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ABSTRACT SUPPLEMENT

2014 ACR/ARHP ANNUAL MEETING

November 14–19, 2014

Boston, MA

American College of Rheumatology
Education • Treatment • Research

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AMERICAN COLLEGE OF RHEUMATOLOGY
ABSTRACT SUPPLEMENT

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

ASSOCIATION OF RHEUMATOLOGY HEALTH PROFESSIONALS
A DIVISION OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

AMERICAN COLLEGE OF RHEUMATOLOGY
78th Annual Meeting

ASSOCIATION OF RHEUMATOLOGY HEALTH PROFESSIONALS
49th Annual Meeting

November 14–19, 2014
Boston, MA

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TUESDAY, NOVEMBER 18, 2014

WEDNESDAY, NOVEMBER 19, 2014

9:00–10:30 AM

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ACR/ARHP ANNUAL MEETING

Pre-meeting Courses: Nov. 14-15, 2014

Scientific Sessions: Nov. 15-19, 2014

ACR Poster Session A
Antiphospholipid Syndrome
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Lymphocyte Proliferation to a Cross-Reactive Gut Commensal Candidate in Antiphospholipid Syndrome. William Ruff[1], Silvio M. Vieira[1], Cassyanne Aguiar[2], John Sterpka[1], Andrew Goodman[3], Doruk Erkan[2] and Martin Kriegel[1]. [1]Yale School of Medicine, New Haven, CT, [2]New York Presbyterian/Weill Cornell Medical Center, New York, NY, [3]Yale School of Medicine, Microbial Diversity Institute, New Haven, CT.

Background/Purpose: Antiphospholipid syndrome (APS) is an autoimmune clotting disorder of unknown etiology targeting a major autoantigen, β_2-glycoprotein I (β_2GPI). Infectious triggers have been implicated in transient autoantibody production, but the persistent stimuli for anti-β_2GPI antibodies remain unknown. Given the vast antigenic potential of the gut microbiota, we hypothesize that human gut commensal bacteria induce and sustain autoreactivity via cross-reactivity. To this end, we characterized APS PBMC reactivity to *in silico* candidates and determined fecal autoantibody production.

Methods: Protein BLAST and Clustal Omega were used to identify commensal protein sequences with high homology to β_2GPI-dominant epitopes. Using anaerobic cultures, we grew isolated candidate and control strains. Blood and stool samples were obtained from anti-β_2GPI-positive patients, non-autoimmune thrombophilia patients, and healthy controls. Stool DNA was isolated using the MoBio extraction kit. A novel species-specific real-time PCR strategy was developed and validated using isolated strains and defined fecal microbiomes. *In vitro* proliferation of PBMC to bacterial protein extracts was assessed by [^{3}H]-thymidine incorporation. An in-house ELISA was established with high-binding plates to analyze anti-β_2GPI levels in plasma and fecal supernatants.

Results: Systematic *in silico* searches revealed *Roseburia intestinalis* as a major candidate for cross-reactivity. *R. intestinalis* is a common colonic gram-positive, flagellated, mucus adhering commensal containing high homology to the main B and T cell epitopes of β_2GPI. *R. intestinalis* colonization load was semi-quantified in patients and controls using real-time PCR. APS PBMC proliferated significantly more to protein extracts from *R. intestinalis* versus control subjects (n=5–6; p=0.0002), and also compared to the closely phylogenetically related, but mimic-deficient gut commensal *Eubacterium rectale* (n=6, p=0.020). Importantly, we were also able to detect anti-β_2GPI IgA antibodies in APS fecal supernatants, which differed significantly compared to controls (n=14–15; p=0.0019).

Conclusion: We have identified a major cross-reactive commensal candidate *in silico* with high homology to dominant β_2GPI epitopes and developed a highly specific real-time PCR-based screening strategy. APS PBMCs proliferated significantly more to candidate protein extracts compared to controls. Furthermore, we report, to our knowledge, for the first time fecal autoantibody production in a non-gut autoimmune disease. Production of fecal anti-β_2GPI IgA in patients with peripheral blood anti-β_2GPI IgG supports our hypothesis of a gut mucosal, cross-reactive trigger in APS, which we are actively pursuing.

Disclosure: W. Ruff, None; **S. M. Vieira**, None; **C. Aguiar**, None; **J. Sterpka**, None; **A. Goodman**, None; **D. Erkan**, None; **M. Kriegel**, None.

2

Thrombocytopenia in Primary Antiphospholipid Syndrome Is Related to Arterial Thrombosis. Ikuma Nakagawa, Kenji Oku, Olga Amengual, Ryo Hisada, Eri Sugawara, Kazumasa Ohmura, Tomoko Fukui, Sanae Shimamura, Haruki Shida, Toshiyuki Watanabe, Yuka Shimizu, Michihito Kono, Takashi Kurita, Toshiyuki Bohgaki, Tetsuya Horita, Shinsuke Yasuda and Tatsuya Atsumi. Hokkaido University Graduate School of Medicine, Sapporo, Japan.

Background/Purpose: Antiphospholipid-associated syndrome refers to organ dysfunctions developed in the existence of antiphospholipid antibodies (aPL), apart from the typical manifestations of antiphospholipid syndrome (APS) such as thromboembolism and pregnancy morbidities. Thrombocytopenia is one of the aPL-associated manifestations and is reported in 20–40% of APS patients. Patients with thrombocytopenia and aPL are at risk of both bleeding and thrombosis. The evaluation of the coagulation status in patients with thrombocytopenia is particularly difficult and the clinical profile of APS patients with thrombocytopenia has not been fully elucidated. The purpose of this study is to analyze the clinical profile of patients with primary APS and thrombocytopenia and to examine the relation between the risk of thrombosis and thrombocytopenia.

Methods: This study comprised of 57 consecutive patients with primary APS and 72 autoimmune disease control patients (non-systemic lupus erythematosus) who visited Hokkaido University Hospital Rheumatology Clinic between January 2000 and May 2014. Thrombocytopenia was defined as a platelet count less than 100,000 per microliter, persistent on two occasions more than 12 weeks apart and without no underlying causes besides aPL. Primary APS patients were retrospectively followed-up for the incidence of thrombosis. Kaplan-Meier survival probability estimate was performed to analyze the occurrence of thrombotic events in primary APS patients with and without thrombocytopenia.

Results: The median age of patients was 41 years (IQR 32–50) in primary APS patients and 50 years (IQR 31–59) in the control group. Thrombocytopenia was more frequently diagnosed in patients with primary APS 17/57(30%) than in the control group 4/72(6%), p<0.001.

In primary APS group, arterial thrombosis was developed in 9 patients (16%) throughout the follow-up period (106 months [IQR 36–142]); 8 patients had cerebral infarctions and 1 myocardial infarction. Arterial thrombosis was more frequently developed in patients with thrombocytopenia than in those without (6/17(35%) vs. 3/40(8%), p=0.014), while no correlation was found between venous thrombosis and thrombocytopenia. There was no statistically significant difference in the rate of hemorrhagic event between APS patients with and without thrombocytopenia (1/17 (6%) vs. 0/40 (0%), p=0.298). Kaplan-Meier curve revealed that the inferior survival was associated with thrombocytopenia (6/9(67%) vs 11/48(23%), p=0.047 log-rank test: Figure1).

Conclusion: Thrombocytopenia in APS patients represents a risk factor for arterial thrombosis and not for bleeding. The risk of thrombosis associated with thrombocytopenia in primary APS must be carefully evaluated and, if necessary, appropriate antithrombotic therapy administered.

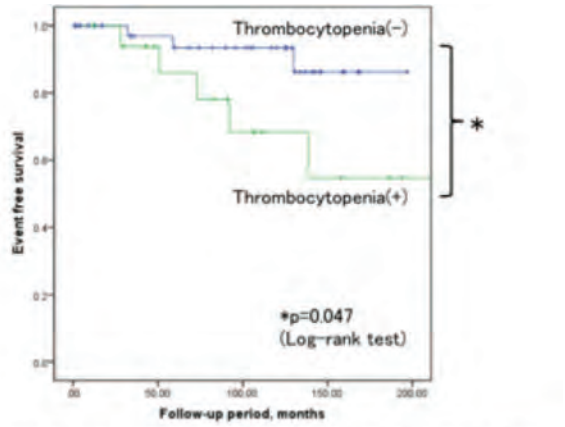

Figure1. Kaplan-Meier curves demonstrating statistically significant difference in arterial thrombosis free survival for primary APS patients with thrombocytopenia(n=17) and without thrombocytopenia(n=40).

Disclosure: I. Nakagawa, None; **K. Oku**, None; **O. Amengual**, None; **R. Hisada**, None; **E. Sugawara**, None; **K. Ohmura**, None; **T. Fukui**, None; **S. Shimamura**, None; **H. Shida**, None; **T. Watanabe**, None; **Y. Shimizu**, None; **M. Kono**, None; **T. Kurita**, None; **T. Bohgaki**, None; **T. Horita**, None; **S. Yasuda**, None; **T. Atsumi**, None.

3

Is There an Association Between Persistently High Positive Antiphospholipid Antibody Profile and Organ Damage Accrual in Lupus Patients? Doruk Erkan[1], Lisa G. Criscione-Schreiber[2], Maria Dall'era[3], Olga Dvorkina[4], Russell Griffin[5], Galina Marder[6], Maureen A. McMahon[7], Jorge Sanchez-Guerrero[8], Amit Saxena[9] and Robert Roubey[10]. [1]Hospital for Special Surgery, New York, NY, [2]Duke University School of Medicine, Durham, NC, [3]University of California, San Francisco, San Francisco, CA, [4]SUNY Health Science Center at Brooklyn, Brooklyn, NY, [5]University of Alabama at Birmingham, Birmingham, AL, [6]North Shore Long Island Health System, Great Neck, NY, [7]UCLA David Geffen School of Medicine, Los Angeles, CA, [8]UHN Toronto Western Hospital, Toronto, ON, [9]New York University School of Medicine, New York, NY, [10]University of North Carolina at Chapel Hill, Chapel Hill, NC.

Background/Purpose: Few studies assessed the impact of antiphospholipid antibodies (aPL) on organ damage in lupus with conflicting results. Our objective was to determine if persistently high positive aPL profiles are associated with organ damage in lupus patients.

Methods: The Lupus Clinical Trials Consortium Inc. (LCTC) Lupus Data Registry consists of consecutively enrolled adults with lupus from 16 US and Canada centers, each contributing ~100 patients. Patients with at least 1 follow-up (f/u) visits who were tested for aPL were analyzed. We investigated the SLICC/ACR Damage Index (SDI) (baseline [BL] and f/u) and the aPL profile (lupus anticoagulant [LA], anticardiolipin antibody [aCL] IgG/M/A, and anti-β_2Glycoprotein-I antibody [aβ_2GPI]) (historically, BL, and f/u). *"High Positive [HP] aPL"* profile was defined as positive LA, aCL IgG/M/A≥40U, and/or aβ_2GPI IgG/M/A≥40U. *"Low Positive [LP] aPL"* profile was negative LA, and aCL or aβ_2GPI IgG/M/A above the laboratory range but <40U. *"Negative aPL"* was negative LA, and aCL and aβ_2GPI IgG/M/A below the laboratory range. *"Persistent aPL"* was based on threshold levels of at least 50%, 60%, or 75% of the tests reported in HP or LP groups (based on ≥2 tests ≥12 weeks apart). A logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals for the association between an increase in SDI (first to last) and aPL-positivity adjusted for SDI at entry.

Results: Among 1506 patients, 1417 (94%) had at least 1 f/u visit, 1392/1417 (98%) had at least 1 aPL result, 1310/1392 (94%) had analyzable aPL (82 excluded; missing aCL/aβ_2GPI levels), and 816/1310 (62%) had ≥2 tests ≥12 weeks apart, or at least 1 triple negative aPL result. Tables demonstrate the crude and adjusted odds ratios for SDI increase based on different SDI accrual points and aPL profiles.

Table 1 Odds ratios* and 95% confidence intervals for the association between aPL profile and SDI accrual of ≥ 1 points from baseline

Persistence threshold	HP-Persistent	LP-Persistent	Negative	p-value$_{trend}$
≥ 50%				
N (% with damage)	**59 (23.7)**	**92 (13.0)**	**632 (24.7)**	
Mean follow-up (years)	1.69±0.78	1.98±0.64	1.65±0.81	
Crude	0.95 (0.51–1.78)	0.46 (0.24–0.86)	Referent	
Adjusted†	0.91 (0.47–1.74)	0.52 (0.27–0.99)	Referent	0.2535
≥ 60%				
N (% with damage)	**14 (28.6)**	**73 (12.3)**	**696 (24.3)**	
Mean follow-up (years)	1.42±0.71	2.01±0.52	1.66±0.81	
Crude	1.25 (0.39–4.03)	0.44 (0.21–0.90)	Referent	
Adjusted†	1.02 (0.30–3.39)	0.49 (0.24–1.03)	Referent	0.1903
≥ 75%				
N (% with damage)	**12 (33.3)**	**70 (12.9)**	**701 (24.1)**	
Mean follow-up (years)	1.38±0.70	2.00±0.63	1.67±0.80	
Crude	1.57 (0.47–5.29)	0.46 (0.23–0.96)	Referent	
Adjusted†	1.38 (0.40–4.80)	0.52 (0.25–1.08)	Referent	0.3458

* Estimated from logistic regression - † Adjusted for SDI at study enrollment

Table 2 Odds ratios* and 95% confidence intervals for the association between aPL profile and damage accrual of ≥ 2 points from baseline

Persistence threshold	HP-Persistent	LP-Persistent	Negative	p-value$_{trend}$
≥ 50%				
N (% with damage)	**61 (13.1)**	**100 (3.0)**	**649 (9.2)**	
Mean follow-up (years)	1.81±0.77	2.07±0.59	1.83±0.77	
Crude	1.48 (0.67–3.26)	0.30 (0.09–0.99)	Referent	
Adjusted†	1.52 (0.67–3.44)	0.36 (0.11–1.19)	Referent	0.8744
≥ 60%				
N (% with damage)	**15 (26.7)**	**78 (3.9)**	**717 (8.9)**	
Mean follow-up (years)	1.46±0.76	2.10±0.56	1.84±0.76	
Crude	*3.71 (1.15–11.99)*	0.41 (0.13–1.33)	Referent	
Adjusted†	3.15 (0.94–10.56)	0.49 (0.15–1.63)	Referent	0.5129
≥ 75%				
N (% with damage)	**13 (30.8)**	**75 (4.0)**	**722 (8.9)**	
Mean follow-up (years)	1.42±0.75	2.09±0.57	1.85±0.76	
Crude	*4.57 (1.37–15.25)*	0.43 (0.13–1.40)	Referent	
Adjusted†	*4.13 (1.19–14.36)*	0.51 (0.15–1.69)	Referent	0.3576

* Estimated from logistic regression - † Adjusted for SLICC at study enrollment

Table 3 Odds ratios* and 95% confidence intervals for the association between aPL profile and SDI accrual of ≥ 3 points from baseline

Persistence threshold	HP - Persistent	LP - Persistent	Negative	p-value$_{trend}$
≥ 50%				
N (% with damage)	**62 (8.1)**	**103 (4.9)**	**651 (4.5)**	
Mean follow-up (years)	1.87±0.74	2.05±0.59	1.88±0.75	
Crude	1.88 (0.70–5.05)	1.09 (0.41–2.89)	Referent	
Adjusted†	1.95 (0.70–5.43)	1.40 (0.51–3.85)	Referent	0.173
≥60%				
N (% with damage)	**17 (17.7)**	**81 (6.2)**	**718 (4.3)**	
Mean follow-up (years)	1.73±0.74	2.08±0.57	1.88±0.75	
Crude	*4.75 (1.30–17.39)*	1.46 (0.55–3.86)	Referent	
Adjusted†	3.77 (0.99–14.39)	1.88 (0.69–5.17)	Referent	*0.0283*
≥75%				
N (% with damage)	**14 (14.3)**	**78 (6.4)**	**724 (4.4)**	
Mean follow-up (years)	1.68±0.73	2.06±0.58	1.89±0.75	
Crude	3.60 (0.77–16.78)	1.48 (0.56–3.92)	Referent	
Adjusted†	2.92 (0.60–14.30)	1.89 (0.69–5.17)	Referent	0.0822

* Estimated from logistic regression -† Adjusted for SDI at study enrollment

Conclusion: Our results suggest that persistently high aPL profiles, particularly those with higher thresholds for persistence, are associated with higher (≥2 or ≥3 points) SDI score accrual in lupus patients. Given the small number of patients with persistently high aPL profiles, limited analysis of potential confounders, and possibility of confounding by indication (more frequent aPL testing in patients with more severe disease/damage), further analysis of the LCTC Lupus Data Registry will clarify if aPL is a risk factor for or rather a marker of organ damage.

Disclosure: D. Erkan, Lupus Clinical Trials Consortium, 2; **L. G. Criscione-Schreiber**, Lupus Clinical Trials Consortium, 2; **M. Dall'era**, Lupus Clinical Trials Consortium LCTC, 2; **O. Dvorkina**, Lupus Clinical Trials Consortium, 2; **R. Griffin**, Lupus Clinical Trials Consortium, 2; **G. Marder**, Lupus Clinical Trials Consortium LCTC, 2; **M. A. McMahon**, Lupus Clinical Trials Consortium LCTC, 2; **J. Sanchez-Guerrero**, Lupus Clinical Trials Consortium LCTC, 2; **A. Saxena**, Lupus Clinical Trials Consortium, 2; **R. Roubey**, Lupus Clinical Trials Consortium LCTC, 2.

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Detection of Anti-Beta2glycoprotein I Domain 1 Antibodies By an Automated Chemiluminescence Assay in a Cohort of 400 Clinically Characterized Consecutive Routine Samples. Laura Andreoli[1], Alessandra Zanola[1], Cecilia Nalli[1], Flavio Allegri[1], Michael Mahler[2], Gary Norman[2] and Angela Tincani[1]. [1]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [2]INOVA Diagnostics, San Diego, CA.

Background/Purpose: Several studies suggested that antibodies to Domain 1 of beta2glycoprotein I (a-B2GPI-D1) represent a promising biomarker for the diagnosis and risk assessment of Antiphospholipid Syndrome (APS). This evidence comes from case-control studies with clinically defined APS patients and disease and healthy controls. This study aims to investigate the performance of a-B2GPI-D1 in a cohort of consecutive, clinically characterized samples derived from a routine diagnostic workup for the detection of antiphospholipid antibodies (aPL).

Methods: A total of 400 samples with a complete aPL panel (aCL IgG/IgM and a-B2GPI IgG/IgM by an in-house ELISA, Lupus Anticoagulant -LA- tested with a DRVVT and aPTT based method) were collected. All the samples were tested for aCL IgG/IgM, anti-B2GPI IgG/IgM, and anti-B2GPI-D1 IgG by QUANTA Flash CIA (INOVA). The clinical diagnosis/reason for aPL detection was retrieved from hospital records. The classification of APS was based on the Sapporo revised criteria. Systemic Lupus Erythematosus (SLE) was defined according to ACR criteria. Undifferentiated Connective Tissue Disease (UCTD) was classified upon international criteria.

Results: Out of 400 samples, 71 (14.5%) were positive for a-B2GPI IgG by either ELISA or CIA. Eighteen samples (4.5%) were positive for both a-B2GPI-D1 and a-B2GPI IgG by either ELISA or CIA assay, with the exception of 2 samples which were positive at low titer for a-B2GPI-D1 only (one positive also for aCL IgG CIA at low titer). These 2 sample derived from one patient with stroke and from one patient with recurrent pregnancy loss, both under investigation. Ten patients displayed a triple aPL positive profile (LA, aCL and anti-B2GPI positive at both ELISA and CIA). A significant association was found between the presence a-B2GPI-D1 (especially at medium-high titer) and triple aPL positivity (Chi Squared=195.468, p< 0.0001). Among 55 patients with positive a-B2GPI IgG (45 at low titer, 10 at medium-high titre) and negative a-B2GPI-D1 IgG, 47 (85.5%) had clinical features compatible with either APS (n=20) and/or systemic autoimmune rheumatic disease (SARD) (n=27).

ID code	a-B2GPI-D1 IgG CIA (<19.9 CU)	a-β2GPI IgG ELISA (<0.130 OD)	a-β2GPI IgG CIA (<20 CU)	aCL IgG ELISA (<10 GPL)	aCL IgG CIA (<20 CU)	LA	Clinical features/ diagnosis
24-Jan	**20.4**	Neg (0.014)	Neg (<6.4)	Neg (2.7)	Neg (<2.6)	Neg	Stroke under investigation
4-Mar	**22.1**	**Pos (0.52)**	**Pos (40.5)**	Neg (2.3)	Neg (7.7)	Neg	Reduction in visual acuity of the right eye
16-May	**23.8**	Neg (0.041)	**Pos (44.4)**	Neg (6.7)	**Pos (25.1)**	**Pos**	UCTD+obstetric APS

Jan-71	**24.1**	**Pos (0.748)**	**Pos (262.3)**	**Pos (37.5)**	**Pos (85.2)**	Neg	Obstetric Primary APS
29-Mar	**36**	Neg (0.029)	Neg (14.0)	Neg (3.9)	**Pos (22.6)**	Neg	Recurrent Pregnancy Loss under investigation
Apr-35	**37.7**	Neg (0.090)	**Pos (21.7)**	Neg (7.3)	Neg (11.5)	Neg	Fibromyalgia
May-54	**64.5**	**Pos (0.534)**	**Pos (157.9)**	**Pos (15.6)**	**Pos (61.3)**	**Pos**	SLE
3-Feb	**71**	**Pos (0.823)**	**Pos (971.5)**	**Pos (26.5)**	**Pos (134.3)**	Neg	UCTD
May-35	**71.8**	**Pos (1.564)**	**Pos (1864.9)**	**Pos (82.5)**	**Pos (459.0)**	**Pos**	UCTD
Feb-73	**86.7**	**Pos (1.248)**	**Pos (1037.9)**	**Pos (15.6)**	**Pos (368.3)**	Pos	SLE+obstetric APS
Mar-54	**108.9**	**Pos (1.734)**	**Pos (2850.0)**	**Pos (51.8)**	**Pos (687.9)**	**Pos**	UCTD
Feb-31	**114.4**	**Pos (0.341)**	**Pos (369.9)**	**Pos (19.4)**	**Pos (85.7)**	**Pos**	SLE+ vascular APS
Feb-69	**137.7**	**Pos (1.037)**	**Pos (488.2)**	**Pos (18.8)**	**Pos (222.0)**	**Pos**	SLE
Jan-72	**206**	**Pos (0.983)**	**Pos (466.6)**	**Pos (17.7)**	**Pos (220.2)**	**Pos**	Obstetric Primary APS
6-Mar	**285.3**	**Pos (0.997)**	**Pos (614.6)**	**Pos (23.7)**	**Pos (193.6)**	**Pos**	Vascular and Obstetric Primary APS
Feb-64	**419.1**	**Pos (2.231)**	**Pos (8893.1)**	**Pos (70.9)**	**Pos (4693.6)**	Neg	Vascular and Obstetric Primary APS
10-Apr	**1003.8**	**Pos (2.398)**	**Pos (8647.2)**	**Pos (68.1)**	**Pos (1760.5)**	**Pos**	UCTD with obstetric APS
Mar-39	**1319.2**	**Pos (2.342)**	**Pos (5764.7)**	**Pos (>140.0)**	**Pos (1294.2)**	**Pos**	SLE+Obstetric APS

Conclusion: In a diagnostic routine setting for aPL, medium-high titer a-B2GPI-D1 were found to cluster in patients with triple aPL positivity. a-B2GPI-D1 were present mainly in patients with APS-related clinical manifestations and in patients with SARD. Nearly 80% of sample positive for a-B2GPI IgG did not display any reactivity toward D1 and the majority of these patients had a diagnosis of APS/SARD, suggesting that clinically significant a-B2GPI IgG antibodies can also be directed against other epitopes of the B2GPI molecule.

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Antiphospholipid-Associated Nephropathy Is a Risk for Developing Arterial Thromboses in Patients with Systemic Lupus Erythematosus. Tomoko Fukui, Shinsuke Yasuda, Toshiyuki Watanabe, Kazumasa Ohmura, Sanae Shimamura, Ikuma Nakagawa, Atsushi Noguchi, Haruki Shida, Yuka Shimizu, Michihito Kono, Takashi Kurita, Kenji Oku, Toshiyuki Bohgaki, Olga Amengual, Tetsuya Horita and Tatsuya Atsumi. Hokkaido University Graduate School of Medicine, Sapporo, Japan.

Background/Purpose: Antiphospholipid-associated nephropathy (APLN) is characterized by coexistence of antiphospholipid antibodies (aPLs) and renal small-vessel vasculopathy/chronic renal ischemia. Consequences of APLN to thrombosis have yet to be known. We aimed in this study to clarify the characteristics and thrombotic risk of APLN in patients with lupus nephritis (LN).

Methods: Patients with LN proven by renal biopsy from January 2000 to February 2014 were included. A total of 90 patients were histologically diagnosed as having LN according to the ISN/RPS classification. APLN was diagnosed when both aPLs and at least one of the following pathological features were present, thrombotic microangiopathy (TMA), fibrous intimal hyperplasia (FIH), fibrocellular arterial occlusion (FAO), focal cortical atrophy (FCA) or tubular thyroidization (TUB) according to the criteria (Miyakis S *et al*. J Thromb Haemost 2006). Patients with antiphospholipid syndrome were excluded. aPLs including lupus anticoagulant, IgG/M anticardiolipin antibody, IgG/M anti-b2-glycoprotein I antibody and IgG/M phosphatidylserine dependent antiprothrombin antibody were measured. Clinical features of APLN patients were retrospectively analyzed. Development of arterial thrombosis was retrospectively observed. Log-rank test was introduced for the comparison between those with APLN and without.

Results: Among 90 patients with biopsy-proven LN, 21 were excluded (10 with APS, 5 without tests for aPLs and 6 for other reasons) and the rest 69 patients were recruited in the study. The median age and mean disease duration was 33 years old and 4.8 years, respectively. Twelve patients (17.4%) were diagnosed as APLN (9 FCA, 5 FIH, 1 FAO and 1 TUB) and 10 as APLN-like disease without aPL and with pathological features. Patients with APLN had higher frequency of hypertension (p-value by chi-square test = 0.002). APLN patients more frequently developed arterial thrombosis during the median observation period of 53 months (p-value by log-rank test = 0.018) compared with patients without APLN. Among patients positive for aPLs, patients with APLN had higher frequency of hypertension (p-value < 0.001) and developing arterial thrombosis (p-value=0.046) than patients without APLN. (Figure)

Conclusion: APLN was found in 17% of LN and associated with hypertension. APLN with LN is a possible risk for developing arterial thrombosis, although prospective study in a larger cohort would be necessary.

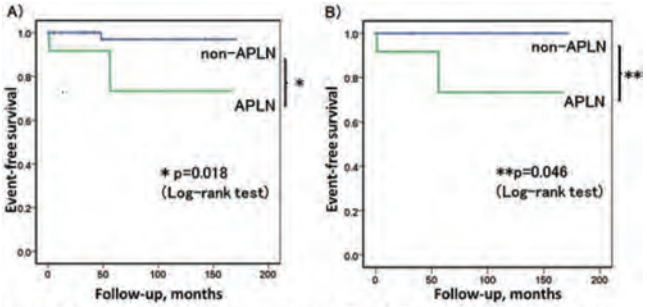

Figure. Kaplan-Meier curves demonstrating significant difference in arterial thrombosis-free survival for patients A) with APLN (n=12) and without APLN (n=57). B) with APLN (n=12) and without APLN (n=19) among patients of positive for aPLs.

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6

Performance Evaluation and Clinical Associations of the Aphl ELISA Compared to Criteria Antiphospholipid Immunoassays in Lupus Patients. Yu Zuo[1], Rohan Willis[2], Emilio Gonzalez[3], Allan Brasier[4], Michelle A. Petri[5], Elizabeth Papalardo[6], E Nigel Harris[7], Hong Fang[8], Karel De Ceulaer[9], Monica Smikle[10], Luis M. Vila[11], John D. Reveille[12], Graciela S. Alarcon[13] and Silvia Pierangeli[14]. [1]UT Southwestern Medical Center, Dallas, TX, [2]UTMB - Galveston, Galveston, TX, [3]University of Texas Medical Branch, Galveston, TX, [4]UTMB-Galveston, Galveston, TX, [5]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [6]Louisville APL Diagnostic, seabrook, TX, [7]The University of the West Ind, Kingston, Jamaica, [8]John Hopkins University School of Medicine, Baltimore, MD, [9]Medicine, Kingston, Jamaica, [10]University of the West Indies, Kgn 7, Jamaica, [11]University of Puerto Rico Medical Sciences Campus, San Juan, PR, [12]University of Texas Health Science Center at Houston, Houston, TX, [13]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [14]Univ of TX Medical Branch, Galveston, TX.

Background/Purpose: Antiphospholipid Syndrome (APS) is characterized by recurrent thrombotic and obstetric manifestations in the presence of 'criteria' antiphospholipid antibodies (aPL) [anticardiolipin (aCL), anti-β2glycoproteinI (anti-β2GPI) and lupus anticoagulant (LA)]. However, aCL assays lack specificity, while anti-β2GPI assays lack sensitivity in the classification/diagnosis of APS. The APhL ® assay (Louisville APL Diagnostics), which detects antibodies against a mixture of negatively charged phospholipids, has been shown to be more specific and as sensitive as aCL in the diagnosis of APS in small observational studies. Our aim was to examine the performance of this assay in a large group of ethnically diverse lupus patients.

Methods: A total of 1178 serum samples from patients with lupus (1997 ACR criteria) from the HOPKINS (n=543), LUMINA (n=588) and Jamaican cohorts (n=47) were examined for IgG and IgM positivity in aCL (in-house), anti-β2GPI (INOVA) and APhL ELISA assays. Chi-squared or Fisher's exact test univariate analysis along with odds ratios/95% confidence intervals were used to evaluate assay correlation with clinical features (SPSS® v20.0). ROC analysis was performed to determine sensitivity, specificity, and likelihood ratios for all assays in predicting clinical features. A case series analysis was also performed of patients in whom criteria aPL assays were negative but the new APhL assay was positive.

Results: Both IgG APHL (OR2.3, 95%CI 1.5–3.7, $p<0.001$) and IgM APHL (OR1.9, 95%CI 1.1–3.4, $p=0.027$) were significantly correlated with thrombosis, while only IgG APHL (OR1.8, 95%CI 1.1–2.9, $p=0.015$) was significantly correlated with pregnancy morbidity. The IgG APHL assay had the greatest performance value as measured by positive likelihood ratio (2.2 for thrombosis and 1.7 for pregnancy morbidity), increased sensitivity as compared to anti-β2GPI, and improved specificity compared to aCL assays (tables 1 and 2). Approximately 2% (23/1178) of our patients tested positive for APHL and negative to criteria assays. Of these, 47.8% (11/23) had APS clinical manifestations, including thrombotic and pregnancy related morbidity.

Conclusion: Overall, APhL antibodies, especially IgG, represent a promising biomarker for the classification of APS patients as well as for risk

assessment in APS patients with regards to pregnancy morbidity and thrombotic manifestations. It has encouraging clinical value and potential to be part of the diagnostic criteria for APS.

Table 1: ROC Analysis: AUC, Sensitivity, Specificity and LR+ of Assays for Predicting Thrombosis

Any Thrombosis	AUC	AUC p-value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+
APHL_IgG	0.558	0.004	13.8	93.8	40.2	78.3	2.2
APHL_IgM	0.531	0.131	6.7	96.2	34.6	77.3	1.8
ACL_IgG	0.477	0.253	25.8	80.1	28.2	78.1	1.3
ACL_IgM	0.377	<0.0001	16.6	75.5	17	74.9	0.8
B2GPI_IgG	0.594	<0.0001	8.9	95.9	39.3	77.7	2.1
B2GPI_IgM	0.578	0.0001	4.1	97.5	33.3	77.1	1.7

Table 2: ROC Analysis: AUC, Sensitivity, Specificity and LR+ of Assays for Predicting Pregnancy Morbidities

Any Preg Morbidity	AUC	AUC p-value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+
APHL_IgG	0.580	<0.0001	9.8	94.2	41.7	70.9	1.7
APHL_IgM	0.523	0.244	4.9	95.7	32.6	70.2	1.1
ACL_IgG	0.456	0.024	19.2	77.9	27.1	69.3	0.9
ACL_IgM	0.417	<0.0001	17.9	73.3	22.3	67.7	0.7
B2GPI_IgG	0.573	0.0002	2.9	94.2	17.6	69.4	0.5
B2GPI_IgM	0.573	0.0002	3.3	97.1	32.3	70.2	1.1

AUC: area under the curve.
PPV: positive predicting value.
NPV: negative predicting value.
LR+: positive likelihood ratio.
Pregnancy morbidity: presence of miscarriage and/or pre-eclampsia/eclampsia.
Thrombosis: PE, DVT, TIA/CVA

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Beneficial Effects of *in Vivo* Ubiquinol Supplementation on Athero-Thrombosis Prevention in Antiphospholipid Syndrome Patients. Chary Lopez-Pedrera[1], Carlos Perez-Sanchez[1], Ángeles Aguirre Zamorano[1], Nuria Barbarroja[1], Patricia Ruiz-Limon[1], Yolanda Jiménez Gómez[1], Munther A. Khamashta[2], Antonio Rodriguez-Ariza[3], Jose Antonio Gonzalez-Reyes[4], Jose Manuel Villalba[4], Eduardo Collantes-Estevez[1] and M[a] Jose Cuadrado[5]. [1]IMIBIC-Reina Sofia University Hospital, Cordoba, Spain, [2]Lupus Research Unit, The Rayne Institute, St Thomas Hospital, Kings College London School of Medicine, London, United Kingdom, [3]IMIBIC-Reina Sofia Hospital, Cordoba, Spain, [4]University of Cordoba, Agrifood Campus of International Excelence (ciA3), Cordoba, Spain, [5]The Rayne Institute, London, United Kingdom.

Background/Purpose: To investigate the beneficial effects of *in vivo* ubiquinol (Q) supplementation on athero-thrombosis prevention in APS patients.

Methods: The study was performed on 10 APS patients randomized to receive either Q (200 mg/day) or placebo for one month. Blood was drawn at time 0 and at the end of the treatment. Studies were conducted in plasma and purified leukocytes subsets. Plasma Q levels and various prothrombotic/proinflammatory parameters and oxidative stress biomarkers were evaluated. Endothelial activity analysis was performed by Laser-Doppler flowmetry measurement of post ischemic reactive hyperemia.

Results: All patients completed the intervention, which increased significantly plasma Q levels. CD14highCD16- classical monocyte count was not significantly changed after Q treatment but CD14highCD16+ intermediate monocytes and CD14dimCD16high non-classical monocytes were decreased. Q treatment decreased significantly Tissue Factor (TF) expression levels in total monocytes, and more notably in CD14highCD16+ intermediate monocytes which also displayed a more robust reduction of intracellular IKK levels. Only this monocytes subset exhibited IL-8 reduction after intervention. Q supplementation produced a significant reduction in both the levels of peroxides and the percentage of monocytes with altered mitochondrial membrane potential ($\Delta\Psi m$), and in six of the ten patients evaluated endothelial function was improved as shown by a significant amelioration in the highest perfusion value after occlusion was released, expressed as a percentage of change vs rest flow value (RF-PF). Q effects were particularly relevant in APS patients suffering from arterial thrombosis (AT) in comparison to those with venous thrombosis (VT) or obstetrical manifestations (OM) since TF expression, being particularly higher at baseline in AT patients, showed a more pronounced decline and endothelial function was better improved.

Correlation studies showed that reduced monocyte TF expression after Q treatment were related to both decreased peroxides levels and increased plasma Q levels. The decrease of CD14dimCD16high non-classical monocytes count was related to the reduction in the percentage of cells with altered $\Delta\Psi m$ as well as with the increase in RF-PF value. Improvement in endothelial function was further related to reduction of peroxide levels and to reduced TF expression on non-classical monocytes.

Conclusion: Q supplementation at 200 mg/d significantly reduced TF expression and oxidative stress markers in monocytes from APS patients, which were further related to an improvement on endothelial function. Our results support the potential impact of Q in the prevention of atherothrombosis in APS patients.

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Safety and Efficacy of New Oral Direct Inhibitors of Thrombin and Factor Xa in Antiphospholipid Syndrome. Nicolas Noel[1], Fabien Dutasta[2], Nathalie Costedoat-Chalumeau[3], Boris Bienvenu[4], Xavier Mariette[5], Loik Geffray[6], Damien Sène[7], Jean-Marie Michot[1], Olivier Fain[8], Luc Darnige[9], Annick Ankri[10], Patrice Cacoub[11], Jean-Charles Piette[11] and David Saadoun[11]. [1]APHP, Hopital Bicêtre, Service de Médecine Interne et Immunologie Clinique, Le Kremlin Bicêtre, France, [2]Hôpital d'Instruction des Armées Percy, Service de Médecine Interne, Clamart, France, [3]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [4]CHU Côte de Nacre, CAEN, France, [5]Université Paris-Sud, Le Kremlin Bicêtre, France, [6]CH Lisieux, Service de Médecine Interne, Lisieux, France, [7]Hopital Lariboisière, service de Médecine Interne, Paris, France, [8]Hôpital Saint Antoine, DHU i2B, Service de Médecine Interne, paris, France, [9]Hôpital Européen Georges Pompidou, service d'hématologie biologique, Paris, France, [10]Groupe Hospitalier Pitié Salpétrière, service d'hématologie biologique, Paris, France, [11]Groupe Hospitalier Pitié Salpétrière, Service de Médecine Interne, DHU i2B, Paris, France.

Background/Purpose: Long term anticoagulation is recommended in antiphospholipid syndrome with thrombosis in order to prevent recurrences. While the current mainstay relies on vitamin K antagonists, their long term maintenance may remain challenging. Our aim was to report on the safety and the efficacy of new oral direct inhibitors of thrombin and factor Xa (ODIs) in antiphospholipid syndrome (APS).

Methods: Descriptive analysis of patients with APS enrolled in a French multicentre observational cohort between January 2012 and March 2014 and receiving ODIs. Clinical, biological, and therapeutic data were retrospectively analyzed. The main primary outcome was the occurrence of a thrombotic recurrence. Secondary outcomes included adverse effects – notably hemorrhagic episodes, and biological tolerance. Kaplan-Meier survival analyses were performed to take into account censored data, using therapeutic interruptions/modifications as events.

Results: Twenty-four patients with APS (primary in 11) received ODIs. The median [IQR] age at APS diagnosis was 41 [23–50] years, and the median duration of disease was 3 [1–11] years at introduction of the anti-thrombotic agent. Antiphospholipid antibodies (Abs) included anticardiolipin Abs (n=21/24, IgG isotype in 20), lupus anticoagulant (n=16/22), and IgG anti-β2glycoprotein I Abs (n=6/24).

ODIs included dabigatran (n=11), and rivaroxaban (n=13). Nineteen patients had been previously treated with VKA (n=18), or fondaparinux (n=1) for a median duration of 3 years. ODIs were introduced as second-line therapy because of INR lability/therapeutic simplification (n=16), recurrent thrombosis (n=1), VKA's associated bleeding event (n=1), atrial fibrillation (n=1). Five patients received ODIs as first-line therapy. After a median follow-up of 15 [8–21] months, one relapse of arterial thrombosis, two bleeding events (hypermenorrhea and rectal bleeding under Rivaroxaban) and one recurrent migraine were reported, leading to discontinuation of therapy in these 4 patients. Overall, the event-free survival rate was of 86.6% at 12 months using Kaplan-Meier curve analysis.

Conclusion: ODIs might be an alternative therapeutic option in APS, especially for patients with INR lability. Prospective studies are warranted to evaluate their safety in this condition.

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A Risk-Stratified Perioperative Management Strategy for Antiphospholipid Antibody Positive Patients Undergoing Kidney Transplantation. Vinicius Domingues[1], Darshana Dadhania[2], Choli Hartono[2], Raymond Pastore[2] and Doruk Erkan[3]. [1]New York Presbyterian Hospital, New York, NY, [2]New York Presbyterian Hospital, new york, NY, [3]Hospital for Special Surgery; Barbara Volcker Center for Women and Rheumatic Diseases, New York, NY.

Background/Purpose: Antiphospholipid antibody (aPL) positive patients undergoing kidney transplantation (Tx) are at increased risk for perioperative complications. The objective of this study was to analyze the outcomes of aPL-positive patients who were managed by a risk-stratified perioperative "standard of care" protocol while undergoing kidney Tx.

Methods: We designed a "standard of care" protocol based on patient's *immunological* and *aPL* risk profiles. *Low Immunological Risk (IR)* was defined as negative donor flow crossmatch (T and B cell XM) with/without donor specific antibodies; *Moderate IR* was defined as positive donor flow crossmatch (T and/or B cell XM) with positive donor specific antibodies; and *High IR* defined as was ABO incompatibility OR positive donor CDC T cell crossmatch with positive donor specific antibodies. *Low aPL Risk* was defined as anticardiolipin antibody (aCL) or anti-β_2Glycoprotein-I (aβ_2GPI) IgG/M/A 20–39U at least twice $\geq$ 12w apart AND negative lupus anticoagulant (LA) test; *High aPL Risk* was aCL/aβ_2GPI IgG/M/A $\geq$40U OR a positive LA test twice $\geq$ 12w apart. We categorized patients into 6 groups and assigned different management strategies to each group (Table). For this descriptive preliminary analysis, we retrospectively reviewed the charts for perioperative and 6-month follow-up thrombosis, graft failure, and glomerular filtration rate (GFR).

Risk Stratification	Low IR Low aPL	Low IR High aPL	Moderate IR Low aPL	Moderate IR High aPL	High IR Low aPL	High IR High aPL
Pre-Tx Immunosuppressive	No	No	Rituximab	Rituximab	Rituximab	Rituximab
Regimen			MMF	MMF	MMF	MMF
Pre-Tx Antiplatelet/	Pre-Transplant Warfarin (+): Bridge Anticoagulation with Heparin					
Anticoagulation	Pre-Transplant Warfarin (−): ASA 81 mg daily for low aPL-risk					
Post-Tx Immunosuppressive	Induction Therapy*					
Regimen	MMF Tacrolimus	MMF Tacrolimus IVIG	MMF Tacrolimus Prednisone	MMF Tacrolimus Prednisone IVIG**	MMF Tacrolimus Prednisone	MMF Tacrolimus Prednisone IVIG**
Post Tx Antiplatelet/ Anticoagulation***	Aspirin 8–12w	UFH to Warfarin 8–12w	Aspirin 8–12w	UFH to Warfarin 8–12w	Aspirin 8–12w	UFH to Warfarin 8–12w

* Induction therapy consists in either Thymoglobulin 5 doses OR Basiliximab 2 doses AND pulse steroids for 4 days; ** The only immunosuppressive agent given for aPL-purposes; *** For patients who are not on long-term warfarin treatment. MMF: Mycophenolate Mofetil; UFH: Unfractionated Heparin.

Results: Eight patients (mean age: 49.2 $\pm$ 19.3; female: 4) underwent kidney transplantation (4 low IR/aPL risk; 2 low IR and high aPL risk; and 2 moderate IR and high aPL risk). Reasons for kidney Tx were lupus nephritis (5), polycystic kidney disease (2), and focal segmental glomerulosclerosis (1). No delayed graft function, thrombosis, or thrombotic microangiopathy were reported in the 6-month postoperative time. Median glomerular filtration rates at 30 days and 6-month post Tx were 70.65 (range 54–86) ml/min and 79.95 (range 36–112) ml/min, respectively. Median spot urine albumin-to-creatinine ratios at 30 days and 6-month post Tx were 53.3 mg/g (range 7–535) and 23.5 mg/g (range 5–244), respectively. One patient had perinephric hematoma on postoperative day one that was drained without further complications.

Conclusion: Our preliminary analysis suggests that a risk-stratified perioperative management strategy based on immunological and aPL risk profiles of aPL-positive patients undergoing kidney transplantation is safe. Future analysis of aPL-positive patients undergoing transplantation with and without risk-stratified management approach will determine if our approach improves clinical outcomes.

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Antiphospholipid Antibodies and Neuropsychiatric Events in Pediatric Patients. Mileka Gilbert[1] and Lenore M. Buckley[2]. [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]Yale School of Medicine, New Haven, CT.

Background/Purpose: An association between anti-phospholipid antibodies (aPL abs) and non-thrombotic neuropsychiatric events has been reported in pediatric and adult patients, including patients who do not have SLE. We reviewed the records of children with aPL abs follow at VCU Health System to assess the prevalence and type of neuropsychiatric events.

Methods: We retrospectively identified all pediatric patients with persistently positive aPLabs (two positive tests 12 weeks apart) followed in the Division of Rheumatology at VCU Health System from 1997 through 2012. Demographic, clinical, and serologic information were collected through chart review including details of clinical presentation, anti-phospholipid antibody testing over time, other autoantibodies, and information about treatment and clinical course.

Results: Twenty nine pediatric patients with aPL abs were identified. The average age at diagnosis was 13 years and average follow up was 6 years (range 1–12 years). Sixty six percent of the children were African American and 92% were female. Sixteen children (55%) met criteria for pediatric lupus (pSLE) and 13 (45%) did not. Of the children who did not meet criteria for pSLE, 4 had a positive ANA and 4 had other autoantibodies (3 with SSA, 1 with low positive DSDNA). Eight patients (28%) met criteria for antiphospholipid antibody syndrome (APS) including 4 (25%) patients with pSLE (1 CVA, 2 with pregnancy loss, 1 thrombotic skin ulcer) and 4 (31%) of those who did not meet criteria for pSLE (1 DVT, 2 with CVA, 1 with catastrophic APS). Of those children with aPL abs who did not meet criteria for pSLE, presenting symptoms included hemolytic anemia in 3 and thrombocytopenia in 7, with some children presenting with both.

Neurologic problems were common in children with aPL abs. 21 (72%) of children with aPL abs had a neurologic diagnosis and headache was the most common (12, 41%). One child had chorea and 2 had a CVA. Of note, 10 (63%) of children with pSLE and 4 (31%) of those with aPL abs alone had a psychiatric diagnosis, including major depression in 14 (with one suicide attempt), obsessive compulsive disorder (1), oppositional defiance disorder (4), schizophrenia (1), and bipolar disorder (1). Two children were in residential care for behavioral disorders (one with pSLE and one without). Among the 41 pSLE patients followed at VCUHS who did not have aPL abs, 17% had a major psychiatric disorder ($p=0.003$ compared to all children with aPL abs).

Conclusion: An association between aPL abs and neuropsychiatric events has previously been reported in adults and children but mood disorders and psychiatric diagnoses have not been consistently found in published series of children with aPL abs. In this cohort followed at VCU, children with both pSLE with aPL abs were more likely to have a psychiatric diagnoses than children with pSLE without aPL abs and children with aPL abs alone also had a high prevalence of psychiatric diagnoses. Although the personal and functional impact of these neuropsychiatric diagnoses is significant, their etiology and responsiveness to treatment is unclear.

Disclosure: M. Gilbert, None; **L. M. Buckley**, None.

11

Sustained Moderate Intensity Levels of Oral Anticoagulant Therapy and the Rate of Recurrent Thrombosis in Patients with Primary Antiphospholipid Syndrome. Alonso Turrent[1], Gabriela Hernandez-Molina[2] and Antonio R. Cabral[2]. [1]Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico.

Background/Purpose: The current recommended anti-thrombotic therapy for patients with anti-phospholipid syndrome (APS) is oral anticoagulants with an INR intensity between 2–3. This recommendation has been mostly derived from retrospective and prospective randomized studies based on INRs determined at time of thrombosis or the closest available one. The current recommended anti-thrombotic therapy for patients with anti-phospholipid syndrome (APS) is oral anticoagulants with an INR intensity between 2–3. This recommendation has been mostly derived from retrospective and prospective randomized studies based on INRs determined at time of thrombosis or the closest available one.

Objective: To evaluate the rate of re-thrombosis in patients with primary APS (PAPS) during a defined anticoagulation index period.

Methods: We studied patients attending a Tertiary Referral Care Center according to the following inclusion criteria: PAPS (Sydney Criteria), a history of one or more episodes of thrombosis, on oral anticoagulants and $\geq$2 INR determinations per year. Index period was defined as either the time elapsed between the first available INR and the next thrombotic event or the time between the first and last available INRs in rethrombosis-free patients. We also analyzed the number of thrombotic episodes before the index period.

Statistical analysis: We used X^2 test, U-Mann Whitney test and Cox survival analysis.

Results: We studied 81 PAPS patients (73% women) with a mean age of 46.8 ± 15.5 years and a median follow-up of 6.4 years (range 0.15–17). Sixty-four patients did not have an episode of re-thrombosis, while 17 had a new episode of thrombosis during follow-up. The latter by definition was longer in thrombotic-free patients (6.7 vs. 1.9 years, p= 0.003). The median INR during the anticoagulation index period was significantly higher in re-thrombosis-free patients (2.5, 1.1–3.6) compared with patients with recurrent thrombosis (1.9, 1–2.9, p=0.001). The median number of INR determinations per years of follow-up was similar in both groups (4.9 vs. 5.7). The number of thrombotic episodes in re-thrombosis-free patients before the index period (1, 1–4) was lower compared with their re-thrombosed counterparts (3, 1–5, p<0.001). Both differences remained statistically different after Cox analysis (median INR: OR 0.13, 95% CI: 0.05–0.32, p<0.001; history of rethrombosis: OR 17.4 (2.2–133.8, p=0.006). No differences were found between the two groups in the frequencies of ant-cardiolipin (IgG or IgM), anti-b_2-glycoprotein-I (IgG or IgM), lupus anticoagulant, triple marker positivity, dyslipidemia, cigarette consumption, aspirin and immunosuppressive therapy, arterial hypertension and diabetes mellitus.

Conclusion: A sustained INR of 2.5 for secondary thromboprophylaxis in patients with PAPS appears to be protective whereas a previous thrombosis confers risk. PAPS patients were more prone to develop recurrent thrombosis if their INR persistently remained beneath that threshold during follow-up.

Disclosure: A. Turrent, None; **G. Hernandez-Molina**, None; **A. R. Cabral**, None.

12

Non-Criteria Antiphospholipid Antibodies in Obstetrical "seronegative Anti-Phospholipid syndrome". Arsene Mekinian[1], Marie Charlotte Bourrienne[2], Lionel Carbillon[3], Sabine Grootenboer[2], Luc Dechaisemartin[4], Sylvie chollet Martin[2], Olivier Fain[5] and Pascale Nicaise-Roland[6]. [1]Internal Medicine, DHUi2B Saint Antoine Hospital, paris, France, [2]Unité Fonctionnelles d'Immunologie <<Autoimmunité et Hypersensibilités>>, AP-HP, Hôpital Bichat-Claude Bernard, Paris, paris, France, [3]Service de gynécologie-obstétrique, Université Paris 13, AP-HP, Hôpital Jean Verdier, 93140, Bondy, France., Bondy, France, [4]Unité Fonctionnelles d'Immunologie Autoimmunité et Hypersensibilités, AP-HP, Hôpital Bichat-Claude Bernard, Paris, PARIS, France, [5]Hôpital Saint Antoine, DHU i2B, Service de Médecine Interne, paris, France, [6]Unité Fonctionnelles d'Immunologie <<Autoimmunité et Hypersensibilités>>, AP-HP, Hôpital Bichat-Claude Bernard, Paris, Paris, France.

Background/Purpose: The aims of our prospective study were to determine the prevalence of non-criteria aPL and their clinical relevance in a seronegative population with pregnancy morbidity according to Sapporo criteria.

Methods: We included 118 women: 73 with history of pregnancy morbidity according to clinical Sapporo's criteria (SN-APS), 38 patients with confirmed obstetrical APS (SP-APS) and 45 with pregnancy without any obstetrical complication (Controls). Other than APS thrombophilia screening was negative in all women (protein C, S, ATIII, V and II mutations).

The IgG/ IgM anti-phosphatidylethanolamine antibodies (aPE), IgG/IgM anti-phosphatidylserin/prothrombin antibodies (aPS/PT) and IgG anti-annexin 5 antibodies (aANX) were measured by commercial ELISAs (Theradiag, Instrumentation laboratory).

Results: Among the SN-APS group, 47% women presented ≥ 3 early miscarriages, 43% mid-to-late pregnancy loss and 22% premature birth <34 weeks of gestation related to placental insufficiency.

Non-criteria aPL were detected in 32% of SN-APS and 72% SP-APS and 13% controls (p<0.05). Among the non-criteria aPL antibodies, only the aPE IgG were more frequent in SN-APS patients than controls (18% vs 2%; p<0.05) and the levels of IgG aPE and IgG aANX were higher in SN-APS patients (median titres 6 U/mL and 8 U/mL, respectively), than in controls (2 U/mL and 2 U/mL, respectively; p<0.0001)(figures 2–3). Non-criteria aPL antibodies were present in 74% SP-APS versus 33% of SN-APS (p<0.05). APS/PT antibodies were more frequent in the SP-APS group: 48% vs 4.4% in controls and 2.2% in SN-APS (p<0.001). IgA anti-β2GPI antibodies were negative in SN-APS vs 23% SP-APS. Antibodies to anti-domain I of β2GPI were absent in SN-APS vs 30% of SP-APS. None of the five aPL antibodies was associated with specific obstetrical feature in SN-APS.

Conclusion: Our results suggest that non-criteria antibodies can be detected in 33% of women with obstetrical complications suggestive of APS with negative aPL.

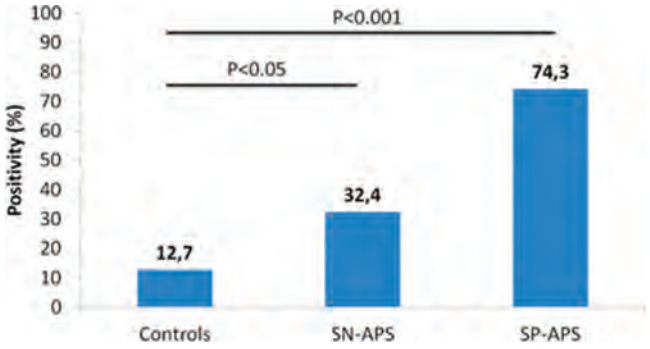

Figure 1. The prevalence of non-criteria APL in SN-APS, SP-APS and controls.

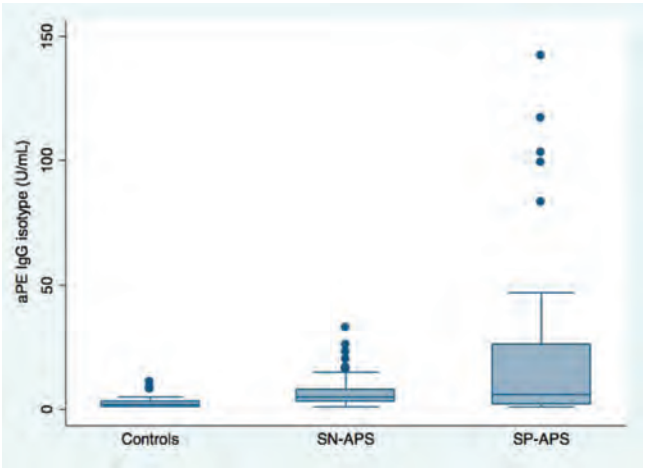

Figure 3. Anti-PE IgG titres in different groups.

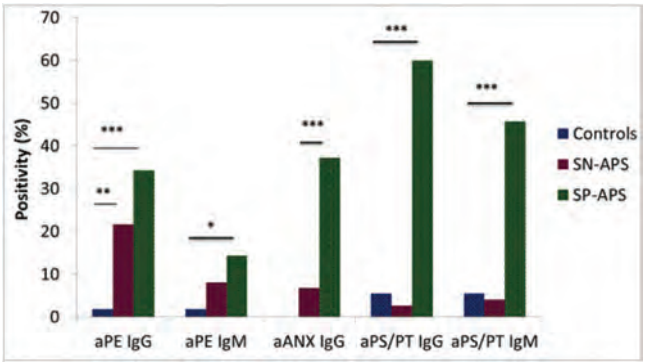

Figure 2. The frequency of different non-criteria APS prevalence in SN-APS, SP-APS and controls.

Disclosure: A. Mekinian, None; **M. C. Bourrienne**, None; **L. Carbillon**, None; **S. Grootenboer**, None; **L. Dechaisemartin**, None; **S. chollet Martin**, None; **O. Fain**, None; **P. Nicaise-Roland**, None.

13

Eculizumab in Antiphospholipid Antibody Syndrome. Ekaterini Zapantis, Richard Furie and Diane Horowitz. North Shore - Long Island Jewish Health System, Great Neck, NY.

Background/Purpose: Antiphospholipid syndrome (APS) is defined as the occurrence of venous or arterial thrombosis and/or pregnancy morbidity, in the presence of serological evidence of antiphospholipid antibodies (including IgM and IgG anticardiolipin antibodies, IgM and IgG anti-beta2-glyoprotein I antibodies, or the lupus anticoagulant). Whereas most patients with focal thrombotic events respond to anticoagulation, occasional patients are refractory to standard therapeutic interventions and continue to have either focal or multifocal occlusive disease. For those with recalcitrant disease or those with the catastrophic antiphospholipid syndrome (CAPS), physicians resort to the addition of anti-platelet agents, steroids, immunosuppressives, IVIG, rituximab, or plasma exchange.

Complement inhibition may be an effective way to prevent thrombosis associated with APS. Eculizumab, a monoclonal antibody that binds to complement protein C5 and prevents the conversion of C5 to C5a and C5b, may potentially be an effective treatment for patients with APS. First studied in patients with systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, and idiopathic membranous nephropathy in the early 2000's, development of the drug for rheumatic diseases was abandoned in favor of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Given the experience of complement inhibition in animal models of APS as well as prior use of eculizumab several years ago in one of our refractory APS patients, we administered eculizumab to three patients with severe refractory APS.

Methods: Two patients with APS, unresponsive to conventional anticoagulant therapy, were treated with a loading dose of eculizumab followed by dosing every other week (Atypical Hemolytic Uremic Syndrome dosing schedule). At the time of submission, the third patient has only received a loading dose. It has been suggested that the platelet count may be used as a surrogate marker of APS activity. During therapy, the patients' platelet counts were monitored and any new thrombotic events documented.

Results: At their lowest values, the patients had platelet counts of 35,000, 22,000 and 18,000 (K/mL). One of the patients was steroid-dependent in order to maintain her platelet count. After initiation of eculizumab, the patient was able to taper steroids as the platelet count had risen from a low of 35,000 to average counts of 100,000. The second patient's platelet count rose to over 200,000 from 22,000 within 10 days of receipt of eculizumab. After receiving one dose of eculizumab, the third patient's platelet count rose from 18,000 to 50,000 within 4 days. For the first two patients, the increases in platelet counts were sustained other than during brief periods when therapy was delayed. During the treatment period (4 and 8 months), there were no new thrombotic events. We will report additional data on the third patient as he proceeds with treatment.

Conclusion: Eculizumab has shown promising results in our patients with refractory APS. Longer follow-up of these patients will be needed in order to discern the effect on thrombosis. Controlled studies are needed to further assess the efficacy of eculizumab in this condition as are mechanistic studies.

Disclosure: E. Zapantis, None; **R. Furie**, None; **D. Horowitz**, None.

14

Rivaroxaban Use in Patients with Antiphospholipid Syndrome Patients and Previous Poor Anticoagulation Control with Vitamin K Antagonists.

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Background/Purpose: Management of antiphospholipid syndrome (APS) centres on attenuating the procoagulant state whilst balancing the bleeding risks of anticoagulant therapy. In a minority of APS patients treated with vitamin K antagonists (VKA) maintaining the INR within the target therapeutic range is still a matter of concern.

Methods: Data from consecutive APS patients attending the Thrombosis and Thrombophilia Center (St Thomas Hospital, London, UK) with poor anticoagulation control with VKA were collected. Inclusion criteria included 1) APS patients treated with VKA with INR target 2–3 for secondary prevention of venous thromboembolism (VTE) 2) Poor Anticogulation Control, defined as 'erratic' pattern (where more time is spent both above and below INR target) or unidirectional pattern (where time out of range is predominantly in one direction-low or high). Time in therapeutic range (TTR) was assed in all the included patients. Included patients were switched to rivaroxaban 20 mg od for secondary thromboprophylaxis.

Results: 18 APS patients were included (13 female, mean age 45.2 ± 10.4 yrs, mean disease duration 8.8 ± 6.7 yrs, mean age at onset of disease 35.1 ± 9.7 yrs). Thirteen had a history of deep vein thrombosis, 5 had both deep vein thrombosis and pulmonary embolism. In all the included patients TTR was 65% or lower. Indication for switching to rivaroxaban was erratic INR control (mean 15 [11–21] INR tests within the last 6 months) in 13 patients and INR constantly in sub-therapeutic range in three patients, respectively. Patients were followed for a mean of 12.9 months [6–24] after starting rivaroxaban. No further VTE or major bleeding events were observed. In two women there was a worsening of menorrhagia, which was treated with conservative management.

Conclusion: In this study, the use of rivaroxaban therapy for secondary thromboprophylaxis for VTE appears safe in APS. A larger trial RAPS (Rivaroxaban in AntiPhospholipid Syndrome, IRSCTN 68222801) is ongoing and results will be available next year. In the interim, rivaroxaban may be considered cautiously as an alternative anticoagulant in APS patients with poor anticoagulant control with VKA.

Disclosure: S. Sciascia, None; **B. Hunt**, None.

15

Performance of an Automated Chemiluminescence Assay for Anti-Cardiolipin and Anti-Beta2glycoprotein I Antibodies Detection in a Cohort of 400 Clinically Characterized Consecutive Routine Samples.

Alessandra Zanola[1], Laura Andreoli[1], Cecilia Nalli[1], Flavio Allegri[1], Michael Mahler[2], Gary Norman[2] and Angela Tincani[1]. [1]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [2]INOVA Diagnostics, San Diego, CA.

Background/Purpose: Several immunoassays are available for the detection of anti-cardiolipin (aCL) and anti-beta2glycoprotein I antibodies (anti-B2GPI), but standardization and harmonization of these tests is an ongoing process. Here we aimed to comparing the performance of an automated chemiluminescence assay with a validated in-house ELISA method, using clinically characterized samples derived from a routine diagnostic workup for the detection of antiphospholipid antibodies (aPL).

Methods: A total of 400 samples with a complete aPL panel (aCL IgG/IgM and anti-B2GPI IgG/IgM determined by an in-house ELISA, Lupus Anticoagulant (LA) tested with a DRVVT and aPTT based method) were collected. All the samples were tested for aCL IgG/IgM and anti-B2GPI IgG/IgM by QUANTA Flash CIA (INOVA). The two assays were compared using a definition of aPL profile for each isotype (single vs double positive samples). The clinical diagnosis/reason for aPL detection was retrieved. Subjects were grouped upon the clinical situation: A) clinical features compatible with Antiphospholipid Syndrome (APS) and/or other systemic autoimmune rheumatic diseases (SARD) (patients considered at risk of aPL-related manifestations); B) clinical features other than A; C) unresolved clinical picture.

Results: The two assays displayed a good overall agreement for both IgG and IgM detection (81% and 84% respectively). Such agreement can be estimated to be higher after reconciliation of discrepant results using clinical features and degree of aPL positivity. The majority of discrepant results for both IgG and IgM assays were due to low titer values. No significant difference was found in the rate of group A patients in the two subgroups of discrepant samples (ELISA pos – CIA neg and *viceversa*) (Chi squared test). LA was positive in 11/75 (15%) for IgG assays and in 9/63 (15%) for IgM assays discrepant samples.

		QUANTA Flash CIA			
	IgG assays	**aCL pos and anti-B2GPI pos (double pos)**	**aCL pos or anti-B2GPI pos (single pos)**	**aCL neg and anti-B2GPI neg (double neg)**	**Total**
In-house ELISA	**aCL pos and anti-B2GPI pos (double pos)**	13 (3.3%)	0	0	13 (3.2%)
	aCL pos or anti-B2GPI pos (single pos)	6 (1.5%)	14 (3.5%)	35 (8.8%)	55 (13.8%)
	aCL neg and anti-B2GPI neg (double neg)	8 (2%)	26 (6.5%)	298 (74.5%)	332 (83%)
	Total	27 (6.8%)	40 (10%)	333 (83.2%)	400 (100%)

		QUANTA Flash CIA			
	IgM assays	**aCL pos and anti-B2GPI pos (double pos)**	**aCL pos or anti-B2GPI pos (single pos)**	**aCL neg and anti-B2GPI neg (double neg)**	**Total**
In-house ELISA	**aCL pos and anti-B2GPI pos (double pos)**	12 (3%)	5 (1.3%)	6 (1.5%)	23 (5.8%)
	aCL pos or anti-B2GPI pos (single pos)	3 (0.8%)	7 (1.8%)	46 (11.5%)	56 (14%)
	aCL neg and anti-B2GPI neg (double neg)	0	3 (0.8%)	318 (79.5%)	321 (80.2%)
	Total	15 (3.8%)	15 (3.8%)	370 (92.4%)	400 (100%)

Discrepant results	**IgG assays (n=75)**	**IgM assays (n=63)**
ELISA pos – CIA neg	Group A: 23/35 (66%)	Group A: 40/57 (70%)
IgG n=35/75 (47%)	Group B: 87/35 (23%)	Group B: 13/57 (23%)
IgM n=57/63 (90%)	Group C: 4/35 (11%)	Group C: 4/57 (7%)
Positive LA n=11 (15%)	Low titer: 27/35 (77%)	Low titer: 45/57 (79%)
ELISA neg – CIA pos	Group A: 30/40 (75%)	Group A: 5/6 (83%)
IgG n=40/75 (53%)	Group B: 7/40 (18%)	Group B: 1/6 (17%)
IgM n=6/63 (10%)	Group C: 3/40 (7%)	Group C: 0 (11%)
Positive LA n=9 (15%)	Low titer: 34/40 (85%)	Low titer: 4/6 (67%)

Conclusion: In-house ELISA assays and the CIA assays displayed a comparable performance in the detection of aCL and anti-beta2GPI. Discrepant results were mostly due to values in the low positive range. The clinical features of the subjects are crucial information to interpret results when comparing different assays for aPL detection.

Disclosure: A. Zanola, None; **L. Andreoli**, None; **C. Nalli**, None; **F. Allegri**, None; **M. Mahler**, Inova Diagnostics, Inc., San Diego, CA, 3; **G. Norman**, Employee of INOVA Diagnostics, 3; **A. Tincani**, None.

16

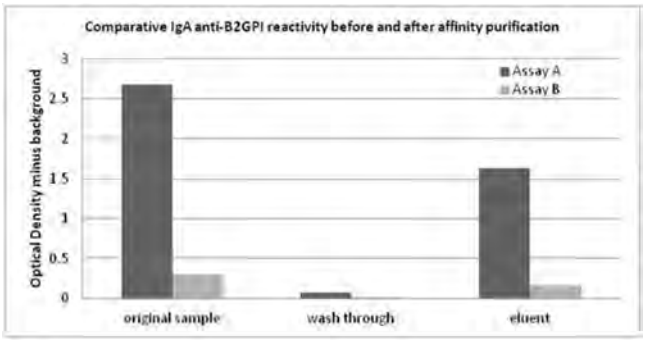
Differential Assay Reactivity of IgA Anti-B_2glycoprotein I Antibodies: Implications for Clinical Interpretation of Antiphospholipid Antibody Testing. David B Hood, Karin R Snyder, Tammy R Buckner, Beth L Hurley, Kelly R Pitts and Luis R Lopez. Corgenix, Inc., Broomfield, CO.

Background/Purpose: IgA anti-β2Glycoprotein I (aβ2GPI) antibodies remain controversial in the assessment of thrombotic risk in spite of several studies indicating an association with thromboembolic events in SLE and antiphospholipid syndrome (APS) patients. In addition, recent proficiency testing revealed widely discrepant results between 2 commonly used IgA aβ2GPI ELISAs on SLE and catastrophic APS samples. This controversy may have contributed to exclusion of IgA aCL and aβ2GPI antibodies from the current classification criteria for APS. One hypothesis is that coated β2GPI of one assay displayed the open (reactive) β2GPI configuration while the other had the closed (non-reactive) configuration.

Methods: Four sera selected from positive SLE and APS patients having discrepant IgA aβ2GPI reactivity; strongly positive in assay A (144–388 A units) and negative in assay B (9.9–18.6 A units). Cut-off was <20 A units in both assays. These samples were also strong IgG aβ2GPI (143–237 G units in assay A). A negative serum was used as control. IgA antibodies were affinity purified (Peptide M, Invivogen, Inc) to investigate β2GPI reactivity. Column wash-through and eluents were tested on both IgA aβ2GPI assays.

Results: were normalized to total protein. To determine the nature of differential reactivity, assay conjugates and controls/calibrators from assay A and B were interchanged.< Results: IgA eluents from IgA aβ2GPI positive samples reacted 10× stronger on assay A compared to assay B (graph). ODs of assay B were within the negative range (<0.200). When normalized to protein content, the eluents showed no cross-reactivity for IgG or IgM aβ2GPI antibodies confirming IgA isotype specificity. IgG aβ2GPI antibodies were detected in the wash-through. Conjugate from assay A reacts with reagents from both assays. However, conjugate from assay B reacts only with assay B reagents. This confirms that β2GPI-coated plates of assay B bind IgA aβ2GPI antibodies, questioning the open/closed hypothesis. When both conjugates were compared in assay B, conjugate from assay A was 4× more reactive, suggesting that the ability of assay A to detect IgA aβ2GPI antibodies is partially dependent on the anti-IgA conjugate and calibration.

Conclusion: These results confirm not only the presence of IgA aβ2GPI antibodies in the selected patient samples but highlight an IgA conjugate reactivity issue for assay B, causing an underestimation of IgA aβ2GPI. This finding may assist in ongoing standardization efforts of APS antibody testing. In addition, conclusions from published clinical studies may need to be revised as some assays may understate IgA significance.



Disclosure: D. B. Hood, Corgenix, Inc., 3; **K. R. Snyder**, Corgenix, Inc., 3; **T. R. Buckner**, Corgenix, Inc., 3; **B. L. Hurley**, Corgenix, Inc., 3; **K. R. Pitts**, Corgenix, Inc., 3; **L. R. Lopez**, Corgenix, Inc., 3.

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Antiphospholipid Syndrome Following Infection: A Systematic Review of Case Reports. Noha Abdel-Wahab[1], Maria A. Lopez-Olivo[1], Paola Patarroyo-Pinto[2] and Maria E. Suarez-Almazor[1]. [1]The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]Baylor College of Medicine, Houston, TX.

Background/Purpose: The occurrence of antiphospholipid syndrome (APS) following an infection has been increasingly reported in the literature. We conducted a systematic review of case reports documenting the development of primary APS, catastrophic APS (CAPS), or APS related features following infection to identify potentially putative agents, and to summarize the patients' clinical and immunologic characters, treatment administered, and patient outcomes.

Methods: We searched the Medline, EMBASE, Web of Science, and Cochrane CENTRAL databases with no language restriction from inception through October 2013 for case reports of patients with APS or CAPS related features after an infection. Study selection, data extraction, and quality appraisal were performed by 2 independent researchers. We extracted data on the related infection, clinical presentation, antiphospholipid (aPL) antibody profiles, treatment, and patient outcomes.

Results: From 2,257 unique citations, 247 publications met our inclusion criteria, reporting on 281 cases. Three different groups of patients were identified according to the clinical presentation reported: 1) patients whose symptoms met the classification criteria for definitive APS or CAPS (24.2%), 2) patients who did not meet the criteria for APS or CAPS but developed transient thromboembolic phenomena with elevated aPL antibodies during an infection and recovered completely (44.8%), and 3) patients who developed transiently elevated aPL antibodies after an infection but no clinical consequences related to APS or CAPS (31%).

The most common preceding infections across all groups was viral (55.5% of cases), including human immunodeficiency virus, hepatitis C virus, and parvovirus B19. Bacterial infections were reported in 36.7% of cases with streptococci, mycoplasma pneumonia, and coxiella burnetii infections being the most common. Parasitic infections were reported in 3.9%, fungal infections in 2.1%, and multiple types of infection in 8.9%. Infection was the sole precipitating factor in 79.7% of reported cases.

Thromboembolic manifestations were the most common presenting feature among patients in groups 1 and 2. Patients across all groups had at least 1 positive aPL antibody with persistent positive antibodies observed mainly among patients in group 1. Anticardiolipin (aCL) antibodies were the most frequently reported, often with coexisting IgG and IgM antibodies. Anticoagulation therapy was the mainstay of treatment in the majority of cases in groups 1 and 2. Clinical outcomes varied considerably and included persistent manifestations of APS or CAPS and death in Group 1. Resolution of clinical events and disappearance of aPL antibodies were most frequently reported in groups 2 and 3.

Conclusion: Development of aPL antibodies, APS, and CAPS can occur after infection with various virus, bacteria, fungus and parasites. Further longitudinal studies should be conducted to better quantify the risk and outcomes of APS or CAPS after infection.

Disclosure: N. Abdel-Wahab, None; **M. A. Lopez-Olivo**, None; **P. Patarroyo-Pinto**, None; **M. E. Suarez-Almazor**, None.

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The Effect of Clinically Significant Antiphospholipid Antibody Positivity on Organ Damage in Systemic Lupus Erythematosus. Mara Taraborelli[1], Laura Leuenberger[2], Wei Zhang[2], Angela Tincani[3], Jane Salmon[2] and Doruk Erkan[2]. [1]Spedali Civili and University of Brescia, Brescia, Italy, [2]Hospital for Special Surgery, New York, NY, [3]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy.

Background/Purpose: The effect of antiphospholipid antibodies (aPL) on organ damage in Systemic Lupus Erythematosus (SLE) patients remains unclear as there are limited number of studies with contrasting conclusions. The aim of this study was to assess the relative contribution of aPL to organ damage in SLE patients.

Methods: SLE patients (based on American College of Rheumatology [ACR] Classification Criteria) with less than 10 years of disease duration at registry entry were identified from an SLE registry. Clinical information retrieved included: demographics, disease duration, organ damage assessed by the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI), and aPL profile. A "clinically significant" aPL profile was

defined as: positive lupus anticoagulant test, anticardiolipin antibody IgG/M/A ≥ 40U, and/or anti-β_2Glycoprotein-I IgG/M/A ≥ 40U on two or more occasions, at least 12 weeks apart, within ± 1 year of registry entry. The outcome variable was any increase of SDI at 5 years of follow-up (time 0 was defined as registry entry). For univariate analysis the demographic and clinical characteristics of patients with and without a SDI increase at 5 years were compared (Chi square or Fisher's exact test for categorical data, Student t test or Mann-Whitney for continuous data as appropriate). The Generalized Estimated Equations (GEE) model was used as multivariate analysis to detect significant factors for increased SDI at 5 years.

Results: Of 394 patients with less than 10 years of disease duration, 112 (28%) had at least 5 years of prospective follow-up and a complete aPL profile (44% Caucasian, 19% African-American, 15% Asian, and 89% female). Mean age at diagnosis was 32 years (±13) and mean age at registry entry was 35 years (±13) with mean disease duration of 3 years (±2). Twenty-one (19%) patients had clinically significant aPL profile (isolated IgA positivity only in 5 patients, 4%). Damage was present (SDI ≥ 1) in 18/112 (16%) of patients with a mean SDI of 1.9 (±1.7) at the registry entry, and in 27/112 (24%) at 5 years follow-up with a mean of 2.4 (±2.0). An increase of SDI (range: 1–5 points) after 5 years of follow-up was observed in 16/112 (14%) of patients. On a univariate analysis, no significant associations were found between any increase of SDI at 5 years and aPL profile, race, gender, age at diagnosis, and disease duration. The GEE model confirmed the lack of an association between the aPL profile and organ damage; African-American (Odds Ratio, [OR]: 7.58, 95% Confidence Interval, [CI]: 1.54–37.27, p: 0.013) and Asian (OR: 8.1, 95% CI: 1.49–44.16, p: 0.016) patients had significantly higher risk of increased SDI at 5 years.

Conclusion: Our preliminary data demonstrate that: a) approximately 15% of SLE patients have new organ damage in 5 years; b) one-fifth of SLE patients have clinically significant aPL profiles; and c) there is no association between organ damage and clinically significant aPL-profile.

Disclosure: M. Taraborelli, None; **L. Leuenberger**, None; **W. Zhang**, None; **A. Tincani**, None; **J. Salmon**, None; **D. Erkan**, None.

ACR Poster Session A
Biology and Pathology of Bone and Joint: Osteoclasts, Osteoblasts and Bone Remodeling
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Adenosine Receptors Stimulate Bone Regeneration. Aranzazu Mediero[1], Tuere Wilder[1] and Bruce N. Cronstein[2]. [1]NYU School of Medicine, New York, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Such orthopedic procedures as spinal fusion and repair of bone defects due to trauma, infection or metastatic disease, require formation of new bone. Adenosine, acting via stimulation of the A_{2A} receptor (A2AR), inhibits osteoclast differentiation. Here we determined whether direct A2AR stimulation or enhancing adenosine concentrations via blockade of purine transport into cells via ent1 with dipyridamole regulates bone formation in a murine calvarial model.

Methods: 6–8-wk male C57Bl/6 mice (WT) or A_{2A}KO were anesthetized; a 3mm trephine defect was formed and covered with a collagen scaffold soaked in saline or CGS21680 (A2AR agonist) or dipyridamole (1mM each) alone or in the presence of ZM241385 1mM (A2AR antagonist). Animals received appropriate treatment daily until sacrifice. Bone Morphogenetic Protein 2 (BMP-2) 200ng was used as a bone formation control. At 0, 2, 4, 6 and 8 weeks calvarias were harvested and prepared for microCT and histology. XenoLight Rediject Bone Probe 680 was injected intravenously at different time points and used to probe bone formation (fluorescence).

Results: 8 weeks after surgery microCT examination of WT mouse calvaria demonstrated that both CGS21680 and dipyridamole markedly enhanced bone regeneration as well as BMP-2 (60±2%, 79±2% and 75±1% bone regeneration, respectively, vs. 32±2% in control, $p<0.001$, n=5 mice per condition). Both CGS21680 and dipyridamole effects were abrogated by ZM241385 (20±3% and 26±4% bone regeneration, respectively, vs. 32±2% in control, p=ns, n=5 mice per condition). Neither CGS21680 nor dipyridamole enhanced bone formation in A_{2A}KO mice. In CGS21680- and dipyridamole-treated WT mice there was increased immunostaining for bone formation markers in the bony defects (Alkaline Phosphatase positive cells/hpf increased from 15±1 for control to 21±1 for CGS21680 and 24±1 for dipyridamole, $p<0.001$). TRAP staining revealed fewer osteoclasts in CGS21680- and dipyridamole-treated defects (17±1 and 16±1 osteoclast/hpf respectively vs. 24±1 Osteoclast/hpf for control, $p<0.001$) 8 weeks after defect formation, an effect blocked by ZM241385 or absent in A2AR KO mice. *In vivo* imaging with XenoLight Rediject Bone Probe 680 (a marker of bone formation) reveals a markedly increased fluorescent signal in treated animals, equivalent to BMP-2, when compared to control as soon as one week after bone defect formation and which lasts for at least 7 weeks.

Conclusion: Stimulation of A2AR increases the rate of new bone formation at sites of surgical bone defects as well as BMP2, a finding which suggests that targeting A2AR may be an effective way to increase bone formation following orthopedic procedures.

Disclosure: A. Mediero, None; **T. Wilder**, None; **B. N. Cronstein**, Canfite Pharma, 1, AstraZeneca, 2, Cellgene, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Reseach Foundation, 6, ACR, 6, Arthritis Foundation, 6.

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High Systemic LDL Cholesterol Levels during Experimental Osteoarthritis Lead to Increased Synovial Activation and Ectopic Bone Formation at End-Stage Osteoarthritis, While Excessive Levels Accelerate Development of Joint Pathology Already at Early-Stage Osteoarthritis. Wouter de Munter, Martijn H. van den Bosch, Annet W. Sloetjes, Peter M. van der Kraan, Wim B. van den Berg and Peter L. van Lent. Radboud university medical center, Nijmegen, Netherlands.

Background/Purpose: A relation between osteoarthritis (OA) and the metabolic syndrome has long been established. One of the characteristics of the metabolic syndrome is increased cholesterol levels. In a recent study, we showed that LDL accumulation by LDL receptor deficient mice resulted in increased ectopic bone formation during experimental osteoarthritis.

In the present study we investigate OA pathology in ApoE deficient ($ApoE^{-/-}$) mice with and without a cholesterol-rich diet, which is a model for extremely high systemic LDL cholesterol levels.

Methods: Wild type (WT) and $ApoE^{-/-}$ mice received a normal or cholesterol-rich diet for 54 days. At day 18, experimental OA was induced by intra-articular injection of collagenase and animals were sacrificed at day 28 and 54. Joint pathology was investigated by histology. LDL levels were measured in serum and synovial wash-outs.

Results: $ApoE^{-/-}$ mice on a normal diet showed markedly higher LDL levels than WT mice (8.90 mmol/L and 0.40 mmol/L, respectively; $p<0.001$). While no differences between the two groups were found at the early time point (day 28), end point OA (day 54) in $ApoE^{-/-}$ mice showed a strong increase of ectopic bone formation, mainly at the medial collateral ligament (fold increase 5.4; $p<0.001$) compared to WT mice. No significant differences in cartilage damage were found between the two groups; a slight increase in synovial thickening, however, was found in $ApoE^{-/-}$mice (arbitrary score 1.9 versus 1.1 in WT mice; $p<0.05$). Furthermore, synovial gene expression of both S100A8 and S100A9 (fold increase 1.8 and 1.4, respectively; $p<0.05$) and S100A8/S100A9 protein levels of synovial wash-outs were increased in ApoE−/− mice (fold increase 5.8; $p<0.05$), suggesting an activated status of synovial lining cells.

In addition, we investigated whether a cholesterol-rich diet could increase joint pathology after induction of OA. The diet increased LDL levels even more in $ApoE^{-/-}$ mice (fold increase 2.1, compared to $ApoE^{-/-}$ mice on a normal diet; $p<0.001$). In both $ApoE^{-/-}$ and WT mice on a cholesterol-rich diet, excessive bone formation was found in the medial collateral ligament at day 54, however, no significant difference was found between the two groups. Interestingly, at the early time point (day 28; 10 days after OA induction), histological differences between the two groups were observed. Synovial thickening was four times increased ($p<0.001$) in $ApoE^{-/-}$mice on a cholesterol-rich diet and also ectopic cartilage formation in the medial collateral ligament was strongly increased (fold increase 2.7; $p<0.01$) compared to WT mice on a cholesterol-rich diet.

Conclusion: LDL cholesterol accumulation by ApoE deficiency or a cholesterol-rich diet results in increased synovial activation and ectopic bone formation in experimental OA. Excessive LDL levels induced by a combination of ApoE deficiency and a cholesterol-rich diet did not affect joint pathology at end-stage OA, but rather accelerates synovial activation and ectopic bone formation, resulting in early pathology.

Disclosure: W. de Munter, None; **M. H. van den Bosch**, None; **A. W. Sloetjes**, None; **P. M. van der Kraan**, None; **W. B. van den Berg**, None; **P. L. van Lent**, None.

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Mendelian Randomization Analysis to Examine for Causal Relationships Between Serum Urate Levels and Bone Mineral Density. Nicola Dalbeth[1], Ruth Topless[2], Tanya Flynn[2], Murray Cadzow[2], Mark Bolland[1] and Tony R. Merriman[2]. [1]University of Auckland, Auckland, New Zealand, [2]University of Otago, Dunedin, New Zealand.

Background/Purpose: In observational studies, serum urate is positively associated with bone mineral density (BMD) and reduced risk of fragility fractures. However, the possibility of unmeasured confounding means that it is uncertain whether urate is a direct mediator of bone density. Mendelian randomization analysis assumes that inherited genetic risk variants for one phenotype are naturally randomized with respect to a second unrelated phenotype, and allows disentangling of cause and effect in the presence of potential confounding. We used Mendelian randomization analysis to examine whether there is a causal relationship between serum urate and BMD.

Methods: We analysed data from the Generation 3 cohort in the Framingham Heart Study (FHS). Inclusion criteria were availability of serum urate, BMD, body mass index (BMI) and genotype data. Exclusion criteria were eGFR<30, and any of the following medications: diuretics, bisphosphonates, oral glucocorticoids and hormone replacement therapy. A weighted urate genetic risk score (GRS) was calculated using SNPs for *SLC2A9, ABCG2, SLC17A1, SLC22A11* and *SLC22A12* based on the genome wide association study by Kottgen et al[1]. Mendelian randomization analysis was done using the two-stage least squares (2SLS) method, this first calculates each individual's genetically determined predictor levels (predicts urate levels based on the urate GRS) then regresses these calculated predictor values against the outcome (BMD). The analysis was adjusted for age, sex, menopause status in women, BMI and the first two principal components from genome-wide genotype data.

Results: There were 2553 eligible participants. The urate GRS accounted for 3.3% of the variance in serum urate in the total group. A strong association between serum urate at Examination 1 and BMD at Examination 2 was observed in the unadjusted ordinary least square analysis ($p<8E-17$ for all BMD measures, Table), which was attenuated but persisted at the spine and total femur following adjustment for potential confounders. In the genetic 2SLS analysis, no significant relationship was observed between urate and BMD, either in the unadjusted or adjusted analysis. For total femur and femoral neck BMD, the effect sizes for the ordinary least square and 2SLS analysis were significantly different (Durbin-Hausman $p<0.02$). Similar findings were observed in both the male and female subgroups. Analysis of a causal role for BMD on serum urate levels using a weighted BMD GRS did not demonstrate evidence for reverse causation (data not shown).

Conclusion: Serum urate is strongly associated with BMD. However, controlling for confounders by Mendelian randomization does not provide evidence that serum urate is causal in increased BMD.

Reference:

Kottgen et al *Nature Genetics* 2013.

Table: Mendelian randomization analysis with BMD as the outcome of interest for all eligible participants.

		Ordinary least square (observational analysis)			Two stage least squares (Mendelian randomization analysis)			
BMD site		Beta	SE	P	Beta	SE	P	Durbin-Hausman P
L2-4 spine	Unadjusted	0.32	0.04	7.94E-17	0.04	0.22	0.87	0.17
	Adjusted	0.21	0.05	5.48E-05	0.14	0.21	0.51	0.7
Femoral neck	Unadjusted	0.3	0.03	8.79E-23	−0.33	0.18	0.07	0.0001
	Adjusted	0.07	0.04	0.06	−0.26	0.16	0.1	0.02
Total femur	Unadjusted	0.48	0.03	1.70E-51	−0.36	0.19	0.06	4.03E-07
	Adjusted	0.11	0.04	0.005	−0.25	0.16	0.1	0.01

Disclosure: N. Dalbeth, Ardea, 5, AstraZeneca, 5, Takeda, 5, Metabolex, 5, Menarini, 8, Savient, 8, Novartis Pharmaceutical Corporation, 8, Fonterra, 2, Novartis Pharmaceutical Corporation, 2, Ardea, 2, Fonterra, 9; **R. Topless**, None; **T. Flynn**, None; **M. Cadzow**, None; **M. Bolland**, None; **T. R. Merriman**, None.

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Adenosine a_{2A} Receptor (A2AR) Stimulation Inhibits Osteoclast Differentiation and Promotes Osteoblast Formation By Regulation of Axon Guidance Proteins. Aranzazu Mediero[1], Miguel Perez-Aso[2] and Bruce N. Cronstein[3]. [1]NYU School of Medicine, New York, NY, [2]New York University, New York City, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Semaphorins (Sema), axonal guidance proteins, play a role in communication between osteoclast and osteoblast. Thus, sema4D, secreted by osteoclasts, binds to its receptor PlexinB1 on osteoblasts to inhibit osteoblast differentiation and function whereas sema3A, produced by osteoblasts, binds to PlexinA1/Neuropilin-1 to both inhibit RANKL-induced osteoclast differentiation and stimulate osteoblast differentiation and function. Because stimulation of A2AR diminishes osteolysis we asked whether $A_{2A}R$ activation regulates bone homeostasis by regulating osteoclast and osteoblast expression of semaphorins.

Methods: Osteoclast and osteoblast differentiation were studied in primary murine bone marrow culture as the number of TRAP-positive or Alizarin Red-positive cells, respectively, after challenge in the presence/absence of CGS21680 (A_{2A} agonist) 1μM and ZM241385 ($A_{2A}R$ antagonist) 1μM together with recombinant Sema4D or Sema3A 10ng/ml each. Sema3A/PlexinA1/Neuropilin-1 and Sema4D/PlexinB1 expression were studied by RT-PCR and Western Blot in bone marrow-derived osteoclasts and osteoblasts in the presence/absence of CGS21680 and ZM241385 1μM each. RANKL and Osteoprotegerin (OPG) levels were studied by RT-PCR. β-catenin activation was studied in primary osteoblast culture. Cytoskeleton changes were studied in osteoclasts.

Results: RANKL induced a 2.5±0.1 fold increase in Sema4D mRNA ($p<0.001,n=4$) in osteoclasts which was blocked by CGS21680 (1.3±0.3 fold change, $p<0.001,n=4$). In contrast, PlexinA1 mRNA was enhanced by CGS21680 (9.3±0.7 fold increase vs 4.9±0.6 for RANKL, $p<0.001,n=4$) but Neuropilin-1 mRNA was unchanged. Sema3A mRNA increased 3.5±0.5 fold during osteoblast differentiation and CGS21680 enhanced this increase (8.7±0.2 fold, $p<0.001,n=4$); PlexinB1 mRNA was increased 2 fold during osteoblast differentiation and was not altered by CGS21680. Similar changes were observed at the protein level. CGS21680 decreased RANKL expression and increased OPG expression in osteoblasts. Total and nuclear β-catenin expression were increased in osteoblasts after CGS21680 treatment and this increase was abrogated by ZM241385. Sema4D increased RhoA phosphorylation and FAK activation in osteoclast precursors and these effectswere reversed in the presence of CGS21680.

Conclusion: A2AR activation diminishes secretion of Sema4D by osteoclasts and enhances secretion of Sema3A by osteoblasts leading to an increase in osteoblast differentiation and function, and, in combination with the suppressive effects of $A_{2A}R$ on osteoclast differentiation and function, diminishes bone osteolysis.

Disclosure: A. Mediero, None; **M. Perez-Aso**, None; **B. N. Cronstein**, Canfite Pharma, 1, AstraZeneca, 2, Cellgene, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Reseach Foundation, 6, ACR, 6, Arthritis Foundation, 6.

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Activation of EPAC1/2 Is Essential for Osteoclast Formation By Modulating NFkB Nuclear Translocation and Actin Cytoskeleton Rearrangements. Aranzazu Mediero[1], Miguel Perez-Aso[2] and Bruce N. Cronstein[3]. [1]NYU School of Medicine, New York, NY, [2]New York University, New York City, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Bisphosphonates inhibit osteoclast differentiation/function via inhibition of Rap1A isoprenylation and cytoskeletal assembly. As Rap1 is the effector of EPAC proteins (exchange *protein* directly activated by cAMP), we determined the role of EPAC in osteoclast differentiation.

Methods: Osteoclast differentiation was studied as the number of TRAP+ multinucleated cells following M-CSF/RANKL stimulation of either primary murine or human bone marrow precursors in the presence of the EPAC-selective cAMP analog 8-CPT-cAMP (100nM) and the EPAC inhibitor BFA (10μM). Rap1 activity assay was performed. Signaling events were studied by Western Blot in EPAC1/2 knockdown (lentiviral shRNA for EPAC1 or EPAC2 or scrambled shRNA) RAW264.7 cells. Osteoclast marker

expression was studied by RT-PCR. Osteoclast morphological characterization was studied by phalloidin staining.

Results: 8-CPT-cAMP significantly increased osteoclast differentiation whereas BFA inhibited differentiation (113±3% ($p<0.05$) and 42±2% ($p<0.001$) of control, respectively, n=6). Rap1 activation was maximal 15 min after RANKL stimulation (136±3% of basal, $p<0.001$, n=4) whereas silencing of EPAC1/2 diminished activated Rap1 (43±2% and 50±5% of control respectively, $p<0.01$, n=4) and NFkB translocation. TRAP staining revealed no osteoclast differentiation in EPAC1/2 KO cells. Cathepsin K, NFATc1 and Osteopontin mRNA expression decreased in EPAC1/2 KO cells when compared to control. Activation of RhoA, cdc42, Rac1 and FAK were observed in an EPAC1/2 dependent manner and there was diminished cytoskeletal assembly in EPAC1/2 KO cells.

Conclusion: EPAC1/2 are critical signaling intermediates in osteoclast differentiation that permit RANKL-stimulated NFkB nuclear translocation and actin rearrangements. Targeting this signaling intermediate may diminish bone destruction in inflammatory arthritis.

Disclosure: A. Mediero, None; **M. Perez-Aso**, None; **B. N. Cronstein**, Canfite Pharma, 1, AstraZeneca, 2, Cellgene, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Reseach Foundation, 6, ACR, 6, Arthritis Foundation, 6.

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Netrin1 Is Highly Expressed and Required in Inflammatory Infiltrates in Wear Particle-Induced Osteolysis. Aranzazu Mediero[1], Bhama Ramkhelawon[1], Ed Purdue[2], Steven R. Goldring[2], Kathryn Moore[1] and Bruce N. Cronstein[3]. [1]NYU School of Medicine, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Osteoclasts play a critical role in homeostatic bone turnover and pathologic bone destruction. Netrin-1, expressed in the marrow only by osteoclast precursors, acts in an autocrine manner via its receptor Unc5b (but not its receptor DCC) to stimulate osteoclast differentiation *in vitro*. Here we tested the hypothesis that blockade of Netrin-1 or Unc5b diminishes wear particle-induced osteolysis in a mouse model.

Methods: A 1-cm midline sagittal incision was made over the anterior calvarium to the line connecting both ears in anesthetized 6–8-wk-old male C57BL/6 mice. 3mg of dried UHMWPE particles were implanted and animals were treated with either 0.9% saline, Netrin-1 antibody, Unc5b antibody or DCC antibody (Rabbit polyclonal for all). 100μg antibodies were injected intraperitonally the day of surgery and then once a week. Animals were sacrificed after 14 days and calvaria were removed, fixed, and prepared for microCT and histology. Netrin-1 immunostaining was performed in human tissue obtained following primary prosthesis implantation or after prosthesis revision for peri-implant osteolysis and aseptic implant loosening.

Results: Weekly ip injection of anti-Netrin-1 or anti-Unc5b antibodies significantly reduced the area of particle-induced bone pitting in calvaria exposed to UHMWPE (46±4 and 49±3% bone pitting, respectively, compared to control, $p<0.001$, n=5) but anti-DCC receptor antibody did not affect UHMWPE-induced pitting and resorption (80±7% bone pitting, p=ns vs control). MicroCT also revealed a significant increase in bone volume (BV) and bone volume/total volume ratio (BV/TV) in both Netrin-1 and Unc5b antibody treated mice. Anti-Netrin-1 or anti-unc5b antibody treatment markedly reduced both the inflammatory infiltrate and the number of TRAP-positive osteoclasts in affected bone (7±1 and 4±1 cells/hpf respectively vs. 12±1 for control, $p<0.001$). In contrast, treatment with anti-DCC antibody did not significantly reduce the number of osteoclasts in affected bone. There were no significant changes in Alkaline Phosphatase positive osteoblasts on bone forming surfaces in any antibody-treated group compared to control (8±1, 10±1 and 10±2 cells/hpf, vs. 10±1 for control, p=ns). The peri-implant tissues of patients undergoing prosthesis revision surgery show a similar increase in Netrin-1 expression whereas there is little Netrin-1 expression by cells in soft tissues removed at the time of primary joint replacement.

Conclusion: These results demonstrate a unique role for netrin-1 in osteoclast biology; netrin-1 is an autocrine and paracrine regulator of osteoclast differentiation and may be a novel target for prevention or treatment of inflammatory osteolysis.

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DC-STAMP Modulates Osteoblast Differentiation and Regulates Bone Repair. Yahui Grace Chiu[1], Tzong-Ren Sheu[1], Jinbo Li[1], Dongge Li[1], Michael Thullen[1], Brendan Boyce[2], Edward Puzas[1] and Christopher T. Ritchlin[3]. [1]University of Rochester, Rochester, NY, [2]University of Rochester, Rocehster, NY, [3]University of Rochester Medical Center, Rochester, NY.

Background/Purpose: Patients with osteoporosis and the elderly have an increased risk of bone fracture. Currently, no biomarker is available to assess bone healing status in fracture patients. Although a coordinated interaction between osteoclasts (OC) and osteoblasts (OB) is required for bone repair after fracture, the molecular mechanisms underlying bone repair are not well understood. We previously demonstrated that DC-STAMP (Dendritic Cell-Specific Transmembrane protein), a 7-pass transmembrane protein essential for cell-to-cell fusion during OC differentiation, is a biomarker of OC precursors (OCP). Intriguingly, an elevated OCP frequency was observed that correlated with an increased frequency of circulating DC-STAMP+ cells in two bone fracture patients 8-week post-fracture. Thus, we hypothesized that multinucleated OC are essential for optimal bone repair and that the frequency of DC-STAMP$^+$cells may serve as biomarkers to assess bone healing. The function of OB and OC in bone fracture and healing was dissected in the DC-STAMP knock-out (KO) mice which lack mature multinucleated OC.

Methods: OB differentiation, bone healing and bone quality were compared between gender- and age-matched wild-type and DC-STAMP KO littermates. OB differentiation was assessed by mineral nodules and ALP$^+$ cells (OB marker) quantification. Bone fracture and callus formation were examined by uCT, x-ray and histology analysis. Bone quality was tested by biomechanical assays including 3-point bending and torsion test. The presence of DC-STAMP$^+$ cells at fresh fracture sites and at healed regions was examined by immunofluorescence. The frequency of circulating DC-STAMP$^+$cells in two bone fracture patients was analyzed by flow cytometry.

Results: In mice, DC-STAMP$^+$ cells were identified at fresh fracture sites and in blood vessels traversing surrounding tissues. DC-STAMP KO mice demonstrated decreased OB differentiation (WT vs. KO: 0.6 +/− 0.1 vs. 0.1 +/− 0, p=0.05 and 0.8 +/− 0.2 vs. 0.15 +/− 0.1 cm^2/well, p=0.01 for mineral nodules and Alp+ cells, respectively) and delayed bone healing (WT and KO mice healed on wk3 and wk6, respectively, post-fracture). Tibias from KO mice have a higher stiffness as demonstrated by torsional analysis (1226 +/− 308 vs. 1762 +/− 527 N/mm for WT and KO, p=0.1). In humans, two bone fracture patients had a significant increase in the frequency of circulating DC-STAMP$^+$cells and elevated OCP frequency (healthy, 185 +/− 62; patients, 1,250 +/− 65 per 10e6 monocytes).

Conclusion: These findings suggest that (1) DC-STAMP is involved in bone healing based on the presence of DC-STAMP$^+$ cells surrounding the fracture sites; (2) Both OB and OC are required for an efficient healing of bone fractures; (3) Elevation of OCP frequency and the number of circulating DC-STAMP$^+$ cells in two patients with recent fracture suggest that an increased DC-STAMP$^+$ cell frequency might serve as a surrogate marker reflecting active ongoing bone remodeling during the course of bone repair. Our data suggest that in addition to its critical role in regulating OC development, DC-STAMP is also involved in OB differentiation and bone repair. Thus, DC-STAMP has potential to serve as a bone-repair biomarker and therapeutic target to promote fracture healing.

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Functional Osteoclasts Differentiate Spontaneously from the Rheumatoid Joint. Stinne Greisen[1], Halldór Bjarki Einarsson[1], Malene Hvid[1], Ellen Margrethe Hauge[2], Bent Deleuran[3] and Tue Kragstrup[1]. [1]Aarhus University, Aarhus, Denmark, [2]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [3]Aarhus University Hospital, Aarhus, Denmark.

Functional osteoclasts differentiate spontaneously from the rheumatoid joint

Background/Purpose: Osteoimmunology is a field of emerging interest in which bone formation and resorption are understood in the context of the immune system. In rheumatoid arthritis (RA) uncontrolled joint inflammation alters the balance between osteoclasts and osteoblasts resulting in bone resorption. The inflamed joint in RA contains multiple factors contributing to the activation of osteoclasts, among these RANKL, M-CSF, TNFα and IL-17 secreted from activated fibroblast-like cells and T-cells. In this study, we

aimed to investigate the potential of synovial fluid mononuclear cells (SFMCs) to develop into functional osteoclasts in vitro.

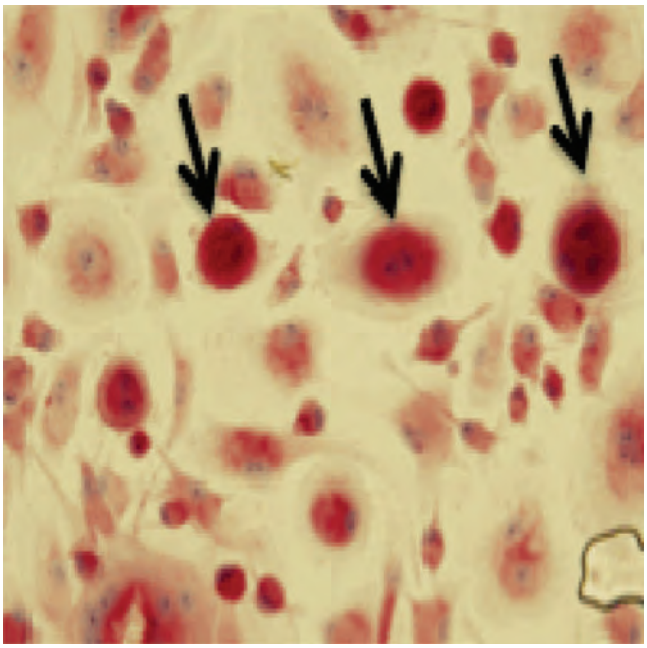
Methods: Synovial fluid was collected from inflamed joints of chronic RA patients at the out patient clinic at Aarhus University Hospital. SFMCs were isolated using ficoll paque and cultured in DMEM (+10% FCS + 2% penicillin/streptomycin + 1% glutamin) at a concentration of 0.5×10^6 cells/cm^2 (n=5). Following 21 days in culture, cells were TRAP stained and examined in light microscopy or lysed for qPCR for the common osteoclast genes calcitoninR, cathepsinK and beta3 integrin. To investigate functionality, SFMCs were also cultured on dentin plates for 21 days. To potentially increase the osteoclast differentiation in the SFMC cultures, culture medium was supplemented with RANKL (50ng/ml) and M-CSF (25ng/ml). As a control, conventional osteoclasts where cultured from healthy control monocytes with RANKL (50ng/ml) and M-CSF (25ng/ml).

Results: SFMCs cultured for 21 days differentiate into both multinucleated TRAP positive osteoclasts (6.7%, SD 4.8%) and mononuclear TRAP positive pre-osteoclasts (43.2%, SD 0.45%) (Fig 1). These cells expressed the common osteoclast genes calcitonin receptor, cathepsin K and beta3 integrin. Both the percentage of TRAP positive multinucleated cells (8.3%) and gene expression were comparable with conventional osteoclasts. Adding RANKL and M-CSF to SFMC cultures increased the percentage of multinucleated TRAP positive cells to 15.3% (SD 1.5%). SFMCs cultured on dentin plates finally confirmed the osteoclast phenotype of these cells, as the dentin was digested in the same manner as observed with conventional osteoclasts cultured on dentin plates.

Conclusion: Here we provide a new and simple method for generating functional osteoclasts from RA SFMCs. This spontaneous differentiation of osteoclasts from cells of the arthritic joint provides a new understanding of the inflamed joint and could explain the increased bone resorption observed in RA. Because osteoclasts are one of the ultimate effector cells in RA, this method could be a new tool to evaluate the effect of novel signaling molecules or the effectiveness of new drugs.

SHAPE * MERGEFORMAT

Fig 1: TRAP+ multinucleated cells differentiated from RA SFMCs.



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CD115$^+$ Osteoclast Precursors Arise before Clinical Onset of Arthritis and Are Regulated By Proinflammatory Cytokines. Antonia Puchner[1], Victoria Saferding[1], Eliana Goncalves-Alves[1], Silvia Hayer[1], Harald Leiss[1], Josef S. Smolen[2], Kurt Redlich[1] and Stephan Blüml[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria.

Background/Purpose: Bone erosions and systemic bone loss in rheumatoid arthritis patients results from an increased activity of osteoclasts, which are derived from precursor cells of the myeloid lineage. Although there is much known about the mechanisms regulating the formation and activation of mature osteoclasts, the identity of an osteoclast precursor population in and its regulation by inflammatory cytokines during arthritis is poorly understood.

Methods: HTNFtg mice were clinically scored once per week for grip strength and swelling. In addition, blood was collected every week starting on week 4. Mice were sacrificed at week 10 - blood, spleen and bone marrow were collected for flow cytometry analysis. IL1/IL6$^{-/-}$ were crossed into hTNFtg mice and blood was also analyzed. K/BxN Arthritis was induced in wild type mice, blood and spleen were collected 14 days after disease induction. Different monocyte subsets were Facs-sorted and cultured in the presence of RANKL and MCSF to induce osteoclasts.

Results: We show that during TNF-driven arthritis CD11b$^+$ CD115$^+$ cells are elevated in blood before the onset of clinical symptoms and remain elevated throughout. In particular, a certain subset of CD11b$^+$ myeloid cells that express intermediate levels of Ly6G expand in blood, spleen and bone marrow during arthritis. Of these, 89% express CD115, the MCSF-receptor. The increase of this population is not only observed in TNF-driven arthritis, but also in K/BxN arthritis. IL-1 and/or IL-6 importantly regulate the expansion of these cells as in IL1/IL-6 double deficient hTNFtg we did not detect an elevation of this subset. After sorting this cells both subsets were able to form mature osteoclasts *in vitro*.

Conclusion: CD115$^+$ CD11b$^+$ cells with osteoclastogenic potential increase during inflammatory arthritis. This process, at least in TNF-driven arthritis is regulated by proinflammatory cytokines IL-1 and or IL-6. Elevated numbers of these cells can be detected before clinical onset of disease and therefore may provide a biomarker for inflammatory arthritis.

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Evidence for Receptor Activator of NF-Kb (RANK)-Independent Bone Erosion in the Cherubism Mouse Model of Inflammatory Arthritis. William R. O'Brien, Julia F. Charles, Kelly Tsang and Antonios O. Aliprantis. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: A gain-of-function mutation in the adaptor Src Homology 3 Binding Protein 2 (SH3BP2) causes Cherubism, a rare pediatric disease marked by aggressive bone remodeling in the mandible and maxilla. Mice homozygous for the most common Cherubism mutation (*Sh3bp2$^{KI/KI}$*) display TNFa-dependent osteopenia and inflammatory arthritis with periarticular bone erosions. We sought to investigate whether bone-resorbing osteoclasts are key cellular mediators of the systemic bone loss and local inflammatory erosion observed in this model. To this end, *Sh3bp2$^{KI/KI}$* mice with an inducible mutation in *Rank*, encoding a master regulator of osteoclast differentiation, were generated.

Methods: We generated *Sh3bp2$^{KI/KI}$* RANK-deficient mice using *Mx1-Cre* driven deletion of floxed *Rank* alleles after intra-peritoneal injection of poly-IC at 10-days of age (referred to as *Sh3bp2$^{KI/KI}$ Rank$^{\Delta/\Delta}$*). Control mice, also treated with poly-IC, included *Sh3bp2$^{KI/KI}$ Rank$^{fl/fl}$* without the *Mx1-Cre* transgene, *Sh3bp2$^{+/+}$Rank$^{fl/fl}$* and *Sh3bp2$^{+/+}$ Rank$^{\Delta/\Delta}$*. Bone mass, periarticular erosions and synovitis were assessed by a combination of microcomputed tomography (mCT) and histology at 12 weeks of age.

Results: Neither *Sh3bp2$^{+/+}$Rank$^{fl/fl}$* nor *Sh3bp2$^{+/+}$ Rank$^{\Delta/\Delta}$* displayed inflammatory arthritis or bone erosion. *Sh3bp2$^{+/+}$ Rank$^{\Delta/\Delta}$* developed severe osteopetrosis, consistent with osteoclast-deficiency. As previously reported, *Sh3bp2$^{KI/KI}$* sufficient for RANK (*Sh3bp2$^{KI/KI}$ Rank$^{fl/fl}$*) developed osteopenia and inflammatory arthritis at the elbow joint with marked peri-articular erosions. Depletion of osteoclasts by genetic deletion of *Rank* reversed the systemic osteopenia observed in *Sh3bp2$^{KI/KI}$* mice but had no effect on synovitis at the elbow. Unexpectantly, peri-articular erosions at the elbow joints were not ameliorated in *Sh3bp2$^{KI/KI}$ Rank$^{\Delta/\Delta}$* mice despite a significant reduction in tartrate-resistant acid phosphatase (TRAP) positive osteoclasts.

Conclusion: Deletion of *Rank* inhibits osteoclastogenesis and reverses systemic osteopenia in *Sh3bp2$^{KI/KI}$* mice. In contrast, while the loss *Rank* reduces classic TRAP-positive osteoclasts at the inflamed elbow joints of *Sh3bp2$^{KI/KI}$* mice, it does not reduce local bone erosion. These intriguing findings suggest an alternative pathway to bone erosion exists in the *Sh3bp2$^{KI/KI}$* model of inflammatory arthritis that is independent of RANK.

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Impaired Bone Healing in Patients Suffering from Rheumatoid Arthritis - Anti-Inflammatory Therapy As Confounder. Annemarie Lang[1], Sarah Fuegener[2], Paula Hoff[2], Anastasia Rakow[2], Manuela Jakstadt[3], Timo Gaber[3], Gerd Burmester[2], Carsten Perka[2] and Frank Buttgereit[2]. [1]Berlin-Brandenburg School of Regenerative Therapies (BSRT), Berlin, Germany, [2]Charité University Medicine, Berlin, Germany, [3]Berlin-Brandenburg Center of Regenerative Therapies (BCRT), Berlin, Germany.

Background/Purpose: Anti-inflammatory treatment of rheumatoid arthritis (RA) with glucocorticoids (GC) and/or non-steroidal anti-inflammatory drugs (NSAIDs) is supposed to negatively influence bone metabolism and healing. It should be noted, however, that RA itself is suspected to promote bone healing complications. However, studies addressing the number of afflicted patients and/or quantifying the negative impact of preexisting comorbidities and treatment with GC and/or NSAIDs on the bone fracture healing process are scarce. Thus, we hypothesized that both (i) suffering from RA and (ii) treatment with either GC or NSAIDs represent risk factors of bone healing disorders.

Methods: To test our hypothesis, we performed a single-center retrospective study based on the database of the Center for Musculoskeletal Surgery at Charité University Hospital Berlin to measure the impact of RA, GC and NSAID on bone healing complications. All patients who underwent surgery at our institution for treating fracture healing complications in 2012 were included. Exclusion criteria were patients with an age below 18 years at initial fracture, open fracture, and metastases close to fracture location. A control group matched for age and type of fracture at the ratio of two was considered for comparison. In parallel, we conducted *in vitro* experiments analyzing the impact of GC and NSAID on osteogenic differentiation of mesenchymal stromal cells (MSC) and the counteracting ability of hypoxia and the hypoxia-inducible factor (HIF) stabilizer deferoxamine (DFO). To this end, human bone marrow derived MSC were cultured, characterized and differentiated into osteoblasts under normoxic (37°C, 5% CO_2, 18% O_2) or hypoxic (37°C, 5% CO_2, 1% O_2) conditions using varying doses of dexamethasone (10^{-3} - 10^{-8} M), ibuprofen ($5x10^{-3}$ - $5x10^{-5}$) and desferrioxamine (DFO; 125–500μM). The calcification process during osteogenesis was analyzed using a quantifiable alizarin red staining method.

Results: Retrospective analysis included 93 patients with fracture-healing complications and 193 controls; both groups equally represented both sexes. We found a 10.6% higher probability ($p=0.036$) of fracture healing disorders in RA patients compared to the controls with a higher rate of these patients being treated with GC and NSAID, respectively. In our *in vitro* studies, we could demonstrate a concentration-dependent significant inhibitory effect of dexamethasone and ibuprofen on the osteogenetic capacity of MSC which could be considerably antagonized by either hypoxia or DFO.

Conclusion: The results we have obtained so far support the hypothesis that both RA and GC medication have a negative impact on the outcome of fracture healing. Our results also demonstrate that GC and NSAID inhibit MSC differentiation which could contribute to explain impaired fracture healing. In addition, we demonstrate a positive effect of (chemically induced) hypoxia promoting osteogenic differentiation and being a promising tool to overcome bone healing disorders which result from anti-inflammatory treatment.

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Inhibiting Autocrine Interleukin-6 (IL-6) Trans-Signalling in Human CD14^{+ve} Monocultures Reduces Osteoclast Differentiation. Lauren A. Jordan[1], Fraser L. Collins[2], Simon A. Jones[1], Ernest H. Choy[1], Ann K. Harvey[1] and Anwen S. Williams[1]. [1]Cardiff University, Institute of Infection and Immunity, School of Medicine, Cardiff, United Kingdom, [2]Michigan State University, Department of Physiology, East Lansing, MI.

Background/Purpose: Interleukin-6 (IL-6) and the inflammatory CC-chemokine CCL3 are highly expressed in rheumatoid arthritis, juvenile idiopathic arthritis and multiple myeloma. While these mediators contribute to bone pain, osteoclast (OC) formation and bone resorption, the relationship of their activities to disease outcome remains unknown. For the first time, we measured the autocrine and paracrine regulation of CCL3 production by OC cultures in response to IL-6 (in combination with the soluble IL-6 receptor; termed IL-6 *trans*-signalling). Experiments identified a novel disease-activity determinant for inflammatory arthritis patients.

Methods: Human CD14^{+ve} monocytes isolated from peripheral blood were grown on ivory disks in medium containing macrophage colony stimulating factor (10 ng/mL; m-CSF) for 7 days. Cells were subsequently differentiated into OC in medium supplemented with m-CSF (5 ng/mL) and receptor activator of nuclear factor kappa-B ligand (5 ng/mL) for 17 days. Conditioned media was recovered on day 0, 3, 7, 10, 14 and 17, and levels of CCL3, IL-6 and sIL-6R were quantified with ELISA. OC formation was visualised by staining with tartrate-resistant acid phosphatase (TRAP) on ivory disks harvested at baseline (day 0), and day 7, 10, 14 and 17 of culture. Add-back studies using anti-CCL3 antibody (0–8 ng/mL) or osteoprotegerin (OPG; 100 ng/mL) were also performed. IL-6 *trans*-signalling was modulated using an engineered chimeric IL-6-sIL-6R fusion protein (HDS agonist; 10 ng/mL) and soluble gp130 (sgp130 antagonist; 500 ng/mL). Cytokine release was reported as mean±SEM and statistical significance through 2-way ANOVA, Spearman's rank co-efficient or student's t-test as appropriate.

Results: No OC or TRAP^{+ve} cells were observed in culture on day 0. OC numbers reached maximum levels after 14 days in culture (338±117 per disk; $P<0.001$). OPG supplementation potently inhibited OC formation on day 14 (8±3 per disk, $P<0.01$). A significant correlation between CCL3 levels and OC number was observed ($P<0.01$, R= 0.32). IL-6 (140±36 pg/mL and 48±28 pg/mL) and soluble IL-6 receptor (30±9 pg/mL and 19±7 pg/mL) levels were maintained throughout the culture period (day 0 and 14 reported). In add-back experiments using a neutralizing CCL3 antibody, OC numbers decreased in a concentration-dependent manner. A maximum 2.4-fold reduction in OC was noted on day 14 (anti-CCL3; 8 ng/mL). Inhibition of IL-6 *trans*-signalling with sgp130 caused a 3.6-fold reduction in OC number ($P<0.01$). Autocrine inhibition of OC differentiation by sgp130 (142±40 pg/mL) halved CCL3 production versus controls (280±86 pg/mL). OC numbers and CCL3 were comparable in control cultures to those exposed to paracrine activation of IL-6 *trans*-signalling by HDS for 14 days.

Conclusion: For the first time, we demonstrate the importance of autocrine versus paracrine regulation of IL-6 *trans*-signalling in controlling OC formation in humans and unmask a hitherto unresolved mechanism involving CCL3. These data identify soluble gp130 as a potentially important disease-modifying therapy, targeting bone destruction for inflammatory arthritis patients.

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Interaction of FGF-8 and TNF-a in the Regulation of BMP-Induced Osteoblast Differentiation. Takayuki Katsuyama, Fumio Otsuka, Mariko Narazaki, Ken-ei Sada, Kenichi Inagaki, Jun Wada and Hirofumi Makino. Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.

Background/Purpose: Osteoblasts and osteoclasts play important roles in the bone remodeling. When the balance between these cells is disrupted, bone loss or aberrant bone formation occur. In rheumatoid arthritis (RA), pro-inflammatory cytokines such as TNF-α play a predominant role in joint destruction. We earlier reported that TNF-α inhibits bone morphogenetic protein (BMP)-induced osteoblast differentiation via activation of JNK and NF-κB pathways.

The fibroblast growth factor (FGF) family constitutes of at least 25 structurally related proteins and known to be involved in various biological processes including cell migration, differentiation, growth and survival. In particular, FGF-2, -8 and -18 have been implicated as key factors for the bone and cartilage homeostasis. It has also been reported that joint destruction of RA patients is involved in the increase of endogenous FGF-2 in synovial fluids.

Among the FGF family, FGF-8 is known to be a key regulator for limb development and cranial formation. However, functional relationship between FGF-8 and BMPs in the osteoblast differentiation and the signal interaction of FGF-8 and proinflammatory cytokines remain unclear. Here we studied the effects of FGF-8 in relation to TNF-α actions on BMP-2-induced osteoblast differentiation.

Methods: Mouse myoblast cell line C2C12, osteoblast precursor cell line MC3T3-E1 and rat primary osteoblast were used to clarify the effects of FGF-8 and TNF-α on BMP-induced osteogenesis. Quantitative real-time PCR was performed to evaluate mRNA levels of osteoblast differentiation markers. Immunoblot analysis for the phosphorylation of Smads and MAPKs was performed to analyze the signal interaction induced by FGF-8, TNF-α and BMP-2.

Results: We found that FGF-8 inhibited BMP-2-induced expression of osteoblast markers in a concentration-dependent manner. The efficacy of

FGF-8 was smaller than that of TNF-α in the experiments using myoblast C2C12, MC3T3-E1 and rat osteoblasts. Of note, the inhibitory effects of FGF-8 on BMP-induced osteoblastic differentiation and Smad1/5/8 activation were enhanced under the co-treatment with TNF-α. FGF-8 also inhibited BMP-2-induced expression of Wnt5a, a non-canonical Wnt signaling, which is known to be involved in Smad-independent signaling induced by BMPs. FGF-8 had no influence on the expression levels of TNFRs, whereas FGF-8 increased the expression levels of ALK3 (BMPR1A) and reduced inhibitory Smads6/7, suggesting a possible feedback activity of FGF-8 to BMPR signaling. Moreover, a MEK inhibitor, but not JNK or NF-κB inhibitors, suppressed the FGF-8 actions on BMP-induced osteoblast differentiation.

Conclusion: Collectively, it was uncovered that FGF-8 inhibits BMP-induced osteoblast differentiation via ERK pathway and the effects were amplified by TNF-α activity. This FGF-BMP interaction may be involved in the regulatory process of inflammatory bone damages as shown in RA.

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Regulation of Senescence and Inflammatory Mediators By N- and C-Terminal Parathyroid Hormone-Related Protein in Osteoarthritic Human Osteoblasts. Maria Isabel Guillén[1], Julia Platas[1], Sergio Portal-Nuñez[2], Pedro Esbrit[2] and M.J. Alcaraz[1]. [1]University of Valencia, Burjasot, Valencia, Spain, [2]Fundación Jimenez Diaz, Madrid, Spain.

Background/Purpose: In osteoarthritis (OA), there is an abnormal remodeling process in subchondral bone associated with an altered osteoblast metabolism. Inflammatory mediators participate in bone remodeling and cartilage degradation during OA progression. Parathyroid hormone (PTH) and its bone counterpart, PTH-related protein (PTHrP), increase bone turnover through interaction of their N-terminal domain with the PTH type 1 receptor in osteoblasts. PTHrP peptides may be a novel approach to treat bone metabolic alterations. The aim of this study was to investigate the effects of different PTHrP peptides, PTHrP (1–37), and the PTH-unrelated peptides, PTHrP (107–139) and PTHrP (107–111) (osteostatin), on osteoblast senescence and the production of inflammatory mediators and degradative enzymes in osteoarthritic human osteoblasts stimulated with interleukin-1β (IL-1β).

Methods: Osteoblasts were obtained from 8 patients undergoing total knee joint replacement. Subchondral bone tissue obtained from tibial plateau was minced into small portions and digested with collagenase under agitation. Collected tissue was seeded in osteogenic medium to obtain osteoblastic cells according to a standard procedure. At first passage, osteoblastic cells were treated with PTHrP (1–37), PTHrP (107–139) and osteostatin (each at 100 nM) with or without IL-1β (10 ng/ml) for 1, 3 and 6 days. Senescence-associated β-galactosidase activity (SA-β-Gal) was assessed by cytochemistry. mRNA expression of matrix metalloproteinases (MMPs) and senescence markers was determined by qPCR. Prostaglandin E_2 (PGE_2) was measured by RIA, pro-inflammatory cytokines by ELISA, and cyclooxygenase-2 (COX-2) expression was determined by immunocytochemistry.

Results: IL-1β increased senescence features and the secretion of inflammatory mediators in osteoarthritic osteoblasts. Increased production of cytokines, MMPs and PGE_2 may contribute to bone sclerosis and degradative processes in the joint. The three PTHrP peptides tested significantly downregulated SA-β-Gal and the expression of caveolin-1, p21, p53, MMP-1 and MMP-3. In addition, these peptides reduced the release of tumor necrosis factor-α into the culture medium. PGE_2 production was significantly decreased by PTHrP (1–37) on days 1, 3 and 6, and also by each C-terminal PTHrP peptide on day 6. This effect on PGE_2 was dependent on the downregulation of IL-1β-induced COX-2 overexpression.

Conclusion: These findings show that both N- and C-terminal PTHrP peptides counteract the effects of IL-1β on the induction of cell senescence and the production of inflammatory and degradative mediators in osteoarthritic human osteoblasts, suggesting a beneficial effect of these peptides in osteoarthritic subchondral bone.

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Stimulation of the Adenosine a_{2A} receptor (A2AR) Regulates the Expression of Netrin1 and Their Receptors (Unc5b, DCC) and Inhibits Osteoclast Differentiation and Inflammatory Bone Destruction. Aranzazu Mediero[1], Bhama Ramkhelawon[1], Miguel Perez-Aso[2], Kathryn Moore[1] and Bruce N. Cronstein[3]. [1]NYU School of Medicine, New York, NY, [2]New York University, New York City, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: A variety of molecules mediate communication between osteoclasts and osteoblasts during bone remodeling. Netrin1 is a member of the family of axonal guidance proteins, that regulates inflammation and macrophage function. Because osteoclasts are derived from myeloid precursors we asked whether osteoclasts expressed Netrin-1 and whether A2AR activation, which diminishes osteoclast differentiation, might regulate Netrin-1 expression and inflammatory osteolysis.

Methods: 1cm midline sagittal incision was made over the calvaria in C57Bl/6 mice age 6–8 weeks. Mice received no particles (Control) or 3mg of UHMWPE with 20μl of saline 0.9% or CGS21680 (A2AR agonist, 1μM, n=4 each) at the surgical site every day up to 14 days. After sacrifice, calvaria were prepared for immunostaining for Netrin1/Unc5b/DCC. Protein and mRNA expression were studied by RT-PCR and WB in mouse and human primary bone marrow-derived OC and OB in the presence/absence of CGS21680 and ZM241385 (A_{2A}R antagonist) 1μM each.

Results: UHMWPE increased expression of Netrin1 and Unc5b, but not DCC, in periosteal inflammatory infiltrates which was reversed by the A2AR agonist CGS21680. RANKL induced 25$\pm$4 and 3$\pm$0.5 fold change, respectively, in Netrin1 and Unc5b mRNA during osteoclast differentiation, changes that were completely blocked by CGS21680 (1.17$\pm$0.1, $p<0.001$, n=4). In contrast, DCC mRNA expression did not significantly change during osteoclast differentiation and DCC expression was unaffected by CGS21680 (1.16$\pm$0.2 fold increase vs 1.9$\pm$0.2 for RANKL, p=ns, n=4). There was no change in Netrin1 or Unc5b expression during OB differentiation. Similar changes were observed in protein expression and secretion.

Conclusion: UHMWPE-induced osteolysis is regulated by Netrin1 activation. Adenosine A_{2A}R stimulation normalizes Netrin1expression and inhibits bony destruction at sites of UHMWPE-induced osteolysis. These results suggest that targeting Netrin1 directly or via stimulation of adenosine A_{2A}R may be a novel approach to preventing osteolysis and joint prosthesis loosening.

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Pro-Nerve Growth Factor (ProNGF) Stimulates Bone Growth By Stimulating Osteoblasts and Inhibiting Osteoclast Differentiation, an Explanation for Anti-NGF-Mediated Osteonecrosis; Prongf Is a Novel Therapeutic Target for Treatment of Osteonecrosis and Charcot's Arthropathy. Aranzazu Mediero[1], Barbara Hempstead[2] and Bruce N. Cronstein[3]. [1]NYU School of Medicine, New York, NY, [2]Weill Cornell Medical College, New York, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Neurotrophins (Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF)) are initially synthesized as pro-neurotrophins (proNGF and proBDNF), which are hydrolyzed to produce the mature proteins. BDNF is reported to be a stimulus for osteoclast differentiation in multiple myeloma. Anti-NGF is currently in trials for relief of chronic pain in patients with osteoarthritis but trials are on hold due to the common occurrence of rapidly progressive osteonecrosis resembling Charcot's arthropathy. We therefore sought to determine whether pro-NGF, which stimulates different receptors than the mature protein, plays a role in bone homeostasis we examined mice that overexpressed poorly hydrolyzed pro-NGF.

Methods: Wild type C57BL/6 (WT) and proNGF/+ (mice that overexpress a poorly hydrolysable proNGF) mice were sacrificed and prepared for microCT. Osteoclast and osteoblast differentiation was studied in primary murine bone marrow precursors as number of TRAP-positive cells or Alizarin Red-positive stain after challenge with the presence/absence of recombinant neurotrophins. Neurotrophin receptors (p75, Sortilin, Sorcs2) were analyzed by Western Blot.

Results: microCT revealed an increase in cortical and trabecular bone in proNGF/+ mice when compare to WT. This change correlated with a decrease in osteoclast differentiation in cells from proNGF/+ mice (30±3% decrease, $p<0.001$, n=4) and increased osteoblast differentiation in proNGF/+ (46±5% increase, $p<0.5$, n=4). Treatment with proNGF markedly inhibits osteoclast differentiation (60±2% decrease, $p<0.001$, n=5) without affecting osteoblast differentiation (10±5% increase, p=ns, n=5). In contrast, recombinant NGF increased osteoclast differentiation (17±2% increase, $p<0.05$, n=5) with a decrease in osteoblast formation (62±3% decrease, $p<0.001$, n=5). p75, Sortilin and Sorcs2 receptors were expressed in osteoclasts and osteoblasts.

Conclusion: These results indicate that the rapid bone destruction seen in patients treated with anti-NGF antibodies is most likely due to reduction of pro-NGF levels required for maintenance of bone homeostasis. Moreover, our results suggest that administering a therapeutically effective amount of proNGF may provide a novel therapeutic approach to promote bone growth and prevent Charcot's arthropathy, a common problem in patients, such as diabetics, with peripheral neuropathy.

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Hydrogen Sulfide Inhibits Human Osteoclast Differentiation *in Vitro* By Triggering Sustained Antioxidant Response and Inhibiting the RANKL/OPG Ratio. Francesco Grassi, Laura Gambari, Andrea Facchini and Gina Lisignoli. ISTITUTO ORTOPEDICO RIZZOLI, BOLOGNA, Italy.

Background/Purpose: Hydrogen sulfide (H_2S) has been recently appreciated as a novel gasotransmitter with an important role in the regulation of tissues and organs. H_2S is produced endogenously in mammalian cells from L-cysteine mainly by the enzymes cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CSE) Several correlations were established between low levels of plasmatic H_2S, reduced activity of H_2S-generating enzymes and diseases, including erosive bone diseases, leading to the hypotheses that disregulation of H_2S levels may be critical in the onset of specific diseases. However, the role of H_2S in the regulation of bone homeostasis has been scarcely investigated. Circulating osteoclasts (OCs) precursors are a population of clinical relevance in erosive bone diseases, such as rheumatoid arthritis or psoriatic arthritis, and a potential pharmacological target.

Our objective was to investigate the role of H_2S in the regulation of OCs differentiation and function *in vitro*, by both direct effect on OCs precursors and indirect regulation of mesenchymal stem cells (MSC).

Methods: human monocytes were isolated and differentiated into osteoclasts in the presence of M-CSF (10ng/ml) and RANKL (75ng/ml) and variable concentrations of NaHS, an H_2S donor. TRAP assay and pit assay were performed to evaluate either h-OCs differentiation or "bone" resorption. h-OCs precursors were tested for cellular apoptosis (Annexin V/ PI staining), acute toxicity (LDH assays), ROS production (DCF staining), mRNA and/or protein expression of NRF2, and NQO1 and PRDX1 (RT-PCR, IHC analyses). RANKL and OPG expression were evaluated by Real-Time PCR in human MSC stimulated with NaHS. GraphPad Prism5 software was used for statistical analysis.

Results: exogenous H_2S (100–300 μM) significantly inhibited the differentiation and function of h-OCs without affecting cell viability. H_2S inhibited RANKL-induced ROS production in OC precursors; moreover, H_2S induced significant nuclear translocation of NRF2, the master regulator of antioxidant response, and significantly increased mRNA and protein expression of PRDX-1 and NQO1, two key NRF-2-dependent antioxidant genes. Furthermore, siRNA-based inhibition of NRF2 in OC precursors completely prevented the NaHS-dependent inhibition of OCs differentiation, showing that NRF2 is critical for H_2S regulation of OCs differentiation. Finally, NaHS stimulation (100mM) significantly inhibited the RANKL/OPG mRNA ratio in human MSC, a key marker of the OCs-supporting ability of these cells.

Conclusion: Our findings show that H_2S inhibits OC differentiation by both direct and MSC-mediated mechanisms, suggesting a possible therapeutical role of H2S donors in erosive bone diseases.

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The Use of Three-Dimensionally Printed β-Tricalcium Phosphate/Hydroxyapatite to Further Understand the Regulation of Adenosine Receptors in Osteoclast Formation and Promotion in Bone Regeneration. Stephanie Ishack[1], Aranzazu Mediero[1], John Ricci[2] and Bruce N. Cronstein[3]. [1]NYU School of Medicine, New York, NY, [2]NYU Dental School, New York, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Bone defects resulting from trauma or infection need timely and effective treatments to restore damaged bone. Using specialized three-dimensional (3-D) printing technology, combined with bioactive molecules, we can design custom 3-D scaffolds for bone repair. The Hydroxyapatite (HA)/Beta-Tri-Calcium Phosphate (B-TCP) scaffold components provide mechanical strength, conduct bone throughout the scaffold and remodel over time. Dipyridamole (DIPY) increases local adenosine levels by blocking cellular uptake of adenosine and stimulates bone regeneration. Because DIPY, adenosine and adenosine A2A receptor-specific agonists stimulate bone regeneration in mice as well as BMP-2, a growth factor currently used to promote bone regeneration, we tested the capacity of DIPY-coated matrices could promote successful bone regeneration.

Methods: 15% HA:85% B-TCP scaffolds were designed usingRobocad software, fabricated using a 3-D Robocasting system, and sintered at 1100°C for 4h. Scanning electron microscopy (SEM), micro-computed tomography (micro-CT), x-ray diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR) and inductive coupled plasma (ICP) were used for material characterization. Vehicle, BMP-2 and DIPY drug scaffolds (scaffold + PBS, scaffold + DIPY or BMP-2, scaffold+ collagen + DIPY or BMP-2) were implanted in C57B6 (wild type, WT) and A2AKO mice with 3mm critical size defect for 2, 4 and 8 weeks. DIPY release from scaffold was assayed spectrophotometrically over time. MicroCT and histological analysis were conducted to determine the degree of new bone formation and remodeling.

Results: Quantitative and qualitative results from microCT showed similar and significant bone formation and remodeling in HA/B-TCP- DIPY and HA/B-TCP-BMP-2 scaffolds when compared to vehicle at 2, 4 and 8 weeks in WT mice (55% bone formation for in HA/B-TCP- DIPY and HA/B-TCP-BMP-2 vs 41% for vehicle, N=5 per group; $P \leq 0.01$). Dipyridamole did not enhance bone formation in A_{2A}KO mice 4 weeks after trephination (31% for HA/B-TCP- DIPY vs 27% for vehicle, N=5, p=ns). Histological analysis of WT mice showed increased bone formation and a trend toward increased remodeling in HA/B-TCP- DIPY and HA/B-TCP-BMP-2 scaffolds. Histologic examination of Dipyridamole treated scaffold in A2AKO mice showed no significant differences in bone formation when compare to vehicle treated scaffolds. Dipyridamole release from collagen coated scaffolds, maintain a constant concentration (10-6M) for up to 10 days.

Conclusion: Dipyridanmole increases adenosine levels and targeting osteoblasts and osteoclasts via activation of the adenosine A2A receptor leads to increased bone regeneration in a murine model. Delivery of Dipyridamole in the 3-D ceramic scaffolds is a an effective approach for bone regeneration following orthopedic, dental and craniofacial procedures.

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Regulation of Osteoclast and T Cell Differentiation By DC-STAMP and TRAF3. Yahui Grace Chiu[1], Jinbo Li[1], Dongge Li[1], Brendan Boyce[1] and Christopher T. Ritchlin[2]. [1]University of Rochester, Rochester, NY, [2]University of Rochester Medical Center, Rochester, NY.

Background/Purpose: DC-STAMP (Dendritic Cell-Specific Transmembrane Protein) is a 7-pass transmembrane protein essential for cell-to-cell fusion during OC differentiation. We have previously shown that DC-STAMP is a specific cell surface marker of OC precursors (OCP) and the frequency of DC-STAMP$^+$cells is elevated in patients with psoriatic arthritis (PsA). Intriguingly, we found that the level of TNF receptor-associated factor 3 (TRAF3) was also significantly elevated in the OCPs of PsA patients. In addition, osteoporosis can be prevented in mice by reducing osteoclastogenesis through inhibition of TRAF3 degradation by chloroquine. Although both DC-STAMP and TRAF3 play critical roles in OC formation, it is unknown if there is an interplay between these two molecules during osteoclastogenesis. Herein, to investigate a possible mutual regulation between them, we

quantified and monitored these two proteins in DC-STAMP knock-out (KO) mice and TRAF3 conditional KO (cKO) mice.

Methods: We analyzed the expression of DC-STAMP and TRAF3 in the spleen, thymus, lymph nodes, bone marrow and skeleton by flow cytometry and Western blotting in the TRAF3 KO and DC-STAMP KO mouse strains. We also examined the effects of chloroquine on the expression of DC-STAMP and TRAF3. The TRAF3 cKO mouse line was established by conditional deletion of TRAF3 in OC lineage cells by crossing $Traf3^{fl/fl}$and CatK-Cre.

Results: In DC-STAMP KO mice, $TRAF3^+$ T cells were identified in the bone marrow, bone, spleen, lymph nodes, but not in the thymus. We showed that the DC-STAMP deficiency blocked the differentiation of $TRAF3^+CD8^+$T cells in thymus, and TRAF3 protein was not present in the thymus by Western blot analysis. In contrast, the expression level of DC-STAMP and DC-STAMP+ cell frequency was unchanged in the TRAF3 cKO mice. Chloroquine treatment increased the expression levels of extracellular DC-STAMP and intracellular TRAF3 and prevented osteoclast formation in human PBMC cell cultures.

Conclusion: The expression of DC-STAMP is normal in the TRAF3 cKO mouse cells, whereas TRAF3 expression was dramatically decreased in the thymus of DC-STAMP KO mice. Our results suggest that (1) DC-STAMP is critical for the regulation of T cell differentiation in the thymus; (2) DC-STAMP and TRAF3 are both required for osteoclastogenesis; (3) chloroquine exerts its negative osteoclastogenic effect by inhibiting the degradation of both TRAF3 and DC-STAMP. Thus, understanding the molecular events that regulate the synthesis and degradation of DC-STAMP and TRAF3 may reveal novel therapeutic targets in metabolic and inflammatory bone diseases.

Disclosure: Y. G. Chiu, None; **J. Li**, None; **D. Li**, None; **B. Boyce**, None; **C. T. Ritchlin**, Eli Lilly and Company, 9, Eli Lilly and Company, 5.

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Angiopoietin-like 4 Is over-Expressed in Rheumatoid Arthritis: A Potential Role in Pathological Bone Resorption. Catherine Swales[1], Nick Athanasou[2] and Helen Knowles[3]. [1]The Botnar Research Centre, Oxford, United Kingdom, [2]Department of Pathology, Oxford, United Kingdom, [3]Botnar Research Centre, Oxford, United Kingdom.

Background/Purpose: In contrast to normal synovial tissue, rheumatoid synovium is hypoxic, and expresses the hypoxia-inducible transcription factors HIF-1α and HIF-2α which allow the transcription of genes involved in angiogenesis, inflammation, apoptosis and regulation of immune function. Hypoxia also stimulates osteoclast differentiation and causes a HIF-1α-dependent 3-fold increase in bone resorption. Angiopoietin-like 4 (ANGPTL4) is a hypoxia- and HIF-inducible pro-angiogenic adipokine that is induced in fibroblast-like synoviocytes in rheumatoid arthritis. This study sought to investigate whether ANGPTL4 is expressed in osteoclasts and other cells within rheumatoid synovial tissue, and to compare serum and synovial fluid levels of ANGPTL4 with those in normal controls and patients with osteoarthritis.

Methods: Serum, synovial fluid and synovial tissue samples were derived from patients with osteoarthritis (OA) and rheumatoid arthritis (RA); serum was obtained from aged-matched normal controls. All donors were recruited from the Nuffield Orthopaedic Centre, Oxford, UK and gave written informed consent. ANGPTL4 and HIF-1α expression was assessed in OA and RA synovial sections by immunohistochemistry and immunofluorescence. Serum and synovial fluid levels of ANGPTL4 were measured by ELISA. Osteoclasts were differentiated from circulating RA monocytes using M-CSF and RANKL, and hypoxic induction of ANGPTL4 mRNA was measured by real-time PCR.

Results: Bone-apposing osteoclasts within the rheumatoid synovium expressed ANGPTL4 and its regulating transcription factor HIF-1α. ANGPTL4 was strongly expressed in synovial lining cells, endothelial cells, stromal cells, CD68+ macrophages and plasma cells within the RA synovium. Little ANGPTL4 was evident in normal synovium, mirroring the expression pattern of HIF-1α in rheumatoid versus normal synovial tissue. ANGPTL4 concentrations were higher in the serum and synovial fluid of RA patients than in OA patients or normal controls. High serum ANGPTL4 correlated with elevated levels of the serum bone resorption marker sRANKL. Finally, ANGPTL4 mRNA was induced 5.5-fold by hypoxia in monocyte-derived osteoclasts from RA patients.

Conclusion: ANGPTL4 is over-expressed in both the serum and the synovial fluid and tissue of RA patients. Expression of ANGPTL4 in bone-apposing osteoclasts and correlation of high serum ANGPTL4 with circulating sRANKL suggests ANGPTL4 as a marker for bone destruction, and a potential target for inhibition of osteoclast-mediated bone resorption in RA.

Disclosure: C. Swales, None; **N. Athanasou**, None; **H. Knowles**, None.

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Human $CD14^+$ Monocytes Stimulated with a Combination of TNFα and IL-6 Differentiate into Osteoclast-like Cells with Bone-Resorption Activity. Kazuhiro Yokota, Kojiro Sato, Yoshimi Aizaki, Yuji Akiyama and Toshihide Mimura. Saitama Medical University, Saitama, Japan.

Background/Purpose: Proinflammatory cytokines play an important role in bone destruction in rheumatoid arthritis (RA), as inferred by the efficacy of biologics. Previously, we reported that mouse osteoclast-like cells were induced, both in vitro and in vivo, by a combination of TNFα and IL-6 from bone marrow-derived monocytes/macrophages. Herein, we examined the differentiation, function, and regulation of osteoclast-like cells that were induced by the combination of TNFα and IL-6 from human $CD14^+$monocytes.

Methods: Human $CD14^+$ monocytes were cultured with IL-6, TNFα, or TNFα plus IL-6. Pit formation assay on dentine slices was performed to assess the bone-resorbing activity. The expression of nuclear factor of activated T-cells cytoplasmic 1 (NFATc1), which is the master regulatory transcription factor for osteoclast differentiation, was detected by a western blot analysis. The effects of osteoprotegerin (OPG), a decoy receptor for RANKL, NFAT inhibitor tacrolimus, or JAK inhibitor tofacitinib were examined.

Results: The tartrate-resistant acid phosphatase positive multinucleated osteoclast-like cells were induced by the combination of TNFα and IL-6 from human $CD14^+$ monocytes in a dose-dependent manner. These osteoclast-like cells had bone resorption activity on dentin slices. The differentiation of conventional osteoclasts induced by RANKL from $CD14^+$ monocytes was inhibited by OPG, whereas that of our osteoclast-like cells was not. Expression of NFATc1 was upregulated by the combination of TNFα and IL-6 compared with TNFα or IL-6 alone. In addition, differentiation of the osteoclast-like cells from $CD14^+$monocytes was completely inhibited by tacrolimus. On the other hand, tofacitinib blocked the differentiation of the osteoclast-like cells through the JAK signaling pathway.

Conclusion: Osteoclast-like cells with bone resorption activity were induced by culturing human $CD14^+$ monocytes with the combination of TNFα and IL-6. These results indicate that not only osteoclasts, but also osteoclast-like cells may be involved in the pathogenic mechanism of inflammatory bone destruction, such as RA.

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ACR Poster Session A
Epidemiology and Public Health: Osteoporosis, Non-Inflammatory Arthritis and More

Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Prevalence of Spondyloarthritis (ASAS Criteria) in First-Degree Relatives of Patients with Ankylosing Spondylitis. Raúl Menor Almagro[1], Carmen Ordas[2], Carlos Montilla[3], Jose Luis Alvarez-Vega[4], Íñigo Hernández-Rodríguez[5], Montserrat Corteguera[6], Santiago MuÑoz Fernandez[7], Claudia Urrego[8], Rafael Ariza-Ariza[9], Mireia Moreno[10], Xavier Juanola[11], Maria Isabel Tévar[12], Eduardo Collantes- Estevez[13], Juan Mulero-Mendoza[14] and Ana Ruiz-Zorrilla[15]. [1]Hospital de Jerez, Jerez de la Frontera, Spain, [2]Hospital de Cabueñes, Gijón, Spain, [3]Hospital Clínico Universitario de Salamanca, Salamanca, Spain, [4]H. de Salamanca, Salamanca, Spain, [5]University Hospital Complex of Vigo, Vigo, Spain, [6]Hospital N^a S^a Sonsoles, Avila, Spain, [7]Sección de Reumatología, Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Madrid, Spain, [8]Hospital G. Segovia, Segovia, Spain, [9]University Hospital Virgen Macarena, Sevilla, Spain, [10]Hospital Universitari Parc Taulí, Sabadell, Spain, [11]University Hospital Bellvitge, Barcelona, Spain, [12]Hospital Vega Baja, Orihuela, Alicante, Spain, [13]Hospital Reina Sofía, Córdoba, Spain, [14]Hospital Puerta de Hierro, Madrid, Spain, [15]Abbvie, Madrid, Spain.

Background/Purpose: Spondyloarthritis (SpA), a group of inflammatory diseases which exhibit similar genetic background, clinical features and symptoms[1], has an estimated prevalence of 0.5–1%[2] in Spain. However, in first-degree relatives positive for the HLA-B27 antigen, this prevalence may reach up to 24%[3–7]. The ASAS (Assessment of SpondyloArthritis international Society) criteria for SpA facilitate the identification of patients throughout the SpA spectrum, helping to potentially diagnose SpA features in first-degree relatives of patients with ankylosing spondylitis (AS). The aim of this study was to determine the prevalence of axial and peripheral SpA in first-degree relatives of AS patients.

Methods: A multicentre, cross-sectional prevalence study was designed in first-degree relatives of patients with AS. Relatives agreeing to participate in the study completed a screening questionnaire to identify the presence of specific SpA characteristics. Relatives whose responses indicated the presence of SpA features were referred to a rheumatologist to collect their medical history and an assessment of disease activity, which included a blood test for the HLA-B27 antigen and C-reactive protein (CRP), a simple pelvic X-ray (Rx) and a pelvic magnetic resonance image (MRI). All the imaging tests were assessed by an expert radiologist.

Results: Of the 486 participants, 290 first-degree relatives were classified as positive for SpA features after the screening questionnaire, and 269 continued in the study. After a rheumatologist's evaluation using the ASAS criteria (table 1), 55 participants had no apparent signs of SpA and 214 were considered to be evaluable by the rheumatologist. Supplementary tests were performed in 195 relatives. Approximately 10.9% (n=53/486) of all the relatives met the criteria for SpA, of whom 60% (n=32) and 40% (n=21) were diagnosed as having? axial SpA and peripheral SpA, respectively. Of the relatives assessed for diagnosis (n=250), 21.2% (n=53) met the criteria for SpA; 12.8% (n=32) were diagnosed with axial SpA, 8.4% (n=21) with peripheral SpA (table 2).

Approximately 62.5% (n=20) of the 32 relatives with axial SpA met criteria for axial SpA through the clinical arm, 15.6% (n=5) met the imaging criteria, and 21.9% (n=7) met both the clinical and imaging criteria (table 2).

Conclusion: The incidence of SpA in first-degree relatives of Spanish patients with AS was 10.9%, which is consistent with the published literature.

Table 1: Assessed ASAS criteria rates

Relatives Screening +	n	%	N
Inflammatory back pain	193	39.70%	486
Arthritis	37	7.60%	486
Enthesitis of the heel	50	10.30%	486
Uveitis	6	1.20%	486
Dactylitis	13	2.70%	486
Psoriasis	14	2.90%	486
Crohn's disease/colitis	3	0.60%	486
Good response to NSAIDs	171	35.20%	486
Relatives evaluated	**n**	**%**	**N**
HLA-B27 Positive	79	40.50%	195
Elevated CRP	37	19.00%	195
Sacroiliitis in imaging	18	8.90%	195

Table 2: Distribution of relatives evaluated for SpA diagnosis

	n	1%
Relative screening + assessed for diagnosis	**250**	**100**
Do not meet spondyloarthritis criteria	197	78.80%
Meet spondyloarthritis criteria	53	21.20%
-Axial spondyloarthritis	32	12.8%
-Peripheral spondyloarthritis	21	8.4%
Axial SpA	**32**	**100%**
Only HLA B27+	20	62.5%
Onl y MRI +	5	15.6%
Both	7	21.9%

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The Impact of Ankylosing Spondylitis on Work Impairment: Data from the Scotland Registry for Ankylosing Spondylitis. Linda E. Dean[1], Alan G. MacDonald[2], Roger D. Sturrock[3], John Hunter[4], David Marshall[5], Gary J. Macfarlane[1] and Gareth T. Jones[1]. [1]University of Aberdeen, Aberdeen, United Kingdom, [2]Aberdeen Royal Infirmary, Aberdeen, United Kingdom, [3]Glasgow Royal Infirmary, Glasgow, United Kingdom, [4]Gartnavel General Hospital, Glasgow, United Kingdom, [5]Inverclyde Royal Hospital, Greenock, United Kingdom.

Background/Purpose: The impact of ankylosing spondylitis (AS) on work status is substantial. While the majority of studies focus on the prevalence of absenteeism in this group, impairment (i.e. presenteeism) whilst at work is also an important factor when assessing the impact of disease on work-life yet remains relatively understudied. The aim of the current study was therefore to describe the prevalence of, and factors associated with, work impairment in AS.

Methods: SIRAS collects data on clinically diagnosed AS patients in Scotland. Clinical measures recorded from medical records include disease activity (BASDAI) and physical function (BASFI), while postal questionnaires provide patient-reported data including pain and fatigue (Chalder Fatigue Scale). Work impairment 'during the past 7days' was assessed using the *Work Productivity and Activity Impairment questionnaire – Specific Health Problem*. Logistic regression was used to identify potential clinical and patient-reported factors associated with work impairment. These were assessed further using forward stepwise logistic models to identify independent risk factors. Results: are given as odds ratios with 95% confidence intervals. Additionally, the population attributable risks associated with independent risk factors were calculated.

Results: SIRAS contains both clinical and patient-reported information on 959 patients (male 73%, mean age 52yrs). Of those who answered items on employment (n=946), 55% were currently working, and only 10% of workers had missed work (during the past 7days) due to their AS. However, 71% of workers reported some impairment during this time (any versus none). Factors independently associated with work impairment were: moderate/severe fatigue (4.8; 2.4–9.4), poor physical function (BASFI≥4: 2.6, 1.2–5.6) and chronic widespread pain (3.7, 1.9–7.3). The population attributable risks associated with these factors were 19%, 9% and 13% respectively.

Conclusion: The majority of employed AS patients did not report missing any work, in the previous week, due to their AS. However, many experienced impairment whilst working, the key identifiable drivers of which were fatigue, pain and poor physical function. Targeted, non-pharmacological treatments, such as cognitive behavioural therapy, in addition to traditional therapeutic targets, may help to improve overall work productivity. This may reduce the economic impact of the disease and, ultimately, could improve overall work retention.

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The Prevalence of Ankylosing Spondylitis in Sweden – a Nationwide Register Study. Sofia Exarchou[1], Ulf Lindström[2], Johan Askling[3], Jonas Eriksson[4], Helena Forsblad-d'Elia[5], Lars Erik Kristensen[6], Martin Neovius[4], Carl Turesson[1] and Lennart T. Jacobsson[5]. [1]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [2]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, [3]Clinical Epidemiology Unit, Rheumatology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden, [4]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [5]Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, [6]Lund University, Malmö, Sweden.

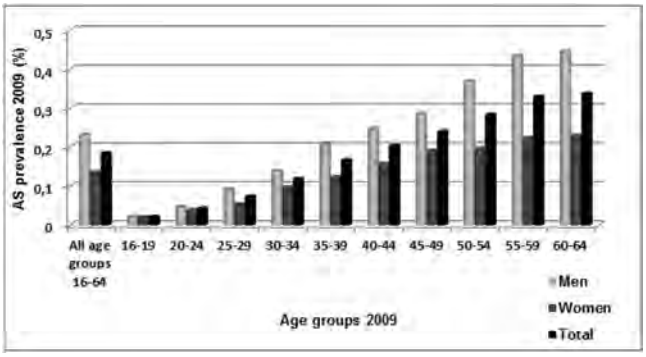
Background/Purpose: Reported Ankylosing Spondylitis (AS) prevalence estimates vary considerably, and there is a lack of nationwide estimates. Previous studies by our group support the validity of WHO International Classification of Disease codes (ICD-codes) for AS in the Swedish National Patient Register (NPR) and indicate that the mean diagnostic delay is about 10 years. This study aims to describe the national prevalence of diagnosed AS in

Sweden, based on data from the NPR, overall as well as stratified by age and sex, and to explore treatment, geographical variation and socio-economic factors in the Swedish AS population.

Methods: All patients given a diagnosis of AS according to ICD-codes in the NPR between 1967 and 2009 were identified. Statistics Sweden, the Swedish biologic register (ARTIS) and the national drug prescription register were used to retrieve data on demographics, drug exposure, level of education and vital status. Our case definition required at least one registered AS diagnosis in inpatient care 1967- present) or specialized outpatient care (2001-present), not including primary care and private practice. Results are presented for individuals 16–64 years old in 2009.

Results: On 31 December 2009, Sweden had a population of approximately 9.3 millions, of which 64% were in the age group 16–64 years old and 50.8% were men. Between 1967 and 2009, 20 044 patients with at least one health care registration in the NPR with a diagnosis of AS were identified. Of those, 11 030 were 16–64 years old, alive and living in Sweden on Dec 31, 2009. The overall prevalence of AS in this age group in 2009 was thus 0.18%. The prevalence increased linearly with age up to the age of 55 years, after which it leveled off. For all investigated age groups combined, men had a higher prevalence compared to women (0.23% vs 0.14%). During 2009, NSAIDs, DMARDs, corticosteroids and TNF-inhibitors had been prescribed to the AS patients in 53.4%, 20.4%, 11.7% and 14.2% respectively. Prevalence estimates by health care region revealed the highest age-/sex-standardized prevalence in the Northern Health Care Region (0.24%; 95% CI 0.23–0.25). The association between level of education and AS prevalence was explored only in those > 30 years old on Dec 31, 2009. The age-/sex-standardized prevalence of AS was lowest among those with > 12 years of education (0.20%; 95% CI 0.19–0.21), while somewhat higher prevalences were observed in the other two strata with a shorter formal education (≤ 9 years and 10–12 years) (0.24%; 95% CI 0.22–0.25 and 0.24%; 95% CI 0.23–0.24).

Conclusion: This nationwide, register-based prevalence estimate of AS in Sweden offers a unique opportunity to better understand the burden of AS to the healthcare system. Moreover, geographic and socio-economic differences in prevalence estimates suggest that genetic and possibly also environmental factors may be important for disease development and detection.



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Deaths Associated with Ankylosing Spondylitis in France from 1969 to 2009. Clement Prati[1], Daniel Wendling[2] and Xavier Guillot[3]. [1]Hopital Jean Minjoz, Besancon, France, [2]CHU J Minjoz, Besancon, France, [3]rheumatology, Besançon, France.

Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory joint disease that can lead to chronic pain in the axial and peripheral joints and to functional impairments. AS is a systemic disease that can cause extraarticular manifestations which could participate to excess mortality. The aim of the study is to describe characteristics of deaths for which AS was mentioned on the death certificate as either the underlying cause or anywhere on the death certificate and to analyze trends in AS related mortality from 1969 to 2009 in France.

Methods: Data were obtained from the Centre of Epidemiology on the Medical Causes of Death (CépiDc) for individuals aged 18 years and over died in France. Owing to implementation of International Classification of Diseases (ICD) 8, ICD-9 and ICD-10 for recording causes of deaths, three separate periods were analyzed (1969–78; 1979–99 and 2000–09). Initial, terminal and associated causes of deaths were analyzed. Initial Causes of deaths were compared with deaths of French general population in the same periods (CIM9 and 10).

Results: In the global period (1969–2009), AS appeared in 2942 deaths certificates, 2292 men (mean age of death 68,7 years) and 650 women (mean age of 75,8), 601 between 1969-78 (ICD8), 1471 between 1979–1999 (ICD9) and 867 between 2000 and 2009 (ICD10). There is a trend that AS decreases life expectancy in men compared with general population. The number of deaths with AS on the death certificates is increasing due to change of ICD and increase of diagnosis. AS is mentioned as initial cause in 38% in 1969–1978, 33% in 1979–1999 and 5% in 2000–2009. Apart from AS, most frequent initial causes are diseases of the circulatory system (28,5 % in ICD8, 23,1% in ICD9 and 26,5% in ICD10; neoplasms (7,8%, 10,2% and 16,3%); diseases of the respiratory system (7,5%, 11,1% and 9,4%) and external causes of mortality (3,5%, 7,8% and 13,1%). Compared to general population there is less deaths caused by neoplasm, but more caused by infectious, genitourinary diseases and external causes of mortality. Most frequent associated causes are diseases of the circulatory system (22,2%, 34,4% and 23,7%).

Conclusion: The manner of death coding varies according to ICD. Our study is the first to analyze data from deaths certificate. Diseases of the circulatory system are the most frequent initial and associated causes of death. But compared to general population, infectious, genitourinary diseases and external causes of mortality are more frequent in AS.

Disclosure: C. Prati, None; **D. Wendling**, None; **X. Guillot**, None.

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Physical Function, Hyperuricemia and Gout in Older Adults. Mara McAdams-DeMarco[1], Bridget Burke[2], Andrew Law[3], Anna Kottgen[4], Alan N. Baer[5] and Josef Coresh[1]. [1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [2]Johns Hopkins University, Baltimore, MD, [3]Johns Hopkins, Baltimore, MD, [4]University Hospital Freiburg, Freiburg, Germany, [5]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: The prevalence of gout is higher in older adults than in younger adults and these patients are at risk of physical disability. We sought to determine the prevalence of and risk factors for impaired physical function in relation to gout status and hyperuricemia.

Methods: We studied gout, hyperuricemia, and function in 5,819 older adults (age >65) using the Atherosclerosis Risk in Communities cohort, a prospective US population-based cohort study of middle-aged adults enrolled between 1987–1989 with ongoing annual follow-up through 2012. Differences in lower (Short Physical Performance Battery (SPPB) and 4 meter walk test, measured in 2011–2013) and upper extremity function (grip strength) by gout status and by hyperuricemia prevalence were estimated: adjusted ordinal logistic regression for SPPB and modified Poisson regression for 4 meter walk test and grip strength. The risk of poor physical function (lowest quartile of grip strength, lowest quartile of SPPB and highest quartile of 4 meter walk test) was estimated using modified Poison regression. Characteristics of gout participants with poor physical function were identified using modified Poisson regression.

Results: There were 595 (10.2%; women: 7.1% and men: 14.6%) participants with gout and 1,242 (21.3%; women: 16.2% and men: 28.4%) with hyperuricemia. There was no difference in grip strength by history of gout (mean difference = -0.29, 95% CI: -0.90, 0.32; P=0.36) nor risk of poor grip strength by history of gout (RR=1.07, 95% CI: 0.95–1.21; P=0.27). Participants with gout had 0.70-times (95% CI: 0.60, 0.82; P<0.001) the odds of 1-unit increase in the SPPB score, such that those with gout had worse performance on the SPPB and participants with gout were 1.28-times (95% CI: 1.15–1.42; P<0.001) more likely to have poor SPPB performance. Participants with gout had slower 4 meter walk test by history of gout (mean difference = 0.23, 95% CI: 0.12, 0.33; P<0.001) and were at 1.24-fold (95% CI: 1.10–1.41; P=0.001) increased risk of poor 4 meter walk test performance. Results were similar when comparing grip strength, SPPB and 4 meter walk test by hyperuricemia (Table). Among participants with gout, older participants (for every 5 year increase in age, RR=1.42, 95% CI: 1.28, 1.59), black participants (RR=1.58, 95% CI: 1.25, 2.00), participants with higher BMI (for every 5 kg/m^2 increase in BMI, RR=1.18, 95% CI: 1.07, 1.29), and participants who were current smokers (RR=1.65, 95% CI: 1.14, 2.38) were at highest risk of poor 4 meter walk time; similar results were observed for poor SPPB score.

Conclusion: Older adults with gout and hyperuricemia are more likely to have poor lower but not upper body function. Additionally, we identified a

group of gout participants with high risk of poor lower extremity function, namely, older age, men, with higher BMIs, and current smokers.

Table: Independent association of physical function in older adults, by gout and hyperuricemia status

	Grip strength (kg)	SPPB score	4 meter walk (seconds)
Adjusted mean difference in physical function			
No gout (n = 5,224)	Reference	Reference	Reference
Gout (n = 595)	−0.29 (−0.90, 0.32)	0.70 (0.60, 0.82)	0.23 (0.12, 0.33)
P-value	0.36	<0.001	<0.001
No hyperuricemia (n = 4,577)	Reference	Reference	Reference
Hyperuricemia (n = 1,242)	−0.10 (−0.56, 0.37)	0.82 (0.73,0.93)	0.14 (0.06, 0.22)
P-value	0.68	0.001	<0.001
Poor physical function			
No gout (n = 5,224)	Reference	Reference	Reference
Gout (n = 595)	1.07 (0.95, 1.21)	1.28 (1.15, 1.42)	1.24 (1.10, 1.41)
P-value	0.27	<0.001	0.001
No hyperuricemia (n = 4,577)	Reference	Reference	Reference
Hyperuricemia (n = 1,242)	0.98 (0.89, 1.07)	1.15 (1.06, 1.26)	1.21 (1.09–1.33)
P-value	0.65	0.001	<0.001

Ordinal logistic regression was used for SPPB score 5,548 with available 4 meter walk test without assistance.
Adjusted for: Age, sex, race, BMI, smoking status, education level, hypertension and alcohol intake.
Grip strength: higher scores are indicative of better function. SPPB score: higher scores are indicative of better function. 4 meter walk test: lower time is indicative of better function.
Low physical function was defined as the lowest quartile for grip strength (≤22 kg) and SPPB (≤7) as well as the highest quartile for normal walking pace (>5.2 seconds).

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Body Mass Index Across the Lifespan and Lifetime Incidence of Gout in Men. Allan C. Gelber, Lucy Meoni, Michael Klag and Joseph Gallo. Johns Hopkins University, Baltimore, MD.

Background/Purpose: Gout is the leading cause of inflammatory arthritis in men and is linked to higher levels of body weight and obesity in mid-adult life. However, few, if any, observational cohorts have examined the association of body weight across the life span with incident gout. We sought to determine whether weight, assessed in young, mid and late-adult life, predicted the subsequent development of gout.

Methods: Body mass index [BMI] was first calculated at a mean age of 23 (+2) years among 1040 male former medical students who graduated from 1948–1964. Thereafter, BMI was re-assessed in each decade of adult life. Incident gout was ascertained during follow-up using self-administered questionnaires and confirmed in a subset of participants according to American College of Rheumatology criteria. Survival analysis techniques were used to examine the association of BMI in each age interval with incidence of gout, with adjustment for comorbid hypertension at time of BMI, cholesterol level and alcohol consumption at cohort entry.

Results: In this prospective cohort study, the mean weight at cohort entry was 75.6 (+9.8) kilograms, height was 1.81 (+0.06) meters, corresponding to mean BMI of 23.1 (+2.6) kg/m^2. During a median follow-up of 45 years, a total of 158 men developed gout. Notably, the youngest age at which gout first occurred was 28 years. Thereafter, 6 men developed gout by age 35 years, an additional 36 developed gout by age 50 years, 36 more between ages 50–65 years, and finally, 70 men developed gout between 65 to 88 years of age. The cumulative incidence of gout by age 45 years was 2.2%, by 55 years was 5.4%, by 65 years was 8.5%, by age 75 years was 14.4%, and the cumulative incidence of gout by 85 years was 21.0%. Further, at each period in the adult life spectrum, a dose-response association was observed between successively higher tertiles of BMI with gout incidence (Table; each logrank p<0.06). Moreover, those men in the highest tertile of BMI (at ages 35, 50 and 65) experienced a heightened risk to develop gout over the next 15–20 year period (between ages 35–50, 50–65, and 65–85, respectively,) compared to those in the lowest BMI tertile, an association largely explained in the late adult period by comorbid hypertension.

Conclusion: The incidence of gout in men rises during each decade of the lifespan. Body weight in young, mid and late adult life, each predicted gout incidence during the subsequent age period. These findings imply that across the lifespan, overweight and obesity are potential modifiable targets in the primary prevention of gout.

BMI at age 35 years	n	Incident cases of gout	Cumulative incidence at specified age (%)	P value	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Upper tertile (24.5 to 36.8 kg/m^2)	387	18	4.8		3.1 (1.2–7.7)	5.7 (1.7–19.7)
Middle tertile (22.8 to 24.4 kg/m^2)	386	12	3.3	0.04	2.1 (0.8–5.5)	3.7 (1.0–13.2)
Lowest tertile (16.6 to 22.7 kg/m^2)	387	6	1.6		1.00	1.00
BMI at age 50 years						
Upper tertile (25.2 to 41.8 kg/m^2)	347	24	7.5		2.8 (1.3–6.0)	3.1 (1.3–7.4)
Middle tertile (23.2 to 25.2 kg/m^2)	348	15	4.7	0.02	1.7 (0.7–3.8)	1.2 (0.5–3.3)
Lowest tertile (15.9 to 23.2 kg/m^2)	347	9	2.8		1.00	1.00
BMI at age 65 years						
Upper tertile (25.8 to 46.6 kg/m^2)	275	29	18.3		1.9 (1.1–3.5)	1.4 (0.8–2.7)
Middle tertile (23.4 to 25.8 kg/m^2)	276	21	12.9	0.06	1.2 (0.6–2.2)	0.8 (0.4–1.6)
Lowest tertile (17.2 to 23.4 kg/m^2)	275	18	10.2		1.00	1.00

Disclosure: A. C. Gelber, None; **L. Meoni**, None; **M. Klag**, None; **J. Gallo**, None.

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Xanthine Oxidase Inhibitors and Risk of Type 2 Diabetes in Patients with Gout. Seoyoung C. Kim[1], John D. Seeger[2], Jun Liu[1] and Daniel H. Solomon[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital/Harvard Medical School, Boston, MA.

Background/Purpose: Hyperuricemia and gout are associated with an increased risk of type 2 diabetes (T2D). Xanthine oxidase inhibitors (XOI), allopurinol and febuxostat, are the main therapy to treat gout patients with hyperuricemia. Little is known whether treating hyperuricemia with a XOI has any effect on future risk of T2D. We examined the risk of T2D in gout patients initiating a XOI versus untreated patients with hyperuricemia.

Methods: We conducted a cohort study using a U.S. commercial insurance claims database. Patients aged ≥40 years with gout and hyperuricemia (≥ 6.8mg/dl) who had an enrollment period for ≥ 365 days were eligible. Propensity score (PS) matching was used to simultaneously control for baseline demographic factors, comorbidities, medications, health care utilization, and time trend. From January 2004 to December 2012, XOI initiators and non-initiators matched on a PS were identified with a 1:2 ratio in each calendar month (a total of 108 calendar months). The first day of each month was the index date for both groups. We excluded patients with diabetes, use of XOI or anti-diabetic drugs, end-stage renal disease and renal transplantation prior to the index date. Follow-up continued until the outcome occurrence, discontinuation or initiation of XOI, disenrollment, or administrative censoring. We calculated incidence rates (IR) of T2D based on a new diagnosis of T2D and a receipt of anti-diabetic medication. Due to violation of the proportional hazards assumption, Cox proportional hazards models stratified by treatment duration compared the risk of T2D in XOI initiators versus non-initiators.

Results: There were 4,045 XOI initiators and 8,090 non-initiators. Baseline characteristics were well-balanced between the matched groups. Mean age was 54 years and 89% male in both groups. Common comorbidities include hypertension (64%), hyperlipidemia (61%), CVD (10%), obesity (10%) and chronic kidney disease (8%). Use of systemic steroids at baseline was common (33%). The mean serum uric acid level at baseline was 8.9 mg/dl in XOI initiators and 8.3 mg/dl in non-initiators. The mean HgbA1c level at baseline was 5.9% in XOI initiators and 5.8% in non-initiators. The IR of T2D per 100 person-years was 1.88 (95% CI 1.41–2.51) in XOI initiators and 1.57 (95% CI 1.36–1.81) in non-initiators. XOI treatment for 0–90 days was associated with an increased risk of T2D versus non-initiators, whereas the use of XOI for longer than 360 days may be associated with a decreased risk of T2D (**Table**).

Conclusion: Nearly 2% of gout patients were newly diagnosed with T2D during follow-up. Short-term use of XOI was associated with a greater risk of T2D in gout patients compared to non-initiators, but a potential long-term beneficial effect of XOI on T2D cannot be excluded. Future research such as a randomized clinical trial ensuring treatment adherence may be needed to examine the long-term effect of XOI on T2D.

Table Risk of type 2 diabetes by the duration of xanthine oxidase inhibitor treatment in gout patients: PS-matched analysis

	Xanthine oxidase inhibitor initiators (n = 4,045)				Non-initiators (n = 8,090)			
Follow-up time (days)	Cases	Person-years	IR* (95% CI)	HR (95% CI)	Cases	Person-years	IR* (95% CI)	HR (95% CI)
All	46	2,449	1.88 (1.41–2.51)	1.26 (0.90–1.76)	189	12,035	1.57 (1.36–1.81)	Ref
0–90	22	903	2.44 (1.60–3.70)	2.53 (1.35–4.71)	18	1,908	0.94 (0.59–1.50)	Ref
90–180	5	448	1.15 (0.46–2.68)	0.71 (0.27–1.85)	25	1,583	1.58 (1.07–2.34)	Ref

181–270	8	279	2.86 (1.43–5.73)	1.63 (0.73–3.64)	23	1,331	1.73 (1.15–2.60)	Ref
271–365	3	209	1.44 (0.46–4.45)	0.96 (0.28–3.25)	18	1,181	1.52 (0.96–2.42)	Ref
366–545	3	240	1.25 (0.40–3.88)	0.7 (0.21–2.29)	30	1,710	1.75 (1.23–2.51)	Ref
546+	5	380	1.31 (0.55–3.16)	0.75 (0.30–1.86)	77	4,342	1.77 (1.42–2.22)	Ref

*per 100 Person-years, IR: incidence rate, HR: hazard ratio, CI, confidence interval

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The Risk of Aplastic Anemia and Pancytopenia with Colchicine: A Retrospective Study of Integrated Health System Database. Jasvinder Singh[1], Shuo Yang[1] and Jeff Foster[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Colchicine is a commonly used medication, sometime associated with bone marrow toxicity. The objective of this study was to examine the risk of severe hematologic side effects including pancytopenia and aplastic anemia with colchicine.

Methods: This retrospective study utilized the Veterans Affairs (VA) administrative and clinical databases from fiscal year 2001 to 2012. Colchicine use was defined as at least 30-day filled prescription. Prevalent gout was defined as the presence of >=1 International classification of diseases, ninth revision (ICD-9) codes for gout during an inpatient visit or during $^{3}2$ codes during outpatient visits. Aplastic anemia was captured with an ICD-9 code of 284.9 and Pancytopenia with a code of 284.1. We used Cox proportional hazards models that assessed hazards of aplastic anemia or pancytopenia adjusted for the following factors: Model 1: drug exposure, age, gender, body mass index, race, marital status, region; Model 2: variables in model 1, plus baseline Charlson comorbidities.

Results: 198 gout patients had aplastic anemia, of which 59 occurred in patients exposed to colchicine. 2047 gout patients had pancytopenia, of which 582 occurred in patients exposed to colchicine. The incidence rate of aplastic anemia was 0.5/1000 person years and of pancytopenia was xx/ in patients taking colchicine.

Conclusion: Colchicine increases the risk of aplastic anemia 3–4 fold and pancytopenia 2–3 fold in gout patients. Predictive models that can identify coexisting conditions that increase the risk of these side effects need to be developed to screen out patients at high-risk of these severe hematologic side effects.

Table 1 Association of colchicine with severe hematologic side effects

	Model 1 (demographics)		Model 2 (demographics + comorbidity)	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Aplastic anemia	3.72 (2.61, 5.31)	<0.0001	3.32 (2.32, 4.76)	<0.0001
Pancytopenia	2.88 (2.58, 3.22)	<0.0001	2.26 (2.02, 2.53)	<0.0001

Disclosure: J. Singh, Savient, 2, Takeda, 2, Degeneron, 5, Allergan, 5; **S. Yang**, None; **J. Foster**, None.

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Osteoporotic Women at High Risk for Fractures Despite Two Years of Oral Bisphosphonate Therapy: Analysis Using the Canadian Multicentre Osteoporosis Study. Jonathan D. Adachi[1], David Goltzman[2], Ankita Modi[3], Jackson Tang[4], Chun-Po S. Fan[4] and Jessica Weaver[3]. [1]Division of Rheumatology, McMaster University, Hamilton, ON, [2]McGill University, Montreal, QC, [3]Merck & Co., Inc., Whitehouse Station, NJ, [4]Asclepius Analytics, New York, NY.

Background/Purpose: Individuals with osteoporosis (OP) have an increased susceptibility to fractures. Prevention and treatment of postmenopausal OP is critical to decreasing the risk of non-traumatic bone fractures. These fractures cause medical and personal hardships, particularly among older individuals, and are a burden on health care systems (Adachi 2003). The objective of this study was to quantify the number of osteoporotic women 55 years of age or older that remain at high risk of fracture despite benefits of prior oral bisphosphonate (BIS) therapy.

Methods: This study retrospectively analyzed a subset of participants in The Canadian Multicentre Osteoporosis Study (CaMos). CaMos is a prospective cohort study of 9,423 selected from community dwelling men and women older than 25 years of age. A subset of women from the CaMos dataset were studied who were 55 years of age or older with OP, who did not have Paget's disease and who reported receiving BIS therapy for at least two consecutive years. Additionally, patients must have had at least three years of follow-up data from the index date (start of 2 years of BIS therapy), and be considered osteoporotic at baseline for inclusion. Patients with lumbar spine or hip BMD of < -2.5 at baseline, or with prior vertebral or hip fractures, were classified as osteoporotic. Two consecutive years of BIS therapy was utilized as a proxy for adherence to BIS therapy, and was based on annual self-reported patient questionnaire responses regarding BIS therapy. High risk for fracture was determined by the following three criteria: 1.) Fractures during the first year following the BIS treatment period. 2.) Any decline in BMD at the hip (femoral neck) or lumbar spine (L1-L4) from baseline BMD (the most recent BMD prior to the treatment period) to the "study BMD" (i.e. the closest BMD after the 2-year treatment period). 3.) A "study BMD" less than -2.5 at the hip (femoral neck) or lumbar (L1-L4) spine. Descriptive analysis was conducted to characterize the fracture risk profile in this patient population.

Results: 628 women with a mean age of 71.6 years met the eligibility criteria. 24 participants (3.8%) experienced fractures during the first year following the two consecutive years of BIS therapy. Of the 24 patients with fractures during this time, 3 had fractures during the two years of BIS therapy. Almost two thirds (59.2%) of participants (372) experienced a decline in BMD from baseline following two years of therapy. Additionally, 71.3% of patients (448) were classified as osteoporotic after two years of OP therapy.

Conclusion: This study demonstrates that despite the benefits of OP treatment with BIS, a considerable proportion of women represented in the CaMos database who reported taking oral BIS therapy for two years remained at high-risk for OP fractures. In light of this finding, alternative treatments should be considered for many osteoporotic women who remain at high risk for OP or non-traumatic fractures.

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Long-Term Oral Bisphosphonate Use for Osteoporosis Among Older Women – US and Canadian Perspective. Nicole C. Wright[1], Wilson Smith[2], Amy H. Warriner[1], Jeff Foster[1], Ruth McConnell[2], Huifeng Yun[3], Mary H Melton[1], Jeffrey R. Curtis[1] and Kenneth G. Saag[1]. [1]The University of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Alabama at Birmingham School of Public Health, Birmingham, AL.

Background/Purpose: Bisphosphonates (BPs) have been widely used for the treatment and prevention of osteoporosis for two decades. Although new parenteral preparations have been introduced, oral BPs still represent the vast majority of osteoporosis treatments. Little is known about the characteristics of or regional differences in long-term oral BP users.

Methods: We evaluated the long-term use of oral BPs in the national US Medicare and Ontario (ON) Canada data systems. The US Medicare cohort consisted of women aged ≥65 years with an osteoporosis or fracture diagnosis code, or BP prescription fill. The ON data consisted of women aged ≥66 years who were new users of oral BPs. We identified women with three years of continuous medical and pharmacy coverage. Long-term BP users were those with exposure to an oral BP (alendronate, risedronate, ibandronate, and etidronate) in each of the three most recent years of available data (2009–2011). We evaluated demographic and BP utilization data including, BP exclusivity (no exposure to another BP agent in three year period) and compliance to therapy using proportion of days covered (PDC) *(*days of drug supplied in 3 years/3*365.25). Users with a PDC of ≥*70%* were considered compliant.

Results: We identified 888,704 US and 99,530 ON women meeting the inclusion criteria with at least one oral BP prescription in the most recent data. We then identified 698,012 US and 54,656 ON long-term oral BPs users (Table). Alendronate was primarily used by Medicare patients (78.0%), whereas risedronate was the primary oral BP in ON (56%). Based on the available data, the mean duration of us among the long-term BP users was five years in both US (SD: 1.1) and ON (SD: 2.2). In the US, risedronate users were more likely to be exclusive users (83%) compared to alendronate users; whereas in ON, a higher proportion of alendronate users were considered exclusive users than risedronate users. All ibandronate users were exclusive

users in US data. Compliance was higher in ON (80% alendronate, 78% risedronate) than in US (63% alendronate, 63% risedronate).

Conclusion: Although alternative preparations of BPs and new non-BP drugs have emerged in the market, the prevalence of oral BP use is high. In the data evaluated, the prevalence of long-term use (≥3years), was also high in both countries. However, compliance differed by country. Evaluations in more recent data would determine if and how drug holidays have altered these characteristics.

Table. Characteristics of Long-term Oral Bisphosphonate Users

	US, 2009–2011 (n = 698,012)	ON, 2009–2011 (n = 54,656)
Age, mean (SD)	79.3 (7.4)	74.0 (6.4)
Mean BP duration[a], yrs (SD)	5.0 (1.1)	4.9 (2.2)
Most recent BP, (n,%)	544,656 (78.0)	24,056 (44.0)
Alendronate	96,795 (13.9)	30,600 (56.0)
Risedronate	56,561 (8.1)	–
Ibandronate		
Exclusive BP users[b]**,** (n,%)	419,496 (77.2)	22,596 (93.9)
Alendronate	80,314 (83.0)	26,981 (88.2)
Risedronate	56,561 (100.0)	–
Ibandronate		
Compliant BP users[c]**,** (n,%)	262,125 (62.5)	18,173 (80.4)
Alendronate	50,880 (63.4)	20,981 (77.8)
Risedronate	33,981 (60.1)	–
Ibandronate		

[a]Mean duration based on first BP dispensed in each data system. US = 2006–2011; ON: 2002–2011
[b]Exclusive users are those who only filled a prescription for each oral BP among most recent BP users
[c]Compliance estimated at proportion of days covered (PDC) of ≥70% among exclusive BP users

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Incidence and Risk Factors for Osteoporotic Vertebral Fracture in Low-Income Community-Dwelling Elderly: A Population-Based Prospective Cohort Study in Brazil. the São Paulo Ageing & Health (SPAH) Study. Diogo S. Domiciano[1], Luana G. Machado[2], Jaqueline B. Lopes[2], Valéria Caparbo[2], Liliam Takayama[2], Ricardo M. Oliveira[3] and Rosa M. R. Pereira[1]. [1]Faculdade de Medicina, University of São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]RDO Diagnosticos Medicos, São Paulo, Brazil.

Background/Purpose: Vertebral fractures are associated with increased future fracture risk and mortality. No data on incidence of osteoporotic vertebral fracture have been reported in low-income countries where the population's aging has been faster. Thus, we sought to describe the incidence and predictors of radiographic vertebral fracture in a longitudinal prospective Brazilian population-based elderly cohort - the São Paulo Ageing & Health (SPAH) Study.

Methods: From 2005–2007, all residents ≥65 years living in the Butantã community, located in the Western part of the city of São Paulo, were identified through census records. In total, 1025 subjects were included in the fracture prevalence study. Until 2012, 132 individuals had died during follow-up, and 725 subjects agreed to take part in this longitudinal evaluation (response rate in surviving subjects, 81.2%). Eighteen subjects were excluded due to cancer; thus, 449 women and 258 men were evaluated. A new vertebral fracture was considered as a distinct alteration in morphology of vertebrae resulting in higher grade of deformity when the second radiograph was compared to the same vertebra on the baseline radiograph. Clinical questionnaire, bone mineral density (BMD) and laboratorial tests were performed at baseline. Multivariate Poisson regression models were used to identify independent predictors of vertebral fracture.

Results: After a mean follow-up of 4.3±0.8 years, the age-standardized incidence of vertebral fracture was 40.3/1000 person-years in women and 30.6/1000 in men. In women, three possible models of risk factors for fracture were fitted:1. age (RR:2.46, 95%CI 1.66–3.65), previous osteoporotic fracture (RR: 1.65, 95% CI 1.00–2.71) and lumbar spine BMD (RR: 1.21, 95% CI 1.03–1.41); 2. age (RR: 2.25, 95%CI 1.52–3.34) and femoral neck BMD (RR: 1.42, 95% CI 1.11–1.81); 3. age (RR: 2.11, 95% CI 1.41–3.15) and total hip BMD (RR: 1.56, 95% CI 1.21–2.0). In men, the highest quartile of serum type I collagen C-telopeptide (CTX) (RR: 1.96, 95% CI 0.98–3.91) and prior fracture (RR: 2.10, 95% CI 1.00–4.39) were predictors of new vertebral fracture.

Conclusion: This is the first population-based study to ascertain the incidence of vertebral fracture in elderly Latin Americans, confirming the high frequency of the disorder. Age, prior fracture, BMD and bone turnover were predictors of the short-term incidence of vertebral fracture.

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High Incidence of Non-Vertebral Osteoporotic Fracture and Hip Fracture in Brazilian Low-Income Community-Dwelling Elderly: A Population-Based Prospective Cohort Analysis from the São Paulo Ageing & Health (SPAH) Study. Diogo S. Domiciano[1], Luana G. Machado[2], Jaqueline B. Lopes[2], Camille P. Figueiredo[2], Valéria Caparbo[2], Liliam Takayama[2], Ricardo Oliveira[3], Paulo R Menezes[1] and Rosa M. R. Pereira[1]. [1]Faculdade de Medicina, University of São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]RDO Diagnósticos Médicos, São Paulo, Brazil.

Background/Purpose: There is considerable variability in the incidence of hip fracture among countries, even among different geographical areas within the same country. In Brazil, population differences in occurrence of hip fracture are probably related to the huge size of the country, the substantial ethnical miscegenation and distinct lifestyle habits within the Brazilian territory. Longitudinal studies on incidence of hip fracture in the Brazilian population are scarce and the results are hampererd by incomplete capture of cases and short follow-up time. Moreover, there is no prospective study on incidence of non-vertebral fractures beyond the hip. Thus, our aim was to describe the incidence of hip and non-vertebral fracture in elderly community from a prospective population-based study.

Methods: Incidence of hip and non-vertebral fracture were determined in 707 women and men from community, aged 65 years or older. Specific questionnaire (clinical and anthropometric data), including personal history of fragility fracture in non-vertebral osteoporotic sites (hip, humerus, wrist, rib) was performed at baseline and after an average of 4.3 years. All incident fractures during the study period were confirmed by radiograph of the affected site.

Results: 449 women (mean age 72.9 ± 4.8 years) and 258 men (mean age 72.3 ± 4.7 years) were included in the study. The age-adjusted incidence of non-vertebral fracture was 1710/100.000 person-years in women and 630/100.000 person-years in men (female/male ratio: 2.6). The age-adjusted incidence of hip fracture was 420/100.000 person-years in women and 90/100.000 person-years in men (female/male ratio: 4.7). The incidence increases with age, particularly in women.

Conclusion: The incidence of non-vertebral osteoporotic fracture in the Brazilian elderly population was high, especially among women. Concerning hip fracture, these results emphasize that the incidence in the southern and southeastern regions of the country seems to be higher than the rates in the northern/northeastern population. Furthermore, our results reinforce the notion that the incidence of hip fracture in Brazilian older adults, particularly in women, is higher than in other Latin American populations, except Argentina.

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Visceral Fat Measured By Dual-Energy X-Ray Absorptiometry Is Associated with Increased Risk of Non-Spine Fractures in Nonobese Elderly Women: a Population-Based Prospective Cohort Analysis from the São Paulo Ageing & Health (SPAH) Study. Luana G. Machado[1], Diogo S Domiciano[1], Camille P. Figueiredo[1], Jaqueline B. Lopes[1], Valéria Caparbo[1], Liliam Takayama[1], Ricardo M. Oliveira[2] and Rosa M R Pereira[1]. [1]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]RDO Diagnosticos Medicos, São Paulo, Brazil.

Background/Purpose: The protective role of obesity on bone health has currently been questioned, since it has been demonstrated that visceral fat have a deleterious effect on bone. However, there are no studies evaluating the association between visceral fat measured by DXA with fracture risk. The aim of this study was to investigate the association of visceral fat with incident non-spine fractures in community-dwelling elderly women.

Methods: This is a longitudinal prospective population-based cohort study evaluating 433 community-dwelling women aged 65 years or older. Specific questionnaire (clinical and anthropometric data), including personal history of fragility fracture in non-spine osteoporotic sites (hip, humerus, wrist, rib) was performed at baseline and after an average of 4.3 years. All incident fractures during the study period were confirmed by affected site radiography. Bone mineral density (BMD) and laboratory tests were also performed at baseline. Visceral fat was measured by a new software of dual-energy X-ray absorptiometry (DXA) in the android region of a total body DXA scan. Logistic regression models were used to estimate the relationship between visceral fat and non-spine fractures.

Results: The mean age was 72.8 ± 4.7 years and 28 incident non-spine osteoporotic fractures were identified after a mean follow-up time of 4.3 ± 0.8 years. According the Lipschitz classification for nutritional status in elderly, 61.4% of women were considered obese/overweigth (BMI > 27 kg/m^2) and 38.6% were nonobese (7.4% underweight- BMI < 22 kg/m^2 and 31.2% normal weight- BMI ≥ 22 and ≤ 27 kg/m^2). After adjusting for age, previous fracture and BMD (parameters with significance at univariate analysis), visceral fat area had a significant association with incident non-spine fractures in nonobese (BMI ≤ 27 kg/m^2) elderly women (p=0.009).

Conclusion: Higher visceral fat was associated with the risk for non-spine fractures in nonobese elderly women. This study supports a potential negative effect of visceral adiposity on bone health.

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Spine-Hip Diagnostic Discordance in the United Arab Emirates. Nicholas Wilson, Lidia Sanchez Riera, Iman Hobeldin, Salman Waheeduddin, Nehad Ibrahim, Suneetha Gonuguntla, Tahir Khan, Ritu Aneja, Samer Nuhaily and Mustafa Al Maini. Mafraq Hospital, Abu Dhabi, United Arab Emirates.

Background/Purpose: Diagnostic discordance for osteoporosis is the presence of different T-scores in two skeletal sites in the same subject leading to different WHO diagnostic categories. Discordance is defined as minor when the difference between two sites is no more than one WHO diagnostic class and major when one site is osteoporotic and the other is normal[1]. This study examines to determine the percentage of minor and major diagnostic discordance and identify associated factors in patients undertaking osteoporosis screening.

Methods: Details of the first Dual-X-Ray-Absorptiometry test (DXA) during 2011–2013 were extracted, including weight, height, T score at femoral neck and total hip in the right side (RFN, RTH) and left side (LFN, LTH) and T score at lumbar spine (LS). Only complete data for individuals over 18 years old, with nationality of North Africa Middle East (as per WHO definition) were analysed. Differences in T scores and degree of discordance between sites were calculated. Age and BMI were analysed as contributing factors.

Results: One thousand, four hundred and forty four patients with complete data were identified. The mean age was 59.1 (±13.2 SD) and 86.3% were females. Diagnostic agreement among all skeletal sites was found in 415 (28.7%) patients, while 631 (43.7%) and 398 (27.6%) showed at least one major or minor discordance, respectively. Maximum concordance was found between right total hip and left total hip (86.6%) and minimum between lumbar spine and left total hip (40.7%). Minor discordance was present in about 40% of the patients when comparing spine to any hip site. Major discordance in LS compared to all hip regions ranged from 19.2 to 21.3%. All comparisons of skeletal sites, including trend of direction is shown below in table 1. A significant correlation with discordance was observed with both age and BMI (p >0.001).

Conclusion: Results show a high level of major diagnostic discordance, higher than previously reported in published studies[1–3]. This high prevalence of discordance could produce some problems for the physicians in decision-making regarding these patients. This reiterates the understanding that multiple site measurements are mandatory for osteoporosis diagnosis, including BMD measurements at both hips. High prevalence of discordance between lumbar spine and hip T-scores suggests some defects in the cut-off values for the definition of osteoporosis and osteopenia proposed by the WHO. BMD should be used as only one of the factors in making therapeutic decisions when evaluating patients with osteoporosis.

Table 1. Number (percentage) of cases categorised as normal, minor and major discordance and the directional trend and weight between the different skeletal sites

Comparison	Normal	Discordance Minor	Major	Trend	Direction	Number of comparisons
LS-RTH; n (%)	581 (41.2)	544 (38.5)	285 (20.2)	93.30%	LS lower	1410
LS-LTH; n (%)	570 (40.7)	532 (38)	298 (21.3)	93.70%	LS lower	1400
LS-RFN; n (%)	579 (40.9)	561 (39.9)	270 (19.2)	92.10%	LS lower	1407
LS-LFN; n (%)	575 (41.2)	469 (40.8)	242 (20.1)	89.50%	LS lower	1396
RTH-RFN; n (%)	1150 (80.9)	260 (18.2)	12 (0.9)	56.90%	RFN Lower	1422
LTH-LFN; n (%)	1097 (77.8)	297 (21)	16 (1.2)	67.90%	LFN Lower	1410
RTH-LTH; n (%)	1219 (86.6)	177 (12.6)	11 (0.8)	51.60%	RTH Lower	1407
RFN-LFN; n (%)	1121 (80)	261 (18.6)	19 (1.2)	64.30%	LFN Lower	1401
RTH-LFN; n (%)	1058 (75.4)	319 (22.7)	26 (1.9)	65.80%	LFN Lower	1403
RFN-LTH; n (%)	1085 (77.2)	297 (21.1)	23 (1.7)	56.50%	RFN Lower	1405

LS, Lumbar Spine. LTH, Left Total Hip. RTH, Right Total Hip. LFN, Left Femoral Neck. RFN, Right Femoral Neck

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Concordance with the National Osteoporosis Foundation Treatment Guidelines. Nicole Wright[1], Xin Lu[2], Stephanie Edmonds[2], Fredric Wolinsky[2], Douglas Roblin[3], Peter Cram[4] and Kenneth G. Saag[5]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Iowa, Iowa City, IA, [3]Kaiser Permanente Georgia, Atlanta, GA, [4]University of Toronto, Toronto, ON, [5]The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: The National Osteoporosis Foundation (NOF) published treatment guidelines to help guide clinicians on which patients should be considered for osteoporosis (OP) therapy. We examined patient factors associated with non-concordance among older adults participating in the PAADRN study.

Methods: The PAADRN study (NCT01507662) is a large, NIH funded, randomized trial currently being conducted in the Iowa City, IA, Birmingham, AL, and Atlanta, GA metro areas. Immediately following DXA, participants ≥50 years of age are recruited and randomized. We used data from the control arm, usual care group, (n=2,711 as of 6/14/14) for our analyses. We defined guideline concordant OP therapy as the report of any FDA approved OP therapy at the 12-week post-DXA survey along with one of the following criteria: 1) baseline self-report of fracture after the age of 40, 2) T-score at or below the OP threshold (<−2.5), or 3) T-score within the low bone mass range (−1.5 to -2.5) and a FRAX score ≥20%. Non-concordance was examined among participants who 1) were indicated for OP therapy who did not report OP therapy at 12 weeks (N=1,170), and 2) were not indicated for OP therapy who reported OP therapy at 12 weeks (N=1,541). We used logistic regression to assess the association of baseline demographic and comorbidity factors with non-concordance in both groups.

Results: Our study population was 85% female, 20% from minority backgrounds, and 60% ≥ 65 years of age. At baseline, 760 (28%) reported having a fracture after 40 years of age, 576 (21%) had DXA defined OP, and 188 (7%) had low bone mass with a FRAX ≥ 20%. At the 12-week survey, 38% of patients with indications for OP therapy reported medication use, and 15% of patients without indications for OP therapy reported medication use. When treatment was indicated, we found that being Black was associated with higher odds of treatment non-concordance in the crude analyses (Table). Factors associated with higher odds of non-concordance among those not indicated for treatment included: being a woman, Hispanic, having comorbidities related to secondary OP, being a pre-menopausal woman, the self-report of low bone mass and OP, calcium and multi-vitamin supplementation use, and having spoken to provider by 12-week survey (Table).

Conclusion: In this study of usual OP treatment, 38% of those indicated for OP treatment reported medication use, and 15% of those not indicated for treatment reported medication use. We found that race was associated with non-concordance when treatment was indicated. When treatment was not indicated, non-concordance was associated with conditions related to low BMD, potentially being used as preventative therapy. However, demographic and lifestyle factors were also associated with high non-concordance in this group, suggesting that additional education on the benefits and risks of OP therapies for both patients and providers is needed.

Table Factors Associated with Non-Concordant Use of Osteoporosis Medications

	Treatment Indicated but Not Received (n=723/1,170)			No Treatment Indicated But Received (n=237/1,541)		
	OR*	95% CI	p-value	OR*	95% CI	p-value
Women vs. Men	0.75	(0.52, 1.08)	0.117	4.13	(2.32, 7.34)	<0.001
Hispanic vs. Non-Hispanic	0.79	(0.29, 2.14)	0.646	2.39	(1.17, 4.91)	0.017
Black vs. White	1.71	(1.14, 2.56)	0.009	0.40	(0.27, 0.60)	<0.001
Site A vs. Site C	0.74	(0.55, 0.99)	0.044	1.39	(0.98, 1.95)	0.062
Site B vs. Site C	1.32	(0.95, 1.83)	0.099	0.55	(0.38, 0.81)	0.003
Self-report of LBM	0.45	(0.35, 0.57)	<0.001	3.35	(2.50, 4.48)	<0.001
Self-report of Osteoporosis	0.33	(0.26, 0.43)	<0.001	2.61	(1.82, 3.74)	<0.001
Pre-menopausal	0.67	(0.51, 0.89)	0.006	1.43	(1.02, 2.00)	0.038
Secondary Osteoporosis	0.74	(0.57, 0.96)	0.022	1.59	(1.17, 2.17)	0.003
Calcium Supplementation	0.53	(0.41, 0.69)	<0.001	3.07	(2.24, 4.19)	<0.001
Vitamin D Supplementation	0.52	(0.39, 0.69)	<0.001	3.02	(2.10, 4.34)	<0.001
DXA defined Low vs. Normal BMD	0.23	(0.12, 0.47)	<0.001	2.34	(1.69, 3.25)	<0.001
Spoke to Doctor by 12 week survey	0.58	(0.45, 0.73)	<0.001	1.81	(1.36, 2.41)	<0.001

*Crude associations from logistic regression models
DXA – dual energy X-ray absorptiometry, LBM – low bone mass

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Validation of the Diagnosis of Avascular Necrosis of Bone in Administrative Data. Medha Barbhaiya[1], Yan Dong[2], Jeffrey A. Sparks[1], Elena Losina[2], Karen H. Costenbader[1] and Jeffrey N. Katz[2]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Avascular necrosis (AVN) of bone is a painful, disabling condition. Studies aimed at improving the diagnosis or treatment of AVN require accurate case-finding methods. We examined the sensitivity, specificity, positive predictive value (PPV) and positive likelihood ratio (LR^+) of alternative algorithms that use claims data to identify cases of AVN of the upper and lower extremities.

Methods: Using a centralized clinical data registry from a large academic hospital, we identified all adults aged ≥18 years who underwent MRI of an upper and/or lower extremity joint for any indication between January 1, 2010 and June 1, 2011. We examined the performance characteristics (sensitivity, specificity, PPV, and LR^+) of four algorithms (A – D) using International Classification of Diseases, 9th edition (ICD-9) codes for AVN (ICD-9, 733.4X) **(Table)**. The algorithms ranged from least stringent (Algorithm A, requiring ≥1 1 ICD-9 code) to most stringent (Algorithm D, requiring ≥ 3 ICD-9 codes at least 30 days apart). Only ICD-9 codes within 6 months of MRI diagnosis were included. We compared cases identified by each algorithm to the gold standard of a clinical MRI reading by a radiologist confirming "avascular necrosis" or "osteonecrosis." We calculated 95% confidence intervals (CI) using the normal approximation of the binomial distribution.

Results: A total of 11,878 patients who underwent MRI of the upper and lower extremities during the 1.5 year period were included in this study. The prevalence of AVN using the gold standard of MRI was 0.7%, with 83 total cases of AVN. Algorithm A had a sensitivity of 81.9% (95% CI 71.9–89.5), with a PPV of 48.6% (95%CI 40.0–57.2) and a LR^+ of 134 (95% CI 104–173). The PPV of algorithm D increased to 61.4% (95% CI 47.6–74.0) with a LR^+ of 226 (95% CI 139–368), although the sensitivity decreased to 42.2% (95% CI 31.4–53.5) **(Table)**. The specificity of all four algorithms ranged from 99.0 to 99.8%.

Conclusion: In this study, we demonstrated that the PPV for AVN among patients who underwent MRI ranged from 49–61% in different ICD-9 code-based algorithms. Given its high sensitivity, Algorithm A (requiring at least 1 ICD-9 code for AVN) appears best suited for situations in which it would be problematic to miss AVN cases, and confirming cases to exclude false positives with further chart review is feasible. Algorithm B, requiring ≥2 ICD-9 codes at least 7 days apart, had the highest PPV and might be recommended when further validation is not feasible, although misclassification may occur. These algorithms provide an efficient way to identify AVN cases in administrative data, and the PPVs will be greater in populations with higher disease prevalence such as SLE or orthopedic cohorts. Of note, since all patients in this study underwent MRI, cases of asymptomatic or mild AVN that did not prompt MRI evaluation would not be detected with these methods.

Table Performance characteristics of ICD-9 code algorithms for the diagnosis of avascular necrosis (AVN) of bone

Algorithms	Sensitivity (95% CI),%	Specificity (95% CI), %	PPV (95% CI),%	LR^+ (95% CI)
A: ≥1 ICD-9 code for AVN	81.9 (71.9–89.5)	99.4 (99.2–99.5)	48.6 (40.0–57.2)	134.2 (104.4–172.6)
B: ≥2 ICD-9 codes for AVN at least 7 days apart	56.6 (45.3–67.5)	99.8 (99.7–99.8)	62.7 (50.7–73.6)	238.5 (157.5–361.3)
C: ≥2 ICD-9 codes for AVN at least 30 days apart	42.2 (31.4–53.5)	99.8 (99.7–99.9)	60.3 (46.6–80.0)	216.3 (133.9–349.4)
D: ≥3 ICD-9 codes for AVN at least 30 days apart	42.2 (31.4–53.5)	99.8 (99.7–99.9)	61.4 (47.6–74.0)	226.1 (138.8–368.2)

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High Prevalence of Cervical Malignant and Premalignant Lesions Among Women with Rheumatoid and Psoriatic Arthritis. Majed Khraishi[1], Rana Aslanov[2] and Sarah Khraishi[3]. [1]Nexus Clinical Research, St John's, NF, [2]Memorial University of Newfoundland, St.John's, NF, [3]NL Research Technologies (NLRT), St. John's, NF.

Background/Purpose: Rheumatic diseases have been associated with an increased prevalence of malignancy. We aimed to examine the prevalence of precancerous lesions and malignancy in the entire cohort of patients with Inflammatory Arthritides; to compare the prevalence of malignancy between Rheumatoid (RA) and Psoriatic (PsA) Arthritis patients and to investigate correlations that may explain the high prevalence of cervical lesions that we noted.

Methods: Patients were recruited prospectively from a rheumatology clinic specializing in treating patients with arthritis and followed from January 2011 to December 2013. The prevalence of premalignant lesions and malignancy was evaluated and compared to the data provided by Statistics Canada, Canadian and Provincial Cancer Registries. Disease severity was assessed using the TJC/SJC, CRP, ESR, DAS28, and CDAI scores.

Results: A cohort of 700 (67.9% females) patients with Inflammatory Arthritis was included in this study with mean (SD) age 55.0 (12.4) years and mean (SD) duration of disease 8.4 (8.3) years. Overall, 116 (16.6%) precancerous lesions and cancers were analysed. Hundred and ten patients (15.7%) had at least one malignancy; three patients had a history of 2 malignancies. The most frequently observed cancers were: Cervical (37-7.8% of female population; OR (95%CI)=2.5 (1.0–6.2); P=0.042), Breast (20-4.2% of female population; OR (95%CI)=1.1 (1.0–1.1); p=0.001), Bowel (11-1.6%), and Lung Cancer (10-1.4%).

We identified 37 cases with cervical lesions. Of them, six females had a history of cervical cancer (SCC), 18- High Grade Squamous Intraepithelial Lesions (HSIL), 8-Low Grade SIL cannot exclude HSIL, and in 5 cases it was impossible to trace the type of cervical dysplasia. Six cases belonged to women aged 49 years and younger, 31 cases of dysplasia and cancer belonged to women aged 50 years and older. All of them underwent hysterectomy prior to enrolment in the study. Prevalence of cervical lesions was strongly correlated with: females' age (R=0.151, p=0.033), Health Assessment Questionnaire (HAQ: R=0.226, p=0.001) in PsA cohort; and with: females' age at RA diagnosis (R=0.100, p=0.026), Tender Joint Count (TJC: R=0.108, p=0.016), and Clinical Disease Activity Index (CDAI: R=0.140, p=0.002) in RA cohort. Cervical lesions were strongly correlated with the total number of comorbidities in the both cohorts (PsA: R=0.161, p=0.023 & RA: R=0.088, p=0.049). The treatment of RA women with NSAIDs showed significant association with cervical lesions (r=0.123, p=0.006). No correlation with PASI score was detected in PsA patients. No definite association with treatment with biologic disease modifiers was documented.

Conclusion: The prevalence of cervical dysplasia and cancer among affected women was higher than the tumor-based 10-year prevalence of cervicouterine cancer cases among females reported by the Canadian Cancer Registry, Statistics Canada and Provincial/ Territory Cancer Registries (7.8% vs. 3.0%, respectively). Our data suggested their possible correlation with disease activity. Closer surveillance will be warranted if the reported increased prevalence is confirmed in larger cohorts.

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Risk of Hospitalized Infection in a Psoriasis/Psoriatic Arthritis Cohort. Kevin L. Winthrop[1], Lang Chen[2], John Baddley[2], Allison Taylor[2], Benjamin Chan[3], Huifeng Yun[4], Sarah Siegel[1] and Jeffrey R. Curtis[5]. [1]Oregon Health & Science University, Portland, OR, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Oregon Health and Science University, Portland, OR, [4]University of Alabama at Birmingham School of Public Health, Birmingham, AL, [5]The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Psoriasis (PsO)/Psoriatic arthritis (PsA) often requires treatment with systemic immunosuppressive agents, some of which may increase hospitalized infection risk. Few population-based studies to date have evaluated the incidence of hospitalized infections this population.

Methods: We used the US Medicare data from 2006–2011 to identify a large cohort of PsA and PsO patients. We defined PsA and PsO patients as those with >1 rheumatologist-diagnosis code for psoriatic arthritis (ICD 9 696.0), or >1 dermatologist-diagnosis code for psoriasis (ICD 9 696.1) respectively, followed by a prescription for etanercept (ETA), cyclosporine (CIC), ustekinumab (UST), adalimumab (ADA), methotrexate (MTX) or ultraviolet light (UV) therapy. Patients had at least 6 months of continuous Medicare enrollment prior to the first date of exposure to these therapies. We excluded patients with organ transplantation, human immunodeficiency virus infection, advanced kidney and liver disease, or cancer with a 183-day period prior to cohort inception. We used validated-claims based algorithms to identify hospitalized infections among all exposure groups. Patient exposures were censored at time of serious infection, death, end of study, loss of coverage, or 90 days following end of treatment exposure whichever came first. Pairwise propensity scores (PS) were calculated and used to control for potential differences between comparator treatments. We calculated crude incidence rates for exposure groups, and used Cox-proportional hazard regression models to calculate hazard ratios for hospitalized infection between exposure groups while adjusting for PS quintile.

Results: We identified 10,261 PsA individuals and 31,052 PsO individuals. Within the PsA cohort, we identified 185 hospitalized infections for an overall incidence rate of 36.2 (95% CI 31.1–41.8) per 1,000 py. The rate of hospitalized infections ranged from 13.2 (95% CI 4.3–41.0) per 1,000 py for the UV group to 38.7 (95% CI 28.8–52.0) per 1,000 py for the ETA group. In Cox modeling, incidence rates were similar between exposure groups, with the exception of patients starting ETA as compared to UV therapy (HR 3.1 [95% CI 0.9–1.9]) where a non-statistically significant trend was noted. Within the PsO cohort, there were 1,198 hospitalized infections yielding an overall incidence rate of 37.0 (95% CI 35.0–39.1) per 1,000 py. The rate of such infections ranged from 27.2 (95% CI 23.1–31.9) per 1,000 py for the UV group to 40.5 (95% CI 36.9–44.5) per 1,000 py for the MTX group. After adjustment for possible confounders, patients on ADA had higher incidence rates as compared to those on CIC (HR 1.4 [95% CI 1.0, 2.0]), or UV therapy (HR 1.4 [95% CI 1.1–1.9]), respectively. Patients on MTX were also at higher risk for infection than those using UV therapy (HR 1.3 [95% CI 1.1, 1.6]). Incidence rates between all other exposure comparisons were similar.

Conclusion: Among Medicare enrollees with PsA or PsO, rates of hospitalized infections varied across therapies but were largely similar. PsA patients were at similar risk no matter their therapy, although PsO patients starting ADA or MTX were at higher risk for infection than those using UV therapy.

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What Does the Patient Global Assessment (PGA) Mean for Patients with Psoriatic Arthritis? a Post-Hoc Analysis of 223 Patients with Psoriatic Arthritis. Sandra Tälli[1], Adrien Etcheto[2], Bruno Fautrel[3], Andra Balanescu[4], Jürgen Braun[4], Juan D. Cañete[5], Kurt de Vlam[4], Maarten de Wit[4], Turid Heiberg[4], Philip S. Helliwell[4], Umut Kalyoncu[4], Uta Kiltz[6], Mara Maccarone[4], Dora Niedermayer[4], Kati Otsa[4], Rossana Scrivo[4], Josef S. Smolen[4], Tanja Alexandra Stamm[4], Douglas J. Veale[7], Tore K. Kvien[4] and Laure Gossec[3]. [1]GRC UPMC Paris 06 University, Pitie-Salpétriere hospital, Paris, France, [2]Paris Descartes University, Paris, France, [3]UPMC GRC08, Paris 06 University, Pitié Salpétrière Hospital, Paris, France, [4]PsAID taskforce, EULAR, Zurich, Switzerland, [5]Hospital Clinic, Barcelona, Spain, [6]Rheumazentrum Ruhrgebiet, Herne, Germany, [7]St. Vincent's University Hospital, Dublin 4, Ireland.

Background/Purpose: Patient global assessment (PGA) is one of the most widely used patient reported outcomes (PROs) in psoriatic arthritis (PsA). PGA should reflect the global impact of the disease from the patient's perspective, however we lack information on the concepts encompassed in PGA. In addition the Group of Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has proposed to use also two specific (joints, skin) patient assessments but their scope is also unclear. (1) Recently the European League Against Rheumatism (EULAR) developed the PsAID (Psoriatic Arthritis Impact of the Disease) which includes 12 domains of health important for patients. (2)

Objective: to explore PGA in PsA from the patient's point of view by comparing it to the PsAID domains of health and also to explore the two specific (joints, skin) patient assessments in relation to PGA.

Methods: Post-hoc analysis of the cross-sectional PsAID study (2) for patients with definite PsA (according to the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria). Data collection included PGA ("Considering all the ways PsA has affected you during the last week, circle the number that best describes how you have been doing"), skin and joint patient assessments (patient global assessments of these 2 aspects) and PsAID questions covering physical (including joints and skin), psychological and social impact of PsA. The concepts covered by PGA were explored by univariate (Spearman correlation coefficient) and multivariate linear regression, and intra-class correlation between PGA and joint and skin patient assessments was calculated.

Results: Among 223 patients (mean age 51.0 (standard deviation, ±13.3) years, mean disease duration 9.9 (±10.1) years, mean swollen joint count 4.1 (±5.1), 84.3% with current psoriasis (mainly of less than 5% body surface area)), 51.1% were females. Mean patient assessment values were for PGA 4.8 (±2.7), joint patient assessment 5.6 (±2.5) and skin patient assessment 4.1 (±3.0). Multivariate linear regression indicated that PGA was well explained (R^2 of model 0.754) by coping (β= 0.287); pain (β= 0.240); work and/or leisure activities (β= 0.141); and anxiety (β= 0.109). Intra-class correlation between PGA and joint or skin patient assessment was respectively 0.71 [95% confidence interval, 0.64–0.77] and 0.52 [95% confidence interval, 0.42–0.60].

Conclusion: PGA in PsA is explained by coping, then as expected physical aspects of impact which may reflect joint involvement: pain and work/leisure activities; and psychological impact: anxiety. In this population, skin related issues were not additional explanatory elements of PGA in multivariate analysis. Finally, joint patient assessment may be redundant with PGA whereas skin patient assessment gives additional information in characterizing the disease and its impact.

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Assessing Dietary Habits in a Large Cohort of Rheumatoid Arthritis and Psoriatic Arthritis Patients: Results of the Spanish *Imid* Consortium. Maria López Lasanta[1], Jesús Tornero[2], Juan D. Cañete[3], Antonio Fernandez Nebro[4], Francisco Blanco[5], Jesus Rodriguez[6], Isidoro González-Alvaro[7], Jordi Gratacós[8], Joan Maymo[9], Rubén Queiro[10], Mercedes Alperi-López[11], Carlos Montilla-Morales[12], Benjamin Fernandez Gutierrez[13], Juan Carlos Torre-Alonso[14], Alejandro Olive[15], Jose Javier Perez Venegas[16], Hector Corominas[17], Alba Erra[18], Santiago Muñoz[19], Carlos M. Gonzalez[20], Daniel

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Background/Purpose: Rheumatoid arthritis (RA) and Psoriatic arthritis (PsA) are complex diseases of unknown etiology and its pathogenesis results from the combination of genetic susceptibility and environmental factors (smoking, alcohol consumption, diet, . . .etc). Among the environmental factors, diet habits are of particular interest since they are modifiable factors. To date, information about dietary habits in this group of patients is very limited. The aim of this study was to analyze dietary habits in a large cohort of patients with RA and PsA from the Spanish population.

Methods: A multicentre cross-sectional comparative study of RA and PsA patients was performed. All patients were recruited through the *Immune-Mediated Inflammatory Diseases Consortium* (*IMIDC*) from 2007 to 2012. The *IMIDC* is a network of Spanish biomedical researchers focused in the study of the molecular basis of immune-mediated inflammatory diseases. All patients included in the present study were selected from the outpatient clinics of the Rheumatology departments at 20 different Spanish University Hospitals. An epidemiological questionnaire developed by experts at DNA National Bank was applied to obtain all data. The dietary questionnaire included the assessment of the number of days per week in which patients consumed certain foods: fresh fruit, meat, fish, legumes, vegetables, pasta, rice, bread, dairy products, sausage and sweets.

Results: From a total number of 3,941 patients surveyed n=3,229 patients were included in the present study: n=1,128 (65%) had Rheumatoid arthritis and n=1,128 (35%) Psoriatic arthritis. The proportion of women was 77% in RA patients and 47% in PsA patients. We observed that the mean number of days per week eating fish and fruit was significantly higher in RA than in PsA patients ([5.58 *vs* 5.09; *P*=8x10E-12] [2.65 *vs* 2.52; *P*=2x10E-2]). Pasta, rice and potatoes intake was also significantly increased in RA patients ([3.41 *vs* 3.22; *P*=7x10E-3]. In this group, the mean of vegetable weekly intake was 4.23 days and in PsA group was 3.97 days (*P*=6x10E-4). Dairy products consumption was also significantly higher in RA than in PsA patients (5.89 *vs* 5.62; *P*=3x10E-5). Among PsA patients the mean number of days per week of intake meat, sausage and sweets was significantly higher comparing to RA patients ([3.17 *vs* 2.72; *P*=3x10E-13], [2.02 *vs* 1.58; *P*=9x10E-10], [2.98 *vs* 2.72; *P*=5x10E-3]).

Conclusion: In our large cohort of patients we describe for the first time the dietary habits differences between rheumatoid arthritis and psoriatic arthritis patients in Spanish population. Significant differences in the consumption of several foods have been observed. Fruit, fish, pasta, rice, potatoes and vegetables were the group of aliments that RA patients intake more days per week; while meat, sausage and sweets are eaten more often in PsA patients. Our findings could provide insights about the possible implication of dietary factors in the development and prognosis of these diseases. It would be also interesting to study if these factors could contribute to disease prevention strategies.

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Epidemiology of Polymyalgia Rheumatica in Korea. In young Kim[1], Seulkee Lee[1], Hemin Jeong[1], Hyungjin Kim[1], Jiwon Hwang[1], Jaejoon Lee[1], Eun-Mi Koh[2] and Hoon-Suk Cha[1]. [1]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

Background/Purpose: Polymyalgia rheumatica (PMR) is a chronic inflammatory disease affecting people older than 50 years. Diagnosis is made based on clinical features and the current standard of treatment is low-dose glucocorticoids. PMR is known to be more frequent in Caucasian ethnicity and females. But up to date, there has been a scant epidemiologic study of PMR in Asian countries including Korea. We aimed to estimate incidence and prevalence rates of PMR and current treatment state in Korea.

Methods: We performed nationwide retrospective review of PMR using the Korean National Health Insurance (NHI) and Health Insurance Review and Assessment (HIRA) database from 2007 to 2012. NHI is the sole public medical insurance system in Korea, which covers 100% of the Korean population and HIRA is a government incorporated organization to build an accurate claims review and quality assessment system for the NHI. We defined PMR cases by both diagnostic codes and medication codes simultaneously, in other words, by proper ICD code (M 35.3) and concurrent appropriate prescription codes (glucocorticoids).

Results: We identified total 1,463 newly diagnosed cases of PMR for the 5 years. The annual incidence rate of PMR per 100,000 Korean individuals was estimated as 2.06 (1.45 in male, 2.59 in female), and the prevalence rate was 8.21 per 100,000 individuals in 2012 (5.60 in male, 10.42 in female). Among the 1,463 cases, 992 (67.8%) were female and 471 (32.2%) were male and the median age at the time of diagnosis was 67 years old. The incidence rate according to age appeared to increase with advancing age peaking 70 years old, as similar as previous reports of western studies. The most frequently prescribed agent was prednisolone, and the starting daily dosage of glucocorticoids as prednisolone equivalent was between 5 to 15 mg daily in 74.5 % of the patients.

Conclusion: This is the first study that evaluated epidemiologic data of PMR in Korea, and included population was the largest among those of studies published in East Asia so far. The incidence and prevalence rates of PMR are estimated considerably lower than that of Western populations. And this result supports that both genetic and environmental factor would play important roles in pathogenesis of PMR.

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Advocating for Pediatric Rheumatology Care in the Mid-Canadian Provinces: Large Geographic Area, Large Pediatric Population, Low Number of Pediatric Rheumatologists and Allied Health Workers Identified As Unique Challenges. Paivi Miettunen[1], Nadia Luca[1], Susanne Benseler[1], Janet Ellsworth[2], Tommy Gerschman[3], Nicole Johnson[1], Heinrike Schmeling[1] and Natalie J. Shiff[4]. [1]Department of Pediatrics/University of Calgary, Calgary, AB, [2]University of Alberta, Edmonton, AB, [3]Alberta Children's Hospital, Calgary, AB, [4]University of Saskatchewan, Saskatoon, SK.

Background/Purpose: Advocacy for pediatric rheumatology care for Mid-Canadian (MC) provinces (Alberta, Manitoba, Northwest Territories, Nunavut and Saskatchewan) represents a challenge. Although these provinces comprise a large geographic area (>52% of Canada), patient characteristics and pediatric rheumatology workforce are not known.

Our objective was to collect and report data for pediatric population, number of pediatric rheumatologists, patient diagnoses, wait times, allied health support and pediatric rheumatologists' work-life balance in MC provinces.

Methods: Canadian 2012 Statistical data was used to identify population between 0–14 years (Defined as "children" by Statistics Canada) in MC provinces. A survey monkey was sent to each MC pediatric rheumatology center to identify 1) the number of pediatric rheumatology full time equivalents (FTEs) per province for clinical care, education, research and administration; 2) Distribution of pediatric rheumatology diagnoses and wait times, and 3) perceived work-life balance of participants.

Results: All 3 currently active pediatric rheumatology centers in MC provinces responded (2 in Alberta and 1 in Saskatchewan). Total pediatric

MC population aged 0–14 years (% of all Canadian) was 1.1 million (21.4%). There were a total of 7.7 FTE pediatric rheumatologists: 5.7 in Alberta (0.7 at one center, 5 at the other), 2 in Saskatchewan and 0 in Manitoba, Nunavut and Northwest Territories. Out of 7.7 FTEs, 4.74 were devoted to for clinical care, 1.08 for education, 3.58 for research and 0.8 for administration. Night–time on-call service frequency varied from "not mandatory" to 1:5. Allied health support was variable: nursing, physiotherapy and occupational therapy were available at 2/3 centers, 1/3 center had a social worker and a pharmacist, and 0/3 center had a psychologist. Individual outpatient data was available for Alberta and Saskatchewan and included 1225 active outpatients. The most common diagnoses (% total) were juvenile idiopathic arthritis (65–82%), systemic lupus erythematosus (4–6%), autoinflammatory disorders (3–7%) and vasculitis (2–4%). Wait time data was available for Saskatchewan and Alberta and ranged from 1 to 8 weeks for patients classified as "urgent" and from 2 weeks to 6 months for "semi-urgent". One center was not able see routine patients. Regarding wellness, 30% of responders reported their work and personal lives were "well balanced", 50% "struggled occasionally", 40% reported adverse impact on personal life and non-clinical work activities, and 60% reported their family/friends had commented on their "stress levels".

Conclusion: The MC provinces provide a unique challenge for provision of pediatric rheumatology care due to the vast geographic area and high proportion of children and low numbers of pediatric rheumatologists. Currently 3 out of 5 provinces are without a pediatric rheumatologist. The small number of rheumatologists per individual center resulted in unequal wait-times, and had an adverse impact on physician wellness. Our results underline a need for a network/collaboration to help address pediatric rheumatology care in these provinces.

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Severe Spine Osteoarthritis in Older Men Is Associated with the Risk of Incident Fragility Fracture. Roland Chapurlat[1], Charline Estublier[2] and Pawel Szulc[3]. [1]Hopital Edouard Herriot, Lyon, France, [2]Hôpital Edouard Herriot, Pavillon F, Lyon, France, [3]INSERM UMR 1033, Lyon, France.

Background/Purpose: Data on the association of osteoarthritis (OA) with bone fragility are limited. In particular, data on the fracture risk in older men with spine OA are scarce. Our aim was to study the association of baseline severity of spine OA with bone mineral density (BMD), bone loss and risk of fragility fracture in a prospective study of a cohort of older men.

Methods: Men aged >50 (n=766) had lateral spine radiographs at baseline. Spine OA was assessed by Lane's score *(J Rheumatol, 1993)*. We calculated the total osteophyte score by adding up osteophyte scores for 6 intervertebral levels. We calculated total disc narrowing score (DSN) and total overall grade score similarly. BMD was measured by DXA using a HOLOGIC QDR1500 device. Abdominal aortic calcification (AAC) was assessed by Kauppila's semiquantitative score *(Atherosclerosis, 1997)*. Men were followed up for 7.5 yr to assess bone loss (every 18 mo) and incident vertebral fractures. Incident peripheral fractures were assessed for 10 yr.

Results: Moderate and severe osteophytes were found in 85% of men, 72% of men had DSN. After adjustment for age and weight, BMD (hip, forearm, whole body) was 2–7% higher ($p<0.05$ to <0.001) in men with severe spine OA in comparison with men with or without mild spine OA. For instance, men with severe DSN (total score >4, highest quartile) had 5% (0.4SD, $p<0.001$) higher total hip BMD compared with men without DSN. The rate of bone loss did not differ according to the severity of spine OA regardless of the measure of the spine OA (DSN, osteophytosis) and regardless of the skeletal site ($p>0.4$).

During the follow-up, 27 men sustained radiographic vertebral fractures. After adjustment for age, BMI, lumbar spine BMD, AAC, prior falls and fractures, risk of vertebral fracture increased with the DSN severity (HR= 1.15 per increase by 1 unit, 95%CI: 1.01–1.31, $p<0.05$). In this multivariable model, the risk of vertebral fracture was higher in the highest quartile of total DSN score vs. the three lower quartiles combined (HR= 2.47, 95%CI: 1.04–5.86, $p<0.05$).

During the follow-up, 61 men sustained non-vertebral fragility fractures. The incidence of non-vertebral fracture was lower above the median of total DSN score (4.6 vs 10.2%, $p<0.005$). After adjustment for the confounders (including hip BMD and leg disability), the risk of peripheral fracture was lower in men above the median total DSN score vs. below the median (HR= 0.44, 95%CI: 0.24–0.80, $p<0.01$).

Other measures of spine OA were not associated with the risk of fracture.

Conclusion: Men with severe spine OA have fewer non vertebral fractures but more vertebral fractures. This may be due to better bone quality but abnormal spine biomechanics.

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Spine Osteoarthritis Is Associated with All Cause Mortality in Older Men. Charline Estublier[1], Roland Chapurlat[2] and Pawel Szulc[3]. [1]Hôpital Edouard Herriot, Pavillon F, Lyon, France, [2]Hopital Edouard Herriot, Lyon, France, [3]INSERM UMR 1033, Lyon, France.

Background/Purpose: Hip and knee osteoarthritis (OA) was associated with higher cardiovascular morbidity and mortality. Data on the cardiovascular status in men with spine OA are scarce. We assessed the association of spine OA with all cause mortality and with abdominal aortic calcification (AAC) severity and its progression rate in older men.

Methods: Men aged >50 (n=766) had lateral spine radiographs and blood collection and were followed up prospectively. Spine OA was assessed by Lane's score *(Lane et al., J Rheumatol, 1993)*. We calculated the total osteophyte score by adding up osteophyte scores for 6 intervertebral levels. We calculated total disc narrowing score (DSN) and total overall grade score similarly. AAC was assessed by Kauppila's semiquantitative score *(Atherosclerosis, 1997)*. We assessed the association of spine OA with all cause mortality (10 years), AAC severity and AAC progression (7.5 years).

Results: Moderate and severe osteophytes were found in 85% of men, 72% of men had DSN. During the follow-up, 176 men died. After adjustment for confounders (age, BMI, AAC, smoking, physical activity, leg disability, diabetes, pulmonary diseases, Parkinson disease, 17b-estradiol, 25OHD, GFR, fat mass, vitamin D supplementation, vitamin K antagonists), the total overall grade spine OA score predicted all cause mortality (hazard ratio [HR]= 1.20 per SD increase, 95% confidence interval [95%CI]: 1.01–1.43, $p<0.05$). After adjustment for confounders, men who had both severe AAC (AAC >2) and severe OA (total overall grade score >8, highest tertile) had higher mortality than the reference group (AAC score ≤2 and total overall grade score ≤8): 51.8 vs 10.3 /1000 person-years; HR= 2.30, 95%CI: 1.34–3.96, $p<0.005$).

After adjustment for confounders, the odds of severe AAC (AAC >5) increased with total DSN score (HR= 1.44 per SD, 95%CI: 1.11–1.87, $p<0.05$). The highest tertile of total DSN score was associated with higher odds of severe AAC (adjusted HR= 2.42 versus two lower tertiles combined, i.e. >3 vs 0–3, 95%CI: 1.24–4.73, $p<0.005$). Finally, probability of long-term AAC stability decreased with increasing total osteophyte score (adjusted HR= 0.66 per SD, 95%CI: 0.49–0.88, $p<0.05$). The highest tertile of total osteophyte score (>10) was associated with lower probability of AAC stability (adjusted HR= 0.35 versus the lowest tertile, i.e. 0–6, 95%CI: 0.18–0.71, $p<0.01$).

OA therapy (non-steroidal anti-inflammatory drugs, analgesics) had no impact on the results of all the above analyses.

Conclusion: Older men with severe spine OA have greater AAC severity, faster AAC progression and higher all-cause mortality. Higher mortality may be partly mediated by lower physical activity and metabolic abnormalities.

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Effect of Family Support on Short-and Intermediate Term Pain and Function Outcomes after Knee or Hip Replacement. Jasvinder Singh[1], Kenneth G. Saag[2], Celeste Lemay[3], Jeroan Allison[4] and Patricia D. Franklin[4]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]The University of Alabama at Birmingham, Birmingham, AL, [3]University of Massachusetts Medical School, Worchester, MA, [4]University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Patients who undergo total knee replacement (TKR) and total hip replacement (THR) need significant help in the immediate post-operative period, when discharged to home. Limited or no data are available regarding the impact of family support on short and intermediate term pain and function outcomes after THR or TKR.

Methods: A subset of patients from a national joint registry undergoing primary TJR between 5/2013 and 6/2014 were queried patients at 2- and 8-weeks regarding pain severity and level of family support, assessed with validated single-item (0–10; 10=highest family support) and dichotomized, as previously into deficient (scores 5 or less) or non-deficient family support

(6–10). Frequency distributions were used to describe the cohort; bivariate statistical tests to compare groups included the chi-square, Fisher's exact, t tests and Wilcoxon-Mann-Whitney test.

Results: There were 1,502 primary TKR or primary THR respondents at 2-weeks and 1,514 respondents at 8-weeks. 1416 patients reported good level of family support and 86 reported deficient family support (level 5 or less; 5.7%) on the 2-week survey; 1,418 reported good family support 96 reported deficient family support (6.3%) on the 8 week survey. Patients with higher family support were older (66.4 vs. 63.0), more likely to be males (41% vs. 31%), and less likely to have income <45K (25% vs. 43%).

At 2-weeks, compared to patients with non-deficient family support (scores 6–10), those with deficient family support had significantly higher levels of pain severity (3.9 vs. 3.2), pain frequency (4.6 vs. 3.2) and lower levels of satisfaction with pain control (0.68 vs. 0.83), treatment satisfaction (5.6 vs. 6.0) and participation in decision-making (6.9 vs. 8.1). At 8-weeks, similar differences were noted: significantly higher levels of pain severity (2.5 vs. 1.8), pain frequency (4.4 vs. 2.9); and lower levels of current satisfaction with pain control (0.71 vs. 0.83), treatment satisfaction (5.4 vs. 6.0) and participation in decision making (6.9 vs. 8.4).

Conclusion: To our knowledge, this is the first study examining the association of family support with pain and other outcomes after TKR and THR. A positive association of non-deficient family support with better pain and satisfaction outcomes is a novel finding. Further research into how to translate these findings into improved outcomes after TKR/THR for those with deficient family support are needed.

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Impact of Dropout and Total Knee Replacement on Joint Space Narrowing Estimation: Data from Osteoarthritis Initiaive. Jamie E. Collins and Elena Losina. Brigham and Women's Hospital, Boston, MA.

Impact of dropout and TKR on Joint Space Narrowing estimation: data from Osteoarthritis Initiative

Background/Purpose: Structural progression in knee osteoarthritis (OA) is often measured by Joint Space Narrowing (JSN). In longitudinal studies, it is common for subjects to drop out before the scheduled end of follow-up. In OA, subjects might undergo total knee replacement (TKR), and consequently drop out of a study evaluating structural progression. Our objective was to estimate the impact of dropout due to TKR on estimates of structural progression in OA and investigate whether information about TKR could be used to improve these estimates.

Methods: We used data from the Osteoarthritis Initiative (OAI), a multicenter, longitudinal, observational study of knee OA. We selected knees with radiographic, symptomatic OA at baseline (KL ≥ 2, WOMAC Pain >0), selecting the knee with the worst pain for subjects with two knees with OA. We compared the estimate of change in JSN over time in persons who did and who did not undergo TKR. Further, we estimated JSN without taking into account dropout and compared to the model that took into consideration time of the dropout and timing of TKR among those that underwent TKR.

Results: We used data from 2,058 subjects with radiographic, symptomatic knee OA at baseline. 377 subjects (18%) dropped out before the 48 month visit; 231 dropped out and did not undergo TKR while 146 underwent TKR. Among those who had TKR, they were distributed evenly between 24, 36 and 48 months visits. The estimates of annual joint space narrowing ranged from 0.116 mm for those who completed the 48 month follow up to 0.28 among those who had TKR between baseline and 24 months visit (Table). Additional analyses showed that not accounting for dropout and TKRs led to underestimation of JSN (0.46 mm over 4 years) compared to the estimation of joint space narrowing using the model that took into consideration both timing of dropout and timing of TKR (0.51 mm over the course of 4 years).

Conclusion: In longitudinal studies restricting analysis to 'completers' may lead to underestimation of structural changes. Subjects with OA who drop out of the study to undergo TKR tend to have much more pronounced structural progression. Investigators studying disease progression in OA should consider the potential impact of dropout due to TKR, particularly when a large proportion of subjects undergo the procedure.

Table. Annual JSN stratified by dropout and timing of TKR

Group	Annual JSN/mm	% of cohort
No dropout/No TKR	−0.116	82.0%
Dropout/No TKR	−0.129	11.0%
TKR after 36M	−0.232	2.1%
TKR after 24M	−0.268	2.3%
TKR between BL and 24M	−0.276	2.5%

Disclosure: J. E. Collins, None; **E. Losina**, None.

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Association of Knee Osteoarthritis and Limitations in Physical Function in a Rural Chinese Population: The Wuchuan OA Study. Xu Wu[1], Jingbo Niu[2], Yan Ke[3], Qiang LIU[1], Xu Tang Sr. [1], Zhengming Cao[3], Rujun Li[3], Hu Li[3], Kai Wang[3], Xin Zhi[3], Daniel White[4] and Jian Hao Lin[1]. [1]Peking University Health Science Center, Beijing, China, [2]Boston University, Boston, MA, [3]Peking University People's Hospital, Beijing, China, [4]Boston Univ School of Med, Boston, MA.

Background/Purpose: knee osteoarthritis (OA) causes more limitations in physical function than other chronic conditions in Caucasians. Knee OA is known to be more prevalent among Chinese than among Caucasians. However, little is known about the effect of knee OA on physical function among Chinese living in rural areas.

Methods: Wuchuan OA Study was a population-based cohort study conducted in the rural areas of Wuchuan, Inner Mongolia of China. Subjects completed a baseline home-interview in 2005, including knee symptoms and 8 physical function questions on daily-living activities (e.g., walking, going up or down stairs, bending or kneeling, chair standing, preparing meals, cleaning house, making beds, getting up bed) with 1: no difficulty, 2: some difficulty, 3: very difficult, and 4: unable to do. Subjects had bilateral weight-bearing posterior-anterior and patellar skyline radiographs taken. Whole radiographic knee OA (ROA) was defined as either tibiofemoral K/L score≥2 or presence of patellofemoral OA. Symptomatic OA (SxOA) was defined as presence of both ROA and knee pain for most days in the last month. We identified distinct groups of limitation in physical function based on subject's response to each of 8 physical function questions using a latent class model (SAS PROC LCA) and examined the relation of ROA and SxOA to the latent groups of limitation in physical function adjusting for potential confounders.

Results: Among 1025 subjects of Wuchuan OA study (men: 49.3%, mean age: 56.4 years, mean BMI: 22.4 kg/m^2) prevalence of knee ROA and SxOA was 17.7% and 6.2%, respectively, at baseline. For KL grading, the weighted kappa for inter-rater reliability was 0.80 (95% confidence interval (CI): 0.72–0.88) and the intra-rater reliability was 0.92 (95% CI: 0.86–0.99).We identified 4 distinct physical function groups: no limitation (n=543, 53.0%), mild limitation (n=252, 24.6%), moderate limitation (n=128, 12.5%), and severe limitation (n=102, 9.9%). Worse limitation was characterized by increasing difficulty in performing 8 daily-living activities. The mean posterior probability of subgroup assignment was 0.90, suggesting a good-fit of model Compared with those without knee ROA, multivariable adjusted odds ratios (OR) of no, mild, moderate and severe limitation in physical function among subjects with ROA was 1.6 (1.0, 2.5), 1.9 (1.1, 3.3) and 3.3(1.9, 5.7), respectively. Association of SxOA with limitation in physical function was even stronger, with ORs being 1.0, 2.7, 3.6, and 11.3, respectively, for each increasing difficulty on activity limitations.

Conclusion: Knee OA was strongly associated with limitation in physical function among people in rural areas of China. Knee OA is likely to become a major public health problem given the limitation in physical functioning associated with this disease among Chinese elderly.

	Limitations in Physical Function			
Knee OA Status	No	Mild	Moderate	Severe
No ROA (N=844)	57.2	24.2	11.6	7.0
ROA (N=181)	33.2	26.5	16.7	23.8
OR (95% CI)*	1.0	1.6 (1.0, 2.5)	1.9 (1.1, 3.3)	3.3 (1.9, 5.7)
No SxOA (N=962)	55.4	24.7	12.2	7.7
SxOA (N=63)	15.9	22.2	17.5	44.4
OR (95% CI)*	1.0	2.7 (1.2, 6.3)	3.6 (1.5, 8.9)	11.3(4.9, 25.7)

*Adjusted for age, sex, BMI, years of education, annual income, physical activity, and number of comorbidities

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Effects of Exercise on Depressive Symptoms in Adults with Arthritis: A Systematic Review with Meta-Analysis. George A. Kelley[1], Kristi S. Kelley[1] and Jennifer Hootman[2]. [1]West Virginia University, Morgantown, WV, [2]Centers for Disease Control and Prevention, Atlanta, GA.

Background/Purpose: Previous randomized controlled trials have led to conflicting findings regarding the effects of exercise on depressive symptoms in adults with arthritis and other rheumatic diseases (AORD). The purpose of this study was to use the meta-analytic approach to try and reach some general conclusions regarding these discrepancies.

Methods: The *a priori* inclusion criteria were: (1) randomized controlled trials, (2) exercise (aerobic, strength training, or both) >/= 4 weeks, (3) comparative control group, (4) adults with osteoarthritis, rheumatoid arthritis, fibromyalgia or systemic lupus erythematosus, (5) published and unpublished studies in any language since January 1, 1981, (6) depressive symptoms assessed. Studies were located by searching 10 electronic databases, cross-referencing, hand searching and expert review. Dual selection of studies and data abstraction were performed. Hedge's standardized effect size (g) was calculated for each result and pooled using random-effects models, an approach that accounts for heterogeneity. Non-overlapping 95% confidence intervals (CI) were considered statistically significant. Heterogeneity based on fixed-effect models was estimated using Q and I^2 with alpha values </= 0.10 for Q considered statistically significant. Small-study effects were examined using funnel plots and Egger's regression test, with adjustment for statistically significant results (non-overlapping one-tailed 95% confidence intervals). In addition, the number-needed-to-treat (NNT), percentile improvement, and 95% prediction intervals (PI) were calculated. Risk of bias was assessed using the Cochrane Risk of Bias Assessment Instrument. Training program characteristics were reported as mean +/− standard deviation.

Results: Of the 500 studies screened, 2,449 participants (1,470 exercise, 979 control) from 29 studies met the criteria for inclusion. Length of training averaged 19.1 +/− 16.0 weeks, frequency 3.6 +/− 2.0 times per week and duration 33.6 +/− 16.9 minutes per session. Overall, statistically significant exercise minus control group improvements were found for depressive symptoms (g = -0.41, 95% CI, -0.58, -0.24, Q = 196.2, p<0.0001, I^2 = 82.7%). The NNT was 8 with percentile improvements of 16.0%. Overlapping 95% PI (−1.33, 0.50) were observed. When adjusted for statistically significant small-study effects, improvements were reduced by 54.7% but remained statistically significant (g= -0.19, 95% CI, -0.37, -0.003). The NNT increased to 15 while percentile improvements were reduced to 7.4%. All studies were considered to be at high risk of bias with respect to blinding of participants and personnel to group assignment. Given the lack of information provided, greater than 50% of the studies were at an unclear risk of bias with respect to (1) incomplete outcome reporting (86%), (2) allocation concealment (72%), (3) blinding of outcome assessors (62%) and (4) subjects not exercising regularly prior to enrollment (52%).

Conclusion: Exercise may improve depressive symptoms in selected adults with AORD. However, a need exists for additional, well-designed, randomized controlled trials on this topic.

Disclosure: G. A. Kelley, None; **K. S. Kelley**, None; **J. Hootman**, None.

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Physical Inactivity to Activity Associated with Less Decline in Physical Function. Abigail Gilbert[1], Jing Song[2], Pamela A. Semanik[1], Rowland W. Chang[2] and Dorothy D. Dunlop[2]. [1]Northwestern University, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Regular physical activity has been demonstrated to improve quality of life for adults with chronic disease including osteoarthritis. Despite these benefits, half of adults with arthritis are inactive. An inactive lifestyle is associated with disability, loss of motion, pain, and stiffness. We analyzed longitudinal data from the Osteoarthritis Initiative (OAI) to evaluate the effect of transitioning from inactivity to activity on changes in function over a 2-year follow-up to assess the benefit of increasing physical activity in persons at high risk for disability.

Methods: The Osteoarthritis Initiative enrolled adults who had or were at risk of developing knee osteoarthritis. Longitudinal physical activity accelerometer monitoring was conducted on a subgroup at baseline (48 month OAI visit) and at 2 years (72 month OAI visit). We evaluated two-year activity transitions on 565 individuals identified as being inactive at baseline (zero 10 minute bouts of moderate-to-vigorous [MV] intensity physical activity during a week). We examined the relationship of becoming active (that is, a transition from inactive to insufficient activity or inactive to meeting guideline levels [meeting DHHS Guidelines of at least 150 minutes/week MV activity]) versus remaining inactive in relationship to change in function as measured by gait speed, chair stand rate, and WOMAC function. Analyses used multiple regression analysis controlling for baseline modifiable factors (smoking, knee pain, depressive symptoms, and overweight/obesity), and descriptive factors (age, gender, race/ethnicity, education, income, arthritis severity as measured by K-L grade, knee injury, medical comorbidities, hip pain, foot or ankle pain, and chronic knee symptoms).

Results: Of the 565 adults who were inactive at baseline, 141 (25%) became active (but insufficient to meet guidelines) while 15 (2.7%) became active enough to meet activity guidelines. Over two years, this group of adults characterized by baseline inactivity on average had worse function compared to baseline levels. However, people who became more active over two years compared to those who remained inactive lost less gait speed (2.6 versus 6.1 loss in feet/second), had improved chair stand (0.6 gain versus 1.0 loss repetitions/minute) and had less decrease in WOMAC function (0.7 versus 1.0 loss). This functional benefit remained after accounting for other modifiable and descriptive covariates. (See Table.)

Conclusion: While this inactive group of individuals on average lost function over two years, those who increased their activity lost less function compared to those who remained inactive. Promoting increased physical activity, even to levels not meeting DHHS guidelines, may help inactive persons with arthritis minimize loss of function.

Table Increased activity versus remaining inactive two-year function loss among adults with/ at high risk for knee OA who were inactive at baseline

	Function measure		
	Gait speed loss feet/ minute **n = 528**	Chair Stand rate **loss** N=534	Loss in WOMAC function N=561
	Mean* ± SE		
Become more active	−2.60±26.83	0.63±8.92	−0.68±8.69
Remain inactive	−6.06±24.06	−1.01±9.85	−0.99±10.11
	More Active versus Remain Inactive difference in functional loss Regression coefficient (95% Confidence Interval)**		
Unadjusted Average Difference	3.46 (−1.23, 8.16)	1.63 (−0.17, 3.44)	0.31 (−1.50, 2.12)
Difference adjusted for descriptive + modifiable factors#	0.79 (−4.39, 5.97)	1.03 (−0.93, 3.00)	0.02 (−1.76, 1.79)

* Negative/positive values in means indicate function loss/gain.
** Negative/positive values in regression coefficient indicate better/worsening function among those who became more active compared to those who remained inactive.
# Descriptive factors: age, gender, race/ethnicity, education, income, K-L grade, knee injury, comorbidity, hip pain, foot/ankle pain, chronic knee symptoms
Modifiable factors: smoking, knee pain, depressive symptoms, overweight/obesity

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Assessment of Exercise Status in Routine Care Using Patient Reported Outcomes: Initiating Exercise Is Associated with Better Outcomes Than No Exercise. Isabel Castrejón[1], Selda Celik[2], Theodore Pincus[1] and Yusuf Yazici[3]. [1]Rush University Medical Center, Chicago, IL, [2]NYU School of Medicine, New York, NY, [3]New York University School of Medicine, New York, NY.

Background/Purpose: Extensive evidence indicates major benefits of exercise in rheumatoid arthritis[1] and many other rheumatic diseases,[2] not only for cardiovascular and general fitness, but also for better rheumatologic clinical status. Most reported exercise data are derived from structured research studies rather than from usual care. A multidimensional health assessment questionnaire (MDHAQ) designed for usual care includes a query concerning exercise status for the rheumatologist to analyze possible associations with clinical outcomes. The objective of this study was to compare baseline demographic and clinical data and changes in status over 1 year, in patients classified into 4 categories according to the level of exercise.

Methods: Each patient seen at an academic rheumatology setting completes an MDHAQ at each visit while waiting to see the rheumatologist. The MDHAQ includes scores for physical function, pain, patient global estimate (PATGL), and RAPID3 (Routine Assessment of Patient Index Data), an index of these 3 measures, each scored 0–10; total=0–30. Patients were classified into 4 groups according to exercise 3 times a week at baseline and 1 year: EX at baseline & 1 year later, no EX at baseline but EX 1 yr later, EX at baseline but no 1 yr later and no EX at baseline or 1yr later. Mean baseline data and percentage change from baseline to 1 year were analyzed and compared by analysis of variance (ANOVA), with multivariate adjustment

for age, disease duration, education, sex and baseline physical function (MANOVA).

Results: 795 patients, including 221 with RA, were classified into 4 exercise groups: EX at baseline & 1 year later, no EX at baseline but EX 1 yr later, EX at baseline but no 1 yr later and no EX at baseline or 1yr later. Patients doing exercise at baseline were younger with a higher level of education than the NO exercise group (data not shown). Patients reporting no exercise at baseline and exercise 1 year later had greater improvement in scores than those in all other groups. Patients reporting exercise at baseline but not 1 yr later were the only group with poorer status. A potential limitation for our study is that it was unknown if change in exercise status preceded or resulted from change in clinical status.

	EX at baseline & 1 year later N=268 (33.7%)		No EX at baseline but EX at 1 year N=126 (15.8%)		EX at baseline No EX at 1 year N=77 (9.7%)		No EX at baseline or 1 year later N=324 (40.7%)	
	Baseline Mean (SD)	Mean change (%)	Baseline Mean (SD)	Mean change (%)	Baseline Mean (SD)	Mean change (%)	Baseline Mean (SD)	Mean change (%)
MDHAQ-FN (0–10)	1.5 (1.8)	−0.2 (−13.3)	2.3 (2.1)	−0.8 (−34.7)	2.0 (1.9)	0.3 (15.0)	2.7 (2.1)	−0.01 (−0.4)
MDHAQ-PN (0–10)	3.9 (2.9)	−0.5 (−12.8)	5.0 (3.1)	−1.7 (−34.0)	4.4 (2.9)	−0.2 (−4.5)	5.6 (3.0)	−0.8 (−14.3)
PATGL (0–10)	3.6 (2.7)	−0.4 (−11.1)	4.5 (2.8)	−1.8 (−40.0)	4.2 (2.8)	0.2 (4.8)	5.4 (2.7)	−0.8 (−14.8)
RAPID3 (0–30)	9.0 (6.5)	−1.2 (−13.3)	11.8 (7.3)	−4.4 (−37.3)	10.5 (6.3)	0.3 (2.8)	13.7 (6.9)	−1.7 (−12.4)
RADAI (0–48)	7 (9)	−2.1 (−28.0)	10 (10)	−3.9 (−37.9)	10 (8)	0.1 (1.2)	12 (11)	−0.3 (−2.4)

P<0.0001 for all comparisons. *Negative change indicates improvement & positive change worsening*

Conclusion: Exercise 3 times a week is associated with better clinical status. The best status was seen for patients who report no EX at baseline but performing EX 1yr later while poorest status was seen in patients reporting exercise at baseline but no 1 yr later. Regular exercise may be of therapeutic relevance in the management of rheumatic diseases by reducing pain and improving physical function. This clinically relevant information concerning exercise is available on MDHAQ for routine care settings.

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The Odds of Work Disability, Unemployment and Depending on Living Allowances Are More Influenced By the Number of Morbidities Than By the Presence of a Musculoskeletal Disease. Antje van der Zee-Neuen[1], Polina Putrik[2], Sofia Ramiro[3], Andras Keszei[4], Rob de Bie[1], Astrid M. Chorus[5] and Annelies Boonen[2]. [1]Maastricht University, Maastricht, Netherlands, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Amsterdam Rheumatology Center, University of Amsterdam & Hospital Garcia de Orta, Almada, Portugal, Amsterdam, Netherlands, [4]RWTH Aachen University, Aachen, Germany, [5]Netherlands Organization for Applied Scientific Research, Leiden, Netherlands.

Background/Purpose: The prevalence of multimorbidity (≥ 2 chronic morbidities in 1 person), is increasingly common also in patients at working age. Musculoskeletal diseases (MSKD) are among the most frequently occurring chronic diseases and comorbidities. However, little is known about the association of multimorbidity with official work disability and even less about its association with economic unemployment or dependence on living allowances (LA). Also, the additional influence of MSKD as comorbidity is unclear. We aimed to explore 1) whether an increasing number of morbidities is associated with increased odds to be work disabled (WD), unemployed or depending on LA & 2) whether presence of MSKD is associated with these outcomes or has an important additional contribution when combined with other morbidities.

Methods: In a Dutch epidemiological study, 8904 subjects (≥18 years old) completed a questionnaire on socio-demographic and lifestyle factors, self-reported physician-diagnosed diseases & work status. Persons at working age (18–65 years) who were either employed, formally WD, economically unemployed or receiving LA were included in the analyses (n=5396). Two multinomial regression models were computed with work status (i.e. employed, WD, unemployed or LA) as outcome and adjusted for age, gender, education, body mass index and smoking status. In model 1 the number of morbidities was the independent variable of interest and in model 2 either the single diseases (distinguishing MSKD from all other single diseases) or combinations of 2 or ≥3 diseases, including and excluding MSKD. Paid employment was used as reference outcome and estimates were compared to the healthy.

Results: MSKD occurred in 925 cases (17%) of the sample. Multimorbidity was present in 755 cases (14%). Of all cases with 2 morbidities 265/490 (54%) reported a MSKD. In cases with ≥3 morbidities 198/265 (75%) reported a MSKD.The odds to be WD increased steeply with every additional morbidity and the same trend but less pronounced was seen for unemployment and dependence on a LA (Table 1). Small (but no significant) increments were seen when exploring the role of MSKD in multimorbidity (e.g. the odds to be WD were 9.2 times higher than to be employed for persons suffering from 2 morbidities including MSKD and these odds were somewhat lower (8.8) when none of the 2 morbidities was MSKD). The odds to be unemployed or to receive a LA were slightly (but not significantly) higher for persons suffering from 2 co-occurring morbidities when 1 of these was a MSKD compared to 2 co-occurring morbidities without MSKD. (Table 1)

Conclusion: An increasing number of morbidities is associated with increased odds of WD, and to a lesser extent also with unemployment and dependence on a LA. There is a small additional adverse influence of the co-occurrence of MSKD in those suffering from 2 morbidities on all work outcomes. Multimorbidity requires more attention in considering patients' work outcome.

Table 1 Association of multimorbidity and combinations with and without MSKD with employment status

	N=5396		
Number of morbidities†	OR [95% CI]	Type of morbidities (in- or excluding MSKD)†	OR [95% CI]
Unemployed*	**n=184**	**Unemployed***	**n=184**
1	1.32 [0.92; 1.88]	1 morbidity (MSKD)	1.23 (0.71; 2.14)
2	**2.55 [1.63; 4.00]**	1 morbidity (no MSKD)	1.36 (0.91; 2.02)
3	**3.08 [1.60; 5.92]**	2 morbidities (+ MSKD)	**2.66 (1.51; 4.68)**
≥4	**4.50 [1.58; 13.62]**	2 morbidities (no MSKD)	**2.43 (1.31; 4.51)**
		≥3 morbidities (+ MSKD)	**3.21 (1.62; 6.35)**
		≥3 morbidities (no MSKD)	**3.58 (1.34; 9.54)**
Work disabled*	**n=350**	**Work disabled***	**n=350**
1	**3.31 [2.35; 4.65]**	1 morbidity (MSKD)	**2.00 (1.19; 3.39)**
2	**9.16 [6.32; 13.27]**	1 morbidity (no MSKD)	**3.91 (2.73; 5.60)**
3	**14.03 [8.88; 22.16]**	2 morbidities (+ MSKD)	**9.22 (5.98; 14.23)**
≥4	**30.33 [14.87; 61.85]**	2 morbidities (no MSKD)	**8.84 (5.59; 14.00)**
		≥3 morbidities (+ MSKD)	**23.73 (15.42; 36.53)**
		≥3 morbidities (no MSKD)	**14.89 (7.73; 28.71)**
Living allowance*	**n=57**	**Living allowance***	**n=57**
1	1.46 [0.69; 3.10]	Musculoskeletal disease	1.39 (0.49; 3.99)
2	**3.76 [1.67; 8.46]**	1 morbidity (no MSKD)	1.48 (0.64; 3.47)
3	**6.37 [2.46; 16.51]**	2 morbidities (+ MSKD)	**5.61 (2.32; 13.55)**
≥4	**16.29 [4.94; 53.67]**	2 morbidities (no MSKD)	1.74 (0.47; 6.54)
		≥3 morbidities (+ MSKD)	**7.70 (3.05; 19.45)**
		≥3 morbidities (no MSKD)	**10.45 (2.86; 38.13)**

** Paid work is reference outcome* **(n=4805)**
† No morbidity is reference category
Significant results are bold (p≤0.05)
Models adjusted for age, gender, education, body-mass index & smoking status

Disclosure: A. van der Zee-Neuen, None; **P. Putrik**, None; **S. Ramiro**, None; **A. Keszei**, None; **R. de Bie**, None; **A. M. Chorus**, None; **A. Boonen**, None.

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Prevalence of Pain Reporting in Different Ethnic Groups in the UK: Results from a Large Biobank. Marcus Beasley, Gareth T. Jones, Tatiana Macfarlane and Gary J. Macfarlane. University of Aberdeen, Aberdeen, United Kingdom.

Background/Purpose: Very large epidemiological studies designed to investigate genetic and environmental influences on disease, known as 'biobanks' can be used to look at associations between rare exposures and health for which smaller studies may lack power. The purpose of this study was to look at the association between ethnicity and pain in the UK Biobank.

Methods: UK Biobank recruited ½ million people across Great Britain. Participants attended assessment centers and answered questions on health and lifestyle by touch-screen questionnaire. They were asked "In the last month have you experienced any of the following that interfered with your usual activities?", and could indicate: headache, face pain, neck/shoulder pain, back pain, abdominal pain, hip pain, knee pain, or pain all over. For each positive answer, participants were asked if the pain had lasted at least three months, which was defined as chronic. Questions were also asked on gender, age, ethnicity, income, employment status, adverse life events and mental health. Self-reported ethnicity was classed as white, mixed, south Asian,

black, Asian (Chinese), or other. Life events recorded were: serious illness, injury, or death to a partner or close relative, marital separation, and financial difficulties. Mental health included mood swings, feelings of guilt and loneliness, and being tense. Prevalence of any pain, chronic pain, and regional pains was calculated for each ethnic group, standardised to age/gender structure in the UK 2011 Census. Risk ratios adjusted for age and sex with 99% confidence intervals were calculated using white as the referent group. Risk ratios for any pain and chronic pain were adjusted for income, employment status, life events, and mental health.

Results: Pain questions were answered by 498,071 participants between the ages of 40 and 69. Compared to the white group (prevalence 60.3%), persons identified as mixed (66.3%), south Asian (71.8%), black (70.2%), or other (71.5%) were more likely to report pain (see table). Relationships were similar for chronic pain, although less strong. Asian (Chinese) were no more likely to report pain (61.0%) and less likely to report chronic pain. After adjustment for potential confounders differences between groups remained but were smaller. Excess prevalence of regional pains was observed for all groups compared to whites apart from Asian (Chinese), who were more likely than whites to report neck or shoulder pain, and less likely to report hip pain and facial pain.

Conclusion: This study has shown differences in pain reporting according to self-reported ethnicity. These are partly explained by socio-economic and psychosocial factors, and adverse life events. The large numbers of centers in this study means the results are more generalizable compared to those from single center studies. Difference in pain prevalence between groups has implications for allocation of healthcare resources where populations differ.

		Ethnic group specific prevalence (%)					
		White	Mixed	South Asian	Black	Asian (Chinese)	Any other
Any Pain	Standardised Prevalence	60.3	66.3	71.8	70.2	61	71.5
	RR (99% CI)[1]	1	1.09 (1.05–1.13)	1.19 (1.17–1.21)	1.15 (1.13–1.18)	1.00 (0.95–1.06)	1.18 (1.15–1.21)
	RR adj (99% CI)[2]	1	1.03 (0.99–1.08)	1.11 (1.08–1.14)	1.06 (1.03–1.09)	0.98 (0.91–1.06)	1.09 (1.05–1.13)
Chronic Pain	Standardised Prevalence	42.6	46.7	47.7	45.2	36.5	47
	RR (99% CI)1	1	1.11 (1.05–1.17)	1.15 (1.12–1.19)	1.08 (1.05–1.12)	0.86 (0.79–0.95)	1.13 (1.08–1.18)
	RR adj (99% CI)2	1	1.04 (0.98<>1.11)	1.05 (1.01–1.09)	0.95 (0.91–0.99)	0.89 (0.79–1.004)	1.01 (0.95–1.07)
Headache	Standardised Prevalence	22.02	25.5	30.2	28.4	23.7	31.8
	RR (99% CI)[1]	1	0.99 (0.91–1.08)	1.29 (1.23–1.34)	1.13 (1.07–1.18)	0.94 (0.83–1.06)	1.29 (1.21–1.37)
Facial Pain	Standardised Prevalence	1.9	2.7	1.6	2.1	0.8	1.7
	RR (99% CI)[1]	1	1.25 (0.93–1.70)	0.87 (0.70–1.09)	1.04 (0.84–1.28)	0.36 (0.16–0.80)	0.86 (0.63–1.16)
Shoulder/ neck Pain	Standardised Prevalence	23	28.7	30.7	25.5	28.7	28.7
	RR (99% CI)[1]	1	1.24 (1.15–1.35)	1.35 (1.30–1.41)	1.11 (1.05–1.17)	1.24 (1.11–1.39)	1.25 (1.17–1.33)
Back pain	Standardised Prevalence	25.8	27.6	33.4	31.3	27.3	34.7
	RR (99% CI)[1]	1	1.07 (0.99–1.16)	1.28 (1.23–1.33)	1.21 (1.16–1.27)	1.06 (0.95–1.19)	1.34 (1.27–1.42)
Abdominal Pain	Standardised Prevalence	9.3	14	11.1	14.5	10.2	14.4
	RR (99% CI)[1]	1	1.31 (1.15–1.48)	1.13 (1.04–1.22)	1.39 (1.28–1.50)	0.98 (0.80–1.21)	1.40 (1.27–1.56)
Hip Pain	Standardised Prevalence	10.3	10	8.3	10.8	6.7	8.9
	RR (99% CI)[1]	1	1.10 (0.95–1.27)	0.92 (0.85–1.01)	1.19 (1.09–1.30)	0.72 (0.56–0.92)	0.97 (0.86–1.10)
Knee Pain	Standardised Prevalence	20.4	21.9	25.4	25.3	17.9	23.1
	RR (99% CI)[1]	1	1.19 (1.09–1.29)	1.35 (1.30–1.41)	1.40 (1.33–1.46)	0.96 (0.84–1.10)	1.25 (1.17–1.34)

[1]RR adjusted for age/sex, standardised
[2]RR (adj) additionally adjusted for income, employment, adverse life events, and mental health

Disclosure: M. Beasley, None; **G. T. Jones**, None; **T. Macfarlane**, None; **G. J. Macfarlane**, None.

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The Association Between Doctor-Diagnosed Arthritis and Falls and Fall Injuries Among Middle-Aged and Older Adults. Kamil E. Barbour[1], Louise Murphy[2], Kristina A. Theis[3], Charles G. Helmick[2], Jennifer Hootman[2] and Judy A. Stevens[2]. [1]CDC, Atlanta, GA, [2]Centers for Disease Control and Prevention, Atlanta, GA, [3]Centers for Disease Control and Prevention, Atlanta, Georgia.

Background/Purpose: Falls are the leading cause of injury-related morbidity and mortality among older adults (age ≥65 years), with more than one in three falling each year, resulting in direct medical costs of nearly $30 billion. Arthritis can lead to poor neuromuscular function (i.e., gait speed and balance), a major risk factor for falling. Although the association between arthritis and increased falls risk among older adults is well documented, little is known about arthritis and falls among middle-aged adults (45–64 years).

Methods: We analyzed data from the 2012 Behavioral Risk Factor Surveillance System (BRFSS), an annual, random-digit–dialed landline and cellphone survey representative of the noninstitutionalized adult population aged ≥18 years from the 50 states, DC, Puerto Rico, and Guam (n=338,734 respondents age ≥45 years). Respondents were considered to have arthritis if they answered "yes" to, "Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?" They were considered to have fallen if they answered one or more to, "In the past 12 months, how many times have you fallen?" Those reporting one or more falls were also asked, "How many of these falls caused an injury? By an injury, we mean the fall caused you to limit your regular activities for at least a day or to go see a doctor?" We analyzed number of falls as a categorical (zero, one, or two or more) and binary variable (no falls, or one or more falls). Fall injury was categorized as a binary variable (yes or no). Prevalence ratios (PRs) and 95% confidence intervals (CIs) were estimated in log binomial and multinomial regression models which adjusted for age, sex, race, education, body mass index (BMI), self-rated health status, physical activity, heart disease, and stroke.

Results: Among middle-aged adults, the prevalence of arthritis, falls, and fall injuries was 33.8%, 25.6%, and 9.7%, respectively, whereas the prevalence among older adults was 53.4%, 27.1%, and 9.6%, respectively. Among middle-aged adults with arthritis, the prevalence of one or more falls, two or more falls, and fall injuries was 1.58 (95% CI: 1.53, 1.63), 1.92 (95% CI: 1.82, 2.02), and 2.10 (95% CI: 1.97, 2.23) times higher compared with middle-aged adults without arthritis. Among older adults with arthritis, the prevalence one or more falls, two or more falls, and fall injuries was 1.38 (95% CI: 1.34, 1.45), 1.69 (95% CI: 1.59, 1.80), and 1.63 (95% CI: 1.52, 1.75) times higher compared with older adults with arthritis.

Conclusion: These findings establish the significant relationship between arthritis and falls and fall injuries among middle-aged adults and demonstrate that these associations are similar in magnitude to those already recognized among older adults. Raising awareness of falls and fall injuries among middle aged adults is an important first step in mitigating negative fall consequences in this population. The high burden of falls and fall injuries among middle-aged and older adults with arthritis can be addressed through greater dissemination of arthritis management and fall prevention programs in clinical and community practice.

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Frequency and Risk Factors for Recurrent Falls in Community-Dwelling Elderly: A Population-Based Prospective Cohort Study in Brazil. the São Paulo Ageing & Health (SPAH) Study. Ketty LLL Machado[1], Diogo S. Domiciano[1], Luana G. Machado[2], Camille P. Figueiredo[2], Jaqueline B. Lopes[2], Valéria Caparbo[2], Liliam Takayama[2], Ricardo M. Oliveira[3] and Rosa Maria Pereira[2]. [1]Faculdade de Medicina, University of São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]RDO Diagnosticos Medicos, São Paulo, Brazil.

Background/Purpose: Falls are among the leading external causes of mortality in the elderly. This issue acquires substantial importance in low-income countries where the population's aging has been faster. Several clinical factors (including age, drugs and previous fracture) have been associated with increased fall risk. However, few studies performed a concomitant evaluation of clinical data, laboratory bone exams and bone mineral density (BMD) to determine more accurately the contribution of each of these variables to fall risk in community-dwelling elderly. Our aim was to investigate the association between bone parameters and falls in a population-based prospective cohort of community-dwelling older adults.

Methods: Risk factors for recurrent falls were determined in 705 community-dwelling individuals (448 women and 257 men) aged ≥ 65 years. Specific questionnaire (clinical data), BMD and laboratory tests -including 25-hydroxyvitamin D (25OHD), intact PTH (iPTH) and serum cross-linked C-telopeptide (CTX) were performed at baseline and after a mean follow-up of 4.3±0.8 years. Individuals with recurrent falls (2 or more falls in the last year from the date of the second evaluation) were considered chronic fallers. Potential risk factors for recurrent falls were compared between fallers and non-fallers. Logistic regression models were used to used to identify independent predictors of recurrent falls.

Results: The frequency of chronic fallers was 16.5% (95% CI: 13.8–19.2). In multivariate analysis, independent risk factors for recurrent falls were visual impairment (OR = 2.49, 95% CI 1.30–4.74, p = 0.006), chronic use of psychotropic drugs (OR = 2.47, 95% CI 1.37–4.49, p = 0.003), previous fracture (OR = 2.78, 95% CI 1.48–5.20, p = 0.001), persistently low serum 25OHD (<20ng/mL) (OR = 1.71, 95% CI 1.10–2.64, p = 0.020)

and loss of total hip BMD between the two assessments (OR = 1.21, 95% CI 1.17–1.25, p = 0.03 for each 5%-decrease).

Conclusion: In addition to traditional clinical risk factors for falls, significant loss of total hip BMD and persistently hypovitaminosis D were associated with recurrent falls in Brazilian community-dwelling elderly. In this way, recognizing these factors is essential to recommend preventive actions to reduce recurrence of falls and might improve the health outcomes in this population.

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ACR Poster Session A
Genetics, Genomics and Proteomics I
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Influence of the Polymorphism IL1β (−511 A/C) and IL6 (- 174 G/C) on the Activity, Radiographic Damage and Clinical Forms of Patients with Psoriatic Arthritis (PSA). Tatiana Carranco[1], Noelia Cubino[1], Clara Cieza-Borrela[1], Ismael Calero[1], Maria Dolores Sanchez[1], C. Hidalgo-Calleja[2], Alba Quesada[1], Andres Plata[1], Agustin Diaz Alvarez[1], Ricardo Usategui[3], Rogelio Gonzalez[3], C.a. Montilla-Morales[2] and J. Del Pino-Montes[2]. [1]HOSPITAL CLINICO UNIVERSITARIO DE SALAMANCA, SALAMANCA, Spain, [2]University of Salamanca Hospital, Salamanca, Spain, [3]IBSAL, SALAMANCA, Spain.

Background/Purpose: PSA is a chronic inflammatory disease associated to psoriasis which affects the joints, vertebrae and enthesis. Interleukin-1 is an inflammatory cytokine. A higher expression of IL-1 has been observed in the synovial fluid of patients with PSA. Interleukin-6 promotes synovitis and enhances bone resorption. No studies have analyzed the relation between PSA patients with polymorphisms of IL-1β (−511 A/C) and IL-6 (−174 G/C) and the activity, the presence of erosions or the clinical form of presentation. We relate the polymorphisms of IL-1β (−511 G/A) and IL-6 (−174 G/C) with inflammatory activity, radiographic damage and clinical forms in a group of PSA patients.

Methods: We studied 125 patients diagnosed with PSA according to the CASPAR criteria. The patients were classified depending on whether they presented peripheral, axial or mixed. The activity in the peripheral or mixed forms was measured according to the number of swollen, painful joints, visual analogue scale, ESR and CRP. The DAS 28 index was calculated. For the axial and mixed forms, the BASDAI index, the visual analogue scale, ESR and CRP were used. In the assessment of radiographic damage we used the SvH and mSASSS. All patients underwent an analysis of the polymorphism in the promoter region of IL-1β (−511 G/A) and IL-6 (−174 G/C).

Results: 59.2% of the patients were men. 13 patients showed axial involvement (10.4%), 38 a mixed involvement (30.4%), and 74 a peripheral involvement (59.2%). The distribution and genotype of the polymorphism of IL-1β (−511 G/A), with regard to the number of swollen joints and DAS >3.2 are included in Table 1. In the logistic regression model: DAS >3.2 (p=0.018; OR: 3.46). In the allele analysis, 30.92% of the carriers of the G allele showed DAS over 3.2, compared with 12.5% of the patients with the A allele (OR: 3.13); p<0.0004; 95% CI: 1.43–6.82; adjusted p<0.008). No differences were found regarding the distribution of the polymorphism in the different clinical forms of the disease or the radiographic damage. With regard to the polymorphism of IL-6 (−174 G/C) in the group of G/G homozygous patients, compared with the combined group of G/A and A/A patients, we found differences in the clinical forms of PSA and in the frequency of appearance of HLA-B27 antigen (Table 1). In the logistic regression analysis: types of disease (p=0.007; OR=2.741) and HLA-B27 (p=0.001; OR=0.103). The G allele was not more frequently found in peripheral forms (70.86%) than in mixed forms (57.42%) (OR=1.89; p<0.03; 95% CI: 1.06–3.39; adjusted p<0.05). We did find a lower association of the G allele with HLA-B27 (15.78%) compared with the C allele (28.57%) (OR= 0.469; p=0.02; 95% CI: 0.238–0.923; adjusted p<0.03).

Conclusion: The G allele of polymorphism IL-1β (−511 A/C) was associated with the presence of more inflammatory activity. We found a trend in patients who carried the G allele of the polymorphism IL-6 (−174 G/C) to present with a peripheral form of the disease.

Table 1.

	IL1β (−511 A/C)	Mean (SD)	p
NSJ	G/G	2.09 (1.99)	0.03
	G/A	1.49 (1.56)	
	A/A	1.45 (1.50)	
DAS>3.2	Yes	No	
	G/G 20	31	0.005
	G/A 7	43	
	A/A 1	10	
	IL6 (−174 G/C)	Patients	
AXIAL	G/G	6	0.009
	G/C+C/C	7	
PERIPHERAL	G/G	39	
	G/C+C/C	35	
MIXED	G/G	10	
	G/C+C/C	28	
HLAB27	POSITIVE	NEGATIVE	
	G/G 3	46	0.003
	G/C+C/C 19	43	

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Robust Identification of Anti-TNF Non-Responders in RA from Blood. Ty Thomson, Reynald Lescarbeau, David Drubin, David Fryburg, David de Graaf, Renée Deehan, Daphna Laifenfeld and Aaron Van Hooser. Selventa, Cambridge, MA.

Background/Purpose: The number of biologic therapies approved for use in treating rheumatoid arthritis (RA) has grown steadily over the past 15 years. While many patients are treated with anti-TNF therapies, 30–40% of these patients fail to respond adequately as their disease progressively worsens. Tools to guide disease management and identify a priori which patients are likely to be non-responsive to anti-TNF therapies would allow these patients to seek alternative therapies to achieve faster relief from symptoms, avoid unnecessary treatment side effects, and avoid further disease progression.

Methods: Four published gene expression data sets containing a total of 91 patients were used to train a classifier to identify anti-TNF non-responders. Gene expression measurements, collected prior to patient treatment with the anti-TNF infliximab, were grouped into disease-relevant biological signaling mechanisms to provide a stable, quantitative representation of biological state. Regularized logistic regression was used to train a classifier to identify non-responders, and a classifier score threshold was selected to optimize for detection of non-responders with high specificity.

Results: Repeated 10-fold cross-validation resulted in highly-specific prediction of non-response (specificity = 92%; likelihood ratio = 5.53; area under the receiver operator characteristic curve (AUROC) = 78%, p-value<0.00001; Figure 1), while still correctly identifying a significant fraction of non-responders (sensitivity = 45%). Prediction of non-response on independent infliximab treated cohorts, consisting of an independent 27 patient cohort as well as each of the four training when left out in turn from training, resulted in AUROCs between 63% and 80% and associated p-values between 0.029 and 0.15. Specificity of the classifier for infliximab and its therapeutic target TNF was supported by a lack of association with responses in small rituximab (anti-CD20) and tocilizumab (anti-IL6R) treated cohorts.

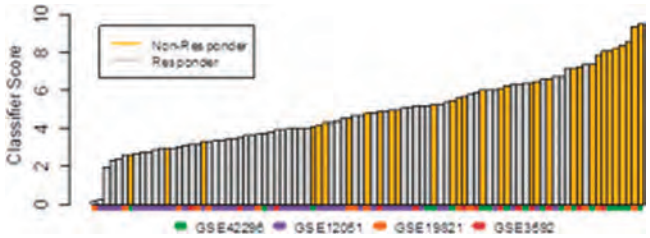

Figure 1. A representative patient stratification from 10-fold cross validation, matching the mean AUROC of 78% across all cross validation repeats, shows the classifier score for each patient. Patients were sorted by classifier score and colored by their clinical response calls.

Conclusion: The classifier developed in this study identifies RA patients who are unlikely to respond to infliximab, and thus are good candidates for

alternative biologic therapies. The test robustly predicts non-response across multiple patient cohorts. Future iterations of the test could include additional training cohorts and expansion to include complementary prediction of response to other RA therapies.

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Identification of Synovial Genes and Pathways Associated with Disease Progression in a Cohort of Early Symptomatic Osteoarthritis Using a Transcriptomic Approach. Arjen B. Blom[1], Peter L. van Lent[1], Martijn H. van den Bosch[1], Hans Cats[2], Frank H.J. van den Hoogen[3], Floris P.J.G. Lafeber[4], Wim B. van den Berg[1] and Peter M. van der Kraan[1]. [1]Radboud university medical center, Nijmegen, Netherlands, [2]Sint Maartenskliniek, Ubbergen, Netherlands, [3]Rheumatology Centre Sint Maartenskliniek and Radboud university medical center, Ubbergen (Nijmegen), Netherlands, [4]University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: If and how the synovial activation that is observed in over 50% of osteoarthritis (OA) patients contributes to irreversible joint pathology, is not known. The purpose of this study was to identify pathways that may determine progression of cartilage damage in this disease.

Methods: From 25 patients with knee OA that entered the CHECK Cohort study (Cohort Hip and Cohort Knee) and 6 controls, synovial biopsies were collected at baseline. CHECK is a prospective 10-year follow-up study on participants with early osteoarthritis-related complaints initiated by the Dutch Arthritis Association. Progression was determined based on change of joint space width (JSW) and osteophyte formation in radiographs, as analyzed using the KIDA (Knee Image Digital Analysis) system. Synovial samples from baseline were studied using histology and affymetrix U133-plus-2.0 chips, which were analyzed using Partek Genomics Suite software and DAVID.

Results: Histologically, lining thickness and synovitis were enhanced in the CHECK biopsies compared to control synovia. Next we compared synovial tissue of CHECK-patients with radiological damage with CHECK-patients without joint damage at baseline. Among the genes that were strongest associated with cartilage damage were *MMP1* (18-fold), *MMP3* (10-fold), and *S100A8* (6-fold). Immunohistochemical staining revealed that expression of MMP-1 and MMP-3 was highest in the synovial lining layer. Enrichment analysis showed that chemotaxis, innate immune response and MMPs were significantly associated with joint damage at baseline. To determine whether any of the regulated genes and pathways were predictive for progression of joint damage between baseline and t=5 yrs, we identified 13 patients that were marked progressors and 8 non-progressors, based on JSW and osteophyte size. At baseline, neither minimum JSW nor osteophyte size differed between the groups. Approximately 200 genes were expressed more than 2-fold higher in synovium of progressors, versus non-progressors. Among these genes were genes from the wnt-signaling pathway: *WISP1*, *FZD1*, *FZD8* and *FZD10*, whereas *FRZB* was downregulated. In addition, pro-inflammatory factors like *IL1*, *IL6*, *S100A9* and *MMP1* were increased. Macrophage markers like *CD14*, MHC class II genes, scavenger receptor A3 and *CXCR2*were positively associated with progression. This indicates that expression of these factors may predict, or even be involved in, progression of joint damage in OA patients. Using DAVID we identified inflammatory response, macrophage differentiation, blood vessel formation, ossification and cell migration to be enriched in patients that show progression of damage 5 yrs later. Histologically, the progressors showed a higher thickness of the lining layer at baseline compared to non-progressors, 2.0 vs 1.2 respectively on an arbitrary scale from 0–3.

Conclusion: These data suggest an active role for the synovium in OA pathology, and identify pathways that may be involved. From histology and the expression data, it appears that presence of macrophages is associated with progression of joint damage in OA. In addition, synovial expression of wnt-signaling genes seems important in progression of damage.

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Epigenome Profiling Reveals Robust Hypomethylation of Interferon Signature Genes in Lupus Neutrophils. Patrick Coit[1], Sri Yalavarthi[1], Wenpu Zhao[2], Mariana J. Kaplan[2] and Amr H. Sawalha[1]. [1]University of Michigan, Ann Arbor, MI, [2]National Institutes of Health, Bethesda, MD.

Background/Purpose: Lupus neutrophils play an important role in tissue damage (including glomerulonephritis and lupus skin involvement), as well as endothelial damage in lupus patients. Several studies have suggested altered functional capacity of lupus neutrophils compared to healthy controls, and the expansion of a neutrophil subset with a lower density (low density granulocytes or LDGs) in lupus. We characterized the DNA methylome of normal-density neutrophils and LDGs from lupus patients, and age-, sex-, and ethnicity-matched healthy controls to gain insight into chromatin architectural differences and how these differences might alter neutrophil function and induce pathogenicity in lupus.

Methods: We included 8 lupus patients and 8 healthy age-, sex-, and ethnicity-matched controls for these studies. Low density granulocytes (LDGs) and normal-density neutrophils were isolated from each lupus patient, and normal-density neutrophils were isolated from healthy controls. Neutrophils and LDGs were extracted using density gradient centrifugation and magnetic bead separation with over 95% purity in every sample. DNA was extracted and bisulfite conversion performed. A genome-wide DNA methylation study was performed using the Illumina HumanMethylation 450 BeadChip array, which includes over 485,000 methylation sites across the entire genome. The array covers 99% of RefSeq genes, including promoter regions, 5'-UTR, first exon, gene body, and 3'-UTR. 96% of all CpG islands are also covered. Statistical and bioinformatics analysis was performed to identify differentially methylated loci, gene ontologies, and pathways.

Results: We identified 619 differentially methylated CpG sites in normal-density neutrophils between lupus patients and healthy matched controls. Very interestingly, we find a robust and consistent demethylation of interferon signature genes in both normal-density neutrophils and LDGs in lupus patients. The top 30 hypomethylated CpG sites in lupus neutrophils are presented in **Table 1**. These data suggest that the chromatin structure in lupus granulocytes supports the expression of higher levels of type-1 interferon regulated genes, and that neutrophils directly contribute to the interferon signature in lupus. Curiously, however, our data so far suggest that LDGs and normal-density neutrophils from lupus patients are virtually identical in their chromatic architecture with no methylation differences across the genome between these two distinct granulocyte subsets.

Table 1: Top 30 hypomethylated CpG sites in lupus normal-density neutrophils compared to age-, sex-, and ethnicity-matched healthy control neutrophils. Significant and consistent hypomethylation in interferon signature genes is noted

CpG ID	Chr	Position (Hg19)	Gene(s)	Methylation Patients	Methylation Controls	Fold Change (patients/controls)	*P* value
cg21549285	21	42799141	*MX1*	0.218	0.716	0.30	1.84E-34
cg14864167	8	66751182	*PDE7A*	0.322	0.666	0.48	1.84E-34
cg05696877	1	79088769	*IFI44L*	0.279	0.611	0.46	1.84E-34
cg08122652	3	122281939	*PARP9; DTX3L*	0.410	0.741	0.55	1.84E-34
cg23570810	11	315102	*IFITM1*	0.381	0.710	0.54	1.84E-34
cg22930808	3	122281881	*PARP9; DTX3L*	0.204	0.526	0.39	1.84E-34
cg22862003	21	42797588	*MX1*	0.268	0.585	0.46	1.84E-34
cg01079652	1	79118191	*IFI44*	0.444	0.758	0.59	1.84E-34
cg11946459	6	29911558	*HLA-A*	0.371	0.678	0.55	1.84E-34
cg05552874	10	91153143	*IFIT1*	0.200	0.499	0.40	1.84E-34
cg07839457	16	57023022	*NLRC5*	0.217	0.515	0.42	1.84E-34
cg18136963	6	139013146	*N/A*	0.063	0.353	0.18	1.84E-34
cg20045320	11	319555	*N/A*	0.300	0.588	0.51	3.82E-30
cg03038262	11	315262	*IFITM1*	0.396	0.679	0.58	1.6E-29
cg13304609	1	79085162	*IFI44L*	0.503	0.785	0.64	1.34E-33
cg02331830	8	145008288	*PLEC1*	0.394	0.673	0.59	2.14E-28
cg08993878	12	98151379	*N/A*	0.301	0.580	0.52	4.64E-28
cg01028142	2	7004578	*CMPK2*	0.505	0.782	0.65	3.13E-32
cg03607951	1	79085586	*IFI44L*	0.142	0.416	0.34	9.87E-34
cg06872964	1	79085250	*IFI44L*	0.161	0.432	0.37	1.04E-31
cg06864789	6	139012992	*N/A*	0.124	0.390	0.32	2.05E-33
cg18025438	1	228756789	*N/A*	0.410	0.674	0.61	5.15E-25
cg06188083	10	91093005	*IFIT3*	0.317	0.575	0.55	2.7E-23
cg26312951	21	42797847	*MX1*	0.185	0.439	0.42	1.39E-26
cg16672562	19	46801672	*HIF3A*	0.202	0.452	0.45	7.77E-25
cg05883128	4	169239131	*DDX60*	0.294	0.544	0.54	4.91E-22
cg20098015	22	50971140	*ODF3B*	0.178	0.419	0.43	6.25E-24
cg17608381	6	29911550	*HLA-A*	0.407	0.647	0.63	9.27E-20
cg22259797	11	118986860	*C2CD2L*	0.246	0.484	0.51	1.04E-20
cg14293575	22	18635460	*USP18*	0.612	0.846	0.72	7.65E-28

Conclusion: We characterized the DNA methylome in lupus neutrophils for the first time and showed a pattern of robust demethylation of interferon signature genes in lupus patients supporting a pathogenic role for neutrophils in lupus.

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a HPLC-SRM-MS Based Method for the Detection and Quantification of Methotrexate Used at Doses in Clinical Practice for Patients with Rheumatological Disease in Urine. James Bluett[1], Isabel Riba-Garcia[2], Richard Unwin[2], Suzanne Verstappen[3] and Anne Barton[4]. [1]Arthritis Research UK Centre for Genetics and Genomics, The University of Manchester, Manchester, United Kingdom, [2]Centre for Advanced Discovery and Experimental Therapeutics (CADET), Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [3]Arthritis Research UK Centre for Epidemiology, University of Manchester, Manchester, United Kingdom, [4]Arthritis Research UK Centre for Genetics and Genomics, University of Manchester, Manchester, United Kingdom.

Background/Purpose: Methotrexate (MTX) is a recommended first-line therapy in 2013 EULAR guidelines for active rheumatoid arthritis (RA). Despite this, up to 54% do not adequately respond to MTX. Non-adherence rates vary depending on the method used to measure adherence. Currently there is no gold standard for measurement of MTX adherence. Whilst an ELISA method exists to detect MTX levels at the doses used for chemotherapy regimes, this is not sensitive enough for the low dose MTX used to treat patients with rheumatological conditions. Detection of MTX and its major metabolite 7-OH-MTX in urine may be an improved method to detect adherence in routine practice, when used in the lower dose range (7.5 – 30 mg/wk). The aim, therefore, was to develop a liquid chromatography-selected reaction monitoring mass spectrometry (HPLC-SRM-MS) method to determine the presence of low concentrations of MTX and 7-OH-MTX in urine.

Methods: Donated drug-free samples from RA patients were frozen at −80°C after collection. Samples were thawed at room temperature and then prepared by spiking purchased MTX, 7-OH-MTX and the internal standard MTX-d_3. Samples were diluted and protein removed by precipitation. Supernatent was subsequently analysed using HPLC with a reversed-phase column on line to a triple quadrupole mass spectrometer operated in positive mode. Analytes were measured in selected reaction monitoring mode for the following mass transitions: 455.1 >308.1 *m/z* for MTX 471.1 >324.1 *m/z* for 7-OH-MTX and 458.1 >311.1 *m/z* for MTX-d_3. Method validation consisted of accuracy, lower limit of quantification, recovery, linearity, precision and stability at room temperature and -80°C. All samples were measured in triplicate.

Results: For MTX and 7-OH-MTX respectively, average recovery of analyte following sample preparations was 118%±8.9% and 86%±18.6%. The lower limit of quantitation (LLOQ) was 2.5 and 5nM. The coefficient of variance for intraday run was 3.0% and 2.5% respectively. The method was linear from the LLOQ up to 1000nM (r^2=0.99, 1.00 respectively). Stability testing revealed no loss at 7 days when samples were stored at -80°C, although storage at room temperature produced an average loss of 27%±6% and 10%±39% respectively within 24 hours.

Conclusion: We have developed a rapid, simple and cost effective HPLC-SRM-MS method to measure MTX and 7-OH-MTX concentrations in urine, which is sensitive to the low doses used to treat RA and other musculoskeletal diseases. The method requires limited sample preparation and may be a novel biochemical assay for measurement of adherence to MTX therapy.

Disclosure: J. Bluett, None; **I. Riba-Garcia**, None; **R. Unwin**, None; **S. Verstappen**, None; **A. Barton**, None.

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PECAM-1 GENE Polymorphisms and Soluble PECAM-1 LEVEL in Rheumatoid Arthritis and Systemic LUPUS Erythematosus Patients Is There a Link with Clinical Atherosclerotic Events? Omer Nuri Pamuk[1], Hilmi Tozkir[2], Mehmet Sevki Uyanik[1], Hakan Gurkan[2], Julide Duymaz[2], Salim Donmez[3], Metin Yazar[2] and Gulsum Pamuk[1]. [1]Trakya University Medical Faculty, Edirne, Turkey, [2]Trakya University Medical Faculty, EDIRNE, Turkey, [3]Trakya University School of Medicine, Edirne, Turkey.

Background/Purpose: Platelet-endothelial cell adhesion molecule-1 (PECAM-1/CD31) which plays a role in the transmigration of leucocytes into tissues is a member of the immunoglobulin (Ig) superfamily. It was reported that the expression of PECAM-1 on synovial tissue in inflammatory arthritis is enhanced. The genetic polymorphisms of PECAM-1 were found to play roles in atherosclerotic events. We determined PECAM-1 polymorphisms, soluble PECAM-1 and CD40L levels in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE); and evaluated their associations with clinical atherosclerotic complications.

Methods: We included 100 RA and 81 SLE patients and 94 healthy controls into the study. The clinical features about patients were obtained from medical records. Past cardiovascular complications were recorded. The most frequent gene polymorphisms of PECAM-1 were studied in our genetics laboratory. Soluble PECAM-1 and CD40L levels in serum were determined with ELISA.

Results: The frequencies of 373C (rs668) and 1688A (rs12953) alleles were higher in RA patients when compared to controls (p values, 0.03 and 0.023). RA and SLE patients had significantly higher allele frequencies for 2008A (rs1131012) when compared to controls (p values, 0.021 and 0.001). SLE patients had significantly more frequent AA genotype for rs1131012 polymorphism than RA patients and controls (p values, 0.007 and <0.001). Soluble PECAM-1 level was significantly higher in RA patients than in SLE patients and healthy controls (p values <0.001). The sCD40L level was also significantly higher in RA group than in SLE and control groups (p values, 0.006 and 0.047). The levels of sPECAM-1 and sCD40L were significantly higher in RA patients with AA genotype (rs1131012) than in patients with AG genotype (p values, 0.046 and 0.008). Atherosclerotic complications were more frequent in SLE patients with AG genotype (rs12953) than those with AA genotype (p=0.021). SLE patients with CC genotype (rs668) had a significantly lower frequency of atherosclerotic complications than those with CG genotype (p=0.045).

Conclusion: We found associations between various PECAM-1 polymorphisms and RA, SLE; PECAM-1 and sCD40L levels were significantly higher in RA patients than in SLE and control groups. Soluble PECAM-1 level in RA was found to be linked to a certain genotype; PECAM-1 polymorphisms in SLE were protective against atherosclerotic complications.

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Cellular Responses of IL6 Inhibition (Tocilizumab) in Rheumatoid Arthritis Using High-Accuracy Tandem Mass Spectrometry. Michael Kruse Meyer[1], Marlene Andersen[2], Grethe N. Andersen[1] and Allan Stensballe[3]. [1]Hospital of Vendsyssel/Aalborg University, Hjørring, Denmark, [2]Aalborg University, Hjørring, Denmark, [3]Aalborg University, Aalborg, Denmark.

Background/Purpose: In this study we are analyzing leukocyte subtype responses from patients with rheumatoid arthritis (RA) to IL6 inhibition. A large contribution to RA immunopathogenesis is caused by the pleiotropic effects of interleukin 6 (IL6), which we are investigating directly on the biological active constituents of the cell, i.e. the proteins, using *state-of-the-art*mass spectrometry. This has enabled us to quantify changes in protein expression of thousands of proteins as a result of biologic treatment, and mapping of post-translational modifications such as citrullination, and phosphorylation.

Methods: 10 ACA positive RA patients fulfilling the ACR criteria are being enrolled prior to monotherapy IL6 inhibition and 4 months after compared to 10 healthy controls. PBMC were isolated and subdivided into $CD14^+$, $CD4^+$, $CD8^+$, $C19^+$, and $CD56^+$cells using immunoaffinity Dynabeads. Each cell type was prepared for mass spectrometry analysis (Thermo Q Exactive Plus), by a filter-aided sample preparation (FASP) method. MS data was searched against a human isoform database derived from UNIPROT using the Matrixscience MASCOT, and MaxQuant search engines. Differentially expressed proteins were filtered by requiring 2 peptides pr. protein, ANOVA (P-value) cutoff 0.05, q-value (false discovery adjusted p-value using multiple hypothesis testing) cutoff 0.05, and a power of at least 80%. The method was validated using known expression responses to IL6 inhibition. While responses have been shown via array and RT-qPCR, we obtained a broader quantitative differential protein expression profile.

Results: The initial results provided the identification of 4258 different proteins obtained by combining 3 technical replicates of the

5 cell types. In brief, several pro-inflammatory proteins were down regulated, while anti-inflammatory proteins were up regulated. For example in $CD14^+$cells, interferon-induced guanylate-binding protein 1 (belonging to the TRIFF pathway), and CXCL2 (also known as macrophage inflammatory protein 2-α) were relatively down regulated by 8.04 fold and 1.14*10$\hat{4}$ fold, respectively while TGFβ was up regulated by 16.8 fold. Myeloid differentiation primary response protein (MyD88) was relatively down regulated by 2.3 fold, which could be explained by IL6 inhibition. The down regulation of both the TRIFF pathway, and MyD88 indicates a down regulation of CD14 (monocyte differentiation antigen) dependent signaling, and hence a reduction in the NFκB signaling and TNFα production. Of note, we found that STAT6 was relatively down regulated by 4.7 fold, which has recently been suggested to correlate with decreased CD14 signaling in CD14−/− mice.

Conclusion: Our proteomics driven strategy enable detection and mapping of valuable information of pro-, and anti-inflammatory responses to IL6 inhibition treatment on the protein level. This detailed insight into in vivo individual cell responses in patients will improve diagnostic and treatment optimization and drive personalized medicine. Our method may reveal hidden mechanisms in treatment success or failure.

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Elevated Peripheral Blood Leukocyte Inflammatory Gene Expression in Radiographic Progressors with Symptomatic Knee Osteoarthritis: NYU and OAI Cohorts. Mukundan Attur[1], Alexander Statnikov[1], Svetlana Krasnokutsky Samuels[1], Virginia B. Kraus[2], Joanne Jordan[3], Braxton D. Mitchell[4], Michelle Yau[5], Jyoti Patel[1], Constantin F. Aliferis[1], Marc C. Hochberg[4], Jonathan Samuels[1] and Steven B. Abramson[1]. [1]NYU Langone Medical Center, New York, NY, [2]Duke University Medical Center, Durham, NC, [3]The University of North Carolina at Chapel Hill, Chapel Hill, NC, [4]University of Maryland School of Medicine, Baltimore, MD, [5]University of Maryland, Baltimore, MD.

Background/Purpose: We and others have demonstrated low grade inflammation exists in OA joint tissues, where it may contribute to disease pathogenesis. In the current studies we assessed whether inflammatory events occurring within joint tissues were reported in the peripheral blood leukocytes (PBLs) of patients with symptomatic knee OA (SKOA).

Methods: PBL inflammatory gene expression (IL-1, TNFα, COX-2) was assessed in two independent cohorts of patients with SKOA, and a cohort of healthy control subjects: 1) 111 patients with tibiofemoral medial OA and 21 healthy volunteers from the NYUHJD Cohort, and 2) 200 patients from the OAI progression cohort who had "high quality radiographs", at both baseline and 24 months, and had KL2 or 3 in the signal knee at baseline. Radiographic progression was defined as narrowing of medial joint space width (JSW) in the signal knee between baseline and 24-months in each cohort. Fast progressors were defined as subjects who had JSN >0.5mm over 24 months. For measuring predictive performance, we used the area under the curve (AUC) of a receiver operating characteristics (ROC). OAI SKOA subjects were dichotomized as radiographic non-progressors (JSN <0.0 mm) and progressors (JSN >0.0mm) for association studies.

Results: Elevated PBL expression of IL-1, TNFα or COX-2 at baseline identified SKOA patients who were "fast progressors" (mean JSN 0= 0.71, 0.75 and 0.71 mm / 24 months, respectively) compared to patients with levels below the median (Table 1). In a multivariable model, anthropometric traits alone (BMI, gender, age) did not predict progression, whereas addition of PBL gene expressions improved prediction of fast progressors (JSN >0.5mm). We next examined inflammatory gene expression in PBLs of radiographic progressors in the OAI cohort. Similar to the NYUHJD cohort, elevated expression of IL-1β, TNFα and COX-2 mRNA at baseline distinguished radiographic progressors from non-progressors (Table 2).

Conclusion: We identified, and confirmed in two cohorts, increased inflammatory gene expression (IL-1, TNFα or COX-2) by PBLs that predict radiographic progression in patients with SKOA. The data indicate that inflammatory events within joint tissues of patients with SKOA are reported in the peripheral blood. These PBL transcriptome signals of local joint inflammation merit further study as potential biomarkers for OA disease progression.

Table 1 Association of PBL transcriptome IL-1β, TNFα and COX-2 (relative gene expression levels were dichotomized by median), with joint space narrowing (JSN) at 24 months in NYUHJD cohort.

	IL-1β (PBL mRNA)			TNFα (PBL mRNA)			COX-2 (PBL mRNA)		
	OA^{IL-1} (n = 54)	OA^{n} (n = 55)	*p value*	$OA^{TNF\alpha}$ (n = 54)	OAnl (n = 55)	*p value*	OA^{COX-2} (n = 54)	OA^{nl} (n = 55)	*p* value
Baseline									
Medial knee JSW (mm)	3.85 (1.39)	3.46 (1.29)	0.13	3.60 (1.28)	3.70 (1.45)	0.71	3.76 (1.43)	3.55 (1.27)	0.42
24 month									
Medial knee JSW (mm)	3.14 (1.58)	3.12 (1.49)	0.93	2.85 (1.58)	3.41 (1.43)	0.06	3.05 (1.57)	3.21 (1.49)	0.57
JSN (mm)	0.71 (0.93)	0.34 (0.82)	0.032*	0.75 (1.03)	0.30 (0.67)	0.007*	0.71 (0.90)	0.34 (0.86)	0.027*

Table Area under the curve (AUC) of a receiver operating characteristics (ROC) of PBL inflammatory gene expression for distinguishing radiographic progressors from non-progressors in the OAI cohort. For multivariable models, we used 10-fold stratified cross-validation repeated with 100 different splits of data into 10-folds.

Progressors (JSN>0.0mm) vs. non-progressors (JSN<0.0mm)	AUC	CI	p value
IL-1β	0.781	0.71–0.85	<0.0001
TNFα	0.692	0.61–0.77	<0.0001
COX-2	0.664	0.58–0.75	<0.0001
IL-1β + TNFα + COX-2	0.813		<0.0001

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***HLA-DPB1*04:01* Confers Risk for PR3-ANCA Positive ANCA-Associated Vasculitis (AAV), but Protects Against MPO-ANCA Positive AAV, in a Japanese Population.** Aya Kawasaki[1], Misaki Hidaka[1], Narumi Hasebe[1], Ken-ei Sada[2], Shigeto Kobayashi[3], Hidehiro Yamada[4], Hiroshi Furukawa[5], Kunihiro Yamagata[1], Takayuki Sumida[1], Nobuyuki Miyasaka[6], Shigeto Tohma[5], Shoichi Ozaki[4], Seiichi Matsuo[7], Hiroshi Hashimoto[8], Hirofumi Makino[2], Masayoshi Harigai[6] and Naoyuki Tsuchiya[1]. [1]Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [2]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, [3]Juntendo University Koshigaya Hospital, Tokyo, Japan, [4]St. Marianna University School of Medicine, Kawasaki, Japan, [5]Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan, [6]Tokyo Medical and Dental University, Tokyo, Japan, [7]Nagoya University Graduate School of Medicine, Nagoya, Japan, [8]Juntendo University School of Medicine, Tokyo, Japan.

Background/Purpose: Epidemiologic difference between European and Asian populations is observed in antineutrophil cytoplasmic antibody (ANCA) – associated vasculitis (AAV). Granulomatosis with polyangiitis (GPA) is prevalent in European populations, while microscopic polyangiitis (MPA) is common in Japanese. Genetic factors appear to contribute to the difference in epidemiology, which was supported by a recent genome-wide association study (GWAS) (Lyons et al., 2012). The GWAS indicated that GPA / proteinase 3 (PR3)-ANCA was associated with *HLA-DP* region, whereas MPA / myeloperoxidase (MPO) – ANCA was associated with *HLA-DQ* region. These results were consistent with the previous studies showing the association of GPA with *HLA-DPB1*04:01* in European populations, as well as our study that reported *HLA-DRB1*09:01-DQB1*03:03* haplotype was associated with MPA in Japanese (Tsuchiya et al., 2006). However, due to the rarity of AAV, contribution of *HLA-DPB1* to either MPA or GPA has not been reported in a Japanese population.

In this study, by means of multicenter collaborative study in Japan, we investigated whether *HLA-DPB1* is associated with susceptibility to AAV in Japanese, and whether the differences in *HLA-DPB1* allele frequency can in part account for the population difference in AAV subsets.

Methods: Association of *HLA-DPB1* was examined in 356 Japanese patients with AAV and 580 healthy controls. According to the European Medicines Agency algorithm, 220 patients were classified as MPA, 69 as GPA and 35 as eosinophilic granulomatosis with polyangiitis (EGPA). Among the patients, 300 were positive for MPO-ANCA and 41 were positive for PR3-ANCA. *HLA-DPB1* typing was performed by the PCR-SSOP (Sequence Specific Oligonucleotide probes) method.

Results: *HLA-DPB1*04:01*, which was reported to be a risk allele to GPA in European populations, is decreased in MPA (dominant model,

P=0.031, odds ratio [OR] 0.53), and more strikingly in MPO-ANCA positive AAV (P=0.0026, OR 0.44). *DPB1*05:01* was also decreased in MPA (allele model, P=0.0063, OR 0.72). On the other hand, *DPB1*04:01* was increased in PR3-ANCA positive AAV (allele model, P=0.010, OR 2.38). Interestingly, although significant association was not detected in GPA as a whole, *DPB1*04:01* was significantly increased when only PR3-ANCA positive GPA was examined (P=5.7E-4, OR 3.18), but not in MPO-ANCA positive GPA.

Conclusion: This study demonstrated that *DPB1*04:01* is a risk allele to PR3-ANCA positive AAV also in the Japanese population. In contrast. *DPB1*04:01* was protective against MPO-ANCA positive AAV. In view of the population difference in the *DPB1*04:01* allele frequency in the Japanese (6.1%) and in the European populations (42.5% in USA, The Allele Frequency Net Database), *DPB1*04:01* may in part account for the epidemiological difference in the prevalence of MPO-ANCA and PR3-ANCA positive AAV, in addition to the *DRB1*09:01-DQB1*03:03* haplotype.

Table 1 Association of *DPB1*04:01* with AAV in a Japanese population

	n	Allele frequency	P	OR (95%CI)	Carrier frequency	P	OR (95%CI)
MPA	220	16 (0.036)	0.050	0.58 (0.33–1.00)	15 (0.068)	0.031	0.53 (0.30–0.95)
GPA	69	12 (0.087)	0.24	1.46 (0.77–2.76)	10 (0.145)	0.56	1.23 (0.60–2.52)
MPO+ GPA	39	2 (0.026)	0.32	0.40 (0.10–1.68)	2 (0.051)	0.30	0.39 (0.09–1.67)
PR3+ GPA	32	11 (0.172)	5.7×10^{-4}	3.18 (1.65–6.15)	9 (0.281)	0.0084	2.85 (1.31–6.21)
MPO+ AAV	300	18 (0.030)	0.0046	0.47 (0.28–0.79)	17 (0.057)	0.0026	0.44 (0.26–0.75)
PR3+ AAV	41	11 (0.134)	0.010	2.38 (1.23–4.60)	9 (0.220)	0.066	2.05 (0.95–4.41)
Healthy control	580	71 (0.061)		70 (0.121)			

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Whole Exome Sequencing Analysis Performed on a Patient with Fibroblastic Rheumatism. Michal Feldon MD[1], Keith A. Sikora[1], John B. Harley[2], Jennifer L. Huggins[1], Hermine I. Brunner[3] and Kenneth M. Kaufman[4]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center; US Department of Veterans Affairs Medical Center, Cincinnati, OH, [3]PRCSG, Cincinnati, OH, [4]Cincinnati Children's Hospital Medical Center and the University of Cincinnati, Cincinnati, OH.

Background/Purpose: Fibroblastic Rheumatism is a rare disease, first described in 1980 with almost 30 cases reported thus far. One-third of the patients are children. The disease is characterized by sudden and rapidly progressive symmetric arthritis in large and small joints with cutaneous nodules over hands and para-articular sites. Sclerodactyly with thickened palmar fascia and Raynaud's phenomenon can also be seen. Laboratory tests are usually normal and the diagnosis is based on the histology of the nodules. The etiology of the disease is unknown and no genetic testing has been published on patients with fibroblastic rheumatism to date.

The objective of this study was to identify possible causative candidate genes for this disease using whole exome sequencing.

Methods: We performed exome sequencing analysis on the DNA of a 14 year old patient with biopsy-proven fibroblastic rheumatism and her unaffected brother. It was performed at Perkin Elmer DNA Sequencing and Analysis Branford, CT. Target enrichment was performed using Illumina TruSeq Exome capture. Sequencing was performed on an Illumina HiSeq 2000. Alignment and variant calls were made using the Broad Institute's Genome Analysis Toolkit (GATK). Variant calls were analyzed using Golden Helix SNP and Variation Suite ver 7.7.5.

We focused on candidate variations that altered the amino-acid sequence of a protein and followed either a recessive homozygous, compound heterozygous or dominant model. Genotypes common with the unaffected sibling were removed as candidates.

Results: After quality control filtering and requiring a minor allele frequency of ≤1% in the general population, we identified 191 different candidate variations. Of those, 156 mutations fit a dominant model in which the patient was heterozygous for the polymorphism; 6 were recessive homozygous and 29 were compound heterozygous variants in 14 genes.

Several interesting candidate genes causing variants in the dominant model were identified (Table).

Conclusion: Although we did not identify one strong candidate gene, these results will form a basis for comparison to variants identified in other patients. If this is, indeed, a disorder with genetic etiology, we believe the identification of one responsible gene can assist in future genetic research of other arthritic syndromes.Table

Mutation	Gene name	Amino acid	Protein function	Related to disease
1:151804213 Stopgain	RORC [RAR related orphan receptor C]	Arg10	DNA-binding transcription factor and member of the NR1 subfamily of nuclear hormone receptors. In mice this gene inhibits the expression of FAS ligand and IL2	Dermatitis; one suspect gene for Systemic lupus Erythematosus (SLE).
4:99027142 Stopgain	C4orf37/STPG2 [Sperm-Tail PG-Rich Repeat-Containing 2]	Arg192	No known function	Rheumatoid arthritis and response to anti TNF alpha medication
1:201182308 Stopgain	IGFN1 [immunoglobulin-like and fibronectin type III domain containing 1]	Gln2763	protein-coding gene	Muscular dystrophy; bone repair.
5:70860710 Stoploss	BDP1/PTPN18 [Protein Tyrosine Phosphatase, Non-Receptor Type 18]	Glu12	The protein encoded by this gene is a member of the protein tyrosine phosphatase (PTP) family. The encoded protein localizes to aggregates in the nucleus, and is required for transcription from all three types of polymerase III promoters	Rheumatoid arthritis and response to anti TNF alpha medication; Pyoderma gangrenosum

Disclosure: M. Feldon MD, None; **K. A. Sikora**, None; **J. B. Harley**, None; **J. L. Huggins**, None; **H. I. Brunner**, None; **K. M. Kaufman**, None.

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Amerindian Ancestry Influences Polyautoimmunity. Nicolás Molano-González, John Castiblanco, Ruben-Dario Mantilla, Adriana Rojas-Villarraga and Juan-Manuel Anaya. Center for Autoimmune Diseases Research (CREA), Universidad del Rosario., Bogota, Colombia.

Background/Purpose: Polyautoimmunity [i.e., the presence of two or more autoimmune diseases (ADs) in a single patient] is a frequent phenomenon in autoimmunity, ranging from 10% to 40%. Since polyautoimmunity is most frequently observed in Latin Americans than in Europeans and the diverse population of Latin America and the Caribbean is a powerful resource for elucidating the genetic basis of complex traits due to its high admixture, we aimed to study the effect of ancestry on polyautoimmunity in a Latin American population.

Methods: A total of 508 subjects were examined [240 cases with a single AD, 87 with polyautoimmunity, of whom 36 presented with multiple autoimmune syndromes (MAS, i.e., 3 or more ADs), and 181 matched-controls with no AD]. Genotyping of 32 ancestry informative markers was performed. The individual admixture profile was built in STRUCTURE 2.3.4 by using data of people from known ethnic groups: African (n=148), European (n=160) and Native American (n=278). Different models were calculated varying the number of ancestral populations. The estimated logarithm P(X⎮ and the mean value of the log-likelihood were used to choose the most parsimonious model. Ancestry differences between cases (AD, polyautoimmunity and MAS) and controls were assessed by a MANOVA model on ARL transformed ancestral profiles, and fitted in R software 3.0.2.

Results: A high European profile (50%) followed by a similar contribution of the remaining ancestral populations (African 26%, Amerindian 24%) was observed in the studied population. Significant differences of ancestry profiles among the four groups analyzed were detected (Pillai test, p-value: 0.001). The MAS group carried a higher Amerindian composition than the other three groups (p-value: 0.01) along with a lesser European ancestry (p-value: 0.003).

Conclusion: The Amerindian ancestry component affect the development of polyautoimmunity. These results increase the understanding of genetics of autoimmunity and may contribute to design strategies to characterize patients at risk of polyautoimmunity.

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Protective Association of *HLA-DRB1*13:02* Against MPO-ANCA Positive ANCA-Associated Vasculitis in a Japanese Population. Naoyuki Tsuchiya[1], Narumi Hasebe[1], Ken-ei Sada[2], Shigeto Kobayashi[3], Hidehiro Yamada[4], Hiroshi Furukawa[5], Kunihiro Yamagata[1], Takayuki Sumida[1], Nobuyuki Miyasaka[6], Seiichi Matsuo[7], Shigeto Tohma[5], Shoichi Ozaki[4], Hiroshi Hashimoto[8], Hirofumi Makino[2], Masayoshi Harigai[6] and Aya Kawasaki[1]. [1]Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [2]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, [3]Juntendo University Koshigaya Hospital, Tokyo, Japan, [4]St. Marianna University School of Medicine, Kawasaki, Japan, [5]Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan, [6]Tokyo Medical and Dental University, Tokyo, Japan, [7]Nagoya University Graduate School of Medicine, Nagoya, Japan, [8]Juntendo University School of Medicine, Tokyo, Japan.

Background/Purpose: Epidemiology of antineutrophil cytoplasmic antibody (ANCA) – associated vasculitis (AAV) is substantially different between European and Asian populations. In the Japanese population, the majority of AAV patients are positive for myeloperoxidase (MPO) – ANCA. In studies with a small sample size, we previously reported significant association of *HLA-DRB1*09:01-DQB1*03:03*, a haplotype common in Asians but rare in other populations, with MPO-ANCA positive AAV (Tsuchiya et al., 2003; Tsuchiya et al., 2006). In the present study, we substantially increased the sample size, and compared *HLA-DRB1* associations among AAV subgroups, and also made an attempt to detect other *DRB1*alleles associated with risk or protection.

Methods: *HLA-DRB1*genotypes were determined by using WAK Flow HLA-typing kit (Wakunaga, Hiroshima, Japan) in 356 Japanese AAV and 596 healthy controls. Among the patients, 220 were classified as microscopic polyangiitis (MPA), 69 as granulomatosis with polyangiitis (GPA), 35 as eosinophilic granulomatosis with polyangiitis (EGPA), and 32 were unclassifiable, according to the European Medicines Agency algorithm. Among all patients, 300 were positive for myeloperoxidase (MPO)-ANCA and 41 for proteinase 3 (PR3)-ANCA. The second risk allele and protective allele were examined by relative predispositional effects (RPE) method. Bonferroni correction was employed to correct for the number of compared alleles.

Results: Positive association of *DRB1*09:01* carrier frequency was confirmed in MPA (P=0.0036, Pc=0.0076, odds ratio [OR] 1.81). In addition, significant negative association with *DRB1*13:02* was detected in MPA (P=0.001, Pc=0.0244, OR 0.43). In GPA, tendency toward positive association was detected in *DRB1*08:02* (P=0.031, Pc=0.65, OR 2.56) and negative association in *DRB1*13:02* (P=0.037, Pc=0.77, OR 0.38). The associations were more striking when the patients were classified according to the specificity of ANCA. In MPO-ANCA positive patients, *DRB1*09:01* was increased ($P=2.3x10^{-5}$, $Pc=4.8x10^{-4}$, OR 1.89), while *DRB1*13:02* was decreased ($P=3.7x10^{-5}$, $Pc=7.8x10^{-4}$, OR 0.38). RPE method confirmed negative association of *DRB1*13:02* ($P_{RPE}=7.3x10^{-4}$, OR_{RPE} 0.47), and also suggested *DRB1*08:02* as the second risk allele ($P_{RPE}=0.025$, OR_{RPE} 1.82). In PR3-ANCA positive patients, suggestive association was observed for *DRB1*11:01* (P=0.021, Pc=0.65, OR 3.80), but not for *DRB1*09:01* (P=0.86, OR 1.02). Genotype comparison suggested that carriage of *DRB1*13:02* cancels the risk of *DRB1*09:01* to MPO-ANCA positive AAV in **09:01/*13:02* heterozygotes.

Conclusion: *DRB1*09:01* is associated with MPO-ANCA positive, but not with PR3-ANCA positive, AAV. Because *DRB1*09:01* is a very common *HLA-DRB1* allele in East Asian bur rare in European populations, such a difference in the genetic background may be associated with the difference in the prevalence of MPO-positive and PR3-positive AAV in both populations. In addition, *DRB1*13:02* was identified as a protective allele against MPO-ANCA positive AAV.

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Association of Leukocyte Immunoglobulin-like Receptor A3 (*LILRA3*) with Systemic Sclerosis. Yuki Hachiya[1], Aya Kawasaki[1], Takashi Matsushita[2], Hiroshi Furukawa[3], Shouhei Nagaoka[4], Kota Shimada[5], Shoji Sugii[5], Takayuki Sumida[1], Shigeto Tohma[3], Minoru Hasegawa[6], Manabu Fujimoto[1], Shinichi Sato[7], Kazuhiko Takehara[2] and Naoyuki Tsuchiya[1]. [1]Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [2]Kanazawa University, Kanazawa, Japan, [3]Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan, [4]Yokohama Minami Kyousai Hospital, Yokohama, Japan, [5]Tokyo Metropolitan Tama Medical Center, Tokyo, Japan, [6]University of Fukui, Yoshida-gun, Fukui, Japan, [7]The University of Tokyo, Tokyo, Japan.

Background/Purpose: The leukocyte immunoglobulin-like receptors (*LILRs*) are a gene family located in leukocyte receptor complex at 19q13.4. LILRs are expressed mainly in immune cells as transmembrane receptors, and some of LILRs have been shown to regulate immune cell activation. LILRA3 is the only secreted protein among LILRs, but its function remains unclear. Furthermore, *LILRA3* has a 6.7-kb deletion polymorphism which lacks most of the coding region, and its frequency is especially high in the East Asian populations (71.0% in the Japanese, 18.5% in the German)(Hirayasu et al., 2006, Koch et al., 2005). Previous studies in European populations reported association of the deletion allele with multiple sclerosis (MS) (Koch et al., 2005) and Sjögren's syndrome (SS) (Kabalak et al., 2009), while recent studies from China reported association of homozygous non-deletion genotype with rheumatoid arthritis (Du et al., 2014a), systemic lupus erythematosus (SLE) and SS (Du et al., 2014b). In this study, we examined whether *LILRA3* deletion polymorphism is associated with systemic sclerosis (SSc) in a Japanese population.

Methods: 373 Japanese patients with SSc and 867 healthy Japanese controls were examined. All patients fulfilled the American College of Rheumatology criteria. 124 were classified as having diffuse cutaneous (dc) SSc, while 201 as limited cutaneous (lc) SSc from available clinical data, according to the classification by LeRoy et al. 82 were positive for anti-topoisomerase 1 antibody (ATA+) and 158 for anti-centromere antibody (ACA+). Six patients were positive for both ATA and ACA. 140 patients were classified as having interstitial lung disease (ILD) based on high resolution CT. The *LILRA3* deletion was genotyped by PCR-sequence specific primers. This study was reviewed and approved by the ethics committees of each participating institute. Informed consent was provided by all subjects.

Results: We observed higher frequency of *LILRA3* deletion in ATA+ SSc patients compared with healthy controls (P=0.015, OR= 1.68 under the allele model, P=0.014, OR=1.83 under the recessive model) (Table1). This association was not observed in ACA+ SSc. In the case-only analysis, the deletion allele frequency of ATA+ACA- SSc was significantly increased when compared with ATA-ACA+ SSc (P=0.0094, OR=1.93).

Conclusion: Our study demonstrated the first evidence for the association between the *LILRA3* deletion and ATA+ SSc. The risk allele was in agreement with that of MS and SS in the German population, but was the opposite to that of RA and SLE in the Chinese population. This study supported the association of *LILRA3* with genetic susceptibility to multiple autoimmune diseases, and its role requires further study.

Table 1. Association between *LILRA3* deletion polymorphism and SSc

	n	Genotype frequency			del allele frequency	Allele model		Recessive model		Dominant model	
		−/− (%)	+/− (%)	+/+ (%)	(%)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)
all SSc	373	228 (61.1)	125 (33.5)	20 (5.4)	77.9	0.060	1.22 (0.99–1.49)	0.065	1.26 (0.99–1.62)	0.34	1.29 (0.77–2.17)
dcSSc	124	78 (62.9)	41 (33.1)	5 (4.0)	79.4	0.083	1.33 (0.96–1.85)	0.12	1.36 (0.92–2.00)	0.24	1.74 (0.69–4.37)
lcSSc	201	121 (60.2)	65 (32.3)	15 (7.5)	76.4	0.40	1.12 (0.87–1.44)	0.22	1.21 (0.89–1.66)	0.74	0.91 (0.50–1.63)
ATA+	82	57 (69.5)	22 (26.8)	3 (3.7)	82.9	0.015	1.68 (1.11–2.54)	0.014	1.83 (1.13–2.97)	0.27	1.92 (0.60–6.15)
ACA+	158	86 (54.4)	59 (37.3)	13 (8.2)	73.1	0.64	0.94 (0.72–1.23)	0.81	0.96 (0.68–1.35)	0.52	0.81 (0.44–1.52)
ILD+	140	87 (62.1)	48 (34.3)	5 (3.6)	79.3	0.076	1.32 (0.97–1.80)	0.14	1.32 (0.91–1.90)	0.15	1.97 (0.79–4.92)
HC	867	481 (55.5)	327 (37.7)	59 (6.8)	74.3	ref		ref		ref	

−: deletion allele, +: non-deletion allele, OR: odds ratio, 95%CI: 95% confidence interval. dcSSc: diffuse cutaneous SSc, lcSSc: limited cutaneous SSc, ATA+: anti-topoisomerase I antibody positive SSc, ACA+: anti-centromere antibody positive SSc, ILD+: SSc with interstitial lung disease, HC: healthy controls. allele model: comparison of – vs +, recessive: comparison of −/− vs (+/− or +/+), dominant: comparison of (−/− or +/−) vs +/+.

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Association of *TRIM21* (*RO52*) Polymorphisms with Systemic Lupus Erythematosus in a Japanese Population. Misaki Hidaka[1], Aya Kawasaki[1], Hiroshi Furukawa[2], Yuya Kondo[1], Satoshi Ito[3], Isao Matsumoto[1], Makio Kusaoi[4], Hirofumi Amano[4], Akiko Suda[5], Keigo Setoguchi[6], Tatsuo Nagai[7], Kota Shimada[8], Shoji Sugii[8], Akira Okamoto[9], Noriyuki Chiba[10],

Eiichi Suematsu[11], Masao Katayama[12], Akiko Okamoto[13], Hajime Kono[13], Shigeru Ohno[5], Shunsei Hirohata[7], Shouhei Nagaoka[14], Yoshinari Takasaki[15], Hiroshi Hashimoto[15], Shigeto Tohma[2], Takayuki Sumida[1] and Naoyuki Tsuchiya[1]. [1]Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [2]Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan, [3]Niigata Rheumatic Center, Shibata, Japan, [4]Juntendo University, Tokyo, Japan, [5]Yokohama City University Medical Center, Yokohama, Japan, [6]Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan, [7]Kitasato University School of Medicine, Sagamihara, Japan, [8]Tokyo Metropolitan Tama Medical Center, Tokyo, Japan, [9]Himeji Medical Center, National Hospital Organization, Himeji, Japan, [10]Morioka Hospital, National Hospital Organization, Morioka, Japan, [11]Clinical Research Institute, Kyushu Medical Center, National Hospital Organization, Fukuoka, Japan, [12]Nagoya Medical Center, National Hospital Organization, Nagoya City, Aichi, Japan, [13]Teikyo University School of Medicine, Tokyo, Japan, [14]Yokohama Minami Kyousai Hospital, Yokohama, Japan, [15]Juntendo University School of Medicine, Tokyo, Japan.

Background/Purpose: TRIM21, also referred to as Ro52 or SS-A1, belongs to the tripartite motif-containing (TRIM) family. TRIM21 is not only important as an autoantigen, but also as a component of the signaling pathway relevant to the disease processes of autoimmune rheumatic diseases. TRIM21 is induced by type I interferon, ubiquitylates proteins of the interferon-regulatory factor (IRF) family, and regulates type I interferon and proinflammatory cytokines. Furthermore, TRIM21 has also been reported to function as an intracellular Fc receptor. To date, it is not clear how these different aspects of TRIM21 are functionally related. Until now, several very small scale studies suggested the association of some SNPs in *TRIM21* with susceptibility to systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS). However, to our knowledge, systematic association study covering all the tagSNPs has not been reported. In this study, we conducted a systematic association study between SLE and*TRIM21*in a Japanese case-control set with more than 1,000 individuals.

Methods: Nine tagSNPs in *TRIM21* region were selected based on JPT HapMap data with the criteria of minor allele frequency > 0.05 and r^2 threshold of 0.80. 530 Japanese SLE and 518 healthy Japanese controls were genotyped for the tagSNPs using TaqMan allele discrimination assay, and case-control association study was performed. Prediction of functional relevance of the SNPs was done by using SNP Function Prediction (FuncPred) website (http://snpinfo.niehs.nih.gov/snpinfo/snpfunc.htm). This study was reviewed and approved by the ethics committees of each participating institute. Informed consent was provided by all subjects.

Results: Among the 9 tagSNPs, association was detected in 3 SNPs. At rs7947461 in intron 1, the frequency of T allele (P=0.04, odds ratio [OR] 0.76, 95% confidence interval [CI] 0.58–0.98) and that of the T/T genotype (P=0.04, OR 0.72, 95% CI 0.53–0.99) were decreased. At rs9261010 in exon 2 coding for a synonymous substitution, T allele frequency (P=0.04, OR 0.81, 95%CI 0.67–0.99) and T/T genotype frequency (P=0.05, OR 0.62, 95% CI 0.39–1.00) were decreased. Furthermore, at rs4144331 in the 3' untranslated region (UTR), decrease in T allele frequency (P=0.04, OR 0.76, 95%CI 0.58–0.98) and in T/T genotype frequency (P=0.04, OR 0.75, 95% CI 0.56–0.99) were observed. A bioinformatic analysis predicted that rs4144331 may affect binding of miRNA hsa-miR-1300.

Conclusion: These results suggested that of *TRIM21* polymorphisms may be associated with susceptibility to SLE. Further replication studies as well as functional studies are required.

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Microbiomes of Inflammatory and Non-Inflammatory Thoracic Aortic Aneurysms. Pauline Funchain*[1], Gary S. Hoffman*[2], Lars Svensson[3], Eric Roselli[3], Gosta Pettersson[3], Douglas Johnston[3], Edward Soltesz[3], Ritu Chakravarti[4], Alison Clifford[3] and Charis Eng[5]. [1]Genomic Medicine Institute, Lerner Research Institute, Cleveland, OH, [2]Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, OH, [3]Cleveland Clinic Foundation, Cleveland, OH, [4]Cleveland Clinic, Cleveland, OH, [5]Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH.

Background/Purpose: Aortitis may occur in the context of multifocal large and medium-sized vessel diseases such as giant cell arteritis (GCA) or Takayasu arteritis (TAK) and as an isolated focal finding (focal idiopathic aortitis, FIA). In each setting, the aortic root and arch are the most common locations for aortic injury that is presumed to be autoimmune. It is not clear whether the propensity to affect the proximal aorta in these diseases suggests common pathways in pathogenesis that could include infection, abnormalities in immune tolerance or response, presence of neo-antigens, or alterations in substrate microbiome. A better understanding of disease pathogenesis may lead to new therapies and improved outcomes. Thus, we sought to describe the microbiome of inflammatory and non-inflammatory thoracic aortic aneurysms (TAA).

Methods: Patients with TAA who underwent surgical reconstruction were prospectively enrolled over a period of 3 years. TAA specimens were sterilely collected and snap frozen. Clinicopathologic data were gathered on all patients. Patients who had histologic evidence of inflamed aortas and diagnoses of GCA, TAK or who were found at surgery to have FIA were matched by age, gender and race to patients with non-inflammatory lesions including bicuspid aortic valves, chronic hypertension, Marfan syndrome and other causes of cystic medial degeneration. Total DNA, including human and bacterial, was isolated from TAA. V1–4 regions of the gene encoding bacteria-specific 16S rRNA were amplified and Sanger sequenced. Principal-coordinate analysis (PCoA) plots were created based on de novo operational taxonomic unit classification via the MacQIIME 1.7 toolkit. Hierarchical taxonomic composition of sequences was performed using a custom pipeline and visualized with Krona.

Results: Twenty-seven TAA were analyzed: 7 GCA, 5 FIA, 2 TAK, and 13 non-inflammatory. Hypertension and hyperlipidemia were the most common comorbidities, and were not significantly different between inflammatory and non-inflammatory groups. All TAA hosted bacterial communities of varying abundance. Autoimmune-associated TAA microbiomes cluster on PCoA plots according to type of aortitis, with the clearest separation seen between FIA and TAK samples. GCA and non-inflammatory TAA microbiomes overlap on PCoA plots, but are separate from FIA and TAK. Both GCA and non-inflammatory TAA microbiomes appear to contain sub-group clusters. Gross visualization of taxonomic composition using Krona plots shows differences between GCA specimens compared to non-inflammatory samples at the phyla level, with a tendency toward increased Proteobacteria, decreased Actinobacteria, and minimal Bacteroidetes in GCA. Overall, TAA microbiomes did not show clustering by age, sex, or prednisone use. Some clustering was seen with tobacco use.

Conclusion: TAA are not sterile. Specimens from patients with different disease associations host distinct microbial communities. Further analysis is needed to assess whether differences in microbial communities play etiologic roles or are secondary results of different types of aortic injury.

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Global miRNA Expression Profiling in Peripheral Blood and Synovial Fluid Mononuclear Cells of Patients with Enthesitis Related Arthritis. Sushma Singh, Ramnath Misra and Amita Aggarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: Enthesitis related arthritis (ERA) is the most common category of JIA in India. MicroRNA dysregulation has been associated with arthritis and autoimmune diseases. In rheumatoid arthritis (RA) over-expression of miR-146a, miR-155 miR-132 and miR-16 has been found in PBMC. Data on miRNA profiling in serum of patients with systemic lupus erythematosus (SLE) shows over-expression of miR-142-3p and miR-181a whereas miR-106a, miR-17, miR-20a, miR-203, and miR-92a were found to be down-regulated. No such data is available in case of ERA. Thus we studied global miRNA expression profile of ERA patients using peripheral blood mononuclear cells and synovial fluid mononuclear cells (PBMCs and SFMCs). PBMCs from healthy subjects were used as controls.

Methods: Total RNA was isolated from PBMCs and SFMCs of ERA patients (n= 8 each) and PBMCs of healthy controls (n= 8). miRNA profiling was done using Agilent Human miRNA Microarray G4470A chips. Log_2-transformed expression values of miRNAs were analysed using RMA algorithms. Differential expression analyses were done using Empirical Bayes moderated t statistics. Highly dysregulated miRNAs were validated by quantitative RT-PCR by comparing fold change (in relation to Let-7a as internal control) in 13 PBMCs with 11 SFMCs from ERA patients. Targets of

dysregulated miRNAs were predicted by computational analysis using databases like DIANA LAB, miR Base, Target Scan, etc.

Results: The miRNAs profiling of ERA PBMCs were not significantly different from healthy controls. While comparing ERA SFMCs 38 miRNAs were down-regulated and 52 were up-regulated at cut offs of 0.05 as compared to ERA PBMCs. Among them miR-34a, miR-210, miR-29b, miR-155, miR-21, miR-27a, miR-132, miR-140-5p, miR-15a, and miR-660 were upregulated and miR-146a, miR-126, miR-130a, miR-150, miR-26a, miR-23b, miR-199a, miR-451, miR-151 and miR-221 were down-regulated in SFMCs. Among these 5 down-regulated and 5 up-regulated miRNAs were validated by RT-PCR using 11 ERA SFMCs and 13 ERA PBMCs.The comparison of fold change between ERA SFMCs and ERA PBMCs (p value) of dysregulated miRNAs showed: miR-34a ($p=$**0.035**), miR-210 ($p=0.424$), miR-29b ($p=0.865$), miR-155 ($p=0.072$), miR-21 ($p=$**0.047**), miR-146a ($p=$**0.006**), miR-126 ($p<$**0.001**), miR-130a ($p<$**0.001**), miR-150 ($p=0.150$) and miR-26a ($p=$**0.011**). The targets of dysregulated miRNAs formed a part of multiple immune pathways like MAPK signaling pathways, TLR signaling pathways, T cell receptor signaling pathways, mTOR signaling pathways, Wnt signaling pathways, etc.

Conclusion: ERA SFMC has a distinct miRNA gene expression profile compared to ERA PBMCs. miR-34a and miR-21 are significantly up-regulated whereas miR-146a, miR-126, miR-130a and miR-26a are significantly down-regulated in ERA SFMCs and all these dysregulated miRNAs are involved in multiple immune pathways. This difference in SFMC may be related to difference in composition of cells, cytokine mileu that modulates miRNA expression as well as differential expression of miRNAs as they have feedback regulatory function.

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Genetic Variants in *IL-6, IL-10, C5-TRAF1* and *FCRL3* and Progression of Joint Damage in Rheumatoid Arthritis; A Study on Six Cohorts. H.W. van Steenbergen[1], L. Rodriguez-Rodriguez[2], E. Berglin[3], A. Zhernakova[4], R. Knevel[1], J. Ivorra-Cortes[5], T.W.J. Huizinga[1], B. Fernández-Gutiérrez[6], P.K. Gregersen[7], S. Rantapää-Dahlqvist[8] and A.H.M. van der Helm-van Mil[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Department of Rheumatology, Hospital Clínico San Carlos, Madrid, Spain, [3]Institution of Public health and clinical medicine/ Rheumatology, University of Umeå, Umeå, Sweden, [4]University Medical Center Groningen, Groningen, Netherlands, [5]University Hospital la Fe, Valencia, Spain, [6]Hospital Clínico San Carlos, Madrid, Spain, [7]The Feinstein Institute for Medical Research, Manhasset, NY, [8]Umeå University Hospital, Umeå, Sweden.

Background/Purpose: Understanding the mechanisms underlying the inter-individual differences in radiographic progression is relevant and heritability studies have shown that genetic factors explain part of these inter-individual differences. Indeed, some genetic variants have been identified and replicated in independent studies or found significant in meta-analyses. The literature on genetic variants and joint destruction in RA was systematically reviewed recently; for genetic variants in *IL-6*, *IL-10*, *C5-TRAF1*, and *FCRL3* the existing literature was indefinite on whether these variants are associated with joint destruction. We aimed to clarify associations of genetic variants in *IL-6*, *IL-10*, *C5-TRAF1* and *FCRL3* with radiographic progression by evaluating six independent cohorts.

Methods: In total 5,895 sets of radiographs of 2,493 RA patients included in the Leiden EAC, Umeå, HCSC-RAC, Wichita, NDB and NARAC cohorts were studied in relation to rs1800795 (*IL-6)*, rs1800896 (*IL-10)*, rs2900180 (*C5-TRAF1)* and rs7528684 (*FCLR3)*. Associations with radiographic progression rates were tested per cohort using an additive model, adjusting for age, gender and treatment when appropriate. The results on yearly radiographic progression rates were combined in inverse variance weighted meta-analyses. Analyses were done on the total RA population and after stratification for anti-citrullinated peptide antibodies (ACPA). Furthermore, the associated region *C5-TRAF1* was fine-mapped.

Results: No associations were found for rs1800795 (*IL-6)*, rs1800896 (*IL-10)* and rs7528684 (*FCLR3)* in the total RA population and after stratification for ACPA. Also the directionality of the effects was diverse. Although for rs2900180 in *C5-TRAF1* no significance was obtained in the total population or in ACPA-positive RA, an association was observed in ACPA-negative RA (p value meta-analysis $5.85\text{x}10^{-7}$). In all data sets with ACPA-negative RA, the minor allele was associated with more radiographic progression. Fine-mapping revealed a region of 66 Kb that was associated with radiographic progression; the lowest p-value was for rs7021880 in *TRAF1*. The p-value for rs7021880 in meta-analysis was $6.35\text{x}10^{-8}$. Previous studies indicate that the region of rs7021880 was associated with RNA expression of *TRAF1* in monocytes after lipopolysaccharide stimulation.

Conclusion: In contrast to initial reports, variants in *IL-6*, *IL-10* and *FCLR3* were not associated with radiographic progression in the present large meta-analyses. Although an association between rs2900180 in *C5-TRAF1* and joint destruction was initially identified in the total RA population, we here replicated an association of rs2900180 in *C5-TRAF1* and linked variants in a 66 Kb region with radiographic progression in ACPA-negative RA.

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Quantitative Proteomics Using Dimethyl Isotope Labeling for Comparison of Fresh Frozen Versus Formalin-Fixed, Paraffin-Embedded Tissue for Lupus Nephritis. Abhimanyu Amarnani, Joseph Capri, Puneet Souda, David Elashoff, Ivan Lopez, Julian Whitelegge and Ram Singh. University of California, Los Angeles, Los Angeles, CA.

Background/Purpose: Lupus nephritis (LN) progresses from mild focal inflammation, to diffuse proliferative nephritis, to fibrosis and end-stage renal disease. Though the understanding of LN has progressed, there is a need to use global, data-driven research methodologies to elucidate its molecular pathogenesis. As a foundation for this goal, we aimed to develop a quantitative proteomics workflow that can directly study formalin-fixed, paraffin-embedded (FFPE) archived clinical tissues. This applicable workflow could therefore provide a powerful tool to study the progression of LN, albeit if we can trust that data obtained are without substantial sample processing bias.

Methods: To obviate the need for large pieces of human LN tissue, we used kidney tissues from lupus-susceptible NZM.2328 mice that develop glomerulonephritis that mimics LN in humans. Identical transverse kidney tissue cuts from 10-month-old female NZM-2328 mice with high-grade proteinuria were processed as FFPE and fresh frozen tissue (FFT). FFPE and FFT sections were digested with trypsin and stable isotope labeled for protein identification and quantification. Our workflow includes a combination of methodologies including filter aided sample preparation (FASP), in-solution dimethyl isotope labeling, strong cation exchange StageTip fractionation, along with nano-LC MS/MS through an Orbitrap XL mass spectrometer. Two separate experiments were run where three conditions were studied in each: two exact technical replicate FFT conditions and one FFPE condition. Within our workflow, combining FASP and in-solution dimethyl isotope labeling, relative quantitative values were obtained via direct comparison of each pair of conditions within each experiment.

Results: We developed and validated a workflow that allows for a direct comparison of FFPE tissue to FFT. Through our workflow validation experiments, we observed an almost 100% protein identification overlap between FFPE and FFT from a LN kidney. A consistent identification of over 1400 proteins in both FFPE and FFT indicate no selection bias with tissue processing. Although, quantification differences did exist when comparing FFPE-to-FFT, the quantitative changes (quantification ratios) of proteins in FFPE tissues were consistent across replicate experiments. This reliability is seen with global hierarchical clustering as well as with specific protein categories such as TGFβ signaling, the KEGG SLE annotated pathway, the GSEA annotated lupus CD4 T cell vs. myeloid function upregulation, and B cell function related proteins, which have been implicated in LN pathogenesis.

Conclusion: Our methodology is the first to directly compare FFT and FFPE tissue in a manner that can be readily applied to archived clinical samples. Our results demonstrate the utility of this workflow by its ability to equally identify proteins between FFPE and FFT, minimizing sample processing bias, and by providing consistent protein quantification values of FFPE tissue between technical replicates and across separate experiments. We conclude that this clinically oriented proteomics workflow, when applied to archived, FFPE tissue can be reliably utilized to study LN pathogenesis.

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Long Noncoding RNA Nron Regulates the Activity of NFAT5 through Ubiquitin-Independent Proteasome Pathway in Rheumatoid Arthritis. Kunihiko Umekita[1], Michelle Trenkmann[1], Christoph Kolling[2], Akihiko Okayama[3], Renate Gay[1], Steffen Gay[1] and Mojca Frank Bertoncelj[4]. [1]Center of Experimental Rheumatology, University Hospital Zurich and Zurich Center of Integrative Human Physiology (ZIHP), Zurich, Switzerland, [2]Schulthess Clinic, Zurich, Switzerland, [3]University of Miyazaki, Miyazaki, Japan, [4]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: Long noncoding RNAs (lncRNAs) are increasingly recognized as master regulators of gene expression. The lncRNA NRON, noncoding repressor of nuclear factor of activated T cells (NFAT) can repress the cytoplasmic-nuclear translocation and function of NFAT1–4 transcriptional factors. Recently, we have reported that NRON regulates also the activity of NFAT5, affecting thereby the function of rheumatoid arthritis synovial fibroblasts (RASF). In addition, the ubiquitin-independent proteasome system has been shown to play an important role in regulating the cellular levels of NFAT5. Our objective was to investigate the regulation of NRON levels in RASF and to explore the role of NRON in protein turnover of NFAT5.

Methods: The levels and subcellular localization of NFAT5 protein in RASF were analyzed by Western blotting using α-tubulin for normalization. RASF were transfected with siRNA targeting NRON or scrambled siRNA using Lipofectamine 2000. RASF were treated with TNFα (10ng/ml), p38MAPK inhibitor (p38i, 10uM) SB202190, and/or proteasome inhibitor MG132 (1.0uM). Gene expression was measured by quantitative real-time PCR with normalization to GAPDH or β2-microglobulin. ELISA was used to measure IL-6 secretion from RASF.

Results: The levels of NRON were significantly decreased and the levels of NFAT5 protein were increased in RASF after 2hr of TNFα stimulation, while the levels of NFAT5 mRNA were not changed. Down regulation of NRON after silencing or TNFα stimulation was accompanied by the translocation of NFAT5 from the cytoplasm to the nucleus of RASF, increasing the transcription of known NFAT5 target genes, such as IL-6 (x-fold$\pm$SD: 3.0$\pm$2.2, p=0.03, n=4;) and MMP13 (x-fold$\pm$SD: 4.7$\pm$2.0, p=0.03, n=4). The secretion of IL-6 in the culture medium of RASF was also significantly increased (mean$\pm$S.D: 1676$\pm$479 vs 2433$\pm$504 pg/mL, p=0.007, n=5). The treatment of RASF with p38i significantly repressed not only the TNFα-induced up regulation of IL-6 but also the TNFα-induced down regulation of NRON (p= 0.001 and p= 0.04, n=5, respectively). Additionally, the proteasome-dependent degradation of NFAT5 was significantly enhanced by p38i (p= 0.01, n=5). Blocking the proteasome activity by MG132 inhibited the p38-induced degradation of NFAT5. Furthermore, the p38i-induced degradation of NFAT5 was inhibited also after silencing of NRON in RASF.

Conclusion: Our data show that TNFα down regulates the expression of lncRNA NRON in RASF by enhancing the activity of p38MAPK. Down regulation of NRON not only enhances the nuclear translocation and transcriptional activity of NFAT5 but also increases the total amount of NFAT5 in RASF by influencing the turnover of NFAT5 via ubiquitin-independent proteasome system. This novel data show the complex and multilevel capacities of the lncRNA NRON in regulating the function of NFAT5, thereby promoting proinflammatory and matrix-destructive responses of RASF.

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Protein Profiling of Secretome Human Cartilage to Identify Potential EARLY Specific Biomarkers in Osteoarthritis. Lucia Lourido, Valentina Calamia, Patricia Fernandez-Puente, Jesus Mateos, Francisco J. Blanco Garcia, Beatriz Rocha, Carolina Fernández-Costa, Carlos Fernandez-Lopez, Natividad Oreiro and Cristina Ruiz-Romero. Grupo de Proteomica-PBR2-ProteoRed/ISCIII-Servicio de Reumatologia. Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC). As Xubias, 15006., A Coruña, Spain.

Background/Purpose: Osteoarthritis (OA) is characterized by the progressive loss of cartilage structural extracellular matrix (ECM) components. The release of these proteins from the tissue can vary according to the stage of the disease and the specific joint affected. The aim of this study was to perform a quantitative proteomics approach to identify and quantify those proteins released from normal (N) and OA human articular cartilages capable of predicting the early stage of hip and knee OA.

Methods: Tissue explants were obtained from the dissection of 4 N and 4 OA cartilages, both from 2 femoral heads and 2 tibial condyles. Among the OA samples, we differentiated the wounded zones (WZOA) from those corresponding to the area adjacent to the lesion, or unwounded zones (UWOA). Cartilage shavings from each donor were cut into 6 mm discs and three discs/donor were placed into 96-well plates and cultured during 6 days. The conditioned media from each condition (N, WZOA and UWOA) were collected and their proteins were digested with trypsin. The resulting peptides were labelled with different isobaric tags using the iTRAQ reagents (ABSciex). Then, labelled peptides from the different conditions were mixed, desalted and separated by liquid chromatography (LC). The resulting fractions were grouped and resolved by reversed-phase nano-LC coupled to mass spectrometry (MS). The identification and relative quantification of the proteins was carried out with Protein Pilot 3.0 software.

Results: Globally we were able to identify 186 proteins released from the cartilage explants. After statistical analysis we found secreted proteins showing differences in abundance ($0.7 \leq$ ratio ≥ 1.3, $p \leq 0.05$) between the different OA zones (WZOA and UWOA) and N samples from the different joints. We classified them into 3 sets of proteins: a first group of proteins modulated specifically in UWOA sample (early OA biomarkers); a second group of proteins altered only in WZOA samples (late OA biomarkers), and finally a third group modified in both OA zones (progression biomarkers). Some of these modulated proteins are common early and progression biomarkers for both hip and knee OA (Table1). Furthermore, we also identified that the release of cartilage intermediate layer protein 1 (CILP1), a protein involved in cartilage scaffolding, is increased in UWOA from hip OA cartilage but not in UWOA from knee OA, being a possible early specific biomarker for hip OA. This specific modulation was confirmed by Real-time PCR and western blot in other human cartilage samples (n=3).

Conclusion: We describe a novel panel of cartilage-secreted proteins with potential biomarker value. Interestingly, we have identified a specific protein, which specifically indicates hip OA onset. This protein is now being explored in biological fluids (synovial fluid and serum) for the development of early diagnosis and/or anti-OA therapy monitoring strategies.

Table 1: A panel of different types of potential protein biomarkers of hip (H) OA and knee (K) OA is listed in the table. Proteins showing a gradual increase among OA samples (UWOA and WZOA) compared to normal cartilage (N) are indicated as early and progression biomarkers. CILP1 specifically indicates hip OA onset.

Protein Name	Uniprot symbol	Joint	Peptides (95%)	Ratio UWOA/N	*p* value	Ratio WZOA/N	*p* value	OA biomarker type
Pigment epithelium-derived factor	PEDF	H	25	2,35	0,00	4,73	0,00	Earlyandprogression
		K	32	2,31	0,00	3,16	0,00	
Tenascin	TENA	H	60	2,99	0,00	5,03	0,00	Earlyandprogression
		K	65	1,68	0,00	6,01	0,00	
Tenascin-X	TENX	H	28	3,21	0,00	6,84	0,00	Earlyandprogression
		K	52	1,34	0,02	2,38	0,00	
Tetranectin	TETN	H	15	2,63	0,00	3,68	0,00	Earlyandprogression
		K	16	1,96	0,01	3,52	0,00	
Transforming growth factor-beta-induced protein ig-h3	BGH3	H	24	5.34	0.00	6.12	0.00	Earlyandprogression
		K	23	1,57	0,00	3,55	0,00	
Vimentin	VIME	H	22	3,69	0,00	5,13	0,00	Earlyandprogression
		K	30	1,40	0,00	4,85	0,00	
Cartilage intermediate layer protein 1	CILP1	H	142	2,27	0,00	1,02	0,83	Early
		K	102	1,27	0,00	1,06	0,46	–

Disclosure: L. Lourido, None; **V. Calamia**, None; **P. Fernandez-Puente**, None; **J. Mateos**, None; **F. J. Blanco Garcia**, None; **B. Rocha**, None; **C. Fernández-Costa**, None; **C. Fernandez-Lopez**, None; **N. Oreiro**, None; **C. Ruiz-Romero**, None.

ACR Poster Session A
Health Services Research
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Possible Effects of Medicare-Only Insurance Coverage on the Use of Biologics in Patients with RA. Marcia Genta. Dallas Arthritis Center, Dallas, TX.

Background/Purpose: Biologics, a relatively new widely used class of medication that can substantially improve the course of RA, are expensive and their use is not reimbursed by all insurances. The aim of this study was to determine whether there was a difference in the usage of biologics between RA patients with only Medicare or Medicare-replacement and those who had other insurance coverage.

Methods: Demographic and clinical information.medication history, and insurance data were extracted from the electronic records of all patients with a diagnosis of RA managed at the Dallas Arthritis Center (DAC) for at least 3 months in 2013. Patients were then stratified into the following categories, based on their type of insurance coverage: *1) Medicare only*: Medicare coverage with no supplemental insurance of any kind, and no medication-specific financial support from charitable organizations; *2) Medicare-Medicaid:* both Medicare and Medicaid coverage; *3) Medicare integrated:* supplemental insurance in addition to Medicare (private or public insurances or Medicare part D); and *4) Private only:* private insurance only. Unadjusted odds ratio were used to determine the likelihood of patients with different types of insurance coverage as compared to patients covered exclusively by Medicare. This latter group was arbitrarily assigned an Odds Ratio of 1.

Results: Our search yielded 529 unique patients (median age 62 years, range 19 to 91; 79% female) with a confirmed diagnosis of RA; 13 patients who received financial support from private foundations to purchase the needed medications were excluded from the analysis. The remaining 516 patients represent our study group. Table 1 depicts the distribution of the insurance coverage amongst the study patients:

Insurance	Total patients	Median age	Female (%)
Medicare only	118	70 (41–88)	91 (77.1)
Medicare-Medicaid	67	66 (28–91)	56 (83.6)
Medicare Integrated	52	68 (36–87)	40 (76.9)
Private only	279	56 (19–91)	231 (82.8)

Table 2 shows the relative usage of biologics amongst the different groups

Insurance	Total RA patients	RA patients on any biologic	% RA patients on any biologic	OR (95% CI)	*p*
Medicare only	118	22	20%	1	
Medicare-Medicaid	67	25	37%	2.44 (1.23–4.81)	$p<.05$
Medicare-Integrated	52	20	38%	2.56 (1.24–5.29)	$p<.05$
Private only	279	102	37%	2.36 (1.39–3.99)	$p<.001$

Conclusion: Patients with Medicare only coverage who received no assistance from private foundations were significantly less likely to be treated with biologics than patients with any other type of coverage. In this study, we did not evaluate each patient's disease activity. Therefore, the possibility that fewer Medicare-only patients needed biologics than patients with other types of coverage must be considered. A study designed to include disease activity as a variable is currently under way. If confirmed, these results suggest that efforts are needed to increase Medicare patients' access to medications that can significantly improve the course of their disease and quality of life.

Disclosure: M. Genta, None.

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Comparison of Patient Characteristics, Healthcare Costs, and Biologic Persistence Between Patients with Rheumatoid Arthritis Initiating First- or Second-Line Subcutaneous Abatacept, Adalimumab, or Etanercept. S Johnston[1], F Lobo[2], D McMorrow[1], R Fowler[1], D Smith[1] and A Nadkarni[2]. [1]Truven Health Analytics, Bethesda, MD, [2]Bristol-Myers Squibb, Plainsboro, NJ.

Background/Purpose: There are currently very limited comparative published data on the characteristics, healthcare costs, and biologic persistence among patients with RA who have been treated with SC abatacept in a real-world care setting. This study compared patient characteristics, healthcare costs, and biologic persistence among patients with RA initiating SC abatacept or one of the two most commonly used SC anti-TNF-α agents, adalimumab and etanercept.

Methods: This was a retrospective, observational cohort study using a large US administrative claims database. Patients included in the study had initiated SC abatacept, adalimumab, or etanercept between 1/1/2009 and 10/1/2012 (index), were continuously enrolled for 12 months before (baseline) and ≥3 months after index, were aged ≥18 years at index, and had ≥1 baseline medical claim with an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis code for RA (714.0x). First-line initiators used no biologic pre-index; second-line initiators used only one biologic pre-index. Patient characteristics were measured at baseline. Biologic persistence (follow-up) was defined as the period extending from index until the first occurrence of switch to another biologic, censoring at disenrollment from health insurance, or 12/31/2012. Total healthcare costs (medical and pharmacy) were measured during baseline and follow-up on a per-patient-per-month basis. Changes in healthcare costs from baseline to end of available follow-up were compared using multivariable regression (difference-in-difference method). Biologic persistence was compared using multivariable survival analyses.

Results: The study results are shown in the Table. Patients treated with SC abatacept had baseline characteristics indicative of the poorest health status (e.g., higher baseline number of unique diagnoses and baseline costs). In all analyses, SC abatacept had the numerically lowest increase from baseline in healthcare costs and hazards of non-persistence, with differences often being statistically significant.

Table

		First-line			Second-line	
	SC abatacept (n=163)	Adalimumab (n=7098)	Etanercept (n=8776)	SC abatacept (n=256)	Adalimumab (n=2055)	Etanercept (n=1303)
Baseline number of unique diagnoses, mean (SD)	17.1 (12.8)	14.0 (8.7) p<0.001	14.3 (8.9) p<0.001	15.9 (10.4)	14.2 (8.9) p<=0.006	14.3 (8.5) p<=0.011
Baseline number of unique medications, mean (SD)	18.0 (10.4)	15.3 (9.3) p<0.001	15.4 (9.5) p<0.001	18.7 (9.9)	17.5 (9.7) p<=0.082	18.1 (10.1) p<=0.44
Baseline healthcare costs, mean (SD)	$2025 ($2843)	$1153 ($1725) p<0.001	$1199 ($1944) p<0.001	$2663 ($2462)	$2162 ($1779) p<0.001	$2231 ($1941) p<0.001
Adjusted healthcare cost difference*	ref.	$640 p<=0.0012	$657 p<=0.0010	ref.	$120 p<=0.0425	$94 p<=0.1304
Adjusted hazard ratio of non-persistence*	ref.	1.504 p<=0.1241	1.691 p<=0.0466	ref.	1.982 p<=0.0003	1.737 p<=0.0057

*As calculated using difference-in-difference; positive $ value indicates lower increase from baseline in healthcare costs for SC abatacept; hazard ratio >1 indicates lower hazards of non-persistence (longer durations of persistence) for SC abatacept.

Conclusion: In this study of patients with RA initiating first- or second-line biologics, SC abatacept was initiated in patients with poorest health status and therefore higher baseline healthcare costs compared with adalimumab or etanercept. Despite this, SC abatacept often had the lowest increase from baseline in healthcare costs and longest duration of biologic persistence.

Disclosure: S. Johnston, Truven Health Analytics, 3; **F. Lobo**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 3; **D. McMorrow**, None; **R. Fowler**, Truven Health Analytics, 3; **D. Smith**, Truven Health Analytics, 3; **A. Nadkarni**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3.

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Comparison of Cardiovascular Risk Factor Management in Patients with RA and Matched Non-RA Patients. H Cawston[1], E Alemao[2], F Bourhis[1], T Le[3], M Al[4], M Rutten-van Molken[4], KP Liao[5] and DH Solomon[5]. [1]OptumInsight, Nanterre, France, [2]Bristol-Myers Squibb, Princeton, NJ, [3]Bristol-Myers Squibb, Hopewell, NJ, [4]Erasmus University, Rotterdam, Netherlands, [5]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: The relative risk of acute myocardial infarction in RA patients (pts) has been shown to range from 1.5 to 2.0, with a 1.4–2.7-fold higher risk of stroke. This study aimed to compare management of traditional cardiovascular (CV) risk factors such as lipids and blood pressure in pts with and without RA.

Methods: A retrospective cohort study was conducted from 1987 to 2010, using the GOLD database from the Clinical Practice Research Datalink. Pts presenting with ≥1 RA read diagnosis code after January 1 1988 (index code), with no RA or juvenile RA codes before the RA index code with ≥12 months of data reported before the first RA code, and without any psoriatic arthritis-related codes over the entire period were included. Pts with RA were matched 1:4 to non-RA pts, based on their year of entry in the database, CV risk category (National Cholesterol Education Program classification), CV treatment status and a risk score measuring the probability of having RA. The index code of non-RA pts was defined as the closest health encounter to the index code of their match. Prescriptions for antidyslipidemic, hypertensive and diabetic treatments were evaluated for up to 5 years post index code. The percentage of pts attaining UK CV targets was also evaluated.

Results: Between 1987 and 2010, 24,859 RA pts were identified and matched to 87,304 non-RA pts. RA pts were followed for an average (SD) of

5.8 (4.4) years, were 60.0 (15.1) years old; 69% were female, 39% were hypertensive and 27% dyslipidemic at index date, based on diagnoses, prescriptions and tests. Similarly, non-RA pts were followed for an average of 5.7 (4.4) years, were 60.2 (15.9) years old; 66% were females, 38% hypertensive and 28% dyslipidemic. The percentage of RA pts prescribed antihypertensives increased from 38.2% at diagnosis to 45.7% at 5 years, from 14.0% to 20.6% for antidyslipidemics, and from 5.1% to 6.4% for antidiabetics (Table). Index rates and changes over time were similar in non-RA pts, although slightly lower for antihypertensives. There was no difference between RA and non-RA pts reaching hypertension targets at 1 year (25.8% vs 26.9%, $p=0.50$) although there was for dyslipidemia and diabetes (16.4% vs 18.5%, $p<0.01$; and 48.7% vs 44.3%, $p<0.01$, respectively). Blood pressure, lipids and diabetes-related testing were similar in both groups over time since diagnosis, although CRP and ESR were higher in RA pts at diagnosis (24.6 mg/L and 31.9 mm/hr, respectively), decreasing over time. These values were lower and did not vary over time in non-RA pts.

Conclusion: There were no differences between RA and non-RA patients in the frequency of prescriptions and testing, although there was a modest 2% lower achievement in lipid targets. Based on this analysis, it seems the higher CV risk in RA patients is unlikely to be driven by differences in traditional CV risk factor management alone.

Table Summary of treatment received, by time since index

	Time point	RA patients (N=24,859)	Non-RA patients (N=87,304)
Antihypertensive treatment	At index date	38.2%	37.4%
	At 5 years	45.7%	43.0%
	Absolute increase (95%CI)	+7.5% (6.5%; 8.6%)	+5.6% (5.1%; 6.2%)
Lipid-lowering treatment	At index date	14.0%	14.8%
	At 5 years	20.6%	21.4%
	Absolute increase (95%CI)	+6.7% (5.8%; 7.5%)	+6.6% (6.1%; 7.0%)
Antidiabetic treatment	At index date	5.1%	5.8%
	At 5 years	6.4%	6.7%
	Absolute increase (95%CI)	+1.3% (0.8%; 1.8%)	+1.0% (0.7%; 1.2%)

Disclosure: H. Cawston, OptumInsight, 3, Bristol Myers-Squibb, 5; **E. Alemao**, BMS, 3, BMS, 1; **F. Bourhis**, None; **T. Le**, BMS, 3; **M. Al**, None; **M. Rutten-van Molken**, None; **K. Liao**, None; **D. Solomon**, None.

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Identification of Tuberculosis in Rheumatoid Arthritis Patients Initiating Therapy with Biologic or Non-Biologic Disease-Modifying Anti-Rheumatic Drugs Using Health Insurance Claims Data. T Simon[1], N Liu[2], N Baker[3], N Lin[2] and V Hoffman[4]. [1]Bristol-Myers Squibb, Hopewell, NJ, [2]Optum Epidemiology, Waltham, MA, [3]Bristol-Myers Squibb, Hopewell, MA, [4]Optum Epidemiology, Ann Arbor, MI.

Background/Purpose: Biologic DMARDs used for the treatment of RA may increase the risk of tuberculosis (TB). [1] Large healthcare claims databases are useful in assessing rare events such as TB, but confirmation of these events can be challenging. As part of an ongoing post-marketing safety evaluation, we sought to characterize potential TB cases in claims data among RA patients initiating biologic and non-biologic DMARDs.

Methods: A prospective cohort study of adults who initiated biologic or non-biologic DMARDs and who had at least 6 months' prior continuous health plan enrollment (baseline) and a baseline claim for RA (International Classification of Diseases, 9th Revision [ICD-9] 714.xx) between December 1, 2005 and March 31, 2013 was conducted using administrative data from a large United States healthcare insurer. Potential TB events following drug initiation were identified with diagnosis codes associated with healthcare claims (ICD-9 010.xx- 018.xx) and characterized using criteria from a published validation algorithm for TB detection by Calderwood et al. (2010)[2], including the presence of claims suggestive of at least two TB treatments (e.g., pyrazinamide, rifampin, isoniazid, ethambutol) within 60 days, prescription for pyrazinamide, and acid-fast bacilli (AFB) testing in the preceding 60 days or subsequent 14 days. Potential TB events were also characterized by the presence of chest x-ray claims within 60 days.

Results: We identified 15,183 biologic DMARD initiators and 50,492 non-biologic DMARD initiators contributing 32,230 and 100,580 person-years of follow-up, respectively. Biologic DMARD initiators were more likely than non-biologic DMARD initiators to have previously used another biologic during the baseline period (20% vs 9%) and more likely to have a baseline claim for a TB skin test (26% vs 4%). A total of 251 potential TB events were identified during follow-up, 59 among biologic DMARD initiators and 192 among non-biologic DMARD initiators. Among the potential cases, 2 (3%) biologic DMARD initiators and 2 (1%) non-biologic DMARD initiators had claims for pyrazinamide, and 4 (7%) biologic DMARD initiators and 4 (2%) non-biologic DMARD initiators had claims for at least 2 different anti-TB medications. A total of 5 (8%) potential cases among biologic DMARD initiators and 6 (3%) potential cases among non-biologic DMARD initiators had an AFB test claim. A total of 28 (47%) potential cases among biologic DMARD initiators and 103 (54%) potential cases among non-biologic DMARD initiators had a claim for chest x-ray.

Conclusion: Few potential TB events identified on the basis of diagnosis codes had additional supporting claims. Claims-based algorithms based on diagnosis codes alone are likely insufficient for accurate identification of TB cases in administrative data. Consideration of claims indicative of TB treatment or diagnostic work-up in combination with diagnosis codes may improve identification of TB events in safety surveillance.

1. Brassard P, et al. *Clin Infect Dis* 2006;**43**:717–22.
2. Calderwood MS, et al. *Public Health Rep* 2010;**125**:843–50.

Disclosure: T. Simon, Bristol-Myers Squibb, 3; **N. Liu**, None; **N. Baker**, Bristol-Myers Squibb, 3; **N. Lin**, Bristol-Myers Squibb, 2; **V. Hoffman**, Optum Epidemiology, 3.

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Costs of Musculoskeletal Diseases in the United States, 1996–2011: Population Growth, Population Aging, Health Care Utilization, or Prices? Edward H. Yelin[1], Miriam G. Cisternas[2], Laura Trupin[1] and Stuart Gansky[1]. [1]University of California, San Francisco, San Francisco, CA, [2]MGC Data Services, Carlsbad, CA.

Background/Purpose: Medical care costs have been a major concern for public policy for a generation. Concern about costs of musculoskeletal conditions (MUSC) has been fueled by the aging of the population which puts a growing fraction of the population at risk for these conditions. We document the growth in medical care costs of MUSC from 1996–2011 and analyze the role that aging of the population, age-specific prevalence of the conditions, increased medical care utilization, and increased prices for services play in this growth.

Methods: We analyzed the 1996–1998 and 2009–2011 Medical Expenditure Panel Survey (MEPS).Using three-year periods provides more stable estimates of long-term trends. In MEPS, persons self-report conditions causing utilization, disability, or symptoms. Responses are coded to ICD-9-CM 3-digit codes; musculoskeletal codes included arthritis and joint pain, spine conditions, osteoporosis, musculoskeletal injuries, and other musculoskeletal conditions. We calculated per person and aggregate costs in constant 2011 dollars, by type (ambulatory, hospital, prescription medications, and "other" which includes devices, ED visits, personal assistance, and other services).

Results: Between 1996–1998 and 2009–2011 prevalence of musculoskeletal conditions rose by 35%, from 76.0 to 102.5 million while costs rose 117%, from $367.2 to $796.2 billion (Table 1). The increased costs resulted from larger populations aged 45–64 and ≥ 65, increased prevalence of MUSC in these age groups, higher unit prices for ambulatory care, hospital admissions, and prescriptions as well as increased numbers of prescriptions used (Table 2). Hospital admissions and ambulatory care utilization did not increase appreciably during this time.

Conclusion: The aging of the baby boom generation will lead to short term increases in the population at greatest risk for MUSC. Reducing costs of these conditions will require public health approaches to reduce the prevalence of MUSC through such mechanisms as weight control and exercise programs as well as change in the organization of health care to attenuate the increases in the unit prices of services, especially of prescription medications.

Table 1 Number and Percent of US Population with Musculoskeletal Conditions and Mean and Aggregate Health Care Costs in 1996–1998 and 2009–2011

			Health Care Costs (in 2011 dollars) for Musculoskeletal Conditions									
	Musc. Conditions		Ambulatory		Hospital		Prescription Meds		Other		Total	
Years	# (mils)	% of Pop.	Mean $s	Agg $bils	Mean $s	Agg $bils	Mean $s	Agg $bils	Mean $s	Agg $bils	Mean $s	Agg $bils
1996–1998	76.0	28.0	1,522	115.7	1,758	133.6	665	50.5	887	67.4	4,832	367.2
2009–2011	102.5	33.2	2,614	267.9	2,237	229.3	1,778	182.3	1,139	116.7	7,768	796.2
Pct Change	35%	19%	72%	132%	27%	72%	167%	261%	28%	73%	61%	117%

Table 2: Percent Change in US Population at Risk for Musc. Conditions, Prevalence of Musc. Conditions by Age, and Utilization and Unit Price of Ambulatory Visits, Hospital Admissions, and Prescription Medications

	Population and Prevalence Factors				Health Care Utilization and Prices					
	US Population		MUSC Prevalence		Ambulatory Visits		Hospital Admissions		P rescriptions	
	% 45–64	% ≥ 65	% 45–64	% ≥ 65	Mean/Yr	Unit Price	Mean/Yr	Unit Price	Mean/Yr	Unit Price
Pct Change	47%	20%	22%	27%	13%	51%	0%	27%	59%	68%

Disclosure: E. H. Yelin, None; **M. G. Cisternas**, None; **L. Trupin**, None; **S. Gansky**, None.

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Impact of Comorbidities on Health Resource Utilization in Patients with Spa. Mariano Andrés[1], Francisca Sivera[2], Sabina Pérez-Vicente[3], Loreto Carmona[4] and Paloma Vela[1]. [1]Hospital General Universitario de Alicante, Alicante, Spain, [2]Hospital General Universitario de Elda, Alicante, Spain, [3]Unidad de Investigación de la Sociedad Española de Reumatología, Madrid, Spain, [4]Instituto de Salud Musculoesquelética, Madrid, Spain.

Background/Purpose: Similar to other rheumatic disorders, patients with spondyloarthritis (SpA) show an increased prevalence of comorbidities compared to the general population [1]. Comorbidities influence management, prognosis and quality of life of SpA patients [2], but their impact on the utilization of health resources has been scantly explored so far.

Methods: The emAR II was a descriptive, multi-center, cross-sectional study, performed in Spain between 2009 and 2010. The records of patients with a SpA diagnosis plus at least a visit to the Rheumatology department within the previous two years were selected using an equiprobabilistic method. Health care utilization was collected during the previous 2-year period as: a) hospital admissions; b) visits to the rheumatology clinics; c) referrals to other medical specialists by the rheumatologist; and d) diagnostic procedures ordered due to SpA. The following comorbidities were registered: hypertension, diabetes, coronary heart disease, chronic heart failure, stroke, neoplasm, infections, peptic ulcer disease, chronic kidney disease, liver disease, and anticoagulation therapy. Additional descriptive and confounding variables were collected. Association between use of resources and comorbidities was assessed by lineal regression for continuous variables and logistic regression for binary variables, accounting for Poisson distribution.

Results: 1,168 patients' records from 45 centres were reviewed in detail (recruitment rate: 73%), mean (±SD) age 50.1 (±13.8) years. 68% males. Main SpA forms were ankylosing spondylitis and psoriatic arthritis. The use of resources was as follows: 248 admissions in 196 patients (19.2%, rate 12.1 per 100 patient-years), 5908 visits to rheumatology clinics (median (IQR) 4 visits per patient (3–6), rate 254 per 100 patient-years), 844 referrals to other specialists (rate 200 per 100 patient-years), and 85560 diagnostic procedures (rate 1753 per 100 patient-years). Analysis results are shown in Table 1. Hypertension, diabetes, coronary heart disease, chronic heart failure, infections, neoplasms, chronic kidney disease, and anticoagulation showed a positive, significant association with hospital admissions. The occurrence of infections was the only comorbidity significantly associated to visits, while no comorbidity showed a significant association to referrals. Infections and neoplasms were significantly associated to the diagnostic procedures.

Conclusion: Comorbidities in SpA influence health resources utilization, except for referrals to other specialties. This finding, added to the known impact in other areas of the disease, makes the identification of comorbidities advisable.

References:

[1] J Rheumatol; 33:2167.
[2] Rheum Dis Clin North Am 2012; 38:523.

Table 1. Association between comorbidities and health resources utilization (univariate analysis).

	N (%)	Admissions (OR; 95%CI)	Visits (b; 95%CI)	Referrals (OR; 95%CI)	Diagnostic Procedures (b; 95%CI)
Hypertension	203 (17.4)	2.563 (1.789–3.673)	−0.152 (−0.835,0.530)	1.023 (0.709–1.477)	0.600 (−2.613,3.813)
Diabetes	71 (6.1)	1.883 (1.059–3.348)	−0.259 (−1.341,0.824)	1.622 (0.905–2.907)	3.614 (−1.477,8.7006)
Coronary heart disease	41 (3.5)	6.472 (3.271–12.806)	−1.355 (−2.758,0.049)	0.781 (0.378–1.615)	0.848 (−5.768,7.464)
Chronic heart failure	17 (1.5)	9.866 (3.006–32.381)	−0.673 (−2.832,1.487)	0.453 (0.145–1.421)	3.244 (−6.921,13.409)
Stroke	13 (1.1)	1.405 (0.282–7.017)	−0.497 (−2.962,1.969)	−[+]	−5.201 (−16.803,6.402)
Peptic ulcer	79 (6.8)	1.267 (0.709–2.266)	0.136 (−0.895,1.166)	1.373 (0.797–2.366)	2.775 (−2.071,7.621)
Neoplasm	39 (3.3)	9.826 (4.702–20.533)	−0.720 (−2.160,0.719)	0.919 (0.435–1.940)	8.261 (1.500,15.022)
Chronic kidney disease	24 (2.1)	5.906 (2.452–14.223)	−0.822 (−2.645,1.001)	1.575 (0.600–4.134)	3.624 (−4.956,12.205)
Liver disease	52 (4.4)	0.811 (0.355–1.850)	0.331 (−0.923,1.586)	1.786 (0.908–3.512)	5.687 (−0.207,11.582)
Infections	55 (4.7)	5.092 (2.823–9.184)	1.418 (0.199,2.636)	1.165 (0.630–2.153)	6.225 (0.488,11.962)
Anticoagulation therapy	24 (2.1)	3.557 (1.453–8.707)	−0.567 (−2.390,1.257)	0.336 (0.111–1.017)	−2.587 (−11.169,5.995)

OR: odds ratio. CI: confidence interval. [+]Not analysed due to few registered cases (n=5). Significance level $p<0.05$.

Disclosure: M. Andrés, None; **F. Sivera**, None; **S. Pérez-Vicente**, None; **L. Carmona**, Roche Pharmaceuticals, 2, Pfizer Inc, 2, Abbott Immunology Pharmaceuticals, 2; **P. Vela**, None.

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Evaluation of Real World Experience with Non-Biologic DMARD in the Treatment of RA: Data from an Electronic Health Record Database. D. Wiederkehr[1], J. Harnett[1], R. Gerber[2], D. Gruben[2], E.Y. Mahgoub[3], G. Wallenstein[1] and A. Koenig[3]. [1]Pfizer Inc, New York, NY, [2]Pfizer Inc, Groton, CT, [3]Pfizer Inc, Collegeville, PA.

Background/Purpose: Non-biologic (NB) disease-modifying antirheumatic drugs (DMARD) such as methotrexate (MTX) are commonly used to treat rheumatoid arthritis (RA). However, NB-DMARD can have adverse events or inadequate response that lead to premature discontinuation. Up to 50% of patients initiating MTX may discontinue at 2 years. [1–3] The objective of this exploratory analysis was to evaluate real world treatment patterns and impact on healthcare resource use (HCRU) among patients whose first DMARD regimen was select NB-DMARD as monotherapy or in combination with other NB-DMARD.

Methods: This retrospective cohort study evaluated patients aged ≥18 years at index with ≥3 physician visits ≥30 days apart for RA (ICD-9 code: 714.xx) who were newly prescribed/administered a select NB-DMARD (MTX, leflunomide, sulfasalazine, hydroxychloroquine) from 2007–2011 in a de-identified electronic health record (EHR) database (Humedica). The index date was the date of the first select NB-DMARD prescription/administration in the EHR (ie, no DMARD in ≥6 months pre-index), and patients were followed for ≥1 year. Patients were categorized by initial treatment with NB-DMARD monotherapy (NBmono) or ≥2 select NB-DMARD at index (NBcombo). Patient baseline characteristics, 1-year post-index treatment patterns and HCRU were evaluated in EHR. RA-related costs were evaluated for a subset of patients with clinical information linked to healthcare claims (Optum) of commercial and Medicare Advantage health plans.

Results: Of 10,338 RA patients receiving any DMARD therapy, 73% received NBmono and 6% NBcombo; patient characteristics are presented in the Table. NBcombo patients tended to have a lower DCCI score, fewer were treated by a rheumatologist, and tended to have more NSAIDS/steroids/opioids at index; <1% of patients had other NB-DMARDs within 30 days of index. During the 1-year follow-up, NBcombo patients were less likely than NBmono patients to continue their index NB-DMARD treatment regimen; treatment patterns are presented in the Table. NBcombo patients had fewer RA-related emergency room (mean difference -0.01) and office (−0.46) visits but more prescriptions (1.1), other outpatient visits (0.04), and inpatient admissions (0.01) in the post-index period. In 204 NB-DMARD patients with claims data, the mean monthly cost was $267 (49% attributed to prescriptions, 42% to office/outpatient visits); costs for NBcombo were 6% higher vs NBmono.

Conclusion: Among RA patients treated with DMARDs, 79% received NB-DMARD (92% initiated as monotherapy). Approximately one third of NB-DMARD pts did not continue with any DMARD therapy in the 1-year follow up. NBcombo pts were less likely to continue their index treatment regimen, and only 14% initiated a biologic DMARD.

1. Lie E et al. *Rheumatology* 2012; 51: 670–678.
2. Lie E et al. *Ann Rheum Dis* 2010; 69: 671–676.
3. Bernatsky S et al. *Drugs and Aging* 2008; 25: 879–994.

Table. Patient characteristics and treatment patterns

	NBmono (N = 7598)	NBcombo (N = 621)
Patient characteristics		
Females, %	5594 (74)	463 (75)
Mean (SD) age, years	61.3 (13.8)	60.8 (12.7)
Geographic region, n (%)		
Midwest	3867 (51)	293 (47)
Northeast	680 (9)	32 (5)
South	2638 (35)	261 (42)
West	253 (3)	31 (5)
Other/unknown	160 (2)	4 (1)

Deyo-Charlson Comorbidity index, mean (SD)	0.93 (1.2)	0.77 (1.0)
Index prescriber (if known), n (%)		
Primary care physician	1288 (17)	85 (14)
Rheumatologist	4385 (58)	270 (43)
Other	1002 (13)	165 (27)
RA medication use on Day 0, n (%)		
NSAIDs	1114 (15)	180 (29)
Corticosteroids	2265 (30)	235 (38)
Opioids	961 (13)	117 (19)
Treatment patterns		
Continued index regimen, n/N (%)	3257/ 7598 (43)	241/ 621 (39)
Did not continue index regimen, n/N (%)	4341/ 7598 (57)	380/ 621 (61)
Next regimen: NB-DMARD, n/N (%)	1300/ 7598 (17)	46/621 (7)
Next regimen: Biologic, n/N (%)	835/ 7598 (11)	87/ 621 (14)
Next regimen: Biologic + NB-DMARD, n/N (%)	23/ 7598 (0.3)	2/ 621 (0.3)
Next regimen: No DMARD, n/N (%)	2183/ 7598 (29)	245/ 621 (39)
Mean RA-related Healthcare Resource Use		
Inpatient admission	0.10	0.11
ER visits	0.06	0.05
Office visits	5.17	4.71
Other outpatient visits	0.59	0.63
Pharmacy	7.70	8.81

Disclosure: D. Wiederkehr, Pfizer Inc, 1, Pfizer Inc, 3; **J. Harnett**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Gerber**, Pfizer Inc, 1, Pfizer Inc, 3; **D. Gruben**, Pfizer Inc, 1, Pfizer Inc, 3; **E. Y. Mahgoub**, Pfizer Inc, 1, Pfizer Inc, 3; **G. Wallenstein**, Pfizer Inc, 1, Pfizer Inc, 3; **A. Koenig**, Pfizer Inc, 1, Pfizer Inc, 3.

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Country of Residence and Its Wealth Determine Disease Activity Levels in RA: Results from Multi-National Study Across 17 Countries (COMORA). Polina Putrik[1], Sofia Ramiro[2], Andras Keszei[3], Ihsane Hmamouchi[4], Maxime Dougados[5], Till Uhlig[6], Tore K. Kvien[6] and Annelies Boonen[1]. [1]Maastricht University Medical Center, Maastricht, Netherlands, [2]Amsterdam Rheumatology Center, University of Amsterdam & Hospital Garcia de Orta, Almada, Portugal, Amsterdam, Netherlands, [3]Uniklinik RWTH Aachen University, Aachen, Germany, [4]Mohamed V Souissi University, Rabat, Morocco, [5]Paris Descartes University, Paris, France, [6]Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: Socio-economic (SE) inequalities in health persist both between and within countries and even increased in the recent years. Therefore, it is important to explore whether country level factors may contribute to health inequities in patients with RA. The objectives of this study was to (1) investigate whether country level factors contribute to explain Disease Activity Score (DAS28) (2) explore whether uptake of biologic disease modifying anti-rheumatic drugs (bDMARDs) mediates the relationship between country welfare and DAS28.

Methods: Data from a cross-sectional multinational (17 countries) study (COMORA) was used. The outcome was DAS28. Contribution of country to DAS28 was explored in multivariable linear regression models, adjusting for potential confounders, using forward selection and accounting for multiple testing. The country with lowest DAS28 (Netherlands (NL)) was used as reference. Next, the country of residence was replaced by GDP (dichotomized in low and high GDP), to investigate the contribution of socio-economic welfare. Improvement in R^2(model fit) of the two models that included either country or GPD was compared. Finally, the mediating role of uptake of bDMARDs in the relationship between GDP and DAS28 was explored by testing indirect effects.

Results: A total of 3920 RA patients from 17 countries (range 30–411) were included in COMORA dataset. Mean age was 56 y.o. (SD13), 82% females. Mean DAS28 was 3.7 (range 2.6 (NL) – 5.2 (Morocco)), and 32% of patients were currently treated with bDMARDs (range 3%(Uruguay) – 74% (UK)). Country differences in DAS28 varied from 0.2 (France) to 2.3 (Morocco) compared to NL, after adjustment for individual factors (Figure 1A). In societies with low GDP disease activity was on average 0.98 units higher, compared to high GDP countries (Figure 1B). Additional contribution of country to $R^2$was 0.15 and of GDP 0.08. Seven percent of the differences in DAS28 between low and high GDP countries were mediated by (lower) uptake of bDMARDs (Figure 2).

Conclusion: Substantial differences in DAS28 between countries were observed after adjusting for individual factors. In countries with low GDP disease activity was higher than in countries with high GDP. Lower uptake of biologics mediated part of the relationship between (low) GDP and (high) disease activity. Inequities across countries should come at focus of international societies of rheumatology and policy-makers.

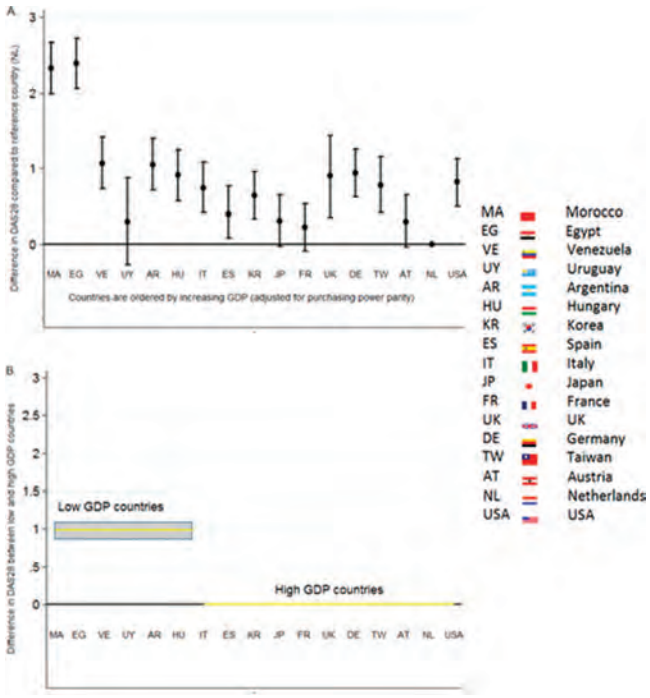

Figure 1. Differences in average DAS28 between individual countries (Figure 1A) and countries grouped by GDP (Figure 1B). Estimates are derived from models adjusted for age, gender, education, high rheumatoid factor or anti-citrullinated protein antibody, and comorbidities.

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Real-World Utilization, Patient Characteristics and Persistency of Certolizumab Pegol Vs Other Anti-TNFs for the Treatment of Rheumatoid Arthritis in the United Kingdom. Frances Humby[1], Stephen Kelly[1], Angela V. Bedenbaugh[2], Nawab Qizilbash[3], Jochen Dunkel[4], Belén San-Jose[5], Ignacio Mendez[5], Jennifer Timoshanko[6] and Jeyanesh Tambiah[2]. [1]William Harvey Research Institute, Queen Mary University of London, London, United Kingdom, [2]UCB Pharma, Smyrna, GA, [3]London School of Hygiene & Tropical Medicine, London, United Kingdom, [4]UCB Pharma, Monheim, Germany, [5]OXON Epidemiology, London, United Kingdom, [6]UCB Pharma, Slough, United Kingdom.

Background/Purpose: Several anti-TNFs are currently approved in Europe for RA treatment including certolizumab pegol (CZP), adalimumab (ADA), etanercept (ETN), golimumab and infliximab. UK NICE guidance recommends CZP as a first-line biologic therapy for patients (pts) with RA, in conjunction with a Pt Access Scheme that provides CZP free of charge for the first 12 weeks (wks). The objective was to assess real-world CZP, and other subcutaneous anti-TNFs (ADA or ETN), RA pt characteristics and treatment utilization in the UK.

Methods: A descriptive, retrospective, observational chart analysis was conducted in 4 UK rheumatology clinics. Medical data were collected over 52(−6/+9) wks for biologic-naïve pts initiating an anti-TNF (N=187); visit schedule was not prescribed therefore exact visit timing varied across pts. Data are reported for CZP pts and those receiving Other Anti-TNFs. Treatment persistency was assessed up to Wk52 using Kaplan-Meier estimates with pts censored at treatment discontinuation (ie. stop first anti-TNF treatment and switch to another/stop anti-TNFs) and excluding reinitiators (ie. pts with a gap in therapy returning to treatment within follow-up period).

Results: Baseline (BL) data were available for 110 CZP pts and 77 pts receiving Other Anti-TNFs (Figure 1A). At initiation, 14.5% (16/110) and 20.8% (16/77) pts received CZP and Other Anti-TNF monotherapy, respectively. Of those receiving combination therapy, 79.8% (75/94) CZP and 78.7% (48/61) Other Anti-TNF pts received concomitant MTX.

Due to the retrospective nature of data collection, not every pt had all data available; data were collected for 110, 108, 82 CZP pts and 77, 74, 50 Other Anti-TNF pts over 12, 24, 52 wks, respectively. Treatment persistency was 95.5%, 82.6%, 71.8% for CZP and 90.9%, 73.5%, and 65.0% for Other Anti-TNF pts at 12, 24, 52 wks, respectively (all lower bounds above 60% for corresponding CIs) (Figure 1B). Mean treatment persistency was 46.3 (95% CI: 43.2–49.4) and 43.1 (95% CI: 38.5–47.7) wks for CZP and Other Anti-TNF pts, respectively. Of pts initiating CZP, 2.7% switched therapy to another anti-TNF at any time during follow-up (n=3; 1 pt each 0–11, 12–24, 25–52 wks). Similarly, 6.5% of Other Anti-TNF pts switched to another anti-TNF (n=5; 4 pts before Wk12, 1 pt 12–24 wks). Compared to CZP pts, the risk of discontinuation in the Other Anti-TNF group was 37.4% greater (Hazard Ratio=1.374; 0.820–2.302). The majority of discontinuations occurred within the first 24 wks for both groups.

Conclusion: In this descriptive study, BL demographics/disease activity for pts treated with anti-TNFs in the UK were broadly similar between groups. Treatment persistency in this real-world observational study was also similar between CZP and Other Anti-TNFs in anti-TNF naïve pts. Interpretation of data is limited due to general caveats inherent to retrospective analyses.

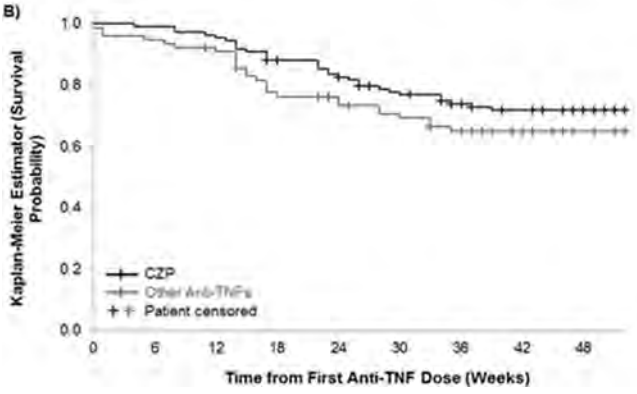
Figure 1: Baseline patient demographics/disease characteristics (A) and persistency on treatment up to 52 weeks (B) for patients receiving CZP (n=110) and Other Anti-TNFs (n=77)

A)

	CZP	Other Anti-TNF
Age, mean (SD) years	57.4 (11.8)	57.4 (13.1)
Gender, n (%)		
Male	38 (34.6)	20 (26.0)
Female	72 (65.5)	57 (74.0)
Disease Duration, mean (SD) years	7.9 (8.3)	11.4 (10.4)
DAS28(ESR), mean (SD)	6.1 (0.9)	6.2 (0.9)
Missing, n	14	18
Disease Activity, n (%)		
Low [a]	0 (0.0)	1 (1.3)
Moderate [b]	6 (5.5)	1 (1.3)
High [c]	90 (81.8)	57 (74.0)
Missing	14 (12.7)	18 (23.4)
Concomitant Medications at BL, n (%)		
Monotherapy	16 (14.6)	16 (20.8)
Combination therapy with non-biologic DMARD	94 (85.5)	61 (79.2)
MTX	75 (68.2)	48 (62.3)
Not MTX	19 (17.3)	13 (16.9)

[a] DAS28(ESR) ≤3.2; [b] DAS28(ESR) >3.2 and ≤5.1; [c] DAS28(ESR) >5.1

B)



Disclosure: F. Humby, None; **S. Kelly**, Abbvie, MSD, Roche, UCB Pharma, 8; **A. V. Bedenbaugh**, UCB Pharma, 3, UCB Pharma, 1; **N. Qizilbash**, OXON Epidemiology, 3; **J. Dunkel**, UCB Pharma, 3; **B. SanJose**, OXON Epidemiology, 3; **I. Mendez**, Employee OXON Epidemiology, 3; **J. Timoshanko**, UCB Pharma, 3; **J. Tambiah**, UCB Pharma, 3, UCB Pharma, 1.

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Rheumatology e-Consult Services: a Rheumatology Workforce Management Model. Thomas Schmidt[1], Charles Lappan[2] and Daniel Battafarano[3]. [1]SAUSHEC/ Brooke Army Medical Center, San Antonio, TX, [2]United States Army, San Antonio, TX, [3]San Antonio Military Medical Center, JBSA - Ft Sam Houston, TX.

Background/Purpose: The regional distribution of adult rheumatologist in the United States (U.S.) was recently analyzed by the American College of Rheumatology (ACR)[1]. Regional workforce shortages were recognized with suggested options to address this concern. Electronic digital consultation (e-Consult) is one proposed solution. An e-Consult service was implemented by the U.S. Army to assist providers in remote global areas.

Methods: A retrospective analysis of rheumatology e-Consults from May of 2006 to May of 2014 was performed. Military providers from all services submitted consultation requests via a secure email site with digital file attachments. Patient identifiable information was excluded. A total of 24 rheumatology staff and fellows provided e-Consult services, and a program manager monitored and aggregated data for rheumatology. Collaboration with other e-Consult services was available and facilitated through the program manager.

Results: A total of 193 rheumatology e-Consults were processed. The average response time was 5.3 hours with 98% answered within 24 hours. There were 122 requests (63%) from Iraq and Afghanistan. Diagnoses included: inflammatory arthritis (65; 22 polyarticular, 18 RA, 14 gout, 8 infectious, 3 monoarticular), seronegative spondyloarthropathy (27; 9 psoriatic arthritis, 6 reactive, 6 undifferentiated, 1 inflammatory bowel disease), arthralgias/myalgias (24), elevated CPK (8), lupus (7; 4 SLE, 2 discoid, 1 pernio), Raynaud's phenomenon (7), mechanical pain (7), positive ANA (6), sicca syndrome (4), DM (1) and 37 other. e-Consult collaboration was common and primarily with dermatology (29) and infectious disease (13).

Conclusion: Over an 8-year period an Army rheumatology e-consult service successfully assisted remote providers with diagnosis and management of rheumatic diseases. This global, collaborative model provided timely subspecialty care and input to providers that did not have immediate access to a rheumatologist. A similar digital and collaborative management model may facilitate rheumatology support for non-rheumatologists in underserved or remote areas.

1. American College of Rheumatology Committee on Rheumatology T, Workforce I, FitzGerald JD, et al. Regional distribution of adult rheumatologists. *Arthritis and rheumatism.* Dec 2013;65(12):3017–3025.

Disclosure: T. Schmidt, None; **C. Lappan**, None; **D. Battafarano**, None.

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Reasons for Leaving an Academic Career in Research Among Rheumatologists in the United States. Alexis Ogdie[1], Ami Shah[2], Una Makris[3], Alfred Kim[4], Sheila Angeles-Han[5], Amit Golding[6], J. Michelle Kahlenberg[7], Eyal Muscal[8], Flavia V. Castelino[9] and Amanda Nelson[10]. [1]University of Pennsylvania, Philadelphia, PA, [2]John Hopkins University, Baltimore, MD, [3]Dallas VA Medical Ctr, Dallas, TX, [4]Washington Univ School of Med, Saint Louis, MO, [5]Emory University School of Medicine, Atlanta, GA, [6]Baltimore VA and University of Maryland School of Medicine, Baltimore, MD, [7]University of Michigan, Ann Arbor, MI, [8]Texas Children's Hospital, Houston, TX, [9]Massachusetts General Hospital, Boston, MA, [10]University of North Carolina at Chapel Hill, Chapel Hill, NC.

Reasons for leaving an academic career in research among rheumatologists

Background/Purpose: Retention of academic rheumatologists in research careers is increasingly challenging in the current funding environment. However, beyond funding, reasons for leaving a career in research remain unknown. The objective of this study was to examine factors for leaving a career in research among rheumatologists.

Methods: A web-based survey was conducted among the domestic ACR membership from Jan-Mar 2014. Inclusion criteria were current or previous fellowship in rheumatology, ACR membership, and an available email address. Non-rheumatologist members were excluded. The survey assessed demographics, research participation, barriers/facilitators to a career in research, and free text response for reasons for leaving a career in research. After excluding incomplete surveys and duplicates, demographics were summarized. Content analysis was used to extract relevant themes from free text comments.

Results: Ninety-seven respondents (among 430 complete responses) indicated that they had previously pursued a career in research but decided to switch career paths. This career change occurred a median of 10 years ago (interquartile range [IQR] 3–20) and a median of 7 years after completing fellowship (IQR 2–14). Previous research types and current positions are presented in the **Table**. Approximately half of respondents were female. The most commonly cited reasons for leaving a research career were difficulty obtaining funding and lack of department or division support (**Table**). Among 27 free text comments, respondents noted additional reasons for leaving research including new opportunities in administration, teaching and clinical care, great clinical burden and insufficient protected time to be successful in research endeavors, increasing age, difficulty financially supporting a family, difficulty covering loans with low salary, need for increased job security, lack

of mentorship, unsupportive environment or institution, need to move to a new geographic area without opportunities for research, and fear of having to move if not successful in obtaining funding or achieving tenure. When asked what would have kept these investigators in research, the most common responses included increased protected time and availability of internal grant funding mechanisms.

Conclusion: This is the largest known study examining reasons for leaving a career in academic research. While financial reasons were the most commonly cited reason for leaving a career in research, division support and protected time were similarly important. These results suggest that enhancing institutional support of academic research in rheumatology should be an important emphasis in order to support and sustain research careers.

Table: Participants who decided to leave a research career (N=97)

Female (N(%))		45 (46%)
Year of fellowship completion (median and IQR)		1993 (1983–2005)
Years Since Transition (median and IQR)		10 (3–20)
Years after fellowship when transition occurred (median and IQR)		7 (2–14)
Current Position	Adult Rheumatologist	78 (80%)
	Pediatric Rheumatologist	14 (14%)
	Adult Fellow	5 (5%)
	Pediatric Fellow	0 (0%)
Current Place of Employment	Academic Medical Center	52 (54%)
	Clinical Practice	24 (25%)
	Industry	17 (18%)
	Government	2 (2%)
	Retired	2 (2%)
Academic Appointment	Instructor or other Junior Faculty	6 (6%)
	Assistant Professor	14 (14%)
	Associate Professor	21 (22%)
	Professor	22 (23%)
	Other (or no academic appointment)	34 (35%)
Previous Type of Research	Clinical	47 (48%)
	Epidemiology/Health Services	8 (8%)
	Translational	36 (37%)
	Basic Science	49 (51%)
Factors Contributing to Decision to Leave	Difficulty obtaining grant funding	55 (57%)
	Lack of division/department support	51 (53%)
	Better compensation	38 (39%)
	Lack of mentorship	38 (39%)
	Tired of writing grants	33 (34%)
	Personal reasons*	26 (27%)
	Desire to spend more time in clinical care	20 (21%)
	Exciting opportunities in industry	10 (10%)
	Did not enjoy research work	6 (6%)
What would have retained you in a research career?	Provide internal grant funding mechanisms	54 (56%)
	Increase protected time	50 (52%)
	Increase income	31 (32%)
	Increase work flexibility	25 (26%)
	Provide greater leadership opportunities	25 (26%)
	Nothing would have incentivized me to stay in academics	9 (9%)

*Personal reasons included desire to move geographically (N=16) or desire to spend more time with family (N=15).

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Resource Use and Health Related Quality of Life Burden of Gout Exacerbated By Common Comorbidities: Results from the 2012–2013 National Health and Wellness Survey. Robert Morlock[1], Natalia M. Flores[2], Kathy Annunziata[3], J. Chapnick[4] and Sulabha Ramachandran[5]. [1]Ardea Biosciences, San Diego, CA, [2]Kantar Health, Foster City, CA, [3]Kantar Health, Princeton, NJ, [4]Kantar Health, Horsham, PA, [5]AstraZeneca, Wilmington, DE.

Background/Purpose: Gout is caused by chronic high serum uric acid (SUA) levels (i.e., hyperuricemia), which leads to the deposition of monosodium urate crystals in musculoskeletal structures (e.g., joints), kidneys, and other connective tissues and urate crystal deposition disease, which can result in chronic inflammation leading to acute gout flares and tophi. Hyperuricemia is a metabolic disorder caused mainly by inefficient renal excretion of uric acid. Because SUA levels are often not at target, it is important to examine how this may relate to resource use and health utility. Additionally, this study examines other factors such as comorbidities and how they may exacerbate the relationship between high SUA levels, resource use, and health utility.

Methods: The data are from the combined 2012 and 2013 U.S. National Health and Wellness Survey (NHWS), a representative, cross-sectional general health survey (2012 NHWS: $N = 71{,}157$; 2013 NHWS: $N = 75{,}000$) of which 3,729 self-reported being diagnosed with gout. Those diagnosed were categorized into uncontrolled ($N = 2{,}215$) and controlled ($N = 344$) gout ("controlled gout" defined as: SUA ≤6 mg/dL and no flares in past year), omitting those whose control status was unknown ($N = 1{,}170$). Weights were calculated to be representative of the U.S. adult population and analyses were based on the weighted data. Resource use in the past six months, health related quality of life (SF-36v2: mental and physical component summary (MCS, PCS) and SF-6D (health utility), and work productivity loss (WPAI) were assessed across the two groups. Comorbidities (e.g., diabetes, hypertension) and their relationship to resource use and health utility were also examined.

Results: Those with uncontrolled gout reported being hospitalized (13.8% vs. 8.1%) and visiting the ER (22.3% vs. 11.7%) more than those with controlled gout. Additionally, those with uncontrolled gout reported lower MCS (Mean = 47.22 vs. Mean = 51.96), PCS (Mean = 41.95 vs. Mean = 46.32), and health utility (Mean = 0.66 vs. Mean = 0.73) scores than those with controlled gout. Furthermore, those with uncontrolled gout reported higher work productivity loss (24.5% vs 16.2%) and activity impairment (40.2% vs. 28.2%) than those with controlled gout. Having a common comorbidity with uncontrolled gout increased resource usage compared with either 1) those uncontrolled without the comorbidity or 2) with controlled gout, as was shown with diabetes (ER visits: 27.2% vs. 13.7% and 22.6%, respectively).

Conclusion: These findings support that uncontrolled gout results in greater hospitalization and twice as many ER visits than controlled gout. This, combined with lower health utility than controlled gout, suggests a significant humanistic and economic impact. These impacts may be further compounded when comorbidities are present.

Disclosure: R. Morlock, Ardea Biosciences, Inc., 1, Ardea Biosciences, Inc., 3; **N. M. Flores**, Kantar Health, 3; **K. Annunziata**, Kantar Health, 3; **J. Chapnick**, Kantar Health, 3; **S. Ramachandran**, AstraZeneca, 1, AstraZeneca, 3.

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Patient Reported Outcomes Following Upper Extremity Arthroplasties in RA -a Report from the Swedish National Register of Rheuma Surgery (RAKIR). Ann Bremander[1], Sofia Forsberg[2], Emelie Gull[2] and Anna Nilsdotter[2]. [1]Spenshult Research and Development Center, Halmstad, Sweden, [2]Halmstad Central Hospital, Halmstad, Sweden.

Background/Purpose: RAKIR, the Swedish National Register of Rheuma Surgery was created to follow joint surgery in patients with RA (rheumatoid arthritis). The aim of this study was to analyze PROMs (patient reported outcome measures) from RAKIR concerning HRQoL (health related quality of life), pain and function in RA patients admitted for arthroplasty in the upper extremity. A secondary aim was to study expectations and satisfaction related with these procedures.

Methods: 106 (87 women, age mean 63, SD 13 years) patients with RA admitted for arthroplasty in the upper extremity, followed in RAKIR, were included (2007–2011). All patients answered the questionnaires SF-36, HAQ and QDASH preoperatively, 6 months postoperatively and at a 2–6 year follow-up (2013). Questions concerning expectations and satisfaction were asked at the same time.

Results: RA patients operated on with arthroplasty in the upper extremity (shoulder n=36, elbow n=20, wrist n=21 and MCP n=29) showed a significant improvement in HRQoL, pain and function 6 months after surgery ($p \leq 0.05$, n=61). The improvement remained 2–6 years later (n=50). The patients' expectations concerning pain relief was fulfilled, the expectations concerning improvement in ADL and function was surprisingly low but in an even greater extent fulfilled.

Conclusion: Long term follow-up with PROMs showed that patients with RA, in need of arthroplasty in the upper extremity, are satisfied, experience pain relief as well as improved function and HRQoL as long as 2–6 years after surgery. However, the response rate in a register is dependent on the patients' benignity and may influence the results.

Disclosure: A. Bremander, None; **S. Forsberg**, None; **E. Gull**, None; **A. Nilsdotter**, None.

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Use of Internet in Adolescents and Young Adults with JIA. Philomine A. van Pelt[1], Constance H.C. Drossaert[2], Radboud JEM Dolhain[3], A.a. Kruize[4], Jaap Huisman[5] and Nico Wulffraat[4]. [1]Erasmus MC, Rotterdam, Netherlands, [2]University of Twente, Enschede, Netherlands, [3]Erasmus MC University Medical Center Rotterdam, Rotterdam, Netherlands, [4]University Medical Center Utrecht, Utrecht, Netherlands, [5]Wilhelmina's Children Hospital UMC Utrecht, Utrecht, Netherlands.

Background/Purpose: Internet-use is increasing since it is an efficient way to find information. Information obtained via Health Related Internet (HRI) sites, or online peer support groups might increase knowledge and self-management in adolescents and young adults with Juvenile Idiopathic Arthritis (JIA). This study evaluates the frequency of use and perceived relevance of HRI use and its association with demographic, disease-related and psycho-social variables.

Methods: In a cross-sectional study, all consecutive JIA patients from the outpatient clinic (age 10 – 27 years) who gave informed consent were asked to complete a self-reported questionnaire. Frequency of using HRI-sites (regarding information about JIA, medication-use and aspects of JIA related to social life) as well as having online contact with fellow patients were evaluated. Perceived relevance of HRI use and contact with fellow patients were also investigated. Demographic variables, disease activity, medication and emotional behavior and coping were assessed as possible predictors.

Results: 142 patients were included and 98% had access to internet. 71% had used internet to search general information on JIA, but specific topics such as medication, were less searched for (6–35%). Most favorite sites to look for information were www.reumafonds.nl (Dutch Arthritis Foundation; 20%); www.google.com (16%); www.jong-en-reuma.nl (UMCU hospital site for rheumatic diseases; 14%) and www.printo.it (Pediatric Rheumatology European Society information site; 3%). One in four adolescents had ever visited a forum or had online contact with peers. Most favorite discussion fora were www.reumaforum.nl (peer support for general rheumatic diseases; 14%); www.jeugdreuma.com (parents of children support forum; 5%) and www.Youth-R-Well.com (peer support information and forum for 16–30 year old patients; 5%). Whereas most had used the internet to find information about JIA, the perceived relevance of HRI-sites and of opportunities for online peer contact was rated low (medians respectively 2,0 and 1,0 on a scale 0–10).

Female gender was positively associated with HRI use ($P<0.01$), other demographic and disease related factors were not associated with HRI use. Coping styles "confrontation" and "reassuring thoughts" were associated with increased HRI use, but only in males. Internalizing and externalizing problem behavior were not significantly associated.

Conclusion: Frequency of Health Related Internet use in young people with JIA was less than expected and considered of low relevance. Besides female gender no demographic and disease related factors were associated. HRI in present form cannot replace regular information as an additional source to increase knowledge.

Disclosure: P. A. van Pelt, None; **C. H. C. Drossaert**, None; **R. J. Dolhain**, None; **A. A. Kruize**, None; **J. Huisman**, None; **N. Wulffraat**, Abbvie, GSK, Roche, 2, Genzyme, Novartis, Pfizer, Roche, 5.

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Patient Reported Outcomes Following Total Knee Arthroplasty in Rheumatoid Arthritis and Osteoarthritis. Anand Dusad[1], Sofia Pedro[2], Kevin Garvin[1], Curtis Hartman[1], James O'Dell[1], Ted R. Mikuls[1] and Kaleb Michaud[3]. [1]University of Nebraska Medical Center, Omaha, NE, [2]National Data Bank for Rheumatic Diseases, Wichita, KS, [3]University of Nebraska Medical Center and National Data Bank, Omaha, NE.

Background/Purpose: Due to the progressive and debilitating nature of knee arthritis, total knee arthroplasty (TKA) is the ultimate outcome. TKA is an effective surgical intervention for relieving pain and restoring function in patients with end-stage knee arthritis. Even though the beneficial impact of TKA is well documented, its effect on patient reported indices of pain and health related quality of life (HRQoL), especially in the RA population, are scarce. We examined the effects of TKA on pain and HRQoL in RA and OA patients.

Methods: Rheumatologist-diagnosed RA (n=834) and OA (n=315) patients undergoing primary TKA during 1999–2012 were identified. Measures of pain, function and HRQoL were obtained in three consecutive 6-month intervals: pre-operative (baseline), peri-operative and post-operative (recovery). Descriptive statistics and one-way ANOVA were used to compare TKA outcomes by diagnosis. Effect sizes were calculated between baseline and recovery period for each measure and graphs were plotted to follow these over time (±3 years of TKA), for both RA and OA patients.

Results: Patients with RA and OA were similar in age (65 vs. 68 years, respectively) and elapsed time [baseline sampling to TKA and TKA to recovery] (4.4 vs. 4.5 and 10.4 vs. 10.3 months). Post TKA, significant improvements were observed for most domains of pain, function and HRQoL indices within both disease groups ($p<0.001$). The beneficial effects of TKA were more profound in OA patients, as compared to RA, for all measures of pain and HRQoL indices except for RADAI/total joint count [RA (−0.42) vs. OA (−0.30)] and EQ-5D [RA (0.07) vs. OA (0.06)]. By effect size, maximum significant ($p<0.001$) improvement was shown in index knee pain (RA -1.69 vs. OA -1.85). Beyond pain outcomes, EQ-5D and SF-36 PCS were the most responsive HRQoL measures in detecting post-TKA improvement in RA and OA ($p<0.001$ in both groups), respectively (Table 1). For all outcomes examined, improvements were greatest in the first post-operative year, showing gradual declines thereafter.

Conclusion: TKA is highly effective in reducing clinically relevant index knee pain to a greater extent than other subjective HRQoL indices in patients with RA, although this improvement is less marked than that observed in OA patients. Gains observed in pain, function, and HRQoL are most striking in the first 12 months following TKA, paralleling levels reported often years prior to joint replacement. From our results, TKA acts as a "time machine" by which a patient returns to a reduced pain and less disabled lifestyle, before the arthritic process catches up, which is strikingly faster in RA.

Table 1. Mean change (SD) and effect size between baseline and recovery period

	RA	Effect size	OA	Effect size
Index knee pain (0–3)#	**−1.47 (0.88)**	−1.69	**−1.47 (0.79)**	−1.85
VAS Pain (0–10)#	**−1.12 (2.67)**	−0.42	**−1.74 (2.60)**	−0.67
RADAI-Total joint count (0–16)@	**−0.40 (4.92)**	0.08	−0.31 (4.61)	−0.07
RADAI-Total joint score (0–48)@	**−1.41 (10.07)**	−0.14	**−1.88 (8.47)**	−0.22
HAQ@	**−0.09 (0.66)**	−0.14	**−0.15 (0.59)**	−0.25
HAQ II	**−0.18 (0.64)**	−0.29	**−0.19 (0.58)**	−0.32
SF-36 PCS (0–100)	**3.59 (9.80)**	0.37	**4.57 (9.89)**	0.46
EQ-5D (US) (0–1)	**0.07 (0.20)**	0.40	**0.06 (0.20)**	0.32

and @ represent indices with significantly ($p<0.05$) less and more severe scores, respectively, in RA (vs. OA) patients undergoing TKA at baseline. Bold numbers represent significant ($p<0.05$) values between baseline and recovery within the respective groups

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Knee Arthroscopy in an International Training Centre: An Audit of Safety and Impact on Work Days. Carl Orr[1], Paul MacMullan[1], Phil Gallagher[2], Mairead Murray[1], Madeline O'Neill[1] and Douglas J. Veale[3]. [1]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]St. Vincent's University Hospital, Dublin, Ireland, [3]St. Vincent's University Hospital, Dublin 4, Ireland.

Background/Purpose: The utility of synovial biopsy has been confirmed as an important research tool in increasing our understanding of the pathogenesis of RA, evaluating new treatments and identifying potential therapeutic targets (1, 2). More rheumatology units are introducing arthroscopy as part of their research programs,(3). In 2004, we published data showing that complication rates are very low (4), however it is critically important to continue to monitor safety and audit our outcomes.

All procedures are performed under local anaesthesia in a state of the art, built-for-purpose facility.

We collected and analysed the experience reported by patients following arthroscopy in our unit, examining parameters such as overall tolerability, pain, time out of work post-arthroscopy and complications.

Methods: Consecutive patients returning to the arthroscopy programme since July 2013 completed a questionnaire including 16 questions, three visual analogue scales (VAS 0mm-100mm), as well as binary questions.

Results: 136 (47 male) respondents are included, age 20–82 years (mean 53.76, SD 13.86).

91.2% (124/136) of patients felt they had received adequate information before the procedure. 84.6% (115/136) reported that the procedure matched

their expectations. The main concern before the arthroscopy was potential pain during the procedure cited by 78.7% (107/136).

The mean VAS for pain during the procedure was 50mm (SD 34.6); in the first 48 hours after the procedure 31mm (SD 28.2); and 15mm (SD 24.1) in the month following the procedure. There was no correlation between diagnosis, age or sex to VAS.

64.0% (73/114) were out of work for less than 2 days, 29.8% (34/114), and 6.1% (7/114). The remainder of patients left this field blank. No significant complications were reported. 66.9% (91/136) felt improvement in their knee symptoms following arthroscopy.

Conclusion: Knee arthroscopy remains a safe and well tolerated research procedure. The procedure is well tolerated under local anaesthesia, and many patients experience an improvement in their knee symptoms. Patients are out of work for very short periods following arthroscopy and no significant complications were reported.

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Use of Smartphones in Collecting Patient Reported Outcomes: Can Passively-Collected Behavior Determine Rheumatic Disease Activity? Early Results from a Nation-Wide Pilot Study. Kaleb Michaud[1], Sofia Pedro[1], Rebecca Schumacher[1], Karim Wahba[2] and Sai Moturu[2]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]ginger.io, San Francisco, CA.

Background/Purpose: Rheumatoid arthritis (RA) and other rheumatic diseases (RD) are associated with depression, fatigue, and disturbed sleep, symptoms that often impact behavior. Many smartphone apps allow patients with RDs to regularly report their disease activity for better self-management and clinical followup. Recent advances in reality mining technology combined with the growing use of smartphones have shown measurable changes in phone behavior due to health issues like depression, stress, and influenza. We sought to learn if there are associations of phone behavior with RD patient reported outcomes.

Methods: We invited 700 patients in the National Data Bank for Rheumatic Diseases to participate by installing a custom app on their smartphone and answering questions regularly: a daily pain VAS for 60 days and a weekly Patient Activity Scale-II (PAS-II) for 6 months. Passive data collected included mobility distance, number of unique calls and text messages, call durations, call counts, and number of missed calls. A principal component analysis (PCA) based on the correlation data was performed on the passive data. The scree plot and the Kaiser criterion were used to select the number of components. A hierarchical cluster analysis was also performed using Euclidean dissimilarity metric and the average linkage criterion, with Calinski/Haralasz rule for the optimal choice of number of clusters. In addition, GEE models examined the association of passive data with weekly PAS-II components. Possible confounders included age, sex, disease, education, income, employment, smoking, and marital status in addition to variables such as season, holiday weekend, and time of day. QIC criterion was used to select the best models.

Results: While 150 patients participated, we limited our analysis to the 55 with Android phones due to more extensive passive data. Three components were extracted, explaining a total variation of 81%. The first was an overall measure of the use of the phone (50% explained variance); the second was a contrast between the use of text messages vs. calls (20%); and a third was a function of mobility and radius. The cluster analysis found 2 groups with a larger cluster (N=42) mostly of RA patients, with a lower overall use of the phone, lower time on the phone, and lower radius, and a second cluster having a greater overall use of the phone, higher radius, and having mostly OA and Fibromyalgia. The use of texting compared to calls was always preferred in both groups. Multivariable models suggested that patients with worse disease activity tended to answer less calls and talk for less time, but compensated with more text messages. They also tended to have greater mobility but less overall travel radius. Holidays and the summer were comparatively better for their diseases. Worse-off patients also left the study sooner.

Conclusion: With our exploratory analysis, we were able to characterize phone behavior in 3 components and 2 profiles that well-distinguished RD diagnosis. Our longitudinal models showed significant association of phone behavior with pain and PAS-II scores over time. This pilot study holds promise for passive behavior to be used in patient self-management and clinical followup.

Disclosure: K. Michaud, None; **S. Pedro**, None; **R. Schumacher**, None; **K. Wahba**, None; **S. Moturu**, None.

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Low Rates of Bone Mineral Density Testing in Medicare Beneficiaries with Breast Cancer Starting Aromatase Inhibitor Therapy. Mamatha Siricilla, Ruili Luo, Linda Elting and Maria E. Suarez-Almazor. The University of Texas, MD Anderson Cancer Center, Houston, TX.

Background/Purpose: Aromatase inhibitors (AI) are increasingly used as adjuvant hormonal therapy in postmenopausal women with estrogen receptor-positive breast cancer. It is well recognized that therapy with AI increases the risk of bone loss and fractures. Therefore, it has been recommended that women who are beginning AI therapy undergo bone mineral density (BMD) measurement at baseline and periodic intervals. The objective of our study was to determine the rates and predictors of dual-energy x-ray absorptiometry (DXA) scan use in breast cancer patients started on AI in the state of Texas who were Medicare beneficiaries.

Methods: In a retrospective cohort study, we identified all Medicare female beneficiaries diagnosed with breast cancer in the period 2005–2010 from the Texas Cancer Registry/Medicare claims-linked database available through the Comparative Effectiveness Research on Cancer in Texas (CERCIT) consortium. Claims for DXA were obtained from Medicare part B for a period from one year before to 6 months after AI initiation. We also evaluated the use of bone-conserving agents (BCA). We collected data for prescription drugs from Medicare part D claims. We used multivariate logistic regression models to determine the association of sociodemographic variables with DXA use after controlling for disease stage and type of AI.

Results: Our breast cancer study cohort included 3587 women. Of these, 1999 (55.7%) underwent DXA between 1 year before and 6 months after AI initiation. Women aged 75 and above were less likely to receive DXA (odds ratio [OR], 0.80 (0.70–0.91) and less likely to receive either DXA or BCA (OR, 0.80; 95% CI, 0.70–0.92) than were women aged 66–74 years. African American women were less likely to receive DXA (OR, 0.70; 95% CI, 0.53–0.92) and less likely to receive either DXA or BCA than were non-Hispanic white women (OR, 0.68; 95% CI, 0.52–0.90).

Women living in urban areas were less likely to undergo DXA than women living in big metropolitan areas (OR, 0.71; 95% CI, 0.53–0.97). Women with state buy-in enrollment plans were less likely to receive DXA (OR, 0.61; 95% CI, 0.51–0.73) and less likely to receive either DXA or BCA (OR, 0.62; 95% CI, 0.51–0.74) than were women with no such enrollment.Of 3587 patients, 681 (18.98%= 19%) received BCA and 2162 (60.3%) either received either BCA or DXA when starting AI.

Conclusion: Slightly more than 50% of Texas Medicare female beneficiaries with breast cancer beginning AI treatment received DXA. Rates of DXA varied with the patient's age, size of area of residence, and socioeconomic status. Differences between ethnic groups in the use of DXA/BCA were noted, with fewer African American women compared to white women receiving DXA or BCA.

Disclosure: M. Siricilla, None; **R. Luo**, None; **L. Elting**, None; **M. E. Suarez-Almazor**, None.

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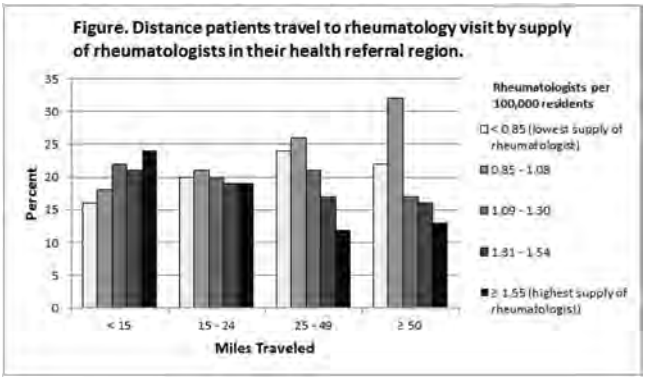
Relationship Between Rheumatology Physician Supply and Travel Distances to Rheumatologists for Medicare Beneficiaries in the United States. Gabriela Schmajuk[1], Chris Tonner[2] and Jinoos Yazdany[2]. [1]UCSF / San Francisco VA, San Francisco, CA, [2]University of California, San Francisco, San Francisco, CA.

Background/Purpose: Workforce shortages in rheumatology have been reported in the face of an aging population and increased number of people gaining insurance under the Affordable Care Act. Population-wide studies of rheumatology supply and the distances that patients travel to see a rheumatologist have not been performed. We used national Medicare data to examine the actual distances patients travel for rheumatology care and hypothesized that patients travelling farthest would reside in low-supply areas.

Methods: Data derive from nationwide Medicare fee-for-service medical claims for 2009 for a 5% random sample of beneficiaries. All patients ≥ age 18 with 12 months of continuous enrollment in Medicare Parts A and B who had at least 1 visit to a rheumatologist were included. We calculated distance between the center of the patient's 5-digit ZIP code and the center of the rheumatologist's office 5-digit ZIP code for the first rheumatologist seen during the calendar year. We averaged distances according to health referral regions (HRRs), regional health care markets for tertiary medical care, and compared average distance with the supply of rheumatologists per HRR (publically available data through the Dartmouth Atlas). Individuals from HRRs with fewer than 40 eligible beneficiaries were censored from this analysis to increase the precision of our estimates.

Results: We studied 44,043 Medicare patients who had at least one visit to a rheumatologist during 2009, representing 245 HRRs. Median distance traveled was 9.3 miles (IQR 4–22). 10% of patients travelled ≥50 miles to see a rheumatologist. Of those traveling long distances, 22% resided in an HRR with the lowest supply of rheumatologists (<0.85 per 100,000 residents) but over 25% resided in an HRR in the 2 highest quintiles of supply (> 1.30 per 100,000 residents). When distances were averaged according to HRR, 13 (4%) of HRRs had an average travel distance of ≥50 miles; only 4 of these HRRs had a supply of rheumatologists in the lowest quintile (Figure).

Conclusion: A substantial proportion of patients in the United States travel significant distances to visit a rheumatologist, although a minority of these patients resides in areas with the lowest supply of rheumatologists. These findings are contrary to our original hypothesis that rheumatologist supply is the main reason for long travel distances. Whether factors such as physician participation in health plans, tertiary care referral patterns, and patient preferences affect travel distance will require additional study.



Disclosure: G. Schmajuk, None; **C. Tonner**, None; **J. Yazdany**, None.

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Dermatologic Rheumatism: Our Experience with a Multidisciplinary Dermatology/Rheumatology Clinic. Archana Sharma[1], Lin A. Brown[2], Dorothea Barton[3] and John Mecchella[4]. [1]Dartmouth-Hitchcock Medical Center, Lebanon, NH, [2]Dartmouth-Hitchcock Med Ctr, Lebanon, NH, [3]Dartmouth Hitchcock Medical Center, Lebanon, NH, [4]Giesel school of medicine and Dartmouth Hitchcock Medical Center, Lebanon, NH.

Background/Purpose: Multidisciplinary clinics are becoming increasingly common as a way to bring together multiple specialists to care for patients with complex diseases. While multidisciplinary clinics commonly involve pulmonologist and cardiologist for patients with pulmonary hypertension, rheumatology and dermatology combined clinic are thought to be less common. Managing skin lesions in patients with known or possible autoimmune diseases can be a diagnostic and therapeutic challenge which often requires the combined expertise of dermatology and rheumatology. Previous studies have shown the benefit of managing patients with psoriasis and psoriatic arthritis in a combined dermatology and rheumatology clinic but to our knowledge there have not been any studies reporting the experience of a general dermatology/rheumatology clinic. We feel that our multidisciplinary clinic adds significant value to complex patients and this study sought to evaluate the clinical experience of a dermatology/rheumatology clinic.

Methods: We performed a retrospective chart review of all patients presenting to our dermatology / rheumatology combined clinic between July 2008 to April 2014 at Dartmouth-Hitchcock Medical Center. A total of 126 patients were seen over 158 visits. We reviewed demographic data, initial diagnosis, treatment modalities including procedures like skin biopsy, change in initial diagnosis and treatment.

Results: Of the 126 patients evaluated, 73% were referred by rheumatology and 27% by dermatology. The majority of participants were females (75%) and the mean age of the patients was 52 years. The average wait period to be seen in the clinic after the referral was made was 3.8 weeks. A skin biopsy was done in 24% patients during the visit and 19% had a skin biopsy reviewed at the visit. The most common initial diagnosis were connective tissue disease related rash (9.5%), SLE (9%) and vasculitis (9%). This was followed by drug rash, psoriasis and psoriatic arthritis. Seventy-seven patients (61%) had a change in diagnosis and treatment as a result of this combination clinic visit. Of the 77 patients who had a treatment change, 18% received DMARD therapy and 8% received biologics. On follow-up, 28.5% patients had significant or complete improvement, 43.5% patients had partial improvement, 12% reported no improvement at all and 16% were lost to follow up.

Conclusion: This study shows that the majority of patients seen in our multidisciplinary clinic had a change in the diagnosis and/or treatment. We believe that this clinic brings value to patients by simplifying the care of these complex patients by having multiple specialists in the same room with the patients. This integrated care approach improves the quality of care for our patients with skin and musculoskeletal diseases. Moreover this combined clinic increases access for these patients and as patients may receive appropriate treatment sooner, it may reduce the overall health care costs for these patients.

Disclosure: A. Sharma, None; **L. A. Brown**, None; **D. Barton**, None; **J. Mecchella**, None.

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Treat-to-Target (T2T) and Measuring Outcomes in RA Care: a 2014 Longitudinal Survey of US Rheumatologists. John J. Cush[1] and Jeffrey R. Curtis[2]. [1]Baylor Research Institute and Baylor University Medical Center, Dallas, TX, [2]University of Alabama at Birmingham, Division of Clinical Immunology and Rheumatology, Birmingham, AL.

Background/Purpose: Changes in US rheumatologic practice for rheumatoid arthritis (RA) patients in the past decade have been influenced by novel therapies, increasing disease metric use and practice economics. This survey of US rheumatologists (Rheums) examined how commonly disease activity measures are used in clinical practice and if they inform decision-making or alter clinical practices over time.

Methods: In 2014, 2027 US Rheums were invited (via 2 emails) to an online survey that included 26 questions on demographics, practice characteristics, RA care practices, DMARDs/biologic use and the use of disease activity metrics. This 2014 cross-sectional survey of Rheums was compared with 2005 and 2008 responses (Table) to assess changes over time. Rheums doing metrics (Metric Rheums) were compared to those who do not (Non-Metric Rheums) with regard to their treatments and practices.

Results: Recruitment for this survey is ongoing. Thus far there are 317 respondents (18% response), with responders being mostly male (71%) with a mean age of 52.8 yrs. 40% of Rheums were in practice >25 yrs; up from 18.2% in 2005. Respondents were largely from private practice (67%) or academics (24%). Compared to 2005, US Rheums do fewer annual x-rays (16 vs 48%), MRI (1.7 vs 8%), or ultrasound (3.9 vs 1.9%). Rheums reported they achieve high rates of ACR 20-like responses (72.6%) and remission (39%) in their patients. Disease activity measures increased since 2005, with the HAQ or its variants being most measured at each visit, followed by the RAPID3 and the CDAI (Table). Metrics were done by 45% of Rheums - owing to improved care (76%), decision making (67%) and ease of use (50%). More than half (55%) did not collect formal measures largely because of the time required (63%), not on their EMR (32%) or just not needed (32%). Metric and non-Metric Rheums were equally committed to research, joint exams and lab testing. Metric and non-Metric Rheums did not differ in the number of patients on TNF inhibitors (47.1 vs 47.4%), or in the management of 3 clinical vignettes differing only in the amount of metric data provided. All rheums were more likely to inject joints when less data was provided and more likely to change or add biologics when more metrics were available. For those failing their first TNFi, 66.7% would choose another TNFi (down from

74.5%), while with others switched to abatacept (19%), tocilizumab (7%), rituximab (2%) or tofacitinib (1%). While a minority (20%) of Rheums don't believe in the T2T "hype", 43% assert they have always practiced in a T2T manner and 37% have adopted a T2T strategy for RA care.

Conclusion: Routine use of RA disease activity measures has become a practice standard in less than half of US rheumatologists. Despite their collection, there is little evidence that metrics are changing how patients are managed.

Changes over time in practice, TNFi and clinical metric use*

	2005	2008	2014
N	1140	446	317
Mean Age (yrs)	49	53	58
TNFi use > 50%	44.2	69	75
Use of RA Disease Activity Metrics at Routine Visits			
HAQ or MDHAQ	17.6	22.9	36.1
RAPID3	ND	3.1	26.7
DAS28	5.9	12.2	16.5
CDAI	ND	2.3	16.2
Vectra MBDA	ND	ND	11.7
SDAI	ND	0.8	3.5
ACR20	1.7	3.9	1.4
None of the above	ND	ND	55

*all results expressed as percents unless noted

Disclosure: J. J. Cush, Pfizer, Celgene, CORRONA, Amgen, NIH, Novartis, UCB Pharma, 2; **J. R. Curtis**, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

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Biologic Dmards Modify the Association Between Patient Expectations and Outcomes of Total Knee Replacement in Rheumatoid Arthritis Patients. Hassan Ghomrawi[1], Lisa Mandl[2], Mark P. Figgie[2], Michael Alexiades[2] and Susan M. Goodman[2]. [1]Weill Cornell Medical College, New York, NY, [2]Hospital for Special Surgery, New York, NY.

Background/Purpose: Unmet patient expectations of total knee replacement (TKR) correlate with postsurgical dissatisfaction, and are linked to outcomes. Patients with rheumatoid arthritis (RA), may have lower expectations than patients with osteoarthritis (OA), due to the systemic nature of the disease and its other manifestations such as fatigue. Biologic DMARDs enhance RA patient quality of life. The effect of pre-operative use of these medications on patient expectations and outcomes of TKR is not known. The purpose of this study was to assess the correlation of preoperative expectations with TKR outcomes in RA patients on biologics and those not on biologics, compared to matched OA patients undergoing TKR.

Methods: Validated RA patients were identified from an institutional TKR registry and their use of biologics was recorded from chart review. RA patients were matched to OA patients on age, sex, prior TKR, and preoperative activity level using the Lower Extremity Activity Scale (0–18, 18 highest level of activity). Preoperative patients completed the validated Hospital for Special Surgery (HSS) Knee Expectations Survey (19 items, score range 0–100, 100 is highest expectation). At 2 years, patients completed the WOMAC pain and function. Preoperatively, expectation scores between RA patients on biologic DMARDS, conventional therapy and matched OA patients were compared. We used regression to determine the association between expectation scores and 2-year WOMAC pain and function subscale scores, adjusted for baseline score.

Results: One hundred fourteen RA cases, 46.5% on biologics, were matched to 228 OA cases. The RA cases were 11.8% male and the average age was 62.6 +/−12.2 years. The average pre-operative LEAS score was 8.3 +/−2.9, which corresponds to being able to walk around the house and walk for several blocks at a time without any assistance. 16.7% of the patients had a prior contralateral TKA. The mean duration of RA was 19.7 +/− 13.4 years. RA patients on biologics had expectations similar to matched OA patients (total expectation score 76.3 ± 8.1 vs. 77.4 ± 17.4, p = 0.71), while RA patients not on biologics had expectations that were clinically and statistically significantly lower (69.9 ± 22.4 vs. 77.1 ± 19.0, p-value = 0.03). Higher expectations scores were associated with better 2-year WOMAC function and pain scores (2-year WOMAC pain coefficient=0.393, p-value<0.001, 2-year WOMAC function coefficient=0.441, p-value<0.001) in RA patients not on biologics therapy but not in RA patients on biologic DMARDS (2-year WOMAC pain coefficient=−0.126, p-value=0.426, 2-year WOMAC function coefficient=0.005, p-value=0.977) nor matched OA patients (2-year WOMAC pain coefficient=−0.037, p-value=0.614, 2-year WOMAC function coefficient=0.060, p-value=0.460).

Conclusion: Expectations of post-operative outcomes are only significantly related to post-operative pain and function in RA patients not on biologic DMARDS; there is no relation in RA patients on biologics or in OA patients. The reasons for this are unclear, and whether this is due to unrealistic expectations in OA and RA patients on DMARDS or that biologics reduces the need to manage expectations needs to be explored.

Disclosure: H. Ghomrawi, None; **L. Mandl**, None; **M. P. Figgie**, None; **M. Alexiades**, None; **S. M. Goodman**, None.

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Is Socioeconomic Status at Diagnosis Associated with Long-Term Direct Medical Costs in Systemic Sclerosis? a General Population-Based Cohort Study. Natalie McCormick[1], Mohsen Sadatsafavi[2], Wenjia Chen[2], Carlo A. Marra[3] and J. Antonio Avina-Zubieta[4]. [1]University of British Columbia/Arthritis Research Centre of Canada, Vancouver, BC, [2]University of British Columbia, Vancouver, BC, [3]Univ of British Columbia, Vancouver, BC, [4]Arthritis Research Centre of Canada, Richmond, BC.

Background/Purpose: Low socioeconomic status (SES) is associated with negative health outcomes and higher healthcare costs in general populations, but the impact of SES on costs in systemic sclerosis (SSc) is unknown. To address this knowledge gap, we examined the relationship between SES at diagnosis, and direct medical costs for 5 years after diagnosis, in a general population-based context. We hypothesized that baseline SES would be associated with higher costs.

Methods: Data Source: Our administrative data captured *all* provincially funded outpatient encounters and hospitalizations (1990–2010), and *all* dispensed medications (1996–2010) regardless of funding source, in the province of British Columbia.

Sample: We assembled a general population-based cohort of all incident cases of SSc who received care from 1996–2010, based on the following validated algorithm: a) two ICD-9-CM codes for SSc at least 2 months apart but within a 2 year period by a non-rheumatologist physician; or b) one ICD code by a rheumatologist or hospitalization. Statistics Canada neighborhood income quintile data for the year of SSc diagnosis was used to define SES.

Cost Calculation: Costs for outpatient services and prescriptions were summed directly from billing data. Case-mix methodology was used for hospitalizations.

Statistical Analysis: Early mortality is common in SSc and likely associated with high costs before death, but failure to account for this censoring will underestimate the long-term costs of SSc. To address this, follow-up was divided into 90-day periods with costs per-period weighted by the person-specific inverse probability of being alive in each period. A generalized linear model was used to

1) Evaluate the relationship between SES and direct medical costs, after adjusting for sex, age and baseline Charlson's comorbidity index; and

2) Predict the cumulative 5-year costs (adjusted for censoring) for cases in each SES group.

Parametric bootstrapping was used to obtain 95% confidence intervals (CI). Costs are reported in 2010 Canadian dollars.

Results: We identified 1,116 incident SSc cases (83% female, mean age 56.2 years) contributing 3,392 person-years. 5-year costs totaled $36,559,914 with 24% from outpatient, 48% from hospital and 28% from medications.

Age (p=0.0278), Charlson's co-morbidity score (p < 0.0001) and being in the lowest (p=0.0364) or middle (p=0.0015) SES quintile (vs. the highest) were significantly associated with costs. Predicted cumulative 5-year costs for the lowest-SES cases were 42% greater than the highest-SES ($55,035 vs. $38,664). Highest-SES cases had the lowest medication costs (**see Table**). Cases in the middle SES quintile at diagnosis had the highest outpatient, hospital and overall costs.

Conclusion: The long-term healthcare costs of SSc cases are substantial (averaging $51,643 per-person over 5 years), and associated with SES, being 42% greater, on-average, for the lowest-SES than the highest.

Socioeconomic Quintile at Diagnosis	N Cases	N Female (%)	Mean Age at Diagnosis (SD)	Median Baseline Charlson Comorbidity Score (IQR)	N Months of Follow-Up	N 90-Day Costing Periods	N Ever-Hospitalized (%)	Unadjusted Overall Costs	Covariate-Adjusted Mean Per-Person Predicted Costs (95% CI) Outpatient	Hospital	Medication	Overall
All	1,116	922 (83%)	56.2 (14.6)	0 (1)	40,707	13,569	595 (53%)	$51,643	–	–	–	–
1=Lowest	220	178 (81%)	55.0 (14.1)	1 (2)	7,899	2,633	134 (61%)	$55,680	$11,373 ($11,005–$11,741)	$14,899 ($12,380–$17,418)	$17,161 ($16,340–$17,982)	$55,035 ($52,516–$57,554)
2	212	176 (83%)	55.0 (15.0)	0 (1)	7,599	2,533	118 (56%)	$43,680	$10,607 ($10,104–$11,111)	$8,750 ($7,167–$10,332)	$13,377 ($12,769–$13,985)	$43,169 ($41,369–$44,968)

3=Middle	239	204 (85%)	56.6 (15.3)	0 (1)	8,688	2,896	116 (49%)	$59,872	$14,251 ($13,536–$14,965)	$15,801 ($13,403–$18,199)	$14,963 ($14,477–$15,449)	$65,054 ($60,939–$69,170)
4	230	189 (82%)	56.4 (14.4)	1 (1)	8,484	2,828	125 (54%)	$54,007	$10,670 ($10,265–$11,075)	$10,230 ($8,405–$12,056)	$17,794 ($16,975–$18,612)	$51,381 ($49,054–$53,708)
5=Highest	215	175 (81%)	58.0 (14.0)	0 (1)	8,037	2,679	102 (47%)	$43,870	$11,033 ($10,632–$11,434)	$9,124 ($7,768–$10,481)	$11,979 ($11,557–$12,402)	$38,664 ($37,159–$40,169)

Disclosure: N. McCormick, None; **M. Sadatsafavi**, None; **W. Chen**, None; **C. A. Marra**, None; **J. A. Avina-Zubieta**, None.

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Predictors of Gout Flares in a US Managed Care Setting. Robert Jackson[1], Aki Shiozawa[1], Erin Buysman[2], Aylin Altan[2], Stephanie Korrer[2] and Hyon K Choi[3]. [1]Takeda Pharmaceuticals International, Inc, Deerfield, IL, [2]Optum, Eden Prairie, MN, [3]Boston University School of Medicine, Boston, MA.

Background/Purpose: Gout is the most common inflammatory arthritis in the US, and acute gout flares are among the most painful events experienced by humans. The goal of this study was to assess gout flares in a managed care setting to better understand the patient characteristics that are associated with frequent flares.

Methods: This was a retrospective cohort study using administrative claims data from a large US health plan of commercially insured and Medicare Advantage enrollees. Patients had evidence of gout based on medical and pharmacy claims indicating gout between January 1, 2009 and April 30, 2012. The 12 months prior to the index gout claim was used to assess baseline confounders including demographics, comorbid conditions, baseline health care resource utilization, and baseline serum uric acid (sUA) levels. Gout flares were assessed in the 12 months following the index gout claim based on diagnoses for gout or joint pain followed within 7 days by claims for NSAIDs, colchicine, corticosteroids, or joint aspiration/drainage. A negative binomial model was used to assess the relationship between patient characteristics and the count of gout flares in the 12-month follow-up period.

Results: Our study included 102,703 patients with gout; 56,611 patients (55%) had evidence of at least one gout flare in 12 months of follow-up, and 13,502 (13%) had multiple flares. Patients had on average 0.73 flares per year, and the average time between flares in patients with multiple flares was 115 days. Characteristics associated with a higher count of flares included Black race, lower net worth, residing in the South census region, high levels of baseline ambulatory utilization, new initiation of urate lowering drugs (ULT) during follow-up, and higher baseline sUA (Table). Cardio-metabolic-renal comorbidities appeared to be associated with fewer flares; however, this may be due to our definition of flares in the claims based on medication use (e.g., NSAIDs) that is often contraindicated with these conditions. Age and gender were not significantly associated with flare frequency after controlling for other confounders.

Conclusion: This large contemporary study of gout patients in a managed care setting indicates over half of patients experiencing at least one flare in a 12-month period, and nearly a quarter of those patients experiencing multiple flares. Black race, lower economic status, Southern region of residence, initiation of urate lowering therapy, and higher baseline sUA were associated with a higher risk for flares. These data may help identify patients at high risk for flares who could be targeted with a gout management plan aimed at preventing flares.

Table. Adjusted Incidence Rate Ratios for Gout Flares According to Patient Characteristics

Variable	Adjusted Incidence Rate Ratio (95% Confidence Interval)
Gender × Age Interaction	
Male, 18–44	reference
Male, 45–64	0.98 (0.93, 1.03)
Male, 65+	0.94 (0.87, 1.02)
Female, 18–44	0.94 (0.80, 1.09)
Female, 45–64	0.95 (0.87, 1.03)
Female, 65+	1.02 (0.93, 1.11)
Geographic Region	
West/Other	reference
Northeast	1.07 (0.98, 1.16)
Midwest	1.09 (1.00, 1.18)
South	1.12 (1.05, 1.19)
Race	
Black	reference
Other Race	0.86 (0.81, 0.90)
Net Worth	
≥ $250,000	reference
Less than $250,000/Unknown	1.06 (1.02, 1.11)
Baseline Comorbidities	
Cardiovascular Conditions (not including Hypertension)	0.84 (0.80, 0.88)
Hypertension	0.96 (0.92, 1.01)
Diabetes	0.86 (0.81, 0.90)
Renal Impairment	0.89 (0.85, 0.93)
All-Cause Healthcare Resource Utilization	
Inpatient Stay or ER Visit	1.04 (0.99, 1.09)
Ambulatory Visits ('9)	1.14 (1.09, 1.20)
Baseline sUA Level (mg/dL)*	
<5.0	reference
5.0–<6.0	1.01 (0.91, 1.12)
6.0–<7.0	1.34 (1.22, 1.47)
7.0–<8.0	1.51 (1.38, 1.65)
8.0–<9.0	1.59 (1.45, 1.74)
9.0+	1.79 (1.63, 1.95)
Follow-up ULT Medication Initiation	1.46 (1.40, 1.52).

* Based on 14,641 patients with baseline sUA levels in the database.

Disclosure: R. Jackson, Takeda Pharmaceuticals International, Inc., 3; **A. Shiozawa**, Takeda Pharmaceuticals International, Inc., 3; **E. Buysman**, Takeda Pharmaceuticals International, Inc, 9; **A. Altan**, Takeda Pharmaceuticals International, Inc., 9; **S. Korrer**, Takeda Pharmaceuticals International, Inc, 9; **H. K. Choi**, Takeda Pharmaceuticals International, Inc;, 5, AstraZeneca, 5.

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Difficult to Treat Gouty Arthritis Associated with Poor Health Related Quality of Life and High Resource Utilization: Post- Hoc Analysis. Louis Bessette[1], Frédéric Lioté[2], Carmen Moragues[3], Rüdiger Moericke[4], Zhang Zhiyi[5], Alberto Ferreira[6], Pascal Lecomte[6], Sophia Kessabi[6], Haijun Tian[7] and Jasvinder Singh[8]. [1]CHUL, Quebec, QC, [2]Hôpital Lariboisière & University Paris Diderot, Paris, France, [3]Hospital Platón, Barcelona, Italy, [4]Institut für Präventive Medizin & Klinische Forschung GbR, Magdeburg, Germany, [5]The First Affiliated Hospital of Haerbin Medical University, Haerbin, China, [6]Novartis Pharma AG, Basel, Switzerland, [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [8]Mayo Clinic, Rochester, MN.

Background/Purpose: Difficult-to-treat (DTT) group in the MOTION study included symptomatic refractory gouty arthritis (RGA) patients with ≥3 flares, refractory to NSAIDs/colchicine/steroids or to uric acid lowering therapy (ULT) due to contraindication, intolerance, or lack of efficacy. There is lack of evidence on burden of illness in DTT patients. The study assessed burden of illness in DTT patients over 1 year.

Methods: A post hoc descriptive comparison was done between DTT vs the other refractory gout (ORG) patients using data from the MOTION (1 year, multinational, non-interventional, prospective, observational) study. Among DTT patients, outcomes for patients with tophi at baseline and patients who discontinued ULT prior to study entry were also summarized. The study outcomes (evaluated at baseline, by time point and pooled yearly) included health status using EuroQol Group 5-Dimension (EQ-5D) questionnaire, the Gouty arthritis Assessment Questionnaire–Gouty arthritis Impact Scale (GAQ-GIS), pain assessment, healthcare utilization over 1 year and lost work productivity. Patient and physician satisfaction with treatment were measured by the Patient Global Assessment of Response to Treatment and Investigator Global Assessment of Response to Treatment. Continuous and categorical variables were reported as (mean ± SD) and as proportions, respectively, for the DTT and ORG patient groups.

Results: Among 454 patients enrolled in the MOTION study, 64 DTT patients (tophaceous group=29, discontinued ULT=35) were included in the analysis (mean age 55.2, males 85.9%). DTT patients had lower mean EQ-5D utility score and EQ-5D VAS score compared to ORG group, with worse scores in the tophaceous group (Table 1). Tophaceous group patients experienced greater difficulty on all EQ-5D dimensions and pain/discomfort was the most affected dimension in all groups. DTT patients expressed greater overall gouty arthritis concern compared to ORG patients (76.5 vs 72.4%), with highest score in the tophaceous group (85.5%) for pooled data. Tophaceous group reported a higher score on all five dimensions of GAQ GIS. About 45.3% of DTT patients reported severe pain during last flare vs 37.2% ORG patients. Healthcare utilization was greater among DTT than ORG patients (35.9 vs 21.1%). A higher proportion in the tophaceous group visited emergency unit (55.2%), hospital (41.4%) and doctors (89.7%) over one year. Physicians and patients in DTT group were more likely to report poor response to treatment compared to ORG group. DTT group missed 23.4% of their working days compared to 15.6% in ORG patients at baseline, the highest being the tophaceous group (31%).

Conclusion: DTT patients had worse health status and reported higher resource utilization with significantly poorer outcomes reported in tophaceous gout patients, suggesting a high unmet medical need in such patients.

Table-1: Mean EQ-5D utility score and EQ-5D VAS pooled for all visits

	EQ-5D utility score (Mean ± SD)	ED-5D VAS (Mean ± SD)
DTT patients (N = 64)	0.78±0.23	73.37±20.40
DTT with tophi at baseline (N = 29)	0.65±0.24*	66.32±18.09*
DTT with discontinued ULT (N = 35)	0.78±0.24	74.02±18.38
Other refractory gout (ORG) (N = 390)	0.81±0.21	75.12±20.96

* $p<0.05$ *vs.* other refractory gout patients

Disclosure: L. Bessette, Novartis, 2; **F. Lioté**, Novartis, Ipsen, Sanofi, 1, Novartis, SOBI, Astra-Zeneca, Savient, Ipsen, Menarini, Mayoly-Spindler, 2, Novartis, Ipsen, Menarini, Savient, Astra-Seneca, Mayoly-Spindler, 5; **C. Moragues**, Novartis, 2; **R. Moericke**, Novartis, 2; **Z. Zhiyi**, Novartis, 2; **A. Ferreira**, Novartis Pharma AG, Basel, 3; **P. Lecomte**, Novartis Pharma AG, Basel, 3; **S. Kessabi**, Novartis Pharma AG, Basel, 3; **H. Tian**, Novartis Pharmaceuticals Corporation, East Hanover NJ, 3; **J. Singh**, Takeda, Savient, Novartis, 2, Savient, Takeda, Regeneron and Allergan, 5.

ACR Poster Session A
Imaging of Rheumatic Diseases: Ultrasound
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Sonographic Evaluation of the Fifth Metatarsophalangeal Joint Erosion in Rheumatoid Arthritis. Nevsun Inanc[1], Gulsen Ozen[1], Sibel Z. Aydin[2], Esen Kasapoglu Gunal[3] and Haner Direskeneli[1]. [1]Marmara University School of Medicine, Istanbul, Turkey, [2]Koc University Faculty of Medicine, Istanbul, Turkey, [3]Goztepe Medeniyet University Faculty of Medicine, Istanbul, Turkey.

Background/Purpose: Joint erosions in RA correlate with structural damage progression and functional capacity. Therefore, detection and the follow-up of erosions are of paramount importance for RA diagnosis, monitoring and prognostication. The 5th MTP is usually the first and most commonly destructed joint in RA. Ultrasound (US) is a useful and as good tool as MRI to detect 5th MTP erosions especially in early RA patients. Although a few MRI studies revelaed that most of the MTP erosions were located at the plantar aspect of the joint, it is unknown whether plantar or dorsal or lateral plane US better detects 5th MTP erosions. In this study we aimed to determine the best ultrasonographic plane for detection of 5th MTP joint erosion in RA patients and to assess clinical characteristics of patients with 5thMTP erosions.

Methods: The 5thMTP of 92 feet of 48 RA patients were evaluated by B-mode and power- Doppler US for signs of erosion. US images were obtained from 3 different aspects, the dorsal, lateral and the plantar surface of the foot, in longitudinal and tranverse scans. The presence of erosion was determined according to OMERACT definition. Patients were also assessed clinically (tender/swollen joint count, DAS28, HAQ scores) along with disease characteristics. Each erosion in each aspect were recorded seperately.

Results: The study cohort consisted of 48 RA patients (F/M=35/13, mean age 50.7±12.3 years, mean DAS28 score 4.04±1.47, HAQ score 0.94±0.88) with mean disease duration of 8.2±7.3 years. RF and anti- CCP positivity were 66.7% and 60.4% respectively. The 5th MTP erosions were detected in 35 of 48 patients (72.9%) and 62 of 92 feet (67.4%). Of the erosions 15 (16.3%) were observed at dorsal plane whereas plantar and lateral planes revelaed majority of the erosions, 53 (57.6%) and 52 (56.5%), respectively. In 26 feet (28.3%), erosions were observed on both plantar and lateral planes, in 15 feet (16.3%) erosions were observed in all three planes. None of the patients had erosion just in dorsal plane examination of the 5th MTP. The presence of 5th MTP erosion in plantar aspect of foot was significantly higher than both lateral and dorsal aspect ($P<0.0001$, $P=0.002$, respectively). Patients with dorsal erosion had significantly higher disease duration (13.8 years vs 6.5 years, $P=0.005$). Patients with erosions in any aspects have similar disease characteristics including RF, anti-CCP positivity, disease duration, HAQ scores and current biologic requirement, when compared to patients without erosions.

Conclusion: The 5th MTP erosions in RA patients can be better detected with plantar plane US than dorsal and lateral aspect evaluations. These data also indicate that dorsal aspect US of foot may miss erosions in early disease and insufficient when performed solely.

Disclosure: N. Inanc, None; **G. Ozen**, None; **S. Z. Aydin**, None; **E. Kasapoglu Gunal**, None; **H. Direskeneli**, None.

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Can We Use Ultrasound to Identify Rheumatoid Arthritis Patients in Remission Who Cannot Taper Their Medication? Myrthe van der Ven[1], T. Martijn Kuijper[1], A. H. Gerards[2], Ilja Tchetverikov[3], A.E.a.M. Weel[1], D. van Zeben[4], J.M.W. Hazes[1] and J.J. Luime[1]. [1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]Vlietland Hospital, Schiedam, Netherlands, [3]Albert Schweitzer Ziekenhuis, Dordrecht, Netherlands, [4]Sint Franciscus Gasthuis, Rotterdam, Netherlands.

Background/Purpose: Tapering medication in rheumatoid arthritis (RA) patients is becoming increasingly important due to the effectiveness of both biological therapy and tight-controlled treatment. Patients are able to reach the state of remission in which they may be able to taper their medication. Whom to taper and when to taper (amount of time in remission) is unclear. Ultrasound (US) data from cross-sectional studies suggest that the presence of subclinical synovitis might increase the risk of disease flare preventing patients to be tapered. Our objective was to detect subclinical synovitis by US and to relate this to the occurrence of flare in RA patients that continue synthetic and biological DMARDs for 3 months while being in remission.

Methods: Patients who are participating in the TARA (TApering strategies in Rheumatoid Arthritis) study and were examined by US were selected for this analysis. TARA is a single-blinded randomized controlled trial that includes RA patients (aged >17 years) who are treated with the combination of a synthetic DMARD and adalimumab or etanercept and are in remission (DAS44<2.4 & SJC ≤1). In the first 3 months of this study patients continue their medication and if they maintain their disease state, are randomized to (i) tapering the synthetic DMARD or (ii) tapering their TNF blocker. US examination included 26 joints (MCP2–5, PIP2–5, wrists, MTP2–5) graded on greyscale (GS; 0–3) and power Doppler (PD; 0–3). A joint with subclinical synovitis was defined as GS >1 and/or PD >0, while flare was captured by DAS44≥2.4 or SJC >1.

Results: For this analysis we included 67 patients. In total 39 patients (58%) had subclinical synovitis. Three patients (8%) with subclinical synovitis experienced a flare while continuing their combination of synthetic and biological treatment. Patients without subclinical synovitis did not differ from patients with subclinical synovitis if we compared clinical features such as tender joints, serology or acute phase reactants. ACPA was slightly higher in the patients without subclinical synovitis but did not reach statistical significance.

Conclusion: In 58% of the patients we detected subclinical synovitis. However, after three months a low flare rate (4%) was observed among patients in remission continuing their combination therapy of synthetic and biological DMARDs. Although the patients who flared had subclinical synovitis, using GS >1 and/or PD >0 in at least one joint might not be sufficient to discriminate who will clinically flare.

Table 1: Baseline characteristics of patients without and with subclinical synovitis (n=67)

	No subclinical synovitis (n=28)	Subclinical synovitis (n=39)
Women (%)	66	69
Age, years (mean, SD)	52 (12)	58 (12)
PD (%)	*NA*	73
Sum score GS>1 and/ or PD>0 (median, IQR)	*NA*	4 (2–8)
SJC (median, IQR)	0 (0–0)	0 (0–0)
TJC (median, IQR)	0 (0–1)	0 (0–1)
RF positive (%)	56	56
ACCP positive (%)	74	60
ESR (median, IQR)	7 (4–15)	9 (5–16)
DAS score (mean, SD)	1.0 (0.6)	1.2 (0.6)
Disease flare after 3 months (%)	0	8

SD = standard deviation; IQR = interquartile range; NA = not applicable.

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Predictors of Persistence of Power Doppler Ultrasound Synovitis in Rheumatoid Arthritis Patients in Clinical Remission. Nathalie Filippi[1], Cédric Lukas[1], Jacques Morel[2], Bernard Combe[2] and Gael Mouterde[1]. [1]Hopital Lapeyronie, Montpellier, France, [2]Hôpital Lapeyronie, Montpellier, France.

Background/Purpose: Ultrasound (US) is a sensitive tool for the evaluation of joint inflammation in patients with RA, and can detect synovitis even when clinical remission is present [1]. Predictors of persistence of such subclinical power Doppler ultrasound (PDUS) synovitis, like potentially severity of the disease, concomitant treatments, or duration of the remission, remain undetermined. The aims of this study were: (1) to assess the proportion of patients with persistent PDUS synovitis in a cohort of patients with RA in clinical remission (DAS28-ESR<2.6 and without clinically active synovitis); (2) to determine predictors of persistence of PDUS synovitis in these patients.

Methods: RA patients fulfilling 2010 *ACR-EULAR* classification criteria, treated with DMARDS or biologic and in clinical remission (DAS28-ESR<2.6 and without clinically active synovitis, i.e. no joint showing both pain and swelling), were included in this transversal study. Following data were collected: clinical and biological characteristics of arthritis, socio economic factors, and radiographs of hands, wrist and feet. A standard US examination on 40 joints for the presence of synovial hypertrophy and power Doppler signal was performed by an independent investigator blinded to clinical data. A subclinical US synovitis was defined by the presence of a power Doppler signal≥2 in at least one joint. Logistic regression was performed to evaluate the association between subclinical US synovitis and baseline variables at the patient level. The reliability was evaluated with intraclass correlation coefficients (ICCs) based on independent assessments of 30 patients by two investigators.

Results: The 94 patients included had a mean (standard deviation) age of 61.2 years (11.2), mean disease duration of 9.6 years (8.1), a mean duration of remission of 11.9 months (15.4). 60% and 68% of the patients were rheumatoid factor and anti-CCP antibody positive respectively. The mean DAS28-C reactive protein was 1.71 (0.47), median 1.67, and 57.4% of the patients had erosive disease. 61.7% received methotrexate, 57.4% biologic treatment and 11.7% corticosteroids. Inter-observer reliability of assessment of synovial hypertrophy and PD signal were very good (ICC=0.954 and 0.985 respectively). Baseline clinical characteristics and US findings were similar whatever the duration of remission (<6 months, n=47 and ≥6 months, n=47). In multivariate analysis, presence of antiCCP (OR=3.68 [95% CI 1.21–11.1], p=0.021), DAS28-CRP >1.67 (OR=2.97 [95% CI 1.12–7.87], p=0.028) were predictors of persistence of PDUS synovitis, whereas current smoking was negatively associated (OR=0.07 [95% CI 0.01–0.59], p=0.015). The duration of the remission was not associated with PDUS synovitis after adjustment in this cohort.

Conclusion: Our results suggest that RA patients in clinical remission are more likely to have persistence of PDUS synovitis if they have anti-CCP antibodies and higher DAS28-CRP value. Current smoking appears to be a protective factor in this cohort, which might potentially be due to vasoconstriction induced by tobacco.

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Disclosure: N. Filippi, None; **C. Lukas**, None; **J. Morel**, None; **B. Combe**, None; **G. Mouterde**, None.

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The Use of Ultrasound to Detect Residual Joint Inflammation in Patients with Rheumatoid Arthritis in Clinical Disease Remission.

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Background/Purpose: Patients (pts) with rheumatoid arthritis (RA), who achieve clinical disease remission by treatment with disease- modifying agents may have residual joint inflammation and vascularization, which can be detected by Power Doppler (PD) ultrasonography. The aim of this analysis was to evaluate the proportion of RA pts with PD activity, 24 weeks (wks) after the addition of adalimumab (ADA) to methotrexate (MTX).

Methods: MUSICA (NCT01185288), a 24 wk double-blind, randomized, controlled trial evaluated the efficacy of 2 different dosages of MTX (7.5 or 20 mg/wk) plus ADA (40 mg every other wk) in RA pts with inadequate response to MTX. For this analysis, the MTX dosage groups were combined. Synovial vascularization was assessed by PD US at 10 joints (bilateral dorsal and volar views of metacarpophalangeal joints 2, 3, 5; dorsal images alone of metatarsophalangeal joint 5 and wrists), at baseline (BL), wks 4, 8, 12, 16, 20 and 24. Images were scored by ultrasound-experienced rheumatologists using a semi-quantitative 4-grade scale.Joint swelling was assessed for the same 10 joints (SJC10). Disease activity was assessed by 28-joint count disease activity score using C-reactive protein (DAS28[CRP]) (remission < 2.6, LDA < 3.2, MDA 3.2- < 5.1, HDA ≥ 5.1), and simplified disease activity index (SDAI) (remission ≤3.3, LDA ≤11, MDA 11-≤26, HDA >26). Pearson's coefficient (ρ) was used to assess correlation between continuous variables.

Results: After 24 weeks of treatment with ADA +MTX, 44/309 pts (14%) were in DAS28 (CRP) remission (mean PD score, 3.3); 18/309 (5.8%) pts were in SDAI remission (mean PD score, 2.7). 23/44 pts (52%) in DAS28 remission, and 9/18 (50%) in SDAI remission had a PD score ≥ 2, indicating inflammatory activity. At wk 24, for the 10 joints selected, 30/44 (68%) pts in DAS28(CRP) remission had positive PD scores, while only 15 pts (34%) had ≥ 1 swollen joint, and only 5 pts (13.6%) had ≥ 1 tender joint. Ten out of 18 (55%) pts in SDAI remission had a positive PD score, while none had swollen/tender joints. A poor correlation (ρ<0.2) was observed between PD scores and clinical disease scores such as DAS28, SJC66, SJC28, TJC68, TJC28, CDAI, SDAI, PhGA, PGA-pain and disease duration. There was poor correlation (ρ=0.184) between the change from BL to wk 24 in PD scores, and the change from BL to wk 24 in DAS28(CRP) or SDAI. The corresponding shifts in disease activity, mean PD score and SJC10 scores are presented (Table).

Table 1. Mean changes in PD score, DAS28(CRP) score and SJC10 from BL to wk 24

DAS disease state shift (BL→wk 24)	N	Mean change in PD score	Mean change in DAS28(CRP) score	Mean change in SJC10
MDA→MDA	24	−0.5	−0.6	−1.1
MDA→LDA	29	−0.8	−2.2	−2.4
HDA→HDA	41	−1.0	−0.6	−1.3
HDA→MDA	94	−1.8	−2.0	−2.7
HDA→LDA	57	−2.3	−3.6	−4.3

Mean changes in PD score, SDAI score and SJC10 from BL to wk 24

SDAI Disease state shift (BL→wk 24)	N	Mean change in PD score	Mean change in SDAI score	Mean change in SJC10
MDA→MDA	9	−0.7	−7.1	0.2
MDA→LDA	15	−0.4	−15.0	−1.9
HDA→HDA	55	−1.1	−12.6	−1.1
HDA→MDA	85	−1.9	−26.4	−2.7
HDA→LDA	81	−1.9	−35.9	−4.1

PD, power Doppler; DAS28(CRP), disease activity state 28 using c-reactive protein; SJC10, swollen joint count (10 joints); SDAI, simplified disease activity index; LDA, low disease activity; MDA, moderate disease activity; HDA, high disease activity.

Conclusion: In agreement with other studies, residual joint inflammation was detected by PD US in pts in clinical remission; therefore ultrasound can offer additional information to that obtained from clinical disease measures.

Disclosure: G. S. Kaeley, AbbVie, 5; **M. J. Nishio**, AbbVie, 8; **J. Goyal**, AbbVie, 5; **D. MacCarter**, AbbVie, 5, AbbVie, 8; **A. Wells**, AbbVie, 5; **A. Cardoso**, AbbVie, 1, AbbVie, 3; **S. Liu**, AbbVie, 1, AbbVie, 3; **J. Kalabic**, AbbVie, 1, AbbVie, 3; **H. Kupper**, AbbVie, 3, AbbVie, 1.

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Combination with Joint Power Doppler Signals with Anti-Citrullinated Peptide Antibody Predicts Joint Destruction in Rheumatoid Arthritis.

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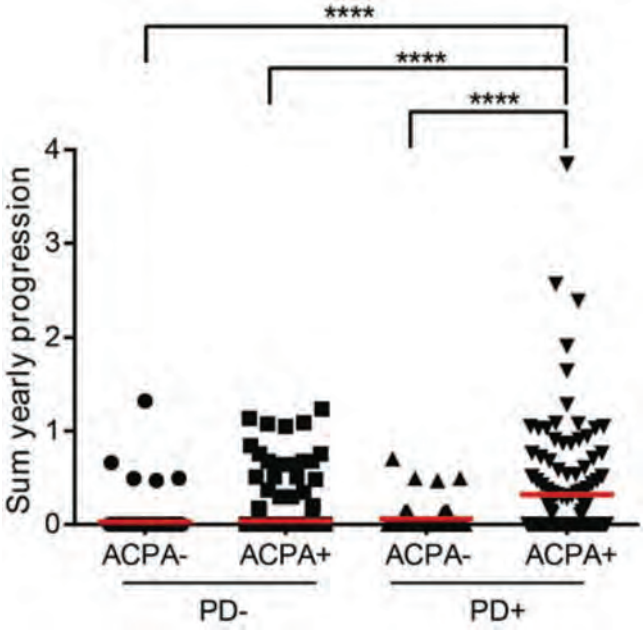
Background/Purpose: Categorizing RA patients who require intensive treatments is highly warranted to optimize the therapy and to avoid overtreatments. We here evaluated the use of predicting joint destruction with joint power Doppler (PD) signal in musculoskeletal ultrasonography (MSUS).

Methods: We performed a retrospective study of 331 RA patients (female n = 280 and male n = 51, mean age 57.9 ± 13.2 y.o) who underwent MSUS from 2002 to 2012. Correlations of progression of joint destructions in 1,308

2nd and 3rd MCP joints with analysis of PD signals of the same joints, clinical findings, age, and disease duration at the study entry, gender, observation period, ACPA, and RF were analyzed in patient- and joint-based fashions, using univariate and multivariate logistic regression analyses and generalized linear mixed model.

Results: Patients' characteristics were as follows: mean disease duration 5.7 ± 7.5 years, observation period 4.6 ± 2.6 years, RF positivity 79.9%, ACPA positivity 76.4%. PD positive 2nd and 3rd joints showed higher rate of joint destruction, especially in ACPA positive patients. Moreover, PD positive joints in ACPA positive patients showed joint destruction even in joints without swelling. Multivariate analysis determined PD, SJ, observation period, and ACPA as independent risks for joint destruction.

Conclusion: PD, SJ, and ACPA are independent predictors for the joint destruction of 2nd and 3rd MCPs in RA. Progression of joint destruction was maximal in PD positive joints in ACPA positive patients, raising the possibility that RA patients are categorized by MSUS findings.



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Ultrasound Power Doppler Findings in the Wrists and Hands Joints of Anti-CCP Antibody Positive Individuals with Non-Specific Musculoskeletal Symptoms and the Development of Inflammatory Arthritis. Jackie L. Nam, Laura Hunt, Elizabeth M.A. Hensor, Philip G. Conaghan, Richard J. Wakefield and Paul Emery. NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom.

Background/Purpose: The use of musculoskeletal ultrasound is increasing in rheumatology practice. Recently we have shown that use of power Doppler signal (PD) on ultrasound in the wrists and hands in patients who present with non-specific musculoskeletal symptoms and are anti-CCP antibody positive can aid the identification of those who will develop an inflammatory arthritis (IA). [1]The aim of this study was to investigate the ultrasound findings at a joint-level in these patients and the use of PD in identifying patients who progressed to inflammatory arthritis (IA).

Methods: In a prospective observational cohort study, patients with new non-specific MSK symptoms and positive anti-CCP underwent imaging with ultrasound at baseline and were followed up for the development of IA. Patients attended for regular follow-up assessments and if necessary were seen earlier if joint symptoms changed. PD findings of the wrists, MCPs and PIPs were scored using a semi-quantitative method from 0 to3 PD using a standard method. Using multilevel binary logistic regression we modelled the association between presence of PD score >0 at baseline and presence of IA in that joint at follow-up; joints (level 1) were nested within patients (level 2).

Results: Our first 100 consecutive patients (73 females, mean age 51 years) were followed up for median 19.8 months (range 0.1–69.0); 50 developed IA after a median 7.9 months (range 0.1–52.4), 34 within 12 months. The majority who progressed to IA in at least 1 joint (43/50) fulfilled the 2010 ACR/EULAR criteria for rheumatoid arthritis. A total of 2200 joints were scanned. The majority of patients (67%) did not have any PD signal present; maximum score in any joint was 1 in 17% and 2 in 16%. None had a joint scoring 3. Progression to clinical synovitis was rare in joints scoring 0 (5% progressed) compared to joints scoring 1 (16%) or 2 (59%). The presence of positive PD signal (any score >0) in a joint at baseline was associated with a 10-fold increase in odds of the joint developing clinical swelling [OR=10.6 (5.3, 21.1), p<0.001].

Conclusion: Our findings suggest that in patients presenting with non-specific MSK symptoms and are anti-CCP antibody positive, ultrasound features of inflammation at a patient- and at a joint-level can aid the identification of patients at risk of developing IA. Results of our larger cohort will be presented.

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PD Signal Detected By Ultrasonography Relates to Joint Destruction in Rheumatoid Arthritis Under Biologics Therapy in Real World. Maasa Hama[1], Yumiko Sugiyama[1], Naomi Tsuchida[1], Yosuke Kunishita[1], Daiga Kishimoto[1], Reikou Kamiyama[1], Kaoru Minegishi-Takase[1], Ryusuke Yoshimi[1], Yohei Kirino[1], Mitsuhiro Takeno[2], Atsuhisa Ueda[1] and Yoshiaki Ishigatsubo[1]. [1]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]Yokohama City University Hospital, Yokohama, Japan.

Background/Purpose: Biologic DMARD (biologics) therapy for rheumatoid arthritis (RA) strongly suppresses joint destruction regardless of its efficacy for disease activity. On the contrary power Doppler (PD) signal detected by ultrasonography (US) is said to be the most potent predictive factor for subsequent radiologic progression. This study aimed to clarify whether PD signal predicts joint destruction of RA patients under biologics therapy in daily practice.

Methods: RA patients who began and continued to receive biologics for more than six months were included. Clinical, laboratory, and US examinations were conducted sequentially from baseline (1st) to the last observation (last). Bilateral wrists and all of the MCP and PIP joints were examined by PDUS and the PD signals were graded from 0 to 3 in each joint. The total PD score was defined as the sum of scores of individual joint, and mean score of several assessments during observational period was also calculated. Structural damage of hands at baseline and at the last was measured by using modified Sharp scoring method for hand X-ray (TSS). Patients having the change in TSS (delta TSS) exceeded 0.5 U per year were defined as showing radiologic progression.

Results: Objectives were 100 RA patients (female 85%, age 59.1±13.4 y.o., disease duration 8.0±8.2 years, 1st DAS28 4.84±1.43). Sixty-three patients continued the same drug (anti-TNF 31, tocilizumab 26, abatacept 6) whereas 37 patients switched biologics. During continuing biologics therapy for 25.3±16.8 months, structural damage progressed in 51% of the patients, who were classified into progressive group, including 18 patients with achieving clinical remission. The progressive group contained more patients who switched agents, and showed higher 1st DAS28 and higher last DAS28 as well as higher last total PD score, compared to the other group. Furthermore, yearly radiologic progression (delta TSS) weakly related to 1st, last, and mean total PD score in addition to 1st DAS28, 1st CRP, and 1st and last MMP-3. Multiple regression analysis using stepwise method revealed that both 1st CRP and mean total PD score were independently associated with joint destruction. For joint-based analysis of total 2200 joints, radiologic progression were seen in 155 joints (7.0%), of which wrists were mainly affected joints, and the existence of PD signal in a joint at any time during observational period was the potent risk for subsequent destruction of the joint (Table).

Conclusion: To practice 'Treat to Target' for achieving radiologic remission in real world, monitoring individual joint by PDUS will be helpful in carrying out optimal intervention even under biologics treatment.

n=2200	Progression	Non-progression	OR (95% CI)	P value
1st PD (+) joint, n (%)	74 (48.1%)	223 (10.9%)	7.81 (5.52, 11.1)	<0.0001
last PD (+) joint, n (%)	36 (24.8%)	83 (4.5%)	6.97 (4.51, 10.8)	<0.0001
mean PD (+) joint, n (%)	91 (59.1%)	282 (13.8%)	9.04 (6.40, 12.8)	<0.0001

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Asymptomatic Versus Symptomatic Ankle Joints in Rheumatoid Arthritis: A High Resolution B-Mode and Power Doppler Ultrasound Study. Mohammed Alsuwaidi[1], Boris P. Ehrenstein[1], Wolfgang Hartung[1] and Martin Fleck[2]. [1]Asklepios Clinic Bad Abbach, Bad Abbach, Germany, [2]University Medical Center of Regensburg, Regensburg, Germany.

Background/Purpose: Despite a crucial role for RA patients' mobility, the ankle joints are frequently clinically neglected, and omitted in activity scoring systems including DAS 28. In addition, only few studies have assessed pathologies detected by ultrasonography of the ankle in symptomatic RA patients (1). Therefore, the type and degree of involvement of the ankle joints were evaluated in established RA patients regardless of symptomatology utilizing standardized high resolution musculoskeletal ultrasound (MSUS) including power Doppler ultrasonography (PDUS).

Methods: A total number of 160 ankle joints of 80 consecutive RA patients fulfilling the ACR/EULAR classification criteria 2010 were examined using MSUS (*Logic E9, GE Healthcare, Buckinghamshire, GB with a ML6–15 linear probe with 6– 15 MHz*) and PDUS according to the EULAR MSUS guidelines (2). In addition, the talonavicular joint, and the flexor and extensor tendons were investigated. Furthermore, ankle pain (VAS score 0–10) was recorded for each patient on joint level. Only VAS = 0 was determined as asymptomatic.

Results: 80 RA patients (52 female, 28 male) with a median age of 60 years (range 28 –81) and a disease duration of 5 years (range 0 – 44) were enrolled in our study. The median DAS28 was 5,0 (range 0,8 -7,8). 97 ankles were painfull (VAS 1–10), whereas 63 ankles were asymptomatic (VAS = 0). Overall, the predominant pathology was arthritis of the tibiotalar and/or talonavicular joint in 124 ankles (77%), followed by tenosynovitis of the flexor tendons in 44 ankles (28%). In symptomatic ankles 59% showed arthritis of the tibiotalar joint (TTJ) and 35% synovitis in the talonavicular joint (TNJ). In 35% of the asymptomatic ankles TTJ synovitis could be detected and 18% TNJ arthritis. PDUS activity was higher in the subgroup of symptomatic ankles (10% of symptomatic ankles (10/97) compared to 2% of asymptomatic patients (3/63). For detailed information see table 1.

Conclusion: Most frequent pathologies detected by MSUS were arthritis of the tibiotalar and talonavicular joint, followed by tenosynovitis of the flexor tendons. Pathologic findings are significantly more frequent in symptomatic ankles but also common in completely asymptomatic ankles of RA patients, whereas overall PDUS activity is low and if present predominately observed in symptomatic patients.

Table 1:

Pathologies	Arthritis tibiotalar (%)	Arthritis talonavicular	Tenosynovitis (M. tibialis posterior +/or M. flexor digitorum)	PDUS positive Arthritis
All ankles (n = 160)	79 (66%)	45 (28%)	44 (27%)	12 (7,5%)
Symptomatic ankles (n=97)	57 (59%)	34 (35%)	32 (33%)	10 (10%)
Asymptomatic ankles (n=63)	22 (35%)	11 (18%)	12 (19%)	2 (3%)
Chi^2	p = 0.003	p = 0.016	n.s.	n.s.

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Metacarpophalangeal Cartilage Loss in Rheumatoid Arthritis. a Simple and Fast Ultrasonographic Assessment Comparing Patients and Healthy Controls. Tomas Cazenave[1], Christian A. Waimann[1], Marwin Gutierrez[2], Emilio Filippucci[3], Gustavo Citera[1] and Marcos G. Rosemffet[1]. [1]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Università Politecnica delle Marche, Jesi, Italy, [3]University of Ancona, Jesi, Italy.

Background/Purpose: There is evidence supporting the use of ultrasonography (US) as a valid and reliable imaging tool to evaluate cartilage in patients with arthritis. The aims of our study were to measure cartilage thickness in rheumatoid arthritis (RA) patients compared with Healthy Subjects (HS) and evaluate the relationship between US findings and clinical variables.

Methods: We designed a cross-sectional study including patients with diagnosis of RA (ACR/EULAR 2010) and HS. Data collected included clinical and demographic characteristics, Body Mass Index (BMI), 28-joint disease activity score (DAS28) and labor characteristics. US evaluation was performed by two rheumatologist with experience on US who were blind to clinical data. The hyaline cartilage of the metacarpal heads for fingers 2–5 was bilaterally scanned from the dorsal aspect with metacarpophalangeal joints in a full flexed position. Two perpendicular measurements at the central cartilage area (transverse and longitudinal views) were obtained and average cartilage thickness recorded. The association between RA characteristics and cartilage thickness was assessed using univariate and multivariate models, adjusted for sex, age, BMI and labor characteristics. Differences between HS and RA patients were compared using t-test. A two-sided P value of 0.05 was considered statistically significant.

Results: We included 98 subjects: RA=45 and HS=53. Mean age was 49 ± 13 years, mean BMI was 25± 4 and 70% were female. Patients with RA were significantly older and had lower BMI than HS. Patients with RA had a mean disease duration of 8 ± 7 years, 60% had erosive disease and mean DAS28 of 4.8 ± 1.4. A total of 784 joints were evaluated (RA=360 and HS=424). Time to perform US examination was 6 minutes per patient. Correlation between transverse and longitudinal view was 0.97 ($p<0.01$). Interobserver correlation was very good (ICC >0,92). Patients with RA had significantly lower cartilage thickness than HS (mean: 0.43 mm versus 0.58 mm, $p<0.01$). After adjusting for sex, age, BMI and type of job, RA was independently associated with cartilage thinning (β -0.51, $p<0.01$).

In patients with RA, those who were older, had longer disease duration, women and erosive disease, had significantly lower values of cartilage thickness. On multivariate regression analysis, only longer disease duration remained significantly associated with lower values of cartilage thickness.

Conclusion: Patients with RA showed significantly lower values of cartilage thickness as compared to healthy controls, having disease duration the highest impact on this fact. The impact of cartilage thinning on pain and functional capacity deserves further investigation.

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A Rapid 4- Joint Ultrasonographic Score to Daily Monitoring Disease Activity in Patients with Rheumatoid Arthritis: Validity and Sensitivity to Change. Tomas Cazenave[1], Christian A. Waimann[2], Gustavo Citera[3] and Marcos G. Rosemffet[3]. [1]IREP, Buenos Aires, Argentina, [2]Hospital Olavarria, Olavarria, Argentina, [3]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina.

Background/Purpose: Ultrasound has demonstrated to be a sensitivity and specific tool to assess patients with Rheumatoid Arthritis (RA). However, the feasibility of this technology in daily clinical practice is still under debate. The purpose of our study was to evaluate the validity and sensitivity to change of a rapid 4-joint ultrasonographic score that could be applied to daily monitoring disease activity in patients with RA.

Methods: We included patients with RA (ACR/EULAR 2010). Data was collected at baseline, 3 and 12 months. Each patient underwent clinical (DAS28) and ultrasonographic (US) evaluation of 28-joints. Power Doppler (PD) and gray scale (GS) were graded from 0 to 3, according to OMERACT standards. Three ultrasonographic scores were calculated: 4-joints (bilateral radio and intracarpal joint and second metacarpophalangeal), 6-joints (4-joints plus bilateral fifth metatarsophalangeal), and 28- joints. US scores come as the result of the addition of PD and GS score, with a total score ranged from 0 – 36, 0 – 48, 0 – 174, respectively. We evaluated psychometric properties of

4-joints score in comparison with others US scores, including criterion, construct validity and internal consistency (Cronbach's α coefficients). Sensitivity to change was measured at 12 months using standardized response mean (SRM) and classified according Cohen's effect size. The minimal important change (MIC) was defined as a change of 1.96 times the standard error of measurement.

Results: 49 patients were included. All patients completed annual visits. Mean age was 53 ± 10 years, 85% were female, and disease duration was 8 ± 5 years. Baseline DAS28 score was 4.8 ± 1.5. Mean 4-joints ultrasonographic score was 12 ± 6 (Doppler subscale 5 ± 3; Synovitis subscale 6 ± 3). The score showed an acceptable confiability and a moderate to good correlation with DAS28, 6 and 28 joints US scores (Table 1). The 4-joint US examination was able to measures change in clinical status (SRM=0.98, large effect size). A change in score ≥5 was defined as a minimal important change. The ultrasonographic evaluation of 4-joint US score was fast, taking 5 minutes per patient, in comparison with 8 and 35 minutes for 6 and 28 joints scores, respectively.

Table 1.

							Correlation matrix (r)		
US score	Baseline mean±SD	Floor effect	Celling effect	Cronbach's α coefficients	MIC	SRM	US 6-joints score	US 28-joints score	DAS28
4-joints	12 ± 6	0%	0%	0.84	4.9	0.98	0.96*	0.80*	0.60*
6-joints	14 ± 7	0%	0%	0.84	5.5	0.94	—	0.83*	0.65*
28-joints	34 ± 20	0%	0%	0.94	5.0	0.72	—	—	0.77*

* P-value <0.05

Conclusion: A reduced US score of 4 joints showed to be a valid tool to detect and monitor disease activity in patients with RA. The quickness and high ability to detect clinical changes make this score a feasible and useful tool in daily rheumatology practice.

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Seven Joints Ultrasound Scoring System May be Useful and Effective in Assessing Disease Activity in Patients with Rheumatoid Arthritis in the State of Remission in Daily Clinical Practice. Petra Hanova[1], Jakub Zavada[1], Jana Hurnakova[1], Martin Klein[1], Olga Sleglova[1], Marta Olejarova[1], Martin Komarc[2], Ladislav ŠEnolt[1] and Karel Pavelka[3]. [1]Institute of Rheumatology, Charles University, 1st Medical Faculty, Prague, Czech Republic, [2]Institute of Biophysics and Informatics, Prague, Czech Republic, [3]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic.

Background/Purpose: To evaluate if the 7-joint ultrasound scoring system (US7) is able to find synovitis in patients in remission of RA.

Methods: Patients with rheumatoid arthritis (RA) in the state of remission according to DAS 28 < 2,6 criteria with duration at least 3 months were identified. HAQ, SJC, TJC were evaluated for 1 year in 3 months interval. The US7 was assessed by every visit. US7 scoring system was well described and uses semiquantitative assessment of grey scale (GS) and power-doppler (PD) synovitis and incorporates erosion count together with evaluation of soft tissue parts (tenosynovitis) on the dominant hand and foot. Participating sonographers were blinded to clinical assesments and used the same US machine with not changed settings during the study follow up and reached reasonable interobserver and intraobserver reliability in using US7 scoring system. Spearmann coefficient was used to calculate statistical correlations.

Results: 73 patients were registered, 212 patient visits were made and 1484 joints were investigated. 13 patients (17,3%) in clinical remission according to DAS28<2,6 had no synovitis in US7 (GS0, PD0), only tenosynovitis was present in 3 patients (4,1%). 62 patients (82,7%) had subclinical synovitis in US7 at the baseline (GS/PD >0). In 34 patients (46%) PD ≥2 was found. Relapse rate during one-year observation (DAS28 >2,6) was 17% both in 3rd and 6th months, 9% in 9th month and 18% in 12thmonth. Total score of GS and PD synovitis on US7 significantly correlated with DAS28 and SDAI in months 3,6 and 12 (all p<0,01). This statistical significance was not reached at baseline and in month 9 with relapse rates of 0 and 9% respectively, thus only subclinical synovitis was more frequently seen while DAS28<2,6. There was observed a strong correlation between presence of synovitis and tenosynovitis (TS) on US7 (p<0,01) but no correlation of TS itself and other disease activity was found (DAS28, SDAI, HAQ, CRP). Number of erosions increased during one-year observation.

Conclusion: It was possible to find a high percentage of subclinical synovitis in patients in remission of RA according to previous studies published using other scoring systems. PD signals were in majority of investigations absent or very low (0 or 1), what is in good correlation with data published. There was no statistical difference in disease activity found in US7 score between patients with DMARDs and biological therapy in our sample. US7 may be a simple and effective tool to evaluate the disease activity of RA not only in active disease but also in the state of remission in daily clinical practice. Other studies are needed to confirm these findings with US7.

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Inter-Rater Reliability of the US-7 Score in a Population of Volunteers: Is a Post-Hoc Analysis of Still Images Comparable to the Dynamic Analysis? Results from the German "Rheuma-Truck" Cohort. Dr. Philipp Sewerin[1], Dr. Stefan Vordenbäumen[1], Sarah Ohrndorf[2], Marina Backhaus[2], Dr. Oliver Sander[1], Prof. Dr. Matthias Schneider[3], Prof. Dr. Benedikt Ostendorf[1] and Aiko Liedmann[1]. [1]Univ. Duesseldorf, Düsseldorf, Germany, [2]Charite University Hospital, Berlin, Germany, [3]Univ. Duesseldorf, Duesseldorf, Germany.

Background/Purpose: To investigate the value of a follow-up analysis of ultrasonographic still images versus dynamic investigation using the US-7 ultrasound score.

Methods: "Rheuma-Truck" was a mobile rheumatology office located in different city center of North Rhine Westphalia, Germany offering a screening for rheumatic diseases including Rheuma-Check questionnaire, lab-tests (MCV capillary test), imaging (US, capillaroscopy), and if positive a consultation with a rheumatologist to everybody free of charge. Ultrasound (MyLab 25 Gold, Esaote linear scanner, 15, Typ LA435) of the dominant hand of 605 volunteers was performed. Moreover in 236 of these volunteers the foot was obtained by ultrasound. Thus a total of 3497 joints were examined by ultrasound. Live images were analyzed according to the US-7 scoring system dynamically on site by a trained rater. Still images were stored in a standardized manner in section planes according to US7. These images were assessed by 3 additional experts blinded to the dynamic scoring. The agreement upon all four raters is assessed in two measures a(0) and a(1). These are the percentages of study subjects who are rated equally (a(0)) or equally up to +/− 1 score point (a(1)) by all four raters.

Results: The mean age of the investigated cohort was 52.72 years (min. 10, max. 89 years). Sex distribution shows 72.2% females and 27.8% males. 181 (29.9%) volunteers displayed any inflammatory sign according to US-7 scoring. Using a(0) (all raters rated all subject equal) dorsal wrist showed an accordance between all 4 raters of 62%, the palmar wrist of 98%, the ulnar wrist of 87%, MCP-2 of 77%, MCP-3 85%, PIP-2 70%, PIP-3 81%, MTP -2 72% and MTP-5 96%. Using a(1) (up to +/−1) we obtained accordance's of the dorsal wrist of 87%, palmar wrist 100%, ulnar wrist 94%, MCP-2 94%, MCP-3 94%, PIP-2 91%, PIP-3 91%, MTP-2 89% and MTP-5 98%.

The accordance between still images and dynamic assessment according to a(1) was 100% for the palmar wrist, 100% for the ulnar wrist, 100% for MCP-2, 100% for MCP-3, 97% for PIP-2, 100% for PIP-3, 100% for MTP -2, and 100% for MTP-5 using the US-7 scoring system.

Conclusion: Inter-rater reliability (between all 4 raters) was good with an average of 93.1%. The accordance between still images and dynamic interpretation by using the US-7 scoring system was excellent with 99.6% consensus. Post-hoc evaluation of still images is a valid and reliable tool for the evaluation and interpretation of the US-7 scoring system as shown here in a population of volunteers.

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Detection of Synovitis and Erosions with an Automated Ultrasound System: Data from a Prospective Cohort with Early and Established RA.
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Background/Purpose: Arthrosonography has proven to be a sensitive and reliable, but time-consuming method for the evaluation of arthritis in small joints of patients with RA (1, 2). The automated breast volume scanner (ABVS) was developed to acquire series of consecutive B-mode pictures of the female breast. In a pilot study, we have recently described the possible application of this system to finger joints of RA patients (3). This study was performed to confirm the value of ABVS in detecting swelling and erosions of the finger, wrist and foot joints in patients with RA in comparison to conventional manual ultrasound (mUS).

Methods: Patients with RA were assessed by clinical and sonographic examination of the MCP, PIP, wrist and MTP joints. In addition, data for DAS-28, SDAI, CDAI and HAQ was gathered. ABVS was conducted using the ACUSON S2000 (Siemens, Germany), mUS was performed on MyLab 70 (Esaote, Italy). The ABVS transducer was equipped with a linear array of 11 MHz and each automatic sweep of the scanner generated 15.4 × 16.8 cm × 2.5 cm volume data sets. The system was set to perform an automatic scanning time of 65 seconds per scan with a slice thickness of 0.5 mm. mUS was performed with a 8–18 MHz linear transducer.

Results: We included 44 patients with established (n=30) and early (n=14) RA with a mean DAS28 of 4.4 ± 1.8 and a mean swollen joint count of 8 ± 6.3. In total, 1548 small joints were assessed. ABVS revealed synovitis in 20,7 % of the examined joints, compared to 18.4 % with mUS. Erosions were seen in 196 joints with ABVS and in 168 joints with mUS. Correlation of US findings with clinical activity parameters were weak for both methods except for the swollen joint count with 0.41 for ABVS and 0.73 for mUS and physicians' global assessment with 0.43 and 0.57 for ABVS and mUS, respectively. Defining mUS as gold standard, the sensitivity of ABVS for the detection of joint swelling was 0.64 with a specificity of 0.88. Concerning erosions, sensitivity and specificity were 0.64 and 0.88. The negative predictive value was 0.91 for joint swelling and 0.92 for erosions. The interrater and intrarater agreements were 0.83 and 0.85 for ABVS and 0.84 and 0.88 for mUS, respectively.

Conclusion: ABVS is a simple and time-sparing method for the detection of joint swelling and erosions. Compared to manual ultrasound as gold standard, ABVS has an acceptable sensitivity and a very good negative predictive value which makes it a promising screening method for small joint synovitis in RA.

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Do Ultrasound (PDUS) and DAS28 Measure Different Aspects of Disease Activity? Analyses from the First Prospective International Phase IIIb Study of PDUS Response in Abatacept-Treated Patients with Rheumatoid Arthritis (RA).
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Background/Purpose: A composite (power Doppler/grayscale ultrasound [PDUS]) synovitis score, developed by the OMERACT-EULAR-Ultrasound Task Force, was shown to be responsive in RA patients with inadequate response to MTX who were treated with abatacept (ABA); a rapid parallel change in PDUS and DAS28 was demonstrated. [1] Data from clinical studies that have utilized PDUS indicate that it could be useful in monitoring RA treatment effects;[2] however, discordant correlations have been found between ultrasound scores and clinical outcomes measured at the same time point. [3–7] In this secondary analysis of the APPRAISE study, we explored correlations between changes in PDUS and clinical scores.

Methods: Individual joint PDUS scores were combined in the Global OMERACT-EULAR Synovitis Score (GLOESS) of metacarpophalangeal joints 2–5 (primary objective), reduced joint set (9 paired) and all examined joints (22 paired). Correlation between changes in GLOESS and clinical scores were assessed through: effect size, expressed as standardized response means of GLOESS and mean changes in DAS28 from baseline to Weeks 1, 12 and 24; Pearson's correlation coefficient, for assessing correlation between early and late changes in DAS28, and early and late changes in all GLOESS scores; and Spearman's correlation coefficient, for assessing correlation between early changes in GLOESS and lower levels of synovitis at Week 24. Furthermore, the relationship between GLOESS and clinical response was explored by analyzing the correlation between changes from baseline in the number of tender and swollen joints and matched joint GLOESS.

Results: No significant correlations were found between: changes from baseline in DAS28 and GLOESS, or component scores (synovial hypertrophy, PD, joint effusion) at any time point; or between early (baseline to Weeks 1, 2 or 4) changes in GLOESS, or components, and changes in the sum of swollen joints from baseline to Weeks 12 or 24. Within the assessment method, i.e. between clinical scores, or between GLOESS at different time points, moderate-to-high correlations were found between early (to Week 12) and late (Week 24) improvements in DAS28, and similarly between changes in GLOESS (any joint set): Pearson's coefficient range 0.37–0.71. Only changes in GLOESS at Week 12 were able to differentiate between early versus late clinical responders: Pearson's coefficient (95% CI): 22 joint: 0.71 (0.57, 0.80); 9 joint: 0.62 (0.46, 0.74).

Conclusion: PDUS is a responsive measure of joint activity in patients starting abatacept, but the extent of PDUS response does not correlate with extent of clinical response. Early PDUS changes could differentiate early versus late clinical responders, suggesting that PDUS adds independent information on response to treatment which needs to be explored further.

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On-Demand Ultrasonography Assessment in the Most Affected Joint Is Efficient for Management of RA Patients in Daily Practice.
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Background/Purpose: Musculoskeletal ultrasonography (US) is recognized as a useful tool for the diagnosis and monitoring of rheumatoid arthritis (RA). Although several sets of power Doppler (PD) US assessment procedures in arbitrary combinations of selected joints have been proposed, they do not always cover all of the affected joints. Here we investigated whether US

assessment in a selected joint on demand from patients is useful for monitoring RA in daily practice.

Methods: PDUS was performed in 8 joints, including bilateral MCP 2, MCP 3, wrist and knee joints, as a routine examination in a cumulative total of 207 patients with RA. At the examination, patients declared the most symptomatically affected joint. In patients who had the most affected joint except the routine 8 joints, the joint was additionally scanned. PD signals were scored semiquantitatively from 0 to 3 in each joint, and total PD score-8 was calculated by summing up PD scores of the routine 8 joints. Patients with positive PD signals in any joints were regarded as having active synovitis. The sensitivity and specificity of assessment in the most affected joint for detection of active synovitis in any of the routine 8 joints were evaluated.

Results: The patients were divided into three groups based on the most affected joints. Group A consisted of 110 patients having the most affected joint among the routine 8 joints, whereas 69 patients having the most affected joint other than the routine 8 joints were included in Group B. The remaining 28 patients were asymptomatic and categorized into Group C. Total PD score-8 was significantly higher in the symptomatic groups (Group A and B) than the asymptomatic group (Group C) (3.41 ± 3.19 vs 1.25 ± 1.80, $P = 5.9 \times 10^{-4}$). In the symptomatic groups, PD scores of the most affected joints showed high correlation with total PD score-8 (Figure 1; $r = 0.52$, $P = 5.8 \times 10^{-14}$). For detection of active synovitis of any of the routine 8 joints, the sensitivity and specificity of assessment in the most affected joint were 66.2% and 94.6%, respectively, in the symptomatic groups (Group A and B), 82.6% and 100%, respectively, in Group A, and 36.0% and 89.5%, respectively, in Group B. In two patients (2.9%) who were classified into Group B, PD signals were detected in the most affected joints (left ankle and right elbow), despite the negative results in the routine 8 joint assessments. These data suggested that US finding in the most affected joint represents those of routine 8 joint examination in Group A, whereas it gives supplemental information to the routine 8 joint examination in Group B.

Conclusion: This study suggests that on-demand US assessment in the most affected joint is efficient for management of RA patients in daily practice.

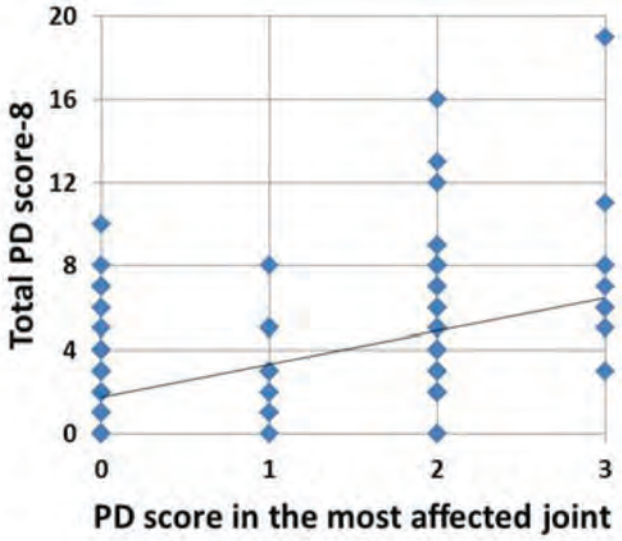

Figure 1 The PD score in the most affected joint correlates well with Total PD score-8.

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Histopathological Correlation of Ultrasound-Defined Active Synovitis in Patients with Rheumatoid Arthritis in Clinical Remission. Preliminary Results.

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Background/Purpose: We recently demonstrated that 45.4% of patients with RA in clinical remission have ultrasound (US)-defined active synovitis (synovial hypertrophy (HS) grade 2 or higher and Power Doppler [PD] signal) (Ramírez J et al, arthritis Research and Therapy 2014). Here we analysed the histological correlate of US-defined active synovitis in a subset of patients in whom synovial biopsy was performed.

Methods: By protocol, we obtained at baseline 6–8 ultrasound-guided synovial biopsies of all patients with (PD) signal who had signed the informed consent. Immunohistochemical staining was performed by the the peroxidase technique for the following antibodies: CD3 (T lymphocytes), CD20 (B lymphocytes), CD31 (vessels), CD68 (macrophages), CD117 (mast cells), Hsp47 (Fibroblast-like synoviocytes)(Izquierdo E et al, Arthritis Rheum 2011) and basic FGF. Quantifications were perfomed by Digital Image Analysis (Olympus). Serum bFGF was analyzed by Quantibody® Human Array (RayBiotech). US scans of both knees and hands (wrists, metacarpophalangeal [MCP], proximal interphalangeal [PIP]) were performed by an experienced rheumatologist using a high sensitivity equipment (Acuson Antares®, Siemens AG, Erlangen, Germany) with a 8–12 MHz linear probe. We quantified the presence of synovial hypertrophy (grades 0–3) and (PD) signal (grades 0–3) in all patients.

Results: We have included 24 patients with synovial biopsy. Regarding US assessment, 100% of patients had PD signal (by protocol), 79.2 % had Synovial HS grade 2 or higher, while 70.8% met criteria for US-defined active synovitis (HS > 2 + [PD] signal) at least in one joint.

The number of B cells (CD20+)/mm2 (p=0.017) and immunostained fractional area of Hsp47+ fibroblasts (p=0.035) in synovial tissue were significantly higher in patients with *US-defined active synovitis*. Furthermore, these patients had a non-significant greater number of CD31+ vessels per area (p=0.061).

The expression of bFGF in the synovial tissue showed a strong trend to correlation with its concentration in serum (p = 0.064). We also analyzed the expression of bFGF in synovial tissue in two control populations (19 patients with active RA and 8 healthy controls). bFGF expression was higher in patients with active rheumatoid arthritis (DAS28 >3.2) than in patients in remission. Furthermore, bFGF expression was lower in healthy controls than in patients in remission. Thereby, these preliminary results point to bFGF expression is parallel to disease activity.

Moreover, a significant correlation of *global US score* of each patient with the number of T cells (CD3+)/mm^2 (p=0.010) and B cells (CD20+)/mm2 (p=0.001), and a strong trend to significance in mast cells CD117+ (p=0.064) were found.

Conclusion: These preliminary results support that US-defined active synovitis has a histopathological substrate which is associated with fibroblasts and B cells. Also, the grade of infiltration of the synovium by T and B lymphocytes is associated with the US global score of the patient. Finally, correlation between synovial tissue expression and serum levels of bFGF, a mainly fibroblast-derived factor, point.

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Comparison of the Ultrasonography Images and Synovial Pathology of the Joints in Patients with Rheumatoid Arthritis Treated with Biological Agents.

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Background/Purpose: An early diagnosis and tight disease control have increased in importance in the era of biological therapy for rheumatoid arthritis (RA). Ultrasonography (US) of the various joints permits an evaluation of synovitis and bone erosion in real time. It has proven to be useful to detect synovitis in the early stage of the disease.The objectives of this study were to investigate whether the ultrasonography (US) images of a surgically-treated joint reflect synovial pathology or clinical indicators, and to compare the results in patients using non-biological agents (NB) and biological agents (Bio) for disease control.

Methods: Rheumatoid arthritis (RA)-related orthopedic surgery was performed in 301 joints, including five shoulders, 43 knees, 36 elbows, 90 wrists, 75 fingers, nine ankles and 43 toes between January 2011 and September 2013. US was performed preoperatively, and the grade of the Power Doppler (PD) signal was weighted. The Rooney score of the synovial pathology, the DAS28-ESR (4), and the MMP-3 and CRP levels were investigated. The Bio treatments were IFX in 13, ETN in 22, TCZ in 18, ADA in seven, ABT in one, GLM in four and CZP in three.

Results: The PDS, DAS28, MMP-3 and Rooney score in the patients using Bio were significantly lower than those in the patients using NB. The MMP-3 values for the patients using ETN were higher than those for the patients using IFX, and the DAS28 was higher for patients using ETN than for patients using TCZ. The DAS28 and fibrosis (as a Rooney score item) in the patients using TCZ were significantly lower than those in patients using TNF-α inhibitors. The PDS, CRP, MMP-3 and Rooney score in the patients using IFX were significantly lower than those in the patients using NB. The PDS, DAS28 and Rooney score in the patients using TCZ were significantly lower than those in the patients using NB. However, there were no significant differences in any items between patients using NB and patients using ETN or ADA.

Conclusion: The activity of RA synovitis at the surgically-treated site was suppressed in patients using Bio. There were some differences in the clinical data, pathological scores, PDS and DAS28 among the patients receiving different types of Bio.

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Serum Calprotectin (S100A8/9) Is an Independent Predictor of Ultrasound Synovitis in Patients with Rheumatoid Arthritis. Jana Hurnakova[1], Jakub Zavada[1], Petra Hanova[2], Hana Hulejova[1], Martin Klein[1], Herman F. Mann[1], Olga Sleglova[1], Martina Olejarova[1], Sarka Forejtova[3], Olga Ruzickova[1], Martin Komarc[4], Karel Pavelka[1] and Ladislav Senolt[3]. [1]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Prague, Czech Republic, [2]Institute of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Prague, Czech Republic, [3]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [4]Institute of biophysics and informatics, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic.

Background/Purpose: Serological biomarkers specifically reflecting pathological processes may have added value in assessing joint inflammation in rheumatoid arthritis (RA). Calprotectin (S100A8/9 protein) has been demonstrated as an important marker of clinical and laboratory disease activity and structural joint damage in RA[1]. Matrix metalloproteinase-3 (MMP-3) is directly involved in progressive joint damage; however, its role as a marker of disease activity in RA remains unclear[2]. Musculoskeletal ultrasound has superior sensitivity over clinical examination in evaluating synovial inflammation in RA. The aim of this study was to evaluate the associations between serum calprotectin, MMP-3, clinical and ultrasound parameters of RA disease activity in a cross-sectional study.

Methods: A total of 37 patients with RA (24 females, median disease duration 18 months), underwent clinical examination (DAS28) and 7-joint ultrasound score (US-7) of clinically dominant wrist, second and third metacarpophalangeal and proximal interphalangeal, and second and fifth metatarsophalangeal joints to assess synovitis and tenosynovitis by gray-scale (GS) and power Doppler (PD) ultrasound using semiquantitative grading (0–3). Blood samples were taken at the same day as ultrasound examination was performed and levels of serum calprotectin, MMP-3 and C-reactive protein (CRP) were subsequently measured. Clinical and laboratory measures were correlated with ultrasound findings using Spearman's correlation coefficient. A multiple regression analysis adjusted for age and sex was used to determine the predictive value of calprotectin, MMP-3 and CRP for PD synovitis.

Results: Calprotectin significantly correlated with DAS28 ($r=0.385$, $p<0.05$) and in particular with CRP levels ($r=0.629$, $p<0.001$) and swollen joint count ($r=0.465$, $p<0.005$). In addition, calprotectin was significantly associated with GS ($r=0.359$, $p<0.05$) and PD synovitis ($r=0.497$, $p<0.005$). On the other side, no such association was found for MMP-3. Using adjusted multiple regression analysis, calprotectin was the only independent predictor of active PD synovitis ($p<0.05$).

Conclusion: This study show a significant association between calprotectin and clinical, laboratory as well as ultrasound assessment of RA disease activity. Circulating calprotectin, but not MMP-3, may represent an important biomarker for monitoring synovial inflammation in RA.

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Evaluation of Metalloproteinase-3 As a Soluble Biomarker of Synovitis Using Weighted Joint Counts Assessed Clinically and on Ultrasound Imaging. Agata Burska[1], Elizabeth Hensor[2], Jackie L. Nam[2], Lukasz Kozera[3], Richard J. Wakefield[2], Paul Emery[2] and Ann W Morgan[4]. [1]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds., Leeds, United Kingdom, [2]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [3]Faculty of Pharmacy and Laboratory Diagnostics, Wroclaw Medical University, Wroclaw, Poland, Wroclaw, Poland, [4]University of Leeds, Leeds, United Kingdom.

Background/Purpose: Synovial inflammation is known to play a central role in articular cartilage degradation in rheumatoid arthritis (RA); it could be a passive marker of disease, or the driving force in the onset of early joint damage. In this study we aimed to determine if circulating metalloproteinase-3 (MMP-3) and hyaluronic acid (HA) would outperform CRP as surrogate biomarkers for synovitis detection.

Methods: Patients fulfilled 1987 ACR RA classification criteria, had 3–12mth symptom duration, active disease (DAS44 >2.4) and were DMARD naïve. In a subset, grey scale (GS) and power Doppler (PD) ultrasound (US) semi-quantitative scores (0–3) were assigned to wrists, MCPs & PIPs 2&3 and MTPs 1–5 bilaterally at baseline[1]. For this analysis both counts (joints scoring GS >1, PD >0, simultaneously GS >1 & PD >0) and score totals were created. To reflect burden of synovitis, clinical and US counts and totals were weighted by first multiplying each joint's score by a weight, determined by its relative area[2], before summating. Samples were tested for MMP-3 and HA using a novel research use only multiplex platform IMPACT(Immunological Multi-Parameter Chip Technology)(Roche Professional Diagnostics, Germany)[3]. We calculated bootstrapped confidence intervals(CI) for the differences in the strength of Kendall's tau-a associations between markers and joint assessments in Stata 13.1.

Results: Data were available for 59 patients: mean age 52.7 (range 19–78); 71% female; 64% RF +ve; median disease duration 1mth. Median (IQR) values for markers were CRP 27mg/L (10, 100); MMP-3 59ng/mL (42, 119); HAμg/mL 37 (20, 70).

None of the associations were particularly strong (Table 1); the strongest were between the weighted clinical joint counts and MMP3 and CRP. Most of the associations with MMP3 were numerically stronger than with CRP, but the differences were neither substantive nor statistically significant.

In patients with normal CRP (<10 mg/L) there appeared to be substantive associations between total GS and MMP-3 (tau-a=0.34) and between total PD and HA (tau-a=0.35); however, sample size was small (n=14).

Table1: Associations between markers of inflammation and clinical and ultrasound measures of synovitis, weighted for joint area (n=59).

	Kendall's Tau-a			Differences between tau-a values (95% CI)		
Weighted joint assessment	MMP-3	HA	CRP	MMP-3 minus HA	CRP minus MMP-3	CRP minus HA
GS total	0.30	0.26	0.24	0.03 (−0.15, 0.21)	−0.06 (−0.25, 0.13)	−0.03 (−0.27, 0.22)
GS count (score>1)	0.23	0.20	0.21	0.04 (−0.16, 0.23)	−0.03 (−0.22, 0.17)	0.01 (−0.23, 0.25)

PD total	0.32	0.30	0.28	0.02 (−0.17, 0.22)	−0.04 (−0.21, 0.13)	−0.02 (−0.25, 0.22)
PD count (score>0)	0.31	0.26	0.28	0.05 (−0.13, 0.24)	−0.03 (−0.20, 0.15)	0.02 (−0.20, 0.25)
'Active' count (GS>1&PD>0)	0.34	0.26	0.26	0.09 (−0.11, 0.28)	−0.08 (−0.25, 0.09)	0.01 (−0.21, 0.23)
SJC28	0.39	0.22	0.42	0.17 (0.00, 0.34)	0.02 (−0.17, 0.22)	0.19 (−0.01, 0.40)
SJC44	0.39	0.21	0.37	0.18 (−0.01, 0.36)	−0.02 (−0.22, 0.18)	0.16 (−0.07, 0.38)

Conclusion: This is the first time that weighted joint counts, which account for joint surface area, have been used in the assessment of soluble synovial biomarkers in RA. Neither MMP3 nor HA performed better as surrogate biomarkers of synovitis than CRP when elevated. Further studies are underway to evaluate the clinical utility of MMP3 as a soluble biomarker of subclinical synovitis at CRP levels<10mg/L.

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Can Ultrasonography of Peripheral Entheses Play a Role in the Diagnosis and Understanding of Diffuse Idiopathic Skeletal Hyperostosis (DISH)? Reuven Mader[1], Irina Novofastovski[2], Salvatore Iervolino[3], Alex Pavlov[4], Leonid Chervinsky[5], Naama Schwartz[5] and Nicola Pappone[3]. [1]Technion Institute of Technology, Haifa, Israel, [2]Ha Emek Medical Ctr, Afula, Israel, [3]"Salvatore Maugeri" Foundation, IRCCS Scientific Institute, Telese Terme, Italy, [4]Bnai Zion Medical Center, Haifa, Israel, [5]Ha'Emek Medical Center, Afula, Israel.

Background/Purpose: to investigate musculoskeletal ultrasound (MSUS) as a diagnostic modality in DISH and to explore if it might help in elucidating its pathogenesis and events that precede the calcification/ossification process.

Methods: Fifty patients with DISH and 34 patients with osteoarthritis of the lower limbs without DISH were investigated. Data regarding demographics and traditional cardiovascular risk factors was collected from all patients. An ultrasonography was performed according to the Glasgow Ultrasound Enthesitis Scoring System (GUESS) by observers who were blinded to the diagnosis or the clinical findings in the patients.

Results: The total mean GUESS score for patients with DISH was 14.12 ±5.2 and for patients without DISH 5.32 ±4.99 ($p<0.0001$). Univariate logistic regression analysis found a strong association between the GUESS and the probability of having DISH ($p<0.0001$). The area under the ROC curve (AUC) revealed that the GUESS accuracy in diagnosing DISH was 88.53% with sensitivity and specificity of 92% and 70.6% respectively, at a cutoff value of 6.36. A stepwise logistic regression analysis of the statistically significant items in the GUESS, isolated 4 items, the presence of either all of them or, the first 3 items yielded the likelihood of having DISH to be 98.8%, and 90.6% respectively.

Conclusion: The GUESS and the stepwise logistic regression analysis demonstrated a high likelihood of having DISH. MSUS might shed light on the early entheseal changes in DISH, and the temporal relationship between the spinal and peripheral involvement in this condition. Further studies are needed to confirm these results.

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Ultrasound Enthesitis in Primary Care Psoriasis Patients with Musculoskeletal Complaints. M. van der Ven[1], M.C. Karreman[1], A.E.a.M. Weel[1], I. Tchetverikov[2], M. Vis[1], T.E.C. Nijsten[1], J.M.W. Hazes[1] and J.J. Luime[1]. [1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]Albert Schweitzer Hospital, Dordrecht, Netherlands.

Background/Purpose: Psoriasis patients with enthesitis can classify as psoriatic arthritis since the introduction of the CASPAR classification criteria in 2006. However, the presence of a tender enthesis is not necessarily indicative for underlying inflammatory disease as it could be related to overuse, metabolic disease or ageing. Therefore, we need a better way to identify the inflammatory component of entheseal involvement in psoriasis. To detect these inflammatory components and structural changes in the entheses, ultrasonographic examination can be applied to identify inflammatory disease of the entheses. Our objective was to determine the prevalence of ultrasound abnormalities among psoriasis patients in primary care.

Methods: Adult patients with psoriasis (ICPC S91) were identified from 97 general practitioners in the Rotterdam area. These patients were invited to participate in the SENSOR study. Patients who reported pain in joints, entheses or the lower back were eligible and invited for clinical evaluation. If physical examination indicated a painful enthesis on the LEI/MASES or arthritis, ultrasonographic examination of the entheses was performed. The six entheses of the Madrid Sonographic Enthesis Index (MASEI) and the lateral epicondyle tendon insertion (elbow) were evaluated according to the MASEI scoring system. Positive inflammatory components on ultrasound included the presence of power Doppler signal (<2mm of the bony cortex) and increased thickness of the enthesis of the plantar fascia (>4.4mm).

Results: In total, 527 patients with psoriasis who reported musculoskeletal symptoms were clinically evaluated. 83 patients (47 female, mean age: 54 years) had at least one tender enthesis on the LEI/MASES and were evaluated by ultrasound. Another 23 patients (9 female, mean age: 54 years) suspected for presence of arthritis were evaluated by ultrasound as well. In 98 (92%) patients we detected ultrasound abnormalities [Table 1]. In 47 (44%) patients we found abnormalities indicating inflammatory disease at the enthesis. 28 (26%) patients were power Doppler positive on ultrasound, 4 (4%) patients had a thickened plantar fascia and in 15 (14%) patients both inflammatory components were present. In 51 (48%) patients we found structural changes without indication for inflammatory disease. There was no difference in ultrasound findings between patients suspected for enthesitis and patients suspected for arthritis.

Conclusion: In 44% of primary care psoriasis patients (n=106) we observed ultrasound abnormalities (presence of power Doppler and/or thickened plantar fascia) indicating inflammatory disease. Additionally, one or more structural ultrasound changes in the enthesis were observed in the majority of the patients. Whether this also indicates inflammatory disease requires further exploration.

Table 1 Ultrasound abnormalities in the entheses using the MASEI score (n=106)

Insertion	PD signal	Structure	Thickness	Bursitis	Erosion	Calcification
Lateral epicondyle tendon (elbow)*	**20 (19)**	*17 (16)*	47 (44)		*34 (32)*	44 (42)
Triceps tendon*	**0**	*25 (24)*	18 (17)		*9 (8)*	25 (24)
Quadriceps tendon*	**12 (11)**	*12 (11)*	50 (47)		*3 (3)*	62 (58)
Proximal patella tendon*	**2 (2)**	*3 (3)*	28 (26)		*2 (2)*	14 (13)
Distal patella tendon*	**5 (5)**	*2 (2)*	70 (66)	1 (1)	3 (3)	22 (21)
Achilles tendon*	**3 (3)**	*0*	11 (10)	0	1 (1)	63 (59)
Plantar aponeurosis*	†	*1 (1)*	**19 (18)**		*0*	19 (18)

*N (%); PD = power Doppler; † = not detectable.

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Are Entheses Ultrasound Findings Similar in Axial Spa Patients and in Athletes? Marie-Alix Lanfranchi[1], Olivier Leluc[2], Alice Tavano[1], Vincent Pradel[1], Sophie Morange[1], Christophe Chagnaud[1], Pierre Lafforgue[1] and Thao Pham[1]. [1]APHM, Aix Marseille University, Marseille, France, [2]APHM, Marseille, France.

Background/Purpose: Spondyloarthritis (SpA) are characterized by inflammatory and structural changes in the entheses (enthesitis). However, enthesitis is not only observed in SpA and can also be seen after a hypersollicitation of the enthese as during intensive sport.

The purpose of the study was to compare ultrasound (US) findings of entheses between 3 groups: axial SpA patients, athletes and healthy controls.

Methods: We conducted a prospective cross-sectional study of 30 axial SpA (2009ASAS criteria), 30 athletes and 30 controls. Athlete subjects practiced a sport resulting in a strain on lower limbs, such as running or soccer, at least 6 hours per week. Controls practiced less than an hour per

week. Clinical evaluation and US were performed at the same day. Physicians performing clinical and US examination were blinded to each other. The US was performed at by two radiologists, using both grey scale (GS) and power Doppler (PD) for calculation of the MASEI index (Madrid Sonographic Enthesis Index) and the analysis of its subitems (bursistis, calcification, erosion, power doppler, thicknening of tendon, structural change) (Toshiba Aplio 500, linear transducer, frequency of 6–18 MHz). *Analysis*: To compare groups we used chi-square and one-way analysis of variance (ANOVA) with Bonferroni correction for post-hoc tests (depending on categorical/continuous variables), and Mann Whitney test for correlation (SPSS 17.0 version).

Results: Patients and controls demographic and clinical characteristics are shown in table 1. In SpA patients mean (SD) BASDAI and ASDAS were 3,14 (1,9) and 1,78 (1,01), respectively. Mean MASEI and each sub-item scores were significantly different between SpA patients and both healthy control groups. There was no difference between athlete and non-athlete groups. No correlation between heel pain and MASEI score or PD of the calcaneal enthese was found. The inter-reader correlation for MASEI scoring was 0.68 (Cohen's kappa coefficient).

Conclusion: The MASEI score was significantly higher in patients with SpA compared to healthy control, athletes and non-athletes. Even if the MASEI score was somewhat higher in the athlete group than in the non-athlete control group, the difference was not significant. The 17-cutoff seems relevant to distinguish SpA from control, whatever their physical activity.

	SpA (n = 30)	Athletes (n = 30)	Non-athlete controls (n = 29)	p
Age, years (mean, SD)	36 (7)	29 (9)	30 (8)	
Gender, male (%)	70.0	70.0	41.4	
Heel pain, ever (%)	55.2	20.7	0	
CRP (mg/l) (mean, SD)	4 (11)	2 (7)	2 (3)	
HLA B27 + (%)	51.1	3.4	3.4	
X-rays sacroiliitis ≥3 (%)	86.7	3.6	10.3	
ASAS criteria + (%)	100	0	0	
MASEI score (mean, SD)	26.3 (13)	12.2 (7)	10.4 (6)	<0.0001
MASEI > 17 (%)	70.0	16.7	14.3	<0.0001

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Prevalence of Subclinical Enthesopathy in Asymptomatic First Degree Relatives of Patients with Spondyloarthritis. Tomas Cazenave[1], Natalia Zamora[2], Marcelo Audisio[3], Ana M. Bertoli[4], Guillermo Py[3], Walter Spindler[5], Javier Rosa[6], David A. Navarta[7], Teresita de Alvarellos[8], Luciana Mas[9], Gustavo Citera[10] and Marcos G. Rosemffet[10]. [1]IREP, Buenos Aires, Argentina, [2]Echeverría 955, Buenos Aires, Argentina, [3]Servicio de Reumatología del Hospital Nacional de Clínicas, Córdoba., Cordoba, Argentina, [4]Instituto Reumatológico Strusberg, Cordoba, Cordoba, Argentina, [5]Centro Médico Privado de Reumatología, Tucumán, Argentina, [6]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [7]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [8]Hospital Privado de Córdoba, Córdoba, Argentina, [9]Hospital Privado Centro Medico De Córdoba, Cordoba, Argentina, [10]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina.

Background/Purpose: There are no studies evaluating enthesis involvement detected by US in relatives of spondyloarthritis (SpA) patients. **Objectives:** 1) To evaluate and compare the prevalence of subclinical enthesopathy detected by US in first degree relatives of patients with spondyloarthritis and healthy controls (HC), 2) To evaluate associations between US findings, clinical variables and presence of HLA-B27.

Methods: We designed a multicenter cross-sectional study including asymptomatic first-degree relatives of patients with Ankylosing Spondyitis (RAS) or Psoriatic Arthritis (RPsA), and a group of sex-age matched healthy controls (HC). Each subject underwent clinical and ultrasonographic evaluation. All RAS subjects were tested for the presence of HLA-B27. Demographic and clinical data were recorded including presence of comorbidities, physical activity and body-mass index. Two rheumatologists who were blinded to clinical examination performed the ultrasound evaluation. Ten enthesal sites were evaluated: bilateral quadriceps tendon, proximal and distal patellar ligament, Achilles tendon and plantar aponeurosis. Ultrasonographic enthesopathy (UE) was defined as the presence of at least one of the following characteristics: thickening, erosion, enthesophytes and/or bursitis. The Glasgow Ultrasound Enthesitis Scoring System (GUESS) was calculated, which range from 0 to 36, being 36 the highest involvement. An alternative model was tested, evaluating the addition of Power Doppler (PD) assessment to the GUESS. Differences among groups were compared using chi-squared test and ANOVA with post-hoc analysis (Games Howell) Interobserver agreement between both ultrasonographers was estimated by the intraclass correlation coefficient (ICC).

Results: We included 101 subjects from 5 rheumatology centers (RAS=44, RPsA= 13, HC=44). Clinical and demographic findings were comparable among groups. Fifty-two perecent were men with a median age of 32 years (IQR: 24.5–41.5). Eighteen RAS subjects (40.9%) were HLA-B27 positive. A total of 1010 enthesal sites were evaluated. Eighty-nine out of 101 subjects (88.1%) showed at least one UE, being enthesophyte at the Achilles tendon, thickening at the proximal and distal insertions of the patellar tendon (51%, 46% and 40%, respectively) the most frequent findings. US evaluation demonstrated a higher frequency of enthesal involvement in Spondyloarthritis relatives (RAS and RPsA) when compared to HC at the following sites: Left sub-quadricipital bursa (15.8% vs 2.3% p=0.04), thickening at the proximal insertion of the left patellar tendon (12.3% vs 0% p=0.018) and thickening of the left Achilles tendon (15.8% vs 0% p=0.005). The mean GUESS score in the three groups were: RAS: 5.16 ±3.22, RPsA: 4.15 ± 5.33 and HC: 3.52 ±2.69. The mean GUESS score was significantly higher in RAS group as compared to HC (p=0.031). Mean GUESS was higher in HLA-B27 subjects as compared with those negatives (5.50 ±3.34 vs 4.92 ±3.18, p value =0.56).

Conclusion: First degree relatives of patients with SpA had a higher frequency of enthesopathy and a higher GUESS score than healthy controls.

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Prevalence of Subclinical Entheseal Involvement in Patients with Paediatric Inflammatory Bowel Disease: An Ultrasonographic Study. Alberto Batticciotto[1], Dario Dilillo[2], Marco Antivalle[3], Martina Nugnes[2], Valentina Varisco[1], Matteo Ferrari[2], F. Atzeni[3], Gian Vincenzo Zuccotti[2] and P. Sarzi-Puttini[3]. [1]L. Sacco University Hospital, Milano, Italy, [2]Pediatric Department, L. Sacco University Hospital of Milan, Milan, Italy, [3]Rheumatology Unit, L. Sacco University Hospital of Milan, Milan, Italy.

Background/Purpose: Joint involvement is the most frequent extra-intestinal manifestation of paediatric inflammatory bowel disease (IBD). Various recent studies focused on the clinical prevalence of enthesitis in children and adults with IBD[1], and others have demonstrated the ability of ultrasound (US) to visualise the acute and chronic signs of entheseal inflammation with greater sensitivity than a clinical examination, although there is a lack of consensus concerning the US definition of entheseal abnormalities and their prognostic value especially in the paediatric field[2]. The aim of this study was to evaluate the prevalence of subclinical entheseal involvement in patients with pediatric IBD using a high frequency ultrasound probe.

Methods: Twenty-seven pediatric IBD patients (13 with Crohn's disease [CD] and 14 with ulcerative colitis [UC]; 15 females and 12 males; mean age 13.7 years, range 7–21 years) without any clinical signs or symptoms of musculo-skeletal involvement and 24 healthy age- and gender-matched controls (14 females and 13 males; mean age 14.2 years, range 8–20 years) underwent an US examination (ESAOTE MyLAB 70 6–18 MHz linear array transducer). Brachial triceps, femoral quadriceps, Achilles, plantar fascia, and proximal and distal patellar entheses were all scored using the 0–136 Madrid Sonographic Enthesis Index (MASEI). Clinical and clinimetrical variables were assessed in both groups (MASES, BASDAI, BASFI, cHAQ, PCAI/PCDAI).

Results: None of the patients had a MASEI score suggesting early spondyloarthritis involvement but their average score was significantly higher than controls (3.15±2.84 *vs* 0.96±1.12, p=0.0006). There was also a significantly higher percentage of patients with at least one enthesis with power Doppler (PD) score ≥2 (37% *vs* 16%; p= 0.037) and at least one enthesis with dishomogeneous echostructure (59% *vs* 0%; p= 0.000). There were no between-group differences in terms of erosions (0% *vs* 0%), calcifications (7.4% *vs* 12.5%; p=0.656) or structural thickness (37% *vs*33.3%; p=0.507). In paediatric IBD group we cannot find correlation

between the total MASEI score and gender (p=0.12), age (p=0.20), disease duration (p=0.18) or IBD activity (p=0.83).

Conclusion: US detectable enthesopathy is frequent in paediatric IBD patients without any clinical signs or symptoms of musculo-skeletal involvement. Further studies involving a larger number of patients are needed to confirm these preliminary data.

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Detailed Anatomical Distribution of Synovial Inflammation Revealed By Ultrasound in Patients with Blau Syndrome. Kei Ikeda[1], Naotomo Kambe[2], Syuji Takei[3], Taiji Nakano[2], Yuzaburo Inoue[2], Minako Tomiita[4], Natsuko Oyake[5], Takashi Satoh[2], Tsuyoshi Yamatou[3], Tomohiro Kubota[3], Ikuo Okafuji[6], Nobuo Kanazawa[7], Ryuta Nishikomori[8], Naoki Shimojo[2], Hiroyuki Matsue[2] and Hiroshi Nakajima[1]. [1]Chiba University Hospital, Chiba, Japan, [2]Chiba University Graduate School of Medicine, Chiba, Japan, [3]Kagoshima University Hospital, Kagoshima, Japan, [4]Chiba Children's Hospital, Chiba, Japan, [5]Hitachinaka General Hospital, Hitachinaka, Japan, [6]Kobe City Medical Center General Hospital, Kobe, Japan, [7]Wakayama Medical University, Wakayama, Japan, [8]Kyoto University Graduate School of Medicine, Kyoto, Japan.

Background/Purpose: Arthritis is the most frequent manifestation of Blau syndrome, an autoinflammatory disorder caused by the genetic mutation of *NOD2*. However, the detailed information on arthritis in Blau syndrome which the therapeutic strategy should be based on was lacking. This multi-center study aimed to accurately characterize the articular manifestation of Blau syndrome and also to demonstrate the utility of musculoskeletal ultrasound in Blau syndrome.

Methods: Patients who had been diagnosed with Blau syndrome by genetic analysis of *NOD2* were recruited. A total of 102 synovial sites in 40 joints were assessed semiquantitatively by ultrasound for gray-scale synovitis and synovial power Doppler (PD) signal.

Results: Ten patients whose age ranged from 10 months to 37 years enrolled in this study. Although only four joints (0.8 %) were tender on physical examination, 81 joints (16.9 %) were clinically swollen. Moreover, 240 (50.0 %), and 124 (25.8 %) joints showed GS synovitis and synovial PD signal on ultrasound, respectively. Importantly, GS synovitis was present in 168 out of 399 non-swollen joints, in which 61 also exhibited synovial PD signal. Among 40 joint regions, the ankle, the wrist, and the proximal interphalangeal joints were the most frequently and severely affected joints (Figure). Comparisons between different synovial tissues demonstrated a significantly higher proportion of the joints with tenosynovitis as compared with that with intra-articular synovitis (41.5 % vs. 27.9 %, $P < 0.0001$). In respect of age and treatment, synovial PD signals were minimal in the youngest patient and in the oldest two patients, and were relatively mild in patients receiving treatment with methotrexate plus TNF antagonists. In two patients who underwent the 2nd ultrasound examination, total PD scores markedly decreased after initiating the treatment with a TNF antagonist.

Conclusion: The detailed information on synovial inflammation obtained by ultrasound confirms the dissociation between pain and inflammation and the frequently involved joint regions and synovial tissue in the arthritis of Blau syndrome. Our data also demonstrate that ultrasonography can be a potent tool in monitoring the activity of synovial inflammation and in investigating the pathophysiology of arthritis in this rare but archetypical autoinflammatory condition.

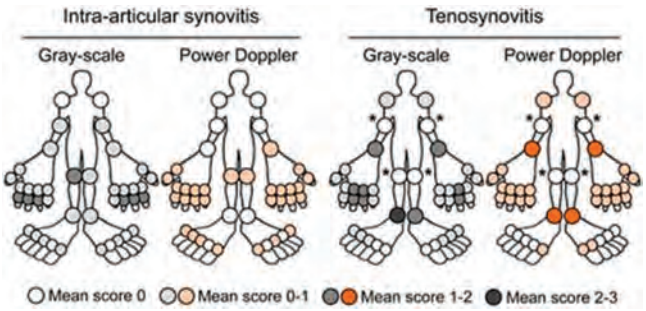

Figure. Mean gray-scale and power Doppler scores for intra-articular- and teno-synovitis in each joint

Mean ultrasound scores for each joint in 10 patients are shown in color grades. Only 1st ultrasound examinations in Patient 5 and 6 are included.

* Ultrasound scores for tenosynovitis are not applicable in elbows and knees where typical tenosynovium does not exist.

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Sonographic Differentiation of Heel Pain: Focal Degenerative Versus Systemic Inflammatory Enthesitis. Patrick Hook[1], Diana Vradii[2], Maureen Dubreuil[3], Hau Pham[3] and Eugene Y. Kissin[1]. [1]Boston University School of Medicine, Boston, MA, [2]Mid Coast Hospital Medical Center, Brunswick, ME, [3]Boston University Medical Center, Boston, MA.

Background/Purpose: Plantar fasciitis and Achilles tendonitis are commonly encountered in a rheumatologic practice due to either degenerative (DG) or systemic inflammatory conditions (SYS). While sonographic findings in both DG and SYS have been described in numerous studies, no study has systematically compared these two causes of heel pain. The aim of our study is to determine whether sonographic findings in the Achilles tendon and plantar fascia can be used to differentiate DG from SYS states.

Methods: Patients over the age of 18 with pain at the Achilles tendon or plantar fascia presenting to the Podiatry, Dermatology or Rheumatology clinics were enrolled. Exclusion criteria: previous heel trauma, surgery or recent corticosteroid heel injections. Medical chart review, a focused history, and a comprehensive musculoskeletal physical examination determined patient categorization as DG, SYS, or undetermined cause of heel pain. Patients' Achilles tendons and plantar fascia were imaged with a GE Logiq e ultrasound and 12MHz linear array transducer. Doppler settings: PRF 0.8, low wall filter and Doppler gain set to maximize signal with minimal artifact. We evaluated tendon thickness, retro-calcaneal bursal size, cortical erosions, and Doppler signal at the enthesis and at the cortical margin. Continuous variable were compared between the degenerative and inflammatory groups using t tests, and proportions were compared using Chi squared or Fischer's exact tests.

Results: Interim analysis of the first 46 patients recruited includes 20 in the SYS group and 22 in the DG group (4 undetermined). SYS group consists of 15 patients with psoriatic arthritis, 4 with non-psoriatic spondyloarthritis, and 1 with rheumatoid arthritis. Male:female ratio was 15:5 in the SYS group, and 6:16 in the DG group. While there were no significant differences in tendon thickness between the groups (Table), both the presence of erosions (SYS 70% vs. DG 23%, p=0.002), and the presence of Doppler at the enthesis (SYS 55%, vs. DG23%, p=0.03) were significantly more common in the SYS group (Table). Surprisingly, erosion size and degree of Doppler signal did not help distinguish the groups (Table). Doppler signal at the cortical margin was not more specific to the inflammatory group than enthesis Doppler overall (Table).

Conclusion: While there were no significant differences in tendon thickness, degenerative causes of heel enthesitis were less likely to show Doppler signal and erosive changes than systemic inflammatory enthesitis. However, erosions were seen in some heel enthesitis not associated with systemic inflammatory disease.

Table. Clinical characteristics and sonographic findings for subjects included in the study

	Inflammatory (N = 20)	Degenerative (N = 22)	P value
Male, % (N)	75.0% (15)	27.2% (6)	
Body Mass Index (kg/m^2)	32.3 +/− 5.9	33.9 +/− 8.5	
Age (range)	46 (20–69)	47 (25–77)	
Plantar fascia pain, % (N)	65.0% (13)	77.3% (17)	
Achilles pain, % (N)	90.0% (18)	59.1% (13)	
Achilles Proximal Thickness (cm)	0.55 +/− 0.16	0.45 +/− 0.11	0.09
Presence of Erosions	70.0% (14)	22.7% (5)	0.0021
Presence of Erosions > 2 mm	35.0% (7)	18.2% (4)	0.30

Presence of Doppler at Enthesis	55.0% (11)	22.7% (5)	0.03
Presence of Doppler > 1 at Enthesis	25.0% (5)	13.6% (3)	0.45
Presence of Doppler at Cortical Margin	40.0% (8)	13.6% (3)	0.052

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A Cut-Off Value Analysis By Ultrasound for the Diagnosis of Giant Cell Arteritis (GCA). Hisayo Horiuchi, Kenta Misaki, Rintaro Saito, Yuri Nakamura, Yoshie Gon, Takumi Nagamoto, Hirotaka Yamada and Toshihiko Yokota. Kurashiki Central Hospital, Kurashiki, Japan.

Background/Purpose: Ultrasonography (US) of the superficial temporal arteries was introduced in the 1990s. The diagnostic value of US of the superficial temporal artery wall in giant cell arteritis (GCA) has been extensively reported. In order to clarify the effectiveness of US preceding pathological diagnosis, we examined cut-off values of ultrasonography-derived halo signs (intima-media thickness, IMT).

Methods: Twenty-eight patients with suspected GCA were examined by US before biopsy from October 2010 to June 2014, inclusive. US was performed unilaterally or bilaterally by two ultrasonographers and the greatest analyzed. Superficial temporal artery biopsy was used as the reference standard. The Cohen's Kappa test for Inter-Observer variation was 0.703 (95%CI: 0.390 to 1.015).

Results: Unilateral halo sign had a sensitivity of 83.3 % and specificity of 40.0 %. In ROC analysis, a cut-off of greatest dimension of halo > 0.51 mm was the most accurate for prediction with a sensitivity of 66.7 % and specificity of 80.0 %. The diagnostic odds ratio was 8.0 (95% CI, 1.28 – 50.04).

Conclusion: This is the first report that examined the cut-off values of IMT in diagnosing GCA. The measurement of the greatest dimension of the ultrasonography-derived halo sign (IMT) increased the diagnostic yield for pathological diagnosis.

Disclosure: H. Horiuchi, None; **K. Misaki**, None; **R. Saito**, None; **Y. Nakamura**, None; **Y. Gon**, None; **T. Nagamoto**, None; **H. Yamada**, None; **T. Yokota**, None.

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Ultrasonographic Evaluation of Joint and Tendon Involvement in Patients with Early Systemic Lupus Erythematosus (SLE) in Comparison with Early Rheumatoid Arthritis (RA). Takehisa Ogura, Ayako Hirata, Norihide Hayashi, Rie Kujime, Hideki Ito, Sayaka Takenaka, Sumie Nakahashi, Kennosuke Mizushina, Naoko Yamashita, Yuki Fujisawa and Hideto Kameda. Toho Univ, Tokyo, Japan.

Background/Purpose: Although both systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) may lead to the joint deformity, different characteristics such as the absence or the presence of bone destruction have been recognized as well: lupus arthritis is typically non-erosive and often accompanied by Jaccoud's deformity. Therefore, we examined characteristics of joint and tendon lesions in SLE patients as compared with RA patients by using ultrasonography.

Methods: Thirteen SLE and 32 RA patients were selected from the treatment-naïve patients with joint symptoms, visiting Toho University Ohashi Medical Center between January 2011 and March 2014. Enrolled patients had at least one swollen or tender joint. The wrist, metacarpophalangeal and proximal interphalangeal joints and related extensor/flexor tendons were ultrasonographically examined from both palmar and dorsal sides. Their joints and tendons including tendon sheaths were evaluated using a gray-scale (GS) for synovial thickening and synovial fluid retention, and power Doppler (PD) for blood flow according to a semiquantitative method based on a scale of grades 0 to 3, and patients graded with GS ≥ 2 or PD ≥ 1 were judged as having joint synovitis and or tendinitis/tenosynovitis.

Results: Joint synovitis and tendinitis/tenosynovitis were observed in 11 (79%) and 12 (86%) of 13 SLE patients, respectively, and in 31 (91%) and 18 (53%) of 32 RA patients, respectively. Thus, SLE patients had tendinitis/tenosynovitis more frequently ($p=0.034$) as compared with RA, and particularly in the wrist joints ($p=0.008$, Table 1). Moreover, the concordance of joint synovitis and tendinitis/tenosynovitis in the same region was less in SLE patients ($\kappa=0.18$) as compared with RA ($\kappa=0.44$).

Conclusion: Joint synovitis was similarly observed ultrasonographically in both SLE and RA patients, while tendinitis/tenosynovitis was more frequently observed in SLE patients than in RA patients. In addition, tenosynovitis in SLE patients may develop rather independently from synovitis.

	SLE number	n=13 (%)	RA number	n=32 (%)	p
Joint synovitis	11	(78.6)	31.0	(91.2)	0.196
Wrist	10	(71.4)	27.0	(79.4)	0.672
MCP	9	(64.3)	25.0	(73.5)	0.704
PIP	3	(21.4)	18.0	(52.9)	0.056
Tenosynovitis	12	(85.7)	18.0	(52.9)	0.034
Wrist	10	(71.4)	10.0	(29.4)	0.008
Finger extensor tendons	6	(42.9)	9.0	(26.5)	0.305
Finger flexor tendons	8	(57.1)	14.0	(41.2)	0.337

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US Lung Examination in SSc Patients: A Comparison of Two Different Scoring Systems. Andrea Delle Sedie[1], Cristina Lodato[1], Elisa Cioffi[1], Linda Carli[2], Stefano Bombardieri[1] and Lucrezia Riente[1]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]GenOMeC PhD, University of Siena, Siena, Italy.

Background/Purpose: Systemic sclerosis (SSc) is a disease characterized by a progressive fibrosis of the skin and internal organs, which can lead to death. Lung involvement includes a wide range of disorders and interstitial lung disease (ILD) is the most common manifestation, being clinically significant in about 40% of patients. Recently, the role of US in the assessment of ILD (counting the B-lines, generated by the reflection of the US beam from thickened sub-pleural interlobar septa) has been confirmed after comparison with high-resolution computed tomography (HRCT) and a few scoring systems proposed. The comprehensive examination of lung intercostal spaces (LIS) is time consuming (54 LIS in each patient) (1) and a previous attempt to give a simplified US B-line scoring system has been made in patients with connective tissue diseases (2), an evaluation on 8 different thoracic areas is also performed (3–4).

Aim of the study was to compare the comprehensive examination and the 8-area scoring system and define which could be more effective in clinical practice.

Methods: 79 SSc patients were enrolled independently of the presence of any dispnoea. Each patient underwent a lung US with comprehensive US B-line assessments by an experienced rheumatologist. A cut-off of >12 B-lines was decided based on the correlation between US and HRCT in 76 patients, then US was performed alone in the rest of the SSc patients. The presence/absence of B-lines was registered in each LIS. The second scoring system was positive when ≥3 B-lines were present in a single LIS in ≥1 area.

Results: 46 patients were positive for ILD (ILD+) and 33 negative when using the comprehensive examination; the 8-area scanning protocol showed 44 ILD+ and 35 negative. Using the two different scoring systems ILD+ and ILD- patients were the same in 67 cases. Seven of the remaining patients were ILD+ only using the comprehensive scan (in 4 of them the total B-lines score was <16, so really close to the cut-off) and 5 only using the 8-area scan. The time needed for the comprehensive assessment was longer than the one for the 8-area scanning protocol (the latter does not assess posterior thorax and, if a LIS is positive, there is no need to scan the other LIS in the same area).

Conclusion: The results provided by the two scoring systems are largely overlapping in the identification of ILD+ patients. Considering the shorter time needed for the assessment, the 8-area scanning protocol could be more useful for screening.

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Value of Ultrasonography Parotid Glands in Patients with Suspected Primary Sjögren's Syndrome. Marina Oliver[1], Lida Santiago[2], Paula Gonzalez[1], Diego Vila[1], Sebastian fernandez Nacul[1], Santiago Scarafia[3], Marta Mamani[4] and Anastasia Secco[3]. [1]Rivadavia Hospital, Buenos Aires, Argentina, [2]hospital rivadavia, CABA, Argentina, [3]Hospital Bernardino Rivadavia, Buenos Aires, Argentina, [4]Hospital Rivadavia, Capital Federal, Argentina.

Background/Purpose: Primary Sjogren's syndrome (pSS) is an autoimmune disorder characterised by chronic lymphocytic infiltration of exocrine tissues. Currently new non-invasive techniques are being continuously introduced as a diagnosis tool. Ultrasonography (US) of salivary glands in these patients merits special interest as a rapid, inexpensive, non-radiating and widely accessible modality.

Methods: The aim of the study is to assess the diagnostic value of ultrasonography (US) in those patients underwent minor salivary gland biopsy (MSGB) by suspected Primary Sjögren Syndrome (pSS).

All patients underwent bilateral parotid glands US and MSGB. The same expert blinded examiner performed the US. All patients were scanned using an MyLab 25 US scanner (Esaote Italy) with a 10–18 MHz linear-array transducer. The following parameters were assessed: homogeneity, hypoechoic areas, hyperechoic foci, Power Doppler (PD) and margins graded from 0 to 2 (0: well-defined, 1: ill-defined, 2: blurred) and gland size was measured. The gold standard was the MSGB. According to the quantity and type of US variables, we determined the following cut-off values (at least unilateral parotid finding) A: presence or absence of heterogeneity on unilateral or bilateral parotid glands B: presence or absence of any variable (not more than one and excluding heterogeneity) on unilateral or bilateral parotid glands. C: presence or absence of three or more variables (any variable) on unilateral or bilateral parotid glands.

Results: We included a total of forty-five biopsies (32 negative and 13 positive). 95.56% were female, the median symptoms length was 2 years (IQR 1–7), no differences were observed between both groups. According to A cut-off values had 30. 77 % sensitivity (S) (CI 17.28– 44.25), 78.13% specificity (Sp) (CI 66.05–90.20), 36.36 % positive predictive value (PPV) (22.31–50.42), 73.53% Negative Predictive Value(NPV) (CI 60.64–86.42), likelihood ratio (LR) + 1.41 (CI 0.49–4.0), and the area under the curve (AUC) 0.54 (CI 0.40–0.69). B findings showed 46.15% S (CI 41.59– 60.72), 68.75% Sp (CI 55.21–82.29), 37.50% PPV (CI 23.36–51.64), 75.86% NPV (CI 63.86–88.36%), LR + 1.48 (CI 0.68–3.22), AUC 0.57 (CI 0.41–0.74). We observed C findings with a 30.77% of Sensitivity (CI 17.28–44.25), 90.63% Specificity (CI 82.11–99.14), 57.14% PPV (CI 42.78– 71.60), 31% NVP (CI 63.89–88.74), LR + 3.28 (CI 0.85–12.67), AUC 0.61(CI 0.47–0.77).Bilateral parotid US showed an AUC similar to B findings.

Conclusion: We considered that C findings are the best cut-off values because it demonstrated greater specificity and slightly better AUC. Nevertheless, in our study the US of parotid gland not prove to be an appropriate diagnostic tool to replace the MSGB.

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Automated Digital Analysis of Major Salivary Gland Ultrasound Images. Daniel S. Hammenfors[1], Preben G. Nes[2], Johan G. Brun[1], Roland Jonsson[1] and Malin V. Jonsson[3]. [1]Haukeland University Hospital, Bergen, Norway, [2]Sogn and Fjordane University College, Førde, Norway, [3]University of Bergen, Bergen, Norway.

Background/Purpose: Primary Sjögren's syndrome (pSS) is an autoimmune chronic inflammatory disease mainly affecting the salivary and lacrimal glands, with symptoms such as dryness of the mouth and eyes as well as fatigue. The diagnosis is based on the objective findings of reduced secretion of saliva- and/or tears, the detection of auto-antibodies against Ro/SSA and/or La/SSB in serum, and the observation of focal mononuclear cell infiltration in minor labial salivary gland biopsies. In the recent years, interest in major salivary gland ultrasonography as a diagnostic tool for pSS has increased. Several scoring systems evaluating glandular homogeneity and echogenicity have been suggested, presenting a challenge for both researchers and clinicians. The aim of this study was to develop a reliable automated digital evaluation of ultrasound images as a useful tool for the clinician and as an objective method for the researcher.

Methods: The parotid glands of patients (n=26) fulfilling the AECG criteria (Vitali et al 2002) had previously been examined using a GE LogiqE9 with a linear high-frequency transducer (6–15MHz) and the images evaluated using a simplified grading system (0–3) (Hocevar et al, 2005). The stored images were analysed digitally with a pilot version of the software developed for this study. Briefly, the software analyses local variability in grayscale values. The algorithm used for the digital analysis was developed using MATLAB (MathWorks, Natick, Massachusetts).

The patients were randomly selected from a previously characterized cohort (n=97) where the ultrasound findings correlated with objective findings such as reduced saliva secretion, minor salivary gland inflammation and elevated autoantibody titers, as well as sicca symptoms of the mouth (manuscript found acceptable for publication in *Clinical and Experimental Rheumatology* 2014).

Results: Preliminary findings show an excellent correlation between the scores obtained with the simplified grading system (0–3) and the automated digital evaluation ($p > 0.05$, $r = 0.816$, $n = 26$). Mean digital score for images graded 0–3 were -9.833 (grade 0), -6.018 (grade 1), 2.752 (grade 2) and 6.850 (grade 3), respectively.

Conclusion: The preliminary results of ultrasound image analysis show an excellent correlation between the automated digital analysis and the evaluation by a trained clinician. In future studies, automated analysis will enable an objective and reproducible analytic method for the researcher as well as provide a useful diagnostic and possibly prognostic tool for the clinician.

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Ultrasonographic Evaluation of Major Salivary Glands in Primary Sjogren's Syndrome: Comparison of Two Scoring Systems and Diagnostic Value of Sonoelastography. Xia Zhang, Jing He and Zhanguo Li. Peking University People's Hospital, Beijing, China.

Background/Purpose: Primary Sjogren's syndrome (pSS) is a chronic systemic autoimmune disease characterized by clinically xerophthalmia and xerostomia. Those standard tests of salivary glands involvement has some deficiency. To date, a precise and feasible evaluation method for primary Sjogren's syndrome (pSS) remains to be established. Ultrasonography (US) is a promising technique, as it is convenient, economic, and non-invasive. A consensus has not been reached regarding the evaluation of typical SGUS changes for pSS, and at present, two main scoring systems exist (range 0–16, 0–48, respectively). To date, it's unknown which one is more practical and useful. On the other hand, sonoelastography (SE) is a rapidly developping technique by which the tissue elasticity can be measured. SE has been investigated in the differential diagnosis of focal nodule of breast, thyroid, prostate and salivary gland and liver fibrosis, as an accurate and reproducible method. However, the application of sonoelastography to salivary diffuse pathologic lesions never reported. We aimed to assess and compare the usefulness of two existing SGUS scoring systems for primary pSS and explore the performance of SE in the diagnosis of pSS.

Methods: US and SE examination of major salivary glands was conducted for 105 pSS patients and 41 non-SS patients with 10 Sicca syndrome, 5 hypothyroidism, 19 rheumatoid arthritis, 7 systemic lupus erythematosus and 16 healthy subjects. The ultrasonographic features were graded using two different scoring systems (0–16, 0–48, respectively) obtained from the grades of bilateral parotid and submandibular glands. On the other hand, elastographic images was determined with a qualitative 4-point scoring method (range 0–16).Receiver operating characteristic (ROC) curves were used to describe and compare the diagnostic accuracy of the two US echostructure scoring systems for pSS, simutaneously, to evaluate the performance of qulalitative elasticity scoring by sonoelastography.

Results: 1) SGUS scores for the pSS group were significantly higher than those for the non-pSS group ($P < 0.001$). The maximal combination of sensitivity and speciality was 80% and 93% at an optimal US cut-off value of 7 in the 0–16 system, and was 88.6% and 84.2% at a best cut-off of 15 in the 0–48 system. For the 0–48 system, the sum of the scores of all four glands provided the best diagnostic accuracy. 2) Scores of elasticity for pSS group were significantly higher than those for non-pSS group by different calculated qulalitative methods ($p < 0.001$). Referring to the ROC curves, the sum of the scores of all four glands provided the largest AUC-ROC (0.916, 95% CI 0.87 – 0.962). The maximal sensitivity and specificity were 81% and 87% at an optimal cut-off value of 9 for the sum of the scores of all four glands.

Conclusion: SGUS showed good sensitivity and specificity for noninvasive assessment of salivary glands for pSS diagnosis. Moreover, compared to the 0–16 system, the 0–48 system had a slightly higher sensitivity. The qualitative assessment of salivary elasticity with SE was of diagnostic value to pSS.

Disclosure: X. Zhang, None; **J. He**, None; **Z. Li**, None.

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Sonographic Measurements Can be Misleading for Diagnosing Carpal Tunel Syndrome in Patients with Rheumatoid Arthritis. Ilker Yagci[1], Merve Akdeniz Leblebicier[2], Basak Mansiz Kaplan[2], Demet Ozturk Gokbakan[2] and Gulseren Akyuz[1]. [1]Marmara University School of Medicine, Istanbul, Turkey, [2]Marmara School of Medicine, Istanbul, Turkey.

Background/Purpose: To compare the nerve cross sectional areas (CSA) in patients with RA without any sign of peripheral neuropathy to healthy controls.

Methods: The study group was generated from referrals to Rheumatic Diseases Outpatient Clinics. Clinical, electrophysiological and sonographic assessments were done by three blinded resarchers. Clinical assessment included Tinnel's sign, Phalen test, tenar atrophy and Flick sign, KATZ hand diagram and Boston Questionnaire. Median, ulnar and tibial motor, median, ulnar and sural sensory nerve conduction studies (NCS) were performed. The patients who had an electrodiagnostic or clinical peripheral neuropathy were excluded from the study. Nerve CSA's were measured in various levels; hamatum hook, psiform bone, radio-ulnar joint, distal 1/3 of forearm, and elbow levels for median nerve; radio-ulnar joint, psiform bone, distal 1/3 of forearm, and medial epicondyle for ulnar nerve. Three different measurements were obtained and the average measure was used for the each level.

Results: The study was completed with 30 women with RA and 30 healthy women. There were no statistical significance according to age, and body mass index. Despite both of the groups had no clinical and electrophysiological neuropathy, the sonographic measurements showed that median nerve CSA's at radioulnar joint, psiform and hamatum levels of patients with RA were larger than healthy controls. Ulnar nerve CSA's of all levels statistically increased in patients with RA ($p<0.05$). If the psiform level median nerve CSA >10 mm2 was used as sonographic carpal tunnel syndrome (CTS) criterion, 23/60 hands of 30 patients with RA and 5/60 hands of 30 healthy controls could be misdiagnosed as CTS.

Conclusion: Median and ulnar nerve CSA's were larger than healthy control in patients with rheumatoid arthritis without clinical and electrophysiological peripheral neuropathy. The rheumatologists should be careful to diagnose CTS in patients with RA with using US.

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Subclinical Synovial Inflammation in Gout. Priya Chowalloor[1], Patrick Cheah[2] and Helen I. Keen[1]. [1]The University of Western Australia, Crawley, Australia, [2]Sir Charles Gairdner Hospital, Nedlands, Australia.

Background/Purpose: Gout is poorly managed in the community. Long standing poorly controlled gout can lead into progressive destructive arthropathy, decreased quality of life and increased mortality. Aims of this study is to assess the burden of subclinical synovitis in gout both in acute and intercritical phases. Subclinical synovitis may have implications for the long term outcome of patients with gout.

Methods: This pilot study included 30 participants with gout according to either ACR or EULAR criteria. Subjects with any other inflammatory joint disorders were excluded. Subjects were examined twice. One visit was during the period of acute gout and second was during the intercritical phase. The intercritical phase visit was done at least four weeks after the resolution of symptoms of acute gout. Examinations performed during each visit include tender and swollen joint count, musculoskeletal ultrasound (US) of 52 peripheral joints for gray scale synovitis and power Doppler (PD). Blood was collected for ESR, high sensitivity CRP (hs CRP) and uric acid.

Results: Median age of the subjects was 69 (IQR 52.5–74) and BMI was 26.40(IQR 23.12–29.40). Females were 7.4%. Median disease duration was 3 years (IQR 11-2). The mean interval between visits was 3.6 months (SD 2.4).

	Flare visit	Intercritical visit	P value
Number of subjects seen	27	27	
Hs CRP	8.19 (3.57–37.45)*	5.15 (1.39–8.46)*	0.054
ESR	28 (14.5–44.75)*	13.5 (5.75–33)*	0.031
Serum uric acid	0.44 (0.36–0.5)*	0.38 (0.2975–0.485)*	0.405
Number of joints clinically involved	1 (1–2)*	0 (0–0)*	0.007
Number of joints involved on US (defined as a PD score of >/= 2)	5 (3–11)*	4 (3–7)*	0.139
Number of joints involved only by US and not clinically	4 (2–9)*	4.5 (3–7.25)*	0.901
Most commonly involved joints by US	1st MTP (n = 30), knee (n = 17), wrist (n = 17) and 2nd MCP (n = 16)	1st MTP (n = 21), wrist (n = 17), 2nd MCP (n = 17) and knee (n = 14)	

*Median (IQR)

Conclusion: Ultrasound demonstrates subclinical synovitis during acute and intercritical periods. Interestingly, whilst there were significantly less clinically active joints during the intercritical period ($p=0.007$) there was not less joints involved by US ($p=0.139$). Ultrasound may be important in the monitoring of inflammation in the management of gout.

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Musculoskeletal Ultrasound of Finger and Foot Joints in a Population of Volunteers: Is Osteoarthritis an Underestimated Problem? Results from the German "Rheuma-Truck" Cohort. Dr. Philipp Sewerin[1], Dr. Stefan Vordenbäumen[1], Aiko Liedmann[1], Sarah Ohrndorf[2], Marina Backhaus[2], Dr. Oliver Sander[1], Prof. Dr. Matthias Schneider[3] and Prof. Dr. Benedikt Ostendorf[1]. [1]Univ. Duesseldorf, Düsseldorf, Germany, [2]Charite University Hospital, Berlin, Germany, [3]Univ. Duesseldorf, Duesseldorf, Germany.

Background/Purpose: To investigate the frequency of osteoarthritis (OA) in musculoskeletal ultrasound of the MCP, MTP and PIP joints in a volunteer population using the US-7 score.

Methods: "Rheuma-Truck" was a mobile rheumatology office located in different city center of North Rhine Westphalia, Germany offering a screening for rheumatic diseases including Rheuma-Check questionnaire, lab-tests (MCV capillary test) and imaging (US, capillaroscopy). Musculoskeletal ultrasound (MyLab 25 Gold, Esaote linear scanner, 15, Typ LA435) of the dominant hand of 605 volunteers (Rheuma-Truck-Cohort) was performed, using US-7 score for the detection of inflammatory joint alteration. Additionally, the foot joints were investigated according to US-7 criteria in 236 volunteers. Osteoarthritis in US was defined as the presence of osteophyte formations (discrete, moderate or severe). Due to the US-7 scoring system DIP joints were not assessed. Descriptive statistics for the patients were obtained and are reported as means $\pm$ standard deviation, ranges, frequencies or proportions as appropriate. Correlation coefficients are Pearson-correlations.

Results: 605 volunteers of the "Rheuma-Truck" Cohort were screened by musculoskeletal ultrasound according to the US-7 scoring system. The mean age of the investigated population was 52.72 years (min. 10 years; max. 89 years). Sex distribution shows 72.2% females and 27.8% males. 181 volunteers were displayed arthritis by ultrasound. Moreover 337 (55.7%) probands showed sonographically detectable sings for osteoarthritis in the investigated joints. The mean age of the OA-positive probands was 57.78 years (min. 12, max. 89 years). The sex distribution reflected that of the entire cohort (72.4% f; 27.6% males). 73.1% of the sonographically positive OA volunteers were older than 50 years, 13% between 40–50 years, 5.2% between 30–40 years and 8.7% under 30 years. MCP-2 was the most frequently involved joint, wherein 36.6% of the sonographically positive OA volunteers showed osteophytes. The MCP-3 was sonographyically positive in 15.4% followed by the wrist (10.4%), PIP-2 (9.3%), PIP-3 (7.6%), MTP-2 and 5 (each 7.2%). Of all volunteers enrolled, 16.8% (102 of 605) were diagnosed with both, OA an RA. Of all patients diagnosed with RA, 56.4% (102 of 181) also showed sonographically detectable OA-sings.

Conclusion: In the "Rheuma-Truck" Cohort, nearly 3 of 4 volunteers over 50 y of age exhibited sonographic findings compatible with osteoarthritis. Also nearly 14% of newly diagnosed OA according to ultrasonographic findings were below the age of 40. Strikingly, MCP joints were the most frequently involved joints within the US-7 scoring, which however ignores the DIP-joints. Thus, this study highlights a previously unrecognized high burden of hand OA.

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Cimt in Individuals with Rheumatoid Arthritis Compared to Individuals with Type2 Diabetes. Helen Pahau Sr. [1], Leanne Short[2], Brian Haluskas[3], Vibeke Videm[4] and Ranjeny Thomas[5]. [1]The University of Queensland, Woolloongabba, Australia, [2]University of Queensland, Woolloongabba, Australia, [3]the University of Queensland, Woolloongabba, Australia, [4]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, and Department of Immunology and Transfusion Medicine, Trondheim University Hospital,, Trondheim, Norway, [5]University of Queensland Diamantina Institute, Brisbane, Australia.

Background/Purpose: It is well known that patients with RA or Type 2 diabetes (T2DM) have increased risk of atherosclerosis and CVD. Carotid ultrasound measurement of the intima media thickness is the most commonly used method to validate progression of atherosclerosis. We aim to investigate the characteristics of cardiovascular risk and progression of carotid intima media thickness in individuals with Rheumatoid Arthritis compared to individuals with type2 diabetes.

Methods: Participants with T2DM were recruited from hospital clinics and the community in the same geographic area as RA participants. The participants with T2DM participated in a randomised trial of exercise intervention for 4 weeks and patients with previous CV events were excluded in that study. All participants were subjected to B-Mode ultrasonography of the common carotid artery to measure Carotid intima media thickness, and to undertake a physical assessment, routine laboratory investigations and history of CV risk profile. Average CIMT were measured on individuals with RA and individuals with Type2 diabetes at two time points, separated by a mean of 4.8 and 2.4 years respectively, using carotid duplex scanning and automated software.

Results: The study comprised 290 individuals: 78 with RA and 212 with T2DM. The RA patients were significantly older and had a higher proportion of smokers and previous CV events. The T2DM had higher BMI, diastolic blood pressure (BP) and triglycerides, lower HDL cholesterol and higher statin use.

At baseline, CIMT measurements were similar in the RA and T2DM cohorts at baseline (0.88mm (0.19) vs. 0.86 (0.21) $p=0.80$). Despite a shorter follow-up, 91 % of the T2DM cohort had CIMT at follow-up compared to 54 % of the RA cohort ($p<0.0005$). In a regression model for yearly rate of CIMT change, the only significant variables were diabetes ($p<0.0005$) and ever use of statins ($p=0.01$). Baseline CIMT was not significantly associated with the yearly rate of CIMT change. In a supplementary adjusted logistic regression analysis where the outcome was CIMT progression compared to unchanged or reduced CIMT, the OR for progression in T2DM compared to RA was 11.4 (5.2–25.0). In the RA cohort, DMARD use at baseline was associated with significantly lower CIMT values at follow-up ($p=0.04$).

Conclusion: Diabetes patients have a much higher risk of CIMT progression than RA patients when adjusting for relevant risk factors and baseline CIMT.

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ACR Poster Session A
Metabolic and Crystal Arthropathies: Clinical Aspects
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Cost-Effectiveness Analysis of HLA-B5801 Genotyping in the Treatment of Gout Patients with Chronic Renal Insufficiency in Korea. Dong-Jin Park[1], Kyung-Eun Lee[1], Sung-Hwan Park[2] and Shin-Seok Lee[1]. [1]Chonnam National University Medical School, Gwangju, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea.

Background/Purpose: Allopurinol-induced severe cutaneous adverse reactions (SCARs) are relatively rare, but cause high rates of morbidity and mortality. Studies have shown that the HLA-B5801 allele and renal impairment are strongly associated with SCARs. Recent American College of Rheumatology guideline recommends that, prior to treatment with allopurinol, the HLA–B5801 genotype of gout patients at high risk for SCARs, including Korean patients with chronic renal insufficiency, should be determined. However, whether such genotyping is cost-effective is unknown. This study evaluated the cost-effectiveness of HLA-B5801 genotyping for treatment of gout in patients with chronic renal insufficiency in Korea.

Methods: A decision analytic model over a time period of 12 months was employed to compare the cost and outcomes of treatment informed by HLA-B5801 genotyping with that of a conventional treatment strategy using a hypothetical cohort of gout patients with chronic renal insufficiency. Direct medical costs were obtained from real SCAR patients from two tertiary hospitals. Outcomes were measured as a total expected cost and an incremental cost-effectiveness ratio.

Results: In the base model, the total expected cost and probability of continuation of gout treatment without SCARs with the conventional and HLA-B5801 screening strategies were US $1,193 and US $1,055, and 97.8% and 100%, respectively. The result was robust according to sensitivity analyses.

Conclusion: Our model suggests that gout treatment informed by HLA-B5801 genotyping is less costly and more effective than treatment without genotyping, and HLA-B5801 genotyping could considerably reduce the occurrence of allopurinol-induced SCARs and related deaths.

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Colchicine and the Risk of Acute Cardiovascular (CV) Events Among Gout Patients: The New York Department of Veterans Affairs Retrospective Cohort Study. Daria B. Crittenden[1], Jessica N. Kimmel[1], Virginia C. Pike[1], Rebecca Boas[1], Daniel Diaz[1], Cilian J. White[1], Michael DeBerardine[2], Grace Kim[1], Pajazit Morina[1], Avni Shah[1], Binita Shah[2], Steven P. Sedlis[3], Jeffrey D. Greenberg[4], Craig T. Tenner[2], Christopher J. Swearingen[5], Svetlana Krasnokutsky Samuels[2], Bruce N. Cronstein[1] and Michael H. Pillinger[1]. [1]NYU School of Medicine, Division of Rheumatology, New York, NY, [2]VA New York Harbor Health Care System, New York, NY, [3]NYU School of Medicine, Division of Cardiology, New York, NY, [4]NYU School of Medicine, New York, NY, [5]University of Arkansas for Medical Sciences, Little Rock, AR.

Background/Purpose: Gout patients are at increased risk for CV disease, possibly owing to chronic inflammation. Colchicine is commonly used in gout, and inhibits inflammatory cell types that are also implicated in atherosclerosis. In a cross-sectional study, we observed an association between colchicine use and decreased myocardial infarction (MI) among gout patients (Crittenden et al, J Rheum 2012). To further assess colchicine's possible effect on CV risk in this population, we performed a retrospective cohort study of gout patients taking or not taking colchicine at the VA NY Harbor Health Care System.

Methods: We identified all active patients with ICD-9 codes for gout or hyperuricemia from 2000-09. Charts were manually screened to confirm gout (based on ACR criteria) and pharmacy records used to identify subjects taking daily colchicine for >30 continuous days (colchicine group). Gout patients who never received colchicine formed the control group. Among the colchicine group, we defined colchicine lapse as any period of colchicine non-use ≥ 2 weeks after medication cessation (to account for drug elimination time). Outcomes included a composite incidence rate of MI+stroke+transient ischemic attack (TIA); individual components of the composite outcome; and C-reactive protein level (CRP; lowest level attained during the period observed).

Results: Of 7,819 potential subjects, 1638 patients met gout criteria. 381 were excluded for <30 days colchicine use, leaving 1257 to be analyzed. 804 colchicine users had 3,630 years of follow-up (2270 years of active use and 1360 years of lapse). 453 patients never used colchicine, with 2,087 years of follow-up. Colchicine users had significantly more hyperlipidemia (60 vs 49%, $p=0.003$), and history of MI (14 vs 9 %, $p=0.01$) and percutaneous intervention (10 vs 6%, $p=0.006$) than controls, as well as higher urate levels (8.5 vs 8.0 mg/dL, $p=0.05$) and allopurinol use rates (23 vs 18%, $p=0.03$). We observed no significant difference between colchicine users and non-users for the composite outcome (control, 0.011 events/subject-year; colchicine, 0.016 events/subject-year, $p=0.23$) or individual component outcomes (adjusted for allopurinol use), but due to a low event rate we were not able to adjust fully for patient risk factors. However, within the colchicine group we observed a significant, 57% reduction in the composite outcome event rate during times of active colchicine use vs lapse (0.012 vs 0.021 events/subject-year, $p=0.04$). When colchicine users were divided into consistent (medication possession ratio ≥ 0.9) vs inconsistent (MPR <0.9) users, consistent

colchicine users had lower CRP levels (0.7 mg/dL) than either never users (2.7 mg/dL) or inconsistent users (1.9 mg/dL) (never vs consistent $p<0.001$, inconsistent vs consistent $p<0.001$), despite higher background CV risk.

Conclusion: Among gout patients prescribed colchicine on an ongoing basis, composite CV event rates were significantly lower during colchicine use vs colchicine lapse, and consistent colchicine use was associated with lower CRP concentrations. Additional studies are underway to clarify the possible benefit of colchicine in reducing acute CV events among gout patients.

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Can We Diagnose Acute Gout without Joint Aspiration? Results of a Prospective Study of 112 Patients Presenting with Acute Arthritis.

Pascal Zufferey, Roxana Valcov, Isabelle Fabreguet, Alexandre Dumusc and Alexander So. RHU/CHUV, Lausanne, Switzerland.

Background/Purpose: The gold standard for the diagnosis of acute MSU induced arthritis is crystal identification by microscopy after joint aspiration. Alternative diagnostic tools that have been proposed include joint ultrasonography (US) and a clinical score for gout (Nijmegen Score – NS) that has been validated in a primary care setting. Most US studies have been performed in patients with known gouty arthritis. The primary objective was to compare the performance of US as diagnostic tool with the NS in the diagnosis of suspected acute gouty arthritis, using synovial fluid analysis as a gold standard. The secondary objective was to evaluate whether the performance of NS could be enhanced by combining with US data.

Methods: All consecutive patients who presented with acute arthritis suspected to be of microcrystalline origin between October 2012 and May 2014 were prospectively included. The duration of arthritis symptoms was <10 days. All patients underwent a clinical and an US evaluation of the symptomatic joint as well as of the knees, the ankles and the first MTP joints (multiple joints). Joint aspiration of the symptomatic joint was performed within 24 hours.. US was performed by2 rheumatologists skilled in US who were blinded to the clinical data. The NS was calculated "a posteriori" by a clinician not implicated in the primary evaluation of patients. We applied a cut-off value of > 8 as proposed by the authors of the NS for the diagnosis of gout (1). US diagnosis of gout was evaluated firstly on typical US signs ("Double contour" and or tophi) in the symptomatic joint and secondly on signs of gout in all the other joints.

Results: 117 patients were included. Joint fluid was obtained in 112 patients. MSU crystals were detected in 61 patients (54%), CCP crystals were found in 29 (26%) and no crystals were found in 22 (20%). The mean ($\pm$ SD) NS scores differed significantly between gout 8.8 ($\pm$2.4) and non-gout groups 4.6 ($\pm$2.8) ($p < 0.05$). In CPP patients, the mean NS score was 4.3($\pm$2.3). US signs of gout were found in symptomatic joints of 40 patients, and by multiple joints US, signs of gout were found in 68 patients.

The table describes the sensitivity, the specificity, and the positive predictive value (PPV)of the NS, US and the combination of both US and NS in the diagnosis of gouty arthritis. NS score alone or US of the affected joint alone had moderate sensitivity but reasonable specificity for diagnosis of gout in our cohort. The best diagnostic performance was obtained with either US in multiple joints or the NS + US in the symptomatic joints.

	Clinical score (>8)	USSymptomatic joint	US Multiple joints	Clinical score +US symptomatic joint	Clinical score+US multiple joints
Sensitivity: %	62	60	84	80	90
Specificity %	86	92	78	82	74
PPV%	84	90	84	84	81

Conclusion: The NS score alone or US alone of the affected joints were moderately sensitive in the diagnosis of acute gout, but had good specificity. Combining the NS score with US evaluation of the symptomatic joint enhanced the diagnostic performance but does not replace the need for crystal-identification by microscopy in the diagnosis of acute gouty arthritis.

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Performance of Joint Ultrasonography in the Diagnosis of Suspected Acute Crystal Arthritis: Results of a Prospective Study of 112 Patients.

Pascal Zufferey[1], Isabelle Fabreguet[1], Roxana Valcov[1], Alexandre Dumusc[1] and Alexander K. So Sr.[2]. [1]RHU/CHUV, Lausanne, Switzerland, [2]CHUV, Lausanne, Switzerland.

Background/Purpose: The gold standard for diagnosing gout and CCP arthritis is the identification of monosodium urate (MSU) crystals in joint fluid. Ultrasound (US) features of gouty and CPP arthritis have been described (1,2), and the technique has been proposed as a diagnostic tool in acute arthritis. There have been limited studies on the performance of this technique as a diagnostic tool when applied to the setting of acute arthritis.

The primary objective was to determine the performance of ultrasound as a diagnostic tool for CCPD and urate acute crystal arthritis, using crystal identification by microscopy as a gold standard.

Methods: 117 consecutive patients who presented an acute arthritis of <10 days duration of suspected microcrystalline origin between October 2012 and January 2014 were prospectively included in the study. Aspiration of the symptomatic joint was performed and crystals identified by polarizing light microscopy. All patients underwent an US of the symptomatic joint as well as both knees, ankles and 1stMTP joints that was performed by a rheumatologist who was "blinded" to the clinical history within 24 hours of joint aspiration. An "US diagnosis" was made based of the findings in the symptomatic joint as well as the other joints examined by US.

Results: In 112 patients joint fluid was obtained. 53 had MSU, 27 CCPD and 9 had both crystals. No crystals were detected in 23. US signs of gout, CCP or mixed crystal deposition were found in symptomatic joints of 40/38/7 patients respectively, and by multiple joints US, in 68/59/16 patients.

Table 1 describes the sensitivity, the specificity, and the positive predictive value (PPV) and negative predictive values (NPV)

	Gout US Symptomatic joint	Gout US Multiple joints	CCP US symptomatic joint	CCP US multiple joints
Sensitivity : %	60	84	60	81
Specificity %	92	76	80	62
PPV%	92	82	60	52
NPV%	62	77	80	87

The sensitivity of US signs in the symptomatic joint for both gout and CCP is poor. US is more specific for the diagnosis of gout that CCP arthritis (PPV >90% against 60%).

By US of multiple joints, the sensitivity of US for both diagnoses rose significantly but the specificity and the PPV decreased, especially for CCP (PPV52%). In absence of US signs in all the joints, CCP arthritis is highly unlikely (NPV 87%).

Conclusion: In patients with a clinical suspicion of acute microcrystalline arthritis, US examination may be of assistance in the diagnosis if joint aspiration is not feasible. The examination of multiple joints is required to obtain the best clinical utility.

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Canakinumab in Frequently Flaring Gouty Arthritis Patients, Contraindicated, Intolerant or Unresponsive to non-Steriodal Anti-Inflammatory drugs and/or Colchicine: Safety and Efficacy Results from Long Term Follow-up.

Naomi Schlesinger[1], Rieke Alten[2], Thomas Bardin[3], H. Ralph Schumacher Jr. [4], Mark Bloch[5], Karine Lheritier[6], Dominik Richard[6], Andrea Stancati[6] and Alexander So[7]. [1]Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, [2]Charité University Medicine, Berlin, Germany, [3]Hôpital Lariboisière, Paris, France, [4]University of Pennsylvania VA Medical Center, Philadelphia, PA, [5]Holdsworth House Medical Practice, Sydney, Australia, [6]Novartis Pharma AG, Basel, Switzerland, [7]Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland.

Background/Purpose: Frequently flaring acute gouty arthritis (GA) patients (pts), in whom NSAIDs and/or colchicine are contraindicated, not tolerated or ineffective, need effective alternative treatments.[1] Canakinumab

(CAN) is a selective, human anti-interleukin-1β antibody, the only biologic approved (in the European Union) for the treatment of difficult-to-treat GA pts. Here, we present the cumulative results from a single long-term extension of two phase III studies. The primary objective is to evaluate the long-term safety of CAN (s.c.) in GA pts with frequent flares. Frequency of new flares, mean number of doses/pt, pts' assessments of gouty pain intensity and pts' global assessment (PGA) of response (both on Likert scale) were measured as secondary objectives. The effectiveness of CAN enabling successful urate lowering therapy (ULT) was explored by assessing serum uric acid (SUA) level in pts' initiating or modifying their ULT while exposed to CAN.

Methods: GA pts, who completed two multicenter randomized (CAN and triamcinolone acetate [TA]) phase III core and respective randomized extensions (E1) of the same design, rolled over into respective open-label extensions, E2, followed by a single extension phase, E3. In E2 and E3, all pts were treated with CAN 150 mg on demand upon new flare. These treatment groups were analyzed as 'CAN Group' [CG] and 'TA Group' [TG], i.e. all patients who were initially randomized to receive CAN or TA, respectively, and received at least one dose of study drug. Safety was assessed in terms of exposure-adjusted incidence of adverse events (AEs) per 100 patient-years (pyr). Maximum total cumulative duration of the study was 3 years.

Results: Of the 456 pts randomized in core studies, 335 entered the E1s. After E1 completion, 272 pts entered E2s. Following E2 completion, 136 pts entered and 122 completed E3. In CG, the mean number of doses/pt was 2.68 over 3 years. Overall, the exposure adjusted incidence of AEs in CG was lower (264.6/100 pyr) than in TG (308.8/100 pyr). Re-treatment with CAN did not result in any increased incidence of AEs. Overall, the incidence of exposure adjusted SAEs in CG and TG was 17.3 and 17.7 per100 pyr, respectively. The overall incidence of SAEs did not change in pts re-treated with CAN in CG (15.2 vs 15.1 per 100 pyr). Overall 4 deaths (2 in CG, 2 in TG) were reported: 1 intracranial hemorrhage [pt not re-treated with CAN]; 1 pneumonia [pt re-treated with CAN], 1 sudden cardiovascular death and 1 pneumococcal sepsis [TG pt who never received CAN]). None of these deaths were suspected to be study drug related. Thirty percent (n=12) of the pts initiating or modifying ULT during the E3 (n=40) reached target SUA levels (<6mg/mL). Mean flare rate per year was lower in CG compared with TG (1.109 vs 2.459). All CAN-treated pts' maintained pain intensity and PGA response scores upon 'on demand' retreatment over 3 years.

Conclusion: These results support the long-term safety of CAN treatment in pts' with frequent GA flares. AEs in CG were lower than in TG. The safety profile was consistent with that observed in the previous studies. Over the cumulative duration of 3 years, efficacy of CAN was maintained.

[1]Schlesinger N, et al. *Ann Rheum Dis*. 2012;71:1839–48.

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All Men with Gout Should be Screened for Erectile Dysfunction. Naomi Schlesinger[1], Diane C. Radvanski[2] and John Kostis[3]. [1]Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, [2]Robert Wood Johnson Medical School, New Brunswick, NJ, [3]Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ.

Background/Purpose: Erectile dysfunction (ED) is common in the general population. The likelihood of ED increases progressively with age; however, it is not an inevitable consequence of aging. The importance of cardiovascular disease (CVD), as an underlying cause of ED is well established. Patients who present with ED have an increased rate of CVD and silent coronary artery disease (CAD). ED and gout share common risk factors such as age, metabolic syndrome, hyperuricemia and inflammation.

Our aim was to determine whether men with gout may have an increased prevalence of ED as compared to men without gout.

Methods: In this cross sectional study, men aged 18–89 presenting to the Rheumatology clinic between 8/26/10 and 5/13/2013, were asked to participate. The presence of ED was determined by filling out a Sexual Health Inventory in Men (SHIM). SHIM scores correlate with ED severity: 22–25 Normal erectile function (no ED); SHIM score $\leq$ 21 ED and a score of $\leq$ 10 denotes severe ED. The patient's history, physical examination and recent laboratory studies were reviewed as well.

Descriptive statistics and subgroup analyses were used to summarize the data. We used chi-square tests for independence to compare categorical variables.

Results: 201 men completed the SHIM questionnaires; 83 had gout. A significantly greater proportion of gout patients had ED (n=63; 76%) compared with patients without gout (n=61; 52 %) (p= 0.0007). A significantly greater proportion of gout patients (43%) had severe ED compared with patients without gout (30%) (p=0.007). The mean SHIM score of all patients was 16.88 (SD$\pm-$0.83). Gout patients had an average SHIM score of 14.38 (SD$\pm$1.01) versus 18.53 (SD$\pm$ 0.964) in patients without gout ($p < 0.0001$). In a multivariate analysis the association between gout and ED remained statistically significant even after adjusting for age (p=0.0009), hypertension, LDL, GFR, obesity, depression (p=0.0154) and diabetes (p=0.0085).

Conclusion: ED is present in most men with gout and is frequently severe. Increasing awareness of the presence of ED in gout patients should in turn lead to earlier medical attention and treatment for this distressing condition as well as evaluation of possible silent CAD. We propose that all men with gout be routinely screened for ED.

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Ultrasonographic Measurement of Renal and Carotid Artery Resistive Indices and Diastolic Function of the Heart in Gout Patients. Rada Gancheva[1], Atanas Kundurdjiev[2], Mariana Ivanova[1], Todor Kundurzhiev[3], Rasho Rashkov[1] and Zlatimir Kolarov[1]. [1]University Hospital "St. Iv. Rilski", Clinic of Rheumatology, Sofia, Bulgaria, [2]University Hospital "Alexandrovska", Clinic of Nephrology, Sofia, Bulgaria, [3]Medical University, Faculty of Public Health, Sofia, Bulgaria.

Background/Purpose: Our aim was to assess the impact of gout on kidneys, diastolic function of the heart and carotid arteries. We examined ultrasonographic parameters that reflect resistance and compliance of the vessels and diastolic function of the left ventricle. Renal resistive index (RRI) and common carotid artery resistive index (CCARI) were measured. Diastolic function of the heart was assessed by parameters of the transmitral blood flow: E/A ratio and deceleration time (DT) which depend on preload and may give false negative results (pseudonormalization of mitral blood flow). That is why with the use of tissue doppler Em was determined which does not depend on preload and helps to differentiate normal from pseudonormal mitral blood flow as it decreases progressively with the worsening of diastolic dysfunction.

Methods: A total of 117 patients (pts) were included in the study: Healthy controls without conventional CV risk factors – 37 pts, 18 males and 19 females in a mean age 47.4$\pm$13.8 years, asymptomatic hyperuricemia pts – 24 pts, 13 males and 11 females in a mean age 55.8$\pm$13.5 years and gout pts – 56 pts, 50 males and 6 females in a mean age 57$\pm$11.6 years, 36 of the pts with gout were without tophi and 20 were gouty tophi pts. All pts included in the study underwent a complex multimodal ultrasonography: 1. RRI was measured in both kidneys at the level of interlobar arteries with 3.5MHz transducer working with pulse repetition frequency (PRF) of 2.5MHz. 2. Echocardiography was performed with 2.5MHz transducer Phased Array working with Pulsed doppler frequency of 2.5MHz. 3. Carotid arteries were examined with 10MHz linear transducer working with PRF of 5MHz. Ultrasonographic examinations were performed once by one researcher who was unaware with the protocol of the study. Statistical analyses were done by ANOVA, Post-Hoc Tukey, Kruskal-Wallis and Mann-Whitney tests.

Results: There was no significant difference in serum uric acid levels between asymptomatic hyperuricemia and gout pts (p=0.865). In all examined ultrasonographic parameters there was statistically significant difference between healthy controls and the other groups of pts with $p<0.001$. Comparing parameters between asymptomatic hyperuricemia and gout pts we estimated no significant difference in RRI (p=0.692), E/A (p=0.195), DT (p=0.611), but we observed a tendency of lower Em (mean$\pm$SD, 0.13$\pm$0.17 vs 0.09$\pm$0.03, p=0.084) and higher CCARI (mean$\pm$SD, 0.69$\pm$0.05 vs 0.71$\pm$0.05, p=0.057) in gout pts. Comparing gouty tophi pts to gout pts without tophi we observed that tophi pts had significantly higher RRI (mean$\pm$SD, 0.69$\pm$0.06 vs 0.65$\pm$0.05, p=0.013) and significantly higher CCARI (mean$\pm$SD, 0.74$\pm$0.05 vs 0.70$\pm$0.05, p=0.027). Tophi pts also had significantly lower Em compared to gout pts without tophi (mean$\pm$SD, 0.07$\pm$0.02 vs 0.09$\pm$0.03, p=0.014). We did not estimate a significant

difference in E/A ratio (p=0.233) and DT (p=0.419) between these two groups.

Conclusion: We suggest that with the progression of the disease arteriosclerotic type vessel changes progress and diastolic function of the heart worsens.

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Development of Preliminary Remission Criteria for Gout Using Delphi and 1000Minds Consensus Exercises. Hugh de Lautour[1], Nicola Dalbeth[2] and William Taylor[3]. [1]Auckland District Health Broad, Auckland, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]University of Otago, Wellington, New Zealand.

Background/Purpose: There are currently no agreed remission criteria for gout. The aim of this study was to establish consensus for elements of potential remission criteria for use in clinical trials of gout.

Methods: Experts in gout from multiple countries (n=88) were invited by email to participate in this web-based questionnaire study to identify remission criteria as an outcome measure for gout clinical trials. For the purposes of this project, remission was defined as the absence of symptoms and signs attributable to gout, when these symptoms or signs can or are expected to return in the future (for example, if the patient stopped treatment). Three rounds of a Delphi consensus exercise were conducted by online survey. Questions focused on domains for inclusion in remission criteria, based on the OMERACT core domains for chronic gout studies. Respondents were then asked to choose which option would indicate remission for each domain. Consensus in the Delphi exercise was defined as >80% agreement in responses. The Delphi exercise was followed by a discrete choice experiment using 1000Minds to further explore the extent of variation in relative weighting for components of remission (particularly the time over which no flares should be observed).

Results: There were 49 respondents (56% response rate). There was consensus about which domains should be included in remission criteria from the Delphi exercise; 98% agreement for serum urate, 96% for flares, 92% tophi, 83% pain due to gout and 93% patient global assessment of gout disease activity (PGA). Consensus was reached that serum urate measurements should be measured at least twice over a set timeframe and that all measurements should be <6mg/dL (94% agreement). There also was consensus that, for both pain and PGA measurements, the results of two separate measurements over a set timeframe would be averaged. There was agreement that timeframes of three months or less were not suitable for measurement of remission. However, consensus was not achieved in the Delphi exercise about the timeframe for remission with equal responses for six months (51%) and one year (49%). In the discrete choice experiment, the range of opinions remained widely distributed, indicating an ongoing lack of consensus between the 6 and 12 month timeframe. The difference in relative weighting accorded to 'no flares observed over 12 months' compared to 'no flares observed over 6 months' ranged from 0.04 to 0.26 (out of a total weighting available of 1.0), with the middle 80% of respondents ranging from 0.04 to 0.24.

Conclusion: These consensus exercises have identified domains for remission criteria for gout, and methods for reporting these domains. Additional analysis is required to determine the relative advantages of a 6 or 12 month timeframe, particularly for the observation of no flare.

Disclosure: H. de Lautour, None; **N. Dalbeth**, None; **W. Taylor**, None.

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Is the Rate of Skin Reactions to Febuxostat Increased in Patients with a History of Skin Intolerance to Allopurinol? a Retrospective, Hospital-Based Study Involving 101 Patients Consecutively Treated with Allopurinol and Febuxostat. Thomas Bardin[1], Gérard Chales[2], Tristan Pascart[3], René-Marc Flipo[4], Jean-Claude Roujeau[5], Aurélie Delayen[6] and Pierre Clerson[7]. [1]Hôpital Lariboisière, Paris, France, [2]CHR - Hopital Sud, Rennes, France, [3]Saint-Philibert Hospital, LOMME, France, [4]Rene Salengro hospital, Lille, France, [5]University Paris Est, Créteil, France, [6]Orgamétrie biostatistiques, Roubaix, France, [7]Orgametrie, Roubaix, France.

Background/Purpose: Allopurinol can lead to skin toxicity. Minor skin reactions are reported in 2–4% of patients and life threatening severe cutaneous reactions (SCARs) in 0.1–0.4%. SCARs are more frequent in patients with a history of minor reaction to allopurinol, precluding re-challenge with the drug. Febuxostat is structurally distinct from allopurinol and could be an interesting option in patients who developed skin reaction to allopurinol. However, the frequency of skin reactions to febuxostat has been suggested to be increased in patients with skin intolerance to allopurinol, therefore challenging the value of this option. The aim of our study was to investigate the cutaneous tolerance of febuxostat in gouty patients who had experienced skin intolerance to allopurinol as compared to those who had not.

Methods: We exhaustively identified gouty patients who had sequentially received allopurinol and febuxostat in the Rheumatology departments of 4 French university hospitals and collected data from hospital files using a predefined protocol. Patients who had not visited the prescribing physician at least two months after the initiation of febuxostat were excluded. The odds ratio (OR) for skin reaction to febuxostat in patients who had a cutaneous reaction to allopurinol as compared to those who had not, was calculated. For estimating the 95% confidence interval (CI) we used two methods: Miettinen's method and a bootstrap method. For bootstrapping, 5000 random subsamples having the same size than the study population were drawn with replacement. An OR was calculated for each replicate. The limits of the 95% CI correspond to the antilog of the 2.5^{th} and 97.5^{th} of log(OR) considered as a randomly distributed variable.

Results: The hospital files of 554 gouty patients were examined. 113 had sequentially been treated with allopurinol and febuxostat. Among them 12 did not visit the prescribing physician after the initiation of febuxostat and were excluded from analysis. The analyzed population therefore included 101 patients (86 males, mean age 61±14 years). 22 patients had a history of cutaneous adverse event to allopurinol (16 minor reactions and 6 severe reactions including 2 systemic epidermal necrosis, 1 DRESS, 2 severe drug-induced skin rash and 1 angioedema). 2 (9.1%) of these 22 patients experienced skin reactions to febuxostat (one diffuse rash in a patient with a history of systemic epidermal necrosis and one localised pruritus in a patient who had the same reaction with allopurinol). Among the 79 patients without history of skin reaction to allopurinol, 2 (2.5%) had a minor skin reaction to febuxostat (one localized vesicular eruption and one pruritus). OR was statistically not significant: 3.85 [0.51–29.04] with the Miettinen's method and 3.86 [0.80–18.74] with the bootstrap method. In addition, renal failure did not modify the risk of skin reaction to febuxostat (P=0.97 in univariate analysis and 0.98 in a multivariate model combining renal failure and intolerance to allopurinol).

Conclusion: These results suggest that the risk of skin reaction to febuxostat is moderate and not significantly increased by a history of cutaneous adverse event to allopurinol nor by renal failure.

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Gouty Patients with History of Adverse Reaction to Allopurinol Are Not at Higher Risk of Reaction to Febuxostat. Thomas Bardin[1], René-Marc Flipo[2], Pascal Richette[3] and Pierre Clerson[4]. [1]Hôpital Lariboisière, Paris, France, [2]Rene Salengro hospital, Lille, France, [3]INSERM 1132, Université Paris-Diderot, Hôpital Lariboisière, Paris, France, [4]Orgametrie, Roubaix, France.

Background/Purpose: Allopurinol is the standard drug for urate-lowering management of gout. Allopurinol is safe in most patients. The most frequent side effects are minor cutaneous reactions, which occur in approximately 2–4 % of patients. Severe, life-threatening cutaneous adverse reactions are observed in 0.1%-0.4% of patients. They include toxic epidermal necrolysis, Steven Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS). They are more frequent in patients with a history of minor reaction to allopurinol, precluding re-challenge with the drug. Febuxostat is a non-purine xanthine oxidase inhibitor which is structurally distinct from allopurinol. Febuxostat is an interesting alternative to allopurinol, especially in patients who do not reach the serum urate target, because of renal impairment or intolerance to allopurinol. The potential for cross reactivity between febuxostat and allopurinol is of obvious clinical importance when assessing treatment alternatives to allopurinol. Skin reactions have been reported in 0.5% to 1.6% of patients treated by febuxostat (Ernst 2009) and have been suspected to be more frequent in patients with previous cutaneous intolerance to allopurinol.

Methods: CACTUS was a non-interventional cross-sectional multicentre study conducted in France by GP from November 2010 to May 2011, with the aim to describe characteristics of gouty patients according to the achieved

urate-level. The study involved 2762 adult gouty patients. Among them 1513 had a history of consecutive treatments with allopurinol and febuxostat and were involved in a post-hoc analysis aiming at answering two questions: 1) Was the risk of adverse reaction to febuxostat increased in patients with prior adverse reactions to allopurinol? 2) If yes what was the magnitude of the risk? History of reaction with allopurinol was cross-tabulated with history of reaction with febuxosat, allowing calculation of the odds ratio as a measure of risk. This post-hoc analysis was initially aimed at assessing skin reaction rates. Details on adverse events were not collected. Assuming that any discontinuation of either allopurinol or febuxostat for adverse event was related to a skin reaction obviously led to overestimate the rate of skin reactions with both treatments, but still gave some insight into the existence of drug cross-reactivity.

Results: Among 92 patients who had a history of adverse event to allopurinol, only one (1.1%) experienced a reaction with febuxostat. Among 1421 patients who had no history of allopurinol adverse event, two (0.1%) experienced a reaction with febuxostat resulting in a non-significant odds ratio of 7.8 [0.7–86.8].

Conclusion: In a post-hoc analysis of the CACTUS study, patients with a history of adverse reaction to allopurinol did not carry significantly higher risk of adverse reaction to febuxostat. Most patients intolerant to allopurinol tolerated febuxostat. Absence of cross-reactivity between allopurinol and febuxostat need to be confirmed by other studies.

Disclosure: T. Bardin, AstraZeneca, Ipsen, Menarini, Novartis, Sobi, 8; **R. M. Flipo**, Ipsen, Menarini, 5; **P. Richette**, None; **P. Clerson**, Ipsen, Menarini, 5.

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Prevalence of Gout in the Adult Population of France in 2013. Thomas Bardin[1], Pierre Clerson[2], Stéphane Bouée[3], Gerard H. Chales[4], Michael Doherty[5], René-Marc Flipo[6], Charles Lambert[7], Frédéric Lioté[8], Thierry Poireaud[9], Thierry Schaeverbeke[10] and Pascal Richette[11]. [1]Hôpital Lariboisière, Paris, France, [2]Orgametrie, Roubaix, France, [3]Cemka, Bourg la Reine, France, [4]CHR - Hopital Sud, Rennes, France, [5]University of Nottingham, Nottingham, United Kingdom, [6]Rene Salengro hospital, Lille, France, [7]Ipsen, Boulogne Billancourt, France, [8]Hôpital Lariboisière & University Paris Diderot, Paris, France, [9]Menarini, Rungis, France, [10]Bordeaux University Hospital, Bordeaux, France, [11]INSERM 1132, Université Paris-Diderot, Hôpital Lariboisière, Paris, France.

Background/Purpose: The prevalence of gout has been studied in several Western countries by various methods to approach gout diagnosis, and has been estimated to vary from 0.9 to 3.9 %. The prevalence of gout remained unknown in France. The aims of our study was to design a tool that would allow a confident diagnosis of gout in an epidemiological setting and to assess the current prevalence of gout in France.

Methods: This was a two phase study. In phase one, we designed a questionnaire to detect gout that would be suitable for telephone interviews by non-physicians. A 62-item questionnaire covering clinical features, co-morbidities and treatment of gout was administered by phone, by non physicians unaware of the patient diagnoses in a case control study. 102 people with crystal-proven gout and 142 controls who had other types of arthritis with no urate crystal in their synovial fluid were included. Logistic regression analysis and classification and regression trees (CARTs) were used to select items discriminating cases from controls. In phase two, a random sample of adults resident in metropolitan France (including Corsica) was derived from the national telephone (fixed and mobile) directory, using the next birthday method in cases of multiple users. The telephone questionnaire was administered by non-physicians to subjects who acknowledged present or past non traumatic acute pain in a peripheral joint. The target size for the interview survey was 10,000 participants. Statistical analysis took into account several factors (area, size of the urban centre, sex, age, occupation, known distribution of fixed or mobile users).

Results: In phase one, two logistic regression models (sensitivity 88.0% and 87.5%; specificity 93.0% and 89.8%, respectively) and one CART model (sensitivity 81.4%; specificity 93.7%) revealed 11 informative items that allowed correct classification of 90.0%, 88.8% and 88.5% of patients respectively. In the second phase the response rate varied between 34 % (fixed phone sample) and 38 % (mobile sample). 10,026 participants were interviewed between March and June 2013. 373 declared having suffered from acute, non traumatic joint pain, of whom a diagnosis of gout was made in 84 to 102 subjects, according to the algorithm used. This led to an estimated prevalence of gout of 0.9% (95% CI: 0.8, 1.1) in the general population, with no significant geographic variation. Prevalence was greater in men and increased with age. Interestingly prevalence estimate on self declaration only gave a much higher prevalence estimate (3.7%).

Conclusion: Gout prevalence in the adult population of metropolitan France in 2013 was estimated to be 0.9%. Studies using self declaration might grossly overestimate the prevalence of gout.

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Risk Factors for Gout Attack Recurrence during Urate-Lowering Allopurinol Treatment. Myeong Jae Yoon[1], Ji Ae Yang[2], Sang Hyun Joo[1], Sang Jin Lee[1], Jin Young Moon[1], Hyun Mi Kwon[1], Dong Jin Ko[1], Yeong Wook Song[1] and Eun Bong Lee[1]. [1]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea.

Background/Purpose: Gout is a recurrent inflammatory arthritis caused by crystal deposition of monosodium urate, which can be prevented urate-lowering agents such as allopurinol. However, gout attack can still recur during urate-lowering therapy. In this study we investigated the risk factors associated with recurrence of gout attacks during allopurinol treatment.

Methods: A total of 527 gout patients were enrolled, who took allopurinol at least for 6 months at Rheumatology Clinic of Seoul National University Hospital between March 2001 and March 2013. The patients were divided into those who have ever experienced recurrence of gout attack (recurrence group) and those who haven't (non-recurrence group) during allopurinol treatment. To reveal the risk factors for gout recurrence, we compared baseline deomographic characteristics, concomitant diseases, uric acid level, creatinine level, presence of tophi, type of prophylactic treatment (non-steroidal anti-inflammatory drugs, colchcine, glucocorticoids) and concomitant treatment. Multiple logistic regression analysis was applied to find the best model to explain the recurrence.

Results: The mean (SD) age of the enrolled patients was 58.7 (14.9) years and 96.2% were male. The patients were followed-up for mean (SD) duration of 3.17 (2.64) years. During urate-lowering therapy, 323 patients (61.3%) experienced recurrence of gout attack. In recurrence group, baseline uric acid level was significantly higher than non-recurrence group (8.6 $\pm$ 2.0 vs 8.1 $\pm$ 1.9 mg/dL, p=0.0043 by Student t-test). The presence of tophi was more commonly observed in recurrence group (29.4% vs 18.6%, p=0.006 by chisquare test). The other variables showed no difference between recurrence and non-recurrence groups, which include age, sex, concomitant diseases, the presence of urinary stone, the type of prophylaxis treatment and initial creatinine level. In multivariate logistic regression analysis, high uric acid level (Uric acid $>$ 8.5 mg/dl) and the presence of tophi were found to be risk factors for gout attack during allopurinol treatment (Table 1).

Conclusion: Our study revealed that patients who show uric acid level $>$ 8.5 mg/dL and/or tophi at baseline have higher risk for recurrence of gout attack during allopurinol treatment. Adequate education and closer follow-up will be required for those risky patients when allopurinol is started.

Table 1. Risk factors for recurrence of gout attack during allopurinol treatment, multivariate logistic regression analysis

Clinical variables	Odds ratio	95% confidence interval	P-value
Tophi	1.78	1.16–2.74	0.009
Serum uric acid ^{3}8.5 mg/dL	1.54	1.07–2.21	0.019
Prophylaxis			
NSAID	0.72	0.36–1.44	0.3555
Colchicine	1.03	0.648–1.628	0.911
NSAID+colchicine	2.57	0.897–7.381	0.079
Glucocorticoid	0.82	0.45–1.50	0.522

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Target Serum Urate: Do Patients Know Their Goal? Brian W. Coburn[1], Kayli A. Bendlin[2], Harlan Sayles[1], Kathryn S. Hentzen[2], Michaela M. Hrdy[2] and Ted R. Mikuls[1]. [1]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [2]Omaha VA Medical Center, Omaha, NE.

Background/Purpose: Treat-to-target approaches are used to achieve therapeutic goals in conditions such as diabetes and rheumatoid arthritis. This strategy has also been widely endorsed in gout using urate lowering therapy (ULT). However, suboptimal rates of serum urate (sUA) goal achievement and ULT dose titration in clinical data indicate that providers are not routinely adopting treat-to-target strategies in gout. According to the Chronic Care Model a viable strategy for improving outcomes may be to directly engage gout patients in their care, an approach that requires patient knowledge of sUA goals. The objective of this study was to examine knowledge of sUA goals among gout patients treated with ULT and to identify factors associated with this knowledge.

Methods: Questionnaires were mailed to 1437 gout patients receiving an allopurinol prescription between August 1, 2011 and July 31, 2012. Of these, 886 (62%) surveys were returned. Patients were asked in a multiple choice format "What is the ideal blood uric acid level to aim for when treating gout?" In addition to sociodemographic, health, and gout-related factors, analysis included Patient Activation Measure (PAM™) scores which quantifies an individual's self-perceived combination of skills, knowledge and confidence necessary to become engaged in their own care (range 0 to 100). A continuous measure, PAM™ scores are categorized into 4 levels from low activation (1) to high activation (4). Associations of factors with knowledge were examined using multivariable logistic regression.

Results: Only 13% of patients correctly identified a sUA goal for ULT (< 6.0 mg/dl); 78% reported that they "didn't know" and 9% chose an incorrect answer (Table 1). This was despite a generally high level of knowledge about gout including its cause (87% correct), cause of acute flares (69%), classic symptoms (93%), use of allopurinol as ULT (83%) and indefinite duration of ULT (69%). Older age and PAM™ score were independently associated with knowing the target sUA. An increase of 15 points was associated with a 32% increase in the odds of knowing goal sUA.

Table 1 Association of Patient Characteristics with Knowledge of Target Serum Urate Among Gout Patients Receiving Urate Lowering Therapy

	Bivariate			Multivariable	
	Knew	Did not know	P	Odds Ratio (95% CI)	P
N = 886	109 (13%)	755 (87%)			
Age, mean (SD)	69.6 (10.3)	72.8 (10.2)	<0.01	0.974 (0.954–0.994)	0.011
Male	108 (99%)	744 (99%)	0.54		
Non-Hispanic Caucasian *	95 (89%)	677 (91%)	0.54		
Married *	63 (59%)	425 (57%)	0.64		
High school graduate *	99 (93%)	661 (88%)	0.12		
Body mass index	32.7 (5.1)	32.2 (6.3)	0.31		
Age at first gout attack	47.4 (15.8)	50.3 (15.4)	0.07		
Serum urate at diagnosis	7.3 (2.0)	7.0 (2.1)	0.16		
Patient activation score (0–100 scale)	62.6 (11.5)	59.4 (11.6)	0.01	1.019 (1.001–1.037)	0.044
Confidence (0–10 scale)†, median (SD)	8.8 (2.0)	8.8 (2.4)	0.32		

Values in bivariate analysis are frequency (%) or mean (±SD) except where noted. * The following variables were dichotomized for analysis: non-Hispanic Caucasian vs. other, currently married vs. not married and high school graduate vs. less than high school graduate. † Composite average confidence in 4 aspects of the treatment plan: discussion of medication, discussion of lifestyle and diet, able to summarize the plan and able to do all the tasks in the plan.

Conclusion: In this population, we observed a lack of knowledge among ULT-treated gout patients about target sUA levels. Younger patients and those demonstrating lower activation were more likely to be deficient in knowledge of their sUA goal. Interventions to improve outcomes among gout patients may benefit from improving activation.

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Positive Association Between Tomato Consumption and Serum Urate: Investigating an Anecdotal Trigger of Gout Flares. Tony R. Merriman[1], Nicola Dalbeth[2], Peter B. B. Jones[3], Lisa K. Stamp[4], Murray Cadzow[1], Ruth Topless[1] and Tanya Flynn[1]. [1]University of Otago, Dunedin, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]Waikato Clinical School, Waikato Hospital, Hamilton, New Zealand, [4]University of Otago, Christchurch, Christchurch, New Zealand.

Background/Purpose: Gout is characterised by intermittent flares of inflammation in response to monosodium urate crystals in the joints. Gout flares can be triggered by dietary factors that raise serum urate. Tomato consumption is an anecdotal trigger of gout flares. This study aimed to measure the frequency of tomato consumption as a self-reported trigger of gout flares in a New Zealand gout sample set, and to use publically available data to test the hypothesis that tomato consumption is associated with levels of serum urate.

Methods: 1324 New Zealand people (of Māori, Pacific Island, European or other ancestry) with clinically ascertained gout were asked about dietary triggers of gout. European individuals from the Atherosclerosis Risk In Communities (ARIC, n=7517), Cardiovascular Health Study (CHS, n=2151) and Framingham Heart Study (FHS, n=3052) were used to test for association between serum urate and self-reported tomato intake using two models. Model 1 was adjusted for age, BMI, average calorie intake (kcal/day), principal components analysis vectors 1 and 2 from genome-wide genotype data and model 2 additionally adjusted for meat, seafood/fish, sugar sweetened soft drinks/juices, dairy products, coffee, vitamin C and alcohol consumption.

Results: At least one dietary trigger was reported by 970/1324 (73.3%) of the New Zealand participants with gout. Tomatoes as a dietary trigger was mentioned by 178/970 (18%) participants, making this the 4th most commonly reported dietary trigger in New Zealand men and women. Seafood or fish (634/970; 65%), alcohol (501/970; 52%) and red meat (374/970; 39%) were more frequently reported than tomatoes. In the analysis of the ARIC, CHS and FHS datasets, there was association between tomato intake and serum urate levels (β=0.66 μmolL^{-1} per weekly serving; P=0.006), which was evident in both men and women (Table; Model 1). This association was also maintained after adjustment for consumption of all other urate associated dietary exposures (all: β=0.66 μmolL^{-1}, P=0.008) (Table; Model 2).

Conclusion: Tomatoes are a common self-reported trigger of gout flares. Whilst our descriptive and observational data are unable to support the claim that tomato consumption is a trigger of gout attacks, the positive association between tomato consumption and serum urate levels suggests that the self-reporting of tomatoes as a dietary trigger by people with gout has a biological basis.

Table 1: Association Between Serum Urate Levels (μmolL^{-1}) And Tomato Consumption (serves/week) in the European meta-analysis combined cohort

	Model 1			Model 2		
	β [95% CI]	P	Het P	β [95% CI]	P	Het P
Men	0.84 [0.06; 1.62]	0.035	0.15	0.67 [−0.12; 1.45]	0.099	0.11
Women[1]	0.59 [0.02; 1.16]	0.041	0.51	0.63 [0.05; 1.22]	0.035	0.78
All[2]	0.664 [0.19; 1.13]	0.006	0.54	0.66 [0.17; 1.14]	0.008	0.33

[1]Adjusted for menopause status.
[2]Adjusted for sex and menopause status.

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Is Gout a Coronary Heart Disease Risk Equivalent, Similar to Diabetes? Jasvinder A. Singh[1], Rekha Ramachandaran[2], Jie Zhang[3], Fenglong Xie[2], Shuo Yang[2], Huifeng Yun[4] and Jeffrey R. Curtis[2]. [1]University of Alabama, Tuscaloosa, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Univ. of Alabama at Birmingham, Birmingham, AL, [4]University of Alabama at Birmingham School of Public Health, Birmingham, AL.

Background/Purpose: Diabetes is a well-recognized risk factor for heart disease, increasing the risk of heart disease by 2–3 fold in many studies. Recent ACC/AHA lipid guidelines have a different pathway for diabetes

patients. Gout has been shown to be a risk factor for myocardial infarction and stroke in some cohort studies. It is not known whether gout is as strong a risk factor for acute myocardial infarction as diabetes, a question we attempted to answer with the current study. We compared the incidence of hospitalized acute myocardial infarction (MI) between patients with DM and or RA.

Methods: We used claims data from 2006 to 2010 that included a mix of private and public health plans with medical and pharmacy coverage. Four mutually exclusive cohorts were identified: 1) Gout and DM; 2) Gout only; 3) DM only; and 4) neither gout nor diabetes. Patients with prior CHD during a baseline period of ≥ 1 year were excluded using relevant diagnosis codes. Outcomes were defined as at least one overnight stay, unless the patient died, plus the presence of ≥ 1 inpatient hospital claim with a discharge ICD-9 code 410.x1 in any position for Acute MI or presence of ICD-9 code for stroke (430.XX, 431.xx, 433.x1(433.01, 433.11, 433.21, 433.31, 433.81, 433.91), 434 (434.01, 434.11, 434.91,excluding 434.x0), 436.XX) in any position. We compared the age- and gender-specific incidence of acute MI and stroke rates across the four cohorts. We assessed univariate and multivariable-adjusted hazard rates of acute MI and stroke.

Results: A total of 298,929 patients had diabetes, 91999 had gout, 37573 had both and 1,099,373 had neither. Compared to patients with neither, those with gout or DM or both were older. Incidence of acute MI was lowest in patients with neither, followed by patients with gout, diabetes and both –e.g. in men, respective rates/1000 person-years were 0.0138, 0.0271, 0.0291 and 0.0475. Similar trend were noted for stroke. In unadjusted analyses, both gout and DM increased the risk of acute MI and stroke by a similar magnitude (**Table 1**). In multivariable-adjusted analyses, gout was associated with significantly lower risk of acute MI than diabetes, but no significant differences were noted between gout and DM for the risk of stroke (**Table 1**). Patients with both gout and DM had 1.26 and 1.29-times higher hazard of acute MI and stroke, compared to patients with diabetes only (**Table 1**).

Conclusion: Gout increases the risk of incident MI significantly but does not appear to be a CHD risk equivalent comparable to DM for incident MI. Gout is a CHD risk equivalent comparable to DM for stroke. Having both gout and DM confers incremental risk compared to DM alone for both MI and stroke.

Table 1. Unadjusted and multivariable-adjusted hazards of MI and stroke with gout and diabetes

	Unadjusted, MI	Multivariable-adjusted, MI	Unadjusted, Stroke	Multivariable-adjusted, Stroke
	Hazard ratio (95% CI); p-value	Hazard ratio (95% CI); p-value	Hazard ratio (95% CI); p-value	Hazard ratio (95% CI); p-value
Gout and diabetes	**1.92 (1.82, 2.04) p<0.0001**	**1.26 (1.19, 1.34) p<0.0001**	**1.88 (1.74, 2.02) p<0.0001**	**1.29 (1.20, 1.40) p<0.0001**
Gout, no diabetes	1.02 (0.96, 1.07) p=0.57	**0.82 (0.77, 0.86) p<0.0001**	**1.28 (1.21, 1.36) p<0.0001**	1.00 (0.94, 1.06) p=0.96
No diabetes, no gout	0.37 (0.36, 0.38) **p<0.0001**	0.55 (0.53, 0.57) **p<0.0001**	0.42 (0.41, 0.44) **p<0.0001**	0.58 (0.56, 0.60) **p<0.0001**
Diabetes, no gout	**ref**	**ref**	**ref**	**ref**

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Increased Risk of Skin Reactions with Gout Medications: An Analysis of VA Databases. Jasvinder A Singh[1], Shuo Yang[2] and Jeff Foster[3]. [1]University of Alabama and VA Medical Center, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Dermatologic side effects to use of gout treatments are concerning to patients. The goal of the study was to assess the risk of occurrence of Drug Rash with Eosinophilia and Systemic Symptoms (**DRESS**) with gout medications.

Methods: This retrospective study utilized the Veterans Affairs (VA) administrative and clinical databases from fiscal year 2001 to 2012. Patients with considered to have prevalent gout based on the presence of >=1 International classification of diseases, ninth revision (ICD-9) codes for gout during an inpatient visit or during [3]2 codes during outpatient visits. We defined exposure to allopurinol, febuxostat, colchicine as at least 30-day filled prescription; since pegloticase is given as a set of infusions, exposure was defined 1 or more infusion. Control population included patients not exposed to any of the four medications, i.e., Urate-lowering therapies (ULT) including Xanthine oxidase inhibitors (allopurinol, febuxostat) and pegloticase or anti-inflammatory medication, colchicine. DRESS was defined as the 1st presence of a code 995.27 in either inpatient or outpatient encounter, that occurred on or after filling the index prescription. Each patient contributed to exposed and non-exposed periods. Switching from one ULT to another led to censoring the patient from contributing to that medication and beginning to contribute the person-time to the current/new ULT. ULT and colchicine did not censor each other, since both can be used together. We used Cox proportional hazards models that assessed hazards of DRESS adjusted for the following factors: Model 1: drug exposure, age, gender, body mass index, race, marital status, region; Model 2: variables in model 1, plus baseline Charlson comorbidities.

Results: There was 198839/220184.7 patients/PYs exposed to allopurinol, 3116/2093.7 patients/PYs to febuxostat; 30/10.2 patients/PYs to pegloticase and 150623/144225.4 patients/PYs to colchicine.

In the multivariable-adjusted Cox proportional hazards model that adjusted for demographics (Model 1), compared to controls allopurinol, febuxostat, colchicine and pegloticase were each associated with statistically significantly higher risk of DRESS (**Table 1**). Results were similar when models were additionally adjusted for comorbidity (Model 2).

Conclusion: Allopurinol and colchicine were associated with a 2-fold increase in hazards of DRESS. With much smaller numbers, pegloticase was associated with dramatic increase in the risk. Febuxostat did not reach statistical significance for increased risk of DRESS in full model, although the odds were similar to allopurinol and it was significantly associated with the risk of DRESS in smaller model. More research is needed to define the risk factors for these reactions with gout medications to allow a more judicious and safer use in high-risk populations.

Table 1. Risk of DRESS with gout medications

	Model 1 (demographics) Hazard ratio (95% CI)	p-value	Model 2 (demographics + comorbidity) Hazard ratio (95% CI)	p-value
Allopurinol	1.97 (1.65, 2.36)	<0.0001	1.86 (1.55, 2.24)	<0.0001
Febuxostat	2.54 (1.04, 6.16)	0.04	2.17 (0.90, 5.26)	0.086
Pegloticase	141 (32, 613)	<0.0001	105 (23.2, 474)	<0.0001
Colchicine	2.08 (1.69, 2.55)	<0.0001	1.89 (1.53, 2.33)	<0.0001

Disclosure: J. A. Singh, takeda, savient, 2, takeda, savient, regeneron, allergan, 5; **S. Yang**, None; **J. Foster**, None.

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High-Protein Diet (Atkins Diet) and Uric Acid Response. Na Lu[1], Iris Shai[2], Yuqing Zhang[1], Gary Curhan[3] and Hyon Choi[3]. [1]Boston University School of Medicine, Boston, MA, [2]Harvard School of Public Health, Boston, MA, [3]Harvard Medical School, Boston, MA.

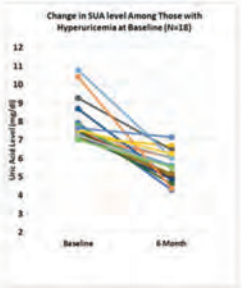
Background/Purpose: The conventional low-purine dietary approach to gout offers limited efficacy, palatability, and sustainability, and promotes increased consumption of refined carbohydrates and saturated fat that can actually worsen gout's cardiovascular (CV)-metabolic comorbidities. In contrast, effective dietary approaches to reduce CV-metabolic conditions (including obesity) could also lower serum uric acid (SUA) levels by lowering adiposity and insulin resistance. Similarly, high-protein, low-carbohydrate diets such as the Atkins diet may lower SUA despite substantial purine loading and ketogenesis. Indeed, a small study (n=13) that employed a high-protein diet with reduced calories found that mean SUA levels decreased from 9.6 to 7.9 mg/dL, with reduced gout attacks over 16 weeks (Ann Rheum Dis 2000). Additional benefits included an improved lipid profile. We investigated the SUA response to the Atkins diet among overweight or obese individuals over a 6 month period.

Methods: Our study population was derived from the Dietary Intervention Randomized Controlled Trial (DIRECT) of overweight or obese participants (BMI ≥ 27). The Atkins diet (i.e., high protein, low-carbohydrate, no calorie restriction) was one of DIRECT's intervention groups and was a focus of the current analysis. We used serum samples at -80°C to compare SUA levels at baseline and 6 months among 74 participants with complete datasets and analyzed the SUA level response as well as lipid profile, weight change, fasting insulin levels, and glucose levels.

Results: The mean age was 51 years and the mean BMI was 31. Most participants (91%) were men. The overall rate of adherence to the diets in DIRECT was > 95% during our 6-month study period. Baseline SUA level was 6.0 mg/dL and the overall SUA change at 6 months was -0.8 mg/dL. This change varied substantially according to baseline characteristics (**Table**), particularly baseline SUA levels. Individuals (N=18) with SUA levels > 7mg/dL (above the saturation point) showed a decrease in mean SUA levels from 7.9 to 5.5 mg/dL (p <.0001). Of the 18, 11 (61%) reached SUA < 6mg/dL (the usual anti-gout SUA therapeutic target) and 6 (33%) reached SUA level < 5mg/dL (the SUA therapeutic target for advanced gout) (**Figure**). Those with obesity and younger individuals (<50 years) tended to have a larger SUA decline. Additional benefits included significant improvements in HDL-cholesterol, total cholesterol/HDL-C ratio, triglyceride levels, and fasting insulin levels (p <.0001).

Conclusion: Our findings suggest that the Atkins diet (i.e., a high protein diet without calorie restriction) can reduce SUA levels despite substantial purine loading. This effect may be more pronounced and clinically meaningful among those with hyperuricemia or obesity. Comparative effectiveness research with other proven CV-metabolic diets would help determine the optimal dietary approach to lower SUA levels.

Overall Analysis	N	Baseline (Mean ± SD)	6-Month Change, Mean (95% CI)	p-value
Uric Acid Level (mg/dl)	74	6.0 ± 1.5	-0.8 (-1.2, -0.4)	<.0001
Weight (kg)	74	91.5 ± 14.6	-7.2 (-8.8, -5.5)	<.0001
Serum triglycerides (mg/dl)	74	172.1 ± 84.2	-46.2 (-63.9, -28.6)	<.0001
Total cholesterol/HDL-C ratio (mg/dl)	74	5.6 ± 1.5	-0.9 (-1.2, -0.7)	<.0001
HDL cholesterol (mg/dl)	74	37.3 ± 8.7	5.1 (3.5, 6.8)	<.0001
Fasting plasma insulin (uU/ml)	74	14.5 ± 11.1	-7.7 (-10.1, -5.2)	<.0001
Subgroup Analysis				
Uric Acid Level (mg/dl)				
<6	35	4.8 ± 0.9	-0.1 (-0.4, 0.2)	0.39
6 - 7	21	6.4 ± 0.2	-0.6 (-1.3, 0.2)	0.12
≥7	18	7.9 ± 1.1	-2.4 (-3.1, -1.7)	<.0001
Obesity				
Yes	34	6.2 ± 1.1	-1.0 (-1.5, -0.5)	0.0004
No	40	5.9 ± 1.8	-0.6 (-1.2, -0.1)	0.016
GFR (mL/min/1.73 m²)				
≥90	51	6.1 ± 1.4	-0.8 (-1.2, -0.4)	0.0002
<90	23	6.0 ± 1.8	-0.8 (-1.6, 0.0)	0.044
Coronary Heart Disease				
Yes	21	5.8 ± 1.3	-0.9 (-1.5, -0.3)	0.0041
No	52	6.1 ± 1.6	-0.8 (-1.3, -0.3)	0.0011
Hypertension				
Yes	18	6.1 ± 1.0	-0.8 (-1.2, -0.5)	0.0003
No	56	6.0 ± 1.7	-0.8 (-1.3, -0.3)	0.0010
Sex				
Female	7	4.2 ± 1.4	-0.3 (-0.7, -0.1)	0.080
Male	67	6.2 ± 1.4	-0.9 (-1.3, -0.5)	<.0001
Age (years)				
>50	40	5.7 ± 1.3	-0.4 (-0.9, 0.0)	0.06
≤50	34	6.4 ± 1.7	-1.2 (-1.8, -0.7)	<.0001



Disclosure: N. Lu, None; **I. Shai**, None; **Y. Zhang**, None; **G. Curhan**, None; **H. Choi**, Takeda, 5, AstraZeneca, 5.

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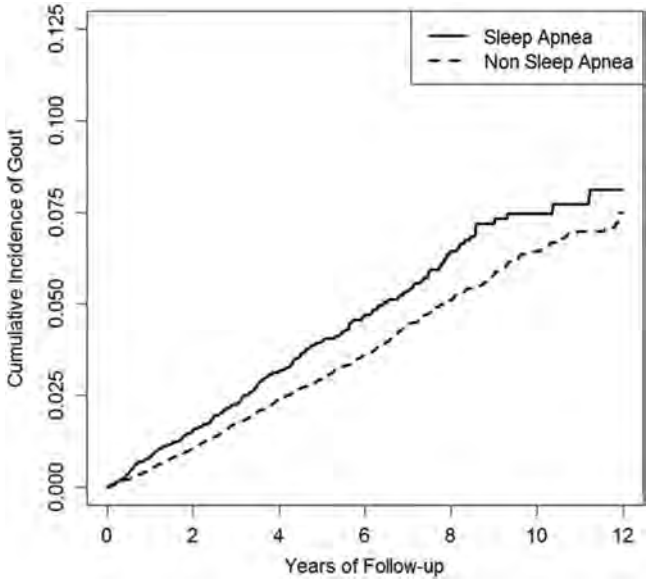
Sleep Apnea and Risk of Incident Gout: A Population-Based Body-Mass Index Matched Cohort Study. Yuqing Zhang[1], Christine Peloquin[1], Maureen Dubreuil[2], Edward Roddy[3], Na Lu[1], Tuhina Neogi[1] and Hyon Choi[4]. [1]Boston University School of Medicine, Boston, MA, [2]Boston University Medical Center, Boston, MA, [3]Keele University, Keele, United Kingdom, [4]Harvard Medical School, Boston, MA.

Background/Purpose: Sleep apnea is common among obese individuals with comorbidities (up to ~30%), a typical profile of gout patients. Since hypoxia associated with sleep apnea can enhance nucleotide turnover (thereby generating purines, which are metabolized to uric acid), sleep apnea could predispose individuals to gout. Furthermore, previous studies have reported that patients with sleep apnea have a higher prevalence of hyperuricemia. All of these findings suggest that patients with sleep apnea may experience an increased risk of incident gout. We evaluated the risk of developing gout in individuals with incident sleep apnea in a general population context.

Methods: We conducted a matched cohort study in a UK general practice database (The Health Improvement Network, THIN) to test proposed hypothesis. We identified individuals aged 20–89 years with the first diagnosis of sleep apnea from Year 2000 to 2013. For each sleep apnea patient, up to four comparators were selected and matched on sex, age, year of birth, body mass index (BMI) (± 0.5kg/m^2), and year of index date (i.e., year of sleep apnea diagnosis). We excluded subjects with sleep apnea or gout prior to study entry as well as subjects without at least one GP visit within the two years prior to study entry. We identified all cases of incident gout based on diagnosis Read code. We estimated the incidence rates of gout and used a Cox-proportional hazard model to assess the association of sleep apnea and the risk of incident gout, after further adjusting for the number of physician visits, alcohol use, BMI, age, use of aspirin, diuretics and losartan, and chronic renal disease, diabetes, hypertension and ischemic heart disease.

Results: Included in this analysis were 9865 newly diagnosed sleep apnea patients (women: 28%, mean age: 53 years, mean BMI: 33.4 kg/m^2) and 43,598 comparators (women: 28%, mean age: 54 years, mean BMI: 32.2 kg/m^2). Over the follow-up period, 1353 incident gout patients were diagnosed. The incidence rate of gout was higher in sleep apnea patients (7.9/1000 person-years) than in the comparators (6.1/1000 person-years) (Figure). After adjusting for all potential confounders, patients with sleep apnea had a 20% higher risk of developing gout than the comparators (hazard ratio =1.2, 95% CI: 1.0–1.4). The corresponding hazard ratios over 6-months, 1-year, and 2-years were 1.7 (95% CI: 1.1–2.8), 1.6 (95% CI: 1.2–2.1), and 1.4 (95% CI: 1.1–1.7), respectively.

Conclusion: This large general population-based study indicates that sleep apnea is associated with a high risk of incident gout. As sleep apnea is common in patients with a typical profile of gout patients and its associated hypoxia is treatable (e.g., with non-invasive ventilation Continuous Positive Airways Pressure), further clarification of the role of sleep apnea on gout attacks among gout patients could add considerably to effective management of gout.



Disclosure: Y. Zhang, None; **C. Peloquin**, None; **M. Dubreuil**, None; **E. Roddy**, None; **N. Lu**, None; **T. Neogi**, None; **H. Choi**, Takeda, 5, AstraZeneca, 5.

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Self-Management Education for Patients with Gout: A Review of Existing Resources. Megan Johnston[1], Gareth Treharne[2], Peter T. Chapman[3] and Lisa K. Stamp[1]. [1]University of Otago, Christchurch, Christchurch, New Zealand, [2]University of Otago, Dunedin, New Zealand, [3]Christchurch Hospital, Christchurch, New Zealand.

Background/Purpose: Inadequate patient self-management education resources may contribute to poor management and outcomes for gout. Patient education resources need to be easy to read and should provide clear and consistent messages regarding lifestyle, diet, and treatment recommendations for gout patients to implement. The aim of this project was to review existing educational resources for gout patients in order to identify strengths and weaknesses and to compare resources cross-nationally.

Methods: Twenty-four patient education resources for gout were identified: 12 print items and 12 websites. The print items are those given to patients by health professionals in New Zealand or are provided by relevant health

organizations in New Zealand, Australia, the United States, Canada, and the United Kingdom. The top ten websites based on a Google search using the keyword "gout" were included, as well as two interactive websites aimed at gout patient self-management. Resources were assessed for coverage of essential information, ease of reading, and dietary recommendations.

Results: All identified resources provided some information about the nature of gout (e.g. caused by too much uric acid in the body) and lifestyle issues (e.g. body weight, nutrition). However, inconsistent messages were given regarding the relative influence of diet on gout, with some resources suggesting little impact of diet and others implicating diet as a major factor in gout management. There was also discordance in certain dietary recommendations, particularly regarding non-meat proteins such as legumes. 50.0% of the resources identified a target serum urate level but only 29.1% recommended checking serum urate levels. Co-morbidities associated with gout not universally discussed included: kidney problems (87.5%), heart disease (58.3%), and diabetes (41.7%). Resources were largely consistent cross-nationally although some differences were found (see Table 1). New Zealand resources were more likely to mention target serum urate levels and to advise patients to continue taking urate-lowering therapies during acute attacks than American or British resources. Certain dietary recommendations also differed within resources from different countries. 50.0% of the resources were written at a highly complex reading level.

Conclusion: A considerable amount of room for improvement exists in current self-management educational resources for gout patients. Inconsistent messages, lack of information on key topics, and inaccessible writing styles were the primary issues identified. Examining resources developed internationally may provide additional information useful for developing educational resources for gout patients. Further research with gout patients is required to determine the resources that patients perceive as most informative and actionable.

Table 1. Content of Gout Patient Education Resources by Country

Content Category	New Zealand (n = 10)	United States (n = 7)	United Kingdom (n= 4)
	Mean Scores		
Readability†	62.6	65.7	61.4
Reading grade level‡	8.4	8.29	9.0
	Percent of Resources Covering Each Category		
Uric acid	100%	100%	100%
Crystal formation	90%	100%	100%
Long term treatment	100%	86%	50%
Acute treatment	100%	100%	50%
Uric acid <. 36 mmol/L	70%	43%	25%
Check uric acid	40%	29%	25%
Non-drug treatments	70%	86%	50%
Not to stop medication	50%	14%	0%
Heart disease	70%	57%	25%
Diabetes	40%	43%	25%
Kidney problems	90%	100%	50%
Weight	100%	100%	100%
General diet	100%	100%	100%
Foods to avoid	100%	100%	100%
Alcohol	100%	100%	100%
Add low-fat dairy	70%	57%	50%

NOTE: Three resources are not included in the table: 1 from Australia, 1 from Canada, and 1 international resource

†Higher Flesch-Kincaid readability scores indicate greater ease of reading (i.e. scores above 90 indicate easy to read, scores <30 indicate difficult to read)

‡Grade level indicates reading grade level based on the United States school system (the majority of American adults read at an eighth to ninth grade level)

Disclosure: M. Johnston, None; **G. Treharne**, None; **P. T. Chapman**, None; **L. K. Stamp**, Astra Zenec, 5, Abbvie, 9, PHARMAC, 6.

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Long Term Safety and Efficacy of Canakinumab Liquid Formulation in Acute Gouty Arthritis Patients: Results from a 36 Week Extension Study. P Sunkureddi[1], E Tóth[2], J. P Brown[3], R Moericke[4], D. Richard[5], K Lheritier[5], A Stancati[5] and A Kivitz[6]. [1]Clear Lake Rheumatology, Nassau Bay, TX, [2]Flór Francis Hospital Rheumatology Department, Kistarcsa, Hungary, [3]CHU de Québec Research Centre and Laval University, Québec, QC, [4]Institut für Präventive Medizin & Klinische Forschung GbR, Magdeburg, Germany, [5]Novartis Pharma AG, Basel, Switzerland, [6]Altoona Center for Clinical Research, Duncansville, PA.

Background/Purpose: Gouty arthritis (GA) patients who experience frequent flares and have comorbidities have limited treatment options. Canakinumab (CAN), a selective, human, anti-interleukin1β monoclonal antibody, has been approved in the European Union for the treatment of difficult-to-treat GA patients. A liquid formulation, presented as pre-filled syringe (CAN-PFS) has been developed to improve upon the lyophilized form (CAN-LYO) that requires reconstitution. Cumulative safety and efficacy results covering a total of 48 weeks are presented.

Methods: GA patients completing the 12 week core study[1] were enrolled in a 36 week open label extension (E1) study. All patients entering E1 received CAN-PFS 150 mg sc on demand upon new GA flare irrespective of assigned treatment during randomization [CAN-PFS, CAN-LYO or triamcinolone acetonide 40 mg (TA)]. The primary objective was to confirm long term safety of CAN-PFS vs TA. Secondary objectives included evaluation of CAN-PFS vs TA and CAN-LYO vs PFS for the time to first new flare over 48 weeks. Long-term safety outcomes and safety upon re-treatment were assessed as exposure-adjusted incidence rate of adverse events (AEs) and serious AEs (SAEs).

Results: Of 397 patients randomized in the core study, 232 (58.4%) entered E1, of which 198 (50%) completed E1. Baseline characteristics were comparable between the treatment groups. The exposure-adjusted incidence of AEs was lower for both CAN-PFS (254.9/100 pyr) and CAN-LYO (224.8/100 pyr) groups when compared with TA (362.7/100 pyr) over the 48 weeks. The exposure-adjusted incidence of AEs in patients randomized to TA was lower after switching to CAN-PFS compared with the incidence prior to switching treatment (218.9/100 vs 319.7/100 pyr, respectively). In patients randomized to TA, the exposure-adjusted incidence rates of infections were similar before and after switching from TA to CAN-PFS (36.5/100 vs 37.2/100 pyr, respectively). The exposure-adjusted incidence of SAEs was 14.7/100, 16.1/100, 15.5/100 pyr in patients randomized to CAN-PFS, CAN-LYO and TA groups, respectively. SAEs increased from 0/100 pyr to 4.1/100 pyr in patients who switched from TA to CAN-PFS. Infections and infestations were the most frequently reported SAE in the CAN-PFS (3.4/100 pyr), CAN-LYO (3.2/100 pyr), TA (0/100 pyr) groups. Over the cumulative duration of 48 weeks, one death (cardiac failure), not suspected to be related to study drug, was reported in a patient randomized to CAN-PFS who was not re-treated over 48 weeks. CAN-PFS treatment significantly delayed time to first new flare vs TA patients with a relative risk reduction of 55% (HR, 0.45; 95% CI, 0.32 to 0.64; $p<0.0001$) over 48 weeks.

Conclusion: These results support the long term safety and efficacy of canakinumab liquid formulation in patients with frequent GA flares compared with a potent long acting corticosteroid, TA. The safety profile of on-demand retreatment was consistent with the one observed in the core study and no new safety signals were observed. Canakinumab significantly reduced the risk of new flares compared to TA.

References:

Sunkureddi et al. Arthirits & Rheumatism. 2013;65(10):S498.

Disclosure: P. Sunkureddi, Abbvie, Takeda, UCB, BMS, Pfizer, 8, Pfizer, Takeda, UCB, Novartis, Eli Lilly, 9; **E. Tóth**, None; **J. P. Brown**, Amgen, Eli Lilly, Merck, Novartis, Pfizer, Roche, 2, Amgen, Eli Lilly, Merck, 5, Amgen, Eli Lilly, Merck, 8; **R. Moericke**, None; **D. Richard**, Novartis Pharma AG, 1, Novartis Pharma AG, 9; **K. Lheritier**, Novartis, 1, Novartis, 3; **A. Stancati**, Novartis, 1, Novartis, 3; **A. Kivitz**, None.

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Efficacy and Safety of Canakinumab in Acute Gouty Arthritis Patients with Chronic Kidney Disease Stage Greater Than or Equal to 3: A Post-Hoc Analysis of 12-Week Data. P Sunkureddi[1], E Tóth[2], J. P Brown[3], A Kivitz[4], A Stancati[5], D. Richard[5], K. Lheritier[5] and R Moericke[6]. [1]Clear Lake Rheumatology, Nassau Bay, TX, [2]Flór Francis Hospital Rheumatology Department, Kistarcsa, Hungary, [3]CHU de Québec Research Centre and Laval University, Québec, QC, [4]Altoona Center for Clinical Research, Duncansville, PA, [5]Novartis Pharma AG, Basel, Switzerland, [6]Institut für Präventive Medizin & Klinische Forschung GbR, Magdeburg, Germany.

Background/Purpose: Chronic kidney disease (CKD) limits the treatment options in acute gouty arthritis (GA) patients due to intolerance and contraindications to available therapies. Efficacy and safety of canakinumab (CAN), a selective, human, anti-IL-1β monoclonal antibody, formulated as a

lyophilized (LYO) powder requiring reconstitution with water vs triamcinolone acetonide (TA) in patients with acute GA was demonstrated in previous phase III trials. Here, we report the efficacy and safety of CAN liquid formulation (CAN-PFS) vs TA in a subgroup of patients with CKD stage ≥3.

Methods: This was a 12-week, multicenter, double-blind, active controlled study. Pts (≥18-≤85 yrs) meeting the ACR 1977 preliminary criteria for acute GA and contraindicated, intolerant or refractory to NSAIDs and/or colchicine, with ≥3 flares in the previous year, were randomized 1:1:1 to receive a single dose of CAN- PFS 150 mg sc or CAN- LYO 150 mg sc or TA 40 mg im and re-dosed "on demand" upon each new flare. Here, we report results from a *post-hoc* analysis of the 12-week data for GA patients with CKD stage ≥3 (estimated Glomerular Filtration Rate (eGFR) <60ml/min). The primary endpoint was pain intensity in the target joint, measured on 0–100 mm VAS scale at 72 h. Secondary endpoints included time to first new flare, and safety over 12 weeks.

Results: Of 388 patients, 76 had CKD stage ≥3 at baseline (CAN-PFS, n=24; CAN-LYO, n=28; TA, n=24). CAN-PFS provided a statistically significant reduction in pain intensity in the target joint vs TA from 72h post dose (estimated difference, -14.6mm; 95% CI:−29.0,-0.1, p≤0.05) until 7 days post dose (−16.1mm; 95% CI: -28.4, -3.7, p=0.0115). The two CAN treatment arms were comparable. Over 12 weeks, a single dose of CAN-PFS showed a significant relative risk reduction of 90% for time to first new gout flare vs TA [HR 0.10, 95% CI (0.01, 0.78); p≤0.05]. Adverse events (AEs) were reported in 12 (50%), 11 (39.3%) and 10 (41.7%) patients in CAN-PFS, CAN-LYO and TA groups, respectively. The most frequent AEs were infections (CAN-PFS, n=3 (12.5%); CAN-LYO, n=6 (21.4%); TA, n=2 (8.3%). Serious AEs were reported in a total of 7 patients (CAN-PFS, n=2 (8.3%); CAN-LYO, n=4 (14.3%); TA, n=1 (4.2%), with infections (CAN-PFS, n=1 (4.2%); CAN-LYO, n=2 (7.1%); TA, n=0), being the most common SAEs. No deaths were reported during the study.

Conclusion: This post-hoc analysis provides evidence for the efficacy of CAN-PFS compared with a potent long-acting corticosteroid in providing significant pain relief and reducing incidence of new flares in gouty arthritis patients with CKD stage ≥3 with limited treatment options. The safety profile in this sub-population was consistent with that of the overall study population and with that known from previous studies.

Reference:
Sunkureddi et al. Arthirits & Rheum 2013; 65.

Disclosure: P. Sunkureddi, Pfizer Inc, BMS, Abbvie, Takeda, UCB, 8, Pfizer Inc, Novartis, Eli Lilly, Takeda, UCB, 9; **E. Tóth**, None; **J. P. Brown**, Amgen, Eli Lilly, Merck, Novartis, Pfizer, Roche, 2, Amgen, Eli Lilly, Merck, 5, Amgen, Eli Lilly, Merck, 8; **A. Kivitz**, None; **A. Stancati**, Novartis, 1, Novartis, 3; **D. Richard**, Novartis Pharma AG, 1, Novartis Pharma AG, 9; **K. Lheritier**, Novartis, 1, Novartis, 3; **R. Moericke**, None.

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Comparative Cardiovascular (CV) Risk and Outcomes Among Patients with Gout, Osteoarthritis (OA), or Both. Svetlana Krasnokutsky[1], Robert T. Keenan[2], Laura Schneck[1], Craig Tenner[3], Helene Strauss[3], Daria Crittenden[4], Aaron Lehmann[1] and Michael H. Pillinger[1]. [1]NYU School of Medicine, Division of Rheumatology, New York, NY, [2]Duke University, Durham, NC, [3]NYU School of Medicine, New York, NY, [4]Amgen, Thousand Oaks, CA.

Background/Purpose: Gout is associated with increased CV risk, both dependent on, and independent of traditional CV risk factors. Recent studies suggest that OA, traditionally considered non-inflammatory, may also carry increased CV risk. To date, few studies have directly compared the relative CV risk of individual rheumatologic diseases. We used the VA NY Harbor Health Care System electronic medical record to compare the rates of CV risk factors and prevalence of CV outcomes among patients with gout versus OA, the two most common forms of arthritis in the US. We also determined CV outcome prevalence in patients with both gout and OA concurrently.

Methods: We identified male patients with an active medical record between January 2007 and June 2008 and an ICD-9 code for gout. We further separated the cohort into gout patients who did (gout+OA), or did not (gout-only) have a concurrent ICD-9 code for OA. Additionally, we identified patients with diagnostic codes for OA but no gout (OA-only). For each group we collected demographics, diagnoses of CV risk factors, and diagnoses of CV events. The primary outcome was a composite index (CV4) consisting of any diagnosis of MI, angina, CABG surgery, and/or CAD. Secondary outcomes included the individual diagnoses within the CV4, as well as CHF and death (all causes). One-way ANOVA with Tukey post-hoc comparisons were used to test for differences between groups.

Results: 1280 subjects had an ICD-9 diagnosis of gout. Of these, 297 had gout+OA, and 983 had gout-only. We further identified 1231 OA-only subjects. Gout+OA, gout-only, and OA-only subjects were similar in age and ethnicity. Gout subjects, with or without OA, had higher baseline rates of CV risk factors including HTN, HLD, and chronic kidney disease (p<0.0001 for each comparison) than OA-only subjects. Gout-only subjects had higher rates of DM vs OA-only subjects (p=0.011). Gout subjects, with or without OA, had higher prevalence rates of CV4 events versus OA-only subjects; individual component outcomes were also more prevalent among the gout subjects with or without OA (Table 1). Gout subjects, with or without OA, had higher rates of CHF and death compared with OA-only patients. Gout+OA subjects demonstrated non-significant trends towards increased CV4, CAD, CHF and death vs. gout-only subjects. Patients with gout+OA, but not gout-only, had increased rates of death compared to OA alone.

Conclusion: Adverse CV outcomes occur more commonly among gout patients compared with patients with OA only, at least partly due to greater prevalence of traditional risk factors. We also observed non-significant trends towards increased risk of some CV outcomes (CV4, CAD, CHF, death) in patients with both gout+OA compared to patients with gout-only, and only gout+OA patients had increased mortality compared to OA alone. Larger sample sizes may clarify whether there is an additive effect of gout and OA on CV outcomes.

Table 1 1" endpoint: composite of CV outcomes (CV4)
2" endpoints: CABG, MI, Angina, CAD CHF, Death

	Group 1 OA-only (n = 1231)	Group 2 Gout-only (n = 983)	Group 3 Gout + OA (n = 297)	Significance, ANOVA
Composite Endpoint	23.7	28.2	30.3	p = 0.047 for groups 1 vs 2; p = 0.054 for groups 1 vs 3
CABG, %	1.6	4.3	3.0	p<0.0001 for groups 1 vs 2
MI, %	1.9	2.2	2.0	NS
Angina, %	0.6	3.5	3.0	p<0.0001 for groups 1 vs 2; p = 0.024 for 1 vs 3
CAD, %	22.7	25.0	29.6	p = 0.003 for groups 1 vs 2; p = 0.041 for 1 vs 3
CHF, %	4.6	10.8	12.1	p<0.0001 for groups 1 vs 2 and 1 vs 3
Death, %	2.4	4.0	6.4	NS for groups 1 vs 2; p = 0.003 for 1 vs 3

Disclosure: S. Krasnokutsky, None; **R. T. Keenan**, AstraZeneca, 5, Takeda, 5, Crealta, 5; **L. Schneck**, None; **C. Tenner**, None; **H. Strauss**, None; **D. Crittenden**, Amgen, 3; **A. Lehmann**, None; **M. H. Pillinger**, Takeda, Savient, Crealta, 2, Crealta, 5.

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Increase in Thyroid Stimulating Hormone (TSH) Levels in Patients with Gout Treated with Inhibitors of Xanthine-Oxido-Reductase. Fernando Perez-Ruiz[1], Ana M. Herrero-Beites[1], M. Angeles Aniel-Quiroga[2] and Sandra P Chinchilla[2]. [1]BioCruces Health Research Institute, Baracaldo, Spain, [2]Hospital Universitario Cruces, Baracaldo, Spain.

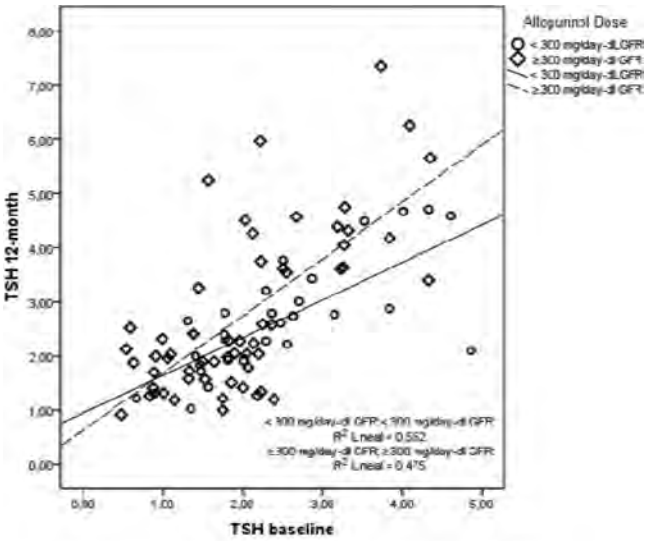
Background/Purpose: Increase in thyroid stimulating hormone (TSH) levels over upper normal limit has been reported in a small percentage of patients treated with febuxostat, but a mechanistic explanation is not yet available.

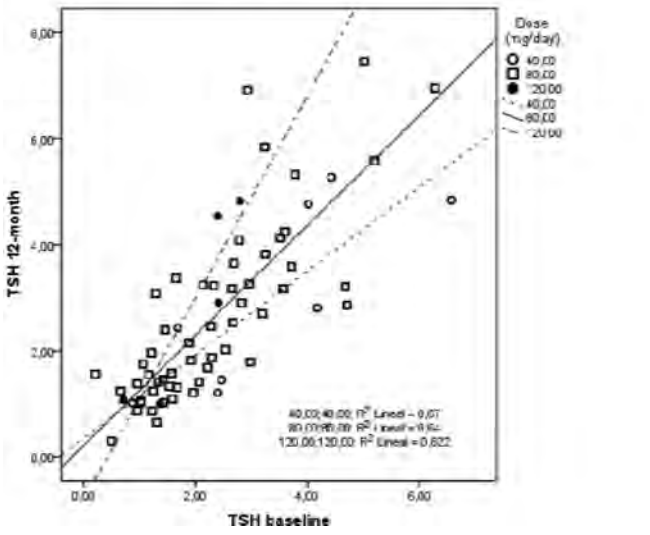
Methods: In a case-control design study, we tested TSH levels in patients with gout at baseline with that every 6-month during follow-up during treatment with febuxostat. Patients to be started allopurinol and an available measurement of TSH 6 months prior to baseline evaluation were used as controls, a follow-up TSH level being measured at 12-month follow-up. Patients with abnormal TSH levels or previous thyroid disease were not included.

Results: Eighty-eight patients treated with febuxostat and 87 with allopurinol were available for comparison. Patients with febuxostat had more severe hyperuricemia and gout, renal impairment, and previous treatment, but were similar in other characteristics. A similar increase in TSH levels was observed in both groups (0.4 and 0.5 μUI/mL for febuxostat and allopurinol, respectively). At 12-mo, 7/88 (7.9%) of patients on febuxostat and 4/87 (3.4%) of patients on allopurinol showed TSH levels over 5.5 μUI/mL, but the upper quartiles for baseline TSH distribution were higher in patients on febuxostat (Table). Doses prescribed (corrected for estimated glomerular filtration rate in patients on allopurinol) and baseline TSH levels were determinants of TSH levels at 12-month follow-up (Figures). No impact on clinical status or free T4 levels was observed in patients with TSH levels over the normal limit.

Table. TSH levels at baseline evaluation and 12-month follow-up. Doses for allopurinol are shown as prescribed and corrected per dL of estimated glomerular filtration rate

Allopurinol Dose	Baseline TSH (μUI/ml)	12-mo TSH (μUI/ml)	p
≤ 300 mg/d (N=81)	2.1±1.0	2.7±1.3	0.000
>300 mg/d (N=6)	2.3±1.3	2.4±1.7	0.760
≤ 300 mg/d-dL EGFR (N=29)	2.5±1.0	2.8±1.0	0.079
> 300 mg/d-dL EGFR (N=58)	2.0±0.9	2.7±1.5	0.000
Febuxostat Dose			
40 mg/d (N= 10)	3.3±1.8	3.0±1.7	0.381
80 mg/d (N= 73)	2.3±1.3	2.6±1.7	0.033
120 mg/d (N=5)	2.0±0.9	2.9±1.8	0.032





Conclusion: both allopurinol and febuxostat increase TSH levels in a dose-dependent, with no apparent impact on free T4 levels, suggesting a class (xanthine-oxidase inhibition) effect with no apparent impact on free T4 levels.

Disclosure: F. Perez-Ruiz, ASOCIACION DE REUMATOLOGOS DE CRUCES, 2, Astra-Zeneca, 5, Menarini, 5, Pfizer Inc, 5, Novartis Pharmaceutical Corporation, 5, SOBI, 5, AstraZeneca, 8, Menarini, 8; **A. M. Herrero-Beites**, ASOCIACION DE REUMATOLOGOS DE CRUCES, 2; **M. A. Aniel-Quiroga**, None; **S. P. Chinchilla**, None.

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The Effect of Initiating Pharmacologic Insulin on Serum Uric Acid Levels in Patients with Diabetes. Lindsey MacFarlane[1], Chih-Chin Liu[2] and Daniel H. Solomon[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA.

Background/Purpose: Substantial evidence links gout and hyperuricemia to diabetes. Previous studies report an association between increasing uric acid (UA) levels, insulin resistance, and type 2 diabetes (T2DM). Elevation in serum insulin is purported to increased serum UA levels through increased renal urate absorption. This study sought to evaluate the effect of initiating insulin for T2DM on serum UA levels.

Methods: We conducted a retrospective analysis on patients with both T2DM and gout. Patients were selected from a linked dataset from an electronic medical record (EMR) and Medicare claims data. This data set includes patients at one academic medical center with diagnoses of gout and hyperuricemia as confirmed in the EMR who also had T2DM (defined as hemoglobin A1c (HbA1c) > 6.5%, ICD-9-CM code 250.x or use of diabetic medications). An insulin-initiating cohort and a non insulin-initiating cohort were compared for changes in UA. Cohorts were matched on sex, age at first UA measurement, and length of time between UA measurements. The first UA measurement occurred before insulin initiation and the second at least 3 months later; matched time points were used in the non-initiators.

Potential cofounders including HbA1c, creatinine, body mass index, length of time between UA measurements and medications (allopurinol, hydrochlorothiazide, losartan, tacrolimus, cyclosporine) were adjusted for in a series of linear regression models.

Results: 23 patients met criteria for insulin initiation and 23 were matched non-insulin initiators. Mean age was 59 and 57 years for the insulin and non-insulin cohorts, respectively, both cohorts were 52% female. Patients initiating insulin had a larger increase in mean UA levels, 6.41mg/dl to 7.66mg/dl (mean change 1.25 mg/dl, interquartile range, IQR: -0.7,2.3) compared to non-insulin initiators, mean increase from 6.17mg/dl to 6.23mg/dl (mean change 0.06 mg/dl, IQR: -1.1,0.9 p = 0.06). Of the covariates, only length of time between UA measurements had an unadjusted p-value < 0.05 and was advanced to the final adjusted model. The final linear regression showed that insulin use was associated with a 1.25mg/dl greater increase in UA levels when compared to non-insulin initiators (p value = 0.02). Adjusting for allopurinol did not attenuate results. (Table)

Conclusion: Insulin initiation in patients with T2DM was associated with a statistically significant increase in serum UA levels. This may have clinical implications, including risk of gout flares. Gout attack prophylaxis might be useful in the setting of insulin initiation among patients with gout. A prospectively designed study would help overcome potential limitations of our retrospective design.

Table 1 Regression analysis of covariate effects on change in uric acid in insulin initiators

	Model	β	95% CI	P
A	Crude Model: Insulin + UA1	1.29	0.15, 2.44	**0.03**
B	Model A + age + months between UA1 & UA2	1.25	0.16, 2.34	**0.03**
C	Model B + hemoglobin A1c	1.47	−0.06, 3.00	0.06
D	Model C + creatinine + body mass index	1.33	−0.28, 2.94	0.10
E	Insulin+UA1+months between UA1 & UA2	1.25	0.18, 2.33	**0.02**
	Addition of relevant medications	**β**	**95% CI**	**P**
F	Model D + Allopurinol	1.36	−0.12, 2.84	0.07
G	Model D + Hydrochlorothiazide	1.41	−0.17, 2.99	0.08
H	Model D + Losartan	1.45	−0.07, 2.96	0.06
I	Model D + Tacrolimus	1.48	−0.04, 3.00	0.06
J	Model D + Cyclosporine	1.61	0.03, 3.20	0.05

β= beta co-efficient from linear regression model, represents the change in uric acid among insulin initiators compared to matched non-initiators; 95% CI=95% confidence interval; UA1=1st uric acid measurement; UA2= 2nd uric acid measurement

Disclosure: L. MacFarlane, None; **C. C. Liu**, None; **D. H. Solomon**, Pfizer Inc, 2, Amgen, 2, Lilly, 2, Corrona, 2, UpToDate, 7.

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Effect of Allopurinol on All-Cause Mortality in Adults with Incident Gout: Propensity Score Matched Landmark Analysis. Chang-Fu Kuo[1], Matthew J. Grainge[2], Christian Mallen[3], Weiya Zhang[2] and Michael Doherty[2]. [1]Chang Gung Memorial Hospital, Taipei, Taiwan, [2]University of Nottingham, Nottingham, United Kingdom, [3]Keele University, Keele, United Kingdom.

Background/Purpose: Although current guidelines recommend allopurinol as a first-line urate-lowering treatment for gout patients, whether the balance of potential benefits and risks can translate to any influence on survival in gout patients remains unclear. The objective of this study was to examine the association between allopurinol use and all-cause mortality for patients with incident gout.

Methods: This study was conducted using the UK Clinical Practice Research Data-link. Patients were included if they were aged 20 years or older, were given first ever gout diagnosis between 1995 and 1999, and had no evidence of gout or prescription for ULT prior to the time of diagnosis. We used propensity score matched landmark analysis to compared incident gout patients who received allopurinol for at least 6 months within exposure window and those did not for all-cause mortality.

Results: Of 23,332 incident gout patient identified, the propensity-matched cohorts contained 1,016 patients exposed to allopurinol on the date one year from diagnosis (landmark date) and 1,016 allopurinol non-users. They were significantly older and had more comorbidity and multiple medications than the overall incident gout patients. Over a median follow-up period of 10 years after the landmark date, there were 437 allopurinol users and 443 allopurinol non-users who died during follow-up. Allopurinol users and non-users had similar risk for all-cause mortality (hazard ratios 0.99; 95% confidence interval. 0.87–1.12). In the three-year landmark analysis, 3,519 allopurinol users (1,280 died) were compared with 3,519 non-users (1,265 died). The hazard ratio for all-cause mortality was 1.01 (95% confidence interval 0.92–1.09).

Conclusion: This propensity score matched landmark analysis in a population of incident gout patients in the UK primary care setting found a neutral effect on the risk of all-cause mortality. Our study provides reassurance for prescription of allopurinol in gout patients early in their disease course to prevent untoward consequences of chronic uncontrolled hyperuricaemia.

Disclosure: C. F. Kuo, None; **M. J. Grainge**, None; **C. Mallen**, None; **W. Zhang**, None; **M. Doherty**, Manarini, 5.

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Analytical Comparison Between Point of Care Uric Acid Testing Meters. Jonathan Paraskos[1], Zsofia Berke[2], Jason Cook[1], Jeffrey N. Miner[3], Martin Braddock[1], Adam Platt[1] and Glen Hughes[1]. [1]AstraZeneca R&D Alderley Park, Macclesfield, United Kingdom, [2]AstraZeneca, Mölndal, Sweden, [3]Ardea Biosciences, Inc., San Diego, CA.

Background/Purpose: Gout is a chronic, painful, debilitating form of arthritis resulting from elevated levels of serum uric acid (SUA), termed hyperuricemia. Hyperuricemia is caused by either overproduction or, more commonly, inadequate excretion of uric acid. Resultant monosodium urate crystal deposition in joints/soft tissue can cause attacks of severe pain, swelling, and inflammation (i.e., flares), as well as the development of tophi. A key goal in gout treatment is achievement of sustained lowering of SUA. A point-of-care (POC) test meter that gives accurate and reliable SUA measurements may have the ability to improve patient care through more frequent testing and improving individualized gout management. Such a device can provide a convenient and rapid measure of a patient's SUA levels to monitor and immediately adjust therapy to achieve SUA targets recommended in international guidelines. In addition, a device for home use could enhance patient disease understanding and may promote treatment compliance.

Methods: Five commercially available uric acid meters were acquired (UASure, Benecheck-Plus, Kernel MultiCheck, EasyTouch-GU, and HumaSens-Plus). All devices were CE marked and approved for European market use only. Analytical performance in all experiments was determined using a single batch of manufacturer test strips. Precision characteristics of each meter were identified by using each device to measure the same finger prick blood samples using 6 replicates taken from 3 healthy volunteers repeated over 3 consecutive days. Meters identified with a precision coefficient of variation (CV) <17% then had accuracy determined by comparing SUA measurements with a laboratory uricase reference method, as well as the linearity of measurement determined by blood spiking with known UA concentrations. Ease of use observations were also made on each instrument.

Results: Performance of the UASure device was found to be suboptimal from precision and ease-of-use perspectives, due to difficulty experienced in obtaining SUA readings. Ease of operation of a POC meter is essential to ensure successful adoption by patients, and so, this meter was not evaluated further. The Kernel and EasyTouch meters, which in appearance seem to be similar devices, demonstrated CVs of 25.9 and 27.2%, respectively. Due to the high CVs, these 2 meters were discontinued from further evaluation. Both BeneCheck and HumanSens had acceptable precision values across the 54 samples measured (CVs: 9.5 and 11.5%, respectively). In 3 healthy volunteers, the BeneCheck and HumanSens meters gave SUA values that were concordant with the uricase test (mean accuracy of 103% and 107%, respectively) and had averaged spiked blood recoveries across 4 sUA concentrations of 114% and 129%, respectively.

Conclusion: The HumaSens and BeneCheck meters were easy to use and have appropriate analytical characteristics to allow reliable SUA monitoring. These POC uric acid testing meters may help with detection of hyperuricemia, thereby assisting in the assessment of urate lowering therapy effectiveness, achievement of target SUA levels, and potentially preventing complications of hyperuricemia and gout.

Disclosure: J. Paraskos, AstraZeneca, 3; **Z. Berke**, AstraZeneca, 3; **J. Cook**, AstraZeneca, 3; **J. N. Miner**, AstraZeneca, 1, Ardea Biosciences, Inc., 3, ARTA Bioscience, 6; **M. Braddock**, AstraZeneca, 1, AstraZeneca, 3; **A. Platt**, AstraZeneca, 3; **G. Hughes**, AstraZeneca, 3.

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Adherence to Treatment Recommendations of Gout: A Patient Survey in China. Feng Sheng, Xuejun Zeng and Weigang Fang. Peking Union Medical College Hospital, Beijing, China.

Background/Purpose: The prevalence of gout appeared to be increasing in China as its economy developed rapidly in the past three decades. Though efficacious and affordable treatment of gout was widely available, the disease was not well controlled in many countries of the world including China. Poor adherence to treatment recommendations was one major reason leading to unsatisfactory management. Patients' adherence to medical treatment of gout was reported to be 17–44% in developed countries, but the data were unknown in China.

Methods: A structured survey was carried out by telephone interview in 349 patients recruited from Gout Clinic at Peking Union Medical College Hospital in 2014. They all satisfied the ACR classification criteria for gout, 1977, and had dietary education when their diagnosis was made or confirmed in our clinic as baseline. 271 patients with urate lowering therapy (ULT) indications were also provided with medication recommendations and/or prescriptions according to the ACR and EULAR guidelines. Demographic data and clinical characteristics were collected at baseline. Patients' adherence to dietary and medication recommendations was measured by food frequency questionnaire and proportion of accumulative days of ULT medication consumption, respectively in the survey. Consumption of alcohol (beer, wine, spirit and yellow rice wine), seafood and internal organs less than once a month and limited intake of red meat was defined as dietary adherence, and ULT ≥80% of time since baseline was defined as medication adherence. Multivariable logistic regression models were used to estimate the independent association between patient characteristics and adherence. Patients' explanations for medication non-adherence were also asked.

Results: The dietary and medication adherence were 44.2% and 21.9%, respectively. Older patients (age ≥60), high serum urate levels (>642umol/L) and tophi at baseline were associated with dietary adherence independently. Tophi and chronic kidney disease at baseline were associated with medication adherence independently, but the longer the time between baseline and the survey was, the less proportion of patients were adherent to ULT medication (Table 1). The main reasons patients reported leading to their medication non-adherence included remission after treatment (35.1%), concern of side effects (22.7%), insufficient patient education (9.5%) and adverse events (8.1%).

Conclusion: Patients' adherence to treatment recommendations of gout was poor in China.Older age, high serum urate levels and comorbidity (tophi and chronic kidney disease) at baseline were associated with treatment adherence. As time elapsed, less patients were adherent to ULT medications.

Table 1. Characteristics associated with treatment adherence of gout

Characteristics	Adjusted OR(95%CI)	p
Dietary adherence		
Age		
<30	1 (Ref.)	
30–39	0.44 (0.12–1.57)	0.20
40–49	0.86 (0.26–2.99)	0.81
50–59	0.83 (0.22–3.19)	0.79
≥60	4.67 (1.07–20.36)	0.04
Serum urate levels		
1st Quartile (0–498umol/L)	1	

2nd Quartile (499–569 umol/L)	1.05 (0.39–2.83)	0.92
3rd Quartile (570–642 umol/L)	0.97 (0.37–2.52)	0.95
4th Quartile (>642 umol/L)	4.23 (1.47–12.16)	<0.01
Tophi	2.39 (1.06–5.37)	0.04
Medication adherence		
Tophi	4.60 (1.37–15.42)	0.01
Chronic kidney disease	8.39 (2.02–34.84)	<0.001
Time interval between baseline and the survey		
<1year	1 (Ref.)	
1–3year	0.09 (0.03–0.30)	<0.001
≥3year	0.03 (0.003–0.37)	<0.01

Disclosure: F. Sheng, None; **X. Zeng**, None; **W. Fang**, None.

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Effect of Urate-Lowering Therapy on Radiographic Changes in Gout Patients. Seulkee Lee, Inyoung Kim, Hyemin Jeong, Jiwon Hwang, Hyungjin Kim, Jaejoon Lee, Hoon-Suk Cha and Eun-mi Koh. Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

Background/Purpose: The aim of this study was to investigate the radiographic changes in patients with gout in association with the control of serum uric acid level.

Methods: A retrospective observational study in a single tertiary medical center was performed. Sixty one patients who had at least one erosive change on baseline radiography or tophus on physical examination were included. Follow up radiography was taken at least 5 years apart from baseline radiograph. The primary endpoint was the changes in the radiographic damage scores based on modified Sharp/van der Heijde (mSvH) score in association with the control of serum uric acid level during the study period. Patients were divided by three groups which consist of improved, no change, aggravated patients for subgroup analysis. The changes in the size of soft tissue density in radiograph were also measured.

Results: The mean age was 55±13 years and 60 (98%) patients were male. Disease duration was 11±7 years and mean serum uric acid level was 8.8±1.9 mg/dL at baseline. Follow up duration between two radiographies was 10.8±3.6 years. All patients were receiving urate-lowering therapy. The change in the mean mSvH score between baseline and follow visit was not statistically significant (6.77 vs. 6.69, respectively). The patient number of improved, no change, aggravated groups was 22, 14, and 25 and the baseline plain radiographic damage score was 12.1, 4.85, and 3.7 respectively. As expected, the change in damage scores was positively correlated to AUC of uric acid level ($r = 0.32$, $p=0.01$). The patients with longer disease duration at baseline were more likely to have improvement in the follow up radiograph. ($r = 0.46$, $p=0.004$). In subgroup analysis, only the baseline radiographic damage score was significantly different from each other. In improved group, the change of damage scores was negatively associated with disease duration at baseline ($r = 0.48$, $p = 0.024$).

Conclusion: Our study demonstrated that radiographic damage in gout may be reversible to some extent and that the magnitude of improvement depends on the degree of serum uric acid control.

Disclosure: S. Lee, None; **I. Kim**, None; **H. Jeong**, None; **J. Hwang**, None; **H. Kim**, None; **J. Lee**, None; **H. S. Cha**, None; **E. M. Koh**, None.

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Musculoskeletal Ultrasound Reveals Calcific Deposition Arthropathy in Seronegative Inflammatory Arthritis Patients. Sheila L. Arvikar[1], Janice Lin[2] and Minna J. Kohler[3]. [1]Massachusetts General Hospital, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Massachusetts General Hospital / Harvard Medical School, Boston, MA.

Background/Purpose: Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) have vastly improved the diagnosis of rheumatoid arthritis (RA), but the diagnosis and management of seronegative RA patients remains a challenge. Musculoskeletal ultrasound (US) can improve the diagnosis of synovitis, and also reveal crystalline deposition potentially contributing to arthritis in a subset of patients.

Methods: We retrospectively reviewed clinical and US characteristics of 26 consecutive seronegative RA patients found to have crystalline deposits by US performed by 1 US-trained rheumatologist over 1 year. Images from 7 age-matched disease controls (4 osteoarthritis (OA), 2 seropositive RA, and 1 seronegative RA) were also reviewed. All images were reviewed by a 2nd rheumatologist.

Results: Typical of RA cohorts, the 26 patients were predominantly female (62%), with a median age of 57. RF and ACPA were by definition negative. Median levels of inflammatory markers were in normal ranges. 62% of the patients met 2010 ACR/EULAR classification criteria for RA. Median symptom duration was 1.4 years, and only 5 patients were receiving disease-modifying antirheumatic drugs (DMARDs) at the time of US. Metacarpophalangeal (MCP) joints were most commonly symptomatic (65%). By X-ray, only 2 patients had chondrocalcinosis, and 1 had erosion.

There was 100% inter-reader agreement of the US images, encompassing 7 anatomic sites (shoulder, elbow, wrist, hand, knee, ankle, and foot). Images in all 26 patients revealed multiple hyperechoic densities consistent with the US appearance of calcium pyrophosphate dihydrate (CPPD) vs. calcium hydroxyapatite crystals, and were not typical of gout. Calcific deposits, in all cases associated with synovitis, were identified in joints, tendons, and/or tendon sheaths. By comparison, control imaging demonstrated few scattered calcifications without synovitis in only 1 OA patient.

Nearly all 26 patients (90%) had calcifications in both joints and tendons. Calcification pattern in joints was most commonly round (79%), followed by punctate (45%), whereas calcification pattern in tendons was more frequently punctate (79%) followed by linear (42%). Over half (58%) of patients had all 3 patterns. Nine (35%) patients had US evidence of bony erosions. There were no effusions amenable to aspiration. Subsequent testing of 10 patients revealed elevated parathyroid hormone levels in 4 patients, a risk factor for CPPD.

Conclusion: Our findings of hyperechoic deposits associated with synovitis on US suggests that crystalline disease, such as CPPD arthropathy, may be an explanation for arthritis in a subset of seronegative RA patients. Although microscopic analysis is the gold standard in diagnosis of crystalline arthropathy, US may be valuable, particularly when X-rays are unrevealing and effusions amenable to aspiration are lacking. Detection of crystals may reveal abnormalities such as hyperparathyroidism, and may affect treatment strategies. Studies with synovial tissue or fluid crystal analysis prospectively evaluating the prevalence of crystal deposition are needed to evaluate the role for US in the screening of seronegative RA patients.

Disclosure: S. L. Arvikar, Arthritis Foundation, 2; **J. Lin**, None; **M. J. Kohler**, None.

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Ultrasound Versus X-Rays Versus Synovial Fluid Analysis for the Diagnosis of Calcium Pyrophosphate Dihydrate Deposition Disease: Is It CPPD? Georgios Filippou[1], Antonella Adinolfi[1], Sauro Lorenzini[2], Ilaria Bertoldi[1], Valentina Di Sabatino[1], Valentina Picerno[1], Luca Sconfienza[3], Mauro Galeazzi[1] and Bruno Frediani[1]. [1]University of Siena, Siena, Italy, [2]Rheumatology Unit, Azienda Ospedaliera Universitaria Senese, Siena, Italy, [3]University of Milan, Milan, Italy.

Background/Purpose: The diagnosis of calcium pyrophosphate crystal (CPP) deposition disease (CPPD) is mainly based on the synovial fluid analysis and Xrays. US has demonstrated high sensitivity and specificity values for diagnosing CPPD compared to synovial fluid analysis as the gold standard, but less is known about sensitivity and specificity of synovial fluid analysis itself. Aim of the study is to compare ultrasonography, synovial fluid analysis and X-rays performances in the diagnosis of CPPD using a real gold standard.

Methods: We enrolled in our study all patients waiting to undergo knee replacement surgery due to severe osteoarthritis. Each patient underwent US examination of the knee, focusing on the menisci and the hyaline cartilage, the day prior to surgery, scoring each site according to the presence/absence of CPP as defined previously. The day of the surgery, synovial fluid of the knee (if present) was aspirated by the surgeon. After surgery, the menisci, condyles and the synovial fluid were retrieved and examined microscopically. Synovial fluid analysis was performed on wet preparations. For the meniscus and cartilage microscopic analysis, six samples were collected, either from the surface and from the internal of the structure trying to cover a large part of it. All slides were observed under transmitted light microscopy and by compensated polarised microscopy. A dichotomous score was given for the presence/absence of CPP. US and microscopic analysis were performed by different operators, blind to each other's findings. X-rays of the knees were collected and assessed for the presence of CPPD by a Radiologist expert in musculoskeletal imaging, blind to other findings. Sensitivity and specificity of US, synovial fluid and X-Rays were calculated using microscopic findings of the menisci and cartilage as the gold standard.

Results: We enrolled in the study 42 patients (14 males), mean age of 74 years old (±8.4). All patients underwent US of the knee, synovial fluid was present in 32 patients and X-rays have been collected form 34 patients. 2x2

contingency tables and diagnostic accuracy values for each exam are summarized in table 1.

Count

		Reference Standard positive	Reference Standard negative	Total
US	positive	24	2	26
	negative	1	14	15
Total		25	16	41

Count

		Reference Standard positive	Reference Standard negative	Total
X-Rays	positive	15	1	16
	negative	5	13	18
Total		20	14	34

Count

		Reference Standard positive	Reference Standard negative	Total
Synovial Fluid	positive	14	0	14
	negative	4	14	18
Total		18	14	32

	Sensitivity (CI 95%)	Specificity (CI 95%)	PPV	NPV	Accuracy
US	96% (±0.07)	87% (±0.16)	92%	93%	93%
Xrays	75% (±0.18)	93% (±0.13)	94%	72%	82%
Synovial fluid analysis	77% (±0.19)	100% (0)	100%	78%	88%

Conclusion: US demonstrated higher sensitivity values for identifying CPP deposits in the knee joint than synovial fluid analysis. Specificity values on the other hand were higher for the microscopic analysis as expected. Globally we believe that for its intrinsic characteristics, the non invasive nature, for the high values of both specificity and specificity, and last but not least, for the capability to address differential diagnosis US should be the first exam to be performed when CPPD disease is suspected. As this study demonstrates, the presence of CPP crystals in the synovial fluid, definitely confirms the diagnosis but a negative microscopic exam does not exclude it.

Disclosure of Interest: None Declared

Disclosure: G. Filippou, None; **A. Adinolfi**, None; **S. Lorenzini**, None; **I. Bertoldi**, None; **V. Di Sabatino**, None; **V. Picerno**, None; **L. Sconfienza**, None; **M. Galeazzi**, None; **B. Frediani**, None.

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Distribution of Haemochromatosis Arthropathy. High Ankle and Mid Foot Prevalence; A Diagnostic Clue? Patrick Kiely[1] and Alex Richardson[2]. [1]St. Georges Healthcare NHS Trust, London, United Kingdom, [2]St George's Healthcare NHS Trust, London, United Kingdom.

Background/Purpose: Long delays in diagnosis of haemochromatosis are frequent and lead to an adverse affect on hepatic and cardiac outcome. Arthropathy is a highly prevalent and early feature, which could act as a trigger for diagnosis if sufficiently distinctive. We conducted a survey of patients with haemochromatosis to assess the prevalence and distribution of joint symptoms and their relation to the diagnosis.

Methods: A questionnaire was sent to members of the UK Haemochromatosis Society (~1500) in December 2013. Questions assessed how the diagnosis of haemochromatosis was made; symptoms, duration, the prevalence and distribution of affected joints, and the role of a rheumatologist.

Results. Questionnaires were returned by 470 people with haemochromatosis, 97% white, 53% male. The genotype was C282Y homozygous 52%, C282Y/H63D heterozygous 7%, C282Y/wild type heterozygous 5%, unknown 33%. The diagnosis was made at a mean age of 56 years, following family member screening in 20%, well man/woman screening in 23% and as result of symptoms in 57%. At diagnosis the most frequent symptoms attributed to haemochromatosis were fatigue 65% and joint pain 60% (Fig 1), with a mean duration of 8 years (0–65) and mean Ferritin 1752 mg/L. The diagnosis was most frequently made by a GP 38%, Haematologist 24%, Gastroenterologist 21.5% and Rheumatologist 7%.

88% of respondents reported joint pain, stiffness or swelling. Joint symptoms preceded the diagnosis of haemochromatosis by more than 5 years in 47%, by more than 1 year in 78.5% and post dated the diagnosis in 14.5%. The most prevalent areas affected were hand or wrist 66%, ankle or mid foot 49%, and knee 44% (Fig 2). In the hands the prevalence of symptoms was 1st CMC 60%, wrist 52%, MCP 47%, PIP 48%, and DIP joints 41%. No formal arthritic diagnosis was given to 45%, OA 29%, haemochromatosis arthropathy 11.5%. Dupuytrens disease was reported by 13% of men and 8% of women. Venesection was reported to have helped joint symptoms in 5%, made no impact in 20% and in 51% new joints had become affected following de ironing. A negative impact on employment from arthropathy was reported by 21%, with 9% losing their job.

Conclusion: In haemochromatosis, joint symptoms are highly prevalent at diagnosis, with the ankle and mid foot involved in 49%. In addition to MCP joint disease, an osteoarthritis-like presentation at a relatively young age in the hind or mid foot might be a distinguishing feature to prompt investigations leading to an earlier diagnosis.

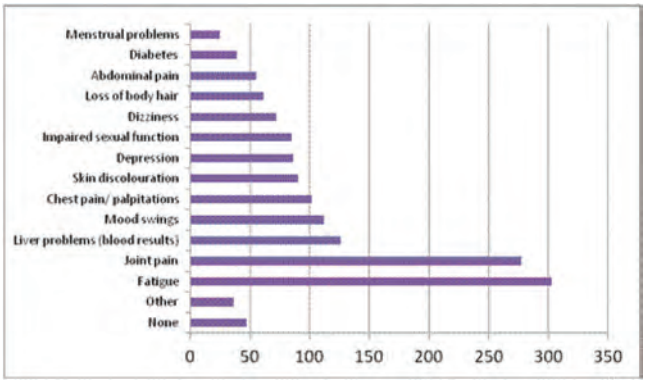

Figure 1 Symptoms at diagnosis

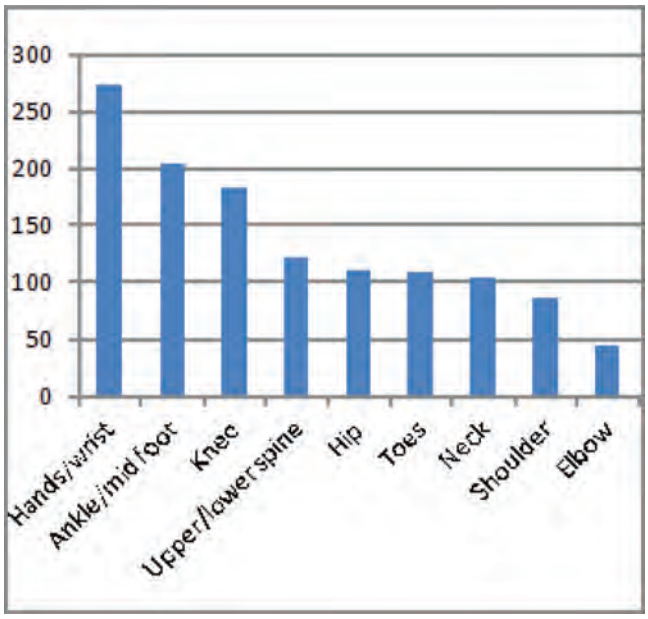

Figure 2 Distribution of joint symptoms

Disclosure: P. Kiely, None; **A. Richardson**, None.

ACR Poster Session A
Orthopedics, Low Back Pain and Rehabilitation
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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The Association Between Low Back Pain and Radiographic Features: A Systematic Review with Meta-Analysis. Joachim Raastad[1], Michael Reiman[2], Remy Coeytaux[2], Leila Ledbetter[3] and Adam P. Goode[2]. [1]Bergen University College, Bergen, Norway, [2]Duke University, Durham, NC, [3]Duke University, Durahm, NC.

Background/Purpose: Low back pain (LBP) is a prevalent condition. Plain film radiography is a commonly used imaging technique for this condition. Radiographic features (RF) such as disc space narrowing (DSN), osteophytes, spondylosis, endplate sclerosis, spondylolisthesis and facet joint osteoarthritis have all been debated as potential pain generators in the lumbar spine. The aim of this study is to: 1) determine the association between LBP and lumbar spine RF in both community and occupation-based groups; and 2) to determine if there are differences in these associations between these two groups.

Methods: A systematic electronic search of PubMed, EMBASE, CINAHL and Cochrane was conducted with keywords related to LBP and lumbar spine RFs. The search was restricted from inception of each respective

database to April 2014. Inclusion criteria consisted of observational studies of adults (≥18 years) with and without non-specific LBP. Studies were excluded if they investigated LBP related to infection, malignancy or rheumatologic nature or were conducted in cadavers. Quality assessment was conducted with the Item Bank for Assessment of Risk of Bias and Precision for Observational Studies of Interventions or Exposures. Random effect models were used for all pooled analyses with associations represented by odds ratios (OR) and 95% confidence intervals (95% CI). Statistical heterogeneity was indicated with an I^2 value >50%.

Results: Twenty-eight (22 community-based and 6 occupation-based) studies met the eligibility criteria consisting of 26,107 subjects. A significant, positive association was found between DSN and LBP that did not differ (p=0.22) between community (OR=1.47 ((95% CI 1.36–1.58)) and occupation-based studies (OR=1.76 ((95% CI 1.34 –2.33)). No significant statistical heterogeneity was present in either estimate (I^2=0.0%). A significant association was found between spondylolisthesis and LBP in occupation-based studies (OR=2.21 ((95% CI 1.44 – 3.39)) that differed significantly (p<0.01) from community based studies (OR=1.12 ((95% CI 1.03 – 1.23)). These individual estimates were also homogeneous (I^2<1.0%). The association between other radiographic features was modest (i.e., spondylosis and osteophytes) or non-significant (i.e., endplate sclerosis and facet joint osteoarthritis). Quality of included studies varied with the majority of studies demonstrating good quality.

Conclusion: A significant positive association was found with DSN and LBP that did not differ between community and occupational-based studies. The fact that no differences exist between these two groups may be related to the influence that genetic factors have on disc degeneration. A significant strong association was found between spondylolisthesis and LBP among the occupational group but was weakly associated in the community-based group, supporting spondylolisthesis as a potential unique pain generator in the lumbar spine.

Disclosure: J. Raastad, None; **M. Reiman**, None; **R. Coeytaux**, None; **L. Ledbetter**, None; **A. P. Goode**, None.

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Revision Arthroplasty in Rheumatoid and Osteoarthritis: Does Methotrexate Decrease Radiographic Lucency in RA Patients? Mike Wei[1], Douglas N. Mintz[2], Lisa A. Mandl[2], Arielle Fein[2], Jayme C. Burket[2], Yuo-Yu Lee[2], Wei-Ti Huang[2], Vivian P. Bykerk[2], Mark P. Figgie[2], Edward F. DiCarlo[2], Bruce N. Cronstein[3] and Susan M. Goodman[2]. [1]Weill Cornell Medical College, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Rheumatoid arthritis (RA) patients have excellent total hip arthroplasty (THA) survival, and methotrexate (MTX), an anti-inflammatory disease modifying drug which may affect bone reabsorption, may play a role. The purpose of this study is to determine the diagnosis leading to revision THA (rTHA) in RA patients and to assess the association of radiographic lucency with MTX use.

Methods: All patients with validated diagnosis of RA in the institution's THA registry undergoing rTHA from May 2007 - February 2011 were eligible. Diagnosis leading to rTHA and medication use was determined by chart review. Osteolysis was evaluated on available radiographs by measuring maximum lucency in each Gruen zone. Differences within RA patients with/without MTX in osteolysis, demographics, and medications were assessed with chi-squared, Fisher's exact tests or Mann-Whitney U tests as appropriate. The error rate for multiple comparisons of lucency in the different Gruen zones was corrected via false discovery rate methods. A secondary analysis was performed to determine differences in diagnoses leading to revision between RA and matched OA controls (2:1 match by sex age +/− 5 years). OA exclusion criteria included presence of rheumatic diseases, use of MTX, and lack of records.

Results: 51 RA rTHA were identified and compared with 103 OA **(Table 1).** Mean age for RA was 57.7 v 59.4 years for OA (p = 0.240). 82.4% RA were female v 83.5% OA (p = 0.859). RA had lower BMI than OA (25.5 v 28.2; p = 0.166). There was no difference in diagnosis leading to rTHA, including infection (RA 3.9 v OA 6.8%; p = 0.719) or dislocation (RA 23.5 v OA 23.3%; p = 0.975). There was no significant difference in the length of time the implant was in before revision: RA 11.0 v OA 8.8 years (p = 0.060). Among RA with/without MTX, **(Table 2)** there was no difference in use of biologics (30.0 v 43.3%, p = 0.283), steroids (47.6 v 50.0%, p = 0.867) or bisphosphonates (23.8 v 33.3%, p = 0.543). There was no difference in rTHA diagnosis with/without MTX, including loosening (52.4 v 56.7%, p = 0.762). There was no significant difference in lucencies with MTX use in any Gruen zone. Patients with MTX had femoral stem subsidence of 3.7mm v no subsidence without MTX (p = 0.006).

Conclusion: There was no difference in the diagnosis leading to rTHR in RA and OA, although RA trended longer prior to rTHA. In this small retrospective study, there were no significant differences associated with MTX exposure or radiographic lucency among RA patients. The significance of subsidence is not clear. Further study of arthroplasty survival in RA patients is warranted.

Table 1: Demographic characteristics and reason for revision for OA vs. RA patients*

	RA, N=51	OA, N=103	p-value
Age, Mean (Std Dev)	57.7 (14.1)	59.4 (15.0)	0.240
BMI, Mean (Std Dev)	25.5 (5.2)	28.2 (11.4)	0.166
Female, N (%)	42 (82.4)	86 (83.5)	0.859
Years Implanted, Mean (StDev)	11.0 (8.3)	8.8 (8.8)	0.060
Diagnosis, N (%)			
Infection	2 (3.9)	7 (6.8)	0.719
Loosening	28 (54.9)	59 (57.3)	0.779
Fracture	7 (13.7)	7 (6.8)	0.232
Wear	12 (23.5)	19 (18.4)	0.459
Dislocation	12 (23.5)	24 (23.3)	0.975
Mech Failure	2 (3.9)	7 (6.8)	0.862
Other	1 (2.0)	0 (0.0)	0.331

*28 patients were ascribed more than 1 diagnosis.

Table 2: Demographic characteristics and radiographic analysis of RA patients with/without MTX*

	MTX, N=20	No MTX, N=30	p-value
Age, Mean (Std Dev)	59.3 (14.9)	56.6 (13.7)	0.461
BMI, Mean (Std Dev)	27.2 (5.9)	24.2 (4.3)	0.059
Years Implanted, Mean (Std Dev)	10.7 (9.1)	11.3 (7.9)	0.737
Diagnosis, N (%)			
Infection	1 (4.8)	1 (3.3)	>0.999
Loosening	11 (52.4)	17 (56.7)	0.762
Fracture	3 (14.3)	4 (13.3)	>0.999
Wear	6 (28.6)	6 (20.0)	0.351
Dislocation	6 (28.6)	6 (20.0)	0.581
Mech Failure	0 (0.0)	2 (6.7)	0.506
Other	0 (0.0)	1 (3.3)	>0.999
Medication, N (%)			
Bisphosphonates	5 (23.8)	10 (33.3)	0.543
Biologics	6 (30.0)	13 (43.3)	0.283
Prednisone	10 (47.6)	15 (50.0)	0.867
Cemented Cup, N (%)	3 (18.8)	5 (22.7)	>0.999
Cemented Femur, N (%)	5 (31.3)	13 (59.1)	0.112
Lucency, Mean (Std Dev) [mm]			
Femur Zone 1	11.4 (16.8)	7.4 (10.2)	0.954
Femur Zone 2	0.0 (0.0)	0.9 (1.7)	0.225
Femur Zone 3	0.2 (0.8)	0.5 (1.8)	0.954
Femur Zone 4	2.7 (8.7)	0.0 (0.0)	0.189
Femur Zone 5	0.3 (0.9)	0.7 (2.6)	0.954
Femur Zone 6	1.3 (3.3)	0.8 (2.8)	0.954
Femur Zone 7	3.7 (5.6)	3.0 (5.5)	0.954
Femur Zone 8	5.7 (7.9)	5.0 (6.3)	0.954
Femur Zone 9	0.0 (0.0)	1.8 (3.5)	0.189
Femur Zone 10	0.2 (0.9)	0.0 (0.0)	0.954
Femur Zone 11	0.8 (2.3)	0.7 (2.4)	0.954
Femur Zone 12	0.1 (0.4)	0.8 (3.6)	0.954
Femur Zone 13	2.2 (5.0)	1.3 (3.6)	0.954
Femur Zone 14	3.5 (6.1)	3.3 (6.3)	0.954
Subsidence (mm)	3.7 (7.1)	0.0 (0.0)	**0.006**

*11 patients were ascribed more than 1 diagnosis.

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Time Trends in Total Ankle Arthroplasty in the U.S.: A Study of the Nationwide Inpatient Sample. Jasvinder Singh and Rekha Ramachandaran. University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: To assess the time-trends in utilization, clinical characteristics and outcomes of patients undergoing total ankle arthroplasty (TAA) in the U.S.

Methods: We used the Nationwide Inpatient Sample (NIS) data from 1998 to 2010 to examine time-trends in the utilization rates of TAA. We used the Cochran Armitage test for trend to assess time-trends across the years and the analysis of variance (ANOVA), Wilcoxon test or chi-squared test (as appropriate) to compare the first (1998–2000) and the last time periods (2009-10).

Results: TAA utilization rate increased significant from 1998 to 2010: 0.13 to 0.84 per 100,000 overall, 0.14 to 0.88 per 100,000 in females and from 0.11 to 0.81 per 100,000 in males ($p<0.0001$ for each comparison for time-trends). Compared to the 1998–2000, those undergoing TAA in 2009-10: were older (41% fewer patients <50 years, $p<0.0001$); less likely to have RA as the underlying diagnosis (55% fewer patients, $p=0.0001$); more likely to have Deyo-Charlson index of two or more (197% more, $p=0.0010$); and had a shorter length of stay at 2.5 days (17% reduction, $p<0.0001$). Mortality was rare, ranging 0 to 0.6% and discharge to inpatient facility ranged 12.6–14.1%; we noted no significant time-trends in either ($p>0.05$).

Conclusion: The utilization rate of TAA increased rapidly in the U.S. from 1998 to 2010, but post-arthroplasty mortality rate was stable. Underlying diagnosis and medical comorbidity changed over time and both can impact outcomes after TAA. Further studies should examine how the outcomes and complications of TAA have evolved over time.

Disclosure: J. Singh, Savient, 2, Takeda, 2, Degeneron, 5, Allergan, 5; **R. Ramachandaran**, None.

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Sex Differences in Characteristics, Utilization and Outcomes of Patient Undergoing Total Elbow Arthroplasty: A Study of the U.S. Nationwide Inpatient Sample. Jasvinder A Singh[1] and Rekha Ramachandaran[2]. [1]University of Alabama and VA Medical Center, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: To compare patient characteristics, utilization rates and outcomes after total elbow arthroplasty (TEA) by sex.

Methods: We used the nationwide Inpatient Sample from 1998–2011 to study sex-related time-trends in patient characteristics, comorbidity and outcomes after TEA. We used chi-square test, analysis of variance and the Cohran-Armitage test to assess differences in utilization rates and characteristics over time by sex and logistic regression to compare mortality, discharge disposition and the length of hospital stay.

Results: Overall TEA utilization increased significantly from 0.45 in 1998 to 0.96 per 100,000 in 2011 ($p<0.0001$). The utilization rates were significantly higher in females compared to males throughout the study period: 0.62 vs. 0.29 in 1998 ($p<0.0001$) and 1.31 vs. 0.70 in 2011 ($p<0.0001$). Compared to males, females undergoing TEA were more likely to be White (79.7% vs. 71.4%; $p<0.0001$), have rheumatoid arthritis (16.7% vs. 8.1%; $p<0.0001$) and have Deyo-Charlson index of 2 or more (11.3% vs. 5.9%; $p<0.0001$) and were older (63.5 vs. 51.4 years; $p<0.0001$). Compared to males undergoing TEA, females had significantly lower mortality, 0.1% vs. 0.4% ($p=0.03$); lower proportion were discharged to home, 81.9% vs. 89.6% ($p<0.0001$) and fewer has index hospital stay above the median, 30.0% vs. 33.0% ($p=0.01$); most differences were significant after multivariable adjustment.

Conclusion: TEA utilization in the U.S. more than doubled in the last 14 years, with rates higher in females than males. Females had better outcomes after TEA than men. Preoperative risk communication should be sex-specific based on these data.

Disclosure: J. A. Singh, takeda, savient, 2, takeda, savient, regeneron, allergan, 5; **R. Ramachandaran**, None.

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Hospital Volume Predicts Outcomes and Complications after Total Shoulder Arthroplasty. Jasvinder A Singh[1] and Rekha Ramachandaran[2]. [1]University of Alabama and VA Medical Center, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: To assess the association of hospital procedure volume for total shoulder arthroplasty (TSA) with patient outcomes and complications.

Methods: We used the Nationwide Inpatient Sample (NIS) from 1998–2011 to study the association of hospital annual TSA procedure volume with patient characteristics and TSA outcomes, including discharge disposition (home vs. inpatient facility), length of index hospitalization, post-arthroplasty periprosthetic fracture and revision. Annual hospital TSA volume was categorized as <5, 5–9, 10–14, 15–24 and ≥25 TSA procedures annually.

Results: Patients receiving TSA at higher volume hospitals were more likely to be female ($p<0.0001$), of White race ($p<0.0001$). Compared to low volume hospitals (<5, 5–9, 10–14 procedures annually), patients receiving TSA at higher volume hospitals (15–24, ≥25) had significantly lower likelihood of: (1) being discharged to an inpatient medical facility, 16.5%, 13.4%, 13.0%, 12.7% and 11.5% ($p<0.0001$); (2) hospital stay >median, 46.6%, 40.4%, 36.6%, 34.4% and 29.2% ($p<0.0001$); (3) post-arthroplasty fracture, 1.2%, 0.8%, 0.9%, 0.6% and 0.8% ($p=0.0004$); (4) transfusion, 8%, 7.1%, 6.7%, 7.1% and 5.5% ($p=0.006$); and (5) TSA revision, 0.5%, 0.3%, 0.2%, 0.3%, 0.3% ($p=0.045$), respectively.

Conclusion: In this study, we found that higher annual hospital TSA volume was associated with better TSA outcomes. These findings document the impact of annual hospital TSA volume on TSA outcomes. Patients, surgeons and policy-makes should be aware of these findings and take them into account in decision-making, policy decisions and resource allocation.

Disclosure: J. A. Singh, takeda, savient, 2, takeda, savient, regeneron, allergan, 5; **R. Ramachandaran**, None.

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Utilization and Outcomes Following Total Shoulder Arthroplasty in Elderly and Non-Elderly Patients. Jasvinder A Singh[1] and Rekha Ramachandaran[2]. [1]University of Alabama and VA Medical Center, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: To assess the age-related differences in total shoulder arthroplasty (TSA) outcomes and utilization and associated time-trends.

Methods: Nationwide Inpatient Sample (NIS) from 1998–2010 was used to study the time-trends in TSA utilization and outcomes, overall and by age. Age was categorized as <50, 50– 64, 65–79 and ≥80. Time trends in TSA utilization were compared using logistic regression or the Cochran Armitage test.

Results: The overall TSA utilization increased from 2.96 in 1998 to 12.68/100,000 in 2010. Compared to 1998–2000, significantly lower rates were noted in 2009-10 for: mortality, 0.2% vs. 0.1% ($p=0.0041$); discharge to an inpatient facility, 14.5% vs. 13.3% ($p=0.039$); and hospital stay >median, 51.2% vs. 29.4% ($p<0.0001$). TSA utilization rates/100,000 by age groups, <50, 50–64, 65–79 and ≥80 years were: 0.32, 4.62, 17.82 and 12.56 in 1998 ($p<0.0001$); and 0.65, 17.49, 75.27 and 49.05 in 2010 ($p<0.0001$) with increasing age-related difference over time ($p<0.0001$). Across the age categories, there were significant differences in the proportion: discharged to inpatient facility, 3.2% vs. 4.2% vs. 14.7% vs. 36.5% in 1998 ($p<0.0001$) and 1.8% vs. 4.3% vs. 12.5% vs. 35.5% in 2010 ($p<0.0001$) and the proportion with hospital stay >median, 39.7% vs. 40.2% vs. 53% vs. 69% in 2008 ($p<0.0001$) and 17.2% vs. 20.6% vs. 28.7% vs. 50.7% in 2010 ($p<0.0001$).

Conclusion: In a nationally representative sample, we noted increasing age-related differences indicate a changing epidemiology of TSA. Age-related differences in outcomes can guide us to focus on those with worst outcomes.

Disclosure: J. A. Singh, takeda, savient, 2, takeda, savient, regeneron, allergan, 5; **R. Ramachandaran**, None.

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Title: Use of Non-Traditional Modalities for Pain Management after Knee or Hip Joint Replacement. Jasvinder Singh[1], Celeste Lemay[2], Jeroan Allison[3] and Patricia D. Franklin[3]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Massachusetts Medical School, Worchester, MA, [3]University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Pain management is a major focus of the post-arthroplasty rehabilitation. A variety of pain treatments are used, including narcotics and non-narcotic analgesics. To our knowledge, there are limited or

no data regarding the use of non-pharmacologic treatment modalities in post-total joint replacement (TJR) period.

Methods: A subset of patients from a national joint registry undergoing primary TJR (total knee or hip replacement, TKR/THR) between 5/2013 and 6/2014 were queried at 2- and 8-weeks regarding pain severity and use of non-pharmacologic modalities. Frequency distributions were used to describe the cohort. We used bivariate statistical tests to compare groups including the chi-square, Fisher's exact, t tests and Wilcoxon-Mann-Whitney test.

Results: There were 969 primary TKR and 584 primary THR respondents at 2-weeks and 1,022 primary TKR and 563 primary THR respondents at 8-weeks. The use of non-medication modalities was common in primary TKR patients at 2-weeks: cold packs (86%), meditation (6%), deep breathing (20%), heat (15%), relaxation (20%), walking (33%), distraction (51%), prayer (32%), massage (28%), listening to music (11%) and imagery (2%); numbers were similar and slightly lower for the 8-week follow-up. Use of most non-medication modalities was significantly lower in primary THR patients.

Compared to non-users, users of non-medication pain management strategies at 2-weeks were significantly: younger (65.6 vs. 68.8 years), more likely to be female (61% vs. 51%), White (93% vs. 89%), have college education or higher (70% vs. 62%) and had household income of $45K or higher (55% vs. 48%). There were no significant differences in race distribution or mean body mass index (30.6 vs. 30.0).

Compared to non-users, patients who reported using non-medication pain management strategies at 2-weeks and 8-weeks had significantly higher mean pain levels (3.0 vs. 2.0 on 0–10 scale; $p<0.0001$) and pain interference with activities of daily living (p-values <0.02) and physical therapy ($p=0.007$).

Conclusion: Use of non-medication pain management strategies was common 2- and 8-weeks after primary TKR and THR. Certain patient groups used these modalities more than others. Use of these strategies was associated with more pain and pain interference, which might indicate that patients with higher pain severity and impact were more likely to use these strategies. This hypothesis needs to be tested with examination of longitudinal data.

Disclosure: J. Singh, Savient, 2, Takeda, 2, Degeneron, 5, Allergan, 5; **C. Lemay**, None; **J. Allison**, None; **P. D. Franklin**, None.

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Pre-Operative Pain and Function: Profiles of Patients Selected for Total Knee Replacement Among Surgeons in the United States. Uyen Sa D.T. Nguyen, David C. Ayers, Wenjun Li, Leslie Harrold and Patricia D. Franklin. University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: When knee pain is severe and frequent, or mobility and daily activities become difficult, a total knee replacement (TKR) remains the most effective treatment to relief pain and to improve function. In the US, the annual rate of TKRs in people 65 years or older increased almost 9-fold between 1979 and 2006. The latest US hospital-discharge data indicated a significant increase in use among the younger patients (< 65 years of age). Among the 719,000 TKRs performed in 2010, about 50% were in people < 65. It remains unclear the reasons for such increased TKR use. We examined profiles of patients selected for TKR in a recently established US national registry of total joint replacements (TJR).

Methods: We used data from the Function and Outcomes Research for Comparative Effectiveness in TJR (FORCE-TJR), a national cohort of TJR patients operated by more than 130 surgeons in 22 sites nationwide. The current study included participants with primary and unilateral TKRs that were not indicated by rheumatoid arthritis. Participants were enrolled between April 2011 and Feb 2014, and had completed a pre-operative Knee Injury and Osteoarthritis Outcome Score (KOOS) and Short-Form 36-item (SF-36) functional health survey. Data were also collected on patient demographics, body mass index, general health and comorbid conditions. We classified patients as having high or low pain (KOOS Pain<70 vs. ≥70), and low or high physical function (SF-36 PCS <40 vs. ≥40). We then classified patients into four groups: 1) low pain-high function, 2) high pain-high function, 3) low pain-low function, and 4) high pain-low function. Descriptive statistics including patient demographic and clinical characteristics of the four groups were compared.

Results: The majority (95%) of patients had high pain and/or low physical function. A small percentage of people (5%), however, had low pain and high function. Many in this latter group reported pain fairly daily (49%) or were aware of their knee problem daily or constantly (85%) despite a very small percentage having experienced severe or extreme pain on stairs (4%) or pain in bed (1%). Moreover, over half had a lot of limitations or difficulties in vigorous activities such as running. Compared with the group with high pain and low function, the group with low pain and high function on average were older, less obese, more highly educated, more likely men, and were generally healthier. Differences for all characteristics by groups were statistically significant at $P<0.05$, except for race.

Conclusion: The overwhelming majority of TKRs were performed to relieve pain and/or restore physical function. However, a small percent of TKR utilization was in patients with low pre-operative pain and high function, probably for quality of life issues. Further investigation is needed to determine the reasons for TKR use among these patients as this may have an important policy implication.

Characteristics*	Group 1 Low Pain High Function (n=288)	Group 2 High Pain High Function (n=931)	Group 3 Low Pain Low Function (n=228)	Group 4 High Pain Low Function (n=4,582)
Demographics				
Age (Years, Mean (SD))	69.8 (7.4)	66.6 (8.6)	70.1 (8.9)	66.2 (9.3)
BMI (Mean (SD))	29.1 (5.2)	29.7 (5.4)	30.8 (5.7)	32.0 (6.2)
Sex (Female)	45%	49%	56%	65%
Race (White)	94%	94%	93%	90%
Post-High School Education	74%	73%	68%	63%
Insurance Type (Medicare)	66%	51%	64%	54%
General Health SF36 GH, Mean (SD)	56.4 (6.1)	55.0 (6.1)	50.9 (8.7)	48.6 (9.0)
Excellent/Very Good	74%	68%	49%	39%
Pain Frequency				
Daily/Always	49%	93%	54%	97%
Awareness of Knee Problem				
Daily/Constantly	85%	98%	91%	99%
Pain, KOOS Mean (SD)	80.4 (7.7)	53.5 (11.9)	79.5 (7.6)	41.8 (15.5)
Pain on stairs (severe/extreme)	4%	33%	8%	69%
Pain in bed (severe/extreme)	1%	11%	1%	22%
Stiffness Late in Day (severe/extreme)	5%	24%	8%	47%
Function, SF36 PCS, Mean (SD)	47.2 (4.7)	44.4 (3.5)	33.8 (4.5)	29.9 (6.1)
Vigorous Activities - Limited a lot	58%	59%	86%	89%
Walking > 1 mile - Limited a lot	28%	29%	76%	82%
Function, KOOS-Sports, Mean (SD)	44.3 (22.4)	27.7 (18.4)	29.0 (22.3)	13.9 (15.9)
Running - Severe/Extreme Difficulty	56%	80%	77%	93%
Jumping - Severe/Extreme Difficulty	53%	79%	78%	93%

***All P values were < 0.05, except race**

Disclosure: U. S. D. T. Nguyen, None; **D. C. Ayers**, None; **W. Li**, None; **L. Harrold**, None; **P. D. Franklin**, None.

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Differences in Total Knee Replacement Outcomes Based on Age. Leslie Harrold[1], David Ayers[1], Wenjun Li[1], Vincent Pellegrini[2], John Grady-Benson[3], Jeroan Allison[1] and Patricia D. Franklin[1]. [1]University of Massachusetts Medical School, Worcester, MA, [2]Medical University of South Carolina, Charleston, SC, [3]Connecticut Joint Replacement Institute, Hartford, CT.

Background/Purpose: The fastest growing segment of the population undergoing total knee replacements (TKR) are patients younger than <65 years, yet little is known regarding their outcomes as compared to older patients. We examined, from a national sample of TKR patients, differences in clinical outcomes of pain and function following surgery based on age.

Methods: Patients undergoing primary TKR from 7/1/11 through 8/30/13 for osteoarthritis were identified from a national research consortium which enrolls patients from >130 surgeons across 22 states in the US. The registry gathers data from patients, surgeons and hospitals on patient demographics, underlying type of arthritis, body mass index, non-arthritis comorbid conditions, arthritis in non-operative hip and knee joints, back pain, global function based on the Short Form 36 Physical Component Score (PCS), and mental health using the SF-36 Mental Component Score (MCS). We evaluated both change in operative joint pain and function as well as the 6-month post-operative pain and function score based on the estimated Western Ontario and McMaster Universities Arthritis Index (WOMAC) using the Knee Injury and Osteoarthritis Outcome Score (KOOS; range of 0–100 with higher being better). Descriptive statistics were performed as well as linear and mixed model multivariable regressions examining differences based on age.

Results: There were 1164 patients <65 years and 2012 patients ≥ 65 years who underwent primary TKR. Younger patients were more likely to be nonwhite (8.7% vs. 5.0%, $p<0.001$), heavier (body mass index 33 vs. 30,

p<0.001), with worse emotional health (51.5 vs. 53.9, p<0.001), fewer comorbid conditions (p <0.001), and greater number of non-operative painful hip and knee joints (p<0.03). At the time of surgery, younger patients had greater pain (50.5 vs. 55.7, p<0.001) and functional impairment (53.2 vs. 54.9). Overall both younger and older patients had substantial pain relief and functional gain, improvement of 30.4 – 32.6 and 28.7 – 29.4 respectively based on the KOOS. In adjusted analyses, at 6-months post-operatively younger patients had slightly greater pain (−2.5, p <0.002) and less improvement in function (−2.2, p<0.016).

Conclusion: Both younger and older TKR patients had substantial pain and disability at the time of TKR and achieved substantial pain relief and functional gain following surgery. However, younger patients had statistically significant less improvement in pain and function, although the clinical significance of this difference is unknown.

Disclosure: L. Harrold, None; **D. Ayers**, None; **W. Li**, None; **V. Pellegrini**, None; **J. Grady-Benson**, None; **J. Allison**, None; **P. D. Franklin**, None.

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Dependence on Walking Aids and Patient-Reported Outcomes after Total Knee Arthroplasty. Jasvinder A Singh[1] and David Lewallen[2]. [1]University of Alabama and VA Medical Center, Birmingham, AL, [2]Mayo Clinic college of medicine, Rochester, MN.

Background/Purpose: To examine whether function and pain outcomes of patients undergoing primary total knee arthroplasty (TKA) are changing over time.

Methods: The Mayo Clinic Total Joint Registry provided data for time-trends in preoperative and 2-year post-operative activity limitation and pain in primary TKA patients from 1993–2005. We used chi-square test and analysis for variance, as appropriate. Multivariable-adjusted analyses were done using logistic regression.

Results: In a cohort of 7,229 patients who underwent primary TKA during 1993–2005, mean age was 68.4 years (standard deviation (SD), 9.8), mean BMI was 31.1 (SD, 6.0) and 55% were women. Crude estimates showed that preoperative moderate-severe overall limitation were seen in 7.3% fewer patients and preoperative moderate-severe pain in 2.7% more patients in 2002-05, compared to 1992-95 (p<0.001 for both). At 2-years, crude estimates indicated that compared to 1992-95, moderate-severe post-TKA overall limitation was seen in 4.7% more patients and moderate-severe post-TKA pain in 3.6% more patients in 2002-05, both statistically significant (p^{2}0.018) and clinically meaningful. In multivariable-adjusted analyses that adjusted for age, sex, anxiety, depression, Deyo-Charlson index, body mass index and preoperative pain/limitation, patients had worse outcomes 2-year post-TKA in 2002–2005 compared to 1993-95 with an odds ratio (95% confidence interval (CI); p-value) of 1.34 (95% CI: 1.02, 1.76, p=0.037) for moderate-severe activity limitation and 1.79 (95% CI: 1.17, 2.75, p=0.007) for moderate-severe pain.

Conclusion: Patient-reported function and pain outcomes after primary TKA have worsened over the study period 1993-95 to 2002-05. This time-trend is independent of changes in preoperative pain/limitation and patient characteristics.

Disclosure: J. A. Singh, takeda, savient, 2, takeda, savient, regeneron, allergan, 5; **D. Lewallen**, Zimmer, Orthosonic and Osteotech, 8, Pipeline Biomedical, 5, DePuy, Stryker, Biomet and Zimmer., 2.

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Dependence on Walking Aids Is Associated with Pain and Mobility Limitation after Total Hip Arthroplasty. Jasvinder A Singh[1] and David Lewallen[2]. [1]University of Alabama and VA Medical Center, Birmingham, AL, [2]Mayo Clinic college of medicine, Rochester, MN.

Background/Purpose: To assess the association of dependence on walking aids with pain and function outcomes after total hip arthroplasty (THA).

Methods: We used the Mayo Clinic Total Joint Registry to study patients who underwent primary or revision THA between 1993–2005 and completed a 2-year or 5-year pain and function outcomes survey. Multivariable-adjusted logistic regression assessed the associations, adjusting for clinical/demographic variables and preoperative pain and function.

Results: Primary THA cohort had 5,707 patients at 2-year and 3,289 at 5-years; revision THA included 2,667 patients at 2-year and 1,627 patients at 5-years. Compared to patients with no dependence on walking aids, patients with some or complete dependence on walking aids had significantly higher odds (95% confidence interval) of: (1) moderate-severe pain post-primary THA at 2-years: 3.40 (2.06, 5.62) and 4.79 (2.88, 7.97); (2) moderate-severe pain post-primary THA at 5-years: 3.92 (2.21, 6.95) and 3.47 (1.97, 6.11); (3) moderate-severe pain post-revision THA at 2-years, 4.67 (2.76, 7.91) and 2.95 (1.65, 5.27); (4) moderate-severe pain post-revision THA at 5-years: 3.95 (1.86, 8.38) and 5.16 (2.59, 10.3); (5) moderate-severe mobility limitation post-primary THA at 2-years: 10.7 (6.78, 17.0) and 14.2 (8.32, 24.3); (6) moderate-severe mobility limitation post-primary THA at 5-years: 13.2 (7.34, 23.7) and 21.4 (10.6, 43.2); (7) moderate-severe mobility limitation post-revision THA at 2-years: 4.90 (2.87, 8.37) and 8.26 (4.12, 16.6); (8) moderate-severe mobility limitation post-revision THA at 5-years: 5.12 (2.32, 11.3) and 10.1 (4.53, 22.7), respectively.

Conclusion: Post-THA dependence on walking aids is associated with worse pain and function outcomes post-THA.

Disclosure: J. A. Singh, takeda, savient, 2, takeda, savient, regeneron, allergan, 5; **D. Lewallen**, Zimmer, Orthosonic and Osteotech, 8, Pipeline Biomedical, 5, DePuy, Stryker, Biomet and Zimmer., 2.

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Differences in Total Hip Replacement Outcomes Based on Age. Leslie Harrold[1], David Ayers[1], Wenjun Li[1], Courtland Lewis[2], Philip Noble[3], Regis O'Keefe[4], Jeroan Allison[1] and Patricia D. Franklin[1]. [1]University of Massachusetts Medical School, Worcester, MA, [2]Hartford Hospital, Hartford, CT, [3]Baylor College of Medicine, Houston, TX, [4]University of Rochester Medical Center, Rochester, NY.

Background/Purpose: The fastest growing segment of patients who undergo total hip replacement (THR) are younger than <65 years, yet little is known regarding their outcomes as compared to older patients. We examined, from a national sample of THR patients, differences in clinical outcomes of pain and function following surgery.

Methods: Patients undergoing primary THR from 7/1/11 through 12/30/13 for osteoarthritis were identified from a national research consortium which enrolls patients from >130 surgeons across 22 states in the US. The registry gathers data from patients, surgeons and hospitals on patient demographics, underlying type of arthritis, body mass index, non-arthritis comorbid conditions, arthritis in non-operative hip and knee joints, back pain, global function based on the Short Form 36 Physical Component Score (PCS), and mental health using the SF-36 Mental Component Score (MCS). We evaluated both change in operative joint pain and function as well as the 6-month post-operative pain and function based on the estimated Western Ontario and McMaster Universities Arthritis Index (WOMAC) using the Hip Disability and Osteoarthritis Outcome Score (HOOS; range 0–100 with higher being better). Descriptive statistics were performed as well as linear and mixed model multivariable regression models examining differences based on age.

Results: There were 1030 patients <65 years and 1242 patients ≥ 65 years who underwent primary THR. Younger patients were more likely to be nonwhite (6.7% vs. 4.1%, p<0.01), heavier (body mass index 29.3 vs. 28.2, p<0.001), with worse emotional health (50.1 vs. 53.1, p<0.001), and fewer comorbid conditions (p <0.001). At the time of surgery, younger patients had greater pain (47.2 vs. 51.7, p<0.001) and functional impairment (45.2 vs. 47.0, p=0.02). Overall both younger and older patients had substantial pain relief and functional gain, mean improvement of 40.1 – 43.2 and 39.1 – 42.2 respectively based on the HOOS. In adjusted analyses, both younger and older patients had similar levels of improvement in pain and function as well as similar mean post-operative 6-month pain (90.4 vs. 91.9, p=0.15) and function scores (86.2 vs. 87.4, p=0.42).

Conclusion: Both younger and older THR patients had substantial pain and disability at time of THR, and achieved significant pain relief and functional gain at 6 months following surgery. In this national sample of THR patients, both younger and older patients had good clinical outcomes following surgery with respect to pain relief and functional gain.

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Implant Survival and Patient-Reported Outcomes after Total Hip Arthroplasty in Young Patients with JIA. Ishaan Swarup, Ella Christoph, Lisa A. Mandl, Susan M. Goodman and Mark P. Figgie. Hospital for Special Surgery, New York, NY.

Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is a common rheumatologic disease in children that often persists into adulthood. The hip joint is commonly involved, and total hip arthroplasty (THA) is the standard treatment for patients who fail non-operative management. This study evaluates implant survival in JIA patients who underwent a primary THA at our institution before the age of 35. It also describes patient-reported outcomes for JIA patients after THA.

Methods: Patient characteristics and implant data were collected by a retrospective chart review. Follow-up surveys were used to determine implant survival and patient-reported outcomes. Kaplan-Meier survival analysis was performed to evaluate implant survival, and the hip disability and osteoarthritis outcome score (HOOS) was used to describe patient-reported outcomes.

Results: Patient data was reviewed for 91 JIA patients under the age of 35 that underwent a primary THA at our institution between 1982 and 2011. Follow-up data was available for 56 patients. A preliminary analysis of 35 patients (60 primary THAs) revealed a mean time to follow-up of 12 years (Range: 2–23 years). The 10-year and 20-year implant survival was 80% (95% CI: 66%-89%) and 64% (95% CI: 46%-77%), respectively. Primary THA with standard implants had a longer survival compared to custom implants (p-value=0.02) with no other significant differences in implant survival stratified by patient age and sex, implant bearing surface, and use of cement for implant fixation. The mean HOOS scores were 89 (95% CI: 84–94) for pain, 87 (95% CI: 83–91) for symptoms, 86 (95% CI: 79–93) for ADLs, and 76 (95% CI: 69–83) for sports. Male patients reported better HOOS-Symptom scores compared to female patients (96 vs. 85, p-value=0.026), and patients with standard implants reported better HOOS-Pain (95 vs. 73, p-value <0.001) and HOOS-Symptom (91 vs. 78, p-value=0.016) scores compared to patients with custom implants.

Conclusion: THA is an excellent treatment option for JIA patients under the age of 35 with very good long-term implant survival and favorable patient-reported outcomes after surgery.

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Increasing Complexity of Patients Undergoing Primary Total Hip Arthroplasty in the U.S. Jasvinder A Singh[1] and David Lewallen[2]. [1]University of Alabama and VA Medical Center, Birmingham, AL, [2]Mayo Clinic college of medicine, Rochester, MN.

Background/Purpose: To examine the time-trends in key demographic and clinical characteristics of patients undergoing primary total hip arthroplasty (THA).

Methods: We used the data from the Mayo Clinic Total Joint Registry from 1993–2005 to examine the time-trends in demographics (age, body mass index (BMI)), medical (Deyo-Charlson index) and psychological comorbidity (anxiety, depression) and underlying diagnosis of patients undergoing primary THA. Chi-square test and analysis for variance were used. Multivariable-adjusted logistic regression (age, sex, comorbidity-adjusted) compared 1993-95 to other study periods. Odds ratio (OR) and 95% confidence interval (CI) are presented.

Results: The primary THA cohort consisted of 6,168 patients with 52% women. Compared to 1993-95, significantly more patients (by >2-times for most) in 2002-05 had: BMI≥40, 2.3% vs. 6.3%; depression, 4.1% vs. 9.8%; and anxiety, 3.4% vs. 5.7%; and significantly fewer had an underlying diagnosis of rheumatoid/inflammatory arthritis, 4.2% vs. 1.5% ($p^2$0.01 for all). In multivariable-adjusted models, compared to 1993-95, significantly more patients in 2003-05 had (all p-values^{2}0.01): BMI≥40, OR, 2.79 (95% CI: 1.85, 4.22); Deyo-Charlson Index≥3, 1.32 (1.07, 1.63); depression, 2.25 (1.66, 3.05); and anxiety, 1.71 (1.19, 2.15). Respectively, fewer patients had a diagnosis of RA/inflammatory arthritis: 0.28 (0.17, 0.46; p<0.01). Over the 13-year study period, Deyo-Charlson index increased by 22% (0.9 to 1.1) and the mean age decreased by 0.7 years (65.0 to 64.3) (p<0.01 for both).

Conclusion: Obesity, medical/psychological comorbidity and underlying diagnosis changed rapidly in primary THA patients over 13-years. Studies of THA outcomes and utilization should take these rapidly changing patient characteristics into account.

Disclosure: J. A. Singh, takeda, savient, 2, takeda, savient, regeneron, allergan, 5; **D. Lewallen**, Zimmer, Orthosonic and Osteotech, 8, Pipeline Biomedical, 5, DePuy, Stryker, Biomet and Zimmer., 2.

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Leg Length Inequality and Hip Osteoarthritis. Chan Kim[1], Jingbo Niu[1], Mary Clancy[2], Ali Guermazi[3], Michael C. Nevitt[4], Neil A. Segal[5], William F. Harvey[6], Cora E Lewis[7] and David T. Felson[8]. [1]Boston University, Boston, MA, [2]Boston University Sch Med, Boston, MA, [3]Boston University School of Medicine, Boston, MA, [4]UCSF (University of California, San Francisco), San Francisco, CA, [5]University of Iowa, Iowa City, IA, [6]Tufts Medical Center, Boston, MA, [7]University of Alabama Birmingham School of Medicine, Birmingham, AL, [8]University of Manchester, Manchester, United Kingdom.

Background/Purpose: Leg length inequality (LLI), a side-to-side difference in lower limb lengths, is common. In the Multicenter Osteoarthritis Study (MOST), in persons with LLI, the shorter limb was found to have an increased incidence, prevalence and progression of knee osteoarthritis (OA) compared to the longer limb. The shorter leg is likely to sustain increased impact force of the foot during gait thus transmitting a greater impulse up the ipsilateral leg. LLI is easily treatable and therefore could be a potentially modifiable risk factor for disease. However, the association of LLI and hip OA has not been prospectively studied. Therefore, we examined the association of LLI with hip OA in the MOST cohort.

Methods: The MOST cohort is a multicenter, longitudinal community based study of 3026 recruited for studying knee OA. Long limb films were obtained at baseline and 60 months, which were used to assess LLI and radiographic hip OA. Radiographic measurement of LLI is the gold standard measure. We defined LLI ≥ 1 cm based on previous literature, but we also assessed LLI ≥ 2 cm.

Radiographic hip OA was defined using UCSF criteria. Hips with prevalent JSN were defined as hips with any JSN at either superolateral or superomedial joint space at baseline. Hips with progressive JSN were defined as any with worsening JSN at 60 month follow-up. Associations between LLI and radiographic hip OA were assessed using logistic regression models with generalized estimating equations.

First, we examined cross-sectional baseline data. Because LLI may be generated by the existence of unilateral hip OA (which may slightly shorten the limb), we examined the longitudinal relationship of baseline LLI with incident hip OA and progressive JSN.

Results: Of the 3026 subjects, 125 subjects with either knee or hip replacements at baseline were excluded. Then, 55 subjects with missing LLI measurements were excluded (mostly due to poor quality films). We used radiographic OA data on both hips for all subjects, but for 17 subjects who had missing OA status for one hip, the contralateral hip was used in analyses. At baseline, neither LLI ≥ 1 cm nor 2 cm were associated with prevalent radiographic hip OA. In the longitudinal analyses, LLI ≥ 1 cm was not associated with incident radiographic hip OA. However, LLI ≥ 2 cm was associated with increased risk of incident radiographic hip OA (adjusted OR 7.13 [CI 95% 1.74,29.18]) for the shorter leg, but this was based on a small number in the group with LLI ≥ 2 cm (13 hips). LLI ≥ 2 cm increased risk for prevalent ipsilateral JSN (adjusted OR 5.49 [CI 95% 1.94,15.52]), LLI did not increase risk for progressive JSN (not shown).

Conclusion: LLI ≥ 1 cm was not associated with prevalent or incident radiographic hip OA or prevalent or progressive JSN. Although the sample size was small, LLI ≥ 2 cm was associated with increased risk for incident radiographic hip OA in the shorter leg and prevalent JSN in the shorter leg.

Tables

		Leg Length Inequality		
		< 1 cm	**≥ 1 cm**	**≥ 2 cm***
Prevalent Radiographic Hip OA (excluded total hip replacement as outcome)†				
Shorter leg	Hips, *n/n* (%)	202/3404 (5.9)	19/255 (7.5)	3/16 (18.8)
	Adjusted OR* (95% CI)	(reference)	1.09 (0.65, 1.83)	2.33 (0.66, 8.23)
Longer leg	Hips, *n/n* (%)	202/3404 (5.9)	14/256 (5.5)	3/17 (17.6)
	Adjusted OR* (95% CI)	(reference)	0.78 (0.44, 1.38)	2.25 (0.58, 8.73)
Incident Radiographic Hip OA (included total hip replacement as outcome)‡				
Shorter leg	Hips, *n/n* (%)	103/3169 (3.3)	10/234 (4.3)	3/13 (23.1)
	Adjusted OR* (95% CI)	(reference)	1.26 (0.66, 2.37)	**7.13 (1.74, 29.18)**
Longer leg	Hips, *n/n* (%)	103/3169 (3.3)	13/239 (5.4)	1/14 (7.1)
	Adjusted OR* (95% CI)	(reference)	1.58 (0.87, 2.84)	2.06 (0.31, 13.74)

Hips with prevalent JSN (excluded total hip replacement as outcome)†				
Shorter leg	Hips, *n/n* (%)	475/3404 (14.0)	45/255 (17.6)	8/16 (50.0)
	Adjusted OR* (95% CI)	(reference)	1.21 (0.85, 1.73)	**5.49 (1.94, 15.52)**
Longer leg	Hips, *n/n* (%)	475/3404 (14.0)	29/256 (11.3)	6/17 (35.3)
	Adjusted OR* (95% CI)	(reference)	0.71 (0.47, 1.07)	2.74 (0.85, 8.78)

n/n = hips with outcome/hips in leg-length inequality category
Adjusted for age, sex, BMI, and height
† Any subjects with either total knee or hip replacement at either leg excluded
‡ Any subjects with total knee at either leg excluded
* For ≥ 2 cm analysis, the group with ≥ 1 cm and < 2 cm is not shown.

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Measures of Hip Morphology Are Related to Development of Incident Radiographic Hip Osteoarthritis over 6 to 13 Year Follow-up: The Johnston County Osteoarthritis Project. Amanda E. Nelson[1], Jamie L. Stiller[1], Xiaoyan A. Shi[2], Kirsten M. Leyland[3], Jordan B. Renner[4], Todd A. Schwartz[5], Nigel K. Arden[3] and Joanne M. Jordan[6]. [1]University of North Carolina Thurston Arthritis Research Center, Chapel Hill, NC, [2]SAS Institute, Inc, Cary, NC, [3]NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, United Kingdom, [4]University of North Carolina Department of Radiology, Chapel Hill, NC, [5]University of North Carolina Gillings School of Global Public Health, Dept of Biostatistics, Chapel Hill, NC, [6]University of North Carolina, Chapel Hill, NC.

Background/Purpose: Alterations in hip morphology, such as femoroacetabular impingement, have been associated with incident hip OA and total hip replacement (THR), but have rarely been assessed in community-based samples and have never been assessed in African Americans (AA).

Methods: This case-control study was nested within a large community-based cohort. Case hips had Kellgren Lawrence grade (KLG)<3 on baseline supine pelvis radiographs and KLG≥3 (mild/moderate hip OA, or THR for OA) at the 1st or 2nd follow-up (mean 6 and 12.7 years, respectively) visit. Control hips had KLG<3 at both baseline and follow-up, with a gender/race distribution similar to cases. Validated software (Oxmorf) was used to assess 27 aspects of hip morphology. Unadjusted analyses comparing cases and controls included chi-squared and t-tests, as appropriate. Generalized estimating equations regression models, adjusted for age, race, BMI, and side were employed, accounting for within-person correlation.

Results: A total of 263 hips, 76 case and 187 control, were included from 136 individuals (25% male, 29% AA, mean age 62 ± 9 years and BMI 30 ± 6 kg/m^2). Case hips were more often right hips (67%, p<0.001), with no differences by age or BMI. Reliability for all measures was acceptable (intra-[ICC 0.7–1.00] and inter-reader ICC 0.5–1.00). Nearly all measures were significantly different by sex (p<0.03 in t-tests) so further analyses were sex-stratified; no interactions were seen for age, race, BMI, or baseline KLG.

For analyses by case/control status, we focused on 7 continuous and 3 categorical hip morphology measures (Table). Among men, higher baseline AP alpha angle, extrusion index, acetabular index, and modified triangular index height were associated with case status at follow-up, while greater baseline minimum joint space width (mJSW) and coxa profunda had a protective effect. Among women, higher AP alpha angle, lower mJSW, presence of protrusio acetabuli and the triangular index sign were significantly associated with case vs. control status. Strength of some associations varied by side (data not shown). With all measures simultaneously included in the model, the associations between AP alpha angle and mJSW remained significant for both men and women, as did the triangular index sign among men only.

Conclusion: Cam-type morphology (higher AP alpha angle and triangular index) and smaller mJSW were associated with incident radiographic hip OA in both men and women, with no differences by race. Newly identified variations in these associations by side are of interest and will be the subject of future work.

Table. Associations between measures of hip morphology and case/control status for men (left) and women (right)

	MEN				WOMEN			
Hip morphology measure	Case (n=18)	Control (n=49)	p values	Adjusted*	Case (n=58)	Control (n=138)	p Values	Adjusted*
Continuous	*mean(SD)*	*mean(SD)*	*p*[a]	*OR (95% CI)*	*mean(SD)*	*mean(SD)*	*p*[a]	*OR (95% CI)*
AP Alpha angle (°)	69.64 (21.1)	57.01 (16.0)	0.012	1.05 (1.02, 1.08)[c]	65.34 (24.3)	50.27 (15.4)	<0.001	1.04 (1.02, 1.06)[c]
Minimum JSW (mm)	3.50 (1.0)	3.97 (0.7)	0.038	0.50 (0.23, 1.12)[c]	3.11 (0.9)	3.63 (0.8)	<0.001	0.38 (0.22, 0.67)[c]
Extrusion index (ratio)[f]	0.23 (0.1)	0.20 (0.1)	0.029	2.84 (0.91, 8.90)	0.15 (0.1)	0.14 (0.1)	0.248	0.94 (0.58, 1.53)
Femoral shaft angle (°)	128.5 (5.8)	130.0 (5.9)	0.387	0.96 (0.88, 1.04)	131.5 (6.4)	131.9 (5.8)	0.678	0.98 (0.93, 1.04)
Acetabular index (mm)	8.88 (10.1)	2.75 (5.9)	0.042	1.21 (1.05, 1.40)	2.61 (9.6)	1.14 (6.6)	0.222	1.02 (0.97, 1.07)
Lateral Center Edge Angle (°)	28.65 (9.8)	31.01 (6.7)	0.267	0.93 (0.83, 1.03)[c]	32.84 (10.4)	32.84 (7.5)	0.998	1.01 (0.97, 1.05)
Modified Triangular Index (mm)	27.60 (2.6)	26.44 (2.8)	0.138	1.21 (1.03, 1.46)	21.38 (3.0)	21.08 (2.2)	0.424	1.08 (0.93, 1.24)
Categorical	*n(%)*	*n(%)*	*p*[a]	*OR (95% CI)*	*n(%)*	*n(%)*	*p*[a]	*OR (95% CI)*
Crossover sign	7 (39)	28 (57)	0.185	0.45 (0.15, 1.31)	16 (28)	40 (29)	0.843	1.03 (0.50, 2.13)
Deep acetabulum	-	-	0.022[e]	-	-	-	0.025[e]	-
Protrusio	0 (0)	0 (0)	-	-	9 (17)	6 (4)	-	4.55 (1.13, 18.33)
Profunda	5 (28)	29 (59)	-	0.23 (0.07, 0.74)	38 (70)	112 (82)	-	0.99 (0.40, 2.44)
Triangular Index	3 (18)	3 (6)	0.172[e]	3.41 (0.66, 17.54)	6 (10)	2 (1)	0.009[e]	8.05 (2.36, 27.47)

*adjusted for age, BMI, race, side
[a] p value from t-test comparing case and control by sex
[b] p value from chi-squared test comparing case and control by sex
[c] Extrusion index (ratio) was multiplied by 10 in adjusted analyses
[d] p value from Fisher exact test due to small cell counts
[e] significant interaction between FAI measure and side
SD=standard deviation; OR=odds ratio; AP=anteroposterior; JSW=joint space width

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Is Schuss View Alone Enough for the Diagnosis of Femorotibial Osteoarthritis ? the Khoala Cohort Study. Christian Roux[1], Bernard Mazieres[2], Evelyne Verrouil[2], Anne-Christine Rat,[3], Patrice Fardellone[4], Bruno Fautrel[5], Jacques Pouchot[6], Alain Saraux[7], Francis Guillemin[8], Liana Euller Ziegler[9] and Joel Coste[10]. [1]Hopital Archet 1 - Université Nice Sophia Antipolis, Nice, France, [2]CHU Toulouse, Toulouse, France, [3]Université de Lorraine, Université Paris Descartes, Apemac, EA 4360, Nancy, France, [4]Hôpital Nord, C.H.U. d'Amiens, Amiens, France, [5]CHU - Hôpital Pitié-Salpêtrière, Paris, France, [6]Hopital Louis Mourier, Colombes, FRANCE, France, [7]CHU de la Cavale Blanche and Université Bretagne occidentale, Brest Cedex, France, [8]INSERM, Centre d'Investigation Clinique - Epidémiologie Clinique (CIC-EC) CIE6, Nancy, France, [9]CHU de Nice -Université Nice Sophia Antipolis, Nice, France, [10]CHU Hotel Dieu, Paris, France.

Background/Purpose: Associating an anteroposterior (AP) extended-knee X-ray with a semiflexed AP or posteroanterior (PA) view is considered the gold standard for radiologically diagnosing tibiofemoral osteoarthritis (OA), but limited data only support the diagnostic value of this approach. Our objective is to compare the contribution of these different views to diagnosis.

Methods: From 2007 to 2009, a population-based two-phase prevalence study was conducted to create the KHOALA cohort (Knee and Hip OA long-term assessment) (1). It was conducted in 6 French centers (Amiens, Brest, Nancy, Toulouse, Nice, and Paris). For the current work, we included the first 350 participants aged 40 to 75 years old regardless of their Kellgren Laurence (KL) stage.

A first reading of Schuss + standard AP views was carried out by an expert rheumatologist (BM). A second reading of Schuss X rays only was carried out remotely, (blinded to the results of the first lecture), by the same examiner. Analysis focused on the comparison of KL stage of each knee, as well as on osteophytes detection and localization: Medial Condyle (MC), Lateral (LC), Medial Tibial Plateau (MTP) or Lateral (LTP) (all ranked from 0 to 3), Joint space narrowing (JSN) (ranked from 0 to 4) and bone sclerosis (MC, LC, MTP, LTP).

Results: 350 subjects were included. Mean age was 58 years (8.6), Body Mass Index (BMI) was 29.8 (5.4). Time between the two readings was 2 years.

	Standard AP + Schuss		Schuss		Standing AP view	
KL stage	Right Knee n (%)	Left Knee n (%)	Right Knee n (%)	Left Knee n (%)	Right knee n (%)	Left knee n (%)
KL≥ 2	**110 (31)**	**87 (25)**	**83 (24)**	**64 (18)**	**95 (27)**	**72 (21)**
Osteophytes						
MC	**31 (9)**	**30 (9)**	**32 (9)**	**32 (9)**	**29 (8)**	**28 (8)**
LC	**10 (3)**	**12 (3)**	**20(6)**	**17 (5)**	**17 (5)**	**10 (3)**
MTP	**39 (11)**	**35 (10)**	**38 (11)**	**28 (8)**	**22 (9)**	**32 (9)**
LTP	**25 (7)**	**23 (6)**	**21 (6)**	**16 (5)**	**21 (6)**	**18 (5)**
JSN	**71 (20)**	**60 (17)**	**60 (17)**	**52 (15)**	**42 (12)**	**37 (11)**

Comparing two readings showed a significantly higher proportion of KL ≥ 2 patients when the two X-ray views were combined (right knee: p < 0.0001; left knee: p < 0.001). In contrast, a more in-depth analysis taking into account JSN, osteophytes, and bone condensation did not confirm this difference. A comparison of Schuss versus AP alone demonstrated the superiority of the Schuss view in evaluating JSN (p=0.0001 and p=0.0001) with no difference in osteophyte detection. A lower rate of JSN detection with Schuss view X-ray alone in high-BMI patients is suggested.

Conclusion: In our study, Schuss is superior to AP view to detect knee OA. Adding an AP view to the Schuss view leads to higher number of grades 1(not confirmed osteophytes). The marked differences in KL are probably due to KL scale limitations. No differences appear in JSN and osteophyte detection, the main features of OA. Due to the higher cost and radiation exposure involved in associating views, the Schuss view alone tends to be used for OA diagnosis in the general population.

Ref.

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Predictors of Radiographic Progression of Interphalangeal Finger Joints in Erosive Osteoarthritis: A Prospective Study. Paulien Meersseman, Celine Van De Vyver, Gust Verbruggen, Dirk Elewaut and Ruth Wittoek. Department of Rheumatology Ghent University Hospital, Ghent, Belgium.

Background/Purpose: Predictors of radiographic progression in erosive osteoarthritis (OA) are important in identifying patients with high risk of disease activity and consequently functional loss. Disease duration, number of tender joints and number of joints with palpable effusion at baseline are already identified as clinical predictors of radiographic progression. The aim of this study is to confirm the existing predictors in a prospective cohort. Additionally, potentially other clinical and radiographic predictors will be identified.

Methods: One hundred and twelve patients with erosive OA were selected from an already existing cohort that was recruited from April 2007 through January 2010 at the Ghent University Hospital. X-rays, clinical and demographic data of the 1st assessment were present. All patients were reassessed between January 2014 and March 2014. All interphalangeal finger joints on both radiographs were scored according to the Verbruggen and Veys method. Radiographic progression was defined as a joint progressing from at least one anatomical phase, excluding the progression from a 'N' phase to a 'S' phase. A generalized estimating equation (GEE) model with a binary logistic function was used to explore the following potential clinical and radiographic predictors on joint level: disease duration (≤5 years, >5 years), presence of erosive joints in the dominant hand, presence of painful joints, tender joints, or joints with palpable effusion, the presence of a joint in 'J' phase and in 'E' phase. All variables were dichotomous (present or absent).

Results: Three clinical and two radiographic predictors were retained: a painful joint, a tender joint, a joint with palpable effusion, a joint in 'J' phase and a joint in 'E' phase. A joint with palpable effusion was the strongest clinical predictor (odds ratio (OR): 2.474) (table 1). A joint in 'E' phase was the strongest radiographic predictor (OR: 90.628) (table 2).

Table SEQ Table * ARABIC 1: Clinical predictors for radiographic progression by GEE modeling

Variables	GEE-OR (95% CI)	P-value
Disease duration (≤5 years, >5 years)	1.028 (0.711–1.487)	0.882
Erosive joint in dominant hand	0.879 (0.671–1.151)	0.348
Painful joint	1.529 (1.013–2.310)	0.043
Tender joint	1.973 (1.344–2.897)	0.001
Joint with palpable effusion	2.474 (1.419–4.314)	0.001

CI: confidence interval.

Table SEQ Table * ARABIC 2: Radiographic predictors for radiographic progression by GEE modeling

Variables	GEE-OR (95% CI)	P-value
Presence of 'J' phase	17.418 (8.785–34.538)	<0.001
Presence of 'E' phase	90.628 (40.109–204.781)	<0.001

Conclusion: A painful joint, a tender joint, a joint with palpable effusion, 'J' phase and 'E' phase were identified as predictors of radiographic progression in erosive OA. The strongest clinical and radiographic predictor was a joint with palpable effusion and the presence of an 'E' phase respectively. These predictors should be considered when selecting patients for therapeutic trials with potential disease-modifying osteoarthritic drugs.

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Ultrasonographic Predictors for Clinical and Radiological Progression in Knee Osteoarthritis after 2 Years Follow up. Karen Bevers[1], Johanna E. Vriezekolk[2], J.W.J. Bijlsma[3], Els van den Ende[2] and Alfons A. den Broeder[2]. [1]St Maartenskliniek, Nijmegen, Netherlands, [2]Sint Maartenskliniek, Nijmegen, Netherlands, [3]University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Pathophysiology of osteoarthritis (OA) is not completely understood. Identifying patients with progression might help to direct future research on therapeutic interventions. As OA is known to affect the entire joint including soft tissue structures, structural changes in these tissues, visualised by ultrasound (US), might predict progression. The aim of this study was to investigate the association between a set of US features and radiographic and clinical progression of knee OA after two years of follow up.

Methods: A total of 125 patients fulfilling American College of Rheumatology clinical criteria for knee OA[1] underwent US examination of the most symptomatic knee. The US protocol included assessment of synovial hypertrophy, joint effusion, infrapatellar bursitis, Baker's cyst, medial meniscus protrusion and cartilage thickness. Clinical progression was defined using the inverse OARSI responder criteria [2]or progression to total knee replacement. A 2-point or more increase in Altman score or progression to total knee replacement was considered radiologic progression. Regression analyses were performed with US features as independent variables and progression (two separate models for clinical progression and radiographic progression) as dependent variable.

Results: A total of 31 (25%) patients fulfilled the criteria of clinical progression and 60 (48%) patients fulfilled the criteria of radiologic progression. Presence of Baker's cyst showed a statistically significant association with clinical (OR: 3.07; 95% CI: 1.21 – 7.78) as well as radiological (OR: 2.84; 95% CI: 1.17 – 6.90) progression. Synovial hypertrophy showed a weaker but consistent association with clinical- as well as radiologic progression (OR: 2.11; 95% CI: 0.80 – 5.57)

Conclusion: We demonstrated a longitudinal association between Baker's cyst (and to a lesser extent synovial hypertrophy) at baseline and radiological and clinical progression after two years. When confirmed, these inflammatory variables might be candidate features to help define knee OA patients with worse prognosis.

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Natural History and Clinical Significance of Meniscal Tears over 8 Years in a Largely Non-Osteoarthritic Cohort. Hussain Ijaz Khan[1], Dawn Aitken[1], Changhai Ding[2], Leigh Blizzard[3], Jean-Pierre Pelletier[4], Johanne Martel-Pelletier[4], Flavia Cicutinni[5] and Graeme Jones[2]. [1]Menzies Research Institute Tasmania, University of Tasmania, Hobart, 7000, Australia, [2]Menzies Research Institute Tasmania, University of Tasmania, Hobart,7000, Australia, [3]Menzies Research Institute Tasmania, University of Tasmania, Hobart, Tasmania, Australia, [4]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [5]Monash University, Melbourne, Australia, Melbourne, Australia.

Background/Purpose: Meniscal tears are a key player in knee osteoarthritis (OA) and family history of the disease has been shown to play an important role. However, there is limited longitudinal data on the natural history of meniscal tears. The aim of this study was to track natural history of meniscal tears over 8 years, describe the association with change in pain and describe structural and non-structural predictors of change in meniscal tears.

Methods: 220 participants [mean age 47 (28–63); 57% female] were studied at baseline and 8 years. Approximately half were the adult offspring of subjects who had a knee replacement performed for knee OA and the remaining half were randomly selected controls without a family history of OA. Meniscal tears were evaluated, using T-1 weighted fat saturated MRI, on a 0–2 (0=absence; 1=simple; 2=complex tear) scale within 6 defined regions: anterior horn, body, and posterior horn at both medial and lateral menisci. Cartilage volume/defects, bone marrow lesions (BMLs), meniscal extrusion and effusion were assessed on MRI and joint space narrowing (JSN) and osteophytes on radiographs using standard protocols. Pain was assessed using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Results: Using updated methodology, 22% of the participants had a meniscal tear at any site at baseline, without a significant difference between the two groups at any site. 16% of the participants had any increase in meniscal score (incident tears + increase from baseline score) over 8 years. Offspring had a significantly higher change in mean meniscal score compared to controls over 8 years **(total knee score: offspring= 0.493, controls= 0.164, p=0.034)**. Change in meniscal tears was independently associated with worsening pain over 8 years (Table 1). There was also a significant offspring-control interaction **(all p<0.05)** at all sites, with offspring having a significantly higher increase in pain on WOMAC scale per unit change in tears compared to controls (Table 1). Higher BMI at baseline was independently associated with a greater risk of increase in mean meniscal score **(total**

knee: RR= 1.10 (1.04, 1.16)). Change in total medial tears was associated with cartilage loss over 8 years in the medial (tibial + femoral) compartment **(β= -176 (−302, -49))** only. Change in tears at all sites was associated with change in compartment specific and total knee BMLs **(total knee: β=+0.39 (+0.26, +0.53))**. Furthermore, change in tears showed the strongest independent correlation with change in both JSN **(ρ=+0.37, p= <0.01)** and osteophytes **(ρ=+0.31, p= <0.01)** in the medial compartment.

Conclusion: In this midlife cohort, meniscal tears are common. Change in tears is independently associated with change in pain, BMLs, cartilage volume and radiographic OA. In turn, change in tears is influenced by family history of OA and BMI but not history of knee injury.

Table 1: Association between change in meniscal tears and change in pain over 8 years

	Change in pain over 8 years	
Change in tears (site)	**Unadjusted β (95%CI)**	**Adjusted[a] β (95%CI)**
Total medial meniscus	**+3.81 (+2.45, +5.20)**	**+2.84 (+1.1, +4.57)**
Offspring	**+4.93 (+3.41, +6.46)**	**+3.72 (+1.64, +5.79)**
Controls	−0.87 (−3.91, +2.17)	−1.19 (−4.35, +1.96)
Total lateral meniscus	**+2.16 (+0.19, +4.14)**	+1.60 (−1.40, +4.55)
Offspring	**+3.14 (+0.52, +5.75)**	+2.52 (−0.89, +5.92)
Controls	−0.02 (−3.20, +3.20)	+0.93 (−2.31, +4.17)
Total (medial + lateral) anterior	**+6.76 (+4.23, +9.29)**	**+6.62 (+3.72, +9.54)**
Offspring	**+7.78 (+4.94, +10.6)**	**+8.10 (+1.49, +11.02)**
Controls	+0.17 (−6.36, +6.70)	+0.84 (−6.09, +7.76)
Total (medial + lateral) body	**+4.21 (+1.95, +6.47)**	**+3.20 (+0.44, +5.96)**
Offspring	**+8.18 (+5.24, +11.13)**	**+6.44 (+2.83, +10.05)**
Controls	−1.43 (−4.66,+1.79)	−1.80 (−5.81, +2.20)
Total (medial + lateral) posterior	**+5.37 (+2.52, +8.22)**	**+3.76 (+0.37, +7.15)**
Offspring	**+5.78 (+2.38, +9.18)**	+2.79 (−1.33, +6.92)
Controls	+2.07 (−5.54, +9.69)	−0.96 (−10.33, +8.41)
Total knee	**+2.87 (+1.84, +3.90)**	**+2.94 (+1.49, +4.37)**
Offspring	**+3.73 (+2.56, +4.89)**	**+3.13 (+1.35,+4.93)**
Controls	−0.48 (−2.72, +1.75)	−1.27 (−4.49, +1.95)

[a] =Adjusted for age, sex, bmi, offspring-control status, change in BMLs, change in cartilage defects, change in extrusion, change in effusion, history of knee injury, bone area and ROA at baseline
(Note: Significant offspring-control interaction at all sites for the association between change in meniscal tears and change in pain)

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Risk Factors for Increased Extrusion of the Meniscus Body in Subjects Free of Radiographic Knee Osteoarthritis: 6-Year MRI Data from the Osteoarthritis Initiative. Fan Zhang[1], Jaanika Kumm[2], Fredrik Svensson[1], Aleksandra Turkiewicz[1], Richard Frobell[1] and Martin Englund[1]. [1]Lund University, Lund, Sweden, [2]Tartu University, Tartu, Estonia.

Background/Purpose: Meniscal body extrusion on knee MRI is strongly associated with the development and progression of knee osteoarthritis (OA). However, there is very limited evidence of risk factors for the development of meniscal extrusion.

Thus, our objective was to determine risk factors associated with increased meniscal body extrusion using quantitative measurements from knee MRIs in subjects free of radiographic OA at baseline. We hypothesized that body mass index (BMI), sex, age, and incident ipsilateral meniscal tear are possible risk factors.

Methods: Data for these analyses are from the OAI public use data. A cohort of 340 subjects with age between 45 and 55 (mean age 50 years, 51% women, mean BMI 26.7) with bilateral knee MRIs available at the baseline, 24 months, 48 months, and 72 month exam and no radiological signs of knee OA (both knees' KL grade = 0 at baseline) were selected. We assessed mid-coronal IW 3-Tesla MR images from baseline and the 72 month follow-up visit. One observer measured widths of the tibia plateau and meniscal body extrusion to the closest 0.1 mm using Sante DICOM Editor (64-bit) software (intraobserver ICC ranging from 0.75 to 0.99). One reader assessed meniscal integrity (presence of tear) at all four time points. To take into account knee size, we calculated an extrusion index as ([meniscal body extrusion]/[tibia width]*100). We evaluated risk factors for increased meniscal body extrusion index from baseline to the 72-month exam by a multivariable linear regression mixed model for medial and lateral compartment, respectively, adjusting for the fact that the same person contributed with two knees and with the covariates: clinical site, age, sex, baseline BMI, baseline extrusion index, and incident meniscal tear.

Results: Mean (SD) medial extrusion index in the right knee at baseline and 72-month follow-up was 3.43 (1.23) and 3.32 (1.30), respectively (similar values in the left knee). The corresponding values for lateral compartment were 1.54 (1.31) and 1.13 (1.52). In the medial compartment we found that female sex (0.35; 95% confidence interval [CI] 0.16–0.53), incident meniscal tear (0.29; 95% CI 0.22–0.55), and the baseline value of the extrusion index (0.63; 95% CI 0.56–0.70) were associated with increased extrusion index by the 72 month follow-up. Results were similar for the lateral compartment (data not shown).

Conclusion: We found female sex, incident meniscal tear, and higher baseline value of extrusion to be risk factors for increased meniscal body extrusion in middle-aged subjects free of radiographic OA. Findings provide new evidence of the causal chain of events in the "meniscal pathway" to knee OA.

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Changes in Knee Compartment Distriubtion of Cartilage Loss and Bone Marrow Lesions over 7 Years: The MOST Study. Joshua Stefanik[1], Ali Guermazi[2], Jingbo Niu[1], Frank Roemer[3], C.E. Lewis[4], Neil A. Segal[5], Michael Nevitt[6] and David T. Felson[2]. [1]Boston University, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Klinikum Augsburg, Augsburg, Germany, [4]University of Alabama at Birmingham, Birmingham City, AL, [5]University of Iowa, Iowa City, IA, [6]UCSF, San Francisco, CA.

Background/Purpose: Knee osteoarthritis (OA) occurs in both the patellofemoral joint (PFJ) and tibiofemoral joint (TFJ). Little is known about the natural history of OA and it has been hypothesized, based on findings from radiographic studies, that OA occurs first in the PFJ and subsequently progresses to involve the TFJ. This has not been evaluated using MRI, which is more sensitive than radiographs to identify structural damage, particularly in the PFJ. The purpose of this study was to describe patterns of change in cartilage loss and bone marrow lesions (BMLs) among knee joint compartments over 7 years. Specifically, we describe whether disease remains isolated to one compartment or develops in the other, and which compartment tended to be initially involved.

Methods: The Multicenter Osteoarthritis (MOST) Study is a NIH-funded longitudinal cohort study of 3,026 individuals with or at risk for knee OA. Participants had MRI of their knee at baseline and 84-month of follow up. Two musculoskeletal radiologists used the Whole Organ Magnetic Resonance Score (WORMS) to assess cartilage morphology and BMLs in the PFJ and TFJ at baseline and 7 years. At baseline and 84-months, knees were categorized as having full-thickness cartilage loss (any region within a compartment with WORMS 2.5, 5 or 6) isolated to the PFJ, isolated to the TFJ, mixed (both PFJ and TFJ) or no full-thickness loss in either compartment. In sensitivity analyses any cartilage loss (WORMS ≥2) and any BML (WORMS ≥1) were used to categorize disease in knee compartments.

Results: 994 knees had complete MRI readings at baseline and 84-months. The mean age and BMI at baseline were 61.7 (±7.5) years and 29.7 (± 4.7) kg/m^2, respectively, and 61% were female. Among 570 knees without full-thickness cartilage loss at baseline, the incidence of isolated PFJ, isolated TFJ and mixed full-thickness cartilage loss was 12, 13 and 5%, respectively. The remaining 70% did not develop full-thickness cartilage loss at follow up. Among 334 knees that had full-thickness cartilage loss isolated to the PFJ or TFJ at baseline, only 62 (19%) developed full-thickness cartilage loss in the other compartment while 272 (81%) continued to only have the initial compartment affected with full-thickness cartilage loss. Among 62 knees that started with isolated full-thickness loss in the PFJ or TFJ and developed full-thickness cartilage loss in the other compartment, it more often progressed from the PFJ 44 (71%) than from the TFJ 18 (29%). Similar patterns were seen in sensitivity analyses when disease was defined using any cartilage loss and any BML.

Conclusion: Over 7 years of follow-up it is uncommon for cartilage loss and BMLs to "spread" to the other compartment in the knee. Furthermore, of knees that develop cartilage loss and BMLs in the other compartment, most knees start with damage isolated to the PFJ, suggesting that mixed disease may start in the PFJ.

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Correlates of Knee Bone Marrow Lesions in Younger Adults. Benny Samuel Eathakkattu Antony[1], Graeme Jones[2], Alison Venn[3], Lyn March[4], Flavia Cicutinni[5], Andrew Halliday[6], Leigh Blizzard[3], Marita Cross[7], Terry Dwyer[8] and Changhai Ding[2]. [1]Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia, [2]Menzies Research Institute Tasmania, University of Tasmania, Hobart,7000, Australia, [3]Menzies Research Institute Tasmania, University of Tasmania, Hobart, Tasmania, Australia, [4]Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, Australia,

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Background/Purpose: Bone marrow lesions (BMLs) of the knee joint are a key player in osteoarthritis of the knee. However, little is known of their determinants, especially in young adults. The aim of this study was to examine the structural and functional correlates of BMLs in younger adults including physical activity and to determine whether bone mass, cholesterol and hormones measured 5 years prior are associated with current BMLs.

Methods: Subjects broadly representative of the Australian population (n=330, aged 31–41 years, female 48.7%) were selected from the Childhood Determinants of Adult Health study. They underwent T1 and T2-weighted fat- suppressed magnetic resonance imaging in their knee. BMLs, cartilage defects, meniscal tears and cartilage volume were measured. Knee pain was assessed by self-administered Western Ontario and McMasters osteoarthritis index (WOMAC) questionnaire. Physical activity was measured by IPAQ questionnaires at the time of MRI. Heel bone mass, cholesterol and hormone levels (in females) were assessed 5 years prior.

Results: The prevalence of any BMLs in the knee joint was 17%. Cross-sectionally, any BML in the knee was associated with age (PR: 1.09, 95% CI: 1.00, 1.19), previous knee injury (medial tibiofemoral BMLs PR: 2.20, 95% CI: 1.03, 4.71) and total WOMAC knee pain (PR: 1.05, 95% CI: 1.02, 1.09). BMLs were associated with other structural abnormalities such as total knee cartilage defects (PR: 2.65, 95% CI: 1.47, 4.80) and total meniscal tears (PR: 1.70, 95% CI: 0.99, 2.94).

High Density Lipoprotein (HDL) cholesterol measured 5 years prior was negatively associated with any BML (PR: 0.36, 95% CI: 0.15, 0.87). Testosterone measured 5 years prior in females (PR: 0.99, 95% CI: 0.99, 1.00) and speed of sound in both sexes (bone mass, PR: 0.98, 95% CI: 0.97, 0.99) were negatively associated with femoral BMLs. Moderate physical activity was protective (PR: 0.93, 95% CI: 0.87, 0.99) while vigorous activity showed a deleterious trend (PR: 1.01, 95% CI: 1.00, 1.02) with BMLs as we reported in older and middle aged adults. All these models were adjusted for age, gender, BMI, duration of follow-up and injury.

Conclusion: BMLs in young adults are associated with increased knee symptoms, a history of injury and other knee structural lesions. Moderate physical activity (not vigorous) may be protective with BML. A higher bone mass and HDL cholesterol in both sexes and testosterone in women may be protective with the development of BMLs in young adults.

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Physical Performance and Obesity Measures Are Associated with Tibial Cartilage Volume and Explains the Sex Difference in Cartilage Volume.

Benny Samuel Eathakkattu Antony[1], Alison Venn[2], Flavia Cicutinni[3], Lyn March[4], Leigh Blizzard[2], Terry Dwyer[5], Marita Cross[6], Graeme Jones[7] and Changhai Ding[7]. [1]Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia, [2]Menzies Research Institute Tasmania, University of Tasmania, Hobart, Tasmania, Australia, [3]Monash University, Melbourne, Australia, Melbourne, Australia, [4]Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, Australia, [5]Murdoch Children's Research Institute, Melbourne, Australia, [6]University of Sydney Institute of Bone and Joint Research, Royal North Shore Hospital, Sydney, Australia, [7]Menzies Research Institute Tasmania, University of Tasmania, Hobart,7000, Australia.

Background/Purpose: The factors associated with knee cartilage volume in younger population are insufficiently explored. The aims of this study were to describe the associations between physical activity, physical performance, body composition, inflammatory and hormonal factors and tibial cartilage volume and to explore if these factors explained the sex difference in tibial cartilage volume observed in young adults.

Methods: Subjects broadly representative of the Australian population (n=328, aged 31–41 years, female 48.7%) were selected from the Childhood Determinants of Adult Health study. They underwent T1 and T2 weighted fat-suppressed magnetic resonance imaging (MRI) scans of their knees. Tibial bone area and cartilage volume were measured from MRI. Physical activity (long version of IPAQ questionnaires) and physical performance measures such as long jump, leg muscle strength, and physical work capacity at 170 heartbeats per minute (PWC_{170}) were measured. Sex hormone binding globulin (SHGB, females only), testosterone (females only), C-reactive protein and fibrinogen were measured 5 years prior. Fat mass and lean mass were calculated from skinfold.

Results: After adjustment for age, sex, BMI, injury, tibial bone area and duration of follow-up, physical performance measures including PWC_{170} (β: 3.4 mm^3, 95% CI: 1.1, 5.8) and long jump (β: 4.3 mm^3, 95% CI: 0.5, 8.0) measured 5 years prior were positively associated with tibial cartilage volume. Physical activity measures (hr/week) including total physical activity (β: 18.0 cm^3, 95% CI: 7.9, 28.2), vigorous (β: 32.1 mm^3, 95% CI: 7.9, 56.4), moderate (β: 20.6 mm^3, 95% CI: 0.8, 40.3) and walking (β: 23.7 mm^3, 95% CI: 4.4, 43.1) measured 5 years prior were positively associated with tibial cartilage volume. The associations of physical activity were independent of fitness levels and current physical activity level.

Lean body mass (β: 26.4 mm^3, 95% CI: 13.6, 39.1) was positively and fat mass (β: -11.8 mm^3, 95% CI: -22.2, -1.4) was negatively associated with cartilage volume. Fibrinogen was negatively associated with the cartilage volume (β: -0.15 mm^3, 95% CI: -0.28, -0.018). SHBG in females was positively (β: 0.67 mm^3, 95% CI: 0.14, 1.2) and free androgen index in females was negatively associated with tibial cartilage volume.

Males had greater tibial cartilage volume than females in adjusted analysis. The magnitude of this association (β of adjusted analysis) decreased by 54%, 47%, 42%, 37%, and 24% after further adjustment for lean body mass, leg strength, fat mass, $PWC_{170}$and fibrinogen, respectively, but remained largely unchanged after adjustment for other factors.

Conclusion: Lean mass, physical activity and physical performance measures are beneficially, while obesity measures and fibrinogen are negatively associated with tibial cartilage volume in young adulthood. The sex difference in tibial cartilage volume is largely explained by variations in body composition and physical performance measures. Physical activity measured 5 years prior was independent of the fitness and current physical activity levels, suggesting cartilage development in younger life can be modified by environmental intervention.

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Preliminary Assessment of Predictive Validity of Cartilage Thickness MRI Biomarkers in Knee OA - the Fnih OA Biomarkers Consortium.

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Background/Purpose: We sought to investigate if cartilage thickness change over 24 months predicts clinically relevant progression (radiographic and/or symptomatic) in knee OA over a 48 month period.

Methods: The OA Biomarkers Consortium undertook a nested case-control study of progressive knee OA within the Osteoarthritis Initiative (OAI). Main inclusion criteria were KLG 1, 2 or 3 at baseline and availability of knee radiograph and magnetic resonance imaging (MRI) at baseline and 24 months. The primary case group (n=194) was defined by the combination of knee radiographic progression (medial tibiofemoral joint space loss (mTF JSL) >= 0.7mm) **AND** pain progression (persistent worsening in WOMAC pain score, reaching a MCID threshold of 9 points on a 0–100 scale), each achieved for the first time at the 24, 36 or 48 month follow-up compared to baseline; referred to as "JSL and pain progressor". We defined two additional case subsets in order to distinguish structural from pain progression: 103 subjects with JSL but no pain increase comprised "JSL only progressors": and 103 with a persistent increase in pain but no JSL comprised "Pain only progressors". "Nonprogressors" (n=200) were participants with a knee eligible for the study that did not meet either progression definition (pain or mTF JSL). Manual segmentation of the femorotibial cartilages was performed by trained readers to generate cartilage thickness. The measures used in this analysis were (i) change in cMFTC (central medial femorotibial compartment), and (ii) change in ccMF (central medial femur) and cMT (central medial tibia). Association between cartilage thickness measures and progressors vs nonprogressors was assessed using a logistic regression model

adjusting for baseline age, sex, BMI, KLG and baseline pain level. Additional analyses were conducted to detect marginal effects of cartilage thickness on changes in pain and mTF JSL.

Results: Participants had mean age of 61.5 years, 59% female and the majority were obese. Changes in cartilage thickness from BL to 24 months in the cMFTC, ccMF and cMT were greater for all three progressor groups combined compared to nonprogressors and significantly associated with increased odds of being a progressor (Table). The ORs for cartilage thickness changes ranged from 1.6 to 2.8, with the largest ORs associated with cartilage thickness changes in the ccMF OR 2.8 (95%CI 2.1 to 3.7). Further analysis suggested that these associations were with structural progression and not pain progression.

Table. Change in cartilage thickness at 24 months and prediction of case control status *OR (95% CI) p value*. ORs represent the change in odds of being a progressor per 1SD increase of normalized changes in cartilage thickness.

Region	All progressors (n=400) vs. nonprogressors (n=200)	Nonprogressors (n=200)	Pain only progressor (n=103)	JSL only progressor (n=103)	JSL and pain progressor (n=194)
Change in cMFTC	**2.5 (1.9, 3.3)**	ref	0.9 (0.6, 1.3)	**3.8 (2.7, 5.4)**	**3.8 (2.7, 5.3)**
Change in ccMF	**2.8 (2.1, 3.7)**	ref	1.0 (0.6, 1.5)	**4.0 (2.8, 5.7)**	**3.8 (2.7, 5.4)**
Change in cMT	**1.6 (1.3, 1.9)**	ref	0.8 (0.6, 1.2)	**1.8 (1.4, 2.4)**	**1.9 (1.5, 2.5)**

Conclusion: Changes in cartilage thickness markers over 24 months clearly differentiate progressors from nonprogressors. These associations are largely attributable to mTF JSL and not to pain increases.

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Association Between Baseline External Knee Adduction and Flexion Moments during Gait and Medial Tibiofemoral Cartilage Thickness Loss over Two Years in Persons with Knee Osteoarthritis (OA).

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Background/Purpose: The external knee adduction moment (KAM) during gait has been characterized as a surrogate for dynamic medial knee load and is believed to be a risk factor for medial knee OA disease progression. By incorporating both load magnitude and duration, KAM impulse may provide a cumulative measure of KAM sustained during each step of walking. A reduction in KAM may be accompanied by a deleterious increase in the external knee flexion moment (KFM). Few longitudinal studies have evaluated the association between KAM impulse and peak KFM and subsequent medial OA disease progression. We hypothesized that in persons with knee OA, greater baseline peak KAM, KAM impulse, and peak KFM during gait are each associated with baseline-to-2-year worsening of medial cartilage thickness loss.

Methods: Participants had knee OA (K/L grade equal or greater than 2 in at least 1 knee). Baseline knee kinematics and kinetics during gait were recorded using an 8-camera Digital Real-Time Eagle motion analysis system, and 6 AMTI force plates; inverse dynamics used to compute peak KAM, KAM impulse, and peak KFM. MRI scans of both knees were done at baseline and 2-year visits. Regions of interest (ROI) were the entire medial tibial and weightbearing femoral surfaces; tibial external, central, and posterior subregions and femoral external and central subregions. Disease progression in each ROI was analyzed as: 1) baseline-to-2-year cartilage thickness loss equal or greater than 5%, and 2) % cartilage loss from baseline to 2 years later. We used logistic and continuous outcome regression models with GEE, adjusting for gait speed, age, and gender, then further adjusting for radiographic disease severity.

Results: The study sample included 385 knees (203 persons): mean age 64.2 years (SD 9.9); BMI 28.4 kg/m^2 (5.7); 156 (76.8%) women. In Table 1, peak KAM and KFM were not associated with cartilage thickness loss at least 5% in the fully adjusted models. In contrast, KAM impulse was associated with thickness loss at both medial surfaces and in all but the tibial posterior subregions. For the continuous outcomes, greater peak KAM and KAM impulse were each associated with greater mean 2-year % thickness loss at the medial tibial surface, particularly the external and central subregions, and at the weightbearing femoral surface, particularly the central subregion (Table 2).

Conclusion: Higher baseline KAM impulse was associated with 2-year medial tibiofemoral cartilage thickness loss using both definitions of progression. Peak KFM was not associated with cartilage loss. These findings support targeting KAM parameters, particularly KAM impulse, in an effort to delay disease progression.

Table 1 Adjusted odds ratios (95% CI) for medial tibiofemoral cartilage thickness loss outcomes (n = 385 knees; 203 persons)

		Cartilage thickness loss (defined as ≥ 5%) at 2-year follow-up (n=385 knees)						
		Medial tibial surface				Medial central weight bearing femoral surface		
Baseline predictor variable	Covariables included in the adjusted models	Whole (74/385) (19.2%)	Central subregion (103/384) (26.8%)	External subregion (93/378) (24.6%)	Posterior subregion (74/385) (19.2%)	Whole (103/384) (26.8%)	Central subregion (124/380) (32.6%)	External subregion (98/373) (26.3%)
Peak KAM (% body wt*ht)	Gait speed, age, and gender	1.49 (0.94, 2.36)	1.40 (0.94, 2.08)	1.43 (0.94, 2.18)	1.25 (0.87, 1.78)	**1.77 (1.05, 2.99)**	**1.77 (1.06, 2.95)**	1.50 (0.96, 2.35)
	Gait speed, age, gender, and K/L grade	1.28 (0.96, 1.71)	1.26 (0.93, 1.69)	1.29 (0.94, 1.77)	1.16 (0.87, 1.54)	1.50 (0.99, 2.27)	1.56 (0.97, 2.52)	1.32 (0.94, 1.85)
KAM impulse (s*% body wt*ht)	Gait speed, age, and gender	**3.43 (1.58, 7.45)**	**2.30 (1.21, 4.37)**	**2.50 (1.25, 4.98)**	**2.26 (1.07, 4.80)**	**4.24 (2.14, 8.42)**	4.39 (2.08, 9.24)	3.12 (1.54, 6.33)
	Gait speed, age, gender, and K/L grade	**2.29 (1.25, 4.17)**	1.81 (1.05, 3.12)	1.99 (1.09, 3.61)	1.85 (0.996, 3.42)	**3.05 (1.73, 5.39)**	3.51 (1.78, 6.95)	2.40 (1.28, 4.49)
Peak KFM (% body wt*ht)	Gait speed, age, and gender	0.98 (0.67, 1.43)	0.98 (0.71, 1.34)	1.12 (0.84, 1.50)	0.97 (0.69, 1.37)	1.19 (0.87, 1.62)	1.21 (0.90, 1.65)	1.21 (0.89, 1.63)
	Gait speed, age, gender, and K/L grade	1.00 (0.71, 1.41)	1.00 (0.74, 1.35)	1.15 (0.88, 1.51)	0.99 (0.71, 1.36)	1.25 (0.95, 1.66)	1.26 (0.94, 1.67)	1.28 (0.98, 1.68)

95% CI excluding 1 is significant

Table 2 Adjusted coefficients (95% CI) for medial tibiofemoral cartilage thickness loss outcomes (n = 385 knees; 203 persons)

		% Cartilage thickness loss at 2-year follow-up (n=385 knees)						
		Medial tibial surface				Medial central weightbearing femoral surface		
Baseline predictor variable	Covariables included in the adjusted models	Whole (n=385)	Central subregion (n=384)	External subregion (n=378)	Post. subregion (n=385)	Whole (n=384)	Central subregion (n=380)	External subregion (n=373)
Peak KAM (% body wt*ht)	Gait speed, age, and gender	**1.48 (0.08, 2.88)**	**2.98 (0.19, 5.78)**	**5.06 (0.77, 9.36)**	1.01 (−0.10, 2.13)	**3.28 (0.36, 6.19)**	**5.19 (0.46, 9.93)**	−3.57 (−19.77, 12.62)
	Gait speed, age, gender, and K/L grade	**1.22 (0.03, 2.41)**	2.41 (0.08, 4.74)	4.29 (0.64, 7.95)	0.83 (−0.14, 1.80)	**2.72 (0.24, 5.20)**	4.38 (0.31, 8.46)	−3.97 (−19.30, 11.36)
KAM impulse (s*% body wt*ht)	Gait speed, age, and gender	**3.67 (1.36, 5.99)**	**6.95 (2.50, 11.40)**	**12.09 (5.18, 18.99)**	2.28 (−0.02, 4.57)	**8.53 (4.47, 12.58)**	13.11 (5.80, 20.42)	−13.36 (−61.38, 34.65)
	Gait speed, age, gender, and K/L grade	**3.22 (1.24, 5.20)**	5.92 (2.19, 9.65)	10.77 (4.94, 16.60)	1.94 (−0.08, 3.96)	**7.55 (4.26, 10.85)**	11.70 (5.52, 17.87)	−14.09 (−60.85, 32.68)
Peak KFM (% body wt*ht)	Gait speed, age, and gender	0.15 (−0.79, 1.08)	0.55 (−1.36, 2.45)	0.73 (−2.44, 3.90)	0.26 (−0.60, 1.12)	0.61 (−1.14, 2.35)	0.94 (−2.10, 3.99)	−1.46 (−7.35, 4.42)
	Gait speed, age, gender, and K/L grade	0.19 (−0.69, 1.06)	0.66 (−1.10, 2.42)	0.87 (−2.13, 3.87)	0.29 (−0.54, 1.13)	0.71 (−0.81, 2.23)	1.06 (−1.63, 3.76)	−1.35 (−7.48, 4.79)

95% CI excluding 0 is significant

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Relation of Shoe Stability to Risk of Knee Cartilage Damage: The Multicenter Osteoarthritis Study.

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Background/Purpose: Clinical guidelines recommend that "every patient with knee osteoarthritis should receive advice concerning appropriate footwear", yet the recommended content of this advice is not specified. Some studies suggest that highly flexible shoes can protect the tibiofemoral (TF) joints against excessive load during gait, while other studies underscore the importance of stable or supportive shoes as a means of protecting the patellofemoral (PF) joint against maltracking brought about by foot pronation. The purpose of this observational study was to determine the relationship between the stability characteristics of a person's usual walking shoe and the 2-year risk of worsening cartilage damage in the medial TF, lateral TF, and PF knee compartments.

Methods: The Multicenter Osteoarthritis Study (MOST) includes middle aged and older adults that have or are at risk of knee OA. Subjects were asked to bring their usual walking shoes and, adapting the methods of Barton et al.,

examiners at the 60-month visit scored the sagittal, torsional, and heel counter stability of each subject's shoe as 0= flexible or 1= stable / supportive (kappa ≥ 0.69). A Summative Shoe Stability Score (0–3) was calculated as the sum of the three component test scores. 1.0T MRIs were obtained at the 60 and 84-month exams, and one knee per subject was scored using Whole Organ MRI Scores (WORMS) to indicate the extent of cartilage damage (0–6) in each of 5 sub-regions of the medial and lateral TF compartments, and each of 4 sub-regions of the PF compartment (kappa ≥ 0.63). Using separate logistic regression models for each compartment, we estimated the relative odds of worsening knee cartilage damage in categories of increasing shoe stability, while adjusting for covariates. Generalized estimating equations accounted for non-independence between sub-regions of a compartment.

Results: 1126 subjects (mean +/− sd age 66.8 +/− 7.5 yrs, BMI 29.6 +/− 4.8 kg/m^2; 61.7% female, 89.8% white) contributed 1124, 1123, and 1116 knees to the analysis of cartilage damage in the medial TF, lateral TF, and PF compartments, respectively. A majority of shoes (64.3%, 68.3%, and 55.0%, respectively) were scored as stable / supportive during sagittal, torsional, and heel counter stability tests, with 47.8% of shoes obtaining the maximum Summative Shoe Stability Score of 3 and only 25.5% obtaining the minimum score of 0. Relative odds of worsening cartilage damage in the medial TF, lateral TF, and PF knee compartments did not change across categories of increasing shoe stability ($p > 0.05$ for all comparisons).

Conclusion: These observational findings do not confirm an association between usual walking shoe stability and 2-year risk of worsening cartilage damage in medial TF, lateral TF, or PF knee compartments. Future studies are needed to clarify the shoe characteristics that are most relevant for persons with knee OA.

Table. Relative odds of worsening knee cartilage damage in categories of increasing shoe stability

	Medial TF Cartilage Damage		Lateral TF Cartilage Damage		PF Cartilage Damage	
Shoe Stability Test	**Sub-regions with worsening n/N (%)**	**Adj* OR (95% CI)**	**Sub-regions with worsening n/N (%)**	**Adj* OR (95% CI)**	**Sub-regions with worsening n/N (%)**	**Adj* OR (95% CI)**
Sagittal Stability						
Flexible	144/1862 (7.7%)	1.0 (ref.)	100/1920 (5.2%)	1.0 (ref.)	100/1356 (7.4%)	1.0 (ref.)
Stable/ Supportive	214/3295 (6.5%)	0.9 (0.7, 1.2)	186/3493 (5.3%)	1.1 (0.8, 1.5)	176/2407 (7.3%)	1.0 (0.8, 1.3)
Torsional Stability						
Flexible	118/1648 (7.2%)	1.0 (ref.)	87/1712 (5.1%)	1.0 (ref.)	88/1202 (7.3%)	1.0 (ref.)
Stable/ Supportive	240/3509 (6.8%)	1.0 (0.7, 1.4)	199/3701 (5.4%)	1.2 (0.8, 1.7)	188/2561 (7.3%)	1.0 (0.8, 1.4)
Heel Counter Stability						
Flexible	164/2318 (7.1%)	1.0 (ref.)	124/2438 (5.1%)	1.0 (ref.)	136/1686 (8.1%)	1.0 (ref.)
Stable/ Supportive	194/2839 (6.8%)	1.0 (0.8, 1.4)	162/2975 (5.4%)	1.2 (0.9, 1.7)	140/2077 (6.7%)	0.8 (0.6, 1.1)
Summative Shoe Stability Score						
0	95/1323 (7.2%)	1.0 (ref.)	72/1374 (5.2%)	1.0 (ref.)	77/961 (8.0%)	1.0 (ref.)
1	33/487 (6.8%)	0.9 (0.5, 1.6)	21/491 (4.3%)	0.8 (0.4, 1.5)	24/355 (6.8%)	0.8 (0.5, 1.4)
2	75/885 (8.5%)	1.3 (0.8, 2.0)	53/966 (5.5%)	1.2 (0.7, 1.9)	45/651 (6.9%)	0.8 (0.6, 1.3)
3	155/2462 (6.3%)	0.9 (0.7, 1.4)	140/2582 (5.4%)	1.2 (0.8, 1.8)	130/1796 (7.2%)	0.9 (0.7, 1.3)

*Adjusted for age, sex, BMI, race, and clinic site.

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Foot Center of Pressure in Knee Osteoarthritis (OA) and Its Association with Knee Load Reduction with Barefoot Walking. Christopher Ferrigno, Roy H. Lidtke, Markus Wimmer, Anjali Nair, Laura E. Thorp, Louis F. Fogg, Joel A. Block and Najia Shakoor. Rush University Medical Center, Chicago, IL.

Background/Purpose: Biomechanical factors including excessive knee loading have been shown to be important in the pathophysiology, severity and progression of knee osteoarthritis (OA). Several biomechanical interventions reduce knee loads by altering foot mechanics, and there is a great deal of interest in better understanding mechanical relationships between the foot and knee. We have previously shown that barefoot walking in OA is associated with a significant reduction in knee loading compared to conventional footwear. Here we evaluate the role of foot center of pressure (COP) in predicting the unloading response of the knee when walking barefoot.

Methods: Participants with radiographic (KL grades ≥ 2) and symptomatic (at least 30mm pain of 100mm scale while walking) medial compartment knee OA underwent gait analyses with their own shoes and while walking barefoot. For simultaneous COP and 3-D ground reaction force acquisition, a pressure platform (Emed, Novel, Munich, Germany) was mounted onto a force plate (Bertec, Columbus, OH) and the stacked assembly was leveled with the walkway. All capture systems were run at 100 Hz to allow for accurate syncing of stance phase, knee moments, and plantar pressures. Foot COP was quantified by determining a custom Medial to Lateral Pressure Index (MLPI) while barefoot. The peak knee adduction moment (KAM) was evaluated as a surrogate of medial knee loading. Linear regression was used to evaluate the relationship between foot COP and percent reductions in the KAM with walking barefoot compared to own shoes. The relationships between foot COP and other gait parameters and OA severity were also evaluated.

Results: 22 participants (15 women, mean age (SD) of 62±11) were evaluated. 10 had a KL grade of 2 and 12 had a KL grade of 3 at the affected knee. Barefoot walking was associated with a 15% reduction in the KAM compared to walking with participants own shoes (2.55±1.00 vs 2.17±1.01%BW*ht, $p<0.001$); notably, the magnitude of reduction of the KAM with barefoot walking was associated with a more medial foot COP after adjusting for speed and stride length (adjusted $r^2=0.509$, $p=0.049$). A medialized foot COP was associated with worse KL grade, slower walking speed and shorter strides during gait ($r^2=0.564$, $p=0.002$). Radiographic severity explained 9 to 26% of the variance in the foot COP while speed and stride length explained 17 to 47%.

Conclusion: Foot mechanics are important contributors to knee loading in OA. There is controversy in the literature regarding the foot COP and how it may relate to various foot-targeted interventions in OA. This study suggests that a more medial foot COP is associated with greater reductions in the KAM during barefoot walking. Thus, foot COP may help predict knee loading responses to walking barefoot or an intervention that simulates barefoot walking.

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Knee Instability and Advanced Function Decline in Persons with Knee Osteoarthritis. Leena Sharma, Joan S. Chmiel, Orit Almagor, Kirsten Moisio, Alison H. Chang, Yunhui Zhang, Laura Belisle and Karen W. Hayes. Northwestern University, Chicago, IL.

Background/Purpose: Knee instability in the setting of osteoarthritis (OA) encompasses a spectrum of symptoms and phenomena, including a feeling of low overall confidence in the knees, low confidence that the knees will not buckle or give way (buckling confidence), actual episodes of buckling, and excessive frontal plane motion. Current treatment for knee OA does little to address instability. Given the central role of the knee in weightbearing activity, confidence and buckling in particular may influence nature and intensity of activity, and could be important proximal factors in a chain of events leading to function decline and disability. It is unclear whether these factors are more important to outcome than instability objectively measured during gait. We hypothesized that overall confidence, buckling confidence, buckling, and excessive frontal plane motion during gait are each associated with poor 2-year function outcome.

Methods: Persons with OA in at least one knee were queried at baseline about overall knee confidence using the KOOS question (how troubled are you by the lack of confidence in your knees, higher worse), buckling confidence (i.e., confidence that knees will not buckle or give way, higher better), and any knee buckling in the past 3 months, and underwent quantitative gait analysis (3-dimensional knee kinematics and kinetics during ambulation recorded using an 8-camera Digital Real-Time Eagle motion analysis system, and 6 AMTI force plates). Physical function was assessed using the Late-Life Function Instrument – Advanced Lower Extremity Domain scaled score; quintiles were used to categorize these scores into groups. Poor outcome was defined as moving into a worse function group or remaining in the 2 worst function groups between baseline and 2 years. Logistic regression was used to evaluate the relationship between baseline instability measures, knee confidence and poor baseline-to-2-year function outcome, adjusting for potential confounders.

Results: 212 persons [163 (77%) women, mean age 65 (10, SD), BMI 28.5 (5.7)] comprised the sample.

98 (46%) had a poor outcome. As shown in the Table, buckling in the past 3 months, buckling confidence, and overall knee confidence, but neither varus-valgus excursion nor maximal varus-valgus angular velocity during gait were associated with the outcome in univariate analyses. In fully-adjusted models, these findings persisted (except for buckling confidence which

approached significance). Age and self-efficacy were also consistently associated with the outcome.

Conclusion: Worse baseline overall knee confidence and recent buckling, but neither varus-valgus excursion nor angular velocity using quantitative gait analysis were associated with greater risk of poor 2-year function outcome. Interventions to address confidence and buckling may improve outcome in knee OA.

TABLE. Results from logistic regression models to evaluate associations of each instability variable with odds of a poor function outcome; unadjusted and adjusted odds ratios (OR) and associated 95% confidence interval (CI). 95% CIs that exclude 1 are statistically significant

Instability variable (baseline)	Unadjusted OR (95% CI)	Fully adjusted* OR (95% CI)
Varus-valgus excursion during gait	0.95 (0.85, 1.06)	1.01 (0.89, 1.15)
Maximum varus-valgus angular velocity during gait	0.99 (0.98, 1.01)	0.99 (0.97, 1.01)
Buckling, past 3 months (yes/no)	***2.27 (1.28, 4.03)***	***2.05 (1.01, 4.16)***
Confidence knees will not buckle (higher better, continuous)	***0.63 (0.47, 0.85)***	0.68 (0.46, 1.01)
Overall knee confidence (higher worse, continuous)	***1.80 (1.27, 2.56)***	***1.66 (1.02, 2.70)***

*adjusted for age, gender, BMI, pain (ICOAP), function self-efficacy, depressive symptoms, disease severity (K/L, worse of 2 knees), knee extensor strength (better of 2 knees)

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External Hip Adduction Moment and Progression of Medial Tibiofemoral Cartilage Damage and Bone Marrow Lesions in Persons with Knee Osteoarthritis. Kirsten Moisio[1], Alison H. Chang[1], Ali Guermazi[2], Joan S. Chmiel[1], Orit Almagor[1], Pottumarthi Prasad[1], Yunhui Zhang[1], Karen W. Hayes[1], Laura Belisle[1], Jamie Rayahin[3] and Leena Sharma[1]. [1]Northwestern University, Chicago, IL, [2]Boston University School of Medicine, Boston, MA, [3]University of Illinois at Chicago, Chicago, IL.

Background/Purpose: Gait mechanics at the hip may affect medial joint loading at the knee in persons with knee OA. Greater external hip adduction moment (reflecting torque generation by hip abductor muscles) during gait may limit excessive hip drop or trunk lean. This, in turn, may prevent excessive medial knee joint loading and eventual progression of knee OA. Little is known about the relationship between hip adduction moment and progression of medial tibiofemoral OA by MRI. We hypothesized that greater baseline external hip adduction moment is associated with reduced risk of baseline-to-2-year progression of medial tibiofemoral cartilage damage and bone marrow lesions in persons with knee OA.

Methods: Participants with knee OA, defined by osteophyte presence in at least one knee, underwent quantitative gait analysis at baseline. Both knees underwent 3.0T MRI at baseline and two year follow-up using double oblique coronal and axial FLASHwe, coronal T1weighted spinecho, and sagittal, axial and coronal fat suppressed turbo spin echo sequences. Cartilage damage and bone marrow lesions assessed using WORMS, blinding readers to hypotheses and all other data. Logistic regression with GEE used to account for correlation between limbs, assess the association between baseline hip adduction moment and baseline-to-2-year cartilage damage progression and bone marrow lesion progression, defined as any worsening of score in medial compartment or joint surface. Analyses adjusted for gait speed, age, gender, and disease severity (K/L grade). Results reported as ORs and 95% CIs.

Results: 204 persons [64.2 years (±9.9), BMI 28.5 kg/m^2 (±5.7), 76.5% women] contributing 391 knees comprised the study sample. Mean hip adduction moment was 4.43 (±0.9) %BW*HT. Table 1 shows a greater hip adduction moment was significantly associated with reduced likelihood of cartilage damage progression in the medial tibiofemoral compartment and medial femoral surface. After adjustment for covariables, these associations were no longer significant. Table 2 shows means (SD) of the hip adduction moment at baseline for knees with/without cartilage damage and bone marrow lesion progression in specific subregions.

Conclusion: In persons with knee OA, greater hip adduction moment was associated with reduced likelihood of 2-year medial tibiofemoral cartilage damage progression and bone marrow lesion progression, but findings were no longer significant in adjusted analyses. The consistently protective direction of findings at compartment, joint surface, and subregional levels warrants further evaluation at longer follow-up.

Table 1 Unadjusted and adjusted ORs (95% CIs) for medial tibiofemoral OA progression at 2 years

		Medial Tibiofemoral Compartment		Medial Femoral Surface		Medial Tibial Surface	
		Cartilage damage progression	Bone marrow lesion progression	Cartilage damage progression	Bone marrow lesion progression	Cartilage damage progression	Bone marrow lesion progression
	Number of knees (%) with progression	61/391 (16%)	87/391 (22%)	48/391 (12%)	53/391 (14%)	29/391 (7%)	48/391 (12%)
Baseline predictor							
External Hip Adduction Moment (%BW*HT)	Unadjusted	**0.70 (0.51, 0.97)**	0.75 (0.55, 1.01)	**0.68 (0.50, 0.93)**	0.72 (0.48, 1.08)	0.88 (0.59, 1.32)	0.96 (0.67, 1.37)
	Adjusted*	0.82 (0.58, 1.15)	0.85 (0.61, 1.17)	0.79 (0.56, 1.12)	0.80 (0.53, 1.21)	1.07 (0.70, 1.64)	1.20 (0.83, 1.75)

Results are per 1 unit (%BW*HT) of external hip adduction moment (n=391 knees from 204 persons)
*adjusted for gait speed, age, gender, and K/L grade

Table 2 Means (SD) for the external hip adduction moment in medial tibial and femoral subregions

		Posterior femur	Central femur	Posterior tibia	Central tibia	Anterior tibia
		Cartilage damage progression at 2-year follow-up				
External Hip Adduction Moment (%BW*HT), mean (SD)	Number of knees (%) with progression	20/391 (5%)	33/391 (8%)	7/391 (2%)	25/391 (6%)	8/391 (2%)
	Knees without progression, mean (SD)	4.45 (0.88)	4.44 (0.90)	4.43 (0.89)	4.43 (0.89)	4.43 (0.89)
	Knees with progression, mean (SD)	3.97 (0.85)	4.36 (0.67)	3.98 (0.57)	4.32 (0.79)	4.61 (0.87)
		Bone marrow lesion progression at 2-year follow-up				
	Number of knees (%) with progression	19/391 (5%)	38/391 (10%)	12/391 (3%)	33/391 (8%)	21/391 (5%)
	Knees without progression, mean (SD)	4.43 (0.87)	4.47 (0.87)	4.43 (0.89)	4.44 (0.89)	4.43 (0.88)
	Knees with progression, mean (SD)	4.38 (1.19)	4.05 (0.92)	4.38 (0.84)	4.34 (0.79)	4.52 (0.96)

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Hip Adiposity, Not Local Knee Adiposity, Is Associated with Knee Pain Independent of Radiographic Osteoarthritis Severity. Grace H. Lo[1], Ajay Balasubramanyam[2], Jeffrey B. Driban[3], Lori Lyn Price[3], Charles B. Eaton[4] and Timothy E. McAlindon[3]. [1]Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, [2]Baylor College of Medicine, Houston, TX, [3]Tufts Medical Center, Boston, MA, [4]Memorial Hospital of Rhode Island, Pawtucket, RI.

Background/Purpose: Elevated body mass index (BMI) is associated with pain in knee OA. However, it is unclear if adiposity closer in proximity to the knee might have a greater influence on pain in that joint. To address this question, we assessed whether fat measured around the knee or around the hip was associated with prevalent knee pain.

Methods: We performed a cross-sectional study of a subgroup of the incidence subcohort of the Osteoarthritis Initiative (OAI) who had DXA scans from the 72-month visit analyzed for knee and hip adiposity. Participants from 2 clinical sites were included. DXA scans of the right knee and one hip (usually the right) were acquired on identical GE Lunar Prodigy scanners, generating knee fat and hip fat percentages. Knee pain was assessed using the question from the 72-month visit, "In the past 12 months, have you had pain, aching or stiffness in or around your knee on most days for at least one month?" Posterior-anterior semiflexed knee radiographs were read for Kellgren-Lawrence (KL) grade (0–4) from the 48-month visit. We performed logistic regression with knee fat percent quartiles as the predictors and frequent knee pain as the outcome. Adjusted results included KL grade as a covariate. We repeated these analyses evaluating hip fat percent quartiles as the predictor.

Results: 359 participants, 51% female, were included with a mean age of 64.8 (8.0) years and BMI of 28.1 (4.9) kg/m^2. The frequency of KL grades 0 – 4 included were 44%, 19%, 21%, 13%, and 3% respectively. Table 1 illustrates that increasing knee fat percent quartiles were minimally associated with knee pain though both unadjusted and adjusted odds ratios were not statistically significant. In contrast, hip fat percent quartiles were associated with knee pain with the p for trend for both unadjusted and adjusted odds ratios being statistically significant.

Table 1 Fat percentiles of the knee and hip as predictors for frequent knee pain.

Knee Fat Percent Quartiles	Prevalence of Knee Pain	Unadjusted OR	Adjusted OR (for KL Grade)
Quartile 1 (6–25%)	12/88 (14%)	Referent	Referent
Quartile 2 (25–34%)	21/90 (23%)	1.4 (0.7–2.8)	1.2 (0.6–2.7)
Quartile 3 (35–44%)	18/90 (20%)	1.3 (0.5–2.4)	1.0 (0.5–2.3)
Quartile 4 (44–64%)	22/90 (24%)	1.4 (0.7–3.0)	1.3 (0.6–2.9)
		p for trend = 0.13	p for trend = 0.40
Hip Fat Percent Quartiles	**Prevalence of Knee Pain**	**Unadjusted OR**	**Adjusted OR (for KL Grade)**
Quartile 1 (10–21%)	10/86 (12%)	Referent	Referent
Quartile 2 (22–26%)	20/88 (23%)	2.1 (1.0–4.7)	1.8 (0.8–4.2)
Quartile 3 (26–32%)	19/88 (22%)	2.0 (0.9–4.4)	1.8 (0.8–4.2)
Quartile 4 (32–44%)	27/88 (31%)	3.2 (1.5–6.9)	2.4 (1.1–5.6)
		p for trend = 0.005	p for trend = 0.05

Conclusion: Hip adiposity, not local knee adiposity, was associated with knee pain independent of radiographic OA severity. These findings suggest that local adiposity may not have a clinically relevant influence on knee pain. Instead adiposity of the hip, one adjacent joint away, has a greater influence on knee pain. Understanding whether the mechanism of this relationship is biomechanically driven or driven by adipokines will be instructive in better understanding the causes of knee pain and identifying new targets of therapy.

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The Relationship of Quadriceps and Hamstrings Intramuscular Fat and Lean Muscle with Power in Women with Knee Osteoarthritis. Michael J. Davison[1], Monica R. Maly[1], Karen A. Beattie[1], Peter J. Keir[1] and Jonathan D. Adachi[2]. [1]McMaster University, Hamilton, ON, [2]Division of Rheumatology, McMaster University, Hamilton, ON.

Background/Purpose: Reduced quadriceps and hamstrings strength is a risk factor for knee osteoarthritis (OA). This strength loss is partly due to the loss of lean muscle mass, increased pain and neuromuscular inhibition. Intramuscular fat, or fat within a muscle belly, is related to poor physical performance and radiographic disease progression in OA. We investigated the relationship between intramuscular fat fraction and lean muscle volume of the quadriceps and hamstrings with isotonic knee extensor and flexor power in women with knee OA.

Methods: Women (n=20) with radiographic and symptomatic knee OA had the thigh of their most symptomatic knee imaged using 3.0T magnetic resonance imaging (MRI). The iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) sequence obtained 60 fat-separated images (3 mm slice thickness). Images were analyzed using SliceOmatic® software with a region-growing algorithm to quantify intramuscular fat and lean muscle tissue volumes (cm^3) separately for the quadriceps and hamstrings (Figure 1). Intramuscular fat was represented as a fraction (%) of total muscle volume. Using a dynamometer, participants completed ten isotonic knee extensions and flexions, with resistance at 20% of maximum voluntary isometric contraction. Mean peak power (W or N×m/s) was calculated using the five highest contractions. Electromyography (EMG) measured the activation of the vastus lateralis and biceps femoris during contractions. Mean peak EMG amplitude was calculated from the five highest activations.

Results: Mean sample characteristics (±SD): age 65±5 yrs; Body Mass Index (BMI) 30±5 kg/m^2. There was a positive relationship between quadriceps lean muscle volume and knee extensor power (B=0.634; p=0.004), controlling for vastus lateralis activation. Also, there was a positive relationship between hamstrings lean muscle volume and knee flexor power (B=1.173; p=0.010), controlling for biceps femoris activation. No relationships were found between quadriceps or hamstrings intramuscular fat fractions and isotonic knee extensor (B=4.351; p=0.764) or knee flexor (B=−4.793; p=0.645) power, respectively.

Conclusion: Lean muscle volume of the quadriceps and hamstrings, but not intramuscular fat fraction, were significant factors in the knee extensor and flexor powers of women with knee OA. Our findings suggest that the volume of thigh lean muscle is of primary importance in the physical performance of women with knee OA, independent of neuromuscular activation. Although intramuscular fat has been implicated in radiographic disease progression, its role in thigh strength and power is uncertain. Further investigation is needed of intramuscular fat and its relationship to other factors of physical performance, such as neuromuscular activation.

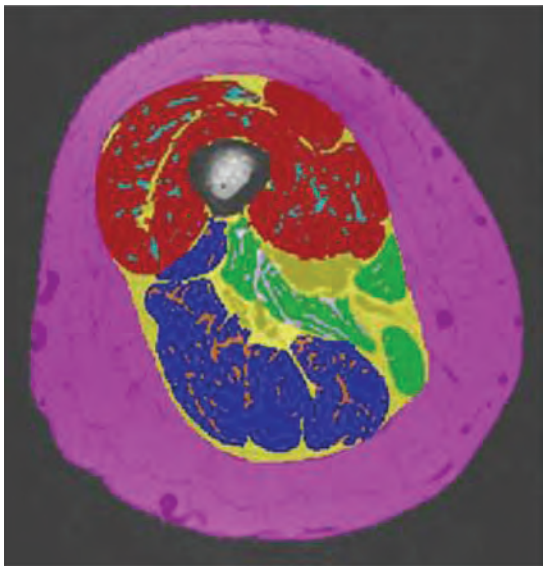

Figure 1. Red=quadriceps muscle, blue=hamstrings muscle, cyan=quadriceps intramuscular fat, orange=hamstrings intramuscular fat.

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Surface Area and Fatty Infiltration of Vastus Medialis Measured By Magnetic Resonance Imaging Are Risk Factors for the Progression of Knee Osteoarthritis and Discriminate Two Osteoarthritis Phenotypes. Johanne Martel-Pelletier[1], Jean-Pierre Raynauld[1], François Abram[2], Marc Dorais[3], Yuanyuan Wang[4], Jessica Fairley[4], Flavia Cicuttini[4] and Jean-Pierre Pelletier[1]. [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [2]Medical Imaging Research & Development, ArthroLab Inc., Montreal, QC, [3]StatSciences Inc., Notre-Dame de l'Île Perrot, QC, [4]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.

Background/Purpose: Osteoarthritis (OA) is the most common arthritic condition but its treatment still remains symptomatic. Understanding factors affecting the progression of this disease may enable the development of disease-modifying therapies. Vastus medialis (VM) muscle surface has been proposed in recent OA studies to be associated with cartilage volume loss over time. However, the VM may include a significant proportion of fatty infiltration, which could also influence knee metabolism and mechanics. These two parameters can be visualized and quantified by MRI. Using data from a recent randomized clinical trial in knee OA[1], this study contrasted the VM surface area and fatty infiltration (% Fat) with cartilage volume loss and changes in bone marrow lesions as assessed by MRI.

Methods: OA patients, diagnosed according to American College of Rheumatology clinical and radiological criteria, were from the according-to-protocol population (n=143) of a 2-year randomized clinical trial, and had MRI acquisitions at baseline and 2 years. MR images of the VM (mm^2) were assessed semi-automatically and VM % Fat by a fully automated software. Univariate and multivariate analyses were performed to assess the relationship between VM area and its % Fat, cartilage volume loss, and bone marrow lesion changes over 2 years.

Results: The median baseline of the VM area and % Fat were chosen to stratify patients. Female ($p \leq 0.001$), higher BMI ($p \leq 0.008$), and disability ($p \leq 0.040$) were associated with both a higher baseline VM surface area and % Fat. Higher baseline VM area was associated with greater cartilage volume loss in the medial compartment, medial femur, and lower cartilage volume loss in the lateral plateau (all $p \leq 0.048$). Change in % Fat, but not in surface area, was associated with an increase in the bone marrow lesion score in the global knee and cartilage volume loss in the global knee, lateral compartment, lateral femur, and medial plateau (all $p \leq 0.035$). Multivariate analyses revealed correlations between % Fat, but not surface area, and cartilage volume loss in the global knee (p=0.011) and most subregions studied. Importantly, % Fat change was independently associated with bone marrow lesion change at 2 years (p=0.001). All of the above changes were found irrespective of the treatment the patients had during the clinical trial.

Conclusion: This study is the first to demonstrate that the % Fat in the VM is strongly associated with cartilage volume loss and the presence and progression of bone marrow lesions. Importantly, two different OA phenotypes were evidenced: i) low VM area phenotype comprising female patients with lower BMI, being more symptomatic at baseline, having more cartilage volume damage at baseline, and at 2 years less cartilage volume loss in the medial femur and more cartilage volume loss in the lateral plateau; ii) higher VM % Fat phenotype comprises female patients with higher BMI, having more disability at baseline, more cartilage volume damage at baseline, and at 2 years more cartilage volume loss in the medial plateau and lateral femur.

Reference:

1) Raynauld JP, et al. Ann Rheum Dis 2009;68:938–47.

Disclosure: J. Martel-Pelletier, ArthroLab, 9; **J. P. Raynauld**, ArthroLab, 5; **F. Abram**, ArthroLab, 3; **M. Dorais**, ArthroLab, 5; **Y. Wang**, None; **J. Fairley**, None; **F. Cicuttini**, None; **J. P. Pelletier**, ArthrioLab, 9.

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DXA Body Composition, Sarcopenia and Knee and Hip Osteoarthritis: Results from the Khoala Cohort. Clémence Jeanmaire[1], Isabelle Chary-Valkenaere[1], Damien Loeuille[2], Lorraine Bernard[3] and Anne-Christine Rat,[4]. [1]CHU Nancy, Vandoeuvre Les Nancy, France, [2]CHU Brabois, Vandoeuvre les Nancy, France, [3]INSERM, CIC-EC, CIE6, Vandoeuvre Les Nancy, France, [4]Université de Lorraine, Nancy, F-54000, France; Inserm,, CIC-EC, CIC 1433, Nancy, F-54000, France; CHU de Nancy, Clinical Epidemiology and Evaluation Department, Nancy, F-54000, France; CHU de Nancy, Rheumatology department, Nancy, France.

Background/Purpose: Obesity is a well known risk factor for the development and progression of knee osteoarthritis (OA), and to a lesser extent of hip OA. However, types of obesity and body composition abnormalities could have different impact on OA severity. Body composition has rarely been studied in hip OA and has never been compared to knee OA.

The purpose of this study was to analyze the associations between body composition and sarcopenia and OA location and severity (clinical and structural), in patients with symptomatic hip and/or knee OA.

Methods: Skeletal muscle and fat mass were measured using dual X-ray absorptiometry (DXA) in a subset of patients of the Knee and Hip OsteoArthritis Long term assessment (KHOALA) cohort[1].

Skeletal muscle mass index (SMI) was defined as appendicular skeletal muscle mass (ASM) / body weight. The SMI cutoff values used for sarcopenia were 26.8% for men and 21.0% for Women [2].

Pain and function were measured by WOMAC index and quality of life (QoL) by SF36. Structural severity was graded on X-Ray according to Kellgren and Lawrence's classification.

Percentages of patients in each group of body composition defined by presence or absence of obesity (BMI ^{3} 30 kg/m^2)) and/or sarcopenia were compared in knee and/or hip OA.

We also compared severity of OA (Xrays grade, pain, function and quality of life) in each group of body composition.

Results: *A DXA was performed in 381 patients among the* 878 patients included in the cohort*: women 254 (66.7%), mean (STD) age 63.6 (8.4), Hip OA 91 (23.9%), knee OA 267 (70.1), obesity 146 (38.8%), sarcopenia 105 (27.6%).*

Associations between joint and OA severity according to body composition *group are presented in table.*

	Normal body composition N=205 N (%)	Non obese patients with sarcopenia N=25 N (%)	Obese patients without sarcopenia N=65 N (%)	Obese patients with sarcopenia N=80 N (%)	p
Joint					
Hip	66 (74.1)	9 (10.1)	5 (5.6)	9 (10.1)	<0.001
Knee	127 (48.2)	16 (6.1)	55 (20.9)	65 (24.7)	
Hip and knee	12 (52.2)	0	5 (21.7)	6 (26.1)	
Kellgren stage					
2	103 (56.3)	10 (5.5)	31 (16.9)	29 (15.8)	0.05
3	48 (52.2)	10 (10.9)	14 (15.2)	20 (21.7)	
4	34 (43.6)	4 (5.1)	18 (23.1)	22 (28.2)	
SF36 PCS (mean (std))	44.3 (8.4)	39.7 (9.1)	38.7 (9.4)	38.2 (9.1)	<0.001
SF36 MCS (mean (std))	48.1 (10.5)	45.8 (10.7)	46.2 (10.7)	44.6 (11.7)	0.09
WOMAC Function (mean (std))	24.1 (17.3)	36.2 (24.3)	34.7 (21.5)	35.9 (20.5)	<0.001
WOMAC Pain (mean (std))	27.0 (18.5)	36.8 (25.7)	38.7 (20.8)	39.6 (22.1)	<0.001

WOMAC [0,100], 0=best, 100=worse), SF36 PCS: Physical component summary, MCS: Mental component summary, 0=worse, 100=best

Normal body composition was significantly more frequent in patients with hip than knee OA, but frequency of patients with sarcopenia was not different in hip or knee OA.

Normal body composition seemed to decrease in more severe Kellgren stages but the associations did not reach statistical significance.

Physical component summary score was higher and pain score lower in patients with normal body composition than in patients with obesity. In patients with normal BMI, scores did not differ with or without sarcopenia.

Function score was lower in patients with normal body composition than in other patients. No difference was found between obese patients with or without sarcopenia. No difference was found between patients with sarcopenia and normal BMI and obese patients.

Conclusion: Impact of OA on pain, function and QoL was not different between obese patients and patients with sarcopenia and normal BMI. Impact of OA was worse in obese patients with or without sarcopenia than in patients with normal body composition.

Guillemin F et al. Joint Bone Spine. 2012
Lee S et al. Arthritis and Rheumatism

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Lower Extremity Presarcopenia Is Associated with the Severity of Knee Pain. Yun-Hong Cheon[1], Wan-Hee Yoo[2], Young Sun Suh[3], Hyun-Ok Kim[3], Ki-Soo Park[3], Sang-Il Lee[3] and Hye-Ji Jeon[3]. [1]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [2]Chonbuk National University School of Medicine, Jeonju, South Korea, [3]Gyeongsang National University School of Medicine, Jinju, South Korea.

Background/Purpose: Presarcopenia, which is defined as skeletal muscle mass loss, and knee pain have been gained attention with ageing. Little is known about the association of lower extremity presarcopenia (LEPS) and severity of knee pain. Thus, this study was conducted to the relationship between severity of self-reported knee pain and LEPS.

Methods: From the 5th Korean National Health and Nutrition Examination Survey (KNHNES V1–2, n=17,476), the data of 721 participants, who underwent dual x-ray absorptiometry (DXA) and bilateral knee plain radiographs, and complained knee pain were analyzed. LEPS was defined as a lower extremity skeletal muscle mass index below -2SD of the value in sex-matched young reference groups. Participant were categorized into 4 groups; normal, LEPS, non-LEPS with obesity (NLEPSO), LEPS with obesity (LEPSO).

Results: LEPS and LEPSO are significantly associated with the severity of knee pain (LEPS 6.9±0.4, LEPSO 7.2±0.5, $P<0.05$). These results did not change after adjusting for various confounding factors. In participants with non-radiographic knee OA (n=268), the severity of knee pain was related with LEPS (7.2±0.6, $P<0.05$). In radiographic knee OA participants (n=452), LEPSO was related with severity of knee pain (7.3±0.5, $P<0.05$). Sex, smoking status, osteoporosis, and vitamin D levels were not related with the severity of self-reported knee pain.

Conclusion: LEPS is directly associated with severity of knee pain. This attribution supports increasing muscle mass is very important to reduce knee pain. Thus, early detection of LEPS may help physicians to detect pain-sensitive LEPS patients who can benefit from early intervention such as exercise.

Disclosure: Y. H. Cheon, None; **W. H. Yoo**, None; **Y. S. Suh**, None; **H. O. Kim**, None; **K. S. Park**, None; **S. I. Lee**, None; **H. J. Jeon**, None.

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An Analysis of Age-Related Loss of Skeletal Muscle Mass and Its Significance on Osteoarthritis in a Korean Population. Hyunje Kim, Minjung Kim, Choong Ki Lee and Young Hoon Hong. Yeungnam University, Daegu, South Korea.

Background/Purpose: This study was conducted in order to analyze the effects of sarcopenia and sarcopenic obesity on age-related OA of the knee in a Korean population.

Methods: All the subjects who visited Yeungnam University Hospital Health Promotion Center between 2008 and 2012 in order to undergo a routine medical examination, including BIA, were enrolled. BMR was calculated using the Cunningham equation, BMI as weight/height^2 (kg/m^2), SMI as ASM/body mass●100 (%), and PBF as FM/body mass●100 (%). The body components were evaluated by BIA using InBody 720 (Biospace, Seoul, Korea). A total of 522 knees with antero-posterior X-rays from 381 subjects in the population were enrolled in this study. The presence and severity of

bony changes for OA were measured and graded twice according to the Kellgren-Lawrence (K/L) grade.

Results: The mean and SD of SMI, BMI and PBF in healthy subjects aged 18 to 39 (total of 5,723 subjects; 2,959 males, 2,764 females) are shown at Table 1-1. Table 1–2 revealed characteristics and BIA parameters of this study population. Negative correlation was observed between SMI and age ($r=-0.157$, $p<0.01$), which was more prominent in females ($r=-0.313$, $p<0.01$) than in males ($r=-0.164$, $p<0.001$) (Table 2). Members of the population aged over 50 showed a significant decrease of SMI ($r=-0.166$, $\beta=-0.112$, $p<0.01$). The population over 50 years of age showed a significant increase of PBF as compared with that of the population under 50 ($r=0.117$, $\beta=0.125$, $p<0.01$).

A cross-tab analysis was done according to sarcopenia classification and body composition by PBF in the aspect of K/L grades (Table 3-1). Knees with sarcopenia class I and class II, and obesity showed a trend toward the higher K/L grade in the higher sarcopenia class and sarcopenic obesity ($p<0.01$). Results of logistic regression analysis between SMI and K/L grade showed a significantly high incidence of a higher K/L grade in subjects with a lower SMI, and significantly high incidence of a lower K/L grade was observed in those with a higher SMI ($p<0.01$) (Table 3-2).

Conclusion: This study provides evidence that sarcopenia and sarcopenic obesity are correlated with development of and progression to severe OA. Thus, the results of this study may indicate interactive correlation of SMI and PBF as age-related alteration of body composition with age related OA.

Table 1-1. Reference values for the classification of sarcopenia from a sex-matched, healthy Korean population aged between 18 and 39 years

		BIA				
	n	BMI (kg/m^2)	BMR (Kcal)	PBF (%)	SMM (kg/m^2)	SMI (%)
males (18≤age≤39)	2,959	24.90 ± 3.71	1400.58 ± 207.78	22.90 ± 6.24	10.74 ± 1.04	43.53 ± 3.55
male-arcopenia class I						36.43≤, <39.98
male-arcopenia class II						<36.43
females (18≤age≤39)	2,764	21.84 ± 3.40	140.87 ± 206.71	29.56 ± 5.94	8.22 ± 0.86	37.99 ± 3.19
female-sarcopenia class I						31.61≤, <34.80
female-sarcopenia class II						<31.61

Table 1-2. characteristics and BIA parameters of study populations

	males				females				
			sarcopenia				sarcopenia		
	total	normal SMI	class I	class II	total	normal SMI	class I	class II	total
n	13,006	11,165	1,575	266	10,467	7,730	2,178	559	23,473
age (yr)	47.92 ± 11.16	47.55 ± 10.70	50.38 ± 12.86	48.72 ± 16.33	47.58 ± 11.91	45.76 ± 11.13	52.07 ± 12.23	55.33 ± 13.30	47.77 ± 11.50
height (cm)	170.67 ± 5.95	170.97 ± 5.82	168.92 ± 6.07	168.76 ± 8.16	158.10 ± 5.76	158.93 ± 5.51	156.19 ± 5.61	154.14 ± 6.19	165.07 ± 8.57
weight (kg)	71.84 ± 10.38	70.53 ± 9.08	78.10 ± 11.18	89.48 ± 21.47	57.88 ± 8.44	55.89 ± 6.84	61.86 ± 8.27	69.91 ± 12.70	65.62 ± 11.81
BMI (kg/m^2)	24.62 ± 2.99	24.09 ± 2.52	27.27 ± 2.78	31.11 ± 5.51	23.16 ± 3.19	22.12 ± 2.39	25.30 ± 2.55	29.29 ± 3.95	23.97 ± 3.16
BMR (kcal)	1405.28 ± 206.81	1404.57 ± 207.00	1412.70 ± 206.16	1390.95 ± 201.89	1404.55 ± 206.39	1405.72 ± 206.65	1401.68 ± 205.25	1399.49 ± 207.27	1404.95 ± 206.62
AC (cm)	86.92 ± 7.52	85.51 ± 6.41	94.09 ± 6.25	103.51 ± 12.21	82.48 ± 9.05	79.23 ± 6.68	89.34 ± 6.68	100.82 ± 9.44	84.94 ± 8.53
W/H ratio	0.90 ± 0.03	0.89 ± 0.03	0.95 ± 0.02	0.98 ± 0.03	0.91 ± 0.06	0.89 ± 0.05	0.95 ± 0.05	1.00 ± 0.06	0.91 ± 0.05
fat mass (kg)	16.98 ± 5.88	15.55 ± 4.22	24.17 ± 4.47	34.45 ± 11.33	18.61 ± 5.71	16.40 ± 3.79	23.28 ± 3.94	30.84 ± 7.09	17.70 ± 5.86
PBF (%)	23.20 ± 5.36	21.78 ± 4.16	30.80 ± 1.90	37.93 ± 3.85	31.61 ± 5.86	29.07 ± 4.26	37.48 ± 1.84	43.82 ± 2.74	26.95 ± 6.98
PBF median	23.12				31.65				
FMI (kg/m2)	5.83 ± 1.97	5.31 ± 1.39	8.43 ± 1.25	11.95 ± 3.30	7.47 ± 2.33	6.50 ± 1.48	9.511 ± .32	12.91 ± 2.46	6.56 ± 2.30
LBM (kg)	18.79 ± 1.56	18.77 ± 1.52	18.84 ± 1.64	19.15 ± 2.51	15.69 ± 1.31	15.62 ± 1.26	15.78 ± 1.31	16.37 ± 1.67	17.41 ± 2.11
SM (kg)	30.83 ± 3.91	30.93 ± 3.76	30.15 ± 4.25	30.63 ± 6.59	21.19 ± 2.61	21.34 ± 2.47	20.73 ± 2.71	20.96 ± 3.61	26.53 ± 5.87
SMM (kg/m^2)	10.56 ± 0.98	10.55 ± 0.95	10.53 ± 1.03	10.65 ± 1.58	8.47 ± 0.79	8.43 ± 0.76	8.48 ± 0.81	8.78 ± 1.04	9.62 ± 1.38
SMI (%)	43.11 ± 3.10	43.95 ± 2.37	38.63 ± 0.95	34.41 ± 2.08	36.86 ± 3.26	38.28 ± 2.35	33.54 ± 0.87	30.06 ± 1.39	40.32 ± 4.44

BIA; bioelectrical impedance analysis, BMI; body mass index, BMR; basal metabolic rate, AC; abdominal circumference, W/H ratio; waist/hip ratio, PBF; percent body fat, FMI; fat mass index, LBM; lean body mass, SM; skeletal muscle, SMM; skeletal muscle mass, SMI; skeletal muscle mass index

Table 2 Correlations and regression analyses of SMI and PBF with age

	age(yr) <50			50 ≤ age (yr)						
	n	SMI	PBF	n	SMI	PBF	SMI/age (r)	ΔSMI/yr (β)	PBF/age (r)	ΔPBF/yr (β)
total population	14,352	40.86 ± 4.24	26.33 ± 6.66	9,121	39.08 ± 4.62	28.10 ± 7.32	−0.157**	−0.061**	0.134**	0.081**
males	7,961	43.45 ± 3.14	22.93 ± 5.50	5,045	42.59 ± 2.97	23.64 ± 5.11	−0.164**	−0.046**	0.078**	0.038**
females	6,391	37.64 ± 3.06	30.33 ± 5.61	4,076	35.64 ± 3.18	30.62 ± 5.70	−0.313**	−0.085**	0.285**	0.140**
value/age (r)		0.007	0.006		−0.166**	0.117**				
Δvalue/ur (β)		−0.004	0.005		−0.112**	0.125**				

SMI; skeletal muscle mass index. PBF; percentager body fat
SMI/age (r); correlation coefficients between SMI and age
ΔSMI/yr (β); β coefficients between SMI and age

Table 3-1. Cross-tab analysis between the classifications of sarcopenia and obesity and the K/L grade of the knee joints

	SMI classification				PBF classification			
		sarcopenia				Obesity		
	normal	class I	class II	total	normal	obesity	SO	total
Total (n)	401	105	16	522	217	184	119	522
K/L grade 0 (n)	186	38	2	226	115	71	40	226
n/total of K/L grade 0 (%)	82.3	16.8	.9	100.0	50.9	31.4	17.7	100.0
n/total of class (%)	46.4	36.2	12.5	43.3	53.0	38.6	33.6	43.3
residual	12.4	−7.5	−4.9		21.0	−8.7	−11.5	
K/L grade 1 (n)	99	19	1	119	56	43	20	119
n/total of K/L grade 1 (%)	83.2	16.0	.8	100.0	47.1	36.1	16.8	100.0
n/total of class (%)	24.7	18.1	6.3	22.8	25.8	23.4	16.8	22.8
residual	7.6	−4.9	−2.6		6.5	1.1	−7.1	
K/L grade 2 (n)	76	24	5	105	29	47	27	103
n/total of K/L grade 2 (%)	72.4	22.9	4.8	100.0	43.8	37.5	21.7	100.0
n/total of class (%)	19.0	22.9	31.3	20.1	13.4	25.5	22.7	19.7
residual	−3.5	10.3	−6.8		−14.6	10.0	3.1	
K/L grade 3 (n)	20	10	4	34	5	15	14	34
n/total of K/L grade 3 (%)	58.8	29.4	11.8	100.0	14.7	44.1	41.2	100.0
n/total of class (%)	5.0	9.5	25.0	6.5	2.3	8.2	11.8	6.5
residual	−6.1	3.2	3.0		−9.1	3.0	6.2	
K/L grade 4 (n)	20	14	4	38	12	8	18	38
n/total of K/L grade 4 (%)	52.6	36.8	10.5	100.0	31.6	21.1	47.4	100.0
n/total of class (%)	5.0	13.3	25.0	7.3	5.5	4.3	15.1	7.3
residual	−9.2	6.4	2.8		−3.8	−5.4	9.3	

SMI; skeletal muscle mass index, PBF; percentager body fat, SO; sarcop[enic obesity, K/L grage; Kellgren-Lawrence grade
*p < 0.05, **p < 0.01

Table 3-2. Logistic regression analyses of SMI and PBF with the K/L grade of the knee joints

		SMI				PBF		
		n (%)	mean	B	OR (95% CI)	n (%)	mean	B	OR (95% CI)
K/L grade	0	226 (43.3)	40.72 ± 4.81	0	1	226 (43.3)	28.76 ± 7.83	0	1
	1	119 (22.8)	29.99 ± 4.40	−0.023	0.977 (0.932~1.024)	119 (22.8)	28.28 ± 7.77	0.01	1.01 (0.980~1.041)
			normal SMI	0	1		normal PBF	0	1
			sarcopenia class I		.939		obesity	0.218	1.244
			sarcopenia class II		.939		sarcopenic obesity	0.026	1.027
	2	105 (20.1)	29.58 ± 4.29	−0.007	0.864** (0.818–0.913)	105 (20.1)	29.02 ± 7.72	0.084	1.088** (1.051~1.126)
			normal SMI	0	1		normal PBF	0	1
			sarcopenia class I		1.546		obesity	0.965	2.625**
			sarcopenia class II		6.118**		sarcopenic obesity	0.985	2.677**
	3	34 (6.5)	27.34 ± 4.18	−0.172	0.842** (0.772~0.919)	34 (6.5)	32.78 ± 7.48	0.068	1.106** (1.047~1.169)
			normal SMI	0	1		normal PBF	0	1
			sarcopenia class I		2.447**		obesity	1.581	4.859**
			sarcopenia class II		18.600**		sarcopenic obesity	2.086	8.050**
	4	38 (7.3)	26.18 ± 3.97	−0.308	0.735** (0.664−0.814)	38 (7.3)	34.36 ± 7.35	0.127	1.135** (1.074−1.200)
			normal SMI	0	1		normal PBF	0	1
			sarcopenia class I		.478		obesity	0.077	4.312**
			sarcopenia class II		.000		sarcopenic obesity	1.462	1.08

*p<0.05, **p<0.01

Disclosure: H. Kim, None; **M. Kim**, None; **C. K. Lee**, None; **Y. H. Hong**, None.

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OA Phenotypes Rather Than Disease Stage Drive Structural Progression – Identification of Structural Progressors from 2 Phase III Randomized Clinical studies with Symptomatic Knee OA. Morten Asser Karsdal[1], Anne C. Bay-Jensen[2], Asger Bihlet[3], Peter Alexandersen[4], Inger Byrjalsen[3], Bente J. Riis[3] and Claus Christiansen[3]. [1]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [2]Cartilage Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, [3]Nordic Bioscience, Herlev, Denmark, [4]Center for Clinical and Basic Research, Vejle, Denmark.

Background/Purpose: Osteoarthritis (OA) is a heterogeneous disorder, with several possible drivers of disease progression. Up to 50% of OA patients do not structurally progress, emphasizing the importance for identification of fast progressors, and the phenotypes associated with that. There is therefore a medical need for in-depth, post-hoc analysis of clinical studies in OA. The aim of the analysis was to investigate the associations between JSW, KL-score, pain and JSN (joint space narrowing), as well as BMI, by combining data from two phase III studies (N=2,206) to identify key characteristics for disease progression.

Methods: This is a post-hoc analysis of two randomized, double-blind, multi-center, placebo-controlled trials NCT00486434 and NCT00704847 evaluating the efficacy and safety of 2-years treatment with oral salmon calcitonin in subjects with painful knee OA, enrolling 1,176 and 1,030 subjects. The analysis includes baseline data on KL-score, JSW, pain and function scores from the WOMAC questionnaire, as well as demographics.

Results: *Diagnostic measures;* At baseline, combined analysis of signal and non-signal knees, the mean JSW was comparable in knees of KL-0 and -1 and significantly decreased with increasing KL-2, -3 and -4 ($p<0.01$). JSW (KL2/3) was significantly lower in the non-target knees as compared to the target knees (3.32 ± 0.03mm vs. 3.42 ± 0.02mm, $p<0.0001$, mean±SEM). There was a clear positive and significant correlation between KL-score and WOMAC pain and total WOMAC, albeit the variance in pain measures was from min-to-max for all KL categories, emphasizing the heterogeneity of this patient population and pain perception. Prognostic measures; 32% of target knees did not progress, and only 51% had changes over minimum significant change (MSC). Only minor differences were observed between target and non-target and KL-2 versus KL-3. The mean JSN at 2-years for the non-target knee was 0.25 ± 0.02mm and 0.32 ± 0.02 for the target knee ($p<0.01$). Patients were stratified in quartiles for WOMAC pain and BMI, as well as WOMAC pain and KL-scores, and investigated for JSN. Q3 WOMAC pain progressed more than Q2 and Q4 in both scenarios.

Conclusion: These data from the largest clinical trial dataset in OA to date clearly describe significant associations between KL-score, JSW, pain and BMI in patients with symptomatic knee OA. 50% of patients did not progress

more than MSC, highlighting the importance for identification of structural progressors and the phenotypes associated with these. Patients with symptomatic OA at baseline progressed significantly faster than patients with asymptomatic disease, however with important variations that need accounting for when designing clinical trials, such as relations to pain, BMI and JSN. Different levels of progression were observed in relation to KL score and pain, in which the third WOMAC pain quartile (Q3), but not the fourth quartile (Q4), progressed significantly faster than the first and second pain quartiles. These results suggest that disease phenotypes rather than disease status are responsible for disease progression. Consequently, this dataset is ideally suited for identification of different phenotypes of OA, and biomarkers associated with those.

Disclosure: M. A. Karsdal, Nordic Bioscience Diagnostic, 3; **A. C. Bay-Jensen**, Nordic Bioscience Diagnostic, 1; **A. Bihlet**, Nordic Bioscience Diagnostic, 1; **P. Alexandersen**, CCBR, 3; **I. Byrjalsen**, Nordic Bioscience Diagnostic, 3; **B. J. Riis**, Nordic Bioscience Diagnostic, 1; **C. Christiansen**, Nordic Bioscience Diagnostic, 1.

ACR Poster Session A

Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis: Osteoporosis: Pathogenesis, Epidemiology and Diagnosis

Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Risk Factors for Clinical Vertebral Fractures in Japanese Men and Women with Rheumatoid Arthritis: Results from a Large Prospective Observational Cohort Study.

Osamu Ishida[1], Takefumi Furuya[1], Eisuke Inoue[2], Kensuke Ochi[1], Katsunori Ikari[1], Atsuo Taniguchi[2], Hisashi Yamanaka[1] and Shigeki Momohara[2]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) are at high risk of developing vertebral fractures. Previously, utilizing data from our Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort study, we reported clinical risk factors for clinicalvertebral fractures in Japanese patients with RA. However, in our previous studies, which analyzed data from 2000 to 2005, the number of patients with verified clinical vertebral fractures was only 40. The aim of this study was to re-evaluate the associations between potential risk factors and the occurrence of clinical vertebral fractures in a larger number of Japanese patients with RA.

Methods: IORRA is a prospective observational cohort study of Japanese patients with RA established in 2000 at the Institute of Rheumatology, Tokyo Women's Medical University. A total of 10,240 Japanese patients with RA (82% female; mean age, 56 years) were enrolled in IORRA cohort study from 2000 to 2011. Self-reported vertebral fractures were verified with patient medical records and radiographs. Independent contributions of various risk factors to clinical vertebral fracture occurrence were analyzed with Cox proportional hazards models.

Results: During a mean follow-up of 4.9 years, 399 patients reported 638 clinical vertebral fractures. Among these patients, 187 clinical vertebral fractures in 187 patients (18 men, 169 women) were verified with medical records (n = 95) and radiographs (n =92). The vertebral fractures were mainly caused by spontaneous events (65%) and falls (25%). Vertebral fractures occurred at lumbar (36%), thoracic (37%), and both (27%) levels of the spine. In men with RA, multivariate Cox regression analyses estimated that the risk of sustaining a clinical vertebral fracture increased by 2.51 for every 10 years of increased age, 2.96 for Japanese version of Health Assessment Questionnaire-Disability Index (J-HAQ-DI), and 1.17 for daily prednisolone dose (Table 1). In women with RA, multivariate Cox regression analyses estimated that the risk of sustaining a clinical vertebral fracture increased by 1.30 for Disease Activity Score 28 (DAS28), 2.35 for history of any previous fractures, 1.67 for every 10 years of increased age, 1.39 for J-HAQ-DI, and 1.08 for daily prednisolone dose (Table 1). Among the eight domains of the J-HAQ-DI, J-HAQ-DI (arising) was significantly associated with the clinical vertebral fractures in Japanese patients with RA (hazard ratio 1.26, 95% confidence interval [CI] 1.02–1.54).

Conclusion: We confirmed the associations between clinical vertebral fractures and advanced age, J-HAQ-DI, and high daily prednisolone dose in a larger number of patients and found significant correlations between clinical vertebral fractures and DAS28, history of any previous fractures, and J-HAQ-DI (arising) in Japanese patients with RA. These clinical risk factors appear to be different between men and women in Japanese RA patients.

Table 1 Hazard ratios (95% confidence interval) for the occurrence of clinical vertebral fractures in Japanese men and women with RA: Multivariate analyses.

Risk factors	Men	Women
DAS28	0.73 (0.36–2.48)	1.30 (1.05–1.63)
History of any prior fracture	1.32 (0.45–3.81)	2.35 (1.69–3.27)
Age, per 10 years	2.51 (1.34–4.73)	1.67 (1.42–1.97)
Japanese HAQ-DI	2.96 (1.02–3.60)	1.39 (1.08–1.79)
Daily prednisolone dose, mg/day	1.17 (1.06–1.29)	1.08 (1.05–1.12)

Disclosure: O. Ishida, None; **T. Furuya**, None; **E. Inoue**, None; **K. Ochi**, None; **K. Ikari**, None; **A. Taniguchi**, None; **H. Yamanaka**, Abbott, AbbVie, Asahikasei, Astellas, AstraZeneca, Bristol-Myers Squib, Chugai, Daiichi Sankyo, Eisai, Glaxo-SmithKline, Janssen, Mitsubishi Tanabe, MSD, Nippon Kayaku, Pfizer, Santen, Taishotoyama, Takeda, Teijin,, 2, Abbott, AbbVie, Astellas, AstraZeneca, Bristol-Myers Squib, Chugai, Daiichi Sankyo, Eisai, Mitsubishi Tanabe, Nippon Kayaku, Pfizer, Takeda, Teijin, 5, Abbott, AbbVie, Astellas, Bristol-Myers Squib, Chugai, Eisai, Mitsubishi Tanabe, Pfizer, Takeda, Teijin, 8; **S. Momohara**, Abbvie Japan, Chugai Parmaceutical, Eisai, Mitsubishi Tanabe Parma, Takeda Parmaceutical, 8.

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Is the Protective Effect of Obesity Against Hip Fracture Due to Changes of Proximal Femur Shape?

Alexander Oldroyd and Marwan Bukhari. Lancaster University, Lancaster, United Kingdom.

Background/Purpose: The association between increasing body mass index (BMI), increasing bone mineral density (BMD) and lower hip fracture risk has been demonstrated by previous research. Studies have implicated variations of proximal femur shape in hip fracture risk. Research has indicated that BMI affects hip fracture risk by its associations with both BMD and proximal femur shape.

This study aims to investigate if variations of proximal femur shape associated with BMI are associated with hip fracture risk, independent of BMD, in a large population of women aged over 50 years.

Methods: Data of women aged over 50 years that attended for a DXA scan at a UK hospital were collated. The following Hip Structural Analysis (HSA) measurements were used to characterise the shape of the proximal femur: distance from centre of femoral head to centre of femoral neck (d1), distance from centre of femoral head to inter-trochanteric line (d2), mean femoral neck diameter (d3), distance from centre of mass of femoral neck to superior neck margin (y), hip axis length (HAL), cross-sectional moment of inertia (CSMI) and the neck/shaft angle. Multiple regression analysis was used to investigate for associations between BMI and each HSA measurement, adjusted for age, femoral neck BMD and significant osteoporosis risk factors. Logistic regression analysis modelling was used to investigate for associations between previous contralateral hip fracture and each HSA measurement, adjusted for age, BMI, femoral neck BMD and significant osteoporosis risk factors.

Results: Data of 8,788 women was analysed. Analysis revealed that a wider (d3, y) and shorter (d1) femoral neck with increased cortical thickness (CSA, CSMI) were associated with a clear significant relationship with increasing BMI (tables 1 and 2). Further analysis revealed that proximal femur shape was not significantly associated with previous contralateral hip fracture (table 2).

Conclusion: This study of a large population of older women identified that a wider and shorter femoral neck with increased cortical thickness was associated with increasing BMI; however, variations of proximal femur shape associated with BMI were not associated with previous hip fracture status.

	BMI category (Kg/m^2)				
	<19	19–25	25–30	30–35	>35
Number in category	552	3046	3149	1421	620
Mean BMI/Kg/m^2 (SD)	18.56 (1.11)	22.89 (1.36)	27.26 (1.41)	32.09 (1.40)	38.46 (3.04)
Mean age/years (SD)	67.99 (10.24)	66.61 (9.82)	67.35 (9.25)	67.39 (8.98)	65.07 (8.76)
Mean number of OP risk factors (SD)	2.89 (1.52)	2.40 (1.31)	2.44 (1.32)	2.40 (1.33)	2.40 (1.32)
Femoral neck BMD (SD)	0.73 (0.12)	0.79 (0.12)	0.83 (0.12)	0.86 (0.13)	0.90 (0.15)
Proportion with previous hip fracture/%	5.62	2.95	2.95	3.24	2.41
HAL/mm (SD)	106.07 (7.25)	105.69 (6.34)	105.68 (6.08)	105.90 (5.96)	106.19 (5.82)
CSMI/m^4 (SD)	8.07 (2.12)	8.82 (2.22)	9.27 (2.53)	9.56 (2.64)	9.91 (2.88)
CSA/mm^2 (SD)	109.76 (19.92)	121.56 (19.96)	126.99 (21.36)	131.88 (23.37)	137.38 (25.48)
d1/mm (SD)	16.83 (3.25)	16.27 (3.19)	15.92 (3.26)	15.61 (3.23)	15.86 (3.33)
d2/mm (SD)	47.68 (6.31)	48.08 (5.71)	48.48 (5.62)	48.75 (5.75)	48.88 (5.90)
d3/mm (SD)	32.87 (2.84)	32.90 (2.50)	33.17 (2.55)	33.23 (2.58)	33.18 (2.65)
Y/mm (SD)	16.95 (1.82)	16.81 (1.48)	16.99 (1.57)	17.09 (1.60)	17.05 (1.69)
Neck/shaft angle/^{0}	125.93 (5.41)	125.02 (5.28)	124.88 (5.22)	124.84 (5.47)	124.63 (5.51)

Table 1 – BMI categories and mean age, number of OP risk factors, mean femoral neck BMD, proportion that have previously sustained a hip fracture and mean HSA measurements

HSA measurement	Coefficient against BMI	p-value	Coefficient against previous hip fracture	p-value
HAL/mm (SD)	−0.02	0.764	−0.06	0.61
CSMI/m^4 (SD)	0.07	0.02	−0.09	0.78
CSA/mm^2 (SD)	0.01	0.01	0.04	0.53
d1/mm (SD)	−0.15	<0.01	−0.20	0.21
d2/mm (SD)	0.01	0.26	−0.01	0.92
d3/mm (SD)	0.13	<0.01	0.58	0.06
y/mm	0.32	<0.01	0.08	0.10
Neck/shaft angle/^{o}	−0.01	0.24	−0.30	0.79

Table 2 – coefficient and p-value of each HSA measurement against BMI, adjusted for age, number of OP risk factors and femoral neck BMD; coefficient and p-value of each HSA measurement against previous hip fracture, adjusted for age, number of OP risk factors, BMI and femoral neck BMD

Disclosure: A. Oldroyd, None; **M. Bukhari**, None.

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Association Between Lean Mass and Hip Bone Mineral Density. Charlotte Beaudart, Jean-Yves Reginster, Justine Slomian, Fanny Buckinx and Olivier Bruyere. University of Liège, Liège, Belgium.

Background/Purpose: Fat mass and lean mass (LM) represent 95% of body weight. However, the role of each component on bone mineral density (BMD) is not clear. In this study, we aimed to investigate the correlation between LM mass and hip BMD.

Methods: Voluntary subjects aged 65 years or older were recruited in an outpatient clinic in Liège, Belgium. Hip BMD as well as LM were measured by dual X-ray absorptiometry.

Results: 123 subjects were recruited for this study (88.5% of women, mean age 74.6 ± 6.4 years). LM was positively correlated with hip BMB (r=0.40; p<0.001). In a multiple regression analysis adjusted for sex, age, body mass index (BMI), physical activity, alcohol and tobacco consumption and presence of prior fracture, this relationship was still significant (b=0.35; p=0.02). In line with this result, we found a higher correlation between LM and hip BMD in men than in women (r=0.60 versus r=0.32 respectively), but also in subjects presenting a BMI higher than 25 kg/m^2 compared to the others (r=0.51 versus r=0.09), in subjects aged between 65 years and 80 years compared to older (r=0.38 versus r=0.29) and in subjects spending at least 1000 kcal/week for their leisure time activity (i.e. Minnesota test) compared to the others (r=0.44 versus r=0.28).

Conclusion: A positive association was found between LM and hip BMD. Strategies aiming to increase lean body mass in subjects aged 65 years or older could be of great public health interest in the field of bone health.

Disclosure: C. Beaudart, None; **J. Y. Reginster**, None; **J. Slomian**, None; **F. Buckinx**, None; **O. Bruyere**, None.

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Improved Prediction of Hip Fracture Using the Health Assessment Questionnaire-Disability Index and FRAX® in Japanese Patients with Rheumatoid Arthritis: A Prospective Observational Study. Takefumi Furuya[1], Eisuke Inoue[2], Kensuke Ochi[1], Osamu Ishida[1], Atsuo Taniguchi[2], Shigeki Momohara[2] and Hisashi Yamanaka[1]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: The World Health Organization Fracture Risk Assessment Tool (FRAX®) algorithm can be used to estimate 10-year probabilities of hip and major osteoporotic fractures. Previously, we and others have reported a significant association between the Health Assessment Questionnaire-Disability Index (HAQ-DI) and clinical fracture risk in patients with rheumatoid arthritis (RA). This has generated interest in the possible role the HAQ-DI could play in improving fracture risk assessment for Japanese patients with RA. The aim of this study was to evaluate the prognostic accuracy of the Japanese version of FRAX® to predict the 10-year probability of hip and major osteoporotic fractures in Japanese patients with RA, and investigate whether the HAQ-DI can further improve the prediction of hip and major osteoporotic fractures.

Methods: We analyzed the database of the Institute of Rheumatology Rheumatoid Arthritis (IORRA) study, our large prospective observational cohort study in Japanese patients with RA. IORRA study subjects included 3,095 women and 703 men with RA ranging in age from 40 to 90 years. The mean (± standard deviation) age was 60.6 ± 9.6 years. Self-reported major osteoporotic fractures of the hip, vertebrae, humerus, and wrist were verified using patient medical records. The association of FRAX® with fractures was evaluated by the Cox model, and C-statistics were used in the risk prediction model to account for censored *survival*data. The Japanese version of HAQ-DI (J-HAQ-DI) was used in the assessment in conjunction with FRAX®, without considering bone mineral density (BMD) values, and C-statistics were used for the 10-year risk calculated by the Cox model.

Results: A total of 3,789 Japanese patients with RA were followed for an average of 5.8 years. Using FRAX® without BMD, the mean 10-year predicted fracture probability for hip and major osteoporotic fractures was 5.3% and 14.5%, respectively. Among the patients, 52 (1.4%) and 216 (5.7%) presented with hip and major osteoporotic fractures (including n=52 hip, n=85 vertebral, n=41 humeral, and n=38 distal radial fractures), respectively. For hip fractures, the C-statistic was 0.735 (95% CI: 0.665, 0.804) for the statistical model prediction based on both J-HAQ-DI and FRAX®, and it was 0.688 (95% CI: 0.613, 0.762) for FRAX® alone. For major osteoporotic fractures, the C-statistic was 0.678 (95% CI: 0.636, 0.719) for both J-HAQ-DI and FRAX®, and 0.664 (95% CI: 0.624, 0.704) for FRAX®alone.

Conclusion: We evaluated the performance of FRAX® in Japanese patients with RA using our longitudinal study data. Our results were similar to those in other previously reported FRAX® studies. However, the J-HAQ-DI improved hip fracture risk assessment when used in conjunction with this conventional risk assessment tool in Japanese patients with RA.

Disclosure: T. Furuya, None; **E. Inoue**, None; **K. Ochi**, None; **O. Ishida**, None; **A. Taniguchi**, None; **S. Momohara**, Abbvie Japan, Chugai Parmaceutical, Eisai, Mitsubishi Tanabe Parma, Takeda Parmaceutical, 8; **H. Yamanaka**, Abbott, AbbVie, Asahikasei, Astellas, AstraZeneca, Bristol-Myers Squib, Chugai, Daiichi Sankyo, Eisai, Glaxo-SmithKline, Janssen, Mitsubishi Tanabe, MSD, Nippon Kayaku, Pfizer, Santen, Taishotoyama, Takeda, Teijin,, 2, Abbott, AbbVie, Astellas, AstraZeneca, Bristol-Myers Squib, Chugai, Daiichi Sankyo, Eisai, Mitsubishi Tanabe, Nippon Kayaku, Pfizer, Takeda, Teijin, 5, Abbott, AbbVie, Astellas, Bristol-Myers Squib, Chugai, Eisai, Mitsubishi Tanabe, Pfizer, Takeda, Teijin, 8.

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Increasing Fat-Mass May Reverse Bone Loss As Detected By DXA Scan. William Hedges[1] and Marwan Bukhari[2]. [1]Royal Lancaster Infirmary, University Hospitals of Morecambe Bay NHS Foundation Trust, Lancaster, United Kingdom, [2]Lancaster University, Lancaster, United Kingdom.

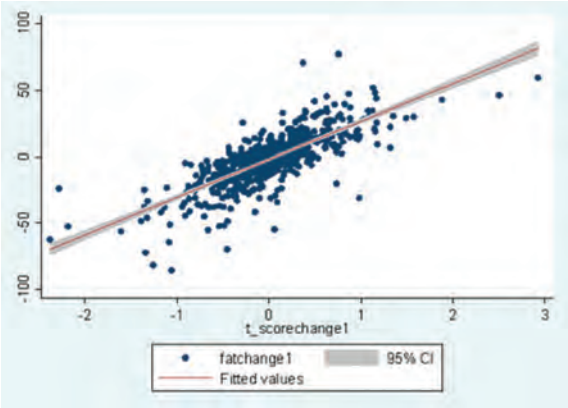
Background/Purpose: Low body mass index (BMI) is a known risk factor for loss of bone mineral density (BMD). It is a part of the FRAX ™ 10-year fracture risk stratification tool developed by the World Health Organisation. It is also known that weight loss through dieting decreases BMD, whilst weight loss through exercise preserves it. The effects of fat-mass and change in fat-mass have not been examined extensively. This could have implications for health advice given to those at significant risk of fragility fractures. This study aimed to identify factors influencing change in bone density related to fat-mass and any confounders.

Methods: Data were analysed from patients having dual-energy X-ray absorptiometry (DXA) assessment between 2007 and 2010. Patients were included if they had multiple scans which included measurements of lean mass and fat mass. Our scanners limited these to scans of the AP spine. Linear regression was performed to determine the relationship between changes in fat mass and BMD. A backwards stepwise linear regression model was fitted with inclusion of confounders including: sex, risk factors, previous fractures, baseline BMI and age at menopause.

Results: 23,239 patients were included in the study, of which 702 met our inclusion criteria. This included 93 males (13%) and 609 females (87%). Mean age at first scan in the whole cohort was 64.5 years (SD11.2). The mean interval between scans was 3.0 years (SD 0.89). Step-wise linear regression identified a positive correlation between increasing fat-mass and t-score per unit time between scans (coefficient 28.4, p<0.01 95%CI 26.6–30.1). Controlling for the above factors didn't alter the results. We identified previous pelvic and femur fractures (p<0.05) and history of inflammatory diseases (p<0.05) as independent risk factors influencing bone density related to fat mass. This relationship was true for patients that were underweight (BMI <18.5), normal weight (BMI 18.5–25), and overweight patients (BMI >25).

Conclusion: Increasing fat mass between DEXA scans is associated with an increase in t-scores. Other factors associated with increasing fat-mass include previous pelvic and femur fractures, as well as history of inflamma-

tory disease. However, excessive fat-mass is associated with increased cardiovascular (CVD) and metabolic disease states. Increasing fat-mass is therefore not viable for all patients. Those at particular risk of fragility fractures and not CVD, e.g. BMI<18.5, may be able to improve their long-term risk by gaining weight.



Disclosure: W. Hedges, None; **M. Bukhari**, None.

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Is Adult Hypophosphatasia a Cardiovascular Risk Factor? Leyre Riancho-Zarrabeitia[1], Maria T. García-Unzueta[1], Alfonso Corrales[1], Juan Gómez-Gerique[1] and José A. Riancho[2]. [1]Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [2]Hospital Universitario Marqués de Valdecilla. IDIVAL. University of Cantabria, Santander, Spain.

Background/Purpose: Mild forms of adult hypophosphatasia may have subtle manifestations, and may go unrecognized. The aim of this study was to get a better knowledge of its clinical spectrum.

Methods: We performed a computerized search of low total alkaline phosphatase among laboratory records. The diagnosis of hypophosphatasia was confirmed by measuring serum pyridoxal phosphate (PLP) and bone alkaline phosphatase. Carotid ultrasonography was performed in patients and controls with a MyLab 70 scanner (Esaote; Genoa, Italy), equipped with 7–12 MHz linear transducer.

Results: Over a 31 month period, we identified 130 individuals with at least one determination of serum alkaline phosphatase less than 26 u/l. After reviewing the clinical records, unexplained persistently low levels were found in 42 individuals who accepted to participate in the study (10 men, 32 women). Age range was 20–77 yr (mean 51). Total alkaline phosphatase levels were positively correlated with bone alkaline phosphatase ($r=0.52$, $p<0.001$). Serum PLP was inversely correlated with bone alkaline phosphatase. Ten individuals (24%) had PLP levels above the reference range of 175 nmol/l, consistent with hypophosphatasia. In comparison with those with normal PLP levels, these individuals had higher frequency of hypertension (50 vs 12%, $p=0.02$). Likewise, individuals with hypophosphatasia showed a trend to have early atherosclerotic disease. Carotid ultrasound showed bilateral plaques in 4 out of 9 patients (44%), and only in 26% of the age and sex-matched controls. The intima-media thickness also tended to be increased in the patients (670 ± 70 vs. 648 ± 110 microns; $p=0.18$).

Conclusion: These preliminary data suggest that individuals with adult hypophosphatasia may be at increased cardiovascular risk. The results should be confirmed in larger studies.

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Correlates of Heel Bone Mass in Young Adults: The Role of Cholesterol over 20 Years from Childhood to Early Adulthood. Benny Samuel Eathakkattu Antony[1], Changhai Ding[2], Alison Venn[3], Terry Dwyer[4] and Graeme Jones[2]. [1]Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia, [2]Menzies Research Institute Tasmania, University of Tasmania, Hobart,7000, Australia, [3]Menzies Research Institute Tasmania, University of Tasmania, Hobart, Tasmania, Australia, [4]Murdoch Children's Research Institute, Melbourne, Australia.

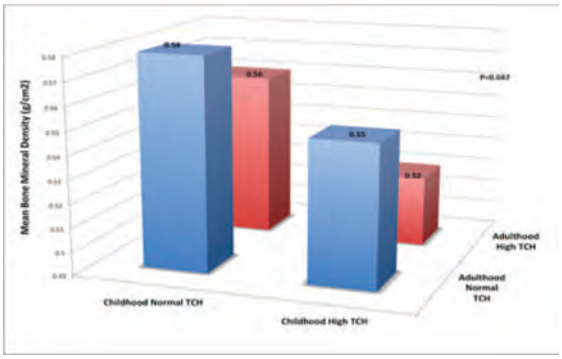
Background/Purpose: The association between lipids and bone mass in adult life is controversial and there is limited evidence in childhood. The aim of this study was to describe the association between cholesterol measured in childhood and young adult life and bone mineral density (BMD) in younger adults.

Methods: Subjects broadly representative of the Australian population ($n=1431$, female=52%, age=26–36) were selected from the Australian Schools Health and Fitness Survey of 1985. They underwent various measurements including leg strength, standing long jump, and physical work capacity at 170 heart beats per minute (PWC_{170}). Physical activity, smoking and alcohol history were recorded using questionnaires. Fasting lipid profiles were assessed in childhood and 20 years later in adulthood. A single Sahara bone ultrasound densitometer was used to determine heel bone mass in adulthood.

Results: In multivariable analysis, childhood High Density Lipoprotein (HDL) was positively (β: 0.056 g/cm^2, 95% CI: 0.005, 0.108) and total cholesterol (TCH, normal Vs high β: -0.042 g/cm^2, 95% CI: -0.081, -0.003) and Low Density Lipoprotein (LDL, normal Vs high β: -0.019 g/cm^2, 95% CI: -0.039, 0.000) were negatively associated with BMD in adulthood. Similarly, adulthood TCH (β: -0.007 g/cm^2, 95% CI: -0.015, -0.001) and LDL (β: -0.011 g/cm^2, 95% CI: -0.019, -0.003) were negatively associated with adult life BMD. The association between childhood HDL and adulthood BMD remained significant after further adjustment for adulthood HDL levels. Subjects who remained in the abnormal category of TCH from childhood to adulthood (high-high) had the least bone mass compared to other category changes of TCH from childhood to adulthood.

These results were independent of gender, alcohol consumption and duration of follow-up from childhood to adulthood. The other confounders included in this analysis were independently associated with BMD, such as age (negatively associated with BMD, β: -3.58 mg/cm^2 per year, 95% CI: -6.14, -1.01), physical activity (vigorous activity, β: 0.04 mg/cm^2 per min/week, 95% CI: 0.01, 0.08), BMI in childhood and adulthood (both positively associated with BMD) and smoking (β: -18.34 mg/cm^2, 95% CI: -27.35, -9.34). Duration and pack year of smoking were independently and negatively associated with BMD while performance measures including PWC_{170} (β: 0.33 mg/cm^2 per Watts, 95% CI: 0.15, 0.51), leg muscle strength (β: 0.24 mg/cm^2 per Kg, 95% CI: 0.02, 0.45) and long jump (β: 0.71 mg/cm^2 per cm, 95% CI: 0.40, 1.02) were positively associated with BMD.

Conclusion: HDL in childhood was beneficially and high TCH was detrimentally associated with adulthood BMD. LDL and TCH in adulthood were detrimentally associated with BMD. The effect of childhood HDL was independent of the adulthood HDL levels. These results indicate that cholesterol may have long-term effects on bone mass from childhood to early adulthood.



Disclosure: B. S. Eathakkattu Antony, None; **C. Ding**, None; **A. Venn**, None; **T. Dwyer**, None; **G. Jones**, None.

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Risk Factors That Predict Poor Bone Health in Those Aged over 75 Years - a Cross Sectional Study. James Fowler[1], Christopher Varley[2], Alexander Oldroyd[2] and Marwan Bukhari[2]. [1]University Hospitals of Morecambe Bay NHS Foundation Trust, Lancaster, United Kingdom, [2]Lancaster University, Lancaster, United Kingdom.

Background/Purpose: .No studies have been conducted into the over 75 population specifically to assess the risk factors that predict BMD loss. The Framingham Osteoporosis Study (age range 69–90) found that gender, weight loss, alcohol use and smoking were the only risk factors that predicted significant increase in the loss of BMD(1). However that study did not analyse

other risk factors such as glucocorticoid use, previous fragility fracture, family history of osteoporosis and rheumatoid arthritis. Furthermore we have shown that bone loss in the lumbar spine and the femoral neck could differ and this was not examined in the elderly.

The aim of this study was to establish which risk factors would predict BMD loss in the over 75 year old population in the lumbar spine and the femoral neck.

Methods: A cohort of patients referred between 2004 and 2011 to a DEXA scanner in the North West of England who over the age of 75 were identified. The sites of bone that were scanned for BMD loss were the L1-L4 vertebrae and the non dominant femoral neck. The risk factors collated included age, gender, BMI, current smoking, family history of osteoporosis, rheumatoid arthritis, current corticosteroid use, history of fragility fracture and current alcohol excess. A regression model was then fitted to determine predictors of BMD loss in those aged over 75. This was done at both the femoral neck and the lumbar spine adjusting for age and gender.

Results: 4,655 patients over the age of 75 were identified; the mean age of the cohort was 79.2 (SD 3.9), with 3732 (80%) females The following risk factors were found to be significantly associated with increased BMD loss in the hip when adjusted: height with a beta coefficient of 0.004 (95% CI 0.003, 0.004), weight 0.005 (95% CI 0.004, 0.006), BMI 0.012 (95% CI 0.011, 0.013) and history of fragility fracture -0.034 (95% CI -0.045, -0.023). The following risk factors were found to be significantly associated with increased bone loss in the lumbar spine after adjusting: height with a beta coefficient of 0.006 (CI 95% 0.004, 0.007), weight 0.007 (95% CI 0.006, 0.0074), BMI 0.014 (CI 95% 0.0135, 0.016), rheumatoid arthritis 0.036 (95% 0.007,0.06) and history of fragility fracture -0.05 (−0.066, -0.04). Glucocorticoid use, tobacco use, alcohol use and family history of osteoporosis were not found to be associated.

Conclusion: Risk factors for increased BMD loss in patients over 75 years old were height, weight, BMI and history of fragility fracture in both the hip and the lumbar spine with rheumatoid arthritis being a risk factor for only the lumbar spine. The results from this study suggest that assessing bone health in the elderly is complex and assuming that risk factors do not change with age is not the case.

References

1. Journal of bone and mineral research. 2000;15(4):710–20. Epub 2000/04/26.

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Factors Predicting Fracture in the over-75s: An Observational Case-Control Study. Christopher Varley[1], James Fowler[2], Alexander Oldroyd[1] and Marwan Bukhari[3]. [1]Lancaster University, Lancaster, United Kingdom, [2]Lancaster Univeristy, Lancaster, United Kingdom, [3]Royal Lancaster Infirmary, Lancaster, United Kingdom.

Background/Purpose: In the over 75s the diagnosis of osteoporosis may be assumed following a fracture, making the need for a dual energy absorptiometry scan (DEXA) optional [1]. In those presenting without fracture, it has been suggested that referral for a DEXA scan in the over 75s should require the presence of 2 risk factors for osteoporotic fracture[2]. However, the strength of these risk factors for predicting fractures in this specific age range has not been properly assessed. This study aims to assess the sensitivity of the risk factors in predicting fractures in patients aged 75 and over.

Methods: Using a nested case-control approach, a cohort of patients aged over 75 and referred between 2004 and 2011 to a DEXA scanner were indentified. The patients were divided into two cohorts depending on their fracture history. The risk factors assessed were hip and spine BMD, family history of fragility fracture, smoking, alcohol excess, steroid use, body mass index (BMI) and rheumatoid arthritis. Logistic models were fitted predicting fractures in the group, adjusting for age and gender.

Results: 4,663 patients over the age of 75 were identified; the median age of the cohort was 79.2 years (SD 3.1 years), with 3732 (80%) females. Fracture was the presenting feature in 1830 (39.25%) of the subjects. The only risk factors which were significantly increased in the fracture group, when adjusted for age and gender, were reduced BMD in the hip (OR: 1.65, CI: 1.21 – 2.42), reduced BMD in the spine (OR: 3.81, CI: 2.81 – 5.16) and rheumatoid arthritis (OR: 6.42 CI: 3.56 – 11.58). The other risk factors of smoking, alcohol excess, family history, steroids and BMI were not significantly associated with fractures when adjusted for age and gender with steroids showing an apparent protective effect (OR 0.74 95%CI 062, 0.87).

Conclusion: Most of the traditional risk factors which predict bone mineral density loss and fracture, such as smoking, alcohol, low BMI and steroid use do not predict fragility fracture in the over 75s, with a curious beneficial effect of steroids. This study has found that the factors which most predict fracture in the elderly are a low BMD in both the hip and spine, and rheumatoid arthritis. This shows that the current clinical advice to not routinely DEXA scan the over 75 year old patients is potentially incorrect; in this age group a patient's hip and spine BMD can provide useful information for judging fracture risk. Limitations of this study include it's observational design, but this association should be studied further.

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2. Excellence NICE. Osteoporosis: assessing the risk of fragility fracture. 2012.

Disclosure: C. Varley, None; **J. Fowler**, None; **A. Oldroyd**, None; **M. Bukhari**, None.

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Significance of Serum Srankl and Osteoprotegerin Concentration in Patients with Rheumatoid Arthritis. Kotaro Shikano, Kaichi Kaneko, Mai Kawazoe, Shotaro Masuoka, Hiroshi Sato, Emiko Shindo, Natsuki Fujio, Makoto Kaburaki, Sei Muraoka, Nahoko Tanaka, Tatsuhiro Yamamoto, Kenji Takagi, Natsuko Kusunoki, Tomoko Hasunuma and Shinichi Kawai. School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan.

Background/Purpose: Rheumatoid arthritis (RA) is known as a cause of secondary osteoporosis. The previous studies reported that receptor activator for nuclear factor κB ligand (RANKL) and osteoprotegerin (OPG) were involved in patients with osteoporosis of various causes. Serum soluble RANKL (sRANKL) is a molecule that may possibly be related to RANKL expression in osteoblasts. The purpose of this study is to investigate serum levels of sRANKL, OPG and several bone metabolism markers in patients with RA.

Methods: RA patients and healthy controls were recruited at Toho University Omori Hospital and the Research Center for Clinical Pharmacology of Kitasato University, respectively. 360 patients with RA [mean age 61.5±13.4 (SD) years, male 66 and female 294 (menopause 229), mean disease duration 119±6.0 (SD) months] were included. We measured serum levels of sRANKL and OPG in RA patients and healthy controls. Serum levels of bone formation markers [intact aminoterminal propeptide of type I procollagen (P1NP) and bone specific alkaline phosphatase (BAP)], and bone resorption markers [type I collagen cross-linked N- telopeptide (NTX) and tartrate-resistant acid phosphatase form 5b (TRACP-5b)] were measured in the same subjects. In addition to these, we observed the background of the RA patients, such as age, sex, disease duration, stage classification, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Disease Activity Score (DAS) 28-ESR, Health Assessment Questionnaire (HAQ), Sharp score, and bone mineral density (BMD).

Results: The serum level of sRANKL [median (25th to 75th percentile range)] in patients with RA [0.09 (0.01–0.21) pmol/L] was significantly increased compared to that of healthy controls [0.03(0–0.19) pmol/L]. As well, the serum level of OPG of RA [5.24 (4.04–5.67) pmol/L] was significantly increased in comparison to healthy subjects [3.61(3.04–4.13) pmol/L]. The serum sRANKL level was negatively correlated with age, CRP and ESR by univariate analysis. In multivariate analysis, sRANKL was negatively correlated with age and disease duration, whereas, it was positively correlated with HAQ. The serum level of OPG was positively correlated with CRP, DAS28-ESR and MMP-3 as well as age by univariate analysis. In multivariate analysis, OPG was positively correlated with age and MMP-3. Both of serum sRANKL and OPG did not correlate with Sharp score and BMD in RA patients. There was no statistical correlation between the serum levels of sRANKL and OPG in RA patients and healthy controls.

Conclusion: In this study, we showed that both of the serum levels of sRANKL and OPG were significantly higher than those in healthy controls. Since sRANKL was correlated with disability index of HAQ, it is suggested that we should pay attention to deterioration of osteoporosis especially in the RA patients with severely impaired activities of daily living. On the other hand, OPG was correlated with disease activity of RA, suggesting that further attention to osteoporosis will be necessary even for the RA patients with the lower disease activities or remission.

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Significance of Serum Marker Levels of Wnt/β-Catenin Signaling Pathway in Patients with Systemic Autoimmune Diseases Under Glucocorticoid Therapy; A Prospective Study. Mai Kawazoe, Kotaro Shikano, Kaichi Kaneko, Shotaro Masuoka, Hiroshi Sato, Emiko Shindo, Natsuki Fujio, Sei Muraoka, Makoto Kaburaki, Nahoko Tanaka, Tatsuhiro Yamamoto, Kenji Takagi, Natsuko Kusunoki, Tomoko Hasunuma and Shinichi Kawai. School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan.

Background/Purpose: Glucocorticoids are widely used to treat a variety of diseases, including systemic autoimmune diseases. Although glucocorticoids improve the outcome for patients with these diseases, various side effects of long-term treatment, such as osteoporosis, have become an important problem. Glucocorticoids decrease bone density through multiple mechanisms by inhibition of bone formation and by enhancement of bone resorption. Recently, the identification of the Wnt/β-catenin signaling pathway has led to considerable interest as one of the mechanism of osteoporosis in postmenopausal women. Wnt/β-catenin signaling pathway is mediated by Wnt3a and plays an important role in bone formation. Sclerostin and Dickkopf1 (Dkk-1) have been identified as antagonists of Wnt signaling. Therefore the purpose of this study is to clarify the clinical significance of the Wnt signaling pathway by measuring the serum levels of sclerostin, Dkk-1, Wnt3a and bone turnover markers in patients with recent onset of glucocorticoid therapy.

Methods: Patients were recruited at Toho University Omori Medical Center. This study was approved by the Ethics Committee of the Medical Center. Forty patients (25 females [14 postmenopausal], 55.2 ± 2.9 yr [mean ± SD]) with systemic autoimmune diseases (vasculitis syndrome 16, systemic lupus erythematosus 12, polymyositis / dermatomyositis 9, and adult-onset Still's disease 3) who received initial glucocorticoid therapy with prednisolone daily (30–60 mg) were prospectively enrolled in this study. Their mean bone mineral density at starting of prednisolone therapy was 0.944 g/cm2. Mean C -reactive protein was 4.08 ± 0.51 (S.D.) mg/dl. Regular doses of bisphosphonates (alendronate or risedronate) were co-administered in all patients. We measured serum sclerostin, Dkk-1, Wnt3a and bone turnover markers at 0, 1, 2, 3 and 4 weeks after start of glucocorticoid therapy.

Results: Serum sclerostin level was significantly ($p<0.05$) increased from 1st to 2nd weeks after starting of glucocorticoid therapy in comparison to previous value. Serum Dkk-1 level had a tendency to decrease, but there was no significant difference. Serum Wnt3a level had a trend to decrease after glucocorticoid therapy. Serum bone formation markers, osteocalcin and procollagen type I N-terminal peptide, decreased from 1st to 4th weeks, whereas bone alkaline phosphatase did not change. Serum bone resorption markers, tartrate-resistant acid phosphatase isoform 5b and N-telopeptide crosslinked of type I collagen did not change.

Conclusion: We found that glucocorticoid therapy caused increased level of serum sclerostin and a trend of decreased Wnt3a level. It is suggested that suppression of Wnt/β-catenin signaling pathway might, at least in part, be a cause of severe osteoporosis in patients with systemic autoimmune diseases under glucocorticoid therapy.

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The Decrease in Prescription of Anti-Osteoporotic Drugs Has No Impact on Hip Fracture Incidence. Karine Briot[1], Milka Maravic[2] and Christian Roux[3]. [1]Paris Descartes University, Paris, France, [2]Hopital Leopold Bellan, Paris, France, [3]Paris Descartes University, Cochin Hospital, Paris, France.

Background/Purpose: Controversies exist about the change in hip fracture incidence among countries. In France, we previously showed that the incidence of hip fractures decreased in both genders, especially in the elderly from 2002 to 2008 in parallel with availability of bone densitometry and effective antiosteoporotic treatments. However these prescriptions are decreasing, since 2009 (1), and recent studies show declining of osteoporosis management after fragility fractures. The aim of this study was to assess the incidence of hip fractures in men and women aged 60 years and over, from 2008 to 2013 in France.

Methods: Data were drawn from the French Hospital National Database which includes all hospitalizations. Hospital data for hip fractures between 2002 and 2013 were numbered and the incidence rates per 1,000,000 adjusted on age (60–74; 74–84, and ≥ 85 years), and gender was calculated using the data of the French population.

Results: The number of hip fractures increased in women (+5%; from 49,287 in 2002 to 50,215 in 2013) and in men (+22%, from 12,716 to 15,482 in 2013). Between 2002 and 2013, the French population increased by 21 and 29% in women and in men. Incidence of hip fractures over 60 years decreased by -14% in women (6,929 and 5,987 per million in 2002 and 2013, respectively) and a slight decrease of -1%was observed in men (2,344 and 2,316 per million in 2002 and 2013, respectively). An age-specific incidence decrease was also confirmed, in particular, in the elderly in both genders (≥ 85 years) with a decrease of -29% in women and -24% in men ($p<0.00001$).

Conclusion: Over the last 12 years, the incidence of hip fractures decreased in France in women and men aged over 60 years. This decrease is particularly important in the elderly in both genders. This is observed in parallel with the decrease in prescription of antiosteoporotic treatments. Further studies are needed to assess potential changes in hip fractures risk factors during the last decade.

Reference:

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Disclosure: K. Briot, None; **M. Maravic**, None; **C. Roux**, None.

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Lower P1NP Serum Levels: a Predictive Marker of Bone Loss after One-Year Follow-up in premenopausal SLE Patients. Luciana Seguro[1], Caio B. Casella[1], Valéria Caparbo[1], Ricardo M. Oliveira[2], Alessandra C Bonfa[1], Eloisa Bonfa[1] and Rosa M R Pereira[1]. [1]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]RDO Diagnosticos Medicos, São Paulo, Brazil.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is associated with high risk of low bone mass/fractures but this risk is still controversial in premenopausal women. Our aim was to determine the one-year incidence of bone mineral density (BMD) loss in premenopausal SLE women and the value of bone turnover markers as predictors of this complication.

Methods: This study enrolled a convenience sample of 63 premenopausal SLE patients. BMD was evaluated by dual X-ray absorptiometry at lumbar spine and hip at baseline and after 12 months. BMD changes above the least significant change were considered significant. Serum levels of P1NP and CTX (electrochemiluminescence), OPG and RANKL (ELISA) were determined at baseline.

Results: Mean age was 31.1±6.8years, disease duration was 5.25±3.8years. 36.5% of patients presented BMD loss and 17.5% BMD gain at lumbar spine and/or hip. Patients were divided in three groups: BMD loss (BL), no BMD change (NC) and BMD gain (BG). Patients with BL and NC received similar cumulative/mean/maximum glucocorticoid doses during the study, but patients with BG received lower doses ($p<0.05$). Baseline P1NP levels were different in the groups (BL:36.95±23.37 vs. NC:54.63±30.82 vs. BG:84.09±43.85 ng/ml; $p=0.031$ BL vs. NC, $p<0.001$ BL vs. BG and $p=0.039$ NC vs. BG). There was no difference in CTX, OPG or RANKL levels. After multivariate analysis P1NP remained as an independent risk factor for BMD loss ($p<0.03$).

Conclusion: This study provides original evidence that lower levels of P1NP, the most specific bone formation marker, are predictive of BMD loss over 12 months in premenopausal SLE patients.

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Risk Factors for Prevalent and Progressive Bone Deficits Among Adult Men and Women with Cystic Fibrosis. Joshua Baker[1], Putman Melissa[2], Karen Herlyn[3], Angela S. Pizzo[4], Allen Lapey[5], Joel Finklestein[2] and Peter A. Merkel[6]. [1]Philadelphia VA Medical Center, Philadelphia, PA, [2]Harvard University, Boston, MA, [3]University Hospital Schleswig-Holstein, Lübeck, Germany, [4]Mercy Hospital, Portland, ME, [5]Massachusetts General Hospital, Boston, MA, [6]Vasculitis Center, University of Pennsylvania, Philadelphia, PA.

Risk Factors for Prevalent and Progressive Bone Deficits Among Adult Men and Women with Cystic Fibrosis

Background/Purpose: Cystic Fibrosis (CF) is associated with an increased risk of osteoporosis and incident fracture. Factors associated with prevalent and

progressive bone deficits in adults with CF have not been comprehensively studied. This study assessed the independent predictors of baseline bone mineral density (BMD) and 2-year changes BMD in adults with CF.

Methods: Sixty-four adult patients with CF, ages 18–57, were recruited from the Massachusetts General Hospital Cystic Fibrosis Care Center. Dual energy absorptometry (DXA) was performed at the spine and radius at baseline and 2-years. Estimates of fat-free mass index (FFMI) and fat mass index (FMI) were determined using height, weight, and tetrapolar bioelectric impedance analysis. All subjects underwent lung spirometry within 1 month of the study visit to measure forced vital capacity (FVC) and forced expiratory volume (FEV1). Linear regression models evaluated predictors of baseline BMD Z-scores and change in anterior-posterior (AP) spine BMD Z-score over the 2-year follow-up. Osteopenia was defined as a BMD Z-score of $^{2}-1.0$.

Results: Osteopenia was present in 52% of subjects. Compared to patients without osteopenia, subjects with osteopenia were more likely to be male (67% v. 32%, $p=0.009$), more likely to be current users of glucocorticoids (21% v. 0%, $p<0.001$), had lower percent body fat (19% v. 23%, $p=0.04$), and were more likely to have had a previous fracture (60% v. 46%, $p=0.007$). In multivariable models, greater estimated FFMI and greater height, but not greater FMI, were associated with greater BMD after adjusting for sex (Table 1). Low FVC and greater adiposity were associated with greater loss of BMD at the A/P spine over two years ($p<0.05$) (Table 2).

Conclusion: Male sex, short stature, and low lean mass at baseline are associated with low BMD among adults with CF. Greater adiposity and lower lung function in women are predictors of negative change in BMD Z-score at the A/P spine at 2-years of follow-up.

Table 1: Multivariable associations between baseline body composition factors and baseline bone density Z-score at different measurement locations.

	β (95% CI)	p-value
DXA AP Spine (n=54)*		
Height (cm)	0.073 (−0.014, 0.13)	0.02
eFFMI (kg/m^2)	0.19 (−0.019, 0.39)	0.07
eFMI (kg/m^2)	−0.072 (−0.25, 0.11)	0.4
DXA Radius (n=20)*		
Height (cm)	0.12 (0.045, 0.20)	0.004
eFFMI (kg/m^2)	0.34 (0.11, 0.56)	0.006
eFMI (kg/m^2)	−0.11 (−0.19, −0.035)	0.2

*Also adjusted for sex. DXA: Dual Electron Absorptometry; eFFMI: Estimated Fat-Free Mass Index; eFMI: Estimated Fat Mass Index

Table 2: Univariate associations between baseline factors and change in BMD Z-score over 2-years (N=39). Body composition variables adjusted for sex*.

	ÆDXA A/P Spine Z β (95%CI)	p-value
Male Sex	0.0065 (−0.28, −0.29)	1
BMI*	−0.015 (−0.061, 0.030)	0.5
% Fat*	−0.019 (−0.036, −0.00075)	0.04
eFFMI*	0.0041 (−0.078, 0.086)	0.9
eFMI*	−0.059 (−0.11, −0.0048)	0.03
FVC	0.0065 (0.0015, 0.013)	0.05
FEV1	0.0051 (−0.00056, 0.011)	0.08
Prednisone Use	0.12 (−0.16, 0.40)	0.4
Baseline Z-Score	−0.033 (−0.13, −0.068)	0.5

Disclosure: J. Baker, None; **P. Melissa**, None; **K. Herlyn**, None; **A. S. Pizzo**, None; **A. Lapey**, None; **J. Finklestein**, None; **P. A. Merkel**, Genentech and Biogen IDEC Inc., 2, Bristol-Myers Squibb, 2, GlaxoSmithKline, 2, Actelion Pharmaceuticals US, 2, Actelion Pharmaceuticals US, 5, Sanofi-Aventis Pharmaceutical, 5, Chemocentryx, 5.

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Analysis of Vitamin D Receptor Gene Polymorphisms and Bone Mineral Density in a Population of Women with Rheumatoid Arthritis in Use of Steroid. Juliana Lucena[1], Fernanda G. G Chaer[2], Rogerio Castro Reis[3] and Branca Souza[1]. [1]Santa Casa Sao Paulo, sao paulo, Brazil, [2]Santa Casa de Sao Paulo, São Paulo, Brazil, [3]Santa Casa de Sao Paulo, São Paulo, Brazil.

Background/Purpose: To determinate the association between vitamin D receptor (VDR) gene alleles and bone mineral density (BMD), comparing a group of healthy pre-menopausal white women to a group of pre-menopausal white women with rheumatoid arthritis (RA), treated with corticosteroid (CE). In the RA group, analysis of the correlation between BMD and VDR genotypes, RA activity, severity, and duration of CE treatment was also performed.

Methods: forty healthy volunteers and 50 patients with RA were recruited. The VDR genotypes were assessed by PCR amplification followed by Bsml digestion on DNA isolated from blood leukocytes.

Results: There was no association between the genotypes of VDR and BMD in both groups, nor any association of genotype BB with subgroups of RA and osteopenia in femoral neck or lumbar spine. The RA group had an average BMD lower than the control group ($p=0.004$ in L2-L4 and $p=0.007$ in femoral neck). The patients with RA and femoral neck osteopenia had a higher rate of joint destruction ($p=0.03$). The correlation analysis confirmed the influence of the joint destruction rate in BMD of femoral neck and showed a negative correlation between duration of CE treatment and BMD in L2-L4 ($p=0.003$).

Conclusion: results indicate that in this populations of RA women, VDR gene polymorphism should not predict the BMD. This study on RA suggests that the severity of joint destruction is associated with lower femoral neck BMD, and that the duration of CE treatment is correlated with lumbar spine BMD.

Disclosure: J. Lucena, None; **F. G. G. Chaer**, None; **R. C. Reis**, None; **B. Souza**, None.

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RANKL and OPG Gene Polymorphisms: Association with Vertebral Fractures and Bone Mineral Density in Premenopausal Systemic Lupus Erythematosus. Alessandra C. Bonfa, Luciana P.C. Seguro, Valéria Caparbo, Eloisa Bonfa and Rosa M R Pereira. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: To evaluate single nucleotide polymorphisms (SNPs) of the receptor activator of NF-κB ligand (RANKL), RANK and osteoprotegerin (OPG) genes in premenopausal systemic lupus erythematosus (SLE) patients and their association with sRANKL and OPG serum levels, vertebral fractures and bone mineral density(BMD).

Methods: 211 premenopausal SLE patients (ACR criteria) and 154 healthy controls were enrolled. SNPs of RANKL 290A >G (rs2277438), OPG 1181G >C (rs2073618), 245T >G (rs3134069), 163 A >G (rs3102735) and RANK A >G (rs3018362) were obtained by real-time PCR. sRANKL/OPG serum levels were determined by ELISA. BMD and vertebral fractures were evaluated by dual energy X-ray absorptiometry.

Results: SLE patients and controls had similar frequencies of the RANKL 290 G allele ($p=0.91$), OPG 1181 C allele ($p=0.83$), OPG 245 G allele ($p=0.80$), OPG 163 G allele ($p=1.00$) and RANK G allele ($p=0.75$). Further analysis of SLE patients revealed that the frequency of the RANKL 290 G allele was lower in patients with fractures than in patients without fractures (28.1 vs. 46.9%, $p=0.01$). In addition, the frequency of the OPG 245 G allele was higher in patients with low BMD than in patients with normal BMD (31.4 vs. 18.1%, $p=0.04$). No association of OPG 1181 G >C, OPG 163 A >G and RANK A >G SNPs with BMD/fractures was found. Additionally, no association was observed between RANKL/OPG/RANK SNPs and sRANKL/OPG serum levels.

Conclusion: Our study provides novel data demonstrating that RANKL/OPG genetic variations play a role in bone remodeling and, particularly, in its major complication, fracture, in premenopausal patients with SLE.

Disclosure: A. C. Bonfa, None; **L. P. C. Seguro**, None; **V. Caparbo**, None; **E. Bonfa**, None; **R. M. R. Pereira**, None.

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Does Adjusting BMI for Lean Mass Deficits Affect Calculated Fracture Risk Using FRAX in Rheumatoid Arthritis? Brittany Adler[1] and Joshua F. Baker[2]. [1]Hospital of the University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania and Philadelphia VAMC, Philadelphia, PA.

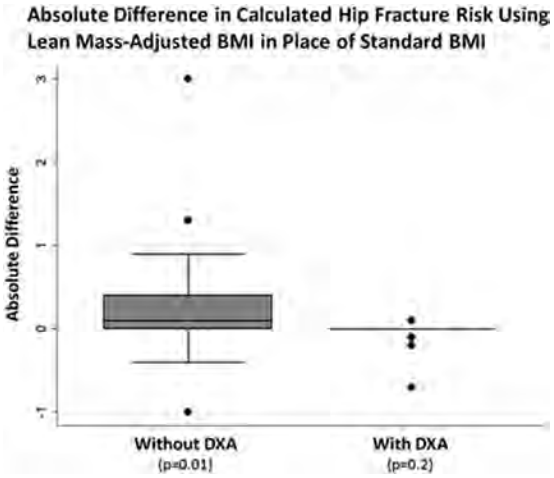
Background/Purpose: Osteoporotic fractures are a cause of morbidity in rheumatoid arthritis (RA) and low body mass index (BMI) is a risk factor for osteoporotic fractures in RA. Emerging evidence suggests that low lean mass is responsible for bone structural deficits among those with low BMI. Therefore we hypothesized that adjusting BMI for lean mass deficits commonly seen in RA would alter prediction of risk using the FRAX tool. We studied the effect of utilizing a lean mass-adjusted BMI as an independent variable in the FRAX tool in the determination of fracture risk.

Methods: Whole-body dual energy absorptiometry (DXA) was previously performed in 40 RA subjects and 500 controls. We have previously identified independent associations between the total fat mass index (FMI)

and appendicular lean mass index (ALMI) among 500 healthy control subjects. Based on our published model, we determined the expected ALMI for RA subjects based on their age, sex, race, and FMI. We then multiplied the actual BMI by the ratio of the actual to expected ALMI to determine a lean mass-adjusted BMI. We calculated fracture risk among RA subjects using the FRAX calculator, and evaluated the differences in fracture risk prediction using the lean mass-adjusted BMI compared to the standard BMI both with and without using bone density results from DXA.

Results: Using the lean mass-adjusted BMI in place of standard BMI, the calculated risk of a major osteoporotic fracture increased in 21 (52.5%), decreased in 8 (20%), and was unchanged in 11 (27.5%) subjects. The mean absolute change in calculated 10-year major osteoporotic fracture risk using lean mass-adjusted BMI was 0.28% ± 0.70 (p=0.02). Similarly, the calculated risk of hip fracture using lean mass-adjusted BMI was increased in 23 (57.5%), decreased in 6 (15%), and unchanged in 11 (27.5%) subjects. The mean absolute change in calculated 10-year hip fracture risk was 0.25% ± 0.60 (p=0.01). The calculated risk of hip fracture using lean mass-adjusted BMI was most increased among subjects with a BMI <25 kg/m^2. For subjects with a BMI<25 (n=11) the estimated fracture risk was significantly increased by 0.67% ± 0.87 (p=0.03), as compared to -0.09% ±0.37 (p=0.2) for subjects with a BMI >25 (n=29) (p for comparison=0.005). When bone density at the hip was included into the FRAX calculation, the differences in calculated fracture risk using the lean mass-adjusted BMI and standard BMI were completely attenuated (Figure 1).

Conclusion: Using lean mass-adjusted BMI in place of standard BMI in the FRAX equation results in an increase in calculated fracture risk for most patients with RA, particularly among those with a normal BMI (BMI<25). Incorporation of bone density measures significantly reduced these differences in risk prediction, which suggests that use of a lean mass-adjusted BMI would not affect risk prediction when bone density is available.



Disclosure: B. Adler, None; **J. F. Baker**, None.

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An Observational Study on the Influence of Glucocorticoid Exposure on Bone. Joseph Heath[1], Alexander Oldroyd[1], Maarten Boers[2] and Marwan Bukhari[1]. [1]Lancaster University, Lancaster, United Kingdom, [2]VU University Medical Center, Amsterdam, Netherlands.

Background/Purpose: It is well known that glucocorticoids are detrimental to bone health and has been postulated that their influence is more than their effect on reduction of bone mineral density (BMD). This has not been localised to type of bone involved as trabecular bone and cortical bone differ. The FRAX ™ tool uses the hip BMD as a predictor of future fracture risk, which is a measure of cortical rather than trabecular bone. Recently, we have shown that hip structure analysis (HSA) is also e predictor of fracture. We aimed to study in an observational manner the effect of corticosteroid (CS) use on the bone in the lumbar spine (trabecular bone) and the hip (cortical bone), in addition to any differences in HSA.

Methods: Patients who are identified from a cohort recruited from the North West of England referred for a bone densitometry (DEXA) scan and receiving CS. Patients were divided into those that had sustained a fragility fracture (cases) and compared to those who had not (controls). Analysis was carried out using the student t-test for continuous variables and the Chi^2 test for categorical variables. Logistic regression analysis was carried out to investigate any significant association between BMD and bone fracture in patients receiving CS. HSA variables were also included in the model.

Results: There were 3,360 patients (73.46% female) identified as receiving CS, of which 779 (23.18%) had suffered from a facture. Mean age of patients who suffered a fracture was significantly higher than those who did not; 62.33 (SD=13.09) vs 67.39 (SD=11.75) respectivly (p value = <0.001). Females were significantly more likely to suffer a fracture compare to males; 33.86% vs 20.00% respectively (p.value=<0.001). After adjusting for age and sex, the mean difference in BMD between patients on steroids who suffered a facture compared to those who did not suffer a fracture at the femoral neck was 0.06 g/cm2 (95%CI=0.05–0.08) and at the lumbar spine was 0.09 g/cm2 (95%CI=0.07–0.10). Logistic regression analysis after adjustment showed that patients who were on steroids were likely to have a lower BMD at the femoral neck (OR=0.13, 95%CI=0.06–0.34) and the lumbar spine (OR=0.13, 95%CI=0.08–0.21). Modelling HSA showed that after adjustment, Cross sectional moment of inertia and not hip axis length was different between the cohorts (OR 0.95 95%CI 0.95,0.98 vs OR 0.99 95%CI 0.98,1.01 respectively).

Conclusion: In this cohort of patients fractures in those taking steroids are associated with increasing age, female sex, and lower BMD. Patients who are taking CS and suffer from a fracture are significantly more likely to have a lower BMD. Differences in Hip structure are also seen. This study does not support the theory that CS are an independent variable in fracture risk in patients. Further prospective studies are needed.

Disclosure: J. Heath, None; **A. Oldroyd**, None; **M. Boers**, None; **M. Bukhari**, None.

ACR Poster Session A
Pain: Basic and Clinical Aspects
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Reduced Estimated Glomerular Filtration Rate Was Improved after Cessation of NSAID and Switching to Tramadol Hydrochloride/Acetaminophen Tablets (Ultracet™) in Patients with Chronic Musculoskeletal Pain. Kenji Miki[1], Hiroshi Kajiyama[2], Kenrin Shi[3], Shigeshi Mori[1], Masao Yukioka[4] and Masao Akagi[1]. [1]Faculty of Medicine, Kindai University, Osaka-Sayama, Japan, [2]Saitama Medical University, Saitama, Japan, [3]Osaka University Hospital, Suita, Japan, [4]Yukioka Hospital, Osaka, Japan.

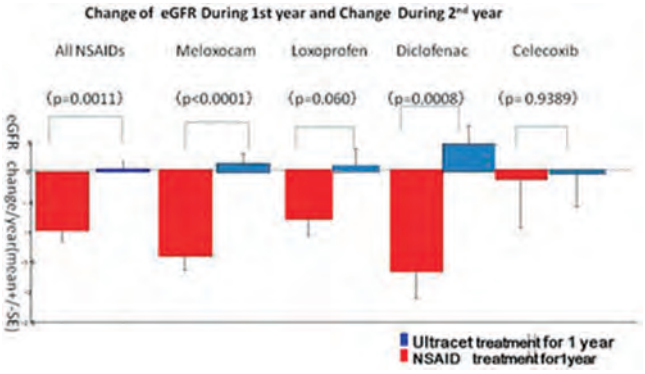
Background/Purpose: NSAID is widely used in patients with chronic musculoskeletal pain, but often deteriorates renal function with acute decline of estimated glomerular filtration rate (eGFR). However, there is little evidence on the long-term effect of chronic NSAID use, whether the eGFR decline is irreversible or not.

Methods: We studied 100 patients with chronic musculoskeletal pain (age 66.8 ± 18.4 years; 29 men, 71 women; 46 patients with lumbago, 28 with osteoarthritis, 26 with other complaints) over a followup period of 2 years. The baseline eGFR of the 100 patients was 85.13±25.63 mL/min/1.73m^2. We compared eGFR change during the first year with daily NSAID administration and that during the following year with daily administration of tramadol hydrochloride/acetaminophen tablets, in the same patient. eGFR was calculated as follows; male,194*Scr O-1.094*age O-0.287; female: eGFR (male)*0.739. As for the NSAID during the first year, meloxicam was administered in 33 patients, loxoprofen in 29, diclofenac in 19, and celecoxib in 11.

Results: eGFR change was -0.973 mL/min/1.73m^2 during the first year with NSAID administration, whereas it was +0.047 mL/min/1.73m^2 during the following year with tramadol hydrochloride/acetaminophen tablets administration. The difference of eGFR change between the two medications was statistically significant (paired t test, p=0.002; Figure), suggesting the cessation of NSAID and switching to tramadol hydrochloride/acetaminophen tablets can improve the renal function deteriorated by NSAID. As for the specific NSAIDs during the first year, cessation of diclofenac and meloxicam followed by switching to tramadol hydrochloride/acetaminophen tablets resulted in a significant improvement in eGFR (paired t test, p=0.0008 and p<0.0001, respectively; Figure), whereas switching from loxoprofen just showed a tendency of improvement (paired t test, p=0.0604; Figure). On the other hand, cessation of celecoxib and switching to tramadol hydrochloride/acetaminophen tablets did not show significant improvement in eGFR (paired t test, p=0.9389; Figure). Improvement of eGFR after switching to tramadol hydrochloride/acetaminophen tablets was also recognized in 4 patients with diabetes and 12 patients with intake of angiotensin receptor blockers, but did

not reach statistical significance. There was no correlation between age and eGFR change over the one year either with NSAID or with tramadol hydrochloride/acetaminophen tablets.

Conclusion: Our findings suggest that reduced eGFR due to one year administration of NSAID could be reversible to a certain degree by cessation of NSAID and switching to tramadol hydrochloride/acetaminophen tablets. The degree of eGFR improvement was different depending on the types of NSAID.



Disclosure: K. Miki, None; **H. Kajiyama**, None; **K. Shi**, None; **S. Mori**, None; **M. Yukioka**, None; **M. Akagi**, None.

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WOMAC Pain Score Reflects Preceding Daily Pain Ratings in Knee Osteoarthritis Interventional Randomized Clinical Trials. Michael H. V. Nguyen[1], Renita Evonne Yeasted[2] and Thomas J. Schnitzer[2]. [1]University of Washington School of Medicine, Seattle, WA, [2]Northwestern University, Chicago, IL.

Background/Purpose: The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a validated and widely used instrument for assessing osteoarthritis (OA) knee and hip pain, stiffness and physical function. The recall period for specific outcome measures is 48 hours. This study aimed to examine the correlation between WOMAC pain score and reported actual pain levels one, two and 5 days prior to completing the WOMAC instrument.

Methods: Data were obtained from three OA studies: an observational study (OBS) convenience sampling of OA and the placebo arm of two interventional randomized control trials (IRCTs). All participants were ≥ 40 years of age, met the ACR definition for OA, and self-reported a minimum pain intensity of ≥ 4 on Numeric Rating Scale (NRS) for pain (0 – no pain; 10 – worst pain possible). Participants were asked to report pain twice daily (IRCTs, electronic tablet) or three times daily (OBS, smartphone) over a 12–16 week period, and WOMAC was completed at regular clinic visits. For each participant, mean pain ratings were calculated for the day of clinical exam, as well as 1 day, 2 days, and 5 days prior and compared to the WOMAC pain score for question 1. Pearson's correlation was computed to assess the relationship between WOMAC pain score and self-reported pain using Stata 13.

Results: In total, data were collected from 162 participants (123 studied in clinical trials and 39 studied in the observational study). The demographics for all three groups were similar and typical of adults with OA. Among clinical trial participants, there was a strong, positive correlation between WOMAC and self-reported pain for all time points [r=0.8505, n=392 (exam day); r=0.8482, n=474 (1 day prior); r=0.8575, n=415 (2 day prior); r=0.8173, n=267 (5 day prior); all values $p < 0.05$] (Figure 1). Among observation study participants, there was a moderate, positive correlation between WOMAC and self-reported pain significant only at 1 day prior to exam [r=0.3741, n=56] (Figure 2).

Conclusion: The findings of this study demonstrate a high correlation within individuals between WOMAC pain scores and self-reported daily preceding pain intensity in ICRT. This correlation was independent of the look-back period (one, two or five days). Less strong correlations were observed in OBS study settings. These findings are consistent with lower daily pain variability in interventional trials than in the observational setting and have implications on assessing and managing pain in non-IRCT settings.

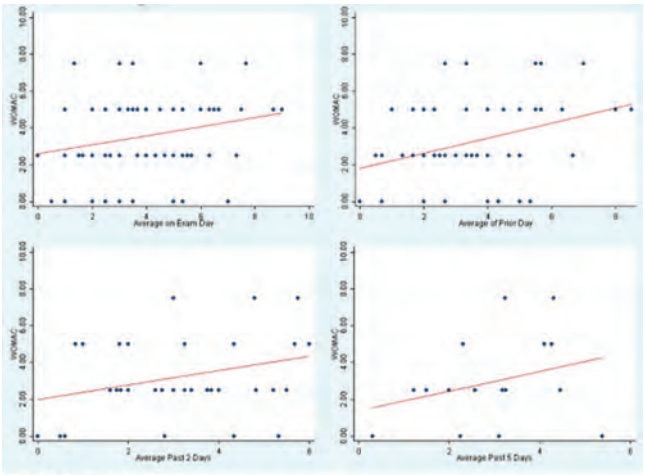

Figure 1: Observational Graph

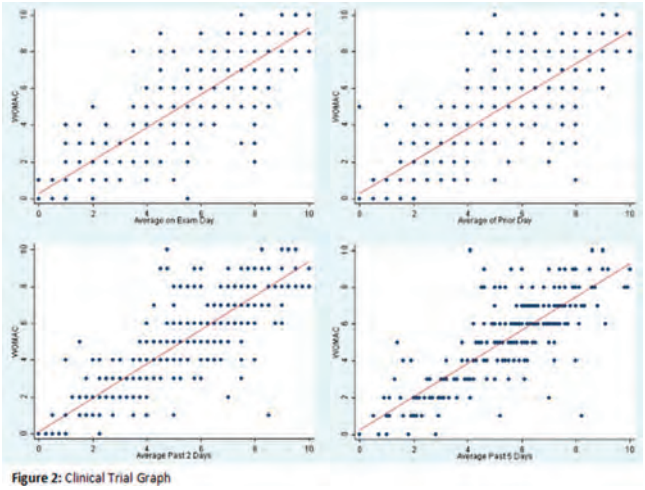

Figure 2: Clinical Trial Graph

Disclosure: M. H. V. Nguyen, None; **R. E. Yeasted**, None; **T. J. Schnitzer**, None.

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Safety of Solumatrix Diclofenac in Adults with Osteoarthritis: Results of a 12-Month, Phase 3 Study. Roy Altman[1], Allan Gibofsky[2], Marc C. Hochberg[3], Byron Cryer[4], Alan J. Kivitz[5], Vibeke Strand[6], Olaolu Imasogie[7] and Clarence Young[8]. [1]University of California–Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [2]Hospital for Special Surgery, New York, NY, [3]University of Maryland School of Medicine, Baltimore, MD, [4]University of Texas Southwestern Medical Center, Dallas, TX, [5]Altoona Center for Clinical Research, Duncansville, PA, [6]Stanford University, Palo Alto, CA, [7]Iroko Pharmaceuticals LLC, Philadelphia, PA, [8]Iroko Pharmaceuticals, LLC, Phila, PA.

Background/Purpose: Osteoarthritis (OA) is a frequent cause of disability in adults. NSAIDs such as diclofenac are often prescribed to treat OA pain. However, NSAIDs are associated with serious dose-related gastrointestinal (GI) and cardiovascular adverse effects, leading the FDA to recommend NSAID use at the lowest dose for the shortest duration necessary to achieve treatment goals. SoluMatrix® diclofenac has been developed using SoluMatrix Fine Particle Technology™ to provide efficacy at low doses and is approved for treatment of mild to moderate acute pain in adults. We report results from a 12-month, open-label phase 3 study investigating SoluMatrix diclofenac in patients with OA.

Methods: This multicenter study treated 601 chronic NSAID/acetaminophen users, aged ≥40 years with knee and/or hip OA. Patients initially received SoluMatrix diclofenac 35-mg capsules BID; the dosing regimen could be increased to TID if necessary and subsequently reduced as needed. Safety analyses included incidence of adverse events (AEs), serious AEs (SAEs), AEs leading to discontinuation, and clinical laboratory test results.

Results: Most patients were women (372/601, 61.9%) with a mean (± SD) age of 59.7 ± 8.9 years. Mean (± SD) trial drug administration duration

was 274.9 ± 125.7 days. AEs were reported by 451/601 (75.0%) patients (**Table**). The most frequently reported events included: upper respiratory tract infection (47/601, 7.8%), headache (46/601, 7.7%) and urinary tract infection (44/601, 7.3%). GI ulcer was reported in 1 patient (0.2%), considered related to study medication. Hypertension was reported in 17/601 (2.8%) patients, and serum creatinine increased in 7/601 (1.2%). SAEs were reported in 42/601 (7.0%) patients. Two patients (2/601, 0.3%) experienced myocardial infarction; both considered unrelated to study drug (**Table**). AEs led to discontinuation in 99/601 (16.1%) patients. Alanine aminotransferase or aspartate aminotransferase ≥3× the upper limit of normal was noted in 20 patients (3.3%), which was associated with elevated bilirubin in one patient and improved following treatment discontinuation.

Conclusion: SoluMatrix diclofenac was generally well tolerated. These data extend the SoluMatrix diclofenac experience to include patients requiring extended treatment for OA pain.

Table.

Adverse Event	SoluMatrix Diclofenac 35 mg TID (n =302)[a]	SoluMatrix Diclofenac 35 mg BID (n =601)[a,b]	Combined SoluMatrix Diclofenac (n =601)[a,c]
Most Frequent (>5% in Any Treatment Group) Adverse Events			
Any AE	186 (61.6)	340 (56.6)	451 (75.0)
URI	21 (7.0)	27 (4.5)	47 (7.8)
Headache	11 (3.6)	36 (6.0)	46 (7.7)
UTI	10 (3.3)	34 (5.7)	44 (7.3)
Diarrhea	14 (4.6)	24 (4.0)	37 (6.2)
Nasopharyngitis	11 (3.6)	24 (4.0)	34 (5.7)
Nausea	11 (3.6)	22 (3.7)	33 (5.5)
Most Frequent (≥2 Patients) Serious Adverse Events			
Any SAE	15 (5.0)	26 (4.3)	42 (7.0)
Osteoarthritis	1 (0.3)	2 (0.3)	3 (0.5)
Carotid artery stenosis	0	2 (0.3)	2 (0.3)
Chest Pain	0	2 (0.3)	2 (0.3)
COPD	0	2 (0.3)	2 (0.3)
Diverticulitis	1 (0.3)	1 (0.2)	2 (0.3)
Lumbar spinal stenosis	1 (0.3)	1 (0.2)	2 (0.3)
Myocardial infarction	0	2 (0.3)	2 (0.3)

Data presented as n (%). AE = adverse event; BID = twice daily; COPD = chronic obstructive pulmonary disease; SAE = serious adverse event; TID = three times daily; URI=upper respiratory tract infection; UTI = urinary tract infection. [a]AEs were assigned to the dose regimen the patient received at the AE start date. Post-treatment AEs were assigned to the last dose regimen received. [b]All treated patients were included in the SoluMatrix diclofenac twice-daily group for ≥4 days. [c]AEs with missing start dates and pretreatment AEs are listed in the 'Combined SoluMatrix Diclofenac' column.

Disclosure: R. Altman, Participant in advisory boards for Iroko Pharmaceuticals, consultant to Pfizer, Teva Pharmaceutical Industries Ltd., Petah Tikva, Oletec, Novartis, Johnson & Johnson, consultant and member of the speaker's bureau for Ferring Pharmaceuticals, 5; **A. Gibofsky**, Stock shareholder of GlaxoSmithKline plc, Bristol-Myers Squibb, Johnson & Johnson, Amgen, Pfizer, AbbVie, Johnson and Johnson, 1, consultant for Takeda, Amgen, AbbVie, UCB Inc., Genentech, Horizon, and Iroko Pharmaceuticals LLC, 5; **M. C. Hochberg**, Iroko Pharmaceuticals LLC, Amgen, AstraZeneca, Covidien, Eli Lilly, EMD Serono, Genentech/Roche, Merck & Co, Inc., Novartis Pharma AG, Pfizer, and Pozen., 5; **B. Cryer**,: Consulting fees received from Ritter Pharmaceuticals, Sanofi, Sandoz, Sucempo, and Iroko Pharmaceuticals, LLC, 5; **A. J. Kivitz**, None; **V. Strand**, Consultant for AbbVie, Afferent, Amgen, Biogen Idec, Bioventus, BMS, Carbylan, Celgene, Celltrion, CORRONA, Crescendo, Genentech/Roche, GSK, Hospira, Iroko, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi, SKK, Takeda, UCB, Vertex, 5; **O. Imasogie**, IBoko Pharmaceuticals LLC, 3; **C. Young**, Iroko Pharmaceuticals, LLC, 3.

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Onset, Magnitude, and Durability of Pain Relief in Patients with Knee OA Receiving a Fixed-Dose Combination Tablet of Enteric-Coated (EC) Naproxen Plus Immediate-Release (IR) Esomeprazole Magnesium Versus Celecoxib and Placebo: Pooled Results from Two Randomized Controlled Trials. John Fort[1], Robert Holt[2], Amy Y. Grahn[3], Jana Steinmetz[4], Ying Zhang[1] and Jeffery Kent[5]. [1]Pozen, Inc, Chapel Hill, NC, [2]University of Illinois-Chicago, Vernon Hill, IL, [3]Horizon Pharma, Inc., Deerfield, IL, [4]Premier Research, Naperville, IL, [5]Horizon Pharma, Inc, Deerfield, IL.

Background/Purpose: Over 40% of patients with OA report having significant knee pain every day. (1) Previously published data have demonstrated the overall comparable efficacy of EC naproxen/IR esomeprozole to celecoxib and superiority to placebo in the management of knee OA. (2) EC naproxen/IR esomeprazole also significantly reduced the incidence of endoscopic ulcers and improved UGI tolerability compared with EC naproxen alone in previous trials and maintained GI protective effect with low-dose aspirin (3). This new analysis characterizes time-to-first pain relief, effect size, and sustainability of naproxen/IR esomeprazole and celecoxib with placebo.

Methods: Two double-blind, double-dummy, placebo-controlled trials in patients aged ≥50 years with knee OA randomized to either EC naproxen 500mg/IR esomeprazole 20mg BID (n=487) or celecoxib 200mg/day (n=486) or placebo (n=246). Acute response endpoints assessed: 1) Time to first significant response during days 1–7 as measured by Patient Global Assessment Likert scale, 2) Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain subscale using a visual analog scale (VAS) during days 1–7, and 3) American Pain Society Patient Outcome Questionnaire (APS-POQ) scores over the first 7 days. Endpoints to assess sustainability of naproxen/esomeprazole included: 1) Routine Assessment of Patient Data (RAPID)-3 and 2) WOMAC Stiffness, Total and Pain VAS at 6/12 weeks. Time to first significant response was analyzed using the log-rank test and estimated using the Kaplan-Meier analysis method. Other endpoints were analyzed using ANCOVA models with baseline values as covariates. Least square means, confidence intervals, and p-values were generated on change from baseline differences compared to placebo. Effect sizes (Cohen's D) and correlation coefficients (Spearman, Pearson) were estimated descriptively.

Results: EC Naproxen/IR esomeprazole produced statistically significant decreases in WOMAC Pain on Days 2–7 (Figure) and at Weeks 6 and 12; APS-POQ pain assessments were significantly improved on Days 2–7. RAPID and WOMAC Total/Pain/Stiffness scores decreased significantly at Weeks 6 and 12. Responses were comparable to celecoxib. Pain relief effect sizes were moderate and median days to good-excellent response was 6 days. Total RAPID-3 to WOMAC and WOMAC to RAPID Pain were highly correlated with each other (correlation > 0.80) at 6 and 12 weeks.

Conclusion: EC naproxen/IR esomeprazole produces a moderate-large early pain response which is maintained for 12 weeks. RAPID-3 was found to be highly correlated with the typical OA measure (WOMAC) and might be a useful clinical tool for measuring NSAID response.

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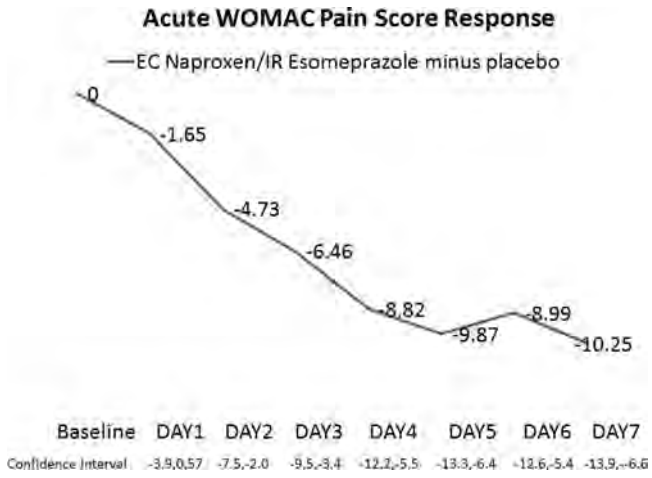
(3) Cryer, et. a. Ann Med 2011;43:594–605.



Disclosure: J. Fort, Pozen, Inc, 3; **R. Holt**, Horizon Pharma, Inc, 5, Pozen, Inc., 5; **A. Y. Grahn**, Horizon Pharma, Inc, 3; **J. Steinmetz**, Horizon Pharma, Inc, 5; **Y. Zhang**, Pozen, Inc, 5; **J. Kent**, Horizon Pharma, Inc, 3.

245 WITHDRAWN

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Neuropathic PAIN in Patients with Ankylosing Spondylitis. Pinar Borman[1], Ferda Kaygisiz[2], Aysegul Yaman[1] and Aynur Karagoz[2]. [1]University of Hacettepe Faculty of Medicine, Ankara, Turkey, [2]Ankara Training and Research Hospital, Ankara, Turkey.

Background/Purpose: There is only one study in the literature indicating that neuropathic pain occurs in ankylosing spondylitis (AS) (1).

Methods: The aim of this cross sectional study was to evaluate frequency of neuropathic pain in AS patients and to determine the relation with disease variables and occurrence of neuropathic pain. Fifty-eight AS patients who were not having any comorbid disease and/or using drugs that would cause neuropathy, were recruited to the study. Demographic properties (age, sex,

disease duration) and clinical characteristics (functional status and disease activity assessed by BASFI and BASDAI respectively, ESR, CRP and quality of life determined by ASQoL questionnaire) were recorded. The neuropathic property of back pain was assessed by both LANSS and DN4 scales. Descriptive statistics was used for clinical variables and frequency of neuropathic pain. The difference of clinical variables between patients with and without neuropathic pain, were examined using t tests and chi square tests. Spearman test was used for correlation analyses. The significance threshold was set as $p < 0.05$.

Results: Fifty-eight AS patients (17 female, 41 male) with a mean age of 45±18 years were included to the study. 33 patients (56.9%) and 31 patients (53.4%) were defined as having neuropathic pain depending on the LANSS (scores >12) and DN4 (scores >4) questionnaire scores respectively. The mean score of LANSS scale was correlated with ASQoL, BASFI, BASDAI, and DN4; and the mean score of DN4 scale was correlated with ASQoL, BASFI, LANSS and BMI. The mean levels of BASFI and ASQoL were significantly higher in patients having neuropathic pain than in patients not having ($p<0.05$) (Table 1). The percentage of patients with neuropathic pain was higher in female than in male patients (58.8% vs 51.2% by DN4, 64.7% vs 53.6% by LANSS).

Conclusion: Neuropathic pain is determined in more than half of the patients with AS and related with functional status and quality of life. In conclusion neuropathic pain is common in AS patients. Diagnosis and treatment of neuropathic pain are warranted in order to increase functional ability and quality of life in patients suffering from AS.

References

1. Wu Q, Inman RD, Davis KD. Neuropathic pain in ankylosing spondylitis: a psychophysics and brain imaging study. Arthritis Rheum. 2013 Jun;65(6):1494–503. doi: 10.1002/art.37920.

Table 1. The difference of demographic and clinical properties, in patients having and lacking neuropathic pain, determined by LANSS.

	Neuropathic pain (+) n=33	Neuropathic pain (−) n=25	p
Age (years)	40,12 ± 10,67	39,68 ± 11,41	0,880
Duration of disease(years)	8,69 ± 7,17	8,77 ± 6,55	0,965
BASFI (mean+SD)	3,57 ± 2,43	2,02 ± 2,06	0,013
BASDAI (mean+SD)	3,80 ± 1,80	2,84 ± 2,07	0,064
ESR (mean+SD)	14,00 ± 9,78	11,64 ± 9,68	0,365
CRP (mean+SD)	1,02 ± 1,24	0,79 ± 1,02	0,470
ASQoL (mean+SD)	8,81 ± 4,48	4,36 ± 4,23	0,000

Table 2. The difference of demographic and clinical properties, in patients having and lacking neuropathic pain, determined by DN4.

	Neuropathic pain (+) n=33	Neuropathic pain (−) n=25	p
Age (years)	39,93 ± 9,59	39,92 ± 12,43	0,997
Duration of disease(years)	9,33 ± 7,05	8,02 ± 6,67	0,475
BASFI (mean+SD)	3,42 ± 2,43	2,30 ± 2,24	0,077
BASDAI (mean+SD)	3,51 ± 1,72	3,24 ± 2,24	0,606
ESR (mean+SD)	13,83 ± 10,11	12,00 ± 9,34	0,477
CRP (mean+SD)	1,06 ± 1,24	0,76 ± 1,03	0,337
ASQoL (mean+SD)	8,35 ± 4,82	5,22 ± 4,46	0,013

Disclosure: P. Borman, None; **F. Kaygisiz**, None; **A. Yaman**, None; **A. Karagoz**, None.

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Cognitive Task Related Hypoperfusion of Frontal Gyrus in Patients with Chronic Fatigue. Jason Craggs[1], Song Lai[1], Ricky Madhavan[1], Donald Price[1], Michael Robinson[1] and Roland Staud[2]. [1]University of Florida, Gainesville, FL, [2]Univ of Florida Med Ctr/JHMHC, Gainesville, FL.

Background/Purpose: Patient with Chronic Fatigue Syndrome (CFS) frequently report cognitive complaints, including lack of concentration and forgetfulness. Previous neuropsychological studies reported attentional and memory dysfunction in CFS patients. We wanted to determine the association between mental fatigue and brain activity as measured by arterial spin labeling (ASL). The perception of mental fatigue was induced with the Paced Auditory Serial Attention test (PASAT) that involves attention, working memory and executive function. We measured cerebral blood flow (CBF) changes in CFS patients and compared them to healthy controls (HC).

Methods: CFS was determined using the CDC Criteria. 15 CFS patients (age = 50.5±13.0)) and 12 HC (age = 49.2±12.2) underwent a 3 Tesla Achieva MRI during rest using a pseudo-continuous arterial spin labeling (pCASL) sequence. pCASL can quantify CBF without using exogenous contrast agents by magnetically labeling inflowing blood. Individual scans were corrected for motion and spatially smoothed, then label and control pairs were subtracted to create a perfusion image. The perfusion image was used to calculate a quantified CBF map, which was then normalized to standardized space. After practice trials, participants were placed in the MRI scanner where they viewed a computer screen and listened to PASAT stimuli. Subjects continuously rated their level of exhaustion on a VAS. Groups were compared using voxel-wise independent samples t-tests. Statistical parametric maps were thresholded using a cluster forming t-statistic greater than 4.0 ($p < 0.00025$) and a spatial extent of 20 contiguous voxels (160 mm^3) to control for multiple comparisons.

Results: Fatigue ratings were 0.4 (0.6) and 3.9 (2.1) for HC and CFS patients, respectively ($p < 0.01$). Overall cerebral blood flow was similar between groups ($p > .05$). CFS patients showed reduced blood flow in the right hemisphere superior frontal gyrus. In the significant cluster, HC participants had a mean (SD) CBF of 66.12 (7.89) compared to 63.24 (6.22) (ml/100g/min) in CFS patients ($t(25) = 4.73$, $p = 0.007$, Cohen's $d = 1.80$).

Conclusion: More reduced cerebral perfusion was observed in the right superior frontal gyrus of CFS patients compared to HC during PASAT. The superior frontal gyrus plays a major role in the Attention Network. Reduced blood flow of this area may be a cause or consequence of chronic fatigue as well as impaired attention and cognition often observed in CFS.

Disclosure: J. Craggs, None; **S. Lai**, None; **R. Madhavan**, None; **D. Price**, None; **M. Robinson**, None; **R. Staud**, None.

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Is the Basdai Score Driven By Pain in Ankylosing Spondylitis Patients Treated with Anti-TNF? Proton Rahman[1], Algis Jovaisas[2], William Bensen[3], Wojciech Olszynski[4], Anna Jaroszynska[5], Philip Baer[6], Maqbool Sheriff[7], Dalton Sholter[8], Eliofotisti Psaradellis[9], John S. Sampalis[9], Francois Nantel[10], Allen J Lehman[10], Susan Otawa[10] and May Shawi[10]. [1]Memorial University of Newfoundland, St. John's, NF, [2]University of Ottawa, Ottawa, ON, [3]Division of Rheumatology, McMaster University, Hamilton, ON, [4]University of Saskatchewan, Saskatoon, SK, [5]Private Practice, Burlington, ON, [6]Private Practice, Scarborough, ON, [7]Nanaimo Regional General Hospital, Nanaimo, BC, [8]University of Alberta, Edmonton, AB, [9]JSS Medical Research, Montreal, QC, [10]Janssen Inc., Toronto, ON.

Background/Purpose: The present standard for measuring disease activity in AS is the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) which focuses on five major symptoms including fatigue, axial pain, peripheral pain, enthesitis and morning stiffness (severity and duration). Given that the BASDAI instrument contains two pain questions, the objective was to assess whether pain symptoms are the main drivers of BASDAI scores among AS patients treated with anti-TNFs in routine clinical practice.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with infliximab (IFX) or golimumab (GLM) as first biologics or after having been treated with a biologic for <6 months. Patients with AS treated with IFX or GLM and enrolled between 2005 and 2014 were included in this analysis. A modified weighted BASDAI score (m-BASDAI) was calculated excluding the axial (Q2) and peripheral (Q3) pain questions of the BASDAI. The correlation of BASDAI, each of its components, and the modified BASDAI (m-BASDAI) was assessed with the Pearson correlation coefficient. BASDAI low disease activity (LDA) and m-BASDAI LDA were defined as a score ≤3. The association between the number of administered analgesics (0, 1, >1) and BASDAI/m-BASDAI was assessed with one-way ANOVA.

Results: A total of 413 AS patients with 1,709 assessments were included in this analysis. Correlation analysis showed a strong correlation between the full BASDAI and m-BASDAI scores ($r=0.98$, $P<0.001$). With respect to the individual BASDAI questions, a strong positive linear correlation was observed between all questions and the BASDAI score as well as the m-BASDAI score (Table 1). As expected, a lower correlation was observed between Q2 and Q3 with the m-BASDAI relative to BASDAI. Axial pain was most strongly correlated with the severity of morning stiffness, whereas the highest correlation of peripheral pain was observed with localized tenderness. The cross-tabulation of BASDAI LDA and m-BASDAI LDA showed a strong measure of agreement (kappa=0.871, $P<0.001$). Omission of the pain questions from BASDAI resulted in a comparable proportion of LDA cases (41.7% vs. 40.9%) when using the same LDA definition.

Increased use of analgesics (0 vs. 1 vs. >1) over 2 years of follow-up was associated with significantly ($P<0.05$) higher mean scores in BASDAI, m-BASDAI, and each of the BASDAI components. No significant association was observed between increased use of analgesics and treatment retention.

Table 1: Correlation between individual BASDAI Questions and BASDAI Outcomes

BASDAI Question	BASDAI*	m-BASDAI*	Q2:Spinal Pain*	Q3: Joint Pain/Swelling*
Q1: Fatigue	0.85	0.88	0.76	0.61
Q2: Spinal pain	0.92	0.87	–	0.68
Q3: Joint pain/Swelling	0.84	0.75	0.68	–
Q4: Areas of localized tenderness	0.89	0.89	0.76	**0.73**
Q5: Morning stiffness severity	0.89	0.90	**0.82**	0.67
Q6: Morning stiffness duration	0.75	0.78	0.64	0.55

$P<0.001$ for all correlations

Conclusion: Higher levels of AS pain are significantly associated with a higher BASDAI score and increased use of analgesic medications among patients treated with anti-TNFs. In addition to pain, fatigue, tenderness, and morning stiffness are likewise important contributing components in the BASDAI score and the disease burden of AS.

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A Phase 3 Open-Label Trial of Low-Dose Solumatrix Diclofenac in Patients with Osteoarthritis Pain: Impact of Long-Term Administration on Patient-Reported Outcomes. Vibeke Strand[1], Allan Gibofsky[2], Marc Hochberg[3], Roy Altman[4], Byron Cryer[5], Alan Kivitz[6], Olaolu Imasogie[7] and Clarence Young[8]. [1]Stanford University, Palo Alto, CA, [2]Hospital for Special Surgery, New York, NY, [3]University of Maryland School of Medicine, College Park, MD, [4]University of California–Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [5]University of Texas Southwestern Medical Center, Dallas, TX, [6]Altoona Center for Clinical Research, Duncansville, PA, [7]Iroko Pharmaceuticals LLC, Philadelphia, PA, [8]Iroko Pharmaceuticals, LLC, Phila, PA.

Background/Purpose: Diclofenac is used for the treatment of osteoarthritis (OA), but, like other NSAIDs, it is associated with serious dose-related adverse events. The FDA has encouraged providers to prescribe NSAIDs at the lowest effective dose. SoluMatrix® diclofenac was developed to provide efficacy at low doses and is approved for treatment of mild to moderate acute pain in adults. A 1-year, open-label, multicenter, phase 3 study in patients with OA evaluated the safety and patient–reported outcome measures associated with SoluMatrix diclofenac.

Methods: The study treated 601 patients age≥40, with knee and/or hip OA, who were chronic NSAID/acetaminophen users. Patients initially received SoluMatrix diclofenac 35-mg capsules BID. The dose could be increased to TID, and subsequently reduced back to BID as needed. Health-related quality of life (HRQOL) was evaluated by the Short Form-36™ version 2 (SF-36v2), which was completed at baseline and at weeks 12, 24, 32, 40, 48; and 52/early termination visit (ET).

Results: During the study, 299/601 (49.8%) patients remained on the SoluMatrix diclofenac 35-mg BID and 302/601 (50.2%) patients increased their SoluMatrix diclofenac dosage to 35-mg TID at least once (316 events), mostly due to the need for more analgesia (214/316, 67.7% events). In total, 20.6% (65/316) of the dosing increases from BID to TID were reduced back to BID, mainly due to satisfactory analgesia (21/65, 32.3%). Patients receiving SoluMatrix diclofenac treatments reported clinically meaningful improvement (≥2.5) in SF-36v2 Physical Component Score from baseline at 12 throughout 52 weeks dosing period (**Table**). Based on values that exceed normative scores at baseline, SF-36v2 Mental Component Scores were not expected to improve (**Table**). Clinically meaningful improvements from baseline to week 52/ET (≥5) were reported for the SF-36v2 Bodily Pain domain scores (+5.5). Improvements in Physical Functioning (+4.3) and Role Physical (+3.6) were also observed (**Table**). Only 12 patients (2%) withdrew from the study due to lack of efficacy.

Conclusion: Low-dose SoluMatrix diclofenac capsules 35-mg BID or TID were associated with improved HRQOL in patients with OA pain and represent a potentially promising treatment option for these patients.

Table.

SoluMatrix Diclofenac 35 mg BID and TID Combined

	Baseline	Week 52/ ET	Change From Baseline to Week 52/ ET
Number of Patients	601	555	–
SF-36v2 Physical Component Score Mean (SD)	39.5 (7.72)	44.2 (8.29)	4.5 (6.89)[a]
SF-36v2 Mental Component Score Mean (SD)	52.0 (9.60)	52.3 (9.44)	0.1 (8.41)
SF-36v2 Domain Scores Mean (SD)	**Baseline**	**Week 52/ ET**	**Change From Baseline to Week 52/ ET**
Physical Functioning	37.8 (8.64)	42.2 (9.48)	4.3 (8.14)
Role Physical	41.3 (8.64)	45.1 (8.79)	3.6 (7.99)
Bodily Pain	40.1 (6.72)	45.8 (8.27)	5.5 (8.55)[b]
General Health	51.2 (8.87)	51.5 (8.97)	0.1 (6.04)
Vitality	48.1 (8.89)	50.4 (9.25)	2.3 (8.00)
Social Functioning	46.5 (9.43)	48.9 (9.12)	2.1 (8.97)
Role Emotional	45.2 (10.57)	47.1 (10.22)	1.5 (10.04)
Mental Health	51.2 (8.71)	51.9 (9.19)	0.5 (8.06)

BID= twice daily; ET = early termination; TID= three times daily
[a]Change from baseline in scores ≥ minimally clinically important difference (MCID) ≥2.5 for physical component score.
[b]Change from baseline in scores ≥ minimally clinically important difference (MCID) ≥5.0 for SF-36v2 domain scores.

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Early Gout Pain Response at 28 Hours Predicts Response at 5 Days on Both Patient Pain and Physician Global Assessment. Paul M. Peloso[1], Ted R. Mikuls[2], Brian W. Coburn[3], H. Ralph Schumacher Jr. [4], Davis F. Gates[1], Zoran Popmihajlov[1], Walter L. Straus[1] and R. Andrew Moore[5]. [1]Merck & Co., Inc., Whitehouse Station, NJ, [2]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [3]Omaha VA and University of Nebraska Medical Center, Omaha, NE, USA, Omaha, NE, [4]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [5]University of Oxford, Nuffield Division of Anaesthetics, Oxford, England.

Background/Purpose: This *post-hoc* analysis from a randomized trial[1] in acute gout asked whether early pain responses predict subsequent pain and investigator global responses.

Methods: Patient assessment of pain captured at 28 hours (the first measurement after 24 hours of dosing) was considered as the "early onset" timepoint and was compared to the patient's subsequent pain and investigators global assessment of response to therapy (IGART) at Day 5. Pain was assessed on a Likert scale (none = 0, mild = 1, moderate = 2, severe = 3, extreme = 4) and IGART was assessed on a 0–4 point scale (excellent to none). All patients had moderate or greater pain at entry. Early onset of pain relief was defined as "No worse than mild pain" when patients reported pain as "None = 0 or Mild Pain = 1". Of the 150 gout patients, all of whom met the 1977 ACR criteria, randomization assigned patients to either etoricoxib 120 mg daily or indomethacin 150 mg daily in a 1:1 ratio. As the analgesic response was similar for etoricoxib and indomethacin in the primary trial, these arms were pooled for this analysis. The 141 patients with complete follow up data were included. Analyses were conducted in SAS® v.9.3.

Results: Ninety percent (90.1%) of patients with mild or no pain at 28 hours continued with mild or no pain at Day 5, vs. 66.7% of those not reaching mild or no pain at 28 hours. More patients with monoarticular than polyarticular gout reached mild or no pain at 28 hours (Breslow-Day, $p=0.008$). Monoarticular gout patients with mild or no pain at 28 hours (98.3%) continued to have mild or no pain at Day 5 vs. 70.6% who did not reach mild or no pain at 28 hours ($p<0.001$). Patients with polyarticular gout reporting mild or no pain at 28 hours continued with mild or no pain at Day

5 (66.7%), vs. 61.5% who attained mild or no pain at 5 Days without reporting mild or no pain at 28 hours (p=NS). Polyarticular gout responded less well early and late vs. monoarticular gout (Table 1‘). Mild or no pain at 28 hours correlated with IGART scores of “very good or excellent” at Day 5. Mild or no pain patients at 28 hours had very good or excellent IGART scores at Day 5 (92.6%) vs. 71.7% without mild or no pain at 28 hours (p<0.001). The trend of early pain response with very good/excellent IGART was consistent for monoarticular and polyarticular gout (Breslow-Day p=0.869). Supportive correlations (Pearson’s) for pain and IGART were r=0.498 at 28 hours and r=0.651 at Day 5 (both p <0.0001).

Table 1. 28-Hour Pain Onset vs Subsequent Pain Response at Day 5

28-Hour Pain Response	Moderate or Greater Pain at Day 5	Mild or No Pain at Day 5	Percent Responder	Patient Population
NO (Mod. or > pain)	20	40	66.7%	All Patients With Gout
YES (Mild or no pain)	8	73	90.1%	
		CMH Test[a]	0.003	
		Breslow-Day Test	0.008	
NO	10	24	70.6%	Monoarticular Gout
YES	1	59	98.3%	
		Chi-Squared Test	<0.001	
		Fisher’s Exact Test	<0.001	
NO	10	16	61.5%	Polyarticular Gout
YES	7	14	66.7%	
		Chi-Squared Test	0.716	
		Fisher’s Exact Test	0.768	

[a]CMH test controls for monoarticular/polyarticular gout comparison.

Conclusion: Early patient pain response of mild or no pain appeared to predict subsequent pain and investigator responses at 5 Days in monoarticular gout. Early response among polyarticular gout patients did not predict subsequent pain response indicating a potentially less stable pain response. This analysis suggests early re-evaluation after 24 hours and modification of gout treatment would benefit patients

[1]Schumacher HR et al. *BMJ*. 2002;324:1488–92.

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Chronic Fatigue Is Associated with Hypoperfusion of Parahippocampal Gyrus. Andrew O’Shea[1], Jason Craggs[1], Ricky Madhavan[1], Donald Price[1], Song Lai[1], Michael Robinson[1] and Roland Staud[2]. [1]University of Florida, Gainesville, FL, [2]Univ of Florida Med Ctr/JHMHC, Gainesville, FL.

Background/Purpose: Cerebral hypoperfusion of the whole brain has previously been reported in chronic fatigue syndrome (CFS) patients. However, discrepancies exist in the literature in regards to the spatial extent of such abnormal brain perfusion, as well as the effect sizes of these abnormalities as previously used methods did not allow precise localization of such perfusion abnormalities. We measured global and local resting state cerebral blood flow (CBF) in CFS patients and compared them to healthy controls (HC).

Methods: CFS was determined using the CDC Criteria. 15 CFS patients (age = 50.5±13.0)) and 12 HC (age = 49.2±12.2) were MRI scanned with a 3 Tesla Achieva during rest using a pseudo-continuous arterial spin labeling (pCASL) sequence. pCASL can quantify CBF without using exogenous contrast agents by magnetically labeling inflowing blood. Individual scans were corrected for motion and spatially smoothed, then label and control pairs were subtracted to create a perfusion image. The perfusion image was used to calculate a quantified CBF map, which was then normalized to standardized space. Groups were compared using voxel-wise independent samples t-tests. Statistical parametric maps were thresholded using a cluster forming t-statistic greater than 4.0 ($p < 0.00025$) and a spatial extent of 20 contiguous voxels (160 mm^3) to control for multiple comparisons.

Results: Overall cerebral blood flow was similar between groups (p >.05). CFS patients showed reduced blood flow in the right hemisphere parahippocampal gyrus. In the significant cluster, HC participants had a mean (SD) CBF of 40.51 (7.89) compared to 27.69 (6.22) (ml/100g/min) in CFS patients ($t(25) = 4.73$, $p = 0.00008$, Cohen’s $d = 1.80$).

Conclusion: Reduced cerebral perfusion was observed in the right parahippocampal gyrus of CFS patients. The parahippocampal gyrus plays a major role in the processing of memory and cognition. Reduced blood flow of this area may be a cause or consequence of chronic fatigue as well as impaired memory and cognition often observed in CFS.

Disclosure: A. O’Shea, None; **J. Craggs**, None; **R. Madhavan**, None; **D. Price**, None; **S. Lai**, None; **M. Robinson**, None; **R. Staud**, None.

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Preliminary Validation of the Michigan Body Map. Chad M. Brummett[1], Jenna Goesling[2], Rishi Bakshi[1], Jennifer Wolfe[2], Stephanie Moser[1], David A. Williams[3] and Afton L. Hassett[4]. [1]University of Michigan Medical School, Ann Arbor, MI, [2]University of Michigan Health System, Ann Arbor, MI, [3]Univ of MI Hlth System-Lobby M, Ann Arbor, MI, [4]University of Michigan, Ann Arbor, MI.

Background/Purpose: One of the hallmark features of fibromyalgia and other centralized pain states is widespread body pain. We developed the Michigan Body Map (MBM) to assess widespread body pain in clinical care and in epidemiological studies. The MBM is a one-sided body image with check boxes for 35 body areas and a box for “No Pain.” The aim of the present study was to assess patients’ understanding of and accuracy when completing the MBM, as well as to assess preference when compared to the 2011 Survey Criteria for Fibromyalgia widespread pain index (WPI) and the body map from the Brief Pain Inventory (BPI).

Methods: 85 patients from the University of Michigan’s Physical Medicine and Rehabilitation Spine Center were included in this study. Written informed consent was obtained. The first phase (n=25) assessed how well participants understood the questionnaire and concurrent validity when compared to a standardized verbal assessment. In the second phase, the MBM’s reliability was assessed using a test-retest assessment 1–2 weeks after the first assessment (n=20). In the third phase, participants were randomized to complete the MBM and either the WPI (n = 20) or BPI (n = 20) to assess construct validity and were also asked preference questions about the body maps.

Results: In the first phase, participants completed the MBM quickly (76.8+/− 64.5 sec). The majority of participants correctly noted right and left, marked only areas of chronic pain (3 months or more), and felt that the measure allowed them to note all of their areas of pain (Table 1). Of the 875 potential check boxes (25 patients × 35 body areas), 63 (7.2%) were incorrectly endorsed as either missed or reversed right/left. In the second phase, the majority of participants had slight discrepancies in the test-retest (ICC =.60, median 1.5 body areas different); however, these differences did not lead to significant changes in the calculated widespread pain score. In the third phase, the MBM was preferred when compared to the 2011 Survey Criteria for Fibromyalgia WPI (Table 2). There were no differences in participant preferences between the MBM and BPI (Table 2).

Conclusion: Overall, participants demonstrated good understanding of the MBM and preferred it to the WPI from the Fibromyalgia Survey Criteria. When compared to the BPI body map, the MBM offers advantages in quantifying, as there is no ambiguity as to the area that was checked. Some participants confused right and left in the MBM and body areas tended to be underreported when compared to verbally assessing each of the 35 possible body areas individually.

Table 1. First phase: Assessment of understanding

	N (%)
Identified right/left correctly	
Yes	16 (64%)
No	5 (20%)
Missing	4 (16%)
Pain present for 3 months or more	
Yes	19 (76%)
No	1 (4%)
Missing	5 (20%)
Able to indicate all areas of pain	
Yes	21 (84%)
No	4 (16%)

Table 2. Third phase: Questionnaire preference

	MBM vs. BPI		MBM vs. WPI	
	MBM	BPI	MBM	WPI
Preference	45%	45%	70%	15%
Best depicts areas of pain	30%	55%	70%	5%
Easier to complete	20%	40%	50%	30%
Best distinguishes left from right	20%	40%	45%	25%

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Evaluating Neuropathic Complaints By DN4 and Lanss Scales after Local Corticosteroid Therapy in Carpal Tunnel Syndrome. Taner Dandinoglu[1], Murat Karadeniz[2], Volkan Yılmaz[3], Levent Tekin[4] and Ümit Dinçer[4]. [1]Bursa Military Hospital, Bursa, Turkey, [2]Çorlu Military Hospital, Tekirdağ, Turkey, [3]Mevki Military Hospital, Ankara, Turkey, [4]Gülhane Military Medical Academy, Haydarpaşa Training Hospital, İstanbul, Turkey.

Background/Purpose: The purpose of this study was to evaluate the neuropathic symptoms after local steroid injection in CTS. Since 2001, neuropathic pain scales have been used in the assessment and follow-up of neuropathic pain. DN4 and LANSS pain questionnaires have been applied to groups, mostly consisted of radiculopathy and polyneuropathy cases, before and after various treatments and the results have been compared with the electrophysiologic findings. However to our knowledge there is yet no such study focusing on neuropathic complaints and the relationship between neuropathic pain and electrophysiological findings before and after local corticosteroid injection.

Methods: Forty-one patients aged 22–65 years and diagnosed with carpal tunnel syndrome by nerve conduction studies who were also found to have a neuropathic symptoms were included in the study. All patients received local steroid injection into the carpal tunnel while the questionnaires and nerve conduction studies were performed before and 2 months after the injection.

Results: Local steroid injection was found effective on clinical and electrophysiologic parameters as well as on DN4 and LANSS scores in CTS patients ($p<0.05$) (Table 1). Electrophysiologic severity exhibited no statistically significant relationship with DN4 and LANSS scores, before and after treatment ($p>0.05$).

Conclusion: These findings suggests that the treatment of neuropathic complaints should be planned independently from the electrophysiologic findings and minimally invasive local steroid injection appears to be effective with regard to clinical and electrophysiologic aspects in CTS patients with neuropathic complaints.

Table 1. DN4 and LANSS Scores Before and After the Treatment

	Pre-Treatment Mean±SD	Post-Treatment Mean±SD	Difference Mean±SD	P
DN4	6.12±1.50 (6.00)	1.46±1.96 (1.00)	**−4.65±1.51**	**0.001****
LANSS	15.85±2.71 (16.00)	3.22±5.16 (0.00)	**−12.63±4.83**	**0.001****

*Wilcoxon Signed Ranks Test **p<0.01*
DN4: Douleur Neuropathique 4
LANSS: Leeds Assessment of Neuropathic Symptoms and Signs

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The Effect of Milnacipran on Pain in Rheumatoid Arthritis Patients with Widespread Pain: a Randomized Blinded Crossover Trial. Yvonne C. Lee[1], Elena Massarotti[2], Robert R. Edwards[3], Bing Lu[1], Chih-Chin Liu[4], Yuanyu Lo[1], Alyssa Wohlfahrt[1], Nancy Kim[5], Daniel J. Clauw[6] and Daniel H. Solomon[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham & Women's Hosp, Boston, MA, [3]Brigham & Womens Hospital, Chestnut Hill, MA, [4]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [5]Massachusetts General Hospital, Charlestown, MA, [6]University of Michigan, Ann Arbor, MI.

Background/Purpose: Clinical trials have shown that serotonin norepinephrine reuptake inhibitors, such as milnacipran, decrease pain in chronic non-inflammatory pain conditions like fibromyalgia and osteoarthritis. We examined the effect of milnacipran on self-reported pain intensity and experimental pain sensitivity among rheumatoid arthritis (RA) patients with widespread pain on a stable treatment regimen.

Methods: Thirty-two subjects with RA completed a double-blind, crossover study. Subjects were randomized to receive milnacipran 50 mg twice daily or placebo for 6 weeks, followed by a 3-week washout and crossed over to the other arm for the remaining 6 weeks. Subjects completed the Brief Pain Inventory – short form (BPI-sf) to assess self-reported pain intensity and the Symptom Intensity Scale (SIS) to assess symptoms of fibromyalgia. Subjects also underwent quantitative assessments of pressure pain thresholds at joint and non-joint sites, using a Wagner FPK 20 algometer. Pain thresholds at the trapezius were measured before and after a noxious conditioning stimulus to assess conditioned pain modulation, a measure of the descending analgesic pain pathways. The primary outcome was change in self-reported pain, measured by the BPI-sf average pain intensity. Secondary outcomes included changes in the SIS score, pain thresholds and conditioned pain modulation. Changes in pain measures were compared between milnacipran and placebo using Wilcoxon signed rank tests and linear mixed models.

Results: After 6 weeks of milnacipran, BPI-sf average pain intensity decreased 0.7 (SD 1.7) points on a 0–10 scale, compared to a decrease of 0.3 (SD 2.0) after 6 weeks of placebo ($P = 0.37$) (Table). Thumbnail pressure pain threshold increased by 0.7 (SD 1.4) during milnacipran treatment compared to -0.02 (SD 1.4) during placebo ($P = 0.04$). None of the other secondary outcome measures differed significantly between treatment periods. In the subgroup of subjects with swollen joint count less than or equal to 1, BPI-sf average pain intensity decreased 1.0 (SD 1.6) points, compared to an increase of 0.1 (SD 1.9) during placebo ($P = 0.04$). In this subgroup, the increase in thumbnail pressure pain threshold was also significantly higher during milnacipran treatment compared to placebo ($P = 0.003$).

Conclusion: This randomized, blinded cross-over trial of milnacipran vs. placebo revealed no overall differences in improvements in pain intensity, fibromyalgia symptoms and experimentally assessed pain measures. Subgroup analyses among patients with 0–1 swollen joints suggested that milnacipran may have a role in diminishing overall pain among RA patients who have minimal evidence of inflammatory disease activity. This finding needs to be replicated in a larger study, designed specifically to examine the effects of milnacipran among RA patients in remission or with low disease activity.

Table: Means (standard deviations) for measures of pain

	Placebo			Milnacipran			*P*-values	
	Baseline	6-weeks	Change	Baseline	6-weeks	Change	Unadjusted[b]	Adjusted[c]
BPI-sf Average Pain Intensity[a]	5.2 (2.1)	4.9 (2.1)	−0.3 (2.0)	5.6 (2.0)	4.8 (2.2)	−0.7 (1.7)	0.42	0.37
Symptom Intensity Scale	5.1 (2.1)	4.3 (2.4)	−0.8 (1.9)	5.2 (2.0)	4.5 (8.3)	−0.7 (1.6)	0.89	0.83
Thumbnail Pain Threshold	5.8 (3.0)	5.8 (2.8)	−0.02 (1.4)	5.3 (2.7)	6.0 (2.8)	0.7 (1.4)	**0.04**	0.04
Trapezius Pain Threshold	4.9 (2.8)	5.5 (3.1)	0.6 (1.5)	5.1 (3.1)	5.5 (3.1)	0.4 (1.3)	0.89	0.44
Wrist Pain Threshold	5.3 (2.7)	5.9 (3.0)	0.6 (1.6)	5.0 (2.4)	5.9 (2.9)	0.9 (1.5)	0.35	0.34
Knee Pain Threshold	7.0 (3.1)	7.3 (3.1)	0.3 (1.8)	6.9 (3.2)	7.3 (3.2)	0.3 (1.4)	0.72	0.82
Conditioned Pain Modulation	0.8 (1.0)	0.9 (1.3)	0.1 (1.2)	0.8 (1.1)	0.9 (1.1)	0.1 (1.5)	0.39	0.96

Abbreviations: BPI-sf, Brief Pain Inventory – short form.
[a] Based on a 0–10 scale with 10 being worse pain.
[b] *P*-values for the difference between the values during milnacipran vs. placebo using Wilcoxon signed-rank tests.
[c] *P*-values for the difference between the values during milnacipran vs. placebo using linear mixed models including treatment, crossover period and treatment sequence.

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Pain As Predictor of Organ Involvement in Fabry Disease. Pierre Kaminsky[1], Frederic Barbey[2], Roland Jaussaud[3], Francis Gaches[4], Vanessa Leguy-Seguin[5], Eric Hachulla[6], Thierry Zenone[7], Christian Lavigne[8], Claire Douillard[9], Isabelle Marie[10], Boris Bienvenu[11], Bertrand Dussol[12] and Olivier Lidove[13]. [1]CHU Nancy, Vandoeuvre, France, [2]CHU Vaudois, Lausanne, Switzerland, [3]CHU de Reims, Reims, France, [4]Hôpital Ducuing, Toulouse, France, [5]CHU Dijon, Dijon, France, [6]Lille University, Lille, France, [7]CH de Valence, Valence, France, [8]CHU d'Angers, Angers, France, [9]CHU Lille, Lille, France, [10]CHU de Rouen, Rouen, France, [11]CHU Côte de Nacre, CAEN, France, [12]AP Marseille, Marseille, France, [13]Hôpital Croix-Saint-Simon, PARIS, France.

Background/Purpose: Fabry disease (FD) in a X-linked hereditary lysosomal disorder due to alphagalactosidase A deficiency, leading to the accumulation of its substrate (globotriaosylceramide) in vessels, neurons, and heart. Pains are the most clinical dishabiliting symptom in children and young adults, characterized by chronic or acute burning sensation in the extremities. These acroparesthesias are often misdiagnosed as rheumatological disorders. Angiokeratomas, hypohidrosis and cornea verticillata are other common early clinical symptoms while hearing loss, hypertrophic cardiomyopathy, renal involvement and cerebrovascular disorders are the main complications, occurring after the second decade. Early diagnosis is crucial since the sooner enzyme replacement therapy (ERT) is prescribed in FD patients, the more efficient it is. The goal of this study was to determine the clinical

pertinence of acroparesthesia to predict organ involvement in Fabry patients.

Methods: Two hundred Fabry patients were systematically investigated for clinical symptoms i.e. acroparesthesia (ACR), angiokeratoma (AGK), hypohidrosis (HHD), and cornea verticillata (CV) and for organ complications i.e. hypoacousia (HAC), cerebrovascular (CER), renal (KDN) and heart (HEA) complications. Statistical analysis included Fischer'exact test and multiple stepwise logistic regression, a p-value lower than 0.01 being considered a significant.

Results: Patients were 78 males, aged 37.7 ± 14.3 years and 122 females, aged 42.2 ± 16.4 years. Male patients were more symptomatic than women for pain (70.5% vs 50.0%; p=0.004) but also for other clinical symptoms: AGK (64.% vs 27.9%; p<0.0001), HHD (66.7% vs 18.0%, p<0.0001), CV (62.8% vs 45.9%, p= 0.02). They were also more severely affected: HAC (40.0% vs 20.8%, p= 0.004)), HEA (53.8% vs 31.1%, p= 0.001), KDN (39.7 vs 16.3%; p<0.001), but not for CER. Compared with others, patients who presented pains had a rik of HAC 3.03 higher (1%CI: 1.41 – 6.50), of KDN 2.12 higher (1%CI 1.02 – 4.38), of HEA 1.80 higher (1%CI 1.08 – 3.00) than others. Presence of HHD, AGK and CV also correlated with organ complications. In multivariate analysis, after adjustement for age and gender, the absence of pain was an independent predictor for the absence of HAC (p< 0.0001), of HEA (p< 0.001), and of KDN (p= 0.008). The same results were obtained after inclusion of AGK, HHD and CV in multivariate analysis.

Conclusion: Fabry patients who exhibited chronic or acute acroparesthesia are at higher risk of organ involvement. Pains appear the best clinical predictor for Fabry complications. This early clinical symptom should be recognized by clinicians in order to start ERT as soon as possible.

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Characteristics of Pain in Fabry Disease. Olivier Lidove[1], Esther Noel[2], Eric Hachulla[3], Francis Gaches[4], Claire Douillard[5], Bernadette Darne[6], Kim Heang Ly[7], Christian Lavigne[8], Agathe Masseau[9], Laurent Aaron[10], Boris Bienvenu[11], Thierry Zenone[12], Philippe Vitielli[6], Vanessa Leguy-Seguin[13] and Jean Marc Ziza[14]. [1]Hôpital Croix-Saint-Simon, PARIS, France, [2]CHU de Strasbourg - Hopital Civil, Strasbourg, France, [3]Université Lille Nord de France, Faculté de Médecine Henri Warembourg, Lille, Lille, France, [4]Hopital Joseph Ducuing, Toulouse, France, [5]CHU Lille, Lille, France, [6]Monitoring Force, Maisons-Laffitte, France, [7]CHU Dupuytren, Limoges, Limoges, France, [8]CHU d'Angers, Angers, France, [9]Nantes University Hospital, Nantes, France, [10]Hôpital Jacques Coeur, Bourges, Bourges, France, [11]CHU Côte de Nacre, CAEN, France, [12]CH de Valence, Valence, France, [13]CHU Dijon, Dijon, France, [14]Hopital Croix-Saint-Simon, Paris Cedex 20, France.

Background/Purpose: Fabry disease (FD) is an X-linked disorder caused by a deficiency of lysosomal alpha-galactosidase A resulting in accumulation of glycosphingolipids. Clinical manifestations include a small-fiber neuropathy associated with debilitating pain. Because enzyme therapy (ERT) is available, early diagnosis in FD is crucial. The objective of this study is to characterize the pain in male (M) and female (F) FD patients.

Methods: An observational, non-interventional, retrospective, multicentre, national study was performed in France between January 2013 and April 2014. This study was approved by the ethics committee (CNIL approval: 1588616). All FD patients were eligible. FD was confirmed in all cases by enzyme alpha-galactosidase A activity and/or gene mutation analysis. Characteristics of pain were reported by the patient and by a referent physician in each case. The Neuropathic Pain Symptom Inventory (NPSI) was assessed at time of evaluation and at the moment in life when "pain was at its worst".

Results: A total of 79 patients were analyzed, median age 43 + 14 yrs.

Table 1: Summary of results

	Males	Females	p value
N (%)	33 (42)	46 (58)	
Index case	21	7	
Age at pain onset	10.9 + 8.3	19.3 + 15.4	
Maximal intensity	Median 7 (quartiles 5,9)	Median 6 (quartiles 5,8)	NS
Frequency of crisis > 10/year	54.5%	34.8%	NS
Associated symptoms: (joint pain, fever, abdominal pain)	18, 16, 9	21, 15, 9	
Aggravating factors (temperature change/humidity, effort/ sport, infectious episodes)	22, 19, 20	33, 25, 20	
Persistent burning pain	18	15	
Pain at its worst	8.2 + 2.2	7.4 + 2.5	NS
Persistent burning pain	Median 3 (quartiles 0,5)	Median 5 (quartiles 2,6)	0.04
Persistent pain in adulthood	22	34	NS
Previous or current ERT	91%	50%	<0.0001
Age at first infusion	31 + 11.1	42.1 + 15	<0.01
Efficacy of carbamazepine (pain crisis)	21	10	
Efficacy of physiotherapy (pain)	6	7	
Depression	11	18	
School attendance	66.7%	82.6%	<0.01
Part-time work	3%	23.9%	<0.01
Handicap expertise	51.5%	21.7%	<0.01

Before diagnosis of FD, other causes of pain were considered (M: n=15; F: n=8): anxiety (n=25), growing pain (n=17), rheumatic fever (n=7), rheumatoid arthritis (n=1), Still disease (n=1). Raynaud's phenomenon was present in 25 patients (30%). Only 18% of M and 15% of F had no pain according to the physician. The association of crisis and persistent pain was the most frequent phenotype (M: 51%, F: 43%). Pain crisis corresponded to burning sensation (M=F), tingling (M=F), electric discharge (M only). Pain crisis duration ranged from few minutes (one third) to few days (M: 18.2%, F: 11%). Other symptoms were more frequent in M than in F: sweating disorders (p=0.02), lymphedema (p=0.02), high creatinine level (p=0.04). Intra-familial other cases of pain in extremities were found with differences between genders: father's pain only in F (p=0.002), children's and cousin's pain more frequently found in F (p=0.003 and p=0.002, respectively). NPSI questionnaire was performed in 75 cases. Agreement between patient and physician was good (kappa 0.73, CI95% 0.57–0.90). Patients with pain were treated with ERT in 69.4% of cases whereas patients without pain were treated with ERT in 61.5%. ERT was the most effective therapy on pain in only two males.

Conclusion: Diagnosis and treatment of neuropathic pain are important in FD. Burning pain in the extremities, and frequent pain in relatives may be a tool for an early diagnosis. The higher frequency of chronic pain in females may imply clinical, psychological, and social components of pain. Treatment of pain in FD patients should not be limited to pharmacological therapies, but include personal and family management, to address psychosocial functioning.

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Quality of Life Assessment of Adults Patients with X-Linked Hypophosphoremia. Karine Briot[1], Hélène Ché[1], Adrien Etcheto[1], Anya Rothenbuhler[2], Peter Kamenicky,[2], Agnès Linglart[2] and Christian Roux[3]. [1]Paris Descartes University, Paris, France, [2]Hôpital Bicêtre, Kremlin Bicêtre, France, [3]Paris Descartes University, Cochin Hospital, Paris, France.

Background/Purpose: X-Linked Hypophosphatemia (XLH) is the most common form of heritable rickets. Although disease severity is variable, adults with XLH may suffer from skeletal symptoms leading to function disability. There are no data on the consequences of these symptoms on quality of life (QoL) of adults with XLH. The objective was to evaluate the QoL and the variables associated with low QoL in adult patients with XLH.

Methods: We conducted a cross sectional study in adult patients with XLH, who consulted in rheumatology, for skeletal symptoms, between 2013 and 2014. We assessed the intensity of pain (VAS Visual Analogic Scale) and QoL using 3 Patient Reported Outcomes: HAQ (Health Assessment Questionnaire, high if >0.5), RAPID3 (Routine Assessment of Patient Index Data 3, high if >6) and 36-item short-form health (SF36) survey. We also collected demographic and disease characteristics, radiographic features and data on treatments of XLH. We described the QoL of XLH patients and analysed the variables associated with low QoL.

Results: Thirty two patients with XLH (27 women; mean age of 42.8 yrs) with PHEX mutations were included. 15 (48.4%), 16 (51.6%), 12 (40%) received respectively phosphate supplements, vitamin D analogues, and 25 OH-vitamin D supplements, at the time of assessment. X-rays showed osteoarthritis (knee, hip or spine) (n=27, 90%), enthesopathies (n=19, 61.3%) and sequelae of insufficiency fractures (n=4, 14.8%). Skeletal pain

was reported by 64.3% of patients with a mean VAS of 4.6 (+/−2.6). Age is significantly associated with low QoL ($p \leq 0.05$), indicated by high scores of HAQ (mean value 0.71±0.6, HAQ >0.5 in n=19), RAPID3 (mean value 11.32 ± 6.4, RAPID3 >6 in n=23), and physical domains of SF36 (physical functioning (mean value 58.4± 23.6) and physical role (mean value 37.5± 39.1)). Osteoarthritis was associated with low QoL indicated by high HAQ ($p \leq 0.05$). Radiographic enthesopathies were significantly higher in patients with high RAPID3 and low bodily pain scale of SF36 (mean value 55± 24) ($p \leq 0.05$). Phosphate supplements, vitamin D analogues and physiotherapy treatments were associated with high general health (mean value 40.23±17.1) and social functioning (mean value 70.31±21.7) scales of SF36 ($p \leq 0.05$).

Conclusion: This study showed that QoL of adults with XLH is altered; age and radiographical involvement (osteoarthritis and enthesopathies) are significantly associated with low QoL; adults treated for XLH reported better general health and social functioning scores.

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Pain Characteristics Among Patients with Rheumatoid Arthritis in the Context of Patient-Physician Discordance in Disease Activity Assessments. John M. Davis III, Cynthia S. Crowson, Tim Bongartz, Clement J. Michet, Eric L. Matteson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN.

Background/Purpose: Healthcare must be patient-centered to achieve optimal outcomes and quality of life. From this perspective, it is significant that patients with rheumatoid arthritis (RA) sometimes rate their disease activity as much higher than their rheumatologists. This 'discordance' is mediated in part by patient-reported pain. In this study, our objective was to characterize the qualities of pain reported by patients in the context of patient-physician discordance.

Methods: We conducted an observational study of consecutive patients with RA recruited between July 2008 and December 2010. A physician joint assessor, who was independent from treatment decision-making, performed a standardized clinical evaluation. Positive discordance was defined as the patient global assessment being ≥25-mm higher than the physician global assessment of disease activity. Patients completed the pain visual analog scale (VAS; range: 0 – 100 mm) and the Short Form McGill Pain Questionnaire (SF-MPQ), including the sensory (range: 0 – 33) and affective (range: 0 – 12) scales. Examples of sensory characteristics are "sharp, aching or throbbing," and examples of affective characteristics are "sickening, fear-causing, or punishing-cruel." We abstracted electronic medical records to collect demographics, laboratory data, smoking status, and body mass index (kg/m^2). Correlations between explanatory variables and the presence of positive discordance were determined using Spearman methods, adjusting for RA characteristics.

Results: A total of 127 patients with RA were recruited (mean age 55.6 years; mean disease duration 6.8 months; 63% female). The mean (SD) pain VAS was 47 (26) mm. The median (range) scores for the SF-MPQ sensory and affective scales were 10 (0 to 29) and 2 (0 to 9). Positive discordance (i.e., patient high) was associated with higher pain ($r = 0.37$, $p = <0.001$) and fatigue ($r = 0.32$, $p<0.001$). The SF-MPQ data showed that positive discordance was more strongly associated with affective characteristics of pain ($r = 0.30$, $p <0.001$) than sensory characteristics of pain ($r = 0.23$, $p = 0.013$). The association of positive discordance with SF-MPQ affective pain was independent of age, sex, rheumatoid factor, anti-CCP antibodies, body mass index, smoking status, and use of prednisone or disease-modifying drugs.

Conclusion: The significance of this study is that in the context of positive discordance, patients are more likely to describe their pain using words that have affective or emotional connotations. This finding could reflect activation of pain, mood, and fear networks in the brain. Future research should evaluate the connectivity between these brain networks in the setting of patient-physician discordance and determine their relationship to subclinical immune/inflammatory status. The positive impact could be the development of new approaches that better alleviate pain and improve quality of life in our patients.

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Development of Pediatric Item Banks to Measure Pain Behavior in the Patient Reported Outcomes Measurement Information System. Esi Morgan DeWitt[1], Kimberly Barnett[1], Wen-Hung Chen[2], Jennifer Farrell[1], Dennis Revicki[2], Adam Carle[1], Karon Cook[3], Kenneth Goldschneider[1], Carlton Dampier[4], David D. Sherry[5] and Susmita Kashikar-Zuck[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Evidera, Bethesda, MD, [3]Northwestern University Feinberg School of Medicine, Chicago, IL, [4]Emory University School of Medicine, Atlanta, GA, [5]Children's Hospital of Philadelphia, Philadelphia, PA.

Background/Purpose: The NIH Patient Reported Outcomes Measurement Information System (PROMIS) has created publicly available patient reported outcomes measures in several domains of physical, social and emotional health. Measurement of pediatric pain in PROMIS is currently limited to pain interference. Pain behaviors are observable actions or reactions that communicate pain including verbal, non-verbal and pain reducing behaviors. Numerous validated parent/provider-rating scales of pain behavior in children exist but there are currently no validated self-report measures of pain behavior in school-age children and adolescents. Such measures could be useful in establishing targets for treatment and assessing outcomes. The aim of this study is to enhance PROMIS pediatric pain assessment by developing and testing pediatric pain behavior item banks for self- and proxy-report.

Methods: Candidate items were developed through a qualitative item review process, and were in the format, "In the past 7 days, when I was in pain. . ." Patients ages 8 to 17 years, or parents/guardians of children, with a chronic painful condition (fibromyalgia, juvenile idiopathic arthritis, sickle cell disease) were recruited through outpatient clinics at 3 centers. Child participants completed approximately 100 PROMIS items concerning their pain (including 47 candidate pain behavior items), physical function, fatigue, and psychosocial well-being. Proxies responded to socio-demographic and health history items and 51 new candidate proxy-report pain behavior items were collected. A confirmatory factor analysis (CFA) was performed on the child and guardian pain behavior data, with model fit assessed by the comparative fit index (CFI) and root mean square error of approximation (RMSEA). Item response theory (IRT) analysis was performed on the pain behavior items based on the graded response model. Differential item functioning (DIF) was assessed by age group and disease group.

Results: 450 children (71% female, M_{age} 13.54), and 232 proxies participated. CFA indicated unidimensionality in the child (CFI=0.962; RMSEA=0.079) and proxy pain behavior responses (CFI=0.970; RMSEA=0.080). The responses for the child and proxy data had good IRT model fit and were free of local dependence. Slopes for the pediatric responses ranged from 1.81 ("rubbed body where hurt") to 4.40 ("moved slower"), and thresholds ranged from -2.00 to 4.95. For the proxy data, slopes ranged from 1.51 ("think of something fun") to 3.48 ("tried not to move"), and thresholds ranged from -3.02 to 2.43. Items performed well across disease groups and age. There was little DIF either by age group (8–12, 13–18) or by sample (child vs. proxy). Child and proxy scores were correlated at 0.70. Correlations between pain behavior and pain intensity were 0.60 in children and 0.65 in proxy sample.

Conclusion: The PROMIS pediatric pain behavior item-banks for self and proxy report are suitable for use in non-adaptive format as short forms or in dynamic format as computerized adaptive tests in clinical research with the potential for adoption into clinical care.

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Validation of the Dutch-Flemish Promis Physical Functioning Item Bank in Patients with Chronic Pain. Martine Crins[1], Caroline Terwee[2], Niels Smits[3], Anton de Vries[3], Henrica de Vet[2], Joost Dekker[2], Rene Westhovens[4], David Cella[5], Karon Cook[5], Dennis Revicki[6], Jaap van Leeuwen[7], Maarten Boers[2] and Leo D. Roorda[8]. [1]Amsterdam Rehabilitation Research Center | Reade, Amsterdam, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]VU University Medical Center EMGO Institute for Health and Care Research, Department of Epidemiology and Biostatistics,

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Background/Purpose: In the assessment of chronic pain patients it is important to measure physical functioning. The National Institutes of Health's Patient-Reported Outcomes Measurement Information System (PROMIS) initiative developed an item bank for measuring physical functioning. This PROMIS physical functioning item bank was translated into Dutch-Flemish language according to the FACIT methodology. The aim of current study was to validate the Dutch-Flemish translation of the PROMIS physical functioning item bank (DF-PROMIS-PF) in patients with chronic pain.

Methods: A paper-and-pencil or web-based survey including the full DF-PROMIS-PF (121 items), was completed by 857 chronic pain patients (77% female, mean age 49y) satisfying the ACR classification criteria of chronic pain and referred to an outpatient secondary care center for rheumatology and rehabilitation in the Netherlands. One-dimensionality was evaluated by one-factor confirmatory factor analysis. With the future strategy to develop computer adaptive tests (CAT), item response theory (IRT) models were used to evaluate the item characteristics of the two item banks. A graded item response model (GRM) was fitted and Differential Item Functioning (DIF) was evaluated for e.g. language (Dutch vs. English), by ordinal regression models. Furthermore, construct validity was studied.

Results: Through computer technical limitation, the item bank was separated during statistical analysis into DF-PROMIS-PF_A (50 PFA-items) and DF-PROMIS-PF_{BC} (45 PF_B- and 26 PF_C-items). These interim analysis showed that the DF-PROMIS-PF_A and DF-PROMIS-PF_{BC} demonstrated good fit to a one-dimensional model (both CFI=0.976 and TLI=0.975). The first factor accounted for 57% of the questionnaire variance. The results showed acceptable test information (SE<0.3) for theta between -2.3 and 3.8 for DF-PROMIS-PF_A and between -1.6 and 4 for DF-PROMIS-PF_{BC}. The items demonstrated no DIF with respect to survey version. DIF was present with respect to gender (2 items), age (4 items) and language (11 items). However, the impact of DIF on the total item scores was minimal. The analyses of the full DF-PROMIS-PF are in progress and will be presented at the ACR conference.

Conclusion: The first results indicate that the DF-PROMIS-PF fits a GRM and demonstrates good coverage across the range of the physical functioning domain. Nearly all Dutch item parameters match the American item parameters and likely Dutch-specific item calibrations are not needed. The DF-PROMIS-PF can be used to develop a CAT.

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Validation of the Dutch-Flemish Promis Pain Behavior and Pain Interference Item Banks in Patients with Chronic Pain. Martine Crins[1], Leo D. Roorda[2], Niels Smits[3], Henrica de Vet[4], Rene Westhovens[5], David Cella[6], Karon Cook[6], Dennis Revicki[7], Jaap van Leeuwen[8], Maarten Boers[4], Joost Dekker[4] and Caroline Terwee[4]. [1]Amsterdam Rehabilitation Research Center | Reade, Amsterdam, Netherlands, [2]Amsterdam Rehabilitation Research Center | Reade, Amsterdam, the Netherlands, Amsterdam, Netherlands, [3]VU University Medical Center EMGO Institute for Health and Care Research, Department of Epidemiology and Biostatistics, Amsterdam, Netherlands, [4]VU University Medical Center, Amsterdam, Netherlands, [5]University of Leuven, Skeletal Biology and Engineering Research Center, Department of Development and Regeneration; Rheumatology, University Hospital Leuven, Leuven, Belgium, [6]Northwestern University Feinberg School of Medicine, Chicago, IL, [7]Outcomes Research, United BioSource Corporation, Bethesda, MD, [8]CEO Leones Group BV, Amsterdam, Netherlands.

Background/Purpose: In the assessment of chronic pain patients it is important to measure pain behavior and pain interference. The National Institutes of Health's Patient-Reported Outcomes Measurement Information System (PROMIS) initiative developed item banks for measuring pain behavior and pain interference. These PROMIS item banks were translated into Dutch-Flemish language according to the FACIT methodology. The aim of current study was to validate the Dutch-Flemish translation of the PROMIS pain behavior item bank (DF-PROMIS-PB) and the Dutch-Flemish PROMIS pain interference item bank (DF-PROMIS-PI) in patients with chronic pain.

Methods: A paper-and-pencil or web-based survey, including the full DF-PROMIS-PB (39 items, 6-point Likert scale) and DF-PROMIS-PI (41 items, 5-point Likert scale), was completed by 1042 chronic pain patients satisfying the ACR classification criteria of chronic pain and referred to an outpatient secondary care center for rheumatology and rehabilitation in the Netherlands. One-dimensionality was evaluated by one-factor confirmatory factor analysis. With the future strategy to develop computer adaptive tests (CAT), item response theory (IRT) models were used to evaluate the item characteristics of the two item banks. A graded item response model (GRM) was fitted and Differential Item Functioning (DIF) was evaluated for e.g. language (Dutch vs. English), by ordinal regression models. Furthermore, construct validity was studied.

Results: DF-PROMIS-PB and DF-PROMIS-PI demonstrated good fit to a one-dimensional model (CFI=0.960; 0.988 resp. and TLI=0.958; 0.987 resp). The first factor accounted for 42% (DF-PROMIS-PB) and 66% (DF-PROMIS-PI) of the questionnaire variance. The results showed acceptable testinformation (SE<0.3) for theta between -1.9 and 3.6 for DF-PROMIS-PB and between -3.3 and 2.8 for DF-PROMIS-PI. 14 out of 741 (1.9%) DF-PROMIS-PB item pairs and 62 out of 820 (7.6%) DF-PROMIS-PI item pairs were marked as possibly locally dependent. The items demonstrated no DIF with respect to age, gender, and survey version. DIF with respect to language was present for 6 DF-PROMIS-PB items and 2 DF-PROMIS-PI items. However, the impact of DIF on the total item scores was minimal.

Conclusion: The DF-PROMIS-PB and the DF-PROMIS-PI fit a GRM and demonstrate good coverage across the range of the pain behavior and pain interference domain. Nearly all Dutch item parameters match the American item parameters and likely Dutch-specific item calibrations are not needed. The DF-PROMIS-PB and DF-PROMIS-PI can be used to develop a CAT.

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Longitudinal Assessment of Promis Pediatric Item Banks in Children with Chronic Musculoskeletal Pain. Esi Morgan DeWitt[1], Adam Carle[1], Kimberly Barnett[1], Jennifer Farrell[1], Kenneth Goldschneider[1], Carlton Dampier[2], David D. Sherry[3] and Susmita Kashikar-Zuck[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Emory University School of Medicine, Atlanta, GA, [3]Children's Hospital of Philadelphia, Philadelphia, PA.

Background/Purpose: Assessing clinical status in musculoskeletal pain syndromes requires self-report of pain and function. Yet, the field suffers from a lack of psychometrically sound, consistently applied measurement tools, limiting clinical practice and research. In this study, we used longitudinal data to evaluate the validity and responsiveness of the Patient Reported Outcomes Measurement Information System (PROMIS) pediatric item banks (physical function (PF), pain impact, fatigue, emotional distress, social role) among children receiving treatment for chronic musculoskeletal pain at two clinics. We expected each domain to improve across time, but we expected domains most closely aligned with treatment (i.e., pain and fatigue) to improve more and domains more distally related (i.e., peer relationships) to improve less. Additionally, we expected scores to improve more quickly among children receiving intensive, inpatient treatment vs. those receiving treatment at an outpatient clinic.

Methods: Across 2 multi-disciplinary pediatric pain clinics, we collected data from patients receiving treatment for a chronic painful condition (n= 145: aged 8–18 years). Across 3 visits, patients completed PROMIS self-report short form measures (~7 items each) that assessed: pain impact, PF-upper extremity, PF-mobility, fatigue, anger, anxiety, depressive symptoms, and peer relationships. PROMIS measures are normed in the general population and have a mean of 0 and standard deviation (SD) of 1. For each measure, higher values reflect more of the measured domain (e.g., higher pain impact scores reflect more pain impact, higher PF-mobility scores reflect better mobility). We used longitudinal growth models (LGM) to examine change across time.

Results: At study's start, mean domain levels ranged from -1.26 SDs below the general population (mobility) to 0.97 SDs above (pain), indicating more pain and poorer function. LGM revealed that each domain demonstrated statistically significant improvement across time. The average monthly change ranged from 0.014 (peer relationships) to -0.074 (pain). Fatigue, PF-mobility and showed changed at rates similar pain impact's. PF-upper extremity's, anxiety's, and depression's changed at rates similar to peer relationships'. In all models, rates of change showed statistically significantly differences across site in the expected directions.

Conclusion: We tested responsiveness to change of PROMIS pediatric domains in youth with chronic musculoskeletal pain. Consistent with expectations, 1) children in the pain clinics reported poorer quality than general population; 2) domains most closely related to treatment (pain impact, fatigue, and mobility) demonstrated the most change, 3) domains more distally related to treatment (e.g., peer relationships) showed the least improvement, and 4) across domains, the measures indicated intensive, inpatient treatment resulted in more rapid improvement than outpatient treatment. Results support the construct validity and responsiveness of PROMIS instruments. Future clinical research in pediatric pain should consider utilizing the PROMIS pediatric items banks.

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Nutraceutical Products and Pain or Non-Pain Medications Use in Patients with Knee Osteoarthritis. Mei Chung[1], John B. Wong[2], Shaoyu Chang[2] and Chenchen Wang[2]. [1]Tufts University School of Medicine, Boston, MA, [2]Tufts Medical Center, Boston, MA.

Background/Purpose: Knee osteoarthritis (OA) causes substantial health burden and economic costs including medications and neutraceuticals for pain. The aim of this analysis was to describe contemporary use of medications and nutraceutical products in patients with knee OA.

Methods: Knee OA patients meeting ACR criteria for enrollment into a randomized clinical trial reported their use of prescription and over-the-counter medications and nutraceutical products during the prior 6 months using the HAQ health utilization form. We analyzed the number of pain medications, non-pain medications, and nutraceutical products taken by each patient and WOMAC questionnaire measures of pain and physical function. The T-test, Fisher's exact test and multivariable ordered logistic regression were used to assess statistical differences between groups and associations. All p-values were two tailed, and results were reported as mean±standard deviation.

Results: In 204 knee OA patients (mean age 60.2 years, 70% female, mean WOMAC pain 254±95 and WOMAC function 899±352), 157 (77%), 166 (81%), 150 (74%) reported taking at least one pain, non-pain medication, or nutraceutical (7% glucosamine), respectively (**Table 1**). On average, each patient used 1.2±0.9 pain medications, 2.8±2.5 non-pain medication, and 2.4±2.3 nutraceutical products. Nutraceutical product use was higher in Whites (3.0±2.4) than in Blacks (1.8±2.0) or Asians (1.7±2.0). Patients using nutraceuticals were significantly older (+3.9, P=0.02) than those who did not without any significant differences by gender. Similarly patients who using non-pain medications were older than those who did not (+3.7 years, P=0.05. In contrast, pain medication users were significantly younger (−4.4 years, P=0.01) than those did not, and more women used pain medications than men (81% vs. 67%, P=0.05). WOMAC pain and function scores were significantly lower in nutraceutical users than in non-users (pain: 241±97 vs. 291±96, P=0.001; function: 859±357 vs. 1011±316, P=0.006). After controlling for age and sex, a higher number of nutraceuticals was associated with an improved WOMAC pain (P=0.05) and function (P=0.03) scores, but the number of pain and non-pain medications were not significantly associated WOMAC pain or function.

Conclusion: Nutraceutical and pain-medication use in OA patients is quite common and much higher in our patient population than in the Osteoarthritis Initiative (*Arthritis Research & Therapy 2013, 15:R106*). Concomitant and frequent uses of NSAIDs pain medications, nutraceutical products, and other medications for comorbidities in older knee OA patients is an area of concern, given the increased potential for side effects and drug-drug or drug-nutrient interactions.

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Table 1 Self-reported uses of non-pain and pain medications, and nutriceutical products in knee OA patients

Nutriceutical products (patient n = 150)	Freq	Percent	Non-pain medication classes (patient n = 166)	Freq	Percent
Vitamin D and/or Calcium	201	41.4%	Hypertension	138	24.2%
Multivitamins & minerals	82	16.9%	Heart disease	112	19.6%
Glucosamine/Chondroitin/MSM	36	7.4%	Hyperlipidemia	47	8.2%
Fish oil	29	6.0%	Depression	36	6.3%
Vitamin B	22	4.5%	Diabetes mellitus	35	6.1%
Flaxseed oil	17	3.5%	Peptic ulcers	30	5.3%
Vitamin C	17	3.5%	Thyroid disorders	19	3.3%
Magnesium	7	1.4%	Insomnia	17	3.0%
Folate	5	1.0%	Respiratory disorders	14	2.5%
Vitamin E	5	1.0%	Constipation	11	1.9%
Coenzyme q10	4	0.8%	Rhinitis	10	1.8%
Probiotic	4	0.8%	Epilepsy	10	1.8%
Biotin	3	0.6%	Glaucoma	9	1.6%
Iron	3	0.6%	Asthma	8	1.4%
Krill oil	3	0.6%	Psychosis	8	1.4%
Tumeric	3	0.6%	HIV	7	1.2%
Chromium	2	0.4%	Anxiety	7	1.2%
Garlic	2	0.4%	Muscle spasm	7	1.2%
L-lysine	2	0.4%	Gout/hyperuricemia	6	1.1%
Red yeast rice	2	0.4%	Cancer	5	0.9%
Ubiquinol	2	0.4%	Rheumatoid arthritis	4	0.7%
Zinc	2	0.4%	Hypokalemia	4	0.7%
Miscellaneous nutraceuticals	31*		Neurologic disorders	3	0.5%
Subtotal	**483**	**100%**	Prostatic hyperplasia	3	0.5%
			Gastrointestinal disorders	2	0.4%
			Xerostomia	2	0.4%
Pain medications (patient n = 157)	**Freq**	**Percent**	Migraine	2	0.4%
NSAIDs	147	58.6%	Incontinence	2	0.4%
Acetaminophen	88	35.1%	Osteoporosis	2	0.4%
Opioids	16	6.4%	Miscellaneous non-pain medications	8*	
Subtotal	**251**	**100%**	**Subtotal**	**567**	**100%**

Legends: Freq = Frequency; MSM = Methylsulfonylmethane. *Total number of unique miscellaneous nutraceuticals and non-pain medications that was reported once in our study population.

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Efficacy and Safety of Cannabinoid Treatments in the Rheumatic Diseases: A Systematic Review of Randomized Controlled Trials. Tara Landry[1], Mary-Ann Fitzcharles[2], Peter A. Ste-Marie[2] and Yoram Shir[2]. [1]Mcgill University Health Centre, Montreal, QC, [2]McGill University Health Centre, Montreal, QC.

Background/Purpose: The endocannabinoid system functions to maintain homeostasis in the human body and thereby has effects on modulation of pain and inflammation. Cannabinoid preparations are available as synthetic or plant derived products and may be effective for the management of pain associated with musculoskeletal conditions. We have conducted a systematic review to examine the evidence on the efficacy and side effects of cannabinoids (phyto- and syntheto-) in the management of rheumatic pain.

Methods: A comprehensive literature search of the following databases was conducted in September 2013: MEDLINE; Embase Classic + Embase; BIOSIS Previews; Scopus; CENTRAL; DARE; CINAHL; PsycINFO; AMED. Additional searches for ongoing clinical trials were also run in ClinicalTrials.gov, International Clinical Trials Registry Platform, Current Controlled Trials, Natural Standard, as well as various Drug and Device Regulatory Approval Sites. Further studies were identified in Web of Science and Scopus (March 2014) by citations searches for studies citing included studies, as well as by examining their reference lists. Randomized controlled trials (RCT's) with outcomes investigating pain and sleep disturbance in rheumatic conditions, with comparison of an active therapy with placebo were included. Study quality was assessed using the JADAD scale (out of 5). In view of a paucity of studies, heterogeneous populations, and different products, only a systematic review is reported.

Results: Of the 1407 articles screened, 12 underwent full text examination. Excluded were survey reports, observational studies, case series, case reports and commentaries, with 7 remaining articles. Of these 3 were excluded: two included patients with non-rheumatic diseases, 1 was an open-label study of effect of THC on experimentally induced pain. The remaining 4 studies comprised 201 patients (58 RA, 72 FM, and 74 OA). One study examined the effect of nabiximols in RA, two studies examined nabilone in FM (one a non-inferiority study with amitriptyline as comparator), and one examined effect of a fatty acid amide hydrolase-1 (FAAH1) inhibitor in OA. The quality of the trials was good, with a mean 3.75

JADAD score. The study of FAAH1 inhibitor was stopped at interim analysis for futility. For the remaining 3 trials, duration was from 5–8 weeks, with significant analgesic effect in two, significant sleep effect in two, and one in FM reporting improved quality of life. No serious adverse events were reported, with dizziness and drowsiness the most common adverse effects for about a quarter of patients. There were no studies of inhaled herbal cannabis identified.

Conclusion: Small sample sizes, heterogeneity of rheumatic conditions and products, only a single comparative trial and absence of any study of herbal cannabis allow for only limited conclusions. The results suggest that pain relief and positive effect on sleep may have some potential for therapeutic benefit for rheumatic patients, but in view of this small body of current evidence cannabinoid treatments cannot be recommended for management of rheumatic complaints.

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Prevalence of Medicinal Marijuana Use Among 1000 Rheumatology Patients Attending a Community-Based Rheumatology Clinic: A Prospective Cross-Sectional Study. Peter A. Ste-Marie[1], Yoram Shir[1], Emmanouil Rampakakis[2], John S. Sampalis[2], Martin Cohen[3], Michael Starr[1], Mark A Ware[1] and Mary-Ann Fitzcharles[1]. [1]McGill University Health Centre, Montreal, QC, [2]JSS Medical Research, Montreal, QC, [3]Mcgill University Health Centre, Montreal, QC.

Background/Purpose: With a worldwide groundswell of interest in cannabinoids as a possible treatment option for persons with rheumatic diseases, and with few pharmacologic cannabinoid options available, patients may be using marijuana mostly to self-medicate. “Severe arthritis” was cited as the diagnosis for 65% of persons legally authorized to possess medicinal marijuana in Canada in 2014. With knowledge that most medicinal marijuana is obtained illegally, and by extrapolating from Canadian census data of 2011, conservative estimates are that 4% of persons with rheumatic complaints may be using cannabis, with an even higher rate expected for those in rheumatology care. As there is currently no knowledge of the prevalence of use of marijuana in a defined rheumatology population, we have prospectively examined the use of herbal cannabis for 1000 rheumatology attenders.

Methods: The study was approved by the Institutional Ethical Review board and informed consent was obtained from every participant. During a two month period (April-May 2014), consecutive patients attending an academic, community based rheumatology clinic staffed by 3 rheumatologists were invited to participate. Patients were either newly referred or attending for a follow up visit. The study comprised 2 questionnaires completed at the time of the visit: 1) demographic and disease related information completed by the rheumatologist, 2) patient anonymous report of current health status, pain severity and past or current marijuana use for either recreational or medicinal purposes, or both.

Results: Of the 1067 patients attending, 1000 (96%; 74% females; mean age 63 ± 15 yrs) agreed to participate. Thirty seven patients refused to participate and 30 were not eligible. Disease categories were as follows: inflammatory arthritis 516 (52%), osteoarthritis or back pain, 489(49%) soft tissue rheumatism or fibromyalgia, 218 (22%), and other condition, 99(10%) with some overlap of diagnoses. Medicinal marijuana was reportedly used by 28 patients (2.8%; 95% CI: 1.9–4.2). Users vs. non users were more likely to be younger, 53.vs.63 yrs ($p=0.0003$), unemployed or disabled 46% vs. 8% ($p<0.0001$), and with a trend to be male. Diagnoses did not differ between the users and nonusers, but users reported poorer global well-being 5.5 vs. 3.9 ($p=0.0029$), more pain 6.3 vs 4.8 ($p= 0.0088$), and previous recreational cannabis use 82% vs 19% ($p< 0.0001$). The Physician global assessment of health status did not differ significantly between the groups 3.2 vs 2.8 ($p=0.2991$).

Conclusion: Contrary to the expected rate, only 2.8% of patients, receiving rheumatology care for multiple rheumatic disease categories, reported current use of medicinal marijuana. With use observed across all disease categories, familiarity with marijuana as a recreational product may explain use for some. Perceived health status was poorer for users, with almost half not working.

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An Examination of the Interaction of Opioid Use, Pain, and Depression. Jenna Goesling[1], Matthew Henry[1], Stephanie Moser[2], Paul Hilliard[2], Afton L. Hassett[1] and Chad Brummett[2]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan Medical School, Ann Arbor, MI.

Background/Purpose: In the past two decades there has been an increase in the use of opioids to treat chronic pain. Despite this trend, there is little empirical evidence to support the use of long-term opioid therapy in clinical practice. Chronic pain and psychiatric disorders are highly comorbid, yet patients with psychiatric diagnoses are typically excluded from opioid efficacy trials. Clinically, patients with depression and anxiety are more likely to receive opioid therapy. We hypothesized that patients taking opioids would present with a worse clinical phenotype (i.e., more pain, less functioning, and more symptoms of depression and anxiety). We also hypothesized that the relationship between opioid use and pain severity and pain interference would be moderated by depression.

Methods: A total of 2,104 new patients seeking treatment for chronic pain at the University of Michigan’s Back & Pain Center were included. Pain severity and pain interference were measured with the Brief Pain Inventory (BPI), symptoms of depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS), catastrophizing was assessed using the related subscale from the Coping Strategies Questionnaire (CSQ), and physical functioning was assessed using PROMIS SF1. Chi-square, t-tests, and analysis of covariance tests were conducted.

Results: Opioid use was associated with a worse clinical phenotype (Table 1). Depression moderated the relationship between opioid use and pain interference (Figure 1) and pain severity (Figure 2). There was no difference in pain interference by opioid group for depressed patients, but non-depressed opioid users reported more pain interference than non-depressed non-opioid users ($p<.001$) (Figure 1). The same moderated effect was found for pain severity ($p<.001$) (Figure 2).

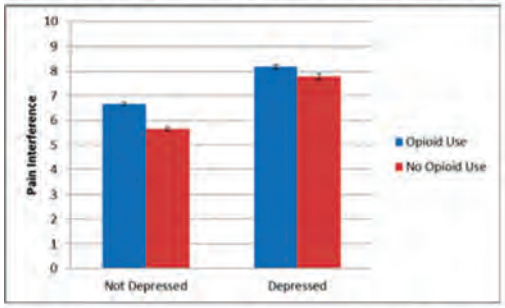
Conclusion: The relationship between opioid use, pain, and depression is complex. Understanding the interaction at a biopsychosocial level is important in order to inform clinical practice. Although causal conclusions cannot be made, this study found patients using opioids present with a worse clinical phenotype. Future longitudinal studies are needed to assess directionality of the relationship and determine whether opioids are the best course of treatment for depressed patients.

Table 1 Phenotypic profiles of opiold and non-opiold users.

	Opiold use		
	Yes N = 1,176	No N = 928	p^a
Male	484 (41.2%)	378 (40.7%)	.844
Caucasian	1,073 (91.2%)	817 (88.0%)	.016
Age	49.03 (14.2)[b]	48.9 (15.3)	.806
HADS Depression	9.70 (4.3)	7.77 (4.6)	<.001
HADS Anxiety	9.06 (4.4)	7.99 (4.3)	<.001
CSQ	17.6 (9.4)	14.5 (9.5)	<.001
PROMIS	29.9 (7.7)	33.9 (8.5)	<.001
BPI Pain Interference	7.33 (1.8)	6.20 (2.3)	<.001
BPI Pain Severity	6.58 (1.6)	5.97 (1.9)	<.001

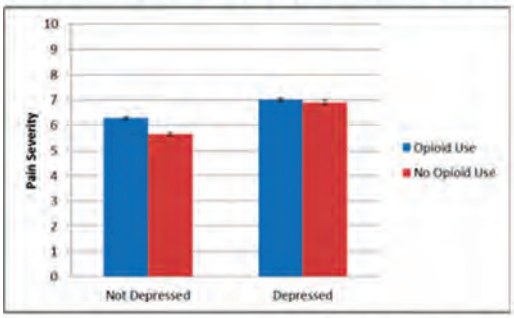
a. Chi-square tests were conducted for categorical variables and independent samples t-tests were conducted for continuous variables.
b. Mean and standard deviation reported for continuous variables.

Figure 1. Relationship between opioid use and pain interference moderated by depression.



Note: A 2*2 analysis of covariance model was conducted and found that the relationship between opioid use and pain interference was moderated by depression ($F(1,2103) = 12.88$, $p < .001$). Gender, race, age, and HADS Anxiety scores were included as covariates. Participants with a score of 11 or higher on the HADS Depression subscale were considered depressed.

Figure 2. Relationship between opioid use and pain severity moderated by depression.



Note: A 2*2 analysis of covariance model was conducted and found that the relationship between opioid use and pain severity was moderated by depression ($F(1,2103) = 11.95$, $p = .001$). Gender, race, age, and HADS Anxiety scores were included as covariates. Participants with a score of 11 or higher on the HADS Depression subscale were considered depressed.

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Selective and Peripheral-Specific Trk Inhibitor Shows Potent Analgesic Effect Comparable to Morphine in Rat Osteoarthritis Model without CNS Toxicity. Takeshi Nagaura, Tetsuya Yasuhiro, Keisuke Oda, Yuya Ezaki, Takashi Koyanagi, Satoshi Itadani, Hiroyuki Nitta, Hiroshi Wakazono, Seishi Katsumata and Yasushi Hirota. Ono Pharmaceutical Co., Ltd., Osaka, Japan.

Background/Purpose: Tropomyosin receptor kinase (Trk) receptors are a family of three closely related receptor tyrosine kinases; TrkA, TrkB and TrkC. Especially, the peripheral TrkA in sensory neuron is a promising target for musculoskeletal pain such as osteoarthritis (OA) since the activation of TrkA receptor by nerve growth factor (NGF) induces hyperalgesia and anti-NGF antibodies show potent analgesic effects in moderate to severe OA patients. However, sustained inhibition of TrkA in brain raises concerns about deteriorating cognitive impairment such as Alzheimer's disease, because NGF/TrkA signal is important to maintain the function of cholinergic neuron. We discovered a highly selective and orally available Trk inhibitor which shows potent *in vivo* TrkA inhibitory activities at low plasma concentrations with a low brain penetration. In this study, we evaluated the analgesic effects of peripheral-specific Trk inhibitor on monosodium iodoacetate (MIA)-induced OA pain in rats.

Methods: Male SD rats (215~265 g) were briefly anaesthetized with isoflurane, and 3 mg MIA solution or saline was intra-articularly injected into right knee. The peripheral-specific Trk inhibitor or vehicle (distilled water containing 20% Wellsolve) was orally administrated twice a day for 8 days from 14 day after MIA injection. Morphine was subcutaneously administrated 1 hour before evaluation of pain-related behavior. Pain-related behavior was evaluated by the percent weight borne on right leg.

Results: The peripheral-specific Trk inhibitor does-dependently inhibited the pain-related behavior of MIA-treated rats in which acetaminophen and nonsteroidal anti-inflammatory drugs did not show analgesic effects. The analgesic effect of it at 1 mg/kg b.i.d. or more was comparable to that of morphine at 3 mg/kg which significantly impaired motor coordination in rats. Although repeated administration of high doses of peripheral-specific Trk inhibitor for 14 days increased food consumption and weight gain in normal rats, there was at least 36-fold margin calculated by area under the concentration-time curve between effective dose in MIA model and no affecting dose to them.

Conclusion: The selective and peripheral-specific Trk inhibitor will be a potent and safer medication for OA pain.

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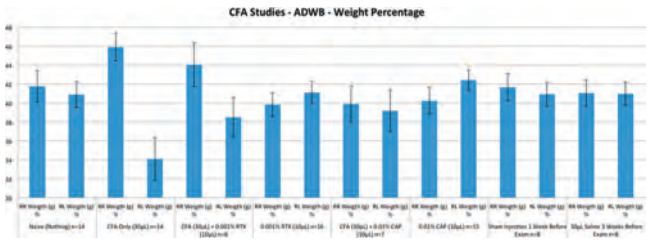
The Effect of Treatment with Resiniferatoxin and Capsaicin on Dynamic Weight Bearing Measures and Evoked Pain Responses in a Chronic Inflammatory Arthritis Murine Model. Joseph Bert[1], Christopher W. Dorman[2], Sandra Frizelle[2], Sonia C. Funkenbusch[2], Hollis E. Krug[3] and Maren L. Mahowald[4]. [1]University of Minnesota Internal Medicine Residency, Minneapolis, MN, [2]Minneapolis VA Health Care System, Minneapolis, MN, [3]VA Health Care System, Minneapolis, MN, [4]University of Minnesota Medical School and Minneapolis VA Health Care System, Minneapolis, MN.

Background/Purpose: Capsaicin (CAP) and Resiniferatoxin (RTX) are vanilloid receptor agonists that when given by intra-articular injections, can normalize Evoked Pain Scores (EPS) and Automated Dynamic Weight Bearing (ADWB) measures in carrageenan-induced acute inflammatory arthritis. To determine whether these vanilloid receptor agonists might have benefit in chronic inflammatory arthritis pain, we measured changes in ADWB and EPS due to joint pain in mice with Complete Freund's Adjuvant (CFA) induced chronic inflammatory arthritis with and without treatment with intra-articular (IA) injections of CAP and RTX.

Methods: Chronic Inflammatory arthritis was produced by intra-articular injection of 30 μl of Complete Freund's Adjuvant (CFA) into the left knee of C57BL6 male mice 3 weeks prior to pain behavior testing. One group of mice was injected with IA RTX (10μl of 0.001%) 7 days prior to measurement of EPS and ADWB. Similarly, another group of mice were injected with 10μl of 0.01% IA CAP 7 days before pain behavior testing. Evoked pain behavior was measured by tallying fights and vocalizations per one minute with repeated palpation of the knee at 15.6 psi. ADWB (weight on each limb and time on each limb) was measured using an Automated Dynamic Weight Bearing apparatus (Bioseb, Vitrolles, France).

Results: Chronic Inflammatory arthritis pain is demonstrated by increased EPS and reduced ADWB measures in the affected limb of arthritic mice. Na●ve mice have low EPS (0.5) and equal left to right DWB ratios for weight (1.01) and time (1.006). Chronic inflammatory arthritis induced by IA CFA resulted in a significantly increased EPS (3.5) and a decrease in left to right ADWB ratios for weight (0.76) and time (0.93) when compared with controls. Treatment with IA CAP 7 days prior to pain behavior testing resulted in improvement in EPS (1.38) and near normalization of left to right ADWB ratios for weight (0.99) and time (1.01) when compared to the chronic inflammatory arthritis model. Treatment with IA RTX 7 days prior to the exam led to improved EPS (1.67) and improved left to right ADWB ratios for weight (0.90) and time (0.98) when compared to the chronic inflammatory arthritis model. IA CAP alone and IA RTX alone did not have an impact on EPS or ADWB ratios when given 7 days prior to pain behavioral testing.



Conclusion: Using ADWB and EPS, we were able to quantitate pain in a murine chronic arthritis model. Intra-articular CFA administration resulted in a significant increase in EPS and decreased ADWB measures in the affected limb. Treatment with CAP and RTX in these mice improved pain measures as assessed by EPS and ADWB measures. These results are comparable to those previously reported when mice were pretreated in an acute inflammatory arthritis model. The optimal dose of RTX and CAP for therapeutic benefit and duration of response has yet to be determined.

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ACR Poster Session A
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Juvenile Idiopathic Arthritis
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Discontinuation of Concomitant Medication for Enthesitis-Related Arthritis during 52 Weeks of Treatment with Adalimumab. Shirley ML Tse[1], Rubén Burgos-Vargas[2], Gerd Horneff[3], Aileen L. Pangan[4], Jasmina Kalabic[5], Kristina Unnebrink[5] and Jaclyn K. Anderson[4]. [1]The Hospital for Sick Children, University of Toronto, Toronto, ON, [2]Hospital General de Mexico, Universidad Nacional Autonoma de Mexico, Mexico City, Mexico, [3]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [4]AbbVie Inc., North Chicago, IL, [5]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany.

Background/Purpose: Children with enthesitis-related arthritis (ERA) require medical therapy to control inflammation and restore normal function; however, the use of multiple medications and for longer periods than needed is of special concern in the pediatric population. The objective of this analysis is to evaluate the proportion of patients (pts) who discontinued one or more concomitant medications for pediatric ERA during the first 52 weeks (wk) of adalimumab (ADA) treatment.

Methods: This is a phase 3, multicenter, randomized, double-blind study in pts aged ≥6 to <18 years (yr) with active ERA not responsive to ≥1 NSAID and ≥1 DMARD. Pts were randomized 2:1 to receive blinded ADA (24 mg/m^2 BSA up to 40 mg every other wk) or placebo (PBO) for 12 wks followed by open-label (OL) ADA up to 144 wks. Active disease was defined as: ≥3 active joints (AJC; swelling not due to deformity or joints with loss of motion plus pain and/or tenderness) and evidence of enthesitis in ≥1 location (documented in the past or present at baseline [BL]). Pts could enter the study on stable doses of concomitant NSAIDs, DMARDs (methotrexate [MTX] or sulfasalazine [SSZ]), and corticosteroids (CSs); doses remained stable during the first 12 wks except as medically required due to adverse event (AE). Dose adjustment or treatment induction with these agents was permitted after wk 12. Discontinuation of concomitant ERA medications was not required in the protocol and was at the discretion of the treating physician. Concomitant use was defined as use of the drug at any time during the study through wk 52.

Results: 46 pts were randomized (PBO 15, ADA 31). At BL, mean duration of ERA symptoms was 2.6 yrs; mean AJC was 7.8, and mean enthesitis count was 8.1. Mean % change from BL to wk 12 in AJC (primary endpoint) was greater in the ADA group vs. PBO (−63% vs -12%, $P=0.039$), with 89% overall reduction in AJC from BL through wk 52. Prior use of NSAIDs, DMARDs, and CSs was reported in 100%, 91%, and 57% of pts, respectively. Concomitant use of ERA drugs at BL is shown in the table. 16 pts (35%) stopped NSAIDs, 5 pts (11%) stopped DMARDS (2 SSZ, 3 MTX), and 7 pts (15%) stopped CSs without restarting prior to wk 52; NSAIDs were stopped in 3 pts due to AEs. 3 pts discontinued the study due to AE (2) or inefficacy (1) during OL period. Of those remaining in the study at wk 52, 8/43 (19%) were completely off concomitant ERA drugs. At wk 52 mean % change from BL in AJC was -81.8% in pts who stopped NSAIDs, -72.4% in pts who stopped DMARDs, -97.1% in pts who stopped CSs, and -82.9% in pts who stopped all NSAIDs and DMARDs.

Table Concomitant Medications for Enthesitis-Related Arthritis

	Placebo/ Adalimumab N = 15 n (%)	Adalimumab/ Adalimumab N = 31 n (%)	Total N = 46 n (%)
NSAIDs			
At baseline	13 (87)	24 (77)	37 (80)
At week 52[a]	8 (57)	14 (48)	22 (51)
DMARDs			
At baseline	11 (73)	21 (68)	32 (70)
At week 52[a]	9 (64)	18 (62)	27 (63)
Corticosteroids			
At baseline	4 (27)	8 (26)	12 (26)
At week 52[a]	3 (21)	4 (14)	7 (16)
NSAID +DMARD			
At baseline	10 (67)	15 (48)	25 (54)
At week 52[a]	5 (36)	7 (24)	12 (28)
ADA Monotherapy[b]			
At baseline	0	1 (3)	1 (2)
At week 52[a]	3 (21)	5 (17)	8 (19)

[a]Observed data; includes pts who started ERA concomitant medication after the double-blind period; includes 3 pts who discontinued the study after week 12 and prior to week 52; N=14/29/43, PBO/ADA/total.
[b]ADA monotherapy = no concomitant NSAID, DMARD, or corticosteroid.
ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; NSAID, nonsteroidal anti-inflammatory drug.

Conclusion: Clinical improvement with ADA through 52 wks allowed some pts to discontinue concomitant NSAIDs, DMARDs, or CSs for ERA at the investigator's discretion. Clinical response was generally maintained in pts who stopped 1 or more concomitant medications. Standardized discontinuation of concomitant ERA medications in ADA responders may have resulted in a higher number of pts able to discontinue concomitant ERA therapies.

Disclosure: S. M. Tse, AbbVie, 2, AbbVie, Pfizer, 5; **R. Burgos-Vargas**, AbbVie, 2, AbbVie, BMS, Janssen, Pfizer, and Roche, 5, AbbVie, BMS, Janssen, Pfizer, and Roche, 8; **G. Horneff**, AbbVie, Pfizer, and Roche, 2, AbbVie, Novartis, Pfizer, and Roche, 8; **A. L. Pangan**, AbbVie, 1, AbbVie, 3; **J. Kalabic**, AbbVie, 1, AbbVie, 3; **K. Unnebrink**, AbbVie, 1, AbbVie, 3; **J. K. Anderson**, AbbVie, 1, AbbVie, 3.

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Disease Burden Is Comparable in Children with Enthesitis-Related Arthritis and Polyarticular Juvenile Idiopathic Arthritis. Pierre Quartier[1], Jasmina Kalabic[2], Zbigniew Zuber[3], Kirsten Minden[4] and Jaclyn K. Anderson[5]. [1]IMAGINE Institute, Hôpital Necker-Enfants Malades, Assistance Publique Hôpitaux de Paris, Université Paris-Descartes, Paris, France, [2]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany, [3]St. Louis Children's Hospital, Krakow, Poland, [4]Charité Universitätsmedizin Berlin, Berlin, Germany, [5]AbbVie Inc., North Chicago, IL.

Background/Purpose: To compare baseline disease characteristics of pediatric patients (pts) with enthesitis-related arthritis (ERA) and polyarticular juvenile idiopathic arthritis (pJIA) from clinical trials with adalimumab (ADA).

Methods: Baseline (BL) data were derived from 1 study in ERA (M11–328) and 2 studies in pJIA (M10–444, DE038). M11–328 was a Phase 3, double-blind (DB), placebo-controlled, multicenter study in pediatric pts aged 6–17 years (yrs) at BL with ERA as defined by International League of Associations for Rheumatology (ILAR). Disease activity was defined by 1) ≥3 active joints (swelling not due to deformity or joints with limitation of motion (LOM) plus pain and/or tenderness) AND evidence of enthesitis in ≥1 location (either past or present at BL). Pts were inadequate responders or intolerant to ≥1 nonsteroidal anti-inflammatory drug (NSAID) and ≥1 disease-modifying antirheumatic drug (DMARD). M10–444 was a Phase 3b open-label multicenter study in pts aged 2 to <4 yrs and age ≥4 yrs weighing <15 kg with moderately to severely active pJIA (ILAR categories: polyarticular rheumatoid factor (RF) positive, polyarticular RF negative, extended oligoarthritis, undifferentiated, and systemic arthritis). Active disease was defined as arthritis affecting ≥5 joints at BL. EU pts must have previously failed, had insufficient response to, or intolerance to ≥1 DMARD. Study DE038 was a multicenter, Phase 3, randomized, DB study in pts aged 4–17 yrs with pJIA by American College of Rheumatology (ACR) criteria (onset may have been systemic, polyarticular, or oligoarticular/pauciarticular). Active disease was defined as ≥5 swollen joints (SJC) and ≥3 joints with LOM at screening. A trial of NSAIDs was required, and pts were stratified according to methotrexate use.

Results: 203 pJIA pts (M10–444, n=32, DE038, n=171) and 46 ERA pts were evaluated. Polyarticular JIA pts were predominantly female compared to ERA pts (pJIA, 79–88% vs ERA, 33%). (Table) C-reactive protein (CRP) was elevated at BL in 66% of pts in DE038 compared to about 39% of the 2–4 year-old pJIA pts and ERA pts. Mean active joint count (AJC) at BL was greater in pJIA pts than in ERA pts (10 and 17.2 vs 7.8 joints). Mean BL tender joint count (TJC) was similar in pJIA study DE038 and M11–328 compared to a lower TJC in the younger age group enrolled in M10–444. Mean physician's global assessment of disease activity, parent's global assessment (PaGA) of pt's overall well-being, PaGA of pt's pain, and childhood health assessment questionnaire scores were similar across JIA subtypes.

Table Baseline Demographics and Disease Characteristics

	Polyarticular JIA		ERA
	M10–444 N = 32	DE038 N = 171	M11–328 N = 46
Demographics			
Age, years	3.0 (0.7)	11.3 (3.5)	12.9 (2.9)
Female, n (%)	28 (87.5)	135 (78.9)	15 (32.6)
White, n (%)	25 (78.1)	157 (91.8)	35 (76.1)
Body mass index, kg/m^2	15.5 (1.3)	19.4 (5.1)	19.7 (4.4)
HLA-B27 positive, n (%)	1 (3.1)	37 (22.0)[a]	29 (67.4)[b]
RF positive, n (%)	1 (3.1)	37 (22.0)	0
Prior JIA medications, n (%)	31 (96.9)	−*	46 (100)
Prior NSAIDs, n (%)	20 (62.5)	−*	46 (100)
Prior DMARDs, n (%)	25 (78.1)	110 (64,3)	42 (91.3)
Methotrexate, n (%)	25 (78.1)	103 (60.2)	29 (63.0)
Prior corticosteroids, n (%)	22 (68.8)	−*	21 (45.7)
Disease duration, years	1.0 (0.8)	3.8 (3.9)[c]	1.9 (2.1)
Disease Characteristics			
AJC (0–73)	10.0 (7.5)	17.2 (10.4)	7.8 (6.6)[d]
TJC (0–75)	3.8 (5.0)	11.4 (12.4)	12.9 (10.1)[d]
SJC (0–66)	8.9 (7.4)	14.8 (9.4)	6.2 (6.4)[d]
LOM (0–69)	8.6 (7.7)	13.5 (9.2)	4.9 (3.5)[d]
PGA of disease activity (0–10 cm VAS)	5.5 (2.0)	5.9 (1.8)	5.3 (2.2)
PaGA of pt's overall well-being (0–10 cm VAS)	4.8 (2.6)	4.8 (2.3)	5.1 (2.4)
PaGA of pt's pain (0–10 cm VAS)	4.6 (2.6)	5.0 (2.5)[c]	5.6 (2.3)
CHAQ (0–3)	1.2 (0.7)	1.1 (0.7)	0.8 (0.6)
Elevated CRP, n (%)	12 (38.7)[e]	112 (65.9)[c]	18 (39.1)
CRP (mg/dL)	1.6 (2.4)[e]	2.6 (4.1)[c]	9.0 (16.0)[f]

Values are the mean (standard deviation) unless otherwise stated. *Data not available. [a]N=168. [b]N=43. [c]N=170. [d]AJC 0–68, TJC 0–72, SJC 0–68, LOM 0–66. [e]N=31. [f]high-sensitivity CRP, mg/L. AJC, active joint count; CHAQ, childhood health assessment questionnaire; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; ERA, enthesitis-related arthritis; JIA, juvenile idiopathic arthritis; LOM, limitation of motion; PaGA, parent's global assessment; PGA, physician's global assessment; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale.

Conclusion: In this comparison of JIA pts enrolled in ERA and pJIA studies, at baseline the burden of inflammatory disease as measured by AJC and SJC was slightly higher in pJIA as compared to ERA. However, AJC and SJC do not encompass all aspects of disease in JIA and overall, physicians and parents assessed disease burden similarly with similar impairment in physical function observed in children with ERA and pJIA.

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Predicting Treatment Response to Etanercept in Juvenile Idiopathic Arthritis: Results from the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN). Lianne Kearsley-Fleet[1], Rebecca Davies[1], Mark Lunt[1], Taunton R. Southwood[2], Kimme L. Hyrich[3] and on Behalf Of The BSPAR Etanercept Cohort Study[1]. [1]University of Manchester, Manchester, United Kingdom, [2]Institute of Child Health, University of Birmingham and Birmingham Children's Hospital, Birmingham, United Kingdom, [3]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom.

Background/Purpose: Etanercept (ETN) is licensed in Europe for use in children with Juvenile Idiopathic Arthritis (JIA) and is routinely prescribed after failure of other DMARDs. Previous findings regarding response to treatment for JIA suggest that patients with less severe disease at start of treatment are those patients who are more likely to respond to treatment. The objectives of this study were to (1) investigate the influence of ETN on disease activity in patients with severe JIA over the initial first year of treatment and (2) explore factors associated with treatment response over this same period.

Methods: This analysis used patients in the British Society for Paediatric and Adolescent Rheumatology ETN Cohort study (BSPAR-ETN) with JIA starting ETN therapy who had follow up records at baseline and 1 year. Only patients with ILAR criteria of systemic arthritis, oligoarticular arthritis, polyarticular arthritis, and psoriatic arthritis were included. Univariable and multivariable backward stepwise logistic regression was performed to identify factors associated with (1) a good treatment response (ACR Pedi 50) and (2) achieving minimal disease activity (MDA) at 1 year. Patients who stopped ETN therapy within the 1st year for an adverse event or unknown reason were excluded from the model as initial treatment response on therapy was not captured. Patients who stopped for inefficacy were classified as non-responders. Imputation was used to account for missing baseline and 1 year disease activity measures.

Results: A total of 422 patients were included in this analysis; 73% female, median age at start of ETN therapy 11.0 years (interquartile range (IQR) 7.3, 13.3), disease duration at start of ETN 4 years (IQR 2, 7); 14 stopped ETN due to inefficacy, 8 due to adverse events and 7 for other reasons. No child stopped for remission within the 1st year. Median baseline JADAS-71 was 17 (IQR 12, 26). At 1 year this decreased to 3 (IQR 1, 10; $p<0.001$). Of the 407 patients included in the model, at 1 year, 75%, 70%, 59%, and 41% had reached ACR Pedi 30, 50, 70 and 90 respectively, and 49% had achieved MDA. Independent predictors of achieving MDA at 1 year included a history of uveitis (Odds Ratio (OR) 2.60 [95% CI 1.06, 6.37]), younger age (OR age ≥ 9 years old compared to <9 years 0.57 [95% CI 0.35, 0.92]) and lower disability (OR 0.59 per unit CHAQ increase [95% CI 0.40, 0.87]). In addition, as age increased, patients had reduced odds of achieving ACR Pedi 50 at 1 year (OR 0.93 per unit increase [95% CI 0.88, 0.99]).

Conclusion: Among this "real-world" cohort of children with severe JIA, a significant proportion of children achieve MDA and good ACR Pedi response scores within 1 year of starting ETN although few clinical factors could predict this outcome. The finding of a lesser response in older children warrants further investigation and may relate to differences in disease phenotype, drug pharmacokinetics or adherence.

	MDA at 1 year		ACR Pedi 50 at 1 year	
Baseline characteristics at start of etanercept therapy	**Univariable Analysis Odds Ratio (95% CI)**	**Adjusted Analysis Odds Ratio (95% CI)**	**Univariable Analysis Odds Ratio (95% CI)**	**Adjusted Analysis Odds Ratio (95% CI)**
Female	1.15 (0.70, 1.91)		1.16 (0.68, 1.96)	
Age [years] – continuous	0.95 (0.90, 1.00)		0.93 (0.88, 0.99)*	0.93 (0.88, 0.99)*
Aged ≥ 9 years old	0.59 (0.37, 0.95)*	0.57 (0.35, 0.92)*	0.55 (0.33, 0.93)*	
Disease Duration [years]	0.97 (0.91, 1.03)		0.95 (0.89, 1.02)	
Systemic arthritis	0.74 (0.40, 1.37)		0.98 (0.51, 1.89)	
Concurrent Oral Corticosteroid Use	0.55 (0.33, 0.91)*		0.72 (0.40, 1.28)	
Concurrent Methotrexate Use	1.00 (0.61, 1.63)		1.11 (0.68, 1.80)	
History of Uveitis	2.49 (1.13, 5.49)*	2.60 (1.06, 6.37)*	1.93 (0.68, 5.47)	
Any Comorbidities	0.95 (0.60, 1.51)		1.07 (0.64, 1.77)	
Disease Activity				
Active Joint Count	0.98 (0.95, 1.00)		1.01 (0.99, 1.04)	
Limited Joint Count	0.98 (0.96, 1.01)		1.00 (0.98, 1.03)	
Physician Global of Disease	0.97 (0.93, 1.02)		1.04 (0.96, 1.13)	
Parent/Patient Global of Well Being	0.97 (0.93, 1.02)		1.01 (0.98, 1.04)	
Childhood Health Assessment Questionnaire (CHAQ) [scale 0–3]	0.64 (0.46, 0.91)*	0.59 (0.40, 0.87)*	0.99 (0.73, 1.33)	
Pain VAS	0.95 (0.86, 1.04)		1.01 (0.97, 1.06)	
ESR	0.99 (0.98, 1.00)		1.01 (1.00, 1.02)	
CRP	1.00 (0.99, 1.00)		1.01 (1.00, 1.02)	
Juvenile Arthritis Disease Activity Score (JADAS-71)	0.99 (0.97, 1.00)		1.01 (1.00, 1.03)*	

*$p<0.05$

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Factors Associated with Choice of First Biologic Among Children with Juvenile Idiopathic Arthritis: A Combined Analysis from 2 UK Paediatric Biologic Registers. Rebecca Davies[1], Lianne Kearsley-Fleet[1], Eileen Baildam[2], Michael W. Beresford[3], Helen E. Foster[4], Taunton R. Southwood[5], Wendy Thomson[6], Kimme L. Hyrich[7], on Behalf Of The BSPAR Etanercept Cohort Study[1] and The Biologics for Children with Rheumatic Diseases (BCRD) study[1]. [1]University of Manchester, Manchester, United Kingdom, [2]Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [3]Institute of Translational Medicine (Child Health), University of Liverpool, Liverpool, United Kingdom, [4]Newcastle University, Newcastle upon Tyne, United Kingdom, [5]Institute of Child Health, University of Birmingham and Birmingham Children's Hospital, Birmingham, United Kingdom, [6]Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [7]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom.

Background/Purpose: The management of juvenile idiopathic arthritis (JIA) has been revolutionised by the introduction of biologics such as etanercept (ETN), approved in the UK in 2002. Since that time, the use of biologics in children and young people (CYP) has expanded, including the use of those licensed for JIA (adalimumab (ADA), tocilizumab (TCZ),

abatacept) as well as those licensed for rheumatoid arthritis (rituximab, infliximab (IFX) and anakinra (ANA)). ETN is most often the first choice biologic in the treatment of JIA; however there may be occasions where ETN is not the preferred choice, for reasons of either efficacy or safety. Understanding how biologics are being selected will help inform future practice and research. Therefore, the aim of this analysis was to describe the choice of first-line biologics in UK CYP with JIA and explore possible reasons behind this choice.

Methods: Both the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN), established 2004, and the Biologics for Children with Rheumatic Diseases (BCRD) study, established 2010, are ongoing prospective observational cohorts, collecting detailed information on CYP starting either ETN (BSPAR-ETN) or any other biologic (BCRD) for JIA. At start of therapy, demographic and disease information is collected. Biologic-naive patients registered on or after 01/01/2010 starting their first biologic were identified and baseline disease characteristics compared between therapies, using descriptive statistics. An additional cohort of children starting ETN <2010 were also included to analyse changes in ETN prescribing since initial approval.

Results: To 07/04/2014, 870 patients were recruited starting a first-line biologic (123 BCRD; 747 BSPAR-ETN (582<2010, 165≥2010) (Table). From 2010, children with systemic JIA (sJIA) were almost exclusively prescribed ANA or TCZ. Choice between anti-TNF therapies was largely driven by prevalence of uveitis (5% ETN versus 70% ADA and 72% INF). Children starting ETN were also more likely to have a polyarticular subtype. Only half of the patients starting ETN received concomitant methotrexate compared to the other biologics (69–90%). Compared to ETN patients pre-2010, CYP starting ETN from 2010 had shorter disease duration and were less likely to be receiving corticosteroids, have lesser prevalence of sJIA and lower rates of uveitis.

Conclusion: Although ETN remains the most common biologic prescribed for JIA, there has been a clear shift towards the use of alternative biologics, including unlicensed biologics, in certain patient situations, largely driven by disease subtype and the presence of uveitis. This channelling of certain children towards specific therapies will need to be considered both in terms of future comparative effectiveness studies and also as a guide to ongoing research priorities within rheumatology.

*All values median(IQR) or n(%)	Biologic Start post 01/01/2010					Pre-2010
	Etanercept	Adalimumab	Infliximab	Tocilizumab	Anakinra	Etanercept
N	**165**	**45**	**29**	**32**	**15**	**582**
Female	109 (67%)	30 (67%)	17 (59%)	14 (44%)	11 (73%)	384 (66%)
Age, years	11 (8, 14)	10 (6, 14)	8 (5, 10)	8 (4, 11)	3 (2, 13)	11 (8, 14)
Disease Duration, years	2 (1, 5)	4 (2, 6)	3 (2, 6)	1 (1, 2)	0 (0, 1)	4 (2, 7)
ILAR subtype						
Systemic arthritis	5 (3%)	1 (2%)	1 (3%)	28 (88%)	15 (100%)	70 (12%)
Oligoarthritis: persistent	13 (8%)	14 (31%)	8 (28%)	0	0	15 (3%)
Oligoarthritis: extended	26 (16%)	10 (22%)	8 (28%)	0	0	102 (18%)
Polyarthritis: RF(−)	66 (40%)	7 (16%)	9 (31%)	3 (9%)	0	195 (34%)
Polyarthritis: RF(+)	17 (10%)	2 (4%)	0	0	0	58 (10%)
Enthesitis Related Arthritis	10 (6%)	5 (11%)	2 (7%)	0	0	50 (9%)
Psoriatic arthritis	10 (6%)	5 (11%)	1 (3%)	0	0	44 (8%)
Undifferentiated arthritis	6 (4%)	0	0	1 (3%)	0	39 (7%)
Not Recorded	12 (7%)	1 (2%)	0	0	0	9 (2%)
Concomitant MTX	77 (47%)	31 (69%)	26 (90%)	28 (88%)	12 (80%)	322 (55%)
Concomitant Corticosteroids	15 (9%)	7 (16%)	5 (17%)	23 (72%)	7 (47%)	146 (25%)
Ever had Chronic Anterior Uveitis	7 (5%)	31 (70%)	21 (72%)	0	0	54 (11%)
Disease activity						
Active joint count	5 (2, 9)	2 (0, 4)	2 (0, 5)	3 (0, 6)	5 (2, 12)	5 (2, 10)
Limited joint count	3 (1, 8)	2 (0, 3)	0 (0, 5)	2 (0, 5)	3 (0, 13)	5 (2, 9)
Physician Global Assessment (10cm VAS)	3 (2, 5)	3 (1, 4)	2 (1, 4)	3 (0, 6)	4 (2, 6)	4 (2, 6)
Parent Global Assessment (10cm VAS)	4 (1, 6)	3 (1, 6)	3 (0, 5)	4 (1, 8)	5 (4, 5)	5 (2, 7)
CHAQ [0–3]	1 (0, 2)	1 (0, 1)	0 (0, 1)	1 (0, 2)	2 (1, 2)	1 (0, 2)
Pain (10cm VAS)	4 (1, 7)	3 (1, 7)	4 (2, 5)	3 (1, 6)	6 (4, 6)	5 (2, 7)
ESR, mm/hr	10 (5, 25)	7 (5, 34)	8 (4, 14)	39 (9, 54)	58 (8, 96)	18 (7, 40)
JADAS-71	13 (8, 21)	10 (7, 17)	6 (3, 12)	19 (1, 22)	23 (7, 30)	16 (9, 23)

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Long-Term Safety and Effectiveness of Adalimumab in Children with Moderately to Severely Active Polyarticular or Polyarticular-Course Juvenile Idiopathic Arthritis.

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Background/Purpose: Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases of childhood. Adalimumab (ADA) is approved for moderate to severe polyarticular JIA (pJIA) in patients (pts) ≥4 years (yrs) in the US**,** Australia, and Japan and in the EU for pts ≥2 yrs. The study objective was to evaluate long-term safety and effectiveness of ADA in pts with moderately to severely active pJIA who are prescribed and treated with ADA in routine clinical practice. 5 yr interim data will be presented.

Methods: This is an ongoing, multicenter, non-interventional, observational registry of pts with moderately to severely active pJIA who are treated with either ADA±methotrexate (MTX) or MTX alone as part of their routine clinical care. 800 pts (500 in ADA arm/300 in MTX arm) were to be enrolled in the US, EU, and Australia. The follow-up observational period is 10 yrs from enrollment into one of the treatment arms. Observational adverse events (AEs) were recorded from the first day in the registry through last contact, irrespective of the duration of registry treatment. Clinical outcomes were assessed by 27-joint juvenile arthritis disease activity score (JADAS27), based on C-reactive protein (CRP).

Results: As of January 2014, enrollment is complete. 842 pts (540 in ADA arm/302 in MTX arm) were treated in the registry as of the March 28, 2014 cutoff date. The mean pJIA disease duration at registry enrollment was 1.3 and 3.7 yrs and the mean duration days of study exposure was 643 and 653 for MTX and ADA arms, respectively. At baseline, mean AJC73 was 5.8 and 5.4 for MTX and ADA, respectively, and childhood health assessment questionnaire disability index (CHAQ-DI) was 0.6 for both groups. Overall, 153 pts (50.7%) in the MTX arm and 132 pts (24.4%) in the ADA arm discontinued registry drug. Of those, 22 (7.3%) and 23 (4.3%) pts in the MTX and ADA arm, respectively, discontinued due to an AE, and 39 of the 153 pts in the MTX arm discontinued as they switched to the ADA arm of the registry. The observational AEs are summarized in the Table. No deaths, malignancies, or opportunistic infections were reported. In the ADA arm, there were 13 (2.4%) pts with serious infectious AEs (including abdominal abscess, acute tonsillitis, appendicitis, cellulitis, gastroenteritis, mononucleosis, viral meningitis, pneumonia, pyelonephritis, scarlet fever, subcutaneous abscess, tonsillitis, urinary tract infection, and varicella). Frequencies and rates of treatment-emergent AEs were similar to those reported for observational AEs. Mean JADAS27 improved from 12.1 at baseline to 9.4, 6.1, 5.1, 4.4 at months 1, 3, 6, and 12 for pts in the MTX arm and from 12.1 at baseline to 7.4, 5.5, 4.4, 4.5 in the ADA arm, respectively (observed data).

Table Overview of Observational Adverse Events (AEs)

	MTX		ADA ± MTX	
	N=302 n (%)	PYs=863.9 E (E/100 PYs)	N=540 n (%)	PYs=1226.8 E (E/100 PYs)
Any AE	135 (44.7)	351 (40.6)	169 (31.3)	447 (36.4)
At least "possibly drug related" per the investigator	68 (22.5)	121 (14.0)	80 (14.8)	147 (12.0)

Severe AE	11 (3.6)	15 (1.7)	19 (3.5)	31 (2.5)
Serious AE	17 (5.6)	26 (3.0)	35 (6.5)	56 (4.6)
AE leading to discontinuation of study drug	20 (6.6)	26 (3.0)	27 (5.0)	39 (3.2)
Infectious AE	75 (24.8)	133 (15.4)	93 (17.2)	149 (12.1)
Serious infectious AE	8 (2.6)	11 (1.3)	13 (2.4)	15 (1.2)
Injection site-related AE	6 (2.0)*	8 (0.9)	24 (4.4)	29 (2.4)

E, events; PYs, patient years.

*3 patients experienced injection site-related AEs with etanercept injections.

Conclusion: Overall, ADA is well-tolerated in these pts with active pJIA. No new safety signals were observed, and based on this interim analysis, the known safety profile of ADA remains unchanged.

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Treatment Prescribing Patterns in a Cohort of Patients with Juvenile Idiopathic Arthritis (JIA). Data from the Childhood Arthritis Prospective Study. Rebecca Davies[1], Roberto Carrasco[2], Helen Foster[3], Eileen Baildam[4], Alice Chieng[5], Joyce Davidson[6], Yiannis Ioannou[7], Lucy R. Wedderburn[8], Wendy Thomson[9], Kimme L. Hyrich[10] and on Behalf Of Childhood Arthritis Prospective Study (CAPS)[11]. [1]University of Manchester, Manchester, United Kingdom, [2]The University of Manchester, Manchester, United Kingdom, [3]Newcastle University, Newcastle, United Kingdom, [4]Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [5]Manchester Children's Hospital, Manchester, United Kingdom, [6]Royal Hospital for Sick Children, Glasgow, United Kingdom, [7]Arthritis Research UK Centre for Adolescent Rheumatology, University College London, London, United Kingdom, [8]Arthritis Research UK Centre for Adolescent Rheumatology at University College London, Great Ormond Street Hospital and UCLH, University College London, London, United Kingdom, [9]Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [10]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, [11]university of Manchester, Manchester, United Kingdom.

Background/Purpose: Juvenile idiopathic arthritis (JIA) is a heterogenous disease, classified according to the International League of Associations for Rheumatology (ILAR). Initial treatment is based largely on disease severity; intra-articular injections for oligoarthritis, methotrexate (MTX) for polyarthritis and systemic presentations. The recent licensing of biologic therapies for use in JIA has revolutionised treatment. It is not known what proportion of children who present with polyarthritis will require biologic therapy. Although not studied formally, it is recognised a proportion of children with oligoarthritis, may also require systemic therapy to control symptoms. Therefore, the aim of this study was to describe prescribing patterns within new onset JIA patients over the first 3 years following presentation to rheumatology.

Methods: Children with at least 3 years of follow-up within the Childhood Arthritis Prospective Study (CAPS), a prospective observational inception study of inflammatory arthritis, were included.

For analysis, children were grouped into a disease pattern according to the physician-assigned ILAR category and number of active joints at first presentation (baseline): oligoarticular, polyarticular, systemic (sJIA) and enthesitis-related arthritis (ERA). Treatment exposures over the 3 year period were determined and categorised into NSAID, intra-articular steroids, disease modifying anti-rheumatic drug (DMARD) including MTX and biologics including etanercept (ETN) and infliximab (INF).

Results: 790 children had 3 years of follow-up. Of these, 78 had missing ILAR subtype data and were excluded, leaving 712 in total (406 oligoarticular, 221 polyarticular, 42 sJIA and 43 ERA). Over a 3 year period, almost 100% of children with polyarticular and 50% with oligoarticular presentation received a DMARD. 46% with polyarticular and 17% with oligoarticular presentation also received a biologic (Figure 1). The most recent ILAR category among children with oligoarticular onset who received a biologic included 39% extended oligoarthritis, 19% polyarthritis, 4% ERA, 11% other; 27% had persistent oligoarthritis. All sJIA patients were treated with DMARDs with 36% having biologics, primarily ETN and INF. 63% of ERA patients received a DMARD, with 26% later receiving a biologic.

Conclusion: Over a three year period almost all patients with a polyarticular presentation received treatment with MTX and almost 50% also received a biologic therapy. A high proportion of children with an oligoarticular presentation also went on to receive DMARDs and biologics, with many children receiving this treatment for persistent oligoarthritis. This is despite the lack of clinical trial evidence for effectiveness in this subtype. Further studies on the efficacy/effectiveness in this subtype should be undertaken to ensure appropriate use of advanced therapies in this population.

Arthritis pattern at presentation	N	Ever had a DMARD, n(%)	Ever had a biologic, n(%)
Oligoarthritis	406	204 (50)	70 (17)
Polyarthritis	221	217 (98)	98 (44)
Systemic arthritis	42	42 (100)	15 (36)
Enthesitis-related arthritis	43	27 (63)	11 (26)

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Environmental Risk Factors and Development of Juvenile Idiopathic Arthritis. Susan Shenoi[1], Kathryn B Whitlock[2] and Carol A Wallace[3]. [1]Seattle Childrens Hospital, seattle, WA, [2]Seattle Children's Hosptial, Seattle, WA, [3]Seattle Children's Hospital/Univ of Washington, Seattle, WA.

Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is a heterogenous group of disorders that is characterized by chronic arthritis in children without known etiology. Environmental factors that act as triggers in a genetically susceptible host are one of the current postulated etiologies of JIA. Although research that focusses on environmental risk factors in JIA is scant, to date there has been some data to suggest a role of infections, exposure to smoking and lack of breastfeeding. This case control study examines the association of selected environmental risk factors in children with JIA.

Methods: JIA cases were identified at outpatient rheumatology clinic visits over 18 months (2012 to 2013) at a major Children's facility. Enrolled JIA cases were asked to identify three control playmates of similar age and gender without JIA. Both cases and controls completed a one time questionnaire on environmental risk factors in reference to critical time period (at JIA case symptom onset). Controls who responded were frequency-matched to cases by age and gender. Logistic regression adjusted for age and gender was used to determine associations with JIA, and odds ratios are reported with 95% confidence intervals.

Results: 223 JIA cases and 86 controls submitted data that was analyzed. Baseline demographic characteristics were similar between cases and controls. Approximately 5% of mothers smoked during pregnancy among cases and controls with OR 0.8 (95% CI: 0.3 –2.4; p value 0.7). Maternal smoking at JIA onset had OR 1 (95% CI: 0.5 –2.3). The odds of JIA for other selected environmental risk factors were as follows: breastfeeding in first year of life: 1.1 (95% CI: 0.6 –2.1), hospitalization with infection in first year of life: 1.7 (95% CI: 0.5 – 5), daycare attendance <6 years of age 1.3 (95% CI: 0.8 – 2.1), household pets 1.2 (95% CI: 0.7 – 2), urban residence 0.7 (95% CI: 0.4 –1.1), stressors in family (death, divorce, move, new school, unemployment) 1 (95% CI: 0.6 –1.7). Limitations of the study include selection bias as cases were identified though outpatient rheumatology visits and overmatching that was accounted for in the analysis.

Conclusion: There was no association between maternal smoking during pregnancy or subsequent maternal smoking at JIA symptom onset, infections

in first year of life, daycare attendance, household pets, urban residence or family stressors and development of JIA in this case control study.

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Growth during Tocilizumab Therapy for Polyarticular-Course Juvenile Idiopathic Arthritis: 2-Year Data from a Phase 3 Clinical Trial. Kamal N. Bharucha[1], Hermine I. Brunner[2], Nicola Ruperto[3], David A. Cabral[2], Abraham Gedalia[2], Valeria Gerloni[3], Christian Jorgensen[3], Athimalaipet Ramanan[3], Daniel Lovell[2], Alberto Martini[4], James Frane[5], Chris Wells[6] and Fabrizio De Benedetti Sr. [7]. [1]Genentech, South San Francisco, CA, [2]PRCSG, Cincinnati, OH, [3]PRINTO, Genoa, Italy, [4]Istituto Giannina Gaslini, Genova, Italy, [5]Consultant, Santa Monica, CA, [6]Roche Products Ltd., Welwyn Garden City, United Kingdom, [7]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy.

Background/Purpose: Elevated interleukin-6 (IL-6) levels have been associated with low growth velocity in patients with juvenile idiopathic arthritis (JIA). [1] The efficacy of tocilizumab (TCZ), an IL-6 receptor inhibitor, in patients with polyarticular-course JIA (pcJIA) was demonstrated up to 104 weeks in the phase 3 CHERISH trial. [2] Growth was evaluated in patients with pcJIA treated with TCZ for up to 104 weeks in CHERISH.

Methods: Patients with active pcJIA for ≥6 months and inadequate responses to methotrexate received open-label (OL) TCZ intravenously every 4 weeks (randomly assigned 1:1 to receive 8 or 10 mg/kg for body weight [BW] <30 kg or 8 mg/kg for BW ≥30 kg) for 16 weeks. At week 16, patients with ≥JIA ACR30 response were randomly assigned 1:1 to receive placebo or to continue TCZ double-blind for 24 weeks. At week 40, all patients entered an OL extension and received TCZ according to BW through week 104. Height velocity and height standard deviation scores (SDS) were measured in patients with Tanner stage <4 (the subset of study patients with the highest growth potential) provided they did not receive the growth hormone somatotropin during the study.

Results: Of 188 patients who received ≥1 dose of TCZ, 123 patients with Tanner stage <4 were included in the growth population (1 patient received somatotropin and was excluded from the growth population). At baseline, the growth population had a mean World Health Organization (WHO) height SDS ± SD of –0.5 ± 1.2. The baseline height SDS was not related to age or disease duration (Spearman's rank correlations $r = 0.08$ and $r = –0.12$, respectively). For patients with Tanner stage <4 at baseline and height data at year 2 of the study (n = 103), baseline mean height SDS increased significantly (by 0.40) from baseline to year 2 of treatment ($p < 0.0001$ vs baseline). At year 2, 71.8% (74/103) of these patients had an increased height SDS compared with their baseline height SDS, with a mean height velocity of 6.7 ± 2.0 cm/year (n = 103). For patients with available data at year 2 (n = 103), the mean daily oral corticosteroid doses (± SD) at baseline and year 2 of treatment were 0.05 mg/kg (± 0.08) and 0.02 mg/kg (± 0.05), respectively.

Conclusion: Mean height SDS of patients with pcJIA was below normal at baseline. The majority of patients who were Tanner stage <4 at baseline (71.8%) had an increased height SDS at year 2 (end of study).

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2. Brunner HI et al *Arthritis Rheumatol.* 2013:65(suppl):S335.

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Nearly 20% of Children ARE NOT Correctly Classified According to Current ILAR Classification in a Printo Dataset of More THAN 12,000 Juvenile Idiopathic Arthritis Patients. Alessandro Consolaro[1], Francesca Bovis[2], Ekaterina Alekseeva[3], Violeta Vladislava Panaviene[3], Jordi Anton[3], Susan Nielsen[3], Gordana Susic[3], Maria Trachana[4], Troels Herlin[5], Nico Wulffraat[3], Pavla Dolezalova[3], Yosef Uziel[6], Nahid Shafaie[3], Ingrida Rumba-Rozenfelde[3], Valda Stanevicha[3], Nicolino Ruperto[3], Daniel Lovell[7], Angelo Ravelli[8] and Alberto Martini[1]. [1]Istituto Giannina Gaslini, Genova, Italy, [2]PRINTO - Istituto Giannina Gaslini, Genoa, Italy, [3]Istituto Giannina Gaslini, Genoa, Italy, [4]Aristotle University, Thessaloniki, Greece, [5]Aarhus, Genoa, Italy, [6]Tel-Aviv University, Sackler School of Medicine, Tel-Aviv, Israel, [7]PRCSG, Cincinnati, OH, [8]Istituto Gaslini-PRINTO, Genova, Italy.

Background/Purpose: Juvenile idiopathic arthritis (JIA) is an exclusion diagnosis that encompasses all forms of arthritis that begin before the age of 16 years, persist for more than 6 weeks, and are of unknown origin. In the ILAR classification, this heterogeneous group of chronic arthritides has been categorized on clinical and laboratory grounds to try to identify homogeneous, mutually exclusive categories suitable for etiopathogenic studies. However, the ILAR classification is complex and includes several inclusion and exclusion criteria. As a result, the correct placement of a patient in a specific category is not simple.

Methods: Patients enrolled in the multinational study of the EPidemiology, treatment and Outcome of Childhood Arthritis (EPOCA study) and in the Pharmacovigilance in patients treated with biologics± methotrexate study (Pharmachild) were merged in a single database, after exclusion of overlapping patients. The reasons that led to a "provisional" ILAR classification (i.e. lack of fitting into an ILAR category despite ILAR category attribution by the attending physician) in the two datasets and the queries regarding classification raised to the investigators by the PRINTO staff were analyzed and grouped into major categories according to the inclusion or exclusion criterion involved.

Results: A total of 12,141 patients were included in the study. The Table shows, for each JIA subtype, the most frequent drawbacks leading to a provisional classification. Most problems were related to the lack of 2 determinations of rheumatoid factor (RF) at least 3 months apart, the missing data in the indication of the presence or absence of psoriasis in the patient or in the presence or absence of a history of psoriasis in a first degree relative, the lack of assessment of HLA-B27 antigen, or the discrepancies in data results in the indication of a family history of spondyloarthropathies.

	N	Provisional diagnosis N (%)	Reasons for provisional diagnosis N (%)			
			Rheumatoid factor	Psoriasis	Spondylitis features	HLA-B27
Systemic arthritis	1365	295 (21.6)	219 (74.2)	83 (28.1)	67 (22.7)	34 (11.5)
Oligoarthritis	4887	1127 (23.1)	837 (74.3)	353 (31.3)	314 (27.9)	144 (12.8)
Polyarthritis RF-negative	2991	379 (12.7)	273 (72)	183 (48.3)	157 (41.4)	69 (18.2)
Polyarthritis RF-positive	492	277 (56.3)	266 (96)	33 (11.9)	28 (10.1)	10 (3.6)
Psoriatic arthritis	433	101 (23.3)	63 (62.4)	22 (21.8)	23 (22.8)	7 (6.9)
Enthesitis related arthritis	1323	217 (16.4)	118 (54.4)	90 (41.5)	–	–
Total	12141	2396 (19.7)	1776 (74.1)	764 (31.9)	589 (24.6)	264 (11)

Conclusion: In current clinical practice nearly 20% of JIA patient were categorized according to physician diagnosis attribution despite the lack of fulfillment of the ILAR exclusion criteria. Most frequently, this was related to the lack of assessment of RF or the inconsistency in indication of the presence of psoriasis in a first-degree relative.

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Is It Worth Allowing the Presence of Morning Stiffness in the Definition of Inactive Disease in Juvenile Idiopathic Arthritis? Alessandro Consolaro[1], Maddalena Allegra[1], Maria C. Gallo[1], Benedetta Schiappapietra[1], Serena Calandra[1], Cristina Robbiano[1], Federica Mongelli[2], Cecilia Bava[2], Alberto Martini[1] and Angelo Ravelli[3]. [1]Istituto Giannina Gaslini, Genova, Italy, [2]University of Genova, Genova, Italy, [3]Istituto Giannina Gaslini and University of Genova, Genova, Italy.

Background/Purpose: Morning stiffness is a major symptom of juvenile idiopathic arthritis (JIA) and it is usually associated with active disease. However, it is common view that children with disease quiescence may have some degrees of residual morning stiffness. The 2004 preliminary criteria for inactive disease (ID) in JIA did not include the assessment of morning stiffness, whereas the 2011 revision of the criteria has allowed the presence of morning stiffness lasting ≤ 15 minutes. However, it is still uncertain whether the disease status of children with ID who have or do not have morning stiffness is comparable. Aim of the study was to compare the disease status of children with JIA who meet the 2011 revised criteria for ID and have or do not have a minutes morning stiffness lasting ≤ 15.

Methods: A database at the study center including 785 patients who had undergone a total of 2957 visits, which included a parent report of the presence and duration of morning stiffness, was analyzed to identify all visits in which patients met the criteria for ID. In each visit, the duration of morning stiffness was categorized as follows: ≤15 min, 15–30 min, 30–60 min, 1–2 hr, > 2 hr. Clinical assessments included demographic features, and parent-reported outcomes. In case a patient met the ID criteria in more than 1 visit, only the first visit was retained.

	Patients meeting 2004 ID criteria Patients meeting 2011 ID criteria			
	No MS N = 390	MS ≤ 15 min N = 41	MS > 15 min N = 29	p-value
Median (IQR) disease duration	3.8 (1.8; 7.3)	2.8 (1.4; 6)	5.7 (2.6; 7.9)	0.30
Functional ability (JAFS score) ≥1, N (%)	64 (16.4)	18 (43.9)	23 (79.3)	<0.001
Physical health (PRQL PhS) ≥1, N (%)	173 (44.4)	32 (78)	28 (96.6)	<0.001
Psychosocial health (PRQL PhS) ≥1, N (%)	188 (48.2)	29 (70.7)	24 (82.8)	<0.001
VAS well-being ≥1, N (%)	155 (40.4)	32 (82.1)	28 (100)	<0.001
VAS pain ≥1, N (%)	102 (26.8)	28 (68.3)	21 (87.5)	<0.001
Acceptable symptom state, N (%)	366 (95.6)	33 (80.5)	16 (57.1)	<0.001

MS: morning stiffness; IQR: interquartile range

Results: A total of 460 visits in which the patient met the criteria for ID were evaluated. Absence of morning stiffness was reported in 390 (84.8%) visits, whereas in 70 visits (15.2%) there was morning stiffness. Among the visits with morning stiffness, in 41 (8.9%) duration was ≤15 min, and in 29 (6.3%) duration was >15 min. Table shows the comparison of disease duration and parent-reported outcomes between patients with absence or presence of morning stiffness.

Conclusion: Among patients who met the 2011 criteria for ID, those with morning stiffness ≤15 min had worse parent-reported outcomes than those without morning stiffness. This finding suggests that parents may not perceive their child's disease state as true remission when lower degrees of morning stiffness are present. Notably, a sizeable proportion (6.3%) of children meeting the 2004 ID criteria had morning stiffness lasting > 15 min. The change of the criterion "Duration of morning stiffness of ≤ 15 minutes" to "Absence of morning stiffness" in the definition for ID should be considered.

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Focus on Patient Reported Outcomes in Juvenile Idiopathic Arthritis: There Is Room to Improve Care. Alysha Taxter[1], Keshia Maughn[1], Edward M. Behrens[2] and Pamela F. Weiss[3]. [1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]Childrens Hospital of Philadelphia, Philadelphia, PA, [3]The Children's Hospital of Philadelphia, Philadelphia, PA.

Background/Purpose: National registry cross-sectional data show significant differences in patient-reported outcomes (PROs) across juvenile idiopathic arthritis (JIA) subtypes. This study aimed to assess predictors of PROs in JIA in a tertiary care clinic setting.

Methods: This is a retrospective study of children meeting ILAR JIA criteria evaluated in a tertiary pediatric rheumatology clinic between 2010–2012. Pain over the past week was assessed with a visual analogue scale (VAS; 0,10). Function was estimated with the childhood health assessment questionnaire (CHAQ; 0, 3). Physician global disease activity was measured using a VAS (0,10). We tested the association of clinical characteristics with pain and function using multivariable linear and ordinal logistic regression, accounting for clustering by subject. Pair-wise correlation was used to compare the association of physician disease assessment and each PRO.

Results: During the study period there were 542 subjects evaluated at 2,689 visits. The distribution of JIA categories was oligoarticular (37%), polyarticular RF+ (3%), polyarticular RF- (19%), systemic (8%), psoriatic (9%), enthesitis-related arthritis (ERA) (18%), undifferentiated (6%). Patients with ERA and undifferentiated reported higher pain intensity ($p<0.01$), higher pain prevalence ($p<0.01$), and poorer function ($p<0.01$) than other JIA categories. In multivariable analyses, older age, female sex, higher active joint count, NSAID use, DMARD use, and the ERA and undifferentiated categories were associated with higher pain scores (Table). Higher active joint count, NSAID use, glucocorticoid use, and ERA were associated with worse function. In patients with ERA, higher tender enthesitis count and female sex were significantly associated with higher pain intensity and poorer function. In patients with undifferentiated arthritis, higher active joint count and glucocorticoid use were associated with worse function. Correlation between the physician assessment of disease activity and patient-reported pain intensity and function were low (r=0.5, 0.4, respectively).

Conclusion: At our tertiary care center children with ERA and undifferentiated JIA had higher pain intensity and more frequent pain than other JIA categories. These results suggest that current treatment regimens may not be equally effective across JIA categories or as efficacious for particular disease attributes that are more common in the ERA and undifferentiated categories.

Table Association of clinical characteristics with pain and function

	Pain B-Coefficient (95% CI)	Function B-Coefficient (95% CI)
JIA category	Reference	Reference
Oligoarticular	0.45 (−0.10, 0.99)	0.08 (−0.07, 0.23)
Systemic	−0.07 (−0.71, 0.57)	0.14 (−0.02, 0.31)
Polyarticular RF+	0.02 (−0.34, 0.38)	0.07 (−0.01, 0.15)
Polyarticular RF-	0.41 (−0.01, 0.82)	0.08 (−0.03, 0.18)
Psoriatic	0.70 (0.26, 1.14) **	0.12 (0.03, 0.21) **
Enthesitis Related	0.72 (0.25, 1.18) **	0.09 (−0.03, 0.22)
Undifferentiated		
Older age (each year)	0.06 (0.03, 0.08) ***	–
Female	0.64 (0.22, 0.95) ***	–
Active joint count	0.15 (0.07, 0.22) ***	0.03 (0.01, 0.04) **
NSAIDs	0.95 (0.72, 1.18) ***	0.12 (0.07, 0.17)***
DMARDs	−0.29 (−0.52, −0.06) *	–
Glucocorticoids	–	0.08 (−0.01, 0.12)*

Legend. Results of multivariable ordinal and linear regression models. Significant predictors in univariate analysis ($p < 0.05$) were included in the multivariable models. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. NSAIDs = non-steroidal anti-inflammatory drugs. DMARD = disease modifying anti-rheumatic drugs.

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Biologic Treatment of Adult Patients with Juvenile Idiopathic Arthritis Followed in the National Registry. Katerina Jarosova[1], Karel Hejduk[2], Michal Uher[2] and Jiri Vencovsky, MD, DSc[3]. [1]Institution of Rheumatology, Prague, Czech Republic, [2]Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic, [3]Charles University Institute of Rheumatology, Prague, Czech Republic.

Background/Purpose: To analyze the efficacy and safety of biologic agents in adult patients with juvenile idiopathic arthritis (JIA).

Methods: ATTRA is the Czech national registry of patients with different forms of chronic arthritis who are treated with biologic drugs. Using this registry, we have analyzed adult JIA patients, who switched their treatment between biologic agents. Patients were treated in recommended doses for RA and the first drug was infliximab (44.3%), etanercept (36.7%), adalimumab (18.1%), or golimumab (0.9%). Those patients, who failed to improve in DAS28 by at least 1.2 after 3 months at 2 consecutive visits, who lost the response during the treatment, or who had to be discontinued due to adverse event, were switched to an alternative TNF inhibitor (TNFi) or to rituximab, abatacept or tocilizumab. Survival on therapy after 1st and 2nd biologic agents was calculated. Clinical efficacy was assessed with DAS28. Safety assessments were done for all patients during the whole follow-up period. No guidelines have been issued for the preference between the 1st or 2nd drug type and this was left solely to treating physician decision and was based on the assessment of overall clinical situation.

Results: Two hundred and ten adult JIA patients were treated with anti-TNF agents in the 1st instance. Mean age of patients was 22.4 years, duration of disease was 12.7 years and 62% were women. Ninety (42.9%) patients received more than one biologic agent. DAS28 showed excellent and persistent improvement for those patients who remained on the first drug. The treatment responses to a second biologic agent were also significant, although with smaller differences to baseline DAS28 values. DAS28 at the initiation of the first TNFi was 6.01±1.28 and decreased significantly to 2.69±1.47 after 12 months and to 2.21±1.46 after 24 months; DAS28 at initiation of the

second TNFi or other biologic agent was 5.59±1.53 and decreased to 2.77±1.39 and 2.74±1.00 after 12 and 24 months, respectively. Survival on the treatment was shorter in patients who switched the biologic agent in comparison with the first users (p = 0.017). The survival on the drug in first users and in switched patients was as follows: 0.93 (95% CI: 0.90–0.97) and 0.89 (95% CI: 0.82–0.95) in the first year; 0.87 (95% CI: 0.83–0.92) and 0.77 (95% CI: 0.68–0.86) in the second year. Adverse events that lead to treatment discontinuation were seen in 4% and 6% after one year and in 6% and 10% after 2 years therapy in the first and subsequent biologic agents groups, respectively. Treatment discontinuation due to inefficacy was observed in 1% and 6 %, and in 5% and 12% with the 1st and 2ndline treatment in years 1 and 2.

Conclusion: biologic treatment in adult patients with juvenile idiopathic is effective and safe. Similarly to patients with RA, it is possible to regain efficacy after switching to second biologic drug in a majority of patients, although with somewhat lower difference between the entry and 2 years DAS28 evaluations. Good adherence to therapy was observed for both first and second biologic agents.

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Retrospective Review of Immobilization Vs. Immediate Resumption of Activity in Patients with Oligoarticular Juvenile Idiopathic Arthritis and Corticosteroid Knee Injections. Elaine Ramsay[1], Heather Benham[2], Jenna Tress[3], Janille Diaz[4] and David D. Sherry[3]. [1]The Children's Hospital of Philadelphia, Philadelphia, PA, [2]Texas Scottish Rite Hospital for Children, Dallas, TX, [3]Children's Hospital of Philadelphia, Philadelphia, PA, [4]The Children's Hospital of Philadelphia, Philadelphia, PA.

Background/Purpose: Intraarticular corticosteroid injection (IACI) is one of the most common treatment modalities in oligoarticular Juvenile Idiopathic Arthritis (JIA). There is widespread use of IACI in the treatment of arthritis, but recommendations following the procedure vary, as there are no published studies on splinting patients post-IACI. Post-injection, Texas Scottish Rite Hospital for Children (TSRHC) splints patients for 24 hours while The Children's Hospital of Philadelphia (CHOP) does not. The aim of this study was to compare the number of cases of recurrent arthritis and re-injection following IACI.

Methods: Data (see Table) were retrospectively collected at CHOP and TSRHC. All patients diagnosed with oligoarticular JIA according to ILAR criteria (2nd revision, 2001) between 2008–2010 were included. Chi square and T test were utilized for preliminary analysis.

Results: 131 patients at CHOP and 70 patients at TSRHC received a knee IACI. The average age was 9.1 (CHOP) v. 6.7 (TSRHC) (p=0.0002). There were more Hispanics at TSRHC (6 v. 10, p=0.055), and a higher number of ANA positive patients (54 v. 74, p=0.003). Overall mean joint disease severity scores (sum of range of motion restriction, joint swelling and tenderness) at CHOP were higher (3.4 v. 2.3, p <0.001). Mean dose of triamcinolone hexacetonide was higher at CHOP (1.4 mg/kg v 0.8 mg/kg, p<0.001). Arthritis reoccurred in 37 (28%) at CHOP v. 30 (43%) at TSRHC (p=0.041). 37 patients at CHOP received re-injection of the same knee v. 5 at TSRHC (p <0.001).

Conclusion: TSRHC patients were younger and more frequently ANA positive and Hispanic. Joint disease severity scores were higher at CHOP, and patients received a higher mean dose of triamcinolone hexacetonide IACI. The number of recurrent arthritis cases was similar between institutions and there was a trend toward more recurrent arthritis at TSRHC, but CHOP completed a larger amount of repeat injections. This may indicate that TSRHC begins systemic immunosuppression if IACI fails to clinically remit the knee. Future plans include comparison of time to recurrent arthritis to see if splinting extends remission. If it does, the practice of splinting knees following IACI may be beneficial in children with oligoarticular JIA. Examining co-variables such as age, ethnicity, ANA status, disease activity, steroid type and dose, and concomitant medications are planned. Limitations of this study include: 1) possibility that some subjects with oligoarticular JIA were missed; 2) some subjects were lost to follow-up; 3) variation in recording and practice styles. Also, the study only examined knee IACIs, splinting duration was less than reported in adults, and adherence was not monitored.

Table

		CHOP n=131 (%)Not splinted post injection	TSRHC n=70 (%) Splinted post injection	P
Mean Age (yrs)		9.1	6.7	0.0002
Female		108 (82)	58 (83)	>0.999
Race				0.220
	White	110 (86)	66 (94)	
	Black	6 (5)	4 (6)	
	Asian	1 (1)	0	
	Other*	11 (8.6)	0	
Ethnicity				
	Hispanic	6 (5%, n=117)	10 (14%, n=70)	0.055
	Not Hispanic	111 (95%, n=117)	60 (85%, n= 70)	
Labs				
	ANA +	74 (57%, 130 tested)	54 (78%, 69 tested)	0.003
	RF +	3 (2.3%, 131 tested)	2 (3%, 70 tested)	0.741
	HLA B 27+	7 (5.5%, 128 tested B27)	3 (4.3%, 70 tested)	0.750
	ESR>20	13 (25%, 52 tested)	22 (35%, 63 tested)	0.310
Iritis present		4 (3.1%, n=131)	2 (3%, n=70)	0.6344
Injection dose (mg/kg)	Triamcinolone Hexacetonide	1.4 (112)	0.8 (68)	<0.001
Total joint activity (sum of ROM, swelling, tenderness) (mean)		3.4	2.3	<0.001
Arthritis reoccurred		37 (28)	30 (43)	0.041
Patients receiving re-injection		37 (31%, n=119)	5 (7%, n=69)	<0.001

Legend: CHOP=The Children's Hospital of Philadelphia, TSRHC=Texas Scottish Rite Hospital for Children, NSAID=non-steroidal anti-inflammatory drug, ROM=range of motion, CHAQ=Children's Health Assessment Questionnaire, * Includes: Native American, Hawaiian, other, not specified.

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Pharmacovigilance in Juvenile Idiopathic Arthritis Patients (PHARMACHILD) Treated with Biologic Agents and/or Methotrexate. Consolidated Baseline Characteristics from Pharmachild and Other National Registries. Joost F. Swart[1], Alessandro Consolaro[2], Gerd Horneff[3], Kimme L. Hyrich[4], Francesca Bovis[5], Bo Magnusson[6], Jose Melo-Gomes[7], Ekaterina Alexeeva[8], Stefano Lanni[9], Gerd Ganser[10], Violeta Vladislava Panaviene[11], Jordi Anton[12], Ivan Foeldvari[13], Valda Stanevicha[14], Susan Nielsen[15], Ralf Trauzeddel[16], Constantin Ailioaie[17], Pierre Quartier[18], Toni Hospach[19], Gordana Susic[20], Maria Trachana[21], Frank Weller-Heinemann[22], Alberto Martini[23], Nico Wulffraat[1] and Nicolino Ruperto[9]. [1]Wilhelmina Children's Hospital/ UMC Utrecht, Utrecht, Netherlands, [2]Istituto Giannina Gaslini, Genova, Italy, [3]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [4]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, [5]PRINTO - Istituto Giannina Gaslini, Genoa, Italy, [6]Karolinska University Hospital, Stockholm, Sweden, [7]Pediatric Rheumatology, Lisbon, Portugal, [8]Scientific Centre of Children's Health of RAMS, Moscow, Russia, [9]Istituto Giannina Gaslini, Genoa, Italy, [10]Sankt Josef Stift, Sendenhorst, Germany, [11]Children's Hospital, Affiliate of Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania, [12]Hospital Sant Joan de Déu, Barcelona, Spain, [13]Department of Pediatric Rheumatology, Hamburger Zentrum für Kinder und Jugendrheumatologie, Hamburg, Germany, [14]Riga Stradins University, Riga, Latvia, [15]University Clinic of Pediatrics II, Rigshospitalet, Copenhagen, Denmark, [16]Helios Clinics, Berlin, Germany, [17]Alexandru Ioan Cuza University, Iasi, Romania, [18]Necker-Enfants Malades Hospital, Paris, France, [19]Olgahospital, Stuttgart, Germany, [20]School of Medicine, University of Belgrade, Belgrade, Serbia, [21]Aristotle University, Thessaloniki, Greece, [22]Klinikum Bremen-Mitte, Bremen, Germany, [23]PRINTO-IRCCS, Genova, Italy.

Background/Purpose: The availability of methotrexate (MTX) and biological agents has provided a major change in the treatment of children with juvenile idiopathic arthritis (JIA). However, limited information exists on the safety of the current available treatements. An international registry named Pharmachild (European Union grant 260353) has been set up by the Pediatric Rheumatology International Trials Organisation (PRINTO)/ Paediatric Rheumatology European Society (PRES). In parallel several national registries with the same purpose have been set up in different European Countries for the follow-up of these patients.

Methods: We merged into a unified database the baseline demographic data of JIA patients treated with MTX or biologicals coming from the Pharmachild registry and from the national registries of Germany, United Kindgom, Sweden and Portugal. Events of special interest (ESI) and moderate/severe/serious adverse events (AE) related to the drugs were

collected. Data are presented as frequencies (%) or medians with 1st and 3rd quartiles.

Results: About 61% of the patients have been treated with biologicals alone or in combination with MTX, and 29% only with MTX. The events of special interest ranged from 0.1 to 15.0% and the other adverse events from 4.8% to 69.9%.

	Pharmachild N = 5571	NR UK N = 1537	NR Germany N = 3243	NR Portugal N = 112	NR Sweden N = 1403	TOTAL N = 11866
Age at onset	5.4 (2.4 – 10.0)	-	7.2 (3.1-11.4) N=3094	6.3 (2.5-10.9)	6.6 (2.7-11.1)	-
Age at JIA Diagnosis	6.2 (2.8 – 11.0)	5.5 (2.1-10.2) N=1495	8.2 (4.0-12.3)=2067	7.3 (3.3-12.3)	-	-
Disease duration at the last available follow up	4.9 (2.5 – 8.2)	5.4 (2.7 – 8.8) N=1383	5.2 (3.1-8.4) N=3090	3.0 (0.5-9.6)	4.2 (2.2-7.7)	-
Therapy with MTX only	1365 (24.5)	503 (32.7)	1132/3134 (36.1)	0 (0.0)	408/1308 (31.2)	3408/11662 (29.2)
Therapy with only one Biologic Drug	204 (3.7)	31 (2.0)	104/3134 (3.3)	1 (0.9)	88/1308 (6.7)	428/11662 (3.7)
Therapy with only one Biologic Drug + MTX	2378 (42.7)	862 (56.1)	1545/3134 (49.2)	27 (24.1)	388/1308 (29.7)	5200/11662 (44.6)
Therapy with more than one Biologic	35 (0.6)	0 (0.0)	13/3134 (0.4)	6 (5.4)	43/1308 (3.3)	97/11662 (0.8)
Therapy with more than one Biologic + MTX	872 (15.6)	141 (9.2)	340/3134 (10.8)	78 (69.6)	8/1308 (0.6)	1439/11662 (12.3)
Nr. patients with ESI or moderate/severe/serious AE	1070 (19.2)	1093 (71.1)	1163(37.1)	27 (24.1)	11 (0.8)	3364 (28.4)
Nr. patients with ESI	496 (8.9)	230 (15.0)	249 (7.9)	5 (4.5)	2 (0.1)	982 (8.3)
Nr. patients with AE or moderate/severe/serious AE	729 (13.1)	1075 (69.9)	1069 (34.1)	24 (21.4)	68 (4.8)	2965 (25.0)

Conclusion: Combination of information from different data sources is a recommended task and will provide a powerful tool for the future analysis of safety events coming from different registries.

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Agreement Between Enthesitis Evaluation By Manual Palpation and Dolorimetry in Juvenile Spondyloarthritis. Lauren Minor[1], Keith Sikora[2], April D. Brundidge[3], Robert A. Colbert[4] and Hemalatha Srinivasalu[5]. [1]NIAMS, NIH, Bethesda, MD, [2]NIAMS, NIH, Bethesda, DC, [3]NIAMS NIH, Bethesda, MD, [4]NIAMS/NIH, Bethesda, MD, [5]Children's National Medical Center, Washington, DC.

Background/Purpose: Enthesitis is a characteristic feature of spondyloarthritis (SpA). Clinical evaluation of enthesitis by palpation is subject to differences in pressure used at different sites or by different examiners over time. Use of a dolorimeter allows calibration of the exact pressure used in assessment of tenderness. The purpose of this study was to assess agreement between manual and dolorimetric testing of entheseal points in juvenile SpA (JSpA).

Methods: Patients less than 18 years of age and diagnosed with JSpA based on ILAR criteria for ERA (over 75%), and Psoriatic arthritis and ESSG criteria for undifferentiated arthritis were included in the study. Forty JSpA patient encounters (age range 7–18 y) and 10 healthy controls (range 10–25 y) were included in the study. Thirty-three entheseal sites were assessed by manual palpation followed by dolorimetry by the same examiner. Three different examiners participated in the study. Tenderness elicited at less than 4 kg pressure using a 20 lb dolorimeter was considered positive by dolorimetry; tenderness with thumb pressure with blanching of the examiner's nail bed was considered positive by manual palpation. Kappa statistics were performed by SPSS to assess agreement between manual and dolorimetric testing. Kappa value (k) > 0.6 indicates substantial agreement; $0.41 < k < 0.6$ is considered moderate, and $0.21 < k < 0.4$ shows fair agreement.

Results: The table displays kappa values for all 33 entheseal sites indicating the degree of agreement, for all 40 JSpA encounters. Substantial agreement between manual and dolorimetric assessment was noted in 42% of sites (14/33); moderate agreement was seen in 39% of sites (13/33) and fair agreement in 12% (4/33). Kappa values of corresponding right and left entheseal sites showed no statistical difference (paired t-test = 0.6). Of a total of 10 positive entheseal sites by manual palpation and 5 sites by dolorimetry in the 10 healthy controls, only one entheseal site showed agreement by both methods. Similar analysis on 30 adult SpA patients yielded 57% sites with substantial and 15% with moderate agreement.

Conclusion: There was substantial to moderate agreement between clinical enthesitis evaluation by manual and dolorimetric methods in 81% of sites, with fair agreement in another 12% in JSpA. Since a single exam was performed at each visit, inter-rater reliability was not assessed. Although manual testing standardized for nail blanching and dolorimetry exhibited considerable agreement, use of dolorimetry may enhance objectivity for enthesitis evaluation among JSpA patients in clinical trials. Future studies are needed to address inter-rater reliability between the two methods and to correlate with ultrasound and/or MRI.

	Kappa statistics	
Entheseal site	**R**	**L**
1st Costosternal junction	0.063	0.072
7th Costosternal junction	0.457	0.5
Supraspinatus to greater tuberosity of humerus	0.844	0.778
Lateral epicondyle	0.645	0.588
Medial epicondyle	0.688	0.581
Anterior superior iliac spine	0.32	0.36
Posterior superior iliac spine	0.588	0.78
Greater trochanter	0.624	0.56
Iliac crest	0.5	0.534
Ischium	0.805	0.725
Upper pole of patella	0.358	0.419
Lower pole of patella	0.63	0.713
Tibial tuberosity	0.541	0.383
Plantar fascia insertion to MTP	0.583	0.63
Plantar fascia insertion to calcaneus	0.61	0.608
Achilles insertion to calcaneus	0.545	0.684
L5 spinous process	0.405	

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Single Hub and Access Point for Paediatric Rheumatology in Europe (SHARE)– Evidence Based Recommendations for Diagnosis and Treatment of Juvenile Idiopathic Arthritis. S.J. Vastert[1], Victor Boom[1], Jordi Anton[2], Tamás Constantin[3], Pavla Dolezalova[4], Gerd Horneff[5], Pekka Lahdenne[6], Bo Magnusson[7], Kirsten Minden[8], K. Nistala[9], Pierre Quartier[10], Ingrida Rumba-Rozenfelde[11], Nicolino Ruperto[12], Vanessa Remy Piccolo[13], Ricardo A. G. Russo[14], Yosef Uziel[15], Carine Wouters[16], Alberto Martini[17], Angelo Ravelli[18], Helen Foster[19] and Nico Wulffraat[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Pediatric Rheumatology Unit. Hospital Sant Joan de Déu. Universitat de Barcelona, Barcelona, Spain, [3]University Childrens Hospital, Budapest, Hungary, [4]General University Hospital, Prague, Czech Republic, [5]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [6]Helsinki University Central Hospital, Helsinki, Finland, [7]Astrid Lindgren Children's Hospital, Stockholm, Sweden, [8]German Rheumatism Research Center, Berlin, Germany, [9]University College London, London, United Kingdom, [10]IMAGINE Institute, Hôpital Necker-Enfants Malades, Assistance Publique Hôpitaux de Paris, Université Paris-Descartes, Paris, France, [11]University of Latvia, Riga, Latvia, [12]Istituto Giannina Gaslini, Genoa, Italy, [13]Hopital Necker Enfants Malades, Paris, France, [14]Hospital de Pediatria Garrahan, Buenos Aires, Argentina, [15]Tel-Aviv University, Sackler School of Medicine, Tel-Aviv, Israel, [16]University of Leuven, Laboratory of Pediatric Immunology, University Hospital Leuven, Leuven, Belgium, [17]Istituto Giannina Gaslini, Genova, Italy, [18]University of Genova, Genova, Italy, [19]Newcastle University, Newcastle, United Kingdom.

Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is one of the most common chronic pediatric rheumatic diseases (PRD). As is the case for most PRD's, evidence-based guidelines are sparse and management is based to great extent on physician's experience. Moreover, there are differences between nations regarding availability and financing of biological therapies. In 2012, a European initiative called SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) was launched to optimize and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases. One of the aims of SHARE was to provide evidence based recommendations for diagnosis and treatment of JIA.

Methods: Evidence based recommendations were developed using the European League Against Rheumatism (EULAR) standard operating procedure[1]. An expert committee was instituted, consisting of pediatric rheumatologists from across Europe with expertise in JIA. The expert committee defined search terms for the systematic literature review. Two independent experts scored articles for validity and level of evidence. Recommendations

derived from the literature were evaluated by an online survey. Those with less than 80% agreement during the online survey were reformulated. Subsequently, all recommendations were discussed by the experts at a consensus meeting using the nominal group technique[2]. Recommendations were accepted if more than 80% agreement was reached.

Results: The literature search yielded 4723 articles, of which 174 were considered relevant. The included articles were scored for validity and level of evidence. Recommendations were formulated based on the valid papers and were discussed and adjusted where needed during the consensus meeting. In total, 10 recommendations for diagnosis and 31 for treatment were accepted with more than 80% agreement. Topics covered for diagnosis and for treatment are shown in *Table 1*.

Table 1 Juvenile Idiopathic Arthritis

Diagnosis	Treatment
The value of MRI in the diagnosis arthritis	Steroids (locally and systemically administered)
The value of ultrasound in the diagnosis of arthritis	DMARDS
Biomarkers for diagnosis of JIA	Biologicals
Diagnosis of complications	Treatment of complications

Conclusion: The SHARE initiative provides recommendations for diagnosis and treatment of JIA and thereby facilitates improvement and uniformity of care throughout Europe. In the subsequent phase of the project, best practices identified from literature will be completed with the 'experts opinion' in order to formulate diagnostic and management guidelines as best practices for care of JIA patients throughout Europe.

References:

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[2] Van de Ven, A. H., and A. L. Delbecq, The nominal group as a research instrument for exploratory health studies. *American Journal of Public Health*, 1972

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Drug Safety in Treatment of Juvenile Idiopathic Arthritis (JIA): Biologic Therapy Compared with MTX. Gerd Horneff[1], Hans Huppertz[2], Gerd Ganser[3], Johannes Peter Haas[4], Ivan Foeldvari[5] and Kirsten Minden[6]. [1]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [2]Prof Hess Children's Hospital, Bremen, Germany, [3]Sankt Josef Stift, Sendenhorst, Germany, [4]German Center for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany, [5]Department of Pediatric Rheumatology, Hamburger Zentrum für Kinder und Jugendrheumatologie, Hamburg, Germany, [6]German Rheumatism Research Center, Berlin, Germany.

Background/Purpose: Drug surveillance of biologics in juvenile patients using registries is of immense importance as patient numbers and duration in clinical trials are limited. There is a special interest in allergic, autoimmune, hematologic, infectious, thrombotic, vascular and malignant disorders.

Methods: Patients with JIA were prospectively observed in the German JIA biologic registry BiKer. Predefined adverse events of special interest (AESI) were recorded by physicians. Total Rate per exposure year (EY) and risk ratio (RR) were calculated with 95 % confidence intervals. Differences were analyzed using the Wald test. Biologics naïve patients were recruited from JIA patients receiving methotrexate (controls). In all three biologics cohorts, methotrexate as well as other DMARDS were allowed to be given concomitantly.

Results: Methotrexate (without a biologic agent) was applied to a total of 1517 patients, Etanercept (ETA) to 1925, Adalimumab (ADA) to 498 and Tocilizumab (TOC) to 104 patients for a total exposure time or 3019; 3958; 561 and 103 years, respectively. A total of 1227 adverse events (AE) were reported In the control group (406/1000 PY[389–424]) with 44 classified as serious (15/1000PY[11–20]). In the ETA cohort there were 1131 AE (286/1000PY [272–300]) and 149 SAE (38/1000PY[32–44]), in the ADA cohort 373 AE (665/1000 PY [625–703]) and 28 SAE (50/1000 PY [35–71] and in the TOC cohort there were 97 AE (941/1000 PY [878–973]) with 10 SAE (97/1000 PY [54–170]. In the control cohort, a total of 252 AE qualified as ESI, upon ETA 234, upon ADA 60 and upon TOC 13 (table).

Thus, compared to the control group the incidence of severe infections is significantly higher upon ETA and ADA, that of autoimmunity and uveitis are significantly higher upon ADA, and MAS is significantly more frequent upon TOC, while the incidence of hepatic events is lower in all the biologics cohorts than with MTX alone. A higher RR failing to reach level of significance was found for chronic inflammatory bowel disease with ETA, and anaphylaxis with TOC. Further ESI including malignancies revealed no differences.

Conclusion: This progress report from the ongoing BiKeR-registry showed a higher incidence for several adverse events of interest including severe infections, autoimmunity, uveitis, anaphylaxis and MAS while the total rate is surprisingly low. In general, JIA patients tolerated biologic treatment very well. Differences between the cohorts are at least in part biased by differences in JIA category distribution and preexisting uveitis risk.

	MTX (3019 years)	ETA(3959 years)			ADA (561 years)			TOC (103 years		
	Rate*	rate	RR (95% CI)	p-Wert	rate	RR (95% CI)	p-Wert	rate	RR (95% CI)	p-Wert
Anaphylaxis	1.32	0.25	0.2 (0.02-1.7)	0.138	3.56	2.7 (0.5-14.7)	0.253	9.71	7.3 (0.8-65.6)	0.074
Autoimmunity	0.33	0			10.69	33.3 (3.9-333.3)	0.001	0		
Bleeding	0.66	0.76	1.1 (0.2-6.9)	0.882	3.56	0.2 (0.03-1.3)	0.092	0		
Chronic inflammatory bowel disease	0.99	3.28	3.3 (0.9-11.6)	0.061	1.78	1.8 (0.2-17.3)	0.613	0		
Cytopenia	3.64	5.81	1.6 (0.8-3.3)	0.202	1.78	2.1 (0.36-16.7)	0.494	29.12	8.0 (2.2-28.7)	0.001
Demyelination	0	0.51			0			0		
Hepatic events	51.67	13.39	0.26 (0.2−0.4)	<0.001	17.82	2.9 (1.5-5.5)	0.001	29.12	0.6 (0.2-1.8)	0.352
Severe infection	9.60	15.66	1.6 (1.1-2.5)	0.029	24.95	2.6 (1.4-4.9)	0.003	29.12	3.0 (0.9-10.0)	0.067
Malignant disease	0.99	1.77	1.8 (0.5-6.9)	0.403	0					
MAS	0.33	0.25	0.8 (0.1-12.5)	0.848	0			29.12	90.9 (9.2-1000)	<0.001
Pregnancy	0	0.25			0			0		
Thrombotic disorders	0	0			1.78			0		
Uveitis	13.91	16.92	1.2 (0.8-1.8)	0.318	40.99	3.0 (1.8-4.9)	<0.001	0		
Stroke	0	0			0			0		

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Using the 2011 ACR Recommendations for the Treatment of Juvenile Idiopathic Arthritis (JIA) to Evaluate a Single Centre Treatment Pathway: A Feasibility Study. Katherine Green[1], Marinka Twilt[2] and Taunton R. Southwood[3]. [1]Birmingham Children's Hospital, Birmingham, United Kingdom, [2]Aarhus University Hospital, Aarhus, Denmark, [3]Institute of Child Health, University of Birmingham and Birmingham Children's Hospital, Birmingham, United Kingdom.

Background/Purpose: The 2011 ACR recommendations for the treatment of Juvenile Idiopathic Arthritis (ACR-JIA) are evidence-based, consensus-approved therapeutic pathways for the safe and effective treatment of JIA. Our aim was to determine the feasibility of applying ACR-JIA to evaluate the treatment pathway in a single centre JIA polyarthritis cohort.

Methods: We conducted a retrospective analysis of a single-centre paediatric JIA cohort by reviewing case notes, investigations and treatment databases of all newly diagnosed JIA polyarthritis patients in the 2 years after ACR-JIA publication. 35 patients with multiple joint arthritis fulfilled ILAR criteria for the diagnosis of JIA: systemic arthritis (n=5, analysed separately), polyarthritis (n=25) and Extended Oligoarthritis (n=5, analysed together with polyarthritis (total n=30) as these groups are managed similarly in the ACR Recommendations). Using the Recommendations, disease severity and poor prognostic features were used to categorize the patients and critical therapeutic time points (disease duration of 8–12 weeks from diagnosis to starting methotrexate, and if methotrexate was ineffective, 14–28 weeks from starting methotrexate to starting etanercept) were calculated. Drug monitoring frequency was also determined.

Results: 25 females and 10 males (median age at onset 13, range 1.5–15 years) were included in the evaluation. Median age at disease onset for

poly/extended oligoarthritis was 10 years (1.5–16), with a median of 12 joints (12–38) active at presentation, and for the systemic group median age at onset was 6 years (2–7), with a median number of 6 active joints (2–10). 3 polyarthritis patients were rheumatoid factor positive. In the polyarthritis/extended oligoarthritis group, 2 patients with polyarthritis had poor prognostic features, 23 had moderate and 6 had high disease severity. None of the systemic patients had poor prognostic factors, 2 had moderate and 2 had high disease severity.

22/30 patients with polyarthritis/extended oligoarthritis followed the ACR recommendations for treatment according to their disease severity, commencing methotrexate therapy within a median of 6 weeks (3–32 weeks) of diagnosis. Etanercept was commenced in a total of 9 patients (30%) within a median of 6 months (1.5–24 weeks) subsequent to commencing methotrexate. This was due to intolerance in 5 patients (56%), inefficiency in 2 cases (22%) and both intolerance and inefficiency in 2 cases (22%). A total of 7 patients did not follow ACR-JIA guidelines due to excessive length of time between diagnosis and commencing methotrexate or etanercept treatment, most commonly due to delays in funding approval or insufficient regular drug monitoring tests. All patients with systemic arthritis followed the ACR-JIA recommendations.

Conclusion: Overall, 28/35 patients followed ACR-JIA. This study demonstrates the feasibility of using the ACR-JIA recommendations to evaluate a clinical pathway. It also highlights the potential influence of the local health economy in achieving rapid commencement of new JIA therapies and the challenges of ensuring regular drug monitoring in all patients.

Disclosure: K. Green, None; **M. Twilt**, None; **T. R. Southwood**, None.

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Role of Joint Status in Decreased Accelerometer-Assessed Daily Physical Activity in Juvenile Idiopathic Arthritis. Mette Noergaard, Marinka Twilt and Troels Herlin. Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is often associated with decreased physical activity (PA). Although improved disease control has opened up the possibilities for JIA-children to participate in dynamic sport activities, various limitations secondary to the disease seem to restrict an adequate integration in sport activities. Accurate, objective measurements of PA and identification of specific factors limiting PA in JIA-children are therefore needed.

This study aimed to: 1. Compare accelerometer-assessed PA in JIA-children with normative data of age- and gender-matched healthy controls. 2. Relate accelerometer-assessed PA to joint status in the lower extremities (LE) in JIA-children regarding active arthritis as well as persistent LOM (contractures) and exceeded range of motion (ROM) (hypermobility).

Methods: In 61 patients with JIA PA was assessed using the hip-worn GT1M Actigraph accelerometer during wakening hours for one week, providing at least 3 separate days each of 8 hours of valid recording accelerometer using 10 second intervals of recording (epochs).

Joint status was valuated using a joint activity count of 71 joints. Also, LE-joints (hips, knees, ankles, toes) were examined for persistent LOM and exceeded ROM (Beighton score-items including alternative items to cover all LE-joints). Demographic, disease- and pain-related parameters were also obtained.

Results: For each age-group between 10–16 years accelerometer data of the 61 JIA patients were compared with 239±93 normative controls. Values of mean counts per minute (c/min), recorded minutes with moderate and high PA (>1000 c/min) and high PA (>2500 c/min) were significantly lower in patients than in normative controls ($p \leq 0.004$), with the more severe JIA-subcategories having the lowest values.

PA of JIA-children was significantly correlated to joint swelling ($p=0.004$) and LOM of the hips and the ankles, but not the knees; no matter if due to active arthritis or contractures. No significant correlations were found between PA of JIA-children and reported pain ($p=0.59$) and hypermobility ($p=0.58$).

Conclusion: Accelerometer-assessed PA-levels of JIA-children were significantly lower than those of normative controls. LOM of hips and ankles, but surprisingly not the knees, were significantly associated with impaired PA. This emphasizes the importance of obtaining full ROM specifically in hips and ankles of JIA-children for the purpose of adequately participating in sport activities.

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Establishing Clinical Meaning and Defining Important Differences in Patient Reported Outcome Measures of Physical Function, Fatigue and Pain Interference in Juvenile Idiopathic Arthritis. Esi Morgan DeWitt[1], Bin Huang[2], Kimberly Barnett[1], Adam Carle[1], Constance Mara[1] and Karon Cook[3]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center/University of Cincinnati School of Medicine, Cincinnati, OH, [3]Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Patient reported outcome measures (PROs) are used increasingly in clinical care. A framework to interpret scores according to degree of clinical severity would enhance their practical use. Furthermore, use of PROs in evaluation of treatment effectiveness over time requires establishment of minimal important differences (MID) in change scores.

Methods: We identified clinical severity thresholds and MID for measures of mobility, upper extremity function, fatigue, and pain interference working with patients with juvenile idiopathic arthritis (JIA) and parents of JIA patients using standard setting methodology modified from educational testing. Data from Patient-Reported Outcomes Measurement Information System (PROMIS) item bank longitudinal validation collected on 121 JIA patients was used to develop clinical vignettes across a range of symptom severity. Vignettes were created based on most likely item responses at different levels on the T score metric [mean = 50; SD = 10]. Vignettes were anchored at 5-point intervals (0.5 SDs). Parents and patients participated in separate one-day meetings. Vignettes were ordered and placed on cards. Panelists identified adjacent vignettes considered to represent upper and lower boundaries separating category cut points (i.e., none /mild problems, mild/moderate, moderate/severe). Cut scores were defined as mean score for boundary vignettes. To define MIDs panelists responded to items to represent "just enough improvement to make a difference". Average change scores served as estimates of MID.

Results: For pain interference, mobility, and upper extremity function patients set higher cut points for severity than parents, typically by 0.5 SD. Parents tended to set higher MID scores than JIA patients. Size of MID varied according to severity classification of the symptom. MIDs estimated by the panelists were typically larger than the MIDs determined using statistical methods.

Conclusion: We used a modified educational standard setting method to estimate clinically relevant cut points to classify severity for PROMIS measures of mobility, upper extremity, fatigue and pain interference. Parallel exercises identified these cut points from the perspectives of patients with JIA and parents of a child with JIA. We explored a novel means of determining MID from the patient/parent perspective. This allows for meaningful interpretation of PROMIS measures in a clinical setting. In summer 2014, the method will be repeated with clinicians serving as panelists. Results will be compared across panel groups. MIDs generated by the 3 panelist groups and those generated statistically from the longitudinal study sample will be compared.

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Patient-Reported Outcomes in Children with Moderately to Severely Active Polyarticular or Polyarticular-Course Juvenile Idiopathic Arthritis Who Are Prescribed and Treated with Adalimumab. Gerd Horneff[1], Carol A. Wallace[2], Pierre Quartier[3], Daniel J. Kingsbury[4], Kirsten Minden[5], Mareike Bereswill[6], Vishvas Garg[7], Hartmut Kupper[6] and Jasmina Kalabic[6]. [1]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [2]University of Washington School of Medicine and Seattle Children's Hospital, Seattle, WA, [3]IMAGINE Institute, Hôpital Necker-Enfants Malades, Assistance Publique Hôpitaux de Paris, Université Paris-Descartes, Paris, France, [4]Randall Children's Hospital at Legacy Emanuel, Portland, OR, [5]Kinderklinik der Charite, Otto-Heubner Centrum, Berlin, Germany, [6]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany, [7]AbbVie Inc., North Chicago, IL.

Background/Purpose: Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases of childhood and adolescents, and improvement in health-related quality of life and functional disability is an important therapeutic goal in the treatment of patients (pts) with JIA. The objective was to evaluate pt-reported outcomes (PROs) in pts with moderately to severely active polyarticular or polyarticular-course JIA (pJIA) who are prescribed and treated with adalimumab (ADA) ± methotrexate (MTX) in routine clinical practice.

Methods: This is an ongoing, multicenter, non-interventional, observational registry of pts diagnosed with moderately to severely active pJIA that are prescribed and treated in a routine clinical setting with either ADA±MTX or MTX alone. Pts with resistant disease, that had received prior MTX treatment, were prescribed and treated with ADA as second line therapy. A cohort of pts with prescribed MTX, naïve to biologics, served as controls. Physical function was measured by the Disability Index of Childhood Health Assessment Questionnaire (DICHAQ), which ranges from 0 (no disability) to 3 (worst disability), and the minimal clinically important difference for improvement is -0.188. Quality of life was assessed by the Child Health Questionnaire-Parent Form (CHQ-PF50), with a scale of 0 (worst possible health state) to 100 (best possible health state). The currently study is limited using data up to 12 months, and all data are as observed.

Results: 842 pts (540 in ADA arm/302 in MTX arm) were enrolled and treated in the registry. The majority of the pts were female (76% and 69% for MTX and ADA, respectively). The mean age at baseline was 9.6 and 12.2 yrs and the mean pJIA disease duration at baseline was 1.3 and 3.7 yrs for MTX and ADA arms, respectively. At baseline mean DICHAQ was 0.62 for both MTX and ADA treatment arms. For those pts with data at both baseline and 12 months, the mean change in DICHAQ was -0.24 and -0.22 for the MTX and ADA arms, respectively, indicating a clinically meaningful difference. From baseline to 12 months, the scores of the individual health concepts in the CHQ-PF50 increased for both the MTX and ADA treatment arms, with the exception of Family Cohesion, as the scores had little change over time (Table). Parental emotional impact had a substantial increase as mean scores changed from 57.8 to 73.0 and 57.0 to 68.8 in the MTX and ADA treatment arms from baseline to 12 months, respectively.

Table Summary of Child Health Questionnaire Parent Form (CHQ-PF50)

	Baseline		Month 12	
	MTX	ADA ± MTX	MTX	ADA ± MTX
Global Health				
Mean (SD)	73.1 (22.7)	63.1 (25.6)	80.8 (17.6)	73.5 (21.4)
n	287	466	158	282
Physical Functioning				
Mean (SD)	73.1 (27.5)	71.8 (28.2)	86.1 (21.1)	81.8 (25.9)
n	295	473	171	297
Role/Social Limitations – Emotional/ Behavioral				
Mean (SD)	84.7 (26.1)	79.9 (27.9)	92.3 (17.7)	89.8 (20.1)
n	293	472	170	296
Role/Social Limitations – Physical				
Mean (SD)	78.9 (29.7)	75.0 (30.3)	90.7 (20.6)	86.9 (25.9)
n	292	472	170	295
Bodily Pain/Discomfort				
Mean (SD)	54.8 (26.4)	53.3 (28.3)	75.1 (24.2)	70.2 (27.0)
n	295	473	171	296
Behavior				
Mean (SD)	75.3 (17.2)	77.2 (16.3)	80.5 (14.7)	80.4 (17.2)
n	293	472	170	296
Global Behavior				
Mean (SD)	80.3 (19.6)	79.6 (19.8)	81.9 (18.8)	80.9 (19.7)
n	276	441	140	263
Mental Health				
Mean (SD)	74.8 (16.3)	74.7 (17.6)	79.6 (15.1)	78.8 (16.6)
n	293	470	171	295
Self Esteem				
Mean (SD)	78.6 (19.9)	75.5 (20.9)	84.7 (17.2)	9.5 (20.8)
n	290	470	169	294
General Health Perceptions				
Mean (SD)	60.0 (18.1)	53.0 (17.4)	61.2 (17.7)	55.5 (18.1)
n	295	471	171	294
Change in Health				
Mean (SD)	2.8 (1.3)	3.3 (1.4)	4.3 (0.9)	4.2 (1.0)
n	291	463	166	280
Parental Impact – Emotional				
Mean (SD)	57.8 (26.3)	57.0 (26.9)	73.0 (21.5)	68.8 (25.6)
n	294	472	169	295
Parental Impact – Time				
Mean (SD)	77.5 (25.6)	76.6 (27.2)	87.1 (19.9)	83.7 (22.1)
n	294	472	169	293
Family Activities				
Mean (SD)	77.6 (22.0)	78.6 (21.7)	86.8 (16.4)	85.0 (18.9)
n	294	472	169	295
Family Cohesion				
Mean (SD)	80.7 (19.4)	76.8 (20.9)	79.5 (21.3)	77.4 (22.1)
n	293	469	169	291

Conclusion: Over the course of 12 months of treatment, pts with pJIA in the ADA treatment arm demonstrated clinically meaningful improvements in functional disability as well as an increase in the scores of the individual health concepts, indicating an improvement in health-related quality of life. The extent of improvement was comparable to that in the MTX treatment arm.

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Patterns of Active Joint Involvement in JIA. Simon W.M. Eng[1], Mira Van Veenendaal[2], Alan M. Rosenberg[3], Kiem Oen[4], Quaid Morris[1] and Rae S.M. Yeung[2]. [1]University of Toronto, Toronto, ON, [2]The Hospital for Sick Children, Toronto, ON, [3]University of Saskatchewan, Saskatoon, SK, [4]University of Manitoba, Winnipeg, MB.

Background/Purpose: JIA encompasses a set of heterogeneous diseases with chronic joint inflammation. Although the ILAR criteria consider joint counts, they do not reflect specific joint involvement patterns. We sought to study these patterns, through unsupervised pattern recognition techniques, to better characterize homogeneous subpopulations of children with JIA.

Methods: Principal component analysis was conducted on baseline joint involvement data from 807 treatment-naive patients satisfying the ILAR criteria to identify composite variables, or principal components (PCs), that distinguish patients from each other. Cluster analysis was conducted on patient PC scores to identify signatures of joint involvement.

Results: 4 PCs were identified that explained 46% of variance among patients. The PCs summarized (1) overall joint count, (2) finger vs. toe involvement, (3) large vs. small joint involvement, and (4) SI joint involvement. On these PCs, 12 distinct signatures were identified whose "fingerprints" or defining characteristics are depicted in Figure 1. These signatures described joint involvements based on clinically meaningful combinations of characteristics given by the PCs. The signatures were clearly able to distinguish homogeneous patient subpopulations both within and between ILAR subtypes based on joint involvement (Figure 2).

Conclusion: Our analysis recovered distinct patterns of joint involvement in an assumption-free manner that will be useful in defining homogeneous patient subpopulations within and across the ILAR subtypes in JIA.

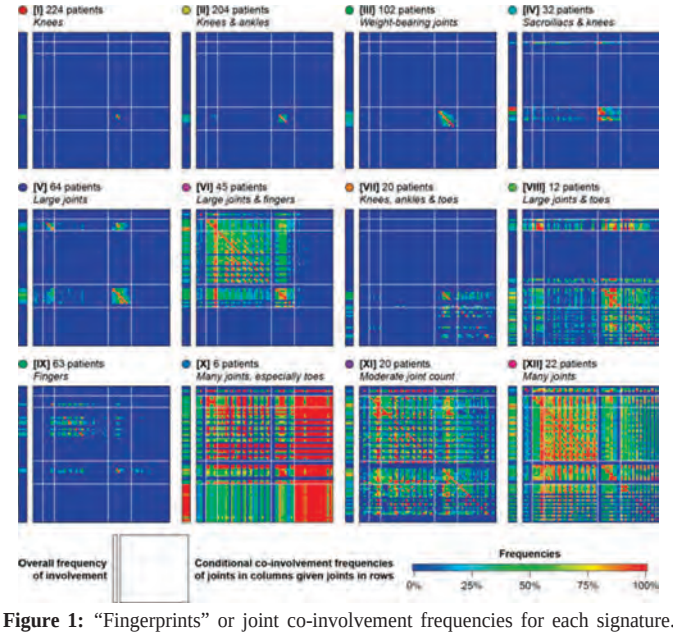

Figure 1: "Fingerprints" or joint co-involvement frequencies for each signature. Vertical heat maps represent overall frequencies of joint involvement among patients in each signature. Square matrices represent frequencies of involvement of joints in columns given the involvement of joints in rows.

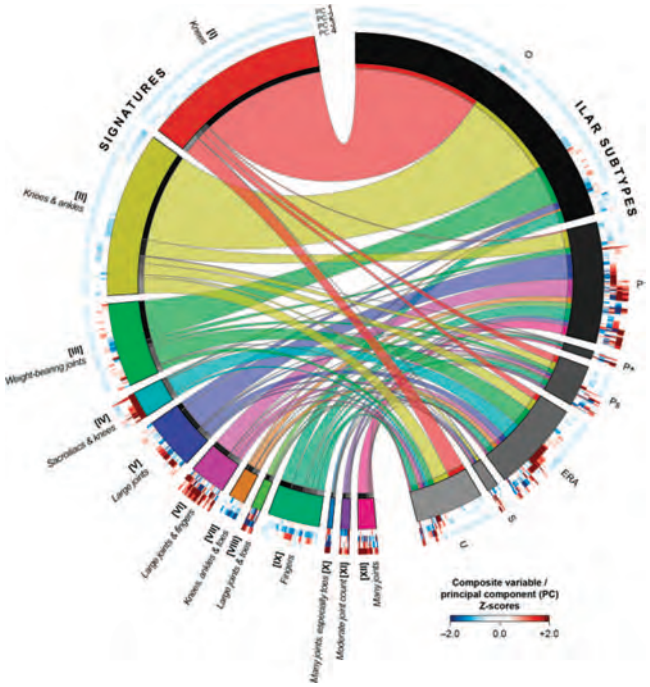

Figure 2: Relationships between the signatures and ILAR subtypes. Heat maps (outermost rings) depict PC scores for each patient. The innermost ring depicts the ILAR subtype composition of each signature and signature composition of each ILAR subtype. Ribbons link patients between signatures (left) and ILAR subtypes (right).

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Development of a Serious Game Designed for Children with Juvenile Idiopathic Arthritis. Jean-David Cohen[1], Damien Bentayou[2], Marcantoine Bernard-Brunel[2] and Sonia Tropé[3]. [1]CHU LAPEYRONIE, MONTPELLIER, France, [2]CG Artist, PESSAC, France, [3]ANDAR, Paris, France.

Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is the most common chronic paediatric rheumatic disease and cause of physical and psychological disability, with family and school consequences.

If the advances in therapeutics as biologicals have revolutionized the outcome of children with JIA, it is necessary to develop educational materials to increase their independence and improve their quality of life.

Information about the disease and treatments, the ability to cope with difficult situations, having good reflexes concerning biotherapies are all skills needed to live well the disease every day.

Democratization of computers and smart phones has led us to develop a serious game for children as an educational learning instrument.

Methods: The game was developed according to the steps of Assessment, Design, Development, Implementation, and Evaluation (ADDIE model).

A steering committee was formed with a pediatric rheumatologist, a patient organization and an agency of video game developers including an art director, a lead programmer and a graphist.

Decisions were strained by a limited budget support.

The National Association against Rheumatoid Arthritis initiated the project and provides funding, manages logistics and monitoring.

The pediatric rheumatologist initially established a series of themes to be developed in accordance with the association and transmitted scientific data to developers.

The developers have proposed animations and graphics, game plays.

The committee has defined the specifications at different points during physical meetings and conference calls:

- Format
- Themes and key messages
- Graphics (places, people)

Results:

The committee has decided to create an adventure game with differents interactives activities.

The following directions have been validated:

- Development of a serious game powered by Unity¨ for computers, smartphones and tablets to allow use in all places (waiting rooms), designed to run on the IOS (apple) and Android operating systems.
- Definition of key messages and themes: family, school, sport, hospital, rehabilitation, treatment, further investigations.
- Graphic choices:

á Hospital (single place with the greatest number of possible themes)

á Two avatars (one boy, one girl) to facilitate the identification of players.

Conclusion: To our knowledge, this is the first application dedicated to JIA.

To ensure the appropriateness of its speech, its ergonomics and ease of use, the global level of satisfaction, a neuropsychiatrist and the KOURIR organization (parents of children with JIA), will evaluate the beta version.

Adaptations would be made prior to the release of the game. Eventually, other game trays could complement this version in the future (adding school and home).

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Flares in Children with JIA: Results from the Reacch-out Cohort. Lori B. Tucker[1], Jaime Guzman[1], Kiem Oen[2] and ReACCh Out Investigators[3]. [1]BC Children's Hospital and University of British Columbia, Vancouver, BC, [2]Children's Hospital of Winnipeg and University of Manitoba, Winnipeg, MB, [3]BC Children's Hospital, Vancouver, BC.

Background/Purpose: Disease flares are a concern to patients with JIA, their parents, and caregivers alike; but little is known of disease manifestations during a flare in children who have achieved inactive disease (ID) or whether flares differ among subtypes. The aim of this study is to describe flares in children with JIA and determine differences in flare characteristics among JIA subtypes.

Methods: We studied children diagnosed with JIA between 2005 and 2010 who had at least one visit with ID (no active joints, no extra-articular manifestation, and a physician global assessment $<$ 10mm) while being prospectively followed in the Research in Arthritis in Canadian Children

emphasizing Outcomes (ReACCh-Out) cohort. They received usual pediatric rheumatology care at 16 Canadian centres. Flare was defined as loss of any criteria for ID. In addition a flare was imputed on the basis of an intra-articular injection alone in absence of other documentation of disease activity. Treatment of flares were recorded if there was a change, addition, or restart of anti-rheumatic or anti-uveitis treatment.

Results: Of 1492 children recruited in ReACCh-Out, 1146 had at least one visit with ID, with median follow-up of 24 mo (IQR 12,39) following first record of ID. A total of 1,191 flares were observed in 531 children (46.3%) after their first ID episode: 31% with systemic JIA and 44–50% with other subtypes. Arthritis was a feature of the majority of flares but there were significant differences in frequencies across subtypes ($p=0.001$). Frequencies of nonarticular flares also differed among subtypes ($p<0.001$) and were most common in children with systemic, enthesitis related arthritis and undifferentiated subtypes. Flares due to uveitis were seen in patients with oligoarticular, rheumatoid factor negative, and undifferentiated subtype most commonly. The majority of flares occurred while patients were still on treatment for their JIA and overall 45% were not associated with treatment changes (Table).

Table: Characteristics of disease flare across JIA subtypes

Feature	All	Systemic	Oligo	RF neg	RF pos	Psoriatic	ERA	Undiff
# subjects	1146	68	488	212	35	75	155	113
# subjects with flare	531	21	232	106	17	36	69	50
# flares	1191	82	483	233	56	70	133	134
Flare signs (% of flares):								
Arthritis flares	79	58.5	83	85	93	86	63	72
Non-articular flares	18	41.5	13	12	7	14	35	22
PGA $\geq$ 1 without other signs	10	29	8	7	7	9	13.5	7.5
Treatment at time of flare (% of flares):								
Flare on treatment	70	91.5	56.5	83	86	60	78	71
Flare off treatment	27	7	39	15.5	14	40	19.5	25
No change in treatment following flare	45	66	40	48	50	46	48	37

Conclusion: Flare characteristics in JIA differ among disease subtypes. An increase in PGA alone accounts for flare some patients, suggesting that PGA includes consideration of disease manifestations not included in our flare definition. Our results suggest that while disease flares occur in approximately half of children with JIA managed with usual care, many are mild and require no treatment change.

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Long Term Functional Outcome and Quality of Life of Patients with Refractory Juvenile Idiopathic Arthritis Treated with Etanercept: Results of the Dutch Arthritis and Biologicals in Children Register. Janneke Anink[1], Femke Prince[1], Maryanne Dijkstra[1], Marieke H. Otten[1], Marinka Twilt[2], Rebecca ten Cate[3], Simone Gorter[4], Yvonne Koopman-Keemink[5], Marion A.J. Van Rossum[6], Esther P.A. Hoppenreijs[7] and Lisette W.A. van Suijlekom-Smit[1]. [1]Erasmus MC Sophia Children's Hospital, Rotterdam, Netherlands, [2]Aarhus University Hospital, Aarhus, Denmark, [3]Leiden University Medical Center, Leiden, Netherlands, [4]Maastricht University Medical Center, Maastricht, Netherlands, [5]Hagaziekenhuis Juliana Children's Hospital, The Hague, Netherlands, [6]Reade, location Jan van Breemen, Amsterdam, Netherlands, [7]Radboud University Medical Center, Nijmegen, Netherlands.

Background/Purpose: Juvenile idiopathic arthritis patients refractory to methotrexate are eligible for treatment with biologic agents. A longitudinal sub-analysis (n=53) of the Dutch Arthritis and Biologicals in Children register previously showed that disability and health related quality of life (HRQoL) improved shortly after treatment with etanercept. Our aim was to investigate long term functional outcome, HRQoL and treatment changes in the same patients, who started etanercept >5 years ago.

Methods: Patients were traced and questioned on education and employment. Data on recent disease status, comorbidities and structural damage were retrieved. Disability was assessed by (Child) Health Assessment Questionnaire ((C)HAQ), HRQoL was measured by Child Health Questionnaire, Short Form 36 and Health Utilities Index Mark 3. Linear mixed models were used to analyze changes over time.

Results: 43 patients (81% response) started etanercept median 8.5 years (IQR: 7.7–10.3) ago. Median age was 22 years (IQR: 18–24). 42% had a (C)HAQ of 0.00. HRQoL was similar to HRQoL shortly after start of etanercept, except for the domains bodily pain and general health perception, which deteriorated to levels comparable to those at start of etanercept. VAS pain also worsened (median 12 (IQR:2–43)), but not to the extent as the bodily pain domain on the SF-36.The unemployment rate (12%) was comparable to the general population; educational level was higher (77% of patients >17 years had achieved at least upper secondary education). 40% of patients switched to other biologic agents, 40% were still using etanercept and 20% were off anti-rheumatic treatment. 14% had had joint surgery. There were no reports of malignancies.

Conclusion: The improvement in HRQoL after start of etanercept was sustained after 8.5 years. Disability was low. On many aspects of daily life, patients functioned comparably to or better than the general population. The need for surgery for 14% of patients stresses the importance of early treatment of JIA. Chronic pain - even when the disease is inactive - remains an important issue that should not be overlooked.

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Long-Term Pharmacokinetics of Body Surface Area-Adjusted Doses of Golimumab Following Repeated Subcutaneous Administrations in Pediatric Patients with Polyarticular Juvenile Idiopathic Arthritis. Jocelyn H. Leu, Alan M. Mendelsohn, Joyce Ford, Hugh M. Davis, Honghui Zhou and Zhenhua Xu. Janssen Research & Development, LLC., Spring House, PA.

Background/Purpose: To assess the pharmacokinetics (PK) and PK-efficacy correlations of body surface area (BSA)-adjusted dosing of 30 mg/m^2 golimumab administered subcutaneously (SC) every 4 weeks (q4w) + methotrexate (MTX) through Week 48 in pediatric patients (ages 2 to <18 years) with juvenile idiopathic arthritis (JIA).

Methods: GO-KIDS is a randomized-withdrawal, double-blind, placebo-controlled, parallel-group, multicenter Phase 3 trial of SC golimumab 30 mg/m^2 (maximum 50 mg) q4w + MTX (10–30 mg/m^2/week) in pediatric patients with active JIA despite current MTX therapy (median 15 mg/week). PK, safety, and efficacy evaluations were performed q4w through week 16. At Week 16, patients who were ACR JIA 30 responders were randomized (1:1) to 30 mg/m^2 golimumab or placebo q4wks through Week 48 with GLM reinstituted upon flare (defined as per JIA ACR flare criteria) or initiation of new DMARDS, biologics, systemic immunosuppressives. Serum trough concentrations were also obtained at Weeks 12, 16, 24 and 48. Serum golimumab trough concentrations for 154 patients were determined via a validated immunoassay. The relationships of ACR pediatric 30 response and disease flare status with steady-state trough levels at Week 48 were assessed.

Results: Trough serum golimumab concentrations in patients receiving SC 30 mg/m^2 golimumab q4w through Week 48 were maintained over time. Steady-state trough golimumab levels were similar across different age groups, and were also similar to those seen in adult RA patients who received 50 mg SC q4w in Phase III clinical trials. There were no apparent differences in pediatric ACR JIA 30 response rates and disease flare rates among the 4 groups of JIA patients categorized by the 4 quartiles of steady-state trough golimumab levels at Week 48. In addition, there were no apparent PK differences between patients who did and did not experience disease flares in the randomized golimumab group. Mean (SD) and median trough serum golimumab concentrations (mg/mL) by age groups and body weight quartiles are presented in the table.

Conclusion: Treatment with 30 mg/m^2 SC golimumab q4w + MTX resulted in sustained steady-state trough serum golimumab concentrations over time. The PK/efficacy correlation analyses demonstrated that the BSA-adjusted dosing regimen of 30 mg/m^2 SC golimumab q4w provided adequate drug exposure for the desired efficacy.

	Age Groups (Years)			
	2-6	≥6 to 12	≥12	Combined
Week 12				
Mean (SD)	1.42 (0.744)	0.95 (0.593)	1.21 (0.711)	1.14 (0.685)
Median	1.77	0.92	1.29	1.16
Week 16				
Mean (SD)	1.17 (0.650)	0.96 (0.721)	1.24 (0.836)	1.13 (0.780)

Median	1.22	0.89	1.23	1.10
Week 24				
Mean (SD)	1.30 (0.833)	1.08 (0.876)	1.23 (1.003)	1.19 (0.927)
Median	1.57	1.12	1.08	1.12
Week 48				
Mean (SD)	0.86 (0.574)	0.95 (0.715)	1.19 (0.777)	1.08 (0.736)
Median	0.87	0.73	1.25	0.95
		Body Weight Quartiles (kg)		
	≤26.80	>26.80 to ≤43.00	>43.00 to ≤56.80	>56.80
Week 12				
Mean (SD)	1.09 (0.723)	1.09 (0.622)	1.54 (0.649)	0.90 (0.642)
Median	1.13	1.09	1.49	0.83
Week 16				
Mean (SD)	0.99 (0.622)	1.07 (0.739)	1.60 (0.845)	0.99 (0.806)
Median	0.90	1.12	1.76	0.89
Week 24				
Mean (SD)	0.91 (0.799)	1.38 (0.780)	1.52 (1.243)	1.05 (0.844)
Median	0.61	1.37	1.42	1.00
Week 48				
Mean (SD)	0.74 (0.468)	1.22 (0.852)	1.59 (0.498)	0.94 (0.789)
Median	0.75	1.10	1.55	0.81

Disclosure: J. H. Leu, Janssen Research & Development, LLC., 3; **A. M. Mendelsohn**, Janssen Research & Development, LLC., 3; **J. Ford**, Janssen Research & Development, LLC., 3; **H. M. Davis**, Janssen Research and Development, LLC, 3; **H. Zhou**, Janssen Research and Development, LLC., 3; **Z. Xu**, Janssen Research and Development, LLC, 3.

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Intra-Articular Corticosteroid Injections in Juvenile Idiopathic Arthritis: Results from a UK Prospective Collaborative Study. Eileen Baildam[1], Roberto Carrasco[2], Susannah Holt[3], Helen Foster[4], Lucy R. Wedderburn[5], Alice Chieng[6], Joyce Davidson[7], Yiannis Ioannou[8], Kimme L. Hyrich[9] and Wendy Thomson[10]. [1]Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [2]The University of Manchester, Manchester, United Kingdom, [3]Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [4]Professor of Paediatric Rheumatology, Newcastle Upon Tyne, United Kingdom, [5]UCL, UCLH, GOSH NHS Trust, London, United Kingdom, [6]Royal Manchester Children's Hospital, Manchester, United Kingdom, [7]Royal Hospital for Sick Children, Glasgow, United Kingdom, [8]Arthritis Research UK Centre for Adolescent Rheumatology, University College London, London, United Kingdom, [9]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, [10]Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Intra-articular corticosteroid injections (IACI) are a standard treatment in juvenile idiopathic arthritis (JIA). This study assessed response to IACI in a large prospective cohort of children and young people (CYP) recruited at initiation of treatment.

Methods: Participants were in the Childhood Arthritis Prospective Study (CAPS), an on-going prospective inception cohort study in 7 UK paediatric rheumatology centres, recruiting CYP <16 years with new inflammatory arthritis persisting for ≥ 2 weeks. Demographics, disease features, joint count, treatment details, Childhood Health Assessment Questionnaire (CHAQ), physician's global assessment (PGA), parent's general evaluation of well-being (PGE), ESR are collected at first presentation, 6 months, then yearly.

Results: Of 1477 CYP recruited to CAPS 759 completed 3 years follow-up and 603 (79.5%) were treated with IACIs. 185 (24.4%) required IACI alone (with a single episode of injection as the only treatment in 100, (13 % of the total cohort) usually the knee in 80 %. Most injected patients required additional treatments, 393 (69.3%) commenced a DMARD or biologic agent. Of these, 93 patients received both DMARD/ biologic and IACI at the same time.

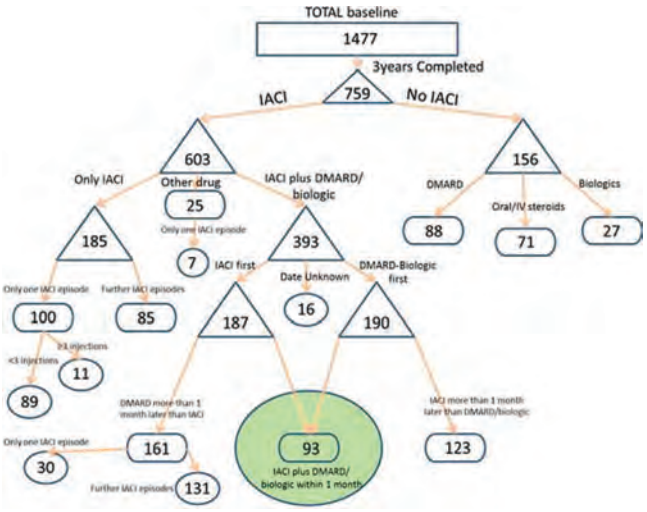
Of the 185 patients treated only with IACI, 85 had more than one episode of injections. For this group the median time to first injection was 14 days (IQR 6.36) and time from first to second injection was 318 days (IQR 162–525) illustrating a prolonged effect from the first injection.

390 of the 759 patients completing 3 years of follow-up had oligoarticular JIA of whom 332 (85%) received steroid injections, 163 (42%) treated exclusively with IACI 85 (25%) receiving only one episode of injection.

Baseline predictors of the need for DMARD in addition to IACI were a higher total active and limited joint counts, ESR, physician's global and the CHAQ score ($p<0.0001$), and pain scores ($p<0.003$).

Conclusion: Approximately one quarter of patients required monotherapy with IACI alone. Only 13% of all patients and 25% of oligo-articular course patients were managed with a single injection. Higher measures of disease activity were significantly associated with the need for DMARD therapy in addition to IACI.

Baseline Characteristics	Only IACI, only 1 episode (N=100)	Had IACI plus DMARD (N=393)	P value
Age (Median, IQR)	6.75 (3.82, 11.2)	7.05 (3.3, 10.9)	0.9
Female (n, %)	57 (57)	276 (70.4)	0.01
Ethnicity (White, n, %)	96 (96)	364 (92.8)	0.09
Disease duration (Median, IQR), months	5.5 (3.07, 10.4)	5.4 (2.9, 10.6)	0.99
Active joint counts (Median, IQR)	1 (1, 2)	4 (1, 8)	<0.0001
Limited joint counts (Median, IQR)	1 (0.5, 1)	2 (1, 5)	<0.0001
PGE (Median, IQR) (100mm VAS)	19.5 (3, 49)	27 (9, 50)	0.1
PGA (Median, IQR) (100mm VAS)	20.5 (10, 30)	36 (21, 60)	<0.0001
ESR (Median, IQR)	9 (5, 25)	30 (12, 56)	<0.0001
CHAQ (Median,IQR) (0-3)	0.5 (0.125, 1.625)	1 (0.375, 1.625)	0.0001
Pain (Median, IQR) (100mm VAS)	23 (8, 50)	45 (16, 65)	0.003
Time to 1st steroid injection (days)	36 (13, 82)	38.5 (14, 135.5)	0.60



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Countermeasures Against Methotrexate Intolerance in Juvenile Idiopathic Arthritis Instituted By Parents Show No Effect. Andrea Scheuern, Nadine Fischer, Johannes-Peter Haas and Boris Hugle. German Center for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany.

Background/Purpose: Methotrexate (MTX) is the mainstay treatment in the therapy of children with juvenile idiopathic arthritis (JIA) and can lead to prolonged remission and improved quality of life. However, JIA patients frequently develop intolerance to MTX, with anticipatory and associative gastrointestinal adverse effects before drug intake arising as a conditioned response. Parents frequently try to alleviate these symptoms with a variety of countermeasures reported to help against nausea.

The objective of this study was to investigate the course of MTX intolerance in pediatric patients over a period of 6 months, as well as the effect of countermeasures by parents on the severity of MTX intolerance.

Methods: Consecutive patients admitted to the German Center for Pediatric and Adolescent Rheumatology from October 2012 until April 2014 were included in this study. MTX intolerance was measured using the validated Methotrexate Intolerance Severity Score (MISS) questionnaire. Inclusion criteria were 1) diagnosis of JIA, 2) treatment with MTX for at least 3 months prior to inclusion, and 3) confirmation of MTX intolerance by a MISS value of ≥ 6. Exclusion criteria were other diseases leading to nausea and/or abdominal complaints, and concomitant medications possibly inducing nausea (excepting biologics and non-steroidal anti-inflammatory drugs).

Methotrexate dose, MISS and countermeasures instituted by the parents were determined at 4 time points (at inclusion, at 6 weeks, 3 months and 6 months). Countermeasures were classified into 4 criteria: antiemetic drugs, covert dosing, taste masking and complementary medicine. **Results** were analyzed using descriptive statistics and non-parametric testing (Wilcoxon signed rank test).

Results: 38 patients were included (63% female, median age at inclusion 11.7 years, median disease duration 7.1 years). Average MISS at inclusion was 10.8 ± 4.1, and after 6 months 12.2 ± 7.2 (p = 0.316). In 6/38 patients (16%), MTX was reduced or discontinued during the study. In 89 time intervals between study visits, 40 countermeasures were introduced by the parents.

Countermeasure	n	MISS before introduction	MISS after introduction	p
Antiemetic drugs	9	10.56	13.78	.080
Covert dosing	11	12.64	12.64	.766
Taste masking	9	11.67	13.22	.120
Complementary medicine	11	12.73	14.18	.089

Conclusion: If MTX intolerance is present, symptoms will not decrease over the course of 6 months. Various modalities used by the parents as countermeasures against nausea show no discernible effect.

Disclosure: A. Scheuern, None; **N. Fischer**, None; **J. P. Haas**, None; **B. Hugle**, None.

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S100 Proteins in Oligoarticular Juvenile Idiopathic Arthritis. Alexandra R Aminoff[1], Carol A Wallace[1], Sarah Ringold[1], Anne Stevens[2] and Jessica M Foster[3]. [1]Seattle Children's Hospital/Univ of Washington, Seattle, WA, [2]Seattle Children's Hospital, Seattle, WA, [3]Seattle Children's Research Institute, Seattle, WA.

Background/Purpose: There is a lack of reliable biomarkers that correlate with active juvenile idiopathic arthritis (JIA). The S100A8/A9 heterodimer (calprotectin) and S100A12 are proinflammatory molecules that have been shown to correlate with risk of relapse in JIA. Our objectives were to compare calprotectin and S100A12 levels in children with newly diagnosed oligoarticular JIA to those of healthy controls and to determine whether baseline levels of these proteins in oligoarticular JIA are associated with disease course.

Methods: This was a prospective, observational cohort study of newly diagnosed oligoarticular JIA patients at Seattle Children's Hospital. Plasma calprotectin and S100A12 levels were measured using commercially-available enzyme-linked immunosorbent assay (ELISA) kits and compared to healthy pediatric controls using the Wilcoxon rank sum test.

Results: The oligoarticular JIA cohort (n=25) was 68% female, with a mean age of 5.6 years (range 2.1–14.4 years) and the historic pediatric control group (n=30) was 67% female, with a mean age of 9.1 years (range 1.3–13.4 years). The oligoarticular JIA cohort had significantly elevated calprotectin levels (median 1246 ng/ul, range 202–5694) compared to controls (median 730 ng/ul, range 124–1668), p value 0.005. For S100A12, the oligoarticular JIA cohort again had significantly elevated levels (median 48,800 pg/ml, range 0–350,400) compared to controls (median 13,400 pg/ml, range 0–178,700), p value=0.002.

Conclusion: Patients with oligoarticular JIA have significantly higher calprotectin and S100A12 levels at the time of diagnosis compared to healthy controls. A longitudinal analysis is underway to determine if these baseline S100 protein levels correlate with subsequent disease course. A reliable biomarker to aid in the prediction of disease course at diagnosis would potentially allow providers to identify children who would benefit from earlier aggressive therapy.

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Long-Term Impact of Juvenile Idiopathic Arthritis in the Greek adults' Psychosocial Life. Despoina Dimopoulou[1], Maria Trachana[2], Polyxeni Pratsidou-Gertsi[3], George Garyfallos[4], Prodromos Sidiropoulos[5], Athina Theodoridou[1] and Alexandros Garyfallos[1]. [1]4th Department of Internal Medicine, Aristotle University, Hippocratio Hospital, Thessaloniki, Greece, [2]Aristotle University, Thessaloniki, Greece, [3]1st Department of Pediatrics, Aristotle University, Thessaloniki, Greece, [4]2nd Department of Psychiatry Aristotle University, Thessaloniki, Greece, [5]University of Crete, Heraklion, Greece.

Background/Purpose: Juvenile idiopathic arthritis (JIA) seems to have a negative impact on patients' life style mostly due to the disease chronicity. No relevant data have been published for Greek young adults so far. /To capture the impact of disease burden in the psychosocial profile of adults with JIA, 17.2 years after disease onset.

Methods: A total of 96 (66 females) patients were enrolled. Psychosocial distress was assessed by the Greek version of the self-completed paper-based General Health Questionnaire (GHQ-28). A second questionnaire regarding marital status, education level and employment status was completed by all patients. Disease activity status at the last follow-up visit was assessed according to the Wallace's criteria while the level of disease activity by the Disease Activity Score-28 (DAS-28). The patient's assessment of global disease activity was measured on a Visual Analogue Scale (VAS) 0 to 10. Structural damage was scored by the the Juvenile Arthritis Damage Index-Articular (JADI-A) and by the Total modified Sharp/van der Heijde Score (TmSvdHS). Physical ability was assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI).

Results: The GHQ-28 case score depicted impaired psychosocial status in 18 patients (18.7%). The level of psychosocial distress was significantly correlated with DAS28 at the last follow up visit ($r=0.446$, $p<0.001$). The presence of disease activity was correlated with higher degree of depression ($p=0.032$) and social dysfunction ($p=0.008$). Interestingly, patients without or with mild physical disability (HAQ-DI=0–0.49) differed from those with moderate-to-severe disability (HAQ-DI=0.5–3) in the fields of somatization ($p=0.004$) and social dysfunction ($p<0.001$), but not of depression. Higher degree of depression was recorded in the unemployed patients ($p=0.018$) and in those with mandatory education ($p=0.018$). In contrast, structural damage (JADI-A, TmSvdHS), marital status and current use or duration of corticosteroid treatment didn't find to influence patients' psychosocial profile. Global disease activity rated by the patient was found to be the only significant predictor of psychosocial distress in the multivariate analysis [B=0.057 95%CI (0.017, 0.097), P=0.005].

Conclusion: Psychosocial distress is evident in a considerable proportion of the patients (~19%), indicating a constant impact of the disease on every-day life. The tight control of disease activity is therefore crucial in order to prevent symptoms of depression in these JIA adults.

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A Controlled Trial of Intra-Articular Corticosteroids with or without Methotrexate in Oligoarticular Juvenile Idiopathic Arthritis. Angelo Ravelli[1], Giulia Bracciolini[2], Sergio Davì[2], Angela Pistorio[2], Alessandro Consolaro[2], Sara Verazza[2], Bianca Lattanzi[2], Giovanni Filocamo[2], Sara Dalprà[2], Maurizio Gattinara[3], Valeria Gerloni[3], Antonella Insalaco[4], Fabrizio De Benedetti[5], Adele Civino[6], Luciana Breda[7], Loredana Lepore[8], Maria Cristina Maggio[9], Franco Garofalo[10], Silvia Magni-Manzoni[5], Donato Rigante[11], Antonella Buoncompagni[2], Marco Gattorno[2], Clara Malattia[1], Stefania Viola[2], Paolo Picco[2], Nicolino Ruperto[12] and Alberto Martini[1]. [1]Istituto Giannina Gaslini and University of Genova, Genova, Italy, [2]Istituto Giannina Gaslini, Genova, Italy, [3]Istituto Ortopedico Gaetano Pini, Milano, Italy, [4]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, [5]Ospedale Pediatrico Bambino Gesù, Roma, Italy, [6]Ospedale Cardinale G. Panico, Tricase, Italy, [7]Ospedale Policlinico, Chieti, Italy, [8]Istituto Burlo Garofolo, Trieste, Italy, [9]University of Palermo, Palermo, Italy, [10]Ospedale degli Infermi, Biella, Italy, [11]Università Cattolica Sacro Cuore, Rome, Italy, [12]Istituto Giannina Gaslini, Genoa, Italy.

Background/Purpose: In contrast with the numerous randomized controlled trials conducted in polyarticular or systemic juvenile idiopathic arthritis (JIA), little evidence-based information is available for oligoarticular JIA. As a result, the management of children with this subtype, which is the most prevalent in Western countries, is largely empiric. Intra-articular corticosteroid (IAC) injection is the therapy of first choice for oligoarthritis in many pediatric rheumatology centers. However, although IAC injections are usually highly efficacious, relapses of synovitis are common and sometimes occur only a few months after the procedure. It is still unclear whether concomitant administration of methotrexate (MTX) may increase and prolong the effectiveness of IAC injections. The aim of the study was to compare the efficacy of IAC injection administered as monotherapy or in association with MTX in children with oligoarticular JIA in a phase II, randomized, actively controlled, multicenter trial.

Methods: Inclusion criteria were oligoarticular JIA by ILAR criteria, age < 18 years, and parent informed consent. Patients who were previously treated with synthetic or biologic DMARDs, had undergone an IAC injection < 3 months, were newly injected only in 1 knee, or had active uveitis were excluded. Patients enrolled were randomized 1:1 to receive either IAC therapy alone (Arm 1) or IAC therapy plus MTX (Arm 2). MTX was given orally at 15 mg/m2/week (maximum 20 mg/week). All patients were followed for 12 months and were assessed at 3, 6 and 12 months. The primary outcome was synovitis flare, defined as recurrence, persistence or new onset of synovitis in 1 or more injected or uninjected (i.e. previously unaffected) joints. Flare rate/probability was compared by chi-square and Kaplan-Meier methods.

Results: A total of 207 patients (50 boys and 157 girls) were enrolled, 102 in Arm 1 and 105 in Arm 2. Fifteen patients lost to follow-up <6 months were included only in the intention-to-treat (ITT) cohort. Patients in arms 1 and 2 were comparable for demographic features and median number of injected joints (2 vs. 2). In the ITT cohort (n=207) flare of synovitis occurred in 133 patients (64.2%), 69 (67.6%) in Arm 1 and 64 (60.9%) in Arm 2 (p=0.31), whereas in the as-observed (AO) cohort (n=192) flare of synovitis occurred in 118 patients (61.4%), 64 (66%) in Arm 1 and 54 (56.8%) in Arm 2 (p=0.19). By Kaplan-Meier analysis, the probability of synovitis flare in the 2 treatment arms was comparable in both ITT and AO cohorts (log-Rank test: p=0.18 and 0.07, respectively). However, among the 118 patients who flared in the AO cohort, flare in injected joints occurred more frequently in Arm 1 than in Arm 2 (46/64, 71.9% vs. 29/54, 53.7%; p=0.04).

Conclusion: Flare of synovitis in injected joints occurred less frequently in patients who received concomitant MTX. However, the association of oral MTX did not increase the overall effectiveness of IAC therapy, owing to the high frequency of new onset of synovitis in uninjected joints. Trial registration identifying number: FARM7Y279L, AIFA, Italy.

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Patient-Reported Joint Count in Juvenile Idiopathic Arthritis: The Reliability of a Mannequin Format. Maryanne Dijkstra[1], Janneke Anink[1], Philomine A. van Pelt[2], Johanna M.W. Hazes[2] and Lisette W.A. van Suijlekom-Smit[1]. [1]Erasmus MC Sophia Children's Hospital, Rotterdam, Netherlands, [2]Erasmus MC, Rotterdam, Netherlands.

Background/Purpose: Juvenile idiopathic arthritis (JIA) is a common chronic disease, requiring regular monitoring. Patient-reported outcomes can assist monitoring, may promote patient self-management and can be useful in epidemiological surveys. Our objective was to evaluate reliability of a mannequin-format patient-reported joint-count in JIA, and to detect changes in agreement at a follow-up visit.

Methods: JIA patients aged 12–21 marked joints with active arthritis on a mannequin (see Figure 1) before their regular clinic visit. The physician performed a joint-count without having seen the patient's assessment. For two subsequent clinic visits, agreement between the physician and patient-reported joint-counts was assessed using Intraclass Correlation Coefficient (ICC) and kappa statistics. The ability of the patient-reported joint-count to discriminate between active and inactive disease was evaluated using positive and negative predictive values. Sensitivity to change was estimated using Pearsons's rho and standardized response mean (SRM).

Results: 75 JIA patients were included. In general, patients had a low number of active joints (median 1 joint, indicated by the physician). ICC was moderate (0.61) and kappas ranged from 0.3–0.7. At the follow-up (n= 53), kappas were similar; the ICC was 0.19. When a patient scored 0 joints, the physician confirmed this in 93–100%. When the patient marked ≥ 1 joints, the physician confirmed arthritis in 59–76%. Sensitivity to change was moderate (Pearson's rho: 0.44, p=0.001, SRM in worsening patients: 0.67).

Conclusion: Agreement between physician and patient on joint-counts was reasonable. Untrained patients tended to overestimate presence of arthritis when they marked active joints on a mannequin-format joint-count. When the patient indicated absence of arthritis, the physician usually confirmed this. The sensitivity to change was moderate for patients who worsened over time.The agreement did not improve at follow-up; future research should focus on the possibility of achieving this through training. For now, the patient-reported joint-count cannot fully replace the physicians' joint-count in clinical practice; it may be used in epidemiological studies with caution.

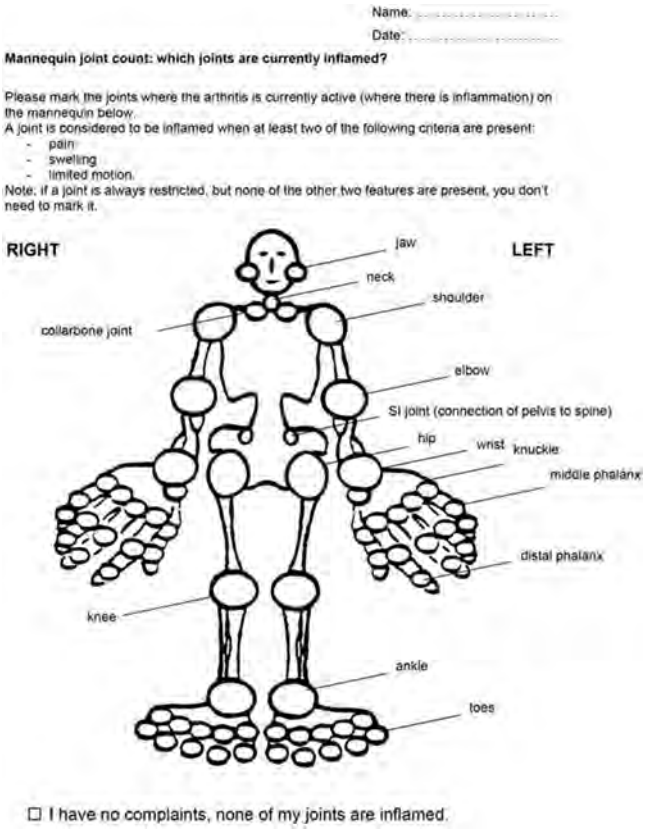

Figure 1 Mannequin (translated from Dutch)

Disclosure: M. Dijkstra, None; **J. Anink**, None; **P. A. van Pelt**, None; **J. M. W. Hazes**, None; **L. W. A. van Suijlekom-Smit**, Pfizer Inc, 2.

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Pregnancies in Females with Juvenile Idiopathic Arthritis (JIA) Who Were Exposed to Biologics and/or Methotrexate – Results from a Biologic Register. Katrin Stüdemann[1], Martina Niewerth[1], Jens Klotsche[1], Angela Zink[2], Gerd Horneff[3] and Kirsten Minden[4]. [1]German Rheumatism Research Center, Berlin, Germany, [2]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, [3]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [4]Charité University Medicine, Berlin, Germany.

Background/Purpose: JIA often continues into adult life and affects about 1 in 1,000 people of childbearing age. Little is known about the impact of JIA and its treatment with non-biologic (nb) and biologic (b) disease modifying antirheumatic drugs on pregnancy and its outcome. We therefore investigated pregnancy outcomes in females with JIA exposed to DMARDs.

Methods: Patients with a pregnancy history, who were enrolled in the JIA biologic registers BiKeR and JuMBO, were interviewed regarding pregnancy complications and outcomes. Prospectively collected patient-reported data on disease activity and functional status, and physician-reported data on treatment and pregnancy-related adverse events were also considered in the analyses.

Results: Out of 875 JIA patients followed into adulthood, 91 pregnancies were reported in 70 patients (58 females patients, 12 partners of male patients). Until June 2014, reports on pregnancies were evaluable for 50 females with 60 pregnancies. The majority had polyarticular JIA (72%), another 16% enthesitis-related arthritis. The median age at conception was 20.9 years (ys, range 13.8–29.0), the median disease duration 11.6 ys (range 3.3–26.1).

All patients were ever treated with bDMARDs (94%) and/or nbDMARDs (100%), 48% were exposed at conception (10 to

bDMARDs only, 10 to b and nbDMARDs, 4 to nbDMARDs only). In the group of DMARD exposed (n=25 pregnancies) and unexposed patients (n=35 pregnancies), pregnancy outcomes were as follows: 13 (52%) and 26 (74%) live births, 0 and 1 stillbirth, 1 and 0 extrauterine gravidity, 3 and 3 spontaneous abortions, 8 and 5 elective pregnancy terminations, respectively. DMARDs were discontinued in the exposed patients 4.9 weeks (median, range 2.7–22.3) after conception.

Of 39 pregnancies with live births, complications were reported in two-thirds of the cases, with similar frequency in exposed and unexposed patients. Most frequently reported complications were hyperemesis gravidarum, pregnancy diabetes, urinary obstruction, preterm contractions and hemorrhages (n=5 each). Almost half of the patients (48%) were delivered by Cesarean section. There were 3 pre-term deliveries and 3 small for gestational age neonates. The median birth weight was 3,110 grams (range: 1,080-4,150) after a median gestational age of 39.0 weeks (range: 30–42). No birth defects were reported. Two neonates required intensive neonatal care.

During pregnancy, disease activity of JIA remained stable or even improved in two-thirds of patients. Within the first 6 months after delivery, about half of women experienced a disease flare. Patients on DMARDs within the 3 months before conception had more often a disease flare than those not being exposed.

Conclusion: Exposure to DMARDs did not seem to increase the risk of adverse pregnancy outcomes, however, that needs to be confirmed in larger patient cohorts. Data suggest that severely affected JIA patients are at risk of pregnancy morbidity and instrumental delivery.

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Qualitative Assessment of Important Long-Term Outcomes in Juvenile Idiopathic Arthritis. Melissa L. Mannion[1], Michelle Williams[1], Gerald McGwin Jr. [1], Kenneth G. Saag[2] and Timothy Beukelman[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: JIA is not a childhood disease, but a chronic disease that begins in childhood. Long term outcomes that physicians and patients care most about may not be reflected by short term surrogate outcomes. The aim of this study was to identify and characterize the factors that pediatric rheumatologists use to define a successful disease outcome for JIA patients in young adulthood, with the ultimate goal of creating an outcome assessment tool to provide a gold standard for comparing different treatment approaches for JIA.

Methods: In depth interviews were conducted with pediatric rheumatologists to generate themes regarding successful treatment, acceptable disease states, and optimal disease management outcomes for young adults with JIA. Interviews were recorded and transcribed then coded via *in vivo* coding based on grounded theory resulting in mutually exclusive categories. Initial coding was for outcome themes and recoding for outcome descriptions to maintain the depth and meaning of the qualitative data.

Results: 13 pediatric rheumatologists from the US were interviewed; 8 were female, there was representation of all census regions and 54% had been practicing for more than 10 years. Coding for outcome theme identified 507 descriptive codes in 65 categories. These codes were regrouped into 14 outcome topics and quantized; chronic arthritis/joint damage, physical/functional, medication, pain/fatigue, expectations, vocation/profession, social/participation, daily life/activities of daily living, health, vision, family, independence, appearance, and mental health. The themes with the most codes were chronic arthritis/joint damage, physical/functional, and medication. The median number of outcome theme codes per physician was 28 with a range of 14 to 55. The outcome theme categories were quantized based on the number of participants who mentioned the category; the categories mentioned by all 13 practitioners were chronic arthritis/joint damage, physical/functional, and expectations followed by medication and pain/fatigue mentioned by 12 practitioners. Recoding for outcome description resulted in 157 codes in 9 mutually exclusive description categories; ability, active disease/remission, feel normal, everything that they want to do, understanding, satisfaction, indistinguishable from peers, and acceptance. The description categories with the most codes were ability and burden/interference. The median number of outcome description codes per physician was 12 with a range of 7 to 18. Ability and burden/interference were mentioned by all 13 physicians.

Conclusion: This study begins to characterize the factors that pediatric rheumatologists use to define a successful disease outcome for JIA in young adulthood. Physicians prioritized physical outcomes, function and medication adverse effects in the definition of successful JIA management. Further studies are needed to characterize the factors that the patients prioritize. With additional studies, the definition of a gold standard based on physician and patient input will enable patients to be better informed about their treatment options and expected future outcomes.

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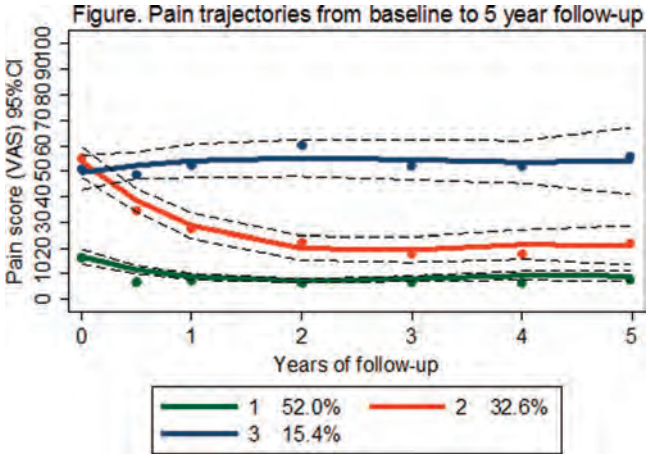
Predicting Chronic Pain in Children with Juvenile Idiopathic Arthritis: Results from the Childhood Arthritis Prospective Study. Amir Rashid[1], Kate Holliday[1], Lis Cordingley[2], Roberto Carrasco[1], Bo Fu[1], Helen E. Foster[3], Eileen Baildam[4], Alice Chieng[5], Joyce Davidson[6], Lucy Wedderburn[7], Kimme Hyrich[8] and Wendy Thomson[9]. [1]The University of Manchester, Manchester, United Kingdom, [2]Centre for Musculoskeletal Research, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [3]Newcastle University, Newcastle upon Tyne, United Kingdom, [4]Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [5]Royal Manchester Children's Hospital, Manchester, United Kingdom, [6]Royal Hospital for Sick Children, Glasgow, United Kingdom, [7]University College London (UCL), London, United Kingdom, [8]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [9]Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom.

· **Background/Purpose:** Pain is the most common symptom of JIA and has been associated with disease activity. However, disease activity has only accounted for a small amount of the variance in pain. This suggests predictors beyond clinical factors may be important in determining pain. The objectives of this study were to predict, at first presentation, children who are likely to have poor pain outcomes and how these children differ from those that improve.

· **Methods:** Participants were children with new inflammatory arthritis who were recruited into the CAPS cohort and followed systematically with baseline data for the 100mm visual analogue scale (VAS) for pain available. A two-stage approach was used for the analysis. Firstly, pain trajectories were modelled in children with pain VAS at presentation and at one or more follow-up visits (up to five years post baseline) using a discrete mixture-model. Secondly, multinomial logistic regression was used to determine the association between baseline variables and trajectory groups (95%CI). These variables included the core outcome variables (active and limited joint counts, physician's global assessment (PGA), parent/patient general evaluation (PGE), childhood HAQ (CHAQ) score), gender, age at onset and disease duration.

· **Results:** 957 children were included. A three group trajectory model of pain was selected as the most clinically relevant model (Figure) and included a Low-Low pain group (trajectory 1), a High-Low pain group (trajectory 2) and a High-High pain group (trajectory 3). Children in the High-Low group and High-High group had significantly older age at onset, longer disease durations, more involved joints, higher PGE, PGA, pain and CHAQ scores at presentation, compared to children in the Low-Low group. Higher pain at baseline predicted membership of the High-High group (RRR 1.1 (95% CI 1.05, 1.1) and High-Low Pain (RRR 1.1 (95% CI 1.1, 1.1) compared to Low-Low group; and predicted membership in the High-Low group compared to the High-High group (RRR 0.98 (95% CI 0.97, 0.99). Both Higher CHAQ scores and older age at onset predicted membership in the High-High group compared to both the Low-Low group and the High-Low group. Longer disease duration at presentation predicted membership in the High-High group (RRR 1.03 (95% CI 1.01, 1.04) and the High-Low group (RRR 1.02 (95% CI 1.001, 1.03) compared to Low-Low group.

· **Conclusion:** Even when adjusting for core outcome variables at presentation, participants who present earlier in their disease, are younger at disease onset and report less pain and functional problems upon presentation are less likely to report pain over time. Age at onset, functional problems and pain at presentation differentiated between high levels of pain which improved or persisted over time.



Disclosure: A. Rashid, None; **K. Holliday**, None; **L. Cordingley**, None; **R. Carrasco**, None; **B. Fu**, None; **H. E. Foster**, Pfizer Inc, 9, Abbott Immunology Pharmaceuticals, 9, Roche Pharmaceuticals, 9, Novartis Pharmaceutical Corporation, 9; **E. Baildam**, None; **A. Chieng**, None; **J. Davidson**, None; **L. Wedderburn**, None; **K. Hyrich**, None; **W. Thomson**, None.

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Juvenile Rheumatoid Arthritis and Future Risk for Cardiovascular Disease; A Multicenter Population-Based Study. Jason Anderson[1], Katelyn Anderson[1], Hanne Aulie[2], Cynthia S. Crowson[1], Thomas Mason II[1], Stacy P. Ardoin[3], Ann M. Reed[1] and Berit Flato[2]. [1]Mayo Clinic, Rochester, MN, [2]Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway, [3]Ohio State University College of Medicine, Columbus, OH.

Background/Purpose: Several studies suggest an increased frequency of cardiovascular disease (CVD) in patients with rheumatoid arthritis, but little is known about CVD risk in patients with juvenile rheumatoid arthritis (JRA). The objective of this study was to evaluate the frequency of CVD and CVD risk factors in adults with a prior diagnosis of JRA compared to controls.

Methods: A retrospective, partly population-based cohort study was independently conducted utilizing patients at two major academic institutions (Cohorts 1 and 2). Each institution employed a unique methodology to evaluate for the common endpoint of clinical CVD outcomes and risk factor development with comparison to control groups of similar age and sex. Cohort 1 was an inception cohort of residents of a geographically defined area who were diagnosed with JRA in 1960–1993. CVD and CVD risk factors were ascertained via medical record review and telephone survey for the subset of patients currently aged ≥30 years. Cohort 2 included patients diagnosed with JRA in 1980–1985 who participated in a clinical exam or completed a survey in 2011–2012 (i.e. 29 year follow-up).

Results: Among 41 patients with JRA and 28 controls in cohort 1, 3 patients (7%) had CVD, compared to 0 controls ($p = 0.43$). Of these, 1 patient had CVD prior to age 30 with ages at time of CVD diagnosis ranging from 21–39 years. Types of CVD included 1 patient with venous and arterial thrombosis, 1 patient with coronary artery disease and myocardial infarction, and 1 patient with angina pectoris. Analysis for the presence of CVD risk factors in Cohort 1 demonstrated 15 patients (56%) with hyperlipidemia, compared to 0 controls ($p = 0.019$). Twenty patients (49%) were ever smokers, compared to 10 controls (36%) ($p = 0.004$). Other risk factors including hypertension, diabetes mellitus, and family history of CVD were elevated in the JRA cohort but did not obtain statistical significance. Among 170 JRA patients with 29 year follow-up and 91 controls in Cohort 2, 2 patients (2%) had CVD, compared to 0 controls ($p = 0.29$). Types of CVD included 1 patient with myocardial infarction and 1 patient with angina pectoris and myocardial infarction. Analysis for the presence of CVD risk factors in Cohort 2 demonstrated 14 patients (8%) with hypertension, compared to 2 controls (2%) ($p = 0.049$). Ninety patients (54%) were ever smokers, compared to 36 controls (40%) ($p = 0.028$). Other CVD risk factors measured and elevated in the JRA cohort included use of antilipemic medication, use of antihypertensive medication, and CVD in first degree relative, but statistical significance was not obtained. The presence of diabetes mellitus was equal in the JRA cohort and control group for Cohort 2.

Conclusion: Certain CVD risk factors including hyperlipidemia, hypertension, and smoking appear to be more common among patients with JRA than in age-matched controls. There may be a trend toward increased numbers of CVD events, and occurrence of CVD at younger ages in patients with JRA, although statistical significance was not demonstrated in this study. Continued longitudinal follow-up of these cohorts and larger population-based studies are needed to establish a definitive relationship between JRA and CVD.

Disclosure: J. Anderson, None; **K. Anderson**, None; **H. Aulie**, None; **C. S. Crowson**, None; **T. Mason II**, None; **S. P. Ardoin**, None; **A. M. Reed**, None; **B. Flato**, None.

ACR Poster Session A
Pediatric Rheumatology - Pathogenesis and Genetics
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Understanding the Molecular Pathogenesis of and Response to Canakinumab Treatment in TNF Receptor-Associated Periodic Syndrome By Gene Expression Profiling of Whole Blood from Patients. R. Torene[1], M. Gattorno[2], H. Lachmann[3], L. Obici[4], A. Meini[5], V. Tormey[6], R. Caorsi[2], L. Baeriswyl[7], U. Affentranger[7], S. Starck-Schwertz[7], M. Letzkus[7], N. Hartmann[7], K. Abrams[8] and N. Nirmala[1]. [1]Novartis Institutes for BioMedical Research, Cambridge, MA, [2]G. Gaslini Institute, Genova, Italy, [3]Royal Free Hospital, London, United Kingdom, [4]IRCCS Policlinico San Matteo, Pavia, Italy, [5]Spedali Civili, Brescia, Italy, [6]Galway University Hospitals, Galway, Ireland, [7]Novartis Institutes for BioMedical Research, Basel, Switzerland, [8]Novartis Pharmaceutical Corporation, East Hanover, NJ.

Background/Purpose: TNF receptor-associated periodic syndrome (TRAPS) is an autoinflammatory disease causing unprovoked fevers, myalgia, abdominal pain, rash, headaches, and, in severe cases, AA amyloidosis. It is an autosomal dominant condition resulting from variants in the TNF super family receptor 1A (*TNFRSF1A*) gene. [1] A hallmark of TRAPS is a huge activation of the inflammatory response in the absence of autoantibodies or antigen-specific T-cells. [1] Canakinumab is a high-affinity, human, selective, anti-IL-1β monoclonal antibody, developed for the treatment of autoinflammatory diseases. [2] The objective of this analysis is to determine whether gene expression in whole blood can support a molecular mechanism for the activity of canakinumab in TRAPS patients.

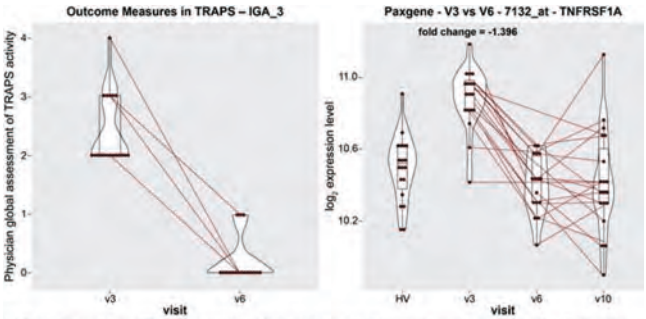
Methods: Twenty patients with active TRAPS received open-label canakinumab 150mg sc/month for 4 months in an efficacy and safety study. These patients were assessed at Day 15 for response by physician global assessment (PGA) disease activity scale. Whole blood was collected at baseline, Day 15 and Day 113 from 19 of these patients and 1 sample each from 19 untreated age-matched healthy volunteers for analysis of gene expression levels by microarrays.

Results: All 20 patients showed improvements in PGA score (Figure 1-left). Gene expression profiles of these patients were altered by treatment with canakinumab. Forty-six differentially expressed genes showed a >2-fold change after treatment with expression levels that shifted towards that of healthy volunteers. The disease-causing gene (*TNFRSF1A*, Figure 1-right), drug target gene (*IL-1β*), and other inflammation related genes (e.g., *MAPK14*) were downregulated after treatment and several inflammation related pathways were evident among the differentially expressed genes. Many of the high confidence differentially expressed genes had expression levels that correlated with neutrophil count, however, neutrophil count alone could not account for the expression differences observed.

Conclusion: Altogether, the gene expression data support a model in which canakinumab increases neutrophil apoptosis and reduces pro-inflammatory signals through its inhibition of IL-1β. Canakinumab is able to reverse the overexpression of several genes associated with inflammatory response, including IL-1β. Interestingly, IL-1β blockade normalized the overexpression of the disease-causing gene, *TNFRSF1A*, at the RNA level, suggesting a direct impact on the main pathogenic mechanism of TRAPS.

References

1. McDermott MF, et al. *Cell* 1999; 97(1):133–44.
2. Lachmann HJ, et al. *J Exp Med*.2009; 206(5):1029–36.



Left–Physician's assessment score of TRAPS patients at baseline and after canakinumab treatment. Higher scores indicate a more severe condition. Right–Gene expression levels for TNFRSF1A for healthy volunteers (HV) and TRAPS patients for whole blood. Note how expression levels are elevated in TRAPS patients at baseline compared to HV, however, after treatment with canakinumab, expression levels are comparable to that of HV. Lines connect samples across different visits derived from the same patient.

Disclosure: R. Torene, Novartis institute for biomedical research, 3; **M. Gattorno**, Novartis, SOBI, 2, Novartis, SOBI, 8; **H. Lachmann**, Novartis, Celtic, 2, Novartis., 5; **L. Obici**, Pfizer Inc, 5, Novartis Pharmaceutical Corporation, 8; **A. Meini**, None; **V. Tormey**, None; **R. Caorsi**, None; **L. Baeriswyl**, Novartis institute for biomedical research, 3; **U. Affentranger**, Novartis institute for biomedical research, 3; **S. Starck-Schwertz**, Novartis institute for biomedical research, 3; **M. Letzkus**, Novartis institute for biomedical research, 3; **N. Hartmann**, Novartis institute for biomedical research, 3; **K. Abrams**, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 1; **N. Nirmala**, Novartis institute for biomedical research, 3.

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Association of Kawasaki Disease with Tropospheric Winds in Central Chile: Is Wind-Borne Desert Dust a Risk Factor?. Arturo Borzutzky[1], Alvaro García[2], Rodrigo Hoyos-Bachiloglu[1] and Hector Jorquera[3]. [1]Millennium Institute on Immunology and Immunotherapy, Pontificia Universidad Católica de Chile, Santiago, Chile, [2]Pontificia Universidad Católica de Chile School of Medicine, Santiago, Chile, [3]Centro de Desarrollo Urbano Sustentable (CEDEUS), Santiago, Chile.

Background/Purpose: Kawasaki disease (KD) has been reported to have seasonal variations in many different countries, as well as geographical and temporal clustering. It has been found that KD cases diagnosed in Japan, Hawaii and San Diego, USA increase when tropospheric wind patterns arrive from central Asia, suggesting a common, wind-borne causal agent.

Methods: We analyzed KD cases hospitalized in Santiago, Chile to look for associations with local, regional and large scale meteorological variables. We compiled monthly data of KD incidence rates, local meteorological variables, regional winds and several El Niño Southern Oscillation (ENSO) indices for 2001–2010; we considered standardized anomalies in all analyses. We used dynamic linear regression models to account for data autocorrelation.

Results: Zonal (U) winds at 1000 and 925 mb above Santiago show a strong correlation with KD data on univariate linear regression ($P<0.001$), but no significant association was observed for other unlagged meteorological variables. We then fitted multivariate dynamical regressions using time series ARX models; model selection was carried out by minimizing Akaike's Information Criterion (AIC) and several model structures — using different lags in meteorological variables — were explored. This multivariate dynamic regression showed that meteorological variables explain 38% of variance in KD rates. A unit increase in northerly wind at 3 lagged months, temperature at 1 and 3 lagged months and monthly change of ENSO 4 index are associated with changes in KD rates of 0.203 (95% CI 0.049 – 0.358), 0.181 (95% CI 0.014 – 0.347], 0.192 (95%CI 0.030 – 0.353) and -0.307 (95% CI -0.458 -0.156), respectively.

Conclusion: We found a statistical association of KD at Santiago, Chile with tropospheric, northerly wind patterns suggesting dust transported from the Atacama Desert could include a causative agent. A novel result is that ENSO dynamics also explain part of KD variability with a decrease in KD when La Niña is dissipating or El Niño is on the rise; hence climate scale dynamics might be taken into account in future studies worldwide — at least as a potential explanatory variable that may confound KD seasonality on a global scale.

Disclosure: A. Borzutzky, None; **A. García**, None; **R. Hoyos-Bachiloglu**, None; **H. Jorquera**, None.

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Sibling Exposure and Risk of Juvenile Idiopathic Arthritis. Jessica Miller[1], Anne-Louise Ponsonby[2], Angela Pezic[1], Jonathan Akikusa[3], Roger Allen[4], Jane Munro[4] and Justine Ellis[1]. [1]Murdoch Childrens Research Institute, Parkville, Australia, [2]The University of Melbourne, Parkville, Australia, [3]Royal Childrens Hospital, Parkville, Australia, [4]Royal Children's Hospital, Melbourne, Australia.

Background/Purpose: Susceptibility to juvenile idiopathic arthritis (JIA) is presumed to be determined by the interplay of genes and environment. Our understanding of the genetic basis of JIA risk has increased markedly over the last few years, but the environmental factors remain largely unknown. The hygiene hypothesis suggests that exposure to microbes in early life may protect against the development of immune disorders. Measures of early life hygiene have been associated with asthma, allergy, multiple sclerosis (MS) and type 1 diabetes. Exposure to siblings may be a marker of exposure to childhood infection, and we have previously shown that higher infant sibling exposure prior to school age is associated with a decreased risk of MS. We therefore hypothesised that sibling exposure may also be associated with JIA.

Methods: Participants were drawn from the CLARITY JIA biobank in Victoria, Australia. Cases (n = 302; mean age 8.5y ± 4.7 SD; 67% female) were children born in Victoria who were diagnosed with JIA by a paediatric rheumatologist at the Royal Children's Hospital (RCH), Melbourne. Systemic JIA cases were excluded. Controls (n = 676; mean age 7.1y ± 4.1 SD; 41% female) were healthy children born in Victoria and visiting the RCH day surgery unit for a minor surgical procedure. At recruitment, families completed a questionnaire that collected birthdates of the index child and siblings, along with data on other potential confounders including index child age and sex, maternal age at birth, gestational age at birth, child sleeping arrangements and socio-economic status. We compared birth order, only-child status, total number of siblings, and cumulative years of sibling exposure by age six, between cases and controls using logistic regression.

Results: We found that, compared to being an only child, having any siblings conferred a protective effect on JIA risk (adjusted OR = 0.46, 95% CI 0.28 – 0.74, p = 0.001). The protective effect appeared to increase with increasing number of siblings (Table 1).

Table 1: Total number of siblings born within 18 years of the index child

	JIA Cases No. (%)	Controls No. (%)	Adjusted OR (95% CI)	P
0	47 (16.5)	79 (12.0)	1.00	
1	123 (43.3)	327 (49.8)	0.46 (0.28, 0.76)	0.002
2	86 (30.3)	165 (25.1)	0.50 (0.29, 0.87)	0.014
≥ 3	28 (9.9)	86 (13.1)	0.25 (0.13, 0.48)	< 0.001

A protective effect of siblings was also observed when we considered cumulative sibling years by age 6 (e.g. ≥ 3y exposure vs no exposure, adjusted OR = 0.49, 95% CI 0.30 – 0.79, p = 0.003). There was no association between birth order and JIA risk. We also compared cases to a second control sample (n = 341, mean age 8.1 years ± 3.6 SD; 45% female) collected from the community and weighted to represent the Victorian child population. JIA odds ratios were found to be similar by this approach, although confidence intervals were wider, reflecting the smaller size of the community control sample.

Conclusion: In the CLARITY JIA case-control sample, increased exposure to siblings is associated with a reduced risk of disease. This suggests that increased microbial exposure in childhood may confer protection against the development of JIA.

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Tenascin-C, a TLR4 Ligand Levels in Enthesitis Related Arthritis Category of Juvenile Idiopathic Arthritis: Cross-Sectional and Longitudinal Study. Anuj Shukla, Priyanka Gaur and Amita Aggarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: Tenascin-C (TNC) is an extracellular matrix glycoprotein, which binds to TLR4 and leads to its activation. Monocytes of children with Enthesitis related arthritis (ERA) show TLR4 overexpression. TNC may serve as an endogenous stimulator of TLR4 in ERA. Thus we

studied the serum and synovial fluid levels of TNC in children with ERA and its association with disease activity.

Methods: TNC levels were measured in serum of 80 children with ERA satisfying ILAR criteria. 15 children were followed-up while on regular NSAID treatment and levels were reassessed at 3 months. 17 paired serum-synovial fluid samples and 25 healthy control serum samples were also analyzed. Disease activity was assessed by physician global assessment; tender, swollen and damaged joint counts; enthesitis score, ESR and CRP.

Results: Patients were mainly boys (9:1) with average age at disease onset of 11.2 years and duration of disease of 4.4 years. 80% had peripheral arthritis, 63% active enthesitis, 43% clinical sacroilitis, 39% inflammatory back-pain, and 8% had a history of acute anterior uveitis. Most of the children were HLA-B27 positive (90%, n=72) and 29% had positive history of JIA-ERA or spondyloarthritis in the family.

The average physician global assessment (0–10) was 4.5±2.2. Average early morning stiffness was 50±57 minutes with 4±4-tender and 3±3-swollen joints. Average ESR and CRP were 72±37 mm at 1 hour and 6.9±5.6 mg/dl. 25% children had at least one damaged joint with an average count of 2±2. 16 children out of 80 had no tender and swollen joints and were classified as inactive disease.

The mean serum TNC level in children with active disease was 67.1±44.9 ng/ml and was significantly higher than the inactive 40.6±36.7 ng/ml ($p=0.01$) and healthy control 21±15.2 ng/ml ($p<0.001$). Median levels were higher in HLA-B27 positive 70.1 ng/ml vs. negative disease 22.8 ng/ml ($p=0.003$).

Serum levels correlated positively with disease activity parameters like physician global assessment (r=0.4, 95%CI=0.15 to 0.58, p=0.001), early morning stiffness (r=0.34, 95% CI = 0.1 to 0.55, p=0.005), tender joint count (r=0.4, 95%CI=0.2 to 0.6, p=0.0003), swollen joint count (r=0.46, 95%CI=0.27 to 0.6, $p<0.0001$), ESR (r=0.42, 95%CI=0.21 to 0.6, p=0.0002) and CRP (r=0.32, 95%CI=0.1 to 0.5, p=0.007) and negatively with duration of disease (r=−0.33, 95%CI=−0.5 to -0.17, p=0.003). TNC levels did not correlate with enthesitis scores and damaged joint counts. In ROC analysis for active vs. inactive disease, TNC (AUC=0.754) was equivalent to ESR (AUC=0.787) and CRP (AUC=0.789).

Treatment with regular and adequate dose of NSAIDs lead to a significant fall in the serum levels at 3 months of follow-up (p=0.0003). The median synovial fluid TNC level in JIA-ERA was 17.39 ng/ml. Synovial fluid levels were significantly lower than the paired serum values (p=0.01).

Conclusion: Circulating TNC levels are significantly raised and correlate with various clinical and laboratory parameters of disease activity in children with ERA. It is equivalent to ESR and CRP as a measure of disease activity. Regular NSAID treatment results in significant fall in the levels at 3 months probably related to control of disease activity.

Disclosure: A. Shukla, None; **P. Gaur**, None; **A. Aggarwal**, None.

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Clinical Significance of Cytokine Profile with Interleukin-18 and -6 in Systemic Juvenile Idiopathic Arthritis. Masaki Shimizu, Natsumi Inoue, Yuko Tasaki, Sayaka Ishikawa, Kazuyuki Ueno and Akihiro Yachie. School of Medicine, Institute of Medical, Pharmaceutical, and Health Sciences, Kanazawa University, Kanazawa, Japan.

Background/Purpose: Innate proinflammatory cytokines interleukin (IL)-6 and IL-18 are critical for perpetuating the inflammatory processes in systemic juvenile idiopathic arthritis (s-JIA) and macrophage activation syndrome (MAS). To assess the role of IL-6 and IL-18 in the pathogenesis of s-JIA and MAS, and to investigate the clinical significance of serum cytokine profile with IL-6 and IL-18 in s-JIA and MAS, we analyzed the serum IL-6 and IL-18 in patients with s-JIA and compared them with the clinical features of s-JIA.

Methods: 71 patients with s-JIA including 23 patients with MAS were analyzed. Levels of IL-6 and IL-18 were quantified in serum by enzyme-linked immunosorbent assay. **Results** were compared with clinical features of s-JIA.

Results: Two distinct s-JIA patient subsets based on their serum IL-6 and IL-18 levels were identified: an IL-18 dominant (IL-18/IL-6 >1000) and an IL-6 dominant (IL-18/IL-6<1000). The IL-6 dominant subset had a significantly greater number of joints with active disease and higher serum levels of matrix metalloproteinase-3, whereas the IL-18-dominant subset was more likely to develop MAS. The cut off value of serum IL-18 to predict the development of MAS was 52500pg/ml with 91.3% of sensitivity and 81.3% of specificity. The patients with IL-18 dominant pattern were likely to have monophasic or polycyclic disease course, whereas the patients with IL-6 dominant pattern were likely to have persistent disease course. Serum IL-18 levels in patients achieved remission decreased to the levels <1,000 pg/mL in inactive phase and normalized in remission phase. In contrast, serum IL-18 levels in patients experienced relapse during withdrawal of steroid within 12 months after disease onset demonstrated a sustained elevation of serum IL-18 levels (>1,000 pg/mL) during the inactive phase.

Conclusion: Two subsets of patients with s-JIA, one which is prone for arthritis and another with prone for MAS, can be identified on the basis of their serum IL-6 and IL-18 levels. These two subsets appear to be characterized by certain distinct clinical features. Monitoring the cytokine profile with IL-18 and IL-6 might be useful to predict disease course. Furthermore, serum IL-18 levels reflect the biological activities of the immune system in s-JIA and may predict the development of MAS and the prognosis of s-JIA.

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Differential Expression of microRNA in Monocytes from Children with Systemic Juvenile Idiopathic Arthritis: Implications for Polarized Phenotype. Grant Schulert[1], Ndate Fall[1], Nan Shen[2] and Alexei Grom[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Shanghai Institutes for Biological Sciences Chinese Academy of Sciences & Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Background/Purpose: Systemic juvenile idiopathic arthritis (SJIA) is an autoinflammatory disease of childhood, and the predominant effector cells are mononuclear phagocytes rather than lymphocytes as in autoimmune diseases such as rheumatoid arthritis (RA). Previous gene expression data has shown that monocytes in SJIA have a novel phenotype with clear proinflammatory activation as well as features of alternative activation. This aberrant phenotype may contribute to the potential of these children to develop macrophage activation syndrome (MAS). What controls monocyte/macrophage differentiation in SJIA is unknown. MicroRNA are small, non-coding RNA that serve as transcriptional negative regulators to fine-tune gene expression programs involved in cell differentiation, metabolism and immunity. There is growing evidence that miRNA contribute to the pathogenesis of human disease, including RA. These regulators have also been implicated in controlling differentiation of monocytes and macrophages. However, miRNA expression in SJIA has not been examined. Here, we examine miRNA expression profiles in peripheral blood monocytes from children with SJIA.

Methods: We enrolled children with active SJIA, defined as presence of active arthritis or systemic features, as well as those with new-onset disease or clinically inactive disease (CID). Freshly isolated CD14+ monocytes were isolated by magnetic beads separation, and used to generate RNA which in turn was used to quantitate the expression of 384 miRNA and controls on the TaqMan ™ MicroRNA Array A.

Results: We found that monocyte expression of mir-125a-5p was significantly elevated in children with active SJIA compared to those with CID (relative expression 16.8 vs. 3.0, $p<0.05$). In addition, expression of mir-125a-5p was significantly correlated with markers of disease activity including ferritin ($R=0.73$, $p<0.001$) as well as presence of systemic features such as hepatosplenomegaly. Recently miR-125a-5p has been suggested to play an essential role in monocyte polarization. We also found several specific miRNA with differential expression in monocytes from children with new-onset disease compared to those with active established disease. One of these, miR-187, has been implicated in negative regulation of inflammatory cytokines including IL-6. We find that miR-187 expression strongly correlates with markers of disease activity including C-reactive protein ($R=0.813$, $p<0.05$), ferritin ($R=0.644$, $p<0.05$) and soluble IL-2 receptor ($R=0.779$, $p<0.05$) as well as presence of systemic features. Interestingly, while monocyte expression of miR-146a has been correlated with disease activity in RA, we found no difference in expression between monocytes from patients with active SJIA and those with CID.

Conclusion: These results provide the first report of miRNA expression profiles in children with SJIA. Taken together, these data suggest that differential miRNA expression contributes to the phenotype of monocyte/macrophages in SJIA, and may have implications for disease pathogenesis and development of MAS. Further work will examine impact of miRNA expression on monocyte function and differentiation.

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Inhibition of Natural Killer (NK) Cell Cytotoxicity By Interleukin-6 (IL-6): Implications for the Pathogenesis of Macrophage Activation Syndrome. Loredana Cifaldi[1], Giusi Prencipe[2], Ivan Caiello[2], Claudia Bracaglia[2], Raffaele Strippoli[3] and Fabrizio De Benedetti Sr. [2]. [1]Paediatric Haematology/Oncology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, [2]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, [3]Cellular Biotechnologies and Haematology, Sapienza Rome University, Rome, Italy.

Background/Purpose: MAS occurs frequently in patients with active systemic juvenile idiopathic arthritis(s-JIA) and because of the similarities with Haemophagocytic Lymphohistiocytosis (HLH) is classified among secondary HLH. s-JIA is characterized by high levels of Interleukin-6 (IL-6). Impairment of natural killer (NK) cell function and decrease perforin expression have also been reported in sJIA. Aim of this study was to evaluate the effect of IL-6 on NK cell cytotoxic function.

Methods: Following in vivo treatment with poly(I:C), splenic NK cell cytotoxic activity from wild-type (WT) or IL-6 transgenic (IL-6TG) mice was evaluated using the chromium51 release assay. NK cell number, perforin, granzymeB, CD69 and CD107a expression were evaluated by flow cytometric analysis. Human polyclonal NK cells were expanded from peripheral blood mononuclear cells (PBMCs) in co-cultures with the feeder cell line RPMI8866 in the presence of tocilizumab, an IL-6 receptor blocker, or isotype control. IL-6 production in the supernatants of human polyclonal NK cells was measured by ELISA. PBMCs from healthy donors were treated with IL-6. NK cell cytotoxic activity, perforin and CD107a expression were evaluated as above.

Results: Following poly(I:C) administration, in vivo generation of splenic NK cell cytotoxicity was markedly reduced in IL6TG mice compared to WT mice. In IL6TG mice number of NK cells, number of CD69+ NK cells and degranulation were comparable to WT mice. Defective expression of both perforin and granzymeB were found in NK cells from IL6TG mice. High levels of IL-6 were found in the supernatants of human polyclonal NK cells. Neutralization of IL-6 effects with tocilizumab in co-cultures of human PBMCs increased human NK cell cytotoxicity and perforin expression. Addition of IL-6 to human PBMCs decreased perforin expression in NK cells.

Conclusion: Both in vivo in mice and in vitro in humans, IL-6 inhibits NK cytotoxicity down-regulating perforin expression. In patients with prominent inflammatory response, such as that present in s-JIA, high levels of IL-6 may contribute to the induction of MAS also by inhibiting cytotoxicity inducing a defect similar to that of primary HLH.

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Mutations in the MTHFR Gene Are Not Associated with Methotrexate Intolerance in Patients with Juvenile Idiopathic Arthritis. Andrea Scheuern, Nadine Fischer, Johannes-Peter Haas and Boris Hugle. German Center for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany.

Background/Purpose: Methotrexate (MTX) is the drug used most frequently in the therapy of juvenile idiopathic arthritis (JIA). However, long-term treatment in children frequently leads to intolerance, with marked revulsion and refusal of treatment. Mutations in the gene for methylenetetrahydrofolate reductase (MTHFR) can lead to increased toxicity of MTX and could possibly represent an initial stimulus for this conditioned response.

The objective of this study was to investigate the relation of common mutations in the MTHFR gene and occurrence of MTX intolerance in pediatric patients with juvenile idiopathic arthritis treated with MTX.

Methods: Consecutive patients admitted to the German Center for Pediatric and Adolescent Rheumatology from October 2012 until April 2014 were included in this study. Inclusion criteria were 1) diagnosis of JIA and 2) treatment with MTX for at least 3 months prior to inclusion. Exclusion criteria were other diseases leading to nausea and/or abdominal complaints, and concomitant medications possibly inducing nausea (excepting biologics and non-steroidal anti-inflammatory drugs). Intolerance to MTX was determined using the validated Methotrexate Intolerance Severity Score (MISS) questionnaire; presence of MTX intolerance was assumed for MISS values of $\geq$ 6. Presence of the two most common mutations in the MTHFR gene (C677T and A1298C) was tested using a polymerase chain reaction assay, as described previously. **Results** were analyzed using descriptive statistics and univariate analysis.

Results: 114 patients were included (71% female, median age at inclusion median 12.6 years, median disease duration 4.1 years). Of those, 49 (43%) showed MTX intolerance. 42% of patients were heterozygous, and 7% homozygous for the C677T mutation of the MTHFR gene, 45% of patients were heterozygous, and 12% homozygous for the A1298C mutation; frequencies of both mutations are comparable to published data. Compared to the homozygous wild type, MTX intolerance was not found significantly more frequent in patients with hetero- and homozygous ($p = 1.000$) or homozygous ($p = 0.125$) C677T mutations, nor in patients with hetero- and homozygous ($p = 0.775$) or homozygous ($p = 0.444$) A1298C mutations. Compound heterozygous mutations for C677T and A1298C were also not found significantly more frequently in patients with MTX intolerance ($p = 0.809$).

Conclusion: Mutations in the MTHFR gene are not found significantly more frequently in JIA patients with intolerance to MTX. Development of MTX intolerance appears not to be causally related to toxicity associated with the MTHFR gene.

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Elevated Cardiovascular Disease Burden and Inflammatory Biomarker Levels in Adults with Juvenile Idiopathic Arthritis. Siobhan Crittenden[1], Elizabeth Coulson[1], Vijay Kunadian[2], Wan-Fai Ng[2] and H. E. Foster[3]. [1]Institute of Cellular Medicine, Newcastle upon Tyne, United Kingdom, [2]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, [3]Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom.

Background/Purpose: Rheumatoid Arthritis (RA) is associated with a 50 % greater cardiovascular mortality rate than the general population, attributable to the increased prevalence of traditional risk factors and inflammatory molecules involved in coronary atherosclerosis. Many young people with Juvenile Idiopathic Arthritis (JIA) have their disease persisting into adulthood. Since persistent systemic inflammation is known to accelerate the atherosclerotic process, individuals with JIA and especially those with persistent inflammation may have a greater cardiovascular risk. This study was to assess the prevalence of traditional cardiovascular risk factors and carotid artery Intima-Media Thickness (cIMT) as a surrogate cardiovascular outcome. Additionally, potential biomarkers for predicting and monitoring of cardiovascular risks will be sought.

Methods: 51 adults with JIA (median age: 34.0 years, range: 18 – 63 years) were recruited from an adult continuity clinic along with 27 age- and gender- matched controls (median age 35.5 years, range: 18 – 62 years). JIA subtypes were defined by ILAR classification. After informed consent, cIMT was examined using B-mode ultrasound by one observer (EJC), and clinical data and blood samples were collected. cIMT images were analysed using the M'ath software package (Intelligence in Medical Technologies). Serum levels of potential cardiovascular risk biomarkers previously indentified in other adult inflammatory arthritides, such as systemic inflammatory and adhesion molecules, were quantified using ELISA kits (R&D Systems) or Cytometric Bead Arrays (BD Biosciences). Data were analysed using FCAP Array software.

Results: A significantly higher proportion of adults with JIA compared to controls had a pre-existing diagnosis of hypertension (12 % vs. 1 %, $p = 0.029$). Mean CRP and cIMT were significantly greater in patients than in controls (9.0 mg/ml vs. 5.6 mg/l, $p=0.006$, and 0.540 mm vs. 0.492 mm, $p=0.039$ respectively), especially among those with systemic JIA and RF+ polyarticular JIA. cIMT correlates with age (Pearson's coefficient 0.67, $p < 0.001$). Serum levels of MPO, IL-12p70, IL-12/23p40, IL-4, IL-8, TNFα and IL-21 were significantly different between the adult JIA and control group. Among the JIA subgroups, the polyarticular JIA group has the highest level of LTA, while the oligoarticular JIA group has the highest level of CD40L. Extended oligoarticular JIA has higher levels of IP10 and IL-8. After correcting for age, hypertension and smoking, IL-12/23p40 ($p < 0.01$) and IL-12p70 ($p = 0.035$) remain independent predictors for the differences in cIMT between patients and controls.

Conclusion: Adults with JIA have increased cIMT, as well as serum levels of CRP and several pro-inflammatory cytokines compared to healthy controls. Furthermore, IL-12p70 and IL-12/23p40 could potentially be used as biomarkers for cardiovascular risk. IL-12 plays an important role in JIA pathogenesis, promoting Th1 response and inflammatory cytokines such as TNFα. It is noteworthy that MPO, which is linked with plaque development, thrombus formation and is a predictor of CVD in healthy individuals, is upregulated in adults with JIA.

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Next Generation Sequencing Reveals Restriction of the Treg Cell Repertoire and an Abundance of Shared Synovial Treg Clonotypes in JIA. Lauren A. Henderson[1], Stefano Volpi[1], Francesco Frugoni[1], Susan Kim[1], Robert P. Sundel[1], Fatma Dedeoglu[1], Mindy S. Lo[1], Erin Janssen[1], Melissa M. Hazen[1], Mary Beth Son[1], Ronald Mathieu[1], David Zurakowski[2], Robert C. Fuhlbrigge[1], Jolan E. Walter[3], Yu Nee Lee[1], Peter A. Nigrovic[1] and Luigi D Notarangelo[1]. [1]Boston Children's Hospital, Boston, MA, [2]Boston Children's Hospital, Boston, MA, [3]Massachusetts General Hospital for Children, Bpstpm, MA.

Background/Purpose: Regulatory T cell (Treg) dysfunction has been documented in juvenile idiopathic arthritis (JIA), but the basis for this lapse in suppressive capacity is incompletely understood. Animal models of autoimmunity demonstrate that a diverse and polyclonal Treg repertoire is essential for immune system homeostasis and Treg cell function. We therefore employed next generation sequencing (NGS) to analyze the repertoires of synovial fluid (SF) and peripheral blood (PB) Treg and effector T cells (Teff) in JIA.

Methods: Paired SF and PB samples were obtained from patients with JIA. Control samples included PB from age-matched, healthy children and SF from patients with Lyme arthritis. Treg ($CD4^+CD25^+CD127^{lo}$) and Teff ($CD4^+CD25^-$) cells were isolated from SF and PB mononuclear cells by fluorescence-activated cell sorting. The T cell receptor (TCR) β chain was amplified by multiplex PCR with genomic DNA serving as the template (ImmunoSEQ™). The PCR products were sequenced using the Illumina HiSeq platform. Subsequently, the data was analyzed using the ImmunoSEQ™ set of online tools, the International ImMunoGeneTics system (IMGT) HighV-QUEST platform, and the Immunoglobulin Analysis Tool (IgAT). The pre-specified primary aim was to evaluate the clonality of SF and PB Treg and Teff populations in JIA patients. Based on data evaluating the Treg repertoire and autoimmunity in animal models, we calculated that a sample size of 5 JIA patients would provide sufficient power for this study.

Results: 5 patients with JIA, 3 healthy controls, and 2 patients with Lyme arthritis were studied. In the PB of controls, the Treg and Teff repertoires were equally polyclonal. In contrast, JIA PB Treg cells were more clonal than control PB Treg, control PB Teff, and JIA PB Teff cells (ANOVA $p<0.0001$ with Bonferroni correction). JIA disease severity, as measured by the active joint count, correlated with the PB Treg clonality ($\rho=0.95$, $p=0.005$). Clonal abnormalities were not observed in the JIA PB Teff repertoire. In SF, JIA Treg cells were significantly more clonal than JIA PB Treg and Teff cells, JIA SF Teff cells, and control PB Treg and Teff cells (ANOVA $p<0.0001$with Bonferroni correction). JIA patients shared a substantial portion of SF Treg clonotypes, significantly more than SF Teff cells (Wilcoxon $p=0.0002$). In some JIA patient pairs, up to 19% of SF Treg clonotypes were shared. Further, these shared SF Treg clonotypes were private to JIA patients and were not identified in Lyme arthritis. In further support of disease specific TCRs in JIA SF, convergent recombination was seen preferentially in the SF Treg compared to the PB Treg compartment (Wilcoxon $p=0.002$). Skewed TCRβ variable family and joining gene usage, including overuse of gene segments that have been associated with other autoimmune conditions, was observed in JIA Treg and Teff cells.

Conclusion: Our data identified an unexpected restriction of the SF and PB Treg repertoires in JIA with sharing of SF Treg clonotypes across arthritis patients. These findings suggest that inadequacy in the Treg repertoire may contribute to Treg cell dysfunction and the perpetuation of inflammation in JIA, possibly in response to shared antigenic triggers.

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NLRC4-Related Macrophage Activation Syndrome (NLRC4-MAS): A Novel Primary Autoinflammatory Syndrome Caused By Activating Mutations in NLRC4. Scott Canna[1], Adriana Almeida de Jesus[2], Sushanth Gouni[1], Stephen Brooks[1], Kristien J. Zaal[1], Bernadette Marrero[1], Yin Liu[2], Michael Dimattia[1], Gina A. Montealegre Sanchez[2], Hanna Kim[2], Dawn C. Chapelle[2], Nicole Plass[2], Yan Huang[2], Angelique Biancotto[3], J. Alex Duncan[4], Susanne Benseler[5], John J. O'Shea[1], Alexei A. Grom[6], Zuoming Deng[2], Ronald M. Laxer[7] and Raphaela Goldbach-Mansky[2]. [1]NIAMS/NIH, Bethesda, MD, [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, [3]NHLBI/NIH, Bethesda, MD, [4]University of North Carolina School of Medicine, Chapel Hill, NC, [5]Alberta Children's Hospital Research Institute/University of Calgary, Calgary, AB, [6]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [7]The Hospital for Sick Children, University of Toronto, Toronto, ON.

Background/Purpose: Macrophage Activation Syndrome (MAS) is a life-threatening systemic inflammatory complication of many rheumatic diseases and its causes are unknown. While genetic defects causing impaired cytotoxicity result in a similar entity called primary Hemophagocytic Lymphohistiocytosis (HLH), MAS has no known primary genetic cause.

Methods: We performed detailed clinical, genetic, and immunologic evaluation of a patient with early onset, recurrent MAS-like disease including whole exome sequencing, serum cytokine analysis, and whole blood transcriptional profiling. We also tested monocyte and macrophage inflammasome activation, cytokine production, and cell death. We also evaluated the inflammatory effects of this mutation in a transduced monocytic cell line.

Results: We identified a 7 year-old female with recurrent MAS-like episodes, including pancytopenia and hyperferritinemia, since 2 months of age. Genetic testing identified a *de novo* threonine to serine conversion in *NLRC4*, a cytosolic danger sensor, Nod-like Receptor (NLR), and component of the NLRC4 inflammasome. The patient's serum and transcriptional profiles were distinct from NOMID and similar to MAS-prone diseases, with high, constitutive IL-18 elevation. Patient monocytes and monocyte-derived macrophages showed over-production of IL-1β and IL-18, enhanced cell death, and spontaneous ASC aggregate formation. These findings were reproduced in THP1 monocytes constitutively expressing mutant NLRC4. The patient has weaned from steroids and colchicine and has been flare-free after six months of IL-1 receptor antagonist (anakinra) therapy.

Conclusion: Like mutations in NOD2 causing Blau Syndrome and in NLRP3 causing the cryopyrinopathies, activating mutations in the nucleotide-binding region of NLRC4 cause a novel "inflammasomopathy". However, *NLRC4* mutations uniquely manifest as recurrent MAS. Strengthening the NLRC4-MAS association, our findings have been independently corroborated in an unrelated kindred[1]. Ongoing investigation of NLRC4-MAS to determine its unique inflammatory characteristics will shed light on the pathogenesis of MAS and related systemic inflammatory disorders.

[1] Romberg N et al., *Nature Genetics*, Under Review

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Cytokines in Systemic Juvenile Idiopathic Arthritis and Macrophage Activation Syndrome: Tipping the Balance Between Interleukin-18 and Interferon-Gamma. Karen Put[1], Anneleen Avau[1], Ellen Brisse[1], Tania Mitera[1], Stéphanie Put[1], Paul Proost[2], Brigitte Bader-Meunier[3], Rene Westhovens[4], Benoît Van den Eynde[5], Ciriana Orabona[6], Francesca Fallarino[6], Lien De Somer[7], Thomas Tousseyn[8], Pierre Quartier[3], Carine Wouters[7] and Patrick Matthys[1]. [1]University of Leuven, Laboratory of Immunobiology, Rega Institute, Leuven, Belgium, [2]University of Leuven, Laboratory of Molecular Immunology, Rega Institute, Leuven, Belgium, [3]IMAGINE Institute, Hôpital Necker-Enfants Malades, Assistance Publique Hôpitaux de Paris, Université Paris-Descartes, Paris, France, [4]University of Leuven, Skeletal Biology and Engineering Research Center, Department of Development and Regeneration; Rheumatology, University Hospital Leuven, Leuven, Belgium, [5]Institut de Duve, Université catholique de Louvain, Brussels, Belgium, [6]Department of Experimental Medicine and Biochemical Sciences, University of Perugia, Perugia, Italy, [7]University of Leuven, Laboratory of Pediatric Immunology, University Hospital Leuven, Leuven, Belgium, [8]University of Leuven, Department of Imaging and Pathology, Leuven, Belgium.

Background/Purpose: To study the role of interferon-gamma (IFN-γ) in the pathogenesis of systemic juvenile idiopathic arthritis (sJIA) and macrophage activation syndrome (MAS) by searching for an IFN-γ profile and assess its relation with other cytokines.

Methods: Patients with inactive (n=10) and active sJIA (n=10), MAS (n=5) and healthy controls (n=16) were enrolled in the study. Cytokines and IFN-γ-induced proteins were determined in plasma by ELISA and HPLC-MS, in patient peripheral blood mononuclear cells (PBMCs) (qPCR, flow cytometry, western blot and ELISA) and in lymph node biopsies of one patient during both sJIA and MAS episodes (immunohistochemistry). IFN-γ responses were investigated in healthy donor PBMCs, primary fibroblasts and endothelial cells.

Results: Plasma IFN-γ, IL-6 and IL-18 were elevated in active sJIA and MAS. Levels of IFN-γ and IFN-γ-induced proteins (IP-10/CXCL-10, IL-18BP and IDO) in MAS were highly surpassing levels in active sJIA. Free IL-18 and ratios of IL-18/IFN-γ were higher in active sJIA versus MAS. MAS PBMCs showed a hyporesponsiveness to IFN-γ *in vitro*. Endothelial cells and fibroblasts expressed IFN-γ-induced proteins *in situ* in lymph node stainings of a MAS patient and *in vitro* upon stimulation with IFN-γ.

Conclusion: Patients with active sJIA and MAS show distinct cytokine profiles with highly elevated plasma levels of IFN-γ and induced proteins typically found in MAS. In addition to PBMCs, histiocytes, endothelial cells and fibroblasts may contribute to an IFN-γ profile in plasma. Increasing levels of IFN-γ compared to IL-18 may raise suspicion for development of MAS in sJIA.

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Myeloid Related Proteins 8 and 14 (MRP 8/14) - Potential Biomarkers of Disease Activity of Arthritis in Children with Trisomy 21. Charlene Foley, Orla Killeen and Emma Jane MacDermott. The National Centre for Paediatric Rheumatology, Dublin, Ireland.

Background/Purpose: JIA is an umbrella term used to describe a heterogeneous group of diseases.To date no specific markers exist in clinical practice to predict disease activity & outcome. MRP8/14 are calcium-binding proteins secreted by infiltrating phagocytes in synovial inflammation.Studies have shown that their serum concentrations correlate sensitively & specifically with synovial inflammation in JIA. It is believed that they are predictive biomarkers that can indicate subclinical disease activity & identify patients at risk of relapse during times of clinically inactive disease.They have also been shown to identify patients more likely to respond to treatment with Methotrexate.To date there have been no studies looking specifically at their use in Down's Arthropathy (DA).

Objectives: To evaluate the use of standard (ESR&CRP) & novel (MRP8/14) inflammatory markers as biomarkers of disease activity in DA & JIA.

Methods: Between May 2013-May 2014 new cases of JIA & DA attending the NCPR had blood drawn to measure their CRP, ESR & MRP 8/14 levels at diagnosis.Corresponding Active Joint Count (AJC) was documented. Paired synovial fluid (SF) samples were taken for analysis from children requiring steroid joint injections as treatment for their arthritis. Serum (Se) & SF concentrations of MRP 8/14 were determined by sandwich ELISA.The reader of laboratory assays was blinded for diagnosis & inflammatory activity.CRP & ESR were measured as part of routine clinical assessment.

Results: 32 children (20 JIA,12 DA) had serum samples taken for CRP, ESR & MRP8/14 levels at diagnosis. 14 of these children had paired synovial fluid samples taken.The average AJC was 4 (range 1–11).Table1 highlights accuracy of each measurement as a marker of disease activity.In DA, a significant correlation was detected between AJC & both ESR and MRP 8/14 (SF).Combining results for the DA & JIA cohort, a significant positive correlation was noted between paired samples of MRP8/14 in Se & SF.

Table 1 *(n=32 Serum, n=14 Synovial Fluid)*

Dx	StatisticalTest	Variable1	Variable2	Correlation	p value
DA	Correlation	Active Joint Count	ESR	Positive	p<0.05
			MRP 8/14 SF	Positive	p<0.05
			CRP	No Correlation	ns
		MRP 8/14 SF	ESR	Positive	p<0.01
JIA & DA	Correlation	MRP 8/14 synovial fluid	MRP 8/14 serum	Positive	p<0.05

Dx	Statistical Test	Variable 1	Variable 2	Outcome	p value
JIA & DA	Paired t test	MRP 8/14 SF	MRP 8/14 Se	SF MRP8/14 signif.higher than matched SeMRP8/14	p<0.01

Conclusion: MRI with contrast remains the gold standard for diagnosis of synovitis.In reality, clinical assessment is the major diagnostic tool.DA is a more challenging condition than JIA, in light of confounding illness & the often-associated non-verbal state.In DA a simple biomarker of disease would be invaluable. We have shown that CRP is a poor marker of disease activity in JIA & DA so the need for a more specific biomarker is evident.Our preliminary results suggest that children with DA have elevated SF levels of MRP 8/14 that correlate to disease activity.SF concentrations of MRP 8/14 are significantly higher than their paired Se samples, however our results show significant positive correlation between the two.This suggests that Se MRP 8/14 levels are potential accurate markers of SF levels.MRP 8/14 may be a useful biomarker of disease activity in DA, aiding timely diagnosis & instigation of appropriate treatment, in turn, helping to improve clinical outcomes for this patient group.

Disclosure: C. Foley, None; **O. Killeen**, None; **E. J. MacDermott**, None.

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HLA-B27 Subtypes in Enthesitis Related Arthritis Category of Juvenile Idiopathic Arthritis. Rajni Srivastava, Shikha Agnihotry, Rakesh Aggarwal and Amita Aggarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: HLA-B27 has a high degree of genetic polymorphism, with more than 105 known subtypes. Enthesitis Related Arthritis (ERA) is most common form of Juvenile Idiopathic Arthritis (JIA) in Asian and Indian population. It has strong association with HLA B27 similar to the adult ankylosing spondylitis (AS). Since the disease occurs in children and different HLA B27 subtypes confer different susceptibility to AS we studied the HLA-B27 subtypes associated with ERA and AS to see if there is any difference.

Methods: Samples were collected from 135 patients with ERA and 121 patients with AS. Genomic DNA was isolated from whole blood using salting out technique and HLA B27 typing was done using ARMS-PCR. Primers for intronic region of HLA-DR were used as internal control. HLA-B27 subtyping was done by sequencing using a group-specific amplification of the second and third exon region of HLA B27 gene.

Results: Hundred and seven out of 135 patients with ERA (79%) and 102/121 (84%) of AS patients were HLA B27 positive. HLA B*2705 and 04 were the most common subtypes. HLA B2*27:02, 07 and 018 were seen rarely. The frequency of HLAB*27:05 was 70% in ERA as compared to 56.8% in AS (p=0.032) whereas HLAB*27:04 was 21.4% in ERA and 36.2% in AS (p=0.013). No correlation was seen between B*27 subtypes (B*2704 and B*2705) and clinical features of JIA-ERA.

Conclusion: HLAB*27 subtype frequencies are different in ERA and AS. It is possible that the presence of ancestral subtype HLA B*27:05 leads to early onset of disease.

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Systemic Juvenile Idiopathic Arthritis and Exposure to Fine Particulate Air Pollution. Andrew Zeft[1], Sampath Prahalad[2], Rayfel Schneider[3], Alexei Grom[4], Fatma Dedeoglu[5], Pamela F. Weiss[6], Carter Mix[7] and C. Arden Pope[7]. [1]The Cleveland Clinic, Cleveland, OH, [2]Emory University, Atlanta, GA, [3]The Hospital for Sick Children, Toronto, ON, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]on behalf of CARRAnet Investigators, Palo Alto, CA, [6]The Children's Hospital of Philadelphia, Philadelphia, PA, [7]Brigham Young University, Provo, UT.

Background/Purpose: Environmental factors are understood to play a pathogenic role in the etiology of Systemic Onset Juvenile Idiopathic Arthritis (SJIA). Fine particulate matter (aerodynamic diameter £2.5-mm cut point, $PM_{2.5}$) is a measurable component of ambient urban pollution, and positive associations of short-term $PM_{2.5}$ exposure with the reported clinical presentation of SJIA in young children have been described in a regional cohort. Our objective was to further establish associations between short-term ambient pollution exposures and the reported clinical event dates of SJIA onset in cases residing from multiple metropolitan regions.

Methods: A case-crossover study design was used to analyze associations of short-term $PM_{2.5}$ exposures with the event date of SJIA symptom onset from cases residing in the metropolitan regions of Boston, Philadelphia, Atlanta, Cincinnati, and Toronto. Time trends, seasonality, month, and weekday were controlled for by matching. Selected exposure windows (up to 14 days) of $PM_{2.5}$ were examined.

Results: Positive, statistically significant associations between $PM_{2.5}$ concentrations and elevated risk of SJIA onset were not observed. The most positive associations of short-term $PM_{2.5}$ exposure with the reported clinical onset of SJIA were in children <5.5 years of age (RR 1.75, 95% CI 0.85–3.62). An ad hoc extended pooled analysis including previously reported cases residing from Utah's metro areas identified an increased risk of SJIA for children <5.5 years of age (RR = 1.76, 95% CI 1.07–2.89 per 10 $\mu g/m^3$ increase in 3-day lagged moving average of $PM_{2.5}$).

Conclusion: Even in this multi-city, multi-period study only small, statistically insignificant $PM_{2.5}$-SJIA associations are observed. However, similar to previously observed results, the $PM_{2.5}$-SJIA association is most suggestive in preschool aged children. More subjects with spatial and temporal specificity may be required by the analysis to demonstrate effects, and further research may be useful in larger numbers of SJIA cases and in geographic areas which experience a greater ambient particulate burden.

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Autoantibodies in Juvenile Systemic Sclerosis. Katharine Moore[1], J. Lee Nelson[1], Marvin J. Fritzler[2], Marisa S. Klein-Gitelman[3], Ann M. Reed[4], Tzielan C. Lee[5] and Anne M. Stevens[6]. [1]University of Washington, Seattle, WA, [2]Mitogen Advanced Diagnostics Laboratory, Faculty of Medicine, University of Calgary, Calgary, AB, [3]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [4]Mayo Clinic, Rochester, MN, [5]Stanford University School of Medicine, Stanford, CA, [6]Seattle Children's Research Institute, Seattle, WA.

Background/Purpose: There are no known biomarkers for organ involvement, response to therapy, or prognosis in juvenile systemic sclerosis (jSSc). In adults with systemic sclerosis, a number of serum autoantibodies have been described, many of which have been associated with clinical phenotypes. Knowing the pattern of organ involvement associated with a particular autoantibody can be of benefit, with implications for both treatment and screening. The objective of this study was to determine the frequency and clinical significance of an extended panel of both scleroderma-specific and scleroderma-associated autoantibodies in patients with jSSc.

Methods: Stored plasma samples from 28 pediatric patients with systemic sclerosis, 26 with localized scleroderma and 35 age-matched healthy controls were tested for antinuclear antibodies (ANA) as well as antibodies against Ro52, platelet-derived growth factor receptor, Ku, PMScl-75, PMScl-100, Th/To, hUF/NOR-90, fibrillarin, RP155, RP11, centromere proteins A/B (CENP-A, CENP-B), and topoisomerase I/Scl-70 RNA. The majority of the stored samples were obtained after the initiation of treatment. Line immunoassay was used, with the exception of Th/To, which were assessed for by chemiluminescence.

Results: Of the 28 patients with jSSc, the most common antibodies detected were anti-PMScl-100 (17.9%), anti-Scl-70 (14.3%), anti-CENPB (10.7%) and anti-CENPA (7.1%). Anti-PMScl-75 and anti-RP155 were found in one patient each. By comparison, no autoantibodies were detected in the plasma from either healthy pediatric controls or juvenile localized scleroderma patients, except for ANA in five (17.9%) of the localized scleroderma samples and one control. Of the patients with jSSc, 15 (53.6%) were ANA positive but negative for both anti-Centromere (CENP-A /B) and Ant-Scl70. Of these, three carried antibodies to PMScl-100. There were no significant differences in antibody profile between limited and diffuse systemic disease, or with specific clinical disease manifestations.

Conclusion: In this cohort, the presence of autoantibodies targeting PMscl-100, Scl-70, and CENPA/B were highly specific for systemic sclerosis compared to localized scleroderma or controls. Testing for PMscl-100 helped capture additional patients who were ANA positive but anti-Centromere/anti-Scl70 negative, but there remained jSSc patients with ANA of unknown antigen specificity. Furthermore, the association of autoantibodies with systemic but not with localized scleroderma reinforces the concept of two distinct disease processes.

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Mutations of Familial Hemophagocytic Lymphohistiocytosis (FHL) Related Genes and Abnormalities of Cytotoxicity function tests in Patients with Macrophage Activation Syndrome (MAS) Occurring in Systemic Juvenile Idiopathic Arthritis (sJIA). Claudia Bracaglia[1], Elena Sieni[2], Martina Da Ros[2], Carmela De Fusco[3], Concetta Micalizzi[4], Valentina Cetica[2], Benedetta Ciambotti[2], Maria Luisa Coniglio[2], Antonella Insalaco[1], Fabrizio De Benedetti Sr. [1] and Maurizio Arico' Sr. [5]. [1]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, [2]Department of Pediatric Hematology-Oncology, Meyer Children's Hospital, Florence, Italy, [3]Department of Pediatric Hematology-Oncology, Pausillipon Children's Hospital, Naple, Italy, [4]Department of Pediatric Hematology-Oncology, G. Gaslini Children' s Hospital, Genoa, Italy, [5]Istituto Toscano Tumori (I.T.T.), Florence, Italy.

Background/Purpose: MAS is a severe complication of rheumatic diseases, mostly sJIA. Clinical and laboratory features are similar to those of FHL resulting from mutations in selected genes involved in the cytotoxicity pathway. We investigated the presence of mutations of FHL-related genes and of abnormalities in degranulation and perforin expression, in patients with MAS occurring in the context of sJIA.

Methods: From the HLH Italian National Registry, we selected patients with MAS defined according to the HLH 2004 criteria and with confirmed diagnosis of sJIA based on ILAR criteria. Mutation analysis was performed by Sanger sequencing of FHL-related genes. Perforin expression and degranulation were analyzed using flow-cytometry.

Results: We identified 31patients (17 females; 25 Southern European, 6 Indian) with MAS and sJIA. Eleven patients (35.5%) had 14 monoallelic mutations in *PRF1* (n=7), *UNC13D* (n=1), *STX11* (n=1), *STXBP2* (n=4), and *Rab27a* (n=1). Three patients had mutations in 2 genes. Both degranulation and perforin expression were evaluated in 18 patients. At least one test was defective in 11 patients (61%). The clinical and laboratory features of patients with monoallelic mutation and/or with abnormalities in at least one functional test, were not different from those of the remaining patients. However, re-occurrence of MAS tended to be more frequent in patients carrying mutations (mutated 27% versus non-mutated 10%) and in patients showing abnormalities in at least 1 functional test (abnormal 18% versus 0%). One patient died of MAS: she carried the N252S *PRF1* variant and showed reduced perforin expression.

Conclusion: Monoallelic mutations in FHL-related genes and partial defect in either perforin expression or degranulation capacity are frequently observed in patients with sJIA who develop MAS. Additional genetic studies are warranted to identify additional genes potentially linked to MAS development.

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ACR Poster Session A
Rheumatoid Arthritis - Animal Models
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Superior Therapeutic Efficacy of a Novel Oral Small Molecule Retinoic Acid Receptor-Related Orphan Receptor Gamma T [Rorgt] Inverse Agonist Inv-17: A Promising Safe & Efficacious Treatment for Rheumatoid Arthritis. Anderson Gaweco[1], Samantha Palmer[1], Rambon Shamilov[1], Caroline Stremnitzer[1], Katie Matthews[1], Michael Fisher[1], William Windsor[1], James Blinn[1], Ellen M. Ginzler[2] and Jefferson Tilley[1]. [1]Innovimmune Biotherapeutics, Brooklyn, NY, [2]SUNY-Downstate Medical Center, Brooklyn, NY.

Background/Purpose: T helper 17 [T_H17] cells and its production of T_H17 cytokines IL-17A and IL-17F play a critical role in the pathogenesis of RA and collagen-induced arthritis [CIA]. Retinoic acid receptor-related orphan receptor gamma t [RORgT] is a nuclear hormone receptor that specifically regulates T_H17 cells by acting as a control switch for T_H17 differentiation, function and cytokine production. Lead development efforts of several proprietary novel chemical scaffolds of the INV-17 portfolio of small molecule RORgT inverse agonists led to the identification of an INV-17 clinical compound candidate demonstrating potent *in vitro* pharmacological effects against T_H17 cells and cytokines coupled with optimal druggable properties. To establish the preclinical Proof of Concept in RA prior to advancing to IND-enabling development, the *in vivo*treatment efficacy of INV-17 was assessed in the mouse CIA model.

Methods: Disease was induced in DBA1 mice according to a standard protocol. Prior mouse *in vivo*pharmacokinetic [PK] studies determined the optimal oral bioavailability and drug exposure of INV-17 enabling p.o. dosing in this study. To assess the preclinical efficacy in a mouse CIA model, INV-17 was administered orally for 28 days as a therapeutic treatment regimen following chicken collagen CII/CFA disease induction on day 0 and CII/IFA booster immunization on day 15 in DBA1 mice. Upon disease-onset, mice with a clinical arthritis score > 1 (Scale: 0–16) were randomized to receive 28-day dosing with INV-17 at 30 mg/kg (n=10) or comparator controls: Vehicle (n=11) or Dexamethasone [Dex] (n=9).

Results: Successful disease amelioration following INV-17 and Dex treatments was observed with statistically significant reduction of cumulative arthritis score of 6.02 +/− 0.26 [mean +/− SEM] ($p<0.001$) and 0.42 +/− 0.2 ($p<0.001$), respectively, in contrast to the vehicle group of 8.81 +/− 0.43. Significant improvement in clinical disease scores in INV-17 treated mice was evident starting on arthritis day 13 ($p=0.04$) with maximal therapeutic effects observed on arthritis day 16 ($p=0.0007$) through day 26 ($p=0.0003$) until end of study ($p=0.01$). INV-17 drug levels were assessed in peripheral blood and hind joints confirming optimal INV-17 pharmacokinetic exposures and oral bioavailability. INV-17 was well tolerated and INV-17-treated mice were unremarkable with optimal body conditions.

Conclusion: The superior safety and therapeutic efficacy data following 28-day treatment of an orally bioavailable small molecule INV-17 clinical candidate compound provide the first report establishing the preclinical POC in RA with pharmacological intervention of RORgT inverse agonism. This compelling evidence supports advancing INV-17 into IND-enabling development stage and highlights the potential promise of INV-17 as a safe & efficacious novel RA DMARD treatment.

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Anti-Inflammatory Marine Compound, Lyy-B2, Ameliorates Rheumatoid Arthritis through Inhibition of Osteoclast Differentiation. Yen-You Lin[1], Hsin-Pai Lee[1], Shi-Ying Huang[1], Han-Chun Hung[1], Chien-Wei Feng[1], Chun-Hong Chen[1], Jui-Hsin Su[2], Ping-Jyun Sung[3], Jyh-Horng Sheu[1], Yen-Hsuan Jean[4] and Zhi-Hong Wen[1]. [1]National Sun Yat-Sen University, Kaohsiung, Taiwan, [2]National Dong Hwa University, Pingtung, Taiwan, [3]National Museum of Marine Biology & Aquarium, Pingtung, Taiwan, [4]Pingtung Christian Hospital, Pingtung, Taiwan.

Background/Purpose: Osteoclasts are multinucleated giant cells of macrophage/monocyte lineage, and are believed to play major roles in joint destruction caused by rheumatoid arthritis (RA). Nuclear factor of activated T cells, cytoplasmic 1 (NFATc1) is a key transcription factor which up regulates the osteoclastic-related protein expression of cathepsin K, matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), and tartrate-resistant acid phosphatase (TRAP), and promotes osteoclast differentiation resulting in bone resorption. In recent years, a significant number of natural products with anti-inflammatory activity have been discovered from marine organisms, and several of these compounds are now under clinical trials. In the present study, we evaluated a culture of LYY-B2, a soft coral-derived compound with anti-inflammatory and anti-arthritic properties.

Methods: We used lipopolysaccharide (LPS)-stimulated murine macrophages to evaluate the anti-inflammation and anti-osteoclast formation properties of LYY-B2, *in vitro*. Lewis rats (180–220g) were used to evaluate the possible effects of LYY-B2, *in vivo*, on adjuvant-induced arthritis (AIA) and collagen-induced arthritis (CIA) animal models. We also examine the joint features of LYY-B2 attenuation of RA by histology and immunohistochemistry.

Results: LYY-B2 significantly inhibited pro-inflammatory induced nitric oxide synthase protein expression in LPS-stimulated macrophages. Moreover, it also attenuated multinucleated cell formation, osteoclast-related gene expression (MMP9 and cathepsin K) and expression of osteoclast-related proteins (TRAP and actin ring). Our animal experiments revealed that LYY-B2 (5mg/kg) significantly inhibited AIA and CIA joint characteristics in rats. Moreover, using histological analysis, we have found that LYY-B2 also improved the histopathologic features of RA. Immunohistochemical results show that LYY-B2 inhibited expression of osteoclast-related proteins cathepsin K, MMP 2, MMP 9, CD11b, and NFATc1 in ankle tissues of AIA- and CIA-rats.

Conclusion: The present findings indicated that LYY-B2 could be of potential use as a therapeutic agent to treat rheumatoid arthritis through inhibition of osteoclast differentiation.

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Regulation of TNF-α-Mediated Activation of Rheumatoid Synovial Fibroblasts By Transcription Factor Snail. Chrong-Reen Wang, Shih-Yao Chen, Ai-Li Shiau, I-Ming Jou, Ming-Fei Liu and Chao-Liang Wu. National Cheng Kung University Medical College, Tainan, Taiwan.

Background/Purpose: Transcription factor Snail plays active roles in various biological functions and is involved in many disease states. We hypothesized that this molecule regulates TNF-α-mediated activation of rheumatoid synovial fibroblasts (SF), and examined its roles in expression of Cadherin-11 (Cad-11) and α-smooth muscle actin (α-SMA, a myofibroblast marker), invasive ability and IL-6 production.

Methods: Synovial tissues were obtained from patients with rheumatoid arthritis (RA), a diagnosis according to 2010 RA classification criteria, and an experimental arthritis model of collagen-induced arthritis (CIA) in rats. SF were treated with TNF-α or a Wnt signaling inducer, and CIA joints were injected with a TNF-α antagonist. The expression of Snail in SF and joints was modulated by lentiviral vector-mediated transfer of cDNA or short hairpin RNA.

Results: There were higher expression levels of Snail and Cad-11 with a positive correlation in synovial tissues from RA patients and CIA rats. Stimulation with TNF-α or activation of Wnt signaling up-regulated the expression levels of Snail, Cad-11 and α-SMA in SF, and TNF-α antagonist therapy down-regulated their expression levels in CIA joints. While Snail-overexpressed SF transfectants had increased expression levels of Cad-11 and α-SMA and enhanced TNF-α-mediated invasive capacity and IL-6 production, Snail-knockdowned CIASF transfectants had decreased expression levels and the opposite effect on these functions. In addition, Snail-overexpressed normal rat joints had hyperplastic synovium with increased expression levels of Cad-11 and α-SMA. In CIA joints, silencing the expression of Snail ameliorated arthritis with reduced Cad-11 expression and extracellular matrix (ECM) deposition, whereas overexpressing Snail exacerbated arthritis with increased Cad-11 expression and ECM deposition.

Conclusion: This study demonstrates for the first time that transcription factor Snail regulates TNF-α-mediated activation of rheumatoid SF, and these findings might contribute to the pharmacological development of therapeutics targeting SF in RA patients.

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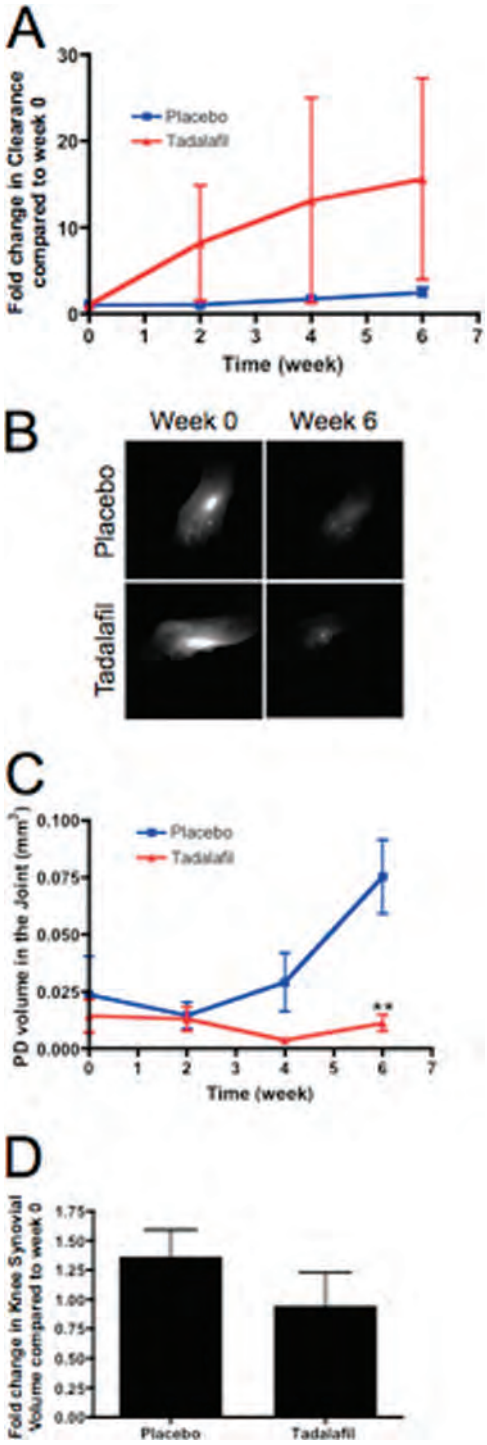
Tadalafil Decreases Joint Inflammation in TNF-Tg Mice By Restoring Passive Lymphatic Transport. Echoe M. Bouta[1], Igor Kuzin[2], Ronald Wood[3], Christopher T. Ritchlin[3], Andrea Bottaro[2] and Edward M. Schwarz[1]. [1]University of Rochester, Rochester, NY, [2]Cooper Medical School, Camden, NJ, [3]University of Rochester Medical Center, Rochester, NY.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with enigmatic episodic flares. Using longitudinal imaging, we recently demonstrated that arthritic knee flare in tumor necrosis factor transgenic (TNF-Tg) mice is associated with the loss of the lymphatic pulse and B-cell clogging of the lymphatic sinuses in the adjacent popliteal lymph node (PLN), which is ameliorated by B-cell depletion therapy that restores passive lymphatic flow from inflamed joints. To test the hypothesis that similar efficacy can be obtained via vasodilatory therapy that opens lymphatic vessels parallel to the clogged PLN, we evaluated the effects of tadalafil, a FDA-approved PDE5 inhibitor, on lymphatic transport, synovitis and bone erosion in TNF-Tg mice experiencing knee flare.

Methods: TNF-Tg mice with collapsed PLN underwent contrast enhancement MRI (CE-MRI), power Doppler (PD) ultrasound, near infrared indocyanine green (NIR-ICG) imaging prior to and after treatment via gavage every other day with tadalafil or placebo for six weeks.

Results: Fold change in ICG clearance from the footpad, a marker of lymphatic transport, was found to be higher in tadalafil treated animals compared to placebo (15.62$\pm$23.25 vs. 2.77$\pm$1.17) (Figure 1A and B). As expected, lymphatic contraction frequency decreased over time in the placebo and tadalafil treatment groups, consistent with progression of the disease and lymphatic dilation respectively. Lymph node contrast enhancement (LNCE), an alternative biomarker of lymphatic transport to the PLN that is measured via CE-MRI, decreased slightly (0.87$\pm$0.10 fold change) in the placebo group, indicating further PLN collapse. In contrast, tadalafil induced a slight increase (1.05$\pm$0.12 fold change) in LNCE, indicating a halt in PLN collapse. Additionally, mice treated with tadalafil showed a greater PLN volume compared to placebo (15.56$\pm$10.15 mm^3 vs. 9.97$\pm$6.09 mm^3), indicative of increased transport to the PLN. PD within the joint, a measure of inflammation, was found to be significantly lower after tadalafil treatment compared to placebo (0.011$\pm$0.01 mm^3 vs. 0.08$\pm$0.02 mm^3) (Figure 1C). Placebo treated animals were shown to have a 1.36$\pm$0.23 fold change in knee synovial volume, while tadalafil treatment showed a lower fold change, 0.95$\pm$0.28 (Figure 1D).

Conclusion: Tadalafil treatment increases passive lymphatic transport, as evidenced by increased ICG clearance, PLN volume and LNCE; in conjunction with decreased lymphatic contraction. In addition, this increase in lymphatic transport results in decreased PD volume within the joint, indicative of decreased joint inflammation. These results in addition to flow cytometry and histology of joints and PLNs will be presented.



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IL-1 Receptor Antagonis (IL-1Ra)-Fc Ameliorate Autoimmune Arthritis By Regulation of the Th17 Cells/Treg Balance and Arthrogenic Cytokine Activation. Hong Ki Min[1], Sung Hwan Park[2], Mi-La Cho[3], Ji Hyeon Ju[1], Seung-Ki Kwok[1], Seon-Yeong Lee[3], Seung Min Jung[1], Kyung-Su Park[4] and Jennifer Lee[1]. [1]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [2]The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea, [3]Catholic University of Korea, Seoul, South Korea, [4]St. Vincent Hospital, SuWon Gyeonggi-do, South Korea.

Background/Purpose: IL-1β signalling has critical role on pathogenesis of various inflammatory arthritis including rheumatoid arthritis (RA). We aimed to investigate the therapeutic effects of human IL-1 receptor antagonist with Fc fragment (hIL-1Ra-Fc) on autoimmune arthritis and find out the possible mechanisms by which hIL-1RA-Fc has anti-arthritic effects in a murine model of RA and arthritis patient.

Methods: Collagen-induced arthritis (CIA) murine model was induced in DBA/1J mice. The levels of various cytokines were determined by using enzyme-linked immunosorbent assay. The joints of mouse were assessed for clinical arthritis score and histologic features. Th17 cells and Treg cells were stained by using antibodies specific for CD4, IL-17, CD25, and FoxP3. Osteoclastogenesis was determined by TRAP stain and real-time PCR.

Results: hIL-1RA-Fc reduced the clinical arthritis, histological inflammation and cartilage score in CIA model. The expression of proinflammatory cytokines, VEGF, and RANK were reduced in affected joint of hIL-1Ra-Fc treated mice. hIL-1Ra-Fc treated mice showed decreased number of Th17 cells with increased Treg cells in spleens. hIL-1Ra-Fc reduced Th17 cell differentiation by inactivation of STAT-3 signalling, reciprocally induced Treg cell differentiation through STAT-5 signalling. In addition, Suppression of gene expression of IL-17, TNF-α, RANKL and VEGF were decreased, while increased Foxp3 gene expression in PBMC of RA patients after administration of hIL-1Ra-Fc.

Conclusion: The anti-arthritis effects of hIL-1RA-Fc are associated with regulating balance between Th17 cells and Treg cells and with suppressing osteoclastogenesis and angiogenesis in affected joints.

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AMPK Activation in Inflammatory Arthritis. Monica Guma[1], Yun Wang[2] and Ru Liu-Bryan[2]. [1]University of California, San Diego, La Jolla, CA, [2]UCSD/VAMC, La Jolla, CA.

Background/Purpose: AMP-activated protein kinase (AMPK) is a serine/threonine protein kinase involved in the regulation of cellular energy homeostasis. It is a central regulator of both lipid and glucose metabolism. Many studies have suggested that AMPK activation can also exert significant anti-inflammatory and immunosuppressive effects. We evaluated whether modulating this pathway altered pathogenic mechanisms in inflammatory arthritis.

Methods: The AMPK agonist A-769662 (60mg/kg/bid) was tested in two arthritis models: In antigen induced arthritis (AIA), mice were primed with mBSA in complete Freund's adjuvant and then given an intraarticular challenge with mBSA in the knee on day 21. In passive serum arthritis, K/BxN serum was injected on day 0. Joints were harvested and prepared for histological assessment. IL-6 expression in joints and sera was measured by ELISA. Human fibroblast-like synoviocyte (FLS) and bone marrow derived macrophage (BMDM) function was tested using A-769662 (250uM) as follows: 1) phosphorylation of p65 NF-kappaB by Western Blot, 2) IL-6 secretion by ELISA, 3) NO secretion by Griess method, 4) cell survival in H_2O_2 treated cells by phase contrast light microscopy.

Results: AMPK pathway activation by A-769662 reduced inflammatory infiltration and joint damage in both animal models. In passive K/BxN model, day 8 scores were 8.2 ± 3 and 2.4 ± 3 ($P<0.05$) for vehicle and A-769662-treated mice, respectively. In AIA model joint histology scores for vehicle and A-769662-treated mice for synovial hypertrophy were 2.9 ± 0.9 and 1.6 ± 1.1 ($p=0.01$), bone erosion scores were 2.2 ± 1 and 1.5 ± 1.1 ($p<0.05$), and cartilage damage scores were 2 ± 0.6 and 1.2 ± 0.6 ($p<0.05$), respectively. IL-6 expression in serum and arthritic joints was significantly decreased in A-769662 treated mice. The mechanism of AMPK action was evaluated in FLS and BMDM. AMPK activation with A-762664 reduced IL-6 and NO secretion by $52\pm5.6\%$ and 76 ± 7.5 %respectively ($p<0.05$), and p65 NF-kappaB phosphorylation after TLR stimulation in BMDM. Additionally, AMPK activation also significantly increased H_2O_2-induced apoptosis in FLS.

Conclusion: Activating AMPK pathway suppressed inflammatory arthritis in mice as well as IL-6 expression in serum, arthritic joints and cultured BMDM. These data suggest that AMPK signaling activation could be an effective therapeutic strategy for IL-6 dependent inflammatory arthritis.

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Etanercept, Abatacept and Anakinra Treatment Ameliorates Inflammation and Pain in a Novel Mono-Arthritic Multi-Flare Model of Streptococcal Cell Wall Induced Arthritis: Further Characterization in a Rodent Model of Collagen Induced Arthritis. Kalyan Chakravarthy, Robert Faltus, Anwar Murtaza and Milenko Cicmil. Merck Research Laboratories, Boston, MA.

Background/Purpose: We developed a novel mono-arthritic multi-flare Rat Streptococcal Cell Wall (SCW) model which captures certain aspects of disease with flares and remission of inflammation similar to Rheumatoid Arthritis (RA). To delineate the role of TNF, T cells, and IL-1 in pathogenesis of SCW-induced arthritis, we investigated the activity of clinical agents, Etanercept, Abatacept and Anakinra. Comparative evaluation of these targeted therapies was also performed in the rat Collagen Induced Arthritis (CIA) model.

Methods: SCW arthritis was induced in female Lewis rats with an intra-articular injection in the hind ankle joint on day 1 (flare 1) followed by two intravenous challenges on days 21 (flare 2) and 42 (flare 3) of SCW extract PG-PS 100p. CIA was induced using methods previously described in literature. Inflammation and pain were monitored by measuring paw swelling (mechanical calipers) and withdrawal threshold (von-Frey assay) respectively. Additional biomarkers assessed by cytokine profiling, cell phenotyping, bioluminescence/μCT imaging and histopathology were also performed in the local joint.

Results: In the SCW model late prophylactic administration of Etanercept, Abatacept and Anakinra significantly inhibited paw swelling by $\geq60\%$ ($p<0.001$), $\geq60\%$ ($p<0.001$), 88% ($p<0.001$) and pain by 37% ($p<0.05$), $\geq28\%$ ($p<0.05$) and 64% respectively in flare 2. Etanercept in flare 3 inhibited paw swelling by 60% ($p<0.001$) and partially inhibited pain by 27%. Interestingly, prior treatment with Etanercept in flare 2 followed by a wash out period of 14 days and re-administration in flare 3 led to a loss in efficacy, potentially due to immunogenicity. Abatacept administration in flare 3 had no effect on either paw swelling or pain in rats that were treated in flare 3 alone or in rats that were treated previously in flare 2. In the CIA model, both late prophylactic and therapeutic treatment with Etanercept inhibited paw swelling by 50% ($p<0.001$). A loss of efficacy with Etanercept was also observed in the CIA model when administered prophylactically possibly due to immunogenicity. Prophylactic, late prophylactic and therapeutic administration of Abatacept in the CIA model significantly inhibited paw swelling by 100% ($p<0.001$), 42% ($p<0.001$) and 34% ($p<0.001$) respectively. The additional biomarkers corroborated with efficacy in both models.

Conclusion: We developed a novel multi-flare SCW model that can be used to evaluate clinically relevant parameters of inflammation and pain simultaneously. Using clinical agents Etanercept, Abatacept and Anakinra targeting TNF, T cells and IL-1 respectively we have delineated distinct pathogenic mechanisms of inflammation and pain at different stages of disease in the SCW model. We also show similar profiles of efficacy in late prophylactic and therapeutic regimens in the CIA model. The flaring mechanism in the SCW model allows for drug washout periods in between compound administration. This might provide useful pre-clinical insights on potential immunogenicity mechanisms that may be relevant in a clinical setting. Our novel model can facilitate innovative assessment of anti-rheumatic agents in multiple flares and offers a powerful tool for drug discovery.

Disclosure: K. Chakravarthy, Merck Pharmaceuticals, 3; **R. Faltus**, Merck Pharmaceuticals, 3; **A. Murtaza**, Merck Pharmaceuticals, 3; **M. Cicmil**, Merck Pharmaceuticals, 3.

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A Novel, Small Molecule Cyclin-Dependent Kinase 4/6 Inhibitor As the New Option for Treatment of Rheumatoid Arthritis. Hiroshi Takahashi[1], Tsuyoshi Mizuno[1], Toshimichi Nakamura[1], Yuri Sakai[1], Yumiko Muroga[1], Kyohei Horie[1], Naoki Hase[1], Hitoshi Kohsaka[2] and Tsuyoshi Kimura[1]. [1]Teijin Pharma Limited, Hino, Tokyo, Japan, [2]Tokyo Medical and Dental University (TMDU), Tokyo, Japan.

Background/Purpose: The pathogenesis of rheumatoid arthritis (RA) is characterized by infiltration of immune cells to the synovial tissues and their hyperplasia. Therapeutic strategies to inhibit proin-

flammatory cytokines or immune cells with biological agents and methotrexate are the mainstay in the current treatment of RA. However, they cannot induce complete remission in all of the patients. Combination therapy of two biologics such as etanercept and abatacept failed to show the synergistic effects. Cyclin-dependent kinases (CDK) are key regulators of the cell cycle progression, and several CDK inhibitors have been developed for treatment of cancer. Recently, it was reported that cell cycle inhibition of synovial fibroblasts with a small molecule CDK4/6 inhibitor ameliorated progression of arthritis without attenuating acquired immune responses in an animal model of RA. Although CDK4/6 is thus an attractive target for treatment of RA, its inhibitors have not yet been developed for clinical use in RA treatment. In this study, we show that we have developed a novel and potent CDK4/6 inhibitor, Compound T and its derivatives for RA treatment. We examined Compound T for its anti-arthritic effects in monotherapy and in combination therapy with TNF blockade in animal models of RA.

Methods: Novel synthetic compounds were evaluated in kinase assays to determine in vitro CDK4/6 inhibitory activity and selectivity for CDKs and other kinases. The effects of these compounds on cell cycle were tested by the SubG1 method. Pharmacokinetic (PK) studies and hERG channel binding assay were performed to determine PK and safety profiles of the test compounds. In vivo efficacy of Compound T was tested in collagen induced arthritis (CIA) as well as anti-collagen antibody induced arthritis (CAIA) of mice. Compound T was orally administered to both models to see the effects on the arthritis score. The effect of combination treatment of Compound T with etanercept was tested in the CAIA model.

Results: Compound T inhibited CDK4 and 6 potently (IC50 is about 1 nM) and selectively to other kinases in the cell free assay. Compound T inhibited cell cycle at the G0/G1 phase without inducing cell death in the cell based assay. Oral administration of Compound T alone suppressed the arthritis score, compared to vehicle treatment, in the CAIA and CIA models. In the CAIA model, combination of oral Compound T with intraperitoneal etanercept synergistically suppressed the progression of arthritis compared to monotheray with Compound T or with etanercept at maximum effective dose. In hERG binding assay, Compound T had binding activity at the high concentration range, but several compounds among its derivatives showed low binding affinity against hERG.

Conclusion: Compound T we synthesized is a potent inhibitor of CDK4/6 and selective to other kinases. Oral treatment with Compound T suppressed the arthritis score in both CAIA and CIA models of mice. CDK4/6 inhibitors should offer a new option for better treatment of RA.

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Prolactin Reduces Bone Erosion in Adjuvant-Induced Arthritis. Maria G. Ledesma-Colunga, Norma Adan, Ana L. Reyes-Lopez, Fernando Lopez-Barrera, Gonzalo Martinez de la Escalera and Carmen Clapp. Institute of Neurobiology, National University of Mexico (UNAM), Queretaro, Mexico.

Background/Purpose: Bone erosion is an important feature of rheumatoid arthritis (RA) that frequently results in lifelong crippling. The receptor activator of NFkB ligand (RANKL)/osteoprotegerin (OPG)/RANK receptor (RANK) system triggers bone loss in arthritis and is activated by proinflammatory cytokines such as TNFa. Prolactin (PRL), the hormone essential for lactation, may protect against bone loss in RA. PRL stimulates bone formation and frequently increases in the circulation of patients with RA. Moreover, hyperprolactinemia reduces chondrocyte apoptosis, proinflammatory cytokine expression, pannus formation, joint swelling, and pain in adjuvant-induced arthritic (AIA) rats (Adan et al., J Clin Invest 123:3902, 2013). Here, we investigate whether eliciting hyperprolactinemia before or after inducing AIA reduces the systemic levels of TNFa and inhibits the expression of the RANKL/OPG/RANK system and bone erosion in arthritic ankle joints.

Methods: Progression of inflammation (joint swelling) was analyzed in rats implanted or not with osmotic minipumps delivering PRL beginning 3 days before of 15 days after the injection of Complete Freunds' adjuvant (CFA). At maximal inflammation (21 days post CFA), bone erosion was evaluated histochemically, RANKL/OPG/RANK, TNFa, and PRL receptor (PRLR) mRNA levels in arthritic joints were quantified by qRT-PCR; and systemic TNFa protein levels were determined by ELISA.

Results: Expression of the PRLR was significantly elevated in the joints of AIA rats. Treatment with PRL before or after inducing AIA reduced local (hind paw) expression and serum levels of TNFa. Moreover, PRL reduced the AIA-induced increase of RANKL and RANK expression in joints, but did not modify that of the RANKL inhibitor OPG. Consistent with these findings, treatment with PRL before inflammation onset significantly reduced the AIA-induced loss of cortical and trabecular bone.

Conclusion: PRL-induced down-regulation of TNFa/RANKL/RANK expression may protect against bone destruction in arthritis, supporting the therapeutic potential of hyperprolactinemia in RA. Funded by UNAM grant IN200312.

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Improvement of the Stability of RNA Aptamers Against Interleukin-17A. Natsuki Otaki[1], Asako Sasaki[1], Shinsuke Hiramoto[1], Masakazu Nagamine[1], Shigeyuki Mori[1], Tomoyoshi Kayo[1], Kuniyoshi Hota[1], Masayuki Takahashi[1], Kazuhiko Haruta[1] and Yoshikazu Nakamura[2]. [1]Zenyaku Kogyo Co., Ltd., Tokyo, Japan, [2]RIBOMIC Inc., Tokyo, Japan.

Background/Purpose: Aptamers are RNA or DNA oligonucleotides selected for their capacity to specifically bind and inhibit the function of a target protein. The effect is similar to neutralizing antibodies that defend the body against pathogenic antigens. These potentially therapeutic oligonucleotides often have short half-lives, however, because they are rapidly degraded by nucleases in peripheral blood and excreted by the kidneys. Here we describe an RNA aptamer against IL-17A that resists degradation in serum and decreases the severity of collagen-induced arthritis in DBA/1 mice.

Methods: *In vitro assay of serum stability*. After substituting a methoxy group for the 2′ hydroxyl group of ribose, we incubated the RNA aptamers in mouse serum for 0.5 to 72 hours at 37°C. Controls were incubated in phosphate buffered saline. Next, samples were added to quenching buffer (8 M urea, 10 mM EDTA, 0.05% bromophenol blue). Then, the RNA fragments were electrophoresed in 20% polyacrylamide gels that contained 8 M urea in TBE buffer. Bands were visualized by staining the gel with SYBR Green II. Each fraction of intact aptamer was normalized to its corresponding control. *Pharmacokinetic studies in mice.* Aptamers were PEGylated with 40-kDa polyethylene glycol and conjugated with 3′-inverted deoxythymidine. Then, these aptamers were infused as a single bolus into the tail vein of a C57BL/6J *mouse* at 1 mg/kg. Aptamer concentrations in plasma were measured by enzyme-linked oligosorbent assay. *Collagen-induced arthritis in mice.* Mice were immunized with bovine type II collagen in Freund's complete adjuvant on day 1. On day 22, they were boosted with bovine type II collagen in Freund's incomplete adjuvant. PEGylated aptamers were injected intraperitoneally at 5 mg/kg once a day from day 22 to day 37. Objective signs of arthritis for each paw were scored using a scale of 0 to 4.

Results: *In vitro* assay of aptamer 17M-340 for serum stability showed very little degradation after 72 hours incubation. By contrast, prototype aptamer Apt21-2 or 17M-4 were rapidly degraded within 24 hours. *In vivo*, the plasma half-life of 17M-340 was 9.3 hours, more than ten-fold that of 17M-4. Finally, intraperitoneal injection of 17M-340 but not 17M-4 reduced the objective score of collagen-induced arthritis significantly ($p \leq 0.05$).

Conclusion: The anti-IL-17A aptamer is 31-base oligoribonucleotide that forms a stem-loop structure. Substitution of a methoxy group for the 2' hydroxyl group of ribose at three positions in the stem and one position in the loop markedly increased stability of the aptamer *in vivo*. Our findings raise the

possibility that RNA aptamers such as 17M-340 may be effective treatments for patients with chronic inflammatory diseases.

Disclosure: N. Otaki, Zenyaku Kogyo Co., Ltd., 3; **A. Sasaki**, Zenyaku Kogyo Co., Ltd., 3; **S. Hiramoto**, Zenyaku Kogyo Co., Ltd., 3; **M. Nagamine**, Zenyaku Kogyo Co., Ltd., 3; **S. Mori**, Zenyaku Kogyo Co., Ltd., 1; **T. Kayo**, Zenyaku Kogyo Co., Ltd., 1; **K. Hota**, Zenyaku Kogyo Co., Ltd., 3; **M. Takahashi**, Zenyaku Kogyo Co., Ltd., 1; **K. Haruta**, Zenyaku Kogyo Co., Ltd., 1; **Y. Nakamura**, TODAI TLO, Ltd., 7.

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Deletion of the Prolactin Receptor Aggravates the Course of Antigen-Induced Arthritis. Norma Adan, Maria G. Ledesma-Colunga, Ana L. Reyes-Lopez, Fernando Lopez-Barrera, Gonzalo Martinez de la Escalera and Carmen Clapp. Institute of Neurobiology, National University of Mexico (UNAM), Queretaro, Mexico.

Background/Purpose: Prolactin (PRL), the hormone essential for lactation, may protect against joint damage in rheumatoid arthritis. PRL frequently increases in the circulation of patients with rheumatoid arthritis, and eliciting hyperprolactinemia in rats before or after inducing the adjuvant model of inflammatory arthritis reduced chondrocyte apoptosis, proinflammatory cytokine expression, pannus formation, joint swelling, and pain (Adan et al., J Clin Invest 123:3902, 2013).

Methods: To better understand the role of PRL in inflammatory arthritides, antigen-induced arthritis (AIA) was induced in PRL receptor-deficient ($Prlr^{-/-}$) mice from two susceptible genetic backgrounds (C57BL/6 and 129Svj). On day 0, preimmunized or control animals were injected into the knee joint with methylated-BSA antigen (mBSA) or vehicle, respectively, and parameters of inflammation were evaluated at days -1, +1, +3, and +5 post-mBSA.

Results: In the 129Svj strain, $Prlr^{-/-}$ mice showed an earlier onset of AIA but similar clinical severity (joint swelling and pain) compared to wild type mice. However, PRLR-deficient mice had a two-fold increase in synovial hyperplasia and higher levels of circulating IL-6. In the C57BL/6 strain, $Prlr^{-/-}$ mice displayed similar joint swelling but increased mechanical allodynia compared to $Prlr^{-+/+}$ mice. Consistent with augmented pain, a two-fold enhanced synovial hyperplasia occurred in the absence of the PRLR, although circulating levels of IL-6 were similar between $Prlr^{-/-}$ and $Prlr^{-+/+}$ mice.

Conclusion: Loss of the PRLR correlates with an aggravated AIA phenotype with different symptoms depending on the genetic background. These findings support the protective role of the PRL system in inflammatory arthritis. Work supported by UNAM-Grant IN200312.

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Inflammatory Arthritis in K/BxN Mice Is Associated with Abnormal HDL Function. C. Charles-Schoeman, Ani Shahbazian, Yuen Yin Lee and Srinivasa T. Reddy. UCLA David Geffen School of Medicine, Los Angeles, CA.

Background/Purpose: Patients with rheumatoid arthritis (RA) have significantly increased cardiovascular (CV) morbidity and mortality. Abnormal function of high density lipoprotein (HDL) has been implicated as a mechanism for this increased CV risk. The current work investigated HDL function in the K/BxN mouse model of RA.

Methods: Male KRN mice were crossed with NOD female mice expressing the MHC class II molecule A^{g7} to generate K/BxN mice. 29 mice were assessed for arthritis activity using caliper measurements of hindlimbs and clinical scores 3 times weekly until sacrifice/serum collection at 21 weeks. HDL function was assessed by a previously published cell free assay (*A&R* 2009; 60: 2870) and paraoxonase 1 (PON1) activity was assessed using both paraoxon and dihydrocumarin as substrates (*A&R*2013; 65: 2765). Total and HDL cholesterol (HDL-C) were assessed by standard assays.

Results: Greater arthritis activity measured by higher hind limb scores in K/BxN mice was significantly associated with decreased ability of HDL to inhibit LDL oxidation (higher HDL inflammatory index (HII)); $r = 0.5$, $p=0.01$ for correlation of hind limb scores with HII at 21 weeks), and decreased PON1 activity measured using both paraoxon and dihydrocumarin as substrates ($r = -0.6$, $p=0.0001$ and $r = -0.7$, $p<0.0001$ respectively). Higher arthritis activity in K/BxN mice (hind limb scores) was also associated with greater suppression of total cholesterol (TC) and HDL-C, (r values $= -0.6$, p values $=0.001$). A marked correlation was observed between the suppression of HDL-C levels and impairment in HDL function ($r = -0.8$ for correlation of HDL-C with HII, $p<0.0001$).

Conclusion: Inflammatory arthritis in K/BxN mice is associated with suppression of HDL- C levels and the generation of more pro-inflammatory, dysfunctional HDL particles. These results are consistent with our prior work showing an association of higher disease activity in RA patients with worse HDL function. This model will be used for further evaluation of mechanisms linking abnormal HDL function to CV risk in RA.

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Interleukin-33 Suppresses Experimental Arthritis through Promoting $Foxp3^+$ Regulatory T-Cells and Type-2 Immune Responses in Mice. Jerome Biton[1], Allan Thiolat[1], Sara khaleghparast Athari[1], Delphine Lemeiter[2], Roxanne Herve[1], Patrice Decker[1], Jean-Philippe Girard[3], Stephane Roga[3], André Herbelin[4], Anais Levascot[4], Marie-Christophe Boissier[2] and Natacha Bessis[1]. [1]INSERM UMR 1125, Li2P, University Paris 13, Sorbonne Paris Cité and Rheumatology Department, Avicenne Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Bobigny, France, [2]INSERM UMR 1125, Li2P, University Paris 13, Sorbonne Paris Cité, Bobigny, France, [3]Centre National de la Recherche Scientifique, Institut de Pharmacologie, dUniversité de Toulouse, Université Paul Sabatier, Institut de Pharmacologie et de Biologie Structurale et de Biologie Structurale, toulouse, France, [4]INSERM U1082, Pôle Biologie Santé,, poitiers, France.

Background/Purpose: Interleukin (IL)-33 is a new member of the IL-1 family that exerts pleiotropic activities in innate and adaptive immunity. With its receptor ST2, they have newly emerged as key molecules strongly involved in several inflammatory and autoimmune disorders. Recent evidence suggests that the IL-33/ST2 axis is strongly involved in the pathophysiology of rheumatoid arthritis (RA). However in RA models, the role of IL-33 and its receptor is still controversial. We aimed at deciphering IL-33 mode of action after administration in an experimental model of RA, namely collagen-induced arthritis (CIA).

Methods: CIA was induced by immunization of C57Bl/6 mice with type 2 collagen. IL-33 was ip administrated in CIA mice and cells were analyzed by flow cytometry on day 28 after CIA induction.

Results and Conclusion We show a previously unshown dramatic inhibition of mouse collagen-induced arthritis (CIA) development after repeated administration of IL-33. This therapeutic effect was related to an enhanced type-2 immune response, including the expansion of eosinophils, Th2 cells, innate type 2 lymphoid cells (ILC2, defined as $CD25^+$ c-Kit^+ Lin^- Sca-1^+ $ST2L^+$) and an increase in Th2 cytokines levels in the serum of treated mice. Moreover, our work brings out the interplay between Treg and IL-33. Since IL-33 acts directly on Treg via ST2L, we showed that IL-33 treatment of CIA majors Treg frequency and increases the suppressive capacities of those cells. IL-33 also induces the emergence of a $CD39^{+/high}$ Treg population in a ST2L dependant manner In the light of our present study, IL-33 can exert powerful anti-inflammatory properties in CIA, integrating the establishment of a type-2 immune response, the expansion and the activation of Treg. Our study reveals an undescribed mechanism by which IL-33 inhibits arthritis development, thus updating and strengthening the crucial role of IL-33 in RA.

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The Additive Inflammatory *in Vivo* and *in Vitro* Effects of Thymic Stromal Lymphopoietin (TSLP) and IL-7 in Arthritis Underscore the Therapeutic Rationale for blockade of Their Common Receptor Subunit. M.R. Hillen[1], S.A.Y. Hartgring[1], T.R.D.J. Radstake[2], C.E. Hack[1], F.P.J.G. Lafeber[1] and J.a.G. van Roon[1]. [1]UMC Utrecht, Utrecht, Netherlands, [2]University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Interleukin (IL)-7 and thymic stromal lymphopoietin (TSLP) are cytokines that signal through the IL-7Ra subunit and play proinflammatory roles in experimental arthritis and rheumatoid arthritis (RA). IL-7R blockade can potentially block signalling of both cytokines. In this study the potential of IL-7R and TSLPR signalling inhibition as well as simultaneous inhibition was investigated in murine experimental arthritis. In

addition, the additive effects of IL-7 and TSLP in human RA *in vitro* dendritic cell (DC)/T-cell co-cultures were studied.

Methods: Proteoglycan-induced arthritis was induced in wildtype mice (WT) and mice deficient for the TSLP receptor subunit (TSLPR) and mice of both genotypes were treated with anti-IL-7R or PBS. Arthritis severity was assessed and paw lysate and serum were collected for cytokine analyses. CD1c DCs and CD4 T-cells were isolated from blood of RA patients and were co-cultured in presence of IL-7, TSLP or the combination of both cytokines and proliferation and cytokine production were assessed.

Results: Arthritis severity and synovitis were significantly decreased in TSLPR−/− mice treated with anti-IL-7R compared to control mice (Arthritis severity; mean area under the curve ± SEM: 25 ± 5.9 vs. 50.7 ± 6.9; $p<0.01$). This was associated with strongly reduced radiographic joint damage and osteoclast activity, which were significantly lower in TSLPR−/− mice treated with anti-IL-7R compared to WT mice treated with anti-IL-7R, PBS treated TSLPR−/− mice or PBS treated WT mice (Radiographic joint damage: Mean score ± SEM: 0.1 ± 0.1, 0.6 ± 0.1, 0.3 ± 0.1, 1.4 ± 0.2 respectively; all $p<0.001$). This was associated with decreased levels of IL-17, IL-6, IL-1β and CD40L, which were all robustly downregulated by combined blockade of IL-7 and TSLP signalling (all $p<0.05$). In DC/CD4 T-cell co-cultures from RA patients, TSLP and IL-7 additively increased T-cell proliferation ($p<0.01$) and production of Th17-associated cytokines (IL-17, IL-22, IL-6; all $p<0.05$) and T-cell attracting chemokines (all $p<0.05$).

Conclusion: TSLP and IL-7 additively promote production of Th17-specific and Th17-associated cytokines, linked with enhanced inflammation and immunopathology. As both cytokines signal via the IL-7Ra, these data emphasize the need for drugs that target this subunit to abrogate activity of both ligands and prevent immunopathology in RA.

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Effect of Etanercept on Endothelial Dysfunction in Rat Adjuvant-Induced Arthritis. Perle Totoson[1], Katy Maguin-Gaté[1], Daniel Wendling[2] and Céline Demougeot[1]. [1]EA 4267 « Fonctions et Dysfonctions Epithéliales », Faculté de Médecine-Pharmacie, Besançon, France, [2]CHU J Minjoz, Besancon, France.

Background/Purpose: Growing evidence indicate that Rheumatoid Arthritis (RA)-associated increase in cardiovascular risk is secondary to the presence of endothelial dysfunction (ED). Although Tumor Necrosis Factor inhibitors are unanimously approved for the treatment of RA, their effect on ED is still controversial. The present study aimed to determine the impact of etanercept on ED as well as the mechanisms involved in the model of adjuvant-induced arthritis (AIA) rats.

Methods: AIA was induced by an intradermal injection of *Mycobacterium butyricum* in the tail of male Lewis rats. At the first signs of arthritis, AIA rats received etanercept (10 mg/kg/ 3 days, s.c) or saline (controls AIA) for 21 days. Arthritis score was daily evaluated. At the end of experiment, preconstricted isolated aortic rings were relaxed with acetylcholine (Ach, $10^{-11}-10^{-4}$moles/liter) in the presence or not of inhibitor of nitric oxide (NO) synthase (L-NAME), cyclooxygenase-2 (NS398), arginase (nor-NOHA), endothelium-derived hyperpolarizing factor (EDHF) (apamin/charybdotoxin) and superoxide anions production (Tempol). Blood pressure was measured by invasive method.

Results: Compared to controls AIA, etanercept significantly reduced arthritis score (−34%, $p<0.001$). This was associated with an improvement of Ach-induced relaxation ($p<0.05$). These beneficial effects of etanercept on ED were mediated by a decrease in cyclooxygenase-2 and arginase activity, a decrease in superoxide anions production and an increase in NO synthase activity. EDHF production was unaffected by the treatment. Surprisingly, no correlation was found between the arthritis score and Ach-induced relaxation (Emax) ($r=-0.195$; $p=0.246$). Last, etanercept significantly increased systolic blood pressure (125.2 ± 5.7 vs 107.1 ± 5.5 controls AIA, $p<0.05$), but not diastolic blood pressure.

Conclusion: Our study demonstrated that etanercept decreases endothelial dysfunction in conduit arteries despite increasing blood pressure. The beneficial effects involved the modulation of vascular NO synthase, cyclooxygenase-2, arginase and superoxide anions production pathways. Our data suggested that these effects are, at least in part, independent on arthritis severity reduction.

Disclosure: P. Totoson, None; **K. Maguin-Gaté**, None; **D. Wendling**, None; **C. Demougeot**, None.

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Bombina Variegate peptide8/Prokineticin 2: A Novel Arthritis-Inducible Chemokine. Haruyasu Ito, Ken Yoshida, Kentaro Noda and Daitaro Kurosaka. Jikei University School of Medicine, Tokyo, Japan.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by the joint destruction. Chemokines play important roles as monocyte and neutrophil recruiters in RA. *Bombina variegate* peptide 8 (Bv8), one of such chemokines is highly expressed in various tissues including the brain, testis, and bone marrow. Bv8 has a diversity of functions, being involved in angiogenesis, neurogenesis, circadian rhythm, and pain threshold. We have previously reported that Bv8 expression level was elevated in the synovial tissue of collagen induced arthritis (CIA) mice. However, it is still unknown whether Bv8 can induce arthritis. Therefore, in this study, we investigated the expressions of Bv8 and its receptors (PKR1, PKR2) in CIA mice. And, we also examined whether Bv8 recruits polymorphonuclear neutrophils (PMNs) and monocytes *in vitro* and induces inflammatory arthritis *in vivo*.

Methods: CIA was induced in 6-week-old DBA/1j male mice. PKR1 and PKR2 mRNA expression levels of joints in CIA mice were measured by real-time PCR on days 28 and 35 and compared to those in normal mice. Immunohistochemical (IHC) staining was performed to semi-quantitate PKR1 or PKR2 expression on day 28 in the synovial tissue. We performed monocyte and neutrophil chemotaxis assays in response to recombinant Bv8 (rBv8) using Boyden chambers. Resuls were expressed as the fold increase of the number of migrated cells compared to PBS. To test Bv8 for inflammatory activity *in vivo*, we injected PBS or rBv8 (10^{-10}M, 20μl) into knee joints. The knee circumference measurements were taken in a blinded manner before and 24 hours after the intraarticular injection for all mice. IHC stainings for PMNs (Gr-1/Ly6G) and monocytes (F4/80) were performed on paraffin sections from mouse knee joints to quantify Gr-1/Ly6G and F4/80 positive cells in the Bv8 group compared to the PBS group, respectively.

Results: In the CIA group, PKR1 mRNA expression level was significantly higher on days 35 than the control group ($p<0.05$), and PKR2 mRNA expression level was significantly higher on days 28 and 35 than the control group ($p<0.05$). IHC stainings for PKR1 and PKR2 both showed significantly higher expressions of receptors in synovial tissue in the CIA group compared to the control group. PMN chemotaxis assays showed that rBv8 had significantly increased PMN chemotactic activity at 10^{-12} M compared to PBS ($p<0.05$). Joints injected with rBv8 had significantly increased knee circumference than those injected with PBS ($p<0.05$). The number of Gr-1/Ly6G positive cells was significantly higher in mouse knee joints injected with rBv8 compared to PBS ($p<0.05$). There was no significant difference in the number of F4/80 positive cells in both groups.

Conclusion: As well as Bv8, PKR1 and PKR2 expression levels were elevated in the synovial tissue of the CIA group. Bv8 recruited PMNs *in vitro* and induced neutrophil-driven inflammatory arthritis. These results indicate that Bv8 may have a previously unrecognized pathogenesis in RA by recruiting neutrophils. Targeting Bv8 may provide a new therapeutic strategy to treat inflammatory arthritis.

Disclosure: H. Ito, None; **K. Yoshida**, None; **K. Noda**, None; **D. Kurosaka**, None.

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Toll-like Receptor Dependent Autoantigens and Vesicles from P.Gingivalis in Animal Models of RA to Modulate Collagen and Collagen Antibody Induced Arthritis. Christina Grimm, Bianka Marklein, Gerd Burmester and Karl Skriner. Charité - Universitätsmedizin Berlin, Berlin, Germany.

Background/Purpose: A variety of animal models suggest that TLR signaling is important in the pathogenesis of RA and the generation of specific autoantibodies. This study was conducted with sera from patients with rheumatoid arthritis, as well as with arthritis animal models to identify identical autoantigens dependent on TLR 7 and 9 in human and animal models for disease modifying use. Moreover TLR2 and TLR 4 modulating bacterial vesicles from P gingivalis containing PAD (Peptidyl-Arginine Deiminase) which is involved in citrullination was used to study the TLR2/4 in arthritis.

Methods: Using protein filter technology (28000 human protein filter) the autoantigen profile of RA patients, mouse collagen and zymosan induced

arthritis, as well as collagen and pristan induced arthritis in rats and TLR7, TLR9 deficient double-deficient and MyoD88 and Tir8 deficient mice of the MRL-lpr/lpr background were obtained. Cationic liposomes transferring siRNAs, bacterial vesicles, lipomannan and LPS were used for the validation of their potential as therapeutic target in collagen or collagen antibody induced arthritis (CAIA).

Results: We found 18 identical proteins targeted in human and animal situations of arthritis. These data identify mRNA binding hnRNPs proteins which are part of P bodies, stress granules and components of messenger RNA stability complex as well as CRP binding proteins as target molecules in mice, rats and humans with RA. Moreover, we found MyoD88 independent autoantigens which are not expressed in the thymus or proteins such as high mobility group box proteins 1 and 2 which are MyoD88 independent sensors of nucleic-acid-mediated innate immune responses. Systemic administration of siRNAs with cationic liposomes inhibiting expression of Toll dependent autoantigens overexpressed and targeted by autoantibodies in the human and mouse synovial tissue were used for the validation of their potential to inhibit collagen induced arthritis in C57BL/6J mice. Moreover P.gingivalis vesicles containing the the PAD induce a mild inflammatory response in the CAIA model of arthritis. P.gingivalis LPS and lipomannan treated animals show a 80% reduction of athrithis score compared to E. coli LPS in a C57BL/6J CAIA model.

Conclusion: Systemic blocking of common RNA or DNA binding proteins overexpressed in synovial target tissue appears to modify arthritis. *P. gingivalis* vesicles evolved the ability to intercept and undermine a subset of TLR2/4 signalling events for corrupting innate immunity and modulate RA.

Disclosure: C. Grimm, None; **B. Marklein**, None; **G. Burmester**, AbbVie, Pfizer, Roche, UCB, 2, AbbVie, BMS, MSD, Medimmune, Novartis, Pfizer, Roche, Sandoz, UCB, 5, AbbVie, BMS, MSD, Pfizer, Roche, Sandoz, UCB, 8; **K. Skriner**, None.

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Role of Beta-Catenin Signaling to Control Dendritic Cell Function in Collagen-Induced Arthritis. Celso Henrique Alves[1], Julia L. Ober-Blöbaum[2], Inge Brouwers-Haspels[1], Patrick S. Asmawidjaja[1], Anne-Marie Mus[1], Björn E. Clausen[2] and Erik Lubberts[3]. [1]Erasmus MC, University Medical Center, Rotterdam, Netherlands, [2]Institute for Molecular Medicine, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany, [3]Erasmus Medical Center, Rheumatology, Rotterdam, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation and synovial infiltration of immune cells. T-cell priming by activated dendritic cells (DCs) contributes to the pathogenesis of RA. DCs are professional antigen presenting cells that have the dual ability to stimulate immunity and maintain tolerance. Microbial and pro-inflammatory stimuli trigger their maturation into immunostimulatory DCs that express high levels of MHC/peptide complexes, costimulatory molecules and pro-inflammatory cytokines to induce an adaptive immune response. DCs are also important to establish self-tolerance either via the generation of regulatory T cells (Tregs) or via the induction of apoptosis or anergy of auto-reactive effector cells. However, the signaling pathways mediating the tolerogenic DC function *in vivo* remain largely unknown. Recently, the b-catenin pathway has been suggested to promote a regulatory DC phenotype *in vitro*. While activation of β-catenin causes the phenotypic maturation of bone marrow-derived DCs, these cells fail to produce immunogenic cytokines and instead drive Treg differentiation *in vitro*and protection from autoimmune disease in mice.

The aim of this study was to unravel the *in vivo*role of β-catenin signaling to control DC function in collagen-induced arthritis (CIA).

Methods: C57BL/6 mice with a conditional deletion or activation of the β-catenin gene specifically in DCs were generated by crossing CD11c-Cre transgenic mice to *β-catenin*$^{FL/FL}$ and *β-catenin*$^{FL(EX3)/FL(EX3)}$animals, respectively. CIA was induced in the mutant mice and littermate controls by intra-dermal immunization with 100 μg chicken type II collagen in complete Freund's adjuvant on days 0 and 21. CIA incidence and severity was monitored macroscopically using a clinical score. On day 35, the animals were sacrificed, and spleen, draining lymph nodes, serum, ankles and knees were collected. The profiles of different T-cell and DC populations as well as their cytokine production were analyzed by flow cytometry.

Results: Deletion or overexpression of *β-catenin* in CD11c$^+$cells did not affect the onset, progression and severity of CIA.

CD11c-specific deletion of *β-catenin* resulted in an increased frequency of splenic CCR6$^-$CXCR3$^+$CD4$^+$ T cells and in an increase of naturally occurring Tregs (FoxP3$^+$CD25$^-$CD4$^+$) as well as of adaptive Tregs (FoxP3$^+$CD25$^+$CD4$^+$).

Overexpression of *β-catenin* in DCs caused an increase of splenic CCR6$^+$CXCR3$^-$CD4$^+$ (Th17) and CCR6$^-$CXCR3$^+$CD4$^+$ (Th1) T-cells. The latter produced elevated levels of the Th1 cytokine IFNγ and of the immunosuppressive cytokine IL-10. We also observed an increased frequency of naturally occurring FoxP3$^+$CD25$^-$CD4$^+$ and of adaptive FoxP3$^+$CD25$^+$CD4$^+$Tregs.

Conclusion: Our preliminary data indicate that changes in the levels of β-catenin expression in DCs did not alter the course and severity of CIA. However, the increase in IL-10 and in the Treg frequency during arthritis suggests that activation of β-catenin signaling may enhance the regulatory function of DCs.

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Death Receptor 3 Causes Vascular Dysfunction in a Murine Model of Rheumatoid Arthritis. Jessica O Williams[1], Eddie C.Y. Wang[2], Derek Lang[1] and Anwen S. Williams[2]. [1]Institute of Molecular and Experimental Medicine, Cardiff University School of Medicine, Cardiff, United Kingdom, [2]Institute of Infection and Immunity, Cardiff University School of Medicine, Cardiff, United Kingdom.

Background/Purpose: Increased cardiovascular (CV) risk is prevalent in several forms of inflammatory arthritides. The mechanisms that regulate CV disease during early inflammatory arthritis are ill-defined. Studies in humans and animal models identify matrix metalloproteinase 9 (MMP-9) as a potential regulator of CV pathology. Macrophages are early sentinels of both joint inflammation and vascular dysfunction. They are considered a major source of MMP-9 and can be induced *in vitro* to produce this metalloproteinase in response to Death Receptor 3 (DR3) signalling. Ablation of DR3 expression reduces MMP-9 levels in arthritic joint tissues during experimental arthritis. Here, for the first time, we measure DR3-dependent vascular dysfunction, associated macrophage infiltration and MMP-9 expression in vascular and perivascular adipose tissues (PVAT) with a view to understanding DR3's role in initiating early CV damage during inflammatory arthritis.

Methods: Murine collagen-induced arthritis (mCIA) was induced in DBA/1 mice (WT). Constriction responses to serotonin (5HT) were used to assess vascular function in isolated sections of thoracic aorta (±PVAT) in non-mCIA and mCIA mice with mild disease. DR3-dependent changes in vascular function were analysed using age-matched DBA/1 DR3 deficient mice (DR3$^{-/-}$). Region specific (thoracic aorta and PVAT) leukocyte infiltration was determined using haematoxylin and eosin staining, whilst localisation of F4/80$^+$ macrophages were visualised and MMP-9 expression quantified after immunohistochemical staining.

Results: The onset of mild arthritis was associated with inflammatory changes in the aortic vessel wall, characterised by increased macrophage infiltration ($p<0.05$) and DR3 expression ($p<0.001$). Total MMP-9 expression was unaltered (non-mCIA vs. mCIA mice). Macrophages (F4/80+), DR3 and total MMP-9 expression were all significantly elevated in PVAT ($p<0.05$ for all). The mCIA vascular tissues (±PVAT) exhibited significant contractile dysfunction compared to non-mCIA controls ($p<0.001$). The presence of PVAT was associated with a significant ($p<0.001$) dextral shift in constriction response curves but had no effect on maximal constriction. In DR3$^{-/-}$ non-mCIA mice, leukocyte infiltration ($p<0.05$) and total MMP-9 ($p<0.01$) levels were increased in PVAT but not in the aortic vessel wall. Vascular function was unaltered (WT versus DR3$^{-/-}$) and PVAT retained its ability to shift the constriction response curve to the right ($p<0.001$) in both genotypes. mCIA had no impact on the leukocyte ingress or MMP-9 production in the aortic vessel wall or PVAT (WT versus DR3$^{-/-}$). However, loss of DR3 further impaired vascular function (±PVAT) in comparison to WT ($p>0.001$).

Conclusion: The onset of mCIA drives an inflammatory response in the PVAT; associated with macrophage infiltration, increased expression of DR3 and MMP-9, and is detrimental to vascular function. Loss of DR3 perpetuates vascular dysfunction independently of leukocyte ingress and MMP-9 production. Further studies are justified to deduce the impact of DR3 on vascular function, in particular, the potential link with cardiovascular co-morbidities allied to arthritis.

Disclosure: J. O. Williams, None; **E. C. Y. Wang**, None; **D. Lang**, None; **A. S. Williams**, None.

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Vascular Permeability As an Imaging Biomarker for Chronic Inflammatory Arthritis: A Dynamic Contrast Enhanced Magnetic Resonance Imaging Study. Eon Jeong Nam[1], Yongmin Chang[1], Jang-Woo Park[1], Shijin Sung[1], Jungwan Hong[1], Md. Hasan Al Faruque[1], Jongmin Lee[1] and Young Mo Kang[2]. [1]Kyungpook National University School of Medicine, Daegu, South Korea, [2]Kyungpook National Univ Hosp, Daegu, South Korea.

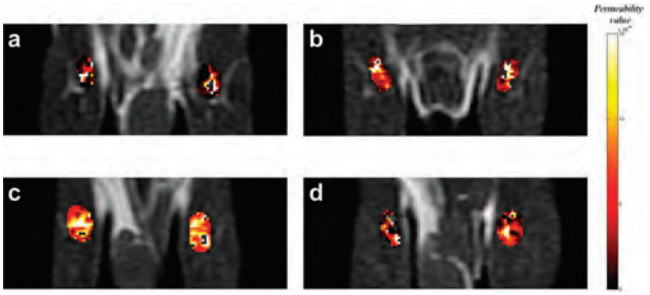
Vascular permeability as an imaging biomarker for chronic inflammatory arthritis: A dynamic contrast enhanced magnetic resonance imaging study.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease in which adequate diagnosis of disease activity is particularly important for optimizing treatment outcomes. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is used to detect inflammatory changes in synovial joints, and to discriminate active and inactive stages of disease. However, DCE-MRI has not been previously used to evaluate quantitative kinetic parameters, such as vascular permeability. The aim of this study was to investigate the quantitative changes in vascular permeability associated with chronic inflammatory arthritis.

Methods: Arthritis was induced in DBA/1J mice by immunization with bovine type-II collagen emulsified in complete and incomplete Freund's adjuvants. The severity of arthritis was monitored using the clinical arthritis index (CAI). R images of mice were obtained at different stages of arthritis progression, and 3 weeks after methotrexate (MTX) treatment. Immunohistochemical staining with an anti-CD31 antibody was used to assess vessel density.

Results: Permeability maps on the knee joint revealed less heterogeneity during the active stage, compared to early and late stages of arthritis. Vascular permeability increased progressively until the active stage of arthritis was reached, and thereafter declined gradually. The pattern of permeability changes quantified using DCE-MRI was consistent with the vascular densities and disease activity. Furthermore, vascular permeability and densities decreased significantly in a dose-dependent manner after treatment with MTX.

Conclusion: Vascular permeability assessed by DCE-MRI can be used as an imaging biomarker for tracking disease progression, and for monitoring therapeutic efficacy in inflammatory arthritis.



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The Caspase 8/RIPK3 Signaling Axis Has Opposing Roles in Myeloid and Dendritic Cells during Progression of a Murine Model of Acute Inflammatory Arthritis. Carla M. Cuda[1], Alexander Misharin[2], George Kenneth Haines III[3] and Harris R. Perlman[1]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]The Mount Sinai Hospital, New York, NY.

Background/Purpose: Rheumatoid arthritis (RA) manifests in persistent synovial inflammation, cellular infiltration and pro-inflammatory cytokine production, and results in progressive joint destruction. Both myeloid cells and dendritic cells (DCs) have been implicated in RA progression and persistence: DCs through either antigen presentation to autoreactive T cells or differentiation into synoviocytes and myeloid cells (including macrophages and neutrophils) through the production of degradative enzymes, cytokines, and chemokines. However, the mechanisms underlying these activities are not fully elucidated. We recently identified that caspase 8, an enzyme that initiates apoptosis and suppresses necroptosis by inhibition of RIPK1/3 signaling in a multitude of cells, is a novel DC and myeloid cell-specific inhibitor of inflammatory processes independent of its known role in cell survival. Recently, a genome-wide association study identified an RA risk single nucleotide polymorphism within the locus that contains the gene that encodes for caspase 8. However, the impact of DC and myeloid cell-specific loss of caspase 8 on arthritis progression has yet to be examined.

Methods: Mice with caspase 8 flanked by *loxP* sites ($Casp8^{fl/fl}$, WT) were bred to mice expressing Cre under control of the lysozyme M gene promoter (Cre^{LysM}) expressed by myeloid cells or the CD11c gene promoter (Cre^{CD11c}) expressed by dendritic cells. $Cre^{LysM}Casp8^{fl/fl}$ and $Cre^{CD11c}Casp8^{fl/fl}$ mice were crossed with RIPK3$^{-/-}$ mice to determine the involvement of this signaling partner. The K/BxN serum-transfer model of arthritis was utilized and clinical severity was assessed. Ankle sections were stained with H&E and scored by a pathologist blinded to the study to assess pathology. Flow cytometric analysis was used to characterize naïve joints.

Results: The expression of CD206 (mannose receptor, involved in phagocytosis) was decreased on macrophages of naïve $Cre^{LysM}Casp8^{fl/fl}$ joints, and CD86 was elevated on CD11b^{+} DCs from naïve $Cre^{CD11c}Casp8^{fl/fl}$ joints. $Cre^{LysM}Casp8^{fl/fl}$ presented with accelerated resolution of arthritis, as assessed by reduced changes in ankle width on day 4, 7, 9 and 11 and clinical scores on day 7 and 9, as well as reduced pathology compared to WT. In stark contrast, $Cre^{CD11c}Casp8^{fl/fl}$ mice showed accelerated initiation of arthritis, as evidenced by increased changes in ankle width and clinical scores on day 2 and 4, as well as increased joint damage compared to WT. However, the in both cases, knockout of RIPK3 in $Cre^{LysM}Casp8^{fl/fl}$ and $Cre^{CD11c}Casp8^{fl/fl}$mice was sufficient to reverse the effect of caspase 8 deletion alone on arthritis initiation and resolution.

Conclusion: While deletion of caspase 8 specifically in myeloid cells promotes the acceleration of arthritis resolution, DC-specific caspase 8-deletion exacerbates arthritis initiation. In both situations, blockade of RIPK3 reverses the effect of caspase 8 deletion, indicating that the caspase 8/RIPK3 signaling axis plays an important cell-specific role in disease pathogenesis. These data have implications for RA by elucidating previously unknown cell-specific functions of a potentially useful target for therapy.

Disclosure: C. M. Cuda, None; **A. Misharin**, None; **G. K. Haines III**, None; **H. R. Perlman**, None.

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Reduced Macrophages in the Synovium Contribute to the Effective Treatment of Spontaneous Arthritis Observeded in Human TNF-Transgenic Mice. Robert Birkett, Qi Quan Huang, Bo Shi and Richard Pope. Northwestern University Feinberg school of Medicine, Chicago, IL.

Background/Purpose: Macrophages in rheumatoid arthritis (RA) synovial tissue (ST) produce high levels of inflammatory cytokines/chemokines and exhibit enhanced differentiation into osteoclasts in the pannus, playing the pivotal role in promoting inflammation and joint destruction. Recent observations demonstrate that effective therapy employing a TNF inhibitor results in a selective reduction of sublining RA ST macrophages within 24 hours. However, neither ingress of monocytes into the tissue nor apoptosis of macrophages in the RA tissue accounted for the reduction of macrophages. Therefore, employing a murine model, studies were performed to define the role of CCR7 expression to promote macrophage egress from inflamed joints as a potential mechanism for therapeutic response.

Methods: CCR7 expression in RA synoival macrophages was determined by two color immunohistochemistry employing anti-CCR7 and anti-CD68, RT-PCR and immunoblotting. A human TNF transgenic (hTNF-tg) mouse line which spontaneously develops arthritis was employed, and treated with infliximab, administered intraperitoneally (10mg/kg, 1–3 doses). The clinical severity of the arthritis was defined as the sum score of joint swelling, inflammation, deformity and grip strength. Ankle histology was performed. The immune cell phenotypes and apoptosis were determined by flow cytometry. Ankle cell migration was tracked by PKH26 intra-articular injection and cell identification by flow cytometry.

Results: CCR7 was increased in macrophages in RA ST and synovial fluid. CCR7 expression on normal human macrophages was significantly increased at the mRNA and protein levels following incubation with TNFa, Pam3 or LPS. As expected the hTNF-tg mice developed arthritis beginning at week 4, progressing through week 12. The hTNF-tg mice treated with infliximab for 72 or 168 hours demonstrated significant clinical improvement. Histologic analysis identified significant reduction of inflammation, bone erosion and pannus formation after 168 hours of therapy. Flow cytometric analysis demonstrated that ST macrophages were significantly reduced at 24 hours, prior to clinical improvement, and 72 and 168 hours following the initiation of therapy. In contrast, other cell types including granulocytes, B or T lymphocytes and dendritic cells were not consistently or not significantly reduced. No increase of macrophage apoptotosis or necrosis in ankle ST was

observed following treatment. Futher, although there was a reduction of PKH26 labeled macrophages in the ankles following therapy, there was also a reduction of macrophages in the popliteal lymph nodes and no increase in the percentage of PKH26 labeled macrophages was detected.

Conclusion: These observations demonstrate increased CCR7 on macrophages in the RA joint and that CCR7 on macrophages was increased by inflammation. Macrophages, but not other cell types, in the inflamed synovium of hTNF-Tg mice were reduced early prior to clinical or histologic improvement, but we have yet to document egress as the mechanism. The role of CCR7 in the therapeutic reduction of macrophages is being pursued by crossing hTNF-Tg mice with those deficient in CCR7−/−.

Disclosure: R. Birkett, None; **Q. Q. Huang**, None; **B. Shi**, None; **R. Pope**, None.

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A Low Salt Diet Ameliorates Clinical Manifestations in Collagen-Induced Arthritis. Bettina Sehnert[1], Sandy Pohle[2], Agnes Schröder[2], Jens Titze[3] and Reinhard E. Voll[1]. [1]University Hospital Freiburg, Freiburg, Germany, [2]University of Erlangen-Nürnberg, Erlangen, Germany, [3]Vanderbilt University School of Medicine, Nashville, TN.

Background/Purpose: A genetic predisposition, but also environmental factors including infections and smoking modulate manifestation and severity of inflammatory autoimmune disease like rheumatoid arthritis (RA). Recently, the induction of pathogenic Th17 cells as a consequence of increased salt intake was demonstrated in an animal model of multiple sclerosis. The impact of dietary factors such as low salt consumption on the inflammatory status in arthritis has not yet fully characterized. The aim of the study was to investigate the association between salt intake and clinical manifestations in a mouse model of arthritis.

Methods: DBA/1 mice were immunized with *bovine* type II *collagen* (CII) in complete Freund's adjuvant (CFA). Two weeks before immunization experimental diet was started and the mice were divided in two groups. The LS (low-salt) group (n=9) received a diet containing a sodium content <0.03% and tap water. The HS (high-salt) group (n=10) were fed with a diet containing 4 % NaCl in combination with 0.9% NaCl supplemented tap water. The feeding lasted 62 days. Arthritis severity was assessed by clinical scoring to a graded scale (0–4). At the end of the experiment hind paws were removed for histological analysis. The stained sections (hematoxylin/eosin, toluidine blue and tartrate-resistant acid phosphatase) were graded on a scale from 0–3. Levels of *IgG1 and IgG2a* antibodies against bovine collagen type were measured by ELISA.

Results: Administration of a low salt diet resulted in a decreased arthritis severity compared to the HS-group. Further, the incidence of arthritis was significantly lower in the LS group. The histopathological analysis revealed reduced infiltrations with inflammatory cells in the group fed with the low salt diet. Also the destruction of cartilage and bone was less pronounced in the LS compared to the HS group. ELISA experiments showed that the level of pathogenic IgG2a antibodies against CII was markedly increased in HS-mice, whereas low salt consumption reduced anti-CII IgG2a levels significantly. The titers of CII-specific IgG1 were similar in both groups. This resulted in decreased IgG2a:IgG1 ratio in the LS group and indicates a shift toward a more Th2-dominated immune response.

Conclusion: Low salt diet ameliorates clinical and histological signs in murine collagen-induced arthritis. The low salt consumption inhibits the humoral IgG2a response against CII and protects against antibody-mediated joint destruction. We conclude that a low salt diet might ameliorate RA and support treatment of immune-mediated arthritides.

Disclosure: B. Sehnert, None; **S. Pohle**, None; **A. Schröder**, None; **J. Titze**, None; **R. E. Voll**, Investigator, 5.

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Treatment of Collagen Induced Artritis with Human Embrionic Stem Cell-Derived Multipotent Mesenchymal Stromal Cells (hESC-MSC). Gabriel Criado[1], María J. Pérez-Lorenzo[1], María Galindo[1], Jose L. Pablos[1], Pablo Menéndez[2] and Elena Gonzalo-Gil[3]. [1]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [2]Josep Carreras Leukemia Research Insitute, Barcelona, Spain, [3]Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain.

Background/Purpose: Inhibition of TGFβ signaling in human Embryonic Stem Cells (hESC) generates mesenchymal stromal cells (hESC-MSC) with osteogenic, adipogenic and chondrogenic potential. These cells have immunosuppressive and anti-inflammatory properties in vitro and have shown a protective effect in experimental models of acute inflammation. The aim of the present study was to test their therapeutic potential in an experimental setting of chronic inflammation, the collagen-induced arthritis model (CIA).

Methods: Arthritis was induced in 8–10 weeks old male DBA/1 mice by intradermal immunization with 200 mcg of chicken type II collagen (CII) in Complete Freund's Adjuvant (CFA). Mice were treated starting on the day of arthritis onset with three doses of 10^6 cells / mouse hESC-MSC every other day and arthritis severity was evaluated daily during ten days. Effect of in vivo treatment was assessed by flow cytometry to detect Treg ($FoxP3^+$), Th1 ($IFNg^+$) and Th17 ($IL17^+$) CD4 T cells in lymph nodes. To analyze T cell responses in vitro, lymph node cells were stimulated with CII, proliferation was measured by incorporation of the colorimetric reagent WST-1 and IFNg and IL17 levels were quantified by ELISA. Serum levels of anti-CII antibodies were determined by ELISA. Detection of ehESC-MSC in mouse tissues was performed by quantitative PCR (qPCR) of HLA-C and quantification of murine and human indoleamine 2,3 dioxygenase (IDO) was performed by quantitative PCR. Statistical differences were analyzed by ANOVA and Mann-Whitney U-test using GraphPad Prism software. P values < 0.05 were considered significant.

Results: Treatment of CIA mice with hESC-MSC reduced diseased severity compared to control-treated mice. Differences appeared the first day after treatment and were significant and sustained in the group receiving 3 doses. Therefore, administration of 3 doses was the schedule used for subsequent experiments. Anti-CII antibodies levels were not affected by treatment. Analysis of CD4 T cell populations in treated mice showed an enrichment in $FoxP3^+$ Treg cells (8.56 ± 0.89 % vs 5.89 ± 0.81% in control mice, *P= 0.026) in inguinal lymph nodes. IFNg producing cells were also increased (0.88 ± 0.09 % vs 0.54 ± 0.02 %, **P= 0.008) but not IL17 producing cells (0.93 ± 0.09 % vs 0.84 ± 0.05 %, P= 0.54). In vitro stimulation with CII caused higher production of IFNg and IL17 in lymph node cultures from hESC-MSC treated mice although not statistically significant (IFNg: 539.0 ± 219.3 pg/ml vs 147.8 ± 93.55 pg/ml, P= 0.09, IL17: 238.3 ± 134.1 pg/ml vs 72.39 ± 72.39 pg/ml, P= 0.24) and proliferation was not affected. hESC-MSC treated mice that showed MSC colonization in lymph nodes, as detected by HLA- expression, had significantly higher expression of murine indoleamine 2,3 dioxygenase than their treated non-colonized and not treated counterparts ($6.88 \pm 0{,}94$ Units vs $1.049 \pm 0{,}36$ in non-colonized and $1.82 \pm 0{,}24$ in non-treated mices, **P= 0.009 and * *P= 0.004, respectively).

Conclusion: Treatment with hESC-MSC ameliorates CIA by inducing IFNg and indoleamine 2,3 dioxygenase.

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Salt Aggravates Arthritis By Th17 Polarization. Seung Min Jung[1], Hong Ki Min[1], Jung Hee Koh[1], Jin Young Kang[1], Jennifer Lee[1], Seung-Ki Kwok[1], Kyung-Su Park[2], Hyeok-Jae Ko[3], Wan-Uk Kim[4], Ho-Youn Kim[1], Sung-Hwan Park[1] and Ji Hyeon Ju[1]. [1]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [2]St. Vincent Hospital, SuWon Gyeonggi-do, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Daejeon, South Korea, [4]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea.

Background/Purpose: Sodium chloride (NaCl) recently has been shown to drive autoimmune diseases through the induction of pathogenic interleukin 17-producing T helper (Th17) cells. This study investigated the effect of NaCl on Th17 cell differentiation in human and murine arthritis.

Methods: To evaluateth *in vivo* arthritogenic effect of NaCl, collagen-induced arthritis (CIA) mice were fed a normal or high-salt diet *ad libitum*, and paw swelling was scored visually. Splenocytes were analysed by flow cytometry for RORgt expression, and splenic $CD4^+$ T cells were differentiated into Th17 cells. Peripheral blood mononuclear cells obtained from patients with rheumatoid arthritis (RA) and osteoarthritis (OA) were cultured under Th17 cell-differentiating conditions in a high-salt environment and were analysed by flow cytometry to quantify the Th17 cell population.

Results: NaCl increased murine and human Th17 cell differentiation in a dose-dependent manner and aggravated arthritis in CIA mice. Joint inflammation was more severe in the high-salt-fed CIA mice. T cells from high-salt-fed CIA mice expressed a higher level of RORgt and were more

likely to differentiate into Th17 cells. Th17 cells were located primarily in arthritic joints, and also observed the intestinal tract of high-salt-fed CIA mice. Na^+ and IL-17 concentrations were higher in synovial fluid from RA patients than in fluid from OA patients. There was a tendency towards increased RORgt expression after NaCl treatment in arthritic patients.

Conclusion: This study suggests that NaCl can aggravate arthritis by affecting Th17 differentiation. Limiting salt intake might be helpful in the management of arthritis.

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ACR Poster Session A
Rheumatoid Arthritis - Clinical Aspects: Novel Biomarkers and Other Measurements of Disease Activity
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Smoking Status Is Associated with Inflammatory Cytokine Profile and Disease Activity: Decreased Inflammation and Disease Improvement with Smoking Cessation? Jeremy Sokolove[1], Harlan Sayles[2], Catriona Wagner[3], Lauren J. Lahey[1], Geoffrey M. Thiele[2], William H. Robinson[1], Andreas Reimold[4], Gail S. Kerr[5], Grant W. Cannon[6] and Ted R. Mikuls[2]. [1]VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA, [2]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [3]VA Palo Alto Heatlh Care System and Stanford University, Palo Alto, CA, [4]Dallas VA and Univ of TX Southwestern Med Ct, Dallas, TX, [5]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [6]Salt Lake City VA and University of Utah, Salt Lake City, UT.

Background/Purpose: Cigarette smoking is a risk factor for RA and has been associated with increased disease severity and lower rates of disease remission. We examined whether smoking cessation might be associated with reduced disease activity and investigated the association of autoantibody levels with smoking status.

Methods: RA patients from the Veterans Affairs RA (VARA) registry were studied (n = 1468, 76.9% anti-CCP2+, 90.7% male, median age 63 [IQR 57–72], median disease duration 8.45 years [IQR 2.8–18]). Baseline serum samples were evaluated for levels of 19 distinct ACPA and 17 cytokines using the BioPlex platform. Baseline smoking status was recorded as current, former, or never. Cross-sectional associations of baseline smoking status with disease activity (DAS28) and its constituents as well as baseline levels of ACPA, and baseline levels of cytokines were assessed.

Results: Multiple measures of RA disease activity including DAS28 were significantly higher among current smokers compared with either former or never smokers ($P<0.01$), an effect limited to the seropositive (anti-CCP2 positive) population (Table 1). The number of inflammatory cytokines found in high concentration was significantly higher among current smokers compared with both former and non-smokers (FDR q-value <0.1%). Levels of both anti-CCP2 as well as ACPA subtypes were lower in never smokers but similar between current and former smokers while levels of RF were highest in current smokers, and lower in both former smokers and lowest in never smokers (Table 2).

Conclusion: Current smoking is strongly associated with increased RA disease activity as well as elevation in pro-inflammatory serum cytokines compared to both former and never smokers. Our findings suggest that continued tobacco exposure promotes greater RA disease activity, particularly in ACPA positive patients though independent of titer or specificity. The observation of reduced disease activity among former smokers, approaching that of never smokers, suggests that the effects of smoking may be reversed by smoking cessation. Whether RF may be a mediator of this effect remains to be clarified.

Table 1: Measures of disease activity, ACPA, and cytokine expression among anti-CCP2 positive RA patients; *p-values among smoking groups generated using Scheffe's method for multiple comparisons

	DAS28	Log(CRP)	ACPA #Pos	ACPA Score	Cytokine #Pos	Cytokine score	CCP2 level	RF level
Current smoker	4.6	1.9	2.7	24.3	1.8	22.9	395.9	593.1
Former smoker	3.9	1.7	2.6	23.2	1.1	18.9	360.9	350.5
Never smoker	3.7	1.7	2.1	19.7	1.1	14.6	278.1	239.0
P-values*								
Global ANOVA	< 0.001	0.044	0.043	0.019	0.001	0.085	0.020	<0.001
Current vs. Never	< 0.001	NS	NS	< 0.05	< 0.01	NS	<0.05	<0.001
Current vs. Former	< 0.001	NS	NS	NS	< 0.01	NS	NS	<0.001
Former vs. Never	NS	NS	NS	NS	NS	NS	NS	NS

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Galectin-3 in the Systemic Circulation Is Increased in Newly Diagnosed Rheumatoid Arthritis and Is Associated with Anti-CCP and Bone Marrow Edema. Saida Farah Issa[1], Anne Friesgaard Christensen[2], Hanne M. Lindegaard[1], Merete Lund Hetland[3], Kim Hoerslev-Petersen[4], Kirsten Junker[5], Kristian Stengaard-Pedersen[6], Tine Lottenburger[2], Torkell Ellingsen[1], Ib Hansen[6], Jens Kristian Pedersen[1], Ulrik B. Lauridsen[7], Anders Svendsen[8], Ulrik Tarp[6], Jan Pødenphant[9], Mikkel Østergaard[10] and Peter Junker[1]. [1]Department of Rheumatology, Odense University Hospital, Odense, Denmark, [2]Department of Rheumatology, Vejle Hospital, Vejle, Denmark, [3]DANBIO, Center for Rheumatology and Spine Diseases, Glostrup Univ Hospital, Glostrup, Denmark, [4]Research Unit at King Christian X Hospital for Rheumatic Diseases, Graasten, Denmark, [5]Institute of Molecular Medicine, Cardiovascular & Renal Research, University of Southern Denmark, Odense, Denmark, [6]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [7]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup Hospital, Glostrup, Denmark, [8]The Danish Twin Registry, Epidemiology, Institute of Public Health, Odense, Denmark, [9]Department of Rheumatology, Copenhagen University Hospital at Gentofte, Gentofte, Denmark, [10]Copenhagen Center for Arthritis Research, Copenhagen University Hospital at Glostrup, Glostrup, Denmark.

Background/Purpose: Galectin-3 (Gal-3), a 26kD beta-galactoside binding protein, has been implicated as a pro-inflammatory mediator in animal arthritis and rheumatoid arthritis (RA) in humans. Thus, Gal-3 is overexpressed by fibroblast-like synoviocytes in the rheumatoid synovium, particularly upon adhesion to cartilage components. Moreover, Gal-3 is increased in serum in animal arthritis and in serum and synovial fluid in patients with long-standing RA as compared with osteoarthritis and healthy individuals.

The aims of this investigation were to quantify the serum level of Gal-3 in a large cohort of patients with newly diagnosed RA before treatment, and to study possible associations with clinical, serological and imaging findings.

Methods: One hundred and sixty DMARD naïve patients with RA of recent onset were included (the CIMESTRA cohort)(1). One hundred and nineteen volunteer blood donors served as healthy controls. Variables included demographics, clinical disease measures (Disease Activity Score in 28 joints-DAS28, Health Assessment Questionnaire-HAQ, Visual Analog Scales– patients global assessment, pain and physicians assessment), autoantibody status and MRI of the non-dominant wrist. Gal-3 was measured by ELISA (R&D).

Results: Gal-3 was significantly increased in RA patients, 4.49 ug/L (*95% CI 4.17;4.81*) compared with healthy controls, 3.96 ug/L (*3.70;4.22*; p = 0.02).

Gal-3 correlated positively with Capsular Reactive Protein (CRP), Erythrocyte Sedimentation Rate(ESR), and HAQ, but not with joint counts, DAS28 or rheumatoid nodules (table 1.a). Stratification according to autoantibody seropositivity and smoking showed that Gal-3 was significantly higher in seropositive than in seronegative RA, particularly in smokers (table 1.b). A similar pattern was observed in IgM-RF only and IgM-RF+anti-CCP positive subsets (p = 0.01 and p = 0.03). There was no association between Gal-3 and anti-ccp titer. By contrast, Gal-3 was positively correlated with bone marrow edema in patients (p = 0.03).

Table 1 a. Galectin-3 correlations according to autoantibody status

Characteristic	Total RA (n = 159)	Anti-CCP positive (n = 93)	Anti-CCP negative (n = 66)
CRP	*rho = 0.22 p < 0.01*	*rho = 0.26 p = 0.01*	rho = 0.10 p = 0.42
ESR	*rho = 0.28 p < 0.01*	*rho = 0.27 p < 0.01*	*rho = 0.25 p = 0.04*
MR bone marrow edema	*rho = 0.18 p = 0.03*	*rho = 0.22 p = 0.05*	rho = 0.07 p = 0.63
MR erosion	rho = 0.03 p = 0.72	rho = 0.03 p = 0.78	rho = −0.05 p = 0.73
MR synovitis	rho = 0.10 p = 0.26	rho = 0.11 p = 0.32	rho = 0.08 p = 0.56
HAQ-score	*rho = 0.24 p < 0.01*	rho = 0.17 p = 0.10	*rho = 0.27 p = 0.03*
DAS28	rho = 0.14 p = 0.08	rho = 0.20 p = 0.06	rho = 0.07 p = 0.57
Total joint count	rho = 0.00 p = 0.96	rho = 0.05 p = 0.64	rho = −0.01 p = 0.96

Gal-3 mean (ug/L)	4.49#	4.78*#	4.08*	
(*95 CI*)	(4.17; 4.81)	(4.35; 5.21)	(3.60; 4.55)	

*: Significant differences between anti-CCP subgroups #: Significant differences between RA subgroups and healthy controls

Table 1 b. Galectin-3 correlations in RA subsets according to antibodies and smoking habits

	Total RA (n = 159)		Anti-ccp positive (n = 93)		Anti-ccp negative (n = 66)	
Characteristic	**Smokers n = 108**	**Never smokers n = 51**	**Smokers n = 71**	**Never smokers n = 22**	**Smokers n = 37**	**Never smokers n = 29**
CRP	*rho = 0.23 p = 0.02*	rho = 0.18 p = 0.20	*rho = 0.24 p = 0.05*	rho = 0.24 p = 0.29	rho = 0.06 p = 0.72	rho = 0.15 p = 0.44
ESR	*rho = 0.34 p<0.01*	rho = 0.18 p = 0.22	*rho = 0.25 p = 0.04*	rho = 0.33 p = 0.15	*rho = 0.41 p = 0.01*	rho = 0.07 p = 0.71
MR bone marrow edema	*rho = 0.23 p = 0.03*	rho = −0.00 p = 0.99	rho = 0.24 p = 0.06	rho = 0.16 p = 0.50	rho = 0.23 p = 0.25	rho = −0.20 p = 0.34
MR erosion	rho = 0.14 p = 0.18	rho = −0.19 p = 0.21	rho = 0.07 p = 0.59	rho = −0.05 p = 0.85	rho = 0.26 p = 0.18	rho = −0.32 p = 0.12
MR synovitis	rho = 0.14 p = 0.18	rho = 0.08 p = 0.62	rho = 0.15 p = 0.26	rho = 0.05 p = 0.83	rho = 0.13 p = 0.52	rho = 0.07 p = 0.73
HAQ-score	*rho = 0.22 p = 0.02*	*rho = 0.30 p = 0.03*	rho = 0.09 p = 0.48	rho = 0.40 p = 0.07	*rho = 0.35 p = 0.03*	rho = 0.24 p = 0.20
DAS28	rho = 0.12 p = 0.21	rho = 0.23 p = 0.11	rho = 0.15 p = 0.22	*rho = 0.44 p = 0.05*	rho = 0.06 p = 0.71	rho = 0.13 p = 0.49
Total joint count	rho = −0.05 p = 0.60	rho = 0.14 p = 0.33	rho = −0.05 p = 0.71	*rho = 0.46 p = 0.03*	rho = 0.08 p = 0.63	rho = −0.08 p = 0.69
Gal-3 mean (ug/L)	4.73*#	4.00*	5.01#	4.05	4.17	3.96
(*95 CI*)	(4.32; 5.13)	(3.49; 4.51)	(4.52; 5.51)	(3.20; 4.91)	(3.48; 4.87)	(3.28; 4.63)

*: Significant differences between smoking subgroups #: Significant differences between RA subgroups and healthy controls

Conclusion: In this study we show that Gal-3 is increased in DMARD naïve patients with RA of recent onset. The associations with autoantibody seropositivity and bone marrow edema provide additional evidence for a role of Gal-3 in the RA disease pathway and hence that Gal-3 has potential as a seromarker for synovial pathology in RA.

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Rho-Associated Protein Kinase (ROCK) Activity Is Elevated in Rheumatoid Arthritis (RA) Patients and May be Responsive to RA Therapies. Reena Khianey, Cristina Rozo, Sanjay Gupta, Vivian P. Bykerk, Susan M. Goodman and Alessandra B. Pernis. Hospital for Special Surgery, New York, NY.

Background/Purpose: Rho-associated protein kinases (ROCKs) regulate cytoskeletal reorganization and gene expression through protein phosphorylation, and are implicated in the pathogenesis of a wide range of disorders including SLE. ROCK activation is associated with TH17 differentiation and production of interleukin 17 (IL17) and IL21, two cytokines associated with SLE and RA. We aimed to 1) evaluate ROCK activity and cytokine profile in RA patients, and 2) correlate ROCK activity with use of disease modifying anti-rheumatic drugs (DMARDs), smoking status, erosions, disease duration, and disease activity.

Methods: We performed a cross-sectional analysis of 26 RA patients meeting 2010 ACR/EULAR criteria compared to 18 age±5 years, gender, and race/ethnicity matched healthy controls. ROCK activity in peripheral blood mononuclear cells (PBMC) lysates was determined by an ELISA. Plasma samples were analyzed by specific ELISAs for IL-17 and IL21. Statistical analyses were performed using GraphPad Prism 6.0 using appropriate non-parametric tests.

Results: Clinical characteristics of RA patients are noted in Table 1. RA PBMCs expressed significantly higher levels of ROCK activity than did healthy control PBMCs (0.4085 vs. 0.3303; $P = 0.0023$). DMARD untreated RA patients had a trend towards higher ROCK activity compared to DMARD treated RA patients, (0.6935 vs. 0.3925; $P = 0.0867$), (Figure 1). Spearman's correlation revealed no association of ROCK activity levels with disease duration (r= 0.277, $P = 0.171$) or disease activity as measured by Clinical Disease Activity Index (CDAI) (r=0.162, $P = 0.429$). There was no significant difference in ROCK levels based on erosions ($P = 0.440$) or smoking status ($P = 0.651$). Patients with moderate or high disease activity (CDAI ≥10.1) had increased ROCK levels (OR=1.96, 95% CI 0.3866–9.938), but this was not statistically significant. No statistically significant differences in IL17 and IL21 levels between RA patients and healthy controls were detected.

Conclusion: ROCK levels were higher in RA patients compared to healthy controls suggesting ROCK deregulation in RA pathogenesis. There was a trend towards higher ROCK activity in DMARD untreated RA patients suggesting that ROCK activity is sensitive to RA therapies. Further studies are needed to understand the role of ROCK activity in RA.

Table 1: Clinical Characteristics of RA Patients, n=26

Mean Age, ±SD, range	**57.5±13.8 (23–79)**
Female, n, (%)	23 (88.5)
Race, n, (%)	
White	15 (57.7)
Black	3 (11.5)
Mixed	4 (15.4)
Asian	4 (15.3)
Mean Disease Duration in months, ±SD, range	56.0±55 (3–240)
Erosive Disease, n, (%) [imaging available on 15 patients]	4/15 (26.7)
Autoantibody Status	
IgM RF or ACPA positive, n, (%)	3 (11.5)
IgM RF and ACPA negative, n, (%)	3 (11.5)
IgM-RF and ACPA positive, n, (%)	20 (76.9)
Mean ACPA titer (U),* ± SD, range	195.1±67.9 (60–250)
Mean IgM-RF titer (IU/mL)* ± SD, range	143.8±166.8, (21.1–587)
*[titers available on 20 patients]	
Disease Activity Parameters	
Mean ESR (mm/hr) ± SD, range	22.5 ± 14.5 (5–44)
Mean CRP (mg/dL) ±SD, range	1.2 ± 0.5 (1 – 3.2)
CDAI,Mean ± SD, Range	13.0 ± 7.3, (6–30)
Current smokers, n, (%)	4 (15.4)
Current Medications, n, (%)	
NSAIDs alone	8 (30.8)
Hydroxychloroquine alone	1 (3.8)
Conventional DMARDs (Methotrexate ± Leflunomide)	8 (30.8)
Anti TNF agents (Etanercept, Adalimumab)	8 (30.8)
Prednisone	1 (3.8)

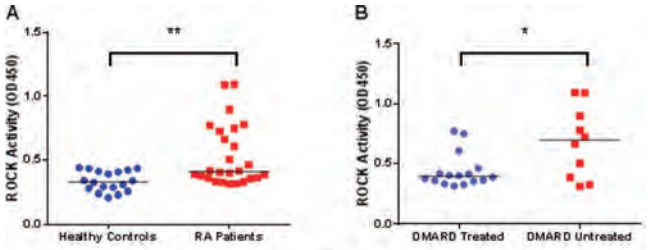

Figure 1 – Rho associated protein kinase (ROCK) activity in rheumatoid arthritis (RA) patients as compared with healthy control subjects. A. Peripheral blood mononuclear cells (PBMCs) were derived from heparinized blood samples obtained from 26 RA patients and compared to 18 matched healthy control subjects. ** = $P = 0.0023$ by Mann Whitney U test. B. ROCK activity in PBMCs from RA patients treated with DMARDs and RA patients untreated. * $P = 0.0867$ by Mann Whitney U test. Each data point in A and B represent a single subject; horizontal lines show the median.

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Doctor, Will My Fatigue be Better If I'm in Remission? an Exploratory Analysis of 1284 Rheumatoid Arthritis (RA) Patients Indicates Fatigue Is the Only Aspect of Patient-Perceived Impact to Remain Significant in ACR/EULAR Boolean Remission. Laure Gossec[1], Bruno Fautrel[1], John Kirwan[2], Andra Balanescu[2], Maarten de Wit[3], Ben A.C. Dijkmans[2], Matthias Englbrecht[2], Philippe Gaudin[4], Feride Gogus[2], Turid Heiberg[3], Tore Kristian Kvien[2], Emilio Martín-Mola[5], Marco Matucci-Cerinic[2], Kati Otsa[3], Adeline Ruyssen-Witrand[4], Tuulikki Sokka-Isler[2], Martin Soubrier[4] and Maxime Dougados[2]. [1]UPMC GRC08, Paris 06 University, Pitié Salpétrière Hospital,

Paris, France, [2]RAID working group for EULAR, Zurich, Switzerland, [3]PsAID taskforce, EULAR, Zurich, Switzerland, [4]COMEDRA trial group, Paris, France, [5]Hospital Universitario La Paz, Madrid, Spain.

Background/Purpose: Fatigue is an important issue for patients with rheumatoid arthritis (RA). The ACR/EULAR Boolean definition of remission comprises values <=1/10 for joint counts, CRP and patient global assessment; fatigue is not specifically assessed. Near-remission (defined as remission for joint counts and CRP but with patient global assessment > 1/10) is a status which may, or may not, be an acceptable objective for patients. Fatigue levels in this status are unknown.

Objectives: To assess fatigue levels and other aspects of impact, in patients in ACR/EULAR remission, compared to patients in near-remission and not in remission.

Methods: Ancillary analysis of the RAID database, based on an international multicenter cross-sectional study of consecutive RA patients from 12 European countries, and the baseline data in COMEDRA, a French national study in stable RA patients (refs 1, 2). Remission, near-remission and non-remission were assessed cross-sectionally and patient-reported impact of RA including fatigue was assessed using the RA Impact of Disease (RAID) score (ref 1). The RAID assesses pain, function, fatigue, sleep, coping and well-being; each component of the RAID score ranges from 0 (no impact) to 10 (high impact). Patients in remission were compared to those in near-remission and not in remission for mean levels and the proportion of patients with a score <=1/10, in each of the RAID components. The discriminant capacity of fatigue and of the other RAID components for the status of remission was assessed by Cohen's effect size.

Results: In total, 1284 patients had complete data for this analysis: mean (±standard deviation) age 57±11 yrs, disease duration 13±10 yrs, 78% women. Mean RAID score was 3.3±2.2. Mean fatigue in this population was 4.1±2.7. With the ACR/EULAR Boolean definition, only 87 (6.8%) were in remission and 84 (6.5%) were in near-remission. In remission patients, all the components of the RAID were very low (mean value below 1), except fatigue (mean value of 1.2±1.8; i.e., fatigue was above 1/10 in 25% of the patients in remission, versus 9–21% for the other aspects of RA impact. Near-remission was characterised by more impact of RA for all components of the RAID but particularly fatigue (mean fatigue 4.0±2.3, similar to patients not in remission: 4.3±2.7). Fatigue levels, psychological well-being and sleep had the lowest discriminant capacity to distinguish patients in remission versus not.

Conclusion: The ACR/EULAR definition of remission is extremely stringent and rarely attained for patients with long-standing RA. Fatigue was the only aspect of the impact of RA to remain at significant levels for many patients in Boolean remission, and was much higher in patients in near-remission. More work is needed to understand the link between fatigue and disease activity.

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Remaining Pain in Spite of Suppressed Inflammation in Early Rheumatoid Arthritis – Long-Term Strongly Increased Risk for Widespread Pain and Fatigue. Maria E.C. Sandberg[1], Saedis Saevarsdottir[2], Reem Altawil[3], Lars Klareskog[4], Lars Alfredsson[1] and Jon Lampa[3]. [1]The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [4]Karolinska Institute, Stockholm, Sweden.

Background/Purpose: Pain is common in rheumatoid arthritis (RA), even after adequate inflammatory disease control. Important long-term health effects of RA are fatigue, sleeping disturbances and a significant portion of patients also develop generalized pain, often leading to decreased quality of life. The aim of the present study was to investigate the distribution of remaining pain dimension in RA, which patients that may be at increased risk, and whether it is a risk factor for long-term generalized (widespread) pain and fatigue.

Methods: We used the cases (incident RA patients aged 18–70 recruited 1996–2009) from the Swedish population-based case-control study; EIRA, linked to the Swedish Rheumatology Quality Register (N=1633). Three years after diagnosis an additional questionnaire was sent out, assessing fatigue, pain outside joints and sleeping problems (N=186). Remaining pain was defined as pain on visual-analog scale (VAS) ≥20 mm and CRP <10 g/L at the 12 month follow-up visit. Logistic regression was used both to calculate the odds ratio (OR) of baseline clinical parameters as possible predictors of remaining pain, adjusted for sex, age and period and also OR of widespread pain (WSP; pain outside joints in all four quadrants)/any pain outside joints/sleeping problems/fatigue, as an effect of remaining pain.

Results: 35% of the patients had remaining pain at 12 months after diagnosis. Several factors at diagnosis significantly and independently increased the risk for remaining pain at 12 months: higher HAQ (ORs per additional unit; OR=1.28 [95%CI: 1.02 – 1.60]), tender joint count (OR=1.04 [95%CI: 1.02 – 1.06]) and patient global assessment (OR=1.25 [95%CI: 1.12 – 1.38] per 20 units). A higher CRP, ESR and swollen joint count all significantly and independently decreased the risk for remaining pain. (OR=0.84 [95%CI: 0.76 – 0.92] per 10 units), (OR=0.89 [95%CI: 0.80 – 0.99] per 10 units), (OR=0.97 [95%CI: 0.94 – 1.00] per joint); respectively. After 3 years; 7% had WSP, 36% had any pain outside joints, 17% had sleeping problems (defined as quite big/very big problem by the patient) and 26% had significant fatigue (VAS ≥40). Regarding the effect of remaining pain at 12 months on WSP/any pain outside joints/sleeping problems/fatigue we, despite our somewhat few observations, found strongly increased risk for these conditions after 3 years in those with remaining pain after 12 months: OR: WSP=3.48 [95%CI: 1.24–9.73], any pain outside joints= 2.67 [95%CI:1.44–4.94], sleeping problems=3.82 [95%CI:1.61–9.06], fatigue=2.43 [95%CI:1.25–4.72]. All these ORs remained after adjustment for very high baseline pain levels (VAS > 70), indicating that presence of WSP/fibromyalgia at diagnosis had no major impact on the results.

Conclusion: More than a third of all RA-patients have remaining pain despite satisfactory inflammation control 12 months after diagnosis. This condition is a very strong predictor for development of widespread pain 3 years after diagnosis. Moreover, we found strong associations with long-term non-joint-related pain, sleeping problems and fatigue. These observations stress the importance to acknowledge and optimize pain treatment also in patients with adequate inflammation control early in RA.

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Sensitivity of Unique Multidimensional Health Assessment Questionnaire Items Compared to Items on Both the HAQ and MDHAQ in Patients with RA and SLE. Narender Annapureddy[1], David Giangreco[1], Isabel Castrejón[1], Nisha Shetty[2], Theodore Pincus[1], Joel Block[1] and Meenakshi Jolly[1]. [1]Rush University Medical Center, Chicago, IL, [2]St. Anthony's Hospital, St. Louis, MO.

Background/Purpose: Patients with rheumatic diseases have significantly better clinical status in recent years than in previous decades, including rheumatoid arthritis (RA)[1] and systemic lupus erythematosus (SLE). [2] Therefore, many items in the health assessment questionnaire (HAQ) which were almost always elevated in 1980 when the HAQ[3] was reported may be normal at this time. In 1999, 16% of patients were reported to have HAQ scores of zero, suggesting "no difficulty" in function, but most nonetheless reported problems with function as well as psychosocial issues reflecting "floor effects." Therefore, a multidimensional HAQ (MDHAQ) was developed to include 13 queries in the user-friendly HAQ format, 8 simple activities of daily living (ADL) from (and identical to) the HAQ, and 5 not on the HAQ: 2 complex activities – "walk 2 miles or 3 kilometers" and "participate in recreation and sports as you would like", and 3 "psychological" queries – sleep quality, anxiety and depression. We analyzed mean scores for each of the 13 MDHAQ items in patients with RA and SLE in routine care in an academic rheumatology setting.

Methods: An MDHAQ is completed in an academic rheumatology setting by each patient at each visit. The MDHAQ queries 13 items (Table) in the patient-friendly HAQ format, all scored 0–3, with 4 response options: without any difficulty=0, with some difficulty=1, with much difficulty=2 and unable to do=3. Mean scores were analyzed in 140 female patients, 70 who met criteria for RA and 70 for SLE. Mean scores for each item was computed and compared using a t-test with a p-value of ≤ 0.05 considered significant on 2-tailed tests. Exploratory factor analysis (Principal Component analysis with varimax rotation) on the 13 items was performed.

Results: Mean scores for the 8 items a-h found on the HAQ were <0.70 in patients with RA and <0.50 in patients with SLE (Table), but scores were

>0.70 in patients with RA and >0.50 in patients with SLE for all 5 items i-m found only on the MDHAQ. Scores of 0 (floor effects) were seen in >49% of RA and >63% of SLE patients for the HAQ and MDHAQ items vs <47% for RA and <54% of SLE patients for the unique MDHAQ items. Most items loaded into 3 Components: A: activities of simple living (a-h in SLE and items a-c, e-g in RA), B: complex activities (i and j) and C: psychological (k-m). Differences between RA and SLE patients were significant only for items a, b and j.

MDHAQ Item	RA patients			SLE patients		
* = Found on HAQ and MDHAQ # = Found only on MDHAQ	Mean (SD)	% 0 (Floor effect)	Factor loading	Mean (SD)	% 0 (Floor effect)	Factor loading
a. Dress yourself, including tying shoelaces and doing buttons?*	0.67 (0.63)	50	A	0.43 (0.79)	64	A
b. Get in and out of bed?*	0.70 (0.79)	49	A	0.37 (0.57)	67	A
c. Lift a full cup or glass to your mouth?*	0.39 (0.66)	70	A	0.27 (0.56)	77	A
d. Walk outdoors on flat ground?*	0.66 (0.76)	50	B	0.42 (0.69)	70	A
e. Wash and dry your entire body?*	0.50 (0.70)	60	A	0.36 (0.64)	72	A
f. Bend down to pick up clothing from the floor?*	0.69 (0.77)	49	A	0.46 (0.65)	63	A
g. Turn regular faucets on and off?*	0.46 (0.69)	66	A	0.28 (0.45)	72	A
h. Get in and out of a car, bus, train, or airplane?*	0.64 (0.70)	49	A/B	0.49 (0.70)	63	A
i. Walk 2 miles, if you wish? #	1.26 (1.06)	29	B	1.03 (1.03)	39	B
j. Participate in recreational activities and sports as you would like, if you wish? #	1.59 (1.13)	23	B	1.13 (1.14)	41	B
k. Get a good night's sleep? #	1.28 (0.97)	23	C	1.13 (0.99)	31	C
l. Deal with feelings of anxiety or being nervous? #	0.79 (0.91)	47	C	0.54 (0.65)	54	C
m. Deal with feelings of depression or feeling blue? #	0.76 (0.85)	46	C	0.56 (0.67)	54	C

Conclusion: Scores of 0 are seen on considerably more HAQ items than MDHAQ items. The MDHAQ identifies patient problems, which are not captured by the HAQ, similar in RA and SLE. Documentation of improvement is not possible when baseline scores are zero. The MDHAQ might be considered for usual clinical care as well as in clinical trials.

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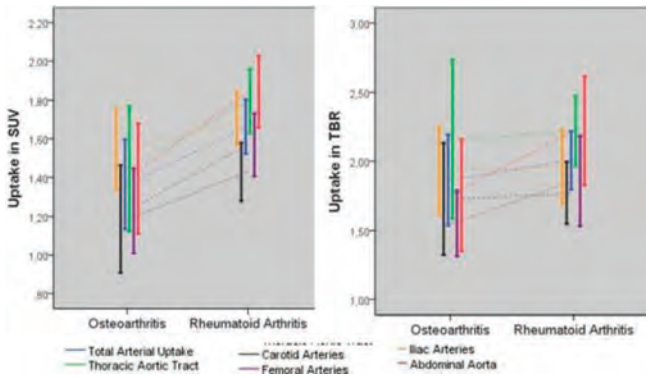
Increased Vascular Wall Inflammation in Patients with Active Rheumatoid Arthritis As Measured By an 18F-FDG-PET/CT Scan. Rabia Agca[1], Alper M. van Sijl[1], Yvo M. Smulders[1], Alexandre E. Voskuyl[1], Connie J. van der Laken[1], Ronald Boellaard[1], Karel-Jan D.F. Lensen[1] and Michael T. Nurmohamed[2]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Jan van Breemen Research Institute Reade, Amsterdam, Netherlands.

Background/Purpose: Patients with rheumatoid arthritis (RA) have an elevated risk of developing cardiovascular disease (CVD). Like active RA, atherosclerosis is an inflammatory process. There are indications that aortic inflammation in atherosclerosis can be detected on an ^{18}F-Fluorodeoxyglucose-positron emission tomography/computed tomography scan (^{18}F-FDG-PET/CT).

Objective: To quantify ^{18}F-FDG uptake in large arteries of RA patients using PET/CT, as potential reflection of vascular wall inflammation in areas of atherosclerosis, and its association with disease activity in patients with RA as compared to controls.

Methods: ^{18}F-FDG-PET/CT scan was performed in patients with active RA (DAS28 > 4.0; n=29) and in controls with osteoarthritis (n=11). Semi-quantitative FDG-uptake was determined by calculation of the mean standardized uptake value (SUV) and tissue-to-background ratio (TBR) using ^{18}F-FDG activity in the vena cava as background. One volume of interest (VOI) of an arterial segments with maximum ^{18}F-FDG uptake was used for SUV calculation (focal arterial uptake). Total arterial uptake was estimated by using the mean of all focal arterial uptakes in all arteries.

Results: Focal as well as total arterial uptake of ^{18}F-FDG was the highest in patients with RA. SUV was significantly higher in RA for the thoracic aortic tract, the abdominal aorta and the femoral arteries as compared to OA controls. C-reactive protein was associated with an increased total arterial uptake as well as an increased focal arterial uptake in the thoracic aortic tract, the abdominal aorta, the iliac arteries and the femoral arteries. DAS28 >2,6 was also correlated to total arterial uptake and uptake in the thoracic aortic tract, the abdominal aorta and the iliac arteries. There were no significant differences in TBR between RA and OA.



Conclusion: Increased focal vascular wall uptake of ^{18}F-FDG as sign of vascular inflammation was found in several arterial segments of RA patients. C-reactive protein and clinical RA activity were correlated with ^{18}F-FDG uptake in most of these arteries. Overall, total arterial uptake was higher in RA patients and it was correlated with C-reactive protein and disease activity. The lack of differences in TBR measurements requires further study.

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Increased Left Ventricular Mass Index and Decreased Ejection Fraction Are Associated with Disease Activity in Rheumatoid Arthritis Patients without Cardiac Symptoms; Comparison Between Non-Biologic and Biologic Dmards Treatment Groups, Using a Cardiac Magnetic Resonance Imaging. Hitomi Kobayashi[1], Yasuyuki Kobayashi[2], Atsuma Nishiwaki[1], Hirotake Inomata[1], Noboru Kitamura[1], Hidetake Shiraiwa[1], Takamasa Nozaki[1], Natsumi Ikumi[1] and Masami Takei[3]. [1]Nihon University School of Medicine, Tokyo, Japan, [2]St.Marianna University School of Medicine, Kawasaki, Japan, [3]Nihon University School of Medicine, Itabashi Tokyo, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) experience an excess risk of congestive heart failure (CHF), but effects of disease-modifying anti-rheumatic drugs (DMARDs) on cardiac structure and function are uncertain. Cardiac magnetic resonance imaging (CMR) has been used to identify early functional and structural changes in the left ventricle (LV) before development of clinically overt CHF. We evaluated LV function and structure using a CMR in RA patients (pts) without cardiac symptoms, and determined the impact of non-biologic and biologic DMARDs (bDMARDs).

Methods: Consecutive RA pts and healthy control without a history or clinical findings of hypertension, cardiovascular disease, diabetes, or dyslipidemia were enrolled. RA pts received biologic or non-biologic DMARDs (nbDMARDs). All subjects underwent evaluation of LV function and structure using non-contrast CMR. LV function was based on LV ejection fraction (EF), end-systolic volume (ESV), end-diastolic volume (EDV), stroke volume (SV), and cardiac output (CO). LV hypertrophy was measured by absolute LV mass (LVM) and LV mass index (LVMI) determined by LVM/body surface area. Subjects were classified into four categories based on LVMI and LVM/EDV of control subjects, with the mean + 2 SD of each measure defined as elevated LVMI and LVM/EDV.

Results: We compared 90 female RA pts (mean age, 55.9±7.1 years) with a matched 20-patient control group (mean age, 52.7±4.6 years). 46 RA pts received nbDMARDs [43, methotrexate (MTX) (8.1±2.1mg); 3, other drugs)] and 44 RA pts received bDMARDs [(18, infliximab (3 mg/kg); 26, tocilizumab (8 mg/kg) plus MTX (8.0±1.4 mg)]. Among the RA groups, there were no significant differences in characteristics such as age, cardiovascular risk factors, RA duration, MTX dose, and proportion of corticosteroid users. The Simplified Disease Activity Index (SDAI) was significantly

higher in the nbDMARDs group than in the bDMARDs group (22.3±1.5, 5.6±1.9. $p=0.002$). Compared to the control group, the nbDMARDs group showed significantly higher LVMI and lower EF ($p<0.001$, $p=0.003$, respectively). There were no significant differences in LVMI and EF between the control and the bDMARDs groups. LV structure was classified as (1) concentric remodeling (LVMI<66.9 and LVM/EDV >1.02); (2) concentric hypertrophy (LVMI >66.9 and LVM/EDV >1.02); (3) eccentric hypertrophy (LVMI >66.9 and LVM/EDV <1.02); and (4) normal geometry (LVMI<66.9 and LVM/EDV<1.02). Among those with abnormal LV geometry, 32% of RA patients in the nbDMARDs group showed eccentric hypertrophy. 98% of RA patients in the bDMARDs group showed normal geometry. LVMI and EF were significantly associated with SDAI (r=0.567, $p<0.001$; r=−0.312, $p=0.003$, respectively). Mass/EDV tended to be associated with SDAI ($p=0.07$). Adjustment for ESR did not modify the association of SDAI with EF and LVMI ($p=0.017$, $p=0.005$, respectively).

Conclusion: Our results showed that increased LV mass Index and decreased EF were associated with SDAI. Biologics treatment may reduce progression of subclinical LV abnormalities in association with the reduction in disease activity. It can be presumed that disease activity may be an important contributor to the development of LV abnormalities in RA.

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The Rheumatoid Arthritis Impact of Disease Score Is Associated with Disease Activity By Clinical, Laboratory and Ultrasonographic Measures: Validation in an inception Cohort of DMARD naïve Patients with Rheumatoid Arthritis. Lena Bugge Nordberg, Elisabeth Lie, Anna-Birgitte Aga, Marthe Thoresen Maehlen, Inge Olsen C, Till Uhlig, Tore K. Kvien, Espen A. Haavardsholm and the Arctic study Group. Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: The Rheumatoid arthritis impact of disease (RAID) score is a relatively new patient-derived composite score assessing the seven most important domains of the impact of rheumatoid arthritis (RA). It is unknown how the RAID score correlates with other disease measures in patients with early RA. We aimed to examine associations between the RAID score and different clinical, laboratory and ultrasonographic disease measures as well as other patient reported outcome measures (PROMs) in an inception cohort of DMARD naïve patients with early RA.

Methods: Consecutive patients from 11 rheumatology centers in Norway who fulfilled the 2010 ACR/EULAR classification criteria for RA were included from October 2010 to April 2013. All patients had symptom duration (from first swollen joint) <2 years and were DMARD naïve with indication for DMARD treatment. Patients were stratified according to level of RAID score at baseline, and a RAID score of ≤3 was considered low, >3–6 moderate and >6 high. Disease measures were compared across RAID levels using either Kruskal-Wallis or ANOVA, and we assessed the correlation between the RAID score and other measures using Pearson or Spearman correlation coefficients, as appropriate.

Results: A total of 229 patients were included, 61.1% female, 81.2% ACPA-positive and with mean (SD) age 51.0 (13.6) years. At baseline, mean (SD) RAID score was 4.5 (0.7), and 28.4%/47.6%/24.0% of the patients had low/moderate/high RAID score according to the above specified cut-offs. Differences in disease measures were all statistically significant across the low, moderate and high RAID groups, with the exception of the power Doppler ultrasonography score (table). Correlation analysis revealed statistically significant correlations between RAID score and all other measures, again with the exception of the power Doppler ultrasonography score. Correlations between RAID and Patient global, EQ-5D and Pain (VAS), respectively, were strong (r≥0.70), and the correlations between RAID and Ritchie, DAS44, Physician global, fatigue and SF-36 Physical and Mental Components Summary measures were moderate (r ≥0.4–0.7). The remaining correlations were weak (r<0.4).

	Low RAID≤3, n=65	Moderate RAID>3-6, n=109	High RAID>6, n=55	P
Disease duration,months*†	6.3 [3.6–12.0]	5.4 [2.7–9.8]	4.3 [2.2–9.3]	0.057
Age**	52.2 (14.4)	49.7 (13.7)	52.0 (12.5)	0.41
Female, n (%)	37 (56.9)	67 (61.5)	36 (65.5)	0.63
DAS-44**	2.71 (0.96)	3.53 (0.89)	4.27 (1.08)	<0.001
44-Swollen joint count*	7 [3–13]	9 [5–13]	12 [7–18]	0.003
ESR (mm/h)*	14 [9–26]	21 [12–30]	29 [15–45]	<0.001
CRP (mg/L)*	4 [2–7]	8 [4–18]	12 [6–28]	<0.001
Ritchie tender joint score*	4 [2–7]	8 [4–13]	12 [6–17]	<0.001
Patient global VAS (mm)**	27.9 (16.4)	48.4 (17.3)	77.2 (15.1)	<0.001
Physician global VAS (mm)**	29.6 (16.5)	41.6 (20.0)	51.4 (20.3)	<0.001
GSUS score ††	14 [9–23]	17 [10–28]	23 [16–30]	0.008
PDUS score*††	6 [2–13]	6 [3–13]	9 [4–14]	0.11
Total US score*††	20 [12–36]	24.5 [15–38]	33 [21–45]	0.015
EQ-5D (UK)*	0.76 [0.69−0.80]	0.66 [0.52−0.69]	0.06 [−0.2−0.18]	<0.001
Pain VAS (mm)**	26.5 (15.8)	45.8 (18.0)	75.6 (11.3)	<0.001
Fatigue VAS (mm)**	19.1 (20.8)	40.8 (24.9)	63.1 (24.7)	<0.001
SF-36 PCS**	43.3 (8.5)	33.9 (7.9)	23.8 (7.9)	<0.001
SF-36 MCS**	52.9 (9.3)	48.2 (10.9)	42.1 (10.3)	<0.001

*Median [25–75 percentiles]. **Mean(SD). †Time from patient reported first swollen joint. ††Ultrasonography (US) examinations were performed by experienced sonographers using a validated gray-scale (GS) and power-Doppler (PD) semi-quantitative scoring system with ranges 0–3 for GS and PD in each of the following 32 joints: MCP I-V, radio-carpal (RCJ), distal radio-ulnar (DRUJ), inter-carpal (ICJ), elbow, knee, talo-crural and MTP I-V bilaterally. PCS = Physical Components Summary, MCS = Mental Component Summary.

Conclusion: The RAID score was associated with both patient-reported and objective disease measures in this inception cohort of DMARD naïve RA patients. These findings support the use of RAID as a valid PROM in patients with early RA, covering a wide variety of disease manifestations and reflecting the patient perspective.

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Development and Validation of a Diagnostic Bead-Based Multiplex Autoantibody Assay:Screening for Autoantibodies to Detect "Seronegative" Rheumatoid Arthritis. Stefan Vordenbäumen[1], Angelika Lueking[2], Carmen Theek[2], Ralph Brinks[1], Rebecca Fischer-Betz[1], Jutta Richter[1], Ellen Bleck[1], Jacqueline Detert[3], Gerd Burmester[4], Peter Schulz-Knappe[2] and Matthias Schneider[1]. [1]Heinrich-Heine-University, Düsseldorf, Germany, [2]Protagen AG, Dortmund, Germany, [3]Charité - University Medicine Berlin, Berlin, Germany, [4]University Medicine, Berlin, Germany.

Background/Purpose: Autoantibodies (auto-Ab) against citrullinated peptides (ACPA) and rheumatoid factor (RF) are important biomarkers in the diagnostic process of rheumatoid arthritis (RA). However, RF or ACPA are undetectable in up to 30% of RA patients who can be referred to as „seronegative". In these cases, the diagnosis is often challenging. Early diagnosis in turn is important for improved outcome. In search for an optimized serologic diagnostic strategy, a comprehensive auto-Ab screening was performed in RA patients.

Methods: 5,892 recombinant human antigens were covalently coupled to fluorescent beads, incubated with patients' sera and detected by a secondary, fluorescent antibody using Luminex xMAP technology. In an explorative phase, auto-Ab profiles were compared between 72 established RA patients according to ACR/EULAR criteria, 71 matched healthy controls, and 129 systemic lupus erythematosus (SLE) patients in an age- and gender-adjusted manner. Predefined multi- and univariate analyses were employed to generate a diagnostic panel of auto-Ab for further testing. In a validation phase, the diagnostic potential of this panel was assessed in 116 RA patients from a randomized controlled trial (HIT-HARD) against 116 matched healthy controls employing logistic regression modelling.

Results: A panel of 11 auto-Ab (including ACPA) showed the best diagnostic properties and was further assessed. In the explorative phase sensitivity/specificity/area under the curve (AUC) were 0.9/0.9/0.97 for RA patients against healthy controls and 0.79/0.92/0.93 against SLE. Omitting ACPA resulted in slightly weaker test performance with sensitivity/specificity/AUC of 0.9/0.86/0.95. When only seronegative (ACPA and RF negative) patients were considered, sensitivity/specificity/AUC was 1.0/1.0/1.0 against healthy controls. In the validation phase on early RA patients from the HIT-HARD study, the panel showed sensitivity/specificity/AUC of 0.71/0.53/0.68 with ACPA and only slightly weaker performance at 0.71/0.52/0.67 without ACPA. Seronegative patients were detected with sensitivity/specificity/AUC of 0.09/0.96/0.78.

Conclusion: The multiplex bead-based approach showed promising results concerning the identification of potential diagnostic markers for seronegative RA. The need for rigorous validation of such explorative approaches to control for over-fitting is clearly demonstrated. Future improvements of the technology such as citrullination of recombinant antigens may further enhance detectability of "seronegative" patients.

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Parity and Severity of ACPA-Positive/Negative Rheumatoid Arthritis. Results from the Swedish EIRA Study. Mitra Pikwer[1], Cecilia Orellana[2], Henrik Källberg[2], Andreas Pikwer[3], Carl Turesson[4], Lars Klareskog[5], Lars Alfredsson[6], Saedis Saevarsdottir[7] and Camilla Bengtsson[8]. [1]Institute of Environmental Medicine, Eskilstuna, Sweden, [2]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Centre of Clinical Research Sörmland, Eskilstuna, Sweden, [4]Rheumatology, Department of Clinical Sciences, Malmö, Sweden, [5]Rheumatology Unit, Karolinska University Hospital, Karolinska institutet, Stockholm, Sweden, [6]Centre of Occupational and Environmental Medicine, Stockholm, Sweden, [7]Institute of Environmental Medicine, Karolinska Institutet,, Stockholm, Sweden, [8]The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Female sex and older age are known risk factors for rheumatoid arthritis (RA). The disease is however heterogeneous, and a common division occurs between the presence/absence of autoantibodies to citrullinated peptide antigens (ACPA) where ACPA-positive disease generally has a worse outcome. In a recent study we reported that parous women of reproductive age (18 to 44 years at diagnosis) had an increased risk of ACPA-negative, but not of ACPA-positive RA, and that this association was stronger closer to partum[1]. There are diverging results regarding the effect of parity on the severity of RA.

Our purpose was to explore if parity has impact on disease severity of RA, stratified into different phenotypes.

Methods: We studied female RA cases aged 18–70, who participated in the Epidemiological Investigation of Rheumatoid arthritis, EIRA, a population-based case-control study from the middle and southern parts of Sweden. All patients included fulfilled the American Collage of Rheumatology (ACR) 1987 criteria for RA and were diagnosed by a rheumatologist, and included within 1 year of diagnosis. Information on disease severity (Health Assessment Questionnaire, HAQ and disease activity score 28, DAS28) was gathered from the Swedish Rheumatology Register, SRQ at inclusion, 3, 6, 12 and 24 months after diagnosis. Mixed models for repeated measurements over time were used to take account of the variation at different time point at individual level and to compare mean DAS28 and HAQ-scores over time. ANCOVA analysis was used to compare mean differences of clinical outcome measures at all time points.

Results: A total of 1237 female cases, with complete information, were included in the study with a mean age of 51 at inclusion. In all, 82% had ever given birth to a child before diagnosis and 65 % were ACPA-positive. Mixed models analysis showed associations between parity and ACPA negative but not ACPA positive disease. Parous women, aged 18–44, who would develop ACPA negative disease, had on average 1.17 higher DAS 28 ($p < 0.001$) and 0.43 higher HAQ ($p < 0.001$) compared to nulliparous women during the follow up time, adjusted for age. These findings remained after individually adjustment for smoking, living area and level of education. There was an opposite trend among parous ACPA negative women (aged 45 to 70), were parous women had 0.26 lower DAS 28 ($p=0.14$) and 0.06 lower HAQ ($p=0.46$). ANCOVA analysis for different time points noted an association between higher DAS 28 and HAQ levels and parity in the ACPA negative reproductive age group at all time points, except at baseline. In ACPA negative older age group we observed a milder disease in parous women, although only significant at baseline.

Conclusion: Parity influenced ACPA negative disease, where parous women who developed RA during their fertile years had on average higher DAS 28 and HAQ compared to nulliparous women. Parity was not a predictor of severity in ACPA positive disease.

References

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14-3-3η Cit:Arg Antibody Ratios: Are We Overlooking the Prognostic Utility of Citrullinated Antibodies By Only Looking at Titers? Anthony Marotta[1], Samina Turk[2], Mairead Murphy[1], WP Maksymowych[3] and Dirkjan van Schaardenburg[2]. [1]Augurex Life Sciences Corp., North Vancouver, BC, [2]Reade, Amsterdam, Netherlands, [3]University of Alberta, Edmonton, AB.

Background/Purpose: Citrullination is a post-translational modification whereby arginine (Arg) is deiminated by PAD enzymes to form citrulline (Cit). In RA, there are auto-antibodies (AAb) to Cit and native proteins[1, 2]. With other types of PTM, such as phosphorylation, modifications are assessed as a degree of change in reactivity from the native state to inform biochemically relevant and potentially deleterious events. Current ACPA assays are designed to measure reactivity to the Cit form of a peptide without accounting for the relative change in Cit:Arg reactivity. This may overlook important information related to citrullination and its relationship with clinical outcomes. 14-3-3η is a ubiquitous intracellular protein whose extracellular expression in RA leads to its citrullination and the development of specific cit-reactive AAb. In this study we investigated whether anti-cit 14-3-3η AAbs inform joint damage prognosis in early RA.

Methods: Anti-cit 14-3-3η levels were measured in 139 DMARD-naïve early RA patients from the READE cohort using the MSD ECL platform, 4 highly reactive 14-3-3η cit/arg peptides formed the basis of the assay. For each of the 4 sites, citrullination reactivity was defined as a 50% increase in Cit:Arg read units. Overall anti-cit-14-3-3η positivity was defined as reactivity to at least one of the four sites. Contingency analysis was used to assess the association between ACPA and 14-3-3η anti-cit:arg ratio positivity. Univariate and stepwise multivariate analyses were performed to identify predictors of radiographic damage progression (DSHS year 3 $\geq$ 3.0).

Results: Of 139 patients, 71% were ACPA positive and 51% were 14-3-3η anti-cit:arg ratio positive. A univariate analysis evaluating the association of anti-cit-14-3-3η titres and cit:arg ratios with radiographic progression revealed that the ratios were significantly associated ($p<0.01$) while titres were not. Contingency analysis revealed a strong association between APCA and 14-3-3η anti-cit:arg ratios, LR=19.1 $p<0.0001$. By Fisher Exact test, ACPA and 14-3-3η anti-cit:arg ratios were associated with radiographic progression at yr 3; LR=5.3 $p=0.02$ and 6.4 $p=0.01$, respectively. In a model incorporating ACPA and 14-3-3η anti-cit:arg ratio controlling for baseline total sharp score, the ratios independently predicted radiographic progression Chi-Sq=6.4 $p=0.01$, while ACPA did not. In a multivariate model including baseline TSS, disease duration, age, ESR, gender together with RF, 14-3-3η and 14-3-3η anti-cit:arg ratio positivity, the only independent predictors of radiographic damage progression were 14-3-3η protein and the cit:arg ratios; Chi-Sq=5.2 ($p=0.02$) and 4.0 ($p=0.05$), respectively.

Conclusion: Both the 14-3-3η protein and 14-3-3η anti-cit:arg ratios are independent predictors of radiographic progression. The ratios (but not anti-cit-14-3-3η titres) are a stronger predictor than ACPA. These data underscore 1) the potential benefit of accounting for cit:arg ratios rather than only cit titres in cit assays and 2) that the prognostic utility of 14-3-3η anti-cit:arg ratios should be further investigated.

1. Brink et al. ARD 73.7 (2014): e46.
2. van de Stadt et al. ARD 70.1 (2011): 128.

Disclosure: A. Marotta, Augurex Life Sciences Corp., 3; **S. Turk**, None; **M. Murphy**, Augurex Life Sciences Corp, 3; **W. Maksymowych**, Augurex Life Sciences Corp, 5; **D. van Schaardenburg**, Augurex Life Sciences Corp, 5.

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88% of Recent Onset Polyarthritis Patients Are Positive for 14-3-3η Markers and 14-3-3η Auto-Antibodies Inform a Favourable Prognosis. Gilles Boire[1], Nathalie Carrier[2], Artur Jose de Brum-Fernandes[2], Patrick Liang[3], Ariel Masetto[4], Yuan Gui[5], Mairead Murphy[5], WP Maksymowych[6] and Anthony Marotta[5]. [1]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [2]Universite de Sherbrooke, Sherbrooke, QC, [3]CHUS, Sherbrooke, QC, [4]CHUS, Fleurimont, QC, [5]Augurex Life Sciences Corp., North Vancouver, BC, [6]University of Alberta, Edmonton, AB.

Background/Purpose: The 14-3-3η protein has been described as a mechanistic marker that is detectable in serum during the very early stages of RA development. A specific anti-14-3-3η autoantibody response is present in RA serum and is postulated to be protective when it effectively clears systemic 14-3-3η. This study examined the baseline expression of 14-3-3η

markers (protein and pan-autoantibodies) in a recent onset polyarthritis cohort and their association with the progression of joint damage.

Methods: 335 subjects were evaluated; 40 DMARD-naïve patients from the Sherbrooke EUPA cohort and 295 controls. Median age was 50 yrs, 2 months median disease duration, 75% were female and 60% were positive for RF and 55% for ACPA. Controls included 106 healthy and 189 disease controls consisting of connective tissue disease, OA, AS or autoimmune disorders. 14-3-3η protein levels were previously tested in this cohort using the Augurex 14-3-3η ELISA (cut-off $\geq$0.19 ng/ml) and 50% of the recent onset polyarthritis patients were positive. 14-3-3η AAb levels were measured on the MSD ECL platform using an established positive cut-off $\geq$380 U/ml. The group that was 14-3-3η AAb-only positive, in whom the 14-3-3η protein would have been cleared, was compared to the remainder of the cohort in terms of differences in radiographic progression over 30 months using the Mann-Whitney U-test. The Fisher Exact test was used to determine the association between marker positivity and radiographic progression (SHS$\geq$3 at 30 months).

Results: Median (IQR) 14-3-3η AAb values were significantly higher in early RA 617 U/ml (473–742) vs all controls 264 U/ml (200–348), $p<0.0001$ delivering a ROC AUC of 0.89 (95%CI:0.85–0.94). When compared to healthy subjects, the ROC AUC was 0.95 (95%CI:0.92–0.99), $p<0.0001$ delivering 93% specificity and 85% sensitivity with a likelihood ratio (LR) of 11.3. Thirty-four patients (85%) were 14-3-3η AAb positive, 88% were positive for either of the 14-3-3η markers and a Pearson correlation between the two 14-3-3η markers of $r < 0.01$ highlighted their complementary nature. Of the 40 patients, 15 (38%) were only positive for the 14-3-3η AAbs and had significantly less joint damage progression at 30 months, median (IQR) ΔSHS 0 (0–3.5) vs the rest of the cohort, 5 (−0.3–11.5), $p<0.03$. The Fisher exact test revealed that 14-3-3η AAb positivity (in the absence of the 14-3-3η protein) is associated with less radiographic progression at 30 months yielding an Odds Ratio of 5.3 (95%CI 1.2–23.9). $p=0.03$.

Conclusion: 14-3-3η and anti-14-3-3η biomarkers identify 88% of recent onset polyarthritis patients and those who are only positive for 14-3-3η AAbs have a more favorable radiographic prognosis. This is potentially due to the more effective clearance of deleterious 14-3-3η protein by anti-14-3-3η antibodies in these patients.

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Citrullinated 14-3-3η Antibodies Are Specific for Early and Established RA and Are Complementary to ACPA. Anthony Marotta[1], Dirkjan van Schaardenburg[2], Gilles Boire[3], Désirée van der Heijde[4], Robert Landewé[5], Maarten Boers[6], C.F. Allaart[4], Mairead Murphy[1], Samina Turk[2], Vivian P. Bykerk[7], Edward Keystone[8], Katherine A. Siminovitch[8] and WP Maksymowych[9]. [1]Augurex Life Sciences Corp., North Vancouver, BC, [2]Reade, Amsterdam, Netherlands, [3]CHUS - Sherbrooke University, Sherbrooke, QC, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [6]Jan van Breemen Research Institute/Reade, Amsterdam, Netherlands, [7]Divison of Rheumatology, Hospital for Special Surgery, New York, NY, [8]Mount Sinai Hospital, Toronto, ON, [9]University of Alberta, Edmonton, AB.

Background/Purpose: Citrullination is a post-translational modification whereby arginine (Arg) is deiminated by PAD enzymes to form citrulline (Cit). In RA, current ACPA assays measure the ACPA titer without determining whether the observed reactivity is specific for the citrullinated or arginilated form of the peptide. Brink showed that autoantibodies (AAb) directed to uncitrullinated peptides may occur prior to the development of cit specific antibodies. Consequently, important information related to citrullination and its relationship to clinical outcomes might be overlooked. 14-3-3η is normally an intracellular protein whose extracellular expression in RA leads to the development of specific pan-reactive AAb to the native protein that inform joint damage prognosis, and also cit-14-3-3η-reactive AAbs. In this study we examined 14-3-3η cit:arg reactivity and its complementarity to ACPA in diagnosing RA.

Methods: A total of 623 subjects were evaluated; 190 DMARD-naïve early RA patients (READE n=139, Sherbrooke n=40, iCOBRA n=11), 115 with classified established RA (n=65 from the RAPPORT cohort; 50 from the year 3 time point of the BeSt study). 318 controls constituted 106 healthy and 212 disease controls with connective tissue disease, OA, AS and autoimmune conditions. AAb levels were measured using the MSD ECL platform. Seven (7) cit/arg sites on 14-3-3η were examined for differential AAb reactivity between RA and controls using the Kruskal-Wallis test and ROC curve analysis. The paired t-test was used to determine differences in cit:arg reactivity. Anti-cit-14-3-3η positivity at an individual cit site was defined by a 50% increase in reactivity to the cit site over the corresponding arg site, with overall anti-cit positivity defined as positive at a least one cit site.

Results: The significantly higher reactivity of anti-cit 14-3-3η in RA versus controls, based on ROC analysis and assessment of cit:arg fold reactivity, resulted in the prioritization of 4 cit sites (1, 2, 4, 7) which reside on the protein surface. Reactivity was not confined to the cit form of the peptide since significantly higher reactivity to the arg peptide was also apparent in RA versus controls. Importantly, 50% of early and 54% of established RA patients were anti-cit-14-3-3η positive. While the Fisher Exact test revealed a significant association between anti-cit-14-3-3η and ACPA positivity (LR = 19.1 $p<0.0001$), in ACPA negatives, 25% of early and 41% of established RA patients were positive for anti-cit-14-3-3η. Combining ACPA and anti-cit-14-3-3η reactivity improved the early RA capture rate (table).

	Early RA (n=190)		Established RA (n=115)	
Based on ACPA	**ACPA -ve (n=60)**	**ACPA +ve (n=130)**	**ACPA -ve (n=27)**	**ACPA +ve (n=88)**
Cit-14-3-3η eta Ab, % (n)	25% (15)	62% (80)	41% (11)	58% (51)
Combination of Markers				
ACPA	68% (130)		77% (88)	
Cit-14-3-3η	50% (95)		54% (62)	
Either Marker	76% (145)		86% (99)	

Conclusion: In RA, AAbs exist against 14-3-3η native and citrullinated protein. Anti cit-14-3-3η AAbs are expressed in early and established RA and complement ACPA as a diagnostic aid. Relative cit:arg AAb reactivity should be accounted for in citrullination assays to properly assess the burden of citrullination in RA.

Ref.
Brink M et al. ARD. 2014 Jul;73(7):e46.

Disclosure: A. Marotta, Augurex Life Sciences Corp., 3; **D. van Schaardenburg**, Augurex Life Sciences Corp, 5; **G. Boire**, Augurex Life Sciences Corp, 5; **D. van der Heijde**, Augurex Life Sciences Corp, 5; **R. Landewé**, Augurex Life Sciences Corp, 5; **M. Boers**, Augurex Life Sciences Corp, 5; **C. F. Allaart**, Augurex Life Sciences Corp, 5; **M. Murphy**, Augurex Life Sciences Corp, 3; **S. Turk**, None; **V. P. Bykerk**, Augurex Life Sciences Corp, 5; **E. Keystone**, Augurex Life Sciences Corp, 5; **K. A. Siminovitch**, None; **W. Maksymowych**, Augurex Life Sciences Corp, 5.

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14-3-3η Early RA Biomarkers: Does Seronegative RA Exist? Dirkjan van Schaardenburg[1], WP Maksymowych[2], Maarten Boers[3], Samina Turk[1], Mairead Murphy[4] and Anthony Marotta[4]. [1]Reade, Amsterdam, Netherlands, [2]University of Alberta, Edmonton, AB, [3]Jan van Breemen Research Institute/Reade, Amsterdam, Netherlands, [4]Augurex Life Sciences Corp., North Vancouver, BC.

Background/Purpose: RF and ACPA are used for early diagnosis and in prediction models for the risk of RA development in arthralgia patients. There remains a high unmet need for biomarkers in the earliest stages of RA to assist with detection and prognosis to enable therapy initiation within the first 6–12 weeks of symptom onset. The 14-3-3η serum protein and its corresponding anti-14-3-3η auto-antibodies are early complementary markers to RF/ACPA. This study describes their expression and diagnostic utility as well as their complementarity to RF/ACPA in early RA.

Methods: 14-3-3η plasma protein levels were measured on the Augurex ELISA and 14-3-3η auto-antibody levels on the Meso-Scale-Discovery electro-chemiluminescent platform in 409 consecutive early RA patients (Reade cohort) according to the 2010 ACR/EULAR RA classification criteria. Patients were DMARD-naïve, had a rheumatologist-confirmed diagnosis, median symptom duration was 4 months, mean age was 54 years and 73% were female. For 14-3-3η auto-antibody level determination, a composite score of six (6) peptides was generated. Peptides were selected based on their individual highest sensitivity for 100% specificity and their complementarity to maximize patient capture. An auto-antibody score of $\geq$380 U/ml was determined to be the best positive cut-off. Serum 14-3-3η protein levels were previously determined in these subjects with a positive diagnostic cut-off of $>$ 0.19 ng/ml. Positive baseline status for each of the 14-3-3η markers and RF and ACPA were compared to examine the extent of early RA patient capture rate versus RF/ACPA.

Results: In the 409 patients, 67% (n=275) were positive for the 14-3-3η protein with median (IQR) titres of 0.63 (0.10–5.13) ng/ml

and 77% (n=313) were positive for 14-3-3η auto-antibodies with median (IQR) values of 527 (387–753) U/ml. RF and ACPA positive rates in this cohort were 63% (n=259) and 69% (n=282), respectively. 76% (n=310) of patients were positive for one or both of RF and ACPA, 93% (n=394) were positive for either of the 14-3-3η markers and 96% for any one of the four markers. This represents 23% more patients identified by 14-3-3η markers alone compared to RF/ACPA, and 27% more when the four markers are used together.

Conclusion: 14-3-3η markers identify 93% of early RA patients compared to RF/ACPA alone at 76%. The combination of all four markers captures 96% of early RA patients which creates the opportunity to treat more patients within the therapeutic window and improve clinical outcomes.

Disclosure: D. van Schaardenburg, Augurex Life Sciences Corp, 5; **W. Maksymowych**, Augurex Life Sciences Corp, 5; **M. Boers**, Augurex Life Sciences Corp, 5; **S. Turk**, None; **M. Murphy**, Augurex Life Sciences Corp, 3; **A. Marotta**, Augurex Life Sciences Corp., 3.

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Increased Prevalence of Plasma Anti-Nuclear, Anti-SSA, and Connective Tissue Disease Associated Antibodies in African American Patients with Rheumatoid Arthritis. Rayford R. June[1], Douglas P. Landsittel[2], Bruce Rabin[3], S. Louis Bridges Jr. [4], CLEAR Investigators[4], TEAR Investigators[4], Thomas A. Medsger Jr. [1] and Larry W. Moreland[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, Center for Health Care Research Data Center, Pittsburgh, PA, [3]University of Pittsburgh Medical Center, Pittsburgh, PA, [4]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: African American (AA) patients with rheumatoid arthritis (RA) have been shown to have worse disability scores, increased disease activity scores, and reduced use of disease modifying anti-rheumatic drugs. The frequency of antinuclear antibodies (ANA) in Caucasian (CAU) RA has been reported, but ANA occurrence in AA RA patients is unknown. ANA positive CAU RA patients have an increased autoimmune genetic risk score and this phenotype is associated with coexistent Sjögren syndrome (SS). There is a high frequency of anti-SSA antibodies in SS. We hypothesized that AA RA patients have an increased frequency (compared to CAU RA patients) of ANA, anti-SSA, and other connective tissue disease (CTD) associated autoantibodies.

Methods: We assayed plasma samples from two published RA cohorts: (1) AA patients in the Consortium for the Longitudinal Evaluation of African-Americans with Early Rheumatoid Arthritis (CLEAR II) and (2) CAU patients from the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) Trial. All patients met the revised 1987 American College of Rheumatology classification criteria for RA. A total of 587 CLEAR and 390 TEAR samples were tested for ANA by indirect immunofluorescence (IIF) and the multiplex bead array (MBA) Bioplex 2200 ANA Screen. Differences in prevalence between AA and CAU RA patients was assessed using tests of proportions with chi-square and Fisher's exact tests. Multivariable logistic regression was used to adjust results for age, sex, body mass index (BMI), modified HAQ, RF and anti-CCP positivity.

Results: ANA by IIF was positive (≥ 1:80) significantly more frequently in AA RA patients (187/587 or 32%) compared with CAU RA patients (65/390 or 17%, p<0.001). The pattern of nuclear staining among patients with a positive ANA significantly differed by racial/ethnic group (p<0.001), with AA RA patients having higher frequencies of speckled staining (64% vs. 46%; p=0.01) where as CAU RA patients had higher frequencies of nucleolar staining (10% vs. 3%; p=0.03). Anti-SSA was detected in twice as many AA RA patients (80/587 or 14% vs. 22/390 or 6%, p<0.001). Systemic lupus associated antibodies (anti-Sm, anti-RNP, anti-Sm/RNP, and anti--chromatin) were also higher in this population (see Table 1). Higher prevalence of ANA and anti-SSA remained significant (p<0.001) after adjustment. In the AA RA patients, logistic regression showed only RF was associated with ANA and anti-SSA without previous TNF use or disease duration significant.

Conclusion: We found that the prevalence of ANA, anti-SSA, and other CTD associated autoantibodies is higher in AA RA patients than in a CAU RA cohort. The increase in ANA prevalence is greater than the published difference in ANA by race (15% vs. 3%) and suggests the existence of a meaningful serological subset of AA RA patients beyond the currently recognized serologic subsets identified by RF and anti-CCP antibodies.

Table 1 ANA and Multiplex Bead Array Prevalence in AA and CAU RA Patients

	AA % Positive	CAU % Positive	P-Value
ANA IIF ('1:80)	31.9	16.7	p<0.001
SSA	13.6	5.6	p<0.001
SSB	2.7	1.3	p=0.123
SSA AND/OR SSB	14.1	5.9	p<0.001
DS DNA	3.7	2.7	p=0.237
Sm	1.5	0	p=0.014
Sm/RNP	4.8	0.3	p<0.001
RNP	5.3	2.6	p=0.038
Chromatin	3.1	0.8	p=0.015
Ribosomal P	0.2	0	p>0.99
Centromere B	2.9	0.8	p=0.021
SCL-70	1	0.5	p=0.488
Jo-1	0.2	0.3	p>0.99

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In Early Rheumatoid Arthritis, the Multi-Biomarker Disease Activity Score at Different Time-Points Is Predictive of Subsequent Radiographic Progression. Karen Hambardzumyan[1], R.J. Bolce[2], Saedis Saevarsdottir*[3], Kristina Forslind[4], Ingemar F. Petersson[5], Pierre Geborek[6], Eric H. Sasso[2], David Chernoff[2], Scott Cruickshank[7] and Ronald F. van Vollenhoven[8]. [1]the Karolinska Institute, Stockholm, Sweden, [2]Crescendo Bioscience Inc., South San Francisco, CA, [3]Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [4]Karolinska Institute, Stockholm, Sweden, [5]Lund University, Lund, Sweden, [6]Section of Rheumatology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden, [7]Scott Cruickshank and Associates, Inc., Santa Barbara, CA, [8]Unit for clinical therapy research (ClinTrid), Karolinska Institute, Stockholm, Sweden.

Background/Purpose: The prediction of radiographic progression in early rheumatoid arthritis (eRA) patients is important for optimal treatment. We previously demonstrated that a multi-biomarker disease activity (MBDA) score (Vectra DA®) at baseline (BL) was predictive for radiographic progression over the first year of treatment of eRA patients from the Swedish Farmacotherapy (SWEFOT) trial. The objective of this study was to evaluate the MBDA score, at different time-points and its change during treatment, as a predictor of radiographic progression over the first two years of treatment in eRA patients.

Methods: The analyses were performed on radiographic progression of patients from the SWEFOT trial, assessed by van der Heijde modified Sharp scores (SHS) from BL to years 1 and 2 (n=220) and from Year 1 to Year 2 (n=133); and on the MBDA and disease activity scores (DAS28) and C-reactive protein (CRP) at BL (n=220), Month 3 (n=220) and Year 1 (n=133). Radiographic progression was defined as ΔSHS >5. Mann-Whitney U and Chi-square tests were used for comparisons of disease activity measures between progressors and non-progressors, and for determining significance of proportion of radiographic progressors.

Results: The median values for year 1-progressors (n=41) and non-progressors (n=179) were MBDA score, 70 and 58 (p=0.001); CRP (mg/L) 28 and 18 (p=0.049); and DAS28, 6.1 and 5.7 (p=0.136), respectively. After 3 months of MTX therapy the corresponding values were 48 and 40 (p=0.001), 9 and 9 (p=0.213), and 4.8 and 4.0 (p=0.009), respectively. At BL, 3 months and 1 year, patients with low MBDA score had a lower mean ΔSHS and a smaller proportion of subsequent radiographic progressors than those with low CRP or low DAS28 (table).

The highest risk for progression from BL to year 1 or 2 (25% and 41%, respectively), or from year 1 to year 2 (32%), was observed among patients with high MBDA score at BL which remained high at 3 or 12 months. In contrast, much lower risk of radiographic progression from BL to year 1 and 2 was detected among those patients whose BL high MBDA score dropped to low by month 3 (6% and 18% respectively) and very low risk of radiographic progression from Year 1 to Year 2 was among those patients who achieved low MBDA score by month 12 (4%). All patients with persistent low MBDA score throughout 1 year did not progress radiographically over 2 years. Those who had a moderate MBDA score at BL and achieved low MBDA at months 3 or 12 did not progress either.

Disease activity time-point	Time-period for radiographic progression	Proportion of Radiographic progressors (DSHS>5) MBDA score Low (<30)	Moderate (>29–44)	High (>44)	CRP (mg/L) Low (≤10)	Moderate (>10–30)	High (>30)	DAS28 Low (≤3.2)	Moderate (>3.2–5.1)	High (>5.1)
BL	*From BL to year 2 (n=220)*	0/5 0.0%	5/28 17.9%	60/187 32.1%	13/66 19.7%*	18/72 25.0%*	34/82 41.5%*	NA	18/64 28.1%	47/156 30.1%
Month 3	*From BL to year 1 (n=220)*	1/33 3.0%*	14/91 15.4%*	24/96 25.0%*	23/157 14.6%	5/39 12.8%*	11/24 45.8%	10/78 12.8%	14/87 16.1%	15/55 27.3%
	From BL to year 2 (n=205)	3/33 9.1%*	21/82 25.6%*	37/90 41.1%*	34/147 23.1%*	16/38 42.1%*	11/20 55.0%*	17/72 23.6%	26/82 31.7%	18/51 35.3%
Year 1	*From year 1 to year 2 (n=133)*	2/60 3.3%*	3/36 8.3%*	12/37 32.4%*	10/112 8.9%*	4/14 28.6%*	3/7 42.9%*	4/66 6.1%*	8/54 14.8%*	5/13 38.5%*
		ΔSHS Mean (median)								
BL	*ΔSHS from BL to year 1*	0.8 (0)	1.1 (0)	3.4 (1)	2.1 (0)	2.1 (0)	4.7 (2)	NA	2.4 (1)	3.3 (1)
Month 3	*ΔSHS from BL to year 1*	0.5 (0)	2.3 (1)	4.7 (3)	2.1 (0)	3.9 (3)	7.6 (4.5)	2.1 (0)	2.7 (1)	5.0 (1)
	ΔSHS from BL to year 2	1.5 (0)	3.6 (2)	7.2 (4.5)	3.5 (1)	6.1 (4.5)	12.3 (6)	3.7 (1)	3.9 (2)	8.0 (3)
Year 1	*ΔSHS from year 1 to year 2*	0.6 (0)	1.0 (0)	4.8 (2.5)	1.3 (0)	4.5 (2.5)	8.4 (4)	1.2 (0)	2.3 (0)	6.1 (3)

*Significantly different proportions of progressors (defined by Chi-square test).
NA – not applicable.

Conclusion: MBDA scores at BL and at 3 and 12 months of treatment, as well as change in MBDA category were predictive of subsequent radiographic progression during up to 2 years. At all measured time points, having a low MBDA score was associated with low risk for subsequent radiographic progression.

Disclosure: K. Hambardzumyan, None; **R. J. Bolce**, Crescendo Bioscience, 4, Crescendo Bioscience, 3; **S. Saevarsdottir***, None; **K. Forslind**, None; **I. F. Petersson**, UCB Pharma, Pfizer, AbbVie, 8; **P. Geborek**, None; **E. H. Sasso**, Crescendo Bioscience, 4, Crescendo Bioscience, 3; **D. Chernoff**, Crescendo Bioscience, 4, Crescendo Bioscience, 5; **S. Cruickshank**, Crescendo Bioscience, 5; **R. F. van Vollenhoven**, AbbVie, BMS, GSK, Pfizer, Roche, UCB, 2, AbbVie, Biotest, BMS, Crescendo, GSK, Janssen, Lilly, Merck, Pfizer, Roche, UCB, Vertex, 5.

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Differential Relative Contribution of Individual Components on DAS28 over Time: An Analysis from the Prospective, Observational, Biological Treatment Registry Across Canada. Denis Choquette[1], Dalton Sholter[2], Isabelle Fortin[3], Michael Starr[4], Carter Thorne[5], Milton Baker[6], Regan Arendse[7], Philip Baer[8], Michel Zummer[9], Jude Rodrigues[10], Maqbool Sheriff[11], Emmanouil Rampakakis[12], John S. Sampalis[12], Francois Nantel[13], Allen J Lehman[13], Susan Otawa[13] and May Shawi[13]. [1]Notre Dame Hospital, Montreal, QC, [2]University of Alberta, Edmonton, AB, [3]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, [4]Montreal General Hospital, Montreal, QC, [5]Southlake Regional Health Centre, Newmarket, ON, [6]University of Victoria, Victoria, BC, [7]University of Saskatchewan, Saskatoon, SK, [8]Private Practice, Scarborough, ON, [9]Université de Montréal, Montreal, QC, [10]Clinical Research and Arthritis Centre, Windsor, ON, [11]Nanaimo Regional General Hospital, Nanaimo, BC, [12]JSS Medical Research, Montreal, QC, [13]Janssen Inc., Toronto, ON.

Background/Purpose: DAS28 is an important outcome for clinical research and practice assisting with therapeutic decisions. The main contributors to DAS28 are joint tenderness and acute-phase reactants. A simulation analysis showed that, due to its logarithmic transformation in the DAS28 formula, the ESR contribution is greater in the lower than in the higher DAS28 range. This analysis assessed the relative contribution of individual DAS28 components and examined its clinimetric properties in rheumatoid arthritis (RA) patients treated with infliximab in a Canadian real-world setting.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with infliximab or golimumab as first biologics or after treatment with a biologic for <6 months (M). RA patients treated with infliximab between 2002–2012 and with ≤60M of follow-up were included. The association between treatment duration and parameter improvement was assessed using linear regression. Slope correlation was assessed with the Pearson's correlation coefficient.

Results: 832 patients evaluated over 4,002 visits were included. Longer treatment duration was associated with significant (P<0.001) improvements in DAS28, TJC28, SJC28, PtGA, ESR, and CRP. Correlation analysis of the rate of change over time showed a high correlation (0.7–0.9) of DAS28 with TJC28, SJC28, and PtGA but low correlation with ESR (r=0.418) and CRP (r=0.411).

Overall, the relative contribution of TJC28, SJC28, PtGA, and ESR in DAS28-ESR was 22%, 9%, 12%, and 57%, respectively. For DAS28-CRP, the relative TJC28, SJC28, PtGA, and CRP contributions were 25%, 10%, 12%, and 20%. Over 60M of treatment, the mean relative contribution of TJC28 (M0:31%, M60:17%), SJC28 (M0:15%, M60:5%), and PtGA (M0:15%, M60:9%) significantly (P<0.001) decreased whereas the weight of ESR contribution increased (M0:39%, M60:69%). Similar results were obtained with DAS28-CRP although the CRP contribution was lower compared to ESR.

Increased DAS28-ESR was associated with higher relative contributions (per unit of DAS28-ESR increase) of TJC28 [parameter estimate (B) = 5.3], SJC28 (B=2.1), and PtGA (B=0.7) but lower ESR contribution (B=−8.1). Similarly, increased DAS28-CRP was associated with lower relative CRP contribution (B=−2.0).

Conclusion: This analysis shows that TJC28 and acute-phase reactants have a greater weight than SJC28 and PtGA within DAS28. Furthermore, the relative contribution of acute-phase reactants is greater with lower DAS28, due to their logarithmic nature. These findings suggest that biologic variability and variability in laboratory techniques may have significant impact on classifying remission or DAS28 changes among patients with low DAS28 and on therapeutic plan changes.

Disclosure: D. Choquette, Notre-Dame Hospital, Quebec, Canada, 3, AbbVie, 5, Amgen, 5, Celgene, 5, BMS Canada, 5, Janssen Pharmaceutica Product, L.P., 5, Pfizer Inc, 5; **D. Sholter**, Janssen Inc., 5; **I. Fortin**, Janssen Inc., 5; **M. Starr**, Janssen Inc., 5; **C. Thorne**, Janssen Inc., 5; **M. Baker**, Janssen Inc., 5; **R. Arendse**, Janssen Inc., 5; **P. Baer**, Janssen Inc., 5; **M. Zummer**, Janssen Inc., 5; **J. Rodrigues**, Janssen Inc., 5; **M. Sheriff**, Janssen Inc., 5; **E. Rampakakis**, None; **J. S. Sampalis**, None; **F. Nantel**, Janssen Inc., 3; **A. J. Lehman**, Janssen Inc., 3; **S. Otawa**, Janssen Inc., 3; **M. Shawi**, Janssen Inc., 3.

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Soluble 4-1BB Is a Marker of Joint Involvement and Disease Activity in Rheumatoid Arthritis. Morten Aagaard Nielsen[1], Thomas Andersen[1], Kristian Stengaard-Pedersen[2], Kim Hoerslev-Petersen[3], Merete Lund Hetland[4], Peter Junker[5], Mikkel Ostergaard[6], Malene Hvid[1] and Bent Deleuran[2]. [1]Aarhus University, Aarhus, Denmark, [2]Aarhus University Hospital, Aarhus, Denmark, [3]Research Unit at King Christian X Hospital for Rheumatic Diseases, Graasten, Denmark, [4]DANBIO, Center for Rheumatology and Spine Diseases, Glostrup University Hospital, Glostrup, Denmark, Glostrup, Denmark, [5]University of Southern Denmark, Odense, Denmark, [6]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark.

Background/Purpose: 4-1BB is induced on T cells after antigen encounter and promotes clonal expansion and accumulation of high numbers of antigen-specific effector-type T cells primarily in the joint. This leads to survival of CD4 T cells and CD8 T cells and enhance TCR-dependent activities such as cytokine production. 4-1BB has previously been linked to rheumatoid arthritis (RA). We examined the role of 4-1BB in early treatment naïve RA (eRA, the OPERA cohort) and chronic RA (cRA).

Methods: Soluble 4-1BB was measured by ELISA in plasma from 77 treatment naïve eRA patients (disease < 3 month), at baseline, after 3 months, and after 12 months of treatment in addition to age and gender matched healthy volunteers (HV) (n=54). Treatment was methotrexate + placebo (MTX) (n=41) or MTX + Adalimumab (ADA) (n=36). Clinical disease was assessed by: DAS28, CRP, number of swollen (SJ40) and tender joints (TJ40), IgM-RF and ACPA. In addition s4-1BB was also measured by ELISA in both plasma and synovial fluid (SF) from 8 cRA patients (disease duration > 6 years (24 (7–48) years) with active disease.

Membrane bound 4-1BB was measured on peripheral blood mononuclear cells (PBMC) and synovial fluid mononuclear cells (SFMC) by flow cytometry in cRA, and in PBMC from HV (n=9). Paired samples were compared by Wilcoxon signed rank test, non-paired samples by Mann-Whitney rank sum test. Correlations were tested using Spearman's rho (ρ). Data are expressed as median (IQR).

Results: In eRA plasma levels of s4-1BB were significantly elevated at baseline (9.8 (4.0–23.0) pg/ml) compared with HV (4.0 (4.0–4.9) pg/ml) (P < 0.01). After 12 months treatment 4-1BB levels were similar to levels in HV. No differences were seen in the s4-1BB plasma levels over time between the ADA and MTX group. We observed correlation with baseline s4-1BB with SJ40 (ρ =0.3) and DAS28 at 24 month (ρ =0.3) (both p<0.05)). A significant association with the presence of IgM-RF was observed.

In cRA patients significantly elevated levels were measured in the SF ((102 (44.9 –134.4) pg/ml) compared with plasma ((5.24 (3.91–40.3) pg/ml) (P < 0.01). Further, plasma s4-1BB showed a strong correlation with the corresponding levels in the synovial fluid. (ρ=0.7, p< 0.01).

In cRA the expression of 4-1BB on the total number of T cells was significantly higher in SFMCs (4.12% (2.24–12.52) %) compared with PBMCs (1.55% (0.93–3.57) %) and PBMCs from HV (0.91 (0.53–2.35) %)

(both $p < 0.01$). Further 4-1BB was primarily expressed by CD45RO+ T-cells.

Conclusion: 4-1BB plasma levels were significantly elevated in treatment naïve eRA patients and decreased to levels comparable with HV within 12 months of successful treatment.

The discovery that s4-1BB is association with number of swollen joints and DAS28 as far as 2 years post treatment initiation, and since the s4-1BB in plasma reflects the levels seen in the SF in active cRA, all points to 4-1BB being a potential marker of disease activity. 4-1BB expression is mainly present on activated T cells in the joint of patients with active cRA. This confirms that 4-1BB is present in the inflamed joint in cRA.

Taken together this supports a central role of 4-1BB in the T cell activity in the inflamed joint; the centre of disease development in eRA.

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In Early Rheumatoid Arthritis Patients with Non-Response to Methotrexate Monotherapy the Change in Multi-Biomarker Disease Activity Score Is Differentially Associated with Subsequent Response to Non-Biological Versus Biological Therapy. Karen Hambardzumyan[1], R.J. Bolce[2], Saedis Saevarsdottir[3], Kristina Forslind[4], Ingemar F. Petersson[5], Pierre Geborek[6], Eric H. Sasso[2], David Chernoff[2], Scott Cruickshank[7] and Ronald F. van Vollenhoven[8]. [1]the Karolinska Institute, Stockholm, Sweden, [2]Crescendo Bioscience Inc., South San Francisco, CA, [3]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [4]Karolinska Institute, Stockholm, Sweden, [5]Lund University, Lund, Sweden, [6]Section of Rheumatology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden, [7]Scott Cruickshank and Associates, Inc., Santa Barbara, CA, [8]Unit for clinical therapy research (ClinTrid), Karolinska Institute, Stockholm, Sweden.

Background/Purpose: For patients with early RA (eRA), methotrexate (MTX) is recommended as first-line treatment and in non-responders both the addition of conventional non-biological disease modifying anti-rheumatic drug therapy (triple DMARD therapy) and of biological (anti-TNF) therapy are supported by data. Identification of patients with a higher likelihood of responding to one or the other of these options would lead to more personalized medicine and an increased effectiveness of therapy. The objective of this study was to evaluate the change in the multi-biomarker disease activity (MBDA) score (Vectra DA®) during MTX therapy as a predictor of response to subsequent non-biological triple versus biological therapy.

Methods: Patients with eRA and DAS28 >3.2 entered the Swedish Farmacotherapy (SWEFOT) clinical trial and received MTX monotherapy for 3 months, at which time clinical non-responders (DAS28 >3.2) were randomized to receive non-biological triple DMARD therapy (arm A) or anti-TNF (infliximab) therapy with MTX (arm B). For this study, 129 non-responders at month 3 (n=62 from arm A and n=67 from arm B) were analyzed by MBDA score at baseline (BL) and month 3. The assessment of changes in the MBDA score (ΔMBDA) from BL to month 3 as a predictor for response (according to DAS28 and EULAR response criteria) to triple or anti-TNF therapy at year 1 was done by defining small (≤6), moderate (7–20) and large (>20) decreases by tertiles. Small and moderate decreases were combined together (small/moderate) and compared versus large decreases for arms A and B. The proportion of patients in arm A versus arm B with response at year 1 was evaluated by the odds ratio (OR) for patients with small/moderate versus large decreases. Homogeneity of the odds ratios between the two cohorts was assessed by Breslow-Day test.

Results: The mean (median) decreases in MBDA score from BL to month 3 for year 1 responders (n=66) and non-responders (n=63) were 12.9 (10) and 10.8 (9), respectively (p=0.431), and Month 3 mean (median) MBDA scores were 47.1 (45) and 50.3 (47), respectively (p=0.336). Of patients who had small/moderate decreases in MBDA score during MTX monotherapy, 43% responded to subsequent triple therapy and 57% responded to anti-TNF (OR=0.577). In contrast, among patients with a large decreases in MBDA score from BL to month 3, 67% responded to subsequent triple therapy and 37% to anti-TNF treatment (OR=3.33). Thus the relative treatment effect of arm A versus arm B differed according to the degree of change in the MBDA score from BL to 3 months (p=0.032). Similarly, good EULAR response was achieved by the majority (67%) of patients from arm A, who had large decrease in MBDA score and also the majority (57%) of patients from arm B, who had small/moderate decrease of the MBDA score.

Conclusion: Among patients with early RA who did not achieve low disease activity on MTX monotherapy, those patients with the greatest decrease in MDBA score were more likely to respond to triple therapy whereas patients with lesser decrease of the MBDA score were more likely to respond to anti-TNF therapy. These findings suggest that in MTX non-responders, the changes in MBDA score may help guide subsequent therapy.

Disclosure: K. Hambardzumyan, None; **R. J. Bolce**, Crescendo Bioscience, 4, Crescendo Bioscience, 3; **S. Saevarsdottir**, None; **K. Forslind**, None; **I. F. Petersson**, UCB Pharma, Pfizer, AbbVie, 8; **P. Geborek**, None; **E. H. Sasso**, Crescendo Bioscience, 4, Crescendo Bioscience, 3; **D. Chernoff**, Crescendo Bioscience, 4, Crescendo Bioscience, 5; **S. Cruickshank**, Crescendo Bioscience, 5; **R. F. van Vollenhoven**, AbbVie, BMS, GSK, Pfizer, Roche, UCB, 2, AbbVie, Biotest, BMS, Crescendo, GSK, Janssen, Lilly, Merck, Pfizer, Roche, UCB, Vertex, 5.

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Serum C1M Level Predicts Disease Progression and Early Treatment Efficacy in Rheumatoid Arthritis. Anne C. Bay-jensen[1], Anne Sofie Siebuhr[1], Inger Byrjalsen[2], Claus Christiansen[2] and Morten Asser Karsdal[1]. [1]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [2]Nordic Bioscience, Herlev, Denmark.

Background/Purpose: Rheumatoid arthritis (RA) is partly characterized by joint destruction. Personalized health care is needed in RA to enable i) prediction of those patients that will progress most rapidly and in most need of aggressive intervention, and ii) prediction of those that will respond to a given treatment and those that will not, and thereby limiting the cases of serious side effects. Serum C1M is specific measure of connective tissue degradation, which originates from the down-stream signaling pathways of inflammatory cytokines IL-6, IL-1 and TNFα. The aims of the study were to investigate: i) whether levels of C1M could predict who would structurally progress over 1-year, ii) to which level C1M was suppressed by tocilizumab (TCZ), and iii) whether baseline levels or early changes of C1M could predict responders to TCZ either on disease activity or structural protection.

Methods: The LITHE Biomarker study (NCT00106535) was a 1-year phase III, double-blind, placebo-controlled, parallel group study of TCZ 4mg/kg+MTX (n=200), 8mg/kg+MTX (n=186) or PBO+MTX (n=199) in patients with moderate-severe active RA, but MTX-IR. All patients had radiographically confirmed joint erosion at baseline. Fasting serum was collected at baseline and week 4, 16, 24 and 52 weeks. Patients who failed to respond to treatment (≤ 20% improvement in both swollen and tender joint counts) at week 16 were designated early non-responders. Radiographs (total Genant-modified Sharp scoring system (mTSS) and joint space narrowing (JSN)) and DAS28 were obtained at baseline, week 24 and 52. The study was approved by ethical committees at each participating institution. All patients provided written informed consent. C1M was measured in samples taken at baseline and week 4. Spearman's ranked correlation was done on baseline level and 4-week change of C1M, age, body mass index (BMI), disease duration, DAS28, JSN and mTSS weeks 24 and 52. Multiple regression analysis was performed on log-transformed data for delta structural progression (JSN and mTSS) and C1M, adjusted for age, BMI, disease duration, baseline CRP and radiography.

Results: At baseline, C1M was significantly correlated to DAS28 (ρ=0.25, P<0.0001), mTSS (ρ=0.14, P=0.0006), and JSN (ρ=0.12, P=0.0056). C1M was at correlated to change in JSN and mTSS (p<0.0001). The level of C1M was at the level of the placebo group when treated with 4mg/kg TCZ, whereas the 8mg/kg TCZ suppressed the level by 49.2% lower than at baseline, p<0.0001). The level of C1M remained at a significantly lower level in the 8 mg/kg TCZ + MTX than in PBO group throughout the study (p<0.0001). The difference in C1M between early responders and non-responders when treated with 8 mg/kg were significant (AUC 0.71, p=0.0010). C1M was not correlated to age, BMI or disease duration.

Conclusion: Baseline C1M levels correlated to worsening joint structure over one year, demonstrating this as the first structural progression marker for RA. Early changes in C1M were associated with structural efficacy. These data in combination with other technologies may be a part of the identification of those RA patients that are in most need of aggressive treatment, and the monitoring of these patients.

Disclosure: A. C. Bay-jensen, Nordic Bioscience Holding A/S, 1, Nordic Bioscience Diagnostic, 3; **A. S. Siebuhr**, Nordic Bioscience A/S, 3; **I. Byrjalsen**, Nordic Bioscience Diagnostic, 3; **C. Christiansen**, Nordic Bioscience Diagnostic, 1; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 3.

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Validation of Snapshot, a Rheumatoid Arthritis Assessment Tool, Against CDAI, DAS28 (ESR), and DAS28 (CRP) in Canadian Patients with Rheumatoid Arthritis. William G Bensen[1], Wynn Bensen[2], Melissa Deamude[2], Cynthia Mech[2], Robert Bensen[2], Arthur N. Lau[3] and Alpesh Shah[4]. [1]St Josephs Hospital and McMaster University, Hamilton, ON, [2]Rheumatology Health Team, Dr. Bensen's Rheumatology Clinic, Hamilton, ON, [3]Division of Rheumatology, McMaster University, Hamilton, ON, [4]MSc in Clinical Epidemiology, University of Western Ontario, London, ON.

Background/Purpose: Measuring disease activity in Rheumatoid Arthritis (RA) remains an elusive goal. Both DAS and CDAI have an inherent weakness because similar numbers can result from dissimilar clinical situations. Snapshot, a hands on immediate clinical tool, shows where a patient stands with SJC, TJC, MD and Patient Global, and visualizes the discrepancies between MD and patient assessments. We have validated Snapshot Traditional (SS-T) (SJC-PtGlobal), Snapshot MD (SS-M) (SJC-MD global) and Snapshot Patient (SS-P) (TJC-Pt. global) to DAS28 (ESR), DAS28 (CRP) and CDAI. in 96 Canadian RA patients, at onset, and disease control.

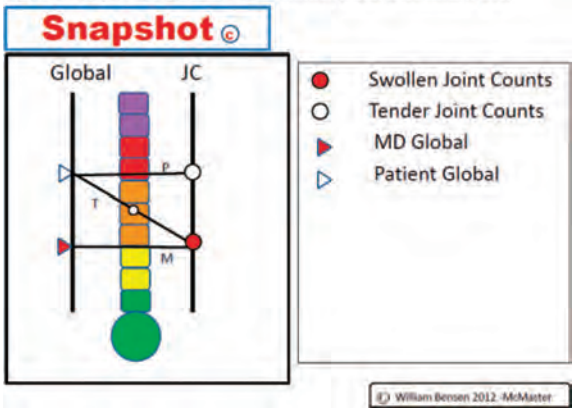
Methods: We validated Snapshot (SS-T, SS-M and SS-P) in data from 96 patients of active RA using SAS version 9.3. The Snapshot scores were validated against DAS28 (ESR), DAS28 (CRP) and CDAI scores. We used Pearson correlation coefficients to assess the correlation (r) and ordinary linear regression analysis to estimate regression coefficients (β) between Snapshot and other measures (DAS28 and CDAI). We also assessed the extent of agreement between Snapshot and other measures DAS28 using Bland-Altman plots.

Results: The results revealed direct significant linear correlation of Snapshot with DAS28 and CDAI (r=0.83 with DAS28 (ESR), 0.92 with DAS28 (CRP), 0.94 with CDAI for SS-T, r=0.82 with DAS28 (ESR), 0.91 with DAS28 (CRP), 0.91 with CDAI for SS-P and r=0.70 with DAS28 (ESR), 0.79 with DAS28 (CRP), 0.89 with CDAI for SS-M). In a linear regression model with DAS28 (ESR) as a predictor, regression coefficients (β) were 1.33 (p<0.001), 0.98 (p<0.001) and 1.27 (p<0.001) for SS-T, SS-M and SS-P respectively with good model fit. Bland-Altman plots showed high degree of agreement between Snapshot and DAS28 (ESR) with 96.7% (SS-T), 96% (SS-M) and 95.6% (SS-P) of the observations of the difference between Snapshot and DAS28 lying between mean±2SD. Similar results were observed for change score data (for disease control).

	SS change score (Pt. Global and SJC)		SS change score (MD Global and SJC)		SS change score (Pt. Global and TJC)	
	Pearson's correlation (P-value)	Regression coefficient (95% confidence interval)	Pearson's correlation (P-value)	Regression coefficient (95% confidence interval)	Pearson's correlation (P-value)	Regression coefficient (95% confidence interval)
DAS28 (ESR) change score	0.839 (<0.0001)	1.47 (1.26, 1.68)	0.751 (<0.0001)	1.15 (0.93, 1.37)	0.824 (<0.0001)	1.32 (1.12, 1.52)
DAS28 (CRP) change score	0.896 (<0.0001)	1.68 (1.49, 1.86)	0.813 (<0.0001)	1.33 (1.12, 1.53)	0.885 (<0.0001)	1.51 (1.34, 1.69)
CDAI change score	0.915 (<0.0001)	0.16 (0.14, 0.17)	0.921 (<0.0001)	0.14 (0.13, 0.15)	0.911 (<0.0001)	0.15 (0.13, 0.16)

Conclusion: All Snapshots (SS-T, SS-M, SS-P) validated well with DAS28 and CDAI in measuring RA disease activity with the benefit of one second visual recognition for patient and MD at the clinical visit and without calculation. The discrepancy between MD and patient values is obvious and prompts an alternative therapeutic decision. Some patients understate their disease as compared to their SJC and need more RA therapy, while others overstate because of soft tissue pain, or depression. We prefer Snapshot Traditional. Snapshot offers an immediate and validated clinical tool for doctors and patients allowing better understanding of disease activity and need for therapeutic intervention.

Figure 1: Snapshot, A Rheumatoid Arthritis Clinical Assessment Tool.



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Double Positivity of RA Serologies More Prevalent Yet Associated with Clinical Response in Ethnic Minority Patients with Rheumatoid Arthritis. Mercedes Quinones[1], Sharon Dowell[2], Ignacio Garcia-Valladares[3], Gail S. Kerr[4], Christopher Swearingen[5], Luis R. Espinoza[6], Yusuf Yazici[7], Edward L. Treadwell[8], Theresa Lawrence Ford[9], Yvonne Sherrer[10], Angelia Mosley-WIlliams[11], Rodolfo Perez Alamino[12], Chunqiao Luo[13], Akgun Ince[14], Adrian Godoy[2] and John Amatruda[2]. [1]Howard University Hospital, Washington, DC, [2]Howard University, Washington, DC, [3]Hospital General de Occidente, Zapopan, Jal., Mexico, [4]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [5]University of Arkansas, Little Rock, AR, [6]LSU Medical Center, New Orleans, LA, [7]New York University School of Medicine, New York, NY, [8]East Carolina University, Greenville, NC, [9]North Georgia Rheumatology Group, PC, Lawrenceville, GA, [10]Centre Rheum Immunol Arthritis, Fort Lauderdale, FL, [11]Detroit VAMC, Detroit, MI, [12]LSUHSC, New Orleans, LA, [13]University of Arkansas for Medical Sciences, Little Rock, AR, [14]St. Louis University, St. Louis, MO.

Double Positivity of RA Serologies More Prevalent But Associated with Clinical Response in a Diverse Ethnic Cohort with Rheumatoid Arthritis

Background/Purpose: The presence of both the anti-citrullinated peptide antibody (ACPA) and a rheumatoid factor (RF) are associated with RA disease severity and portend a poor prognosis. Whether ethnic minorities differ in the prevalence of RA-related serologies from Caucasian RA counterparts is unknown, as is their role as determinants of a clinical response in this patient subset.

Methods: Ethnic Minority RA Consortium (EMRAC) patients with at least one follow up visit were evaluated. Comparisons of demographic (age, gender, race, education, smoking), RA disease status (RF, ACPA, nodules/erosions), RA treatment (prednisone, DMARD, biologics) variables amongst ethnic subsets were made as well as frequencies of clinical response (D MDHAQ – 0.3 and D RAPID3 –3.6) from baseline. Baseline differences between ethnic subsets were compared using Chi-square for categorical and Kruskal-Wallis for continuous variables. Logistic regression associating outcome at follow up and between ethnic subsets were estimated, adjusting for age, smoking, race, education, baseline RAPID3, and double positivity of RA-related serologies.

Results: Follow up visits in 671 EMRAC patients provided data for analyses (Table). African American patients were older (p=0.02), and had longer follow up compared to either Caucasians or Hispanics (p< 0.001). Either a positive ACPA (60%, 46.3% vs 14.3%, respectively, p<0.001) or RF (79.6%, 71.7%, respectively vs 42.1%, p<0.001) were more frequent in AA and Hispanics versus Caucasian patients. In patients who were double positive, the odds ratio for a clinical response was 2.7 (95% CI 1.37, 5.35) for MDHAQ and 3 fold (95% CI 1.37, 6.76) for RAPID3. There was a greater frequency of both ACPA+/RF+ in ethnic subsets who had a clinical response in both MDHAQ (AA 57.9%, Hispanics 46.9% vs Caucasian 16.7%) and RAPID3 (AA 64.9%, Hispanic 55% vs Caucasian 17.9%). Hispanic patients with RF+/CCP+ had a 67% increased odds of a RAPID response compared to Caucasians and 8% to AA, while AA had a 55% increase in odds for clinical response compared to Caucasians – but none achieving statistical significance.

Conclusion: In a diverse cohort, double positivity of RA-related serologies while more prevalent, are associated with increased odds of a clinical response regardless of ethnicity.

RAPID3 Outcomes by Race and Double Positive RA Serology Status

	Caucasian	African-American	Hispanic
		HAQ Response	
RF-ACPA-	40 (66.7%)	15 (15.8%)	11 (34.4%)
RF+ACPA-	10 (16.7%)	20 (21.1%)	5 (15.6%)
RF-ACPA+	0 (0%)	5 (5.3%)	1 (3.1%)
RF+ACPA+	10 (16.7%)	55 (57.9%)	15 (46.9%)
		RAPID Response	
RF-ACPA-	27 (69.2%)	11 (19.3%)	6 (30%)
RF+ACPA-	4 (10.3%)	6 (10.5%)	3 (15%)
RF-ACPA+	1 (2.6%)	3 (5.3%)	0 (0%)
RF+ACPA+	7 (17.9%)	37 (64.9%)	11 (55%)

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The Impact of Missing Anti-Citrullinated Protein Antibody (ACPA) on Outcomes in Early Rheumatoid Arthritis: From the Canadian Early Arthritis Cohort. Jenny Shu[1], Vivian P. Bykerk[2], Gilles Boire[3], Carol A. Hitchon[4], J. Carter Thorne[5], Diane Tin[5], Edward C. Keystone[6], Boulos Haraoui[7] and Janet E. Pope[8]. [1]University of Western Ontario, London, ON, [2]Hospital for Special Surgery, New York, NY, [3]CHUS - Sherbrooke University, Sherbrooke, QC, [4]University of Manitoba, Winnipeg, MB, [5]Southlake Regional Health Centre, Newmarket, ON, [6]University of Toronto, Toronto, ON, [7]Institut de rhumatologie de Montréal (IRM), Montréal, QC, [8]St Joseph Health Care, London, ON.

Background/Purpose: The impact of missing ACPA in early inflammatory arthritis patients was studied to determine if failure to perform ACPA testing could cause a care gap.

Methods: 2191 patients recruited to CATCH were allocated to 3 groups: 1. seropositive (rheumatoid factor positive (RF+) and/or ACPA+), 2. seronegative (RF- /ACPA-) and 3. missing ACPA (RF negative [RF-]). Analyses were adjusted for age, sex, symptom duration, and smoking status if $p<0.1$. Data were also imputed to determine effect on results. One-third of ACPA were missing as this test is not reimbursed in all jurisdictions.

Results: More seropositive patients fulfilled 2010 ACR/EULAR RA criteria. Group 3 was slightly older, less: % female, symptom duration, and smoking. At 3 months, group 3 was treated with less DMARDs and methotrexate ($P<0.00002$), but there were no significant differences in DAS28, HAQ-DI, proportion receiving corticosteroids, or physician/patient global assessments. See table for full results.

Conclusion: Patients with missing ACPAs were less likely to fulfill RA criteria and were treated differently with fewer medications but had similar outcomes at three months. Cost-effectiveness of ensuring ACPA testing availability in suspected RA is unknown. Imputed data did not alter results. There could be a care gap in the unknown ACPA group who were RF negative, but there were no significant differences in DAS28, 3 month change in DAS28, or HAQ-DI despite less treatment. We cannot determine whether performing ACPA in RF positive suspected ERA adds value as we combined the seropositive group into any seropositive result. The cost effectiveness of performing ACPA in RF negative patients could be debated if early RA is already suspected.

	Total	Seropositive	Seronegative	Missing anti-CCP, RF neg	p-value
Number of Patients (%)	2191	1276 (58.2)	497 (22.7)	225 (10.3)	N/A
Baseline 3 months	1743	1062 (60.9)	359 (20.6)	171 (9.8)	
Age, mean ± SEM	53.04± 0.34	51.63 ± 0.44	54.04 ± 0.67	55.58 ± 0.80	0.000009*
Rheumatoid factor serology at baseline, no. (%)		1110 (50.7)	813 (37.1)	268 (12.2)	N/A
Anti-CCP serology at baseline, no. (%)		736 (33.6)	724 (33.0)	731 (33.4)	N/A
Female, no. (%)	1445 (72.6)	958 (75.5)	336 (67.6)	151 (67.4)	0.0007*
Symptom duration at baseline, mean ± SEM (months)	6.04 ± 0.08	6.24 ± 0.11	5.89 ± 0.18	5.26 ±0.21	0.0008*
Swollen joint count (ACR 28), mean ± SEM	7.23 ± 0.14	7.05 ± 0.17	7.44 ± 0.30	7.74 ± 0.38	0.19
Baseline 3 months	3.46 ±0.11	3.44 ± 0.14	3.51 ± 0.21	3.42 ± 0.25	0.95
DAS28, mean ± SEM	4.89 ± 0.04	4.92 ± 0.05	4.81 ±0.07	4.90 ± 0.10	0.45
Baseline 3 months	3.55 ± 0.04	3.51 ± 0.05	3.60 ± 0.09	3.70 ± 0.13	0.33
Change in DAS28 over 3 months, mean ± SEM	-1.35 ± 0.05	-1.38± 0.05	-1.21 ± 0.10	-1.41 ± 0.15	0.29
Proportion in DAS28 remission at 3 months, no. (%)	343 (28.2)	248 (29.8)	62 (24.3)	33 (25.2)	0.17
HAQ-DI	1.00 ± 0.02	1.01 ± 0.02	0.98 ± 0.03	0.97 ± 0.05	0.57
Baseline 3 months	0.63 ± 0.16	0.61 ± 0.02	0.69 ± 0.04	0.67 ± 0.05	0.12
Meets 2010 ACR/ EULAR RA Classification Criteria no. (%)	1569 (78.8)	1138 (89.7)	293 (59.0)	138 (61.6)	0.000001*
On Methotrexate, no. (%)	1296 (64.9)	889 (69.7)	283 (56.9)	124 (55.1)	0.000001*
Baseline 3 months	1194 (75.0)	830 (78.2)	250 (69.6)	114 (66.7)	0.0002*
Number of DMARDs, mean ± SEM	1.31± 0.02	1.41 ± 0.02	1.17 ± 0.04	1.05 ± 0.05	0.000001*
Baseline 3 months	1.60 ± 0.02	1.67 ± 0.03	1.51 ± 0.05	1.36 ± 0.06	0.00002*
On cortico-steroid, no. (%)	966 (48.3)	614 (48.1)	234 (47.1)	118 (52.4)	0.40
Baseline 3 months	559 (35.1)	370 (34.8)	133 (37.0)	56 (32.7)	0.59

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Diagnostic Accuracy and Associated Costs of Rheumatoid Factor Testing in Primary Care: A Population-Based Cohort Study in Spain. Raashid Luqmani[1], Klara Morsley[2], Anne Miller[3], Christopher J. Edwards[4], M. Kassim Javaid[5], Daniel Prieto-Alhambra[6], Rafael Pinedo-Villanueva[7], Manuel Medina Peralta[8], Sebastian Calero Munoz[8], Nigel Arden[9], Francesc Fina-Aviles[8] and Cyrus Cooper[10]. [1]Oxford NIHR Musculoskeletal Biomedical Research Unit, Oxford, United Kingdom, [2]Nuffield Orthopaedic Centre, Oxford, United Kingdom, [3]Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust, Oxford, United Kingdom, [4]University Hospital Southampton, Southampton, United Kingdom, [5]Oxford NIHR Musculoskeletal Biomedical Research Unit, University of Oxford, Oxford, UK, Oxford, United Kingdom, [6]NIHR Musculoskeletal Biomedical Research Unit, Oxford, United Kingdom, [7]MRC Lifecourse Epidemiology Unit, Southampton, United Kingdom, [8]Institut Català de la Salut, Barcelona, Spain, [9]NIHR Musculoskeletal Biomedical Research Unit University of Oxford, Oxford, United Kingdom, [10]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom.

Background/Purpose: To assess the sensitivity, specificity, and predictive values of rheumatoid factor (RF) as a test for rheumatoid arthritis (RA) in primary care, and to estimate the costs associated with the use of RF in primary care settings.

Methods: Design: a retrospective cohort study using electronic data from the Information System for the Development of Research in Primary Care (SIDIAP database), which contains the complete primary care records and laboratory results of more than 5 million people (over 80% of the population) in Catalonia, Spain.

Setting: primary care.

Participants: patients aged 18 or above registered in the SIDIAP database with at least one RF test performed between 01/01/2006 and 31/12/2011, excluding those who had a diagnosis of RA at the start of the study period.

Outcome measures: RA diagnosis (as coded in medical records) within the first year after RF testing, and cost of RF testing per case of RA.

Results: 495,434 patients out of an eligible 4,796,498 (10.3%) people were tested for RF at least once during the study period. 107,362 (21.7%) were sero-positive of which 2,768 (2.6%) of these were diagnosed with RA in the following year. Similarly, 1,141/388,072 (0.3%) sero-negative participants were subsequently diagnosed with RA. RF testing had a sensitivity of 70.8% (95% CI 69.4 to 72.2), specificity 78.7% (78.6 to 78.8), and positive and negative predictive values of 2.6% (2.5 to 2.7) and 99.7% (99.6 to 99.7) respectively. An estimated €3,963,472 was spent on RF testing in the duration of the study, with a cost of €1,432 per true positive case.

Conclusion: The low prevalence of RA in this primary care population resulted in a very high cost of testing for every case of RA diagnosed. Limiting RF testing to patients with a higher pre-test probability would significantly reduce the overall cost of testing.

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Biomarkers of Cardiac Dysfunction and Inflammation in Plasma Predict Occult Coronary Plaque Burden and Composition in Rheumatoid Arthritis. George A. Karpouzas[1], Joel Estis[2], John Todd[2] and Matthew Budoff[1]. [1]Harbor-UCLA Medical Center, Torrance, CA, [2]Singulex, Alameda, California, Alameda, CA.

Background/Purpose: Rheumatoid arthritis (RA) is associated with accelerated coronary atherogenesis, myocardial infarction, and mortality. We previously reported a higher prevalence, severity, and different composition of occult coronary plaque in patients with RA compared to age and gender matched non-rheumatic disease controls (NRD). We now explore whether various plasma inflammatory biomarkers, or their combinations, predict occult coronary plaque presence, various burden outcomes, and composition in the same cohort of patients with RA.

Methods: One hundred and fifty RA subjects without symptoms or prior diagnosis of cardiovascular disease underwent 64-slice computed tomography angiography (CTA). Coronary artery calcium score (CAC), segment involvement score (SIS- n of segments with plaque), stenosis severity score (sum of individual segmental stenosis- SSS) and plaque burden score (sum of segmental plaque burden- PBS) were computed. Plaques were further characterized as non-calcified (NCP), mixed (MP), or calcified (CP). High-sensitivity cardiac Troponin-I (cTnI), tumor necrosis factor-alpha (TNFα), vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), interleukin-17A and F (IL-17A, IL-17F), were quantified at the time of CTA, using Erenna immunoassay (Singulex, Alameda, CA). Associations of individual biomarkers with all plaque outcomes were evaluated with linear regression models. Ability of individual or combinations of binarized biomarkers to predict plaque outcomes was explored in logistic regression models adjusted for age and gender (model 1), or additional cardiac risk factors (CRFs, model 2).

Results: Higher tertiles of cTnI correlated with plaque prevalence, as well as increasing CAC, SIS, SSS, and PBS (p-values 0.006, 0.005, 0.01, and 0.009 respectively- not shown). IL-6 and cTnI individually and independently predicted various plaque parameters after age and gender adjustments (model 1, table 1). The combination of high cTnI with high IL-6 predicted plaque burden after adjustments both for age and gender, as well as additional CRFs (model 2- table 1). Very high-risk plaque outcomes for future cardiac events (CAC >100, SIS >5, SSS >5, obstructive plaque, or composite outcome) were best predicted by cTnI alone. Similarly, cTnI was the only biomarker predicting presence of higher-risk NCP or MP [OR (95% CI) of 2.37 (1.13–4.94)], however, significance was lost after age and gender adjustments [1.97 (0.92–4.24)].

Conclusion: In patients with RA, biomarkers of cardiac dysfunction (cTnI) and inflammation (IL-6) may predict the presence, various burden outcome severity, and composition of occult coronary plaque as evaluated by CTA. Their associations and prognostic implications for atherosclerosis deserve further evaluation.

Table 1

	outcome	Unadjusted OR (95% CI)	Model 1[1] OR (95% CI)	Model 2[2] OR (95% CI)
c-TnI	CAC (>0 vs. 0)	*2.5 (1.2–5.2)*	1.8 (0.8–4.0)	1.7 (0.8–4)
	CAC>100 vs.≤100	*7.1 (2.5–20.7)*	*6 (1.9–19)*	*10.4 (2.4–45.5)*
	SIS (>0 vs. 0)	*2.8 (1.2–6.2)*	2.0 (0.8–4.8)	2.3 (0.8–6.9)
	SIS>5 vs. SIS≤5	*4 (1.2–13.6)*	2.5 (0.7–9.4)	3.6 (0.9–14.7)
	SSS (>0 vs. 0)	*2.8 (1.2–6.2)*	2.0 (0.8–4.8)	2.3 (0.8–6.9)
	SSS>5 vs. SSS≤5	*2.9 (1.1–7.7)*	2.2 (0.8–6.3)	2.6 (0.9–8)
	PBS (>2 vs. ≤2)	*3.6 (1.7–7.4)*	*2.9 (1.3–6.5)*	*3.2 (1.4–7.5)*
	Obstructive plaque	*3.9 (1.2–12.5)*	3.1 (0.9–10.7)	3.6 (0.9–13.9)
	Composite outcome*	*3.2 (1.2–8.3)*	2.4 (0.9–6.8)	2.8 (0.9–8.2)
IL-6	CAC (>0 vs. 0)	1.6 (0.8–3.2)	2.0 (0.9–4.4)	1.6 (0.7–3.7)
	SIS (>0 vs. 0)	2.1 (0.9–4.9)	*3.0 (1.1–7.8)*	2.0 (0.8–5.0)
	SSS (>0 vs. 0)	2.1 (0.9–4.9)	*3.0 (1.1–7.8)*	2.0 (0.8–5.0)
	PBS (>2 vs. ≤2)	*2.1 (1.0–4.2)*	*2.8 (1.2–6.2)*	2.0 (0.8–4.7)
c-TnI+IL-6	CAC (>0 vs. 0)	*2.7 (1.1–7.0)*	2.1 (0.7–5.9)	1.9 (0.6–5.5)
	SIS (>0 vs. 0)	*2.7 (1.1–6.3)*	2.1 (0.9–5.3)	1.7 (0.7–4.6)
	SSS (>0 vs. 0)	*2.7 (1.1–6.3)*	2.1 (0.9–5.3)	1.7 (0.7–4.6)
	PBS (>2 vs. ≤2)	*5.1 (1.9–13.8)*	*4.4 (1.5–12.7)*	*3.9 (1.3–11.6)*

1. adjusted for age, gender, cTnI, IL-6
2. Adjusted for age, gender, hypertension, diabetes, dyslipidemia, smoking, body mass index, prednisone use, cTnI, IL-6
* composite outcome: SIS>5, or SSS>5, or obstructive plaque

Disclosure: G. A. Karpouzas, None; **J. Estis**, Singulex, 3, Singulex, 1; **J. Todd**, Singulex, 1, Singulex, 3; **M. Budoff**, None.

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IL-33 and Soluble ST2 Levels As Novel Predictors for Remission and Progression of Carotid Plaque in Early Rheumatoid Arthritis: A Prospective Study. Jiayun Shen[1], Qing Shang[1], Ying Ying Leung[2], Shui Lian Yu[1], Chun-Kwok Wong[3], Edmund Li[1], Tracy Y. Zhu[1] and Lai-Shan Tam[1]. [1]Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Hong Kong, Hong Kong, [2]Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, Singapore, [3]Department of Chemical Pathology, The Chinese University of Hong Kong, Hong Kong, Hong Kong.

Background/Purpose: Clinical remission is achievable for patients with early rheumatoid arthritis (ERA). Identification of predictors for response of treatment may provide risk estimation and help for the development of personalized medicine. On the other hand, patients with ERA die prematurely primarily because of cardiovascular disease. The aim of this study is to study the association between the baseline IL-33 and soluble ST2 (sST2) levels with disease remission and progression of carotid atherosclerosis in ERA patients.

Methods: Ninety-eight ERA patients were enrolled. Disease activity and the presence of carotid plaque were evaluated at baseline and 12 months later. Plasma IL-33 and sST2 levels were determined using enzyme-linked immunosorbent assay kits.

Results: Baseline IL-33 and sST2 levels were associated with inflammatory markers and cardiovascular (CV) risk factors. 44(45%), 18(18%) and 21(21%) patients achieved remission based on 28-joint disease activity score (DAS28), Boolean and simplified disease activity score (SDAI) criteria at 12 months. Patients with detectable IL-33 at baseline were less likely to achieve DAS28 (P=0.010) and SDAI remission (P=0.021), while a lower baseline sST2 level was able to predict DAS28, Boolean and SDAI remission (P=0.005, 0.001 and <0.001, respectively). By multivariate analysis, a lower baseline sST2 level independently predict Boolean (OR: 0.789, P=0.005) and SDAI remission (0.812, P=0.008). Regarding carotid atherosclerosis, 9/98(9.2%) patients with plaque progression were observed. Baseline IL-33 was detectable in 8/9(89%) and 42/83(51%) of patients with and without plaque progression (P=0.029). Baseline detectable IL-33 was an independent predictor for plaque progression after adjusting for traditional CV risk factors (27.523, P=0.017).

Conclusion: Lower baseline sST2 levels independently predict disease remission and baseline detectable IL-33 independently predicts carotid plaque progression in ERA patients. This study suggests that inflammation induced by the IL-33/ST2 axis may play a significant role in the development of cardiovascular disease in RA.

Table 1. Multivariable analysis for remission of disease and progression of carotid plaques

Events at month 12	Factors*	OR	95% CI	*P* value
DAS28 remission	Disease duration	2.371	1.050−5.353	0.038
(Event**: n=42, 47%)	ESR	0.970	0.953−0.988	0.001
	Prednisolone use during study	0.202	0.055−0.751	0.017
Boolean remission	sST2	0.789	0.669−0.932	0.005
(Event**: n=17, 18%)				
SDAI remission	Pain	0.766	0.606−0.969	0.026
(Event**: n=19, 21%)	sST2	0.812	0.696−0.948	0.008
Plaque progression	Age	1.217	1.063−1.393	0.004
(Event**: n=9, 11%)	Detectable IL-33	27.523	1.805−419.6	0.017

* Variables were determined at baseline except where specifically indicated.
** Number/percentage of event in the multivariate analysis after cases with unavailable data excluded, may be different from total number/percentage in the text.

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Evaluation of RAPID3 with Minimal Joint Count and ACR/EULAR Provisional Remission Definitions As Predictors of Future Good Radiographic + Functional Outcome in a Double-Blind, Phase 3, Randomized Controlled Trial of Tocilizumab. Martin J. Bergman[1], Jeffrey Yourish[2], Jinglan Pei[2], Jenny Devenport[2], William Reiss[2] and Edward Keystone[3]. [1]Taylor Hospital, Ridley Park, PA, [2]Genentech, South San Francisco, CA, [3]University of Toronto and Mount Sinai Hospital, Toronto, ON.

Background/Purpose: Based on treat-to-target guidelines, the goal of treatment should be remission. Definitions for remission recommended by the ACR/EULAR task force include joint counts and a laboratory test and were selected to predict later good radiographic and functional outcomes. [1] Despite these guidelines, rheumatologists still do not regularly measure disease activity. RAPID3, developed as a tool for monitoring disease activity, is advantageous because it requires only patient input. This analysis evaluated the performance of RAPID3 with minimal joint count (for physician input), compared with ACR/EULAR proposed remission definitions, to predict future good radiographic + functional outcome.

Methods: LITHE was a 5-year, double-blind, phase 3 study of tocilizumab (TCZ) in patients with moderate to severe RA who had inadequate responses to MTX therapy. [2] Patients were randomly assigned 1:1:1 to receive placebo + MTX, TCZ 4 mg/kg + MTX, or TCZ 8 mg/kg + MTX for 24 weeks, with an option to escape starting at week 16. Associations between various year 1 measures were evaluated against rates of good radiographic + functional outcome at year 2, specifically no worsening of Genant-Sharp Score (GSS) and HAQ-DI, and HAQ-DI $\leq$0.5. [1] Logistic regression was used to estimate odds ratio (OR), positive predictive value (PPV), negative predictive value (NPV), and sensitivity/specificity of the measures.

Results: In total, 690 patients had sufficient 2-year data to evaluate year 2 outcome: 73% of patients had no worsening of GSS score, 58% had no worsening of HAQ-DI, 22% had HAQ-DI $\leq$0.5, and 15% met all 3 criteria. ORs with 95% confidence intervals (CIs) for all year 1 measures were >1, indicating that all were statistically significantly associated with year 2 outcome, though no one measure had superior association ($p < 0.05$ for all; overlapping 95% CIs for OR). NPV and specificity were high (>80%), but PPV and sensitivity for all measures were low (range, 28–49% and 16–39%, respectively), which meant the measures could successfully identify patients who did not achieve the year 2 outcome but were not very good at identifying patients who achieved the outcome (Table).

Conclusion: Consistent with publications on other therapies/populations,[3–5] these results suggest the RAPID3 plus $\leq$1 joint count performed similarly to more complex measures. However, given that no single measure had especially high PPV or sensitivity, it is important that the patient be fully evaluated to understand what individual factors might contribute to his or her long-term prognosis.

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Table. Performance of Year 1 Measures for Predicting Year 2 Outcome of Good Radiographic + Functional Outcome[a]

Year 1 Measure	Odds Ratio	95% CI	n[b]	PPV, %	NPV, %	Sensitivity, %	Specificity, %
RAPID3 $\leq$6 with SJC66 $\leq$1	3.461	2.098, 5.692	683	28.8	87.5	34.0	84.6
RAPID3 $\leq$3 with SJC66 $\leq$1	3.973	2.182, 7.148	683	35.3	86.7	22.6	92.4
RAPID3 $\leq$6 with SJC28 $\leq$1	3.149	1.951; 5.068	681	28.5	87.9	38.7	82.1
RAPID3 $\leq$3 with SJC28 $\leq$1	4.257	2.403; 7.486	681	36.8	87.1	26.4	91.7
SDAI $\leq$3.3 only	3.956	2.230; 6.969	623	37.3	86.0	26.7	90.9
ACR/EULAR Boolean criteria only	5.246	2.539; 10.792	687	47.4	86.4	17.0	96.6
SDAI $\leq$3.3 or Boolean criteria	3.932	2.240; 6.861	624	37.2	86.1	27.6	90.6
SDAI $\leq$3.3 and Boolean criteria	5.422	2.555; 11.473	686	48.6	86.3	16.0	96.9

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count; VAS, Visual Analogue Scale.
Boolean criteria are SJC $\leq$1, TJC $\leq$1, CRP $\leq$1 mg/dL, and patient global assessment (0–10 VAS scale) $\leq$1.
Each odds ratio is estimated from a separate logistic regression for predicting year 2 outcome, all with these covariates: age, treatment at baseline, and region.
Sensitivity and specificity are based on basic 2 $\times$ 2 tables of measure vs outcome.
[a]Year 2 outcome (good radiographic + functional outcome): no worsening of Genant-Sharp Score and HAQ-DI at year 2 vs year 1, and HAQ-DI $\leq$0.5 during year 2.
[b]Patients who had sufficient data to evaluate the year 2 outcome (n = 690) plus each year 1 measure are shown; patients failing 1 of the criteria were included even if other criteria were missing, whereas patients achieving each measure/outcome had all criteria observed.

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Using the Multi-Biomarker Disease Activity Score As a Complementary Inclusion Criterion for Clinical Trials in Rheumatoid Arthritis May Enhance Recruitment. Ronald F. van Vollenhoven[1], Rebecca J. Bolce[2], Karen Hambardzumyan[3], Saedis Saevarsdottir[4], Kristina Forslind[4], Ingemar Petersson[5], Eric H. Sasso[2], CC Hwang[2], Oscar Segurado[2] and Pierre Geborek[6]. [1]Unit for clinical therapy research (ClinTrid), Karolinska Institute, Stockholm, Sweden, [2]Crescendo Bioscience Inc., South San Francisco, CA, [3]the Karolinska Institute, Stockholm, Sweden, [4]Karolinska Institute, Stockholm, Sweden, [5]Lund University, Department of Orthopedics, Clinical Sciences Lund, Lund, Sweden, [6]Section of Rheumatology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden.

Background/Purpose: Clinical trials in rheumatoid arthritis (RA) often require elevated C-reactive protein (CRP) as an inclusion criterion, which may limit recruitment by excluding some patients with active disease. The multi-biomarker disease activity (MBDA) score (Vectra® DA) quantifies disease activity with a score of 1 to 100 and can be high (>44) when CRP is low, e.g., $\leq$1 mg/dL. This study explored the hypothesis that, by using MBDA score >44 as a clinical trial inclusion criterion complementary to CRP >1 mg/dL, the number of eligible patients can be increased while maintaining ability to detect treatment responses and radiographic progression.

Methods: The Swedish Farmacotherapy (SWEFOT) trial, disease modifying anti-rheumatic drugs (DMARD)-naïve patients with early RA were enrolled without a CRP requirement, and received methotrexate (MTX) monotherapy from baseline (BL); at 3 months, non-responders to MTX (NR, DAS28 >3.2) received treatment intensification with triple therapy or MTX plus infliximab. For the present study, we analyzed two populations from SWEFOT: 1) DMARD-naïve patients, based on enrollment at BL, and 2) MTX non-responders, based on the Month 3 assessment. In both analyses, patients were grouped according to CRP ($\leq$1 vs. >1 mg/dL) and MBDA score ($\leq$44 vs. >44) at the defining time point, and clinical outcomes were assessed from BL to 3 months for DMARD-naïve patients treated with MTX; and from 3 to 12 months for MTX NRs receiving triple therapy or anti-TNF. Radiographic progression was assessed by change (Δ) in Sharp van der Heijde score (SHS) from BL to 1 year for both analyses.

Results: In the DMARD-naïve population (N=220), BL values, changes in clinical disease activity from BL to Month 3, and ΔSHS from BL to year 1 were similar for patients with MBDA score >44 and CRP $\leq$1 mg/dL (n=37) vs. patients with CRP >1 mg/dL (n=154). If the two groups are combined, the resulting group (n=191) has 24% more patients and similar clinical and radiographic outcomes, compared with the CRP >1 mg/dL group. For the MTX NRs (N=127), values at Month 3 and their changes to Month 12 were also similar for patients with MBDA score >44 and CRP $\leq$1mg/dL (n=23) vs. those with CRP >1 mg/dL (n=49). Combining these two groups results in a group with 47% more patients (n=72) and similar outcomes, compared with the CRP >1 mg/dL group. (See table) In comparison, for patients with MBDA score $\leq$44 and CRP $\leq$1 mg/dL, there is less change in clinical disease activity at Month 12 for the MTX NRs, and less

radiographic progression at Month 12 for the DMARD-naïve and MTX NR groups.

Table: Mean changes in disease activity measures from BL to 3 months for DMARD-naïve patients and from Month 3 to 12 months for MTX non-responders

	DMARD-Naïve Patients			
			Conventional approach	New approach
Response Measurement	CRP ≤1 mg/dL and MBDA ≤ 44	CRP ≤1 mg/dL and MBDA >44	CRP >1 mg/dL	CRP >1 mg/dL or MBDA >44
N	29	37	154	191
MBDA	−5.5	−11.9	−16.4	−15.6
DAS28	−1.5	−1.6	−1.8	−1.8
TJC	−5.2	−5.0	−4.6	−4.6
SJC	−5.0	−5.9	−5.8	−5.8
CDAI	−12.2	−12.9	−13.2	−13.2
ΔSHS >3 at Year 1 (%)	10%	35%	33%	34%

	MTX Non-responders			
			Conventional approach	New approach
Response Measurement	CRP ≤1 mg/dL and MBDA ≤44	CRP ≤1 mg/dL and MBDA >44	CRP >1 mg/dL	CRP >1 mg/dL or MBDA >44
N	55	23	49	72
MBDA	−4.2	−15.4	−23.2	−20.7
DAS28	−1.1	−1.4	−2.0	−1.8
TJC	−3.0	−4.3	−4.0	−4.1
SJC	−3.3	−4.2	−6.7	−5.9
CDAI	−8.0	−10.5	−13.6	−12.6
ΔSHS >3 at Year 1 (%)	24%	39%	53%	49%

Conclusion: These analyses suggest that if a clinical trial of DMARD-naïve or MTX-NR patients with RA were to include patients with MBDA score >44 even though CRP was ≤1mg/dL, the number of eligible patients would be increased by 24% and 47%, respectively, compared with the conventional approach to enrollment based on CRP >1 mg/dL alone, while maintaining clinical and radiographic outcomes.

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Fatigue Fluctuates Substantially over Time in Rheumatoid Arthritis Patients Despite Stable Disease Activity during Treatment with Biological Agents. Emilie Lund Egsmose, René Cordtz and Ole Rintek Madsen. Copenhagen University Hospital Gentofte, Hellerup, Denmark.

Background/Purpose: Fatigue (FTG) is a symptom commonly reported by patients with rheumatoid arthritis (RA). Little is known about its nature and etiology. The number of studies including FTG as an outcome measure has increased rapidly during recent years and FTG is considered a potential marker of RA disease activity in the clinic (1). In order to judge whether a given change in any disease marker in the individual patient is due to "measurement error" or to real change it is essential to know how large the natural variation of the disease marker is when the disease activity is constant.

The purpose of the present study was to examine intra-individual FTG fluctuations in patients with stable RA during treatment with a biological agent.

Methods: 233 RA patients treated with a biological agent and with stable disease activity were identified in the Danish registry for biological treatment in rheumatology (DANBIO). Stable disease activity was defined as a change in DAS28-CRP ≤ 0.6 between two consecutive visits with complete clinical data sets available including FTG. Paired data from a single set of such two consecutive visits were extracted for each patient. Data comprised DAS28-CRP and its individual components, HAQ and global assessment of the patient (PaGl) and the physician (PhGl) as well as patient reported FTG scored on 0–100 visual analogue scales (VAS). Bland-Altman analyses were used to assess the lower and upper 95 % limits of agreement between the two consecutive FTG assessments and the corresponding bias (the mean of individual differences). Associations between intra-individual inter-visit differences (Δ) in FTG and in other measures of disease activity were evaluated using Pearson's linear correlation analyses and by stepwise multiple regression with ΔFTG as the dependent variable. A p-value ≤ 0.05 was considered statistically significant.

Results: Mean age was 60±15 years, female/male ratio 3.2, mean time from treatment start to the first visit 136.1±117.8 (range 0–485) weeks, mean inter-visit duration time 22.3 ± 20.7 weeks, mean DAS28 3.1±1.2 and mean FTG 43.3±27.6. Mean ΔDAS28-CRP was 0.0±0.3 (range −0.6 to 0.6) (NS). The bias for FTG was 0.9 ±18.8 (NS) and the lower and upper limits of agreement −35.9 and 37.7, respectively. No significant correlation was found between the absolute value of ΔFTG and the inter-visit duration time ($r = 0.043$, NS). ΔFTG was weakly correlated with ΔPain ($r = 0.33$, $p < 0.01$) and ΔPaGl ($r = 0.39$, $p < 0.001$) and were not significantly correlated with change in any other single measure of disease activity or ΔDAS28-CRP. In a multiple regression analysis including Δ of all disease activity measures including DAS28-CRP as independent variables, ΔFTG was significantly predicted by only ΔPaGl (beta = 0.26, $p < 0.001$) and ΔPain (beta = 0.15, $p < 0.05$). No statistically significant difference in FTG or ΔFTG was found between males and females.

Conclusion: In individual RA patients, large fluctuations in FTG were observed over time although the disease activity was stable. If FTG is considered to reflect disease activity, changes in FTG less than approximately 35 on a VAS-scale may be interpreted as natural variation or pure measurement error.

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The Use of Week 12 CDAI, RAPID3 and DAS28(CRP) Responses to Predict Optimal Response to Methotrexate. Gerd Burmester[1], Gurjit S. Kaeley[2], Jeffrey R. Curtis[3], Yusuf Yazici[4], Benoit Guerette[5], Xin Wang[5], Alan Friedman[5] and Vibeke Strand[6]. [1]Charité University Medicine, Berlin, Germany, [2]University of Florida, Jacksonville, FL, [3]University of Alabama at Birmingham, Birmingham, AL, [4]New York University School of Medicine, New York, NY, [5]AbbVie, Inc., North Chicago, IL, [6]Stanford University, Palo Alto, CA.

Background/Purpose: The prediction of treatment outcomes based on early response could guide treatment decisions in patients (pts) with rheumatoid arthritis (RA). The objective was to determine if disease state at wk 12 in pts treated with a lower dose of methotrexate (MTX) + adalimumab (ADA), assessed by CDAI, DAS28(CRP) and RAPID3, was predictive of an SDAI response at a later time point, comparable to that achieved by pts receiving a high dose of MTX+ADA.

Methods: Data for this post hoc analysis originated from 2 randomized controlled trials. In CONCERTO, pts with early RA received ADA + 2.5, 5, 10 or 20 mg/wk MTX. In MUSICA, pts with moderate to severe RA and an inadequate response to MTX, received ADA + 7.5 or 20 mg/wk MTX. "Achievers" were defined as pts achieving optimal SDAI responses comparable to those in the top 40thpercentile (pct) receiving 20 mg/wk MTX + ADA. For CONCERTO, achievers had SDAI scores at wk 16 ≤6.8, wk 20 ≤5.0 and wk 26 ≤4.2; for MUSICA, achievers had SDAIs at wk 16 ≤15.4, wk 20 ≤11.8 and wk 24 ≤11. The following outcomes at wk 12 were compared in achievers vs non-achievers: CDAI, DAS28(CRP) and RAPID3. The likelihood of predicting optimal SDAI responses was assessed by ROC analysis using logistic regression with wk 12 CDAI, DAS28(CRP) and RAPID3 as predictors. Optimal ROC thresholds based on sensitivity and specificity, as well as those with satisfactory negative and positive predictive values (N/PPV), were calculated.

Results: In CONCERTO, 11/98 (11.2%), 10/100 (10%), 21/99 (21.2%) and 21/98 (21.4%) of pts receiving 2.5, 5, 10 and 20mg/wk MTX, respectively, were achievers; In MUSICA, 29/154 (18.8%) and 28/155 (18.1%) in 7.5 and 20 mg /wk MTX groups, respectively, were achievers. ROC-AUC, PPV and NPV indicated that wk 12 CDAI, DAS28(CRP), and RAPID3 were good predictors of optimal SDAI responses (table). Across selected thresholds, all three criteria provided good NPV for all MTX groups. In CONCERTO, non-achievers in CDAI remission/LDA at wk 12 achieved SDAI remission (≤3.3) or LDA (≤11) at wk 26; most pts in CDAI MDA or HDA at wk 12 did not. In MUSICA, in the 7.5 mg MTX treatment group, non-achievers in CDAI remission/LDA at wk 12 reached SDAI LDA (≤11) or MDA (11–26) at wk 24; 72.5% of pts in wk 12 CDAI MDA did not achieve optimal SDAI responses.

Table: AUC, PPV and NPV of wk 12 CDAI, RAPID3 and DAS28 (CRP) for prediction of optimal SDAI response

MTX dose (mg/wk)	Wk 12 criterion	Area under curve (95%CI)	ROC thres-hold	Sensitivity	1-specificity	PPV	NPV
CONCERTO							
2.5	CDAI	0.907 (0.837, 0.977)	3.6	0.455	0.038	0.625	0.926
5*		0.758 (0.562, 0.953)	7.3	0.700	0.190	0.304	0.958
10		0.902 (0.841, 0.963)	2.5	0.571	0.056	0.750	0.881
20		0.923 (0.870,0.976)	2.6	0.631	0.082	0.666	0.905
2.5	RAPID3	0.879 (0.796, 0.962)	0.6	0.450	0.038	0.625	0.925
5*		0.807 (0.711, 0.902)	6.3	0.900	0.265	0.290	0.984
10		0.863 (0.784, 0.943)	2.6	0.570	0.100	0.600	0.872
20		0.839 (0.738, 0.941)	1.9	0.631	0.111	0.600	0.901
2.5	DAS28	0.870 (0.790, 0.950)	1.6	0.180	0.012	0.667	0.895
5*		0.755 (0.566, 0.944)	2.8	0.700	0.167	0.333	0.959
10		0.890 (0.818, 0.960)	2.0	0.619	0.098	0.650	0.888
20		0.923 (0.870, 0.976)	2.5	0.894	0.150	0.608	0.968
			MUSICA				
7.5	CDAI	0.822 (0.749, 0897)	4.1	0.222	0.19	0.750	0.833
20		0.946 (0.908, 0.983)	8.7	0.851	0.056	0.793	0.962
7.5*	RAPID3	0.765 (0.673, 0.858)	7.9	0.740	0.243	0.444	0.919
20		0.839 (0.764, 0.914)	3.4	0.444	0.077	0.600	0.865
7.5	DAS28	0.814 (0.740, 0.888)	2.7	0.330	0.050	0.600	0.849
20		0.940 (0.901, 0.979)	3.3	0.925	0.121	0.658	0.979

For CONCERTO, optimal SDAI response was SDAI at wk 16 '6.8, wk 20 ≤5.0 and wk 26 ≤4.2; for MUSICA, optimal SDAI response was SDAI at wk16 ≤15.4, wk20 ≤11.8 and wk 24 ≤11.
ROC thresholds with NPV≥0.8 and PPV≥0.6 are presented, except for the groups indicated by the asterisk, where the optimal ROC cut-off is presented.

Conclusion: CDAI and RAPID3 are quick, convenient tools to assess treatment response, and correlated well with DAS28(CRP) as predictors of later outcome in the CONCERTO and MUSICA trials. In pts with early RA receiving lower doses of MTX, the achievement of remission or LDA targets at wk 12 was predictive of a subsequent optimal SDAI treatment response comparable to pts receiving higher MTX doses. Based on these data, pts in MDA/HDA at wk 12 might benefit from an adjustment of therapy.

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What Level of Disease Activity at 6 Months Predicts Achieving or Sustaining Remission at 12 Months? Edward Keystone[1], Philip Baer[2], Boulos Haraoui[3], J Antonio Avina-Zubieta[4], Andrew Chow[5], Dalton Sholter[6], Denis Choquette[7], Emmanouil Rampakakis[8], John S. Sampalis[8], Francois Nantel[9], Allen J Lehman[9], May Shawi[9] and Susan Otawa[9]. [1]Mount Sinai Hospital, University of Toronto, Toronto, ON, [2]Private Practice, Scarborough, ON, [3]University of Montreal Hospital Centre, Montreal, QC, [4]University of British Columbia, Department of Experimental Medicine, Vancouver, BC, [5]McMaster University, Hamilton and Credit Valley Hospital, Mississauga, ON, [6]University of Alberta, Edmonton, AB, [7]Institut de rhumatologie de Montréal (IRM), Montréal, QC, [8]JSS Medical Research, Montreal, QC, [9]Janssen Inc., Toronto, ON.

Background/Purpose: Achievement of clinical remission in rheumatoid arthritis (RA) is a process that may take several months. Identification of clinical signs predicting future remission may assist physicians in clinical decision making. The aim of this analysis was to describe the association between DAS28-ESR scores at 6 months and remission at 12 months in RA patients treated with infliximab (IFX) in a real-world, clinical practice setting.

Methods: BioTRAC is an ongoing, prospective Canadian registry of patients initiating treatment for RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with IFX or golimumab as first biologics or after having been treated with a biologic for <6 months. Eligible patients for this analysis included RA patients treated with IFX who were enrolled between 2002 and 2012 and had available DAS28 data at 6 and 12 months of follow-up. The association between DAS28-ESR score at 6 months and remission achievement at 12 months was assessed with logistic regression. Receiver operator curve (ROC) analysis was used to determine the optimal cut-off points for achieving and maintaining remission.

Results: A total of 293 patients were included with a mean (SD) age of 56 (13.5) years and disease duration of 10.0 (9.7) years. Mean (SD) DAS28 was 3.8 (1.5) and 3.5 (1.5) at 6 and 12 months, respectively, and the percent with DAS28-ESR remission was 24.6% and 27.0%. Of the patients in remission at 6 months, 65.3% sustained the remission at 12 months, while of those not in remission at 6 months, 14.5% achieved remission at 12 months ($P<0.001$). Logistic regression analysis showed a significant inverse association between DAS28-ESR score at 6 months and the likelihood of achieving remission at 12 months [for each increase in DAS28-ESR score by one unit there was a 64.6% lower probability of achieving remission; $P<0.001$]. ROC curve analysis identified a DAS28 score at 6 months ≤ 3.54 as most accurately predicting remission at 12 months with a sensitivity of 82% and a specificity of 70% (Figure 1A). Stratified analysis showed that, among patients in remission at 6 months, a DAS28 score of ≤2.13 was the optimal cut-off for predicting sustained remission at 12 months (68% sensitivity, 64% specificity) (Figure 1B).

Conclusion: The results of this analysis demonstrate that a DAS28-ESR target of ≤3.54 at 6 months maximizes the likelihood of remission at 12 months while a value of ≤2.13 should be targeted for optimal sustainment of remission.

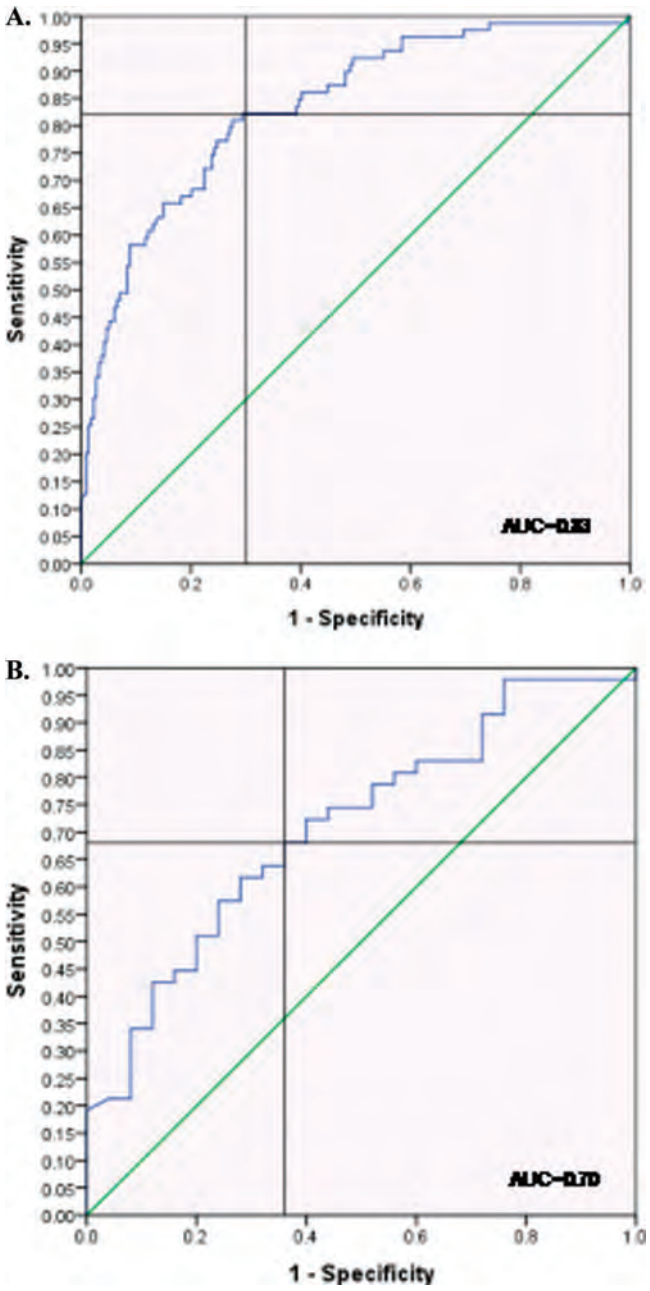

Figure 1. ROC curves showing the optimal DAS28-ESR cut-offs at 6 months for achieving (A) or sustaining (B) remission at 12 months

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In Palindromic Rheumatism, Older Age, Shorter Interval Between Attacks and Positive Anti-CCP Antibodies May Predict Progression to RA. Masatoshi Hayashi[1], Jackie L. Nam[2], Laura Hunt[2], Elizabeth Hensor[2], Toshihisa Kanamono[1], Toshihisa Kojima[3], Naoki Ishiguro[3] and Paul Emery[4]. [1]Nagano Red Cross Hospital, Nagano, Japan, [2]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [3]Nagoya University Graduate School of Medicine, Nagoya, Japan, [4]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds., United Kingdom, Leeds, United Kingdom.

Background/Purpose: Palindromic rheumatism (PR) is a clinical syndrome characterised by episodes of joint swelling that settle spontaneously. A proportion of patients with PR progress and develop rheumatoid arthritis (RA). Understanding the factors associated with progression would have value for management and understanding pathogenesis. We therefore identified potential factors associated with the development of RA in these patients.

Methods: A retrospective analysis was done on 55 patients with PR followed up in our rheumatology early arthritis clinics. For inclusion, patients had either a history or physical examination findings consistent with synovial swelling that returned to normal between episodes in the absence of an alternative diagnosis. Medical history, clinical examination and laboratory findings were compared between the group that progressed to ACR/EULAR 2010 RA (progression) and the group that did not (non-progression). Comparisons between groups were made with Mann-Whitney U tests or Pearson's chi-square tests, according to data type.

Results: Of the 55 patients, 28 (51%) developed RA and 27 (49%) did not over a mean (SD) period of 28.3 (40.0) and 17.2 (19.0) months of follow-up. Factors that differed between the groups were: age at PR onset (non-progression vs. progression median 39 vs. 48 years; table), duration of interval between attacks (30 vs. 45 days), anti-cyclic citrullinated peptide (anti-CCP) positivity (96% vs. 73%), and anti-CCP titre (164 vs. 57 U/ml).

Conclusion: In our cohort of patients with PR, a relatively high proportion progressed to RA. Features on history and anti-CCP anti-body positivity, particularly high antibody titres, were found to be associated with evolution to RA. These data should be of value in managing therapy and follow-up of PR patients.

Table Characteristics of patients with palindromic rheumatism who progressed to RA in comparison with those without progression to RA at the first visit.

Characteristics	Non-progression	Progression	OR (95% CI)	p
Number (%)	27 (49)	28 (51)		
Age, yrs	39 (32, 45)	48 (39, 59)		0.009*
Female, no. (%)	17 (63)	19 (68)	1.2 (0.4–3.8)	0.703
Symptom duration[a], wks	57.0 (28.0, 108.5)	86.0 (36.0, 138.0)		0.418
Followup, mo	9.0 (2.0, 22.0)	16.0 (10.3, 29.8)		0.107
Duration of one attack, hours	60.0 (30.0, 60.0)	36.0 (33.0, 51.0)		0.356
Interval of attacks, days	45.0 (30.0, 90.0)	30.0 (12.3, 30.3)		0.007*
Gout crystal arthropathy, no. (%)	0 (0)	4 (14)	1.2 (1.0–1.4)	0.041
Smoker (current or previous), no. (%)	16 (59)	22 (79)	2.5 (0.8–8.2)	0.121
Smoker (current), no. (%)	8 (30)	10 (36)	1.3 (0.4–4.1)	0.631
FDRRA, no. (%)	9 (33)	5 (18)	0.4 (0.1–1.5)	0.188
RF +, no. (%)	13 (57)	15 (68)	1.6 (0.5–5.6)	0.420
Anti-CCP +, no. (%)	16 (73)	24 (96)	9.0 (1.0–82.0)	0.025*
Anti-CCP titre (U/ml)	57.0 (0.5, 142.9)	164.0 (57.0, 300.0)		0.010*
CRP (mg/l)	4.0 (3.0, 11.7)	4.2 (2.2, 9.3)		0.637
ESR (mm/h)	10.0 (4.0, 22.0)	17.0 (6.0, 32.0)		0.181
ANA +, no. (%)	4 (17)	5 (19)	1.2 (0.3–5.1)	0.814

Data are median (inter-quartile range). *RA* rheumatoid arthritis, *PR* palindromic rheumatism, *MTX* methotrexate, *Anti-CCP* anti-cyclic citrullinated peptide, *FDRRA* first degree relative with RA, *RF* rheumatoid factor, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *ANA* antinuclear antibodies.

[a]Period between patient-reported symptom onset and date of first anti-CCP test
*p<0.05

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Distribution and Clinical Significance of Anti-Heterogenic Nuclear Ribonucleoprotein A2 Antibody in Connective Tissue Diseases. Wang Yong Sr., Mu Fangxiang, Wu Hong and Fang Yongfei. Southwest Hospital, Third Military Medical University, Chongqing, China.

Distribution and clinical significance of anti-heterogeneous nuclear ribonucleoprotein A2 antibody in connective tissue diseases

Background/Purpose: The heterogeneous nuclear ribonucleoprotein A2 (hnRNP-A2) has been described as an important autoantigen in rheumatoid arthritis (RA) since it is targeted by autoantibodies. To explore clinical significance of anti-heterogeneous nuclear ribonucleoprotein A2 (hnRNP-A2) antibody, we dectect the distribution of anti-hnRNP-A2 antibody in 1888 patients with connective tissue diseases.

Methods: Serum anti-hnRNP A2 antibody level was measured by solid-phase enzyme linked immunosorbent assay (ELISA) in 1464 patients with RA, 209 patients with systemic lupus erythematosus (SLE), 63 patients with mixed connective tissue disease (MCTD), 60 patients with Sjogren syndrome (SS), 47 patients with polymyositis/dermatomyositis (PM/DM), and 45 patients with systemic sclerosis (SSc). The positivity rate of anti-hnRNP-A2 antibody was compared among various patient groups, and its correlation to clinical and laboratory parameters and its diagnostic significance were analyzed.

Results: The positivity rate of anti-hnRNP-A2 antibody was 38.0%(556/1464), 36.8%(77/209), 52.4%(33/63), 5.0%(3/60), 4.3%(2/47), and 8.9%(4/45) in RA, SLE, MCTD, SS, PM/DM and SSc, respectively. The rate differed insignificantly between the RA, SLE and MCTD groups ($P > 0.05$), but was significantly higher than in other disease groups ($P < 0.01$). The titers of anti-hnRNP-A2 antibody were significantly higher in the RA, SLE, MCTD groups than in other disease groups ($P < 0.01$), but differed insignificantly between the RA, SLE, MCTD groups ($P > 0.05$). In RA patients, anti-hnRNP-A2 antibody weakly correlated negatively to anti-Cyclic citrullinated peptide (CCP) antibody ($r = -0.135$, $P < 0.01$), but correlated insignificantly to age, course of disease, time of morning stiffness, erythrocyte sedimentation rate, C reactive protein, rheumatoid factor (RF), anti-keratin antibody (AKA) and glucose phosphate isomerase (GPI) ($P > 0.05$).

Conclusion: Anti-hnRNP-A2 antibody can be found in various connective tissue diseases, and its positivity rate is relatively high in RA, SLE and MCTD. It is not a RA-specific antibody. In RA, anti-hnRNP-A2 antibody does not coincide with other RA-related serological indicators; hence, it may serve as an adjunctive indicator for RA diagnosis.

Key Words: heterogeneous nuclear ribonucleoprotein A2 (hnRNP-A2); Rheumatoid Arthritis (RA); Connective Tissue Diseases.

Disclosure: W. Yong Sr., None; **M. Fangxiang**, None; **W. Hong**, None; **F. Yongfei**, None.

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What Is More Predictive of Achieving Remission at 12 Months: The Percentage of Baseline Improvement or the Actual Disease State Achieved at 6 Months? Edward C. Keystone[1], Carter Thorne[2], Michael Starr[3], Jude Rodrigues[4], Philip Baer[5], Regan Arendse[6], J. Antonio Avina-Zubieta[7], Denis Choquette[8], Emmanouil Rampakakis[9], John S. Sampalis[9], May Shawi[10], Francois Nantel[10], Allen J Lehman[10] and Susan Otawa[10]. [1]University of Toronto, Toronto, ON, [2]Southlake Regional Health Centre, Newmarket, ON, [3]McGill University Health Centre, Montreal, QC, [4]Clinical Research and Arthritis Centre, Windsor, ON, [5]Private Practice, Scarborough, ON, [6]University of Saskatchewan, Saskatoon, SK, [7]Arthritis Research Centre of Canada, Richmond, BC, [8]Institut de rhumatologie de Montréal (IRM), Montréal, QC, [9]JSS Medical Research, Montreal, QC, [10]Janssen Inc., Toronto, ON.

Background/Purpose: The aim of rheumatoid arthritis (RA) treatment is to optimize symptom control and, when possible, achieve sustained remission. Therefore, identification of clinical signs predicting future remission is valuable to clinical decision making. One question faced by clinicians is whether the achievement of a lower disease activity value or a higher rate of change of disease activity is indicative of better future disease outcomes. The purpose of this analysis was to determine whether change in disease activity measures or the actual values achieved at 6 months were more predictive of remission at 12 months in RA patients treated with infliximab (IFX) in a real-world, clinical practice setting.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA with IFX or golimumab as first biologics or after

having been treated with a biologic for <6 months. Eligible people for this study included RA patients treated with IFX enrolled between 2002–2012 with available 12-month information on remission. Multivariate logistic regression models with the parametric Wald statistic and the log-likelihood ratio were used to assess the independent contribution of the actual value and the change at 6 months in predicting 12-month remission as defined by DAS28 (<2.6), SDAI (≤3.3) and CDAI (≤2.8) criteria. These two statistics assess the extent of contribution of an individual predictor to an outcome of interest - higher values signify greater contribution - and can be used to compare the contribution of different predictors in a standardized fashion.

Results: 436 patients were included with mean age of 56.1 yrs and disease duration of 10.4 yrs. With respect to 12-month DAS28 remission, a stronger association was observed with the actual DAS28 score compared to the percent improvement in DAS28 at 6 months. The Wald statistic for the percent change and actual value of DAS28 at 6 months was 5.38 and 46.88, respectively, while the change in log-likelihood was 4.98 (P=0.026) and 61.64 (P<0.001), respectively, indicating that the actual DAS value achieved is significantly more predictive of remission when compared to percent change in DAS from baseline.

For SDAI remission at 12 months, the respective Wald values for percent change and actual value at 6 months were 0.075 and 18.28 and log-likelihood changes were 0.07 (P=0.788) and 24.08 (P<0.001). For CDAI remission at 12 months, the Wald statistic was 0.01 and 34.42 for 6 month percent change and actual value, respectively, and change in log-likelihood was 0.01 (P=0.934) and 34.23 (P<0.001). Similar results were obtained when predicting low disease activity at 12 months.

Conclusion: These results demonstrate that the actual disease outcome value achieved at 6 months is a stronger predictor of remission at 12 months than the percent change in disease activity. These findings suggest that the treatment target in a real-world setting should be set as specific endpoints and not as change over time.

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How Low Is Low Disease Activity? an Analysis from a Prospective, Observational Registry. Edward C. Keystone[1], Boulos Haraoui[2], John Kelsall[3], Carter Thorne[4], Philip Baer[5], William Bensen[6], Denis Choquette[7], Regan Arendse[8], Dalton Sholter[9], Niall Jones[9], Algis Jovaisas[10], Emmanouil Rampakakis[11], John S. Sampalis[11], Francois Nantel[12], May Shawi[12], Allen J Lehman[12] and Susan Otawa[12]. [1]University of Toronto, Toronto, ON, [2]University of Montreal Hospital Centre, Montreal, QC, [3]The Mary Pack Arthritis Centre, Vancouver, BC, [4]Southlake Regional Health Centre, Newmarket, ON, [5]Private Practice, Scarborough, ON, [6]St Josephs Hospital and McMaster University, Hamilton, ON, [7]Institut de rhumatologie de Montréal (IRM), Montréal, QC, [8]University of Saskatchewan, Saskatoon, SK, [9]University of Alberta, Edmonton, AB, [10]University of Ottawa, Ottawa, ON, [11]JSS Medical Research, Montreal, QC, [12]Janssen Inc., Toronto, ON.

Background/Purpose: Composite measures of disease activity can facilitate clinical decision-making to achieve treatment goals, and treating-to-target has been shown to improve outcomes. Both CRA and ACR/EULAR recommend that treatment target should be remission or, when not possible, low disease activity (LDA). Low levels of acute phase reactants, patient-reported disease activity (PtGA), or tender joints included in such measures may result in meeting LDA criteria while having significant residual disease activity. This analysis examined the levels of individual components of composite measures in RA patients with LDA.

Methods: BioTRAC is an ongoing, prospective registry of RA, AS, or PsA patients initiating treatment with infliximab or golimumab as first biologics or after having been treated with a biologic for <6 months. In this analysis, data from RA patients treated with infliximab for 6–18 months who were enrolled between 2002–2012 were used. LDA was defined using the DAS28-ESR (2.6–3.2), CDAI (2.8–10.0), and SDAI (3.3–11.0) criteria.

Results: 321 RA patients with mean age of 57.1 years and mean duration since diagnosis of 10.5 years were included, providing information from 488 instances of LDA. Among patients with DAS28 LDA, mean (min, max) TJC28 was 1.3 (0,9), SJC28 was 1.2 (0,7), PtGA was 2.1 (0.0,10.0), and ESR was 21.0 (1.0,75.0). Similarly, disease parameters in patients with CDAI and SDAI LDA were, respectively: TJC28 [1.4 (0,6); 1.5 (0,8)], SJC28 [1.1 (0,7); 1.0 (0,6)], PtGA [2.3 (0.0,8.5); 2.3 (0.0,9.6)], MDGA [1.7 (0.0,9.0); 1.6 (0.0,9.0)], and CRP [6.7 (0.0, 68.0)]. More than two swollen joints were present in 18.2%/14.1%/14.5% of DAS28 / CDAI / SDAI instances, respectively, and MDGA was >2 in 24.0%% / 18.6% / 18.2% of instances. With respect to HAQ-DI, patients with DAS28, CDAI and SDAI LDA had a mean (min, max) score of 0.96 (0.00,2.88), 1.00 (0.00,2.88), and 0.96 (0.00,2.88), respectively; with 8.5%, 11.3%, and 9.8% of cases having HAQ-DI≥2.0 indicating severe to very severe disability.

Conclusion: Despite meeting the LDA criteria, significant residual disease may exist as indicated by the number of swollen joints and MDGA. Furthermore, a significant proportion of patients in LDA may have severe to very severe disability, although this may be due to long disease duration and irreversible damage. Altogether, although targeting LDA results in improved outcomes, it may not be an appropriate target for a significant portion of patients. Furthermore, treatment decisions should not be based solely on composite measures, but also take into consideration the global patient picture.

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Using Patient Reported Outcome Measures to Classify Disease Activity States in Rheumatoid Arthritis: A Comparison of Patient Activity Score (PAS) and Routine Assessment of Patient Index Data (RAPID). Erin Carruthers[1], Noura AL Osaimi[2], Charles H Goldsmith[3], Paul Adam[4] and Diane Lacaille[5]. [1]Arthritis Research Centre of Canada, Richmond, BC, [2]University of Ottawa, Ottawa, ON, [3]Simon Fraser University, Burnaby, BC, [4]Mary Pack Arthritis Centre, Vancouver, BC, [5]Arthritis Research Centre of Canada, Vancouver, BC.

Background/Purpose: In RA the target for treatment is clinical remission or minimal disease activity. Patient involvement in monitoring their disease activity could enhance treatment by providing early warning when targets are not met, indicating the need to re-evaluate treatment. Several patient reported outcome measures of disease activity have been developed and validated. The objective of this study is to compare the agreement between patient and rheumatologist (MD) derived disease activity states using these measures.

Methods: Consecutive RA patients seen by 7 rheumatologists were invited to participate. Patients completed a questionnaire before their visit. MD joint count and lab values were obtained from charts. We evaluated 4 patient reported disease activity measures: i) PASII; ii) RAPID with 3 measures (RAPID3); iii) RAPID with 4 measures (RAPID4); iv) modified-RAPID4 (m-RAPID4) using HAQII instead of MDHAQ. The following MD derived measures served as gold standards: i) Clinical Disease Activity Index (CDAI); ii) Simplified Disease Activity Index (SDAI); iii) Disease Activity Score 28 (DAS28). Disease states were categorized into remission, low, moderate or high, according to published cut points. Because change in treatment is recommended with moderate or high disease activity, we also compared two categories: remission or low vs. moderate or high. Agreement between patient and MD derived disease states was evaluated using *Agreement Coefficient 1 (AC1)* for two category comparisons and *Agreement Coefficient 2 (AC2)*, weighted with quadratic weights, for four category

comparisons. AC values > 0.62 were considered good agreement. Z tests were used to evaluate the significance of the difference between pairs of ACs.

Results: We recruited 150 RA patients [mean (SD) RA duration: 11.9 (11.3) y; age: 57.8 (16.3) y; 81% female]. See **Table 1** for agreement between patient and MD derived disease activity states. Overall, PASII showed the best agreement with MD measures. When comparing ACs for four category disease activity states, all pairwise comparisons were significantly different (all but one $p < 0.001$), except when comparing agreement between RAPID4 and m-RAPID4 with CDAI ($p = 0.054$), and between RAPID3 and RAPID4 with SDAI ($p = 0.075$). When comparing ACs for two categories, significant differences were detected in the agreement between PASII and RAPID3 with CDAI, RAPID3 and 4 with CDAI, PASII and RAPID3 with DAS28, PASII and RAPID5 with DAS28, RAPID3 and 4 with DAS28, and RAPID4 and m-RAPID4 with DAS28) (all $p < 0.05$).

Table 1. Agreement between patient and MD derived indices measured across four and two disease activity categories.

A	Comparison across four categories (remission vs. low vs. moderate vs. high)		
PATIENT MEASURES	**RHEUMATOLOGIST MEASURES**		
	CDAI-MD	**SDAI-MD**	**DAS28-MD**
	AC2 [95% CI]	**AC2 [95% CI]**	**AC2 [95% CI]**
PASII	**0.67 [0.55, 0.79]**	**0.67 [0.54, 0.79]**	0.47 [0.33, 0.62]
RAPID3	0.54 [0.40, 0.68]	0.60 [0.46, 0.73]	0.29 [0.14, 0.45]
RAPID4	0.60 [0.47. 0.73]	**0.65 [0.52, 0.78]**	0.39 [0.24, 0.54]
m-RAPID4	0.58 [0.45, 0.91]	**0.64 [0.51, 0.77]**	0.33 [0.18, 0.49]
B	**Comparison across two categories (remission or low vs. moderate or high)**		
PATIENT MEASURES	**RHEUMATOLOGIST MEASURES**		
	CDAI-MD	**SDAI-MD**	**DAS28-MD**
	AC1 [95% CI]	**AC1 [95% CI]**	**AC1 [95% CI]**
PASII	**0.86 [0.83, 0.90]**	**0.86 [0.82, 0.90]**	**0.67 [0.59, 0.75]**
RAPID3	**0.70 [0.63, 0.76]**	**0.73 [0.67, 0.79]**	0.29 [0.13, 0.44]
RAPID4	**0.77 [0.71, 0.83]**	**0.78 [0.72, 0.84]**	0.43 [0.29, 0.56]
m-RAPID4	**0.73 [0.66, 0.79]**	**0.75 [0.68, 0.81]**	0.35 [0.20, 0.49]

AC1 = agreement coefficient 1; AC2 = quadratic weighted agreement coefficient 2
All p-values 2 tailed, $p < 0.001$
Bolded values (AC > 0.62) are considered good agreement

Conclusion: Our results suggest that patients can self-monitor disease activity. PASII shows the best agreement with all MD measures. Given the similarities in the components of the measures compared, this difference may be due to cut points used to categorize disease states.

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Validation of a Prognostic Model to Predict Structural Damage Assessed By X-Ray in Patients with RA Using MRI Data from a Clinical Trial. EA Alemao[1], S Joo[2], S Banerjee[1], P Allison[3], P Emery[4], M Weinblatt[5] and KP Liao[5]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]Bristol-Myers Squibb, Hopewell, NJ, [3]University of Pennsylvania, Philadelphia, PA, [4]University of Leeds, Leeds, United Kingdom, [5]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: We developed and validated a prognostic model for rapid radiographic progression (RRP) using X-ray data to identify RA patients (pts) at risk of structural joint damage. The objective of this study was to determine the RRP model performance using MRI as the outcome for structural joint damage.

Methods: We analyzed data from a Phase IIB clinical study with the anti-IL-6 monoclonal antibody clazakizumab. This was a randomized, comparator-controlled, double-blind study of moderate-to-severe RA pts with inadequate response to MTX. Outcome data were available for MRI scans of the hands (12 wks) as well as disease activity and functional status (12 and 24 wks). MRI outcomes of synovitis, erosions and bone edema were evaluated using the RA-MRI scoring system (RAMRIS). We applied our prognostic model for RRP to pts in this study. The model includes seropositivity status, body weight, disease duration, DAS28 (CRP) and Total Sharp Score to determine the probability of RRP for each pt. The external validity of the model was evaluated for discrimination (receiver operating characteristic [ROC]) and calibration (Hosmer–Lemeshow goodness-of-fit chi-square). Based on the calculated probability of RRP, pts were categorized by probability into low (0–0.25), moderate (>0.25–0.75) and high (>0.75) risk of RRP. Analysis of variance was used to study the association between predicted probability of RRP at baseline to MRI outcome at 12 wks. Additionally, we examined the association between RRP prediction and disease activity [SDAI, DAS28 (CRP)] and functional status (HAQ) at 12 and 24 wks.

Results: There were 418 pts in the clazakizumab Phase IIB study; average age was 50.4 yrs (SD 12.3); 82.1% were female. The RRP model when applied to clazakizumab Phase IIB had an overall ROC of 0.73 (95% CI 0.62, 0.83) and Hosmer–Lemeshow chi-square of 13.5 (df=8; p=0.1). Baseline probability of RRP was evaluated in 387 (92.6%) pts with available data. Of these, the majority (96.1%) were in the moderate- and high-risk (48.1% each) RRP groups. Pts in the moderate-risk group, when compared with those in the high-risk group, tended to be younger (mean age [SD] 48.3 [12.9] vs 52.2 [11.0] yrs). Compared with the moderate-risk RRP group, pts at high risk of RRP had significantly higher MRI measures of erosion, synovitis and joint space narrowing. In addition, pts at baseline in the high–risk group compared with the moderate-risk group had significantly higher disease activity scores and higher physical activity scores as measured by HAQ at 12 and 24 wks (Table).

Table Differences between MRI, disease activity, and functional outcomes in pts at high risk versus moderate risk of RRP

	12 weeks		24 weeks	
Outcomes	**Δ (high versus moderate) risk of RRP**	**95% CI**	**Δ (high versus moderate) risk of RRP**	**95% CI**
MRI scores				
Erosion (MRI)	**10.84**	7.03, 14.66	–	–
Synovitis (MRI)	**2.63**	1.54, 3.71	–	–
Edema (MRI)	1.06	–0.90, 3.02	–	–
Joint space narrowing (MRI)	**6.54**	3.59, 9.50	–	–
Disease activity and functional outcomes				
DAS28 (CRP) C	**0.72**	0.36, 1.09	**0.78**	0.42, 1.14
SDAI	**8.22**	4.38, 12.05	**8.11**	4.63, 11.58
HAQ	**0.43**	0.25, 0.60	**0.47**	0.29, 0.65

Each line represents a mutivariable linear regression model of outcomes

Conclusion: The RRP model based on X-ray progression had good validity in predicting structural joint damage measured by MRI. In line with clinical thinking, we observed that patients at high baseline risk of RRP compared with those with moderate risk tended to have higher disease activity and worse functional status in the longer term.

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Association of Pharmacogenetic Markers with Treatment Response in Patients with Rheumatoid Arthritis. Ute I. Schwarz[1], Janet E. Pope[1], Edward Keystone[2], Boulos Haraoui[3], Carter Thorne[4], Yun-Hee Choi[1], Melanie Poulin-Costello[5], Nabil Bayan[5] and Richard B. Kim[1]. [1]Western University, London, ON, [2]Mount Sinai Hospital, University of Toronto, Toronto, ON, [3]University of Montreal Hospital Centre, Montreal, QC, [4]Southlake Regional Health Centre, Newmarket, ON, [5]Amgen Canada Inc., Mississauga, ON.

Background/Purpose: In the **CA**nadian **M**ethotrexate and **E**tanercept **O**utcome Study (CAMEO) continued therapy with etanercept (ETN) and methotrexate (MTX) led to better outcomes at month 24 than the withdrawal of MTX in MTX inadequate responders (MTX-IR) with active rheumatoid arthritis (RA). Patients had to tolerate MTX at a dose of ≥ 15 mg/wk or 10 mg/wk if intolerant. Similar disease activity was observed in both treatment arms at 12 months in the subgroup of patients who achieved low disease activity (disease activity score [DAS28] < 3.2) at 6 months of combination therapy, whereas if not in low DAS28 combination therapy was more effective. Recent evidence suggests that polymorphisms in genes related to metabolism and cellular transport pathways of MTX and to the biological targets of ETN may help predict clinical response in RA. This pre-defined CAMEO sub-study explored pharmacogenetic markers as novel predictors of treatment outcome in patients failing MTX prior to starting ETN.

Methods: All patients were treated with ETN+MTX for 6 months, followed by randomization to either ETN+MTX or ETN alone for an

additional 18 months. After consent, DNA extraction and genotyping was performed using TaqMan Genotyping Assays. Fifteen genetic variants in 12 genes related to MTX and 4 variants in 3 genes related to TNF were analyzed. The contribution of genetic variants to therapeutic response (improvement in DAS28 [ΔDAS28] from baseline to months 6, 12, 18 and 24; total Sharp score [TSS] at 12 and 24 months) was assessed using mixed models with adjustments for age and sex.

Results: Assessments were performed in 111 patients (mean age 55.2 years, 73% female, 98% Caucasians). Univariate analyses did not suggest an association of genetic variants related to response to ETN ($p > 0.25$). Patients receiving ETN+MTX after randomization (N=64) were included for multivariate analyses at 12, 18 and 24 months. Patients expressing the *ATIC* 347GG, *GGH* 452CC, *MTHFD1* 1958A, *ABCB1* 3435C, or *SLCO1B1* 521C alleles were more likely to have an improvement with combined therapy as reflected by a significantly higher ΔDAS28 from baseline to follow-up (Table 1). At 12 and 24 months, patients having the *ATIC* 347GG and *ABCB1* 3435CC alleles showed moderately higher TSS (Table 2). Radiographic assessments also indicated that *ABCC2* 1249A carriers appear to be less responsive compared with GG carriers.

Conclusion: Genetic polymorphisms in drug transporters and metabolic enzymes related to MTX pathways were associated with clinical response after combined treatment in MTX-IR patients. No association between response to ETN and TNF gene variants was observed.

Table 1 Association of genotype with treatment response assessed as DAS28 improvement from baseline

	Genotype	N	LS Mean ΔDAS28 (95% CI)	*P* value*
Month 6, N = 108				
ABCB1 3435C>T	TT	23	1.90 (1.30, 2.50)	0.0074
	CC and CT	85	2.70 (2.20, 3.20)	
ATIC 347C>G	GG	11	3.00 (2.18, 3.82)	0.0013
	CC and CG	97	1.64 (1.28, 2.00)	
GGH 452C>T	CT and TT	24	2.00 (1.34, 2.66)	0.0352
	CC	84	2.64 (2.18, 3.10)	
Month 12, N = 61				
GGH 452C>T	CT and TT	12	1.48 (0.57, 2.39)	0.0136
	CC	49	2.73 (2.23, 3.23)	
Month 18, N = 58				
GGH 452C>T	CT and TT	10	2.06 (1.14, 2.98)	0.0186
	CC	48	3.09 (2.57, 3.61)	
ATIC 347C>G	GG	8	3.11 (2.08, 4.15)	0.0059
	CG	29	1.81 (1.21, 2.41)	
	CC	21	2.81 (2.08, 3.54)	
MTHFD1 1958G>A	GA and AA	42	2.97 (2.32, 3.61)	0.0343
	GG	16	2.19 (1.42, 2.96)	
SLCO1B1 521T>C	TC and CC	14	3.02 (2.14, 3.89)	0.0315
	TT	44	2.14 (1.59, 2.69)	
Month 24, N = 59				
GGH 452C>T	CT and TT	11	1.10 (0.08, 2.13)	0.0145
	CC	48	2.45 (1.88, 3.02)	

CI, confidence interval; DAS28, disease activity score; LS, least squares
*P values are from multivariate comparisons by genotype.

Table 2 Association of genotype with treatment response assessed as TSS

	Genotype	N	LS Mean TSS (95% CI)	*P* value*
Month 12, N = 62				
ABCB1 3435C>T	CT and TT	48	18.7 (17.95, 19.47)	0.0123
	CC	14	20.1 (18.87, 21.38)	
ATIC 347C>G	GG	8	20.1 (18.72, 21.63)	0.0334
	CC and CG	54	18.7 (18.01, 19.32)	
ABCC2 1249G>A	GA and AA	16	20.1 (18.96, 21.32)	0.0088
	GG	46	18.7 (17.84, 19.55)	
Month 24, N = 56				
ABCB1 3435C>T	CT and TT	43	20.7 (19.73, 21.62)	0.0244
	CC	14	22.2 (20.76, 23.68)	
ATIC 347C>G	GG	6	22.4 (20.65, 24.33)	0.0309
	CC and CG	56	20.4 (19.72, 21.17)	
ABCC2 1249G>A	GA and AA	14	22.1 (20.72, 23.51)	0.0492
	GG	42	20.8 (19.76, 21.79)	

CI, confidence interval; LS, least squares; TSS, total Sharp score
*P values are from multivariate comparisons by genotype.

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Levels of IgG Autoantibodies to Oxidation-Associated MDA Neo-Determinants Are a Biomarker for Systemic Inflammation and Disease Activity in SLE and RA. Caroline Grönwall, Lelise Getu, Jeffrey D. Greenberg, Robert M. Clancy and Gregg J. Silverman. New York University School of Medicine, New York, NY.

Background/Purpose: Monitoring disease activity in patients with autoimmune rheumatic disease is an essential part of clinical care. Highly reactive malondialdehyde (MDA) arise from reactive oxygen species and lipid peroxidation and can covalently modify proteins and increased levels of MDA may be associated with the inherent autoimmune pathogenic process. We therefore hypothesized that levels of IgG-autoantibodies to MDA-modified proteins may reflect core disease activity.

Methods: In the current study, serum IgG anti-MDA levels were compared in 71 healthy controls, 30 OA, and 15 PsA, 283 SLE and 162 RA patients identified by ACR criteria. IgG anti-MDA was measured by sandwich ELISA using MDA-modified BSA. Statistical differences were assessed by Mann-Whitney test and Spearman analysis.

Results: Compared to controls (5±3 RU/ml), IgG anti-MDA was significantly increased in patients with PsA (7.4±4 RU/ml, p=0.01), SLE (17±21 RU/ml, p<0.0001) and RA (13±11 RU/ml, p<0.0001). In SLE patients, IgG anti-MDA significantly correlated with the disease activity assessed by SELENA-SLEDAI (p<0.0001, R=0.34, n=219) and levels were higher in SLE patients with active disease (SLEDAI≥6, 18.9±17.3 RU/ml, p=0.001) than with low disease activity (SLEDAI >6, 11.5±16.6). In RA, IgG anti-MDA was significantly higher in new onset RA (<6 mo, 21±13 RU/ml, p<0.0001) than in chronic RA (>2 yr, 10±8 RU/ml). Notably, new onset RA patients had more active disease by DAS28 (5.7±1.2, p=0.01) than chronic RA patients generally on therapy (4.8±1.5). Importantly, IgG anti-MDA significantly correlated with DAS28-ESR (p<0.0001, R=0.35, n=157; with 16 seroneg), and compared to RA patients with more controlled disease (DAS28<3.2, 6±3) the levels were higher in moderate disease (DAS28 3.2–5.1, 12±11 RU/ml, p=0.005) and further elevated in active disease (DAS28 >5.1, 15±12 RU/ml, p=0.001). IgG anti-MDA also correlated with TNFα (p=0.002, R=0.39), IL-6 (p=0.03, R=0.27), and CRP levels (p=0.003, R=0.37) in DMARD naïve RA patients (n=62).

Conclusion: IgG autoantibodies to MDA-modified determinants may provide a biomarker for disease activity in rheumatic autoimmune diseases. These autoantibodies could therefore provide a valuable early objective metric for diagnosis and for assessing disease activity. The potential mechanisms responsible for induction of IgG anti-MDA autoantibodies during the pathogenesis of systemic inflammation merits further study.

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Soluble TREM-1 Is a Biomarker of Anti-CCP-Positive, DMARD-Naive Early Rheumatoid Arthritis. Shachaf Ofer-Shiber[1], Elisheva Pokroy-Shapira[1], Yair Molad[2], Shirly Oren[1], Hagit Shay-Aharoni[1] and Ilan Babai[3]. [1]Rabin Medical Center, Beilinson Hospital and Sackler Faculty of Medicine, Tel Aviv University, Petach Tikva, Israel, [2]Rabin Medical Center, Beilinson Hospital and Sackler Faculty of Medicine, Tel Aviv University, Petah Teqva, Israel, [3]Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel.

Background/Purpose: Triggering receptor expressed on myeloid cells-1 (TREM-1) is a cell-surface receptor, expressed mainly on monocytes and neutrophils and involved in amplification of the inflammatory response. Previous studies have shown an upregulation of TREM-1 in synovium of patients with rheumatoid arthritis (RA) as

well as increased levels of soluble TREM-1 (sTREM-1) in synovial fluid and blood of patients and animal model of RA. We sought to determine the serum sTREM-1 levels in disease-modifying anti-rheumatic drug (DMARD)–naïve early rheumatoid arthritis (ERA), to investigate the association of sTREM-1 levels with Disease Activity Score in 28 joints (DAS28) and seropositivity for anti- cyclic citrullinated peptide *(*CCP) antibody, and to determine the predictive value of sTREM-1with respect to clinical response to DMARD therapy.

Methods: Twenty-two consecutive patients with DMARD-naïve ERA were prospectively evaluated for serum sTREM-1 by means of ELISA at diagnosis and at the following clinic visit after low dose prednisone and/or DMARD have been administered, and related to DAS28 and serum level of anti-CCP Ab'. We compared the sTREM-1 level to that of 31 patients with established RA as well as to 24 controls.

Results: Serum sTREM-1 level was significantly higher in the DMARD-naïve ERA group (2,122.9±388.9 ρg/ml) compared to established RA group (1,478.0±280.0 ρg/ml, $p = 0.001$) and normal control (34.4±7.4 ρg/ml, $p < 0.001$). In the ERA group, elevated basal sTREM-1 level was significantly associated with DAS28-CRP ($p = 0.001$, HR3.23, 95% CI 1.4 – 8.12), DAS28-ESR ($p = 0.04$, HR 2.34 95%CI 0.1–8.12), as well as predicted higher DAS28 at the following encounter after DMARD treatment was administered ($p = 0.001$, HR 3.2 95% CI 1.1–7.2), as well as in patients with established RA. Higher serum sTREM-1levels were significantly associated with higher titers of anti-CCP antibody ($p < 0.001$).

Conclusion: Our results suggest that serum sTREM-1 may provide a novel biomarker of DMARD-naïve ERA as well as of disease activity and seropositivity for anti-CCP antibody in RA.

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High 11B-HSD1 Activity Is Associated with Progression to Rheumatoid Arthritis in Patients with a New Onset of Inflammatory Arthritis. Dominika Nanus[1], Andrew Filer[2], Lorraine Yeo[1], Dagmar Scheel-Toellner[3], Rowan Hardy[1], Gareth Lavery[1], Paul Stewart[4], Christopher Buckley[1], Mark Cooper[5] and Karim Raza[1]. [1]University of Birmingham, Birmingham, United Kingdom, [2]Rheumatology Research Group, MRC Centre for Immune Regulation, School of Immunity and Infection, University of Birmingham, Birmingham, United Kingdom, [3]Rheumatology Research Group, Centre for Translational Inflammation Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK, Birmingham, United Kingdom, [4]University of Leeds, Leeds, United Kingdom, [5]ANZAC Research Institute, Sydney, Australia.

Background/Purpose: Inadequate endogenous glucocorticoid (GC) synthesis during inflammation has been proposed as an aetiological factor in the development of rheumatoid arthritis (RA). It has been shown that inflamed synovial tissue from patients with RA can generate active GCs through the expression of the 11β-hydroxysteroid dehydrogenase type 1 enzyme (11β-HSD1), which converts cortisone to cortisol. We examined whether the total body activity of 11β-HSD1 was associated with the risk of developing persistent arthritis in patients first presenting with joint inflammation.

Methods: Blood and urine, were obtained from 76 patients with early arthritis (symptoms ≤ 12 weeks duration). The final diagnostic outcome was determined after 18 months clinical follow up when patients were assigned to one of the following three outcome groups. (1) Persistent inflammatory arthritis that did not fulfil 1987 ACR classification criteria for RA, n=13. (2) Persistent RA, according to 1987 ACR classification criteria, n=18. (3) Resolving inflammatory arthritis, n=24. Patients were classified as having a resolving inflammatory arthritis if they had no clinically apparent joint swelling at final follow-up, were not receiving disease modifying drugs or steroids and had not received such drugs in the previous 3 months. In addition, patients who fulfilled 1987 ACR classification criteria for RA and had a symptom duration of more than 12 weeks at initial assessment were recruited as patients with 'established RA', n=20. Total body 11β-HSD1 activity was determined by urinary gas chromatography/mass spectrometry and calculated as the tetrahydrocortisol+allotetrahydrocortisol/tetrahydrocortisone ((THF+alloTHF)/THE) and the cortols/cortolones ratios. Urinary 11β-HSD2 activity was measured as the UFF/UFE ratio. Arthritis severity was assessed by ESR, CRP and DAS28.

Results: Systemic measures of 11β-HSD1 activity were significantly higher in patients with early arthritis whose disease went on to persist, and also in the subgroup of patients with persistent disease who developed RA, when compared with patients whose synovitis resolved over time (persistent RA, 1.34 (0.013) and resolving inflammatory arthritis, 0.96 (0.07), P=0.012), mean (SEM). Levels of ESR at baseline were not significantly different between the different outcome groups. However the levels of CRP in patients with early synovitis that persisted were higher than that in patients whose synovitis resolved. We observed a significant positive correlation between systemic 11β-HSD1 activity and both ESR and CRP in patients with established RA but not in any of the early arthritis patients group.

Conclusion: The present study demonstrates that patients with a new onset of synovitis whose disease subsequently resolved had significantly lower levels of systemic 11β-HSD1 activity when compared with patients whose synovitis developed into RA or other form of persistent arthritis. This observation is contrary to that predicted on the basis of previous work and raises the possibility that a high total body 11β-HSD1 activity during early arthritis may reduce the probability of disease resolution.

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Prevalence and Correlates of Patient-Physician Discordance in Early Rheumatoid Arthritis. John M. Davis III, Cynthia S. Crowson, Tim Bongartz, Clement J. Michet, Eric L. Matteson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN.

Background/Purpose: Patients with rheumatoid arthritis (RA) sometimes rate their global disease activity differently than their rheumatologists. Previous studies describing this 'discordance' have primarily included patients with established disease (i.e., mean disease duration >10 years). The objective of this study was to evaluate the prevalence and correlates of patient-physician discordance in patients with early disease (i.e., duration <3 years).

Methods: We conducted an observational study of consecutive patients with RA recruited between July 2008 and December 2010. RA was defined by the Leiden early RA prediction rule or the 1987 ACR criteria. A physician joint assessor, who was independent from treatment decision-making, performed a standardized clinical evaluation. Discordance was defined by a ≥25-mm difference between the patient and physician global assessments of disease activity. A higher patient-than-physician global assessment defined positive discordance, and a higher physician-than-patient global assessment defined negative discordance. Patients completed visual analog scales for pain and fatigue, the Health Assessment Questionnaire (HAQ), and the Medical Outcomes Study Short Form 36 (SF-36). We abstracted the electronic medical records to collect demographics, laboratory data, smoking status, and body mass index (kg/m^2). Correlations between explanatory variables and the presence of positive or negative discordance were determined using Spearman methods.

Results: A total of 127 patients with RA were recruited. The mean age was 55.6 years, mean disease duration was 6.8 months, and 63% of patients were female. The prevalence of positive (i.e., patient high) and negative (i.e., physician high) discordance was 10.2% and 16.5%, respectively. Positive discordance was associated with higher pain ($r = 0.37$, $p = <0.001$), fatigue ($r = 0.32$, <0.001) and HAQ disability ($r = 0.31$, $p<0.001$). Poor health-related quality of life on the SF-36 physical component scale ($r = -0.29$, $p = 0.001$) and mental component scale ($r = -0.20$, $p = 0.02$) also correlated with positive discordance. Notably absent were associations of discordance with age, sex, radiographic damage, body mass index, smoking, anti-CCP antibodies, or use of prednisone or disease-modifying medications. In contrast, negative discordance (i.e., physician high) was associated with higher numbers of swollen joints ($r = 0.19$, $p = 0.03$), positive rheumatoid factor ($r = 0.18$, $p = 0.046$), and with lower pain and better overall physical and mental health on the part of the patient.

Conclusion: The contribution of this study is that prevalence and correlates of patient-physician discordance are similar in early and established RA. Patients with early RA take into account their pain, fatigue and adverse quality of life when making their global disease assessments whereas physicians emphasize objective inflammation and laboratory markers. As 'treat-to-target' algorithms increasingly focus on quantitative targets, these data behoove clinicians to fully consider the disease experience to provide optimal patient care.

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Self-Assessment Tool of Rheumatoid Arthritis Disease Activity: Handgrip Strength Measured By a Smartphone Connected to a Dynamometer. Francisco Espinoza Sr. [1], Yves-marie Pers Sr. [2], Pierre LeBlay Sr. [2] and Christian Jorgensen[2]. [1]Rheumatology Department, Division of Internal Medicine, School of Medicine, University of Los Andes, Santiago, Chile, [2]Clinical Immunology and Osteoarticular Diseases Therapeutic Unit, CHU Lapeyronie., Montpellier, France.

Background/Purpose: Patient self-management should become a key component of rheumatology care. Development of modalities using personal technologies resources represents an attractive way to assess periodic disease's activity. We previously developed a Smartphone application and a software to measure the dominant handgrip strength in rheumatoid arthritis (RA) patients. This pilot-study was performed in healthy and RA volunteers for testing and calibrating the system with a classical dynamometer. Then using this novel handheld device, we conducted an exploratory study to correlate RA disease activity with handgrip strength. Here we present our preliminary results.

Methods: We included 50 patients with RA. All patients fulfilled the 2010 ACR/EULAR criteria for RA. We excluded patients with health issues that could affect the test (hand or wrist surgery, myopathy, carpal tunnel syndrome, etc). Patients received visual and audio instructions from the Smartphone application and one-trained operator was present. The 28-joint disease activity score (DAS28) and modified Health Assessment Questionnaire (mHAQ) were measured for all participants. Linear regression and Two-Way ANOVA test were performed. The results were adjusted by age and sex.

Results: 96% of patients were females. Mean age was 62,59 + 12,9. Mean DAS28 was 3,41 ± 1,38 and 38% of patients were in remission (DAS28<2,6). 22% were treated with Methotrexate or Leflunomide and 76% were treated with a bDMARD in association or not with a sDMARD. No patients reported difficulties or pain performing the test. Mean duration of the test was 3.5 minutes ± 0.22 and handgrip strength level was 9,63 ± 5,49 Kg. A significantly negative correlation between the index of handgrip strength test and DAS28 was identified ($r=-0.79, -0.85$ to -0.34, $p<0,01$). We observed a significant correlation with the mHAQ ($r=0.85$, 0,67 to 0,96, $p<0,01$). In a subgroup of 15 patients we evaluated the handgrip strength after treatment modifications or disease flare-up exacerbations and we founded a significantly correlation with DAS28 changes ($r=-0.93$, -0.76 to -0.54, $p<0.001$). Ultimately we observed a tendency to correlate index of handgrip strength, adjusted by age and sex, and the presence of ultrasonography synovitis in a subgroup of 10 patients ($p=0.076$).

Conclusion: Our preliminary data showed that Smartphone self-evaluation of handgrip strength is a feasible way to assess RA disease activity. Moreover, we will continue to follow longitudinally our RA patients in order to determinate if this test could be used to detect flare-up or response to treatment. Then, we will validate this simple tool of self-assessment RA activity in a larger outpatients cohort.

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Neuroendocrine Hormone and Metabolic Peptide Levels in the Earliest Phases of Rheumatoid Arthritis – Do Free Fatty Acids Play a Role? Man Wai Tang[1], Frieda A. Koopman[2], Jan P.M. Visscher[2], Marjolein J.H. de Hair[2], Danielle M. Gerlag[2] and Paul P. Tak[2]. [1]Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with several neuroendocrine hormones and metabolic peptides. The crosstalk between the hormones and the immune system is important for homeostasis during inflammation. Therefore, we hypothesize that disturbances in hormones may gradually result in an inflammatory disease and hormones may be even disturbed years before onset of arthritis. The aim of this study is to determine the hormone levels in RA patients and individuals at risk for developing RA and compare those with the levels in healthy controls.

Methods: In total 18 neuroendocrine hormones and metabolic peptides (triglycerides (TG), free fatty acids (FFAs)) and pancreatic polypeptide (PP) were measured in fasting serum samples from 22 RA patients, 45 individuals at risk for developing RA by the presence of RA-specific autoantibodies and 16 healthy controls.

Results: The median (IQR) PP level was significantly higher in RA patients (34 (23–58) pmol/L) and individuals at risk (31 (24–45) pmol/L) compared to healthy controls (10 (6–27) pmol/L), respectively $P=0.004$ and $P=0.002$. The TG level was significantly higher in RA patients (1.03 (0.75–1.29) mmol/L) and a trend towards elevated TGs in individuals at risk (0.94 (0.72–1.15) mmol/L) compared to healthy controls (0.70 (0.59–1.02) mmol/L), respectively $P=0.036$ and $P=0.09$. The FFA level was significantly higher in RA patients (0.59 (0.47–0.65) mmol/L) compared to healthy controls (0.40 (0.35–0.50 mmol/L; $P=0.011$) and a trend towards elevated FFAs in individuals at risk (0.53 (0.40–0.59) mmol/L; $P=0.06$)compared to healthy controls. In RA patients, the FFA level was positively correlated with disease activity parameters, but not confounded by body mass index or other variables. All other hormones and peptides were comparable between the three study groups.

Conclusion: FFA, TG and PP levels were higher in RA patients than in healthy controls. PP levels were higher in at risk individuals than in healthy controls and FFA and TG levels showed a similar trend. Moreover, the FFA level was positively correlated with disease activity parameters. This may support a role for FFAs, TGs and PPs in the pathogenesis of RA and these peptides may contribute, even in the at risk phase of RA, to the increased risk of cardiovascular diseases. Furthermore, PPs and FFAs can be potential biomarkers to identify individuals in the at risk phase of RA, who may develop RA later on.

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Influence of Body Mass Index on Disease Activity and Radiographic Joint Damage in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Celine Vidal[1], Thomas Barnetche[2], Jacques Morel[3], Bernard Combe[3] and Claire Daien[1]. [1]Hopital Lapeyronie, Montpellier, France, [2]Rheumatology department, Bordeaux University Hospital, bordeaux, France, [3]Hôpital Lapeyronie, Montpellier, France.

Background/Purpose: Overweight and obesity in patients with rheumatoid arthritis (RA) are rising conditions. Adipose tissue has pro inflammatory properties by producing adipokines which could play a role in RA activity. The prognosis of overweight and obese patients with RA is not well established.

Methods: We conducted a systematic review and meta-analysis to assess the influence of body mass index on disease activity (DAS 28) and radiographic joint damage (RJD) in patients with RA. We searched MEDLINE and The Cochrane Database publications up to April 2014 with MeSH terms ("body mass index" OR "obese") AND "rheumatoid arthritis". Studies reporting DAS 28 and/or its components, Health Assesment Questionnaire (HAQ) and RJD according to body mass index (BMI)groups were included. Two investigators abstracted data and rated study quality and applicability. Statistical analysis used weighted mean differences with a fixed or random effects model, except for radiographic analysis in which standardized means were used as different radiographic scores were assessed in studies.

Results: Among the 579 citations retrieved with MeSH terms, 52 articles suited inclusion criteria and 7 of them were included in meta-analysis. Activity was assessed in 4 studies, involving 1402 patients, and revealed an association between obesity in RA and higher DAS 28 (+ 0.14, $p=0.04$, $I^2=0\%$).Health Assessment Questionnaire (HAQ) was evaluated in 2 studies, involving 1264 patients, and also revealed a positive association with obesity (+ 0.1, $p=0.03$, $I^2=0\%$). RJD was reported in 4 studies, involving 1465 patients, revealing a negative association with obesity ($p=0.03$, $I^2=38\%$). According to the systematic review, the increase of DAS 28 could be explained by an increase of tender joint counts and global health assessment.

Conclusion: Obesity in RA is associated with higher DAS 28 and HAQ. However, obese patients with RA have lower RJD. This increase of DAS28 in obese patients could be explained by pro inflammatory fat cytokines or the general tendency of higher pain levels due to comorbidities resulting from obesity. Conversely, the increase of adiponectine observed in obese patients

may play a protective role on joint damage. Altogether, this work highlights the importance of obesity on RA prognosis and supports the need of future studies to better understand the mechanisms behind.

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Very Low or High Body Mass Index Negatively Affects patients' Ability to Achieve Sustained Remission in Early RA in a Multicenter Canadian Cohort. Susan M. Goodman[1], Yan Ma[1], Wei Zhang[1], Elizabeth Schulman[2], Janet E. Pope[3], Carol Hitchon[4], Susan J. Bartlett[5], Boulos Haraoui[6], Daming Lin[7], Gilles Boire[8], Diane Tin[9], J. Carter Thorne[10], Shahin Jamal[11], Edward C. Keystone[12] and Vivian P. Bykerk[1]. [1]Hospital for Special Surgery, New York, NY, [2]New York Presbyterian - Cornell Campus - HSS, New York, NY, [3]St Joseph Health Care, London, ON, [4]University of Manitoba, Winnipeg, MB, [5]Johns Hopkins University, Baltimore, MD, [6]University of Montreal Hospital Centre, Montreal, QC, [7]Mount Sinai Hospital, University of Toronto, Toronto, ON, [8]CHUS - Sherbrooke University, Sherbrooke, QC, [9]Southlake Regional Health Centre, Newmarket, ON, [10]Southlake Regional Health Centre, Newmarket, Newmarket, ON, [11]Vancouver General Hospital, Vancouver, BC, [12]University of Toronto, Toronto, ON.

Background/Purpose: To determine if patients with a very low body mass index (BMI) (<18.5) or high BMI (≥ 25) are able to achieve sustained remission (susREM) in an early RA (ERA) cohort.

Methods: Initial BMI and disease activity (DAS28) were prospectively measured over 3 years in patients from CATCH (Canadian Early Arthritis Cohort). Patients were categorized into 6 groups based on World Health Organization BMI classifications (class 1–6) Differences between BMI groups in patients' demographics and clinical outcomes were assessed using Chi-square/Fisher's exact tests or Kruskal-Wallis tests. Multivariate regression based on generalized estimating equations (GEE) methods was used to compare the likelihood of achieving susREM between groups, where susREM was defined as DAS28<2.6 × 2 at consecutive visits 3–12 months apart.

Results: 944/2524 eligible patients with a measured BMI and ≥ 2 consecutively measured DAS28 scores over 3 years formed the study cohort. Only 15 (2%) patients were underweight (category (Cat) 1). Overall 65% were either overweight (34% in Cat 3) or obese (31% in Cat 4–6), representing a rate higher than the WHO reported 47% national average. Patient characteristics in the 6 BMI categories were studied (**Table 1**). Univariate analysis, presented for BMI strata show patients with higher BMI were older (p<0.0001), more often female (p<.001) with worse function at baseline by HAQ-DI (p<001). Those with very low or high BMI had a higher CRP (p=0.0004) and ESR (p<0.001), and those with low or normal BMI were more often smokers (p<0.0001). Patients in the highest BMI strata had higher Patient Global Assessments of disease (PtGA) (p=0.03) and pain (p=0.04). Variables that did not differ among groups included Physician's Global assessments (MDGA)(p=0.9), ACPA and RF positivity [(p=0.16)],(p=0.26)], symptom duration (p=0.66), DAS28 (p=0.06) at study entry, or steroid (p=0.3) or methotrexate (MTX) use (p=0.9) over the first 3 months. In the multivariate analysis patients in all BMI categories except for class 4 (p value=0.678 were significantly less likely to achieve susREM compared to normal BMI. Early MTX use, not smoking, being Caucasian and achieving a low disease activity state (LDAS) by 6 months increased the odds of achieving susREM (**Table 2**).

Conclusion: The chance of achieving sustained remission is decreased in underweight, and overweight / obese ERA patients, more so in the morbidly obese (class 5–6). Early use of MTX, an early response to treatment, and non-smoking status improve the odds of sustained remission independent of BMI. BMI should be considered among the modifiable risk factors for poor RA outcomes.

Table 1: Characteristics of ERA patients in CATCH based on WHO BMI Categories (Univariate Analysis)

WHO Category	BMI 1 (<18.5)	BMI 2 (18.5 ≥ and <25)	BMI 3 (25 ≥ and <30)	BMI 4 (≥ 30 and <35)	BMI 5 (≥ 35 and <40)	BMI 6 (≥ 40)	
Baseline Variables*	**Underweight (N=15)**	**Normal (N=314)**	**Overweight (N=323)**	**Obese I (N=175)**	**Obese II (N=74)**	**Obese III (N=42)**	**p-Value****
Age	**47.4 (17.8)**	**49.7(16.6)**	**55.2 (14.5)**	**54.9 (13.2)**	**51.5(13.9)**	**52.3(10.3)**	**0.0001**
DAS28	**5.4 (1.5)**	**4.8 (1.6)**	**5.0 (1.5)**	**5.1 (1.4)**	**5.3(1.5)**	**5.2(1.3)**	**0.0610**
Female	**16 (100%)**	**255 (82%)**	**205(64%)**	**112(64%)**	**57(77%)**	**34(81%)**	**<.001**
Caucasian	**12 (75%)**	**241 (77%)**	**264 (82)%**	**137(79%)**	**58(78%)**	**33(78%)**	**0.0004**
Smoker***	**3 (18.8%)**	**62 (19.8%)**	**55 (17%)**	**27(15.4%)**	**6(8.1%)**	**6(14.3)**	**0.0001**
ESR(mm/h)	**42.7(27.8)**	**24.9 (24.3)**	**27.8 (23.4)**	**26. 7 (20.6)**	**28.6(22.1)**	**31.8(21.7)**	**0.0014**
RF	12 (75%)	163 (57%)	187 (63%)	104(63%)	36(52%)	26(65%)	0.2616
Anti-CCP	12 (86%)	147 (64%)	149 (67%)	80(64%)	29(54%)	16(53%)	0.1682
Caucasian	**12(75%)**	**241(77%)**	**264(81.7%)**	**137(79%)**	**58(78%)**	**33(78%)**	**0.0004**
CRP (U/L)	**18.3(22.6)**	**12 (18.1)**	**16.8 (21.8)**	**13.6 (17.1)**	**11.5(13.3)**	**17.6(17.8)**	**0.0004**
PtGA (0–10)	5.2(3.3)	5.6 (3)	5.8 (2.9)	6.1(3)	6.3(2.8)	6.5(2.4)	0.1873
Pain (0–10)	**5(3.2)**	**5.2(2.8)**	**5.5 (2.9)**	**5.5(2.9)**	**6.3(2.6)**	**6.2(2.3)**	**0.0416**
HAQ-DI	**0.8 (0.7)**	**0.9 (0.7)**	**1.0 (0.7)**	**1.0(0.8)**	**1.2(0.6)**	**1.2(0.7)**	**0.0011**
MDGA	5.3 (2.7)	5.0 (2.5)	5.1 (2.5)	5.0(2.5)	5.4(2.6)	5(2.2)	0.9392
MTX use	12 (75%)	226 (72%)	243 (75%)	130(74%)	55(74%)	32(76%)	0.9588

*Results presented as mean(SD) or n(%); **groups compared using Chi-square/Fisher's exact tests or Kruskal-Wallis tests; ***current smoker

Table 2: Multivariate regression (GEE): Both high and low BMI were associated with a lower odds of achieving sustained remission

Variables*	OR (95% CI)	p-value**
BMI Category 1 vs. 2* **	**0.55(0.31–0.96)**	**0.0361**
BMI Category 3 vs. 2	**0.75(0.63–0.90)**	**0.0022**
BMI Category 4 vs. 2	0.82(0.67–1.01)	0.0678
BMI Category 5 vs. 2	**0.50(0.37–0.67)**	**<.0001**
BMI Category 6 vs. 2	**0.36(0.24–0.53)**	**<.0001**
Function (HAQ-Di) 0–3	**0.54(0.45–0.64)**	**<.0001**
Pain (0–10)	**0.94(0.89–0.99)**	**0.0369**
Achieved LDAS by 6 months (DAS28<3.2)	**5.36(4.57–6.29)**	**<.0001**
Age	**0.98(0.98–0.99)**	**<.0001**
Female Gender	**0.55(0.46–0.66)**	**<.0001**
Non-Caucasian vs. Caucasian	**0.45(0.35–0.56)**	**<.0001**
Never/Ex-Smoker	**1.52(1.23–1.87)**	**<.0.0001**
Received Methotrexate over first 3 months	**1.72(1.43–2.05)**	**<0.0001**

Variables remaining significant using multivariable regression using generalized estimating equations (GEE) controlling for BMI categories, function, pain, LDAS, age, gender, race, income, smoking, MTX use* Statistical significance measured using Chi-Square; ** Comparison of BMI groups where normal BMI is referent ***

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Could Osteoprotegerin and TNF-Related Apoptosis-Inducing Ligand Assessments Help Us to Manage Early Rheumatoid Arthritis? Results from the Espoir Cohort. Rachel Audo[1], Claire I. Daien[2], Laura Papon[1], Cédric Lukas[3], O Vittecoq[4], B Combe[5] and Jacques Morel[5]. [1]IGMM, CNRS UMR5535, Montpellier, Montpellier, France, [2]Lapeyronie Hospital, Montpellier, France, [3]Hopital Lapeyronie, Montpellier, France, [4]Rouen University Hospital & Inserm U905, Rouen, France, [5]Hôpital Lapeyronie, Montpellier, France.

Background/Purpose: TNF-Related Apoptosis Inducing Ligand (TRAIL) is a member of the TNF familly. Its soluble receptor Osteoprotegerin (OPG) also inhibits Receptor activator of nuclear factor kappa-B ligand (RANKL). We previously reported that, in a cohort of early arthritis (< 2 years), a high OPG/TRAIL ratio at baseline was associated with remission (DAS28<2.6) at 6 months, suggesting that OPG and TRAIL could be used to predict outcomes in early arthritis.

Methods: The aim of this study was to confirm these results in the larger French cohort ESPOIR. To be included, patients should have an early arthritis (< 6 months). We studied patients clinical status at 12 months (M12) and radiographic progression (Sharp's score) at 24 months (M24). TRAIL and OPG concentrations in serum were measured at baseline (M0). Values of TRAIL and OPG were log transformed to be normalized. We first compared TRAIL and OPG between patients with arthritis responding to ACR/EULAR

2010 criteria (RA) and undifferentiated arthritis (UA). We then compared logOPG, logTRAIL and logOPG/logTRAIL using general linear model adjusted for DAS28, rheumatoid factor and anti-citrullinated protein antibodies positivity, and total Sharp score at M0. Logistic regression was used to determine predictive value for remission (DAS28 ≤2.6) and radiographic progression (DSharp score >0).

Results: TRAIL, OPG and TRAIL/OPG at M0 were not different between RA (n = 641) and UA patients (n = 53). Among RA patients, patients in remission at M12 had a significantly lower concentration of M0 logOPG than those with DAS28 >2.6 (2.93±0.18 (n=204) vs 2.98±0.16 pg/ml (n=341), respectively, p=0.002 and p=0.026 after adjustment). M0 TRAIL and M0 OPG/TRAIL were not significantly different between patients in remission at M12 and others. Logistic regression adjusted for DAS28, rheumatoid factor and anti-citrullinated protein antibodies positivity, and total Sharp score at M0 showed that logOPG≥3.1 (=1259 pg/ml) was predictive of absence of M12 remission (B=0.55, CI: 0.33–0.90, p=0.018), with a sensibility of 21%, a specificity of 87%, a positive predictive value of 75% and a negative predictive value of 38%.

Patients with progression of Sharp score erosion at M24 had significant lower M0 logTRAIL (2.96±0.22 vs 3.00±0.19, p=0.009 and p=0.002 after adjustment). M0 OPG and M0 OPG/TRAIL were not significantly different between patients with or without radiographic progression at M24. Logistic regression adjusted for DAS28, rheumatoid factor and anti-citrullinated protein antibodies positivity, and total Sharp score at M0 showed that logTRAIL≤2.95 (891 pg/ml) was predictive of erosion progression (B=0.47, CI: 0.30–0.72, p=0.001) with a sensibility of 52%, a specificity of 63%, a VPP of 39% and a VPN of 74%.

Conclusion: Concentrations of TRAIL and OPG could not help in distinguish UA and RA. Low M0 OPG is associated with remission at M12 and low TRAIL is associated with erosion progression at M24 after multiple adjustments for usual prognosis factors. This suggests a promoting effect of OPG on disease activity and a protective role of TRAIL on bone erosion. However, no relevant threshold could be determined to use OPG and TRAIL in daily practice to identify early RA patients at risk of poor outcomes.

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Disease Activity Scoring: Comparing Patient and Physician Global Assessment of Disease Activity in Rheumatoid Arthritis. Boulos Haraoui[1], Denis Choquette[1], Jean-Pierre Raynauld[1], Jean Pierre Pelletier[1], Louis Bessette[2], Edith Villeneuve[1], Marie-Anaïs Rémillard[1], Isabelle Fortin[3], Diane Sauvageau[1] and Louis Coupal[1]. [1]Institut de rhumatologie de Montréal (IRM), Montréal, QC, [2]Centre d'ostéoporose et de rhumatologie de Québec (CORQ), Québec, QC, [3]Centre de rhumatologie de l'est du Québec (CREQ), Rimouski, QC.

Background/Purpose: Visual analogue scales (VAS) are routinely used in daily clinical practice and are part of the different composite outcome measures. Studies often report weak to moderate positive correlations between physician and patient assessment of disease activity. It is thought that they are driven by different considerations such as pain, fatigue and mental status for patients and objective measures such as joint counts and CRP/ESR for physicians. While absolute values of patient and physician global disease activity do not always correlate, changes may offer a better correlation. We evaluated those changes in RA patients initiating a first anti-TNF.

Methods: We extracted from the RHUMADATA® clinical database and registry patient and physician global assessments of disease activity of RA patients treated for at least 6 months with a first anti-TNF agent (adalimumab, etanercept or infliximab). Pearson correlations coefficients between pre, post and pre-post changes in patient and physician assessments were computed (SAS v 9.13) and compared. We used t-tests to verify if pre-post differences in global assessments were related to disease duration (less or equal to two years vs greater than two years), age (less or equal to 50 years vs greater than 50 years), gender and DAS 28 (less or equal to 3.2 vs greater than 3.2). A general linear model (GLM) was used to further assess if disease duration, age, gender and DAS score explained the discrepancies in physician and patients pre-post global assessments differences.

Results: The global disease activity scores from 83 patient-physician pairs were available for this analysis. Pre-treatment assessments were made within 0 and 176 days (mean 33 days) of biologic initiation while post treatment assessments occurred between 182 and 799 days (mean 268 days). Patient and physician pre, post, and pre-minus-post global assessment means and standard deviations are presented. The pre and post and change treatment Pearson correlations coefficients between patient and physician assessments are respectively r2=0.34 (p=0.001), r2=0.19 (p=0.08) and 0.15 (p=0.19).

Physician and patient global disease activity assessment

	Physician		Patient		Difference (patient-physician)	
	Mean	StdDev	Mean	StdDev	Mean	StdDev
Pre-treatment	5.27	1.98	5.58	2.96	0.31	2.94
Post-treatment	1.42	1.79	3.79	2.81	2.37	3.02
Difference (post-pre)	−3.85	2.31	−1.79	2.95	–	

Physician pre-post differences in global assessment were not significantly different across disease duration, gender, age and DAS scores. Similar results were observed in the patient assessments except for disease duration. Smaller differences were observed in subjects having a disease duration of two years or less. The GLM revealed that no factors other than rater (physician or patient) explained the observed differences.

Conclusion: While the pretreatment initiation global disease activity assessments showed moderate correlation, the change in these assessments exhibited a weak relationship. Both physicians and patients agree on disease activity improvement although their magnitudes differ. Of the factors explored, only rater (physician or patient) seem to explain these differences.

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Th9 Lymphocytes in Rheumatoid Arthritis. Rossella Talotta[1], Angela Berzi[2], Fabiola Atzeni[1], Donata Dell'Acqua[1], Piercarlo Sarzi-Puttini[1] and Daria Trabattoni[2]. [1]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy, [2]Chair of Immunology, Department of Biomedical and Clinical Sciences "L. Sacco, Milan, Italy.

Background/Purpose: Th9 cells are IL-9-secreting Th lymphocytes that are involved in the immunological responses underlying parasitic infections and allergic diseases. In the case of autoimmune diseases, Th9 cells seem to be involved in the pathogenesis of experimental autoimmune encephalomyelitis. No study has yet evaluated the effects of Th9 responses in rheumatic diseases such as rheumatoid arthritis (RA). The aim of this study was determine the prevalence of Th9 lymphocytes in RA patients and identify their possible association with the discontinuation of biological treatment with infliximab (IFX).

Methods: We enrolled 55 consecutive RA outpatients: 15 not receiving any immunosuppressive drug; 20 responders to IFX treatment; and 20 who had discontinued IFX because of adverse events or inefficacy and were being treated with other biological agents (ABA, TCZ, ETN or CTZ) and traditional immunosuppressive drugs. The matched control group consisted of 10 healthy subjects. After giving their informed consent, the subjects underwent blood sampling for the isolation of peripheral blood mononuclear cells (PBMCs). The PBMCs were cultured with/without IFX 50 ƒÝg/L for 18 hours, and the percentage of Th9 cells was assessed by means of flow cytometry. Th9 lymphocytes were identified as IFNγ-, IL4-, IL17-, IL9-secreting CD4+ T cells.

Results: Cytometric analysis revealed no significant decrease in the percentage of Th9 cells after IFX exposure in any of the groups, but there were significantly fewer cells in the healthy controls than the RA patients both before and after the IFX stimulation assay (Fig.1). The higher frequency of Th9 cells in the patients was not associated with higher levels of anti-nucleus autoantibodies or other auto-antibody subsets, or with a higher likelihood of experiencing an adverse event or lack of efficacy on IFX treatment.

Conclusion: IL-9 levels are increased in RA patients, in whom it plays a crucial role. Th9 cells are the major producers of IL-9, and their prevalence is higher in RA patients than in healthy subjects, although they do not seem to affect the outcome of biological therapies.

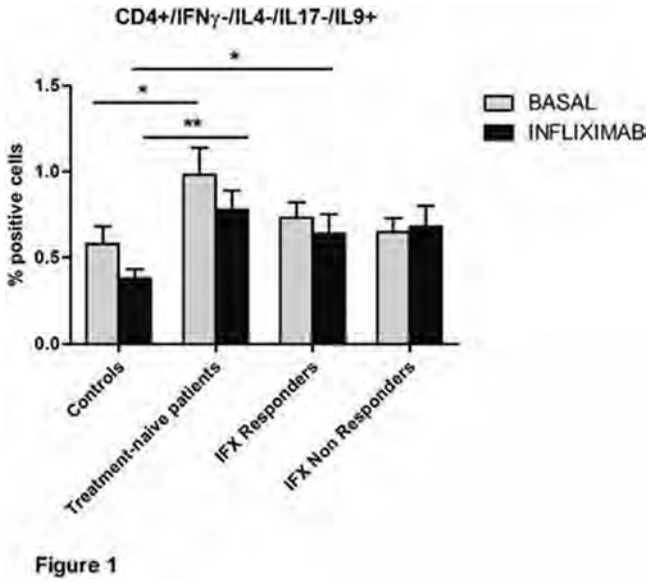

Figure 1

Figure 1. The percentage of IFNγ-, IL4-, IL17-, IL9-secreting CD4+ T cells in RA patients and healthy controls under unstimulated and IFX-stimulated conditions. Mean values ±SE. *p <0.05; **p <0.01 (Student's t test)

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Anti-Rheumatic Therapy Decreases Syndecan-1 Shedding in Rheumatoid Arthritis (RA). Ivana Hollan[1], Gunnbjørg Hjeltnes[2], Torstein Lyberg[3], Stefan Agewall[3], Allan Wiik[4], Knut Mikkelsen[1], Øystein T. Førre[5], Tram T. Vuong[3] and Svein O. Kolset[3]. [1]Lillehammer Hospital for Rheumatic Diseases, Lillehammer, Norway, [2]Innlandet Hospital Trust, Lillehammer, Norway, [3]University of Oslo, Oslo, Norway, [4]Statens Serum Institute, Copenhagen S, Denmark, [5]Oslo University Hospital, Oslo, Norway.

Background/Purpose: Intact glycocalyx is of importance for healthy endothelial function. Changes in the endothelial glycocalyx, characterized by increased levels of circulating syndecan-1, might be related to accelerated atherosclerosis in RA. The aim of this study was to examine the level of serum (s-) syndecan-1 in patients with RA, and the effect of anti-rheumatic treatment on the s-syndecan-1 levels.

Methods: We selected 32 patients with active RA from the Norwegian observational PSARA study. Due to clinical decision, the patients should start either with methotrexate or methotrexate (MTX) and anti-tumor necrosis factor (TNF) regimen. The patients were examined before the treatment initiation (visit 1) and after 6 weeks (visit 2) of the treatment. S-syndecan-1 was measured by ELISA.

Results: The mean age of the patients was 59±8 years, and 27% were men. 12 patients recieved MTX and 20 recieved MTX and anti-TNF treatment. S-syndecan-1 levels significantly decreased from visit 1 (49 ± 52 ng/ml) to visit 2 (45±50 ng/ml), p=0.047. The difference was independent of age, sex and difference in DAS28. The s-syndecan-1 reduction was greater in the MTX than MTX and anti-TNF group (10 ± 13 vs. 1 ± 1 ng/ml), p=0.048.

Conclusion: Anti-rheumatic treatment reduces s-syndecan-1 in RA. Thus, a glycocalyx ameliorating effect may contribute to the reduction of cardiovascular morbidity and mortality due to anti-rheumatic treatment. In theory, the greater reduction of s-syndecan-1 in the MTX than in the combined group might be due to differences in patient population, as patients starting with MTX are likely to have a less severe RA, with a shorter disease duration, than those starting with anti-TNF. Interestingly, although MTX is considered as a less potent anti-rheumatic drug than anti-TNF, it may have a protective effect on glycocalyx, which may explain its cardioprotective effect observed in previous studies. This effect might be at least partially independent of its anti-inflammatory properties.

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Lipid Concentrations and Particle Sizes in Drug Naive Patients with Rheumatoid Arthritis. Aulikki Kononoff[1], Hannu Kautiainen[2], Pasi Soininen[3], Antti Kangas[4], Leena Laasonen[5], Leena Arstila[1], Pia Elfving[1], Elina Savolainen[6], Helena Niinisalo[7], Mika Ala-Korpela[4] and Oili Kaipiainen-Seppanen[1]. [1]Department of Medicine, Kuopio University Hospital, Kuopio, Finland, [2]Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland, [3]Computational Medicine, Institute of Health Sciences, University of Oulu, Oulu, Finland, [4]NMR Metabolomics Laboratory, School of Pharmacy, University of Eastern Finland, Kuopio, Finland, [5]Helsinki Medical Imaging Center, Helsinki University Hospital, Helsinki, Finland, [6]Kuopio Municipal Hospital, Kuopio, Finland, [7]Suonenjoki Health Center, Suonenjoki, Finland.

Background/Purpose: Excess mortality attributed to cardiovascular causes has been described among patients with rheumatoid arthritis (RA). Atherosclerotic lipid profile has been reported in patients with drug naïve RA without comorbidities. In a European study on inflammatory and atherogenic lipoprotein markers, patients with RA had significantly higher levels of small, dense LDL and lower levels of large, light LDL than controls. The size of LDL particles was smaller in RA patients compared to controls. We have investigated lipid concentrations and particle sizes among patients with newly diagnosed RA in a population based cohort.

Methods: Concentrations and sizes of lipoprotein subclass particles were analyzed by proton nuclear magnetic resonance spectroscopy of native serum samples from patients with RA participating in Northern Savo 2010 Study.

Results: Sixty-three patients, 34 female and 29 male patients with RA satisfying the ACR/Eular 2010 classification criteria were divided into tertiles according to the disease activity measured by DAS28 (<3.9, 3.9–4.7, >4.7). Small LDL concentrations were lowest in the tertile with the highest disease activity, p= 0.031, and the particle size in LDL also increased with increasing disease activity, p<0.001. In HDL, the total, medium and small particle concentrations showed a linear decrease along with the disease activity, p=0.0012, 0.0079 and <0.001, respectively.

Conclusion: Marked changes in lipid concentrations and particle sizes occurred in drug naïve patients with RA and they were associated with disease activity.

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Clinical Utility of 14-3-3η in the Evaluation of Inflammatory Arthritis. Lance Feller[1], Paul Tuttle IV[2] and Terry L. Moore[2]. [1]Saint Louis University, St. Louis, MO, [2]Saint Louis University, Saint Louis, MO.

Background/Purpose: 14-3-3 proteins are chaperonins found in all eukaryotic cells. There are multiple isoforms which are thought to be involved in intracellular signaling and transcription regulation. Among their targets are phosphatases, kinases and transmembrane receptors. There are seven known isoforms in mammals. Recent work has implicated the η (Eta) isoform as having diagnostic potential in inflammatory arthritis. In this study we investigated the utility of measuring 14-3-3η when evaluating of inflammatory arthritis.

Methods: Measurements of 14-3-3η were obtained during evaluation of joint pain in patients presenting between July 2013 and May of 2014. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP Ab) were measured. Joint imaging was evaluated for erosive changes. A chart review was later conducted to evaluate the utility of standard measures versus 14-3-3η.

Results: 120 patients were evaluated. 21 had RA, 8 had juvenile idiopathic arthritis (JIA), and 6 had psoriatic arthritis (PsA). 30 patients had connective tissue disease (CTD). 10 had fibromyalgia (FMS), 3 had mono-

clonal gammopathies, 1 had enteropathic arthritis, and 1 had erosive osteoarthritis (OA). 8 had only OA, 2 had benign hypermobility syndrome, 1 had amyopathic dermatomyositis, 2 had celiac disease, and 2 had crystal induced arthropathies. 7 were antinuclear antibody (ANA) positive without synovitis or CTD. 3 patients had granulomatosis with polyangiitis, 2 had suspected PsA, 2 had chronic urticaria, and 11 had no associated condition.

Of the 21 RA patients, 18 were RF positive, 16 were anti-CCP Ab positive, and 16 were 14-3-3η positive. All 16 14-3-3η positive patients with RA were RF positive. 9 had joint erosions, of which 8 were RF, anti-CCP Ab and 14-3-3η positive. 14-3-3η was 76.2% sensitive for RA, and 89% specific. Its positive predictive value (PPV) was 61.5%, and negative predictive value (NPV) was 94.2%. 4 of the 8 JIA patients were 14.3.3η and RF positive. 4 were also anti-CCP Ab positive, of which 2 had measurable 14-3-3η. 3 JIA patients had joint erosions. When JIA and RA were considered together, the sensitivity and specificity of 14-3-3η was 68.9 and 89% respectively, while PPV and NPV were 66.7 and 90%. The correlation of 14-3-3η and RF titers in RA was 0.63 ($p<0.01$) and 0.65 ($p<0.001$) in the combined RA/JIA cohort.

All 6 patients with PsA were seronegative. 2 had joint erosions.

30 patients had CTD; 6 were RF positive, 2 were anti-CCP Ab positive, and 5 were 14-3-3η positive. 3 of the five 14-3-3η positive patients also produced RF, while 1 had anti-CCP Ab.

All FMS patients were seronegative. Of the 8 patients with purely OA, 1 had 14-3-3η. 1 patient with celiac disease had 14-3-3η. 1 patient with a positive ANA and joint pain had 14-3-3η. 1 patient with joint pain and no evidence of synovitis produced 14-3-3η.

Of the 17 patients with RF without RA, 10 were positive for 14-3-3η, while 6 produced anti-CCP Ab.

Conclusion: 14-3-3η protein titers are associated with RA. Their general trend follows RF. Based upon the results from our study, 14-3-3η is both sensitive and specific for RA, with value in evaluating JIA as well. A larger sample size is necessary to evaluate utility with JIA.

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Association of Anti-Thyroid Autoantibodies with Fibromyalgia in Rheumatoid Arthritis. Jowairiyya Ahmad[1], Helena Blumen[2], Claudene George[3], Asha Shrestha[1] and Clement Tagoe[4]. [1]Albert Einstein College of Medicine/Montefiore Medical Centre, Bronx, NY, [2]Albert Einstein College of Medicine, Bronx, NY, [3]Albert Einstein College of Medicine/Montefiore Medical centre, Bronx, NY, [4]Albert Einsetin College of Medicine/Montefiore Medical Centre, Bronx, NY.

Background/Purpose: Autoimmune thyroiditis has been linked independently with fibromyalgia and chronic widespread pain. We studied how the presence of autoimmune thyroiditis affects the clinical presentation of rheumatoid arthritis with particular reference to chronic pain syndromes.

Methods: We studied a cohort of 203 patients with a diagnosis of rheumatoid arthritis for whom the presence or absence of autoimmune thyroid antibodies was documented. The relationships between thyroid autoantibodies and the presence fibromyalgia and chronic widespread pain were examined. Logistic regression analyses were performed to determine the statistical significance of these associations.

Results: In our sample of 203 patients, we identified 34% of patients who tested positive for anti-thyroid peroxidase antibodies (anti-TPO). Thirty five percent of patients tested positive for anti-thyroglobulin antibodies (anti-TG). Among the thyroid autoantibody-positive patients, 37 % had a diagnosis of fibromyalgia or chronic widespread pain. Additional patient variables considered included age, sex, body mass index (BMI) and the presence of comorbidities, including type II diabetes.

Logistic regression analyses (adjusted by age, sex, diabetes and BMI) indicated that anti-TPO positive patients were more likely to be diagnosed with fibromyalgia and report the presence of chronic widespread pain, with an odds ratio of 3.42, 95% *CI* (1.665–7.017), $p < .001$. The odds ratio between anti-TG and fibromyalgia was not significant, $p > .05$. Patients who were either anti-TPO or anti-TG positive were more likely to be diagnosed with fibromyalgia with an odds ratio of 2.70, *CI* (1.193–6.082), $p < .05$.

When adjusted for degenerative disc disease, patients who were either anti-TPO or anti-TG positive were more likely to be diagnosed with fibromyalgia with an odds ratio of 2.508, CI (1.094–5.749), $p < .05$. Similarly patients with anti-TPO were more likely to have fibromyalgia with an adjusted OR of 3.356, CI (1.608–7.003), $p < .05$.

Conclusion: There is a strong positive association between the presence of anti-thyroid autoantibodies and hence autoimmune thyroiditis, with fibromyalgia syndrome and chronic widespread pain in patients with established rheumatoid arthritis.

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Can GP88 (Progranulin) be Used As a Biomarker for the Diagnosis and Therapy Evaluation of Rheumatoid Arthritis? Masao Sato[1], Masao Takemura[1], Kuniaki Saito[2] and Yasuko Yamamoto[2]. [1]Matsunami Reserch Park, Gifu, Japan, [2]Kyoto University, Kyoto, Japan.

Background/Purpose: GP88 (progranulin; PGRN), a glycoprotein with a molecular weight of approximately 88000, is suggested to play an important role in the immune response and growth of tumors. Recently, its high affinity for the tumor necrosis factor receptor has been reported and there have been studies on its anti-inflammatory effects in autoimmune diseases. The objectives of the present study were to measure serum PGRN levels in rheumatoid arthritis (RA) patients, to analyze the changes of PGRN levels in RA patients treated with biological products, and to analyze whether PGRN is useful as a biomarker for the diagnosis and therapy evaluation of RA.

Methods: Serum PGRN levels were measured using ELISA in 149 healthy subjects (78 men and 71 women) who underwent health checkups (controls) and in 68 RA patients and 24 knee osteoarthritis (OA) patients before the start of treatment, who met the 2010 ACR/EULAR classification criteria and visited the arthritis outpatient clinic. Among RA patients who were non-responsive to methotrexate (MTX), the cryopreserved serum samples of 11 patients who were administered infliximab (IFX) were analyzed to determine the PGRN levels during the course of treatment (at baseline, week 6, week 14, week 22, and week 48).

Results: PGRN levels in the controls were 40.5 $\pm$ 14.3 ng/mL in men (mean age, 54.2 years; range, 25–68) and 41.0 $\pm$ 10.9 ng/mL in women (mean age, 51.0 years; range, 28–69), and there were no sex and age differences. PGRN levels were significantly higher in RA patients (51.2 $\pm$ 12.5 ng/mL) than in OA patients (43.9 $\pm$ 5.8 ng/mL) ($p<0.01$) and controls ($p<0.001$). Among the RA patients, 10 women and 1 man (mean age, 62.0 years; range, 27.0–78.0) received IFX treatment. MTX was administered orally at 6–8 mg/week, and IFX was administered at 3 mg/kg. Mean PGRN levels at the different time points were as follows: baseline, 45.0 ng/mL; week 6, 46.4 ng/mL; week 14, 50.8 ng/mL; week 22, 48.9 ng/mL; and week 48, 50.4 ng/mL, and there were no significant changes. Because disease activity was high at week 48 and IFX was considered ineffective, 2 cases received a different biological product. Mean PGRN levels in these 2 cases were as follows: baseline, 60.1 ng/mL; week 6, 61.3 ng/mL; week 14, 68.3 ng/mL; week 22, 74.9 ng/mL; and week 48, 79.5 ng/mL, showing an increasing tendency with the treatment course.

Conclusion: Serum PGRN levels were found to be significantly higher in RA patients than in OA patients and controls. Further, no changes in the PGRN levels were found in the group that showed a good response to IFX treatment. However, in cases resistant to IFX, PGRN levels were high when IFX was introduced, followed by an increasing tendency with the treatment course. Owing to the small number of cases in the present study, it is difficult to obtain a clear result. However, the findings showed the possibility of using PGRN levels for the differential diagnosis of RA patients and the therapy evaluation of IFX.

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Metaflammation, PEDF and Chemerin: Potential Systemic Factors Which Link Obesity to Response to Therapy in Early Rheumatoid Arthritis. Elisa Gremese, Barbara Tolusso, Anna Laura Fedele, Maria Rita Gigante, Silvia Canestri, Clara Di Mario, Angela Carbonella and Gianfranco Ferraccioli. Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy.

Background/Purpose. Obesity per se is a systemic, low-grade inflammatory state and the adipose tissue is an endocrine organ that releases bioactive substances, including pro-inflammatory cytokines, like TNFα and IL6 and specific adipokines. There are only few data about early RA (ERA), suggesting that obesity associates with disease outcomes. In this work we aimed to evaluate whether the body weight, and fat metabolic (PEDF-Pigment Epithelium-Derived Factor) and

meta-inflammatory parameters (Chemerin), could be associated with the outcomes in terms of disease remission and treatment in ERA patients (symptoms duration <12 months).

Methods. 164 ERA patients, treated according to a treat-to-target strategy, were enrolled. At each visit the ACR/EULAR core data set was registered. Baseline BMI was collected and baseline interleukin-6, PEDF and Chemerin plasma levels were evaluated by ELISA's methods.

Results. Of the 164 ERA patients (75.9% female, age 55.4±14.6 years, 34.3% very ERA, 66.9% seropositive, baseline DAS 3.4±1.0), 75 (45.7%) were normal weight, 66 (40.2%) overweight and 23 (14.0%) obese. Overweight and obese patients showed a higher disease activity at baseline compared to normal-weight patients (DAS: 3.6±1.0 vs 3.3±0.9, p=0.02). At baseline, BMI values correlated with baseline PEDF (r=0.33, p<0.001) and chemerin (r=0.31, p<0.001) plasma levels. Moreover, chemerin plasma levels correlated with age (r=0.31, p<0.001), baseline inflammatory markers (IL-6: r=0.28, p<0.001; ESR: r=0.39, p<0.001, CRP: r=0.35, p<0.001), swollen joint count (r=0.26, p<0.001), tender joint count (r=0.23, p<0.001), HAQ (r=0.24, p=0.002), DAS (r=0.34, p<0.001), CDAI (r=0.28, p<0.001) and SDAI (r=0.32, p<0.001). On the other hand, PEDF plasma levels correlated only with age (r=0.35, p<0.001) and baseline inflammatory markers (ESR: r=0.17, p=0.03, CRP: r=0.22, p=0.01). At 6 and 12 months none of the patients had a significant reduction of body-weight. A significant reduction of the disease activity at 6 and 12 months follow-up was observed in the three subgroup of ERA patients (normal-weight, overweight and obese patients). In the same manner, circulating chemerin levels significantly decreased over time; conversely, the circulating levels of PEDF remained unchanged. These findings were observed both in patients reaching and not reaching remission at 12 months of follow up.

Fourteen obese RA patients (BMI 35.3±3.2) with an active disease (DAS 3.5±0.7) underwent a dietary regimen for weight loss for six months, with no change in RA treatment. At the sixth month, the mean reduction in percentage of BMI was 8.9±5.3% and the average percentage of DAS reduction was 46.8±20.2% (DAS T6: 1.8±0.6, p=0.01 with respect to DAS T0).

Conclusion. In ERA patients, PEDF and chemerin seem to be biomarkers of obesity and metaflammation, respectively. Chemerin seems to be linked to RA disease activity and to treatment response, irrespective of body weight category, supporting its dual role in inflammation and metabolism and providing a link between chronic inflammation and obesity.

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The Relationship Between Disease Activity and Levels of HMGB1 in Patients with Rheumatoid Arthritis. David S. Pisetsky[1], Diane Spencer[2], Stephen R. Wisniewski[3], Jason Lyons[3], Melissa Saul[4], Mandy J. McGeachy[5], Yong Gil Hwang[6], Heather Eng[3] and Larry W. Moreland[6]. [1]Durham VAMC, Durham, NC, [2]Duke University Medical Center, Durham, NC, [3]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [4]University of Pittsburgh, School of Medicine, Pittsburgh, PA, [5]Univeristy of Pittsburgh, Pittsburgh, PA, [6]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: HMGB1 (High Mobility Group Box 1), a non-histone nuclear protein, is a prototypic alarmin that displays immunological activity following release during cell death or immune cell activation. As shown in studies of patients with rheumatoid arthritis (RA) and animal models, HMGB1 plays a key role in pathogenesis; HMGB1 has increased expression in synovial tissue and blockade of HMGB1 can attenuate disease in animal models. While the role of HMGB1 in mediating disease has been well studied, its role as a biomarker has received less attention. The present study therefore explored the expression of HMGB1 in the blood of RA patients, investigating correlations with various clinical features.

Methods: This study utilized samples from the RACER (Rheumatoid Arthritis Comparative Effectiveness Research) cohort. Patients varied in disease duration and received therapy determined by clinical response. Disease activity was assessed by DAS 28 scores using C-reactive protein as the acute phase reactant. The samples, selected to provide a range of disease activity, were divided into 4 groups: remission; low activity; moderate activity; and high activity. Levels of HMGB1 were determined by ELISA using the Shino-test kit. The concentrations of HMGB1 in the plasma from 10, non-RA control subjects were also measured.

Results: Among 100 patients with RA, HMGB1 levels varied from 1.1 to 19.3 ng/ml (median value = 5.73 ng/ml) which was significantly higher than those of the control population (range = 0.72–3.28; median value = 1.93 ng/ml). Despite the increase in HMGB1 levels in the RA population, the median values of the 4 disease activity groups were similar (remission, 5.98; low 5.09; moderate 5.64; high, 6.02). These differences did not reach statistical significance by a non-parametric ANOVA. In contrast, CRP levels showed a statistically significant association with disease activity by a non-parametric ANOVA (<0.0001). As a previous study suggested a relationship with disease duration, the results were analyzed in terms of duration less than 5 years, 5–10 years, 15–20 years and greater than 20 years. This analysis failed to reveal a relationship with disease duration. Values of males and females were also similar.

Conclusion: These studies demonstrate that levels of HMGB1 are elevated in the blood of patients with RA and show a relationship to disease activity distinct from that of CRP. As HMGB1 levels were increased in patients either in remission or with low disease activity, these findings suggest ongoing inflammation that may not be apparent with either the DAS 28 or CRP. Furthermore, since HMGB1 can also arise from cell death, the elevation of HMGB1 levels, even with remission or low disease activity, may reflect tissue destruction that persists even with inflammation restrained.

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14-3-3η: A Mechanistic Biomarker That Supports the Concept of "Uncoupling" of Inflammation and Joint Damage. Dirkjan van Schaardenburg[1], Mairead Murphy[2], Yuan Gui[2], Samina Turk[1], WP Maksymowych[3], Kelly Young[4] and Anthony Marotta[2]. [1]Reade, Amsterdam, Netherlands, [2]Augurex Life Sciences Corp., North Vancouver, BC, [3]University of Alberta, Edmonton, AB, [4]Rheumatoid Patient Foundation, Cocoa, FL.

Background/Purpose: In RA, irreversible joint damage often begins within the first year of symptom onset. A compelling and growing body of data describing the "uncoupling" of inflammation and joint destruction indicates that radiographic monitoring is important in all RA patients, regardless of clinical response. C-reactive protein (CRP) is an acute phase reactant that is routinely used alongside clinical assessment to evaluate response to treatment in RA although ~30–40% of patients have normal levels. 14-3-3η is a modifiable serum/plasma mechanistic biomarker that is a potent regulator of MMP expression and its positive status in early RA predicts radiographic progression. This study examines 14-3-3η's relationship with CRP in an early RA cohort and whether its baseline expression in CRP-normal patients relates to radiographic outcome at year 1.

Methods: Baseline serum 14-3-3η protein titres were measured in a cohort of 409 early RA patients from the Reade Institute; all patients were treatment naive at baseline. Median patient age was 56 years and 73% were female. Patient plasma was tested on the 14-3-3η ELISA (cut-off ≥0.19 ng/ml) and differences in joint damage progression over three years along 14-3-3η positive/negative status groups was evaluated within the whole cohort and between CRP-normal (≤10 mg/L) and elevated groups. Statistical analyses were performed (GraphPad Prism 5.0) using Spearman correlations to compare relationships between variables and the Mann-Whitney u-test to assess median differences between groups.

Results: 67% of patients were positive for the 14-3-3η protein and 60% of patients had elevated CRP (> 10mg/L). The Spearman correlation of baseline CRP and 14-3-3η titres showed no relationship between the two variables (r= 0.06). Baseline CRP titres correlated with TSS at year 1 (r=0.17, p=0.0007) as well as the change in TSS from baseline to year 1 (r=0.17, p=0.0005) but not with baseline TSS. Patients who were 14-3-3η protein positive had more radiographic progression than 14-3-3η negative patients over years 1, 2 and 3; p-values = 0.006, 0.008 and 0.009, respectively (Table). In patients with normal CRP (≤10 mg/L), 14-3-3η positive patients (n=105) had a higher mean (SD) radiographic progression at year 1 of 1.4 (3.4) versus the 14-3-3η negative group (n=55), 0.7 (2.3), p<0.05.

Median (min-max)	14-3-3η Negative[n]	14-3-3η Positive[n]	p-value
SHS Y1	0(0–3)[131]	1(0–5)[273]	0.02
SHS Y2	1(0–5)[133]	2(0–8)[271]	0.02
SHS Y3	1.5(0–6)[128]	3(0–10)[264]	0.01
Δ SHS Y1	0(0–1)[131]	0(0–2)[274]	0.006
Δ SHS Y2	0(0–2.5)[133]	1(0–6)[271]	0.008
Δ SHS Y3	0(0–4)[127]	2(0–7)[264]	0.009

Conclusion: 14-3-3η is a mechanistic joint damage marker that does not correlate with the acute phase reactant CRP in early RA. These two markers provide unique information to assist in the clinical management of RA patients informing the uncoupling of inflammation and joint damage.

Disclosure: D. van Schaardenburg, Augurex Life Sciences Corp, 5; **M. Murphy**, Augurex Life Sciences Corp, 3; **Y. Gui**, Augurex Life Sciences Corp, 3; **S. Turk**, None; **W. Maksymowych**, Augurex Life Sciences Corp, 5; **K. Young**, None; **A. Marotta**, Augurex Life Sciences Corp., 3.

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The Utility of HLA-DR Genotypification As a Complementary Tool to Discriminate Undifferentiated and Rheumatoid Arthritis Patients in Early Arthritis. Fernando Dal Pra[1], Gustavo Citera[2], Margarita Landi[3], Christian A. Waimann[4], Luis Alejandro Cayetti[2], Sergio Paira[5], Federico Ceccatto[6], Teresita Alvarellos[7], Luciana Mas[7], Josefina Marcos[8], Mercedes García[8], A Salas[8], Alejandro Martinez[9], Rafael Chaparro[10], Oscar Luis Rillo[9], Edson Veloso[11], Ricardo V. Juárez[12], Maria Elena Crespo[13], Antonio Catalán Pellet[14], Anastasia Secco[14], Lucila Marino[14] and V Martire[14]. [1]Instituto de Rehabilitacion Psicofisica, Buenos Aires, Argentina, [2]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [3]Instituto Rehabilitacion Psicofisica, Buenos Aires, Argentina, [4]Hospital Olavarria, Olavarria, Argentina, [5]Hospital Jose Maria Cullen, Santa Fe, Argentina, [6]Hospital Jose María Cullen, Santa Fé, Argentina, [7]Hospital Privado Centro Medico De Córdoba, Cordoba, Argentina, [8]HIGA San Martín, La Plata, Argentina, [9]Hospital General de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [10]Hospital Gral. de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [11]Sanatorio y Universidad Adventista Del Plata, Entre Rios, Argentina, [12]Hospital Señor del Milagro, Salta, Argentina, [13]Hospital Señor Del Milagro, Salta, Argentina, [14]Hospital Bernardino Rivadavia, Buenos Aires, Argentina.

Background/Purpose: Only half of patients with undifferentiated arthritis (UA) will progress to rheumatoid arthritis (RA) after two years of follow-up. Particular human leukocyte antigens class II-DR (HLA-DR) alleles have been associated with a higher risk to develop RA, however these alleles may vary among ethnic groups. The aim of our study was to investigate the frequency of HLA-DR alleles and evaluate the association with the development of rheumatoid arthritis in an early arthritis cohort in Latin America.

Methods: We designed a case-control study. Cases were defined as patients with diagnosis of RA from an early arthritis cohort (<2 years of disease duration). Two control groups were selected. First group was obtained from the mentioned cohort and included patients with UA. The second control group was obtained from the national register of cadaveric organ donors (Healthy Subjects, HS). HLA-DR genotypes frequencies were estimated for each group. We calculated the odds ratio (OR) to develop RA in general population and undifferentiated arthritis. Statistical analysis was performed with two-tailed Pearson's chi-squared test with Bonferroni adjustment (p-value after Bonferrroni adjustment, Pc). A stepwise logistic regression model using RA vs UA diagnosis as dependent variable was performed to identify the association of HLA-DR alleles and RA development in patients with UA, adjusted by smoking, gender and presence of rheumatoid factor (variable significance entry criteria $P < 0.15$). A p-value less than 0.05 was considered statistically significant.

Results: We included a total of 1859 subjects: AR=347; UA=52; Cs=1460. When comparing with HS, RA patients had an increased frequency of DR4 [RA=50% vs HS=31%, OR 2.3 (1.7 – 2.8), Pc<0.0001], DR9 [RA=12% vs HS=7%, OR 1.9 (1.3 – 2.8), Pc=0.02], and lower frequency of DR7 [RA=13% vs 21%, OR 0.6 (0.4 – 0.8), Pc=0.02], DR11 [RA=10% vs 21%, OR 0.4 (0.3 – 0.6), Pc<0.0001], DR15 [RA=9% vs 15%, OR 0.5 (0.4 – 0.8), Pc=0.04]. Among patients with early arthritis, being heterozygote or homozygote for DR-4 allele could not differentiate between patients with RA and UA. On the other hand, patients with UA showed higher frequency of DR7, DR11 and DR15 than RA (23%, 21%, 17% vs 13%, 11% 9%, respectively), but did not reach statistical significance after adjustment for multiple comparisons. Stepwise regression indicated that the presence of DR15 was significantly associated with lower risk of RA [OR=0.35 (0.12–0.97, p=0.04].

Conclusion: In our cohort of patients with early arthritis, the genotypification of HLA-DR alleles was not useful to discriminate between RA and UA. Only the presence of DR15 allele was associated with a lower probability of RA, however the poor precision of the estimates makes it difficult to address the utility of this determination in daily clinical practice.

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Serum 14-3-3η Protein Supplements Traditional Rheumatoid Arthritis Biomarkers. Olga Zhukov[1], Jonnielyn Rivera[1], Charles M. Rowland[2], Joanna M. Popov[1] and Stanley J. Naides[3]. [1]Quest Diagnostics Nichols Institute, San Juan Capistrano, CA, [2]Celera, Alameda, CA, [3]Quest Diagnostics Nichols Institute, San Juan Capistrano, Albania.

Background/Purpose: The 14-3-3 family of chaperonin proteins consists of 7 isomers. The tissue distribution of the 14-3-3η (eta) isoform is limited to synovial tissue and brain. 14-3-3η is released from synovial tissue into the synovial fluid and serum in patients with rheumatoid arthritis (RA) and, to a lesser extent, erosive psoriatic arthritis (ePsA). Extracellular 14-3-3η induces signaling pathways that lead to production of proinflammatory mediators including metal η loproteinases, RANKL, IL1, TNFα, and additional 14-3-3η, thereby exacerbating disease. Serum 14-3-3η measurement has been shown to aid diagnosis and prognosis of rheumatoid arthritis, and may have utility in assessing disease activity. The purpose of this study was to investigate the potential value of adding 14-3-3η to traditional biomarkers of rheumatoid factor (RF) and citrullinated cyclic peptide antibody (CCP).

Methods: Consecutive serum samples (n=1944) referred to an esoteric diagnostic laboratory for a "Rheumatoid Arthritis Diagnostic Panel" were tested for RF by nephelometry, CCP by immunoassay (INOVA QUANTA Lite™ CCP3.0 IgG ELISA), and 14-3-3η by a proprietary laboratory-developed test (ELISA).

Results: Of 1944 sera tested, 248 (12.8%; 95% CI 11.3%–14.3%,) were positive for 14-3-3η. 1483 of the 1944 samples (76.3%; 95% CI 74.3%–78.1%) were negative for both RF and CCP. Of these seronegative samples, 91 (6.1%; 95% CI 5.0%–7.5%) were positive for 14-3-3η. 14-3-3η was also in positive in 46 of 245 RF+/CCP- samples (18.8%; 95% CI 14.4%–24.1%); 107 of 161 RF+/CCP+ samples (66.5%, 95% CI 58.9%–73.3%); and only 4 of 55 RF-/CCP+ samples (7.3%, 95% CI 2.9%–17.3%).

Conclusion: Serum 14-3-3η was positive in 12.8% of individuals tested for RA biomarkers. The population likely includes individuals without RA, with seropositivity for RF and/or CCP but no joint disease, or with other rheumatic diseases; these factors may account for the lower rate of 14-3-3η positivity relative to that reported in clinically defined early RA. Further, 14-3-3η was positive in 18.8% of RF+/CCP- samples, suggesting that this marker may be useful in further demonstrating joint specificity of an isolated positive RF result. Adding 14-3-3η testing to RF and CCP increases detection of individuals warranting further evaluation for RA and possibly ePsA, and may assist primary care physicians in triaging referrals to rheumatologists. Subsequent studies with detailed clinical correlation are warranted.

Disclosure: O. Zhukov, Quest Diagnostics, 3; **J. Rivera**, Quest Diagnostics, 3; **C. M. Rowland**, Celera/Quest Diagnostics, 3; **J. M. Popov**, Quest Diagnostics, 3; **S. J. Naides**, Quest Diagnostics, 3.

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14-3-3η Auto-Antibody Positivity Informs Better Clinical Outcomes in RA. D. van Schaardenburg[1], Mairead Murphy[2], Samina Turk[3], Walter P Maksymowych[4] and Anthony Marotta[2]. [1]Jan van Breemen Research Institute, Amsterdam, Netherlands, [2]Augurex Life Sciences Corp., North Vancouver, BC, [3]Reade, Amsterdam, Netherlands, [4]University of Alberta, Edmonton, AB.

Background/Purpose: We have previously reported pilot data that patients who are only positive for 14-3-3η auto-antibodies (AAb) and negative for the 14-3-3η protein have a lower radiographic trajectory over 3 years. 14-3-3η AAbs have been described as "protective" based on their currently understood mechanism of clearing "harmful" extracellular 14-3-3η protein. In this study, we investigated how 14-3-3η AAb plasma expression informs clinical variables at baseline and over 3 years in a substantial cohort of patients with early RA.

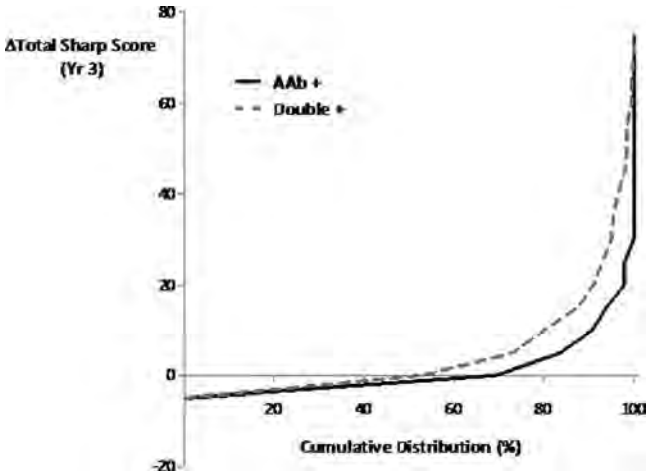
Methods: Baseline serum 14-3-3η protein and AAb levels were measured in a cohort of 409 early RA patients; all patients were treatment naive

at baseline. Median patient age was 56 years and 73% were female. 14-3-3η protein levels were tested using the Augurex 14-3-3η ELISA (cut-off ≥0.19 ng/ml) and 67% of patients were positive. 14-3-3η AAb levels were measured on the MSD ECL platform and using a diagnostic cut-off of 380 U/ml, 77% of patients were +ve. Patients were grouped into 4 groups: 1) Negative for both markers, 2) Positive for the 14-3-3η protein only, 3) Positive for the 14-3-3η AAb only and 4) Positive for both markers. Assessment of differences across these 4 groups was performed using Kruskal-Wallis Analysis of Variance (ANOVA) with Dunn's post-hoc testing to identify differences between individual groups.

Results: Across the four 14-3-3η biomarker expression groups (table), ANOVA revealed significant differences in RF and CCP positive rates and titers ($p<0.0001$), baseline TSS, SJC28 and ESR (≤0.01). Patients who were only 14-3-3η auto-antibody positive had significantly lower positivity rates and titers of RF and CCP ($p<0.0001$).

	ANOVA (4 groups)	Double −	Protein +	AAb +	Double +	P-value
Baseline						
RF +	< 0.0001	14%	81%	34%	79%	< 0.0001
CCP +	< 0.0001	41%	79%	35%	87%	< 0.0001
SJC28	0.0007	7	7	9	7	0.0002
ESR	0.02	18	27	31	32	NS

Over the 3 years, 14-3-3η auto-antibody +ve patients had significantly lower radiographic progression compared to patients who were double positive ($p=0.004$). 14-3-3η auto-antibody +ve patients also had significantly greater changes in response to treatment in SJC28 ($p=0.0004$) and DAS28 (0.006) compared to the double positive patient group.



Conclusion: At baseline, the combination of a positive 14-3-3η auto-antibody test and a negative 14-3-3η protein test is significantly associated with a less severe RA disease profile and a better prognosis in regards to radiographic progression, SJC and DAS outcomes at 3 years. This data supports a protective role for 14-3-3η auto-antibodies.

Disclosure: D. van Schaardenburg, Augurex Life Sciences Corp, 5; **M. Murphy**, Augurex Life Sciences Corp, 3; **S. Turk**, None; **W. P. Maksymowych**, Augurex Life Sciences Corp, 5; **A. Marotta**, Augurex Life Sciences Corp., 3.

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Soluble CD163 Is a Marker of Disease Activity in Early Rheumatoid Arthritis and Reflects TNFα Levels. Stinne Greisen[1], Holger Jon Møller[2], Kristian Steengaard-Petersen[2], Merete Lund Hetland[3], Kim Hoerslev-Petersen[4], Peter Junker[5], Mikkel Ostergaard[6], Malene Hvid[7] and Bent Deleuran[7]. [1]Aarhus University, Aarhus C, Denmark, [2]Aarhus University Hospital, Aarhus, Denmark, [3]DANBIO, Center for Rheumatology and Spine Diseases, Glostrup University Hospital, Glostrup, Denmark, Glostrup, Denmark, [4]Research Unit at King Christian X Hospital for Rheumatic Diseases, Graasten, Denmark, [5]Odense University Hospital, Odense, Denmark, [6]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [7]Aarhus University, Aarhus, Denmark.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation and eventually destruction, where TNFa is a central mediator of both processes. Soluble CD163 is a plasma marker of macrophage activation. CD163 is a scavenger receptor specifically expressed by macrophages and responsible for binding hemoglobin-haptoglobin complexes. The soluble form is cleaved from the cell surface by TACE/ADAM17, the metalloproteinase also responsible for the cleavage of TNFa, suggesting a close association between sCD163 and TNFa. In RA, sCD163 has been suggested as a marker of disease activity and progression [1]. We aimed to investigate plasma sCD163 in very early RA (eRA) patients.

Methods: Soluble CD163 was measured by ELISA in plasma samples from 154 eRA patients belonging to the OPERA cohort[2]. Age 53.5 years (51–56), 70% females, average disease duration: 3 months. Patients were randomized to conventional methotrexate and placebo (MTX+PLA) or MTX and adalimummab (MTX+ADA) treatment. Clinical disease was assessed by: Disease activity index (DAS28), health assessment questionnaire (HAQ), CRP, swollen joints (SJC40), tender joints (TJC40), simple disease activity index (SDAI), clinical disease activity index (CDAI), visual analogue scale (VAS) for pain, total sharp score (TSS), IgM-RF and ACPA. Statistical analysis was performed by student's t-test, Spearman's Rank correlation and linear regression.

Results: Plasma concentration of sCD163 at baseline was 2.40 mg/l (CI: 2.21 mg/l-2.56 mg/l)) corresponding to the upper part of the HV reference interval (0.69mg/l - 3.86mg/l). After three months of treatment sCD163 had decreased significantly in both treatment groups (to 1.81 mg/l (1.68mg/l – 1.95 mg/l), $p<0.001$). Though the decrease in the MTX+ADA group was more prominent than in the MTX+PLA group. Withdrawal of ADA after 12 months of treatment was followed by incremental sCD163 levels during the subsequent 12 months (1.73mg/l (1.55mg/l -1.94mg/l to 2.07mg/l (1.88mg/l – 2.28mg/l ($p<0.001$)). At baseline sCD163 correlated with CRP and all investigated markers of disease activity (ρ = 0.16–0.28, $p<0.05$). We observed no correlation with TSS, IgM-RF and ACPA. The correlation between sCD163 and CRP at baseline could be fitted to a linear regression model ($\beta=8.28$, $p<0.001$). In the MTX+PLA group, this linear regression was also observed after 6 months and 1 year of treatment ($\beta=7.5$ and 9.9, respectively, both $p<0.001$). In the MTX+ADA group the close association was only observed after 3 months of treatment ($\beta=10.9$, $p<0.007$).

Conclusion: Soluble CD163 correlated with markers of disease activity in eRA. The correlation with CRP was very close and followed a linear regression model. Our results also indicate that sCD163 is associated with TNFa, as withdrawal of anti-TNF treatment was clearly reflected in increased sCD163 levels and correlation with CRP is diminished in the MTX+ADA treatment group. Plasma sCD163 thus reflects anti-TNF treatment and is a potential new disease activity marker in eRA.

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Vascular Endothelial Function Changes during Treatment in Patients with Rheumatoid Arthritis. Johana Zacariaz[1], Eliana Lancioni[1], Tomas Cazenave[2], Florencia Marengo[2], Emilce Edith Schneeberger[2], Lucas Aparicio[3], Margarita Morales[3], Jorge Norscini[4], Gabriel Waisman[3], Javier Rosa[5], Gustavo Citera[2] and Enrique R. Soriano[6]. [1]Rheumatology Unit, Internal Medicine Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [3]Hypertension Section, Internal Medicine Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [4]Neurology Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [5]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [6]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina.

Background/Purpose: Rheumatoid Artrhitis (RA) patients have an increased risk for accelerated atherosclerosis. Endothelial dysfunction and arterial stiffness, assessed by measurement of carotid-femoral pulse wave velocity (PWV) and common carotid artery intima-medial thickness (CCA-IMT), respectively, are proven surrogate markers of premature and potentially reversible atherosclerosis. Disease modifying anti-rheumatic drugs (DMARDs), and particularly biologic treatments, because of their higher capacity for controlling inflammation, might improve these surrogate markers of atherosclerosis. To assess the short-term effect (1 year) of treatment with conventional synthetic DMARDs, TNF-inhibitors, or Abatacept, on endothelial function and arterial stiffness in RA patients.

Methods: Consecutive patients meeting 1987 ACR classification criteria for RA in whom their treating Rheumatologist prescribed a new DMARD or a change in DMARD (including biologics), were included. Patients with history of cardiovascular disease were excluded from the study. Common carotid artery (CCA) intima-medial thickness (IMT) and carotid plaques (CP) were measured in the right common carotid artery using high-resolution B mode ultrasound with a 10 MHz linear transducer. Carotid-femoral pulse wave velocity (PWV) was measured using a hand-held tonometry probe. Clinical evaluation included assessment of disease activity using the Disease Activity Score including 28 joint count (DAS28), the Argentinean validated HAQ-DI, blood pressure measurement, and 10-year risk for coronary events using the Framingham 2010 risk equation. All measurements were performed at baseline, and after one year of treatment. In patients switching or stopping treatment, measurements were completed within one month of treatment stop/change.

Results: Thirty-four patients were included. Baseline characteristics and follow up outcomes, according to treatment at the initiation of the study are shown in the table. After a mean follow up of 12.1 (SD: 2,2) months there was a significant reduction in DAS28 in all three treatment groups, [mean 4.7 (SD:1.3) vs 4 (SD: 1.2); p=0.0425], while there was no difference in HAQ [1.2 (SD:0.8) vs 1.1 (SD:0.7); p=0.3244], in any of them. All patients had normal baseline PWV, and there were no significant changes after one year in any of the treatment groups. In a similar way, there were no differences between baseline and follow up mean CCA-IMT. No patient developed new carotid plaques.

Conclusion: After one year of treatment, there were no significant changes in surrogate markers of atherosclerosis in long standing RA patients, with low basal cardiovascular risk. Parameters of endothelial dysfunction and arterial stiffness remained within normal values after one year of follow up.

Variable	DMARDs (n = 15)	TNFα inhibitors (n = 10)	ABATACEPT (n = 9)
Female, n (%)	11 (73)	11 9 (90)	11 8 (89)
Mean age, years (SD)	53.8 (14)	56.9 (12.4)	56.7 (6.6)
Mean Disease duration, years (SD)	7.4 (9.5)	18.5 (11.8)	13.7 (9.2)
Rheumatoid Factor positivity, n (%)	13 (87)	6 (60)	9 (100)
Previuos TNFα inhibitors, n (%)	0 (0)	1 (10)	7 (78)
DAS 28, mean (SD)	4.4 (1.3)	4.9 (1.5)	4.9 (1.3)
Mean HAQ (SD)	0.9 (0.7)	1.6 (0.7)	1.4 (0.9)
Mean Systolic Blood Pressure, mmHg (SD)	131 (18.7)	142.6 (13.7)	129.4 (18.2)
Mean Framingham 2010 10 years, Cardiovascular Risk	5.7%	3.1%	2.4%
Mean PWV, m/sec (SD)	8.1 (2.4)	8.3 (1.5)	7.3 (1.2)
Mean CCA-IMT, mm (SD)	0.85 (0.3)	0.83 (0.2)	0.78 (0.2)
Carotid Plaques, n (%)	6 (40)	2 (20)	3 (33)
Mean time to follow up study, months (SD)	12.3 (2.4)	12.4 (0.7)	11.4 (2.9)
Patients stopping/Switching treatment, n (%)	8 (53)	7 (70)	5 (55)
Mean time to stop/switch treatment, months (SD)	8 (6)	8.5 (3)	8.4 (5)
Mean PWV, m/sec (SD) at follow up	8 (1.6)	7.95 (1.3)	8 (1.3)
Mean CCA-IMT, mm (SD) at follow up	0.87 (0.28)	0.88 (0.22)	0.8 (0.2)

Disclosure: J. Zacariaz, Bristol-Myers Squibb, 2; **E. Lancioni**, Bristol-Myers Squibb, 2; **T. Cazenave**, Bristol-Myers Squibb, 2; **F. Marengo**, Bristol-Myers Squibb, 2; **E. E. Schneeberger**, Bristol-Myers Squibb, 2; **L. Aparicio**, Bristol-Myers Squibb, 2; **M. Morales**, Bristol-Myers Squibb, 2; **J. Norscini**, Bristol-Myers Squibb, 2; **G. Waisman**, Bristol-Myers Squibb, 2; **J. Rosa**, Bristol-Myers Squibb, 2; **G. Citera**, None; **E. R. Soriano**, None.

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ABCB1 and ABCG2 Drug-Efflux Transporters Function and Its Association with Disease Activity in a Cohort of Patients with Rheumatoid Arthritis. Yemil Atisha-Fregoso[1], Hilda Fragoso-Loyo[2], Juan Jakez-Ocampo[3], Guadualupe Lima[4], Miguel Baños[2], Virginia Pascual-Ramos[1], Irazu Contreras-Yañez[2] and Luis Llorente[5]. [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico, [3]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México, Mexico, [4]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubirán, Mexico City, Mexico, [5]Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico.

Background/Purpose: ABCB1 (P-gp) and ABCG2 (BCRP) are part of the adenine triphosphate (ATP)-binding cassette (ABC) transporter proteins. These proteins mediate efflux of drugs from inside the cells and can confer a multidrug resistance phenotype. Since among its substrates are included drugs that are part of the treatment in Rheumatoid Arthritis (RA) such as prednisone and chloroquine (for ABCB1) and methotrexate and sulfasalazine (for ABCG2), these transporters might contribute to the resistance to treatment observed in some patients.

The objective of this study was to determine the activity of these transporters in patients with active and inactive rheumatoid arthritis.

Methods: We included patients with Rheumatoid Arthritis (2010 ACR/EULAR criteria) from the early rheumatoid arthritis cohort of our Institute. ABCB1 (P-gp) and ABCG2 (BCRP) functional activity was measured in peripheral mononuclear cells by flow cytometry. The percentage of cells able to extrude substrates for ABCB1 (daunorubicin) and ABCG2 (mitoxantrone) were recorded. The specificity of the assay was confirmed with specific inhibitors (verapamil for ABCB1 and KO143 for ABCG2). Thirty healthy controls were also evaluated to established normal values. The study was approved by our local ethics committee. For the statistical analysis continuous variables were compared with Student t or Mann-Whitney U tests and categorical variables with chi square or Fisher exact test as appropriate.

Results: Thirty seven patients (all women) had been included. The mean age was 38.3 ± 12.3 years and a disease duration of 5 ± 3.3 years. Twenty patients had inactive and 17 active disease according to DAS28 (1.2 ± 1.5 vs 4.1 ± 1; p<0.001). There were no differences in age, disease duration or use of prednisone (76.5 vs 80%), methotrexate (94.1 vs 95%), antimalarials (41.2 vs 40%) or sulfasalazine (35.3 vs 25%) among active and inactive patients (respectively, all with p >0.05).

The median percentage value of cells able to extrude daunorubicin in active patients was 4.4% (IQR 0.7–19.7%) vs 0.9 (IQR 0.5–3.4) in inactive patients, while the median percentage of cells that extruded mitoxantrone in active patients was 1.7% (IQR 0.4–11.4%) vs 0.7% (IQR 0.4–1.8) in the inactive patients. These differences were no statistically significant.

Only 2 of 20 (10%) inactive patients were positive for ABCG2 and 8 of 17 (47%) active patients were positive (p=0.023) while for ABCB1 9/17 (53%) of active patients were positive and 6/20 (30%) of inactive patients were positive (p=0.157).

Conclusion: Patients with active RA have a higher percentage of positivity for the ABCG2 transporter compared with those in remission independently of treatment and disease duration. Follow up of these patients is currently ongoing to determine if the functional activity of these efflux pumps entails a higher risk of persistent activity or risk of RA reactivation.

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Determinants of Radiological Progression in Rheumatoid Arthritis: Relationship with Serum Levels of OPG, RANKL and DKK-1. Carmen Gómez-Vaquero[1], Irene Martín-Esteve[1], Jose Ivorra[2], Jose Antonio Narvaez[1], Javier Hernandez Gañan[1], Pedro Alia[1] and Javier Narváez[3]. [1]Hospital Universitari de Bellvitge - IDIBELL, Barcelona, Spain, [2]Department of Rheumatology, Hospital Universitario y Politécnico La Fe., Valencia, Spain, [3]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain.

Background/Purpose: Osteoprotegerin (OPG), RANKL, and DKK-1 act as regulators of bone resorption and formation. The uncoupling of bone remodelling that occurs in rheumatoid arthritis (RA) originates generalized bone loss and joint erosions.

Our aims are: 1) In patients with RA, to determine the serum levels of OPG, RANKL and DKK-1 and its relationship with radiological progression in hands. 2) To assess their relations with the activity and disability parameters of RA.

Methods: From a previous study in which we had radiographs of hands and frozen sera from all patients (T0), we selected the ones controlled since the diagnosis of the disease in an Early Arthritis Clinic of a university hospital through a strategy of tight control. They came back to make radiographs of hands and collection of sera (T1). Study variables were: 1) Demographics: age, sex, body mass index (BMI); 2) RA history: duration, RF, anti-CCP antibodies; 3) Disease activity: mean DAS28 and CRP between T0 and T1; 4) Disability: mean HAQ; 5) RA treatment; 6) Serum levels of OPG, RANKL and DKK-1; and 7) Sharp-van der Heijde Index (SHI) of hands, analyzing together and separately erosions (SHI-Ero) and joint space (SHI-Spa).

Results: Ninety-seven patients (60 women) were included with a mean age of 53 ± 14 years and a mean BMI of 25.9 ± 4.9 kg/m2. At T0, mean RA duration was 1.6 ± 1.5 years. Sixty-one percent of the patients had RF + and 62%, anti-CCP antibodies +. Mean DAS28 was 2.61 ± 0.96; CRP, 5.9 ± 7.1 mg/L; and HAQ, 0.330 ± 0.331. Seventy-six percent of the patients had low activity (DAS28 < 3.2) and 23%, moderate activity (DAS28 ≥ 3.2 and <

5.1); only one patient presented high activity (DAS28: 5.21). Mean time between T0 and T1 was 3.3 ± 1.5 years.

	SHI	SHI-Ero	SHI-Spa	OPG pmol/L	RANKL* pmol/L	OPG/RANKL*	DKK-1 pmol/L
T0	5.2 ± 7.1	0.8 ± 2.3	4.5 ± 5.9	3.9 ± 1.8	0.3 ± 0.3	53.5 ± 55.1	29.9 ± 11.0
T1	7.8 ± 10.9	1.4 ± 3.7	6.3 ± 8.1	4.1 ± 2.2	0.4 ± 0.4	29.7 ± 39.4	26.4 ± 18.9

* RANKL levels were below the limit of detection in 82 (T0) and 72 (T1) patients.

Mean annual progression of SHI was 0.9 ± 2.2; SHI-Ero, 0.2 ± 0.6, and SHI-Spa, 0.7 ± 1.7. The annual progression of SHI, SHI-Ero and SHI-Spa correlated with CRP levels ($p < 0.01$) and with the titer of anti-CCP antibodies; SHI-Spa progression correlated also with age ($p < 0.05$). We found no relation between SHI and OPG, RANKL or DKK-1.

Patients whose ISH worsened (48%) were older and had higher BMI and RA activity than patients in which ISH didn't worsen (52%).

Conclusion: The progression of radiological damage in a series of RA patients controlled in an Early Arthritis Clinic is dependent on the activity of the disease and the titer of anti-CCP antibodies. Serum levels of OPG, RANKL and DKK-1 do not seem useful to predict progression of radiographic damage.

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Association of Antinuclear Antibodies with Lung Disease, Malignancy and Joint Replacement in Rheumatoid Arthritis. Reshmi Raveendran[1], Bobby Kwanghoon Han[2], Quan-Zhen Li[3] and Nancy J. Olsen[1]. [1]Penn State MS Hershey Medical Center, Hershey, PA, [2]Cooper Medical School of Rowan University, Camden, NJ, [3]University of Texas Southwestern Medical Center, Dallas, TX.

Background/Purpose: Antinuclear antibodies (ANAs) are present in a significant proportion of patients with rheumatoid arthritis (RA). Positivity for ANA in RA has been associated with use of TNF inhibitor therapies and with the presence of overlapping disorders such as Sjogren's syndrome. We hypothesized that ANA positivity might be associated with other clinical or immunologic manifestations of RA.

Methods: Peripheral blood samples were obtained from CCP-positive RA patients (N=50) and 8 patients with systemic lupus erythematosus (SLE) who were seen in outpatient clinics. Clinical and laboratory features of disease were determined by chart review. Serum was used for measurement of ANA by ELISA and for detection of IgG and IgM autoantibodies on an 84-component protein array. Whole blood samples were used for quantitation of expression levels of 3 genes in the Type I interferon signature (MX1, OAS1, IFI27) using real-time PCR. Groups were compared for significant differences using 2-tailed t and Fisher's exact tests. Continuous variables were analyzed for correlations with Pearson's test.

Results: ANA positivity was present in 23/50 (46%) of the RA patients and this group tended to be older (60 vs 52 years; P=0.02), have longer mean disease duration (10 vs 7 years; P = 0.09), a lower prevalence of smoking (30% vs 63%; P=0.027), and somewhat higher prevalence of TNF inhibitor therapies (48% vs 26%; p=0.14) than the ANA negative group. Gender distributions were similar. The erythrocyte sedimentation rate was modestly correlated with ANA level (R=0.3; P=0.038). Malignancies were exclusively seen in the ANA+ group (8 cancers in 6 patients; P=0.008 vs ANA-). Only 2 of these were after starting TNF inhibitor therapy. 9 patients had lung disease, including interstitial fibrosis and bronchiectasis, and 6 of these were in the ANA+ group (NS), but lung disease in nonsmokers was only observed in ANA+ patients (P=0.038). Two of the 27 ANA-negative patients had had a single joint replacement each, compared to 6/23 ANA-positive patients, 4 of whom had more than one replaced joint (P=0.027). Other connective tissue diagnoses including Sjogren's Syndrome and thyroid conditions were not different in the two groups. On the autoantigen array, ANA + and – subgroups of RA did not show any significant differences for IgM autoantibodies while 12 IgG autoantibodies were higher in the ANA+ group (P £ 0.04). Compared to SLE, the ANA+ RA group had significant elevation of 13 IgM autoantibodies, but did not show any elevated IgGs. ANA positivity in the RA patients was not associated with elevation of the Type I IFN genes.

Conclusion: ANA positivity in patients with CCP+ RA may define a clinical subset that has a greater risk of lung disease, malignancy and joint replacement surgery. The presence of ANA was associated with elevation of the Type I IFN signature. The paradoxical observation that smoking was less prevalent in the ANA+ group that had higher malignancy rates is not explained. If ANA expression in RA is not associated with the Type I IFN signature as in SLE, then other pathogenetic pathways may be involved, possibly including those involved in immune surveillance.

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Relationship Between Range of Motion of Joints in Upper Limbs and Physical Function in Patients with Long-Standing Rheumatoid Arthritis: Multicenter Prospective Cohort Study for Evaluation of Joint Surgery on Physical Function. Toshihisa Kojima[1], Hajime Ishikawa[2], Keiichiro Nishida[3], Jun Hashimoto[4], Hisaaki Miyahara[5], Sakae Tanaka[6], Nobuhiko Haga[6], Yasuo Niki[7], Masayo Kojima[8] and Naoki Ishiguro[1]. [1]Nagoya University Graduate School of Medicine, Nagoya, Japan, [2]Niigata Rheumatic Center, Niigata, Japan, [3]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama city, Japan, [4]National Hospital Organization, Osaka Minami Medical Center, Kawachinagano, Japan, [5]National Hospital Organization Kyushu Medical Centre, Fukuoka, Japan, [6]The University of Tokyo Hospital, Tokyo, Japan, [7]Keio University School of Medicine, Tokyo, Japan, [8]Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

Background/Purpose: Even now, in clinical practice, most of RA patients have long-standing disease and structural damage in their joints. Reconstructive joint surgery should be needed for further improvements of physical function for long-standing RA patients. It is very important to understand how much range of motion (ROM) should be needed to gain better physical function in each case.

The purpose of this study is to explore the characteristics of functional impairment and relationship ROM of joints and physical function in RA patients who were needed joint surgery using multicenter prospective cohort.

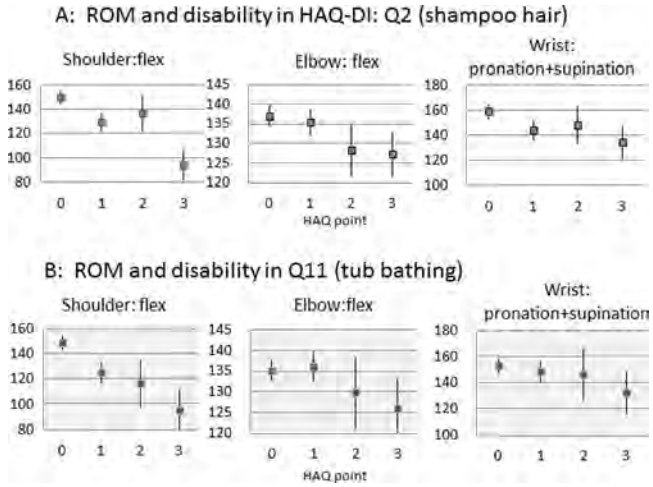
Methods: We started the prospective study in September, 2012 (Study registration: UMIN000012649). We collected data on age, sex, disease duration, drug therapies, and disease activity. Functional evaluations were made using the HAQ-DI, DASH (Disability of Arm, Shoulder and Hand; upper limb function), and JSSF-RA (foot and ankle function), and patient subjective evaluations using the EQ-5D (QOL) and BDI-II (depression). Joint range of motion was also measured as part of this evaluation. This study is supported by grant from the Japanese Ministry of Health, Labour and Welfare.

Results: 347 surgical patients were registered. Mean values for age, disease duration, and sex were 65.2 years, 18 years, and 88% female, respectively. Actually, even long-standing RA patients who were needed joint surgery had remission or low disease activity in this baseline data (median values for DAS28 (3.0) and CRP (0.33 mg/dl). 23.8% of the patients were treated with biologics. We confirmed the significant correlation between HAQ-DI and EQ-5D, BDI-II; DASH and BDI-II ($P<0.05$). Assistive use of upper limb was required for arising, climbing stairs, standing up from the sofa, and walking outside by 52%, 51%, 44%, and 29% of patients, respectively.

We found significant relationship between ROM of joints in upper limb (shoulder, elbow and wrist) and the level of disability in HAQ-DI: Question 2 (shampoo hair), Q4 (arising), Q11 (tub bathing), and Q16 (opening and closing a wide mouth jar).

ROMs of the joints [age-adjusted mean values (95% CI)] which represented nearly non-existent levels of disability in each questioner of HAQ-DI, are as follows; wrist; flexion-extension 69.9 (61.4–78.5)°, pronation and supination 151.0 (145.4–158.6)°, elbow; flexion 135.3 (131.9–138.7)°, and shoulder; flexion 129.6 (122.2–137.0)°. (Fig. A and B).

Conclusion: ROMs of the joints in upper limbs were significantly associated with many kinds of daily activity including arising and bathing. The information should be important for assessment of disability in patients with long-standing RA. The ROM as shown in this study could be target of surgical procedure. It will be validated by further analysis of longitudinal data of this study.



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a Dual-Center, Double Blind Randomized Study for a New Scientific Approach in Assessment of Tender Joints in Inflammatory Arthritis Using the Smart Joint Assessor Glove Device (Smart JAG Device). Mohammad Khan[1], Larry Willis[2], Swapan Nath[3], Cheryl Guest[2], Lindsey Gillispie[4] and Mary Jane Rorick[4]. [1]Arthritis & Rheumatology Center of Oklahoma, Oklahoma City, OK, [2]Arthritis & Rheumatology Center of Oklahoma, PLLC, Oklahoma City, OK, [3]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [4]McBride Orthopedic Hospital, Oklahoma City, OK.

Background/Purpose: Tender Joint Count (TJC) is a vital quality measure to assess the progression of Inflammatory Arthritis both from a therapeutic and a diagnostic standpoint. To date no scientific instruments are available to validate and standardize a Joint Count and these assessments remain largely subjective to the Joint Assessor. Physician variability, depending upon the technique and the force used in Tender joint count assessments, can significantly impact the Disease Activity Scores. Both inter and intra-observer variability bias in assessing Tender Joint Count can be pivotal in impacting the outcome of a trial.

Objectives: Primary Objective Tender Joint Count Assessments are significantly accurate using the Smart JAG Device than with conventional Joint Assessments.

Secondary Objective Establishing a high degree of consistency over time to monitor therapeutic response and improved joint function.

Methods: We present a smart hand held glove device for Tender Joint Count Assessment. The first of its kind that allows standardizing a joint exam based on scientific rationale.

We examined 100 patients (2800 joints) with moderate to severe inflammatory arthritis as defined by ACR criteria for their respective disease states maintained on DMARD therapy. A standardized 28 Joint Count was performed on all subjects. Each subject underwent a Tender Joint Exam by a total of 4 different assessors that were blindly randomized to the device. Two Joint Assessors performed the joint count using the device and two performed without the device. All joint assessors were blinded. Each joint count was performed after approximately 30 minute intervals. All assessors were blindly randomized to the device. The device was programmed at 4kg pressure to beep as a signal so that the same amount of pressure was applied consistently throughout on all the joints measured. The device beeped every time on reaching the desired pressure. This smart device has the capability of connecting via wireless connection to computer software with a built-in voice recognition system. Tender Joints are captured based on voice recognition of the Assessor in real time. The software has LED mode feature for the hearing impaired. At the conclusion of the Joint Assessment, this software is able to give a total Tender Joint Count with memory capability that can be retrieved. It can also calculate a CDAI and DAS-28 if needed.

Results: There was striking difference in consistencies between the 2 groups. We found only 4.5% discrepancy within the device users as compared to 15% in non-device users. We performed a "paired t-test" between the discrepancy measures from the 2 groups. We found strong statistical significance between the 2 groups. ($p<9.8 \times 10\text{-}8$).There were no significant differences in the overall mean tender joints in either group.

Conclusion: The device measures tender joints with high accuracy and has less discrepancy between different users. Can be used by other health care personnel as joint assessors and has a high yield to assess therapeutic efficacy over time. It is also much less time consuming and standardizes tender joint exams by keeping the pressure as constant with less inter and intra observer variability.

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Using Patient Reported Outcome Measures to Classify Disease Activity States in Rheumatoid Arthritis: A Comparison of Patient-Derived Versions of Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI) and Disease Activity Score 28 (DAS28). Erin Carruthers[1], Noura AL Osaimi[2], Charles H Goldsmith[3], Paul Adam[4] and Diane Lacaille[5]. [1]Arthritis Research Centre of Canada, Richmond, BC, [2]University of Ottawa, Ottawa, ON, [3]Simon Fraser University, Burnaby, BC, [4]Mary Pack Arthritis Centre, Vancouver, BC, [5]University of British Columbia, Vancouver, BC.

Background/Purpose: In RA the target for treatment is clinical remission or minimal disease activity. Patient self- monitoring of disease activity may enhance treatment by providing early warnings when targets are not met, indicating the need to re-evaluate treatment. The objective of this study is to compare agreement between patient and rheumatologist (MD) derived disease activity states using Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI) and Disease Activity Score 28 (DAS28).

Methods: Consecutive RA patients presenting for follow-up to seven rheumatologists were invited to participate. Consenting patients completed a questionnaire and performed a self-report joint count before their visit. MD joint count and lab values were obtained from charts. Disease activity was evaluated using patient and MD versions of CDAI, SDAI and DAS28. In patient versions, patient joint counts were used and MD global assessments were replaced with patient global assessments (for CDAI and SDAI). Disease states were categorized into remission, low, moderate or high, according to published cut points. Because change in treatment is recommended with moderate or high disease activity, we also compared instruments using two categories: remission or low vs. moderate or high. Agreement between patient and MD derived disease states were evaluated using Agreement Coefficient 1 (AC1) for two category comparisons and Agreement Coefficient 2 (AC2), weighted with quadratic weights, for four category comparisons. AC values > 0.62 were considered good agreement. Z tests were used to evaluate the statistical significance of the difference between pairs of ACs. All p values were 2 tailed.

Results: We recruited 150 RA patients [mean (SD) RA duration: 11.9 (11.3) y; age: 57.8 (16.3) y; 81% female]. **Table 1** shows agreement between patient and MD derived disease activity measures (all p values < 0.001). There was good agreement between patient and MD derived disease activity states from the same measure, except when comparing patient and MD DAS28 across four categories, which had slightly lower agreement. There was no significant difference in the agreement between the patient and MD versions of the three measures when using four categories [CDAI vs. SDAI AC2: $p = 0.480$; CDAI vs. DAS28 AC2: $p = 0.633$; SDAI vs. DAS28 AC2: $p = 0.915$] or two categories [CDAI vs. SDAI AC1: $p = 0.580$; CDAI vs. DAS28 AC1: $p = 0.052$; SDAI vs. DAS28 AC1: $p = 0.062$].

Conclusion: Our results suggest that patients can self-monitor disease activity using patient derived CDAI, SDAI or DAS28 measures. Good agreement was found between the disease activity states derived from patient data and MD data from the corresponding measure, except for DAS28 when using four categories. There was no statistically significant difference in the agreement across measures.

Table 1. Agreement between patient and MD derived indices measured across four and two disease activity categories.

A	Comparison across four categories (remission vs. low vs. moderate vs. high)		
PATIENT MEASURES	RHEUMATOLOGIST MEASURES		
	CDAI-MD AC2 [95% CI]	SDAI-MD AC2 [95% CI]	DAS28-MD AC2 [95% CI]
CDAI-Pt	**0.67 [0.55, 0.79]**	**0.67 [0.54, 0.79]**	0.43 [0.29, 0.58]
SDAI-Pt	**0.62 [0.49, 0.75]**	**0.68 [0.56, 0.81]**	0.39 [0.24, 0.55]

DAS28-Pt	0.55 [0.42, 0.69]	0.50 [0.35, 0.64]	0.58 [0.45, 0.71]

B — **Comparison across two categories (remission or low vs. moderate or high)**

PATIENT MEASURES	RHEUMATOLOGIST MEASURES		
	CDAI-MD	**SDAI-MD**	**DAS28-MD**
	AC1 [95% CI]	**AC1 [95% CI]**	**AC1 [95% CI]**
CDAI-Pt	**0.80 [0.75, 0.85]**	**0.80 [0.75, 0.86]**	0.43 [0.29, 0.57]
SDAI-Pt	**0.77 [0.72, 0.82]**	**0.79 [0.74, 0.85]**	0.38 [0.24, 0.53]
DAS28-Pt	**0.71 [0.64, 0.79]**	**0.67 [0.58, 0.75]**	**0.79 [0.72, 0.86]**

AC1 = agreement coefficient 1; AC2 = quadratic weighted agreement coefficient 2
All AC values have 2 tailed p-values of $p < 0.001$
Bolded values (AC > 0.62) are considered good agreement

Disclosure: E. Carruthers, None; **N. AL Osaimi**, None; **C. H. Goldsmith**, None; **P. Adam**, None; **D. Lacaille**, None.

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Normal Scores of "0" (floor effects) Are Seen in 33–83% of Patients with Rheumatoid Arthritis (RA) on 8 HAQ Activities Which Also Are Found on the MDHAQ, but in Fewer Than 32% of Patients on 2 Unique MDHAQ Complex Activities "Walk 2 Miles or 3 Kilometers," and "Participate in Recreation and Sports." Isabel Castrejón[1], Martin J. Bergman[2], Kathryn A. Gibson[3], John Meyerhoff[4] and Theodore Pincus[1]. [1]Rush University Medical Center, Chicago, IL, [2]Taylor Hospital, Ridley Park, PA, [3]Liverpool Hospital, Liverpool, Australia, [4]Sinai Hospital, Baltimore, MD.

Background/Purpose: Patients with rheumatoid arthritis (RA) have significantly better clinical status in recent years compared with previous decades. [1] Health assessment questionnaire (HAQ) scores were almost always elevated in 1980 when the HAQ was reported. [2] In a 1999 report, 16% of patients had HAQ scores of zero, suggesting "no difficulty" in function, but most nonetheless reported problems with function as well as psychosocial issues, reflecting "floor effects". [3] Therefore, a multidimensional HAQ (MDHAQ) was developed to include 13 queries in the user-friendly HAQ format, 8 simple activities of daily living (ADL) from the HAQ, and 2 unique complex activities: "walk 2 miles or 3 kilometers" and "participate in recreation and sports as you would like," and 2 psychological items. We analyzed mean scores and percent of patients with scores of "0", suggesting normal function, for each of the 10 MDHAQ activities in patients with RA in 3 rheumatology settings, 2 in the USA and one in Australia.

Methods: All patients at 3 settings in Ridley Park, PA, USA, Baltimore, MD, USA, and Liverpool, NSW, Australia, complete an MDHAQ at each visit in the reception area before seeing the physician. The MDHAQ queries 10 activities, 8 simple activities on the HAQ and 2 unique complex activities only on the MDHAQ (Table), all scored 0–3, with 4 response options: without any difficulty=0, with some difficulty=1, with much difficulty=2 and unable to do=3. Mean scores were analyzed in RA patients. Statistical significance was evaluated using Wilcoxon signed rank tests.

Results: A total of 314 patients were analyzed. A similar pattern was observed at each of the three sites. Mean scores were less than 0.92 (0–3 scale) for all 8 HAQ items in all patient groups; 33%-83% scored "0" on these items. Mean scores were greater than 1.27 on the 2 complex activities, "walk 2 miles/3 kilometers" and "participate in recreation/sports as you would like." Fewer than 32% of patients scored "0" on these items.

	Questionnaire items	USA, PA: RA (n=224 pts) Mean (% 0)	USA, MD: RA (n=27 pts) Mean (% 0)	Australia: RA (n=63 pts) Mean (% 0)
Traditional HAQ items	a. Dress yourself	0.49 64%	0.65 46%	0.62 55%
	b. Get in and out of bed	0.43 64%	0.52 54%	0.53 67%
	c. Lift a cup to your mouth	0.18 83%	0.27 71%	0.33 75%
	d. Walk outdoors on flat ground	0.58 58%	0.81 37%	0.39 67%
	e. Wash/dry one's body	0.39 70%	0.73 42%	0.52 64%
	f. Bend down to pick up clothing	0.57 57%	0.61 46%	0.60 54%
	g. Turn on taps/faucets	0.29 77%	0.50 54%	0.64 54%
	h. Get in and out of car/bus	0.57 55%	0.92 33%	0.54 59%
Unique MDHAQ items	i. Walk 2 miles/3 kilometers	1.48 30%	1.85 8%	1.27 32%
	j. Participate in recreation/sports	1.48 24%	1.77 4%	1.64 20%

Conclusion: The 2 unique MDHAQ complex activities identify patient problems which are not captured by the 8 items from the HAQ, similarly in USA and Australia. This information may be valuable in clinical management and documentation of improvement over time, which is not possible when baseline scores are zero. The MDHAQ might be considered for usual clinical care as well as in clinical trials.

References:

1) Arthritis Rheum 2005;52:1009–19.
2) Arthritis Rheum 1980;23:137–45.
3) Arthritis Rheum 1999;42:2220–30.

Disclosure: I. Castrejón, None; **M. J. Bergman**, None; **K. A. Gibson**, None; **J. Meyerhoff**, None; **T. Pincus**, None.

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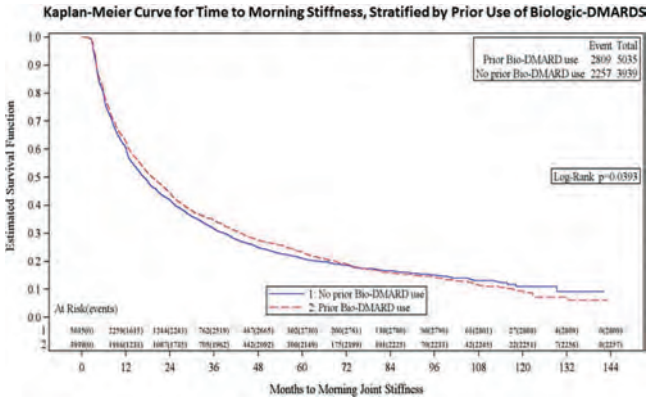
Prevalence of Morning Stiffness in a US Registry Population of Rheumatoid Arthritis Patients. Vibeke Strand[1], Robert J. Holt[2], Katherine C. Saunders[3], Jeffery D. Kent[4], Ping Xu[5], Amy Y. Grahn[4], Marc Mason[3] and Carol J. Etzel[3]. [1]Stanford University, Palo Alto, CA, [2]University of Illinois - Chicago, Chicago, IL, [3]Corrona, LLC., Southborough, MA, [4]Horizon Pharma, Inc., Deerfield, IL, [5]Axio Research LLC, Seattle, WA.

Background/Purpose: Morning stiffness is a symptom of rheumatoid arthritis (RA) that is frequently reported and thought to reflect disease activity, but its etiology is poorly understood.

Methods: Using the Corrona RA registry, data from RA patients enrolled from October 2001–February 2014 were evaluated cross sectionally at: enrollment and last visit between January 2013 and February 2014 for those with at least one visit during that interval. Longitudinal data from 2003 to 2014 were summarized to estimate changes in prevalence of morning stiffness over time reported by all Corrona RA patients.

Results: Prevalence of morning stiffness at enrollment was 74.1% and at last visit was 69.9%; mean (SD) duration 1.7 hours (± 3.1) and 1.5 hours (± 3.0), respectively. Approximately 50% of patients reporting morning stiffness with a duration ≥ 1 hour at last visit. Patients with morning stiffness were significantly less likely to be working 39.2% vs 47.3% and were more likely to have a BMI ≥ 30 (42.2% vs 29.9%) at last visit. Similar rates of treatment with biologic DMARDs as mono therapy or in combination with non-biologic DMARDs were observed in patients with and without morning stiffness. Among patients with no reported morning stiffness at time of enrollment, time in months to first visit with reported morning stiffness was not significantly different between patients with or without prior biologic DMARD experience(Figure 1).

Conclusion: Morning stiffness continues to be reported by a high proportion of US patients despite treatment with non-biologic and biologic DMARDs and the overall prevalence has remained relatively stable over the past 10 years. Patients reporting this symptom were also more likely to be not working. More research is needed to better understand how to manage morning stiffness in clinical practice.



Disclosure: V. Strand, AbbVie, Afferent, Amgen, Biogen Idec, Bioventus, BMS, Carbylan, Celgene, Celltrion, CORRONA, Crescendo, Genentech/Roche, GSK, Hospira, Iroko, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi, SKK, Takeda, UCB, Vertex, 5, Up to Date, 7; **R. J. Holt**, Horizon Pharma, Inc., 5; **K. C. Saunders**, Corrona, LLC., 3; **J. D. Kent**, Horizon Pharma, Inc., 1, Horizon Pharma, Inc., 3; **P. Xu**, Axio Research, LLC, 3; **A. Y. Grahn**, Horizon Pharma, Inc, 1, Horizon Pharma, Inc., 3; **M. Mason**, Corrona, LLC., 3, NIH, 6; **C. J. Etzel**, Corrona, LLC., 3.

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Comparative Dynamics of Rheumatoid Arthritis Disease Activity and Disease Severity Measures Using Rarbis, Ciras and DAS28 in a Population Based Cohort of Patients with RA. Arun K. Chandran[1], Cynthia S. Crowson[1], Birkan İlhan[2], C. John Michet[1], Eric L. Matteson[1] and Elena Myasoedova[1]. [1]Mayo Clinic, Rochester, MN, [2]Marmara University School of Medicine, Istanbul, Turkey.

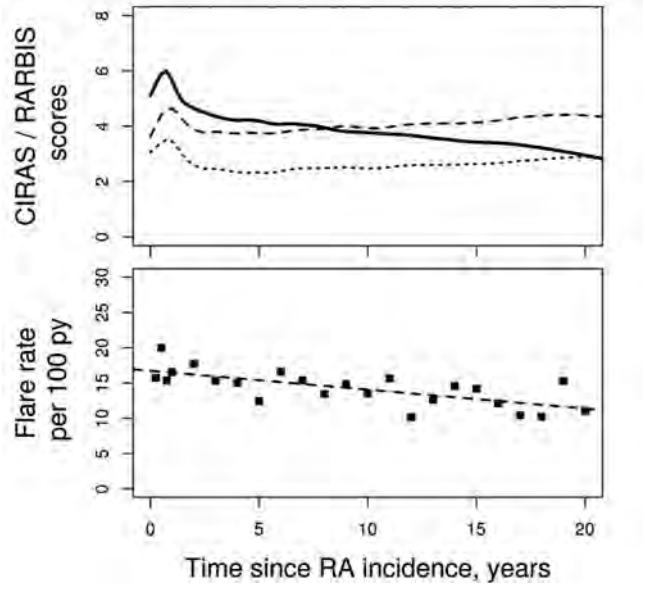
Background/Purpose: There is an extensive list of composite scores of rheumatoid arthritis (RA) activity status for the use in clinical practice including Disease Activity Score (DAS) and DAS-28. Much less common are validated definitions and scores of RA activity and severity for use in healthcare databases. The Record based Index of Severity (RARBIS) and the Claims-based Index for RA Severity (CIRAS) are methods used for this purpose. Our objective was to assess the dynamics of the CIRAS and RARBIS as measures of RA disease severity over time and to assess their correlation with DAS28.

Methods: A population-based inception cohort of 525 patients with incident RA (as per the 1987 ACR Criteria) in 1988–2007 was retrospectively identified and followed until 7-1-2012. The available data to calculate the RARBIS (joint surgeries, erosions, extra-articular manifestations, arthritis flares, morning stiffness, rheumatoid factor [RF] positivity, acute phase reactants and antirheumatic medications) were collected at every visit via medical record review. Claims data were used to calculate the CIRAS at every visit using 1 year prior data on number of inflammatory marker tests, platelet counts, chemistry panels, rheumatology visits, rehabilitation visits, assessment of RF, and Felty's syndrome. DAS28 was also collected, when available. RA flare was defined based on OMERACT 9 definition. Scores were compared using Spearman's correlation.

Results: The 525 patients (mean age 55; 71% female) in our cohort had 15,649 visits (mean 30 visits per patient) with an average of 10.3 years follow-up. The mean RARBIS with medication at RA incidence was 3.3 (SD 1.4) and the CIRAS was 4.5 (SD 1.9). There was an increase in both, CIRAS and RARBIS scores during the first year of disease (Figure). Thereafter, the CIRAS scores tended to decrease, but the RARBIS values showed little change over the disease course. The flare rate decreased significantly during the follow-up by 0.3 per 100 person-years per year ($p<0.001$). There was a statistically significant correlation between RARBIS and CIRAS scores ($r=0.19$, $p<0.001$). DAS28 was available in only 278 visits. There was a moderate correlation between DAS28 and RARBIS ($r=0.40$; $p<0.001$) and a weaker correlation between CIRAS and DAS28 ($r=0.16$; $p=0.008$).

Conclusion: The uniform increase in CIRAS and RARBIS values during the first year after index date may reflect initial spike of RA activity and initial extensive work up of RA disease. Subsequent decline in CIRAS scores is concordant with decreasing flare rates, and could be due to the gradual decrease in the need for comprehensive laboratory workup and decreased frequency of rheumatology visits in patients with established disease. CIRAS and RARBIS scores were found to be significantly correlated with DAS28 suggesting that these indices may be helpful measures of RA activity/ severity in healthcare database research.

Figure 1. Trends in CIRAS (solid line) RARBIS with medications (dashed line) and RARBIS without medications (dotted line) [upper panel] and flare rate [lower panel].



Disclosure: A. K. Chandran, Roche Pharmaceuticals, 2; **C. S. Crowson**, Roche Pharmaceuticals, 2; **B. İlhan**, None; **C. J. Michet**, None; **E. L. Matteson**, None; **E. Myasoedova**, Roche Pharmaceuticals, 2.

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Less Is More: The Shorter Physical Function Measure Promis-PF10a Outperforms HAQ in an Ethnically Diverse, Urban Rheumatoid Arthritis Clinic Population. Elizabeth R. Wahl, Andrew J. Gross, R Krishna Chaganti, Lianne S. Gensler, Vladimir Chernitskiy, Laura Trupin, Patricia P. Katz and Jinoos Yazdany. University of California, San Francisco, San Francisco, CA.

Background/Purpose: Patient-reported outcome measures are important tools that assess the impact of disease on patients' lives; in RA, patient-reported physical function is especially relevant. In contrast to legacy measures such as the Health Assessment Questionnaire (HAQ) or Short Form 36 Health Survey (SF-36), the Patient-Reported Outcome Measurement Information System (PROMIS) scales are brief and intended to address psychometric flaws in earlier measures such as ceiling effects. However, use of PROMIS in clinical practice has been limited. The current study evaluates the ceiling and floor effects of the PROMIS Physical Function short form 10a (PROMIS-PF10a) relative to the HAQ, and compares the construct validity of these measures to a commonly used measure of disease activity (Clinical Disease Activity Index, CDAI), among patients with RA in an ethnically diverse urban clinic.

Methods: We abstracted demographic and clinical data from the electronic health record (EHR) of patients from a university-based rheumatology clinic. Eligible patients had 2 ICD-9 codes for RA between February 2013 and March 2014, had completed PROMIS-PF10a and HAQ, and had CDAI scores recorded by a clinician. We characterized score distributions for PROMIS T-scores and HAQ, including percent of patients with minimum and maximum possible scores. Construct validity was evaluated by examining the matrix of correlation coefficients (Pearson's r) among PROMIS-PF10a, HAQ and CDAI.

Results: Analyses included 78 patients. 78% were female, mean age was 57.0± 14.4 years, 59% were Caucasian, 15% Hispanic/Latino, and 10% Asian. 82% were RF or CCP positive, 51% had erosive disease and mean disease duration was 12± 11 years. The mean PROMIS-PF10a score was 44.3; the mean HAQ score was 0.82. The distribution of PROMIS-PF10a scores more closely approximated a normal distribution (Figure), and had a lower proportion of scores at the ceiling (Table). There was a statistically significant correlation between PROMIS-PF10a and HAQ scores of $r = -0.61$, and a modest significant correlation between PROMIS-PF10a and CDAI scores of $r = -0.48$. The relationship between HAQ and CDAI was not statistically significant ($r = 0.19$).

Conclusion: In this ethnically diverse RA clinic population, the shorter PROMIS-PF10a had a distribution closer to normal with less ceiling effect, which enables better discrimination at higher levels of functioning. PROMIS-PF10a also had a higher correlation with CDAI scores than HAQ. Further studies are needed to understand the relative responsiveness of changes in PROMIS physical function scores compared to legacy measures.

Table. Score Characteristics and Floor/Ceiling Effects for PROMIS-PF10a and HAQ.

		Scores			Floor (poorest function)	Ceiling (best function)
MEASURE	Mean ± SD	Median	Min	Max	N (%)	N (%)
PROMIS-PF10a	44.3 ± 9.3	41.4	27.1	61.7	0	10 (12.8%)
HAQ	0.82 ± 0.66	0.88	0	2.25	0	15 (19.2%)

Higher PROMIS-PF10a scores reflect better function while higher HAQ reflects poorer function. Normalized PROMIS-PF10a scores can range from 14.1–61.7. A score of 50 represents average function in a healthy individual; each 10-point decrement represents one standard deviation from this norm. HAQ scores range from 0–3. A score of 0 represents no limitation in functioning.

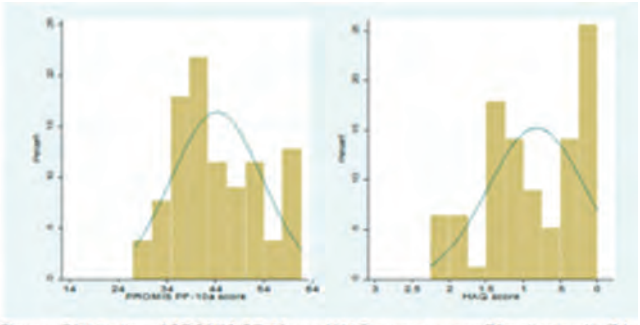

Figure. Distribution of PROMIS PF-10a and HAQ scores among 78 patients with RA.

Disclosure: E. R. Wahl, None; **A. J. Gross**, None; **R. K. Chaganti**, None; **L. S. Gensler**, UCB, 5, AbbVie, 5, Celgene Corporation, 9; **V. Chernitskiy**, None; **L. Trupin**, None; **P. P. Katz**, None; **J. Yazdany**, None.

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Prediction of Remission By Patients and Physicians: Does the Doctor Know Best? WG Bensen[1], Boulos Haraoui[2], Carter Thorne[3], Edward Keystone[4], Michel Zummer[5], Isabelle Fortin[6], Rafat Faraawi[7], Andrew Chow[8], Milton Baker[9], Niall Jones[10], Emmanouil Rampakakis[11], John S. Sampalis[11], May Shawi[12], Francois Nantel[12], Allen J Lehman[12] and Susan Otawa[12]. [1]St Josephs Hospital and McMaster University, Hamilton, ON, [2]University of Montreal Hospital Centre, Montreal, QC, [3]Southlake Regional Health Centre, Newmarket, ON, [4]Mount Sinai Hospital, University of Toronto, Toronto, ON, [5]Université de Montréal, Montreal, QC, [6]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, [7]McMaster University, Hamilton, ON, [8]McMaster University, Hamilton and Credit Valley Hospital, Mississauga, ON, [9]University of Victoria, Victoria, BC, [10]University of Alberta, Edmonton, AB, [11]JSS Medical Research, Montreal, QC, [12]Janssen Inc., Toronto, ON.

Background/Purpose: Patient (PtGA) and physician (MDGA) assessment of global disease activity have been used as outcome measures individually or as part of composite scores in the measurement of rheumatoid arthritis (RA) disease severity and the evaluation of treatment effectiveness. However, discordance between the two is common[1]. The question arising is which global measure is a more valid predictor of disease remission.

The aim of the analysis was to compare PtGA and MDGA with respect to their association with remission based on DAS-28, SDAI and CDAI, using a sequential cross-sectional analysis.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with infliximab (IFX) or golimumab as first biologics or after having been treated with a biologic for <6 months. Eligible patients for this study included RA patients treated with IFX who were enrolled between 2002 and 2012 with available information on 6-, 12-, or 18-month remission. Logistic regression analysis with the parametric Wald statistic was used to compare the independent association of MDGA and PtGA with remission at 6, 12 and 18 months. The WALD statistic assesses the extent of contribution of an individual predictor to an outcome of interest and can be used to compare the contribution of different predictors.

Results: A total of 657 patients were included with mean (SD) age of 56.2 (13.5) years and disease duration of 10.1 (10.0) years. Significant ($P<0.001$) associations were observed between both PtGA and MDGA and achievement of remission at the corresponding assessments regardless of remission type. For DAS28 remission, the Wald statistic at 6, 12 and 18 months for MDGA vs. PtGA was 26.9 vs. 39.2, 12.7 vs. 35.9, and 19.8 vs. 22.5, respectively. For SDAI remission the MDGA and PtGA Wald statistics were 27.7 vs. 24.5, 27.8 vs. 28.5, and 32.4 vs. 23.4, respectively, at 6, 12 and 18 months. For CDAI remission, the Wald statistic for MDGA vs. PtGA at these time points was 34.8 vs. 26.9, 38.1 vs. 37.2, and 39.5 vs. 27.1. Similar results were obtained for predicting low disease activity.

Conclusion: The results of this analysis show that PtGA is a better predictor of DAS28 disease remission compared to MDGA. This could be explained by the fact that DAS28 includes PtGA and not MDGA. However, for CDAI and SDAI, physicians were better in predicting remission although the superiority of the MDGA was not consistent over time.

References:

1. Bensen WG et al. Identification of Four Parameters that Drive the Discordance Between the Patient and Physician Global Assessment in Rheumatoid Arthritis. Canadian Rheumatology Association Annual Scientific Meeting, 2013, Ottawa, ON, Canada.

Disclosure: W. Bensen, None; **B. Haraoui**, AbbVie, 2, AbbVie, 5, Amgen, 2, Amgen, 5, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5, Janssen Pharmaceutica Product, L.P., 2, Janssen Pharmaceutica Product, L.P., 5, Pfizer Inc, 2, Pfizer Inc, 5, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5, UCB, 2, UCB, 5; **C. Thorne**, Janssen Inc., 5; **E. Keystone**, Abbott, Amgen, AstraZeneca, BMS, F. Hoffmann-La Roche, Janssen, Lilly, Novartis, Pfizer Sanofi-Aventis, UCB, 2, Abbott Laboratories, AstraZeneca, Biotest, BMS, F. Hoffmann-La Roche, Genentech, Janssen, Lilly, Merck, Pfizer, UCB, 5, Abbott, AstraZeneca, BMS Canada, F. Hoffmann-La Roche, Janssen, Pfizer, UCB, Amgen, 8; **M. Zummer**, Janssen Inc., 5; **I. Fortin**, Janssen Inc., 5; **R. Faraawi**, None; **A. Chow**, Janssen Inc., 5; **M. Baker**, Janssen Inc., 5; **N. Jones**, None; **E. Rampakakis**, None; **J. S. Sampalis**, None; **M. Shawi**, Janssen Inc., 3; **F. Nantel**, Janssen Inc., 3; **A. J. Lehman**, Janssen Inc., 3; **S. Otawa**, Janssen Inc., 3.

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Correlation of RAPID3, DAS28 and CDAI in Disease Activity and Effects of Education Level and Co-Morbid Diseases on This Assesment in RA. Kubilay Sahin[1], Yasar Karaaslan[2], Zeynep Ozbalkan[1], Ahmet Omma[1] and Nesibe Yesil[1]. [1]Ankara Numune Education and Research Hospital, Ankara, Turkey, [2]Hitit University, Corum, Turkey.

Background/Purpose: RAPID3 is an activity index based on only the patient's report in RA. It doesn't require joint counts and it isn't time consuming. Therefore this situation makes the index very attractive for physicians. It has been shown in clinical studies that RAPID3 gives corralated information with DAS28 and CDAI.

In this study, we aimed to determine the correlation of RAPID3, DAS28 and CDAI in the assesment of disease activity and effects of education level and co-morbid diseases on this assesment in RA patients who were followed in a tertiary rheumatology clinic of Turkey.

Methods: 246 RA patients (80.1% female, mean age: 53.2±12.1 years) followed up for at least 3 months between January-June 2013 were included to the study. All patients were asked to fill out RAPID3 questionnaires. Uneducated patients completed the survey with the help of medical secretary. RAPID3, DAS28 and CDAI was calculated in all patients. Patients were subdivided according to disease severity as group A (remission-minimal disease activity) and group B (medium-severe disease activity) for all scoring systems. All data were analyzed using statistical software; SPSS (Statistical Package For Social Sciences) for Windows 20 (SPSS Inc, Chicago, IL). One way Annova, Kruskal Wallis analysis, kappa analysis and Spearman correlation were used for statistics. A level of $p < 0.05$ was considered significant.

Results: 27.2% of the patients were uneducated, the rest were educated graduating from 50.8% primary school, 16.6% secondary/high school and 5.3% university. Mean training period of the patients was 4.9 years. 47.6% of the patients had at least one comorbid disease (i.e. hypertension, diabetes, hypo/hyperthyroidism, coronary artery disease, lung disease or obesity). Correlation of RAPID3 with the DAS28 and CDAI score was statistically significant ($p<0.001$). Similarly, educational status and the presence of comorbid disease didn't effect this correlation ($p<0.001$). Kappa analysis showing compliance of RAPID3 with DAS28 and CDAI scores was also significant ($p<0.001$).

100% of the patients with severe disease activity according to DAS28 also had moderate/severe disease activity according to the RAPID3. 77% of patients who were in remission according to DAS28 have near remission–minimal disease activity according to RAPID3. Patients with high disease activity according to the CDAI also had severe disease activity (100%) according to RAPID3, while 97% of patients who were in remission according to the CDAI have near remission-minimal disease activity according to RAPID3.

Conclusion: Similar to previous studies, RAPID3 was significantly correlated with DAS28 and CDAI score. Even though RAPID3 could be effected by patients educational status, when we compared the patients as educated/uneducated, there was no significancy. At the same time, presence of co-morbid diseases didn't effect the correlation of RAPID3 with DAS28 and CDAI. RAPID3 can provide quantitative information in uneducated patients and with presence of comorbid diseases just like DAS28 and CDAI.

Disclosure: K. Sahin, None; **Y. Karaaslan**, None; **Z. Ozbalkan**, None; **A. Omma**, None; **N. Yesil**, None.

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Circulating Anti-Citrullinated Peptide Antibodies and Cytokines As Biomarkers of Response to Disease-Modifying Antirheumatic Drugs Therapy in Early Rheumatoid Arthritis. Mahmood MTM Ally[1], Pieter Meyer[2], Bridget Hodkinson[3], Eustasius Musenge[4], Gregory Tintinger[2], Mohammed Tikly[5] and Ronald Anderson[1]. [1]University of Pretoria, Pretoria, South Africa, [2]university of pretoria, pretoria, South Africa, [3]University of the Witwatersrand, Johannesburg, South Africa, [4]University of Witwatersrand, Johannesburg, South Africa, [5]C H Baragwanath Hospital, Johannesburg, South Africa.

Background/Purpose: Serial measurement of circulating anti-citrullinated peptide antibodies (ACPA) and cytokines is of potential importance in the management of patients with rheumatoid arthritis (RA). However, the utility of this strategy in monitoring responses to traditional disease-modifying antirheumatic drugs (DMARDs) in early RA is largely untested.

Methods: A cohort of 140 predominantly (88.5%) black female South African patients with early RA median (IQR) symptom duration 9.7 (11.4)

months was treated with synthetic DMARDs, mostly methotrexate (MTX), either as monotherapy or combination DMARD therapy, mostly combined with low-dose oral corticosteroids (CS). The simple disease activity index (SDAI) was used to evaluate clinical response, while circulating ACPA and a panel of circulating cytokines/chemokines/growth factors were measured using immunofluorimetric and multiplex suspension bead array procedures respectively at baseline and after 6 months of therapy. Shared epitope genomic analysis was done using PCR typing of the HLA-DRB1 allele.

Results: Following 6 months of therapy, the median SDAI declined from a baseline of 41.39 to 16 ($p=0.0001$) for the entire cohort. This decline in disease activity was paralleled by significant falls in median serum ACPA levels (516.6 vs. 255.65 units, $p=<0.0001$) and several of the circulating cytokines (IL-4, IL-6, IL-7, IL-8, G-CSF, VEGF, CCL4; $p<0.023$ – $p<0.0001$) which were most evident in the subgroup of patients treated with a combination of MTX and CS. No significant correlations between these biomarkers and disease activity were observed. Baseline ACPA levels, but not SDAI or cytokines, were significantly higher in the subgroup of risk allele-positive patients (594.1 vs. 255.7 units, $p<0.05$), while no associations with ACPA and a smoking history were evident.

Conclusion: The use of synthetic DMARDs in early RA is associated with significant decreases in SDAI, paralleled by a decrease in ACPA and predominantly pro-inflammatory cytokines. However, the lack of correlation of ACPA and the other biomarkers with therapy-associated alterations in disease activity in the short term appears to preclude the utility of serial measurement of these biomarkers to monitor early responses to therapy, while the long-term, prognostic potential remains to be established.

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The Comparison Between Physical and Ultrasound Joint Examination for the Hand Joints in Patients with Rheumatoid Arthritis. Norihide Hayashi, Takehisa Ogura, Ayako Hirata, Rie Kujime, Munetsugu Imamura, Sayaka Takenaka, Kennosuke Mizushina, Sumie Nakahashi, Hideki Ito, Naoko Yamashita and Hideto Kameda. Toho Univ, Tokyo, Japan.

Background/Purpose: To establish the importance of joint examination by ultrasound (US) in daily clinical practice of patients with rheumatoid arthritis (RA), we compared the US findings with the joint examination findings sorted by the presence of tenderness and/or swelling in the hand (proximal) interphalangeal (IP/PIP), metacarpophalangeal (MCP) and wrist joints.

Methods: A total of 208 RA patients (158 female, the mean age of 66 years) completed clinical, laboratory and US assessments between October 2011 and December 2013. Clinical joint assessments determined the presence of tenderness alone (T) or swelling alone (S), both (TS) or none (N) of them. US synovitis was defined as gray-scale (GS) imaging score ≥ 1 (graded 0–3) or a synovial power Doppler (PD) signal score ≥ 2 (graded 0–3).

Results: Among total joints assessed, US synovitis was observed in 146 of 178 TS joints (82%), 50 of 128 T joints (28%), 130 of 201 S joints, and 309 of 3710 N joints. Therefore, joint swelling is more closely associated with US synovitis than joint tenderness. Next, even among TS joints, US synovitis was observed only in 50% (23/46) of IP/PIP joints, which was significantly less than 95% (55/58) and 92% (68/74) for the wrist and MCP joints, respectively ($p<0.01$). Among N joints, conversely, US synovitis was observed in 32% (92/286) of the wrist joints, which was greater than 9%(56/624) for the MCP joints and 9% (52/1898) of IP/PIP joints ($p<0.0001$).

	TS	T	S	None
Wrist (n = 416)				
US+	55	13	37	92
US-	3	7	15	194
MCP (n = 2080)				
US+	68	25	73	165
US-	6	40	33	1670
IP/PIP (n = 2080)				
US+	23	12	20	52
US-	23	81	23	1846
Total (n = 4576)				
US+	146	50	130	309
US-	32	128	71	3710

Conclusion: Based on the US findings, physical joint examination of the IP/PIP and the wrist joints tends to overestimate and underestimate synovitis, respectively. Thus, clinical importance of US examination in daily clinical practice may differ among joint sites, probably due to the structural complexity in the wrists and the co-existing osteoarthritis in IP/PIP joints.

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Beyond Disease Activity: Patient Global Scores Also Reflect Treatment Expectations and Emotional Reactions to Living with Rheumatoid Arthritis. Susan J. Bartlett[1], Maria Celia Bazan Bardales[2] and Ines Colmegna[3]. [1]Johns Hopkins University, Baltimore, MD, [2]McGill University, Montreal, QC, [3]McGill University - Royal Victoria Hospital, Montreal, QC.

Background/Purpose: Illness perceptions (IP) are the beliefs and expectations that an individual has about medical conditions. IP have been found to cluster around five coherent themes (identity; cause; time-line; consequences; and cure/control). Positive IPs have been associated with higher adherence, better disease outcomes and wellbeing in several chronic diseases. Relatively less is known about how illness perceptions impact patient perceptions of wellbeing and other disease outcomes in rheumatoid arthritis (RA).

Methods: Consecutive English speaking RA patients seen at an academic center between 2013– 2014 were asked to complete the Illness Perception Questionnaire – Revised (IPQ-R). Clinical RA indicators were obtained at each visit. Spearman correlations were calculated between IPQ-R scales and CDAI. Adjusted regression models evaluated the effect of IPQ-R on patient global scores.

Results: 50 RA patients completing the survey were mostly female (n=38;76%) with a mean (SD) education of 15 (4) yrs, and median (IQR) HAQ score of.25 (1.0). Eight (16%) had an RA duration $\leq$ 1 year and 20 (40%) of 1–5 years. Most were seropositive for RF (61%) and anti-CCP (66%); 15 (30%) were on biologics. CDAI scores classified 13 (26%) in remission and 18 (36%), 13 (26%) and 6 (12%) with low, moderate and high disease activity levels, respectively.

Timeline-Cyclic (rho =.32) and Personal Control (rho =.28) were significantly (p's <.05) and directly associated with CDAI; Treatment Control (rho = -.40) was inversely related to CDAI in a dose response manner (mean difference 2.3 and 3.8 between remission, low, and mod-high levels). After controlling for disease activity, Treatment Control and Emotional Representations were independent additional predictors (p's <.05) explaining 62% of the variance in patient global scores. Genetic risk factors (39%), altered immunity (26%) and psychological factors (24%) were viewed as the primary reason or an important contributing factor for developing RA. Patients who attributed their RA to psychological factors had significantly higher mean Cyclical Timeline scores (14.8 vs. 12.1; p=.004) reflecting attitudes of greater unpredictability and uncertainty around their disease.

Conclusion: Understanding patients' beliefs about the cause of their RA, as well as expectations about controllability, may offer insight into patient behaviors (e.g., adherence to treatment) that impact long-term outcomes. Beliefs about causes of RA may also affect expectations of whether and how the disease can be controlled. Clinicians may find useful to directly explore patients' expectancies around treatment, and to provide hope, encouragement and ongoing support when expectations are low.

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Exploring the DAS: What Is the Level of Agreement in the Classification of Remission and Low Disease Activity (LDA) Among the Various Versions of the Disease Activity Score (DAS) and Their Correlation? an Analysis from a Prospective, Observational Registry. WG Bensen[1], Edward Keystone[2], Philip Baer[3], Jude Rodrigues[4], J. Antonio Avina-Zubieta[5], Wojciech Olszynski[6], Denis Choquette[7], Suneil Kapur[8], Manisha Mulgund[9], John S. Sampalis[10], Emmanouil Rampakakis[10], Francois Nantel[11], Allen J Lehman[11], May Shawi[11] and Susan Otawa[11]. [1]St Josephs Hospital and McMaster University, Hamilton, ON, [2]Mount Sinai Hospital, University of Toronto, Toronto, ON, [3]Private Practice, Scarborough, ON, [4]Clinical Research and Arthritis Centre, Windsor, ON, [5]Arthritis Research Centre of Canada, Richmond, BC, [6]University of Saskatchewan, Saskatoon, SK, [7]Institut de rhumatologie de Montréal (IRM), Montréal, QC, [8]University of Ottawa, Ottawa, ON, [9]Private Practice, Hamilton, ON, [10]JSS Medical Research, Montreal, QC, [11]Janssen Inc., Toronto, ON.

Background/Purpose: Two versions of DAS28 are available, DAS28-4 comprising 4 variables [tender and swollen joint counts, acute phase reactant (APR), and patient global assessment] and DAS28-3 where patient global has been omitted. Despite the difference between DAS28-4 and DAS28-3 thresholds for remission and low disease activity (LDA) are the same. Additionally, the APR used to calculate the DAS may be either ESR or CRP. The aim of this analysis is to describe the agreement between these four possible indices, DAS28-4 ESR, DAS28-4 CRP, DAS28-3 ESR and DAS28-3 CRP and to compare them in terms of classifying remission and LDA in a real-world, routine clinical care setting.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with infliximab or golimumab. In this analysis, data from RA patients who were treated with infliximab between 2002–2014 or with golimumab between 2010–2014 and had available information in all indices were used. The definitions for remission were as follows: DAS28-3/4 <2.6; LDA was defined as: DAS28-3/4 <3.2. Correlation between the different indices was assessed with the Pearson's correlation coefficient (r) and classification agreement was assessed with Cronbach's alpha (CA) and the kappa statistic.

Results: Eight hundred sixty nine RA patients who had 3,517 complete assessments were included in the analysis. Non-remission was classified by all indices in 61.4% of cases, while remission was achieved in one (5.9%), two (10.3%), three (5.3%), or all four (17.2%) indices. Similarly, non-LDA was classified by all indices in 46.1% of cases, while LDA was achieved in one (6.2%), two (10.9%), three (5.4%), or all four (31.3%) indices.

Overall, a strong linear positive correlation ($r > 0.8$) was observed between all indices. When looking at the internal consistency in terms of classifying disease state, the CA was 0.905 for remission and 0.923 for LDA suggesting an overall high internal consistency. However, when looking at the individual inter-item correlations (Table 1), the agreement between indices was variable with DAS28-3 CRP and DAS28-4 CRP showing the highest correlation and DAS28-3 ESR and DAS28-4 CRP showing the lowest correlation. When comparing DAS28-4 ESR with DAS28-3 ESR, the latter categorized 16.5% of DAS28-4 ESR remission cases as non-remission and 3.0% of DAS28-4 ESR non-remission cases as remission. With respect to LDA, DAS28-3 ESR categorized 9.1% of DAS28-4 ESR LDA cases as non-LDA and 4.7% of DAS28-4 ESR non-LDA cases as LDA. Similar results were observed with DAS28 CRP.

Conclusion: The results of this analysis show that, despite being highly correlated, variability exists in the classification of remission and LDA by the various DAS indices. These results suggest that decision making based on disease state achieved may vary significantly based on the type of APR used in the DAS index.

Table 1 Inter-Item Correlation Matrix of DAS Remission / LDA Types

Remission	*DAS28-4 ESR*	*DAS28-4 CRP*	*DAS28-3 ESR*	*DAS28-3 CRP*
DAS28-4 ESR	–	0.678	0.824	0.670
DAS28-4 CRP	0.678	–	0.589	0.846
DAS28-3 ESR	0.824	0.589	–	0.631
DAS28-3 CRP	0.670	0.846	0.631	–
LDA				
DAS28-4 ESR	–	0.728	0.864	0.702
DAS28-4 CRP	0.728	–	0.670	0.846
DAS28-3 ESR	0.864	0.670	–	0.696
DAS28-3 CRP	0.702	0.846	0.696	–

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Multimedia Patient Education Tool for Patients with Rheumatoid Arthritis. Maria A. Lopez-Olivo[1], Aparna Ingleshwar[1], Robert Volk[1], Andrea Barbo[1], Maria Jibaja-Weiss[2], Heather Lin[1] and Maria E. Suarez-Almazor[1]. [1]The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]Baylor College of Medicine, Houston, TX.

Background/Purpose: Effective patient education provides individuals with essential information about their disease and treatment alternatives, and aids informed decision-making. The purpose of our study was to test the efficacy of a multimedia patient education tool (MM-PtET) including storylines and testimonials for patients with rheumatoid arthritis (RA).

Methods: Patients were recruited from 5 centers and through advertisement. Inclusion criteria were: (i) age $\geq$18 years (ii) diagnosis of RA by a rheumatologist (iii) disease duration $\leq$10 years (iii) adequate cognitive status and, (iv) ability to communicate in English or Spanish language. After completion of a baseline questionnaire, participants reviewed materials of the group to which they Patients were randomized to receive a MM-PtET or a written booklet, both with the same written information. They completed self-report questionnaires before and after viewing the assigned materials. Primary outcome measures included: a) Disease knowledge, and b) Decisional conflict. Secondary outcomes included: a) Acceptability, and b) Educational tool evaluation. We compared differences between and within groups for outcomes of interest. Linear regression was performed to assess the influence of the intervention and patient characteristics on the knowledge score.

Results: 221 participants were randomized (111=MM-PtET, 110=written booklet). Mean age was 51 ± 13 years, mean disease duration was 5 ± 3 years, 85%were female 24% had inadequate health literacy levels and 41(%) were Spanish speaking. Post randomization, both, intervention and control groups, showed significantly higher knowledge scores (Intervention: 5.5 ± 2.1 vs 7.6 ± 1.5 and, Control: 5.5 ± 2.1 vs 7.1 ± 2.0; $p<0.05$ for both groups) and, significantly lower "Informed" and "Values clarity" scores ($p<0.05$ for both scales). No statistically significant differences was observed between the two groups for knowledge improvement and decisional conflict scales ($p > 0.10$ for both measures). The majority of the participants in both groups gave a favorable response to all evaluation questions, with no significant differences in response options observed between the two groups ($p > 0.05$). Regarding acceptability, MM-PtET group participants were more likely to rate the presentation as "Excellent" for the following items: impact of RA, medication options, evidence about medications, benefits of medication, and self-care options ($p<0.05$ for all). Also, compared to the control group, more participants in the MM-PtET group found the length of the material presented as "just right" (Intervention vs Control: 92% vs 80%, $p=0.03$). Regression analysis indicated that, being in MM-PtET group, shorter disease duration and being Hispanic compared to White, was predictive of greater knowledge improvement ($p<0.05$, Adjusted $R^2=0.08$).

Conclusion: Viewing of the MM-PtET was as effective and more acceptable than reading written materials in RA patients. Hispanics and patients with shorter disease duration may achieve the greatest benefit from multimedia tools incorporating narratives and stories.

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Patient-Physician Discordance of Disease Activity Assessments Predicts Inadequate Treatment Response in Early Rheumatoid Arthritis. John M. Davis III, Cynthia S. Crowson, Tim Bongartz, Clement J. Michet, Eric L. Matteson and Sherine E. Gabriel. Mayo Clinic, Rochester, MN.

Background/Purpose: Discordance between patients' and physicians' global assessments of disease activity occurs in up to a third of clinical evaluations for rheumatoid arthritis (RA). In this study, we sought to determine the association between the presence of patient-physician discordance at baseline and clinical disease activity after the 24 weeks of disease-modifying therapy.

Methods: We conducted an observational study of consecutive patients with newly diagnosed RA recruited between July 2008 and December 2010. RA was defined by the Leiden early RA prediction rule. The primary rheumatologist prescribed disease-modifying therapy, which did not follow any study protocol. Standard disease activity assessments were performed by a single joint assessor, who was independent of treatment decision-making, at baseline and at 24 weeks of follow-up, including tender and swollen joint counts, patient and physician global assessments of disease activity (0 – 100 mm visual analog scales), and the C-reactive protein. Discordance was defined by $\geq$25-mm difference between the patient and physician global assessments. A higher patient-than-physician global assessment defined positive discordance, and a higher physician-than-patient global assessment defined negative discordance. The outcome variable of interest for this analysis was the Disease Activity Score in 28 joints, 3-variable version (which excludes the patient global assessment), using the C-reactive protein

(DAS28-CRP). The association between discordance and DAS28-CRP at 24 weeks was determined using linear regression models, adjusting for multiple study covariates.

Results: A total of 66 patients were included in this study. The mean age was 56.4 years, and 66% was female. As initial treatment, 51% of patients received methotrexate, 25% hydroxychloroquine, and 58% prednisone. Patient-physician discordance was present at 27% of the baseline visits, 10% with positive discordance (i.e., patient high) and 17% with negative discordance (i.e., physician high). The presence of positive discordance was predictive of higher DAS28-CRP after 24 weeks of disease-modifying therapy (β coefficient = 1.58; p = 0.017) whereas negative discordance was not predictive (β coefficient = 0.65; p = 0.091), after adjusting for age, sex, disease duration, rheumatoid factor, anti-CCP antibodies, baseline tender joint count, baseline swollen joint count, baseline CRP, initial DMARD, prednisone use, and smoking status.

Conclusion: In conclusion, discordance in which patient's assessment of disease activity is higher than the physician's assessment is predictive of significantly higher DAS28-CRP after 24-weeks of disease-modifying therapy. Further research is necessary to explicate factors underlying patient-physician discordance and to develop strategies for managing these factors. This work is anticipated to improve treatment outcomes for patients with RA.

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Investigation of MRI Bone Changes in Early-Stage RA Patients Achieved in Sustained Clinical Good Response: Sub-Analysis from Nagasaki University Early Arthritis Cohort. Mami Tamai[1], Kazuhiko Arima[2], Yoshikazu Nakashima[1], Masataka Umeda[1], Shoichi Fukui[1], Ayako Nishino[1], Takahisa Suzuki[1], Yoshiro Horai[1], Akitomo Okada[3], Tomohiro Koga[1], Shin-ya Kawashiri[2], Naoki Iwamoto[1], Kunihiro Ichinose[1], Hideki Nakamura[1], Tomoki Origuchi[4], Masataka Uetani[5], Kiyoshi Aoyagi[2] and Atsushi Kawakami[1]. [1]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan, [4]Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [5]Department of Radiological Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Background/Purpose: Given the improved detection of joint injury by MRI than by clinical examination, EULAR recommendations for the use of imaging of the joints in the clinical management of RA states that MRI may be useful in monitoring disease activity. However, few data have been established that specifically address how MRI should be applied to consider the outcome of RA. We have tried to examine whether MRI is useful to predict the development of radiographic progression in patients with early-stage RA from Nagasaki University Early Arthritis Cohort.

Methods: This is a sub-analysis from the 1-year observational study from seventy-six early-stage RA patients recruited consecutively from Nagasaki University Early Arthritis Cohort in which the subjects received Gd-enhanced MRI of both wrists and finger joints. All of the patients had been received DMARDs during 1 year after entry and we have selected 36 patients in which the favorable clinical response was obtained by DMARDs. The favorable clinical response was defined by decrement of DAS28 $\geqq$ 1.2 at 3 months as well as achievement of DAS28 low disease activity or remission at 6 months. Synovitis, osteitis and bone erosion determined by Gd-enhanced MRI were scored by Rheumatoid Arthritis Magnetic Resonance Imaging score (RAMRIS). Plain radiographic progression was studied by Genant-modified Sharp score. The association of MRI findings with plain radiographic progression at 1 year was investigated.

Results: Median age, disease duration and Genant-modified Sharp score at entry from 36 patients were 55 y.o., 2.4 months and 0, respectively. Although all of the 36 patients showed the favorable clinical response, radiographic progression was found in 7 patients at 1 year. Although there were no significant differences between the patients with radiographic progression (N = 7) and those without radiographic progression (N = 29) in age, gender, disease duration, RF, ACPA, CRP, matrix metalloproteinase-3 and DAS28 at entry, the significant differences were found in the rate (100% vs 51.7%, p < 0.05) and RAMRIS score of osteitis (median score 5 vs 1, p = 0.0012) at baseline, the rate (100% vs 31.0%, p = 0.001) and RAMRIS score of bone erosion (median score 3 vs 0, p = 0.004) at baseline. In addition, initial therapy with MTX was significantly less in the patients with radiographic progression as compared those without radiographic progression (14.3% vs 69.0%, p = 0.013). Multivariate logistic regression analyses, the most appropriate model is selected on the basis of Akaike's information criteria in the SAS system®, version 9.2, have shown that MRI osteitis at entry, MRI bone erosion at entry and initial MTX therapy tended to associate with plain radiographic progression.

Conclusion: MRI bone changes appear to predict poor radiographic outcome in patients with early-stage RA despite the favorable clinical response is achieved. Our present data indicate again the importance of MTX as initial DMARDs in early RA patients.

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Minimally Important Difference in the European Quality of Life-Five Dimensions in Patients with Rheumatoid Arthritis. Daisuke Hoshi, Eiichi Tanaka, Eisuke Inoue, Kumi Shidara, Yoko Shimizu, Akiko Kobayashi, Naoki Sugimoto, Eri Sato, Yohei Seto, Ayako Nakajima, Shigeki Momohara, Atsuo Taniguchi and Hisashi Yamanaka. Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Patient-reported outcomes (PROs) have been recognized as important in evaluating disease status of rheumatoid arthritis (RA). The minimally important difference (MID) in PROs has been studied in RA for physical function, however, the MID for quality of life assessed by European Quality of Life-Five Dimensions (EQ-5D) has not yet been analyzed. Thus, we conducted this study to elucidate MID for EQ-5D.

Methods: Participants were patients with RA who enrolled in the IORRA study conducted in October 2011 and April 2012. The IORRA study was established as a large observational cohort of RA patients.in October 2000 and the data collection was conducted biannually. The database includes the EQ-5D, the disease activity score in 28 joints (DAS28), and the Japanese version of the Health Assessment Questionnaire (J-HAQ) for physical disability. Patients self-rated their change in overall status in April 2012 as much better, somewhat better, the same, somewhat worse, or much worse compared to that in October 2011 using a 5-point Likert scale. In this study, the MID for EQ-5D in patients who rated themselves as somewhat better were analyzed. The MID is the means of each patient's change in the EQ-5D, and the responsiveness to change was evaluated using effect size (ES) which of 0.2 to 0.5 is usually considered as relevant value for the MID.

Results: A total of 4,847 patients in this study had a mean (standard deviation [SD]) age of 60.4 (13.4) years, disease duration of 14.2 (10.0) years, DAS28 score of 2.9 (1.1), J-HAQ score of 0.64 (0.73), and EQ-5D of 0.800 (0.18), and 85.0% were women. Among them, 745 patients self-rated themselves somewhat better. The mean (SD) change in EQ-5D was 0.018 (0.17) with ES of 0.11 for patients who self-rated themselves somewhat better. When patients rated themselves somewhat better were stratified by baseline DAS28 into groups of remission, low, moderate and high disease activity, the mean (SD) changes in EQ-5D were −0.0002 (0.15), 0.017 (0.15), 0.032 (0.13) and 0.58 (0.12) with ES of 0.001, 0.11, 0.23 and 0.49, respectively. When stratified by baseline J-HAQ into groups of low (J-HAQ<0.5), moderate (0.5≤J-HAQ<1.5) and high (J-HAQ≥1.5) physical disability, the mean (SD) changes in EQ-5D were 0.004 (0.13), 0.027 (0.12) and 0.032 (0.13) with ES of 0.03, 0.21 and 0.24, respectively. When stratified by baseline disease duration into groups of < 2 years, 2–5 years, 5–10 years and ≥10 years, the mean changes (SD) in EQ-5D were 0.043 (0.12), 0.021 (0.16), 0.015 (0.16) and 0.014 (0.16) with ES of 0.33, 0.16, 0.09 and 0.08, respectively. Finally, the MID in EQ-5D in patients with baseline DAS28 >3.2, baseline J-HAQ >0.5 and disease duration <5 years was demonstrated as 0.036 with ES of 0.39.

Conclusion: This study demonstrated the MID in EQ-5D in RA patients from the IORRA cohort. The MID in EQ-5D varies in concordance with disease activity, physical disability and disease duration.

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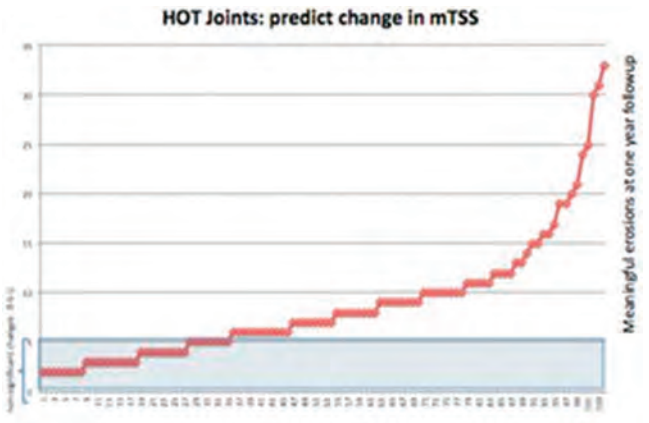
Joint Dermal Temperature Specifically Identifies the Individual RA Patient Most Likely to Develop Radiographic Change on Sharp Score; An Exam in Less Than a Minute Can Predict Who Specifically Needs Biologic Therapy. Maria Greenwald[1], Joann Ball[2] and Harold Paulus[3]. [1]Desert Medical Advances, PALM DESERT, CA, [2]Desert Medical Advaces, Palm Desert, CA, [3]UCLA, Los Angeles, CA.

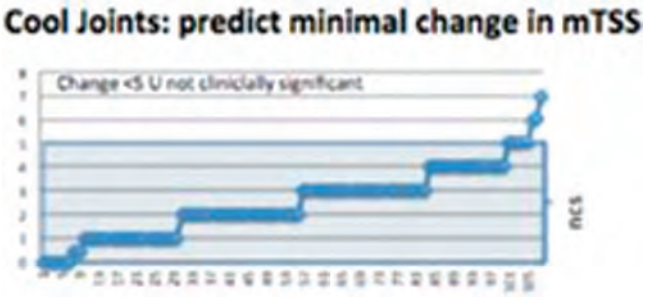
Background/Purpose: Joint dermal temperature (temp) measured in less than a minute can identify specifically the individual RA patient most likely to develop radiographic change on Sharp Score in the next year. There is great debate regarding which patients should be treated with expensive therapies for rheumatoid arthritis (RA). Certain subsets of RA patients are more likely to cripple, such as sero-positive disease, those earlier in disease onset, and earlier age at onset, and higher inflammatory non-specific markers (like amyloid, fibrinogen). However, can we identify a specific patient at most risk for radiographic changes. We evaluated the power of touch to determine disease. It has long been noted in the literature that skin over a gout joint is "hot", which we define as a temp equal to or above central temp. Elevated skin temps occur also over septic joints and RA. The hot joint will identify which individual is destined for new xray erosions.

Methods: A digital clinic dermal thermometer was used to record vital signs, both at skin on the forehead and over any painful joint, most often the wrist. The dermal temp can be measured accurately and in less than a minute (accuracy ±0.1 F). Sequentially 208 sero-positive RA patients on MTX (15–25 mg/week) and with baseline plus one year follow up hand/feet xrays were enrolled. No biologic therapy was permitted. Xrays were scored by a single reader (MG) with a modified van der Heijde total Sharp score (mTSS) without sequence order or identifiers. Medical history, WESR, CRP, baseline medications and xray were performed at screening. A small group of subjects without RA (n=25) were used as controls to evaluate the usual range of joint temp.

Results: The dermal temp at a wrist of normal persons without RA is −12.0±4.6 F. The "hot" joint RA group had a joint temp in excess of central temp +1.06±0.69 (CI 0.23) and neared a 4-fold higher individual risk of new erosions compared to those RA "cool" joints. Results were highly significant, $p<0.001$. Sensitivity for joint temp predicting erosions is 91.7% and specificity for joint temp predicting erosions 78%. Newer onset of RA, younger age, and WESR were mildly significant ($P<0.05$) but had poor specificity and sensitivity.

Conclusion: A simple dermal temperature taken with a standard digital thermometer can quickly and accurately identify RA patients who are at high risk for further destructive change on MTX alone. This can be submitted to insurers, national health registries, and provides objective data to what we have known for centuries, that the human hand can detect active disease.





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Rheumatoid Arthritis-Associated Interstitial Lung Disease: Risk Factors for Disease Progression. Yashaar Chaichian, Imre Noth, Mary Strek, Tammy O. Utset and Rekha Vij. University of Chicago Medical Center, Chicago, IL.

Background/Purpose: Rheumatoid arthritis (RA) is the most common systemic connective tissue disease in the U.S. Interstitial lung disease (ILD) is a frequent extra-articular manifestation of RA that contributes significantly to morbidity and mortality. While risk factors for developing ILD have been identified, less is known about factors that predict prognosis. The objectives of this study were to identify factors associated with RA-ILD progression and determine how often RA-ILD pulmonary activity parallels joint disease activity.

Methods: We performed a retrospective analysis of adult patients with RA-ILD at the University of Chicago Medical Center. Demographic and clinical information were extracted from medical records. All patients met ACR 1987 classification criteria for RA. ILD diagnosis required interstitial abnormalities on high-resolution chest CT plus confirmation by a pulmonologist, with or without restrictive pattern on pulmonary function tests (PFTs) or compatible lung biopsy. Progressive RA-ILD was defined as decrease in forced vital capacity of ≥10% or diffusing capacity for carbon monoxide of ≥15% on serial PFTs ≥8 weeks apart. Progressive joint disease was defined as evidence of new erosion or persistent flare by rheumatologist on successive visits ≥8 weeks apart. Patients with parallel ILD and joint activity had worsening in PFTs and joint disease activity within 3 month overlapping period. Subgroups of patients were compared using Fisher's exact tests for categorical variables and ANOVA for continuous variables.

Results: We identified 47 RA-ILD patients. Thirty six (77%) had progressive RA-ILD and 11 (23%) had stable RA-ILD. High-titer rheumatoid factor (RF), >3 times upper limit of normal, was associated with progressive RA-ILD ($p=0.0394$) while high-titer cyclic citrullinated peptide (CCP) antibody ($p=0.0973$) and smoking history ($p=0.0933$) trended towards association. Twenty eight patients had serial rheumatology assessments coinciding with PFTs: 9 (32%) had parallel ILD and joint disease activity, and 19 (68%) had non-parallel disease activity. Usual interstitial pneumonia (UIP) was the most common radiographic pattern in patients with progressive and stable RA-ILD. There was a slight predominance of UIP as the radiographic pattern in patients with non-parallel ILD and joint disease activity. Radiographic patterns other than pure UIP were slightly more frequent in patients with parallel ILD and joint disease activity.

Conclusion: High-titer RF was associated with RA-ILD progression in this cohort. High-titer CCP antibody and smoking history trended towards

association with progressive RA-ILD. Thus, we propose that RA-ILD patients with these risk factors merit closer monitoring for disease progression. For the majority of our RA-ILD cohort, ILD and joint disease activity did not parallel one another. This finding highlights the importance of monitoring joint and lung disease separately, as different factors may contribute to articular and pulmonary disease flares in RA-ILD patients. Furthermore, these results suggest that articular and pulmonary disease activity should be considered separately for therapeutic decision-making.

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ACR Poster Session A
Rheumatoid Arthritis - Human Etiology and Pathogenesis
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Bronchiectasis: A Model for Chronic Bacterial Infection Inducing Autoimmunity in Rheumatoid Arthritis. Anne-Marie Quirke[1], Elizabeth Perry[2], Alison Cartwright[1], Clive Kelly[3], Anthony De Sozya[4], Paul Eggleton[5], David Hutchinson[2] and Patrick Venables[1]. [1]University of Oxford, Oxford, United Kingdom, [2]Royal Cornwall Hospital, Truro, United Kingdom, [3]Queen Elizabeth Hospital, Gateshead, United Kingdom, [4]The Freeman Hospital, Newcastle, United Kingdom, [5]University of Exeter, Exeter, United Kingdom.

Background/Purpose: Anti-citrullinated peptide antibodies (ACPA) are associated with smoking in patients with rheumatoid arthritis (RA). Bronchiectasis (BR), which tends to occur in non-smokers, has been recognised as an uncommon, but potent risk factor for RA for 50 years. Here we examine the potential of BR in generating ACPA in patients with BR alone and in patients with BR and RA (BRRA).

Methods: The multi-centre study included 122 patients with BR alone, 50 BRRA, 50 RA without lung disease, compared with 87 asthma and 79 healthy subjects as controls. All RA patients met the 2010 ACR criteria for RA. ACPA were measured using CCP2 and fine specificities to citrullinated α-enolase (CEP-1: ^{4}KIHA-cit-EIFDS-cit-GNPTVE^{21}), citrullinated vimentin (cVim: ^{59}VYAT-cit-SSAV-cit-L-cit-SSVP^{74}) and citrullinated fibrinogen, β chain (cFib: ^{36}NEEGFFSA-cit-GHRPLDKK^{52}), with their arginine control peptides (REP-1, Vim, and Fib) by ELISA. The cut-off for positivity for CCP2 was 5 U/ml as per manufacturers instructions and for the remaining peptides was calculated using the 95th percentile of the healthy controls. The Mann-Whitney U test was used to calculate p-values for differences between the results for each assay and Spearman non-parametric correlations between datasets were calculated.

Results: In the BR patients without RA, there was an increased antibody reponse to the uncitrullinated variants of the antigens tested in this study. Anti-CCP2 antibodies were positive in 5% of patients, significantly increased above the healthy ($p< 0.001$) and asthma ($p<0.01$) controls. The anti-CCP2 arginine control test (anti-CPArg) was also significantly increased in 19%. Similarly, antibodies to the arginine control peptides from the specific citrullinated antigens were also increased: REP-1 19% ($p <0.01$), Vim 16% ($p<0.01$) and Fib 9% (p ns), compared to both healthy and asthma controls. There was a corresponding increase in antibodies to the citrullinated peptides which in each case strongly correlated with their uncitrullinated variants (Spearman ρ values $=0.512– 0.798$), further supporting the findings of a citrulline-independent autoantibody response in BR.

In contrast to the BR patients, the BRRA patients had a highly citrulline specific ACPA response and the rate of seropositivity in BRRA vs RA was significantly increased for each ACPA tested: anti-CCP, 88% vs 48%; anti-CEP-1, 60% vs 24%; anti-cVim, 56% vs 20% and anti-cFib 74% vs 40% (each $p<0.001$) despite a lower frequency of smoking (42% vs 58%; $p=0.06$). The citrulline specificity of the RA ACPA response was confirmed by the lack of correlation with response to the arginine-containing peptides (Spearman ρ values < 0.298). Collectively, these data show that the citrulline specificity of ACPA in BRRA is increased compared to BR alone and its magnitude is increased compared to RA without any lung disease.

Conclusion: These findings provide further evidence linking BR to RA by indicating that BR may generate ACPA in two stages: firstly a citrulline independent B-cell response to host or bacterial antigens in the lungs with a subsequent evolution of citrulline specificity in the cases where BR evolves into BRRA.

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Characterization of Lung Inflammation in the Lungs of Early Rheumatoid Arthritis. Gudrun Reynisdottir[1], Vijay Joshua[2], Aase Haj Hensvold[2], Lars Klareskog[3] and Anca I Catrina[2]. [1]Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet,, Stockholm, Sweden, [2]Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Karolinska University Hospital, Karolinska institutet, Stockholm, Sweden.

Background/Purpose: We have previously demonstrated that lung abnormalities are present already at disease onset in ACPA positive RA patients. We aimed to further investigate lung changes in patients with rheumatoid arthritis (RA) in dynamic in a follow-up clinical study.

Methods: 105 RA patients (with patient-reported symptom duration less than 1 year and naive to DMARD treatment) were investigated by lung HRCT and functional pulmonary testing at disease onset and 6 months after. All patients were started on methotrexate. A smaller subgroup of these patients (n=24) were subjected to bronchoscopy and mucosal large bronchial biopsies and bronchoalveolar lavage (BAL) samples were retrieved at disease onset (n=24) and after 6 months (n=21). Additional 16 large bronchial biopsies and 79 BAL samples from healthy volunteers were available. Histological analysis for identification of inducible bronchia associated lymphoid tissues (iBALT) and lymphocyte infiltration were performed. Further immunohistochemical analysis was performed in RA biopsies to detect PAD enzymes, CD3, HLA-DQ and HLA-DR and to identify citrullinated targets.

Results: Both parenchymal and airway HRCT abnormalities were more frequent among RA patients than controls (54% as compared to 30%, OR 2.7, $p<0.05$ for parenchymal changes and 66% as compared 42%, OR 2.7, $p<0.05$ for airway changes). Fibrosis (12/105, 11%) was solely detected in RA patients. At follow up 4 out of these 12 patients show some progress signs while the remaining 8 were stable.

Bronchial lymphocyte infiltration and iBALT formation was observed at baseline in half of the ACPA+ RA patients but only 1 out of 6 ACPA- patients (17%) and 1 out of 9 healthy volunteers (10%). Signs of such infiltration were still present at 6 months. Higher expression of HLA-DR, HLA-DQ and citrullinated targets was observed in bronchial biopsies of ACPA+ as compare to ACPA- RA ($p<0.05$). CD3 expression also showed a tendency to higher expression in the ACPA+ as compared to ACPA- RA patients. HLA-DR expression showed a tendency to decrease at 6 months but no significant changes were observed.

ACPA+ RA patients had significantly higher proportions of BAL lymphocytes and neutrophils as compared to healthy controls ($p<0.05$). The increased relative numbers of BAL lymohcoytes at disease onset was found reduced after 6 months of treatment ($p<0.05$). Markers of T cell activation (CD69 and CD103) were expressed by significantly more CD4+ BAL T cells in ACPA+ RA patients as compared to healthy controls, but no significant changes were observed at follow-up.

Conclusion: HRCT changes, signs of inflammation and accumulation of highly activated and differentiated BAL CD4+ T cells are present early in the lungs of ACPA+ RA patients and show relatively minimal changes during 6 months follow-up.

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Smoking Functions As a Negative Regulator of IGF-1 Levels and Adipokine Network in Patients with Rheumatoid Arthritis. Maria Bokarewa[1], Malin Erlandsson[2], Sofia Töyrä Silfverswärd[3], Andreea Ioan-Fascinay[4] and Roberto Doria Medina[3]. [1]University of Goteborg, Goteborg, Sweden, [2]University of Gothenburg, Gothenburg, Sweden, [3]University of Göteborg, Göteborg, Sweden, [4]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Smoking is an important player in the pathogenesis of rheumatoid arthritis (RA) being tightly connected to the genetic (carriage of HLA-DRB1 shared epitope) and serological (production of autoantibodies) risk factors for the development of RA. The molecular events connecting cigarette smoking to severe joint inflammation and low efficacy of

anti-rheumatic drugs, are poorly understood. Adipokines is a family of signalling molecules originating from adipose tissue and regulating carbohydrate metabolism and soft tissue regeneration. In RA, adipokines are connected to the disease activity and progressive radiological joint damage. Numerous effects of adipokines are mediated through insulin receptor/insulin-like growth factor-1 receptor (IGF-1R) complex.

Here we address a potential connections between cigarette smoking and changes in IGF-1 signalling and adipokine network function in patients with RA.

Methods: 543 patients from 2 independent RA cohorts (Göteborg, n=350 and Leiden, n=193) were included in this observational study. Patients were divided by their smoking habits defined as present smokers (n=126), ex smokers (n=177) and never smokers (n=240). Serum levels of total IGF-1 and adipokines (adiponectin, leptin, resistin and visfatin) were measured with sandwich ELISAs. The patient groups were compared by quantitative statistics and the association between smoking and serum parameters were evaluated by bivariate and multivariate correlation analysis.

Results: The two studied cohorts differed in disease duration, where the Leiden cohort consisted of early RA patients (DD md 0.4 years), higher disease activity (DAS28 md 5.1) and higher VAS-pain (md 46mm), while the Göteborg cohort consisted of patients with established RA (DD md 7.5 years), low DAS28 (md 3.0) and VAS-pain (md 27mm). In both cohorts the smokers were more often men ($P<0.001$).

Serum levels of IGF-1 were significantly lower in the present smokers followed by ex smokers. RA patients who never smoked had significantly higher serum levels of IGF-1 ($P<0.001$). Levels of adiponectin were also higher in never smokers ($P=0.002$). The correlation between leptin and resistin observed in the whole material was significantly weaker in the present smokers (rho=0.357) compared to the never smokers (rho=0.520). The present smokers had stronger correlations between IGF-1 and leptin (rho=0.233, $P=0.009$), resistin (rho=0.210, $P=0.018$). These correlations were not observed in the never smokers or the ex smokers.

The logistic regression analysis showed that low levels of IGF-1 were associated with low levels of leptin and visfatin and with current smoking. Neither age, gender, DAS28 nor BMI was contributing significantly in the regression model. Clinical impact of low leptin levels evaluated in a different logistic regression model showed an association with high DAS28, male gender and high BMI.

Conclusion: Smoking is associated with lower serum levels of IGF-1 in RA patients. The link between IGF-1 and the adipokines network is dependent on the smoking habit of the patient, and potentially supporting sustained disease activity and reducing regeneration processes in the damaged arthritic joints in RA patients.

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Increasing Cartilage Turnover in Smokers Developing Rheumatoid Arthritis Is Associated with High Disease Activity in Early Disease. Carl Turesson[1], Christina Book[2], Ulf Bergström[2], Lennart Jacobsson[2] and Tore Saxne[3]. [1]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [2]Lund University, Malmö, Sweden, [3]Dept of Clinical Sciences Lund, Section of Rheumatology, Lund, Sweden.

Background/Purpose: Autoantibodies and other biomarkers of rheumatoid arthritis (RA) that may be detected years before disease onset in a subset of investigated individuals could be affected by exposures such as smoking. Changes in biomarker levels from the pre-clinical phase to early RA may reflect mechanisms that determine the disease phenotype. Cartilage oligomeric matrix protein (COMP) is a marker of cartilage turnover that has been shown to predict progression of joint damage in RA. Our purpose was to investigate the relation between COMP and smoking, as well as changes in COMP from the pre-clinical phase to early RA, and how these relate to early disease activity.

Methods: Between 1991 and 1996, 30 447 subjects from a defined catchment area were included in a health survey. From this population, individuals who developed RA after inclusion were identified by linking the health survey database to a community based RA register and local and national patient administrative databases. In a structured review of the medical records, patients were classified according to the 1987 ACR criteria for RA. One control for each validated case, matched for sex, year of birth and year of screening, who was alive and free of RA when the index person was diagnosed with RA, was selected from the health survey database. Furthermore, the identified sample of incident cases of RA was linked to an inception cohort of early RA patients (symptom duration <12 months) from the same area. Serum COMP in pre-RA cases and controls, as well as in patients with early RA, was measured with a sandwich ELISA (AnaMar).

Results: Serum was available from 167 individuals (131 women, mean age at screening 63 years) who were diagnosed with RA after inclusion in the health survey (a median of 5 years later (range 1–13)). COMP levels were significantly lower among current smokers compared to non-smokers in pre-RA cases (mean 10.1 vs. 11.5 U/L; $p=0.009$) as well as in controls (mean 10.7 vs 11.9 U/L; $p=0.046$). Fifty-seven cases (44 women) were also included in the early RA cohort after a median of 4.9 years (interquartile range 3.6–6.7). At inclusion, their mean age was 65 years, 56 % were anti-CCP positive and the mean DAS28 was 4.6 (SD 1.1). COMP levels increased significantly from the pre-RA sample to inclusion in the early RA cohort (mean change 1.6 U/L (SD 4.2); $p=0.006$). An increase in COMP tended to be associated with higher DAS28 at inclusion in the early RA cohort (β 0.09; 95 % confidence interval (CI) −0.01 to 0.18; adjusted for age, sex and baseline COMP). This association was observed in particular among smokers at baseline (n=22) (adjusted β 0.22; 95 % CI 0.04 to 0.39) and to a lesser extent in non-smokers (n=35) (adjusted β 0.06; 95 % CI −0.07 to 0.19).

Conclusion: COMP levels were lower in smokers among pre-RA cases as well as in controls who did not develop RA. Increasing COMP in the pre-clinical phase of RA appeared to be associated with a severe RA phenotype, in particular among smokers. The relation between early changes in cartilage turnover and long term outcomes in RA should be further studied.

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Anti-Citrullinated Heat Shock Protein 90 Antibodies Identified in Bronchoalveolar Lavage Fluid Are a Marker of Lung-Specific Immune Responses. Lisa Harlow[1], Bernadette Gochuico[2], Ivan Rosas[3], Tracy Doyle[3], Juan Osorio[3], Timothy Travers[4], Carlos Camacho[4], Chester V. Oddis[4] and Dana P. Ascherman[1]. [1]University of Miami Miller School of Medicine, Miami, FL, [2]National Institutes of Health, Bethesda, MD, [3]Brigham and Women's Hospital, Boston, MA, [4]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Previous work has demonstrated an association between serum anti-citrullinated HSP90 antibodies and rheumatoid arthritis-associated interstitial lung disease (RA-ILD). To further investigate this potential pathogenic relationship, we assessed anti-citrullinated HSP90 antibody profiles in bronchoalveolar lavage fluid (BALF) isolated from RA patients with and without ILD.

Methods: BALF and corresponding serum samples were collected from a well-defined cohort of RA patients with various stages of ILD. Specimens obtained from these subjects were then subjected to enzyme-linked immunosorbent assays (ELISAs) using recombinant HSP90 isoforms and derivative peptides as substrate antigens. While comparison of resulting BALF-associated antibody profiles to those identified in healthy controls and patients with idiopathic pulmonary fibrosis (IPF) permitted assessment of disease specificity, evaluation of matching serum specimens provided insight regarding relative antibody production in lung and extra-pulmonary tissue compartments.

Results: 9/21 RA-derived BALF specimens demonstrated either IgG or IgA antibodies targeting citrullinated HSP90 proteins/peptides, highlighting disease specific immune responses (with a predilection for RA-ILD) that did not occur in IPF patients (0/5) or healthy control subjects (0/5). Discordance between these antibody responses and BALF anti-CCP2 reactivity (IgG, IgA) provided clear evidence of antigen specificity (as only 3/21 BALF samples possessed antibodies recognizing both CCP2 and citrullinated HSP90 derivatives). Furthermore, comparison of antibody profiles between BALF and matching serum specimens revealed several different recognition patterns favoring predominant production of anti-citrullinated HSP90 antibodies within the lung microenvironment.

Conclusion: IgG and IgA anti-citrullinated HSP90 antibodies occur preferentially in BALF derived from patients with RA-ILD, supporting the connection between this antibody specificity and parenchymal lung disease. Moreover, qualitative as well as quantitative differences in anti-citrullinated HSP90 profiles between BALF and serum indicate that the lung plays a direct role in shaping the immune repertoire of RA/RA-ILD.

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Distinct Profiles of Proinflammatory Macrophages in Rheumatoid Arthritis and Coronary Artery Disease. Tsuyoshi Shirai[1], Eric L. Matteson[2], David G. Harrison[3], Barbara B. Wallis[4], Themistocles L. Assimes[1], Jorg J. Goronzy[1] and Cornelia M. Weyand[1]. [1]Stanford University School of Medicine, Stanford, CA, [2]Mayo Clinic, Rochester, MN, [3]Vanderbilt University School of Medicine, Nashville, TN, [4]Veterans Affairs Palo Alto Health Care System, Palo Alto, CA.

Background/Purpose: Patients with RA have an increased risk of developing coronary artery disease (CAD) compared to the general population. The underlying pathological process of CAD is atherosclerosis, which is a chronic inflammatory disease caused by maladaptive inflammatory responses. Macrophages are key players in the progression of atherosclerosis, contributing through proinflammatory effector functions, such as cytokine production. It is currently unknown whether accelerated CAD in RA results from similar or distinct pathomechanisms that underlie non-RA CAD. This study was designed to define and compare proinflammatory macrophages in patients with CAD and RA to clarify their potential contribution to the process of atherosclerosis.

Methods: Healthy controls, patients with RA who satisfied the ACR classification criteria, and patients with CAD who had a history of at least one myocardial infarction in the absence of co-existent autoimmune disease, were enrolled into this study. Monocytes isolated from peripheral blood mononuclear cells were differentiated into macrophages with M-CSF for 5 days. Macrophages were further differentiated into M1 or M2 with IFN-γ and lipopolysaccharide or IL-4 and IL-13, respectively, for 2 days. RNA was purified from macrophages, and the expressions of 55 genes were measured using quantitative PCR. Cytokine production was quantified by multi-parametric flow cytometry.

Results: The gene expression signatures of macrophages derived from healthy controls, RA and CAD were significantly different ($p<0.01$). CAD macrophages were characterized by high production of IL-6 and IL-1β (7.8 and 6.4-fold upregulation compared to controls, $p=0.04$ and $p=0.03$, respectively), a phenotype that RA macrophages did not share. CAD macrophages expressed high levels of chemokine receptors including CCR2, CCR5, and CCR7, while RA macrophages expressed similar levels of chemotactic receptors as healthy macrophages. The expression of the transcription factors Kruppel-like factor (KLF)-2 and KLF-4 also distinguished CAD and RA macrophages. KLF-2 and KLF-4 were distinctly low in CAD macrophages ($p=0.04$ and $p= 0.02$, respectively), but well maintained in RA macrophages. A characteristic feature of RA macrophages was the high expression of CCL18, a CC chemokine attracting predominantly T lymphocytes. The signature of RA macrophages included the suppression of activation-induced IFN-β, indicating a down-regulation of type 1 IFN-dependent immunity.

Conclusion: CAD macrophages have a signature of super-inflammatory effector cells, characterized by the loss of negative regulators of inflammation (KLF-2; KLF-4) and the gain of cytokine production capability, releasing high amounts of IL-6 and IL-1β. Because of high expression of chemotactic receptors, they can efficiently navigate through the atherosclerotic plaque to enhance inflammation. In contrast, RA macrophages appear less mobile and are able to amplify inflammation through the CCL18-dependent recruitment of T cells. The data suggest that macrophage-dependent immune responses are fundamentally different in RA and CAD.

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The Anti-IL-6 Antibody Sirukumab Inhibits Vascular Inflammation in a Human Surrogate Model of Atherosclerosis. Ryan Feaver[1], Sol Collado[2], Stephen Hoang[2], Erica Berzin[2], Allison Armstrong[3], Debbie Gardner[4], Paul Fisher[5], Hao Liu[6], Aaron Mackey[2], David Manka[2], Brian Wamhoff[2], David Shealy[4] and Brett Blackman[2]. [1]HemoShear, LLC, Charlottesville, VA, [2]HemoShear, LLC., Charlottesville, VA, [3]HemoShear, LLC., Virginia, VA, [4]Janssen Research & Development, LLC, Spring House, PA, [5]Janssen Research & Development, LLC., Spring House, PA, [6]Immunology Research, Janssen Research and Development, LLC., Spring House, PA.

Background/Purpose: Rheumatoid arthritis (RA) and atherosclerosis are chronic inflammatory diseases that share many biological features. Prevalence of atherosclerosis is increased by approximately 2-fold in RA, with at least 2 prominent molecular links between the two diseases: IL6 and TNFα signaling. Elevated circulating IL6 is an independent risk factor for cardiovascular disease and correlates with RA disease progression in patients. To test the hypothesis that compounds used for the treatment of RA decrease vascular inflammation under atherogenic conditions.

Methods: To elucidate the impact of RA treatments on vessel wall health, a novel *in vitro* human surrogate system that co-cultures human endothelial (EC) and smooth muscle cells (SMC) was used. Atheroprone flow conditions were applied, based upon human hemodynamic blood flow from the carotid bifurcation, a site prone to developing atherosclerosis. Atherogenic risk factors were added to the culture medium, including *in vivo* circulating concentrations of oxidized LDL (oxLDL) and TNFα. In addition, soluble IL-6 receptor (sIL6R) was added at a concentration typically seen in patient sera. RNA sequencing and multiplex protein assays were used to perform transcriptomic and bioanalytical pathway analyses of the response of the human surrogate system. We compared treatments that target pathogenic RA pathways including anti-IL6 and anti-IL6 receptor antibody (sirukumab or tocilizumab, respectively), anti-TNFα antibody (adalimumab) and a small molecule inhibitor of JAK (tofacitinib) at C_{min} doses.

Results: Using this model, the combination of sIL6R, TNFα and oxLDL induced a robust transcriptional response of inflammatory genes under atheroprone hemodynamics compared to control conditions without sIL6R or TNFα and with non-oxidized LDL. The anti-IL6/IL6R treatments (sirukumab, tocilizumab) significantly improved the vascular health phenotype relative to control IgG treatment. Both sirukumab and tocilizumab dramatically decreased adhesion molecule gene expression and NFkB-dependent genes while simultaneously increasing vasculoprotective responses such as eNOS and KLF2 expression, and promoting a contractile SMC phenotype. Adalimumab showed a weaker but similar trend compared to IL6 inhibition, while tofacitinib was not effective in suppressing inflammation or promoting vascular health. Sirukumab and tocilizumab were more effective in suppressing TNFα signaling than adalimumab. Although broadly comparable, sirukumab was more potent than tocilizumab in suppressing inflammation and promoting vascular health.

Conclusion: These data suggest that the IL6 pathway inhibitors (sirukumab and tocilizumab) potently suppress inflammation and promote vascular health in an *in vitro* model of RA-associated cardiovascular disease. In contrast the TNFa inhibitor, adalimumab, and JAK inhibitor, tofacitinib, were less effective in alleviating the disease phenotype. Collectively, the data suggest that IL6 inhibition may provide vascular protection in patients with RA.

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Comparison of C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) with Estimated Glomerular Filtration Rate (eGFR) in Patients with Rheumatoid Arthritis (RA). Ilias Oikonomopoulos[1] and John D. Carter[2]. [1]University of South Florida Morsani College of Medicine, Tampa, FL, [2]University of South Florida, Tampa, FL.

Background/Purpose: It has previously been demonstrated that the ESR and CRP correlate in patients with RA but with a high degree of variability. Reasons for this variability are not completely understood, but anemia, adiposity, and age can play a role. It has previously been suggested that ESR and CRP are inversely related to renal function in a non-RA population; it is felt that underlying inflammation is the explanation for the negative correlation with the CRP, specifically. The aim of this study is to see if the CRP and/or ESR inversely correlate with renal function in patients with RA.

Methods: This is a retrospective chart review of RA patients followed at USF Health. Subjects were identified by ICD-9 code (714.0) and they had to have a CRP, ESR, hemoglobin (Hgb) and eGFR performed on the same day. The most recent labs were utilized and no patient was included twice. Patients were excluded if they were <18 years of age or had a history of blood cancers known to affect inflammatory markers. The co-primary endpoints were the correlation between CRP and eGFR as well as ESR and eGFR. Secondary endpoints included correlation between CRP and ESR as well as both inflammatory markers with Hgb and the patients' age. Spearman correlation coefficients (rho) were utilized to determine significance.

Results: 158 patients met the inclusion criteria; 136 (86%) were females with a mean age of 58.82 years (+/− 11.44 SD; range 26–84 years). 93/130 (71.5%) of these subjects were seropositive; status was unknown on 28

patients. The mean CRP and ESR in these subjects was 0.89mg/dL (+/− 1.37mg/dL SD) and 16.07mmHg (+/− 16.61mmHg SD), respectively; the mean eGFR and Hgb was 82.76 mL/min/1.73m^2 (+/− 20.92 mL/min/1.73m^2 SD) and 12.77g/dL (+/− 1.31g/dL SD), respectively. There was no correlation between the CRP and the eGFR (rho = 0.041; p = 0.60) [Fig 1]; there was also no correlation between the ESR and the eGFR (rho = −0.037; p = 0.64) [Fig 1]. There was a correlation between the CRP and ESR but with a high degree of variability (rho = 0.596; p < 0.0001) [Fig 1]. The ESR correlated weakly with Hgb and it did so in an inverse fashion (rho = −0.348; p<0.0001); the CRP did not appear to correlate with the Hgb (rho = −0.115; p = 0.15). There was no correlation with either CRP or ESR and age (rho = −0.075 and 0.006 respectively).

Conclusion: This retrospective chart review of 158 patients with RA suggests there is no correlation between CRP and/or ESR with renal function. Renal function does not appear to be an explanation for some of the variability that is documented between CRP and ESR in patients with RA.

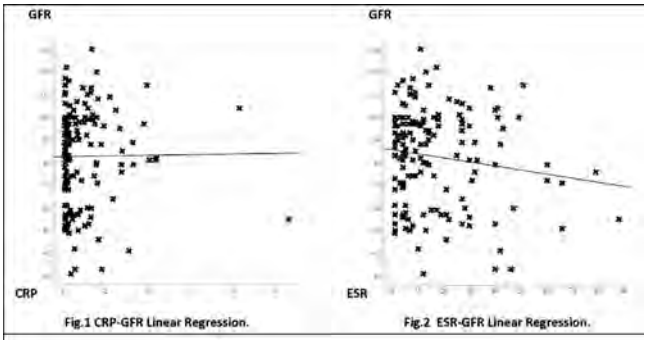

Fig.1 CRP-GFR Linear Regression.

Fig.2 ESR-GFR Linear Regression.

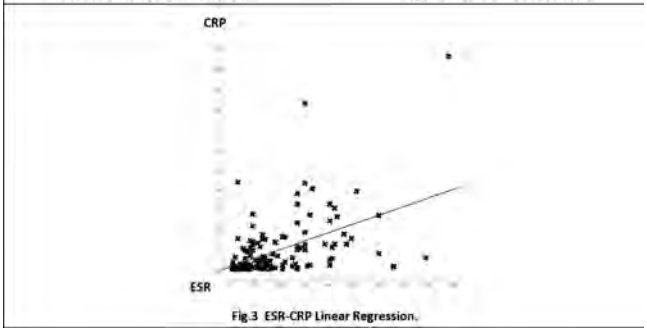

Fig.3 ESR-CRP Linear Regression.

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Arthritis Associated Autoantibodies in Non-Rheumatoid Arthritis Patients with Mucosal Inflammation. Koen M. J. Janssen[1], Menke J. de Smit[1], Elisabeth Brouwer[1], Berber Doornbos-van der Meer[1], Arie Jan van Winkelhoff[1], Arjan Vissink[2], Josje Altenburg[3], Nivine Levarht[4], Marije K. Verheul[4], Leendert A. Trouw[4] and Johanna Westra[1]. [1]University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [2]University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [3]Medical Center Alkmaar, Alkmaar, Netherlands, [4]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) associated autoantibodies, such as anti-citrullinated protein antibodies (ACPA), rheumatoid factor (RF) and anti-carbamylated protein antibodies (anti-CarP), can be present in serum years before clinical manifestation of RA. High ACPA-levels have been associated with a negative disease outcome. Recently, initiation of ACPA-response has been hypothesized to occur at inflamed mucosal surfaces, e.g., in the oral cavity. Therefore, it is of particular interest to investigate the IgA ACPA response and other IgA autoantibodies. The aim was to assess ACPA and anti-CarP autoantibodies levels (IgG and IgA) in serum of patients with mucosal inflammation at different sites, namely in periodontitis, cystic fibrosis and bronchiectasis patients, all without a diagnosis of RA.

Methods: Autoantibody levels were assessed in periodontitis, cystic fibrosis and bronchiectasis patients. As controls, healthy subjects without periodontitis (HC) and a cohort of established RA-patients were added (Table 1). IgG anti-CCP2 levels were measured by ELISA (EuroDiagnostica, cut-off mean +2SD of HC). IgA anti-CCP2 levels were measured by a modified anti-CCP2 ELISA. Citrulline specificity of the anti-CCP2 response was assessed by measuring antibody levels against the arginine control peptide CAP (EuroDiagnostica). Serum IgM and IgA RF levels (cut-off >15, >25 IU/ml, respectively) and IgG antibodies against carbamylated FCS (cut-off mean +2SD of a distinct healthy control cohort) were measured by an in-house ELISA. IgG and IgA antibody levels against four citrullinated peptides (fibrinogen-1, 2, α-enolase and vimentin) were measured by ELISA in which the reactivity was corrected for the native peptides and positivity was defined as mean + 2SD of HC.

Results: Although RA autoantibody levels in periodontitis, cystic fibrosis and bronchiectasis patients were overall low, IgG seropositivity for anti-CAP (9.6%, 9.8% and 13.8%, respectively), anti-CCP2 (13.2%, 24.4% and 21.3%, respectively), and anti-CarP (3.5%, 7.3% and 3.8%, respectively) tended to be more prevalent in these groups compared to HC (5.6%, 5.6% and 0%, respectively). Comparable results were observed for IgA seropositivity. No increased seropositivity was observed for antibodies against the four citrullinated peptides. In bronchiectasis patients, seropositivity for IgM and IgA RF was significantly increased (18.8%, 23.8%) compared to HC (0%, 2.8%).

Table 1: Characteristics of patients and healthy controls assessed for presence of autoantibodies.

	Healthy controls	Periodontitis patients	Cystic fibrosis patients	Bronchiectasis patients	Rheumatoid arthritis patients
No. of subjects	36	114	41	80	88
Age, mean ± SD	34 ± 15	51 ± 9**	29 ± 8*	63 ± 11**	60 ± 11**
Female, sex (%)	56	59	49	63	69

Group characteristics were compared to healthy controls using Mann Whitney test. *p< 0.05, **p< 0.0001

Conclusion: Presence of anti-CCP2 and anti-CarP is slightly more prevalent in serum of non-RA patients with mucosal inflammation. The increased levels of anti-CAP indicate that at least part of the increased anti-CCP2 reactivity might not be citrulline specific. In conclusion, our observations might be clinically relevant as we presume that once ACPAs are initiated they can mature in individuals that are genetically pre-disposed for RA.

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Anti-Carbamylated Protein Antibody Levels Are Elevated in Seropositive Rheumatoid Arthritis and Correlate with Anti-Sa/Citrullinated Vimentin Antibody Levels. Gregory J. Challener[1], Jonathan D. Jones[1], B. JoNell Hamilton[1], Gilles Boire[2], Artur José de Brum-Fernandes[2], Pierre Cossette[2], Patrick Liang[2], Ariel Masetto[2], Nathalie Carrier[2], Henri A. Ménard[3] and William F.C. Rigby[1]. [1]Geisel School of Medicine at Dartmouth College, Lebanon, NH, [2]Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC, [3]Research Institute of the McGill University Health Center, Montreal, QC.

Background/Purpose: Recent studies indicate that the breach of immune tolerance that occurs in rheumatoid arthritis (RA) extends beyond the citrullination of arginines (as recognized by anti-citrullinated protein antibodies; ACPA) to homocitrullination of lysines. Since 2011, humoral responses to homocitrullinated proteins (subsequently referred to as anti-carbamylated protein antibodies; ACarP Ab) have been reported in both early and established seropositive RA. We analyzed the relationship of serum/plasma levels of ACarP Ab to several clinical and serologic parameters, using both established and early RA cohorts.

Methods: Carbamylation of fetal calf sera was performed as previously described [1]. Patients with established RA (n=212) were recruited at Dartmouth-Hitchcock Medical Center (Lebanon, NH, USA). Serum and/or plasma ACarP Ab, anti-Sa Ab, CXCL13, rheumatoid factor (RF), ACPA (specifically, anti-CCP2 Ab) and total IgG were measured by ELISA. Seropositivity (positive for RF, anti-CCP or both) and C-Reactive Protein

level were determined by the clinical lab. A confirmatory analysis was performed using samples from early RA patients included in the Sherbrooke, QC (Canada) cohort. T-test, ANOVA and correlation analysis were utilized to evaluate relationships between variables. 63 healthy controls were also evaluated for levels of ACarP Ab.

Results: Among seropositive patients in the Dartmouth cohort (n=164), 46.6% exhibited elevated levels of ACarP Ab. ACarP Ab titers correlated with levels of ACPA (p=0.004) and IgM-RF (p=0.04). Seropositive patients in the early RA Sherbrooke cohort (n=173) displayed similar trends; 38.2% had elevated ACarP Ab levels, and ACarP Ab titer was highly associated with levels of ACPA (p=0.005) and weakly associated with IgM-RF (p=0.06). The relationship of ACarP Ab levels with baseline clinical parameters (age, DAS28-CRP, erosions, etc.) was either weak or absent in both cohorts. Intriguingly, we observed a highly significant correlation between anti-Sa status and ACarP Ab titer among seropositive patients in the Sherbrooke cohort ($p<0.0002$), with 47.9% of anti-Sa-positive patients harboring elevated levels of ACarP Ab versus 25.4% of anti-Sa-negative patients. This observation led us to test seropositive RA samples in the Dartmouth cohort for anti-Sa status; once again, a highly significant relationship was observed ($p<0.000001$); 62.6% of anti-Sa-positive patients showed elevated ACarP Ab levels versus 26.9% of anti-Sa-negative patients.

Conclusion: This is the first investigation of ACarP Ab levels in a population of established RA patients in the US, comparing it with an early RA Canadian cohort. A large proportion of each seropositive RA cohort exhibited elevated levels of ACarP Ab (38.2–46.6%). Most compellingly, we identified a strong relationship between levels of ACarP Ab and anti-Sa reactivity that raises the mechanistic question of how antibody responses to carbamylated proteins and citrullinated vimentin (Sa) are linked *in vivo*.

1. Shi, J., et al., *Autoantibodies Recognizing Carbamylated Proteins Are Present in Sera of Patients with Rheumatoid Arthritis and Predict Joint Damage*. PNAS, 2011. **108**(42): p. 17372–77.

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Sputum Anti-Citrullinated Protein Antibodies in Patients with Long Standing Rheumatoid Arthritis. Ari Polachek[1], Wilma Vree Egberts[2], Elizabeth Fireman[3], Daphna Paran[3], Ido Drokman[4], Ilana Kaufman[4], Irena Wigler[5], Dan Caspi[6], David Levartovsky[7], Ger JM Pruijn[8] and Ori Elkayam[9]. [1]Tel Aviv Medical Center, Tel Aviv, Israel, [2]Radboud University Medical Centre, Nijmegen, Israel, [3]Tel-Aviv Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel, [4]Sourasky Medical Center, Tel-Aviv, Israel, [5]Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [6]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [7]Tel Aviv Medical Ctr, Tel Aviv, Israel, [8]Department of Biomolecular Chemistry, Radboud University, Nijmegen, Netherlands, [9]Tel-Aviv Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel.

Background/Purpose: The lung has been implicated in the pathogenesis of rheumatoid arthritis (RA). The aim of this study was to evaluate the presence of autoantibodies to citrullinated (Cit) and non-citrullinated (Arg) forms of 2 cyclic synthetic peptides (ACPA) in the sputum of patients with long standing rheumatoid arthritis.

Methods: Twenty RA patients (80% female, mean age 62 years) and 15 age/gender matched healthy controls (81% female, mean age 58 years) participated in this study. Demographic and epidemiological data, including age, gender, disease duration and smoking habits, were collected. All the subjects underwent complete lung function tests, and provided induced sputum. The severity of the disease was evaluated in the RA patients by means of DAS score, and hand and feet X rays. Antibodies to Cit and Arg peptides in the sputum of the RA patients and healthy controls, as well as in the serum of the RA patients, were determined by ELISA.

Results: The RA patients suffered from long standing disease (mean disease duration of 12 years), displayed moderate disease activity (mean DAS 3.44), and showed a mean Sharp van der Heijde score of 57.5. Seventy % of the patients were on DMARDs and 65% on biologics, mainly TNF alpha blockers. Sixty % and 68 % of the RA and healthy controls, respectively, were defined as "ever smoker". Eleven of the 20 RA patients showed in most cases high titers of ACPA in their sera. Six of the seropositive (55%) and none of the seronegative RA patients and none of the healthy controls showed detectable levels of ACPA in their sputum. The ratio between the reactivity with Cit and Arg peptides in the sputum was significantly higher in RA sputum than in control sputum (1.33 +/− 1.2 vs. 0.64 +/− 0.14, p=0.02). A positive correlation was found between sputum ACPA and age and serum ACPA in RA patients, as well as between sputum anti-Cit/Arg reactivity ratio and the proportion of neutrophils and lymphocytes in the sputum. No significant correlation was found between sputum ACPA and disease severity, smoking or lung function tests.

Conclusion: ACPA can be detected in the sputum of RA patients and are correlated with the presence in the serum. These findings further strengthen the hypothesized role of the lungs in RA pathogenesis.

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Evidence for Citrullination of the Nuclear Transciption Factor Inhibitor of DNA Binding 1 (Id1) in Rheumatoid Arthritis. Ray A. Ohara[1], Gautam Edhayan[1], Christine M. Ha[1], M. Asif Amin[1], Ali S. Arbab[2], Phillip L. Campbell[1], David A. Fox[1] and Jeffrey H. Ruth[1]. [1]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [2]Georgia Regents University, Augusta, GA.

Background/Purpose: Citrullination is a post-translational modification mediated by peptidyl arginine deiminase (PAD) enzyme in which arginine is converted to citrulline. Inhibitor of DNA binding 1 (Id1) is known to be actively transcribed in endothelial progenitor cells (EPCs) and cells that exhibit hyperproliferative responses. Previously, we showed that Id1 is expressed in rheumatoid arthritis synovial tissues (RA STs) and upregulated in RA synovial fluids (SFs), suggesting that Id1 may be post-translationally modified in RA. A more detailed analysis of the structure of Id1 reveals a relatively small protein of approximately 16kDa, but containing 10 modifiable arginines. We show that Id1 can be citrullinated, and that RA STs and SFs contain citrullinated Id1 (cit-Id1), suggesting that cit-Id1 may be pathogenic in the course of RA. We also show that by immunodepletion of Id1, we can reduce the angiogenic potency and overall amount of citrullinated protein in RA SF.

Methods: Id1 concentrations in RA SFs were measured by enzyme-linked immunosorbent assay (ELISA). To further explore the role of Id1 in RA SF, we immunodepleted Id1 with a neutralizing antibody or non-specific IgG ("sham depleted"), and used this in the severe combined immunodeficient (SCID) mouse chimera. Mice grafted with human RA ST were injected i.v. with fluorescently dye-tagged EPCs while receiving simultaneous intragraft injections with the treated SFs. To examine Id1 citrullination, we modified recombinant human (rhu) Id1 by incubation with rabbit PAD enzyme. Cit-Id1 was measured for deimination by a cit-ELISA using an anti-modified citrulline antibody. Citrullinated bovine serum album (BSA) was used as a relative standard. RA SFs imunodepleted with either Id1 or sham depleted were also measured by cit-ELISA to determine the total amount of citrullinated protein contained in RA SFs before and after Id1 depletion. Finally, we homogenized RA ST and performed immunoprecipitation (IP) of Id1 to determine the presence of Id1 and cit-Id1 by Western blotting using anti-human Id1 and anti-modified citrulline antibodies.

Results: We found a 50% reduction in EPC recruitment to intragraft injections of RA SF immunodepleted of Id1 compared to sham depleted RA SF (*$p<0.05$). We measured the amounts of total citrullinated protein in RA SF, and found that by removal of Id1, we could significantly reduce the total amount of citrullinated protein in RA SF (*$p<0.05$). Western blot analysis of Id1 and cit-Id1 confirmed that we could discriminate cit-Id1 from non-cit-Id1, and that we could successfully modify Id1 in vitro. Similarly, Id1 isolated by IP from RA ST homogenates showed that we could detect both Id1 and cit-Id1 in RA ST homogenates, and that a significant portion of the total Id1 in RA ST was in modified form.

Conclusion: We identify Id1 as an angiogenic factor, capable of recruiting EPCs to RA ST. We also show for the first time that Id1 can be modified using rabbit PAD enzyme. The significant shift downward in total citrullination in RA SFs depleted of Id1 indicates that cit-Id1 is present and elevated in the RA SF. We also show that Id1 in the RA ST is also citrullinated. Taken together, we show that Id1 functions as an angiogenic mediator and is robustly deiminated in RA tissues.

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Differing Specificities of Anticitrullinated Peptide/Protein Antibodies in Palindromic Rheumatism and Rheumatoid Arthritis: A Case-Control Study. Sonia Cabrera-Villalba[1], María José Gomara[2], Julio Ramirez[1], Georgina Salvador[3], Virginia Ruiz-Esquide[1], M. Victoria Hernández[1], José Inciarte-Mundo[1], Andrea Cuervo[1], Celia Saura[1], Juan D. Cañete[1], Isabel Haro[2] and Raimon Sanmarti[1]. [1]Hospital Clínic of Barcelona, Barcelona, Spain, [2]IQAC-CSIC, Barcelona, Spain, [3]Hospital Universitario Mutua Terrassa, Barcelona, Spain.

Background/Purpose: Palindromic rheumatism (PR) may evolve to rheumatoid arthritis (RA), particularly in patients with citrullinated peptide/protein antibodies (ACPA), although a significant number of patients do not progress to RA in the long term. Differences in ACPA specificities have been shown between patients with established and preclinical RA. It is unclear whether ACPA specificities differ between patients with longstanding PR and RA. To determine whether there are differences in the recognition of epitopes between patients with longstanding PR and established RA by analysis of different ACPA specificities.

Methods: Case-control study. Cases: patients with pure PR, with no evolution to RA or other rheumatic disease at study entry. Controls: patients with established RA (ACR-87) matched by sex, disease duration and ACPA positivity (commercial CCP2 test [Eurodiagnostica]; NV<50U). ACPA specificity in sera was determined by ELISA test using a synthetic citrullinated peptide of *fibrin* as antigen: [Cit^{630}] α-Fibrin (617–631)(p18), two peptides of *vimentin* ([Cit^{71}] Vim (47–72)(p48), [$Cit^{64,69,71}$] Vim (47–72)(p55)) and one peptide of *α-enolase*: [$Cys^{4,22}$, $Cit^{9,15}$] Enolase (5–21)(CEP-1). The cut off for each ELISA test was established by ROC curves, with a specificity of 98% compared to a healthy population (blood donors, n=64). The presence and number of different ACPA specificities in the two groups was analyzed.

Results: We included 108 patients: 54 PR and 54 RA. 62.9% were female and 66.7% in both groups were CCP2 positive. No significant differences between groups in mean age (51.2±11.3 y vs 54.7±11.8 years) and disease duration (11.6±10.7 y vs. 8.3±6.1 years) were found. PR patients had a lower frequency of some ACPA specificities than RA, which was significant in the case of p 48 vimentin (1.9% RP vs. 14.8% AR, p: 0.015) and, especially, p 55 vimentin (PR 24.1% vs. 59.3% RA, p: <0.001). The mean number of ACPA specificities was lower in PR than in RA patients (0.9±0.9 PR vs. 1.4±1.03 AR, p=0.008). The percentage of sera with no ACPA specificity was greater in PR than in RA patients (42.6% vs 22.2% p= 0.02) (see Table). No differences between groups in the levels of different ACPA specificities were observed.

Conclusion: Patients with PR had a lower frequency of some antigenic specificities of ACPA in comparison with RA patients, especially in the case of citrullinated vimentin**.** PR patients also had a lower total number of specificities than RA patients. PR patients with fewer ACPA specificities and no recognition of citrullinated vimentin may have a better prognosis, without progression to RA.

Table: ACPA specificities in patients with PR and RA

	PR n = 54	RA n = 54	p
CCP2, n,%	36 (66.7)	36 (66.7)	1
CCP2, levels	392.6 ± 527.6	487.4 ± 584.4	0.37
p18 α-fibrin n, %	19 (35.2)	26 (48.1)	0.17
CEP-1 enolase n, %	16 (29.6)	21 (38.9)	0.31
p48 vimentin n, %	1 (1.9)	8 (14.8)	**0.015**
p55 vimentin n, %	13 (24.1	32 (59.3)	**<0.001**
Number of Vimentin specificities, mean	0.26 ± 0.4	0.74 ± 0.7	**<0.001**
Total number of ACPA specifies	0.91 ± 0.96 (min0–max3)	1.43 ± 1.03 (min0–max3)	**0.008**
Total number of ACPA specificites			
0	23 (42.6)	12 (22.2)	**0.024**
1	17 (31.5)	17 (31.5)	1
2	10 (18.5)	15 (27.8)	0.25
≥2	14 (25.9)	25 (46.3)	**0.028**

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Immunoglobulin a Antibodies to Cyclic Citrullinated Protein Predominate in Individuals at-Risk for Future Rheumatoid Arthritis. Gregory M. Ingolia[1], M. Kristen Demoruelle[1], Mark C. Parish[1], Ryan W. Gan[2], Jason R. Kolfenbach[1], Michael H. Weisman[3], Jane H. Buckner[4], Peter K. Gregersen[5], Ted R. Mikuls[6], James R. O'Dell[7], Richard M. Keating[8], Alvin Yee[9], Michael Mahler[9], Jill M. Norris[2], Kevin D. Deane[1] and V. Michael Holers[1]. [1]University of Colorado School of Medicine, Aurora, CO, [2]Colorado School of Public Health, Aurora, CO, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]Benaroya Research Institute at Virginia Mason, Seattle, WA, [5]Feinstein Institute Medical Research and North Shore-Long Island Jewish Health System, Manhasset, NY, [6]University of Nebraska Medical Center, Omaha, NE, [7]Veteran Affairs Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, [8]Scripps Clinic, La Jolla, CA, [9]INOVA Diagnostics, San Diego, CA.

Background/Purpose: Immunoglobulin A (IgA) autoantibodies (Abs) to citrullinated proteins (ACPAs) are present in the preclinical period of RA development, a finding that suggests a mucosal site of Ab generation (Kokkonen 2011). IgA ACPAs have also been found in subjects at-risk for future RA based on a family history of disease (Arlestig 2012; Barra 2013). In addition, we have identified apparent local lung mucosal generation of IgA RA-related Abs in at-risk subjects (Willis, Demoruelle 2013). Additional findings that serum IgA ACPA predominates during the early natural history of RA would further support initial mucosal generation of RA-related autoimmunity.

Methods: Three groups from the Studies of the Etiology of RA (SERA) project were evaluated: 77 AtRisk subjects who were first-degree relatives of patients with RA or subjects identified through health fair screening and all were serum positive for ≥1 Ab including CCP2 (IgG, Axis-Shield), CCP3.1 (IgG/IgA, INOVA) and rheumatoid factor IgA/M/G (INOVA) without inflammatory arthritis, 53 subjects with seropositive RA (1987 criteria), and 71 blood donor controls. Each subject was tested for ACPA IgA/M/G using CCP3 antigen ELISAs (research use only; donated by INOVA), and by a technician blinded to group status. Positivity for CCP isotypes was mean levels +2 standard deviations in a separate set of 70 random blood donors. Shared epitope (SE) status was determined in AtRisk and RA subjects using published methods (Kolfenbach 2009).

Results: When comparing isotype proportions, IgA-CCP was positive in a higher number of AtRisk subjects than IgM (46.8% vs. 27.3%, p=0.03) (Table), and the prevalence was higher than IgG, although this was not statistically significant (46.8% vs. 39.0%; p=0.33). In contrast, in RA IgG-CCP was more common than IgA and IgM (86.8% vs. 69.8% and 47.2%, respectively; p's^{2}0.03). In Controls, IgA-CCP was also positive in a higher number of subjects than IgM or G (12.7% vs. 2.8% and 1.4%, respectively; p's^{2}0.03). In AtRisk, smoking was associated with positivity for ≥1 CCP isotype; this was not seen in RA, however, RA subjects were more likely to be current smokers than AtRisk. In AtRisk and RA there was no association between CCP isotypes the SE.

Conclusion: The high IgA ACPA positivity in AtRisk and high IgG APCA in RA suggest that mucosal processes may be an early feature of RA-related autoimmunity that later transition to an IgG-dominant process. IgA ACPA positivity in controls also suggests that IgA-CCP is present in wider populations and perhaps related to non-disease-specific immune responses. These findings as well as the association of smoking with ACPA isotypes in AtRisk subjects and current smoking with RA status need exploration in larger studies that examine the genetic, environmental and mucosal factors that may be involved in the evolution of ACPA isotypes in transition from preclinical to clinically apparent RA.

	Controls	AtRisk	RA
N	71	77	53
Age* (mean, SD)	54.9 (12.5)	50.3 (14.5)	58.5 (14.1)
%Female*	79%	71%	83%
%Non-Hispanic White*		71%	85%
Ever smoker*		36%	45%
Current smoker*		8%	45%
≥1 allele with the shared epitope (SE)*		56%	76%
Proportions of CCP positive subjects using commercial assays			
CCP2 (Axis-Shield)**	0.0%	18.2%	83.0%
CCP3.1 (INOVA)**	0.0%	51.9%	84.9%
Proportions of CCP isotype positive subjects			
IgA ACPA**	12.7%	46.8%	69.8%
IgM ACPA **	2.8%	27.3%	47.2%
IgG ACPA **	1.4%	39.0%	86.8%
≥1 ACPA isotype	16.9%	75.3%	88.7%

Comparisons of proportions of CCP isotype positivity within groups

IgA ACPA vs. IgM	**12.7% vs. 2.8%; p = 0.03**	**46.8% vs. 27.3%; p = 0.01**	**69.8% vs. 47.2%; p = 0.02**
IgA ACPA vs. IgG	**12.7 vs. 1.4%; p = 0.01**	46.8% vs. 39.0%; p = 0.33	–
IgG ACPA vs. IgA	–	–	**86.8% vs. 69.8%; p = 0.03**
IgG ACPA vs. IgM	1.45 vs. 2.8%; p = 0.56	39.0% vs. 27.3%; p = 0.12	**86.8% vs. 47.2%; p<0.01**

*Race, smoking and SE status were unavailable for blood donor controls; none of the AtRisk or RA subjects were related. The mean age of AtRisk subjects was less than than RA ($p<0.01$) although there were no significant differences in groups in sex or race. RA subjects were more likely to be current smokers and have ≥1 allele with the SE when compared to AtRisk ($p<0.05$).
**Positivity for all autoantibodies was significantly higher in RA than other groups, and higher in AtRisk when compared to controls. Within the AtRisk subjects, smoking was associated with positivity for ≥1 ACPA isotype (odds ratio 2.4; 95% CI 1.2–33.3; $p<0.01$); in RA, there was no significant association between smoking and any specific ACPA isotype. In AtRisk and RA, there was no association between any ACPA isotype and the presence of ≥1 SE allele.

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Rheumatoid Factor Isotypes in Relation to Antibodies Against Citrullinated Peptides in Individuals before Onset of Rheumatoid Arthritis. Mikael Brink[1], Monika Hansson[2], Linda Mathsson-Alm[3], Johan Rönnelid[3], Lars Klareskog[2] and Solbritt Rantapää-Dahlqvist[4]. [1]Umeå University, Umeå, Sweden, [2]Karolinska Institute, Stockholm, Sweden, [3]Uppsala University, Uppsala, Sweden, [4]Institution of Public health and clinical medicine/ Rheumatology, University of Umeå, Rheumatology, Sweden, Umeå, Sweden.

Background/Purpose: The presence of rheumatoid factor (RF) and antibodies against citrullinated peptides (ACPA) has been shown to precede the development of rheumatoid arthritis (RA) by several years. The relationships between the separate antibody development of RF and ACPAs are unclear.

Methods: Three isotypes (IgA, IgG and IgM) of RF has been analyzed in samples from 333 pre-symptomatic individuals (contributing with 596 samples), who subsequently developed RA and 495 population controls, all donors to the Biobank of Northern Sweden. The pre-symptomatic samples were collected in median 6.1 (IQR 7.1) years before symptom onset. Cut-offs for RF isotypes were set at 95% specificity using ROC-curves. Data from the RF-isotypes were compared against ten ACPA specificities previously analyzed on a microarray based on the ImmunoCAP ISAC system (Phadia). RF isotypes were analyzed using the EliA on the ImmunoCAP 2500-system (Phadia).

Results: The frequency of RF isotypes in pre-symptomatic individuals were 25.7% for IgA, 17.6% for IgG and 26.7% for IgM, significantly more prevalent compared with controls ($p<0.0001$). The concentrations for each isotype increased gradually the closer to onset of symptoms the sample was collected.

All three isotypes were associated with smoking (Odds ratio (OR) IgA= 2.5 (95%CI 1.8–3.6), IgG 2.1 (1.4–3.2) and IgM 2.4 (1.7–3.4), respectively) but not with HLA-SE or PTPN22 T-variant. The combinations of each of the RF isotypes with ACPA specificities (a-Enolase (CEP-1/Eno5–21), fibrinogen (Fib)β36–52, Fibα591, filaggrin (CCP-1/Fil307–324), vimentin ((Vim) 60–75 or Vim2–17) were associated with significantly shorter time to onset of symptoms ($p<0.001$–0.05). The OR (95%CI) for disease development in IgA, IgG and IgM positive individuals were in combination with Fib36–52, CEP-1 or Fil307–324 further increased from 7.1 (4.5–11.2), 4.5 (2.8–7.3) and 7.4 (4.7–11.7), respectively to OR= 12.5–19.6 for IgA, 7.5–16.2 for IgG and 17.4–20.7 for IgM.

Conclusion: RF isotypes predicted development of RA and in particular using combinations of both ACPAs and RF isotypes the association with disease development was high and the predating time shorter.

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Citrulline-Specific Autoimmunity Resides in Quiescent Circulating Memory B Cells in Rheumatoid Arthritis. Adam Pelzek, Caroline Grönwall, Jeffrey D. Greenberg and Gregg J. Silverman. New York University School of Medicine, New York, NY.

Background/Purpose: The detection of anti-citrullinated protein antibodies (ACPA) aids RA diagnosis, while B cell depletion by anti-CD20 can provide clinical benefits. We therefore undertook investigations of the phenotypic and functional properties of citrulline (Cit)-specific B cells in the bloodstream of RA patients.

Methods: RA met 2010 ACR/EULAR criteria. PBMC were cultured +/− CpG2006/IL-21/sCD40L, and ELISpots performed. CD19+ B cell subsets were FACS sorted and cultured with CD40L-cell line/CpG2006/IL-21. Sera and supernatants were evaluated for total IgG, and for IgG1 and IgG4 subclasses by bead-based multiplex analysis, against 8 sets of paired Cit/native cyclic self-peptides, plus CCP3, CQP3 (Cit to Q), Cit/native fibrinogen (Fib), tetanus toxoid (TT) and control ligands. We also surveyed 87 CCP3-seropositive and 50 seronegative RA serum samples, plus panels of disease specific control samples (SS, OA, PsA, SLE).

Results: ELISpots documented the presence of circulating anti-Cit B cells, as seropositive RA had 41.3+/−0.5 CCP3+ IgG (mean +/−SE) but only 1.9+/−0.6 CQP+ spots/$10^{(6)}$ PBMC, while these were undetectable in seronegative RA and healthy adults. Anti-TT ISC were detected at 71.1+/−2.6 and 65.4+/−1.2 spots/$10^{(6)}$PBMC in seropositive RA and controls, respectively. By multiplex assay, ACPA fine specificity reactivities in sera were compared with supernatant antibodies from stimulated PBMC. In 36 PBMC from seropositive RA, highly significant correlations by ACPA fine specificity were found in comparisons with sera ACPA by Spearman correlations. From sorted B cells, we found ACPA-secreting B cells were enriched among CD19+IgD-CD27+ switched-memory (0.019 – 0.059% of CD19+CD27+IgD-), and included highly CCP3-reactive IgG. Yet, only rare weakly CCP3-reactive naïve B cells (IgD+CD27-) were detected, and none amongst pre-switched memory (IgD+CD27+). From subclass-specific sera multiplex assays, amongst IgG1 ACPA-expressing seropositive RA, about half showed anti-CCP3 IgG1 only, while the remainder had both anti-CCP3 IgG1 and IgG4. Whereas reactivity levels were generally greater for IgG1 than IgG4, IgG1 responses usually displayed great Cit than native antigen-specific responses, while the IgG4 displayed greater reactivity with the native (non-Cit) form in 5/9 antigen sets.

Conclusion: In seropositive RA PBMC, IgG ACPA in vitro secretion was detected across all treatment groups tested (MTX, MTX+TNFi, MTX+abatacept), suggesting these cells persist despite therapeutic intervention. DAS28 score correlated with neither the level nor specificity of supernatant or sera ACPA. Pilot studies also suggest ACPA-secreting B cells predominantly reside within peripheral switched memory. Our data therefore suggest that seropositive RA patients have recirculating but quiescent memory B cells with repertoires akin to serum ACPA patterns. Furthermore, while IgG1 autoantibodies in RA are predominantly Cit-specific, with subclass switch to IgG4 there may be epitope spreading with progression to include recognition of determinants on the native forms of the self-antigens. Our studies highlight defects in B cell tolerance in RA that may help guide development of better therapy.

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Citrullinated-Vimentin-Specific Regulatory T-Cell Responses Associate with ACPA Positive Individuals with Non-Specific Musculoskeletal Symptoms. Aamir Aslam[1], Jackie L. Nam[1], Laura Hunt[1], Chadi Rakieh[1], Ann W. Morgan[2] and Paul Emery[1]. [1]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [2]University of Leeds, Leeds, United Kingdom.

Background/Purpose: The pathogenesis of RA can be conceptualised by sequential phases that precede the development of synovitis. Autoimmune antibody responses, including ACPA, can precede clinical synovitis. Our demonstrating a role for T-regs in ACPA-positive individuals without synovitis, may focus the development of treatments that can strengthen T-reg function.

Methods: 21 ACPA+ individuals with arthralgia but without clinically detectable inflammatory arthritis, 20 individuals with ACPA+ early RA (<12months after starting DMARD) and 20 healthy volunteers were recruited from clinical studies. Peripheral blood mononuclear cells were incubated with peptide pools covering the entire sequence of citrullinated vimentin (CitVim); in some incubations, anti-IL-10 neutralising antibody was added. After 72 hours, IL-10 and IFN-g T-cell responses were enumerated by ELISpot. A positive response was defined by a stimulation index (ratio of spots with peptide to spots with negative control) >3.

Results: CitVim-reactive T-cells were readily detected in healthy volunteers, ACPA+ arthralgia and RA and there was a significant difference in the quality of this response between these groups: there was a sequential reduction in the percentage of individuals who had IL-10 CitVim-specific T-cell responses and an increase in IFN-g responses as we move from health to ACPA+ arthralgia to RA (Fig. 1). In order to determine whether IL-10 from CitVim specific T-cells had a regulatory role, we blocked IL-10 function

with a neutralising antibody and found an increase in the magnitude of the IFN-g CitVim responses in the ACPA+ arthralgia, whereas in health there were no IFN-g responses (Fig. 2).

Conclusion: We demonstrate a sequential change from a regulatory (IL-10-predominant) to an inflammatory (IFN-g) CitVim-specific T-cell response as we move from health to ACPA+ arthralgia to RA. We have also shown that autoreactive IL-10 T-reg responses are actively inhibiting IFN-g responses in ACPA+ arthralgia individuals. It is plausible that such regulatory T-cell responses prevent progression to disease in health and in pre-clinical RA.

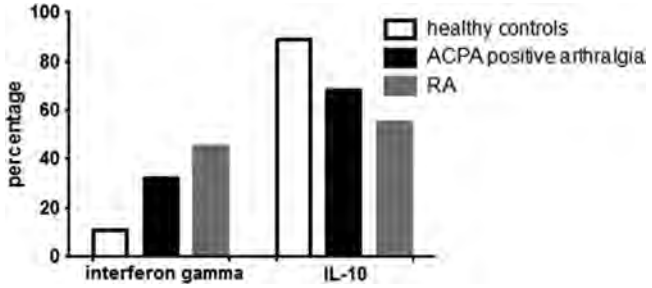

Fig. 1. IL-10 and IFN-g responses to CitVim peptide pools can be detected by ELISpot. The percentage of individual with IL-10 and IFN-gamma cit-vim specific T-cell responses differed between RA, ACPA+ arthralgia and healthy volunteers (c^2=28.4, p<0.0001).

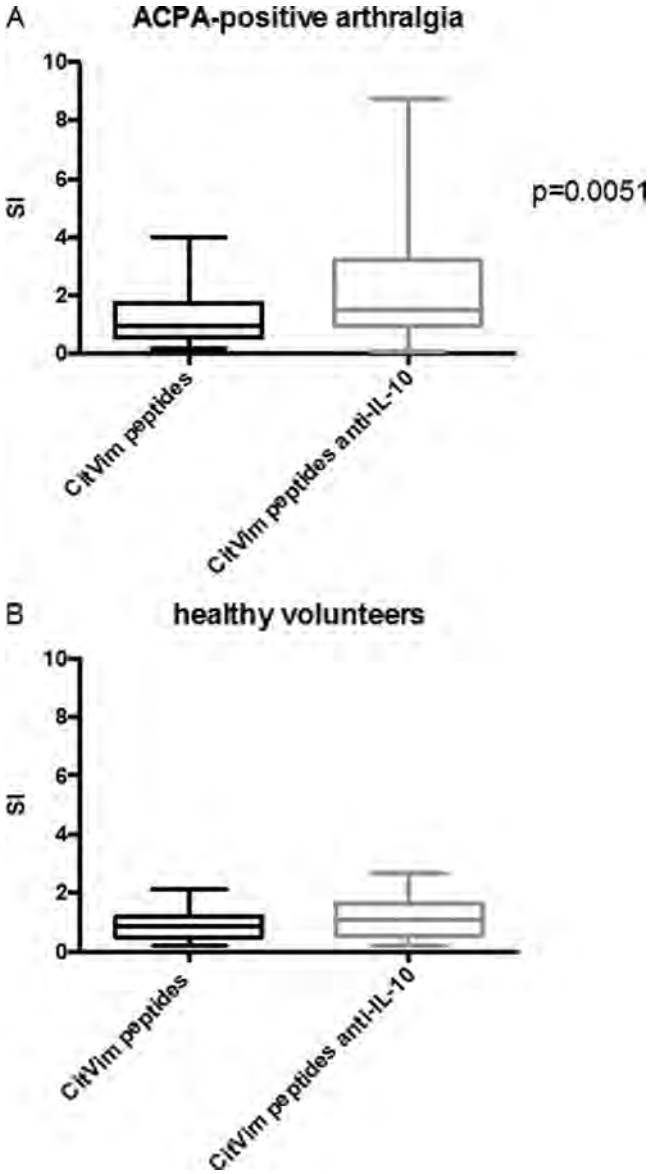

Fig. 2. IL-10 mediated suppression of CitVim IFN-g T-cell responses. **A.** There was an increase in CitVim IFN-g T-cell responses after IL-10 blockade in ACPA+ arthralgia (N=5, p=0.0051). **B.** In healthy volunteers there was no increase (N=5).

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The Mucosal Anti-Citrullinated Protein Antibody Response in Pre-Clinical Rheumatoid Arthritis. Anneke van der Horst[1], Ivy Y.K. Choi[2], Dirkjan van Schaardenburg[3], D.M Gerlag[2], Paul Tak[2], Dörte Hamann[1] and Rogier M. Thurlings[2]. [1]Sanquin Diagnostic Services, Amsterdam, Netherlands, [2]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [3]Reade, Amsterdam, Netherlands.

Background/Purpose: Recent data suggest rheumatoid arthritis (RA) may originate from an autoimmune response in inflamed mucosa. RA is associated with gingival and airway inflammation and alterations in the microbiomal composition in the gut. Furthermore, anti-citrullinated (cit) protein antibodies (ACPA) of the IgA class, the main secreted mucosal antibody, precede arthritis by years in a proportion of RA patients. When aiming to prevent arthritis it is critical to understand the source and regulation of autoantibody production in preclinical RA.

Objective to determine whether ACPA are produced at mucosal sites in ACPA positive individuals at risk for RA and to compare the ACPA isotype and fine specificity in mucosal fluids to peripheral blood.

Methods: Saliva, sputum, faeces and peripheral blood were collected from 15 individuals with anti-cyclic cit protein (anti-CCP2) antibody positive arthralgia who are part of a cohort that is being prospectively followed for the possible development of arthritis. Saliva and sputum were collected during an early morning visit. Sputum was induced by inhalation of sodium chloride aerosols 4.5%. Mucus plugs were selected from sputum for extraction of supernatants. Faeces was collected at the same visit using stool collection kits and extracted using 6% BSA phosphate buffered saline. ACPA of IgA and IgG class were measured in mucosal fluids and blood using two cit fibrinogen peptides, one enolase peptide and one vimentin peptide and their respective arginine peptides as control.

Results: Thirteen of 15 individuals tested positive for the anti-CCP2 test and ACPA in their blood at the day of mucosal fluid collection. Two patients tested positive for anti-CCP2 but negative for ACPA. Two other patients had high reactivity against both cit peptides and arginin controls and were also considered ACPA negative. Anti-cit fibrinogen, enolase and vimentin antibodies were detected in respectively 11, 4 and 3 individuals. The saliva of 4 patients contained IgA ACPA with positive tests for anti-cit enolase and anti-cit fibrinogen. The saliva of another patient tested positive for IgG anti-cit enolase and anti-cit fibrinogen. Other saliva, sputum and faeces samples tested negative for ACPA. All 5 patients with ACPA in saliva tested positive for the same antibodies in blood. In addition, in 3 of 5 patients ACPA were detected in blood that were not detected in saliva, including anti-cit fibrinogen, anti-cit vimentin and anti-cit enolase antibodies.

Conclusion: Collection of saliva allows for the detection of ACPA in the saliva of a proportion of anti-CCP positive individuals at risk for RA. In these patients, IgG ACPA in blood are directed against more peptides compared to IgA ACPA in saliva. Future analyses should focus on further defining the precise source and regulation of mucosal ACPA compared to systemic ACPA.

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The Association of Fine Specificities of Anti-Citrullinated Protein Antibodies (ACPA) with disease Severity in African-Americans with RA. Maria I. Danila[1], Richard Reynolds[1], Gordon Wu[1], Hemant Tiwari[1], William H. Robinson[2], Jeremy Sokolove[3], CLEAR Investigators[1] and S. Louis Bridges Jr. [11]University of Alabama at Birmingham, Birmingham, AL, [2]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [3]VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA.

Background/Purpose: RA is characterized by the presence of autoantibodies to citrullinated proteins (ACPA) and joint damage. The role of fine specificities of ACPA in radiographic severity has not been defined. The purpose of the current study was to evaluate whether fine specificities of ACPA are associated with radiographic severity of RA in African Americans.

Methods: Using a custom Bio-Plex™ bead-based autoantibody assay platform, we measured anti-CCP antibody and 19 autoantibodies targeting citrullinated proteins and peptides (vimentin, fibrinogen, histone 2A, histone 2B, and apolipoprotein E, clusterin, biglycan, enolase, fillagrin). We analyzed sera from 692 African-American patients with RA. A total antibody score was defined for each patient as the standardized sum of the log transformed autoantibodies. The total antibody score was used as predictor variable for radiographic severity. Radiographic severity defined as total Sharp/van der Heijde scores of hands/feet was the dependent variable. Zero-inflated negative binomial regression models were used to test the association of the autoantibody score with radiographic severity defined as total Sharp/van der Heijde scores of hands/feet given the covariates gender, BMI, smoking status and disease duration.

Results: High correlation coefficients among the autoantibodies were observed. Using zero-inflated negative binomial regression, the total sum of standardized antibodies had a statistical significant (p-value =0.002) effect among patients with a total RA radiographic severity (total score >0). For each unit increase in the total sum of standardized autoantibodies, the total radiographic score increases by 0.3 units. In addition, disease duration was found to be statistically significant (p-value <0.0001).

Conclusion: Autoantibodies against citrullinated autoantigens are associated with joint damage in this cross sectional study of African Americans with RA. Future work will focus on longitudinal aspects of antibodies to specific peptides/proteins and their role in progression of radiographic damage.

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The Use of Multiplex Bead Array to Follow the Effect of Rituximab on IgG and IgA Serum Autoantibody Responses to Citrullinated Epitopes in Patients with Rheumatoid Arthritis. Geraldine Cambridge[1], Lauren J. Lahey[2], Maria J. Leandro[1], William H. Robinson[2] and Jeremy Sokolove[2]. [1]Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom, [2]VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA.

Background/Purpose: The majority of patients with established Rheumatoid arthritis (RA) have autoantibodies against the Fc of IgG (Rheumatoid factors-RhF) and to citrullinated protein antigens (ACPAs). As ACPAs recognize epitopes on many different proteins, the full complement of reactivity is unknown so they are usually detected using cyclic citrullinated peptides (CCP). Seropositivity for RhF and/or ACPA is a strong predictor of a positive clinical response to rituximab (RTX) therapy. Although playing an important pro-inflammatory role in RA, ACPA, measured using CCP as substrate, are less dynamic than RhF in relation to RTX treatment. Using an antigen array comprising citrullinated antigens identified as present in RA synovia we have explored changes in fine specificity and levels of IgG- and IgA-ACPAs following RTX.

Methods: 17 patients with active RA (DAS28 ≥ 5.1) fulfilling ACR criteria were included. All had undergone one cycle of RTX (2 weekly infusions of 1g), showed adequate depletion in the peripheral blood (<5 CD19+ cells/μl) at 1–3 months, and had clinically responded (ΔDAS28≥1.2) at 3 months. Follow-up was from 4–13 months up to re-treatment or relapse. A custom, bead-based, antigen array comprising 30 putative RA-associated citrullinated, and 20 corresponding native antigens was used for measurement of ACPA (assessed using mean fluorescence intensity-MFI). To compensate for number of binding sites per antigen, MFI were Z-normalised. Positive results were regarded as those with SD >1 above population mean.

Results: Before RTX, IgG- and IgA-ACPA often shared specificities to a variable number of citrullinated and native antigens. Post-RTX, the overall median % decrease in MFI for ACPA from baseline to when B-cells were depleted, was modest for IgG-CCP (7.3%) and more pronounced for IgA-CCP (20.0%). At relapse, median % decrease in MFI for IgG-CCP was 3.3% but IgA-CCP remained high at 20.5%. The patterns of antibody binding to individual peptide or protein epitopes were considerably more dynamic than those to CCP. In general, the same citrullinated epitopes were recognized by both IgA- and IgG-ACPA in each sample but additional specificities could be present in either autoantibody class. IgG- and IgA-ACPA also tended to respond in parallel to RTX treatment. Prior to relapse, steep rises in IgG- or IgA-ACPA recognizing individual, or several, epitope specificities were observed, particularly when relapse occurred several months after B cell return (9/17 patients). Rises usually occurred in ACPA specificities present before RTX but new epitope specificities could emerge.

Conclusion: The use of multiplex antigen arrays for analysis of the ACPA response in RA patients after RTX has revealed that populations of ACPA-producing cells behave differently in response to B cell depletion therapy. Recognition of particular epitopes was highly variable and dynamic, suggesting some derivation from short-lived parent plasmablasts, which were not reflected in the relatively static, 'global' IgG-CCP measurements. IgA-ACPA responses to RTX therapy were also varied and did not necessarily recognize the same epitopes although patterns of response were similar to those of IgG-ACPA.

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In a Periodontal Disease Cohort without RA, Indeterminate or Low-Positive Anti-CCP-2 Antibodies Are Associated with Multiple Distinct ACPA. Jerry A. Molitor[1], Bryan S. Michalowicz[2], Ryan T. Demmer[3], Jane H. Buckner[4], Mark H. Wener[5] and William H. Robinson[6]. [1]University of Minnesota, Minneapolis, MN, [2]University of Minnesota School of Dentistry, Minneapolis, MN, [3]Columbia Univ. Mailman School of Public Health, New York, NY, [4]Benaroya Research Institute at Virginia Mason, Seattle, WA, [5]University of Washington, Seattle, WA, [6]Stanford University School of Medicine, Stanford, CA.

Background/Purpose: Periodontal disease (PD) and RA share the risk factors HLA DR B1 shared epitope (SE) and tobacco exposure (TE). PD may represent a risk factor for subsequent RA. Individuals with multiple ACPA have increased risk of subsequent RA. We developed a prospective cohort with moderate to severe PD but no clinical features of RA, determining: i) the prevalence of HLA-DRB1 alleles; ii) seropositivity to CCP-2 antibodies (CCP-2) and ACPA; iii) whether HLA-DRB1 alleles were associated with CCP-2 or ACPA; and iv)if HLA-DRB1 alleles modified the association between CCP-2 and ACPA.

Methods: CCP-2 and IgM RF were performed by CLIA–certified assays. CCP-2 or RF+ individuals were offered clinical assessment to ensure they were free of RA by 2010 ACR/EULAR criteria. Sera were analyzed by multiplex assay for distinct ACPA. Positive cutoffs for ACPA were established by ROC analysis of prior studies. HLA DRB1 SE alleles were assayed by PCR. Proportions and 95% confidence intervals (CI) were estimated using Fisher's Exact Test. Mantel-Haenszel odds ratios (OR) were computed as appropriate. Interaction was assessed via the Breslow-Day test.

Results: Median age was 60 years. Key findings;

Characteristic	# (181 total)	Percentage
Male	120	66.3
Ever used tobacco	131	72.3
Detectable CCP-2 (> 0.5 u)	30	16.6
CCP-2 indeterminate or greater (> 1.5 u)	11	6.1
RF positive (> 10)	10	5.5
≥1 ACPA	62	34.3
≥3 ACPA	12	6.6
HLADRB1*0401	33	18.2
HLADRB1*0101	34	18.8

The most common ACPA was anti-citrullinated histone 2A; n=44(24%), all other ACPA occurred in < 7% of participants. There was a significant relationship between the presence of an indeterminate or low positive CCP-2 and the presence of ≥ 3 distinct ACPA (OR [95%CI] = 23.4[5.5, 100.1], p=0.0001). The presence of DRB1*0401 was marginally associated with an indeterminate or low positive CCP-2 (OR= 3.2[0.8, 12.3], p=0.09), and with the presence of ≥ 3 ACPA (OR= 5. 3[1.6, 17.5, p=0.01). RF was not associated with any specific ACPA, nor was it associated with indeterminate or low positive CCP-2. No relationships between tobacco exposure and any specific ACPA or RF were seen. Among DRB1*0401 negative individuals, prevalence estimates of ≥ 3 ACPA among those with an indeterminate or low positive CCP-2 vs. negative CCP-2 were 17% vs. 4%.This relationship was markedly stronger among DRB1*0401 positive individuals; prevalence estimates of ≥ 3 ACPA among those with an indeterminate or low positive CCP-2 vs. negative CCP-2 were 100% vs. 7% (p for interaction=0.06).

Conclusion: In this PD cohort, indeterminate or low positive CCP-2 is associated with the presence of ≥ 3 distinct ACPA. HLA DRB1*0401 alleles

were associated with an increased risk of ≥ 3 ACPA, and with the presence of an indeterminate or higher CCP-2. These results have implications for the follow-up of individuals with RA risk factors and indeterminate or low positive CCP-2 findings, and for the design of RA prevention trials.

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The Specificity of Anti-Carbamylated Protein Antibodies for Rheumatoid Arthritis in a Setting of Early Arthritis. Jing Shi, H.W. van Steenbergen, J. a. B. van Nies, E.W.Nivine Levarht, Annette H. M. van der Helm- van Mil, Tom W. J. Huizinga, René E.M. Toes and Leendert A. Trouw. Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Anti-carbamylated protein (anti-CarP) antibodies have been described in rheumatoid arthritis (RA) and arthralgia patients [1;2] and occur in subsets of the anti-CCP2 positive and negative patients [1;3]. In anti-CCP2 negative RA patients the presence of anti-CarP was associated with more severe joint destruction [1]. Here we investigated the sensitivity and specificity of anti-CarP antibodies for RA in a setting of early arthritis.

Methods: Anti-carbamylated fetal calf serum (anti-Ca-FCS), anti-CCP2 antibodies and rheumatoid factor (RF) IgM were measured by ELISA using serum samples available from a large inception cohort; the Leiden Early Arthritis Clinic cohort (EAC). For the anti-CarP antibodies we used as a cut-off for positivity the mean + 2 times the standard deviation of the healthy controls [1].

Results: In total 2086 sera of Leiden EAC patients suffering from early arthritis were analyzed for the presence of anti-Ca-FCS antibodies. Anti-CarP antibodies were present in 26% of the patients and in 2% of the controls. We observed that the sensitivity and specificity of anti-Ca-FCS in the EAC cohort for RA are 44% and 89%. As a reference the sensitivity and specificity of anti-CCP2 antibodies are 54% and 95% and for RF IgM are 59% and 90%. Analyzing the early arthritis patients that did not fulfil the EULAR/ACR 2010 criteria for RA that were anti-CarP positive (n=127) revealed that these patients were mainly diagnosed as undifferentiated arthritis (45%), reactive arthritis (9%), psoriatic arthritis (9%) or peripheral spondyloarthritis (8%).

Conclusion: Anti-CarP antibodies, as determined by the reactivity to carbamylated FCS, are predominantly present in RA but can also be detected in other forms of arthritis. The prognostic relevance of anti-CarP antibodies in these latter patients will have to be determined.

1. Shi J *et al.* Autoantibodies recognizing carbamylated proteins are present in sera of patients with rheumatoid arthritis and predict joint damage. Proc. Natl. Acad. Sci. U.S.A 2011; 108:17372–7.

2. Shi J, van de Stadt LA, *et al.* Anti Carbamylated Protein Antibodies (anti-CarP) are present in arthralgia patients and predict the development of rheumatoid arthritis. Arthritis Rheum. 2012.

3. Jiang X, Trouw LA, *et al.* Anti-CarP antibodies in two large cohorts of patients with rheumatoid arthritis and their relationship to genetic risk factors, cigarette smoking and other autoantibodies. Ann. Rheum. Dis. 2014.

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Clinical and Tissue Specificity of Antibodies Against Carbamylated Proteins in Patients with Rheumatoid Arthritis. Antonio Gonzalez[1], Ariana Montes[1], Eva Perez-Pampin[1], Maria Dolores Boveda[2] and Juan J. Gomez-Reino[3]. [1]Instituto Investigacion Sanitaria- Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [2]Insitituto Investigacion Sanitaria- Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [3]University of Santiago de Compostela, Santiago de Compostela, Spain.

Background/Purpose: Antibodies against carbamylated proteins (CarP) are a new type of autoantibodies specific of patients with rheumatoid arthritis (RA) relative to healthy controls, but their specificity in relation with other rheumatic diseases has not been established. In addition, they have been analysed with CarP from Fetal Calf Serum (FCS) raising doubts about their protein specificity.

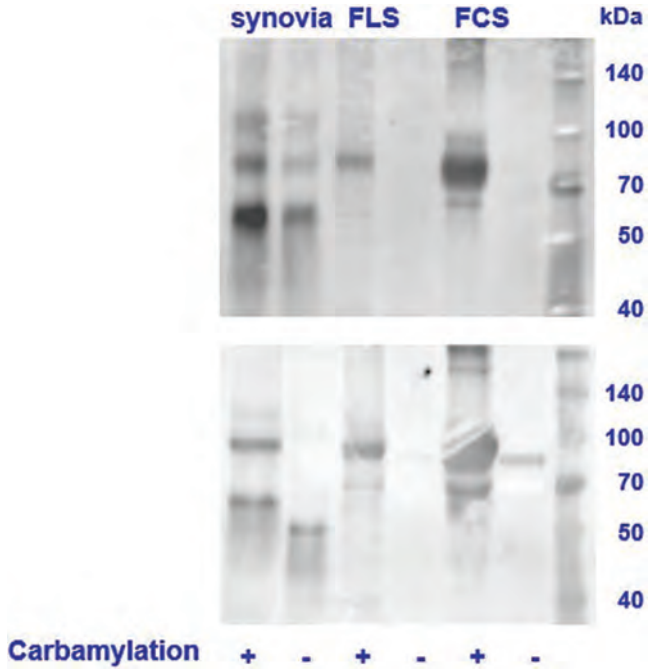
Methods: Anti-CarP FCS from 520 patients with RA was compared with reactivity in 208 healthy donors and 90 patients with each of the following diseases: osteoarthritis (OA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). In addition, anti-CarP-FCS from 97 patients with RA was correlated with reactivity against CarP from seven human tissues.

Results: Anti-CarP-FCS antibodies were found in 35.9 % of the patients with RA. These antibodies were also observed in 4.8 % of the healthy controls, 4 % of the OA patients, 6 % of the PsA patients and 24.4 % of the AS patients. Therefore, their specificity was high in relation with healthy controls and in relation with OA and PsA patients, but not in relation with patients with AS. These results reinforce the nature of anti-CarP as an independent autoantibody system that will be worth to study in AS patients.

Protein extracts from FCS and the 7 analysed tissues were carbamylated with similar efficiency allowing for meaningful comparisons of the serum reactivities against them. There were at least some sera showing reactivity against each of the tissues analysed, but the frequencies and titers showed clear differences in function of the tissue used as source of CarP (Table 1).

			Titer correlation		Concordance	
Tissue	**Positive, %**	**% of the FCS+**	**ρ Spearman**	***P-value***	***Gamma***	***P-value***
FCS	57.7	–	Ref.	Ref.	Ref.	Ref.
FLS	49.5	91.7	0.76	$<10^{-15}$	0.94	$<10^{-15}$
synovia	40.2	89.7	0.48	$<10^{-7}$	0.88	$<10^{-14}$
Liver	52.6	70.6	0.64	$<10^{-10}$	0.72	$<10^{-7}$
Tyroid	29.9	82.8	0.31	$<10^{-3}$	0.69	$<10^{-4}$
Kidney	45.4	77.3	0.46	$<10^{-4}$	0.65	$<10^{-5}$
Spleen	16.5	68.8	0.19	n.s	0.38	n.s
Lung	26.8	61.5	–0.08	n.s	0.09	n.s

In addition, the reactivities that best correlated with anti-CarP-FCS were against CarP from FLS and synovia. However, Western blot analysis showed a different pattern of binding of RA patient sera when the CarP were from synovia or from FCS in Western blots (Figure 1).



These results indicate the protein specificity of the anti-CarP antibodies present in RA sera.

Conclusion: The anti-CarP-FCS antibodies are moderately prevalent in patients with RA and highly specific of them in comparison with healthy controls, or patients with OA or PsA, but not with AS. Furthermore, analysis of reactivity against CarP from different tissues shows that the anti-CarP reactivity is dependent of specific CarP, which are different depending on the tissue. Fortunately, results with FCS, which has been used as source of CarP for testing RA sera, strongly correlate with synovia. This correlation contributes to confidence in the previously reported clinical and genetic associations of this new type of autoantibodies.

Disclosure: A. Gonzalez, None; **A. Montes**, None; **E. Perez-Pampin**, None; **M. D. Boveda**, None; **J. J. Gomez-Reino**, None.

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AAA-Atpase p97 Regulates Autophagy-Associated Cell Death in Arthritis. Masaru Kato[1], Kerstin Klein[2], Caroline Ospelt[3], Christoph Kolling[4], Michihito Kono[1], Shinsuke Yasuda[1], Renate E. Gay[5], Steffen Gay[3] and Tatsuya Atsumi[1]. [1]Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]University Hospital Zurich, Zurich, Switzerland, [3]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [4]Schulthess Clinic, Zurich, Switzerland, [5]Zurich University Hospital, Zurich, Switzerland.

Background/Purpose: Recently we described a hypersensitivity of rheumatoid arthritis synovial fibroblasts (RASF) compared to osteoarthritis synovial fibroblasts to autophagy under conditions of severe endoplasmic reticulum (ER) stress, leading to a massive cytoplasmic vacuolization, the formation of poly-ubiquitinated protein aggeregates and non-apoptotic cell death. Valosin containing protein (p97/VCP) is an ATPase implicated in the degradation of ubiquitin-labelled proteins through the proteasome. We hypothesized that the inhibition of p97 further sensitizes RASF to autophagy-associated cell death due to impaired proteasomal degradation and subsequent overloaded autophagy.

Methods: RASF were transfected with siRNA targeting p97 or treated with the selective p97 inhibitor DBeQ (5 μM). To induce ER stress, RASF were treated with thapsigargin (TG, 5 nM-5 μM). 3-methyladenine (5 mM) was used as an autophagy inhibitor. The distribution of poly-ubiquitinated proteins was evaluated by immunofluorescence microscopy. Cell death was evaluated by flow cytometry using annexin V/propidium iodide staining. Collagen-induced arthritis (CIA) was induced in Lewis rats. Scrambled or p97 siRNA-atelocollagen complexes were injected into ankle joints of rats. Three, seven and eleven days after the injection, CIA was scored from 0 to 4 according to paw thickness and ankle diameter.

Results: Both siRNA-mediated knockdown and inhibition of p97 in RASF boosted a cytoplasmic vacuolization, the formation of poly-ubiquitinated protein aggeregates and cell death under 5 μM TG treatment, and this cell death was inhibited by 3-methyladenine. Smaller amounts of TG (50 or 500 nM) induced a cytoplasmic vacuolization and the formation of poly-ubiquitinated protein aggeregates in p97-inhibited RASF but not in control RASF. Intra-articular injection of p97 siRNA significantly suppressed CIA (Day 3, $p = 0.002$; Day 7, $p = 0.002$; Day 11, $p = 0.04$; $n = 6$) in rats.

Conclusion: Our data indicate that the inhibition of p97 promotes autophagy-associated cell death in RASF and suppresses CIA in vivo. p97 may be a new potential target in the treatment of arthritis.

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ACR Poster Session A

Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy: Safety of Biologics and Small Molecules in Rheumatoid Arthritis

Sunday, November 16, 2014, 8:30 AM–4:00 PM

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First Confirmation Data of Long Term Safety for Tocilizumab in Real-World Setting; 3 Year Follow-up Postmarketing Surveillance of 5573 Patients with Rheumatoid Arthritis in Japan. Kazuhiko Yamamoto[1], Hajime Goto[2], Kenzo Hirao[3], Atsuo Nakajima[4], Hideki Origasa[5], Nobuhiro Takagi[6], Minako Tomobe[6] and Kyoichi Totsuka[7]. [1]Univ Tokyo Gr School of Med, Tokyo, Japan, [2]Fukujuji Hospital, Tokyo, Japan, [3]Heart Rhythm Center, Tokyo Medical and Dental University, Tokyo, Japan, [4]Tokyo Metropolitan Police Hospital, Tokyo, Japan, [5]University of Toyama School of Medicine, Toyama, Toyama, Japan, [6]Chugai Pharmaceutical, Tokyo, Japan, [7]Kitatama Hospital, Tokyo, Japan.

Background/Purpose: To evaluate the long-term safety of tocilizumab (TCZ) for the treatment of rheumatoid arthritis (RA) in a real-world clinical setting in Japan.

Methods: In this long-term extension of the single-arm, observational postmarketing surveillance study of TCZ, patients who received at least 1 dose of intravenous TCZ (8 mg/kg) between April 2008 and August 2010 were observed for 3 years. Patient characteristics and the incidences of mortality, serious infection, malignancy, GI perforation and serious cardiac dysfunction were evaluated during observation period. The analyses included the adverse events (AEs) after discontinuation of TCZ. Data were summarized as the proportion (95% CI) of patients experiencing each event or as incidence rates presented as the number of patients per 100 patient-years (PY).

Results: In total, 5573 patients were enrolled, with a total observation of 15,106 PY. Excluding patients who died, transferred hospitals, or were lost to follow-up, a total of 5327 patients (95.59%) completed 1 year, 4850 (87.03%) completed 2 years, and 4527 (81.23%) completed 3 years of observation. The mean and median treatment duration was 2.1and 2.9 years, respectively. The overall mortality rate during the observation period was 2.58% (144/5573 patients). The most common cause of death was infection (28.47%), followed by respiratory disease (15.97%), malignancy (14.58%), and cardiac dysfunction (9.03%). The standardized mortality ratio (SMR) in comparison with the general Japanese population was 1.27 (95% CI, 1.08–1.50), which is comparable to the SMR reported in a large observational cohort of Japanese patients with RA (all-patient mortality between 1.46 [95% CI, 1.32–1.60] and 1.90 [95% CI, 1.75–2.07]).[1] The incidence rate of malignancy during the observation period was 2.24% (0.83/100 PY), and the standardized incidence ratio (SIR) was 0.79 (95% CI, 0.66–0.95), which was stable over time. Only malignant lymphoma had a significantly higher incidence compared to the general Japanese population, with a SIR of 3.13 (95% CI, 1.82–5.39) which is comparable to that of all RA patients compared with the general population (SIR, 6.07; 95% CI, 3.71–9.37).[2] There was no increase in rate of any AEs with prolonged observation, while incidence of fatal events, serious infection, GI perforation and serious cardiac dysfunction decreased over time. (Table).

Conclusion: The safety profile of TCZ was consistent over time with respect to mortality, serious infections, malignancy, gastrointestinal perforation, and serious cardiac dysfunction. These data confirm the long-term safety of TCZ use in patients with RA in a real-world clinical setting in Japan.

Ref 1; Nakajima et. al. *Scand J Rheumatol.* 2010;39(5):360–367.
Ref 2; Yamada et. al. *Rheumatol Int.* 2011;31(11):1487–1492.

Table. Changes in the incidence of fatal events, serious infections malignancy GI perforation and serious cardiac dysfunction during observation period

Incidence rate [95%CI]	0–52 wk (n=5573)	53–104 wk (n=5168)	105–156wk (n=4721)
Mortality	1.18 [0.92–1.50]	0.85 [0.62–1.14]	0.47 [0.29–0.70]
Malignancy	0.68 [0.48–0.93]	0.81 [0.59–1.10]	0.66 [0.45–0.93]
Serious infections	5.67 [5.08–6.31]	3.25 [2.78–3.77]	2.16 [1.77–2.62]
Gastrointestinal perforation	0.36 [0.22–0.55]	0.15 [0.07–0.30]	0.15 [0.06–0.31]
Serious cardiac dysfunction	0.61 [0.42–0.85]	0.41 [0.25–0.62]	0.11 [0.03–0.25]

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Meta-Analysis of Serious Infections with Tofacitinib and Biological Treatment in Rheumatoid Arthritis Clinical Trials. V. Strand[1], S. Ahadieh[2], J. French[3], J. Geier[4], S. Krishnaswami[5], S. Menon[5], T. Checchio[2], R. Riese[6] and J. Gomez-Reino[7]. [1]Biopharmaceutical Consultant, Portola Valley, CA, [2]Pharmacometrics, Pfizer Inc, Groton, CT, [3]Metrum Research Group, Tariffville, CT, [4]Pfizer Inc, New York, NY, [5]Clinical Pharmacology, Pfizer Inc, Groton, CT, [6]Pfizer Inc, Groton, CT, [7]Hospital Clinico, Universitario de Santiago, Santiago, Spain.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Serious infection events (SIEs) have been reported in the tofacitinib RA trials. Limited head-to-head comparator data are available within the tofacitinib RA development program to directly compare rates of events relative to approved biologic therapies. Here we present a meta-analysis of published randomized controlled trials (RCTs) and corresponding long-term extension (LTE) studies to contextualize the risk of SIEs for tofacitinib relative to biologics approved for treatment of moderate to severe RA.

Methods: A systematic literature search (Medline, Embase, PubMed, and regulatory submission documents for approved therapies) was conducted through October 2013. A total of 66 RCTs and 22 LTE trials met the inclusion criteria for the meta-analysis. Incidence rates (per 100 patient-years) of SIEs for each therapy across trials were estimated based on RCT and LTE data using a random effects model. Relative and absolute risk comparisons to placebo were made using RCT data only, based on Mantel-Haenszel methods. Placebo-controlled data ranging between 3–12 months for biologics and 3 months for tofacitinib were assessed. Statistical heterogeneity was assessed using I^2 statistic.

Results: Incidence rate (per 100 patient-years [95% CI]) estimates from the meta-analysis were 3.04 (2.49, 3.72) for abatacept, 3.72 (2.99, 4.62) for rituximab, 5.45 (4.26, 6.96) for tocilizumab, and 4.90 (4.41, 5.44) across TNF inhibitor (TNFi) therapies. The tofacitinib incidence rates from the five Phase (P) 3 trials only were 3.02 (2.25, 4.05) and 3.00 (2.24, 4.02) for 5 mg twice daily (BID) and 10 mg BID, respectively. The incidence rates in the ongoing LTE studies (as of August 2013) were 2.50 (2.05, 3.04) for 5 mg BID and 3.19 (2.74, 3.72) for 10 mg BID. The risk ratio (RR; [95% CI]) for TNFi relative to placebo in methotrexate inadequate responder (MTX-IR) trials (n=24) was 1.50 (1.00, 2.25). The tofacitinib RRs, relative to placebo, in P3 were 2.21 (0.60, 8.14) for 5 mg BID and 2.02 (0.56, 7.28) for 10 mg BID. Risk differences (expressed as difference in incidence percent; RD; [95% CI]) relative to placebo were 0.94% (0.25%, 1.63%) for TNFi therapies, 0.38% (−0.24%, 0.99%) for tofacitinib 5 mg BID, and 0.40% (−0.22%, 1.02%) for tofacitinib 10 mg BID. Separate analyses of MTX-naïve studies (n=10) showed a RR of 1.24 (0.87, 1.77) for TNFi relative to MTX. RRs from the tofacitinib ORAL Start (A3921069) study vs. MTX were similar to the TNFi estimates for both tofacitinib doses (i.e. 1.10 [0.39, 3.11] for 5 mg BID and 0.75 [0.25, 2.26] for 10 mg BID).

Conclusion: This meta-analysis provided an indirect quantitative assessment of the SIEs for biological therapies to contextualize data from the tofacitinib RA clinical development program. Comparisons of incidence rates, RRs and RDs suggest that risk of SIEs with tofacitinib is comparable to published rates for biologic therapies in the treatment of moderate to severe RA.

Disclosure: V. Strand, AbbVie, Afferent, Amgen, Biogen Idec, Bioventus, BMS, Carbylan, Celgene, Celltrion, CORRONA, Crescendo, Genentech/Roche, GSK, Hospira, Iroko, Janssen, Lilly, Merck, Novartis, Pfizer Inc, Regeneron, Sanofi, SKK, Takeda, UCB, Vertex, 5, 9; **S. Ahadieh**, Pfizer Inc, 1, Pfizer Inc, 3; **J. French**, Pfizer Inc, 5; **J. Geier**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Krishnaswami**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Menon**, Pfizer Inc, 1, Pfizer Inc, 3; **T. Checchio**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Gomez-Reino**, Pfizer Inc, 5, Pfizer Inc, 8.

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Evaluation of the Effect of Tofacitinib on Measured Glomerular Filtration Rate in Patients with Active Rheumatoid Arthritis. J. Kremer[1], A.J. Kivitz[2], J.a. Simon Campos[3], E.L. Nasonov[4], H. Tony[5], B. Vlahos[6], C. Hammond[6], J. Bukowski[6], H. Li[6], S. Schulman[6], S. Raber[7], A. Zuckerman[8] and J. Isaacs[9]. [1]Albany Medical College and The Center for Rheumatology, Albany, NY, [2]Altoona Center for Clinical Research, Duncansville, PA, [3]Hospital CEM/BIOCEM, Merida, Mexico, [4]Nasonova State Institute of Rheumatology, Moscow, Russia, [5]University Hospital Würzburg, Würzburg, Germany, [6]Pfizer Inc, Collegeville, PA, [7]Pfizer Inc, San Diego, CA, [8]Pfizer Inc, Groton, CT, [9]National Institute for Health Research Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, Newcastle, United Kingdom.

Background/Purpose: In the clinical development program of the oral Janus kinase inhibitor tofacitinib for the treatment of rheumatoid arthritis (RA), small mean increases in serum creatinine (SCr) (<4 μmol/L least mean squares difference from placebo [PBO] for tofacitinib 5 and 10 mg twice daily [BID] at Month 3) were observed and plateaued early. Further analyses using pooled data from five Phase 3 and two long-term extension (LTE) studies suggested that tofacitinib had a small and reversible effect on mean SCr in patients (pts) with RA; the mean SCr changes plateaued, remained within normal limits and did not appear to be associated with acute renal failure or progressive worsening of renal function in the LTE studies. This study aimed to assess changes in measured glomerular filtration rate (mGFR) with tofacitinib relative to PBO in pts with active RA.

Methods: In this double-blind, PBO-controlled, Phase 1 study (NCT01484561) RA pts were randomized 2:1 to oral tofacitinib 10 mg BID in Period 1 (P1) then PBO BID in Period 2 (P2) (tofacitinib→PBO); or oral PBO BID in both P1 and P2 (PBO→PBO). P1 and P2 were 6–7 and 4–5 weeks in duration, respectively. Each pt underwent mGFR evaluations by iohexol serum clearance at 4 time points (run-in, pre-dose 1 in P1, end of P1, and end of P2); estimated GFR (eGFR) was calculated using the Cockcroft-Gault equation. The primary endpoint was the geometric mean change in mGFR from baseline to end of P1. Secondary endpoints included the geometric mean change in mGFR from baseline to end of P2 and from end of P1 to end of P2, change in eGFR and SCr, RA clinical efficacy and safety.

Results: 148 pts were randomized to tofacitinib→PBO (N=97) and PBO→PBO (N=51). Baseline characteristics were similar between groups. In tofacitinib→PBO, tofacitinib treatment in P1 was associated with a reduction of 8% (90% confidence interval [CI]: 2%, 14%) from baseline in geometric mean mGFR vs PBO→PBO. The reduction in geometric mean mGFR associated with tofacitinib in P1 reversed on PBO in P2, and there was no difference vs PBO→PBO in the adjusted geometric mean fold change of mGFR at the end of the study (tofacitinib→PBO: PBO→PBO: 1.04; 90% CI: 0.97, 1.11). Similar results were observed for eGFR and SCr (Table). Of note, during P2 there was a 5% reduction (90% CI: 1%, 10%) in mGFR (but not eGFR) in PBO→PBO. Clinical efficacy and safety were consistent with prior studies.

Conclusion: This study suggests that small mean increases in SCr and mean decreases in eGFR in pts with RA treated with tofacitinib may occur in parallel with small mean decreases in mGFR, and that changes in these parameters with short-term tofacitinib treatment appear reversible after discontinuation. Safety monitoring will continue in ongoing and future clinical trials and routine pharmacovigilance.

1. Isaacs JD et al. Ann Rheum Dis 2012; 71 (Supplement 3): 672.
2. Wollenhaupt J et al. Arthritis Rheum 2013; 65(suppl 10): S993.

Table: Renal endpoints (ANCOVA) in Full Analysis Set (observed case)

Period	Treatment Sequence	N	Adjusted Geometric Mean Fold Change (90% CI)	Ratio of Adjusted Geometric Mean Fold Change (Tofacitinib→PBO vs PBO→PBO) (90% CI)
mGFR (mL/min/1.73 m^2)				
Baseline to Period 1	Tofacitinib→PBO	91	0.91 (0.88, 0.95)	0.92 (0.86, 0.98)
	PBO→PBO	46	0.99 (0.94, 1.04)	
End Period 1 to Period 2	Tofacitinib→PBO	86	1.03 (0.99, 1.07)	1.09 (1.02, 1.16)
	PBO→PBO	45	0.95 (0.90, 0.99)	
Baseline to Period 2	Tofacitinib→PBO	86	0.96 (0.92, 1.00)	1.04 (0.97, 1.11)
	PBO→PBO	45	0.92 (0.87, 0.97)	
eGFR (Cockcroft-Gault) (mL/min/1.73m^2)				
Baseline to Period 1	Tofacitinib→PBO	92	0.96 (0.95, 0.98)	0.95 (0.92, 0.98)
	PBO→PBO	46	1.01 (0.99, 1.04)	
End Period 1 to Period 2	Tofacitinib→PBO	87	1.03 (1.01, 1.05)	1.04 (1.01, 1.07)
	PBO→PBO	44	1.00 (0.97, 1.02)	
Baseline to Period 2	Tofacitinib→PBO	87	1.00 (0.98, 1.01)	0.99 (0.97, 1.02)
	PBO→PBO	44	1.01 (0.98, 1.03)	
Serum creatinine (mg/dL)				
Baseline to Period 1	Tofacitinib→PBO	92	1.04 (1.02, 1.06)	1.05 (1.02, 1.08)
	PBO→PBO	46	0.99 (0.97, 1.01)	
End Period 1 to Period 2	Tofacitinib→PBO	87	0.97 (0.95, 0.99)	0.97 (0.94, 1.00)
	PBO→PBO	44	1.00 (0.98, 1.03)	
Baseline to Period 2	Tofacitinib→PBO	87	1.00 (0.99, 1.02)	1.01 (0.98, 1.04)
	PBO→PBO	44	1.00 (0.97, 1.02)	

ANCOVA, analysis of covariance; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; mGFR, measured glomerular filtration rate; OC, observed case.
FAS (OC) include available data from all randomized patients who took at least one dose of study medication (tofacitinib→PBO or PBO→PBO). Data collected after patients (one in Period 1 and two in Period 2, all in to facitinib→PBO) took a wrong treatment bottle were excluded. Missing data were not imputed.
ANCOVA model included treatment and baseline of the endpoint as a covariate. The analysis was performed on the log-transformed scale and then exponentially back-transformed to derive the geometric mean fold change and 90% confidence intervals on the original scale.

Disclosure: J. Kremer, Pfizer Inc, 2, Pfizer Inc, 5; **A. J. Kivitz**, Pfizer Inc, 2, Pfizer Inc, 5, Pfizer Inc, 8; **J. A. Simon Campos**, None; **E. L. Nasonov**, None; **H. Tony**, None; **B. Vlahos**, Pfizer Inc, 1, Pfizer Inc, 3; **C. Hammond**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Bukowski**, Pfizer Inc, 1, Pfizer Inc, 3; **H. Li**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Schulman**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Raber**, Pfizer Inc, 1, Pfizer Inc, 3; **A. Zuckerman**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Isaacs**, Pfizer Inc, 2, Pfizer Inc, 5.

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Analysis of Non-Melanoma Skin Cancer Across the Tofacitinib Rheumatoid Arthritis Clinical Program. J.R. Curtis[1], E.B. Lee[2], G. Martin[3], X. Mariette[4], K.K. Terry[5], Y. Chen[6], J. Geier[7], J. Andrews[5], M. Kaur[6], K. Kwok[7] and C. Nduaka[5]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Seoul National University College of Medicine, Seoul, South Korea, [3]Dermatology and Laser Center of Maui, Kihei, HI, [4]Paris-Sud University, Paris, France, [5]Pfizer Inc, Groton, CT, [6]Pfizer Inc, Collegeville, PA, [7]Pfizer Inc, New York, NY.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). The incidence of non-melanoma skin cancer (NMSC) in the tofacitinib RA program was evaluated using data from randomized Phase (P) 1, 2, 3, and open-label long-term extension (LTE) studies (P1P2P3LTE studies).

Methods: NMSC data (cut-off date: August 30, 2013) were pooled from two P1, eight P2, six P3, and two LTE studies; LTE data collection and analyses are ongoing; study databases have not yet been locked. Patients in P1, P3 and LTE studies were treated with tofacitinib 5 mg or 10 mg twice daily (BID) either as monotherapy or with background disease-modifying antirheumatic drugs (DMARDs). LTE patients rolled over from qualifying P1, P2, and P3 studies; patients from P2 studies were treated with tofacitinib 1 to 30 mg BID or 20 mg once daily. Incidence rates per 100 patient-years (py) of exposure (IRs) for first new NMSC were calculated for combined doses (all doses) of tofacitinib in the P1P2P3LTE patient population. The overall NMSC IR was analyzed as well as IRs for subgroup analyses according to the following conditions: dose of tofacitinib (5 mg vs 10 mg); tofacitinib monotherapy vs tofacitinib + background DMARDs; previous treatment with tumor necrosis factor inhibitors (TNFi); age of patients (≥65 vs <65); ethnic background; and time period.

Results: A total of 6,092 tofacitinib-treated patients (representing 15,103 py of exposure) received tofacitinib (all doses) in the P1P2P3LTE studies. One or more events of NMSC occurred in 83 patients receiving tofacitinib (all doses). Of these 83, squamous cell carcinomas (SCC) occurred in 39 patients, and basal cell carcinomas (BCC) occurred in 52 patients. A total of five patients had a history of NMSC prior to tofacitinib exposure compared with 78 patients who did not. In the whole P1P2P3LTE population, the IR for NMSC overall was 0.55 (95% confidence interval [CI] 0.45, 0.69); the IRs for SCC and BCC were 0.26 (0.19, 0.35) and 0.35 (0.26, 0.45), respectively. The IRs for patients from the P1/2/3 and LTE cohorts receiving tofacitinib 5 mg BID were 0.61 (0.34, 1.10) and 0.41 (0.26, 0.66), respectively; for patients receiving tofacitinib 10 mg BID, the IRs were 0.47 (0.24, 0.90) and 0.79 (0.60, 1.05), respectively. Patients on background DMARDs had a numerically higher IR (IR 0.64, 95% CI 0.49, 0.84) than patients on tofacitinib monotherapy (IR 0.43, 95% CI 0.30, 0.64). There was a higher rate of NMSC in patients previously treated with TNFi (IR 1.01, 95% CI 0.67, 1.51) vs TNFi-naïve patients (IR 0.47, 95% CI 0.37, 0.61). Patients ≥65 years old had a higher rate of NMSC (IR 1.67, 95% CI 1.19, 2.35) vs patients <65 years old (IR 0.38, 95% CI 0.29, 0.51). Patients of White ethnicity had the highest IR of NMSC vs patients of Asian, Black, or Other ethnicity (0.86 vs 0.03, 0.00, or 0.14). The IRs for NMSC, analyzed in 6-month intervals (through >42 months), were stable over time.

Conclusion: The overall IR for NMSC in the tofacitinib clinical development program remained stable over time. The NMSC IRs appear to be consistent with published estimates in patients with RA treated with TNFi (IR 0.22–0.66).[1]

1. Askling J et al. Pharmacoepidemiol Drug Saf 2011; 20: 119–130.

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Comprehensive Summary of the Efficacy and Safety of Tofacitinib 5mg Twice Daily in Patients with Rheumatoid Arthritis and an Inadequate Response to Disease-Modifying Antirheumatic Drugs.

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Background/Purpose: Tofacitinib has been approved in the US and other countries at the recommended dose 5 mg BID in patients (pts) with rheumatoid arthritis (RA) and an inadequate response (IR) to prior DMARDs. Several Phase 3 studies have been conducted as part of the tofacitinib clinical development program. Here we provide a comprehensive summary of efficacy and safety outcomes with the 5 mg BID dose from five DMARD-IR Phase 3 studies.

Methods: Week 12 efficacy and safety data for tofacitinib 5 mg BID and placebo (PBO) were compiled from five Phase 3 studies (NCT00814307, ORAL Solo; NCT00856544, ORAL Sync; NCT00853385, ORAL Standard; NCT00847613, ORAL Scan; and NCT00960440, ORAL Step). Pts with RA received tofacitinib as monotherapy (ORAL Solo) or with background DMARDs (ORAL Sync, ORAL Standard, ORAL Scan, ORAL Step). All pts in ORAL Standard and ORAL Scan had an IR to MTX, those in ORAL Step had an IR to TNFi, those in ORAL Solo were biologic or nonbiologic DMARD-IR, and those in ORAL Sync were nonbiologic DMARD-IR. Endpoints evaluated included ACR20, ACR50, ACR70 response rates, DAS remission (DAS28-4[ESR]<2.6), change in Health Assessment Questionnaire-Disability Index (HAQ-DI), adverse events (AEs), discontinuations due to AEs, serious adverse events (SAEs), and serious infection events (SIEs). For binary variables, such as ACR20/50/70 and DAS28-4(ESR)<2.6, non-responder imputation (NRI) was used.

Results: Baseline demographics and disease characteristics were generally similar within and between studies, except TNFi-IR pts having a longer history of RA than DMARD-IR. ACR20 rates were significantly improved with tofacitinib vs PBO either as monotherapy or with background DMARDs; ACR50 and ACR70 rates demonstrated similar patterns (Table 1). After only 12 weeks of treatment, significantly more pts receiving tofacitinib 5 mg BID than PBO achieved DAS28-4(ESR)<2.6, apart from those in ORAL Solo (Table 1). Significant changes from baseline in HAQ-DI were also observed with tofacitinib vs PBO, both as a monotherapy or with background DMARDs (Table 1).

Frequencies of AEs and SAEs were similar between tofacitinib and PBO across all studies (Table 1). Discontinuations due to AEs, by pts receiving tofacitinib, were ≤7% in all groups. Pooled and long-term analyses of Phase 3 and long-term extension studies have further described the AE profile associated with tofacitinib therapy.[1]

Conclusion: This comprehensive summary demonstrates that, regardless of prior therapy, short-term treatment with tofacitinib 5 mg BID significantly reduced signs and symptoms of RA, as measured by ACR20/50/70, DAS28-4(ESR)<2.6, and HAQ-DI. There were no unexpected safety findings at the US-recommended dose.

1. Wollenhaupt J et al. J Rheumatol 2014; 41: 837–52.

Table 1. Efficacy and safety outcomes of 5mg BID tofacitinib treatment vs placebo at Week 12

	ORAL Solo		ORAL Sync		ORAL Standard		ORAL Scan		ORAL Step	
	5 mg BID	PBO	5 mg BID	PBO	5 mg BID	PBO	5 mg BID	PBO	5 mg BID	PBO
Baseline Characteristics										
Mean (range) disease duration, years	N = 243 8.0 (0.2–42.3)	N = 122 7.7 (0.1–28.0)	N = 315 8.1 (0.2–39.9)	N = 159 9.9 (0.3–49.0)	N = 204 7.6 (0.3–39.0)	N = 108 8.0 (0.3–49.4)	N = 321 8.9 (0.3–43.0)	N = 160 9.2 (0.4–43.5)	N = 133 13.0 (1.2–55.0)	N = 132 11.3 (0.4–47)
Mean (SD) DAS28-4(ESR)	N = 237 6.7 (0.9)	N = 115 6.7 (0.9)	N = 309 6.3 (1.0)	N = 158 6.3 (0.9)	N = 193 6.6 (0.9)	N = 103 6.5 (0.9)	N = 316 6.4 (0.9)	N = 154 6.3 (1.0)	N = 126 6.5 (1.0)	N = 130 6.5 (1.0)
Efficacy	N = 241	N = 120	N = 311	N = 157	N = 196	N = 106	N = 309	N = 154	N = 132	N = 131
ACR20, n (%)	144 (59.8)†***	32 (26.7)	175 (56.3)***	43 (27.4)	119 (60.7)***	28 (26.4)	174 (56.3)***	42 (27.3)	55 (41.7)†*	32 (24.4)
ACR50, n (%)	75 (31.1)***	15 (12.5)	85 (27.3)***	9.6 (2.3)	67 (34.2)***	7 (6.6)	89 (28.8)***	12 (7.8)	35 (26.5)***	11 (8.4)
ACR70, n (%)	37 (15.4)*	7 (5.8)	26 (8.4)**	3 (1.9)	24 (12.2)**	2 (1.9)	33 (10.7)**	4 (2.6)	18 (13.6)**	2 (1.53)
DAS28-4(ESR) <2.6, n (%)	N = 229 13 (5.6)†	N = 104 5 (4.4)	N = 260 28 (10.8)***	N = 140 1 (0.71)	N = 177 9 (5.1)*	N = 92 1 (1.1)	N = 265 14 (5.3)*	N = 129 2 (1.6)	N = 119 8 (6.7)†*	N = 120 2 (1.7)
LS mean (SE) change from baseline in HAQ-DI	N = 237 −0.50 (0.03)†***	N = 109 −0.19 (0.05)	N = 292 −0.46 (0.03)†***	N = 147 −0.21 (0.04)	N = 188 −0.55 (0.04)†**	N = 98 −0.24 (0.05)	N = 294 −0.40 (0.03)†***	N = 146 −0.14 (0.04)	N = 117 −0.43 (0.04)†***	N = 118 −0.18 (0.04)
Safety	N = 243	N = 122	N = 315	N = 159	N = 204	N = 108	N = 321	N = 160	N = 133	N = 132
AEs, n (%)	124 (51.0)	67 (54.9)	166 (52.7)	97 (61.0)	106 (52.0)	51 (47.2)	157 (48.9)	73 (45.6)	71 (53.4)	75 (56.8)
Discontinuations due to AEs, n (%)	2 (0.8)	5 (4.1)	13 (4.1)	2 (1.3)	14 (6.9)	3 (2.8)	15 (4.7)	5 (3.1)	8 (6.0)	7 (5.3)
SAEs, n (%)	0	6 (4.9)	9 (2.9)	6 (3.8)	12 (5.9)	2 (1.9)	12 (3.7)	5 (3.1)	2 (1.5)	6 (4.5)

†Primary endpoint of the study; *p<0.05, ** p<0.001, *** p<0.0001 vs placebo
ACR, American College of Rheumatology Scale response rates; AE, adverse events; BID, tofacitinib twice daily; DAS28, disease activity score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; PBO, placebo; SAE, severe adverse events; SD, standard deviation; SE, standard error; SIE, serious infection events

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Infections and Gastrointestinal Side Effects in a Comparison of Rheumatoid Arthritis Therapies. Bei-Hung Chang[1], Lien Quach[1], Mary Brophy[2], Keri Hannagan[2], Edward C. Keystone[3], Ted R. Mikuls[4] and James R. O'Dell[5]. [1]VA Boston Healthcare System, Boston, MA, [2]VA Boston Heathcare System, Boston, MA, [3]University of Toronto, Toronto, ON, [4]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [5]Veteran Affairs Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: TNF inhibitors and combinations of conventional disease-modifying antirheumatic drugs are commonly added to treat methotrexate non-responsive rheumatoid arthritis patients. In the 48-week double blind, RACAT trial (NEJM 2013;369:307–18), 353 methotrexate suboptimal-responders were randomized to two treatment strategies, either first adding sulfasalazine and hydroxychloroquine, triple therapy (T, N=178), or etanercept (E, N=175) to methotrexate. Participants without significant improvement in DAS28 at 24 weeks switched treatment while maintaining the blind. We examined differences between T and E in the most common adverse events reported in the trial, gastrointestinal (GI) toxicity and infections, taking into account possible confounding factors.

Methods: All adverse events during the trial were recorded and coded by blinded reviewers. Serious (SAE) or non-serious (NAE) infectious and GI events reported during the intervention period and for 4 weeks after completing the intervention were included in the analysis. The trial design posed challenges for analysis for 13 switcher patients who had infection (N=8) or GI (N=5) events occur both before and after switching treatment (either T to E or E to T). For these switchers we included in the analysis only the infections that occurred when patients were currently on T and GI events that occurred when patients were currently on E. This is a conservative approach because infections were the most common side effect for E and GI events were for T. We calculated the rate of event, total number of events, and the mean duration in the treatment when events occurred. Logistic and linear regression models were used for treatment comparison with and without controlling for participant characteristics (age, sex, race, BMI, smoking) and comorbidities.

Results: Participants who were on E were more likely to have infection NAEs (OR= 1.68, p=0.02) and had a higher total number of events (mean of 0.7 vs. 0.4, p=0.004) than participants who were on T. Participants who were on T had a higher number of GI NAEs than those on E (mean 0.55 vs. 0.34, p=0.02). Furthermore, the amount of time on the treatment when the GI events occurred was shorter for T than E (mean duration 10.0 vs. 17.7 weeks, p=0.001). The same conclusions remain after using regression models to control for patient characteristics and comorbidities. Serious infections and GI events were rare for both treatments. However, there were a greater number of SAE infections that occurred when receiving E than T (12 vs. 4). Pneumonia was the most common SAE infection for both treatments (6 E and 2 T).

Conclusion: In RACAT, infectious NAEs were significantly increased in participants receiving E compared with T even after controlling for participant demographics and comorbidities. GI NAEs were significantly more frequent in T and occurred earlier in the course of therapy. Though numbers of SAE were small, there was a trend toward greater number of infectious SAEs when receiving E, which were predominately pneumonias. Our study findings might help clinicians when prescribing medications by considering patients' tolerance of each treatment's more common adverse events.

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Golimumab 5-Year Safety: an Analysis of Pooled Data from the Long Term Extensions of Randomized, Double-Blind, Placebo-Controlled Studies in Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis. Jonathan Kay[1], Roy Fleischmann[2], Edward C. Keystone[3], Elizabeth C. Hsia[4], Neil Goldstein[4], Benjamin Hsu[4], Yiying Zhou[4], Jürgen Braun[5] and Arthur Kavanaugh[6]. [1]UMass Memorial Medical Center, Worcester, MA, [2]Metroplex Clinical Research Center, University of Texas, Dallas, TX, [3]Mount Sinai Hospital, Toronto, ON, [4]Janssen Research & Development, LLC., Spring House, PA, [5]Rheumazentrum Ruhrgebiet, Herne, Germany, [6]University of California San Diego, La Jolla, CA.

Background/Purpose: To present an analysis of pooled data through approx 5yrs of follow-up from 5 completed golimumab(GLM) Ph3 SC trials across rheumatological indications.

Methods: SC placebo (PBO) or GLM (50mg or100mg) was administered q4wks in Ph3 trials. After wk24/52, pts in the Ph3 studies entered LTE and received GLM50mg or 100mg q4wks in an unblinded fashion. Dose adjustment from 50mg to 100mg and 100mg to 50mg was allowed once. Concomitant meds included DMARDs (mostly MTX). AEs were analyzed based on treatment received by a pt during the course of the study; PBO, 50mg only, 100mg only, or 50mg and 100mg. Because pts could cross-over from PBO to GLM, a pt may appear in both PBO and GLM columns. Due to the short duration of the PBO-controlled portion, comparisons between GLM and PBO grps are limited.

Results: In Ph3 trials, 639pts received PBO, 671 GLM50mg, 765 GLM50mg and GLM100mg, and 792 GLM100mg through 5yrs. In Ph3, 5.2%, 15.4%, 9.5% and 19.9% of PBO, GLM50 only, GLM50 and GLM100mg, and GLM100mg only pts, respectively, discontinued due to AE through 5yrs. The incidences per 100PY of deaths, serious infections (including TB, opportunistic infections [OI]), demyelination, and malignancies are presented. Injection site reactions were low; most were mild, and 2 cases led to discontinuation. No GLM SC-treated pt developed anaphylaxis/serum sickness-like reaction. Malignancies occurring during the 5 Ph3 trials included skin cancers, solid tumors, and lymphoma. In comparison to SEER, overall incidence of malignancies in GLM-and PBO-treated pts was similar to that expected in the general US population. Incidence of lymphomas per 100 pt-years of follow-up was greater in the GLM100mg dose grp through 5yrs and higher than that expected in the general US population.

Conclusion: The safety of continued SC GLM exposure demonstrates that GLM was generally well-tolerated with overall low rates of discontinuation due to AEs. Safety profiles were generally similar between GLM dose with exception of higher rates of serious infections, including TB and opportunistic infections, and lymphoma in the GLM100mg grp. Results are confounded by LTE design in which pts could receive GLM100mg after being exposed to GLM50mg with higher GLM dose used for pts with more refractory disease and by limited exposure to PBO making the comparisons between PBO and treatment grps of less value.

	PBO +/− MTX	GLM50mg +/− MTX	GLM50mg and GLM100mg +/− MTX	GLM100mg +/− MTX
Pts treated (n)	639	671	765	792
Total pt/yrs of follow-up	350	2375	3346	2983
Deaths	0.29(0.01, 1.59)	0.46(0.23, 0.83)	0.27(0.12, 0.51)	0.54(0.31, 0.87)
All serious infections	4.86(2.83, 7.78)	2.48(1.89, 3.20)	3.26(2.67, 3.93)	3.96(3.27, 4.74)
Tuberculosis (TB)	0.00(0.00, 0.86)	0.17(0.05, 0.43)	0.21(0.08, 0.43)	0.30(0.14, 0.57)
Opportunistic infections(not TB)	0.00(0.00, 0.86)	0.13(0.03, 0.37)	0.12(0.03, 0.31)	0.34(0.16, 0.62)
Demyelination*				
Total pt/yrs of follow-up	350	2375	3346	2979
Incidence/100 pt yrs(95%CI)	0.00(0.00, 0.86)	0.00(0.00, 0.13)	0.03(0.00, 0.17)	0.20(0.07, 0.44)
Malignancy				
Nonmelanoma skin cancers (NMSC)				
Total pt/yrs of follow-up	347	2371	3319	2947
Observed # of pts with event	6	6	16	15
Incidence/100 pt yrs (95%CI)	1.73(0.63,3.76)	0.25(0.09,0.55)	0.48(0.28,0.78)	0.51(0.28,0.84)
Lymphoma				
Total pt/yrs of follow-up	350	2374	3346	2982
Observed # of pts with event	0	1	2	6

Incidence/100 pt yrs (95% CI)	0.00(0.00,0.86)	0.04(0.00,0.23)	0.06(0.01, 0.22)	0.20(0.07,0.44)
Expected # of pts with event	0.09	0.59	0.95	0.78
SIR (95% CI)	0.00(0.00,33.23)	1.71(0.04,9.50)	2.11(0.26, 7.61)	7.71(2.83, 16.78)
Other malignancies				
Total pt/yrs of follow-up	349	2369	3345	2977
Observed # of pts with event	3	20	11	17
Incidence/100 pt yrs (95% CI)	0.86(0.18,2.51)	0.84(0.52,1.30)	0.33(0.16, 0.59)	0.57(0.33, 0.91)
Expected # of pts with event	1.98	12.34	20.63	16.70
SIR (95% CI)	1.52(0.31,4.44)	1.62(0.99,2.50)	0.53(0.27, 0.95)	1.02(0.59,1.63)

GLM SC program including 3RA, 1 PsA, 1 AS studies;*Based on data through end of studies (approximately 5 years)

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Analysis of Pooled Data from Two Randomized Controlled Trials and Their Open-Label Extensions: Long-Term Safety in Rheumatoid Arthritis before and after Certolizumab Pegol Dose Increase/Decrease. Boulos Haraoui[1], Vivian P. Bykerk[2], Ronald van Vollenhoven[3], Marc de Longueville[4], Kristel Luijtens[4], Pauline Ralston[5] and Arthur Kavanaugh[6]. [1]Centre Hospitalier de l'Université de Montréal, Montréal, QC, [2]Hospital for Special Surgery, New York, NY, [3]The Karolinska Institute, Stockholm, Sweden, [4]UCB Pharma, Brussels, Belgium, [5]Giant Professional Ltd, London, United Kingdom, [6]University of California San Diego, La Jolla, CA.

Background/Purpose: Certolizumab pegol (CZP) is approved for adult patients (pts) with rheumatic diseases (RA, PsA and AS) at a maintenance dose of 200mg every 2 wks (Q2W) or 400mg every 4 wks (Q4W). In RAPID1[1] (52 wks) and RAPID2[2] (24 wks) randomized clinical trials (RCTs; NCT00152386 and NCT00160602), CZP was administered at a loading dose of 400mg at Wks 0, 2, and 4, followed by CZP 200mg Q2W, or at CZP 400mg Q2W in pts with active RA. All pts entering open-label extensions (OLEs; NCT00175877 and NCT00160641) received CZP 400mg Q2W for ≥6 months. The dose was subsequently reduced to CZP 200mg Q2W for all pts[3,4] as feeder studies revealed that the null hypothesis of no difference between doses could generally not be rejected. We present safety data evaluating the potential effect of CZP dose change over 12 wks prior to and post dose-escalation or dose-reduction, in line with treat-to-target.

Methods: Post-hoc analysis was performed on pooled RAPID1 and RAPID2 CZP data: 1) dose-escalation from CZP 200mg Q2W to CZP 400mg Q2W, 2) dose-reduction from CZP 400mg Q2W to CZP 200mg Q2W (Figure).

Results: 557 pts randomized to CZP 200mg Q2W in the RCTs entered the OLEs, with dose-escalation to 400mg Q2W. Of these, 210 pts (37.7%) experienced an adverse event (AE) in the 12 wks prior to dose-escalation versus 203 pts (36.4%) in the 12 wks post dose-escalation (Table). 94.4% of AEs were mild-moderate: 65 and 71 pts, respectively, experienced AEs considered to be drug-related. Serious AEs are reported in the table. The incidence of infections increased post dose-escalation. Malignancies were reported in 3 pts during 12 wks prior to (1 testis, 2 basal cell carcinoma [BCC]) and post (testis, lung, and peritoneal) dose-escalation. During OLEs, 1110 pts received CZP 400mg Q2W for ≥6 months before dose-reduction. Of these, 365 pts (32.9%) experienced an AE in the 12 wks prior to dose-reduction versus 342 pts (30.8%) in the 12 wks post dose-reduction; 94.1% of AEs were mild-moderate: 102 and 91 pts, respectively, experienced AEs considered drug-related. Incidence of SAEs and infections was similar prior to and post dose-reduction. 2 pts reported malignancies in the 12 wks post dose-reduction (1 gastric, 1 BCC). 2 cases of opportunistic infection (including tuberculosis) were reported in the 12 wks post dose-reduction. Overall, the number of AEs leading to withdrawals was low and no deaths were reported during the dose-escalation and dose-reduction study periods evaluated.

Conclusion: Overall, despite a modest infection rate increase after dose-escalation, no new safety concerns emerged during dose-escalation or dose-reduction, and AE rates were generally similar between periods. However, the natural trend of a decreasing rate of AEs was observed over time, as is usual in RA clinical trials.

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Figure: Schematic of RAPID1 and RAPID2 study design showing periods of dose-escalation and dose-reduction

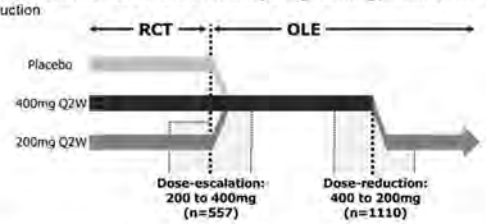

Table: SAEs reported in ≥3 pts by SOC during 12-wk periods prior to and post CZP dose increase/decrease

Event, n (%)	Dose-escalation		Dose-reduction	
	CZP 200mg, prior to dose-escalation (n=557)	CZP 400mg, post dose-escalation (n=557)	CZP 400mg, prior to dose-reduction (n=1110)	CZP 200mg, post dose-reduction (n=1110)
Total AEs	210 (37.7)	203 (36.4)	365 (32.9)	342 (30.8)
Total SAEs	13 (2.3)	25 (4.5)	31 (2.8)	41 (3.7)
Most frequent SAEs:				
Cardiac Disorders [a]	1 (0.2)	1 (0.2)	1 (0.1)	3 (0.3)
Ischemic coronary artery [b]	1 (0.2)	0	1 (0.1)	3 (0.3)
Gastrointestinal Disorders [a]	2 (0.4)	0	4 (0.4)	0
Infections and Infestations [a, c]	1 (0.2)	12 (2.2)	13 (1.2)	13 (1.2)
Lower respiratory tract and lung infections [b]	0	4 (0.7)	5 (0.5)	2 (0.2)
Injury, Poisoning and Procedural Complications [a]	1 (0.2)	2 (0.4)	3 (0.3)	4 (0.4)
Musculoskeletal and Connective Tissue Disorder [a]	4 (0.7)	1 (0.2)	4 (0.4)	8 (0.7)
Rheumatoid arthropathies [b]	1 (0.2)	0	1 (0.1)	4 (0.4)
Respiratory, Thoracic and Mediastinal Disorders [a, d]	0	2 (0.4)	3 (0.3)	2 (0.2)
Pneumothorax and pleural effusions NEC [b]	0	1 (0.2)	3 (0.3)	0

SAEs presented by [a] SOC, and [b] high level term, MedDRA v9.0; [c] All other infections and infestations refer to singular events of a wide range of infections. [d] Does not include SAEs listed under infections and infestations; AEs, adverse events; NEC, not elsewhere classified; SAEs, serious AEs; SOC, system organ class

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18-Month Worldwide Post-Marketing Surveillance Experience of Tofacitinib. S. Cohen[1], J.R. Curtis[2], Roy Fleischmann[1] and Y. Chen[3]. [1]Metroplex Clinical Research Center, Dallas, TX, [2]University of Alabama, Birmingham, AL, [3]Pfizer Inc, Collegeville, PA.

Background/Purpose: Post-marketing surveillance is an important part of monitoring adverse events (AEs) following the approval of new drugs. Tofacitinib is an oral Janus kinase inhibitor approved in the United States in November 2012 for the treatment of rheumatoid arthritis (RA). An analysis of the post-marketing spontaneous (PMS) reports, covering a period of 18 months, was conducted to evaluate the safety of tofacitinib in the post-marketing setting.

Methods: Tofacitinib worldwide PMS reports received in the Pfizer safety database from 6 November 2012 to 5 May 2014 were analyzed. The type and estimated reporting rate of serious AEs of interest, including infections, neoplasm events, gastrointestinal (GI), and hepatobiliary disorders, by 6-month interval were reviewed. The reporting rate of SAEs was calculated by dividing the number of SAEs by the estimated patient-years of exposure (PYs). The PYs were estimated based on estimated worldwide sales and an estimated daily regimen of 5 mg twice daily.

Results: A total of 2,496 case reports with 6,295 AEs were received. The majority of reported AEs were non-serious (83.4%). Of the 1,043 SAEs, 21.8% of the events were related to infections, 8.7% were GI disorders, 3.55% were neoplasm events, and 0.6% were hepatobiliary disorders. The reporting rate of serious infections (SIs) was 5.1, 6.2, and 2.48 per 100 PYs for the

first/second/third 6-month interval, respectively. The most commonly reported SI events (n ≥ 10) include pneumonia (33), urinary tract infection (26), sepsis (15), diverticulitis (11), and herpes zoster (HZ) infections (10). A small number of opportunistic infections (OI) were reported including reactivation of tuberculosis (2), disseminated HZ (1), histoplasmosis (1), Cytomegalovirus gastritis/ oesophagitis (1), and unspecified OI (1). The reporting rate of serious neoplasm events across the first/second/third intervals was 0.14, 1.02, and 0.54 per 100 PYs, respectively. The commonly-reported serious neoplasm events (n ≥2) include lymphoma (6), bladder cancer (3), brain neoplasm (3), lung neoplasm malignant (2), basal cell carcinoma (2), and unspecified neoplasm malignant (2). Most of the case reports did not have sufficient information for a causality assessment. In the reports where time to onset was provided, eight events were diagnosed before or within 2 months of the initiation of tofacitinib. Across the reporting period, no significant change in reporting rate was noted for GI and hepatobiliary disorders. Of the 91 reported serious GI events, the most commonly reported events (n ≥ 5) including diarrhea (11), nausea (6), vomiting (6), GI hemorrhage (5), and hematochezia (5).

Conclusion: Review of AEs from PMS reports did not reveal any new safety signal compared with the safety profile identified from tofacitinib RA clinical studies during its development program. SAEs including SIs and malignancy have been reported in the post-marketing setting and the safety profile of tofacitinib will continuously be monitored via pharmacovigilance. Limitations of PMS reports (such as under-reporting and reporting bias) and estimated reporting rate due to lack of denominators should be considered when interpreting these results.

Disclosure: S. Cohen, Pfizer Inc, 5, Pfizer Inc, 2; **J. R. Curtis**, Pfizer Inc, 2, Pfizer Inc, 5; **R. Fleischmann**, Pfizer Inc, 2, Pfizer Inc, 5; **Y. Chen**, Pfizer Inc, 1, Pfizer Inc, 3.

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Should Anti-Tnfa treatment of RA be Stopped before Orthopedic Surgery? Charlotte Mabille[1], Adeline Ruyssen Witrand[2], Thomas Barnetche[3], Arnaud Constantin[2] and Alain G. Cantagrel[2]. [1]hopital Purpan, Toulouse, France, [2]CHU Purpan - Hôpital Pierre-Paul Riquet, Toulouse, France, [3]Rheumatology department, Bordeaux University Hospital, bordeaux, France.

Background/Purpose: Anti-TNFs have greatly contributed to improve RA prognosis. Hence, the needs for orthopedic surgery have considerably decreased in the past years. However, surgery, whether programmed or not, whether orthopedic or not, is sometimes necessary in patients treated with TNF inhibitors. Current recommendations are to discontinue biologic DMARDs to reduce the risk of surgical site infection. The guidelines for periopetrative cessation periods of biologic DMARDs differ among countries but generally a stop of the biotherapy 2 to 6 weeks before programmed surgery is recommended. Anti-TNF can be resumed after wound healing.

The purpose of this current study was to ask:

1. Whether patients treated with anti-TNF are really at risk for infection upon surgery.

2. Whether stopping anti-TNF treatment increases the risk of infection upon surgery.

Methods: We have conducted a systematic review of the literature indexed in Pubmed, Embase, and Cochrane using the following keywords: "Rheumatoid arthritis AND surgery AND infection AND (adalimumab OR certolizumab OR etanercept OR golimumab OR infliximab)". This search was conducted up to February 2014 and was limited to papers in English and French languages. Reviews and case reports were excluded.

We selected studies reporting numbers of infections observed post-surgery by

i) comparing patients using anti-TNF with patients using DMARDS without biologicals and

ii) comparing patients keeping up with anti-TNF with patients who interrupted anti-TNF before surgery.

Results: Fourteen studies reported the frequency of post-surgery infections of RA patients undergoing orthopedic surgery, most often joint replacement.

Eleven studies were pooled in order to evaluate the infection risk in patients treated with anti-TNF compared with patients treated with DMARD without biologics. There were 4,925 surgeries and 121 infections in patients using anti-TNF and 60,678 surgeries and 711 infections in patients with DMARD alone. Thus, patients treated with anti-TNF are at higher risk of post-surgery infection (OR = 1.95 [1.34–2.85]). Some joints such as foot, ankle and elbow seem to be at higher risk.

Six studies were pooled for meta-analysis evaluating the benefits of stopping anti-TNF as post-infection risk is concerned. Two studies were not informative, as no infection was reported in any of them. Stopping the anti-TNF treatment did not modify the infection risk: OR = 0.70 [0.39–1.25].

Conclusion: This meta-analysis shows that patients treated with anti-TNF are more exposed to risks of infection after orthopedic surgery. The increased rate of infection in those patients was not ameliorated by stopping anti-TNF before surgery. This could lead clinicians, at least in surgeries with lower risks of infection, to reconsider stopping anti-TNF before surgery since this may expose patients to a flare-up.

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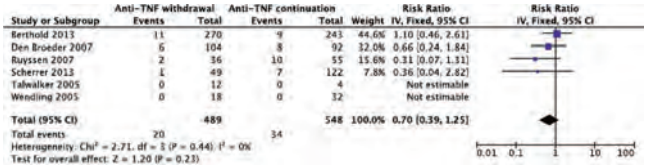

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Evaluation of the Rabbit Risk Score for Serious Infections in a UK Anti-TNF Treatment Cohort. Lucia Silva-Fernandez[1], Mark Lunt[1], Kath D. Watson[1], BSRBR Control Centre Consortium[1], Deborah P. Symmons[1], Kimme Hyrich[1] and On behalf of the BSRBR[2]. [1]Arthritis Research UK Centre for Epidemiology, University of Manchester, Manchester, United Kingdom, [2]British Society for Rheumatology, London, United Kingdom.

Background/Purpose: Serious infections (SI) are a major concern in patients treated with tumour necrosis factor inhibitors (TNFi). The RABBIT Risk Score (RRS) (1) allows a calculation of the expected number of SI over a one year period of TNFi treatment according to patient characteristics. This score was developed in a cohort of German patients with rheumatoid arthritis (RA) enrolled in the RABBIT biologics register and then validated in a second cohort from the same register. The aim of the present study is to assess the reliability of the RRS in two cohorts of patients with RA treated with TNFi from the British Society for Rheumatology Biologics Register (BSRBR)-RA.

Methods: The BSRBR-RA is an ongoing national prospective cohort study of subjects with RA starting biologic therapy. Patients were recruited to a first TNFi cohort (old) between 2001 and 2008 and to a second TNFi cohort (new) from 2010 to date. Risk factors included in the RRS include age. Health Assessment Questionnaire (HAQ) score, chronic lung disease, chronic renal disease, previous serious infection, number of treatment failures, mean daily glucocorticoid dose and treatment with TNFi. As the BSRBR-RA does not capture the dose of oral steroids or intramuscular injections (common in the UK), we applied a modified version of the score to both cohorts assuming that all patients receiving steroids would take between 7.5–14 mg of prednisolone per day. We calculated the expected number of patients with at least one SI in the first year of therapy and compared to the observed numbers in each cohort. To evaluate the predictive performance of the RRS we calculated the area under the curve (AUC).

Results: 13,121 patients were recruited to the old cohort and 1,475 patients were recruited to the new cohort. There were significant differences between cohorts (Table). Patients from the old cohort had a longer disease duration, higher DAS28 and HAQ score, and more likely to be receiving steroids compared to newer patients. The crude incidence rate of SI was lower in the new cohort (29.3 new vs 62.3 old/1000 patient-years) as was the expected and observed number of patients with ≥1 SI during the first year of therapy. The predictive performance of the RRS was better for the new cohort (AUC=0.82) than for the old cohort (AUC=0.62).

	Old cohort (n=13,121)	New cohort (n=1,475)	p
Age (years), mean (SD)	56.1 (12.3)	56.5 (12.6)	0.128
Gender: n (%) female	10,010 (76.3)	1,116 (75.7)	0.591
RA disease duration (years), Median (IQR)	11 (6 – 19)	6 (2 – 14)	0.0001
DAS28, mean (SD)	6.5 (1.0)	5.9 (1.0)	0.0001
HAQ score, mean (SD)	2.0 (0.6)	1.6 (0.7)	0.0001
RF +, n (%)	8,493 (64.8)	821 (55.6)	<0.0001
Steroid use (%)	5,867 (44.7)	358 (24.3)	<0.0001
Smoking			0.065
Current, n (%)	2,861 (22.0)	279 (20.2)	
Ex-smoker, n (%)	4,922 (37.8)	505 (36.5)	
Never smoked, n (%)	5,238 (40.2)	600 (43.4)	
More than 5 previous DMARDs, n (%)	325 (2.5)	4 (0.3)	<0.0001
Diabetes, n (%)	750 (5.8)	115 (7.9)	0.001

Chronic lung disease, n (%)	2,060 (15.9)	252 (18.5)	0.012
Chronic renal disease, n (%)	330 (2.5)	28 (1.9)	0.149
Crude incidence rate of serious infections in the first year per 1,000 patient-years (95% Confidece Interval)	63.3 (59.0 – 67.9)	29.3 (20.8 – 41.3)	
Number of observed first serious infections in the first year	771	33	
Number of expected first serious infections in the first year	496	27	
Area under the curve (95% Confidence Interval)	0.62 (0.60 – 0.64)	0.82 (0.73 – 0.91)	

Conclusion: TNFi are being used earlier in RA patients with lesser disease activity, steroid use and disability. These patients are also experiencing lower SI rates. Among these cohorts of UK patients, the RRS underestimated the total number of SI, although some misclassification of steroid dose and differential access to TNFi resulting in other unmeasured patient differences may have contributed. The predictive power improved in a more recent cohort which strengthens the utility of this score in current routine clinical practice.

Reference:

(1) Zink A et al. Evaluation of the RABBIT risk score for serious infections. Ann Rheum Dis 2013 Jun 28 (doi:10.1136/annrheumdis-2013–203341)

Disclosure: L. Silva-Fernandez, None; **M. Lunt**, None; **K. D. Watson**, None; **BSRBR Control Centre Consortium**, None; **D. P. Symmons**, None; **K. Hyrich**, Pfizer, Abbvie, 8; **On behalf of the BSRBR**, Pfizer Inc, Abbvie, UCB, Merck, Roche, 2.

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Identification of Baseline Risk Factors for Adverse Events in Certolizumab Pegol Treated Rheumatoid Arthritis Patients. Boulos Haraoui[1], John Wade[2], Marc de Longueville[3], Pauline Ralston[4] and Jeffrey R. Curtis[5]. [1]Centre Hospitalier de l'Université de Montréal, Montréal, QC, [2]University of British Columbia, and Vancouver General Hospital, Vancouver, BC, [3]UCB Pharma, Brussels, Belgium, [4]Giant Professional Ltd, London, United Kingdom, [5]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Despite efficacy of anti-tumor necrosis factors (anti-TNFs) in treating chronic immune conditions, some patients (pts) report serious adverse events (SAEs) highlighting a need to identify at risk pts before starting treatment.[1,2] We examine safety data for rheumatoid arthritis (RA) pts treated with the anti-TNF, certolizumab pegol (CZP), in the RAPID1 and RAPID2 randomized clinical trials (RCTs; NCT00152386/NCT00160602) and their open-label extensions (OLEs) to identify baseline (BL) risk factors for specific SAEs, with the goal of risk stratifying pts for adverse outcomes to provide more personalized estimates of expected risks and benefits of therapy.

Methods: Post-hoc analysis was performed on CZP safety data pooled across RCTs (RCT CZP data) and RCT+OLE periods (All CZP data). Pts with prior anti-TNF/biologicals use (4.1%) were excluded from analyses due to limited pt numbers in this group. 3 non-sequential stepwise multivariate Cox proportional hazards models were used to estimate relative risk (Hazard Ratio [HR]; entry $p \leq 0.2$, stay $p \leq 0.25$) of BL covariates to the first serious infectious event (SIE), major cardiovascular event (MACE), or all-cause death. Any event between first CZP dose and 84 days after the last study dose or pt withdrawal was included. BL covariates included age ($<$ or $\geq$65 years), presence of comorbidity (any treated cardiac disorder, diabetes or COPD), systemic steroid use (0, $>$0–5, $>$5 mg/day), methotrexate dose ($\leq$ or $>$15 mg/week), RA disease duration ($<$ or $\geq$2 years), and a range of BL disease activity measures.

Results: A total of 311 placebo (PBO) pts (130.5 pt-years [PY]) and 1224 CZP pts (798.5 PY) were included in the RCT analyses, with 3 and 50 pts, respectively, reporting $\geq$1 SAE of interest. 1 and 2 PBO pts experienced $\geq$1 SIE or MACE, respectively, and 1 died while 40 and 8 CZP pts experienced $\geq$1 SIE or MACE, respectively, and 7 died. BL predictors of SIEs for the RCT data were treated comorbidities and systemic steroid use (Figure A). For All CZP data, 246/1506 RA pts (5778.6 PY) reported SIE/MACE/death: 201 and 32 pts reported $\geq$1 SIE or MACE, respectively, with 38 deaths. Time to first SIE was associated with several covariates screened as potential risk factors. BL treated comorbidity had marked associations with time to first SIE (Figure B). No other covariates examined were considered relevant to the outcome. Age was a predictor of MACE and death but the low number of events limits interpretation of this finding.

Conclusion: CZP-treated pts with certain comorbidities were twice as likely to experience SIEs and the risk remained elevated when data were pooled across RCT +OLEs. Knowledge of BL characteristics related to an increased risk of SAE of interest should help clinicians to better identify those pts and help manage some of the risks related to anti-TNFs.

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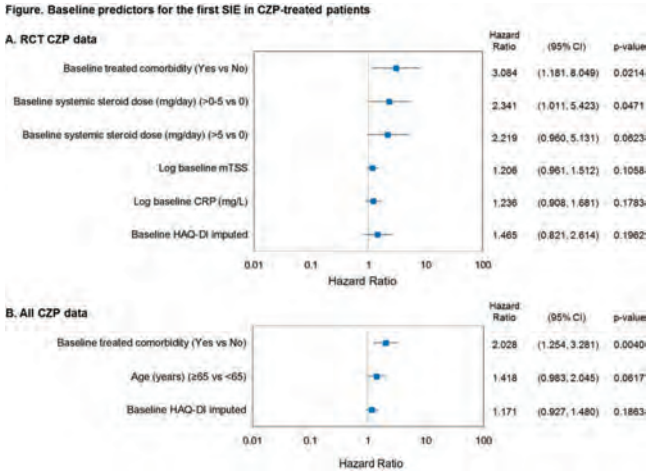

Disclosure: B. Haraoui, Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 2, Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 8, Abbott, Amgen, BMS, Janssen, Pfizer, Roche and UCB Pharma, 5; **J. Wade**, UCB Pharma, 5; **M. de Longueville**, UCB Pharma, 3; **P. Ralston**, UCB Pharma, 5; **J. R. Curtis**, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

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Safety of Rituximab in Patients with Chronic Inflammatory Arthritis. Seven-Year Follow-up Observational Study. Andrea Cuervo[1], M. Victoria Hernández[1], Sonia Cabrera[1], Jose Inciarte-Mundo[1], Julio Ramirez[1], Virginia Ruiz-Esquide[1], Juan D. Cañete[2] and Raimon Sanmarti[1]. [1]Hospital Clínic of Barcelona, Barcelona, Spain, [2]Hospital Clinic, Barcelona, Spain.

Background/Purpose: Rituximab (RTX) is a biologic therapy approved for the treatment of active rheumatoid arthritis (RA) refractory to tumour necrosis factor antagonists. It causes B cell depletion, with a progressive reduction of the levels of immunoglobulin (Ig) that may be associated with an increased risk of infection. Our objective was to analyse the long-term safety of treatment with RTX in patients with RA and other inflammatory arthritis, and especially the risk of severe infections.

Methods: We made a retrospective descriptive study including patients treated by the Rheumatology Department of a tertiary hospital from June 2006 to December 2013 who had received at least one cycle of treatment with RTX. We analysed: demographic data (age, sex), diagnosis and disease duration, positive rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibodies (anti-CCP); previous biologic treatment; concomitant treatment: disease-modifying antirheumatic drugs (DMARD) and/or concomitant glucocorticoids (GC); number of cycles received; levels of immunoglobulin (Ig) and adverse effects, especially severe infections.

Results: 53 patients were included (85 % female, mean age 58.9 $\pm$ 12.9) until December 2013, who received a total of 169 cycles of RTX (mean: 3.3 $\pm$ 2.2 cycles/patient) during 7 years. Diagnoses were: RA (75.5 %), overlap syndrome (11.3 %), systemic lupus erythematosus (5.7 %), psoriatic arthritis (3.7 %), seronegative oligoarthritis (1.9 %) and juvenile idiopathic arthritis (1.9 %). Mean disease duration was 15.1 $\pm$ 8.4 years, 79.2 % were RF/anti-CCP positive, 67.9 % had received prior biological treatment, 37.7 % had received $\geq$ 2 or more biologic drugs, 77.3% received concomitant DMARDs (47.2% methotrexate, 30.2 % leflunomide, 11.3% hydroxychloroquine and 3.8 % mycophenolate mofetil) and 79.2% received GC. A progressive, significant decrease in IgG levels ($p = 0.018$), IgM ($p = 0.018$) and IgA (0.05), already evident after the first RTX cycle, was observed, although only 13.2% of patients had Ig levels below the normal range. Twenty-five adverse events were reported, of which 19 were considered drug-related: 2 infusion reactions, 2 cases of leukopenia and 15 infections (7 respiratory tract, 5 urinary tract, 1 soft tissue infection, 1 case of bacteremia and 1 septic shock), and 4 of which were considered serious according to medical criteria, although no patient discontinued RTX for those reasons. No opportunistic infection or malignancy was reported. Patients with low Ig levels did not have a greater number of infections than those with normal Ig levels.

Conclusion: After prolonged exposure to RTX, serious adverse events, including infections, were stable over time and multiple treatment courses, and showed a good safety profile, even in patients with reduced Ig levels.

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Safety Profile of Biologic Agents for Rheumatoid Arhtisitis Treatment after the Complication with Methotrexate-Related Lymphoproliferative Disorder.

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Background/Purpose: Lymphoproliferative disorder (LPD) is a rare complication in patients with rheumatoid arthritis(RA) treated with methotrexate(MTX). Although not a few patients experience exacerbation of RA disease activity after withdrawal of MTX, there have been very few reports referring how to treat RA with MTX-LPD. This study is to investigate the safety profile of biologic agents as a RA treatment after the diagnosis of MTX-LPD.

Methods: We retrospectively studied all 32 RA patients regarded as being complicated with MTX-LPD from 2007 to 2013 in our institution. The patients were classified into 2 groups: patients treated with biologic agents after MTX withdrawal (Biologics group) and patients treated with conventional synthetic disease modifying anti-rheumatic drugs (csDMARD) other than MTX or prednisolone (PSL) (non-biologics group). The rates of LPD recurrence after these RA treatments were compared. The recurrence rates were analyzed by Kaplan-Meier curves and compared by log-rank test.

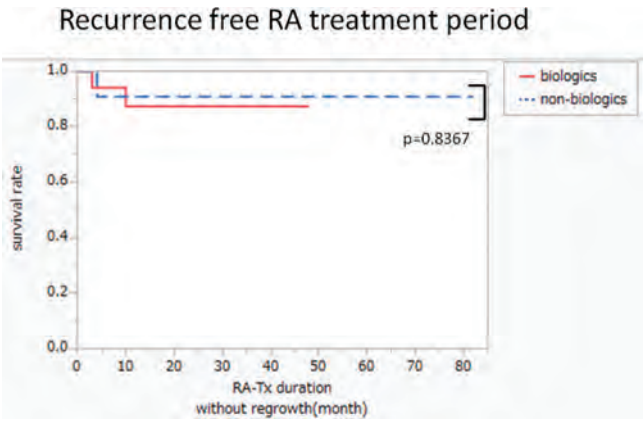
Results: Four patients were excluded because three died before the restart of RA treatment and one needed no treatment, so twenty eight patients were analyzed in this study. Baseline characteristics of 28 patients were following: age,65; Female, 89%; duration of MTX administration, 7.5 years; RA disease duration,14.1years; disease activity score (DAS) 28, 2.95. Of 28 patients, 22 patients were pathologically diagnosed as LPD, and 10 were highly suspected of LPD with imaging tests. Seven patients were treated of LPD with chemotherapy prior to restart of RA therapy. 17 Patients were treated with biologic agents and the drugs used were following; tocilizumab (TCZ) in 9 patients, tumor necrosis factor inhibitors (TNFi) in 6, abatacept in 1, rituximab in 1. Eleven patients were treated with PSL and/or csDMARDs; PSL alone in 5, salazosulfapyridin (SASP) in 3, bucillamin in 2, tacrolimus (Tac) in 1 patient. LPD relapsed in 2 patients in biologics group, and in 1 in non-biologics group. No significant difference in recurrence rates between the two groups analyzed by Kaplan-Meier curves and Log-rank test (Figure, p=0.84).

Among 7 patients who had been treated with chemotherapy before the RA disease activity exacerbation, 3 were treated with biologics and 4 with non-biologic; PSL alone in 2, SASP in 1, Tac in 1. No LPD recurrence was observed in these 7 patients in follow up duration (mean 33 months).

Additional analysis with 22 patients that were pathologically diagnosed of LPD showed similar results.

Conclusion: Biologics agents did not increase LPD recurrence compared to csDMARD, and could be the choice of RA treatment in post-MTX-LPD.

<Figure> Recurrence free RA treatment period [months]



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Improving of Safety in Treatment with Biologics during First Seven-Years Experiences; Long-Term Results from Observational Cohort Study of Clinical Practice Using Multicenter Registry in Japan.

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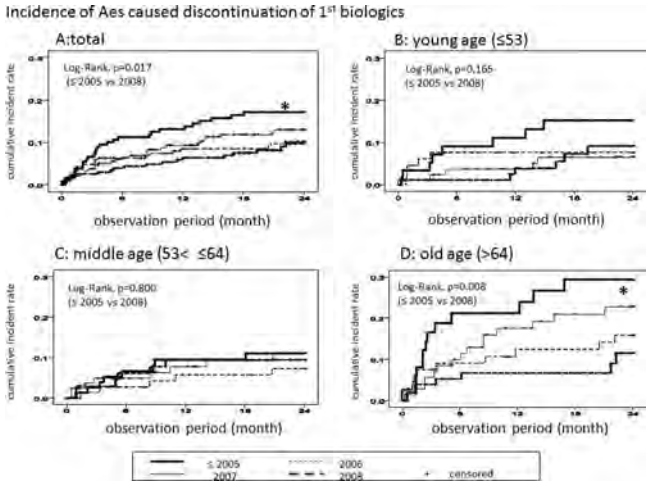
Background/Purpose: Many evidences including clinical trials of biologics lead us earlier and more aggressive treatment strategy for patients with rheumatoid arthritis (RA). It is stated as "treat-to-target", that is remission. It is critical issue in clinical practice how to evaluate risks and to balance between safety and efficacy of treatment, which could be related to experience.

The aims of this study are to explore the learning curve of treatment with biologics during the first 7 years in Japan (2003–2010) based on safety results associated with the changes in baseline characteristics according to treat-to-target strategy in RA patients treated with biologics using multicenter registry; Tsumumai Biologics Communication Registry (TBCR).

Methods: We analyzed changes in baseline characteristics by initiation year of 1st biologics and the incidence rate of adverse event (AE) caused discontinuation of 1st biologics in patients who were registered in TBCR from 2003 to 2008 and followed up to 2010. Predictive factors at baseline for incidence of adverse event were determined using multivariable Cox's proportional-Hazards regression model.

Results: A total of 874 cases (2052 person-years) were observed. Patients with younger age (≤53 ys) had significantly shorter disease duration (<2 years), less dysfunction, joint damage, and disease activity (DAS28-CRP) at 2008, compared to 2003–2005 while patients with older age (>64 ys) had no significant changes. During total observation, 122 AEs (6.0 events/100 person-years) were occurred. The incidence rate of AEs were significantly higher in older age group than in younger age group (p<0.001, log-rank test). Kaplan-Meier curves showed that the incidence rate of AEs was significantly decreased with year of initiation, especially in older age group and that the differences was remarkable up to 6 months. Actually, multivaliable analysis showed that, during 2 years observation, older age [OR 1.8, 95%CI (1.1–3.0)], worse physical function [OR 2.1, 95%CI (1.4–3.1)], MTX use [OR 0.4, 95%CI (0.3–0.7)], and etanercept use (vs infliximab use) [OR 0.4, 95%CI (0.3–0.7)] had significant impacts on incidence of the AEs. Interestingly, initiation year had significant impacts on incidence of AEs up to 6 months [initiation at 2008: OR 0.3, 95%CI (0.1–0.7), compared to initiation 2003–2005] and while the impact disappeared up to 2 years observation. The impact of MTX use and etanercept use was not detected up to 6 months observation. Incident rate of the AEs in pateints with older age who were initiated biologics at 2008 was comparable to patients with younger age. These results suggested that, during first 3 years (2003–2005), we could not evaluate risk factors properly, especially in respiratory system, with inadequate experience.

Conclusion: We clearly demonstrated improving of safety of 1st biologics with first 7-years experiences in real clinical practice using multicenter registry of biologics in Japan.



Disclosure: T. Kojima, Takeda Pharma Corporation, Janssen Pharmaceutical, and Astellas Pharma Corporation., 2, Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Eisai Pharma Corporation, Abbvie, Bristol-Myers Squibb, Pfizer and Chugai Pharma Corporation, 8; **N. Takahashi**, Abbott Japan Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Co. Ltd, Chugai Pharmaceutical Co. Ltd., and Bristol-Myers Squibb Co. Ltd., 8; **K. Funahashi**, None; **S. Asai**, None; **Y. Yoshioka**, None; **K. Terabe**, None; **N. Asai**, None; **T. Takemoto**, None; **N. Ishiguro**, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 5, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 8; **A. Kaneko**, Janssen Pharmaceutica Product, L.P., 8, Astellas Pharma, 8, Mitsubishi-Tanabe Pharma, 8, Chugai, 8, Eisai, 8, Abbott Immunology Pharmaceuticals, 8, Bristol-Myers Squibb, 8; **Y. Hirano**, AbbVie Inc.; Eisai Co. Ltd.; Mitsubishi Tanabe Pharma Corporation; Takeda Pharma Corporation; Pfizer Co. Ltd; Chugai Pharmaceutical Co. Ltd. and Bristol-Myers Squibb Co. Ltd., 8; **Y. Yabe**, Abbott Immunology Pharmaceuticals, 8, Mitsbishi-Tanabe Pharma, 8, Eisai, 8, Chugai, 8, Bristol-Myers Squibb, 8, Pfizer Inc, 8; **Y. Kanayama**, Astellas Pharma, 8, Eisai, 8, Mitsubishi Tanabe Pharma Corporation, 8, AbbVie Inc, 8, Chugai, 8.

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Abatacept Can be Used Safely for RA Patients with Interstitial Lung Disease. Shinji Motojima[1], Tamao Nakashita[2], Akira Jibatake[3] and Katsutoshi Ando[4]. [1]Kameda Medical Center, Kamogawa City, Japan, [2]Kameda Medical Center, Kamogawa-city, Japan, [3]Kameda Medical Center, Kamogawa city, Japan, [4]Juntendo university, tokyo, Japan.

Background/Purpose: Interstitial lung disease (ILD) associated with RA is a big concern particularly in Japanese patients evidenced by the reports that the cause of death in approximately 10 % of patients with RA is ILD compared with only few percent in western countries. We have reported that ILD exacerbated in 24 % (14/58) of RA patients associated with ILD when TNF-inhibitors were administrated and 2 of 14 died of ILD, although the degree of exacerbation was minimal in half of the patients (ACR 2012). Here we retrospectively analyzed the effects of abatacept (ABT), a CTLA4-Ig fusion protein, on RA associated with ILD.

Methods: Subjects were 16 patients with RA (male/female = 6/10, mean age 71 years-old) associated with ILD who were administrated with ABT for longer than 52 weeks and analysis was done for the changes between 0 to 52 weeks, because the exacerbation of ILD developed between 4 to 52 weeks of administration of TNF-inhibitors with the mean of 24 weeks in our previous study. Chest CT scan was done before and 52 weeks after administration of ABT. Chest X-ray film (CXR) was taken at least every 3 months. When newly developed shadows were found on CXR or when patients complained of respiratory symptoms for more than 2 weeks, chest CT scan was done. The severity of ILD was graded into 4, grades 0 to grade 3, according to the extent of ILD on chest CT by the method of Gochuico et al. (Arch Intern Med 2008). Chest CT images were graded by 2 independent respirologists.

Results: All the patients completed 52 weeks administration and no-one abandoned ABT due to the exacerbation of ILD. The grades of ILD (grade 0/1/2/3) before and at 52 weeks were 0/9/4/3 and 2/7/4/3, respectively. In 2 patients with grade 1, the grade decreased to 0, suggesting the improvement of ILD. We further attempted to analyze more in detail the CT images according to the method by Kondoh et al. (Respirology 2013), and obtained what % of lung fields have findings of ILD. All the abnormalities suggestive of ILD before and at 52 weeks were 12.9 +/− 12.7 (mean +/− SD) and 12.2 +/− 13.9, respectively, and no significant differences were found. Mean DAS28-ESR and SDAI decreased from 4.47 +/− 1.44 to 2.84 +/− 0.85, and from 16.9 +/− 11.7 to 8.1 +/− 4.2, respectively, and the differences were statistically significant. The mean dose of PSL decreased from 6.6 mg/day to 5.6 mg/day significantly (n = 15). KL-6, a biomarker of ILD, did not change significantly.

Conclusion: ABT can be used safely for RA patients with ILD. ABT even may improve ILD and is an appropriate treatment option for such patients.

Authors do not have any COI.

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Complications of Varicella Zona Virus Infections Are More Frequent in Patients Treated with Biologic Drugs When Combined with Steroids. Jacques Morel[1], Florence Tubach[2], Yannick Allanore[3], Daniel Wendling[4], Celine Cozic[5], Emmanuelle Dernis Labous[6], Eric Legangneux[7], Thao Pham[8], Sophie Odoit[9], Isabelle Roitg[10], Isabelle Koné-Paut[11], Pierre Quartier[12], Jean Sibilia[13] and Severine Guillaume Czitrom[14]. [1]Hopital Lapeyronie, Montpellier, France, [2]Universite Paris Diderot, Paris, France, [3]Paris Descartes University, Rheumatology A Department and INSERM U1016, Cochin Hospital, Paris, France, [4]CHU J Minjoz, Besancon, France, [5]CHD la Roche sur Yon, La Roche Sur Yon, France, [6]Ch Du Mans, Le Mans, France, [7]Centre Hospitalier Public du Cotentin, 50100, France, [8]Sainte Marguerite Hospital, Marseille, France, [9]CHU de la Réunion, Saint Denis, France, [10]Hopital De Perpignan, Perpignan, France, [11]CHU Bicêtre, Le Kremlin Bicêtre, France, [12]IMAGINE Institute, Hôpital Necker-Enfants Malades, Assistance Publique Hôpitaux de Paris, Université Paris-Descartes, Paris, France, [13]University Hospital of Strasbourg, Strasbourg, France, [14]Ch De Bicetre, Le Kremlin Bicetre Cedex, France.

Background/Purpose: To assess varicella zona virus (VZV) infection features under biological drugs.

Methods: A call for observations was sent from april 2013 to april 2014 by email through the Club Rheumatism et Inflammation website to collect varicella zona virus (VZV) infections in adults and children under biologic DMARDs (bDMARDs). Cases collected between february 1st 2004 and january 31th 2007, by the french observational study RATIO were added. Khi-two or Fisher tests were used for qualitative variables when appropriate.

Results: 103 VZV infections were collected in 76 adults and 27 children receiving anti-TNF (71), anti-IL-1 (10), rituximab (10), tocilizumab (8) and abatacept (4) for rheumatoid arthritis (46), spondyloarthritis (15), juvenile induced idiopathic arthritis excluding Still's diseases (11), Still's disease (11), Crohn's disease (8), psoriasis or psoriatic arthritic (3), connectivite connective tissue disease (2) and other chronic inflammatory diseases (6). Adult patients were mainly women (72.4%), 56% aged 19–60 years old and the others were over 60. At the time of infection, associated to bDMARDs were NSAIDs in 5 patients were on NSAID, steroids in 43 on steroids, conventional synthetic (cs) DMARDs in 54 on conventional synthetic (cs) DMARDs and 9 immunosuppressive drugs in 9. VZV infections occurred late after drug onset (> 6 months for 97.2% of patients with steroids, 70.2% for bDMARDs and after 3 years for cs DMARDs for 70.4%. 27 children aged less than 18, mainly girls (74.1%) were treated with methotrexate (15) or immunesuppressive drugs (2) combined with NSAIDs for 10 patients in addition to bDMARDs. Most children were on steroids (11), or bDMARDs (16) for at least 6 months when VZV infection occurred. None of the patients had been vaccinated against VZV. Zoster was more frequently observed in adults (68/76 adults), whereas varicella was most often reported in children (18/27). For varicella, 4 complications were reported in adults (2 skin and 2 disseminated) and 2 in children (1 ophthalmic and 1 disseminated). Complications were more frequent for zoster: 40 in adults (28 skin, 6 neurological, 6 ophthalmic) and 2 in children (1 neurological and 1 ophthalmic). Complications were significantly higher in patients on steroids (p=0.02 vs non steroid group) and tend to be more elevated in anti-TNF group (p=0.055 vs non TNF inhibitor bDMARDs). None received IV immunoglobulin. 90 patients (71 adults and 19 children) were treated with an anti-herpes virus (HSV) drug usually prescribed oral for 1 to 2 weeks and intravenously in 28 patients. NSAIDs were pursued in 11% of the children and 83% of the adults. bDMARDs were at least transiently interrupted in 63 patients (62%) and csDMARDs were stopped for 17 patients. Outcome was favourable for 98 patients with no death.

Conclusion: In this retrospective study, VZV infections were mainly varicella in children and zoster in adults. Outcome was favourable in most cases even when bDMARDs or NSAIDs were pursued and remarkably, even when no specific treatment of VZV infection was applied. Under bDMARDS, complications of VZV infections occurred more frequently in patients treated with steroids.

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Assessment of 12-Month Efficacy and Safety of 168 Certolizumab-pegol Rheumatoid Arthritis Treated Patients from a Multicenter Retrospective National Study in Spain. Vicente Torrente-Segarra[1], Ana Urruticoechea[2], Héctor Corominas[1], Amalia Sánchez[3], Juan

Víctor Tovar[4], Alejandro Muñoz[5], Anna Martínez[6], José Antonio González[4], Manuel Fernández[7] and Noelia Vázquez on behalf of RENACER Study Group[8]. [1]Hospital General Hospitalet-Sant Joan Despí Moisès Broggi, Hospitalet Llobregat, Barcelona, Spain, [2]Hospital de Can Mises, Ibiza, Spain, [3]Hospital Universitario Lucus Augusti, Lugo, Spain, [4]Hospital General Universitario de Elche, Alicante, Spain, [5]Hospital Universitario de Valme, Sevilla, Spain, [6]Hospital La Ribera, Alzira, Valencia, Spain, [7]Hospital Universitario de Guadalajara, Guadalajara, Spain, [8]Hospital Universitario de Ceuta, Ceuta, Spain.

Background/Purpose: There's scant data of CertolizumabPEGol (CZP) in clinical practice. Study goal: assess efficacy and safety of CZP in RA patients at 3, 6,12-month (m), and clinical / serological variables that predict 12-m clinical CZP response.

Methods: Observational, retrospective study of RA patients (ACR 2010), 35 sites in Spain. Patients on CZP, either anti TNF naïve / after other Biological Therapies (BT) failure. Study approved by a local Ethics Committee. Efficacy variables: Tender Joint Count (TJC) and Swollen Joint Count (SJC) reductions, European League against Rheumatism (EULAR) Response, Simplified Disease Activity Index (SDAI) response, steroids dose, CRP, ESR. Safety variables: discontinuation due to side effects. Statistical analysis: SPSS v19.0. Comparative: Mann Whitney / Chi-square tests. Longitudinal: Friedman Cochran's test. Logistic regression analyses performed.

Results: 168 patients: 79.2% women, mean age 54.5 (±13.2), mean disease time 7.5 (±7.3), prior DMARD (25.6% none; 32.1% 1, 42.3% ≥2): MTX 55.4%, leflunomide 36.9%, gold 25.6%, SSZ 11.3%, HCQ 10.7%. Mean number (nr) prior DMARD: 1.4 (±1.2). Prior BT (54.2% none, 28.6% 1, 17.2% ≥2): etanercept 23.8%, adalimumab 19.0%, infliximab 16.1%, rituximab 6.5%, tocilizumab 5.4%, abatacept 4.2%, golimumab 3.0%. Mean nr prior BT 0.8 (±1.1). Mean time on CZP 9.8 m (±3.4), 93.5% induction dose. Concomitant treatment: 11.9% oral steroids, 24.4% DMARD, 50.0% DMARD + steroids (69.6% 1 DMARD, 4.8% 2 DMARDs).

Table 1: Basal, 3-m, 6-m, 12-m clinical variables

	Basal	3-m	6-m	12-m	P value
RF	70.8% (mean RF: 124.2 ± 183.2)				
Anti-Cyclic citrulinated Protein (CCP)	59.8% (mean CCP:275.1 ± 454.9)				
CRP	9.0 (±12.7)	5.7 (±11.7)	4.7 (±9.9)	4.6 (±9.9)	<0.001
ESR	32.3 (±25.3)	25.7 (±21.2)	23.7 (±21.9)	23.5 (±19.9)	<0.001
TJC	8.0 (±5.2)	4.7 (±5.3)	3.6 (±5.0)	3.3(±5.2)	<0.001
SJC	6.0 (±4.5)	3.1 (±4.2)	2.1 (±3.7)	2.2 (±3.9)	<0.001
Disease Activity Score (DAS28)	5.1 (±1.3)	4.0 (±1.6)	3.5 (±1.7)	3.4 (±1.7)	<0.001
DAS28 remission	4.2%	23.8%	35.7%	44.0%	
EULAR		19.6% / 29.8%	27.4% /38.7%	25.0% / 46.4%	
Moderate/Good Response					
SDAI	35.8 (±18.1)	22.1 (±20.7)	17.8 (±19.3)	17.1 (±19.6)	<0.001
Steroids (mg)	8.8 (±6.9)	6.6 (±5.7)	5.7 (±5.7)	4.8 (±5.2)	<0.001

19 patients had mild side-effects, 6 at 3-m (1 varicella zoster reactivation), 8 at 6-m (1 mild respiratory tract infection, that led to CZP withdrawn), 5 at 12-m (1 infectious otitis). 48 withdrawn (28.6%): 31 lack efficacy, 15 intolerance, 2 other causes, 11.9% 3-m and 16.7% 6-m. 120 patients (71.4%) went on CZP at 12-m visit.

Looking responders versus non responders for DAS28/EULAR Response/SDAI we saw some predictors of response ($p<0.05$): lower nr of prior DMARD / BT; higher CRP, ESR, TJC, SJC, DAS28, SDAI. No differences in BT-naive / monotherapy

Conclusion: CZP showed clear benefit in severe refractory to DMARD / BT RA patients with a significant reduction of CRP, ESR, TJC, SJC, DAS28. 75% patients achieved moderate/good EULAR response, either RF/antiCCP (+) or (−). 12-m predictors of response: CRP, ESR, nr of prior DMARD / BT, TJC, SJC, DAS28, SDAI. CZP was well tolerated, no serious side effects. On clinical practice, CZP showed benefit in 71% of RA after 12-m, even in a 45.8% of patients with prior antiTNF.

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Risk Analysis of a First Adverse Event and Recurrent Infections during Biological Therapy in Chronic Inflammatory Arthritis. G. Avila[1], Arnald Alonso[1], Andrea Pluma-Sanjurjo[2], Carolina Diaz[2], Roxana Juverdeanu[2], María América López-Lasanta[1] and Sara Marsal[1]. [1]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [2]University Hospital Vall d'Hebron, Barcelona, Spain.

Background/Purpose: Biological therapies (BT) have significantly improved the prognosis of chronic inflammatory arthritis (CIA) patients. Although they are characterized by a good safety profile, the presence of adverse events (AE) might limit their use. Despite their importance, neither the distribution of AE during treatment nor the risk of a recurrent event has been adequately estimated. The **objective** of this study was to analyze the incidence, distribution in time and the risk of recurrence of infectious AE (IAE) in CIA patients during BT.

Methods: 290 CIA patients (i.e. rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis) treated with at least 1BT during the period between December '99 – March '13 were included. From all these patients a large retrospective clinical data set of 615 BTs could be collected.

The incidence rate (IR) was calculated as the total number of AE per 1,000 patients / year. The difference in the risk of an AE between the 3 CIA was analyzed using the Cox and Poisson regression models. To evaluate temporal distribution and recurrence of IAE, the IR was analyzed at multiple time intervals. Only those IAE with at least 10 recurrences were included.

The analysis of the recurrence was based on a regression model of Cox proportional hazards. Time to failure (TTF) was defined as the time interval between the initiation of the BT and the first IAE. For recurrent events, was defined as the time interval between a recurrent event and the previous one.

Results: A total of **1,361 AE** were found. Comparing the 3 CIA, the risk of a first AE was higher for RA, although this was not significant. The Cox and Poisson regression models showed a high degree of concordance between the 3 CIA.

738 IAE with at least 10 recurrences were identified. From these, 485 were respiratory infections (RI), 73 urinary infections (UI), 67 gastrointestinal infections (GII), 58 herpetic infections (HI) and 55 oral cavity infections (OCI).

The probability of a first **RI** was greatest during the first 48 wks of BT. When all RI (first event and recurrences) were considered, we found a homogeneous distribution over time. In the Cox model, we observed that RI was significantly associated with an increased risk of recurrence (p-value = 7.99e-03, HR = 1.08 [95% CI 1.2–1.14]).

UI showed a less homogeneous distribution over time and there was a greater risk of UI in the first 48 wks of treatment. The probability of recurrence was highly significant (p-value = 1.67e-10, HR = 1.96 [95% CI 1.59–2.41]).

The probability of a first **GII** showed a maximum in the first 12 wks and he risk of recurrence was not significantly (p-value =6.81e-02; HR=1.55 [95% CI 0.97–2.49]).

In the distribution of the **HI**, we found a maximum during the first 48 wks, and a significant risk of recurrence (p-value = 2.78E-03, HR = 1.91 [95% CI 1.25–2.91]).

The distribution of **OCI** showed two maxima, and the risk of recurrence was highly significant (p-value = 5.21e-06, HR [95% CI 1.53–2.92]).

Conclusion: In our series of Chronic Inflammatory Arthritis treated with BT we found no significant differences in the risk of a first AE between the three CIA. In the recurrence analysis, UI and OCI had a highly significant risk of recurrence, whereas the recurrence risk in GII was minimal.

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Medium-Term Safety of TNF-Alpha Inhibitors in Rheumatoid Arthritis: A Meta-Analysis of Randomized Controlled Trials. Lucile Poiroux[1], Yannick Allanore[2], Andre Kahan[3] and Jerome Avouac[1]. [1]Cochin Hospital, Paris, France, [2]Rheumatology A, Paris Descartes University, Cochin Hospital, APHP, Paris, France, Paris, France, [3]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France.

Background/Purpose: TNF-a inhibitors have changed the prognosis of rheumatoid arthritis (RA). The number of molecules and the time of exposure have increased. However, few studies have compared the safety of the five TNF-alpha inhibitors between them, and their medium term safety. The aim of our study was to compare medium term safety (particularly death and severe infection) obtained from randomized controlled trials for the five TNF alpha inhibitors used in the treatment of RA.

Methods: A systematic review of articles published from January 2000 to January 2013 was performed using MEDLINE, EMBASE and COCHRANE

databases. We included randomized, controlled, double-blind trials, with a follow-up period of at least 6 months, comparing TNF-a inhibitors to placebo, with or without concomitant Methotrexate. The primary outcome measure was the occurrence of a serious adverse event, defined by the occurrence of death or of a severe infection (with the requirement of hospitalization). The MedCalc software was used for the statistical analysis.

Results: Among the 396 articles initially identified, 22 were finally selected. These articles included 6682 patients in the anti-TNF-a group (Adalimumab: 2507, Golimumab: 575, Certolizumab: 1512, Infliximab: 1087 and Etanercept: 1001) and 3607 in the placebo group. The duration of patient follow-up ranged from 24 to 78 weeks.

There was no excess of risk of serious adverse event (death or severe infection) in the TNF-a inhibitors compared to placebo (Odds Ratio OR: 1.14, 95% Confidence Interval CI: 0.91–1.44). Nevertheless, we noticed an increased risk of serious event under Certolizumab (OR: 2.06, CI: 1,35–3,15).

There was no increases risk of death in the TNF-a inhibitor group compared to the placebo group (OR: 1.27). We referenced 36 deaths among 6208 patients under TNF alpha inhibitors (0,58%) and 10/3282 deaths under placebo (0,30%). However, increased risk of severe infections in the TNF alpha inhibitor group was observed compared to the placebo group (OR: 1.66) with 192 serious infections among 5889 patients under TNF alpha inhibitors (3,26%) versus 63 serious infections among 3398 patients under placebo (1,85%). Sensibility analysis revealed that adalimumab had an increased risk of severe infection (OR: 2.10)

	Total	Adalimumab	Golimumab	Certolizumab	Infliximab	Etanercept
Death	1.27	2.27	2.02	1.19	0.47	1.28
(CI 95%)	0.71–2.25	0.84–6.16	0.22–18.19	0.27–5.18	0.16–1.40	0.22–7.24
Serious infections	1.66	2.10	2.47	3.47	1.59	0.75
(CI 95%)	1.24–2.23	1.28–3.46	0.93–6.54	0.94–12.78	0.87–2.90	0.40–1.41
SAE	1.14	0.91	1.82	2.06	1.13	0.80
(CI 95%)	0.91–1.44	0.68–1.23	0.45–7.29	1.35–3.15	0.80–1.59	0.57–1.12

Conclusion: This meta-analysis has been performed on a large number of patients and included the five TNF-a inhibitors currently available. It allowed an indirect comparison between the different molecules according to their medium-term safety. We did not find an increased risk of serious adverse events or deaths in patients treated with TNF-a inhibitors. However, we observed an increased risk of severe infections. Further studies aiming at the evaluation of the long-term safety are now needed to confirm these results.

Disclosure: L. Poiroux, None; **Y. Allanore**, None; **A. Kahan**, None; **J. Avouac**, None.

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Leflunomide Use Is Not Associated with an Increased Risk of Lung Disease in Rheumatoid Arthritis: A Meta-Analysis of Randomised Controlled Trials. Richard Conway[1], Candice Low[2], Robert J. Coughlan[1], Martin O'Donnell[1] and John J. Carey[1]. [1]Galway University Hospitals, Galway, Ireland, [2]St. James Hospital, Dublin, Ireland.

Background/Purpose: Leflunomide is an effective treatment for rheumatoid arthritis. An association between pulmonary adverse events, in particular interstitial lung disease, and leflunomide use has been reported. Incident respiratory events may result in cessation of leflunomide treatment. Clarification of its potential role in pulmonary disease is therefore of clinical importance.

Methods: We performed a systematic literature search of Pubmed and Cochrane databases with no date limits for double-blind randomised controlled trials of leflunomide versus placebo or active comparator agents in adults with rheumatoid arthritis. We evaluated the association between leflumonide use and pulmonary adverse events by performing a meta-analysis of the results. Studies with less than 50 subjects, of less than 12 weeks duration, or with no reporting of respiratory adverse events were excluded. Random effects meta-analysis using the Mantel-Haenszel method was used to assess total respiratory adverse events, infectious respiratory adverse events, non-infectious respiratory adverse events, pneumonitis, and death. **Results** were expressed as relative risks (RR) with 95% confidence intervals.

Results: Our literature search returned 884 results. A total of 8 studies, 4 with placebo comparators, met our inclusion criteria. Seven hundred and eight respiratory adverse events were documented in 4579 participants. Six cases of pneumonitis occurred, all in the comparator group. Four pulmonary deaths were reported, none in the leflunomide group. Leflunomide was not associated with an increased risk of total adverse respiratory events, RR 0.99 (95% CI 0.56–1.78), or infectious respiratory adverse events, RR 1.02 (95% CI 0.58–1.82). Leflunomide was associated with a decreased risk of non-infectious respiratory adverse events, RR 0.64 (95% CI 0.41–0.97).

Conclusion: Our study found no evidence of increased respiratory adverse events with leflunomide treatment.

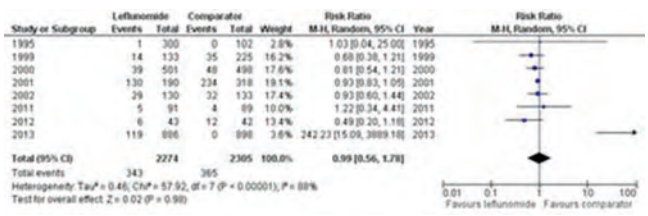

Figure 1: Forest Plot of Total Adverse Respiratory Events

Disclosure: R. Conway, None; **C. Low**, None; **R. J. Coughlan**, None; **M. O'Donnell**, None; **J. J. Carey**, None.

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Adverse Events and Infections in Patients with Rheumatoid Arthritis Treated with Conventional Drugs or Biologic Agents: A Real World Study. Christos E. Lampropoulos[1], Philippos Orfanos[2], Vasiliki-Kalliopi Bournia[3], Theofilos P. Karatsourakis[1], Clio P. Mavragani[4], Dimitrios Pikazis[1], Menelaos N. Manoussakis[5], Athanasios G. Tzioufas[1], Haralampos M. Moutsopoulos[6] and Panayiotis G. Vlachoyiannopoulos[3]. [1]School of Medicine, National University of Athens, Athens, Greece, [2]Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National University of Athens, Athens, Greece, [3]First Department of Propedeutic Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece, [4]School of Medicine, University of Athens, Athens, Greece, Athens, Greece, [5]School of Medicine, National University of Athens, Greece, Athens, Greece, [6]School of Medicine, University of Athens, Athens, Greece.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic, inflammatory disease with joint destruction and permanent disability. Biologic agents (BAs) offer a better outcome when disease is not adequately controlled by DMARDs. Nevertheless, many doubts still exist about the safety of BAs compared to classical treatment. Purpose of the study was to test the hypothesis that adverse events (AEs), including infections, are rather common in patients receiving BAs than in those with DMARDs.

Methods: Analysis of the medical records of patients with RA followed in a single outpatient clinic was performed. In total, 1403 adults (295 men, 1108 women) were included in the analysis (969 treated with DMARDs only, 434 with biologics). All AEs and infections were recorded and their severity was graded according to international criteria. Cox proportional-hazards models were performed to examine the association of treatment groups and other confounding factors with the risk of first AE or infection. Incident rates were calculated as number of events/100 person-years.

Results: The risk of first AE or infection, mild or serious, was significantly increased in patients with biologics (Figure 1, $p<0.001$). Hazard ratios ranged from 1.93 (95% CI: 1.59 to 2.34) for any AE to 5.92 (95% CI: 2.55 to 13.75) for serious infection (Table 1). Age, ESR >40mm/h and total steroid dose >500mg were significant detrimental risk factors. The risk for infection was equal across biologic agents, but infliximab and adalimumab were marginally significantly associated with AEs in general (Figure 2, $p<0.05$).

There were 519 AEs in the biologic group with an IR of 35.5 events/100 PY (IRR=2.24 95% CI: 1.96 to 2.55), as compared with 407 and 15.9 events/100 PY with DMARDs only. When only the follow-up time up until the first AE or infection in both treatment groups was counted in, the IRR for the biologic group was 2.14 for any first AE (95% CI: 1.78 to 2.58), 4.43 for first serious AE (95% CI: 2.83 to 7.09), 5.27 for any first infection (95% CI: 3.62 to 7.8) and 7.93 for first serious infection (95% CI: 3.60 to 19.83).

Conclusion: Biologic agents are associated with a higher frequency and severity of AEs and infections compared to conventional DMARDs.

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Long Term Safety of Intravenous Golimumab and Comparison with Subcutaneous Golimumab in Rheumatoid Arthritis: Results through 2 Years. Rene Westhovens[1], Edward C. Keystone[2], Clifton O. Bingham III[3], Elizabeth C. Hsia[4], Lilianne Kim[4], Yiying Zhou[4], Alan M. Mendelsohn[4] and Michael E. Weinblatt[5]. [1]University Hospital KU Leuven, Leuven, Belgium, [2]Mount Sinai Hospital, University of Toronto, Toronto, ON, [3]Johns Hopkins University, Baltimore, MD, [4]Janssen Research & Development, LLC., Spring House, PA, [5]Brigham and Women's Hospital, Boston, MA.

Long Term Safety of Intravenous Golimumab and Comparison with Subcutaneous Golimumab in Rheumatoid Arthritis: Results through 2 Years

Background/Purpose: To describe the safety profile of IV GLM in RA (MTX nonresponders) from the Ph3 GO-FURTHER trial. AE rates of interest are indirectly compared to those observed in the SC GLM GO-FORWARD trial in a similar pt population.

Methods: In GO-FURTHER, pts with active RA despite MTX were randomized to MTX + IV PBO or GLM 2mg/kg at wks 0, 4, and q8wks. In GO-FORWARD, pts with active RA despite MTX were randomized to SC PBO+MTX or SC GLM 100mg+PBO, GLM 50 mg+MTX, or GLM 100 mg+MTX administered q4wks. Observed safety findings through wk 112 for GO-FURTHER and wk 104 in GO-FORWARD are reported; incidence rates/100 pt-yrs are reported for AEs of interest from data through the August 15, 2012 cut-off (120-day safety update) in GO-FURTHER and from the wk160 CSR in GO-FORWARD. Comparison of targeted safety events between IV and SC GLM are reported. Pts who received ≥1administration were included.

Results: Baseline demographic and disease characteristics were similar in GO-FURTHER and GO-FORWARD. 584 pts received IV GLM, with a mean follow-up of 95.9 wks. 434 pts received SC GLM, with a mean follow-up of 89.9 wks. Overall AEs observed in GO-FURTHER and GO-FORWARD are summarized (Table). Similar proportions of pts in GO-FURTHER (wk 112) and GO-FORWARD (wk 104) had an AE (79.1% and 89.4%, respectively), an SAE (18.2% and 22.6%, respectively), or discontinued due to an AE (7.0% and 9.4%, respectively). Infections/infestations were the most common type of AE in both trials. Rates of selected SAEs per 100 pt-years through the August 15, 2012 cut-off in GO-FURTHER and wk 160 in GO-FORWARD showed no difference in AE rates or significant SAEs between GLM IV and SC in RA pts previously treated with MTX with the exception of patients with ALT abnormalities (>1 – < 3 × ULN). Similar differences were noted through all ALT tertiles (≥3 – <5 × ULN; ≥5 × ULN). (Table). Incidence of nonserious infusion reactions (median 30 minute infusions) remained low regardless of infusion length, and no serious infusion reactions, requiring study discontinuation, were reported. NMSC (incidence/100 pt-yrs of f/u: 0.10[95% CI: 0.00,0.58] vs. 0.81 [95%CI: 0.37,1.54] for GLM IV vs GLM SC) and lymphoma rates were numerically lower in GO-FURTHER vs. GO-FORWARD.

Conclusion: Overall safety profile of IV GLM in pts with RA despite MTX observed through wk 112 in GO-FURTHER was similar to that for SC GLM in a similar pt population (GO-FORWARD). Rates/100 pt-yrs (through August 15, 2012 in GO-FURTHER and wk 160 in GO-FORWARD) for events of interest such as malignancies and serious infections in GO-FURTHER were comparable to or lower than rates in GO-FORWARD.

Overall AE summary: GLM-treated patients in GO-FURTHER (IV;through wk 112) and in GO-FORWARD (SC; through week 104)

	GO-FURTHER GLM IV 2 mg/kg + MTX	GO-FORWARD All GLM SC 50 mg +MTX or 100 mg +/− MTX
Pts treated/Mean duration of f/u (wks)	584/95.9	434/89.9
AE/Serious AE/D/c due to AE	79.1%/18.2%/7.0%	89.4%/22.6%/9.4%
Overall infection/Serious infection	49.1%/6.2%	67.5%/6.7%
Infusion or injection reactions	3.5%	8.3%

AEs of interest in pts receiving IV or SC GLM: Incidence per 100 pt-years of follow-up (95% CI)

	GO-FURTHER (IV)[a] (n= 584)	GO-FORWARD (SC)[b] (n=434)
Total pt/yrs of follow-up	958	1127
Deaths	0.52 (0.17, 1.22)	0.35 (0.10, 0.91)
Sepsis	0.42 (0.11, 1.07)	0.71 (0.31, 1.40)
Tuberculosis	0.31 (0.06, 0.92)	0.27 (0.05, 0.78)
Opportunistic Infections	0.42 (0.11, 1.07)	0.27 (0.05, 0.78)
Cellulitis	2.19 (1.36, 3.35)	3.28 (2.31, 4.52)
Postbaseline ALT ↑ (>1 to <3 × ULN)	98.86 (92.66, 105.36)	69.02 (64.26, 74.05)
Postbaseline ALT ↑ (≥3 to <5 × ULN)	3.76 (2.63, 5.20)	1.51 (0.88, 2.41)
Postbaseline ALT ↑ (≥5 × ULN)	2.30 (1.44, 3.48)	0.71 (0.31, 1.40)
Lymphoma:		
Observed # of pts/Incidence/ 100 pt-yrs (95%CI)[c] Observed/Expected #of pts/SIR (95% CI)[d]	0/0.00 (0.00, 0.31) 0/0.27/0.00 (0.00, 11.14)	1/0.09 (0.00, 0.49) 1/0.29/3.40 (0.09, 18.94)
Other malignancies:		
Observed # of pts/Incidence/ 100 pt-yrs(95% CI)[c] Observed/Expected #of pts/SIR (95% CI)[d]	3/0.31 (0.06, 0.92) 2/6.03/0.33 (0.04, 1.20)	5/0.44 (0.14, 1.04) 5/6.81/0.73 (0.24, 1.71)
All malignancies:		
Observed # of pts/Incidence/ 100 pt-yrs (95%CI)[c] Observed/Expected #of pts/SIR (95% CI)[d]	4/0.42 (0.11, 1.07) 2/6.28/0.32 (0.04, 1.15)	15/1.35 (0.76, 2.23) 6/7.08/0.85 (0.31, 1.84)

[a]Based on data cut-off of August 15, 2012 (GO-FURTHER).[b]Through Wk 160 (GO-FORWARD). [c]Includes nonmelanoma skin cancer (NMSC). [d]Excludes NMSC, which are not included in the SEER database. SIR=Standardized Incidence Ratio

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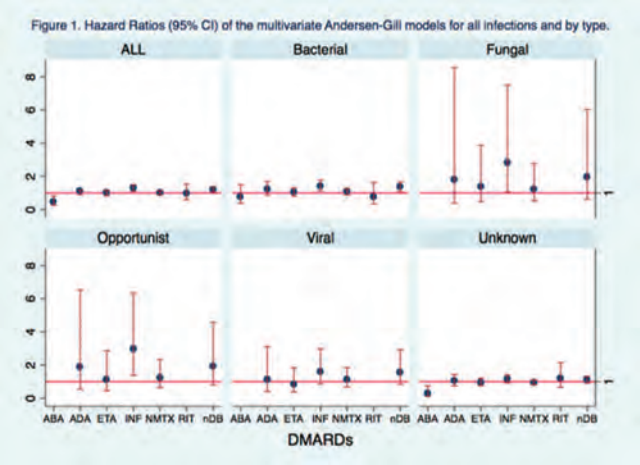
Serious Infection Risk By Treatments and Types in Patients with RA. Kaleb Michaud[1], Sofia Pedro[1], Andre Kalil[2], Ted R. Mikuls[2] and Frederick Wolfe[1]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: Recent studies provide conflicting results on the impact of DMARDs on the risk of serious infections for patients with RA. We examined these infection risks by type, site, and treatment in a real world setting.

Methods: Participants were followed biannually from 1998 through 2013 in a large US longitudinal observational study. Serious infections were defined as those requiring hospitalization or intravenous antibiotics, or led to death within a year after the patient's last observation. Infections were validated from hospitalization, physician, and death records. Infections were categorized as opportunist, by cause and by syndrome. Survival analysis methods (Cox regression, time to first infection using time-varying covariates and Andersen-Gill multiple failures model) were applied, both in a univariate and multivariate manner. Confounders included demographics, clinical status, disease severity and medications. DMARDs and biologics were grouped using different categorizations: methotrexate (MTX), non-MTX DMARDs (NMTX), anti-TNF (TNF), and no DMARD/biologic (nDB). Individual drugs included abatacept (ABA), adalimumab (ADA), etanercept (ETA), infliximab (INF), rituximab (RIT), and leflunomide (LEF). An at-risk window of 3 months was considered for all drugs (except RIT with 12 months).

Results: We had 21,727 RA patients participate, with 21% male, a mean (SD) age of 59.0 (13.7) yrs, and 1.7 (1.5) comorbidities. During 92,138 patient-yr follow-up, the treatment exposures included: prednisone (53%), MTX (61%, median 2.4 yrs), NMTX (53%, 1.9 yrs), TNF (50%, 1.5 yrs), and NTNF (8%, 1.4 yrs). There were 2530 serious infections of any type (69 opportunist, 881 bacterial, 114 viral, 43 fungal and 1048 were unable to classify). The most frequent by syndrome were pneumonia (1017), skin (424), and sepsis (367). From the univariate and multivariate analyses, no differences between treatments were found when compared to MTX monotherapy in any group of infections considered. Some exceptions were found: patients who were on INF seemed to be at a higher risk of any infection (HR: 1.29 (1.10–1.50)) and opportunistic infections (2.96 (1.38–6.33)). Patients who took ETA or INF were also at higher risk for skin infections (1.38 (1.04–1.38) and 1.32 (1.00–176), respectively) (Figure 1). When decomposing DMARDs into 5 classes, the results also didn't change but patients on LEF seemed to be at higher risk for bacterial infections (1.4 (1.12–1.75)), bone/joint (2.01 (1.37–2.94)) and skin (1.48 (1.11–1.95)). HCQ was protective for pneumonia (0.82 (0.69–0.98)).

Conclusion: Our preliminary results indicated little differences between treatments in risk of serious infections in RA. Next steps will include propensity scores to adjust for possible channeling and to adjust for previous infections and geographical region.



Disclosure: K. Michaud, None; **S. Pedro**, None; **A. Kalil**, None; **T. R. Mikuls**, None; **F. Wolfe**, None.

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Efficacy and Safety of Etanercept in Rheumatoid Arthritis Patients over 75 Years Old. Satoru Kodama, Satoshi Ito, Akira Murasawa, Kiyoshi Nakazono and Daisuke Kobayashi. Niigata Rheumatic Center, Shibata, Japan.

Background/Purpose: Early introductions of biologics in early rheumatoid arthritis (RA) patients are well documented, but there are few reports of biologics use in established elderly RA patients. We used etanercept (ETN), which has a short half-life and was considered safe, for elderly RA patients who had many complications.

Methods: Out of 330 patients treated with ETN at Niigata Rheumatic Center from May 2008 to June 2013, clinical course and data of the patients who started ETN at 75 years old (YO) or older were analyzed. Tender joint counts (TJC) and swollen joint counts (SJC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), matrix metalloprotease-3 (MMP-3), rheumatoid factor (RF), Disease Activity Score for 28-joint counts based on ESR (DAS28-ESR), simplified disease activity index (SDAI), and major adverse events were obtained from their medical records. The efficacy and safety of ETN was evaluated at 24 months.

Results: Forty five patients (17 males, 28 females), a mean age of 79.0 ±2.9 YO and a mean disease duration of 17.0±10.2 years were analyzed. Eighty four point four percent of them had complications such as hypertension, diabetes mellitus, osteoporosis, interstitial pneumonia, or amyloidosis. ETN was used at a dose of 20 mg/week in 1 patient, 25 mg/week in 31, 50 mg/week in 13. Twenty six percent of the patients did not inject by themselves and were injected by family or by the general practitioners. Prophylaxis of tuberculosis (TB), pneumococcal pneumonia (PP), pneumocystis jiroveci pneumonia (PCP) were done in 64%, 40%, and 62 % respectively. TJC, SJC, CRP, ESR, MMP-3 and RF decreased significantly as follows: TJC, 6.3±4.77 to 3.1±3.34 ($P < 0.01$); SJC, 5.1±4.57 to 2.1±2.53 ($P < 0.01$); ESR, 54.2±19.48 mm/h to 34.5±24.25 mm/h ($p < 0.01$); CRP, 4.3±3.19 mg/dL to 1.2±1.68 mg/dL ($p < 0.01$); MMP-3, 330.7±236.44 ng/mL to 212.7±123.81 ng/mL ($p < 0.05$); RF, 189.4±219.67 IU/mL to 117.5±140.38 IU/mL ($p < 0.05$); DAS28-4[ESR], 5.3±1.18 to 3.9±1.33 ($p < 0.01$); SDAI, 27.3±12.63 to 12.0±9.08 ($p < 0.01$) (Last Observation Carried Forward). Thirty four percent of the patients achieved remission or low disease activity score and 50% achieved them by SDAI. Adverse events occurred in 10 patients. Six patients stopped ETN and 4 out of them had infection. One patient (85YO) died due to TB and another (80YO) died due to PCP.

Conclusion: We considered that ETN is an effective end relatively safe treatment for elderly RA patients. Prevention of TB, PP and PCP should be done in all elderly patients treated with ETN.

Disclosure: S. Kodama, None; **S. Ito**, None; **A. Murasawa**, None; **K. Nakazono**, None; **D. Kobayashi**, None.

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Incidence of Opportunistic Infections in Rheumatoid Arthritis Treated with Biological Agents. Alejandro Gomez-Gomez, Zulema Rosales, Leticia Leon, Juan A Jover, Luis Rodriguez-Rodriguez and Lydia Abasolo. Instituto de Investigación Sanitaria San Carlos (IdISSC), Madrid, Spain.

Background/Purpose: With the expanding use of Biological Agents (BA), in particular TNF inhibitors, opportunistic infections (OI) are a major concern in Rheumatology. Our purposes were to describe the incidence of OI global and by periods in Rheumatoid Arthritis (RA), and comparing the risk of OI by BA.

Methods: We performed a retrospective longitudinal observational study from 2000 to 2013. We included subjects followed in our outpatient clinic, diagnosed with RA according to ACR criteria 87, whom started treatment with a BA [etanercept (ETN), golimumab (GOLI), certolizumab (CTZ), infliximab (IFX), adalimumab (ADA), rituximab (RTX), abatacept (ABA), or tocilizumab (TCZ)]. Our primary endpoint was OI that involved the suspension of the BA. We consider OI when there was a positive culture (for Virus, Fungus, and bacterial) or compatible symptoms that responded to specific treatment. We also collected secondary variables: sociodemographic (age, sex); clinical (disease duration, type of BA, hospital admission, previous BA). We used survival techniques to estimate the incidence of OI, expressed per 1000 patient-year [CI 95 %]. The exposure time was defined from the start date of each BA to its suspension, loss of follow up or end of study (23/11/2013). We performed Cox regression models (adjusted by age, duration of RA, sex, calendar time and prior BA) to compare the risk of OI between each BA.

Results: 453 RA patients were included in the study; they started 853 different courses of BA treatment. Of these, 81% were women with a mean age at diagnosis of 52.4 ± 14 years. The median time from onset of BA until onset of OI was 1.7 years [0.48–2.8]. Except for one all patients with OI took steroids. The most frequently used drug was ADA (33%), followed by ETN (25%), IFX (19%) and RTX (14%). There were 33 OI [22 Virus (18 Herpes Zoster, 2 virus B reactivation, 1 Avian flu), 10 Fungus (Candida, 2 Aspergillus), and 1 Bacterian (Legionella)], 36% required hospitalization and 4 died (2 fungus infection, 1 Legionella and 1 virus B reactivation with a myelodisplasic syndrome). The global incidence of OI was 17.7 [12.5–24.8]. TZC had 1 OI, with a incidence of 68.1 [9,6–483,5], followed by RTX, with 4 OI, Incidence 22.2 [8.3 to 59]; ADA, with 14 OI, Incidence: 19.9 [11,8–33,6]; IFX with 9 OI, Incidence: 19.4 [10,1–37,3], and ETN with 5 OI, Incidence: 11.6 [4,8–27,9]. We not find statistical differences in the rate of OI between BA. Age was found a predictor of OI in the multivariate analysis.

Conclusion: The incidence of OI and its evolution over time in real life conditions is described. Incidence found was near 18 cases per 1000 patients -year. Four of them resulted in death. Incidence of opportunistic infections showed no variance during the years. We did not find statistical differences in the rate of OI between BA. Doctors using Biological Agents should be concerned about this problem and be aware for the detection and management of OI.

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Risk of HBV Reactivation in Rheumatoid Arthritis Patients Undergoing Treatment with Newer Biological Dmards, Tocilizumab and Abatacept: A Single-Center Real Life Experience. Francesca De Nard[1], Vittorio Grosso[2], Monica Todoerti[1], Carlomaurizio Montecucco[3] and Roberto Caporali[3]. [1]University of Pavia, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy, [2]University of Pavia, Foundation IRCCS Policlinico S. Matteo, Pavia, Italy, [3]Rheumatology and Translational Immunology Research Laboratories (LaRIT), Division of Rheumatology, IRCCS Policlinico S.Matteo Foundation/University of Pavia, Pavia, Italy.

Background/Purpose: HBV infection represents a major issue in patients with rheumatoid arthritis (RA) undergoing biological disease-modifying anti-rheumatic drugs (bDMARDs) (1). While the risk of hepatitis reactivation under anti-TNF agents has been well described, experience with drugs as tocilizumab (TCZ) and abatacept (ABA) is still limited (2). Aim of this study is to retrospectively assess the risk of HBV reactivation in real-life RA patients treated with ABA and TCZ.

Methods: RA patients with a past HBV infection history ('chronic inactive carriers' with HBsAg+ and undetectable or <2,000 IU/mL viral load + normal liver function tests (LFT) and 'occult carriers' with only

HBcAb+) and treated with ABA or TCZ, have been retrospectively analyzed for the risk of 'viral re-activation' (rise in viral load≥1 log10 IU/mL compared with baseline values, or detection of previously undetected serum HBV-DNA) and/or 'viral hepatitis B' (increase in LFT and serum HBV-DNA, necroinflammation and/or fibrosis in liver biopsy) by regularly detecting HBsAg, HBV-DNA, LFT throughout follow-up.

Results: Out of a total of 125 RA patients, 17 (13,6%) were HbcAb+: 16 occult carriers (8 treated with ABA+8 treated with TCZ), and 1 chronic inactive carrier treated with ABA. Patients have been followed for a median time (IQR) of 1.2 (0.7–1.5) years. They were previously treated with a median (IQR) number of 2 (1–3) synthetic DMARDs (sDMARDs) and 0 (0–1) bDMARDs. The mean age (sd) was 54.7 (13.8) years, the median disease duration was 5.8 (1.8–7.6) years. Most patients were treated with concomitant methotrexate (8/9 in the ABA group, 5/8 in the TCZ group) and corticosteroids. In the ABA group, 1 patient with chronic HCV co-infection (HCV-RNA+) started lamivudine, due to LFT elevation (<2-fold ULN) occurring 2 months after ABA initiation; amelioration of LFT along with undetectable viral load occurred throughout 12 months of follow-up. 2 patients (1 occult carrier and 1 chronic inactive carrier) underwent lamivudine before ABA with no HBV-related adverse events; among the other 6 ABA patients not receiving lamivudine only 1 experienced a temporary positivization of viral load (85 UI/mL) without LFT elevation at 12 months of follow-up: spontaneous negativization of viral load was registered at 18 months. In the TCZ group, no patient received lamivudine with no HBV reactivation.

Conclusion: Despite limited to few patients and short follow-up, the use of ABA and TCZ in RA patients with past history of HBV infection seems relatively safe. However, periodic monitoring of liver function tests and viral load is mandatory. According to scientific literature, viral prophylaxis might be considered mainly in patients undergoing ABA. Further data are needed to clarify long-term safety issues.

References:

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Table 1. Characteristics of patients with RA and past HBV infection treated with ABA and TCZ.

	TCZ group	ABA group	TOT
N of patients	8	9	17
Sex (M/F)	2/6	2/7	4/13
Age, mean±SD (ys)	49.5±8.4	59.2±16.3	54,7±13,8
Disease duration, median (IQR) (ys)	4,7 (1,7–7,5)	5,8 (2,2–7,9)	5,8 (1,8–7,6)
Duration of follow-up, median (IQR) (ys)	1,2(0,9–1,5)	1,2 (0,7–1,5)	1,2 (0,7–1,5)
Number of previous sDMARDs, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)
Number of previous bDMARDs, median (IQR)	1 (0–1)	0 (0–2)	0 (0–1)
Co-treatment: steroids	7	8	15
Co-treatment: methotrexate	5	8	13
Chronic inactive infection	0	1	1
Occult carrier	8	8	16
Antiviral prophylaxis	0	3	3

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Reactivation of Hepatitis B Virus in Patients with Rheumatoid Arthritis after Anti-TNF Therapy. Seung Min Jung[1], Hong Ki Min[1], Jung Hee Koh[1], Jin Young Kang[1], Jennifer Lee[1], Seung-Ki Kwok[1], Ji Hyeon Ju[1], Hyeok-Jae Ko[2], Kyung-Su Park[3], Ho-Youn Kim[1] and Sung-Hwan Park[1]. [1]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Daejeon, South Korea, [3]St. Vincent Hospital, SuWon Gyeonggi-do, South Korea.

Background/Purpose: Anti-TNF therapy was known to increase the risk of certain infection. There are only limited data about the reactivation of hepatitis B virus (HBV) after anti-TNF therapy. The study was aimed to investigate the clinical course of hepatitis B in patients with rheumatoid arthritis (RA) after the introduction of anti-TNF therapy.

Methods: We retrospectively reviewed to identify patients infected with HBV treated with TNF inhibitors between October, 2004 and September, 2013. For patients with HBV infection, the liver enzyme and the viral status were monitored. The HBV reactivation was defined according to the Korean guideline by hepatology.

Results: Of 536 patients who were treated with TNF inhibitors, 17 patients had comorbidities of HBV infection. Thirteen patients were treated with etanercept, three with adalimumab, and one with infliximab. Seven patients received pre-emptive antiviral prophylaxis before anti-TNF therapy: 4 with entecavir, 1 with telbivudine, 1 with tenofovir, and 1 with lamivudine. Among 17 patients with HBV infection, 4 (23.5 %) patients experienced the reactivation of HBV, which occurred in 3 patients without prophylaxis and 1 patient with lamivudine prophylaxis. In the latter case, YMDD mutation was identified and addition of adefovir resulted in virological response. The other three patients were treated successfully with entecavir or tenofovir. There was no subsequent events associated with HBV infection.

Conclusion: This study indicates the risk of HBV reactivation during anti-TNF therapy. Careful management is mandatory for patients who planned to be treated with TNF inhibitors.

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Incidence of Clinical and Serological Lupus-like Disease during Anti-Tnfα-Treatment – a Two-Year Prospective Study in an Interdisciplinary Patient Cohort. Simon Julius Winkelmann[1], Rainald A. Zeuner[1], Dörte Schuldt[1], Johannes Bethge[1], Ulrich Mrowietz[2], Matthias Laudes[1], Stefan Schreiber[1] and Johann Schroeder[1]. [1]University of Kiel, Kiel, Germany, [2]Univ Schleswig-Holstein, Kiel, Germany.

Background/Purpose: TNFα-Inhibitors are the most widely used biological agents in rheumatic conditions or other chronic inflammatory diseases. Over the last ten years, the occurrence of lupus-like disease and the induction of antinuclear antibodies have been observed in more than 800 individuals receiving anti-TNFα-treatment worldwide. However, the exact incidence of serological changes and the frequency of associated clinical manifestations are unknown.

Methods: We conducted a single center, interdisciplinary prospective study on patients with RA, spondyloarthropathies and inflammatory bowel diseases who were elected for anti-TNFα-therapy as their first biological treatment. Clinical and serological parameters were collected before the first application and thereafter at six-monthly intervals. The evaluation included a clinical questionnaire and serological testing for ANA, dsDNA-antibodies and ANCA. We calculated the incidence rates based upon duration of drug exposure. The odds ratios within the subgroups were adjusted to the diagnosis or the compound with the lowest event rate, respectively.

Results: Between January 2011 and February 2014, 223 patients entered the study. The underlying diseases of these patients were RA (68), spondyloarthropathies (67), inflammatory bowel disease (84) and JIA (4). During the follow-up, 318 serum samples were collected, 117 of these were allotted to week 26, 89 to week 52, 51 to week 78 and 61 to week 104 of follow-up. – During the entire observation period, there was a continuous rise in ANA-titers and in the concentration of dsDNA-antibodies. The proportion of samples tested positive for ANA increased from 20 or 9.0% at baseline to 21 out of 56 or 37.5% respectively at week 104 ($p=0.001$). The proportion of samples with dsDNA-antibodies above the normal range (20 IU/ml) rose from none at baseline to 16 of 49 or 32.7% at the two year evaluation ($p=0.0002$), the average anti-dsDNA value increasing from 5.6 IU/ml to 18.5 IU/ml ($p=0.004$). These results were confirmed by a crithidia luciliae assay in 51.4% of these cases. 5 individuals or 2.5% of the study population additionally developed musculoskeletal symptoms assessed as lupus-like disease. These events required temporary termination of anti-TNFαtreatment and the application of corticosteroids. - When analyzing the impact of the various biologics and the co-medication, the highest seroconversion rate was observed in patients receiving infliximab (46.1%), followed by adalimumab (15.6%), certolizumab (8.2%) and etanercept (6.1%). In patients being treated with concomitant MTX (only rheumatic conditions were considered), the risk was lower (odds ratio 0.87) than in patients without MTX.

Conclusion: The present data confirm the capability of TNFα-inhibitors to induce both, clinically relevant lupus like disease and a high rate of seroconversion towards a lupus like antibody profile in a substantial proportion of patients. Our prospective study thus substantiates the hypothesis that these phenomena represent a systematic effect of TNFα-inhibitors, and that their incidence is higher than assumed by estimates based upon case reports.

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Tofacitinib Improves Arterial Stiffness Despite up-Regulating Serum Cholesterol with Chronic Cardiovascular Disease in Methotrexate-Resistant Active Rheumatoid Arthritis Patients. a Cohort Study. Kensuke Kume[1], Kanzo Amano[2], Susumu Yamada[2], Toshikatsu Kanazawa[3], Hiroshi Komori[3], Kazuhiko Hatta[4], Kuniki Amano[5] and Noriko Kuwaba[6]. [1]hiroshima clinic, Hiroshima, Japan, [2]Hiroshima Clinic, Hiroshima, Japan, [3]hiroshima clinic, hiroshima, Japan, [4]Hatta Clinic, Kure, Japan, [5]Sky Clinic, Hiroshima, Japan, [6]Sanki Clinical Link, Hiroshima, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) have an increased cardiovascular (CV) risk. We should have strategies for primary cardiovascularprevention in RA. Tofacitinib (Tofa) could possibly play a role in up-regulating levels of serum cholesterol[1].But there is no evidence of CV risk management about Tofa. To examine the effect of Tofa plus methotrexate (MTX) on arterial stiffness with CV disease in MTX resistant RA patients in a cohort study design.

Methods: 18 RA patients with moderate to severe active disease despite MTX treatment (disease activity score: DAS28 >3.2) were received Tofa plus MTX. All patients have previous history of CV. Arterial stiffness was assessed with cardio-ankle vascular index (CAVI) and augmentation index corrected for a heart rate of 75 beats per minute (AIx@75) at baseline and 24 weeks follow-up. Clinical data were collected at regular visits. CAVI is very similar to pulse wave velocity (PWV), and CAVI measures arterial wall stiffness independent of blood pressure and it is superior to brachial ankle PWV as an index of arterial stiffness[2]. No new all treatments(statin, low lipids drug, and etc.) were allowed.

Results: Treatment with Tofa attenuated the CAVI significantly from baseline to 24 weeks follow up(12.68 ± 1.77 and 10.48± 1.28%; p = 0.016). Treatment with Tofa attenuated the Aix@75 significantly from baseline to 24 weeks follow up(38.7 ± 8.6, 33.2 ± 3.6 %; p = 0.018). DAS 28-ESR score improved significantly from baseline to 24 weeks(5.11±1.33, 2.43±1.43: p=0.01). On the other hand, fasting serum total cholesterol TC was significantly increased from baseline to follow-up at 24 weeks (195±21.2mg/dL, 211±24.2mg/dL, p = 0.03). No patients suffered from new CV disease.

Conclusion: These findings suggest that combination therapy, Tofa with MTX not only reduced RA disease activity but also limited vascular damage despite up-regulating serum cholesterol with CV disease in patients MTX resistant active RA.

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Assessment of Lipid Changes in Patients with Early Rheumatoid Arthritis Treated with Tofacitinib or Methotrexate over 24 Months. C. Charles-Schoeman[1], A. Dikranian[2], J. Taylor[3], B. Wilkinson[4], T. Jones[5], K. Kwok[6] and C. Nduaka[4]. [1]University of California, Los Angeles, CA, [2]San Diego Arthritis Medical Clinic, San Diego, CA, [3]Anderson Arthritis and Rheumatology Center, Meridian, MS, [4]Pfizer Inc, Groton, CT, [5]Pfizer Inc, Collegeville, PA, [6]Pfizer Inc, New York, NY.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Post-baseline (BL) increases in mean low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were observed in Phase 3 (Ph 3) studies of tofacitinib (mostly with background DMARDs). In the Ph 3, 24-month (mo) ORAL Start study (NCT01039688), methotrexate (MTX)-naïve patients (pts) treated with tofacitinib monotherapy had significant and clinically meaningful improvements in RA signs and symptoms, physical function, and inhibition of radiographic progression vs MTX-treated pts. Here, the lipid profile during tofacitinib monotherapy treatment over 24 mos was investigated in these MTX-naïve pts with RA.

Methods: Pts were randomized 2:2:1 to receive tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID, or MTX (mean dose by Mo 3, 18.5 mg/week). LDL-C, HDL-C, and triglyceride (TG) levels were measured at BL and Mos 3, 6, 9, 12, 18, and 24, and descriptive statistics provided. Categorical changes (defined by National Cholesterol Education Program Adult Treatment Panel III) in LDL-C, HDL-C, and TG levels from BL to maximum on-treatment values through Mo 6 were compared using shift analyses.

Results: 956 pts were treated: tofacitinib 5 mg BID, n=373; tofacitinib 10 mg BID, n=397; and MTX, n=186. With both tofacitinib doses, median increases in LDL-C, HDL-C, and TG levels were observed at Mo 3 (first time point for analysis) but generally stabilized thereafter (Fig 1). Median increases and decreases in LDL-C, HDL-C, and TG levels were observed with MTX treatment (Fig 1). The total cholesterol (TC)/HDL-C ratio remained unchanged from BL through Mo 24 in all treatment groups. Categorical increases in lipid profile (ie shifts from a lower to higher lipid category) from BL through Mo 6 in pts receiving tofacitinib 5 mg BID, tofacitinib 10 mg BID, or MTX, respectively, were reported in: 52.2%, 57.3%, and 27.7% of pts for LDL-C; 5.7%, 10.2%, and 1.1% of pts for HDL-C; and 24.0%, 21.6%, and 14.7% of pts for TG levels. A similar percent of pts in each treatment group had BL LDL-C <130 mg/dL (tofacitinib 5 mg BID: n=251/362 [69.3%]; tofacitinib 10 mg BID: n=277/391 [70.8%]; MTX: n=132/184 [71.7%]). A minority of these pts had maximum on-treatment LDL-C ≥160 mg/dL by Mo 6 (tofacitinib 5 mg BID: n=32/251 [12.7%]; tofacitinib 10 mg BID: n=38/277 [13.7%]; MTX: n=4/132 [3.0%]).

Conclusion: Tofacitinib monotherapy was associated with increases in LDL-C, HDL-C, and TG levels by Mo 3 (first time point measured) which generally stabilized thereafter. TC/HDL-C ratios were unchanged across all treatment groups. These changes were consistent with changes observed in the tofacitinib Ph 3 program. Most pts had LDL-C <130 mg/dL at BL and a minority of these had maximum on-treatment LDL-C ≥160 mg/dL by Mo 6.

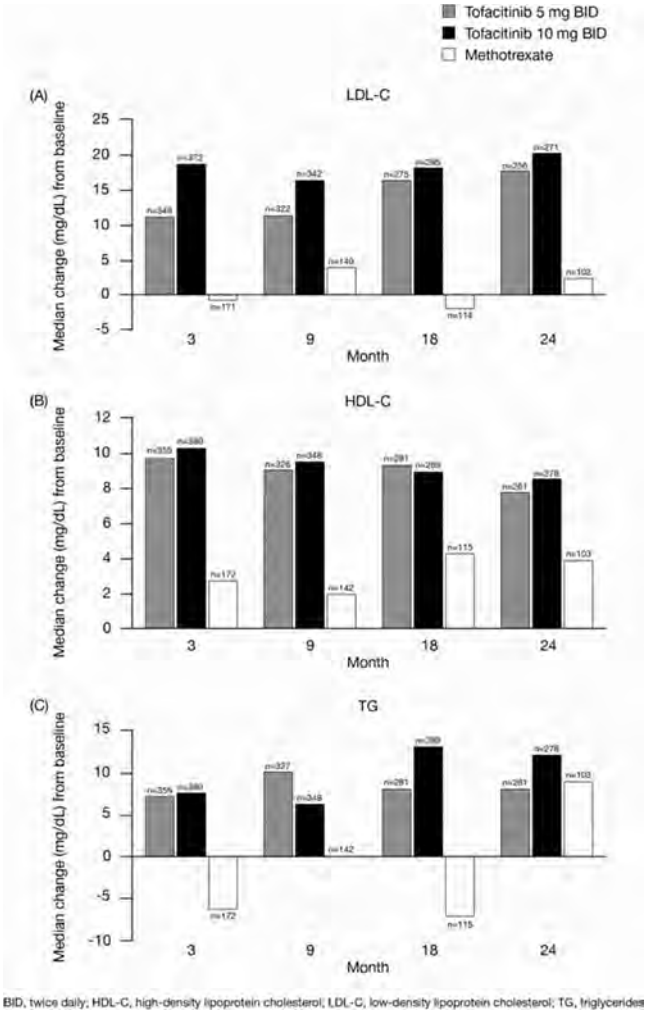

Fig 1. Median change (mg/dL) from BL in LDL-C (A), HDL-C (B), TG (C) at Mos 3, 9, 18, and 24 by treatment group

Disclosure: C. Charles-Schoeman, Pfizer Inc, 2, Pfizer Inc, 5; **A. Dikranian**, Pfizer Inc, 8, Pfizer Inc, 9; **J. Taylor**, Pfizer Inc, 8; **B. Wilkinson**, Pfizer Inc, 1, Pfizer Inc, 3; **T. Jones**, Pfizer Inc, 1, Pfizer Inc, 3; **K. Kwok**, Pfizer Inc, 1, Pfizer Inc, 3; **C. Nduaka**, Pfizer Inc, 1, Pfizer Inc, 3.

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Increases in Serum Cholesterol with Baricitinib Treatment Are Associated with Favorable Changes in Apolipoprotein Content and with Improvement in DAS28-CRP in Patients with Rheumatoid Arthritis.

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Background/Purpose: Treatment with baricitinib (bari), an oral inhibitor of JAK1/JAK2, demonstrated improvements in signs and symptoms of RA through 52 wks in a Phase 2b study[1]. Bari treatment also resulted in dose- and time-dependent changes in serum lipids detectable by Wk 2 and persisting through Wk 24 and was associated with increases in LDL particle size and HDL and VLDL particle numbers[2]. Increases in HDL, but not LDL cholesterol, correlated with decreases in CRP at Wk 12. Changes from baseline in serum cholesterol through 52 wks of bari treatment as well as changes in the apolipoprotein content of LDL, VLDL, and HDL particles with bari treatment at Wks 4 and 12 were evaluated. The relationship between cholesterol changes and measures of clinical efficacy was also explored.

Methods: Patients (pts) with RA were randomized to QD doses of placebo (PBO) (n=98) or bari 1 mg (n=49), 2 mg (n=52), 4 mg (n=52), or 8 mg (n=50) for 12 wks. Pts assigned to 2-, 4-, or 8-mg bari continued blinded treatment for an additional 12 wks. Pts who completed the 24-wk study could enter a 2-yr, open-label extension. Serum samples were collected through 52 wks for conventional lipid determinations (total cholesterol, LDL, HDL, and triglycerides). Apolipoprotein content was assessed at Wks 4 and 12 for PBO, 4-, and 8-mg bari groups. Pearson correlations and partial correlations, adjusted for assigned treatments, between changes in cholesterol and efficacy measures were evaluated at 12 wks.

Results: Pts treated with bari through 52 wks maintained a stable cholesterol and triglyceride profile with no further changes beyond Wks 12 and 24. Increases in apolipoprotein A-I, apolipoprotein B, and total apolipoprotein CIII were observed with 4- and 8-mg bari with no increase in LDL-associated apolipoprotein CIII. Bari treatment also demonstrated a significant reduction in HDL-associated SAA at the 4- and 8-mg doses compared to PBO while a significant reduction in Lp(a) was observed only in the 8-mg bari group (all $p<0.05$). These changes in apolipoproteins coincided with the increases in serum lipids apparent by Wk 4. In pts treated across all doses of bari, a significant correlation was observed between change in HDL cholesterol and absolute DAS28-CRP score at Wk 12 ($r=-0.33$, $p<0.001$) as well as the change from baseline to Wk 12 in the DAS28-CRP ($r=-0.29$, $p<0.001$). Specifically, pts achieving DAS28-CRP <2.6 and larger decreases in DAS28-CRP demonstrated larger increases in HDL cholesterol. No significant correlations were observed in the PBO arm between HDL and disease activity measures and no significant correlations were observed between disease activity and total cholesterol or LDL levels in the bari arms.

Conclusion: In addition to increases in serum cholesterol and lipoprotein particle number (HDL and VLDL) and size (LDL), there were changes in apolipoprotein content of these particles in pts treated with bari. The increase in HDL cholesterol with bari treatment correlated with an improvement in DAS28-CRP. Further studies are necessary to determine if these changes influence long-term cardiovascular outcomes.

[1] Taylor P, et al. *Ann Rheum Dis* 2013;72:A65–A66
[2] Kremer J, et al. *Ann Rheum Dis* 2013;72(Suppl 3):241

Disclosure: J. M. Kremer, Eli Lilly and Company, 2, Eli Lilly and Company, 5; **M. C. Genovese**, Eli Lilly and Company, 2, Eli Lilly and Company, 5; **E. C. Keystone**, Abbott Laboratories, 2, Amgen Canada, 2, Astrazeneca Pharmaceuticals LP, 2, Bristo-Myers Squibb, 2, F. Hoffman La-Roche Inc., 2, Janssen Pharmaceutica Product, L.P., 2, Eli Lilly and Company, 2, Novartis Pharmaceutical Corporation, 2, Pfizer Inc, 2, Sanofi-Aventis Pharmaceutical, 2, Abbott Laboratories, 5, AstraZeneca, 5, Biotest, 5, Bristol-Myers Squibb, 5, F. Hoffman-La Roche Inc., 5, Genentech and Biogen IDEC Inc., 5, Janssen Pharmaceutica Product, L.P., 5, Eli Lilly and Company, 5, Merck Pharmaceuticals, 5, Pfizer Inc, 5, Abbott Laboratories, 8, AstraZeneca, 8, Bristol-Myers Squibb, 8, F. Hoffman La-Roche Inc., 8, Janssen Pharmaceutica Product, L.P., 8, Pfizer Inc, 8, UCB, 8, Amgen, 8; **P. C. Taylor**, Eli Lilly and Company, Pfizer Inc, AstraZeneca, 5; **S. H. Zuckerman**, Eli Lilly and Company, 3, Eli Lilly and Company, 1; **D. E. Schlichting**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **E. P. Nantz**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **S. D. Beattie**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **W. L. Macias**, Eli Lilly and Company, 1, Eli Lilly and Company, 3.

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Rosuvastatin Improves Arterial Stiffness in Patients with Inflammatory Joint Diseases.

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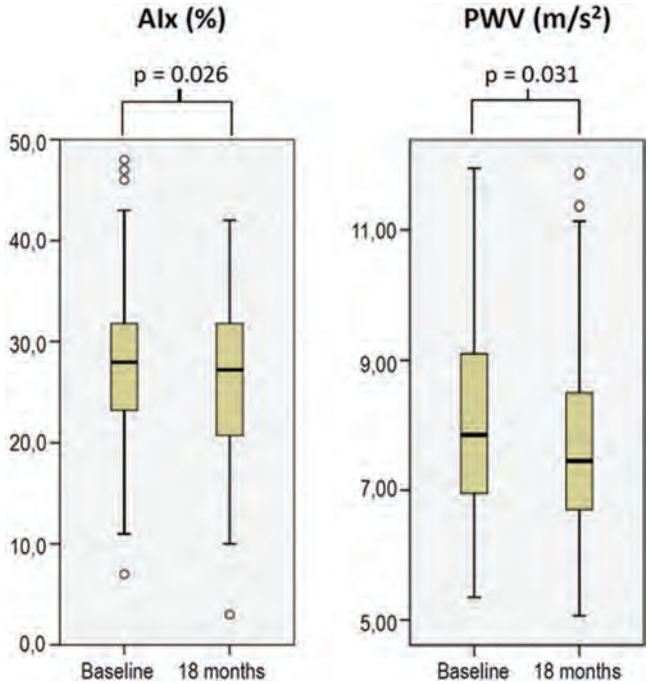
Background/Purpose: Arterial stiffness, as pulse wave velocity (PWV) and augmentation index (AIx) has emerged as early risk markers of cardiovascular disease (CVD) in patients with inflammatory joint diseases (IJD). In IJD patients, statin treatment has demonstrated a significant improvement in arterial stiffness. Furthermore, we have shown that statin treatment induced carotid plaque (CP) regression in IJD patients. However, the effect of statins on arterial stiffness in IJD patients with established atherosclerosis is still not elucidated. The aim of the present study was therfore to evaluate the effect of rosuvastatin on arterial stiffness in patients with IJD who had CP. We also evaluated the association between the change in arterial stiffness and change in inflammation markers, disease activity, low-density lipoprotein cholesterol (LDL-c), blood pressure (BP), CP height and intima-media thickness (IMT) after 18 months of rosuvastatin treatment.

Methods: The study population included 89 statin naïve patients with IJD (55 with rheumatoid arthritis, 23 with ankylosing spondylitis and 11 with psoriatic arthritis). All patients had B-mode ultrasound verified CP and received rosuvastatin therapy over 18 months to obtain LDL-c goals (<1.8mmol/L). The arterial stiffness variables PWV and AIx were measured prior to, and at the end of the study, using the Sphygmocor device. We used paired-samples t-tests to assess change from baseline, and regression analysis to assess the association between change in arterial stiffness and other outcome measures.

Results: Study population demographics are presented in table 1. After 18 months rosuvastatin therapy, a significant reduction in Aix was observed, from mean (SD) 27.9 (7.7) % to 26.2 (8.2) % ($p=0.026$). Furthermore, PWV decreased from 8.1 (1.6) m/s^2 to 7.8 (1.5) m/s^2 ($p=0.031$). In a logistic regression model where change in arterial stiffness was the dependent variable (defined as either increasing or decreasing related to baseline value), change in and exposure of systolic blood pressure during the study period influenced PWV significantly: odds ratio (95% CI): 1.06 (1.02, 1.09)($p=0.005$) and 0.97 (0.94; 1.00)($p=0.035$). Change in CP height and rosuvastatin dose predicted change in AIx 5.72 significantly: odds ratio (95% CI): (1.25, 26.25)($p=0.025$) and 1.22 (1.05, 1.41) ($p=0.009$).

Conclusion: This is the first clinical trial showing that rosuvastatin treatment improves arterial stiffness in IJD patients with atherosclerosis.



Legends Fig 1: AIx: augmentation index, PWV: pulse wave velocity

	RA	AS	PsA	All	p-value RA/AS/PsA
Number n (%)	55 (61.8)	23 (25.8)	11 (12.4)	89	–
Age median (IQR)	62.0 (57.0–68.0)	59.0 (53.0–64.0)	60.0 (52.0–64.0)	61.0 (56.0–67.0)	0.07
Sex male/female n (%)	14/41 (25.5/74.5)	15/8 (65.2/34.8)	5/6 (45.5/54.5)	34/55 (38.2/61.8)	0.004
Disease duration median (IQR)	16.0 (6.5–22.3)	22.0 (16.0–30.0)	13.0 (2.0–30.0)	16.0 (8.0–26.0)	0.11
CV risk factors					
Smoke n (%)	11 (20.0)	3 (13.0)	3 (27.3)	17 (19.1)	0.59
Body mass index mean±SD	25.0±2.9	25.2±2.7	26.1±3.7	25.2±2.9	0.55
Total cholesterol (mmol/L) mean±SD	6.43±1.24	6.19±0.90	6.62±1.07	6.39±1.13	0.54
HDL-c (mmol/L) mean±SD	1.78±0.48	1.53±0.45	1.60±0.51	1.69±0.49	0.09
Triglycerides (mmol/L) median (IQR)	1.2 (0.9–1.6)	1.4 (0.9–1.9)	1.1 (0.7–2.9)	1.2 (0.9–1.8)	0.67
LDL-c (mmol/L) mean±SD	3.95±0.96	3.97±0.86	4.32±1.00	4.00±0.94	0.48
Systolic blood pressure (mm Hg) mean±SD	142.6±19.8	144.8±14.2	147.4±24.6	143.7±19.0	0.71
Diastolic blood pressure (mm Hg) mean±SD	82.7±8.9	85.2±8.2	87.9±10.8	84.0±9.0	0.16
***Co morbidities* n (%)**					
Hypertension	31 (56.4)	16 (69.6)	6 (54.5)	53 (59.6)	0.52
Diabetes	3 (5.5)	2 (8.7)	0 (0.0)	5 (5.6)	0.59
Cardiovascular disease	6 (10.9)	2 (8.7)	0 (0.0)	8 (9.0)	0.51
Carotid artery plaque median (range)	1 (1–5)	1 (1–3)	2 (1–3)	1 (1–5)	0.34
***Haematology* mean±SD**					
ESR (mm/h)	15.8±10.3	12.9±9.8	13.9±5.7	14.8±9.7	0.47
CRP (mg/L) median (IQR)	3.0 (1–4)	1 (1–3)	3 (2–6)	2 (1–4)	0.22
***Medication* n (%)**					
Prednisolone	21 (38.2)	2 (8.7)	2 (18.2)	25 (28.1)	0.02
NSAIDs	21 (38.2)	12 (52.2)	5 (45.5)	38 (42.7)	0.52
Synthetic DMARDs	36 (65.5)	5 (21.7)	9 (81.8)	50 (56.2)	0.002
Biologic DMARDs	15 (27.3)	8 (34.8)	5 (45.5)	28 (31.5)	0.53
Antihypertensive medication	16 (29.1)	4 (17.4)	2 (18.2)	22 (24.7)	0.48

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A Randomised Controlled Trial Evaluating the Effect of Humira upon Endothelial Function in ACPA Positive Rheumatoid Arthritis – an Interim Analysis. Stephen Oakley[1], Niloofar Esmaili[2], Gabor Major[2], David Mathers[3], Siva Ratnarajah[4], John van der Kallen[3], Mark Collins[4], Marc Toh[4] and John Glass[2]. [1]Hunter Medical Research Institute, Newcastle, Australia, [2]Newcastle Bone & Joint Institute, Newcastle, Australia, [3]Georgetown Arthritis Centre, Newcastle, Australia, [4]Private Practice, Newcastle, Australia.

Background/Purpose: Rheumatoid arthritis (RA) is associated with elevated cardiovascular (CV) risk not explained by traditional risk factors. Increased CV risk may develop prior to the onset of arthritis. Amongst RA patients Shared Epitope (SE) positivity is associated with increased CV mortality but it is unclear if this is mediated by inflammation. Observational studies suggest that TNF-inhibition improves endothelial dysfunction and lowers CV risk but RCT data are lacking. HEART-RA is a single-site RCT evaluating the effect of Humira upon endothelial function in ACPA positive RA.

Methods: ACPA positive RA patients with moderate disease activity were enrolled in a 24-week trial of Humira versus placebo on a background of usual care undergoing assessments of disease activity and endothelial function (reactive hyperaemic index - RHI) at baseline, 2, 4, 12 and 24 weeks. Serum lipids were evaluated when deemed appropriate by the treating clinician. Improvements RHI in Humira and placebo arms were compared by t test. Secondary analysis evaluated influences upon RHI by univariate analysis and multivariate time-series regression modelling.

Results: 23 subjects included 9 early (<6months) and 14 established RA underwent a total 138 assessments. 1 patient carried none, 10 one and 12 two SE. 12 patients (4 Humira and 3 placebo) withdrew after week 12 and were assessed open label at 24 weeks. HDL was available for 28 and LDL for 24. There were non-significant trends to greater RHI improvements in the Humira arm. Secondary analysis found better RHI in patients currently receiving Humira distinct from more general negative effects of higher disease activity and SE dose. Paradoxically ever-smokers had better RHI. Limited data suggested positive effects from HDL and negative from LDL.

Conclusion: Several disease-specific factors appear to contribute to endothelial dysfunction in RA. RHI is clearly better in patients receiving Humira distinct from the broader effects of disease activity. The paradoxical effect of smoking is not consistent with previous studies and is likely due to the small number of patients. However, negative effects of the SE are consistent with previous work. Furthermore, the effect appears to be quite distinct from inflammatory mechanisms seen in RA and introducing the possible role of antigen processing and lipid transport with implications for subjects with Pre-RA and therapies that that adversely influence lipids.

Input Variables	Mean RHI	Mean RHI	Raw Difference	t test p value	Adjusted Difference	Adjusted p value
Humira vs No Humira	2.23	2.11	0.12	0.016	0.19	0.041
3VDAS28CRP (<3.88 vs >3.88)	2.22	2.00	0.22	0.016	0.17	0.056
Shared Epitope (2 vs 0 or 1 copy)	2.20	2.04	0.16	0.080	0.25	0.045
Smoking (Ever versus Never)	2.20	1.79	0.24	0.001	0.44	0.004
Established vs Early RA	2.21	1.97	0.24	0.010	0.20	0.119
HDL Choilesterol (>1.20 vs <1.20)	2.23	2.06	0.17	0.448		Insufficient data
LDL Cholesterol (<3.00 vs >3.00)	2.13	2.07	0.06	0.226		Insufficient data

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Do Patients with Congestive Heart Failure Treated with Biologics for RA Have a Lower Risk of Fatal Outcome of Serious Infections? Anja Strangfeld[1], Adrian Richter[1], Yvette Meissner[1], Matthias Schneider[2], Michael Zaenker[3], Wolfgang Ochs[4], Thomas Klopsch[5], Angela Zink[6] and Joachim Listing[1]. [1]German Rheumatism Research Center, Berlin, Germany, [2]Heinrich-Heine-University, Düsseldorf, Germany, [3]Immanuel Klinikum Bernau, Rheumatology Center Northern Brandenburg, Bernau, Germany, [4]Rheumatologist in private practice, Bayreuth, Germany, [5]Rheumatologist in private practice, Neubrandenburg, Germany, [6]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany.

Background/Purpose: Patients with multimorbid conditions are at high risk of developing serious infections (SI) and of premature mortality. TNF inhibitors increase the infection risk (1) in patients with rheumatoid arthritis (RA). However, they are likely to decrease all-cause mortality (2). We aimed to examine a) the infection risk and b) the outcome of SI in a group of patients at high mortality risk: RA patients with congestive heart failure (CHF).

Methods: We used data from the German biologics register RABBIT with 10,671 RA patients included at start of a synthetic or biologic DMARD (bDMARD) after at least one DMARD failure. In 242 patients, CHF was reported as comorbid condition at enrollment (NYHA grade III: 16%, NYHA IV: none). We investigated the incidence of SI in CHF patients compared to a matched control sample and the rest of the cohort. Age, sex and comorbidity (chronic lung disease, chronic kidney disease, hypertension) were used as matching criteria for the nested case control study. For 238 CHF patients exactly matching controls without CHF were found. Multiple logistic regression was applied to investigate the risk of fatal outcome of the first SI in CHF patients.

Results: Compared to the rest of the cohort (n=10,429), CHF patients were older (mean age 68 vs. 56), more frequently males (34% vs. 23%), at baseline they had a higher level of disease activity (DAS28: 5.9 vs. 5.2), considerably more comorbidities (e.g. chronic lung disease: 7% vs. 3%, kidney disease: 24% vs. 3%) and lower functional capacity (FFbH (mean % of full function): 44% vs. 63%). These patient characteristics predispose CHF patients to develop SI. Compared to the rest of the cohort, we observed a nearly five times higher incidence per 100 patient-years (PY) (16 [95%CI: 13, 19] vs. 3.4 [3.2, 3.6]). In addition we found a higher risk of fatal outcome of SI in CHF patients.

In the sample of 238 CHF patients with exact matched controls, the difference in incidence rates of SI in CHF patients vs. controls was considerably smaller: 13.0 [10.7;15.8] vs. 10.3 [8.2;13.0] per 100 PY.

In patients of the matched sample who developed SI we observed a significantly lower risk of fatal outcome in those who were treated with biologics at the time of the infection: The odds ratio for bDMARD treatment (adjusted for age, sex, CHF and physical function) was 0.4 [0.2, 0.96].

Conclusion: Patients with CHF are at increased risk of SI with a high lethality risk. Our data suggest that SI occurring in RA patients on biologic therapy tend to have a lower risk of fatal outcome.

(1) Strangfeld et al., Ann Rheum Dis 2011;70(11):1914–20
(2) Listing J et al. Ann Rheum Dis 2013 Nov 29 [Epub ahead of print]

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Patient-Reported Outcomes from a Canadian Study of Patients Taking Methotrexate and Etanercept. J. Carter Thorne[1], Edward C. Keystone[2], Janet E. Pope[3], Melanie Poulin-Costello[4], Krystene Phan-Chronis[4] and Boulos Haraoui[5]. [1]Southlake Regional Health Centre, Newmarket, ON, [2]University of Toronto, Toronto, ON, [3]St Joseph Health Care, London, ON, [4]Amgen Canada Inc., Mississauga, ON, [5]Institut de rhumatologie de Montréal (IRM), Montréal, QC.

Background/Purpose: The Canadian Methotrexate and Etanercept Outcome Study (CAMEO) evaluated etanercept (ETN) monotherapy vs ETN plus methotrexate (MTX) in biologic-naïve patients with rheumatoid arthritis (RA) who had an inadequate response to MTX.

Methods: This phase 4, randomized, open-label, noninferiority study enrolled patients who had an inadequate response to MTX. All patients received ETN+MTX for 6 months; they were then randomized at month 6 to ETN monotherapy or remained on ETN+MTX for an additional 18 months. Patient-reported outcomes (PROs) were assessed at baseline and at 6, 12, 18, and 24 months and included the Short Form-36 (SF-36) Health Survey questionnaire (higher scores represent better health); Health Assessment Questionnaire Disability Index (HAQ-DI; 0=no disability to 3=severe disability), and pain based on visual analog scale (VAS; 0=no pain to 100=severe pain). The minimal clinically important difference (MCID) for the SF-36 physical and mental component scores is a change ≥2.5; for HAQ-DI is a change ≥0.22; and for the pain VAS is a change ≥10mm.

Results: Of 258 patients enrolled, 205 were randomized at month 6 to ETN (n=98) or ETN+MTX (n=107); 53 were not randomized. These PROs through month 24 are shown (Table). As expected, on average, PROs demonstrated improvements at 6 months, when all patients had been on ETN+MTX. From month 6 (randomization) to month 24, mean improvements were maintained in both treatment arms.

	All Patients (N = 258)	ETN (N = 98)	ETN+MTX (N = 107)
HAQ-DI, mean score (SD)			
BL		1.2 (0.7)	1.5 (0.5)
M6 (randomization)		0.8 (0.7)	1.0 (0.7)
M24		1.0 (0.8)	1.0 (0.8)
HAQ-DI, mean score change* (SD)			
BL to M6	−0.4 (0.6)		
M6 (randomization) to M24		0.2 (0.4)	0.0 (0.5)
Patients with improvement in HAQ-DI ≥ 0.22 (MCID) from BL to M24, n (%)		53 (54.1)	69 (64.5)
Pain VAS (0–100), mean score (SD)			
BL		56.2 (24.4)	59.3 (24.6)
M6 (randomization)		32.5 (25.4)	34.1 (27.7)
M24		41.2 (28.4)	39.7 (28.7)
Pain VAS, mean score change (SD)			
BL to M6	−20.6 (28.7)		
M6 (randomization) to M24		8.7 (26.1)	5.1 (27.3)
Patients with improvement in pain VAS ≥ 10 mm (MCID) from BL to M24, n (%)		54 (56.3)	65 (61.3)
SF–36 domain scores			
Physical component, mean score (SD)			
BL		30.4 (7.8)	29.0 (8.8)
M6 (randomization)		38.3 (10.5)	36.9 (10.9)
M24		35.2 (11.3)	36.1 (11.6)
Physical component score, mean score change† (SD)			
BL to M6	7.9 (8.7)		
M6 (randomization) to M24		−3.1 (9.0)	−0.8 (9.4)
Patients with improvement in physical component score ≥ 2.5 (MCID) from BL to M24, n (%)		25 (25.5)	16 (15.1)
Mental component, mean score (SD)			
BL		44.7 (10.8)	43.1 (10.8)
M6 (randomization)		50.3 (9.9)	48.5 (11.3)
M24		49.0 (10.8)	48.7 (11.2)
Mental component score, mean score change† (SD)			
BL to M6	5.5 (11.6)		
M6 (randomization) to M24		−1.3 (10.5)	0.1 (10.7)
Patients with improvement in mental component score ≥ 2.5 (MCID) from BL to M24, n (%)		53 (54.1)	60 (56.6)

*Negative change indicates improvement; †Positive change indicates improvement. BL, baseline; M6, month 6; M24, month 24; MCID, minimum clinically important difference. Last observation carried forward imputation was used for missing data.

Conclusion: Clinically meaningful improvements in PROs were demonstrated from baseline to month 6. In general, patients who discontinued MTX at month 6 and those who remained on ETN+MTX, maintained improvements to month 24.

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Efficacy and Safety of Tofacitinib Following Inadequate Response to Nonbiologic DMARD or Biologic DMARD. C. Charles-Schoeman[1], Gerd Burmester[2], P. Nash[3], C.a.F. Zerbini[4], S. Anway[5], K. Kwok[6], T. Hendrikx[7], E. Bananis[8] and Roy Fleischmann[9]. [1]University of California, Los Angeles, CA, [2]Charité – University Medicine Berlin, Berlin, Germany, [3]Rheumatology Research Unit, Nambour Hospital, Sunshine Coast and Department of Medicine, University of Queensland, Queensland, Australia, [4]Centro Paulista de Investigação Clinica, Sao Paulo, Brazil, [5]Pfizer Inc, Groton, CT, [6]Pfizer Inc, New York, NY, [7]Pfizer BV, Capelle aan den IJssel, Netherlands, [8]Pfizer Inc, Collegeville, PA, [9]Metroplex Clinical Research Center, University of Texas Southwestern Medical Center, Department of Medicine, Dallas, TX.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Here we compare the efficacy and safety of tofacitinib 5 mg and 10 mg twice daily (BID) vs placebo (PBO) in patients (pts) who had an inadequate response (IR) to nonbiologic/conventional synthetic DMARDs only (csDMARDs; biologic-naïve) and pts with an IR to previous anti- TNF drugs or other biologic DMARDs (biologic-IR pts).

Methods: Efficacy comparisons were performed on pooled data from 4 Phase (Ph) 2 and 5 Ph 3 randomized, controlled studies of tofacitinib in RA pts. Pts received tofacitinib 5 mg or 10 mg BID or PBO as monotherapy, or with background MTX or other csDMARDs. In this analysis, efficacy in biologic-naïve and biologic-IR subpopulations was assessed by American College of Rheumatology (ACR) 20/50/70, disease activity score (DAS)28-4(ESR [erythrocyte sedimentation rate]), Health Assessment Questionnaire-Disability Index (HAQ-DI), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI). Safety was assessed in pooled Ph 3 pts from 5 studies.

Results: A total of 1071, 1090 and 651 biologic-naïve pts were randomized to tofacitinib 5 mg BID, 10 mg BID and PBO, respectively. For biologic-IR pts, 259, 253, and 193 were randomized to tofacitinib 5mg BID, 10 mg BID and PBO, respectively. Baseline demographics and disease characteristics were similar between tofacitinib and PBO groups within subpopulations. Biologic-IR pts were heavier, with a higher proportion of white pts, had longer disease duration and had slightly greater disease activity at baseline compared with biologic-naïve pts. In both biologic-naïve and biologic-IR pts in the pooled Ph 2 and 3 studies, clinical response was significantly greater for tofacitinib 5 and 10 mg BID vs PBO; significantly more pts achieved low disease activity and remission with both tofacitinib doses vs PBO by DAS28-4(ESR), SDAI or CDAI (Table 1). Clinical response appeared numerically greater with biologic-naïve vs biologic-IR pts. Rates of safety events of special interest in pooled Ph 3 studies were generally similar between tofacitinib doses and subpopulations (Table 2). Confidence intervals (CI) for safety events were wide and overlapping for all events and treatment groups due to the limited sample size in PBO and biologic-IR groups.

Conclusion: Tofacitinib reduced signs and symptoms of RA in pts who were biologic-naïve and biologic-IR. Tofacitinib had a numerically greater clinical response in the biologic-naïve population compared with the biologic-IR population. The safety profile appeared similar between the pt subpopulations in Ph 3 studies.

Table 1. Efficacy responses at Month 3 (pooled Ph 2 and Ph 3 studies) within each subpopulation. All measures were significantly improved with tofacitinib 5 mg or 10 mg BID vs PBO ($p<0.05$)

	Biologic-naïve			Biologic-IR		
Parameter	Tofacitinib 5 mg BID N=1046	Tofacitinib 10 mg BID N=1068	PBO N=640	Tofacitinib 5 mg BID N=258	Tofacitinib 10 mg BID N=251	PBO N=191
ACR20/50/70 (%)	60.3/32.7/12.9	66.2/36.6/18.4	26.6/9.7/2.8	43.4/24.4/9.7	51.8/27.9/12.4	24.6/10.5/3.1
CDAI ≤10*/ ≤2.8† (%)	32.4/6.4	39.9/9.0	14.4/0.7	29.5/5.9	35.9/6.5	14.4/1.2
SDAI ≤11*/ ≤3.3† (%)	34.5/6.3	41.1/9.3	14.1/0.7	29.8/6.8	38.3/8.3	13.8/0.6
DAS28–4(ESR) ≤3.2*/<2.6† (%)	16.6/7.3	22.9/11.4	4.5/2.3	12.7/6.6	17.8/8.4	5.1/2.3

LS mean change in DAS28–4(ESR)	−1.90	−2.12	−0.79	−1.62	−1.98	−0.67
HAQ-DI '0.5 (%)	40.4	46.2	18.1	31.0	39.2	20.1
LS mean change from baseline in HAQ-DI	−0.46	−0.54	−0.14	−0.31	−0.42	−0.09

*Low disease activity
†Disease remission
Ns represent the numbers of subjects with available ACR data at Month 3
ACR, American College of Rheumatology criteria; BID, twice daily; CDAI, Clinical Disease Activity Index; DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; IR, inadequate responders; LS, least squares; PBO, placebo; Ph, Phase; SDAI, Simplified Disease Activity Index

Table 2. Incidence rates (95% CI) of safety events in Ph 3 studies

	Biologic-naïve Incidence rate, per 100 pt-yr (95% CI) (number of pts with event)			Biologic-IR Incidence rate, per 100 pt-yr (95% CI) (number of pts with event)		
	Tofacitinib 5 mg BID N=893 Pt-yr=885.5	Tofacitinib 10 mg BID N=898 Pt-yr=917.4	PBO N=465 Pt-yr=149.5	Tofacitinib 5 mg BID N=247 Pt-yr=170.5	Tofacitinib 10 mg BID N=241 Pt-yr=154.8	PBO N=181 Pt-yr=42.5
Serious adverse events	12.2 (10.0, 14.8) (103)	9.5 (7.7, 11.8) (85)	15.0 (9.9, 22.7) (22)	13.0 (8.5, 20.0) (21)	11.3 (7.0, 18.1) (17)	19.0 (9.5, 38.0) (8)
All-cause mortality*	0.6 (0.2, 1.4) (5)	0.4 (0.2, 1.2) (4)	0.7 (0.1, 4.7) (1)	1.2 (0.3, 4.7) (2)	0	0
Adjudicated MACE	0.6 (0.2, 1.4) (5)	0.8 (0.4, 1.6) (7)	1.3 (0.3, 5.4) (2)	1.2 (0.3, 4.7) (2)	0.6 (0.1, 4.6) (1)	0
Malignancies excluding NMSC	0.6 (0.2, 1.4) (5)	0.8 (0.4, 1.6) (7)	0	1.2 (0.3, 4.7) (2)	1.9 (0.6, 6.0) (3)	0
Serious infection events	3.4 (2.4, 4.9) (30)	3.5 (2.5, 4.9) (32)	2.0 (0.6, 6.2) (3)	2.3 (0.9, 6.3) (4)	3.2 (1.3, 7.8) (5)	0

*30-day rule - deaths occurring within 30 days of the last dose
BID, twice daily; CI, confidence interval; IR, inadequate responders; MACE, major adverse cardiac events; NMSC, non-melanoma skin cancer; PBO, placebo; pt-yr, patient-years of drug exposure

Disclosure: C. Charles-Schoeman, Pfizer Inc, 2, Pfizer Inc, 5; **G. Burmester**, Pfizer Inc, 8, Pfizer Inc, 2, Pfizer Inc, 5; **P. Nash**, Pfizer Inc, 2, Pfizer Inc, 5; **C. A. F. Zerbini**, Pfizer Inc, 2, Pfizer Inc, 5; **S. Anway**, Pfizer Inc, 3; **K. Kwok**, Pfizer Inc, 1, Pfizer Inc, 3; **T. Hendrikx**, Pfizer Inc, 3; **E. Bananis**, Pfizer Inc, 3; **R. Fleischmann**, Pfizer Inc, 2, Pfizer Inc, 5.

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Estimation of Cost per Effectively Treated Patients with Biologic Disease Modifying Anti-Rheumatic Drugs in US Veterans with Rheumatoid Arthritis. Grant W. Cannon[1], Chia-Chen Teng[1], Tao He[1], Jianwei Leng[2], Chao-Chin Lu[1], Derek Tang[3], Neel Shah[3], David J. Harrison[3] and Brian Sauer[1]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]Salt Lake City VA and University of Utah, Salt Lake Citty, UT, [3]Amgen Inc., Thousand Oaks, CA.

Background/Purpose: An algorithm based on administrative claims data (in lieu of clinical measures) was validated using data from the Veteran's Affairs (VA) Rheumatoid Arthritis (RA) Registry (VARA). It can be used to evaluate effectiveness of biologic disease modifying anti-rheumatic drugs (DMARDs) and cost per effectively treated patient.

Methods: National VA pharmacy and administrative claims for US veterans initiating biologics (abatacept (ABA) (intravenously [IV]), adalimumab (ADA), etanercept (ETN), infliximab (INF), or rituximab (RIT)) from Jan 1, 2008 to Jan 1, 2011 were evaluated. Patients were included if they newly initiated biologic treatment ≥365days after VA enrollment and were followed for 1-year. Only biologics with ≥100 patients were evaluated.

Clinical effectiveness was estimated using an algorithm based on claims data. Patients who did not fail any of the six algorithm criteria; biologic dose escalation, switching biologics, adding a new non-biologic DMARD, receiving >1 intra-articular glucocorticoid injection, increasing glucocorticoid dose, or low treatment compliance (<80%) were categorized as effectively treated. Cost per effectively treated patient was calculated using annual medication and administration cost divided by the percentage of patients categorized as effectively treated.

Subgroup analyses stratified by age, smoking status, serologic status, and body mass index (BMI) were conducted.

Results: A total of 4,696 patients (mean age 61 years, 87% male) met all inclusion and exclusion criteria. Demographic characteristics were similar across groups. The percentage of patients categorized as effectively treated ranged from 25% to 33% and was higher for self-injected than IV biologics. Annual cost was higher for INF and RIT compared to ABA, ADA, and ETN.

Outcomes were similar across all subgroups other than gender. Men had higher drug cost, but a higher percentage were categorized as effectively treated and the cost per effectively treated patient was lower, ($40.7k vs. $57.5k). Cost per effectively treat patient was lower for current non-smokers, patients with positive rheumatoid factor, positive anti-cyclic citrullinated peptide antibodies (aCCP), and BMI ≥30, but the differences were not statistically significant.

Conclusion: In US veterans, the percentage of patients categorized as effectively treated using the algorithm was highest for ADA (33%) and ETN (32%) and the cost per effectively treated patient was lowest for ETN ($39.4k) and ADA ($41.5k). Male gender was associated with higher annual drug cost but lower cost per effectively treated patient.

	All (n=4,696)	ABA (n=117)	ADA (n=1,989)	ETN (n=2,069)	INF (n=254)	RIT (n=267)
	n (%) (95% confidence interval)					
Demographics						
Age (mean) at index (years)	61 (61–61)	62 (60–64)	61 (60–61)	61 (60–61)	62 (60–63)	63 (61–64)
Gender						
Male	87% (86–88%)	80% (73–88%)	87% (85–88%)	87% (86–89%)	85% (80–89%)	85% (80–89%)
Smoking Status						
Current	34% (32–35%)	28% (20–36%)	33% (31–35%)	35% (33–37%)	31% (25–37%)	31% (25–36%)
Former	37% (36–39%)	40% (31–49%)	37% (35–40%)	37% (35–39%)	35% (29–41%)	39% (33–45%)
Never	16% (15–17%)	20% (12–27%)	17% (15–18%)	16% (14–17%)	17% (12–21%)	16% (12–21%)
Unknown	13% (12–14%)	12% (6–18%)	12% (11–14%)	13% (12–14%)	17% (13–22%)	14% (10–18%)
CCP						
Positive	47% (45–48%)	46% (37–55%)	47% (45–49%)	47% (45–50%)	43% (36–49%)	46% (40–52%)
Negative	20% (19–21%)	19% (12–26%)	21% (19–22%)	21% (19–23%)	17% (12–22%)	16% (12–21%)
Unknown	33% (32–34%)	35% (26–44%)	33% (30–35%)	32% 30–34%)	41% (35–47%)	37% (32–43%)
Rheumatoid Factor						
Positive	61% (59–62%)	57% (48–66%)	61% (58–63%)	61% (59–63%)	51% (45–57%)	66% (60–71%)
Negative	28% (27–30%)	26% (18–34%)	572 (29%) (27–31%)	28% (26–30%)	32% (27–38%)	25% (20–30%)
Unknown	11% (10–12%)	16% (10–23%)	212 (11%) (9–12%)	11% (10–12%)	17% (12–22%)	9% (6–13%)
BMI (kg/m^2)	30 (30–30)	30 (29–31)	30 (29–30)	30 (29–30)	30 (29–31)	29 (28–30)
Outcomes						
Effectively treated	32% (31%–33%)	25% (17%–33%)	33% (31%–35%)	32% (30%–34%)	26% (21%–32%)	27% (22%–32%)
Annual Drug Cost ($1,000/patient)	13.5 (13.3–13.7)	13.8 (12/5–15.2)	13.9 (13.5–14.2)	12.8 (12.4–13.1)	14.4 (13.4–15.4)	15.7 (14.8–16.7)
Cost per effectively treated patient ($1,000/patient)	42,2 (41.1–43.4)	55.8 (44.8–66.7)	41.5 (39.8–43.2)	39.4 (37.8–41.1)	54.5 (47.0–62.1)	58.32 (51.5–65.0)

	Gender	
Data presented with 95% CI	**Male(n=4,068)**	**Female(n=628)**
Annual Drug Cost ($1,000/patient)	13.7 (13.4–13.9)	12.3 (11.0–12.0)
Patients Effectively Treated	34% (32%–35%)	21% (18%–25%)
Cost per Effectively Treated Patient ($1,000/patient)	40.7 (39.6–41.9)	57.5 (51.9–63.0)
	Smoking Status	
	Smoker (n=1,575)	**Nonsmoker (n=2,510)**
Annual Drug Cost ($1,000/patient)	13.2 (12.8–13.5)	13.7 (13.5–14.0)
Patients Effectively Treated	29% (27%–32%)	33% (31%–35%)
Cost per Effectively Treated Patient ($1,000/patient)	45.00 (42.8–47.3)	41.5 (40.0–43.0)
	aCCP Status	
	Positive (n=2,199)	**Negative (n=949)**
Annual Drug Cost ($1,000/patient)	13.8 (13.4–14.1)	13.4 (12.9–13.8)
Patients Effectively Treated	33% (31%–35%)	29% (26%–32%)
Cost per Effectively Treated Patient ($1,000/patient)	41.1 (39.5–42.7)	45.8 (42.7–48.8)
	Rheumatoid Factor Status	
	Positive (n=2,843)	**Negative (n=1,326)**
Annual Drug Cost ($1,000/patient)	13.5 (13.2–13.8)	13.4 (13.0–13.8)
Patients Effectively Treated	33% (31%–35%)	30% (28%–32%)
Cost per Effectively Treated Patient ($1,000/patient)	41.0 (39.6–42.5)	44.5 (42.1–46.9)
	BMI (kg/m^2)	
	≥ 30 (n=1,857)	**<30 (n=2,468)**
Annual Drug Cost ($1,000/patient)	13.8 (13.4–14.1)	13.6 (13.1–13.6)
Patients Effectively Treated	33% (31%–35%)	31% (30%–33%)
Cost per Effectively Treated Patient ($1,000/patient)	41.9 (40.2–43.7)	42.5 (40.8–44.1)

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Discontinuation of Biologics in Patients with Rheumatoid Arthritis after Achieving Low-Activity Disease Status. Moeko Ochiai, Eri Sato, Eiichi Tanaka, Eisuke Inoue, Ayako Nakajima, Shigeki Momohara, Atsuo

Taniguchi and Hisashi Yamanaka. Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Several clinical trials have reported bio-free remission or discontinuation of biologic DMARDs; however, these findings have not been confirmed in a real-world setting. The aim of this study is to evaluate the discontinuation of biologics after achieving low -activity disease status among patients with rheumatoid arthritis (RA) undergoing treatment in daily practice.

Methods: Among 1,775 patients (infliximab [IFX], 418 patients; etanercept [ETN], 690 patients; adalimumab [ADA], 267 patients; tocilizumab [TCZ], 318 patients; and abatacept [ABT], 82 patients) who had been treated with biologics in our clinic between 2003 and 2012, we extracted data on 43 patients with RA (IFX, 26 patients; ETN, 9 patients; ADA, 4 patients; TCZ, 2 patients; and ABT, 2 patients) who discontinued biologics since their disease activity were well controlled. In these patients, DAS28 scores were $<$ 3.2 at the time of biologics discontinuation. Those 43 patients were divided into two groups (bio-free or bio-reuse) on the basis of biologic usage 1 year after discontinuation. Those 43 patients were also divided into bio-free success and bio-free failure groups on the basis of disease activity (DAS28 $<$ 3.2 or DAS28 $\geqq$ 3.2, respectively) 1 year after discontinuation. The clinical features of the patients at the time of initiation and discontinuation of biologics were compared between the bio-free and bio-reuse groups and between the bio-free success and bio-free failure groups.

Results: The percentages of patients who discontinued biologics due to well-controlled disease activity and in the bio-free success group among biologics users in our clinic were 2.4% (43/1775) and 1.4% (25/1775), respectively. The number of patients in the bio-free and bio-reuse groups was 34/43 (79.1% [IFX, n = 20; ETN, n = 8; ADA, n = 3; TCZ, n = 1; and ABT, n = 2) and 9/43 (20.9%), respectively. There were no significant differences between the two groups with respect to age (bio-free vs. bio-reuse [47.5 vs. 39.0 years]), disease duration (3.0 vs. 2.0 years), DAS28 (4.17 vs. 5.10), J-HAQ (0.75 vs. 0.56), dose of MTX (8.0 vs. 8.0 mg/week), and dose of glucocorticoids (4.0 vs. 0 mg/day) at initiation of biologics, or DAS28 at discontinuation of biologics (2.09 vs. 1.80), or duration of biologics use (591.5 vs. 851.0 days). In addition, most clinical features did not differ significantly between the bio-free success (n=25 [58.1%]; IFX, n = 13; ETN, n = 6; ADA, n = 3; TCZ, n = 1; and ABT, n = 2) and bio-free failure groups (n=18 [41.9%]). The median DAS28 at initiation of biologics was significantly lower in the bio-free success group than the bio-free failure group (3.95 vs. 5.04, *p=0.04*). The bio-free success group was significantly decreased the average dosage of glucocorticoid during the biologics use than that in the bio-free failure group (−3.0 vs 0 mg/day, *p=0.01*).

Conclusion: We showed that the 1-year discontinuation rate of biologics after achieving low-activity disease status was high (79.1%) in patients with RA being treated in an outpatient setting. A lower DAS28 score at initiation of biologics and decreasing the dose of glucocorticoid before discontinuation of biologics were important factors leading to bio-free success in patients with RA irrespective of biologic type.

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Efficacy and Safety of Induction Therapy for Rheumatoid Arthritis with Simultaneous Administration of Methotrexate and Low-Dose Tacrolimus: A Retrospective Study. Takashi Nakanishi[1], Hideyuki Horikoshi[1], Reiko Takahashi[1], Kanami Tongu[2], Junko Nishioka[2], Fumihiko Kimura[1], Yuichi Nishioka[2] and Kenji Itoh[1]. [1]National Defense Medical College, Tokorozawa, Japan, [2]Nishioka Clinic for Rheumatic Diseases and Allergic Diseases, Kofu, Japan.

Background/Purpose: Additional administration of low-dose tacrolimus (LD-TAC) at 0.5–1.0 mg daily was reported to be quite effective for rheumatoid arthritis (RA) patients with inadequate response to methotrexate (MTX). This study evaluated the efficacy and safety of induction therapy with simultaneous administration of MTX and LD-TAC for RA.

Methods: Clinical records of 147 RA patients initially treated with MTX alone or MTX with LD-TAC were retrospectively analyzed. We classified the patients into the MTX monotherapy group (patients who continued to receive MTX alone during the entire investigation), LD-TAC add-on group (patients with inadequate response to MTX who initially received MTX monotherapy and then an add-on LD-TAC), and simultaneous combination group (patients who initially received concomitant administration of MTX and LD-TAC). Patients who needed to receive other disease-modifying antirheumatic drugs, biological agents, or prednisone $>$ 10 mg daily were excluded from the study. Treatment efficacy was evaluated every 12 weeks for 1 year from the initial treatment, using the Disease Activity Score in 28 joints and erythrocyte sedimentation rate (DAS28-ESR) and Boolean-based remission rate.All adverse events observed in each group were also evaluated.

Results: A total of 26, 18, and 28 patients in the MTX-monotherapy, LD-TAC add-on, and simultaneous combination groups, respectively, were evaluated. The initial DAS28-ESR scores were 4.73, 4.58, and 4.63, respectively. No differences in baseline patient characteristics were found between the groups, except the higher initial prednisone dose in the MTX-monotherapy group.Of the patients in the simultaneous combination group, 92.9% achieved low disease activity at the 48th week, which was a significantly higher rate than that for those in the MTX-monotherapy and LD-TAC add-on groups (65.4% and 66.7%, respectively; $p < 0.01$). The achievement rates for good response according to the DAS28-based European League of Associations for Rheumatology response and Boolean-based remission criteria were also significantly higher in the simultaneous combination group. In addition, the prednisone dose was lower in the simultaneous combination group than in the MTX monotherapy group at the 48th week.No significant difference in the incidence of adverse events was observed between the groups. No serious adverse event was observed during the study period.

Conclusion: This study demonstrates the efficacy and safety of induction therapy with simultaneous administration of MTX and LD-TAC for RA. Large-scale prospective cohort studies are required for a more precise understanding of the treatment.

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Efficacy and Safety Study of a Sequential Therapy of Tocilizumab and, If Initially Inadequately Responded to Tocilizumab, Followed By Rituximab in Patients with Rheumatoid Arthritis and Inadequate Response to Traditional Disease Modifying Anti-Rheumatic Drugs. Thomas Dörner[1], Hans-Peter Tony[2], Gerd Burmester[1], Hendrik Schulze-Koops[3], Jörg Kaufmann[4], Peter Kästner[5], Herbert Kellner[6], Reiner Kurthen[7], Sylke Wagner[8], Marvin A. Peters[9] and Christoph Iking-Konert[10]. [1]Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]University Clinic Wuerzburg, Wuerzburg, Germany, [3]University Clinic Munich, Munich, Germany, [4]Rheumatology Practice, Ludwigsfelde, Germany, [5]MVZ Out-patient Rheumatogy Unit Erfurt, Erfurt, Germany, [6]Specialist Practice for Rheumatology and Gastroenterology, Munich, Germany, [7]Rheumatology Practice, Aachen, Germany, [8]Practice for Internal Medicine specialized in Rheumatology, Halle, Germany, [9]Roche Pharma AG, Grenzach-Wyhlen, Germany, [10]University Clinic Hamburg-Eppendorf, Hamburg, Germany.

Background/Purpose: The MIRAI study evaluated a sequential exposure to 2 defined biologics under rigorous study conditions within a homogeneous population of biological naïve patients (pts) with moderate/severe active RA who inadequately responded to traditional DMARDs. This study investigated the early response to the IL-6 inhibitor tocilizumab (TCZ); non-responders to TCZ subsequently received 1 cycle of rituximab (RTX; anti-CD20 therapy).

Methods: We report the results of the final analysis (first-pat-in: MAR-2011; last-pat-out: FEB-2014) of MIRAI (NCT01332994), a German, multicenter, two-arm, open-label, phase-III-study. All pts received 4 TCZ infusions (8 mg/kg, q4w; 1st treatment period) until week 16. Partial responders (ΔDAS28 $>$1.2 or DAS28$\geq$2.6 and $\leq$3.2) received further 4 TCZ infusions (8 mg/kg, q4w); non-responders (ΔDAS28$\leq$1.2 and DAS28 $>$3.2) received subsequent RTX treatment (1g each at weeks 16 and 18). All pts with a 2nd treatment period (TCZ or RTX) completed study at week 32. Primary endpoint: pts in remission (DAS28 $<$2.6) at week 16 (expected 45%). Secondary endpoints: DAS28/ACR response at week 32, patient-reported outcomes, B-cells, adverse events (AE).

Results: 519 pts (ITT-Main/Safety; mean age: 56 years, females 67.8%) received TCZ in the 1st treatment period. 504 pts received concomitant DMARDs (mostly MTX, 365 pts). At week 8, a clinically relevant DAS28

reduction (>1.2) from baseline was seen in 81.5% of pts. At week 16, 222 pts (42.8%) were in remission and completed study, 213 pts received a 2nd TCZ period (ITT-TCZ2), only 27 non-responder initiated subsequent RTX (ITT-RTX). At week 32, 117 of 213 pts achieved remission under continued TCZ therapy, and 10 of 27 pts showed a clinically relevant DAS28 reduction from week 16 after 1 cycle RTX.

Total incidence of drug related AEs/SAEs: 38.3%/4.4%. Drug-related serious infections occurred in 10 pts (1.9%). One death possibly related to TCZ was reported (fall plus craniocerebral injury). No RTX related SAEs were reported.

Conclusion: Early response to TCZ was demonstrated by a rapid improvement of RA symptoms until week 16. Initially partial responders to TCZ benefited from a continued TCZ therapy. Notably, the proportion of TCZ non-responders was low (27 of 519 pts); about 1/3 of these pts clearly benefited from subsequent RTX therapy with lasting effects until week 66.

All patients (ITT-main/Safety), 1st treatment period TCZ: results from baseline to week 16

Parameter	Baseline N=519	Week 8 N=519	Week 16 N=519
DAS28, mean ± SD (n)	5.7 ± 1.0 (516)	3.0 ±1.4 (491)	2.6 ± 1.3 (485)
DAS28 <2.6, n (%)	0 (0.0)	208 (40.1)	222 (42.8)
DAS28 ≤3.2, n (%)	1 (0.2)	295 (56.8)	357 (68.8)
ΔDAS28 >1.2, n (%)*	–	423 (81.5)	447 (86.1)
EULAR-Response good, n/N (%)*	–	291 (56.1)	354 (68.2)
EULAR-Response moderate, n (%)*	–	159 (30.6)	105 (20.2)
SDAI, mean ± SD (n)	32.6 ± 11.6 (512)	14.6 ±10.7 (492)	11.7 ± 10.1 (475)
SDAI ≤3.3, n (%)	0 (0.0)	59 (11.4)	89 (17.1)
CDAI, mean ± SD (n)	30.9 ± 11.2 (519)	14.3 ±10.6 (497)	11.4 ± 9.9 (485)
CDAI ≤2.8, n (%)	0 (0.0)	56 (10.8)	86 (16.6)
ACR20, n (%)*	–	317 (61.1)	348 (67.1)
ACR50, n (%)*	–	174 (33.5)	237 (45.7)
ACR70, n (%)*	–	79 (15.2)	127 (24.5)
HAQ-DI, mean ± SD (n)	1.24 ± 0.67 (513)	0.85 ± 0.66 (490)	0.75 ± 0.67 (472)
ΔHAQ-DI >0.22, n (%)*	–	299 (57.6)	317 (61.1)

* Compared to baseline.
CDAI = Clinical disease activity index; SD = Standard deviation; SDAI = Simplified disease activity index.

Partial TCZ responder (ITT-TCZ2), 2nd treatment period TCZ: results from week 16 to week 32

Parameter	Week 16 N=213	Week 24 N=213	Week 32 (EOS) N=213
DAS28, mean ± SD (n)	3.3 ± 0.6 (213)	2.6 ±1.1 (197)	2.5 ± 1.2 (193)
DAS28 <2.6, n (%)	3 (1.4)**	109 (51.2)	117 (54.9)
DAS28 ≤3.2, n (%)	133 (62.4)	145 (68.1)	142 (66.7)
ΔDAS28 >1.2, n (%)*	208 (97.7)	195 (91.5)	181 (85.0)
EULAR-Response good, n/N (%)*	130 (61.0)	145 (68.1)	142 (66.7)
EULAR-Response moderate, n (%)*	80 (37.6)	51 (23.9)	44 (20.7)
SDAI, mean ± SD (n)	15.3 ± 7.6 (207)	11.1 ±8.8 (190)	10.0 ± 9.9 (189)
SDAI ≤3.3, n (%)	0 (0.0)	23 (10.8)	47 (22.1)
CDAI, mean ± SD (n)	15.0 ± 7.5 (213)	10.9 ±8.6 (199)	9.7 ± 9.8 (194)
CDAI ≤2.8, n (%)	0 (0.0)	21 (9.9)	41 (19.2)
ACR20, n (%)*	145 (68.1)	155 (72.8)	161 (75.6)
ACR50, n (%)*	69 (32.4)	106 (49.8)	117 (54.9)
ACR70, n (%)*	18 (8.5)	46 (21.6)	73 (34.3)
HAQ-DI, mean ± SD (n)	0.86 ± 0.67 (209)	0.84 ± 0.66 (190)	0.82 ± 0.68 (191)
ΔHAQ-DI >0.22, n (%)*	130 (61.0)	113 (53.1)	122 (57.3)

* Compared to baseline.
** Despite being in remission at week 16, 3 pts. erroneously received a TCZ infusion.
CDAI = Clinical disease activity index; EOS = End of study; SD = Standard deviation; SDAI = Simplified disease activity index.

TCZ non-responder (ITT-RTX), 2nd treatment period subsequent RTX: results from week 16 to week 32 incl. SFU at week 66

Parameter	Week 16 N=27	Week 32 (EOS) N=27	Week 66 (SFU) N=27
DAS28, mean ± SD (n)	5.1 ± 1.2 (27)	4.0 ±1.5 (26)	3.9 ± 1.5 (25)
DAS28 <2.6, n (%)	0 (0.0)	4 (14.8)	6 (22.2)
DAS28 ≤3.2, n (%)	0 (0.0)	9 (33.3)	8 (29.6)
ΔDAS28 >1.2, n (%)*	–	10 (37.0)	10 (37.0)
EULAR-Response good, n/N (%)*	–	7 (25.9)	8 (29.6)
EULAR-Response moderate, n (%)*	–	8 (29.6)	3 (11.1)
SDAI, mean ± SD (n)	32.2 ± 14.9 (27)	16.5 ±15.8 (24)	16.6 ± 13.8 (25)
SDAI ≤3.3, n (%)	0 (0.0)	5 (18.5)	5 (18.5)
CDAI, mean ± SD (n)	31.4 ± 14.4 (27)	16.6 ±16.5 (25)	15.5 ± 13.7 (26)
CDAI ≤2.8, n (%)	0 (0.0)	4 (14.8)	5 (18.5)
ACR20, n (%)*	–	11 (40.7)	12 (44.4)
ACR50, n (%)*	–	9 (33.3)	7 (25.9)
ACR70, n (%)*	–	6 (22.2)	4 (14.8)
HAQ-DI, mean ± SD (n)	1.26 ± 0.74 (27)	1.09 ± 0.68 (26)	n.a.
ΔHAQ-DI >0.22, n (%)*	–	9 (33.3)	n.a.

* Compared to week 16.
CDAI = Clinical disease activity index; EOS = End of study; n.a. = not applicable; SD = Standard deviation; SDAI = Simplified disease activity index; SFU = Safety follow-up.

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Patient Experience with Initiation of SQ and Oral MTX. Jeffrey R. Curtis[1], David Mackey[1], Noam Gerber[2], Aseem Bharat[1], Lang Chen[1], Fenglong Xie[1], Ben Nowell[2], Kenneth G. Saag[3] and Seth Ginsberg[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Creaky Joints/ Global Healthy Living Foundation, Upper Nyack, NY, [3]The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Methotrexate is the anchor drug used for the treatment of rheumatoid arthritis (RA). Despite its prominent position in RA therapeutics, its real-world effectiveness may be influenced by a relative lack of tolerability or other side effects that physicians may not be aware of but that are bothersome to patients.

Methods: We conducted a prospective, compensated ($25), online survey among RA patients who were members of Creakyjoints, a large arthritis patient community. Eligible participants must have recently initiated a new biologic, SQ MTX, or oral MTX in the last 12 months and were uniquely assigned to one of these 3 exposure cohorts. Patients eligible for more than 1 cohort were assigned in the hierarchy above. **Results** were stratified by exposure cohort: SQ MTX, oral MTX, and biologic. Descriptive statistics were used to compare patient-reported side effects and tolerability related to MTX use, comparing SQ vs. oral formulations and referent to biologic initiation. Recruitment is still ongoing to an expected sample size of 550 pts and results are reported through June 5th, 2014.

Results: A total of 783 patients were screened for the survey, and 346 were eligible. Of these, 287 (83.0%) completed the survey, distributed to the biologic (n=175, including 85 initiating SQ biologics), SQ MTX (n=33), and oral MTX (n=79). Demographics were similar across treatment arms; overall, mean (SD) age was 47.91 (13.01) years, 90.2% women. Commonly-reported side effects were included in the table and showed differences between exposure groups in diarrhea, nausea, fatigue, and other adverse events. Pain initiating SQ biologics compared to SQ MTX reported greater pain, particularly with SQ etanercept and adalimumab compared to SQ MTX. The mean pain score (0–10 scale) for patients on SQ MTX was 2.18, lower than mean score for etanercept (4.21, $p = 0.002$) and adalimuamb (4.43, $p < 0.0001$). Patients reported a monthly co-payment of $0 with the following frequencies: oral MTX - 13%, SQ MTX – 0%, and biologic users - 23%; and monthly co-payments between $0 and $25: oral MTX – 61%, SQ MTX - 61%, and biologics - 30%.

Conclusion: Results: from this real-world RA patient cohort suggest that oral MTX is accompanied by many patient-reported side effects and tolerability problems that may be under-recognized by physicians. These may impact both treatment satisfaction and medication adherence that adding or switching to biologics or SQ MTX may attenuate.

Table: Patient Reported Side Effects and Tolerability Associated with use of Biologics and MTX

	Biologic N=175	SQ MTX N=33	Oral MTX N=79	P value for difference between the 3 treatments
Diarrhea	6 (3%)	3 (9%)	17 (22%)	<0.0001
Vomiting	7 (4%)	1 (3%)	5 (6%)	0.64
Other stomach problems	13 (7%)	2 (6%)	4 (5%)	0.77
Fatigue	42 (24%)	27 (82%)	42 (53%)	<0.0001
Malaise	26 (15%)	16 (48%)	26 (33%)	<0.0001
Mental fog	26 (15%)	13 (39%)	21 (27%)	0.002
Infection	22 (13%)	3 (9%)	4 (5%)	0.18
Any pain with injections	83/99* (84%)	20 (71%)	N/A	0.008

*limited to the 99 patients using SQ biologics

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Biologic Discontinuation in Rheumatoid Arthritis: Experience from a Canadian Clinic. Denis Choquette[1], Louis Coupal[1], Marie-Claude Laliberté[2] and Olivier Desjardins[2]. [1]Institut de rhumatologie de Montréal (IRM), Montréal, QC, [2]AbbVie, St. Laurent, QC.

Background/Purpose: Adherence and persistence to treatment are a cornerstone of treatment success in chronic diseases such as rheumatoid arthritis (RA). The purpose of this study was to describe biologic treatment discontinuation and assess the predictors of discontinuation in RA patients followed at a Canadian clinic.

Methods: In this prospective cohort study, adult patients included in the RHUMADATA computerized database with a diagnosis of RA and treated with at least one biologic agent since 2003 were selected. The RHUMADATA database includes clinical, laboratory and socioeconomic information of patients with rheumatic diseases followed at the *Institut de Rhumatologie de Montréal*, a rheumatology clinic in Montreal (Quebec, Canada). Patients were followed for three years after therapy initiation or until treatment discontinuation. Biologic therapies considered include abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and anakinra. Treatment discontinuation was measured using pharmacy records. Time to discontinuation and predictors of treatment discontinuation were explored using Cox proportional hazards models.

Results: A total of 623 eligible patients were treated with at least one biologic. The average age was 53.2 years (SD=12.4), 77% were women and patients had been diagnosed for an average of 7.7 years. The average time on treatment for the first biologic agent was 1.7 years (SD=2.1). In all, 233 (37%), 326 (52%), 405 (65%), and 438 (70%) patients had stopped their first biologic treatment after 6, 12, 24, and 36 months, respectively. In time-to-event analyses (Cox proportional hazard models), type of work [part time vs. full time; hazard ratio (HR): 1.57; 95% confidence interval (CI): 1.05–2.34] and income [$20,000 to $40,000 vs. less than $20,000 (HR: 1.35; 1.01–1.80) and $80,000 to $100,000 vs. less than $20,000 (HR: 2.16; 1.23–3.80)] were significantly associated with biologic discontinuation over the complete treatment duration. The number of disease-modifying antirheumatic drugs (DMARDs) used (HR: 0.89; 0.80–0.99) and the use of methotrexate (yes vs. no; HR: 0.80; 0.64–0.99) were associated with a reduced risk of biologic discontinuation.

Conclusion: In this real-life Canadian study, high biologic discontinuation rates were observed over three years. This study also suggests that many clinical and socioeconomic variables are predictors of biologic therapy discontinuation in RA patients. These results may help design interventions aiming at improving treatment adherence in RA, a chronic and progressive disease.

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Prediction of Successful Dose Reduction or Discontinuation of Adalimumab or Etanercept Using Serum Drug Levels and Antidrug Antibody Measurement. Noortje van Herwaarden[1], Chantal Bouman[1], Aatke van der Maas[1], Ronald F. van Vollenhoven[2], Johannes W.J. Bijlsma[3], Frank H.J. van den Hoogen[4], Alfons A. den Broeder[1] and Bart van den Bemt[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]Unit for clinical therapy research (ClinTrid), Karolinska Institute, Stockholm, Sweden, [3]University Medical Center Utrecht, Utrecht, Netherlands, [4]Rheumatology Centre Sint Maartenskliniek and Radboud university medical center, Ubbergen (Nijmegen), Netherlands.

Background/Purpose: Dose reduction and discontinuation of TNF inhibitors (TNFi) is feasible in many rheumatoid arthritis (RA) patients, but leads to (temporary) worsening of disease activity in some patients. We evaluated the predictive value of baseline adalimumab and etanercept serum levels and antidrug antibodies for successful dose reduction or discontinuation in patients with RA and low disease activity.

Methods: Patients with RA and a stable low disease activity, included in the intervention arm of an 18 months randomised controlled trial (DRESS study) assessing non-inferiority of a dose reduction strategy of adalimumab or etanercept compared to usual care were analysed[1]. Dose was reduced by stepwise increasing the interval between injections every 3 months until flare or discontinuation of the TNFi. Serum levels of adalimumab or etanercept and antidrug antibodies were measured before start of dose reduction[2,3]. Receiver-operator-curves (ROC) and optimal cut-off drug serum levels were calculated. A sensitivity analyses was done for timing of serum sampling (days after last injection), per tertile. Sensitivity/specificity of anti-drug antibodies were calculated for successful discontinuation and for successful dose reduction separately.

Results: Data was available for 118 of 121 included patients. Mean DAS28-CRP at baseline was 2.2 (SD 0.6). At 18 months follow up TNFi could be stopped in 19% (95%CI 12–27) of patients, the interval increased in 44% (95%CI 35–53) and in 37% (95%CI 29–47) of patients no dose reduction was possible. Mean drug levels and anti-drug antibodies were not different per subgroup (table 1). ROC analyses showed no predictive value of drug levels for successful dose reduction or discontinuation (figure 1). Sensitivity analyses showed no influence of serum sample timing, with the exception of adalimumab trough level (last tertile) predicting successful dose reduction (AUC 0.86, 95% CI 0.58–1.00, optimal cut-off 7.8 μg/ml).

Anti-adalimumab antibodies were detected in 4 patients (10%), and were not predictive for successful discontinuation. No anti-etanercept antibodies were detected.

Conclusion: Adalimumab and etanercept serum levels and antidrug antibodies have no predictive value for successful dose reduction or discontinuation in RA patients with low disease activity, with a possible exception of adalimumab trough levels for predicting successful dose reduction.

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Figure 1. Serum level predicting successful discontinuation or dose reduction

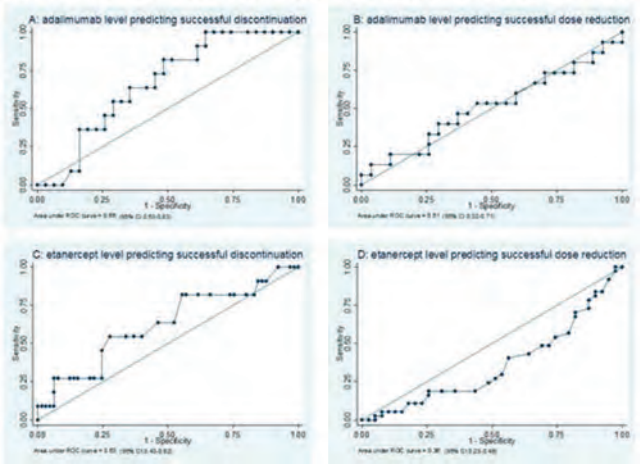

Table 1 Mean drug levels and anti-drug antibodies at baseline

A: adalimumab

Outcome at 18 months	Mean drug level at baseline μg/ml (SD)	Anti-drug antibodies (%)
Stopped (n = 11)	8.5 (2.8)	0
Dose reduced (n = 15)	8.1 (5.2)	1 (7)
No dose reduction possible (n = 16)	6.8 (4.1)	3 (19)

B: etanercept

Outcome at 18 months	Mean drug level at baseline μg/ml (SD)	Anti-drug antibodies (%)
Stopped (n = 11)	2.7 (1.3)	0
Dose reduced (n = 37)	2.0 (0.9)	0
No dose reduction possible (n = 28)	2.4 (1.0)	0

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Bio-naïve Patients with Rheumatoid Arthritis Benefit More from Abatacept Treatment Compared to Those Who Are Inadequate Responders to Other Biologics – Results from the National Swedish Rheumatology Quality Register. Carl Turesson[1], Leszek Stawiarz[2], Staffan Lindblad[2] and Saedis Saevarsdottir[3]. [1]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Department of Medicine, Karolinska institutet and Karolinska University Hospital, Stockholm, Sweden.

Background/Purpose: Abatacept is a biological anti-rheumatic drug used in Rheumatoid Arthritis (RA). Data on patient characteristics, diagnosis, previous treatment and outcomes of abatacept have been collected in the Swedish Rheumatology Quality register (SRQ) which comprises the Swedish Biologics Register (ARTIS; Arthritis Treatment In Sweden), since the drug was first available in 2006. The objective of this study was to evaluate drug survival probability and short term outcome of abatacept in clinical practice for patients with RA, using a national register.

Methods: Observational data from the SRQ were collected for the period from April 1st, 2006 to May 20, 2014. Analyses were stratified by previous exposure to biologics, regardless of the cause of discontinuation. Kaplan-Meier survival analysis with right censoring and log-rank test of equality across strata were performed and Šidák multiple-comparison adjustments applied. EULAR good or moderate response rates at 6 and 12 months were calculated, and corrected for survival on drug using the Lundex method (proportion still on drug x proportion responding(1)).

Results: A total of 1291 patients with RA (1023 females, 79.2%) started abatacept treatment between April 2006 and May 2014. The mean age at start of abatacept was 59.2 years, and the median duration of RA was 11.2 years. Abatacept was prescribed as the first biologic treatment in 200 cases (15.5 %), after inadequate response (IR) to one other biologic in 349 cases (27.0 %) and after IR to ≥ 2 other biologics in 742 cases (57.5 %). The baseline disease activity was slightly lower in bio-naïve patients starting abatacept compared to those who had received one or ≥2 previous biologics (mean DAS28 5.01, 5.16 and 5.37 respectively). The bio-naïve patients treated with abatacept were older at baseline (mean 62.0 vs 60.6 and 57.8 years, respectively), and less likely to be female (71 % vs. 80 % and 81 %). Survival on drug was significantly longer in patients treated with abatacept as the first biologic compared to those previously exposed to 1 biologic (p=0.002) or ≥ 2 biologics (p=0.002). The corresponding estimated survival rates were 91%/77%/78% at 6 months and 75%/60%/62% at 12 months. There was no significant difference in drug survival between those with IR to one vs two biologics (p=0.94). After 6 months, among those still on treatment, a EULAR good or moderate response was achieved in 74 % of patients in the bio-naïve subset compared to 62 % among those with previous IR to one biologic, and 57 % among those exposed to ≥ 2 biologics. The Lundex corrected EULAR good/moderate responses were 67%/48%/45% at 6 months and 47%/41%/37% at 12 months.

Conclusion: In this observational study of RA patients treated with abatacept in clinical practice, a greater proportion of bio-naïve patients had a significant clinical response and remained on treatment compared to those with a previous IR to other biologic drugs. These results are compatible with reports from clinical trials, and indicate that a substantial number of RA patients treated with abatacept as their first biologic in clinical practice have a favorable outcome.

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Tocilizumab Use in Patients with Rheumatoid Arthritis Having Failed One Previous Anti-TNF Agent: Comparison with Adalimumab, Etanercept and Infliximab. Denis Choquette[1], Marie-Pier Payette[1], Jean-Pierre Raynauld[1], Jean-Pierre Pelletier[2], Louis Bessette[3], Edith Villeneuve[1], Boulos Haraoui[1], Isabelle Fortin[4], Marie-Anaïs Rémillard[1], Diane Sauvageau[1] and Louis Coupal[1]. [1]Institut de rhumatologie de Montréal (IRM), Montréal, QC, [2]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [3]Centre d'ostéoporose et de rhumatologie de Québec (CORQ), Québec, QC, [4]Centre de rhumatologie de l'est du Québec (CREQ), Rimouski, QC.

Background/Purpose: Tocilizumab, as an intra-venous agent, has been approved for rheumatoid arthritis (RA) in Canada in April 30th, 2010. It was the sixth approved agent after adalimumab, etanercept, abatacept, infliximab and rituximab. It has been demonstrated effective in the treatment of RA either in monotherapy or combo therapy after non-biologic or biologic DMARDS [1–3]. The goal of this analysis is to describe its effectiveness in patients with RA failing a first anti-TNF DMARDs and to compare its retention rate versus adalimumab, etanercept and infliximab in the same clinical situation.

Methods: All patients with RA having failed a first anti-TNF agents and subsequently exposed to tocilizumab after the 1stof January 2005 were extracted from the Rhumadata® database. 4 cohorts were created according to the time tocilizumab or the subsequent anti-TNF agents was introduced: One cohort of patients starting tocilizumab and 3 other cohorts starting either adalimumab, Etanercept or infliximab. Demographics and baseline characteristics including age, gender, disease duration, Rheumatoid factor and anti-CCP antibodies, CRP and ESR, previous failed treatment number, DAS 28 ESR and CDAI, HAQ-DI were included for each cohorts.

Results: The data from 259 patients prescribed either tocilizumab (53=20%), adalimumab (97=37%), etanercept (82=33%) or infliximab (27=10%) as a second biologic agent were extracted from the Rhumadata® registry and clinical database. Mosts subjects were female (75%) and the average age of cohort subjects was 58.2 (StD=14.3). Mean CRP and ESR were respectively 17.0 (StD=29.5) mg per L and 26.6 (StD=24.1) mm per hour. No clinically significant differences at baseline were observed between groups. The four year retention rates of tocilizumab, adalimumab, etanercept and infliximab as second line biologic agents were 44.3%, 27.2%, 37.1% and 34.0% respectively. Kaplan-Meier survival analysis revealed significant differences in the drug retention rates (logrank p=0.0249).

Conclusion: In RA patient having failed their first anti-TNF agent, tocilizumab, an Il-6 inhibitor, could be a more valuable alternative than cycling to a second anti-TNF agent.

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Does a Higher Dose of Folic Acid Reduce Adverse Effects of Methotrexate in Rheumatoid Arthritis? a Randomized Controlled Trial. Varun Dhir[1], Amit Sandhu[1], Jasbinder Kaur[2], Nidhi Gupta[1], Prabhdeep Kaur[1], Ankita Sood[1], Aman Sharma[1] and Shefali Sharma[1]. [1]Postgraduate Institute of Medical Education and Research, Chandigarh, India, [2]Government Medical College and hospital Sector 32, Chandigarh, India.

Background/Purpose: There is good evidence that folic acid 5–10mg per week leads to reduction in methotrexate (MTX) toxicity in rheumatoid arthritis (RA). However, this data comes from old studies using a lower dose of MTX. There is limited data of folic acid doses with contemporary usage of MTX, i.e., when MTX is started at a high dose and rapidly escalated. We wondered whether a higher dose of folic acid i.e. 30mg per week (approx. 1:1 MTX) would be better, in this context, in reducing toxicity than 10 mg per week.

Methods: This was a single-center double-blind randomized controlled trial of 24 weeks duration. Included patients 18–75 years of age, who fulfilled 1987 ACR criteria for RA and had active disease (DAS28(3) >3.2). MTX was started at 15mg/week and escalated by 8 weeks to 25 mg/week. At 16 weeks, a new DMARD could be added on the physician's discretion. Folic acid was given at a dose of 10 mg (FA-10) or 30 mg per week (FA-30), as 6 identical tablets for every day of the week except the day of taking MTX. Patients were seen every 8 weeks. Co-primary endpoints were incidence of toxicity and change in disease activity by 24 weeks. Toxicity included undesirable symptoms (evaluated by questionnaire) and laboratory abnormalities (cytopenias: WBC<4000 or platelet<100x10^3/ul or transaminitis:

>2ULN). Disease activity was evaluated using modified disease activity score using 3 variables (DAS28(3)). In addition, HAQ, serum and RBC folate and MMP-3 were done at 0 and 24 weeks. Intention-to-treat and per-protocol analyses were performed. Trial # NCT01583959

Results: This study included 100 patients, having a mean±SD age of 44.3±10.9 years, disease duration of 4.8±4.7 years and DAS28(3) of 5.8±0.9. At enrolment 13 patients were on steroids and 4 on other DMARDs. FA-10 and FA-30 groups had 51 and 49 patients respectively, with similar baseline characteristics. Similar numbers of patients were lost to follow up (6,6). At 24 weeks, the mean±SD dose of MTX in both groups (22.8±4.4, 21.4±4.6mg/week) was similar (p=0.1). Leflunomide was added in 18 and 10 patients at 16 weeks and SSZ in 1 patient. Among patients with at least 1 follow up, there were no significant differences between groups in the frequency of undesirable symptoms or laboratory abnormalities. Lung toxicity was suspected in 2 patients in the FA10 group (Table 1). DAS28(3) declined similarly from baseline to 24 weeks (p=0.2) in FA10 (−1.1±1.0) and FA30 (−1.3±1.0) groups. At 24 weeks, serum folic acid was significantly (p<0.001) higher in FA30 (45.1±39.7) compared to FA10 group (20.4±17.1ng/ml), but there was no difference in RBC folate, HAQ and MMP-3.

Conclusion: We did not find any significant difference in toxicity or efficacy of MTX with higher dose of folic acid even when starting MTX at a high dose and escalating rapidly. The finding of 2 cases of suspected lung toxicity with folic acid 10 mg/week warrants larger studies.

Table 1: Frequency of MTX related toxicity in patients who had at least one follow up visit

	Folic acid 10 mg per week (N=47) N(%)	Folic acid 30 mg per week (N=46) N(%)	P value
Laboratory abnormalities			
Cytopenias	2 (4.3)	2 (4.3)	0.99
Transaminitis	20 (42.6)	21 (45.7)	0.76
Undesirable symptoms			
Nausea	10 (21.3)	17 (37)	0.10
Dizziness	6 (12.8)	1 (2.2)	0.11
Fatigue	2 (4.3)	3 (6.5)	0.98
Loss of appetite	2 (4.3)	3 (6.5)	0.98
Uneasiness	4 (8.5)	3 (6.5)	0.99
Headache	0 (0)	4 (8.7)	0.11
Oral ulcers	0 (0)	2 (4.3)	0.99
Altered taste	1 (2.1)	1 (2.2)	0.99
Other adverse effects			
Herpes Zoster	2 (4.3)	1 (2.2)	0.99
Suspected lung toxicity	2 (4.3)	0 (0)	0.25

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Abatacept after Rituximab in Rheumatoid Arthritis. a Pan-European Collaboration of RA Registries. Axel Finckh[1], David Neto[2], M. Victoria Hernández[3], Florenzo Iannone[4], Elisabeth Lie[5], Helena Canhao[6], K Pavelka[7], Carl Turesson[8], Xavier Mariette[9], Merete Lund Hetland[10] and Jacques Gottenberg[11]. [1]Geneva University Hospital, Geneva, Switzerland, [2]University of Geneva, Geneva, Switzerland, [3]Hospital Clínic of Barcelona, Barcelona, Spain, [4]Reumatologia Universita e Policlinico di Bari, Bari, Italy, [5]Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, [6]Instituto de Medicina Molecular, Universidade de Lisboa, Lisbon, Portugal, [7]Institute of Rheumatology, Prague, Czech Republic, [8]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [9]Université Paris-Sud, Le Kremlin Bicêtre, France, [10]DANBIO, Center for Rheumatology and Spine Diseases, Glostrup Univ Hospital, Glostrup, Denmark, [11]Strasbourg University Hospital, Strasbourg, France.

Background/Purpose: Some observations have suggested that the effectiveness of abatacept (ABA) may be decreased in rheumatoid arthritis (RA) patients (pts) who previously failed rituximab (RTX).(1) The objective of this study was to compare the effectiveness of ABA started after prior inadequate response (IR) to RTX (RTX-IR) versus prior IR to anti-TNF agents only (aTNF-IR) in routine care.

Methods: This is a pooled observational database analysis of 9 prospective registries of RA pts (Czech Republic, Denmark, France, Italy, Norway, Portugal, Spain, Sweden, Switzerland). We included all RA pts treated with ABA with information on prior use of specific bDMARDs and who experienced either a RTX-IR or a aTNF-IR. The primary outcome was drug retention of ABA, defined as the time between first and last administration plus one dispensation interval, and analyzed using a Cox proportional hazards model. A secondary endpoint was EULAR good or moderate response rate at one year, estimated by longitudinal interpolation and corrected for drug retention (Lundex(2)). All analyses were adjusted for potential confounders, such as calendar year, demographics, country, number of prior bDMARDs and other disease characteristics.

Results: We identified 1994 pts initiating ABA with 3105 pt-years of follow-up. Of these, 486 pts (24%) received ABA after failing RTX and 1508 pts (76%) after failing > 1aTNFs, but never RTX. RTX-IR pts had significantly higher disease activity at baseline, longer disease duration, more functional disability, more prior bDMARDs and used more concomitant glucocorticoids than had aTNF-IR pts. (Table)

Baseline characteristics*	RTX-IR (N=486)	aTNF-IR (N=1508)	p-value
Age, (yrs)	57	57	0.08
Female, (%)	84	82	0.41
DAS28	5.2	4.9	<0.001
Dis. Duration (yrs)	13.9	12.1	<0.001
HAQ	1.4	1.2	<0.001
BMI	26	26	0.91
CRP (mg/L)	24.8	22.7	0.11
ESR (mm/1h)	34	32	0.25
RF+, (%)	70	74	0.10
N° prior bDMARDs, med (IQR)	3[2–4]	2[1–2]	<0.001
Oral Glucocorticoid use, (%)	74	59	<0.001

* Values are the means, unless stated otherwise

The crude median retention time of ABA after RTX-IR was 1.65 y (IQR: 1.42 – 2.13) compared to 2.05 y (IQR: 1.87 – 2.27) after aTNF-IR (p = 0.11). After adjustment for potential confounders no difference between ABA retention rates was found (Hazard Ratio (HR) RTX-IR vs aTNF-IR: 1.00 (95%CI: 0.83 – 1.21)). Similar results were found when examining only ABA treatment discontinuations due to ineffectiveness (HR: 1.04 (95%CI: 0.84 – 1.29)). However, response rates at one year were slightly lower in pts with RTX-IR compared to pts with aTNF-IR (73% EULAR good or moderate responses versus 83% in aTNF-IR (p=0.001); Lundex-adjusted EULAR good or moderate response 45% versus 56% in aTNF-IR, p=0.003, respectively).

Conclusion: The results of this large pooled RA population of inadequate responders to bDMARDs suggest that the slightly decreased effectiveness of ABA in patients having experienced a RTX-IR may be largely driven by a selection of pts with more treatment refractory disease.

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A Structured Approach for Comparative Benefit-Risk Assessment of Rituximab for the Treatment of Rheumatoid Arthritis. Ani John[1], George Quartey[1], Patricia B. Lehane[2], Nicole Mairon[3], Michael Schulte[3], Ashwini Shewade[1], Carol Chung[1] and Dominic Borie[1]. [1]Genentech, Inc, South San Francisco, CA, [2]Roche Products Ltd, Welwyn Garden City, United Kingdom, [3]F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Background/Purpose: Rituximab in combination with methotrexate (MTX) is indicated for the treatment of adult patients with moderate to severe active rheumatoid arthritis (RA) who have an inadequate response to tumor necrosis factor therapies (TNF-IR). A structured systematic assessment of a drug's benefit-risk profile is useful to inform decisions at each developmental milestone, and could meaningfully inform multiple stakeholders, physicians, patients, payors and researchers on the trade-offs between benefits and risks during the lifecycle of a drug product. The objective of this post-hoc analysis

was to apply a structured descriptive approach to compare the benefit-risk profile of rituximab from the REFLEX 24-week placebo (PBO)-controlled trial and to produce a graphical representation of this profile in TNF-IR patients with RA.[1]

Methods: Presentations of data were based on the Benefit Risk Assessment Tool Framework developed for pharmaceutical benefit-risk decision-making in drug development and post-approval settings.[2,3] Key benefits and risks of rituximab were identified and organized in a hierarchical manner to construct a 'value tree' as a basis for potential treatment benefits and risks. Absolute differences in efficacy outcome measures and safety event rates between (rituximab+MTX) and (PBO+MTX) treated patients were calculated to summarize key benefit-risk metrics and then presented graphically in a descriptive manner.

Results: Key benefits of rituximab treatment in TNF-IR patients identified included measures of clinical response (ACR and EULAR response and DAS28-ESR) and patient-oriented outcomes (Health Assessment Questionnaire Disability Index [HAQ-DI]). Safety assessments included rates of overall adverse events (AEs), serious AEs, all infections and serious infections. Mean (95% CI) efficacy differences and adverse event rate differences between the rituximab and PBO arms of the 24-week trial were calculated and displayed in the **Figure**. Overall, patients receiving rituximab treatment demonstrated meaningful clinical and statistically significant improvement compared with PBO in ACR20/50/70 response rates, EULAR response rates, DAS28-ESR and HAQ-DI, with no meaningful differences in safety events including serious AEs and infections.[1]

Conclusion: A graphical representation of key benefits and risks was generated to present the positive benefit-risk profile of rituximab in TNF-IR patients with RA. Future applications of this structured approach could include interpretation of the benefit-risk profile of longer term outcomes and of subpopulations of patients with RA receiving rituximab or a similar structured assessment of other drugs in a consistent manner.

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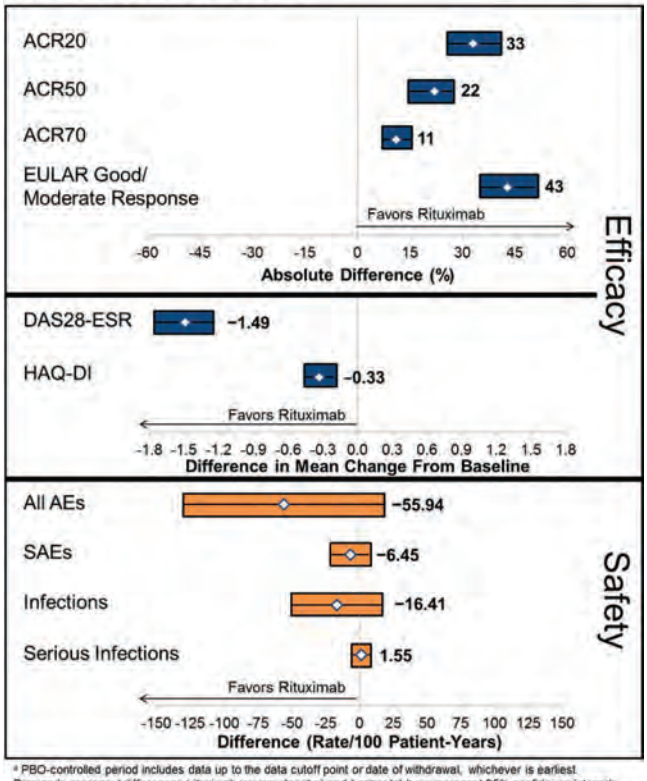
Figure. Comparative Benefit-Risk Plot of Efficacy and Adverse Event Rate Differences (95% CI) Between Rituximab and PBO in the 24-Week PBO-Controlled Period[a] of the REFLEX Trial



[a] PBO-controlled period includes data up to the data cutoff point or date of withdrawal, whichever is earliest. Diamonds represent differences (rituximab versus placebo) and horizontal bars represent 95% confidence intervals. ACR, American College of Rheumatology; AEs, adverse events; DAS28-ESR, Disease Activity Score in 28 joints using erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire Disability Index; PBO, placebo; SAEs, serious adverse events.

Disclosure: A. John, Genentech, Inc, 3; **G. Quartey**, Genentech, Inc, 3; **P. B. Lehane**, Roche Products Ltd, 3; **N. Mairon**, F. Hoffmann-La Roche Ltd, 3; **M. Schulte**, F. Hoffmann-La Roche Ltd, 3; **A. Shewade**, Genentech, Inc, 3; **C. Chung**, Genentech, Inc, 3; **D. Borie**, Genentech, Inc, 3.

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Trial of Six Weeks Interval of Tocilizumab Infusion in Patients with Rheumatoid Arthritis. Osamu Saiki, Hiroshi Uda and Koji Shigematsu. Higashiosaka City General Hospital, Higashiosaka, Japan.

Background/Purpose: For active rheumatoid arthritis (RA) patients with inadequate response to synthetic DMARDs, biologic agents, such as TNF inhibitor and IL-6 receptor inhibitor, are indicated. However, all biologics are very expensive, and, therefore all patients with high disease activities always can not receive biologics. Indeed, the interval of administration is fixed in most of biologics, but the interval is flexible in some biologics such as etanercept and infliximab. Tocilizumab (TCZ) is one of useful biologics, and the interval of TCZ infusion is fixed for 4 weeks. In the course of treating active RA patients by TCZ with 4 weeks interval, sometimes we experienced that longer interval was also effective. In preliminary study, we found that six weeks interval was effective in these patients. The present study is carried out to clarify the efficacy of six weeks interval of TCZ infusion in the patients with active RA.

Methods: The patients who showed inadequate response to DMARDs and the patients who showed inadequate response to biologics other than TCZ and who agreed with TCZ therapy of six weeks interval were enrolled in the present study. In addition to oral medicines, the patients were infused 8mg/kg of tocilizumab in every six weeks (SIWETO study). The clinical assessments and blood tests were also carried out in every 6 weeks. To the patients who did not achieve clinical remission by 6 weeks interval of TCZ, prednisolone (PSL) and/or methotrexate were added with increasing the dose. The patients who achieved clinical remission in 12 months were estimated as responder and others were as non-responders. We followed up the patients at least for 3 years.

Results: Total of 74 patients was enrolled in the present study. Male and female were 18 and 56 respectively. Forty-four patients achieved clinical remission with 6w interval, and the rest of the patients were non-responder. To the patients who did not achieve clinical remission with 6w interval, TCZ infusion with 5w or 4w interval was carried out. Nineteen patients achieved clinical remission by 5w interval and four patients by 4w interval, respectively. The rest of 7 patients could not achieve clinical remission by TCZ infusion. In 44 patients who achieved clinical remission with 6w interval of TCZ infusion, 10 patients were treated by TCZ alone without any oral medicines for rheumatoid arthritis and kept the condition throughout the observation and the rest of patients received either or both PSL (1 to 7.5 mg) and MTX (2 to 8mg). It is generally accepted in Japanese rheumatologist that the effective dose of MTX in Japanese is lower than that in Caucasian. Severe adverse events including tuberculosis and death were not found. The frequency of other adverse events of 6w interval of TCZ was less than those of regular use (4w interval).

Conclusion: The SIWETO study provides evidence that 6w interval of TCZ infusion is also effective in active rheumatoid arthritis patients. The finding of SIWETO study is quite useful for taking care of active rheumatoid arthritis patients, especially in financial aspects. The cost of 6 weeks interval of TCZ became two thirds of that of 4 weeks regular use.

Disclosure: O. Saiki, None; **H. Uda**, None; **K. Shigematsu**, None.

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Efficacy and Safety of Adalimumab Therapy in Japanese Patients with Rheumatoid Arthritis. Yosuke Hattori. National Hospital Organization Nagoya Medical, Nagoya, Japan.

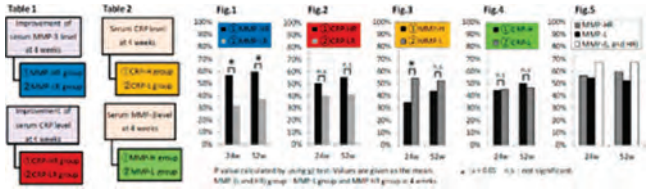
HIGH RATE OF IMPROVEMENT IN SERUM MATRIX METALLOPROTEINASE-3 LEVELS AT 4 WEEKS PREDICT REMISSION AT 52 WEEKS IN RA PATIENTS WITH ADALIMUMAB THERAPY

Background/Purpose: Serum Matrix metalloproteinase-3 (MMP-3) is a specific inflammatory marker of the synovium in patients with rheumatoid arthritis (RA). Our aim in this study is to investigate whether serum MMP-3 is the predictor for remission in treatment for RA patients with biologics.

Methods: All RA patients (n=269) who underwent Adalimumab (ADA) treatment in the multicenter study group (Tsurumai Biologics Communication Registry; TBCR) were enrolled in this study. We analyzed 114 patients in continuation with ADA therapy for 52 weeks. We divided into 2 groups based on the improvement of serum level of MMP-3 and CRP: high rate of improvement (MMP-HR group) and low rate of improvement (MMP-LR group) in serum MMP-3 levels at 4 weeks.and: high rate of improvement (CRP-HR group) and low rate of improvement (CRP-LR group) in serum CRP levels at 4 weeks (Table1). We also divided into 2 groups based on the serum level of MMP-3 and CRP: high value (MMP-H group) and low value (MMP-LR group) in serum MMP-3 levels at 4 weeks, and: high value (CRP-H group) and low value (CRP-L group) in serum CRP levels at 4 weeks (Table2). We evaluated the rate of remission at 24, and 52 weeks in 2 groups.

Results: In patients continuing at 52 weeks, the rate of remission at 24 and 52 weeks in MMP-HR group is 56% and 60%, and MMP-LR group is 32% and 37%. The rate of remission at 24 and 52 weeks in MMP-HR group is significantly higher than in MMP-LR group (Fig.1). However, the rate of remission at 24 and 52 weeks had no significance in CRP-HR group and CRP-LR group (Fig.2).The rate of remission at 24 and 52 weeks in MMP-H group is 35% and 44%, and MMP-L group is 55% and 53%. The rate of remission at 24 weeks in MMP-L group is significantly higher than in MMP-H group (Fig.3). However, the rate of remission at 24 and 52 weeks had no significance in CRP-H group and CRP-L group (Fig.4). Moreover, the rate of remission at 24 and 52 weeks in MMP-(L and HR) group is very high (Fig.5). In patients continuing at 52 weeks, the best cut-off rate of improvement in MMP-3 at 4 weeks for determining remission at 52 weeks was 40% determined by ROC analysis (sensitivity: 47%, specificity: 83%, accuracy: 64%).

Conclusion: We considered that high rate of improvement in serum MMP-3 at 4 weeks can be useful for predicting the remission at 52 weeks in RA patients with ADA therapy.



Disclosure: Y. Hattori, None.

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Relationship Between NK Cell Count and Important Safety Events in Rheumatoid Arthritis Patients Treated with Tofacitinib. R. van Vollenhoven[1], Y. Tanaka[2], R. Riese[3], M. Lamba[3], T. Kawabata[3], T. Hirose[4], S. Toyoizumi[4], A. Hazra[3] and S. Krishnaswami[3]. [1]The Karolinska Institute, Stockholm, Sweden, [2]University of Occupational and Environmental Health, Kitakyushu, Japan, [3]Pfizer Inc, Groton, CT, [4]Pfizer Inc, Tokyo, Japan.

Background/Purpose: Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Cytokines (e.g. interleukin [IL]-2, -4, -7, -15, -21) involved in lymphocyte development, function and homeostasis are known to signal through JAK. Objectives were to characterize changes in natural killer (NK) cell counts following tofacitinib treatment and evaluate the relationship between NK counts and rates of infection and malignancy.

Methods: Lymphocyte subset data, enumerated by flow cytometric analyses, were pooled from 3 double-blind, placebo-controlled, Phase 2 (P2) studies (two monotherapy and one background methotrexate [MTX]) in MTX inadequate responders, and from a sub-study of an ongoing long-term extension (LTE) study (study is ongoing; database not locked). RA patients (pts) received tofacitinib (1 to 30 mg twice-daily [BID]) or placebo for 6 to 24 weeks in P2 and tofacitinib 5 or 10 mg BID for 22 months (median) in LTE. 928 and 161 pts contributed NK cell data in P2 and LTE, respectively. Correlations between baseline or nadir NK cell count and serious infection (SIE, any infection that requires hospitalization for treatment or parenteral antimicrobial therapy), herpes zoster (HZ) and malignancy (excluding non-melanoma skin cancer) were assessed by sub-dividing NK cell data into deciles and calculating incidence rate (events/100 pt years) of adverse events for each decile.

Results: Following tofacitinib administration, NK cell counts decreased in a dose-dependent manner by Week 2 (Figure 1). Median NK cells counts returned to baseline 2 to 6 weeks after treatment discontinuation (dc). At the 5 mg BID dose, pts with the largest (>90th percentile) decrease in NK cell counts recovered from ~70% below baseline to ~18% by 6 weeks after treatment dc (n=4). The estimated median decrease for 5 mg BID at Week 24 was ~35%. Cross-sectional analyses in different groups of pts showed similar median NK cell count in the LTE (141 cells/μL) compared to pre-treatment baseline (135 cells/μL). No clear association between baseline or nadir NK cell counts (predominantly collected within first 6 months of treatment) and the incidence of SIE, HZ or malignancy (Figure 2) was seen over the period of observation (median duration 1.9 years).

Conclusion: Tofacitinib treatment is associated with a dose-dependent decrease in NK cell counts. No association between baseline or nadir NK cell counts and the incidence of SIE, HZ or malignancy was observed. Long-term lymphocyte subset data are being collected in the ongoing LTE study to confirm these relationships.

Figure 1: Time course of NK cell counts in Tofacitinib or Placebo Treated RA Patients

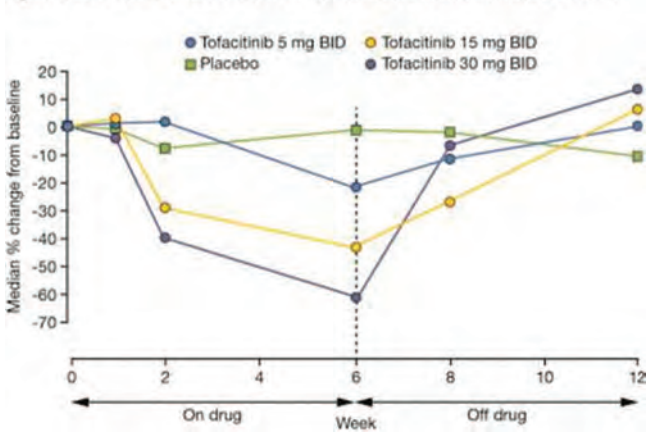
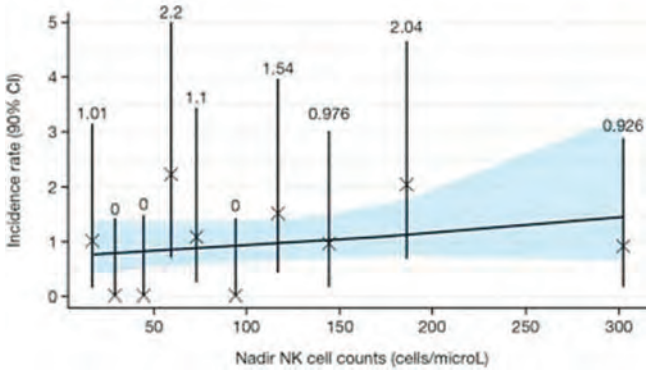


Figure 2: Lack of correlation between NK cell counts and Malignancy excluding non-melanoma skin cancer



Disclosure: R. van Vollenhoven, Pfizer Inc, 2, Pfizer Inc, 5; **Y. Tanaka**, Abbvie, Chugai, Astellas, Takeda, Santen, Mitsubishi Tanabe, Pfizer, Janssen, Eisai, Daiichi-Sankyo, UCB Japan, GlaxoSmithKline, and Bristol-Myers-Squib, 5, Abbvie, Chugai, Astellas, Takeda, Santen, Mitsubishi Tanabe, Pfizer, Janssen, Eisai, Daiichi-Sankyo, UCB Japan, GlaxoSmithKline, and Bristol-Myers-Squib, 8, Abbvie, Chugai, Astellas, Takeda, Santen, Mitsubishi Tanabe, Pfizer, Janssen, Eisai, Daiichi-Sankyo, UCB Japan, GlaxoSmithKline, and Bristol-Myers-Squib, 9; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3; **M. Lamba**, Pfizer Inc, 1, Pfizer Inc, 3; **T. Kawabata**, Pfizer Inc, 1, Pfizer Inc, 3; **T. Hirose**, Pfizer Japan Inc, 1, Pfizer Japan Inc, 3; **S. Toyoizumi**, Pfizer Japan Inc, 3; **A. Hazra**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Krishnaswami**, Pfizer Inc, 1, Pfizer Inc, 3.

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Etanercept Have Better Drug Survival Than Monoclonal Antibodies in Rheumatoid Arthritis: Results of Single Center Hur-BIO Registry. Umut Kalyoncu[1], Murat Torgutalp[2], Hakan Babaoglu[2], Sadettin Kilickap[2], Sedat Kiraz[3], Ali Akdogan[1], Omer Karadag[1], Abdulsamet Erden[2],

Sule Apras Bilgen[2] and Ihsan Ertenli[1]. [1]Hacettepe University Faculty of Medicine, Ankara, Turkey, [2]Hacettepe University, Faculty of Medicine, Ankara, Turkey, [3]Hacettepe Unv.Tip Fakultesi-Romatoloji Servis, Ankara, Turkey.

Etanercept have better drug survival than monoclonal antibodies in Rheumatoid Arthritis: Results of single center HÜR-BÝO registry

Background/Purpose: In routine practice, observational registries may show retention rates of TNFi drugs in rheumatoid arthritis (RA). The objective of this study was to compare TNF inhibitors regarding the drug survival rate in RA patients.

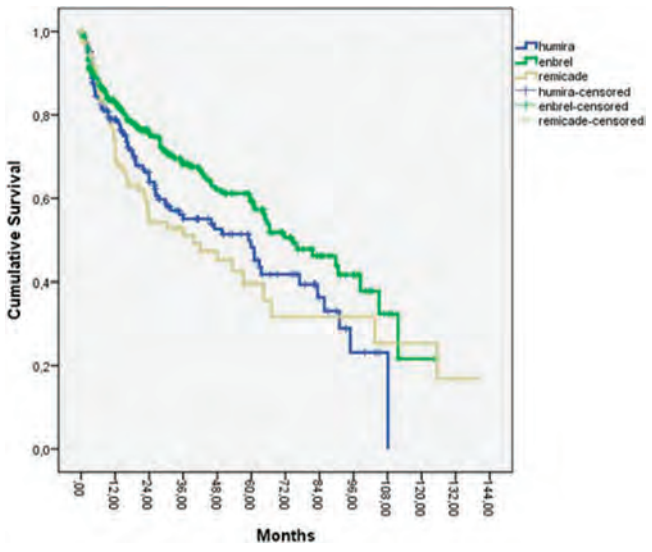
Methods: HÜR-BIO (Hacettepe University Rheumatology Biologic Registry) is a single center biological registry since 2005. Data collected includes demographic data, switch ratio, baseline and follow-up disease activity parameters (if available). Patients with regularly follow-up status were recorded systematically. Patients with lost of follow-up searched regarding to last TNFi prescription date either local computer system or national social security institution database. Inition and last date of TNFi were noted from those systems. First TNFi drug switch date (either advers event or inefficacy) was accepted as main variable for drug survival. Kaplan-Meier plots and log rank tests were used to assess drug survival. HÜR-BIO is not sponsored by any pharmaceutical company.

Results: HÜR-BIO includes 815 RA patients, however 156 of 815 patients excluded because of other biological agents such as rituksimab, abatecept and golimumab. Of 659 patients 77,7% was female. Mean age was 50±13 years and mean disease duration was 11±8 years. TNFi drug duration was 3,2±2,8 years and 176 (26,7%) patients were used TNFÝ drugs more than 5 years. Positive ACPA and RF were 216/356 (60,6%) and 353/601 (58,7%), respectively. First TNFi drugs were etanercept 321 (48,7%), adalimumab 223 (33,8%) and infliximab 115 (17,5%). TNFi switch was found in 246 (37,3%) patients. Patients were divided as regularly follow-up (either first biological drugs or another biological drugs) 487 (73,9%), lost of follow-up 114 (17,3%), drug cessation 35 (5,3%), exitus 15 (2,3%) and not first control performed 8 (1,2%). Patients with etanercept had better drug retention than monoclonal antibodies (log rank p=0.014), figure 1.

Conclusion: In this single center observational registry, etanercept had better drug retention rate than monoclonal antibodies. Our result is similar with another registry such as DANBIO (1). On the other hand, certain confounder factors such as baseline disease activity, functional status, socioeconomic status were not known in whole patients, thus our results should evaluate in this limitation.

Reference

1. Arthritis Rheumatism 2010;62:22–32.



Disclosure: U. Kalyoncu, None; **M. Torgutalp**, None; **H. Babaoglu**, None; **S. Kilickap**, None; **S. Kiraz**, None; **A. Akdogan**, None; **O. Karadag**, None; **A. Erden**, None; **S. Apras Bilgen**, None; **I. Ertenli**, None.

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Similar Short Term Survival on Drug for Patients with Rheumatoid Arthritis Treated with Subcutaneous and Intravenous Abatacept - Results from the National Swedish Rheumatology Quality Register. Carl Turesson[1], Leszek Stawiarz[2], Staffan Lindblad[2] and Saedis Saevarsdottir[3]. [1]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Department of Medicine, Karolinska institutet and Karolinska University Hospital, Stockholm, Sweden.

Background/Purpose: Abatacept is a biological anti-rheumatic drug used in Rheumatoid Arthritis (RA). Data on patient characteristics, diagnosis, previous treatment and outcomes of abatacept have been collected in the Swedish Rheumatology Quality register (SRQ) which comprises the Swedish Biologics (ARTIS; Arthritis Treatment In Sweden) register, since the drug was approved in 2006. In early 2013, subcutaneous treatment with abatacept became available. The objective of this study was to investigate baseline characterstics and drug survival probability in clinical practice for patients with RA treated with subcutaneous (sc) vs. intravenous (iv) abatacept, using a national register.

Methods: Observational data from the SRQ for the period when both iv and sc abatacept were available, January, 2013 to May 20, 2014, were obtained. Kaplan-Meier survival analysis with right censoring and log-rank test of equality across strata were performed and Šidák multiple-comparison adjustments applied.

Results: A total of 371 patients with RA were started on their first treatment with abatacept during the study period (252 with sc administration and 119 with iv treatment). Age (mean 58.7 vs 59.7 years), RA duration at treatment initiation (median 12.8 vs 13.2 years) and sex distribution (79 % vs 81 % women) were similar in the two groups, and there was no major difference in baseline disease activity (DAS28; mean 5.10 vs. 4.98). Among those receiving sc treatment, 21 % were bio-naïve, 26 % had previously been exposed to one biologic drug, and 53 % to ≥ 2 biologics. The corresponding figures among those treated with iv abatacept were 17%/ 30%/ 53 %. There was no significant difference in the survival on drug for those on sc, compared to iv treatment (p=0.19). The estimated survival rates at 6 months were 76 % (sc) and 81 % (iv). Furthermore, there were no significant differences in drug survival in analyses stratified by previous exposure to biologics (p=0.73 for bio-naïve patients, p=0.19 for those with 1 previous biologic, and p=0.32 for those with ≥ 2 previous biologics).

Conclusion: In this observational study of a real-life national cohort, the majority of patients with RA started on abatacept since the subcutaneous administration form became available received that form of treatment. There were no major differences in baseline characteristics or short term survival on drug between patients treated with subcutaneous or intravenous abatacept. This supports clinical trials that have demonstrated similar efficacy and safety for the two routes of administration of abatacept.

Disclosure: C. Turesson, Unrestricted research grants from Abbvie, Pfizer and Roche, 2, Abvisory Boards: Bristol-Myers Squibb, MSD, Pfizer, Roche, 5; **L. Stawiarz**, None; **S. Lindblad**, None; **S. Saevarsdottir**, None.

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First and Second Line Continuation Rates of Non Anti-TNF-α Biological DMARD for the Treatment of Rheumatoid Arthritis. Tristan Pascart[1], Rene-Marc Flipo[2], Xavier Deprez[3] and Eric Houvenagel[4]. [1]Saint-Philibert Hospital, Lille, France, [2]University Hospital Lille, Lille, France, [3]Ch De Valenciennes, Valenciennes, France, [4]Saint-Philibert Hospital, LOMME, France.

Background/Purpose: The 2013 update of the EULAR recommendations for the management of RA with synthetic and biological DMARDs set non-anti-TNF- α as first-line biological treatments. Yet, available data regarding treatment after rituximab, abatacept and tocilizumab failure is weak. The objective of this study was to compare continuation rates of second line non-anti-TNF- α treatments after a first non-anti-TNF- α failure.

Methods: This retrospective multicentre study included patients treated for RA with rituximab, abatacept or tocilizumab after having received in a previous line abatacept, tocilizumab or rituximab from 2002 to 2013. Data were collected from patients' file including baseline and final DAS28-ESR and DAS28-CRP for both lines of treatment, motives for treatment introduction and discontinuation. Follow-up of the second line of treatment was one year. The primary endpoint was the continuation rate at the end of the first year of treatment.

Results: A total of 100 patients were included. Patients had previously received an average of 2.6 (+/− 0.9) biological DMARDs. Patients were aged 55.4 (+/− 11.5) years and disease duration was 14.3 (+/− 9.4) years. In first line, 29 patients were treated with tocilizumab, 26 with abatacept and 45 received rituximab. In second line of treatment, 49 patients were treated with abatacept, 36 received tocilizumab and 15 rituximab. Methotrexate was associated in 36% of cases. The first line of treatment was continued for 15.6 (+/− 14.4) months. At baseline, DAS28-ESR was 5.57 (+/− 1.19) and DAS28-CRP was 5.25 (+/− 1.15) for the first line and DAS28-ESR was 5.00 (+/− 1.41) and DAS28-CRP was 4.84 (+/− 1.22) for the second line of treatment. Treatment continuation rates at the end of the first year was 45.9% in first line and 58.6% in second line of treatment (p=0.10). In patients without Methotrexate, continuation rates at the end of the first year was 37.5% for the first line of treatment and 64.3% in the second line (p=0.009). In the first line of treatment, 66.6% of patients that interrupted their treatment for a reason of intolerance in the first year of treatment versus 15.5% in the second line of treatment.

Conclusion: After a first non-anti-TNF- α biological DMARD failure, continuation rates at one year are similar in the second line of non-anti-TNF-α treatment. Association to Methotrexate does not seem to bring any benefits in the second line of treatment.

Disclosure: T. Pascart, None; **R. M. Flipo**, Roche Pharmaceuticals, 5, Bristol-Myers Squibb, 5; **X. Deprez**, Roche Pharmaceuticals, 5, Bristol-Myers Squibb, 5; **E. Houvenagel**, Roche Pharmaceuticals, 5, Bristol-Myers Squibb, 5.

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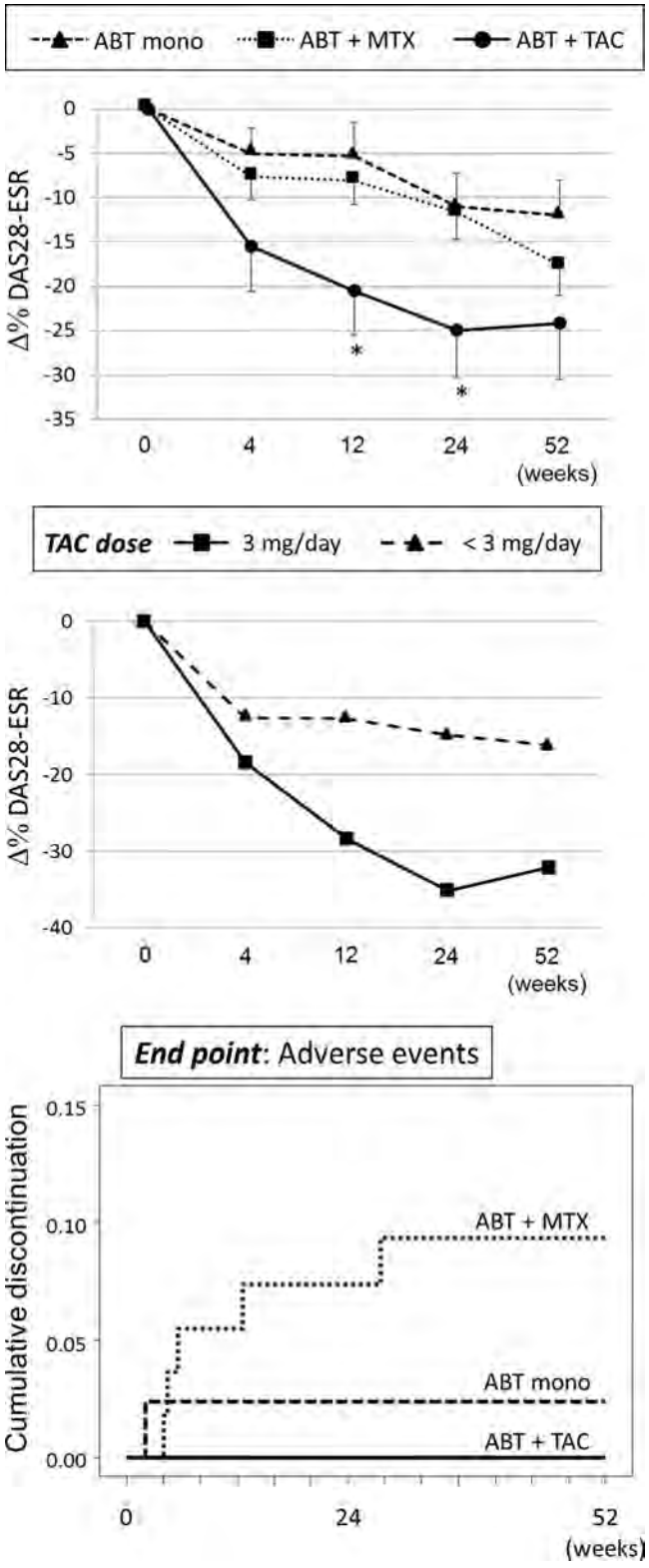
Effect and Safety of Concomitant Methotrexate and Tacrolimus on Clinical Response of Abatacept in Rheumatoid Arthritis Patients with Prior Use of Biological Dmards. Nobunori Takahashi[1], Toshihisa Kojima[1], Yuji Hirano[2], Yasuhide Kanayama[3], Koji Funahashi[1] and Naoki Ishiguro[1]. [1]Nagoya University Graduate School of Medicine, Nagoya, Japan, [2]Toyohashi Municipal Hospital, Toyohashi, Japan, [3]Toyota Kosei Hospital, Toyota, Japan.

Background/Purpose: Abatacept (ABT) is a new class of biologic agents for the treatment of rheumatoid arthritis (RA) that inhibits T cell activation by binding to CD80/86. It has been reported that ABT was less effective in the patients with previous biological DMARDs and concomitant MTX had only little enhancing effect on ABT efficacy. Tacrolimus (TAC) was approved in Japan for the treatment of RA (oral dosage of ≤ 3 mg/day). It down-regulates the synthesis of inflammatory cytokines activated by T cells mainly via inhibition of a calcineurin. In this study, we investigated whether concomitant TAC had enhancing effect on ABT efficacy in the patients with previous biological DMARDs, using data from a Japanese multicenter registry system (TBCR).

Methods: The present study included all patients who had previous biological DMARDs and were initiated intravenous ABT and prospectively observed for longer than 52 weeks at TBCR-affiliated institutes (n = 121). Demographic data and the following parameters of disease activity were collected; tender joint count (TJC) and swollen joint count (SJC), patient global assessment (VAS), ESR, and serum CRP at baseline, 4, 12, 24, and 52 weeks. We compared these clinical data between the patients treated without concomitant MTX or TAC (ABT-mono, n=42), those treated with concomitant MTX (ABT-MTX, n=56), and those treated with concomitant TAC (ABT-TAC, n=18). The last observation carried forward (LOCF) method was used in each analysis.

Results: In the baseline characteristic data, the ABT-mono group had higher pulmonary comorbidity rate (23.8%, p = 0.030) compared to the ABT-MTX (5.4%) and ABT-TAC (16.7%) group while no other clinical parameters showed significant difference including all disease activity indices such as DAS28-ESR (5.10, 5.30, and 5.30, p = 0.949). The ABT-TAC group demonstrated significantly lower f¢% of DAS28 score compared to the ABT-mono group while no difference between the ABT-mono and ABT-MTX group (Left panel). The patients taking 3 mg/day dosage of TAC demonstrated apparently lower f¢% of DAS28 score compared to those taking < 3 mg/day (Middle panel). Kaplan-Meier analysis demonstrated that the ABT-MTX group showed significantly higher discontinuation rate due to adverse events compared to the ABT-mono group while no difference between the ABT-TAC and ABT-mono group (Right panel).

Conclusion: We clearly demonstrated that concomitant TAC treatment had dose-dependent enhancing effect on the ABT efficacy, while there seemed to be little combinational effect of ABT and MTX. Since both ABT and TAC are the agents targeting T cells, there is concern regarding safety issue when used in combination. However, in our results, the ABT-TAC group did not show increased discontinuation due to adverse events. We would suggest that combination of ABT and TAC treatment should be helpful when we treat the patients with previous biological DMARDs history.



Disclosure: N. Takahashi, Abbott Japan Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Co. Ltd, Chugai Pharmaceutical Co. Ltd., and Bristol-Myers Squibb Co. Ltd., 8; **T. Kojima**, Takeda Pharma Corporation, Janssen Pharmaceutical, and Astellas Pharma Corporation., 2, Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Eisai Pharma Corporation, Abbvie, Bristol-Myers Squibb, Pfizer and Chugai Pharma Corporation, 8; **Y. Hirano**, Abbott Immunology Pharmaceuticals,

8, Mitsbishi-Tanabe Pharma, 8, Pfizer Inc, 8, Eisai, 8, Chugai, 8, Bristol-Myers Squibb, 8, Astellas Pharma, 8; **Y. Kanayama**, Astellas Pharma, 8, Eisai, 8, Mitsubishi Tanabe Pharma Corporation, 8, AbbVie Inc, 8, Chugai, 8; **K. Funahashi**, Abbott Japan Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Co. Ltd, Chugai Pharmaceutical Co. Ltd., and Bristol-Myers Squibb Co. Ltd., 8; **N. Ishiguro**, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 5, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 8.

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Analysis of Shoulder Joint Destruction in Rheumatoid Arthritis Patients Treated with Biologics. Yukio Yonemoto, Koichi Okamura, Tetsuya Kaneko, Chisa Okura and Kenji Takagishi. Gunma University Graduate School of Medicine, Maebashi, Japan.

Background/Purpose: The assessment of joint destruction in rheumatoid arthritis (RA) patients being treated with biologics is normally mainly carried out for small joints. There are a few reports that have so far assessed joint destruction of large joints, and no reports that assess joint destruction of the shoulder joint. The aim of this study was therefore to assess the risk factors for shoulder joint destruction in RA patients being treated with biologics based on the findings of both the magnetic resonance imaging (MRI) and 18F-fluorodeoxy glucose positron emission tomography (PET).

Methods: Twenty-nine shoulders (5 male shoulders, 25 female shoulders; 16 right shoulders, 14 left shoulders) in 30 patients with RA were assessed using PET and MRI before starting biologics and then again six months later. The mean age (range) was 54 (18–72) years and the mean disease duration was 7 (0.8–30) years. The XP findings were assessed before starting biologics and then again three years later. The CRP, ESR and MMP-3 levels, and the DAS28-ESR, DAS28-CRP, CDAI and SDAI scores were also assessed. We compared these parameters between the progression of joint destruction group (P group) and the no progression group (N group).

Results: The SUV max, the rates of synovitis and the rates of rotator cuff tear on MRI before biologics treatment were significantly higher in the P group than in the N group. The SUV max and synovitis detected by MRI after biologics were also significantly higher in the P group. The CRP, ESR and MMP-3 levels and disease activity showed no significant differences between the two groups. RA patients who had severe joint destruction (Larsen grade ≧ III) before starting biologics demonstrated a significantly greater progression of shoulder joint destruction than the patients who had mild joint destruction (Larsen grade ≦ II) before starting biologics.

Conclusion: The detection of synovitis by PET or MRI is thus considered to be more important than the disease activity and serum inflammation markers when assessing the potential for a progression of shoulder joint destruction. In addition, a previous history of joint destruction and rotator cuff tears is also an important factor for the evaluation of shoulder joint destruction in RA patients.

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Methotrexate Reduces the Frequency of Prediabetes in Patients with Rheumatoid Arthritis or Psoriatic Arthritis. Katja Perdan-Pirkmajer[1], Sergej Pirkmajer[2], Alojzija Hocevar[1], ŽIga Rotar[1], Natasa Gaspersic[1], Sonja Praprotnik[1], Matija Tomsic[3] and Ales Ambrozic[1]. [1]University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]Faculty of Medicine Ljubljana, Ljubljana, Slovenia, [3]University Medical Centre Ljubljana, Ljubljana, Slovenia, Ljubljana, Slovenia.

Background/Purpose: Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are associated with an increased risk of diabetes mellitus (DM). Disease-modifying anti-rheumatic drugs, including methotrexate (MTX), may exert protective metabolic effects conducive to reduced incidence of DM. Whether MTX mitigates metabolic risk factors in non-diabetic RA and PsA patients has not been determined unequivocally. In this study we assessed metabolic parameters in RA or PsA patients during the first six months of MTX therapy.

Methods: Newly diagnosed, MTX-naïve RA (2010 ACR/EULAR criteria) and PsA (CASPAR criteria) patients were included between December 2012 and June 2013. Patients with DM or hypothyroidism were excluded. The initial assessment included DAS28ESR, BMI, fasting plasma glucose and insulin, HbA_{1c}, TSH, triglycerides, HDL, LDL and urate. Disease activity and the metabolic parameters were followed 1, 2, 3 and 6 months after MTX initiation. Uninterrupted MTX treatment with dose escalation according to the treat to target approach was required. HOMA-IR (glucose (mM) × insulin (μU/ml)/22.5), HOMA-B (20 × insulin (μU/ml)/[glucose (mM)-3.5]) and QUICKI ($[\log_{10}$glucose (mg/dl) + $\log_{10}$insulin (μU/ml)$]^{-1}$) were used as surrogate indices of insulin sensitivity and β-cell function. ANOVA or the Kruskal-Wallis test, followed by an appropriate *post hoc* test was used to establish statistical significance.

Results: Inclusion criteria were fulfilled by 16 RA and 10 PsA patients (16 female, 10 male). Mean age was 52.5±12.2 (range: 27–76), BMI 28.4±4.8 kg/m^2 (range: 19.7–39.4) and the initial DAS28ESR 5.23±1.27 (range: 2.95–7.71). Eighteen patients had prediabetes according to the American Diabetes Association criteria (HbA_{1c}: 5.7–6.4%), while 11 patients had insulin resistance as assessed by HOMA-IR (>2.5). After six months of MTX (±methylprednisolone) therapy remission or low disease activity (DAS28ESR<3.2) was achieved in 76%. BMI, fasting plasma glucose, insulin, triglyceride, cholesterol or urate levels remained unaltered. Conversely, HbA_{1c} (%) decreased in a time-dependent manner from the baseline value of 5.80±0.29% to 5.55±0.31% (n=26, P=0.017) at 6 months. HbA_{1c} (%) was reduced in 17 out of 26 patients. The decrease in HbA_{1c} (%) was especially pronounced in patients without insulin resistance at inclusion (5.82±0.35% vs. 5.42±0.32%, P=0.013, 12 out of 14 patients). Overall, the number of patients with prediabetes was reduced from 18 to 8. HOMA-IR, HOMA-B and QUICKI remained unaltered in patients receiving MTX or MTX and methylprednisolone, indicating co-therapy with methylprednisolone did not impair insulin sensitivity.

Conclusion: MTX reduces serum HbA_{1c} in non-diabetic RA or PsA patients during the initial 6 months of treatment. As assessed by HbA_{1c} MTX also reduces the prevalence of prediabetes, consistent with the notion that MTX protects against the development of DM. According to recent data HbA_{1c} is not only an established predictor of CV risk in diabetic patients, but also an independent CV risk predictor in non-diabetics. Taken together, our findings support a possible role of MTX in reducing DM and CV risk in RA as well as PsA patients.

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Dosing of Intravenous Tocilizumab in a Real-World Setting—Analyses from a US RA Registry. Dimitrios A. Pappas[1], Ani John[2], Jeffrey R. Curtis[3], George W. Reed[4], Chitra Karki[5], Robert Magner[6], Joel M. Kremer[7], Ashwini Shewade[2] and Jeffrey D. Greenberg[5]. [1]Columbia University, New York, NY, [2]Genentech, Inc, South San Francisco, CA, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Corrona, LLC., Southborough, MA, [5]Corrona, LLC, Southborough, MA, [6]University of Massachusetts Medical School, Worcester, MA, [7]Albany Medical College and The Center for Rheumatology, Albany, NY.

Background/Purpose: In the US, the recommended starting dose of intravenous tocilizumab (TCZ) in combination with DMARDs or as monotherapy is 4 mg/kg every 4 weeks and increased to 8 mg/kg based on clinical response for patients with moderate to severe rheumatoid arthritis (RA)[1]; however, data on actual dose escalation patterns are limited. The objective of this analysis was to evaluate how intravenous TCZ is dosed in a real-world setting using data from the Corrona registry.

Methods: All patients enrolled in the comparative effectiveness substudy (CERTAIN) nested within Corrona who initiated TCZ and had 3- and 6-month follow-up data available were eligible for inclusion in this analysis. Data were collected from patients who remained on their initial TCZ dose of 4 mg/kg at 3 months (Group 1) and patients who had their TCZ dose escalated to 8 mg/kg by or at 3 months (Group 2). Unadjusted efficacy response data were provided for patients at 3 and 6 months, including Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP), Clinical Disease Activity Index (CDAI), CRP, modified Health Assessment Questionnaire, patient pain, patient fatigue and EULAR response.

Results: Of the 196 patients included in this analysis, 56.1% (95% CI, 48.9% to 63.2%) escalated their TCZ dose by or at 3 months (Group 1, n = 86; Group 2, n = 110). Baseline characteristics were similar between dosing groups, except patients in Group 2 were older (58.3 vs 54.0 years) and a lower proportion were female (75.5% vs 89.4%) compared with patients in Group 1. At baseline, the mean (SD) CDAI was 32.4 (13.9) and 31.3 (12.9), mean (SD) DAS28-CRP was 5.1 (1.1) and 5.0 (1.2) and mean (SD) CRP was 10.4 (15.1) mg/L and 13.0 (20.2) mg/L in Group 1 and Group 2, respectively. The median (IQR) number of prior biologics was 2.0 (1.0, 4.0) and 2.0 (1.0, 3.0) in Group 1 and Group 2, respectively, suggesting a rather refractory disease. Unadjusted disease activity response outcomes at 3 months were mostly

similar between the 2 groups, except median (IQR) decrease from baseline in CRP was significantly greater in Group 2 vs Group 1 (−3.4 [-12.8, -0.8] mg/L vs -1.0 [-5.0, 1.0] mg/L; $P = 0.001$). At 6 months, efficacy outcomes remained similar between the 2 groups (**Table**); however, a numerically higher proportion of patients in Group 2 achieved EULAR good responses, CDAI low disease activity and DAS28-CRP low disease activity and remission vs Group 1, and median decrease from baseline to 6 months in CRP was significantly greater in Group 2 vs Group 1.

Conclusion: Real-world data show that physicians escalate the dose of TCZ at varying frequencies. In slightly more than one half of TCZ initiators in this refractory to therapy population, the TCZ dose was escalated by 3 months. The majority of patients in both groups achieved moderate or good EULAR response.

Reference:

1. ACTEMRA [Highlights of Prescribing Information]. South San Francisco, CA: Genentech, Inc; 2013.

Table. Summary of Efficacy at 6 Months by Dosing Pattern

Outcome	Group 1 - No Dose Escalation (n = 86)[a]	Group 2 - Dose Escalated (n = 110)	*P*-Value[b]
CDAI remission, n (%)	8 (9.30)	8 (7.55)	0.79
CDAI LDA, n (%)	29 (33.72)	37 (34.91)	0.88
CDAI MCID[c], n (%)	55 (67.90)	68 (67.33)	1.00
DAS28 remission, n (%)	14 (17.95)	28 (27.18)	0.16
DAS28 LDA, n (%)	21 (26.92)	41 (39.81)	0.08
EULAR response, n (%)			0.13
Good	16 (22.54)	33 (35.87)	
Moderate	30 (42.25)	28 (30.43)	
No response	25 (35.21)	31 (33.70)	
Median change from baseline to 6 months, median (IQR)			
CDAI	−14.0 (−23.0, −5.5)	−13.0 (−19.3, −5.2)	0.69
DAS28	−1.3 (−2.3, −0.7)	−1.7 (−2.4, −0.7)	0.36
CRP, mg/L	−1.7 (−7.9, 0.3)	−3.3 (−15.7, −0.8)	0.04
mHAQ	0.0 (−0.4, 0.0)	0.0 (−0.3, 0.0)	0.78
Patient pain (0–100)	−10.0 (−30.0, 5.0)	−10.0 (−35.0, 0.0)	0.64
Patient fatigue (0–100)	−10.0 (−25.0, 3.0)	−5.0 (−30.0, 5.0)	0.65

[a] Of the 86 patients in Group 1, 45 patients remained on TCZ 4 mg/kg throughout the 6-month period and 41 patients escalated their dose to 8 mg/kg by or at 6 months.
[b] *P*-values between groups were calculated using Fisher's exact test for categorical outcomes and the Wilcoxon Rank-Sum test for continuous outcomes.
[c] MCID is defined as a decrease in CDAI of 2 in patients with baseline CDAI < 10 (low disease), as a decrease in CDAI of 6 in patients with a baseline CDAI between 10 and 22 (moderate disease) and as a decrease in CDAI of 11 in patients with a baseline CDAI > 22 (high disease).
CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; EULAR, European League Against Rheumatism; IQR, interquartile range; LDA, low disease activity; MCID, minimal clinically important difference.

Disclosure: D. A. Pappas, Corrona, LLC, 3, Novartis, 9; **A. John**, Genentech, Inc, 3; **J. R. Curtis**, AbbVie, Amgen, BMS, Corrona, LLC, Crescendo, Janssen, Pfizer, Roche/Genentech and UCB, 5, AbbVie, Amgen, BMS, Corrona, LLC, Crescendo, Janssen, Pfizer, Roche/Genentech and UCB, 2, AbbVie, Amgen, BMS, Corrona, LLC, Crescendo, Janssen, Pfizer, Roche/Genentech and UCB, 9; **G. W. Reed**, Corrona, LLC, 3; **C. Karki**, Corrona, LLC, 3; **R. Magner**, University of Massachusetts Medical School, 3; **J. M. Kremer**, Corrona, LLC, 3, Corrona, LLC, 1, Genentech, Inc, 5, Genentech, Inc, 2; **A. Shewade**, Genentech, Inc, 3; **J. D. Greenberg**, Corrona, LLC, 3, Corrona, LLC, 1, AstraZeneca, Celgene, Novartis and Pfizer, 5.

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The Safety and Treatment Efficacy of Abatacept in Rheumatoid Arthritis Patients with Pulmonary Complications: From the Tsurumai Biologics Communication Registry (TBCR) Multicenter Study.

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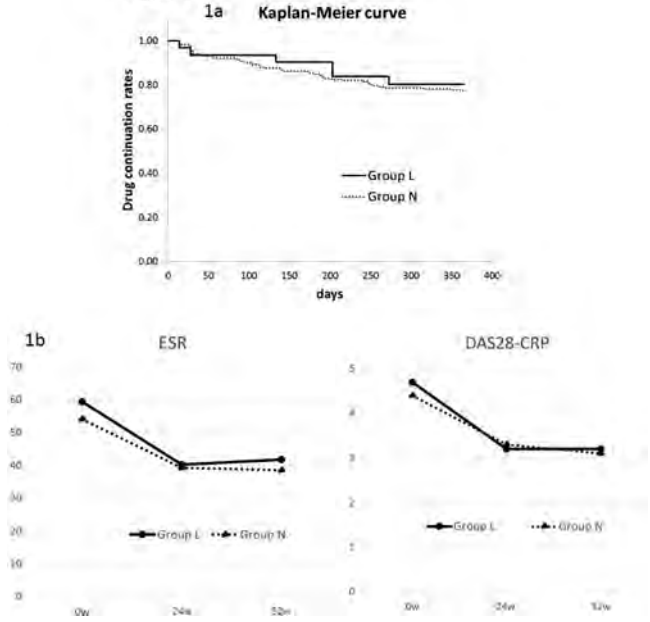
Background/Purpose: Roughly 10–30% of rheumatoid arthritis (RA) patients reportedly develop pulmonary complications. These patients are at increased risk of MTX or biologics-induced damage, which often becomes problematic for RA treatment. Abatacept (ABT) has been reported to have relatively few adverse events, and is often used in clinical settings in patients with pulmonary complications. Given the paucity of studies on the safety of ABT, however, accumulation of safety data under actual clinical settings is warranted. In the present study, we examined the persistence rates and treatment effects of ABT in patients with pulmonary complications.

Methods: We divided 250 RA patients registered in the Tsurumai Biologics Communication Registry who used ABT for ≥52 weeks according to whether they had pulmonary complications (L group: n=32) or not (N group: n=218). We then compared the persistence rates, incidence of adverse events, and disease activity between the two groups.

Results: No significant differences were found between groups with regard to mean age (L group, 67.7±6.9; N group, 64.0±12.8), disease duration (L group, 12.6±9.8; N group, 11.8±8.8), concomitant use rates of steroid (L group, 62.5%; N group, 60.5%), CRP (L group, 2.6±2.9; N group, 2.1±2.8), DAS28-CRP (L group, 4.7±1.5; N group, 4.4±1.3), or SDAI (L group, 28.8±16.5; N group, 24.5±14.0) at the time ABT was initiated, but significant differences were found in the percentage of women (L group, 65.6%; N group, 83.5%) and concomitant use rates of MTX (L group, 25%; N group, 53.2%). The persistence rates for 52 weeks were 73.1% and 74.3% in the L and N groups, respectively (Figure 1a). Adverse events occurred in 1 (3.13%) and 7 (3.83%) patients in the L and N groups, respectively. No pulmonary complications occurred after ABT administration in the L group, but 2 patients in the N group had interstitial pneumonia. Treatment was discontinued due to insufficient response in 6 (18.8%) and 29 (15.9%) patients in the L and N groups, respectively. None of these were significantly different by group. Mean DAS28-CRP significantly improved in both groups (Figure 1b), from 4.7 at ABT initiation to 3.2 at 52 weeks in the L group (P<0.01), and from 4.4 to 3.1 in the N group (P=0.034). Achievement of those with low disease activity also increased, from 9.4% at ABT initiation to 53.3% at 52 weeks in the L group, and from 8.3% to 47.7% in the N group.

Conclusion: The safety, treatment effects, and persistence rates of ABT were similar among RA patients with and without pulmonary complications. Use of ABT is beneficial even in patients with pulmonary complications, under close consideration of the risks involved.

Figure 1



Disclosure: S. Hirabara, None; **T. Kojima**, Takeda Pharma Corporation, Janssen Pharmaceutical, and Astellas Pharma Corporation., 2, Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Eisai Pharma Corporation, Abbvie, Bristol-Myers Squibb, Pfizer and Chugai Pharma Corporation, 8; **N. Takahashi**, Abbott Japan Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Co. Ltd, Chugai Pharmaceutical Co. Ltd., and Bristol-Myers Squibb Co. Ltd., 8; **Y. Hirano**, AbbVie Inc.; Eisai Co. Ltd.; Mitsubishi Tanabe Pharma Corporation; Takeda Pharma Corporation; Pfizer Co.

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Real-World Use of Tocilizumab in Rheumatoid Arthritis Patients in Canada: Interim Results. Boulos Haraoui[1], Shahin Jamal[2], Vandana Ahluwalia[3], Tarang Manchanda[4] and Majed Khraishi[5]. [1]Centre Hospitalier de l'Université de Montréal, Montréal, QC, [2]University of British Columbia, Vancouver, BC, [3]William Osler Health Center, Brampton, ON, [4]Hoffmann-La Roche Canada, Mississauga, ON, [5]Nexus Clinical Research, St John's, NF.

Background/Purpose: Tocilizumab (TCZ) has been approved for the treatment of adults with rheumatoid arthritis (RA) either as monotherapy or as combination with disease-modifying antirheumatic drugs (DMARDs). However, to date, data on its real-world utilization and durability are limited. The aim of this analysis is to describe the pattern of TCZ use at baseline (BL) and after 6 months (mos) of treatment in Canadian patients enrolled in ACT-UP, a multi-national observational study in moderate-to-severe RA patients treated with TCZ.

Methods: ACT-UP is an ongoing, multi-national, observational study with TCZ. As of June 2014, 1,375 patients have been enrolled from 14 countries. In this analysis, data from the 200 Canadian patients participating in ACT-UP were used. Descriptive statistics were produced and between-group comparisons were performed with the independent samples t-test (continuous variables) and the chi-square test (categorical variables).

Results: Among the 200 patients included, 67 (33.5%) started TCZ as monotherapy and 133 (66.5%) in combination with DMARD(s) (mean methotrexate dose: 19.9 mg/week). BL age (55.2 vs 55.6 years, respectively), gender (79.1% vs 80.5% females) and disease duration (13.8 vs 12.0 years) were similar in the two groups. No difference in the initial TCZ dose was observed between groups with 91.0% in each receiving 8 mg/kg and the remaining receiving <8 mg/kg. Similarly, concomitant use at BL of a corticosteroid (38.8% vs 36.1%; mean prednisone dose: 10.7 vs 9.2 mg/day) and prior exposure to a biologic (80.6% vs 82.0% in monotherapy vs combination therapy) were also comparable in TCZ monotherapy vs combination therapy. Lack of efficacy (70.4% vs 68.2%) and intolerance (12.2% vs 10.9%) were the most common reasons for stopping a previous biologic in both treatment groups. However, a significantly higher proportion of patients in the monotherapy group had been previously treated with >1 traditional DMARD (90.8% vs 66.9%; P<0.001). Overall, BL disease parameters were statistically comparable between treatment groups with the exception of patient global assessment which was significantly higher in the TCZ monotherapy group (68.1 vs 60.6 mm; P=0.017).

Upon 6 mos of treatment, 86.6% of patients in the monotherapy group and 85.0% in the combination therapy group were still on TCZ. Over that period no change in TCZ dose was reported in 80.6% patients (76.9% vs 82.5% in mono- vs combination therapy), while the TCZ dose was down-titrated in 14.7% patients (18.5% vs 12.7%, respectively). Seven of 67 (10.4%) patients in the TCZ monotherapy group added a concomitant DMARD to TCZ within 6 mos. Regardless of treatment group significant improvements were observed over 6 mos in all disease parameters examined (BL vs 6 mos DAS28: 5.3 vs 3.4; P<0.001).

Conclusion: In this real-world observational study, TCZ was used as monotherapy in 33.5% of patients. Despite the fact that 81.5% of patients had been previously treated with a biologic, more than 85% of patients remained on TCZ treatment after 6 mos of treatment. TCZ treatment alone or in combination with DMARD(s) over 6 mos was effective in inducing significant improvements in all disease parameters studied.

Disclosure: B. Haraoui, AbbVie, 2, AbbVie, 5, Amgen, 2, Amgen, 5, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5, Janssen Pharmaceutica Product, L.P., 2, Janssen Pharmaceutica Product, L.P., 5, Pfizer Inc, 2, Pfizer Inc, 5, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5, UCB, 2, UCB, 5; **S. Jamal**, AbbVie, Amgen, BMS, Roche, Merck, Pfizer, and UCB, 6; **V. Ahluwalia**, None; **T. Manchanda**, Hoffmann-La Roche Canada, 3; **M. Khraishi**, Roche Canada, 2.

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Risk of Infection Associated with Subsequent Biologic Use Following Rituximab—Results from a National RA Patient Registry. Leslie R. Harrold[1], George W. Reed[2], Chitra Karki[3], Robert Magner[1], Ashwini Shewade[4], Ani John[4], Joel M. Kremer[5] and Jeffrey D. Greenberg[3]. [1]University of Massachusetts Medical School, Worcester, MA, [2]Corrona, LLC., Southborough, MA, [3]Corrona, LLC, Southborough, MA, [4]Genentech, Inc, South San Francisco, CA, [5]Albany Medical College and The Center for Rheumatology, Albany, NY.

Background/Purpose: Rituximab is a chimeric monoclonal antibody for the treatment of rheumatoid arthritis (RA). Prolonged B-cell depletion from repeated doses of rituximab may be associated with increased risk of infection during subsequent biologic use; however, there are limited data on rates of infection in patients (pts) with RA who switched to a subsequent biologic following rituximab. [1–3] The objectives of this analysis were to assess whether time between last rituximab infusion and switching to a biologic with a different mechanism of action and intensity of rituximab use influenced risk of infection in a large, national RA pt registry (Corrona).

Methods: Pts with RA who newly initiated rituximab within Corrona were included if they switched to a (non-rituximab) biologic and had ≥ 1 follow-up visit within 12 months of switching. Pts were followed from the time they switched to a subsequent biologic to either the first infectious event or 12 months. The primary outcome was time to the first infectious event. Pts were categorized by the duration of time between their last rituximab infusion and switching to a subsequent biologic (≤ 5 months, 6–11 months and ≥ 12 months). Additionally, the number and rate of rituximab retreatments prior to starting the subsequent biologic were evaluated. Cox regression models estimated the association between time to starting a subsequent biologic and infection, and were adjusted for potential confounders.

Results: A total of 215 pts who switched to a subsequent biologic following rituximab use were included in this analysis (≤ 5 months [N = 104], 6–11 months [N = 67] and ≥ 12 months [N = 44]). Baseline characteristics were similar between the groups except for higher tender joint count and rate of rituximab retreatment in those pts who switched to a subsequent biologic earliest. Fewer than 50% of patients experienced an infection; of those patients who had an infection during the 12-month follow-up, the median (IQR) time to infection was 4 (2, 5) months. The overall rates of infection (95% CI) per person-year were 0.34 (0.22, 0.52), 0.30 (0.17, 0.52) and 0.41 (0.22, 0.77) in the ≤ 5 months, 6–11 months and ≥ 12 months groups, respectively. After adjusting for potential confounders, time to switch to a subsequent biologic was not associated with infection, which remained unchanged when including the number and rate of rituximab retreatments in the models (**Table**).

Conclusion: Duration of time between last rituximab infusion and switching to a biologic with a different mechanism of action was not associated with an increased rate of infection in pts with RA. Additionally, the number and rate of rituximab retreatments did not influence the risk of infection associated with the subsequent biologic.

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Table. Multivariate Models Estimating Association of Time to Switching to a Subsequent Biologic and Infection Adjusted for Potential Confounders[a]

HR (95% CI)	Months to Initiation of Second Biologic		
	≤ 5 (Reference)	6–11	≥ 12
Adjusted HR	1	0.94 (0.42, 2.10)	1.09 (0.43, 2.76)
Adjusted HR-Including No. of Rituximab Retreatments	1	1.00 (0.45, 2.23)	1.09 (0.44, 2.71)
Adjusted HR—Including Rate of Rituximab Retreatment	1	0.85 (0.37, 1.94)	0.94 (0.36, 2.43)
Adjusted HR—Including No. and Rate of Rituximab Retreatment	1	0.79 (0.32, 1.96)	0.81 (0.28, 2.37)

[a] Potential confounders were defined as covariates associated with infection from the unadjusted analysis (duration of RA, CDAI, tender joint count, swollen joint count, patient pain, patient global assessment of disease activity, physician global assessment of disease activity, mHAQ, subcutaneous nodules, history of liver disorder, history of cardiovascular disease and number of prior DMARDs [including current]) and additional characteristics deemed potentially clinically relevant to incidence of infections (age, sex, smoking history/status and history of serious infections).
CDAI, Clinical Disease Activity Index; DMARD, disease-modifying antirheumatic drug; HR, hazard ratio; mHAQ, modified Health Assessment Questionnaire.

Disclosure: L. R. Harrold, Corrona, LLC, 2; **G. W. Reed**, Corrona, LLC, 3; **C. Karki**, Corrona, LLC, 3; **R. Magner**, University of Massachusetts Medical School, 3; **A. Shewade**, Genentech, Inc, 3; **A. John**, Genentech, Inc, 3; **J. M. Kremer**, Corrona, LLC,

3, Corrona, LLC, 1, Genentech, Inc, 5, Genentech, Inc, 2; **J. D. Greenberg**, Corrona, LLC, 3, Corrona, LLC, 1, AstraZeneca, Celgene, Novartis and Pfizer, 5.

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Patterns of Tocilizumab Use and Safety in Patients with Rheumatoid Arthritis: Interim Results from a Multinational Observational Study. Boulos Haraoui[1], Gustavo Casado[2], Elke Theander[3], Laszlo Czirják[4], Andrew Taylor[5], Peter Button[6], Lykke Hinsch Gylvin[7] and Roberto Caporali[8]. [1]Centre Hospitalier de l'Université de Montréal, Montréal, QC, [2]Hospital Militar Central, Buenos Aires, Argentina, [3]Skane University Hospital Malmö, Lund University, Malmö, Sweden, [4]University of Pécs, Pécs, Hungary, [5]Royal Perth Hospital, Perth, Australia, [6]Roche Products Pty Limited, Dee Why, Australia, [7]F. Hoffmann-La Roche, Basel, Switzerland, [8]Division of Rheumatology, University of Pavia, IRCCS Policlinico San Matteo, Pavia, Italy.

Background/Purpose: Tocilizumab (TCZ) is indicated for the treatment of patients with RA who have had inadequate responses to DMARDs either as monotherapy (Mono) or in combination with DMARDs (Combo). ACT-UP is an umbrella project with data pooled from several international, observational, postmarketing studies investigating intravenous TCZ use in patients with RA in routine care. Interim observations of patterns of TCZ use, adherence to label recommendations, and safety are reported.

Methods: Adult patients with moderate to severe RA who started TCZ within 8 wk of enrollment were observed in clinical practice for 6 mo. There were no specified dosing regimens (concomitant RA treatments were permitted) and no interventional procedures, clinic visits, or laboratory analyses outside routine practice.

Results: Of 961 patients who received their first TCZ dose by June 30, 2013, 352 (37%) started Mono and 609 (63%) started Combo; 94% and 95% of Mono and Combo patients, respectively, started TCZ at 8 mg/kg, and 93% and 94% of patients, respectively, who received TCZ at 6 mo received 8 mg/kg. TCZ dose changes were reported for 34 (10%) Mono patients (7 increased, 11 decreased, 16 both increased and decreased) and 68 (11%) Combo patients (13 increased, 20 decreased, 35 both increased and decreased). Reasons for dose changes were AEs for 4% of Mono and 5% of Combo patients and lack of efficacy for 2% of Mono and 1% of Combo patients. Median MTX dose for Combo patients was 15.0 mg/wk. Sixty-three patients changed MTX dose during the study at a median dose change of –5.0 mg/wk. Twenty-eight (8%) patients who started TCZ Mono added a DMARD during the study. Corticosteroids were used by 57% of Mono and 70% of Combo patients (median prednisone-equivalent dose of 7.5 and 5.0 mg/d, respectively, at baseline). At 6 mo, 72% of Mono and 84% of Combo patients were still receiving TCZ. Overall, 100 (10%) patients discontinued TCZ in the first 3 mo and another 94 (10%) discontinued in the next 3 mo. Reasons for discontinuations included lack of efficacy (11% Mono; 27% Combo), adverse events (AEs; 27% Mono, 29% Combo), and other (62% Mono, 44% Combo). Regarding safety, AEs occurred in 53% of patients in each group. AEs classified as infections were less common in Mono than Combo patients (Table). No gastrointestinal perforations were reported in either group. Among patients for whom an AE required TCZ dose modification or an abnormal laboratory test result required follow-up, the investigator reported that local label/protocol recommendations were followed for 98% of Mono and 95% of Combo patients.

Conclusion: In this multinational observational study, 37% of patients started TCZ as monotherapy in clinical practice. Most patients continued TCZ treatment 6 mo after initiation whether they started it as monotherapy or in combination with DMARDs. TCZ was well tolerated in both groups, and adherence to local label recommendations was high.

Table. Safety

	TCZ Mono n = 352	TCZ Combo n = 609	All Patients n = 961
AEs, n (%) [rate per 100 PY]	185 (52.6) [193]	324 (53.2) [205]	509 (53.0) [201]
AEs by SOC[a]			
Infections and infestations	56 (15.9)	132 (21.7)	188 (19.6)
Investigations	38 (10.8)	71 (11.7)	109 (11.3)
Musculoskeletal and connective tissue disorders	33 (9.4)	52 (8.5)	85 (8.8)
Gastrointestinal disorders	29 (8.2)	49 (8.0)	78 (8.1)
Skin and subcutaneous tissue disorders	28 (8.0)	44 (7.2)	72 (7.5)
General disorders and administration site conditions	22 (6.3)	34 (5.6)	56 (5.8)
Blood and lymphatic system disorders	20 (5.7)	44 (7.2)	64 (6.7)
Nervous system disorders	18 (5.1)	32 (5.3)	50 (5.2)
Metabolism and nutrition disorders	18 (5.1)	23 (3.8)	41 (4.3)
SAEs, n (%) [rate per 100 PY]	34 (9.7) [23]	49 (8.0) [19]	83 (8.6) [21]
Infection SAEs	6 (1.7)	15 (2.5)	21 (2.2)
Total AEs leading to withdrawal, n (%) [rate per 100 PY]	32 (9.1) [21]	42 (6.9) [14]	74 (7.7) [16]
AEs leading to withdrawal by SOC[b]			
Skin and subcutaneous tissue disorders	6 (1.7)	5 (0.8)	11 (1.1)
Infections and infestations	5 (1.4)	6 (1.0)	11 (1.1)
Gastrointestinal disorders	4 (1.1)	1 (0.2)	5 (0.5)
Cardiac disorders	4 (1.1)	–4 (0.4)	
Blood and lymphatic system disorders	3 (0.9)	7 (1.1)	10 (1.0)

PY, patient-years; SAEs, serious AEs; SOC, system organ class.
n refers to number of patients with event. Rate per 100 PY is based on total number of events during TCZ exposure, determined for each patient as date of last TCZ dose - date of first TCZ dose + 28 days.
Numbers in parentheses are percentages.
[a]Reported in ≥5% of patients in a treatment group. [b]Reported in ≥1% of patients in a treatment group.

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ACR Poster Session A
Sjögren's Syndrome: Pathophysiology
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Genetic Variant and High Levels of CCL11 in Serum Are Associated with the Occurrence of Lymphoma and Disease Activity in Primary Sjögren's Syndrome Patients (pSS). Gaetane Nocturne[1], Olivier Fogel[2], Joanne Nititham[3], Kimberly E. Taylor[4], Philippe Dieude[5], Jean Jacques Dubost[6], Anne-Laure Fauchais[7], Vincent Goëb[8], Eric Hachulla[9], Claire Larroche[10], Véronique Le Guern[11], Jacques Morel[12], Aleth Perdriger[13], Xavier Puéchal[11], Stephanie Rist Bouillon[14], Alain Saraux[15], Damien Sène[16], Olivier Vittecoq[17], Lindsey A. Criswell[4], Corinne Miceli-Richard[18], Jacques Gottenberg[19] and Xavier Mariette[20]. [1]Paris sud university, Le Kremlin Bicetre, France, [2]Paris sud university, Le Kremlin Bicêtre, France, [3]374 Parnassus Avenue, San Francisco, CA, [4]University of California, San Francisco, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, San Francisco, CA, [5]Hopital Bichat Claude Bernard, Paris, France, [6]CHU G.-Montpied, Clermont-Ferrand, France, [7]Department of Internal Medicine A, Dupuytren Hospital, Limoges University Hospital, Limoges, France, [8]Amiens University Hospital, Amiens, France, [9]Université Lille Nord de France, Faculté de Médecine Henri Warembourg, Lille, Lille, France, [10]Assistance Publique des Hôpitaux de Paris, Bobigny, France, [11]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [12]Hôpital Lapeyronie, Montpellier, France, [13]Rhumatologie, Rennes, France, [14]Hopital La Source, La Source, France, [15]CHU Brest and EA 2216, UBO, Brest, France, [16]Hopital Lariboisière, service de Médecine Interne, Paris, France, [17]Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France, [18]Université Paris-Sud 11, Bicêtre Hospital, Kremlin Bicêtre, France, [19]Strasbourg University Hospital, Strasbourg, France, [20]Université Paris-Sud, Le Kremlin Bicêtre, France.

Background/Purpose: Development of non-Hodgkin lymphoma (NHL) is one of the most severe complications of pSS. It occurs in 5–10% of the patients. A more accurate detection of the high risk patients is mandatory to enable a more individualized approach. Presence of ectopic germinal center (GC) in salivary glands biopsy has been shown to be a predictor of NHL occurrence in pSS patients[1]. Interestingly, 2 single nucleotide polymorphisms (SNPs) located within *CCL11 (Eotaxin)*gene are associated with GC structures in pSS patients[2]. CCL11 is a chemokine that plays a role in chemotaxis of eosinophils and in allergy. In this study, we decided to assess the role of CCL11 both at the genetic and proteic level in the occurrence of pSS-associated NHL.

Methods: Genotyping of the 2 SNPs (rs3091328 and rs1860184, located on chromosome 17) known to be associated with GC structures was performed in 562 pSS cases (ASSESS cohort and Paris-Sud teaching hospital cohort) and 435 healthy controls, both of them of European ancestry as assessed by 47 ancestry informative markers. Among patients, 25 had a history of NHL. CCL11 serum levels at inclusion in the ASSESS cohort were evaluated in 385 pSS patients by multiplex assay. Among them, 21 patients had a NHL (history or future). Case-only associations (i.e., pSS patients with vs. without lymphoma) were tested with logistic regression adjusting for the top two Immunochip principal components. Association between CCL11 levels and genotype was assessed with the Kruskal-Wallis test. Levels of

CCL11 were compared in the different subsets of patients with a Mann-Whitney test.

Results: The 2 *CCL11* SNPs were not significantly associated with risk of pSS. However, we found a significant association between the rs1860184A located within the first intron of *CCL11*and pSS complicated by NHL: OR 1.87 CI95% [1.07–3.27], p= 0.03 compared to pSS patients without NHL and OR 1.84 CI95% [1.02–3.31], p= 0.04 compared to healthy controls. The median [range] serum level of CCL11 was 106.5 [13.2–283.5]pg/ml in the 385 pSS patients from the ASSESS cohort. We did not find any association between the CCL11 levels and the rs1860184 genotype (p=0.36). We found a trend for an association between CCL11 levels and the occurrence of NHL: (median [range]): 105 [13.23–283.5] in patients without NHL vs 141.3 [46.76–211] in patients with NHL (p=0.053). Interestingly we found a significant increased serum level of CCL11 in patients with an active disease defined by an ESSDAI ≥ 5 vs patients with inactive disease (112.2 pg/ml [13.23 – 283.5] vs 103.1 pg/ml [14.13 – 281.5] respectively, p=0.01). Last, we found significant correlations between CCL11 serum levels and B cells biomarkers (RF titer: p=0.01; free light chain kappa/lambda ratio: p=0.02 and β2-microglobulin level: p=0.0003).

Conclusion: This study highlights the potential implication of CCL11 in the occurrence of NHL in pSS patients. We show that the rs1840186 SNP is associated with NHL occurrence. An increased serum level of CCL11 tends to be associated with NHL occurrence and is associated with increased disease activity and B cells bio-markers. Further studies will be mandatory to determine the functional role of CCL11 in this phenomenon.

1. Theander et al ARD, 2011 2.Reksten, ARD 2014.

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CXCL13 Serum Levels Is Associated with Lymphoma, High B Cells Markers and Diseases activity in Primary Sjögren 's Syndrome Patients.

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Background/Purpose: Development of non-Hodgkin lymphoma (NHL) is one of the most severe complications associated with pSS. It affects 5–10% of the patients. Definition of predictive factors is mandatory to enable a more individualized approach. CXCL13 is a chemokine also known as B lymphocyte chemo-attractant (BLC) involved in the homing of B cells within germinal centers. High CXCL13 serum levels have been shown to be predictive of NHL occurrence in the general population outside the context of autoimmunity [1]. Given this association with NHL in the general population, we decided to assess a possible association between CXCL13 serum levels and lymphoma and B-cell biomarkers in our cohort of pSS patient.

Methods: CXCL13 serum levels at inclusion were evaluated in 385 pSS patients included in the ASSESS cohort by multiplex assay. Among them, 21 patients had a NHL (history of or future). Levels of CXCL13 were compared in the different subsets of patients with a Mann-Whitney test. Association between CXCL13 levels and B cells markers was assessed by the Pearson's r correlation test.

Results: The median [range] levels of CXCL13 was 108 [6.33–4040] pg/ml in the 385 pSS patients from the ASSESS cohort. We found an increased CXCL13 serum level in pSS patients with NHL vs pSS patients without NHL (191.1 [43.7–3251] vs 105 [6.33–4040], p=0.008). CXCL13 was also increased in patients with active disease (ESSDAI ≥5) compared to patients with inactive disease (ESSDAI < 5) (98.5 [6.3–3251] vs 66.9 [11.1–4040], p=0.009). Last we found significant correlations between CXCL13 serum levels and B cells biomarkers such as gammaglobulinemia (r=0.11, p=0.04), β2-microglobulin level (r=0.22, p< 0.0001), BAFF serum level (r=0.18, p=0.0006), free light chain kappa/lambda ratio (r=0.21, p<0.0001) and rheumatoid factor titer (r=0.22, p<0.0001) and an increased level in patients with anti-SSA vs patients without (138.3 [7.2–4040] vs 76.5 [6.3–1515], p<0.0001).

Conclusion: This study demonstrates that CXCL13 may be involved in lymphomagenesis in pSS patients. We demonstrated that CXCL13 serum level is increased in pSS patients with NHL, in patients with active disease and is associated with B cells markers. Further studies will be needed to investigate the functional role of this chemokine in the disease.

Reference:

1. Purdue et al. Blood, 2014

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Whole Blood microRNA Signature for Primary Sjögren's Syndrome-Related Lymphoma.

Jessica Tarn[1], Simon Cockell[1], Colin Gillespie[1], Shereen Al-Ali[2], Katherine James[1], James Locke[1], Simon Bowman[3], Bridget Griffiths[4], David Young[1] and Wan-Fai Ng[1]. [1]Newcastle University, Newcastle upon Tyne, United Kingdom, [2]University of Basrah, Basrah, Iraq, [3]University Hospital Birmingham, Birmingham, United Kingdom, [4]Freeman Hospital, Newcastle Upon Tyne, United Kingdom.

Background/Purpose: Micro RNAs (miRNAs) are 18–25nt non-coding RNAs that bind target/complementary sequences within the 3'UTR of RNA molecules steering them towards degradation or translational repression, and play a key role in the regulation of gene expression. Better understanding of the expression pattern of miRNAs in diseases may improve our understanding of the biological basis of the disease and identify potential biomarkers. The role of miRNAs in primary Sjögren's syndrome (PSS) and PSS-related lymphoma remains poorly understood. The aim of this project is to identify a miRNA signature for PSS-related lymphoma.

Methods: We profiled the expression of miRNAs in whole blood (PaxGene) total RNA preparations using the Exiqon miRCURY LNA array which encompasses >1400 miRNAs and other small non-coding RNAs. A discovery cohort comprised of 36 samples from the United Kingdom Primary Sjögren's Syndrome Registry (UKPSSR) (12 PSS patients with lymphoma, 12 PSS patients without lymphoma, 12 healthy controls) were used in the initial analysis. We also explored different normalisation strategies and developed an approach which we considered most appropriate for analysing these data. Real-Time PCR was used to validate the most highly differentially expressed miRNAs between groups. A miRNA signature for PSS-related lymphoma was identified using cluster analysis followed by validation with a second independent cohort of 36 patients and controls.

Results: The initial miRNA array profiling revealed a clear clustering of the 3 subject groups. Between the 'High Function' and 'Lymphoma' patient groups, 44 miRNAs were found to be differentially expressed. The differential expressions of these miRNA were validated by RT-PCR in 3 out of 9 miRNAs with the highest fold-changes between the two groups. Indeed, based on the expression levels of these 3 miRNAs were sufficient to distinguish PSS patients with lymphoma from those without. Two out of these 3 miRNAs were also differentially expressed between the same two groups in the validation cohort.

Conclusion: We have identified 2 miRNAs that are differentially expressed in peripheral blood between PSS patients with lymphoma and those without lymphoma. Identifying the mRNA targets of these miRNAs in PSS may improve our understanding of the pathogenesis of PSS-related lymphoma. Furthermore, miRNAs may be useful biomarkers for PSS-related lymphoma.

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Serum CXCL4 Is Increased in Patients with Primary Sjögren's Syndrome and Is Associated with Features of Microvascular Impairment. Rosaria Irace[1], Antonella Riccardi[1], Daniela Iacono[1], Luciana Pellecchia[1], Lucia Vicedomini[1], Gabriele Valentini[2] and Serena Vettori[1]. [1]Second University of Naples, Naples, Italy, [2]Second University of Naples, Napoli, Italy.

Background/Purpose: CXCL4 is a pleiotropic antiangiogenic and immunomodulatory chemokine. We aimed to investigate CXCL4 serum levels in primary Sjögren's syndrome (pSS) and looked for associations with disease features, with a focus on parameters of microvascular involvement.

Methods: Thirty-nine consecutive pSS patients meeting the 2012 classification criteria for the disease were enrolled and underwent clinical assessment, nailfold videocapillaroscopy (NVC), and autoantibody profiling. Additional serum to measure levels of CXCL4 and soluble E-selectin (sE-selectin) was available from 36 pSS patients and 30 healthy controls (HC). At NVC, enlargement, density, and tortuosity of capillaries, and microhemorrhages were scored on a 0 to 3 scale (0 = normal, 3 = high grade). Plexus visualization and neoangiogenesis were also considered as present/absent. Autoantibodies were assayed by ELISA, while CXCL4 and sE-selectin were measured by multiplex suspension immunoassay.

Results: Serum levels of CXCL4 were increased in pSS patients (median 1.79 ng/ml [0.2–11.18], vs 1.023 ng/ml [0.02–14.45] in HC, $p < 0.05$), the highest found in anti-La/SSB autoantibody-negative patients (2.89 mg/ml [1.01–11.18] vs 1.69 [0.2–2.72] ng/ml, $p < 0.05$), and correlating with a longer disease duration ($r = 0.35$, $p < 0.05$). Most interestingly, we found a higher prevalence of CXCL4 levels above the 95° percentile of the HC group (10.91 ng/ml) in pSS patients with Raynaud's phenomenon (RP) (11/14 vs 4/18, $p < 0.001$). This prompted us to look for associations of serum CXCL4 with microvascular abnormalities at NVC and/or correlations with serum levels of sE-selectin, a marker of endothelial activation. Indeed CXCL4 positively correlated with sE-selectin ($r = 0.45$, $p < 0.01$), but was not associated with any NVC finding. However, a reduced capillary density and high grade enlarged capillaries were more prevalent in patients with RP (14/15 vs 6/21 and 16/16 vs 8/23, respectively; both $p < 0.0001$). An NVC "scleroderma pattern" was observed only in 3 patients (megacapillaries), and neoangiogenesis in 2 (both $p > 0.05$).

Conclusion: Here we show for the first time that pSS patients have increased serum CXCL4 levels, which correlate with disease duration and serum sE-selectin levels, and are associated with the presence of RP. These data suggest that CXCL4 might be implicated in microvascular/endothelial impairment in pSS. Actually, our pSS patients with RP had microvascular damage, as a reduced capillary density and high grade enlarged capillaries showed. Lastly, we detected higher CXCL4 levels in anti-La/SSB autoantibody-negative patients. This negative association might be related to the role played by pSS specific autoantibodies in promoting pathological angiogenesis in human salivary glands. Taken together this data provide preliminary evidence of a role for circulating CXCL4 as a marker of microvascular damage in pSS on larger cohorts of patients.

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Distinct Patterns of DNA Methylation in Labial Salivary Gland Tissue Based on Sjögren's Syndrome Disease Status. Michael Cole[1], Xiaorong Shao[1], Diana Quach[1], Hong L. Quach[1], Lisa F. Barcellos[1] and Lindsey A. Criswell[2]. [1]University of California, Berkeley, Berkeley, CA, [2]University of California, San Francisco, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, San Francisco, CA.

Background/Purpose: Sjögren's Syndrome (SS, OMIM #270150) is a chronic, multi-system autoimmune disease characterized by progressive destruction of the exocrine glands, with subsequent mucosal and conjunctival dryness. A growing body of evidence indicates that epigenetic changes contribute to the development of this complex disease. In particular, altered patterns of DNA methylation may modulate both risk and severity.

Methods: We report an expanded case-control study of DNA methylation differences within labial salivary gland tissues, using biopsies sampled from 12 primary SS cases, 2 secondary SS cases, and 14 controls in the Sjögren's International Collaborative Clinical Alliance (SICCA; http://sicca.ucsf.edu/; HHSN268201300057C) collection. These subjects are part of a larger, 36-subject study group for which blood, gland tissue, and cell-sorted blood samples have been methylotyped (110 samples total). We generated genome-wide DNA methylation profiles using Illumina HumanMethylation450 BeadChips and further characterized full genome SNP profiles using the Illumina HumanOmni2.5-Quad platform. All methylation results were background subtracted via out-of-band normal-exponential convolution (NOOB) and normalized via all sample mean normalization (ASMN) and beta-mixture quantile normalization (BMIQ).

Results: Multidimensional Scaling (MDS) applied to the 360,546 CpG sites passing strict QC criteria visibly separates primary SS cases from controls within the first 2–3 components, and this clustering changes substantially with the inclusion of a subset of 9 symptomatic SICCA control subjects (control status based on SICCA's extensive clinical and serologic data). We demonstrate significant gene-centered mean hypomethylation across *IL10* and *IRF5* in SS cases (False Discovery Rate $\leq .05$). Mean methylation levels within 15 other putative SS-associated genes were similar between cases and controls. We report median methylation levels in specific *BLK* and *KLHL24* CpGs that are 15–25% hypermethylated in primary SS cases versus controls; other sites in *IRF5* and *BLK* display 10–20% hypomethylation. Single-site methylation differences across 7 of the 17 genes retain significance after multiple-testing correction, with 6 of the 7 genes exhibiting hypomethylation at a majority of sites.

Conclusion: Our results emphasize the utility of DNA methylation as a potential biomarker of disease status. Additional research, including studies of pathway-specific gene expression will be required to fully define the role of DNA methylation in SS-affected salivary glands.

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The Genetic Basis of Sjögren's Syndrome (SS) Clinical Manifestations from Genome-Wide Association Analysis of Subphenotype Extremes in an International Cohort. Lindsey A. Criswell[1], Kimberly E. Taylor[1], Quenna Wong[2], David M. Levine[2], Caitlin McHugh[2], Cathy Laurie[2], Kimberly Doheny[3], Mi Y. Lam[4], Alan N. Baer[5], Stephen Challacombe[6], Yi Dong[7], Hector Lanfranchi[8], Morten Schiødt[9], M. Srinivasan[10], Susumu Sugai[11], Hisanori Umehara[11], Frederick B. Vivino[12], Zhao Yan[13], Stephen Shiboski[4], Troy Daniels[4], John S. Greenspan[4], Caroline H. Shiboski[4] and Sjögren's Syndrome Collaborative Clinical Alliance (SICCA)[4]. [1]University of California, San Francisco, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, San Francisco, CA, [2]University of Washington, Biostatistics, Seattle, WA, [3]Center for Inherited Disease Research, Baltimore, MD, [4]University of California San Francisco, San Francisco, CA, [5]Johns Hopkins University School of Medicine, Baltimore, MD, [6]Kings College London, London, United Kingdom, [7]Peking Univ Med Coll Hospital, East City Beijing, China, [8]University of Buenos Aires, Buenos Aires, Argentina, [9]Rigshospitalet, Copenhagen, Denmark, [10]Aravind Eye Hospital, Madurai, India, [11]Kanazawa Medical University, Ishikawa, Japan, [12]Penn Presbyt Med Ctr, Philadelphia, PA, [13]Peking Union Medical College Hospital, Beijing, China.

Background/Purpose: Our goal is to define the contribution of genetic factors to two hallmark manifestations of SS, keratoconjunctivitis sicca (KCS) and focal lymphocytic sialadenitis (FLS), in an international cohort.

Methods: We studied 3,334 participants in the Sjögren's International Collaborative Clinical Alliance (SICCA; contract # HHSN 268201300057C) registry who were characterized for the Illumina HumanOmni 2.5-Quad marker set. SICCA participants were enrolled according to standardized protocols at 9 international sites, including Argentina (n=428), China (n=304), Denmark (n=583), India (n=127), Japan (n=367), the UK (n=296) and the US (total n=1229 from 3 sites). QC measures included filters based on SNP and sample missingness ($\geq 2\%$), unexpected relatedness, non-Mendelian inheritance, and chromosomal regions of anomaly (> 10Mb). SICCA participants were assessed for presence and severity of FLS defined by focus score (FS, positive ≥ 1) on minor salivary gland biopsy and degree of KCS based on ocular staining pattern measured by ocular staining score (OSS, positive ≥ 3). In order to investigate the genetic basis of these manifestations, we compared patients with high values (OSS ≥ 7, FS ≥ 2.5) to patients with normal values (OSS < 3, FS < 1) via logistic regression. Principal components analysis (PCA) was used to characterize each participant for genetic ancestry, and PCs 1 – 5 were included as covariates in all

association analyses. We analyzed the entire group and also the two largest strata by ethnicity (European and Asian, with outliers removed outside of PCA clusters).

Results: Out of 3284 unrelated subjects with post-QC genotypes and sufficient clinical data, patients were categorized for analysis as follows: high FS (n=636), normal FS (n=1968), high OSS (n=1333), normal OSS (n=857). A total of 1,550,200 SNPs with MAF ≥ 1% passed all QC filters and were fully analyzed. Not surprising in autoimmunity, the MHC was the most significantly associated with both traits in the full dataset (FS p=3e-22; OSS p=6e-12) and in Europeans (FS 375 SNPs p<5e-8, lowest 3e-17; OSS 60 SNPs p<5e-8, lowest p=4e-11). However, in Asians the MHC appears to have much less importance. There was only one suggestive MHC SNP (p=8e-6) for FS; the most associated FS gene in Asians was *PTPRD*, with 12 SNPs p<5e-6 (lowest p=1.8e-7). Outside of the MHC, some genes appear to influence both phenotypes while others are trait-specific. For example, *IRF5* is the highest-associated region for FS (p=2e-7) but not suggestive for OSS. The *XYLT1* region is the highest-associated region for OSS (p=1e-6) but is not implicated in FS. On the other hand, *STAT4* is among the most-associated regions for both FS (p=1e-6) and OSS (p=3e-6).

Conclusion: These results demonstrate that the ocular (OSS) and oral (FS) manifestations of SS are influenced by both shared and trait-specific genetic factors. Furthermore the genetic profile appears to be quite different for both depending on ancestry, in particular when comparing European and Asian SS patients. Additional work including imputed genetic data and more extensive ancestry analysis will provide more power for extending these findings and fully characterizing the genetic contribution to SS.

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A Descriptive and Comparative Study of the Transcriptome from Salivary Exosomes of Sjögren's Syndrome Patients Using RNA-Seq. Alessia Gallo[1], Mayank Tandon[2], Shyh-Ing Jang[2], Ana Paola Cotrim[1] and Ilias Alevizos[3]. [1]NIH, Bethesda, MD, [2]NIDCR, Bethesda, MD, [3]NIDCR/NIH #10 1N110, Bethesda, MD.

Background/Purpose: Saliva is a biofluid secreted by the salivary glands (SGs) that is critical for the health of the oral cavity. In Sjögren's Syndrome (SS), changes in salivary biomarkers are not only useful for diagnosis, but may also elucidate the mechanisms underlying SG dysfunction. The RNA content of saliva has been shown to be useful for monitoring the health of oral tissue and the oral microbiome. Next-Generation Sequencing (NGS) offers a high throughput method for comparing the salivary transcriptomes of SS patients and healthy volunteers (HV). We have previously shown that RNA is protected within exosomes and we focused this study in using salivary exosomes isolated from the parotid. Parotid saliva has the advantage of being pure without the contamination generated from all type of cells found in the whole saliva.

Methods: Total RNA was extracted from exosomes isolated from parotid saliva from 4 healthy volunteers and 4 primary SS patients. The amount and the quality of the RNA were assessed using Nanodrop, Qubit and Bioanalyzer. The Ion Torrent Proton sequencer was used sequencing according to manufacturer protocols. Reconstructed reads were aligned using the TMAP (Torrent Mapper) algorithm sequentially to miRBase 19, hg19, viral, and bacterial genomes, i.e. reads left unmapped were used as input for each subsequent step. The bacterial reference included 14,549 contigs representing 1,132 genomes retrieved from the Human Oral Microbiome Database, and the viral reference included 1,741 viruses retrieved using the NCBI assembled genomes FTP website. Read counts were generated using the HTSeq python module, and differential expression analysis was done in R using the DESeq2 package. Ingenuity Pathway Analysis (IPA) was used to analyze pathway enrichment and visualization. Microbial expression and taxonomy were analyzed used Pathosystems Resource Integration Center (PATRIC).

Results: Overall the percentage of all reads mapping to each reference were similar between SS and HV: miRBase (5.96% in HV, 5.427% in pSS), hg19 (81.82% HV, 81.96% pSS), viral (6.94% HV, 3.26% pSS), and bacterial (1.121% HV, 1.737% pSS). On average, 4.14% of the input was left unmapped in HVs and 7.62% in pSS patients after all mapping. The differences between percent input reads in patients and HVs was only significant for the bacterial reference, and for unmapped reads. Expression pairing between miRNAs and their target genes using IPA showed significant enrichment for canonical pathways for pancreatic adenocarcinoma signaling, and estrogen-mediated S-phase Entry. Top differentially regulated bacterial genera (fold-change greater than or less two and FDR-corrected p-value less than 0.01) include Streptococcus, Selenomonas, and Actinomyces. Notable upregulated viruses include Tomato yellow leaf curl virus and streptococcus phage Cp-1. Human papillovirus, type 41 was found to be significantly downregulated in pSS patient saliva.

Conclusion: This is the first known effort to compare the transcriptome of SS patients' salivary exosomes versus healthy controls. Using RNA-Seq, we were able to identify important human genes as well as alterations in the salivary microbiome that could shed light on the mechanisms of salivary dysfunction in pSS.

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Salivary Expression of S100A7/Psoriasin and Oral Damage in Primary Sjögren's Syndrome and Overlapping Disorders. Francesca Sernissi[1], Chiara Baldini[1], Daniela Martini[1], Leonardo Lorenzini[1], Laura Bazzichi[1], Antonietta Raffaella Maria Sabbatini[1], Giada Marchi[1], Camillo Giacomelli[1], Marta Mosca[2] and Stefano Bombardieri[2]. [1]Rheumatology Unit, Pisa, Italy, [2]Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: S100A7/psoriasin, a 11.4kDa protein belonging to the S100A family of Ca2+-binding proteins, is known to exhibit an antimicrobial activity at skin level, but has also been implicated in the regulation of cell proliferation, differentiation, invasion and metastasis. By using a proteomic approach, S100A7/psoriasin has been recently identified in the whole saliva of patients with Systemic Sclerosis as a potential disease biomarker. The aims of the present study were (1) to compare the expression of salivary S100A7/psoriasin in patients with Sjögren's Syndrome associated to anti-centromere antibodies (ACA) positive Systemic Sclerosis (SS-SSc), versus patients with primary Sjögren's Syndrome (pSS), and (2) to explore any correlation between salivary S100A7/psoriasin and oral damage.

Methods: Unselected pSS and SS-SSc patients (AECG 2002) were consecutively recruited in the study. Unstimulated salivary flow (USF) rate were measured according to the sialometry protocol, and saliva samples were collected on ice, centrifuged and stored at -80°C. S100A7/psoriasin levels were determined by CircuLex S100A7/psoriasin ELISA kit (MBL International Corporation), according to manufacturer's instructions. All subjects had a standardized evaluation for pSS which included oral and ophthalmologic examinations, laboratory testing and a rheumatologic evaluation.

Results: Eighteen SS-SSc and 33 pSS female patients were included in the study. SS-SSc patients had a mean age ± standard deviation (SD) of 65.6 ± 11.3, which did not differ from that of pSS (59.8 ± 11.3). S100A7/psoriasin levels were significantly higher in SS-SSc subjects (p=0.02). S100A7/psoriasin salivary levels negatively correlated with the USF rate (r=−0.27, p<0.05), particularly in pSS subjects (r=−0.508, p=0.003), and were significantly higher in patients with a USF <1.5 ml/15 minutes (p=0.006). Regarding the relationship between S100A7/psoriasin and patients' oral damage, we found that the salivary expression of the protein was significantly associated with the Sjögren's Syndrome disease damage index (SSDDI) (p<0,05) and specifically with the complete loss of teeth (p=0.02).

Conclusion: Salivary S100A7/psoriasin might be useful in differentiating pSS from SS-SSc and seems to be able to reflect oral damage in both pSS and SS overlapping disorders. The potentially predictive value of this biomarker for oral damage accrual in SS calls for further studies.

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Calcium-Calcineurin-NFAT Signaling Pathway Regulates AQP5 Expression in Primary Salivary Gland Acinar Cells. Shyh-Ing Jang[1], Hwei Ling Ong[1], Indu Ambudkar[2] and Illias Alevizos[1]. [1]NIDCR, Bethesda, MD, [2]NIH, Bethesda, MD.

Background/Purpose: Aquaporin (AQP) 5 belongs to a family of small integral membrane proteins which function as a water channels in cells. AQP5

plays a critical role in mediating the secretion of fluid in salivary gland. Decrease or no saliva flow is one of the key symptoms in Sjögren's syndrome patients. Towards understanding the molecular basis of the loss of salivary secretion, here we have studied the regulation of AQP5 expression in primary human salivary gland epithelial cells (phSG).

Methods: cell culture, Western blot, qPCR, siRNAs, site-directed mutagenesis, chromatin immunoprecipitation.

Results: We observed that the phenotype of the cells depended largely on the calcium levels in the culture conditions. AQP5 transcript showed more than 3-fold increase in phSG cells grown in high calcium (0.8 mM) medium compared to that in low calcium (0.05 mM) condition. This was confirmed by both immunofluorescence staining and Western blot studies. Evaluation of expression transcripts of calcium signaling proteins in phSG cells revealed that NFAT1 expression was dependent on calcium in a dose-response manner. Furthermore, when cells were switched to a high calcium medium pGFP-NFAT1 was translocated from the cytoplasm into the nucleus. Expression of AQP5 was also reduced when phSG cells were treated with cyclosporine A confirming the involvement of calcineurin-NFAT1 signaling pathway in regulation of AQP5 expression. Since NFAT activation has been linked to calcium influx, we examined the role of the calcium entry regulatory proteins STIM1 and STIM2 as well as the channel protein Orai1. Knockdown of NFAT1 and STIM1, but not STIM2 or Orai1, resulted in 70% decrease of AQP5 expression. Further analysis revealed that several NFAT binding motifs were identified in the AQP5 promoter and these were validated using AQP5-promoter-luciferase assays. Mutagenesis of putative NFAT-binding regions as well as chromatin immunoprecipitation analyses revealed the presence of functional NFAT binding sites within the proximal AQP5 promoter region.

Conclusion: These data demonstrate that AQP5 expression in phSG cells is regulated by a calcineurin-NFAT-dependent signaling pathway. Importantly, STIM1, but not Orai1 is involved in this mechanism. We propose that external Ca^{2+}-dependent Ca^{2+} entry triggers activation of AQP5 expression in phSG cells. Thus alterations in calcium signaling could lead to alterations in AQP5 expression and function in pSS. Further studies are being directed towards determining the status of calcium signaling in pSS salivary glands.

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IP3R3 Deficit Underlies the Loss of Fluid Secretion in Salivary Glands from Sjögren's Syndrome Patients. Leyla Y Teos[1], Bill Swaim[2], Margaret Grisius[1], Ana Paola Cotrim[1], Shyh-Ing Jang[3], Lolita Bebris[1], David Yule[4], Gabor G. Illei[5], Indu Ambudkar[1] and Ilias Alevizos[6]. [1]NIH, Bethesda, MD, [2]NIH/NIDCR, Bethesda, MD, [3]NIDCR, Bethesda, MD, [4]University of Rochester, Rpochester, NY, [5]NIDCR/ NIH, Bethesda, MD, [6]NIDCR/ NIH #10 1N110, Bethesda, MD.

Background/Purpose: Sjögren's syndrome (SS) is a chronic autoimmune disease with unknown etiology. Affecting from 0.2% to 3.0% of the total population, with a 9:1 female to male ratio, Sjögren's patients suffer from a reduction in salivary flow which leads to tenacious dry mouth and dry eyes symptoms causing debilitating oral complications, in addition to extraglandular systemic manifestations. Our focus has been to assess the possible mechanism(s) underlying the reduction in salivary flow by examining cellular volume regulation and the trigger to this regulation which is calcium signaling. Saliva is an orchestrated process initiated by neurotransmitter stimulation which is critically regulated by an increase in cytosolic calcium. This increase in calcium triggers ion channel activities, leading to the secretion of fluid which can be detected as a decrease in cell volume. We hypothesized that alterations in calcium signaling in acinar cells (where secretion is produced) accounts for the reduction in salivary flow seen in SS.

Methods: A non-enzymatically dispersed organotypic tissue preparation was used to maintain the microenvironment. Human minor salivary gland biopsies were finely minced (0.5mm) to obtain cell clusters which were loaded with cytosolic calcium indicator (Fluo-2AM) or cell-volume indicator, calcein. The loaded cell clusters were then used for live-cell imaging using confocal microscopy. In addition we performed immunoflourescence to label key proteins involved in calcium and volume regulation in salivary glands such as AQP5, STIM1, and IP3 receptor 3 (IP3R3).

Results: Acinar cells from SS patients displayed significant attenuation of agonist-stimulated cytosolic calcium increases when compared to the function in cells from normal healthy volunteers. Both intracellular release and Ca^{2+} influx were substantially reduced. This was correlated with a loss of agonist stimulated decrease in cell volume. Decrease in cell volume is indicative of fluid secretion and is completely dependent on increase in $[Ca^{2+}]_i$. There was a significant correlation between agonist – induced volume decrease and saliva secretion within the patient population. Together these data demonstrate that the reduced salivary secretion in the SS patients is due to reduced Ca^{2+} signaling in acinar cells. To further determine underlying factors causing the functional defect we examined the expression of critical components involved in calcium mobilization and fluid secretion; AQP5, STIM1, and IP3R. Within the area of infiltration, there was cell damage and all proteins were disrupted. In the area around the infiltrate there was no change in AQP5. STIM1 was reduced in cells around the infiltrate, but not in areas further away infiltrating site. Importantly, IP3R was uniformly decreased in all areas of the gland.

Conclusion: Our findings reveal an underlying defect in IP3R in acinar cells that can account for loss of salivary secretion in patients with low levels of lymphocytic infiltration and minimal tissue damage. Further studies are required to determine what causes loss of IP3R.

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Downregulation of Microrna-183 in Sjogren's Syndrome Minor Salivary Glands. Implications in Control of Ezrin Expression and Salivary Gland Function. Paola Perez Riveros[1], Mayank Tandon[1], Salman Kazmi[2], Alessia Gallo[2], Gabor G. Illei[3] and Ilias Alevizos[4]. [1]NIDCR, Bethesda, MD, [2]NIH, Bethesda, MD, [3]NIDCR/ NIH, Bethesda, MD, [4]NIDCR/ NIH #10 1N110, Bethesda, MD.

Background/Purpose: Sjogren's syndrome (SS) is an exocrinopathy, which is mainly characterized by salivary glands (SG) hypofunction. SGs from SS patients present dilated lumen in acini and loss of microvilli in the acinar cell SG. Previously, we reported that these changes correlate with an **aberrant location in the basal pole of the acinar cells** and **an overexpression of ezrin**. Ezrin is a cytoplasmic peripheral membrane protein that regulates the microvilli organization and secretion of exocrine cells. The mechanism of gene expression and specific function of ezrin in SG is unknown. We also proved that microRNA hsa-miR-183 is down regulated in SG from SS patients and it can modify the expression of ezrin SG cell culture in 3D. Here we are further confirming the function of hsa-miR-183 in vivo, its implication in saliva secretion and exploring a mechanism by which ezrin mislocalization produce saliva hyposecretion.

Methods: LNA-antimir-183 was transfected into mice parotid SG. The effect of the blockage of hsa-mir-183 was assessed evaluating the volume of saliva secretion after stimulation with isoproterenol and ezrin protein expression. Proximity ligation assay was performed to determine the interaction of ezrin with three possible targets: Sodium-hydrogen antiporter 3-regulator1 (SLC9A3R1), Anotacmin1 (ANO1) and Rab27A.

Results: The *in vivo* transfection of the LNA-antimir produced an increase of protein levels of ezrin and a decrease in the saliva secretion. ANO1 did not appear to form complex with ezrin in human SG. The complex ezrin/SLC9A3R1 was decreased in apical pole acinar cells of SS patient. A similar change was observed for ezrin/Rab27.

Conclusion: These experiments suggest that in SG of SS patients the overexpression of ezrin is produced by the down regulation hsa-miR-183 and propose a role of ezrin in the mechanism of SG hyposecretion. In this mechanism the mislocalization of ezrin affect the localization of the sodium-hydrogen antiporter 3-regulator1, altering the activation of the SLC9A3R1 and the electrolyte balance to regulate water secretion. Additionally, the change in the interactionof ezrin- Rab27A would affect the fusion of the secretory granules with apical plasma membrane.

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Expression of Indoleamine 2,3 Dioxygenase-1 and -2 in Focal Sialoadenitis of Patients with Sjögren's Syndrome. Claudio Vitali[1], Antonina Prafioriti[2], Domenico Sambataro[2], Andrea Di Bernardo[2], Elisabetta Admiraglio[2], Saba Nayar[3], Francesca Barone[3] and Nicoletta Del Papa[2]. [1]Istituto San Giuseppe, Como, Italy, [2]Istituto G.Pini, Milan, Italy, [3]University of Birmingham, Birmingham, United Kingdom.

Background/Purpose: The role of indoleamine 2,3 dioxygenase 1 and 2 (IDO1-IDO2) enzymes in modulating the immune response has not been so far completely clarified. IDO1 may induce immune-tolerance by suppressing antigen-specific T-cell response, directly or by activating T-reg cells, as shown in some cancer cells and in the placental tissue. IDO1 and IDO2 function in autoimmune diseases is controversial. In collagen-induced arthritis of DBA/1 mice, IDO1 limits the arthritis phenotype, as suggested by arthritis worsening after IDO1 inhibition. Conversely, IDO2 is critical for arthritis development in K/BxN transgenic mice, since IDO2-null mice display less aggressive joint inflammation.

This study was aimed at investigating whether IDO1/IDO2 are expressed in focal sialoadenitis of Sjögren's syndrome (SS), and possibly at identifying the inflammatory cells where these enzymes are active.

Methods: Minor salivary gland biopsies from 22 patients (21 F) with SS (according to the AECG classification criteria) were examined for IDO1 and IDO2 expression by using monoclonal antibodies, and immunohistochemical (IH) and immuno-fluorescence (IF) methods. In IH-stained sections the prevalence (or number) of CD3+T-cells, CD20+B-cells, CD123+dendritic cells (DC), IDO+cells was semi-quantitatively scored. Co-localization of IDO+cells and of the other inflammatory cells was investigated by IF methods.

Results: IH studies showed that IDO1 was notably expressed within the focal infiltrates. Correlations were found between the amount of IDO1+cells and the focus score ($R=0.52$, $p<0.02$), the prevalence of B-cells ($R=0.79$, $p<0.0005$), and the number of DCs ($R=0.64$, $p<0.005$). IDO2 was expressed in the vessel walls and ductal cells surrounded by infiltrates, but not in the CD3+T-cell area.

In germinal centre-like foci, IF studies showed that IDO1+cells were noticed around the B-cell area, at the boundaries of the T-cell zone. IDO2 was expressed only in a part of samples within the B-cell area, and in both CD138+plasma cells and CD68+macrophages.

Conclusion: In focal infiltrates of patients with SS, different areas and different cells may express IDO1 and IDO2 enzymes, thus suggesting that activity and function of these molecules in this context could be different.

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Adipose Tissue Is Prominent in Salivary Glands of Sjögren's Syndrome Patients and Appears to Influence the Autoimmune Microenvironment in These Organs. Kathrine Skarstein[1], Lara Adnan Aqrawi[1], Roland Jonsson[1] and Janicke Cecilie Liaaen Jensen[2]. [1]University of Bergen, Bergen, Norway, [2]University of Oslo, Oslo, Norway.

Background/Purpose: A positive salivary gland (SG) biopsy with a focus score of ≥1 is the only widely accepted pathological finding confirming the salivary gland component of Sjögren's syndrome (SS). SG biopsies can yield important information about the autoimmune activity and severity of the disease process including identification of germinal centers that may be possible predictors of lymphoma development. Moreover, adipocytes can occupy a large percentage of the gland area, and at present, little is known about their significance in SS lesions. The aim of the present study was to characterize adipose tissue infiltration in labial SG biopsies of patients under evaluation for SS.

Methods: 3–5 SGs were excised from the lower lip following a standard procedure. Evaluation of the glands was performed by one oral pathologist and included area assessment and counting of foci (dense aggregates of 50 or more mononuclear cells), as well as evaluation of acinar atrophy, fatty replacement, interstitial fibrosis, nonspecific chronic inflammation, and scattered or focal infiltrates of mononuclear cells adjacent to tissue not appearing normal. Patients were classified according to the AECG classification criteria and included 28 SS patients and 28 subjects evaluated for SS but not fulfilling the criteria (non-SS controls). IL-6 (rabbit polyclonal, Abcam-ab6672) expression was assessed by immunohistochemical staining of paraffin embedded salivary gland biopsies from SS patients and non-SS controls.

Results: Fatty replacement was evident in all SS patients possessing autoantibodies (RoSS-A and/or LaSS-B) as well as a positive SG biopsy (focus score ≥1), whereas 62% of the SS patients having autoantibodies but a negative biopsy showed fatty infiltration. Less than one third of the non-SS controls demonstrated fatty replacement. Overall, the SS group (mean age 53.0 years) had a significantly higher degree (p-value 0.0003) of fatty infiltration than the non-SS controls (mean age 54.8 years). Interestingly, adipocytes were located in IL-6 rich areas, and scattered IL-6 positive adipocytes were detected.

Conclusion: Our observations indicate that although fatty infiltration may occur in the repair process of glandular epithelium, fat deposition seems to be more extensive in salivary glands affected by SS. The important finding of IL-6 positive adipocytes supports the notion that adipocytes have the potential to secrete IL-6, thus being active contributors to immune reactions. Further analysis to delineate possible roles of adipocytes in the autoimmune salivary gland microenvironment is needed. Moreover, assessing the adipose tissue replacement may be helpful for diagnostic accuracy in SS.

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Predictive Significance of CCL21 and CXCL13 Levels in the Minor Salivary Glands of Patients with Sjögren's Syndrome. Kyung-Eun Lee, Dong-Jin Park and Shin-Seok Lee. Chonnam National University Medical School, Gwangju, South Korea.

Background/Purpose: Chemokines, which control inflammatory cell migration, have been shown to play important roles in the inflammatory processes associated with Sjögren's Syndrome (SS). CCL21 and CXCL13 within the lymphocytic infiltrate characteristic of the condition have been reported to contribute to ectopic lymphoneogenesis. In the current study, we investigated whether the laboratory and clinical manifestations of SS patients were associated with CCL21 and CXCL13 expression levels in the minor salivary gland.

Methods: We obtained sociodemographic data on a total of 106 SS patients, documented glandular and extraglandular manifestations of the disease, performed minor salivary gland biopsies, and analyzed laboratory findings. EULAR index values of SS disease activity (ESSDAI values) at the time of biopsy, and SS disease damage index (SSDDI) values, were also noted. An immunohistochemical approach was used to (semiquantitatively) measure the expression levels of CCL21 and CXCL13 in the minor salivary glands.

Results: The minor salivary glands of SS patients stained positively for CCL21 and CXCL13 in 46.2% (49/106) and 70.7% (75/106) of all cases, respectively. Higher-level expression of CCL21 was associated with an elevated ESR, an increased IgG level, elevated anti-SS-A and -SS-B titers, a higher focus score, and a greater ESSDAI value at the time of biopsy. Higher-level expression of CXCL13 was associated with an elevated ESR, an increased IgG level, elevated anti-SS-A and -SS-B titers, a rise in the level of rheumatoid factor, a higher focus score, and a greater ESSDAI value at the time of biopsy. In patients with extraglandular manifestations of SS, the prevalence of lymphadenopathy tended to rise with an increase in the level of CCL21.

Conclusion: The expression levels of CCL21 and CXCL13 within the lymphocytic infiltrates of SS patients were associated with several laboratory features of the disease, lymphadenopathy, and the extent of clinical disease activity. CCL21 and CXCL13 levels should serve as useful markers predicting SS disease activity and prognosis.

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Serum Biomarkers of Inflammation and Fibrosis in Advancing Diagnosis, Prognosis and Treatment of Anti-Ro Associated Congenital Heart Block. Amit Saxena, Peter M. Izmirly, Sung Won Han, Andrew Markham, Robert M. Clancy and Jill P. Buyon. New York University School of Medicine, New York, NY.

Background/Purpose: Women with Sjogren's Syndrome (SS) and anti-Ro antibodies face the risk of a pregnancy complicated by fetal congenital heart block (CHB). Identification of maternal and fetal biomarkers which associate with development and morbidity of CHB should provide clues to pathogenesis with translational implications for management. Several candidates were chosen based on potential roles in cardiac disease, inflammation and fibrosis: 1) C-reactive Protein (CRP), elevated in fetal sepsis and hypoxia 2) NT-proBNP, elevated in neonates with congenital heart disease 3) Matrix Metalloproteinase-2 (MMP2), a proinflammatory/profibrotic factor associated with heart failure in adults 4) Urokinase plasminogen activator, its receptor and plasminogen (UPA, UPAR, PGN), proteins in a cascade induced by anti-Ro binding to apoptotic cardiocytes, resulting in TGFb activation 5) Vitamin D, negative regulator in TGFb signaling and fibrosis.

Methods: Sera from anti-Ro positive mothers and cord blood from their CHB and unaffected children in the Research Registry for Neonatal Lupus

were analyzed. Cord CRP and NT-proBNP were assessed on Luminex and MMP2, UPA, UPAR and PGN by ELISA. Maternal vitamin D 25-OH was analyzed by LC-MS. Logistic regression was applied to identify predictors of CHB, fetal echo endocardial fibroelastosis (EFE) and hydrops, need for and age at pacemaker (PM) placement, and requirement of B-Blocker, digoxin, and/or ACE-I on long term follow up. Confounders were added stepwise, including maternal steroid, HCQ and IVIg use, race, maternal SS/lupus, child's gender, gestational week (GW) of delivery, and GW of greatest disease vulnerability during winter. Skewed data were log transformed for normalization.

Results: Log transformed levels of cord CRP positively associated with CHB and hydrops in 50 affected and 62 unaffected cases (adjusted OR 1.65, p=0.02, OR 3.7, p=0.02). Log cord NT-proBNP positively associated with CHB and hydrops in 57 affected and 65 unaffected (OR 2.24, p<0.001, OR 2.46, p=0.02). Log cord MMP2 positively associated with CHB in 36 affected and 28 unaffected (OR 20.23, p=0.01). Cord UPA (OR 45.42, p<0.001), UPAR (OR 12.99, p=0.03) and log PGN (OR 38.28, p=<0.001) were positively associated with CHB in 27 affected and 22 unaffected. UPA and log PGN (OR 1.22, p=0.02, OR 1.27, p=0.03) were positively associated with cardiac meds (mean age at follow-up 7.34 ± 4.93 y) in 18 affected cases. Other cord biomarkers did not associate with PM, timing of PM or cardiac meds. Although maternal vitamin D at GW 20 of CHB and healthy pregnancies were equivalent (34.3 ± 11.8 in 50 CHB and 34.1 ± 14.5 ng/mL in 81 unaffected), levels were negatively associated with fetal EFE (OR 0.89, p=0.03), and positively associated with later age at PM (p=0.01) in CHB cases.

Conclusion: Elevated inflammatory markers in neonates with CHB and extranodal disease support close follow up to identify worsening heart function. The association of NT-proBNP supports consideration of this maker as a diagnostic during amniocentesis. Elevations of MMP2, UPA, UPAR and PGN in CHB children suggest therapies aimed at decreasing fibrosis. Optimizing maternal vitamin D levels could become routine in the management of all anti-Ro positive pregnancies.

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535 WITHDRAWN

ACR Poster Session A
Spondyloarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Secukinumab, a Monoclonal Antibody to Interleukin-17A, Significantly Improves Signs and Symptoms of Active Ankylosing Spondylitis: Results of a Phase 3, Randomized, Placebo-Controlled Trial with Subcutaneous Loading and Maintenance Dosing. Joachim Sieper[1], Jürgen Braun[2], Xenofon Baraliakos[2], Dominique L. Baeten[3], Maxime Dougados[4], Paul Emery[5], Atul A. Deodhar[6], Brian Porter[7], Mats Andersson[8], Shephard Mpofu[8] and Hanno Richards[8]. [1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [4]INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France., Paris, France, [5]University of Leeds, Leeds, United Kingdom, [6]Oregon Health and Sciences University, Portland, OR, [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [8]Novartis Pharma AG, Basel, Switzerland.

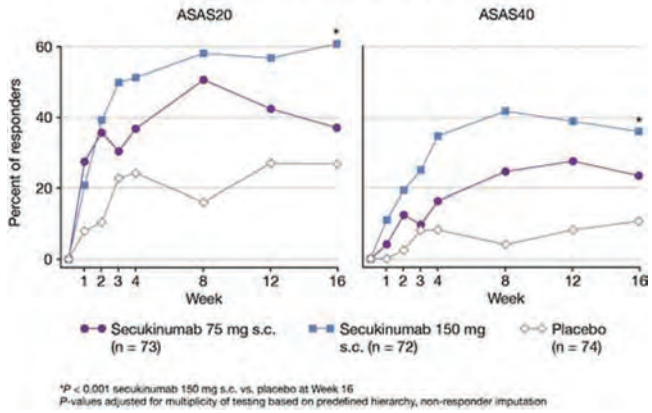
Background/Purpose: Previous data indicate that interleukin (IL)-17, a key pro-inflammatory cytokine, might play a role in the pathogenesis of ankylosing spondylitis (AS). We assessed the efficacy and safety of two different doses of secukinumab, a fully human anti–IL-17A monoclonal antibody, in a randomized, multicenter, double-blind, placebo (PBO)-controlled, phase 3 trial in patients with AS (MEASURE 2; NCT01649375).

Methods: Adults with active AS fulfilling modified New York Criteria and a BASDAI ≥ 4, despite adequate NSAID therapy, were randomized to receive weekly subcutaneous (s.c.) secukinumab 75 mg, 150 mg, or PBO for 4 weeks followed by dosing every 4 weeks. Subjects naïve to anti-TNF agents (61.6%) and subjects with prior intolerance or inadequate response to anti-TNF agents (TNF-IR; 38.4%) were included. The primary endpoint was the proportion of subjects achieving an ASAS20 response at Week 16. Secondary endpoints included ASAS40, hsCRP, BASDAI, ASAS 5/6, SF-36, ASQoL, and ASAS partial remission. Statistical analyses used non-responder imputation and followed a pre-defined hierarchical hypothesis testing strategy to adjust for multiplicity.

Results: 219 subjects were randomized. Demographics and baseline disease characteristics were comparable between study arms: mean age 43.3 years, mean time since diagnosis 6.2 years and mean BASDAI 6.65. The primary endpoint was met with secukinumab 150 mg at Week 16: ASAS20 response rate was 61.1% vs. 27.0% with PBO ($P < 0.001$; Figure), with significant improvements seen as early as Week 1. Secukinumab 150 mg also significantly improved hsCRP, ASAS40, ASAS 5/6, BASDAI, SF-36 PCS and ASQoL compared with PBO. Efficacy of secukinumab 150 mg vs. PBO was observed in both TNF-naïve and TNF-IR subjects for ASAS20 (68.9% vs. 31.1% and 48.1% vs. 20.7%, respectively; both $P < 0.05$) and ASAS40 (44.4% vs. 17.8% and 22.2% vs. 0%, respectively; both $P < 0.05$). Secukinumab 75 mg provided numerically greater responses than PBO at Week 16, but these did not reach statistical significance for any of the pre-specified primary or secondary endpoints based on hierarchical testing. Similar adverse event (AE) rates were reported up to Week 16 for secukinumab 75 mg (57.5%), 150 mg (62.5%), and PBO (63.5%). Serious AEs were reported in 5.5% of subjects in the secukinumab 75 mg group, compared with 5.6% in the secukinumab 150 mg group and 4.1% in the PBO group.

Conclusion: Secukinumab 150 mg s.c. was effective at rapidly reducing the signs and symptoms of disease and improving health-related quality of life in subjects with active AS, regardless of prior anti-TNF exposure. Secukinumab was well tolerated, with no unexpected safety findings.

Figure. ASAS response over 16 weeks



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Secukinumab, a Human Anti–Interleukin-17A Monoclonal Antibody, Significantly Reduces Psoriasis Burden in Patients with Psoriatic Arthritis: Results from a Phase 3 Randomized Controlled Trial. Alice B. Gottlieb[1], Philip Mease[2], Iain B. McInnes[3], Bruce Kirkham[4], Arthur Kavanaugh[5], Proton Rahman[6], Peter Nash[7], Luminita Pricop[8], Jiacheng Yuan[8], Hanno Richards[9] and Shephard Mpofu[9]. [1]Tufts Medical Center, Boston, MA, [2]Swedish Medical Center and University of Washington, Seattle, WA, [3]University of Glasgow, Glasgow, United Kingdom, [4]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [5]UCSD School of Medicine, La Jolla, CA, [6]Memorial University of Newfoundland, St. John's, NF, [7]University of Queensland, Brisbane, Australia, [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [9]Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: Reducing the burden of skin manifestations of psoriatic arthritis (PsA) is an important aspect of disease management. Secukinumab, a human anti–IL-17A monoclonal antibody, has demonstrated rapid and sustained efficacy in the treatment of psoriasis in phase 3 trials, including in the subset of patients (pts) with PsA. Here we present the effect of secukinumab on dermatological parameters in pts enrolled in FUTURE 1 (NCT01392326), the first phase 3 trial to evaluate the efficacy of IL-17A inhibition in pts with PsA.

Methods: Adults with moderate to severe PsA according to ClASsification of Psoriatic ARthritis criteria were randomized to a secukinumab 10 mg/kg intravenous (i.v.) loading dose at baseline (BL), Week (Wk) 2, and Wk 4, then either 75 mg subcutaneously (s.c.; 10 IV→75 SC) or 150 mg s.c. (10 IV→150 SC) every 4 wks from Wk 8, or placebo (PBO) on the same i.v. and s.c. schedules. Assessments of psoriasis burden included 75% and 90% improvement in Psoriasis Area and Severity Index (PASI 75/90), Investigator's Global Assessment (modified 2011) score of 0 or 1 (IGA 0/1), target lesion score (TLS), modified Nail Psoriasis Severity Index (mNAPSI), and the Dermatology Life Quality Index (DLQI). The effect of treatment on high-sensitivity C-reactive protein (hsCRP) levels, a marker of skin and joint inflammation, was also monitored.

Results: From the full analysis set (FAS) of 606 pts, 325 (53.6%) had psoriasis affecting ≥ 3% of body surface area at BL (psoriasis subset), 510 (84.2%) had a psoriatic target lesion ≥ 2 cm in diameter (TLS subset) and 435 (71.8%) had nail involvement (nail subset). Improvements in dermatology parameters with secukinumab vs. PBO at Wk 24 are presented in the table. In the psoriasis subset, 10 IV→75 SC and 10 IV→150 SC significantly improved the proportion of PASI 75, PASI 90, and IGA 0/1 responders vs. PBO at Wk 24, and provided clinically meaningful improvement (≥ 4-point change from BL) in DLQI, with most pts having a decline in DLQI score from > 10 (severe) at BL to < 4 at Wk 24. Pts in the TLS subset experienced a rapid (from Wk 1) and significant improvement in TLS with secukinumab vs. PBO at Wk 24, while mNAPSI was significantly improved with secukinumab in the nail subset. hsCRP values were significantly lower with secukinumab vs. PBO from Wk 1 through Wk 24 (FAS).The improvements in dermatological parameters observed with secukinumab at Wk 24 were sustained through Wk 52.

Table. Effect of treatment on skin and involvement at Week 24

BL and Wk 24 Data	Secukinumab10 mg/kg IV → 75 mg SC	Secukinumab10 mg/kg IV → 150 mg SC	Placebo
[a]PASI Responses	6.4	9.2	8.9
BL score	64.8*/49.1*	61.1*/45.4*	8.3/3.7
PASI 75/90, % responders			
[a]IGA 0/1, % responders	54.6*	49.1*	3.7
[b]TLS	5.5	6.0	6.1
BL	–4.46*	–4.64*	–1.31
Mean change from BL			
[c]mNAPSI	18.6	18.7	17.5
BL	–12.3*	–10.9*	–4.1
Mean change from BL			
[a]DLQI total score	11.2	12.6	12.5
BL	–7.87*	–8.80*	0.70
Mean change from BL			

*$P < 0.0001$ vs. placebo; [a]Data from patients with psoriasis affecting ≥ 3% of body surface area at BL (n=325); [b]TLS data from patients with psoriatic target lesion ≥ 2 cm in diameter (n=510); [c]Data from patients with nail psoriasis (n=435).
BL, baseline; DLQI, Dermatology Life Quality Index;IGA, Investigator's Global Assessment; IV, intravenous; mNAPSI, modified Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; SC, subcutaneous; TLS, target lesion score

Conclusion: This is the first phase 3 trial in pts with active PsA to demonstrate that selective IL-17A inhibition with secukinumab significantly reduces the severity of plaque and nail psoriasis and improves quality of life in those pts with a significant concomitant psoriasis burden in addition to their joint disease.

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Secukinumab, a Monoclonal Antibody to Interleukin-17A, Significantly Improves Physical Function and Quality of Life in Subjects with Active Ankylosing Spondylitis: Results of a Phase 3 Randomized, Placebo-Controlled Trial with Intravenous Loading and Subcutaneous Maintenance Dosing. Atul A. Deodhar[1], Dominique L. Baeten[2], Jürgen Braun[3], Xenofon Baraliakos[3], Joachim Sieper[4], Maxime Dougados[5], Paul Emery[6], Brian Porter[7], Ruvie Martin[7], Shephard Mpofu[8] and Hanno Richards[8]. [1]Oregon Health and Sciences University, Portland, OR, [2]Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [3]Rheumazentrum Ruhrgebiet, Herne, Germany, [4]Charité Universitätsmedizin Berlin, Berlin, Germany, [5]Descartes University, Cochin Hospital, Paris, France, [6]University of Leeds, Leeds, United Kingdom, [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [8]Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: Ankylosing spondylitis (AS) can have a profound negative effect on an individual's physical functioning, health status and quality of life (QoL), affecting the ability to work (Sieper J et al. Ann Rheum Dis. 2002). Since interleukin (IL)-17A is implicated in the pathogenesis of AS (Dougados M, Baeten, D. Lancet 2011), inhibition of this cytokine with secukinumab, a fully human anti-IL-17A monoclonal antibody, may help reduce the burden of disease. Here we present the impact of high-dose intravenous (i.v.) loading with secukinumab followed by subcutaneous (s.c.) maintenance dosing on patient-reported outcomes (PROs) in a phase 3 trial (MEASURE 1; NCT01358175) over 52 weeks.

Methods: 371 adults with active AS fulfilling modified New York Criteria and Bath Ankylosing Spondylitis Disease Activity Index ≥ 4 were randomized to receive i.v. secukinumab 10 mg/kg (Week 0, Week 2, Week 4) followed by s.c. secukinumab 75 mg every 4 weeks (10 IV → 75 SC); i.v. secukinumab 10 mg/kg (Week 0, Week 2, Week 4) followed by s.c. secukinumab 150 mg every 4 weeks (10 IV → 150 SC); or i.v. placebo (Week 0, Week 2, Week 4) followed by s.c. placebo every 4 weeks (placebo group; PBO). PBO subjects were re-randomized to either 75 mg or 150 mg s.c. secukinumab based on ASAS20 response at Week 16, with non-responders switched to secukinumab at Week 16 and responders at Week 24. PROs were measured every 4 weeks using the following questionnaires: short form 36 (SF-36), EuroQoL (EQ-5D), AS QoL (ASQoL), Functional Assessment of Chronic Illness Therapy — Fatigue (FACIT-Fatigue) and Work Productivity and Activity Impairment — General Health (WPAI-GH). PROs to Week 16 are reported using a mixed-effect model repeated measures (MMRM) analysis, except WPAI-GH domains which are observed data.

Results: Demographics and disease severity were comparable among the three groups with subjects experiencing moderate to severe levels of fatigue and impaired health-related QoL at baseline. Secukinumab 10 IV →75 SC and 10 IV → 150 SC significantly improved scores on the SF-36 physical and mental component summaries, ASQoL, EQ-5D and FACIT-Fatigue vs. PBO at Week 16 (Table), with significant differences in these parameters seen with both doses in all assessments starting at Week 4. Mean changes from baseline at Week 16 were greater than the minimum clinically important difference (MCID) for SF-36

PCS, MCS, ASQoL and FACIT-Fatigue (Table). Reductions in the impact of disease on work productivity (WPAI-GH) were observed with secukinumab vs. PBO at Week 16. Improvements in PROs observed with secukinumab were sustained or increased beyond Week 16 through Week 52.

Conclusion: In subjects with active AS, selective inhibition of IL-17A with secukinumab provided rapid and sustained improvements in PROs, including fatigue, general and AS-specific QoL measures, and illness-associated reductions in work productivity.

Table. Mean baseline scores and mean change from baseline in patient-reported outcomes (PROs) at Week 16 and 52 by treatment group

PROs		Secukinumab 10 mg/kg i.v. → 75 mg s.c. n = 124	Secukinumab 10 mg/kg i.v. → 150 mg s.c. n = 125	Placebo n = 122
SF-36 PCS[a]	BL	37.57	36.81	36.30
	Change[c] at Wk 16	5.64 ± 0.595*	5.57 ± 0.586*	0.96 ± 0.612
	Change[d] at Wk 52	7.03	7.53	N/A
SF-36 MCS[a]	BL	41.54	39.99	39.21
	Change[c] at Wk 16	3.29 ± 0.841*	3.40 ± 0.828*	0.61 ± 0.865
	Change[d] at Wk 52	5.78	5.32	N/A
ASQoL[b]	BL	10.82	10.85	11.67
	Change[c] at Wk 16	−3.61 ± 0.424*	−3.58 ± 0.420*	−1.04 ± 0.437
	Change[d] at Wk 52	−4.49	−4.68	N/A
EQ-5D health state assessment[a]	BL	47.1	45.2	46.5
	Change[c] at Wk 16	15.24 ± 1.923*	13.26 ± 1.908*	2.01 ± 1.991
	Change[d] at Wk 52	21.9	19.6	N/A
FACIT-Fatigue[a]	BL	27.46	25.60	24.51
	Change[c] at Wk 16	6.58 ± 0.850*	6.77 ± 0.837*	2.50 ± 0.875
	Change[d] at Wk 52	7.69	10.24	N/A

*$P < 0.05$ vs. PBO.
SF-36 PCS MCID ≥ 2.5, SF-36 MCS MCID ≥ 2.5, ASQoL MCID ≥ 1.8, FACIT-Fatigue MCID ≥ 4
P-values at Week 16 are from mixed-effect model repeated measures (MMRM) analysis.
[a]Increase in score represents improvement; [b]Decrease in score represents improvement. [c]LSM ± SE, LSM = Least square means; SE = std. error. [d]Observed data.
MCID, Minimum Clinically Important Difference; ASQoL, Ankylosing Spondylitis Quality of Life; EQ-5D, EuroQoL 5-Dimension health status index; i.v., intravenous; s.c., subcutaneous; SF-36 MCS, Short Form 36 mental component summary; SF-36 PCS, Short Form 36 physical component summary

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Efficacy and Safety of Ustekinumab in Psoriatic Arthritis Patients with Spondylitis and Peripheral Joint Involvement: Results from a Phase 3, Multicenter, Double-Blind, Placebo-Controlled Study. Arthur Kavanaugh[1], Lluís Puig Sanz[2], Alice B. Gottlieb[3], Christopher T. Ritchlin[4], Yin You[5], Yuhua Wang[5], Alan M. Mendelsohn[5], Michael Song[5], Proton Rahman[6] and Iain B. McInnes[7]. [1]University of California San Diego, La Jolla, CA, [2]Universitat Autònoma de Barcelona, Barcelona, Spain, [3]Tufts Medical Center, Boston, MA, [4]University of Rochester Medical Center, Rochester, NY, [5]Janssen Research & Development, LLC., Spring House, PA, [6]Memorial University of Newfoundland, St. John's, NF, [7]University of Glasgow, Glasgow, United Kingdom.

Background/Purpose: IL-23 may be implicated in spondylitis. A substantial number of pts with spondylitis and peripheral joint involvement were enrolled in PSUMMIT. We evaluated the efficacy of SC UST 45/90 mg in a subgroup of psoriatic arthritis (PsA) pts with physician diagnosed spondylitis and peripheral joint involvement through wk108, from PSUMMIT 1.

Methods: Adult PsA patients (n=615) with active disease (≥5 SJC and ≥5 TJC;CRP≥0.3mg/dL) despite DMARD and/or NSAIDs were randomized to UST45mg, 90mg, or PBO at wks 0, 4, and q12wks. Pts treated with prior anti-TNF agents were excluded. Stable concomitant MTX was permitted but not mandated. At wk16, pts with <5% improvement in TJC & SJC entered blinded early escape (PBO→UST45mg; UST45mg→90mg; 90mg→90mg). PBO pts subsequently crossed over to UST45mg at wk24. Pts received q12w dosing to wk88, with final efficacy evaluation at wk100 and safety assessment at wk108. Pts with spondylitis and peripheral joint involvement as their primary arthritis presentation of PsA also had BASDAI assessments at wks12 and 24.

Results: 186 randomized pts (70 PBO, 116 UST combined) had spondylitis with peripheral joint involvement at baseline (30% of overall population); mean baseline characteristics were similar to the overall population (age 45.6yrs, weight 82.8kg, PsA duration 6.3yrs, SJC/TJC 14.3/24.1, HAQ-DI 1.3; BASDAI 6.5, and 26% were HLAB27 positive. Mean baseline scores among pts with dactylitis (n=100), enthesitis (148), and skin disease (147) were 8.3, 5.6, and PASI 14.2, respectively. At wk24, greater proportions of combined UST45/90mg treated pts had improvements in dactylitis/enthesitis measurements, HAQ-DI and ACR20/50/70 responses than PBO (Table). Clinical improvements were generally maintained through wk100. A significantly higher proportion of UST-treated pts achieved BASDAI20/50/70 responses vs. PBO at wk24 (54.1%/27.9%/14.4% vs. 26.2%/13.1%/0.0%). Peripheral structural damage assessed by total vdH-S mean change from baseline also showed improvement in the UST groups vs PBO at wk24. Of the 135 patients with ≥3% BSA involvement and spondylitis with peripheral arthritis at baseline, PASI75 responses were also maintained through wk100. During the PBO-controlled period, the proportion of pts with AEs were comparable between the PBO and combined UST-treated groups (AEs 32.9% vs 24.1%; SAEs 1.4% vs 0.9%; discontinuations due to AEs 2.9% vs 0.9%; serious infections 14.3% vs 7.8%). Through 2yrs, safety observations were consistent with the overall PsA population.

Conclusion: In this post-hoc subgroup analysis, UST significantly improved signs and symptoms, and demonstrated improvements in BASDAI and peripheral radiographic progression compared with PBO through wk24; efficacy was maintained through wk100. UST was well-tolerated and demonstrated a safety profile similar to that observed in the overall PsA study population.

Table: PSUMMIT 1-Efficacy Outcomes in Patients with Spondylitis and Peripheral Joint Involvement at Baseline (BL)

	Wk 24		Wk 52		Wk 100	
	PBO	UST Combined	PBO→ 45mg	UST Combined	PBO→ 45mg	UST Combined
n	70	116	63	116	63	116
ACR20/ACR50/ACR70 (%)	20.0/2.9/1.4	38.8[†]/26.7/12.1 [†]P=0.006	N=63 65.1/41.3/15.9	N=111 62.2/36.9/21.6	N=62 62.9/35.5/16.1	N=109 61.5/43.1/22.9
Mean % change (median) from BL entheses score (MASES index)*	N=50 –5.81(0.00)	N=92 –46.14(–48.33) P=0.009	N=48 –53.88(–100.00)	N=88 –58.39(–88.31)	N=47 –50.70(–100.00)	N=87 –49.58(–100.00)
Mean % change(median) from BL dactylitis score**	N=33 2.47(0.00)	N=63 –64.05(–94.44) P<0.001	N=31 –65.38(–100.00)	N=62 –75.58(–100.00)	N=31 –73.66(–100.00)	N=61 –81.15(–100.00)
Mean (SD) change from BL HAQ-DI	N=70 –0.10(0.41)	N=116 –0.36(0.56) P<0.001	N=63 –0.42(0.39)	N=111 –0.41(0.58)	N=62 –0.38(0.48)	N=109 –0.39(0.63)
PASI 75 response ***	N=52 11.5%	N=95 65.3% P<0.001	N=47 66.0%	N=92 73.9%	N=44 63.6%	N=91 78.0%
Total vdH-S mean change from BL (peripheral joints)	1.92(7.26)	0.05(1.77) P<0.001	2.03(10.15)	0.34(2.41)	4.28(21.03)	1.46(5.07)

Patients who did not receive UST are excluded at wk52 and wk100; *Enthesitis with spondylitis and peripheral joint involvement at baseline; **Dactylitis with spondylitis and peripheral joint involvement at baseline; ***Among randomized patients with ≥3% BSA psoriasis skin, spondylitis and peripheral joint involvement at BL

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Two Years Sacroiliac Radiographic Progression Rate and Influence of Baseline Markers of Inflammation in Recent Onset Spondyloarthritis. Maxime Dougados[1], Christophe Demattei[2], Rosaline van den Berg[3], Viet Vo Hoang[4], Fabrice Thévenin[5], Monique Reijnierse[3], Damien Loeuille[6], Antoine Feydy[7], Pascal Claudepierre[8] and Désirée van der Heijde[9]. [1]INSERM

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Background/Purpose: According to the ASAS axial spondyloarthritis (SpA) criteria, patients suffering from inflammatory back pain (IBP) can be recognized as suffering from axial SpA even in the absence of structural damage of the sacroiliac joints (SIJ) but the natural history of these patients is not well known.The objective of this study was to evaluate 1) the rate of SIJ structural progression over a 2 years period and 2) the influence of baseline objective signs of inflammation on this progression rate in patients suffering from recent onset inflammatory back pain suggestive of SpA.

Methods: *Patients:* IBP < 3 years duration suggestive of axial SpA according to the treating rheumatologist (DESIR cohort) *Outcome measures:* **Pelvic X-rays** collected both at baseline and at the 2 year follow up visit and **MRI of the SIJ** collected at baseline were stored after anonymizing and blinding for the visit. Radiographic structural damage was defined as the fulfillment of the modified New-York (mNY) criteria and inflammation on MRI ("positive MRI") was defined according to the ASAS criteria. The radiographs and MRIs were read centrally by two pairs of well calibrated central readers blinded for clinical, laboratory and other imaging data. In case of disagreement, images were adjudicated by an experienced radiologist. **CRP**at baseline was defined as abnormal if >6mg/l.

Results: Of the 708 enrolled patients, 449 had a complete radiological data set (34 + 9 years old, 53 % females, HLA B27 positive: 61%). At baseline, 123 of 449 (27%) fulfilled the mNY criteria. Of the remaining 326 patients, 16 (4.9%) progressed (fulfilling the mNY criteria at the 2 year visit). Among these 326 patients, baseline MRI, CRP and both MRI and CRP were available in 307, 314 and 303 patients respectively. The table summarizes the main findings of this study. MRI positivity, CRP abnormality and either MRI positivity or CRP abnormality was observed in 14/15 (93%) *versus* 67/292 (23%), 7/15 (46%) *versus* 61/299 (20%) and 14/15 (93%) *versus* 111/288 (39%) of the patients with *versus* without a radiographic progression after the 2 year follow-up visit. A normal MRI and CRP at baseline almost excluded the development of sacroiliitis according to the mNY criteria after two years.

Table: SIJ structural progression among the 326 patients not fulfilling SIJ mNY criteria at baseline

		SIJ structural progression		
Baseline Variable		**mNY Positive at year 2**	**mNY negative at year 2**	
MRI	positive	14*	67	OR: 47.0[6.1–364.1] PPV: 0.17
	negative	1	225	NPV:0.004
CRP	abnormal	7	61	OR:3.4[1.2–9.8] PPV:0.10
	normal	8	238	NPV:0.033
Inflammation**	presence	14	111	OR:23.3[2.9–172.1] PPV:0.11
	absence	1	177	NPV: 0.006

*values given are the number of patients and OR []: Odds ratio [95% confidence interval]; PPV: positive predictive value; NPV: negative predictive value.
**baseline inflammation: either MRI positive or abnormal CRP

Conclusion: These data suggest that 1) SIJ structural progression to fulfillment of mNY criteria in this cohort was low after a two years follow-up period 2) the presence of objective signs of inflammation are a predisposing factor of structural progression keeping in mind that the majority of patients with baseline signs of inflammation did not progress.

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Collagen II Neo-Epitopes in Spondyloarthritis. Heidi Lausten Munk[1], Natasja Staehr Gudmann[2], Anne Friesgaard Christensen[3], Leif Ejstrup[4], Grith Lykke Sørensen[5], Anne Gitte Loft[3], Anne C. Bay-Jensen[2], Anne Sofie Siebuhr[2] and Peter Junker[1]. [1]Department of Rheumatology, Odense University Hospital, Odense, Denmark, [2]Cartilage Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, [3]Department of Rheumatology, Vejle Hospital, Vejle, Denmark, [4]Department of Rheumatology, Esbjerg Hospital, Esbjerg, Denmark, [5]Institute of Molecular Medicin, University of Southern Denmark, Odense, Denmark.

Background/Purpose: Spondyloarthritis (SpA) is characterized by aseptic inflammation of the axial skeleton which may ultimately lead to irreversible deformities due to bony ankylosis. Occasionally, peripheral joints and extraskeletal sites are also involved. The etiology is unknown, but there is a well-established association with HLA-B27. Intervertebral discs and diarthrodial joints of the spine are targeted by the disease, and studies on cartilage have indicated increased turnover of several extracellular matrix components, mainly collagen, in active ankylosing spondylitis (AS). Thus, C2M, a matrix metalloproteinase derived collagen type II fragment has been found to be increased in AS. Procollagen IIA, an alternatively spliced collagen II variant, is preferentially expressed during embryogenic skeletal patterning where it is supposed to participate in the regulation of chondro- and osteogenesis. In adults PIIANP is present in damaged cartilage and osteophytes.

The aims of this investigation were to assess collagen II turnover in SpA by studying C2M and PIIANP concomitantly in patients treated with or without TNF inhibitors (TNFi).

Methods: One hundred and ten patients (age 18–63 years) with SpA according to the ASAS criteria were recruited from two secondary and one tertiary center. Demographic and clinical disease measures were recorded. Ninety six volunteer blood donors served as healthy controls. C2M and PIIANP were quantified in serum by ELISA. Mann–Whitney U test for intergroup comparisons and Spearman's rank test for correlations were applied. The discriminative power of the serum markers between healthy and diseased was calculated by receiver-operator characteristics (ROC) and expressed by the area under the curve (AUC).

Results: The serum level of C2M was higher in SpA patients compared to healthy controls ($p<0.01$)(table). The PIIANP level did not differ between SpA patients and controls. There was no correlation between C2M and PIIANP. C2M correlated negatively with smoking ($r=-0.22$;$p=0.02$) and PIIANP correlated positively with sex ($r=0.31$;$p=0.001$), CRP ($r=0.31$; $p=0.001$), HLA-B27 ($r=0.21$;$p=0.03$) and negatively with treatment ($r=-0.23$;$p=0.02$). Patients were categorized according to TNFi treatment (TNFi-/TNFi+). PIIANP and C2M were increased in TNFi- patients compared to controls ($p<0.05$–0.001). Using ROC calculation for C2M AUC was estimated to 0.67.

Characteristics	**SpA (n=110)**	**TNFi- (n=57)**	**TNFi+ (n=53)**
Sex (% male)	72%	63%*	81%
Age	36.6 (35.3–38.0)	35.7 (33.4–37.9)	37.7(36.1–39.3)
BMI	25.5 (24.8–26.3)	25.4 (24.1–26.6)	25.7 (24.8–26.6)
Smoker	36%	32%	42%
HLA-B27 (%)	87%	84%	91%
Disease duration (y)	6.4 (5.4–7.5)	5.0 (3.7–6.3)**	8.1 (6.4–9.7)
Patient global VAS	34 (29–39)	43 (35–50)**	25.8 (19.3–32.3)
Patient pain VAS	32 (27–37)	40 (33–48)***	23.4 (17.4–29.4)
Patient fatigue VAS	40 (34–45)	48 (40–55)**	32.8 (25.7–39.9)
Physician global VAS	4 (1;16)	10 (1;24)***	1 (0;7)
BASDAI	31 (26–35)	38 (32–44)***	23.5 (17.9–27.6)
BASFI	23 (19–27)	25 (20–30)	21.2 (14.8–27.6)
BASMI	10 (0;20)	10 (0;20)	10 (0;30)
ASDAS(CRP)	2.0 (1.8–2.3)	2.5 (2.1–2.8)***	1.6 (1.3–1.8)
Swollen joint (%)	9%	11%	9%
hs-CRP (mg/l)	3 (1;7)	5.5 (1.3–9.3)***	2 (0.9;3.9)
PIIANP(ng/ml) 2142 (1742;2658)	2252 (1888;2770)	2459 (1916;2983)#	2171 (1852;2522)
ROC PIIANP (AUC)	0.56 (0.48–0.64)	0.60 (0.50–0.69)	0.52 (0.43–0.62)
C2M(ng/ml) 0.36 (0.30;0.43)	0.41 (0.34;0.50)##	0.44 (0.35;0.50)###	0.39 (0.31–0.5)
ROC C2M (AUC)	0.62 (0.54–0.69)	0.67 (0.58–0.76)	0.56 (0.46–0.66)

#Denotes SpA vs. controls *Denotes TNFi- vs. TNFi+

Conclusion: These findings indicate that active SpA is associated with enhanced cartilage turnover as reflected by increased collagen II degradation and repair. Conversely, this sero-marker profile was normal during TNFi treatment. In addition, C2M discriminates well between healthy subjects and SpA.

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Predictors for Cardiovascular Events in Patients with Psoriatic Arthritis – a Cohort Study. Lihi Eder[1], Arane Thavaneswaran[1], Vinod Chandran[1], Hua Shen[2], Richard J. Cook[2] and Dafna D. Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Waterloo, Waterloo, ON.

Background/Purpose: The prevalence of cardiovascular (CV) morbidity is increased in patients with psoriatic arthritis (PsA). CV risk is only partially explained by traditional CV risk factors. We aimed to identify predictors for CV events in a cohort of patients with PsA.

Methods: A retrospective cohort analysis was conducted in patients attending a large PsA clinic from 1978 to 2013. Patients were assessed at 6–12 month intervals according to a standard protocol. The collected information included demographics, lifestyle habits, medical history and disease-related outcomes. The following factors were assessed as candidate predictors of CV events: traditional CV risk factors, measures of PsA disease activity and laboratory biomarkers of inflammation. The primary outcome was the time to the first major CV event that comprised myocardial infarction (MI), ischemic stroke, re-vascularization or CV death. The secondary outcome was the time to any first CV event that included major CV events, angina, transient ischemic accident (TIA) and congestive heart failure (CHF). Each event was confirmed by reviewing hospital records and death certificates. Cox proportional hazard model, with time-dependent explanatory variables and date of birth as the time of origin, was used to compute the multivariate relative risk (RR) for incident CV events adjusting for sex and duration of PsA.

Results: The analysis included 1103 patients with PsA for a combined follow-up time of 10,751 person-years, during which 104 cardiovascular events occurred (57 MI, 9 stroke, 19 revascularization, 2 CV death, 10 angina, 1 TIA and 6 CHF). The mean follow-up period was 9.8±8.5 years. The mean age at the first visit was 44±12.9 years and 56.3% of the patients were males. The incidence rate of CV events did not change significantly across the three decades from 1978 to 2013 (p=0.65). The following variables were associated with a higher incidence rate of major CV events: diabetes (RR 2.7, p=0.002), hypertension (RR 1.93 p=0.003), high triglycerides (RR 1.95 p=0.005), high cholesterol (RR 1.58 p=0.05), erythrocyte sedimentation rate (ESR) (RR 1.36 p=0.009), leukocyte count (RR 2.19 p=0.007) and tender joint count (RR 1.34, p=0.01). The variables that were associated with a higher incidence rate of any CV event were: diabetes (RR 2.68 p=0.0007), hypertension (RR 1.99, p=0.0008), high triglycerides (RR 1.71 p=0.02), ESR (RR 1.3 p=0.02) and tender joint count (RR 1.34 p=0.007). Achieving a minimal disease activity state was associated with a lower incidence rate of major CV events (RR 0.56, p=0.009) and any CV event (RR 0.62, p=0.02). No association was found between the use of non-steroidal anti-inflammatory drugs, disease modifying anti rheumatic agents or TNFα blockers and CV events.

Conclusion: Cardiovascular morbidity in patients with PsA is explained by the combined effect of elevated inflammatory burden and traditional CV risk factors. The achievement of a minimal disease activity state may decrease CV risk in patients with PsA.

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Disease Activity and Clinical Response Early in the Course of Treatment Predict Long-Term Outcomes in Axial Spondyloarthritis Patients Treated with Certolizumab Pegol. Désirée M. van der Heijde[1], Atul A. Deodhar[2], Owen Davies[3], Tommi Nurminen[4] and Martin Rudwaleit[5]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Oregon Health and Science University, Portland, OR, [3]UCB Pharma, Slough, United Kingdom, [4]UCB Pharma, Monheim, Germany, [5]Endokrinologikum, Berlin, Germany.

Background/Purpose: Early response to anti-TNF therapy has been shown to be a strong predictor of good long-term outcomes in ankylosing spondylitis (AS). [1] However, early identification of patients (pts) unlikely to achieve good long-term disease control by anti-TNF therapy has been less well characterized, although identifying such pts may help avoid unnecessary exposure, increase cost-effectiveness and improve the chance of achieving long-term treatment goals. Here we aim to assess the association between disease activity (DA) during the first 12 weeks (wks) of treatment, and attainment/lack of attainment of treatment targets at Wk48 in axial spondyloarthritis (axSpA) pts, including AS and non-radiographic (nr-) axSpA pts, receiving certolizumab pegol (CZP).

Methods: The relationship between DA during the first 12 wks of treatment and achievement of the Wk48 treatment targets: ASDAS Inactive Disease (ID) or BASDAI <2 with or without CRP levels equal to or below the upper limit of normal (ULN=7.9mg/L), was assessed post hoc using CZP data from the RAPID-axSpA trial (NCT01087762). [2] DA state was defined for ASDAS as: ID, moderate (MD), high (HD) or very high DA (vHD), and for BASDAI as Low (<2), Moderate (≥2 to <4), High (≥4 to ≤6) or Very High (>6). BASDAI thresholds have not been validated. Analyses are based on all pts randomized to CZP (200mg Q2W or 400mg Q4W) in the overall axSpA population and also the AS and nr-axSpA subpopulations. Predictability analyses for a given wk are based on all pts continuing treatment at that wk. For these pts, LOCF was applied for withdrawals before, or missing evaluation at, Wk48.

Results: ASDAS DA state at Wk2 was associated with likelihood of achieving ID at Wk48, with 71% (22/31) of pts with ID at Wk2 achieving ID at Wk48, compared with 0% (0/27) of pts with vHD at Wk2 achieving ID at Wk48. A similar trend was observed at Wk12, although fewer pts had HD and vHD, and more pts had ID at this time point (Table A). BASDAI Very High DA also successfully predicted the lack of attainment of the treatment target BASDAI <2 + CRP ≤ULN (Tables B and C), and results were not altered if only BASDAI <2 (and not CRP level) was the target. Lack of clinical response (CR) to CZP was also an effective negative predictor of Week 48 DA (Table C), with 3/45 (6.7%) pts with Wk12 BASDAI improvement <1 achieving Wk48 DA of BASDAI <2, and 12/65 (18.5%) pts with Wk12 ASDAS improvement less than clinically important improvement (<CII) achieving Wk48 ASDAS ID. Similar trends were observed in the AS and nr-axSpA subpopulations (Table C).

Conclusion: Using ASDAS or BASDAI DA state or CR during the first 12 wks of CZP treatment, it was possible to identify a subset of pts who are unlikely to achieve long-term treatment goals. This approach may enable physicians adopting a treat-to-target strategy to determine early on when to change therapy in pts not responding to CZP.

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Table A: Proportion of pts achieving ASDAS ID at Wk48 based on ASDAS classification of DA at Baseline, Wk2, Wk8 and Wk12

Visit	ASDAS ID n/N (%)	ASDAS MD n/N (%)	ASDAS HD n/N (%)	ASDAS vHD n/N (%)
Baseline	0/0	1/3 (33.3)	32/70 (45.7)	34/145 (23.4)
Week 2	22/31 (71.0)	30/59 (50.8)	15/100 (15.0)	0/27 (0.0)
Week 8	35/49 (71.4)	22/57 (38.6)	10/89 (11.2)	0/20 (0.0)
Week 12	34/50 (68.0)	20/54 (37.0)	13/86 (15.1)	0/21 (0.0)

Table B: Proportion of pts achieving BASDAI <2 + CRP ≤ULN at Wk48 based on BASDAI DA at Baseline, Wk2, Wk8 and Wk12

Visit	Low BASDAI <2 n/N (%)	Moderate BASDAI ≥2 to <4 n/N (%)	High BASDAI ≥4 to ≤6 n/N (%)	Very High BASDAI >6 n/N (%)
Baseline	0/0	2/9 (22.2)	36/79 (45.6)	28/130 (21.5)
Week 2	20/31 (64.5)	30/62 (48.4)	12/63 (19.0)	4/61 (6.6)
Week 8	30/45 (66.7)	30/74 (40.5)	5/59 (8.5)	1/37 (2.7)
Week 12	37/58 (63.8)	19/61 (31.1)	10/54 (18.5)	0/38 (0.0)

Key to probability: Light grey: 10–20% | Dark grey: 0–10%

Table C: Proportion of pts achieving Wk48 treatment targets based on DA or CR at Wk12

Target	Wk12 Predictor	Proportion of pts achieving target at Wk48		
		axSpA n/N (%)	AS n/N (%)	nr-axSpA n/N (%)
ASDAS ID	ASDAS vHDA	0/21 (0.0)	0/9 (0.0)	0/12 (0.0)
	ASDAS <CII	12/65 (18.5)	7/31 (22.6)	5/34 (14.7)
BASDAI <2 + CRP ≤ULN	BASDAI Very High DA (>6)	0/38 (0.0)	0/18 (0.0)	0/20 (0.0)
	BASDAI Change <1	3/45 (6.7)	2/24 (8.3)	1/21 (4.8)

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Observed Incidence Rates of Uveitis over 96 Weeks of Certolizumab Pegol Treatment in Patients with Axial Spondyloarthritis. James T. Rosenbaum[1], Martin Rudwaleit[2], Robert B. M. Landewé[3], Helena Marzo-Ortega[4], Joachim Sieper[5], Désirée M. van der Heijde[6], Owen Davies[7], Christian Stach[8], Tommi Nurminen[8] and Atul A. Deodhar[9]. [1]OHSU, Portland, OR, [2]Endokrinologikum, Berlin, Germany, [3]Amsterdam Rheumatology Center, Amsterdam, Netherlands, [4]University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [5]University Hospital Charité, Berlin, Germany, [6]Leiden University Medical Center, Leiden, Netherlands, [7]UCB Pharma, Slough, United Kingdom, [8]UCB Pharma, Monheim, Germany, [9]Oregon Health and Sciences University, Portland, OR.

Background/Purpose: Axial spondyloarthritis (axSpA) is characterized by inflammation in the spine and sacroiliac joints, but can also manifest as inflammation at extra-spinal sites, most commonly inflammation of the uvea (uveitis).[1] Here we aim to estimate the incidence of uveitis flares in patients (pts) with axSpA following certolizumab pegol (CZP) treatment in the RAPID-axSpA trial.

Methods: RAPID-axSpA (NCT01087762)[2] was double-blind and placebo (PBO)-controlled to Week (Wk) 24, dose-blind to Wk48 and open-label to Wk204. Pts fulfilled ASAS criteria and had active axSpA, including ankylosing spondylitis (AS) and non-radiographic (nr-)axSpA. Pts were randomized 1:1:1 to either CZP 200mg Q2W, 400mg Q4W (following 400mg loading dose [LD] at Wks 0, 2, 4) or PBO. PBO pts entering dose-blind phase were re-randomized to CZP LD followed by CZP 200mg Q2W or 400mg Q4W after Wk24 or, for non-responders, Wk16. Uveitis events were recorded on extra-articular manifestation forms or adverse event forms (preferred term "Uveitis"). Events were analyzed in pts with or without a history of uveitis (defined using standard medical history, ASAS classification criteria screening assessment and baseline extra-articular assessment). At Wk24, combined CZP dosing regimens were compared with PBO; for Wk96 analyses all pts exposed to CZP were considered. Incidence rates (IR) are reported per 100 pt-yrs (PY) with censoring at time of event. No analyses of statistical significance were carried out on these data.

Results: At baseline, 38/218 (17.4%) CZP-randomized pts had a history of uveitis, as did 31/107 (29.0%) PBO-randomized pts. The proportion of pts with history of uveitis was similar in AS (20.8%) and nr-axSpA (21.1%) subpopulations. During the 24-wk double-blind phase, overall IR of uveitis flares (regardless of previous history) was lower in CZP pts (IR=2.0/100 PY) than PBO pts (IR=10.6/100 PY). There were no *de novo* cases of uveitis flares observed to Wk24 – ie. all cases were observed in pts with history of uveitis; in these pts, IR was 11.9/100 PY for CZP and 42.1/100 PY for PBO (Table A). To Wk96, 22 uveitis flares occurred in 19 pts, 11 in AS pts and 11 in nr-axSpA pts. The IR of uveitis flares (regardless of prior history of uveitis) remained low to Wk96 in CZP-treated pts (IR=4.0/100 PY; Table B). The incidence of uveitis flares in CZP-treated pts (IR=4.0/100 PY) was comparable to rates observed for other anti-TNFs in AS pts including adalimumab (IR=6.9/100 PY)[3] and etanercept (IR=6.7/100 PY).[4]

Conclusion: The IR of uveitis flares was lower for axSpA pts treated with CZP than with PBO during the randomized controlled phase, and was comparable to the rate reported for AS pts receiving anti-TNF therapy.

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Table A: Incidence of uveitis flares in axSpA patients treated with CZP or placebo to Week 24

	CZP			Placebo		
	All Patients (n = 218)	History of Uveitis (n = 38)	No History of Uveitis (n = 180)	All Patients (n = 107)	History of Uveits (n = 31)	No History of Uveitis (n = 76)
IR per 100 pt-yrs	2.0	11.9	0.0	10.6	42.1	0.0
Pts (Exposure, pt-yrs)	2 (97.6)	2 (16.8)	0 (80.7)	4 (37.7)	4 (9.5)	0 (28.2)

Table B: Incidence of uveitis flares in axSpA patients treated with CZP to Week 96

	All Patients (n = 315)	History of Uveitis (n = 63)	No History of Uveitis (n = 252)
IR per 100 pt-yrs	4.0	16.3	1.3
Pts (Exposure, pt-yrs)	19 (469.4)	14 (86.0)	5 (383.4)

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Long-Term Safety and Efficacy of Certolizumab Pegol over 96 Weeks in Patients with Psoriatic Arthritis with and without Prior Tumor Necrosis Factor Inhibitor Exposure. Philip Mease[1], Roy Fleischmann[2], Jurgen Wollenhaupt[3], Atul A. Deodhar[4], Dafna D. Gladman[5], Bengt Hoepken[6], Luke Peterson[7] and Désirée M. van der Heijde[8]. [1]Swedish Medical Center and University of Washington, Seattle, WA, [2]University of Texas Southwestern Medical Center and Metroplex Clinical Research Center, Dallas, TX, [3]Schoen-Klinik Hamburg-Eilbek Teaching Hospital of the University of Hamburg, Hamburg, Germany, [4]Oregon Health and Sciences University, Portland, OR, [5]University of Toronto, Toronto Western Hospital, Toronto, ON, [6]UCB Pharma, Monheim, Germany, [7]UCB Pharma, Raleigh-Durham, NC, [8]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Previous reports of RAPID-PsA (NCT01087788) demonstrated efficacy and safety of certolizumab pegol (CZP) over 48 weeks (wks) in psoriatic arthritis (PsA) patients (pts), including pts with prior anti-TNF therapy.[1] Here, we report the efficacy and safety of CZP in PsA from a 96-wk interim data cut of RAPID-PsA.

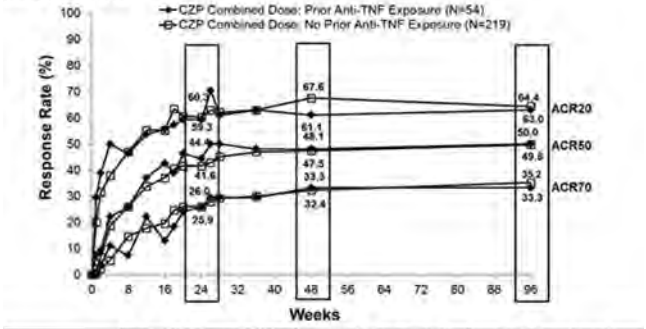
Methods: RAPID-PsA[1] is double-blind and placebo (PBO)-controlled to Wk24, dose-blind to Wk48 and open-label (OL) to Wk216. Pts had active PsA and had failed ≥1 DMARD. Pts originally randomized to CZP (200mg Q2W/400mg Q4W, following 400mg loading dose [LD] at Wks 0, 2, 4) continued on assigned dose in the OL phase; PBO pts entering dose-blind phase were re-randomized to CZP LD followed by CZP 200mg Q2W or 400mg Q4W after Wk24 or, for non-responders, Wk16. We present efficacy data for pts originally randomized to CZP (combined dose regimens). Primary clinical endpoint was Wk12 ACR20 response.[1] Other endpoints included ACR and PASI responses, HAQ-DI, pain and minimal disease activity (MDA)[2] at Wk96, and ACR responses in pts with/without prior anti-TNF exposure. Data are shown as observed case and with imputation (NRI for categorical measures; LOCF for continuous measures). Safety set consists of pts treated with ≥1 dose of CZP to Wk96.

Results: 409 pts were randomized and 273 received CZP from Wk0. 54 (19.8%) CZP pts had prior anti-TNF exposure with similar baseline (BL) characteristics to pts without. Of CZP-randomized pts, 91% completed Wk24, 87% Wk48 and 80% Wk96. ACR and MDA responses were maintained in both dosing regimens from Wk24 to Wk96 (Figure). ACR responses were similar in pts with/without prior anti-TNF exposure (Figure). Pts randomized to PBO who switched to CZP displayed rapid clinical improvements that were maintained to Wk96. In pts with ≥3% skin involvement at BL (N=166, 60.8% CZP pts) PASI responses were maintained to Wk96 (Table). Improvements in PROs were maintained to Wk96 (Change from BL at Wk24 and Wk96: HAQ-DI: -0.48 vs -0.52; pain: -28.5 vs -31.3). In the safety set (N=393) total CZP exposure was 606 pt-yrs. Adverse events (AEs) occurred in 345 pts (87.8%; event rate [ER] per 100 pt-yrs=329.8) and serious AEs (SAEs) in 67 (17.0%; ER=14.5). SAEs included malignancies in 4 pts (1.0%; ER=0.7) (2 cases of breast cancer, 1 lymphoma, 1 stage 0 *in situ* cervix carcinoma) and serious infections in 16 pts (4.1%; ER=3.3). 6 deaths were reported in the overall 96-wk period (1.5%) (2 cardiac disorders, 1 sudden death, 1 infection, 1 breast cancer, 1 lymphoma).

Conclusion: Clinical efficacy of CZP was maintained through both the dose-blind and OL phases of RAPID-PsA. Efficacy was maintained in both dosing regimens and in both TNF-naïve and TNF-experienced pts. The safety profile was in line with previous reports from RAPID-PsA, with no new safety signals observed with increased exposure.

References:
1. Mease P.J. Arthritis Rheum 2013;65(10):S132–S133
2. Coates L. Ann Rheum 2010;69(1):48–53

Figure: Maintenance of CZP efficacy in clinical outcomes to Wk96 of the RAPID-PsA trial



	CZP 200mg Q2W (n=138)			CZP 400mg Q4W (n=135)			CZP Combined (n=273)		
Outcome (%)	Wk24 (NRI)	Wk96 (NRI)	Wk96 (OC)	Wk24 (NRI)	Wk96 (NRI)	Wk96 (OC)	Wk24 (NRI)	Wk96 (NRI)	Wk96 (OC)
ACR20	63.8	68.8	84.8	56.3	59.3	76.2	60.1	64.1	80.6
ACR50	44.2	50.7	62.5	40.0	48.9	62.9	42.1	49.8	62.7
ACR70	28.3	34.1	42.0	23.7	35.6	45.7	26.0	34.8	43.8
MDA	34.8	39.9	49.1	34.8	42.2	54.3	34.8	41.0	51.6
PASI75[a]	62.2	58.9	77.9	60.5	46.1	66.0	61.4	53.0	72.7
PASI90[a]	46.7	48.9	64.7	35.5	38.2	54.7	41.6	44.0	60.3

[a]PASI response rates reported in pts with ≥3% body surface area skin involvement at baseline (CZP 200mg Q2W, N=90; CZP 400mg Q4W, N=76). OC: Observed Case; NRI: Non-Responder Imputation

Disclosure: P. Mease, Abbott, AbbVie, Amgen, BiogenIdec, BMS, Celgene, Crescendo, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB Pharma, Vertex, 2, Abbott, AbbVie, Amgen, BiogenIdec, BMS, Celgene, Covagen, Crescendo, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB Pharma, Vertex, 5, Abbott, AbbVie, Amgen, BiogenIdec, BMS, Crescendo, Genentech, Janssen, Lilly, Pfizer, UCB Pharma, 8; **R. Fleischmann**, Genetech Inc, Roche, Abbott, Amgen, UCB Pharma, Pfizer, BMS, Lilly, Sanofi-Aventis, MSD, Novartis, BiogenIdec, Astellas, AstraZeneca, Janssen, 2, Roche, Abbott, Amgen, UCB Pharma, Pfizer, BMS, Lilly, Sanofi-Aventis, Novartis, Astellas, AstraZeneca, Janssen, 5; **J. Wollenhaupt**, UCB Pharma, 5, UCB Pharm, 2; **A. A. Deodhar**, Abbott, Amgen, Janssen, Novartis, Pfizer and UCB Pharma, 2, Abbott, Amgen, Janssen, Novartis, Pfizer and UCB Pharma, 5; **D. D. Gladman**, Abbott, Bristol Myers Squibb, Celgene, Johnson & Johnson, MSD, Novartis, Pfizer, and UCB Pharma, 2, Abbott, Bristol Myers Squibb, Celgene, Johnson & Johnson, MSD, Novartis, Pfizer, and UCB Pharma, 5; **B. Hoepken**, UCB Pharma, 3; **L. Peterson**, UCB Pharma, 3; **D. M. van der Heijde**, AbbVie, Amgen, AstraZeneca, Augurex, BMS, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Vertex, 5, Imaging Rheumatology bv, 9.

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Psoriatic Arthritis Mutilans: Characteristics and Radiographic Progression. Deepak R. Jadon[1], Gavin Shaddick[2], William Tillett[1], Graham Robinson[3], Charlotte Cavill[1], Nicola Waldron[1], Eleanor Korendowych[1] and Neil J McHugh[4]. [1]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]University of Bath, Bath, United Kingdom, [3]Royal United Hospital, Bath, United Kingdom, [4]Department of Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom.

Background/Purpose: Psoriatic arthritis mutilans (PAM) is a rare extreme subtype of psoriatic arthritis (PsA). Our objectives were to: (1) compare clinical characteristics of PsA patients with PAM and without PAM (non-PAM); (2) determine the rate of PAM radiographic progression.

Methods: A retrospective cohort study was conducted of all PsA patients attending a teaching hospital. Clinical characteristics were recorded. Most recent radiographs of hands and feet were evaluated for PAM, defined as osteolysis affecting ≥50% of the articular surface on both sides of the joints. All available radiographs (earliest to most recent) were quantitatively scored for osteolysis, erosion, joint space narrowing, and osteoproliferation. Radiographic progression was analysed using random effects models to allow for patient differences, and additive models for all joints.

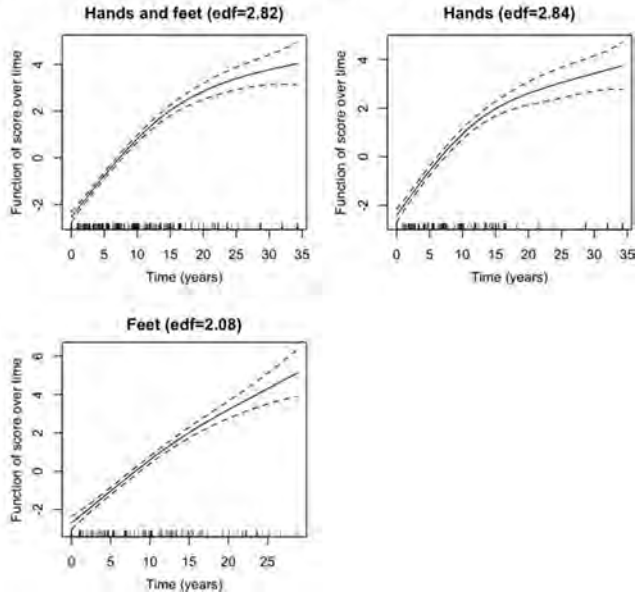
Results: 610 PsA cases fulfilling CASPAR criteria were screened: 36 PAM (35 with serial radiographs); 483 non-PAM; 91 had insufficient radiographs to determine PAM.

PAM cases were younger at diagnosis of PsA than non-PAM cases (33 *vs.* 40 years; p=0.04). Psoriatic nail dystrophy was more prevalent in PAM than non-PAM cases (83.33 *vs.* 47.95%; p=0.0002). At most recent assessment, PAM cases had a higher HAQ than non-PAM cases (median 1.25 *vs.* 0.63; p=0.05), especially in domains relating to hand / feet function: HAQ-grip (p=0.02); HAQ-eating (p=0.03). In cases with ACPA serology available, PAM cases were no more likely to be ACPA positive (0/16) than non-PAM cases (8/226; p=0.44). 16/28 PAM cases had radiographic sacroiliitis, often bilateral (14/16) and of grade ≥3 (15/16). During their disease course, PAM cases were more likely than non-PAM cases to have used a DMARD (91.67 *vs.* 50.21%; p<0.0001), but no more likely to have used a Biological (p=0.53). 87.50% of PAM cases had used a DMARD before PAM-occurrence.

A median of 5 radiographs were scored for each PAM case (IQR 3–7). 22/35 patients developed PAM during the course of their follow-up. PAM was most commonly monoarticular (21/35) at first observation, and polyarticular most recently (28/35). The most frequently affected joints were: feet IPJ1, MTPJ2–5; hand DIPJ2, PIPJ5, MCPJ1. Significant changes in osteolysis scores over time were observed for all joints (p<0.008). There was strong indication of differences in the patterns of deterioration over time for different joints (p<0.001). An initial increase in score, followed by a slower rate of deterioration was seen (effective degrees of freedom; edf 2.82), with the change in rate more marked for hands (edf 2.84) than feet (edf 2.08) (*Figure 1*).

Conclusion: PAM is associated with worse physical function, more prevalent nail dystrophy, high-grade bilateral sacroiliitis, greater DMARD use and earlier diagnosis when compared to cases without PAM. Osteolysis progresses most rapidly in early disease, slowing in established disease.

Figure 1. **Osteolysis progression over time in PAM cases**



Disclosure: D. R. Jadon, None; **G. Shaddick**, None; **W. Tillett**, None; **G. Robinson**, None; **C. Cavill**, None; **N. Waldron**, None; **E. Korendowych**, None; **N. J. McHugh**, None.

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Comparison of Clinical and Imaging Characteristics of Axial Psoriatic Arthritis and Axial Spondyloarthritis. Neha Garg[1], Abhijeet Danve[2], Kiana Vakil-Gilani[3] and Atul A. Deodhar[4]. [1]Oregon Health and Sciences University, Portland, OR, [2]Oregon Health & Science University, Portland, OR, [3]OHSU, Portland, OR, [4]Oregon Health and Science University, Portland, OR.

Background/Purpose: Few studies have compared the clinical and imaging (x-ray and MRI) characteristics between axial psoriatic arthritis (axPsA) and axial spondyloarthritis patients without psoriasis (axSpA). We compared the clinical and imaging characteristics in these two groups.

Methods: AxSpA patients were identified by searching electronic medical records of our university, and axPsA patients were identified from our existing cohort. Demographic and clinical data were collected by chart review. Disease activity was measured using BASDAI and RAPID3. For

imaging comparisons, the patients were divided into 2 gender and disease duration matched subgroups – 1) AS: ankylosing spondylitis patients without psoriasis fulfilling mNY criteria 2) axPsA: PsA patients fulfilling mNY criteria. Symmetry of sacroiliitis was defined as having same grade of sacroiliitis on each side. Bilateralism was defined as having any grade sacroiliitis on either side. Categorical and continuous variables were reported using proportions and means. Statistical significance was estimated using Mann-Whitney, two mean comparison t-tests, and two sample proportion comparison tests as applicable.

Results: Of 168 SpA patients, 135 axSpA patients were compared with 33 axPsA patients (Table1). Mean age, symptom duration, BMI were similar between the two groups. axSpA had lesser number of females compared to axPsA (33% vs. 57%, $p<0.01$), higher prevalence of uveitis (29% vs. 12%, $p<0.04$), higher HLA B27 (80% vs. 50%, $p<0.007$) and higher BASDAI and RAPID3 scores (BASDAI 4.4 vs 3.8, RAPID3 4.3 vs 3.6, p = ns). These scores were numerically higher in HLA-B27 positive compared to HLA-B27 negative patients (4.3 vs. 3.7, and 4.4 vs. 3.6, respectively; p = ns). Eighteen patients with axPsA were gender and disease duration matched with 86 patients with AS. Radiographic grading of sacroiliitis, symmetry or bilateralism were not significantly different between AS and axPsA. RAPID 3 and BASDAI scores did not correlate with radiographic grading in any group. No significant clinical or imaging differences were found between patients positive and negative for HLA B27.

Conclusion: In this comparative study between axPsA and axSpA patients, we found a higher prevalence of female gender, uveitis and positive HLA-B27 in the axSpA group. Our findings do not confirm the previous reports of more symmetry and more severe disease in AS compared to axPsA patients.

Table 1: Demographic and clinical characteristics of axSpA and axPsA patients

	All patients N=168 % or means (standard deviation)	axSpA N=135 (80.4%) % or means (standard deviation)	axPsA N=33 (19.6%) % or means (standard deviation)	P value
Age (years)	39.6 (13.4)	38.7 (13.7)	43.1 (11.2)	0.09
Female	64 (38.1%)	45 (33.3%)	19 (57.6%)	**0.01**
Symptom duration (years)	12.8 (10.6)	13 (10.9)	12.2 (9.6)	0.87
BMI ($kg/m^{2)}$	27.5 (6.8)	27.7 (6.9)	26.85 (6)	0.54
Smoking status	60 (35.7%)	47 (34.8%)	10 (30.3%)	0.14
Sacroiliitis on x-rays*	150/163(92%)	118/131(90.1%)	32/32 (100%)	**<0.0001**
Sacroiliitis on MRI**	49/54 (90.7%)	33/37 (89.2%)	16/17 (94.1%)	0.56
HLA B27	91/119 (76.5%)	83/103 (80.6%)	8/16 (50%)	**0.007**
BASDAI	4.31 (2.4)	4.41 (2.5)	3.82 (2)	0.4
RAPID 3	4.18 (2.20)	4.32 (2.21)	3.67 (2.16)	0.15
ESR mm/hr	28 (25.7)	27.4 (24.8)	29.5 (28.4)	0.81
CRP mg/dl	2.6 (5.8)	2.89 (6.5)	1.88 (3)	0.28
Peripheral arthritis	42 (25%)	31 (22.9%)	11 (33%)	0.22
Uveitis	44 (26.2%)	40 (29.6%)	4 (12.1%)	**0.04**
IBD	26 (15.5%)	22 (16.3%)	4 (12.1%)	0.55
Depression	44 (26.2%)	34 (25.2%)	10 (30.3%)	0.55
Fibromyalgia	15 (8.9%)	11 (8.2%)	4 (12.1%)	0.47
Spinal Fractures	7 (4.2%)	7 (5.2%)	0 (0%)	0.18
Ischemic Heart Disease	5 (2.9%)	5 (3.7%)	0 (0%)	0.26
NSAIDs	129 (77.7%)	109 (81.9%)	20 (60.6%)	**0.008**
DMARDs any	68 (40.5%)	51 (37.8%)	17 (51.5%)	0.15
TNF inhibitors (%)	70.8	95 (70.4%)	24 (72.7%)	0.79

*Sacroiliitis on X-Ray defined as either present or absent irrespective of Modified NY grading.
**Sacroiliitis on MRI defined as presence of edema, erosions, sclerosis or ankylosis as reported by the radiologist

Table 2: Comparison of data for radiographic disease: AS vs axPsA, gender and duration matched

Variable	AS (N=86) N (%); Mean (SD)	axPsA (N=18) N (%); Mean (SD)
X ray Grade Right	100%	100%
1	3 (3.5)	0
2	22 (25.6)	3 (16.7)
3	41 (47.7)	10 (55.6)
4	20 (23.3)	5 (27.8)
X ray Grade Left	88%	100%
1	1 (1.2)	0
2	18 (20.9)	5 (29.4)
3	48 (55.8)	8 (47.1)
4	17 (19.8)	4 (23.5)
Symmetry on x-ray	63/86 (73.3)	13/17 (76.5)
Bilateral on x-ray	84/86 (97.7)	17/17 (100)
Sacroiliitis on x ray*	86/86 (100)	18/18 (100)
Sacroiliitis on MRI**	18/21 (85.7)	6/6 (100)
MRI fatty change	12%	16%
Right	1 (5.9)	0
b/l	1 (5.9)	1 (16.7)
MRI edema	66%	100%
Left	1 (5.6)	0
Right	1 (5.6)	2 (33.3)
b/l	10 (55.6)	4 (66.7)
MRI structural changes β	78%	50%
Right	1 (5.6)	0
b/l	13 (72.2)	3 (50)

*Sacroiliitis on X-Ray defined as either present or absent irrespective of Modified NY grading.
**Sacroiliitis on MRI defined as presence of edema, erosions, sclerosis or ankylosis as reported by the radiologist

Disclosure: N. Garg, None; **A. Danve**, None; **K. Vakil-Gilani**, None; **A. A. Deodhar**, Abbott, Amgen, Janssen, Novartis, Pfizer and UCB Pharma, 2, Abbott, Amgen, Janssen, Novartis, Pfizer and UCB Pharma, 5.

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Apremilast, an Oral Phosphodiesterase 4 Inhibitor, Is Associated with Long-Term (52-Week) Improvement in Measures of Disease Activity in Patients with Psoriatic Arthritis: Results from 3 Phase 3, Randomized, Controlled Trials.

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Background/Purpose: Apremilast (APR) is an oral phosphodiesterase 4 inhibitor that helps regulate the immune response that causes inflammation and skin disease associated with psoriatic arthritis (PsA). The PALACE 1, 2, and 3 trials compared the efficacy and safety of APR with placebo (PBO) in patients with active PsA despite prior conventional disease-modifying antirheumatic drugs (DMARDs) and/or biologics, including biologic failures. We evaluated the impact of APR over 52 weeks on PsA disease activity.

Methods: Patients were randomized (1:1:1) to receive PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline DMARD use (yes/no). Patients whose swollen and tender joint counts had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if they were initially randomized to PBO, or continued on their initial APR dose. At Week 24, all remaining PBO patients were re-randomized to APR20 or APR30. This analysis reports data over 52 weeks. Disease activity was evaluated using a modified American College of Rheumatology 20 (ACR20) response, 28-joint count Disease Activity Scale (DAS-28; C-reactive protein [CRP]), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), dactylitis count, and 75% reduction from baseline Psoriasis Area and Severity Index (PASI-75) response.

Results: At Week 16, a significantly greater proportion of patients treated with APR achieved a modified ACR20 response vs PBO (primary endpoint). In patients initially randomized to APR and completing 52 weeks, ACR20 response was sustained over 52 weeks. APR20 and APR30 demonstrated improvement in disease activity vs PBO at Week 16, as measured by the

mean change in DAS-28 (CRP), achievement of DAS-28 <2.6, median percent changes in MASES/dactylitis score, and PASI-75 response. Among patients who were continuously treated with APR through 52 weeks, sustained improvements were observed at Week 52 (Table). The most common adverse events reported during the PBO-controlled period (PALACE 1–3; pooled) were diarrhea (12.2%), nausea (10.1%), and headache (8.0%). The safety profile of APR through 52 weeks was similar to that observed with APR for up to 24 weeks of treatment (PBO-controlled period). Marked laboratory abnormalities generally were infrequent and returned to baseline with continued treatment or were associated with a concurrent medical condition.

Conclusion: APR demonstrated sustained clinically meaningful improvements in measures of PsA disease activity through Week 52. APR demonstrated an acceptable safety profile and was generally well tolerated through 52 weeks.

	Week 16									Week 52					
	PALACE 1			PALACE 2			PALACE 3			PALACE 1		PALACE 2		PALACE 3	
	PBO	APR20	APR30	PBO	APR30	APR30	PBO	APR20	APR30	APR20	APR30	APR20	APR30	APR20	APR30
ACR20, % achievement	19.0	30.4*	38.1‡	18.9	37.4μ	32.1*	18.3	28.4*	40.7‡	63.0	54.6	52.9	52.6	56.0	63.0
ACR50, % achievement	6.0	15.5μ	16.1μ	5.0	14.7μ	10.5	8.3	12.4	15.0	24.8	24.6	26.7	18.6	25.2	30.2
ACR70, % achievement	1.2	6.0*	4.2	0.6	3.7	1.2	2.4	4.7	3.6	15.4	13.8	9.8	6.8	9.2	10.4
DAS–28, mean change from baseline	−0.29	−0.72‡	−0.81‡	−0.30	−0.78‡	−0.73μ	−0.28	−0.57*	−0.77‡	−1.40	−1.31	−1.11	−1.30	−1.21	−1.41
DAS–28 (CRP) <2.6, % achieved	3.6	13.1μ	13.1μ	8.2	17.8*	11.7	7.7	17.2*	18.0*	32.5	23.3	28.0	17.8	28.1	29.9
MASES, median % change	−20.0	−50.0*	−34.8	−33.3	−33.3	−50.0	−25.0	−20.0	−28.6	−100.0	−66.7	−63.3	−60.0	−60.0	−66.7
Dactylitis score, median % change	−66.7	−70.7	−50.0	−66.7	−50.0	−70.8	−50.0	−66.7	−80.2	−100.0	−100.0	−100.0	−100.0	−100.0	−100.0
PASI–75, % achievement	4.4	20.8μ	22.0μ	2.7	18.8μ	22.1μ	7.9	20.9*	22.2*	24.5	36.8	27.1	39.3	28.6	39.1
Good/moderate EULAR response, % achieved	29.8	46.4μ	48.8μ	31.4	53.4‡	48.8μ	29.0	40.2*	51.5‡	75.0	74.4	68.0	67.5	69.4	74.8

For Week 16 (intent-to-treat analysis:*$P<0.05$; μ$P\leq0.005$; ‡$P\leq0.0001$ vs PBO, based on an analysis of covariance model for change from baseline in DAS–28 and a Cochran-Mantel-Haenszel test for DAS–28 (CRP) <2.6, and good/moderate European League Against Rheumatism (EULAR) response. Note: Missing data were handled using the last-observation-carried-forward methodology for continuous data and the non-responder imputation approach for categorical data. Week 52 was analyzed using data as observed.

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Reliability and Construct Validity of the Psoriasis Symptom Inventory in Subjects with Psoriatic Arthritis. Philip Mease[1], Mark C. Genovese[2], Alex Mutebi[3], Hilary Wilson[4], Dennis Revicki[4], Ngozi Erondu[3], Ajay Nirula[3], JingYuan Feng[3] and Hema Viswanathan[3]. [1]Swedish Medical Center and University of Washington, Seattle, WA, [2]Stanford University Medical Center, Palo Alto, CA, [3]Amgen Inc, Thousand Oaks, CA, [4]Evidera, Bethesda, MD.

Background/Purpose: The Psoriasis Symptom Inventory (PSI) is an 8-item patient-reported outcome measure of psoriasis symptom severity. Data from a Phase 2 study of Brodalumab in subjects with plaque psoriasis demonstrated that the PSI has good reliability, validity, and ability to detect change. Psoriasis related symptoms are an important component of psoriatic arthritis (PsA). However, the measurement properties of the PSI have not been evaluated in the PsA population. This analysis sought to evaluate the reliability and construct validity of the PSI in subjects with PsA.

Methods: This was a secondary analysis of pooled data from treatment arms of a Phase 2 clinical trial (NCT01516957) evaluating the efficacy of Brodalumab, an anti-IL-17 R monoclonal antibody in subjects with PsA. Confirmatory factor analysis (CFA) and Rasch analysis were used to assess the dimensionality of the PSI. Item evaluation and internal consistency (Cronbach's α) were conducted on baseline PSI data. Test-retest reliability was assessed using intraclass correlation coefficients (ICC) between PSI scores at week 2 and week 4 in stable subjects (i.e., -1≤ change ≤1 on the subject global assessment of disease [SGA]). Construct validity was evaluated based on correlations between PSI scores and body surface area (BSA) affected by psoriasis, and selected domains of the SF-36. Known groups validity was explored based on BSA severity categories (<5%, 5–10%, >10%) using analysis of variance. Ability to detect change was explored using t-tests comparing mean PSI scores in subjects reporting ≥30% versus <30% improvement from baseline to week 12 on the SGA.

Results: The analysis sample included 154 subjects; 93.5% White, 63.0% females, mean (SD) age was 52.2 (11.47) years. Mean (SD) duration of PsA and BSA at baseline was 8.8 (7.84) years and 10.4% (15.61%) respectively. At baseline, 12% of subjects had no skin involvement and 63% had ≤5% skin involvement. Mean (SD) PSI total score at baseline was 12.2 (7.89). CFA and Rasch analysis supported unidimensionality. Rasch analysis also indicated good item fit and correctly ordered categories. The PSI had excellent internal consistency (α=0.95) and good test-retest reliability (ICC=0.70 for total scores and ranging from 0.67 to 0.81 for items). Convergent validity was supported by moderate correlations with BSA (r=0.50). Discriminant validity was supported by small correlations (r<−0.3) for SF-36 domains of mental health and role emotions. Known groups validity was supported by significantly lower mean PSI scores ($p<0.001$) between subjects with BSA<5% compared to those with BSA >10%). Mean change in PSI score was significantly greater ($p<0.001$) in subjects with ≥30% SGA improvement than subjects with <30% SGA improvement.

Conclusion: This study provides evidence that the PSI is unidimensional, with excellent internal consistency, good test-retest reliability, construct validity, and ability to detect change in subjects with PsA. Based on the findings, the PSI is a robust yet simple and practical measure of psoriasis-related symptoms for use in PsA clinical trials.

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Secukinumab, an Anti–Interleukin-17A Monoclonal Antibody, Improves Physical Function, Quality of Life and Work Productivity in Patients with Active Psoriatic Arthritis: Results from a Phase 3, Randomized, Controlled Trial. Vibeke Strand[1], Philip Mease[2], Iain B. McInnes[3], Bruce Kirkham[4], Arthur Kavanaugh[5], Proton Rahman[6], P. Nash[7], Luminita Pricop[8], Jiacheng Yuan[8], Hanno Richards[9] and Shephard Mpofu[9]. [1]Stanford University, Palo Alto, CA, [2]Swedish Medical Center, Seattle, WA, [3]University of Glasgow, Glasgow, United Kingdom, [4]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [5]University of California San Diego, La Jolla, CA, [6]Memorial University of Newfoundland, St. John's, NF, [7]Rheumatology Research Unit, Nambour Hospital, Sunshine Coast and Department of Medicine, University of Queensland, Queensland, Australia, [8]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [9]Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: Psoriatic arthritis (PsA) has a significant adverse effect on patients' health-related quality of life (HRQoL), affecting their physical and emotional functioning and psychological health. Here we present the impact of treatment with secukinumab on patient-reported outcomes (PROs) in patients enrolled in FUTURE 1 (NCT01392326), the first phase 3 trial to evaluate interleukin (IL)-17A inhibition in subjects with PsA.

Methods: Adults with active, moderate to severe PsA were randomized to secukinumab 10 mg/kg i.v. at baseline, Weeks 2 and 4, then either 75 mg s.c. (10 IV → 75 SC; n = 202) or 150 mg s.c. (10 IV → 150 SC; n = 202) at Week 8 and every 4 weeks until end of study, or placebo (PBO; n = 202) on the same i.v. and s.c. schedules. PROs were measured using: Health Assessment Questionnaire – Disability Index (HAQ-DI); Short Form-36 Health Survey (SF-36); EuroQoL (EQ-5D); PsAQoL; Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F); and Work Productivity and Activity Impairment – General Health (WPAI). PROs were reported using a mixed-effect model repeated measures analysis, except WPAI and SF-36 domains which were assessed using an observed analysis.

Results: At baseline, dose groups were comparable with respect to demographics and disease activity; subjects had moderate to severe physical impair-

ment, fatigue levels and impaired HRQOL. Secukinumab 10 IV → 75 SC and 10 IV → 150 SC significantly improved HAQ-DI ($P < 0.0001$), SF-36 physical component summary [PCS] score ($P < 0.0001$), EQ-5D ($P < 0.001$ and $P < 0.0001$) and PsAQoL ($P < 0.0001$) vs. PBO at Week 24; only 10 IV → 150 SC significantly improved FACIT-F ($P < 0.05$). Mean changes from baseline reported in HAQ-DI, PCS, mental component summary (MCS) and all domains of SF-36 and FACIT-F exceeded minimum clinically important differences (MCID; Table, in bold): physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Various aspects of work productivity, as assessed by WPAI, were also improved with secukinumab vs. PBO. Improvements in all PROs were sustained or further increased over 52 weeks.

Table. Mean baseline scores and mean change from baseline (BL) in patient-reported outcomes (PROs) at Week 24 by treatment group

PROs		Secukinumab 10 mg/kg i.v. → 75 mg s.c. n = 202	Secukinumab 10 mg/kg i.v. → 150 mg s.c. n = 202	Placebo n = 202
HAQ-DI[a]	**BL**	1.25	1.23	1.19
(MCID ≥ 0.35)	**Change from BL at Week 24**	**–0.41***	**–0.40***	–0.17
EQ–5D (VAS)[b]	**BL**	52.80	52.60	52.60
	Change from BL at Week 24	11.91‡	13.36*	2.45
PsAQoL[a]	**BL**	10.65	10.27	10.65
	Change from BL at Week 24	–3.19*	–3.49*	–0.36
FACIT-Fatigue[b]	**BL**	27.59	28.90	27.82
(MCID ≥ 4)	**Change from BL at Week 24**	**6.03**	**6.74†**	4.0
SF–36 PCS[b]	**BL**	36.90	36.16	36.63
(MCID ≥ 2.5)	**Change from BL at Week 24**	**5.41***	**5.91***	1.82
SF–36 MCS[b]	**BL**	42.04	42.82	43.49
(MCID ≥ 2.5)	**Change from BL at Week 24**	**3.67**	**5.66§**	2.39
SF–36 Domains[c]				
(MCID ≥ 5)				
PF	**BL**	45.66	42.62	46.94
	Change from BL at Week 24[c]	**14.23**	**15.73**	**7.08**
RP	**BL**	47.32	45.99	47.01
	Change from BL at Week 24[c]	**13.68**	**18.52**	**9.27**
BP	**BL**	36.47	36.01	36.84
	Change from BL at Week 24[c]	**18.68**	**19.78**	**12.92**
GH	**BL**	40.91	42.42	41.72
	Change from BL at Week 24[c]	**8.81**	**12.03**	**6.33**
VT	**BL**	39.31	41.31	41.94
	Change from BL at Week 24[c]	**12.32**	**13.86**	**9.62**
SF	**BL**	56.71	56.15	57.81
	Change from BL at Week 24[c]	**13.80**	**17.41**	**10.53**
RE	**BL**	58.29	56.93	58.24
	Change from BL at Week 24[c]	**9.73**	**14.30**	**5.68**
MH	**BL**	56.28	58.97	61.09
	Change from BL at Week 24[c]	**8.25**	**10.35**	**5.60**

*$P < 0.0001$, ‡$P < 0.001$, §$P < 0.01$, †$P < 0.05$ vs. PBO
[a]Decrease in score represents improvement; [b]Increase in score represents improvement; [c]Observed data with no statistical analysis performed (n = 192, 191 and 184 for secukinumab 10 mg/kg i.v. →75 mg s.c., secukinumab 10 mg/kg i.v. →150 mg s.c. and PBO, respectively, for BP, GH, MH, PF, SF and VT assessments; n = 191, 190 and 182, respectively, for other SF–36 domains [RE and RP]).
P-values are from a mixed model repeated measures analysis.
BP, bodily pain; EQ–5D (VAS), EuroQoL health questionnaire (visual analogue scale); GH, general health; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; HAQ-DI, Health Assessment Questionnaire – Disability Index; i.v., intravenous; MCID, minimum clinically important difference; MH, mental health; PsAQoL, psoriatic arthritis quality of life questionnaire; PF, physical functioning; RE, role emotional; RP, role physical; s.c., subcutaneous; SF, social functioning; SF–36 MCS, short form–36 health survey – mental component summary; SF–36 PCS, short form–36 health survey – physical component summary; VT, vitality.

Conclusion: In patients with active PsA, selective inhibition of IL-17A with secukinumab improved physical function (HAQ-DI), fatigue (FACIT), and HRQOL by generic (SF-36, EQ-5D) and disease-specific (PsAQoL) measures, and reduced the impact of disease on work productivity (WPAI).

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Predictors Associated with Rheumatologist Referral Time in Patients with Ankylosing Spondylitis. Atul A. Deodhar[1], Manish Mittal[2], Patrick Reilly[2], Yanjun Bao[2], Shivaji Manthena[2], Jaclyn K. Anderson[2] and Avani D. Joshi[2]. [1]Oregon Health and Sciences University, Portland, OR, [2]AbbVie Inc., North Chicago, IL.

Background/Purpose: Average delay between symptom onset and diagnosis of ankylosing spondylitis (AS) has been reported as 8–12.8 years[1,2]. This study assessed delay in AS diagnosis following diagnosis of back pain (BP), and sought to identify factors affecting time from BP diagnosis to rheumatologist referral in AS patients (pts).

Methods: This longitudinal study used claims data from the large US MarketScan® commercial insurance claims databases (total number of pts n = 127,137,195 between Jan 2000–Dec 2012). Pts aged 18–64 years with diagnosis of BP in a non-rheumatology setting followed by AS diagnosis in any setting were selected. Pts with a rheumatologist visit on/before AS diagnosis were considered to have been referred. A time-dependent Cox proportional hazard model was used to determine factors associated with referral time after adjusting for age, sex, comorbidities, physician specialty, drug therapy and imaging procedures.

Results: Out of 3,336 pts diagnosed with AS after a diagnosis of BP, 1,244 (37%) were referred to and diagnosed by rheumatologists; remaining were diagnosed in a primary care (PCP; 25.7%), chiropractor/physical therapy (7%), orthopedic (3.8%), pain (3.6%), acute care (3.4%) or other (19.2%) setting. More referred pts were prescribed NSAIDs, DMARDs, corticosteroids and anti-TNF prior to diagnosis of AS, suggesting potentially more severe AS (**Table 1**). In the time between the diagnoses of BP and AS, 75 (6%) of referred patients were prescribed anti-TNF therapy by rheumatologists and 42 (2%) of non-referred patients were prescribed anti-TNFs by PCPs. Referred pts were also more likely to have had spinal/pelvic imaging procedures (x-ray, MRI, CT scan). Median time from BP diagnosis to rheumatologist referral was 307 days and median time from first rheumatologist visit to AS diagnosis was 28 days. Referred pts were more likely to be younger, male, diagnosed with uveitis, referred by PCPs, prescribed NSAIDs, DMARDs, and anti-TNF prior to referral, and to have had spinal/pelvic x-ray **(Table 2)**.

Conclusion: During 2000–2012, the majority of AS patients who presented with BP were diagnosed without rheumatologist referral. Among those referred, there was a delay of approximately 10 months before a rheumatologist referral was made. After a rheumatologist visit, diagnosis of AS generally followed within a month. Predictors of referral time included young age, male sex, presence of uveitis, use of drug therapy and imaging procedures, and referring physician specialty.

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Table 1. Patient Characteristics

Characteristic	Patients referred to rheumatologist (n=1,244)	Patients not referred to rheumatologist (n=2,092)
Age, years	42.9	45.8
Female, %	50.7%	50.0%
Comorbid condition, %		
Diabetes	5.1%	9.8%
Cardiovascular disease	7.1%	10.2%
Hypertension	18.4%	23.5%
Renal disease	0.5%	1.1%
Cancer	17.3%	19.0%
Uveitis	4.3%	3.9%
Prescribed Drug Therapy, %		
NSAID	64.8%	53.9%
DMARD	28.0%	13.9%
Corticosteroid	58.3%	41.5%
Opiate	57.5%	56.3%
Anti-TNF	10.2%	3.4%
Spinal/Pelvic Imaging Procedure, %		
x-ray	71.3%	56.4%
MRI	42.3%	38.7%
CT scan	18.4%	17.0%

DMARDs=disease-modifying antirheumatic drug; MRI=magnetic resonance imaging; NSAIDS=non-steroidal antiinflammatory drug; TNF=tumor necrosis factor.

Table 2. Factors Associated with Rheumatologist Referral Time for Patients with Ankylosing Spondylitis in multivariate analysis

Predictor	HR (95% CI)
Age	0.986 (0.981, 0.991)
Sex (M vs F)	1.15 (1.03, 1.29)
Uveitis	1.49 (1.13, 1.96)
Specialty	
PCP	1.96 (1.64, 2.35)
Pain management	0.79 (0.69, 0.91)
Prescribed Drug Therapy	
NSAID	1.55 (1.35, 1.77)
DMARD	1.33 (1.16, 1.54)
Opiate	0.82 (0.72, 0.94)
Anti-TNF	1.40 (1.12, 1.76)
Spinal/Pelvic Imaging Procedure	
x-ray	1.28 (1.12, 1.46)
CT scan	0.71 (0.58, 0.87)

CI=confidence interval; DMARDs=disease-modifying antirheumatic drug; HR=hazard ratio; MRI=magnetic resonance imaging; NSAIDS=non-steroidal antiinflammatory drug; PCP=primary care physician; TNF=tumor necrosis factor.

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Sustained Improvement in Physical Function, Health-Related Quality of Life, and Work Productivity with Adalimumab Treatment in Non-Radiographic Axial Spondyloarthritis. Désirée van der Heijde[1], Manish Mittal[2], Naijun Chen[2], Aileen L. Pangan[2] and Avani D. Joshi[2]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]AbbVie Inc., North Chicago, IL.

Background/Purpose: In the ABILITY-1 trial, adalimumab (ADA) treatment for 12 weeks was associated with improved clinical and health-related quality of life (HRQOL) outcomes among patients with nonradiographic axial spondyloarthritis (nr-axSpA). [1] We aimed to evaluate physical function, HRQOL and work productivity over 3 years of ADA treatment in ABILITY-1.

Methods: ABILITY-1 was a 3-year, phase 3, multicenter, randomized, controlled trial of ADA vs placebo in patients with nr-axSpA (classified using the Assessment of SpondyloArthritis international Society axial SpA criteria). After a 12-week double-blind phase, all patients switched to open-label ADA for an additional 144 weeks (156 total). This post hoc analysis evaluated patient-reported outcomes through year 3 among 185 patients overall and among subgroups of 142/43 patients with/without elevated C-reactive protein (CRP) and/or MRI evidence of inflammation at baseline. Physical function was assessed using the disability index of the Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S) and HRQOL using the Short Form 36 Health Survey (SF-36) Physical Component Summary (PCS) score. Productivity was assessed using the Work Productivity and Activity Impairment Questionnaire (WPAI). Changes in HAQ-S, SF-36 PCS, and WPAI from baseline to years 1, 2, and 3 were reported for the ITT populations (LOCF).

Results: No significant differences were observed between patient cohorts in baseline HAQ-S, SF-36 PCS, or WPAI domain scores. Mean change from baseline in HAQ-S indicated sustained improvement over time among patients in the overall population at years 1, 2, or 3 (−0.39, -0.40, and -0.39, respectively); a majority of patients (56%, 55%, and 54%, respectively) achieved the minimum clinically important difference (MCID) of -0.26[2] (**Table**). Trends were similar for SF-36 PCS score; approximately 68% of patients achieved the MCID of 3.0[3] at each time point; mean scores were 41.8, 41.9, and 41.9 at years 1, 2, and 3, respectively, compared to the US general population norm of 50[4]. Mean changes from baseline in overall work impairment and activity impairment were stable over time, and >60% of patients achieved the MCID of -7.0%[5] at each time point. Improvements were sustained among patients with and without elevated CRP and/or positive MRI, and in observed case analysis.

Mean Change From Baseline Through Week 156 in HAQ-S, SF-36 PCS, and WPAI Domain Scores Among nr-axSpA Patients[a], Mean ± SD, MCID (%)

	Overall Population (n=185)			MRI+/elevated CRP at baseline (n=142)			MRI- and normal CRP at baseline (n=43)		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
HAQ-S[b]	−0.39 ± 0.50 55.7%	−0.40 ± 0.54 55.1%	−0.39 ± 0.55 54.1%	−0.40 ± 0.49 57.8%	−0.41 ± 0.53 57.8%	−0.40 ± 0.54 55.6%	−0.36 ± 0.55 48.8%	−0.35 ± 0.58 46.5%	−0.36 ± 0.58 48.8%
SF-36 PCS[c]	8.3 ± 10.0 69.2%	8.4 ± 10.3 68.1%	8. 5 ± 10.7 68.1%	9.1 ± 9.9 73.9%	9.2 ± 10.2 72.5%	9.1 ± 10.8 71.1%	5.6 ± 9.8 53.5%	5.5 ± 10.2 53.5%	6.2 ± 10.3 58.1%
Overall Work Impairment[d]	−18.9 ± 31.8 60.8%	−17.3 ± 35.0 59.8%	−16.0 ± 37.4 59.8%	−20.1 ± 32.5 62.2%	−17.1 ± 34.5 57.3%	−16.8 ± 37.3 59.8%	−14.8 ± 29.6 56%	−18.1 ± 37.5 68%	−13.5 ± 38.4 60%
Activity Impairment[d]	−24.3 ± 29.5 75.3%	−23.5 ± 28.9 72.5%	−23.7 ± 29.6 73.1%	−24.6 ± 30.2 75%	−23.0 ± 29.3 70.7%	−23.9 ± 29.8 71.4%	−23.3 ± 27.6 76.2%	−25.0 ± 28.0 78.6%	−23.1 ± 29.3 78.6%

[a]ITT population. Missing data were imputed using last observation carried forward (LOCF).
[b-d]MCID = −0.26, 3.0, and −7.0%, respectively.

Conclusion: Treatment of nr-axSpA with ADA was associated with significant and sustained improvements in physical function, HRQOL, and work productivity over 3 years of the ABILITY-1 trial among patients with and without elevated CRP and/or positive MRI as well as the overall nr-axSpA population.

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Comparison of Baseline Extra-Articular Manifestations, Comorbidities, and Long-Term Safety in Patients Treated with Adalimumab for Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis. Joachim Sieper[1], Désirée van der Heijde[2], Nupun A. Varothai[3] and Jaclyn K. Anderson[3]. [1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]Leiden University Medical Center, Leiden, Netherlands, [3]AbbVie Inc., North Chicago, IL.

Background/Purpose: To compare 1) extra-articular manifestations, 2) baseline comorbidities, and 3) adverse event (AE) rates with long-term adalimumab (ADA) therapy in patients (pts) treated in clinical trials for established ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA).

Methods: This *post hoc* analysis was performed in 3 studies: 1) ATLAS, a phase 3, randomized, double-blind (DB), multicenter study in US and Europe in pts with active AS who had inadequate response, or were intolerant to ≥1 nonsteroidal anti-inflammatory drug (NSAID); 2) M03–606, conducted in Canada with the same study design as ATLAS, and 3) ABILITY-1, a phase 3, multinational, randomized, DB, multicenter study in pts with active nr-axSpA (pts with past/present diagnosis of psoriasis were excluded). Pts were randomized to receive ADA 40 mg every other week (wk) or placebo for 24 wks followed by open-label ADA for up to 260 wks in ATLAS and M03–606, and up to 156 wks in ABILITY-1. Pts who received ≥1 dose of

ADA at any time during the study were analyzed (Any ADA set). AE frequency and events/100 patient-years (E/100 PY) of ADA exposure were summarized by study indication with the AS studies combined.

Results: The Any ADA population in the ATLAS/M03–606/ABILITY-1 studies was n=311/82/183, respectively. The Any ADA safety population was n=393 for AS and n=190 for nr-axSpA. Mean age was similar in AS and nr-axSpA pts, ranging from 37–42 yrs and about 80% of both AS and nr-axSpA pts were HLA-B27 positive. AS pts were predominantly male and had longer duration of disease diagnosis compared to nr-axSpA pts. Mean duration of SpA symptoms was >10 yrs in the nr-axSpA study; however, it was not collected in the AS studies (Table 1). At BL uveitis and IBD were less frequent in nr-axSpA pts compared to AS pts. Among pts exposed to ADA (1543.9 PY of exposure in AS, 412.2 PY in nr-axSpA), the incidence of serious AEs was similar in both populations (10.8 vs. 10.9 E/100 PY, AS vs. nr-axSpA). The malignancy rate in AS studies was 0.8 E/100 PY and 0 in nr-axSpA. There was 1 death in the AS studies (<0.1 E/100 PY) and 2 in nr-axSpA pts (0.5 E/100 PY); none were considered related to ADA. (Table 2)

Table 1. Baseline Demographic and Disease Characteristics

	AS		nr-axSpA
	ATLAS N = 311	M03-606 N = 82	ABILITY-1 N = 183
Demographics			
Age, mean (years)	42.3	40.9	37.9
Male, n (%)	233 (74.9)	65 (79.3)	83 (45.4)
HLA-B27 +, n (%)	245 (78.8)	69 (84.1)	144 (78.7)
Duration of disease diagnosis, mean (years)	10.9	13.3	2.8
Symptom duration, mean (years)	-	-	10.1
SpA Disease Characteristics			
CRP elevated, n (%)	211 (67.8)	60 (73.2)	65 (35.5)
BASDAI, mean (0–10)	6.3	6.3	6.5
PtGA, mean (VAS 0–10)	6.4	6.7	6.8
PGA, mean (VAS 0–10)	5.7	6.5	5.7
Total back pain, mean (VAS 0–10)	6.5	7.0	7.0
Uveitis, n (%)	95 (30.2)	32 (39.0)	22 (12.0)
Inflammatory bowel disease, n (%)	27 (8.6)	9 (11.0)	8 (4.3)
Psoriasis*, n (%)	34 (10.9)	11 (13.4)	0

*A past or present diagnosis of psoriasis was an exclusion criterion for ABILITY-1. AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; nr-axSpA, non-radiographic axial spondyloarthritis; PGA; physician global assessment of disease activity; PtGA, patient global assessment of disease activity; SpA, spondyloarthritis.

Table 2. Adverse Events

	AS[a] Any ADA Safety Population (N = 393; 1543.9 PY) E/100 PY	nr-axSpA[b] Any ADA Safety Population (N = 190; 412.2 PY) E/100 PY
Any AE	343.5	320.7
Any Serious AE	10.8	10.9
Any Infection	92.4	102.6
Serious Infections	1.4	2.4
Cardiac Disorder	1.0	0.2
Any Malignancy	0.8	0
Lymphoma	<0.1	0
Hematologic Disorders	1.0	1.5
Psychiatric Disorders	7.8	9.9
Gastrointestinal Disorders	27.0	33.7
Liver Events	0.8	0.5
Inflammatory bowel disease (new onset or worsening)[c]	0.6	0.5
Psoriasis (new onset or worsening)	2.7	0.5
Uveitis (new onset or worsening)[d]	3.0	1.5
Deaths	<0.1	0.5

[a]ATLAS + M03-606 studies. [b]ABILITY-1 study. [c]Includes inflammatory bowel disease, Crohn's disease and colitis ulcerative. [d]Includes uveitis, iritis and iridocyclitis. Any ADA = patients who received ≥1 dose of ADA at any time during the study. Not all events within larger system organ categories are reported in this table. MedDRA version 15.1. ADA, adalimumab; AE, adverse event; AS, ankylosing spondylitis; E, event; nr-axSpA, non-radiographic axial spondyloarthritis; PY, patient-year.

Conclusion: Enrolled pts with AS and nr-axSpA were generally similar in terms of demographics and BL disease activity. Although the SpA-related comorbidities of IBD and uveitis were more commonly reported in AS pts as compared to nr-axSpA pts at BL, reported AE rates were generally similar between pts with AS and nr-axSpA. This indicates a similar safety profile for ADA treatment in all pts with axial SpA.

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Myocardial Infarction Risk with Diclofenac Use in Spondyloarthropathy Versus Non-Inflammatory Low Back Pain. Maureen Dubreuil. Boston VA HealthCare System, Boston, MA.

Background/Purpose: Spondyloarthropathies (SpA) have been associated with increased risk of myocardial infarction (MI), however it remains unclear if the risk is related solely to the underlying inflammatory disease, or also due to use of medications that increase MI risk, such as certain non-steroidal anti-inflammatory drugs (NSAIDs). Alternatively, NSAIDs may reduce MI risk through reduction in systemic inflammation. Although diclofenac is commonly prescribed for treatment of SpA symptoms, its effect on MI in the SpA population has not been well quantified. By comparing risk of MI with diclofenac use in the SpA population with that in non-inflammatory back pain, we aimed to determine if the increased MI risk is solely due to the inflammatory disease or also the result of NSAID use.

Methods: We performed a cohort study assessing the effect of diclofenac on MI risk using 1995–2013 data from The Health Improvement Network, a medical record database from the United Kingdom, comprising records of over 11 million patients from over 600 general practitioners. We included adults with at least 1 year enrollment in the database, followed by a diagnosis of ankylosing spondylitis or psoriatic arthritis (combined SpA population) or who had a low back pain (LBP) diagnosis without any prior SpA history. From the SpA and LBP populations.we identified subjects who used either diclofenac or naproxen after SpA or LBP diagnosis and followed them until diagnosis of MI, death or end of the study period. We divided subjects into four categories: SpA/diclofenac, SpA/naproxen, LBP/diclofenac, and LBP/naproxen. We used Cox proportional hazards models with adjustment for potential confounders. The risk of MI in each cohort was compared to that in the LBP/naproxen cohort to estimate the effects of diclofenac and SpA on MI independently.

Results: We identified 2590 naproxen users and 3573 diclofenac users with SpA, as well as 147510 naproxen users and 280442 diclofenac users with LBP. SpA subjects tended to be younger, and less commonly female than LBP subjects. In all cohorts, baseline smoking, obesity, hypertension and use of cardioprotective medications was common. After adjustment for potential confounders, relative to the LBP/naproxen cohort, hazard ratios were 1.02 (985% CI 0.91–1.14) for LBP/diclofenac, 1.26 (0.71–2.23) for SpA/naproxen, and 1.50 (1.02–2.22) for SpA/diclofenac (Table).

Conclusion: Diclofenac use among SpA patients was associated with 50% increased risk of MI, while naproxen use did not significantly increase risk relative to its use in LBP patients. Notably in LBP patients, diclofenac use did not increase MI risk, potentially reflecting different patterns of use among LBP and SpA populations (eg- dose, frequency). These findings suggest that diclofenac use in SpA increases MI risk beyond any potential risk conferred by the underlying inflammatory disease.

Table. Risk of Myocardial Infarction (MI) according to low back pain or spondyloarthropathy diagnosis and use of naproxen or diclofenac.

Cohort	Subjects, N	MI, N (%)	Follow-up time (PY)	Incidence rate (/1000 PY)	Crude RR (95% CI)	Age-sex adjusted HR (95% CI)	Multivariable adjusted HR* (95% CI)
LBP/Naproxen	147510	1156 (0.8%)	518282	2.23	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
LBP/Diclofenac	280442	3797 (1.4%)	1798810	2.11	0.93 (0.87,1.00)	1.03 (0.96,1.10)	1.02 (0.91,1.14)
SpA/Naproxen	2590	27 (1.0%)	10375	2.60	1.16 (0.79,1.70)	1.30 (0.89,1.91)	1.26 (0.71,2.23)
SpA/Diclofenac	3573	61 (1.7%)	23498	2.60	1.14 (0.88,1.48)	**1.34 (1.04,1.74)**	**1.50 (1.02,2.22)**

LBP= low back pain, SpA=spondyloarthropathy, PY=person-years, RR=risk ratio, HR=hazard ratio, CI=confidence interval. *Adjusted for presence of hypertension, diabetes, gastrointestinal bleeding, kidney disease, hyperlipidemia and ischemic heart disease within 1 year prior to study entry; use of ACE inhibitors, aspirin, beta-blockers and lipid-lowering drugs within 2 years prior to study entry, and most recent value of body mass index, smoking status and alcohol use within 5 years prior to study entry.

Disclosure: M. Dubreuil, None;

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Urinary Excretion of Type II Collagen C-Telopeptide and Glucosyl-Galactosyl-Pyridinoline As Prognostic Biomarkers in Early Spondyloarthritis. Elisa Trujillo[1] and Maria del Mar Trujillo[2]. [1]Hospital Universitario de Canarias, La Laguna, Tenerife, Spain, [2]Servicio Canario de la Salud, Tenerife, Spain.

Background/Purpose: The search for biomarkers in spondyloarthritis (SpA) is of great interest because of their diagnostic and prognostic role in the treatment of these diseases. In recent years cartilage has been shown to be a major target organ in spondyloarthritis. In other diseases of the joints, elevated levels of urinary CTX-II (C-telopeptide fragments of type II collagen) and Glc-Gal-PYD (glucosyl-galactosyl-pyridinoline) have been associated with progression of radiological damage. *Objectives:* 1. To compare the level of urinary CTX-II and Glc-Gal-PYD in patients with early-stage SpA with urinary levels in healthy people of similar age and gender. 2. To analyze the association between the level of urinary CTX-II and Glc-Gal-PYD with patient variables and diagnosis at 3 years of follow up.

Methods: We included 68 patients aged <45 years who came to the service with some of the suggestive information of ESP of the table and who later completed three years of follow-up and they fulfill nowadays criteria for the Classification of Spondyloartropathy of The European Spondyloarthropathy Study Group (ESSG):

- inflammatory back pain,
- asymmetrical arthritis especially in lower limbs, dactylitis,
- raquialgia or arthralgia, plus one of the following; psoriasis, enthesitis, IBD, anterior uveitis, family history of spondyloarthritis, radiographic sacroiliitis, HLA-B27+, cervicitis/urethritis/diarrehea in the previous month.

Urine samples were taken from all patients attending for the first time with suspected early SpA. Urinary excretion of CTX-II was determined by immunoassay (ELISA). Urinary excretion of Glc-Gal-PYD was determined by High performance liquid chromatography. We also determined CTX-II and Glc-Gal-PYD urinary excretion in a healthy control group (n = 25) of similar age and sex.

Association analysis was performed with the following variables at 3 years: final diagnosis, HLA-B27, SpA axial / peripheral ASAS, early involvement of large joints (hips/knees), presence of extra-articular manifestations (anterior uveitis, psoriasis or IBD) and anti-TNF therapy.

Results: Urinary excretion of CTX-II and Glc-Gal-PYD in patients presenting for the first time with suspected early SpA was significantly higher than in the healthy control group matched for age and sex ($p < 0.001$).

The levels of urinary excretion of CTX-II and Glc-Gal-PYD in patients presenting for the first time with suspected early SpA were significantly higher in those who had predominantly peripheral involvement (SpA peripheral ASAS) versus axial involvement and in those due to high clinical activity and functional deficits (BASDAI and BASFI) required biological treatment at 3 years follow up. Urinary excretion of CTX-II was also significantly higher in patients developed early large joint involvement at 3 years follow up.

Conclusion: Urinary excretion of CTX-II and Glc-Gal-PYD in patients with early SpA may be a prognostic biomarker since in our series it was associated with peripheral involvement and early large joint involvement, and the need for biological treatment in the first three years of follow-up.

Disclosure: E. Trujillo, None; **M. D. M. Trujillo**, None.

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Defining Flare in Spondyloarthritis: Thresholds of Disease Activity Variations. Marie Godfrin-Valnet[1], Marc Puyraveau[1] and Daniel Wendling[2]. [1]CHRU, Besançon, France, [2]CHU J Minjoz, Besancon, France.

Background/Purpose: Spondyloarthritis (SpA) activity varies with time and treatment, but to date no clear definition of a flare of the disease is available.

The aim of this study was to evaluate thresholds of disease activity variations using validated composite indexes.

Methods: SpA patients fulfilling ASAS criteria and prospectively followed with at least two visits were evaluated using BASDAI, ASDAS-CRP and ASDAS-ESR. Patients and physician answered at each visit the question: "do you consider your SpA in a state of flare ?". Variations of BASDAI and ASDAS between visits were assessed and associated to the change of perception of a flare (yes/no). ROC curves were built to assess thresholds of variation in BASDAI and ASDAS associated with the change Flare: no to yes between visits.

Results: The patients were issued from a prospective series of 250 SpA. 99 situations with at least 2 visits were analyzed. The main characteristics of this cohort were: 67 % men, mean age 45 ± 12 years; disease duration: 16 ± 10 y; 84 % HLA-B27 positive; purely axial SpA: 81 %; PASS at baseline: 56 %; mean CRP: 8.6 ± 13.5 mg/l. Mean BASDAI and ASDAS-CRP at baseline were 4.3 ± 2.2 and 2.5 ± 1.1 respectively. The kappa coefficient of agreement between patient and physician for considering a flare was 0.68. The main results of the ROC curves are reported in the table:

Variation of the activity score	Flare considered by Patient and physician	Flare considered by Physician	Flare considered by Patient
BASDAI	**2.1**	**2.1**	2.1
Number of 2 visits	67	97	76
AUC	0.715	0.671	0.694
Specificity %	83	82	83
Sensitivity %	59	53	55
ASDAS-CRP	**1.3**	**0.7**	**1.3**
Number of 2 visits	30	45	34
AUC	0.74	0.698	0.682
Specificity %	100	72	100
Sensitivity %	47	59	40
ASDAS-ESR	**0.8**	**0.8**	**0.8**
Number of 2 visits	28	28	31
AUC	0.779	0.779	0.759
Specificity %	91	91	92
Sensitivity %	56	56	50

Conclusion: According to these results, an increase from a non-flare state of at least 2.1 units in BASDAI, 0.8 units in ASDAS-ESR or 1.3 units in ASDA-CRP is associated to (and may define) a flare, as considered by the patient and the physician.

This is the first study assessing, in current practice, thresholds of variation of activity score associated with a flare in SpA. This may help physicians in the evaluation and management of the patients with SpA.

Disclosure: M. Godfrin-Valnet, None; **M. Puyraveau**, None; **D. Wendling**, None.

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Translation and Cross-Cultural Adaptation of the ASAS Health Index and the environmental Item Set into 15 Languages. Uta Kiltz[1], Désirée van der Heijde[2], Annelies Boonen[3], Wilson Bautista - Molano[4], Ruben Burgos-Vargas[5], Praveena Chiowchanwisawakit[6], M Tuncay Duruoz[7], Bassel El-Zorkany[8], Inna Gaydukova[9], Ivette Essers[10], Pál Géher[11], Laure Gossec[12], Simeon Grazio[13], Jieruo Gu[14], Muhammad Asim Khan[15], Tae-Jong Kim[16], Walter P. Maksymowych[17], Helena Marzo-Ortega[18], Victoria Navarro-Compan[19], Ignazio Olivieri[20], Dimos Patrikos[21], Fernando Pimentel-Santos[22], Filip van Den Bosch[23], Jane Zochling[24] and Juergen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Maastricht University Medical Center, Maastricht, Netherlands, [4]Spondyloarthritis Group. Rheumatology Division. Hospital Militar Central/Universidad de La Sabana. Bogotá. Colombia, Bogotá, Colombia, [5]Universidad Nacional Autónoma de México, Mexico, Mexico, [6]Siriraj Hospital, Bangkok, Thailand, [7]Marmara Univ Med Schl, Istanbul, Turkey, [8]Cairo University, Cairo, Egypt, [9]Saratov State Medical University, Saratov, Russia, [10]Maastricht University, Maastricht, Netherlands, [11]Budai Irgalmasrendi Korhaz, Budapest, Hungary, [12]UPMC GRC08, Paris 06 University, Pitié Salpétrière Hospital, Paris, France, [13]Clinical Hospital Center Sestre Milosrdnice, Zagreb, Croatia, [14]The Affiliated Third Hospital of Sun Yat-san University, Rheumatology, Guangzhou, China, [15]CASE at MetroHealth Med Center, Cleveland, OH, [16]Chonnam Nat'l University Medical School&Hospital, Chonnam, South Korea, [17]University of Alberta, Edmonton, AB, [18]University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [19]University Hospital La Paz, Madrid, Spain, [20]Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Potenza, Italy, [21]401 Military Hospital Of Athens, Athens, Greece, [22]Centro Hospitalar de Lisboa Ocidental, Hospital Egas Moniz, Lisboa, Portugal, [23]Department of Rheumatology Ghent University Hospital, Ghent, Belgium, [24]Menzies Research Institute Tasmania, Hobart, Australia.

Background/Purpose: The ASAS Health Index (ASAS HI) is a unidimensional questionnaire measuring health and impairment in functioning in patients with spondyloarthritis (SpA). The ASAS HI is accompanied by a multidimensional item set aiming at measuring environmental factors (EF Item Set). These two disease-specific questionnaires are the first questionnaires which have been developed based on the International classification of functioning, disability and health (ICF). The ASAS HI contains 17 dichotomous items addressing categories of pain, emotional functions, sleep, sexual function, mobility, self care, and community life and the EF Item Set contains 9 dichotomous items addressing categories of support/relationships, attitudes and health services. The objective is to translate and adapt the ASAS HI and

the EF Item Set cross-culturally into 15 languages with 17 versions and to field test the new versions in patients with axial SpA (axSpA).

Methods: Translation and cross-cultural adaptation was done in 20 countries according to published recommendations (forward-backward procedure) in 5 steps: translation, synthesis of translation, back translation, expert committee review and pre-testing in a field test. The field test was conducted in patients with axSpA to test its applicability in patients with all forms of SpA.

Results: The ASAS HI and EF Item Set was translated into Arabic, Chinese, Croatian, Dutch/Flemish, French, German, Greek, Hungarian, Italian, Korean, Portuguese, Russian, Spanish (Colombia, Mexico, Spain), Thai, and Turkish. 206 patients (approximately 10 patients/country, 59.7% male, mean (SD) age 42.4 (13.9) years, mean (SD) BASDAI 3.8 (2.3)) with axSpA underwent qualitative interviews during field testing in 23 countries (19 non-English speaking countries, 4 English-speaking countries). 65% of the patients were diagnosed with AS, 35% with non-radiographic axSpA and 33% of the total sample size suffered from peripheral involvement. Interviews showed the English questionnaire and the translations to be clear, relevant and comprehensive. All versions were accepted with minor modifications. The total sum of the ASAS HI (range 0–17, with a lower score indicating a better health status) was 7.1 ± 4.4 (mean ± SD). Completion times for ASAS HI and for EF Item Set were respectively, 2.6 ± 1.6 and 2.1 ± 1.5 (mean ± SD) minutes.

Conclusion: The ASAS HI and the EF Item Set were successfully translated into 15 languages with 17 versions. This study showed the ASAS HI items to be readily adaptable throughout countries, indicating the concepts covered may be meaningful in many cultures. In the other hand, more difficulties were experienced with the contextual factors indicating these concepts may be more culture-dependent. The field test suggested that the English and the non-English versions have high face and content validity. By investigating patients with axSpA with and without peripheral manifestations it could be shown that the ASAS HI and the EF Item Set are valid to be applied in patients with all forms of SpA. Further validation is underway to test the psychometric properties of this new disease-specific questionnaire.

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Therapeutic Response in Adalimumab-Treated Patients with Non-Radiographic Axial Spondyloarthritis Is Similar Regardless of Body Mass Index.

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Background/Purpose: C-reactive protein (CRP), an objective measure of active inflammation, has been associated with obesity, with both overweight and obese individuals more likely to have elevated CRP levels than their normal-weight counterparts. The objective of this analysis was to assess the relationship of elevated CRP with clinical response in non-overweight and non-obese subgroups of non-radiographic axial SpA (nr-axSpA) patients (pts).

Methods: This *post hoc* analysis was performed in ABILITY-1, a phase 3, randomized, double-blind, multicenter study in pts with active nr-axSpA. Pts were randomized to receive adalimumab (ADA) 40 mg every other week (wk) or placebo (PBO) for 12 wks followed by open-label (OL) ADA for up to 156 wks. The MRI+/elevated CRP subpopulation included pts with a positive baseline MRI (Spondyloarthritis Research Consortium of Canada [SPARCC] score ≥2 for either the sacroiliac joints or spine) and/or elevated baseline CRP. Pts with BMI ≥25 kg/m^2 were considered overweight; pts with BMI ≥30 kg/m^2 were considered obese. Clinical response variables were analyzed by BMI subgroups at wk 12.

Results: BMI was <25 in 85/185 (45.9%) pts in the overall population (PBO/ADA, n=43/42) and in 57/142 (40.1%) in the MRI+/elevated CRP subpopulation (PBO/ADA, n=30/27); BMI was <30 in 149/185 (80.5%) pts in the overall population (PBO/ADA, n=70/79) and in 110/142 (77.5%) in the MRI+/elevated CRP subpopulation (PBO/ADA, n=52/58). In the overall population CRP was elevated in 43/100 (43%) pts with BMI ≥25 and in 22/36 (61.1%) pts with BMI ≥30. BMI and CRP were weakly correlated (0.23, P=0.002); however, in pts with elevated CRP, mean BMI was significantly higher than in pts with normal CRP (28.8 vs 25.0; P<0.0001). ASAS40 response at wk 12 was similar in the overall population and when excluding overweight and obese pts. (Table 1) A comparable effect was seen in the MRI+/elevated CRP subpopulation with the exception of a slightly higher ASAS40 response in the MRI+/elevated CRP subgroup with BMI <25; however, this should be interpreted with caution due to small sample size. (Table 2) ASAS40 response for the subgroup BMI ≥25 for the overall and MRI+/elevated CRP populations was consistent with the overall population (PBO 15.7% vs ADA 34.7%, and PBO 16.3% vs ADA 33.3%, respectively).

Table 1. Clinical Response in the Overall Population at Week 12

	Overall Population (N = 185)		BMI <25 kg/m^2 (N = 85)		BMI <30 kg/m^2 (N = 149)	
	PBO N = 94	ADA N = 91	PBO N = 43	ADA N = 42	PBO N = 70	ADA N = 79
Response Rate, n (%)[a]						
ASAS40	14 (14.9)	33 (36.3)	6 (14.0)	16 (38.1)	9 (12.9)	31 (39.2)
ASAS20	29 (30.9)	47 (51.6)	12 (27.9)	18 (42.9)	18 (25.7)	41(51.9)
BASDAI50	14 (14.9)	32 (35.2)	5 (11.6)	15 (35.7)	7 (10)	30 (38.0)
ASAS PR	5 (5.3)	15 (16.5)	1 (2.3)	9 (21.4)	1 (1.4)	15 (19.0)
ASAS5/6	6 (6.4)	28 (30.8)	1 (2.3)	14 (33.3)	3 (4.3)	28 (35.4)
Change from Baseline[b,c]						
hs-CRP (mg/L)	n=70 −0.4 (6.5)	n=67 −5.0 (12.5)	n=35 0.4 (5.8)	n=32 −5.7 (15.7)	n=52 0.1 (5.2)	n=60 −5.0 (12.9)
SF-36v2 PCS	n=93 2.0 (7.0)	5.5 (9.0)	n=42 1.7 (8.1)	5.4 (10.1)	n=69 1.1 (7.2)	6.0 (9.4)
HAQ-S	n=90 −0.1 (0.4)	n=88 −0.3 (0.5)	n=41 −0.2 (0.5)	n=41 −0.3 (0.5)	n=66 −0.1 (0.5)	n=76 −0.3 (0.5)
SPARCC MRI Score, SI Joints	n=84 −0.6 (6.2)	n=84 −3.2 (8.3)	n=40 −0.1 (6.1)	n=39 3.4 (7.4)	n=62 −0.6 (7.1)	n=74 −3.6 (8.8)
SPARCC MRI Score, Spine	n=83 −0.2 (3.3)	n=85 −1.8 (4.5)	n=39 0.2 (2.3)	n=40 −1.0 (2.3)	n=60 0.3 (2.1)	n=75 −1.2 (2.7)

[a]Non-responder imputation. [b]Mean (standard deviation). [c]Observed case analyses. ADA, adalimumab; ASAS, Assessment of SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; HAQ-S, Health Assessment Questionnaire modified for the Spondyloarthropathies; hs-CRP, high sensitivity C-reactive protein; MRI, magnetic resonance imaging; PBO, placebo; PR, partial remission; SI, sacroiliac; SPARCC, Spondyloarthritis Research Consortium of Canada; SF-36v2 PCS, Short Form-36 Health Status Survey Version 2 Physical Component Summary.

Table 2. Clinical Response in the MRI+/elevated CRP Subpopulation at Week 12

	MRI+/elevated CRP Subpopulation (N = 142)		BMI [2] (N = 57)		BMI [2] (N= 110)	
	PBO N = 73	ADA N = 69	PBO N = 30	ADA N = 27	PBO N =52	ADA N = 58
Response Rate, n (%)[a]						
ASAS40	10 (13.7)	28 (40.6)	3 (10.0)	14 (51.9)	5 (9.6)	26 (44.8)
ASAS20	23 (31.5)	41 (59.4)	8 (26.7)	15 (55.6)	13 (25.0)	35 (60.3)
BASDAI50	10 (13.7)	27 (39.1)	2 (6.7)	13 (48.2)	3 (5.8)	25 (43.1)
ASAS PR	4 (5.5)	13 (18.8)	0	7 (25.9)	0	13 (22.4)
ASAS5/6	6 (8.2)	24 (34.8)	1 (3.3)	12 (44.4)	3 (5.8)	24 (41.4)
Change from Baseline[b,c]						
hs-CRP (mg/L)	n=52 −0.9 (7.5)	n=49 −6.8 (14.3)	n=24 0.4 (7.1)	n=19 −9.7 (19.6)	n=36 −0.2 (6.1)	n=43 −7.0 (14.8)
SF-36v2 PCS	n=72 2.3 (6.8)	6.9 (9.3)	n=29 1.6 (7.7)	8.3 (10.7)	n=51 1.2 (6.9)	7.6 (9.8)
HAQ-S	n=69 −0.1 (0.4)	n=68 −0.3 (0.5)	n=28 −0.1 (0.4)	n=27 −0.4 (0.6)	n=48 −0.1 (0.4)	n=57 −0.4 (0.5)
SPARCC MRI Score, SI Joints	n=64 −0.9 (7.1)	n=64 −4.3 (9.3)	n=27 −0.2 (7.5)	n=25 −5.6 (8.5)	n=44 −0.9 (8.4)	n=55 −5.0 (9.8)
SPARCC MRI Score, Spine	n=63 −0.5 (3.7)	n=65 −2.3 (5.0)	n=26 −0.3 (2.4)	n=26 −1.6 (2.7)	n=42 0 (2.2)	n=56 −1.7 (2.9)

[a]Non-responder imputation. [b]Mean (standard deviation). [c]Observed case analyses. ADA, adalimumab; ASAS, Assessment of SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; HAQ-S, Health Assessment Questionnaire modified for the Spondyloarthropathies; hs-CRP, high sensitivity C-reactive protein; MRI, magnetic resonance imaging; PBO, placebo; PR, partial remission; SI, sacroiliac; SPARCC, Spondyloarthritis Research Consortium of Canada; SF-36v2 PCS, Short Form-36 Health Status Survey Version 2 Physical Component Summary.

Conclusion: In ABILITY-1, ADA showed similar clinical responses in subgroups excluding overweight and obese pts compared to the overall study population. These data suggest nr-axSpA pts have a general inflammatory

state which is unrelated to obesity-related CRP elevations and that response to ADA is not driven by CRP elevations related to obesity.

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Ultra Sonographic Evaluation of the Anterior Chest Wall in Spondyloarthritis. a Prospective Study. Frank Verhoeven[1], Xavier Guillot[2], Marie Godfrin-Valnet[3], Clément Prati[4] and Daniel Wendling[4]. [1]CHU jean Minjoz, Besançon, France, [2]rheumatology, Besançon, France, [3]CHRU, Besançon, France, [4]CHU J Minjoz, Besancon, France.

Background/Purpose: Anterior chest wall (ACW) involvement is a characteristic feature of spondyloarthritis (SpA), even in early stages, but its paraclinic exploration is not standardized.The aim of this study was to evaluate prevalence and type of ultrasonic (US) ACW involvement in SpA, and to look for factors associated to this involvement.

Methods: This prospective monocentric study included consecutive SpA (ASAS criteria) patients and a control group (healthy subjects, discal sciatica). Clinical (pain, swelling) and US evaluation (synovitis, joint effusion, erosion, joint space narrowing, ankylosis, power Doppler activity) were performed on manubrio sternal and sternoclavicular joints. The main characteristics of SpA were recorded (disease duration, biologic features, BASDAI, ASDAS, radiographic and extra articular involvement). Patients were compared to controls (C).

Results: 131 SpA and 49 control patients (same age and sex ratio) were included. Clinical and US ACW involvement was found respectively in 36 and 39 % of SpA and 10 and 15 % of controls ($p< 0.01$). US findings were:synovitis (9 SpA vs 2 C), joint space narrowing (12 vs 0), erosions (34 vs 0), manubrio sternalankylosis (24 vs 3), power Doppler activity (12 vs 2). US involvement in SpA is associated to smoking ($p< 0.05$), history of ACW pain ($p < 0.05$), to radiographic changes of sacro iliac joint ($p = 0.05$), to age (45 vs 41 y, $p = 0.004$), disease duration (14.9 vs 11.1 y, $p = 0.04$) and presence of inflammatory bowel disease ($p = 0.03$). US involvement is not associated to HLA-B27, enthesitis, psoriasis or uveitis, whereas clinical ACW involvement is associated with higher BASDAI (47 vs 32; $p = 0.0009$) and ASADAS (2.9 vs 2.2; $p = 0.006$). There is only a weak correlation between clinical and US involvement of ACW in these patients and controls.

Conclusion: US involvement of ACW is frequent in SpA, associated to disease duration, smoking and bowel involvement.

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High Sensitivity of the ASAS Classification Criteria in Patients with HLA-B27 Positive Undifferentiated Spondyloarthritis with Onset of Disease after Age 45. Ignazio Olivieri[1], Michele Gilio[1], Salvatore D'Angelo[1], Angela Padula[1], Pietro Leccese[1], Silvana Di Bello[1], Norullah Akkoc[2], Nicola Ferrara[3] and Carlo Palazzi[1]. [1]Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Potenza, Italy, [2]Department of Internal Medicine, Division of Rheumatology, Dokuz Eylul University School of Medicine, Izmir, Turkey, [3]Department of Translational Medical Sciences, Federico II University, Naples, Italy.

Background/Purpose: The spondyloarthritis (SpA) complex also includes forms that do not meet criteria for the definite forms and are called undifferentiated SpA (uSpA). Recently the Assessment in SpondyloArthritis international Society (ASAS) suggested criteria for axial and peripheral SpA that have substituted the Amor and the European Sondylarthropathy Study Group (ESSG) criteria for all forms of SpA. In the ASAS criteria for axial disease the entry criterion is chronic low back pain in a patient with an age less than 45 years. Only 15% of the patients included in the study for the ASAS criteria for peripheral disease were older than 45 years. The objective of our study was to evaluate the sensitivity of the ASAS criteria for axial and peripheral SpA in a cohort of consecutive patients with HLA-B27-positive uSpA with onset of disease after the age of 45 (late onset uSpA) consecutively recruited in a 12-year period in comparison with a cohort of consecutive patients with HLA-B27-positive uSpA with onset before age 45 (ordinary onset uSpA) recruited in the same period.

Methods: Patients HLA-B27-positive with at least one clinical manifestation of SpA and not meeting the New York criteria for ankylosing spondylitis (AS) and with a negative personal history for psoriasis, inflammatory bowel disease and preceding infection seen since January 2001 were entered in a special register and were followed prospectively. Each patient was examined at 6-month interval even if asymptomatic.

Results: During the 12-year recruitment period, 93 patients (35 M, 58 F; age 58.4±9.8) with late onset uSpA were seen. The first 93 consecutive patients (54 M, 39 F; age 29.6 ± 8.6) with ordinary onset uSpA seen in the same period were evaluated for comparison. Compared to the 93 patients with ordinary onset uSpA, the 93 patients with late onset uSpA were more frequently females (62.4% *vs.* 41.9 %, $p < 0.05$) had a significant shorter diagnostic delay (time elapsed between the day of onset and the day of diagnosis) (24.2 ± 45.6 *vs.* 65.1±97 months, $p < 0.05$) and showed more frequently increased levels of ESR (Erythrocite Sedimentation Rate)(57% *vs.* 33.3%, $p < 0.05$) and CRP (C-reactive proteine) (62,4% vs. 48,4%, p=0,07). In addition, patients with late onset uSpA developed more frequently inflammatory extremity swelling with pitting edema (IESPE) over the dorsum of hands and/or of the feet (25.8% *vs.* 4.3%, $p < 0.01$) and peripheral enthesitis (48.4% *vs.*31.2%, $p < 0.05$). In contrast, patients with ordinary onset uSpA showed more frequently acute anterior uveitis (20.4% vs. 7.5%, $p <0.05$). The sensitivity of the ASAS criteria was similar in the ordinary onset (90.3%) and the late onset (91.4%) cohorts of patients with uSpA.

Conclusion: The ASAS classification criteria for axial and peripheral SpA showed a similar high sensitivity in patients with ordinary and late onset uSpA. In addition, this study confirms that some clinical and laboratory features of SpA may differ with the age at onset of the disease.

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A Psychometric Analysis of Outcome Measures in Trials of Peripheral Spondyloarthritis. Sofia Ramiro[1], Maureen C. Turina[2], Dominique L. Baeten[3], Philip Mease[4], Jacqueline E. Paramarta[2], In-Ho Song[5], Aileen L. Pangan[6] and Robert Landewé[2]. [1]Amsterdam Rheumatology Center/University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [3]Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [4]Swedish Medical Center and University of Washington, Seattle, WA, [5]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany, [6]AbbVie Inc., North Chicago, IL.

Background/Purpose: We assessed the discriminatory aspects of disease activity measures and response criteria between adalimumab (ADA) and placebo (PBO) in 2 studies of patients (pts) with peripheral spondyloarthritis (pSpA).

Methods: ABILITY-2 is an ongoing randomized controlled trial of ADA in pts with pSpA fulfilling ASAS peripheral SpA criteria. Primary endpoint was peripheral SpA response criteria (PSpARC)40 at wk 12, defined as ≥40% improvement from baseline (BL) (≥20 mm absolute improvement on a visual analog scale) in Patient Global Assessments of Disease Activity (PGA) and Pain (PGA-pain) and ≥40% improvement in ≥1 of the following: swollen joint (SJC) and tender joint counts (TJC); enthesitis count; or dactylitis count. In an investigator-initiated study (AMC) in the Netherlands, pts fulfilling ESSG and/or AMOR criteria for SpA for ≥3 months but not criteria for ankylosing spondylitis or psoriatic arthritis were randomized to ADA or PBO. Primary endpoint was change in PGA at wk 12. Analyses to determine the discriminatory capacity of disease activity measures between ADA and PBO groups included standardized mean difference (SMD) of the mean change from BL; for categorical response criteria Pearson's χ^2 between treatments were calculated. The higher the SMD and χ^2, the higher the discriminatory capacity. Variables evaluated included PGA, PGA-pain, Physician's Global Assessment of Disease Activity (PhGA), CRP, TJC, SJC, BASDAI, SF-36, HAQ-S, ASDAS, PSpARC40/50/70, ACR20/50/70, ASDAS major improvement/inactive disease, and BASDAI50.

Results: ABILITY-2 randomized 165 pts (ADA 84, PBO 81); AMC enrolled 40 pts (ADA 20, PBO 20). Among the continuous variables, ASDAS

discriminates better than BASDAI or individual measures such as CRP as shown by higher SMD values (Table). For clinical response criteria, PSpARC40, PSpARC50, ASDAS inactive disease and BASDAI50 performed well in differentiating between ADA vs. PBO treatment as shown by the χ^2 in the table. ACR20 and ACR50 performed better than ACR70 in differentiating between ADA vs. PBO.

Discrimination between patients on adalimumab vs. placebo at week 12

	ABILITY-2				AMC			
Mean Change from Baseline	ADA (n)	PBO (n)	SMD	Guyatt's ES	ADA (n)	PBO (n)	SMD	Guyatt's ES
ASDAS	−1.1 (80)	−0.5 (77)	−0.63	−1.18	−1.5 (19)	−0.6 (19)	−0.89	−1.90
BASDAI	−2.1 (82)	−1.0 (80)	−0.50	−0.976	−1.9 (19)	−0.3 (19)	−0.73	−1.26
PGA (0–100 mm VAS)	−28.0 (81)	−16.2 (80)	−0.47	−1.14	−31.0 (19)	−5.9 (19)	−1.12	−1.45
PhGA (0–100 mm VAS)	−32.7 (82)	−18.2 (81)	−0.64	−1.43	−19.8 (19)	−4.1 (19)	−0.87	−1.21
CRP (mg/L)	−5.8 (80)	−2.9 (80)	−0.18	−0.52	−5.7 (19)	4.0 (19)	−0.53	−0.25
SJC 76	−3.6 (82)	−3.1 (81)	−0.10	−0.64	−2.5 (19)	−0.4 (19)	−0.67	−1.40
TJC 78	−6.0 (82)	−1.8 (81)	−0.50	−0.72	−1.8 (19)	1.7 (19)	−0.45	−0.28
n (%)	ADA	PBO	Pearson's χ^2	*P-value*	ADA	PBO	Pearson's χ^2	*P-value*
PSpARC40	33 (41)	16 (20)	8.18	0.004	7 (37)	0 (0)	8.58	0.008
PSpARC50	29 (36)	9 (11)	13.46	<0.001	6 (32)	0 (0)	7.13	0.020
PSpARC70	19 (24)	3 (4)	13.49	<0.001	3 (16)	0 (0)	3.26	0.230
ASDAS Major Improvement	18 (23)	5 (6)	8.04	0.005	5 (26)	2 (11)	1.58	0.405
ASDAS Inactive Disease	27 (34)	12 (15)	7.2	0.007	8 (42)	0 (0)	10.13	0.003
BASDAI50	35(43)	15 (19)	10.9	0.001	8 (42)	1 (5)	7.13	0.019
ACR20	47 (57)	21 (26)	16.05	<0.001	9 (47)	0 (0)	11.79	0.001
ACR50	28 (34)	8 (10)	13.66	<0.001	7 (37)	0 (0)	8.58	0.008
ACR70	15 (18)	2 (3)	10.75	0.001	4 (21)	0 (0)	4.47	0.105

Observed analyses. SMD: Standardized Mean Difference

Conclusion: Composite indices (ASDAS and BASDAI) outperformed individual measures (TJC, SJC, CRP) in sensitivity to change and discriminatory properties. The PSpARC response criteria developed for pSpA, as well as ACR20 and ACR50, have good discriminatory ability in patients with pSpA. Although the ASDAS and to some extent BASDAI, which were developed for AS, performed reasonably well in being able to discriminate between active treatment and placebo in patients with peripheral SpA, there may be problems regarding face validity.

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Clinical Response and Remission in Patients with Non-Radiographic Axial Spondyloarthritis after Three Years of Adalimumab Therapy.

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Background/Purpose: Adalimumab (ADA) has been previously shown to be effective for the treatment of non-radiographic axial spondyloarthritis (nr-axSpA) patients (pts) in the ABILITY-1 trial. [1] Week (wk) 12 results were further supported by sustained clinical response and remission data through Year 2 of the study. [2] We evaluate the final Year 3 long-term response/ remission and durability of response with ADA in pts with nr-axSpA.

Methods: ABILITY-1 was a phase 3, double blind (DB), randomized, controlled trial in pts with nr-axSpA who had an inadequate response, intolerance, or contraindication to NSAIDs. A 12-wk DB period of ADA 40 mg every other week (eow) or placebo was followed by an open-label period in which pts could receive ADA 40 mg eow for up to an additional 144 wks. This *post hoc* analysis evaluated the final Year 3 (wk 156) efficacy and safety results for both the overall population and the MRI+/elevated CRP subpopulation defined as those with a positive MRI at baseline (BL) (SPARCC score ≥2 for either the SI joints or spine) or an elevated CRP at BL. ASAS, BASDAI and ASDAS responses were calculated. Clinical remission was defined by ASDAS inactive disease (ASDAS ID, ASDAS <1.3) or by ASAS partial remission (ASAS PR).

Results: Of the 185 pts enrolled in ABILITY-1, 122 (66%) had data available at wk 156 and 97 of 142 (68%) from the MRI+/elevated CRP sub-population. Clinical responses and remission rates were generally sustained between Year 2 and Year 3 of the study (Table). Through 412.2 patient-years (PYs) of exposure to ADA, the serious infection rate observed was 2.4 events/100 PYs, including 1 case of disseminated TB. There were 2 deaths – 1 due to suicide and another due to opiate toxicity. There were no malignancies reported.

Table. Long-term clinical response and remission at Years 2 and 3

	Overall Population				MRI+/elevated CRP Sub-population			
	Year 2		Year 3		Year 2		Year 3	
%	NRI N=185	Observed Data N=138	NRI N=185	Observed Data N=122	NRI N=185	Observed Data N=107	NRI N=185	Observed Data N=97
ASAS20	61	81	55	83	62	82	58	86
ASAS40	48	64	44	66	50	66	47	69
ASAS PR	28	39[a]	28	43[d]	32	44[f]	32	47[i]
BASDAI50	49	65	46	70	52	69	49	72
ASDAS CII	49	69[b]	44	69[e]	56	77[g]	48	73[j]
ASDAS MI	27	38[b]	25	40[e]	30	41[g]	27	42[j]
ASDAS ID	34	46[c]	30	46[d]	36	49[h]	32	47[k]

[a]N=135; [b]N=131; [c]N=136; [d]N=120; [e]N=118; [f]N=104; [g]N=103; [h]N=105; [i]N=96; [j]N=93; [k]N=95.

ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CII, clinically important improvement; ID, inactive disease; MI, major improvement; NRI, non-responder imputation; PR, partial remission.

Conclusion: Almost half of the pts who remained on long-term ADA therapy in ABILITY-1 were in remission at the end of the study (Year 3), whether measured by ASAS PR or ASDAS ID. Results were similar between the overall population and the MRI+/elevated CRP sub-population.

References:

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2. Sieper J et al. Ann Rheum Dis 2013;72(Suppl3):88.

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Evaluation of Clinical Parameters and Quality of Life in Smokers with Ankylosing Spondylitis: Results from the Scotland Registry for Ankylosing Spondylitis.

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Background/Purpose: Several studies have shown that smoking is associated with increased disease activity, worse physical function and poor quality of life in ankylosing spondylitis (AS). However, other than as part of general health advice, recommendations on smoking cessation are not commonly given by physicians, nor perceived as of high importance by AS

patients. The aim of the current study was to examine the effect of smoking cessation on various clinical and patient-reported parameters in AS.

Methods: SIRAS collects data on clinically diagnosed AS patients in Scotland. Clinical measures are obtained from medical records, and postal questionnaires provide patient-reported data, including smoking status and quality of life. Differences between current and ex-smokers were assessed using linear regression models, adjusted for potential confounders (age, sex, education, socio-economic status, and alcohol consumption). **Results** are given as regression coefficients with 95% Confidence Intervals.

Results: SIRAS includes clinical and patient-reported information on 959 AS patients: 73% male; mean age 52yrs; 22% current smokers and 38% ex-smokers. Compared to current smokers, ex-smokers initially reported significantly lower disease activity (BASDAI) and physical function (BASFI) scores (−0.7 (−1.2, -0.2) and -0.4 (−0.95, 0.2), however, after adjusting for potential confounders this was no longer statistically significant (although still lower): -0.4 (−0.98, 0.1), and -0.4 (−0.97, 0.3), respectively. Additionally, ex-smokers reported significantly better quality of life: ASQoL score -1.4 (−2.5, -0.4). There were no other statistically significant differences between current and ex-smokers with any other clinical or patient-reported outcome.

Conclusion: Ex-smokers with AS, in comparison to smokers, have lower disease activity and function in addition to better disease-related quality of life. For comparison, the difference in disease activity is around 30% of the expected effect one might achieve with intensive physiotherapy, and 16% that of biologic therapy. Rather than being part of generic health advice, clinicians should actively promote smoking cessation as an adjunct to usual therapy.

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Cardiovascular Events in Ankylosing Spondylitis. an Updated Meta-Analysis. Sylvain Mathieu[1] and Martin Soubrier[2]. [1]Hopital Gabriel Montpied, Clermont Ferrand, France, [2]CHU G.-Montpied, Clermont-Ferrand, France.

Background/Purpose: Rheumatoid arthritis is associated with increased cardiovascular risk. In the guidelines, ankylosing spondylitis (AS) is considered to have an equally high cardiovascular risk. The literature findings remain controversial. Objectives of this study were to assess the risk of myocardial infarction (MI) and stroke in AS patients in 2013.

Methods: An updated meta-analysis with a new systematic literature review using PubMed was conducted up to December 2013. Incidence of MI or stroke was calculated by metaproportion.

Results: In addition to the eleven previously included studies, five new studies assessed the occurrence of MI or stroke in AS patients.

1. MI. 726 MI were reported in AS patients (N=18,916) over mean follow-up of sixteen years: incidence 5.5% [3.9%, 7.4%], i.e. 0.44/100 pyrs. Seven studies revealed 17,410 MI (2.5% (95% CI [1.8%, 3.4%])) in the control group (N=1,349,964). Meta-analysis of the seven longitudinal studies showed a significant increase in MI (RR=1.46 [1.33, 1.60]) in AS patients. **2. Stroke.** In ten longitudinal studies (N=43,374), 1,370 strokes were reported in AS patients over 18.5 years of follow-up: incidence 3.4% [1.2%, 6.8%], i.e. 0.1/100 pyrs. Three studies reported 22,899 strokes in controls (N=1,239,041), giving an incidence of 1.78% [1.75%, 1.80%]. A significant increase in stroke (RR=1.50 [1.39, 1.62]) in AS patients was found.

Conclusion: AS patients appear to have a higher risk of MI and stroke. Management of cardiovascular risk factors and control of systemic inflammation should be taken into account in AS.

Disclosure: S. Mathieu, None; **M. Soubrier**, None.

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Effect of Certolizumab Pegol over 96 Weeks of Treatment on Inflammation of Spine and Sacroiliac Joints Measured By Magnetic Resonance Imaging in Patients with Axial Spondyloarthritis. Jürgen Braun[1], Walter P. Maksymowych[2], Robert B. M. Landewé[3], Christian Stach[4], Owen Davies[5], Tommi Nurminen[4] and Desiree van der Heijde[6]. [1]Ruhr-University Bochum, Herne, Germany, [2]University of Alberta, Edmonton, AB, [3]Amsterdam Rheumatology Center, Amsterdam, Netherlands, [4]UCB Pharma, Monheim, Germany, [5]UCB Pharma, Slough, United Kingdom, [6]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Previous results from RAPID-axSpA (NCT01087762) demonstrated that certolizumab pegol (CZP) reduced inflammation in the sacroiliac joints (SIJ) and spine, as assessed by Magnetic Resonance Imaging (MRI), after 12 weeks (wks) of therapy in patients (pts) with axial spondyloarthritis (axSpA) and in both ankylosing spondylitis (AS) and non-radiographic (nr-) axSpA subpopulations. [1] The objective of this report is to present MRI outcomes from RAPID-axSpA to Wk96.

Methods: RAPID-axSpA,[2] a Phase 3 study in axSpA pts, is double-blind and placebo-controlled to Wk24, dose-blind to Wk48 and open-label (OL) to Wk204. Pts originally randomized to CZP (200mg Q2W or 400mg Q4W, following 400mg loading dose at Wks 0, 2, 4), continued on their assigned dose in dose-blind and OL phases. MRI scans of the SIJ and spine,[3] using short-tau-inversion recovery sequences, were performed at baseline (BL) (±3 days), Wk12, Wk48 and Wk96. MRI endpoints were change from BL in the Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ score for inflammation and in the Berlin modification of AS spine MRI score for disease activity in the spine (ASspiMRI-a). MRIs were recorded in a subset of pts, and results reported for pts randomized to CZP using all observed MRI measurements.

Results: 218 pts were randomized to receive CZP, of which 109 were included in the MRI set. 27 pts (24.8%) reported inflammation of SIJ (SPARCC≥2), but no spinal involvement (ASspiMRI-a≤2); 17 (15.6%) reported spine inflammation without SIJ involvement; and 31 (28.4%) reported inflammation of spine and SIJ. Mean BL SPARCC was similar between AS and nr-axSpA pts (7.2 in both groups), but mean BL ASspiMRI-a score was higher in AS pts (AS: 5.3 vs nr-axSpA: 2.8). Rapid improvement in SPARCC SIJ and ASspiMRI-a scores was observed at Wk12 and sustained to Wk96 (Table). Similar results were observed for both CZP dose regimens (data not shown). Similar improvement in SPARCC SIJ score was observed in AS and nr-axSpA pts. While improvement in spinal inflammation was observed in both AS and nr-axSpA pts, nr-axSpA pts had a lower mean ASspiMRI-a score at all time points.

Conclusion: Previously reported improvements in MRI scores at Wk12 were maintained to Wk96 in axSpA, AS and nr-axSpA pts.

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Table: Mean change from BL in SPARCC and ASspiMRI-a in patients with axSpA

	Week 12			Week 48			Week 96		
	N	Mean score (SD)	Mean change from BL (SD)	N	Mean score (SD)	Mean change from BL (SD)	N	Mean score (SD)	Mean change from BL (SD)
SPARCC									
axSpA	97	2.1 (4.1)	−4.8 (8.6)	76	2.6 (5.1)	−5.4 (10.4)	81	2.5 (7.5)	−5.0 (10.9)
AS	58	1.5 (3.6)	−5.0 (9.1)	41	2.6 (5.4)	−6.3 (10.7)	48	1.8 (7.0)	−6.4 (10.7)
nr-axSpA	39	2.9 (4.8)	−4.4 (7.9)	35	2.7 (4.8)	−4.4 (10.1)	33	3.7 (8.1)	−3.0 (11.1)
ASspiMRI-a									
axSpA	99	1.4 (2.4)	−3.0 (4.2)	76	1.4 (2.8)	−2.5 (4.1)	82	1.4 (2.5)	−3.2 (4.6)
AS	60	1.8 (2.8)	−3.6 (4.7)	41	1.9 (3.7)	−3.3 (4.4)	49	1.7 (3.0)	−4.1 (5.0)
nr-axSpA	39	0.9 (1.4)	−2.0 (3.2)	35	0.9 (1.1)	−1.6 (3.6)	33	0.9 (1.5)	−2.0 (3.9)

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Structural Progression of the Spine Measured By X-Ray in Patients with Axial Spondyloarthritis Treated with Certolizumab Pegol over 96 Weeks, Including Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis. Désirée M. van der Heijde[1], Walter P. Maksymowych[2],

Robert B. M. Landewé[3], Christian Stach[4], Owen Davies[5], Tommi Nurminen[4] and Jürgen Braun[6]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]University of Alberta, Edmonton, AB, [3]Amsterdam Rheumatology Center, Amsterdam, Netherlands, [4]UCB Pharma, Monheim, Germany, [5]UCB Pharma, Slough, United Kingdom, [6]Ruhr-University Bochum, Herne, Germany.

Background/Purpose: The impact of certolizumab pegol (CZP) on clinical and Magnetic Resonance Imaging outcomes in patients (pts) with axial spondyloarthritis (axSpA), including ankylosing spondylitis (AS) and non-radiographic (nr-) axSpA, has been described previously.[1] However, structural progression in these pts measured by X-ray has not been previously reported. The objective of this report is to present structural progression, assessed using X-ray, over 96 weeks (wks) of CZP treatment in the RAPID-axSpA study (NCT01087762).[2]

Methods: RAPID-axSpA, a Phase 3 study in axSpA pts, is double-blind and placebo-controlled to Wk24, dose-blind to Wk48 and open-label (OL) to Wk204. Pts had adult-onset active axSpA. Pts originally randomized to CZP (200mg Q2W or 400mg Q4W, following 400mg loading dose at Wks 0, 2, 4), continued on their assigned dose in dose-blind and OL phases. X-ray assessment of the anterior vertebral edges of the cervical and lumbar spine was conducted using the modified Stokes Ankylosing Spondylitis Spine Score (mSASSS) at baseline (BL) and Wk96. X-rays were recorded in a subset of pts, and results reported for pts initially randomized to CZP with both available BL and Wk96 X-ray measurements (observed case). Definite mSASSS progression was defined as an mSASSS increase ≥2 units, and was assessed over 96 wks. Unadjusted descriptive analyses investigated mSASSS disease activity and response in subgroups of pts.

Results: 218 pts were randomized to receive CZP, of which 109 were included in the imaging set, and 89 had both BL and Wk96 X-rays available for analysis. 22.2% of CZP pts in the imaging set had evidence of structural changes in the spine (mSASSS≥2, with ≥1syndesmophyte) at BL (32.3% of AS and 8.7% of nr-axSpA pts). Mean mSASSS at BL was 8.0 in axSpA pts. As expected, BL damage was more severe in AS pts compared to the nr-axSpA population (11.1 vs 3.2, Table). Over 96 wks of CZP treatment, mean mSASSS score of the axSpA population increased by 0.4 units, and 9.0% of pts experienced definite mSASSS progression ≥2 units. Radiographic progression was greater in AS pts compared to nr-axSpA pts (change from BL: 0.6 vs 0.2, definite mSASSS progression 13.0% vs 2.9%). A number of BL characteristics appeared to influence mSASSS progression over 96 wks (Table). However, these are unadjusted analyses, therefore further investigation is underway to determine whether these observations are influenced by confounding BL factors.

Conclusion: Limited radiographic progression was seen over 96 wks in CZP-treated pts. Further analyses are needed to confirm which subgroups of pts have an increased risk of progression.

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Table: BL structural changes, and mean BL mSASSS, change from BL and mSASSS progression rate at Wk96 of CZP treatment, by subgroup

	BL[a]		Week 96 mSASSS[b]		
Subgroup	mSASSS≥2 and ≥1 syndesmophyte % (n/N)	N	Mean BL score (SD)	Mean change from BL (SD)	% progression ≥2
axSpA	22.2 (24/108)	89	8.0 (14.3)	0.4 (1.6)	9.0
AS	32.3 (20/62)	54	11.1 (15.7)	0.6 (1.8)	13.0
nr-axSpA	8.7 (4/46)	35	3.2 (10.2)	0.2 (0.9)	2.9
HLA-B27 positive	23.3 (20/86)	73	8.4 (14.0)	0.5 (1.7)	11.0
HLA-B27 negative	16.7 (3/18)	13	7.8 (17.4)	0.0 (0.1)	0.0
BL SPARCC <2	21.4 (9/42)	36	8.8 (15.1)	0.4 (1.2)	11.1
BL SPARCC ≥2	20.7 (12/58)	49	6.7 (13.2)	0.3 (1.5)	4.1
BL ASspiMRI ≤2	7.8 (4/51)	41	3.7 (11.0)	0.0 (0.3)	0.0
BL ASspiMRI >2	32.7 (16/49)	43	10.2 (14.2)	0.6 (1.7)	11.6
Male	32.8 (22/67)	56	11.9 (16.8)	0.7 (1.9)	14.3
Female	4.9 (2/41)	33	1.4 (2.4)	−0.1 (0.3)	0.0
Current Smoker	28.6 (8/28)	23	9.3 (15.2)	1.0 (2.8)	21.7
Never/Former smoker	20.0 (16/80)	66	7.5 (14.1)	0.2 (0.7)	4.5
CRP ≤ULN	18.0 (16/89)	73	7.6 (13.7)	0.4 (1.5)	8.2
CRP >ULN	42.1 (8/19)	16	9.8 (17.1)	0.8 (1.9)	12.5
ASDAS <2.1	14.9 (10/67)	57	6.1 (12.4)	0.3 (1.0)	7.0
ASDAS ≥2.1	34.1 (14/41)	32	11.3 (16.9)	0.7 (2.3)	12.5
BL BMI <30	16.9 (13/77)	62	5.5 (10.5)	0.2 (0.8)	6.5
BL BMI ≥30	37.9 (11/29)	25	14.8 (20.1)	1.1 (2.6)	16.0

[a] All pts with BL X-ray measurements (N = 108), [b] Pts with both BL and Wk96 X-ray measurements (N = 89) only

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Use of Monotherapy Anti-Tnf Agents in Ankylosing Spondylitis Patients from the rhumadata® Registry: 8-Year Comparative Effectiveness of Adalimumab, Etanercept and Infliximab.

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Background/Purpose: Anti-TNF agents namely adalimumab (ADA), etanercept (ETA) and infliximab (INF) are approved for the treatment of signs and symptoms of ankylosing spondylitis. Their efficacy has been demonstrated in randomized controlled trials against placebo. They have also been shown effective in the treatment of extra-articular features such as enthesitis, inflammatory bowel entities such as Crohn's disease and ulcerative colitis and uveitis. Antibodies and soluble receptors may have a different efficacy profile. Our objective is to assess the retention rates of adalimumab (ADA), etanercept (ETA) and infliximab (INF) in patients diagnosed with ankylosing spondylitis (AS) and to compare patient reported response over time.

Methods: Data of AS patients who had been prescribed adalimumab (ADA), etanercept (ETA) or infliximab (INF) in monotherapy on or after January 1st 2004 was extracted. Baseline demographics included age, gender, disease duration, HAQ-DI, fatigue and pain visual analog scale evaluations (VAS), morning stiffness, BASDAI, BASFI, ASDAS and HLA-B27. Eight-year drug retention rates were estimated and compared using Kaplan-Meier survival estimates. BASDAI improvement over time was assessed using proportional hazard model adjusted for age and disease duration at TNF initiation. Other differential measures of effectiveness were tested using general linear models (GLM). For these analyses, patients with baseline BASDAI of 4 or more were included. Statistical analysis was performed using SAS version 9.3. RHUMADATA® is a clinical database and registry used in daily clinical practice at the IRM, CORQ and CREQ.

Results: Data from 170 patients diagnoses with AS was extracted and no significant differences in baseline characteristics were observed between treatment groups except for age and disease duration. The 8-year retention rate of ADA, ETA and INF were 62%, 55% and 54% respectively and were not statistically different (Log-Rank p=0.90). Seventy-five patients were used to analyse time required to reach a BASDAI of 2 and compare rates of response. At baseline, ADA, ETA and INF BASDAI were 6.6, 6.2, 6.5 respectively. The adjusted hazard ratio for reaching a BASDAI of two was found to be 0.77 (95% CI = [0.32, 1.87]) and 0.92 (95% CI = [0.40, 2.14]) when comparing ETA and INF to ADA respectively. Overall 42%, 61% and 64% of ADA, ETA and INF patients reached a target BASDAI of 2 in average adjusted times of 9.6, 19.0 and 15.6 months (p-value=0.31).

Conclusion: Monotherapy adalimumab, etanercept and infliximab in AS patients show similar 8-years retention rates and similar improvement in BASDAI. They all represent good options for the treatment of AS in monotherapy.

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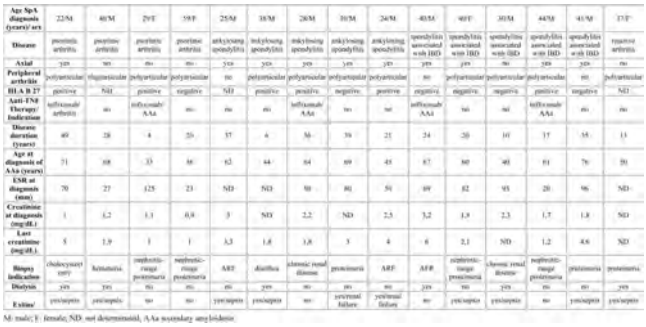
Secondary Amyloidosis Complicating Spondyloarthritis: Still Present after All These Years. Samantha Rodriguez-Muguruza[1], Melania Martínez-Morillo[1], Susana Holgado[1], Maria Lourdes Mateo[1], Juana Sanint[1], Anne Riveros-Frutos[2], Jeronima Cañellas[1], Xavier Tena[1] and Alejandro Olivé Marqués[1]. [1]Hospital Universitari Germans Trias i Pujol, Barcelona, Spain, [2]Hospital Universitario Germans Trias i Pujol, Badalona, Spain.

Background/Purpose: Secondary amyloidosis (AA) is a disorder caused by deposition of insoluble amyloid A fibrils in different tissues and organs. It is a rare and serious complication of rheumatic diseases including spondyloarthropathies (SpA).

The aim of this study was to determine the clinical features, laboratory data, treatment and clinical outcome of patients with SpA who developed AA amyloidosis.

Methods: Design: retrospective (1984–2013). Hospital: academic tertiary hospital. Referral area: 850,000 inhabitants. We reviewed the medical records of 1125 patients with SpA: 509 (45%) psoriatic arthritis (PsA), 263 (23%) ankylosing spondylitis (AS), 128 (11.3%) spondylitis associated with inflammatory bowel disease (IBD), 190 (16.8%) undifferentiated spondyloarthropathies, and 35 (3.1%) reactive arthritis. We selected patients who had a histological diagnosis of AA amyloidosis. Patients with comorbidities that might be associated with AA amyloidosis were excluded.

Results: Fifteen (1.3%) patients with AA amyloidosis were recruited: 11 (73.3%) males and 4 (26.7%) females. Five (33.3%) AS, 5 (33.3%) spondylitis associated with IBD, 4 (26.7%) PsA, and 1 (6.7%) reactive arthritis. Mean age at SpA and AA amyloidosis diagnosis: 35.13 and 57.7 years, respectively. Mean disease duration: 23.9 years. Eleven patients with AA amyloidosis were diagnosed in 1984–2000 and 4 in 2001–2013. Amyloid deposits were observed on biopsy of: rectum (6 cases), kidney (3 cases), subcutaneous fat (4 cases) and bladder (1 case). In one case diagnosis was made incidentally (gallbladder), in the others diagnosis was symptomatic and suspected due to nephrotic syndrome (4), acute renal failure (ARF) (3), non-nephrotic-range proteinuria (3), chronic renal failure (CRF) (2), diarrhoea (1) and macroscopic haematuria (1). The mean values of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at diagnosis of amyloidosis were 65.4 mm and 25.22 mg/L, respectively. Five patients were treated with infliximab: three showed a clinical improvement, with decreased proteinuria and improved renal function. Ten patients did not receive an anti-TNF treatment, 9 of whom died (2 of CRF, 7 of sepsis). Mortality at one and five years was 30 and 50% respectively. Clinical and analytical parameters are described in Table 1.



Conclusion: The frequency of clinically apparent AA amyloidosis in our patients was 1.3%. There was a marked male predominance. Clinical AA amyloidosis was diagnosed at a relatively late stage in SpA. The predominant clinical picture was nephrotic syndrome. The frequency of AA amyloidosis decreases between decades, reflecting better control of the disease with novel therapies. Mortality is high.

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Better Outcomes in Ankylosing Spondylitis: The Synergistic Association Between Exercise and Tumor Necrosis Factor Inhibitors. Sarah L. Patterson[1], John D. Reveille[2], MinJae Lee[2], Michael M. Ward[3], Mohammad H. Rahbar[4], Matthew A. Brown[5], Michael H. Weisman[6] and Lianne S. Gensler[1]. [1]University of California, San Francisco, San Francisco, CA, [2]University of Texas Health Science Center at Houston, Houston, TX, [3]NIAMS/NIH, Bethesda, MD, [4]The University of Texas Health Science Center at Houston, Houston, TX, [5]University of Queensland Diamantina Institute, Brisbane, Australia, [6]Cedars-Sinai Medical Center, Los Angeles, CA.

Background/Purpose: Exercise is an important component of Ankylosing Spondylitis (AS) management. The purpose of this study was to determine if the amount patients exercise associates with better functional outcomes and to assess if medication use contributes to this relationship.

Methods: This is a prospective cohort of 623 AS patients, meeting modified New York criteria followed up to 4 years. We collected demographic, clinical and self-reported outcomes every 6 months. Participants were queried about exercise habits including number of days per week and minutes per time exercised. A moderate exercise dose was defined as ≥120 minutes per week. Using a mixed effects Poisson regression model, we assessed multivariable associations between independent variables and the Bath Ankylosing Spondylitis Functional Index (BASFI). This accounted for correlation of repeated measures over time. Potential confounding, including baseline function, and effect modifications were examined and addressed while developing a final longitudinal multivariable model.

Results: The mean age of patients was 43 ± 14.0 years. The cohort was 72% male and 78% of patients were white. Mean disease duration was 19 ± 13.4 years. Findings from our final multivariable model indicated BASFI scores for the moderate exercise group were significantly lower than those who exercised less than 120 minutes per week at 1, 2, 3, and 4 years of follow-up (Table 1). Additionally, there was a significant interaction between exercise and Tumor Necrosis Factor (TNF) inhibitor use on function ($p=0.046$). When we looked at the effect based on level of exercise, there was a significant association between TNF inhibitor use and better function regardless of exercise status, but a greater benefit in function in those who were both on a TNF inhibitor and exercising above the defined threshold (Figure 1).

Conclusion: AS patients who exercise for at least 120 minutes per week have significantly better long-term function than those who do not. Additionally, there is a greater likelihood of functional improvement in those on both a TNF inhibitor and moderate exercise program compared to those using a TNF inhibitor alone.

Table 1. Adjusted Associations of Exercise and Other Covariates on Function (BASFI)

Independent Variable	Adjusted Rate Ratio[a]	95% Confidence Interval	P-value
Exercise & Time Interaction			0.0349
Exercise > 120[b]			
Baseline	1.00	0.96–1.05	0.96
Year 1	0.93	0.90–0.96	<0.0001
Year 2	0.95	0.91–0.99	0.01
Year 3	0.93	0.88–0.97	<0.001
Year 4	0.95	0.90–1.00	0.04
Exercise & TNF inhibitor Interaction			0.0464
Exercise > 120			
TNF inhibitor Use	0.99	0.93–1.06	0.83
No TNF inhibitor	1.04	0.97–1.11	0.32
TNF inhibitor Use			
Exercise > 120	0.87	0.84–0.91	<0.0001
Exercise < 120	0.91	0.88–0.95	<0.0001
BASFI at Baseline	1.03	1.03–1.03	<0.0001
Age at least 50 years	1.12	1.05–1.19	0.0003
Male	1.01	0.91–1.13	0.85
Postgraduate Education	0.96	0.84–1.10	0.58
BASDAI score at least 40	1.33	1.29–1.36	<0.0001
Total CES-D score at least 8	1.14	1.11–1.16	<0.0001
Current Smoker	0.93	0.79–1.08	0.32
At least 1 comorbidity	1.04	0.93–1.18	0.48
Disabled	0.91	0.76–1.08	0.28
NSAID Use	1.07	1.04–1.09	<0.0001

[a] Rate Ratio of a higher BASFI score based on the independent variables in column 1 adjusted for BASFI at baseline, and all other covariates above.
[b] Report of exercise for at least 120 minutes per week.

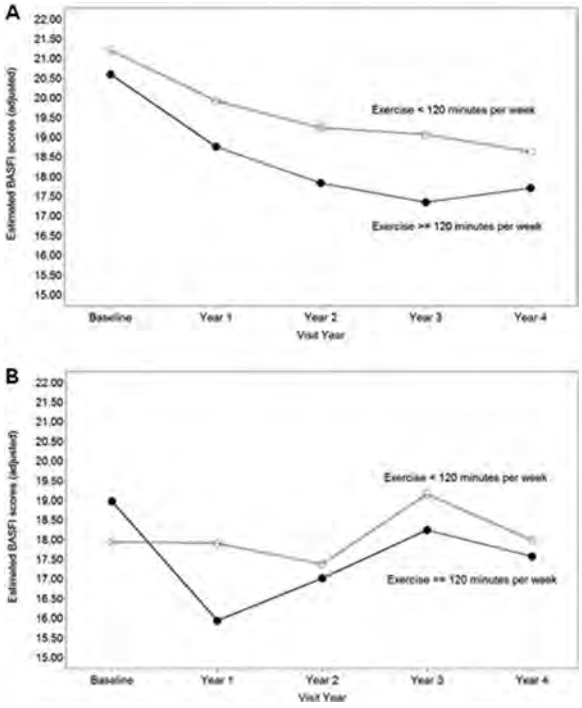

Figure 1A: In TNF inhibitor users: estimated BASFI Scores by Exercise Group Over Time

B: In TNF inhibitor non-users: estimated BASFI Scores by Exercise Group Over Time

Disclosure: S. L. Patterson, None; **J. D. Reveille**, None; **M. Lee**, None; **M. M. Ward**, None; **M. H. Rahbar**, None; **M. A. Brown**, None; **M. H. Weisman**, None; **L. S. Gensler**, UCB, 5, AbbVie, 5.

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Sleep Disturbances in Korean Patients with Ankylosing Spondylitis Are Associated with Increased Disease Activity.

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Background/Purpose: Sleep problems have been reported to be more frequent in rheumatic disease than normal population. Other studies indicate various sleep problems have been reported in ankylosing spondylitis (AS). Inadequate sleep in AS patients is associated with multiple factors including pain, fatigue, disease activity and depression. In this study, we evaluated the prevalence of sleep disturbance in Korean patients with ankylosing spondylitis, and its association with disease activity and depression.

Methods: Forty patients with AS and eighty healthy controls were included in the study. Participants completed questionnaires. Sleep quality was assessed using the Korean version of the Pittsburgh sleep quality index (PSQI). Depression was assessed by the Korean version of the Beck depression inventory second edition (BDI-2). The Bath ankylosing spondylitis disease activity index (BASDAI) and ankylosing spondylitis disease activity score-C-reactive protein (ASDAS-CRP) were used to evaluate disease activity. Patients were dichotomized into a good sleeper group ($PSQI \leq 5$) and a poor sleeper group ($PSQI > 5$).

Results: The mean total PSQI score of patients with AS was 7.23 ± 3.84. It was higher than that of control subjects ($p < 0.001$). AS patients had higher scores in the subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance and daytime dysfunction components. 60% of the AS patients classified as poor sleeper group. The mean ASDAS-CRP and BDI-2 score of poor sleeper group were higher than that of good sleeper group. Significantly, higher disease activity according to ASDAS-CRP was associated with poor sleep quality and depression. Stepwise multiple regression analysis revealed that duration of morning stiffness and depression were independent risk factors that influenced poor sleep quality.

Conclusion: Sleep disturbances are prevalent amongst Korean patients with AS. Lower quality of sleep is significantly associated with higher disease activity and depression. Morning stiffness and depression were independent risk factors that influenced poor sleep quality. Therefore, evaluation and optimal management of morning stiffness and depression to improve sleep quality in patients with AS is important.

Disclosure: H. J. Jeong, None; **Y. S. Kim**, None; **C. N. Son**, None; **J. M. Kim**, None; **S. H. Kim**, None.

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Unraveling the Familial Tendency for Ankylosing Spondylitis in Korea.

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Background/Purpose: Despite of the evidence of familial aggregation of ankylosing spondylitis (AS), familial tendencies are not fully explored. The purpose of this study was to examine the recurrence risk (RR) ratios in different degrees of relatives for Korean AS patients.

Methods: 526 consecutive unrelated AS probands (101 female, 425 male, mean age 35.5 years, mean disease duration 12.3 years, 88.7% HLA-B27 positive) fulfilling the modified New York criteria were face-to-face-interviewed by physicians, with elaborated questionnaire to investigate AS in other family members by the same criteria. A total of 12,051 relatives (2284, 5342 and 4425 for first, second and third-degree relatives (TDR), respectively) were included. The RR ratios for different degrees of relatives were elicited and subsequently stratified by gender and HLA-B27 status. The prevalence of AS among Korean in 2013 was estimated by the Korean National Health Insurance Service at 0.07%.

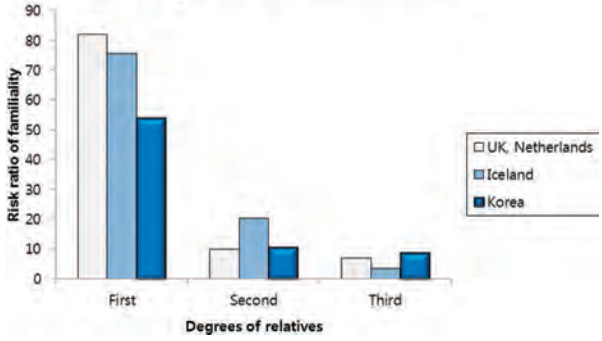
Results: The RR ratio was 53.8 for first-degree relatives (FDR) followed by 10.8, 9.0 for second-degree relatives (SDR) and TDR, respectively, indicating strictly decreasing in familiality. Among FDRs, siblings were more frequently affected than offspring or parents. For male probands, the overall RR ratio for FDR was 55.5, and 65 for female, implying higher familiality of female over male. Remarkably, all of affected SDRs and beyond were relatives of HLA-B27 positive probands.

Conclusion: We demonstrated strongest familiality of AS in FDRs, particularly in siblings. Despite of similar sharp decline pattern of familiality beyond SDR, lower RR ratio in FDR in our study, compared to previous Caucasian reports, indicates ethnic difference in inheritance of the same disease. This study suggests familial tendency for AS can be explained by degrees of relationship, gender and HLA-B27, warranting further studies.

Table. The relative recurrence risk ratio by gender in Korean AS patients

	Female		Male		All	
Korean population prevalence (%)	0.04		0.09		0.07	
	RR % (95% CI)	RR ratio	RR % (95% CI)	RR ratio	RR % (95% CI)	RR ratio
Overall familial AS	0.8 (0.5–1.0)	19.3	1.8 (1.4–2.1)	19.5	1.3 (1.1–1.5)	18.3
First degree	2.6 (1.7–3.5)	65.0	5.0 (3.8–6.3)	55.5	3.8 (3.0–4.5)	53.8
Parent	1.8 (0.6–3.0)	45.0	3.7 (2.0–5.3)	41.1	2.7 (1.7–3.8)	39.2
Offspring	2.5 (0.1–4.9)	62.5	5.1 (1.9–8.4)	56.6	3.9 (1.8–5.9)	55.3
Sibling	3.3 (1.7–4.8)	82.5	6.6 (4.3–8.9)	73.3	4.8 (3.4–6.1)	68.1
Second degree	0.4 (0.2–0.7)	10.0	1.1 (0.7–1.5)	12.2	0.8 (0.5–1.0)	10.7
Third degree	0.2 (0.0–0.4)	5.0	1.0 (0.6–1.4)	11.1	0.6 (0.4–0.9)	9.0

Figure. Recurrence risk ratios of familiality in different countries. It shows familial tendencies are decreasing as familial degree extends in order, though with lesser risk for FDR in our study.



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Objective Evaluation of Physical Functioning after TNFi Therapy in Ankylosing Spondylitis Patients; A Selection of Three Feasible Performance-Based Tests. Salima F.E. van Weely[1], Joost Dekker[2], Martijn P.M. Steultjens[3], Christiaan J. Van Denderen[1], Mike T. Nurmohamed[1], Ben A.C. Dijkmans[4] and Irene E. van der Horst-Bruinsma[4]. [1]Reade, centre for Rehabilitation and Rheumatology, Amsterdam, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]Glasgow Caledonian University, Glasgow, Scotland, [4]VU University Medical Centre, Amsterdam, Netherlands.

Background/Purpose: Physical functioning is considered an important outcome domain for the evaluation of the effectiveness of therapy and the course of the disease. In an effort to find objective outcome measures that assess limitations in physical functioning in Ankylosing Spondylitis (AS) patients, eight performance-based tests based on items of the Bath AS Functional Index (BASFI) were developed. However, in research and clinical practice it is important to eliminate redundant testing in order to safe energy, time and money. Therefore, this study aimed (i) to select a limited number of performance-based tests that are reliable, show improvement in physical functioning after TNFi therapy and generate the equivalent information as the full set of tests and (ii) are feasible for use in daily clinical practice.

Methods: Eight performance-based tests were evaluated ((1) climbing stairs, (2) bending, (3) reaching up, (4) putting on socks, (5) rising up and sitting down on a chair, (6) getting up from the floor, (7) looking over the shoulder and (8) a physically demanding activity). The tests that showed adequate reliability, highest Standardized Response Means (SRM) and the largest proportion of patients with an improved performance-based physical functioning were selected. The selected tests were combined into a new criterion for improvement in physical functioning (AS Performance-based Improvement, ASPI). The number and percentage improved patients identified with the ASPI and identified with the full set of performance tests were compared.

Results: Reliability for all tests was adequate to excellent (Intraclass Correlation Coefficients 0.73–0.96). The tests for bending, putting on socks and getting up from the floor had the highest SRM's (0.52–0.74) and showed the largest proportion of improved patients after TNFi therapy. The combination of these three tests is feasible in daily clinical practice and showed improved physical functioning after TNFi therapy in 67% of the patients.

Conclusion: The tests for bending, putting on socks and getting up from the floor are recommended for use in daily practice, because they generate comparable information as the full set and are feasible for use in daily clinical practice. A new criterion, the ASPI, using a combination of these three tests showed an improved physical functioning after TNFi therapy in 67% of the patients. By performing only three instead of all performance-based tests, redundant testing is eliminated. In future, evaluations of the effectiveness of TNFi therapy in AS patients might be improved by adding these tests to other outcome measures.

Disclosure: S. F. E. van Weely, None; **J. Dekker**, None; **M. P. M. Steultjens**, None; **C. J. Van Denderen**, None; **M. T. Nurmohamed**, None; **B. A. C. Dijkmans**, None; **I. E. van der Horst-Bruinsma**, None.

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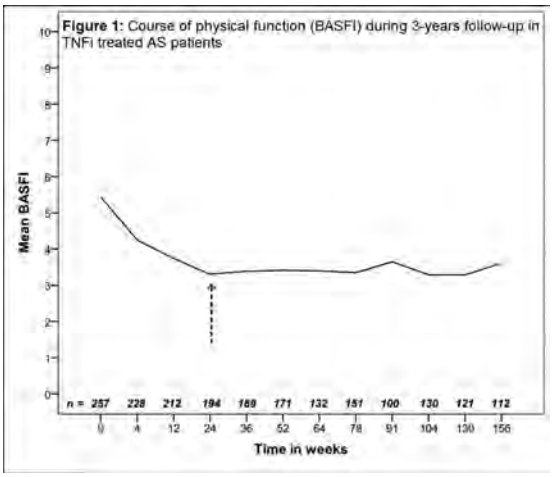
Three-Year Course and Prediction of Physical Functioning in Ankylosing Spondylitis Patients Treated with TNF-Inhibitors. Salima F.E. van Weely[1], Eva L. Kneepkens[1], Mike T. Nurmohamed[1], Joost Dekker[2] and Irene E. van der Horst-Bruinsma[3]. [1]Reade, centre for Rehabilitation and Rheumatology, Amsterdam, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands, [3]VU University Medical Centre, Amsterdam, Netherlands.

Background/Purpose: Currently, only limited information is available on the long-term course of limitations in physical functioning and spinal mobility in Ankylosing Spondylitis (AS) patients receiving TNF inhibiting (TNFi) therapy in daily clinical care. Therefore this study aimed (i) to examine the 3-years course of physical functioning and spinal mobility impairments in patients routinely treated with TNFi; (ii) to predict the 3-years level and (iii) to predict the 3-years course of physical functioning and spinal mobility.

Methods: AS patients eligible for TNFi were followed in a prospective observational cohort for 3 years. Prediction models were developed with linear mixed modelling using 18 baseline variables. The Bath AS Functional Index (BASFI) and Bath AS Metrology Index (BASMI) were used as outcome measures for physical functioning and spinal mobility, respectively.

Results: At baseline 257 patients were included and treated with etanercept (n=174) or adalimumab (n=83). Physical functioning improved significantly during the first 24 weeks after the start of TNFi. The BASFI score decreased from 5.4±2.4 to 3.3±2.6 in week 24, and stabilised thereafter (BASFI 3-years 3.6±2.5; see figure-1). The BASMI showed a stable course over time. Lower baseline BASFI and BASMI-scores predicted a better physical functioning and spinal mobility after 3-years of TNFi therapy. Other predictors for a higher 3-years level and better 3-years course of physical functioning included absence of comorbidity, physical activity, younger age and lower body mass index (BMI) at baseline. However, large between-patient variations were observed.

Conclusion: Improvement of physical functioning in TNFi treated AS patients continues up to 24-weeks and stabilises thereafter. Therefore, the efficacy of treatment should be determined at 6 months. Predictors for the level and course of physical functioning and spinal mobility after 3-years of TNFi treatment include baseline BASFI, BASMI, absence of comorbidity, physical activity and BMI.



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Do Extra-Articular Manifestations Influence Outcome in Ankylosing Spondylitis? a 12 Year Follow-up Study. Ivette Essers[1], Sofia Ramiro[2], Carmen Stolwijk[1], Marc Blaauw[3], Robert Landewé[4], Désirée M. van der Heijde[5], Filip van Den Bosch[6], Maxime Dougados[7] and Astrid van Tubergen[8]. [1]Maastricht University, Maastricht, Netherlands, [2]Amsterdam Rheumatology Center/University of Amsterdam, Amsterdam, Netherlands, [3]Catharina Hospital, Eindhoven, Netherlands, [4]Atrium Medical Center, Heerlen, Netherlands, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Department of Rheumatology Ghent University Hospital, Ghent, Belgium, [7]Hopital Cochin, Descartes University, Paris, France, [8]Maastricht University Medical Center, Maastricht, Netherlands.

Background/Purpose: Extra-articular manifestations (EAMs), such as acute anterior uveitis (AAU), inflammatory bowel disease (IBD), and psoriasis contribute to diagnosis, classification criteria, and choice of treatment in patients with ankylosing spondylitis (AS). Therefore, the aim of the present study is to assess whether the presence of EAMs is associated with more functional disability, worse quality of life (QoL), and more radiographic damage in patients with AS over time.

Methods: Twelve-year follow-up data from all patients included in the Outcome in Ankylosing Spondylitis International Study (OASIS) were used. The presence of EAMs was extracted from medical charts by two independent extractors. Function was assessed by the Bath AS Functional Index (BASFI), and the physical component of the Short Form-36. QoL was assessed by the ASQoL, and EuroQoL. Radiographic damage was assessed by the modified Stoke AS Spinal Score. Time adjusted univariable and multivariable generalized estimating equations analyses were performed to assess whether prevalent and incident EAMs, respectively, were associated with functional disability, QoL, and radiographic damage over time. Patients with prevalent EAMs were excluded from the analysis involving incident EAMs.

Results: 216 Patients were included (154 (71%) men, mean age 43.6 years (SD 12.7), mean symptom duration 20.5 years (SD 11.7), and mean follow-up 8.3 years (SD 4.1)). At baseline, 39 (18%) patients had AAU, 15 (7%) IBD, and 9 (4%) psoriasis (prevalent cases). During follow-up, 19 patients developed AAU, 9 IBD, and 5 psoriasis (incident cases). Psoriasis was excluded from further analyses, because of a low prevalence and incidence in this cohort. Prevalent AAU was univariably associated with more radiographic damage (B=7.19, 95%-Confidence Interval [CI] 0.19 to 14.19, p=0.04) over time, but in a multivariable model this association was no longer significant (B=1.22, 95%-CI -3.81 to 6.26, p=0.64). Prevalent IBD was not associated with any of the clinical outcomes over time. Incident AAU was also not associated with clinical outcomes over time. Incident IBD, however, showed a trend towards worse function (BASFI) over time in a univariable model (B=1.86, 95%-CI -0.08 to 3.80, p=0.06), and also in a multivariable model (B=1.40, 95%-CI -0.04 to 2.84, p=0.06).

Conclusion: Prevalent AAU and IBD at baseline were not associated with a worse course of QoL, function, or radiographic damage over time. However, patients with new-onset IBD tended to have more functional disability over time in comparison with patients who do not develop IBD.

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Disease Activity Strongly Influences Work Productivity and Physical Health Related Quality of Life in Early Axial Spondyloarthritis: Data from the SPACE-Cohort. A Roeterink[1], M de Hooge[1], R. van den Berg[1], H Dagfinrud[2], R Landewé[3], M. van Oosterhout[4], R Ramonda[5], D. van der Heijde[1] and F van Gaalen[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]Groene Hartziekenhuis, Gouda, Netherlands, [5]University of Padova, Padova, Italy.

Background/Purpose: In early onset axial spondyloarthritis (axSpA), not much is known about the relationship between disease activity and work productivity loss (WPL) or disease activity and health-related quality of life (HRQoL) In this study we assessed the relationship between disease activity and WPL and HRQoL in early axSpA.

Methods: The SPACE cohort recruited patients (n=345) with chronic back pain (≥3 months, ≤2 years, onset <45 years) in 5 European centres. In patients fulfilling the ASAS axSpA criteria (n=131), the following assessments were done: ASDAS and BASDAI (disease activity), BASFI (functional ability), SF-36 (HRQoL) and Work Productivity and Activity Impairment (WPAI). Patients were grouped according to ASDAS: inactive disease (<1.3), moderate disease (1.3–2.1), high disease (2.1–3.5) and very high disease activity (>3.5). BASDAI and BASFI scores ≥4 were considered as high disease activity and impaired function, respectively. HRQoL was reported as the SF-36 physical (PCS) and mental component summary (MCS) scores. Lower scores indicate decreased quality of life compared to the general population. Impact of disease on work productivity (WP) was defined as percentage of absenteeism and presenteeism and WPL (combines absenteeism and presenteeism) with greater scores indicating greater impairment.

Results: Figure 1 shows that physical health-related quality of life (PCS) decreased significantly with increasing ASDAS. For example, in patients with inactive disease, the PCS was 42.5 compared to 17.3 in patients with very high disease activity. Moreover, absenteeism, presenteeism and WPL increased as ASDAS increased (figure 1b). MCS was not influenced by disease activity. PCS and WPL had a similar association with BASDAI (not shown) and BASFI (low vs.high BASFI; PCS 46.3 vs. 47.2, P=0.76; WPL; 30.9% vs. 66.7%; absenteeism; 7.1% vs. 24.9%; presenteeism; 28.9% vs. 61.1%, all P <0.001).

Conclusion: In early axial SpA, disease activity highly influences physical health-related quality of life and work productivity. These findings support aiming for clinical remission in patients with early axial SpA.

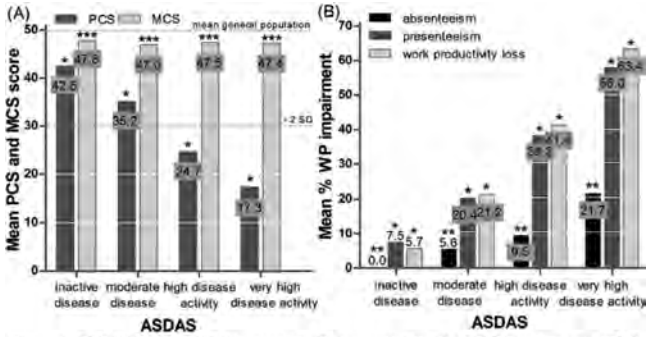

Figure 1. PCS, MCS (A) and WPAI components (B) in association with ASDAS in patients with axSpA. * $P < 0.001$ ** $P = 0.02$ *** $P = 0.97$.

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Dikkopf-1 (Dkk-1) Serum Levels in Axial Spondyloarthritis (axSpA) Are Related to Disease Duration. Victoria Navarro-Compán[1], Enrique Melguizo-Madrid[2], Concepción González-Rodríguez[2], Federico Navarro-Sarabia[2] and Rafael Ariza-Ariza[2]. [1]University Hospital La Paz and Leiden University Medical Center, Madrid, Spain, [2]University Hospital Virgen Macarena, Sevilla, Spain.

Background/Purpose: Tumor necrosis factor (TNF) alpha is responsible for induction of dkk-1 which down-regulates bone formation. Therefore, it was expected that TNF-blocker therapy would inhibit radiographic progression in patients with axSpA but this effect has not been observed yet. Nevertheless, most of the studies have included patients with long disease duration and it is unknown whether or not this effect would be the same in patients with an early stage of the disease. The objective of this study was to investigate if disease duration influences on the serum levels of dkk-1 in patients with axSpA.

Methods: Observational study including consecutive patients with axSpA according to ASAS criteria visiting a tertiary hospital between January 2011 and June 2013. All patients were receiving NSAIDs and none of them was under biologic therapy. The following characteristics were recorded at one visit: Demographic (age, gender), symptoms duration, HLA-B27, disease activity indices (BASDAI, CRP, ESR) and function (BASFI). Blood samples to determine dkk-1 serum levels by enzyme immunoassay were collected at the same visit too. Patients were classified as early axSpA (symptoms duration ≤ 5 years) and established axSpA (>5 years) and the characteristics enumerated above were compared between both groups. Univariate and multivariate linear regression models were employed to identify the characteristics related to dkk-1 serum levels.

Results: Fifty one patients (31 with early axSpA and 21with established disease) were included this study. Patients with early axSpA were younger (32.6 ± 9.3 vs 41.0 ± 10.2 years; p<0.01), had lower degree of disease activity (BASDAI: 4.6 ± 2.7 vs 6.6 ± 1.9; p<0.01 and ESR: 7.7 ± 9.2 vs 18.1 ± 15 mmHg; p<0.05) and worst function (3.2 ± 2.9 vs 5.8 ± 2.5; p<0.01) compared with patients with established disease. Serum levels of dkk-1 were significantly higher in patients with early disease (25.9 ± 11.5 vs 13.9 ± 13.5; p<0.001 ng/dl). No statistically significant differences were found between both groups for the rest of characteristics. In the univariable analysis, symptoms duration and BASDAI were inversely related to dkk-1 levels (std β: -0.435; p<0.01 and Std β: -0.283; p<0.05, respectively). However, only the relationship with symptoms duration remained statistically significant in the multivariable analysis (std β: -0.415; p<0.01).

Conclusion: Serum Dkk-1 levels in patients with axSpA depend on disease duration, being higher in patients with recent onset of the disease. The effect of TNF-blocker therapy on radiographic progression may be different in patients with an early stage of the disease compared with patients with established disease.

Disclosure: V. Navarro-Compán, None; **E. Melguizo-Madrid**, None; **C. González-Rodríguez**, None; **F. Navarro-Sarabia**, None; **R. Ariza-Ariza**, None.

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A Substantial Decrease in Work Productivity and Physical Health-Related Quality of Life in Chronic Back Pain of Recent Onset: Data from the SPACE-Cohort. A Roeterink[1], M de Hooge[1], R. van den Berg[1], H Dagfinrud[2], M Turina[3], M. van Oosterhout[4], D. van der Heijde[1] and F van Gaalen[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [4]Groene Hartziekenhuis, Gouda, Netherlands.

Background/Purpose: Ankylosing spondylitis is associated with work productivity (WP) loss and a decreased health-related quality of life (HRQoL). Little is known about WP loss and HRQoL in early axial spondyloarthritis (SpA). Aim of the study was to determine the impact of chronic back pain (CBP) of recent onset on HRQoL and work productivity in young patients.

Methods: The SPACE-cohort includes patients with CBP (≥3 months, ≤2 years, onset <45 years) in 5 European centers (n=345). Patients who met the ASAS axial SpA criteria were classified as axSpA (n=131). Patients with 1 SpA feature were defined as possible SpA (n=167), and those with no SpA features as no SpA (n=47). The 36-item Short-Form (SF-36) and Work Productivity and Activity Impairment (WPAI) surveys were used to assess HRQoL and WP. SF-36 physical (PCS) and mental component summary (MCS) scores were compared to the general population (a score of 50±10 SD represents the general population). Impact of disease on WP was defined as percentage of absenteeism, presenteeism and WP loss (which combines absenteeism and presenteeism) with greater scores indicating greater impairment.

Results: 304 patients completed the SF-36 and 230 the WPAI. Figure 1 shows a significant reduction of ≥2 SD in mean physical component scores (PCS) in all subgroups compared to the general population (25.9 in no SpA, 23.5 in possible SpA and 28.3 in axial SpA). Mental components scores (MCS) were not significantly reduced in patients with CBP compared to the general population. Considerable absenteeism and presenteeism was present in all subgroups with CPB. Absenteeism was highest in no SpA and possible SpA (21.6% and 18.5%; compared to axSpA (10.3%) (p=0.10 and p=0.05, respectively),. Presenteeism was highest in no SpA and possible SpA (46.9% and 44.7%), compared to axSpA (34.7%). Total WPL was highest in no SpA and possible SpA (55.2% and 48.3%) compared to axSpA (37.5%).

Conclusion: Work productivity and physical health-related quality of life are already greatly reduced in young patients with chronic back pain of less than two years duration.

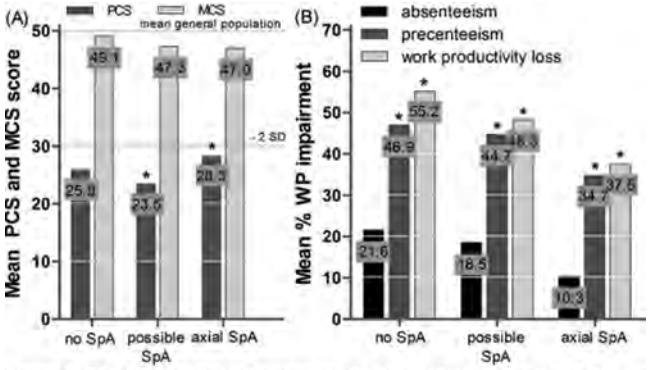

Figure 1. PCS, MCS (A) and WPAI components (B) in patients with chronic back pain ≥3 months but ≤2 years and <45 years of age. * *P*<0.05 axSpA vs. possible SpA and axSpA vs. no SpA.

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Female Patients but Not Male Patients with Ankylosing Spondylitis Are at Increased Risk of Developing Ischemic Heart Disease: A Population-Based Cohort Study. Ivette Essers[1], Carmen Stolwijk[1], Annelies Boonen[2], Marie L. De Bruin[3], Marloes Bazelier[3], Frank de Vries[1] and Astrid Van Tubergen[1]. [1]Maastricht University, Maastricht, Netherlands, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands.

Background/Purpose: It is well recognized that rheumatoid arthritis is an independent risk factor for cardiovascular disease. For ankylosing spondylitis (AS), the literature on this risk is relatively scarce, and shows conflicting results. Furthermore, these studies did not explore the role of non-steroidal anti-inflammatory drugs (NSAIDs) use on this risk. Therefore, the aim of the present study was to investigate the incidence and risk of ischemic heart disease (IHD) and acute myocardial infarction (AMI), including the role of NSAIDs, in patients with AS compared with matched population controls.

Methods: All patients with newly diagnosed AS from the British Clinical Practice Research Datalink (1987–2012) were matched with up to 7 persons without AS by year of birth, gender and practice. Incidence rate ratios (IRRs) and hazard ratios (HR) for development of IHD and AMI were calculated. Stepwise analyses were performed adjusting for age, gender, comorbidity, and drug use, including NSAIDs.

Results: In total, 3,809 patients with AS were matched with 26,196 population-based controls. The number of men (70.5% vs 70.7%), and the mean age (43.7 years vs. 43.3 years) were comparable for patients with AS and controls. The mean duration of follow up for patients and controls was 6.6 years. At baseline, 4.3% of the patients had a history of IHD, and 1.8% had a history of AMI, compared with 3.4% and 1.4% of the controls, respectively (p<0.01 and p=0.02, respectively). After excluding subjects with pre-existing cardiovascular disease, the overall IRR for IHD was 1.18 (95%-confidence interval [CI] 0.96–1.46) and for AMI 0.91 (95%-CI 0.65–1.27). Compared with controls, the age-gender adjusted HR for developing IHD was 1.20 (95%-CI 0.97–1.48), and for AMI 0.91 (95%-CI 0.65–1.28) for patients with AS. In female patients, the increased risk of developing IHD was statistically significant (HR 1.81, 95%-CI 1.18–2.79), but after adjustment for all possible risk factors only a non-significant trend towards increased risk was found (HR 1.36, 95%-CI 0.86–2.14). In particular, recent NSAID use explained the change in risk (female HR IHD adjusted for age-gender-NSAID use 1.47, 95%-CI 0.93–1.36). After stratification for the use of NSAIDs, the overall risk of IHD in patients with AS was 1.36-fold (95%-CI 1.00–1.87) increased with recent use of NSAIDs. This was particularly increased in female patients (HR fully adjusted 2.52, 95%-CI 1.41–4.51), but not in male patients (HR fully adjusted 1.13, 95%-CI 0.78–1.64).

Conclusion: Female patients with AS are at increased risk of developing IHD, but this effect is associated with recent NSAID use. However, it cannot be excluded that NSAID use is (partly) a reflection of active disease.

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Patients with Ankylosing Spondylitis Do Not Adapt to Their Disease: Evidence from the 'then Test' in Patients Treated with TNF-Inhibitors. Ivette Essers[1], Astrid Van Tubergen[1], Jurgen Braun[2], Xenofon Baraliakos[2], Frank Heldmann[2] and Annelies Boonen[3]. [1]Maastricht University, Maastricht, Netherlands, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Maastricht University Medical Center, Maastricht, Netherlands.

Background/Purpose: Although never formally studied, rheumatologists feel that patients with ankylosing spondylitis (AS) tend to adjust to their disease. Response shift is one of the theories to demonstrate that adaptation takes place and makes use of the 'then test'. A 'then test' asks patients to re-rate their past health in a situation where change in health occurred. This theory states that patients with a treatment response would re-rate their former health as worse as initially thought, and that the magnitude of treatment response is associated with a larger gap between the initial and retrospective assessment of health. The aim of the present study was to understand whether patients with AS adapt to their disease, using the 'then test', in patients in whom infliximab (INF) was started. It was hypothesized responders to therapy would re-rate retrospectively their initial health as worse.

Methods: Data were used from 103 European patients who participated in the AS Study for the Evaluation of Recombinant INF Therapy (ASSERT) and continued in the European AS INF Cohort (EASIC). The Bath AS Global Score (BAS-G) last week was used to assess patient global well-being. A BAS-G 'then test' was integrated in EASIC, and asked patients to re-rate their initial well-being (i.e. before the start of INF in ASSERT). Treatment response between ASSERT and EASIC was assessed with the Assessment of SpondyloArthritis International Society 20 (ASAS20) response criteria. The baseline BAS-G of ASSERT and retrospective BAS-G of ASSERT were compared using paired t-test. Limits of agreement were calculated. A linear regression analysis was performed to identify whether response influenced the difference between the initial and retrospective BAS-G of ASSERT (i.e. gap) after adjusting for other covariates.

Results: 86 Patients contributed to the current analyses (mean age 39.6 years (SD 10.6); mean disease duration 9.7 years (SD 8.1), and 68/96 (79.1%) patients had an ASAS20 response). At baseline, the BAS-G in ASSERT was 7.0 (SD 1.6), and patients retrospectively re-rated their BAS-G, using the 'then test', at 7.2 (SD 2.3), revealing a non-significant and non-relevant gap of 0.2 (SD 2.7) ($p=0.45$). Limits of agreements show that the gap varied between -5.1 and 5.5. In a multivariable model, the difference between the baseline BAS-G of ASSERT and retrospective BAS-G of ASSERT was irrespective of treatment response, and was only associated with the baseline BAS-G of ASSERT ($p<0.01$) and the BASDAI ($p=0.02$) before the start of INF.

Conclusion: Patients with AS were able to retrospectively judge their well-being, even if substantial time relapsed between the start of the treatment and this retrospective assessment, and irrespective of treatment response. In this setting, the 'then test' could not prove adaptation by response shift in AS.

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MRI Is Often Negative in Clinically Suspected Non-Radiographic Axial Spondyloarthritis. M.L. John[1], M.a.C. van der Weijden[2], C.M.a. van der Bijl[1], S.T.G. Bruijnen[1], C.J. van der Laken[1], M.T. Nurmohamed[1] and I.E. van der Horst-Bruinsma[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Jan van Breemen Research Institute Reade, Amsterdam, Netherlands.

Background/Purpose: The diagnosis of ankylosing spondylitis (AS) is based on disease specific bone damage seen on plain radiography of the pelvis. Recent developments in magnetic resonance imaging (MRI) techniques have demonstrated that active inflammation in the sacroiliac joints (SIJ) and/or spine is detectable by MRI and might even be visible before the appearance of chronic changes on plain radiography. However, the current literature discussing the actual diagnostic properties of MRI in early spondyloarthritis (SpA)/non-radiographic axial SpA remains controversial and its prognostic value regarding the future development of AS has yet to be determined.

Methods: In this cross-sectional study, we recruited 70 patients with chronic inflammatory back pain (mean disease duration of 5 years) and high disease activity (BASDAI$\geq$4) who had to be either HLA-B27 positive with $\geq$1 SpA-feature or HLA-B27 negative with $\geq$2 SpA-features. All patients underwent MRI of the SIJ and 50 patients underwent additional MRI of the spine on baseline. A positive MRI was defined by the presence of either BMO and/or osteitis, a negative MRI by the absence of both. Patients with a negative baseline MRI were asked to undergo a second MRI after 6 months. Eventually, 29 out of 49 patients with a negative baseline MRI SIJ and 22 out of 47 patients with a negative baseline MRI spine were willing and eligible to undergo the second MRI. Additionally, all patients were tested for CRP and ESR levels, X-rays of the pelvis were made and several patient features were recorded. Correlation analysis was performed between the different collected variables.

Results: At baseline, only 21 of the 70 patients (30%) showed signs of inflammation on MRI: 18 had sacroiliitis, 2 had spinal involvement and one patient had both. In total, only 4 patients presented with inflammation of the spine at baseline and six months, of which 2 also suffered from sacroiliitis. Comparison of the two consecutive MRIs revealed that, in two patients, the inflammatory process spread from the SIJ to the spine or the other way around. Only one patient with a negative baseline MRI SIJ developed apparent sacroiliitis over time. Furthermore, three patient characteristics were significantly associated with a positive MRI outcome at any point in time: raised CRP-level ($p=0.032$), family history of uveitis ($p=0.028$) and the number of swollen joints (SJC, $p=0.023$). We also observed a slight difference regarding HLA-B27-status and medical history of uveitis, in favor of the positive MRI-group.

Conclusion: Only a small number of patients with clinically suspected non-radiographic axial SpA showed signs of inflammation on MRI SIJ and/or spine, questioning the sensitivity and with this the value of this new imaging tool in early SpA. Even though, some patient characteristics seem to be positively associated with MRI outcome, defining the right place of MRI in the diagnosis of early SpA remains difficult. The diagnostic properties of MRI in this particular patient group should be weighted carefully because patients with a negative MRI might also have severe complaints.

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Evaluation of the Nonsteroidal Anti-Inflammatory Drug-Sparing Effect of Etanercept in Axial Spondyloarthritis: Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Maxime Dougados[1], Emily Wood[2], Bernard Combe[3], Corinne Miceli-Richard[4], Francis Berenbaum[5], Nandan Koppiker[6], Arnaud Dubanchet[7] and Isabelle Logeart[7]. [1]Université Paris René Descartes and Hôpital Cochin, Paris, France, [2]Quanticate, Hitchin, England, [3]Hôpital Lapeyronie, Montpellier, France, [4]Université Paris-Sud 11, Bicêtre Hospital, Kremlin Bicêtre, France, [5]Saint-Antoine Hospital, Paris, France, [6]Pfizer PGRD, Sandwich, United Kingdom, [7]Pfizer, Paris, France.

Background/Purpose: Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line pharmacotherapy in axial spondyloarthritis (axSpA) but are recommended for use at the lowest effective dose for the shortest possible time due to safety concerns. Although NSAID discontinuation is common in clinical practice after response to biologic therapy in axSpA patients, its impact has not been evaluated in prospective controlled trials. The SPARSE trial was conducted to assess the effects of etanercept (ETN) on NSAID intake as measured by the ASAS-NSAID score[1]and conventional clinical outcomes in axSpA.

Methods: In the initial 8-week, double-blind (DB), placebo (PBO)-controlled period, patients with active (mini BASDAI $\geq$4) axSpA (ASAS criteria) despite optimal NSAID intake were randomized to ETN 50 mg or PBO once weekly for 8 weeks. All patients were advised to taper/stop their NSAID intake (self-reported diary) during the study treatment period. Completers were eligible for ETN 50 mg in the subsequent 8-week open-label (OL) period. ASAS-NSAID scores were calculated according to ASAS recommendations. [1] The primary endpoint, the change from baseline (BL) to week 8 in the ASAS-NSAID score, was analyzed using an analysis of covariance (ANCOVA).

Results: In 90 randomized patients at BL, mean age ($\pm$SD) was 38.9$\pm$11.8 years; disease duration, 5.7$\pm$8.1 years; 62% were male; 66% were HLA-B27 positive; and 50% were MRI sacroiliitis positive. Mean ASAS-NSAID scores at BL (ETN vs PBO: 98.2$\pm$39.0 vs 93.0$\pm$23.4), BASDAI (6.0$\pm$1.7 vs 5.9$\pm$1.5), and BASFI (5.2$\pm$2.1 vs 5.1$\pm$2.2) were similar between groups. A between-group difference in changes in ASAS-NSAID scores of -27.3 ($P=0.002$) favoring ETN was observed at week 8 (table). Significantly more patients in the ETN vs PBO group achieved BASDAI50 and ASAS40 at week 8. Significant reductions in ASAS-NSAID scores were seen in the ETN/ETN group from BL to week 16 and in the PBO/ETN group from week 8 to 16 (table); response rates increased in the ETN/ETN and PBO/ETN groups for most clinical endpoints in the OL period.

Table. Effects of ETN vs PBO in patients with axSpA (ITT).

	Wk 8 (DB), N/n (%)		Wk 16 (OL), N/n (%)	
Endpoint	**ETN (n=42)**	**PBO (n=48)**	**ETN/ETN (n=39)**	**PBO/ETN (n=44)**
NSAID-free[a]	16/33 (48)	8/40 (20)*	—	—
BASDAI50[a]	16/41 (39)	8/45 (18)†	15/28 (54)	18/37 (49)
ASAS20[a]	16/36 (44)	10/42 (24)	18/28 (64)	23/36 (64)
ASAS40[a]	16/36 (44)	9/42 (21)†	16/28 (57)	20/36 (56)
Parameter	**Mean Change (95%CI/SD)**			
	BL to Wk 8		**BL to Wk 16**	**Wk 8 to Wk 16**
ASAS-NSAID score[b]	−63.9 (−76.0, −51.8)	−36.6 (−48.3, −24.9)*	−65.9 (−87.0, −44.9)‡	−39.2 (−52.9, −25.5)‡
	BL to Wk 8		**BL to Wk 16**	
BASDAI[c]	−2.0 (−2.6, −1.4)	−1.1 (−1.7, −0.5)	−2.6 (1.8)	−3.0 (2.1)
BASFI[c]	−1.7 (−2.3, −1.1)	−0.8 (−1.3, −0.2)†	−1.8 (2.5)	−2.3 (1.9)

*$P<0.01$, ETN vs PBO; $^{\dagger}P<0.05$, ETN vs PBO; $^{\ddagger}P<0.0001$, BL vs wk 16.
[a]DB period: logistic regression with relevant BL score and treatment in model; OL period: descriptive statistics, observed cases (OC). [b]DB: ANCOVA, with BL score and treatment in model, LOCF, with imputation of missing data; OL: linear regression, OC, no imputation. [c]DB: ANCOVA, LOCF; OL: descriptive statistics, OC.

Conclusion: In this population of patients with axSpA, etanercept was associated with clinically relevant NSAID-sparing effects in addition to significant improvements in conventional clinical outcomes.

Reference:

1. Dougados M, et al. *Ann Rheum Dis* 2011;70(2):249–51.

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Non-Steroidal Anti-Inflammatory Drugs in Axial Spondyloarthritis: A Cochrane Review. Féline Kroon[1], Lennart van der Burg[1], Sofia Ramiro[2], Robert Landewé[3], Rachelle Buchbinder[4] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Amsterdam Rheumatology Center/University of Amsterdam, Amsterdam, Netherlands, [3]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [4]Monash Department of Clinical Epidemiology at Cabrini Hospital, Department of Epidemiology and Preventive Medicine, Monash University, Malvern, Victoria, Australia.

Background/Purpose: We performed a Cochrane systematic review to determine the benefits and harms of non-steroidal anti-inflammatory drugs (NSAIDs) in axial spondyloarthritis (axSpA).

Methods: We included all published randomised controlled trials (RCTs) of NSAIDs versus any comparator in adult patients with axial SpA identified by searches in MEDLINE, EMBASE and CENTRAL (until April 2014). The comparisons investigated were traditional NSAIDs versus placebo, COX-2 NSAIDs versus placebo, traditional NSAIDs versus COX-2 NSAIDs, NSAIDs in low versus high dose and NSAIDs versus NSAIDs. Main efficacy outcomes were pain, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI) and radiographic progression. Main safety outcomes were number of withdrawals due to adverse events and number of serious adverse events. Risk of bias of included studies was assessed according to the Cochrane risk of bias tool.

Results: Forty-one trials (n=6073) with a median duration of 12 weeks (range 1 week to 2 years) met inclusion criteria. Thirty-one studies (n=5317) with a median duration of 12 weeks (range 2 to 26 weeks) could be included in quantitative data-analysis. Most studies were at unclear risk of selection bias, although blinding was adequate in most trials and many trials had low risk of attrition and reporting bias.

In 5 RCTs (n=1165), comparing conventional NSAIDs versus placebo (duration 2 to 12 weeks), there was a consistent significant effect in all efficacy variables favouring NSAIDs, for example pain on VAS: mean difference (MD) -16.5 (95% CI -20.8 to -12.2) in 4 trials (n=850). There were no significantly more (serious or any) adverse events or withdrawals due to adverse events, except for more gastrointestinal adverse events in patients taking NSAIDs (RR 1.92 (95% CI 1.41 to 2.61), 5 trials, n=1289). We found similar results in the comparison COX-2 versus placebo (3 studies, n=669). When comparing conventional NSAIDs to COX-2 we found no difference in either efficacy or safety (4 studies, n=995). In general we found no clear dose-effect on efficacy or safety. When comparing different NSAIDs to each other, no important difference in efficacy could be determined. However, 11 studies (n=1135) showed that indomethacin resulted in more adverse events than other NSAIDs (RR 1.25 (95% CI 1.06 to 1.49)), in particular neurological adverse events like headache and dizziness (RR 1.96 (95% CI 1.06 to 3.57), 9 trials, n=963), although there were not more withdrawals due to adverse events.

Conclusion: In patients with axial SpA, overall high quality trials indicate that traditional and COX-2 NSAIDs are consistently more efficacious than placebo, without a significant difference between the two NSAIDs classes. Various NSAIDs do not differ in efficacy in low to moderate quality trials, although indomethacin seems to result in more, mainly neurological, adverse events, even though this did not lead to more withdrawals. Results of this review support current recommendations for treatment of axial Spa with NSAIDs.

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What Is the Correlation of Individual HAQ and Basdai Questions with Disease Activity Measures in Ankylosing Spondylitis? Implications for Instrument Reduction. Proton Rahman[1], Michel Zummer[2], Wojciech Olszynski[3], Majed Khraishi[4], Dalton Sholter[5], Rafat Faraawi[6], William Bensen[7], Milton Baker[8], Andrew Chow[9], Julie Vaillancourt[10], John S. Sampalis[10], Francois Nantel[11], Allen J Lehman[11], Susan Otawa[11] and May Shawi[11]. [1]Memorial University of Newfoundland, St. John's, NF, [2]Université de Montréal, Montreal, QC, [3]University of Saskatchewan, Saskatoon, SK, [4]Nexus Clinical Research, St John's, NF, [5]University of Alberta, Edmonton, AB, [6]McMaster University, Hamilton, ON, [7]Division of Rheumatology, McMaster University, Hamilton, ON, [8]University of Victoria, Victoria, BC, [9]Credit Valley Rheumatology, Mississauga, ON, [10]JSS Medical Research, Montreal, QC, [11]Janssen Inc., Toronto, ON.

Background/Purpose: Despite the importance of the Health Assessment Questionnaire (HAQ) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in assessing patient-reported functional status and disease activity, they have been critiqued for being time-consuming, not convenient on a daily-basis and thus not contributing to decisions in routine care. The aim of this analysis was to describe the correlation of individual HAQ and BASDAI questions with patient and physician reported measures used in ankylosing spondylitis (AS) and to examine whether the instruments could be reduced to better reflect routine clinical practice.

Methods: BioTRAC is an ongoing prospective registry of patients initiating infliximab or golimumab as first biologics or after <6 months of biologic treatment. Data from AS patients treated in 2005–2014 were used. The correlation of individual HAQ and BASDAI questions with patient (pain, BASDAI, HAQ and BASFI) and physician (MDGA) reported measures was described with the Pearson's correlation coefficient. The impact of each question on the need for help in each HAQ domain was assessed with logistic regression. Factor analysis was used to assess the variability due to each individual question in HAQ and BASDAI.

Results: A total of 413 AS patients with 1660 BASDAI and 1654 HAQ assessments were included. HAQ and BASDAI questions correlated at different extents with each AS measure (Table 1). Questions related to "eating" and "gripping" showed the lowest correlation with patient and physician reported measures. All HAQ questions had higher correlations with patient reported measures than with MDGA. The BASDAI question on "fatigue and tiredness" showed the highest correlation with BASFI, while the question on "other joints pain/swelling" showed the lowest correlation with MDGA. None of the HAQ and BASDAI questions were associated with needing help for eating. All other HAQ individual questions were significantly associated with the need for help within their corresponding category, with the exception of Q5C and Q7A. BASDAI question on level of discomfort was significantly associated with the need for help in all HAQ categories, with the exception of "eating" and "walking". Q2A and Q7C accounted for 59.6% of the HAQ variance. The level of morning stiffness accounted for 73.8% of the BASDAI variance. When combining the HAQ and BASDAI, Q2A and Q3A from HAQ and Q1 from BASDAI accounted for 63.5% of the variance.

Conclusion: Variability exists in the correlation of HAQ and BASDAI questions with patient and physician reported AS measures. The results suggest that "standing up straight from an armless chair" and "turning faucets on/off" are the main drivers of HAQ, while the level of morning stiffness drives the BASDAI. Three questions were found to drive the combined HAQ and BASDAI which may have implications in the design of self-report instruments.

Table 1. Correlation between Individual HAQ / BASDAI Questions and Disease Activity Measures

HAQ Questions	Pain	BASDAI	BASFI	MDGA
Dressing and Grooming (Q.1 A/B)	0.56/0.41	0.53/0.45	0.68/0.52	0.47/0.37
Arising (Q.2 A/B)	0.60/0.63	0.63/0.66	0.74/0.66	0.50/0.54
Eating (Q.3 A/B/C)	0.32/0.27/0.34	0.36/0.31/0.39	0.36/0.36/0.42	0.24/0.22/0.25
Walking (Q.4 A/B)	0.52/0.54	0.55/0.58	0.63/0.68	0.43/0.45
Hygiene (Q.5 A/B/C)	0.51/0.40/0.50	0.54/0.44/0.53	0.63/0.65/0.60	0.43/0.35/0.44
Reach (Q.6 A/B)	0.47/0.53	0.52/0.57	0.68/0.72	0.37/0.44
Grip (Q.7 A/B/C)	0.33/0.33/0.28	0.28/0.40/0.35	0.38/0.40/0.33	0.26/0.26/0.25
Activities (Q.8 A/B/C)	0.56/0.57/0.60	0.58/0.58/0.62	0.67/0.67/0.72	0.46/0.48/0.52
HAQ-DI score	***0.67***	***0.71***	***0.87***	***0.55***
BASDAI Questions	**Pain**	**HAQ-DI**	**BASFI**	**MDGA**
Fatigue and tiredness (Q. 1)	0.74	0.58	0.87	0.62
Neck, back or hip pain (Q. 2)	0.85	0.66	0.77	0.67
Other joints pain/swelling (Q. 3)	0.66	0.60	0.67	0.53
Level of discomfort (Q. 4)	0.72	0.63	0.71	0.60
Level of morning stiffness (Q. 5)	0.80	0.64	0.76	0.69
Morning stiffness duration (Q. 6)	0.63	0.60	0.65	0.60
BASDAI score	***0.85***	***0.71***	***0.82***	***0.72***

** Levels of correlation are Weak: r <0.30; Moderate: r =0.30 - 0.39; Strong: r =0.40 - 0.69; and Very Strong: r ≥0.70*

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Flare in Spondyloarthritis: Proposal of a Meaningful Change in Symptomatic Outcome Measures in Axial Spondyloarthritis. Maxime Dougados[1], Emily Wood[2], Laure Gossec[3], Désirée van der Heijde[4] and Isabelle Logeart[5]. [1]Université Paris René Descartes and Hôpital Cochin, Paris, France, [2]Quanticate, Hitchin, England, [3]UPMC GRC08, Paris 06 University, Pitié Salpétrière Hospital, Paris, France, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Pfizer, Paris, France.

Background/Purpose: Recognition of flare is important in both daily practice and clinical trial setting. However, there is no clear definition of flare in patients with axial spondyloarthritis. SPARSE was a randomized controlled trial evaluating the NSAID-sparing effect of etanercept in axial spondyloarthritis. All patients had to be on NSAIDs prior to screening and were requested to discontinue their NSAID therapy at screening. The objective of this post-hoc analysis was to evaluate the threshold in the changes in symptomatic outcome measures in case of a restart of NSAID, which was considered as a flare.

Methods: Patients: Axial spondyloarthritis (ASAS criteria) with active disease (BASDAI $\geq$ 4) refractory to NSAIDs and justifying anti-TNF therapy. Design: Prospective randomized controlled trial. Study period of interest: This analysis was focused on the period between screening and baseline. During this period, patients were requested to stop their NSAID therapy and to restart the NSAID only if they experienced clinical deterioration. In this case, patients were asked to complete a diary. Analysis: The proposal of a meaningful change in symptomatic outcome measures was based on the 75th percentile technique. The 75thpercentiles of the change in the evaluated outcome measures between screening and re-starting NSAIDs were examined for the subgroup of patients who were able to stop NSAID therapy for at least 2 consecutive days and subsequently had to restart their NSAID therapy (i.e. those patients who flared). Evaluated outcome measures: The BASDAI score and each component of the BASDAI.

Results: Of the 128 screened patients, 91 (71.1%) had an available BASDAI at the screening visit and 45 (35.2 %) were able to stop their NSAID therapy for at least 2 consecutive days. Of these 45 patients, 32 optimally completed their diary the day they had to restart their NSAID. The table summarizes the observed values for the study variables at screening and flare (time of NSAID restarting) in these 32 patients.

			Changes from Screening to Flare	
Variable		**Screening**	**Absolute**	**Percentage**
BASDAI total score	Mean ± SD	5.8 ± 1.2	0.7 ± 1.2	13 ± 21
	(Median)	(5.8)	(0.8)	(14)
	75th Percentile [95% CI]		1.5 [1.2, 1.9]	28 [20, 38]
BASDAI question #1 (fatigue)	Mean ± SD	6.7 ± 1.6	0.8 ± 1.9	23 ± 54
	(Median)	(7.0)	(1.0)	(13.0)
	75th Percentile [95% CI]		2.0 [1.0, 3.0]	25 [17, 67]
BASDAI question #2 (axial)	Mean ± SD	6.6 ± 1.5	0.8 ± 1.6	16 ± 27
	(Median)	(7.0)	(1.0)	(14)
	75th Percentile [95% CI]		2.0 [2.0, 2.0]	33 [29, 43]
BASDAI question #3 (peripheral)	Mean ± SD	4.3 ± 2.8	0.1 ± 2.5	16 ± 80
	(Median)	(5.0)	(0.0)	(0)
	75th Percentile [95% CI]		2.0 [1.0, 3.0]	50 [13, 100]
BASDAI question #4 (enthesitis)	Mean ± SD	5.0 ± 2.3	0.9 ± 2.5	43 ± 128
	(Median)	(5.0)	(1.0)	(17)
	75th Percentile [95% CI]		2.0 [1.0, 3.0]	43 [25, 100]
BASDAI question #5/6 (morning stiffness)	Mean ± SD	6.5 ± 1.7	0.6 ± 1.3	12 ± 23
	(Median)	(6.5)	(0.5)	(7)
	75th Percentile [95% CI]		1.5 [1.0, 2.5]	27 [11, 43]

Conclusion: This study suggests that there is no universal change that is applicable to all variables. However, an absolute change of at least 2 on a scale of 10 or a relative change of 30% is indicative of a meaningful symptomatic deterioration for most of the symptomatic variables included in the BASDAI score.

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Optimism Levels Are Moderate and Similar in Patients with Axial Spondyloarthritis and Chronic Low Back Pain, and Are Related to Mental Quality of Life but Not Physical Quality of Life. a Cross Sectional Study of 277 Patients. Sarah Kreis[1], Anna Molto[1], Florian Bailly[1], Sabrina Dadoun[2], Stephanie Fabre[3], Christophe Hudry[2], Franck Zenasni[4], Sylvie Rozenberg[1], Edouard Perthuiset[3], Bruno Fautrel[2] and Laure Gossec[2]. [1]Pitié-Salpêtrière Hospital, AP-HP, Rheumatology department, paris, France, [2]Sorbonne Universités, UPMC Univ Paris 06, GRC-08, Institut Pierre Louis d'Epidémiologie et de Santé Publique, paris, France, [3]Pontoise University Hospital, pontoise, France, [4]Institut de Psychologie, Laboratoire de Psychopathologie et Processus de Santé EA4057, Université Paris Descartes, Paris, France, Boulogne-Billancourt, France.

Background/Purpose: Axial Spondyloarthritis (AxSpA) and chronic low back pain (LBP) are very different chronic rheumatic diseases in terms of physiopathology and prognosis but both have a strong impact on patients' health-related quality of life (HRQoL). Dispositional optimism is defined as a stable personality trait consisting of a general positive mood or attitude about the future with a tendency to expect favorable outcomes in life situations. It has been shown in some chronic disease groups (e.g cancer) that dispositional optimism is related to both physical and psychological outcomes and seems to lead to better HRQoL. The objective of this study was to explore the relationship between optimism and HRQoL in both chronic diseases: AxSpA and LBP.

Methods: A cross-sectional study was performed in two tertiary care hospitals and two private practices in France. Patients were diagnosed with definite AxSpA or chronic LBP according to the rheumatologist. HRQoL was collected using a generic HRQoL questionnaire (Short Form, SF-12) with physical and mental composite scores (PCS and MCS respectively) and optimism was collected using the Life Orientation Test-revised (LOT-R) questionnaire. Analyses included descriptive statistics, non-parametric correlations and multiple regression analyses to study the effect of optimism on physical and mental HRQoL.

Results: In all, 277 patients (188 AxSpA and 89 LBP) were included: mean age, 47.3±11.9 years, 49.1% were males. BASDAI in AxSpA was 3.8±2.0 and the LBP patients' pain visual analog scale was 4.3±2.3. HRQoL was similarly altered in both diseases, for both physical and mental composite scores (mean PCS: 43.4±8.4 vs. 41.9±7.1; mean MCS: 45.7±7.9 vs. 46.7±8.1 for AxSpA and LBP respectively). Optimism was moderate and similar in both populations. Optimism was positively correlated to MCS in both diseases (r=0.57 vs. 0.54, for AxSpA and LBP respectively, both $p<0.0001$) and these relations persisted in multivariate analyses (beta=0.77 vs. 1.21, both $p<0.0001$).

Conclusion: Optimism was similar in these two chronic diseases and was an explanatory factor of mental HRQoL, but not physical HRQoL. Physical HRQoL may reflect more the disease process than character traits.

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Helplessness in Coping Is Associated with Worse Patient Reported Outcomes Among Patients with Ankylosing Spondylitis: A Longitudinal Multi-Country Cohort Study. Walter P Maksymowych[1], Annelies Boonen[2], Helena Marzo-Ortega[3], Marina N. Magrey[4], Manish Mittal[5], Michael Halpern[6], Jeannette Renaud[6], Yanjun Bao[5] and Avani D. Joshi[5]. [1]University of Alberta, Edmonton, AB, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]LMBRU, Chapel Allerton Hospital, and University of Leeds, Leeds, United Kingdom, [4]Case Western Reserve University, MetroHealth Medical Center, Cleveland, OH, [5]AbbVie Inc., North Chicago, IL, [6]RTI International, Washington, DC.

Background/Purpose: Ankylosing spondylitis (AS) causes pain, joint damage and reduced function, which contribute to a substantial burden on affected patients and their families. A feeling of helplessness (self-perceived lack of control over the disease) can have an impact on coping[1,2]. We aimed to understand associations between helplessness in coping with AS and patient-reported outcomes, including depression, work productivity, disease activity, functional impairment and health-related quality of life (HRQoL).

Methods: A prospective Patient Reported Outcomes Survey of Employment in Patients with AS (PROSE-AS) was conducted at rheumatologists' clinical practice sites in Canada (n=234), the Netherlands (n=131), the

United Kingdom (n=144) and the United States (n=46). Patients ≥18 years of age completed surveys at baseline, 3, 6, 9 and 12 months. Helplessness was assessed using the helplessness subscale of the Rheumatology Attitudes Index (RAI; scale 5–25), and patients were stratified according to low (RAI <11), moderate (RAI 11–19) or high (RAI ≥20) helplessness for analysis[3]. Depression was assessed using the Center for Epidemiological Studies Depression (CES-D) scale. Work outcomes were assessed using the Work Productivity and Activity Impairment (WPAI) questionnaire. Disease activity and functional impairment were assessed using the Bath AS Disease Activity Index (BASDAI) and Bath AS Functional Index (BASFI) scales, respectively. HRQoL was assessed using the Physical Component Summary (PCS) and Mental Component Summary (MCS) of the Short Form 36 Health Survey (SF-36) and the AS Quality of Life (ASQoL) questionnaires. Associations between helplessness and outcome variables over time were analyzed using multivariable generalized estimating equations (GEE), with adjustment for baseline patient socio-demographics, disease characteristics, medication use and country.

Results: Mean AS duration among 553 patients was 13.9 years; 194 (35.1%), 317 (57.3%) and 42 (7.6%) were classified with low, moderate and high helplessness, respectively. Patients with moderate and high helplessness were significantly more likely than patients with low helplessness to be depressed, unemployed and exhibit overall work and activity impairment (**Table**). High helplessness was also significantly associated with greater clinical severity as measured by BASDAI and BASFI, and with greater HRQoL impairment as measured by ASQoL, SF-36 PCS and MCS scores, compared with low helplessness.

Association Between RAI Helplessness Category and Outcome Variables Over Time[a]

Outcome Variables (Categorical)	Moderate vs Low Helplessness (OR, 95% CI)	High vs Low Helplessness (OR, 95% CI)
CES-D (scale 0–60) (a) Depressed (≥16, n=182) vs Not Depressed (<16, n=371)	3.56 (2.72 to 4.64)	12.91 (8.20 to 20.32)
Work Status (a) Unemployed (n=177) vs Employed (n=376)	1.14 (0.99 to 1.33)	1.69 (1.30 to 2.21)
WPAI (a) Absenteeism (n=60) vs no absenteeism (n=312) (b) Presenteeism (n=287) vs no presenteeism (n=86) (c) Overall work impairment (n=286) vs no overall work impairment (n=83) (d) Activity impairment (n=317) vs no activity impairment (n=59)	3.41 (2.07 to 5.62) 2.49 (1.86 to 3.34) 2.54 (1.89 to 3.41) 2.93 (2.06 to 4.17)	5.16 (2.35 to 11.33) 4.57 (1.76 to 11.86) 4.65 (1.75 to 12.35) 4.46 (1.33 to 14.91)
Outcome Variables (Continuous)	**Moderate vs Low Helplessness (β, 95% CI)**	**High vs Low Helplessness (β, 95% CI)**
BASDAI Score (n=553, scale 0–10)	1.01 (0.85 to 1.16)	2.28 (1.98 to 2.58)
BASFI Score (n=552, scale 0–10)	0.88 (0.73 to 1.02)	2.01 (1.74 to 2.28)
SF-36 PCS Score (n=553, scale 0–100)	−4.40 (−5.04 to −3.75)	−8.31 (−9.56 to −7.07)
SF-36 MCS Score (n=553, scale 0–100)	−4.03 (−4.88 to −3.17)	−9.92 (−11.57 to −8.28)
ASQoL Score (n=552, scale 0–18)	2.77 (2.47 to 3.07)	5.34 (4.76 to 5.92)

[a]Adjusted for age, sex, race, country, education, comorbidities, NSAIDs, DMARDs, anti-TNF, and AS duration. CI, confidence interval; DMARD, disease-modifying antirheumatic drug; MCS, Mental Component Summary; OR, odds ratio; PCS, Physical Component Summary; β, regression coefficient

Conclusion: High helplessness in coping with AS was associated with depression, poor work productivity and employment outcomes, greater disease activity and functional impairment, and worse HRQoL. Helplessness should receive more attention in clinical care.

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Clinical Characteristics of Nonradiographic Axial Spondyloarthritis in Korea: A Comparison with Ankylosing Spondylitis. Hyungjin Kim[1], Hyemin Jeong[2], Seulkee Lee[1], Inyoung Kim[1], Jiwon Hwang[3], Jaejoon Lee[2], Jinseok Kim[4], Eun-Mi Koh[2] and Hoon-Suk Cha[2]. [1]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [4]Jeju National University Hospital, Jeju, South Korea.

Background/Purpose: To evaluate the clinical characteristics and outcomes of nonradiographic axial spondyloarthritis (nr-axSpA) in Korean patients.

Methods: A retrospective analysis evaluated 155 patients with nr-axSpA at a single tertiary hospital between January 2001 and January 2011. Baseline characteristics and clinical courses were reviewed and compared with those of patients with ankylosing spondylitis (AS).

Results: The mean age at disease onset was 29.5 ± 10.8 years, and 52 (33.5%) patients were female. The mean age at symptom onset was older (29.5 ± 10.8 vs. 25.9 ± 9.2, respectively, $p < 0.001$) and the male to female ratio was lower (2:1 vs. 5:1, respectively, $p = 0.001$) in patients with nr-axSpA compared with patients with AS. The proportion of females was higher among patients with late onset-SpA than early-onset nr-axSpA (55.0 vs. 30.1%, respectively, $p = 0.029$). Among 74 patients with nr-axSpA, whose follow-up duration was more than 1.5 years, 29 (39.2%) patients progressed to AS during the follow-up period. The proportion of females was lower in progressors that that of non-progressors (13.8 vs. 44.4%, respectively, $p = 0.010$). Presence of syndesmophyte and minimal X-ray changes at baseline were frequently observed in progressors compared with non-progressors (26.7 vs. 0.0 %, $p = 0.006$ and 69.0 vs. 35.6%, $p = 0.005$, respectively).

Conclusion: The predominance of male patients is more prominent among Korean patients with SpA compared with Caucasians. Female nr-axSpA patients had late symptom onset and less progression to AS. X-ray changes at baseline were associated with radiographic progression.

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Blacks with As Have Greater Disease Severity Than Whites. Farokh Jamalyaria[1], Michael M. Ward[2], MinJae Lee[1], Lianne S. Gensler[3], Laura A. Diekman[4], Mohammad H. Rahbar[4], Amirali Tahanan[4], Shervin Assassi[1], Michael H. Weisman[5] and John D. Reveille[1]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]NIAMS/NIH, Bethesda, MD, [3]University of California, San Francisco, San Francisco, CA, [4]The University of Texas Health Science Center at Houston, Houston, TX, [5]Cedars-Sinai Medical Center, Los Angeles, CA.

Background/Purpose: To compare clinical parameters in African American (AA) patients with ankylosing spondylitis (AS) to white patients.

Methods: 539 AS patients (47 B, 492 W), meeting the modified New York criteria f enrolled in a longitudinal outcome study were assessed cross-sectionally at the baseline visit. Disease activity was defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), functional outcomes by the Bath Ankylosing Spondylitis Functional Index (BASFI) and radiographic severity by the Bath Ankylosing Spondylitis Radiographic Index (BASRI) and the modified Stokes Ankylosing Spondylitis Scoring System (mSASSS). Univariable comparisons of clinical characteristics for African-American and White patients were done using Chi-square test and Student t test and their non-parametric counterparts when necessary in both cohorts. We compared the baseline BASRI total score for African-American and White patients by constructing multivariable mixed effect models to account for intra-family correlation (539 patients from 449 families). Possible confounders were examined by identifying variables that were significantly associated with race and effect modifications were also tested while developing a final multivariable model. Analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC) at a statistical significance level of 0.05.

Results: Blacks had greater radiographic severity as seen by higher BASRI scores (9.12 versus 6.41, $p=0.0001$), greater functional impairment as measured by the BASFI (53.65 versus 31.94, $p=0.0001$) and higher disease activity as determined by the BASDAI (5.52 versus 4.11, $p=0.007$) compared to whites. There was no difference between disease duration or age. A significant interaction effect was found between race and disease duration. Table 1 shows the associations between baseline BASRI score and race at different levels of disease duration from the unadjusted and adjusted mixed effect model. Sex, B27+, study site and comorbidities (heart attack and diabetes) were adjusted in the final multivariable model. Subjective disease activity (BASDAI) and functional impairment (BASFI) were not included

because data for African-American subjects were missing n some subjects. BASRI scores for African-American subjects were higher than those for Whites and this association got stronger as disease duration increased in both unadjusted and adjusted models.

Table 1. Associations between Baseline BASRI Score and Race at Different Levels of Disease Duration

Outcome=BASRI	Disease Duration	Beta coefficient	SE	p
		unadjusted model		
Black vs. White	5 years	**1.2907**	**0.9859**	**0.2046**
	15 year	**2.5696**	**0.6331**	**0.0006**
	25 year	**3.8484**	**0.7087**	**<.0001**
	40 year	**5.7666**	**1.3842**	**0.0004**
		adjusted model		
Black vs. White	DD=5 year	**0.8247**	**1.0393**	**0.4408**
.DD=15 year		**1.923**	**0.7758**	**0.0265**
.DD=25 year		**3.0213**	**0.8555**	**0.0033**
.DD=40 year		**4.6688**	**1.4379**	**0.0058**
Male vs. Female			2.6606	0.3535	<.0001
B27+ vs. B27 -			0.07704	0.4337	0.8616
Heart attack vs. no			2.5047	0.9595	0.0206
Diabetes vs. no			1.5079	0.6768	0.0428

Conclusion: Although we cannot rule out the possibility that the more severely affected AA with AS are properly diagnosed and/or volunteer for study, these data confirm and extend prior subjective assessments of greater disease severity in African Americans using objective clinical and radiographic measurements and validated outcome tools.

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Patients with Nr-Axspa Show a Statistically Higher Disease Burden in Clinical Practice Compared with Patients with Radiographic Axial Spa. Lennart TH Jacobsson[1], Tomas Husmark[2], Elke Theander[3], Kenneth Henriksson[4], Katharina Büsch[5] and Martin Johansson[5]. [1]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, [2]Falu Hospital, Falun, Sweden, [3]Skane University Hospital Malmö, Lund University, Malmö, Sweden, [4]Rheumatology city clinic, Stockholm, Sweden, Stockholm, Sweden, [5]AbbVie AB, Stockholm, Sweden, Stockholm, Sweden.

Background/Purpose: The ASAS axial SpA classification criteria was published in 2009 but so far there has been limited research on axial SpA patients in clinical practice. There is no diagnose code for non-radiographic axial SpA (nr-axSpA) and it is unclear which diagnosis these patients receive in clinical practice. Characterization of nr-axSpA patients in clinical practice is lacking in comparison with radiographic axial SpA (rad-axSpA). The aim of this study was to characterize patients with axial SpA in clinical practice and to investigate similarities/differences between radiographic and non-radiographic axial SpA.

Methods: This is a prospective, cross-sectional, multi-center cohort study from Sweden. SpA patients (diagnosed with Psoriatic Spondylitis (M07.2), Ankylosing Spondylitis (M45), Spinal entesopathy (M46.0), Sacroiliitis, not elsewhere classified (M46.1), Other specified inflammatory spondylopathies (M46.8), or Inflammatory spondylopathy, unspecified (M46.9)) were consecutively recruited from the clinical settings of the participating study centers. Patients were followed for three months via an online questionnaire. At baseline, the rheumatologist assessed the ASAS axial SpA criteria and registered information on disease history, extra articular manifestations, and treatments. The patients answered online questionnaires capturing patient demographics, disease activity and function (BASDAI, BASFI, HAQ-S, etc.), QoL (EQ-5D, AS-QoL), health care resource use, and work ability (WPAI). P-values, unadjusted for covariates, were calculated using chi-square tests for categorical variables and t-tests for continuous variables.

Results: 251 patients were included of whom 197 (78%) were classified as axial SpA. Of those, 125 (63%) were classified as rad-axSpA and 72 (37%) were classified as nr-axSpA according to the ASAS axial SpA criteria. The nr-axSpA patients were diagnosed with AS (35%), other specific inflammatory spondylopathies (31%), inflammatory spondylopathy unspecified (19%), psoriatic spondylitis (11%), and sacroilitis, not elsewhere classified (4%). Time between symptom onset and diagnosis was 9.0 (8.4) years for rad-axSpA and 6.7 (7.1) years for nr-axSpA. The nr-axSpA patients showed a higher disease burden compared with rad-axSpA patients, e.g. higher BASDAI (4.1 vs. 2.7), VAS global (4.3 vs. 2.9), VAS pain (4.4 vs. 2.9), and ASDAS(CRP) (2.3 vs. 1.9) (Table).

Variable	Radiographic Axial SpA N = 125	Non-radiographic Axial SpA N = 72	p-value
BASDAI, mean, n (%)	2.7 (65)	4.1 (61)	<0.001
BASDAI >4.0, %, n (%)	28 (65)	55 (61)	0.004
BASFI, mean, n (%)	2.5 (65)	3.0 (61)	0.29
VAS global, mean, n (%)	2.9 (65)	4.3 (61)	0.006
VAS pain, mean, n (%)	2.9 (65)	4.4 (61)	0.003
ASDAS CRP, mean, n (%)	1.9 (58)	2.3 (57)	0.03
ASDAS ESR, mean, n (%)	1.8 (58)	2.3 (56)	0.007
Current NSAID use, %, n (%)	60 (100)	71 (100)	0.13
Current MTX or SSZ use, %, n (%)	28 (100)	22 (100)	0.37
Current anti-TNF use, %, n (%)	50 (100)	40 (100)	0.17

Conclusion: In this study, from Swedish clinical practice, we included patients from rheumatology clinics with pre-specified diagnoses most likely to be classified as axial SpA. The results show that the nr-axSpA patients have a statistically higher burden of disease than patients with rad-axSpA.

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Factors Associated with a Poor Functional Prognosis in Early Inflammatory Back Pain: Results from the DESIR Cohort. Cédric Lukas[1], Maxime Dougados[2] and Bernard Combe[1]. [1]Hopital Lapeyronie, Montpellier, France, [2]Descartes University, Cochin Hospital, Paris, France.

Background/Purpose: Spondyloarthritis is a heterogeneous disease, with various and hardly predictable potential courses. We aimed at determining prognostic factors of a bad functional outcome at 2 years in patients with early inflammatory back pain.

Methods: Data from patients included in the French multicenter DESIR cohort, i.e. suffering from inflammatory back pain (IBP) starting before 50 years of age and lasting for between 3 months and 3 years, were used in this work. A bad functional outcome was defined as an increase in BASFI superior to 75th percentile of observed progression in the cohort from inclusion visit to 24-months assessment, or a BASFI at 2 years higher than 75th percentile at this latter timepoint. Demographic, clinical, biological andradiological data collected at inclusion were compared in patients with bad functional outcome versus others, first by Chi2 test (numeric data were dichotomized according to observed median values), then by multivariate logistic regression model with stepwise selection of relevant factors.

Results: 513 patients (54.4% females, mean age 34±8.8 years, 72.2% fulfilling ASAS criteria) were assessed. Of those, 130 (25.3%) fulfilled the aforementioned criteria of a bad functional outcome (with BASFI increase of at least 4 units or value at 2 years ≥6). A bad outcome was more frequently observed in "older" patients aged over 33 years at disease onset, or with educational level lower than college (both $p<0.0001$). Smoking patients ($p<0.001$) and female patients ($p<0.008$) also had more frequently an unfavourable course of disease. Patients not fulfilling ASAS criteria, having negative X-Rays or MRI of sacroiliac joints, with a history or active peripheral arthritis were also more prone to have poor functional outcome (all $p<0.05$). A high disease activity at baseline (ASDASCRP >3.5 and BASDAI >45) was also associated with a bad functional evolution ($p<0.0001$). Multivariate analysis revealed that not fulfilling ASAS criteria, a female sex, an age >33 years, a lower educational level, an active smoking status and a high disease activity according to BASDAI at baseline were independently associated with a bad functional outcome at 24 months follow-up (Table).

Factors associated with a bad functional outcome at 24 months

	OR [95% confidence interval]	p
ASAS criteria fulfilled	0.59 [0.34–0.99]	0.049
Female sex	1.94 [1.16–3.23]	0.012
Age>33 years	2.27 [1.37–3.77]	0.002
Education > college	0.33 [0.20–0.55]	0.0001
Active smoking	3.20 [1.89–5.39]	0.0001
Baseline BASDAI>45	3.74 [2.21–6.32]	0.0001

Conclusion: We confirmed, in a large prospective cohort of early IBP patients, bad prognostic factors formerly described in ankylosing spondylitis, especially a low educational level, a (relatively) older age and a high disease

activity at onset, and revealed that an active smoking status was also independently associated with a poor outcome. Fulfilment of ASAS criteria on the other hand was predictive of a better outcome, likely due to more consensual management of a defined disease. Female sex however, usually regarded as a protective factor in AS, was related with a (self-assessed) poorer functional outcome after 2 years of follow-up.

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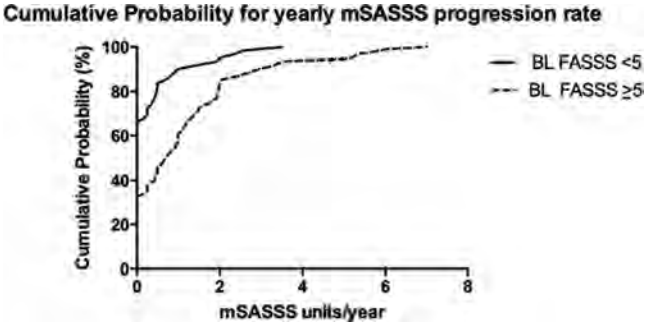
The Fat Spondyloarthritis Spine Score (FASSS) Independently Predicts Radiographic Progression in Patients with Ankylosing Spondylitis. Susanne Juhl Pedersen[1], Stephanie Wichuk[2], Praveena Chiowchanwisawakit[3], Zheng Zhao[4], Robert GW Lambert[2] and Walter P. Maksymowych[2]. [1]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [2]University of Alberta, Edmonton, AB, [3]Mahidol University, Bangkok, Thailand, [4]PLA General Hospital, Beijing, China.

The Fat Spondyloarthritis Spine Score (FASSS) independently predicts radiographic progression in patients with ankylosing spondylitis.

Background/Purpose: Vertebral corner fat lesions have been shown to be associated with later development of new syndesmophytes in the same vertebral corners[1,2]. The aim of this study was to investigate the association between fat lesions and radiographic progression at the patient level using the novel Fat Spondyloarthritis Spine Score (FASSS)[3]. This could lead to an important target for therapeutic intervention.

Methods: 157 patients with AS (N (%) male sex: 121 (77%); receiving TNFα inhibitor: 93 (59%); mean (SD) age: 39.4 (11.7); symptom duration: 15.9 (10.2)) had MRIs and X-rays performed with a mean (SD) follow-up of 2.3 (0.7) years and 2.2 (0.68) years. Status and change in fat lesions were assessed with FASSS and radiographic progression with the modified Stoke AS Spine Score (mSASSS). Two readers independently read MRIs scans and radiographs, and an adjudicator re-assessed discrepant cases according to pre-specified rules. Multivariate stepwise regression analysis included variables significant in univariate analyses (age, sex, symptom duration, baseline CRP, baseline mSASSS) and treatment.

Results: When mSASSS progression was dichotomized (mSASSS progression yes/no), baseline FASSS scores were significantly higher in the progression group as compared to the non-progression group (20.0 (21.6) vs. 12.9 (22.5), $p<0.001$). When a pre-specified FASSS cut-off of 5 was used, which has been suggested as a definition of a "positive spine MRI"[4], higher rates of radiographic progression were seen in patients with score ≥ 5 vs. <5 (1.19 (1.52) vs 0.34 (0.72), $p<0.001$). In the regression analyses baseline FASSS score was the only independent predictor of radiographic progression ($\beta=0.008$, $p=0.0004$). Figure 1 shows patients with a baseline FASSS scores ≥ 5 had a higher cumulative probability of radiographic progression.



Conclusion: A positive spine MRI for fat assessed with FASSS, and the degree of spinal fat are significantly associated with radiographic progression in patients with AS.

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Clinical and Psychological Correlates of Sleep Difficulties in Patients with Spondyloarthropathies Compared to Patients with Rheumatoid Arthritis. Konstantinos Kotsis[1], Thomas Hyphantis[2], Paraskevi V. Voulgari[3], Andre F. Carvalho[4] and Alexandros A. Drosos[5]. [1]Department of Psychiatry, Medical School, University of Ioannina, 45110, Ioannina, Greece., Ioannina, Greece, [2]Department of Psychiatry, Medical School, University of Ioannina, Ioannina 45110, Greece., Ioannina, Greece, [3]Associate Professor of Rheumatology, Ioannina, Greece, [4]Department of Clinical Medicine, Faculty of Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil., Fortaleza, Brazil, [5]Professor of Medicine/Rheumatology, Ioannina, Greece.

Background/Purpose: Sleep difficulties are common in patients with rheumatological disorders. Patients with Rheumatoid Arthritis (RA) report frequently poor quality sleep, numerous night awakening and difficulty falling asleep; complaints of patients with Spondyloarthropathies (SpA) often include poor sleep quality, sleep-onset insomnia and difficulty awakening. The aim of the present study was to test whether the clinical and psychological factors associated with sleep difficulties are different in patients with SpAs compared to RA patients.

Methods: In 138 consecutive SpA patients (55 with Ankylosing Spondylitis (AS) and 83 with Psoriatic Arthritis) we assessed disease's parameters, pain, depressive symptom severity (PHQ-9), Illness Perceptions (B-IPQ) and sleep difficulties (SCL-90-R). One hundred and ninety-nine consecutive RA patients served as disease control group. Multiple regression models determined the associations of clinical and psychological variables with sleep difficulties separately for each disease-group.

Results: SpA patients reported more waking up early in the morning ($p=0.012$) and less difficulties in falling asleep ($p<0.001$) and restless sleep ($p=0.002$) compared to RA patients. Depressive symptoms were associated with sleep difficulties in both disease-groups. In RA, older age ($p=0.038$) and female gender ($p=0.016$) were associated with more difficulties in falling asleep; female gender was correlated with waking up early in the morning ($p=0.028$), and disease activity, as measured by the DAS-28, was associated with restless sleep ($p=0.004$). However, pain was associated with troubles falling asleep ($p=0.009$) and sleep restlessness ($p<0.001$) only in patients with SpA. In addition, in patients with SpA, the higher the number of bodily symptoms attributed to the illness (illness identity), the greater the waking up early in the morning ($p=0.05$).

Conclusion: Apart from early recognition and treatment of depressive symptoms in both SpA and RA, addressing pain issues should be considered a priority in patients with SpA, as axial pain and stiffness in the latter half of the night are an important characteristic of the inflammatory back pain in those patients with AS, resulting in sleep disturbances, as the present findings showed. Attention to patients' illness perceptions and their concerns about numerous bodily symptoms attributed to the illness may also enable rheumatologists to identify and manage treatable aspects of sleep difficulties in patients with SpA.

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The Clinimetric Outcomes of Two Bath Ankylosing Spondyltis Metrology Indices in Treatment with TNF-á Blockers. Eon Jeong Nam[1], Jeong Soo Eun[1], Sang Hoon Kwon[1] and Young Mo Kang[2]. [1]Kyungpook National University School of Medicine, Daegu, South Korea, [2]Kyungpook National Univ Hosp, Daegu, South Korea.

Background/Purpose: Bath Ankylosing Spondyltis Metrology Index (BASMI) was developed to quantify the accurate axial status and to assess the clinical changes in spinal movement. The original BASMI was a 3-point scale (range 0–2; $BASMI_2$), which was refined to an 11-point scale, $BASMI_{10}$ (range 0–10) to increase the sensitivity to changes of axial status in ankylosing spondylitis (AS). In this study, we compared these BASMI scoring methods in AS patients who were treated with TNF-α blockers.

Methods: A retrospective study was conducted in a total of 116 patients who were treated with TNF-α blockers (137 cases; 96 patients with single agent, 19 patients with two, and 1 patient with three). Clinical efficacy was assessed using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), ASAS20, ASAS40, ASAS5/6, BASDAI50, and acute phase reactants including ESR and CRP at baseline and month 3, and then every six months up to 27 months. Metrology outcome was also evaluated by chest expansion, $BASMI_2$ and $BASMI_{10}$ methods at the same time.

Results: Three TNF-α blockers including etanercept (60 cases), adalimumab (62 cases), and infliximab (15 cases) showed a similar clinical efficacy. ASAS20 response rate was 87.3%, 91.3%, 91.9%, 90.3%, and 90.9% at months 3, 9, 15, 21, and 27, respectively. ASAS20 responders at month 3 (3MoASAS20) showed a significant improvement of $BASMI_2$ and $BASMI_{10}$ scores and chest expansion, compared to those of baseline, while 3MoASAS20 non-responders did not show a significant change until month 27. $BASMI_2$ scores at baseline and months 3, 9, 15, 21, and 27, were not significant different from those of $BASMI_{10}$ scores at the same time points. Both $BASMI_2$ and $BASMI_{10}$ scores were significantly correlated with components of ASAS20 response criteria including Bath Ankylosing Spondylitis Functional Index (BASFI), BASDAI-spinal inflammation (BASDAI-SI), patient's global assessment, and pain. The change of $BASMI_2$ and $BASMI_{10}$ in 3MoASAS responders was most prominent from baseline to month 3, but still significant from month 3 to month 9. The change of lumbar flexion and lumbar side flexion components of both $BASMI_2$ and $BASMI_{10}$ in 3MoASAS20 responders were statistically significant until month 9, while that of other components was only significant until month 3. The improvement of both $BASMI_2$ and $BASMI_{10}$ was significantly associated with changes of BASDAI-SI, BASFI, and pain at month 3, 9, 15, 21, and 27.

Conclusion: The $BASMI_2$ method showed similar sensitivity to changes in range of axial motion in patients with AS who were treated with TNF-α blockers. Further studies are required to determine whether $BASMI_2$ method is as sensitive as $BASMI_{10}$ method for assessment of axial involvement in AS patient with TNF-α blocker treatment.

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Do Bone Marrow Edema Lesions in the Sacroiliac Joint Change into Fatty Lesions over a 1-Year Period in Patients with Axial Spondyloarthritis or Possible Spondyloarthritis. Pauline Bakker[1], Rosaline van den Berg[1], Manouk de Hooge[1], Floris van Gaalen[1], Monique Reijnierse[1], T.W.J. Huizinga[1] and Désirée van der Heijde[2]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: Bone marrow edema (BME) lesions in the sacroiliac joint (SIJ) may change into fatty lesions over time. Fatty lesions are regarded as the earliest sign of chronic changes as a consequence of inflammation but are sometimes also found healthy controls.[1] At the moment, there is little information on the course over time in patients without treatment of TNF-inhibitors. The aim is to investigate whether BME lesions in the sacroiliac joint change into fatty lesions over 1 year time in patients with axial SpondyloArthritis (axSpA) or possible SpA and to evaluate the volatility of both lesions general.

Methods: Patients in the SPACE cohort (back pain: $\geq$ 3 months, $\leq$ 2 years, onset $<$ 45 years) with (suspicion of) axSpA underwent MRI of the SIJ at baseline and 1-year follow-up (n=76). MRIs were scored independently by 3 well-calibrated readers, blinded for time sequence and patient characteristics (STIR and MRI T1-weighted sequences viewed simultaneously). The presence of BME and fatty lesions was scored. Both lesions were defined present if 1 lesion was seen on $\geq$2 consecutive slices or if $>$1 lesion was seen on a single slice and scored in 4 quadrants per SI joint. For the two readers individually, scores of baseline and 1 year were compared on quadrant level (Q). The sum of all 8 Qs was calculated to obtain total scores per patient.

Results: 76 patients were completed in the analyses (number of Q=608); of which 39 (51%) were classified axSpA at baseline (ASAS classification criteria), and 37 (49%) as possible SpA. BME or fatty lesions at any time point was found in 27/76 (36%) and 20/76 (26%) patients respectively (reader 1, reader 2). Reader 1 indicated no lesions at baseline or follow-up in 519/608 Qs (85%) and in 45/608 Qs (7%) a change in lesions was visible (new lesions occurred, former lesions disappeared or the type of lesions changed over time). Similar trends were visible amongst the two readers (table). In both readers, fatty lesions newly occurred in 8/76 patients (11%) over 1 year time with agreement on 5 patients. In 3 patients, a transition of BME to fat occurred. On the other hand, fatty lesions disappeared in 2/76 patients (3%, reader 1) and in 5/76 patients (7%, reader 2). In reader 2, concomitant occurrence and disappearance of fatty lesions was observed in 2/76 (3%) of patients. In reader 1, this was not seen.

Conclusion: About one third of the patients showed BME/fatty lesions in the SIJ at any time point. There was not much change in site and/or type of lesions visible over 1-year period of time. Fatty lesions occurred more frequently de novo than in quadrants with previous BME and fatty lesions and can also resolve over time. The incremental value of fatty lesions in the SIJ needs to be further re-evaluated.

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Volatility of BME and fatty lesions in the SIJs over 1 year time

			1 year		
	Reader 1	**no lesions**	**BME**	**FAT**	**BME & FAT**
Baseline	no lesions	519	10	5	1
	BME	14	17	3	3
	FAT	0	1	20	1
	BME & FAT	0	1	6	7
			1 year		
	Reader 2	**no lesions**	**BME**	**FAT**	**BME & FAT**
Baseline	no lesions	524	10	7	1
	BME	18	10	2	1
	FAT	5	0	9	1
	BME & FAT	5	1	6	8

8 quadrants per patient (n = 76); 608 quadrants in total

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Radiographic Sacroiliitis Progression in an Early Axial Spondyloarthritis Cohort. Concepcion Castillo-Gallego[1], Jesus Sanz[2], Carmen Martin-Hervas[3], Mireia Moreno[4], Victoria Navarro-Compán[5], Diana Peiteado[1], Jorge Gratacos-Masmitja[6], Eugenio De Miguel[7] and Emilio Martín-Mola[1]. [1]Hospital La Paz - IdiPaz, Madrid, Spain, [2]Hospital Puerta de Hierro Majadahonda, Madrid, Spain, [3]Hospital Universitario La Paz, Madrid, Spain, [4]University Hospital Parc Taulí, Sabadell, Spain, [5]Rheumatologist, Madrid, Spain, [6]Hospital Parc Tauli, Sabadell, Spain, [7]Department of Rheumatology, Hospital Universitario La Paz, Madrid, Spain.

Background/Purpose: The current concept of axial Spondyloarhtritis (axSpA) considers non-radiographic axSpA (nr-axSpA) and Ankylosing Spondylitis (AS) as two stages of one disease. There are limited data available regarding rate of radiographic progression of the sacroiliac joints (SIJ) and the rate of transition from nr-axSpA to AS. The aim of the current study was to investigate radiographic progression in the SIJ in an early axSpA cohort.

Methods: Patients included in the study came from an early SpA cohort, from three centers of the ESPERANZA programme, a Spanish nationwide health management programme designed to provide excellence in care for early SpA. One of the inclusion criteria was symptom duration between 3 and 24 months. Every patient had a complete examination at baseline that included ESR, CRP, ASDAS-CRP, ASDAS-ESR, BASDAI, HLA-B27, pelvis x-Rays and Magnetic resonance (MRI) of SIJ. Pelvis x-Rays at baseline and at follow up were performed for every patient. These x-Rays were centrally digitized, anonymised and the SIJ were scored independently by two trained readers, according to the grading system of the modified New York criteria (mNYc). The readers scored images of both time points randomly and were blinded for all clinical data. MRI of SIJ were assessed independently and blinded by two trained readers, according to ASAS definition for bone marrow oedema (BME). Descriptive analysis was performed using SPSS program v.21.0. Cohen's kappa coefficients were also calculated to assess agreement between the two readers (mNYc for x-Rays and ASAS definition for a positive MRI).

Results: Forty four patients (52% male) were included. Mean age was 34.4 years (range: 21–45) and 52.3% were HLA-B27 positive. Mean time since symptoms onset until baseline visit was 10.4 months (range: 3–24). Mean (SD) follow up period (between baseline x-Ray and last follow up x-Ray) was 3.6 (1.4) years (median 4 years). All patients fulfilled ASAS criteria for axSpA and 16 of them had AS according to mNYc at baseline, in the opinion of both readers. Interobserver agreement for the x-Ray reading at baseline visit (44 x-Rays) was at the limit between moderate and good (kappa 0.62), but it increased to very good agreement (kappa 0.90) at the x-Rays reading corresponding to the follow-up visit. Regarding MRI, data from 27 images were available for analysis and the kappa value for the ASAS definition of BME was 0.76 at baseline. Progression of sacroiliitis over follow up period by at least one grade at one side was found in 43.2% (19/44), in the opinion of both readers. Among the 28 nr-axSpA patients at baseline, 3 of them (11%) progressed to AS according to NYmc in the opinion of both readers. We also analyzed the possible association between all variables

collected at baseline with radiographic progression but we did not find any statistically significant association for any of them.

Conclusion: Progression of radiographic sacroiliitis by at least one grade after a mean time of follow-up of 3.6 years occurs in almost half of the patients. The rate of progression from nrax-SpA to AS was 11%. The inter-reader reliability of pelvis x-Ray improves as disease progresses. Regarding to these results, pelvis x-Ray has a limited utility at early stages of axSpA.

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Clinical Value of ASDAS Index in Spanish Patients with Ankylosing Spondylitis. Agusti Sellas-Fernandez[1], Jose Luis Guerra Vázquez[2], Jose Luis Casals[3], Carlos Gonzalez Fernandez[4], Roberto Miguelez[5], José Rosas[6], Antonio Fernandez-Nebro[7], Cilia Peralta Ginés[8], Carlos Montilla-Morales[9], Xavier Juanola[10], Miguel Ángel Abad[11], Alberto Alonso[12], Azucena Hernández-Sanz[13], Luis Francisco Linares[14], Julio Medina[15], Joana Rovira[16], Juan Carlos Torre-Alonso[17], Alfredo Willisch[18], Eduardo Collantes-Estevez[19] and Ana Ruiz-Zorrilla[20]. [1]H. Vall d'Hebron, Barcelona, Spain, [2]H. Arquitecto Marcide, La Coruña, Spain, [3]H. Virgen de la Victoria, Málaga, Spain, [4]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [5]H. de Móstoles, Madrid, Spain, [6]Hospital Marina Baixa, Villajoyosa, Valencia, Alicante, Spain, [7]Hospital Regional Universitario Carlos Haya, Málaga, Spain, [8]H. Clínico Lozano Blesa, Zaragoza, Spain, [9]H. de Salamanca, Salamanca, Spain, [10]University Hospital Bellvitge, Barcelona, Spain, [11]Hospital Virgen del Puerto, Cáceres, Spain, [12]Hospital de Cruces, Bilbao, Spain, [13]H. Virgen de la Salud, Toledo, Spain, [14]Hospital Virgen de la Arrixaca., Murcia, Spain, [15]Hospital Clínico, Valladolid, Spain, [16]Mutua Terrasa, Barcelona, Spain, [17]H. Monte Naranco, Oviedo, Spain, [18]Complexo Hospitalario de Ourense, Ourense, Spain, [19]Hospital Reina Sofía, Córdoba, Spain, [20]Abbvie, Madrid, Spain.

Background/Purpose: The ASDAS (ankylosing spondylitis disease activity score) was developed to overcome some of the deficiencies of BASDAI (Bath Ankylosing Disease Activity Spondyltis Index). In this prospective study merits of both scores are compared.

Methods: Patients with AS according to mNY criteria and BASDAI≥4 were enrolled at 23 Spanish centers and followed during 1 year. Follow-up visits were scheduled every 4 months. Physical examination, CRP and ESR, Patient Global disease activity visual analogue scale (PG-VAS), pain due to AS (VAS), BASDAI, BASMI, BASFI, ASDAS, patient acceptable symptom state (PASS), SF-36, ASQoL, work productivity and activity impairment (WPAI) questionnaire data were recorded at each visit.

Results: A total of 127 evaluable patients, 75.6% men, with median age of 48 years and median time from diagnosis of 10 years, were recruited. *Criterion validity*: across follow-up correlations between ASDAS and PG-VAS ranged from 0.560 to 0.736, and from 0.758 to 0.840 between BASDAI and PG-VAS. *Convergent validity*: ASDAS correlation with BASDAI (0.733 to 0.781), BASMI (0.275 to 0.552), BASFI (0.476 to 0.591), lumbar pain VAS, (0.691 to 0.702) and lumbar night pain VAS (0.648 to 0.702) were found. *Discriminant validity*: mean ASDAS and mean BASDAI were significantly higher in patients with non-acceptable PASS than in patients with acceptable PASS. Patients below median PG-VAS showed significantly lower mean ASDAS and BASDAI than patients above median PG-VAS. ASDAS, but not BASDAI, distinguishes between patients below and above median CRP. Patients in different ASDAS categories showed significant differences in CRP, PG-VAS, BASMI, BASDAI, BASFI and pain VAS across follow-up, but significant differences in TJC and SJC were not found at any visit. *Sensitivity to change*: significant reductions in mean ASDAS and BASDAI were observed in patients changing from non acceptable PASS at baseline to acceptable PASS across the follow-up, and a significant proportion of patients had a reduction in disease activity level according to their ASDAS categories. ASDAS was sensitive to patients achieving a 50% reduction in BASDAI. Concerning treatments, ASDAS and BASDAI were sensitive to changes in PASS in patients treated with biological therapies, but only BASDAI was sensitive to changes in patients treated with DMARDs. An inverse relationship was detected between ASDAS and physical and mental subscales of SF36, and changes in ASDAS were significantly related with changes in ASQoL. Concerning WPAI, the work time missed increased as ASDAS score increased.

Conclusion: ASDAS has shown good metric properties in patients with AS, performing as well as BASDAI, but with higher sensitivity to inflammatory signs. Patients' quality of life and impairment of productive activity are associated with ASDAS scores.

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Inflammatory Burden in Recent-Onset Axial Spondyloarthritis. Juan Jose Aznar Sánchez, Raul Veroz Gonzalez, Adela Gallego Flores, Tamara Libertad Rodriguez Araya, Piter José Cossio Jimenez and Eugenio Chamizo Carmona. Hospital de Mérida, Mérida, Spain.

Background/Purpose: Patients with Non-Radiographic Axial Spondylarthritis (non-Rx AxSpA) don't presnt with different clinical manifestations than patients with Ankilosing Spondylitis (AS), although the inflammatory burden measured by ASDAS and CPR is higher in the latter. Stydies have still yet to discover any difference in inflammatory burden between patients with non-Rx SpA classified by ASAS criteria by the pathway of imaging (active inflammatory lesions in sacroiliac joints detected by MRI) and that classified by the clinical pathway (HLA-B27). The aim of this study is to analyze the clinical characteristics and the inflammatory burden of patients classified of Axial Spondylorarthritis (AxSpA) by ASAS criteria attended in recent-onset Spondyloarthritis Unit (RSpAU).

Methods: We included adult patients younger than 45 years old attended the RSpAU of the General Hospital in Mérida (Spain) between May 2008 and May 2014 with inflammatory low back pain more than 3 months and less than 2 years, asymmetric arthritis and/or mechanical low back pain/arthralgias accompanied by, at least, one of the following: psoriasis, uveitis, inflammatory bowel disease (IBD), entesytis, sacroiliitis on imaging, HLA-B27(+) or familiy history of SpA. Patients with previous diagnosis of SpA were however excluded.

Results: We studied 132 patients, 36 patients fulfilled ASAS criteria for SpA. Of this group, 8 patients fulfilled NY criteria for EA, and 28 were diagnosed with non-Rx SpA. Of the patients with non-Rx SpA, 16 entered through the clinical pathway (HLA-B27) and 12 through the pathway of imaging (MRI of sacroiliac joints with active inflammatory lesions or bone marrow edema). The age at the diagnosis was 29.5 year for both EA and non-Rx SpA. In the group of non-Rx SpA we found female predominance (16 women/12 men), in particular in the group with MRI positive and HLA-B27 negative (4 women/2 men). The measures of BASDAI and BASFI indexes were higher in the group of non-Rx SpA, but without stadistically significance. In patients with non-Rx SpA, the medium level of CRP was higher in patients with positive MRI than patients that entered by the clinical pathway, but without sadistically significance.

Conclusion: In the non-Rx SpA there is a female predominance and a lower rate of HLA B27 (+) than in radiological EA. We didn't find any significant differences in the indexes used to measure the inflammatory burden between both groups. There is a trend to higher inflammatory burden measured by CRP and ASDAS in EA than in non-Rx SpA and in the last group, higher in patients with active inflammatory lesions in sacroiliac joints by MRI.

	n°	H:M	B27+ %	BASDAI Media 95%IC	ASDAS Media 95%IC	BASFI Media 95%IC	EGP Media 95%IC	PCR (mg/L) Media 95%IC
TOTAL	36	0,80	83,33	4,95 (4.26,5.64)	2,83 (2.46,3.20)	2,81 (1.97,3.65)	6,11 (5.2,7.02)	9,02 (3.61,14.43)
AS (NY)	8	1,6	100	4,25 (2.49,6.01)	2,95 (1.72,4.18)	2,425 (0.44,4.40)	5,75 (3.25,8.25)	21,01 (0,43.32)
non-Rx AxSpA	28	0,75	78,6	5,18 (4.40,5,96)	2,8 (2.43,3.31)	2,92 (1.95,3.89)	6,21 (5.21,7.21)	5,61 (2.31,8.91)
HLAB27	16	0,77	100	5,01 (3.86,6.16)	2,72 (2.21,3.23)	2,75 (1.47,4.03)	6,25 (4.86,7.64)	4,87 (0.51,9.23)
RMN	12	0,71	50	5,42 (4.3,6.54)	2,91 (2.3,3.52)	3,14 (1.48,5.80)	6,17 (4.53,7.81)	6,61 (1.12, 12.20)

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Anti-Drug Antibodies As a Predictor for the Discontinuation of Anti-TNF Agents in Patients with Spondyloarthrtis. Jiwon Hwang, In young Kim, Seulkee Lee, Hyemin Jeong, Hyungjin Kim, Jaejoon Lee, Eun-mi Koh and Hoon-Suk Cha. Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

Background/Purpose: Tumor necrosis factor (TNF) blocking agent has shown to be effective in patients with axial spondyloarthritis (SpA) including ankylosing spondylitis (AS) as up to 60–70%. However, the other 30–40% of patients fails to respond. This non-responsiveness to TNF blocking agent has been suggested as the result of the development of antibodies against it, anti-drug antibodies (ADA), which have been described well in patients with rheumatoid arthritis and Crohn's disease. The aim is to assess whether ADA is related to the clinical efficacy in SpA patients on anti-TNF agents.

Methods: According to the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial SpA, consecutive patients were recruited at a single tertiary hospital who received treatment with adalimumab (Ada) or infliximab (Ifx): 86 AS, 11 inflammatory bowel disease associated SpA, 3 psoriatic SpA and 2 undifferentiated SpA. Serum samples were collected at the enrolment for the drug and ADA levels, which were measured by ELISA. Disease activity was assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at baseline (at the beginning of the current anti-TNF agents), at 3 month and then every 6 months. The reactivation of tuberculosis infections, side-effects or infusion reactions, and the cause for discontinuation of therapy were assessed prospectively.

Results: A total of 102 patients were studied (89.2% male; mean age at sampling 35.2 $\pm$ 18.0 years; mean disease duration 11.3 $\pm$ 7.9 years). HLA-B27 was positive in 65 of 76 patients (85.5%). Among 102 patients, 74 were treated with Ada and 28 with Ifx. Eighteen patients (17.6%) had switched from other kinds of anti-TNF agents including Ada, Ifx and etanercept. Latent tuberculosis (TB) infection was detected in 22 patients (21.6%) before starting anti-TNF agents and the treatment regimen with isoniazid and rifampin was commenced by a TB expert. ADA was demonstrated in 8 patients (7.8%) (5 of Ada and 3 of Ifx) and all of them were anti-TNF naïve patients. Patients who developed ADA had lower levels of the corresponding drugs (Ada level: 0.45 $\pm$ 0.68 vs 4.42 $\pm$ 2.12, $p < 0.0001$; Ifx level 0.91 $\pm$ 1.36 vs 3.38 $\pm$ 2.24, $p = 0.076$). At baseline, no differences in BASDAI were found in patients with or without ADA, and neither ESR nor CRP was different. The median period under prospective observation was 15 months (range 0 – 17, mean 12.7 $\pm$ 7.8). ADA-positive patients had a significantly higher cumulative drug discontinuation rate due to inefficacy and adverse events (37.5% vs 6.4%, $p = 0.022$). There was no reactivation of tuberculosis during anti-TNF treatment.

Conclusion: Our result suggests that in SpA patients the presence of ADA to current Ada or Ifx can predict the drug discontinuation in future due to inefficacy or adverse events.

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Is There Any Gender Specific Difference in the Cut Off Values of Ankylosing Spondylitis Disease Activity Score (ASDAS) in Patients with Axial Spondyloarthritis? Erkan Kilic, Gamze Kilic and Salih Ozgocmen. Erciyes University, Faculty of Medicine, Kayseri, Turkey.

Background/Purpose: Axial spondyloarthritis (ax-SpA) consisted patients with advanced axial SpA or ankylosing spondylitis (AS) and non-radiographic axial SpA (nr-axSpA). Evaluation of disease activity in axSpA is complex due to the phenotypic heterogeneity of the disease. Assessment in Spondyloarthritis international Society (ASAS) endorsed the cut off values for ASDAS-CRP. The aim of this study was to assess the validity of AS Disease Activity Score (ASDAS)-CRP and ASDAS-ESR as clinical tools for assessing disease activity in axSpA and to estimate the cut-off values of ASDAS-CRP and ASDAS-ESR for male and female patients with axSpA.

Methods: Patients with axSpA were recruited from Erciyes Spondyloarthritis Cohort (ESPAC) and assessed for BASDAI, ASDAS, BASFI, BASMI, Ankylosing Spondylitis Quality of Life (ASQoL), and VAS-pain. Patients were grouped into low and high disease activity according to the physician's (DrG) and patient's global (PtG) assessment score (>6/10 vs <4/10), ASAS partial remission criteria, treatments and presence of peripheral arthritis. The discriminant ability of ASDAS-CRP and ASDAS-ESR was assessed using standardized mean differences. Receiver operating characteristic (ROC) curves were used for comparisons. Optimal cut-off values of ASDAS-CRP and ESR were calculated for both genders and for the whole group.

Results: Three hundred fifty-eight patients with axSpA (138 F, 220 M) were included in this study. One hundred sixty two patients met criteria for non-radiographic axSpA (nr-axSpA) and 196 for ankylosing spondylitis. Two ASDAS versions and BASDAI had good correlations with PtG and DrG in both groups, however correlation coefficients were relatively higher in men. Women had significantly higher VAS-pain, BASDAI item scores, PG and DrG and ESR. Discriminant ability of ASDAS-CRP, ASDAS-ESR and BASDAI were similar in men and women when patients were assigned into low and high disease activity based on the ASAS partial remission, PtG and DrG scores (assessed by comparing AUC of ROC curves). ASDAS cut-off values are quite similar in all groups indicating that ASDAS-CRP works similarly well in male and female patients with axSpA. The calculated ASDAS-CRP cut-offs in both genders were very similar to predefined values by ASAS except the cut off for in-active to moderate disease activity. The cut-off values for ASDAS-ESR seem to be lower than predefined values and women tent to have higher cut-offs compared to males.

Conclusion: The construct validity of ASDAS-CRP to discriminate low and high disease activity and cut off values are similar in male and female patients with axSpA, however cut offs for ASDAS-ESR need to be redefined.

	ASDAS-CRP			ASDAS-ESR		
	In-active-moderate	Moderate-High	High-Very high	In-active-moderate	Moderate-High	High-Very high
Whole group	1.57–1.69	1.93–2.34	3.40–3.92	1.43	1.82–2.06	3.25–3.57
Females	1.55–1.73	2.00–2.33	3.34–3.83	1.69–1.76	1.99.2.09	3.30–3.66
Males	1.56–1.73	1.91–2.41	3.48–3.96	1.32–1.36	1.61–2.03	3.17–3.55

Disclosure: E. Kilic, None; **G. Kilic**, None; **S. Ozgocmen**, None.

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Differing Patterns of Axial Spondyloarthritis in Females and Males. Ibrahim Almaghlouth[1], Arane Thava[1], Nigil Haroon[2] and Robert D. Inman[3]. [1]Toronto Western Hospital, Toronto, ON, [2]Toronto Western Research Institute, Toronto, ON, [3]Department of Medicine, University of Toronto, Toronto, ON.

Background/Purpose: Sex effects have been noted in axial spondyloarthritis (AS) however controversy still exists regarding male and female clinical manifestations of AS. This includes uncertainty regarding pattern of spinal disease, peripheral joint involvement, and clinical burden of disease. Prior studies have often been limited by numbers and lack of contemporaneous comparators. In this study we examine sex effects on a longitudinal observation cohort of AS.

Methods: A systematic review of 950 AS patients (671 male and 279 female) followed in a longitudinal clinic which entails regular clinic visits using a standardized protocol. Patients were stratified by sex. Descriptive characteristics using means (sd) and frequencies (%) can be seen in Table 1. Tests were used to compare continuous variables and Chi-Squared tests for categorical variables. P-value <0.05 was used to define statistical significance.

Results: We observed that age of onset of back pain was higher in females, and that there was a significant longer delay in diagnosis in females. CRP levels were lower among female patients. This finding parallels previous reports of lower CRP among female with non-radiographic axSpA. We noticed no difference between both sex in terms of affected joints, nor with respect to key extra-articular manifestations (iritis, psoriasis, inflammatory bowel disease). Significant differences in BASMI indicate less impairment of spinal mobility, which may reflect both lower levels of CRP and lower rates of smoking, both of which have been previously associated with structural progression of AS. The use of biologic agents as a surrogate marker of symptomatic burden of disease did not differ between females and males but comparative ASQOL scores reflected greater impact on quality of life in females.

Conclusion: Our large cohort documents later onset of AS symptoms and longer delay in diagnosis in female AS patients compared with males. Difference in inflammatory markers might be a reflection of different disease pathogenesis but environmental factors such as smoking also contribute to the difference in clinical expression of the disease.

TABLE 1: Comparison of Baseline Demographic and Disease Characteristics by Sex (n=950)

	Frequency (%) or Mean(sd)		
Variable	Males n=671	Females n=279	p-value
Age	38.2 (14.1)	37.5 (12.3)	0.45
Age at Joint Pain	23.6 (11.3)	25.8 (11.8)	0.02
Age at Back Pain	24.0 (10.2)	25.7 (10.7)	0.03

Age at diagnosis of AS	29.7 (12.2)	32.2 (11.2)	0.004
Duration of AS	14.5 (11.8)	12.1 (10.6)	0.002
Ever smoked (Yes)	283 (42.2%)	85 (30.5%)	0.0007
Employment status	332 (61.9%)	153 (62.2%)	<0.0001
Employed:	61 (11.4%)	24 (9.8%)	
Disabled:			
HLA-B*27	460 (74.1%)	183 (72.3%)	0.60
Family history of AS	88 (13.6%)	43 (16.4%)	0.28
CRP	12.7 (17.8)	9.5 (21.5)	0.005
Peripheral arthritis	286 (42.6%)	138 (49.6%)	0.048
Iritis/Uveitis	154 (23.0%)	71 (25.5%)	0.41
Psoriasis	56 (9.8%)	13 (5.1%)	0.03
IBD	73 (20.7%)	30 (22.9%)	0.60
BASDAI	4.7 (4.5)	5.0 (4.7)	0.07
BASMI	2.7 (2.6)	1.9 (1.9)	<0.0001
BASFI	3.7 (2.8)	3.7 (2.8)	0.82
BASG	5.2 (2.8)	5.7 (2.6)	0.02
HAQ	0.7 (0.6)	0.7 (0.6)	0.15
SF36- PCS	37.4 (11.3)	36.4 (11.6)	0.30
SF36-MCS	46.7 (11.7)	45.0 (11.9)	0.10
FSS	5.0 (2.8)	5.4 (2.9)	0.08
ASQOL	7.5 (5.8)	8.6 (5.7)	0.02
EQ5D	0.6 (0.2)	0.7 (0.2)	0.38
NSAIDs	412 (61.7%)	203 (73.6%)	0.0005
DMARDs	145 (22.6%)	52 (19.1%)	0.23
Glucorticoids	35 (5.5%)	15 (5.5%)	0.98
Biologics	129 (19.3%)	46 (16.7%)	0.35

Disclosure: I. Almaghlouth, None; **A. Thava**, None; **N. Haroon**, None; **R. D. Inman**, Advisory board and grant, 5.

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Combined Hip Abduction Angle Measured By Using Iphone Compass Application; A Novel Measurement Tool to Asses Hip Mobility. Handan Yarkan, Berrin Zengin, Gokce Kenar, Pinar Cetin, Ismail Sari, Fatos Onen and Nurullah Akkoc. Dokuz Eylul University School of Medicine, Izmir, Turkey.

Background/Purpose: Intermalleolar distance (IMD) is a component of the Bath ankylosing spondylitis metrology index (BASMI) and measures abduction of the hips. New generations of smartphones are equipped with a gyroscope and an accelerometer which in combination with a smartphone's operating system or specific software applications can be used for various inclinometric functions. The purpose of this study was to estimate the intra and inter-rater reliability of using iphone built in compass application, as compared to IMD in the assessment of hip abduction in patients with AS.

Methods: The study sample included 20 AS patients (6 females, 14 males) with a mean age of 47.8 (± 10.2). BASMI scores were obtained from patient charts. Two examiners measured intermalleolar distance as the standard method at two different time points with the patient lying in a supine position. Then combined abduction of the hips angle (CAHA) was measured by iPhone compass application twice. To stabilize the iphone's position during measurements an iphone case and an elastic bandage with velcro patches were used. Intra-rater and inter-rater reliability were examined with intra-class correlation coefficients (ICC). The validity was assessed by Pearson Correlation analysis.

Results: The mean BASMI score was 43 (±22.7). The mean scores for BASDAI, ASDAS and BASFI were 3.7 (± 19.9), 2.9 (± 0.96) and the 3.5 (± 24.02), respectively. The mean IMD was 83.6 cm (± 24.4) for rater 1 and 83.4cm (SD: 23.1) for rater 2. The mean CAHA was 51.2° (±18.3) for rater 1 and 55.6°(±20.5) for rater 2. We observed almost an excellent intra and inter-rater reliability for both methods (Table 1). CAHA measurements showed a strong correlation with IMD (r=0.74)

Conclusion: The results of this study suggest that measurement of combined hip abduction angle using iphone, which is not to be affected by patients' height, can be used as a novel hip mobility measure.

Table: Intra-rater and inter-rater reliability of the two methods to asses the hip mobility

	Intrarater reliability		Interrater reliability
	Rater 1 ICC (95% CI)	Rater 2 ICC (95% CI)	ICC (95% CI)
Intermalleolar distance	0.99 (0.98–0.99)	0.85 (0.66–0.94)	0.93 (0.85–0.97)
Combined hip abduction Angle	0.94 (0.85–0.97)	0.84 (0.64–0.93)	0.94 (0.85–0.97)

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A Phase 3, Randomized, Controlled Trial of Apremilast, an Oral Phosphodiesterase 4 Inhibitor, for Treatment of Psoriatic Arthritis: Long-Term (52-Week) Improvements in Physical Function. Alvin Wells[1], Jacob A. Aelion[2], Adewale O. Adebajo[3], Alan Kivitz[4], Paul Bird[5], ChiaChi Hu[6], Randall M. Stevens[6] and Christopher J. Edwards[7]. [1]Rheumatology & Immunotherapy Center, Franklin, WI, [2]West Tennessee Research Institute, Jackson, TN, [3]University of Sheffield, Sheffield, United Kingdom, [4]Altoona Center for Clinical Research, Duncansville, PA, [5]Combined Rheumatology Practice, Kogarah, Australia, [6]Celgene Corporation, Warren, NJ, [7]University Hospital Southampton, Southampton, United Kingdom.

Background/Purpose: Apremilast (APR) is a phosphodiesterase 4 inhibitor that helps regulate the immune response that causes inflammation and skin disease associated with psoriatic arthritis (PsA). PALACE 4 compared APR efficacy and safety with placebo in patients with active PsA who were DMARD-naïve. We evaluated the impact of APR over 52 weeks on physical function among PALACE 4 patients.

Methods: Patients were randomized (1:1:1) to placebo, APR 20 mg BID (APR20), or APR 30 mg BID (APR30). Patients whose swollen and tender joint counts had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if they were initially randomized to placebo, or continued on their initial apremilast dose. At Week 24, all remaining placebo patients were re-randomized to APR20 or APR30. This analysis reports data for Weeks 0 to 52. Physical function was evaluated using the Health Assessment Questionnaire-Disability Index (HAQ-DI) and 36-item Short-Form Health Survey version 2 (SF-36v2) Physical Function (PF) domain and physical component summary (PCS) scores. Proportions of patients initially randomized to APR achieving minimum clinically important difference (MCID) thresholds at Week 52 for HAQ-DI (≥0.13 or ≥0.30)[1,2] and SF-36v2 PF and PCS (both ≥2.5)[3] were determined.

Results: At Week 16, a significantly greater proportion of patients treated with APR achieved a modified ACR20 response vs placebo (primary endpoint). Mean changes in HAQ-DI at Week 16 (key secondary endpoint) were 0.03 (placebo), -0.17 (APR20; $P=0.0008$), and -0.21 (APR30; $P<0.0001$). Among patients who were treated with APR continuously through 52 weeks, sustained improvement in HAQ-DI was observed. Mean change in HAQ-DI was -0.32 (APR20) and -0.39 (APR30) at Week 52, exceeding MCID thresholds of ≥0.13 or ≥0.30 (Table). At Week 52, 56.8% (APR20) and 59.0% (APR30) achieved HAQ-DI MCID ≥0.13 and 48.5% and 48.9% achieved MCID ≥0.30, respectively. Week 52 mean changes from baseline in SF-36v2 PF (APR20: 4.61; APR30: 6.41) and PCS (APR20: 5.55; APR30: 6.67) exceeded the MCID threshold (≥2.5). At Week 52, 57.6% of APR20 and APR30 patients achieved SF-36v2 PF MCID, and 60.6% (APR20) and 69.1% (APR30) achieved SF-36v2 PCS MCID. The most common adverse events reported during the placebo-controlled period were nausea (12.6%), diarrhea (9.4%), and headache (6.0%). The safety profile of APR for up to 52 weeks was similar to that observed with APR for up to 24 weeks of treatment (placebo-controlled period).

Conclusion: Over 52 weeks, APR continued to demonstrate clinically meaningful improvements in physical function in active PsA patients who were DMARD-naive. APR demonstrated an acceptable safety profile and was generally well tolerated for up to 52 weeks.

Physical Function at Week 52 in Patients Receiving APR From Baseline

	APR20 n=132	APR30 n=139
HAQ-DI*		
Baseline, mean	1.12	1.09
Mean change from baseline	−0.32	−0.39
Patients achieving MCID ≥0.13‡, %	56.8	59.0
Patients achieving MCID ≥0.30‡, %	48.5	48.9
SF-36v2 PF$^{\mu}$		
Baseline, mean	35.8	35.6
Mean change from baseline	4.61	6.41
Patients achieving MCID ≥2.5‡, %	57.6	57.6
SF-36v2 PCS$^{\mu}$		
Baseline, mean	35.6	36.4
Mean change from baseline	5.55	6.67
Patients achieving MCID ≥2.5‡, %	60.6	69.1

Note: The n represents the number of patients with a baseline value and a value at Week 52. *Decrease or $^{\mu}$Increase in score indicates improvement. ‡Pre-specified thresholds based on literature[1–3] at time of protocol and analysis.

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ACR Poster Session A
Spondyloarthropathies and Psoriatic Arthritis - Pathogenesis, Etiology
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Periostin May Have a Role in Ankylosing Spondylitis and It Is Associated with Wnt Signalling Pathway Regulators. Servet Akar[1], Saadettin Uslu[2], Leyla Didem Kozaci[3], Gercek Can[4], Neslihan Karaca[5], Emine Figen Tarhan[4], Mustafa Ozmen[4] and Dilek Solmaz[6]. [1]Izmir Katip Celebi University School of Medicine, Izmir, Turkey, [2]Izmir Katip Celebi University School of Medicine, Izmir, Turkey, [3]Adnan Menderes University School of Medicine, Aydin, Turkey, [4]Izmir Ataturk Education and Reseach Hospital, Izmir, Turkey, [5]Adnan Menderes University, Science Thecnology Research and Application Center, Aydin, Turkey, [6]Namik Kemal University School of Medicine, Tekirdag, Turkey.

Background/Purpose: Ankylosing spondylitis (AS) is a chronic rheumatic disease characterized by sacroiliac and spinal inflammationand new bone formation (syndesmophyte). Molecular mechanisms underlying this process have not been yet fully understood however differentiation of mesenchymal cells into bone-forming osteoblasts appears to be a key pathogenic event. Periostin is an extracellular matrix protein and primarily secreted by osteoblasts. It was shown that periostin has a role in bone anabolism by the regulation of Wnt-β-catenin signaling, therefore it may be one of the pathogenic mechanisms in syndesmophyte formation in AS. To evaluate the serum periostin levels in patients with AS. We also assessed the relationship among periostin levels and other biomarkers of bone formation and the role of periostin in disease outcomes, radiographic changes in particular.

Methods: In total 98 consecutive AS patients (77 males [79%]; with a mean age of 39.3 ± 10.0years) according to the modified New York criteria and 49 healthy controls (37males [76%]; with a mean age of 39.0 ± 5.9 years) from two centers were included in the study. Serum periostin, interleukin (IL)-8, dickkopf-1 (Dkk-1) and sclerostin levels were measured by commercially available ELISA kits. We also determined the serum high-sensitivity C-reactive protein(hs-CRP) levels. Disease related characteristics of patients were assessed by using BASDAI, BASFI, BASMI. Radiographs of the pelvis, cervical and lumbar spine were scored by using the modified New York and modified Stokes ankylosing spondylitis spinal score (mSASSS).

Results: As expected hs-CRP levels and erythrocyte sedimentation rate were higher in AS patients in comparison with controls. Serum periostin and Dkk-1 levels were significantly lower in AS patients compared with controls. Moreover periostin level was particularly lower in patients with active (35.4 ± 25.8 vs 53.9±42.1 ng/mL and P=0.014) disease (BASDAI >4). There was also a trend towards higher periostin levels in patients with syndesmophyte, hip involvement and sacroiliac ankylosis however these were not reached statistical significance. Regression analysis showed that serum periostin levels were independently predicted by Dkk-1, IL-8 levels.

Conclusion: Our results suggested that periostin may be down regulated in AS patients with active disease and the increase in periostin in inactive phase may contribute to the new bone formation along with the Wnt signalling.

	AS patients (n=98)	Controls (n=49)	P
Age at disease onset	27.7 ± 8.6	N/A	N/A
Mean BASDAI	4.2 ± 2.1	N/A	N/A
Mean BASFI	3.4 ± 2.4	N/A	N/A
Mean BASMI	3.8 ± 1.7	N/A	N/A
ASDAS-CRP	3.0 ± 0.9	N/A	N/A
Median m SASSS score	6 (0–72)	N/A	N/A
Serum periostin (ng/mL)	43.8 ± 35.0	72.5 ± 50.0	0.001
Dkk-1 (ng/mL)	48.9 ± 35.1	68.6 ± 37.8	0.040
IL-8 (pg/mL)	103.9 ± 270.9	66.9 ± 60.1	0.390
hsCRP (μg/mL)	5.2 ± 8.4	0.7 ± 1.3	<0.001
Creatinine (mg/dL)	0.76 ± 0.15	0.82 ± 0.14	0.017

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Characterisation of Mucosal-Associated Invariant T (MAIT) Cells in Ankylosing Spondylitis Patients. Ibrahim Almaghlouth[1], Eric Gracey[2], Zoya Qaiyum[2], Robert D. Inman[3] and Ammepa Anton[4]. [1]Toronto Western Hospital, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]Department of Medicine, University of Toronto, Toronto, ON, [4]University Health Network, Toronto, ON.

Background/Purpose: Ankylosing spondylitis (AS) is chronic inflammatory disease of unknown origin. Studies into the molecular basis of AS have demonstrated exaggerated innate and adaptive immune responses mediated though various cytokines. Over-expression of cytokines such as TNFα and IL-17 has provided a rationale for targeted biologic agents for suppressing the disease activity. Identifying the cellular sources of these cytokines is crucial to understand the pillars of inflammation in AS. Recently, mucosal associated invariant T (MAIT)-cells have been implicated in various autoimmune diseases. Their effectors phenotype and preferential localization to peripheral tissue makes them possible contributor in the pathogenesis of AS. Thus we hypothesized that MAIT cells may be increased in AS patients compared to normal controls.

Methods: Peripheral blood mononuclear cells (PBMC) and synovial fluid (SF) mononuclear cells (SFMC) from the AS patients (N=17) and controls (n=11) were isolated. Healthy controls were used for the MAIT cells in the in PBMC while RA and OA were used as controls for the SF MAIT cells. Flow cytometry was used to identify MAIT cells, which were defined as CD3+CD161^{hi}V.α 7.2+CCR6+, with the majority being CD8+. Cytokine production by respective cell populations was assessed indirectly by intracellular straining for IL-4, IL-17, TNFa, IFNg and granzyme B.

Results: The percentage of MAIT cells in PBMC of AS patients and control groups were similar. Whereas CD69+ (activation marker) and CCR6+(homing marker) MAIT cells were comparable in AS and HC, CCR6+ MAIT showed a tendency to be higher in AS PBMC. It was noted that in PBMC, activated MAIT cells (CD69+) represented a small proportion of the total MAIT cells in. In contrast, almost all SF MAIT cells from AS patients were activated (CD69+). We also noticed that the percentage of CD4+ MAIT to total MAIT cells in AS SF is higher than peripheral blood. Similar results were seen in paired patient blood-synovial fluid analysis. In this analysis, IL17 production was similar while an increased granzyme B production and reduction of IL4, IFNγ and TNFα were detected in SF MAIT cells compared to MAIT cells in PBMC.

Conclusion: To our knowledge, this study is the first to look at MAIT cells in both blood and SF of AS patients. Interestingly MAIT cells in the inflamed joints in AS are predominantly activated. This suggests that examining the microenvironment of the joint to define the activating signals for local MAIT cells would be productive.

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Decreased Frequencies of Circulating Follicular Helper T Cell Counterparts and Plasmablasts in Ankylosing Spondylitis Patients Naïve for TNF Blockers. M. Belén Bautista-Caro[1], Irene Arroyo-Villa[1], Concepcion Castillo-Gallego[1], Eugenio de Miguel[2], Diana Peiteado[1], Chamaida Plasencia-Rodriguez[1], Alejandro Villalba[1], Paloma Sanchez-Mateos[3], Amaya Puig-Kröger[4], Emilio Martín-Mola[1] and Maria Eugenia Miranda-Carus[1]. [1]Hospital La Paz - IdiPaz, Madrid, Spain, [2]University Hospital La Paz - IdiPaz, Madrid, Spain, [3]Hospital Gregorio Marañon, Madrid, Spain, [4]Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain.

Background/Purpose: Follicular helper T cells (Tfh), localized in lymphoid organs, promote B cell differentiation and function. Circulating CD4 T cells expressing CXCR5, ICOS and/or PD-1 are counterparts of Tfh. Three subpopulations of circulating CD4+CXCR5+ cells have been described: CXCR3+CCR6- (Tfh-Th1), CXCR3-CCR6+ (Tfh-Th17) and CXCR3-CCR6- (Tfh-Th2). Only Tfh-Th17 and Tfh-Th2 function as B cell helpers.

Our objective was to study the frequencies of circulating Tfh (cTfh), cTfh subsets and plasmablasts (CD19+CD20-CD27+CD38^{high} cells), and the function of cTfh cells, in patients with Ankylosing Spondylitis (AS).

Methods: Peripheral blood was drawn from healthy controls (HC) (n=50), AS patients naïve for TNF blockers (AS/nb) (n=25) and AS patients treated with TNF blockers (AS/b) (n=25). The frequencies of cTfh and plasmablasts were determined by flow cytometry. Cocultures of magnetically sorted CD4+CXCR5+ T cells with autologous CD19+CD27- naïve B cells were established from 3 AS/nb patients and 3 HC, and concentrations of IgG, A and M were measured in supernatants.

Results: AS/nb but not AS/b patients, demonstrated decreased frequencies of circulating CD4+CXCR5+ICOS+PD-1+ cells and plasmablasts together with a decreased (Tfh-Th17+Tfh-Th2)/Tfh-Th1 ratio. The amounts of IgG and IgA produced in cocultures of CD4+CXCR5+ T cells with CD19+CD27- B cells of AS/nb patients were significantly lower than observed in cocultures established from HC.

Conclusion: AS/nb but not AS/b patients, demonstrate a decreased frequency of cTfh and plasmablasts, and an underrepresentation of cTfh subsets bearing a B helper phenotype. In addition, peripheral blood CD4+CXCR5+ T cells of AS/nb patients showed a decreased capacity to help B cells ex vivo.

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The Immunological Basis of the Sex-Bias in Ankylosing Spondylitis: Th17 Expansion Is Restricted to Male Patients and Correlates with Sex-Related Alteration in Vitamin D Metabolism. Eric Gracey[1], Blerta Green[1], Paul Yip[1], Renise Ayearst[1], Ammepa Anton[1], Aifeng Lin[1] and Robert D. Inman[2]. [1]University Health Network, Toronto, ON, [2]University of Toronto and Toronto Western Hospital, Toronto, ON.

Background/Purpose: Ankylosing spondylitis (AS) is an inflammatory arthritis of the spine, which has a major impact on function and quality of life. AS is known to have a sex-bias with a M:F ratio of 3:1. In addition, females have a delayed onset and reduced radiographic severity compared to males. Genetic and immunologic studies have implicated the Th17-axis in AS pathogenesis, and recent clinical trials suggest efficacy of anti-IL-17A therapy. Prior studies have demonstrated a suppressive effect of vitamin D_3 on Th17 cells. In the present study we examine whether there is a sex-bias in the Th17-axis, and its possible relationship to vitamin D metabolism in AS.

Methods: Serum IL-6 and IL-17A were measured by ELISA and 25(OH) vitamin D_3 by mass-spectrometry in a cohort of 39 male AS patients, 36 female AS patients and 34 age- and sex-matched healthy controls. Whole blood gene expression for vitamin D_3-associated and Th17-associated genes was measured by RT-PCR. Th17 cells were measured by flow cytometry of peripheral blood mononuclear cells (PBMC) in a second, overlapping cohort of 14 female AS patients, 24 male AS patients and 30 age- and sex-matched healthy controls. Data was analyzed by Mann-Whitney tests and correlations with Spearman tests.

Results: AS patients had an elevated Th17-axis when compared to healthy controls as demonstrated elevated IL-6 ($p<0.01$), IL-17A ($p=0.06$) and Th17 cell levels ($p<0.05$). When stratified for sex, the elevated Th17-axis was restricted to male patients, as exemplified by higher Th17 cell levels in male AS *vs* female AS (Figure 1). A trend was seen for lower serum 25(OH) vitamin D_3 in male AS patients and healthy controls relative to their respective female counterparts. Gene expression of *VDR* and *CYP27B1* (vitamin D_3 activating enzyme) were equivalent in male and female AS patients, whereas *CYP24A1* (vitamin D_3 degrading enzyme) expression was significantly elevated in male AS patients. This was not seen in male *vs* female healthy controls. In male AS patients, serum 25(OH) vitamin D_3 was inversely proportional to whole blood *IL23R* expression ($r=-0.43$, $p<0.05$) and Th17 cell level ($r=-0.014$, $p=0.085$).

Conclusion: This is the first demonstration that elevated levels of Th17 cells in AS are restricted to male patients, which could inform targeted therapy with anti-IL17 agents. This may be due to a sex-related alteration in the biochemistry of vitamin D_3 which functions as an important inhibitory factor to the Th17 axis. This work demonstrates a biological basis for the observed sex-bias in incidence and in disease expression in AS.

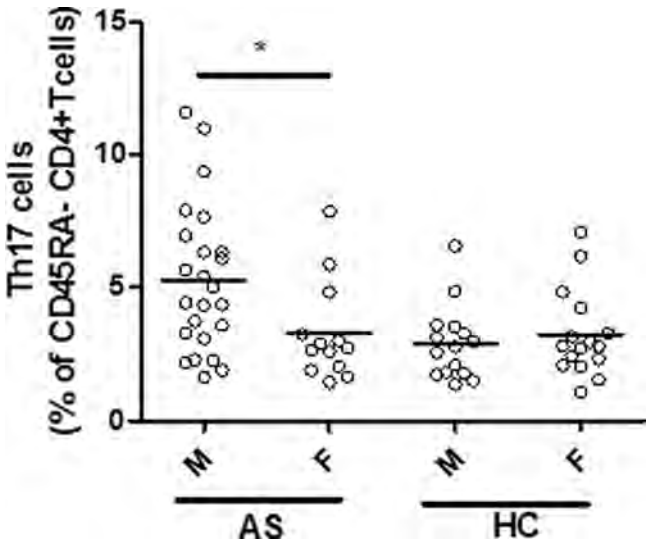

Figure 1: Male AS patients have higher circulating Th17 levels than female AS patients and healthy controls (HC). Results displayed as scatter plot with mean and analyzed by Mann-Whitney test.

Disclosure: E. Gracey, None; **B. Green**, None; **P. Yip**, None; **R. Ayearst**, None; **A. Anton**, None; **A. Lin**, None; **R. D. Inman**, None.

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The HLA-B27 Peptidome in Vivo in Transgenic Rats. Joel D. Taurog[1], Yael Haimovich[2], Eilon Barnea[2], Michal Bassani-Sternberg[2], Shira Yair-Sabag[2], Martha L. Dorris[1], Nimman Satumtira[1], Mylinh Nguyen[1], Robert E. Hammer[1], Tri M. Tran[3], Robert A. Colbert[3] and Arie Admon[2]. [1]UT Southwestern Medical Center, Dallas, TX, [2]Technion-Israel Institute of Technology, Haifa, Israel, [3]NIAMS/NIH, Bethesda, MD.

Background/Purpose. In all current hypotheses for the association of B27 with SpA, the B27 peptide repertoire (peptidome) is likely to play a key role. ERAP1 directly influences the MHC-I peptide repertoire and has strong genetic association with AS. The B27 peptidome has previously been reported only in cell lines. We used mass spectrometry to characterize the in vivo B27 peptidome in spleen cells from rats transgenic (TG) for B27 and human beta-2-microglobulin (hb2m).

Methods. B27 TG rats that develop SpA (males only), the protective Dazl-knockdown (kd) transgene, and rats TG for a B27 C67S mutant have been described (A&R 54,1317, 2006; 64:2518, 2012). ERAP1 knockout (ko) rats were produced by microinjection of LEW rat zygotes with a zinc finger nuclease targeting ERAP1. In ERAP1-ko spleen, absence of ERAP1 protein was confirmed by immunoblotting, and ERAP1 mRNA abundance was 18±3% of wild type. One B27/hb2m/ERAP1-ko male was available for peptide analysis. Frozen spleens were solubilized with 1% octyl-glucoside, B27 molecules were immunoaffinity-purified, and peptides were dissociated in 0.1% TFA and isolated by capillary reverse–phase chromatography. Peptides were analyzed by Orbitrap tandem mass spectrometry and data analyzed for peptide identities and relative intensities by MaxQuant, Sequest and Mascot software.

Results. A total of 20,096 unique peptides fitting the B27 peptide motif were identified, of which 10,587 were shared by all genotypes. The data are summarized in the table. The C67S mutant rats showed fewer B27-motif peptides and had a higher proportion of unique peptides, compared with the groups with wild type B27. The Dazl-kd rats, which have no disease manifestations, carried fewer unique peptides than the other groups.

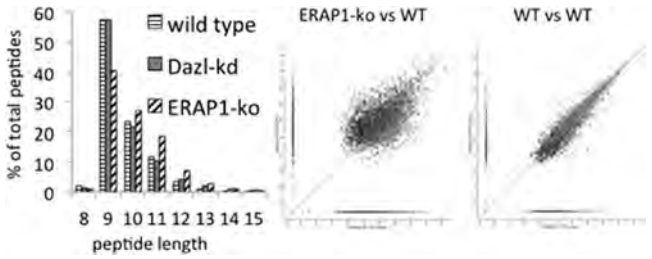
B27-bound peptides isolated from male rat spleens

Group (all B27/hb2m TG)	Age (d)	Phenotype	No. spleens	No. B27 motif peptides	No. group specific peptides
Wild type B27, Dazl, ERAP1	72–109	EO	4	9,808	1,238
	223–236	EO, SpA	4	10,029	
Dazl-knockdown	72–109	healthy	4	9,911	360
	223–236	healthy	4	9,994	
B27 C67S mutant	163–218	EO	12	7,610	1,896
ERAP1 knockout	57	*	1	9,808	781

EO = epididymo-orchitis; *phenotype not yet known

The peptidome from the ERAP1 ko rat was skewed toward longer peptides, compared with the young wild type and Dazl-kd rats (Figure).

Conclusion. HLA-B27 in TG rat spleen carries large numbers of peptides conforming to the B27 peptide motif identified in human cell lines. Rats with disease show more unique B27-bound peptides than healthy rats, suggesting that disease itself alters the B27 peptidome. Whether either specific peptides or the peptidome as a whole play a role is disease initiation is not yet clear, but the data are consistent with alterations in the peptidome playing a role in disease perpetuation. ERAP1 deletion leads to binding of longer peptides, and the effect of the deletion on disease should be known soon.



Disclosure: J. D. Taurog, None; **Y. Haimovich**, None; **E. Barnea**, None; **M. Bassani-Sternberg**, None; **S. Yair-Sabag**, None; **M. L. Dorris**, None; **N. Satumtira**, None; **M. Nguyen**, None; **R. E. Hammer**, None; **T. M. Tran**, None; **R. A. Colbert**, None; **A. Admon**, None.

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Identification of Novel Autoantibodies in Patients with Ankylosing Spondylitis Using Human Protein Microarray. Matthew Presby[1], Mark J. Soloski[1], John A. Flynn[1], Clifton O. Bingham III[1], Michael M. Ward[2] and Grant H. Louie[1]. [1]Johns Hopkins University, Baltimore, MD, [2]NIAMS/NIH, Bethesda, MD.

Background/Purpose: Ankylosing spondylitis (AS) is an immune-mediated disease for which the search for autoantibodies has been elusive. Conventional immunoserological approaches are slow and limited to the analysis of several dozen proteins at a time. In this pilot study, we used large-scale, high-throughput, protein microarrays to identify potential autoantibodies in AS.

Methods: Sera from patients who fulfilled the 1984 modified New York criteria for AS (N=20) were profiled using a human protein array composed of ~17,000 human proteins (CDI Laboratories, MD) and compared with healthy controls (N=18). Proteins were purified from *Saccharomyces cerevisae*, N-terminus tagged with GST-HisX6, spotted in duplicate on the array, imaged using a GenePix 4000B microarray scanner (Molecular Devices, CA), and analyzed using GenePix Pro software. Signal intensity, referred to as an A-score, was computed.

Results: AS patients were age (mean ± SD) 53.5 ± 12.1 years, 80% men, 100% HLA-B27 positive, with a disease duration (mean ± SD) of 28.6 ± 12.8 years. Healthy controls were age 55.7 ± 14.4 years and 50% men. Among 146 potential autoantigens detected in AS patients but not in healthy controls, we identified 6 with the highest frequency and signal intensity. These proteins were microtubule-associated serine/threonine-protein kinase 4 (MAST4), centriole, cilia and spindle-associated protein (CCSAP), SNF related kinase (SNFRK), calcium-binding protein 4 (CaBP4), protein MTG8 (MTG8), and eukaryotic elongation factor 2 kinase (EEF2K). The 3 most frequently targeted autoantigens were the serine/threonine kinases SNFRK, EEF2K, and MAST4. SNFRK and EEF2K were positive in 4/20 patients (20%). Three patients (15%) were positive for autoantibodies against MAST4. Two patients (10%) had antibodies to both MTG8 and CCSAP. The highest A-score observed was reactivity to CaBP4 by 1 patient (5%) (Figure 1). This was the lowest frequency autoantigen observed; however, CaBP4 reactivity was higher in the overall AS population compared to healthy controls. The images of each autoantigen were inspected and can be seen in Figure 2 for the patients with the five highest A-scores.

Conclusion: Using a high-throughput, protein microarray system, we have identified 6 novel autoantigens (SNFRK, EEF2K, MAST4, MTG8, CCSAP, and CaBP4) in AS patients, with an overall frequency of 5–20%. The detection of these AS-specific antibodies may allow for better understanding of disease pathogenesis and potential therapeutic targets. Further validation studies in larger numbers of patients are currently underway.

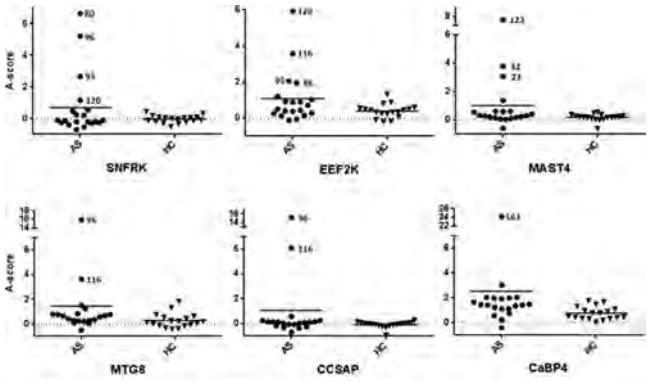

Figure 1. A-scores for 6 autoantigens targeted in AS

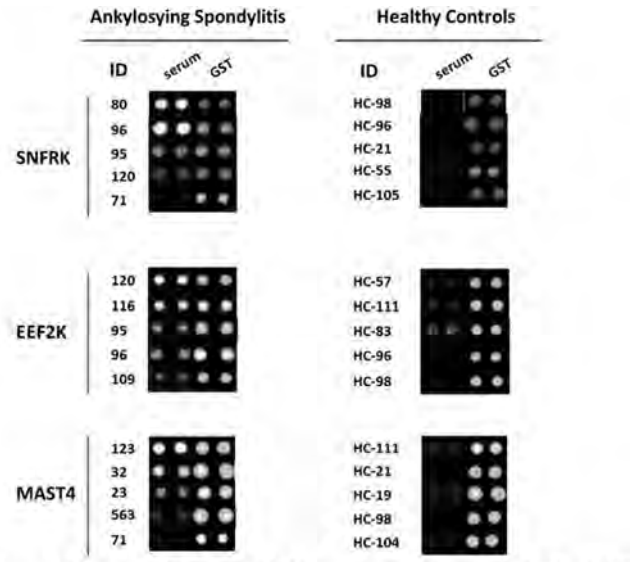

Figure 2. Serum reactivity to ser/thr kinases targeted by autoantibodies in AS

Disclosure: M. Presby, None; **M. J. Soloski**, None; **J. A. Flynn**, None; **C. O. Bingham III**, None; **M. M. Ward**, None; **G. H. Louie**, None.

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Induced Pluripotent Stem Cells (iPSCs) As a Tool for Unraveling the Role of Different Cell Types in the Disease Process of Spondyloarthritis Pathogenesis. Gerlinde Layh-Schmitt, Shjia Lu, Fatemeh Navid, Massimo Gadina and Robert A. Colbert. NIAMS/NIH, Bethesda, MD.

Background/Purpose: Many genetic factors and cell types contribute to the axial inflammation, trabecular bone loss, and aberrant bone formation that result in ankylosing spondylitis. The functional consequences of genetic variants may be manifest in specific cell types and in many cases affected cell types are not readily accessible for evaluation. In order to obtain these cell types we examined the feasibility of reprogramming fibroblasts from patients

with axial spondyloarthritis (AxSpA) into induced pluripotent stem cells (iPSCs) and subsequent re-differentiating iPSCs into various lineages.

Materials and Methods: Dermal fibroblasts from 7 AxSpA patients and 3 healthy controls (HC) were reprogrammed using a Sendai virus vector encoding Oct4, Sox2, Klf4 and Myc. One AxSpA and one HC fibroblast line were reprogrammed in two different labs to assess technical reproducibility. Virus-free iPSCs were differentiated into mesenchymal stem cells (MSCs) using a TGF-β inhibitor. MSCs were differentiated into osteoblasts, chondrocytes, and adipocytes; defined cytokine cocktails were used to differentiate iPSCs into monocytes. IPSC derived monocytes were treated with RANKL to induce osteoclastogenesis. IPSC gene expression patterns were established by RNAseq. Gene expression during MSC-osteoblast differentiation was monitored by Nanostring. Flow cytometry was conducted to evaluate the expression of iPSC, MSC and monocyte specific markers.

Results: All iPSC lines expressed pluripotency markers (OCT4, TRA-1, SSEA-4) and stem cell specific genes. IPSC derived MSCs proved positive for CD105, CD73, CD90 and CD44, but lacked CD45, CD34, CD11b, CD19, and HLA-DR. MSCs exhibited the capacity to induce differentiation of peripheral blood monocytes into osteoclasts in co-culture as demonstrated by tartrate resistant acid phosphatase staining. MSCs could be differentiated into mineralizing osteoblasts, as confirmed by expression of osteogenic genes and Alizarin-Red staining, into chondrocytes (proteoglycan staining with Alcian-Blue), and into adipocytes (lipid staining with Oil Red O). iPSC-derived monocytes/macrophages expressed HLA-DR, CD14, CD86, CD80 and CX3CR1 and CD45, and were capable of phagocytosing beads and differentiating into osteoclasts. Preliminary comparison of mineralization potential revealed that MSCs from AxSpA patients (n=3) exhibited 3-fold higher mineralization than the HC as determined by Alizarin Red staining. Independently-derived iPSC lines behaved similarly.

Conclusion: We have successfully derived iPSCs from AxSpA patient fibroblasts. The iPSCs can be differentiated into functional MSCs capable of differentiating into mature osteoblasts, chondrocytes, and adipocytes, as well as inducing monocytes to become osteoclasts. We have also successfully generated hematopoietic cells that can differentiate into monocytes, macrophages and osteoclasts. Notably, MSCs from AxSpA patients demonstrated greater mineralization capacity. This was observed repeatedly in independently iPSC derived MSCs from the same patient. These cells may provide a powerful system to examine the molecular functional consequences of genetic differences that predispose to SpA.

Disclosure: G. Layh-Schmitt, None; **S. Lu**, None; **F. Navid**, None; **M. Gadina**, None; **R. A. Colbert**, None.

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Functional Implications of the Endoplasmic Reticulum Aminopeptidase 2 (ERAP2) Association with Ankylosing Spondylitis and Crohn's Disease: Impact on the Unfolded Protein Response. Zhenbo Zhang[1], Francesco Ciccia[2], Kirby Yee[3], Giuliana Guggino[2], Hasan Abdullah[4], Ricardo Alessandro[5], Stefania Raimondo[5], Giovanni Triolo[5] and Nigil Haroon[1]. [1]Toronto Western Research Institute, Toronto, ON, [2]Rheumatology Unit, University of Palermo, Palermo, Italy, [3]McMaster University, Hamilton, ON, [4]University of Toronto, Toronto, ON, [5]University of Palermo, Palermo, Italy.

Background/Purpose: Endoplasmic Reticulum Aminopeptidase 2 (*ERAP2*) has found to be associated with AS and Crohn's Disease (CD). The functional implications of this association have not been explained to date. We tested levels of HLA-B27 and MHC-I Free Heavy Chain (FHC) in AS patients with the ERAP2 null allele. We further tested if ERAP2 suppression in an *in vitro* system results in changes in B27 misfolding and UPR.

Methods: A total of 40 B27-positive AS patients were typed for the rs2248374 polymorphism. Peripheral Blood Mononuclear Cells (PBMC) were isolated and stained with antibodies to CD19 (B cells) and CD14 (Monocytes). Staining with HC10 antibodies to assess MHC-I FHC expression and ME-1 antibody for intact HLA-B27 was performed. Mean Fluorescence Intensities (MFI) for FHC and B27 expression was assessed by flow cytometry.

C1R-B27, a human B lymphoblastoid cell line stably transfected with HLA-B27, were treated with 2 separate shRNAs to suppress endogenous ERAP2. Changes in UPR were assessed by PCR for BiP, CHOP and PERK. Protein expression of CHOP was assessed by western blot and semi-quantitative XBP-1 splicing assay was done by PCR.

Results: AS patients with no ERAP2 expression (homozygous for the minor allele of rs2248374) had higher FHC expression on the surface of PBMCs (P=0.019). When corrected for ME1 expression there was significantly lower ratio of intact-B27:FHC ratio in PBMC as well as specifically on monocytes.

PCR showed more than 20-fold increase in CHOP levels with ERAP2 suppression and between 1.2–1.5 fold increase in BiP and PERK. CHOP protein levels increased more than 3 fold while XBP1s increased 20-fold.

Conclusion: This is the first study showing a functional relevance of the ERAP2 association with AS and Crohn's Disease. ERAP2 deficiency in AS patients are associated with higher MHC-I FHC expression on PBMCs. Suppression of ERAP2 in an *in vitro* system led to significant increase in UPR markers. Changes in ERAP2 expression could influence the pathogenesis of AS and CD.

Disclosure: Z. Zhang, None; **F. Ciccia**, None; **K. Yee**, None; **G. Guggino**, None; **H. Abdullah**, None; **R. Alessandro**, None; **S. Raimondo**, None; **G. Triolo**, None; **N. Haroon**, None.

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Autophagy and Unfolded Protein Response: A Fine Balance That Can Influence the Pathogenesis of Ankylosing Spondylitis and Inflammatory Bowel Disease. Nigil Haroon[1], Giuliana Guggino[2], Zhenbo Zhang[1], Kirby Yee[3], Hasan Abdullah[4], Ricardo Alessandro[5], Stefania Raimondo[5], Giovanni Triolo[5] and Francesco Ciccia[2]. [1]Toronto Western Research Institute, Toronto, ON, [2]Rheumatology Unit, University of Palermo, Palermo, Italy, [3]McMaster University, Hamilton, ON, [4]University of Toronto, Toronto, ON, [5]University of Palermo, Palermo, Italy.

Background/Purpose: We have shown an increase in the unfolded protein response (UPR) with decreased ERAP1 or ERAP2 function in an *in vitro*system. Similarly UPR has been demonstrated to correlate with onset of disease in the HLA-B27 rat model. UPR has been difficult to demonstrate in the gut of AS patients but autophagy is upregulated. ERAP2 is associated with both AS and inflammatory bowel disease (IBD). Here we explore the moderating effect of autophagy on UPR.

Methods: Lamina Propria Mononuclear cells (LPMC) were isolated from terminal ileal biopsies of 10 AS patients. Autophagy was suppressed with 2 agents anisomycin and 3-MA. In parallel an in vitro system was established with C1R-B27 cells (B-lymphoblastoid cells with stable HLA-B27 expression) and the presence of autophagy in these cells were established with electron microscopy as well as by transfecting these cells with LC3-RFP followed by confocal microscopy. Autophagy was suppressed in C1R-B27 cells using 3-MA.

In both LPMC and C1R B27 cells, suppression of autophagy was demonstrated by RT-PCR of appropriate markers. Changes in MHC-I free heavy chain (FHC) expression were tested by HC10 staining and flow cytometry. Changes in UPR following inhibition were tested by XBP1 splicing assay and RT-PCR for BiP, CHOP, PERK, GADD34 and PDIA6.

Results: Electron and confocal microscopy demonstrated autophagy in C1R-B27 cells. Autophagy was in a dynamic state in the C1R cells as demonstrated by changes with rapamycin a stimulator of autophagy. Significant suppression of autophagy was noted in both LPMCs and C1R-B27 cells. Following autophagy suppression there was a significant increase in FHC expression in both C1R cells and LPMCs. In parallel we demonstrated increase in UPR markers in both LPMCs and C1R cells.

Conclusion: The inability to demonstrate UPR in some in vivo studies could be due to compensation by autophagy. Inhibition of autophagy led to significant increase in UPR in both LPMC and C1R cells. Autophagy and UPR regulate each other and perturbations of this fine balance can influence the pathogenesis of AS and IBD.

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Association of Platelet Endothelial Cell Adhesion Molecule-1 and beta1 Integrin Gene Polymorphisms with Uveitis Development in Ankylosing Spondylitis. Seong-Wook Kang[1], Seung-Taek Song[1], Su-Jin Yoo[1], Mi-Kyoung Lim[2], Dong-Hyuk Sheen[2], In-Seol Yoo[1], Jinhyun Kim[1] and Seung-Cheol Shim[1]. [1]Chungnam National University School of Medicine, Daejeon, South Korea, [2]Eulji University Hospital, Daejeon, South Korea.

Background/Purpose: Genetic factors provide over 90% of the overall susceptibility to ankylosing spondylitis (AS) and recent studies have focused on non-major histocompatibility complex genes. The etiology of uveitis in AS has been suggested to involve two adhesion molecules including intercellular adhesion molecule (ICAM)-1 and leukocyte functional antigen (LFA)-1.

Platelet-endothelial cell adhesion molecule 1 (PECAM1) is a member of the immunoglobulin superfamily which is expressed on endothelial cells. There is emerging evidence to suggest that PECAM1 may be an important regulator of antigen induced cell activation of lymphocytes. The β1 integrin (ITGB1) can associate with different membrane proteins and cause signal transduction by interactions in the extracellular and trans-membrane domain. Therefore, we examined the association of PECAM1 and ITGB1 gene polymorphisms with development of uveitis in patients with AS.

Methods: We conducted a case–control study where 223 AS patients who met the Modified New York criteria and 239 ethnically matched controls were genotyped for 9 single nucleotide polymorphisms (SNPs) in the PECAM-1 promoter and gene. Genomic DNA was isolated from peripheral blood leukocytes by a standard phenol–chloroform method and a Golden Gate assay (Illumina, http://www.illumina.com) was used for genotyping.

Results: Conditional logistic regression was used to evaluate the association between the PECAM1 or ITGB1 SNPs with susceptibility to AS, and no significant association was found on both genes. However, in the subgroup analyses between AS patients with uveitis and those without, seven SNPs in PECAM1 gene were associated with the presence of uveitis, including rs1050382 (dominant model (DM), p=0.022), rs2812 (recessive model (RM), p=0.013), rs4968721 (DM, p=0.016), rs6808 (DM, p=0.011), rs6809 (DM, p=0.013), rs9899806 (DM, p=0.013) and rs9913080 (DM, p=0.019). In addition, seven polymorphisms in ITGB1 gene including rs11009147 (DM, p=0.012; co-dominant model (CDM), p=0.034), rs17468 (DM, p=0.012; CDM, p= 0.019), rs2153875 (CDM, p= 0.030), rs2230396 (DM, p=0.012; CDM, p=0.034), rs2488330 (DM, p=0.004; CDM, p=0.017), rs3780871 (DM, p=0.031) and rs7079624 (RM, p=0.004; CDM, p=0.017) were associated with uveitis development.

Conclusion: This is the first analysis of the PECAM1 and ITGB1 gene polymorphisms in AS, demonstrating a clear association with uveitis in AS. Given the functional role of PECAM-1 and ITGB1 variants in the immune system, larger studies are now warranted to elucidate the association of PECAM-1 and ITGB1 in the pathogenesis of uveitis in AS.

Table 1. Logistic analysis of PECAM1 polymorphisms and the risk of uveitis among AS patients

	Dominant Model		Recessive Model		Co-dominant Model	
rs No.	Odds (95% CI	P.Value (adj.P.)	Odds (95% CI)	P.Value (adj.P.)	Odds (95% CI)	P.Value (adj.P.)
rs1050382	2.170 (1.116–4.219)	0.022 (0.027)	0.456 (0.129–1.611)	0.223 (0.262)	1.314 (0.824–2.095)	0.250 (0.294)
rs11079538	1.623 (0.745–3.537)	0.222 (0.261)	1.289 (0.568–2.924)	0.543 (0.571)	1.345 (0.821–2.202)	0.238 (0.297)
rs2812	2.190 (0.620–7.736)	0.223 (0.247)	0.424 (0.215–0.837)	0.013 (0.024)	0.732 (0.457–1.173)	0.195 (0.300)
rs4968721	2.302 (1.167–4.541)	0.016 (0.022)	0.412 (0.117–1.446)	0.166 (0.237)	1.304 (0.820–2.075)	0.261 (0.290)
rs6808	2.406 (1.220–4.743)	0.011 (0.020)	0.456 (0.129–1.611)	0.223 (0.278)	1.379 (0.862–2.205)	0.178 (0.298)
rs6809	2.354 (1.193–4.641)	0.013 (0.020)	0.456 (0.129–1.611)	0.223 (0.297)	1.364 (0.852–2.184)	0.195 (0.279)
rs8065316	1.124 (0.490–2.578)	0.781 (0.822)	1.774 (0.908–3.468)	0.093 (0.155)	1.360 (0.848–2.180)	0.201 (0.268)
rs9899806	2.354 (1.193–4.641)	0.013 (0.022)	0.509 (0.143–1.813)	0.297 (0.330)	1.414 (0.876–2.283)	0.155 (0.282)
rs9913080	2.252 (1.141–4.443)	0.019 (0.025)	0.392 (0.112–1.373)	0.143 (0.220)	1.270 (0.800–2.016)	0.310 (0.326)

Table 2. Logistic analysis of ITGB1 polymorphisms and the risk of uveitis among AS patients

	Dominant Model		Recessive Model		Co-dominant Model	
rs number	Odds (95% CI)	P.Value (adj.P.)	Odds (95% CI)	P.Value (adj.P.)	Odds (95% CI)	P.Value (adj.P.)
rs11009147	0.436 (0.226–0.839)	0.012 (0.021)	0.712 (0.273–1.858)	0.488 (0.596)	0.582 (0.353–0.960)	0.034 (0.046)
rs1187078	0.873 (0.261–2.921)	0.826 (0.865)	0.919 (0.486–1.737)	0.796 (0.834)	0.926 (0.560–1.532)	0.767 (0.804)
rs17468	0.436 (0.226–0.839)	0.012 (0.019)	0.563 (0.249–1.272)	0.167 (0.245)	0.589 (0.377–0.918)	0.019 (0.030)
rs2153875	0.527 (0.249–1.117)	0.094 (0.122)	0.465 (0.202–1.071)	0.072 (0.113)	0.582 (0.356–0.949)	0.030 (0.044)
rs2230396	0.436 (0.226–0.839)	0.012 (0.020)	0.712 (0.273–1.858)	0.488 (0.565)	0.582 (0.353–0.960)	0.034 (0.044)
rs2298141	1.340 (0.702–2.559)	0.374 (0.457)	3.718 (1.126–12.28)	0.031 (0.052)	1.508 (0.906–2.511)	0.113 (0.131)
rs2488330	0.390 (0.203–0.748)	0.004 (0.008)	0.712 (0.273–1.858)	0.488 (0.631)	0.546 (0.330–0.901)	0.017 (0.032)
rs2503997	1.278 (0.659–2.477)	0.466 (0.540)	1.308 (0.586–2.920)	0.511 (0.562)	1.205 (0.778–1.865)	0.401 (0.441)
rs3780871	0.268 (0.081–0.888)	0.031 (0.042)	0.745 (0.390–1.424)	0.374 (0.514)	0.662 (0.398–1.103)	0.113 (0.139)
rs7079624	1.403 (0.538–3.662)	0.488 (0.536)	2.560 (1.335–4.909)	0.004 (0.008)	1.830 (1.109–3.021)	0.017 (0.030)

Disclosure: S. W. Kang, None; **S. T. Song**, None; **S. J. Yoo**, None; **M. K. Lim**, None; **D. H. Sheen**, None; **I. S. Yoo**, None; **J. Kim**, None; **S. C. Shim**, None.

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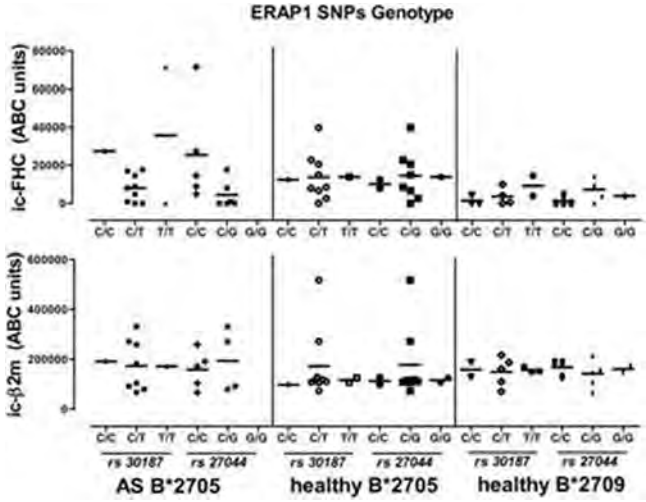
The Amount of Free Heavy Chain and β2-Microglobulin in the Cytoplasm of B*2705 Ankylosing Spondylitis Patients Compared to B*2705 and B*2709 Healthy Subjects Does Not Support the UPR Theory. Influence of ERAP1 Polymorphisms. Alberto Cauli, Grazia Dessole, Giovanni Porru, Matteo Piga, Alessandra Vacca and Alessandro Mathieu. Unit and Chair of Rheumatology, University Hospital of Cagliari, Cagliari, Italy.

Background/Purpose: Ankylosing Spondylitis (AS) is a chronic inflammatory disease of the spine strongly associated with the majority of HLA-B27 alleles, with the exception of B*2709 and B*2706. Genome wide association studies (GWAS) have revealed that besides HLA-B27, other genes are involved in AS pathogenesis, such as ERAP1, an ER aminopeptidase that is implicated in peptide trimming thus influencing B27-peptide-β2microglobulin (β2m) complex stability. Several theories have been proposed to explain the B27 association with AS. Among them, the unfolded protein response (UPR) theory suggests that the tendency of B27 trimeric complex to misfold determines free heavy chain (FHC) accumulation in the endoplasmic reticulum, leading to a stress response and activation of pro-inflammatory pathways.To our knowledge this is the first *ex vivo* study investigating the intracellular (ic) level of FHC and β2m in peripheral blood mononuclear cells (PBMC) and the possible influence of ERAP1 allelic variance in HLA-B27 positive AS patients and healthy subjects (HSs) bearing the AS-associated (B*2705) and the non-AS-associated (B*2709) allele.

Methods: The ic amount of FHC and β2m in CD14+ cells from *ex vivo* PBMC was evaluated in 12 HLA-B*2705 patients with AS, 12 HLA-B*2705 HSs and 12 HLA-B*2709 HSs by flow cytometry analysis. HC10 (gift of Dr. Chella David) and TU99 clone (BD Biosciences, USA) monoclonal antibodies were used to detect FHC and β2m, respectively, and quantified by comparison with standard beads (antibody binding capacity ABC units, Dako Denmark). Cells were fixed and permeabilized by the Intraprep Permeabilization technique (Beakman Coulter, USA) according to standard procedure. Patients and controls were also genotyped for two ERAP1 SNPs associated with AS (rs27044 C/G and rs30187 C/T). Optimized allelic discrimination assays were purchased from Applied Biosystem (Life Technologies, Italy). Values were expressed as mean ± standard deviation. Differences between AS patients and healthy subjects were analyzed by Mann-Whitney U test.

Results. FHC expression in AS patients was 37486 ± 30346 compared to B*2705 HSs 35673 ± 16723 and B*2709 HSs 26683 ± 10592 ABC units (p=ns). β2m quantity was also not significantly different in AS patients 174930 ± 90441 compared to B*2705 HSs 156471 ± 123855 and B*2709 HSs 153478 ± 42117 ABC units (p=ns). The majority of AS patients and HSs were heterozygous for both rs27044 (C/G) and rs30187 (C/T) SNPs; the intracellular amount of FHC and β2m in the PBMC of the analysed cohorts appeared not influenced by ERAP1 allelic distribution, as shown in the figure below:



Conclusion: This study shows equal amount of FHC and β2m in the cytoplasm of B*2705 AS patients compared to B*2705 and B*2709 healthy controls, regardless of ERAP1 allelic variance. These data, therefore, do not provide support to the UPR theory in the pathogenesis of AS.

Disclosure: A. Cauli, None; **G. Dessole**, None; **G. Porru**, None; **M. Piga**, None; **A. Vacca**, None; **A. Mathieu**, None.

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The Association of PPM1A with Inflammasome Activation in Ankylosing Spondylitis. Soo Min Ahn, Seung-Hyeon Bae, Seokchan Hong, Eun-Ju Lee, Eun-Jin Lee, Eun-Ju Chang, Doo-Ho Lim, Yong-Gil Kim, Chang-Keun Lee and Bin Yoo. University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea.

The Association of PPM1A with Inflammasome Activation in Ankylosing Spondylitis

Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory disorder usually affecting axial skeleton and joints. The pathogenesis and mechanism of inflammatory response in AS, however, remains not fully under-

stood. Recently, it has been suggested that AS could be associated with autoinflammatory responses, which are driven by innate immunity through inflammasome activation. We have reported that immunity to protein phosphatase magnesium-dependent 1A (PPM1A), which regulate BMP and Wnt signaling, are associated with AS. In this study, we try to investigate the association of PPM1A with inflammatory response in AS and its role in the inflammasome activation.

Methods: The concentration of PPM1A was measured in the plasma from AS, rheumatoid arthritis (RA) and healthy control (HC) subjects by enzyme-linked immunosorbent assay (ELISA), and addressed the association with inflammatory burden including disease activity in AS patients. Next, the expression of intracellular PPM1A was evaluated in the synovia from patients with AS, RA and osteoarthritis and in peripheral blood mononuclear cells (PBMCs) from patients with AS, RA and HC. To know the role of PPM1A in the inflammasome activation, the production of IL-1β and expression of active caspase-1 were measured with or without PPM1A knockdown in the macrophage. The expression of PPM1A was evaluated after stimulation with various cytokines.

Results: The levels of PPM1A were significantly higher in the plasma of AS patients compared with RA or HC subjects. In addition, there was significant correlation between the levels of PPM1A in plasma and the values of BASDAI, ESR and CRP in AS patients (Figure 1). The expression of PPM1A in the synovia and PBMCs were elevated in AS. Further, IL-1β secretion and activation of caspase-1 was significantly decreased by knockdown of PPM1A. Finally, the expression of PPM1A was enhanced by stimulation with TGF-β in the macrophage.

Conclusion: Our present study suggested that inflammasome activation could be regulated by intracellular PPM1A, which contribute to the pathogenesis of inflammatory responses in AS.

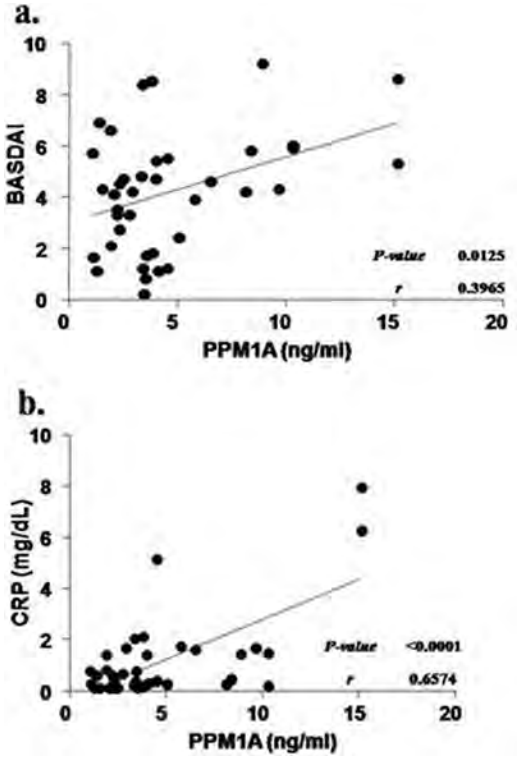

Figure 1. Correlation between BASDAI (a), CRP (b) and the levels of PPM1A in the plasma of patients with AS

Disclosure: S. M. Ahn, None; **S. H. Bae**, None; **S. Hong**, None; **E. J. Lee**, None; **E. J. Lee**, None; **E. J. Chang**, None; **D. H. Lim**, None; **Y. G. Kim**, None; **C. K. Lee**, None; **B. Yoo**, None.

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Analysis of the Gut Transcriptome in HLA-B27 Transgenic Rats By RNA-Seq Reveals Prominent Interferon and IL-23/IL-17 Axis Signatures. Tejpal Gill[1], Mark Asquith[2], Steve Brooks[1], James T. Rosenbaum[2] and Robert A. Colbert[1]. [1]NIAMS/NIH, Bethesda, MD, [2]OHSU, Portland, OR.

Background/Purpose: Expression of HLA-B27 and human beta 2-microglobulin (hb_2m) in rats induces a spontaneous inflammatory disease resembling human spondyloarthritis (SpA). SpA overlaps with IBD in genetic predisposition, pathogenic mechanisms and clinical manifestations. While key components of rat SpA have been studied in great detail, a complete understanding of the associated inflammatory bowel disease (IBD) has not been established. The goal of this project is to determine how HLA-B27 alters gut transcriptome in transgenic rats that develop SpA-like disease. HLA-B27 and hb_2m transgenic (TG) rats (33–3 transgene locus) on a Lewis (LEW), Fischer (F344), and Dark Agouti (DA) background from two different animal facilities are being studied along with strain-specific controls. TG LEW and F344 rats develop SpA beginning with colitis at about 8 weeks of age, while TG DA rats are disease free. Arthritis develops later in LEW and F344 TG animals, and is more variable.

Methods: To assess colitis, tissue samples from colon were assessed by H&E staining and scored for histological differences. Samples were also assessed for transcriptome differences using RNA-Seq. Total poly (A) enriched RNA was reverse transcribed into double stranded complementary DNA (dscDNA) and sequenced on Illumina HiSeq 2000. Raw reads were mapped to Rat rn5 genome using Tophat (2.0.8). Transcript expression levels in Reads per Kilobase Million (RPKM) and ANOVA comparisons were calculated using Partek GS (6.6/6.14.0514). A minimum fold change of 50% (p value $\leq$ 0.05% and q value $\leq$0.2) with Max Mean ≥ -3.3 was used as cutoff criteria for identifying differentially expressed genes between TG and WT animals on LEW, F344 and DA background at 2, 3 and 6 months. These genes were subjected to pathway exploration by Ingenuity Pathway Analysis (IPA) software.

Results: Inflammation in the colon was documented by histopathological analysis. Transcriptome analysis revealed that LEW and F344 TG animals exhibit up-regulation of the genes for IFN response (e.g. *Tap1, Tap2, Irf1, Cxcl10, Oas1 Gbp-2, Stat1*). The *Il17* pathway is highly up regulated at all age groups whereas *Il23* up regulation became statistically significant at 6 months of age. Apoptotic signaling and *iNos* (*Nos2*) pathways as well as the oxidative stress (*Gpx2, Nox1, Duox2*) pathway in colon were up-regulated as compared to their age matched WT controls. Susceptibility genes (*Card9, Nod2*) as well as IBD associated genes (*Tnf, Ltb, Reg3*γ*, Ccl2, Ccr7*) were up regulated in TG F344 and LEW animals. DA background had a protective affect since TG DA did not exhibit significant gene expression changes consistent with the fact that they do not develop either SpA or IBD.

Conclusion: Transcriptome analysis of the TG inflamed colon depicts upregulation of interferon and Il23/Il17 pathways suggesting a shift in the immune microenvironment in the colon. The interferon signature contrasts results recently obtained from isolated dendritic cells, and underscores the role of interferon in this disease process. These results increase our understanding of SpA associated IBD and may lead to the identification of potential biomarkers for use in diagnosis and treatment.

Disclosure: T. Gill, None; **M. Asquith**, None; **S. Brooks**, None; **J. T. Rosenbaum**, None; **R. A. Colbert**, None.

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In Situ Analysis of Mechanisms of New Bone Formation in Zygapophyseal Joints from Patients with Ankylosing Spondylitis. Janine Bleil[1], Joachim Sieper[2], Rene Maier[3], Uwe Schlichting[4], Axel Hempfing[5], Heiner Appel[6] and Uta Syrbe[7]. [1]Charité Medical University, Campus Benjamin Franklin, Berlin, Germany, [2]Charité Universitätsmedizin Berlin, Berlin, Germany, [3]Deutsches Rheumaforschungszentrum, Berlin, Germany, [4]Charite, Berlin, Germany, [5]Werner-Wicker-Klinik, Bad Wildungen, Germany, [6]Rheumatology and Nephrology Practice, Hamm, Germany, [7]Charité, Berlin, Germany.

Background/Purpose: Osteoproliferation leading to joint ankylosis is a characteristic feature of ankylosing spondylitis (AS). In general, there are two ways of bone formation: a) endochondral bone formation via generation of collagen X scaffolds requiring hypertrophic chondrocytes and b) membraneous or direct bone formation mediated by osteoblasts without primary cartilage synthesis.

Using zygapophyseal joints of AS patients (and zygapophyseal joints from autopsy controls and from OA patients for comparison), we determined whether chondrocytes acquire signs of chondrocyte hypertrophy upon joint remodeling or whether direct ossification by osteoblasts could be involved in the process of new bone formation in AS.

Methods: 17 zygapophyseal, i.e. facet joints from 14 patients with AS fulfilling the modified New York Criteria, 22 zygapophyseal joints from 12

patients with OA and 11 zygapophyseal joints of 10 non-AS control patients were included in the study.

The percentage of hypertrophic chondrocytes was determined by immunohistochemistry according to Runx2, MMP13 and collagen X expression in the cartilage of zygapophyseal joints. Activation of the wingless (wnt) pathway controlling chondrocyte hypertrophy was analyzed according to beta-catenin expression. Osteoblasts were identified according to CD56 staining.

Results: The percentage of hypertrophic chondrocytes expressing Runx2, COL10 and MMP13 was significantly increased in OA (mean ± SEM: Runx2 = 55.03 ± 11.83%, COL10 = 8.79 ± 8.88%, MMP13 = 14.55 ± 8.77%) but not in AS joints (Runx2 = 38.49 ± 22.84%, COL10 = 2.71 ± 3.05%, MMP13 = 1.80 ± 2.53%) compared to CO joints (Runx2 = 33.06 ± 17.27%, COL10 = 4.87 ± 4.66%, MMP13 = 1.43 ± 0.87%). Beta-catenin expression was low in AS (0.54 ± 0.84%) and CO zygapophyseal joints (1.83 ± 2.85% of chondrocytes) while in OA joints the number of beta-catenin positive chondrocytes was significantly increased (18.84 ± 18.31%).

Osteoblasts were observed at their typical location, i.e. within the bone marrow, lining the trabecular bone. However, CD56-positive cells were also found at the edges of fibrous tissue which is often observed at subchondral bone marrow sites in AS and OA joints and which invades the subchondral bone. Runx-2 and weak osteocalcin expression of these lining cells further supports their osteoblastic nature. Ossification of cartilage was predominantly found at contact zones between the fibrous tissue and the cartilage in AS joints; i.e. in 71% of AS joints and 27% of OA joints with fibrous tissue-cartilage contacts.

Conclusion: The lack of chondrocyte hypertrophy as an indicator of endochondral bone formation but co-localization of osteoblasts with fibrous tissue and bony transformation at contact zones to cartilage in AS joints suggest that direct ossification is involved in joints ankylosis in AS.

Disclosure: J. Bleil, None; **J. Sieper**, None; **R. Maier**, None; **U. Schlichting**, None; **A. Hempfing**, None; **H. Appel**, None; **U. Syrbe**, None.

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Shared HLA Class I and II Alleles in Susceptibility to Ankylosing Spondylitis Among Three Ethnic Groups. Mark Hwang[1], Xiaodong Zhou[1], Michael H. Weisman[2], Michael M. Ward[3], Jiucun Wang[4], Lianne S. Gensler[5], Hejian Zou[4], Dongyi He[6], Matthew A. Brown[7], Paul Scheet[8] and John D. Reveille[1]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]Cedars-Sinai Medical Center, Los Angeles, CA, [3]NIAMS/NIH, Bethesda, MD, [4]Huashan Hospital, Shanghai, China, [5]University of California, San Francisco, San Francisco, CA, [6]Shanghai Guanghua Hospital, Shanghai, China, [7]University of Queensland Diamantina Institute, Brisbane, Australia, [8]MD Anderson Cancer Center, Houston, TX.

Background/Purpose: The purpose of this study is to examine associations of HLA class I and class II alleles with AS in different patients populations of whites of European ancestry (EA) and African-American (AA) ethnicities, as well as HLA-B locus associations in Han Chinese (HC).

Methods: HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1 alleles were examined by DNA typing in unrelated patients from the Prospective Study of Outcomes in Ankylosing Spondylitis cohort, the North American Spondylitis Consortium and Australo-Anglo-American Spondyloarthritis Consortium. For the HLA-B locus analyses, an additional 578 British and Australian AS patients from the Australo-Anglo-American Spondylitis Consortium and 360 HC AS patients were also analyzed. Included therefore in the study were 1829 EA, 62 AA patients and 360 HC who met modified New York criteria for AS. Controls were North American white and African American as well as Han Chinese subjects without history of rheumatic disease. To remove an associated effect of HLA-B*27 due to linkage disequilibrium, analyses were also conducted on HLA-B*27 non-carriers only. Statistical analysis was done by construction of 2x2 tables and testing the proportion of alleles in cases vs. controls with Fisher's exact test. Other analyses included permutation-based omnibus testing and "relative predispositional effects" (RPE) analysis.

Results: HLA-B27 occurred in 88.7% of EA, 61% of AA, and 93% of HC patients compared to 7.5%, 2% and 7.6%, respectively, of ethnicity matched controls. HLA-B*07 was negatively associated with AS in all three ethnic groups (6.2 % versus 14.9% in EA, p $3.655 \times 10^{-26,}$ 3.2% versus 14% in AA(p=0.02), and 1% versus 12% in HC (p=0.0018). Among EA AS patients, HLA-B27 noncarriers showed positive associations with HLA-B*38 (OR=2.94, p =0.0008) and DRB1*04:04 (OR= 3.02 p = 0.0065) and negative associations with HLA-B*07 and HLA-DRB1*03, HLA-DRB1*15:01 and their respective linked alleles DQB1*02:01 and DQB1*06. Additional associations with HLA-B*14(OR = 1.74, p < 0.001) and HLA-B*40 (OR = 1.32, p = 0.02) were observed via RPE analysis, which excludes the HLA-B*27 alleles. No associations were seen with HLA-DPB1 alleles or with HLA-A*02 (the latter seen in a much larger study where HLA alleles were imputed but not directly genotyped). Among AA patients, positive associations were seen in HLA-B*27 (OR = 75.11, p <0.0001), HLA-B*40 (OR = 8.33, p = 0.01) and HLA-DRB1*13:02 (OR = 2.43, p = 0.02). No statistically significant associations were seen in HLA-DQB1, HLA-DPB1 alleles. In the HC, no association was seen with B*40:01 (B60) although an association was seen by a covariate via logistic regression analysis (p=0.02, OR=2.3) and by RPE analysis (p=0.01, OR=1.56). Negative associations were also demonstrated with HLA-B*13, B*15, B*46 and B*51.

Conclusion: This is the largest directly genotyped HLA study to date. These data, analyzing the largest number of AS patients in three patient populations examined to date, suggest other HLA alleles to be operative in AS predisposition in addition to HLA-B*27. The shared association of certain alleles in all three groups suggests a direct role in AS pathogenesis

Disclosure: M. Hwang, None; **X. Zhou**, None; **M. H. Weisman**, None; **M. M. Ward**, None; **J. Wang**, None; **L. S. Gensler**, UCB, 5, AbbVie, 5, Celgene Corporation, 9; **H. Zou**, None; **D. He**, None; **M. A. Brown**, None; **P. Scheet**, None; **J. D. Reveille**, None.

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A Gender Bias in Gut Microbiota of SKG Mice Colonized with a Limited Bacterial Consortium Associated with Severity of Spondyloarthritis and Ileitis Triggered By Beta-Glucan. Linda Rehaume, Olga Zbarskaya, Alicia Kang, Helen Benham, Paraic O Cuiv, Mark Morrison and Ranjeny Thomas. University of Queensland Diamantina Institute, Brisbane, Australia.

Background/Purpose: Beta-glucan (curdlan)-treated BALB/c ZAP-70^{W163C}(SKG) mutant mice develop IL-23-dependent spondyloarthritis, and curdlan promotes ileitis in SKG mice housed under specific pathogen-free (SPF) but not germ-free (GF) conditions. When GF SKG mice were recolonized with altered Schaedler flora, a limited bacterial consortium known as altered Shaedler microbiota (ASM), SKG mice developed spondyloarthritis and ileitis. Relative to SPF conditions, ASM-SKG mice developed spondyloarthritis and ileitis with reduced severity, and incidence of ileitis was reduced. Relative to female mice, disease severity in male SKG mice was reduced. Our aim was to study SKG mice recolonized with ASM to understand the mechanisms by which certain gut micro-organisms drive SpA-like disease, and their relationship to gender and the curdlan inflammatory trigger.

Methods: GF SKG mice were recolonized at the Walter and Eliza Hall Institute of Medical Research with ASM (*Eubacterium plexicaudatum*, *Lactobacillus murinus*, *Mucispirillum schaedleri*, 2 *Clostridium* sp., *Lactobacillus* sp., *Parabacteroides* sp., *Firmicutes* bacterium) then injected with curdlan or saline. Fecal samples were collected following recolonization and then serially after injection. The microbiota community profile was analyzed by real-time PCR. Arthritis, spondylitis and ileitis were assessed histologically in ASM-SKG mice or SPF SKG-DTR mice depleted or not of regulatory T cells (Treg).

Results: After colonization and before injection, four bacterial strains were detectable in male ASM-SKG mice (*Clostridium* sp, *Lactobacillus murinus*, *Mucispirillum schaedleri*, *Parabacteroides* sp.) with *Parabacteroides* the dominant species. In female ASM-SKG mice before curdlan, this same bacterial profile was observed except that the *Clostridium* species was not detected. After injection, the *Clostridium* species increased in female mice treated with curdlan but not saline-treated mice, and was maintained at similar levels in male mice. Depletion of Treg from curdlan-treated SKG mice under SPF conditions resulted in rapid and severe disease development.

Conclusion: Similar to non-obese diabetic mice, microbiota of ASM-SKG mice show a gender bias. Furthermore, these preliminary data suggest that the absence of a *Clostridium* species in naive female mice and outgrowth of the same species associated with curdlan-induced inflammation correlate with greater disease severity in females. *Clostridium* species derived from mouse and human microbiota have been shown to induce Treg in mouse colon. Together our data suggest a link between gender, microbial environment, mucosal Treg induction and propensity to disease severity, where either a lack of *Clostridium* species in SpA-prone mice or a lack of Treg in mice developing SpA promotes disease severity. Analysis by next generation sequencing methods will further explore gender and treatment differences in mouse gut microbiota associated with phenotype.

Disclosure: L. Rehaume, None; **O. Zbarskaya**, None; **A. Kang**, None; **H. Benham**, None; **P. O Cuiv**, None; **M. Morrison**, None; **R. Thomas**, None.

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Effect of ERAP1 Knockdown on Conformation of HLA-B27 and Other HLA Class I Molecules in Human Monocytic Cells. Tri M. Tran[1], Sohee Hong[1], Jehad H. Edwan[2] and Robert A. Colbert[1]. [1]NIAMS/NIH, Bethesda, MD, [2]NIAMS NIH, Bethesda, MD.

Background/Purpose: Polymorphisms in endoplasmic reticulum (ER) aminopeptidase 1 (ERAP1) are associated with ankylosing spondylitis, Behcet's disease, and psoriasis/psoriatic arthritis, where HLA class I alleles are also implicated in susceptibility. The mechanism by which ERAP1 influences disease is unknown, although ERAP1 trims peptides that are presented by HLA class I. To better define the functional interaction between ERAP1 and HLA-B27 we examined the effect of knocking down ERAP1 (ERAP1 KD) on the conformation of HLA-B27 in human monocytic U937 cells (U937.B27) that also express HLA-A3/31, HLA-B18/51, HLA-C1/7).

Methods: U937.B27 cells stably expressing shRNA for ERAP1 showed a 65% reduction in ERAP1 protein expression. The unfolded and folded forms of HLA class I molecules (including HLA-B27) were assessed by immunoprecipitation with antibodies HC10 and W6/32, respectively, followed by either isoelectric focusing to separate HLA class I heavy chains, or SDS-PAGE under non-reducing or reducing conditions, to assess disulfide-linked (misfolded) complexes of HLA-B27. HLA proteins were visualized by immunoblotting with 3B.10.7. Flow cytometry was employed to measure expression of folded forms of HLA-B27 (HLA.ABC.m3 or ME1), unfolded and folded forms of HLA class I (HC10 and W6/32, respectively), on the cell surface or after permeabilization (cell surface and intracellular). MARB4, which recognizes a subset of HLA-B27 containing longer peptides and also dimers was also used.

Results: The HLA-B27-transfected U937 cells express approximately equal amounts of HLA-B27 and B51 heavy chains, which is greater than the HLA-B18 allele. At steady state, ERAP1 KD resulted in 47% more folded HLA-B27 accumulating on the cell surface (HLA-ABC.m3) and 30% more in total (extra- plus intracellular), whereas there was only an 11% increase in total folded HLA class I (W6/32). When other alleles were examined by focusing, there was no increase in folded forms of HLA-B51 or B18. MARB4-reactive HLA-B27 was increased by 24% on the cell surface in ERAP1 KD cells. ERAP1 KD caused a 53% increase in unfolded HLA class I (B/C) on the cell surface, and led to a 39% increase in the accumulation of high molecular weigh disulfide-linked complexes of HLA-B27 (immunoblots) ($P < 0.05$ for all comparisons).

When cells were treated with IFNg, ERAP1 KD caused a 25% increase in total unfolded HLA-B27 compared to sc shRNA, but no increase in HLA-B51 or B18. High molecular weigh disulfide-linked complexes of HLA-B27 were also increased.

Conclusion: These data demonstrate that reduction of ERAP1 expression significantly increases both folded and unfolded/misfolded forms of HLA-B27. IFNg treatment further increased all forms of HLA-B27 when ERAP1 expression was limited. It is of interest that the effects of ERAP1 KD on HLA-B allele conformation were substantially greater for HLA-B27 than for Behcet's disease associated HLA- B51.

Disclosure: T. M. Tran, None; **S. Hong**, None; **J. H. Edwan**, None; **R. A. Colbert**, None.

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Innate Immune Stimulation Triggers Altered IL-1a/b Gene Expression and Experimental Spondyloarthritis in HLA-B27/huβ2m Transgenic Rats. Melissa N. van Tok[1], Leonie M. van Duivenvoorde[1], Nimman Satumtira[2], Martha L. Dorris[2], Joel D. Taurog[2] and Dominique L. Baeten[1]. [1]Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [2]UT Southwestern Medical Center, Dallas, TX.

Background/Purpose: Spondyloarthritis (SpA) does not display typical features of autoimmune diseases such as female predominance, presence of autoantibodies, or clinical response to T- and/or B cell targeting biologicals. Despite the strong association with MHC class I, CD8 T cells are not required for disease induction in the HLA-B27/huβ2m transgenic rat model. Moreover, the capability of HLA-B27 to misfold and thereby induce endoplasmatic reticulum stress and the direct recognition of HLA-B27 homodimers by NK cells suggest pathogenic mechanisms which may be independent of classical acquired immune responses. Therefore, we and others propose that SpA may be primarily driven by an innate immune response. Using the HLA-B27/huβ2m transgenic rat model,[1] we investigated this hypothesis by studying the effect of innate immune stimulation on ex vivo cytokine expression and in vivo development of arthritis and spondylitis.

Methods: Splenocytes and bone marrow cells isolated from HLA-B27/huβ2m tg rats and controls were stimulated for 6 hours with 50 ng/ml LPS, 5 μg/ml zymosan or 5 μg/ml heat-inactivated *Mycobacterium tuberculosis*. TNF, IL-1, IL-6, IL-10 and IL-23p19 expression was measured by qPCR. In vivo, six week old male and female HLA-B27/huβ2m tg were immunized with a low dose of *M. tuberculosis*in incomplete Freund's adjuvant. Rats were followed up for 60 days and scored clinically for arthritis and spondylitis. At day 60 hind limbs and tails were analysed for inflammation, destruction and new bone formation by histology.

Results: In vitro stimulation of splenocytes with zymosan and with *M. tuberculosis*, but not with LPS, strongly induced gene expression of pro-inflammatory cytokines such as TNF, IL-1a, IL-1b and IL-6 in all 3 groups of rats. IL-1a and IL-1b, but not TNF or IL-6, were increased in the HLA-B27/huβ2m transgenic cells as compared to both HLA-B7/huβ2m tg and wild-type controls upon ex vivo stimulation. IL-10 and IL23p19 expression could not be detected in any of the groups after stimulation. In vivo, non-immunized HLA-B27/huβ2m tg males spontaneously develop arthritis and spondylitis after 4–6 months of age with an incidence of 70% and 40%, respectively, whereas female rats do not develop disease. Immunization of male HLA-B27/huβ2m tg rats with 30 μg of *M. tuberculosis* was sufficient to induce arthritis and spondylitis within 2–3 weeks with an incidence of 80–100%. Moreover, HLA-B27/huβ2m tg females developed similar disease when immunized with 60 μg of *M. tuberculosis*. Control rats were less sensitive to low doses of *M. tuberculosis*. Histologically in both male and female HLA-B27/huβ2m tg rats inflammation, destruction and new bone formation was detected in both peripheral and axial joints.

Conclusion: The transgenic expression of HLA-B27/Hub2m increases the sensitivity to innate immune stimulation as evidenced by increased IL-1a and IL-1b expression ex vivo and development of arthritis and spondylitis in vivo. These data suggest that the B27/Hub2m expression lowers the threshold for innate immune activation of the IL-1 pathway, and this alone may be sufficient to trigger experimental SpA.

References:

1. Tran TM et. al. Arthritis Rheum 2006; 54(4):1317–27

Disclosure: M. N. van Tok, None; **L. M. van Duivenvoorde**, None; **N. Satumtira**, None; **M. L. Dorris**, None; **J. D. Taurog**, None; **D. L. Baeten**, None.

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ERAP1 Knockdown Affects HLA-B27 Misfolding and Endoplasmic Reticulum Stress in HLA-B27 Transgenic Rat Macrophages. Sohee Hong and Robert A. Colbert. NIAMS/NIH, Bethesda, MD.

Background/Purpose: Endoplasmic reticulum aminopeptidase 1 (ERAP1) is a multifunctional enzyme involved in the processing of peptide cargo for major histocompatibility complex (MHC) class I complexes, and can have significant effects on peptide repertoire, and cell surface expression and stability of MHC class I molecules. ERAP1 variants are associated several MHC class I-associated inflammatory diseases, such as ankylosing spondylitis (AS), Behcet's disease, and psoriasis/psoriatic arthritis, with evidence for epistasis with MHC class I susceptibility alleles. Since peptide supply is a critical determinant of MHC class I folding and assembly, we asked whether ERAP1 knockdown would affect HLA-B27 misfolding and endoplasmic reticulum (ER) stress in HLA-B27 transgenic (Tg) rats.

Methods: Bone marrow derived macrophages from HLA-B27 Tg, HLA-B7 Tg and wild type (WT) rats were transduced with lentiviral ERAP1 shRNA or scrambled shRNA as a control. Protein expression including folded, unfolded, and misfolded forms of HLA-B27 was evaluated using immunoblotting of whole cell lysates and immunoprecipitates. To evaluate the effects of cytokines, macrophages were treated without or with IFNg (100 ng/ml) or IFNg and TNFa (30 ng/ml) for 24–48 hr. ER stress was assessed using real time PCR and XBP-1 splicing.

Results: ERAP1 protein expression was reduced 55–77% by ERAP1 shRNA as measured by immunoblotting blotting in several experiments, before and after treatment with cytokines. ERAP1 knockdown led to

increased accumulation of aberrant disulfide-liked HLA-B27 complexes in whole cell lysates and HC10 immunoprecipitates. Interestingly, HLA-B7 heavy chains, which do not misfold under normal conditions, could be detected forming dimers with prolonged exposure in ERAP1 KD cells, although quantitatively much less than for HLA-B27. Expression of Bip and CHOP mRNA and XBP1 splicing were elevated in ERAP1 KD cells compared to sc shRNA. With cytokine stimulation, the there was increased UPR target gene expression and XBP1 splicing consistent with accumulation of aberrant HLA-B27 complexes.

Conclusion: In summary, these results suggest that ERAP1 loss-of-function impacts HLA-B27 misfolding and may affect the pathogenesis of AS via the aberrant biology of HLA-B27 and ER stress.

Disclosure: S. Hong, None; **R. A. Colbert**, None.

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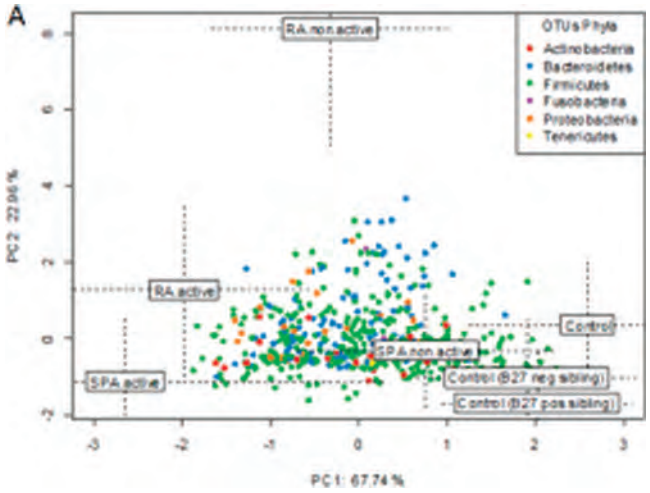
Gut Microbiota Variations Correlate with Disease Activity in Spondyloarthritis (SpA) and Rheumatoid Arthritis (RA). Julien Tap[1], Jad Abou-Ghantous[1], Ariane Leboime[2], Roula Said Nahal[2], Philippe Langella[1], Henri-Jean Garchon[3], Gilles Chiocchia[4], Jean-Pierre Furet[1] and Maxime Breban[2]. [1]UMR INRA-AgroParisTech 1319, Equipe ProbiHote, MICALIS Institute, National Institute for Agronomical research (INRA), Jouy-en-Josas, France, [2]Service de Rhumatologie, Hopital Ambroise Pare, Boulogne-Billancourt, France, [3]INSERM U987, Faculté des Sciences de la Santé Simone Veil, Montigny-le-Bretonneux, France, [4]INSERM U987, UFR des Sciences de la Santé, Montigny-le-Bretonneux, France.

Background/Purpose: Inflammatory bowel diseases (IBD) are associated with changes in microbiota which may be responsible for sustained gut inflammation and/or a consequence of it. Whether variations in microbiota also play a role during the course of inflammatory rheumatic disorders such as SpA or RA, remains to be addressed.

Methods: Targeted metagenomic profiles were established by deeply sequencing the 16S rRNA-encoding bacterial genes amplified by PCR in stools from 97 SpA and 33 RA patients, and 72 healthy controls (including 46 siblings of SpA patients). After pyrosequencing and a denoizing step to remove artefactual reads, bacterial operational taxonomic units (OTUs) were attributed to the remaining sequences (>1.5M reads, 8,000 sequences per sample in average). Supervised analysis (between class co-inertia analysis and L1-regularized logistic machine learning procedure) was carried out to identify factors associated with OTUs variations. Age, gender, disease status and activity (SpA: BASDAI; RA: DAS28) and concomitant treatments (NSAIDs, corticosteroids, DMARDs, biotherapies) were the considered variables.

Results: Neither SpA nor RA status correlated with discrete OTUs variations. Using 600 OTUs represented in at least 1% of the reads mass per sample, disease activity was the main clinical factor explaining variations in OTUs composition, similarly in SpA and RA. Concomitant treatments, and particularly corticosteroids, had also significant impact but of lesser magnitude.



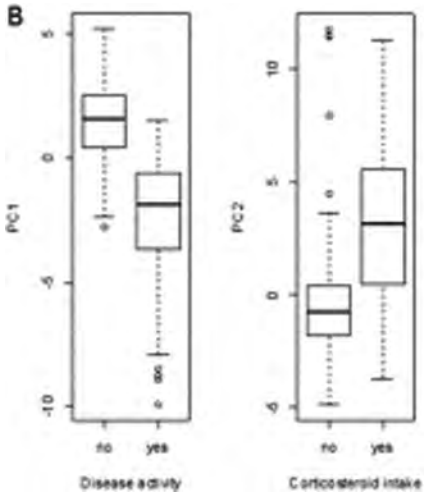


Figure 1: Supervised co-inertia analysis between clinical metadata and microbial OTUs variation as function of health status. A) Health statuses are plotted according the two main components. Monte Carlo test showed that health statuses were significantly linked with clinical metadata and microbiota OTUs variations (colored according their phylum assignation). B) Principal components allowed to significantly separate patients according to disease activity and corticosteroid intake.

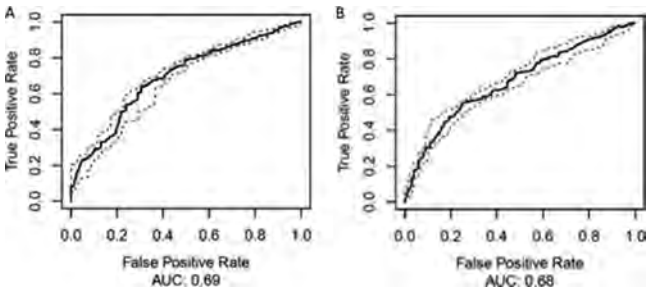


Figure 2: A. Complementary to this signal, SpA and RA could be distinguished from controls by combining 16 OTUs, yielding a statistically significant ROC curve (AUC = 0.69). B. The best model to predict disease activity included 110 OTUs and yielded a statistically significant ROC curve (AUC = 0.68).

Conclusion: Variations in OTUs were found both in SpA and RA, as compared to healthy controls that primarily correlated with disease activity. Whether such variations are cause or consequence of chronic joint inflammation remains to be determined.

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Epigenetic Studies in Maternally Versus Paternally Transmitted Psoriatic Disease. Darren D. O'Rielly[1], Remy Pollock[2], Yuhua Zhang[3], Nayef Al Ghanim[1], Sean Hamilton[1], Dafna D. Gladman[2], Vinod Chandran[2], Rose Ardern[1], Guangju Zhai[3] and Proton Rahman[1]. [1]Memorial University of Newfoundland, St. John's, NF, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, [3]Discipline of Genetics, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NF.

Background/Purpose: Epidemiological studies have noted excess paternal transmission in psoriasis and psoriatic arthritis. To date, there has been no molecular explanation to account for this observation. Differential methylation patterns have long been implicated as a potential mechanism to account for excess paternal transmission. In this pilot study, we investigated the differential methylation pattern among paternally and maternally transmitted PsA.

Methods: Twenty-four (24) patients with maternally transmitted PsA were compared with 24 paternally transmitted PsA cases. For maternally transmitted PsA, the proband's mother had either psoriasis or PsA, and for

paternally transmitted PsA, the proband's father had either psoriasis or PsA. Genome-wide DNA methylation profiling was performed on all these 48 samples by using Illumina HumanMethylation450k Beadchip, which measures up ~480,000 different CpG sites per sample and covers 96% of RefSeq genes. The methylation level at each CpG site was measured by β values varying from 0 (no methylation) to 1 (100% methylation).

Results: Maternally transmitted PsA cases were predominantly females (19/24) with mean age of onset of PsA at 30.6 years. For paternally transmitted PsA, there were slightly more females (13/24) and age of onset of PsA was 22.2 years. Methylation data were normalized using BMIQ method and no batch effects were detected by PCA analysis. Methylation analysis was performed on 382,024 of the 485,512 CpG sites after filtering and revealed 90 significant CpG sites ($p<0.05$). The three most significant CpG sites were hypermethylated regions located on chromosome 8 that did not reside on or adjacent to a gene, with p values ranging from $9x10^{-7}$ to $5x10^{-6}$. Many genes of interest based on current understanding of psoriatic disease were identified including hypermethylation of CPG sites on *MICA* (diff 10.22%; p=0.014), *IRIF1* (diff 10.3%; p=0.016), *PSORS1C3* (diff 11.1%; p=0.005); and *TNFS4* (diff 15.2%; 0.004). Excess hypomethylation at CPG sites was noted on *PSORS1C1* (18.9% diff. p=0.027).

Conclusion: These preliminary results demonstrate that the global DNA methylation pattern in paternally transmitted PsA differs from maternally transmitted PsA. High priority candidate regions and genes identified in this study need further validation.

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Genome-Wide Methylome Investigation Reveals New Candidate Genes Associated with Arthritis Mutilans. Vinod Chandran[1], Darren O'Reilly[2], Amir Haddad[1], Yuhua Zhang[3], Guangju Zhai[3], Dianne Codner[2], Arane Thavaneswaran[1], Proton Rahman[2] and Dafna D. Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]Memorial University of Newfoundland, St. John's, NF, [3]Discipline of Genetics, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NF.

Background/Purpose: Arthritis mutilans is a severe form of psoriatic arthritis (PsA). Why some patients develop this rapidly progressive destructive disease remains unclear. We hypothesized that the epigenetic signature may be different between PsA patients with and without arthritis mutilans. The aim of this study was to investigate DNA methylation in PsA patients with and without arthritis mutilans.

Methods: Arthritis mutilans was defined using the modified Steinbrocker scoring (mSS) method which classifies each of a total of 42 joints on a 0–4 scale where grade 0=normal, 1= juxta-articular osteopenia or soft tissue swelling, 2=erosion, 3=erosion and joint space narrowing and 4=total destruction (severe osteolysis, subluxation, ankylosis, pencil-in-cup change). Patients with at least 1 joint with grade 4 damage were classified as having arthritis mutilans and those with no damage following similar duration of follow up were classified as PsA patients without mutilans. All patients were Caucasians of Northern European Ancestry. Genome-wide DNA methylation profiling was performed on the blood DNA samples from 24 PsA patients with mutilans and 24 patients without arthritis mutilans. The methylation profiling was performed using Illumina HumanMethylation450k Beadchips, which measures up ~480,000 different CpG sites per sample and covers 96% of RefSeq genes. The methylation level at each CpG site was measured by β values varying from 0 (no methylation) to 1 (100% methylation).

Results: PsA patients with arthritis mutilans (50% males) had mean of disease onset at age 31.8 (10.7) years and age at time of assessment was 42.8 (11.4) years Meanwhile, PsA patients with no evidence of arthritis mutilans (50% males) had mean of disease onset at age 32.7 (16.1) years and age at time of assessment was 41.8 (15.1) years. Methylation data were normalized using BMIQ method and no batch effects were detected by PCA analysis. Methylation analysis was performed on 332,530 autosomal CpG sites after applying quality control filtering. Two outliers were identified and excluded in the subsequent analysis. Methylation profiling analysis revealed 37 CpG locations where there was at least 10% difference in β values between patients with and without arthritis mutilans. The three locations that differentiated the most after correction for multiple testing included CpG sites in *WNT3A* (hypermethylated; $p=3.74x10^{-5}$); *NRXN2* (hypomethylated; $p=6.02x10^{-5}$) and an agenic region (hypomethylated; $p=4.53x10^{-5}$). Based on functional relevance to PsA pathology, particularly antigen presentation, cytokine signalling, and bone remodeling, 5 candidate genes (2 hypomethylated; 3 hypermethylated) emerged: *PELI2* (β diff=−0.1249; p=0.001), *SEEK1* (β diff=0.1834; p=0.002), *COL11A1* (β diff=0.1085; p=0.006), *ADAMTS1* (β diff=−0.1030; p=0.005), and *WNT3A* (β diff=0.0752; $3.74x10^{-5}$).

Conclusion: These preliminary results demonstrate that the DNA methylation signature in PsA patients with arthritis mutilans is distinct compared with PsA patients without mutilans. High priority candidate genes identified in this study warrants further validation.

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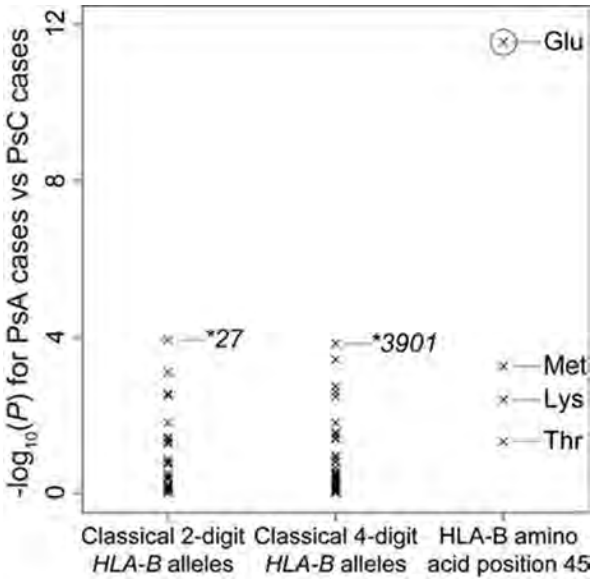
Fine-Mapping Major Histocompatibility Complex Associations Identified Contribution of Multiple Class I and II HLA Genes on Risk of Psoriasis and Its Clinical Subtypes. Yukinori Okada[1], Buhm Han[2], Lam C. Tsoi[3], Philip E. Stuart[4], Eva Ellinghaus[5], Trilokraj Tejasvi[4], Vinod Chandran[6], Fawnda Pellett[7], Remy Pollock[7], Anne M. Bowcock[8], Gerald G. Krueger[9], Michael Weichenthal[5], John J. Voorhees[4], Proton Rahman[10], Peter K. Gregersen[11], Andre Franke[5], Rajan P. Nair[4], Gonçalo R. Abecasis[3], Dafna D. Gladman[6], James T. Elder[4], Paul IW. de Bakker[12] and Soumya Raychaudhuri[13]. [1]Tokyo Medical and Dental University, Tokyo, Japan, [2]Broad Institute of MIT and Harvard, Cambridge, MA, [3]University of Michigan, Ann Arbor, MI, [4]University of Michigan Medical School, Ann Arbor, MI, [5]Christian-Albrechts-University of Kiel, Kiel, Germany, [6]University of Toronto, Toronto Western Hospital, Toronto, ON, [7]University of Toronto, Toronto, ON, [8]Imperial College, London, United Kingdom, [9]University of Utah, Salt Lake City, UT, [10]Memorial University of Newfoundland, St. John's, NF, [11]The Feinstein Institute for Medical Research, Manhasset, NY, [12]University Medical Center, Utrecht, Netherlands, [13]Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Psoriasis vulgaris (PsV) risk is strongly associated with genetic variation within the major histocompatibility complex (MHC) region, although its fine genetic architecture has not been elucidated.

Methods: To fully characterize and fine-map the MHC associations of PsV, we conducted a large-scale fine-mapping study of PsV risk in the MHC region in 9,247 PsV cases and 13,589 controls of European descent. We also evaluated risk of two major clinical subtypes of PsV, psoriatic arthritis (PsA; n = 3,038) and purely cutaneous psoriasis (PsC, defined as 10 years of psoriasis without developing PsA; n = 3,098). We imputed class I and II HLA gene variants by applying SNP2HLA software to the SNP genotype data. In addition, we newly constructed an imputation reference panel of sequence variants for *MICA*, an HLA-like gene within the MHC region that has been implicated for PsA risk. We applied MICA variant imputation to the SNP genotype data and evaluated their risk as well.

Results: As previously described, we observed that *HLA-C*06:02* demonstrated the most significant impact on overall PsV risk (odds ratio [OR] = 3.38, 95% confidence interval [95%CI]: 3.18–3.60, $P = 1.7x10^{-364}$). Stepwise conditional analysis revealed multiple independent risk variants of both class I and class II HLA genes for PsV susceptibility independent of *HLA-C*06:02* (*HLA-C*12:03*, HLA-B amino acid positions 67 and 9, HLA-A amino acid position 95, and HLA-DQα1 amino acid position 53; $P < 5.0x10^{-8}$), but no apparent independent risk conferred by *MICA*. Strikingly, we found that risk heterogeneity between PsA and PsC may be driven by one amino acid position at *HLA-B* (Glu at HLA-B amino acid position 45; OR = 1.46, 95%CI: 1.31–1.62, $P = 2.9x10^{-12}$), which demonstrated much more significant association signals compared to classical *HLA-B* alleles including *HLA-B*27* and *HLA-B*39:01* ($P > 1.0x10^{-4}$).

Conclusion: These results indicate that multiple class I and II HLA genes (*HLA-C*, *HLA-B*, *HLA-A*, and *HLA-DQA1*) contribute to development of PsV, and suggest that different genetic factors, most evident at *HLA-B*, underlie for the differential risk of specific PsV sub-phenotypes. Our study illustrates the value of high-resolution HLA and *MICA* imputation for fine-mapping causal variants in the MHC.



Disclosure: Y. Okada, None; **B. Han**, None; **L. C. Tsoi**, None; **P. E. Stuart**, None; **E. Ellinghaus**, None; **T. Tejasvi**, None; **V. Chandran**, None; **F. Pellett**, None; **R. Pollock**, None; **A. M. Bowcock**, None; **G. G. Krueger**, None; **M. Weichenthal**, None; **J. J. Voorhees**, None; **P. Rahman**, None; **P. K. Gregersen**, None; **A. Franke**, None; **R. P. Nair**, None; **G. R. Abecasis**, None; **D. D. Gladman**, Abbvie, Amgen, Celgene, Janssen, Pfizer, UCB, 2, Abbvie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, UCB, 5; **J. T. Elder**, None; **P. I. de Bakker**, None; **S. Raychaudhuri**, None.

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The Impact of the Interaction Between Human Leukocyte Antigen Alleles and Obesity on Psoriatic Arthritis Risk. Lihi Eder[1], Fatima Abji[1], Cheryl Rosen[1], Proton Rahman[2], Vinod Chandran[1] and Dafna D. Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]Memorial University of Newfoundland, St. John's, NF.

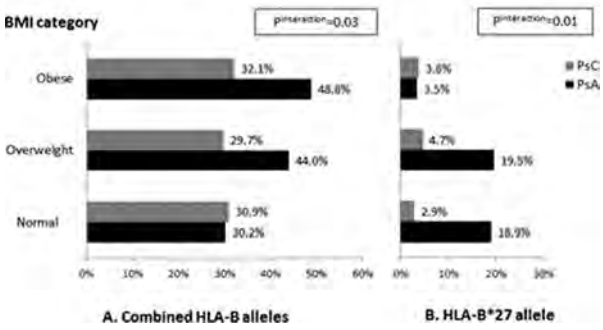
Background/Purpose: Human Leukocyte Antigen (HLA) class I alleles and obesity are risk factors for psoriatic arthritis (PsA). We aimed to assess whether there is an interaction between HLA risk alleles for PsA and obesity in susceptibility to PsA.

Methods: The study comprised two parts: 1) a case-only design that included patients with early PsA (<2 years) from 2 PsA cohorts, 2) a case-control design in which patients with early PsA were compared to those with psoriasis alone (PsC). Body Mass Index (BMI) at the first visit was stratified to normal (<25), overweight (25≤BMI<30) and obese (≥30). HLA genotyping was performed by sequence-specific oligonucleotide probes. The following alleles that were independently associated with PsA were analyzed: HLA-B*08, B*18, B*27, B*38, B*39 and C*06. Due to low frequency and similar structure, the effect of HLA-B*08, B*18, B*39 and B*38 was assessed in conjunction (termed "combined HLA-B alleles"). The interaction between obesity and HLA alleles was assessed by comparing the distribution of the various alleles across the three BMI categories in patients with PsA using trend test (case-only design). The interaction between HLA alleles and obesity was further investigated (case-control design) by assessing a departure from multiplicative combined effect of risk using logistic regression analysis after adjusting for age and sex and by assessing a departure from additivity by calculating the attributable proportion (AP).

Results: 637 Caucasians patients were analyzed (262 PsA, 375 PsC). Obesity was more frequent in patients with PsA compared to those with PsC (p=0.005). In addition, HLA-B*27 (p=0.0001) and the combined HLA-B alleles (p=0.03) were associated with PsA vs. PsC. A differential distribution of HLA-B alleles was observed across the 3 BMI categories in patients with PsA (case-only design) suggesting an interaction. The frequency of B*27 was higher in patients with normal weight compared to those with higher BMI (p^{trend}=0.005). In contrast, PsA patients who carried one of the combined HLA-B alleles tended to be heavier (p^{trend}=0.03). Similar findings were observed in the case-control analysis (Figure 1). A multiplicative interaction was found for the combined effect of B*27 and obesity in logistic regression analysis (OR 0.1 p=0.01) as well as for the joint effect of combined HLA-B alleles and obesity (OR 2.7 p=0.03). A significant additive interaction of combined HLA-B alleles and obesity was found with the proportion of risk due to additive interaction (AP) of 0.62 (95% CI 0.38, 0.93, p=0.0001). No interaction was found between obesity and HLA-C*06 allele.

Conclusion: An interaction was found between HLA-B alleles and obesity in PsA risk thus the effect of obesity on PsA risk may depend on the presence of HLA-B alleles.

Figure 1 - The frequency of HLA alleles in PsA vs. PsC by BMI category



Disclosure: L. Eder, None; **F. Abji**, None; **C. Rosen**, None; **P. Rahman**, None; **V. Chandran**, None; **D. D. Gladman**, None.

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HLA Markers for Disease Severity Are Associated with a Higher Burden of Atherosclerosis in Patients with Psoriatic Disease. Lihi Eder, Fatima Abji, Cheryl Rosen, Vinod Chandran and Dafna D. Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Recent evidence supports the link between the extent of inflammation and cardiovascular risk in patients with psoriatic disease (PsD). We aimed to investigate the association between Human-Leukocyte Antigen (HLA) markers of severe phenotype and the extent of atherosclerosis in PsD.

Methods: Consecutive Caucasian patients with Psoriatic arthritis (PsA) and psoriasis alone (PsC) were recruited from two large cohorts. Patients with PsA met the CASPAR criteria. Patients with PsC were examined by a rheumatologist to exclude the presence of arthritis. Information about the participants' demographics, co-morbidities and skin and joint disease activity was obtained from the cohorts' database. An ultrasound of the carotid arteries was performed and the presence of atherosclerotic plaques was recorded. The size of each plaque was measured and the resulting score, the total plaque area (TPA), represented the extent of atherosclerosis. TPA was classified to 4 categories (No plaques, mild, moderate and severe atherosclerosis). HLA genotyping was performed by sequence-specific oligonucleotide probes. Haplotype information was inferred using an expectation–maximization algorithm. Ten HLA alleles that were previously reported to be associated with severe phenotype of PsD were analyzed. The association between each HLA allele and the severity of atherosclerosis was assessed by ordinal logistic regression models adjusted for age, sex and traditional cardiovascular risk factors.

Results: 411 patients with PsD (273 PsA, 138 PsC) were analyzed. Their mean age was 55.5±11.5 years and 55.7% were males. 254 (61.8%) had at least one atherosclerotic plaque. HLA-B*1302 and HLA-C*0602 were associated with more severe atherosclerosis (age- and sex-adjusted Odds Ratio (OR) 2.31 (95% Confidence Interval (CI) 1.23, 4.32) and OR 1.68 (95% CI 1.12, 2.52), respectively). The haplotype HLA-B*1302-C*0602 was also associated with more severe atherosclerosis (OR 2.49, 95% CI 1.32, 4.72). The association between HLA-C*0602 and B*1302 and atherosclerosis severity remained statistically significant after adjusting for traditional cardiovascular risk factors (OR 1.63 (95% CI 1.08, 2.45) and OR 2.21 (95% CI 1.17, 4.16), respectively). Lower extent of atherosclerosis was found in carriers of HLA-B*3801 allele and the HLA-B*3801-C*1203 haplotype (age- and sex-adjusted OR 0.49 (95% CI 0.28, 0.86) and OR 0.45 (95% CI 0.26, 0.80), respectively). Higher levels of erythrocyte sedimentation rate over time were associated with HLA-B*1302 (p=0.02) and HLA-C*0602 (p=0.0007). No association was found between these alleles and traditional cardiovascular risk factors. No interaction was found between the HLA alleles and disease status.

Conclusion: HLA-C*0602 and B*1302 are markers of more severe atherosclerosis, while HLA-B*3801 is associated with lower burden of atherosclerosis in patients with PsD.

Disclosure: L. Eder, None; **F. Abji**, None; **C. Rosen**, None; **V. Chandran**, None; **D. D. Gladman**, None.

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The Predictive Value of Cardiovascular and Metabolic Biomarkers for Progression of Atherosclerosis in Psoriatic Disease. Lihi Eder, Fatima Abji, Cheryl Rosen, Vinod Chandran and Dafna D. Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: The pathophysiologic mechanisms underlying the accelerated atherosclerosis in patients with psoriatic disease (PsD) are unknown. We aimed to investigate candidate pathways involved in this process by identifying biomarkers that predicted progression of atherosclerotic plaques in patients with PsD.

Methods: A prospective cohort study was conducted in patients with psoriatic arthritis (PsA) and psoriasis alone (PsC) from 2010 to 2014. Patients with PsA met the CASPAR criteria. Patients with PsC were examined by a rheumatologist to exclude the presence of arthritis. Information about demographics, co-morbidities and disease manifestations was collected. The following serum cardiovascular and metabolic biomarkers were assessed at baseline by enzyme-linked immunosorbent assay (ELISA): insulin, adiponectin, leptin, vascular cell adhesion molecule 1 (VCAM-1), intracellular adhesion molecule 1 (ICAM-1), plasminogen activator inhibitor 1 (PAI-1), myeloperoxidase (MPO) and lipoprotein-associated phospholipase A2 (Lp-PLA2). The homeostatic model assessment (HOMA) was calculated using insulin and glucose levels to estimate insulin resistance. Ultrasound assessment of the carotid arteries was performed and Total Plaque Area (TPA) was measured at baseline and after 3 years. This measure represented the extent of atherosclerosis and was considered the outcome of interest. TPA at baseline was classified to 4 categories (No plaques, mild, moderate and severe atherosclerosis). A significant progression in atherosclerosis was defined as an increase in TPA of $> 0.1\ cm^2$ at 3 years (top quartile of TPA progression from baseline). The association between the log-transformed levels of the various biomarkers and TPA at baseline and atherosclerosis progression at 3 years was assessed using logistic regression models adjusted for age, sex and cardiovascular risk factors.

Results: A total of 235 patients with PsD (121 PsA, 114 PsC) were scanned at baseline, 129 of them were re-scanned at 3 years. The mean age of the study population was 52.5 ± 11.9 years and 54% were males. Patients with more severe atherosclerosis at baseline had higher levels of VCAM-1 ($p=0.0002$), ICAM-1 ($p=0.03$), leptin ($p=0.03$) and HOMA ($p=0.0002$), however in the age- and sex-adjusted model only HOMA remained significantly associated with more severe atherosclerosis (Odds Ratio (OR) 1.6, 95% Confidence Interval (CI) 1.2, 2.3, $p=0.006$). 31 of 129 patients had a significant progression of atherosclerosis at 3 years. Higher levels of Lp-PLA2 ($p=0.03$), PAI-1 ($p=0.05$) and HOMA ($p=0.01$) and lower levels of adiponectin ($p=0.04$) predicted progression of atherosclerosis. In the multivariate regression model adjusted for age, sex and cardiovascular risk factors, Lp-PLA2 (OR 5.5, 95% CI 1.4, 22.5, $p=0.02$), adiponectin (OR 0.3, 95% CI 0.1, 0.8, $p=0.008$) and HOMA (OR 2.2, 95% CI 1.1, 4.4, $p=0.03$) predicted progression of atherosclerosis in patients with PsD. No interaction was found between disease status (PsA vs. PsC) and any of the biomarkers.

Conclusion: Biomarkers involved in lipid and glucose metabolism and other metabolic pathways play a role in progression of atherosclerosis in patients with PsD.

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Biomarkers of Chondrocyte Activity Are Increased in Psoriasis Arthritis and Spondyloarthritis. Natasja Stæhr Gudman[1], Heidi Lausten Munk[2], Anne Friesgaard Christensen[3], Leif Ejstrup[4], Grith Lykke Sørensen[5], Anne Gitte Loft[3], Morten A. Karsdal[1], Anne C. Bay-Jensen[6], Yi He[7], Anne Sofie Siebuhr[1] and Peter Junker[2]. [1]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [2]Department of Rheumatology, Odense University Hospital, Odense, Denmark, [3]Department of Rheumatology, Vejle Hospital, Vejle, Denmark, [4]Department of Rheumatology, Esbjerg Hospital, Esbjerg, Denmark, [5]Institute of Molecular Medicin, University of Southern Denmark, Odense, Denmark, [6]Cartilage Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, [7]Nordic Bioscience, Herlev, Denmark.

Background/Purpose: Psoriasis arthritis (PsA) and spondyloarthritis (SpA) are both inflammatory joint diseases in which the pathogenesis is not fully understood. However, both pathologies are associated with extracellular matrix (ECM) remodeling favoring cartilage formation and calcification (type II and X collagen formation) in the affected joints. Treatment of the diseases has improved within recent years, but the therapeutic response at the level of the individual cannot be adequately predicted. Hence, there is an increasing interest in diagnostic and prognostic biomarkers to further characterize the patients to achieve personalized medicine. The biomarker ProC2 measures the level of propeptide type II collagen and C-Col10 measures type X collagen. Collagen type X is exclusively expressed by hypertrophic chondrocytes and is a measure of hypertrophic cartilage. The aim of this study was to evaluate the level of two novel biomarkers of cartilage formation (ProC2) and hypertrophy (C-Col10) in SpA, PsA and healthy controls, and to investigate whether these markers would have diagnostic potential.

Methods: 99 PsA patients, 94 SpA patients and 120 age-matched healthy controls were included in the study. Demographic and clinical disease measures were recorded. ProC2 and C-Col10 were quantified in serum by newly developed and specific competitive ELISAs based on monoclonal antibodies. One way analysis of variance and Tukeys multiple comparison test were performed on log-transformed data. Receiver operator characteristics (ROC) curve analysis was carried out to evaluate the discriminative power of the biomarkers.

Results: The serum levels of P2BNP had a mean level of 0.59ng/ml for healthy controls, but were significantly increased in patients with either SpA (mean 1.25ng/ml) or PsA (mean 1.35) compared to controls ($p<0.001$). When segregating between patients and healthy controls by mean of ROC curves the AUC was 0.78 for SpA (Cl 95% 0.71 to 0.84) and 0.79 (CI 95% 0.73–0.85) for PsA as listed at the table below. Furthermore SpA had a slightly, but significantly increased level of type X collagen (mean 0.60ng/ml) compared the controls (mean 0.56ng/ml) ($p=0.035$). None of the two markers correlated with age, sex, BMI and the markers did not correlate with each other.

Conclusion: These findings indicate that both SpA and PsA arthritis have enhanced cartilage formation reflected by increased levels of PIIBNP levels in serum compared to healthy controls. In addition, an increased level of the hypertrophic chondrocyte collagen X marker was found in SpA only, indicating a difference in cartilage turnover between the two diseases. This difference could aid in the differentiation between SpA and PsA.

The AUC, sensitivity and specificity of each ROC-analysis

	AUC (CI95%)	Sensitivity	Specificity
P2BNP			
Healthy vs PsA	0.793 (0.73–0.85)	65.1	81.7
Healthy vs SpA	0.776 (0.71–0.84)	60.4	83.3
SpA vs. PsA	0.539 (0.46–0.62)	40.4	60.4
Col X			
Healthy vs PsA	0.607 (0.53–0.68)	48.5	60.6
Healthy vs SpA	0.580 (0.50–0.66)	48.6	60.6
SpA vs. PsA	0.525 (0.45–0.60)	40.4	60.6

Disclosure: N. S. Gudman, Nordic Bioscience Diagnostic, 3; **H. L. Munk**, None; **A. F. Christensen**, None; **L. Ejstrup**, None; **G. L. Sørensen**, None; **A. G. Loft**, None; **M. A. Karsdal**, Nordic Bioscience Holding, 1, Nordic Bioscience Diagnostic, 3; **A. C. Bay-Jensen**, Nordic Bioscience Diagnostic, 1; **Y. He**, Nordic Bioscience Diagnostic, 3; **A. S. Siebuhr**, Nordic Bioscience A/S, 3; **P. Junker**, None.

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Biomarkers of Bone Remodeling Are Elevated in Psoriatic Arthritis. Fatima Abji, Arane Thavaneswaran, Vinod Chandran and Dafna D. Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Psoriatic arthritis (PsA) is an inflammatory arthritis that develops in about a third of patients with cutaneous psoriasis (PsC). The identification of biomarkers to aid in the early diagnosis of PsA in patients with PsC may prevent disability and improve the quality of life for those affected. Inflammation in peripheral and/or axial joints in PsA is associated with abnormal bone metabolism, including erosions and bone formation. The goal of the current study was to determine if markers of bone remodeling are associated with PsA patients with active disease compared to patients with PsC only.

Methods: PsA patients with active disease (≥ 3 tender and swollen joints) and PsC patients were identified from the cohort of patients followed prospectively. Patients were matched for age, sex, PASI score and psoriasis duration and were not receiving treatment with biologic agents. PsA patients

satisfied CASPAR criteria and PsC patients were examined by a rheumatologist to exclude arthritis. Patients were not receiving treatment with methotrexate for a minimum of two years before the sampling date. Serum biomarkers measured included DKK1, FGF23, IL-6, IL-1β, leptin, osteocalcin, osteoprotegerin, osteopontin, sclerostin and TNFα. All proteins were measured simultaneously using the Millipore Milliplex MAP human bone magnetic bead panel, according to the manufacturer's instructions. Data was acquired using the Luminex 200 system and analyzed with the Biorad Bio-Plex Manager software. Significant differences were determined by performing paired t-tests between the PsA and PsC cohorts ($p<0.05$).

Results: The levels of bone biomarkers were measured in 60 PsA patients (mean age 51 years, 50% males, psoriasis duration 18 years, PASI 4.24, 11.4 tender joints, 6.3 swollen joints) and 60 PsC patients (mean age 52 years, 50% males, psoriasis duration 20 years, PASI 3.7). DKK1, leptin, osteoprotegerin, osteopontin, and sclerostin were significantly elevated in PsA patients compared to PsC patients (Table 1, paired student's t-test). TNFα levels were significantly reduced in PsA (3.7 pg/ml) patients compared to those with psoriasis only (10.6 pg/ml). Elevation in markers of bone resorption (DKK1, OPN, SOST) and ossification (leptin, OPG) in PsA relative to PsC were found, reflecting the balance in both synthesis and degradation that is disrupted in PsA. Using a reduced conditional logistic regression model that included all markers tested, IL-6, osteopontin, sclerostin and TNFα were independently associated with PsA.

Conclusion: Serum markers of bone remodeling were elevated in PsA patients with active disease compared to patients with PsC only. Future studies will focus on validating these markers in a large, independent cohort, to determine whether these genes can serve as biomarkers of PsA susceptibility.

Table 1: Expression of bone biomarkers ($p<0.05$) in serum of PsA and PsC patients

			Mean (sd) levels (pg/ml)		
Protein	**Description**	**Function**	**PsA Cohort**	**PsC Cohort**	**P-Value**
DKK1	dickkopf WNT signaling pathway inhibitor 1	Resorption	**1940.7 (627.6)**	**1750.6 (483.7)**	**0.045**
FGF23	Fibroblast growth factor 23	Resorption	113.7 (262.7)	76.3 (35.4)	0.28
IL-6	Interleukin-6	Resorption	37.0 (139.5)	49.1 (197.3)	0.71
IL-1β	Interleukin-1 beta	Resorption	2.1 (2.7)	4.1 (10.8)	0.18
LEP	Leptin	Ossification	**22347.5 (22503.2)**	**11279.1 (10508.0)**	**0.002**
OC	Osteocalcin	Ossification	10332.4 (6360.4)	8099.3 (4985.9)	0.05
OPG	Osteoprotegrin	Ossification	**443.4 (218.6)**	**374.3 (162.1)**	**0.04**
OPN	Osteopontin	Resorption	**11486.5 (6780.4)**	**7323.3 (4411.8)**	**0.0001**
SOST	Sclerostin	Resorption	**3655.9 (1306.6)**	**3035.4 (1040.7)**	**0.001**
TNFα	Tumor necrosis factor alpha	Resorption	**3.7 (5.6)**	**10.6 (16.0)**	**0.003**

Disclosure: F. Abji, None; **A. Thavaneswaran**, None; **V. Chandran**, None; **D. D. Gladman**, None.

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Joint and Bone Related Pathways Discriminate Psoriatic Arthritis Lesional Skin from Psoriasis vulgaris Lesional Skin. Jennifer Belasco[1], James S. Louie[2], Nicholas Gulati[1], Nathan Wei[3], Kristine Nograles[1], Hiroshi Mitsui[1], Mayte Suarez-Farinas[1] and James G. Krueger[1]. [1]The Rockefeller University, New York, NY, [2]UCLA School of Medicine, Los Angeles, CA, [3]Arthritis & Osteoporosis Center of MD, Frederick, MD.

Background/Purpose: It is preferable to start therapy as early as possible in psoriatic arthritis (PsA) because of the destructive nature of the arthritis. Starting treatment promptly is complicated because the arthritis component can occur years after the psoriatic skin disease (psoriasis vulgaris, PsV), and the arthritis may not be diagnosed until it is more established. Many patients with PsV are seen in dermatology clinics where early arthritis symptoms may not be diagnosed. Given these issues, it would be useful to have a predictive model that would allow the identification of patients with PsV that will go on to have PsA, possibly even before clinical symptoms of arthritis are apparent. Since the psoriasis lesions of the skin are often the first detected symptom of psoriatic disease, molecular profiles of the skin may provide prognostic value to predict the onset of joint inflammation, We conducted a comprehensive genomic and molecular comparison of lesional skin from subjects with PsA and PsV.

Methods: Lesional psoriatic skin samples were obtained from subjects with PsA (n=6) and PsV (n=10). PsA subjects were diagnosed by Moll and Wright criteria by a rheumatologist. PsV samples were chosen after a retrospective chart review was done to assure subjects denied joint complaints at all visits. Gene expression analysis was conducted using Affymetrix HGU133 2.0+ arrays. Differentially expressed genes (DEGs) were evaluated with a cut-off of fold change >2.0 and false discovery rate <0.01. **Results** were validated using RT-PCR. Ingenuity Pathway Analysis (IPA) was utilized to identify canonical pathways among DEGs.

Results: A comparison of PsA and PsV lesional skin revealed 1569 genes were upregulated and 1838 genes were downregulated. While there are a variety of differences in gene expression, it is notable that genes typically associated with bone formation and cartilage were in the top 50 upregulated genes. These include cartilage oligomeric matrix protein (COMP), secreted frizzled-related protein 1 (SFRP1), and proteoglycan 4 (PRG4). In addition, IPA showed differential expression of several pathways related to joint destruction and dysregulated bone metabolism. These include the "Role of Macrophages, Fibroblasts, and Endothelial Cells in Rheumatoid Arthritis", the "BMP Signaling Pathway", the "Wnt/β-Catenin Signaling Pathway" and "RANK Signaling in Osteoclasts". RT-PCR confirmed a significant difference in BMP2.

Conclusion: In this pilot study we show differences in gene expression of lesional skin from subjects with PsA and PsV. To our knowledge, this is the first study to show that markers linked to the joint and dysregulated bone metabolism could be identified in skin biopsies. This could be useful as both an early predictor of PsV patients who will go on to have PsA and help to guide therapies at a very early stage of disease diagnosis to prevent destructive arthritis. In addition, this could lead to the discovery of key pathogenic molecules in skin that may affect joints and/or entheses, thus suggesting new therapeutic targets.

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IL-23 Mediates Psoriasis-like Inflammation in the SKG Mouse Model of Spondyloarthropathy. Helen Benham[1], Linda Rehaume[1], Athan Baillet[1], Zaied Bhuyan[1], Jaclyn Bowman[1], Dimeng Pang[1], Kristine Kikly[2], Geoffrey Strutton[3], Matthew Brown[1] and Ranjeny Thomas[1]. [1]University of Queensland Diamantina Institute, Brisbane, Australia, [2]Biotechnology Discovery Research, Eli Lilly and Co, Indianapolis, IN, [3]Department of Pathology, Princess Alexandra Hospital, Brisbane, Australia.

Background/Purpose: Psoriasis (Ps) is a common immune-mediated inflammatory skin disease and is a well- recognised extra-articular manifestation of the spondyloathopathies (SpA). Genetic studies implicate IL-23 signalling in the pathogenesis of both Ps and SpA. Spondyloarthritis and psoriasis-like disease develop in an IL-23-dependent fashion in ZAP70-mutant SKG mice, which have deficient T cell receptor signaling. We characterized curdlan (1,3-D β-glucan) induced psoriasis-like inflammation in SKG mice, investigating the role of IL-23, IL-22/IL-17, regulatory T cells (Tregs) and microbiota.

Methods: SKG mice, IL-17A-deficient SKG mice, Germ Free SKG mice and Foxp3-DTR SKG mice were injected intraperitoneally with curdlan (1,3-D β-glucan) to induce disease. Anti-mouse IL-22, anti-IL-23 or isotype control antibodies were given i.p one day before curdlan, and weekly until sacrifice. Recombinant IL-23 or PBS was administered intra-dermally into ear skin. Outcomes were measured by clinical and histological scoring; cytokines and by qRT-PCR and in supernatants of cultured tissue explants by ELISA and CBA.

Results: Curdlan induced psoriasis-like inflammation in addition to spondyloarthritis in 100% of SKG mice. SKG skin lesions showed a histological phenotype similar to human Ps with elevated constitutive levels of *IL-23a(p19)* and increased secretion of both IL-17 and IL-22, 7 days after curdlan. Neutralisation of both IL-23 and IL-22 suppressed development of skin inflammation, in contrast IL-17A-deficient SKG mice were only partially spared. Germ Free (GF) SKG mice failed to develop significant skin inflammation after curdlan, however colonization of GF-SKG mice with a limited microbiota induced mild psoriasis-like inflammation. Tregs modulated the severity of skin inflammation through the suppression of IL-23 secretion. Intradermal injection of IL-23 induced IL-22 mediated, microbiota dependent psoriasis-like inflammation in naïve SKG mice.

Conclusion: In curdlan-treated SKG mice IL-23-driven psoriasis-like inflammation is induced in the setting of spondyloarthritis. The skin inflammation recapitulates several features of human Ps and is dependent on the relative contributions of IL-17, IL-22, microbiota and the balance of Tregs and T effector cells.

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Immunological and Clinical Relationships of Synovial IL-17+ T Cells in Psoriatic Arthritis. Bruce Kirkham[1], Bina Menon[2] and Leonie S. Taams[3]. [1]Guy's & St Thomas NHS Foundation Trust, London, United Kingdom, [2]Guy's and St. Thomas' Foundation Hospital NHS Trust, London, United Kingdom, [3]King's College London, London, United Kingdom.

Background/Purpose: We recently reported elevated numbers of synovial fluid IL-17+CD4- T cells (mainly CD8+ (Tc17) cells) in Psoriatic Arthritis (PsA), correlating with clinical, serological and imaging measures of disease activity (1). These relationships are not found with CD4+ IL-17+ (Th17) synovial cells. Here we report the relationship of synovial fluid T cell cytokine expression with PsA clinical patterns, and the relationships between synovial fluid cytokine-expressing T cells.

Methods: Mononuclear cells from synovial fluid (SF) and peripheral blood (PB) samples from 22 patients with PsA were isolated and stimulated for three hours in vitro with PMA and ionomycin in the presence of GolgiStop. CD3+ T cells were investigated for cytokine expression (IL-17A, IFN-γ, TNF-α, IL-22, IL-21, IL-10) by flow cytometry. Clinical measures and Power Doppler Ultrasound (PDUS) of the affected joint were made at the time of joint aspiration.

Results: Of 22 subjects, 16 (73%) had an oligoarthritis (<5 involved joints) and 6 (27%) a polyarticular pattern of PsA, with 9 (41%) having co-existing axial disease. 2 subjects had a history of dactylitis, 8 of enthesitis and 5 of nail disease.

All clinical subgroup patients had elevated synovial IL-17+CD4- and IL-17+CD4+ T cells compared to PB, which was significant in the oligo ($p=0.001$ and $p=0.02$ respectively) and axial groups ($p=0.01$ for both), with the polyarthritis group increase not statistically significant ($p=0.06$ for both), most likely due to low numbers.

TNF-α+CD4- T-cell frequency positively correlated with DAS28 ($r=0.51$, $p=0.02$) with a trend for TNF-α+CD4+ T-cells and DAS28 ($r=0.43$, $p=0.07$). In contrast to IL-17+CD4- T cells, there was no correlation between TNF-α+ T-cells and ESR, CRP or PDUS. IL-22+CD4- cells correlated with PDUS. No other T cell cytokine expression pattern correlated with clinical measures.

Relationships of cytokine expressing T cells were assessed for the percentages of IL-17+CD4- T cells and IFN-γ+, TNF-α+, IL-22+, IL-21+ and IL-10+ CD4- T-cells in PsA SF. Only TNF-α+ cells positively correlated with IL-17+ cells in the CD4- T-cell compartment ($r=0.55$, $p=0.01$). This relationship may be partly explained by the finding that 60% of IL-17+CD4- cells co-express TNF-α. IL-22 was co-expressed in 22% of IL-17+ CD4- T cells.

Conclusion: These data suggest that IL-17 expressing CD4- (CD8+) T cells are found in all articular patterns of PsA. The correlation of IL-17+ and TNF-α+ CD4- cells suggests that IL-17 and TNF-α may be related in expression as well as synergy of function.

Ref

1. Menon B, et al.Arthritis Rheumatol. 2014;66:1272–81.

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ACR Poster Session A
Systemic Lupus Erythematosus - Animal Models
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Characterization of $CD4^+$ T Cell Response and Effects of Regulatory T Cells in Pristane Induced Lupus (PIL). Harald Leiss, Barbara Schwarzecker, Irina Gessl, Antonia Puchner, Birgit Niederreiter, Carl-Walter Steiner, Josef Smolen and Georg H. Stummvoll. Medical University of Vienna, Vienna, Austria.

Background/Purpose: $CD4^+$ T cells and the Th1 and Th17 subsets in particular play a pivotal role in SLE. Regulatory T cells (Treg) are essential for maintaining peripheral tolerance, but their number and function in SLE is decreased. We herein characterize CD4+T cell and Treg homeostasis and severity of organ involvement in a murine model of SLE and analyze the effects of *in vitro* –induced iTreg.

Methods: Mice were injected i.p. with 0.5ml of pristane or PBS as control and killed after 8 months. Naïve $CD4^+$ thymocytes were cultured under specific conditions and tested for $CD4^+Foxp3^+$ expression by FACS. Cell suspensions with >80% purity for $CD4^+FoxP3^+$ iTreg were injected intravenously either once at start of experiments (iTreg-boost) or monthly (1xiTreg-repeated).

Animals were monitored for clinical signs of arthritis and, in order to analyze and compare disease severity, histological features of arthritis and pneumonitis were quantified by an image analysis system. Lungs were scored for the severity of perivascular inflammation by analyzing the numbers of affected vessels and the area of the inflammatory infiltrate.

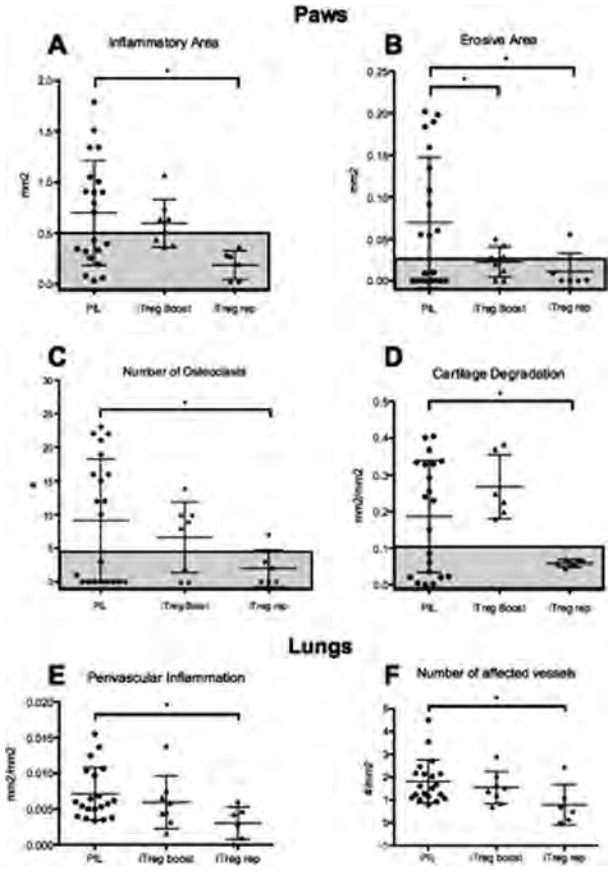
Lymphocytes were isolated from granulomas (intraperitoneal ectopic lymphoid tissue), lymph nodes (LN) and spleens and were analyzed separately by FACS. For analyzes of the Th1, 2 and 17 subsets, cells were restimulated in vivo plate bound with anti-CD3 and anti-CD28abs.

Results: PIL mice presented with involvement of inner organs, most frequently affected were the lungs (100% pneumonitis); 52% of PIL developed arthritis, both clinically and histologically. Monthly iTreg-injection significantly decreased clinical signs of arthritis and histological lung and joint parameters. 66% of treated mice did not show any signs of arthritis at all. (Fig. 1A-F)

The iTreg-boost did not prevent joint manifestations or pneumonitis, but appeared to have a retarding effect (Fig.1A-F) indicated by a delayed onset of clinical symptoms and by a significantly decreased erosive area at the end of observation (Fig.1B).

Intraperitoneal granuloma typical for PIL appeared to be the hotspots of inflammation showing a significantly elevated Teff/Treg ratio of 1.3. Upon re-stimulation, CD4+ cells showed a pronounced Th1 response (27% IFNγ producers) compared to cells from LN and spleens from both PIL and HC (with Th1 percentages ranging from 9–16%). In addition, frequencies of Th2 and Th17 cells were elevated in PIL, again with the highest yield in granuloma. The repeated application of iTreg reduced the Teff/Treg ratio in PIL granuloma to 0.7.

Conclusion: Repeated injections of iTregs reduce severity of pneumonitis and arthritis as well as the T_{eff}/T_{reg} ratio. A single injection of iTregs is not effective, but appears to retard onset of symptoms and progression of arthritis and pneumonitis. Thus, iTreg have significant effects on lupus symptoms, which may have consequence for future therapeutic considerations.



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Mir-663 Impairs the Effects of Bone Marrow-Derived Mesenchymal Stem Cells on MRL/Lpr Mice. Linyu Geng, Xuebing Feng and Lingyun Sun. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

Background/Purpose: Previously we have shown that miR-663 was increased in bone marrow derived mesenchymal stem cells (BMSCs) from SLE patients and involved in the functional deficiency of BMSCs through inhibiting transforming growth factor β1 (TGF-β1) production. This study was undertaken to explore whether the modulation of miR-663 in BMSCs could affect their therapeutic effects on MRL/lpr mice.

Methods: Negative-control-miR-663 (miR-663-C), mimics-miR-663 (miR-663-M) and inhibitor-miR-663 (miR-663-I) eukaryotic expression vector were artificially transfected into BMSCs and intravenous injected (1°Á10^6) into 20 weeks old female MRL/lpr mice. 8 weeks later, mice were sacrificed, with kidneys, lymph node harvested and spleen weighed. Their serum and urinary samples were collected for the measurement of autoantibodies (including IgG, ds-DNA and ANA) and cytokines (TGF-β1, IL-4, IFN-¡Ã, IL-17A and so on) by ELISA, and proteinuria by coomassie blue staining assay. Immune complex deposition including IgG and complement 3 (C3) in kidney sections was performed by immunofluorescence staining. The percentages of Th1, Th2, Th17, regulatory T cells (Treg) and follicular T helper (Tfh) cells in splenic mononuclear cells were detected by flow cytometry.

Results: Compared to the miR-663-C and miR-663-M group, miR-663-I transfected BMSCs displayed enhanced therapeutic effects on MRL/lpr mice, as shown by significantly declined spleens and lymph nodes size as well as reduced serum IgG and anti-dsDNA levels. Compared to miR-663-C and miR-663-I group, mice treated with miR-663-M transfected BMSCs presented enlarged glomerulus with hyper cellularity and meningeal expansion, and greater amounts of immune complex deposition including IgG and C3 in the meningeal and peripheral capillary loops. Meanwhile, Treg cell percentages were increased in miR-663-I group compared with those in miR-663-M and miR-663-C group (13.3±1.12% vs. 6.90±0.82% and 8.25±1.07%, overall $p < 0.05$), while Tfh cell percentages were decreased (8.58±1.09% vs. 22.9±4.24% and 12.40±1.61%, overall $p < 0.05$).

Conclusion: Inhibition of miR-663 in MSCs enhanced the therapeutic effects of MSC transplantation on MRL/lpr mice.

Disclosure: L. Geng, None; **X. Feng**, None; **L. Sun**, None.

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Liposomal-Glucocorticoids: A Novel Approach to the Therapy of SLE. Yaakov Naparstek, Eli Moallem, Rina Ulmansky, Erez Koren and Yechezkel Barenholz. Hadassah - Hebrew University Medical Center, Jerusalem, Israel.

Background/Purpose: Glucocorticoids (GCs) have been known for years to be the most effective therapy in SLE. Their use is however limited by the need of high doses due to the unfavorable pharmacokinetics and biodistribution of the drug. A possible approach to overcome this obstacle is to use liposomal formulation that has a different biodistribution than that of the free GCs. We have previously developed a new liposomal GC formulation and demonstrated its specific accumulation in inflamed tissues, as well as superior therapeutic efficacy over that of free GC in the autoimmune adjuvant arthritis model. In the present study we have tested the effect of the liposomal GC formulation in the murine SLE model of MRL/lpr/lpr mice.

Methods: We used 80 nm sterically stabilized nanoliposomes which were remote-loaded with an amphipathic weak acid GC methylprednisolone hemisuccinate (liposomal GC). Six-weeks old MRL/lpr/lpr mice were injected subcutaneously with either the liposomal GC 25 mg/kg weekly, or free MPS 5 mg/kg daily, or the appropriate solvents and their clinical course, kidney damage and serology, followed until the age of 24 weeks.

Results: No mortality was observed in mice treated with the liposomal GC up to 24 weeks, as compared to 20% and 30% mortality in the free MPS and the solvent-treated groups. Anti-dsDNA levels (OD) were 0.49±0.05 in the liposomal GC group, compared to 1.21±0.22 and 1.7±0.12 in the two other groups. Significant reduction of spleen size was observed in the liposomal GC-treated group, 1.09±0.43 cm^2, compared to 2.98±0.65 cm^2 and 2.82±0.51 cm^2 in the two other groups. A significant improvement in renal histopathology was achieved in the liposomal GC treatment, and mean urea levels were 8.8±1.05 nM/L in the liposomal GC group compared to 18.9±3.86 nM/L and 22.5±2.69 nM/L in the two other groups.

Conclusion: Liposomal GC has significant superiority over daily injections of free MPS in suppressing murine lupus. These results make our liposomal GC formulation a good candidate for the treatment of human SLE.

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Decreased Inflammatory Dendritic Cells in Lupus-Prone Estrogen Receptor Alpha Knockout (ERαKO) Mice Correlate with Increased Survival. Melissa A. Cunningham[1], Jena R. Wirth[2], Jackie G. Eudaly[1], Jennifer L. Scott[1], Osama S. Naga[1] and Gary S. Gilkeson[1]. [1]Medical University of South Carolina, Charleston, SC, [2]MUSC, Charleston, SC.

Background/Purpose: SLE is a disease that disproportionately affects females. The etiology of the sex bias in this disease is unclear. We previously showed that a functional knockout of estrogen receptor alpha (ERαKO) resulted in significantly reduced renal disease and increased survival in murine lupus. Subsequently, we demonstrated a role for ERα in modulating Toll-like receptor (TLR)-induced inflammation, partially explaining the protected phenotype. The mechanism of this effect, however, is not known. Dendritic cell development, which requires both estrogen and ERα is impacted, as is activation status and cytokine production. Due to altered feedback loops, the hormonal milieu of ERα mutant mice is significantly different from WT. ERαKO mice have hypergonadism and partial endocrine sex reversal (elevated estrogen and testosterone levels), and decreased prolactin levels. These hormones may have immunomodulating effects in concert with other intact hormone receptors. Therefore, we investigated the phenotype of the NZM/ERαKO mouse following ovariectomy (OVX) and estrogen pellet (to preserve a physiologic hormonal state).

Methods: ERαKO and Ex3a (ERα null) strains were backcrossed onto the NZM2410 lupus-prone background. Subsets of mice were ovariectomized (at 4 or 8 weeks). Urine and blood were collected at 2–4 week intervals starting at 10 weeks, and mice were sacrificed at 32 weeks, or earlier if they had high proteinuria and >10% weight loss. Bone marrow was isolated and cultured for 7 days with Flt3L to enrich for dendritic cells. Spleen and kidney cells were also isolated. Flow cytometry was utilized to determine number of cDCs (CD11c+/CD11b+) and activated cDCs (CD11c+/CD11b+/MHCII+) from cultured BM-DCs, as well as from *ex vivo* spleen and kidney cells.

Results: Survival at 32 weeks: NZM/ERαKO – OVX + E2: 8/8 (100%) vs. NZM/ERαKO – OVX: 5/9 (56%) vs. NZM/WT – OVX 8/14 (57%) vs. NZM/Ex3a 7/7 (100%) vs. NZM/Ex3a – OVX 3/6 (50%) vs. NZM/Ex3a – OVX + E2 5/8 (63%). Proteinuria (dipstick) correlated with survival as did total and activated cDCs (BM-DCs) which were significantly reduced in NZM/ERαKO – OVX + E2 vs. both NZM/WT – OVX ($p<0.001$) and NZM/ERαKO – OVX ($p<0.05$). To date, analyzed numbers of activated cDCs from both spleen and kidney of NZM/ERαKO mice were also significantly reduced.

Conclusion: Consistent with previous experiments, NZM/ERαKO mice were protected from lupus disease expression (no early deaths; no proteinuria at 32 weeks). This was only true if they were either unmanipulated, or both ovariectomized *and* E2-repleted. These mice had fewer inflammatory and activated cDCs from bone marrow, spleen and kidney, which correlated with increased survival in this group. The protective phenotype was lost after ovariectomy if no E2 pellet was administered, suggesting that the effect requires E2 in the system (despite the lack of a full length ERα). A protective effect was not observed in lupus-prone Ex3a mice (ER$\alpha-/-$) that were OVX'ed and E2-repleted, suggesting that the A/B domain mutant in ERαKO mice potentially modulates disease in the presence of estrogen, rather than ERα deficiency alone being protective.

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Commensal Microbiota Influence Systemic Autoimmune Responses. Jens Van Praet[1], Erin Donovan[2], Michael Drennan[1], Fons Van de Loo[3], Sylvie Rabot[4], Jeroen Raes[5], Tom Van De Wiele[1], Carl Ware[6] and Dirk Elewaut[7]. [1]Ghent University Hospital, Ghent, Belgium, [2]Ghent University Hospital, ghent, Belgium, [3]Raboud University Medical Center, Utrecht, Netherlands, [4]AgroParisTech, Micalis, Jouy-en-Josas, France, [5]Rega Institute, KU Leuven, Leuven, Belgium, [6]Sanford-Burnham Medical Research Institute, La Jolla, CA, [7]Department of Rheumatology Ghent University Hospital, Ghent, Belgium.

Background/Purpose: Antinuclear antibodies are a hallmark feature of generalized autoimmune diseases, including systemic lupus erythematosus and systemic sclerosis. However, the processes underlying the loss of tolerance, particularly the role of lymphoid organs, against nuclear self constituents remains largely unresolved.

Methods: We generated mice lacking all secondary lymphoid organs including spleen by intercrossing lymphotoxin beta receptor deficient mice with HOX11 deficient animals. LTbR-Fc was administered intrauterine and postnatally at various stages of development. *Ltb*$^{-/-}$, T-*Ltb*$^{-/-}$, B-*Ltb*$^{-/-}$ and Rorγt-*Ltb*$^{-/-}$ were generated by crossing LTβ-floxed mice with CD4-cre, mb1-cre, RORgt-cre mice respectively. Thymi were isolated from newborn LTbR$^{-/-}$ or wildtype mice and transplanted under the kidney capsule of adult nude mice. 16S rRNA profiling and analysis was conducted on mucosal, luminal and faecal samples. Germfree versus conventionalized mice were treated with LTbR-Fc intrauterine and postnatally. Germfree mice were monocolonized with SFB or E. Coli species and treated with LTbR-Fc. We screened for autoantibodies using a validated immunodetection system for a broad range of ANA, including anti-U1RNP, anti-Sm, anti Scl70/Topoisomerase-I, anti-Centromere protein B, anti-SSA/Ro52 and anti-Jo1 (INNO-LIA ANA Update, Innogenetics NV).

Results: We found that approximately 25% of mice lacking secondary lymphoid organs spontaneously develop specific antinuclear antibodies. Interestingly, we find this phenotype is not caused by a defect in central tolerance. Rather, cell-specific deletion and *in vivo* lymphotoxin blockade link these systemic autoimmune responses to the formation of gut associated lymphoid tissue in the neonatal period of life. We further demonstrate antinuclear antibody production is influenced by the presence of commensal gut flora, in particular increased colonisation with segmented filamentous bacteria, IL-17 receptor signalling, and IgA production, which appears to have a protective role against autoantibody formation.

Conclusion: Together, these data indicate that neonatal colonization of gut microbiota influences generalized autoimmunity in adult life.

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Lack of Response Gene to Complement-32 Impairs Th17 Differentiation and Attenuates Lupus-like Chronic Graft Versus Host Disease. Vinh Nguyen[1], Cosmin Tegla[1], Cornelia Cudrici[2], Tudor Badea[3], Horea Rus[1] and Violeta Rus[1]. [1]University of Maryland School of Medicine and Veteran Affairs Medical Center, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, MD, [3]NIH, National Eye Institute, Bethesda, MD.

Background/Purpose: Response Gene to Complement (RGC)-32 was cloned and characterized by our group as one of the genes induced by complement activation. It encodes an intracytoplasmatic protein that promotes cell cycle activation via cyclin B1-CDC2 activation and Akt phosphorylation in vascular smooth muscle and endothelial cells. RGC-32 is also a downstream target of TGF-β in fibroblasts and renal proximal tubular cells and plays a role in renal fibrogenesis. The expression and function of RGC-32 in immune cells has not been studied. As Th17 and induced T regulatory cells (iTreg) differentiate under the control of TGF-β, we determined whether RGC-32 plays a role in Th17/Treg balance using RGC-32 KO mice generated in our lab. In addition, using two established models of chronic graft versus host disease (cGVHD), we assessed whether absence of RGC-32 on either donor CD4 cells or host B cells alters autoimmune parameters of disease.

Methods: Naïve CD4$^+$ cells purified from WT or RGC-32 KO splenocytes were cultured under Th1, Th2, Th17 and Treg conditions. The expression of IFN-γ, IL-4, IL-17A, FoxP3, T-bet, RORγt, and GATA-3 were determined by flow cytometry, ELISA and RT-PCR. Lymphocytes isolated from the large intestine lamina propria of WT and RGC-32$^{-/-}$mice were stained for IL-17A. Phosphorylation of STAT3, Smad2 and 3 were assessed by Western blot.

Parent-into-F1 cGVHD was induced with 12x10^6 WT or RGC-32$^{-/-}$ CD4 cells injected into B6D2F1 recipients. Bm12-into-B6 cGVHD was induced by injecting 100x10^6 Bm12 splenocytes into WT or RGC-32$^{-/-}$hosts. In both models, parameters of cGVHD including donor CD4, host B cell number and activation, anti-ssDNA autoAb production were assessed at two weeks after disease induction.

Results: RGC-32$^{-/-}$ CD4$^+$ T cells failed to differentiate normally to Th17 lineage as demonstrated by a significant reduction in IL-17 and RORγt mRNA and protein expression in vitro and a decreased proportion of IL-17$^+$ cells in lamina propria lymphocytes in vivo. Decreased phosphorylation of Smad2 but not of STAT3 and Smad3 was noted in RGC-32$^{-/-}$ CD4$^+$ cells. A trend for increased iTreg differentiation was also noted while Th1 and Th2 differentiation did not differ between WT and RGC-32$^{-/-}$CD4 cells.

In P-into-F1 cGHVD mice, RGC-32$^{-/-}$ donor CD4 cells displayed decreased expansion and proliferation compared to WT donor cells**.** Consistent with the in vitro data, RGC-32$^{-/-}$ donor CD4 cells displayed lower proportion of IL-17$^+$ cells. Bm12-into- B6 cGVHD induced in RGC-32$^{-/-}$ mice was characterized by decreased anti-dsDNA titers versus WT B6 recipients.

Conclusion: RGC-32 is a novel mediator of Th17 differentiation. In cGVHD expression of RGC-32 on CD4 cells is critical for their proliferation, expansion and IL-17 differentiation while expression of RGC-32 on B cells is critical for optimal autoantibody production. These data support the idea that RGC-32 blockade has the potential to attenuate autoimmune parameters of cGVHD and possibly reverse abnormalities in the Th17 and Treg cell pathways that contribute to lupus pathogenesis. These observations provide a compelling rationale for further investigating the therapeutic potential of RGC-32 blockade in murine and human lupus.

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A Peptide Mimic Inhibits the Cross Reaction of Anti-DNA Antibodies with Glomerular Antigens. Yumin Xia, Ertan Eryilmaz, Rahul Pawar, David Cowburn and Chaim Putterman. Albert Einstein College of Medicine, Bronx, NY.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by high titers of multiple autoantibodies. Of those, anti-DNA antibodies play a key role in the pathogenesis of lupus nephritis by cross reacting with renal antigens. Previously, we generated a panel of anti-DNA antibodies from the murine PL9–11 anti-DNA mAb (IgG3), which share identical variable regions of both heavy and light chains but differ in their heavy chain constant region. We demonstrated that the binding affinity of the PL9–11 mAbs to self-antigens (including renal antigens) is isotype-dependent. The present study was designed to further investigate the cross reaction between anti-DNA antibodies and renal antigens, by identifying a peptide mimic that can bind to multiple anti-DNA isotypes.

Methods: A phage display library was used for peptide selection, and identified a 12-mer peptide, ALWPPNLHAWVP or "ALW". The specificity and kinetics of binding affinity of ALW to anti-DNA isotypes were determined by ELISA and surface plasmon resonance. Inhibition and cell surface ELISAs, flow cytometry, and glomerular binding assays were performed to evaluate how well ALW inhibits murine and human anti-DNA antibodies in binding to glomerular antigens in vitro and ex vivo.

Results: The ALW peptide exhibits differential binding affinity to the PL9–11 anti-DNA antibodies in the order of IgG2b >IgG2a >IgG3=IgG1. Pre-incubation with the ALW peptide significantly reduced the binding of anti-DNA IgGs to dsDNA, laminin, matrigel, mesangial cells, and isolated glomeruli. Moreover, the inhibition by ALW of anti-DNA binding was isotype-dependent. Alanine replacement studies and phage binding assays confirmed the specificity of the amino acid sequence in the binding of ALW to the PL9–11 panel. Finally, ALW significantly inhibited the binding of sera from MRL/lpr and B6.Sle1/3 mice and patients with active SLE to nuclear and glomerular antigens.

Conclusion: The ALW peptide significantly inhibits the binding of nephritogenic anti-DNA antibodies and human/mouse lupus sera to multiple self-antigens, presumably by mimicking their antigenic properties. The ALW peptide or its derivatives may potentially be a useful approach in the treatment of lupus nephritis and other autoantibody-mediated disease manifestations, by

inhibiting the binding of polyclonal anti-DNA antibodies to their in vivo targets.

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Peptidylarginine Deiminase Inhibition Mitigates NET Formation and Protects Against Kidney, Skin, and Vascular Disease in Lupus-Prone MRL/Lpr Mice. Jason S. Knight[1], Venkataraman Subramanian[2], Alexander A. O'Dell[1], Srilakshmi Yalavarthi[1], Wenpu Zhao[3], Carolyne K. Smith[3], Jeffrey B. Hodgin[1], Paul Ryan Thompson[2] and Mariana J. Kaplan[3]. [1]University of Michigan, Ann Arbor, MI, [2]The Scripps Research Institute, Jupiter, FL, [3]National Institutes of Health, Bethesda, MD.

Background/Purpose: An imbalance between neutrophil extracellular trap (NET) production and NET degradation has been observed in systemic lupus erythematosus (SLE), potentially contributing to autoantigen externalization, type I interferon production, and endothelial dysfunction. We have previously demonstrated that peptidylarginine deiminase (PAD) inhibition can mitigate NET formation and protect against vascular damage in the New Zealand Mixed model of lupus. However, another strategy for disrupting NET formation—knockout of *NOX2*—accelerates lupus in a different mouse model, MRL/*lpr*. Here, we tested PAD inhibition in MRL/*lpr* mice in an attempt to clarify whether some NET inhibitory pathways may be consistently therapeutic across different models of SLE.

Methods: NET formation, autoantibodies to NETs, interferon signature, and endothelial function were characterized at baseline in MRL/*lpr* mice. MRL/*lpr* mice were also treated for six weeks (daily, from 8 to 14 weeks of age) with two different PAD inhibitors, Cl-amidine and the newly developed BB-Cl-amidine. NET formation, interferon signature, endothelial function, nephritis, and skin disease were examined in treated mice.

Results: Neutrophils from MRL/*lpr* mice demonstrate more NET formation than controls. MRL/*lpr* mice also form autoantibodies to NETs and have evidence of endothelial dysfunction. PAD inhibition with either Cl-amidine or BB-Cl-amidine markedly improves endothelial function, while downregulating expression of type I interferon-regulated genes. PAD inhibition also protects against proteinuria, immune complex deposition in the kidneys, and skin disease.

Conclusion: Chemical PAD inhibition reduces NET formation, while protecting against damage to the endothelium, kidneys, and skin in various lupus models. The strategy by which NETs are targeted will have to be carefully considered if human studies are to be undertaken.

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Treatment with a Glycolipid Ameliorates Lupus Dermatitis and Expands Skin ãä T Cells That Promote the Migration of Langerhans Dendritic Cells. Ram Raj Singh, Anna Eriksson, Darshan Randhawa and Miguel-Angel Gutierrez. UCLA, Los Angeles, CA.

Background/Purpose: Self antigens are taken from tissues to local lymphoid organs to acquire ability to avoid self-reactivity. This important immune function is accomplished by dendritic cell (DC) populations that primarily reside in tissues. We posit that a defect in the migration of tissue-resident DCs may predispose to autoimmunity in a tissue-specific manner; and an improved migration of tissue-specific DC may ameliorate disease in the respective organ. We have previously reported that lupus dermatitis-prone MRL mice exhibit a profound defect in the migration of skin-resident DC. Here, we investigated the effect of improved skin-DC migration on lupus dermatitis and determined mechanisms that regulate the migration of tissue-resident DC from tissues to lymph nodes

Methods: Skin and cutaneous lymph nodes from MRL-lpr mice and MHC-matched control mice and $\gamma\delta$ T cell-deficient mice were analyzed for Langerhans DC and skin-resident invariant $\gamma\delta$ T cells before and after treatment with a glycolipid αGalCer that was previously shown to ameliorate lupus dermatitis, without affecting disease in other organs.

Results: MRL mice that exhibit reduced skin-DC migration had reduced skin-resident $\gamma\delta$ T cells, whereas treatment with αGalCer reduced the severity of lupus dermatitis and restored skin-$\gamma\delta$ T cells and skin-DC migration. This effect of αGalCer was independent of its effect on invariant natural killer T cells, but required the presence of lipid antigen presenting molecule CD1d. We further show that gd T cell-deficient mice had reduced skin-DC migration in vivo, and skin-gd T cells directly promoted the migration of skin-DC in vitro via CD40L–CD40 interaction.

Conclusion: Our data elucidate a new mechanism of regulation of skin-DC homeostasis whereby skin-gd T cells normally facilitate skin-DC migration from skin to cutaneous lymph node. Such 'local' control of migratory behavior of tissue-DC can regulate immune response in a tissue-specific manner. This mechanism of skin-DC homeostasis is disrupted in lupus dermatitis, but can be repaired by treatment with a glycolipid.

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The Effect of TNF Inhibition on the Autoreactive B Cell Repertoire in SLE Prone Mice. Anne Davidson, Weiqing Huang and Ranjit Sahu. Feinstein Institute for Medical Research, Manhasset, NY.

Background/Purpose: TNF inhibitors are widely used for inflammatory diseases but often induce ANAs that sometimes progress to overt SLE. TNF deficient mice fail to generate germinal centers (GCs) but are still able to mount effective humoral responses to exogenous antigens. A similar loss of GCs occurs in the tonsils of RA patients treated chronically with TNF inhibitors. The goal of these studies was to analyze the mechanism of induction of ANAs by TNF inhibition and the nature of the checkpoint between ANA induction and clinical SLE in a mouse model.

Methods: TNF deficient autoimmune prone Sle1 mice were generated and the 3H9 IgVH transgene that confers anti-DNA and anti-cardiolipin specificity was introduced. Mice were followed clinically and sacrificed at the age of 52 weeks. Spleen cells were analyzed by single cell PCR for the repertoire of Vk light chains associated with the 3H9 heavy chain. Selected 3H9/Vk combinations were transfected into 293 cells and supernatants were tested for autoreactivity by ELISA.

Results: TNF deficient Sle1 mice did not spontaneously develop clinical SLE or proteinuria and survived until at least 52 weeks of age. Surprisingly, serum levels of both anti-chromatin and anti-dsDNA antibodies were decreased in TNF deficient mice compared with their TNF sufficient controls, with similar results in the 3H9 TNF deficient mice. By contrast, TNF deficient mice developed high titers of IgG anti-cardiolipin autoantibodies. Similar results were observed in Sle1.TNFR1 deficient but not Sle1.TNFR2 deficient mice. Single cell analysis of the follicular B cell repertoire of 3H9.Sle1 TNF deficient mice revealed a loss of 3H9/Vk12–46.Jk2 encoded B cells that can bind to histones and chromatin.

We have previously shown a preferential selection of Vk5 light chains into the GCs of 3H9 SLE prone mice; these light chains confer anti-chromatin activity in their germline configuration and acquire high affinity anti-DNA and anti-cardiolipin activity as a result of somatic mutations. Since GCs are not present in TNF deficient mice we analyzed the light chain repertoire of splenic class switched B cells and plasma cells. 3H9.Sle1 mice had marked overrepresentation of Vk5 encoded light chains among their class switched B cells and plasma cells. By contrast, 3H9.Sle1 TNF deficient mice had few Vk5 encoded plasma cells and instead had a vast overrepresentation of Vk4–57-1. Co-transfection of this light chain with 3H9 into 293 cells revealed that this combination had anti-cardiolipin but not anti-DNA or anti-chromatin activity. Further analysis of the Vk4–57-1 encoded light chains from class switched B cells of TNF deficient mice revealed that they were all germline encoded.

Conclusion: TNF deficiency has significant effects on the Ig repertoire of mature and antigen activated B cells. The loss of GCs in TNF deficient Sle1 mice alters the spontaneously autoreactive Ig repertoire and is associated with a decrease in somatic mutations in autoreactive B cells suggesting that these cells have matured in an environment that is not exposed to cognate T cell help. The data further suggest that a "second hit" that bypasses the germinal center defect is required for TNF inhibition to induce pathogenic autoimmunity.

Disclosure: A. Davidson, None; **W. Huang**, None; **R. Sahu**, None.

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HM-0523, a Novel Syk Inhibitor Blocks Glomerulonephritis and Extends Life Spans in Lupus Prone MRL/Lpr Mice. Yu Cai, Zhipeng Wu, Ping Ren, Xiaoming Dai, Jianlin He, Fang Yin, Wei Deng, Guangxiu Dai, Weiguo Su and Xiong Li. Hutchison Medipharma Limited, Shanghai, China.

Background/Purpose: Syk is a key mediator of signaling events downstream of a wide array of receptors important for immune functions, including the B cell receptor, immunoglobulin receptors bearing the Fcg or Fce chain. Therefore, modulation of Syk could provide a novel therapeutic approach for autoimmune diseases and cancers. HM-0523, a highly potent and selective, orally available Syk inhibitor, is currently in Phase I clinical trials. The aim of this study is to evaluate the efficacy of HM-0523 in a systemic lupus erythematous (SLE) model in lupus-prone (MRL/lpr) mice.

Methods: HM-0523 was orally administered to MRL/lpr mice before the disease onset. Key lupus features, including skin lesions, proteinuria and blood urea nitrogen levels were examined periodically. Overall survival and renal pathologic parameters were also assessed during the study (8–25 weeks).

Results: Lupus-prone (MRL/lpr) mice, commonly used as a SLE model, spontaneously develop autoimmune disorders that reflect pathologies of human SLE, including enlargement of lymph nodes, elevation of IgG levels, anti-nuclear antibody production, proteinuria, and kidney failure caused by inflammation of the glomeruli.

In this study, *in vivo* efficacy of the orally active HM-0523 was evaluated in the lupus-prone (MRL/lpr) mice. The mice, at the age of 8 weeks, were prophylactically administrated with HM-0523 at 0, 5 and 20 mg/kg (QD), respectively. HM-0523, at 20 mg/kg, significantly blocked skin lesions [skin lesion score: 1.0 ± 0.3 (vehicle control) vs. 0.0 ± 0.0 (HM-0523); $p< 0.05$], delayed the onset of proteinuria and reduced the immune organs to body weight ratios [for example, spleen: 1.744 ± 0.158 (vehicle control) vs. 0.426 ± 0.034 (HM-0523) $p< 0.05$]. HM-0523, at 20 mg/kg, also significantly suppressed production of anti-dsDNA antibodies [408.6 ± 172.6 KU/ML (vehicle control) vs. 156.3 ± 25.8 KU/ML (HM-0523) $p< 0.05$]. Histopathological investigation demonstrated that HM-0523, at 20 mg/kg, greatly alleviated the pathological changes in renal, including glomerulonephritis, interstitial nephritis, and perivascular infiltration. HM-0523, at 20 mg/kg, also significantly inhibited increase of serum BUN and creatinine. Overall survival rate at week 25 in the HM-0523 treated mice was 100% (at 20 mg/kg and 5 mg/kg) compared to 70.0% in controls ($p< 0.01$). These comprehensive data indicate that HM-0523 has significant activity against the development of lupus and could be developed as a novel therapeutic agent for the treatment of SLE.

Conclusion: Our data demonstrated that HM-0523, acting through selective inhibition of Syk activation, exhibited significant beneficial effects in a murine lupus model. HM-0523 is currently in Phase I clinical trials. These new data provided support that HM-0523 could potentially become a novel therapeutic agent for systemic lupus erythematous.

Disclosure: Y. Cai, Hutchison Medipharma Limited, 3; **Z. Wu**, Hutchison Medipharma Limited, 3; **P. Ren**, Hutchison Medipharma Limited, 3; **X. Dai**, Hutchison Medipharma Limited, 3; **J. He**, Hutchison Medipharma Limited, 3; **F. Yin**, Hutchison Medipharma Limited, 3; **W. Deng**, Hutchison Medipharma Limited, 3; **G. Dai**, Hutchison Medipharma Limited, 3; **W. Su**, Hutchison Medipharma Limited, 3; **X. Li**, Hutchison Medipharma Limited, 3.

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The Combination of Metformin and 2-Deoxy-D-Glucose Normalizes CD4 T Cell Metabolism and Functions, and Reverse Disease in Murine Models of Lupus. Laurence Morel, Yiming Yin, Seung-Chul Choi, Eric S. Sobel and Byron Croker. University of Florida, Gainesville, FL.

Background/Purpose: Autoreactive CD4 T cells are key effectors in Systemic Lupus Erythematosus (SLE). Cell metabolism is an important checkpoint for T cell activationand differentiation. Both Anaerobic glycolysis and mitochondrial oxidative phosphorylation are necessary for effector CD4 T cell differentiation and inflammatory cytokine production. We hypothesized that 1) SLE T cells have metabolic defects that impair their functions; 2) Targeting CD4 T cell metabolism may abrogate CD4 T cell inflammatory functions and reduce disease symptoms in SLE mice; 3) The functions of CD4 T cells from SLE patients can be normalized by treatment with metabolic inhibitors.

Methods: CD4 T cells from lupus-prone mice and controls, as well as CD4 T cells obtained from SLE patients and healthy controls were treated with metformin or 2-DG, or a combination of the two. Several models of lupus-prone mice were treated with these drugs, either before or after disease onset. Glycolysis (extracellular acidification rate; ECAR) and oxygen consumption rate (OCR) were measured in CD4 T cells with an Extracellular Flux Analyzer. CD4 T cell activation and effector subsets were analyzed by flow cytometry. Disease progression was assessed by measuring serum anti-dsDNA IgG and anti-nuclear autoantibodies by ELISA and immunofluorescence, as well as renal histopathology.

Results: CD4 T cells from lupus mice have a significantly higher metabolism with increase in both ECAR and OCR, as well as an enhanced mTOR activity as compared to control mice. To normalize T cell metabolism in these mice, we used metformin, which activates the AMPK pathway and inhibits mitochondrial oxygen consumption, and 2-DG, an inhibitor of glycolysis. *In vitro*, metformin blocked IFNγ production and enhanced Treg development. 2-DG also blocked IFNγ production, but only after T cell activation. *In vivo*, a combined treatment with metformin and 2-DG normalized T cell metabolism and reversed disease phenotypes, including T cell activation and effector functions, as well as autoantibody production in the B6.Sle1.Sle2.Sle3 and the NZB/WF1 spontaneous models, as well as the chronic graft-vs-host disease model. Renal pathology is pending. Neither treatment with metformin or 2-DG alone resulted in disease reversal. Further, CD4 T cells from SLE patients showed an enhanced metabolism as compared to healthy controls, and their excessive IFNγ production was significantly reduced by metformin.

Conclusion: The combination of a glucose inhibitor with metformin restores T cell functions and reverses disease in mouse models, while metformin treatment normalizes the function of T cells from lupus patients. We propose that T cell metabolism is a novel target for SLE treatment.

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ONO-4059 - a Highly Potent and Dual Oral Inhibitor of Bruton's Tyrosine Kinase (Btk) and Tec Kinase: Improves Anti-Nuclear Antibodies–mediated SLE in Mice. Yuko Ariza, Toshio Yoshizawa, Yoshiko Ueda, Masayuki Murata and Kazuhito Kawabata. Ono Pharmaceutical Co., Ltd., Osaka, Japan.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a complex and heterogeneous autoimmune disease associated with the over production of high affinity autoantibodies, mainly raised against nuclear antigens and can be considered a B-cell disease. These autoantibodies mediate tissue injury affecting multiple organs such as skin and joints in mild forms of the disease to Central Nervous System (CNS) and kidney damage in severe forms that can be fatal. SLE is a chronic disease with a relapsing and remitting time-course of unknown etiology and the precise understanding of how these auto-antibodies contribute to the disease is still incomplete. However, overactivity of B-cell responsiveness to immune stimulation and direct activation of circulating FcR bearing cells are sufficient to initiate inflammatory responses, which may be an essential feature of SLE pathogenesis. ONO-4059 is a highly potent and dual oral Btk/Tec inhibitor with an IC_{50} in the sub-nmol/L range. We have previously shown that ONO-4059 strongly suppressed B-cell activation, FcγR-induced TNFα production in monocytes and FcεR-induced TNFα production in mast cells (ACR 2012). Given Btk/Tec play a critical role in B-cell development and function, we examined the potential efficacy of ONO-4059 using female NZB/WF1 mice in a model of spontaneous SLE.

Methods: Mice were randomized to two treatment groups and fed a diet containing 0.012% (equivalent to 20 mg/kg/day) and 0.0037% (6 mg/kg/day) ONO-4059 from 12 to 37 weeks. The mice were weighed weekly and the level of anti-dsDNA antibody was examined on weeks of 28, 32 and 37. The level of proteinuria and overall survival were recorded during the treatment period. A subset of mice was sacrificed at 37 weeks for histopathological analysis of the kidney and ELISpot assays for total Ig-secreting cells and anti-dsDNA-secreting B-cells were evaluated in spleens.

Results: The treatment with 0.012% and 0.0037% of ONO-4059 resulted in 100% and 90% survival respectively, while 60% survival was observed in untreated mice. The onset of proteinuria was markedly lower in ONO-4059-treated mice (untreated: 6570.2±2520.5 μg/mL vs 0.012% and 0.0037% of ONO-4059 treated: 366.2±19.2 and 358.3±18.4 μg/mL). ONO-4059 dramatically inhibited the production of anti-dsDNA in serum by 76% ($P<0.05$, 0.0037% diet) and 98.6% ($P<0.01$, 0.012% diet), compared with untreated mice at week 28. Furthermore, the observed inhibition was much stronger at week 37 (95.5% and 98.9% respectively). Significant reductions in the numbers of total IgG and anti-dsDNA-secreting B-cells were apparent in spleens from ONO-4059-treated mice. Germinal center B-cells and plasma cells were also significantly lower in ONO-4059 treated mice.

Conclusion: Recent studies indicate that the pathogenesis of SLE is associated with B-cell activation and circulating FcR bearing cells, in which Btk/Tec may play an important role. Our results demonstrate that treatment

with ONO-4059 may simultaneously target autoantibody producing and effector cells to prevent the spontaneous disease development in NZB/WF1 mice. These data suggest that ONO-4059 may provide promising therapeutic benefit in human lupus and related disorders.

Disclosure: Y. Ariza, Ono Pharmaceutical Co., Ltd., 3; **T. Yoshizawa**, Ono Pharmaceutical Co., Ltd., 3; **Y. Ueda**, Ono Pharmaceutical Co., Ltd., 3; **M. Murata**, Ono Pharmaceutical Co., Ltd., 3; **K. Kawabata**, Ono Pharmaceutical Co., Ltd., 3.

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Helminthes Derivative for Treating Lupus and Colitis in Mice Models. Miri Blank[1], Tomer Bashi[1], Dana Ben-Ami Shor[1], Mati Fridkin[2], Iris Barshack[3], Alexander Volkov[4] and Yehuda Shoenfeld[1]. [1]Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Ramat Gan, Israel, [2]Weizmann Institute for Sciences, Rehovot, Israel, [3]Institute of Pathology, Sheba Medical Center, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Tel-Aviv, Israel, [4]Institute of Pathology, Sheba Medical Center, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Tel-Aviv, Israel.

Background/Purpose: In areas where helminthes infections are common, autoimmune diseases are rare. Treatment with ova from helminthes, improved clinical findings of inflammatory bowel disease and other autoimmune diseases. The tolerogenic properties of the helminthes and their ova were attributed to the phosphorylcholine (PC) molecule. We aimed to decipher the tolerogenic potential of Tuftsin-PC (TPC) compound in experimental Lupus and Colitis.

Methods: 1. Lupus prone NZBXW/F1 mice received subcutaneously TPC (5μg/ml), 3 times a week using preventive protocol. Autoantibodies were tested by ELISA, T-regulatory-cells by FACS, cytokines by RT-PCR and R&D ELISA DuoSet. Glomerulonephritis was addressed by the presence of proteinuria, PAS staining and immunoglobulin deposition in the mesangium by immunofluorescence. 2. Colitis was induced by Dextran-Sodium-Sulfate (DSS) in drinking water. TPC was given by daily oral ingestion (500 μg/mouse or PBS) starting at day (−2). DAI score was followed daily and histology of the colon was performed by H&E staining.

Results: 1. **Lupus** mice treated with TPC attenuated the development of glomerulonephritis, illustrated by a significant diminished proteinuria ($p<0.02$), and reduced immunoglobulin deposits in the kidney mesangium. TPC enhanced expression of TGFbeta and IL-10 ($p<0.001$), and inhibited anti-inflammatory cytokines profile on the level of protein and RT-PCR. Significant enhancement of CD4+CD25+FOXP3+ T-regulatory cells phenotype was documented. 2. Chemically induced **colitic** mice, treated with TPC, developed a significant moderate colitis, in comparison to mice which received the vehicle. The DAI score of the TPC treated mice was 0.9, whereas DAI score of 2.6 was observed in colitis mice which received the vehicle, $p<0.02$. The reduced DAI score in the TPC group was associated with a significant colon shortening and prevention of colon destruction as observed by histological analyses.

Conclusion: TPC delayed lupus development in lupus prone mice and prevented a significant colitis induction in naïve mice.

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Influenza A (H1N1) Virus Infection Triggers Severe Pulmonary Inflammation in Lupus-Prone Mice Following Viral Clearance. Samantha Slight-Webb, Harini Bagavant, Sherry Crowe, Jourdan R. Anderson and Judith A. James. Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Each year, up to one fifth of the United States population is infected with influenza virus. Although mortality rates are low, hundreds of thousands are hospitalized each year. Specific high risk groups, such as those with dysregulated immune systems, are in greater danger for complications from influenza. Further, infections are a common cause of hospitalizations and mortalities in patients with systemic lupus erythematosus (SLE). To understand the influenza immune response in SLE and the effect of infection on autoimmune disease in a controlled setting, we utilized the MRL-Fas(lpr) lupus-prone mouse model.

Methods: Female MRL-Fas(lpr) mice were infected with 200 EID^{50} influenza A virus PR/8/34 H1N1. Mice were weighed daily as a measurement of morbidity and viral burden was determined by quantitative RT-PCR of the influenza M1 gene. Further, lung, kidney, and spleen samples were collected at various time points post infection to analyze pathology by H&E and PAS staining, cytokines by ELISA, and cellular composition by flow cytometry. Total antigen-specific cells were determined by stimulated cells overnight with inactivated influenza virus and intracellular staining for cytokines. Serum was collected to determine autoantibody concentrations by ELISA. Apoptosis was examined in the spleen on paraffin-embedded spleen sections by TUNEL staining. Finally, the role of extrinsic apoptosis in influenza infected lupus-prone mice was examined by administration of 0.1 mM caspase-8 inhibitor (Z-IETD-FMK) and negative control (Z-FA-FMK) daily for six days.

Results: MRL-Fas(lpr) mice accumulated more CD8+ T cells and more TNF-a influenza A virus specific T cells with less neutrophil accumulation in the lung by day 7 post infection ($P<0.05$). Moreover, increased extrinsic apoptosis during influenza infection led to a reduction of autoimmune disease symptoms with decreased splenomegaly ($P<0.0005$) and kidney disease ($P<0.05$). Unlike acute infection, following clearance of the influenza A virus, MRL-Fas(lpr) mice had severe complications during the contraction and resolution phase with widespread severe pulmonary inflammation. Lupus-prone mice had an increased lung severity score ($P<0.05$) with significantly more CD4+ and CD8+ T cells and myeloid cells compared to MRL control mice at day 40 post infection ($P<0.005$). Further, the improvement of autoimmune disease symptoms ceased following clearance of the viral infection and by day 40 was similar to PBS treated MRL-Fas(lpr) mice.

Conclusion: Our findings suggest that autoimmunity drives an enhanced influenza-specific immune response to clear infection, but that severe complications can arise during the resolution of pulmonary inflammation. We propose that problems with pulmonary infection in lupus may arise not from an inadequate antigen-specific immune response, but from sustained pulmonary inflammation and defective cellular clearance causing prolonged symptoms in patients. Additionally, influenza infection diminishes autoimmune disease responses rather than exacerbate autoimmune pathology in mice during the acute infection as a direct result of virus induced apoptosis.

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Enhance Translatability Using Multi-Modality Disease Evaluation Approach in Lupus Model. Jie Zhang-Hoover[1], Alan Byford[1], Mark Zielstorff[1], Robert Faltus[1], Joseph Eckman[1], Kimberly Bettano[1], Gain Robinson[1], Raquel Sevilla[1], Bindu Bennet[2], Lisa LaFranco-Scheuch[2], Franklin Vives[3], Michael Judo[3], Gulesi Ayanoglu[3], Weisheng Zhang[1] and Milenko Cicmil[1]. [1]Merck Research Laboratories, Boston, MA, [2]Merck Research Laboratories, West Point, PA, [3]Merck Research Laboratories, Palo Alto, CA.

Background/Purpose: Rodent models mimic some aspects of human lupus disease manifestations in various tissues, such as kidney, skin, joint, and CNS. NZB/NZW F1 and MRL/lpr models have been used extensively for gaining understanding of disease driving mechanism as well as pharmacological evaluation of new therapies. However, the translatability of therapeutic results from rodent lupus models to human lupus patients is limited. Here, we explored the feasibility of using a combination of clinically relevant methods, such as biochemistry analysis, terminal histology, and *in vivo* imaging modalities, to characterize and/or quantify specific inflammatory pathways/tissue damage and to evaluate treatment effect in MRL/lpr mice.

Methods: Female MRL/lpr mice were treated with cyclophosphamide (50 mg/kg i.p. qw) starting at 6–8 weeks of age. Disease development was monitored by gross skin lesion scoring, conventional blood (anti-dsDNA and blood urea nitrogen) and urine (proteinuria) biochemistry, and terminal skin and kidney H&E histology analyses. Disease phenotypes were also monitored longitudinally *in vivo* using multi-modality imaging. Changes in glomerular filtration rate (GFR) were tracked by contrast agent Omnipaque washout using micro-computed tomography (micro-CT). Myeloperoxidase-dependent reactive oxygen species (ROS) production by neutrophils/myeloid cells was quantified with luminol-bioluminescence imaging (luminol-BLI) to monitor skin and joint inflammation. Finally, changes in cerebral cortical thickness and ventricle size were measured by brain magnetic resonance imaging (MRI).

Results: MRL/lpr mice treated with cyclophosphamide had no detectable production of anti-nuclear antibodies and exhibited with minimal skin and kidney disease phenotype. Neutrophil activation and ROS production in the skin and hind limbs visualized by luminol-BLI was detectable at 12 weeks of age and preceded gross skin lesion observation at 14 weeks of age. MicroCT detected a GFR decrease as early as 14 weeks of age in MRL/lpr mice, compared to the blood urea nitrogen level increase at 16 weeks of age. Skin and kidney imaging

results correlated with the terminal tissue H&E histology evaluation. Furthermore, MRI of the brain detected cerebral cortical thinning as early as 10 weeks of age in MRL/lpr mice. Cyclophosphamide treatment resulted in reduced progression of the cerebral cortical thinning process in these mice.

Conclusion: Here for the first time we have successfully demonstrated that evaluation of disease progression and treatment effect can be achieved by a combination of *in vivo* imaging, blood biochemistry, and terminal histological analysis in MRL/lpr model. The novel non-invasive imaging approach in MRL/lpr model captured disease progression and treatment effect efficiently. This comprehensive approach of combined *in-life* and terminal inflammation pathway/tissue damage evaluation in a pre-clinical lupus model provides a potential platform for translatable biomarkers of lupus diagnosis and treatment evaluation in drug discovery.

Disclosure: J. Zhang-Hoover, Merck Pharmaceuticals, 3; **A. Byford**, Merck Pharmaceuticals, 3; **M. Zielstorff**, Merck Pharmaceuticals, 3; **R. Faltus**, Merck Pharmaceuticals, 3; **J. Eckman**, Merck Pharmaceuticals, 3; **K. Bettano**, Merck Pharmaceuticals, 3; **G. Robinson**, Merck Pharmaceuticals, 3; **R. Sevilla**, Merck Pharmaceuticals, 3; **B. Bennet**, Merck Pharmaceuticals, 3; **L. LaFranco-Scheuch**, Merck Pharmaceuticals, 3; **F. Vives**, Merck Pharmaceuticals, 3; **M. Judo**, Merck Pharmaceuticals, 3; **G. Ayanoglu**, Merck Pharmaceuticals, 3; **W. Zhang**, Merck Pharmaceuticals, 3; **M. Cicmil**, Merck Pharmaceuticals, 3.

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Decreased Severity of Pristane Induced Lupus in miR155 Deficient Mice. Harald Leiss, Wilhelm Salzberger, Irina Gessl, Barbara Schwarzecker, Nicolas Kozakowski, Stephan Blüml, Antonia Puchner, Birgit Niederreiter, Carl-Walter Steiner, Josef Smolen and Georg H. Stummvoll. Medical University of Vienna, Vienna, Austria.

Background/Purpose: MicroRNAs (miRs) are an important class of regulators of gene expression that are associated with a variety of biological functions. Deregulation of endogenous miR155 was observed in many autoimmune conditions, including SLE. We herein examine the role of miR155 in the development of systemic manifestations in murine pristane induced lupus by evaluating the severity of organ involvement and assessing serum antibody-levels and T helper cell homeostasis.

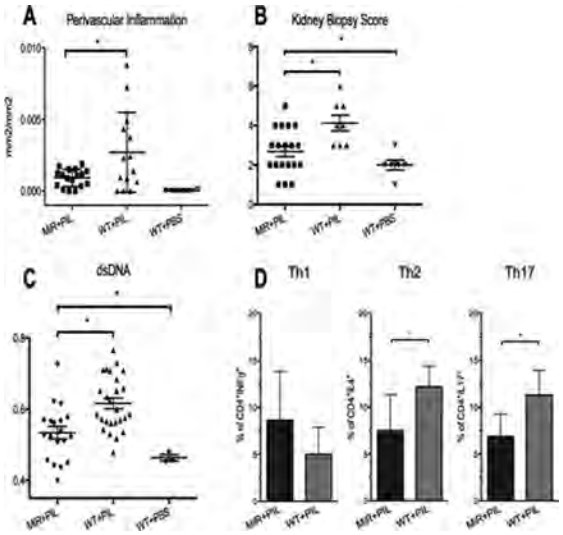
Methods: MiR155-deficient (miR155-PIL) and C57/Bl6 (WT-PIL) mice were injected i.p. with 0.5ml of pristane or PBS as control (WT-PBS). In order to observe the effects of miR155 deficiency in fully developed SLE, we analyzed the mice 8 months after induction.

A blinded specialist appraised histological features of GN using the composite kidney biopsy score (KBS). Histological features of pneumonitis were quantified by an image analysis system: Lungs were scored for the severity of perivascular inflammation by analyzing the numbers of affected vessels and the area of the inflammatory infiltrate. In order to assess the composition of these infiltrates, specimens were stained with B220 (B), CD3 (T), Neu7/4 (neutrophils) and F4/80 (macrophages) and analyzed by cell-identification algorithms for nuclear segmentation (HistoQuest¨).

Lymphocytes were isolated from spleens and analyzed separately for each mouse by standard FACS procedures. For analysis of the Th1, 2 or 17 subsets, respectively, cells were re-stimulated *in vivo* with anti-CD3 and anti-CD28abs.

Results: Lungs were affected in both pristane-treated groups, but not in controls. MiR155-PIL had reduced lupus severity as indicated by significantly decreased perivascular inflammatory area with B cells being the most prominent inflammatory cell type in the HistoQuest analysis (Fig. 1A). Without showing clinical abnormalities WT-PIL had a more severe renal involvement in the kidney biopsy score than miR-PIL (Fig. 1B). Corresponding with reduced severity in organ involvement, miR155-PIL had lower serum levels of anti-dsDNA-abs (Fig. 1C), decreased frequencies of $CD4^+$ cells (14.24 ± 0.7587 vs. 18.04 ± 1.075, $p=0.01$) and slightly lower frequencies of activated $CD4^+CD25^+Foxp3^-$ cells (1.539 ± 0.1279 vs. 1.838 ± 0.2259, p=ns.). Interestingly, also frequencies of $CD4^+CD25^+Foxp3^+$ regulatory T cells were lower in Mir155-PIL (1.689 ± 0.1388 vs. 2.375 ± 0.2320, $p=0.03$). Upon restimulation, $CD4^+$ cells showed a more pronounced Th2 and Th17 response in WT-PIL, but no significant differences in Th1 phenotype (Fig. 1D).

Conclusion: MiR155 deficiency in PIL mice did not prevent the development of disease, but was associated with less severe lung and kidney involvement, lower serum auto-abs levels and lower Th17 and Th2 frequencies when analyzed in fully established PIL after 8 months. Thus, antagonisation of miR155 might be a beneficial future approach in treating SLE.



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Inhibiting Tweak (TNF-like weak inducer of apoptosis) Signaling Improves Blood Brain Barrier Integrity and Protects from Neuronal Damage in Murine Neuropsychiatric Lupus. Jing Wen[1], Jessica Doerner[1], Ariel Stock[1], Jennifer Michaelson[2], Linda Burkly[2], Maria Gulinello[1] and Chaim Putterman[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]Biogen Idec, Cambridge, MA.

Background/Purpose: While neuropsychiatric involvement in systemic lupus erythematosus (NPSLE) is relatively common and appears early, the underlying mechanisms are not fully understood. The disruption of the blood brain barrier (BBB) is believed to be one key pathological feature in NPSLE, allowing the passage of neurotoxic autoantibodies into the brain.

TWEAK is a cytokine member of the TNF superfamily; the TWEAK receptor, Fn14, is expressed in brain endothelial cells, astrocytes, microglia and neurons. We recently found that lupus prone MRL/lpr Fn14 knockout (KO) mice display a markedly attenuated neuropsychiatric phenotype, as revealed by a significant reduction in depressive-like behavior and improved cognitive function. Morever, NPSLE patients demonstrate high levels of TWEAK in the cerebrospinal fluid (CSF). We undertook the current studies to determine the mechanisms by which TWEAK signaling is involved in the pathogenesis of NPSLE.

Methods: Brains from female MRL/lpr Fn14WT and MRL/lpr Fn14KO mice at 20 weeks of age were prepared for qRT-PCR, Western blot and immunohistochemistry (IHC). Cellular infiltrates were quantified by hematoyxlin and eosin staining. To assess BBB integrity, extravascular fibronectin and IgG deposition, VCAM/ICAM, and iNOS expression was evaluated by Western blot, IHC and qPRT-PCR, respectively. Complement activation was assessed by measuring the expression of C3, C4a and C6 by qRT-PCR and Western blot. Fluoro Jade B and TUNEL staining were employed to analyze neuronal damage and apoptosis in the brain. Furthermore, gliosis, neuron loss, and neurogenesis were assessed by immunostaining with GFAP, NeuN and Ki-67, respectively.

Results: We found that MRL/lpr Fn14KO mice had significantly improved BBB integrity, as shown by a lower CSF albumin index, decreased fibronectin and IgG deposition, and reduced brain expression of VCAM, ICAM and iNOS. Furthermore, Fn14KO mice exhibited significantly fewer cellular infiltrates in the choroid plexus compared to the Fn14WT mice. At the same time, a significant reduction in C3, C4a and C6 expression was observed in brains of Fn14KO mice. Neuronal damage, an important pathological change present in lupus animal models, was also ameliorated by Fn14 deficiency. Fn14KO mice displayed reduced apoptosis in the cortex, as well as less neuron loss and less gliosis in the hippocampus. Interestingly, there were no differences in neurogenesis and in microglia activation between Fn14KO and Fn14WT mice.

Conclusion: Our studies indicate that TWEAK/Fn14 interactions can play a central role in the pathogenesis of NPSLE by improving BBB integrity

and reducing neuronal damage, suggesting this pathway as a novel target for therapeutic intervention in this disease.

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Identification of Eat-2 As a Lupus Susceptibility Gene in New Zealand Black (NZB) Mice That Regulates Dendritic Cell Function. Nafiseh Talaei[1] and Joan E. Wither[2]. [1]Toronto Western Research Institute, Toronto, ON, [2]Toronto Western Research Institute, Toronto Western Hospital, University of Toronto, Toronto, ON.

Background/Purpose: We have previously shown that B6 mice with an introgressed homozygous NZB chromosome (c) 1 interval (70 to 100 cM) develop high titres of antinuclear antibodies and severe glomerulonephritis (GN), with approximately 40% of the mice dying by 8 months age. Using subcongenic mice with shorter intervals in this region we found that T cell and dendritic cell (DC) defects, derived from several genetic loci, synergize to convert the preclinical disease in c1(96–100) mice to fatal GN in c1(70–100) mice through expansion of pro-inflammatory T cell subsets. EAT-2, an adapter molecule in the SLAM signaling pathway that is located in the 70–96 cM region, has a promoter polymorphism in NZB mice that is predicted to lead to decreased expression. In this study we examine whether altered expression of this molecule leads to the abnormal DC function observed in these mice.

Methods: Expression levels of EAT-2 were evaluated in bone marrow derived DC from c1 congenic and B6 mice using *q*RT-PCR and Western blots. siRNAs targeting EAT-2 gene were introduced into B6 and c1 congenic DC. Subsequently, naïve OVA-specific TCR transgenic (OTII) T cells from B6 and c1 congenic mice were isolated and co-cultured with EAT-2 silenced or scrambled control treated DC in the presence of OVA peptide. In parallel DC were stimulated with anti-CD40 before and after knock-down of EAT-2. Production of cytokines (IL-12, IL-6, IFN-g) by DC and T cells were analyzed by flow cytometry.

Results: Expression of EAT-2 was reduced by ~70% in DC from c1(70–100) mice as compared to c1(96–100) and B6 mice. Silencing of the EAT-2 gene in DC from B6 and congenic mice resulted in increased production of IL-12 as compared to scrambled control and was associated with increased differentiation of OVA-specific T cells from both B6 and c1 congenic mice to a Th1 phenotype. Knock-down of EAT-2 in DC from all strains of mice did not affect IL-6 production when co-cultured with B6.OTII T cells, however augmented IL-6 production was seen for c1(96–100) and c1(70–100) DC when co-cultured with naïve T cells from c1 congenic mice. This was accompanied by somewhat enhanced production of IL-21, but not IL-17, by c1 congenic OTII T cells. SLAM/SLAM homotypic interactions inhibit production of IL-12 and IL-6 by CD40L-activated DCs. Consistent with a role for EAT-2 in this inhibition, knock-down of EAT-2 resulted in increased production of IL-12 by CD40-stimulated B6 and c1(96–100) DC. This was recapitulated in c1(70–100) DC, which demonstrated increased production of IL-12, and a trend to increased production of IL-6, as compared to B6 or c1(96–100) DC following CD40 stimulation.

Conclusion: EAT-2 negatively regulates cytokine production in DC downstream of the SLAM molecules and a genetic polymorphism leading to low levels of EAT-2 in c1(70–100) mice may contribute to the increased production of IL-12 we have previously observed for their DC.

Disclosure: N. Talaei, None; **J. E. Wither**, None.

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Dermal Injury Promotes Nephritis Flare in Lupus-Prone NZM2328 Mice. Kaitlyn Clark, Tamra J. Reed, Jeffrey B. Hodgin and J. Michelle Kahlenberg. University of Michigan, Ann Arbor, MI.

Background/Purpose: Systemic lupus erythematosus is an autoimmune disease with pleotropic manifestations, including severe skin disease, hematologic abnormalities and nephritis. Clinically, lupus is characterized by episodes of flare and remission, and exposures such as UV light or viral infections have been proposed as flare triggers. However, induction of flare has been difficult to emulate in murine models. Here, we describe a system in which cutaneous injury is able to trigger the development of a lupus nephritis flare in lupus-prone mice.

Methods: 20-week old NZM2328 (NZM) female mice were depilated in a 2x4 cm area on the dorsal skin followed by 25 applications of duct tape under isofluroane anesthesia. NZM mice lacking the type I interferon (IFN) receptor (iNZM) were used as a non-lupus prone control. Skin biopsies were taken prior to and following tape-stripping, and gene expression changes were evaluated via quantitative PCR. Serial blood draws and urine collection were obtained following tape stripping, and anti-double-stranded DNA titers, C3 levels and urine albumin/creatinine ratios were measured via commercially available kits. Inflammatory cells were isolated from whole kidneys and cell populations were measured via flow cytometry. Renal immune complex deposition was assessed via immunofluorescent staining for IgG and C3. Renal inflammation was assessed on Hematoxylin and Eosin stained sections by a blinded renal pathologist.

Results: NZM mice subjected to tape stripping had a rapid dermal upregulation of type I IFN-mediated and inflammatory gene expression. Importantly, tape-stripped NZM mice developed onset of proteinuria and death within 3 weeks of skin injury whereas non-tape stripped littermates remained free of proteinuria. This was coupled with a drop in serum C3. Proteinuria induction did not occur in tape-stripped iNZM mice, suggesting the rapid death was not secondary to skin injury itself. In NZM mice, renal immune complex deposition was enhanced within two weeks of tape stripping, as was renal expression of the B cell chemokine CXCL13. Evaluation of renal inflammatory cell populations revealed an increased infiltrate of B cells in the kidney prior to proteinuria onset.

Conclusion: Cutaneous injury via tape-stripping induces a rapid flare of lupus nephritis that is preceded by enhanced renal immune complex deposition and B cell recruitment. This novel model provides a mechanism to study the communication between the dermal and renal immune systems and how crosstalk between these systems can lead to lupus flare, thus providing potential targets for prevention of flares in human disease.

Disclosure: K. Clark, None; **T. J. Reed**, None; **J. B. Hodgin**, None; **J. M. Kahlenberg**, None.

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Type I Interferon Induces the Depletion and Dysfunction of Endothelial Progenitor Cells in Gld. ApoE−/− C57BL/6 Mice. Linyu Geng, Shiying Wang, Xuebing Feng and Lingyun Sun. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

Background/Purpose: To study whether the accelerated atherosclerosis in SLE is mediated by type I interferon (IFN-I) through the regulation of endothelial progenitor cells (EPCs) in gld. ApoE−/− C57BL/6 mice under normal chow diet.

Methods: The gld. ApoE−/− mice were generated through intercrossing and backcrossing of gld. and ApoE−/− mice on C57BL/6 background. At 20 weeks of age, female gld. ApoE−/− mice were injected with either saline vehicle, synthetic CPG-oligodeoxynucleiotides (CPG-ODN) IRS423 (TLR7/9 agonists) or IRS661 (TLR7 antagonists) twice a week. 4 weeks later, mice were euthanized. Quantitative PCR was applied to detect the mRNA expressions of IFN-I inducible genes. EPCs in peripheral blood and bone marrow were recognized as Sca-1+CD309+ cells by FACS. The capacities of EPC to differentiate into mature endothelial cells, to re-adherent and to form vascular-like structure were measured to determine EPC functions. To find out whether EPC function could be modulated by other cytokines, EPCs from 24 weeks old female gld. ApoE−/− mice were cultured in vitro in the presence of either IFN-α, IL-1β, TNF-α, IRS423 (1μM), IRS954 (1μM) or saline vehicle control for 24 hours.

Results: gld. ApoE−/− C57BL/6 mice displayed both aggravated lupus-like disease and atherosclerosis under normal diet. Decreased percentage of peripheral blood and bone marrow EPCs, impaired EPC functions and increased atherosclerotic lesion area were observed in gld. ApoE−/− mice. IRS661 treatment inhibited the expressions of IFN-I inducible genes (including IRF7, MX1, OAS1, OAS2 and IFIT-2), while IRS423 promoted the expressions of these genes. The number of EPCs and the ability of EPC to form normal endothelial cells monolayer, to form cavity structure and to re-adherent in gld. ApoE−/− mice were restored after IRS661 treatment, and deteriorated after IRS423 treatment. In vitro experiments showed that only recombinant IFN-α could affect EPC functions, while other interventions including IL-1β, TNF-α, IRS423 and IRS661 did not have a direct impact on EPC regulation.

Conclusion: IFN-I, activated through the upregulation of the TLR7/9 signaling, could induce the depletion and dysfunction of both peripheral and BM EPCs in gld. ApoE−/− C57BL/6 mice, thus may contribute to the development of atherosclerosis.

Disclosure: L. Geng, None; **S. Wang**, None; **X. Feng**, None; **L. Sun**, None.

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Hydroxycholorquine Is Cardioprotective in an *In Vivo* Rat Model of Myocardial Ischaemic Reperfusion Injury. Lauren Bourke[1], Valerie Taylor[2], James McCormick[3], Charis Pericelous[1], John Franklin[1], Daniel Stuckey[2], Mark Lythgoe[2], Anastasis Stephanou[4] and Yiannis Ioannou[5]. [1]Centre for Rheumatology Research, University College London, London, United Kingdom, [2]Centre for Advanced Biomedical Imaging (CABI), University College London, London, United Kingdom, [3]Clinical & Molecular Genetics Unit, University College London, London, United Kingdom, [4]Medical and Molecular Biology Unit (MMBU), University College London, London, United Kingdom, [5]Centre for Rheumatology Research, University College Hospital London, London, United Kingdom.

Background/Purpose: A significant amount of myocardial damage during a myocardial infarction (MI) occurs during the reperfusion stage which is known as ischaemic reperfusion (I/R) injury and can account for up to 50% of cell death. Systemic lupus erythematosus (SLE) is associated with increased cardiovascular morbidity and mortality. Many of these patients are treated with the drug Hydroxycholoroquine (HCQ) and whilst retrospective studies have suggested HCQ lowers the risk of suffering an MI, inevitably many still do. This study investigates the effects of HCQ on myocardial survival during reperfusion (I/R injury).

Methods: Male Sprague-Dawley rats (200–220g) were dosed by gavage with 200mg/kg of HCQ once a day for three days which yielded blood concentrations of HCQ in line with that seen in patients (1–2μg/ml). Rats underwent myocardial I/R injury by occlusion of the left anterior descending (LAD) coronary artery, with reperfusion after 40 mins. Twenty-four hours later animals were sacrificed, hearts excised, the LAD re-occluded and the hearts perfused with Evans Blue dye (to label perfused myocardium). Hearts were then cut into 1mm slices and stained with TTC to label viable myocardium). Infarct size (IS) was calculated as entire myocardium area - area of viable tissue. Area at risk (AAR) was then calculated from entire myocardium area - perfused myocardium from the area of viable myocardium. *In vitro* experiments were performed in neonatal rat cardiomyocytes isolated from 1–2 day old rat pups and exposed to simulated I/R injury using a hypoxic chamber. Protein lysates were collected and processed for use in western blot.

Results: *In vivo*, HCQ resulted in a significant reduction in infarct size (IS) presented as a percentage of area at risk (AAR) (area supplied by the LAD). Control rats had an IS/AAR of 20.36% (n=5)), which was significantly reduced in the presence of HCQ to 13.41% (n=5)(p=0.0159). When the hearts were probed for the protective kinase ERK, there was a significant increase in the phosphorylation of ERK in the presence of HCQ - control 0.11 for p-p42 and 0.14 for p-p44 versus HCQ 0.55 (p=0.029) for p-p42 and 0.52 (p=0.020) for p-p44. *In vitro* data has also shown that pre-treatment of neonatal rat cardiomyocytes with HCQ prior to simulated I/R injury was protective, specifically reducing apoptosis. This was observed by a reduction of 43.74% (p value <0.0001) in the number of TUNEL positive cells during reoxygenation and also confirmed thorough probing for cleaved caspase-3. A cell viability assay confirmed that HCQ caused a reduction in total cell death in cells exposed to simulated I/R injury of 57.85% (p value = 0.0213). Correlating with decreased cell death, enhanced ERK phosphorylation in HCQ treated cells was observed in a dose-dependent manner with no significant differences in p38, JNK nor Akt. Cells treated with HCQ and exposed to simulated I/R injury were incubated with the ERK inhibitor U1026 and protective effects of HCQ as assessed via caspase-3 cleavage were completely reversed.

Conclusion: HCQ is cardioprotective in this *in vivo* I/R injury model and phosphorylation of the pro-survival kinase ERK is enhanced in the presence of HCQ. Mechanistic experiments *in vitro* demonstrate that HCQ protection is ERK dependent.

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Breach of B Cell Tolerance in New Zealand Black Chromosome 1 Congenic Mice. Kieran Manion[1], Nan-Hua Chang[2], Yuriy Baglaenko[1] and Joan Wither[2]. [1]University of Toronto, Toronto, ON, [2]Toronto Western Research Institute, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Mapping studies in the lupus-prone New Zealand Black (NZB) mouse strain identified an interval from 170.8–181 Mb on chromosome 1 sufficient to induce B cell-intrinsic increases in B cell activation, germinal center formation and anti-ssDNA autoantibody production when introgressed onto a non-autoimmune C57BL/6 background. It was previously shown that B cells from these mice (denoted c1) expressing a transgene for hen egg lysozyme (HEL)-specific immunoglobulin in the presence of soluble HEL were able to breach anergy. The purpose of the current study was to determine if the autoimmune phenotype in c1 mice similarly resulted from a breach of anergy in DNA-reactive B cells.

Methods: To generate mice with a homogeneous, anergic B cell repertoire, genes for heavy (3H9) and light (Vκ8) chains specific for ssDNA were backcrossed onto the c1 strain (c1.Vκ8/3H9). Mice with both knock-in genes were aged to 8 months, at which time autoantibody production and B cell localization, activation and differentiation were assessed by ELISA and flow cytometry, respectively. Adoptive transfers were conducted by staining 10 million negatively isolated splenic B cells from 8–10 week old B6.Vκ8/3H9 or c1.Vκ8/3H9 mice with carboxyfluorescein succinimidyl ester (CFSE) and injecting them via tail vein into B6 or c1 mice. Splenic B cell subsets were analyzed by flow cytometry 7 days post-injection to assess survival, activation, plasma cell differentiation and germinal center recruitment. Germinal centers and plasma cells were further quantified by immunofluorescence microscopy.

Results: Surprisingly, analysis of autoantibody production and splenic B cell subsets in c1.Vκ8/3H9 mice revealed a reduced breach of tolerance to ssDNA as compared to c1 mice and a failure to recapitulate the cellular defects observed in the HEL model. To examine whether the preponderance of anergic B cells in the repertoire of c1.Vκ8/3H9 mice was suppressing the breach of tolerance that would otherwise occur, adoptive transfers of B6.Vκ8/3H9 and c1.Vκ8/3H9 B cells into recipients lacking the knock-in genes were performed. Supporting the previous observations of a breach of B cell tolerance in the c1 HEL model, transferred c1.Vκ8/3H9 B cells showed significantly increased activation compared to their B6 counterparts. Furthermore, increased marginal zone localization and a corresponding decrease in the size of the mature follicular subset for transferred c1.Vκ8/3H9 B cells were observed. Despite this, preliminary data did not reveal a difference between transferred B6.Vκ8/3H9 B cells and transferred c1.Vκ8/3H9 B cells with respect to recruitment to germinal centers in either B6 or c1 recipients, suggesting that the activation of transferred c1.Vκ8/3H9 B cells may be extra-follicular in nature.

Conclusion: The results reaffirm previous findings that c1 mice breach tolerance to nuclear self-antigen through an intrinsic B cell defect. There is also indication of an active role for anergic B cells in maintaining tolerance through immune suppression.

Disclosure: K. Manion, None; **N. H. Chang**, None; **Y. Baglaenko**, None; **J. Wither**, None.

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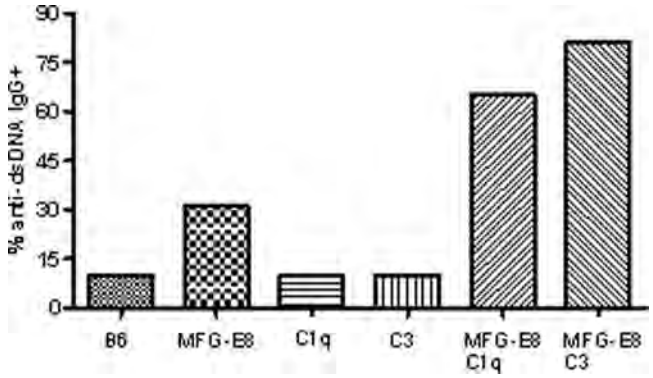
Distinct Contributions of C1q and C3 in Preventing Immunogenicity of Apoptotic Cells in Lupus. Clayton Sontheimer, Yenly Nguyen, Keith B. Elkon and YuFeng Peng. University of Washington, Seattle, WA.

Background/Purpose: Defective clearance of apoptotic cells (AC) and complement deficiency are important contributors to the pathogenesis of systemic lupus. Dead (sunburn) cells and complement activation are also observed in patients with cutaneous lupus. ACs are opsonized by several proteins including C1q, C3 and MFG-E8. MFG-E8 is a soluble milk protein that binds to phosphatidylserine on AC and facilitates their removal through its interaction with avb3 and avb5 integrins on phagocytes. In its absence, AC debris accumulates in germinal centers. In MFG-E8−/− B6 mice, we observed a C1q dependent increase of C3/IgG deposition on MZ B cell and FDCs, suggesting excessive self antigens can activate the classical pathway and be presented as antigen/immune complexes to autoreactive B cells in spleen. In this study, we determined how the interaction between AC and complement contribute to autoantibody production, nephritis and photosensitivity in lupus.

Methods: We introduced MFG-E8−/−, C1q−/− and C3−/− into SLE 1 congenic mice. We created MFG-E8−/−C1q−/− and MFG-E8−/− C3−/− double knock-out in the SLE1 background. We analyzed the titers of anti-chromatin and anti-dsDNA (n =15–20 in each group) by ELISA and confirmed the results by *Crithidia luciliae* staining. We examined T and B cell phenotypes by flow cytometry. Kidney damage was evaluated by blood urea nitrogen, immuno-fluorescence and PAS staining. We exposed respective strains to repeated UVB irradiation and followed development of nephritis and skin lesions.



Results: In 7 month old female B6.SLE1 mice, 10% of mice developed anti-dsDNA IgG. Neither C1q nor C3 deficiency alone changed the percentages of anti-dsDNA IgG+ mice. MFG-E8−/− SLE1 mice had a significantly higher number of germinal center B cells and 30% of females became anti-dsDNA IgG+. Combining MFG-E8−/− with either C1q−/− or C3−/− significantly accelerated the production of anti-dsDNA IgG and increased the percentage of anti-dsDNA IgG+ mice to 65% and 80%, respectively (Figure). Furthermore, 50% MFG-E8−/−C1q−/− but 0% FG-E8−/−C3−/− SLE1 mice showed early mortality due to spontaneous lupus nephritis. When exposed to UVB irradiation, 90% (8 out 9) MFG-E8−/−C3−/− developed either acute nephritis or persistent skin lesions. On the contrary, none of MFG-E8−/−C1q−/− mice (0 out 15) experienced similar symptoms.

Conclusion: Both C1q and C3 are essential in reducing the immunogenicity of apoptotic cells in lupus. The protective mechanisms they provide depend on availability of other opsonins and environmental factors such as sunlight exposure.

Disclosure: C. Sontheimer, None; **Y. Nguyen**, None; **K. B. Elkon**, None; **Y. Peng**, None.

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17β Estradiol Regulates VCAM-1 Expression during Glomerulonephritis. Neelakshi Jog and Roberto Caricchio. Temple University, Philadelphia, PA.

Background/Purpose: The immunomodulating roles of estrogens are not completely understood. Although 17β estradiol (E2) has been shown to promote systemic autoimmunity, it has also been shown to inhibit pro-inflammatory cytokine secretion. We showed previously that treatment of male mice with E2 led to improved survival in nephrotoxic serum induced nephritis (NTN). In this study we aimed at determining the effect of E2 on intrinsic renal cells and to understand the role of E2 in regulating inflammation in vivo in the kidney during nephritis. Vascular Cell Adhesion Molecule, VCAM-1, is an adhesion molecule for leukocytes that is upregulated in vivo in mice with autoimmune nephritis, and in vitro in tubular epithelial cells and mesangial cells (MCs) upon stimulation with tumor necrosis factor alpha (TNFα) and Interferon gamma (IFNγ). In this study we determined whether E2 regulates the extent of renal inflammation by regulating adhesion molecule expression by MCs.

Methods: We used nephrotoxic serum induced nephritis as a model of autoimmune nephritis. Mice were treated with E2 pellets prior to induction of nephritis. We determined the molecular mechanisms of VCAM-1 regulation by E2 using cell and molecular biology techniques such as flow cytometry, immunofluorescence, Chromatin immunoprecipitation (ChIP) assays, and quantitative PCRs in TNFα stimulated MCs.

Results: We show that E2 treatment inhibited VCAM-1 upregulation in kidneys in vivo during NTN in both male and female mice. E2 also inhibited upregulation of VCAM-1 in MC upon TNFα stimulation. The VCAM-1 upregulation in MCs was regulated by the transcription factor NFκB, since inhibition of NFκB inhibited the upregulation. We further determined the molecular mechanism of regulation of VCAM-1 by E2. We show that E2 does not regulate the nuclear translocation of p65 subunit. ChIP assays showed that although E2 does not inhibit p65 binding to the VCAM-1 promoter, it inhibits the recruitment of RNA polymerase II to the promoter, suggesting that E2 may inhibit the formation of pre-initiation complex at the promoter. We showed previously that absence of Poly (ADP-Ribose) Polymerase-1 (PARP-1) inhibited TNFα stimulated VCAM-1 upregulation in mouse MCs. PARP-1 has been shown to interact with estrogen receptor and we showed that E2 inhibits PARP-1 activity in macrophages. PARP-1 has been also proposed as a co-factor for NFkB activation. We therefore determined whether E2 regulates VCAM-1 upregulation through PARP-1. Indeed our data show that PARP-1 interacts with p65 upon TNFα stimulation and this interaction is inhibited in the presence of E2.

Conclusion: Our data show that E2 inhibits upregulation of VCAM-1 in nephritic kidneys. Using mesangial cells we further showed that E2 inhibits VCAM-1 upregulation by inhibiting the formation of pre-initiation complex at the VCAM-1 promoter. E2 inhibits PARP-1 recruitment to p65, further inhibiting the recruitment of RNA polymerase II and transcription at the VCAM-1 promoter. We propose that E2 plays an important role in regulating renal inflammation locally, which may explain why nephritis in systemic autoimmunity tends to be worse in males.

Disclosure: N. Jog, None; **R. Caricchio**, None.

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Breakdown of Tolerance at the Tissue Level in Systemic Autoimmunity: Role of Tissue-Resident Dendritic Cells. Jennifer K. King, Rachael Philips, Anna Eriksson and Ram Raj Singh. UCLA, Los Angeles, CA.

Background/Purpose: Systemic autoimmune diseases such as lupus affect multiple organs including skin and kidneys, usually in a diverse fashion where only certain organs are affected in individual patients. It is unclear whether the breakdown in tolerance manifested by global immune dysregulation can account for the tissue specificity in relation to heterogeneity of disease, or if local factors also contribute. We hypothesized that the local immune environment may regulate tissue specificity and chose to study skin tolerance within a systemic lupus disease model. Here, we investigated whether a subset of skin-resident dendritic cells, namely Langerhans cells (LC), maintain immune tolerance in skin versus other target organs in a model of SLE.

Methods: We used genetically lupus-prone MRL/MpJ-Fas$^{+/+}$ (MRL+/+) and MRL-lpr mice that develop lupus dermatitis, nephritis, arthritis, vasculitis, and dsDNA antibodies as models of systemic autoimmunity. To conditionally ablate LC in these mice, we introgressed the Langerin-DTR-EGFP knockin mutation from the stock B6 onto the MRL by backcrossing >10 generations, and injected diphtheria toxin in adult mice. Recombinant desmoglein 3 (Dsg3) was used as a skin autoantigen to assess tissue-specific tolerance using an epicutaneous tolerization assay. Thymidine uptake/Ki67 expression was used for cell proliferation and Western blot for measuring autoantibodies against skin lysate. Disease was assessed by clinical and histological scoring.

Results: We previously reported that MRL mice have reduced migration of langerin^{+}DC from the skin to the skin-draining lymph nodes (dLN), with a profound defect in the emigration of LC from their epidermis. This migration defect worsens with age and disease onset. We hypothesized that this impaired DC migration observed in MRL mice play a role in the loss of skin tolerance. Indeed, lymphocytes from dLN of MRL-lpr mice spontaneously proliferate to a skin autoantigen, desmoglein 3 (Dsg3), which can be reversed by the epicutaneous application of Dsg3. Such resumption of tolerance to skin antigen, however, is prevented upon a transient ablation of LC in these mice. We then asked that if reduced DC cell migration to the dLN contributes to lupus dermatitis, then the complete ablation of them would further exacerbate dermatitis. Indeed, an inducible LC ablation in adult MRL-lpr and MRL+/+, but not in B6 and B6-lpr mice, accelerated and exacerbated lupus dermatitis and increased circulating antibodies against skin antigens, along with reduced frequency of IL-10-producing CD4 T cells in dLN. However, LC ablation did not affect disease in other organs such as kidneys, lung, or liver, and serum levels of systemic autoantibodies such as anti-dsDNA.

Conclusion: These data indicate that LCs maintain skin tolerance in systemic lupus, and highlight the importance of the local immune milieu in regulating tissue-specific autoimmunity, without affecting systemic immunity. Such immune regulation at the local level may explain the heterogeneity of multiorgan involvement in SLE. Our data have implications for therapy at the local organ level, providing a target for therapy to correct a local breakdown in tolerance rather than attempting correction at a systemic level.

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Microthrombotic Renal Vascular Lesions Are Associated to Increased Renal Inflammatory Infiltration in a Mouse Model of Lupus Nephritis.

María Galindo[1], Elena Gonzalo-Gil[1], Oscar Toldos[2], Carmen García-Herrero[1], Alicia Usategui[1], Sonia Pérez-Yagüe[3], Gabriel Criado[1], Domingo F. Barber[3] and Jose L. Pablos[1]. [1]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [2]Servicio de Anatomia Patologica, Hospital 12 de Octubre, Madrid, Spain, [3]Centro Nacional de Biotecnología (CNB-CSIC), Madrid, Spain.

Background/Purpose: In patients with lupus nephritis (LN), acute renal vascular and atherosclerotic lesions correlate with the degree of inflammation regardless the presence of antiphospholipid antibodies. The aim of this study was to confirm these results in MRL/lpr mice and to analyze the specific effect of blocking inflammatory factors and/or platelet aggregation.

Methods: The pattern of renal vascular disease, acute and chronic glomerular and tubulointerstitial lesions were specifically analyzed with histological staining (H&E, PAS) in 12–20-wk old female MRL/lpr mice with nephritis. Immunohistochemistry (IHC) techniques were used to detect CD41 (platelet aggregates), fibrinogen (FGN), periglomerular macrophagic F4/80 (quantified as the % of positive glomeruli), intraglomerular macrophage infiltration (Mac-2) and C3 deposition. Renal function was assessed by measuring proteinuria, serum creatinine and albumin (sCr, sAlb). Levels of a-dsDNA and anticardiolipin (aCL) antibodies were quantified by ELISA. The specific effect of treatment with steroids and antiaggregation (aspirin or clopidogrel) was analyzed. Association between categorical variables was tested by the X^2 test. For continuous variables, comparisons were carried out using *t*-test for two independent samples. A Spearman's rank was used for correlations among different study parameters. *P* values < 0.05 were considered significant.

Results: In the descriptive phase, 41 mice were analyzed. Histological, IHC and clinical characteristics of lpr mice with lupus nephritis are described in table 1.

Mice with microthrombotic renal vascular lesions showed a greater degree of periglomerular macrophage infiltration (p=0.002). All mice had detectable a-dsDNA or aCL IgG, irrespective of the presence of TMA or CD41+. Proteinuria positively correlated to the proportion of sclerotic glomeruli (r=0.4; p=0.01) and glomerular macrophage infiltration (r=0.46; p=0.004) and was higher in mice with diffuse proliferative glomerular lesions (340.8 vs110.8; p=0.02).

After two weeks of treatment, the specific effect of 15 mg/d dexamethasone, 10 mg/d aspirin or 1.5 mg/d clopidogrel, or combined therapy dexa+ antiaggregation was compared to PBS treatment in 52 mice, and results are detailed in table 2.

Table 1

	Mice (n=41)
Glomerular lesions:	–
Focal and segmental proliferative	53.70%
Diffuse proliferative	46.30%
Interstitial fibrosis	5%
Instertitial inflammation:	–
Medular	7.30%
Cortical	29.30%
Both	36.60%
Mice with sclerotic glomeruli (number of glomeruli)	46% (1–11)
Microthrombotic renal vascular lesions (thrombotic microangiopathy [TMA] or CD41+ microthrombi)	34%
Glomerular/extragomerular FGN (%)	–
Glomerular Mac-2 (%)	4.8 ± 3.6/ 0.8 ± 0.6
Periglomerular F4/80 (+ glom %)	3.9 ± 2.3
Mean sCr (mg/dl)	41.9 ± 21.4
Proteinuria (>300mg/dl)	0.5 ± 0.1
	13.20%

Table 2

	PBS	dexamethasone (15 ug/d)	aspirin/ clopidogrel (10o1,5mg/d)	dexamethasone and antiaggregation
Exp1	N=8	N=9	N=8	N=8
		↓ proteinuria**	↓ proteinuria **	↓ proteinuria*
		↓ a-dsDNA**	↓ a-dsDNA*	↓ a-dsDNA**
		= aCL	↓ aCL*	↓ aCL*
		= sCr and sAlb	= sCr and sAlb	= sCr and sAlb
		↓ CD41 (NS)	↓ CD41 (NS)	↓ CD41 (NS)
		= C3 deposition	↓ C3 deposition*	= C3 deposition
		↓ Mac-2*	↓ Mac-2*	↓ Mac-2*
		↓ F4/80**	↓ F4/80**	↓ F4/80**
Exp2	N=4	N=4	N=6	N=5
		↓ proteinuria*	↓ proteinuria**	↓ proteinuria**
		↓ a-dsDNA*	↓ a-dsDNA*	↓ a-dsDNA (NS)
		= aCL	= aCL	↓ aCL (NS)
		= sCr and sAlb	= sCr and sAlb	= sCr and sAlb
		↓ CD41 (NS)	↓ CD41 (NS)	↓ CD41 (NS)
		= C3 deposition	↓ C3 deposition*	↓ C3 deposition*
		↓ Mac-2*	↓ Mac-2**	↓ Mac-2*
		↓ F4/80*	↓ F4/80**	↓ F4/80*
Both	N=12	N=13	N=14	N=13
		↓ proteinuria***	↓ proteinuria***	↓ proteinuria**
		↓ a-dsDNA*	= a-dsDNA	↓ a-dsDNA*
		= aCL	= aCL	↓ aCL**
		= sCr and sAlb	= sCr and sAlb	= sCr and sAlb
		↓ CD41 (NS)	↓ CD41 (NS)	↓ CD41 (NS)
		= C3 deposition	↓ C3 deposition**	↓ C3 deposition*
		↓ Mac-2***	↓ Mac-2***	↓ Mac-2**
		↓ F4/80***	↓ F4/80***	↓ F4/80***

*: $p<0.05$; **:$p<0.01$; ***: $p<0.001$; NS: no significant

Conclusion: Presence of microthrombotic renal vascular lesions is associated to a higher degree of macrophage infiltration in MRL/lpr model of LN. Both dexamethasone and blockers of platelet aggregation reduce glomerular damage and inflammatory response, suggesting platelets involvement in inflammatory damage.

Disclosure: M. Galindo, None; **E. Gonzalo-Gil**, None; **O. Toldos**, None; **C. García-Herrero**, None; **A. Usategui**, None; **S. Pérez-Yagüe**, None; **G. Criado**, None; **D. F. Barber**, None; **J. L. Pablos**, None.

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Dysfunction of Glycosphingolipid Metabolism in Lupus Nephritis.

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Background/Purpose: Lupus is a chronic autoimmune disease characterized by autoantibody production and aberrant activation and proliferation of lymphocytes. Subsequent deposition of immune complexes in target tissues leads to an inflammatory reaction and tissue damage. Glomerulonephritis (GN) is the most severe complication of lupus, lupus nephritis (LN) affecting up to two-thirds of lupus patients and is associated with high morbidity and mortality. LN is characterized by podocyte dysfunction, proteinuria and a decrease in renal function. Glycosphingolipids (GSLs) are a heterogeneous class of lipids in the sphingolipid family that play a role in the regulation of cellular processes. Highly abundant in the kidney, GSLs play a role in a variety of kidney diseases including GN, nephropathy, and polycystic kidney disease. GSLs are present in most cells and are thought to play roles in signal transduction, cell-cell adhesion and immune responses. GSLs are enriched in the kidney. Loss of sialic acid residues from the surface of podocytes is linked to proteinuria in GN. Neuraminidases (NEUs) remove sialic acids from gangliosides to generate lactosylceramide (LacCer) and glucosylceramide, (GlcCer) ganglioside precursors.

Methods: Kidney homogenates, serum and urine samples were prepared from 11, 14 and 18 week-old MRL/lpr lupus mice and human lupus patients and controls. GSL levels were measured by Supercritical Fluid Chromatography coupled with tandem mass spectrometry. NEU protein and activity were measured by western immunoblot and/or enzyme activity assays. Gene expression was analyzed by real-time RTPCR on RNA isolated from kidney cortex. Matrix-assisted laser desorption/ionization-imaging mass spectrometry (MALDI-IMS) and immunohistochemistry for LacCer was performed on frozen kidney sections.

Results: GlcCer and LacCer levels are significantly elevated 3–5-fold, NEU activity and Neu1 expression levels are significantly elevated 2-fold and

12-fold, respectively, in the kidney of lupus mice with nephritis compared to lupus mice without nephritis and/or normal, healthy controls. Levels of ceramide and other enzymes in the GSL metabolic pathway are unchanged. Urine LacCer levels appear to be significantly elevated prior to significant increases in proteinuria. Using MALDI-IMS, we also observed a striking decrease in the levels of gangliosides GM1 and GM3 in the LN mice compared to controls. Of translational significance, human LN patients compared to controls have a 1) significant 25-fold increase in urine LacCer levels, 2) significant increase in urine Neu1 levels, and 3) observed increased LacCer levels in the mesangial regions in renal biopsy sections. No significant differences were observed in serum LacCer levels in LN patients compared to controls.

Conclusion: Our results demonstrate that elevated LacCer is likely due to an upregulation of the GSL catabolic pathway in the kidney of lupus mice and patients with nephritis. Furthermore, the elevated LacCer levels in the urine of patients may be largely due to kidney rather than systemic contributions and our mouse studies suggest it may be an earlier marker than proteinuria of nephritis.

Disclosure: T. Thiyagarajan, None; **L. Siskind**, None; **J. Oates**, None; **R. Drake**, None; **T. K. Nowling**, None.

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Interferon Regulatory Factor-5 Promotes Disease in the *MRL/Lpr* Mouse Model of Lupus. Amanda Watkins, Ramon Bonegio, Guneet Kochar, Gabriella Wilson, Bari Laskow, Christophe Richez, Ian Rifkin and Kei Yasuda. Boston University School of Medicine, Boston, MA.

Background/Purpose: Interferon regulatory factor 5 (IRF5) polymorphisms are strongly associated with an increased risk of developing Systemic Lupus Erythematosus (SLE). SLE is caused, in part, by the survival of self-reactive B cells which produce autoantibodies that can deposit in tissues such as the kidney leading to tissue injury and significant morbidity.

In murine lupus models, IRF5-deficiency has been shown to reduce disease severity, in part, by ameliorating immune complex-mediated kidney disease. IRF5 is highly expressed in B cells where it is involved in isotype switching to IgG2a and TLR-mediated activation. However, whether IRF5 contributes to lupus pathogenesis by promoting B cell differentiation or plasma cell survival is not fully understood. We hypothesized that IRF5 may contribute to disease in the MRL/lpr lupus mouse model by promoting B cell survival through regulation of B lymphocyte stimulator (BLyS).

Methods: We evaluated the effect of IRF5-deficiency in the MRL/lpr mouse lupus model by measuring splenomegaly, lymphadenophathy, severity of kidney disease, as well as total serum IgG and anti-Sm/RNP and anti-nuclear autoantibodies. In addition we analyzed the splenic and bone marrow lymphocyte populations and measured serum BLyS levels over the course of disease.

Results: We found that IRF5-deficient ($IRF5^{-/-}$) MRL/lpr mice developed much less severe disease compared to their IRF5-sufficient ($IRF5^{+/+}$) littermates. Despite markedly lower serum levels of anti-nuclear autoantibodies and reduced total splenocyte and $CD4^+$ T cell numbers, $IRF5^{-/-}$ MRL/lpr mice had similar numbers of all splenic B cell subsets compared to $IRF5^{+/+}$ MRL/lpr mice, suggesting that IRF5 is not involved in B cell development to the mature B cell stage. However, $IRF5^{-/-}$ MRL/lpr mice had greatly reduced numbers of splenic plasmablasts and bone marrow plasma cells. Despite the marked reduction in serum IgG and plasmablast numbers in $IRF5^{-/-}$ MRL/lpr mice, serum BLyS levels remained highly elevated with no difference observed between groups.

Conclusion: Overall our data demonstrate that IRF5 contributes to disease pathogenesis in the MRL/lpr lupus model and that this is due, at least in part, to the role of IRF5 in plasma cell formation and independently of BLyS production. Our data also suggest that combined therapy targeting both IRF5 and BLyS might be a particularly effective therapeutic approach in lupus.

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STAT3 Inhibition Delays the Onset of Lupus Nephritis in MRL/*Lpr Mice*. Linsday Edwards[1] and Vasileios C. Kyttaris[2]. [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Background/Purpose: The transcription factor Signal transducer and activator of transcription (STAT) 3 is overexpressed and aberrantly activated in patients with SLE as well as lupus-prone mice. More specifically, STAT3 plays a central role in T cell differentiation into pathogenic Th17 as well as T follicular helper cells, two T cell subsets that are thought to orchestrate autoimmune responses in SLE. Our previous studies have shown that STAT3 is also important in SLE T cell migration in response to chemokines. To better understand its role in SLE, we inhibited STAT3 in lupus-prone mice using the small molecule Stattic.

Methods: MRL/*lpr* mice were treated 3 times per week with 10 mg/kg of the STAT3 inhibitor Stattic or vehicle delivered intraperitoneally beginning at 6 weeks of age and continuing through 15 weeks of age. The kidney function was monitored weekly by urinalysis. Levels of anti-dsDNA antibodies, C3 and various cytokines were measured in the serum. At the conclusion of treatment, tissues were harvested for histology and phenotypic analysis. *In vitro* assessment of the effects of Stattic treatment on T cell function was also performed.

Results: Stattic treated mice exhibited a delay in the onset of proteinuria by approximately 3 weeks. Stattic treated mice had lower levels of anti-dsDNA production (mean=1771 U/ml in treated vs. 32174 U/ml in control) and inflammatory cytokine production (serum IL-17 levels approximately 2-fold higher in untreated mice). Inhibitor treatment reduced lymphadenopathy, and resulted in a decrease in the total number of T cells in treated mice. Absolute numbers of T cells were 3–4 fold higher in untreated mice. Furthermore, the numbers of T follicular helper cells were reduced in Stattic treated mice by 4-fold. Complimentary *in vitro* experiments showed that T cells treated with Stattic exhibited a dose dependent decrease in proliferation and an approximately 70% decrease in their ability to migrate in response to CXCL12 stimulation.

Conclusion: From the data generated in this study, we conclude that treatment of lupus prone mice with a STAT3 inhibitor delays the onset of autoimmunity and end-kidney damage. Our *in vivo* and *in vitro* findings suggest that STAT3 inhibition leads to the following: a. decreased T cell proliferation, b. decreased Tfh cells and decreased anti-dsDNA production, and c. decreased cell migration in response to chemokines. We propose that STAT3 inhibition represents a therapeutic target in SLE and in particular lupus nephritis.

Disclosure: L. Edwards, None; **V. C. Kyttaris**, None.

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The Pathogenesis of Neuropsychiatric Systemic Lupus Erythematosus Is Dependent on Brain Intrinsic Factors. Ariel Stock, Jing Wen, Jessica Doerner and Chaim Putterman. Albert Einstein College of Medicine, Bronx, NY.

Background/Purpose: Neuropsychiatric disease is a common manifestation of systemic lupus erythematosus (SLE). Frequent presentations include depression, anxiety, memory loss and cognitive decline. The pathogenesis of neuropsychiatric SLE (NPSLE), however, remains unclear; several potential mechanisms include thrombosis, complement deposition, brain reactive autoantibodies, and cytokine mediated inflammation. The MRL-*fas*$^{lpr/lpr}$ (MRL/lpr) mouse has proven quite valuable to the study of SLE in general, including NPSLE. This is due to development of a disease profile similar to humans including renal and cutaneous manifestations, as well as an early neuropsychiatric phenotype characterized by depression and spatial memory deficit. However, it is not clear whether the neuropsychiatric manifestations of SLE are secondary to systemic disease or a primary pathogenic process.

Methods: In order to distinguish between the relative contributions of the central nervous system (CNS) vs hematopoietic compartments, we generated three groups of bone marrow chimeras between MRL/lpr mice and the congenic control MRL/+ mouse (Table 1). We monitored systemic disease progression through titers of autoantibodies and levels of proteinuria. The mice underwent extensive behavioral testing to characterize their motor, cognitive and emotional states, including open field, object placement, object recognition and the forced swim tests.

Results: MRL/lpràMRL/lpr mice showed increasing autoantibody titers over time, consistent with untransplanted MRL/lpr mice. MRL/+àMRL/+

mice showed consistently low or undetectable levels of autoantibodies. MRL/+àMRL/lpr mice showed early increases in autoantibody titers that decreased over time, indicative of MRL/+ bone marrow engraftment and abrogation of the MRL/lpr systemic disease phenotype. Behaviorally, MRL/+àMRL/lpr mice displayed a phenotype remarkably consistent with MRL/lpràMRL/lpr (as well as untransplanted MRL/lpr) mice, including depression like behavior (Fig 1) and increased spatial memory deficits. MRL/+àMRL/+ mice displayed no behavioral deficits, consistent with untransplanted MRL/+ mice.

Conclusion: Previous studies have shown that MRL/lpr mice develop neuropsychiatric disease similar to human lupus, though have not determined whether this is a primary CNS manifestation or secondary to peripheral immune abnormalities and systemic disease. The data presented herein indicate that the MRL/lpr CNS is responsible for NPSLE development, which can occur absent hematopoietic contributions.

Table 1. Bone marrow transplant scheme

Donor	Host	Chimera	Source of CNS Cells	Source of Hematopoeitic Cells
MRL/+	MRL/+	MRL/+→MRL/+	MRL/+	MRL/+
MRL/lpr	MRL/lpr	MRL/lpr→MRL/lpr	MRL/lpr	MRL/lpr
MRL/+	MRL/lpr	MRL/+→MRL/lpr	MRL/lpr	MRL/+

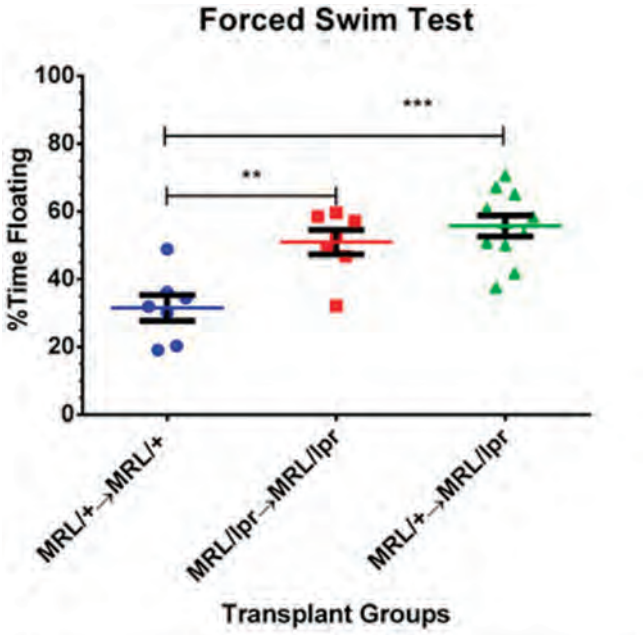

Fig 1. Despite the transplant of MRL/+ bone marrow and resultant resolution of systemic autoimmunity, MRL/+→MRL/lpr mice display depressive like behavior similar to MRL/lpr→MRL/lpr mice, as measured by forced swim test.

Disclosure: A. Stock, None; **J. Wen**, None; **J. Doerner**, None; **C. Putterman**, None.

ACR Poster Session A
Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Treatment and Management Studies
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Safety and Efficiency of Low-Dose Interleukin-2 Treatment in Systemic Lupus Erythematosus. Jing He[1], Xia Zhang[1], Xiaolin Sun[1], Jianping Guo[1], Yunbo Wei[2], Zhaohua Hou[2], Yu Di[3] and Zhanguo Li[1]. [1]Peking University People's Hospital, Beijing, China, [2]Shandong Analysis and Test Center, Shandong Academy of Science, Shandong, China, [3]Monash University, Clayton, Austria.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by loss of tolerance to nuclear self-antigens, production of pathogenic autoantibodies and damage tomultiple organs. While corticosteroids and immunosuppressive agents have improved the outcome of patients, there remains a significant unmet need for safe and more effective treatments. Low-dose Interleukin-2 (IL-2) therapy has recently been shown effective to treat autoimmune disease. We aimed to assess the safety and efficacy of low-dose IL-2 therapy in active SLE.

Methods: We conducted a clinical trail on active SLE patients (NCT02084238). A total of 40 patients were enrolled. Patients with SLE Disease Activity Index (SLEDAI) scores ≥8 received three courses of low dose recombinant human IL-2 (1 million IU every second day for 2 weeks followed by a 2-week hiatus). The primary end point was the response rate at week 10. Both the safety and efficiency of IL-2 therapy were evaluated.

Results: Total 36 patients (36/40, 90%) achieved an SLE Responder Index (SRI) improvement at week 6. No patients demonstrated high grad adverse events; mild injection-site reaction was observed in 5 patients (5/40, 12.5%). Better response was seen in patients with skin involvement (erythema, photo sensibility, Rdynolds, vasculitis), hematologic abnormities (leukopenia, Thrombocytopenia and anemia) and disease-related fever.Patients showed the improvement of major laboratory indicators, including reduced anti-dsDNA autoantibody titres and 24-hour proteinuria, and increased levels of the complement proteins C3 and C4. Immunological analysis showed significant increase of Treg cells and decrease of effector helper T cells after the therapy.

Conclusion: Our results showed that low-dose IL-2 therapy in active SLE was safe and achieved satisfactory efficacywith increasing Treg and decreasing effector helper T cells.

Disclosure: J. He, None; **X. Zhang**, None; **X. Sun**, None; **J. Guo**, None; **Y. Wei**, None; **Z. Hou**, None; **Y. Di**, None; **Z. Li**, None.

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Approach to Discriminate Treatment Impact in Both Moderate and Severe SLE: The Atacicept Phase IIb Trial Design. Joan T. Merrill[1], Yong Li[2], Stephen D. Wax[3] and Christopher Tehlirian[4]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]R&D Global BioStatistics, EMD Serono, Billerica, MA, [3]Global Clinical Development Center - Immunology, EMD Serono Inc, Rockland, MA, [4]EMD Serono, Rockland, MA.

Background/Purpose: Increases in background treatment in SLE trials lead to high placebo group responses in patients with moderate but not those with high disease activity (1–3). The optimal allowance of background medication increase to ensure patient safety and still enable data interpretability over a range of disease severity remains unknown. Since even moderate lupus activity leads to organ damage, disability and poor quality of life (4–6), a goal of the ADDRESS II trial of atacicept (inhibitor of B cell stimulators BLyS and APRIL) is to discriminate treatment effects on both moderate and high SLE disease activity within one trial.

Methods: This 24 week study examines atacicept (75 or 150 mg/wk) versus placebo for the reduction of SLE disease activity. Similar to the Phase III belimumab (BLISS) program, study drug is added to standard of care. Unlike the BLISS design, which allowed temporary unlimited background steroids and permanent increases in immune suppressant doses, after the Week 4 study visit ADDRESS II restricts the corticosteroid dose to ≤ the dose at the Screening visit and ≤30 mg prednisone (or equivalent), and immunosuppressives must be stable from 2 months before screening throughout the duration of the study. Additional treatment defines a non-responder.

Results: The primary endpoint is similar to the BLISS trials as defined by the SRI (≥4 point reduction in SLEDAI-2K, <10% increase in PGA, no new BILAG A score and ≤1 new BILAG B score, at Week 24 compared to the Screening visit). A placebo response rate of 30% (lower than BLISS placebo rates due to more stringent background medication restriction) is predicted, enabling 80% power to detect a 20% absolute difference in proportion achieving an SRI response with 93 patients per arm and a 2-sided α=0.05 with a randomization ratio of 1:1:1. A steroid reduction endpoint, which includes a provision for lack of flare, will also be examined. Patients are stratified by level of disease activity (SLEDAI < 10 vs. ≥ 10), race, and use of mycophenolate at screening, enabling analysis of response in these subpopulations. A 2 year extension study will give all completer patients the option to receive active treatment (placebo patients will be switched to 150 mg atacicept), but the dose will be blinded, allowing longer term evaluation of responses.

Conclusion: Interpretation of SLE trials is hampered by confusing data in patients with moderate disease activity. The ADDRESS II study was

designed to discern treatment impact in both severe and moderate disease patients, who represent a large, underserved population with poor quality of life and progressive damage despite high response rates to increased standard of care in trials.

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Disclosure: J. T. Merrill, EMD Serono, 5, GSK, 5, Lilly, 5; **Y. Li**, EMD Serono, 3; **S. D. Wax**, EMD Serono, 3; **C. Tehlirian**, EMD Serono, 3.

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24-Month Outcomes Associated with Belimumab in Patients with Systemic Lupus Erythematosus in Clinical Practice Settings. Christopher E. Collins[1], Hong Kan[2], Maria Dall'era[3], Cynthia Macahilig[4], Ramesh Pappu[2], Charles T. Molta[5] and Volker Koscielny[6]. [1]MedStar Washington Hospital Center, Washington, DC, [2]GlaxoSmithKline, Research Triangle Park, NC, [3]UCSF, San Francisco, CA, [4]Medical Data Analytics, Parsippany, NJ, [5]GlaxoSmithKline, Philadelphia, PA, [6]GlaxoSmithKline, Brentford, United Kingdom.

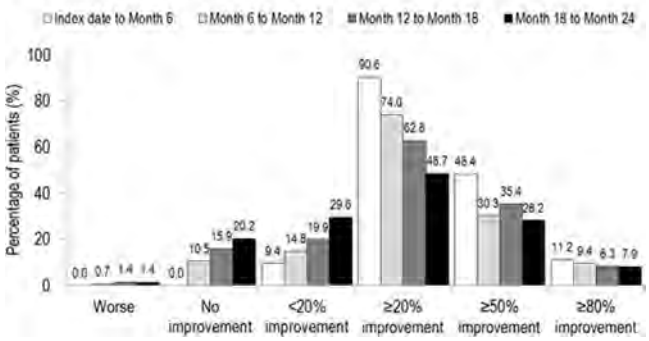
Background/Purpose: The clinical efficacy of belimumab in patients with systemic lupus erythematosus (SLE) has been demonstrated in large randomized clinical trials. We examined clinical outcomes following belimumab treatment in clinical practice settings in the US.

Methods: OBSErve US (evaluation **O**f use of **B**elimumab in clinical practice **SE**ttings in the US; GSK Study: BLM117295) was a multicenter, retrospective, medical chart review study. Rheumatologists from non-academic centers were randomly recruited from a national physician database. Physicians reported retrospective data from medical charts of randomly identified adult SLE patients in their care who had received ≥8 belimumab infusions as part of usual care. Data were reported for 6 months prior to index date (date of first belimumab infusion), and every 6 months thereafter for up to 24 months. The primary outcome measure was physician impression of change in SLE disease manifestations, relative to the previous time point. Here we report the final analyses of patients who had outcomes reported at Month 24.

Results: At index date, 501 patient charts were analyzed. By Month 24, 112 patients were lost to follow-up and 112 patients had discontinued. Most common reasons for discontinuation included patient request (n=44, 40.2%), medication not effective (n=33, 29.5%), disease progression (n=15, 13.4%), loss of insurance or reimbursement (n=14, 12.5%) and lack of patient compliance (n=11, 9.8%). The Month 24 completer analysis included 277 patients: female, 90.6%; mean age, 42.9 (standard deviation [SD]: 12.0) years; Caucasian, 52.7%; African-American, 24.9%; Hispanic, 15.5%; Other, 6.9%.

Of the 277 patients, 134 (48.4%) had ≥50% improvement in overall clinical response between index date and Month 6 according to the physicians' impression (**Figure 1**). Further improvements were observed during Months 6–12 and 12–18. At Month 24, 78 (28.2%) patients had improved by ≥50% since Month 18.

Figure 1. Clinical responses in completers (n=277), according to physicians' impression of overall change in SLE manifestations relative to the previous timepoint



At index date, 218/277 (78.7%) patients received concomitant steroids (mean [SD] dose: 18.0 [12.2] mg/day); by Month 24, the mean (SD) dose among these patients was 2.9 (3.4) mg/day and 95 (43.6%) patients had discontinued steroids. During the 24-month period six patients initiated steroid treatment.

Of the 277 patients who completed to Month 24, 69 (24.9%) had SELENA-SLEDAI scores available at index date and Month 24; the mean (SD) score at index date was 12.5 (3.0), with a reduction of 8.2 (3.8), to 4.4 (3.1) by Month 24.

Conclusion: Overall, physicians reported continued improvements in clinical outcomes throughout the study, among patients who had completed 24 months of treatment with belimumab 10 mg/kg plus usual care (≥8 belimumab infusions). Over 24 months, mean steroid dose among baseline users was reduced by 84%.

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Disclosure: C. E. Collins, GlaoxSmithKline, 5, GlaxoSmithKline, 8, Abbvie, 8; **H. Kan**, GlaxoSmithKline, 3, GlaxoSmithKline, 1; **M. Dall'era**, None; **C. Macahilig**, Medical Data Analytics, 9; **R. Pappu**, GlaxoSmithKline, 3, GlaxoSmithKline, 1; **C. T. Molta**, GlaxoSmithKline, 3, GlaxoSmithKline, 1; **V. Koscielny**, GlaxoSmithKline, 3, GlaxoSmithKline, 1.

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Evolution of Patients with Systemic Lupus Erythematous Treated with Belimumab in Clinical Practice Settings. Josefina Cortes[1], Carlos Marras[2], Jose Luis Andreu[3], Jaime Calvo-Alen[4], Angel M. Garcia-Aparicio[5], Elvira Diez Alvarez[6], Carlos Coronell[7], Elena Morejon[7], Alessandra Perna[8], Volker Koscielny[8] and Josep Ordi-Ros[1]. [1]Vall d'Hebron Hospital, Barcelona, Spain, [2]Virgen de la Arrixaca Hospital, Murcia, Spain, [3]Puerta de Hierro Universitary Hospital, Madrid, Spain, [4]Sierrallana Hospital, Torrelavega, Spain, [5]Virgen de la Salud Hospital, Toledo, Spain, [6]Leon Hospital, Leon, Spain, [7]GlaxoSmithKline, Madrid, Spain, [8]GlaxoSmithKline, Brentford, United Kingdom.

Background/Purpose: After the approval of belimumab for patients with systemic lupus erythematosus (SLE), the objective of this study is to describe the clinical outcomes associated with 6 months of belimumab treatment in clinical practice settings in Spain.

Methods: OBSErve (GSK 200883) is a multi-center and retrospective study from community-based rheumatology practices with high experience in SLE treatment. All adult SLE patients in their practices who had received belimumab (10mg/kg) as part of routine care were identified for chart abstraction. Baseline date is the date of belimumab initiation. The activity of the disease was classified as mild, moderate and severe according the perception of the disease manifestations by the physician or based on SELENA-SLEDAI index. The primary clinical outcome measure is the overall clinical response, reported as change from baseline in SLE disease manifestations, 6 months after belimumab initiation based on physician subjective assessment. Reasons for premature treatment discontinuation were collected as secondary variable of safety, and information about steroid use and dosage within the first 6 months of belimumab therapy was collected as secondary variables of efficacy.

Results: 64 eligible patient charts were included. The mean patient age was 42.7 years±12; 89% were female; 23% were diagnosed with SLE <5 years ago; 6%, 61% and 33% had mild, moderate and severe SLE respectively at baseline; 70% of patients had low C3 or C4, and 69% high anti-dsDNA at baseline. The most frequent reasons for initiating belimumab were an ineffective previous treatment regimen (78%), the intent to decrease steroid use (58%), and worsening patient condition (55%). The most frequent manifestation of SLE in these patients were musculoskeletal (arthritis=56.2%), Immunologic (low complement [C3, C4, or CH50]=53.13), Increased anti-dsDNA antibody levels=48.44%, and Mucocutaneous (Rash=26.56%). In general, belimumab appeared to be well-tolerated; two patients (3%) had discontinued belimumab within the first 6 months of therapy: one due to lack of efficacy, the other due to Pelvic inflammatory disease. After 6 months of belimumab therapy 72%, 52% and 27% of patients had an overall clinical improvement of >20%, >50% and >80% respectively. For the most frequent SLE manifestations, such as in arthritis (69%), low complements (47%), high anti-ds-DNA levels (48%), and fatigue (60%) a >50% improvement was observed. Additionally, the mean score of the SELENA-SLEDAI index decreased from 10.1 to 4.5 ($p<0.0001$) in the first 6 months. In 88% of the patients (n=57), a decrease SELENA-SLEDAI index was observed.

Oral steroids were used concomitantly in 95% of SLE patients at baseline. Patients had a mean reduction in steroid dose of 6.8mg/day from 14.8mg/day

at baseline after 6 months of treatment with belimumab ($p<0.0001$). 75% of patients (n=57) experienced a reduction in steroid use during the 6 months.

Conclusion: Among SLE patients treated with belimumab, clinical and serological improvement was observed in a majority of SLE patients over their first 6 months of routine treatment in a sample of clinical practices in Spain.

Disclosure: J. Cortes, GlaxoSmithKline, 5; **C. Marras**, GlaxoSmithKline, 5; **J. L. Andreu**, GlaxoSmithKline; Eli Lilly, 5; **J. Calvo-Alen**, MSD, GlaxoSmithKline, Eli Lilly, 5; **A. M. Garcia-Aparicio**, None; **E. Diez Alvarez**, None; **C. Coronell**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **E. Morejon**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **A. Perna**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **V. Koscielny**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **J. Ordi-Ros**, GlaxoSmithKline, 5.

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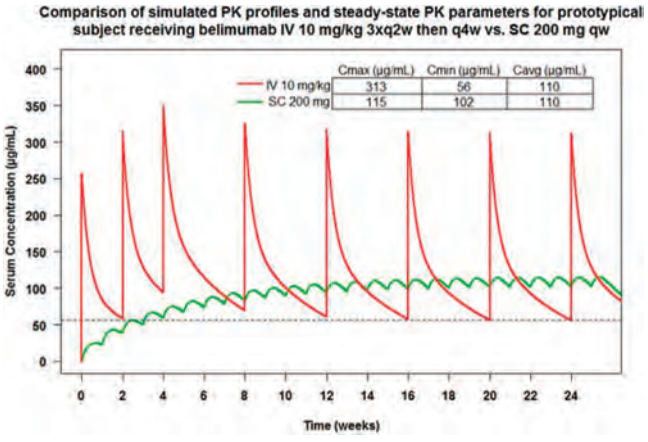
Predicted Chronic Exposure and Dose Selection for Belimumab Administered Subcutaneously to SLE Patients. Herbert Struemper[1], David Roth[2] and David Gordon[3]. [1]GlaxoSmithKline, Research Triangle Park, NC, [2]GlaxoSmithKline, Philadelphia, PA, [3]GlaxoSmithKline, King of Prussia, PA.

Background/Purpose: Monthly (q4w) intravenously (IV) administered belimumab 10 mg/kg is approved for the treatment of adults with active, autoantibody-positive SLE receiving standard therapy. The present analysis was conducted to predict a safe and efficacious weekly (qw) belimumab subcutaneous (SC) dose to be evaluated in a SC Phase 3 trial in adult SLE patients.

Methods: The belimumab IV Phase 3 clinical trials BLISS-52 and BLISS-76 indicated better efficacy with comparable safety for the 10 mg/kg versus the 1 mg/kg dose. A Phase 1 study (BEL114448: NCT#01583530) evaluated the pharmacokinetics (PK) of SC belimumab in healthy subjects as single or multiple doses up to 240 mg. IV and SC PK parameters were estimated using linear, 2-compartment PK models with NONMEM and Pharsight Phoenix modeling platforms, respectively, and chronic exposure profiles were simulated. The target steady-state SC exposure was set to an exposure level approximating the steady-state average belimumab serum concentration (Cavg) for 10 mg/kg IV q4w. Body-size dependent individual clearance values from the population PK analysis of the IV Phase 3 trials were used to predict the range of Cavg for the SC regimen.

Results: Simulation predicted that belimumab Cavg for 200 mg SC qw closely matched the corresponding Cavg for 10 mg/kg IV q4w. The simulated SC profile showed smaller fluctuations compared to the IV regimen, due to the slow absorption and more frequent dosing. At the end of the first month the trough concentration (Cmin) for 200 mg SC dosing is expected to exceed the steady-state Cmin for the 10 mg/kg IV regimen and therefore a loading dose was not deemed necessary.

The predicted body-size dependent steady-state Cavg values for the SC regimen, demonstrated that the Cavg ranges are similar between 10 m/kg IV q4w and 200 mg SC qw dosing. While for the IV regimen patients with large BMI experienced higher exposure, for the SC regimen higher weight patients are predicted to experience lower exposures.



Conclusion: 200 mg SC qw belimumab is predicted to result in a steady-state belimumab Cavg comparable to the Cavg for 10 mg/kg IV q4w dosing. The fixed SC dose is predicted to result in a similar range of Cavg values as compared to the weight-proportional 10 mg/kg IV dose, albeit with an inverse relationship between body size and exposure. This analysis supported the choice of the belimumab dose tested in the BLISS-SC Phase 3 trial.

Disclosure: H. Struemper, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **D. Roth**, GlaxoSmithKline, 3, GlaxoSmithKline, 1; **D. Gordon**, GlaxoSmithKline, 1, GlaxoSmithKline, 3.

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Decreased Disease Activity and Corticosteroid Usage and No Renal Flares during Belimumab Treatment in Patients with Systemic Lupus Erythematosus. Ioannis Parodis[1], Elisabet Svenungsson[1], Magnus Axelsson[2] and Iva Gunnarsson[1]. [1]Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [2]AlbaNova, Stockholm University, Stockholm, Sweden.

Background/Purpose: B cells have a central role in Systemic Lupus Erythematosus (SLE) and autoantibody production. B-Lymphocyte Stimulator (BLyS) is important for the activation and maintenance of B cells. Belimumab is a recombinant monoclonal antibody that specifically binds to soluble BLyS, and the only biologic agent approved for treatment of SLE. Its effects in patients with lupus nephritis (LN) are poorly known.

The aim of this study was to investigate the effects of belimumab given as an add-on to patients with active SLE despite standard-of-care therapy, with focus on patients with renal involvement.

Methods: Twenty-three patients (mean age 39.5 years) have been treated with belimumab at Karolinska University Hospital and have been included in this prospective observational study. Clinical data were acquired at baseline and at week 12, 26, 52 and 104. Disease activity was assessed using SLE Disease Activity Index 2000 (SLEDAI-2K) and Systemic Lupus Activity Measure (SLAM). C3 and C4 levels were determined by nephelometry. The predominant organ manifestations to motivate treatment with belimumab were mucocutaneous (n=14) and muskuloskeletal (n=14). Thirteen patients with history of LN, five of them having signs for nephritis and low-grade proteinuria, were included.

Results: At baseline, all but 2 patients received oral prednisolone (mean dose 9.1 mg/d, range 0–20 mg/d), 17 patients received antimalarials, 6 received azathioprine, 4 mycophenolate mofetil, 1 methotrexate, and 1 cyclosporine. The median SLEDAI and SLAM scores were 9 (range 2–24) and 12 (range 5–26), respectively.

Significant decreases of both SLEDAI-2K and SLAM were seen at week 12 ($p=0.018$ and $p=0.003$, respectively; n=18), 26 ($p=0.008$ and $p=0.002$, respectively; n=15), 52 ($p=0.003$ and $p=0.044$, respectively; n=12) and 104 ($p=0.042$ and $p=0.042$, respectively; n=5), as compared to baseline. Prednisolone dosages were significantly decreased compared to baseline at week 12 ($p=0.012$, n=18), 26 ($p=0.002$, n=16), 52 ($p=0.005$, n=12) and 104 ($p=0.043$, n=5). Eighteen patients had low complement at baseline. We observed no significant increases in C3 or C4 levels, with the exception of a significant increase of C4 levels at week 12 ($p=0.047$, n=18).

The patients with history of nephritis had at baseline a mean 24-h albuminuria of 0.25 g/d (range 0.01–1.16 g/d). No renal flare was observed during the study. The grade of proteinuria remained unchanged compared to baseline at all follow-up occasions.

One patient withdrew due to an allergic reaction. The treatment with belimumab was discontinued in 4 patients after 12 months follow-up due to inadequate or uncertain effect, and in 1 patient after 6 months follow-up due to plans for pregnancy. No severe adverse events were noted during the observation period. One male patient was diagnosed with prostate cancer (age at diagnosis 55 years) 15 months after discontinuation of belimumab.

Conclusion: Belimumab treatment decreased SLE disease activity and reduced corticosteroid usage. Despite the limited number of patients, our observations indicate that belimumab may prevent renal flares and may be used in patients with renal involvement and persistent low-grade proteinuria.

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Belimumab Reduces the Frequency of Flares in Patients with Refractory SLE: DATA from Clinical Practice Setting. Andrea Doria[1], Luca Iaccarino[1], Silvano Bettio[1], Micol Frassi[2], Laura Andreoli[2], Rossella Reggia[2], Margherita Zen[1], Linda Nalotto[1], Mariele Gatto[1], Lara Pea[2], Leonardo Punzi[1] and Angela Tincani[2]. [1]University of Padova, Padova, Italy, [2]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy.

Background/Purpose: To investigate the efficacy and safety of belimumab in patients affected with active systemic lupus erythematosus (SLE) refractory to standard therapy in the clinical practice setting.

Methods: Forty-one patients affected with active SLE (1997 ACR criteria), with low complement and high anti-double stranded DNA (dsDNA) antibody levels, unresponsive to corticosteroids, antimalarials and/or immunosuppressant were treated with belimumab (10 mg/kg at day 0, 14 and 28 and then every 28 days) for a median follow-up of 8.9 months (range 13.1–2.0). A total of 426 infusions of belimumab were performed. The median age of patients was 38.9 years (range 21–62) and mean disease duration 12.2 years (range 1–32). SLE Disease Activity Index 2000 (SLEDAI-2K), anti-dsDNA (tested by ELISA or Farr method), C3 and C4 serum levels, and corticosteroid daily dose were recorded at baseline and every 3 months thereafter. Disease flare was defined according to SLE flare index. Disease flare rate was evaluated in 23 patients prior and during treatment. Adverse events were carefully recorded at each clinical evaluation and were defined severe when hospitalization was required and/or death and/or life-threatening manifestations occurred.

Results: Refractory manifestations requiring belimumab were renal (41.4%), musculoskeletal (36.5%), mucocutaneous (36.5%), hematologic (21.9%), and serositic (4,8%). In the efficacy analysis we considered 34 patients followed for at least 6 months. Decrease in median SLEDAI-2K, anti-dsDNA, and corticosteroid daily dose and increase in C3 and C4 serum levels at baseline, 3, and 6 months of follow-up are reported in Table 1. Notably, a reduction in the frequency of flares was observed: 70 flare/100 patients in the 6 months before the start of belimumab and 18 flares/100 patients during the 6-month belimumab treatment ($p=0.02$).

Adverse events were analyzed in 23 patients. A total of 70 adverse events were obseved. Most frequent non infectious adverse events were fatigue (15%), hypertension (7%), and mild hair loss (5%). Infectious adverse events were 38 (54.2%), 34 were mild and 4 were moderate. Mild infusion reactions was observed in 2 patients (8.7%). No severe adverse events were observed.

Conclusion: These preliminary data confirm the efficacy and tolerability of belimumab in the treatment of patients with active SLE refractory to standard treatment in the clinical practice setting. Belimumab seem to reduce the number of disease flares and this suggest that it might be useful especially in those patients with relapsing remitting pattern of disease.

Table 1. SLEDAI-2K, anti-dsDNA antibody, C3, C4 and corticosteroid daily dose at baseline, 3, and 6 months of follow-up

	Baseline	3 months	P	6 months	P
SLEDAI-2K	8.9	5.4	0.002	5.9	0.004
Anti-dsDNA	459.8	142.6	0.001	140.4	0.003
- ELISA, KIU/L in 23 pts	76.0	37.3	n.s.	27.5	n.s
- Farr method, IU/mL in 18 pts					
C3 (g/l)	0.67	0.73	<0.0001	0.74	0.007
C4 (g/l)	0.11	0.14	<0.0001	0.18	<0.0001
Corticosteroid daily dose (mg/day)	12.1	8.2	0.015	6.0	<0.0001

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Favorable Response to Belimumab in Pediatric-Onset Systemic Lupus Erythematosus. Joyce Hui-Yuen[1], Jennifer Taylor[1], Xiao Qing Li[1], Liza Mariel Bermudez[1], Josephine Isgro[1], Andrew H. Eichenfield[1], Amy J. Starr[1], Lisa F. Imundo[2], Jill P. Buyon[3], Richard Furie[4], Diane L. Kamen[5], Susan Manzi[6], Michelle Petri[7], Rosalind Ramsey-Goldman[8], Ronald van Vollenhoven[9], Daniel J. Wallace[10] and Anca Askanase[1]. [1]Columbia University Medical Center, New York, NY, [2]Pediatric and Adult Rheumatology Columbia University Medical Center, New York, NY, [3]New York University School of Medicine, New York, NY, [4]North Shore-LIJ Health System, Great Neck, NY, [5]Medical University of South Carolina, Charleston, SC, [6]Division of Rheumatology, University of Pittsburgh School of Medicine, Pittsburgh, PA, [7]Johns Hopkins University School of Medicine, Baltimore, MD, [8]Northwestern University and Feinberg School of Medicine, Chicago, IL, [9]Karolinska Institute, Stockholm, Sweden, [10]Cedars-Sinai Medical Center, Los Angeles, CA.

Background/Purpose: Belimumab (Benlysta) is a human monoclonal antibody that inhibits soluble B-lymphocyte stimulator. It was approved by the FDA in 2011 for treatment of active, autoantibody-positive, systemic lupus erythematosus (SLE) in adults. Patients with pediatric-onset SLE (pSLE) have more severe disease requiring more aggressive immunosuppression than adult SLE. To date, there have been no published data on the use of belimumab in pSLE.

Methods: Observational study of patients with SLE diagnosed before their 19thbirthday, and treated with belimumab, from 10 large academic centers. Data were collected on demographic and disease characteristics, clinical manifestations requiring treatment, concomitant medications, disease course, and treatment outcomes. The outcome was defined as the physician's impression of improvement in the initial manifestation(s) being treated without worsening in other organ systems. Chi-square and Student t-tests were used when appropriate.

Results: Of a cohort of 195 patients treated with belimumab, 38 patients had pSLE. The median age at diagnosis was 13.5 years old (range 4–18 years old); the median disease duration at initiation of belimumab was 12.5 years (range 2–43 years). Eighty-nine percent of the patients were female, 39% Black, 39% Caucasian, 11% Hispanic, 5% Asian. All patients were taking other background medications prior to initiation of belimumab (hydroxychloroquine 92%, prednisone 89% compared to 73% in the adult SLE patients, $p=0.005$, mycophenolate mofetil 47%, azathioprine 21%). The most common indications for initiation of therapy were inability to taper steroids (89%, mean prednisone equivalent dose 17.2mg/day compared to 27% in the adult SLE patients, $p<0.0001$), arthritis (61%), and rash (39%), accompanied by worsening serologic activity (increasing anti-dsDNA and hypocomplementemia). At 6 months, 71% of pSLE patients had responded clinically to belimumab compared to 48% of the entire patient population ($p=0.01$), and exhibited improvement in their laboratory abnormalities. Steroids were tapered in 63% of pSLE patients, and discontinued in 22%. Six months after initiation of belimumab, pSLE patients who responded clinically demonstrated an 86% decrease in anti-dsDNA ($p<0.0001$), 15% increase in C3 ($p=$NS), and 27% increase in C4 ($p=$NS). Of note, 100% of blacks with pSLE responded clinically ($p=0.0003$) with improvement in all serologic markers. Thirty-two of 38 pSLE patients tolerated infusions well, with only 6 patients discontinuing treatment.

Conclusion: This is the first study investigating the use of belimumab in pSLE. Our data demonstrate favorable clinical and laboratory outcomes across all ethnic groups: 71% of patients responded clinically within 6 months and steroids were tapered in 63% of our patients, suggesting a more important role for belimumab in pediatric-onset SLE.

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A Comparison of Rheumatoid Arthritis and Systemic Lupus Erythematosus Trial Design: Ways to Improve Positive Trials in Systemic Lupus Erythematosus. Amy Miles[1] and Janet E. Pope[2]. [1]University of Western Ontario and U of Toronto, London, ON, [2]St Joseph Health Care, London, ON.

Background/Purpose: Recent SLE RCTs were examined and compared to rheumatoid arthritis (RA) RCT to suggest modifications to SLE RCTs that could improve the future success of SLE trials.

Methods: RA and SLE biologics RCTs published between 2005 and July 2013 were identified using PubMed. Inclusion criteria, study design, outcome measures, sample size calculations, baseline characteristics, steroid use and results were compared.

Results: Twenty-two RA RCTs and eight SLE RCTs were included. RA RCTs used composite scores (ACR response or DAS28). SLE RCTs used SLEDAI, BILAG, SLAM, SRI and BICLA. RA trials were larger (543 vs. 376 participants). RA measurements of response included patient reported outcomes, SLE trials did not. Concomitant corticosteroid use was stable in 100% of RA trials while all SLE RCTs allowed tapering. RA trials were mostly in methotrexate or DMARD inadequate responders whereas SLE trials allowed for the presence or absence immunosuppressives within all trials. Positive trials were found in 100% of RA RCTs and 25% of SLE RCTs. Table shows suggestions to improve SLE trials.

Conclusion: The potential insensitivity of SLE disease activity index (SLEDAI) to partial improvements may result in type II errors in SLE RCTs, whereas many BILAG flares were recorded with a significant number not considered as important flares by the physician (nonspecificity). Varying concomitant pharmacotherapy, especially corticosteroid use, in SLE may blunt observed treatment effects. Steroid dose must be accounted for within

SLE trials. Sample size calculations in SLE may be unrealistic in some SLE trials. Moving forward, clinical relevance in treatment could be considered by proportional responses similar to ACR20 such as in SLE inflammatory arthritis trials or per cent improvement for skin studies in SLE and/or time to improvement of active urinary sediment in nephritis studies and/or reduction of steroids. SLE trial experts may need to reassess what outcomes and what minimal degree of change should be necessary to consider a treatment effective.

Suggestions of Outcomes in SLE trials: Points to Consider

Organ specific trials in SLE

Inflammatory arthritis	If arthritis is being studied, the SJC and TJC should be the primary outcome and patients with fibromyalgia may need to be excluded.
Rash	If rash is the being studied, MD and patient global assessment of SLE rash and the CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index) may be considered as outcomes.
Renal	In renal SLE, head to head comparisons of standard of care vs. the new treatment or add on to standard of care can be done with active urinary sediment (red blood cell [RBC] casts, total protein/day) and creatinine as the outcomes as well as time to normalizing urinary sediment. WBCs in the urine are not part of lupus nephritis and should not be included as an outcome (unless interstitial nephritis is being studied).
	Likewise, urinary RBCs may not be due to lupus nephritis.
	Many patients will do well on standard of care treatment so longer outcomes such as creatiniine, 24hr proteinuria at one and two years may be needed .
	Time to achieving a certain renal outcome, steroid sparing effect and safety may be the important outcomes.
Flares as an outcome	Flares in SLE patients within trials are frequent and a minimally important flare should be defined as relevant to the drug under study. A flare may need different defintions with a sensitivity analysis – such as MD reported major flare, a major increase in prednisone or a change in SLEDAI by at least 2 or 4 points.
Steroid sparing effects of treatment	A primary outcome could be a steroid sparing effect of a drug where steroids are not strictly mandated in their use and tapering but a suggested protocol of steroid tapering is given and only those with a certain minimum dose of steroids are allowed into the trial.
Head to head trial with active new comparator	The speed of improvement, ability to taper steroids and/or safety may be the primary outcomes or a non-inferiority design.

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A Novel Strategy to Identify and Evaluate Approved Drugs and Treatments for Repositioning As Therapies for Systemic Lupus Erythematosus (SLE). Peter E. Lipsky, Matthew Ryals, Jacob Smearman, Victoria Soler and Amrie Grammer. AMPEL BioSolutions, Charlottesville, VA.

Background/Purpose: Development of new SLE treatments has been slow with only one new treatment approved in the past half century. One way to increase the availability of new therapies for SLE is to consider repositioning agents that have been approved for other indications. The goal of this project was to identify possible therapies that might be useful as therapies for lupus among the hundreds of agents approved for human use.

Methods: Initially, a comprehensive strategy was developed to identify all possible SLE therapies within FDA approved drugs and therapies. First, the lupus community was engaged via a social media site (www.linkedin.com/in/lrxlstat) and queried for recommendations. Secondly, the reported actions of all drugs approved for human used were cross-referenced with a database of known pathway abnormalities in SLE. Finally a comprehensive search of all drugs and therapies showing benefit in murine models of SLE was carried out. After the initial Lupus Treatment List (LRxL) was assembled, a structured research of the available literature on each drug and therapy was carried out focusing on mechanism of action, relevant experience in animals and humans, drug properties and adverse events. Finally, a comprehensive scoring system was developed and employed to score ten features of each drug or therapy on a 28 point scale. Face validity of this scoring system was assessed by ranking available lupus therapies and questioning rheumatologists for their response.

Results: Of the more than 1100 new chemical entities approved by the FDA for 6800 indications, 157 were identified as possible treatments for SLE. All drugs widely used for lupus or known to be in development for lupus by Pharma/Biotech were excluded. Of the 157 therapies initially screened, more than 25 have an appropriate set of characteristics to consider for testing in clinical trials in lupus, including drugs targeting cellular metabolism, kinases, cytokines, immune cell function and regulation, HDACs, complement as well as cellular therapies & non-drug/cell interventions.

Conclusion: This approach has demonstrated that there are numerous FDA-approved candidates for repositioning as new therapies for SLE. Not only have unique treatments that could be useful in SLE and possibly other autoimmune/inflammatory conditions been identified, but a rigorous evidence-based process has been delineated by which therapies can be objectively rated for possible clinical application to treat these conditions, thereby miti

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Use of Rituximab in Systemic Lupus Erythematosus: A Single Center Experience. Renata Aguiar[1], Ana Carolina Araújo[2], Ana Luisa Papoila[3], Marta Alves[4] and David Isenberg[5]. [1]Centro Hospitalar do Baixo Vouga, E.P.E., Aveiro, Portugal, [2]Hospital de Curry Cabral, Centro Hospitalar Lisboa Central, Lisbon, Portugal, [3]Centro Hospitalar Lisboa Central, Lisbon, Portugal, [4]Centro Hospitalar Lisboa Central, Lisboa, Portugal, [5]Centre for Rheumatology Research, University College Hospital London, London, United Kingdom.

Background/Purpose: Rituximab (RTX), an anti-CD20 chimerical monoclonal antibody, has been used as an off-label in patients with systemic lupus erythematosus (SLE) refractory to standard treatment. Although some small, open label and retrospective studies suggest that RTX might be beneficial in SLE treatment, the two randomized controlled trials of RTX in SLE did not meet the primary endpoints.

The purpose of this work was to assess clinical efficacy and safety of RTX in a cohort of SLE patients treated at a single centre for a long period.

Methods: The authors undertook a retrospective in-depth analysis of all patients (>100) with SLE treated with RTX at a single center between June 2000 and December 2013 and followed for upto 14 years. Data collected included BILAG scores AT and 6, 12, 18 and 24 months after, RTX treatment; anti dsDNA antibody and C3 levels before and 6 months after RTX infusions; adverse events, including allergic/anaphylactic reactions, hypogammaglobulinemia, infections, cardiovascular and cerebrovascular events, and death.

Statistical analysis was performed using Wilcoxon and McNemar non-parametric tests.

Results: A total of 115 patients were reviewed; 93.9% female; 43.5% were Caucasian, 32.2% African and 17.4% South Asian; mean age at diagnosis was 26.39±11.90 years and mean disease duration at first RTX treatment was 91.96±84.80 months. The most frequent indications for RTX treatment were refractory musculoskeletal, renal and mucocutaneous involvement. Mean BILAG score before first RTX treatment was 18.29±10.62; after 6 months, 40% of patients had a complete response (loss of all A's and B′s and no new A's or B's) and 27% had a partial response (partial loss of some but not all A's or B's, no new ones.). At 6 months, there was a significant reduction in the BILAG score ($p<0.001$). Also, 6 months after the first treatment, 36,5% of patients had an increase in C3 levels of 25% and 33.5% had a decrease of over 50% from anti dsDNA antibody baseline level. Depletion of CD19+ cells was successfully achieved in 94% of patients. Hypogammaglobulinemia was detected in 14.9%, however, this reduction was only significant for IgM ($p<0.001$) and IgG ($p=0.001$); severe infections, infusion-related and hypersensitivity reactions occurred in 7%, 3.5% and 2.6% of patients, respectively. Of the 115 patients initially treated with RTX, 62 patients had further RTX treatments, maximum of 6, with an average number of 1.95±1.17 cycles per patient and a mean interval between infusions of 21.44±20.11 months. The reason that led to the second RTX treatment was different from the reason leading to the first one in 16 patients, and 25 of the 40 patients who had had partial or complete response at first administration remained partial or complete responders.

At the end of follow-up, 11 patients had died and 6 had cardiovascular events (2 deaths).

Conclusion: In this cohort, RTX treatment was effective in decreasing disease activity and had low incidence of adverse effects.

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Response to Rituximab in Patients with Refractory Systemic Lupus Erythematosus (SLE): Results from a National Multicentre Register. Emily Sutton[1], Kath D. Watson[2], David A. Isenberg[3], Anisur Rahman[4], David Jayne[5], Caroline Gordon[6], Ben Parker[7], David P. D'Cruz[8], Munther A. Khamashta[9], Pamela Lutalo[10], Peter Lanyon[11], Benjamin Rhodes[12], Bridget Griffiths[13], Edward M. Vital[14], Chee-Seng Yee[15], Christopher Edwards[16], Mohammed Akil[17], Nicola Erb[18], Athiveer Prabu[19], Asad A. Zoma[20], Neil McHugh[21], Hazem Youssef[22], Lee-Suan Teh[23], Michael W. Beresford[24] and Ian N. Bruce[25]. [1]Arthritis Research UK Centre for Epidemiology, Manchester, United Kingdom, [2]Arthritis Research UK Centre for Epidemiology, University of Manchester, Manchester, United Kingdom, [3]Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom, [4]University College London, London, United Kingdom, [5]Addenbrookes Hospital University of Cambridge, Cambridge, United Kingdom, [6]Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, [7]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [8]Louise Coote Lupus Unit, Guy's and St Thomas' Hospital, London, United Kingdom, [9]Lupus Research Unit, The Rayne Institute, St Thomas Hospital, Kings College London School of Medicine, London, United Kingdom, [10]King's College London School of Medicine, London, United Kingdom, [11]Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom, [12]Queen Elizabeth Hospital, Birmingham, United Kingdom, [13]Freeman Hospital, Newcastle Upon Tyne, United Kingdom, [14]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds., United Kingdom, Leeds, United Kingdom, [15]Doncaster and Bassetlaw Hospitals NHS Foundation Trust, Doncaster, United Kingdom, [16]NIHR Wellcome Trust Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, [17]Rheumatology Department, Sheffield South Yorkshire, United Kingdom, [18]Russells Hall Hospital, Dudley, United Kingdom, [19]Department of Rheumatology, Worcester Acute Hospitals NHS Trust, Worcester, United Kingdom, [20]Hairmyres Hospital, East Kilbride, United Kingdom, [21]Royal National Hospital, Bath, United Kingdom, [22]NHS Grampian, Aberdeen, United Kingdom, [23]Royal Blackburn Hospital, Blackburn, United Kingdom, [24]Institute of Translational Medicine (Child Health), University of Liverpool, Liverpool, United Kingdom, [25]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Published efficacy data for rituximab in SLE are complex with positive single-centre case series and negative randomised controlled trials. This may be due to heterogeneity of SLE or the populations, design and endpoints of trials. The BILAG Biologic Registry (BILAG BR) is a national, multicentre, prospective study of safety and efficacy of biologics in SLE patients refractory to standard immunosuppressive therapy. The objective of the present analysis was to describe clinical response to rituximab at three and six-months post therapy.

Methods: Patients with SLE (≥ 4 ACR 1997 criteria), ≥ 5 years old, refractory to conventional therapy and newly starting treatment with rituximab, from centres across the UK, were recruited into the BILAG BR. A comprehensive questionnaire collected information on concomitant medications, risk factors for infection, co-morbidities and SLE disease duration. Disease activity was measured using the BILAG 2004 Index and the SLEDAI2K at treatment initiation, 3 and 6 months post therapy.

Results: Baseline, 3 and 6 month disease activity were collected for 80 patients (92.5% women) starting therapy with rituximab. The cohort included 44 (60.3%) white British patients. The median (interquartile range [IQR]) age and disease duration at baseline were 39.5 years (IQR 30.0, 47.3) and 5.7 years (IQR 2.5, 11.6) respectively. The most commonly involved BILAG 2004 index systems were mucocutaneous (33 [41.25%]), renal (28 [35.0%]) and musculoskeletal (25 [31.0%]). The baseline SLEDAI2K was 8 (IQR 4, 13.5). At 3 months follow-up, 47 (58.75%) patients showed an improvement in their overall BILAG 2004 index, 16 (20.0%) had persisting active disease and 12 (15.0%) had deteriorating disease. The majority of patients (11/12 [91.7%]) who deteriorated, did so in one system only. In the same follow-up period, 56 (70.0%) had an improved SLEDAI2K, 15 (18.75%) had no change and 9 (11.25%) worsened. Data at 6 months showed 39 (48.75%) with improvement, 18 (22.5%) with persistent disease and 16 (20.0%) deteriorating. In addition, there was a trend towards steroid dose being reduced over the 6 month period (Table 1).

Conclusion: There was variability in the degree of response to rituximab with respect to both the magnitude and duration of response, in this cohort of SLE patients refractory to standard immunosuppression. Although nearly half of the cohort demonstrated significant reduction in disease activity across all systems at 6 months, there was a sub-group that worsened in either the original system involved, or developed activity in a new system. This may be explained some patients who initially responded to rituximab at 3 months, beginning to flare by 6 months post therapy. Further analysis will attempt to identify predictors of response in this cohort.

Table 1:

N = 80 unless otherwise stated		**N (%)**
Baseline Characteristics		
Female		74 (92.5)
Ethnicity (n = 73)		
White British/other white		44 (60.3)
Indian/Pakistani/Bangladeshi		10 (13.7)
African Ancestry		10 (13.7)
Mixed (white/Caribbean)/other mixed		9 (12.3)
BILAG 2004 Index score at baseline (n = 80)		
≥1 A score and/or ≥2 B score		55 (68.8)
		median (IQR)
Age at diagnosis (years)		30.0 (18.4, 40.2)
Age at baseline (years)		39.5 (30.0, 47.3)
Disease duration at baseline (years)		5.7 (2.5, 11.6)
Prednisolone dose at baseline (mg/day) (n = 70)		10 (8.0, 22.5)
Number of previous immunosuppressant therapies at baseline (n = 78)		2 (1, 3)
Baseline SLEDAI 2K score		8 (4, 13.5)
Baseline SLICC/ACR Damage Index (n=64)		0 (0, 1)
Patient Follow-up		
BILAG 2004 Index	**3M:** N (%)	**6M:** N (%)
Improvement [All As to B/C/D; all Bs to C/D (allowing for 1≤B persisting)]	47 (58.75)	39 (48.75)
Persistent active disease [Any system still A or 2Bs as per previous time point]	16 (20.0)	18 (22.5)
Deterioration [Any system to A from B/C/D or to B from C/D]	12 (15.0)	16 (20.0)
No Change/Inactive [Stable C/D/E with no new A or B]	5 (6.25)	7 (8.75)
SLEDAI2K (n=80)	**3M**	**6M**
Score at follow-up [median (IQR)]	4 (2, 6.5)	4 (2, 7)
Improve: N (%)	56 (70.0)	56 (70.0)
Persist: N (%)	15 (18.75)	13 (16.25)
Worsen: N (%)	9 (11.25)	11 (13.75)
Prednisolone dose at follow-up (mg/day) [median (IQR)]	10 (5, 13.75)	8.5 (5, 12.5)

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Pharmacokinetics, Safety, and Biological Activity of Intravenously or Subcutaneously Administered Tabalumab in Subjects with Rheumatoid Arthritis or Systemic Lupus Erythematosus. Jennifer Witcher[1], Ryan Hansen[1], Leijun Hu[1], David Radtke[1], James Voelker[1] and Juliet McColm[2]. [1]Eli Lilly and Company, Indianapolis, IN, [2]Eli Lilly and Company, Windlesham, United Kingdom.

Background/Purpose: B-cell activating factor (BAFF) promotes B-cell survival and maturation, and increased serum levels are associated with autoimmune disease and disease activity in systemic lupus erythematosus (SLE). Tabalumab is a human anti-BAFF monoclonal antibody that neutralizes both soluble and membrane-bound BAFF. The objectives of 2 Phase 1 studies were to evaluate the pharmacokinetics (PK), safety, and biological activity of tabalumab administered intravenously (IV) or subcutaneously (SC) in subjects with rheumatoid arthritis (RA) or SLE.

Methods: In Study A, subjects with stable RA (n=23) received a single dose of tabalumab ranging from 0.01 to 8.0 mg/kg (0.01, 0.04, 0.125, 0.5, 2.0, and 8.0 mg/kg) or placebo, and subjects with stable SLE (n=6) received 1 of 2 tabalumab doses (0.125 or 2.0 mg/kg) or placebo by IV infusion. In Study B, subjects with RA received a single tabalumab dose SC (20 mg) (n=12) or IV (10 mg infused over 30 min) (n=12). Serum tabalumab and peripheral CD20+ B-lymphocyte levels were evaluated for 36 weeks in Study A and 12 weeks in Study B with optional follow up to monitor B-lymphocyte recovery, if required. Safety was assessed throughout both studies.

Results: Tabalumab PK were nonlinear across the 0.01 to 8.0 mg/kg dose range (Figure A), with a slower clearance (CL) and longer half-life ($t_{1/2}$) at higher doses. The CL decreased from 2.9 to 0.1 L/day over the dose range, resulting in greater than dose-proportional increases in exposure. The terminal $t_{1/2}$ increased from 1.6 to 25 days over the dose range. PK parameters were similar between RA and SLE subjects. SC dosing had a slow absorption phase with time to maximal concentration (t_{max}) of approximately 5.5 days. The estimated bioavailability (F) for the 20-mg SC dose was 62%. Single-dose tabalumab was well tolerated, and the majority of treatment-emergent adverse events (TEAEs) were mild to moderate in severity in both studies. The rate of TEAEs was similar for IV and SC groups in Study B. TEAEs considered related to study drug included headache (n=1), back pain (n=1), dry mouth (n=1), dysgeusia (n=1) dysphagia (n=1), and nausea (n=3) in study A, and injection-site pain (n=1) and flushing (n=1) in the 20-mg SC group in Study B. In general, a tabalumab-dependent transient increase from baseline in CD20+ B lymphocytes followed by a progressive decrease below baseline levels was observed in both studies, with the decrease being significant (P<0.05; overall F-test) for the 2-mg/kg and 8-mg/kg doses. No increases in anti-tabalumab antibodies were detected post-treatment.

Conclusion: A single tabalumab dose administered IV or SC was well tolerated and had non-linear CL over the dose range investigated in subjects with RA and SLE. The non-linearity likely reflects target-mediated CL due to binding to BAFF. Tabalumab showed biological activity based on changes in peripheral CD20+ lymphocyte numbers in both subjects with RA and SLE.

Figure

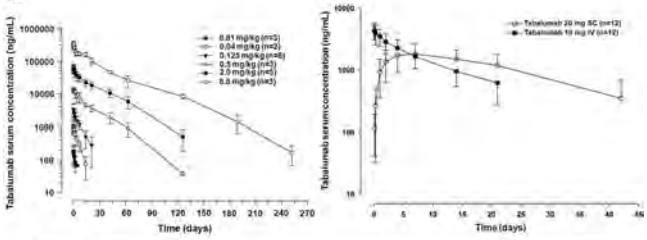

Figure legend: Tabalumab arithmetic mean (±SD) serum concentration-time profiles following a (A) single IV dose of tabalumab in subjects with stable RA or SLE (Study A) (data represent the combined data of RA and SLE groups, n=27) or (B) single IV (n=12) or SC (n=12) dose of tabalumab in subjects with RA (Study B)

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The Effectiveness of Tacrolimus for Minor Flares of the Patients with Systemic Lupus Erythematosus. Haruki Watanabe[1], Ryutaro Yamanaka[2], Ken-ei Sada[1], Eri Katsuyama[1], Takayuki Katsuyama[1], Mariko Narazaki[1], Noriko Tatebe[1], Koichi Sugiyama[1], Katsue S. Watanabe[1], Hiroshi Wakabayashi[1], Tomoko Kawabata[1], Jun Wada[1] and Hirofumi Makino[1]. [1]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, [2]Himeji Red Cross Hospital, Himeji, Japan.

Background/Purpose: Although effectiveness of tacrolimus (TAC) for remission induction or maintenance treatment of patients with lupus nephritis has been reported, there are few reports about its efficacy for the flares of patients with systemic lupus erythematosus (SLE).

Methods: Medical records of 313 outpatients with SLE who fulfilled the revised ACR criteria in Okayama university hospital visited from 2006 to 2013 were assessed retrospectively. We recruited the patients treated with add-on TAC without the intensification of glucocorticoids (GC) for the minor flares (TAC group). The minor flare was defined as an increase of SLE disease activity index (SLEDAI) ranged from 3 to 11 in the patients maintained remission for over 3 months within 10 mg/day of predonisolone and/or immunosuppressants except calcineurin inhibitors. As controls, we also recruited the patients administered with the increased doses of GC for minor flares (GC group). We collected clinical and laboratory data at baseline, 1 month, 3 months, 6 months, and 12 months. We defined responders as the patients whose SLEDAI was improved to the level before the flares within 1 year. We also evaluated the development of the second flare in the responders. The second flare was defined as the reinforcement with other immunosuppressants or higher doses of GC.

Results: There were 14 eligible patients in the TAC group and 20 eligible patients in the GC group. Although SLEDAI at the flare was higher in the TAC group than the GC group (8.2 vs. 6.2, p<0.05), other baseline characteristics (sex, age, serological markers, and the dose of GC) were comparable between the two groups. The initial dose of TAC for the flare was 1.6 mg/day in the TAC group, while the dose of GC for the flare was 13.7 mg/day in the GC group. The proportion of responders was 79% in the TAC group and 75% in the GC group (p=0.92). In the responders, 2 of 11 (18%) patients in the TAC group and 4 of 16 (25%) patients in the GC group developed the second flare (p=0.68). The dose of GC was higher in the GC group than in the TAC group at 12 months (9.7 mg/day vs. 7.1 mg/day, p<0.05). Only 1 patient withdrew TAC because of fatigue after three months.

Conclusion: Adding TAC without increased dose of glucocorticoids may be an effective treatment option for minor flares of patients with SLE.

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Hydroxychloroquine Dosing and Disease Activity in a Large Multi-Racial Lupus Cohort. Jennifer M. Grossman[1], Megan E. B. Clowse[2], Peter M. Izmirly[3], Diane L. Kamen[4], Alana B. Levine[5], Meggan Mackey[6], W. Joseph McCune[7], Jerry McGwin[8], David S. Pisetsky[2], Tammy Utset[9] and Jinoos Yazdany[10]. [1]UCLA David Geffen School of Medicine, Los Angeles, CA, [2]Duke University Medical Center, Durham, NC, [3]New York University School of Medicine, New York, NY, [4]Medical University of South Carolina, Charleston, SC, [5]Hospital for Special Surgery, New York, NY, [6]The Feinstein Institute, Mahasset, NY, [7]University of Michigan, Ann Arbor, MI, [8]UAB, Birmingham, AL, [9]UC Pritzker Schl of Medicine, Chicago, IL, [10]University of California, San Francisco, San Francisco, CA.

Background/Purpose: Treatment with hydroxychloroquine (HCQ) is recommended for all patients with lupus nephritis to prevent further damage and reduce disease manifestations. Some studies suggest that drug levels may be important in medication efficacy. In view of reports of an increased risk of ocular toxicity with HCQ, however, the American Academy of Ophthalmology (AAO) recommends more stringent screening for damage as well as changes in dosing. Specifically, the AAO recommends dosing by ideal and not actual weight, which would decrease the dose of HCQ for many patients. To assess the impact of these dosing recommendations, we explored the patterns of HCQ use in a large patient cohort and the effect of dose levels on the trajectory of disease activity. For this purpose, we analyzed data from the Lupus Clinical Trials Consortium, Inc. (LCTC) Lupus Data Registry, a prospective registry of 1506 patients with SLE from 16 lupus centers in the US and Canada.

Methods: Patients were consecutively enrolled into the Registry and followed at outpatient visits by participating rheumatologists. Medication use, disease activity, and patient global assessment were recorded at each visit. Baseline dose of HCQ was recorded as mg per kg and was analyzed as <4 mg/kg, 4–4.99 mg/kg, 5–5.99 mg/kg and

≥6 mg/kg, with approximately 25% of the cohort falling into each dose group. Associations between HCQ use, disease activity, and patient global assessments were evaluated.

Results: At the baseline visit, 1058 of the 1506 subjects (70.3%) were on HCQ. 80% of patients were on 400 mg daily, 15% on 200 mg daily with the mean dose 5.1 mg/kg. In the 400 mg group, the mean dose was 5.4 mg/kg while the mean dose in the 200 mg group was 3.2 mg/kg. 18% of all the patients on HCQ were on more than 6.5 mg/kg. There were no significant differences in change in disease activity among any of the different mg/kg groups compared to those not on HCQ even when adjusting for baseline disease activity or only evaluating those patients with a SLEDAI of ≥4. The dose of HCQ in mg/kg was not associated with flare risk using the SELENA-SLEDAI flare instrument. When evaluating patient global assessment of their worst score versus their baseline, those patients in the highest ≥6 mg/kg group had the smallest change in patient global assessment (p=0.02) compared to those not using HCQ suggesting better symptom control (table 1).

Conclusion: In this large observational cohort, there is significant variation in prescribed mg/kg dosing of HCQ. For patients on prevalent HCQ before the start of the study, the mg/kg dosing based on actual weight does not appear to impact the incidence of flare as measured by the SELENA flare instrument or overall SLE activity as measured by SLEDAI. Together, these results suggest efficacy with HCQ occurs with various drug dosing regimens although there is some indication for a greater subjective benefit at the higher dose range.

	No HCQ	HCQ <4 mg/kg	HCQ 4–4.99 mg/kg	HCQ 5–5.99 mg/kg	HCQ 6+ mg/kg
Any flare	59%	49%	57%	57%	58%
Severe flare	15%	10%	12%	18%	13%
Any flare in HCQ 400 mg		48%	56%	58%	58%
Severe flare in HCQ 400 mg		9%	11%	18%	18%
Decline in physician global worst-baseline	0.4	0.3	0.4	0.4	0.4
Decline in patient global worst-baseline	20	20	20	18	14

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Influence of Antimalarial doesn′t Modify the Outcome of Cytopenias in Systemic Lupus Erythematosus. Eugenia Enriquez Merayo[1], Maria Galindo Izquierdo[2], Esther Rodriguez-Almaraz[3], Maria Martin Lopez[2], Otto Martin Olivas Vergara[2], Patricia E. Carreira[4] and Isabel Mateo[5]. [1]12 DE OCTUBRE, MADRID, Spain, [2]HOSPITAL 12 DE OCTUBRE, MADRID, Spain, [3]Department of Rheumatology. Hospital Universitario 12 de Octubre, Madrid, Spain, [4]Rheumatology Department. Hospital Universitario 12 de Octubre, Madrid, Spain, [5]Servicio De Reumatología, Hospital 12 De Octubre, Madrid, Spain.

Background/Purpose: To analyze the effect of antimalarials (AM) as preventive factor for the development of severe cytopenias and in their outcome after treatment in a large series of patients with systemic lupus erythematosus (SLE).

Methods: 253 SLE patients followed in rheumatology department (12 de Octubre hospital) between 1976–2014 were included. Demographic, clinical data and patients outcome were obtained from pre-existing databases and from the charts. SLE related cytopenias were defined as: autoimmune haemolytic anemia (AHA): hematocryt<35%, reticulocytes >5% or spherocytosis in peripheral blood smear; leukopenia:WBC<4000x106/l; neutropenia: neutrophils<1000x106/l; thrombocytopenia (TP):moderate 50–100x109/l and severe <50x109/l. The associations between categorical variables were tested using the chi-square or Fisher's exact test, where appropriate. The odds ratios with the corresponding 95% CIs were calculated. For continuous variables, the comparisons were carried out using the t-test for two independent samples. P-values<0.05 were considered significant. The analysis was performed using advanced SPSS software version 11.

Results: 253 patients were included (91.3% women), with a mean age at SLE onset of 30 ± 13 years. Globally, 74.3% of patients developed hematological involvement (HI): 37.2% TP(21% moderate, 21% severe); 26.1% AHA, 75% leukopenia, 68% lymphopenia and 11.2% neutropenia. Evans syndrome was present in 13 patients and secondary antiphospholipid syndrome (APS) was diagnosed in 19.4%. Among patients with severe haematological disease, aggressive treatments (bolus of methylprednisolone, cyclophosphamide, rituximab, intravenous immunoglobulin or esplenectomy) were needed in 9% of patients with TP and in 18% of AHA. Only 20% of the patients had received AM prior to the developement of HI. In 5.5% of cases life-threatening complications appeared because of HI. Relapses occurred in TP (9,1%) and in AHA (2.8%). In 3 cases of neutropenia colony stimulating factor was needed, all relapsed cases. TP was significantly associated with having positive aDNA (p0.035), antiB2GP1IgG, lupus anticoagulant AL +, with APS and venous thrombosis secondary to APS (all p<0.01). AHA was associated with malar rash and discoid lupus, and AL+, ACL IgG +, antiB2GP1IgG and IgM (all p<0,05) but not with APS. AHA was associated with exitus as a result of hematologic involvement (p0,039). Neutropenia was associated with arthritis (p 0.024). Hypocomplementemia (C3, C4) was associated with TP, AHA (all p<0.05) Treatment with hydroxychloroquine was associated with a tendency of complete response to therapy in AHA and a partial response in TP.

Conclusion: Up to 41% of patients had some kind of severe cytopenia. Only AHA was associated with increased mortality from this cause. All cytopenias were associated with hypocomplementemia except neutropenia. AM treatment tended with favorable therapeutic response in AHA and thrombocytopenia. In our series, treatment with antimalarial drugs not proved to be a protective factor for developing severe cytopenias LES related neither for prevent severe complications or to prevent recurrences, although further studies are needed.

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Hydroxychloroquine Use Is Associated Independently with Improved Quality of Life in Systemic Lupus Erythematosus. Meenakshi Jolly[1], Winston Sequeira[2], Sarfraz Hasni[3], Zulfiqar Ali[4], Sergio Toloza[5], Ana M. Bertoli[6], Ivana Blazevic[7], Luis M. Vila[8], Ioana Moldovan[9], Karina D Torralba[10], Berna Goker[11], Josiane Bourré-Tessier[12], S. Navarra[13], Daniel Wallace[14], Michael H. Weisman[15], Ann E. Clarke[16] and Chi Chiu Mok[17]. [1]Rush University Medical Center, Chicago, IL, [2]Rush University, Chicago, IL, [3]NIH, BETHESDA, MD, [4]NIH, Bethesda, MD, [5]Hospital San Juan Bautista, San Fernando del Valle de Catamarca, Argentina, [6]Instituto Reumatológico Strusberg, Cordoba, Cordoba, Argentina, [7]University of Buenos Aires, Buenos Aries, Argentina, [8]University of Puerto Rico Medical Sciences Campus, San Juan, PR, [9]Beaver Medical Group, Redlands, CA, [10]University of Southern California, LA, CA, [11]Gazi University School of Medicine, Ankara, Turkey, [12]Division of Rheumatology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, [13]University of Santo Tomas Hospital, Manila, Philippines, [14]UCLA, LA, CA, [15]Cedars-Sinai Medical Center, Los Angeles, CA, [16]University of Calgary, Calgary, AB, [17]Tuen Mun Hospital, Hong Kong, Hong Kong.

Background/Purpose: Hydroxychloroquine (HCQ) has been shown to be beneficial to patients with Systemic Lupus Erythematosus (SLE), however, its effects on the quality of life (QOL) of patients with SLE has not been evaluated. Interestingly, there is not a clear concordance between pharmacological amelioration of visceral organ damage in SLE and QOL, as reported by patients themselves. LupusPRO is a disease targeted QOL tool that is well validated in English and various other languages, and has two construct: health related quality of life (HRQOL) and non-HRQOL. Here, we test the hypothesis that treatment with HCQ has a beneficial effect on QOL as well as organ function in patients with SLE.

Methods: Cross sectional data from 1,037 SLE patients (USA, Canada, Argentina, Mexico, Philippines, Turkey, and China) was accumulated, after obtaining informed consent and IRB approval. Age, gender, LupusPRO scores, disease activity, and disease damage were analyzed. Disease activity was measured by SLEDAI (physician global assessment and Total), while damage was assessed using SLICC-ACR/SDI. We compared the QOL on the LupusPRO domains using nonparametric independent sample t tests, using two sided p values of ≤ 0.05 as significant. T tests were also used to compare disease activity and disease damage in patients where the data were available. Multivariate linear regression analysis for satisfaction with treatment domain of LupusPRO was performed as the dependent variable, and HCQ use, age, gender, disease activity (SLEDAI), damage (SLICC-ACR/SDI) and current steroid use as independent variables.

Results: 1,037 SLE patients (727 HCQ users and 310 non-HCQ users) data were analyzed. HCQ users and non-users were similar in age and gender (Mean age (SD) 40.1 (13.0 vs. 42.5 (12.9) yrs). SLICC-ACR/SDI was lower, while non-HRQOL was higher among HCQ users as compared to non-HCQ users (Table 1). Specifically non-HRQOL domain of satisfaction with treatment was significantly better among HCQ users than non-HCQ users. On multivariate analysis, HCQ use remained an independent predictor of satisfaction with treatment (non HRQOL LupusPRO domain), even after adjusting for age, gender, disease activity, damage and current steroid use.

Conclusion: Hydroxychloroquine use in SLE has clearly beneficial effects on QOL. This is in addition to the well-recognized ameliorative effects on cumulative damage. The QOL improvement appears to be related to non-HRQOL (satisfaction with treatment) independently. Longitudinal studies with disease targeted QOL tools with use of HCQ are indicated.

	HCQ (n=310)	No HCQ (n=727)	P value
Age (yrs) Mean (SD)	40.1 (13.0)	42.5 (12.9)	0.82
Gender (Female %)	93.6	94.2	0.75
SLEDAI (Mean, SD)	3.4, 4.3	3.5, 4.1	0.92
SLICC-ACR/SDI (Mean, SD)	0.7, 1.1	0.9, 1.3	0.003
LupusPRO HRQOL (Median, IQR)	77.5, 23.7	80.1, 22.7	0.14
LupusPRO non HRQOL (Median, IQR)	68.2, 27.5	65.9, 28.5	0.03
Satisfaction with Treatment (Median, IQR)	75.0, 56.3	62.5. 62.5	<0.001
Multivariate Analysis for Satisfaction with Treatment non HRQOL LupusPRO domain	B co-efficient	95% CI	P value
HCQ use	7.2	2.7 to 11.7	0.002
Age	−0.2	−0.4 to −0.01	0.04
Gender	−3.1	−11.8 to 5.7	0.49
Disease Activity (SLEDAI)	0.7	0.2 to 1.2	0.01
Damage Index (SLICC-ACR/SDI)	1.8	−0.05 to 3.6	0.06
Current Steroid use	4.2	−0.2 to 8.6	0.06

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Impact of Patient's Priorities on the Management of Systemic Lupus Erythematosus. Valérie Leclair[1], Holly O. Witteman[2], Carolyn Neville[3], Isabelle Fortin[4] and Paul R. Fortin[5]. [1]Laval University, Department of Internal Medicine, Quebec City, QC, [2]Laval University, Family and Emergency Medicine, Quebec City, QC, [3]Division of Clinical Epidemiology, Department of Medicine, McGill University Health Centre, Canada, Montreal, QC, [4]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, [5]Laval University, Division of Rheumatology, Centre de Recherche du CHU de Québec and Department of Medicine, Quebec City, QC.

Background/Purpose: Systemic Lupus Erythematosus (SLE) greatly reduces the quality of life (QoL) and satisfaction with life of affected patients. SLE patients can have numerous unmet needs and may feel misunderstood by their health care providers. The aim of this study was to explore what is important to SLE patients when it comes to their care.

Methods: Participants were adults satisfying the ACR classification for SLE, and were recruited by phone, letter or directly by their respective rheumatologist. A qualitative approach based on audio-recorded focus groups was used to collect data. Interview guides were prepared prior to the meetings by an expert panel including: a resident in internal medicine, a psychologist, a rheumatologist, and nurse. The open-ended questions covered SLE patient priorities, their means of conveying these priorities to their medical team, and the impact of these priorities on their disease management. The transcriptions were independently coded by 2 analysts using 2 techniques: 1) a qualitative data analysis software (NVivo 10) and 2) manual analysis. The analytic approach was based on grounded theory.

Results: Nineteen female participants attended 3 focus groups in 2 sites (university and community-based). Participants' ages ranged from 18 to >70 with the majority between 30 and 59 years of age. The average disease duration was 8.8 ± 7,7 years, ranging from 1 to 23 years. 68% were married/or cohabitating with a partner and 63% were employed. Five priorities (Figure 1) were identified: 1) management of disability, in particular, loss of energy that prevents full engagement in daily activities, relationships, and social roles; 2) management of the unpredictable nature of SLE including, preventing flares and worsening of their condition, employment and financial issues associated with chronicity; 3) management of side effects; 4) access to information about lupus and support resources, in particular, support groups; 5) access to health care (improved communication between physicians, shorter wait times and longer consultations with physicians).

Conclusion: SLE patients have multiple complex priorities and may have difficulty articulating them. Health care providers need to develop strategies and communication tools to help SLE patients identify their priorities and support them in the self-management of their disease.

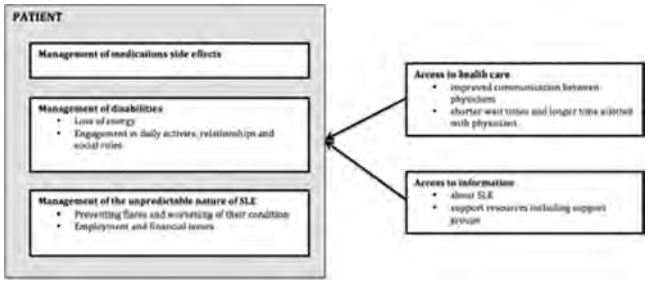

Figure 1 Priorities of SLE patients

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Impact of Lupus on Work Productivity in Patients and Caregivers: Findings from a Cross-Sectional Online Survey in the United States. Sarah Al Sawah[1], R Paola Daly[2], Shonda Foster[1], April Naegeli[1], Katy Benjamin[3], Helen Doll[3], Greg Bond[3], Olga Moshkovich[3] and Graciela Alarcón[4]. [1]Eli Lilly and Company, Indianapolis, IN, [2]Lupus Foundation of America, Inc., Washington, DC, [3]ICON PRO, Bethesda, MD, [4]University of Alabama Birmingham, Birmingham, AL.

Background/Purpose: Lupus imposes a substantial burden on patients' work productivity[1]; however, little is known about its impact on the work productivity of those caring for individuals with lupus. In this study, we examined the impact of lupus on work productivity in a sample of patients with lupus and caregivers.

Methods: An online cross-sectional survey of English-speaking respondents aged ≥18 years with 1) self-reported diagnosis of lupus or 2) self-reported caregivers of individuals with lupus was conducted across the US in partnership with the Lupus Foundation of America between February and March 2014. Demographic and clinical information, as well as other self-reported measures, including the work productivity and activity index (WPAI), were collected. The WPAI is a 6-item, 4-domain questionnaire that measures respondents' levels of impairment in work and general activities over the past 7 days. [1]The four domains are: 1) absenteeism—time missed from work; 2) presenteeism—impairment of productivity while at work; 3) overall loss of work productivity—combination of absenteeism and presenteeism domains; and 4) activity impairment—impairment in activities of daily living outside of work. The responses for each of the four domains are expressed as impairment percentages, with higher numbers indicating greater impairment and reduced productivity.

Results: A total of 827 patients with lupus and 253 caregivers completed the survey. Almost all patients (97.5%) were females; 49.2% of all patient respondents reporting being employed, with 30.7% of them working part time. Around half of the caregivers (54.2%) were males; 68.8% of all caregiver respondents reported being employed, with 14.4% of them working part time. Patients who were employed missed an average of 16.6% of paid work time because of lupus, reported an almost 46.4% reduction in on-the-job effectiveness and a 36.6% impairment in overall work productivity. Caregivers who were employed missed an average of 12.8% of paid work time because of caregiving responsibilities, reported a 33.5% reduction in on-the-job effectiveness and a 27.4% impairment in overall work productivity. Overall, for those who were employed, there was no substantial difference between the number of hours missed from work during the past 7 days because of lupus 6.3 hours and the number of hours missed from work during the past 7 days because of taking care of an individual with lupus 5.2 hours. Overall, all patients reported an average of 64.8% of impairment in activities outside of work, whereas an average of 46.7% was reported by caregivers.

Conclusion: Lupus has a substantial impact on work productivity for not only patients, but also for caregivers. Understanding the extent to which lupus

impacts caregivers and patients will help healthcare professionals and policymakers expand their outreach to consider the well-being of caregivers.

Reference:
[1]Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics. 1993; 4(5): 353–65.

Disclosure: S. Al Sawah, Eli Lilly and Company, 3; **R. P. Daly**, Eli Lilly and Company, 5; **S. Foster**, None; **A. Naegeli**, Eli Lilly and Company, 3; **K. Benjamin**, Eli Lilly and Company, 5; **H. Doll**, Eli Lilly and Company, 5; **G. Bond**, Eli Lilly and Company, 5; **O. Moshkovich**, Eli Lilly and Company, 5; **G. Alarcón**, Eli Lilly and Company, 5.

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Effects of Current Therapies for Lupus on Disease Activity and Renal Flares. Kenneth C. Kalunian[1], Jill P. Buyon[2], Cynthia Aranow[3], Mary Anne Dooley[4], Richard A. Furie[5], Ellen M. Ginzler[6], R. John Looney[7], Joan T. Merrill[8], Jerry McGwin[9] and Bevra H. Hahn[10]. [1]UCSD School of Medicine, La Jolla, CA, [2]New York University School of Medicine, New York, NY, [3]The Feinstein Institute, Manhasset, NY, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC, [5]North Shore - Long Island Jewish Health System, Great Neck, NY, [6]SUNY-Downstate Medical Center, Brooklyn, NY, [7]University of Rochester, Rochester, NY, [8]Department of Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [9]UAB, Birmingham, AL, [10]UCLA David Geffen School of Medicine, Los Angeles, CA.

Background/Purpose: A paucity of data exists that delineates the effect of current medications for lupus on disease activity and the propensity for renal flares in these patients.

Methods: Data from a registry of SLE patients collected from 16 medical centers in the US and Canada in which patients are seen regularly to evaluate the association between specific medications and the incidence of renal flares over an average of 1.8 years of observation. The percentage of patients with low levels of disease activity (SLEDAI ≤ 4) at entry who maintained these same levels of low disease activity was calculated, as was the percentage of patients who entered at higher levels of disease activity (SELENA SLEDAI >4) but became inactive at 6 months and remained at that low level of disease activity during follow-up.

Results: Of the 1299 patients with any follow-up, 103 subjects were taking Azathioprine plus Hydroxychloroquine (AZA+HCQ), 312 were on Mycophenolate Mofetil (MMF) plus HCQ, 111 were on MMF alone, 502 were on HCQ without other immunosuppressant drugs and 271 were on none of these medications. Six-hundred and eleven had a history of renal disease at study entry; mean Prednisone dose did not significantly differ between the five medication groups and the SLEDAI score was significantly lower in the HCQ alone group. The incidence of renal flares ranged from 14%-37% with the lowest incidence in the HCQ group, but no statistically significant differences were noted. The incidence of severe renal flares varied from 7%-13% with the lowest in the MMF alone group and the highest in the MMF+HCQ group, though any differences were not statistically significant. Among subjects with a history of nephritis, the incidence of severe renal flares did not differ between those who were using Prednisone at enrollment compared with those who were not. Logistic regression was used to identify significant, independent risk factors for renal flares; only older age and higher baseline SLEDAI scores were associated with severe renal flares, while race/ethnicity, disease duration, gender and medications were not. Among patients who entered with low levels of disease activity (SLEDAI ≤ 4) and maintained these low levels of activity, the group using HCQ alone was significantly more likely to maintain low levels of disease activity (46% for HCQ group compared to 20%-27% for the other groups).

Conclusion: The results of this study suggest that over a period of almost two years, approximately one-third of SLE patients, even those with nephritis; can be maintained at a low level of disease activity with current maintenance therapies. Over that period, approximately 1/3 of patients have renal flares and approximately 10% have severe renal flares.

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Successful Withdrawal and Discontinuation of Immunosuppressants in Lupus Patients: Outcomes and Predictors. Zahi Touma, Murray B. Urowitz, Dominique Ibanez and Dafna D. Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Physicians and patients (Pts) are hesitant to withdraw immunosuppressant (IS) in Pts in clinical remission as the consequences of this approach are unknown.

We aimed to determine the number of successful withdrawals of IS and their predictors in a large observational cohort study.

Methods: Analysis was conducted on all Pts seen in The Lupus Clinic, from 1987–2012, in whom IS was tapered and stopped. Pts who were in clinical remission and on prednisone (P) $\leq$7.5mg/day were included. Tapering start was defined as the date of the visit with a decrease $\geq$25% in IS dose. IS Stop was the day of IS discontinuation. Study end was the date of flare or last clinic visit following IS stop.

Flare was defined as the introduction of new IS or increase of P dose for active disease. Flare was evaluated within the first 2 years from IS stop and at any time after IS stop.

Kaplan-Meier curve was used to evaluate the time to flare after IS stop. Pts who flared after IS stop were compared to Pts who did not flare (t-test and χ^2 test) at the time of IS tapering start and IS stop.

Covariates evaluated in the univariate analysis were: sex, ethnicity, IS, DNA antibody level and DNA antibody [yes/no], C3/C4 level and low C3/C4 [yes/no], lupus duration, age at IS taper, length of time on IS, disease activity [SLEDAI-2K, AMS year 1 before IS taper] and steroids at IS stop [yes/no]. Forced and stepwise regression models were fitted with covariates with $p<0.1$ in addition to age, sex and ethnicity to predict flare in Pts who discontinued IS.

Results: Of the 1678 lupus Pts, 973 were ever on IS, 179 had tapering attempts and 99 Pts stopped IS. 91% were female and at tapering start age was 40.4$\pm$13.1 and disease duration was 11.4$\pm$9.4 years.

Of the 99 Pts, 25 flared within 2 years (16 AZA; 7 MTX and 2 MMF; p 0.31). The length of time from tapering start to IS stop was 1.8$\pm$1.8 years in the no flare and 0.9$\pm$0.9 years in the flare group; p 0.002.

46 of the 74 Pts who had not flared by 2 years had follow-up available beyond 2 years; 32 were followed beyond 3 years and 24 beyond 5 years. 17 Pts experienced a flared after year 2. Using Kaplan-Meier curve for time to flare showed that at 1, 2, 3, 4 and 5 years, the percent of Pts who flared was 17%, 30%, 46%, 49% and 51% respectively; Figure 1.

The percentage of Pts on P at the time of IS stop was greater among those who flared, 52% compared to 30%; p 0.04. At the time of IS tapering the models were not statistically significant for all studied covariates. At the time of IS stop, the results from the logistic regression showed that Pts off P are more likely not to flare; OR 2.99; 95% CI: 1.13, 7.89; p 0.03.

Conclusion: Within 2 years, successful stopping of IS was possible in about 75% of clinically stable Pts. Half were successful within 3 year and this proportion was stable up to 5 years. At the time of IS stop, Pts who discontinued IS slowly and who were off P were less likely to flare.

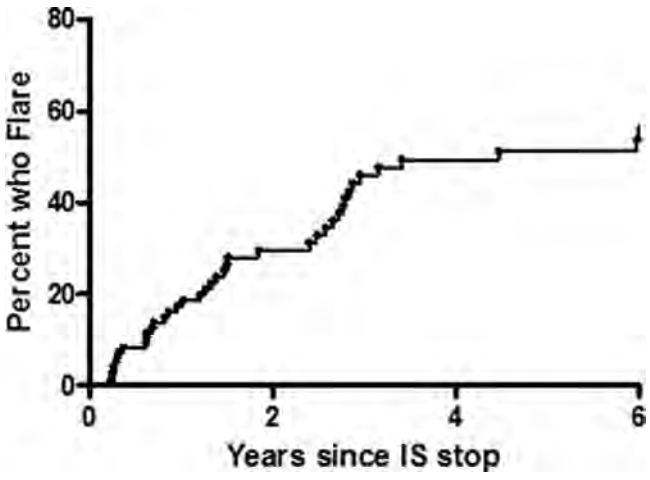

Figure 1: Percent Flared since IS stop

Disclosure: Z. Touma, None; **M. B. Urowitz**, None; **D. Ibanez**, None; **D. D. Gladman**, None.

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Clinicians Approaches to the Management of Background Therapy in SLE Patients in Clinical Remission: Results of an International Survey. Pintip Ngamjanyaporn[1], Ian Bruce[2], Ben Parker[1] and Jamie Sergeant[1]. [1]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, Institution of Inflammation and Repair, University of Manchester, NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals, Manchester Academic Health Sciences Centre, Manchester, United Kingdom.

Background/Purpose: At present there is no consensus on what constitutes a remission in SLE. In particular it is not clear how background therapy should be interpreted in remission studies. We aimed to survey clinicians involved in the care of SLE patients to determine how background therapy is managed in patients in clinical remission and in particular to assess how previous severity, duration of remission and serological parameters influence therapy alterations.

Methods: We undertook an internet-based survey of clinicians involved in the management of SLE. Case scenarios were constructed to reflect different states of clinical remission; previous organ involvement, current serological abnormalities, duration of remission (1, 3 and 5 years) and current therapy (HCQ, steroids and/or immunosuppressives[ISS]). The survey link was sent to (1) the corresponding authors from Lupus Journal published between January 2013 and December 2013 (2) Lupus working groups e.g. BILAG, SLICC. Percentage of responses in each scenario was described and compared between different factors.

Results: 130 clinicians from 30 countries (Europe 54 [41.5%], Asia 53 [40.8%], North America 16 [12.3%]) responded including 113 (86.9%) rheumatologists. The median (range) duration of practice and number of SLE patients seen per month was 13 (2, 42) years and 30 (2, 200) respectively. There was variation in management decisions across all scenarios with increasing caution on therapy reduction with shorter duration of remission, extent of serological abnormalities and previous disease severity. Even with mild disease, normal serology and a 5 year clinical remission 104 (86.7%) clinicians would still continue HCQ, with only 16 (13.3%) stopping the drug. Similarly, when low dose steroid are co-prescribed in this scenario 78 (64.5%) would continue these and 116 (96.7%) would continue HCQ. When MTX is added to this scenario 85 (70.2%), 79 (67.8%), and 116 (96.7%) would continue all therapies. Of interest, persistent abnormal serology in the above scenario led to a higher proportion of respondents continuing HCQ 113 (96.6%). Similarly, 106 (89.1%) would continue steroid and 119 (100%) would continue HCQ when patients were prescribed both. Prescribing in remission scenarios varied geographically, particularly with regard to steroids. For example, in the scenario describing stable, mild disease for 5 years, steroids would be withdrawn by 24 (48%) European respondents, 4 (28.6%) North American respondents and 10 (19.6%) Asian physicians.

Conclusion: Clinicians approach to withdrawing or reducing therapy in patients with SLE in clinical remission varies substantially. Serological abnormalities, previous disease severity and duration of remission all influence a clinician's decision to reduce treatments and anti-malarials are not usually withdrawn. It is unusual for clinicians to withdraw all therapies, even after a very prolonged period of clinical remission and therefore any definition of remission needs to include the continued use of some background maintenance therapies.

Disclosure: P. Ngamjanyaporn, None; **I. Bruce**, None; **B. Parker**, None; **J. Sergeant**, None.

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Effect of Corticosteroid Use By Dose on the Risk of Developing Organ Damage over Time in Systemic Lupus Erythematosus—the Hopkins Lupus Cohort. Sarah Al Sawah[1], Xiang Zhang[1], Baojin Zhu[1], Laurence S. Magder[2], Shonda A Foster[1], Noriko Iikuni[1] and Michelle Petri[3]. [1]Eli Lilly and Company, Indianapolis, IN, [2]University of Maryland, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Reduction of corticosteroid dose remains an important goal in the management of systemic lupus erythematosus (SLE). Current standard of care in SLE relies heavily on corticosteroids, despite what is known about the side effects of corticosteroids and their role in the development of new organ damage.

Methods: We used data from a longitudinal lupus cohort to understand the impact of different levels of exposure to corticosteroids on the risk of developing new irreversible organ damage, as measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Cox proportional hazard models were used to estimate the impact of predictors, including mean prednisone dose, on the risk of developing any new organ damage or any new organ damage by organ system (e.g., ocular, musculoskeletal, cardiovascular, and renal damage) over time.

Results: At cohort entry, the average age of SLE patients was 38 years and the average disease duration was 5.1 years. Patients were followed for an average of 6.2 years. The most frequent types of organ damage, occurring over time, were ocular damage (cataract) and musculoskeletal damage (osteoporotic fractures). Mean prednisone dose, disease activity score, and immunosuppressant use during the follow-up period, as well as SDI score at cohort entry, were significant predictors of the risk of developing any new organ damage. There was a dose-response relationship between mean prednisone dose during the follow-up period and the risk of developing any new organ damage (Models 1 and 2; Table 1). A 1-mg/day increase in prednisone dose increased the risk of developing any new organ damage by 2.8% ($p<0.001$). The risk more than doubled when patients were exposed to a prednisone dose during follow-up of $\geq$20 mg/day versus $<$7.5 mg/day (HR=2.51, 95% CI 1.98, 3.20; $p<0.001$). For individual organ systems, exposure to a mean prednisone dose during follow-up of $\geq$7.5mg/day versus $<$7.5 mg/day significantly increased the risk of developing cataracts (HR=2.41, $p<0.001$), osteoporotic fractures (HR=2.16, $p<0.001$), and cardiovascular damage (HR=1.54, $p=0.041$), but showed no significant difference for renal damage (HR=1.44, $p=0.163$).

Conclusion: Organ damage in SLE is multifactorial, with both corticosteroid treatment and disease activity playing a role. However, even a minimal change in corticosteroid dose (1 mg/day of prednisone) significantly affects the accrual of organ damage over time. These findings may be offset, to some degree, by the impact that prednisone has on damage through the reduction in disease activity.

Table 1. Time-dependent Cox proportional hazard model showing the effect of mean prednisone dose on the risk of any new organ damage in systemic lupus erythematosus

Variable	Model 1		Model 2	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
SELENA-SLEDAI score during follow-up ($\geq$6 vs. $<$6)	1.40 (1.17–1.67)	$<$0.001	1.37 (1.15–1.64)	$<$0.001
Mean prednisone dose, mg/day:				
($\geq$7.5 vs. $<$7.5)	1.74 (1.49–2.04)	$<$0.001	NA	
($\geq$7.5–$<$15 vs. $<$7.5)	NA		1.54 (1.28–1.84)	$<$0.001
($\geq$15–$<$20 vs. $<$7.5)	NA		1.80 (1.35–2.40)	$<$0.001
($\geq$20 vs. $<$7.5)	NA		2.51 (1.98–3.20)	$<$0.001

Abbreviations: CI = confidence interval; HR = hazard ratio; NA = not applicable; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index.
Note: The only difference between Models 1 and 2 is that Model 1 uses mean prednisone dose as a binary variable, while Model 2 uses mean prednisone dose as a 4-level categorical variable. All HRs presented in the table are adjusted for age, race, ethnicity, and SDI score at cohort entry; calendar year of diagnosis; and time-dependent variables, including mean prednisone dose, SELENA-SLEDAI score, immunosuppressant use, and antimalarial use during follow-up.

Disclosure: S. Al Sawah, Eli Lilly and Company, 3; **X. Zhang**, Eli Lilly and Company, 3; **B. Zhu**, Eli Lilly and Company, 3; **L. S. Magder**, None; **S. A. Foster**, Eli Lilly and Company, 3; **N. Iikuni**, Eli Lilly and Company, 3; **M. Petri**, None.

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Corticosteroids in Early Treatment Pathways in SLE. John G. Hanly[1], Amyn Sayani[2], Steve Doucette[1], Sandra Iczkovitz[2] and Jorge Alfonso Ross[2]. [1]Dalhousie University and Capital Health, Halifax, NS, [2]Medical Affairs, GlaxoSmithKline, Mississauga, ON.

Background/Purpose: The treatment algorithm for patients with new onset systemic lupus erythematosus (SLE) is more variable than that for other rheumatic diseases (e.g. rheumatoid arthritis). We examined the treatment

patterns, with a particular emphasis on corticosteroids (CS), in an inception cohort of SLE patients over the first 3 years of disease.

Methods: The study was conducted at a single academic center with a longitudinal lupus database. All patients fulfilled the ACR classification criteria for SLE within 12 months preceding their enrollment and completed at least 3 subsequent annual followup visits during which data since the previous assessment were recorded. Information was collected per protocol at each visit and included patient demographics, SLE manifestations, medications, SLE disease activity index-2K (SLEDAI-2K), SLICC/ACR damage index (SDI) and SF-36 for assessment of health related quality of life (HRQoL). Analysis included descriptive statistics and repeated measures mixed models.

Results: Seventy-nine patients, 86.1% female and 91.1% Caucasian were studied. At baseline the mean ± SD age was 39.8 ± 16.1 years, disease duration was 0.36 ± 0.28 years and SLEDAI-2K was 5.7 ± 4.6. Over 3 years the cumulative exposure to CS, antimalarials (AM) and immunosuppressive (IM) drugs was 53.2%, 77.2% and 40.5% respectively, and CS were virtually always used in combination with AM and/or IM. The use of CS fell between baseline and final assessments (44.3% vs. 15.2%) in contrast to the use of AM (55.7% vs. 70.9%) and IM (26.6% vs. 24.2%). Of the 44/79 (55.7%) patients who were not receiving CS at baseline 84.1% remained off CS for the duration of the study. Thirty-seven of 79 (46.8%) patients never received CS and only 5/79 (6.3%) of patients were taking corticosteroids at all 4 assessments. Patients exposed to CS at baseline had higher mean ± SD daily dose and cumulative dose of CS over 3 years compared to patients not on CS at baseline (9.0 ± 6.8 vs. 0.3 ± 1.3 mg; 10.8 ± 8.5 vs. 0.3 ± 1.2 gr.) The adjusted mean SLEDAI-2K over 3 years was higher in patients exposed to CS regardless of whether group assignment was determined by cumulative dose (none vs > 10 g: 2.7 ± 1.9 vs 6.5 ± 3.5; p=0.0001), CS at baseline visit (none vs present: 2.9 ± 2.1 vs 5.1 ± 3.9; p=0.006) or CS exposure at any time during the study (2.7 ± 1.9 vs 3.8 ± 0.6; p=0.002).Using the same group assignments CS exposure over 3 years was associated with a significant fall in SLEDAI-2K scores ($p<0.05$) compared to patients not exposed to CS. There was no consistent association with baseline SDI or HRQoL or change over time.

Conclusion: Exposure to CS occured in approximately half of the patients with new onset SLE, usually in association with AM and/or IM. It was associated with both higher disease activity, especially at baseline, and a subsequent fall in disease activity over time. In SLE patients who do not receive CS at disease presentation, the introduction of CS is very unlikely over the next 3 years.

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Prednisone, Disease Activity and Hypertension Independently Predict Cataracts in Systemic Lupus Erythematosus (SLE). Khaled Alderaan[1], Vuk Sekicki[2], Laurence S. Magder[3] and Michelle Petri[4]. [1]King Fahad Specilaist Hospital, Dammam, Saudi Arabia, [2]Saint Agnes Hospital, Baltimore, MD, [3]University of Maryland, Baltimore, MD, [4]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Cataract is the most common ocular damage in SLE. It is the second most frequent item in the SLICC/ACR Damage Index. Apart from cumulative corticosteroid doses, there are virtually no reports on other risk factors for cataract in SLE population. We report on a large prospective study of cataract risk factors in SLE.

Methods: The analysis was based on the follow-up experience prior to age 60 of 2109 SLE patients who had not had a cataract prior to cohort entry. Patients saw their ophthalmologist every 6 months. Cataract was defined by the SLICC/ACR Damage Index. The rate of incident cataract was calculated in subsets defined by patient characteristics and history. Multivariable logistic regressions were fit to identify predictors of cataract while controlling for potential confounding variables.

Results: The patients were 93% female, 54% Caucasian, and 39% African-American. The analysis was based on 11,887 persons-years of follow up, with median follow up time of 4.1 years per patient. During this follow-up we observed 157 new cases of cataract, for an incidence of 13.2 per 1000 persons-years. We estimated that the risk of being diagnosed with a cataract by age 60 was 28%. Table 1 shows the results of a multivariate regression model. Adjusting for other predictors, a cumulative prednisone dose equivalent to 10 mg/day for 10 years was a strong predictor of cataract (RR=3.1, P=0.0005). Disease activity measured by SLEDAI (P =0.0005) and higher systolic blood pressure (P =0.0006) were associated with cataract. Duration of SLE, diabetes mellitus, smoking, cholesterol, renal involvement, immunological profile and medication history, other than prednisone, were not associated with cataract.

Conclusion: Cataract development in SLE patients is multifactorial with cumulative prednisone doses, systolic blood pressure and disease activity all playing an independent role.

Table 1: Independent Predictors of Cataract Based on a Multivariable Model

Predictor	Comparisons	Rate Ratio (95% confidence interval)	P-value
Age	Per 10 year increase	2.0 (1.7, 2.4)	<0.0001
Mean Systolic BP during prior cohort visits > 140 mmHg	Yes vs. no	2.2 (1.4, 3.3)	0.0006
Mean total cholesterol	Per 50 mg/dl increase	1.1 (1.0, 1.2)	0.22
Diabetes mellitus	Yes/no	1.3 (0.9, 2.0)	0.22
Mean SELENA-SLEDAI	Per 2 point increase	1.3 (1.1, 1.5)	0.0005
Cumulative Corticosteroid Exposure[1]	<3649[2] mg vs. none	1.1 (0.5, 2.5)	0.77
	3650–10,949[3] vs. none	1.1 (0.5, 2.3)	0.87
	10,950–36,499[4] vs. none	2.3 (1.3, 4.3)	0.0065
	36,500[5] + vs. none	3.1 (1.6, 5.7)	0.0005

1 Includes prednisone history prior to cohort entry
2 Exposure equivalent to <10 mg/day for 1 year
3 Exposure equivalent to 10 mg/day for 1–3 years
4 Exposure equivalent to 10 mg/day for 3–10 years
5 Exposure equivalent to 10 mg/day for 10+ years

Disclosure: K. Alderaan, None; **V. Sekicki**, None; **L. S. Magder**, None; **M. Petri**, None.

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Lupus Patients Requiring First Corticosteroid Intervention Late in Disease Course - a Phenotypic Description. Barry J. Sheane, Dominique Ibanez, Dafna D. Gladman and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: The University of Toronto Lupus Clinic (UTLC) recently described the phenotype of a group of inception patients with SLE who remained naïve of corticosteroid (CS-naïve) for the entire duration of follow-up at the Clinic. One third of those CS-naïve SLE patients accrued damage over time, yet developed less damage and at a slower rate than those exposed to CS.

We have identified a group of patients who remained CS-naïve for at least 3 years but who later required CS intervention. Below we describe the clinical features of this subset of patients.

Methods: Patients with SLE attending the UTLC satisfying the following criteria were included in the study: 3 years or more of follow-up from inception, no exposure to CS for the first 3 years from inception, no organ damage (as per the SLICC Damage Index (SDI) = 0) from inception and at least 5 follow-up visits. Two groups were identified from this cohort: those who remained entirely CS-naïve up to their last visit (CS-naïve) and those exposed to CS at some point after 3 years during follow-up (CS-late). Differences between the 2 groups were examined: in disease activity at inception (SLEDAI-2K) and over time (adjusted mean SLEDAI (AMS)), in the time to first incidence of organ damage (SDI ≥ 1), and the effect of exposure to anti-malarial (AM) medication on organ damage accrual (SDI ≥ 1).

Results: In the CS-late group, 31 patients were identified and 59 in the CS-naïve. The mean time to first CS exposure in the CS-late group was 9.0 ± 5.6 years.

Comparing the CS-late vs. CS-naïve groups, sex distribution (93.6% vs. 94.9% female), mean age at diagnosis (33.3 ± 11.9 vs. 37.8 ± 14.5 years; p = 0.15), years of follow-up (9.1 ± 5.6 vs. 11.0 ± 6.4 years; p = 0.15), mean SLEDAI at first visit (5.68 ± 3.31 vs. 5.25 ± 3.69; p = 0.59), AMS for the first 3 years, time to first damage (3.7 ± 3.9 vs. 4.8 ± 3.1 years; p = 0.36), damage scores over 10 years of follow-up, and the proportion eventually developing damage (11 (35.5%) vs. 23 (39%); p = 0.74) were similar between groups.

73.3% of the CS-late and 50.9% of the CS-naïve received a score on the SLEDAI for immunological activity (p = 0.04), with a mean immunological score of 2.00 ± 1.49 and 1.25 ± 1.38, respectively (p = 0.02). The CS-late had a lesser number with musculoskeletal (MSK) activity (16.1%) at first

visit, compared with the CS-naïve group (27.1%; p = 0.24) with lower MSK scores (0.65 ± 1.50 and 1.08 ± 1.79, respectively; p = 0.25). Arthritis and lupus rash were the cause of CS requirement in the CS-late group in most cases.

AM medication did not delay the onset of organ damage in the CS-late group.

Conclusion: A small group of patients with SLE remain steroid treatment naïve for more than 9 years and then develop a requirement for steroids usually because of arthritis and rash. Patients requiring late intervention with CS have greater immunological activity at baseline than patients who remain CS-naïve, yet accrue damage at similar rates to the CS-naïve. Early AM prescription is not protective of late CS requirement or development of organ damage.

Disclosure: B. J. Sheane, None; **D. Ibanez**, None; **D. D. Gladman**, None; **M. B. Urowitz**, None.

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Prevalence of Subclinical Echocardiographic Abnormalities in Patients with Systemic Lupus Erythematosus (SLE). Sergi Heredia[1], Javier Narváez[2], Andrea Zacarias[1], Eulalia Armengol[1], Gloria Albert[1], Alex Roset[1], Patricia Siguenza[1], Xavier Juanola[3], Manel Rubio Rivas[1] and Joan Miquel Nolla[1]. [1]Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, [3]University Hospital Bellvitge, Barcelona, Spain.

Background/Purpose: To determine the prevalence of unsuspected echocardiographic abnormalities (excluding pericardial effusion) and to identify associated clinical and laboratory features in a large SLE cohort.

Methods: The sample comprised 243 patients with SLE treated between 1980 and 2013 at a tertiary university hospital that does not attend pediatric populations. Patients were registered in a specific database (ACHILLES project). Ninety-one patients who were free of cardiovascular symptoms and had been examined at least once with a transthoracic Doppler echocardiogram (TTE) were selected for analysis. In patients with more than one TTE, only data from the last examination were included in the analysis. Each study investigated the presence of myocardial systolic dysfunction, diastolic myocardial dysfunction, valve disease, segmental wall motion abnormalities suggestive of ischemic heart disease and pulmonary arterial hypertension (PAH) defined as a systolic pulmonary artery pressure (PAP) of 40 mmHg and tricuspid regurgitation velocity (TRV) greater than 2.5 m/s.

Results: The mean age of patients (75 women) was 50 ± 12 years (range, 27–77) and median duration of disease at the time of the echocardiographic study was 83 months (range, 12 – 156). The main findings were:

- *Systolic dysfunction* in 1.1% (1/91) of patients.
- *Diastolic dysfunction* in 5.5% (5/91) of patients; all had arterial hypertension and two had positive antiphospholipid antibodies (aPL).
- *Segmental wall motion abnormalities suggestive of ischemic heart disease*: 3.3% (3/91) of patients.
- *Subclinical valve disease*: 46.2% (42/91) of patients, including 27 cases of tricuspid insufficiency (30%), 26 mitral regurgitation (29%), 5 aortic insufficiency (5.5%), 4 aortic stenosis (4.4%) and 1 verrucous Libman-Sacks endocarditis in mitral valve (1.1%). Some patients presented several different types of injury. Valve dysfunction was mild in all cases.
- *Pulmonary arterial hypertension*: 7.7% (7/91) of patients. Mean PAP was 46.8 ± 4 mmHg (range, 40–56) and mean TRV was 3 ± 0.3 m/s (range, 2.7–3.4). Pulmonale was observed in two patients; neither had dilated inferior vena cava or pericardial effusion. Six out of seven patients (86%) of patients with PAH also had some kind of valve disease.

Of the patients with subclinical valvular disease, 40.5% (17/42) were positive for one or more of the aPL (cardiolipin antibodies Ig or IgM, anti-beta2-glycoprotein IgG or IgM, lupus anticoagulant). Five out of seven patients with PAH (71.4%) were positive for aPL. In the comparative study of 49 SLE controls without valve disease or PAH, there were no statistically significant differences in aPL positivity (45% positivity in controls; p > 0.05). No significant differences were observed in the frequency of Raynaud's phenomenon between patients with PAH and controls.

Conclusion: Echocardiographic abnormalities were frequently detected in asymptomatic patients with SLE. Valve disease (46%) was the most common finding. TTE screening may be indicated in patients with SLE.

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Circulating Anti-Ro/SSA Antibodies Are Associated with the Presence of Severe Mitral Regurgitation in Systemic Lupus Erythematosus. Violeta Higuera[1], Claudia Hübbe[2] and Luis M. Amezcua-Guerra[3]. [1]Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico, [2]Instituto Nacional de Cardiología, Mexico City, Mexico, [3]Mexican Board of Rheumatology, Mexico City, Mexico.

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disorder involving multiple organ systems. The frequency of symptomatic heart disease ranges from 5 to 10%, but noninvasive imaging methods such as transthoracic echocardiography (TTE) may demonstrate subclinical cardiac involvement in up to 95% of SLE patients. In spite of this, intrinsic SLE factors conferring risk to develop cardiac valve involvement have not been adequately defined. Indeed, almost all available information about cardiac valve disease in SLE is related to both circulating antiphospholipid antibodies and the antiphospholipid syndrome.

A recent short study described that anti-Ro/SSA antibodies, one of the most commonly autoantibodies found in SLE (40–50%), could be associated with the presence of valvulopathy.

Objectives: To evaluate the association between anti-Ro/SSA and other antibodies and cardiac valve disease in SLE.

Methods: One-hundred patients fulfilling the ACR classification criteria for SLE were enrolled. Demographics and clinical data were collected and patients underwent to TTE. Also, serum antibodies against nuclear antigens, dsDNA, Sm, Ro/SSA, La/SSB, RNP, cardiolipin, and β2GP1 were measured.

Patients were grouped according to the presence or absence of anti-Ro/SSA antibodies, and clinical, serological and TTE data were compared by chi-square or Mann-Whitney tests as correspond.

Results: Eleven patients were excluded because rheumatic valve disease or congenital heart disorder. Eighty-nine patients were included for analyses, 36 patients (35 female, mean age 37.3±14 years) were positive and 53 negative (43 female,40.1±15) for circulating anti-Ro/SSA antibodies. There were no differences in age, disease duration or co-morbidities between groups. A difference was noted in the presence of anti-dsDNA (67% *vs* 45%; P=0.04) and anti-La/SSB (19% *vs* 2%; P=0.004) antibodies. In the cardiac abnormalities detected by TTE, there was a significant relationship between positive anti-Ro/SSA antibodies and severe mitral regurgitation (27% *vs* 5%; P=0.02). Indeed, anti-Ro/SSA antibodies confer an OR 6.5 (P=0.03) for the presence of severe mitral regurgitation. No other differences in the TTE findings were found.

Conclusion: In SLE, circulating anti-Ro/SSA antibodies are associated with the presence of severe mitral regurgitation.

Disclosure: V. Higuera, None; **C. Hübbe**, None; **L. M. Amezcua-Guerra**, None.

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Acute Myocarditis in Patients with Systemic Lupus Erythematosus: Experience from Affiliated Hospitals of Catholic University of Korea. In-Woon Baek[1], Ki-Jo Kim[2], Yune-Jung Park[3], Chong-Hyeun Yoon[4], Wan-Uk Kim[5] and Chul-Soo Cho[1]. [1]Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [2]St. Vincent's Hospital, The Catholic University of Korea, Suwon, South Korea, [3]St. Vincent's Hospital, The Catholic University of Korea, Suwon, South Korea, [4]Uijeongbu St. Mary's Hospital, The Catholic University of Korea, Uijeongbu, South Korea, [5]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea.

Background/Purpose: To determine the factors associated with occurrence of acute myocarditis (AMC) and its outcomes in patients with systemic lupus erythematosus (SLE).

Methods: This was a retrospective study of hospitalized SLE patients with AMC from 2002 to 2014 at Catholic University affiliated hospitals. A diagnosis of AMC was made on the basis of clinical findings, electrocardiographic changes, elevated cardiac enzymes levels and echocardiographic abnormalities. Eighty-six SLE patients who showed no echocardiographic evidence of myocarditis were enrolled as a control group. The clinical and laboratory data from each patient were collected from the charts and compared between 2 groups.

Results: During these periods, 22 SLE patients were identified to have AMC (male 3, female 19). Patients with AMC, as compared with those without, were found to be associated with shorter disease duration and higher frequency of smoking (P<0.005, P<0.05, respectively). Moreover, they showed significantly higher SLE disease activity index score (P<0.001) and

C-reactive protein levels ($P<0.001$), but lower complement levels (C3, C4 and CH50, all $P<0.005$). Interestingly, antiphospholipid syndrome (APS) was more prevalent in patients with AMC compared with those without ($P<0.01$). In multivariate analysis, shorter disease duration, smoking and presence of APS were independent factors associated with AMC in SLE patients. All patients with AMC received high-dose corticosteroid and 2 of them received intravenous cyclophosphamide; 17 patients completely recovered, but 5 died.

Conclusion: AMC patients are more likely to have high disease activity and its occurrence is associated with shorter disease duration, smoking, and presence of APS.

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Lupus Myocarditis: Clinical, Echocardiographic and Magnetic Resonance Characteristics. Maria del Carmen Zamora Medina[1], Hilda Fragoso-Loyo[2], Martha Morelos[3], Juan Jakez-Ocampo[3], Luis Llorente[4], Juan Rosas Saucedo[3] and Yemil Atisha-Fregoso[5]. [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran, Mexico City, Mexico, [2]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico, [3]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México, Mexico, [4]Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico, [5]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

Background/Purpose: Myocarditis is an uncommon manifestation with important morbidity and mortality in patients with Systemic Lupus Erythematosus (SLE). There are scant information about this manifestation that comes from case series, which include no more than 24 patients. Also, there are not a uniform definition about the criteria for the diagnosis of this manifestation in SLE, and only in few reports the diagnosis was supported by cardiac magnetic resonance (CMR).

Methods: Retrospective study of all cases of myocarditis seen in a single center between 2005 and 2014. Patients with diagnosis of SLE according to the updated 1982 ACR criteria, who met the expanded criteria for myocarditis and had CMR compatible with the diagnosis were included.

The objective of the study was to describe the clinical and laboratorial manifestations, and electrocardiographic, echocardiographic and CMR findings of these patients.

Results: Twenty five patients (24 women, 96%), with a mean age of 29.38 ± 11.36 years, and who presented 26 episodes of myocarditis were included. The mean time to development of myocarditis after SLE diagnosis was 11.5 months (IQR 0–31.2%). The main clinical and imaging findings are shown in tables 1 and 2.

During the episode of myocarditis the activity of SLE at diagnosis measured by SLEDAI was of 8.77 (IQR 4–12). Patients had a SLICC Damage Index at diagnosis of 1.43 ± 1.6. Nine of 26 patients (35%) required admission to the ICU and 6 of 26 (23%) patients were treated with inotropics. There were no deaths during the acute episode, but 4 patients died during the follow-up, three of them secondary to infections. All patients were treated with prednisone, mean dose 50 ± 12 mg/day.

Follow-up MRI was performed on 10 patients, the mean initial LVEF was 49.2% ± 9.2 vs 61% ± 8.1(p=0.007). The SLEDAI score at follow-up was of 2 points (IQR 0–6), and the SLICC Damage Index at follow-up was of 1.71 ± 1.82.

Conclusion: Myocarditis is a severe manifestation of SLE. CMR is a useful study in the diagnosis of myocarditis that can evaluate some parameters that are not detectable in echocardiography e.g., valvulitis, edema, hyperemia and myocardial fibrosis. Further studies are needed to determine the role of CMR and currently follow-up studies are undergoing at our Institute in SLE patients with myocarditis.

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Osteonecrosis in Patients with Systemic Lupus Erythematosus: Risk Factors and Clinical Outcome. Andrea Zacarias[1], Javier Narváez[2], Sergi Heredia[1], Helena Borrell[1], Paula Estrada[1], Alex Roset[1], Nestor Arce Gonzalez[1], Carmen Gomez Vaquero[1], Olga Capdevila[1] and Joan Miquel Nolla[1]. [1]Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain.

Background/Purpose: To study the prevalence of osteonecrosis (ON) in patients with systemic lupus erythematosus (SLE) and to identify the risk factors for development of this complication and predictors of total hip/knee arthroplasty.

Methods: The sample comprised 243 patients with SLE treated between 1980 and 2013 at a tertiary university hospital that does not attend pediatric populations. Patients were registered in a specific database. Patients with ON were selected for analysis. The diagnosis was confirmed in all cases with imaging techniques (conventional radiography and bone scan, CT scan or MRI). The variables associated with the occurrence of this complication were analyzed using a backward logistic regression model.

Results: During the follow-up period, 11 patients (4.5%) had 12 episodes of ON (one patient developed two). The mean age of the patients (nine women) was 52 ± 15 years and median time to progression of SLE at the time of diagnosis of ON was 149 months (range: 24–323). Three out of 11 cases of ON (27%) occurred within the first five years of the course of the disease.

The condition was monoarticular in eight episodes (66%) and multifocal in four (34%); in the latter case it simultaneously affected two or more joints (range 2–4). The most common site was the femoral head (75% of episodes), followed by the knee (33%) and the humeral head (8%). In 90% of the affected joints, ON presented with pain and functional impotence (the asymptomatic joints were detected in the scintigraphic study).

The mean dose of prednisone at the time of diagnosis of ON was 11 ± 8.2 mg/day and the total cumulative dose was 30.4 ± 16.7 g. Seven patients (64%) had received a prednisone dose of at least 0.5 mg/kg/day at some point of the disease; 5 (45%) of these had received a dose of 1 mg/kg/day for serious complications. However, at the time of ON diagnosis, disease was inactive or mild in all patients according to the SLEDAI score (mean 1.3, range 0–4).

Antiphospholipid antibodies were positive in two patients (18%); both were on antiplatelet therapy. We did not identify any other risk factors that have been associated with the development of ON in SLE.

Outcome was unfavorable in seven patients (64%), who required total hip/knee replacement. There was no increase in mortality.

Both in the comparisons between groups using univariate analysis and in the multivariate analysis, the only predictor of risk for development of this complication was the total cumulative prednisone dose (OR = 19.07 [95% CI: 2.7 – 133.7], p = 0.0002). No associations were found with the presence of antiphospholipid antibodies, immunosuppressive therapy, presence of arthritis or degree of disease activity according to the SLEDAI. In the Cox proportional hazards model, advanced radiological stage was the only statistically significant predictor for arthroplasty.

Conclusion: ON is a rare complication in patients with SLE (4.5%). In the majority of the cases it is symptomatic and occurs in advanced stages of the disease. The major risk factor associated with the development of this complication is the cumulative dose of glucocorticoids. ON was not associated with increased mortality, but it was associated with physical disability.

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Clinical Characteristics and Outcome of Intestinal Pseudo-Obstruction in Patients with Systemic Lupus Erythematosus. Lingling Zhang, Mengtao Li, Dong Xu, Na Gao, Li Zhang, Yong Hou, Qian Wang and Xiaofeng Zeng. Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China.

Background/Purpose: Intestinal pseudo-obstruction (IPO) is a rare clinical syndrome characterized by ineffective intestinal motility. IPO has been recently recognized as an uncommon complication of systemic lupus erythematosus (SLE). Though case series of patients with SLE-related IPO (SLE-IPO) have been reported, the epidemiology, characteristics, risk factors and prognosis for SLE-related IPO remain poorly understood.

Methods: To analyze the clinical characteristics and outcome of SLE-IPO, we retrospectively enrolled 68 SLE patients with IPO syndrome as the case group and 323 randomly matched SLE patients without any gastrointestinal manifestations as controls out of 3937 inpatients at Peking Union Medical College Hospital (PUMCH) from 2003 to 2013. IPO was diagnosed according to gastrointestinal symptoms, gaseous small bowel distension with air-fluid levels showed by radiographic signs or thickened gastric wall and dilated small or large bowels showed by CT scan, otherwise, patients were

excluded. The case-control study was conducted to compare the clinical and laboratory data. The outcome of SLE-IPO was also investigated.

Results: Within the last 10 years at PUMCH, the prevalence of IPO in SLE patients was 1.73% and the in-hospital fatality rate was 8.8%. 58.8% of the SLE-IPO manifested as the initial presentation of SLE. Ureterohydronephrosis was the most common complication (60.3%) in SLE patients with IPO and the incidence of biliary tract dilation was 7.9%. SLE patients with IPO were always diagnosed at earlier stage of SLE with higher frequency of hematological disturbance, polyserositis and hypocomplementemia than control patients. Ureterohydronephrosis (OR = 90.322, 95% CI 21.283–383.32, p = 0.000), hypocomplementemia (OR = 10.437, 95% CI 1.341–81.217, p = 0.025) and elevated CRP level in serum (OR = 5.143, 95% CI 1.401–18.876, p = 0.014) were independent risk factors for IPO in SLE disease. However, the positivity of anti-dsDNA antibody was a protective factor for SLE with IPO (OR = 0.222, 95% CI 0.061–0.8, p = 0.021). SLE-IPO patients with long IPO duration, diagnosed at late stage of SLE or concurrent with megacholedochus and ureterohydronephrosis always had unfavorable outcome.

Conclusion: IPO can manifest as a complication of SLE and more commonly, as the initial presentation. SLE-IPO always occurs concomitantly with ureterohydronephrosis and biliary dilatation, and these three complications combined indicate a severe situation of SLE. SLE-IPO patients without systemic smooth muscular involvement could achieve better prognosis with early diagnosis and aggressive treatment.

Table 1 A comparison of demographics, clinical manifestations

Variable	*Cases*	*Control*	*p value*
Demographics			
Female sex n, (%)	66/68(97.1)	221/232(95.3)	0.739
Age, years, mean±SE	32.3±1.4	32.3±0.83	0.975
Clinical manifestations			
Flare age, years, mean±SE	29.7±1.4	32.4±2.7	0.594
Disease duration, months, mean±SE	30.8±5.5	56.2±4.7	0.001
Fatality, n(%)	6/68(8.8)	13/232(5.6)	0.398
Acute or subacute skin lupus	23/66(34.8)	85/232(36.6)	0.79
Mucosal Ulcers	15/67(22.4)	40/232(17.2)	0.338
Arthritis	29/68(42.6)	95/232(40.9)	0.802
Polyserositis	54/66(81.8)	93/232(40.1)	0.0001
Nephropathy	53/68(77.9)	154/232(66.4)	0.064
Nervous system disturbance, n(%)	12/68(17.6)	58/224(25.0)	0.207
Hematological disturbance, n(%)	41/67(61.2)	99/232(42.7)	0.007
Urinary system disturbance	41/68(60.3)	10/232(4.3)	0.0001
Elevated ESR, n(%)	41/60(68.3)	155/226(68.6)	0.97
Elevated CRP, n(%)	32/60(53.3)	63/202(29.9)	0.001
Hypocomplementemia, n(%)	61/68(89.7)	146/219(66.7)	0.0001
ANA, n(%)	63/68(92.6)	183/232(78.9)	0.009
Anti-dsDNAantibody, n(%)	21/68(30.9)	113/224(48.7)	0.009
Anti-Smantibody, n(%)	20/61(32.8)	56/230(24.3)	0.182
Anti-RNP antibody, n(%)	27/67(40.3)	81/230(35.2)	0.45
Anti-SSA antibody, n(%)	38/68(55.9)	124/230(53.9)	0.775
Anti-SSB antibody, n(%)	14/68(20.6)	27/220(11.7)	0.063
Ro-52, n (%)	9/67(13.4)	–	–
Anti-rRNPantibody, n(%)	6/68(8.8)	33/180(18.3)	0.066
ANCA	1/60(1.7)	3/136(2.2)	1
ACL antibody, n(%)	7/59(11.9)	31/196(15.8)	0.455
LA antibody, n(%)	5/45(11.1)	21/171(12.3)	0.843
SLEDAI, mean±SE	13.15±0.827	10.23±0.40	0.001

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Venous and Arterial Thrombosis in SLE: Differences in Natural History. Katharine Hickman[1], Laurence S. Magder[2] and Michelle Petri[3]. [1]University College London, London, United Kingdom, [2]University of Maryland, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Thrombosis is increased in SLE due to disease activity and co-morbid factors including antiphospholipid antibodies. We separately investigated the natural history of venous vs. arterial thrombosis.

Methods: 2250 patients were enrolled in a prospective cohort; 334 had a thrombotic event before cohort entry or diagnosis of SLE. For ALL thrombosis, age over 60 yrs, male gender, African-American ethnicity, SLEDAI greater than 3, and prednisone greater than 0 were risk factors.

Results: In general, rates of venous thrombosis were fairly constant, while rates of arterial thrombosis increased with age. The figure below shows that initially the venous thrombosis rate is higher (including before diagnosis) and later the arterial thrombosis rate is higher.

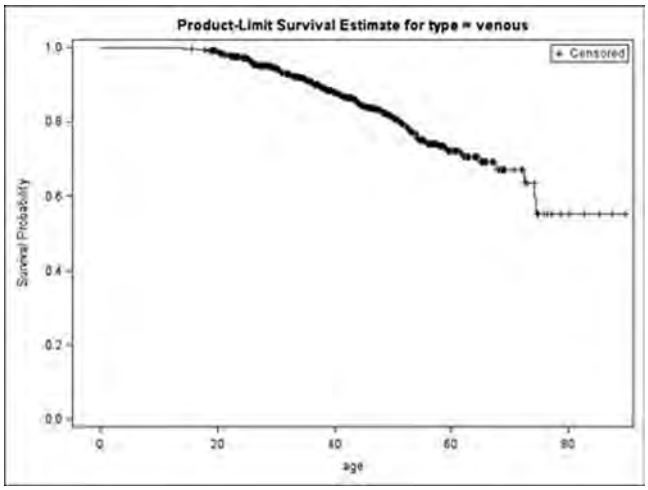

Figure SEQ Figure * ARABIC 1: Probability of remaining thrombosis free, by age

Table 1: Incidence rates (per 1000 patient-years) of thromboses

Characteristic of Person-Month	All Thromboses Rate Ratios (95% CI)	P-values	Arterial Thromboses Rate Ratios (95% CI)	P-values	Venous Thromboses Rate Ratios (95% CI)	P-values
Age	1.0 (Ref Group)	0.47	1.0 (Ref. Group)	0.22	1.0	0.66
18–39	1.1 (0.8, 1.6)	0.46	1.3 (0.8, 2.1)	0.13	0.9 (0.6, 1.5)	0.53
40–49	1.2 (0.8, 1.7)	0.0002	1.5 (0.9, 2.4)	0.0001	0.8 (0.5, 1.5)	0.70
50–59	2.2 (1.4, 3.3)		3.0 (1.8, 4.9)		1.1 (0.6, 2.2)	
60+						
Sex	1.0 (Ref. Group)	0.024	1.0 (Ref. Group)	0.070	1.0 (Ref. Group)	0.27
Female	1.7 (1.1, 2.7)		1.7 (1.0, 3.0)		1.5 (0.7, 2.9)	
Male						
Race	1.0 (Ref. Group)	0.0051	1.0 (Ref. Group)	0.031	1.0 (Ref. Group)	0.068
Caucasian	1.5 (1.1, 2.0)	0.91	1.5 (1.0, 2.1)	0.11	1.5 (1.0, 2.2)	0.24
African Amer.	1.0 (0.5, 1.9)		0.3 (0.1, 1.3)		1.6 (0.7, 3.6)	
Other						
Most Recent SLEDAI	1.0 (Ref. Group)	0.20	1.0 (Ref. Group)	0.021	1.0 (Ref. Group)	0.42
0	1.3 (0.9, 2.0)	0.024	1.9 (1.1, 3.2)	0.0007	0.8 (0.4, 1.4)	0.69
1–2	1.6 (1.1, 2.5)	<0.0001	2.5 (1.5, 4.3)	<0.0001	0.9 (0.4, 1.7)	<0.0001
3–4	3.0 (2.0, 4.4)		3.5 (2.1, 6.0)		2.8 (1.7, 4.6)	
5+						
Current Prednisone Dose	1.0 (Ref Group)	0.038	1.0 (Ref. Group)	0.015	1.0 (Ref. Group)	0.33
0	1.5 (1.0, 2.3)	<0.0001	1.8 (1.1, 3.0)	<0.0001	1.3 (0.7, 2.4)	<0.0001
1–9	3.3 (2.2, 4.8)	<0.0001	3.5 (2.2, 5.7)	<0.0001	3.2 (1.9, 5.6)	<0.0001
10–19	6.7 (4.5, 10.0)		7.0 (4.2, 11.6)		7.2 (4.1, 12.7)	
20+						

Conclusion: Prevention of venous thrombosis remains important throughout the course of SLE. Prevention of arterial thrombosis becomes more important later in the disease course. Disease activity is a risk factor for arterial thrombosis while prednisone is a risk factor for both venous and arterial thrombosis.

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Grip Strength Identifies Increased Physical Disability in Women with Systemic Lupus Erythematosus. James S. Andrews[1], Mary Margaretten[2], Jennifer Barton[2], Jinoos Yazdany[2], Ed Yelin[2] and Patricia P. Katz[3]. [1]University of California San Francisco, San Francisco, CA, [2]University of California, San Francisco, San Francisco, CA, [3]University of California, San Francisco, CA.

Background/Purpose: Muscle weakness is common and contributes to physical disability in women with systemic lupus erythematosus (SLE). Recently, the Foundation for the National Institutes of Health Sarcopenia Project reported grip strength cutpoints that identified weakness associated

with impaired mobility among women aged ≥ 65 years. However, the ability of grip strength to identify SLE patients at increased risk of physical disability is unknown. This study aims to test whether grip strength is associated with increased physical disability in women with SLE.

Methods: Subjects were women in a longitudinal cohort with physician-documented SLE. All measures were collected during an in-person research visit among a subset of the cohort. Grip strength was measured with a handheld dynamometer. Grip strength was classified as "weak" (<16kg), "intermediate" (16–20kg), and "normal" (>20kg). Self-reported physical functioning was assessed using the SF-36 Physical Functioning subscale (range 0–100, mean 50, SD 10) and Valued Life Activities (VLA) Disability (range 0–3) surveys. Higher SF-36 and lower VLA scores indicate higher functioning. Regression analyses controlling for age, SLE duration, prednisone use, SLE disease activity measured with the Systemic Lupus Activity Questionnaire (SLAQ), physical activity level measured by the International Physical Activity Questionnaire (IPAQ), and depressive symptoms measured by the Center for Epidemiological Studies Depression Scale (CES-D) modeled the effects of grip strength on SF-36 and VLA scores.

Results: Of the 146 women, mean age was 48 (±12) years; duration of SLE was 16 (±9) years; SF-36 score was 40.9 (±11.4); VLA disability score was 0.80 (±0.55). Fifteen women (10%) had "weak" grip strength, 31 (21%) "intermediate, 78 (53%) "normal"; and 22 (15%) were missing grip strength data. In both unadjusted and adjusted models, having "weak" compared to "normal" grip strength was associated with significantly worse SF-36 and VLA scores (see Table 1). In sensitivity analyses examining the effects of missing grip strength data and of excluding women aged ≥ 65 years (n=11), the overall trends were unchanged.

Conclusion: Grip weakness was common in our cohort of women with SLE, with a prevalence comparable to that of geriatric populations. Grip weakness successfully identified women with increased physical disability even when adjusting for potential confounders such as disease activity and depression. These findings underscore the high burden of muscle weakness among women with SLE, and they may suggest a clinical role for grip strength testing in identifying women with SLE at greatest risk of physical disability. Further studies will need to examine the ability of grip strength to predict incident disability in SLE.

Table 1. Association between Grip Strength and Disability Scores[#]

	SF-36 Physical Functioning		Valued Life Activities	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Weak (<16kg)	−11.8 (−17.6, −6.1)***	−4.4 (−8.7, −0.1)*	0.68 (0.40, 0.96)***	0.31 (0.11, 0.51)**
Intermediate (16–20kg)	−7.5 (−11.8, −3.2)**	−3.2 (−6.3, 0.01)	0.29 (0.08, 0.50)**	0.08 (−0.06, 0.23)
Normal (>20kg)	ref.	ref.	ref.	ref.

[#]Values are regression beta coefficients (95% CI). Grip strength cutpoints defined per Alley DE et al., J Gerontol A Biol Sci Med Sci 2014 May; 69(5):559–566.
*p<0.05, **p<0.01, ***p<0.001

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Osteonecrosis in Systemic Lupus Erythematosus: Prevalence, Patterns and Outcomes. Nimrit Dhillon, Dominique Ibanez, Dafna D. Gladman and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Osteonecrosis is a serious comorbidity of systemic lupus erythematosus (SLE). The reported frequency of symptomatic osteonecrosis in SLE is variable, ranging from 4% to 15%.

The aim of this study is to provide an update of the prevalence, patterns and outcomes of symptomatic osteonecrosis in SLE.

Methods: SLE patients with osteonecrosis were identified from the Lupus Clinic Database containing patients with 4 ACR criteria of SLE or 3 criteria and a biopsy diagnostic of lupus. Osteonecrosis was defined as those patients with clinical symptoms and confirmed osteonecrosis by imaging (x-ray, bone scan, CT, MRI). Demographic and clinical data of affected patients were collected prospectively, stored in an Oracle database and analyzed using descriptive statistics.

Results: Of the 1729 patients with SLE registered in the database as of 1970, 235 patients (13.6%) developed symptomatic osteonecrosis. 86.0% were female, with a mean age of 34.8 ± 12.8 years at first osteonecrosis diagnosis. This involved a total of 542 joints, 383 joints of which were identified at the time of first osteonecrosis occurrence. The mean time from diagnosis of SLE to diagnosis of first osteonecrosis was 8.2 ± 8.1 years, and the time from first osteonecrosis diagnosis to second osteonecrosis diagnosis was 3.4 ± 4.8 years.

111 out of 235 (47%) patients had multiple site involvement at first osteonecrosis occurrence, affecting from 2 to 6 sites. At the time of first diagnosis affected sites included the hip (245), knee (86), shoulder (28), ankle (15), wrist (3), other joints (3) and elbow (2). Those that progressed to surgical intervention included: hip 131/245 (53.5%), knee 18/86 (19.8%), wrist 1/3 (33.3%), shoulder 1/28 (3.6%), ankle 0/15 (0%), elbow 0/2 (0%), and other joints 1/3 (33%). The mean time from osteonecrosis diagnosis to surgery of the hip was 3.8 ± 5.5 years, while the mean time from osteonecrosis diagnosis to surgery of the knee was 5.5 ± 6.2 years.

Conclusion: To our knowledge, this is the largest cohort of SLE patients with symptomatic osteonecrosis. Osteonecrosis continues to be a significant comorbidity of SLE as 13.6% of patients developed symptomatic osteonecrosis. In patients developing osteonecrosis, the presentation occurred after 8.2 ± 8.1 years of SLE disease duration. 47.2% of patients had multiple site involvement at first ON diagnosis. Large weight-bearing joints, including the hip and knee, were most frequently involved. The majority of hips required surgical intervention. Better strategies to prevent this serious complication are needed.

Disclosure: N. Dhillon, None; **D. Ibanez**, None; **D. D. Gladman**, None; **M. B. Urowitz**, None.

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Decreased Lung Diffusion Capacity in Asymptomatic Patients with Systemic Lupus Erythematosus Does Not Predict Future Lung Disease. Ofir Elalouf, Elizabeth Fireman, David Levartovsky, Ilana Kaufman, Ori Rogovski, Ori Elkayam, Dan Caspi and Daphna Paran. Tel-Aviv Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

Background/Purpose: In a previous study, performed 9±3.6 years ago 74 asymptomatic patients with systemic lupus erythematosus (SLE) and or antiphospholipid syndrome (APS) who fulfilled the ACR criteria for diagnosis, underwent lung function testing. A significantly low diffusion capacity (DLCO) ranging from 45% to 70% was recorded in 28 of the 74 (37.8%) patients who were all free of respiratory symptoms. This study aims to assess the clinical importance and predictive value of a low diffusion capacity in asymptomatic patients with SLE or APS.

Methods: Asymptomatic patients with SLE and /or APS who were found to have a low DLCO in the previous study were contacted. Of the 28 patients, 15 were recruited and reevaluated in the current study [SLE with APS (n=7), SLE without APS (n=7); primary APS (n=1)]. A detailed history, physical examination, nail bed capillaroscopy, current laboratory tests and lung function tests including DLCO were obtained.

Results: During a surveillance period of 9±3.6 years none of the patients developed lung disease. Diffusion capacity corrected for alveolar volume (DLCO/VA) improved in the study group during this period from 61.3% ± 6.3 to 77% ± 12.7% (p=0.006). Lung function tests including total lung capacity (TLC) and forced expiratory volume in 1s (FEV1) remained within normal limits. Capillaroscopy studies did not reveal changes compatible with scleroderma in any of the patients.

Conclusion: Low diffusion capacity findings on lung function testing does not have a positive predictive value for the development of future lung disease in patients with SLE who are free of respiratory symptoms. Our results suggest that a finding of low diffusion capacity in asymptomatic patients with SLE does not necessarily require further evaluation and imaging and may improve spontaneously over time. Further studies in a larger group of patients are needed to validate these findings.

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How Important Is Physical Activity for Patients with Systemic Lupus Erythematodes? -Results of Lula-Study. Isabelle Kloubert[1], Gamal Chehab[1], Jutta Richter[2], Rebecca Fischer-Betz[3], Ralph Brinks[2] and Matthias Schneider[1]. [1]Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany, [2]Heinrich-Heine-University, Düsseldorf, Germany, [3]University of Düsseldorf, Düsseldorf, Germany.

Background/Purpose: Physical activity (PA) plays a decisive role in primary and secondary prevention in various domains of medicine. Our examination aimed to determine association PA and on outcomes in systemic lupus erythematodes (SLE).

Methods: The LuLa-Study is a prospective long-term study since 2001, which systematically collects patients' reported outcomes among members of the German SLE Self-Help Organization. In 2006 and 2009 we analysed data of 750 patients (94.4% female, age 52.3±12.9 years (mean±SD), duration of disease 15.9 years in 2009) with regard to their PA applying the "Freiburger Questionnaire on physical activity". We calculated the Metabolic Equivalent of Task (MET) for every patient. In the univariate analysis we compared 422 patients with low/intermediate PA (<30 MET, n=259) to those with high/very high activity (>30 MET, n=163) in both years. Furthermore, we examined the association of PA to disease activity, HRQoL (SF-12) and clinical symptoms in a multivariate regression analysis with age, sex, BMI and number of comorbidities.

Results: The medium MET of the group with low/intermediate PA was 13.4±7.6 respectively, 73.9±31.5 with high/very high PA. A high PA in 2006 and 2009 was associated with less cephalgia ($p<0.006$) and muscle weakness ($p<0.009$) and with lower disease activity in 2009 (determined with SLE Activity Questionnaire (SLAQ) and VAS; $p<0.001$). No statistically significant relation between PA and myalgia or arthralgia could be found. Patients with high MET in 2006 and 2009 showed a better HRQoL (Physical Component Summary ($p<0.001$) and Mental Component Summary ($p<0.014$) determined with SF 12) in 2009. Both groups of activity improved their emotional HRQoL between 2006 and 2009, whereas the physical HRQoL stagnated in both groups. A higher PA in 2006 and 2009 was connected to a lower damage (determined by System Lupus International Collaborating Clinics/ACR Damage Index for SLE (SLICC-) Score; $p<0.012$) as well as to an improved fatigue (Vanderbilt Fatigue Score (VFS); $p<0.001$) and a different cognition of pain (FSS-Score; $p<0.001$) in 2009. The multivariate analysis included all 750 patients (medium MET in 2006 28.5±26.1, in 2009 34.5±37.7) and affirmed the influence of higher MET to the above outlined scores. It could be shown, that a higher PA of 10 MET is related to a decreasing SLAQ (−0.43 points) three years later ($p<0.001$). This effect remained after adjusting for the covariates. The same activity of 10 MET in 2009 is only associated with a decreasing SLAQ (−0.30 points) ($p<0.001$). A similar observation could be depicted for emotional and physical HRQoL.

Conclusion: PA of SLE patients does have an impact on clinical manifestations and is related to a higher HRQoL. As increased PA has an impact on HRQoL and SLAQ three years later, a recommendation of more PA seems reasonable.

Disclosure: I. Kloubert, GlaxoSmithKline, 9, UCB, 9; **G. Chehab**, GlaxoSmithKline, 9, UCB, 9; **J. Richter**, GlaxoSmithKline, 9, UCB, 9; **R. Fischer-Betz**, GlaxoSmithKline, 9, UCB, 9; **R. Brinks**, GlaxoSmithKline, 9, UCB, 9; **M. Schneider**, GlaxoSmithKline, 9, UCB, 9.

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Protein Losing Enteropathy in Systemic Lupus Erythematosus. Doo-Ho Lim, Seung-Hyn Bae, Soo Min Ahn, Seokchan Hong, Yong-Gil Kim, Chang-Keun Lee and Bin Yoo. University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea.

Background/Purpose: Protein losing enteropathy (PLE), characterized by severe hypoalbuminemia and edema, is rare manifestation of systemic lupus erythematosus (SLE). The study was proposed to identify the distinct features of lupus PLE and to evaluate the factors related with treatment response or outcome of lupus PLE.

Methods: From Mar. 1998 to Mar. 2014, the clinical data of 14 patients with lupus related PLE (lupus PLE) and 7 patients with idiopathic PLE in tertiary center were reviewed. PLE was defined as demonstration of protein leakage from gastrointestinal tract by either technetium 99m-labelled human albumin scan or fecal α1-antitrypsin clearance with no evidence of protein loss from other sources and impaired protein synthesis. Positive steroid response (PSR) was defined as return of serum albumin to ≥ 3.0 g/dl within 4 weeks after initial steroid monotherapy and remission as maintenance of serum albumin ≥ 3.0 g/dl for at least 3 months. High total cholesterol means the serum total cholesterol level of ≥ 240 mg/dl.

Results: The mean age of lupus PLE was 37.0 ± 19.8 years (range: 16 – 72) and 11 patients (78.6%) had PLE as initial manifestation of SLE. The mean follow-up duration was 55.8 ± 16.0 months (range: 6 – 172). There were significant increases in ESR and total cholesterol level in lupus PLE compared with idiopathic PLE. Among 14 patients with lupus PLE patients, 8 patients experienced PSR. Total cholesterol level was significantly higher in PSR group (Table 1). PSR was associated with initial high total cholesterol (OR = 7.0, 95% CI = 1.14 – 42.97) and with achievement of remission in 6 months (OR = 3.0, 95% CI = 0.97 – 9.30). Among 14 patients with lupus PLE, 10 patients who achieved remission in 6 months showed higher total cholesterol level (283.3 ± 79.3 mg/dL) compared to 4 patients who did not (165.3 ± 63.9 mg/dL).

Conclusion: In lupus PLE, high total cholesterol level could be a predictive factor to initial steroid response, expecting good response to steroid therapy alone. Furthermore, we suggest that initial high level of total cholesterol could predict a favorable outcome in patient with lupus PLE.

Table 1 Characteristics of lupus related PLE patients according to steroid response

Characteristic	Positive steroid response (n=8)	Negative steroid response (n=6)
Age, years	37.0 ± 19.8	48.3 ± 7.7
Sex, male (%)	4 (50)	2 (33.3)
Symptom duration before treatment, weeks	6.1 ± 4.5	16.0 ± 11.5
White blood cells, $x10^3$/ul	7.7 ± 3.3	7.0 ± 1.9
Lymphocyte, $x10^3$/ul	1.9 ± 0.7	1.5 ± 0.5
Hemoglobin, g/dl	12.8 ± 1.1	11.5 ± 1.5
Platelets, $x10^3$/ul	202.8 ± 119.9	260.1 ± 107.2
ESR, mm/h[a]	68.3 ± 23.9	70.7 ± 51.2
CRP, mg/dl	0.9 ± 1.9	1.1 ± 1.0
C3, mg/dl	52.8 ± 24.6	44.3 ± 19.4
C4, mg/dl	11.3 ± 5.7	13.2 ± 3.2
Anti-ds DNA antibody, IU/ml	16.6 ± 19.8	20.4 ± 41.5
SLEDAI score	6.5 ± 3.3	7.67 ± 3.7
Protein, g/dl	4.2 ± 1.6	4.23 ± 0.9
Albumin, g/dl	1.3 ± 0.5	1.2 ± 0.35
Total cholesterol level, mg/dl[a]	304.6 ± 74.0	176.6 ± 52.3
High total cholesterol, (%)	7 (87.5)	0 (0)
Remission within 6 months (%)	8 (100)	2 (33.3)

[a]: $p < 0.05$

Disclosure: D. H. Lim, None; **S. H. Bae**, None; **S. M. Ahn**, None; **S. Hong**, None; **Y. G. Kim**, None; **C. K. Lee**, None; **B. Yoo**, None.

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Autoimmune Hepatitis in Systemic Lupus Erythematosus. Doo-Ho Lim, Seung-Hyeon Bae, Soo Min Ahn, Seokchan Hong, Yong-Gil Kim, Chang-Keun Lee and Bin Yoo. University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea.

Background/Purpose: Autoimmune Hepatitis (AIH) is a chronic progressive liver disease of unknown cause, characterized by circulating autoantibodies and hyperglobulinemia. Patients with AIH often have other autoimmune diseases such as autoimmune thyroiditis and ulcerative colitis. However, AIH accompanied by SLE (AIH-SLE overlap) is relatively rare condition. The aims of our study were to identify the distinct features of AIH-SLE overlap compared with primary AIH (PAIH) and to evaluate the factors related with outcome of AIH-SLE overlap.

Methods: From May. 1995 to Feb. 2014, the clinical data of 164 patients with PAIH and 23 patients with AIH-SLE overlap in a tertiary referral center were reviewed retrospectively. AIH was diagnosed if pretreatment or posttreatment score was above 9 or 11, according to AIH diagnostic scoring system of American Association for the Study of Liver Disease in 2002. Liver biopsy was performed in all AIH patients. SLE patients fulfilled at least 4 of the 1997 revised American College of Rheumatology criteria. Progression was defined as occurrence of liver cirrhosis (LC), hepatocellular carcinoma (HCC), liver transplantation (LT) or death from hepatic failure.

Results: The mean follow-up duration of AIH-SLE overlap and PAIH were 7.62 ± 4.13 years (range: 1.5 – 16) and 6.23 ± 4.21 (0.5 –17.5), respectively (Table 1). The age at AIH diagnosis was younger and initial serum IgG level was higher in AIH-SLE overlap ($P < 0.005$). There were no significant differences of histological findings and treatment strategy. Although proportion of overall progression was not different, severe progression such as HCC, LT or death only happened in PAIH patients. Among 23 patients of AIH-SLE overlap, 8 patients with progression showed higher serum IgG level (4077.38 ± 1641.02 mg/dl) compared to 15 patients without progression (2560.71 ± 932.24) ($p=0.017$). Furthermore, progression in AIH-SLE overlap was associated with serum IgG level of above 2 folds upper limit of normal (OR = 11.00, 95% CI = 1.420 – 85.201, P = 0.026).

Conclusion: The clinical course of AIH might be expected less aggressively in AIH-SLE overlap than PAIH. In addition, we could suggest that initial high level of serum IgG is a poor prognostic factor in patients with AIH-SLE overlap.

Table 1. Characteristics of AIH-SLE overlap and PAIH

Characteristic	AIH-SLE overlap (n = 23)	PAIH (n = 164)
Age at AIH diagnosis, years[a]	37.35 ± 12.55	49.98 ± 12.365
Sex, female (%)	23 (100)	149 (90.9)
Follow up, year	7.62 ± 4.13 (1.5 – 16)	6.23 ± 4.21 (0.5 – 17.5)
Other autoimmune disease (%)	4 (17.4)	21 (12.8)
Arthritis (%)[a]	9 (39.1)	27 (16.6)
Leukopenia (%)	3 (13.1)	25 (15.2)
Thrombocytopenia (%)	11 (47.8)	44 (26.8)
Protein, g/dl	8.40 ± 1.10	8.02 ± 4.07
Albumin, g/dl	3.42 ± 0.70	3.53 ± 0.2
AST, IU/l	402.43 ± 444.87	432.40 ± 552.15
ALT, IU/l	372.70 ± 514.39	355.34 ± 468.92
Alkaline phosphatase, IU/l	235.39 ± 176.12	165.20 ± 116.71
GGT, IU/l	168.24 ± 190.10	162.44 ± 250.23
Total bilirubin, mg/dl	5.99 ± 10.60	5.57 ± 6.83
Serum IgG, mg/dl[a]	3112.23 ± 1411.84	2419.23 ± 899.64
Autoantibody	23/23 (100)	141/162 (87)
anti nuclear antibody (%)	8/21 (38.1)	42/161 (26.1)
anti smooth muscle antibody (%)	1/17 (4.3)	0/136 (0)
anti LKM1 (%)	0/22 (0)	6/160 (3.8)
anti mitochondrial antibody (%)		
Biopsy	16 (69.6)	93 (56.7)
interface hepatitis (%)	5 (21.7)	35 (21.3)
plasma cell infiltration (%)	2 (8.7)	3 (1.8)
rosette (%)	6 (26.1)	23 (14)
biliary change (%)		
Progression at AIH diagnosis (%)	4/23 (17.4)	37/164 (22.5)
Progression after AIH diagnosis (%)	4/19 (21.1)	45/127 (35.4)
liver cirrhosis	4 (21.1)	38 (29.9)
hepatocellular carcinoma	0 (0)	1 (0.8)
liver transplatation	0 (0)	3 (2.4)
death from hepatic failure	0 (0)	3 (2.4)

[a]: $p < 0.05$

AST, Aspartate aminotransferase; ALT, Alanine transaminase; GGT, Gamma glutamyltransferse; anti LKM1, anti Liver-Kidney-Microsomes antibody

Disclosure: D. H. Lim, None; **S. H. Bae**, None; **S. M. Ahn**, None; **S. Hong**, None; **Y. G. Kim**, None; **C. K. Lee**, None; **B. Yoo**, None.

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Utility and Associated Risk of Pulmonary Embolism CT Scans in the Michigan Lupus Cohort. Ruba Kado[1], Emily Siegwald[2], Emily Lewis[2], Mitch Goodsitt[2], Emmanuel Christodoulou[2], Ella Kazerooni[2] and W. Joseph McCune[2]. [1]University of Michigan, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI.

Background/Purpose: Ionizing radiation from CT scanning can increase cancer risk. Lupus patients are frequently evaluated for chest pain and may have multiple pulmonary embolism CT (PE-CT) scans in addition to other exposures to diagnostic or therapeutic radiation.

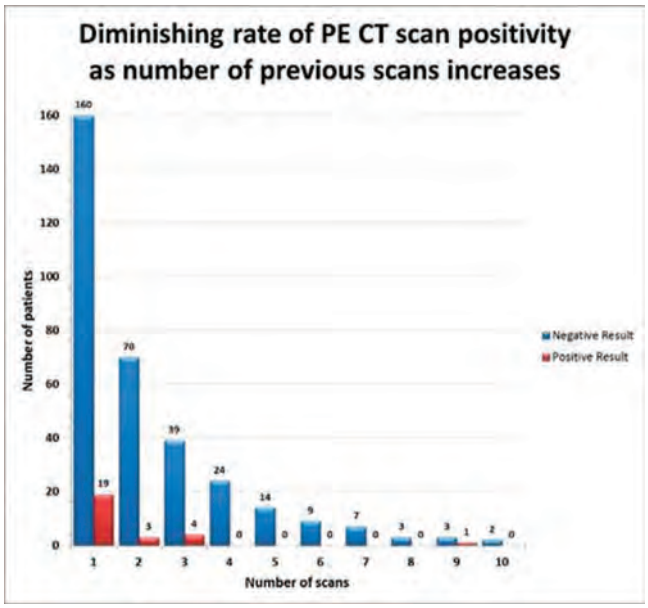
The objective of this study is twofold i) Determine the incidence of PE in University of Michigan Lupus Cohort patients who have undergone PE -CT scans ii) Estimate associated breast and lung cancer incidence.

Methods: We reviewed records of patients in the Michigan Lupus Cohort (N=856), and for each patient determined the number and outcome of PE-CT scans. All patients gave informed consent for review of their records. Based on estimated x-ray exposure from a state of the art GE Discovery CT750 HD CT scanner for an arterial chest scan, we estimated radiation dosage to the breast and lung in an average sized adult woman, utilizing CT-Expo software package.{1] We used the dose information and the patient's age at the time of the CT scan and tabulated risks according to the BEIR VII report to estimate the increased lifetime incidence risks of breast and lung cancer. Risks from multiple CT scans were summed.

Results: 183/856 (21%) patients underwent a total of 358 PE CT scans. The overall rate of positivity was 7.5%. The likelihood of a positive scan decreased in proportion to the number of scans that had been previously performed. (Figure 1) For patients undergoing their first through third CT scans the rate of positivity for PE was 9.2 %, whereas patients undergoing their fourth through tenth CT scans had 1.6% positivity.

We estimated radiation doses of to the breast and lung in female patients from a PE CT arterial scan, as 20mGy and 22mGy respectively. Separating patients based on age and number of CT scans, the estimated lifetime increase incidence risk of breast and lung cancer was calculated. In this simplified model the range of added risk for breast and lung cancer respectively per 100,000 female patients was 0–100 in 72% and 72%; 100– 500 in 25% and 28% and 500– 1000 in 4% and 1%.

Image/graph:



Conclusion: Patients with multiple previous PE CT scans had lower likelihood of a positive result on subsequent scans and higher risks of malignancy. Our conservative estimates of radiation exposure, that do not account for higher radiation doses from older CT scanners, indicate sufficient risk to warrant more precise characterization of radiation exposure in this population; and encourage development of guidelines for PE screening for patients with systemic lupus erythematosus and recurrent chest pain. The magnitude of risk should not discourage performance of PE CT when clinically indicated.

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Disclosure: R. Kado, None; **E. Siegwald**, None; **E. Lewis**, None; **M. Goodsitt**, None; **E. Christodoulou**, None; **E. Kazerooni**, None; **W. J. McCune**, None.

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Lupus Chest Pain in the Emergency Department: a Common Diagnostic Dilemma. Masoom Modi[1], Mariko L. Ishimori[1], Daniel J. Wallace[2] and Michael Weisman[1]. [1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]Cedars-Sinai/David Geffen School of Medicine at UCLA, Los Angeles, CA.

Background/Purpose: Chest pain (CP) is a common symptom reported by SLE patients often leading to presentation to Emergency Departments (ED). The origin of CP can be attributed to many causes, which may or may not be cardiac in nature. It is important to understand the prevalence of CP in SLE, with ED visits being a window of opportunity for early detection of SLE heart disease.

Methods: Billing records of patients who presented to Cedars-Sinai Medical Center ED with ICD-9 codes for SLE between 3/2009–10/2013 were reviewed; this data was then examined for secondary ICD-9 codes for CP (786.50–786.59). Two study groups were formed, based on discharge from ED vs. hospital admission. Visits were evaluated for basic cardiac work up with EKG and cardiac enzymes, and number of visits by individual patient recorded. Hospital admissions were evaluated for CP etiology and discharge

diagnoses. Continuous variables were analyzed by paired t test, and categorical data by chi squared test.

Results: Of 2675 ED visits with ICD-9 codes for SLE; 397 had secondary codes for CP (15%). Of the 397 SLE and CP visits, 173 visits were discharged directly from the ED and 224 visits became hospital admissions.

The ED discharged group was significantly younger ($p<0.0005$) compared with the hospital admitted group.

ED discharge group: The 173 ED visits were accounted for by 127 unique patients. 77% of these visits received a basic cardiac work up. While most patients had just 1 visit, a small number (7%) were frequent users of the ED, with an estimated one fourth of all visits.

Hospital Admitted Group: The 224 admissions were accounted for by 161 unique patients. 92% of admitted patients received a basic cardiac work up.

CP in the hospitalized group: The most commonly listed discharge diagnoses based upon primary physician's work up and opinion, and the listed diagnoses for CP in the discharge summary are shown in Table 1. Rule out of Acute Coronary Syndrome (28.6%) was the most common diagnosis. Over 50% of CP at discharge was attributed to non-cardiac causes.

Conclusion: Of all SLE coded patients presenting to the CSMC ED over a 4.5 year period, 15% had complaints of CP, which is higher than the national average for CP in non-SLE patients (10%). Frequent ED users (3 or more visits) made up only 7% of the total sample, but accounted for 24% of all the ED visits. Over90% of admitted patients had a basic cardiac work up performed. However, only a small percentage had a discharge diagnosis that was related to cardiovascular disease (7.2%). There is a high percentage of a negative cardiac work up with a majority of non-cardiac diagnoses in SLE patients, strengthening the need for more research into improved biomarkers or more specific imaging techniques to assess the etiology of CP. This study was a first step in revealing the high prevalence of CP in SLE patients presenting to the ED, while examining the limited diagnostic capabilities of a traditional cardiac work up.

Table 1: Chest Pain in the Hospitalized Group

Discharge Diagnosis	Percentage of Admissions
Cardiovascular Disease (CAD, MI, Unstable Angina, Microvascular Disease)	7.2%
Pericarditis (SLE related)	3.1%
Other Cardiac NOS (CHF, Arrhytmia, PVD)	4%
Rule out of Acute Coronary Syndrome	28.6%
Musculoskeletal/ Costochondritis	24.6%
Pulmonary (Pulmonary Embolism, Pneumonia, COPD)	13.8%
Gastro-Intestinal	8.9%
Multi-Factorial	9.8%

Disclosure: M. Modi, None; **M. L. Ishimori**, None; **D. J. Wallace**, None; **M. Weisman**, None.

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Humoral Immunodeficiency in Patients Presenting with Clinical Features of Systemic Lupus Erythematosus. W. Winn Chatham[1], Duncan Harmon[1] and Harry W. Schroeder Jr.[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama-Birmingham, Birmingham, AL.

Background/Purpose: Humoral immunodeficiency syndromes including common variable immune deficiency (CVID) are not uncommonly associated with autoimmunity. The spectrum of autoimmune disorders encountered in CVID patients may include features seen in systemic lupus erythematosus (SLE). Studies were undertaken at an academic center managing both disorders to determine the relative prevalence, clinical features, and outcomes of immunodeficiency associated SLE.

Methods: A retrospective review of records of patients seen between 2011 and 2014 with suspected humoral immunodeficiency and SLE was undertaken. Records for review were identified using an electronic medical record search of diagnosis codes for SLE and hypogammaglobulinemia. The clinical and immunologic profile was determined for patients with confirmed or suspected SLE who also had undergone evaluation for humoral immunodeficiency.hods.

Results: We identified 36 patients meeting ACR criteria for SLE with inadequate response to pneumococcal vaccine challenge (failure to generate protective antibody titer to $\geq$ 5/14 pneumococcal vaccine antigens) and/or low serum IgG levels ($<$ 700 mg/dl) not attributable to antecedent immunosuppressive therapy. This comprised 5.5% of our SLE patients meeting ACR SLE criteria in active follow-up. An additional 30 patients with SLE clinical features but not meeting SLE ACR criteria were identified with low serum IgG and/or inadequate vaccine responses. Among the 36 identified patients meeting ACR SLE criteria, serum immunoglobulin levels ranged from 459–744 mg/dl; 33 (92%) had serum IgG levels $<$700 mg/dl, while 19 (53%) had inadequate response to pneumococcal vaccine challenge, including the three patients with serum IgG $>$ 700 mg/dl. Frequent upper/lower respiratory infections requiring antibiotic treatment ($\geq$3 episodes/year) were reported in 24/36 (67%) patients. SLE features developed 2–26 years (mean = 8.9 years) prior to the recognition of low serum IgG in 25 (69%) patients, whereas initial SLE features were noted concurrently with or 3–4 years following first confirmed low IgG levels in 11 (31%). Arthritis (75%), photosensitivity (81%), malar rash (61%) and mucosal ulcers (56%) were the most prevalent SLE features. Only 9 (25%) of patients had low complement C3 or C4 levels, 6 (17%) had cytopenias, and 2 (6%) had elevated levels of anti-dsDNA. The majority of patients were managed with antimalarials (86%), with 8/36 (22%) also using methotrexate; 18/36(50%) were on treatment with IVIG. Disease activity was low (SLEDAI score $\leq$2) in 32/36 (89%) at the last noted follow-up assessment.

Conclusion: SLE may be a presenting feature of patients with humoral immunodeficiency. Serum immunoglobulin levels and assessment of the response to pneumococcal vaccination for patients with low or low normal serum IgG levels should be included as part of the evaluation for suspected SLE, particularly in the context of frequent respiratory infections. Favorable outcomes are seen in the context of standard of care treatment for SLE combined with immunoglobulin replacement therapy.

Disclosure: W. W. Chatham, None; **D. Harmon**, None; **H. W. Schroeder Jr.**, None.

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Characteristics of Lupus Patients with Interstitial Lung Disease and Relationship with Jo-1 Antibody. Samera Vaseer[1], Judith A. James[2], Aikaterini Thanou[2] and Joan T. Merrill[2]. [1]University Of Oklahoma, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Pulmonary involvement is frequent in systemic lupus erythematosus (SLE) and can affect the pleura, pulmonary vasculature, and parenchyma. The prevalence of ILD is lower in SLE than in the other CTDs (3–13%). While ILD in SLE is usually mild, it can be progressive or severe in some patients. We aimed to determine clinical and serological characteristics of SLE patients with symptomatic ILD in an outpatient longitudinal lupus cohort.

Methods: The Oklahoma Lupus Cohort consists of a longitudinal cohort of patients who meet 1997 ACR criteria for SLE. Patients are enrolled after informed consent and their clinical and serological data are collected at routine clinic visits. Patients with pulmonary fibrosis or interstitial lung disease were identified using the database, and matched with 5–6 age and gender matched SLE controls without ILD. Data was collected using retrospective chart review. All patients included (n=110) fulfilled 1997 ACR criteria for SLE.

Results: Fifteen SLE patients with a concurrent diagnosis of pulmonary fibrosis or ILD were identified among 517 in SLE cohort giving a prevalence of 2.9%. Fourteen of 15 patients had imaging reports available for review and all patients had radiographic evidence of parenchymal lung involvement. Most commonly reported abnormalities were ground glass opacities and interstitial thickening or fibrosis mostly involving basilar regions followed by traction bronchiectasis, reticular pattern and fibrotic NSIP. Subpleural honeycombing and UIP were least common.

American Indians were 27% of those with ILD and 13% of controls. African Americans were evenly divided (37% cases, 37% controls). 53% of ILD patients had a diagnosis of anti-phospholipid syndrome vs. 32% of controls. Cases had a high rate of serositis history (78% vs. 38% controls, P value 0.006), anti-dsDNA (53% vs 23% p=0.02) and lymphopenia (47% cases vs. 17% controls, P value 0.016). There was a trend to increased frequency of anti-La (43%), anti-Sm (43%), RNP (53%) and lupus anticoagulant (33%) in ILD vs non-ILD (18%, 24%, 37% and 13% respectively, p= 0.07, 0.2, 0.2 and 0.06).

There were only 2 patients positive for anti-Jo1 among 517 SLE patients (0.4%); one by laser immunobead assay and immunodiffusion (patient A), the other by immunobead assay only (patient B). Both were among the cases with significant ILD. Both were African American females; had cytoplasmic ANA

pattern seen on IFA and were positive for anti ds-DNA. They had marked impairment of lung function with FVC 51% (patient A) and 22% (patient B) respectively. Only patient A had clinically significant myositis.

Conclusion: Clinically significant ILD is seen in a small proportion of SLE patients but can cause significant morbidity. Patients with ILD are more likely to have American Indian heritage, earlier history of serositis and positive anti-ds DNA. They may have a higher prevalence of anti-La (SS-B), anti-Sm, RNP and lupus anticoagulant. Testing for overlap syndromes with antibodies associated with ILD may provide useful prognostic information for these patients.

Disclosure: S. Vaseer, None; **J. A. James**, None; **A. Thanou**, Exagen, 2; **J. T. Merrill**, Genentech, Roche, 5.

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Determining Risk Factors That Increase Hospitalizations in Patients with Systemic Lupus Erythematosis. Hareth M. Madhoun[1], Wael N. Jarjour[1], Peter J. Embi[2], Erinn M. Hade[1] and W Neal Roberts Jr[3]. [1]The Ohio State University Wexner Medical Center, Columbus, OH, [2]The Ohio State University, Columbus, OH, [3]University of Louisville, Louisville, KY.

Background/Purpose: Systemic lupus erythematosis (SLE) is a complex heterogeneous disease which can be associated with significant morbidity and mortality. Hospitalization and readmissions have garnered significant attention in recent years through Medicare reimbursement adjustments. The aim of this study was to determine what factors may increase the risk of hospitalization in patients with SLE. The goal of this project is to develop a lupus specific computerized decision support prompt to improve care and reduce hospitalizations.

Methods: Between 2006–2011, patients with an ICD-9 code of SLE were selected. Additional information that could be relevant to risk profiling were extracted, including: laboratory results, medications, appointments (scheduled and/or kept), and hospitalizations. Patients were divided into two groups: hospitalized and non-hospitalized. Hospitalized patients selected for chart review and inclusion in the cohort, included any with an ICD-9 diagnosis of lupus as the primary reason for admission to the hospital. The non-hospitalized patients included any with an ICD-9 code for lupus who were seen by rheumatology. Patients were selected randomly from among all who met inclusion criteria. The risks associated with hypothesized risk factors, including proportion of missed appointments and creatinine levels, were estimated through weighted Cox regression models to account for patient selection into the study.

Results: 29 patients were selected who met the above lupus hospitalization criteria and 37 patients were randomly selected as non-hospitalized lupus controls. Patients were categorized into three groups based on the percentage of missed appointments (0% missed, >0%-33% missed, 33%-100% missed). Of the 60 patients with appointment data, 12 had no missed appointments, 27 (0–33%), 21 (33–100%). There was a trend toward an elevated risk of hospitalization for those with missed appointments and an elevated creatinine at their last appointment. In a multivariable model accounting for age and last creatinine measurement, patients who missed up to 33% of appointments, were estimated to have 2.92 (95% CI: 0.54–15.76) times the risk of patients who did not miss any appointments. Patients who missed between 33% and 100% of their appointments, the risk was 3.30 (95% CI: 0.52–20.96) times. The estimated risk of hospitalization associated with creatinine measure over 1.25 ml/dl at their last appointment was 4.72 (95% CI: 1.22–18.27) times the risk of those with with lower creatinine.

Conclusion: Patients with SLE appear to have an elevated risk of hospitalization with an increase in missed appointments and higher creatinine. Data about proportion of missed appointments or elevated creatinine might be used to trigger electronic health record-based decision support alerts about such risk that could lead to clinical interventions to help avoid hospitalizations. Further study with larger cohort samples is needed to confirm these findings and potentially identify other risk factors. Ongoing work will incorporate elements from the Systemic Lupus International Correlation Clinics damage index to enhance the predictive value of this model with the goal of helping to reduce hospitalization and readmission.

Disclosure: H. M. Madhoun, None; **W. N. Jarjour**, None; **P. J. Embi**, None; **E. M. Hade**, None; **W. N. Roberts Jr**, None.

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Impact of Sleep Disorders in Quality of Life, Pain and Disease Activity Using Actigraphy and Pittsburgh Sleep Quality Index (PSQI)in Female with Systemic Lupus Ertyhematosus (SLE). Lilian Reis[1], Marco Tulio de Mello[2] and Virginia M. Trevisani[3]. [1]Federal University of Sao Paulo - UNIFESP, SAO PAULO, Brazil, [2]Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil, [3]Federal University of São Paulo, São Paulo Brazil, Brazil.

Background/Purpose: Despite the fact that sleep disorders are poorly studied, they′re a frequent complain by patients with SLE (62 to 80% related) and others found their influence over morning fatigue. *Aim of study:* To assess the impact of sleep disorders in quality of life, pain, fatigue and disease activity in female with SLE.

Methods: *Patients and methods:* The actigraphy and sleep diary was used to measure sleep habits during 15 days in 34 female with SLE and who achieve Pittsburgh Sleep Quality Index (PSQI) equal or above 5. Quality of life was assessed through Short form health survey questionnaire (SF-36). Disease activity was measured with SLEDAI. Patients were divided into two groups, according categorical variables of PSQI scoring: less than 10 and more than 10 points. Mann-Whitney U test was used to compare SF-36 domains and the relationship between disease activity and sleep latency were analyzed with Pearson′s correlation coefficient. Significance level adopted was 5%.

Results: Thirty-four (34) female with SLE was analyzed (n=34; mean=43±10 years), disease time 9,5 ± 6,7 years. It was found some disabilities on SF-36 domain. Results of PSQI >10 had less points for Body pain (BP) (p-value=0,016) and role emotional (RE) (p-value=0,056). There wasn′t significant difference in physical functioning (PF) (p-value=0,730), role physical (RP) (p=*0,131*), general health (GH) (*p = 0,769*), vitality (*p = 0,219*), social functioning (SF) (*p = 0,187*) and mental health (MH) (*p = 0,334*). Furthermore the patients with PSQI >10 had longer sleep latency time when it was compared with the patients with PSQI<10 (p = 0,050). There was correlation between disease activity and sleep latency (r = 0,356; *p = 0,046*).

Conclusion: Our results suggest that the patients with PSQI >10 and disease activity are important factors that can affect the quality of life in patients with SLE.

Table 1. Comparison between SF-36 domains and PSQI categorical groups:

	PSQI		
SF-36 domain	***< 10 points***	***> 10 points***	**p-value**
PF	67,9 (4,4)	64,4 (5,5)	0,73
RP	47,1 (9,8)	27,9 (8,0)	0,131
BP	52,8 (3,2)	35,5 (4,9)	**0,016**
GH	40,7 (3,5)	43,9 (6,7)	0,769
V	60,6 (3,2)	54,1 (4,4)	0,219
SF	70,6 (4,8)	63,3 (4,8)	0,187
RE	74,5 (7,8)	47,1 (10,3)	**0,056**
MH	68,7 (4,1)	62,6 (4,4)	0,334

Teste de Mann-Whitney U

1	Physical functioning	(PF)
2	Role physical	(RP)
3	Bodily pain	(BP)
4	General health	(GH)
5	Vitality	(V)
6	Social functioning	(SF)
7	Role emotional	(RE)
8	Mental health	(MH)

Table 2. Comparison between actigraphy results and PSQI categorical groups:

	PSQI		
Actigraphy	***< 10 points***	***> 10 points***	**p-value**
S_LAT_MEAN	25,8 (4,6)	43,0 (6,0)	0,05
SMIN_MEAN	372,7 (13,2)	383,7 (17,3)	0,624
SEFF_MEAN	91,5 (1,3)	89,7 (1,5)	0,396
WASO_MEAN	38,9 (6,6)	47,2 (6,2)	0,309

Teste de Mann-Whitney U

S_LAT_MEAN	sleep latency mean
SMIN_MEAN	sleep minutes mean
SEFF_MEAN	sleep efficiency mean
WASO_MEAN	wake up after sleep onset mean

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Splenectomy in Systemic LUPUS Erythematosus and AUTOIMMUNE Hematological Diseases. a Comparative Analysis. Luis J. Jara[1], Nahim Barron[2], Jesús Arenas-Osuna[3], Arturo Vélazquez-García[3], Arturo González-Zúñiga[3], Miguel A Saavedra[3] and Pilar Cruz-Domínguez[1]. [1]Hospital de Especialidades Centro Médico La Raza, IMSS, Mexico City, Mexico, [2]Hospital de Especialidades Centro Médico La Raza, México, Mexico, [3]Hospital de Especialidades Centro Médico La Raza, Mexico, Mexico.

Background/Purpose: Acute presentation of severe autoinmune thrombocytopenia, and hemolytic anemia in systemic lupus erythematosus (SLE) is associated with high mortality. Splenectomy is the second line of treatment.

The aim of this study is to investigate the efficacy and safety of splenectomy in refractory thrombocytopenia and hemolytic anemia associated or not with SLE.

Methods: From January 2004 to April 2014, 34 patients underwent splenectomy due to severe autoimmune thrombocytopenia and/or hemolytic anemia. The mean age of patients were 34.6 years old (range 18–62 y.o.) and twenty eight patients were female (82.35%). The patients were divided into two groups: Group 1: 18 patients with thrombocytopenia associated with SLE (9), SLE plus antiphospholipid syndrome, APS, (6), and primary APS (3). Group 2: 16 patients without SLE: Fisher-Evans Syndrome (2), and hemolytic anemia (14). All patients had refractory hematological manifestations, which were defined according to Mayo Clinic Criteria as: 1. If patients did not maintain platelets≥ 50,000 per ml for 2 weeks on medical therapy; 2. Medically dependent. 3. Medically intolerant. Patients with hemolytic anemia were submitted to surgery when they developed 2 hemolytic crisis (fever, jaudice, pallor, abdominal pain, and hemoglobin ≤ 6 grams per ml) despite to conventional treatment in a 6 months period. The response to splenectomy were considered for thrombocytopenia as follows: 1. Complete response: ≥150,000 platelets per ml, 2. Partial response: 50,000 to 149,000 per ml or 3. No response: < 50,000 per ml. The complete response for hemolityc anemia as hemoglobin ≥ 9 gr per ml. The inmediate response were evaluated after 7 days. The mean of follow up were 28.5 months (range3–96 months). Statistical Analysis: descriptive stadistics and Chi square Test.

Results: Open splenectomy was performed in 15/34 patients (44.11%) and laparoscopy in 19/34 patients, 3 converted to open surgery. The complete response were observed in 15/34, (44.11%).Group 1, 4/18 (22.2%) and Group 2, 11/16, (68.8%) (p=.006). After 30 days of surgery a complete response were observed in 11/18, (61.1%) for Group 1 and 13/16, (81.2%) Group 2 (p=NS). The complications in the inmediate post-operative period were observed in 6/34, 5 of Group 2 vs 1 in Group 1 (p=0.05). Infections in 3/34, one patient had bleeding and 2 had mesenteric and portal vein thrombosis respectively. In Group 1, the mean of period between hematologic manifestations and surgery was 17.8 months and in Group 2, 16.5 months. After follow up, in Group 1, the relapse were observed in 7/18 patients, and in Group 2, 3/16. In Group 1, steroids were reduced in 13/18 patients, and 14/16 patients of the Group 2.

Conclusion: This study suggest that patients with SLE, SLE plus APS and primary APS have a similar response to splenectomy compared with organ-specific autoinmune diseases despite a partial response in the inmediate period. Patients with organ-specific autoinmune diseases had a significant increase of complications. The splenectomy is safety and effective in severe and refractory hematologic manifestations.The surgery approach has not influence in the prognosis of splenectomy.

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Is the Disease-Specific Lupusqol Sensitive to Changes of Disease Activity in SLE Patients after Treatment of a Flare? Kathleen McElhone[1], Jane Burnell[2], Chris Sutton[2], Janice Abbott[2], Peter Lanyon[3], Anisur Rahman[4], Chee-Seng Yee[5], Mohammed Akil[6], Yasmeen Ahmad[7], Ian Bruce[8], Caroline Gordon[9] and Lee-Suan Teh[1]. [1]Royal Blackburn Hospital, Blackburn, United Kingdom, [2]University of Central Lancashire, Preston, United Kingdom, [3]Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom, [4]University College London, London, United Kingdom, [5]Doncaster and Bassetlaw Hospitals NHS Foundation Trust, Doncaster, United Kingdom, [6]Sheffield Center Rheumatic Dis, Sheffield South Yorkshire, United Kingdom, [7]Peter Maddison Research Centre, Bangor, United Kingdom, [8]Arthritis Research UK Epidemiology Unit, Institution of Inflammation and Repair, University of Manchester, NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [9]Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom.

Background/Purpose: With improving survival in SLE patients, patient-reported health-related quality of life (HRQoL) has become an important outcome. The LupusQoL is a disease-specific patient-derived HRQoL measure with good psychometric properties. The aim of the UK multi-centre LupusQoL Sensitivity Study is to assess whether the LupusQoL is sensitive to change when disease activity improves or deteriorates.

Methods: Patients with SLE (≥ 4 1997 ACR criteria), experiencing a flare (new A or B by BILAG-2004 Index) & requiring an increase in treatment (either prednisolone ≥ 20mg daily, introduction of methotrexate, parenteral steroids, cyclophosphamide &/or biologics) were recruited from 9 UK centres. Assessments were undertaken at baseline & monthly for 9 months after initiation of therapy & included BILAG-2004 disease activity index & the LupusQoL with 8 domains (physical health, pain, planning, intimate relationships, burden to others, emotional health, body image, fatigue) and scores ranging from 0 (worst) to 100 (best HRQoL). Changes in disease activity are defined (see Table – first column) as *deterioration*: major & minor and *improvement*: major & minor. Changes in LupusQoL domain scores when disease activity improved, deteriorated or was unchanged between consecutive time-points are reported as mean changes, with 95% confidence intervals (CI) constructed using robust standard errors to account for repeated patient assessments.

Results: Mean (SD) age was 40.9 (12.8) & duration since diagnosis was 9.3 (8.1) years for the 101 patients recruited; 94% females, 62.6% white Caucasians, 15.2% south Asians, 8.1% black Caribbean, 4% black Africans, 5% mixed, 1% Chinese. At baseline mean (SD) BILAG2004 score was 16.4 (8.1); all mean LupusQoL domain scores were < 52. LupusQoL physical health, pain & fatigue domain scores increased when BILAG improved (overall, major & minor). Physical health and pain domain scores decreased when there was a major BILAG deterioration but changes with a minor BILAG deterioration were small and non-significant. The effects of improvements & deterioration in BILAG on the LupusQoL domain scores were smaller or not present (Table).

Mean changes in LupusQoL Domain Scores (95% Confidence Intervals) between monthly visits

BILAG change category (Total n_{pat}=1100; n_{obs}=5724)	Physical health	Pain	Planning	Intimate relationships	Burden to others	Emotional health	Body Image	Fatigue
Major & Minor Deterioration (n_{pat}=73; n_{obs}=160)	−0.8 (−3.0 to 1.4)	−2.4 (−5.9 to 1.1)	−1.2 (−3.8 to 1.4)	2.6 (−1.3 to 6.5)	2.3 (−0.6 to 5.2)	−1.1 (−3.5 to 1.3)	0.5 (−2.2 to 3.2)	−1.0 (−3.5 to 1.5)
Major deterioration (any system to A from B/C/D &/or any 2Bs from C/D) (n_{pat}=32; n_{obs}=43)	−4.9 (−9.4 to −0.4)	−6.9 (−12.9 to −0.8)	−3.0 (−8.2 to 2.1)	4.3 (−6.6 to 15.2)	1.4 (−4.6 to 7.5)	−2.8 (−7.7 to 2.2)	−4.1 (−8.7 to 0.5)	−2.4 (−7.6 to 2.7)
Minor deterioration (one B from C/D & no new As) (n_{pat}=63; n_{obs}=117)	0.7 (−1.6 to 2.9)	−0.8 (−4.6 to 3.0)	−0.5 (−3.6 to 2.6)	2.0 (−1.5 to 5.5)	2.7 (−0.6 to 5.9)	−0.5 (−3.3 to 2.3)	2.2 (−1.0 to 5.4)	−0.5 (−3.3 to 2.4)
Major & Minor Improvement (n_{pat}=97; n_{obs}=199)	4.0 (1.9 to 6.1)	7.7 (4.8 to 10.5)	2.6 (0.1 to 5.1)	2.4 (−1.2 to 6.0)	2.4 (−0.1 to 4.8)	3.1 (0.8 to 5.4)	3.1 (0.1 to 6.1)	4.1 (1.7 to 6.5)
Major improvement (all As to B/C/D &/or all Bs to C/D) (n_{pat}=93; n_{obs}=162)	3.8 (1.3 to 6.3)	7.4 (4.2 to 10.5)	1.8 (−0.9 to 4.6)	2.6 (−1.6 to 6.7)	1.8 (−0.9 to 4.5)	2.7 (0.0 to 5.3)	3.4 (0.2 to 6.6)	3.3 (0.6 to 5.9)
Minor improvement (all As to B/C/D, some Bs to C/D but 1 persistent B) (n_{pat}≥4=; n_{obs}=37)	5.0 (0.6 to 9.3)	8.8 (2.2 to 15.5)	5.9 (−1.9 to 13.7)	1.8 (−4.4 to 7.9)	4.9 (−2.1 to 11.9)	5.0 (−0.3 to 10.4)	2.1 (−4.5 to 8.6)	7.8 (2.1 to 13.4)
Persistent active disease (all As or ≥ 2Bs unchanged) (n_{pat}=57;n_{obs}=127)	−0.9 (−2.7 to 0.9)	−0.9 (−3.6 to 1.7)	0.0 (−1.9 to 1.8)	−2.5 (−6.3 to 1.3)	−1.2 (−4.0 to 1.6)	0.3 (−1.7 to 2.3)	0.6 (−2.0 to 3.2)	2.0 (−0.7 to 4.7)
Persistent inactive disease (all systems remaining C/D) (n_{pat}=65;n_{obs}=238)	1.6 (0.6 to 2.7)	2.0 (0.5 to 3.5)	2.5 (0.9 to 4.0)	1.8 (−0.8 to 4.5)	4.1 (2.2 to 6.0)	2.3 (1.1 to 3.5)	0.2 (−1.2 to 1.5)	1.7 (0.2 to 3.2)

Conclusion: Improvement and deterioration of LupusQoL domain scores for physical health, pain & fatigue domain scores was seen in patients with significant changes in disease activity over 1 month. Sensitivity to change of other LupusQoL domains in relation to changes of disease activity may need to be evaluated over a longer interval as the more emotive type of response to the disease & its consequences may be latent and therefore not evident at monthly intervals.

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Mapping the Disease-Specific Lupusqol to the SF-6D. Rachel Meacock[1], Mark Harrison[2], Kathleen McElhone[3], Janice Abbott[4], Sahena Haque[5], Ian N. Bruce[6] and Lee- Suan Teh[3]. [1]The University of Manchester, Manchester, United Kingdom, [2]University of British Columbia, Vancouver, BC, [3]Royal Blackburn Hospital, Blackburn, United Kingdom, [4]University of Central Lancashire, Preston, United Kingdom, [5]University Hospital of South Manchester, Manchester, United Kingdom, [6]NIHR Manchester Musculoskeletal

Biomedical Research Unit, Manchester Academy of Health Sciences, Manchester, United Kingdom.

Background/Purpose: The LupusQoL is a measure of health-related quality of life (HRQoL) developed specifically to assess the impact of systemic lupus erythematosus (SLE) and its treatment. Whilst producing a profile of scores, it is not preference-based, and therefore does not provide utility values. Such utility estimates are necessary to calculate quality-adjusted life years in economic evaluations, which are increasingly needed to guide decisions on how best to allocate health care resources.

The SF-6D (derived from the SF-36/SF-12) is a generic preference-based HRQoL measure which does provide utility scores. Despite evidence to support the validity of the SF-6D in SLE, and growing need for utility data, many trials fail to include a preference-based measure. One solution is empirical mapping; estimating a statistical relationship between a non-preference based and a preference-based measure using a dataset in which both measures have been administered to the same patients.

We aim to derive and test a mapping algorithm to predict SF-6D utility scores from the LupusQoL.

Methods: LupusQoL and SF-6D data were collected from 320 people with SLE at rheumatology outpatient clinics at 7 UK centres. Ordinary least squares regression was used to estimate models of increasing complexity to predict individuals' SF-6D scores from their LupusQoL responses. Model performance was judged on predictive ability through the size and pattern of prediction errors generated, using mean absolute error (MAE) and root mean squared error (RMSE) statistics. Performance of the selected model was externally validated on an independent data set of 113 females with SLE who had completed both the LupusQoL and SF-36. All patients met 4 or more of the ACR criteria for SLE.

Results: Mean age and disease duration of the estimation sample was 44.8 (SD 13.6) and 10.5 (SD 8.7) years respectively. The sample cover the full range of SF-6D scores, mean 0.615 (range 0.296–1.00). Figure 1 shows mean LupusQoL domain scores. Four LupusQoL domains (physical health, pain, emotional health, fatigue) were selected in the final model. The validation dataset were slightly older (mean age 48.6 (SD 9.3) years) with longer disease duration (mean 12.6 (SD 9.7) years), but had comparable range of SF-6D (0.327 – 1.00) and mean LupusQoL scores (Figure 1). Model fit was good in both the estimation data (*R2* 0.7219, MAE 0.0557, RMSE 0.0706) and when applied to the validation sample (*R2* 0.7431, MAE 0.528, RMSE 0.0663). The model predicts mean SF-6D utility in the validation sample extremely well (observed mean 0.624; predicted 0.617).

Conclusion: We provide a method by which utility values can be estimated from patient responses to the non-preference based LupusQoL, generalizable beyond the sample upon which it was estimated. Prediction errors, upon which mapping functions are primarily judged, were lower than those of published studies to date.

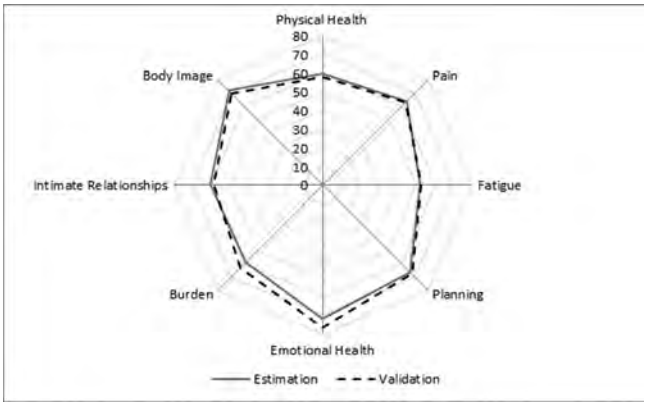

Figure 1:

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Lupuspro Is Responsive to Changes in Disease Activity over Time. David Giangreco[1], Hervé Devilliers[2], Narender Annapureddy[1], Joel A. Block[1] and Meenakshi Jolly[1]. [1]Rush University Medical Center, Chicago, IL, [2]Department of internal medicine and systemic diseases, Dijon, France.

Background/Purpose: Patient reported outcome (PRO) tools are important to understand, educate, manage, and follow patients with systemic lupus erythematosus (SLE). Disease targeted PRO for SLE (LupusPRO) has good reliability and has been validated in several languages and cultural contexts. LupusPRO could be better integrated into routine clinical care and clinical trials in SLE if it was also found to be responsive to physician assessed changes in disease activity. We sought to test the responsiveness of LupusPRO domains to changes in physician disease activity assessments in the routine clinical care setting.

Methods: Longitudinal data on LupusPRO and disease activity assessments were collected in the Rush Lupus Data Repository during routine clinical care visits. We tested only the responsiveness of the health related quality of life domains (HRQOL) as we expect these to change over short periods of time in response to disease activity. Disease activity assessments used as anchors for testing responsiveness included the SLEDAI physician global assessment (PGA), Total SELENA-SLEDAI, and the SELENA-Flare Index (SFI). Cut-offs used to determine change in disease activity were PGA (change of 0.3), SELENA-SLEDAI (change of 4), and SFI (remitting, stable and flaring). Non-parametric analysis of variance was used to compare changes in LupusPRO HRQOL domains against disease activity anchors.

Results: There were 658 visit data available for 185 patients. Consecutive visits were 2–5 months apart with a median number of visits per patient of 7. PGA was available for 651 visits; Total SLEDAI was available for 269 visits; SFI was available for 614 visits. Mean (SD) age and SELENA-SLEDAI were 43.5 (13.2) years and 6.4 (7.3), respectively. PGA changed significantly for 281 visit data (increased in 132, decreased in 142), while 377 visit data had unchanged PGA. LupusPRO HRQOL domains that changed significantly in the appropriate direction included Lupus Symptoms ($p<0.001$), Procreation ($p=0.03$), Pain-Vitality ($p=0.002$), Emotional Health ($p=0.06$), and Body Image ($p=0.03$). SELENA-SLEDAI changed significantly among 73 visits (32 increased, 41 decreased), and remained stable among 196 visits. LupusPRO HRQOL domains of Lupus symptoms ($p=0.0004$) and Pain-Vitality ($p=0.02$) responded significantly and in the appropriate direction. Significant changes in SFI were observed in 151 visit data (79 remitting, 72 flaring), while 463 visit data were unchanged. LupusPRO HRQOL domains that responded significantly in the appropriate direction in response to changes in SFI were Lupus symptoms ($p<0.001$), Procreation (p 0.005), Physical Health ($p=0.0006$) and Pain-Vitality ($p<0.0001$). Mixed model analysis supported similar results.

Conclusion: Most HRQOL domains of LupusPRO are responsive to physician-assessed changes in disease activity in the routine patient care setting. LupusPRO is an appropriate tool to be used not only in clinical trials but also in the clinical care setting.

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The Validity of Patient and Physician Global Disease Activity Assessments of Systemic Lupus Erythematosus: Results from the Lupus Activity Scoring Tool (LAST) As Compared to the Selena Sledai (SS) Modification Multicentre Study. Majed Khraishi[1], Rana Aslanov[2], Sanjay Dixit[3], Ramin Yazdani[4], Vandana Ahluwalia[5] and Sarah Khraishi[6]. [1]Nexus Clinical Research, St John's, NF, [2]Memorial University of Newfoundland, St.John's, NF, [3]McMaster University, Hamilton, ON, [4]St. Clare' Mercy Hospital, St. John's, NF, [5]William Osler Health Center, Brampton, ON, [6]NL Research Technologies (NLRT), St. John's, NF.

Background/Purpose: In our centre, new tools for the assessment of SLE activity: the Lupus Activity Scoring Tool (LAST) and Clinical Lupus Activity Scoring Tool (C-LAST) were developed and validated. We aimed to validate the LAST and C-LAST in multiple clinical settings using their correlation to the SELENA SLEDAI modification, and to investigate the correlation of the specific components of the LAST (e.g. patient's and physician's global assessments of disease activity, steroid use) to the SS.

Methods: This multicenter study was initiated in five Canadian clinics: 3 in Newfoundland and 2 in Ontario. The LAST includes patient (PGA)and physician global assessment of disease activity (PHGA), C3, C4 and Anti-ds Anti-DNA titer abnormalities, and a formula incorporating the current immunomodulating medication. The C-LAST does not include laboratory test results. Patients who met the SLE ACR 1997 criteria update were recruited and evaluated in the study centres using LAST/C-LAST. Some of the patients

were prospectively followed and evaluated by the same tools at each visit. The SS was also calculated for each visit.

Results: Fifty-eight patients (84.5% females) with 98 assessments from five study centers were included in this analysis. The median age was 49.0 (Q1-Q3=33.8–60.3) years with the mean (SD) disease duration 12.1 (6.5) years. Scores from the LAST/C-LAST were obtained at each visit in addition to the SLEDAI scores. The mean (SD) SLEDAI score was 8.2 (5.2). The mean (SD) LAST (with C3, C4 and Anti-ds Anti-DNA) score was 30.5 (17.3) and C-LAST – 32.2 (20.1). The SS scores were consistent and strongly correlated with the LAST and C-LAST scores ($r=0.430$, $p<0.001$ & $r=0.215$, $p=0.034$, respectively) at the baseline and follow-up visits: SS scores 0–4 corresponded to the LAST scores of 0–30 while SS scores of 8 or higher corresponded to 50 and higher, respectively. Both SS and LAST scores were significantly correlated with current treatment with Prednisone ($r=0.305$, $p=0.002$ & $r=0.430$, $p<0.001$, respectively); LAST score was also correlated with Mycophenolate mofetil ($r=0.205$, $p=0.043$) and Azathioprine ($r=0.296$, $p=0.003$) treatments. Patient's (PGA) and Physician's (PHGA) Global Assessments of SLE activity were strongly correlated with each other ($r=0.759$, $p<0.001$) and with the LAST score ($r=0.781$, $p<0.001$ & $r=0.826$, $p<0.001$, respectively); PHGA was also significantly correlated with SELENA SLEDAI score ($r=0.324$, $p=0.001$). The LAST and C-LAST scores concurred in 90% of the assessments with $r=0.898$ and $p<0.001$.

We utilized an electronic application of the LAST which was easy to use and no errors were found with its results as compared to the manually obtained scores with the Pearson's correlation coefficient $r=0.995$ & $p<0.001$.

Conclusion: The Lupus Activity Scoring Tool (LAST) and C-LAST are new disease activity indices that correlate well with the SELENA SLEDAI modification. The use of simple clinical variables as a measure of SLE activity seems to be valid under different clinical settings with different assessors. The inclusion of patient's global assessment and the current use of steroids and immunomodulators can be utilized effectively in assessing disease activity.

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The REAL Life with Lupus Study: Developing a Patient Reported Outcome Measure for Use in Clinical Trials and Clinical Care. R. Paola Daly[1], Sarah Gilman[1], Joan T. Merrill[2], Leslie M. Hanrahan[1], Alisha Ladenburg[1] and Anca Askanase[3]. [1]Lupus Foundation of America, Washington, DC, [2]Department of Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Columbia University Medical Center, New York, NY.

Background/Purpose: The goal of this study is to better understand how people with systemic lupus erythematosus (SLE) in the United States experience the disease. **Results** will be used to develop a patient reported outcome instrument that will form half of the LFA-REAL™ system. The LFA-REAL™ will be a comprehensive system, comprised of complimentary clinician reported outcome (ClinRO) and patient reported outcome measures (PRO). This will be the first system that will allow, from both a physician and patient perspective, both global and organ-specific disease assessment, without complex forms and scoring algorithms. The LFA-REAL™ is undergoing qualification reviews by the United States Food and Drug Administration (FDA) in order to become accepted by the FDA for use in SLE clinical trials. This abstract describes the aims, methods and preliminary findings of the qualitative research used in development of this PRO.

Methods: This exploratory study was designed in two phases. During Phase I, a literature review was conducted, identifying common themes in the experiences of people with lupus. In-depth interviews were then completed with 11 participants, including three men and eight women from a diverse range of demographic and experiential backgrounds, including health history and lupus severity. All study participants were 18 years of age or older and confirmed formal lupus diagnosis by a rheumatologist. The interviews covered the following topics: diagnosis and current treatment, symptoms, experience receiving clinical care, and ideal tool development. Analysis of in-depth interviews was conducted using grounded theory analysis; subsequently a conceptual framework was created to capture emerging codes and themes. This framework was iteratively refined, through a stepwise analytical review. During phase 2, the resulting conceptual framework will be used to create a draft PRO instrument. The conceptual framework and draft PRO will be evaluated through patient and physician focus group discussions, iteratively refined, and finally, tested in tandem with the LFA-REAL™ ClinRO, through a pilot study and large scale validation trial.

Results: Our initial data confirm that, in addition to physical indicators of wellbeing, such as physical functioning, pain, fatigue, and acute and chronic symptoms, mental and emotional indicators of wellbeing are also important to people with lupus. Disease-related factors that cause anxiety or interfere with activities of daily living may be perceived as equally or more limiting than symptoms that indicate severe disease to an MD. Additionally, study subjects indicated that the ideal PRO should be able to track and rate symptoms with visual aids, assess symptoms over time and should also encourage open communication with their healthcare providers.

Conclusion: Findings show that patients view factors that cause anxiety and interfere with daily living as equally or more limiting than symptoms of severe disease. A two part system that addresses both physicians' and patients' views is likely to contribute to reconciling the discordance between physician and patient assessments of disease, improving short and long term outcomes in lupus.

Disclosure: R. P. Daly, Lupus Foundation of America, 3; **S. Gilman**, Lupus Foundation of America, 3; **J. T. Merrill**, Medical Director for the Lupus Foundation of America., 5; **L. M. Hanrahan**, Lupus Foundation of America, 3; **A. Ladenburg**, Lupus Foundation of America., 3; **A. Askanase**, None.

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Simple Disease Assessment for People with Lupus Erythematosus. Meenakshi Jolly[1], Winston Sequeira[2], Sergio Toloza[3], Ana M. Bertoli[4], Luis M. Vilá[5], Ivana Blazevic[6], Ioana Moldovan[7], Karina D Torralba[8], Berna Goker[9], Josiane Bourré-Tessier[10], Sandra V. Navarra[11], Daniel Wallace[12], Michael H. Weisman[13], Ann E. Clarke[14], Chi Chiu Mok[15] and Joel A. Block[1]. [1]Rush University Medical Center, Chicago, IL, [2]Rush University, Chicago, IL, [3]Hospital San Juan Bautista, San Fernando del Valle de Catamarca, Argentina, [4]Instituto Reumatológico Strusberg, Cordoba, Cordoba, Argentina, [5]University of Puerto Rico Medical Sciences Campus, San Juan, PR, [6]University of Buenos Aires, Buenos Aries, Argentina, [7]Beaver Medical Group, Redlands, CA, [8]University of Southern California, LA, CA, [9]Gazi University School of Medicine, Ankara, Turkey, [10]Division of Rheumatology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, [11]University of Santo Tomas Hospital, Manila, Philippines, [12]UCLA, LA, CA, [13]Cedars-Sinai Medical Center, Los Angeles, CA, [14]University of Calgary, Calgary, AB, [15]Tuen Mun Hospital, Hong Kong, Hong Kong.

Background/Purpose: Community rheumatologists treating patients with Systemic Lupus Erythematosus (SLE) typically lack user-friendly tools to effectively track SLE disease activity. Current disease activity tools in SLE are resource and effort intensive, require special training and practice, take time, are difficult to implement in busy clinical practices and are of use almost exclusively to SLE researchers. Nonetheless, patient reported outcomes are recognized as important for patient care, and physician reimbursement (quality initiatives) and resource allocation are becoming tied to these outcomes. Here we report a novel user-friendly tool intended for daily clinical use In SLE.

Methods: Using our dataset of approximately 1,150 SLE patients from multiple countries and ethnicities that was accrued during the development of the LupusPRO, a disease targeted health outcome measure, we created multiple models with self reported SLE health survey items (LupusPRO), clinical variables (medications) and laboratory values that would correlate best with physician disease activity assessments (Physician Global Assessment and SLEDAI). Using stepwise regression methods, we parsed our model to keep it simple, included few and easily accessible laboratory values so it can be performed in most locations, and expected minimal real-time physician involvement. "SIMPLE" index equation was derived from the regression model with the best fit (**Sim**ple disease assessment for **P**eople with **LE**). We then prospectively tested the correlation between SIMPLE Index and Total SLEDAI in an independent dataset (n= 150) of SLE patients.

Results: SIMPLE index has two parts (i) patient self-report 16 items and (ii) two laboratory values obtained within 10 days before/after the visit. Requisite physician input pertains to (1) interpretation of one blood and one urine lab result in the context of SLE diagnosis, and (2) addition of weighted scores using a mobile application on a smart phone/computer by health personnel. The SIMPLE equation is as follows:

SI= 2- (0.03) LSX+ 0.02(LIT)+0.28(DHS)+0.95(CSU)+0.04(CSD)+ 5.6(UL)+2.4(BL), where Simple Index: SI, LupusPRO Lupus Symptom domain: 3 items (LSX), Lupus Impact Tracker: 10 items (LIT), Change in Health Status: 1 Item (DHS), Self Report of Current use of corticosteroid: I item (CSU), Self Report of current daily corticosteroid dose (Prednisone

equivalent in mg): 1 item (CSD), Urine Laboratory-Proteinuria (SLEDAI definition) (UL) and Blood Laboratory-Low complement C3/C4 (BL).

The SIMPLE index explained 55% variance of total SLEDAI score. In the second dataset, correlation of SIMPLE index with Total SLEDAI was strong (0.74, p=0.0001).

Conclusion: SIMPLE Index appears to correlate well with disease activity. It is easy, requires minimal physician training and involvement, and has the potential for quick integration into practice with minimal personnel resources. It also allows active patient engagement in care. Longitudinal studies are ongoing to confirm its utility and acceptability.

Disclosure: M. Jolly, None; **W. Sequeira**, None; **S. Toloza**, None; **A. M. Bertoli**, None; **L. M. Vilá**, None; **I. Blazevic**, None; **I. Moldovan**, None; **K. D. Torralba**, None; **B. Goker**, None; **J. Bourré-Tessier**, None; **S. V. Navarra**, None; **D. Wallace**, None; **M. H. Weisman**, None; **A. E. Clarke**, None; **C. C. Mok**, None; **J. A. Block**, None.

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Comparison of Responsiveness of Lupus Impact Tracker with Lupus Quality of Life to Selena Responder Index. Hervé Devilliers[1], Narender Annapureddy[2], Winston Sequeira[3], Joel A Block[4] and Meenakshi Jolly[2]. [1]Department of internal medicine and systemic diseases, Dijon, France, [2]Rush University Medical Center, Chicago, IL, [3]rush university, chicago, IL, [4]Rush University, Chicago, IL.

Background/Purpose: Lupus Impact Tracker (LIT) is a 10-item patient reported outcome tool to measure the impact of Systemic Lupus Erythematosus (SLE) or its treatment on patients' daily lives. The transformed scores range from 0–100, where higher scores denote greater impact. The tool is responsive to self-reported changes in SLE health status over time. Herein, we compare the responsiveness of the LIT and LupusQoL (34 items) to changes in disease activity as judged by SLE responder index (SRI).

Methods: Adult SLE patients were prospectively recruited from 20 North American Rheumatology clinics for the LIT study- an observational, non-interventional prospective multi center study conducted across the US and Canada. Data (Demographics, LIT, LupusQoL, BILAG, SELENA-SLEDAI) were obtained three months apart. Modified SRI was defined as (1) a decrease in SELENA-SLEDAI (4 points), (2) No new BILAG A and not more than 1 new B and (3) No increase in Physician Global Assessment (PGA). Latter definition was used as our PGA variable was categorical (0/1/2/3). Standardized response mean (SRM) and effect size (ES) for LIT and LupusQoL domains were calculated among SRI responders and non-responders by taking the average difference divided by the standard deviation of the differences between the paired measurements at baseline and 3 month visit LIT scores. Kruskall Walis test was used to compare the SRM among SRI responders (R) and non responders (NR).

Results: 325 patients participated (90% Female); 53% Whites, 33% Black and 17% Hispanic. Mean (SD) age and SELENA-SLEDAI at baseline were 42.3 (16.2) yrs and 4.3 (3.8), respectively. Mean (SD) LIT score at baseline was 39.4 (22.9). SRI data was available for 295 (40 R and 255 NR) at the 3 month timepoint. LIT SRM (ES) was −0.69 (−0.36) and −0.20 (−0.12) among SRI responders and non-responders respectively, (p=0.02).

For LupusQoL, SRM (ES) for Physical health and Pain domains were 0.42 (0.23) and 0.65 (0.44) respectively.

Conclusion: 10 item LIT was modestly responsive to changes in disease activity as assessed by SRI in patients with SLE in this study Two domains (11 items) of LupusQoL showed responsiveness to SRI. Inclusion of the these tools in clinical care and clinical trials may provide further insight into its responsiveness.

	Responders (n=40)					Non-responders (n=255)					
	Mean variation	SRM	95% CI	ES	95% CI	Mean variation	SRM	95% CI	ES	95% CI	p-value
LIT	−7.9	−0.68	[−1.05; −0.28]	−0.36	[−0.54; −0.16]	−2.9	−0.19	[−0.32; −0.06]	−0.12	[−0.2; −0.04]	0.023
LupusQoL domains											
Physical health	+5.7	+0.42	[0.07; 0.74]	+0.23	[0.04; 0.41]	+0.5	+0.03	[−0.09; 0.15]	+0.02	[−0.05; 0.09]	0.042
Pain	+12.6	+0.65	[0.36; 0.91]	+0.44	[0.19; 0.66]	+1.6	+0.08	[−0.04; 0.20]	+0.06	[−0.03; 0.13]	0.002
Planning	+3.5	+0.18	[−0.16; 0.50]	+0.13	[−0.10; 0.37]	+1.2	+0.07	[−0.06; 0.19]	+0.04	[−0.03; 0.12]	NS
Intimate Relationship	−0.7	−0.06	[−0.41; 0.27]	−0.05	[−0.32; 0.24]	+0.4	+0.02	[−0.09; 0.08]	+0.01	[−0.16; 0.14]	NS
Burden to others	+6.0	+0.24	[−0.05; 0.55]	+0.20	[−0.05; 0.44]	+3.9	+0.18	[0.04−0.31]	+0.12	[0.04−0.21]	NS
Emotional health	+4.5	+0.38	[0.07; 0.68]	+0.17	[0.03; 0.32]	+0.3	+0.01	[−0.11; 0.14]	+0.01	[−0.09; 0.11]	NS
Body image	+4.7	+0.29		+0.15		+2.7	+0.13		+0.09		NS
Fatigue	+3.5	+0.26	[−0.07; 0.56]	+0.16	[−0.05; 0.36]	+2.5	+0.13	[0.01; 0.25]	+0.09	[0.01; 0.17]	NS

Disclosure: H. Devilliers, None; **N. Annapureddy**, None; **W. Sequeira**, None; **J. A. Block**, None; **M. Jolly**, None.

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Safety of Gardasil® Vaccine in Systemic Lupus Erythematosu, Trial Update. J. Patricia Dhar[1], Lynnette Essenmacher[1], Renee Dhar[2], Ardella Magee[1], Harpreet Sagar[1], Malini Venkatram[1] and Robert Sokol[1]. [1]Wayne State University, Detroit, MI, [2]Central Michigan University College of Medicine, Mount Pleasant, MI.

Background/Purpose: Cervical neoplasia is increased in women with SLE presumably due to cervical infection with oncogenic Human Papillomavirus (HPV) types which persist in an immunosuppressed host. Vaccinating women with SLE against HPV is thus an important part of health prevention in this population. Gardasil® immunizes against the HPV types that cause the majority of cervical cancer (types 16 and 18) and genital warts (types 6 and 11), and has been shown to be protective against these HPV-related diseases.

Methods: For this ongoing trial**,** 36 women ages 19–50 years with a history of mild to moderate SLE and minimally active or inactive SLE disease received Gardasil® at the standard dosing schedule (0, 2 months, 6 months). This study was approved by the Human Investigation Committee at Wayne State University and the U.S. Food and Drug Administration. Patients were excluded if they had active disease (SELENA-SLEDAI >2), a history of severe disease, deep venous thrombosis, were on >400 mg/day of hydroxychloroquine, were on >15 mg/day of prednisone, or had active infections. To date, all 36 patients have completed the vaccine series shots. Patients were monitored for adverse events (AE), SLE flare, and generation of thrombogenic antibodies and thrombosis.

Results: The women in the study were predominantly African-American (81%), mean age 38.4 years with mean age at diagnosis of SLE at 29.4 years. All patients met American College of Rheumatology (ACR) criteria for SLE; 24.3% had a history of smoking, 92% had 4 or more sexual partners, 38.9% had a history of sexually transmitted diseases, and only 30.6% used condoms on a regular basis. History of abnormal pap smears occurred in 44.4% ranging from ASCUS (atypical glandular cells of undetermined significance) to CIN 3 (cervical intraepithelial neoplasia grade 3). Most of our patients had multiple comorbidities in addition to SLE. Vaccine site reactions (VSRs) occurred in 55%, all being mild, with the most common reaction being pain. This compares favorably to data from the current prescribing label showing frequency of VSRs in normal women to be 83.9% for Gardasil® vs. 75.4% for controls. For the non-vaccine site adverse events (nvAE), 90% of our cohort experienced at least one nvAE; there were 467 nvAEs reported from 36 patients and 90% of these nvAEs were mild. There were 9 serious adverse events, none were related to vaccine or SLE and all resolved. The most common nvAEs reported were musculoskeletal (n=99) followed by nervous system (n=93, mostly headaches), gastrointestinal (n=46), general disorders (n=46) and dermatologic (n=45). None of the nvAEs were related to vaccine or SLE. There was no flare of SLE, thrombosis, or generation of thrombogenic antibodies in any patient.

Conclusion: Preliminary data from our study shows that Gardasil® vaccine is safe to use in women with SLE. Vaccine site reactions are not increased in SLE patients. Other than vaccine site reactions, there were no related short term adverse events. Gardasil® vaccine administration did not result in any lupus flare or thrombosis. Women with SLE should be immunized with Gardasil® vaccine as part of their health prevention program, particularly since this population is at increased risk for HPV-related cervical dysplasia.

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Target Modulation of a Type I Interferon (IFN) Gene Signature with Sifalimumab or Anifrolumab in Systemic Lupus Erythematosus (SLE) Patients in Two Open Label Phase 2 Japanese Trials. Chris Morehouse[1], Linda Chang[2], Liangwei Wang[1], Philip Brohawn[1], Shinya Ueda[3], Gabor Illei[4], Warren Greth[1], Stephen Yoo[1], Lorin Roskos[4], Yihong Yao[5], Gabriel Robbie[5] and Brandon W. Higgs[1]. [1]MedImmune, LLC, Gaithersburg, MD, [2]MedImmune, Hayward, CA, [3]Astrazeneca, Osaka, Japan, [4]Medimmune, Gaithersburg, MD, [5]MedImmune, Gaithersburg, MD.

Background/Purpose: The pharmacokinetic (PK) and pharmacodynamic (PD) effects of two investigational monoclonal antibodies inhibiting type I IFN signaling - sifalimumab or anifrolumab, specific for IFN-α or IFN-α receptor subunit 1 (IFNAR1), respectively were assessed in the blood of adult SLE Japanese patients.

Methods: Two phase 2 randomized, open label, dose-escalation studies were conducted in adult Japanese patients with SLE - AZD2800C (sifalimumab; N=30) and AZD3461C (anifrolumab; N=17). Patients enrolled in both studies satisfied ACR classification criteria. AZD2800C included dose cohorts of 1, 3, and 10 mg/kg (mpk) administered intravenously (IV) every 4 weeks; 100 mg subcutaneously every 2 weeks; and 600 and 1200 mg IV every 4 weeks. AZD3461C included dose cohorts of 100, 300, and 1000 mg administered IV every 4 weeks. In both studies, blood specimens were collected for PK and PD assessment at multiple time points between predose and 169 days (anifrolumab) or 365 days (sifalimumab) after initial administration. Sifalimumab and anifrolumab concentrations were measured using a validated electrochemiluminescence assay and PK parameters were determined by noncompartmental analysis. Transcript profiling was conducted with qRT-PCR on a 21 IFN gene signature (IFNGS).

Results: Sifalimumab exhibited linear pharmacokinetics with a half-life of about 20 days while, anifrolumab exhibited nonlinear pharmacokinetics. Trough concentrations of both sifalimumab and anifrolumab reached steady state by Day 84. In AZD2800C and AZD3461C, 97% and 88% of patients had elevated IFNGSs at baseline, respectively. In AZD2800C, maximum median suppression of the IFNGS was 63% with 1 mpk, 48% with 3 mpk, 67% with 10 mpk, 37% with 100 mg SC, 76% with 300 mg, and 61% with 1200 mg and was observed within 1 to 3 days of dosing with sifalimumab. In AZD3461C, maximum median suppression of the IFNGS by anifrolumab was 6% in the 100 mg (day 85), 85% (day 169) in the 300 mg, and 97% (day 85) in the 1000 mg cohort, with sustained suppression (>70% and >95%) in the 300 and 1000 mg cohorts after days 141 and 29, respectively. The level of suppression correlated well with increased anifrolumab concentrations. There were no major safety issues in the small sifalimumab and anifrolumab Japanese open-label trials (AZD2800C and AZD3461C, respectively) at the dose regimens studied but there is inadequate data to fully characterize the safety profile adequately and overall safety needs to be confirmed in larger double-blind controlled studies.

Conclusion: Both sifalimumab and anifrolumab showed expected mechanism of action in SLE, with anifrolumab having increased and more sustained target suppression of the IFNGS in Japanese SLE patients compared to sifalimumab.

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ACR Poster Session A
Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics: Systemic Sclerosis Measures and Outcomes

Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Measures of Disease Status in Systemic Sclerosis: Systematic Review. Tien Tay[1], Nava Ferdowsi[1], Wendy Stevens[1], Marie Hudson[2], Murray Baron[2], Candice Rabusa[1], David Prior[1], Susanna Proudman[3] and Mandana Nikpour[1]. [1]The University of Melbourne at St Vincent's Hospital, Melbourne, Australia, [2]Lady David Institute for Medical Research and Jewish General Hospital, Montreal, QC, [3]Royal Adelaide Hospital, Rheumatology Unit and University of Adelaide, Discipline of Medicine, Adelaide, Australia.

Background/Purpose: To identify the measures of disease status in systemic sclerosis (SSc) using a systematic review.

Methods: A systematic review of Medline (1966–2014), EMBASE (1974–2014), and Cochrane Library (inception-2014) was undertaken to identify indices of disease status in systemic sclerosis. We focussed on objective measures and excluded non-English articles, animal-only studies and those relating to morphea, localized scleroderma or juvenile systemic sclerosis.

Results: Of the 5687 articles identified through the search, we identified 45 articles for review. We found a further 22 articles through a search of the bibliography of relevant articles. We identified 10 'composite' (multi-organ) indices: two disease activity indices, six disease severity scales, and two combined response indices (Tables 1 and 2). There was no disease damage index for SSc. Furthermore, we found no objective organ-specific index for the gastrointestinal system.

Conclusion: We identified a number of composite and organ-specific indices in SSc, incorporating subjective and/or objective measures, developed to quantify disease activity, severity and response in clinical trials. Most of the existing indices require further evaluation according to the OMERACT filter. None of the indices measures organ damage per se, highlighting this as an area for future research.

Table 1: Features of existing composite measures of disease status in systemic sclerosis

	Disease activity indices				Disease severity indices										Outcome measures			
Features	**Valentini**		**Minier**		**Medsger**		**Geirrson**		**Morita**		**Furst**		**Hughes**		**Casas**		**CRISS^**		**EPOSS~**	
Methodology																				
Consensus-based	Y		?		Y		?		?		?		?		?		Y		Y	
Number of experts	3		?		20		?		?		?		?		?		9		12	
Data-driven	Y		Y		Y		?		?		?		?		?		N		Y	
Variables	10		17		31		5		19		33		7		9		30		14	
Organ systems	5		5		9		5		9		7		5		6		11		6	
	Obj	Sub	Obj	Sub	Obj	Sub	Obj	Sub	Obj	Sub	Obj	Sub	Obj	Sub	Obj	Sub	Obj	Sub	Obj	Sub
Musculoskeletal	Y	Y	Y	Y	Y	N	N*	N	Y	N	Y#	Y	N	N	N	N	Y	Y	N	N
Vascular	Y	Y	Y	Y	Y	N	N*	N	Y	N	Y	N	N	N	Y	Y	Y	Y	N	N
Skin	Y	Y	Y	Y	Y	N	Y	N	Y	N	Y	N	Y	N	N	N	N	N	N	N
Cardiac	N	Y	N	Y	Y	N	N*	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Respiratory	N	Y	N	Y	Y	N	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Gastrointestinal	N	N	N	N	Y	N	Y	N	Y	N	Y	Y	Y	N	Y	Y	N	Y	N	N
Renal	N	N	N	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N	N	N
General lab tests	Y		Y		Y		Y		N		N		N		N		Y		N	
Others	N	N	N	Y	N	N	N*	N	Y	N	N	N	?	?	N	N	Y	Y	Y	Y
Patient-reported outcomes	Y		Y		N		N		N		Y		N		N		Y		Y	
Weighted score	Y		Y		N		N		N		Y		N		N		N		N	
Global assessment score	Y		Y		N		N		N		Y		N		N		N		N	

? Insufficient data to evaluate the item; Obj: objective tests; Sub: subjective tests; * omitted due to lack of recorded data;
includes SJC, TJC, bony erosions, lysis, serum creatine phosphokinase, myositis (EMG) and myopathy (EMG).
^ The Combined Response Index for Systemic Sclerosis; ~ Expert Panel on Outcome Measures in Pulmonary Arterial Hypertension related to Systemic Sclerosis.

Table 2: Summary of composite measures of health status in systemic sclerosis according to the OMERACT filter

	Disease activity indices		Disease severity indices						Outcome measures	
OMERACT filter	**Valentini**	**Minier**	**Medsger**	**Geirrson**	**Morita**	**Furst**	**Hughes**	**Casas**	**CRISS~**	**EPOSS'**
Validity										
Face validity	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Content validity	PV*^	PV*^	Y	N	Y	Y	N	N	Y	Y
Criterion validity#	PV	NT	Y	Y	?	?	N	N	NT	NT
Construct validity$	Y	NT	NT	N	?	?	N	N	NT	NT
Discrimination capacity										
Reliability	Y	NT	NT	NT	?	?	NT	NT	NT	NT
Sensitivity to change	PV*	NT	NT	?	?	NT	NT	NT	NT	NT
Feasibility	Y	NT	Y	Y	Y	N	Y	Y	Y	Y
Validation										
Internal validation	Y	NT	Y	NT	?	?	NT	NT	IPR	IPR
External validation	Y	NT	Y	NT	?	?	NT	NT	IPR	IPR

*PV: partially validated; ^lacks gastrointestinal and renal components; #tested against mortality; NT: not tested; ? insufficient data to evaluate item; $ tested against physician global assessment of disease activity or disease severity;
~ Combined Response Index in Systemic Sclerosis; ' Expert Panel on Outcome Measures in Pulmonary Arterial Hypertension related to Systemic Sclerosis: IPR: in progress.

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Muscle Disease in Systemic Sclerosis Is Associated with an Increased Risk for Cardiac Involvement. Jison Hong[1], Antonia Valenzuela[1], David Fiorentino[2] and Lorinda Chung[1]. [1]Stanford University School of Medicine, Palo Alto, CA, [2]Stanford University, Redwood City, CA.

Background/Purpose: Patients with systemic sclerosis (SSc) and muscle involvement (myopathy/myositis) have more severe disease and worse outcomes. We sought to determine the prevalence of muscle disease in our cohort of SSc patients and to compare these patients to those without muscle disease.

Methods: We conducted a retrospective medical record review of patients with SSc according to 2013 ACR classification criteria, evaluated at Stanford from 2006–2013. We collected demographics, clinical features if ever present, Manual Muscle Test 8 (MMT-8), laboratory data (available autoantibody results and muscle enzymes: CPK, aldolase, LDH, AST and ALT). Muscle involvement was defined by the presence of any of the following criteria: elevation in muscle enzyme(s), physician reported history of myopathy/myositis, and if performed, electromyelogram, MRI, and/or muscle biopsy results consistent with myopathy/myositis. Comparisons between SSc patients with and without muscle disease

were made with Student's t-test for continuous variables and chi-square or Fisher's exact test for categorical variables.

Results: The study included 273 patients (mean age 57.3 years, 88.7% female, 54.6% Caucasian, 37.4% diffuse, and 62.6% limited). Muscle disease was present in 80 patients (29.3%). The most common findings of muscle disease at presentation were elevated muscle enzymes (42.5%) and proximal muscle weakness (42.5%). The first manifestation of muscle disease occurred at a mean time of 7.1±11.1 years after the first non-Raynaud symptom of SSc. As expected, patients with muscle disease were more likely to have diffuse disease, arthralgias, myalgias, muscle weakness, dysphonia, mechanic hands, greater maximum modified Rodnan skin score, lower MMT-8 scores, and positive PM-1 antibody ($p<0.03$). They had less vascular manifestations such as Raynaud's phenomenon (73.8% vs 87.1%; $p=0.008$) and telangiectasias (7.5% vs 21.8%; $p=0.005$) and were less likely to be centromere positive (21.3% vs 36.3%, $p=0.02$). Cardiac disease was more common in patients with muscle disease (13.8% vs 5.7%, $p=0.03$).

Conclusion: 30% of our SSc cohort had muscle disease, which was associated with a higher likelihood of cardiac disease. Obtaining baseline and routine monitoring of muscle enzymes and performing strength exams at every visit may help to identify patients with SSc with muscle involvement who are also at risk for cardiac disease. The current development of a multi-center SSc cohort of patients with muscle disease led by SCTC and EUSTAR will help elucidate the pathophysiology and better define the subtypes of muscle disease in SSc.

Table 1. Baseline characteristics of 80 patients with muscle disease

	Patients n (%)
Disease duration from first Raynaud's symptom to muscle disease diagnosis (years ± SD)*	8.26 ± 10.9
Disease duration from first non-Raynaud's symptom to muscle disease diagnosis (years ± SD)*	7.1 ± 11.1
Symptom at presentation of muscle disease:	34 (42.5)
High muscle enzymes	12 (15)
Myalgias	34 (42.5)
Proximal muscle weakness	
Symptom at any time of muscle disease:	13 (16.25)
Myalgias	21 (26.25)
Subjective muscle weakness	13 (16.25)
Muscle weakness on physical exam	3 (3.75)
Dysphonia	24 (30)
Dysphagia related to muscle weakness	
MRI performed	6 (7.5)
Normal	3 (3.75)
Abnormal	2 (2.5)
Non-specific	1 (1.25)
EMG performed	10 (12.5)
Normal	4 (5)
Neuropaty	1 (1.25)
Myopathy	1 (1.25)
Non-specific	1 (1.25)
Inflammatory myositis	3 (3.75)
Muscle biopsy performed	8 (10)
Normal	1 (1.25)
Abnormal	7 (8.75)
Elevated muscle enzymes	64 (82.5)
Peak CPK (Units/Liter)	1577.7 ± 3116.6
Peak aldolase (Units/Liter)	20.1 ± 26.5
Peak AST (Units/Liter)	264.8 ± 846.4
Peak ALT (Units/Liter)	215.1 ± 240.3
Peak LDH (Units/Liter)	544 ± 316.4
More than one test positive**	12 (15)
Normal muscle enzymes	14 (17.95)
MMT-8	66.38 ± 15.5951

*Information available in 46 patients
**Any combination of MRI, EMG, muscle biopsy and muscle enzymes

Disclosure: J. Hong, None; **A. Valenzuela**, None; **D. Fiorentino**, None; **L. Chung**, None.

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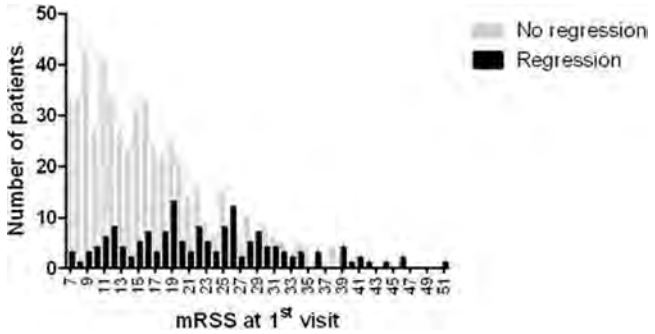
Prediction of Improvement in Skin Fibrosis in Diffuse Cutaneous Systemic Sclerosis. Rucsandra Dobrota[1], Britta Maurer[2], Nicole Graf[3], Carina Mihai[1], Otylia Kowal-Bielecka[4], Yannick Allanore[5] and Oliver Distler on behalf of the EUSTAR investigators and co-authors[2]. [1]Department of Internal Medicine and Rheumatology, Dr. I.Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [2]Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [3]graf biostatistics, Winterthur, Switzerland, [4]Department of Rheumatology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland, [5]Department of Rheumatology, University Paris Descartes and Cochin Hospital, Paris, France.

Background/Purpose: Improvement of skin fibrosis over time is part of the "natural history" of patients with diffuse cutaneous systemic sclerosis (dcSSc). However, in the individual patient, the pattern of change in skin fibrosis varies widely. The extent of skin fibrosis measured by the modified Rodnan skin score (mRSS) is the major outcome measure in clinical trials (CT) in dcSSc. Understanding the factors behind the improvement of skin fibrosis in dcSSc is important to avoid unnecessary use of therapy and medical resources. Moreover, it could improve cohort selection in CT using skin fibrosis as a major outcome.

Methods: A longitudinal analysis including 704 patients with dcSSc from the EUSTAR registry was performed. The inclusion criteria were diagnosis of dcSSc, fulfillment of ACR criteria, mRSS≥7 at baseline and available data for mRSS at 12±2 months follow-up. First entry into the database was defined as baseline. Skin improvement was defined as a decrease in mRSS of >5 points AND ≥25 % within 1 year. Variables with $p<0.2$ in univariate analysis were selected for multivariate analysis through a nominal group technique. To compensate for missing data, a multiple imputation followed by a pooled logistic regression was run. Based on a likelihood ratio test, the full model was compared to a reduced model. The model with the best fit was evaluated in the available data set.

Results: A total of 155/704 patients showed skin improvement. On univariate analysis, cardiac involvement, immunosuppression and ESR<25 mm/h were associated with skin improvement. High baseline mRSS was the strongest parameter ($p<0.001$; Figure 1), with the best sensitivity and specificity for prediction of skin regression at a cut-off of 17.5 points (area under the curve 0.708). In addition, a high skin fibrosis progression rate at baseline was also strongly associated with regression of skin fibrosis at 12-months follow-up. A multivariate pooled logistic regression with 13 variables was run. The likelihood ratio test was in favor of a reduced model: baseline mRSS (Estimate 0.087, $p<0.001$) and ESR >25mm/h (Estimate −0.526, p 0.030). When tested on the available data set, this latter model showed good performance in predicting regression of mRSS (area under the curve 0.726, 95%CI 0.64–0.80). **Figure 1**. Baseline mRSS in patients with and without skin regression: there is a clear trend towards the predominance of regression (black bars) over no regression (grey bars) in patients with high mRSS.



Conclusion: These results show that, opposite to current practice, patients with already advanced skin fibrosis are more likely to regress under standard of care in the next 12 months than patients with milder skin fibrosis. Thus, focus for treatment intervention and recruitment in CT aiming at skin fibrosis should shift from these patients with high baseline mRSS to at risk patients characterized by low to moderate skin fibrosis and high ESR at baseline.

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Early Mortality in Australian, Canadian and Spanish Scleroderma Patients: Rationale for Establishing a Multi-National Inception Cohort of Patients with Systemic Sclerosis. YanJie Hao[1], Marie Hudson[2], Patricia Carreira[3], Wendy Stevens[1], Candice Rabusa[4], Solene Tatibouet[5], Loreto Carmona[6], Beatriz E Joven[7], Susanna Proudman[8], Murray Baron[5] and Mandana Nikpour[9]. [1]St. Vincent's Hospital Melbourne, Melbourne, Australia, [2]McGill University, Montreal, QC, [3]Hospital Universitario 12 de Octubre, Madrid, Spain, [4]The University of Melbourne at St Vincent's Hospital, Melbourne, Australia, [5]Lady David Research Institute, Montreal, QC, [6]Instituto de Salud Musculoesqueletica, Madrid, Spain, [7]Hospital Universitario, Madrid, Spain, [8]University of Adelaide, Adelaide, Australia, [9]The University of Melbourne at St. Vincent's Hospital, Melbourne, Australia.

Background/Purpose: Studies of 'prevalent' cohorts wherein most patients have longstanding disease at recruitment may underestimate mortality in systemic sclerosis (SSc) due to survivor bias. The aim of this study was to quantify mortality in Australian, Canadian and Spanish patients with SSc and to compare patients with prevalent and incident disease.

Methods: We quantified mortality as Standardized Mortality Ratio (SMR) and Years of Life Lost (YLL) in each of the cohorts based on Australian Bureau of Statistics, Statistics Canada and Spain National Statistics Institute data for the general population, and percentage survival in the first decade of disease in the whole combined 'prevalent' cohort and a subset of patients recruited within 4 years of onset of disease (the combined 'incident' cohort). We determined a single primary cause of death (SSc or non-SSc related) and all other SSc organ involvement that contributed to death.

Results: In the combined prevalent cohort of 3218 patients (1411 Australian, 1465 Canadian and 342 Spanish), 53% of the primary causes of 440 deaths (157 Australian, 213 Canadian and 70 Spanish) recorded were SSc related; the most common cause of SSc-related death was heart-lung disease (Table 1). Malignancy, atherosclerotic vascular disease and sepsis were the most common non-SSc related causes. SSc organ involvement contributed to 31% of these non-SSc related deaths. In multivariable regression, the predictors of mortality were male sex, older age at disease onset, diffuse subtype and presence of PAH, ILD, myocardial involvement, or renal crisis. The SMR and YLL were higher (Table 2) in Australian and Canadian incident cohorts compared with the respective prevalent cohorts. Survival was lower (Figure 1) in the combined incident cohort than the prevalent cohort.

Conclusion: Mortality in Canadian, Spanish and Australian SSc patients is substantial. Our results suggest that prevalent cohorts underestimate mortality in SSc by failing to capture early deaths, particularly in diffuse disease. These findings provide a compelling rationale for establishing a large multi-national inception cohort of patients with SSc to more accurately quantify early mortality in this disease.

Table 1 Causes of SSc-related death

	Australian Cohort 01/2007-03/2014		Canadian Cohort 01/2005-03/2014		Spanish Cohort 01/2000-03/2014		Combined cohort	
Organ system	Principal Cause N=87 n (%)	Contributing cause N=157 n (%)	Principal Cause N=94 n (%)	Contributing cause N=213 n (%)	Principal cause N=52 n (%)	Contributing cause N=70 n (%)	Principal cause N=233 n (%)	Contributing cause N=440 n (%)
Heart and Lung	74 (85.0)	44 (28.0)	57 (60.6)	55 (25.8)	35 (67.3)	12 (17.1)	166 (71.2)	111 (25.2)
PAH	41 (47.1)	24 (15.3)	30 (31.9)	22 (10.3)	14 (26.9)	3 (4.3)	85 (36.5)	49 (11.1)
ILD	19 (21.8)	20 (12.7)	17 (18.1)	33 (15.5)	14 (26.9)	9 (12.9)	50 (21.5)	62 (14.1)
PAH and ILD	14 (16.1)		10 (10.6)		7 (13.5)		31 (13.3)	
Myocardial involvement	2 (2.3)	0 (0)	8 (8.5)	7 (3.3)	10 (19.2)	8 (11.4)	20 (8.6)	15 (3.4)
Pericardial involvement	0 (0)	3 (1.9)	4 (4.3)	5 (2.3)	0 (0)	3 (4.3)	4 (1.7)	11 (2.5)
Renal crisis	4 (4.6)	1 (0.6)	9 (9.6)	6 (2.7)	2 (3.8)	3 (4.3)	15 (6.4)	10 (2.3)
Gut involvement	6 (6.9)	14 (8.9)	14 (14.9)	17 (8.0)	4 (7.7)	13 (18.6)	24 (10.3)	44 (10.0)
Sepsis due to ischemic digit or decubitus ulcer	2 (2.3)	22 (14.0)	1 (1.1)	6 (2.8)	1 (1.9)	13 (18.6)	4 (1.7)	41 (9.3)

Table 2 A comparison of mortality in 'prevalent' and 'incident' cohorts

	Australian Patients 01/2007-12/2012		Canadian Patients 01/2005-12/2012		Spanish Patients 01/2000-12/2012	
	'Prevalent' cohort n=1252	'Incident' cohort n=339	'Prevalent' cohort n=1132	'Incident' cohort n=405	'Prevalent' cohort n=342	'Incident' cohort n=183
Number of deaths	110	27	151	53	58	32
SMR(95%CI)						
Women	2.6 (2.1–3.1)	2.4 (1.2–3.5)	3.3 (2.7–3.9)	4.2 (2.9–5.5)	4.1 (3.0–5.3)	3.3 (2.0–4.5)
Men	4.2 (2.4–5.9)	9.1 (3.7–14.5)	5.9 (3.9–7.9)	6.8 (3.1–10.4)	9.5 (3.6–15.4)	8.4 (1.7–15.1)
Overall	2.8 (2.4–3.3)	3.4 (2.3–4.5)	3.7 (3.2–4.2)	4.7 (3.6–5.7)	4.6 (3.7–5.5)	3.8 (2.8–4.9)
YLL (years)						
Women	11.9	11.3	19.8	21.1	22.4	16.4
Men	17.2	25.8	16.7	19.7	24.4	25.7

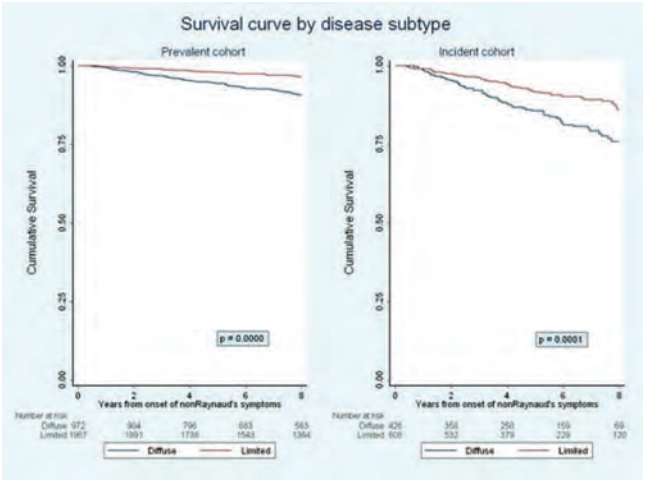

Figure 1 Survival curves in combined cohorts

Disclosure: Y. Hao, None; **M. Hudson**, None; **P. Carreira**, None; **W. Stevens**, None; **C. Rabusa**, None; **S. Tatibouet**, None; **L. Carmona**, None; **B. E. Joven**, None; **S. Proudman**, None; **M. Baron**, None; **M. Nikpour**, None.

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Moderate Decline in Forced Vital Capacity is Associated with a Poor Outcome in Systemic Sclerosis Patients. Anna-Maria Hoffmann-Vold[1], Oyvind Midtvedt[2], Torhild Garen[1], May Brit Lund[3], T. Mogens Aalokken[4], Jan Tore Gran[2] and Oyvind Molberg[5]. [1]Department of Rheumatology, Oslo University Hospital Rikshospitalet, Oslo, Norway, [2]Oslo University Hospital, Oslo, Norway, [3]Department of Respiratory Medicine, Oslo University Hospital Rikshopitalet, Oslo, Norway, [4]Department of Radiology, Oslo University Hospital Rikshospitalet, Oslo, Norway, [5]Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway.

Background/Purpose: Interstitial lung disease (ILD) is a common manifestation in systemic sclerosis (SSc) and the leading cause of morbidity and mortality. Serial pulmonary function tests are useful for monitoring SSc-ILD, and total decline in forced vital capacity (FVC) above 10% predicts mortality. Moderate FVC decline (5–10%) was recently shown to predict poor outcome in idiopathic pulmonary fibrosis, but it is not known if moderate FVC decline has any impact on the outcome of SSc-ILD.

Methods: The study cohort included 305 SSc patients enrolled in the prospective SSc cohort (Norwegian Systemic Connective Tissue Disease and Vasculitis Registry [NOSVAR]) at the Department of Rheumatology, Oslo University Hospital (OUH). Serial pulmonary function test (PFT), lung fibrosis measured on high resolution computed tomography (HRCT) and clinical data were registered at baseline and then prospectively at annual follow-up visits. Patients were segregated in three groups according to annual FVC decline rates; (A) stable or minimal decline (<5%), (B) moderate decline (5–10%) and (C) major decline (>10%). Mortality and disease progression (fibrosis progression, DLCO and total FVC decline) quantified from baseline data were defined as poor outcome. Descriptive statistics and t-tests were applied; Kaplan-Meyer and Cox proportional hazard models were used to analyse survival.

Results: 305 SSc patients were followed for mean 3.8 years (range 1–15) from the baseline FVC. Altogether, 241 patients (79%) had stable FVC, 43 (14 %) had moderate FVC decline and 21 (7%) had major decline (Table 1). Sixty-seven deaths occurred during the observation period. Moderate decline in FVC was significantly associated with mortality (HR 2.5 (95% CI 1.4, 4.6, p-value 0.003). The 1-year survival rates for the three FVC groups were 100%, 100%, 86%, 5-year survival rates were 97%, 85% and 76% and 10-year survival rates were 85%, 66% and 54%, respectively. Compared to the stable FVC group, the moderate FVC decline group were older at disease onset, had more lung fibrosis at baseline and at follow up, higher total decline in DLCO and lower FVC% at follow up (table 1).

Conclusion: In this prospective SSc cohort, annual moderate FVC decline was associated with high total DLCO decline, high lung fibrosis scores and increased mortality. These results highlight the importance of regular PFT measurements in daily clinical practice.

Table 1: Clinical and lung characteristics of 305 SSc patients stratified by FVC decline

	Annual decline in FVC			
	<5%	5–10%	>10%	p-val*
Demographics				
Number of patients (%)	241 (79)	43 (14)	21 (7)	
Age at diagnoses, yrs (SD)	46.6 (15.1)	53.2 (13.6)	53.3 (13.1)	0.007
Disease duration[1], yrs (SD)	5.2 (6.9)	4.9 (7.1)	6.0 (8.0)	0.862
Deceased, n (%)	41 (17)	14 (33)	12 (57)	<0.001
Time to death[2], yrs (SD)	9.6 (9.5)	10.6 (7.4)	9.1 (8.7)	0.328
Male gender, n (%)	49 (20)	11 (26)	3 (14)	0.437
Ever smoker, n (%)	100 (42)	14 (33)	10 (48)	0.436
dcSSc, n (%)	60 (25)	17 (40)	9 (43)	0.056
ATA positive, n (%)	36 (15)	11 (26)	52 (17)	0.161
Lung function and imaging				
Baseline FVC, % (SD)	93.0 (23.4)	91.7 (21.0)	91.4 (22.5)	0.712
FVC at follow up, % (SD)	91.7 (22.9)	77.0 (24.8)	66.9 (19.9)	<0.001
Baseline DLCO, % (SD)	67.3 (20.9)	68.4 (19.7)	52.9 (17.4)	0.759
DLCO at follow up, % (SD)	60.2 (20.2)	55.4 (19.9)	42.5 (18.5)	0.154
Total DLCO decline, % (SD)	6.9 (13.4)	13.0 (12.8)	10.0 (15.4)	0.006
Baseline lung fibrosis, % (SD)	6.0 (12.9)	11.3 (18.3)	6.4 (10.8)	0.015
Fibrosis at follow up, % (SD)	7.6 (13.9)	13.1 (19.2)	7.8 (13.3)	0.026
>20% fibrosis, follow up, n (%)	36 (15)	11 (26)	4 (19)	0.084

Yrs: years; n: number; dcSSc: diffuse cutaneous systemic sclerosis; ATA: anti-topoisomerase antibody, FVC: forced vital capacity; DLCO: diffusing factor for carbon monoxide; * p-value between <5% and 5–10% decline in FVC; [1] time from first non-Raynaud symptom to baseline FVC, [2] time from disease onset to death

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Reduced Diffusing Capacity of Carbon Monoxide Is Independently Associated with Worse Subclinical Left Ventricular Function on Speckle-Tracking Echocardiography in Systemic Sclerosis. Monique Hinchcliff, Vistasp Daruwalla, Lauren Beussink-Nelson, Sofia Podlusky, Mary A. Carns, John Varga, Michael Cuttica and Sanjiv J. Shah. Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Reduced diffusing capacity of carbon monoxide (DLCO) is a predictor of worse outcomes in patients with systemic sclerosis (SSc). Traditionally, the association between low DLCO and mortality in SSc has been attributed to either interstitial lung disease (ILD) or pulmonary vascular disease due to pulmonary arterial hypertension (PAH). However, patients with primary cardiac involvement in SSc may have reduced DLCO due to pulmonary venous hypertension and/or generalized vascular disease in SSc. We sought to determine the association between DLCO and cardiac mechanics (speckle-tracking strain parameters) in patients with SSc.

Methods: We studied 195 patients with SSc who were enrolled in the Northwestern Scleroderma Program. All patients underwent comprehensive echocardiography using a standardized protocol for image acquisition and interpretation. Indices of cardiac mechanics (LV, RV, and left atrial [LA] strain parameters) were measured using speckle-tracking analysis. We used multivariable-adjusted linear regression analyses to determine the association between DLCO and indices of cardiac mechanics.

Results: The mean±SD age was 51±13 years, 84% were female, 59% had limited cutaneous SSc, 31% had diffuse cutaneous SSc, and 10% had other forms of SSc (e.g., overlap syndromes). Prevalence of SSc complications were as follows: PAH in 10%, significant ILD in 18.5%, and LV systolic dysfunction (EF<50%) in 3.6%. DLCO was not associated with global LVEF, but it was associated with LV, RV, and LA strain parameters, and early LV diastolic (e') tissue velocities, on univariate analysis ($P^2$0.001) (Figure). Reduced DLCO remained associated with reduced absolute global longitudinal systolic strain (GLS, a marker of longitudinal LV systolic function) after adjusting for age, sex, SSc subtype, SSc disease duration, PAH, ILD, e' velocity (a marker of LV diastolic dysfunction), and tricuspid annular plane systolic excursion (a marker of RV function): μ-coefficient = −0.9 (95% CI −1.5 to −0.2) %-units, P=0.009. The association between DLCO and GLS persisted in the subset of patients with normal LVEF (>50%), no PAH, and FVC > 60% of predicted (multivariable-adjusted P=0.014).

Conclusion: In patients with SSc, reduced DLCO is associated with subclinical abnormalities in LV mechanics even in patients without evidence of ILD, PAH, or global LV systolic dysfunction. DLCO may be a marker of SSc cardiac disease.

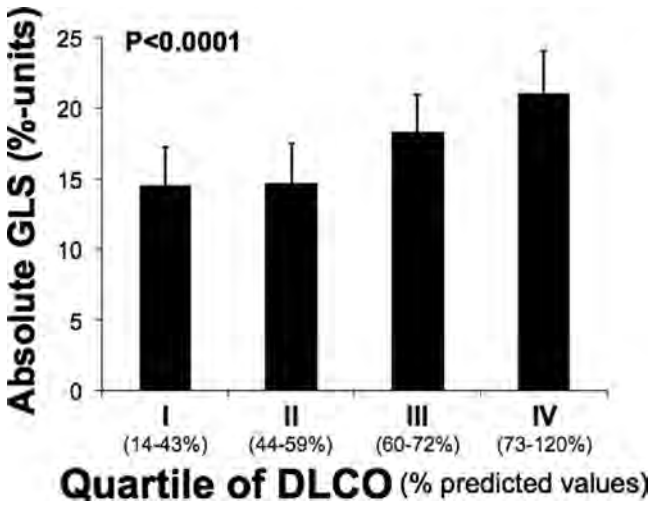

Figure. Diffusing Capacity of Carbon Monoxide (DLCO) Quartiles vs. Absolute Global Longitudinal Strain (GLS). Lower DLCO is associated with worse left ventricular longitudinal systolic function as indicated by lower values of GLS.

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Risk of Ischemic Stroke in Patients with Systemic Sclerosis: A Systematic Review and Meta-Analysis. Patompong Ungprasert[1], Praveen Ratanasrimetha[2], Charat Thongprayoon[3], Wisit Cheungpasitporn[3] and Promporn Suksaranjit[4]. [1]Bassett medical center, Cooperstown, NY, [2]Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [3]Mayo clinic, Rochester, MN, [4]University of Utah School of Medicine, Salt Lake City, UT.

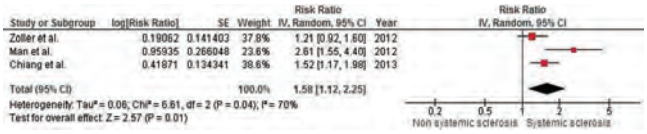
Background/Purpose: Several chronic inflammatory disorders, such as rheumatoid arthritis and systemic lupus erythematosus, have been shown to increase risk of ischemic stroke secondary to accelerated atherosclerosis. However, the data on systemic sclerosis (SSc), another chronic inflammatory disease, remain unclear due to conflicting epidemiological studies. Thus, to further investigate this possible association, we conducted a systematic review and meta-analysis of observational studies that compared the risk of ischemic stroke in patients with SSc versus participants without it.

Methods: Two investigators (P.U. and P.C.) independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception to March 2014 using the terms "systemic sclerosis" and "scleroderma" combined with the terms for cerebrovascular disease. A manual search of references of retrieved articles was also performed. The inclusion criteria were as follows: (1) observational studies published as original studies to evaluate the association between SSc and ischemic stroke and (2) odds ratios (OR's), relative risk (RR's) or hazard ratio (HR's) or standardized incidence ratio (SIR's) with 95% confidence intervals (CI's) were provided. Study eligibility was independently determined by the two investigators noted above. Differing decisions were resolved by consensus with the senior investigator. The quality of each study was, again, independently assessed by the two investigators using Newcastle-Ottawa scale.

RevMan 5.2 software was used for the data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird. Given the high likelihood of between study variance, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran's Q test.

Results: Out of 370 potentially relevant articles, three studies (all were retrospective cohort studies) with 3,861 cases of SSc were identified and included in our data analysis. The pooled risk ratio of ischemic in patients with SSc was 1.58 (95% CI, 1.12 to 2.25). The statistical heterogeneity of this meta-analysis was moderate with an I^2 of 70%.

Conclusion: Our study demonstrated a statistically significant increased ischemic stroke risk among patients with SSc.



Disclosure: P. Ungprasert, None; **P. Ratanasrimetha**, None; **C. Thongprayoon**, None; **W. Cheungpasitporn**, None; **P. Suksaranjit**, None.

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International Classification of Functioning, Disability, and Health (ICF) Core Sets for Connective Tissue Disease Interstitial Lung Disease (CTD-ILD) and Idiopathic Pulmonary Fibrosis (IPF) – a Necessary Map to Health Care Provision in the Era of ICD-11. Reuben Escorpizo[1], Kevin J. Keen[2], Kim Fligelstone[3], Matthew R. Lammi[4], Daphne LeSage[5], Anne-Marie Russell[6], Surinder Birring[7], Catherine Sarver[8], Janos Varga[9], Oliver Distler[10] and Lesley Ann Saketkoo[11]. [1]ICF Research Branch in cooperation with the WHO Collaborating Centre for the Family of International Classifications in Germany (DIMDI), Nottwil, Switzerland, [2]Health Research Institute, Prince George, BC, [3]Royal Free Hospital, Scleroderma Unit and Scleroderma Society, London, United Kingdom, [4]Louisiana State University Health Sciences Center, Pulmonary and Critical Medicine, New Orleans, LA, [5]Center for CCH at State of Louisiana, New Orleans, LA, [6]Royal Brompton Hospital,, London, United Kingdom, [7]King's College Hospital NHS Foundation Trust, London, United Kingdom, [8]Johns Hopkins, Baltimore, MD, [9]National Koranyi Institute for TB and Pulmonology, Budapest, Hungary, [10]University Hospital Zurich, Zurich, Switzerland, [11]Louisiana State University Health Sciences Center, New Orleans, LA.

Background/Purpose: A recent consensus project (Saketkoo et al, Thorax 2014) recommended a minimum core set of outcome measures for use in future clinical trials of CTD-ILD and IPF. The World Health Organization (WHO) introduced the **International Classification of Functioning, Disability, and Health (ICF)** as a scientific method of disability data collection and a universal framework of >1200 categories to describe disability associated with health conditions in terms of the bio-psycho-social model with consideration of environmental and personal factors. For accurate representation of disease, ease of healthcare provision and fair allocation of resources, it is essential that ICF Core Sets be established for rare and complex diseases.

Methods: Per updated ICF linkage rules, each instrument from the published CTD-ILD and IPF core sets were deconstructed to meaningful concepts and independently linked by 2 health professionals experienced in ICF linkage (RE, LAS). Inter-linker agreement on independent linkages was analyzed (KK). Discordant linkages were resolved between linkers. A 3rd linker (OD) arbitrated if irreconcilable linkages occurred.

Results: Eighty-two ICF categories were identified under the 4 ICF domains for 6 patient questionnaires and 3 traditional objective measures. The proportion of agreement ranged from 0.79 (95% CI: 0.62, 0.91) to 0.93 (0.76, 0.99) (Table 1) on the 5 different survey instruments (Table 2) with the overall proportion of inter-linker agreement 0.86 (0.82, 0.89). Any discordant linkages were reconciled between the initial 2 linkers. A previously linked version of the SF-36 had already existed; All-Cause Mortality and Patient Global of Disease Activity were indefinable in ICF terms. 20 new Personal Factors were generated to capture important disease-specific qualities not elsewhere described in ICF, e.g. 'pf_embarrassed by cough' or 'pf_panic/afraid when can't get breath'.

Table 1. Instruments from published CTD-ILD and IPF minimum core sets for clinical trials; with Instrument Comparison and Inter-Reviewer Agreement.

Minimum Core Set Instruments For CTD-ILD and IPF	Number of Items Linked	Number of Categories Identified	Agreement (%)	Agreement 95% Confidence Interval
Medical Research Council (MRC) Dyspnea Scale	27	34	79	(62, 91)
Dyspnea 12 (D-12)	25	27	93	(76, 99)
University of California San Diego-Shortness of Breath Questionnaire (UCSD-SBQ) (for IPF only)	68	83	82	(76, 90)
Leicester Cough Questionnaire	44	56	79	(66, 88)
St Georges Respiratory Questionnaire	126	138	91	(85, 95)
Medical Outcomes Study Short Form 36 (SF-36)		26*	Based on previously linked version	
Visual Analogue Scale-Patient Global Disease Activity		Not defined by ICF (too broad)		
Forced Vital Capacity on Spirometry	2	2*	100	Not done
Diffusion Capacity of the Lung for Carbon Monoxide (DLCO)	1	1*	100	Not done
Overall Extend of ILD on High Resolution CT (HRCT)	1	1*	100	Not done
All Cause Mortality		Not defined by ICF (too broad)		
Overall Agreement on Questionnaires	290	338 (+30*)	86	(82, 89)

Table 2. Distribution of ICF Categories and Instrument Occurrence according to ICF domains with example linkages.

ICF Domain	Description	Instruments Linked	No. of ICF Categories Linked	Examples from CTD-ILD and IPF Core Sets
Body Structure	Relates to involvement of anatomical structures	HRCT	1	s4301, Structure of lungs
Body Function	include physical, mental and emotional functions	D-12, DLCO, FVC, LCQ, MRC-DS, SF-36, SGRQ, UCSD-SOBQ	17	b1300, Energy level b134, Sleep functions b4402, Depth of respiration b455, Exercise tolerance b28011, Pain in chest
Activities and Participation	Execution of task or action; involvement in a life situation	D-12, LCQ, MRC-DS, SF-36, SGRQ, UCSD-SOBQ	56	d330, Speaking d430, Lifting, carrying objects, d4600, Moving around house d510, Washing oneself d8451, Maintaining a job
Environmental Factors	Positive (e.g. family, medications, assistive devices, oxygen, lifts) or Negative (e.g. stairs, lack of income, cold climate, distance from services) influences on performance.	LCQ, SGRQ	8	e260, Air quality e460, Societal attitudes e2100, Land forms, such as mountains, hills, valleys and plains.
Total			82	

Conclusion: This is the first effort to map CTD-ILD and IPF outcome measures to the ICF. A composite of these ICF linkages will be available to clinicians and researchers with validation studies to follow. ICF Core Sets are intended to be stream-lined disease-specific languages that support global, regional and personal health-related parity across cultures, age and socioeconomic status. ICF Core Sets enable fair assessment that may be utilized in policy making and service provision and funding. Familiarity with ICF Core Sets in CTD-ILD and IPF will enable clinicians to experience a smoother transition to ICD-11 which is under development and will meld diagnostic coding with the ICF.

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Prediction and Impact of Attacks of Raynaud's Phenomenon, As Judged By Patient perception. Michael Hughes[1], Amir Snapir[2], Jack Wilkinson[3], Daniel Snapir[2], Fredrick M. Wigley[4] and Ariane Herrick[1]. [1]The University of Manchester, Manchester, United Kingdom, [2]Orion Corporation Orion Pharma, Turku, Finland, [3]Salford Royal NHS Foundation Trust, Salford, United Kingdom, [4]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Our aim was to evaluate (a) whether subjects with Raynaud's phenomenon (RP) can predict RP attacks because if so, then this could have implications for new treatment approaches and (b) the impact of RP attacks on quality of life (QOL).

Methods: Subjects with RP were approached through international patient associations to participate in an online survey. The survey comprised 19 questions including demographic information and details of the RP. Subjects were asked to report their ability to predict (all on an ordinal scale) the occurrence of RP attacks (<20%, 21%–50%, 51%–70% and >70% of times), severity of attacks (very poorly, poorly, fairly well, well, and very well), and their ability to prevent/control RP attacks (very poor, poorly, fairly well, well and very well). Other questions related to medications, how well subjects felt they could control their RP, and the impact of RP on QOL.

Results: A total of 443 responses from subjects with self-reported RP (mean age 41 years, 91% female), from 15 countries were evaluable. 187 subjects (43%) had primary RP (PRP, as judged by self-report), 149 (34%) secondary RP (SRP) and 100 (23%) were not aware of the cause of their RP. 252 (58%) of subjects reported that they could predict at least 51% of RP attacks (66% of subjects with SRP vs. 56% PRP, p=0.03). 248 (57%) subjects reported that they could predict attack severity either 'fairly well' or better (64% of subjects with SRP vs. 58% PRP, p=0.16), with 43% predicting severity only poorly (30%) or very poorly (13%).

64% of all subjects reported either a 'poor' or 'very poor' ability to prevent or control RP attacks. 182 subjects (41%) reported current or previous use of medications for RP: 82% reported at least one currently used medication being tolerated, but only 16% at least one current medication being 'effective'.

Most subjects (78%) reported making at least one life adjustment due to RP, more so in subjects with SRP compared with PRP (87% vs.71%, [P=0.001]). Patients reported the impact of their RP on QOL on a 0–10 scale, where 10 was the best imaginable: the mean QOL for all patients was 6.0 (SD 2.1 [range = 1–10]). PRP subjects' current QOL was higher than SRP subjects (mean QOL 6.5 and 5.2 respectively, difference in means (95% CI): 1.21 (0.76 to 1.66) [P < 0.001]). When asked to imagine their QOL without RP, SRP subjects imagined a greater absolute improvement from their current QOL (2.3 vs. 3.3, difference in means −0.9 (−1.4 to −0.4) [P=0.0002]).

Conclusion: 1. Subjects ability to predict both the occurrence and severity of RP attacks is limited (almost half of patients could predict neither attacks nor their severity), and this must be taken into account when designing clinical trials of future novel, 'PRN' (as required) treatments.

2. Only 16% of subjects currently on medication for RP reported that at least one current medication was 'effective', and most subjects reported a poor ability to prevent/control RP attacks, confirming an unmet need to develop new treatments.

3. RP significantly impacts on QOL, especially in subjects with SRP but also in PRP.

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A Dilated Esophagus Is an Independent Risk Factor for Interstitial Lung Disease in SSc. Carrie Richardson[1], Rishi Agrawal[2], Jungwha Lee[2], Orit Almagor[3], John Varga[2], Rowland W. Chang[2] and Monique E. Hinchcliff[4]. [1]McGaw Medical Center of Northwestern University, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Northwestern University, Chicago, IL, [4]Northwestern University, Feinberg School of Medicine, Chicago, IL.

Background/Purpose: High-resolution computed tomography of the chest (HRCT) performed for assessment of interstitial lung disease (ILD) in patients with systemic sclerosis (SSc) frequently reveals a patulous esophagus, but the significance is unclear. Assuming that the risk of aspiration is directly related to the magnitude of esophageal dilatation, we hypothesized that a greater HRCT esophageal diameter is associated with worse pulmonary outcomes, as measured by severity of ILD on HRCT and pulmonary function tests (PFT).

Methods: A cross-sectional study of Northwestern Scleroderma Registry patients with HRCT was conducted. Subjects met the ACR 1980 SSc or three out of five CREST (**C**alcinosis cutis, **R**aynaud phenomenon, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasias) criteria. The esophageal diameter was measured at three levels: above the aortic arch, between the aortic arch and the right inferior pulmonary vein, and between the right inferior pulmonary vein and the diaphragmatic hiatus. Widest esophageal diameter (WED) was used as the predictor variable. A modified Likert scale (0= none, 1= <5%, 2= 6–25%, 3 for 26–50%, 4=51–75%, 5= >75%) was used to score fibrosis and ground glass opacities. Total ILD (outcome variable) was calculated as the sum of fibrosis and ground glass scores. Secondary outcomes were PFT including total lung capacity (TLC), forced vital capacity (FVC) and diffusing capacity for carbon monoxide adjusted for hemoglobin % predicted (DLCO). Standardized regression coefficients (β) between WED and the outcome variables were calculated adjusting for age, sex, ethnicity, disease subtype (limited or diffuse cutaneous SSc), disease duration (years since first non-Raynaud symptom), proton pump inhibitor use, C-reactive protein and modified Rodnan skin score.

Results: Three hundred eleven subjects had HRCT. Eight subjects without available HRCT images and one subject who had undergone esophagectomy were excluded. Twenty-eight patients who had mixed connective tissue disease, SSc sine scleroderma, or overlap syndromes were excluded, leaving 275 subjects for analysis. Adjusted standardized regressions demonstrated positive associations between WED and total ILD score (β=0.33, p<0.0001), fibrosis (β=0.32, p<0.0001), and ground glass opacities (β=0.28, p<0.0001) (Table). There were negative associations between WED and TLC % predicted (β=−0.24,p=0.0002), FVC % predicted (β=−0.23, p=0.0004), and adjusted DLCO % predicted (β=−0.23; p=0.005).

Conclusion: Increasing esophageal diameter on HRCT in patients with SSc is associated with more severe radiographic ILD, lower lung volumes, and lower DLCO % predicted. Longitudinal studies should be done to elucidate the temporal relationship between esophageal disease and ILD in persons with SSc. Future trials of aggressive management of esophageal disease to prevent ILD may be warranted in persons with SSc.

Table Association between widest esophageal diameter and HRCT findings and pulmonary function test parameters

	Widest esophageal diameter (WED)			
Variables	**Unadjusted β coefficient (SE)**	**p value**	***Adjusted β coefficient (SE)**	**p-value**
Total ILD score	0.36 (0.07)	<0.0001	0.33 (0.08)	<0.0001
Total fibrosis score	0.32 (0.04)	<0.0001	0.32 (0.04)	<0.0001
Total ground glass score	0.32 (0.04)	<0.0001	0.28 (0.04)	<0.0001
TLC, % predicted	−0.34 (0.12)	<0.0001	−0.24 (0.13)	0.0002
FVC, % predicted	−0.31 (0.12)	<0.0001	−0.23 (0.13)	0.0004
Adjusted DLCO, % predicted	−0.29 (0.14)	<0.0001	−0.23 (0.17)	0.0005

ILD=interstitial lung disease, TLC=total lung capacity, FVC=forced vital capacity, DLCO=diffusion capacity for carbon monoxide.
*Adjusted for age, sex, disease subtype, ethnicity, proton pump inhibitor use, disease duration, C-reactive protein, and modified Rodnan skin score.

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Prediction of Cardiac and Vascular Events in Systemic Sclerosis: Input from Endothelin-1 Type a Receptor Antibodies. Jerome Avouac[1], Gabriela Riemekasten[2], Christophe Meune[3], Barbara Ruiz[4] and Yannick Allanore[1]. [1]Paris Descartes University, Rheumatology A Department and INSERM U1016, Cochin Hospital, Paris, France, [2]Charité University Hospital and German Rheumatism Research Centre, a Leibniz Institute, Berlin, Germany, [3]Paris 13 University, University Hospital of Paris-Seine-Saint-Denis, Cardiology Department, Bobigny, France, [4]Paris Descartes University, INSERM U1016, Institut Cochin, Sorbonne Paris Cité, Paris, France.

Background/Purpose: Cardiac and peripheral microvascular alterations are key features of systemic sclerosis (SSc). We have previously reported that angiogenic markers can predict the cardiovascular outcomes in SSc (1). In parallel, a cross-sectional study reported an association between severe cardiovascular complications and functional antibodies against angiotensin II type 1 receptor (AT_1R) and Endothelin-1 type A receptor (ET_AR) (2). Therefore, our aim was to investigate the respective merit of all these markers in a prospective cohort.

Methods: serum levels of anti-AT_1R and anti-ET_AR autoantibodies, placenta growth factor (PlGF) and soluble vascular adhesion molecule (sVCAM) were measured with sandwich ELISA in a prospective cohort of 75 SSc patients. Circulating endothelial progenitor cells (EPCs) were quantified in peripheral blood by flow cytometry after cell sorting. The occurrence of at least one cardiac/vascular event was assessed during a planed 3-year follow-up by a composite index defined by the occurrence of at least one of the following event: a) one or more new ischemic digital ulcer (DU), b) pre-capillary pulmonary hypertension (PH) confirmed by right heart catheterization, c) left ventricular (LV) dysfunction, defined by a LV ejection fraction (EF)<50%, d) scleroderma renal crisis (SRC) (1).

Results: The mean age of SSc patients (64 women) was 55±12 year old and the mean disease duration was 9±8 years at baseline. Twenty-eight patients developed at least one cardiac/vascular event (DU in 18, PH in 5, LV dysfunction in 4 and SRC in a single patient). By univariate analysis, high baseline serum levels of anti-ET_AR were predictive of the occurrence of cardiac/vascular events (p=0.002), together with low EPC counts (p=0.003) and increased levels of PlGF (p=0.0005) and sVCAM (p=0.009). No predictive value of anti-AT_1R antibodies was identified. Multivariate analysis confirmed high serum levels of anti-ET_AR antibodies (hazard ratio, HR: 3.71, 95%CI 1.44–9.52, p=0.03) and PlGF (HR: 5.22, 95%CI 1.96–15.87) as independent predictors of further development of cardiac/vascular events. The combination of high serum levels of anti-ET_AR antibodies and PlGF was highly predictive of cardiac and vascular events occurrence during follow-up (HR 7.27 95%CI 2.49–23.51, P=0.0002).

Conclusion: This study identifies for the first time anti-ET_AR antibodies as an independent predictor of cardiac and vascular events in SSc. This

functional antibody, together with other angiogenic markers and in particular PlGF, may serve as biomarkers to improve cardiovascular risk stratification and therefore allow earlier therapeutic intervention.

Reference:
(1) Avouac et al, Ann Rheum Dis 2012; (2) Riemekasten et al, Ann Rheum Dis 2011

Disclosure: J. Avouac, None; **G. Riemekasten**, None; **C. Meune**, None; **B. Ruiz**, None; **Y. Allanore**, None.

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Performance of the Old ACR and the New ACR-EULAR Systemic Sclerosis Classification Criteria in Patients with Limited Cutaneous Disease: Effect on the Ascertainment of Severe Pulmonary Arterial Hypertension. Beatriz E. Joven[1], M Jesus Garcia de Yebenes[2], Pilar Escribano[3], Estibaliz Loza[4], M Jose Ruiz-Cano[3], Carmen Jimenez Lopez-Guarch[3], Loreto Carmona[5] and Patricia E. Carreira[1]. [1]Rheumatology Department. Hospital Universitario 12 de Octubre, Madrid, Spain, [2]Instituto de Salud Musculoesqueletica, Madrid, Spain, [3]Multidisciplinary Pulmonary Hypertension Unit. Hospital Universitario 12 de Octubre, Madrid, Spain, [4]Institu, Madrid, Spain, [5]Instituto de Salud Musculoesquelética, Madrid, Spain.

Background/Purpose: To analyze the performance of the old ACR1980 and the new ACR-EULAR2013 classification criteria for systemic sclerosis (SSc) in patients with limited disease in clinical practice, and to compare the characteristics of patients with severe pulmonary arterial hypertension (PAH) who fulfilled or did not fulfill the 1980 criteria.

Methods: All patients with clinical diagnosis of limited cutaneous SSc followed in a single center from Jan1990 to May2014 were included. Descriptive analysis and comparisons between groups, according to their performance in new and old criteria, were carried out by parametric or non parametric tests based on the distribution of the variables.

Results: From 321 patients, 202 (63%) fulfilled the 1980 and 297 (93%) fulfilled the 2013 criteria. Compared to those fulfilling 2013 criteria only, patients fulfilling 1980 criteria also were younger at diagnosis (48 vs 52 y), presented higher mRSS (8.5 vs 2.7) and had significantly more aScl70, esophagic involvement, lung fibrosis, ischaemic lesions, calcinosis and telangiectasia. In contrast, patients not fulfilling 1980 criteria had more ACA (61 vs 44%) and severe PAH (17 vs 9%) (Table 1).

Within the group of patients with severe PAH (n=38), all fulfilled the 2013 but only 18 (47%) fulfilled the 1980 criteria. Clinical characteristics between those who fulfilled and did not fulfill 1980 criteria were similar, except for higher frequency of calcinosis (85 vs 22%) and ischaemic lesions (83% vs 0%) in the former group. In hemodynamics, patients not fulfilling 1980 criteria had higher pulmonary vascular resistance (16 vs 7) and lower cardiac index (2.2 vs 3.2). Mortality was high in both groups (72 vs 65%)(Table 2).

Conclusion: The new SSc ACR-EULAR2013 criteria perform better than the old ACR1980 criteria in clinical practice. Patients with mild symptoms, not fulfilling 1980 criteria, are at higher risk of developing severe PAH, with increased mortality. Our study points out: 1) the need to apply the new criteria to all patients with SSc suspicion; and 2) since SSc-PAH has better prognosis if treated early, all SSc patients, even with very mild disease, should be screened to diagnose PAH as early as possible.

Table 1 Characteristics of the limited cutaneous SSc patients according to the fulfillment of the ACR1980 criteria

Variable	Total (n = 321)	Not fulfilling ACR1980 (n = 119)	Fulfilling ACR1980 (n = 202)	p value*
Quantitative variables, mean (SD)				
Age at diagnosis (yr) (n = 321)	49.3 (16.4)	52.0 (16.7)	47.8 (16.0)	0.026
Maximum mRSS (n = 314)	6.4 (5.7)	2.7 (1.6)	8.5 (6.2)	<0.0001
Cualitative variables, n (%)				
Sex (women) (n = 321)	287 (89.4)	110 (92.4)	177 (87.6)	0.176
Antibodies				
Scl-70 (n = 315)	51 (16.2)	10 (8.5)	41 (20.8)	0.004
ACA (n = 314)	159 (50.6)	72 (61.0)	87 (44.4)	0.004
Esophagic involvement (n = 321)	213 (66.4)	66 (55.5)	147 (72.8)	0.002
Lung fibrosis (n = 320)	59 (18.4)	2 (1.7)	57 (28.4)	<0.0001
PAH (confirmed by RHC) (n = 321)	38 (11.8)	20 (16.8)	18 (8.9)	0.034
LV Systolic dysfunction (n = 306)	24 (7.8)	8 (7.3)	16 (8.1)	0.807
Renal (n = 321)	13 (4.0)	2 (1.7)	11 (5.4)	0.098
Myositis (n = 321)	30 (9.3)	7 (5.9)	23 (11.4)	0.102
Joint involvement (n = 321)	149 (46.4)	52 (43.7)	97 (48.0)	0.453
Ischaemic lesions (n = 321)	126 (39.2)	3 (2.5)	123 (60.9)	<0.0001
Calcinosis (n = 250)	58 (23.2)	11 (11.5)	47 (30.5)	0.001
Telangiectasia (n = 293)	151 (51.5)	43 (40.2)	108 (58.1)	0.003
Capillaroscopic changes (n = 267)	220 (82.4)	80 (76.9)	140 (85.9)	0.061

mRSS = modified Rodnan Skin Score; PAH: pulmonary arterial hypertension; RHC: right heart catheterization; LV: left ventriculus

Table 2 Clinical and hemodynamic characteristics of limited cutaneous SSc patients with severe pulmonary hypertension by their fulfillment of 1980 ACR criteria

Variable	Severe PAH (n = 38)	Not fulfilling ACR1980 (n = 20)	Fulfilling ACR1980 (n = 18)	p value*
Quantitative variables, mean (SD)				
Mean PAP, mmHg (n = 32)	54.6 (10.5)	57.4 (11.9)	51.5 (47.2)	0.112
Pulmonary wedge pressure, mmHg (n = 32)	9.5 (8.2)	9.3 (7.4)	9.6 (7.9)	0.850
PVR, Woods Units (n = 29)	12.9 (10.4)	15.7 (11.9)	9.6 (7.0)	0.027
Cardiac output (L/min)	4.3 (1.7)	3.7 (1.5)	4.9 (1.9)	0.078
Cardiac index (L/min/m^2)	2.6 (1.1)	2.2 (0.8)	3.2 (1.3)	0.029
Cualitative variables, n (%)				
ACA + (n = 36)	26 (72.2)	13 (68.4)	13 (76.5)	0.590
Hand edema (n = 38)	17 (44.7)	10 (50.0)	7 (38.9)	0.492
Ischaemic lesions (n = 38)	15 (39.5)	–	15 (83.3)	<0.0001
Sclerodactily (n = 38)	36 (96.7)	18 (90.0)	18 (100)	0.168
Raynaud's phenomenon (n = 38)	38 (100)	20 (100)	18 (100)	–
Capillaroscopic changes (n = 30)	29 (96.7)	18 (94.7)	11 (100)	0.439
Calcinosis (n = 31)	15 (48.4)	4 (22.2)	11 (84.6)	0.001
Telangiectasia (n = 38)	33 (86.8)	16 (80.0)	17 (94.4)	0.188
Esophagic involvement (n = 38)	25 (65.8)	11 (55.0)	14 (77.8)	0.139
Joint involvement (n = 38)	7 (18.4)	3 (15.0)	4 (22.2)	0.566
Death (June 2014) (n = 38)	26 (68.4)	13 (65.0)	13 (72.2)	0.632

PAP = pulmonary artery pressure; PVR = Pulmonary vascular resistance; PAH = Pulmonary artery hypertension

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Predictors of Inpatient Mortality in Patients with Systemic Sclerosis: A Case Control Study. Shiv Tej Sehra[1], Chris T. Derk[1], Andrew Kelly[2] and Joshua Baker[3]. [1]University of Pennsylvania, Philadelphia, PA, [2]Pennsylvania Hospital, Philadelphia, PA, [3]University of Pennsylvania and Philadelphia VAMC, Philadelphia, PA.

Background/Purpose: There are few published studies on predictors of inpatient mortality in patients with systemic sclerosis (SSc). Knowledge of these predictors is important for early identification of patients at high-risk of inpatient death and recognition of potential modifiable factors. Currently available data are mostly from large databases which lack a granular view. The aim of this study was to define factors associated with inpatient mortality in SSc.

Methods: All admissions coded for SSc (ICD-9 710.1) at the Hospital of University of Pennsylvania, between Jan 1, 2001 and Dec 31, 2011 were reviewed. The diagnosis of SSc was confirmed, and deaths were identified by chart review. For each death, an age (±5 years), sex and gender matched control with SSc (who did not die during their hospitalization) was identified. We hypothesized group differences in SSc characteristics, non–SSc comorbidities and admission labs (as summarized in Table 1). Group differences were analyzed using Student's t-test (and non parametric equivalents) as well as Chi^{2}tests for dichotomous variables. Exposures associated with death in univariate analyses were used to form a final parsimonious multivariable logistic regression model.

Results: A total of 593 admissions and 30 deaths were identified. Data was not available on 1 death. A significant difference in non–SSc lung disease ($p = 0.031$), aspiration events ($p < 0.001$), WBC count ($p = 0.048$), Blood Urea Nitrogen (BUN) ($p < 0.001$) and hemoglobin (Hb) ($p = 0.025$) was noted between subjects that died compared to matched controls. Odds of death were higher in patients with a higher BUN (OR = 1.06, CI = 1.02–1.11), non–SSc lung disease (OR = 3.87, CI = 1.26–11.88) and

aspiration events (OR = 30, CI = 3.58–250.80), and lower in patients with a higher Hb (OR = 0.73, CI = 0.54–0.97). High BUN, a history of aspiration events and low Hb were found to be independently associated with mortality.

Conclusion: A high BUN on admission, low Hb, non–SSc Lung disease, and aspiration events are associated with higher in–hospital mortality in patients with SSc. The odds of dying in the hospital were 30 times in patients who aspirated. Therefore, stringent measures should be taken to prevent aspiration in these patients. Also, further study is needed to identify factors that predispose to acute aspiration events.

Table 1

Parameter	Death	Control	p–value
Transfer	6 of 29	8 of 19	0.76
Raynaud's Phenomenon	22 of 23	22 of 23	1
Digital Ulcers	2 of 22	2 of 22	1
SSc – ILD	12 of 28	8 of 28	0.403
Pulmonary Artery HTN	16 of 22	14 of 22	0.747
SSc Reflux	22 of 25	22 of 25	1
Bacterial Overgrowth	2 of 19	3 of 19	1
SSc Renal Crisis	3 of 25	0 of 25	0.235
SSc – MSK	2 of 23	4 of 23	0.665
SSc – Cardiac	4 of 25	3 of 25	1
Coronary Artery Disease	19 of 27	13 of 27	0.176
Arrhythmia	13 of 27	9 of 27	0.277
Hypertension	23 of 29	18 of 29	0.370
Coronary Artery Disease	12 of 22	9 of 22	0.547
Chronic Renal Failure	9 of 29	4 of 29	0.207
Liver Disease	4 of 29	1 of 29	0.352
Diabetes Mellitus	7 of 29	2 of 29	0.144
Non SSc Lung Disease	**16 of 29**	**7 of 29**	**0.031**
Any Cause Lung Disease	18 of 29	14 of 29	0.429
Aspiration Events	**15 of 29**	**1 of 29**	**<0.001**
Parameter	**Mean (SD)**	**Mean (SD)**	**p–value**
Hemoglobin	10.46 (1.72)	11.71 (2.31)	**0.025**
Hematocrit	31.89 (4.93)	35.43 (6.23)	**0.022**
WBC	12.98 (11.1)	8.5 (3.67)	**0.048**
BUN	37.23 (21.84)	19.77 (10.92)	
Creatinine	1.39 (0.71)	1.07 (0.78)	0.133
Sodium	137.86 (4.98)	138.25 (3.79)	0.741
Potassium	4.11 (0.69)	4.16 (0.66)	0.788
Platelets	256.36 (125.71)	228.75 (70.34)	0.315

Table 2

	Univariate Logistic Regression	
Parameter	**Odds Ratio (95% CI)**	**p–value**
Hemoglobin	**0.73** (0.54–0.97)	**0.032**
BUN	**1.06** (1.02–1.11)	**0.004**
Aspiration	**30** (3.58–250.80)	**0.002**
Other Pulmonary	**3.87** (1.26–11.88)	**0.018**
WBC	1.11 (0.99–1.25)	0.066
	Multivariate Logistic Regression	
Parameter	**Odds Ratio (95% CI)**	**p–value**
BUN	**1.09** (1.02–1.17)	**0.007**
Hemoglobin	**0.63** (0.43–0.93)	**0.021**
Aspiration	**41.05** (3.62–464.91)	**0.003**

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Impact of Geographic Variation on the Risk of Digital Ulcers Development in Systemic Sclerosis: A Brazilian Multicenter Registry. Eduardo José do Rosário e Souza[1], Carolina de Souza Muller[2], Andrea Tavares Dantas[3], Henrique A. Mariz[3], Alex Magno Coelho Horimoto[4], Renato Alvarenga Rezende[1], Isabela Guimarães[2], Izaias Pereira da Costa[4], Glauce Rejane Leonardi Bertazzi[5], Luiza Paiola[5], Eutília Andrade Medeiros Freire[6], Roberta Ismael[6], Ana Paula Toledo Del-Rio[7], Juliana Sekiyama[7], Carolina Barros Kahwage[8] and Cristiane Kayser[8]. [1]Hospital Santa Casa, Minas Gerais, Belo Horizonte, Brazil, [2]Universidade Federal do Paraná, Curitiba, Brazil, [3]Hospital das Clínicas - Universidade Federal de Pernambuco, Recife, Brazil, [4]Universidade Federal do Mato Grosso do Sul, Campo Grande, Brazil, [5]Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, Brazil, [6]Universidade Federal da Paraíba, João Pessoa, Brazil, [7]Universidade Estadual de Campinas, Campinas, Brazil, [8]Universidade Federal de São Paulo, São Paulo, Brazil.

Background/Purpose: Digital ulcers (DU) and Raynaud's phenomenon (RP) are a frequent complication in patients with Systemic Sclerosis (SSc). The present study aimed to evaluate the frequency and severity of RP and DU in patients with SSc in four distinct geographic regions of Brazil in order to evaluate the influence of geographic variation on the risk of DU development.

Methods: One hundred and forty-one patients with SSc according to the ACR/EULAR classification criteria of 2013, from centers located in four regions of Brazil (Northeast, Midwest, Southeast and South), were evaluated from January to March 2012. Demographic, clinical, and nailfold capillaroscopy data were collected. The daily mean temperature and the mean temperature in the week before evaluation were also recorded. In order to evaluate a possible association between DUs and climate, the group of patients from the South region (Subtropical climate zone, with lower temperatures), was compared to those from the other regions (Tropical climate zone). Comparisons between groups were made using t-test or chi-square test. Simple and multiple logistic regression models were applied to determine the association between DUs and clinical and demographic variables.

Results: A total of 43 active DUs were observed in 23 (16%) of the 141 patients included. Eighty-six percent were women, with a mean age of 47.8 years, a mean duration of RP of 10.1 years and a mean duration of disease of 5.8 years. Forty-three percent had limited cutaneous SSc, 61.7% had digital pitting scars and 12.1% had a previous history of gangrene or amputation. Twenty-six (18.4%) patients were from the Subtropical climate zone and 115 (81.6%) from the Tropical climate zone, with no difference on age, gender, RP and disease duration between groups. By simple logistic regression model, the presence of DU was associated with a higher modified Rodnan skin score (P=0.023), presence of necrosis or amputation (P=0.008), presence of flexion contracture of the fingers (P=0.002), active smoking (P=0.038), higher avascular score on nailfold capillaroscopy (P=0.019), higher severity of RP in the last week (P=0.007), a higher sHAQ score (P=0.001), and with the Subtropical climate zone patient group (P=0.011). The presence of DU was not significantly associated with the mean daily temperature or the temperature in the week before the evaluation. Using multiple logistic regression model including the significant associations observed in univariate analysis, presence of DU was significantly associated with patients living in the Subtropical climate zone (odds ratio [OR]=3.5, 95% confidence interval [95%CI]=1.10–11.28, P=0.034), with a previous history of necrosis or amputation (OR=4.7, 95%CI=1.20–19.10, P=0.026) and with a higher sHAQ (OR=4.7, 95%CI=1.81–12.5, P=0.002).

Conclusion: This was the first study to evaluate the influence of temperature and geographic variation on DU prevalence in SSc patients. In this multicenter study in a continental country with different climates, patients with SSc living in a colder region (Subtropical climate zone) have a 3.5 times higher risk of developing DU than those patients living in a warmer region (Tropical zone).

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Lower Socioeconomic Status, Male Gender and Diffuse Scleroderma Are Associated with Worse Survival in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Cohort. Jessica K. Gordon[1], Wei Zhang[1], Lorinda Chung[2], Yan Ma[1], Virginia D. Steen[3] and PHAROS Investigators. [1]Hospital for Special Surgery, New York, NY, [2]Stanford University School of Medicine, Palo Alto, CA, [3]Georgetown University Medical Center, Washington, DC.

Background/Purpose: Lower socioeconomic status (SES) and male gender have been associated with worse survival in idiopathic pulmonary arterial hypertension (PAH). Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) is a multicenter, prospective registry of systemic sclerosis (SSc) patients with pulmonary hypertension (PH) or at high risk for the development of PH. In this study we examined whether survival in patients with SSc-PH varied with gender, SES, or race.

Methods: 276 patients with SSc and newly diagnosed PH were enrolled in the PHAROS registry between 2006 and 2014. We used level of education and employment status as surrogates for SES, although more than half of our

patients were retired or medically disabled at the time of PH diagnosis. For employment status we analyzed working versus all other. For level of education, we analyzed 12th grade or less versus some college or more. Statistical analysis was performed using chi-square, univariate and multivariate Cox proportional hazard models.

Results: Baseline characteristics of the patients are described in Table 1. The following variables were examined as prognostic factors for survival: age, scleroderma subtype, disease duration, World Health Organization (WHO) PH Group classification, baseline mean pulmonary artery pressure (mPAP), gender, level of education, and employment status. The univariate and multivariate Cox Proportional Hazard Models are reported in Table 2. Male gender, diffuse subtype, and unemployment were associated with an increased risk of death. WHO group was not a significant predictor. Race was not found to be a significant prognostic factor. Lower level of education was a significant prognostic factor when evaluating the entire group; however, if the analysis is limited to WHO Group 1 PH subtype only, then lower level of education is associated with an increased risk of death with HR 2.1 (95% CI 1.2, 3.6), $p<0.01$ when corrected for age, SSc subtype and mPAP.

Conclusion: Male gender, lower SES, and diffuse SSc are associated with a higher risk of death in the PHAROS cohort. Lower level of education was a risk factor for death only in WHO Group 1 (PAH). Worse survival in males is seen also in idiopathic PAH despite the fact that PAH is more prevalent in females, and the explanation for this is a topic for additional study. Addressing health disparities associated with lower SES may improve the outcomes of patients with SSc-PH.

Table 1 Patient Characteristics

Age-mean ± S.D.	58.4 ± 11.0
Gender-(n=275)	
Male-n (%)	52 (18.9)
Female-n (%)	223 (81.1)
Scleroderma Subtype-(n = 276)	
Diffuse-n (%)	90 (32.6)
Limited-n (%)	171 (61.9)
Duration of Disease from first non RP symptom mean ± S.D.	7.6 ± 8.2
Race (n = 274)	
Caucasian-n (%)	201 (73.4)
African-American-n (%)	45 (16.4)
Other-n (%)	28 (10.2)
Education Status-Â (n = 239)	
8th grade or less-n (%)	13 (5.4)
12th grade-n (%)	78 (32.6)
Associate, technical or some college-n (%)	63 (26.3)
College degree-n (%)	50 (20.9)
Post-graduate degree-n (%)	35 (14.6)
Employment Status-(n=218)	
Working-n (%)	69 (31.7)
Homemaker-n (%)	13 (6.0)
Student-n (%)	1 (0.5)
Medically disabled-n (%)	55 (25.2)
Retired-n (%)	72 (33.0)
Unemployed-n (%)	8 (3.7)
WHO Group-(n = 276)	
1-PAH-n (%)	181 (65.6)
2-PVH-n (%)	49 (17.8)
3-PH-ILD-n (%)	46 (16.7)
Mean Pulmonary Artery Pressure at Baseline-mean ± S.D.	36.2 ± 10.2

Table 2

Factors	HR	95% CI	p-value
Univariate Analyses			
Male Gender	1.948	1.152, 3.292	0.0128
Not working	3.895	1.92, 7.902	<0.001
Education	0.65	0.4, 1.063	0.0863
Education (WHO1 only)	2.09	1.199, 3.641	<0.01
Diffuse scleroderma	1.648	1.017, 2.671	0.043
African American Race	0.925	0.456, 1.877	0.83
Mean PAP	1.044	1.026, 1.062	<0.0001
Multivariate Analyses			
Age	1.004	0.982, 1.027	.07275
Mean PAP	1.044	1.023, 1.064	<0.0001
Male Gender	2.348	1.368, 4.029	.002
Diffuse SSc	2.034	1.202, 3.442	0.0016
Not working	2.835	1.484, 5.415	0.0016

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Sarcopenia in Systemic Sclerosis: Prevalence and Association with Functional Parameters and Quality of Life. Elise Siegert[1], Kristina Norman[2], Emilie Preis[2], Alexander Makowka[2], Gerd Burmester[2] and Gabriela Riemekasten[1]. [1]Charité – University Hospital, Berlin, Germany, [2]Charité – University Medicine Berlin, Berlin, Germany.

Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune disease that characterized by endothelial dysfunction, inflammation and fibrosis. It is associated with high mortality and physical impairment. We assessed the prevalence of sarcopenia in SSc patients and correlated sarcopenia with muscle strength and quality of life, also taking other clinical parameters into account.

Methods: Patients meeting the ACR/EULAR 2013 criteria for SSc were included in this study. Body composition was assessed using bioelectrical impedance analysis. Fat free mass (FFM) was estimated using the equation of Kyle and was normalized to patients' height using the square of body size (FFM/m^2 = FFMI). Sarcopenia was defined as a FFMI value below 17.4 kg/m^2 for men and < 15 kg/m^2 for women. Maximal grip strength was measured using the Jamar Dynamometer, maximal knee extension strength using the Digimax and expiratory peak flow using a peak flow meter. Quality of life was assessed using the SF-36®, while C-reactive protein (CRP), hemoglobin (Hb) and other clinical parameters were quantified by routine laboratory testing or by history taking.

Results: 111 patients were included in this study (101 women and 10 men; age 59.7 ± 13.8 years, BMI 24.5 ± 5 kg/m^2). 53 (47.7%) patients were diagnosed with sarcopenia. Patients with sarcopenia differed significantly from patients without sacropenia with respect to maximal grip strength, knee extension strength, peak flow and CRP. They did not differ in age and select clinical parameters such as gastrointestinal involvement, total number of organs involved, number of comorbidities and number of medical therapies. Absolute FFM correlated significantly with maximal grip, knee extension strength and peak flow ($r = .64$, $r = .366$ and $r = .48$, respectively, $p < 0.0001$). With respect to quality of life there was no significant difference between patients with and those without sarcopenia.

	sarcopenia	no sarcopenia	p-value
sex (m/f)	3/50	7/52	n.s.
age (years)	59.5 ± 15.7	59.9 ± 11.8	n.s.
BMI (kg/m^2)	21.4 ± 2.2	27.3 ± 5.4	.00000000002
anti-Centromer	10	22	.03
anti-Scl-70	21	15	n.s.
mod. Rodnan Skin Score	6.6 ± 7.3	9.8 ± 9.7	.05
hand grip (kg)	13.5 ± 6.6	19.0 ± 8.4	.0003
knee extension (kg)	19.3 ± 14.9	26.4 ± 22.9	.05
peak flow (l/min)	321.0 ± 85.0	360.9 ± 113.2	.05
CRP (mg/l)	6.9 ± 11.7	2.5 ± 2.9	.01
Hb (g/dl)	12.2 ± 1.6	13.2 ± 1.5	.003

Conclusion: There was a high prevalence of sarcopenia among SSc patients in our study. Sarcopenia was associated with an impairment of muscle strength, low hemoglobin and high inflammatory activity.

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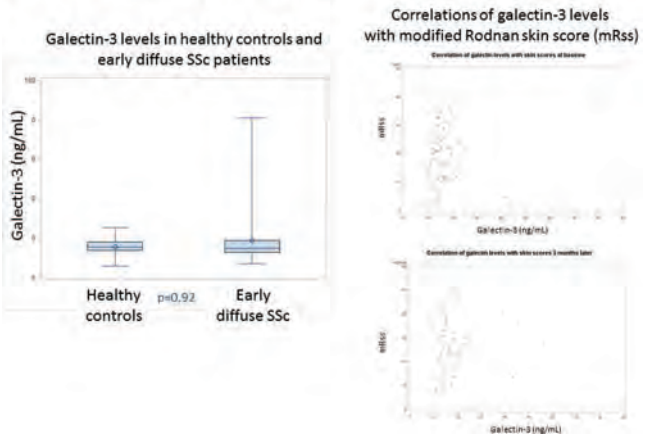
Serum Galectin-3 Levels in Early Diffuse Systemic Sclerosis and the Relationship to Skin Score and Skin Score Change. Siamak Moghadam-Kia, Thomas A. Medsger Jr. and Robyn T. Domsic. University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Galectin-3 is a β-galactoside-binding animal lectin which is associated with inflammation, angiogenesis and fibrosis. Galectin-3 is upregulated in hepatic fibrosis, idiopathic pulmonary fibrosis and in the myocardium of heart failure patients. In heart failure it is a useful biomarker to predict mortality. In systemic sclerosis (SSc), one report (Koca

2013) suggests higher levels compared to healthy controls (HC). In a second study (Taniguchi 2012) suggested down-regulation in diffuse SSc and on subset analysis, the 6 early diffuse SSc patients had the greatest reduction in galectin-3 levels. They also reported a modest correlation between galectin-3 ($r=0.45$) and skin score. The objective of this study was to assess galectin-3 levels in very early diffuse SSc patients and the relationship to skin score and skin score change.

Methods: We identified patients with very early diffuse SSc who were seen for the first time in a dedicated Scleroderma Center between 1990 and 2010 and met the following criteria: (1) seen within 9 months of the first SSc symptom, (2) skin thickening proximal to the elbows and knees (or skin thickening with tendon friction rubs) and (3) had clinical follow-up with repeat skin scores at either 3 months, 6 month or both. HC were also identified. All SSc and HC first visit serum samples underwent ELISA testing (BGMedicine, Waltham, MA). Differences in galectin-3 levels between SSc and HC were assessed by nonparametric tests. Correlations with skin score at first visit, skin thickness progression rate (STPR) and absolute change in skin score at 3 and 6 months were assessed.

Figure 1: Summary of Galectin-3 levels in early diffuse SSc



Results: We identified 114 SSc patients who met all inclusion criteria. Of these, 94 had available samples taken at the same time as the initial skin assessment. The 37 HC were collected on the same day. All SSc patients and HC were Caucasian and 70% female. Mean age was 51 in SSc and 47 in the HC. Of the SSc patients, 50 had f/u at both 3 and 6 months, 20 at 3 months only and 22 at 6 months only. There was no significant difference in serum galectin-3 level between SSc patients and HC ($p= 0.92$), as shown in Figure 1. Baseline serum galectin-3 levels were not correlated with the skin scores taken at the same time ($p=0.29$) or STPR ($p=0.71$). Skin scores at 3 or 6 months follow-up also showed no correlation ($p=0.43$ and 0.76, respectively). There was a weak correlation with baseline galectin-3 levels and absolute skin score change at 3 months ($r=0.26$, $p=0.02$), but not at 6 month follow-up ($p=0.78$).

Conclusion: Contrary to smaller pilot studies suggesting galectin-3 is significantly different in SSc compared to HC, and may modestly correlate with skin score, our study did not confirm this. We used very early patients not on medications, and it may be that the previously reported differences in galectin-3 occur later in disease and represent fibrotic burden, or may be affected by medications.

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Reliability of Nailfold Capillary Density Measurement As a Possible Outcome Measure for Systemic Sclerosis-Related Microangiopathy. Graham Dinsdale[1], Tonia Moore[2], Joanne Manning[2], Andrea Murray[1], Michael Berks[3], Philip Tresadern[3], Chris Taylor[3], Neil O'Leary[4], Chris Roberts[4], John Allen[5], Marina Anderson[6], Maurizio Cutolo[7], Roger Hesselstrand[8], Kevin Howell[9], Paula Pyrkotsch[6], Francesca Ravera[7], Vanessa Smith[10], Alberto Sulli[7], Marie Wildt[8] and Ariane Herrick[1]. [1]Centre for Musculoskeletal Research, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [2]Salford Royal Hospital NHS Foundation Trust, Salford, United Kingdom, [3]Centre for Imaging Sciences, University of Manchester, Institute of Population Health, Manchester, United Kingdom, [4]Centre for Biostatistics, Institute of Population Health, University of Manchester, Manchester, United Kingdom, [5]Regional Medical Physics Department, Freeman Hospital, Newcastle upon Tyne, United Kingdom, [6]Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, United Kingdom, [7]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, [8]Lund University, Lund, Sweden, [9]Institute of Immunity and Transplantation, University College London, Royal Free Campus, London, United Kingdom, [10]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium.

Background/Purpose: Nailfold videocapillaroscopy allows non-invasive assessment of the microcirculation. Image annotation software allows tracking of changes over time; a potential outcome measure for systemic sclerosis (SSc) related microangiopathy. Our objective was to assess the reliability of capillary density measurement, known to be reduced in SSc[1].

Methods: 124 patients (102 SSc, 22 primary Raynaud's phenomenon [PRP]), and 50 healthy controls (HC), underwent high-magnification (300x) videocapillaroscopy mosaic imaging of all 10 digits (1740 images).

Image subsets, sampled across disease categories, were randomly allocated to each of 10 capillaroscopy experts. These 'raters' used custom software to assess images. Each image used in this analysis was assigned to at least 2 raters. To assess intra-rater reliability, each rater performed repeat evaluations on an image subgroup. At least 6 images were assessed from each subject.

Raters marked distal vessel locations in an image. Vessel density was calculated as the total number of distal vessels divided by the Euclidean distance between the vessels at the horizontal extremities.

We examined: (1) the probability of raters marking sufficient (2 or more) distal vessels in an image (logistic mixed-effects model). Conditional on an image evaluation having sufficient distal vessels marked (2) distal vessel density (linear mixed-effects model).

Intra and inter-rater reliability was estimated with intra-class correlation coefficients from fitted model variance components.

Results: 3463 images were evaluated. Each rater assessed a median (range) of 112 (87, 1406) unique images from 14 (9, 174) subjects. Same-rater repeat evaluations were performed on (median) 17% of images, and 904 images from 116 patients were evaluated by at least 2 raters.

Raters marked sufficient distal vessels in 79% of evaluations. Compared to HC, SSc and PRP images had odds ratios [95% CI] of sufficient distal vessels marked of 0.23 [0.14, 1.41] and 3.80 [0.37, 5.23] respectively. The mean vessel density in HC was 9.84 vessels/mm. Compared to HC, vessel density was lower in SSc (6.62) but not significantly different in PRP (9.58); respective differences [95% CI] were -3.22 [-3.88, -2.63] and -0.26 [-1.12, 0.63] vessels/mm.

Estimates of intra-rater reliability [95% CI] were 0.91 [0.89, 0.92] for vessel mark-up and 0.89 [0.87, 0.91] for vessel density. Corresponding estimates of inter-rater reliability were 0.51 [0.39, 0.76] and 0.56 [0.47, 0.64] respectively.

Conclusion: Mark-up rate differences between-groups are most likely due to differences in capillary architecture (capillary loss/damage in SSc patients). Density was unmeasurable in a sizable minority (21%) of image evaluations with potential implications for the representativeness of this measure. The high intra-(compared to inter-) rater reliability suggests that density could serve as outcome measure in prospective studies if the same rater examines images. Research on the impact of training on inter-rater reliability, and into more objective (automated) analysis methods is required to further develop this promising outcome measure.

1. Cutolo M et al. *Nature Rev Rheumatol* 2010;6:578–87

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Troponin T as a Diagnostic and Prognostic Biomarker of Primary Cardiac Involvement in Systemic Sclerosis. Silvia Laura Bosello, Giacomo De Luca, Federico Parisi, Giorgia Berardi, Manuela Rucco, Giovanni Canestrari and Gianfranco Ferraccioli. Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy.

Background/Purpose: Heart involvement is common in Systemic Sclerosis (SSc), even if often clinically silent, and represents one of the leading

cause of death in these patients. The aim of our study was to define the role of cardiac troponin T (cTnT) and NT-proBNP to identify a cardiac involvement.

Methods: cTnT and NT-proBNP levels were evaluated in 200 consecutive SSc patients (mean age: 58.7 ± 13.9 years; mean disease duration: 11.1 ± 9.0 years; diffuse disease: 42.0%; anti-Scl70 positivity: 45.5%) from 2008 and 2013. Data regarding disease subtype and organ involvement were available for the entire cohort and all patients underwent: electrocardiogram (EKG), echocardiography and pulmonary function test (PFTs). All SSc-related deaths were registered during a mean follow-up of 40.8±18.7 months.

Results: cTnT levels were above the normal limit in 79 (39.5%) SSc patients (mean levels in positive patients: 0.06 ± 0.08 ng/ml). NT-proBNP levels were above the cut-off limit of 125 ng/ml, recommended by the manufacturer, in 79 patients (39.5%) and 51 of these patients presented also increased levels of cTnT. The increased cTnT levels were associated with diffuse skin involvement and skeletal myositis ($p<0.0001$; $p=0.006$ respectively) and directly correlated with skin score ($R=0.27$; $p<0.0001$). Patients with high cTnT levels presented a lower left ventricular ejection fraction (LV-EF) (59.5±9.3%) and higher pulmonary arterial systolic pressure on echocardiography (37.7±16.8 mmHg) compared to patients with normal cTnT values (63.1±4.9%, $p=0.04$; 28.3±6.8 mmHg, $p<0.0001$). These patients, furthermore, presented more frequently a right bundle branch block on EKG with respect to patients without increasing of cTnT (19.7% vs.7.0%; $p=0.008$). In our cohort 28 patients (14%) presented a LV-EF <55% and the sensitivity of increased cTnT levels (>0.014 ng/ml) in the detection of depressed myocardial contractility was 67.8% and its specificity was 66.8%. It is also noteworthy that its negative predictive value in the assessment of depressed LV-EF was 92%. During the follow-up, 18 SSc-related death occurred; 10 of these were directly related to cardiac involvement (sudden cardiac death or heart failure) and all occurred in patients with increased cTnT levels. Cumulative survival estimated by Kaplan-Mayer curve was worse in patients with increased baseline levels of cTnT ($X^2=21.2$, $p<0.0001$). Died patients presented higher levels of cTnT (0.11±0.03 ng/ml) and of NT-proBNP (7193±5691.3 pg/ml) and lower LV-EF (52.5±11.9%) with respect to survivors (cTnT: 0.02±0.05 ng/ml; NT-proBNP: 585.8±2517.3 pg/ml; LV-EF: 61.9±6.6%; $p=0.001$ for all comparisons).

Conclusion: The cTnT levels were increased in up to 40% of the SSc patients, revealing that myocardial involvement is more relevant in scleroderma disease than appreciated previously. cTnT may provide an opportunity to screen non-invasively SSc patients for subclinical heart involvement. The more impaired systolic function and more frequent EKG abnormalities in SSc patients with increased TnT levels, suggest that cTnT may be a novel biomarker of cardiac damage. Our data on survival suggest it as a possible prognostic biomarker of SSc-related death.

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Lack of Association Between Esophageal Symptoms and Abnormal Findings in High-Resolution Manometry in a Mexican Mestizo Cohort with Systemic Sclerosis (SSc).

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Background/Purpose: Esophageal involvement is present in 50–70% of SSc patients and it is the most common visceral organ complication. The impact of the esophageal involvement is related with high morbidity and included the association with intersticial lung disease, weight loss and malnutrition, Barretxs esophagus and adenocarcinoma degeneration. Our objectives were characterize motor esophageal impairment in patients with SSc with or without esophageal symptoms using high-resolution manometry (HRM).

Methods: Observational, descriptive, cross-sectional study. We included SSc patients according to American College of Rheumatology classification criteria of the 1980 and patients with Scleroderma variants with esophageal symptoms; with an age ≥ 18 years old, from a clinic of a tertiary hospital. The demographic data, skin manifestations, esophageal symptoms and drugs used were recorded. The Carlsson-Dent questionnaire (CDQ) was used to evaluate gastroesophageal reflux disease and dysphagia was graded on a five-point scale according to Mellow and Pinkas. The modified Rodnan skin score (mRSS) was used in the skin evaluation. A standard HRM was performed and the results were classified according to Chicago Classification. In the analysis we categorized the grade of dysphagia, the mRSS and HRM results. We used 2x2 contingency tables and chi-square or Fisher's exact test according of their distribution to establish an association between each variable and HRM result. A p value < 0.05 was classified as statistically significant.

Results: We included 19 SSc patients, 1 with morphea and 1 with Scleroderma sine scleroderma. Clinical and demographic variables are shown in Table 1. Most of the patients were on normal BMI, had been classified in limited disease, and had used proton-pump inhibitors. The most common symptoms were dysphagia and heartburn. We found an abnormal HRM in 16 (76.2%) patients; the most common abnormality in HRM was absence of peristalsis in 5 (23.8%) patients. Variables analyzed with HRM are shown in Table 2. We did not find association between any variable (Table 1 and 2) and the presence of abnormal HRM.

Conclusion: We found a lack of association between esophageal symptoms and abnormal findings in HRM. There was not association between CDQ and HRM. Although this study is limited by the number of patients analyzed, we think that due to the large impact of the esophageal involvement in SSc patients, we need to do a systematic esophageal study of this patients with the objective to decrease their morbidity.

Table 1 Clinical and demographic variables

Characteristics	n = 21
Age, mean (SD) years	44 (14)
Female n (%)	20 (95.2)
BMI	
- Normal n (%)	7 (33.3)
- Underweight n (%)	5 (23.8)
- Overweight n (%)	5 (23.8)
- Obese n (%)	4 (19)
SSc classification	
- Limited n (%)	17 (80.9)
- Diffuse n (%)	2 (9.5)
- Scleroderma sine scleroderma n (%)	1 (4.8)
- Morphea n (%)	1 (4.8)
mRSS, mean (SD)	9.7 (7.4)
Antibodies	
- Antinuclear n (%)	15 (75)
- Anti-Scl70 n (%)	5 (23.8)
- Anti-centromere n (%)	5 (23.8)
Drugs	
- NSAID n (%)	2 (9.5)
- CCB n (%)	18 (85.7)
- PPI n (%)	20 (95.2)

SSc; Systemic Sclerosis, SD; standard deviation, BMI; body mass index, mRSS; modified Rodnan skin score, NSAID; Nonsteroidal anti-inflammatory drug, CCB; Calcium channel blockers, PPI; Proton-pump inhibitors.

Table 2

Esophageal characteristics and HRM findings

	n = 21
Esophageal symptoms, n (%)	
- Dysphagia	13 (61.9)
- Heartburn	13 (61.9)
- Regurgitation	9 (42.9)
- Cough	10 (47.6)
- Chest Pain	3 (14.3)
- Nausea	4 (19)
- Vomiting	1 (4.8)
CDQ questionnaire, mean (SD)	6.04 (4.4)
Dysphagia classification* n (%)	
- No dysphagia	9 (42.9)
- Dysphagia to normal solids	6 (28.6)
- Dysphagia to soft solids	6 (28.6)
HRM abnormal n (%)	16 (76.2)

SD; standard deviation, CDQ; Carlsson-Dent questionnaire, HRM; esophageal high-resolution manometry.
*according to Mellow and Pinkas

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Right Ventricular Diastolic Impairment Is Common in Systemic Sclerosis and Is a Marker of Several Organ-Target Damage of the Disease.

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Background/Purpose: Heart failure and cardiac dysfunctions both of intrinsic or secondary origin and targeting LV (left ventricule) and/or RV (right ventricule) are critical complications promoting mortality in systemic sclerosis (SSc). While several studies reported possible right ventricule (RV) alterations in SSc patients having pulmonary hypertension, only few and small series investigated RV function in unselected SSc patients. Therefore, the aim of the present study is to investigate LV and RV systolic and diastolic function in a large SSc cohort of unselected patients compared to a control group using comprehensive echocardiographic parameters.

Methods: We examined LV and RV systolic and diastolic functions, using echocardiography and Tissue Doppler echocardiography (TDE) indexes, in a cohort of 212 consecutive SSc patients seen during a 9 month-period at two institutions (Paris, France and Los Angeles, USA) and 50 healthy controls.

Results: Patients' characteristics from the two institutions were very similar allowing combined analyses. When compared to controls, SSc patients had consistently impaired RV indices that include reduced RV contractility ($p<0.001$), larger right atrial area ($p=0.027$) and overall RV diastolic dysfunction ($p<0.001$) (Table 1). Patients also exhibited alterations in LV contractility and diastolic function ($p<0.001$ each) (Table 1). Looking at associated parameters, in multivariate analysis, RV contractility as expressed by the TDE S_T parameter was associated with TDE LV contractility S_M ($p=0.030$), DLCO ($p=0.013$) whereas RV diastolic impairment was associated with systolic pulmonary artery pressure ($p=0.015$). In a subset of 27 patients with proven pre-capillary PAH, comparison between SSc-PAH versus SSc free of PAH patients, revealed reduced LV diastolic function (measured by transmitral E/A ratio ($p=0.045$) and E_A <10cm/s ($p=0.029$)), reduced overall RV contractility (21.5 versus 4.5%; $P=0.03$) and reduced RV diastolic function (transtricuspid E/A ratio; $p=0.014$ and 68% versus 29% with impaired function; $p=0.001$).

Conclusion: Whereas most previous studies focused on the LV, we report in the present controlled study that not only systolic but also diastolic RV dysfunction is common in SSc and that several cardiopulmonary factors seem to influence RV function in this multifaceted disease. Given that RV dysfunction and fibrosis are poor prognosticator, possibly associated with lethal ventricular arrhythmias, sudden death, exercise limitation, and impaired RV cardiac output, we assume that RV function should be closely investigated in SSc patients and that the impact on RV diastolic function of future therapies targeting PAH and/or primary myocardial involvement is to be assessed.

Table 1:

	SSc patients (n=212)	Controls (n=50)	p
Age, years	55.3 ± 13.2	53.1 ± 11.0	0.201
Men/women	40/172	Aug-42	0.637
Heart rate, bpm	76 ± 11	69 ± 15	0.001
Blood pressure, mmHg			
Systolic	122 ± 14	123 ± 14	0.536
Diastolic	70 ± 9	69 ± 9	0.49
LV indexes			
Left ventricular end-diastolic diameter, mm	43 ± 6	47 ± 7	0.002
Interventricular septum thickness, mm	10 ± 3	10 ± 1	0.846
Left ventricular ejection fraction, %	61 ± 7	67 ± 3	<0.001
Left ventricular ejection fraction <55%, n (%)	8 (3.9)	0 (0.0)	0.361
Left atrial area, mm^2	14 ± 4	13 ± 2	0.418
Mitral doppler E/A ratio	1.0 ± 1.0	1.2 ± 0.3	<0.001
S_M, cm/s	9.8 ± 2.2	11.9 ± 2.7	<0.001
S_M <7.5 cm/s, n	23 (10.8)	0 (0.0)	0.010
Ea <10 cm/s, n	76 (35.8)	6 (12.0)	<0.001
RV indexes			
Tricuspid doppler E/A ratio	1.2 ± 0.4	1.3 ± 0.3	0.023
S_T, cm/s	13.2 ± 2.7	14.7 ± 2.7	<0.001
S_T <10 cm/s, n (%)	11 (5.2)	0 (0.0)	0.128
Tricuspid annular plane systolic excursion, mm	21.9 ± 4.0	23.9 ± 2.0	<0.001
Right atrial area, mm^2	15 ± 8	12 ± 2	0.027
RV diastolic dysfunction, n (%)	53 (25.0)	0 (0.0)	<0.001
Pericardial and pulmonary artery measurements			
Pericardial effusion, n (%)	27 (12.7)	4 (9.1)	0.618
Tricuspid regurgitation maximal velocity (m/s)	2.5 ± 0.4	2.4 ± 0.2	0.491
Pulmonary arterial pressure, mmHg	33 ± 10	31 ± 5	0.496
Pulmonary arterial pressure >40 mmHg, n (%)	29 (13.7)	0 (0.0)	0.002

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Abnormal Right Ventricular Longitudinal Strain Detected in Systemic Sclerosis Patients Prior to Abnormalities in Conventional Measures of Right Ventricular Size and Function.

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Background/Purpose: Cardiac involvement in systemic sclerosis (SSc) adversely affects long-term prognosis, remaining undetectable despite frequent echocardiographic monitoring. Speckle tracking derived strain of the RV free wall was utilized to detect whether early changes in regional and global contractility are detectable in SSc patients in comparison to standard 2D measures of RV chamber size and function.

Methods: 138 SSc patients who had technically adequate, clinically indicated 2D echocardiograms were studied, and compared with a cohort of 40 age-matched non-scleroderma controls (C). Conventional 2D and off-line strain analyses were performed. Standard assessment of RV chamber size and function by 2D included linear dimensions of RV base and length, tricuspid annular plane systolic excursion (TAPSE), and RV fractional area change (FAC). RV longitudinal systolic speckle-derived strain (RVLSS) was assessed in the basal, mid and apical free wall. Conventional echo parameters, global RVLSS, and RVLSS in each RV segment were compared between SSc and C by the Student's t test. We also modeled RVLSS as a function of RV segment and disease group (SSc vs C) using GEE analysis to account for the clustering of RV strain values across the 3 RV segments.

Results: Most conventional echo measures of RV size and function were not different between SSc patients and C, including TAPSE (SSc 2.2 ± 0.47 vs C 2.3 ± 0.4 cm; $p=0.119$), linear dimensions of the RV base (SSc 3.6 ± 0.6 vs C 3.4 ± 0.4 cm, $p=0.066$) and RV length (SSc 7.7 ± 0.9 vs C 7.7 ± 0.7 cm, $p=0.832$). While within the normal range, FAC in SSc patients was slightly decreased (48.9 ± 10.9% vs 52.7 ± 8.0, $p=0.045$). In contrast to these conventional parameters, measures of RVLSS were significantly different between SSc and C. Global RVLSS was diminished in SSc compared to C (b 1.5, $p=0.045$). Regional differences in RVLSS were also noted: decreased in the apex (SSc −8.5 vs C −17.2%, $p<0.0001$) and mid (SSc −12.4 vs C −17.8%, $p<0.0001$) segments and increased in the base (SSc −32.2 vs C −22.5%, $p<0.0001$) in SSc vs C. Among C, regional differences in RVLSS were detected in the basal segment relative to the apex (base-apex b −5.4; $p<0.0001$) but not in the mid-apex comparison. In contrast, SSc had significant regional differences throughout (base-apex b −23.6, mid-apex b −3.9, both $p<0.0001$), especially when comparing the basal to apical segments. The base-apex difference was significantly greater in SSc compared to C ($p<0.0001$ for interaction). While SSc had a higher mean PASP than C (SSc 31.4 vs C 22.7 mmHg, $p=0.0001$), the differences observed in regional strain between SSc and C were unchanged when restricting our analyses to those with a PASP<35 mmHg.

Conclusion: Speckle-derived strain reveals a heterogenous pattern of regional longitudinal systolic contraction in scleroderma, that is not detected by conventional echocardiographic measures. These data suggest that significant RV myocardial disease is occult in SSc patients, and may potentially progress with time.

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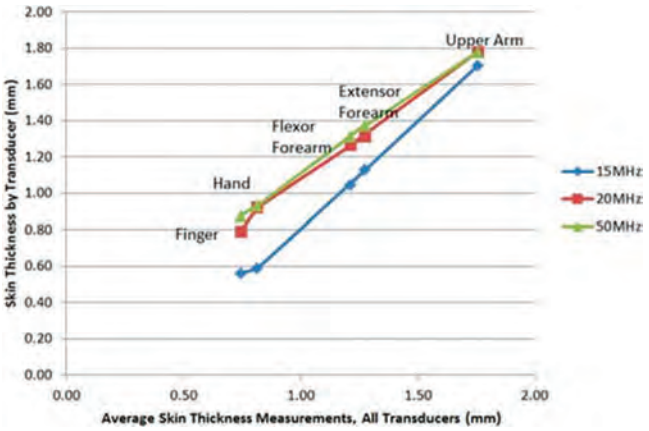
Precision of Ultrasound Skin Thickness Measurements: Influence of Examiner and Ultrasound Transducer. Ingeborg A. Sacksen, P. Scott Pollock and Mark H. Wener. University of Washington, Seattle, WA.

Background/Purpose: Ultrasound has been used to measure scleroderma skin thickness, but it has not been established that routine clinical ultrasound equipment is adequate. We compared skin thickness measured with a common office instrument vs measurements using high frequency research ultrasound equipment, and determined the differences in measurement values and precision.

Methods: Repeated measurement of skin thickness of 1 normal volunteer at 5 reproducible sites on the dorsum of the proximal phalanx of a finger, the dorsum of a hand, the extensor surface and flexor surface of a forearm, and a lateral upper arm. A 15 MHz clinical ultrasound transducer and instrument (Sonosite, Bothell, WA), and 20 MHz and 50 MHz research transducers of a research ultrasound instrument (Sonosite, Bothell, WA) were used. After initial training, 3 examiners independently imaged all 5 sites with each transducer on 3 days over a period of one month. On each image, measurements of dermal thickness were made at 3 representative sites, and averaged to provide the thickness measure of that image.

Results: The overall average coefficient of variation (CV) was 8.6% for the 50 MHz transducer, 5.7% for the 20 MHz transducer, and 14.2% for the 15 MHz transducer. Measurements were more precise at the thicker skin of the arm (CV=5.6%) than at thinner sites. Thickness measured with 15 MHz was smaller than those of the 20 and 50 MHz transducers at all sites, but was generally reproducible at each site. Skin thickness at the finger vs hand differed significantly using the 20 and 50 MHz transducers, but the 15 MHz transducer results at those 2 sites were not statistically distinguishable. Measurements by one examiner were consistently smaller than those of the other 2 observers, whose values matched closely. All showed the expected increase in thickness by site (figure).



Conclusion: The 15 MHz clinical ultrasound instrument is not as precise as higher frequency ultrasound equipment, especially in thin skin such as at the dorsum of the normal finger and hand. However, even at modestly thicker sites, such as the normal arm and forearm, the precision is acceptable. These data suggest that routinely-available mid-range clinical ultrasound equipment can be used to develop ultrasound-based skin thickness measurements, with the potential to improve the ability to monitor changes in skin thickness.

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Outcome of Patients with Systemic Sclerosis Admitted to the Intensive Care Unit. Tarik Hissem[1], Alice Berezne[2], David Grimaldi[3], Alain Cariou[1], Julien Charpentier[1], Jean-Daniel Chiche[1], Yannick Allanore[4], Jean-Paul Mira[1], Frédéric Pène[5] and Luc Mouthon[6]. [1]Intensive care unit - Cochin University Hospital, Paris, France, [2]Paris Descartes University, Internal Medicine department, Cochin Hospital, Paris, France, [3]Intensive Care Unit - Cochin University Hospital, Paris, France, [4]Paris Descartes University, Rheumatology A Department and INSERM U1016, Cochin Hospital, Paris, France, [5]Intensive care unit - Cochin university hospital, Paris, France, [6]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France.

Background/Purpose: Studies on the outcome of patients with systemic sclerosis (SSc) in intensive care unit (ICU) are scarce in the literature.

Objective: To assess the characteristics and outcomes of patients with SSc admitted to ICU.

Methods: We performed a single-center retrospective study over a 4-year period (November 2006-December 2010). All patients with SSc admitted to the ICU were enrolled. The underlying disease's features, reasons for ICU admission and organ failure supports were collected. We studied their short-term (ICU and hospital mortality) and long-term (6-month and 1-year mortality) outcomes, and we sought to identify prognostic factors. Variables were expressed as median (IQR) or number (percentage) as appropriate.

Results: Thirty five patients (age 51 [40–63] years, 77% female, SAPSII 35 [23–51]) were enrolled in the study. Twenty two (63%) and 13 (37%) patients displayed diffuse cutaneous and limited cutaneous SSc, respectively. The time from diagnosis to ICU admission was 80 [27–110] months. Twenty six (74%) patients had pulmonary fibrosis with the following baseline characteristics: diffusion capacity of lung for CO 33% [20–45], forced vital capacity 52% [39–66]. Ten patients had pulmonary hypertension with a systolic pulmonary artery pressure of 55 mmHg [45–63]. Only two (6%) had chronic renal insufficiency requiring long-term hemodialysis.

The main reasons for ICU admission were acute respiratory failure (69%) and acute renal failure (17%). During hospitalisation in ICU, 10 (28%) required endotracheal intubation and mechanical ventilation, 10 (28%) required hemodialysis and 9 (26%) required vasopressors. The overall ICU and hospital mortality rates were 26% and 34% respectively. Six-month and 1-year mortality rates were 40% and 46% respectively. None of the disease characteristics impacted the hospital outcome. Survivors and decedents were mostly different in terms of organ failures, most especially respiratory failure. Invasive mechanical ventilation was associated with a 100-percent hospital mortality rate and was the only independent prognostic factor.

Conclusion: This study reports on the most important cohort of patients with SSc in the ICU. Respiratory failure related to advanced-stage pulmonary fibrosis represents the main reason for ICU admission. In this setting, mechanical ventilation is constantly associated with hospital mortality. These results urge to reappraise the indications for ICU and mechanical ventilation in this high-risk subgroup of patients.

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ACR Poster Session A
Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics
Sunday, November 16, 2014, 8:30 AM–4:00 PM

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Integrin Inhibitor Modulates Pulmonary Fibrosis in the Reactive Oxygen Species Murine Model of Systemic Sclerosis. Gianluca Bagnato[1], Alessandra Bitto[1], Natasha Irrera[1], Gabriele Pizzino[1], Neal Roberts[2], Domenica Altavilla[1], Francesco Squadrito[1], Antonino Saitta[1] and Gianfilippo Bagnato[3]. [1]University of Messina, Messina, Italy, [2]University of Louisville, Louisville, KY, [3]Universita Messina, Villafranca Tirrena, Italy.

Background/Purpose: Systemic sclerosis (SSc) is an acquired connective tissue disorder in which inflammation, immune dysregulation and vascular damage lead to fibroblast activation that results in fibrosis of the skin and internal organs. Development of therapies is hampered by lack of understanding of the underlying mechanism of disease. It has been recently shown that alterations in cell–matrix interactions are sufficient to initiate and sustain inflammatory and pro-fibrotic programmes [1]. Both SSc fibroblasts [2] and pulmonary T cells of patients affected by SSc with interstitial lung disease highly express $\alpha V\beta 3$ and $\alpha V\beta 5$ integrins and they are required for

lymphocytic infiltration and collagen accumulation [3]. The aim of the study is therefore to evaluate the effect of the αVβ3 and αVβ5 inhibitor (cilengitide) on the development of pulmonary fibrosis in the HOCl-induced murine model of systemic sclerosis.

Methods: Chronic oxidant stress SSc was induced in BALB/c mice by daily s.c. injections of HOCl for 6 weeks. 25 Mice were randomized in three arms: HOCl alone (n=10), HOCl + Cilengitide (n=10) or vehicle alone (n=5). Treatment with cilengitide 20 (mg/kg/i.p./day) was started four weeks after the administration of HOCl and maintained throughout the remaining experimental period (2 weeks). Lung fibrosis was evaluated by histological methods. The severity of fibrosis was assessed using ordinal or nominal scales and the results compared nonparametrically. Lung concentrations of focal adhesion kinase (FAK) were evaluated by western blot analysis.

Results: The administration of HOCl induced lung fibrosis as demonstrated by routine histological analysis. Cilengitide significantly reduced the histopathological change of HOCl-induced pulmonary fibrosis (Figure 1A-D). Additionally, pulmonary FAK expression was increased in mice treated with HOCl and significantly modulated by cilengitide administration (Figure 1E).

Conclusion: The inhibition of integrin signaling could prove useful as future therapeutic targets for treatment of SSc. Further confirmatory results in a second animal model are needed to better assess the specific effect of cilengitide on the development of fibrosis and myofibroblasts differentiation.

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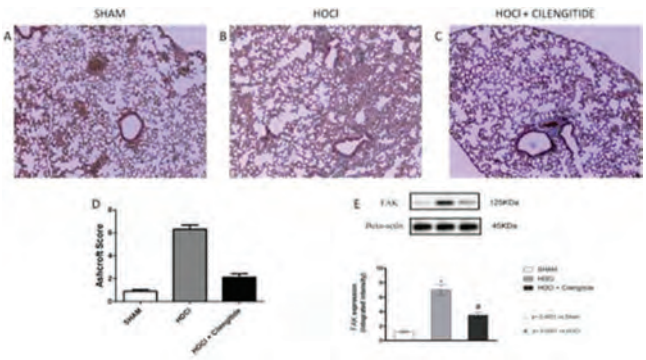

Figure 1

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Genetic Susceptibility Loci of Idiopathic Interstitial Pneumonitis Do Not Represent Risk for Systemic Sclerosis. Minghua Wu[1], Shervin Assassi[1], Gloria Salazar[1], Olga Y Gorlova[2], Wei V Chen[2], Julio Charles[1], Fredrick M. Wigley[3], Laura K. Hummers[3], Ami A. Shah[3], Monique Hinchcliff[4], Dinesh Khanna[5], Elena Schiopu[5], Kristine Phillips[5], Daniel E. Furst[6], Virginia D. Steen[7], Murray Baron[8], Marie Hudson[8], Xiaodong Zhou[1], Janet E. Pope[9], Niall Jones[10], Peter Docherty[11], Nader A. Khalidi[12], David B. Robinson[13], Robert W. Simms[14], Richard Silver[15], Tracy Frech[16], Barri J. Fessler[17], Marvin J. Fritzler[18], Jerry A. Molitor[19], Barbara M. Segal[19], Javier Martín[20], John Varga[4] and Maureen D Mayes[1]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]Geisel School of Medicine at Dartmouth, Hanover, NH, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]Northwestern University Feinberg School of Medicine, Chicago, IL, [5]University of Michigan, Ann Arbor, MI, [6]University of California, Los Angeles, Department of Medicine, Los Angeles, CA, [7]Georgetown University Medical Center, Washington, DC, [8]McGill University, Montreal, QC, [9]St. Joseph's Health Care, University of Western Ontario, London, ON, [10]University of Alberta, Edmonton, AB, [11]The Moncton Hospital, Moncton, NB, [12]St. Joseph's Hospital, McMaster University, Hamilton, ON, [13]University of Manitoba, Winnipeg, MB, [14]Boston University School of Medicine, Boston, MA, [15]Medical University of South Carolina, Charleston, SC, [16]University of Utah, Salt Lake City, UT, [17]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [18]Mitogen Advanced Diagnostics Laboratory, Faculty of Medicine, University of Calgary, Calgary, AB, [19]University of Minnesota, Minneapolis, MN, [20]Consejo Superior de Investigaciones Científicas, Granada, Spain.

Background/Purpose: Systemic sclerosis (SSc) related interstitial lung disease (ILD) has phenotypic similarities to idiopathic interstitial pneumonia (IIP). The objective of this study was to assess whether genetic susceptibility loci which were recently identified in a large idiopathic interstitial pneumonia (IIP) genome-wide association study (GWAS) were also risk loci for SSc overall, for SSc-autoantibody subgroups or for severity of SSc-ILD.

Methods: A total of 2571 North-American Caucasian SSc patients and 4500 unaffected control subjects were investigated in two independent cohorts. The discovery cohort consisted of 1486 SSc cases and 3477 unaffected controls while the confirmation cohort consisted of 1085 additional SSc cases and 1023 unaffected controls. All patients were enrolled in the National Scleroderma Family Registry and DNA Repository and fulfilled the 1980 American College of Rheumatology classification criteria for SSc or had at least three of the five CREST features. Forced vital capacity % predicted (%FVC) as continuous outcome was used as a validated outcome measure for severity of ILD. Single nucleotide polymorphisms (SNPs) rs2736100 (*TERT*), rs2076295 (*DSP*), rs4727443 (*AZGP1*), rs7934606 (*MUC2*), rs2034650 (*IVD*), rs1981997 (*MAPT*), rs12610495 (*DPP9*), rs6793295 (*LRRC34*), rs2609255 (*FAM13A*), rs11191865 (*OBFC1*), rs1278769 (*ATP11A*) and rs1379326 (*CSMD1*), which were identified/confirmed to be associated with IIP in a recently published GWAS (Fingerlin et al. Nat Genetics 2013) were genotyped and analyzed for its association with SSc and severity of SSc-ILD.

Results: In the discovery cohort, we observed nominally significant associations with SSc overall for *LRRC34* rs6793295 (MAF=0.29, OR=1.14, CI 95% 1.03 to 1.25, p value=0.009) and *OBFC1* rs11191865 (MAF=0.52, OR=1.09, CI 95% 1.00 to 1.19, p value=0.043). There were no significant associations in the anti-topoisomerase I (ATA) or anti-centromere (ACA) positive patient subgroups. However, *DSP* rs2076295 (β=−2.29, CI 95% −3.85 to −0.74, p value=0.004) and *MAPT* rs1981997 (β=2.26, CI 95% 0.35 to 4.17, p value=0.02) were associated with forced vital capacity % predicted (% FVC) even after adjusting for ATA status. All SNPs observed to reach nominal significance levels in the discovery cohort were genotyped in the replication cohort. However, none of the above observed associations were confirmed in the replication cohort.

Conclusion: Herein, we add new evidence that SSc and SSc related ILD are genetically distinct from IIP, although they share phenotypic similarities. This finding might have important implications for follow-up mechanistic studies and identification of therapeutic targets. Genetic background of SSc seems to be mainly related to innate and adaptive immunity while IIP genetic susceptibility relates to epithelial cell injury and dysfunction, mucin production, and telomere length. Interstitial lung involvement in SSc-ILD and IIP might be the common end-product of two different pathological backgrounds.

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Elevated Pentraxin 3 in Patients with Systemic Sclerosis: Associations with Vascular Manifestations and Defective Vasculogenesis. Yuichiro Shirai[1], Yuka Okazaki[1], Yumiko Inoue[1], Yuichi Tamura[1], Hidekata Yasuoka[2], Tsutomu Takeuchi[1] and Masataka Kuwana[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Keio Univ School of Medicine, Tokyo, Japan.

Background/Purpose: Pentraxin 3 (PTX3) is a multi-functional pattern recognition protein involved in inflammation, extracellular matrix deposition, and suppression of neovascularization mediated by fibroblast growth factor-2 (FGF2). Several lines of recent evidence suggest that PTX3 is constitutively

overexpressed in fibroblasts and endothelial cells derived from systemic sclerosis (SSc) patients. The aim of this study is to examine roles of PTX3 in pathogenic processes of SSc.

Methods: We enrolled 171 patients with SSc and 19 age- and sex-matched healthy controls. Circulating levels of PTX3 and FGF2 were measured by enzyme immunoassay and their correlations with SSc-related organ involvement were evaluated. Univariate and multivariate analysis was conducted to investigate if PTX3 and FGF2 were correlated with the presence or future development of vascular manifestations, including digital ulcer (DU) and pulmonary arterial hypertension (PAH). Circulating $CD34^+CD133^+$ $CD309^+$ endothelial progenitor cells (EPCs) were enumerated by flow cytometry. Effects of recombinant PTX3 on EPC differentiation were evaluated in pro-angiogenic cultures of mouse bone marrow mononuclear cells, followed by colony formation assay.

Results: PTX3 and FGF2 were significantly increased in SSc patients than in healthy controls ($P < 0.001$ and $P = 0.001$, respectively). When PTX3 and FGF2 levels were compared between two groups stratified by the presence or absence of individual organ involvement, PTX3 was increased in SSc patients with DU or PAH than in those without ($P < 0.001$ and $P = 0.006$, respectively), while FGF2 was reduced in patients with PAH ($P < 0.001$). Multivariate analysis revealed that elevated PTX3 was an independent parameter associated with the presence of DU (odds ratio (OR) = 1.50, $P < 0.001$) and PAH (OR = 1.23, $P = 0.002$), and was useful in predicting future occurrence of DU (hazard ratio = 1.12, $P = 0.04$). In contrast, reduced FGF2 was independently associated with the presence of PAH (OR = 0.91, $P = 0.02$). EPC counts were significantly reduced in patients with DU or PAH than in those without ($P = 0.003$ and 0.003, respectively), and were correlated negatively with circulating PTX3 concentration ($r = -0.53$, $P < 0.001$) and a PTX3/FGF2 ratio ($r = -0.35$, $P = 0.003$). Finally, exogenous PTX3 significantly inhibited differentiation of EPCs from mouse bone marrow stem cells *in vitro*.

Conclusion: PTX3 was elevated in circulation of SSc patients and was a useful biomarker that predicts the presence of DU and PAH as well as future development of DU. In addition, continuous exposure to a high PTX3 concentration may contribute to SSc vasculopathy through inhibition of vasculogenesis by exerting its suppressive effects on FGF2.

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Systemic Sclerosis Patients with Antitopoisomerase Antibodies Showed Significant Association with *CCR6* Polymorphisms. Javier Martin[1], Eguzkine Ochoa[2], Jose Ezequiel Martin[1], Shervin Assassi[3], Lorenzo Beretta[4], Patricia Carreira[5], Carmen Pilar Simeon[6], Eugénie Koumakis[7], Philippe Dieude[8], Yannick Allanore[9], Francisco J. García-Hernández[10], Gerard Espinosa[11], Ivan Castellvi Barranco[12], Luis Trapiella[13], Luis Rodriguez Rodriguez[14], Miguel A González-Gay[15], María-Victoria Egurbide[16], Luis Saez[17], José Luis Callejas[18], JA Vargas-Hitos[19], Nicolas Hunzelmann[20], Gabriela Riemekasten[21], Torsten Witte[22], Jörg HW Distler[23], Alexander Kreuter[24], Claudio Lunardi[25], Alessandro Santaniello[26], Filemon K. Tan[3], Frank C. Arnett[3], Paul Shiels[27], Ariane L. Herrick[28], Jane Worthington[29], Madelon C. Vonk[30], Bobby P.C. Koeleman[31], T.R.D.J. Radstake[31] and Maureen Mayes[32]
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Background/Purpose: Systemic sclerosis (SSc), also known as scleroderma, is an inflammatory autoimmune disease characterized by fibrosis of the skin and internal organs, vascular damage and altered immune responses with autoantibody production (especially anticentromere (ACA) and antitopoisomerase I (ATA)). As a complex disease, SSc, is caused by a combination of genetic and environmental factors. In recent years, the number of new susceptibility loci associated with SSc has remarkably grown due to genome-wide association studies (GWAS). Nevertheless, the current knowledge of the influence of SSc risk loci in the clinical sub-phenoytpes is limited and one of the main reasons is the low sample size in sub-phenotypes that triggers a lower statistical power. In this regard, ATA^+ SSc patients have been recently associated with *CCR6* gene variants and the main limitations of the study was the low sample size due to the low frequency of ATA among SSc patients (around 20%). Thus, in order to confirm the *CCR6* association with ATA^+ SSc, we performed an independent replication study in populations of European ancestry and a meta-analysis with the previous data published.

Methods: We selected for replication SNP rs3093024, in high linkage disequilibrium with the SNPs previously associated with ATA^+ SSc, rs3093023 ($r^2=1$) and rs10946216 ($r^2=0.96$). We designed a replication study with two phases: In phase I, we analyzed 454 ATA^+ SSc cases and 4,867 controls from available GWAS genotyped platform by Radstake *et al.* and in phase II, 446 ATA^+ SSc cases and 2,998 controls from five additional European cohorts were genotyped using TaqMan SNP® genotyping assay. Approval of local ethical committees and informed written consent was obtained for all participants. The meta-analysis of our study with the previous one included 1,548 ATA^+ SSc cases and 14,777 controls and reached statistical power of the analysis to 99% (OR 1.16, MAF 0.43, at the 5% significant level).

Results: Results obtained in meta-analysis showed significant association between SNP rs3093024 and ATA^+ SSc patients ($P = 1.0 \times 10^{-4}$, OR=1.16) (Table 1). Thus we confirm the association previously observed between *CCR6* and ATA^+ SSc patients harnessing the largest cohort of patients. The relevance of *CCR6* gene lies in its function as specific marker for Th17 cells. These cells are characterized by the production of interleukin-17 (IL- 17) which has been found to be increased in patients with SSc. Besides serum levels of IL-17 and ATA presence have been both correlated with disease severity. Interestingly, *CCR6* expression levels and IL-17 levels showed correlation with a *CCR6* functional variant which was in high linkage disequilibrium with SNP rs3093024 in rheumatoid arthritis patients.

Conclusion: Taken all together, our findings suggest that the presence of the risk variant of rs3093024 in *CCR6* gene may acts as a marker of severity in SSc patients.

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Increased Expression of Chemerin in Endothelial Cells Due to Fli1 Deficiency May Contribute to the Development of Digital Ulcers in Systemic Sclerosis. Kaname Akamata, Yoshihide Asano, Takashi Taniguchi, Hayakazu Sumida, Naohiko Aozasa, Shinji Noda, Tetsuo Toyama, Takehiro Takahashi, Yohei Ichimura, Ayumi Yoshizaki and Shinichi Sato. University of Tokyo Graduate School of Medicine, Tokyo, Japan.

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disorder characterized by vascular injuries and fibrosis development. In SSc lesional skin, transcription factor Friend leukemia virus integration 1 (Fli1) is constitutively down-regulated in various cell types, especially by an epigenetic mechanism in dermal fibroblasts, and Fli1 deficiency is deeply related to the pathogenesis of SSc. In particular, endothelial Fli1 deficiency reproduces the histological and functional abnormalities characteristic of SSc vasculopathy *in vivo*. Recently, adipocytokines have drawn much attention in the research field of various autoimmune diseases. Chemerin is a member of adipocytokines with a chemoattractant effect and a pro-angiogenic property, and has been shown to have pivotal roles in the pathogenesis of various autoimmune diseases. To elucidate the role of chemerin in the developmental process of SSc, we investigated the expression levels of chemerin in SSc lesional skin and the mechanism underlying its altered expression, and the clinical correlation of serum chemerin levels in SSc patients.

Methods: Expression of chemerin and its receptor, ChemR23, was evaluated by immunostaining and/or quantitative reverse transcription-real time PCR in human and/or murine skin. The mechanisms regulating chemerin expression in dermal fibroblasts and endothelial cells were examined by gene silencing technique and chromatin immunoprecipitation. Serum chemerin levels were determined by enzyme-linked immunosorbent assay in 64 SSc and 19 healthy subjects.

Results: In SSc lesional skin, chemerin was up-regulated in small blood vessels, down-regulated in activated fibroblasts surrounded with thickened collagen bundles, but not altered in inflammatory cells, while ChemR23 expression was comparable in various cell types. Chemerin expression was also markedly decreased in dermal fibroblasts of bleomycin-treated SSc model mice. Importantly, the decreased expression of chemerin was significantly reversed by blocking autocrine transforming growth factor (TGF)-β signaling with TGF-β1 antisense oligonucleotide in cultured SSc dermal fibroblast. As for endothelial cells, gene silencing of Fli1, which directly bound to the chemerin promoter, induced chemerin expression in human dermal microvascular endothelial cells and *Fli1*$^{+/-}$ mice exhibited elevated chemerin expression in dermal blood vessels. Regarding the correlation of serum chemerin levels with clinical features in SSc patients, serum chemerin levels inversely correlated with estimated glomerular filtration rate in SSc patients with renal dysfunction while, in SSc patients with normal renal function, patients with digital ulcers had higher serum chemerin levels than those without.

Conclusion: Chemerin is down-regulated in SSc dermal fibroblasts by autocrine TGF-β, while up-regulated in SSc dermal blood vessels through endothelial Fli1 deficiency. In SSc, dysregulated chemerin/ChemR23 axis by endothelial Fli1 deficiency may contribute to the development of SSc vasculopathy through altering angiogenic/angiostatic signaling pathways.

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Progranulin Overproduction Due to Fli1 Deficiency Contributes to the Resistance of Dermal Fibroblasts to Tumor Necrosis Factor a in Systemic Sclerosis. Yohei Ichimura, Yoshihide Asano, Kaname Akamata, Shinji Noda, Takashi Taniguchi, Takehiro Takahashi, Tetsuo Toyama, Yayoi Tada, Makoto Sugaya, Shinichi Sato and Takafumi Kadono. University of Tokyo Graduate School of Medicine, Tokyo, Japan.

Background/Purpose: Systemic sclerosis (SSc) is a multisystem fibrotic connective tissue disease characterized by a dysregulated activation of fibroblasts following inflammation, autoimmune attacks, and vascular injuries. Although the pathogenesis of SSc remains currently elusive, chronic activation of wound healing-related gene programs is a hall mark of this disease. Progranulin (PGRN) is a wound healing-associated growth factor with an antagonistic property against tumor necrosis factor (TNF) receptors, regulating fibroblast activation, angiogenesis, and inflammation, i.e. three major pathological components of SSc. Therefore, we hypothesized that PGRN is involved in the mechanism underlying dermal fibrosis of SSc.

Methods: PGRN expression levels were determined by immunohistochemistry and quantitative reverse transcription-PCR in the skin of human subjects and murine SSc models. The role of PGRN in dermal fibroblast activation was examined with gene silencing technique. Serum PGRN levels were determined by ELISA in 60 SSc and 16 healthy subjects.

Results: In immunostaining with human skin samples, the expression levels of PGRN were increased in SSc dermal fibroblasts compared with normal dermal fibroblasts, while comparable in inflammatory cells, endothelial cells, and epidermal keratinocytes between SSc and control subjects. This finding was also confirmed *in vitro* with cultured SSc dermal fibroblasts, showing a significant increase of PGRN mRNA expression compared with normal dermal fibroblasts. Furthermore, bleomycin-treated mice exhibited the up-regulated expression of PGRN in dermal fibroblasts, suggesting the potential contribution of this molecule to the pathological dermal fibrosis, including SSc. Importantly, transcription factor Fli1, whose deficiency due to epigenetic mechanism contributes to the constitutive activation of SSc dermal fibroblasts, bound to the promoter of the *PGRN* gene and gene silencing of Fli1 resulted in a robust increase in mRNA levels of the *PGRN* gene in human dermal fibroblasts. Consistently, the up-regulated expression of PGRN was observed in dermal fibroblasts of *Fli1*$^{+/-}$ mice *in vivo*. Given that PGRN serves as an antagonist of TNF-a, a pro-inflammatory cytokine with a potent anti-fibrotic effect on dermal fibroblasts, we hypothesized that PGRN renders SSc dermal fibroblasts resistant to the anti-fibrotic effect of TNF-a. Supporting our idea, TNF-a suppressed the expression of type I collagen in SSc dermal fibroblasts treated with PGRN siRNA, while not in those treated with non-silencing scrambled RNA. To further assess the role of PGRN in SSc, we measured serum PGRN levels and examined their clinical correlation. Serum PGRN levels were elevated in early diffuse cutaneous SSc patients, especially in those with inflammatory skin symptoms, and positively correlated with C-reactive protein.

Conclusion: PGRN overproduction due to Fli1 deficiency may contribute to the constitutive activation of SSc dermal fibroblasts by antagonizing the anti-fibrotic effect of TNF-a. PGRN may also be involved in the inflammatory process associated with progressive skin sclerosis in early diffuse cutaneous SSc.

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Molecular Characterization of Systemic Sclerosis Esophageal Pathology Identifies Inflammatory and Proliferative Signatures with Few Fibrotic Markers. Jaclyn Taroni[1], Viktor Martyanov[2], Chiang-Ching Huang[3], J. Matthew Mahoney[4], Ikuo Hirano[5], Tammara A. Wood[2], Brandon Shetuni[5], Guang-Yu Yang[5], Darren Brenner[5], Barbara Jung[6], Swati Bhattacharyya[7], Orit Almagor[8], Jungwha Lee[5], Arlene Sirajuddin[5], Rowland W. Chang[5], John Varga[5], Michael Whitfield[2] and Monique Hinchcliff[5]. [1]Giesel School of Medicine at Dartmouth, Hanover, NH, [2]Geisel School of Medicine at Dartmouth, Hanover, NH, [3]University of Wisconsin, Milwaukee, Milwaukee, WI, [4]University of Vermont, Burlington, VT, [5]Northwestern University Feinberg School of Medicine, Chicago, IL, [6]University of Illinois at Chicago, Chicago, IL, [7]Northwestern University, Feinberg School of Medicine, Chicago, IL, [8]Northwestern University, Chicago, IL.

Background/Purpose: Esophageal involvement in patients with systemic sclerosis (SSc) is common, but tissue-specific pathological mechanisms are poorly understood. Esophageal muscle atrophy without concomitant fibrosis is found in the majority of SSc patient autopsy specimens. We hypothesized that detailed characterization of SSc esophageal histopathology and molecular signatures at the level of gene expression would provide insights into SSc esophageal disease pathogenesis.

Methods: Esophageal biopsies were prospectively obtained during esophagogastroduodenoscopy (EGD) in 16 clinically well-characterized SSc patients and 7 subjects without SSc. Upper and lower esophageal biopsies were evaluated for histopathology and gene expression by DNA microarray. Biopsies were scored for basal cell hyperplasia, lymphocyte infiltration, and degree of collagen deposition. The presence of a hiatal hernia and/or esophagitis on gross examination of the esophageal lumen at the time of EGD was considered evidence for esophagitis. Transcripts with the most similar expression between an individual's upper and lower biopsies, but most different expression between individuals, termed 'intrinsic genes,' were identified and hierarchically clustered to define molecular subsets (FDR $<$1.1%). Consensus clustering and SigClust formally confirmed the number of significant clusters within the cohort. Significance Analysis of Microarrays (SAM) identified differentially expressed transcripts between subsets, and g:Profiler identified functional terms enriched in subsets.

Results: Upper and lower esophageal biopsies showed nearly identical patterns of gene expression within an individual. Three groups of patients with SSc were identified molecularly: an inflammatory group (upregulated genes related to immune processes), a proliferative group (upregulated genes indicative of proliferating cells), and a non-inflammatory group (downregulated immune genes). The inflammatory signature was independent of esophagitis as assessed by basal cell hyperplasia grade, infiltrating lymphocyte counts, and presence of gross esophagitis/hiatal hernia indicating im-

mune cell activation may underlie the inflammatory esophageal gene expression signature. Inflammatory patients tended to have more collagen deposition than patients in the combined non-inflammatory/proliferative, but the results were not statistically significant ($p = 0.38$). Molecular classification of esophageal biopsies was independent of SSc subtype ($p=0.62$), serum autoantibodies ($p=0.23$) and esophagitis ($p=1.00$).

Conclusion: Similar to skin, Inflammatory and Proliferative Intrinsic Subsets are present SSc patients' esophagi suggesting that molecular subsets are a global feature of SSc end target organ pathology. SSc esophageal molecular subsets are distinct from subtypes identified clinically. Inflammation rather than fibrosis was the most dominant gene expression signature in SSc esophageal biopsies. The inflammatory signature is observed in biopsies that lack large inflammatory infiltrates suggesting that immune activation is a major driver of SSc esophageal pathogenesis.

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Dissecting the Heterogeneity of Skin Gene Expression Patterns in Systemic Sclerosis. Shervin Assassi[1], William Swindell[2], Minghua Wu[1], Filemon K. Tan[1], Dinesh Khanna[2], Daniel E. Furst[3], Donald Tashkin[3], Richard Jahan-Tigh[1], Maureen D Mayes[1], Johann Gudjonsson[2] and Jeffrey T. Chang[1]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]University of Michigan, Ann Arbor, MI, [3]University of California at Los Angeles, Los Angeles, CA.

Background/Purpose: To examine the heterogeneity of global transcriptome patterns in systemic sclerosis (SSc) skin from a large cohort of patients and controls.

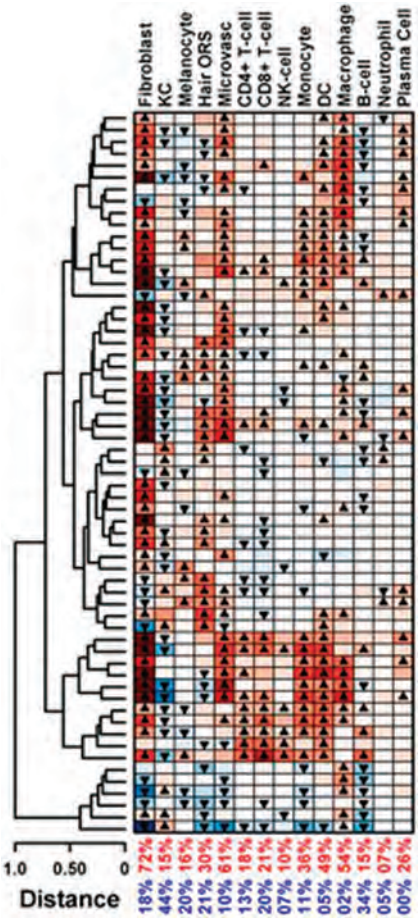
Methods: Skin biopsies from 61 patients (70.5 % diffuse cutaneous involvement) enrolled in the GENISOS cohort or at the baseline visit of an imatinib study, as well as 36 unaffected controls of similar demographic background, were examined by Illumina HT-12 gene expression arrays. Follow-up q-PCR and immunohistochemistry experiments were also performed. Using a novel analytic approach based on expression profiles, we investigated how heterogeneity within SSc samples relates to specific disease-relevant cell types (e.g. fibroblasts or macrophages).

Results: We identified 2754 differentially expressed transcripts in SSc patients compared to controls. Clustering analysis revealed two prominent transcriptomes in SSc patients: Keratin and fibro-inflammatory signatures. Higher keratin transcript scores were associated with shorter disease duration and interstitial lung disease while higher fibro-inflammatory scores were associated with diffuse cutaneous involvement, higher skin score at biopsy site and higher modified Rodnan Skin Score. There were no significant associations with disease-related autoantibodies or concomitant treatment with immunosuppressive agents. A subgroup of patients with significantly longer disease duration had a normal-like transcript pattern.

Further analysis and immunohistochemistry staining indicated that the above-mentioned keratin signature was not a general marker of keratinocyte activation, but was in fact associated with an activation pattern in hair and adnexal structures.

As shown in Figure 1, analysis of cell type-specific signature scores revealed remarkable heterogeneity across patients (each row represents a patient sample). Significantly high scores were observed in the majority of patients for fibroblasts (72% of patients), microvascular (61%), and macrophages (54%). The majority of samples with significant fibroblast scores (35 of 44 = 80%) also had significantly increased macrophage and/or dendritic cell scores. Only a minority of samples showed significantly high CD4+ T-cell, CD8+ T-cell and plasma cell scores (18%, 21%, and 26%).

Conclusion: In this large gene expression data set, a prominent keratin signature was present in addition to a fibro-inflammatory signature, supporting the notion that molecular dysregulations in SSc skin are not confined to the dermal layer but are in fact present in several skin compartments. Furthermore, the novel cell-specific transcript analysis showed significant heterogeneity of inflammatory profiles from SSc skin, which might be useful for stratifying patients for targeted treatment and/or predicting their response to immunosuppression.



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Potential Roles of Toll-like Receptor 4 in the Murine Models of Systemic Sclerosis. Takehiro Takahashi, Yoshihide Asano, Yohei Ichimura, Tetsuo Toyama, Takashi Taniguchi, Shinji Noda, Kaname Akamata and Shinichi Sato. University of Tokyo Graduate School of Medicine, Tokyo, Japan.

Background/Purpose: Bleomycin **(**BLM)-induced fibrosis model and tight skin mice (TSK/+) model are well-established experimental murine models of human systemic sclerosis (SSc). Growing evidence has demonstrated the pivotal role of Toll-like receptors (TLRs) in several autoimmune inflammatory diseases including SSc. The aim of this study is to determine the role of TLR4 in the fibrotic process in these models.

Methods: We generated a BLM-induced SSc murine model with mice deficient for TLR4. The mechanism by which TLR4 contributes to this fibrotic model was investigated with histologic examination, hydroxyproline assay, ELISA, real-time PCR, and flow cytometry. In addition, to examine the role of TLR4 in less inflammatory fibrotic model, we also investigated fibrosis in TSK/+ mice lacking TLR4.

Results: Dermal and lung fibrosis was attenuated in BLM-treated $TLR4^{-/-}$ mice compared with their wild type counterparts. Consistently, inflammatory cell infiltration, expression of various inflammatory cytokines, pathological angiogenesis, hypergammaglobulinemia and elevated titer of anti-DNA topoisomerase I antibody induced by BLM treatment were suppressed with TLR4 deletion. Furthermore, the increased expression of interleukin (IL)-6 in fibroblasts, endothelial cells, and immune cells in response to BLM *in vivo* and to LPS *in vitro*was remarkably abrogated in the absence of TLR4. Moreover, TLR4 deletion was associated with alleviated skew in Th2/Th17 response against BLM treatment. In parallel with these observations, TLR4 abrogation attenuated skin fibrosis in TSK/+ mice as well.

Conclusion: These results indicate the pivotal contribution of TLR4 to the pathogenesis in a BLM-induced SSc murine model and TSK/+ model, two major models which mimic early and late phase of SSc respectively. Our results indicate the critical role of TLR4 signaling in the pathogenesis of fibrosis, suggesting that the biomolecular TLR4 targeting might be a potential therapeutic approach to SSc.

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Identification of *IL12RB1* As a Novel Systemic Sclerosis Susceptibility *Locus*. Elena Lopez-Isac[1], Lara Bossini-Castillo[2], Sandra G Guerra[3], Shervin Assassi[4], Xiaodong Zhou[4], Carmen P. Simeón[5], Norberto Ortego-Centeno[6], Ivan Castellvi[7], Patricia Carreira[8], Olga Gorlova[9], Lorenzo Beretta[10], Alessandro Santaniello[11], Claudio Lunardi[12], Roger Hesselstrand[13], Annika Nordin[14], Gabriela Riemekasten[15], Torsten Witte[16], Nicolas Hunzelmann[17], Alexander Kreuter[18], Jörg HW Distler[19], Alexandre E. Voskuyl[20], Jeska K. De Vries-Bouwstra[21], Bobby P.C. Koeleman[22], Ariane Herrick[23], Jane Worthington[23], Christopher Denton[3], Carmen Fonseca[3], T.R.D.J. Radstake[22], Maureen D. Mayes[4] and Javier Martin[2]. [1]Institute of Parasitology and Biomedicine López-Neyra, IPBLN-CSIC, Granada, Spain, [2]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain, [3]Centre for Rheumatology, Royal Free and University College Medical School, London, United Kingdom, [4]University of Texas Health Science Center at Houston, Houston, TX, [5]Hospital Valle de Hebron, Barcelona, Spain, [6]Medicine Department, Hospital Universitario San Cecilio, Granada, Spain, [7]Hosp. De Sta. Creu i S. Pau, Vilafranca del Pened, Spain, [8]Hospital Universitario 12 de Octubre, Madrid, Spain, [9]The University of Texas MD Anderson Cancer Center, Houston, TX, [10]Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy, [11]Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy, [12]Università degli Studi di Verona, Verona, Italy, [13]Lund University, Lund, Sweden, [14]Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [15]Charité University Hospital and German Rheumatism Research Centre, a Leibniz Institute, Berlin, Germany, [16]Hannover Medical School, Hannover, Germany, [17]University of Cologne, Cologne, Germany, [18]HELIOS St. Elisabeth Hospital, Oberhausen, Germany, [19]Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [20]VU University Medical Center, Amsterdam, Netherlands, [21]Leiden University Medical Center, Leiden, Netherlands, [22]University Medical Center Utrecht, Utrecht, Netherlands, [23]The University of Manchester, Manchester, United Kingdom.

Background/Purpose: A recent large-scale fine mapping study -Immunochip- in systemic sclerosis (SSc) identified 3 novel genome-wide significant hits as well as a wide number of *loci* putatively associated with SSc (*P*-values between $5x10^{-3}$ and $5x10^{-8}$), which might result in real association signals that could be masked owing to a limited power. In this line, one of the *locus* that showed suggestive association signals was *IL12RB1*, which encodes the beta 1 subunit of the interleukin-12 (IL-12) receptor. Interestingly, several IL-12 pathway-related genes are confirmed genetic risk factors for SSc, such as *IL12RB2*, *STAT4* and *IL12A*. Therefore, our aim was to evaluate the genetic contribution of the *IL12RB1*region in SSc through a follow-up strategy.

Methods: Forty-six single-nucleotide polymorphisms (SNPs) within the *IL12RB1* region were screened in a discovery cohort comprising 1,871 SSc cases and 3,636 controls from the previously published Immunochip dense fine-mapping study. Four *IL12RB1* SNPs were selected for genotyping in a large Caucasian replication cohort. A meta-analysis of the data from the original Immunochip discovery cohort and the replication cohort was performed for a combined total of 5,052 SSc patients and 8,712 healthy controls. We also performed *in sillico* functional analyses for SNPs characterization.

Results: In the first phase of our study, 11 out of the 46 SNPs showed nominal association signals (*P*-values between $5x10^{-3}$ and $5x10^{-5}$). After conditional logistic regression analyses, we selected four SNPs (rs8109496, rs2305743, rs436857 and rs11668601) as the genetic variants which better explained the observed signals in the *IL12RB1* region. One SNP, rs2305743, reached the genome-wide significance level in the independent replication cohort ($P_{MH} = 3.936 \times 10^{-8}$, OR= 0.79). Interestingly, the combined analysis (discovery plus replication cohorts) showed that the four selected SNPs were associated with SSc at the genome-wide significance level. Finally, our *in silico* functional analyses showed that the minor allele of rs436857 promoter SNP was in an *IL12RB1* cis-expression Quantitative Trait *Loci* (eQTL) that decreased *IL12RB1* expression (*P*-value = 2.4×10^{-81}, Z-score = −19.10). Additionally, rs436857 showed evidence to affect the binding of several transcription factors. These results pinpoint rs436857 as the most likely causal variant for driving the reported association, narrowing down the signal to the promoter region of the gene.

Conclusion: The present study reports for the first time robust evidence for the implication of *IL12RB1* in SSc genetic background and highlights the importance of the follow-up studies. The results reinforce the relevance of IL-12 pathway in SSc pathophysiology, shedding light on our understanding of the immune system processes implicated in SSc development, and suggest that blocking this pathway could be a possible new therapeutic target.

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The Global miRNA Whole Blood Profile in Systemic Sclerosis and Its Correlation with Serum Cytokine Levels. Gloria Salazar[1], Maureen Mayes[2], John Hagan[3], Minghua Wu[1], John D. Reveille[1] and Shervin Assassi[1]. [1]University of Texas Health Science Center at Houston, Houston, TX, [2]University of TX Health Science Center -Houston, Houston, TX, [3]University of Texas at Houston, Houston, TX.

The Global miRNA Whole Blood Profile in Systemic Sclerosis and its Correlation with Serum Cytokine Levels

Background/Purpose: Several studies have implicated miRNAs in the pathogenesis of systemic sclerosis (SSc). [1–3] Recent advances in quantitative polymerase chain reaction (qPCR) allow simultaneous measurement of hundreds of miRNAs. The objective of this study was to use this technology to identify the unbiased, global miRNA profiling of SSc whole blood and evaluate its correlation with plasma cytokine levels.

Methods: We investigated the miRNA profile in SSc whole blood compared to unaffected controls using multiplex qPCR platform. We obtained blood samples from 10 patients with early SSc (≤5 yrs, on no immunosuppression) and 10 age-, gender- and ethnicity matched controls. Eight patients had diffuse disease and two had limited disease. The mean disease duration was 2.2 years. Levels of 752 miRNAs were determined. Unsupervised hierarchical clustering analysis was performed. Patient and control samples miRNA levels were compared and differences with a $p<0.01$, false discovery rate (FDR) <10% and fold change >2 were considered statistically significant.

A quantitative, multiplexed immunoassay designed to measure 45 cytokines, chemokines and acute-phase reactants was used to determine the serum cytokine levels (myriad human inflammationMAP) in order to correlate expression of miRNA with their predicted targets.

Results: The comparison of patient to control whole blood samples revealed 16 miRNA that were differentially expressed (Table 1). All miRNAs, except for miR-10b-5p, were downregulated in SSc compared to controls. Notably four differentially expressed miRNA in whole blood originate from the same cluster located in 14q32.3. The unsupervised hierarchical clustering analysis of whole blood miRNA profile separated the two groups but three patients clustered along with controls.

In the cytokine analysis, MCP1 (CCL2), IL-10, MMP-9, TNFR2, VCAM1 and ICAM1 were differentially expressed in SSc patients. MiR-370 levels highly correlated with MCP-1 protein levels ($r_s = -0.6$, $p=0.004$) which is a predicted target of this miRNA.

Conclusion: To our knowledge, this is the first global, unbiased examination of miRNA in SSc whole blood and the first correlation of miRNA with SSc plasma cytokine levels. The miRNA profile showed 16 miRNAs that are dysregulated in SSc whole blood. MiR-370 levels were differentially expressed in SSc blood and highly correlated with MCP-1 protein levels. We have previously reported also an upregulation of this miRNA in SSc skin. Furthermore, miR-370 targeted TGFbR-II in two independent studies underscoring its potential role in SSc pathogenesis.

Table 1. SSc whole blood dysregulated miRNA

miRNA	Location	Fold Change	*p*
miR-1238-3p	19p13.2	0.18	<0.001
miR-506-3p	Xq27.3	0.33	<0.001

miR-134	14q32	0.42	0.001
miR-579	5p13.3	0.2	0.001
miR-144-3p	17q11.2	0.27	0.002
miR-320a	8p21.3	0.5	0.002
miR-370	14q32	0.16	0.003
miR-1537	1q42.3	0.3	0.003
miR-2113	6q16.1	0.19	0.004
miR-877-5p	6p21.33	0.48	0.004
miR-101-5p	1p31.3	0.33	0.004
miR-200b-5p	1p36.33	0.33	0.006
miR-511	10p12.33	0.26	0.007
miR-300	14q32	0.26	0.008
miR-584-5p	5q32	0.49	0.009
miR-10b-5p	2q31.1	5.39	0.005

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Increased Degradation of BMPR2 in a TGFβ Dependent Transgenic Mouse Model of Scleroderma with Susceptibility to Pulmonary Arterial Hypertension. Adrian J Gilbane[1], Emma C. Derrett-Smith[2], Andrew Pearce[3], Christopher P Denton[2] and Alan M. Holmes[4]. [1]UCL Medical School, London, United Kingdom, [2]UCL Medical School Royal Free Campus, London, United Kingdom, [3]Novartis, London, United Kingdom, [4]UCL, London, United Kingdom.

Background/Purpose: Scleroderma patients are susceptible to development of pulmonary arterial hypertension (PAH) that has similarities to some forms of heritable PAH. The basis for this susceptibility is unclear and SSc-PAH has a worse clinical outcome. We have previously shown that a TGFβ dependent mouse model of scleroderma (TβRIIΔk-fib) develops PAH in response to pulmonary endothelial cell injury. Using this model as a platform and clinical material form SSc lungs we explored expression and proteasomal degradation of BMPRII that is implicated in development of heritable PAH.

Methods: We investigated BMP signalling in the lung in the TβRIIΔk-fib model of PAH-SSc in which TGFβ signalling is upregulated. The TβRIIΔk-fib mouse develops a structural pulmonary vasculopathy with smooth muscle hypertrophy and raised right ventricular pressures. Experiments were performed on whole lung isolates and explant cultured fibroblasts (n=6) from the TβRIIΔk-fib mouse and compared with wildtype controls. TGFβ/BMP signalling pathways were investigated by Western blot and immunohistochemistry and qPCR. MG132, an inhibitor of proteasomal degradation, was used to explore the role of proteasomal degradation on BMPRII protein levels in vitro.

Results: The TβRIIΔk-fib model has increased levels of pSmad2/3, indicative of enhanced TGFβ signalling. The TβRIIΔk-fib model exhibits a significant reduction in BMPRII protein expression in whole lung isolates (1.43, 0.38) ($p<0.05$), and explant cultured fibroblasts (0.299, 0.09) ($p<0.05$). A reduction of BMPRII was also observed in whole lung (0.095, 0.03) and explant cultured lung fibroblasts from SSc patients compared to healthy controls ($p<0.05$) but there was an increase in BMPRII gene expression. Interestingly, both TβRIIΔk-fib and SSc fibroblasts exhibited refractory responses to BMP4 ($p<0.05$). MG132 was able to restore BMPRII protein levels and restore BMP4 ligand response of SSc fibroblasts.

Conclusion: Here we demonstrate the TβRIIΔk-fib transgenic murine model of PAH-SSc exhibits reduced expression of BMPRII as a reciprocal response to increased TGFβ signalling. Collectively our data suggests loss of BMPRII expression by non-genetic means may contribute to the development of PAH in SSc. Further, our results suggest that use of a proteasomal degradation inhibitor might reduce the risk of developing PAH by restoring BMPRII expression.

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Nucleosome, a Basic Repeating Unit of Chromatin, in Patients with Systemic Sclerosis: Possible Association with Immunological Abnormalities Via Abnormal Activation of T and B Cells. Ayumi Yoshizaki, Yoshihide Asano, Takashi Taniguchi, Ryosuke Saigusa, Kouki Nakamura, Takashi Yamashita, Takehiro Takahashi, Tetsuo Toyama, Yohei Ichimura, Zenshiro Tamaki, Miki Miyazaki and Shinichi Sato. University of Tokyo Graduate School of Medicine, Tokyo, Japan.

Background/Purpose: Nucleosome is the basic repeating units of chromatin. Each nucleosome is composed of an inner core of histones H3 and H4 and an outer portion of histones H2A and H2B. Protruding tails of the histones can establish contact with other nucleosomes. In addition, these tails can be modified by methyl-, acetyl-, or ubiquitin-groups. DNA surrounds the protein core about 1.5 times on the flat outside and is connected with histones at 14 sites. Nucleosomes are released from cells during apoptosis and necrosis. Although elevated serum nucleosome levels have been described in various autoimmune disorders, only one previous study has shown that systemic sclerosis (SSc) exhibits elevated serum nucleosome levels in less than 15 patients. In addition, correlations of serum nucleosome levels with immunological parameters and organ involvement were not investigated. Although nucleosome contains DNA and histone, which are major autoantigens of various autoimmune diseases, the relationship of nucleosome and disease progression are still unknown. Therefore, we investigated the role of nucleosome in SSc and correlation of serum nucleosome levels with immunological parameters, extent of skin and lung fibrosis, vascular damage, and presence of other organ involvements in SSc.

Methods: Serum nucleosome levels were examined in SSc (n=91) and controls (n=20) by enzyme-linked immunosorbent assay. We also examined serum nucleosome levels in bleomycin-induced SSc model mice and phosphate-buffered saline-treated control mice.

Results: Nucleosome levels in limited cutaneous SSc and diffuse cutaneous SSc patients were significantly higher than in normal controls ($p<0.0001$, respectively). Similarly, in bleomycin-induced SSc model mice, serum nucleosome levels were higher than in control mice ($p<0.0001$). SSc patients with elevated nucleosome levels had significantly higher modified Rodnan total skin thickness score, high frequency of diffuse cutaneous SSc, and more frequent involvement of pitting scar/ulcer, pulmonary fibrosis, esophagus, heart, kidneys, joints, and muscle than those with normal levels ($p<0.05$, respectively). Nucleosome levels also significantly correlated inversely with %VC ($r=-0.22$, $p<0.01$) and %DLco ($r=-0.68$, $p<0.001$) and positively with modified Rodnan total skin thickness score ($r=0.58$, $p<0.001$). SSc patients with elevated nucleosome levels had significantly higher frequency of elevated levels of serum IgG and more frequent presence of anti-topoisomerase I and centromere antibodies compared with those with normal levels ($p<0.05$, respectively). Moreover, in this study, we demonstrated that nucleosome could activate T and B cells which were obtained from SSc patients.

Conclusion: These results suggest that elevation of nucleosome levels is associated with the disease severity. In addition, this study is the first to reveal the association of nucleosome levels with various immunological abnormalities in SSc.

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Distinctive Patterns of Telomere Shortening and Apoptosis in Limited and Diffuse cutaneous Systemic Sclerosis. Jasper Broen[1], Liane McGlynn[2], Dagmara McGuinness[2], Rina Wichers[3], Jacqueline Thomson[2], Rajan Madhok[4], Robert Lafyatis[5], Carol A. Feghali-Bostwick[6], Paul Shiels[2] and T.R.D.J. Radstake[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]University of Glasgow, Glasgow, United Kingdom, [3]UMC Utrecht, Utrecht, Netherlands, [4]Glasgow Royal Infirmary, Glasgow, United Kingdom, [5]Boston University, Boston, MA, [6]Medical University of South Carolina, Charleston, SC.

Background/Purpose: Aberrant telomere shortening and DNA damage-responses have been previously described in SSc, here we aim to validate these observations and incorporate them in a functional and clinical relevant framework.

Methods: We measured telomere length in peripheral blood leukocytes, monocytes, B cells, myeloid dendritic cells, T cells and plasmacytoid dendritic cells from a total of 103 healthy controls, 121 lcSSc patients and 83 dcSSc patients. In addition, telomere measurements were performed in 21 monozygotic twin pairs with SSc. We finally analyzed apoptosis and telomere gene expression arrays to investigate underlying pathways and used them to stratify patients.

Results: We found that suffering from dcSSc is an independent risk factor for shorter telomeres in full blood cells, which is on the cellular level reflected by significantly shorter telomeres in T cells and pDCs compared to healthy controls and lcSSc (all $p<0.001$). Based on the analyses of 21 monozygotic twin pairs with SSc we conclude that this seems to be an inborn error in

dcSSc, whereas in lcSSc telomere shortening seems to be caused by disease itself. We establish by gene expression arrays that this seems to be mainly caused by aberrant expression of apoptotic genes, of which expression of *BIRC5* and *P53* have a specificity of 91% to predict dcSSc from a mixed-pool of 72 healthy controls, lcSSc patients, patients with Raynaud's phenomenom, ANA+ patients and early SSc patients identified by nail-capillaroscopy, making these genes clinically relevant.

Conclusion: Telomere shortening and apoptotic pathways are differentially regulated in lcSSc and dcSSc and provide novel avenues for patient stratification.

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Assessment of mRNA Gene Expression Based on Forearm Skin Score in Systemic Sclerosis Patients. Lisa Rice[1], Giuseppina Stifano[1], Jessica Ziemek[2] and Robert Lafyatis[2]. [1]Boston University Medical Center, Boston, MA, [2]Boston University School of Medicine, Boston, MA.

Background/Purpose: The extent of skin disease in patients with systemic sclerosis is typically measured through physical examination of patients at 17 sites and involvement is quantified on a scale from uninvolved to severe involvement (0 to 3). The total of all 17 sites scores is defined as the Modified Rodnan Skin Score (MRSS). We have shown previously that gene expression of skin biopsies taken from the mid-forearm correlates well with overall skin disease as assessed by the MRSS. However, it remained unclear whether the success of such an approach represented a particularly accurate, molecular, quantification of local skin disease or a manifestation of altered gene expression known to occur in all the skin of systemic sclerosis patients, both lesional and non-lesional.

Methods: Skin biopsies (n=42) from the forearms of patients with diffuse cutaneous SSc (dcSSc) and healthy donors (n=5) were assessed for expression of genes we have previously identified as elevated in SSc skin. The results were assessed for difference (one-way ANOVA) in gene expression ($p \leq 0.05$) with forearm skin score (0 to 3) and correlation with forearm skin score (Pearson's).

Results: Expression of all genes examined form patients showing a local skin score of 1 or greater were different from healthy control. Several inflammatory, TGFβ, and WNT regulated genes (CCL2, IL13RA1, COMP, THBS-1, ADAM12, and WIF1) showed a significant correlation with the local forearm score (1 or greater). Other inflammatory and macrophage related genes (IFI44, CD163, SIGLEC1, CD14) showed no significant correlation between the level of gene expression and the local skin score.

Conclusion: The different relationships between local gene expression, and local versus systemic assessment of the skin score (MRSS) suggest a hierarchy of molecular events. Gene expression correlating most highly with the local skin score may represent molecular events closest to clinical manifestations. Altered gene expression that does not correlate with the skin score may represent more molecular events earlier in the pathogenic cascade, or alternatively epiphenomena without direct roles in pathogenesis. These results have particular implications for biomarker selection in clinical trials of drugs delivered by local topical application.

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The Anti-Fibrotic Effect of Endostatin-Derived Peptide Is Mediated By Urokinase. Tetsuya Nishimoto[1], Takahisa Takihara[2], Yunyun Su[1], Roger Chambers[1], Logan Mlakar[1] and Carol Feghali-Bostwick[1]. [1]Medical University of South Carolina, Charleston, SC, [2]Tokai University School of Medicine, Kanagawa, Japan.

Background/Purpose: Fibroproliferative disorders such as systemic sclerosis (SSc) have no effective therapies and result in significant morbidity and mortality as a result of organ fibrosis. We recently demonstrated that the C-terminal domain of endostatin known as E4, corresponding to amino acid sequence 133–180, is a promising therapeutic agent for fibrotic disorders. E4 prevented and reversed both dermal and pulmonary fibrosis. Our goal was to delineate the mechanism by which E4 abrogates fibrosis. Preliminary gene expression data from primary human fibroblasts suggested that E4 treatment resulted in increased expression of urokinase (uPA).

Methods: Bleomycin (60 μg/mice) or Bleomycin in combination with E4 (10 ug/ml) was administered intratracheally to 6 to 8-week-old C57BL/6J male mice to induce lung fibrosis. Bronchoalveolar lavage (BAL) fluid was collected on days 3, 5, 7, and 14 post treatment, and the levels and activity of uPA and plasminogen activator inhibitor-1 (PAI-1), an inhibitor of uPA, were measured. Primary human fibroblasts were treated with TGF-b (10 ng/ml) to induce a fibrotic phenotype or TGF-b in combination with E4 (10 ug/ml). The mRNA and protein levels of uPA, PAI-1, matrix metalloproteinase-1 (MMP-1), and MMP-3 were determined using real-time PCR and immunoblotting, respectively. Secreted uPA activity was also measured in fibroblast supernatants. Since MMP-1 and MMP-3 are downstream effectors of uPA, we assessed MMP-1 and -3 activity using collagen and casein zymography, respectively. The mRNA levels of uPA and PAI-1 in human whole lung tissue and lung fibroblasts from 9 healthy control (HC) and 32 SSc patients were examined using real-time PCR.

Results: *In vivo*, bleomycin reduced uPA levels and activity and increased PAI-1 activity. E4 peptide partially blocked these effects. The reduction of PAI-1 caused by E4 administration preceded the increase in uPA activity, suggesting that a release from inhibition may explain in part the increase in uPA activity. *In vitro*, TGF-b reduced uPA levels and increased PAI-1 levels in primary fibroblasts. E4 peptide cancelled these effects and increased the uPA/PAI-1 ratio. Moreover, the expression and activity of MMP-1 and MMP-3 were increased by E4 treatment. The mRNA levels of uPA both in whole lung tissue and lung fibroblasts were comparable between HC and SSc patients, however, those of PAI-1 were increased in SSc patients, resulting in a decrease of the uPA/PAI-1 ratio.

Conclusion: Our results demonstrated that E4 increases uPA activity by both increasing uPA levels and activity and reducing PAI-1-mediated inhibition. The ability of E4 to reverse fibrosis can be explained by its ability to induce MMP-1 and MMP-3 levels and activity, thus promoting extracellular matrix degradation. In SSc patients, the uPA/PAI-1 balance shifted toward PAI-1. Taken together, our findings suggest that the anti-fibrotic effects of E4 peptide are mediated, at least in part, by the uPA fibrinolytic system, and that E4 peptide exerts its therapeutic effects in organ fibrosis via regulation of the urokinase pathway.

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Use of Multiplex Cytokine Analysis of Dermal Blister Fluid to Assess Local Inflammatory and Immune Activity in Systemic Sclerosis. Kristina E.N. Clark[1], Henry Lopez[2], Xu Shiwen[1], Bahja Ahmed Abdi[1], George Martin[3], Korsa Khan[4], David J. Abraham[1], Christopher P. Denton[5] and Richard J. Stratton[1]. [1]UCL Medical School, London, United Kingdom, [2]Murigenics, Vallejo, CA, [3]Aero Dap, Vallejo, CA, [4]UCL medical School, London, United Kingdom, [5]UCL Medical School Royal Free Campus, London, United Kingdom.

Background/Purpose: Clinical diversity in systemic sclerosis (SSc) suggests complex multifaceted pathogenesis involving interplay of growth factors or cytokines within the lesional microenvironment. We analysed dermal suction blister fluid to investigate protein expression in skin of SSc patients and healthy controls. We compared the levels of key candidate proteins that may be relevant to pathogenesis.

Methods: Blister fluid (BF) samples from the forearm skin of patients (n=25; DcSSc =19, LcSSc=6) or healthy controls (HC)(n=10) were collected using a dermal suction blister method with paired serum samples, and profiled by Luminex array. Permutation analysis was used for statistical testing.

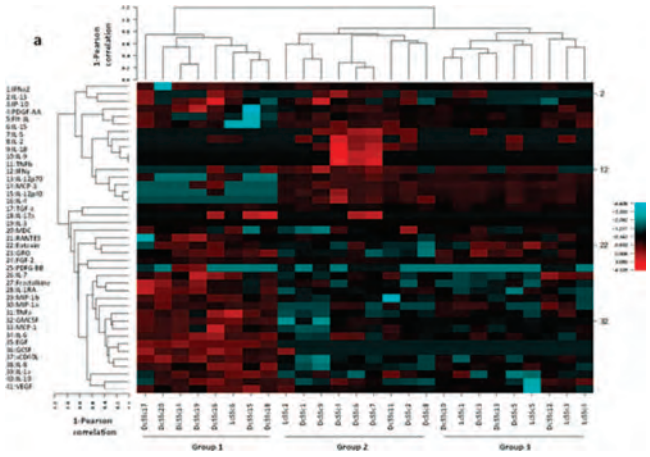
Results: BF: Profiling showed increased inflammatory cytokines (mean IL-6 in SSc- 77.2 pg/ml, HC-17.8 pg/ml, p=0.009, mean IL-17 in SSc-0.61 pg/ml, HC- 0 pg/ml, p=0.03), and vascular growth factors (PDGF-aa 16.4 pg/ml in SSc, HC-0.97 pg/ml, p=0.049). Additionally MCP-3 (CCL7), IL-15 and IFN-g were all significantly increased in SSc ($p<0.05$). Plasma: 19/26 SSc patients, and 8/10 HCs were available. Proteins that were significantly raised ($p<0.05$) in plasma compared to HC, that were also raised in BF were MCP-3 (p=0.025), IL-15 (p=0.02) and IL-6 (p=0.04). Also raised in plasma were IL-1Rα, IL-1a, IL-12p40, GM-CSF, IL-2, IL-4, IL-9, Flt-3L and VEGF (all $p<0.05$). Of interest Th2 cytokines IL-4, 5, and 13, were only detectable in SSc plasma.

Proinflammatory cytokines (IL-6 (p=0.23), IL-17 (p=0.56)), and growth factors (VEGF(,p=0.47), PDGF(p=0.22)) showed no correlation between serum samples and BF. The healthy controls showed greater correlation

between BF and serum, often reaching significance (IL-10,MCP-3,IL1ra, FGF-2).

Heatmaps of BF (Figure 1). Unbiased BF analysis by CIMminer (NIH) revealed clustering of SSc patients into 3 groups; Group 1, high IL-6, IL-10, TNFα, and IL-1α high (innate) consisted of mainly early DcSSc with high skin score. Group 2 comprised late stage DcSSc with increased levels of IFNγ, IL-2, IL-4, IL-5, MCP-3, IL12p40, IL12p70 (adaptive). Group3 quiescent with low levels of cytokines and chemokines, and LcSSc or DcSSc patients with low skin score. Plasma analysis did not cluster into distinct clinical groups. ANOVA showed significant difference between skin scores ($p=0.003$), with Scheffe post hoc analysis showing significant higher skin scores in Group 1 ($p=0.005$).

Conclusion: Our results confirm the value of dermal blister analysis in SSc, and identify key factors expressed locally. Whilst plasma analysis revealed some overlap with the blister fluid analysis, it did not reflect all of the changes present in the dermal microenvironment. This method profiles the local inflammatory process occurring within the skin and complements clinical and gene expression based classification, as well as suggesting markers of disease activity or treatment effect.



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Specific Autoantibody Profiles and Disease Subgroups Correlate with Circulating Micro-RNA in Systemic Sclerosis. Dirk Wuttge[1], Anting L. Carlsen[2], Gabriel Teku[1], Samantha Steen[2], Marie Wildt[1], Mauno Vihinen[1], Roger Hesselstrand[1] and Niels H. H. Heegaard[3]. [1]Lund University, Lund, Sweden, [2]Statens Serum Institut, Copenhagen, Denmark, [3]Odense University Hospital, Odense C, Denmark.

Background/Purpose: Systemic sclerosis (SSc) is a serious autoimmune disease with clinical phenotypes of different prognosis, progression rate, and different extent of involvement of internal organs. Specific circulating autoantibody profiles contribute to forecasting the prognosis of SSc cases. Circulating micro-RNA (miRNA) profiles also are characteristic in SSc but clinical phenotypes, autoantibody profiles, and circulating miRNA profiles have not yet been correlated. The aim of the study, therefore, was to evaluate the expression profiles of cell-free plasma miRNAs in SSc and study their correlation with disease subgroups (limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc)) and with clinical and paraclinical parameters including circulating autoantibody profiles.

Methods: Total RNA was purified from plasma and the abundance of 45 mature miRNAs were measured using quantitative polymerase chain reaction assays after reverse transcription. A total of 95 SSc patients (n=94 fulfilling the ACR criteria for SSc, n=1 with limited SSc) were included (lcSSc, n=63; dcSSc, n=32). The patients represented the following autoantibody subgroups: anti-centromere group (ACA, n=35); anti-DNA topoisomerase I group (ATA, n=20), anti-RNA polymerase III group (ARA, n=20); and anti-U1-RNP group (RNP, n=20). MiRNA expression data, clinical data, autoantibody data, and other paraclinical data were analyzed for correlations. Regression analysis was performed to optimize models for prediction of SSc disease subgroups and autoantibody classes.

Results: A total of 36 miRNAs were measurable in all samples. Six of these miRNAs were statistically significantly differently expressed between the lcSSc and dcSSc groups in univariate tests and three (miRNAs -223, -181b, and 342-3p) remained significant after correction for multiple comparisons. Ten miRNAs exhibited statistically significant different levels in one or more autoantibody groups and three of these miRNAs were also found to differ between the dcSSc and lcSSc groups. Five miRNAs (miRNAs -409-3p, -184, -92a, -29a, and -101) retained significance after correction for multiple comparisons. Analysis of patterns of miRNA levels and clinical and paraclinal parameters showed correlations between C-reactive protein and glomerular filtration rates and the specific regulation of distinct miRNAs.

Conclusion: The profile of circulating miRNAs from plasma samples of SSc patients differ between patients classified as lcSSc and dcSSc and between the four autoantibody groups. Especially the ACA group is distinctive in terms of its specific circulating miRNA profile. This is the first time autoantibody profiles, disease phenotypes, and plasma miRNA profiles have been shown to correlate in an autoimmune disease. The data supports the role of miRNAs in SSc by showing that specific miRNAs are associated with autoantibody profiles of known diagnostic and prognostic value.

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IQGAP1 Enhances Contractility of Scleroderma Lung Fibroblasts and Promotes Bleomycin-Induced Pulmonary Fibrosis. Tanjina Akter[1], Ilia Atanelishvili[1], Yuichiro Shirai[2], Sybil Prince Nelson[2], Alvaro Garcia-Martos[3], Thomas A. Morinelli[2], Richard M. Silver[1] and Galina S. Bogatkevich[1]. [1]Medical University of South Carolina, Charleston, USA, Charleston, SC, [2]Medical University of South Carolina, Charleston, USA, chareston, SC, [3]Hospital la Zarzuela, Madrid, Spain, Madrid, Spain.

Background/Purpose: Scleroderma associated interstitial lung disease (SSc-ILD) is an irreversible and progressive complication and a leading cause of death among SSc patients. Constitutive overexpression of connective tissue growth factor (CTGF) has been observed in both *in vivo* and *in vitro* studies of SSc patients. Proteomic analysis of CTGF-activated lung fibroblasts demonstrated that CTGF induces IQ motif containing GTPase activating protein (IQGAP1). IQGAP1 is a multifunctional scaffold protein that integrates diverse signal transduction pathways and regulates fibroblast migration. Our recent findings demonstrate the profibrotic role of IQGAP1 in the bleomycin-induced murine model of SSc-ILD. Here we report our latest data focusing on the molecular mechanism and pathophysiologic action of IQGAP1 in this mouse model of ILD.

Methods: Lung injury was induced in female C57BL/6 mice by a single intratracheal instillation of bleomycin (0.05U/mouse). IQGAP1-siRNA and CTGF-siRNA were delivered by intranasal instillation every other day. Mice were sacrificed 3 weeks after bleomycin instillation and lungs were harvested. Lungs were perfused with neutral buffered formaldehyde, embedded in paraffin, stained with hematoxylin and eosin (H&E), and scored for fibrosis. Lung tissue was harvested, lyophilized and run on western blot. IQGAP1 knockout mice were challenged with bleomycin and histology was performed. Assessment of collagen was accomplished by Masson's trichrome staining and by Sircol Collagen Assay. The role of IQGAP1 in F-actin filament formation was examined by immunofluorescence staining and by actin polymerization assay. The rate of actin polymerization was measured in terms of fluorescence intensity by Fluorometric Imaging Plate Reader.

Results: A profound antifibrotic effect was observed in the bleomycin lung fibrosis model when IQGAP1-siRNA treatment was combined with CTGF-siRNA treatment. Partial reduction of fibrosis was detected with treatment by either of these two siRNA's alone. Western blot results showed that IQGAP1-siRNA decreased the expression of IQGAP1 by 70% and had no effect on CTGF expression. However, CTGF-siRNA reduced the expression of CTGF by 80% and IQGAP1 by 40%. A similar trend of reduction in fibrosis was observed in IQGAP1 knockout mice. Decreased collagen expression was detected by Masson's trichrome stain and by Sircol Collagen Assay. Immunofluorescence staining of IQGAP1 and F-actin on human SSc lung fibroblasts demonstrated that IQGAP1 co-localizes with globular actin but not with filamentous stress fiber actin, indicating a crucial role of IQGAP1 in actin rearrangement. The actin polymerization assay demonstrated that the rate of actin polymerization is IQGAP1 dependent.

Conclusion: IQGAP1 forms a signal transduction complex with CTGF in lung fibroblasts, regulates the expression of α-SMA, and promotes pulmonary fibrosis. Inhibition of IQGAP1 has a marked antifibrotic effect in a bleomycin model of pulmonary fibrosis and should be considered as a potential new therapeutic target for the treatment of SSc-ILD.

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Caveolin-1 and Peroxisome Proliferator-Activated Receptor Gamma Co-Regulate the Differentiation of Monocytes to Adipocytes and Myofibroblasts in Vivo and in Vitro. Rebecca Lee[1], Charles Reese[1], Michael Bonner[1], Beth Perry[1], Richard M. Silver[2], Richard P. Visconti[1], Stanley Hoffman[1] and Elena Tourkina[1]. [1]Medical University of South Carolina, Charleston, SC, [2]Medical University of South Carolina, Charleston, USA, Charleston, SC.

Background/Purpose: Skin fibrosis in scleroderma is associated with the loss of subcutaneous adipose tissue (lipodystrophy). The mechanisms underlying lipodystrophy and its relationship to fibrosis are not known. Monocytes are precursors of several cell types including myofibroblasts and adipocytes. We recently showed that this myofibroblast differentiation is inhibited by the master regulatory protein caveolin-1. Similarly, caveolin-1-deficient mice are lean with small adipocytes. The nuclear receptor PPARγ also regulates adipose differentiation and lipid homeostasis. Here we examine the coordinate roles of caveolin-1 and PPARγ in adipogenesis and fibrosis.

Methods: Mini-osmotic pumps are implanted into 10 week-old CD1 male mice. The pump delivers 100 U/kg bleomycin or saline and is removed on day 10. Mice are injected i.p. daily with 100 μl caveolin-1 scaffolding domain peptide (CSD, final concentration 0.1 mM) or phosphate-buffered saline (PBS) vehicle over the entire course of the experiment and sacrificed on day 28. Cutaneous fibrosis and lipodystrophy are analyzed histologically and immunohistologically. Monocytes are obtained from scleroderma patients and healthy controls. Monocyte differentiation to adipocytes and myofibroblasts is evaluated using Oil red O stain and ASMA stain. PPARγ and caveolin-1 expression are determined by Western blot and immunohistochemistry.

Results: We previously observed a loss of subcutaneous adipose tissue concomitant with dermal fibrosis in bleomycin treated mice, both of which were blocked by CSD. We now show that levels of caveolin-1 and PPARγ are reduced in adipocytes of SSc patients and bleomycin-treated mice. CSD significantly enhances the expression of PPARγ and FABP4 in adipocytes in bleomycin-treated mice. Low levels of PPARγ are observed in monocytes from SSc patients and are increased by CSD treatment. PPARγ ligand triglitazone (TRLZ) and CSD inhibit, and TGFβ promotes human monocytes differentiation to myofibroblasts. Conversely, these treatments have the opposite effects on monocyte differentiation into adipocytes. These treatments affected PPARγ signaling through their effects on PPARγ levels and localization.

Conclusion: The present studies demonstrate the importance of both caveolin-1 and PPARγ in the regulation of adipogenesis in fibrotic skin. These studies further validate CSD as a novel therapy for both fibrotic disease and lipodystrophy.

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ERG and FLI1 in Systemic Sclerosis-Associated Pulmonary Complications. Rong Han and Maria Trojanowska. Boston University, Boston, MA.

Background/Purpose: Pulmonary arterial hypertension (PAH) and pulmonary fibrosis (PF) are the two major lung complications associated with the autoimmune disease systemic sclerosis (SSc), and constitute the leading causes of mortality and morbidity in patients with SSc. Endothelial dysfunction and inflammation have both been described in these two diseases. We hypothesize that disturbed transcriptional control of endothelial cell function can induce inflammation in the lung, which in turn drives the initiation and progression of PAH and PF in SSc. Deficiency of the ETS family transcription factor FLI1 has been implicated in scleroderma vasculopathy, while its closest homolog, ERG, has been demonstrated to suppress inflammatory gene expression in endothelial cells. The purpose of this study is to determine whether ERG and FLI1 deficiency plays a pathogenic role in SSc-associated lung manifestations.

Methods: Paraffin sections of lung samples from patients with SSc were subjected to immunohistochemical staining for ERG and FLI1. ERG and FLI1 were inhibited in human pulmonary arterial endothelial cells (HPAEC) with siRNA, and gene expression changes were analyzed by microarray and then validated with quantitative RT-PCR. *Erg* and *Fli1* double heterozygote mice were generated and lung samples from these mice were analyzed.

Results: ERG protein level was significantly reduced in the endothelium of lung samples from patients with SSc, while FLI1 was similarly reduced but to a lesser extent, suggesting that the loss of ERG and FLI1 is associated with the vascular changes occurring in the lung of patients with SSc. In HPAECs treated with *ERG* and *FLI1* siRNA, a number of inflammatory genes, including *CXCL10*, *IL8*, *IRF1*, *GBP1*, *IFIT2*, *VCAM1*, were upregulated, whereas genes regulating endothelial homeostasis and cell-cell adhesion, such as *APLN*, *FABP4*, *PECAM1* and *VECADHERIN*, were downregulated. Simultaneous knockdown of both *ERG* and *FLI1* had a synergistic effect on the expression of these genes, suggesting that ERG and FLI1 co-regulate at least a subset of their target genes. Consistent with the upregulation of inflammatory genes seen in vitro with *ERG* and *FLI1* knockdown, *Erg* and *Fli1* double heterozygote mice show increased lymphocyte infiltration in the lung.

Conclusion: Loss of ERG and FLI1 might contribute to the pathogenesis of SSc-associated lung complications through the induction of inflammation in the tissue.

Disclosure: R. Han, None; **M. Trojanowska**, None.

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Gene-Gene Interaction of *IRF5* and *BLK* Polymorphisms in US and Spanish Cohorts of Systemic Sclerosis (SSc). Pravitt Gourh[1], Yoonhee Kim[2], Sandeep K. Agarwal[3], Filemon K. Tan[4], Shervin Assassi[4], Javier Martin[5], Frank C. Arnett[4] and Maureen D. Mayes[4]. [1]National Institutes of Health, Bethesda, MD, [2]NIH, Bethesda, MD, [3]Baylor College of Medicine, Houston, TX, [4]University of Texas Health Science Center at Houston, Houston, TX, [5]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain.

Background/Purpose: Systemic sclerosis (SSc) is a complex autoimmune disease and several genetic loci increasing SSc susceptibility have been identified with small to modest effect sizes. These loci even when taken together are not able to fully explain the heritability of SSc. We believe that genetic epistasis along with rare variants and gene-environment interaction may explain the missing heritability. In this study, we test two seemingly distinct loci, rs2004640 on *IRF5* and rs2736340 on *BLK* both of which have previously been associated with SSc, for genetic epistasis.

Methods: In this study, we combined genetic data from rs2004640 variant on *IRF5* and rs2736340 variant on *BLK* from 1024 patients with SSc and 694 unrelated healthy controls from University of Texas and a Spanish case–control series of 395 SSc patients and 443 healthy controls. Odds ratios (OR) and biologic interactions as departures from additivity or multiplicity were analyzed by logistic regression. To quantify the amount of interaction in terms of departure from additivity of effects, the relative excess risk due to interaction (RERI), proportion attributable to interaction (AP), and the synergy index (S) were calculated. Interaction between the two SNPs was evaluated using the cross-product of the risk factors in a logistic-regression model as interaction criteria (multiplicative interaction). We adjusted for gender and cohort in the analyses. Recoding of *IRF5*, *BLK* genotypes from protective effects to risk effects were done to produce the meaningful measures for departures of additivity. Statistical analyses were performed using SAS 9.3. Gene expression array of PBMCs from PAXgene tubes were analyzed with BRB-ArrayTools.

Results: Both *IRF5*:rs2004640 and *BLK:* rs2736340 variants show independent association with SSc. The OR of single effects was 1.40 for *IRF5*:rs2004640 and 1.44 for *BLK:* rs2736340 (Table 1).

We observed a significant multiplicative interaction between *IRF5* GT/TT & *BLK* CT/TT genotypes as compared to *IRF5* GG & *BLK* CC genotypes ($p=0.02$). The OR of joint effects for *IRF5* GT/TT & *BLK* CT/TT genotypes was higher than the wildtype genotype ($P=0.0003$, OR=2.26; 95%CI 1.7–3.1). RERI<0, AP<0, and S<1 mean negative interaction and less than additivity. P value of S is significant, but 95% CI includes 1.

PBMC RNA gene expression arrays predicted more T & B cell pathways in SSc as compared to controls for *IRF5* GT/TT & *BLK* CT/TT genotypes and PPAR-γ and WNT signaling pathways in SSc as compared to controls for *IRF5* GG & *BLK* CC genotypes.

Conclusion: In an effort to explore genetic epistasis we demonstrate genetic interaction using multiple methodologies between two well-replicated and distinct loci on *IRF5* and *BLK*. We also observed differences in the gene expression pathways based on the *IRF5* and *BLK* genotypes. Additional studies are needed to test them in other autoimmune diseases and discern their role at a molecular level.

Table 1.

	Genotype	No SSc/ Controls	OR (95% CI)
OR of single effect	*IRF5* GG	257/254	1
	IRF5 GT/TT	1162/883	1.40 (1.1–1.7)
	BLK CC	722/670	1
	BLK CC/CT	697/497	1.44 (1.2–1.7)
OR of joint effect	*IRF5* GG/*BLK* CC	123/164	1
	IRF5 GT, TT/*BLK* CC	599/506	1.74 (1.3–2.3)
	IRF5 GG/*BLK* CT, TT	134/90	2.16 (1.5–3.2)
	IRF5 GT, TT/*BLK* CT, TT	563/377	2.26 (1.7–3.1)
Additivity	AP	P = 0.14	−0.28 (−0.7–0.09)
	RERI	P = 0.21	−0.64 (−1.7–0.4)
	S	P = 0.005	0.66 (0.2–1.2)
	Multiplicity		P = 0.02

***IRF5* GG/*BLK* CC SSc v Controls Top 10 Pathways (p<0.01)**	***IRF5* GT/TT & *BLK* CT/TT SSc v Controls Top 10 Pathways (p<0.01)**
Multi-step Regulation of Transcription by Pitx2	Proepithelin Conversion to Epithelin and Wound Repair Control
Control of Gene Expression by Vitamin D Receptor	T Cell Receptor Signaling Pathway
Role of MEF2D in T-cell Apoptosis	CTL mediated immune response against target cells
Role of PPAR-gamma Coactivators in Obesity and Thermogenesis	HIV induced T Cell Apoptosis
Mechanism of Gene Regulation by Peroxisome Proliferators via PPARa (alpha)	IFN gamma signaling pathway
Chromatin Remodeling by hSWI/SNF ATP-dependent Complexes	Selective expression of chemokine receptors during T-cell polarization
Pertussis toxin-insensitive CCR5 Signaling in Macrophage	Antigen Dependent B Cell Activation
WNT Signaling Pathway	IL-10 Anti-inflammatory Signaling Pathway
METS affect on Macrophage Differentiation	TNFR2 Signaling Pathway
ADP-Ribosylation Factor	Lck and Fyn tyrosine kinases in initiation of TCR Activation

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Endothelial Fli1 Deficiency Delays Wound Healing Due to Impaired Anastomosis of Newly Formed Vessels – a Possible Mechanism of Refractory Skin Ulcers in Systemic Sclerosis. Yoshihide Asano[1] and Maria Trojanowska[2]. [1]University of Tokyo Graduate School of Medicine, Tokyo, Japan, [2]Boston University, Boston, MA.

Background/Purpose: Systemic sclerosis (SSc) is a multisystem inflammatory and vascular disease resulting in fibrosis of the skin and certain internal organs. Although the pathogenesis of SSc still remains unknown, we have recently demonstrated that Fli1 deficiency at least partially due to epigenetic suppression contributes to the development of fibrosis and vasculopathy characteristically seen in this disease. A critical complication associated with SSc vasculopathy is refractory and recurrent skin ulcers which largely affect morbidity of SSc patients. To elucidate a potential mechanism rendering skin ulcers refractory to the treatments in SSc, we employed endothelial cell-specific Fli1 knockout (Fli1 ECKO) mice and carried out a wound healing experiment.

Methods: Fli1 ECKO mice were generated by crossing $Fli1^{flox/flox}$ mice with Tie2-Cre transgenic mice under a C57B/6 background. An 8 mm full-thickness skin wound was generated on the back of wild type (WT) and Fli1 ECKO mice with a punch biopsy. Vascular structure was visualized by FITC-dextran injection. The expression levels of target molecules were determined by immunohistochemistry *in vivo* and immunoblotting and quantitative reverse transcription-PCR *in vitro* using murine dermal microvascular endothelial cells (MDMECs). Promoter occupancy was evaluated by chromatin immunoprecipitation in MDMECs

Results: Wound healing was markedly delayed in Fli1 ECKO mice compared with WT mice. When vascular structure around scars was visualized with FITC-dextran injection, newly formed blood vessels were oriented toward the central area of scars in WT mice, while Fli1 ECKO mice lacked blood vessels around the central area of scars, suggesting that angiogenesis is impaired in Fli1 ECKO mice. At day 7 after wounding, many newly formed blood vessels filled with erythrocytes were present in granulation tissue in WT mice, while there were many dilated vessels with a few or no erythrocytes and a small number of vessels filled with erythrocytes in Fli1 ECKO mice. Since day 7 is a time point when newly formed blood vessels connect with pre-existing ones, it suggested that anastomosis may be impaired in Fli1 ECKO mice. In line with this idea, mRNA levels of the *Notch1* and *Dll4* genes, which code key molecules regulating anastomosis, were markedly decreased in ECs derived from Fli1 ECKO mice compared with those from WT mice. Furthermore, Fli1 occupied the promoter region of these genes in MDMECs.

Conclusion: Fli1 deficiency decelerates wound healing by inhibiting anastomosis of newly formed vessels with pre-existing ones and a similar process may contribute to the delayed wound healing associated with SSc.

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The Impact of Plasmacytoid Dendiritc Cells (pDCs) on Fibrosis in bleomycin–induced Murine Model of Systemic Sclerosis (SSc). Suzanne Kafaja[1], Isela Valera[1], Anagha Divekar[2], Daniel E. Furst[3] and Ram Singh[1]. [1]University of California, Los Angeles, Los Angeles, CA, [2]Biolegend, San Diego, CA, [3]University of California, Los Angeles, Department of Medicine, Los Angeles, CA.

Background/Purpose: Pathogenesis of systemic sclerosis (SSc) remains unclear. Alterations in adaptive and innate immune responses, with increased T-cells that produce type 2 cytokines and impaired responsiveness to Toll-like receptors, have been reported in patients with SSc. Dendritic cells (DC) that participate in both innate and adaptive immunity are increasingly being investigated in the pathogenesis and immune intervention in various autoimmune diseases and other immune-mediated conditions. Little is known about the alterations and role of DC in SSc. Our goal in this study is to investigate alterations of DC subsets and their roles in the pathogenesis of SSc.

Methods: In order to investigate the time kinetics of DC alterations in the affected and lymphoid organs and to manipulate DCs in vivo, we used the bleomycin-induced mouse model where the exact timing of pathogenic insult is known. Although, the bleomycin or any of the currently available animal models do not reproduce all aspects of human SSc, bleomycin-induced dermal and pulmonary fibrosis mimics human SSc in many ways. C57BL/6 mice were injected with bleomycin or PBS for 2 weeks, and cells isolated from lung tissue or lavage, skin, lymph nodes, spleen and bone marrow were analyzed for various immune cell types including DC subsets namely myeloid DC (mDC) and plasmacytoid DC (PDC). To directly determine the role of pDC, these cells were depleted using an anti-PDCA1 antibody (Miltenyi Biotec) or an IgG isotype control antibody. Animals were euthanized 2 weeks after treatment. Disease was assessed by clinical and histological scoring.

Results: Both DC subsets were increased in the lungs of bleomycin-injected mice, with a more profound increase in pDCs that were significantly elevated in the lungs ($p<0.008$), skin ($p<0.04$), and their associated draining lymph nodes in bleomycin-injected mice compared to PBS controls. Neither DC susbets differed in the spleen of bleomycin-injected mice when compared to controls. Treatment with anti-PDCA1 antibody significantly reduced pDC numbers in the spleen and lung by two-fold as compared to animals injected with an isotype control antibody. pDC-depleted mice had a significant improvement in combined clinical disease severity score ($p<0.001$) and histopathology ($p<0.009$), along with a reduction in cellular infiltrates comprising of B-cells, T-cells, NK and NK-T cell as compared to control mice. qPCR array analysis of lung tissue for molecules potentially involved in DC function and recruitment thus far shows alterations in chemokines *Ccl2* and *Ccl19*, and in macrophage migration inhibiting factor namely *Cd74*, which have been implicated in fibrosis development.

Conclusion: A more profound accumulation of pDCs, as compared to the other major DC subset, in the affected organs and their draining lymph nodes, but less so in the lymphoid organs, of bleomycin-injected mice suggests a possible role of pDC in SSc process. Indeed, antibody depletion of pDC reduces skin and lung fibrosis in the bleomycin model. A significant reduction in several immune cell types in pDC-depleted mice suggests a major pathogenic role of pDC in inflammatory/fibrosis process.

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Transforming Growth Factor Beta Induces anti Angio and Vasculo-Genesis Phenotype in Dermal Fibroblasts through Secretion of Pigment Epithelium Derived Factor. Vasiliki Liakouli[1], Margherita Scarcia[2], Giuseppina Abignano[3], Emma C. Derrett-Smith[4], Justin Gillespie[5], Paola Cipriani[6], Paul Emery[7], Christopher P. Denton[4], R Giacomelli[8], Georgia Mavria[2] and Francesco Del Galdo[9]. [1]Leeds Institute of Rheumatic and Musculoskeletal Medicine and Department of Biotechnological and Applied Clinical Science, Rheumatology Unit, School of Medicine, University of L'Aquila, Leeds, United Kingdom, [2]Signal Transduction and Angiogenesis group, Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK, Leeds, United Kingdom, [3]Leeds Institute of Rheumatic and Musculoskeletal Medicine and Department of Biotechnological and LTHT Leeds Musculoskeletal Biomedical Research Unit, leeds, United Kingdom, [4]UCL Medical School Royal Free Campus, London, United Kingdom, [5]Leeds Institue of Rheumatic and Musculoskeletal Medicine, Leeds, United Kingdom, [6]Department of Biotechnological and Applied Clinical Science, Rheumatology Unit, School of Medicine, University of L'Aquila, L'Aquila, Italy, [7]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [8]Università degli Studi dell'Aquila, L'Aquila, Italy, [9]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune disorder characterized by tissue fibrosis and vasculopathy. A proteomic analysis of the secretome of SSc dermal fibroblasts (SSc-FBs) identified increased protein levels of Pigment Epithelium Derived Factor (PEDF), which is the major endogenous inhibitor of intraocular angiogenesis. Here we aimed to validate the findings in vitro and in vivo and determine whether PEDF could be involved in SSc vasculopathy.

Methods: PEDF expression was investigated in the skin and FBs of 4 early diffuse SSc patients and 4 healthy controls (HC) by immunohistochemistry (IHC), qRT-PCR and flowcytometry. Functional effects of PEDF on angio/vasculogenesis were examined by Matrigel assays and CD31 IHC on organotypic co-culture assays of endothelial cells and either HC-FBs or SSc-FBs. Vascular tubule number, length and junctions were analyzed by Angiosys software. Caveolin expression was silenced by lentiviral induced shRNA expression. PEDF expression was also investigated by IHC on skin biopsies from wild-type (WT) and TβRIIΔk mice, which have fibroblast-specific constitutive activation of transforming growth factor-beta (TGF-β) signaling.

Results: In SSc skin 52% of FBs showed a strong expression of PEDF vs. 13% in HC skin ($p<0.0006$). Double IHC studies indicated that FBs positive for PEDF showed a decreased expression of cav-1. SSc-FBs *in vitro* showed on average a 5-fold PEDF expression compared to HC-FBs ($p<0.05$). Increased PEDF expression was inducible by either TGF-β stimulation or silencing of cav-1 expression *in vitro*. Concordantly, TβRIIΔk-fib mice showed an increased PEDF expression and decreased CAV-1 expression *in vivo*. Recombinant human PEDF inhibited vasculogenesis in vitro by suppressing >50% of tubule length, number and junctions ($P<0.01$). Consistently, organotypic co-culture assays indicated that SSc- FBs inhibited tubulogenesis in vitro. shCAV-1 FBS displayed a similar phenotype to SSc fibroblasts, which was abrogated by immunodepletion of PEDF from shCAV supernatants.

Conclusion: PEDF expression is increased in SSc biopsies and SSc-FBs and in TβRIIΔk-fib mice. PEDF expression is associated with decreased cav-1 expression *in vivo* and it is induced by silencing cav-1 *in vitro*. Functionally, PEDF can suppress vasculogenesis both in Matrigel and organotypic co-culture assays. This suggest that the decreased expression of cav-1 observed in SSc-FBs may contribute to the SSc vasculopathy through PEDF as well as other factors. Further studies unraveling the mechanisms of the antiangiogenic effect of PEDF may shed light in understanding the molecular events linking the profibrotic phenotype and SSc vasculopathy.

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Anti-Fibrotic Effects of an Investigational Drug: Bis-Oxetanyl Sulfoxide. Logan Mlakar[1], Takahisa Takihara[2], Melissa Sprachman[3], Peter Wipf[4] and Carol Feghali-Bostwick[1]. [1]Medical University of South Carolina, Charleston, SC, [2]Tokai University School of Medicine, Kanagawa, Japan, [3]Massachusetts General Hospital, Boston, MA, [4]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: The hallmark of pulmonary fibrosis is thickening and scarring of the tissue caused by increased deposition of extracellular matrix (ECM) proteins like collagen and fibronectin. Pulmonary fibrosis is a feature of several diseases including systemic sclerosis (SSc). MMS-350, a highly soluble small organic bis-oxetanyl sulfoxide, was recently shown to protect against radiation induced fibrosis. The low toxicity, high solubility and oral bioavailability of MMS-350 make it a promising therapeutic agent. Our goal was to determine the efficacy of this novel drug, MMS-350 and its analogs, in both *in vitro* and *in vivo* models of pulmonary fibrosis.

Methods: Primary human lung fibroblasts from normal donors were treated with TGFβ and MMS-350 for 72 h. Levels of ECM and pro-fibrotic proteins were assessed using immunoblotting. To study the effects of MMS-350 *in vivo*, 8-week old C57BL/6J mice were given bleomycin intratracheally to induce pulmonary fibrosis and PBS or MMS-350 orally on a daily basis for either 5 or 14 days. RNA was isolated from lung tissues and collagen 1A2 mRNA levels were measured by qRT-PCR. Paraffin embedded lung tissues were examined histologically following H&E staining and imaging. Collagen content was measured using the hydroxyproline assay.

Results: Fibroblasts treated with TGFβ and MMS-350 versus TGFβ alone showed a significant reduction in ECM (collagen and fibronectin), secreted (CTGF and IGFBP-3), and intracellular (α-SMA) pro-fibrotic markers. MMS-350 decreased these markers when added at the same time and when added up to 6 hours after TGFβ. One analog that differed from MMS-350 by the replacement of an oxetanyl methylene side chain with a phenyl ring, KRL507-031, showed a decrease in ECM and pro-fibrotic factors at concentrations 10-fold lower than the parent compound. Both the survival and mouse weight improved in the MMS-350 treated mice. Collagen 1A2 mRNA levels were significantly reduced in MMS-350 treated mice. H&E staining of lung tissue from mice treated with bleomycin and MMS-350 exhibited a reduction of scarring, and a significant reduction of collagen content in comparison to bleomycin.

Conclusion: These studies demonstrate that MMS-350 is an anti-fibrotic agent and are consistent with recent data demonstrating the ability of MMS-350 to reduce fibrosis in thoracic irradiated C57BL/6NTac mice. MMS-350 significantly reduced pro-fibrotic factors and ECM proteins both *in vitro* and *in vivo*. A lipophilic analog of MMS-350, KRL507-031, exhibited similar anti-fibrotic effect albeit at lower concentrations. The fact that MMS-350 was effective at reducing pulmonary fibrosis induced by different triggers and that it is orally available make it an attractive lead candidate for the development of a therapy for organ fibrosis.

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Detection of Proteins in Lung Tissues of Patients with Systemic Sclerosis Using Tissue Microarrays. Frank Schneider[1] and Carol A. Feghali-Bostwick[2]. [1]University of Pittsburgh, Pittsburghh, PA, [2]Medical University of South Carolina, Charleston, SC.

Background/Purpose: Research on systemic sclerosis (SSc)-associated interstitial lung disease (ILD) has been hindered by the paucity of lung tissues, as SSc patients with lung involvement are not routinely biopsied. To gain further insights into the pathogenesis of lung fibrosis in SSc, we used lung tissue microarrays (TMAs) for the detection of 4 proteins of interest in SSc-associated ILD and idiopathic pulmonary fibrosis (IPF).

Methods: Lung tissues were obtained from the explanted lungs of patients undergoing lung transplantation. Normal lung tissues were obtained from controls. H&E sections were used for the selection of suitable regions. These regions were used for obtaining 1 mm cores. A TMA was constructed containing 117 cores from patients with SSc-associated ILD, IPF, and normal controls. Sections from the TMA block were used for detection of TTF-1, thrombomodulin, laminin, and Smad4 using immunohistochemistry (IHC). Distribution and levels of expression were qualitatively assessed using light microscopy.

Results: TTF-1, thrombomodulin, laminin, and Smad4 were detected in all cores on the TMA slide. The distribution of the proteins differed in normal lungs compared to fibrotic lungs since the two subepithelial layers in normal lungs are closely apposed in the absence of fibrosis. We observed subtle differences in distribution and levels of protein expression between SSc and IPF. TTF-1 expression appeared reduced in areas of fibrosis and inflammation

in both diseases. Thrombomodulin staining of airway basal cells was weaker and patchier in SSc than IPF. Laminin expression was reduced in areas of fibrosis in both SSc and IPF, but IPF lungs showed stronger laminin staining around vessels compared to SSc lungs. Nuclear Smad4 expression was more prominent and more widespread in perivascular smooth muscle cells of SSc than IPF lungs.

Conclusion: Lung TMAs are useful to simultaneously compare localization and expression levels of proteins in lung tissues from multiple patients and controls. Our initial IHC findings suggest that differences exist in the distribution and levels of TTF-1, thrombomodulin, laminin, and Smad4, and such differences can be identified using TMAs.

Disclosure: F. Schneider, None; **C. A. Feghali-Bostwick**, None.

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Development of a Bifluorescent Lineage Tracker Reporter Mouse Strain to Analyze the Phenotypic Conversion of Endothelial Cells into Myofibroblasts *in Vivo*. Application to Study the Synergistic Effects of Endothelin-1 on TGF-β1-Induced Endothelial-to-Mesenchymal Transition. Peter J. Wermuth and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center, Thomas Jefferson University, Philadelphia, PA.

Background/Purpose: Endothelial-to-mesenchymal transition (EndoMT) may be a crucial pathway in generating activated myofibroblasts, cells that play a pivotal role in the development of tissue and organ fibrosis in diseases such as Systemic Sclerosis (SSc). It has been previously demonstrated that endothelin 1 (ET-1) synergistically enhances TGF-β-induced EndoMT *in vitro* in murine lung endothelial cells (ECs). The purpose of this study was to develop a mouse model expressing a green distinct fluorescent label in ECs (green fluorescent protein; GFP) and a red fluorescent label in fibroblasts (mCherry protein) to allow monitoring of EndoMT *in vivo*.

Methods: Homozygous Tie2GFP transgenic mice expressing GFP under control of the EC specific *Tie2* promoter (Tie2GFP mice) were crossed with homozygous mice expressing a doxycycline inducible red fluorescent mCherry protein in mesenchymal cells and fibroblasts under control of the *Col1a1* promoter (Col1mCherry mice) to generate heterozygous bifluorescent Tie2GFP-Col1mCherry mice. At 4 weeks of age, osmotic pumps containing either saline, 2.5 μg TGF-β, or 2.5 μg TGF-β+5.0 μg ET-1 were implanted subcutaneously in the right intrascapular region of the mice (2 mice per treatment group). The pumps deliver their contents at a rate of 0.5 μl/h over a 2 week period. Mice received IP injections of 1 mg/kg doxycycline every other day starting at 2 weeks post-implantation of the pump and were sacrificed one week later. Both lungs and two skin samples, one at the pump dispersal site and one opposite to the pump site, were isolated. A portion of each tissue was fixed in formalin and processed for histopathologic analysis (hematoxyllin/eosin and Masson's trichrome stains) whereas another portion was frozen and sectioned for evaluation of fluorescence. Another sample portion of each tissue was hydrolyzed for measurement of hydroxyproline content.

Results: Histopathology studies in samples from TGF-β-treated mice showed mononuclear cell infiltration and peribronchial fibrosis and diffuse interstitial fibrosis in lungs. Dermal fibrosis was present in both samples of skin. ET-1 synergistically enhanced the severity of fibrosis in all three tissues. Hydroxyproline levels in skin taken from the site of the osmotic pump demonstrated a 61% increase in response to TGF-β alone and a 113% increase ($\sim$2.2 fold) in response to TGF-β+ET-1 whereas skin from the opposite side of the back displayed a 29% increase in response to TGF-β alone and a 102% increase ($\sim$2 fold) in response to TGF-β+ET-1. In the lung, TGF-β increased hydroxyproline levels by 38% and TGF-β+ET-1 increased hydroxyproline levels by 75%.

Conclusion: Tie2GFP-Col1mCherry mice represent a valuable resource for monitoring EndoMT *in vivo*. ET-1 plays an important *in vivo* role in regulating EndoMT by causing a synergistic potentiation of TGF-β1-induced EndoMT. Since ET-1 plays a crucial role in the pathogenesis of SSc-associated pulmonary arterial hypertension and may play a profibrotic role in skin and lung fibrosis, the results described here identify a novel mechanism supporting the concept that ET-1 plays a key pathogenetic role *in vivo* in SSc-associated tissue fibrosis.

Disclosure: P. J. Wermuth, None; **S. A. Jimenez**, None.

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RNA-Seq and Mir-Seq Analysis of SSc Skin Across Intrinsic Gene Expression Subsets Shows Differential Expression of Non-Coding RNAs Regulating SSc Gene Expression. Zhenghui Li[1], Eleni Marmarelis[1], Kun Qu[2], Lionel Brooks[1], Patricia Pioli[1], Howard Chang[2], Robert Lafyatis[3] and Michael Whitfield[1]. [1]Geisel School of Medicine at Dartmouth, Hanover, NH, [2]Stanford University School of Medicine, Stanford, CA, [3]Boston University, Boston, MA.

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease with a heterogenous and complex phenotype. Previously, our lab has identified four gene expression subsets (fibroproliferative, inflammatory, limited and normal-like) among SSc patients by their gene expression in skin using DNA microarrays. We have extended these findings by using RNA-Seq in a subset of SSc skin biopsies to detect mRNA levels, splice variants, novel non-coding RNAs, and coding region SNPs in a lower background signal over microarray.

Methods: We performed RNA-Seq on eight SSc patients and four healthy controls and skin biopsies. The eight SSc patients included five individuals that mapped to the inflammatory subset and three from the fibroproliferative subset. We sequenced the small and large RNA fraction extracted from each biopsy by Illumina Solexa sequencing. We obtained 90–100 million 50 bp paired-end reads for the mRNA fraction and 25 – 50 million 36 bp reads for the miRNA fraction.

Results: Our analyses reveal significant ($p<0.05$) gene expression differences between healthy controls and SSc patients, as well as between intrinsic subsets. Specifically, we found >1000 genes are significantly expressed in the inflammatory and the fiboproliferative subsets of patients. Many of the significant genes are involved in cellular proliferation or immune responses, consistent with results found by DNA microarray hybridization. We did not observe any significant differential splicing between the healthy controls and the SSc patients. We identified 228 novel long non-coding RNAs (lncRNAs) that are significantly differentially expressed in the inflammatory subset and fibroproliferative subsets. The lncRNAs differentially expressed in the inflammatory subset map to Gene Ontology terms including *inflammatory response*, *immune response*, *response to wounding*, and *defense response* and those in the fibroproliferative group map to *cell cycle*, *M phase*, and *RNA metabolism*. We also identified 54 miRs differentially expressed in the inflammatory subset of SSc patients. These include the well-characterized miR21 that has previously been reported to be differentially expressed in SSc as well as many novel miRs. We have previously shown CCL2 to be highly expressed in the inflammatory subset of SSc and inhibiting its function prevents development of disease in the sclGVHD mouse model. We now identify a novel miR with decreased expression that is predicted to target the 3'UTR of CCL2. We show that transfection of the CCL2-targeting miR, but not a negative control miR, into RAW264.7 macrophage cells expressing a heterologous Luciferase-CCL2 (3'UTR) reduced luciferase activity by 74%.

Conclusion: To summarize, we conducted the first comprehensive RNA-Seq study in SSc skin and identified differentially expressed non-coding RNAs genome-wide. Our findings show that a complex network of regulatory factors controls the disease specific gene expression subsets in SSc skin.

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Functional Autoantibodies from Patients with Systemic Sclerosis Reactive to Angiotensin II Type 1 and Endothelin-1 Type a Receptor Induce Inflammatory Lymphocyte Infiltration into Lungs of Mice. Angela Kill[1], Clement Braesch[1], Anja Kühl[2], Jeannine Guenther[1], Mike O. Becker[2], Gerd Burmester[3], Thomas Walther[4] and Gabriela Riemekasten[5]. [1]Charité University Hospital, German Rheumatology Research Center, a Leibniz Institute, Berlin, Germany, [2]Charité University Hospital, Berlin, Germany, [3]Charité University Medicine, Berlin, Germany, [4]University College Cork, Cork, Ireland, [5]Charité University Hospital and German Rheumatism Research Centre, a Leibniz Institute, Berlin, Germany.

Background/Purpose: Functional autoantibodies reactive to the angiotensin II type 1 receptor (AT_1R) and endothelin 1 type A receptor (ET_AR) were found in elevated levels in systemic sclerosis (SSc) patients, with clinical connections to lung involvement. Functional effects on T-lymphocyte migration were studied previously *in vitro* and first *in vivo* experiments on C57BL/6 mice demonstrated agonistic effects on lung architecture. Here, functional effects of anti-AT_1R and

anti-ET_AR autoantibodies on inflammatory cell infiltration into lungs of mice deficient for the AT receptor and on their respective WT mice (129 × C57BL/6), were studied for the first time.

Methods: Female mice deficient for AT_{1a}, AT_{1b}, and AT_2 receptor (ATR −/−, 129 × C57BL/6, n=5 per group) and WT controls (129 × C57BL/6, n=4 per group) were treated with SSc-IgG with elevated levels of anti-AT_1R and anti-ET_AR autoantibodies. In control experiments same groups were treated with healthy donor IgG (NC-IgG). IgG samples were transferred into ATR −/− and into WT groups five times over three months. Lungs were examined using histological staining and an index-system was developed to assess CD3+T-lymphocyte infiltration around vessels. Samples were analysed in a blinded fashion using imageJ software.

Results: Mice of the ATR −/− and WT group treated with SSc-IgG showed a dramatically decreased survival in both groups, with worst survival rate in the ATR −/− group. Groups with the control treatment NC-IgG showed a better survival compared to SSc-IgG, with a slightly lower survival rate in ATR −/− group, than in the WT group. Histological analyses of lungs revealed a statistically higher T-lymphocyte infiltration in both groups with SSc-IgG than with NC-IgG. Furthermore, ATR −/− group with SSc-IgG showed a statistically higher infiltration rate than WT group with SSc-IgG.

Conclusion: These preliminary experiments demonstrate a dramatic survival reduction by treatment with SSc-IgG containing anti-AT_1R and anti-ET_AR autoantibodies (SSc-IgG) in both groups, ATR −/− and WT. Moreover, a major inflammation in ATR −/− and in WT mice was induced by SSc-IgG, reflected by T-lymphocyte infiltration into lung tissue. Increased inflammation in ATR −/− vs. WT group by SSc-IgG, suggests a possible ET_AR-mediated inflammation in ATR −/− mice. Anti-AT_1R and anti-ET_AR autoantibodies react presumably in a cross-reactive way and mice deficient for angiotensin-receptors could therefore enable detailed studies of ET_AR-mediated effects, providing thereby a deeper understanding of involved mechanisms. Moreover, the data demonstrate the recruitment and activation of immune cells by autoantibodies and could as a result offer deeper insight into autoantibody-mediated T-lymphocyte recruitment and reveal potential therapeutic targets for treatment of SSc.

Disclosure: A. Kill, Actelion Pharmaceuticals US, 2; **C. Braesch**, None; **A. Kühl**, None; **J. Guenther**, None; **M. O. Becker**, None; **G. Burmester**, AbbVie, Pfizer, UCB, Roche, 2, AbbVie, BMS, Pfizer, Merck, MedImmune, UCB, Roche, 5, AbbVie, BMS, Pfizer, Merck, UCB, Roche, 8; **T. Walther**, None; **G. Riemekasten**, Actelion Pharmaceuticals US, 2, CellTrend, 5.

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Endothelin-1 Synergistically Increases TGF-β-Induced Hif1α Expression Under Normoxic Conditions during Endothelial-to-Mesenchymal Transition in Murine Endothelial Cells. A Novel Mechanism for the Fibrogenic Effects of Endothelin. Peter J. Wermuth and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center, Thomas Jefferson University, Philadelphia, PA.

Background/Purpose: Tissue hypoxia is a consequence of vascular damage and Hif-1α accumulation is a major mechanism of hypoxia response pathways. HIF-1α induces the transcriptional upregulation of expression of numerous genes encoding proteins involved in vascular repair including soluble growth factors (TGF-β and VEGF), and extracellular matrix components (type I collagen and fibronectin), rendering HIF-1α as a positive regulator of wound healing and a potential mediator of organ repair and tissue fibrosis, suggesting that HIF1-α may play an important role in the pathogenesis of fibrotic diseases such as Systemic Sclerosis (SSc). Recent studies have shown that TGF-β causes a potent increase in HIF-1α protein levels. Since endothelin 1 (ET-1) synergistically enhances TGF-β mediated endothelial-to-mesenchymal transition (EndoMT), we examined the transcriptional regulation of Hif-1α and of several of its downstream targets in response to TGF-β alone or TGF-β in combination with ET-1 in cultured murine lung microvascular endothelial cells (MVEC).

Methods: Murine pulmonary MVEC were isolated from C57Bl/6J mice employing trypsin/collagenase tissue digestion followed by sequential immunomagnetic selection with anti-CD31 and anti-CD102 antibodies. The purified EC were treated in monolayer cultures with ET-1 (100 ng/mL) in the presence and absence of TGF-β1 (10 ng/mL) and the induction of Hif-1α as well as several Hif-1α targets including lysyl oxidase (Lox), Lox-like 1 protein (Loxl1), Loxl2, Loxl3, and LoxL4 was assessed employing semi-quantitative RT-PCR.

Results: Exposure of murine pulmonary MVEC to ET-1 induced a three-fold increase in Hif-1α levels compared to non-treated controls. TGF-β1, however, induced a nearly 500-fold increase in expression whereas samples treated with TGF-β1 plus ET-1 increased Hif-1α transcript levels nearly 2500-fold compared to the saline control. This profound synergistic increase was abrogated by the dual ET-1 receptor antagonist, Bosentan, demonstrating that the observed effect was indeed mediated by ET-1. Similarly, TGF-β alone induced significant increases in the expression of Hif-1α target genes Lox, LoxL1, LoxL2, LoxL3 and LoxL4. ET-1 alone did not alter the expression of these genes whereas ET-1 in combination with TGF-β synergistically increased their levels. Bosentan abrogated the increased expression levels of these genes observed for TGF-β plus ET-1, indicating that the synergistic increases were mediated by ET-1.

Conclusion: TGF-β potently increased Hif-1α and Hif-1α target gene expression in murine pulmonary MVEC under normoxic conditions. ET-1 synergistically enhanced these effects. Since vascular damage plays a crucial role in SSc-associated pulmonary arterial hypertension pathogenesis and participates in the development of skin and lung fibrosis, the results described here identify ET-1 as a potentially key regulator of TGF-β-mediated activation of Hif-1α in response to vascular damage causing a synergistic enhancement of HIF-1α-mediated profibrotic effects suggesting that this process may play a key pathogenetic role in SSc-associated tissue fibrosis and fibroproliferative vasculopathy.

Disclosure: P. J. Wermuth, None; **S. A. Jimenez**, None.

ACR Poster Session A
Vasculitis

Sunday, November 16, 2014, 8:30 AM–4:00 PM

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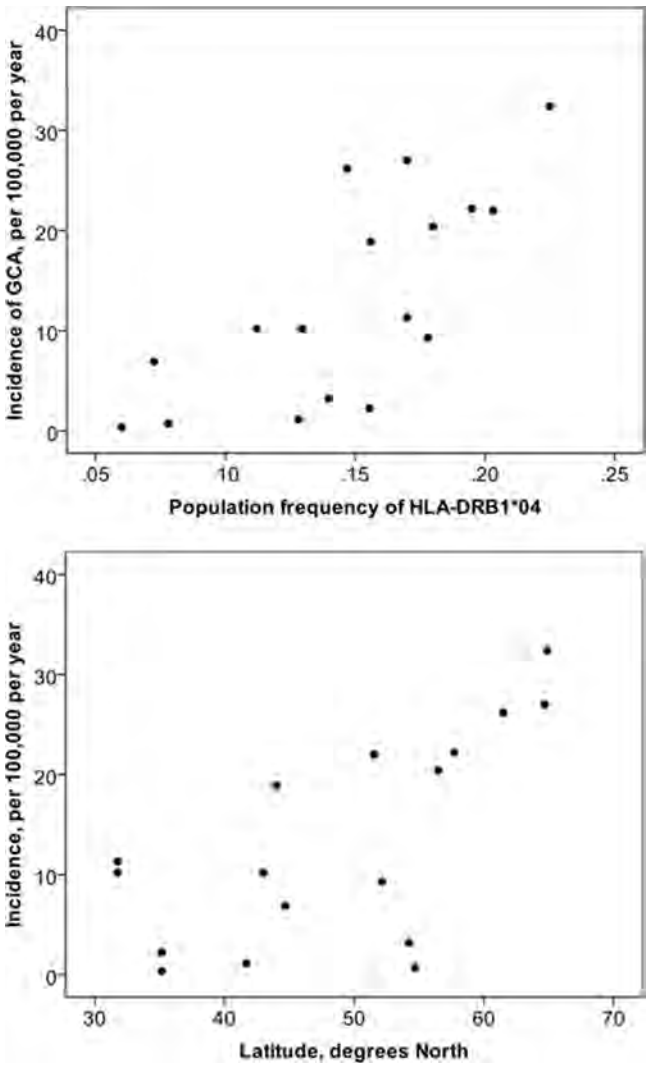
***HLA-DRB1* Alleles in Susceptibility to Giant Cell Arteritis: Literature Review and Meta-Analysis.** Sarah Mackie[1], John Taylor[1], Lubna Shafi[1], Stephen Martin[1], Bhaskar Dasgupta[2], Andrew Gough[3], Michael Green[4], Lesley Hordon[5], Stephen Jarrett[6], Colin T. Pease[7], Jennifer Barrett[1], Richard Watts[8] and Ann W. Morgan[1]. [1]University of Leeds, Leeds, United Kingdom, [2]Southend University Hospital, Essex, United Kingdom, [3]Harrogate and District Foundation Trust, Harrogate, United Kingdom, [4]York Teaching Hospital NHS Foundation Trust, York, United Kingdom, [5]Mid Yorkshire Hospitals NHS Trust, Dewsbury, United Kingdom, [6]Mid Yorkshire Hospitals NHS Trust, Wakefield, United Kingdom, [7]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [8]Norwich Medical School University of East Anglia, Norwich, United Kingdom.

Background/Purpose: Giant cell arteritis (GCA) has been reported by many studies (but not all) to be associated with carriage of *HLA-DRB1**04, with variable results relating to other alleles, but formal meta-analysis has never been performed. Our objective was to study the influence of *HLA-DRB1* alleles on GCA susceptibility and incidence, combining new UK data with a meta-analysis of the literature.

Methods: GCA patients from the UK GCA Consortium were genotyped using single strand oligonucleotide polymerization, allele-specific polymerase chain reaction and direct sequencing. Control data was provided by the UK RA Genetics (UKRAG) Consortium. Meta-analysis was used to combine our results with previously-published data. Finally we determined the relationship of *HLA-DRB1**04 population carrier frequency to the incidence of GCA reported in different countries.

Results: In the new UK data (225 cases, 1378 controls), *HLA-DRB1**04 carriage was associated with GCA susceptibility (OR=2.69, $p=1.5\times10^{-11}$), but *HLA-DRB1**01 was protective (adjusted OR=0.55, p=0.0046). In meta-analysis combined with 14 published studies (an additional 691 cases, and 4038 controls), protective effects were seen from HLA-DR2, comprising *HLA-DRB1**15 and *HLA-DRB1**16 (OR=0.65, $p=8.2\text{x}10^{-6}$), and possibly from *HLA-DRB1**01 (OR=0.73, p=0.037). The incidence of GCA (n=17 countries) was associated with *HLA-DRB1**04 allele frequency in the population (p=0.008; adjusted $R^2=0.51$ on univariable analysis, adjusted $R^2=0.62$ after also including latitude).



Conclusion: This meta-analysis confirms *HLA-DRB1**04 as a GCA susceptibility allele but fails to show a susceptibility effect of *HLA-DRB1**01, despite sharing amino acids in common in the third hypervariable region. Variations in population frequency of *HLA-DRB1**04 might help explain worldwide variations in GCA incidence; latitude appears to make an independent contribution to GCA risk.

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A Candidate Gene Approach Identifies *IL33* as a Novel Genetic Risk Factor for GCA.

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Background/Purpose: IL-33, through binding to its receptor ST2 (suppression of tumorigenicity 2), encoded by the interleukin 1 receptor-like 1 (*IL1RL1*) gene, activates mast cells and Th2 lymphocytes. Additionally, IL-33 acts as an activator of endothelial cells promoting angiogenesis and vascular permeability. Different studies have supported a pathogenic role of IL-33 axis in autoimmunity. Interestingly, an increased expression of this cytokine and its receptor has been detected in the inflamed arteries of GCA patients, mainly in endothelial cells of newly formed vessels, thus suggesting a possible role of IL-33 in the angiogenesis-dependent inflammation in GCA. The aim of the present study was to investigate for the first time the potential influence of the *IL33* and *IL1RL1 loci* on GCA predisposition.

Methods: A total of 1,363 biopsy-proven GCA patients and 3,908 healthy controls from four European case/control sets (Spanish cohort: 894 cases and 2,047 controls, German cohort: 103 cases and 444 controls, Italian cohort: 255 cases and 1,141 controls, and Norwegian cohort: 111 cases and 276 controls) were combined in a meta-analysis. Six genetic variants: rs3939286, rs7025417 and rs7044343, within the *IL33* gene, and rs2058660, rs2310173 and rs13015714, within the *IL1RL1* gene, previously associated with autoimmunity, were genotyped using predesigned TaqMan® assays.

Results: A consistent association between the rs7025417 polymorphism and GCA was evident in the overall meta-analysis, under both allele (P_{MH}=0.041, OR=0.88, CI 95% 0.78–0.99) and recessive (P_{MH}=3.40E-03, OR=0.53, CI 95% 0.35–0.80) models. No statistically significant differences between allele or genotype frequencies for the other *IL33* and *IL1RL1* genetic variants were detected in this pooled analysis.

Conclusion: Our results clearly evidenced the implication of the *IL33 locus* in the genetic network underlying GCA. This study, together with previous findings, supports an important role of this cytokine in the inflammatory process occurring in GCA.

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Influence of the *IL17A Locus* in Giant Cell Arteritis Susceptibility.

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Spain, [8]Department of Rheumatology, Hospital Universitario Marqués de Valdecilla, IFIMAV, Santander, Spain, [9]Systemic Autoimmune Diseases Unit, Hospital Clínico San Cecilio, Granada, Spain, [10]Department of Internal Medicine, Complejo Hospitalario Universitario de Vigo, Vigo, Spain, [11]Department of Rheumatology, Grup de recerca cellular en inflamació i cartílag. IMIM (Institut de Recerca Hospital del Mar), Barcelona, Spain, [12]Department of Rheumatology, Hospital Ramón y Cajal, Madrid, Spain, [13]Department of Internal Medicine, Hospital Universitario Central de Asturias, Oviedo, Spain, [14]Department of Rheumatology, Hospital Universitario La Paz, Madrid, Spain, [15]Hospital Marques de Valdecilla, Santander, Spain, [16]Oslo University Hospital and University of Oslo, Oslo, Norway, [17]Department of Rheumatology, Oslo University Hospital Rikshospitalet, Oslo, Norway, [18]Department of Internal Medicine, Division of Nephrology, Robert-Bosch-Hospital, Stuttgart, Germany, [19]Department of Clinical Immunology and Rheumatology, University of Luebeck, Bad Bramstedt, Germany, [20]Hannover Medical School, Hannover, Germany, [21]Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy, [22]Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy, [23]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [24]Unitá Operativa di Reumatologia, Azienda Ospedaliera ASMN, Istituto di Ricovero e Cura a Carattere Scientifico, Reggio Emilia, Italy, [25]Azienda Ospedaliera ASMN, Istituto di Ricovero e Cura a Carattere Scientifico, Reggio Emilia, Italy, [26]Hospital Universitario Marqués de Valdecilla, IFIMAV, Santander, Spain.

Background/Purpose: A recent study has showed that the number of Th17 lymphocytes is significantly increased in patients with GCA, resulting in an imbalance between Th17 and regulatory T cells. In addition, an increased expression of IL-17A, a Th17 cytokine leading to pro-inflammatory responses, has been detected in temporal artery samples from GCA patients. Considering the proposed crucial role of Th17 cells in this vasculitis, we aimed to assess whether polymorphisms at the *IL17A* gene are involved in the genetic predisposition to GCA and its main clinical subgroups.

Methods: We carried out a large meta-analysis including a total of 1,266 biopsy-proven GCA patients and 3,779 healthy controls from four European populations (Spanish cohort: 931 cases and 1,845 controls, German cohort: 74 cases and 480 controls, Italian cohort: 178 cases and 1,175 controls, and Norwegian cohort: 83 cases and 279 controls). Five *IL17A* polymorphisms (rs4711998, rs8193036, rs3819024, rs2275913 and rs7747909), which tag over 86% of the variability of this *locus*, were genotyped using TaqMan® assays. Allelic combination and dependency tests were also performed.

Results: In the pooled analysis, two of the five analyzed polymorphisms showed evidence of association with GCA (rs2275913: P_{MH}=1.85E-03, OR= 1.17 [1.06–1.29]; rs7747909: P_{MH}=8.49-03, OR= 1.15 [1.04–1.27]). A clear trend of association was also found for the rs4711998 variant (P_{MH}=0.059, OR= 1.11 [1.00–1.23]). An independent effect of rs2275913 and rs4711998 was evident by conditional regression analysis. In addition, the haplotype harboring the risk alleles better explained the observed association than the polymorphisms independently (likelihood P-value$<10^{-05}$).

Conclusion: Our study provides clear evidence of the role of *IL17A* as a novel genetic risk *locus* for GCA, thus contributing to the advance in the knowledge of the genetic network underlying this vasculitis susceptibility.

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PTPN22 rs2476601 and Susceptibility to Biopsy Proven Giant Cell Arteritis (GCA) in an Australian Sample. Susan Lester[1], Alex Hewitt[2], Linda Bradbury[3], Elisabeth De Smit[4], Andrew Harrison[5], Graeme Jones[6], Geoffrey O. Littlejohn[7], Tony R. Merriman[8], Bain Shenstone[9], Malcolm D. Smith[10], Maureen Rischmueller[11], Matthew A. Brown[12] and Catherine L. Hill[13]. [1]Queen Elizabeth Hospital, Woodville South, Australia, [2]University of Western Australia, Perth, Australia, [3]The University of Queensland, Brisbane, Australia, [4]University of Melbourne, Melbourne, Australia, [5]University of Otago, Wellington, New Zealand, [6]University of Tasmania, HOBART, Australia, [7]Monash Medical Center, Melbourne, Australia, [8]University of Otago, Dunedin, New Zealand, [9]Concord Hospital, Sydney, Australia, [10]Repatriation General Hospital, Adelaide SA, Australia, [11]The Queen Elizabeth Hospital, SA, Australia, [12]University of Queensland Diamantina Institute, Brisbane, Australia, [13]University of Adelaide, Adelaide, Australia.

Background/Purpose: The aetiology and genetic background of GCA remains unclear, although genetic susceptibility is known to play a role. Recently, an association with the minor, loss of function, allele of PTPN22 rs2476601 (R620W), was reported in a Spanish cohort of biopsy-proven GCA (odds ratio = 1.62, 95%CI 1.29–2.04, p = 0.0001)[1]. Therefore, dysregulation of TCR signalling may be implicated in the pathogenesis of GCA. The aim of this study was to determine the association between the PTPN22 rs2476601 minor (A) allele and biopsy-proven GCA in an Australian cohort.

Methods: rs2476601 genotyping was performed by a Taqman assay (C-16021387, Applied Biosystems) in 209 GCA cases. Genotype data from 1407 healthy ethnically-matched unrelated postmenopausal women included in the Anglo-Australian Osteoporosis Genetics Consortium study of bone density variation were used as healthy controls. All GCA cases were temporal artery biopsy proven, and were recruited in Australia by the Arthritis Genomics Recruitment Initiative in Australasia (AGRIA). The mean age of GCA patients at diagnosis was 73 yrs (SE 8 yrs), with 68% female.

Results: The frequency of the A allele was 0.093 in GCA cases and 0.103 in the controls. Overall, there was no evidence of an association between GCA and controls, (OR=0.89, 95% CI 0.63, 1.27, p = 0.52). A random effects meta-analysis of replication datasets from Germany[1], Norway[1], UK[1], and Australia, included 769 GCA patients and 14,214 controls, did not reach statistical significance (OR 1.21, 95% CI 0.73, 2.00, p = 0.32). Similarly, a random effects meta-analysis which included the original Spanish dataset (1,392 GCA cases and 15,943 controls), also did not reach statistical significance (OR 1.31, 95% CI 0.90, 1.90, p = 0.11), Figure 1.

Conclusion: There was no statistically significant association between PTPN22 rs2476601 in this Australian GCA cohort. Nor does a meta-analysis of combined, available data reach statistical significance. However, an association with small effect size cannot yet be definitively excluded, and further studies may be required.

1. Serrano et al. Ann Rheum Dis 2013;72:1882–6.

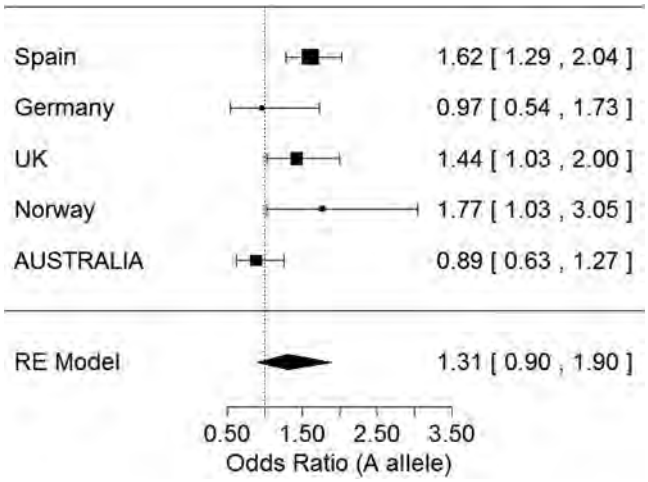

Figure 1. Random Effects Meta-Analysis for the association between PTPN22 rs2476601 A allele and Giant Cell Arteritis

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Toll-like Receptor 2 Agonism Induces Inflammation, Angiogenesis and Cell Migration in Giant Cell Arteritis. Lorraine O'Neill[1], Aoife Maher[1], Jennifer McCormick[2], Conor Murphy[3], Geraldine M. McCarthy[4], Douglas J. Veale[1], Ursula Fearon[2] and Eamonn S. Molloy[1]. [1]St. Vincent's University

Hospital, Dublin 4, Ireland, [2]Translational Rheumatology Research Group, Dublin, Ireland, [3]Royal Victoria Eye and Ear Hospital, Dublin, Ireland, [4]Mater Misericordiae University Hospital, Dublin 7, Ireland.

Background/Purpose: Activation of dendritic cells (DCs) is one of the earliest inciting events in Giant Cell Arteritis (GCA). TLR 2 is expressed on DCs in normal temporal arteries and is also found ubiquitously throughout the macro vasculature. [1] Stimulating temporal arteries implanted into SCID mice with TLR 2 activates dendritic cells. [2] Therefore TLR 2 is likely to play a major role in the pathogenesis of GCA while the exact mechanisms involved are yet to be fully elucidated.

This study examines the functional effects of TLR 2 on induction of pro-inflammatory cytokines, angiogenesis and cell migration in GCA.

Methods: 15 patients with biopsy proven GCA and meeting 1990 ACR classification criteria for GCA were prospectively recruited. To directly examine the effects of TLR 2 on pro-inflammatory cytokines, growth factors and gelatinase expression in GCA, *ex-vivo* temporal artery (TA) whole tissue explant models were established. PBMCs and TA explants were cultured in the presence of Pam3CSK4 (a TLR 2 agonist) (1μg/ml) for 24 hours. Supernatants were harvested and assayed for IL-6, IL-8 Ang2, and VEGF by ELISA and MMP-2 and MMP-9 by gelatin zymography. Endothelial cell tube formation was assessed following culture with TLR 2-induced TA explant conditioned media. To examine the effect of TLR 2 on migration/ invasion in GCA, TA explants were embedded in Matrigel, stimulated with Pam3CSK4 and myofibroblast outgrowths observed. Myofibroblasts were also isolated from TA explants, cultured and wound repair assays performed. To examine the effects of TLR 2 on cytoskeletal architecture, cultured myofibroblasts were treated with Pam3CSK4 and stained for F-actin.

Results: In PBMC cultures, Pam3CSK4 induced a 7.7 and 3.6 fold increase in expression of IL6 and IL8 respectively, from a basal IL-6 level of 34.58 $\pm$ 6.77 pg/ml to 266.1 $\pm$ 117.6 pg /ml and basal IL-8 level of 1769 $\pm$ 731.7 pg/ml to 6388 $\pm$ 1632 pg/ml.

In temporal artery explant cultures stimulation with Pam3CSK4 increased expression of IL- 6 from 26,800 $\pm$ 9209 pg/ml to 47494 $\pm$ 10,946pg/ml ($p=0.01$). Expression of IL-8 was also increased from basal levels of 20,593 $\pm$ 8224 pg/ml to 40,793 $\pm$ 16, 670 pg/ml ($p=0.058$).

Stimulation with Pam3CSK4 significantly increased Ang 2 expression from basal levels of 727.9 $\pm$ 254.5 pg/ml to 1415 $\pm$ 459.6 pg/ml ($p=0.011$). There was a trend towards increased expression of VEGF, from basal levels of 107.5 $\pm$ 33.38 pg/ml to 200 $\pm$ 69.95pg/ml but this was not statistically significant. ($p=0.19$) Differential effects for MMP2/9 expression were observed on zymography. Pam3CSK4 induced endothelial cell tube formation. Pam3CSK4 also promoted myofibroblast outgrowths from the TA explants and cytoskeletal disassembly in the cultured myofibroblasts.

Conclusion: In an *ex vivo* temporal artery culture model, Pam3CSK4, a TLR 2 agonist, enhances production of pro inflammatory mediators, promotes angiogenesis, myofibroblast migration and cytoskeletal rearrangement. TLR2 signalling may therefore play a role in driving vascular inflammation and remodelling in GCA, and may represent a potential therapeutic target in GCA.

[1] Pryshchep et al, Circulation 2008
[2] Makrupa et al, Journal of Exp Med 2006

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Novel Roles for Zyxin in the Pathogenesis of Giant Cell Arteritis. Rie Karasawa[1], Paul A. Monach[2], Mayumi Tamaki[1], Takahiro Okazaki[3], Masamichi Oh-Ishi[4], Yoshio Kodera[4], Toshiko Sato[1], Shoichi Ozaki[3], Kaiyu Jiang[5], Kazuo Yudoh[1], James N. Jarvis[5] and Peter A. Merkel[6]. [1]Institute of Medical Science, St. Marianna University School of Medicine, Kawasaki, Japan, [2]Vasculitis Center, Boston University School of Medicine, Boston, MA, [3]St. Marianna University School of Medicine, Kawasaki, Japan, [4]School of Science, Kitasato University, Sagamihara, Japan, [5]The University at Buffalo, Buffalo, NY, [6]Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA.

Background/Purpose: The mechanisms of the blood vessel injury in giant cell arteritis (GCA), a systemic vasculitis characterized by inflammation of large- and medium-sized vessels, remain to be fully solved. Anti-endothelial cell antibodies (AECA) are antibodies that are detected frequently in vasculitis, including GCA. However, AECA target molecules have been poorly incompletely identified, which hampers our understanding the roles of AECA in disease pathogenesis.

Methods: We identified target antigens for AECA in patients with GCA using agarose 2-dimensional electrophoresis (agarose 2DE) and WB followed by mass spectrometry and accessed to pathophysiological roles in GCA. To detect antigens recognized by GCA sera predominantly in extracted proteins from endothelial cells (EC-specific proteins), the results of agarose 2DE-WB using human aortic endothelial cells (HAEC) were compared with that using human aortic adventitial fibroblasts. Furthermore, to detect antigens on HAEC recognized predominantly in sera with patients with GCA (GCA-specific proteins), the results of 2DE-WB using sera from GCA were compared with that using sera from healthy donors.

Results: A total of 31 proteins identified from 23 protein spots recovered from 2DE gel were determined successfully. Three proteins, Ezrin, Zyxin and FK506-binding protein 4, were EC-specific proteins as well as GCA-specific proteins. Gene Ontology analysis showed the EC-specific protein group was mainly classified into the metabolism and the defense and immunity group. In the GCA-specific protein group, the proteins were classified into broad functional categories except for metabolism group. By IPA analysis, more than half of the identified proteins were closely related ubiquitin. Regarding relationships between the identified proteins and cytokines, chemokines, and adhesion molecules, TNF-α was also involved in this signaling network. Using both proteomics and immunocytochemical analyses, we report here for the first time the identification of a specific target antigen for AECA in GCA, zyxin, a focal adhesion protein. Anti-zyxin antibodies were detected in 37% of patients with GCA and in 15% of patients with Takayasu's arteritis but not in healthy controls. Interestingly, the titer of anti-zyxin antibodies tended to be higher in all untreated patients with GCA than in treated patients. Half of GCA patients with polymyalgia rheumatica had antibodies to zyxin. Using immunocytochemistry analysis, we observed that zyxin translocated from cytoplasm or membrane to the nucleus in ECs stimulated with TNF-α and IL-1β, respectively. Using zyxin siRNA knockdown, zyxin mainly regulates IL-8 production from ECs stimulated with TNF-α and IL-1β, respectively. Furthermore, the increased IL-8 production via zyxin from ECs was inhibited by treatment with glucocorticoids and treatment with anti-zyxin antibodies.

Conclusion: Zyxin is a target antigen for AECA in GCA. Because zyxin is involved in regulating inflammatory responses in ECs via its translocation to the nucleus, the presence of anti-zyxin antibodies in GCA strongly implicates these antibodies in the pathogenesis of GCA or in disease progression.

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Rho Kinase (ROCK) Activity in Aortitis: Comparison of Giant Cell Arteritis (GCA), Takayasu Arteritis (TA) and Isolated Aortitis (IA). Lindsay Lally[1], Navneet Narula[2] and Robert F. Spiera[1]. [1]Hospital for Special Surgery, New York, NY, [2]Weill Cornell Medical College, New York, NY.

Background/Purpose: Aberrant ROCK activity is implicated in the pathogenesis of many autoimmune and vascular disease states as ROCKs promote Th17 differentiation and vascular remodeling. Increased ROCK activity has been demonstrated in temporal artery biopsies from GCA patients and ROCK is proposed to play a role in aortic aneurysm formation; however the role of ROCK in aortitis is unknown. The aim of this study was to assess ROCK activity in aortic specimens from patients with GCA, TA and IA.

Methods: All aortic aneurysm specimens with histopathologic evidence of aortitis diagnosed during a 1 year period at a single institution identified and corresponding medical record reviewed. Patient history and ACR criteria were used to confirm diagnosis of GCA, TA, or IA. Those with IgG4 disease were excluded. Paraffin-embedded specimens were stained for Phospho-Ezrin/Radixin/Moesin (pERM), a surrogate of ROCK activity, using immunohistochemical stain. Sections also stained for the un-phosphorylated ERM protein. Inflammatory cells characterized using CD3/CD20 stain for T/B cells. Aortic specimens without aortitis were also stained for ERM/pERM as controls. Stained slides reviewed by a pathologist blinded to clinical status. pERM intensity in the vasculature and inflammatory infiltrate was assessed.

Results: Of 12 eligible aortitis cases, 4 were in those with prior history of GCA, 3 had TA and 5 had IA. Expected demographic differences noted between groups.

In all compartments, pERM staining was notably more intense than ERM suggesting activation of ROCK. All patients with aortitis had >50% of the inflammatory infiltrate staining positive for pERM, though TA patients had

greater proportion of pERM negative inflammatory cells (CD 163+ histiocytes) than those with GCA or IA. All patients, including 10 with non-inflammatory aortic aneurysms, had intense pERM staining of stromal cells in the adventitia and vasa vasorum, which was not affected by use of medications or co-morbidities known to influence ROCK (Table 1).

Conclusion: The markedly more intense pERM staining compared to ERM in the vasculature and lymphocytic infiltrate from those with GCA, TA, and IA suggest the ROCK pathway is active in these disease states, though no major differences in stain intensity between groups was noted. The pERM intensity in vessels of non-aortitis aneurysm controls supports the idea that ROCK may promote aneurysm development. ROCK activation likely reflects a response to vascular damage and repair regardless of etiologic mechanism, though staining in the infiltrating lymphocytes suggests ROCK is also involved in the inflammatory response in aortitis. These findings may ultimately have therapeutic implications, if confirmed in larger cohorts, especially in GCA as inhibition of ROCK may mitigate the initial inflammatory milieu as well as aneurysm formation, the most significant late disease manifestation.

Table 1: Patient Demographics

Subject	Age (yr)/Sex	Diagnosis/Disease Duration (yr)	Immunosuppression	Symptoms*	Statin Use	ACE-Inhibitor Use	Tobacco Use	Hypertension
1	79/M	GCA/8	Prednisone 10mg	PMR	n	y	former	y
2	71/M	GCA/4	NA		n	y	former	y
3	78/F	IA	NA		y	y	former	y
4	73/M	IA	NA		n	n	former	y
5	60/M	IA	NA		n	y	n	y
6	76/M	GCA/8	NA	vision loss	y	y	n	y
7	64/F	IA	Prednisone 3mg**		n	n	former	n
8	71/M	GCA/5	Prednisone 2mg	HA/PMR	y	n	former	y
9	32/F	TAK	NA		n	n	n	n
10	28/F	TAK/1	Prednisone 40mg	fever/weight loss	n	n	n	n
11	40/F	TAK/1	Remicade 5mg/kg	arthritis, limb claudication	n	n	n	y
12	42/M	IA	NA		n	n	former	y

GCA= Giant Cell Arteritis TAK=Takaysu Arteritis IA=Isolated Aortitis PMR=Polymyalgia Rheumatica HA=headache.
n=no y=yes.
*Symptoms at time of presentation.
**Steroids for congenital adrenal hyperplasia.

Disclosure: L. Lally, None; **N. Narula**, None; **R. F. Spiera**, None.

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Temporal Artery Microbiome in Giant Cell Arteritis. Alison Clifford*[1], Pauline Funchain*[2], Lisa Lystad[3], Charissa Peterson[4], Jessica Altemus[4], Gary S. Hoffman[1] and Charis Eng[2]. [1]Center for Vasculitis Care and Research, Cleveland Clinic Foundation, Cleveland, OH, [2]Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH, [3]Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, OH, [4]Genomic Medicine Institute, Lerner Research Institute, Cleveland, OH.

Background/Purpose: Whether infectious agents play a part in giant cell arteritis (GCA) remains controversial. We have performed the first microbiome study of snap-frozen temporal arteries, collected and processed under sterile conditions, from GCA patients and controls using metagenomic sequencing.

Methods: Patients undergoing temporal artery biopsy for possible GCA were prospectively enrolled. Biopsies were collected under strictly sterile conditions and split, with one part sent for routine histopathological review and one part snap-frozen for microbiome studies. Patients were classified according to clinical presentation as either biopsy-positive GCA (TA+), biopsy-negative clinically classical GCA (TA-) or controls. Long-read 16S ribosomal RNA (rRNA) sequencing was used to describe the entire microbiome of temporal arteries. Total DNA was isolated, and V1-V4 regions of the gene encoding bacteria-specific 16S rRNA were amplified and Sanger sequenced. Taxonomic classification of bacterial sequences was performed using an in-house analysis pipeline and relative abundances of species were calculated. Microbiomes were plotted by principal-coordinate analysis (PCoA) using a de novo operational taxonomic unit (OTU) picking protocol (using the MacQIIME 1.7 toolkit). Functional composition of microbiomes was analyzed using the PICRUSt bioinformatics package.

Results: Eleven patients were enrolled, including 3 TA+ GCA patients, 2 TA- GCA patients and 6 controls. All patients were receiving empiric prednisone therapy at time of biopsy and 1 control patient was also receiving doxycycline. Using PCoA, the microbiomes of control temporal arteries clustered tightly together in the center of the plot, showing high degrees of taxonomic relatedness, while GCA microbiomes (both TA+ and TA – patients) plotted in the periphery, clearly separated from controls. One control outlier was noted. Stratification of the samples by prednisone dosage did not account for the separation of GCA and controls on PCoA. Taxonomic classification revealed a wide variety of bacteria in each temporal artery (mean 10.8 species/control vs 10.6 species/GCA), with no overarching species common to all. Significant upregulation of 4 functional pathways (nucleotide metabolism, steroid hormone biosynthesis, biosynthesis of siderophore group nonribosomal peptides, and electron transport) was identified in the GCA microbiomes (both TA+ and TA-) as compared to controls.

Conclusion: Temporal arteries are not sterile. They are inhabited in both the control and diseased state by a community of bacteria. GCA temporal artery microbiomes (from both TA+ and TA- patients) differ from controls with respect to both the taxonomy and function of bacterial species present. Whether these shifts in the GCA microbiome represent the cause or effect of vascular inflammation remains to be elucidated.

* contributed equally to this work

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Increased Migration and Proliferation Potential Characterize Vascular Smooth Muscle Cells from Patients with Giant Cell Arteritis. Alexis Regent[1], Kim-Heang Ly[2], Matthieu Groh[1], Chabha Khifer[3], Sebastien Lofek[3], Guilhem Clary[4], Philippe Chafey[4], Cédric Broussard[4], Christian Federici[4], Claire Le Jeunne[1], Elisabeth Vidal[5], Antoine Brezin[6], Veronique witko-Sarsat[4], Loïc Guillevin[1] and Luc Mouthon[1]. [1]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [2]Laboratoire d'immunologie, EA3842, Faculté de médecine, Limoges, Limoges, France, [3]Institut Cochin, INSERM U1016, CNRS UMR 8104, Université Paris Descartes, Paris, France, Paris, France, [4]Institut Cochin, INSERM U1016, CNRS UMR 8104, Université Paris Descartes, Paris, France, [5]Laboratoire d'immunologie, EA3842, Faculté de médecine, Limoges, France, [6]Service d'ophtalmologie, hôpital Cochin, AP-HP, Paris, France.

Background/Purpose: The pathophysiology of GCA is poorly understood. Questions remain regarding the mechanisms underlying vascular remodeling.

Methods: Vascular smooth muscle cells (VSMC) were cultured from temporal artery biopsies (TAB) of consecutive patients suspected of GCA. We selected four patients with biopsy proven GCA (TAB^+-GCA), four patients with biopsy-negative GCA (TAB^--GCA), and four patients with another diagnosis than GCA (GCA-control). Normal human aorta VSMC were used as control. Proteomes of VSMC from patients in TAB^+-GCA, TAB^--GCA or GCA-control groups were compared using two-dimension DIGE (2D-DIGE) at pH range of 3–11. Transcriptomic analysis of VSMC from patients within the three GCA groups was performed using affimetrix chips. Proliferation of VSMC was performed with BrDU proliferation assay ELISA kit in unstimulated condition and with paxillin siRNA.

Results: We could identify 16, 28 and 2 protein spots that were differentially expressed between VSMC from TAB^+-GCA and GCA-control patients, between TAB^+-GCA and TAB^--GCA patients and between TAB^--GCA and GCA-control patients respectively (fold change$\geq$1.5 and $p\leq0.05$). Principal component analysis differentiated VSMC proteomes from TAB^+-GCA, TAB^--GCA and GCA-control. Ingenuity analysis comparing TAB^+-GCA and aorta revealed that identified proteins interact with paxillin.

Genes differentially expressed between VSMC from patients with TAB^+-GCA, TAB^--GCA and GCA-control were involved in cellular movement, organismal injury, tissue development, and cancer.

Unstimulated proliferation and in the presence of paxillin siRNA are currently being investigated in order to evaluate its potential involvement in the dysregulated proliferative phenotype observed in VSMC from GCA patients

Conclusion: VSMC from patients with GCA expressed proteins that confer increased proliferation and migration potential. Inhibition of the increased proliferation of VSMC during GCA through paxillin targeting might represent a promising therapeutic approach in patients with GCA.

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Novel Inhibitory Effects of Mast Cells in Aortitis Involves Aortic Expression of Suppressor of Cytokine Signaling-1. Jason Springer, Vineesh Raveendran, Donald Smith, Mehrdad Maz and Kottarappat Dileepan. University of Kansas Medical Center, Kansas City, KS.

Background/Purpose: Early in the pathogenesis of Giant Cell Arteritis (GCA) dendritic cells interact with T cells of both Th1 and Th17 origin. IL-6; released by Th17 T-cells, macrophages and endothelial cells; plays an important role in the pathogenesis of GCA. Mast cells (MCs) are important constituents of the immune system. They possess both pro-inflammatory and anti-inflammatory functions. There is an increased presence of mast cells in the temporal arteries of GCA patients. Furthermore, MCs have been shown to have an immunomodulatory effect in an MPO-associated vasculitis mouse model. The mechanism by which MCs modulate vascular inflammation in large vessel vasculitis, such as GCA, is not known. Suppressor of Cytokine Signaling-1 (SOCS-1), a JAK-STAT inhibitor, plays a role in inhibiting cytokine signaling. The objective of this study was to test the hypothesis that MCs regulate LPS induced aortic IL-6 production through SOCS-1 proteins.

Methods: Two month old male C57Bl/6J mice were randomized into 4 treatment groups. The treatment groups were administered intraperitoneal injections with: saline (control), Compound 48/80 (C48/80, MC degranulating agent, 1mg/kg), LPS (1mg/kg) or C48/80+LPS. Mice were sacrificed at either 24 hours (single injection) or 10 days (serial injections), and blood and aortas were collected for various analyses as presented in '**Results**'. Data were analyzed for statistical significance and $p < 0.05$ was considered significant.

Results: In the single injection groups, LPS significantly enhanced serum IL-6 (350±146 pg/ml vs 21.3±5.5 pg/ml) and aortic IL-6 gene expression (18.0±5.4 fold vs 1.03±0.025 fold) compared to normal saline-injected mice. When MCs were degranulated by C48/80, LPS-induced aortic expression of IL-6 and serum IL-6 were significantly reduced when compared to LPS alone (IL-6: 101±13 pg/ml vs 350±146 pg/ml; IL-6 mRNA: 4.3±0.5 vs 18.0±5.4 fold change). Aortic expression of SOCS-1 mRNA was found to be 2- and 3-fold higher, respectively, in the LPS and C48/80 + LPS groups compared to controls. In mice receiving serial injections, there were significantly higher levels of IL-18 and tissue inhibitor of metalloproteinase-1 ($p<0.0001$) in the LPS and LPS+C48/80 groups compared to controls. Thrombopoetin was significantly higher in the LPS group compared to the C48/80 and control groups but no difference was seen between C48/80 + LPS compared to C48/80 group alone. No significant differences between groups were seen for IL-1 alpha, IL-1 beta, monocyte chemotactic protein (MCP) 1, MCP-3 or VEGF-A.

Conclusion: These results demonstrate that MC degranulation inhibits LPS- induced aortic expression of IL-6 and systemic production of IL-6. The inhibitory effect of MCs was associated with an increased expression of SOCS-1 in the aorta. This suggests that SOCS-1 plays a role in mast cell-mediated regulation of IL-6 as well as other cytokines associated with the pathogenesis of GCA homeostasis. Identifying the MC factor or factors involved in the inhibition of LPS-induced inflammation in the aorta may provide novel therapeutic strategies for GCA.

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Incidence, Prevalence and Survival of Biopsy-Proven Giant Cell Arteritis in Northern Italy. Mariagrazia Catanoso[1], Pierluigi Macchioni[1], Luigi Boiardi[1], Francesco Muratore[1], Giovanna Restuccia[1], Alberto Cavazza[1], Ferdinando Luberto[2] and Carlo Salvarani[1]. [1]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [2]Azienda Usl Reggio Emilia, Reggio Emilia, Italy.

Background/Purpose: To investigate the incidence, prevalence and mortality of biopsy proven giant cell arteritis (GCA) over a 27-year period in a defined area of northern Italy.

Methods: All patients with incident GCA diagnosed from January 1, 1986 to December 31, 2012 living in the Reggio Emilia area were identified through computerized hospital discharge diagnosis and a structured review of all histopahology reports. Patients were followed up from the time of diagnosis until either their death or December 31, 2012.

Results: Two hundred and eighty-five patients (75 men and 210 women) had biopsy proven GCA according to the histopathological examination. Mean+SD age at diagnosis was 74.4+7.3 years. The mean annual incidence rate (IR) of GCA was $58.16/10^6$ (95% CI: 51.4–64.9). The mean IR was $31.1/10^6$ (95% CI: 26.9–35.4) among women and $11.6/10^6$ (95% CI: 8.9–14.2) for men ($p < 0.05$). The estimated incidence for people over 50 y was 78.11 (95% CI: 67.4–88.7) for women and 33.4 (95% CI: 25.7–41) for men. The lowest IR occurred in male patients in the 50–59 years age group ($5.13/10^6$; 95% CI: 1.4–13.1), the highest IR was observed in female patients 80–84 years age group ($215.4/10^6$; 95% CI: 184.7–297.2). IR difference between sex was significant only in the 60–69 age group (IR male/female 14.6/67.1, 95% CI 7.0–26.9 vs 49.8–88.4). The average annual IR increased from $5.63/10^6$ during 1986–1988 to $45.23/10^6$ during 1998–2000 period and was stable thereafter with IR of $30–23/10^6$. Point prevalence on December 31st 2012 was $304.5/10^6$ (95% CI: 258.0–355.7) (women 453.1, 95% CI: 376–541.4, men 148.8, 95% CI: 105.3–204.2).

At histological examination 13.6% (39 pts) had only small vessels perivascular involvement (adventitial vasa vasorum and peri-adventitial capillaries). Prevalence of small vessels involvement was significant higher among male patients (male 30% vs 7%female, $p< 0.001$). One hundred and twenty-nine patients (45.2%) died during the follow-up period (median survival after diagnosis 152 months [range 4–320 months]). Survival did not differ nor between gender or between different histopathological pattern

Conclusion: This population-based study is the first to report the incidence of biopsy proven GCA in Italy. Our average annual IR is similar to that reported in the period 1984–1988 in Finland (1).

Reference

1) Franzén P, Sutinen S, von Knorring J. Giant cell arteritis and polymyalgia rheumatica in a region of Finland: an epidemiologic, clinical and pathologic study, 1984–1988. J Rheumatol. 1992; 19:273–6.

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The Incidence and Mortality Rates of Giant Cell Arteritis in Southern Norway Are Lower Than Previous Reported. Andreas P. Diamantopoulos, Glenn Haugeberg, Lisa Amundsen, Elisabeth Wigaard, Dag Magnar Soldal and Geirmund Myklebust. Hospital of Southern Norway Trust, Kristiansand, Norway.

Background/Purpose: Giant cell arteritis (GCA) is the most common form of vasculitis. The highest incidence rates of GCA have been reported from Southern Norway (29–32/ 100000 >50 years and mortality rates has been reported not to be different from the background population. However, data are from the end of 80's to the early 90's and no recent reports exist.

The aim of this study was to examine the incidence and standardized mortality ratios (SMR) of GCA in Southern Norway in the period of the last 13 years.

Methods: GCA patients were identified by using the hospital records during the years 2000–2013. The ICD-10 coding system (M31.5- 6) was used to identify the patients and the diagnoses were carefully verified. In addition, a retrospective study of the archives of the Department of Pathology was conducted, in order to identify patients with biopsy that were not registered by the ICD-10 system. SMR was calculated by using the death rates of the Norwegian population per 100 000.

Results: Mean age (95% CI) among the 212 identified GCA patients was 73.2 (72.0–74.4) years. Among them, 60 were males [mean age 73.4 years (71.0–75.7)] and 152 females [mean age 73.2 years (71.8–74.5)]. One-hundred fifty-five patients (73.1%) had a positive biopsy of the temporal artery, 42 patients (19.9%) a negative and in 15 patients (7.0%) biopsy was not performed. All the patients with a negative or not performed biopsy satisfied the ACR classification criteria for GCA.

The incidence rate for GCA was 17.2 per 100 000 >50 years (males 10.4 and females 23.4). The incidence rate of the biopsy-proven GCA was 12.6 per 100 000 >50 years. The yearly distribution of the incidence rates of GCA in Southern Norway is displayed in figure 1.

Among the 212 GCA patients, there were 52 deaths during the period 2000–2014. The overall SMR was 0.5 (95%CI 0.3– 0.6) [0.5 for males (95%CI 0.3– 0.7), and 0.4 for females (95%CI 0.3– 0.6)]. For biopsy-proven GCA the SMR rates were 0.7 (95%CI 0.4–1.0) for males and 0.4 (95%CI 0.2– 0.5) for females.

Conclusion: The incidence rate of GCA in Southern Norway during the years 2000–2013 is 45 % lower than this reported in previous studies. However, a rising tendency of the incidence rates has been noticed at the last 5 years (fig 1). Interestingly, the mortality of GCA patients appears to be lower compared to the background population. Better quality of health care in this group of patients could be a reason.

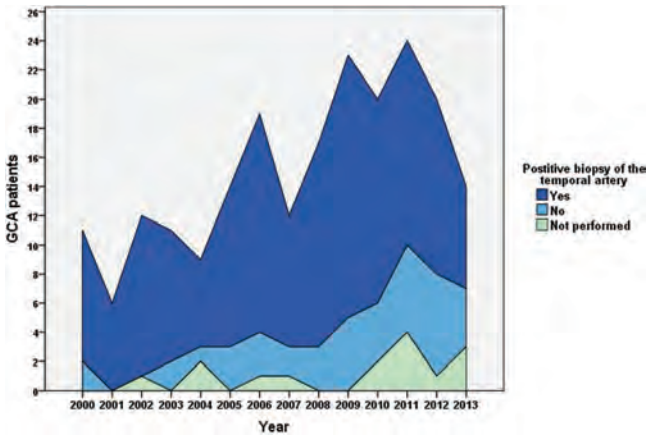

Fig 1

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Cardiovascular Risk Factors and Incident Giant Cell Arteritis. Gunnar Tomasson[1], Jóhannes Björnsson[2], Vilmundur Gudnason[3], Yuqing Zhang[4] and Peter A. Merkel[5]. [1]University of Iceland, Reykiavik, Iceland, [2]Akureyri Hospital, Akureyri, Iceland, [3]The Icelandic Heart Association, Kopavogur, Iceland, [4]Boston University School of Medicine, Boston, MA, [5]Vasculitis Center, University of Pennsylvania, Philadelphia, PA.

Background/Purpose: To assess the effect of cardiovascular risk factors on incidence GCA within a longitudinal cohort study in which detailed information on cardiovascular risk factors has been collected.

Methods: The data source is the Reykjavik Study (RS), a population-based, prospective cohort study with a primary focus on cardiovascular disease. All persons born in 1907–1935 that were living in Reykjavik, Iceland or adjacent communities on December 1, 1967 were invited to participate. Subjects came for a study visit in 1967–1996 and information on cardiovascular risk factors, including smoking habits, blood pressure, diabetes, body mass index, and serum cholesterol was obtained. All temporal artery biopsies (TABs) obtained from 1961–2009 on members of the cohort were identified through all three pathology laboratories in Iceland. All TABs were re-examined in a standardized fashion by a single pathologist with expertise in vascular pathology. Incidence of GCA was calculated for exposed (GCA) and unexposed (no GCA) subjects and incidence rate ratios (IRR) were calculated with 95% confidence intervals adjusted for age and sex.

Results: Data were obtained from 19,241 subjects that were followed for a median 23.1 (IQR: 17.6–29.4) years after the age of 50. During the follow-up of 444,396 person-years, 194 subjects had GCA, corresponding to an incidence rate of 45.0 (95% CI: 38.8–51.2) per 100,000 person-years after the age of 50. Woman had increased incidence of GCA compared to men, IRR= 2.03 (95% CI: 1.49 – 2.76). BMI was inversely associated with GCA; subjects with a BMI >25 had an IRR= 0.68 (95% CI: 0.50–0.90). Smoking was inversely associated with GCA among men IRR= 0.51 (95% CI: 0.30–0.86), but not women IRR=1.12 (95% CI: 0.79–1.57). Hypertension was associated with incident GCA among men IRR= 1.91 (95% CI: 1.12–3.25), but not among women IRR= 0.86 (95% CI: 0.60–1.24). Serum cholesterol was not associated with incident GCA.

Conclusion: This study confirms a high incidence of GCA in Iceland. Lower BMI is associated with the occurrence of GCA. Among men, hypertension is positively associated with GCA and smoking is inversely associated with incident GCA.

Disclosure: G. Tomasson, None; **J. Björnsson**, None; **V. Gudnason**, None; **Y. Zhang**, None; **P. A. Merkel**, None.

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Fast-Track Diagnostic Procedure for Giant Cell Arteritis. Alojzija Hočevar[1], Ziga Rotar[2] and Matija Tomsic[3]. [1]University Medical Centre Ljubljana, 1000 Ljubljana, Slovenia, [2]University Medical Centre Ljubljana, Ljubljana, Slovenia, [3]BioRx.si, University Medical Centre Ljubjana, Ljubljana, Slovenia.

Background/Purpose: Giant cell arteritis (GCA) represents the most common primary vasculitis among adults aged 50 years or above. Recently, the national annual incidence rate in this population was determined at 10.5 per 10^5. GCA may lead to ischemic complications, which among others include permanent visual loss in up to 20% of patients and ischemic stroke in 2–4%. Early diagnosis and initiation of treatment is thus of paramount importance. At our secondary/tertiary level department of rheumatology we examine majority of patients with referral diagnosis of GCA within 24 hours from referral, and those referred during the week-end in up to 72 hours. Also, rheumatologists have been performing temporal artery biopsies (TAB) ourselves for decades with an excellent safety record. Snap frozen TAB specimens are processed and analyzed at the attached university institute of pathology. **Results** are obtained within three hours from TAB. Since September 2011 Color Doppler ultrasonography of temporal arteries (CDS-TA) is routinely performed in every potential case of GCA to aid diagnosis and guide TAB. Our aim was to analyze the performance of this approach to GCA patient work-up.

Methods: We retrieved and analyzed electronic and paper patient charts of patients diagnosed with GCA form September 1, 2011 to May 31, 2014. Appropriate descriptive statistical methods were used describe our cohort.

Results: During the 32 month observation period, 66 new GCA cases were identified. Their characteristics are presented in Table 1. Median (interquartile range (IQR), range) symptom duration prior to presentation was 30 (14–77, range 2–365) days. Patients were referred to our outpatient clinic by their general practitioners (33/66), infectious disease specialists (13/66), specialists of internal medicine (12/66) ophthalmologists (6/66), and neurologists (2/66). Except for two polymyalgia rheumatica patients, all other patients were glucocorticoid naïve at the time of diagnostic procedures. CDS-TA was performed in 65/66, and TAB in 54/66 cases. Median time to CDS-TA (IQR; range) was 0 (0–1; 0–6) days, and 1 (0–1.75; 0–15) day for TAB. CDS-TA, and TAB were performed on the day of referral to our department in 48/66 (73%), and 20/66 (30%) of patients, respectively. Notably, 24/66 (36.4%) patients reported visual manifestations. Unilateral permanent visual loss developed in 4/66 patients (6.1%)—in one patient despite prompt initiation of glucocorticoid treatment, and in the remaining three cases 13 days, 14 days, and 2 months before diagnosis. One patient had an ischemic stroke 8 days prior to diagnosis.

Conclusion: This fast-track pathway enables us to obtain a definitive diagnosis even before the initiation of treatment, and might contribute to a relatively low incidence of irreversible sight loss in our cohort compared to reported data, as well as avoidance of overtreatment with glucocorticoids.

Characteristics	
% female	69.7
age (mean ± SD)	73.2 ± 8.0
smoking # (%)	27 (40.9)
new onset/type headache # (%)	48 (72.7)
scalp tenderness# (%)	16 (24.2)
jaw claudication # (%)	21 (31.8)
visual symptoms # (%)	24 (36.4)
blurred vision # (%)	15 (22.7)
diplopia # (%)	8 (12.1)
transient visual loss # (%)	3 (4.5)
permanent visual loss # (%)	4 (6.1)
ptosis # (%)	1 (1.5)
dry cough # (%)	12 (18.2)
clinically changed TA # (%)	40 (60.6)
symptoms of large vessel disease # (%)	7 (10.6)
general symptoms # (%)	45 (68.2)
fever (≥38°C) # (%)	14 (21.2)
weight loss # (%)	36 (54.5)
polymyalgia rheumatica # (%)	9 (13.6)
ESR (mm/h; ref. <15–32), median (IQR)	80 (57–95)
CRP (mg/l; ref. <5.0), median (IQR)	63 (32–122)
SAA (mg/l; N <6.4), median(IQR)	192 (66.8–468)
positive TAB #/# all biopsies (%)	43/54 (79.6)
positive CDS-TA #/# all CDS-TA (%)	50/65 (76.9)
US signs large vessel disease #/# all CDS (%)	19/58 (32.7)

Disclosure: A. Hočevar, None; **Z. Rotar**, None; **M. Tomsic**, None.

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Association Between Histological Features and Clinical Features of Patients with Biopsy Positive Giant Cell Arteritis. Kimberley Ting[1], Susan Lester[2] and Catherine L. Hill[3]. [1]The Queen Elizabeth Hospital,

Adelaide, Australia, [2]Queen Elizabeth Hospital, Woodville South, Australia, [3]University of Adelaide, Adelaide, Australia.

Background/Purpose: Temporal artery biopsy is the gold standard for diagnosing giant cell arteritis (GCA). The pathology of GCA characteristically involves transmural infiltrates, giant cell formation and intimal hyperplasia. However the significance of histopathology characteristics, in terms of clinical features and complications of GCA, remains unknown. The aim of this study was to investigate the association between histological biopsy features and clinical features, such as blindness, in patients with biopsy positive GCA.

Methods: Positive temporal artery biopsies registered on the South Australian Giant Cell Arteritis Registry were identified between 1991 and 2013 (n=186). Clinical and serological data was recorded using both patient questionnaire and case note review. Patients without clinical data were excluded from the analysis (n=42). Statistical analysis was performed using chi-squared and Wilcoxon's tests.

Results: 144 biopsy positive GCA cases were analysed. The mean age at biopsy was 77 years. 71% were female, and in total 30% experienced blindness. Although not individually significant, transmural inflammation ($p = 0.11$), luminal thrombus ($p = 0.17$) and giant cells ($p = 0.20$) were more frequent in GCA patients with blindness, whereas fragmentation of the internal elastic lamina ($p = 0.04$), and intimal thickening ($p = 0.02$) were more frequent in GCA patients without blindness (Table 1). The presence of giant cells was associated with transmural inflammation ($p = 0.06$), jaw claudication ($p = 0.02$), and higher inflammatory markers. In contrast, characteristics of patients with intimal thickening included a lower frequency of giant cells (0.01) and jaw claudication ($p = 0.01$), and lower inflammatory markers.

Table 1: Association Between Histopathology and Blindness

Histological Feature	*GCA with Blindness n (%)*	*GCA with Blindness n (%)*	*p value*
Giant cells	29/35 (85%)	61/82 (74%)	0.20
Macrophages	9/24 (37.5%)	25/68 (36.7%)	0.95
Lymphocytes	22/24 (91.7%)	64/68 (94.1%)	0.68
Plasma Cells	5/24 (20.8)	8/68 (11.8%)	0.27
Neutrophils	2/24 (8.3%)	6/68 (8.8%)	0.94
Histiocytes	11/24 (45.8%)	31/68 (45.6%)	0.98
Transmural Inflammation	16/24 (66%)	32/67 (47.8%)	0.11
Fragmentation of internal elastic lamina	15/36 (41.7%)	53/85 (62.4%)	0.04
Intimal thickening	13/36 (36.1%)	51/85 (60%)	0.02
Luminal Thrombus	6/36 (16.7%)	7/85 (8.2%)	0.17

Conclusion: Giant cells are strongly associated with jaw claudication and systemic markers of inflammation. We did not find any histological features that were individually significantly associated with an increased risk of blindness in GCA patients. However patients with intimal thickening by histology are less likely to have giant cells, have less acute systemic inflammation, and have a lower risk of blindness. This group may reflect a different disease subgroup or late stages of inflammation, highlighting the challenges in the pathological diagnosis and biopsy reporting of active GCA.

Disclosure: K. Ting, None; **S. Lester**, None; **C. L. Hill**, None.

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Correlations Between Histopathological Findings and Clinical Manifestations in a Large Monocentric Cohort of Patients with Biopsy-Proven Giant Cell Arteritis. Luigi Boiardi, Francesco Muratore, Giovanna Restuccia, Alberto Cavazza, Pierluigi Macchioni, Giuseppe Germanò, Nicolò Pipitone and Carlo Salvarani. Arcispedale S Maria Nuova, Reggio Emilia, Italy.

Background/Purpose: Giant cell arteritis (GCA) is a vasculitis that involves large and medium sized arteries in patients older than 50 years. Temporal artery biopsy (TAB) is the gold standard for the diagnosis of GCA. Cranial symptoms are the most common manifestations of the disease, while permanent visual loss is the most feared ischaemic complication of GCA and is reported in 10–20% of patients. Previous study have tried to correlate histological features of TAB with cranial and visual symptoms, but the results reported are not conclusive. The aim of our stuy was to correlate histological findings of TAB with clinical manifestations in a large monocentric cohort of consecutive patients with biopsy-proven GCA.

Methods: A pathologist with expertise in vasculitis and blinded to clinical data and final diagnosis reviewed all TABs performed for suspected GCA at our hospital between January 1986 and December 2012. Positive TABs showing only small vessel vasculitis and/or vasa vasorum vasculitis without transmural inflammation were excluded from the comparison analysis. Histopathologic features evaluated were: the severity of inflammation and intimal hyperplasia, both graded on a semiquantitative scale (mild=1, moderate=2 severe=3), the presence of intraluminal acute thrombosis, calcifications, giant cells, fibrinoid necrosis and laminar necrosis, consisting in a band of coagulative necrosis sometimes bordered by palisading histiocytes and following the internal elastic lamina.

Results: 271 patients had a final diagnosis of biopsy-proven GCA and were included in the study. More severe inflammation on semiquantitative scale was more frequently seen in patients with any cranial symptoms (88.4% grade 3; 87.5 % grade 2 and 74.7% grade 1, p=0.026), headache (80.4% grade 3; 80% grade 2 and 65.3% grade 1, p=0.038), abnormalities of TA at physical examination (82.6% grade 3; 63.5 % grade 2 and 56.9% grade 1, p=0.001) and halo at TA colour duplex sonography (CDS) (75.5% grade 3; 78.4 % grade 2 and 48.5% grade 1, p=0.011). The presence of laminar necrosis was more frequent in patients with visual symptoms (43.1% vs 24.8%, p=0.005), and in those with abnormalities of TA at physical examination (82.3% vs 65.3%, p=0.012). The presence of calcifications was more frequent in patients with visual symptoms (45.5% vs 25%, p=0.003), and in patients without systemic symptoms (71.3% vs 52.7%, p=0.009). More severe intimal hyperplasia on semiquantitative scale was less frequently seen in patients with polymyalgia rheumatica (PMR) (32.2% grade 3; 53.8 % grade 2 and 56.3% grade 1, p=0.008). The presence of giant cells was more frequent in patients with jaw claudication (49.2% vs 30.8%, p=0.006). Fibrinoid necrosis was present only in 2 cases (0,7%), in both sparing the temporal artery and limited to a small branch

Conclusion: The data of this large monocentric cohort of biopsy-proven GCA patients evidenced that visual symptoms correlate with the presence of laminar necrosis and calcifications. Cranial symptoms and halo at TA CDS correlate with the severity of mural inflammation. PMR inversely correlates with intimal hyperplasia. Fibrinoid necrosis was not a features of GCA.

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Comparison of Clinical Manifestations in Different Histological Subsets of Biopsy-Proven Giant Cell Arteritis. Luigi Boiardi[1], Francesco Muratore[1], Alberto Cavazza[1], Giovanna Restuccia[1], Pierluigi Macchioni[1], Giuseppe Germanò[1], Nicolò Pipitone[1], Gianluigi Bajocchi[2] and Carlo Salvarani[1]. [1]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [2]Arcispedale S Maria Nuova, Reggio Emilia, Japan.

Background/Purpose: Temporal artery biopsy (TAB) showing transmural inflammation is considered the gold standard for the diagnosis of giant cell arteritis (GCA). In some cases of GCA, inflammation is confined to the periadventitial small vessels, the vasa vasorum and/or the adventitia. These patients seem to closely resemble classic GCA, but the final significance of this more limited inflammation need more confirmation. The aim of our study was to describe and correlate the different histological subsets of GCA with demographic and clinical manifestations in a large monocentric cohort of biopsy positive GCA patients

Methods: All TABs performed for suspected GCA between 1986 and 2012 were reviewed by a single pathologist. Based on the localization of the inflammation, positive TABs were classified into 4 categories: small vessel vasculitis (SVV), with inflammation limited to small periadventitial vessels devoid of muscular coat; vasa vasorum vasculitis (VVV), with inflammation surrounding the adventitial vasa vasorum; inflammation limited to adventitia (ILA), with inflammation spreading from vasa vasorum to the adventitia without extension to the media; transmural inflammation (TMI), with external elastic lamina disruption and extension of the inflammation to the medi

Results: 317 TABs were positive for inflammation and were classified as: 253 (79.8%) TMI, 18 (5.7%) ILA, 19 (6.%) VVV and 27 (8.5%) SVV. Compared to patients with TMI, those with SVV and VVV had a significantly lower frequency of headache (55.6% vs 77.9%, p=0.010 for SVV and 57.9% vs 77.9%, p=0.048 for VVV), jaw claudication (7.4% vs 44.7%, p<0.0001 for SVV and 15.8% vs 44.7%, p=0.015 for VVV), abnormalities of TA at physical examination (33.3% vs 71.3%, p<0.0001 for SVV and 47.1% vs 71.3%, p=0.036 for VVV), halo at TA color duplex sonography (CDS) (27.3% vs 72.4%, p<0.0001 for SVV and 16.7% vs 72.4%, p<0.0001 for VVV), systemic symptoms (only for VVV, 42.1% vs 66.8%, p=0.029), a

lower levels of ESR (70.4±30.9 vs 86.5±30.1, p=0.011 for SVV and 64.9±34.7 vs 86.5±30.1, p=0.010 for VVV, mean ± DS mm/hour) and CPR (7.4±8.4 vs 8.9±6.1, p=0.027 for SVV and 3.5±3.7 vs 8.9±6.1, p<0.0001 for VVV, mean ± DS mg/dl) an higher frequency of male gender (63% vs 22.1%, p<0.0001 for SVV and 42.1% vs 22.1%, p=0.048 for VVV) and peripheral arthritis (only for SVV, 22.2% vs 6%, p=0.002) but a similar frequency of polymyalgia rheumatica, large vessel involvement and visual symptoms (including blindness). Patients with ILA were more similar to those with TMI, showing only a lower frequency of headache (55.6% vs 77.9%, p=0.031), abnormalities of TA at physical examination (40% vs 71.3%, p=0.011) and halo at TA CDS (14.3% vs 72.4%, p=0.003).

Conclusion: The histological spectrum of inflammatory lesions that can be found in TAB is broad and constitutes a continuum, ranging from SVV at one extreme, through VVV and the more spread ILA in the middle, to TMI at the other extreme of the spectrum. Despite the differences in cranial symptoms, halo sign at CDS and levels of acute-phase reactants, it is crucial that clinicians be aware that all different histologic TAB patterns are equally associated with a risk of visual loss, thus requiring prompt glucocorticoid treatment.

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Is Temporal Artery Biopsy the Gold Standard for the Diagnosis of Giant Cell Arteritis? Marina Scolnik[1], Aldo Fabian Ojeda[2], Valeria Scaglioni[3] and Enrique R. Soriano[4]. [1]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [2]Departamento de Reumatología, Hospital de Clínicas, FCM-UNA, Asuncion, Paraguay, [3]Rheumatology Unit, Internal Medical Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [4]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina.

Background/Purpose: The only test that confirms diagnosis of Giant Cell Arteritis (GCA) is a temporal artery biopsy showing vasculitis with mononuclear cell inflammatory infiltrates, often with giant cells. Due to the focal and segmental nature of the infiltrates, areas of inflammation may be missed by the biopsy. Some imaging modalities may aid in the diagnosis such as color duplex ultrasonography of the temporal arteries. When the clinical suspicion is strong and temporal biopsy is negative or can't be performed, patients are treated as GCA. Our objective was to analyze all patients with GCA seen at our hospital in order to address value of temporal biopsy result in relation to the clinical course.

Methods: We retrospectively reviewed electronic medical records of patients registered in our hospital between 2000–2013 with the problem: vasculitis, Giant Cell Arteritis or Temporal Arteritis. Patients fulfilling ACR 1990 criteria for GCA were included. Clinical and treatment information was collected. Temporal biopsies were reviewed. Ultrasound of temporal arteries was performed by an experienced vascular sonographer if requested by the treating rheumatologist and the finding of the halo sign was considered compatible with GCA diagnosis.

Results: 101 patients were included with GCA diagnosis, 79 females (78.2%), with a mean age at diagnosis of 74.9 years (SD 8.1). Temporal biopsy was positive in 52 patients, negative in 21 and was not performed in 28. Clinical characteristics are shown in table 1 grouped by biopsy result. Multivariate analysis showed that abnormal temporal pulse on examination had an OR of 19.7 (CI 2.9–131.9) for predicting a positive biopsy. Having symptoms of polymyalgia rheumatica (PMR) and age were also associated with a positive biopsy (OR 4.5, CI 1.03–19.4, and OR 1.11, CI 1.01– 1.24 respectively). No differences were found in clinical presentation, treatment, relapses or recurrences between groups. Ultrasound was performed in 42 patients (41.6%). Results according to temporal biopsy are shown in table 2. Ultrasound had an overall sensitivity of 29%, and a sensitivity of 25% and a specificity of 84% versus temporal biopsy; it helped in diagnosing 2 patients with negative biopsy and 6 patients without biopsy.

Conclusion: Abnormal temporal pulse, PMR symptoms and age were associated with a positive biopsy. Clinical presentation, course, treatment and relapses/recurrences didn't differ between patients with positive or negative or unperformed biopsy. In our experience, clinical judgement continues to be relevant in the diagnosis of GCA, aided partially by biopsy, less so by ultrasound.

Table 1 and Table 2

	Total of GCA patients (n=101)	Positive temporal biopsy (n=52)	Negative temporal biopsy (n=21)	Temporal biopsy not performed (n=28)
Females, n (%)	79 (78.2)	39 (75)	24 (86)	22 (79)
Age at diagnosis, average, years (SD)	74.9 (8)	76 (6)	71 (9)	76 (10)
Follow-up, median, years (IQR)	2.6 (2.3)	3.2 (2.7)	2.2 (3.6)	2 (2.1)
Headaches, % (CI 95%)	80.2 (72–88)	78.8 (67–90)	71.4 (51–91)	88.8 (77–101)
Ocular symptoms, % (CI 95%)	45.5 (36–55)	48 (34–62)	48 (25–70)	39 (21–58)
-Blurred visión, %	20.8 (13.3–30)	28.8 (17.1–43.1)	9.5 (1.2–30.4)	14.3 (4–32.7)
-Diplopia, %	8.9 (4.1–16.2)	5.8 (1.2–15.9)	9.5 (1.2–30.4)	14.3 (4–32.7)
-Partial or total blindness, %	15.8 (9.3–24.4)	13.5 (5.6–25.8)	28.6 (11.3–52.2)	10.7 (2.3–28.2)
Jaw claudication, % (CI 95%)	39.6 (30–49)	48 (34.2–62)	28.5 (8.5–48.6)	33.3 (15–52)
Polymyalgia Rheumatica, % (CI 95%)	44.6 (35–54)	53.8 (40–68)	33.3 (12–54)	33.3 (15–52)
Temporal tenderness, % (CI 95%)	63.4 (53.2–72.7)	65.4 (50.9–78)	57.1 (34–78.2)	64.3 (44.1–81.3)
Abnormal temporal pulse, % (CI 95%)	43.6 (33.7–53.8)	**55.8 (41.3–69.5)**	**9.5 (1.2–30.4)**	46.4 (27.5–66.1)
Temporal tenderness or abnormal temporal pulse, % (CI 95%)	63.4 (54–73)	65 (52–79)	57 (35–79)	64 (46–82)
Erythrocyte sedimentation rate at diagnosis, mm/1 h, average (SD)	67 (31)	71(27)	68 (30)	60 (36)
Methylprednisolone IV pulse, n (%)	15 (14.9)	10 (19,2)	4 (19,1)	1 (3,6)
Initial oral meprednisone dose, mg/day, average (SD)	42.8 (16.9)	44 (20)	42 (14)	39.9 (12)
Duration of treatment, months, median (IQR)	19 (25)	22 (19)	18 (31)	14 (18)
Relapses while tapering steroids, n (%)	31 (30.7)	17 (32.7)	7 (33.3)	7 (25)
Recurrence after finishing initial treatment, n (%)	7 (6.9)	4 (7.7)	1 (4.8)	1 (3.7)
Use of other immunosuppressive agents, n (%)	11 (10.9)	7 (13.5)	3 (14.3)	1 (3.6)

	Total of GCA patients with temporal Doppler ultrasound performed (n=42)	Positive temporal biopsy (n=16)	Negative Temporal Biopsy (n=13)	Temporal biopsy not performed (n=13)
Ultrasound with halo sign	12 (28.6%)	4 (25%)	2 (15.4%)	6 (46.2%)
Ultrasound without halo sign	30 (71.4%)	12 (75%)	11 (84.6%)	7 (53.8%)

Disclosure: M. Scolnik, None; **A. F. Ojeda**, None; **V. Scaglioni**, None; **E. R. Soriano**, None.

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Preliminary Analysis of Histological Findings in GCA Biopsy Positive Patients. Surjeet Singh[1], Andrew Hutchings[2], Wulf Forrester-Barker[3], Bhaskar Dasgupta[4], Andreas P. Diamantopoulos[5], Peter Lanyon[6], Malgorzata Magliano[7], Brendan McDonald[8], Konrad Wolfe[4] and Raashid Luqmani[9]. [1]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [2]London School of Hygiene and Tropical Medicine, London, United Kingdom, [3]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford, United Kingdom, [4]Southend University Hospital, Essex, United Kingdom, [5]Hospital of Southern Norway Trust, Kristiansand, Norway, [6]Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom, [7]Stoke Mandeville Hospital, Aylesbury, United Kingdom, [8]John Radcliffe Hospital, Oxford, United Kingdom, [9]University of Oxford, Oxford, United Kingdom.

Background/Purpose: A positive temporal artery biopsy (TAB) with giant cells, active inflammation and intimal hyperplasia is the gold standard test for diagnosing temporal arteritis. However, a negative TAB does not rule out the disease. In this preliminary analysis we have looked at the histological features of the TAB's assessed in a prospective multicentre study of patients with suspected temporal arteritis (TABUL).

Methods: Temporal artery biopsies were performed in all patients with suspected temporal arteritis from June 2010 to December 2013. All biopsies were taken from the symptomatic side and examined by the local pathologist, recording results on a standardised case report form in addition to a routine pathology report. We describe the key histological features in the intima and internal elastic lamina, the presence of inflammatory infiltrates (including giant cells), thrombus, occlusion and recanalisation. Age, sex, median time to biopsy from starting steroids, biopsy length and clinical diagnosis at baseline assessment were recorded.

Results: In this preliminary analysis, data was available from 350 patients (254 female: 86 male, mean age = 71.1±9.5 (SD), [range 47–96]), of whom 348 received steroids. The mean time to biopsy following initiation of steroids was 5±3 (SD) days with 6 GCA biopsy positive cases greater than 10 days. The mean length of the temporal artery biopsy was 11.9±7.4 (SD) mm. Only 332 biopsies consisted of an artery (94.9%), from which 89 cases were positive for GCA (26.8%). Of the 89 cases, 69 had internal hyperplasia and 11 had both internal hyperplasia and arteriosclerosis in the intima. Fragmentation in the internal elastic lamina was reported in 53 cases, 24 cases reported both fragmentation and reduplication. In 98.9% of GCA biopsy positive cases, inflammatory infiltrate were present, with transmural (41.6%) and adventitia

(18.0%) recorded as the predominant sites of inflammation. Giant cells were seen in 67 (75.3%) of GCA biopsy positive cases. Completely occluded vessels were found in 20 cases, usually due to internal hyperplasia (in 16), although 4 cases had additional thrombus. Furthermore, 7 cases had evidence of recanalisation in at least one section of the biopsy. We analysed the clinician's initial assessment at baseline (prior to biopsy): 88, 189 and 73 out of 350 cases were defined as possible, probable or definite GCA: of these, 7 (8.0%), 45 (23.8%) and 37 (50.7%) respectively had a biopsy consistent with GCA.

Conclusion: Histological features in biopsy positive patients with GCA are not confined to one particular form of inflammation. The most common finding was transmural inflammation. We report a relatively low number of positive biopsies (89/350) which may reflect the low index of suspicion of GCA in this group, technical difficulties in obtaining an adequate sample, or skip lesions missed due to inadequate length of tissue, or the effects of glucocorticoid therapy in changing the biopsy result. Our findings highlight the need for a better diagnostic strategy for patients with suspected temporal arteritis.

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Colour Doppler Ultrasonography Findings in Giant Cell Arteritis (GCA) and Their Relationship with Clinical Manifestations. Cristina Ponte[1], Ruth Geraldes[2], Anthea Craven[1], Andrew Judge[1], Peter C. Grayson[3], Ravi Suppiah[4], Joanna Robson[1], Richard A. Watts[5], Peter A. Merkel[6] and Raashid Luqmani[1]. [1]University of Oxford, Oxford, United Kingdom, [2]Lisbon Academic Medical Centre, Lisbon, Portugal, [3]National Institutes of Health, Bethesda, MD, [4]Auckland District Health Board, Auckland, New Zealand, [5]Rheumatology Department Ipswich Hospital and University of East Anglia, Ipswich, United Kingdom, [6]Vasculitis Center, University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Colour Doppler ultrasonography (CDU) of the temporal (TA), axillary (AA) and common carotid arteries (CA) has excellent sensitivity and specificity for the diagnosis of GCA, typically showing halos (dark areas around the arterial walls) and stenoses or occlusions. The CDU pattern of patients with extra cranial and cranial GCA has been reported to substantially differ; visual impairment and age are inversely correlated to extra cranial GCA. In addition, involvement of the vertebral arteries (VA) is associated with vertebrobasilar stroke. The aim of this analysis was to evaluate the type and frequency of CDU abnormalities in the TA, AA, CA and VA and their relationship with clinical features amongst patients with a submitted diagnosis of GCA in the DCVAS study (a multinational observational study to develop diagnostic criteria and update classification criteria for primary vasculitis, using data from patients with vasculitis and comparators).

Methods: This analysis included data from all patients recruited into DCVAS through April 2014 who had complete 6 month follow-up data, a submitted diagnosis of GCA, and whose tests included a CDU of TA, AA, CA or VA. The presence of halo was considered diagnostic of GCA. Patients were defined as having cranial GCA if they underwent CDU of at least TA and AA but only had abnormities in TA; patients with extra-cranial GCA had involvement of the proximal arm arteries. CDU findings of each artery and cranial/extra cranial pattern were compared to clinical features using Chi-square or Mann-Whitney tests.

Results: GCA was diagnosed in 431 patients; 336 underwent TA biopsy (78%) and 133 (31%) underwent CDU of the following arterial territories: 107 TA, 72 CA, 42 AA and 21 VA. In 8 cases all 4 areas were evaluated; in 27 cases 3 areas; in 31 cases 2 areas; and in 67 cases 1 area. Halo occurred in 75% (TA), 16% (CA), 34% (AA), 41% (VA) of cases; stenosis was seen in 31% (TA), 11% (CA), 16% (AA) and 41% (VA); occlusion was present in 11% (TA), 0% (CA), 3% (AA) and 6% (VA); CDU was normal in 16% (TA), 73% (CA), 58% (AA) and 39% (VA). Table 1 shows that older people were more prone to having a positive TA CDU; headache was less frequent in extra-cranial GCA; PMR occurred in a higher number of patients with CA involvement; and an association between vascular examination and CDU was only found in AA ($p<0.05$). Moreover, no type of CDU involvement correlated to eye symptoms.

Conclusion: Despite the high sensitivity of CDU and its ability to evaluate several vessels, clinicians usually use TA biopsy for the diagnosis of GCA. Extra-cranial involvement is frequent in GCA and inversely correlated to history of headache. The presence of abnormal CDU findings in several arterial territories supports the use of more extensive imaging in GCA. No significant correlation between cranial GCA and eye symptoms was found, but the low number of patients with extra cranial CDU was a limitation in the analysis.

Table 1 Relationship between the CDU findings and clinical features.

CDU findings (n)	Female sex n (%)	Mean age (±SD)	Eye Sympt.[1] n (%)	PMR n (%)	Jaw claudic. n (%)	Headache n (%)	Stroke/ TIA n (%)	Mean ESR (±SD)	TAB positive[2] n (%)	Vasc. examination abnormality[3] n (%)
TA + (70 patients)	40 (57%)	74 ± 9	29 (41%)	16 (23%)	25 (36%)	49 (70%)	3 (4%)	73 ± 31	45 (83%)	39 (59%)
TA - (15 patients)	12 (80%)	70 ± 7	5 (33%)	5 (33%)	4 (27%)	12 (80%)	1 (7%)	66 ± 31	6 (60%)	8 (53%)
p value	0.09	**0.03**	0.56	0.39	0.50	0.44	0.69	0.35	0.09	0.68
VA + (7 patients)	4 (57%)	78 ± 5	5 (71%)	0 (0%)	3 (43%)	6 (86%)	1 (14%)	83 ± 15	7 (100%)	–
VA - (7 patients)	4 (57%)	70 ± 7	2 (29%)	2 (29%)	2 (29%)	7 (100%)	0 (0%)	88 ± 43	3 (50%)	–
p value	1.00	**0.03**	0.11	0.13	0.58	0.30	0.30	0.39	**0.03**	–
CA + (10 patients)	7 (70%)	72 ± 8	3 (30%)	5 (50%)	1 (10%)	1 (10%)	0 (0%)	77 ± 17	3 (100%)	0 (0%)
CA - (45 patients)	31 (69%)	73 ± 8	22 (49%)	7 (16%)	11 (24%)	32 (71%)	2 (4%)	71 ± 30	27 (79%)	3 (8%)
p value	0.95	0.81	0.28	**0.02**	0.32	**0.001**	0.50	0.59	0.38	0.37
AA + (13 patients)	11 (85%)	73 ± 8	6 (46%)	1 (8%)	4 (31%)	7 (54%)	0 (0%)	70 ± 26	7 (78%)	5 (50%)
AA - (22 patients)	13 (59%)	74 ± 5	6 (27%)	2 (9%)	6 (27%)	15 (68%)	1 (5%)	79 ± 30	15 (75%)	0 (0%)
p value	0.15	0.59	0.26	0.87	0.83	0.40	0.44	0.29	0.87	**0.002**
Cranial GCA (19 patients)	13 (68%)	74 ± 8	5 (26%)	2 (11%)	5 (26%)	15 (79%)	1 (5%)	76 ± 31	13 (77%)	–
Extra cranial GCA (17 patients)	15 (88%)	74 ± 6	8 (47%)	3 (18%)	5 (29%)	8 (47%)	0 (0%)	74 ± 24	8 (73%)	–
p value	0.15	0.79	0.20	0.54	0.84	**0.04**	0.34	0.94	0.63	

(+) Positive findings for GCA; (−) Negative findings for GCA; AA - Axillary artery; CA - Carotid artery; CDU - Colour Doppler ultrasonography, ESR - Erythrocyte Sedimentation Rate; GCA - Giant Cell Arteritis; PMR - Polymyalgia Rheumatica; SD - Standard deviation; TA - Temporal artery; TAB – Temporal artery biopsy; TIA - Transient Ischaemic Attack; VA - Vertebral artery.
[1] Eye symptoms were considered when "amaurosis fugax", "sudden visual loss", "blurred vision in either eye", "diplopia" or "optic neuritis" was recorded.
[2] TAB was defined has positive when "definitive vasculitis" or "consistent with vasculitis but not definitive" was recorded.
[3] The presence of a diminished/absent pulse, tenderness, hard 'cord like' or/and bruit in the area scanned.

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High Interobserver Agreement on Ultrasonographic Findings in Patients with Large Vessel Vasculitis. Andreas P. Diamantopoulos[1], Julia Geiger[2], Frode Lohne[3], Geirmund Myklebust[1] and Wolfgang A. Schmidt[4]. [1]Hospital of Southern Norway Trust, Kristiansand, Norway, [2]University Children's Hospital, Zurich, Switzerland, [3]Unilabs Røntgen Kristiansand, Kristiansand, Norway, [4]Immanuel Krankenhaus, Berlin, Germany.

Background/Purpose: Ultrasound has a high sensitivity and specificity regarding the diagnosis of giant cell arteritis (GCA). Ultrasound can also depict extracranial large vessel vasculitis (LVV) in both GCA and Takayasu arteritis (TA) patients. Until now, no studies have examined the inter-observer agreement of the ultrasonographic findings in LVV patients.

Hence, the aim of this study was to examine the inter-observer agreement of the ultrasound examination of temporal arteries and large vessels in LVV patients.

Methods: This study is a part of the MUSES project (Magnetic resonance angiography vs Ultrasonography in Systemic large vEssel vasculitiS), a prospective cross-sectional study. Patients who were diagnosed with LVV by ultrasound, MRA or CTA were identified and included in the study at the Department of Rheumatology, Hospital of Southern Norway Trust in Kristiansand from January 2014 to June 2014. One ultrasonographer experienced in the use of vascular ultrasound (APD) examined and recruited the LVV patients. The common temporal (TC), temporal parietal branch (TP), temporal frontal branch (TF), carotid (AC), subclavian (AS), vertebral (AV), axillary (AA) arteries, abdominal aorta (AAR) and ascending thoracic aorta (TAR) were scanned in all patients. Films of ultrasound evaluation of every artery both in longitudinal and transverse view (TAR-only longitudinal view) were recorded, and these data were surveyed by an expert on vascular ultrasound (WAS) who was blinded to clinical and laboratory data. To calculate the inter-observer agreement the Cohen's kappa test has been used.

Results: Nineteen patients were included in this study [(9 males, 10 females, median age 65 (32–78)]. Eighteen patients were diagnosed with GCA and one with TA. Six patients had new onset LVV and 13 had long lasting [(mean disease duration 3.3 years, 95% CI 1.95–4.67)]. Median CRP was 5 mg/l (1–133) and ESR 25 mm/hr (4–112).

The inter-observer agreement for the various arteries was: TC 0.94 (95% CI 0.82–1.00), TP 0.94 (95% CI 0.83–1.00), TF 0.87 (95% CI 0.70–1.00), AC 0.67 (95% CI 0.45–0.89), AS 0.94 (95% CI 0.84–1.00), AV 0.84 (95% CI 0.54–1.00), AA 1.00, TAR 1.00. None of the patients had affection of the abdominal aorta on ultrasound examination.

Conclusion: Ultrasonographic findings of aorta, temporal and supraaortic arteries in patients with LVV appears to be highly reproducible and can be recorded in films for further evaluation. Nonetheless, experience in the use of vascular ultrasound is required to achieve these promising results.

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Early Halo Sign Features on Ultrasound Examination of Treated Patients with Giant Cell Arteritis. Ana Sofia Serafim[1], Surjeet Singh[1], Jennifer Piper[2], Andrew Hutchings[3], Mike Bradburn[4], Cristina Ponte[5], Bhaskar Dasgupta[6], Wolfgang A. Schmidt[7], Andreas P. Diamantopoulos[8], Eugene McNally[9] and Raashid Luqmani[2]. [1]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [2]University of Oxford, Oxford, United Kingdom, [3]London School of Hygiene and Tropical Medicine, London, United Kingdom, [4]Sheffield University, Sheffield, United Kingdom, [5]Lisbon Academic Medical Centre, Lisbon, Portugal, [6]Southend University Hospital, Essex, United Kingdom, [7]Immanuel Krankenhaus, Berlin, Germany, [8]Hospital of Southern Norway Trust, Kristiansand, Norway, [9]Oxford University, Oxford, United Kingdom.

Background/Purpose: The TABUL study (Temporal Artery Biopsy Vs Ultrasound in diagnosis of Giant Cell Arteritis) is assessing the relative performance of ultrasound and temporal artery biopsy for diagnosing GCA. All patients with newly suspected GCA underwent a single ultrasound scan of both temporal and axillary arteries within 7 days of commencing glucocorticoid therapy. We aimed to examine the ultrasound response to treatment as a potential biomarker in GCA, by measuring differences in the size of the halo around the arteries with different steroid duration within a 7 day period; furthermore we correlated the halo size with ischaemic symptoms of GCA.

Methods: All 415 cases with suspected GCA had an ultrasound examination of the temporal and axillary arteries and a biopsy of the temporal artery within 7 days of inclusion. The 301 patients with clinically defined definite or probable GCA at baseline were included in this analysis. Using the IBM SPSS Statistics package v20, we performed a cross-sectional analysis with linear and logistic regression models to determine the relationship of the halo size with days of steroid treatment and with ischaemic symptoms of GCA (jaw and tongue claudication, amaurosis fugax and reduced, lost or double vision).

Results: We included 214 women and 87 men (mean age 72.6 and 71.2 years old respectively) from 20 different recruitment centres. Fifty percent were scanned on the second day of steroid treatment or before. Forty three per cent (131 patients) had one or more temporal segments with a halo, 48.5% (146 patients) had bilateral temporal artery halos and 12.6% (38 patients) had axillary involvement. The linear regression model showed a consistently smaller halo size over the 7 days of steroid treatment ($p<0.005$) for the temporal arteries. The likelihood of finding a halo diminished with time, which was confirmed in a logistic regression until day 4 of steroid treatment ($p<0.005$), whereas this trend was not possible to predict after that time. At least one ischaemic symptom was present in 42% of the patients: jaw claudication in 48.2% (146 patients), reduced or lost vision in 36.6% (111 patients), double vision in 8.6% (26 patients), tongue claudication in 6.6% (20 patients) and amaurosis fugax in 4% (12 patients). The presence of jaw claudication was more frequent in patients with a halo ($p<0.05$). The symptomatic side of temporal arteries correlated significantly with the ipsilateral ultrasound findings ($p<0.05$ for right and left side findings on physical examination).

Conclusion: In newly diagnosed GCA, ultrasound halo size decreases with steroid treatment and correlates with the presence of ischaemic symptoms, supporting its early use as a diagnostic and potentially prognostic marker. We are exploring the potential value of change in halo size in individual patients over time to determine its value in monitoring response to treatment.

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PET/CT for the Diagnosis of Giant Cell Arteritis: A Prospective Study. Alison Clifford[1], Elana Murphy[1], Steven Burrell[1], Matthew Bligh[1], Godfrey Heathcote[1], Mathieu Castonguay[1], Kara Thompson[2] and John G. Hanly[1]. [1]Dalhousie University and Capital Health, Halifax, NS, [2]Department of Medicine, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, NS.

Background/Purpose: Temporal artery (TA) biopsies are negative in up to 50% of patients with giant cell arteritis (GCA). In such cases, increased uptake in large arteries on PET/CT may support the clinical diagnosis. The objective of this study was to compare vascular (18F)-FDG uptake in patients with clinically diagnosed GCA to controls, and to compare uptake in GCA TA biopsy positive (TA+) patients to those with negative TA biopsies (TA-). Secondary outcomes evaluated the correlation of vascular uptake on PET/CT with clinical and laboratory variables and medications, including use of corticosteroids.

Methods: Patients with a clinical diagnosis of GCA and meeting ACR 1990 classification criteria were prospectively enrolled. Controls were identified from an oncology database, matched for age and sex. All GCA cases were treated per standard of care with high dose corticosteroids and underwent both TA biopsy and PET/CT. Using a 4 point scale, vascular FDG uptake was scored in 8 vascular territories and overall (total) by two nuclear medicine specialists, blinded to the clinical diagnosis. TA biopsies were interpreted by 2 anatomical pathologists with differences resolved by consensus. Statistical analysis used non-parametric Wilcoxon exact tests, Spearman correlations and analysis of variance.

Results: Twenty-eight patients with GCA (61% female, mean age $\pm$ SD: 70 $\pm$ 8.9 yrs) and 28 controls (61% female, 64 $\pm$ 8.2 yrs) were enrolled. TA biopsy was positive in 64% of GCA patients. Mean total PET/CT uptake scores were significantly higher in those with GCA (10.34 $\pm$ 2.72) compared to controls (7.73 $\pm$ 2.56, $p=0.001$.) Six of 8 vascular territories evaluated showed significantly greater uptake in GCA patients. TA+ and TA- GCA patients had similar total PET/CT uptake (10.86 $\pm$ 2.63 vs. 9.4 $\pm$ 2.76, $p=0.2$) and in each specific vascular territory. The optimal cut-off for distinguishing GCA cases from controls by total PET/CT uptake score was 9. This resulted in area under the curve of 0.75, with a sensitivity of 71.4% and specificity of 64.3%. The presence of systemic symptoms ($p=0.015$), lower hemoglobin levels ($p=0.009$) and higher platelet counts ($p=0.008$) were associated with higher PET/CT scores but ESR and CRP levels were not. The only association with corticosteroids was between higher daily dose adjusted for body weight with higher total PET/CT scores ($p=0.033$).

Conclusion: Large vessel disease was identified in the majority (71.4%) of GCA patients by PET/CT despite initiation of corticosteroids, with similar uptake noted in TA+ and TA- patients. The sensitivity of PET/CT was superior to that of TA biopsy for identification of patients with a clinical diagnosis of GCA. Systemic symptoms, in particular, were associated with greater total uptake scores.

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Frequency and Predictive Variables of Relapses in Patients with Biopsy-Proven Giant Cell Arteritis. Luigi Boiardi[1], Giovanna Restuccia[1], Francesco Muratore[1], Alberto Cavazza[1], Luca Cimino[1], Raffaella Aldigeri[2], Pierluigi Macchioni[1], Maria Grazia Catanoso[1], Nicolò Pipitone[1] and Carlo Salvarani[1]. [1]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [2]Università di parma, Parma, Italy.

Background/Purpose: Giant cell arteritis (GCA) is a vasculitis that involves large and medium sized arteries in patients older than 50 years. Relapses and recurrences of the disease have been reported in 40.8–48% of patients, leading to longer duration of glucocorticoids (GCs) therapy and to increased risk of GCs side effects. The aim of our study was to determine the frequency and the predictors of disease relapses in a large monocentric cohort of consecutive patients with biopsy-proven GCA.

Methods: All patients with a diagnosis of biopsy-proven GCA made at our centre between 1986 and 2007 were identified. Only patients with a follow-up period longer than 6 months were included in the study. A pathologist with expertise in vasculitis reviewed all temporal artery biopsies (TABs). Demographic, clinical and laboratory data at presentation and at each follow-up visit were retrospectively collected. Relapse was defined as recurrences of symptoms with rise in inflammatory markers during tapering of GCs or after GCs discontinuation.

Results: 181 patients had a diagnosis of biopsy-proven GCA in the study period. 22 patients had a follow-up shorter then 6 months, and were excluded from further analyses. Median (Q1,Q3) follow-up period for the 159 patients included was 80 (49,125) months. 57/159 (35.8%) patients relapsed during the follow-up period, with a median of 1 (range: 1–7) relapses. Most common clinical manifestation at first relapse was polymyalgia rheumatica (44%), followed by headache (37%). Only 1 patient developed visual loss secondary to disease relapse. Mean (DS) prednisone dose at the time of first relapse was

6.3 (10.1) mg/day. At univariate analysis predictors of relapses were the levels of hemoglobin (Hb) (HR 0.793, p=0.037), fever (HR 1.938, p=0.029), presence of giant cells (HR 2.560, P=0.031), acute thrombosis (HR 2.805, p= 0.003), and a more severe inflammation on a semiquantitative scale (HR 3.973, p=0.011 for moderate inflammation; HR 3.051, p=0.039 for severe inflammation) at TAB. Furthermore total duration of corticosteroid therapy [mean (SD) 64 (46) vs 31 (32) months, p<0.0001] and cumulative dose of prednisone [mean (SD) 16.7 (12.3) vs 9.7 (9.2) grms, p<0.0001) were significantly higher in patients whit disease relapses than in those without. Multivariate analysis confirmed as independent predictors of relapses the levels of Hb, [HR (CI 95%) 0.738 (0.575–0.947), p=0.017], the presence of moderate and severe inflammation at TAB [HR (CI 95%) 4.648 (1.328–16.363), p=0.016; and 3.653 (1.085–12.302), p=0.037 respectively for moderate and severe inflammation] and the presence of acute thrombosis at TAB [HR (CI 95%) 2.29 (0.974–5.383), p=0.05].

Conclusion: The results of the present study confirm that relapses are frequent in patients with biopsy-proven GCA. The levels of hemoglobin at diagnosis, the severity of inflammation and the presence of acute thrombosis at TAB are independent predictors of disease relapses.

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Peripheral Arterial Disease in Patients with Giant Cell Arteritis: A Systematic Review and Meta-Analysis. Patompong Ungprasert[1], Praveen Ratanasrimetha[2], Charat Thongprayoon[3], Wisit Cheungpasitporn[3] and Promporn Suksaranjit[4]. [1]Bassett medical center, Cooperstown, NY, [2]Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [3]Mayo clinic, Rochester, MN, [4]University of Utah School of Medicine, Salt Lake City, UT.

Peripheral Arterial Disease in Patients with Giant Cell Arteritis: A Systematic Review and Meta-analysis

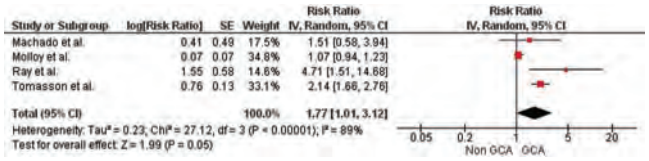
Background/Purpose: Several chronic inflammatory disorders, such as rheumatoid arthritis and systemic lupus erythematosus, have been shown to increase cardiovascular disease risk secondary to accelerated atherosclerosis. Similarly, there are data to suggest that patients with giant cell arteritis (GCA), another common chronic inflammatory condition, have an increased risk of coronary artery disease. However, the data on peripheral arterial disease (PAD) remain unclear due to conflicting epidemiological studies. Thus, to further investigate this association, we conducted a systematic review and meta-analysis of observational studies that compared the risk of PAD in patients with GCA versus participants without it.

Methods: Two investigators (P.U. and P.C.) independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception to March 2014 using the terms “giant cell arteritis” and “temporal arteritis” combined with the terms “peripheral artery disease”, “peripheral vascular disease” and “arterial occlusive disease” A manual search of references of retrieved articles was also performed. The inclusion criteria were as follows: (1) observational studies published as original studies to evaluate the association between GCA and clinically relevant PAD and (2) odds ratios (OR’s), relative risk (RR’s) or hazard ratio (HR’s) or standardized incidence ratio (SIR’s) with 95% confidence intervals (CI’s) were provided. Study eligibility was independently determined by the two investigators noted above. The quality of each study was, again, independently assessed by the two investigators using Newcastle-Ottawa scale.

RevMan 5.2 software was used for the data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird. Given the high likelihood of between study variance, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran’s Q test.

Results: Out of 460 potentially relevant articles, four studies (three retrospective cohort studies and one case-control study) were identified and included in our data analysis. The pooled risk ratio of PAD in patients with GCA was 1.77 (95% CI, 1.01 to 3.12). The statistical heterogeneity of this meta-analysis was high with an I^2 of 89%.

Conclusion: Our study demonstrated a statistically significant increased PAD risk among patients with GCA.



Disclosure: P. Ungprasert, None; **P. Ratanasrimetha**, None; **C. Thongprayoon**, None; **W. Cheungpasitporn**, None; **P. Suksaranjit**, None.

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Hospitalization Rates and Utilization Among Patients with Giant Cell Arteritis: A Population-Based Study from 1987 to 2012. C. John Michet III[1], Sara J. Achenbach[2], Cynthia S. Crowson[2] and Eric L. Matteson[2]. [1]Mayo Clinic College of Medicine, Rochester, MN, [2]Mayo Clinic, Rochester, MN.

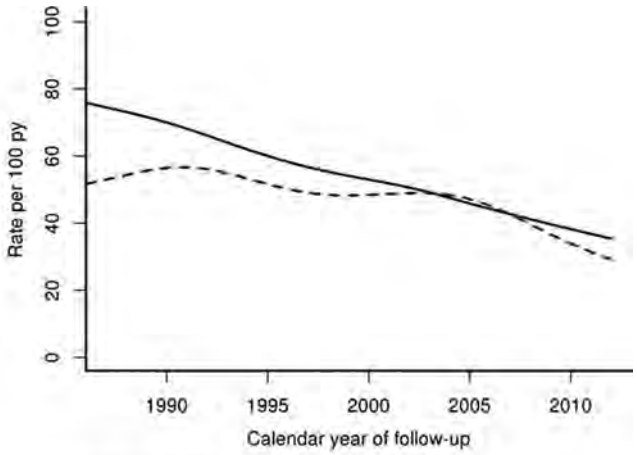
Background/Purpose: Patients with giant cell arteritis (GCA) may experience serious vascular and visual complications. It is unknown, however, to what extent the difficulties of the disease may lead to hospitalization. The goal of this study is to discern whether patients with GCA are at greater risk for all-cause hospitalizations when compared to the general population.

Methods: This retrospective, population-based cohort study utilized patients with large vessel or visual involvement who were diagnosed with GCA (as defined by the 1990 ACR criteria) between 1/1/1950 and 12/31/2009, and a reference cohort of patients without GCA matched on age, sex, and calendar year. Each patient’s medical record was examined for hospitalizations from 1987 through 2012. For this analysis, follow-up began with the latter of index date or 1/1/1987 and ended at the earlier of death, last follow-up, or 12/31/2012. Discharge diagnoses were grouped together using the Clinical Classifications Software (CCS) for ICD-9-CM from Healthcare Cost and Utilization Project (HCUP). Data were analyzed using person-year methods and rate ratios comparing GCA to non-GCA.

Results: The GCA cohort consists of 199 patients with a mean age of 76.2 (79.9% female) and follow-up of 8.2 years. The non-GCA cohort is comprised of 194 patients with a mean age of 75.7 (78.9% female) and follow-up of 8.6 years. The patients with GCA had 816 hospitalizations and the non-GCA patients had 737 hospitalizations. GCA patients proved to be at a marginally greater risk for all causes of hospitalization (Rate Ratio [RR] 1.13, 95% Confidence Interval [CI] 1.02, 1.25); however, the rate of hospitalization for patients with GCA decreased substantially from 1987 to 2012 (Figure 1).

Two specific discharge categories are of interest. First, transient cerebral ischemia (TCI) is a greater risk of hospitalization for patients with GCA who had 16 hospitalizations compared to patients without GCA who only had 5 hospitalizations (RR 3.06, CI 1.27, 9.47),. Second, patients with GCA (21 hospitalizations) are at greater risk of hospitalization for syncope than patients without GCA (5 hospitalizations) (RR 3.98, CI 1.72, 12.14).

Conclusion: In this first ever analysis of all-cause hospitalizations in a population-based cohort, patients with GCA appear to be at a marginally greater risk for hospitalization than patients without GCA, although the rate of hospitalization for GCA patients decreased from 1987 to 2012. Patients with GCA are at increased risk of hospitalization for both transient cerebral ischemia and syncope.



Solid line – patients with GCA
Dashed line – patients without GCA

Disclosure: C. J. Michet III, None; **S. J. Achenbach**, None; **C. S. Crowson**, None; **E. L. Matteson**, None.

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Venothromboembolism in Large Vessel Vasculitis. Sankalp V. Bhavsar[1], Nader A. Khalidi[2], Simon Carette[3], David Cuthbertson[4], Peter C. Grayson[5], Gary S. Hoffman[6], Curry L. Koening[7], Carol A. Langford[8], Carol McAlear[9], Larry Moreland[10], Paul A. Monach[11], Christian Pagnoux[3], Philip Seo[12], Kenneth J. Warrington[13], Steven R. Ytterberg[13] and Peter A. Merkel[9]. [1]Division of Rheumatology, McMaster University, Hamilton, ON, [2]St. Joseph's Hospital, McMaster University, Hamilton, ON, [3]University of Toronto, Toronto, ON, [4]University of South Florida, Tampa, FL, [5]National Institutes of Health, Bethesda, MD, [6]Cleveland Clinic Foundation, Cleveland, OH, [7]University of Utah, Salt Lake City, UT, [8]Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, OH, [9]Vasculitis Center, University of Pennsylvania, Philadelphia, PA, [10]Vasculitis Center, of University of Pittsburgh Medical Center, Pittsburgh, PA, [11]Vasculitis Center, Boston University School of Medicine, Boston, MA, [12]Johns Hopkins Vasculitis Center, Johns Hopkins University, Baltimore, MD, [13]Mayo Clinic, Rochester, MN.

Background/Purpose: Venous thromboembolic disease (VTE) is a recognized characteristic of various systemic vasculitides, particularly small-vessel vasculitis. However, there are no reports describing the frequency of VTE in Takayasu's arteritis (TAK) and no large studies examining VTE in patients with giant cell arteritis (GCA) using a standard case definition. The aim of this study was to determine the prevalence and incidence of VTEs in patients with large-vessel vasculitis (LVV), describe these VTEs, and assess the timing of VTEs in relation to the diagnosis of LVV.

Methods: The data source was the Vasculitis Clinical Research Consortium Longitudinal Studies of TAK and GCA, which enrolled patients with new onset or established disease. At baseline visits any history of VTE is recorded to determine the baseline prevalence of VTE. Also collected are data on traditional VTE risk factors such as history of malignancy, hematological disease, and other autoimmune diseases, and use of oral contraceptives or hormone replacement therapy. In follow-up visits, the occurrence of any new/interval VTEs is recorded. The timing of new VTEs in relation to the diagnosis of LVV or to flares of LVV was also evaluated.

Results: 159 patients with TAK and 256 patients with GCA were included for analysis. In patients with TAK, 5 patients (3.1%) had a history of VTE recorded at the baseline visit. No patients had identifiable traditional risk factors for VTE. 4 of the 5 events occurred within 4 years of diagnosis. New VTEs occurred in 4 patients with TAK over a mean observation period of 2.6 years after the baseline visit (incidence 1.0 per 100 person-years vs. a rate of 0.06 per 100 person-years in age matched controls). No patients experienced a flare of vasculitis when a new VTE was recorded. One patient with TAK with a new VTE had a history of inflammatory bowel disease. The overall prevalence of VTE in patients with TAK was 5.7%. In the GCA group, a history of VTE was recorded at the baseline visit in 12 patients (4.7%). One patient had a history of estrogen use; no other patients with VTE had a history of identifiable traditional risk factors for VTE. Over a mean observation period of 3.2 years after the baseline visit, no patients with GCA experienced a new VTE (incidence 0.0/100 person-years). All 21 VTEs in the patients with LVV occurred in females ($p < 0.05$). 19% of VTEs occurred within one year of diagnosis of LVV.

Conclusion: This is the first large study to describe VTEs in patients with TAK and GCA using a standardized case definition. Patients with TAK but not GCA appear to have an increased risk of developing VTEs after diagnosis, especially among female patients. VTEs in LVV appear likely to occur more frequently around the time of the diagnosis of LVV. In LVV the pathogenesis of VTE, the role of prophylactic antiplatelet/anticoagulation therapy, and determining if VTEs should be considered a criterion for disease relapse are all areas for future study suggested by these results.

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Inpatient Complications in Patients with Giant Cell Arteritis: Increased Risk of Thromboembolism, Delirium and Adrenal Insufficiency. Sebastian Unizony, Mariano Menendez, Naina Rastalsky and John H. Stone. Massachusetts General Hospital, Boston, MA.

Background/Purpose: The morbidity and mortality of hospitalized giant cell arteritis (GCA) patients has been largely unexplored. The aim of this study was to analyze inpatient complications experienced by patients with GCA.

Methods: We used the Nationwide Inpatient Sample (NIS) database to study a large group of patients admitted with medical and surgical problems that commonly affect the elderly (pneumonia, myocardial infarction, ischemic stroke and femoral neck fracture). Patients were divided in 2 cohorts based on whether or not they carried the diagnosis of GCA. Outcomes evaluated included inpatient mortality, the occurrence of adrenal insufficiency (AI), deep vein thrombosis (DVT), pulmonary embolism (PE), and delirium. GCA and non-GCA groups were compared using chi-square tests. Multivariate logistic regression analysis was performed to control for potential confounders such as age, sex, characteristics of the admitting hospital (teaching versus non-teaching; urban versus rural), and the presence of co-morbid conditions such as diabetes, hypertension, chronic kidney disease, coronary artery disease, and congestive heart failure. In order to maintain the family-wise error rate below a significance level of 0.05, adjustment for multiple comparisons was applied using Bonferroni's method.

Results: From 2008 to 2011, 8,203,447 patients older than 50 years of age were discharged from acute care facilities across the US after admission with pneumonia (3,232,939), myocardial infarction (2,180,990), ischemic stroke (1,623,564), or hip fracture (1,165,954). Among these individuals, a group of 9,311 (0.11%) carried the diagnosis of GCA. Compared to the non-GCA cohort, GCA patients were significantly older (mean age 80 versus 74 years, $p < 0.001$) and predominantly female (76% versus 53%, $p < 0.001$). Most hospitalizations in both GCA and non-GCA subjects occurred in urban locations (~80%).

During hospitalization, 4.1% of the patients with GCA died in comparison to 4.8% of the individuals without GCA ($p = 0.006$). After accounting for potential confounding factors, multivariable logistic regression analysis showed that the OR for in-hospital mortality among GCA subjects was 0.73 (95% CI 0.66 – 0.81; $p < 0.001$). In contrast, when compared with the non-GCA population, those with GCA suffered from DVT (1.5% versus 0.7%), PE (0.9% versus 0.6%), delirium (3.1% versus 1.5%), and AI (1.3% versus 0.3%) significantly more often ($p < 0.001$). Multivariate analyses revealed that GCA persisted as an independent risk factor for each of these complications. The OR for DVT was 2.08 (95% CI 1.76 – 2.45, $p < 0.001$); for PE, 1.58 (95% CI 1.27 – 1.96, $p < 0.001$); for delirium, 1.60 (95% CI 1.42 – 1.80, $p < 0.001$); and for AI, 4.95 (95% CI 4.13 – 5.93, $p < 0.001$).

Conclusion: GCA patients admitted for pneumonia, myocardial infarction, ischemic stroke and femoral neck fracture had a slight but significant reduction in inpatient mortality compared to the general population. However, GCA was an independent risk factor for AI, DVT, PE and delirium in the hospitalized population. Increased awareness among providers caring for inpatients with GCA may help prevent, diagnose and treat these important complications.

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Corticosteroid-Related Adverse Events in Patients with Giant Cell Arteritis: A Claims-Based Analysis. Gordon H. Sun[1], Khaled Sarsour[2], Eunice Chang[1], Michael S. Broder[1], Neil Collinson[3], Katie Tuckwell[3], Pavel Napalkov[2] and Micki Klearman[2]. [1]Partnership for Health Analytic Research, LLC, Beverly Hills, CA, [2]Genentech, Inc., a Member of the Roche Group, South San Francisco, CA, [3]Roche Products Ltd., Welwyn Garden City, United Kingdom.

Background/Purpose: Giant cell arteritis (GCA) is an inflammatory vasculitis preferentially affecting large and medium-sized arteries with an incidence of 1 to 30/100,000. High-dose oral corticosteroids (CS) are the mainstay of GCA therapy. We examined the risk of oral CS-related adverse events in a US commercially insured population.

Methods: This was a retrospective cohort study using MarketScan® during 2003–2012. We identified GCA patients who had at least 2 medical claims with a GCA diagnosis (International Classification of Diseases, 9th Revision, Clinical Modification code 446.5), had at least 1 oral CS prescription fill within 6 months before or after the first GCA diagnosis, and were at least 50 years old. Patients were followed for at least 1 year until disenrollment or study end. We measured oral CS use in 3 ways: cumulative number of days, cumulative prednisone-equivalent exposure, and contemporaneous use (time from the date of interest to last oral CS use). We prospectively reviewed published literature to identify adverse events of interest known to

be associated with oral CS use. Adverse events included cataracts, glaucoma, pneumonia, opportunistic infections, peptic ulcer disease, and bone-related conditions. We conducted Cox regression analyses to model oral CS use across time and the resultant risk of developing adverse events.

Results: The cohort contained 2,497 GCA patients with mean age 71 years, 71% women, and mean Charlson comorbidity index 1.5. Median initial oral CS dose in the cohort was 40 mg/day. Patients required a median 190 days to reduce this dose to ≤7.5 mg/day and received a median cumulative oral CS dose of 3,380 mg until this level was reached. They required a median 210 days to reach ≤5.0 mg/day and received a median 3,600 mg until this level was reached.

Patients with any adverse event were prescribed more days of oral CS (median 195 vs. 102.5 days) and received a higher cumulative prednisone-equivalent dose (median 3,400 vs. 2,145 mg) than those without an adverse event.

After adjusting for patient characteristics, each additional 1 gram increase in cumulative prednisone-equivalent exposure increased the hazard ratio of developing a first adverse event by 3% ($p<.001$). Similar patterns of increase were observed for individual adverse events, as well as for adverse event risk regardless of the method used to measure oral CS use (**Table**). Each additional cumulative month of oral CS increased the hazard ratio for first adverse event by 1% ($p=.003$). For current oral CS users, the hazard ratio for first adverse event was 1.47 ($p<.001$) compared to non-users.

Table

Risk of Developing Oral Corticosteroid-Related Adverse Events Based on Model of Oral Corticosteroid Use

Oral Corticosteroid Use Model	Hazard Ratio of First Adverse Event	Hazard Ratio of Osteoporosis	Hazard Ratio of Fracture	Hazard Ratio of Cataract	Hazard Ratio of Glaucoma	Hazard Ratio of Pneumonia	Hazard Ratio of Diabetes Mellitus
Each Additional Gram of Prednisone-Equivalent Exposure	1.03*	1.05*	1.04*	1.03*	1.05*	1.03*	1.05*
Each Additional Month of Oral Corticosteroid Use	1.01*	1.02*	1.01*	1.01	1.02*	1.01*	1.00
Current Oral Corticosteroid Use vs. No Use in 1 Year of Follow-Up	1.47*	2.28*	2.05*	1.39*	1.57	1.63*	1.51*

* p-value <.05

Conclusion: In a large cohort of GCA patients, high-dose oral CS use was near-universal. Patients were maintained on oral CS for a median 7 months before tapering to a daily dose of ≤5.0 mg. By multiple measures, high-dose oral CS use was associated with a significantly increased risk of adverse events.

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Vasculitis and Inflammatory Bowel Diseases: A Study of 32 Patients with Both Conditions and Systematic Review of the Literature. Alice Sy[1], Natasha Dehghan[2], Nader A. Khalidi[3], Lillian Barra[4], Simon Carette[5], David Cuthbertson[6], Gary S. Hoffman[7], Curry L Koening[8], Carol A. Langford[9], Carol McAlear[10], Paul A. Monach[11], Larry W. Moreland[12], Philip Seo[13], Ulrich Specks[14], Steven R. Ytterberg[14], Gert Van Assche[15], Peter A. Merkel[16] and Christian Pagnoux[5]. [1]Medicine Division, London, ON, [2]Rheumatology Division, Vancouver, BC, [3]McMaster University, Hamilton, ON, [4]St. Joseph's Health Care, London, ON, [5]University of Toronto, Toronto, ON, [6]University of South Florida, Tampa, FL, [7]Cleveland Clinic Foundation, Cleveland, OH, [8]George E. Wahlen Department of Veterans Affairs Medical Center Salt Lake City and University of Utah, University of Utah School of Medicine, Salt Lake City, UT, [9]Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, OH, [10]University of Pennsylvania, Philadelphia, PA, [11]Boston University, Boston, MA, [12]University of Pittsburgh, Pittsburgh, PA, [13]Johns Hopkins Vasculitis Center, Rheumatology Division, Johns Hopkins University, Baltimore, MD, [14]Mayo Clinic, Rochester, MN, [15]Mount Sinai Hospital, Toronto, ON, [16]Vasculitis Center, University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Small case series suggested that vasculitis and inflammatory bowel disease (IBD; Crohn's disease [CD] or ulcerative colitis [UC]) can co-occur more commonly than the prevalences of the individual diseases suggest. This study aimed to describe this association through the analysis of a large cohort of carefully studied patients and a systematic literature review.

Methods: Clinical data was available from patients with both IBD and vasculitis with follow-up >6 months enrolled in the Vasculitis Clinical Research Consortium (VCRC) Longitudinal Studies, followed in Canadian Vasculitis research network (CanVasc) centers, and/or in the University of Toronto's IBD clinic. Individuals in which ANCA-associated vasculitis (AAV) and IBD were diagnosed within the same 12-month period were excluded because diagnostic misclassification as IBD is common at initial presentation of ileocolitis due to vasculitis. A systematic review of the literature (through 02/2014) for patients with IBD and vasculitis was conducted through a PubMed search. The main characteristics of patients with Takayasu arteritis (TAK) were compared to those patients in the VCRC with TAK but no IBD.

Results: 32 patients (17 VCRC, 15 CanVasc) with vasculitis and IBD satisfying our study criteria were identified. The main group included 13 patients with large vessel vasculitis (LVV): 12 TAK and 1 giant cell arteritis; 8 patients had CD and 5 had UC. Eight patients had AAV (6 granulomatosis with polyangiitis, GPA), 2 eosinophilic granulomatosis with polyangiitis, EGPA, 5 isolated cutaneous vasculitis, and 6 other vasculitides (Kawasaki, IgA nephropathy, polyarteritis nodosa, or central nervous system vasculitis). Patients with LVV and AAV were mostly female (18/21) with a median age of 20 (8 to 52) and 27 (17 to 58) years at diagnosis of IBD and vasculitis, respectively. The diagnosis of IBD preceded that of vasculitis in 12/13 LVV and 8/8 AAV patients, 3/5 with cutaneous vasculitis and 3/6 with other vasculitides.

305 other patients with IBD and vasculitis were identified in the literature, distributed among 4 similar subsets: LVV (n=143, 116 female, 69 CD, 74 UC, 132 TAK, 87 with IBD preceding vasculitis), cutaneous vasculitis (n=66, 33 with IBD preceding vasculitis), AAV (n=19, 13 GPA, 3 MPA, 3 EGPA), and other vasculitides (n=77, including IgA vasculitis, retinal vasculitis, CNS vasculitis, polyarteritis nodosa, Kawasaki disease, vasculitic neuropathy).

As shown in the Table, no differences other than in ethnicity (likely due to center or publication biases) and age at TAK diagnosis were observed between patients with TAK with or without IBD. Mortality was low.

Characteristic	Patients with TAK but no IBD (VCRC) N = 152	Patients with TAK and IBD from this series N = 12	Patients with TAK and IBD from this series and literature N = 144
Female/Male, No.	143/9	11/1	110/24*
Median age at diagnosis of TAK, years (range)	31 (4 to 63)	19 (8 to 52)	23 (8 to 69)
Ethnicity, No. (%)			
Caucasian	127 (84%)	8 (67%)	18 (24.7%)
Asian	14 (9%)	3 (25%)	48 (65.8%)
Clinical manifestations, No (%)			n = 75*
Claudication of extremities	96 (63%)	8 (67%)	26 (35%)
Decreased brachial pulse	92 (61%)	9 (75%)	47 (63%)
Blood pressure difference between arms	70 (46%)	7 (58%)	45 (62%)
Bruit over subclavian artery or aorta	77 (51%)	5 (42%)	40 (55%)
Renal hypertension	20 (13%)	4 (33%)	15 (21%)
Median number of ACR criteria met	4 (1 to 6)	4.5 (2 to 6)	4 (2 to 6)
Median duration of follow-up, years	6.25 (0.25 to 31)	4.7 (0.75 to 28)	0.6 (0.1 to 28)
Outcomes, No (%)			n = 75*
Remission of vasculitis at last follow-up	108/122 (89%)*	5/8 (63%)	59 (79%)
Stroke	9 (7%)	0	4 (5%)
Myocardial infarction	4 (3%)	0	1 (1%)
Deaths	0	0	6 (8%)

* Complete information was not available for all patients, especially those from the literature.

Conclusion: These findings highlight the risk in patients with IBD (both CD and UC) to develop vasculitis, especially TAK. Further investigation of patients with both vasculitis and IBD may provide intriguing insights into common underlying mechanisms.

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Takayasu Arteritis and Ulcerative Colitis –High Concurrence Ratio and Genetic Overlap. Chikashi Terao[1], Takayoshi Matsumura[2], Hajime Yoshifuji[1], Yohei Kirino[3], Yasuhiro Maejima[4], Yoshikazu Nakaoka[5], Meiko Takahashi[1], Eisuke Amiya[2], Natsuko Tamura[4], Toshiki Nakajima[1], Tomoki Origuchi[6], Tetsuya Horita[7], Mitsuru Matsukura[2], Yuta Kochi[2], Akiyoshi Ogimoto[8], Motohisa Yamamoto[9], Hiroki Takahashi[9], Shingo Nakayamada[10],

Kazuyoshi Saito[10], Yoko Wada[11], Ichiei Narita[11], Yasushi Kawaguchi[12], Hisashi Yamanaka[13], Koichiro Ohmura[1], Tatsuya Atsumi[7], Kazuo Tanemoto[14], Tetsuro Miyata[2], Masataka Kuwana[15], Issei Komuro[2], Yasuharu Tabara[1], Atsuhisa Ueda[3], Mitsuaki Isobe[4], Tsuneyo Mimori[1] and Fumihiko Matsuda[1]. [1]Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [3]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [4]Tokyo Medical and Dental University, Tokyo, Japan, [5]Osaka University Graduate School of Medicine, Osaka, Japan, [6]Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [7]Hokkaido University Graduate School of Medicine, Sapporo, Japan, [8]Ehime University Graduate School of Medicine, Ehime, Japan, [9]Sapporo Medical University School of Medicine, Sapporo, Japan, [10]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [11]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [12]Tokyo Women's Medical University, Tokyo, Japan, [13]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [14]Kawasaki Medical School, Kurashiki, Japan, [15]Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Takayasu arteritis (TAK) is a systemic vasculitis affecting large arteries and large branches of the aorta. Ulcerative colitis (UC) is a prevalent autoimmune colitis. Since TAK and UC share HLA-B*52:01 and IL12B as genetic determinants, and concurrent cases of these two diseases have been reported, we hypothesized that UC is a common complication of TAK. Here, we performed an observational study to evaluate concurrence ratio of TAK and UC followed by genetic analysis of shared susceptibility genes between the two diseases.

Methods: A total of 470 consecutive patients with TAK from 14 Japanese institutions were registered. Concurrence ratio of TAK and UC were searched in each institution. We characterized patients with TAK and UC by analyzing clinical manifestations and genetic components. Genetic overlapping of TAK and UC was evaluated with use of UC susceptibility SNPs by comparing risk directions and effect sizes between susceptibility to the two diseases.

Results: We found that 29 patients out of 470 patients with TAK suffered from UC (6.2% (95%CI:4.2%-8.7%)). This ratio was much higher than expected based on prevalence of UC (0.11%). Patients with TAK and UC developed TAK at an earlier stage of life ($p=0.0051$) and showed significant enrichment of HLA-B*52:01 in comparison to patients without UC ($p=1.9\times10^{-5}$, OR:11.60, 95%CI:2.82–102.65). The patients with the two diseases did not display higher frequency of aortic regurgitation (AR) or severer AR than patients without UC. While the TAK patients with UC displayed high risk allele frequency of rs6871626 in the IL12B region in comparison with patients without UC, the difference did not reach the significant level (88.0% vs 75.7%, $p=0.22$, OR:2.35 (0.68–12.53)). The 103 susceptibility SNPs to UC displayed common risk directions with TAK susceptibility ($p=0.00074$), while the 133 susceptibility SNPs to human height as a non-immunological reference did not show common risk directions with TAK susceptibility ($p=0.13$).

Conclusion: UC is a major complication of TAK. These two diseases share a significant proportion of their genetic background and HLA-B*52:01 may play a central role on the concurrence.

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Association of a Single Nucleotide Polymorphism (SNP) in *IL-12B* Region with Clinical Features and Peripheral T Cell Profiles of Patients with Takayasu Arteritis. Toshiki Nakajima[1], Hajime Yoshifuji[1], Chikashi Terao[2], Koji Kitagori[1], Ran Nakashima[1], Yoshitaka Imura[1], Naoichiro Yukawa[1], Koichiro Ohmura[1], Takao Fujii[1] and Tsuneyo Mimori[1]. [1]Kyoto University Graduate School of Medicine, Kyoto, Japan, [2]Kyoto University, Kyoto, Japan.

Background/Purpose: We preliminarily found a SNP (A vs. C, rs6871626) in *IL-12B* region as a susceptibility gene to Takayasu arteritis (TAK) by genome-wide association study. *IL-12B*encodes IL-12/IL-23 p40 that regulates differentiation and activation of Th1 and Th17. In the present study, we investigated the association of this SNP with clinical characteristics and pathophysiology of TAK.

Methods: We investigated 1) the association of the SNP with clinical features of 84 TAK patients who have visited Kyoto University Hospital and 2) the association of the SNP with expression levels of surface markers and intracellular cytokines in peripheral T cells sampled from 21 TAK patients and 15 healthy controls (HC). We obtained peripheral blood mononuclear cells from the TAK patients and HC, stained them with fluorescent antibodies, and analyzed them with flow cytometry.

Results: 1) In 84 patients with TAK, 68 were the risk group (R-Group; AA+AC) and 16 were the non-risk group (NR-Group; CC). The complication rate of aortic regurgitation (AR) was 51% in R-Group, significantly higher than 13% in NR-Group ($p<0.01$). The ultrasound-evaluated severity of AR was higher in R-Group ($p<0.01$). eGFR tended to be lower in R-Group than in NR-Group (70.5 vs. 80.3 mL/min/1.73m^2, $p=0.2$). The complication rate of abdominal arterial lesions was 58% in R-Group, significantly higher than 27% in NR-Group ($p<0.05$). 2) In 21 patients with TAK analyzing T cells, 14 and 7 were R-Group and NR-Group, respectively. In $CD4^+$ T cells, $CXCR3^+$ (Th1) cells were 6.9% in patients (7.5% in R-Group and 5.7% in NR-Group), tended to be higher than 5.7% in HC ($p=0.16$), while $CCR6^+$ (Th17) cells were 16.0% in patients (16.5% in R-Group and 15.4% in NR-Group), significantly higher than 8.3% in HC ($p<0.01$). In $CD4^+$ T cells, IFN-γ^+ cells in R-Group was significantly higher than in NR-Group (23% vs.7%, $p=0.02$), while IL-17^+cells were not significantly different between R-Group and NR Group (0.7% vs. 1.4%, $p=0.37$).

Conclusion: In TAK patients with the risk allele of *IL-12B*, the complications of aortic valve and abdominal arteries were more frequent than in patients with the non-risk allele. TAK patients showed a tendency to have higher percentage of Th1 and Th17 cells than HC, and R-group had higher percentage of Th1 cells than NR-Group. The results suggested a possibility that this SNP may be involved in the pathophysiology of TAK through increased expression of cytokines.

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Serum Cytokine Profiles in Takayasu's Arteritis: A Search for a Biomarker. Fatma Alibaz-Oner[1], P.Sibel Yentür[2], Guher Saruhan-Direskeneli[3] and Haner Direskeneli[1]. [1]Marmara University, School of Medicine, Istanbul, Turkey, [2]Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey, [3]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey.

Background/Purpose: Assessment of disease activity is one of the main difficulties in patients with Takayasu Arteritis (TAK) during follow-up. In this study, we aimed to investigate serum interleukin (IL)-6, IL-8, IL-10, IL-18, IL-23 and granulocyte-macrophage colony-stimulating factor (GM-CSF), as possible biomarkers of disease activity in patients with TAK.

Methods: The study included 51 patients (age: 40.6±12.2 years, F/M: 45/6) with TAK and 42 age and sex matched healthy controls (age: 38.1±7.4 years, F/M: 38/4). All patients with TAK fulfilled the criteria of American College of Rheumatology (ACR) and were evaluated by physician's global assessment (PGA: active/inactive) and ITAS2010 (Indian Takayasu Clinical Activity Score) in terms of clinical activity at baseline and follow-up visits. Commercial enzyme linked immunosorbent assay (ELISA) kits were used for the measurements of serum IL-6, IL-8, IL-10, IL-18, IL-23 and GM-CSF.

Results: At baseline, 21 (41.2%) patients were active assessed with PGA and 8 (15.7%) with ITAS2010. Serum IL-6, IL-8 and IL-18 levels were significantly higher in patients with TAK (TAK vs HC, respectively; 194.7±485 (0–2555) vs 64.3±156.8 (0–748), 49.4±189 (0–1349) vs 8.4±23.8 (0–97), 535.1±252 vs 268.8±216.2) whereas GM-CSF, IL-10 and IL-23 levels were similar to healthy controls. Comparing baseline and follow-up visits, IL-8 levels significantly decreased in follow-up together with a decrease of clinical activity by PGA, whereas IL-23 levels significantly increased. IL-18 levels were associated with disease activity assessed with ITAS2010, but not with PGA. IL-18 was also the only cytokine correlating with CRP. No association of IL-6 levels were observed with disease activity.

Conclusion: We found significantly increased IL-6, IL-8 and IL-18 levels in patients with TAK compared to healthy controls, suggesting their role in disease pathogenesis. However, no consistent association of any

cytokine is observed with disease activity to use as a biomarker. In addition to anti-IL-6 treatment currently investigated, blockage of other pro-inflammatory cytokines IL-8 and IL-18 might be new therapeutic approaches in refractory TAK.

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Biomarkers of Disease Activity in Vasculitis. Alicia Rodriguez-Pla[1], Roscoe L. Warner[2], David Cuthbertson[3], Simon Carette[4], Gary S. Hoffman[5], Nader A. Khalidi[6], Curry L Koening[7], Carol A. Langford[8], Kathleen Maksimowicz-McKinnon[9], Larry W. Moreland[10], Christian Pagnoux[4], Philip Seo[11], Ulrich Specks[12], Kenneth J. Warrington[12], Steven R. Ytterberg[12], Peter A. Merkel[13], Kent J. Johnson[2], Paul A. Monach[14] and For the Vasculitis Research Consortium[15]. [1]Boston University, Boston, MA, [2]University of Michigan, Ann Arbor, MI, [3]University of South Florida, Tampa, FL, [4]University of Toronto, Toronto, ON, [5]Cleveland Clinic Foundation, Cleveland, OH, [6]McMaster University, Hamilton, ON, [7]George E. Wahlen Department of Veterans Affairs Medical Center Salt Lake City and University of Utah, University of Utah School of Medicine, Salt Lake City, UT, [8]Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, OH, [9]Henry Ford Hospital, Detroit, MI, [10]University of Pittsburgh, Pittsburgh, PA, [11]Johns Hopkins Vasculitis Center, Johns Hopkins University, Baltimore, MD, [12]Mayo Clinic, Rochester, MN, [13]Vasculitis Center, University of Pennsylvania, Philadelphia, PA, [14]Vasculitis Center, Boston University School of Medicine, Boston, MA, [15]U Pennsylvania, Philadelphia, PA.

Background/Purpose: To identify circulating proteins that distinguish between active vasculitis and remission in giant cell arteritis (GCA), Takayasu's arteritis (TAK), polyarteritis nodosa (PAN) and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss), using a panel of markers known to be elevated in ANCA-associated vasculitis.

Methods: 22 serum proteins (MMP-3, NGAL, ACE, sIL-6R, osteopontin, PAI-1, PDGF-AB, RANTES, sICAM-1, TIMP-1, BCA-1, G-CSF, GM-CSF, IFNγ, IL-15, IL-18, IL-18BPa, sIL-2Ra, IL-6, IL-8, IP-10, and sTNFRII) linked to possible pathways relevant to vasculitis were measured using a microarray platform. Disease activity during the past 28 days was classified by physician global assessment (PGA), where remission is indicated by PGA=0 and active disease by PGA 1–10. Spearman's correlation was used to study the association between serum proteins and ESR. To compare marker values between active disease and remission, mixed models were used to account for repeated measures with unequal spacing between visits. Prednisone and immunosuppressive treatments were included as independent variables. Fold-change (FC) in marker values between active and mean remission values was used as the measure of effect.

Results: 479 samples from 174 patients (66 GCA, 35 TAK, 31 PAN, 42 EGPA, with 1 active visit and 1–3 remission visit samples per patient) were tested. 440 samples (92%) were obtained while the patient was on treatment. Disease activity ranged from PGA 1 to 9. In GCA, sIL-6R (FC 1.1, p=0.024), BCA-1 (FC 2.08, p=0.008), GM-CSF (FC 32.5, p=0.04; 7 patients with FC >2), IL-18BPa (FC 1.16, p=0.026), sIL-2Ra (FC 2.03, p=0.018), IL-6 (FC 2.54, p=0.032), and TIMP-1 (FC 1.18, p=0.034) were significantly higher in active than remission samples; in TAK, only IL-18BPa was higher in active than in remission samples (FC 1.16, p=0.029); and in PAN, only MMP-3 was significantly different, being higher in remission samples (FC 0.71, p=0.045). ESR was significantly elevated in active GCA (FC 1.43, p=0.001) and PAN (FC 1.45, p=0.013), and no differences were observed in TAK or EGPA. The correlation of ESR with the majority of the protein markers was weak; the highest correlation was observed in GCA with IL-6 (r=0.34, p<0.0001). FC and p-values were similar when use of prednisone and other immunesuppressive drugs were included in the models. The majority of the samples were obtained while the patients were on prednisone (81.2% of the active and 79.1% of the remission samples). Trajectories of selected markers are shown in Figure 1.

Conclusion: This study identifies several potential biomarkers of disease activity in GCA, although effect sizes were modest in this partially-treated cohort. Promising markers included several cytokines (IL-6, GM-CSF, BCA-1), soluble cytokine receptors (sIL-6R, IL-18BPa), and the metalloproteinase inhibitor TIMP-1. Larger studies are needed to test the utility of these biomarkers for disease monitoring.

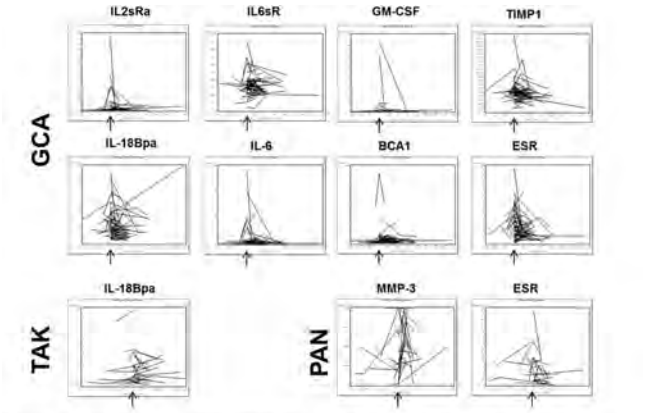

Figure 1. Trajectories of blood protein biomarkers in individual patients. ↑Indicates active visit.

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Risk Factors for Severe Ischemic Complications in Takayasu Arteritis: A French Multicenter Retrospective Cohort of 182 Patients. Cloé Comarmond[1], Tristan Mirault[2], Jean-Emmanuel Kahn[3], Philippe Cluzel[4], Fabien Koskas[5], Laurent Chiche[6], Julien Gaudric[7], Emmanuel Messas[8], Patrice Cacoub[9] and David Saadoun[10]. [1]Internal Medicine and Clinical Imunology, Hôpital Pitié Salpétrière, Paris, France, [2]HEGP vascular department, paris, France, [3]Internal Medicine, Foch Hospital, Suresnes, France, [4]Vascular and Interventional Imaging Department, Paris, France, [5]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [6]Vascular Surgery, Paris, France, [7]Department of Vascular surgery GHPS, Paris, France, [8]Vascular Department, Paris, France, [9]Groupe Hospitalier Pitié Salpétrière, Service de Médecine Interne, DHU i2B, Paris, France, [10]DHU 2iB Internal Medicine Referal Center for Autoimmune diseases Pitie Hospital, Paris, France.

Background/Purpose: Takayasu arteritis (TA) is a chronic inflammatory disease that primarily affects large vessels, such as the aorta and its main branches. To report clinical features, morphologic findings, treatment and long-term outcome of a large cohort of patients with TA, and to determine risk factors for the occurrence of severe ischemic complications (SIC) during follow-up.

Methods: We performed a retrospective multicenter study of characteristics and outcomes of 182 patients with TA fulfilling the American College of Rheumatology criteria. Characteristics at presentation, SIC, relapses and deaths were recorded.

Results: The median age [interquartile range] at onset of symptoms was 31 [24; 45] years and with a predominance of females (85%). The median delay of diagnosis was 10 [0; 47] months. The most common clinical findings were vascular bruits (52%), unequal or absent pulses (47%), and upper extremity blood pressure discrepancy >10 mm Hg (44%). Major complications at diagnosis were hypertension (36%), aneuvrysm (24%), and aortic regurgitation (18%). Forty six percent of patients had extensive disease at diagnosis according to Numano type V. Twenty percent of patients had another inflammatory or auto-immune disease associated to TA, mostly ankylosing spondylitis, crohn disease and sarcoidosis. Stenotic lesions were 3.1-fold more common than were aneuvrysms (78% versus 25%, respectively). Revascularization procedure was required for 49% of patients. The median delay between diagnosis and first surgery or endovascular intervention was 5 [0; 17.5] months. Glucocorticoids were prescribed in 151 (83%) patients. The median delay in initiation of corticosteroids was 1 [0; 5] months. Fifty eight percent of patients required additional immunosuppressive agent. The median delay in initiation of the first immunosuppressor was 11 [2; 29.5] months. Twenty six percent of patients required three or more antihypertensive drugs. SIC occurred in 38 (21%) patients after TA diagnosis. SIC-free

survival at 10 years was 82% in patients without refractory hypertension versus 34% in patients with refractory hypertension (i.e. requiring ≥ 3 antihypertensive drugs) (P = 0.003). SIC-free survival at 5 years was 89% in patients with immunosuppressive agent versus 78% without immunosuppressive agent (P = 0.175). In multivariable analysis, predictive variables for the occurrence of SIC after TA diagnosis were refractory hypertension (OR 12.03 [95%CI 2.78–52.07], P = 0.001), relapse (OR 7.11 [95%CI 1.82–27.78], P = 0.005) and SIC at time of TA diagnosis (OR 4.65 [95%CI 1.10–19.67], P = 0.036). Forty four percent relapsed after a median follow-up of 69 [31; 145] months. The median relapse-free survival was 16 [7; 62] months. The mortality rate was 12%. Five of 7 (71%) deaths were related to cardiovascular complication.

Conclusion: In this cohort of TA patients, risk factors for late-developing SIC were refractory hypertension, relapse and SIC at time of TA diagnosis. Immunosuppressive agents may reduce late-developing SIC. Despite prolonged and intensive therapy, TA remains a major cause of cardiovascular morbi-mortality.

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Damage Assessment in Takyasu Arteritis Using Takayasu Arteritis Damage Score (TADS). Debashish Danda[1], Ruchika Goel[2], Raheesh Ravindran[2] and George Joseph[2]. [1]Christian Medical College, Vellore Tamilnadu, India, [2]Christian Medical College & Hospital, Vellore, India, Vellore, India.

Background/Purpose: Takayasu arteritis (TA) is a prototype large vessel vasculitis. Assessment of disease activity and damage has been challenging in TA due to lack of composite indices and biomarkers. TADS is damage index devised by the Indian Rheumatology Association Vasculitis Group. It consists of 42 items with 8 from cardiovascular system, classified under 7 headings. Only features persistently present for at least the preceding 6 months are scored. Both TADS[1] and DEI.TAK[2] (Disease Extent Index.TA) are derived from Birmingham vasculitis activity score (BVAS). We aimed to assess damage in TA using TADS, a novel composite clinical index.

Methods: TADS and DEI.TAK were calculated prospectively at baseline visit for incident patients with TA (ACR 1990 classification criteria) from our rheumatology and cardiology clinics between May 2012 and May 2014. TADS of this prospective cohort was compared with that calculated retrospectively for TA patients presenting to us prior to May 2012. SPSS version 16 was used; data was depicted as median (Inter Quartile Range) and Pearson's correlation coefficient between TADS and selected parameters were done.

Results: A total of 102 consecutive TA patients (80 females, 22 males) with age of 27.5 (20.7– 36) years, disease duration of 27 (9.8– 65.8) months and diagnostic delay of 12 (6–36) months were recruited. Type 5 was the commonest angiographic type (n=60) with DEI.TAK of 9 (7–13) at presentation. Coronaries and pulmonary artery were involved in 18 and 9 patients respectively. Median TADS score at presentation was 6.0 (4–10) with a third of our patients (n=34) having very high damage score (TADS >8). Absent arterial pulse (59%), persistent claudication (59%), hypertension (56%), persistent dyspnea (41%) and cardiac damage (23.5%) contributed to most of the damage as reflected in TADS. Period of delay in diagnosis and age at presentation did not correlate with the damage score (r= - 0.073 and −0.87 respectively).

A marginally lower TADS [6.0 (4–10)] at presentation in the prospective cohort of 102 patients was noted as compared to that [8(4–11)] of the earlier retrospective cohort of 48 patients whose TADS was calculated from hospital records. No other parameter was different between these two cohorts. A follow up of these 48 patients for 36 (24–57) months showed an insignificant rise in TADS to 9(6–12) at the last recorded visit from 8(4–11) at baseline, in spite of treatment with steroids and 2nd line cytotoxic agents in all.

Conclusion: This is the first study using TADS for damage assessment in a large cohort of TA. Over these years, TA continues to be associated with high damage score right from its initial presentation. Ongoing damage can probably be prevented by aggressive immunosuppression from early disease.

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Biologics in Takayasu Arteritis: Preliminary Data from the French Registry. Arsene Mekinian[1], Chloe Comarmond[2], Mathieu Resche Regon[3], Tristan Mirault[4], Jean-Emmanuel Kahn[5], Marc Lambert[6], Jean Sibilia[7], Antoine Neel[8], Miguel Hié[9], Emmanuel Messas[10], Pascal Cohen[11], Geraldine Muller[12], Sabine Berthier[13], Zahir Amoura[14], Isabelle Marie[15], Christian Lavigne[16], Marie Anne Vandenhende[17], Hervé Devilliers[18], Sébastien Abad[19], Loic Guillevin[20], Mohamed Hamidou[21], Bertrand Godeau[22], Patrice Cacoub[23], Olivier Fain[24] and David Saadoun[2]. [1]DHU2iB, Internal Medicine Saint Antoine Hospital, PARIS, France, [2]DHU 2iB Internal Medicine Referal Center for Autoimmune diseases Pitie Hospital, Paris, France, [3]biostatistics Saint Louis Hospital, paris, France, [4]HEGP vascular department, paris, France, [5]Internal Medicine, Foch Hospital, Suresnes, France, [6]Internal Medicine University Lille Hospital, Lille, Lille, France, [7]University Hospital of Strasbourg, Strasbourg, France, [8]Internal Medicine, Nantes, France, [9]Hôpital Pitié-Salpêtrière, AP-HP, UPMC Univ Paris 06 & French National Reference Center For Systemic Lupus and Antiphospholipid Syndrome, Paris, France, [10]HEGP hospital Vascular and cardiology Department, paris, France, [11]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [12]Internal Medicine, Dijon, France, [13]Dijon Hospital, Dijon, France, [14]Pitié-Salpêtrière Hospital (AP-HP), Paris, France, [15]CHU de Rouen, Rouen, France, [16]CHU d'Angers, Angers, France, [17]Internal Medicine, Bordeaux, France, [18]Department of internal medicine and systemic diseases, Dijon, France, [19]Hôpital Avicenne, Bobigny, France, [20]Service de médecine interne, Centre de Références des Vascularites, Université Paris Descartes, APHP, Hôpital Cochin, 75005 Paris, France., Paris, France, [21]CHU Hôtel Dieu, Nantes, Nantes, France, [22]Service de médecine interne, Université Paris Est Créteil, AP-HP, Hôpital Mondor Créteil, France, Creteil, France, [23]Groupe Hospitalier Pitié Salpétrière, Service de Médecine Interne, DHU i2B, Paris, France, [24]Hôpital Saint Antoine, DHU i2B, Service de Médecine Interne, paris, France.

Background/Purpose: The aim of this registry is to determine: (1) the real-life use of various biological targeted treatments in Takayasu arteritis (TA) in France; (2) to compare the efficacy of different biologics among them; (3) to evaluate the tolerance.

Methods: French practionners from the departments of internal medicine, of vascular medicine and rheumatology were contacted to declare the patients with TA under biologics. Complete response was defined as the NIH<2 with prednisone<10 mg/day, the partial response as NIH and prednisone decrease at least at 50%.

Results: Forty eight patients with TA (age 42 years [20–55], 38 women) were included with 74 treatment lines including various biologics. The biologics were mostly used in second-line (n=21; 29%) and third-line regimen (n=27; 37%) for steroid dependence, non-response or relapses. At the initiation of the biologics, the vascular symptoms were present in 39 (67%) cases, constitutional signs in 25 (46%), with radiological activity in 37 (64%) of cases. NIH was ≥2 in 62 (93%) cases.

Among the biologics, most of the patients were treated by infliximab (59%), and etanercept (8%), adalimumab (8%), tocilizumab (19%), anakinra (3%) and rituximab (3%). The biologics duration was 1.8±1.1 year, with the mean follow-up of 3±1.5 years. A complete/partial response to biologics was shown in 15 (39%) and 17 (44%) of patients at 3 months, and 23 (62%) and 4 (11%) at 6 months, whereas a non-response was noted in 7 (18%) and 10 (27%), respectively. During the follow-up, NIH, C-reactive protein levels and prednisone amount significantly decreased (p<0.001). Only 58% of patients were still under steroids at 3 years versus 82% before biologics.

The comparison of patients treated with TNFa antagonists (n=55) to patients with tocilizumab (n=14) showed that the number of partial/complete responses was similar at 3 and 6 months, as were the NIH scale and the associated immunosuppressive agents.

Six infusion related reactions were noted (infliximab in 5 cases and tocilizumab in one), one EBV reactivation (infliximab) and 5 severe infections (3 with infliximab, one with etanercept and tocilizumab, respectively). One patient under tocilizumab experienced severe neutropenia (<500/mm3), but without any infection or antibiotics needs in relation with tocilizumab.

Two neoplasms occurred during the biologics treatment, one lung cancer (infliximab) and one breast cancer (tocilizumab).

Conclusion: This is the first nationwide registry of TA treated by biologics which show an overall response rate to biologics, with similar response rates between TNFa antagonists and tocilizumab.

	Before Biologics N=74	At 3 months N=42	At 6 months N=32	At 12 months N=39	At 18 months N=31	At 3 years N=19
NIH	2.5 [2–3]	0 [0–1]	0.5 [0–2]	0 [0–1]	0 [0–2]	1 [1–3]
C reactive protein (mg/l)	30 [15–63]	6.5 [2–17]	5 [2–18]	6 [15–21]	5 [1–22]	18 [11–25]
Prednisone (n;%)	61 (82%)	37 (88%)	28 (88%)	35 (89%)	26 (84%)	11 (58%)
Prednisone amount (mg/day)	15 [10–24]	12.5 [7–16]	10 [7–14]	7.7 [5–10]	5 [5–10]	5 [1–6]
Other immunosupressive agent (n;%)	55 (65%)	35 (83%)	23 (72%)	33 (85%)	10 (32%)	16 (84%)
Biologics (n;%)	74	42 (97%)	31 (97%)	33 (85%)	24 (77%)	13 (68%)

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Prognosis of Clinically Inactive Takayasu's Arteritis. Seung-Hyeon Bae, Seokchan Hong, Soo Min Ahn, Doo-Ho Lim, Yong-Gil Kim, Chang-Keun Lee and Bin Yoo. University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea.

Background/Purpose: Takayasu's arteritis (TA) is a chronic inflammatory vasculitis, and immunosuppressants including glucocorticoids are generally required for treatment. Although, some portions of patients with TA have no evidence of active disease at the time of diagnosis, but the prognosis has not been reported. Therefore, aim of our study is to investigate the outcome and to identify the predictors of activation of clinically inactive TA.

Methods: We reviewed data of patients who was diagnosed with TA according to the 1990 ACR classification criteria between January 1990 and December 2012 at the Asan Medical Center. Patients were classified as an inactive disease at the time of diagnosis, based on the NIH definition of active disease in TA. During follow-up, activation of TA was defined based on acquisition of criteria for active disease. The pattern of vascular involvement was classified according to the International Conference on TA in Tokyo, 1994.

Results: Total 199 TA patients were identified, and 59 (29.6%) patients were classified as inactive disease at the time of diagnosis. The mean age of 59 patients was 42.9 ± 12.9 years and 50 (84.7%) patients were female. The median follow-up duration was 58 months (IQR, 37.0–107.0). During follow-up, 13 (22.0%) patients experienced disease activation of TA with median 37.0 months (IQR, 23.5–46.5) after the diagnosis of TA (***activation group***). On the other hand, remaining 46 (78.0%) patients did not experience the activation (***stable group***). There were no significant differences in baseline clinical characteristics and laboratory findings between activation group and stable group. The presence of renovascular hypertension, however, was more commonly observed in activation group than in stable group (4/13, 38.5% vs. 4/46, 8.7%, p=0.019). Further, type V, which is the most extensive type in involved pattern, was found more frequently in activation group (12/13, 92.3%) than in stable group (18/46, 39.1%. p=0.008). In a multivariate analysis, involvement of type V (OR=10.969, 1.144–105.182, p=0.038) was significantly associated with increased risk for disease activation in clinically inactive TA. In addition, the cumulative probability of activation was significantly higher in TA patients with type V than those without type V by Kaplan–Meier analysis (p=0.002) (**Figure 1**).

Conclusion: In the present study, substantial portions of patients with clinically inactive TA at diagnosis experienced an activation of disease during long-term follow-up. We suggested that the type V angiographic pattern can be used as an important predictor for disease activation.

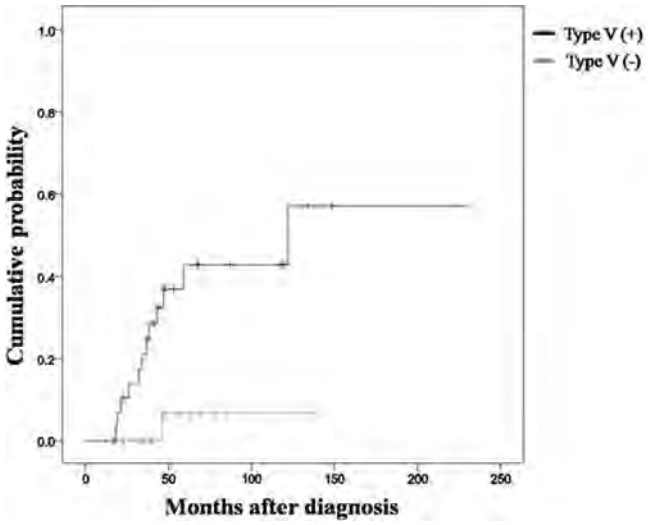

Figure 1. Cumulative probability of activation in patients with clinically inactiva TA

Disclosure: S. H. Bae, None; **S. Hong**, None; **S. M. Ahn**, None; **D. H. Lim**, None; **Y. G. Kim**, None; **C. K. Lee**, None; **B. Yoo**, None.

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Long-Term Outcomes of Takayasu's Arteritis Patients with Renal Artery Involvement. Corisande Baldwin[1], Aladdin Mohammad[2] and David Jayne[3]. [1]University of British Columbia, Vancouver, BC, [2]Lund University, Lund, Lund, Sweden, [3]Addenbrookes Hospital University of Cambridge, Cambridge, United Kingdom.

Background/Purpose: Takayasu's Arteritis (TAK) is a chronic inflammatory large vessel vasculitis characterized by granulomatous inflammation of the aorta and its branches. TAK incidence is 2.6/million annually in Minnesota. Prevalence is higher in Asian and Indian populations. TAK predominantly affects younger woman under 40 years of age. Renal artery involvement (RAI) in TAK is a poor prognostic factor. However, long-term outcomes of TAK patients with RAI have not been reported.

Methods: We performed a retrospective chart review of 37 patients from Addenbrooke's Hospital, UK, and 13 patients from Skane University Hospital, Sweden. Diagnosis of TAK was based on the presence of constitutional symptoms, elevated inflammatory markers, and vascular abnormalities on angiography. RAI was identified based on conventional, CT or MR angiography. Data was collected on patient demographics and presenting symptoms, signs, co-morbidities, blood pressure and medications. Laboratory values including creatinine, erythrocyte sedimentation rate, and c-reactive protein were collected. Disease activity was assessed using the Indian Takayasu Activity Index 2010 (ITAS2010). Irreversible organ damage was assessed using the vasculitis damage index (VDI). Worsening or improved renal function was defined as a drop or increase in eGFR > 20%.

Results: Sixteen of 50 (32%) TAK patients were identified to have RAI. Presenting demographics and disease parameters are summarized in Table 1. Two patients had structural renal disease (PUJ obstruction and prior renal surgery undefined) and are among the 7 patients with renal asymmetry; one was among the nine patients with pre-existing hypertension. The three with eGFR <60 ml/min had moderate renal dysfunction (eGFRs of 45, 57, and 59 ml/min).

Table 1 Presenting Demographics & Disease Parameters

Demographic/Disease Parameter	
Mean Age	32 years (9–68)
Female (%)	15 (94)
White (%)	13 (81)
Comorbidities	
Structural Renal Disease (%)	2 (13)
Inflammatory Bowel Disease (%)	2 (13)
Hypertension (%)	8 (50)
Other (%)	5 (31)
Nil (%)	3 (19)
≥ 3 ACR Criteria Met (%)	14 (88)
Age < 40 (%)	12 (75)
Limb Claudication (%)	7 (44)
Reduced pulses (%)	9 (56)

Assymmetrical blood pressure (%)	10 (63)
Vascular Bruit, (%)	5 (31)
Abnormal Angiography (%)	16 (100)
Unilateral (%)/Bilateral (%) RAI	7 (44)/9 (56)
Median ITAS2010 (range)	13 (5–18)
Prior Therapy	
Systemic (%)	11 (69)
Vascular (%)	2 (13)

Follow-up data is presented in Table 2. Median follow-up duration was 8.8 years (10 months - 30 years). Among the 13 with hypertension including two who developed hypertension over the follow-up period; 11 were on anti-hypertensive drugs. Among the six patients with renal asymmetry; five were known and one developed this over the follow-up period. Among those with eGFR $<$ 60 ml/min at presentation, one improved, one declined (patient with PUJ obstruction), and one remained stable.

Table 2 Follow-up Disease Parameters

Pre and Post Demographics	Presentation	Follow-up
Median ITAS2010 (range)*	13 (9–18)	7 (1–13)
Therapy		
Systemic Therapy (%)	–	15 (94)
Vascular Therapy (%)	–	4 (25)
Angiography**		
Unchanged (%)	–	12 (86)
Improved (%)	–	1 (7)
Complete Resolution (%)	–	1 (7)
Median VDI (range)***	–	5 (0–9)
Renal Parameters		
Renal Assymmetry (%)	6 (38)	6 (38)
Hypertension (%)	11 (69)	13 (81)
eGFR $\geq$ 60 ml/min (%)	13 (81)	14 (88)
eGFR $<$ 60 ml/min (%)	3 (19)	2 (12)
Change in eGFR		
Stable (%)	–	7 (44)
Improved (%)	–	4 (25)
Reduced (%)	–	3 (19)

* Follow-up ITAS2010 score only available for 10 patients
** Follow-up renal angiography available for 14 patients
*** Not calculated at presentation

Conclusion: The prevalence of RAI in this population (32%) is comparable to that in the literature. Hypertension was common. Most patients had normal eGFRs, despite severe disease. Disease progression was minimal. Our results suggest renal prognosis is better than previously thought.

Disclosure: C. Baldwin, None; **A. Mohammad**, None; **D. Jayne**, None.

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Tocilizumab in Giant Cell Arteritis: Multicenter Open-Label Study of 22 Patients. Montserrat Santos-Gómez[1], Javier Loricera[1], Ricardo Blanco[1], Jose L. Hernández[1], Antonio Mera[2], Eva Pérez-Pampin[2], M. Enriqueta Peiró[1], Santos Castañeda-Sanz[3], Alicia Humbría[4], Jaime Calvo-Alen[5], Elena Aurrecoechea[5], Javier Narváez[6], Amalia Sánchez-Andrade[7], Paloma Vela[8], Elvira Díez Álvarez[9], Cristina Mata[10], Pablo Lluch Mesquida[11], Concepcion Moll Tuduri[11], Vanesa Calvo-Río[1], Francisco Ortiz-Sanjuán[1], Trinitario Pina Murcia[12], Carmen Gonzalez-Vela[1], Leyre Riancho-Zarrabeitia[1] and Miguel A. González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [2]Hospital Clínico Universitario de Santiago de Compostela. Spain, Santiago de Compostela, Spain, [3]Hospital Universitario de La Princesa. Madrid. Spain, Madrid, Spain, [4]Hospital Universitario de La Princesa. IIS-Princesa, Madrid, Madrid, Spain, [5]Hospital de Sierrallana. Torrelavega. Spain, Torrelavega, Spain, [6]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, [7]Hospital Universitario Lucus Augusti. Lugo. Spain, Lugo, Spain, [8]Hospital General de Alicante. Spain, Alicante, Spain, [9]Hospital de León. Spain, León, Spain, [10]Hospital Comarcal de Laredo. Spain, Laredo, Spain, [11]Hospital Mateu Orfila. Menorca. Spain, Mahón (Menorca), Spain, [12]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain.

Background/Purpose: Giant cell arteritis (GCA) is a primary vasculitis that involves the aorta and its major branches. It usually affects people aged more than 50 years. GCA may be refractory to standard therapy with corticosteroids that, in turn, may be associated with substantial adverse events. Tocilizumab (TCZ) has demonstrated efficacy in single cases or in small series of patients with GCA. Our aim was to assess the efficacy and side-effects of TCZ in a multicenter study of patients with refractory GCA.

Methods: Multicenter open-label study of patients with refractory GCA. TCZ was used because of inadequate response to corticosteroids and in most cases to other therapies. All the patients meet the 1990 ACR criteria for GCA. TCZ therapy was used at standard dose of 8 mg/kg/monthly.

Results: 22 patients (17 women/ 5 men; mean age$\pm$SD was 69$\pm$8 years) were assessed. Sixteen (73%) of them had a positive temporal artery biopsy. The main clinical features at the time of TCZ onset were: polymyalgia rheumatica (n=15), asthenia (n=7), headache (n=5), constitutional syndrome (n=4), jaw claudication (n=2), visual manifestations (n=2), claudication of the lower limbs (n=1), chest pain (n=1), arthritis (n=1), dyspnea (n=1) and scapular pain (n=1). Fifteen patients also had aortitis. Besides corticosteroids and before TCZ therapy, 19 patients had received several traditional immunosuppressive agents: methotrexate (n=19), azathioprine (n=1) and leflunomide (n=1). In addition, 2 patients had also been treated with other biologic agents before starting on TCZ. One patient received etanercept that was switched to TCZ due to inefficacy. Another patient received infliximab that was switched to rituximab, then to abatacept and finally to TCZ because of inefficacy. Most patients experienced clinical and laboratory improvement within the first 3 months after the onset of TCZ **(TABLE).** After a median [IQR $25^{th}-75^{th}$] follow-up of 6 [3–16] months, the erythrocyte sedimentation rate decreased from a median value of 44 [20–81] to 12 [3–20] mm/1^{st} hour. Similarly, C-reactive protein levels also decreased from a median initial value of 1.9 [1.2–5.4] to 0.2 [0.1–0.9] mg/dL. A corticosteroid sparing effect was also achieved (from a median [IQR] prednisone dose of 18.75 [10–45] mg/day at TCZ onset to 5 [0–7.5] mg/day at last visit). In 3 patients TCZ was discontinued due to severe neutropenia (351 neutrophils/mm^3); recurrent pneumonia; and cytomegalovirus infection, respectively. Also, one patient died after the second infusion of TCZ as the result of a stroke in the setting of an infectious endocarditis.

Conclusion: In our series, TCZ seems to be effective in the treatment of GCA refractory to corticosteroids and other immunosuppressive agents.

Table

Clinical Manifestations	Basal*	Month 3*	Month 6*	Month 12*
Polymyalgia rheumatica, %	68	0*	0*	0*
Constitutional syndrome, %	18	0*	0*	0*
Headache, %	23	10*	0*	0*
Laboratory parameters, median [IQR]				
ESR	44 [20–81]	4 [2–17]*	4 [3–9]*	14.5 [8–30]*
CRP	1.9 [1.2–5.4]	0.1 [0.1–0.3]*	0.1 [0.1–0.2]*	0.3 [0.1–1.8]*
Prednisone dose (mg/day), median [IQR]	18.75 [10–45]	9.37 [5–10]*	5 [5–6.25]*	2.5 [0–5]*

*$p<0.05$ compare to baseline

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ACR Plenary Session I: Discovery 2014

Sunday, November 16, 2014, 11:00 AM–12:30 PM

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Netosis Induced Histone Citrullination Facilitates Onset and Propagation of Rheumatoid Arthritis. Dong Hyun Sohn[1], Kazuhiro Onuma[1], Chris Rhodes[1], Xioayan Zhao[1], Tal Gazitt[2], Rani Shiao[1], Justyna Fert Bober[3], Danye Cheng[1], Lauren J. Lahey[1], Heidi Wong[4], Jennifer van Eyk[3], William H. Robinson[1] and Jeremy Sokolove[1]. [1]VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA, [2]University of Washington, Seattle, WA, [3]Johns Hopkins University and Cedars Sinai Medical Center, Los Angeles, CA, [4]Stanford University School of Medicine, Stanford, CA.

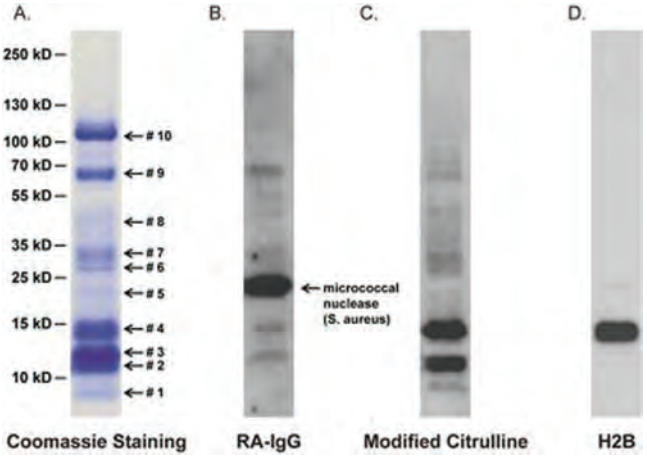
Background/Purpose: Anti-citrullinated protein antibodies (ACPAs) are characteristic of rheumatoid arthritis however, their presence years before onset of clinical RA is perplexing. Although multiple putative citrullinated

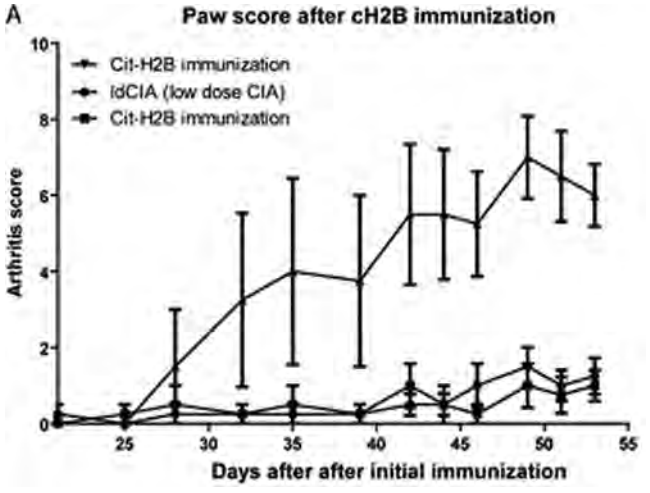
antigens have been identified, including citrullinated products of NETosis, no studies have demonstrated the capacity of these antigens to initiate inflammatory arthritis. We sought to identify citrullinated products of NETosis targeted by the RA immune response and with the capacity to drive inflammatory arthritis.

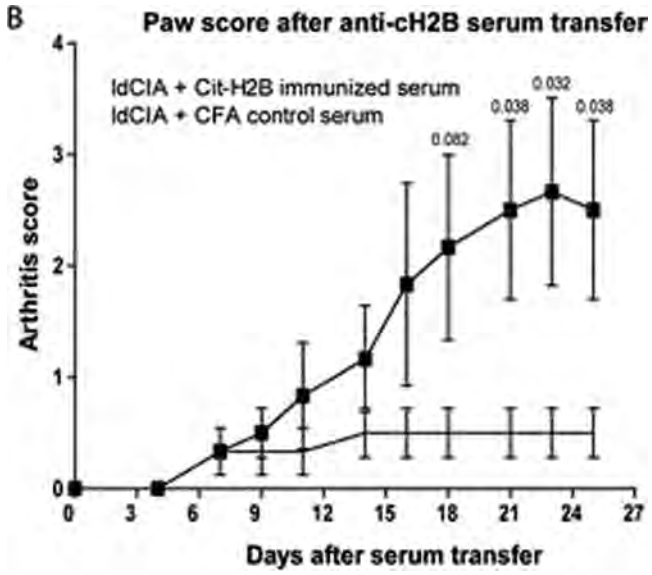
Methods: We performed proteomic analysis of human NETs to identify all citrullinated proteins including those targeted as part of the RA immune response. Using a combination of ELISA and IHC we compared RA and OA serum, synovial fluid and synovial tissue for levels of histone 2B (H2B), anti-H2B antibodies, as well as H2B-containing immune complexes. Using macrophage activation assays we assessed the effect of histone citrullination on immunostimulatory capacity and evaluated the stimulatory capacity of native and citrullinated H2B-containing immune complexes. Finally, we immunized mice with citrullinated H2B (cH2B) with and without the induction of low grade collagen induced arthritis to assess the potential for anti-cH2B antibodies to mediate arthritis *in vivo*.

Results: Proteomic interrogation of NET-derived proteins, RA serum, synovium, and synovial fluid identified robust targeting of NET-derived citrullinated histones by the ACPA immune response. Over 90% of RA patients have anti-cH2B antibodies and over half have measurable levels of synovial fluid H2B immune complexes. We observe that histone citrullination increases innate immunostimulatory capacity and that immune complexes containing citrullinated histones both activate macrophage cytokine production and propagate NETosis. Finally, we demonstrate that autoimmunity to cH2B is arthritogenic, both by primary immunization as well as immune serum transfer, but only in the setting of underlying low grade articular inflammation.

Conclusion: We identify cH2B as an antigenic target of the ACPA immune response and our findings suggest that intra-articular histone citrullination can link innate immunity via NETosis and adaptive immunity via generation of citrullinated histone immune complexes. The generation of citrullinated histone antigens during low grade articular inflammation provides a potential mechanism for the conversion from asymptomatic ACPA seropositivity to clinical RA.







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***TRNT1* Missense Mutations Define a New Periodic Fever Syndrome.** Angeliki Giannelou[1], Qing Zhou[2], Monique Stoffels[3], Amanda Ombrello[4], Deborah Stone[2], Jehad H. Edwan[5], Martin Pelletier[6], Wanxia Tsai[7], Katherine Calvo[8], Sergio Rosenzweig[9], Karyl Barron[10], Massimo Gadina[11], Ivona Aksentijevich[2] and Daniel L. Kastner[2]. [1]National Institute for Arthritis and Musculoskeletal and Skin Diseases, bethesda, MD, [2]National Human Genome Research Institute, Bethesda, MD, [3]National Human Genome Research Institute, bethesda, MD, [4]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [5]NIAMS NIH, Bethesda, MD, [6]Immunoregulation Section, Autoimmunity Branch, Bethesda, MD, [7]NIAMS/NIH, Bethesda, MD, [8]National Institutes of Health Clinical Center, Bethesda, MD, [9]National Institute of Allergy and Infectious Diseases, Bethesda, MD, [10]NIH, Bethesda, MD, [11]NIAMS/NIH, Bethesda, MD.

Background/Purpose: Two thirds of the 1700 patients seen at our NIH clinic for autoinflammatory diseases do not have a genetic diagnosis. Whole exome sequencing permits analysis of most of the protein coding regions of the human genome.

Methods: With the use of whole exome sequencing and candidate gene screening, we identified five children from four unrelated families, who had unexplained autoinflammatory disease and shared mutations in one common gene. One family from Saudi Arabia was consanguineous with two affected daughters. The second family of mixed Czech and British background had one affected boy. The third and fourth families were of mixed European ancestry from the United States and each family had one affected daughter. We performed additional experiments in patients samples including flow cytometry, immunophenotyping, cytokine profiling, mitochondria related function and ribosomal assembly assays. Protein function was studied with morpholino knockdowns in zebrafish embryos.

Results: All patients carried missense recessive mutations in one common gene, the *TRNT1* (tRNA Nucleotidyl Transferase, CCA-Adding, 1), on chromosome 3. The two affected Saudi Arabian sisters were homozygous for a p.H215R missense mutation, while the other three children were compound heterozygous for a missense mutation, p. I223T or p. R99W, and one shared mutation p.D163V. The p.H215R mutation was not found in any public database neither in 1061 Arab control DNA samples. From the three Caucasian mutations, the p.R99W was novel whereas the p. I223T and p.D163V were found at a very low allele frequency (<0.001) at the NHLBI exomedatabase. All mutations affect highly conserved amino acid residues and are predicted to be damaging to the protein function. All children had recurrent episodes of high fevers with negative sepsis work up that occurred in association with microcytic anemia, and a spectrum of multisystem features. Neurologic involvement ranged from mild developmental delay to nystagmus, hypotonia, optic nerve atrophy, and sensorineural hearing loss. Other variables manifestations include dysmorphic fea-

tures, musculoskeletal and gastrointestinal symptoms, B cell immunodeficiency and hypogammaglobulinemia. Studies performed so far, point towards a maturation defect of the B cell lineage in the bone marrow, as a possible cause of the observed immunodeficiency. Preliminary data from cytokine analysis in two patients have shown elevated levels of the proinflammatory cytokines interleukin 6 and type 1interferon, suggesting possible therapeutic targets. Knockdown of the zebrafish *TRNT1* homologue caused hydrocephaly, defects in tail development, anemia and a reduction in the number of hair cells present in the lateral line, that has function resembling human inner ear.

Conclusion: The CCA-adding TRNT1 enzyme catalyzes the addition of the CCA terminus to the 3 prime end of all tRNAs precursors, a step that is essential for tRNA aminoacylation and protein synthesis. The discovery that missense mutations in this essential and ubiquitiously expressed gene cause a newly defined periodic fever syndrome, will allow further understanding of mechanisms underlying inflammation.

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Mortality in a Large Cohort of Patients with Early Rheumatoid Arthritis That Were Treated-to-Target for 10 Years. I.M. Markusse[1], L. Dirven[1], J.H. van Groenendael[2], K.H. Han[3], H.K Ronday[4], P.J.S.M. Kerstens[5], W.F. Lems[6], T.W.J. Huizinga[1] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Fransiscus Hospital, Roosendaal, Netherlands, [3]MCRZ hospital, Rotterdam, Netherlands, [4]Haga Hospital, The Hague, Netherlands, [5]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [6]VU Medical Center, Amsterdam, Netherlands.

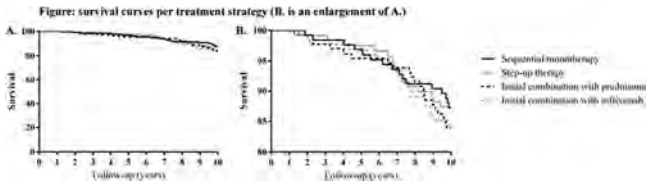
Background/Purpose: Recent studies showed diverging results about mortality trends in patients with rheumatoid arthritis (RA). Our aim was to determine survival after 10 years of treat-to-target therapy in patients with early RA, to compare these survival rates with the general population and to define risk factors for mortality during the 10 years duration of the BeSt study.

Methods: The BeSt study enrolled 508 Dutch patients with recent-onset active RA (1987 criteria) who were randomized to: sequential monotherapy, step-up therapy, initial combination including either prednisone or infliximab. During 10 years, all patients were treated-to-target, aiming at a disease activity score (DAS) ≤2.4. Kaplan-Meier curves and the log-rank test were used to compare survival rates in the four treatment strategies. Standardized mortality ratios (SMR) were calculated to compare the BeSt population to the general Dutch population, matched by age, gender and calendar year. Cox regression was used to calculate hazard ratios (HR) to determine baseline risk factors for increased mortality in the BeSt population.

Results: During 10 years, 72 of 508 patients died at a mean age of 75 years. No difference in survival was observed between the treatment strategies (p=0.805) (figure), with 16/126, 15/121, 21/133 and 20/128 deaths in arm 1 to 4, respectively. Based on the general Dutch population, 62 deaths were expected and 72 deaths occurred, resulting in an overall SMR of 1.16 (95% confidence interval, CI 0.92 – 1.46). Comparing the general population to each of the treatment strategies resulted in a SMR (95% CI) of 1.00 (0.61 – 1.64), 1.02 (0.61 – 1.69), 1.30 (0.85 – 1.99) and 1.32 (0.85 – 2.04) in arm 1 to 4, respectively.

In the BeSt population, baseline age (HR 1.13, 95% CI 1.10–1.16), male gender (HR 1.78, 95% CI 1.06–2.99), smoking at baseline (HR 5.19, 95% CI 3.08–8.75) and health assessment questionnaire at baseline (HR 1.89, 95% CI 1.29–2.76) were associated with an increased risk of mortality. Randomization arm was not associated with an increased risk of mortality (arm 1 as reference category; arm 2 HR 0.99, 95% CI 0.49 – 2.00; arm 3 HR 1.27, 95% CI 0.66 – 2.44; arm 4 HR 1.25, 95% CI 0.65 – 2.41).

Conclusion: After 10 years of continued tight controlled treatment in patients with rheumatoid arthritis in the BeSt study, the survival rate was comparable to the general Dutch population, without differences between the treatment strategies. Higher age, male gender, smoking and worse functional ability were associated with an increased risk of mortality within our study population. These results suggest that treatment targeted at DAS ≤2.4 prevents increased mortality previously associated with RA, and that the medication used in these strategies does not increase mortality.



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Incident Rheumatoid Arthritis and Risk of Mortality Among Women Followed Prospectively from 1976 to 2010 in the Nurses' Health Study. Jeffrey A. Sparks, Shun-Chiao Chang, Katherine P. Liao, Bing Lu, Daniel H. Solomon, Karen H. Costenbader and Elizabeth W. Karlson. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: RA has been associated with increased mortality compared to general population estimates. Previous studies were limited due to the inability to directly compare RA patients to controls, short follow-up, and lack of detailed data on clinical, lifestyle, and serologic factors. We evaluated mortality among women followed prospectively prior to RA diagnosis, directly comparing to women without RA.

Methods: We conducted a study of RA and mortality among 121,700 women followed from 1976 to 2010 in the Nurses' Health Study (NHS). Incident RA was validated by medical record review according to the 1987 ACR RA criteria and classified by serostatus. Women who reported RA or other connective tissue diseases before the start of NHS were excluded. Women were followed from cohort entry to death or end of follow-up and were censored for loss to follow-up. Deaths were validated by the National Death Index; death certificate and medical record review determined cause of death. Cox regression models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause, cardiovascular disease (CVD), cancer, and respiratory mortality for women with RA compared to women without RA. We obtained HRs for mortality by RA duration and serologic RA phenotype. Models were adjusted for age, demographics and other mortality factors, including physical activity, smoking, obesity, comorbidities, and family history of cancer, CVD, and diabetes.

Results: We validated 960 incident RA cases and identified 25,699 deaths in 34 years of NHS follow-up. Of the 261 deaths among women with RA, 75 (29%) were from cancer, 58 (22%) were from CVD, and 43 (16%) were from respiratory causes. Compared to women without RA, women with RA had increased all-cause mortality that remained significant after adjusting for age and other mortality factors (HR 2.07, 95% CI 1.83–2.35, **Table**). Mortality was significantly increased for seropositive (HR 2.33, 95% CI 2.00–2.71) and seronegative RA (HR 1.60, 95% CI 1.30–1.98) compared to non-RA women. Each five years of RA duration conferred a 32% (95% CI 27–36%) increased mortality compared to non-RA. Women with RA had significantly increased risk for mortality from CVD (HR 1.87, 95% CI 1.44–2.43), cancer (HR 1.35, 95% CI 1.07–1.69) and respiratory (HR 4.50, 95% CI 3.28–6.17) causes compared to women without RA. Respiratory mortality for women with seropositive RA was six-fold higher than non-RA women (HR 6.23, 95% CI 4.38–8.85).

Conclusion: In 34 years of prospective follow-up, women diagnosed with RA had a two-fold increased risk of death from any cause compared to women without RA. Respiratory mortality was six-fold higher in seropositive RA and women with RA were significantly more likely to die from CVD and cancer than women without RA. Respiratory mortality appears to be an important but understudied cause of death in RA. These findings provide evidence of high RA mortality burden that is unexplained by traditional mortality predictors.

Table. Hazard ratios for all-cause and cause-specific mortality in RA serologic phenotypes among women in the Nurses' Health Study, 1976–2010 (n = 119,264)

	All-cause mortality		CVD-specific mortality	Cancer-specific mortality	Respiratory-specific mortality†
	Age-adjusted HR (95% CI)	Multivariable HR (95% CI)*	Multivariable HR (95% CI)*	Multivariable HR (95% CI)*	Multivariable HR (95% CI)*
All RA					
No RA	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
RA	**1.42 (1.26–1.61)**	**2.07 (1.83–2.35)**	**1.87 (1.44–2.43)**	**1.35 (1.07–1.69)**	**4.50 (3.28–6.17)**
No RA	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
RA duration (per 5 years)	**1.16 (1.13–1.20)**	**1.32 (1.27–1.36)**	**1.24 (1.15–1.33)**	**1.22 (1.14–1.30)**	**1.55 (1.42–1.69)**

Seropositive RA					
No RA	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
RA	**1.54 (1.33–1.79)**	**2.33 (2.00–2.71)**	**1.80 (1.27–2.55)**	1.25 (0.92–1.70)	**6.23 (4.38–8.85)**
No RA	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
RA duration (per 5 years)	**1.20 (1.15–1.25)**	**1.38 (1.33–1.44)**	**1.26 (1.15–1.39)**	**1.23 (1.13–1.34)**	**1.69 (1.53–1.85)**
Seronegative RA					
No RA	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
RA	1.15 (0.93–1.41)	**1.60 (1.30–1.98)**	**1.84 (1.23–2.73)**	1.40 (0.99–1.98)	1.97 (0.97–3.98)
No RA	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
RA duration (per 5 years)	**1.08 (1.02–1.15)**	**1.20 (1.14–1.28)**	**1.19 (1.06–2.73)**	**1.18 (1.06–1.31)**	**1.23 (1.00–1.51)**

*Adjusted for age, questionnaire period, US region, race/ethnicity, education, husband's education, body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30), cigarette smoking pack-years (never, 0–10, 10.1–20, >20), post-menopausal hormone use, physical activity, healthy eating index, cancer, cardiovascular disease, diabetes mellitus, family history of diabetes, family history of cancer, family history of myocardial infarction <60 years of age, and aspirin use through follow-up. Modifiable factors were adjusted up to RA diagnosis (cigarette smoking pack-years, physical activity, and body mass index).
†Among women with RA, there were a total of 43 respiratory deaths that were due to pneumonia (11), emphysema (8), chronic interstitial lung disease (5), asthma (1), and other respiratory diseases (18).

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Secukinumab, a Monoclonal Antibody to Interleukin-17A, Significantly Improves Signs and Symptoms of Active Ankylosing Spondylitis: Results of a 52-Week Phase 3 Randomized Placebo-Controlled Trial with Intravenous Loading and Subcutaneous Maintenance Dosing. Dominique L. Baeten[1], Juergen Braun[2], Xenofon Baraliakos[2], Joachim Sieper[3], Maxime Dougados[4], Paul Emery[5], Atul A. Deodhar[6], Brian Porter[7], Ruvie Martin[7], Shephard Mpofu[8] and Hanno Richards[8]. [1]Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Charité University Medicine Berlin, Berlin, Germany, [4]Université Paris René Descartes and Hôpital Cochin, Paris, France, [5]University of Leeds, Leeds, United Kingdom, [6]Oregon Health and Sciences University, Portland, OR, [7]Novartis Pharma AG, East Hanover, NJ, [8]Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: A phase 2, proof-of-concept study indicated that secukinumab, an anti–IL-17A monoclonal antibody, suppressed signs and symptoms of active ankylosing spondylitis (AS) by Week (Wk) 6. We present Wk 16 and Wk 52 efficacy and safety data from MEASURE 1 (NCT01358175), a phase 3 study assessing secukinumab vs. placebo (PBO) in patients (pts) with AS.

Methods: Pts with active AS fulfilling modified New York Criteria and BASDAI ≥ 4, despite current or previous therapy with NSAIDs, DMARDs and/or anti-TNF agents, were randomized to receive: i.v. secukinumab 10 mg/kg (Wk 0, 2, 4) followed by s.c. secukinumab 75 mg every 4 wks (10 IV → 75 SC), s.c. secukinumab 150 mg every 4 wks (10 IV → 150 SC), or PBO on same i.v. and s.c. schedules. Endpoints included ASAS20 at Wk 16 (primary), ASAS40, hsCRP, ASAS 5/6, BASDAI, SF-36 PCS, ASQoL and ASAS partial remission. Statistical analyses followed a pre-defined hierarchical hypothesis testing strategy to adjust for multiplicity. PBO pts were re-randomized to secukinumab 75 mg or 150 mg s.c. based on ASAS20 response at Wk 16, with non-responders switched at Wk 16 and responders at Wk 24.

Results: Baseline characteristics of the 371 randomized pts were similar between study arms: mean age 40.1–43.1 years, mean disease duration 6.5–8.3 years, mean BASDAI 6.05–6.51, ~27% inadequate response to anti-TNF agents (TNF-IR). The study met its primary efficacy endpoint with a significantly higher ASAS20 response at Wk 16 in the 10 IV → 75 SC (59.7%) and 10 IV → 150 SC (60.8%) groups vs. PBO (28.7%; $P < 0.01$ for each dose); ASAS20 response rates in TNF-naïve pts were 60.0%, 66.3% and 32.6%, and in the TNF-IR pts were 58.8%, 45.5% and 18.2%, in the 10 IV → 75 SC, 10 IV → 150 SC and PBO groups, respectively ($P< 0.01$ vs. PBO). Significant improvements with both doses of secukinumab vs. PBO were observed for all pre-specified secondary endpoints at Wk 16 (Table), with responses sustained through Wk 52. Onset of action of secukinumab was rapid, with significant improvements in ASAS20, ASAS40, hsCRP, ASAS5/6 and BASDAI seen at Wk 1. Through to Wk 16, drug exposure levels were similar in the secukinumab groups due to the i.v. loading doses. Secukinumab was generally well tolerated. At Wk 16, 66.9% of pts in the 10 IV → 75 SC group and 69.6% in the 10 IV → 150 SC group experienced an AE, vs. 55.7% on PBO; SAE rates were 1.6%, 2.4% and 4.1%, respectively. Through Wk 52 visit of the last pt (average exposure [range]: 451.7 [8–757] days), AE/SAE rates were 76.5%/10.1% and 85.1%/9.4% for pts receiving secukinumab 75 or 150 mg s.c., respectively, at any point in the study.

Table. Summary of 16-week efficacy results

Week 16 Data	Secukinumab 10 mg/kg i.v. → 75 mg s.c. (N = 124)	Secukinumab 10 mg/kg i.v. → 150 mg s.c. (N = 125)	Placebo (N = 122)
ASAS20 response	59.7%*	60.8%*	28.7%
ASAS40 response	33.1%*	41.6%*	13.1%
hsCRP, post-baseline to baseline ratio (LSM±SE)	0.45 ± 1.092*	0.40 ± 1.090*	0.97 ± 1.095
ASAS5/6	45.2%*	48.8%*	13.1%
BASDAI, mean change from baseline score (LSM±SE)	−2.34 ± 0.175*	−2.32 ± 0.172*	−0.59 ± 0.180
SF-36 PCS, mean change from baseline score (LSM±SE)	5.64 ± 0.595*	5.57 ± 0.586*	0.96 ± 0.612
ASQoL, mean change from baseline score (LSM±SE)	−3.61 ± 0.424*	−3.58 ± 0.420*	−1.04 ± 0.437
ASAS partial remission	16.1%*	15.2%*	3.3%

*$P<0.01$ vs. placebo

Table. Summary of 16-week efficacy results

Prespecified hierarchical statistical testing strategy used to account for multiplicity. Missing data for categorical variables were imputed as nonresponse

ASAS, Assessment of SpondyloArthritis International Society Criteria; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; hsCRP, high-sensitivity C-reactive protein; LSM, least square mean; SE, standard error; NS, not significant; SF-36 PCS, short form 36 physical component summary

Conclusion: The selective IL-17A inhibitor secukinumab provided rapid and significant improvement of signs and symptoms in pts with active AS, regardless of prior anti-TNF exposure. Improvements were observed from Wk 1 and sustained through 52 wks. Secukinumab was well tolerated through 52 wks with no unexpected safety findings.

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ACR Concurrent Abstract Session
Epidemiology and Public Health I: Drug and Vaccine Safety
Sunday, November 16, 2014, 2:30 PM–4:00 PM

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Herpes Zoster Infection Risk in Auto-Immune and Inflammatory Diseases: Implications for Vaccination. Huifeng Yun[1], Shuo Yang[2], Lang Chen[2], Fenglong Xie[2], K. L. Winthrop[3], John Baddley[2], Kenneth G. Saag[4], Jasvinder Singh[2] and Jeffrey R. Curtis[2]. [1]University of Alabama at Birmingham School of Public Health, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Oregon Health and Science University, Portland, OR, [4]The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Herpes zoster (HZ) vaccine is recommended for healthy people age >= 60 years in US. It is unclear whether the absolute risk for younger patients (pts) with autoimmune or inflammatory (AI) diseases is high enough to warrant vaccination. We evaluated the overall and age-stratified absolute incidence of HZ infection associated with different AI

diseases compared to healthy older adults who are recommended for vaccination by the CDC.

Methods: Using 2007–2010 Multi-Payer Claims Database, we assembled 7 AI disease cohorts, requiring pts to have ≥ 13 months continuous medical and pharmacy coverage. Pts with at least one prescription and two diagnoses of rheumatoid arthritis (RA), psoriasis arthritis (PsA), psoriasis (PsO), ankylosing spondylitis (AS), inflammatory bowel disease (IBD), lupus (SLE), gout were included and compared with diabetic pts and healthy pts without diabetes or any autoimmune disease. We identified HZ using diagnosis codes and antiviral agent +- 30 days. Age-adjusted incidence rates (AAIR) and age-specific rates for HZ per 1,000 person-years were calculated for each disease and compared to healthy older people age 60–69 using Poisson regression. Based upon external data, we used a non-inferiority margin of an HZ IR ratio (IRR) of 0.62 to establish non-inferiority of HZ rates of younger pts with AIs versus healthy older people. Rates were classified as significantly higher (bold) if the lower limit of the IRR 95% CI >1, comparable (i.e. non-inferior, bold, underlined) if the lower limit of the IRR 95% CI > 0.62 but ≤ 1, or inconclusive.

Results: The study population consisted of 50,646 pts with RA, 2629 with PsA, 4299 with PsO, 1,019 with AS, 7,916 with IBD, 8,395 with SLE, 5893 with gout, 214,631 with diabetes and 330,727 in the healthy cohort. The AAIRs among the 7 disease cohorts ranged from a high of 14.6 per 1,000 person years (SLE) to a low of 5.0 (gout). AAIR was 5.9/1000 for diabetes and 3.9/1000 for healthy cohort. The age-specific rate of HZ for RA, IBD and SLE pts in the 20s, 30s, and 40s, was non-inferior or significantly greater than the corresponding rate in healthy people individuals age >=60 (Table, bold). Compared with the healthy cohort, the adjusted HR for RA (1.4, 95% CI: 1.2–1.5), Gout (1.4, 1.2–1.5), IBD (1.8, 1.5–2.1) and SLE (2.1, 1.8–2.4) were increased significantly.

Conclusion: RA, IBD and SLE are associated with an increased risk of HZ infection compared to healthy people. Based on absolute risk compared to healthy people age >= 60, RA, IBD and SLE patients age >30 may benefit from vaccination for HZ.

Table: Incidence rate of herpes zoster per 1000 person years by 10 year age group and auto-immune disease or comparator cohort

		Cohorts							
	Healthy	SLE	IBD	RA	PSA	PSO	AS	Gout	Diabetes
Age group	IR	IR	IR	IR	IR	IR	IR	IR	IR
21–30	2.7	**24.6**	**11.6**	6.6	N/A	5.9	N/A	2.9	7.8
31–40	3.3	**15.2**	5.6	**8.2**	9.8	3.7	8.1	5.2	5.3
41–50	3.9	**17.5**	**10.4**	**10.0**	8.5	6.4	5.1	6.1	**5.3**
51–60	5.8	**20**	**11.7**	**14.6**	**13.2**	**9.7**	8.3	**6.9**	**8.2**
61–70	***8.5*** ***(referent)***	**22.7**	**19.0**	**17.1**	**15.9**	**13.3**	**14.3**	**9.5**	**11.0**
71–85+	10.6	**20.9**	**23.8**	**21.3**	**19.4**	**21.2**	**26.3**	**13.3**	**13.0**

IR: Incidence per 1000 person years
Compared to healthy older people aged 60–69 (referent), rates were classified as significantly higher (bold), comparable (bold, underlined) and other (i.e. inconclusive or lower)

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Pregnancy Outcome in Women Treated with Adalimumab for the Treatment of Rheumatoid Arthritis. Christina D Chambers[1], Diana L Johnson[2], Yunjun Luo[2], Ronghui Xu[1] and Kenneth L Jones[2]. [1]University of California San Diego Department of Family and Preventive Medicine, La Jolla, CA, [2]University of California San Diego Department of Pediatrics, La Jolla, CA.

Background/Purpose: Adalimumab is a fully human monoclonal antibody to tumor necrosis factor alpha and is approved for several indications including rheumatoid arthritis (RA).

Methods: The OTIS Collaborative Research Group conducted a prospective cohort study in the U.S. and Canada between 2004 and 2013 comparing pregnancy outcomes in women with RA treated with adalimumab for some period of the first trimester to women with RA not treated with any adalimumab in pregnancy. No women in either group were also treated with methotrexate, but women may have been treated with another DMARD or steroid. An additional comparison group included women without any autoimmune disease. All three groups were recruited prior to 19 completed weeks' gestation and followed by extensive telephone interviews throughout pregnancy and after birth. Medical records were reviewed, and a subset of live born infants received dysmorphological examination by a study physician (blinded to the mother's status). Outcomes were compared using logistic regression techniques and survival methods as appropriate with adjustment for confounders using propensity scoring if two or more confounders were identified.

Results: Seventy-four women exposed to adalimumab, 80 disease-matched comparison women, and 218 non-diseased women enrolled in the study. All women in the adalimumab-exposed group had at least one dose of the medication in the first trimester; approximately 43% of those women used the medication in all three trimesters. The overall lost-to-follow up rate was 5.9%. Disease severity, as measured by the HAQ at the time of enrollment and at 32 weeks' gestation, was similar between the two disease-matched groups. The rate of major defects in the exposed, disease-matched, and non-diseased comparison groups was 5.6%, 7.8% and 5.5% respectively. In adjusted analysis, there was no significant difference in the overall rate of major malformations among live births in the adalimumab exposed vs. disease-matched group (adjusted Relative Risk (RR) 1.14, 95% Confidence Interval (CI) 0.26, 4.93). A total of 234 infants (70% of live born infants) received the study-related physical examination. The proportion of children with 3 or more minor malformations in the three groups did not differ, and there was no specific pattern of minor malformations identified. Using Cox Proportional Hazards modeling, the adjusted hazard ratio (HR) for spontaneous abortion was 1.96 (95% CI 0.47, 8.26) comparing the adalimumab vs. disease-matched groups; the rate was elevated in comparison to the non-diseased group (adjusted HR 3.79, 95% CI 1.01, 14.23), although the number of events was small. The rate of preterm delivery did not differ significantly among groups, nor did the proportion of infants who were small for gestational age.

Conclusion: Pregnant women with RA who are treated with adalimumab during the first trimester compared to women with the same underlying condition do not appear to be at increased risk of any of the adverse pregnancy outcomes evaluated. Although the sample size is small, these results provide reassuring data to women with RA who require treatment with adalimumab.

Disclosure: C. D. Chambers, AbbVie Inc., 2, Amgen, 2, Apotex, 2, Barr Laboratories, Inc., 2, Bristol-Myers Squibb, 2, Genentech, 2, Janssen Pharmaceutica Product, L.P., 2, Parr Pharmaceutical, 2, Pfizer Inc, 2, Roche Pharmaceuticals, 2, Sandoz, 2, Sanofi-Aventis Pharmaceutical, 2, Teva Pharmaceuticals, 2, UCB, 2; **D. L. Johnson**, AbbVie Inc., 2, Amgen, 2, Apotex, 2, Barr Laboratories, Inc., 2, Bristol-Myers Squibb, 2, Genentech, 2, Janssen Pharmaceutica Product, L.P., 2, Parr Pharmaceutical, 2, Pfizer Inc, 2, Roche Pharmaceuticals, 2, Sanofi-Aventis Pharmaceutical, 2, Sandoz, 2, Teva Pharmaceuticals, 2, UCB, 2; **Y. Luo**, AbbVie Inc, 2, Amgen, 2, Apotex, 2, Barr Laboratories, Inc., 2, Bristol-Myers Squibb, 2, Genentech, 2, Janssen Pharmaceutica Product, L.P., 2, Parr Pharmaceutical, 2, Pfizer Inc, 2, Roche Pharmaceuticals, 2, Sandoz, 2, Sanofi-Aventis Pharmaceutical, 2, Teva Pharmaceuticals, 2, UCB, 2; **R. Xu**, AbbVie Inc, 2, Amgen, 2, Apotex, 2, Barr Laboratories, Inc., 2, Bristol-Myers Squibb, 2, Genentech, 2, Janssen Pharmaceutica Product, L.P., 2, Parr Phamaceutical, 2, Pfizer Inc, 2, Roche Pharmaceuticals, 2, Sandoz, 2, Sanofi-Aventis Pharmaceutical, 2, Teva Pharmaceuticals, 2, UCB, 2; **K. L. Jones**, AbbVie Inc, 2, Amgen, 2, Apotex, 2, Barr Laboratories, Inc., 2, Bristol-Myers Squibb, 2, Genentech, 2, Janssen Pharmaceutica Product, L.P., 2, Parr Pharmaceutical, 2, Pfizer Inc, 2, Roche Pharmaceuticals, 2, Sandoz, 2, Sanofi-Aventis Pharmaceutical, 2, Teva Pharmaceuticals, 2, UCB, 2.

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Meloxicam and Risk of Myocardial Infarction: A Population-Based Cohort Study. Deepan Dalal[1], Maureen Dubreuil[2], Yuqing Zhang[2], Christine Peloquin[2], Tuhina Neogi[2], Hyon Choi[2] and David T. Felson[2]. [1]Boston Medical Center, Boston, MA, [2]Boston University School of Medicine, Boston, MA.

Background/Purpose: Certain non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with an increased risk of myocardial infarction (MI). MI risk for different NSAIDs varies largely because of different levels of cyclo-oxygenase (COX) 2 inhibition. Given this differential MI risk, it is clinically important to understand which NSAID options are safer vs. which ones confer an increased risk. For example, naproxen has shown no increased risk of MI, whereas diclofenac has shown an increased risk. However, Meloxicam, which is considered to inhibit COX-2 selectively over COX-1, is used widely across the world, but the risk of MI with Meloxicam has not been quantified.

Methods: The Health Improvement Network (THIN) is a national population-based cohort of over 10 million patients from 580 general practices in the UK. We conducted a nested case-control study of patients between 35 and 89 years of age who had at least 1 year of enrollment between 2000 and 2013 in the cohort and at least 1 prescription for an NSAID. Individuals with a history of MI were excluded. Cases of MI were identified by Read codes and the date of MI was considered the index date. Each case

was matched with up to 4 unique controls on age, sex and practice ID. NSAID exposure was categorized as remote (greater than 60 days prior), recent (between 1 and 60 days) or current to the index date. Current NSAID users were further classified as Naproxen, Diclofenac, Meloxicam or other NSAID users. Multivariate logistic regression analysis with 6 categorical variables for NSAID exposure categories was conducted to determine the risk of MI among various current NSAID users compared with that of remote users, adjusting for potential confounders including traditional cardiac risk factors, comorbidities and cardiovascular drug use.

Results: We identified 9817 MI cases and 12860 matched controls from the cohort. The cases had a higher prevalence of traditional cardiac risk factors, more frequent use of cardiovascular medications, and a higher prevalence of chronic kidney disease and inflammatory arthritis (Table 1). The adjusted odds ratio (aOR) for MI with current Meloxicam use was 1.40 (95% CI, 1.15–1.71) as compared with remote NSAID use. While, the aOR with current Naproxen use was 1.01 (95% CI, 0.84–1.22) and with current Diclofenac use was 1.35 (95% CI, 1.21–1.5).

Conclusion: In this large population-based cohort, Meloxicam significantly increased the risk of MI at a level similar to that of Diclofenac. As previously shown, Naproxen was not associated with an increased risk of MI. Drugs like Diclofenac and Meloxicam are widely used across the world should be used cautiously because of the increased risk of MI they pose.

Table 1: Baseline characteristics

		MI Cases	Controls
Subjects (n)		9817	12860
Age (years)		62.8 ± 12.4	63.1 ± 12.2
Female		4039 (41.1%)	5571 (43.3%)
Smoking	Non-smoker	2965 (30.2%)	4914 (38.2%)
	Ex-smoker	2724 (27.7%)	3413 (26.5%)
	Current smoker	2493 (25.4%)	1876 (14.6%)
	Missing	1635 (16.7%)	2657 (20.7%)
BMI	Underweight	206 (2.1%)	283 (2.2%)
	Normal	1572 (16.0%)	2102 (16.3%)
	Overweight	2833 (28.9%)	3561 (27.7%)
	Obese	2426 (24.7%)	2816 (21.9%)
	Missing	2780 (28.3%)	4098 (31.9%)
Diabetes		1699 (17.3%)	1502 (11.7%)
Hyperlipidemia		1547 (15.8%)	1582 (12.3%)
Hypertension		4890 (49.8%)	5483 (42.6%)
History of ischemic heart disease		2464 (25.1%)	1383 (10.8%)
Kidney Disease		926 (9.4%)	733 (5.7%)
Inflammatory rheumatic disease		1984 (20.2%)	2187 (17.0%)
Osteoarthritis		3822 (38.9%)	5003 (38.9%)
ACE Inhibitors		2575 (26.2%)	2342 (18.2%)
Aspirin		3453 (35.2%)	2995 (23.3%)
Beta Blockers		2503 (25.5%)	2336 (18.2%)
Statins		3402 (34.7%)	3188 (24.8%)

Odd Ratios of MI by NSAID Use of Interest

NSAID Use	# Cases	# Controls	Adjusted OR (95% CI)
Referent (Remote use)	4422	6258	1.0
Current Naproxen use	291	383	1.01 (0.84, 1.22)
Current Diclofenac use	1089	1234	1.35 (1.21, 1.50)
Current Meloxicam use	262	291	1.40 (1.15, 1.71)

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Risk of Active Tuberculosis in Patients with Arthritis Receiving TNF-α Inhibitors: A Look Beyond the Baseline Tuberculosis Screening Protocol. Alina Soare, Carina Mihai, Ana Maria Gherghe, Rucsandra Dobrota, Raida Oneata, Simona Pintilie, Mihaela Milicescu, Ioan Ancuta, Andrei Martin, Mariana Sasu, Claudia Ciofu, Liviu Macovei, Victor Stoica and Mihai Bojinca. Carol Davila University of Medicine and Pharmacy & Cantacuzino Hospital, Bucharest, Romania.

Background/Purpose: Tuberculosis (TB) is a major concern in patients receiving TNF inhibitors (TNFi), especially in countries with a high TB burden. Careful TB screening is mandatory before TNFi initiation, and patients with latent TB receive prophylactic treatment. This study aimed to assess the incidence of active TB and the efficacy of TB prevention measures in a cohort of patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS)receiving TNFi, in an academic Rheumatology center.

Methods: Data of all patients who received treatment with TNFi in our clinic between Jan 1st 2001 and June 1st 2014 have been retrospectively analyzed. Demographics, baseline TB screening, TB prophylaxis, duration of TNFi treatment and reported active TB data were extracted from clinical records. The cohort was divided into 3 groups according to the mandatory TB screening method at baseline: tuberculin skin test (TST) with a positive threshold of either >10mm (01.2001–12.2005) = group TST1, or >5mm (01.2006–08.2010) = group TST2, and QuantiFERON®-TB Gold test (09.2010–06.2014) = group QTF. All patients tested positive for latent TB received prophylaxis with isoniazide for 9 months. Cases of TB reactivation were defined as TB occurring at <12 months since TNFi initiation. The incidence of active TB was analyzed for each group and compared to TB incidence data in Romanian general population, retrieved from the World Health Organization (WHO) reports. The impact of the screening method on the incidence of active TB was assessed using Cox proportional hazard regression.

Results: A total of 550 patients were included (304 RA, 43 PsA and 203 AS). According to the initial TB screening method, 77 patients belonged to the TST1, 251 to the TST2 and 222 to the QTF group. The number of active TB cases/ time of exposure to TNFi in person-years (PY) in the 3 groups was 9/477.3, 9/1081.5 and 3/445.5 respectively, accounting for an incidence of 1885.7, 832.2 and 673.4 cases per 100,000 PY. These numbers are significantly higher than the incidence of TB in Romania, which decreased from 147 to 94 per 100,000 PY from 2001 to 2013.

Cases classified as latent TB reactivation/total TB cases in the TST1, TST2 and QTF groups were only 2/9, 2/9 and 1/3 respectively, while the remaining TB cases were more likely new TB infection. Using Cox regression adjusted for age, sex and disease, we found no influence of the TB screening method on the risk of latent TB reactivation. However, the TST1 group had a significantly higher TB risk, with the QTF group as reference, when all cases of active TB were analyzed: hazard ratio [95% confidence interval] were 9.33[1.64–53.10], p=0.012 for TST1 and 1.68 [0.43–6.59], p=0,445 for TST2, suggesting that the period of TNFi initiation in TST1, when the TB incidence in general population was higher than in the later years, determined a higher risk for active TB.

Conclusion: In a country with high TB burden, where all patients initiated on TNFi are screened for latent TB at baseline, new TB infection exceeds latent TB reactivation. TB incidence in these patients is much higher than in the general population and baseline screening does not solve the problem of later infection, suggesting the necessity of yearly TB re-screening.

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Impact of Oral Glucocorticoid Therapy on Mortality in Patients with Rheumatoid Arthritis and Diabetic Mellitus. Mohammad Movahedi and William G Dixon. Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Glucocorticoid (GC) therapy is known to increase the risk of new-onset type 2 diabetes mellitus (DM). Furthermore, GC therapy increases blood glucose in diabetic patients, thereby potentially leading to worse outcomes. This study aimed to examine the impact of GC use on all-cause and cardiovascular (CV) mortality in patients with RA and DM, and to compare to the impact of GC use on mortality in patients with RA but no DM.

Methods: Adult patients with RA were identified from the Clinical Practice Research Datalink, a UK primary care research database. Type 2 DM was defined using READ codes, anti-diabetic treatment or abnormal blood results. GC exposure was identified from oral GC prescriptions. Mortality data, including cause of death, were obtained through linkage to the Office for National Statistics. All-cause and CV mortality rates with 95% confidence Interval (CI) were calculated for ever/ never GC use and categories of cumulative dose. Data were analysed using multivariable time-dependent Cox models to assess the association between GC and death, adjusting for potential confounders.

Results: We studied 3,397 patients with RA and DM and 17,883 patients with RA but no DM with a median follow-up of 3.6 and 5.3 years, respectively, during which 699 (266 from CVD cause) and 2,887 (1,016 from CVD cause) patients died. All-cause mortality rate was 4.6 (95% CI 4.3–5.0) and 2.7 (95% CI: 2.6–2.8) per 100 person-years (pyrs) in DM and non-DM cohorts, respectively.

In patients with RA and DM, the adjusted relative risk (aRR) and absolute risk difference (ARD) of all-cause mortality were 2.0 (95% CI: 1.6–2.4) and 4.2 per 100pyrs (95% CI: 3.5–5.0) in ever GC use compared with never GC use, respectively. There was a dose response relation between both all-cause and CV mortality, and cumulative GC dose category. Patients in the highest category of cumulative GC dose (≥7,299 mg) had an aRR of 3.4 (95%CI: 2.5–4.6) and compared to non GC users for all-cause mortality.

In patients with RA but no DM, the aRR and ARD of all-cause mortality was 2.3 (95% CI: 2.0–2.5) and 2.9 per 100pyrs (95% CI: 2.7–3.2) in ever GC use compared to never GC use, respectively. Risk of all-cause mortality was increased with increasing cumulative dose category. Similar results were observed for risk of CV mortality in association with cumulative GC dose.

Whilst the aRR for all-cause mortality was lower in patients with RA and DM compared to patients without DM (2.0 vs 2.3), the ARD was higher (4.2 vs 2.9 per 100 pyrs). The table below shows the association between GC use patterns and all-cause and CV mortality.

All cause mortality

	RA and DM		RA but no DM	
Oral GC pattern	**aRR**	**ARD Per 100 pyrs**	**aRR**	**ARD Per 100 pyrs**
Never use	Ref	-	Ref	-
Ever use	2.0 (1.6–2.4)	4.2 (3.5–5.0)	2.3 (2.0–2.5)	2.9 (2.7–3.2)
Cumulative dose category				
Non GC use	Ref	-	Ref	-
Low (>0–959.9 mg)	1.7 (1.3–2.2)	0.6 (−0.4–1.7)	1.8 (1.6–2.1)	0.3 (0.1–0.6)
Med (960–3054.9 mg)	1.8 (1.3–2.3)	1.6 (0.4–2.9)	2.2 (1.9–2.6)	1.7 (1.3–2.2)
High (3055–7298.9 mg)	2.3 (1.7–3.0)	3.8 (2.4–5.3)	3.3 (2.8–3.8)	4.5 (3.9–5.1)
Very high (≥7299 mg)	3.4 (2.5–4.6)	5.4 (3.8–7.1)		

CV mortality

	RA and DM		RA but no DM	
Oral GC pattern	**aRR**	**ARD Per 100 pyrs**	**aRR**	**ARD Per 100 pyrs**
Never use	Ref	-	Ref	-
Ever use	2.0 (1.4–2.7)	1.4 (0.9–1.9)	1.8 (1.5–2.2)	0.9 (0.8–1.1)
Cumulative dose category				
Non GC use	Ref	-	Ref	-
Low (>0–959.9 mg)	1.7 (1.2–2.7)	0.3 (–0.3–1.1)	1.4 (1.2–1.9)	−0.02 (−0.2–0.2)
Med (960–3054.9 mg)	1.8 (1.2–2.8)	0.7 (−0.1–1.5)	1.5 (1.2–2.0)	0.4 (0.2–0.7)
High (3055–7298.9 mg)	2.3 (1.5–3.6)	1.7 (0.8–2.6)	2.8 (2.2–3.7)	1.6 (1.2–1.9)
Very high (≥7299 mg)	2.4 (1.5–4.0)	1.0 (0.1–1.9)		

Conclusion: Oral GC therapy is associated with higher all-cause and CV mortality in RA patients with DM, although residual confounding may explain some of the association. Whilst the aRR is slightly lower that that seen in patients with RA but no DM, the higher background mortality rate in patients with DM means this lower aRR is associated with more excess deaths.

Disclosure: M. Movahedi, None; **W. G. Dixon**, None.

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Serious Infections on TNF Inhibitors: Have the Risks Changed over Calendar Time, and How High Are They? Elizabeth V. Arkema[1], Johan Askling[1] and the ARTIS Study group[2]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Karolinska Institutet och Svensk Reumatologisk förening, Solna, Sweden.

Background/Purpose: The rheumatoid arthritis (RA) population starting tumor necrosis factor inhibitors (TNFi) today is much different in terms of accumulated and concurrent disease activity and comorbidity, than patients starting treatment 10 years ago. Still, few studies have investigated time-trends in infection risks and their determinants, on a clinically relevant scale. Our aim was to calculate the absolute risk of serious infection (SI) within 1 year of TNFi-initiation in patients with RA in Sweden and to examine whether the risk changes over calendar time and patient characteristics.

Methods: Patients with RA who initiated a TNFi from 2004 to 2011 were identified from the Anti-Rheumatic Therapies in Sweden (ARTIS) register. Patient demographics, concomitant medications and clinical measures were collected from the patient's first visit (baseline). ICD-10 codes for SI hospitalizations were identified in the inpatient register (2004–2012) and linked to the study population using each patient's unique personal identification number. We calculated the absolute risk of SI hospitalization within 1 year of treatment start using modified Poisson regression models stratified by risk factors previously identified by the German biologics register, RABBIT: concomitant corticosteroid use, total number of risk factors (age≥60, previous serious infection 1 year before TNFi-initiation, COPD or chronic kidney disease). We additionally stratified risks by calendar year of initiation (2004–4007 vs. 2008–2011) and investigated other comorbidities (cardiovascular disease, diabetes, number of hospitalizations, days hospitalized, outpatient visits) and disease activity measurements (DAS-28 and its components, HAQ, disease duration).

Results: We included 8562 biological-initiators with RA. A total of 344 (4.0%) individuals had at least one SI hospitalization within a year of biological initiation (2004–2007 4.4%; 2008–2011 3.7%). Serious infection risk decreased over time in age and sex-adjusted models (p value for calendar year 0.02) but when adjusted for comorbidities, year of TNFi-initiation was no longer significantly associated with a decreased risk of SI (p=0.15). Individuals who were older, male, with longer disease duration, a history of infection and higher disease severity were at an increased risk of SI. Our results from 2004–2007 were very similar to those reported by RABBIT. When examining risks from 2008–2011, the majority of the increased risk was observed in individuals with 3 or 4 risk factors (**Figure**).

Conclusion: Risks of SI within 1 year of TNFi initiation were similar to those reported by the German Biologics Register 2004–2007. Although the population starting TNFi has changed over time, the one-year risks of SI has only dropped modestly, but the relative importance of SI risk factors has changed, such that infection risk calculators need be updated using contemporary data.

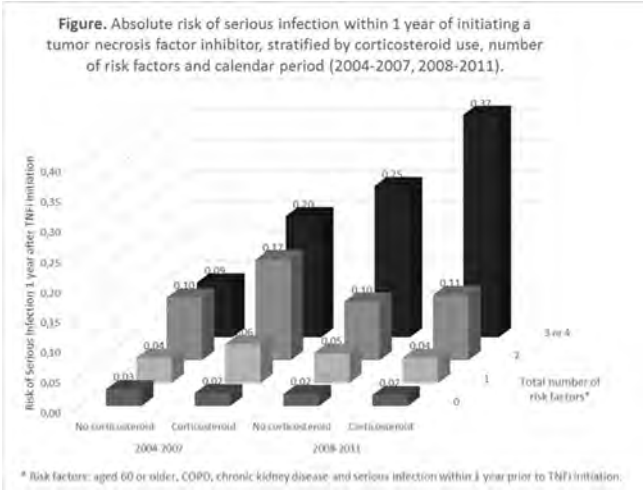

Figure. Absolute risk of serious infection within 1 year of initiating a tumor necrosis factor inhibitor, stratified by corticosteroid use, number of risk factors and calendar period (2004-2007, 2008-2011).

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ACR Concurrent Abstract Session
Metabolic and Crystal Arthropathies I: Clinical Aspects
Sunday, November 16, 2014, 2:30 PM–4:00 PM

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Comparison of Classification Criteria for Gout Using Monosodium Urate Crystal Identification By a Certified Examiner As the Gold-Standard in a Large Multi-National Study. William Taylor[1], Nicola Dalbeth[2], Jaap Fransen[3], Tuhina Neogi[4], H. Ralph Schumacher Jr. [5] and Tim Jansen[6]. [1]University of Otago Wellington, Wellington, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]Radboud University, Nijmegen, Netherlands, [4]Boston University School of Medicine, Boston, MA, [5]University of Pennsylvania VA Medical Center, Philadelphia, PA, [6]Radboud University Medical Center, Nijmegen, Netherlands.

Background/Purpose: Most gout is managed in primary care where the diagnosis seldom relies upon identification of MSU crystals. Several classification criteria for gout have been developed but there is little information on the relative performance of these criteria, especially in comparison to competent identification of MSU crystals in synovial fluid. This study,

undertaken as part of an ACR-EULAR project to update gout classification criteria compares the performance of existing criteria.

Methods: Investigators from 25 sites in 16 countries contributed data on consecutive patients with at least 1 recent swollen joint or subcutaneous nodule that conceivably might be gout. All patients underwent arthrocentesis or tissue aspiration and examination of synovial fluid or tissue with polarizing microscopy by an examiner who had undergone a 2-step certification procedure. Case-control status was defined by the presence or absence of MSU crystals. Data were collected that enabled classification into each of 5 published classification criteria for gout. Both full and survey versions of 1977 American Rheumatism Association (ARA) criteria were used for this analysis. The original NEW YORK and ROME criteria and a modification to contain only clinical items were included. Specificity, sensitivity and AUC were calculated and the differences in test performance were assessed with logistic regression. The reference category was MEX for each regression model.

Results: Data from 983 patients (509 cases, 474 controls) were collected, of whom 702 were male. The mean (SD) age was 58.5 (17.2) and duration of disease since first ever symptoms was 7.8 (24.6) years. Controls had a clinical diagnosis of gout (MSU crystals not observed by microscopy, n=50), CPPD (109), osteoarthritis (67), rheumatoid arthritis (69), septic arthritis (10), SLE (5), spondyloarthritis (71), undifferentiated arthritis (60), other (31). Not all patients could be classified by every criteria because of missing data, particularly radiographs.

The performance of the criteria is shown in the Table. Analysis of subjects without tophi generally led to minor differences in criteria performance. Excluding controls with a clinical diagnosis of gout led to slightly better specificity (54% MEX to 84% NEW YORK).

Overall, sensitivity was very high. The high sensitivity of the ARA (full) and NEW YORK criteria is due to the fact that presence of MSU crystals is sufficient for classification; therefore all cases meet these criteria by study design. The sensitivity of ARA, ROME and NEW YORK criteria are greatly reduced by excluding MSU crystal data. MEX has worse specificity than all other criteria sets and NETH has worse specificity than NEW YORK or ROME.

Conclusion: Although sensitivity of existing criteria is satisfactory, the specificity of every set is less than 80%, which is not ideal. There is a need for better performing criteria.

	Sensitivity	Specificity	AUC (95% CI)	Not classified
ROME[1]	97.6%	+74.5%	0.87 (0.84, 0.89)	8.2%
ROME (clinical 2 of 3)[1]	†77.6%	†74.5%	0.77 (0.73, 0.80)	8.2%
NEW YORK[2]	†100.0%	†78.4%	0.88 (0.85, 0.91)	0.2%
NEW YORK (clinical 2 of 4)[2]	†78.9%	†78.4%	0.78 (0.75, 0.81)	0.5%
ARA (full)[3]	†100%	†64.8%	0.82 (0.79, 0.86)	20.6%
ARA (survey)[3]	†85.7%	†68.1%	0.77 (0.74, 0.80)	19.3%
NETH[4]	93.7%	†60.7%	0.76 (0.73, 0.80)	9.0%
MEX[5]	95.3%	49.5%	0.72 (0.68, 0.76)	9.1%

† p<0.05 for difference in comparison to MEX
[1]The Epidemiology of Chronic Rheumatism 1963; [2]Population Studies of the Rheumatic Diseases - Proceedings of the Third International Symposium New York 1968; [3]Arthritis Rheum 1977; 20:895–900;
[4]Arch Intern Med 2010;170:1120–6; [5]Clin Rheumatol 2012;31:429–34

Disclosure: W. Taylor, Pfizer Inc, 5, Metabolex, 5, Abbvie, 9; **N. Dalbeth**, Ardea, 5, AstraZeneca, 5, Takeda, 5, Metabolex, 5, Menarini, 8, Savient, 8, Novartis Pharmaceutical Corporation, 8, Fonterra, 2, Novartis Pharmaceutical Corporation, 2, Ardea, 2, Fonterra, 9; **J. Fransen**, None; **T. Neogi**, None; **H. R. Schumacher Jr.**, Takeda, 2, Abbvie, 2, Regeneron, 5, AstraZeneca, 5, Novartis Pharmaceutical Corporation, 5, Metabolex, 5, Ardea, 5; **T. Jansen**, Abbvie, 2, UCB, 2, Abbvie, 5, AstraZeneca, 5, UMS, 5, Janssen Pharmaceutica Product, L.P., 5, Menarini, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, Abbvie, 8.

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Gout and the Risk of Alzheimer's Disease: A Population-Based Cohort Study. Na Lu[1], Yuqing Zhang[1], Alberto Ascherio[2], Miguel Hernan[2], Tuhina Neogi[1], Maureen Dubreuil[3] and Hyon Choi[4]. [1]Boston University School of Medicine, Boston, MA, [2]Harvard School of Public Health, Boston, MA, [3]Boston University Medical Center, Boston, MA, [4]Harvard Medical School, Boston, MA.

Background/Purpose: While gout is associated with cardiovascular (CV)-metabolic comorbidities and their sequelae, uric acid's anti-oxidant effects may have neuroprotective benefits. Several studies have found an inverse association between a history of gout and the future risk of Parkinson's disease, but no such evidence is available for the risk of Alzheimer's disease (AD). To that effect, a Rotterdam study has found an inverse association between prior serum uric acid levels and the risk of AD. Thus, we evaluated the potential impact of incident gout on the risk of developing AD in a general population context.

Methods: We conducted a matched cohort study using data from The Health Improvement Network (THIN), an electronic medical records database representative of the UK general population. Study population included individuals aged ≥ 40 who had at least 1 year of active enrollment with the general practice during 1 January 1995 to 31 May 2010. For each case of incident gout patient, up to 5 non-gout individuals were selected and matched on age, sex, date of study entry and year of enrollment. Gout diagnoses, outcomes, and dementia risk factors were identified from electronic medical records. We compared incidence rates (IRs) of AD between the gout and comparison cohorts, excluding individuals with prevalent gout or dementia at baseline. Cox proportional hazards models were used to estimate the hazard ratio (HR), adjusting for body mass index (BMI), smoking, alcohol use, prior comorbid conditions, and use of CV medicines.

Results: Among 55,471 individuals with gout (28% female, mean age 63 years), we identified 179 new cases of AD over a 4-year median follow up. The IR of AD was 0.7 per 1000 person-years (PY) vs. 1.3 per 1000 PY in the comparison cohort, and the multivariate HR of AD among those with gout was 0.69 (95% CI, 0.58 to 0.81). The inverse association was similarly present among men and those < vs ≥ 75 years, but was stronger among those with CV disease (i.e., ischemic heart disease or stroke) than those without (HRs, 0.37 [95% CI, 0.24 to 0.58] vs. 0.76 [95% CI, 0.61 to 0.93]) (p for interaction, 0.02).

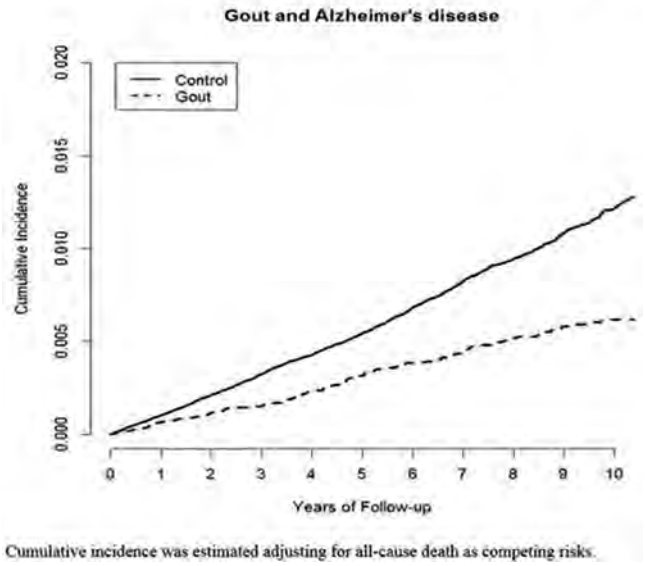
Conclusion: These findings provide the first general population-based evidence that gout is associated with a protective effect against developing AD and support the purported potential neuro-protective role of uric acid. These associations may be more evident among those with CV disease.

Table 1 Incidence Rates and Relative Risks (RR) for Alzheimer's disease by Gout Status (Total and Subgroups)

	Gout Status	N	Cases	Follow-up Time (person-years)	Mean Follow-up (years)	Incidence Rate (cases per 1000 person-years)	Crude RR (95% CI)*	+ GPs visits, BMI, smoking and alcohol Adjusted RR (95% CI)	+ Comorbidity and CVD drug classes Adjusted RR** (95% CI)
Total	Yes	51046	179	232733.7	4.6	0.8 (0.7 to 0.9)	0.58 (0.49 to 0.68)	0.62 (0.52 to 0.73)	0.69 (0.58 to 0.81)
	No	253909	1669	1176367.1	4.6	1.4 (1.4 to 1.5)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Female	Yes	14915	69	65792.1	4.4	1.0 (0.8 to 1.3)	0.49 (0.38 to 0.63)	0.53 (0.40 to 0.68)	0.59 (0.45 to 0.77)
	No	74386	812	339619.6	4.6	2.4 (2.2 to 2.6)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Male	Yes	36131	110	166941.7	4.6	0.7 (0.5 to 0.8)	0.66 (0.54 to 0.81)	0.70 (0.56 to 0.86)	0.77 (0.62 to 0.95)
	No	179523	857	836747.6	4.7	1.0 (1.0 to 1.1)	1.0 (reference)	1.0 (reference)	1.0 (reference)
<75	Yes	37441	75	183804.2	4.9	0.4 (0.3 to 0.5)	0.63 (0.49 to 0.80)	0.65 (0.50 to 0.83)	0.70 (0.54 to 0.91)
	No	186839	646	924476.6	4.9	0.7 (0.6 to 0.8)	1.0 (reference)	1.0 (reference)	1.0 (reference)
75–90	Yes	13605	104	48929.5	3.6	2.1 (1.7 to 2.6)	0.55 (0.44 to 0.68)	0.59 (0.48 to 0.74)	0.67 (0.54 to 0.84)
	No	67070	1023	251890.5	3.8	4.1 (3.8 to 4.3)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Hypertension	Yes	27083	91	114647.3	4.2	0.8 (0.6 to 1.0)	0.53 (0.40 to 0.69)	0.59 (0.45 to 0.77)	0.62 (0.47 to 0.81)
	No	90077	607	370234.5	4.1	1.6 (1.5 to 1.8)	1.0 (reference)	1.0 (reference)	1.0 (reference)
No Hypertension	Yes	23963	88	118086.5	4.9	0.7 (0.6 to 0.9)	0.72 (0.56 to 0.93)	0.74 (0.57 to 0.96)	0.79 (0.61 to 1.03)
	No	163832	1062	806132.6	4.9	1.3 (1.2 to 1.4)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Hyperlipidemia	Yes	17418	53	62199.0	3.6	0.9 (0.6 to 1.1)	0.49 (0.33 to 0.73)	0.55 (0.36 to 0.85)	0.63 (0.41 to 0.99)
	No	64365	344	224040.7	3.5	1.5 (1.4 to 1.7)	1.0 (reference)	1.0 (reference)	1.0 (reference)
No Hyperlipidemia	Yes	33628	126	170534.7	5.1	0.7 (0.6 to 0.9)	0.60 (0.49 to 0.72)	0.63 (0.51 to 0.77)	0.69 (0.56 to 0.85)
	No	189544	1325	952326.4	5.0	1.4 (1.3 to 1.5)	1.0 (reference)	1.0 (reference)	1.0 (reference)
CVD	Yes	13910	51	56181.9	4.0	0.9 (0.7 to 1.2)	0.34 (0.23 to 0.51)	0.35 (0.23 to 0.53)	0.35 (0.23 to 0.55)†
	No	49669	395	205063.5	4.1	1.9 (1.7 to 2.1)	1.0 (reference)	1.0 (reference)	1.0 (reference)
No CVD	Yes	37136	128	176551.9	4.8	0.7 (0.6 to 0.9)	0.66 (0.54 to 0.81)	0.69 (0.56 to 0.85)	0.76 (0.61 to 0.93)†
	No	204240	1274	971303.6	4.8	1.3 (1.2 to 1.4)	1.0 (reference)	1.0 (reference)	1.0 (reference)

* Matched by age, sex, and entry time
** Adjusted for the covariates in Table 1, except for the sub-group variables.
† P for interaction = 0.02. Other p values for interaction for the remaining subgroups were >0.15.

Figure 1. Cumulative Incidence of Alzheimer's disease According to Presence of Gout.



Cumulative incidence was estimated adjusting for all-cause death as competing risks.

Disclosure: N. Lu, None; **Y. Zhang**, None; **A. Ascherio**, None; **M. Hernan**, None; **T. Neogi**, None; **M. Dubreuil**, None; **H. Choi**, Takeda, 5, AstraZeneca, 5.

828

Extent of Urate Deposition in Asymptomatic Hyperuricemia and Symptomatic Gout: A Dual Energy Computed Tomography Study. Nicola Dalbeth[1], Meaghan House[1], Opetaia Aati[1], Paul Tan[1], Christopher Franklin[1], Anne Horne[1], Gregory Gamble[1], Lisa K. Stamp[2], Anthony Doyle[1] and Fiona M. McQueen[1]. [1]University of Auckland, Auckland, New Zealand, [2]University of Otago, Christchurch, New Zealand.

Background/Purpose: Recent studies have reported that ultrasound features of urate crystal deposition are present in some asymptomatic individuals with hyperuricemia, suggesting that subclinical urate deposition occurs prior to presentation with symptomatic disease. Dual energy computed tomography (DECT) allows both specific detection and volume measurement of urate crystals. The aim of this study was to compare the frequency and volume of DECT urate deposits in people with asymptomatic hyperuricemia and symptomatic gout.

Methods: DECT scans of both feet were prospectively obtained from asymptomatic individuals with serum uric acid ≥9mg/dL recruited from community laboratories (n=25), and those with crystal proven gout without clinically apparent tophi (n=33). The gout group was separated into two groups: early gout (pre-defined as onset of symptoms in the preceding 3 years, n=14), and late gout (disease duration >3 years, n=19). Asymptomatic individuals with serum uric acid <6mg/dL (negative controls, n=10) and individuals with crystal proven tophaceous gout (positive controls, n=20) were studied to optimize the DECT settings. Two readers, blinded to all clinical features including gout status and serum uric acid, independently scored the scans for the presence and sites of urate deposition, and measured the urate volume in both feet using automated volume measurement software. For the purposes of analysis, DECT urate deposits were considered to be present if scored by both readers.

Results: DECT urate deposits were observed in 6/25 (24%) participants with asymptomatic hyperuricemia, 11/14 (79%) participants with early gout and 16/19 (84%) participants with late gout ($p<0.001$, Figure 1A). In those with urate deposits, the volume of urate deposition was significantly lower in those with asymptomatic hyperuricemia, compared with the early and the late gout groups (Kruskall-Wallis $p=0.02$, Figure 1B). Similar urate volumes were observed in the early and late gout groups (Figure 1B). DECT urate deposition was observed in both joints and tendons in the asymptomatic hyperuricemia group, but significantly less frequently than in both the early and late gout groups ($p\leq0.001$ for both joint and tendon sites).

Conclusion: Although DECT can detect urate deposition in the feet of some asymptomatic individuals with hyperuricemia, these deposits are far more frequently observed in those with symptomatic gout. Urate deposit volumes are also greater in those with symptomatic disease. These data suggest that a threshold of urate crystal volume may be required before symptomatic gout occurs.

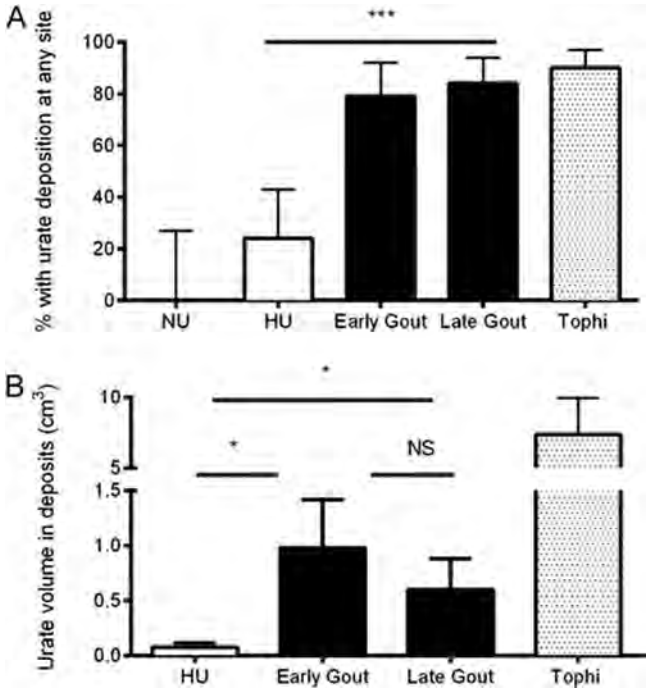


Figure: A. Frequency with urate deposition at any site, ***Chi-Square test $p<0.001$. B. Urate volume in those with deposits detected, *Dunn's multiple comparison test $p<0.05$. NU: asymptomatic normouricemia, HU: asymptomatic hyperuricemia.

Disclosure: N. Dalbeth, Ardea, 5, AstraZeneca, 5, Takeda, 5, Metabolex, 5, Menarini, 8, Savient, 8, Novartis Pharmaceutical Corporation, 8, Fonterra, 2, Novartis Pharmaceutical Corporation, 2, Ardea, 2, Fonterra, 9; **M. House**, None; **O. Aati**, None; **P. Tan**, None; **C. Franklin**, None; **A. Horne**, None; **G. Gamble**, None; **L. K. Stamp**, None; **A. Doyle**, None; **F. M. McQueen**, None.

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Asymptomatic Deposit of Monosodium Urate Crystals Associates to a More Severe Coronary Calcification in Hyperuricemic Patients with Acute Coronary Syndrome. Mariano Andrés[1], María Amparo Quintanilla[1], Francisca Sivera[1], Paloma Vela[2] and Juan Miguel Ruiz-Nodar[3]. [1]Hospital General Universitario de Elda, Alicante, Spain, [2]Universidad Miguel Hernández, Alicante, Spain, [3]Hospital General Universitario de Alicante, Alicante, Spain.

Background/Purpose: Increased cardiovascular (CV) risk in gout relates to crystal-driven inflammation. Monosodium urate (MSU) crystals are found in ~25% of patients with asymptomatic hyperuricemia (AH) by ultrasound (US) [1,2]. Whether AH patients with crystal deposits depict an increased CV risk has not been assessed so far. We aimed to assess the association between the deposit of MSU crystals in AH and the severity and extension of the coronary atherosclerotic disease (CAD).

Methods: Cross-sectional study, approved by the local ethics committee. Consecutive patients with AH (serum uric acid [SUA] >7.0 mg/dL) admitted due to an acute coronary event were selected. Those with current urate lowering treatment (ULT) were excluded. US of both knees and 1st MTP joints was performed to detect signs of MSU crystals deposition: doble contour sign, snow storm sign, tophus or joint effusion. When present, US-guided arthrocentesis was performed to confirm MSU crystals by polarised light microscopy. US and microscopy findings were later reviewed by a blinded rheumatologist. CAD was assessed through the severity of coronary artery calcification (absent, mild, moderate or severe) and the total of significant coronary lesions (>50% of the diameter) at coronariography by a blinded cardiologist. Traditional CV risk factors were also collected. Association between coronariographic features and crystal identification was analysed by logistic regression for binary variables and lineal regression for continous variables.

Results: Fifty-one patients were enrolled, median (p25–75) age 73 years (59–81), 76.5% males. Median SUA at admission was 7.6 mg/dL (7.08–8.6). Moderate-to-severe calcification was present in 21 (41.2%) patients, and the median number of significant coronary lessions was 3.0 (2–5). US found lesions in 49 (96.0%) patients: joint effusion in 94.1%, tophi in 9.8%, doble contour sign in 9.8% and snow storm sign in 3.9%. Arthrocentesis was performed in 48 patients. MSU crystals were identified in 11 patients (21.6% of total). No significant differences between groups were found in traditional CV risk factors or SUA levels. The presence of moderate to severe coronary calcification significantly differed between groups and strongly associate to the detection of MSU crystals [Table]. The number of significant lesions did not associate to MSU crystals identification, though a trend tomards more lesions in MSU+ patients was noted.

Conclusion: Our study found a more severe coronary calcification in those AH patients with deposits of MSU crystals. These patients might benefit from ULT aiming to reduce their CV risk, but this should be addressed in future studies.

References:
[1] Arthritis Res Ther; 13:R4.
[2] Ann Rheum Dis; 71:157.

Table.

	MSU+ patients (n= 11)	MSU- patients (n=40)	p-value	Association analysis
Moderate-severe coronary calcification (n,%)	8 (72.7%)	13 (32.5%)	0.016	OR 9.406+ (95%CI 1.459, 60.637)
Significant coronary lesions (median, p25–75)	4.0 (3.0–5.0)	3.0 (1.3–4.0)	0.137	β 0.693 (95%CI-0.596, 1.982) R^2 0.003

MSU: monosodium urate; OR: odds ratio; CI: confidence interval. + Model adjusted for age, gender, hypertension, diabetes, dyslipemia, smoking, glomerular filtration rate and serum uric acid at admission.

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Profound Hypouricemia Induced in Human Subjects By Novel Bifunctional Inhibitors of Xanthine Oxidase and URAT1. Raymond P. Warrell Jr.[1], Anna Klukovits[2], Keith Barnes[3], Chitkala Satyanarayana[4], Chris Cheeseman[5] and John Piwinski[1]. [1]Relburn-Metabolomics, Inc., Westfield, NJ, [2]SOLVO Biotechnology, Budapest, Hungary, [3]AMRI, Albany, NY, [4]AMRI, Singapore, Singapore, [5]University of Alberta, Alberta, AB.

Background/Purpose: A prototype anticancer drug (RLBN1001) induced marked hypouricemia in studies of > 350 human subjects. Preliminary exploration suggested dual effects on uric acid (UA) production and excretion, whereas studies by others showed the agent was a catalytic (Type 2) inhibitor of topoisomerase-II. Given the unusual clinical potency, we sought to: identify the hypouricemic mechanism(s); clarify structure-activity relationships (SARs) to both the uric acid and genotoxic targets; and develop novel analogs that would enhance the hypouricemic effect and eliminate genotoxicity, thereby discovering potentially useful treatments for gout.

Methods: We verified clinical proof-of-concept by examining biochemical effects in 50 human subjects treated with RLBN1001. We explored SARs in recursive chemical syntheses using four principal bioassays: renal UA transporters URAT1 (SLC22A12) and splice variants of GLUT9a/b (SLC2A9); xanthine oxidase (XO); and *in vitro* mouse micronucleus (MMN) (to detect genotoxicity).

Results: Over a 15-fold dosing range with RLBN1001, nadir levels of clinical hypouricemia (≤ 1.0 mg/dL) were not dose-related, indicating the minimal effective dose was below the lowest administered dose in this study (100 mg/m^2/d × 5d). At both low and high doses, hypouricemia was associated with increased urinary excretion of both UA and total oxypurines, suggesting bifunctional equilibrium effects on both production and excretion. We found that the RLBN1001 prototype was a potent inhibitor of URAT1 but not GLUT9a, a modest inhibitor of XO, and a potent clastogen in the MMN assay. We iteratively synthesized a series of novel analogs and identified new compounds that are potent inhibitors of both XO (i.e., 4-fold more potent than allopurinol) and URAT1 (equipotent to lesinurad), but devoid of genotoxicity. One compound showed moderate inhibition of GLUT9b (data not shown), but other compounds showed minimal effects on this target. Data for reference and selected new compounds are shown in the table.

Conclusion: Having established compelling clinical POC with the RLBN1001 prototype, we have synthesized a library of unique compounds with strongly enhanced activities that both reduce UA production and enhance UA excretion. A lead compound is expected to enter initial clinical trials as a novel, potential first-line treatment for hyperuricemic patients with gout.

Compound	URAT1 Inhibition IC50 mM Mean ± SEM	XO Inhibition IC50 mM Mean ± SEM	MMN
Allopurinol	>300	2.8 ± 0.33	ND
Benzbromarone	0.2	ND	ND
Lesinurad	3.54	>300	ND
RLBN1001	5.4 ± 1.0	274	+
RLBN2022	1.2	>300	+
RLBN2027	6.3	243	+
RLBN2023	2.6 ± 0.6	1.1	Negative
RLBN2024	9.4 ± 0.6	0.7	Negative
RLBN3022	3.5	1.9	Negative
RLBN3050	9.5	0.6	Pending

Disclosure: R. P. Warrell Jr., Relburn-Metabolomics, Inc., 3; **A. Klukovits**, None; **K. Barnes**, None; **C. Satyanarayana**, None; **C. Cheeseman**, None; **J. Piwinski**, Relburn-Metabolomics, Inc., 3.

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Bisphosphonates and Risk of Acute Pseudogout: A Case-Control Study in the Clinical Practice Research Datalink (CPRD). Edward Roddy, Sara Muller, Zoe Paskins, Samantha Hider, Milisa Blagojevic-Bucknall and Christian Mallen. Keele University, Keele, United Kingdom.

Background/Purpose: Acute pseudogout is the most dramatic clinical manifestation of calcium pyrophosphate crystal deposition (CPPD). CPPD is most commonly sporadic and age-related but can rarely occur secondary to metabolic diseases or a familial trait. Published case reports also suggest that acute pseudogout can occur as a consequence of bisphosphonate therapy. This matched case-control study aimed to examine whether acute pseudogout is associated with bisphosphonate prescription with the preceding 60 days.

Methods: The study was nested within the UK Clinical Practice Research Datalink (CPRD) which houses clinical data from over 600 general practices. Cases aged ≥18 years with a first-ever diagnosis of pseudogout between 01/03/1987 and 31/12/2012 were individually matched for age, gender and practice to four controls without pseudogout. The exposure of interest was prescription of an oral bisphosphonate in the 60 days prior to the diagnosis of pseudogout. It was estimated that 2147 eligible cases of pseudogout would be identified conferring 98% power to detect an odds ratio (OR) of 2.0. Unadjusted conditional logistic regression was used to assess the association between oral bisphosphonate prescriptions and pseudogout and then adjusted for hyperparathyroidism, osteoarthritis, rheumatoid arthritis, and prescription of diuretics and corticosteroids. Analyses were then repeated for individual bisphosphonates. In order to address the possibility of misdiagnosis of crystal arthritis, a sensitivity analysis was undertaken excluding cases or controls who had a prior diagnosis of gout. ORs were presented as incident rate ratios (IRR) with 95% confidence intervals (CI).

Results: 2011 cases of incident pseudogout were identified and successfully matched to 8013 controls (mean age 72 years; male 52%). Those with incident pseudogout were more likely than controls to have received a bisphosphonate prescription in the preceding 60 days (6.1% vs 3.8%; IRR 1.69; 95%CI 1.35, 2.11). On multivariate analysis, this association attenuated slightly (IRR 1.33; 95%CI 1.05, 1.69). A similar significant association was seen for prescription of alendronic acid (multivariate IRR 1.35; 95%CI 1.02, 1.79) but not etidronate disodium, risedronate sodium, ibandronic acid or sodium clodronate although the absolute number of prescriptions for these drugs was small. After excluding known cases of gout, multivariate associations with both any bisphosphonate (IRR 1.43; 95%CI 1.11, 1.84) and alendronic acid (IRR 1.53; 95%CI 1.14, 2.06) remained.

Conclusion: Bisphosphonate prescription appears to be a risk factor for pseudogout, independent of co-morbid conditions and medications. Prescribers should be aware of this uncommon cause of acute pseudogout.

Disclosure: E. Roddy, None; **S. Muller**, None; **Z. Paskins**, None; **S. Hider**, None; **M. Blagojevic-Bucknall**, None; **C. Mallen**, None.

ACR Concurrent Abstract Session
Miscellaneous Rheumatic and Inflammatory Diseases
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NOD2-Associated Autoinflammatory Disease: The Largest Cohort Study. Qingping Yao, Min Shen, Christine McDonald, Felicitas Lacbawan and Bo Shen. Cleveland Clinic, Cleveland, OH.

Background/Purpose: *NOD2*-associated autoinflammatory disease (NAID) is an emerging systemic inflammatory disease. The aim is to report our extended study of the phenotypic and genotypic features of the disease.

Methods: A total of 143 adult patients with autoinflammatory phenotypes at presentation were suspected of having NAID over the past 4 years. All patients were genotyped for the *NOD2* mutations. They were then clinically followed and prospectively studied. All patients were divided into two groups predicated on the presence or absence of the *NOD2*mutations. NAID was diagnosed according to our previously reported criteria. The data of the 2 groups were compared and analyzed.

Results: Of 143 patients, we identified 46.9% of patients carrying *NOD2* mutations. The genotype frequencies were significantly higher than historical healthy controls, with IVS8+158 being 35.7%, R702W 11.2% and rare mutations 14.0% (Table 1). The frequency of IVS8+158 was significantly higher than non-Jewish white Crohn's patients. Fifty seven of the 67 *NOD2* positive patients were diagnosed with NAID. The remaining included 5 cases of Crohn's disease, 2 ulcerative colitis, 2 Blau syndrome, and 1 autoimmune disease. The frequency of NAID was estimated to be 3%-7% of our outpatients.

All 57 NAID patients were white with 68.4% of women. The mean age at onset was (33.2 ± 14.0) years, and the mean disease duration at diagnosis was (10.6 ± 8.3) years. NAID was sporadic in 93% of cases. The phenotypic features of this disease included periodic fever (63.2%), dermatitis (91.2%) and inflammatory arthritis/arthralgia (87.7%)(Table 2). Compared with *NOD2* negative patients, the skin disease was overrepresented by dermatitis manifested as erythematous patches or plaques on trunk(Figure 1). Oligo-polyarthritis were common mainly involving the lower extremities. Distal lower extremity swelling was more common(Figure 1). There were gastrointestinal symptoms in 73.7% but without inflammatory bowel disease and sicca-like symptoms in 56.1%. Pericarditis and pleuritis were occasionally

seen. Acute phase reactants were elevated in 40.4%, and autoantibodies are largely absent, with only 8.8% of patients having low titters of ANA. Associated *NOD2* gene mutations were IVS8+158 (80.7%) and/or R702W (26.3%), and rare mutations (24.1%)(Table 2).

Of the 76 *NOD2* mutation negative subjects, 28 patients turned out to have autoimmune diseases and 4 cases of autoinflammatory disease. The remaining were still non-diagnostic. The medications used to treat the disease entailed nonsteroidal anti-inflammatory agents (34.5%), glucorcorticoids (36.4%), sulfasalazine (32.1%) and biologics (7.1%). Prednisone and sulfasalazine were found effective and 2 cases were treated with infliximab and tocilizumab.

Conclusion: The largest cohort study has demonstrated that the *NOD2* genotype frequencies are significantly higher in our study patients and associated with NAID. NAID represents a genetically complex autoinflammatory disorder, and is distinct from Crohn's disease. This disease is more prevalent than initially thought, with an estimated frequency of about 5% in our rheumatology outpatients. This report will further increase awareness of this entity in the medical community.

Disclosure: Q. Yao, None; **M. Shen**, None; **C. McDonald**, None; **F. Lacbawan**, None; **B. Shen**, None.

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Canakinumab Use in Patients with Cryopyrin-Associated Periodic Syndrome: Interim Safety and Efficacy Results from Beta-Confident Registry. Hal M. Hoffman[1], Jasmin B. Kuemmerle-Deschner[2], Philip N. Hawkins[3], T. van der Poll[4], Ulrich A. Walker[5], Ken Abrams[6] and Hugh H. Tilson[7]. [1]University of California at San Diego, La Jolla, CA, [2]University Hospital Tuebingen, Tuebingen, Germany, [3]University College London Medical School, London, United Kingdom, [4]University of Amsterdam, Amsterdam, Netherlands, [5]Department of Rheumatology, University Hospital Basel, Basel, Switzerland, Basel, Switzerland, [6]Novartis Pharmaceutical Corporation, East Hanover, NJ, [7]University of North Carolina, Chapel Hill, NC.

Background/Purpose: The three phenotypes in the order of severity: familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous and articular syndrome/neonatal onset multisystem inflammatory disease (CINCA/NOMID), constitute the cryopyrin-associated periodic syndrome (CAPS). [1] Here we present the interim safety data of canakinumab (CAN) use in CAPS patients (pts) in clinical practice from the on-going observational β–Confident Registry, that involves 40 sites in 13 countries. To monitor and explore the overall safety of CAN with a focus on serious adverse events (SAEs) including serious infections, vertigo, malignancies and hypersensitivity reactions. The secondary objective is to measure efficacy using physician global assessments (PGA).

Methods: β–Confident Registry protocol does not mandate any visits or procedures, but records all observed and reported adverse events (AEs) and serious AE (SAEs) or AEs potentially related to treatment with CAN. Cumulative safety data are reported as incidence rate (number of events) per 100 patient-years (IR/100 pyr) from the date of first pt enrollment (19 November 2009) until the current data cut-off date (15 April 2014). Additional safety data will be updated, as available, at the time of the presentation.

Results: 272 pts (FCAS, n=38; MWS, n=164; NOMID, n=32; others, n=37) were enrolled with a mean±SD duration of 164±61.3 weeks in the registry. Of these, 17 (6.3%) pts discontinued CAN: 5 each due to AE, poor efficacy and patient preference; 2 for unknown reasons. The incidence rate of overall AEs was 100.0 per person-years (pyr). Pts with FCAS, the least severe phenotype, had the lowest AE incidence rate (49.1/100 pyr) as compared with pts with MWS (107.3/100 pyr) and NOMID (130.4/100 pyr), the more severe phenotypes. The most common types of AEs were infections and infestations with an incidence rate of 35.6/100 pyr. A total of 79 SAEs were reported by 47 pts resulting in an incidence rate of 13.2 SAEs/100 pyr. The most common type of SAE was infection (3.5/100 pyr). One death in a 76 yr MWS old pt with metastatic rectal adenocarcinoma was reported. Of 14 (5.1%) pts that received pneumococcal vaccination (PPV), 10 reported a local post-PPV injection site reaction; of which 4 were considered as serious. Based on PGA assessment, nearly half the pts had no disease activity while most others had mild/moderate disease activity, at the current data cut-off. There was no evidence of loss of effect with time.

Conclusion: The safety profile observed with the use of CAN in CAPS registry is consistent with that observed in the clinical trial program. Response rates were as expected based on clinical trial experience with no evidence of loss of efficacy.

[1]Farasat S. et al. Arch Dermatol. 2008;144: 392–402

Disclosure: H. M. Hoffman, Novartis Pharmaceutical Corporation, 5; **J. B. Kuemmerle-Deschner**, Novartis, 2, Novartis, 5; **P. N. Hawkins**, None; **T. van der Poll**, None; **U. A. Walker**, Novartis, 5; **K. Abrams**, Novartis Pharmaceutical Corporation, 3, Novartis Pharmaceutical Corporation, 1; **H. H. Tilson**, Novartis, 5.

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Interleukin-18 (IL-18) As a Biomarker for Diagnosis and Evaluation of Disease Activity in Patients with Adult Onset Still's Disease and Systemic Onset Juvenile Idiopathic Arthritis. Holger Kudela[1], Susanne Drynda[2], Anke Lux[3], Gerd Horneff[4] and Joern Kekow[2]. [1]Univ of Magdeburg, Clinic for Rheumatology, Vogelsang-Gommern, Germany, [2]Univ of Magdeburg, Clinic of Rheumatology, Vogelsang-Gommern, Germany, [3]Univ of Magdeburg, Institute for Biometry and Medical Informatics, Magdeburg, Germany, [4]Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany.

Background/Purpose: Establishing the diagnosis of adult onset Still's disease (AOSD) as well as of systemic onset juvenile idiopathic arthritis (sJIA) is very challenging. Mostly it is still a diagnosis of exclusion. Along with IL-1β, IL-6 and TNFα, IL-18 is one of the cytokines which seem to play a pivotal role in the pathogenesis of both diseases. It has been described as a potential biomarker to support the diagnosis of AOSD and sJIA. Regarding the importance of IL-18 as a marker for disease activity published data are so far conflicting. The aim of the study was to clarify the role of IL-18 as a diagnostic marker and its importance as a measure for disease activity in AOSD and sJIA.

Methods: Thirty adult patients diagnosed with AOSD and twenty children diagnosed with sJIA were included in the study. Twenty adults and three children were analyzed repeatedly. At each visit patients underwent clinical evaluation and laboratory analysis. IL-18 serum levels were determined using an IL-18 ELISA (MBL, Japan) according to the manufacturer's instructions. As comparison groups served 65 adults and 23 children with other rheumatic diseases. To evaluate the disease activity Rau's criteria and CRP values were used. Active disease was defined as a Rau's score ≥2 and/or CRP≥ 2 ULN.

Results: In 83 samples from 30 AOSD patients IL-18 levels were determined. At the time of blood sample collection clinical parameters were obtained as well. In active disease (n=27) patients showed a mean activity score of 3.9±1.4 and a mean CRP value of 106.5±86.1 mg/l. Patients in remission (n=43) showed a mean activity score of 0.14±0.35, and mean CRP value of 5.6±1.5 mg/l. IL-18 levels were significantly increased in patients with active AOSD compared to patients in remission and to the comparison group with a median of 16327 pg/ml, 470 pg/ml, and 368 pg/ml, respectively ($p<0{,}001$). In active disease (n=16) the sJIA cohort showed a mean activity score of 3.4±1.0 and mean CRP value of 133.9±81.8 mg/l. Analogous to AOSD in active sJIA the median IL-18 serum level with 21512 pg/ml was significantly higher than in the comparison group (n=25) with a median IL-18 serum level of 2580 pg/ml ($p<0.001$) and a mean CRP value of 67.6±77.7 mg/l.

For evaluation of IL-18 serum levels as marker for AOSD or sJIA a receiver operating characteristic curve analysis was used. At a cutoff point of 5000 pg/ml IL-18 specificity for AOSD was 96.9 %, and sensitivity 63.3 % (AUC=0.870, $p<0.001$). For diagnosis of sJIA in children a cutoff value of 10000 pg/ml was chosen with a specificity of 100 % and a sensitivity of 60 % (AUC=0.774, $p = 0.003$).

In 11 AOSD patients with active disease at the first visit (Rau's score 4.2±1.5) the reduction of disease activity (Rau's score 0.4±0.7) went along with a significant reduction in IL-18 serum levels from medians of 12500 pg/ml to 402 pg/ml (Wilcoxon sign rank test $p<0{,}001$).

Conclusion: We could confirm earlier publications that highly elevated IL-18 serum levels are common in active AOSD and sJIA, with up to 1000fold higher concentrations compared to other rheumatic diseases. A clear association of IL-18 serum levels with disease activity in AOSD was found. The results give further evidence for the use of IL-18 as diagnostic biomarker in AOSD and sJIA.

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Relapsing Polychondritis Can be Characterized By 3 Different Clinical Phenotypes: Analysis of a Series of 142 Patients. Jeremie Dion[1], Nathalie Costedoat-Chalumeau[1], Damien Sène[2], Judith Cohen-Bittan[3], Gaëlle Leroux[3], Charlotte Dion[4], Camille Francès[5] and Jean-Charles Piette[3]. [1]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin,

AP–HP, Université Paris Descartes, Paris, Paris, France, [2]Hopital Lariboisière, service de Médecine Interne, Paris, France, [3]CHU Pitié-Salpêtrière, Paris, France, [4]Ecole des hautes études en sciences sociales, Paris, France, [5]Hôpital Tenon, Paris Cedex 20, France.

Background/Purpose: We previously described clinical characteristics and evolution of 142 patients with relapsing polychondritis (RP) followed in a single center and seen at least once since 2000 (1). A cluster analysis was performed with the aim to identify different subtypes of RP.

Methods: A cluster analysis using a k-mean clustering method preceded by a multiple correspondence analysis was performed on 142 patients with RP according to Michet's criteria.

Results: We identified 3 clusters corresponding to 3 distinct clinical phenotypes (Table 1). Cluster 1 (n=12, 8%) corresponded to the more severe phenotype, with a mortality rate of 58% and intensive care unit (ICU) admission rate of 50%. This cluster mainly included men (83%), older at diagnosis, with myelodysplasia (83%), cutaneous (92%) and cardiac (58%) involvement, but with rare tracheobronchial involvement. They were more frequently treated with biologics (58%) than with immunosuppressive agents (33%).

Cluster 2 (n=37, 26%) was characterised by patients with predominant tracheobronchial (76%) involvement and abnormal functional respiratory test results (57%). None had myelodysplasia, and cardiac involvement was less frequent (24%). The prognosis was intermediate: mortality was 14%, but these patients with high infection rate (35%) were frequently admitted to ICU (27%). They frequently received immunosuppressive agents (84%).

Cluster 3 (n=93, 65%), the largest and less severe, was mainly composed of women (68%) with infrequent tracheobronchial (3%) and hematological involvement (2% had myelodysplasia and 5% another hematological disease). Few patients died (4%) or were admitted to ICU (2%). All patients with long-lasting remission (n=15) were in this group.

Conclusion: Using cluster analysis, we were able to distinguish three distinct subgroups of RP. Cluster 1 and 2 had the worst prognosis: older men with myelodysplasia were more likely to have a fatal issue and patients with a respiratory tract involvement were more likely to be admitted to intensive care and had an intermediate survival. By contrast, the last group, mainly composed of patients without hematological or respiratory involvement, had a good prognosis. These results need to be confirm in further studies.

1. Dion J, Costedoat-Chalumeau N, Sène D, Piette JC. Description of 142 cases of relapsing polychondritis followed in a single center since 2000 (abstract). ArthritisRheum 2013;10(supplement):S868.

Table 1: Cluster analysis of 142 patients with relapsing polychondritis

	Overall series N=142	Cluster 1 n=12 (8%)	Cluster 2 n=37 (26%)	Cluster 3 n=93 (65%)	p value
Demographical data					
Women (%)	**86 (61)**	2 (17)	21 (57)	63 (68)	**0.003**
Men	**56 (39)**	10 (83)	16 (43)	30 (32)	
Age at onset					**0.02**
≤55 years	**109 (77)**	5 (42)	33 (89)	75 (81)	
>55 years	**33 (23)**	7 (58)	4 (11)	18 (19)	
Clinical phenotype					
Laryngeal	**61 (43)**	2 (17)	25 (68)	34 (37)	**0.001**
Tracheobronchial	**32 (22)**	1 (8)	28 (76)	3 (3)	**<0.0001**
Audiovestibular	**48 (34)**	6 (50)	15 (41)	27 (29)	0.21
Ophthalmological	**80 (56)**	11 (92)	18 (49)	51 (55)	**0.029**
Cutaneous	**40 (29)**	11 (92)	6 (16)	23 (25)	**<0.0001**
Deep vein thrombosis	**15 (11)**	3 (25)	6 (16)	6 (6)	0.06
Myelodysplasia	**12 (8)**	10 (83)	0 (0)	2 (2)	**<0.0001**
Other hematological disease	**6 (4)**	0 (0)	1 (3)	5 (5)	0.59
Cardiac	**38 (27)**	7 (58)	9 (24)	22 (24)	**0.03**
Abnormal functional respiratory test result	**29 (20)**	2 (17)	21 (57)	6 (6)	**<0.001**
Treatments					
Steroids	**133 (94)**	12 (100)	37 (100)	84 (90)	0.08
Biological agents	**22 (15)**	7 (58)	12 (32)	3 (3)	**<0.0001**
Immunosuppressive agents	**56 (39)**	4 (33)	31 (84)	21 (23)	**<0.0001**
Disease evolution					
Death	**16 (11)**	7 (58)	5 (14)	4 (4)	**<0.0001**
Serious infection	**26 (18)**	7 (58)	13 (35)	6 (6)	**<0.0001**
ICU admission	**18 (13)**	6 (50)	10 (27)	2 (2)	**<0.0001**
Long lasting remission	**15 (11)**	0 (0)	0 (0)	15 (16)	**0.02**

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Categorical Change in 6MWD in Patients with Connective Tissue Disease Associated Pulmonary Arterial Hypertension Receiving Ambrisentan over 3-Years. Aryeh Fischer[1], Virginia D. Steen[2], Steven Nathan[3], Hunter Gillies[4], James Tislow[4] and Chris Blair[4]. [1]National Jewish Health, Denver, CO, [2]Georgetown University Medical Center, Washington, DC, [3]Inova Medical Group, Falls Church, VA, [4]Gilead Sciences, Inc., Foster City, CA.

Background/Purpose: The 6MWD is a valuable tool for evaluating response to therapy in patients with pulmonary arterial hypertension and may be considered a surrogate measure for survival in PAH. However, due to musculoskeletal and other non-PAH related factors, there has been a less robust effect on 6MWD in patients with CTD-PAH. We analyzed the ARIES database to determine the percentage of CTD-PAH patients who have achieved categorical changes in 6MWD while receiving ambrisentan.

Methods: Data from the combined ARIES 1 & 2 placebo controlled studies (ARIES-C) as well as the extension study (ARIES-E) were used. Based upon the previously determined MID of 26m in the overall PAH population participating in the ARIES clinical trials (Minnai, ATS 2014), we chose to evaluate the number of patients achieving changes from their baseline 6MWD in 30m intervals. Analysis was broken down by 6MWD at the end of each year through year 3 and observed cases are reported. Patients who discontinued participation prior to completing year three continued to have survival status evaluated and overall survival status is reported. Adverse events over three years are also reported.

Results: There were 124 CTD-PAH patients who participated in the ARIES clinical trials. At the end of year 3, 6MWD data was available for 55 patients and was unavailable for 69 patients (died = 29, missing 6MWD, alive = 29, and missing 6MWD with survival status unknown = 11). Of patients with an evaluable 6MWD at each yearly interval, the majority [57/91 (63%) at year 1, 43/75 (57%) at year 2, and 32/55 (58%) at year 3] demonstrated improvement from baseline and this was maintained throughout the three years. Additionally, of the patients demonstrating improvement in 6MWD, most were categorized as demonstrating an improvement of at least +60m over baseline which is well above the MID. At the completion of 3 years, survival status is unknown for 11 of the 124 CTD-PAH patients participating. Of the 113 patients where survival status is known, 84 (74.3%) were alive at three years. Adverse events occurring over 3 years were consistent with observed AEs in both PAH and CTD, and were consistent with the known profile of ambrisentan.

Table 1.

	Year 1	Year 2	Year 3
CTD-PAH patients with evaluable 6MWD	n = 91	n = 75	n = 55
≥60m improvement	25 (27.5%)	23 (30.7%)	14 (25.5%)
≥30–60m improvement	17 (18.7%)	12 (16%)	6 (10.9%)
0–30m improvement	15 (16.5%)	8 (10.7%)	12 (21.8%)
0–30m worsening	18 (19.8)	11 (14.7%)	5 (9.1%)
>30m–60m worsening	5 (5.5%)	9 (12%)	8 (14.5%)
>60m worsening	11 (12.1%)	12 (16%)	10 (18.2%)
Overall improved	57 (62.6%)	43 (57.3%)	32 (58.2%)
Overall worsening	34 (37.4%)	32 (42.7%)	23 (41.8%)

Conclusion: Although CTD-PAH patients often do not have a robust improvement in 6MWD, among patients with CTD-PAH who received ambrisentan and had evaluable 6MWD, the majority demonstrated increases in 6MWD over 3 years with 58.2% maintaining improvement by the end of year 3.

Disclosure: A. Fischer, Gilead Sciences, Inc., InterMune, 2, Gilead Sciences, Inc., Actelion Pharmaceuticals US, 8, Actelion Pharmaceuticals US, Gilead Sciences, Inc., InterMune, 5; **V. D. Steen**, Actelion Pharmaceuticals US, 8, United Therapeutics, 5, Gilead Science, 8, Roche Pharmaceuticals, 2, Sanofi-Aventis Pharmaceutical, 2, CSL Berhing, 2, Intermune, 2, Bayer, 5; **S. Nathan**, Actelion Pharmaceuticals US, Bayer, Boerhinger-Ingelheim, Gilead Sciences, InterMune, Novartis, Roche, United Therapeutics, 5, Actelion Pharmaceuticals US, Bayer, Gilead Sciences, United Therapeutics, 8, Actelion Pharmaceuticals US, Bayer, Boerhinger-Ingelheim, Gilead Sciences, InterMune, United Therapeutics, 2; **H. Gillies**, Gilead Sciences, Inc., 1, Gilead Sciences, Inc.,

3; **J. Tislow**, Gilead Sciences, Inc., 1, Gilead Sciences, Inc., 3; **C. Blair**, Gilead Sciences, Inc., 1, Gilead Sciences, Inc., 3.

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Progressive Multifocal Leukoencephalopathy Associated with Biologic Therapy in Rheumatic Diseases: Strengthening Association with Rituximab. Eamonn Molloy[1] and Leonard H. Calabrese[2]. [1]St Vincent University Hospital, Dublin, Ireland, [2]Cleveland Clinic Foundation, Cleveland, OH.

Background/Purpose: Progressive Multifocal Leukoencephalopathy (PML) is a rare and often fatal opportunistic infection recently associated with several biologic therapies. However, ascribing risk to individual therapies has been problematic. A previous study of the aggregate experience of PML reported in association with autoimmune rheumatic diseases (ARD) in the FDA Adverse Event Reporting System (AERS) database, through March 31, 2010 identified 15 cases associated with biologic therapies for rheumatic diseases.

Methods: A Freedom of Information Act request was submitted for all cases of PML and/or JC virus infection within the FDA AERS database, updated through August 27, 2012. MedWatch forms with identified ARD were selected for further analysis. Exclusions included: [1] cases where the ARD was not the primary indication for biologic therapy [2] where another condition was the key underlying factor for PML (e.g. HIV positivity) [3] where PML was classified as unconfirmed. A case was considered as confirmed PML once there was a clear description of compatible clinical and neuroimaging findings AND positive identification of the JC virus by PCR in cerebrospinal fluid AND/OR compatible findings on brain biopsy or autopsy. Relevant data collected included drug treatment and disease association cofactors of PML.

Results: 30 confirmed cases of PML associated with biologic therapy in the setting of ARD were identified (11 SLE, 11 RA, 5 dermato/polymyositis, 3 other). Median age was 53 yrs (range 28–76yrs), 25 were female. Rituximab (RTX) and anti-TNF therapies were the most recently administered biologic therapy in 26 and 4 cases respectively. There were no cases in which abatacept, tocilizumab, belimumab or anakinra was the most recently administered biologic therapy.

PML developed after a median of 2 courses of RTX (range 1–5). The median interval between the first and last infusion of RTX and the development of PML was 15 months (range 1–66) and 5 months (range 0–66), respectively. 4 patients were receiving concomitant cyclophosphamide (CYC), 5 additional patients had previously received CYC. 18/26 were receiving one or more additional immunosuppressive therapies at the time of diagnosis of PML. 7/26 had received an anti-TNF therapy prior to treatment with rituxmab. Two RTX-treated patients had received chemotherapy for malignancy (1 oropharyngeal cancer, 1 MALT lymphoma), 1 had a prior history of breast cancer, 5 additional patients had documented significant lymphopenia.

4 patients developed PML during treatment with anti-TNF therapy, 1 receiving concomitant CYC and 1 treated with CYC prior.

Conclusion: PML is a rare event overall in ARD patients treated with biologic immunosuppressive therapies. The small numbers of cases involved and existence of confounders in many cases precludes definitive attribution of causality. However, the relative paucity of confirmed cases in patients recently treated with anti-TNF therapy, despite their widespread use, suggests that a causal relationship is less likely. In contrast, albeit rare, there is a discordant signal regarding the association between rituximab and PML, requiring continued pharmacovigilance.

Disclosure: E. Molloy, GlaxoSmithKline, 5; **L. H. Calabrese**, Genentech and Biogen IDEC Inc., 5, Pfizer Inc, 5, GlaxoSmithKline, 5.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects: Cardiovascular Disease Risk

Sunday, November 16, 2014, 2:30 PM–4:00 PM

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The Impact of Rheumatoid Arthritis Disease Activity on Cardiovascular Disease Risk: What Is the Role of the Flare? Elena Myasoedova[1], Arun K. Chandran[1], Birkan İlhan[2], Brittny T. Major[1], C. John Michet[1], Eric L. Matteson[1] and Cynthia S. Crowson[1]. [1]Mayo Clinic, Rochester, MN, [2]Marmara University School of Medicine, Istanbul, Turkey.

Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk of cardiovascular disease (CVD). Longitudinal studies assessing the effect of changes of RA activity on CVD risk are lacking. We aimed to examine the impact of RA flare, remission, and cumulative burden of RA severity on CVD in RA.

Methods: In a population-based cohort of patients with RA (age≥30 years; 1987 ACR criteria met in 1988–2007) with no history of CVD we performed a retrospective medical records review of each clinical visit to estimate flare/remission status. RA flare was defined as any worsening of RA activity leading to initiation/change/increase of therapy (OMERACT 9). Remission was defined as the absence of disease activity (i.e. tender joint count [TJC]=0 + swollen joint count [SJC]=0 + ESR<10 mm/hr) (OMERACT 7). The previously validated RA medical Records-Based Index of Severity (RARBIS) and Claims-based Index of RA Severity (CIRAS) were used to estimate RA severity. Data on joint surgeries, erosions, extra-articular manifestations, RA flares, morning stiffness, rheumatoid factor (RF), acute phase reactants, antirheumatic drugs were gathered to calculate RARBIS. Claims data were used to calculate the CIRAS based on the number of rheumatology visits, rehabilitation visits; tests for inflammatory markers, RF, platelet counts, chemistry panels. The comparison cohort included age- and sex-matched non-RA subjects without CVD from the same underlying population. Data on CVD risk factors and incident CVD (i.e. myocardial infarction, cardiovascular death, angina, heart failure, stroke, intermittent claudication) were collected. All subjects were followed until death, migration or 07/01/2012. The association of RA activity/severity measures with CVD was examined using Cox models with time-dependent covariates, adjusting for age, sex, calendar year of RA, CVD risk factors and antirheumatic drug use.

Results: The study included 525 RA patients and 524 non-RA subjects (mean age 54.5 yrs; 71% female in both groups). During the mean follow-up of 10.3 years in RA cohort and 8.8 years in the non-RA cohort, 129 RA patients and 77 non-RA subjects developed CVD. There was a significant increase in CVD risk in RA per each acute flare vs remission (hazard ratio [HR] 1.07 per 6-week flare; 95% confidence interval [CI] 1.01–1.15). The CVD risk for RA patients during remission was not significantly different from the non-RA subjects adjusting for age, sex and calendar year (HR 0.90; 95%CI 0.51–1.59). Increased cumulative moving average of daily RARBIS (HR 1.16, 95%CI 1.03–1.30) and CIRAS (HR 1.38, 95%CI 1.12–1.70) was associated with CVD. RA patients who spent more time in medium and high CIRAS tertiles tended to have higher CVD risk vs those in the lower tertile (HR 1.08, 95%CI 0.98–1.20 and HR 1.18, 95%CI 1.06–1.31, respectively, per 1yr increase).

Conclusion: There was a meaningful 7%-increase in CVD risk with the exposure to each acute flare, but not remission, in RA vs general population highlighting the pivotal role of RA flares in shaping CVD risk in RA. Higher long-term burden of RA severity was associated with significantly increased CVD risk in RA suggesting accrued detrimental impact of RA severity over time.

Disclosure: E. Myasoedova, Roche Pharmaceuticals, 2; **A. K. Chandran**, Roche Pharmaceuticals, 2; **B. İlhan**, None; **B. T. Major**, Roche Pharmaceuticals, 2; **C. J. Michet**, None; **E. L. Matteson**, None; **C. S. Crowson**, Roche Pharmaceuticals, 2.

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Cardiovascular Risk with Nsaids in Rheumatoid Arthritis: An Analysis Using Routinely Collected Data. Fowzia Ibrahim[1], Antigoni Grigoriou[2], Khaldoun Chaabo[2], David L. Scott[2], Sophia Steer[2] and James Galloway[2]. [1]King's College London, Department of Rheumatology, London, United Kingdom, [2]King's College Hospital, Department of Rheumatology, London, London, United Kingdom.

Background/Purpose: Atherosclerotic disease increases the morbidity and mortality in Rheumatoid Arthritis (RA). NSAIDs are associated with Cardiovascular (CV) risk in the general population. Data from RA cohorts are limited, but some evidence suggests that the association with CV risk may be less marked when NSAIDs are used in RA. We aimed to assess the extent of prescribing NSAIDs amongst a contemporary RA cohort and to evaluate the relationship between NSAIDs use and hospitalized cardiac events.

Methods: We collected data using the electronic medical record (EMR) at King's College Hospital, United Kingdom, for routine clinical care which contains detailed information on disease as well as drug exposure.

Patients with a consultant diagnosis of RA were classified into regular NSAID users and non-users. Low dose aspirin was not considered an NSAID. Cox-II inhibitors were combined with NSAIDs for this analysis.

Disease activity was analyzed using the mean DAS over the duration of follow up. Patients entered follow up from either March 2008 (when the EMR current coding system was established) or date of diagnosis. Follow up was

censored at date of CV event or October 2013 whichever occurs first. CV events (hospitalization with myocardial infarction, angina, heart failure, TIA or stroke) were identified using the hospital electronic coding system and subsequently validated by a physician (AG).

Cox proportional hazard modeling was used to compare rates. The potential influence of confounding due to age, disease severity or existing IHD was explored using multivariate regression.

Results: The clinical characteristics of the population are presented in table 1. In total, 1089 patients with RA were under follow up during the time period available for analysis. The characteristics are typical of a UK cohort with RA, with a mean age 55 years, a female predominance (78%) and mean DAS28 score of 4.0 and a moderate level of disability as measured by HAQ (median 1.625). 28% of the cohort were treated for hypertension. The median follow up time in whole cohort was 3.7 years.

In our practice NSAIDs use is not associated with a significantly increased rate of CV events. Inclusion of PRN users did not influence estimates.

Exclusion of naproxen raised adj HR to 1.2 (0.54, 2.45). Naproxen use accounted for 24% of NSAIDs prescriptions.

Conclusion: These data are reassuring about the use of NSAIDs in RA in our practice, as these drugs remain an important adjunct to therapy. This approach to analysis using the EMR opens doors to future research, highlighting the power of routine captured data. Important limitations include unmeasured confounding, challenges of potential misclassification as well as left and right censorship. Awareness of these issues can help drive innovative solutions to make the data more robust for future analyses.

Table 1

Characteristic	All patients n=1089	No NSAIDs n=866	NSAIDs n=223	p value
Age, mean (SD)	55 (16)	55 (16)	53 (15)	0.044
Gender, n (%) female	847 (78)	676 (78)	171 (77)	0.659
Average DAS, mean (SD)	4.0 (1.3)	3.9 (1.3)	4.4 (1.3)	<0.001
Average HAQ, median (IQR)*	1.625 (0.875, 2.125)	n/a	n/a	n/a
Disease duration in years, median (IQR)	7 (4, 11)	6.9 (4, 11)	7.3 (4, 11)	0.874
Methotrexate use, n (%)	614 (56)	491 (57)	123 (55)	0.679
Biologic use, n (%)	132 (12)	107 (12)	25 (11)	0.640
Treated hypertension, n (%)	301 (28)	249 (29)	52 (23)	0.106
Exposure time (person years)	4633	3751	882	
Number of CV events	63	53	10	
Incidence CV events/ 1000 person years (95% CI)	12.1 (9.5, 15.5)	12.6 (9.5, 16.5)	10.0 (4.8, 18.5)	
Unadjusted hazard ratio (95% CI)	n/a	ref	0.77 (0.39, 1.51)	
Adjusted hazard ratio (95% CI)*	n/a	ref	0.78 (0.36, 1.68)	

*Missing data for HAQ present preclude meaningful analysis across cohort

Disclosure: F. Ibrahim, None; **A. Grigoriou**, None; **K. Chaabo**, None; **D. L. Scott**, None; **S. Steer**, None; **J. Galloway**, None.

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Vascular Calcifications on Hand and Wrist Radiographs Are Associated with Cardiovascular Risk Factors, Antigen-Specific Anti-Citrullinated Protein Antibodies, and Mortality in Rheumatoid Arthritis.

E. Blair Solow[1], Fang Yu[2], Geoffrey M. Thiele[3], Jeremy Sokolove[4], William H. Robinson[5], Zachary M. Pruhs[3], Kaleb Michaud[3], Alan R. Erickson[3], Harlan Sayles[3], Gail S. Kerr[6], Angelo L. Gaffo[7], Liron Caplan[8], Lisa A. Davis[8], Grant W. Cannon[9], Andreas M. Reimold[10], Joshua Baker[11], Pascale Schwab[12], Daniel Anderson[3] and Ted R. Mikuls[3]. [1]UT Southwestern Medical Center, Dallas, TX, [2]University of Nebraska Medical Center, Omaha, NE, [3]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [4]VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA, [5]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [6]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [7]Birmingham VA Medical Center and University of Alabama at Birmingham, Birmingham, AL, [8]Denver VAMC and Univ of Colorado School of Medicine, Aurora, CO, [9]Salt Lake City VA and University of Utah, Salt Lake City, UT, [10]Dallas VA and University of Texas Southwestern, Dallas, TX, [11]University of Pennsylvania and Philadelphia VAMC, Philadelphia, PA, [12]Oregon Health & Science University, Portland, OR.

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased mortality due to cardiovascular disease (CVD). Select antigen-specific anti-citrullinated protein antibodies (ACPA) are associated with atherosclerotic burden in RA. Furthermore, citrullinated proteins have been localized in atherosclerotic plaque. Vascular calcifications (VC) may be found incidentally on hand and wrist radiographs in RA. This study examined the relationship of VC with CVD risk factors, ACPA subtypes, and all-cause mortality in RA.

Methods: Hand and wrist radiographs from 906 RA patients were scored for the presence of VC as either "positive" or "negative". Patient characteristics associated with VC were assessed using univariate and multivariable logistic regression. ACPAs were measured using an enzyme-linked immunosorbent assay for second generation anti-cyclic citrullinated peptide (CCP2) antibodies, then 19 distinct ACPA subtypes were measured by a bead-based immunoassay and sorted based on q-values calculated by Significance Analysis of Microarrays (SAM). ACPA associations with VC were further examined using multivariable quantile regression. VC and all-cause mortality were examined using Cox proportional hazards regression.

Results: Ninety-nine (11%) patients demonstrated VC on hand and wrist radiographs (Table 1). In multivariable analyses, factors associated with VC included diabetes (OR 2.85; 95% CI 1.43, 5.66, p=0.003), history of CVD (OR 2.48; 95% CI 1.01, 6.09, p=0.047), prednisone use (OR 1.90; 95% CI 1.25, 2.91, p=0.003), current vs. never smoking (OR 0.06; 95% CI 0.01, 0.23, p=0.001) and former vs. never smoking (OR 0.36; 95% CI 0.27, 0.48, p=0.001). In the ACPA subtype analyses using SAM, antibodies to citrullinated forms of Apolipoprotein E (anti-Cit-ApoE), fibrinogen, and vimentin, but not anti-CCP antibody, were differentially expressed in patients with VC (Table 2). The association of anti-Cit-ApoE with VC remained significant following all multivariate adjustments, as well as adjustment for known CVD. After adjusting for significant covariates and stratifying by age and gender, VC were associated with increased all-cause mortality (HR = 1.41; 95% CI 1.12, 1.78, p=0.004).

Conclusion: In this cohort, ~1 in 10 RA patients had VC on hand and wrist radiographs. VC were associated with traditional CVD risk factors and prednisone use and yielded an independent association with all-cause mortality. ACPA targeting Cit-ApoE were increased among patients with VC. Mechanisms underpinning the association of select ACPA with CVD in RA warrant further investigation.

Table 1 Hazard ratios for association of vascular calcification all-cause mortality (top). Demographics of rheumatoid arthritis subjects with and without radiographic vascular calcifications with unadjusted comparisons (bottom).

	Age-adjusted and sex-stratified univariate hazard ratio (95% CI)	Multivariable hazard ratio* (95% CI)	
Vascular calcifications	1.36 (1.06, 1.74) p = 0.016	1.41 (1.12, 1.78) p = 0.004	
Demographics & Health Behaviors	**Vascular Calcifications Present (n = 99)**	**Vascular Calcifications Absent (n = 807)**	**p-value****
Age, years (SD)	72 (9)	64 (11)	<0.001
Men (%)	96 (97)	725 (90)	0.02
Race			
Caucasian (%)	79 (80)	615 (76)	0.53
African American (%)	13 (13)	142 (18)	
Smoking			
Never (%)	38 (38)	146 (18)	
Former (%)	53 (54)	427 (53)	<0.001
Current (%)	8 (8)	234 (29)	
BMI, kg/m^2 (SD)	27 (5)	28 (5)	0.02
Diabetes (%)	38 (38)	139 (17)	<0.001
Hyperlipidemia (%)	45 (45)	343 (43)	0.58
Cardiovascular disease (%)	43 (43)	164 (20)	<0.001
RA-Related Factors			
Disease duration, years (SD)	16 (13)	13 (11)	0.004
Anti-CCP positive (%)	74 (77)	620 (78)	0.79
RAPID-3 score (SD)	2.9 (1.3)	2.5 (1.4)	0.02
DAS-28 score (SD)	3.9 (1.5)	3.8 (1.5)	0.29
CRP, mg/L (SD)	14 (24)	11 (18)	0.21
Prednisone use (%)	53 (55)	313 (41)	0.01

*Adjusted for age, gender, diabetes, cardiovascular disease, smoking, and prednisone use. CI: confidence intervals, SD: standard deviation, BMI: body mass index; anti-CCP: cyclic citrullinated peptide 2; RAPID-3: routine assessment of patient index data; CRP: C-reactive protein. **T-test or chi-square as indicated, p<0.05 significant.

Table 2 ACPA subtypes generated from SAM analysis followed by multivariable quantile regression* examining ACPA associations with radiographic vascular calcifications in rheumatoid arthritis.

ACPA subtype	Fold Change in ACPA VC+ vs. VC−	q-value (%)	Model 1 p-value	Model 2 p-value	Model 3 p-value	Model 4 p-value
Citrullinated Vimentin	1.35	0	0.031	0.021	0.025	0.084
Citrullinated Fibrinogen	1.30	0	0.41	0.49	0.49	0.60
Citrullinated Apolipoprotein E	1.28	0	0.014	0.013	0.018	0.034

**Model 1*: Unadjusted. *Model 2*: Adjusted for age and gender. *Model 3*: Model 2 plus disease duration, RAPID3, prednisone. *Model 4*: Model 3 plus a history of hypertension, hyperlipidemia, and diabetes, body mass index, C-reactive protein, and smoking status (current, former vs never). ACPA: anti-citrullinated protein antibodies; VC: vascular calcifications; SAM: significance analysis of microarrays.

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Lipid Control and Cardiovascular Risk for Patients with Rheumatoid Arthritis Compared with Matched Non-Rheumatoid Arthritis Patients.

J. An[1], E. Alemao[2], K. Reynolds[3], H. Kawabata[2], D. H. Solomon[4], K. P. Liao[4] and T. C. Cheetham[3]. [1]Western University of Health Sciences, Pomona, CA, [2]Bristol-Myers Squibb, Princeton, NJ, [3]Kaiser Permanente Southern California, Pasadena, CA, [4]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Lipid levels are known to be lower in patients with RA compared with the general population; however, differences in cardiovascular (CV) risk associated with lipid control between patients with RA and non-RA patients remain uncertain. The purpose of this study is to evaluate the association between low-density lipoprotein cholesterol (LDL) control and CV outcomes among RA and matched non-RA populations.

Methods: Between 01/01/2007 and 12/31/2011, adult patients with RA were identified within Kaiser Permanente Southern California. Two age- and sex-matched cohorts were identified as non-RA: 1) 1:4 matched general population, and 2) 1:1 matched osteoarthritis (OA) population. Individuals were followed from their index date until the first CV outcome (myocardial infarction, angina, stroke, transient ischemic attack, intermittent claudication, heart failure or CV disease death), end of enrollment or death from other causes. Univariate and multivariate Cox proportional hazard analyses were conducted for patients treated for dyslipidemia who had ≥1 LDL measurement during the follow-up period. LDL measures closest to the end of follow-up were used to define LDL control (mg/dL) stratified by CV risk.

Results: Cohort 1 consisted of 1522 patients with RA and 6511 matched patients from the general population; Cohort 2 had 1746 patients with RA and 2554 matched patients with OA. Median follow-up was 3.1 years for Cohort 1, and 4.0 years for Cohort 2. Mean (SD) age was 63.5 (10.2) years for both cohorts; there were 71.4% females in Cohort 1 and 75.8% in Cohort 2. In addition to dyslipidemia, 74.2% of patients with RA had hypertension, 40.9% had diabetes, 46.7% were obese, 10.5% were smokers, 41.3% had high CV risk, and 51.3% had medium CV risk. Traditional CV risk factors were higher in RA compared with general (Cohort 1) or OA populations (Cohort 2). Mean (SD) LDL levels (mg/dL) were 96.8 (32.7) for RA, 100.1 (35.1) for the general population, and 99.1 (34.3) for the OA population. The rate of LDL control was 78.7% for both the RA and general populations, and 80.0% for the OA population. Adjusting for age, sex, hypertension, antihypertensive medication use, smoking status, and diabetes, controlled LDL was associated with a 33% reduced CV risk compared with uncontrolled LDL in patients with RA (hazard ratio [HR] [95% CI] = 0.67 [0.46, 0.96] for Cohort 2). Controlled LDL was also associated with a reduced CV risk compared with uncontrolled LDL in the general population (HR = 0.72 [0.55, 0.95]). Similar HR results were found in the OA population; however, the association was not statistically significant (HR = 0.76 [0.53, 1.07]) (Table).

Table. Association between LDL Control and Cardiovascular Events for Patients with Treated Dyslipidemia

Cohort	Cohort 1 RA population N=1522		Cohort 2 RA population N=1746	
RA patients	HR (95% CI)	p-value	HR (95% CI)	p-value
LDL control (vs no control)*	0.72 (0.49, 1.07)	0.104	0.70 (0.49, 1.00)	0.053
LDL control (vs no control)μ	0.68 (0.46, 1.02)	0.060	0.67 (0.46, 0.96)	0.028
	General population N=6511		**Osteoarthritis population N=2554**	
Non-RA patients	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
LDL control (vs no control)*	**0.83 (0.63, 1.09)**	**0.179**	**0.93 (0.65, 1.31)**	**0.659**
LDL control (vs no control)μ	0.72 (0.55, 0.95)	0.021	0.76 (0.53, 1.07)	0.118

* Results from univariate analyses μ Results from multivariate analyses adjusting for age, sex, hypertension, antihypertensive medication use, smoking, diabetes

Conclusion: LDL control was associated with a reduced CV risk in the RA and matched general populations. These results suggest an important role for LDL control in preventing CV events among patients with RA as well as non-RA patients.

Disclosure: J. An, BMS, Genentech, Merck, 2; **E. Alemao**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **K. Reynolds**, None; **H. Kawabata**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **D. H. Solomon**, None; **K. P. Liao**, None; **T. C. Cheetham**, BMS, Gilead, 2.

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Is Rheumatoid Arthritis a Coronary Heart Disease Risk Equivalent, Similar to Diabetes?

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Background/Purpose: Recently cholesterol treatment guidelines recommend that diabetes (DM) should be considered a CVD risk equivalent to a history of coronary heart disease (CHD). Despite the well-recognized increased CVD risk in rheumatoid arthritis (RA) patients, the guidelines do not recommend that RA should be considered a CHD risk equivalent. We compared the incidence of hospitalized acute myocardial infarction (MI) among patients with DM alone, RA alone, both conditions and neither of them.

Methods: Using a mix of private and public health plans claims data from 2006 to 2010 with medical and pharmacy coverage; we identified 4 mutually exclusive cohorts: patients with 1) RA and DM; 2) RA only; 3) DM only; 4) Neither RA nor DM. Patients with prevalent CHD during a baseline period of ≥ 1 year were excluded. Acute MI was defined as ≥ 1 inpatient hospital claim with a discharge ICD-9 code in any position for 410.x (excluding 410.x2) and at least one overnight stay, unless the patient died. We compared the age- and gender-specific incidence rates (IRs) of acute MI across the four cohorts and calculated differences in IRs between select cohorts.

Results: We identified 1,070,212 eligible participants in our study. MI IRs were highest among adults with both RA and DM, followed by those with DM alone, with RA alone, and lowest in those without either condition. Findings were consistent for both sexes and across all age strata (Table). Among women 41 years of age or older, the absolute difference in IRs between the two cohorts peaked at 4.3 cases per 1,000 Person-Years (PYs) among those 71 or older. Among men, the peak difference (4.61 cases per 1,000 PYs) was observed among those 51–60 years of age. We found large increases in MI IR among RA patients if they were also diagnosed with DM, especially among women with the greatest difference (9.3 cases per 1,000 PYs) observed among women 51–60 years of age.

Conclusion: In this analysis, the incidence of MI was consistently lower in patients with RA alone than in those with DM alone, which does not support RA as a CHD risk equivalent. Our findings have important clinical implications in the treatment of hyperlipidemia for RA patients.

Table: Comparison of Age- and Gender-Specific MI Risk between Patients with RA, Diabetes (DM) and Both to Healthy Patients

	Both DM and RA		DM Only		RA Only		Neither DM Nor RA		Risk Difference	
Age group	# Person-Years (PYs)	MI Incidence Rate (IR*)	PYs	MI IR*	PYs	MI IR*	PYs	MI IR*	DM Alone – RA Alone	DM and RA – RA Alone
Female										
41–50	754	5.31	16453	3.95	6138	1.96	73179	0.85	1.99	3.35
51–60	1923	11.96	32431	6.08	10558	2.65	84338	1.64	3.43	9.31
61–70	3400	11.47	61620	8.10	18410	5.81	141474	3.13	2.29	5.66
71–85	4038	18.08	106349	15.95	25474	11.66	300340	8.24	4.29	6.42
Male									0	
41–50	215	4.65	17393	4.37	1522	2.63	63340	1.60	1.74	2.02
51–60	459	4.36	28154	7.71	2583	3.10	70147	2.87	4.61	1.26
61–70	997	11.03	47776	10.09	4257	7.75	107472	4.96	2.34	3.28
71–85	928	20.48	54639	16.93	4898	13.68	159464	10.10	3.25	6.8

*Incidence rate, per 1,000 person-years

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Exercise Is Associated with Protective Cardiovascular Risk Profile Including Increased HDL Particle Number in Patients with Rheumatoid Arthritis. Kevin Byram, Annette Oeser, MacRae F. Linton, Sergio Fazio, C. Michael Stein and Michelle Ormseth. Vanderbilt University, Nashville, TN.

Background/Purpose: Patients with rheumatoid arthritis (RA) have increased cardiovascular risk. In the general population, exercise improves several cardiovascular risk factors, including HDL cholesterol concentrations. Although exercise is known to improve quality of life measures in patients with RA, less is known about its effects on cardiovascular risk factors, particularly lipoprotein particle concentrations, which provide information not always concordant to that of lipoprotein cholesterol concentrations. Therefore, we examined the hypothesis that increased exercise is associated with beneficial effects on cardiovascular risk factors, including HDL particle concentration.

Methods: Patient-reported exercise outside of daily activities was quantified as metabolic equivalents measured in minutes per week (METmin/week), according to the 2011 Compendium of Physical Activities, in 165 patients with RA. Hypertension was defined as current use of antihypertensive agents or systolic blood pressure ≥140 mmHg and/or a diastolic pressure ≥90 mmHg. Insulin resistance was measured by the homeostasis model assessment of insulin resistance (HOMA). Standard lipid profiles were measured by our diagnostic clinical laboratory, whereas HDL and LDL particle concentrations were determined by nuclear magnetic resonance spectroscopy (LipoScience). The relationship between METmin/week and cardiovascular risk factors was assessed with Spearman correlation and with linear and logistic regression with adjustment for age, race and sex.

Results: The mean ± standard deviation [range] of exercise was 311 ± 786 METmin/week [0 – 7200 METmin/week]. Exercise was inversely associated with heart rate (P=0.02), waist-hip ratio (P=0.02), and systolic blood pressure (0.03), but not with the degree of insulin resistance (HOMA) or BMI. We found no significant association between exercise and LDL or HDL cholesterol concentrations. Exercise was positively associated with the concentration of both total and small HDL particles (P=0.003 and P=0.001, respectively), but not with LDL particle concentrations (Table). Those who exercised had 2.6 μmol/L greater HDL particle concentration (P=0.002) and 2.8 μmol/L greater small HDL particle concentration (P=0.001), after adjustment for age, race and sex.

Conclusion: The amount of self-reported exercise in patients with RA was independently associated with beneficial changes in several cardiovascular risk factors including heart rate, waist-hip ratio, systolic blood pressure and HDL particle concentration.

Table: Relationship between METmin/week and cardiovascular risk factors in patients with RA

	Spearman rho	P	Adjusted P value
Heart rate, bpm	−0.197	0.011	0.022
Systolic BP, mm Hg	−0.110	0.161	0.027
Diastolic BP, mmHg	−0.076	0.331	0.255
Hypertension, diagnosis	–	–	0.508
Waist circumference, cm	−0.182	0.022	0.019
Waist-hip ratio	−0.154	0.053	0.022
BMI, kg/m^2	−0.105	0.179	0.231
HOMA, units	−0.117	0.023	0.143
Total-Cholesterol, mg/dl	−0.020	0.800	0.741
HDL-Cholesterol, mg/dl	−0.028	0.725	0.690
LDL-Cholesterol, mg/dl	−0.001	0.989	0.938
Triglycerides, mg/dl	−0.026	0.744	0.557
HDL particle concentration, μmol/L	0.174	0.026	0.003
HDL small particle concentration, μmol/L	0.263	0.001	0.001
HDL large particle concentration, μmol/L	−0.086	0.275	0.274
LDL total particle concentration, μmol/L	0.020	0.804	0.793
LDL small particle concentration, μmol/L	0.085	0.280	0.439
LDL large particle concentration, μmol/L	−0.107	0.174	0.258

Disclosure: K. Byram, None; **A. Oeser**, None; **M. F. Linton**, None; **S. Fazio**, None; **C. M. Stein**, None; **M. Ormseth**, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy I: Safety of Biologics and Small Molecules in Rheumatoid Arthritis - Malignancy and Infection

Sunday, November 16, 2014, 2:30 PM–4:00 PM

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Frequency of Significant Infection in Patients with RA Following Initiation of Rituximab with up to 5 Years of Follow-up in a US Observational Study. Kenneth G. Saag[1], Kevin L. Winthrop[2], D. E. Furst[3], Kimberly Alexander[4], Angelika Jahreis[5], Carol Chung[6] and Kurt Oelke[7]. [1]The University of Alabama at Birmingham, Birmingham, AL, [2]Oregon Health & Science University, Portland, OR, [3]University of California at Los Angeles, Los Angeles, CA, [4]Genentech, Inc., South San Francisco, CA, [5]Genentech, South San Francisco, CA, [6]Genentech, Inc, South San Francisco, CA, [7]Rheumatic Disease Center, Glendale, WI.

Background/Purpose: Rituximab (RTX) is an approved treatment for rheumatoid arthritis (RA) in patients (pts) with an inadequate response to anti–TNF therapy (aTNF-IR). Long-term infection risk data of RTX use in real-world settings are limited. The objective of this study was to describe the frequency of significant infections in pts with RA initiating RTX in the US.

Methods: SUNSTONE was a prospective observational cohort study designed to evaluate the safety of RTX in TNF-IR RA pts in a real-world setting. Pts were evaluated and treated according to their physicians' standard practices and followed at visits every 6 months. Pts were followed for 5 years (regardless of RTX discontinuation or start of another biologic DMARD), until death, withdrawal of consent or loss to follow-up. Significant infections were defined as infections that meet FDA serious AE criteria or require IV antibiotics. For calculation of incidence rates (IRs), pts were censored at the time of first event, switch to another biologic DMARD, death, withdrawal of consent or loss to follow-up. IRs by year after RTX initiation and by RTX course are described. Course was defined as 2 × 1000-mg infusions separated by ≤21 days. Pts not treated according to this regimen were excluded from the course analysis. Among pts who switched to another biologic DMARD during follow-up, the IRs of significant infection before and after switch were also calculated. IR calculations after switch were censored at the time of first event, death, withdrawal of consent or loss to follow-up. IRs per 100 pt-yrs (PY) are reported.

Results: Overall, 938 pts (3778 PY) received RTX (82% F; median age, 58 y; median disease duration, 9 y; 72% RF+). Mean duration of follow-up was 4 y and mean number of RTX courses was 4; however, not all pts were treated following the labeled dose regimen. Four pts with insufficient information to calculate IRs were excluded. Significant infections were reported in 160 pts (17%), with an IR of 6.4 (95% CI, 5.5 to 7.4). IRs in 1-y increments following RTX initiation were 7.1 (95%CI: 5.5–9.2), 6.5 (95%CI: 4.8–8.7), 8.0 (95%CI: 5.9–10.9), 9.2 (95%CI: 6.6–12.7) and 7.0 (95%CI: 4.7–10.3) in years 0–1, 1–2, 2–3, 3–4, and 4–5, respectively. See table for IR and 95%CI by course; exposure is less than 100PY from Course 7 onward resulting in wide 95%CIs around IR estimates. Among 338 pts who switched to another biologic DMARD, IRs before and after switch were 4.6 (95% CI, 3.1 to 6.7) and 4.5 (95% CI, 3.3 to 6.2), respectively.

Conclusion: Data from SUNSTONE with up to 5 years of follow-up showed that risk of significant infection among pts with refractory RA that were treated with RTX after an inadequate response to an aTNF agent did not increase over time and with multiple courses. In addition, switch from RTX to another biologic DMARD was not associated with an increased risk of significant infection.

	Course 1 N = 859; PY = 676	Course 2 N = 558; PY = 459	Course 3 N = 378; PY = 282	Course 4 N = 281; PY = 186	Course 5 N = 212; PY = 143	Course 6 N = 158; PY = 100	Course 7 N = 115; PY = 73	Course 8 N = 83; PY = 46	Course 9 N = 57; PY = 28
IR/100 PY	7.4	6.1	7.1	4.8	7.7	6.0	1.4	2.2	7.2
95% CI	5.6–9.8	4.2–8.8	4.6–11.0	2.5–9.3	4.3–13.9	2.7–13.4	0.2–9.7	0.3–15.4	1.8–28.8

Disclosure: K. G. Saag, Amgen, 2, Merck Pharmaceuticals, 2, Takeda, 2, Ardea, 2, Abbott Immunology Pharmaceuticals, 5, AbbVie, 5, Amgen, 5, Ardea, 5, BioCryst, 5, Bristol-Myers Squibb, 5, Eli Lilly and Company, 5, Crescendo, 5, Iroko, 5, Merck Pharmaceuticals, 5, Roche Pharmaceuticals, 5, NOV VP Board of Trustees, 6, ACR Board of Directors, 6; **K. L. Winthrop**, Pfizer Inc, 2, Pfizer, UCB, AbbVie, Genentech, 5; **D. E. Furst**, AbbVie, Actelion, Amgen, BMS, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB, 2, AbbVie, Actelion, Amgen, BMS, Cytori, Janssen, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB, 5, AbbVie, Actelion, UCB, 8; **K. Alexander**, Genentech, Inc, 3; **A. Jahreis**, Genentech and Biogen IDEC Inc., 3; **C. Chung**, Genentech, Inc, 3; **K. Oelke**, Abbvie, Amgen, GSK, crescendo biosciences, Pfizer, UCB, BMS, 8.

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The Risk of Cancer with Tumor Necrosis Factor Inhibitors in Patients Concomitantly Exposed to Non-Biological Immunosuppressants Differs According to the Indication. Layla Saliba[1], Guillaume Moulis[2], Malak Aboutaam[3], Grégory Pugnet[2], Vanessa Rousseau[1], Leila Chebane[1], Nadine Petitpain[4], Bernadette Baldin[5], Jean-Louis Montastruc[1] and Haleh Bagheri[1]. [1]Toulouse University Hospital, Clinical Pharmacology Department, University of Toulouse, Toulouse, France, [2]Toulouse University Hospital, Department of Internal Medicine, University of Toulouse, INSERM UMR 1027, Toulouse, France, [3]Reims University Hospital, Pharmacovigilance Regional Center, Reims, France, [4]Nancy University Hospital, Pharmacovigilance Regional Center, Nancy, France, [5]Nice University Hospital, Pharmacovigilance Regional Center, Nice, France.

Background/Purpose: The risk of cancer with TNF-a inhibitor (TNFi) in patients concomitantly exposed to non-biological immunosuppressants (NBIS) is highly debated in RA, AS and psoriasis/PsA. In contrast, it has been suggested that the excess risk of some lymphomas in IBD was due to NBIS exposure and not to add-on TNFi. The primary objective of this study was to detect a signal of an increased risk of cancer in patients treated with TNFi and NBIS compared with NBIS alone for these diseases. The secondary objective was to compare this risk between the different TNFi.

Methods: We conducted a disproportionality analysis (case/non-case study) in the French National PharmacoVigilance Database. Study population was all the reports of serious adverse drug reactions from 2000 to 2010 in patients treated with NBIS for labeled indications of TNFi. Cases were all the reports of cancer that occurred after a minimal exposure of three months to NBIS. Non-cases were all the other reports. We searched for exposure to TNFi in cases and non-cases, leading to Reporting Odds Ratio (ROR) calculations. The analyses were stratified on the condition and the type of cancer (blood and solid cancer, non-melanoma skin cancers – NMSCs, melanoma), and were adjusted on the age, the gender, the history of cancer, the type of NBIS and the year of reporting. Sensitivity analyses were carried out to detect event- or drug-related competition biases.

Results: Out of the 1,918 reports meeting the study population definition, 217 were cases (135 solid and 82 blood cancers). RA was the leading indication among the study population (n=1200), followed by IBD (n=422), psoriasis or PsA (n=126), and AS (n=92). Exposure to TNFi was found in 156 (72.7%) cases (infliximab, 48.9%, adalimumab, 28.8% and etanercept, 37.2%) and in 698 (43.0%) non-cases (infliximab, 63.5%, adalimumab, 18.8% and etanercept, 18.8%). A safety signal was found as regards the risk of cancer with exposure to both TNFi and NBIS compared with NBIS alone in RA (ROR: 5.43, 95%CI[3.52–8.38]). The signal was significant for every type of cancer, but was the most important for NMSCs (ROR: 20.17, 95%CI[2.49–163.36]). In contrast, no signal was found in AS, psoriasis/PsA and IBD, whatever the type of cancer. As regards the secondary objective, there was no difference between TNFis. Sensitivity analyses confirmed these results.

Conclusion: This study adds strong argument for an increased risk of cancer, and particularly NMSCs, in RA patients exposed to TNFi in addition to NBIS compared with NBIS alone. The signal seems similar with infliximab, adalimumab and etanercept. In contrast, it suggests that there is no signal in AS, psoriasis/PsA and IBD.

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Rheumatoid Arthritis, Anti-Tumor Necrosis Factor Therapy, and Risk of Squamous Cell and Basal Cell Skin Cancer- a Nationwide Population Based Prospective Cohort Study from Sweden. Pauline Raaschou[1], Julia F Simard[2], Charlotte Asker-Hagelberg[3], Johan Askling[4] and the ARTIS Study group[5]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Stanford School of Medicine, Stanford, CA, [3]Swedish Medical Products Agency, SE-751 03 Uppsala, Sweden, [4]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [5]Karolinska Institutet och Svensk Reumatologisk förening, Solna, Sweden.

Background/Purpose: There is a concern that tumor necrosis factor inhibitors (TNFi) may interplay with tumor biology and increase the risk of cancer, in particular cancer types already associated with states of immune perturbation, such as skin cancers. We therefore investigated the risk of first squamous cell (SCC) and basal cell (BCC) cancers in TNFi-treated rheumatoid arthritis (RA) compared to biologics-naïve RA, and also in biologics-naïve RA compared to the general population, taking several potential confounders into account.

Methods: Through register-linkages, we assembled a cohort of biologics-naïve patients with RA (n=54,450), one cohort of patients with RA starting TNFi-treatment as first biologic 1998–2011 (n=10,974), and a general population comparator cohort (matched 5:1 to the biologics-naïve RA-patients). Individuals with a history of organ transplantation and/or invasive malignancy were excluded. The primary outcome was defined as first in situ or invasive SCC (1998–2011), and first BCC (2004–2011) during follow-up. Hazard ratios (HR) were estimated adjusting for several potential confounders including invasive malignancy during follow-up, use of immuno-suppressive medications and history of non-melanoma skin cancer. We performed a series of sensitivity analyses using different definitions of the study population, risk window, and outcome.

Results: Comparing biologics-naïve RA to the general population, the HR of first in situ or invasive SCC in RA was 2.01 (95% CI 1.80–2.33). Based on 168 vs. 803 first invasive or in situ SCC, the adjusted HR was 1.20 (95% CI 0.96–1.51) comparing TNFi-treated to biologics-naïve RA. The HR of SCC was driven mainly by in situ lesions. Similarly, comparing biologics-naïve RA to the general population, the HR of first BCC was 1.22 (95% CI 1.23–1.34). Based on 169 vs. 1,439 first BCC, the adjusted HR was 1.01 (95% CI 0.85–1.21) comparing TNFi-treated to biologics-naïve RA.

Conclusion: RA (in the absence of TNFi-treatment) was associated with a doubled risk of SCC. TNFi-treatment was associated with a further 20% increase in the risk of in situ, but not invasive SCC. For BCC, RA (in the absence of TNFi treatment) was a much weaker risk factor, and TNFi treatment did not increased the risk of BCC. Whilst we cannot exclude surveillance bias as an explanation for our findings regarding SCC, the risks observed call for vigilance of skin lesions in RA, irrespective of treatment.

Table 1. Occurrence and hazard ratios (HR) with 95% confidence intervals (CI), of squamous cell cancer (SCC) in 10,974 TNFi-treated, compared to 41,031biologics-naïve Swedish rheumatoid arthritis (RA)-patients. Occurrence and hazard ratios (HR) with 95% confidence intervals (CI), of basal cell cancer (BCC) in 7,397 TNFi-treated, compared to 38,679 biologics-naïve Swedish RA-patients.

Squamous cell cancer	TNFi (n events/ person-years)	Biologics-naïve RA (n events/ person-years)	HR[1]	HR[2]
First during follow-up	168/66,010	803/221,081	1.24 (1.04–1.47)	1.20 (0.96–1.51)
Invasive	61/66,673	334/223,571	1.12 (0.84–1.50)	0.98 (0.71–1.35)
In situ	126/66,224	580/222,080	1.25 (1.03–1.53)	1.26 (1.02–1.57)
Basal cell cancer				
First during follow-up	169/29,432	1,439/184,441	1.14 (0.97–1.36)	1.01 (0.85–1.21)

HR[1] Stratified for sex, county and civil status. Adjusted for age
HR[2] Stratified for sex, county, civil status, and education level. Adjusted for age, country of birth, co-morbidities during follow-up (chronic obstructive pulmonary disease, psoriatic disease, any benign skin disease, non-melanoma skin cancer, malignant melanoma, all-site cancer, and joint surgery)solid organ transplantation, ever use of cyclosporine, cyclophosphamide or azathioprine.

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Safety of TNF Inhibitor Therapy in Patients Who Have Had a Prior Malignancy. Seung-Hyeon Bae, Doo-Ho Lim, Soo Min Ahn, Seokchan Hong, Yong-Gil Kim, Chang-Keun Lee and Bin Yoo. University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea.

Background/Purpose: A few is known about the effects of biologic therapy in patients with a history of a solid cancer. According to the 2012 updated American College of Rheumatology Recommendations, it is possible to start or resume any biologic agent in patients who have been treated for solid tumor (level of evidence C). But, there is no evidence in patients with history of a solid cancer within the past 5 years because of the lack of studies examining the risk of recurrent cancer in this subgroup. The purpose of this study was to explore the influence of TNF inhibitor (TNFi) therapy in patients with prior cancer treatment within the past 5 years.

Methods: The medical records of all patients (n=859) that received TNFi therapy at a single rheumatology clinic between June 2005 and May 2014 were retrospectively reviewed. Among them, data from patients who had a history of solid cancer treatment before TNFi therapy were collected and patient outcomes were evaluated especially for those who have been treated cancer within the last 5 years.

Results: Of 859 patients who underwent TNFi therapy, 22 patients (1 on infliximab, 11 on etanercept, 7 on adlimumab and 3 on golimumab) had a history of malignancy before initiating TNFi therapy for ankylosing spondylitis (AS) and rheumatoid arthritis (RA) (Table 1). The median AS, RA disease duration was 8 (3.75–12.25) years and median time to TNFi therapy after prior cancer treatment was 62.5 (21.25–140.25) months. Most common site of prior cancer is stomach (36.4%) and followed by thyroid, colorectum, liver, kidney, and breast. There was no recurrence of previous cancer during 40 (7.0–50.75) months of TNFi therapy. Especially, 10 patients started TNFi therapy before 5 years prior cancer treatment (Table 2). All of our 10 cases were limited in an early stage without distant metastasis. When they have been followed for 36 months, recurrence of cancer was not found.

Conclusion: Our results suggest that starting TNFi therapy in patients with history of solid cancer in locally limited stage is safe even less than 5 years after prior cancer treatment.

Table 1 Clinical characteristics of patients with prior cancer history when starting TNFi

Characteristics	Patients (n=22)
Age, mean(range), years	63 (41–81)
Sex, female, n (%)	15 (68.2)
Diagnosis, n (%)	
AS	8 (36.4)
RA	14 (63.6)
Disease duration of AS and RA, median(IQR), years	
Time to TNFi therapy after prior cancer treatment, median(IQR), month	62.5 (21.25–140.25)
TNFi, n (%)	
infliximab	1 (4.5)
etanercept	11 (50)
adalimumab	7 (31.8)
golimumab	3 (13.6)
Site of prior cancer, n (%)	
stomach	8 (36.4)
colon,rectum	2 (9.1)
gallblader	1 (4.5)
liver	2 (9.1)
kidney	2 (9.1)
breast	2 (9.1)
skin (non melanoma)	1 (4.5)
cervix	1 (4.5)
thyroid	3 (13.6)
Duration of TNFi use, median(IQR), month	40.0 (7.0–50.75)
Incidence of cancer recur, n (%)	0 (0)

AS: ankylosing spondylitis, RA: rheumatoid arthritis, IQR: interquartile range, TNFi: TNF inhibitor

Table 2. Clinical characteristics of 10 patients who starting TNFi less than 5 years after prior cancer treatment

Age,years/ sex	Diagnosis	Site of prior cancer	Type/staging	Treatment	Time to TNFi therapy after prior cancer treatment, month	TNF inhibitor	Duration of TNFi use, month	Cancer recur
60/F	RA	liver	HCC T1N0M0	surgical resection	1	A	75	No
41/F	RA	stomach	MALToma low grade	H.pyrori eradication	42	A	64	No
73/F	RA	thyroid	PTC T3N0M0	surgical resection, RAI	8	G	7	No
78/F	RA	skin	BCC	surgical resection	2	E	45	No
44/M	AS	stomach	AGC T2N0M0	surgical resection, adjuvant chemo	22	E	213	No
62/F	AS	kidney	RCC T1N0M0	surgical resection	47	E	56	No
72/M	RA	stomach	AGC (?)	surgical resection	47	E	7	No
51/M	AS	stomach	AGC T2N1M0	surgical resection	19	A	27	No
67/F	RA	thyroid	PTC T1N0M0	surgical resection, RAI	18	I	7	No
63/F	AS	colon	colon cancer T2N1M0	surgical resection, adjuvant chemo	36	G	6	No

TNFi: TNF inhibitor, RA: rheumatoid arthritis, AS: ankylosing spondylitis, HCC: hepatocelluar carcinoma MALToma: extranodal marginal zone B cell lymphoma, PTC: papillary thyroid cancer, BCC: basal cell carcinoma AGC: andvanced gastric cancer, RCC: renal cell carcinoma, RAI: radioactive iodine, chemo: chemotherapy A: adalimumab, E: etanercept, G: golimumab, I: infliximab

Disclosure: S. H. Bae, None; **D. H. Lim**, None; **S. M. Ahn**, None; **S. Hong**, None; **Y. G. Kim**, None; **C. K. Lee**, None; **B. Yoo**, None.

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Malignant Progression of Precancerous Lesions of the Uterine Cervix Following DMARD Therapy in Female Arthritis Patients. René Cordtz[1], Lene Mellemkjær[2], Bente Glintborg[1], Merete Lund Hetland[3] and Lene Dreyer[1]. [1]Copenhagen University Hospital Gentofte, Hellerup, Denmark, [2]The Danish Cancer Society, Copenhagen, Denmark, [3]Copenhagen University Hospital Glostrup. On behalf of all departments of Rheumatology in Denmark., Glostrup, Denmark.

Background/Purpose: Recent studies have found that a high proportion of female rheumatoid arthritis (RA) patients are chronic carriers of high-risk HPV-strains and that these patients are at increased risk of high-grade cervical dysplasia (CD) and cervical cancer. There are uncertainties regarding the safe use of biological DMARDs (bDMARDs) in arthritis patients with premalignant conditions. The aim of the present study was to investigate the occurrence of premalignant lesions of the uterine cervix progressing to a more malignant stage or developing another HPV associated cancer in female RA, ankylosing spondylitis (AS) and psoriatic arthritis (PsA) patients treated with bDMARDs or conventional synthetic DMARDs (csDMARDs).

Methods: In this observational study, we used the nationwide Danish DANBIO Registry covering > 90% of rheumatologic patients treated with bDMARDs in routine care and also patients treated with csDMARDs have been registered since 2006. Patient data from RA, AS and PsA patients registered from 2000–2011 was linked with data from The Danish Cancer Registry. We specifically included patients with a history of mild, moderate and severe cervical dysplasias (CD) or carcinoma in situ (CIS) of the cervix, including both CD/CIS diagnosed before or after DANBIO entry. Patients were followed up for a cancer diagnosis or progression of the premalignant grading of the lesion from the date of diagnosis of CD/CIS of the cervix or first registration in DANBIO, whichever came latest. End of follow-up was date of diagnosis with cervical cancer or other HPV-associated cancer (vulvar, vaginal, anal or oropharyngeal cancer), other cancer diagnosis, death or end of 2011, whichever came first.

Results: We identified 905 arthritis patients with a history of CD or CIS. Of these, 806 were diagnosed with CD/CIS prior to DANBIO entry, while the remaining 99 were diagnosed during their time registered in DANBIO. Overall, 356 had ever been exposed to bDMARDs and 673 to csDMARDs of which 124 patients switched from csDMARD to bDMARD therapy and therefore contributed with person-years of observation in both csDMARD and bDMARD groups. The table shows the number of arthritis patients registered in DANBIO with a history of CD/CIS and characteristics of the RA patients. Only 1 of the 356 bDMARD exposed patients experienced malignant progression from CD to CIS of the cervix. None were diagnosed with cervical cancer or any other HPV-related cancer after DMARD treatment initiation during 2740 person years of observation.

Conclusion: Our findings suggest that DMARD – and bDMARD treatment in particular – has limited harmful effects on precancerous lesions of the uterine cervix in female arthritis patients, but more patients and longer follow-up are required to confirm these findings.

Table: Number of arthritis patients in DANBIO with a diagnosis of cervical dysplasia (CD) or carcinoma in situ of the cervix (CIS) and occurrence of malignant progression. Characteristics of RA patients at first registration according to ever biological DMARD (bDMARD) or conventional synthetic DMARD (csDMARD) exposure, respectively.[#]

		Treatment							
		bDMARD*				csDMARD			
		Total	CIS	CD	Unspecified[§]	Total	CIS	CD	Unspecified[§]
Rheumatologic diagnosis and No. of patients.	All	356	99	211	46	673	170	422	81
	RA	245	77	129	39	499	143	288	68
	AS	22	5	17	0	22	3	19	0
	PsA	49	11	34	4	92	18	65	9
	Other	40	6	31	3	60	6	50	4
Age at start of follow-up, years		52 (18–85)				53 (20–85)			
Age at diagnosis, years		43 (3–74)				47 (1–81)			
Follow-up time, years		3.3 (0.0–11.3)				1.4 (0.0–8.3)			
Person-years of observation		1409				1331			

No. of patients		
with progression of CD or CIS	1	0
developing HPV-associated malignancy§	0	0
Characteristics of RA patients at start of follow-up#		
No. of IgM RF seropositive %	75%	69%
Disease duration, years	6 (0–48)	4 (0–51)
Proportion with disease duration < 2 years	21 %	25%
Tender Joint Count (0–28)	8 (0–27)	4 (0–28)
Swollen Joint Count (0–28)	4 (0–24)	1 (0–28)
CRP, mg/L	9 (0–142)	6 (0–158)
DAS28-CRP	4.4 (0.0–8.2)	2.7 (0.0–7.8)
HAQ	0.9 (0.0–3.3)	0.5 (0.0–3.0)

#Shown are medians (range) unless otherwise indicated.
* First biological treatment for RA patients: adalimumab 114 patients; etanercept 77; infliximab 119, golimumab 10 and certolizumab 8. Number of patients treated with other bDAMRDs: 1 Abatacept, 6 Anakinra, 9 Rituximab, 4 Tocilizumab, 6 Other.
§A total of 127 patients with precancerous cervical lesions had no specified histopathologic grading in The Danish Cancer Registry.
¤ According to International Agency for Research on Cancer (IARC) monograph on HPV; anal, vulvar, vaginal, oropharyngeal cancers were defined as HPV-associated.

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Tofacitinib, an Oral Janus Kinase Inhibitor, in the Treatment of Rheumatoid Arthritis: Safety and Efficacy in Open-Label, Long-Term Extension up to 6 Years. J. Wollenhaupt[1], J. Silverfield[2], E.B. Lee[3], S.P. Wood[4], K. Terry[4], H. Nakamura[5], K. Kwok[6], A. Anisfeld[6], C. Nduaka[4], R. Riese[4] and L. Wang[4]. [1]Schoen-Klinik Hamburg-Eilbek Teaching Hospital of the University of Hamburg, Hamburg, Germany, [2]Healthpoint Medical Group, Tampa, FL, [3]Seoul National University, Seoul, South Korea, [4]Pfizer Inc, Groton, CT, [5]Pfizer Inc, Tokyo, Japan, [6]Pfizer Inc, New York, NY.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Here we report tofacitinib safety, tolerability, and durability of response through 72 months (mo) in long-term extension (LTE) studies.

Methods: Data were pooled from two open-label studies (NCT00413699 [ongoing; database unlocked as of April 2014 data cut-off] and NCT00661661) of patients (pts) with RA who participated in randomized Phase (P)1, P2, or P3 tofacitinib studies. Treatment was initiated with tofacitinib 5 or 10 mg BID as monotherapy or with background DMARDs; data from both doses ± background DMARDs were pooled. Baseline (BL) was that of P1, P2, or P3 studies for pts enrolling within 14 days of participation; for all other pts, BL was the start of the LTE study. Primary endpoints were adverse events (AEs) and laboratory safety data. Confirmed (2 sequential abnormalities) data are reported for decreased hemoglobin (HgB), absolute neutrophil counts, absolute lymphocyte counts, and increases >50% from BL in creatinine. Secondary endpoints included ACR responses, DAS28-4(ESR), and HAQ-DI. Safety data were included over 84 mo and efficacy data up to Mo 72 (limited pt numbers [n≤29] post-Mo 72 for efficacy).

Results: Overall, 4,858 pts were treated for a mean (maximum) duration of 918 (2,535) days. Total tofacitinib exposure was 12,359 pt-years (pt-y). In total, 1747 pts (36.0%) discontinued (AEs: 866 [17.8%]; insufficient clinical response: 133 [2.7%]). The most commonly reported classes of AEs were infections and infestations (63.4%), musculoskeletal/connective tissue disorders (33.9%), and GI disorders (29.9%). The most frequently reported individual AEs were nasopharyngitis (16.3%), upper respiratory tract infection (14.5%), and urinary tract infection (10.3%). Serious AEs (SAEs) were reported in 19.0% of pts with an incidence rate (IR) of 8.1 per 100 pt-y (95% CI 7.6, 8.7). Serious infection events (SIEs) were reported in 7.2% of pts with an IR of 2.9 per 100 pt-y (95% CI 2.6, 3.2). All malignancies excluding NMSC were reported in 2.4% of pts with an IR 1.0 per 100 pt-y (95% CI 0.8, 1.2). IRs for SAEs, SIEs and malignancies through Mo 84 did not increase compared with previously reported data through Mo 72. [1] Decreased Hgb (>2 g/dL change from BL, or Hgb <8 g/dL) was observed in 5.7% of pts. Increased aminotransferases (>3 × ULN) were observed in 4.7% (ALT) and 2.6% (AST) of pts. Moderate to severe neutropenia (absolute neutrophil count [ANC] 0.5–1.5 × 10^3/mm^3) was reported in 1.2% of pts; there were no cases of ANC <0.5 × 10^3/mm^3. Absolute lymphocyte counts <0.5 × 10^3/mm^3were reported in 1.1% of pts. Increases >50% from BL in creatinine were noted in 3.4% of pts. ACR20, ACR50, and ACR70 response rates for tofacitinib were sustained between Mo 1 (72.7%, 48.7%, and 29.0%, respectively) and Mo 72 (80.8%, 62.8%, and 37.2%, respectively). Mean DAS28-4(ESR) was 6.29 at BL, 3.74 at Mo 1, and 3.32 at Mo 72. Mean HAQ-DI score was 1.42 at BL, 0.81 at Mo 1, and 0.77 at Mo 72.

Conclusion: A consistent safety profile and sustained efficacy through 72 mo was observed in patients with RA receiving tofacitinib at either 5 or 10 mg BID in LTE studies.

Reference:

1. Wollenhaupt J. et al. Arthritis Rheum 2013; 65: S2328.

Disclosure: J. Wollenhaupt, Roche, Chugai Pharma, Pfizer Inc, Abbott, and UCB, 5, Roche, Chugai Pharma, Pfizer Inc, Abbott, and UCB, 8; **J. Silverfield**, Pfizer Inc, 2; **E. B. Lee**, Pfizer Inc, 5; **S. P. Wood**, Pfizer Inc, 1, Pfizer Inc, 3; **K. Terry**, Pfizer Inc, 1, Pfizer Inc, 3; **H. Nakamura**, Pfizer Inc, 1, Pfizer Inc, 3; **K. Kwok**, Pfizer Inc, 1, Pfizer Inc, 3; **A. Anisfeld**, Pfizer Inc, 1, Pfizer Inc, 3; **C. Nduaka**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Riese**, Pfizer Inc, 1, Pfizer Inc, 3; **L. Wang**, Pfizer Inc, 1, Pfizer Inc, 3.

ACR Concurrent Abstract Session

Spondyloarthropathies and Psoriatic Arthritis I - Novel Treatments Axial Spondyloarthritis

Sunday, November 16, 2014, 2:30 PM–4:00 PM

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Targeting Synovial Mast Cells in Spondyloarthritis: A Proof-of-Concept Study with the Tyrosine Kinase Inhibitor Nilotinib. Jacqueline E. Paramarta[1], Maureen C. Turina[1], Tanja F. Heijda[1], Iris C. Blijdorp[2], Troy Noordenbos[1], Nataliya Yeremenko[1] and Dominique L. Baeten[2]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: Immunopathological studies on synovitis recently identified the mast cell as potential novel therapeutic target in spondyloarthritis (SpA).[1] Mast cells can be targeted by inhibiting the signalling of c-Kit, which is one of the targets of the tyrosine kinase inhibitor nilotinib. The aim of this study was to evaluate the immunomodulating and clinical effects of nilotinib in the treatment of SpA.

Methods: 28 patients with active peripheral and/or axial SpA were included in a randomized, double-blind, placebo-controlled clinical trial. Patients were treated 1:1 with nilotinib or placebo for 12 weeks, followed by an open label extension for another 12 weeks. Paired synovial tissue biopsies, serum sampling and assessment of clinical symptoms were performed serially.

Results: In peripheral SpA (n=13) synovial inflammation was markedly reduced after 12 weeks of nilotinib treatment as evidenced by histopathology (decrease in number of infiltrating CD68+ and CD163+ macrophages and mast cells). Compared to placebo the mRNA expression of c-Kit as mast cell marker (p=0.037) and of pro-inflammatory cytokines such as IL-6 (p=0.024) were reduced. The improvement of synovial inflammation was paralleled by a decrease in serum biomarkers of inflammation such as C-reactive protein (CRP) from 9.2 (IQR 1.7–33.1) to 5.2 (IQR 1.7–25.1) mg/L (p=0.024) and calprotectin from 359.9 (IQR 183.3–484.9) to 287.9 (IQR 116.7–457.1) ng/mL (p=0.055). Also clinical parameters such as patient's global assessment of disease activity (week 0: 52 (IQR 43–65) vs week 12: 21 (IQR 0–51) mm; p=0.031) and Ankylosing Spondylitis Disease Activity Score (ASDAS) (week 0: 2.2 (IQR 1.2–3.0) vs week 12: 1.1 (IQR 0.7–2.4); p=0.031) showed improvement upon 12 weeks of nilotinib but not placebo treatment, and this improvement was further augmented at week 24. In sharp contrast to peripheral SpA, neither serum biomarkers of inflammation nor clinical parameters improved upon nilotinib treatment in axial SpA. During the trial one serious adverse event occurred, which was considered unrelated to the study drug. There were no unexpected safety signals in comparison with published large scale data on nilotinib in chronic myeloid leukemia (CML).

Conclusion: This proof-of-concept study supports the concept that mast cells can contribute to synovial inflammation in SpA and that tyrosine kinase inhibition targeting these cells has a biological and clinical immunomodulatory effect in peripheral but not axial SpA. These results support further clinical evaluation of nilotinib in larger clinical trials in pure peripheral SpA, as well as evaluation of other drugs targeting mast cells in SpA.

Reference

[1]Noordenbos T, et al. Interleukin-17-positive mast cells contribute to synovial inflammation in spondylarthritis. Arthritis Rheum 2012;64:99–109.

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Disclosure: J. E. Paramarta, None; **M. C. Turina**, None; **T. F. Heijda**, None; **I. C. Blijdorp**, None; **T. Noordenbos**, None; **N. Yeremenko**, None; **D. L. Baeten**, AbbVie, BMS, Boehringer Ingelheim, Centocor, Janssen, MSD, Novartis, Pfizer, and UCB, 2.

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A Tailored Approach to Reduce Dose of Anti-TNF Drugs Is Equally Effective, but Substantially Less Costly Than Standard Dosing in Patients with Ankylosing Spondylitis over One Year: A Propensity Score-Matched Cohort Study.

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Background/Purpose: To compare effectiveness, safety and costs of standard versus individually tailored reduced doses of anti-TNF drugs in patients with Ankylosing Spondylitis (AS) after achieving low disease activity.

Methods: This was a single center prospective observational study performed within the national biologics registry. The anti-TNF dose tapering strategy was chosen by treating physicians, without pre-specified protocol. We used propensity score (PS) methodology to identify 2 cohorts of patients matched for relevant baseline characteristics (table 1) who were treated with either reduced (n=53) or standard (n=83) doses of TNF inhibitors. One year outcomes and costs of anti-TNF drugs were compared between both PS-matched cohorts.

Results: In the reduced dosing group the median dose of TNF inhibitor corresponded to 0.67, and 0.5 of the standard dose initially, and at 12 months resp., and 21% of patients required return to standard dosing regimen. The mean change per year in BASDAI, CRP, HAQ and BASFI, as well as QALY area under the curve were no different between both groups (table 2). The hazard ratio (95% confidence interval) of reduced versus standard dosing group for relapse and any adverse event was 1.46 (0.66; 3.19), and 0.56 (0.22; 1.44) resp. (Figure 1) Mean difference (95% confidence interval) in cost of anti-TNF drugs was −4214 (−4707; −3701) € per year of treatment in favor of reduced dosing strategy.

Conclusion: In AS patients after reaching low disease activity, a tailored approach to reduce doses of anti-TNF drugs produced similar clinical outcomes at 1 year, but was substantially less costly.

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Table 1 Baseline characteristics

		Standard dosing group n=83	Reduced dosing group n=53	p-value
Female	*n (%)*	19 (22.9%)	13 (24.5%)	0.840
Age (years)	*Mean (SD)*	39.5 (9.3)	41.0 (10.8)	0.585
Weight (kg)	*Mean (SD)*	75.3 (13.5)	75.5 (14.9)	0.927
HLA B27 positive	*n (%)*	76 (91.6%)	48 (90.6%)	0.919
Disease duration prior to the start of anti-TNF therapy (years)	*Mean (SD)*	8.1 (7.0)	9.2 (8.5)	0.582
Duration of anti-TNF therapy (months)	*Mean (SD)*	37.4 (20.0)	34.8 (18.6)	0.443
Peripheral joint involvement	*n (%)*	29 (34.9%)	18 (34.0%)	0.911
CRP (mg/l)	*Mean (SD)*	4.4 (5.6)	4.3 (7.8)	0.713
BASDAI	*Mean (SD)*	1.4 (0.9)	1.4 (1.1)	0.796
HAQ	*Mean (SD)*	0.4 (0.5)	0.4 (0.4)	0.833
BASFI	*Mean (SD)*	1.9 (1.4)	1.8 (1.5)	0.644
Concomitant glucocorticoids	*n (%)*	4 (4.8%)	1 (1.9%)	0.460
Concomitant DMARD	*n (%)*	9 (10.8%)	6 (11.3%)	0.954
Anti-TNF agents	*Etanercept, n (%)*	31 (37.3%)	25 (47.2%)	
	Adalumumab, n (%)	19 (22.9%)	11 (20.8%)	0.515
	Infliximab, n (%)	33 (39.8%)	17 (32.1%)	
First anti-TNF treatment	*n (%)*	68 (81.9%)	46 (86.8%)	0.466

Mann-Whitney U test and unconditional z-pooled test are used when comparing continuous and categorical variables, respectively (Fisherxs exact test is used when comparing anti-TNF agents).

Table 2 Measures of activity/function, quality of life, and costs of anti-TNF therapy over one year of observation

		Standard dosing group n=83	Reduced dosing group n=53	p-value
BASDAI at baseline	*Mean (SD)*	1.4 (1.0)	1.4 (1.1)	0.796
BASDAI at 12 M	*Mean (SD)*	1.9 (1.5)	1.7 (1.3)	0.453
Change in BASDAI (per year)	*Mean (95% CI)*	0.47 (0.18; 0.76)	0.36 (0.01; 0.71)	0.615
Difference of mean change (per year)	*Mean (95% CI)*	*reference*	−0.12 (−0.57; 0.34)	
CRP at baseline	*Mean (SD)*	4.4 (5.9)	4.3 (7.9)	0.713
CRP at 12 M	*Mean (SD)*	7.5 (15.6)	5.4 (7.9)	0.992
Change in CRP (per year)	*Mean (95% CI)*	3.42 (−0.16; 7.01)	2.19 (−2.09; 6.47)	0.663
Difference of mean change (per year)	*Mean (95% CI)*	*reference*	−1.23 (−6.81; 4.35)	
HAQ at baseline	*Mean (SD)*	0.4 (0.4)	0.4 (0.4)	0.833
HAQ at 12 M	*Mean (SD)*	0.4 (0.4)	0.4 (0.5)	0.479
Change in HAQ (per year)	*Mean (95% CI)*	0.07 (0.00; 0.14)	0.08 (−0.01; 0.17)	0.942
Difference of mean change (per year)	*Mean (95% CI)*	*reference*	0.00 (−0.11; 0.12)	
BASFI at baseline	*Mean (SD)*	1.9 (1.7)	1.8 (1.7)	0.644
BASFI at 12 M	*Mean (SD)*	2.1 (1.8)	1.9 (1.7)	0.481
Change in BASFI (per year)	*Mean (95% CI)*	0.07 (−0.21; 0.35)	0.09 (−0.24; 0.43)	0.907
Difference of mean change (per year)	*Mean (95% CI)*	*reference*	0.03 (−0.41; 0.46)	
EQ-5D* utility at baseline	*Mean (SD)*	0.80 (0.09)	0.79 (0.11)	0.667
EQ-5D* utility at 12 months	*Mean (SD)*	0.78 (0.14)	0.78 (0.11)	0.901
QALY area under the curve**	*Mean (SD)*	0.78 (0.12)	0.76 (0.14)	0.436
Annual cost of anti-TNF therapy (€)	*Mean (SD)*	12000 (−)	7784 (2254)	
Incremental effectiveness***	*Mean (95% CI)*	*reference*	−0.020 (−0.057; 0.016)	**<0.001**
Incremental cost (€)***	*Mean (95% CI)*	*reference*	−4214 (4707; −3701)	

Mann-Whitney U test was used when comparing continuous variables. Change (per year) was estimated using linear mixed effects regression model and restricted maximum likelihood method. * EQ-5D utility was derived from BASDAI and BASFI. ** QALY was calculated as area under the curve of linearly interpolated values of EQ-5D utility. ***Incremental cost and effectiveness are differences between groups estimated from 10000 bootstrap samples.

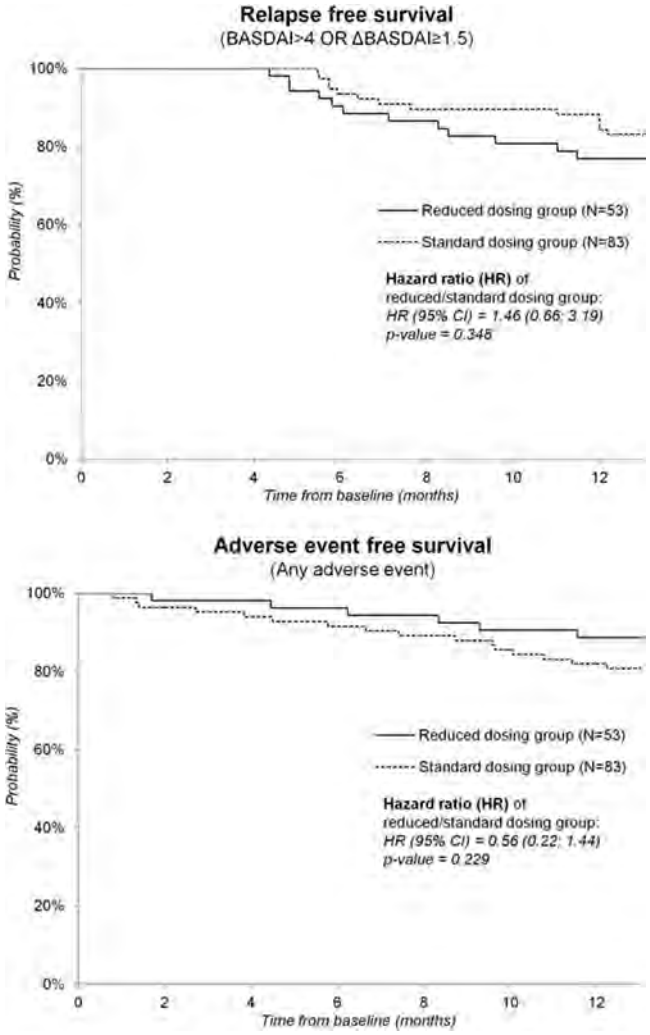

Figure 1

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Safety and Efficacy of Certolizumab Pegol over 96 Weeks in Patients with Axial Spondyloarthritis, Including Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis.

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Background/Purpose: Previous reports of RAPID-axSpA (NCT01087762) demonstrated efficacy and safety of certolizumab pegol (CZP) in patients (pts) with axial spondyloarthritis (axSpA) including pts with ankylosing spondylitis (AS) and pts with non-radiographic (nr-)axSpA to Week (Wk) 48. [1] Here, we report the clinical efficacy and safety of CZP in axSpA from a 96-wk interim data cut of RAPID-axSpA.

Methods: The RAPID-axSpA trial[1] is double-blind and placebo (PBO)-controlled to Wk24, dose-blind to Wk48 and open-label (OL) to Wk204. Pts fulfilled ASAS criteria and had active axSpA. Pts originally randomized to CZP (200mg Q2W or 400mg Q4W, following 400mg loading dose [LD] at Wks 0, 2, 4) continued on their assigned dose in the OL phase; PBO pts entering dose-blind phase were re-randomized to CZP LD followed by CZP 200mg Q2W or CZP 400mg Q4W after Wk24 or, for non-responders, after Wk16. We present efficacy data for all pts originally randomized to CZP (combined dose regimens). Outcome variables assessed included ASAS20/40 and BASDAI50 responses and ASAS PR, ASDAS, ASDAS ID, ASDAS MI, BASDAI, BASFI and BASMI-linear. Data are shown as observed case and with imputation (NRI for categorical measures; LOCF for continuous measures). Safety set consists of all pts treated with ≥1 dose of CZP to Wk96.

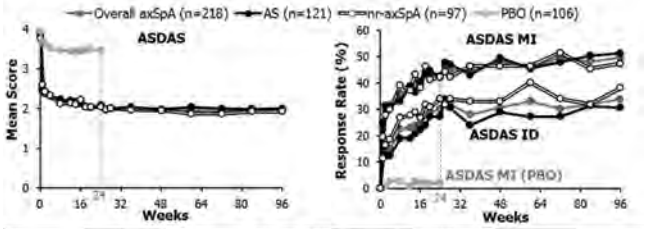
Results: 325 pts were randomized, of whom 218 received CZP from Wk0. Of CZP-randomized pts, 203 (93%) completed to Wk24, 191 (88%) to Wk48 and 174 (80%) to Wk96. The proportion of pts achieving ASAS20/40 and PR responses was maintained from Wk24 through to Wk96 (Figure). Improvements in all ASAS and ASDAS response measures, BASDAI, BASFI and BASMI-linear were maintained to Wk96 (Figure). Similar improvements were seen with both dosing regimens (data not shown) and in both AS and nr-axSpA pts. Rapid clinical improvements were also observed in pts originally randomized to PBO who switched to CZP at Wk16 or Wk24 (data not shown). In the safety set (N=315) total exposure to CZP was 486 pt-yrs. Adverse events (AEs) occurred in 279 pts (88.6%; event rate per 100 pt-yrs [ER/100PY]=360.3). The ER/100PY for serious AEs was 10.9, and for serious infections was 2.7, including 1 confirmed case of active tuberculosis. No deaths or malignancies were reported in the overall 96-wk period.

Conclusion: In RAPID-axSpA, improvements in both CZP dosing regimens observed over 24 wks in clinical efficacy and patient-reported outcomes were sustained throughout the dose-blind and OL study periods to Wk96. Similar sustained improvements were observed in both AS and nr-axSpA subpopulations. The safety profile was in line with that previously reported from the RAPID-axSpA trial, with no new safety signals observed with increased exposure.

Reference:

1. Landewé R. Arthritis Rheum 2013;65(10):S767

Figure: Maintenance of CZP efficacy to Wk96 of the RAPID-axSpA trial



Outcome	Combined CZP 200mg Q2W + 400mg Q4W								
	axSpA (n=218)			AS (n=121)			nr-axSpA (n=97)		
	Wk24 (NRI)	Wk96 (NRI)	Wk96[a] (OC)	Wk24 (NRI)	Wk96 (NRI)	Wk96[b] (OC)	Wk24 (NRI)	Wk96 (NRI)	Wk96[c] (OC)
ASAS20 (%)	67.4	62.8	82.0	66.9	64.5	83.9	68.0	60.8	79.7
ASAS40 (%)	50.9	50.5	65.9	51.2	50.4	65.6	50.5	50.5	66.2
ASAS PR (%)	30.3	28.4	37.1	28.1	24.8	32.3	33.0	33.0	43.2
BASDAI50 (%)	52.3	47.7	60.8	48.8	46.3	57.7	56.7	49.5	64.9
	Baseline (LOCF)	Wk24 (LOCF)	Wk96 (LOCF)	Baseline (LOCF)	Wk24 (LOCF)	Wk96 (LOCF)	Baseline (LOCF)	Wk24 (LOCF)	Wk96 (LOCF)
ASDAS-MI (%)	-	42.2	49.5	-	42.1	51.2	-	42.3	47.4
ASDAS-ID (%)	-	30.3	33.9	-	27.3	30.6	-	34.0	38.1
BASDAI (mean)	6.4	3.3	3.0	6.4	3.4	3.1	6.6	3.3	3.0
BASFI (mean)	5.3	3.0	2.7	5.6	3.3	3.0	5.0	2.6	2.4
BASMI-lin (mean)	3.8	3.2	3.1	4.2	3.6	3.6	3.2	2.6	2.5

[a]n=167; [b]n=93; [c]n=74; Data shown are for Randomised Set, except for PBO data which are shown for Full Analysis Set. LOCF: Last Observation Carried Forward; NRI: Non-Responder Imputation; OC: Observed Case

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Cancer Incidence in TNF Inhibitor Treated Patients with Axial Spondyloarthritis and Psoriatic Arthritis - a Study from the ARTIS and Danbio Registers.

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Background/Purpose: Most studies of the safety profile of TNF inhibitors (TNFi) - in particular in relation to cancer risks - have been performed in patients with rheumatoid arthritis. Today, however, TNFi are widely used in patients with axial spondyloarthritis (AxSpA) and psoriatic arthritis (PsA), i.e., in populations with different age/sex distributions and with potentially different underlying risks for cancer. The aim of this study was to assess risks of overall and site-specific cancers in patients with AxSpA and PsA treated (vs. not) with TNFi, and to compare these risks to the risk in the general population. To do this we used pooled data from two Scandinavian national biologics registers and other population-based data-sources.

Methods: By linking data from the Swedish (ARTIS) and Danish (DANBIO) biologics registers, we assembled a cohort of 8,156 (ARTIS=4,901 and DANBIO=3,255; total person-years=29,011) patients with AxSpA (57%) and PsA (43%) that started a TNFi 2001–2010. From the Swedish National Patient Register we identified a national TNFi-naïve AxSpA/PsA comparator cohort (n=24,058, person-years=112,714), and a Swedish age- and sex matched general population comparator cohort (n=103,380, person-years=535,345). The first invasive cancer for each subject was identified through linkage with the nationwide Swedish and Danish Cancer Registers (2001–2010). Subjects with previous cancers were excluded in all three cohorts. Age- and sex-standardized incidence rates and relative risks (RR) were calculated for cancer overall, and for six specific cancer sites (lung-, colorectal-, female breast-, prostate cancer, malignant melanoma, and lymphoma).

Results: In total we identified 129 cancers among the TNFi treated patients, 744 in the TNFi –naïve cohort, and 3,259 in the general population comparator cohort. TNFi-naïve patients were not at increased cancer risk vs. the general population (RR=1.06), but displayed a lower risk for colorectal cancer (RR=0.70). Based on 129 incident cancers, TNFi treated patients did not have a higher risk of cancer (vs. TNFi-naïve patients), RR=0.80 (95% CI 0.66–0.98). Point estimates below 1 were noted for lung-, colorectal- and prostate cancer though only the latter reached statistical significance (Table).

Conclusion: Based on these nationwide clinical data from Sweden and Denmark, TNFi treatment in patients with AxSpA and PsA was not associated with any significantly increased risks of cancer overall, nor for the six most common cancer types. The tendency towards decreased risks for lung, and prostate cancer following TNFi treatment may reflect selection related to pre-treatment screening. Furthermore, we observed a decreased risk of colorectal cancer in AxSpA/PsA.

Table Age- and sex-adjusted relative risks (RR) of overall and site-specific cancers in patients with axial spondyloarthritis (AxSpA) and psoriatic arthritis (PsA) from ARTIS and DANBIO treated with TNFi (n=8,156, persons-years=29,011) versus a Swedish AxSpA/PsA comparator cohort (n=24,058, person-years=112,714) and a Swedish general population comparator cohort (n=103,340, person-years=535,345) from 2001 to 2010.

	TNFi treated versus TNFi naïve AxSpA and PsA		TNFi treated AxSpA and PsA versus general population		TNFi naïve AxSpA and PsA versus general population	
Cancersite	No. of cancers	RR[1] (95% CI)	No. of cancers	RR[1] (95% CI)	No. of cancers	RR[1] (95% CI)
Overall	129/774	**0.80 (0.66–0.97)**	129/3,259	0.85 (0.71–1.02)	774/3,259	1,06 (0.98–1.14)
Lung	6/42	0.66 (0.32–1.37)	6/225	0.56 (0.24–1.24)	42/225	0.81 (0.70–1.13)

Colorectal	10/60	0.87 (0.42–1.80)	10/364	0.63 (0.36–1.09)	60/364	**0.70 (0.53–0.93)**
Breast	27/129	1.15 (0.75–1.77)	27/509	1.29 (0.93–1.80)	129/509	1.15 (0.95–1.40)
Prostate	17/178	**0.45 (0.27–0.75)**	17/657	**0.53 (0.32–0.86)**	178/657	**1.19 (1.01–1.40)**
Malignant melanoma	10/40	1.16 (0.56–2.43	10/168	1.24 (0.71–2.17)	40/168	1.08 (0.76–1.52)
Lymphoma	8/33	0.99 (0.43–2.08)	8/152	0.96 (0.52–1.76)	33/152	0.99 (0.68–1.44)

[1]Age- and sex-standardized relative risks (RR) with 95% confidence intervals (CI)

Disclosure: J. Askling, AstraZeneca; Pfizer;, 2; **L. Dreyer**, None; **M. Lund Hetland**, None; **L. Jacobsson**, Pfizer, Abbie, Merck, UCB, 2; **L. E. Kristensen**, Pfizer, AbbVie, UCB, and MSD, 5; **B. Glintborg**, None; **ARTIS and DANBIO study groups**, None; **K. Hellgren**, None.

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Golimumab Versus Pamidronate for the Treatment of Axial Spondyloarthropathy (SpA): A 48-Week Randomized Controlled Trial. Chi Chiu Mok, Angela Li, Kar Li Chan and Ling Yin Ho. Tuen Mun Hospital, Hong Kong, Hong Kong.

Background/Purpose: To compare the efficacy of golimumab(GLM) and pamidronate(PAM) in the treatment of SpA.

Methods: Inclusion criteria: (1) patients ≥18 years of age; (2) fulfills the 2009 ASAS classification criteria for axial SpA; (3) Active spondylitis defined by a BASDAI score of ≥4 (with spinal pain score ≥4), despite treatment with NSAIDs for ≥3 months. Exclusion criteria: (1) Hepatitis B/C carriers; (2) Biological treatment in the past year; (3) Major surgery within 8 weeks; (4) Active infection; (5) Pregnancy/lactation; (6) Contraindications to anti-TNF or bisphosphonates. Patients were randomized to receive GLM (50mg subcutaneously monthly) or PAM (60mg intravenously monthly) in a 2:1 ratio on top of existing therapies. Latent tuberculosis was screened and treated in the GLM arm. Assessment for clinical efficacy (BASDAI, BASFI, BASMI, ESR, CRP, ASDAS, VAS pain, global assessment, SF36) was performed at week 0,2,4,8,12,16,20,24,32,40 and 48. MRI of the spine and SIJ was performed at week 0, 24 and 48 and graded by the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system (SIJ score 0–72; spinal score 0–108). The primary efficacy end-point was the proportion of patients who achieved the ASAS20 response at week 48. Intra-group paired data over time were compared by the paired Students' t-test whereas inter-group differences were compared by ANCOVA with adjustment for baseline values.

Results: 30 patients were recruited (83% men; age 33.4±10.9 years; disease duration 4.4±3.4 years) – 20 assigned to GLM and 10 assigned to PAM. Baseline demographic and clinical characteristics were not significant different between the two arms, except for a non-significantly higher mean ASDAS (CRP) (4.07±0.77 vs 3.70±0.65) and SIJ SPARCC (15.8±17.7 vs 7.8±5.93) score in GLM-treated patients. At week 48, a higher proportion of patients achieved ASAS20 (50% vs 20%; p=0.23) and ASAS40 (35% vs 0%; p=0.04) responses in the GLM compared to the PAM group. The ASDAS, BASDAI, BASFI, CRP and ESR levels significantly improved with GLM treatment but not with PAM. Interestingly, patient reported outcomes such as pain score and SF36 improved significantly in both treatment groups. In patients treated with GLM, the SPARCC SIJ (15.8±17.7 to 3.80±5.19; p<0.01) and spine (11.4±10.8 to 3.56±5.65; p<0.01) scores at week 48 decreased significantly compared to baseline. However, there was only a modest but non-significant reduction in the corresponding MRI scores observed in PAM-treated patients. There was no serious adverse events (SAEs) reported and the frequency of any adverse events (AEs) was not significantly different between the two arms. Minor upper respiratory infection (URI) was the commonest AE (30%), followed by dyspepsia (10%) and deranged liver function (10%) in GLM-treated patients. In patients treated with PAM, the commonest AE was post-infusion fever / myalgia / headache (30%), followed by dyspepsia (10%), phlebitis (10%) and minor URI symptoms (10%).

Conclusion: In patients with axial SpA, GLM was more effective than PAM in reducing clinical disease activity and MRI spinal / SIJ inflammation. PAM led to improvement in subjective pain and quality of life but did not have significant effects on MRI inflammation, CRP or ESR.

Disclosure: C. C. Mok, None; **A. Li**, None; **K. L. Chan**, None; **L. Y. Ho**, None.

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Active and Structural Lesions on MRI of the Sacroiliac Joints Predict Major Clinical Responses in Patients with Non-Radiographic Axial Spondyloarthritis Treated with Etanercept. W. P. Maksymowych[1], S. Wichuk[1], H. Jones[2], A. Szumski[2], L. Marshall[2], J. Bukowski[2] and R. G. Lambert[1]. [1]University of Alberta, Edmonton, AB, [2]Pfizer Inc., Collegeville, PA.

Background/Purpose: Previous studies evaluating predictors of major clinical response in patients with non-radiographic axial SpA (nr-axSpA) receiving treatment with anti-TNF agents have been limited by the heterogeneity of patients recruited according to classification criteria and/or disease duration. We aimed to assess the predictive capacity of active and structural lesions on MRI of the sacroiliac joints (SIJ) in a cohort of patients selected according to objective measures of inflammation and limited duration of disease.

Methods: Patients had axial SpA per the Assessment of SpondyloArthritis (ASAS) classification criteria, but did not meet modified NY radiographic criteria. Patients had symptoms for >3 months and <5 years, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and failed ≥2 NSAIDs. Patients were randomly assigned to etanercept 50 mg/week or placebo, then after 12 weeks, all patients received open-label etanercept 50 mg/week. Clinical and health outcomes were assessed throughout the study, and MRI of the SIJ and spine was performed by two central readers at baseline, weeks 12 and 48 to assess bone marrow edema (BME) using the Spondyloarthritis Research Consortium of Canada (SPARCC) score. Additionally, a post-hoc analysis was conducted to score structural lesions using the SPARCC SIJ structural method (SSS), which assesses fat metaplasia, erosion, backfill, and ankylosis on T1-weighted spin echo (T1WSE) MRI. Two independent readers scored baseline and 48 week T1WSE MRI scans from 187 cases blinded to patients and short tau inversion recovery (STIR) MRI scans. Mean scores of the readers were used. Baseline high sensitivity CRP (hsCRP) levels, SPARCC MRI inflammation and SSS erosion scores were analyzed using logistic models of week 48 ASAS40 and ASDAS major improvement (ASDAS MI change ≥2.0), adjusted for treatment.

Results: Mean (SD) age was 32 (7.8) years, 60.5% were male, and mean (SD) duration of disease symptoms was 2.5 (1.8) years. A total of 73% of patients were human leukocyte antigen B27 (HLA-B27) positive and 81% met the ASAS MRI imaging criteria at baseline. Baseline CRP, SPARCC SIJ inflammation, and SSS erosion scores, but not fat metaplasia, backfill, or ankylosis were significant predictors of both ASAS40 and ASDAS MI responses at week 48 in both last observation carried forward and observational data analyses (see table). The higher the baseline value the greater the likelihood of response.

Table: Logistic Models of week 48 ASAS40 or ASDAS MI for each of the baseline SSS components, adjusted for treatment

Week 48 Outcome	Baseline Predictor	Adjusted Odds Ratio (95% CI)	P-value
ASAS40, LOCF	CRP	1.05 (1.02,1.09)	0.0042
ASAS40, LOCF	SSS Erosion Score	1.09 (1.00,1.19)	0.0432
ASAS40, LOCF	SPARCC SIJ	1.06 (1.02,1.09)	0.0006
ASAS40, OC	CRP	1.05 (1.01,1.09	0.0110
ASAS40, OC	SSS Erosion Score	1.09 (1.00,1.19)	0.0412
ASAS40, OC	SPARCC SIJ	1.05 (1.01,1.08)	0.0057
ASDAS MI, LOCF	CRP	1.17 (1.11,1.24)	<0.0001
ASDAS MI, LOCF	SSS Erosion Score	1.11 (1.03,1.21)	0.0099
ASDAS MI, LOCF	SPARCC SIJ	1.07 (1.04,1.10)	<0.0001
ASDAS MI, OC	CRP	1.15 (1.09,1.22)	<0.0001
ASDAS MI, OC	SSS Erosion Score	1.12 (1.03,1.21)	0.0088
ASDAS MI, OC	SPARCC SIJ	1.07 (1.04,1.11)	<0.0001

LOCF=last observation carried forward, OC=observed case, CI=confidence interval

Conclusion: The presence of objective manifestations of active disease as indicated by CRP and inflammatory or erosive lesions on MRI prior to the start of anti-TNF therapy has predictive capacity for major treatment responses.

Disclosure: W. Maksymowych, Pfizer Inc, 2, Pfizer Inc, 5; **S. Wichuk**, None; **H. Jones**, Pfizer Inc, 3, Pfizer Inc, 1; **A. Szumski**, Pfizer Inc, 5; **L. Marshall**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Bukowski**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Lambert**, None.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Animal Models
Sunday, November 16, 2014, 2:30 PM–4:00 PM

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A Pathogenic Role for the Gut Microbiota in Murine Antiphospholipid Syndrome and Lupus. Silvio M. Vieira, Andrew Yu, Michael Hiltesperger, Odelya E. Pagovich, Eleni Tiniakou, William Ruff, John Sterpka and Martin Kriegel. Yale School of Medicine, New Haven, CT.

Background/Purpose: The etiology of lupus-associated antiphospholipid syndrome (APS) is unknown but microbial triggers have been implicated in transient antiphospholipid antibody production in both mice and humans. We hypothesize that a constant trigger of autoreactivity lies within the gut microbiome and tested if persistent reactivity to β_2-glycoprotein I (β_2GPI) and mortality in the spontaneous (NZWxBXSB)F_1 model of lupus-associated APS are sustained by specific members of the gut microbiota.

Methods: (NZWxBXSB)F_1 hybrid male mice were treated orally with combined or single antibiotics (vancomycin, metronidazole, neomycin and ampicillin) targeting different microbial community structures starting at 6 weeks of age. Female TLR7 transgenic C57BL/6 mice were similarly treated with broad-spectrum antibiotics. Sera, urine and fecal pellets were collected longitudinally and analysed for anti-β_2GPI titers, proteinuria from lupus nephritis and eubacterial 16S rDNA load by real-time PCR. H&E slides were prepared from tissues for histologic analysis. Splenocyte proliferation was assessed by [^{3}H]-thymidine incorporation.

Results: Not only broad-spectrum antibiotics but also vancomycin or ampicillin alone lowered anti-β_2GPI antibodies at 4 months of age (n=5 each; p=0.014) and protected mice from deaths due to coronary microthrombi, pulmonary emboli or strokes (n=5 each; p=0.005). Proliferation of splenocytes to the autoantigen (using recombinant β_2GPI) was diminished compared to anti-CD3-induced proliferation (n=8 each; p=0.0012). Proteinuria due to lupus nephritis was also suppressed in microbiota-depleted mice (n=8 each; p=0.026). Furthermore, mortality from systemic lupus-like disease was significantly reduced in lupus-prone TLR7 transgenic C57BL/6 mice treated with antibiotics (n=9–10 each; p=0.0154).

Conclusion: Vancomycin-sensitive gut commensals are necessary for anti-β_2GPI-antibody-induced thrombembolic deaths. Broad-spectrum antibiotics selectively reduced T cell proliferation to β_2GPI but not anti-CD3, suggesting antigen-specific effects of the gut microbiota. These results support that gram-positive members of the gut microbiota are fundamentally involved in the pathogenesis of APS. The gut microbiota modulate also lupus pathogenesis in two spontaneous models, suggesting that not only APS but also SLE is dependent on the gut microbial community composition we are currently defining to identify novel biomarkers and treatment targets.

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Amelioration of Systemic Lupus Erythematosus (SLE) in NZM 2328 Mice By Selectively Blocking Engagement of Two BAFF Receptors. Chaim O. Jacob, Ning Yu and William Stohl. University of Southern California Keck School of Medicine, Los Angeles, CA.

Background/Purpose: BAFF, a potent B cell survival factor, is an established therapeutic target in SLE, with the anti-BAFF antibody, belimumab, being FDA-approved for the treatment of SLE. Nevertheless, large percentages of SLE patients failed to respond to belimumab in the seminal phase-III trials, pointing to an ongoing large unmet therapeutic need. Inhibition of one or more of the individual BAFF receptors (BCMA, TACI, BR3) may, in principle, be more efficacious than global inhibition of BAFF. Indeed, whereas the contribution of BAFF to SLE has been the subject of substantial investigation, the contributions of the individual BAFF receptors to SLE have undergone only limited investigation to date. In the SLE-prone NZM 2328 (NZM) mouse model, NZM mice singly-deficient in any BAFF receptor develop clinical SLE with a time course indistinguishable from that of NZM wild-type (WT) mice, demonstrating sufficient functional redundancy among the BAFF receptors to render any single BAFF receptor dispensable to the development of SLE in these mice. To determine whether elimination of combinations of BAFF receptors could be clinically beneficial, we examined the effect of eliminating discrete pairs of BAFF receptors on the development of disease in NZM mice.

Methods: NZM mice singly-deficient in BCMA, TACI, and BR3 were intercrossed to yield NZM mice deficient two BAFF receptors (NZM.*Br3*$^{-/-}$.*Bcma*$^{-/-}$, NZM.*Br3*$^{-/-}$.*Taci*$^{-/-}$, and NZM.*Bcma*$^{-/-}$.*Taci*$^{-/-}$). These mice were evaluated for BAFF receptor expression and lymphocyte phenotype by flow cytometry, for renal immunopathology by immunofluorescence and histopathology, and for clinical disease by assessment of proteinuria (≥3+ by dipstick) and death.

Results: The only BAFF receptor expressed by NZM.*Br3*$^{-/-}$.*Bcma*$^{-/-}$ mice is TACI; the only BAFF receptor expressed by NZM.*Br3*$^{-/-}$.*Taci*$^{-/-}$ mice is BCMA; and the only BAFF receptor expressed by NZM.*Bcma*$^{-/-}$.*Taci*$^{-/-}$ mice is BR3. All B cell subsets are reduced in NZM.*Br3*$^{-/-}$.*Bcma*$^{-/-}$ and NZM.*Br3*$^{-/-}$.*Taci*$^{-/-}$ mice but are increased in NZM.*Bcma*$^{-/-}$.*Taci*$^{-/-}$ mice. All T cell subsets, other than naive CD4$^+$ cells, are reduced in NZM.*Br3*$^{-/-}$.*Taci*$^{-/-}$ mice but are increased in NZM.*Bcma*$^{-/-}$.*Taci*$^{-/-}$ mice. CD4$^+$ memory cells are reduced in NZM.*Br3*$^{-/-}$.*Bcma*$^{-/-}$ mice. Renal immunopathology and clinical disease are significantly delayed and attenuated in NZM.*Br3*$^{-/-}$.*Bcma*$^{-/-}$ and NZM.*Br3*$^{-/-}$.*Taci*$^{-/-}$ mice but are significantly accelerated in NZM.*Bcma*$^{-/-}$.*Taci*$^{-/-}$ mice (Figure 1).

Conclusion: Elimination of both BR3 and TACI (while retaining BCMA) or both BR3 and BCMA (while retaining TACI) markedly inhibits development of SLE in NZM mice. By extension, selective pharmacologic targeting of BR3 + TACI (while preserving BCMA engagement) or BR3 + BCMA (while preserving TACI engagement) may represent a successful therapeutic approach in human SLE.

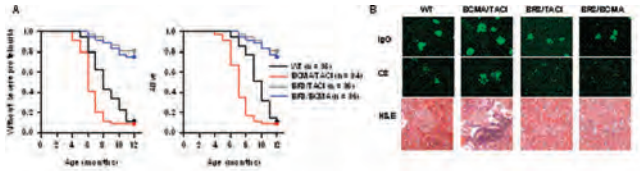

Figure 1. Clinical disease and renal immunopathology among NZM mice deficient in two BAFF receptors. Panel A: WT (n = 35, black lines), BCMA/TACI (n = 34, red lines), BR3/TACI (n = 36, gray lines), and BR3/BCMA (n = 36,blue lines) mice were monitored for 12 months for development of severe proteinuria (left) and survival (right). Data are plotted as the fraction of mice over time that did not develop severe proteinuria (left) or remained alive (right). Panel B: Kidney sections from 6- to 7-month-old NZM WT, BCMA/TACI, BR3/TACI, and BR3/BCMA mice were stained for IgG immunofluorescence (top row) or C3 immunofluorescence (middle row) or with hematoxylin and eosin (H&E) for histologic evaluation. Original magnification 200X.

Disclosure: C. O. Jacob, None; **N. Yu**, None; **W. Stohl**, None.

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ABT-199, a Potent and Selective BCL-2 Inhibitor, Prevents Lupus Nephritis in the Spontaneous NZB/W F1 Mouse Model By Depleting Selective Lymphocyte Populations While Sparing Platelets. Li Chun Wang[1], Stuart Perper[1], Annette Schwartz[1], Christian Goess[1], Liz O'connor[1], Dawna Hartman[1], Candace Graff[1], Andrew Souers[2], Joel Leverson[2], Steven Elmore[2] and Lisa Olson[1]. [1]AbbVie Inc, AbbVie Bioresearch Center, Worcester, MA, [2]AbbVie Inc, North Chicago, IL.

Background/Purpose: Proteins in the BCL-2 family are key regulators of apoptosis, or programmed cell death. Navitoclax, a selective inhibitor of both BCL-2 and BCL-X(L) demonstrated efficacy in the IFN-α induced lupus model in NZB/W F1 mice suggesting that dysregulation of this pathway is operative in lupus disease. However, thrombocytopenia caused by BCL-X(L) inhibition limits the chronic use of this therapeutic agent. We have conducted studies to evaluate a highly potent and orally available BCL-2-selective inhibitor, ABT-199, for efficacy and mechanism of action in the spontaneous NZB/W F1 mouse model.

Methods: 26 week old NZB/W F1 mice were treated daily for 24 weeks with vehicle or ABT-199. Proteinuria and survival data are presented as Kaplan-Meyer survival curves. Changes in lymphocytes and platelets in peripheral blood were assessed by Celldyn 3700 blood analyzer. Renal pathology was evaluated by a board certified pathologist. IgG deposition and changes in leukocyte subsets in the kidney were evaluated by immunohistochemistry. Circulating anti-dsDNA antibody levels were determined using a semi-quantitative ELISA assay. In a separate study NZB/W F1 mice were treated daily with vehicle or ABT-199 at 30mg/kg for 16 weeks, leukocyte subsets in spleen, kidney and bone marrow were analyzed by flow cytometry.

Results: ABT-199 treatment dose-dependently reduced the incidence of severe proteinuria compared to vehicle control and conferred 100% survival at the higher doses in the spontaneous NZB/W F1 lupus model. Treatment with ABT-199 also resulted in attenuated glomerulonephritis, tubular dilatation and IgG deposition in the kidney. ABT-199 treatment resulted in reductions in numbers of B220+, CD3+, F4/80+ and CD138+ cells in the kidneys compared with vehicle-treated mice. Consistent with its BCL-2 selectivity profile, ABT-199 mediated efficacy in NZB/WF1 mice correlated with a dose-dependent reduction of lymphocytes in peripheral blood (45% reduction for ABT-199 11mg/kg vs. vehicle; 70% reduction for ABT-199 100 mg/kg vs. vehicle) with no effect on platelet numbers. ABT-199 also demonstrated a significant reduction in the numbers of splenic T cells (CD4+, CD8+), B cells (transitional 2, germinal center, and mature). Interestingly, other B cell subsets (transitional 1, marginal zone, and B1) were largely unaltered. ABT-199 did not impair early B cell development or the number of CD138+ long-lived plasma cells in the bone marrow. These data were consistent with the unaltered anti-dsDNA titers in these animals.

Conclusion: Treatment of spontaneous lupus in NZB/W F1 mice with the BCL-2 selective inhibitor ABT-199 resulted in preservation of renal function and complete protection against severe proteinuria and mortality. ABT-199 treatment resulted in lymphopenia and a reduction of cell infiltration into the kidney while sparing circulating platelets. Splenic marginal zone B cells, the first line of defense against blood-borne pathogens, were resistant to ABT-199. Taken together, these data underscore the essential role of BCL-2 in the pathogenesis of lupus and support a role for BCL-2 selective inhibition in the treatment of autoimmunity.

Disclosure: L. C. Wang, AbbVie Inc., 3; **S. Perper**, AbbVie Inc., 3; **A. Schwartz**, AbbVie Inc., 3; **C. Goess**, AbbVie Inc., 3; **L. O'connor**, AbbVie Inc., 3; **D. Hartman**, AbbVie Inc., 3; **C. Graff**, AbbVie Inc., 3; **A. Souers**, AbbVie Inc., 3; **J. Leverson**, AbbVie Inc, 3; **S. Elmore**, AbbVie Inc., 3; **L. Olson**, AbbVie Inc., 3.

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TGF-β3-Producing CD4$^+$CD25$^-$LAG3$^+$ Regulatory T Cells Control B Cell Responses. Tomohisa Okamura[1], Kaoru Morita[1], Mariko Inoue[1], Toshihiko Komai[1], Yukiko Iwasaki[1], Shuji Sumitomo[1], Shinichiro Nakachi[1], Hirofumi Shoda[2], Keishi Fujio[2] and Kazuhiko Yamamoto[1]. [1]Graduate School of Medicine, the University of Tokyo, Tokyo, Japan, [2]The University of Tokyo, Tokyo, Japan.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibody production and associated with a wide range of clinical manifestations. Recent case-control association study suggests that polymorphisms in the early growth response gene-2 (*EGR2*), a zinc-finger transcription factor, influence SLE susceptibility in humans. In line with the observation, T-cell-specific Egr-2-deficient mice show lupus-like autoimmune disease. We previously described CD4$^+$CD25$^-$Foxp3$^-$ regulatory T cells (Treg) that characteristically express both lymphocyte activation gene 3 (LAG3, CD223) and Egr2 (hereinafter referred to as 'LAG3$^+$ Treg'). Therefore, we have examined whether LAG3$^+$ Treg suppress the development of follicular helper T cell (T_{FH}) and germinal center B cell (GCB), antibody production, and disease progression in lupus-prone MRL-*Fas*$^{lpr/lpr}$ (MRL/*lpr*) mice.

Methods: B cells from C57BL/6 (B6) mice and helper T (Th) cells from OT-II mice were injected i.v. into Rag1KO mice in combination with or without LAG3$^+$ Treg from B6, Egr2 conditional knockout (CKO) (*Egr2*$^{fl/fl}$ CD4-*Cre*$^+$), or Fas-mutated B6/*lpr* mice. Mice were subsequently immunized with NP-OVA/alum 24 hr after the cell transfer. Mice were re-immunized with NP-OVA/alum 14 days after the first immunization. Serum anti-NP antibody levels were analyzed by ELISA, and splenocytes were analyzed by FACS 7 days after the re-immunization. To examine the therapeutic effects of LAG3$^+$ Treg in lupus-prone mice, 8-week-old MRL/*lpr* mice were randomly assigned to specific treatment groups. Ten-week-old MRL/*lpr* mice in the treatment group were injected i.v. with LAG3$^+$ Treg, CD4$^+$CD25$^+$Treg, or naïve T cells obtained from MRL/+ mice. Mice were sacrificed at 18 weeks of age to examine pathological alterations. Anti-ds DNA antibodies were measured by ELISA.

Results: Transfer of LAG3$^+$ Treg from wild type (WT) mice, but not Egr2 CKO or B6/*lpr* mice, significantly suppressed NP-specific antibody responses and the development of GCB and T_{FH} in Rag1KO mice transferred with B cells and OT-II Th cells. Interestingly, LAG3$^+$ Treg produce high amounts of transforming growth factor-β3 (TGF-β3) in an Egr2- and Fas-dependent manner. Treatment with a TGF-β3 or FasL blocking antibody cancelled the suppressive activity of WT LAG3$^+$ Treg. Adoptive transfer of LAG3$^+$ Treg from control MRL/+ mice significantly suppressed the progression of nephritis and autoantibody production in MRL/*lpr* mice. In contrast, CD4$^+$CD25$^+$ Treg and naïve T cells from MRL/+ mice exhibited no significant therapeutic effect upon transfer to MRL/*lpr* mice. TGF-β3-blockade also abrogated the therapeutic effects of MRL/+ LAG3$^+$ Treg in MRL/*lpr* mice.

Conclusion: These results clarified the molecular basis underlying TGF-β3-producing LAG3$^+$ Treg-mediated B cell regulation, which indicated that LAG3$^+$ Treg may be a suitable target for immune manipulation in autoantibody-mediated autoimmune diseases, including SLE.

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Inhibition of G Protein $\beta\gamma$ Signaling Inhibits Nephritis in Lupus Prone Mice. Teresa Owen, Javier Rangel-Moreno, Jesi To, Bruce Goldman, Alan Smrcka and Jennifer H. Anolik. University of Rochester, Rochester, NY.

Background/Purpose: G protein-coupled receptors (GPCRs), including chemokine receptors on leukocytes, signal through G protein G$\beta\gamma$ subunits. An important target of G$\beta\gamma$ is phosphoinositide 3 kinase γ (PI3Kγ), a major isoform of PI3K whose receptor-dependent activation relies primarily on the G$\beta\gamma$ subunit. We hypothesized that G$\beta\gamma$ inhibition may be an effective treatment for lupus as it will prevent PI3Kγ activation which is upstream of T and B cell survival and the migration and activation of innate immune cells. Here, we evaluated the effects of gallein, a small molecule novel G$\beta\gamma$ inhibitory compound (Lehmann 2008, Mol Pharmacol 73: 410), in lupus prone mice.

Methods: 18 week old NZB/NZW mice were treated daily with 20 mg/kg or 35 mg/kg gallein (intraperitoneal injection) or vehicle (n=8 per group) for 15 weeks. For therapeutic intervention, mice with established disease (26 weeks old) were treated for 4 weeks with gallein at 35 mg/kg. Lymphocytes were enumerated by flow cytometry, auto-reactive antibody secreting cells (ASC) were quantitated by ELISpot, kidney inflammation was evaluated by histology (H&E, immunofluorescence), and renal function was assessed by monitoring changes in proteinuria. To determine the effect of gallein on cell migration, BM neutrophils or Jurkat T cells were stimulated in the presence of fMLP (250nM) or CXCL2 (30 or 100 ng/ml).

Results: In a prevention model, gallein therapy significantly abrogated the progression of proteinuria (35 mg/kg: p=0.0001, 20mg/kg p=0.0116). There was a significant dose dependent reduction in the number of effector T cells (20 mg/kg: p=0.0495, 35 mg/kg: p=0.0001) and central memory T cells (35 mg/kg: p=0.0029) in spleens of lupus prone mice. Mice treated with a high dose of gallein (35 mg/kg) had a significant reduction in the number of T follicular helper cells (p=0.0092) and germinal center B cells (p=0.0411). Although auto-reactive IgG ASC and dsDNA specific ASC were not reduced in the spleen, mice treated with gallein (35 mg/kg) had a reduction in IgG$^+$ and dsDNA$^+$ ASC in the BM (p=0.0029 and 0.0571). Strikingly, both doses of gallein caused a marked reduction in the number of dsDNA$^+$ ASC in the kidneys (20 mg/kg: p=0.0103, 35 mg/kg: p=0.0308). Treated mice also had a significant reduction in glomerular, interstitial inflammation (p=0.01 and 0.03 respectively), perivascular inflammation (35 mg/kg: p<0.0001), and IgG deposition. Treatment of mice with established disease also resulted in a significant reduction in the numbers of IgG$^+$ (p=0.0173) and dsDNA$^+$ASCs (p=0.0031) in the kidneys and reduced proteinuria (p=0.0236). Gallein inhibited the migration of WT murine neutrophils and cultured Jurkat T cells in response to fMLP and CXCL12, respectively. Similarly, in vivo administration of gallein in NZB/NZW mice resulted in a less efficient migratory response of BM isolated neutrophils in response to CXCL2.

Conclusion: These results suggest that G$\beta\gamma$ inhibition with gallein may modulate the generation of PCs in GC reactions as well as alter the kidney inflammatory milieu and PC survival niche in lupus, possibly by influencing the influx and function of inflammatory cells.

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Ultraviolet B Generates Type 1 Interferon and Induces Autoantibody-Mediated Disease in a Mouse Model of Cutaneous Lupus. Clayton Sontheimer and Keith B. Elkon. University of Washington, Seattle, WA.

Background/Purpose: Photosensitivity is a common symptom in patients with systemic lupus erythematosus (SLE) and lupus skin lesions often contain plasmacytoid dendritic cells (pDC). The mechanisms linking ultraviolet (UV) light to inflammation and cutaneous flares is not well understood. While *in vitro* experiments have suggested that UV-induced apoptosis exposes lupus-specific nuclear antigens and immune complex mediated inflammation, this has not been shown *in vivo*. Here, we asked whether, and under what conditions, UVB-induced inflammation could induce Type I interferon (IFN-I) and the roles of pDCs and also autoantibodies in cutaneous lupus.

Methods: Shaved C57BL/6 (B6), IFNAR KO, BDCA2 DTR, and huFcgR2a transgenic mice were irradiated with narrowband UVB at 100 mJ/cm^2/day for 5 consecutive days. To induce interface dermatitis, shaved and depilated mice were subject to 15 strokes of tape stripping using medical tape (3M). Serial punch biopsies (6 mm) were obtained at 3, 24, and 72 hrs following UVB exposure or tape stripping. PDCs were detected in enzyme

digested skin samples by flow cytometry (CD45+, Ly6C+, PDCA1+, CD11c+, Siglec H+). Skin samples were examined for mRNA expression by QPCR of pro-inflammatory cytokines and Interferon Stimulated Genes (ISG). mRNA fold change was calculated by comparison with non-irradiated control mice. In experiments with huFcgR2a Tg mice, mice were irradiated as above but injected i.p. at the time of the final UVB exposure with purified immunoglobulin pooled from human lupus patients and the skin was examined by immunofluorescence for the presence of human IgG.

Results: Whereas tape stripping induced a robust ISG response associated with the presence of pDC in the skin, repeated UVB exposure induced a more modest IFN-I skin response with bimodal peaks at 3 and 72 hrs when compared to control mice ($p<0.05$, $n=20$). UVB-irradiated IFNAR KO mice had increased levels of pro-inflammatory cytokines TNFα and IL-6 at ($p<0.01$ at 3 and 24 hr time points, $n=12–13$) and had increased levels of inflammation by visual scoring suggesting a protective role for IFN-I. Interestingly, pDCs did not appear to be the source of IFN following UVB as pDC-depleted BDCA2 DTR mice maintained moderate expression of ISGs. Immunoglobulin from human lupus patients, but not IVIG, localized to the skin at the dermal/epidermal junction following UVB of FcgR2A transgenic and wild-type mice, but FcgR2a signaling was required for cellular uptake and enhanced Type 1 IFN signaling ($p<0.05$, $n=5–9$).

Conclusion: In the normal host, repeated doses of UVB induce a protective, pDC-independent Type1 IFN response in the skin that attenuates pro-inflammatory signals and limits tissue damage. In contrast, in situations associated with the presence of autoantibodies as occurs in lupus, the antibodies bind to UVB-exposed antigen, deposit in the skin and require Fcgr2a-mediated uptake to produce enhanced expression of IFN-I. This novel FcgR2a mouse model of cutaneous lupus establishes the role of UVB in exposing otherwise sequestered nuclear antigens and in facilitating immune-complex mediated skin disease in lupus.

Disclosure: C. Sontheimer, None; **K. B. Elkon**, None.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Cardiovascular Disease and Pregancy
Sunday, November 16, 2014, 2:30 PM–4:00 PM

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Risk Factors for Changes in Subclinical Atherosclerosis As Measured By Carotid Intima Media Thickness (IMT) and Plaque over 5 Years in Women with Systemic Lupus Erythematosus (SLE). Apinya Lertratanakul[1], Peggy W. Wu[1], Alan Dyer[1], William Pearce[1], Emma Barinas-Mitchell[2], Trina Thompson[2] and Rosalind Ramsey-Goldman[3]. [1]Northwestern University, Chicago, IL, [2]University of Pittsburgh, Pittsburgh, PA, [3]Northwestern University and Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Women with SLE have increased rates of subclinical atherosclerosis. We have investigated which risk factors may be related to the increase in subclinical atherosclerosis, as measured by carotid plaque and IMT in women with SLE (cases) and without SLE (controls), over 5 years.

Methods: Baseline data including demographics and cardiovascular risk factors (CVRF) were collected from 151 cases and 126 controls in the Study of Lupus Vascular and Bone Long-term Endpoints (SOLVABLE). SLE factors measured included the modified American College of Rheumatology/Systemic Lupus International Collaborative Clinics Damage Index (excluding CV outcomes), Systemic Lupus Erythematosus Disease Activity Index 2000, disease duration, complement C3 and C4 levels, and self-reported use of corticosteroids, hydroxychloroquine, and immunosuppressants. Plaque and IMT were measured by B-mode ultrasound at baseline and at a follow-up visit. Plaque progression was defined as any increase in plaque number at follow-up. Logistic and linear regression were used to identify predictors of progression in plaque and increase in IMT, respectively; multivariate models included adjustment for the a priori CV risk factors age, hypertension, and total cholesterol/HDL ratio.

Results: The mean $\pm$ SD follow-up time was 5.36 ± 0.60 years in cases and 5.63 ± 0.66 years in controls. Mean IMT change per year was 0.0037 ± 0.024 in cases and -0.0001 ± 0.029 in controls ($p=0.25$); 71% of cases and 63% of controls had an increase in IMT at follow-up. Of cases, 28% had more plaque at follow-up, compared with 11.9% of controls with a relative risk for plaque progression of 2.34 (95%CI 1.36–4.01) (Table 1). Only in cases, higher fasting glucose ($\beta=0.005$ for glucose higher by one SD, 95%CI 0.0001–0.009) was significantly associated with increase in IMT in adjusted models. In adjusted models, the presence of SLE, higher cumulative and baseline corticosteroid dose were significantly associated with plaque progression in cases (Table 2). No CVRF were associated with either increase in IMT or plaque progression in controls, in the adjusted models.

Conclusion: SLE itself infers a greater risk for subclinical atherosclerosis progression over 5 years in women, as measured by an increase in carotid plaque. Higher baseline and cumulative corticosteroid dose were associated with an increased risk for plaque progression, suggesting that earlier and more aggressive treatment of SLE may be beneficial. No CVRF were associated with plaque progression in controls. Only higher baseline fasting glucose level independently predicted increase in IMT in cases.

Table 1 Plaque Progression at 5-year Follow-up

		Normal, No Change (N(%))	Normal and Progressed (N(%))	Abnormal and Regressed (N(%))	Abnormal, No Change (N(%))	Abnormal with Progression (N(%))	Relative Risk (95% CI)
5-year	Cases (N = 151)	75 (49.7)	20 (13.2)	22 (14.6)*	12 (8.0)	22 (14.6)	2.34 (1.36–4.01)
	Controls (N = 126)	70 (55.6)	6 (4.8)	29 (23.0)**	12 (9.5)	9 (7.1)	

*N = 18 regressed to normal, N = 4 regressed but were still abnormal
**N = 20 regressed to normal, N = 9 regressed but were still abnormal
Relative Risk was calculated as the proportion of cases who progressed compared with the proportion of controls who progressed.

Table 2 Plaque Progression Regressed with Baseline Cardiovascular Risk Factors at 5-year Follow-up

	Unadjusted				Adjusted$^{\delta}$			
	Cases		Controls		Cases		Controls	
	OR$^{\&}$	95% CI	OR$^{\&}$	95% CI	OR$^{\&}$	95% CI	OR$^{\&}$	95% CI
Traditional Risk Factors								
Age	1.77	1.20–2.66	1.95	1.09–3.70	–	–	–	–
Hypertension	2.27	1.10–4.89	2.42	0.75–7.40	–	–	–	–
Total Cholesterol/High-Density Lipoprotein Ratio	1.30	0.93–1.84	1.17	0.67–1.98	–	–	–	–
Waist Circumference	1.57	1.09–2.29	1.32	0.78–2.21	1.33	0.87–20.4	1.19	0.61–1.99
Current Smoking Status	2.91	0.94–9.09	1.98	0.28–9.01	2.32	0.72–1.60	2.52	0.30–11.85
Fasting Glucose	1.94	1.20–3.47	1.45	0.92–2.51	1.53	0.99–2.73	1.27	0.79–2.09
Glomerular Filtration Rate	0.74	0.48–1.12	0.93	0.52–1.59	1.07	0.65–1.79	1.62	0.755–2.24
Lipoprotein (a)	1.29	0.93–1.80	1.33	0.83–2.06	1.20	0.84–1.72	1.21	0.73–1.95
Fibrinogen	1.56	1.08–2.30	1.18	0.64–2.18	1.37	0.90–2.10	1.02	0.54–1.95
Homocysteine	1.52	0.94–2.51	1.26	0.63–2.42	1.23	0.72–2.07	1.09	0.49–2.24
C-Reactive Protein	1.34	0.85–2.43	1.59	1.03–2.62	1.27	0.77–2.14	1.57	0.97–2.84
SLE-Related Factors								
Presence of SLE	2.85	1.54–6.48	–	–	3.10	1.54–6.48	–	–
Modified ACR/SLICC-DI	1.48	1.03–2.15	–	–	1.27	0.84–1.91	–	–
Modified SLEDAI-2K	1.05	0.72–1.49	–	–	1.12	0.75–1.66	–	–
Disease Duration	1.50	1.06–2.15	–	–	1.05	0.96–2.06	–	–
Complement component 3 (C3) (mg/dl)	1.30	0.92–1.87	–	–	1.14	0.71–1.57	–	–
Complement component 4 (C4) (mg/dl)	1.34	0.94–1.94	–	–	1.45	0.77–1.67	–	–
Corticosteroid dose	1.43	0.99–2.06	–	–	1.62	1.08–2.52	–	–
Cumulative Corticosteroid Dose	1.46	1.04–2.10	–	–	1.46	1.02–2.13	–	–
Anti-dsDNA Level	0.94	0.62–1.30	–	–	0.92	0.61–1.29	–	–
Hydroxychloroquine	0.63	0.29–1.42	–	–	0.63	0.27–1.50	–	–
Corticosteroid	1.20	0.58–2.46	–	–	1.47	0.66–3.30	–	–

[?]Adjusted for age, total cholesterol/high-density lipoprotein ratio, and presence of hypertension
Modified SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, excluding complement score
Modified ACR/SLICC-DI: American College of Rheumatology/Systemic Lupus International Collaborative Clinics Damage Index, excluding coronary artery bypass grafting, myocardial infarction, stroke, and angina
[&]Odds ratio, calculated for continuous variables higher by 1 standard deviation

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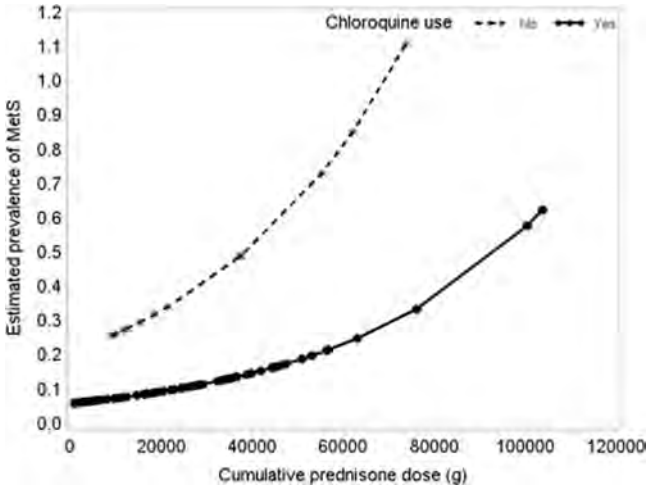
Metabolic Syndrome in Young Premenopausal Female Lupus Patients Is Mainly Influenced By Therapies. Luciana Muniz[1], Rosa M.R. Pereira[1], Thiago Silva[1], Eloisa Bonfá[2] and Eduardo Ferreira Borba[1]. [1]University of São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: A high prevalence of metabolic syndrome (MetS) has been observed in Systemic Lupus Erythematosus (SLE) patients, but there are scarce data about the main factors for MetS in young patients. The aim of the present study was to evaluate MetS frequency in premenopausal SLE patients and to identify factors that could contribute to this condition.

Methods: One hundred and three female SLE patients (fulfilled the revised American College of Rheumatology criteria) with age less than 40 years old were selected. Demographical, clinical, laboratorial and therapeutics data about SLE and MetS were assessed. Thirty-five healthy female age-matched were selected as controls. MetS was defined according to the 2009 Joint Interim Statement. Data analysis (SAS 9.3): t Student's test or Mann-Whitney's test (continuous data) and chi-square test or Fisher's exact test

(categorical variable) was performed as appropriate. Multivariate analysis used the Poisson regression.

Results: A higher frequency of MetS (22.3 *vs.* 5.7%, p=0.03) was observed in SLE group even as higher mean homeostasis model assessment index (HOMA-IR) (1.8 ± 0.9 *vs.* 1.3 ± 1.0, p=0.0008) and mean systematic coronary risk evaluation (SCORE) risk (1.4 ± 0.8 *vs.* 1.1 ± 0.4, p=0.01). Regarding MetS criteria, hypertension (42.7 *vs* 2.9%, p<0.0001) and waist circumference (83.5 *vs* 37.1%, p<0.0001) were most frequently observed in SLE group. The comparison of SLE patients with and without MetS showed no differences in mean disease duration and damage index score but higher SLE Disease Activity Index (SLEDAI) scores (median [range] 2 [0–31] *vs.* 2 [0–14], p=0.006) and more frequently previous (73.9 *vs.* 51.2%, p=0.05) and current renal (34.8 *vs.* 10.0%, p=0.008) disease in MetS-SLE group. MetS-SLE patients had higher current prednisone dose (20 [0–60] *vs.* 5 [0–60] mg/dl, p=0.018), cumulative dose (41.48 ± 27.81 *vs.* 24.7 ± 18.66 g, p=0.023) but no differences in the duration of its use or methylprednisolone pulse use. A higher frequency of chloroquine use was identified in SLE patients without MetS (90.0 vs. 65.2%, p=0.008). In multivariate analysis, only current chloroquine use (prevalence ratio [PR]=0.29; 95% confidence interval [CI] 0.13–0.64) and cumulative prednisone dose (PR=1.02; 95% CI 1.01–1.04) were associated with MetS in SLE. Patients that were not using chloroquine had a 3.48-fold higher risk of MetS and the prevalence of MetS increased by 2% for each increase of one gram of cumulative prednisone dose. The chloroquine use reduced the estimated prevalence of MetS even in patients on steroids and this benefit appears to be greater the higher the cumulative dose of prednisone (figure below):



Conclusion: The prevalence of MetS is high in premenopausal SLE patients and is mainly influenced by lupus therapy with prednisone or chloroquine rather than disease itself. Chloroquine use appears to decrease MetS prevalence even in patients on steroids.

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Association of Coronary Artery Calcification with Brown and White Pericardial Adipose Tissue in SLE. Kelly J. Shields. Lupus Center of Excellence/Allegheny Health Network, Pittsburgh, PA.

Background/Purpose: Women with systemic lupus erythematosus (SLE) have an increased risk of cardiovascular disease (CVD). We have shown that clinically CVD-free women with SLE have an increased volume of descending aortic perivascular adipose tissue, which is also associated with aortic calcification independent of overall adiposity. The relative volumes of brown (BAT) versus white adipose tissue (WAT) may also influence the development of exacerbated CVD. Typically, increased BAT has been associated with a leaner and healthier phenotype.while increased WAT has been associated with an obese-like state. We hypothesized that greater pericardial adipose tissue (PAT) and WAT volumes will be associated with coronary artery calcification (CAC) in clinically CVD-free women with SLE.

Methods: Women participating in the "Heart Effects on Atherosclerosis and Risk of Thrombosis in SLE" (HEARTS) study were clinically CVD-free and diagnosed with SLE for at least 2 years. CAC was measured using electron beam computed tomography (EBCT) and quantified by Agaston scoring. The PAT (epicardial + paracardial adipose tissue) was quantified using commercially available software and attenuation values for overall adipose volume (–190 to –30 HU), WAT (−190 to −75HU), and BAT (−75 to −30 HU). Logistic regression modeling for any CAC was used to evaluate associations. Models were adjusted for CVD risk factors (age, waist-to-hip ratio, menopausal status and hypertension) and circulating inflammatory markers (C3, C4 and CRP).

Results: The study included 156 SLE women and 46% (72/156) had any CAC. SLE women with CAC had higher circulating levels of C3 (p=0.0002), C4 (p=0.001), and CRP (p=0.0001). The WAT to BAT ratio ($r_{Spearman}$=0.35, p=0.006) was significantly correlated with the extent of CAC. In unadjusted logistic regression models PAT (Odds Ratio/OR[95% CI], p-value: 1.02[1.01–1.03], <0.0001), WAT (1.03[1.01–1.04],<0.0001), and BAT (1.05[1.03–1.08],<0.0001) were significantly associated with any CAC. The three volumetric adipose measures maintained significance after adjusting for CVD risk factors (PAT (p=0.006), WAT (p=0.02), and BAT (p=0.002)) and circulating inflammatory markers (PAT (p=0.002), WAT (p=0.007), and BAT (p=0.0005).

Conclusion: Approximately half of the clinically CVD-free SLE women in this study had CAC. Traditional CVD risk factors do not explain the exacerbated CVD risk in the SLE population. We found that PAT and the relative WAT and BAT volumes were independently associated with any CAC even after adjustment for CVD risk factors and circulating inflammatory markers. Small visceral adipose depots surrounding the heart and vasculature may provide localized inflammation promoting CVD.

Disclosure: K. J. Shields, None

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Cardiovascular Events Prior to or Early after Diagnosis of SLE. Murray B. Urowitz[1], Dafna D. Gladman[1], Nicole Anderson[1], Dominique Ibanez[1] and Systemic Lupus International Collaborating Clinics (SLICC)[2]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Toronto, Toronto Western Hospital (Coordinating Center), Toronto, ON.

Background/Purpose: A large multicenter multinational inception cohort was established to study risk factors for atherosclerosis (AS) in SLE. Previous studies have shown a history of cardiovascular events prior to diagnosis of systemic lupus erythematosus (SLE) and rheumatoid arthritis. This study describes the frequency of myocardial infarction (MI) prior to the diagnosis of SLE and within the first 2 years of follow-up.

Methods: An inception cohort of SLE patients from 31 centers in 12 countries has been assembled and followed at yearly intervals according to a standardized protocol between 2000 and 2014. Patients enter the cohort within 15 months of SLE diagnosis (≥4 ACR criteria). MIs were reported and attributed on a specialized vascular event form. MIs were confirmed by one or more of the following: abnormal EKG, typical or atypical symptoms with EKG abnormalities and elevated enzymes (≥2 times ULN), or abnormal stress test, echocardiogram, nuclear scan or angiogram. Descriptive statistics were used.

Results: 31 of 1848 patients that entered the cohort had an MI. Of those, 23 patients had an MI occur prior to SLE diagnosis or within the first 2 years of disease. Of the 23 patients studied 60.3% were female, 82.6% were Caucasian, 4.3% Black, 8.7% Hispanic and 4.3% other. The mean age at SLE diagnosis was 52.5 ± 15.0 years. Of the 23 MIs that occurred, 16 MIs occurred at a mean of 6.1 ± 7.0 years prior to diagnosis and 7 occurred within the first 2 years of follow-up.

Table 1. Cohort Characteristics and CAD risk Factors at Baseline

	Early MI Patients	Non-early MI Patients	p
N	23	1825	
Sex (female)	14 (60.9%)	1626 (89.1%)	<0.0001
Age at SLE Diagnosis (years)	52.5 ± 15.0	34.5 ± 13.2	<0.0001
SLEDAI-2K	3.65 ± 3.54	5.35 ± 5.39	0.03
Anti-dsDNA	7/22 (31.8%)	650/1661 (39.1%)	0.48
Low C3 and C4	8/22 (36.4%)	617/1666 (37.0%)	0.95
HsCRP	3/12 (25%)	141/742 (19.0%)	0.60
ESR	8/14 (57.1%)	519/927 (55.9%)	0.93
On Steroid	19 (82.6%)	1260 (69.1%)	0.16
On Antimalarials	14 (60.9%)	1234 (67.8%)	0.48
On Immunosuppressives	10 (43.5%)	725 (39.8%)	0.72
Family History of MI	4/9 (44.4%)	127/228 (55.7%)	0.51
Hypercholesterolemia	6 (28.6%)	549 (35.7%)	0.50
Hypertension (≥ 140/90)	7 (30.4%)	213 (11.9%)	0.007
BP Diastolic	74.2 ± 12.2	75.2 ± 11.0	0.67

BP Systolic	125.8 ± 18.5	119.6 ± 16.8	0.08
Diabetes	1 (4.6%)	68 (3.8%)	0.85
Metabolic Syndrome	5/19 (26.3%)	238/1647 (14.5%)	0.15
ACL	1.47 ± 6.06	4.23 ± 13.41	0.09

Risk factors associated with early MI in univariate analysis are male sex, older age at diagnosis, lower SLEDAI-2K and hypertension. In multivariate analysis only age (OR=1.07 95% CI (1.04, 1.10)) and male sex (OR=3.2, 95% CI (0.13, 0.78)) remained significant risk factors.

Conclusion: MI prior to or early in diagnosis of SLE may indicate earlier low grade disease activity not diagnosed or a concomitant alternative predisposition to AS and SLE.

Disclosure: M. B. Urowitz, None; **D. D. Gladman**, None; **N. Anderson**, None; **D. Ibanez**, None; **S. L. I. C. C. (SLICC)**, None.

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Heart Rate Variability: An Inflammatory Biomarker in Systemic Lupus Erythematosus. Aikaterini Thanou[1], Stavros Stavrakis[2], John Dyer[2], Stan Kamp[1], Melissa E. Munroe[1], David Albert[3], Judith A. James[1] and Joan T. Merrill[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]AliveCor, Inc., San Francisco, CA.

Background/Purpose: Heart rate variability (HRV) is a marker of vagus nerve activity and can be easily obtained with minimal technical expertise in the outpatient setting, using software calculating the distance between consecutive R waves on the electrocardiogram tracing. Decreased HRV is strongly associated with cardiovascular morbidity and mortality, and measures of HRV have been inversely correlated with inflammatory biomarkers in the general population. The current study evaluates the relationship of HRV with clinical disease activity and cytokine pathways in patients with systemic lupus erythematosus (SLE).

Methods: 58 patients with SLE from the Oklahoma Lupus Cohort were evaluated at two visits with the stipulation that there must be at least mild/moderate disease activity, in the clinician's opinion, at the first visit. Standard of care was rendered to each patient per usual clinic practice. Clinical assessments included the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), the British Isles Lupus Assessment Group (BILAG 2004) index and the Physician Global Assessment (PGA). A 5-minute ECG was obtained at each visit for HRV analysis using the AliveCor iPhone ECG device. Serum cytokine levels, including interleukin 6 (IL-6) and B Lymphocyte Stimulator (BLyS) were measured with an enzyme-linked immunoassay (ELISA). Linear regression analysis and multivariate linear mixed effect models were used.

Results: At baseline, mean SLEDAI was 7.6±0.3, mean cumulative BILAG 2004 index was 10.0±0.6 and mean PGA was 1.4±0.1. Baseline HRV measures were negatively associated with baseline disease activity using the BILAG 2004 index ($p=0.01$), but less consistently with the SLEDAI score ($p=0.60$) and the PGA ($p=0.16$). HRV measures were also negatively associated with baseline IL-6 levels ($p=0.02$). At the follow up visit (median 1 month from the baseline visit), there was a significant decrease in SLEDAI (average decrease −2.3±0.5), BILAG 2004 index (average decrease −3.7±1.0) and PGA (average decrease −0.4±0.1) compared to baseline. Change in HRV measures was negatively associated with change in the BILAG 2004 index ($p=0.03$) and the PGA ($p=0.02$) and less well with change in SLEDAI ($p=0.12$), indicating that an increase in HRV is associated with a favorable change (decrease) in disease activity at follow up. In addition, there was a significant association between the change in HRV measures and improvement in IL-6 ($p=0.04$) and BLyS ($p=0.03$). None of the disease activity indices were correlated with change in IL-6 levels ($p>0.05$ for each); however, the change in BLyS levels was positively associated with change in SLEDAI ($p=0.03$) and BILAG 2004 index ($p=0.02$).

Conclusion: These pilot findings suggest that HRV measures could provide a sensitive marker for lupus disease activity and improvement, and support a role for HRV as an easily measured, non-invasive, in- office procedure. Its relevance to specific clinical or immunologic phenotypes or potential utility as a treat to target endpoint remain to be further explored.

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Specific SLE Disease Manifestations in the Six Months Prior to Conception Predict Similar Manifestations during Pregnancy. Sara K. Tedeschi, Hongshu Guan, Alexander Fine, Bonnie L. Bermas and Karen H. Costenbader. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Active SLE, in particular lupus nephritis, during the six months prior to conception is associated with disease flare during pregnancy. Previous studies, however, have not evaluated how other disease manifestations prior to conception are related to disease activity during pregnancy. We sought to investigate the relationship between SLE organ-specific disease activity in the six months prior to conception and organ-specific disease activity during pregnancy.

Methods: We identified SLE patients with >2 visits to our Lupus Center and ≥1 pregnancy lasting >12 weeks from 1990–2013, who had clinical and lab data available for the six months prior to conception and during pregnancy. All women had confirmed SLE by rheumatologist review for 1997 ACR Criteria for Classification. We collected data on: age, pregnancy outcomes, SLE medication use, history of nephritis, serositis (pleuritis, pericarditis), inflammatory arthritis, skin disease (malar rash, discoid lesions, photosensitivity), antiphospholipid antibody syndrome, hematologic disorder (leukopenia, hemolytic anemia, thrombocytopenia), anti-dsDNA elevation, and low complement, both in the six months preceding and during pregnancy. We analyzed the data using Fisher's exact tests.

Results: Among 1,127 women with SLE, 149 pregnancies occurred in 115 women. Mean age at SLE diagnosis was 23.8 (SD 6.8) years and at conception was 31.1 (SD 5.2) years; average SLE duration prior to pregnancy was 7.8 (SD 5.8) years; 8.7% were diagnosed with SLE during pregnancy. 68.7% were White, 14.8% Hispanic, 9.6% Black, and 7.0% Asian. During pregnancy the most common SLE manifestations were hematologic (15.4%), nephritis (10%), skin (9.4%), arthritis (6.7%), and serositis (4.7%). Activity of each of these SLE manifestations in the six months prior to conception was significantly associated with occurrence of the same manifestation during pregnancy. In contrast, patients without these clinical findings in the six months prior to pregnancy were unlikely to have activity in these organ systems during pregnancy. (Table 1)

Conclusion: Among women with SLE who had any organ system disease activity six months prior to conception, a large proportion had persistent symptoms of the same type during pregnancy. Those patients with quiescent organ-system manifestations six months prior to pregnancy were unlikely to become symptomatic during pregnancy. To our knowledge, this is the first study to reveal that organ-specific SLE manifestations, in addition to nephritis, in the six months prior to conception portend similar disease manifestations during pregnancy.

Table 1. Organ-specific SLE disease activity six months prior to conception and during pregnancy, N=149 pregnancies

	Active 6 months prior		Inactive 6 months prior		
	Active during pregnancy	Inactive during pregnancy	Active during pregnancy	Inactive during pregnancy	p value
Arthritis	n=13		n=136		
	4 (31%)	9 (69%)	6 (4%)	130 (96%)	0.006
Serositis	n=5		n=144		
	2 (40%)	3 (60%)	6 (4%)	138 (96%)	0.024
Skin	n=15		n=134		
	7 (47%)	8 (53%)	7 (5%)	127 (95%)	<0.001
Hematologic	n=17		n=132		
	12 (71%)	5 (29%)	14 (11%)	118 (89%)	<0.001
Nephritis	n=8		n=131		
	7 (88%)	1 (12%)	1 (1%)	130 (99%)	<0.001

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ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis I: Pathways of Inflammation/Injury
Sunday, November 16, 2014, 2:30 PM–4:00 PM

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Protein Phosphatase 5 (PP5) Regulates Methylation Sensitive Gene Expression in CD4+ T Cells. Dipak R. Patel, Gabriela Gorelik and Bruce C. Richardson. University of Michigan, Ann Arbor, MI.

Background/Purpose: CD4+CD28- T cells are enriched in chronic inflammatory diseases like rheumatoid arthritis (RA) and lupus. They are cytotoxic and resistant to apoptosis. Compared to CD28+ cells, CD28- CD4 T cells over-express killer immunoglobulin-like receptors (KIRs) and other pro-

inflammatory molecules. These genes are regulated by DNA methylation, so they are over-expressed by CD4 T cells that are demethylated in vitro. This is a result of decreased signaling through the ERK and JNK pathways and, consequently, decreased activity of the DNA methyltransferase enzymes (DNMTs) responsible for DNA methylation. Protein phosphatase 5 (PP5) is a stress induced regulator of gene expression in multiple signaling pathways, including those involved in aging. It is expressed in CD4+CD28-, but not CD4+CD28+ T cells, and it inhibits both ERK and JNK signaling. We hypothesized that PP5 is over-expressed in CD4+ T cells in patients with RA and lupus, and that over-expressing PP5 in CD4 T cells from healthy donors will induce expression of methylation sensitive genes unique to CD4+CD28- T cells.

Methods: CD4+ T cells were isolated from healthy controls and patients, and PP5 mRNA was measured by RT-PCR. To study the effects of PP5 on gene expression, PBMCs from healthy donors were stimulated with phytohemagglutinin and cultured for 3 days with IL-2. CD4+ T cells were then isolated by negative selection, transfected (Amaxa Nucleofector) with constructs encoding GFP and PP5 or GFP alone, and cultured 24–72 hours. Expression of DNMT1 and methylation sensitive genes was assessed by RT-PCR in sorted CD4+GFP+ T cells. DNMT1 expression was measured 24 hours after transfection, and the other genes were analyzed 72 hours after transfection. Cell surface protein expression was measured by flow cytometry 72 hours after transfection.

Results: Compared to CD4+ T cells from healthy donors, PP5 mRNA is over-expressed in patients with lupus (1.97 fold change $\pm$0.18 SEM, $p=0.03$) and RA (1.6 ± 0.2, $p=0.06$). When transfected into CD4+ T cells from healthy donors, PP5 increased mRNA levels of KIR (2DL4 gene, 2.4 ± 0.7, $n=3$, $p=0.04$), perforin (1.38 ± 0.07 fold, $p=0.03$, $n=3$), CD11a (1.2 ± 0.1 fold, $p=0.047$, $n=5$), and CD70 (10.5 ± 4.1 fold, $p=0.03$, $n=7$). PP5 also increased the percentage of cells expressing surface KIRs ($33\pm7\%$ with control vs. $62\pm7\%$ with PP5, $n=7$, $p<0.01$), CD70 ($18.3\pm7\%$ with control vs. $34\pm10.8\%$ with PP5, $n=3$, $p=0.06$), and CD40L ($15\pm6.1\%$ with control vs. $27.3\pm9\%$ with PP5, $n=3$, $p<0.05$). Finally, PP5 caused a corresponding $20\pm8\%$ decrease ($n=5$, $p=0.02$) in DNMT1 mRNA expression.

Conclusion: CD4+CD28- T cells, which are enriched in lupus and RA, over-express pro-inflammatory methylation sensitive genes. These data demonstrate, for the first time, that PP5 contributes to the regulation of these genes (KIR, perforin, CD70, CD40L, and CD11a) in CD4+ T cells. PP5 is hypothesized to accomplish this by demethylating regulatory elements in the promoters for these genes, and this is currently being tested. PP5 expression is induced by oxidative and replicative stress, so it could provide a mechanistic link between those physiologic stressors and autoimmune disease flares.

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***UBE2L3* genotype Influences Plasma Cell Proliferation in Systemic Lupus Erythematosus By Regulation of NF-κB By the Linear Ubiquitination Assembly Complex.** Myles J. Lewis[1], Simon Vyse[1], Adrian M. Shields[2], Sebastian Boeltz[2], Patrick Gordon[2], Timothy D. Spector[2], Paul J. Lehner[3], Henning Walczak[4] and Timothy J. Vyse[2]. [1]Queen Mary University of London, London, United Kingdom, [2]King's College London, London, United Kingdom, [3]University of Cambridge, Cambridge, United Kingdom, [4]University College London, London, United Kingdom.

Background/Purpose: Genome-wide association studies have identified a strong association between a single risk haplotype of the *UBE2L3*gene and Systemic Lupus Erythematosus (SLE), as well as multiple autoimmune diseases (rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, psoriasis). UBE2L3 is an E2 ubiquitin-conjugating enzyme specific for RING/HECT hybrid or HECT E3 ligases. Linear ubiquitination is a newly described form of ubiquitination, whose only known function is controlling activation of NF-kB, mediated by the linear ubiquitination chain assembly complex (LUBAC).

Methods: *UBE2L3* genotype data from GWAS in SLE was imputed up to 1000 Genomes level. UBE2L3 function was studied *in vitro* using standard molecular biology techniques in HEK293 cells, or *ex vivo* using B cells and/or monocytes from healthy individuals or SLE patients (NF-kB translocation by Imagestream, multicolour flow cytometry of B cell subsets) stratified by *UBE2L3*genotype.

Results: Data from SLE GWAS, imputed to 1000 Genomes level identified rs140490 as the most strongly associated *UBE2L3* SNP, located at -270bp of the promoter region ($P=8.6\times10^{-14}$; OR 1.30, 95%CI: 1.21–1.39). Microarray /western blot studies found that the rs140490 risk allele increased UBE2L3 expression in B cells and monocytes from PBMC. Overexpression of UBE2L3 in combination with LUBAC in HEK293-NF-kB reporter cell line led to a marked upregulation in NF-kB activity, which was abolished by dominant-negative mutant UBE2L3[C86S]. RNAi blockade of UBE2L3 antagonised TNF signalling by inhibiting IκBα processing. *Ex vivo* human B cells and monocytes were isolated from genotyped healthy twins stimulated with CD40L or TNF respectively and NF-kB translocation quantified by Imagestream analysis. rs140490 genotype was correlated with both basal NF-kB activation in healthy human individuals, as well as the sensitivity of NF-kB to CD40 stimulation in B cells and TNF stimulation in monocytes. UBE2L3 expression was 3–4-fold elevated in peripheral blood plasmablasts and plasma cells ($P<0.0001$), with increased UBE2L3 expression in plasma cells from SLE patients compared to controls ($P=0.01$). UBE2L3 expression was significantly elevated in Ki-67^+ B cells consistent with a functional role in B cell proliferation. Consistent with the functional effect of *UBE2L3* on CD40 driven NF-kB activation in human B cells, rs140490 genotype correlated with increasing plasmablast and plasma cell differentiation in SLE patients ($P<0.001$).

Conclusion: Our study is the first to show that the *UBE2L3* risk haplotype exerts a critical rate-limiting effect on TNF and CD40 activation of NF-kB in primary human cells, and that this effect is mediated through LUBAC. By tracking NF-kB nuclear translocation in B cells and monocytes from genotyped individuals, we have shown that the *UBE2L3* risk variant amplifies both basal NF-kB activation and sensitivity of NF-kB to stimulation in *ex vivo* cells, leading to increased plasma cell proliferation in SLE.

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IRF1 Influences on Histone H4 Acetylation in Systemic Lupus Erythematosus. Yiu Tak Leung[1], Lihua Shi[2], Kelly Maurer[2], Li Song[2], Zhe Zhang[3], Michelle Petri[4] and Kathleen E. Sullivan[2]. [1]University of Pennsylvania, Philadelphia, PA, [2]The Children's Hospital of Philadelphia, Philadelphia, PA, [3]Bioinformatics, Children's Hospital of Philadelphia, Philadelphia, PA, [4]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Systemic lupus erythematosus (SLE) is the classical systemic autoimmune disease. Epigenetic processes, such as posttranslational histone modifications, can regulate gene expression without altering the underlying genomic sequence; these disease mechanisms that have had little attention in SLE to date. We previously reported that histone H4 acetylation (H4ac) is globally increased across the genome in monocytes of SLE patients as compared to healthy controls using tiling array. Transcription factor motif analysis then found that 63% of genes with increased H4ac had potential interferon regulatory factor (IRF) 1 binding sites, associating this transcription factor in the dysregulated gene expression. In order to investigate how IRF1 interactions influence H4ac in SLE, we identified the specific hyperacetylated H4 lysine residues, looked for histone acetylatransferases (HATs) and histone deacetylases (HDACs) dysregulation that may lead to the pathological hyperacetylation pattern and examined IRF1 associations with HATs and HDACs.

Methods: Flow cytometry for H4 lysine groups: K5, K8, K12 and K16 were ran using isotype controls. H4ac was defined in monocytes from 21 controls and 34 SLE patients. RNA-Seq studies were performed on monocytes from a different set of 8 controls and 8 SLE patients to look for an imbalance in HAT and HDAC expression; these imbalances were validated using real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR). IRF1 influences on H4ac were evaluated in vitro using D54MG cells overexpressed with IRF1. IRF1 interactions with HATs and HDACs were studied using co-immunoprecipitation assays.

Results: Flow cytometry data showed that H4K5, H4K8, H4K12, and H4K16 acetylation were significantly increased in SLE monocytes. RNA-Seq results identified HDAC3 and HDAC11 with significantly decreased expression in SLE monocytes as compared to controls. HDAC3 can deacetylate all H4 lysine acetyl groups, preferentially acetylated H4K5 and H4K12. In contrast, the expression of PCAF, a HAT, was significantly increased in SLE monocytes as compared to controls. PCAF can place H4K5, H4K8, and H4K16 acetylation marks with a preference for H4K8. qRT-PCR data validated the HAT/HDAC expression patterns seen in the RNA-Seq studies. SLE monocytes had decreased gene expression levels of HDAC3 and HDAC11; PCAF had significantly higher gene expression in SLE than controls. IRF1-overexpressed in D54MG cells was associated with significantly increased H4K8 and H4K12 as compared to vector-only D54MG cells. While there was also some increase in acetylation at H4K5, no increase in acetylation was seen at H4K16 in IRF1-overexpressing D54MG cells. Co-immunoprecipitation studies using D54MG cells revealed IRF1 associations with PCAF, P300, CBP, GCN, ATF2, HDAC3 and SIRT1.

Conclusion: We hypothesize that IRF1 responds to alpha-IFN activation in SLE, and activated IRF1 recruits HATs, which then increases H4ac and leads to the chronic pathological gene expression in SLE. These studies have identified pivotal enzymes participating in the global hyper-acetylation in SLE.

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Antimalarials Regulate TLR7/8 Mediated Macrophage Activation Via Epigenetic Modification at the TNFα Promoter. Androo J. Markham[1], Mark Halushka[2], Cristiana Guiducci[3], Robert M. Clancy[1] and Jill P. Buyon[1]. [1]New York University School of Medicine, New York, NY, [2]John Hopkins Pathology, Baltimore, MD, [3]Dynavax Technologies, Berkeley, CA.

Background/Purpose: Maternal anti-SSA autoantibodies contribute to the pathogenesis of congenital heart block by the formation of immune complexes (IC) comprised of Ro and ssRNA (hY3) which, via FcgR uptake, result in macrophage TLR signaling, a finding also applicable to other cell types and the pathogenesis of lupus in general. Accordingly, antagonists of innate cell drivers such as TLR7/8 and NF-κB would constitute a multi-target approach to the inhibition of proinflammatory and profibrotic mediators and subsequent organ injury. This study examined the role of TLR7/8 ligation and the modulatory effects of antimalarials on the epigenetic signature (methylation state) of histone 3 at lysine 4 (H3K4), a regulatory site in the promoter region of genes such as TNFα whose transcription is augmented by NF-kB binding.

Methods: The approach included both in vitro and in vivo studies. The former employed TLR7/8 stimulated human macrophage cells including THP1 and peripheral blood macrophages and the latter immunohistochemistry of autopsy tissue from the heart of a fetus dying with CHB and an age matched control.

Results: As expected, H3K4me2 (reflecting increased promoter activity) was expressed in both the CHB and control hearts. In the former, highly positive mononuclear infiltrates were identified in the AV nodal region. Based on these novel findings, in vitro experiments were initiated to examine the role of TLR7/8 ligation (hY3, surrogate for IC) on the epigenetic modification at histone 3 using broadly based and specific readouts, the latter for expression of TNFα, a cytokine linked to inflammation and fibrosis. Compared with no treatment, hY3 transfection of THP1 cells (N = 4) and isolated macrophages (N=2) increased the expression of H3K4me2 (but not H3K4me1, H3K4me3) by immunofluorescence, confirmed by immunoblot (IB, pixel values 0.39 ± 0.09 vs. 1.6 ± 0.23, no treatment and hY3, respectively, p=0.024). Since H3K4 dimethylation leads to increased promoter activity, parallel experiments evaluated the secretion of TNFα, which was significantly increased compared with control (1540 ± 234 vs 148 ± 49 pg/ml, respectively, p=0.02). The addition of hydroxychloroquine (HCQ, 5–100 uM) resulted in dose dependent inhibition of TNFα release (63% reduction with 5uM, approaching levels in patients, p =0.04 vs hY3, N=3). In parallel, HCQ treatment reduced hY3-stimulated H3K4me2 expression as assessed by immunofluorescence of THP-1 cells (confirmed by immunoblot). Similar results were obtained with both chloroquine and IRS661 (TLR7/8 inhibitor). ChIP was employed to assess the NF-κB binding site at the TNF promoter. Using hY3-treated THP-1 and H3K4me2-immunprecipitated chromatin, qPCR showed an enrichment of TNFα promoter binding by H3K4me2 (0.64 fold of the total input chromatin) which was attenuated by HCQ (0.31 fold of the total input chromatin).

Conclusion: These data support a link between TLR7 activation and dimethylation of lysine 4 of histone 3 (H3K4me2), which has been shown to increase binding of NF-κB at inflammatory gene promoters. Epigenetic modification by antimalarials supports the benefit of HCQ in the treatment of lupus and potential for prevention of organ damage, inclusive of heart block in an anti-Ro offspring.

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Interferon-α and Angiogenic Dysregulation in Pregnant Lupus Patients Destined for Preeclampsia. Danieli Andrade[1], Mimi Kim[2], Luz P. Blanco[3], S. Ananth Karumanchi[4], Gloria Koo[1], Patricia M. Redecha[1], Kyriakos A. Kirou[1], Angela M. Alvarez[5], Melissa J. Mulla[5], Mary K. Crow[1], Vikki Abrahams[5], Mariana J. Kaplan[3] and Jane E. Salmon[1]. [1]Hospital for Special Surgery, New York, NY, [2]Albert Einstein College of Medicine, Bronx, NY, [3]National Institutes of Health, Bethesda, MD, [4]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [5]Yale School of Medicine, New Haven, CT.

Background/Purpose: Pregnant patients with SLE are at increased risk of placental insufficiency and preeclampsia, disorders associated with angiogenic factor imbalance. IFN-α, a critical element in SLE pathogenesis, is a potent antiangiogenic factor. In a case-control longitudinal study of lupus pregnancies from PROMISSE (Predictors of Pregnancy Outcome: Biomarkers In Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus), we investigated whether elevated IFN-α early in pregnancy might be associated with poor pregnancy outcomes.

Methods: Each of 28 SLE patients with poor pregnancy outcome was matched to an SLE patient with an uncomplicated pregnancy and to a pregnant healthy control. Serum samples obtained monthly through pregnancy were assayed for IFN-α activity using a reporter cell assay, and for antiangiogenic factor, sFlt1, and proangiogenic factor, placenta growth factor (PlGF). Human umbilical vein endothelial cells (HUVEC) were cultured in the presence of IFN-α and/or sFlt1, and gene expression assessed by q-RT PCR. The effect of IFN-α and sFlt1 on endothelial-trophoblast interactions was assessed in an *in vitro* model of spiral artery transformation in which the capacity of human first trimester extravillous trophoblasts to stabilize endometrial endothelial cell tube structures is measured.

Results: Compared to SLE patients with uncomplicated pregnancies, those with preeclampsia had increased IFN-α before clinical symptoms. Non-autoimmune patients destined for preeclampsia did not have increased IFN-α. In SLE patients with low IFN-α, marked angiogenic imbalance (higher sFlt1, lower PlGF and higher sFlt1/PLGF ratios) precedes maternal manifestations of preeclampsia, whereas in SLE with high IFN-α, preeclampsia occurs without evidence of systemic angiogenic imbalance. To investigate this result, we treated HUVEC with exogenous sFlt1 and IFN-α. Treatment with sFlt1 induced the expression of *sFlt1* mRNA, and IFN-α dramatically amplified the endothelial response to sFlt1, leading to a local positive feedback loop. Furthermore, in an *in vitro* model of spiral artery transformation, only IFN-α and sFlt1 together disrupted the ability of trophoblast cells to remodel endothelial tube structures.

Conclusion: Our studies identify a new mechanism by which IFN-α induces an antiangiogenic milieu in the vasculature leading to inadequate spiral artery remodeling and poor placentation early in pregnancy and maternal endothelial dysfunction presenting as preeclampsia later in pregnancy. They suggest that elevated IFN-α may contribute to the pathogenesis of preeclampsia in some pregnant women with SLE.

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The Second Messenger, Cyclic GMP-AMP Dinucleotide (cGAMP) and the Enzyme, Cyclic GMP-AMP Synthase (cGAS), Are Expressed in Systemic Lupus Erythematosus. Jie An, Joshua Woodward, Reynold Karr, Thomas H. Teal and Keith B. Elkon. University of Washington, Seattle, WA.

Background/Purpose: The type I IFNs (IFN-I), are strongly associated with Systemic Lupus Erythematosus (SLE). It is generally considered that IFN-I is induced by immune complexes (IC) containing (ribo)nucleoprotein antigens. However, this conclusion is based on in vitro studies and doesn't address how IFN-I may be induced prior to the formation of IC. Cytosolic DNA induces IFN-I and other cytokines which are important for antimicrobial defense but can also trigger autoimmunity. Cytoplasmic DNA frequently transduces signals via the adaptor protein, STING, and the transcription factor IRF3, however how cytosolic DNA is sensed in eukaryotic cells remains under intense investigation. Recently it was shown that a newly discovered enzyme called cyclic-di-GMP–AMP (cGAMP) synthase (cGAS) detects cytosolic DNA, synthesizes cGAMP which then acts as a second messenger to trigger a signaling pathway through STING and IRF3, resulting in production of IFN-β in mammalian cells. Our research aim is to determine whether the cGAS pathway could contribute to IFN I production in SLE.

Methods: cGAS and Interferon Stimulated Genes (ISGs) mRNA expression was quantified by quantitative PCR (qPCR). IRF3 phosphorylation was determined by anti-phospho-IRF3 antibody and western blot. cGAMP levels were monitored by Selective Reaction Monitoring (SRM) with High Performance Liquid Chromatography-tandem Mass Spectrometry (HPLC-MS/MS).

Results: When compared to normal controls (n=20), SLE patients (n=51) had a significant increase of the expression of cGAS (P=0.0045) in peripheral blood mononuclear cells (PBMC). cGAS expression positively correlated with

ISGs expression and IFN score in SLE patients consistent with it being an IFN signature gene. We further quantified IRF3 activation by phosphorylation in PBMC and found that IRF3 was activated in a higher proportion of SLE patients compared to controls. To quantify c-GAMP in patient PBMC samples we used a reference cyclic GMP-AMP dinucleotide that is comprised of the unusual 2'-5' and 3'-5' phosphodiester linkage and demonstrated the ability to distinguish the cyclic dinucleotide from other species by HPLC-MS/MS. Of 23 SLE patients tested, we could detect cGAMP in approximately one fourth of SLE patients but not in any of the normal controls and RA patients.

Conclusion: Our findings implicate the activation of cGAS pathway in at least some patients with SLE. While increased cGAS gene expression may be induced in response to IFN-I, DNA binding to cGAS is required for synthesis of cGAMP. Defining the molecular mechanisms responsible for activation of the cGAS enzyme, will contribute to our understanding of IFN-I stimulation in SLE patients. Furthermore, since IFN-β primes other cells such as pDC for heightened expression of IFN-α, targeted approaches to reduce DNA/cGAS interaction may be a useful therapeutic strategy in SLE.

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ACR Concurrent Abstract Session

Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics I: Systemic Sclerosis, Advances in Therapy

Sunday, November 16, 2014, 2:30 PM–4:00 PM

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Safety and Efficacy of Subcutaneous Tocilizumab in Adults with Systemic Sclerosis: Week 24 Data from a Phase 2/3 Trial. Dinesh Khanna[1], Christopher P. Denton[2], Jacob M. van Laar[3], Angelika Jahreis[4], Sabrina Cheng[4], Helen Spotswood[5], Jeffrey Siegel[4] and Daniel E. Furst on behalf of FaSScinate Clinical Trial in Patients With SS[6]. [1]University of Michigan Health System, Ann Arbor, MI, [2]University College London Medical School, London, United Kingdom, [3]University Medical Center Utrecht, Utrecht, Netherlands, [4]Genentech, South San Francisco, CA, [5]Roche Products Ltd., Welwyn Garden City, United Kingdom, [6]University of California, Los Angeles, CA.

Background/Purpose: Systemic sclerosis (SSc) is a progressive, debilitating disease with limited treatment options. IL-6 has been implicated in disease pathogenesis.[1,2] IL-6 receptor inhibition prevented and reversed skin fibrosis in a murine scleroderma model.[3] Tocilizumab (TCZ), an IL-6 receptor inhibitor, is under evaluation in the ongoing 2-y faSScinate study, a randomized, double-blind, placebo-controlled trial. Wk 24 efficacy and safety data of TCZ in SSc pts are presented here.

Methods: Pts (≥18 y) with active SSc (1980 ACR criteria,[4] ≤5-y disease duration, mRSS 15–40 units, and elevated acute-phase reactants) were randomized 1:1 to subcutaneous TCZ 162 mg or placebo (PBO) wkly for 48 wks. The primary end point was mean change in mRSS from baseline (BL) at wk 24, with patient and lung responses as secondary/exploratory measures.

Results: Eighty-seven pts (43 TCZ, 44 PBO) were enrolled. BL characteristics were similar between arms, including mean (SD) mRSS (TCZ, 26.4 [7.2]; PBO, 25.6 [5.9]). The primary end point, change in mRSS, and secondary end point, change in HAQ-DI, from BL to wk 24 are displayed in the Table. At 24 wks, a numerically favorable but not statistically significant effect of TCZ over PBO on mRSS was noted (TCZ, –3.9; PBO, –1.2; adjusted mean difference, –2.7 [95% CI, –5.85, 0.45]). In addition, a numerically greater proportion of TCZ pts achieved clinically meaningful reduction in mRSS of ≥4.7[5] (TCZ, 43.2% [16/37]; PBO, 26.3% [10/38]; $p = 0.15$, Fisher exact test). Exploratory analysis of change in forced vital capacity (FVC; liters) showed more PBO than TCZ patients (81% vs 50%) with progression of FVC decline (≤0%) (Table) and 27% of PBO pts vs 3% of TCZ pts with ≥10% FVC decline ($p = 0.009$, Van Elteren test). Adverse events (AEs)/serious AEs were reported in 88.4%/20.9% of TCZ and 90.9%/25.0% of PBO pts. Fewer noninfectious SAEs were reported in the TCZ arm (5 pts) than the PBO arm (10 pts), whereas infection/infestation SAEs were more common in TCZ than PBO pts (6 pts vs 1 pt). By system organ class, the following SAEs, potentially indicative of SSc complications, were reported more frequently in the PBO than in the TCZ arm: cardiac SAE (TCZ, 0 pts; PBO, 3 pts), gastrointestinal SAE (TCZ, 0 pts; PBO, 2 pts), and renal SAE (TCZ, 0 pts; PBO, 2 pts). Three pts in the TCZ arm and 2 pts in the PBO arm discontinued due to AEs. One death occurred in each arm: 1 pulmonary infection in a TCZ pt on day 109 and 1 heart failure in a PBO pt 131 days after withdrawal.

Conclusion: In this phase 2 study, favorable trends in skin score for TCZ were detected though the primary skin score end point was not met. In addition, encouraging changes in FVC were noted. The ongoing double-blind and open-label phases of this trial will provide additional information.

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Table. Change From Baseline in mRSS, HAQ-DI, and FVC at Week 24 (ITT population)

	TCZ	PBO	Difference (95% CI)	*p*
mRSS, adjusted[a] mean (SD)	−3.9 n = 41	−1.2 n = 43	−2.70 (−5.85, 0.45)	0.09
HAQ-DI, adjusted[a] mean (SD)	0.14 n = 41	0.12 n = 42	0.02 (−0.19, 0.23)	0.85
FVC (L) change ≤0%, n (%)	15 (50.0) n = 30	30 (81.1) n = 37		
FVC (L) decline ≥10%, n (%)	1 (3.3) n = 30	10 (27.0) n = 37		

HAQ-DI, Health Assessment Questionaire-Disability Index; ITT, intent to treat.
[a]Mixed-model repeated measures analysis that included treatment, visit, joint involvement at baseline, treatment-by-visit interaction, baseline parameter, and baseline parameter-by-visit interaction.

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Treatment-Related Outcomes in Connective Tissue Disease-Associated Pulmonary Arterial Hypertension: A Pooled Analysis of 12 Randomized Controlled Trials. Rennie L. Rhee[1], Nicole B. Gabler[1], Amy Praestgaard[1], Peter A. Merkel[2] and Steven M. Kawut[1]. [1]University of Pennsylvania, Philadelphia, PA, [2]Vasculitis Center, University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Recent studies have shown that therapies for pulmonary arterial hypertension (PAH) improve exercise capacity, but subgroup analyses suggest that these therapies may be less effective in patients with connective tissue disease (CTD-PAH). The aim of this study was to compare the effect of treatment on the change in six minute walk distance (Δ6MWD) and clinical events in CTD-PAH vs idiopathic PAH (IPAH).

Methods: A pooled analysis was performed on patient-level data from 12 Phase III randomized placebo-controlled trials of advanced therapies for PAH that were submitted to the FDA for approval. Outcomes for this analysis included Δ6MWD from baseline to 12 weeks, the occurrence of clinical worsening (defined as first occurrence of death, hospitalization for PAH, addition of other PAH medications, lung transplant, atrial septostomy, or worsening exercise capacity and/or functional class), and all-cause mortality. Missing 6MWD at 12 weeks was multiply imputed. A robust generalized estimating equation within a linear or logistic regression model was utilized using an exchangeable correlation structure and clustering on study trial. Effect modification of treatment assignment (drug vs placebo) by diagnosis (CTD-PAH vs IPAH) was assessed. All regression models were adjusted for age, sex, race, drug class, baseline 6MWD, functional class, and baseline hemodynamics (right atrial pressure, pulmonary vascular resistance, and cardiac index).

Results: The study sample included 2,736 participants: 824 had CTD-PAH and 1,912 had IPAH. Patients with CTD-PAH were significantly older, more often female, and had a lower baseline 6MWD compared to patients with IPAH (**Table 1**). There was a significant interaction between treatment assignment and diagnosis in terms of the Δ6MWD, such that the treatment-related improvement in Δ6MWD was significantly less in CTD-PAH than in IPAH (difference-in-difference −11.3 meters, [95% CI −20.0, −2.6], p for interaction = 0.011). There was also greater treatment-associated reduction in clinical worsening and mortality in IPAH than in CTD-PAH (**Table 2**).

Conclusion: In clinical trials, treatment for PAH was less effective in CTD-PAH compared to IPAH in terms of increasing 6MWD, preventing clinical worsening, and possibly reducing the risk of death. The differential treatment response in CTD-PAH and IPAH supports the need for stratified analysis in future trials and suggests that a different pathophysiological process may exist in the two phenotypes of disease.

Table 1: Characteristics of Study Participants

	CTD-PAH (n = 824)	IPAH (n = 1,912)	p-value
Age, years	54 ± 14	47 ± 16	<0.001
Female sex, No. (%)	735 (89)	1,402 (73)	<0.001
Race, No (%)	480 (58)	1,155 (60)	0.210
White	33 (4)	54 (3)	
Black	311 (38)	703 (37)	
Other			
WHO functional class, No (%)	374 (45)	847 (44)	0.599
I-II	450 (55)	1,065 (56)	
III-IV			
Baseline hemodynamics	7.9 ± 4.9	9.2 ± 5.7	<0.001
Right atrial pressure, mmHg	45 ± 12	55 ± 15	<0.001
Mean pulmonary arterial pressure, mmHg	2.5 ± 0.8	2.3 ± 0.8	<0.001
Cardiac index, L/min/m^2	9 ± 3	9 ± 4	0.993
Pulmonary capillary wedge pressure, mmHg	9.8 ± 6.0	12.9 ± 7.5	<0.001
Pulmonary vascular resistance, Woods units			
Baseline 6-minute walk distance, meters	338 ± 89	351 ± 86	<0.001
Drug Class, No. (%)	507 (62%)	1,071 (56%)	0.025
Endothelin receptor antagonists	90 (11%)	211 (11%)	
Phosphodiesterase-5 inhibitors	117 (14%)	349 (18%)	
Prostacyclin analogue	110 (13%)	281 (15%)	
Soluble guanylate cyclase stimulator			

Data are presented as mean ± standard deviation unless otherwise indicated.

Table 2: Risk of Clinical Worsening and Death Stratified by Diagnosis

Outcome	Diagnosis	OR	95% CI	p-value	p for interaction
Clinical Worsening	CTD-PAH	0.80	0.63−1.03	0.081	0.011
	IPAH	0.51	0.40−0.65	<0.001	
Death	CTD-PAH	1.73	0.75−4.00	0.198	0.115
	IPAH	0.66	0.27−1.60	0.356	

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SAR100842, an Antagonist of Lysophaphatidic Acid Receptor 1, As a Potential Treatment for Patients with Systemic Sclerosis: Results from a Phase 2a Study. Dinesh Khanna[1], Christopher P. Denton[2], Alexandre Jagerschmidt[3], Martine Jasson[4], Oliver Distler[5] and Yannick Allanore[6]. [1]University of Michigan Scleroderma Program, Ann Arbor, MI, [2]UCL Medical School Royal Free Campus, London, United Kingdom, [3]Sanofi-Aventis, Chilly-Mazarin, France, [4]Sanofi-Aventis, Paris, France, [5]Zurich University Hospital, Zurich, Switzerland, [6]Department of Rheumatology, University Paris Descartes and Cochin Hospital, Paris, France.

Background/Purpose: Preclinical genetic and pharmacological studies suggest a role for Lysophosphatidic acid (LPA) involvement in three key processes of systemic sclerosis: fibrosis, microangiopathy and immunoinflammation. We have assessed SAR100842, a potent selective orally available antagonist of LPA1 receptor and explored safety, skin biomarkers of disease activity and clinical efficacy in patients with diffuse cutaneous SSc (dcSSc) in a phase 2a clinical trial.

Methods: ACT12339, study NCT01651143 sponsored by SANOFI, was an 8-week double-blind, randomized, placebo-controlled study followed by a 16 week open label extension study with SAR100842. 32 patients with dcSSc <36 months since the onset of the first non-Raynaud's SSc manifestation and an mRSS ≥15 were included. Patients with severe organ involvement that was deemed unsafe were excluded. Background stable immunosuppressant therapy was allowed. The primary endpoint was safety. Secondary end-points included effect on potential biomarkers from skin biopsies and blood samples as well as change in mRSS and S-HAQ at week 8 and 24 in the modified intent to treat (ITT) population defined as any patient with a post investigational product evaluation in each part of the study.

Results: 17 patients were randomized to the placebo group and 15 to the SAR100842 group. 30 patients participated in the extension study.

The most frequent adverse events reported under SAR100842 during the blinded period were headache, diarrhea and nausea.

No statistically significant difference between the 2 groups was observed in skin biopsy and blood biomarkers at week 8. However, a greater reduction of some skin LPA-induced marker mRNA levels (e.g. Wnt2, PAI1 and SFRP4) was observed in the SAR100842 group compared to placebo, consistent with sucessful target engagement. At week 8 an improvement in mRSS (median improvement= - 4.0 versus −1.0 units) and in HAQ-DI were observed in the SAR100842 group compared to placebo, respectively.

The safety profile was good during the extension part. The most frequent adverse events in this part were headache, arthralgia, fatigue and nausea. After 24 weeks of treatment with SAR100842 key skin fibrotic biomarkers (COMP and TSP1) were reduced from baseline. LPA-induced biomarker mRNA levels were improved after 16 weeks of treatment with SAR100842 in the group of patients who initially received placebo. In parallel and of interest, there was a clinically meaningful improvement of clinical parameters as indicated in the table below. 78.5% of patients achieved MCID estimate of mRSS.

	Placebo/SAR100842	SAR100842/SAR100842
mRSS total score (0–51) at baseline	25.23 (7.47)	23.07 (8.32)
Mean change to Week 24 (SD)	−7.31 (4.59)	−7.36 (4.24)
HAQ-DI total score (0–3) at baseline	1.32 (0.79)	1.20 (0.79)
Mean change to Week 24 (SD)	−0.23 (0.30)	−0.15 (0.33)

Conclusion: SAR100842 was well tolerated in patients with dcSSc and resulted in a reduction of skin thickness assessed by mRSS. The clinical efficacy was supported by biological evidence of the LPA target engagement. Altogether these data suggests that SAR100842 may be an effective treatment for dcSSc that need to be confirmed in a larger controlled trial.

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Sildenafil Attenuates the Fibrotic Phenotype in Scleroderma Skin Fibroblasts. Tomoaki Higuchi[1], Yasushi Kawaguchi[1], Kae Takagi[1], Akiko Tochimoto[1], Yuko Ota[1], Yasuhiro Katsumata[1], Takahisa Gono[1], Masanori Hanaoka[1], Yuko Okamoto[1], Hidenaga Kawasumi[1] and Hisashi Yamanaka[2]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Systemic sclerosis (SSc) is a connective tissue disease characterized by inflammation, vasculopathy and fibrosis. Tissue fibrosis directly contributes to mortality or quality of life. However, the effective therapy has not been established. Aberrantly activated fibroblasts in the affected area of SSc, which play a main role in the production and remodeling of collagen and other extracellular matrix components, is thought to be a key therapeutic target. Recent researches showed that stimulation of soluble guanylate cyclase (sGC) reverted fibrotic phenotype of SSc and other fibrotic disorders *in vivo* and *in vitro* by increasing levels of intracellular cyclic GMP (cGMP). The purpose of the present study is to assess the anti-fibrotic properties of cGMP in cultured fibroblasts from patients with SSc.

Methods: Skin fibroblasts were obtained from patients with diffuse cutaneous SSc. Intracellular cGMP levels were measured using a commercially available ELISA kit. To increase the intracellular concentration of cGMP, sildenafil, an inhibitor of phosphodiesterase (PDE) 5, was added. Expression of PDE5 and alpha smooth muscle actin (αSMA) were analyzed by immunohistochemistry. Gene expressions related to profibrotic marker were evaluated by quantitative RT-PCR. Western blotting and ELISA were performed to investigate the effects of sildenafil on the downstream pathway of TGF-β.

Results: PDE5 expression on skin fibroblasts was confirmed by immunohistochemistry. Baseline cGMP levels in SSc skin fibroblasts were significantly higher than those in healthy skin fibroblasts. Sildenafil increased cGMP levels in a dose dependent manner in skin fibroblasts, and then our results indicated that sildenafil significantly decreased the expression of profibrotic genes, which were augmented by TGF-β1, including *COL1A1, COL1A2, CTGF and ACTA2* in SSc skin fibroblasts. Conversely, these inhibitory effects of sildenafil were found to be weak in healthy skin fibroblasts. Also, we confirmed using immunohistochemistry that the protein levels of αSMA in SSc skin fibroblasts were down-regulated by sildenafil. Next, we explored the effects of sildenafil on

the signal pathway of TGF-β. Sildenafil significantly reduced phosphorylation of p38 induced by TGF-β1, but did not affect phosphorylation of Smad3. In addition, sildenafil reduced Rho kinase activity.

Conclusion: We demonstrated that sildenafil attenuated the fibrotic phenotype of SSc skin fibroblasts induced by TGF-β1. This effect may be attributed by non-Smad signaling pathways, including MAPK and Rho kinase cascade. Sildenafil has been used for the treatment of SSc -associated pulmonary arterial hypertension and Raynaud phenomenon by its potent vasodilating effect. In addition, our findings would provide the evidence that sildenafil may have the potential to improve fibrotic lesions in SSc.

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Luminex and Autoantigen Microarray Analysis of Sera from Patients with Diffuse Cutaneous Systemic Sclerosis Reveals Changes Associated with Imatinib Mesylate Treatment. D. James Haddon[1], Hannah Wand[1], Paul J. Utz[1], Robert F. Spiera[2], Jessica K. Gordon[2] and Lorinda Chung[3]. [1]Stanford University School of Medicine, Stanford, CA, [2]Hospital for Special Surgery, New York, NY, [3]Stanford University School of Medicine, Palo Alto, CA.

Background/Purpose: Tyrosine kinase inhibitors (TKIs), including imatinib mesylate, have been studied for the treatment of diffuse cutaneous Systemic Sclerosis (dcSSc). In a previously reported single center, open-label study of imatinib for dcSSc, a significant improvement in the modified Rodnan skin score (MRSS) was observed. In this study, we analyzed the patient serum samples collected during the trial by Luminex and autoantigen microarray to investigate the mechanism of action of imatinib in dcSSc, and to identify biomarkers that are predictive of response to imatinib.

Methods: Thirty patients who fulfilled ACR criteria for SSc, with dcSSc, were enrolled in the trial, and 24 completed 12 months of treatment with oral imatinib 400 mg daily. Serum samples were collected at −1, 0, 6, 12, and 15 (post-treatment follow-up) months. Twenty-six patient serum samples were available for analysis at screening/baseline, 25 at 6 months, 20 at 12 months, and 15 at the follow-up time point.

Luminex immunoassays were used to measure the levels of 44 cytokines, chemokines and growth factors in each serum sample in duplicate. Autoantigen microarrays were used to measure the levels of 30 autoantigens known to be associated with dcSSc, in parallel. Luminex and microarray results were analyzed by Significance analysis of microarrays (SAM), a statistical technique that uses permutation to adjust for multiple testing. SAM was used to identify Luminex analytes and autoantibodies that were present at significantly different levels: 1) in healthy controls vs. patients with dcSSc at baseline, 2) during treatment with imatinib vs. baseline; and 3) in the baseline samples of responders vs. non-responders. For this analysis, a decrease in MRSS $\geq$ 5, previously defined as the minimal clinically important difference, was considered a response to treatment.

Results: Luminex analysis identified 18 analytes that were present at significantly higher levels in the serum of patients with dcSSc than in healthy control serum, including previously reported factors IL-6, MCP-1, VEGF, IL-17 and MIP-1β (fold-change $>$ 2, q $<$.001). Autoantigen microarray analysis revealed 7 autoantibodies present at significantly higher levels in dcSSc patient sera than in healthy control sera, including Scl-70 and RNA Pol III (fold-change $>$ 1.5, q $<$.001). We observed significant reductions in 5 autoantibodies following 6 months of treatment with imatinib, including Scl-70 and RNA Pol III, compared to baseline (q $<$.001). Imatinib treatment was also associated with reductions in 8 Luminex analytes, including VEGF, IL-17, MCP-1, PDGF-AA, and PDGF-BB (q $<$.001). Levels of VEGF, IL-17, and MIP-1β were significantly higher in responders than non-responders at baseline.

Conclusion: Treatment with imatinib was associated with a reduction in the serum levels of VEGF and IL-17. Increased serum levels of VEGF, IL-17 and MIP-1β in dcSSc patients at baseline were associated with an increased likelihood of clinical improvement in MRSS with imatinib treatment. Investigation of the utility of the baseline levels of IL-17, VEGF and MIP-1β for patient stratification in the context of future randomized controlled trials of TKIs in SSc is warranted.

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Efficacy of Autologous Hematopoietic Stem Cell Transplantation in Rapidly Progressive Systemic Sclerosis: Prolonged Remission of Disease Activity in a Long-Term Follow up. Eleonora Zaccara[1], Domenico Sambataro[2], Wanda Maglione[1], Gianluca Sambataro[1], Francesco Onida[3], Claudio Annaloro[3], Giorgia Saporiti[3], Elena Tagliaferri[3], Agostino Cortelezzi[3], Rosaria Giordano[3], Claudio Vitali[4] and Nicoletta Del Papa[2]. [1]Osp. G. Pini, Milano, Italy, [2]Istituto G.Pini, Milan, Italy, [3]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico-University of Milan, Milano, Italy, [4]Istituto San Giuseppe, Lecco, Italy.

Background/Purpose: In the recent years, autologous haematopoietic stem cell transplantation (AHSCT) has been shown to represent an effective therapeutic option for patients (pts) suffering from rapidly progressive SSc, although the number of available clinical trials at present is relatively scant. Aim of the study was to retrospectively evaluate the efficacy of AHSCT in a long term in a number of patients with severe diffuse cutaneous SSc after a long lasting period of observation.

Methods: Since 2003, 18 pts affected by diffuse cutaneous SSc (male 5, female 13; median age 40 years, range 20 – 62), underwent AHSCT using positively selected CD34+ cells. Pts were eligible if they had a rapidly progressive disease, a modified Rodnan Skin Score (mRSS) $>$ 14 and a clinical activity score $>$ 3 (evaluated according to the European Scleroderma Study Group – ESSG), in the absence of major organ involvement. Mobilisation was performed with CTX 4000 mg/m2 given over two days and G-CSF 10 μg/m2/day. Conditioning regimen included CTX 50 mg/kg/day on days −5 to −2 and rabbit ATG 2.5 mg/kg/day on days −3 to −1. The major outcome variables were treatment safety and clinical response, in terms of mRSS and ESSG improvements. The long-term follow-up of organ disfunction was evaluated by echocardiographic LEVF or PAPs, and functional respiratory parameters DLCO and VC.

Results: The median follow-up was of 37 months (range 6–138). Ninety-four % (17/18) of the pts demonstrated a beneficial clinical response with significant reduction of mRSS $>$ 30% and ESSG at Month 6, and a further reduction of mRSS at year 1 of the most part of them was observed.

The mean mRSS was 19.8 (SD + 5.3) at baseline, 9.3 + 4.6 at Month 6, 6.21 + 7.4 at year 1 and 3.0 + 2.2 at year 5; all the reductions were statistically significant ($<$ 0.001). The mean ESSG was 5.3 + 0.85 at baseline, 2.1 + 0.8 at Month 6, 2.0 + 1.6 at year 1 and 1.5 + 0.96 at Year 5; all the reductions were statistically significant (p$<$ 0.0001). Organ involvement was nearly unchanged during follow-up: mean value of DLCO at baseline 65.0% + 19%, at Year 1 67.2% + 17.8% and at Year 5 58.0% + 14.7% (p=ns); mean value of VC at baseline 81% + 23.6%, 82% + 15.7%, 89.2% + 26% (p=ns). No echocardiographic changes were identified during follow-up. Two patients died during follow-up of SSc from pulmonary and cardiac complications due to the disease. One patient died from interstitial pneumonia at day + 65, leading to a TRM of 5.6% (1/18).

Conclusion: This study confirms that AHSCT in selected patients with rapidly progressive SSc results in sustained improvement of skin thickening and stabilisations of organ function up to 10 years after transplantation, so leading to a global clinical improvement, as showed by the persistent reduction in the ESSG clinical activity score. According to other experiences, TRM resulted reasonable, as a possible result of patients selection. These finding are in keeping with the view that AHSCT is effective in improving the active phase of SSc, while letting unchanged and stable the fibrosclerotic one. Further studies are needed to evaluate the importance of CD34 selection, the need of immunosuppressive therapy post-AHSCT and the best timing of HSCT in the treatment of SSc patients.

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ACR Concurrent Abstract Session
Vasculitis I
Sunday, November 16, 2014, 2:30 PM–4:00 PM

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An Immunochip Study Confirms a Strong Contribution of HLA Class I and II Genes in the Susceptibility to Giant Cell Arteritis. Francisco David Carmona[1], Sarah Mackie[2], Jose Ezequiel Martin[1], John Taylor[2], Augusto Vaglio[3], Lara Bossini-Castillo[1], Santos Castañeda[4], Maria C. Cid[5], José Hernández-Rodríguez[5], Roser Solans[6], Ricardo Blanco[7], Lorenzo Beretta[8],

Claudio Lunardi[9], Marco A. Cimmino[10], Cisca Wijmenga[11], Torsten Witte[12], Julia Holle[13], Frank Moosig[13], Verena Schönau[14], Andre Franke[15], Øyvind Palm[16], Andreas P. Diamantopoulos[17], Benedicte A. Lie[18], Simon Carette[19], David Cuthbertson[20], Gary S. Hoffman[21], Nader A. Khalidi[22], Curry L. Koening[23], Carol A. Langford[24], Carol McAlear[25], Larry Moreland[26], Paul A. Monach[27], Christian Pagnoux[19], Philip Seo[28], Antoine G. Sreih[29], Kenneth J. Warrington[30], Steven R. Ytterberg[30], Colin T. Pease[31], Andrew Gough[32], Michael Green[33], Lesley Hordon[34], Stephen Jarrett[35], Richard Watts[36], Sarah Levy[37], Yusuf Patel[38], Sanjeet Kamath[39], Bhaskar Dasgupta[40], Paul IW. de Bakker[41], Bobby P.C. Koeleman[41], Jennifer H. Barrett[2], Carlo Salvarani[42], Peter A. Merkel[25], Miguel A. Gonzalez-Gay[7], Ann W. Morgan[2] and Javier Martin[1]. [1]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain, [2]University of Leeds, Leeds, United Kingdom, [3]University Hospital of Parma, Parma, Italy, [4]Hospital Universitario de La Princesa, IISP, Madrid, Spain, [5]Hospital Clínic University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [6]Hospital Vall d'Hebron, Autonomous University of Barcelona, Barcelona, Spain, [7]Hospital Universitario Marqués de Valdecilla, IFIMAV, Santander, Spain, [8]Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy, [9]Università degli Studi di Verona, Verona, Italy, [10]University of Genova, Genova, Italy, [11]University Medical Hospital Groningen, University of Groningen, Groningen, Netherlands, [12]Hannover Medical School, Hannover, Germany, [13]Vasculitis Clinic, Klinikum Bad Bramstedt & University Hospital of Schleswig Holstein, Bad Bramstedt, Germany, [14]Universitätsklinikum Erlangen, Erlangen, Germany, [15]Christian-Albrechts-University of Kiel, Kiel, Germany, [16]Oslo University Hospital and University of Oslo, Oslo, Norway, [17]Hospital of Southern Norway Trust, Kristiansand, Norway, [18]University of Oslo and Oslo University Hospital, Oslo, Norway, [19]University of Toronto, Toronto, ON, [20]University of South Florida, Tampa, FL, [21]Center for Vasculitis Care and Research, Cleveland Clinic Foundation, Cleveland, OH, [22]St. Joseph's Hospital, McMaster University, Hamilton, ON, [23]University of Utah, Salt Lake City, UT, [24]Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, OH, [25]Vasculitis Center, University of Pennsylvania, Philadelphia, PA, [26]Vasculitis Center, of University of Pittsburgh Medical Center, Pittsburgh, PA, [27]Vasculitis Center, Boston University School of Medicine, Boston, MA, [28]Johns Hopkins Vasculitis Center, Johns Hopkins University, Baltimore, MD, [29]The University of Pennsylvania, Philadelphia, PA, [30]Mayo Clinic, Rochester, MN, [31]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [32]Harrogate and District Foundation Trust, Harrogate, United Kingdom, [33]York Teaching Hospital NHS Foundation Trust, York, United Kingdom, [34]Mid Yorkshire Hospitals NHS Trust, Dewsbury, United Kingdom, [35]Mid Yorkshire Hospitals NHS Trust, Wakefield, United Kingdom, [36]Ipswich Hospital NHS Trust, Ipswich, United Kingdom, [37]Croydon Health Service NHS Trust, Croydon, United Kingdom, [38]Hull and East Yorkshire NHS Trust, Hull East Yorkshire, United Kingdom, [39]Staffordshire and Stoke-on-Trent Partnership NHS Trust, Staffordshire, United Kingdom, [40]Southend University Hospital, Essex, United Kingdom, [41]University Medical Center Utrecht, Utrecht, Netherlands, [42]Azienda Ospedaliera ASMN, Istituto di Ricovero e Cura a Carattere Scientifico, Reggio Emilia, Italy.

Background/Purpose: Giant cell arteritis (GCA) is a chronic autoimmune vasculitis with an important genetic component. We aimed to identify relevant risk *loci* for GCA predisposition by performing a large-scale genetic analysis on this disease.

Methods: We genotyped a large cohort of patients with GCA using the Illumina Immunochip. The study cohort was of European ancestry and comprised 1,892 cases of GCA confirmed by temporal artery biopsy or vascular/imaging and 15,306 unrelated controls from 6 different countries (Spain, UK, USA, Italy, Norway and Germany). To test for association, we compared the variation frequencies of cases and controls by logistic regression under a fixed-effects model using the three first principal components (PCs), sex, and country of origin as covariates. We also imputed the HLA region using a previously validated imputation method to perform a more comprehensive analysis of this region.

Results: The strongest association signals were observed in the HLA region, specifically histidine at position 13 of HLA-DRB1 (P=3.46e-38, OR=1.92, 95% CI=1.74–2.12). A multivariate model including 3 amino acids (a histidine in position 13 of DRB1, a leucine in position 69 of DQA1, and a threonine in position 45 of HLA-B) explained most of HLA association with GCA. All 3 amino acids are located in the binding pocket of their corresponding HLA molecule and interact directly with the antigen. Outside the HLA region, the most highly associated SNPs were located within *PTPN22* (rs2476601, P=1.73E-06, OR=1.38, 95% CI=1.21–1.58) and *LRRC32* (rs10160518, P=4.39E-06, OR= 1.20, 95% CI=1.11–1.29). The latter gene is selectively expressed on Tregs.

Conclusion: Our data provide evidence of a strong contribution of HLA Class I and II molecules to susceptibility to GCA. Regarding the non-HLA region, we confirmed a key role for the functional *PTPN22* rs2476601 variant and identified *LRRC32* as a putative risk factor for GCA, suggesting a possible role of Tregs in the pathophysiology of GCA.

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DNA Methylation Analysis of the Temporal Artery Microenvironment Reveals a Robust T Cell Signature and Suggests a Role for TNF-α in Giant Cell Arteritis. Patrick S. Coit, Lindsey B. De Lott, Bin Nan, Victor M. Elner and Amr H. Sawalha. University of Michigan, Ann Arbor, MI.

Background/Purpose: Giant cell arteritis (GCA) is a systemic large vessel vasculitis of unknown etiology. A hallmark of GCA is the presence of granulomatous inflammation of the arterial wall. The DNA methylation status of the arterial environment in GCA patients has not been previously elucidated. This study characterizes the DNA methylation profile of formalin-fixed, paraffin-embedded (FFPE) temporal artery tissue biopsies taken from GCA patients and age, sex, and ethnicity matched controls that presented with similar symptoms, but had normal temporal artery biopsies.

Methods: Temporal artery biopsies performed at the University of Michigan from 1988–2012 were reviewed. Twelve patients with non-equivocal histological evidence for GCA and twelve age, sex, and ethnicity matched controls with normal biopsies were included in this study. All patients fulfilled the ACR classification criteria for GCA and were not taking steroids for more than 48 hours prior to biopsy. DNA was extracted from the affected portions of FFPE temporal artery tissue in GCA patients and from histologically-confirmed normal arteries in controls. Genome-wide DNA methylation status was evaluated using the Illumina Infinium HumanMethylation 450 BeadChip Array, which covers 99% of RefSeq genes and over 485,000 methylation sites across the genome. Differentially methylated loci between affected and unaffected arterial tissues were identified, and subsequent bioinformatic analysis performed.

Results: We identified 1558 hypomethylated CpG sites (853 genes) and 2754 hypermethylated CpG sites (1471 genes) in GCA patients compared to controls. Gene ontology enrichment analysis of hypomethylated genes revealed significant representation in T cell activation and differentiation pathways, including both Th1 and Th17 related cytokine gene signatures (Table 1). Other proinflammatory genes such as *TNF*, *LTA*, and *LTB* were significantly hypomethylated in the cellular milieu of GCA arteries. Of the hypomethylated CpG sites in *TNF*, which is a known genetic susceptibility locus for GCA, two are within 1500bp upstream of the transcription start site, while two CpG sites are in the gene body. In addition, other genetic susceptibility loci for GCA such as *IFNG*, *PTPN22*, and *NLRP1* were also hypomethylated in this study. *CCR7* which is expressed on mature DCs, was amongst the most hypomethylated genes in GCA, consistent with a previously described pathogenic role for mature DCs within GCA affected arteries. Gene ontology analysis of hypermethylated genes displayed enrichment for genes related to actin cytoskeletal arrangement and regulation of GTPase-mediated and Ras protein signal transduction.

Table 1. Biological Process Gene Ontology (GO) Terms Most Enriched Among Hypomethylated Genes in GCA Arterial Lesions

GO Term	GO Term ID	Fold Enrichment	P value (Benjamini)	Genes
Immune response	GO:0006955	3.4	3.78E-26	*TLR1, IL19, TNFSF14, TGFB1, B2M, CFP, S1PR4, IFNG, MS4A1, SPN, PAG1, RAB27A, BST2, NCF4, HLA-A, HLA-E, HLA-DQA1, C1QB, CCR8, CCR7, CCR6, CCR5, CCR4, CST7, LYST, LILRB4, CCR2, CD300LF, HLA-DPA1, GBP4, GBP3, GPB2, HLA-DRA, TNFAIP8L2, ITGAL, OAS2, CCL5, CD74, ICOS, CNR2, ZAP70, ARHGDIB, ST6GAL1, TCF7, IL23R, CD300E, SLAMF7, FOXP1, PSMB8, AIM2, PSMB9, BTLA, LAT, NOTCH1, TNFSF10, CORO1A, RGS1, ETS1, TGFBR3, LY86, FASLG, CLNK, LY9, HLA-DMB, SKAP1, HLA-DMA, MBP, CD96, SH2D1A, LTB, LTA, GZMA, SLA2, CD164, SIGIRR, OSM, LAX1, FAIM3, CTSC, LCP2, TNF, GPSM3, GPR65, TNFRSF4, CCL26, CCL25, CCL22, TNFRSF1B, TAP2, TAP1, IL2RG, CD4, INPP5D, CD28, FYB, PTPRC, IL2RA, THEMIS, CTLA4, TRIM22, CCL18, TNFSF8, IRF8, LIME1, ATP6V0A2*
Cell activation	GO:0001775	3.9	3.03E-13	*GNA13, PREX1, STAT5A, TLR1, PTPN22, TNFSF14, HLA-DMA, CBFB, TGFB1, NLRC3, ITIH1, MS4A1, LTB, SPN, LTA, KIF13B, RAB27A, CD3G, CD3D, BST2, CD3E, SLA2, NCK2, CD80, LAX1, RIPK2, TSHR, LCP2, ITGAL, TNF, TNFRSF4, CD74, BCL11B, BCL11A, ZAP70, CD4, CD28, PTPRC, IKZF1, THEMIS, TGFBR2, SLAMF7, ITGA4, SLAMF1, FOXP1, HDAC4, LAT, NCK2, CD80, FYN, LAX1, IRF1, RIPK2, TSHR, LCP2*
Leukocyte activation	GO:0045321	4.2	6.06E-13	*ITGAL, PREX1, STAT5A, TLR1, PTPN22, TNFSF14, TNFRSF4, HLA-DMA, CD74, TGFB1, CBFB, NLRC3, ITIH1, BCL11B, BCL11A, ZAP70, MS4A1, CD4, SPN, CD28, KIF13B, RAB27A, PTPRC, CD3G, BST2, CD3D, IKZF1, CD3E, THEMI S, SLA2, TGFBR2, SLAMF7, ITGA4, SLAMF1, FOXP1, HDAC4, LAT, NCK2, CD80, FYN, LAX1, IRF1, RIPK2, TSHR, LCP2*
Positive regulation of immune system process	GO:0002684	4.1	6.89E-12	*C3AR1, STAT5A, CD247, PTPN22, TNFSF14, TNFRSF4, SKAP1, HLA-DMA, CD74, TGFB1, B2M, CFP, SH2D1A, HLX, TAP2, IFNG, ZAP70, CD4, IL2RG, INPP5D, CD5, SPN, LAG3, CD28, IRAK2, PTPRC, IL 2RA, IKZF1, CD3E, THEMIS, SLA2, TGFBR2, FOXP1, NCK2, C1QB, PRKCQ, CORO1A, CD80, FYN, LAX1, RIPK2, CD226, HLA-DRA*
Lymphocyte activation	GO:0046649	4.4	7.76E-12	*ITGAL, STAT5A, PTPN22, TNFSF14, TNFRSF4, HLA-DMA, TGFB1, CBFB, CD74, NLRC3, BCL11B, BCL11A, ZAP70, MS4A1, CD4, SPN, CD28, KIF13B, RAB27A, PTPRC, CD3G, BST2, CD3D, IKZF1, THEMIS, CD3E, SLA2, SLAMF7, IT GA4, SLAMF1, FOXP1, HDAC4, NCK2, CD80, FYN, LAX1, IRF1, RIPK2, TSHR*
Regulation of T cell activation	GO:0050863	5.6	5.88E-11	*STAT5A, TNFSF14, HLA-DMA, TGFB1, CD74, HLX, IFNG, ZAP70, IL2RG, CD4, CD5, PAG1, LAG3, SPN, CD28, PTPRC, IL2RA, IKZF1, CD3E, TGFBR2, CTLA4, BTLA, LAT, PRKCQ, NCK2, CORO1A, CD80, LAX1, RIPK2*
Regulation of leukocyte activation	GO:0002694	4.6	9.55E-11	*STAT5A, TNFSF14, RORA, TNFRSF4, HLA-DMA, TGFB1, CD74, HLX, IFNG, ZAP70, CD4, IL2RG, INPP5D, CD5, PAG1, LAG3, SPN, CD28, PTPRC, IL2RA, IKZF1, CD3E, SLA2, TGFBR2, CTLA4, BTLA, LAT, NCK2, PR KCQ, CORO1A, CD80, LAX1, RIPK2, CD226*
Regulation of lymphocyte activation	GO:0051249	4.9	1.03E-10	*STAT5A, TNFSF14, TNFRSF4, HLA-DMA, TGFB1, CD74, HLX, IFNG, ZAP70, IL2RG, CD4, INPP5D, CD5, PAG1, LAG3, SPN, CD28, PTPRC, IL2RA, IKZF1, CD3E, SLA2, TGFBR2, CTLA4, BTLA, LAT, NCK2, PRKCQ, CORO1A, CD80, LAX1, RIPK2*
T cell activation	GO:0042110	5.2	2.82E-10	*ITGAL, STAT5A, PTPN22, TNFSF14, TNFRSF4, HLA-DMA, TGFB1, CD74, NLRC3, BCL11B, BCL11A, ZAP70, CD4, SPN, RAB27A, KIF13B, CD28, PTPRC, CD3G, CD3D, IKZF1, THEMIS, CD3E, SLA2, NCK2, CD80, FYN, IRF1, RIPK2*
Regulation of cell activation	GO:0050865	4.4	3.17E-10	*STAT5A, TNFSF14, RORA, TNFRSF4, HLA-DMA, TGFB1, CD74, HLX, IFNG, ZAP70, CD4, IL2RG, INPP5D, CD5, PAG1, LAG3, SPN, CD28, PTPRC, IL2RA, IKZF1, CD3E, SLA2, TGFBR2, CTLA4, BTLA, LAT, NCK2, PRKCQ, CORO1A, CD80, LAX1, RIPK2, CD226*
Positive regulation of lymphocyte activation	GO:0051251	5.8	8.44E-10	*STAT5A, TNFSF14, HLA-DMA, TNFRSF4, TGFB1, CD74, HLX, IFNG, ZAP70, IL2RG, CD4, INPP5D, CD5, SPN, CD28, PTPRC, IL2RA, IKZF1, CD3E, TGFBR2, PRKCQ, NCK2, CORO1A, CD80, RIPK2*
Positive regulation of leukocyte activation	GO:0002696	5.5	8.67E-10	*STAT5A, TNFSF14, HLA-DMA, TNFRSF4, TGFB1, CD74, HLX, IFNG, ZAP70, IL2RG, CD4, INPP5D, CD5, SPN, CD28, PTPRC, IL2RA, IKZF1, CD3E, TGFBR2, PRKCQ, NCK2, CORO1A, CD80, RIPK2, CD226*
Positive regulation of T cell activation	GO:0050870	6.5	1.63E-09	*PTPRC, IL2RA, IKZF1, CD3E, STAT5A, TGFBR2, TNFSF14, HLA-DMA, CD74, NCK2, PRKCQ, CORO1A, CD80, HLX, IFNG, ZAP70, RIPK2, CD4, IL2RG, CD5, SPN, CD28*

Conclusion: DNA methylation profiling in GCA affected arteries revealed a robust T cell signature and identified key molecules that might help to better understand the pathogenesis of GCA.

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A Signature of microRNAs Overexpressed in Inflamed Temporal Arteries of Patients with Giant Cell Arteritis. Stefania Croci, Alessandro Zerbini, Luigi Boiardi, Francesco Muratore, Alessandra Bisagni, Giulia Pazzola, Luca Cimino, Antonio Moramarco, Davide Nicoli, Enrico Farnetti, Bruno Casali, Alberto Cavazza, Maria Parmeggiani and Carlo Salvarani. Arcispedale S Maria Nuova, Reggio Emilia, Italy.

Background/Purpose: MicroRNAs (miRNAs) are small, non-coding RNAs that suppress gene expression at post-transcriptional level. MiRNAs can regulate innate and adaptive immunity. Moreover, they have been found deregulated in various autoimmune diseases emerging as biomarkers and novel therapeutic targets. Giant cell arteritis (GCA) is an autoimmune inflammatory vasculitis affecting large and medium-sized arteries. Temporal artery biopsy (TAB) showing resident immune cells is the gold standard for the diagnosis of GCA. Nevertheless, a negative TAB does not rule out GCA and some patients receive a diagnosis of TAB-negative GCA according to clinical and laboratory parameters. The present study aimed to identify miRNAs deregulated in GCA and to determine if miRNA levels might allow to discriminate between patients with GCA and those without.

Methods: 48 patients undergoing TAB for suspected GCA were included in the study and divided into 3 groups: GCA with positive TABs (n=23), GCA with negative TABs (n=7) and non-GCA with negative TABs receiving a different diagnosis (n=18). 1990 ACR classification criteria for GCA were satisfied in all GCA patients with positive TABs, in 6 of the 7 GCA patients with negative TABs and in none of the non-GCA patients. To identify candidate miRNAs deregulated in GCA, expression of 1209 miRNAs was profiled with a miRNA array (Ocean Ridge Biosciences, Palm Beach Gardens, FL) in inflamed TABs from 7 GCA patients *versus* normal TABs from 8 non-GCA patients. MiRNAs showing a >2 fold, statistically significant differential expression with a false discovery rate <10%, were selected for further analyses. Their expression was validated by real-time PCR (QIAGEN, Milan, Italy) in different TAB samples as well as PBMCs and PMN cells isolated from GCA and non-GCA patients. To identify which cell type expressed miR-21 in TABs, in situ hybridization (Exiqon, Vedbaek, Denmark) was performed on FFPE tissue sections.

Results: 10 miRNAs emerged deregulated in inflamed TABs from GCA patients by a high throughput miRNA profiling assay. Subsequent real-time PCRs confirmed that miR-146b-5p, -146a, -155, -150 and -21 were significantly more expressed in TABs from GCA patients positive for a transmural inflammatory infiltrate. Negative TABs from GCA patients had a miRNA profile similar to negative TABs from non-GCA patients suggesting that miRNAs might be downstream inflammation. Expression of miR-146b-5p was particularly promising in a diagnostic perspective because it was possible to set a threshold level which correctly classified TABs as inflamed or normal. Within inflamed TABs, miRNA expression levels did not positively correlate with the load of infiltrating immune cells suggesting that miRNAs might be expressed by tissue cells. Indeed, in inflamed TABs, miR-21 was mainly expressed by spindle shaped cells of the media layer and stellate fibroblast-like cells of the intima layer. Moreover, miRNAs were expressed at comparable levels by circulating PBMCs and PMN cells from GCA and non-GCA patients.

Conclusion: miR-146a, -21, -150 and -155 and above all miR-146b-5p emerged as markers of inflammation in TABs from GCA patients, might be involved in GCA pathogenesis thus further investigated as therapeutics targets.

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Accuracy of High Resolution MRI of Scalp Arteries for the Diagnosis of Giant Cell Arteritis: Results of a Prospective Study. Maxime Rhéaume[1], Ryan Rebello[2], Christian Pagnoux[3], Simon Carette[3], Marie Clements-Baker[4], Violette Cohen-Hallaleh[2], David Doucette-Preville[2], B. Stanley Jackson[5], Sam Salama[6], George Ioannidis[7] and Nader A. Khalidi[8]. [1]Division of Rheumatology, St. Joseph's Hospital, McMaster University, Hamilton, ON, [2]Department of Radiology, St. Joseph's Hospital, McMaster University, Hamilton, ON, [3]University of Toronto, Toronto, ON, [4]Queens University, Kingston, ON, [5]Department of Surgery, St. Joseph's Hospital, McMaster University, Hamilton, ON, [6]Department of Pathology, St. Joseph's Hospital, McMaster University, Hamilton, ON, [7]St Joseph's Healthcare Hamilton, Hamilton, ON, [8]St. Joseph's Hospital, McMaster University, Hamilton, ON.

Background/Purpose: Temporal artery biopsy (TAB) remains the gold standard for the diagnosis of giant cell arteritis (GCA). It is invasive and its sensitivity is limited by segmental arterial involvement. We sought to determine the diagnostic accuracy of high-field MRI compared to TAB in patients with suspected GCA.

Methods: All patients referred for TAB at our center were approached for this study. A high-resolution 3T MRI of the scalp arteries was obtained before the TAB was performed. Arterial abnormalities on MRI were assessed according to a previously published grading scheme, evaluating mural thickness and enhancement based on multiplanar postcontrast T1-weighted spin-echo images. Diagnostic accuracy of MRI was evaluated by comparison with TAB results as a primary analysis. Secondary analyses included comparison to clinician diagnosis and ACR criteria.

Results: 191 patients were screened and 171 were included in the study. Exclusions were based on withdrawal of consent (11), contra-indication to MRI (3), non-diagnostic test (3 MRI, 2 TAB) or failure to obtain MRI (1). ACR criteria were met in 137 patients (80.1%). Physician diagnosis was available for 162 subjects, with 78 (48.2%) considered as GCA. The MRI showed abnormal scalp arteries in 60 patients (35.1%) while biopsy was positive in 31 (18.1%). MRI was positive in 29 of those 31 patients with positive TAB (Sensitivity 93.6%). MRI was normal in 109 of those 140 with negative TAB (Specificity 77.9%). Relative to TAB, the negative predictive value of MRI was 98.2%.

Conclusion: High-resolution MRI detects biopsy-positive GCA with high sensitivity. A negative MRI is highly predictive of a negative TAB, such that patients with a negative MRI could safely be spared TAB. The significance of a positive MRI is not as well defined, and this should be the focus of future research.

MRI: Sensitivity, Specificity, Positive predictive value (PPV) and Negative predictive value (NPV)

Index Test	Reference Test	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
MRI	Biopsy	0.936 (0.786,0.992)	0.779 (0.701, 0.844)	0.483 (0.352, 0.616)	0.982 (0.936, 0.998)
MRI	ACR (Fulfillment of at least 3/5 ACR criteria)	0.394 (0.311, 0.481)	0.824 (0.655, 0.932)	0.900 (0.795, 0.962)	0.252 (0.175, 0.344)

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Interleukin 6 Does Not Upregulate Pro Inflammatory Cytokine Expression in an *Ex-Vivo* Model of Giant Cell Arteritis. Lorraine O'Neill[1], Jennifer McCormick[2], Wei Gao[2], Conor Murphy[3], Geraldine M. McCarthy[4], Douglas J. Veale[1], Ursula Fearon[2] and Eamonn S. Molloy[1]. [1]St. Vincent's University Hospital, Dublin 4, Ireland, [2]Translational Rheumatology Research Group, Dublin, Ireland, [3]Royal Victoria Eye and Ear Hospital, Dublin, Ireland, [4]Mater Misericordiae University Hospital, Dublin 7, Ireland.

Background/Purpose: Interleukin 6 (IL 6) is postulated to play a role in the pathogenesis of Giant Cell Arteritis. Several studies have demonstrated increased circulating IL 6 levels and upregulation of IL 6 in the temporal arteries of patients with GCA.

Multiple recent uncontrolled reports have noted improvements in clinical and laboratory parameters in patients with GCA treated with tocilizumab, an IL 6 receptor antagonist. However, persistent vascular inflammation has been reported in some cases.

The aim of this study was to examine the ability of IL 6 to induce pro-inflammatory mediators in *ex -vivo* temporal artery explant cultures.

Methods: 28 patients meeting 1990 ACR classification criteria for GCA were prospectively recruited. To directly examine the effects of IL 6 on pro-inflammatory mediators in GCA, *ex-vivo* temporal artery explant models were established.

Temporal artery explants were cultured in the presence or absence of recombinant human IL 6 (20 or 40 ng/ml) for 24 hours.

IL 6 mediates its effects through gp130 and the IL6 receptor. While gp130 is ubiquitous, the IL 6 receptor is limited to certain cells and therefore cells lacking the IL 6 receptor are unresponsive to the direct effects of IL 6. To overcome this, explants were co-cultured with rIL 6 and its soluble receptor (sIL6R).

Explant supernatants were harvested after 24 hours and assayed for IFNg, TNF, SAA, IL1b, IL 17, IL 8 and VEGF by ELISA. Of the cultured biopsies, 4 were snap frozen, protein was extracted and pSTAT3 expression assessed by Western Blot.

Graphpad Prism Ver 6.0d was used for statistical analysis. **Results** are presented as the mean +/− SEM in pg/ml/mg of biopsy weight.

Results: Stimulation with IL 6 did not induce any of the pro -inflammatory mediators assayed. No differences were observed in the explants cultured in the presence or absence of the sIL6R or between those with a positive (n=11) or negative (n=17) temporal artery biopsy. Increasing the concentration of IL 6 to 40 ng/ml did not alter our findings.

Mean values of VEGF did increase following treatment with IL6, even in the absence of sIL6R in keeping with the known ability of IL 6 to promote angiogenesis.

Western Blot analysis revealed increased expression of pSTAT3 in response to the combination of IL6+sIL6R, but not IL 6 alone, suggesting that the addition of the sIL6R is necessary to induce signal transduction.

	Basal:	Stimulated: IL6 (20 ng/ml)	p value: Wilcoxon signed-rank test
INFg	27.13 ± 8.6	36.10 ± 12.8	0.148
TNF	5.93 ± 1.9	7.39 ± 2.6	0.460
IL1b	2.45 ± 0.6	2.52 ± 0.85	0.945
IL 17	11.08 ± 4.9	16.92 ± 8.20	0.843
IL 8	16, 563 ± 5458	19,118 ± 6698	0.277
SAA * ng/ml/mg	10.42 ± 4.31	7.45 ± 2.54	0.625
VEGF	7.74 ± 3.45	107.3 ± 78.44	0.062

Conclusion: IL6 stimulation of temporal artery explants from patients with GCA, at concentrations sufficient to activate STAT3 and up regulate VEGF, did not result in increased expression of key pro-inflammatory mediators. This data argues against a central role for IL6 in driving vascular inflammation in GCA and raises the hypothesis that anti-IL6 based therapeutic strategies may have a lesser impact on vascular inflammation than on the systemic inflammatory syndrome in patients with GCA.

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A 2-Week Single-Blind, Randomized, 3-Arm Proof of Concept Study of the Effects of Secukinumab (anti-IL17 mAb), Canakinumab (anti-IL-1 b mAb), or Corticosteroids on Initial Disease Activity Scores in Patients with PMR, Followed By an Open-Label Extension to Assess Safety and Effect Duration. Eric L. Matteson[1], Bhaskar Dasgupta[2], Wolfgang A. Schmidt[3], Carlo Salvarani[4], Nagui Gendi[5], Mauro Galeazzi[6], Sylvie Stitah[7], Yue Li[7], Marie-Anne Valentin[7], Bolan Linghu[8] and Stephen J. Oliver[7]. [1]Mayo Clinic, Rochester, MN, [2]Southend University Hospital, Essex, United Kingdom, [3]Immanuel Krankenhaus, Berlin, Germany, [4]Arcispedale-Santa-Maria-Nuova, Reggio Emilia, Italy, [5]Basildon & Thurroch University Hospitals NHS Trust, Basildon, Essex, United Kingdom, [6]Università di Siena, Siena, Italy, [7]Novartis Pharma AG, Basel, Switzerland, [8]Novartis Pharma AG, Cambridge, MA.

Background/Purpose: To assess the effects of a single dose of secukinumab or canakinumab in patients with new onset, untreated polymyalgia rheumatica (PMR).

Methods: In this single-blinded, double-dummy, randomized, active-controlled, parallel-group study, patients with PMR of >1 week duration were randomized 1:1:1 to receive single dose (3 mg/kg/body weight) of either secukinumab or canakinumab, or daily oral prednisone (PRED) at 20 mg a day. The primary endpoint was efficacy after 2 weeks, assessed by the PMR activity score (PMR-AS components: CRP, morning stiffness, ability to elevate arms; 100 mm VAS assessments for patient pain and physician global). Complete response was defined as >70% reduction in patient global assessment VAS compared with baseline, morning stiffness <30 min, and CRP <1.0 mg/dl. Partial response was defined as >50% reduction in patient global assessment VAS compared with baseline and morning stiffness <60 min. Patients treated with biologics failing to achieve criteria for either complete or partial response by Day 15 initiated treatment with PRED 20 mg/day. All patients receiving PRED underwent a scheduled taper after 2 weeks treatment. Patients were followed up to 154 days for safety and duration of treatment effects. Serum levels of IL-6 and VEGF were measured by ELISA.

Results: 16 patients (11 females) were randomized (secukinumab, n=6, mean baseline PMR-AS 46.6; canakinumab, n=5, mean PMR-AS 54.3; PRED n=5, mean baseline PMR-AS 37.5). The primary endpoint was assessed in 13 patients (secukinumab, 6; canakinumab, 3; PRED, 4). PMR-AS reductions from baseline were seen in all patients at day 15: secukinumab =52%; canakinumab =65%; PRED 92%. By Day 15 no biologic-treated patients achieved complete response and only 1 patient in each biologic group achieved a partial response, whereas 1 patient in the PRED arm had complete response and 3 patients had partial responses. CRP reductions were most rapid in the PRED group and more consistent in patients treated with either PRED or secukinumab. In patients treated with PRED, rapid reductions were observed in mean VAS for physician global assessment and patients' assessment of pain compared to only moderate or minimal effects in the secukinumab and canakinumab groups, respectively. PRED induced a rapid and consistent decrease in IL-6 while no consistent effects were noted in patients treated with biologics. Secukinumab induced rapid and consistent decreases in VEGF levels that were not observed in the other two groups. Patients in secukinumab (n=4) and canakinumab (n=3) groups who required switch to PRED with subsequent taper had a 40% and 35% lower monthly average steroid use, respectively, compared to the PRED group (n=4) that had not been exposed to a biologic. All three study treatments were well-tolerated without SAEs or increased infections noted.

Conclusion: In this study PMR-AS reduced more rapidly by Day 15 in prednisone-treated patients than in patients receiving secukinumab or canakinumab. Patients receiving biologics followed by prednisone had overall lower cumulative steroid doses. The therapeutic effects of secukinumab and canakinumab in PMR remains uncertain and deserves further study.

Disclosure: E. L. Matteson, Novartis Pharma AG, 2; **B. Dasgupta**, Novartis Pharma AG, 2; **W. A. Schmidt**, Novartis Pharma AG, 2, Mundipharma, 2; **C. Salvarani**, Novartis Pharma AG, 2; **N. Gendi**, Novartis Pharma AG, 2, Roche Pharma AG, 2, UCB Pharma, 2; **M. Galeazzi**, None; **S. Stitah**, Novartis Pharma AG, 3; **Y. Li**, Novartis Pharma AG, 3; **M. A. Valentin**, Novartis Pharma AG, 3; **B. Linghu**, Novartis Pharma AG, 3; **S. J. Oliver**, Novartis Pharma AG, 1, Novartis Pharma AG, 3.

ARHP Concurrent Abstract Session
Exemplary Abstracts
Sunday, November 16, 2014, 2:30 PM–4:00 PM

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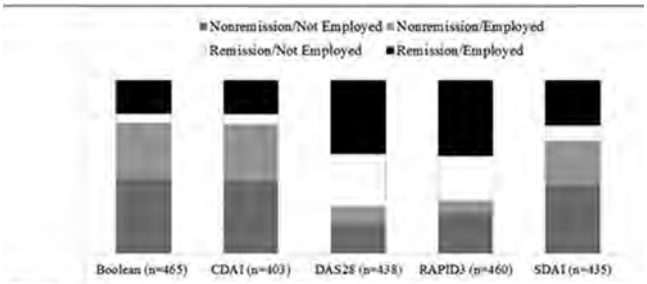
Measuring Rheumatoid Arthritis Remission: Which Index of Disease Activity Best Predicts Work Status? Nancy A. Baker[1], Heather Eng[2], Juan (June) Feng[2], Jason Lyons[2], Yong Gil Hwang[1], Kimberly P. Liang[1] and Larry W. Moreland[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA.

Background/Purpose: Disease remission is the goal of treat-to-target initiatives in rheumatoid arthritis (RA). There are multiple indices to measure disease activity and remission status including those recommended by ACR and EULAR in 2011: the Simplified Disease Activity Index (SDAI) and a Boolean based definition (tender joint count, swollen joint count, C-reactive protein, patient global assessment ≤ 1). The choice of these measures was based on their predictive validity for radiographic damage and the Health Assessment Questionnaire (HAQ), outcomes which are focused on impairment and activity levels. Remission scores should be predictive of community participation, such as employment. As work disability is common for people with RA, it is particularly important that indices can accurately predict work status. This study evaluated each of five common indices of disease activity (Boolean, SDAI, Clinical Disease Activity Index [CDAI], Disease Active Score-28 joint count [DAS28], Routine Assessment of Patient Index 3 [RAPID3]) to identify the best predictor of work status.

Methods: In this cross-sectional study we extracted data on 511 working aged (≤65 year old) RA patients from the Rheumatoid Arthritis Comparative Effectiveness Research (RACER) longitudinal registry based at the University of Pittsburgh. This registry, started in 2010 has enrolled 1,045 RA patients with over 7000 usual care clinic visits. Work status and index data are collected at most visits and we selected the most recent visit that contained information on both. Patients self-identified as "employed" were coded as such; all other categories were coded as not employed. We calculated the Boolean, SDAI, CDAI, DAS28, and RAPID3 scores and coded each patient as in remission/not in remission based on published cut-off scores (Figure 1). We completed 5 separate logistic regressions with work status as the outcome and each index as the predictor variable. Covariates were age, gender, remission duration, disease duration and the presence of any comorbidities (yes/no) measured through the Charlson score, which we dichotomized. We report the C-statistic, which is equivalent to the area under a ROC curve and allows us to judge how well each model discriminated between employed and not employed.

Results and Conclusion: In all models except CDAI, remission status was significantly associated with work status. While all models were moderately good at predicting work status (C-statistic range 0.66 to 0.77), the RAPID3 was the most accurate and the DAS28 and CDAI were the least. A score indicating remission on the RAPID3 would correctly identity that someone would or would not be employed 77% of the time. This superior accuracy may be related to the functional questions included in this index, whereas all other indices rely on symptoms and patient assessment of health without a functional component.



Cut-off	measures ≤1	≤2.8	≤ 2.6	≤1	≤3.3
C-statistic	0.72	0.66	0.67	0.77	0.73
[95% CI]	[0.67, 0.76]	[0.60, 0.72]	[0.61, 0.73]	[0.72, 0.82]	[0.68, 0.78]

Outcome variable: Work status (employed not employed). Predictor variable: Remission status (yes/no). Covariates: Age, gender, remission duration (days), Charlson score (yes/no), disease duration (years).
*All models were significant ($p \leq .05$). Age was a significant predictor in all models, remission status was a significant predictor in all models except the CDAI. Remission duration was a significant predictor in only the RAPID3 model.

Figure 1 – The ability of each index of disease activity to predict work status.

Disclosure: N. A. Baker, None; **H. Eng**, None; **J. Feng**, None; **J. Lyons**, None; **Y. G. Hwang**, None; **K. P. Liang**, None; **L. W. Moreland**, None.

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The Impact of Inadequate Health Literacy on Disease Activity in Patients with Rheumatoid Arthritis. Maria Celeste Orozco[1], Maria Florencia Marengo[1], Christian A. Waimann[1], Ana Inés Marcos[2], Amelia Granel[2], Sofia Velez[3], Federico Zazzetti[3], Juan C. Barreira[4], Paula Kohan[5], Oscar L. Rillo[6], María Victoria Collado[7], Graciela Gómez[8], Ricardo V. Juárez[9], Veronica Lencina[9], Andrea D'Orazio[10], Gustavo Rodriguez Gil[10], Mariana Salcedo[11] and Gustavo Citera[1]. [1]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Hospital San Roque de Gonnet, La Plata, La Plata, Argentina, [3]Hospital Britanico, Buenos Aires, Argentina, [4]British Hospital, Buenos Aires, Argentina, [5]Hospital Gral. de agudos Dr. E. Tornú, Buenos Aires, Argentina, [6]Hospital General de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [7]Instituto de Investigaciones Medicas Alfredo Lanari, Buenos Aires, Argentina, [8]Insituto de Investigaciones Medicas de la UBA, Capital Federal, Argentina, [9]Hospital Señor del Milagro, Salta, Argentina, [10]Hospital Municipal de agudos Dr. Leonidas Lucero, Bahía Blanca, Argentina, [11]Consultorio Privado, San Nicolás, Argentina.

Background/Purpose: Health literacy is the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions. It is being increasingly recognized as important determinant to health outcomes. Patients with low health literacy are less able to manage chronic conditions effectively. The aim of our study was to measure the level of health literacy in patients with Rheumatoid Arthritis (RA) and assess its association with clinical outcomes.

Methods: A multicenter cross-sectional study was conducted. Patient were recruited from 7 outpatients clinics including consecutive patients with diagnosis of RA according to American College of Rheumatology (ACR) 1987 criteria and/or ACR/European League Against Rheumatism (EULAR) 2010 criteria. Health literacy was assessed using the Test of Functional Health Literacy in Adults (S-TOFHLA) (0–36, 0 worst health literacy). Patients were categorized as having low or adequate health literacy using the standard cutoff (<23). Patient reported clinical outcomes included the Clinical Disease Activity Index (CDAI) and the Health Assessment Questionnaire (HAQ). We also collected data regarding patient demographics, comorbidities and treatment adherence -. Adherence to treatment was assessed using the Compliance Questionnaire Rheumatology (CQR; 0 – 100, 0 low adherence). The association between health literacy and clinical/functional outcomes were evaluated using univariate and multivariate models adjusting by age, gender, educational level, disease duration and treatment adherence.

Results: Three hundred and thirty-eight patients were included, 84 % were female, mean age was 53 ± 12 years, disease duration 13 ± 10 years, CDAI 13 ± 11 and HAQ 1.00 ± 0.75. Mean S-TOFHLA score was 26 ±12. Three hundred and two patients (76%) had adequate health literacy. These patients had significantly lower age ($r=-0.22$, $p<0.01$), higher level of education($r=0.40$, $p<0.01$), less number of comorbidities($r=-0.13$, $p<0.01$) and shorter disease duration($r=-0.14$, $p<0.01$). After adjusting for multiple confounders, patients with low level of health literacy showed significantly higher disease activity ($b = 3.7$, $p=0.01$). Health literacy was not associated with HAQ ($b=0.14$, $p=0.14$). Using S-TOFHLA as continuous variables did not affect the results.

Conclusion: A quarter of patients with rheumatoid arthritis had inadequate health literacy, showing higher level of disease activity. Physicians

should recognize that literacy levels of their patients could affect clinical outcomes, and provide appropriate interventions to ease this burden.

Disclosure: M. C. Orozco, None; **M. F. Marengo**, None; **C. A. Waimann**, None; **A. I. Marcos**, None; **A. Granel**, None; **S. Velez**, None; **F. Zazzetti**, None; **J. C. Barreira**, None; **P. Kohan**, None; **O. L. Rillo**, None; **M. V. Collado**, None; **G. Gómez**, None; **R. V. Juárez**, None; **V. Lencina**, None; **A. D'Orazio**, None; **G. Rodriguez Gil**, None; **M. Salcedo**, None; **G. Citera**, None.

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Annual Medical Care Expenditures Among US Adults with Gout, 2005–2011. Miriam G. Cistcrnas[1], Louise Murphy[2], David J. Pasta[3], Edward H. Yclin[4], and Charles Hclrnick[2]. [1]MGC Data Services, [2]Centers for Disease Control and Prevention, [3]DMA Corporation[4]University of California, San Francisco.

Background/Purpose: Costs associated with gout arc of growing interest due to its increasing prevalence, but quantifying those costs has been hampered by its co-occurrence with other highly prevalent, high-cost conditions. We estimated all-cause medical care expenditures and gout-attributable expenditures among US adults with gout age ≥18 years.

Methods: Using the 2005–2011 Medical Expenditure Panel Survc (MEPS), we identified adults with gout by the presence of ICD-9-CM 274. We estimated annual national total (aggregate) and mean per-person all-cause and gout-attributable expenditures overall and for four expenditure categories: ambulatory care (office-based and hospital outpatient); inpatient care; prescriptions; and other (emergency room visits, home health care, vision aids, dental visits, and medical devices). Gout-attributable expenditures were calculated using multis agc regression models that adjusted for demographics (age, sex, race, Hispanic ethnicity, and education), health insurance coverage (any private, public only, or none), and a count of nine costly comorbid conditions. All estimates are in 2011 US dollars.

Results: National total all-cause medical care cxpcnditurcs among the 2.7 million adults reporting gout were $31.8 billion; mean per-person expenditures among US adults with gout were $11,663, compared to $4,643 for all adults. Across expenditure categories, all-cause mean per-person expenditures were: inpatient ($4,329), ambulatory care ($3,704), prescriptions ($2,497), and other ($1,133). National gout-attributable expenditures totaled $7.7 billion (mean per person=$2.805) and accounted for 24% ($7.7 billion/$31.8 billion) of all medical expenditures among US adults with gout. Mean per-person gout-attributable expenditures for inpatient ($1,488) and ambulatory care ($1,349) accounted for essentially all of the attributable expenditures. Attributable expenditures for prescription and other were less than $100 in magnitude and much less than the estimated error.

Conclusion: Mean per-person all-cause medical expenditures were more than 2.5 times higher among adults with gout compared to the entire adult population. Total annual national medical expenditures attributable to gout were $7.7 billion, accounting for almost one of four dollars spent for medical care of US adults with gout. The increasing prevalence of gout suggests increasing costs in the future. Raising awareness about recent therapies and guidelines to identify and treat gout at earlier stages and increase compliance may help moderate those costs.

Disclosure: M. G. Cisternas, None; **L. Murphy**, None; **D. J. Pasta**, None; **E. H. Yelin**, None; **C. Helmick.**, None.

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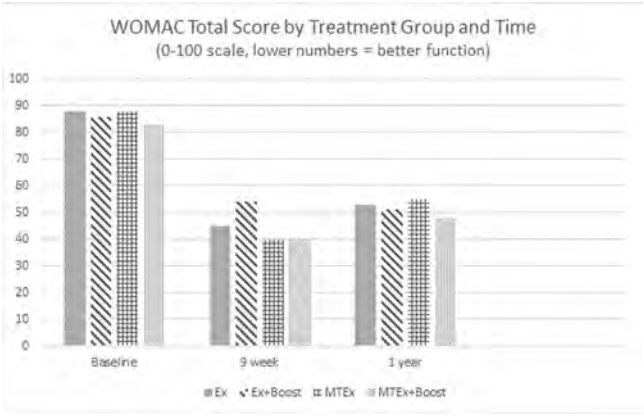
Exercise, Manual Therapy, and Use of Booster Sessions in Physical Therapy for Knee OA: A Multi-Center Randomized Clinical Trial. G Kelley Fitzgerald[1], Julie Fritz[2], John Childs[3], Gerard P. Brennan[4], Douglas P. Landsittel[5], Brett Neilson[6], Alexandra Gil[1] and J. Haxby Abbott[7]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Utah, Salt Lake City, UT, [3]US Army-Baylor University, Schertz, TX, [4]Intermountain Healthcare, Murray, UT, [5]University of Pittsburgh, Center for Health Care Research Data Center, Pittsburgh, PA, [6]Henry M. Jackson Foundation, Bethesda, MD, [7]University of Otago, Dunedin, New Zealand.

Background/Purpose: There is need to improve the magnitude and duration of treatment effects of exercise therapy (ET) for patients with knee osteoarthritis (KOA). There is conflicting evidence that manual therapy (MT) can enhance treatment effect magnitude of ET for pain and function. The use of booster treatment sessions have also been suggested to improve sustainability of these treatment effects, but evidence is lacking. The aims of the study were to: 1) determine if adding MT to ET programs would result in an additive treatment effect on pain and function, and 2) determine if use of booster treatment sessions would result in greater sustainability of these effects in patients with KOA.

Methods: Multi-center randomized clinical trial, including three clinical sites from different regions of the United States. 300 subjects (mean age = 58 ± 9 years; 199 female) meeting the ACR clinical criteria for KOA were randomly allocated to 1 of 4 groups; 1) ET- no booster, 2) ET + booster, 3) MT+EX-no booster, and 4) MT+Ex + booster. Subjects not receiving booster sessions received 12 treatment sessions in 9 weeks. Subjects receiving booster sessions received 8 treatment sessions in 9 weeks then received 4 additional booster treatment sessions distributed over the remaining year. Primary outcome measure was the WOMAC total score. Secondary outcome measures included the numeric knee pain rating, the Timed Up and Go (TUG) test, the 30 sec. chair rising test, and the 40m walk test. Outcome measures were obtained at baseline, 9 weeks, and 1 year. Data was analyzed using a repeated measures linear mixed model of treatment effect and the treatment group by time interaction was performed, adjusting for treatment site location and bilateral knee involvement. Statistical significance was $\alpha = .05$.

Results: The figure summarizes the WOMAC total scores at each time point. There were no statistical or clinically meaningful differences between treatment groups at either follow-up time point. There was no significant treatment group by time interaction. All treatment groups demonstrated meaningful changes in clinical outcome from baseline to the 9 week follow-up (within group effect sizes range =.69 to 1.2; percent change from baseline range = 37%-54%) which was also maintained over the 1 year follow-up period (within group effect sizes range =.70 to.85; percent change from baseline range = 37%-40%). Similar results were observed for all other outcome measures.

Conclusion: Adding MT to ET did not increase the magnitude of treatment effect and use of booster sessions did not exhibit superior sustainability of treatment effects over time. All four treatment approaches tested in this study yield moderate to large improvements in pain and function that were sustained over a one year period.



Disclosure: G. K. Fitzgerald, None; **J. Fritz**, None; **J. Childs**, None; **G. P. Brennan**, None; **D. P. Landsittel**, None; **B. Neilson**, None; **A. Gil**, None; **J. H. Abbott**, None.

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Test of the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) 29-Item Profile in a Large Cohort of Rheumatic Disease Patients. Patricia P. Katz[1], Sofia Pedro[2] and Kaleb Michaud[3]. [1]University of California, San Francisco, San Francisco, CA, [2]National Data Bank, Wichita, KS, [3]University of Nebraska Medical Center and National Data Bank, Omaha, NE.

Background/Purpose: Patient-reported outcomes are routinely used in rheumatology research and clinical care. Yet, often outcomes cannot be compared across studies or diseases because a variety of measures are used in these assessments, and many important health domains are not assessed because of lack of measures or concerns about questionnaire burden. Further, many "traditional" patient-reported outcomes measures are available only in English, which is an increasingly limiting factor. The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) consists of a group of patient-reported outcome measures that span a wide array of physical, social, and emotional health outcomes; are applicable across health conditions; and are available free of charge and in multiple languages. A test of the PROMIS measures has not been undertaken in patients with RA, OA, or

fibromyalgia. This analysis presents an initial psychometric evaluation of PROMIS measures in a large cohort of these patients.

Methods: Data were from a subset of respondents to a single administration of a questionnaire that included the PROMIS 29-item profile. The sample included 528 individuals (RA: 323; OA: 109; fibromyalgia: 96). Using short questionnaires, the PROMIS-29 assesses 7 of the PROMIS health domains: Physical Function, Pain Interference, Fatigue, Depression, Anxiety, Sleep Disturbance, and Ability to Participate in Social Roles. Each section was scored and converted to t-scores, with mean = 50 and SD = 10. Analyses examined correlations of PROMIS measures with scales measuring related constructs (SF-36 subscales, Health Assessment Questionnaire [HAQ], and numeric rating scales for pain, fatigue, and sleep problems), for the total sample and within disease groups. Analyses also examined ability of PROMIS measures to discriminate among levels of satisfaction with health.

Results: PROMIS scales exhibited moderate ($r<0.7$) correlations with most of the comparison measures, with some correlations slightly higher, indicating that similar constructs were being measured (Table 1). Results were similar for each disease group. All PROMIS scales discriminated among levels of satisfaction with health, yielding significant overall ANOVA results and significant non-parametric tests of trend (Table 2).

Conclusion: These PROMIS short forms exhibited strong psychometric properties. Use of PROMIS offers important expansions of current measures so that aspects of health, social functioning, and quality of life that are important to patients can be included without increasing questionnaire burden.

Table 1 Correlation of PROMIS Scales with Related Measures

	PROMIS 29-Item Profile scales*						
	PF	**PI**	**FAT**	**DEP**	**ANX**	**SLP**	**SocR**
SF-36 Physical Function	0.83						
SF-36 Role Physical							0.62
SF-36 Role Emotional							0.43
SF-36 Vitality			−0.77				
SF-36 Bodily Pain		−0.73					
SF-36 Mental Health				−0.69	−0.67		
HAQ	−0.74						
NRS-pain		0.62					
NRS-fatigue			0.71				
NRS-sleep						0.71	

* For all PROMIS scales, higher scores reflect "more" of the construct being measured. E.g., Higher Physical Function scores reflect better functioning; higher Pain Interference scores reflect greater pain interference
PF = Physical Functioning; PI = Pain Interference; FAT = Fatigue; DEP = Depression; ANX = Anxiety; SLP = Sleep disturbance; SocR = Ability to Participation in Social Roles.
HAQ = Health Assessment Questionnaire

Table 2 PROMIS 29-Profile Scores* by Levels of Satisfaction with Health

	PROMIS 29-Item Profile scales*						
Satisfaction with health:	**PF**	**PI**	**FAT**	**DEP**	**ANX**	**SLP**	**SocRole**
Very satisfied (n=61)	46.9	52.7	48.0	45.0	44.6	47.5	52.5
Somewhat satisfied (n=173)	41.1	58.1	53.8	47.9	47.9	51.4	45.8
Neither satisfied nor dissatisfied (n=81)	37.9	61.1	57.9	51.3	51.3	55.0	40.9
Somewhat dissatisfied (n=139)	35.8	63.6	60.9	52.7	52.8	56.0	38.3
Very dissatisfied (n=89)	33.0	66.7	67.2	60.3	58.8	61.7	32.2

* Table presents mean scores for individuals in each satisfaction with health rating group. Differences were tested with ANOVA and non-parametric test for trend. All were significant p<.001.

Disclosure: P. P. Katz, None; **S. Pedro**, None; **K. Michaud**, None.

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Randomized Clinical Trial of Group Vs. Individual Physical Therapy for Knee Osteoarthritis. Kelli D. Allen[1], Dennis Bongiorni[2], Hayden B. Bosworth[3], Cynthia Coffman[3], Santanu Datta[3], David Edelman[3], Jennifer H. Lindquist[2], Eugene Oddone[3] and Helen Hoenig[3]. [1]Durham VA Medical Center and University of North Carolina at Chapel Hill, Durham, NC, [2]Durham VA Medical Center, Durham, NC, [3]Durham VA Medical Center and Duke University Medical Center, Durham, NC.

Background/Purpose: Physical therapy (PT) is a key component of treatment for knee osteoarthritis (OA). There is a high demand for PT services in many healthcare systems, resulting in a need for evidence-based models for delivering PT in an efficient manner. A group-based approach to PT can extend services to more patients with lower staffing requirements than typical individual PT. The objective of this trial was to compare the effectiveness of a group-based PT program (GPT) with usual individual PT (IPT) for knee OA.

Methods: 320 patients with knee OA at the VA Medical Center in Durham, NC (mean age = 60, SD=10; 88% male; 58% non-white) were randomized to either GPT or IPT. GPT included six 1-hour sessions, every other week, co-led by a physical therapist and PT assistant, with 8 participants per group. IPT, modeled after typical outpatient PT care for knee OA at the Durham VAMC, included two 1-hour visits with a physical therapist, 2–3 weeks apart. Both PT interventions included a home exercise program, as well as individual evaluations of functional limitations and needs for braces or assistive devices. GPT sessions also included exercise sessions supervised by the PT assistant. The primary outcome was the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC; range 0–96, higher scores indicate worse symptoms), and the secondary outcome was objective physical function (Short Physical Performance Battery; SPPB, range 0–20, higher scores indicate better function); both were assessed at baseline and 12-weeks, and WOMAC was also assessed at 24-weeks. Linear mixed models were used to assess the difference in improvement in outcomes between arms, adjusting for clustering of group sessions within the GPT arm.

Results: The median numbers of sessions attended for GPT and IPT were 5 (out of 6 possible) and 2 (out of 2 possible), respectively. At 12-week follow-up, WOMAC scores were 2.7 points lower in the GPT group vs. IPT [95% confidence interval (CI) = −5.9, 0.5; p=0.10], indicating no meaningful difference in improvement between arms. However, mean total WOMAC scores declined −4.5 points from baseline across both arms combined [95% CI =−6.8,-2.2; p=0.0001], indicating meaningful improvement. Similarly, for the WOMAC pain and function subscales and SPPB scores there was improvement across both arms at 12-weeks ($p<0.0001$, p=0.001, and p=0.02) but no difference in improvement between arms (p=0.19, p=0.12, and p=0.37). At 24-week follow-up, WOMAC scores across both arms were 3.1 points lower compared to baseline [95% CI = −5.4, −0.7; p=0.01], indicating some sustained improvement in both groups, with no difference between groups (p=0.45).

Conclusion: Results of this study confirm that PT improves pain and functional outcomes in patients with knee OA. Outcomes did not differ substantially between GPT and IPT arms, suggesting that either is an effective means of delivering PT services for knee OA. The GPT approach in this study required less overall staff time per patient to deliver, and it could provide services efficiently to larger numbers of patients. Therefore it should be considered as a viable model for health systems to provide this service to patients with knee OA.

Disclosure: K. D. Allen, None; **D. Bongiorni**, None; **H. B. Bosworth**, None; **C. Coffman**, None; **S. Datta**, None; **D. Edelman**, None; **J. H. Lindquist**, None; **E. Oddone**, None; **H. Hoenig**, None.

ACR Concurrent Abstract Session
Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes I: Research Perspectives
Sunday, November 16, 2014, 4:30 PM–6:00 PM

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Symptom Increase in Fibromyalgia Is Not Consistent with the Central Sensitization or Central Hyperresponsiveness Hypothesis. Frederick Wolfe[1], Brian T. Walitt[2], Johannes Rasker[3], Robert S. Katz[4] and Winfried Häuser[5]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Washington Hospital Center, Washington, DC, [3]University Twente, Enschede, Netherlands, [4]Rush Medical College, Chicago, IL, [5]Klinikum Saarbrücken, Saarbrücken, Germany.

Background/Purpose: The current dominant hypothesis explains fibromyalgia (FM) as a centralized pain state in which the CNS originates or amplifies pain, which is then accompanied by fatigue, memory problems, and sleep and mood disturbances[1]. The often noted "pan-positive review of symptoms" is attributed to central hyperresponsiveness not to psychological factors or "somatization."[1] Surprisingly, this explanation of non-pain symptoms has never been validated. As fibromyalgia and widespread pain (WP) have been accepted as evidence of the presence of central sensitization (CS), we used the widespread pain index (WPI), a non-symptom containing component of the polysymptomatic distress scale (PSD), to test whether the rate of increase in non pain symptoms as WP increased was greater in the presence of PSD defined fibromyalgia and WSP then in their absence.

Methods: We studied 3,562 mixed rheumatic disease patients, and diagnosed FM by modified ACR FM criteria. To preclude bias because of the non-pain symptoms included in the PSD, we used WPI alone and as a surrogate for the PSD. We formed an ad hoc fibromyalgia symptom count

(FSC) (0–19) by summing 19 non-pain related symptoms. We used linear splines and regression models to calculate separate slopes for symptom prediction at WPI levels between 0–6 and 7–19. An increase in the slope of the 7–19 WPI scores compared with the 0–6 WPI scores was accepted as evidence of the effect of CS.

Results: 96% of those with a WPI score ≥7 satisfied WP criteria, and FM was correctly classified in 89% (kappa 0.703). The FSC increased monotonically as WPI increased (Figure 1), and the slope for WPI 0–6 was 0.68 compared with 0.25 for 7–12 ($P<0.001$). For each of the 19 symptoms examined, slopes were compared by odds ratios and were significantly lower in the 7–12 group (Table 1).

Conclusion: Our data show no increase in non-pain symptom slopes in subjects with high WPI. Instead, symptom increase is monotonic, and the rate of increase is greater at lower levels of WPI. Alternative hypotheses for increase in symptoms should include factors such non-CS pain and psychological variables.

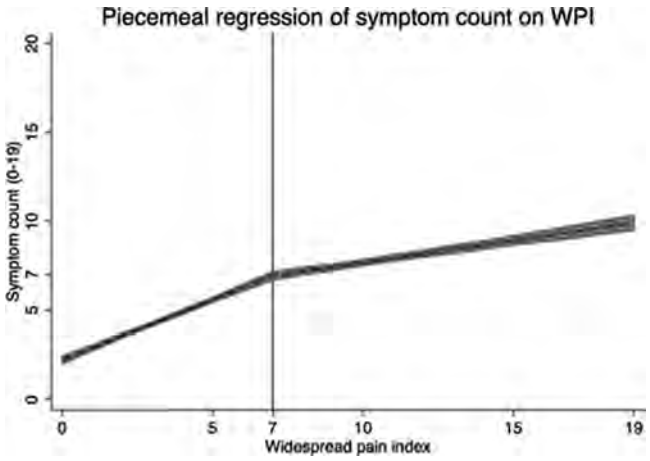
References

1. Clauw DJ. Fibromyalgia: A Clinical Review. JAMA. 2014;311(15):1547–1555.

Table 1. Odds ratios (OR) for rate of symptoms in WPI ≥7 compared with 0–6

Variable	OR	Variable	OR	Variable	OR
Diarrhea	0.85	Nausea	0.79	Tinnitus	0.90
Dizziness	0.83	Paresthesias	0.81	Vision prob	0.83
Dry eyes	0.88	Photosensitivity	0.86	Vomiting	0.87
Dry mouth	0.85	Bruising	0.82	Alopecia	0.89
Dyspnea	0.88	Heartburn	0.85	Anorexia	0.83
Hearing prob	0.87	Rash	0.92*	Asthma	
Urticaria	0.83	Reynaud's	0.91	Constipation	0.84
Oral ulcer	0.84	Seizures	0.89*	Fever	0.84
Muscle weakness	0.77	Dysgeusia	0.82	Itching	0.86

*Not significant



Disclosure: F. Wolfe, None; **B. T. Walitt**, None; **J. Rasker**, None; **R. S. Katz**, None; **W. Häuser**, None.

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Polysymptomatic Distress Categories for Clinical and Research Use.

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Background/Purpose: The polysymptomatic distress (PSD) scale is derived from variables used in the 2010 American College of Rheumatology (ACR) fibromyalgia (FM) criteria as modified for survey and clinical research. The scale is useful in measuring the effect of PSD over the full range of human illness, not just in those who are ACR criteria positive. However, no PSD scale categories have been defined to distinguish severity of illness in FM or in those who do not satisfy criteria. We analyzed the scale and multiple covariates to develop useful clinical categories for PSD and to further validate the scale.

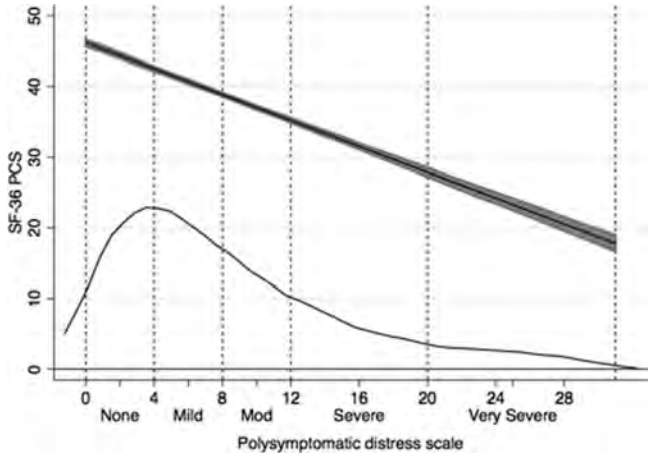
Methods: Fibromyalgia was diagnosed according to the research criteria modification of the 2010 ACR fibromyalgia criteria. We used the 2012 German general population survey (N=2445) to establish "normal" values. We then investigated categories in a large sample of patients with pain: 2,732 with rheumatoid arthritis (RA), and developed categories by utilizing germane clinic variables that had been previously studied for severity groupings. By ACR definition, FM cannot be diagnosed unless PSD is at least 12.

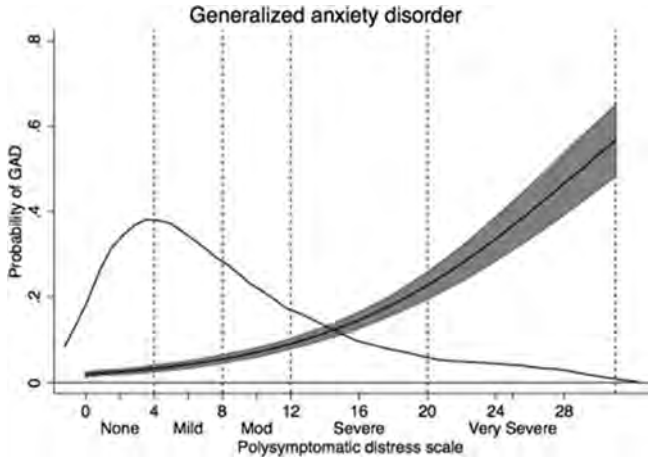
Results: The mean PSD of those with FM in the General population was 16.2 and was 19.2 in the RA clinical sample. Based on population categories and regression analysis and inspections of curvilinear relationships in RA, we established PSD severity categories of None (0–3), Mild (4–7), Moderate (8–11), Severe (12–19) and Very severe (20–31). Categories were statistically distinct, and a generally linear relationship between PSD categories and covariate severity was noted (Table and figures). The thin line in the figures represents the distribution of PSD values.

Conclusion: The described PSD categories are clinically relevant and demonstrate FM type symptoms over the full range of clinical illness, not just in FM positive subjects. Although FM criteria can be clinically useful, no clear-cut distinction between FM (+) and FM (−) subjects can be seen in our data.

Table 1. Clinical variables according to PSD severity groups.

PSD Group	PSD (0–3)	PSD (4–7)	PSD (8–11)	PSD FM (+) (12–19) FM (−) excluded	PSD FM (+) (20–31) FM (−) excluded
Pain (0–10)	1.3	2.7	4	5.3	6.8
Global severity (0–10)	1.4	2.8	3.9	5.2	6.3
HAQ (0–3)	0.4	0.8	1.1	1.4	1.7
PCS score (SF-36)	47.4	40.2	34.6	30.8	27.5
GAD Anxiety case (%)	1.3	3.4	6.8	22.3	30.6
PHQ-2 Depression case (%)	0.1	2.3	5.6	26.1	34.8
Regional Pain Scale (0–19)	0.8	2.6	5	8.2	16.3
Symptom severity (0–12)	0.9	2.8	4.3	7.2	8.2
ACR FM criteria (+) (%)	0.0	0.0	0.0	100.0	100.0
PSD (0–31)	1.7	5.4	9.3	15.4	24.5
Widespread pain (%)	0.8	18.0	57.5	87.8	100.0





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Small Fiber Neuropathy in Women with Fibromyalgia. a Clinical-Pathological Correlation Using Confocal Corneal Biomicroscopy. Manuel Ramírez-Fernández[1], Laura-Aline Martinez-Martinez[2], Angelica Vargas-Guerrero[2], Manuel Martínez-Lavín[2], Everardo Hernandez Quintela[1] and Jorge Velazco-Caspia[1]. [1]Asociación para Evitar la Ceguera en México, Mexico City, Mexico, [2]Instituto Nacional de Cardiologia, Mexico City, Mexico.

Background/Purpose: A consistent line of investigation proposes that fibromyalgia is a sympathetically maintained neuropathic pain syndrome (Semin Arthritis Rheum 2000;29:197). This view has been recently reinforced by several controlled studies describing decreased small nerve fiber density in skin biopsies of patients with fibromyalgia (Brain 2013;136:1857).

Small fiber neuropathy is a disorder of the peripheral nerves that primarily affects small somatic fibers and sympathetic fibers resulting in sensory changes and autonomic dysfunction. The cornea receives the densest small fiber innervation of the body. Confocal corneal biomicroscopy is a new noninvasive method to assess small nerve fiber pathology.

The main objective of this cross-sectional investigation was to assess the corneal small nerve fiber morphology in patients with fibromyalgia using confocal microscopy. The secondary objective was to correlate corneal nerve microscopic features with fibromyalgia severity parameters contained in several validated questionnaires.

Methods: We studied 17 female patients with fibromyalgia (mean age = 43 ± SD 5) and 17 age-matched healthy female control subjects. A central scan of the total corneal thickness was obtained with a confocal microscope (Confoscan 4, Fortune Technologies, Italy). A single ophthalmologist expert in corneal pathology evaluated stromal nerves morphology and thickness using the Navis v. 3.5.0. Software (NIDEK, Multi-Instrument Diagnostic System, Japan). Nerve thickness was defined as the mean between the widest and the narrowest portion of each analyzed stromal nerve. Nerve smoothness was defined as the difference between the widest and the narrowest portions of each analyzed stromal nerve. Measurements were done without knowledge of the clinical diagnosis. All studied subjects filled out different questionnaires assessing fibromyalgia severity, including a neuropathic symptom questionnaire (LANSS).

Results: Corneal stromal nerves were easily identified as bright linear silvery structures. Patients with fibromyalgia had nerve thickness of 5.9 ± 2.2 micrometers (mean ± SD) significantly different from control's values (7.4 ± 2.4) $p < 0.0001$. The difference between widest and narrowest nerve diameter was also dissimilar in patients (1.8 ± 1.3) vs. controls (2.6 ± 1.5) $p < 0.0001$. Remarkably; when patients and controls were grouped together (n = 34), there was a negative correlation between corneal stromal nerve thickness and LANSS neuropathic symptoms questionnaire score (Spearman's r = - 0.36, $p = 0.03$) as well as with tender points number (r = - 0.38, $p = 0.02$), and other non-pain-related fibromyalgia symptoms.

Conclusion: Confocal biomicroscopy demonstrates that women suffering from fibromyalgia have thinner and smoother corneal nerve fibers when compared to healthy controls. When controls and patients are grouped together, there is a correlated continuum between the degree of corneal nerve pathology and fibromyalgia symptoms. Small fiber neuropathy may play a key role in fibromyalgia's pathogenesis.

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The Fibromyalgia Syndrome and Widespread Pain Frequency in Active Duty U.S. Service Members with Posttraumatic Stress Disorder. Bernard Hildebrand Jr. [1], Jay B. Higgs[1], Douglas Williamson[2], Edna Foa[3], Patricia Resick[4], Jim Mintz[2], Antoinette Brundige[2], Kevin Kelly[5], Adam Borah[5], Stacey Young-McCaughan[2], Brett Litz[6], Elizabeth Hembree[3] and Alan Peterson[2]. [1]San Antonio Military Medical Center, JBSA - Fort Sam Houston, TX, [2]The University of Texas Health Science Center at San Antonio, San Antonio, TX, [3]University of Pennsylvania, Philadelphia, PA, [4]Duke University, Durham, NC, [5]Carl R. Darnall Army Medical Center, Fort Hood, TX, [6]VA Boston Healthcare System, Boston, MA.

Background/Purpose: Posttraumatic stress disorder (PTSD) and pain are common amongst US military service members who have deployed to Iraq and Afghanistan. Studies suggest the co-morbidity of PTSD and pain exacerbates somatic symptoms, and the relationship between PTSD and somatic symptom disorders, including the fibromyalgia syndrome (FMS), is a subject of much importance. The STRONG STAR Consortium offers a unique opportunity to study FMS in the context of a series of investigations of PTSD risk factors, features, and treatment methods in active duty personnel during a period of ongoing military conflict. We report the prevalence of FMS and widespread pain (WP) in pre-deployment, active duty US military service members and in post-deployment service members with PTSD.

Methods: Active duty US veterans of the wars in Iraq and Afghanistan enrolled in STRONG STAR Consortium studies were evaluated. A questionnaire screening for WP, symptom severity, symptom duration, and a prior diagnosis of a pain disorder was administered as part of the assessment battery for two treatment studies of PTSD patients and a prospective study assessing the effect of military deployment on PTSD development. The prevalence of WP and FMS were determined using 1990 ACR Criteria and the Wolfe modification to the 2010 ACR criteria, respectively.

Results: Of 4120 active duty military service members assessed pre-deployment, 118 (3%) met study criteria for the classification of FMS and 244 (5.9%) for WP. In a cohort of 181 service members with PTSD, 57 (31%) met criteria for FMS and 48 (27%) had WP. A separate cohort of 171 service members with PTSD identified 67 (37%) patients with FMS and 51 (30%) with WP.

Conclusion: The prevalence of FMS and WP was markedly elevated in active duty military service members seeking treatment for PTSD when compared to a sample of active duty personnel screened just prior to deployment. Further study may help answer questions regarding the intersection of FMS with PTSD and enable development of tailored therapies appropriate for US service members and veterans with PTSD, FMS and related disorders.

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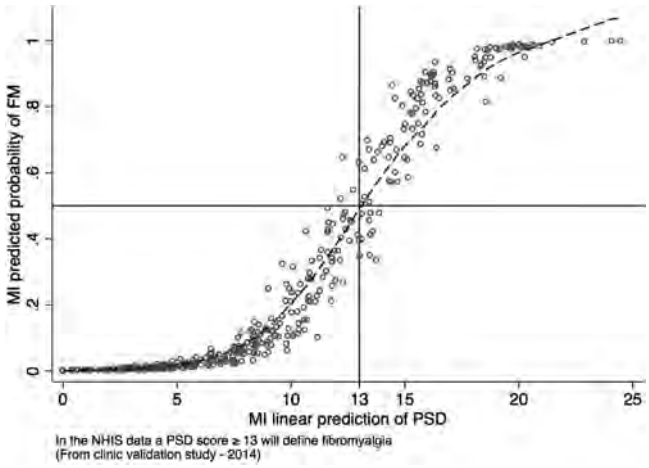
Development of Fibromyalgia and Polysymptomatic Distress Definitions in the National Health Interview Survey. Brian Walitt[1], Richard Nahin[2], Robert S. Katz[3], Martin J. Bergman[4] and Frederick Wolfe[5]. [1]MedStar Health, Washington, DC, [2]National Institutes of Health, Bethedsa, MD, [3]Rush Medical College, Chicago, IL, [4]Taylor Hospital, Ridley Park, PA, [5]National Data Bank for Rheumatic Diseases, Wichita, KS.

Background/Purpose: A detailed understanding of fibromyalgia and its symptoms in the US population would be valuable. The National Health Interview Survey (NHIS) is the principal source of civilian population data in the USA. To study fibromyalgia in the NHIS requires the development of a fibromyalgia definition that uses NHIS questions and a subsequent validation of that definition with a standard fibromyalgia definition. However, the 2011 modified American College of Rheumatology (ACR) criteria and the NHIS questionnaire set evaluate pain differently and over different time periods. In particular, NHIS inquires about joints while the ACR criteria about painful regions. To reconcile and adjust for these differences we administered the ACR criteria and questions from the NHIS at the same time to rheumatic disease patients.

Methods: In 2012, NHIS collected data about joint pain, fatigue, subjective cognitive impairment, mood, headaches, and sleep. A questionnaire was developed that incorporated 2012 NHIS questions along with the questions of the 2011 modified ACR research criteria for fibromyalgia. These questionnaires were sequentially administered to 415 patients during office visits in 2 rheumatology clinics.

Results: For the 415 questionnaires, the average missing items per questionnaire was 1.4, with percent missing for items ranging between 0 and 19.2%. 274 questionnaires were completed without missing data. We used multiple imputation by chained equations and 10 iterations to develop a complete imputed set of 415 questionnaires. We tested a series of matching and regression techniques to identify the optimum set of predictors based on measurements of PSD and ACR criteria as determined by the 2010 modified ACR research criteria. The R-Squared for measured and predicted PSD was 0.781. In a logistic model, we tested NHIS predictors against observed ACR criteria positivity. The area under the receiver-operating curve (AUC ROC) was 94.6. 88.0% of cases were properly classified, and the sensitivity/specificity was 74.7%/93.4%.The NHIS definition found to best approximate 2010 ACR criteria included specific multiple painful joint sites, problems with concentration, fatigue and abdominal pain.

Conclusion: It is feasible to use NHIS questions to approximate both fibromyalgia diagnoses and polysymptomatic distress in 2012 NHIS data. This definition can be used for the epidemiologic study of fibromyalgia in NHIS.



Disclosure: B. Walitt, None; **R. Nahin**, None; **R. S. Katz**, None; **M. J. Bergman**, None; **F. Wolfe**, None.

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Resting State Functional Connectivity Differs Between Chronic Fatigue Syndrome Patients and Healthy Controls. Jason Craggs[1], Charles Gay[1], Andrew O'Shea[1], Ricky Madhavan[1], Donald Price[1], Michael Robinson[1] and Roland Staud[2]. [1]University of Florida, Gainesville, FL, [2]Univ of Florida Med Ctr/JHMHC, Gainesville, FL.

Background/Purpose: Examining neural activity in the absence of task (i.e. resting state) is an active area of research. Functional connectivity, defined as correlations in BOLD signal between two brain regions, is a promising component of fatigue/pain research. Seed to voxel analyses are one approach used to estimate functional connectivity between brain areas. This approach takes the BOLD signal time course of a priori defined seeds and compares their signals to all other voxels in the brain. We determined brain areas of chronic fatigue syndrome (CFS) patients as seeds for connectivity analysis that demonstrated abnormal resting cerebral blood flow during arterial spin labeling (ASL) functional MRI.

Methods: CFS was determined using the CDC Criteria. 15 CFS patients (age = 50.5±13.0)) and 12 HC (age = 49.2±12.2) were MRI scanned with a 3 Tesla Achieva during rest using a pseudo-continuous arterial spin labeling (pCASL) sequence. ASL data were corrected for rigid body motion and smoothed in SPM8. Label and control images were subtracted to create a perfusion time series. The perfusion time series was used to quantify cerebral blood flow (CBF) using the software aslTBX. A mean CBF image was created which was normalized to MNI space and resampled into 2mm isotropic voxels. An independent samples t-test was used to examine voxel-wise differences in CBF between CFS patients and HC. Resulting t-maps were thresholded with a t-statistic > 4.0 and a cluster size > 120 mm^3. 2 distinct clusters passed this threshold and were used to create seed masks for subsequent BOLD functional connectivity analyses. BOLD resting state data were slice-time corrected, realigned and resliced into 3mm isotropic voxels, co-registered to the anatomic volume, warped into MNI standard space and spatially smoothed. Data were spike-corrected to reduce the impact of artifacts using the post-processing Artifact Detection Tool. The final processing steps were then carried out using the functional connectivity toolbox Conn that implements the component-based noise correction method strategy for physiological and other noise source reduction, which included: Temporal (band-pass) filtering, and removal of several nuisance variables, such as CSF and white matter signal, rigid body motion parameters, and outlier data points.

Results: Significantly decreased blood flow was observed in the right parahippocampal gyrus of CFS patients [27.69 (6.22)] compared to HC [40.51 (7.89) (ml/100g/min)]]. Subsequent analyses showed increased connectivity between the parahippocampal seed and the supramarginal gyrus of CFS patients compared to HC.

Conclusion: Our novel method of generating seeds for functional connectivity analyses, using multi-modal neuroimaging data, demonstrated increased connectivity between brain areas involved in memory and language processing of CFS patients.

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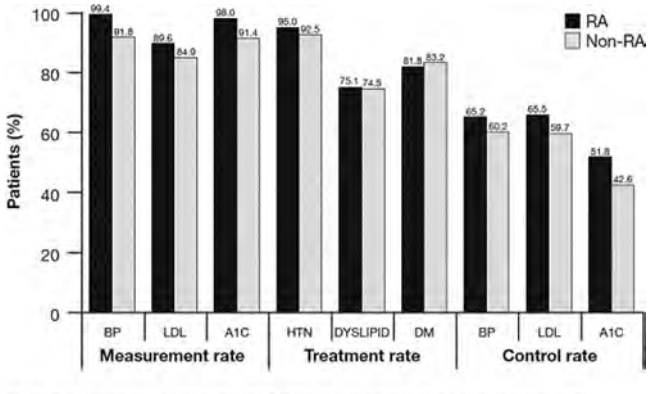
Traditional Cardiovascular Risk-Factor Management in Patients with Rheumatoid Arthritis Compared with Matched Non-Rheumatoid Arthritis Patients in a US Managed Care Setting. J. An[1], K. Reynolds[2], E. Alemao[3], H. Kawabata[3], D. H. Solomon[4], K. P. Liao[4] and T. C. Cheetham[2]. [1]Western University of Health Sciences, Pomona, CA, [2]Kaiser Permanente Southern California, Pasadena, CA, [3]Bristol-Myers Squibb, Princeton, NJ, [4]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Studies have suggested suboptimal care of traditional cardiovascular risk factors (CRF) in patients (pts) with RA as a reason for elevated CV risk compared with the general population. However, these studies lacked a comparison group, laboratory test results and data on blood pressure (BP) measurements. In this study, we compared CRF management for pts with RA with that of matched non-RA pts within an integrated healthcare delivery system with access to electronic medical records.

Methods: Pts aged ≥18 yrs with ≥2 RA diagnoses plus a DMARD were identified as an RA cohort between 01/01/2007 and 12/31/2011 within Kaiser Permanente Southern California. Pts with RA were followed from their first RA diagnosis or prescription date (index). Each pt with RA was matched by age and sex to 4 pts without any RA diagnoses. Non-RA pts were required to have at least one office visit or hospitalization within 12 months from the index date of the matched pair, and the closest encounter date was specified as an index date. Pts without continuous enrollment 12 months prior and post the index date were excluded from the study cohort. Descriptive statistics were used to compare CRF management between RA and non-RA pts. The same analyses were repeated for 1:1 age- and sex-matched osteoarthritis pts as a non-RA group.

Results: A total of 9440 RA and 31,009 matched non-RA pts were included in the study. Mean [SD] age was 56.8 [14.1] for RA and 56.5 [13.9] years for non-RA pts, and 76% were female in both groups. At baseline, 42.9% of RA pts had hypertension, 30.2% had dyslipidemia, 22.9% were obese, and 11.6% were smokers, whereas 32.4% of non-RA pts had hypertension, 35.8% had dyslipidemia, 23.1% were obese, and 10.5% were smokers. Mean [SD] number of office visits during the first yr of follow-up was higher in RA compared with non-RA pts (13.2 [10.8] vs 8.2 [9.1], $p<0.001$). Rates of BP measurement for treated hypertension and low-density lipoprotein (LDL) cholesterol measurement for treated dyslipidemia were higher in pts with RA compared with non-RA pts (BP: 99.4 vs 91.8%, $p<0.001$; LDL: 89.6 vs 84.9%, $p<0.001$). Treatment rates for hypertension were slightly higher in pts with RA compared with non-RA pts (95.0 vs 92.5%, $p<0.001$) and similar for dyslipidemia (75.1 vs 74.5%, $p=0.393$). RA pts and non-RA pts had similar rates of BP control but higher rates of LDL and A1C control (BP: 65.2 vs 60.2%, $p=0.996$; LDL: 65.5 vs 59.7%, $p=0.005$; A1C: 51.8 vs 42.6%, $p<0.001$). These results were consistent with results for pts with osteoarthritis as a matched non-RA group.

Conclusion: CRF management in pts with RA was slightly better than the management in non-RA pts in a US managed care setting. The finding of this analysis indicates that the higher CV risk in pts with RA is unlikely to be driven by poor control of traditional CV risk factors.



BP=blood pressure; LDL=low-density lipoprotein cholesterol; A1C=hemoglobin A1C; HTN=hypertension; DYSLIPID=dyslipidemia; DM=diabetes

Figure. Traditional CRF Management for RA and Matched Non-RA Pts

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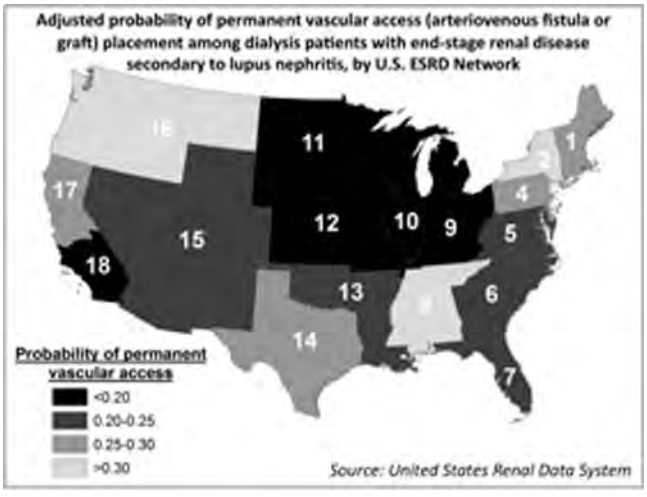
Insurance Status and U.S. Region Associated with Placement of Permanent Vascular Access in Dialysis Patients with End-Stage Renal Disease Secondary to Lupus Nephritis. Laura Plantinga[1], Cristina M. Drenkard[1], Rachel Patzer[1], William McClellan[1], Stephen Pastan[1] and S. Sam Lim[2]. [1]Emory University, Atlanta, GA, [2]Emory University School of Medicine, Division of Rheumatology, Atlanta, GA.

Background/Purpose: Prior data suggest sociodemographic and regional variability in various indicators of quality of end-stage renal disease (ESRD) care, both overall and in the SLE population, but, to our knowledge, no study has addressed the placement of a permanent vascular access prior to the start of hemodialysis in patients with ESRD secondary to lupus nephritis (LN-ESRD). We aimed to describe permanent vascular access placement among hemodialysis patients with LN-ESRD and to examine whether this placement differs by sociodemographic factors and across the 18 U.S. ESRD Networks, which are Centers for Medicare & Medicaid Services-defined regions that implement ESRD quality-of-care initiatives.

Methods: Among 5562 incident U.S. hemodialysis patients with LN-ESRD initiating treatment 7/05–9/11, we estimated the associations between permanent access placement (arteriovenous fistula or graft used or in place on first dialysis, vs. temporary catheter only) and race/ethnicity, insurance at the start of ESRD, and ESRD Network using national surveillance data (United States Renal Data System). Logistic regression models were used to estimate odds ratios (ORs) and confidence intervals (CIs), with adjustment for potential demographic (age, sex, race/ethnicity, insurance) and clinical (BMI, hypertension, cardiovascular disease) confounders.

Results: Fewer than one-quarter (24.4%) of incident hemodialysis patients with LN-ESRD patients had a permanent vascular access placed at start of dialysis, compared to 36.0% of other ESRD patients. Hispanic LN-ESRD patients were less likely than their white counterparts to have a permanent vascular access (20.5% vs. 28.2%), but the association was not statistically significant after adjustment (OR=0.85; 95% CI, 0.69–1.05). Placement did not differ in black vs. white LN-ESRD hemodialysis patients. After adjustment, private, Medicaid, and other insurance were associated with equivalent likelihood of permanent vascular access, but having no insurance was associated with 38% lower likelihood of permanent vascular access among LN-ESRD patients (OR=0.62; 95% CI, 0.49–0.79). There was substantial, statistically significant Network-level variation in likelihood of permanent vascular access, with adjusted probabilities of permanent vascular access used or in place at first dialysis ranging nearly 2-fold, from 0.17 (Network 10, Illinois) to 0.33 (Network 16, Northwest).

Conclusion: The vast majority of LN-ESRD patients on hemodialysis are not initiating treatment with a permanent vascular access. LN-ESRD patients who are Hispanic or uninsured or who live in the Midwest or Southern California at the start of ESRD are less likely to have permanent vascular access. Targeted interventions to increase permanent vascular access among SLE patients with ESRD are warranted to prevent potential morbidity and mortality associated with temporary catheters.



Disclosure: L. Plantinga, None; **C. M. Drenkard**, None; **R. Patzer**, None; **W. McClellan**, None; **S. Pastan**, None; **S. S. Lim**, None.

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Race and Sex Specific Incidence Rates and Predictors of Total Knee Arthroplasty: Data from the Osteoarthritis Initiative, 7 Years Follow up. Jamie E. Collins, Bhushan Deshpande, Jeffrey N. Katz and Elena Losina. Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Total knee arthroplasty (TKA) is used to reduce pain and improve functional status in persons with symptomatic knee osteoarthritis (OA). Several studies point to differential uptake of TKA in women and racial minorities, but most do not distinguish between the effect of demographic factors on the prevalence of knee OA vs. uptake of TKA among those with knee OA. We sought to estimate sex-, race- and age-stratified incidence rates of TKA among persons with symptomatic radiographic knee OA in the Osteoarthritis Initiative (OAI) over 7 years of follow up and document the independent effect of demographic factors on TKA incidence.

Methods: We used data from the OAI, a U.S. multicenter, longitudinal, observational study of knee OA. We selected knees with radiographic, symptomatic OA at baseline (KL 2+, WOMAC Pain at least 1). We determined the TKA incidence rate as the ratio of number of TKAs in a specific subgroup over time at risk for TKA. Time at risk was defined from time of enrollment to time of TKA or to the last available visit date for those without TKA. We computed incidence rate per person-year and used repeated measures Poisson regression to identify the independent contribution of sex, age and race to the incidence of TKA.

Results: We used data from 2,630 knees (1,915 subjects) with radiographic, symptomatic knee OA at baseline. 1,488 (57%) were KL2, 871 (33%) were KL3, and 271 (10%) were KL4. There were 281 TKAs over 84 months of follow-up, for an overall annual incidence rate of 1.7% (95% CI: 1.5 – 2.0). The annual incidence rate of TKA among Whites was estimated at 2.0% (1.8 – 2.3) compared to 1.1% (0.8 – 1.5) in non-Whites. The annual incidence rate of TKA among those who were younger than 65 years was estimated at 1.5% (1.2 – 1.8) compared to 2.1% (1.8 – 2.6) among older persons. In adjusted analysis, higher incidence of TKA was significantly associated with White race and female sex (Table). After adjusting for income and health insurance status, Whites had 1.7 times the rate of TKA compared to non-Whites. Whites were more likely to earn more than $50k annually compared to non-Whites (62% vs. 38%); in income-stratified analysis the racial disparity in TKA incidence persisted: Whites had 1.5 (1.0 – 2.3) times the rate of TKA vs. non-Whites among subjects earning less than $50k and 2.2 (1.2 – 3.8) times the rate among subjects earning more than $50k.

Conclusion: We used a large longitudinal cohort of persons with diagnosed knee OA to determine the incidence of TKA in specific demographic subgroups. This approach overcomes prior estimates from population-based samples that could not distinguish risk factors for OA from risk factors for TKA. In this cohort, with adjustment for age, sex, radiographic severity, income and insurance status, Whites had 1.7 times the TKA incidence of non-Whites. These data confirm the racial disparity suggested by population-based estimates and underscore the need for interventions to address the disparity.

Table: Independent predictors of incident TKA

	RR	95% CI	p-value
Age 65+ vs. <65	1.2	0.9, 1.5	0.255
Sex Female vs. Male	1.6	1.3, 2.1	<.001
Baseline KL 4 vs. 2	8.9	6.4, 12.4	<.001
Baseline KL 3 vs. 2	3.0	2.2, 4.1	<.001
Race White vs. Non-White	1.7	1.2, 2.4	0.002
Yearly Income <$50K vs. >$50K	0.9	0.7, 1.2	0.420
Health Insurance No vs. Yes	0.8	0.4, 1.8	0.596

Disclosure: J. E. Collins, None; **B. Deshpande**, None; **J. N. Katz**, None; **E. Losina**, None.

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Rate of Serum Uric Acid (SUA) Assessment in Gout Patients Treated with Urate-Lowering Therapy: Treating to Target? Robert Morlock[1], David M. Kern[2], Ozgur Tunceli[2], Siting Zhou[2], Laura Horne[3], Sulabha Ramachandran[3] and Hyon Choi[4]. [1]Ardea Biosciences, San Diego, CA, [2]HealthCore, Inc., Wilmington, DE, [3]AstraZeneca, Wilmington, DE, [4]Harvard Medical School, Boston, MA.

Background/Purpose: Gout is the most common form of inflammatory arthritis and is caused by chronic hyperuricemia, leading to urate crystal deposition disease and subsequent intermittent flares and tophi development. ACR guidelines recommend treating to target SUA levels (<6 mg/dL or, in some cases, <5 mg/dL as needed to control signs/symptoms). This study aimed to describe overall rates of SUA testing and differences in patient characteristics, comorbidities, treatments, and flare rates by SUA testing status.

Methods: Gout patients treated with urate-lowering therapy (ULT) were identified between Feb 1, 2011 and Jan 31, 2012 from the HealthCore Integrated Research Environment. Index event was considered to be the earliest of the following: a prescription for ULT; or a gout diagnosis (ICD-9 274.xx) or a claim for colchicine with ULT therapy in the year prior. Patients with <12 months pre- and post-index enrollment or with a diagnosis of cancer, evidence of hematologic cancer, tumor lysis syndrome, Lesch-Nyhan syndrome or juvenile gout, familial Mediterranean fever, or pregnancy in the pre- or postindex periods were excluded. Patient demographics and comorbid conditions were captured during the 12-month pre-index period. SUA laboratory testing, treatment characteristics, and overall gout control (SUA ≤6 mg/dL, no flares, no tophi) were examined during the 12 month post-index period. Target SUA level was ≤6 mg/dL. Flares were defined during the post-index period as either a claim for colchicine, or a healthcare visit recording gout together with ≥1 of the following within 1 week: joint aspiration/injection (corticosteroids), prescription of NSAIDs, corticosteroids, adrenocorticotropic hormone, or IL-1 antagonist.

Results: 50,602 ULT-treated patients met inclusion criteria (average age, 59; 82% male). During follow-up, 90% of patients received allopurinol, 6% febuxostat, and 4% probenecid. SUA testing occurred in 47% of patients during 1-year follow-up. Those with SUA testing were younger (57 vs. 61 years) and had higher rates of colchicine use (23% vs 13%), hyperlipidemia (64% vs. 59%), and chronic kidney disease (15% vs 13%) compared to those without testing. Patients without SUA testing had higher rates of cardiac-related comorbidities: coronary artery disease (21% vs 17% in those with testing), angina (21% vs 16%), and peripheral vascular disease (10% vs 8%). A higher proportion of patients seen by a rheumatologist had testing compared with those not visiting a rheumatologist (75% vs 44%, respectively). Among patients with available SUA results (n=6649), 47% of subjects had SUA levels ≤6 mg/dL, and 30% achieved overall gout control.

Conclusion: Guidelines describe treating to target SUA as appropriate care. This study finds <50% of all gout patients treated with a ULT have SUA assessed at any time during a 12-month period. Patients most likely to have SUA assessments are younger, have more flares, or visit a rheumatologist. In patients with SUA assessment, <50% achieve SUA goal and less than a third achieve overall gout control. These findings suggest that contemporary gout care is suboptimal, leaving considerable room for improvement.

Disclosure: R. Morlock, Ardea Biosciences, Inc., 1, Ardea Biosciences, Inc., 3; **D. M. Kern**, Healthcore, Inc., 3; **O. Tunceli**, Healthcore, Inc., 3; **S. Zhou**, Healthcore, Inc., 3; **L. Horne**, AstraZeneca, 1, AstraZeneca, 3; **S. Ramachandran**, AstraZeneca, 1, AstraZeneca, 3; **H. Choi**, Takeda, 5, AstraZeneca, 5.

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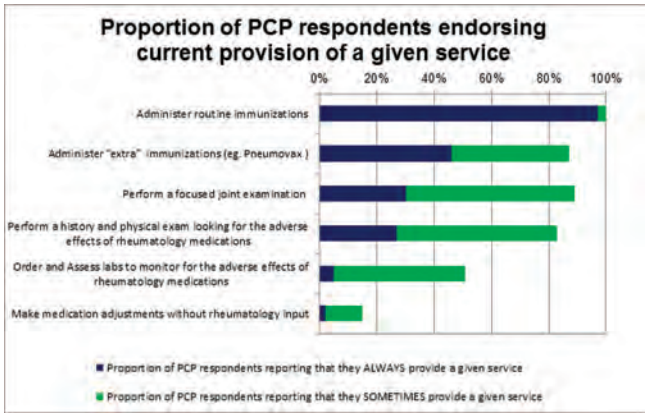
Co-Management for Children with JIA: A Survey of Primary Care Providers Regarding Current Practices and Willingness to Provide Services. Amanda Mroczek, Gary Freed and Meredith Riebschleger. University of Michigan, Ann Arbor, MI.

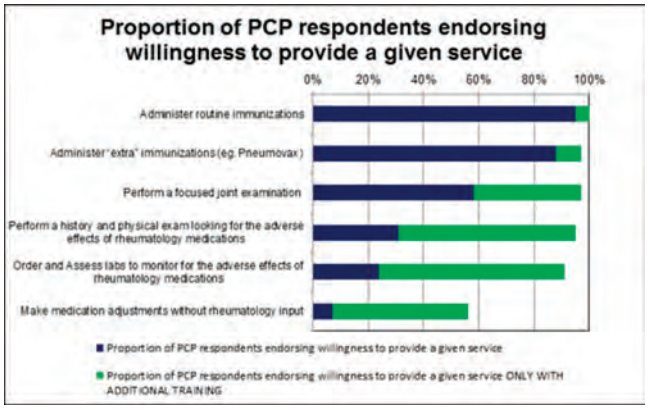
Background/Purpose: Pediatric Rheumatology (PR) is among the smallest and least geographically accessible of the pediatric subspecialties. This problem may be addressed by utilizing the more extensive primary care provider (PCP) workforce, in combination with new technologies such as telemedicine. The objectives of this study were to 1) determine current PCP provision of medical services for children with JIA and 2) determine the willingness of these PCPs to provide services in the future.

Methods: Surveys were mailed to PCPs who had referred ≥2 patients to the University of Michigan Division of PR 2/2012-2/2014. Survey domains included the current provision of and willingness to provide medical services to children with JIA who are also followed by a pediatric rheumatologist. Services assessed included administration of immunizations, performance of a focused joint exam, monitoring for the adverse effects of rheumatology medications, and making medication adjustments. Statistical analyses included proportions and chi square tests.

Results: After 2 of 3 planned mailings, 154/230 PCPs had responded (response rate=67%). The majority of PCPs reported that they already provide many of the assessed services, especially those that are typically performed for all of their patients, such as administering immunizations. Fewer PCPs reported performing services traditionally done by specialists, such as monitoring for adverse effects of medications or making dose adjustments (Figure 1). With the exception of changing medications without PR input, over 90% of PCPs reported willingness to provide the assessed services in the future (Figure 2).

Conclusion: This study found that the majority of PCPs already provide many of the assessed medical services for children with JIA and that an even larger majority are willing to provide these services in the future. Co-management between PCPs and PRs could benefit children and their families by limiting travel expenses and time missed from work and school, while promoting communication and collaboration between PCPs and PRs. The current practices and willingness of PCPs to provide services to their patients with JIA should be used to guide future co-management activities for PCPs and PRs.





Disclosure: A. Mroczek, None; **G. Freed**, None; **M. Riebschleger**, None.

903

Poor Adherence to Medications for Systemic Lupus Erythematosus Predicts Higher Health Care Utilization in U.S. Medicaid Beneficiaries. Jinoos Yazdany[1], Candace H. Feldman[2], Hongshu Guan[3] and Karen H. Costenbader[3]. [1]University of California, San Francisco, San Francisco, CA, [2]Brigham and Women's Hospital, Boston, MA, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Immunosuppressive and antimalarial drugs improve outcomes in systemic lupus erythematosus (SLE), including reducing disease activity, damage and mortality. Although prior studies have found low adherence to medications in SLE, little information is available on the impact of adherence on health utilization and outcomes. In this study, we examined whether poor adherence is associated with higher acute care utilization in a nationwide study of Medicaid beneficiaries.

Methods: We used 2000–2006 U.S. Medicaid Analytic eXtract (MAX) data containing person-level files on Medicaid eligibility, utilization and payments. We identified patients with at least two years of continuous enrollment, who met an administrative definition of SLE and had received either an immunosuppressive (cyclophosphamide, mycophenolate, mycophenolic acid, azathioprine, leflunomide, methotrexate, or tacrolimus) or antimalarial (hydroxychloroquine) drug through an outpatient pharmacy. Pharmacy claims were used to assess adherence by calculating a medication possession ratio (MPR) in the 1st year ("baseline year"), defined as the proportion of days covered by the total days' supply dispensed after the first claim for each drug. Average MPR for SLE drugs in the baseline year was used to examine outcomes in a subsequent one-year

period ("follow-up year"). Outcomes included all cause hospitalizations, SLE-related hospitalizations and emergency room (ER) visits. We used Poisson regression models to evaluate the impact of low adherence (average MPR<80%) on utilization outcomes in the follow-up year, adjusting for baseline age, sex, race/ethnicity, Charlson comorbidity index, SLE-specific risk index (Ward M, *J Rheum,* 2000) and number of SLE drugs taken.

Results: 15,955 patients with SLE were taking at least one immunosuppressive or anti-malarial drug and continuously enrolled in Medicaid over the two-year period. Mean age was 38.6 years (SD 11.3), 95% were female, and 39% were Black, 34% White, 16% Hispanic, 5% Asian, 5% other, 1% Native. The average MPR during the baseline year was 49% (SD 30%). In the follow-up year, 28% had one or more hospitalizations, 17% SLE-related hospitalizations, and 49% ER visits. Lower adherence was associated with significantly increased risks of subsequent hospitalizations and ER visits, even after adjustment for sociodemographic factors, SLE risk index, comorbid disease, and number of SLE drugs taken (**Table**).

Conclusion: We found that lower adherence (MPR<80%) significantly increased risks of subsequent hospitalizations and ER visits in Medicaid beneficiaries with SLE. These results are consistent with past studies highlighting the importance of promoting medication adherence to improve health outcomes and decrease costs. Further research is warranted to gain a better understanding of how disease activity and severity influence this relationship.

Table Relationship between Adherence and Subsequent Hospitalizations and Emergency Room Encounters in U.S. Medicaid beneficiaries with SLE.

	All-cause hospitalizations IRR (95% CI)	SLE-related hospitalizations IRR (95% CI)	Emergency Room visits IRR (95% CI)
Adherence in year one (MPR*≥80%)	Referent	Referent	Referent
Non-adherence in year one (MPR*<80%)	**1.43 (1.33, 1.54)**	**1.36 (1.25,1.46)**	**1.55 (1.45, 1.65)**

*MPR=Medication Possession Ratio IRR= Incidence rate ratio. Poisson regression models were adjusted for baseline age, sex, race/ethnicity, SLE-specific risk index, Charlson comorbidity index and number of concomitant SLE medications. Each column represents a separate Poisson regression model.

Disclosure: J. Yazdany, None; **C. H. Feldman**, None; **H. Guan**, None; **K. H. Costenbader**, None.

ACR Concurrent Abstract Session
Imaging of Rheumatic Diseases: Ultrasound
Sunday, November 16, 2014, 4:30 PM–6:00 PM

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Ultrasound Synovitis Reflects Synovial Inflammation at a Histopathological Level. Nora Ng, Stephen Kelly, Frances Humby, Maria DiCicco, Vidalba Rocher, Rebecca Hands, Michele Bombardieri and Costantino Pitzalis. William Harvey Research Institute, Queen Mary University of London, London, United Kingdom.

Background/Purpose: Ultrasound (US) is widely used by rheumatologists to assess inflammatory burden on patients with inflammatory arthritis. Some studies have shown that US measures of inflammation reflects aspects of histological synovitis in a heterogeneous groups of patients with rheumatoid arthritis (RA). Little work has been done to describe this relationship in an early arthritis population.

Our aim of this study is to investigate, at a single joint level, the correlation of US synovitis with histological synovial inflammation before and after treatment initiation in a homogenous cohort of patients with early RA.

Methods: Data was collected from 54 patients with early RA (fulfills 1987 ACR classification, symptom onset <12 months). Patients were naïve to both disease modifying anti-rheumatic drugs (DMARD) and to steroids. All patients underwent a core data set assessment including clinical, biochemical, imaging and an US guided minimally invasive synovial biopsy of the most inflamed joint. Patients were then initiated on DMARD according to standardised protocol. A repeat assessment and US guided biopsy was performed at 6 months follow up. US images of the joint are scored using a semi quantitative score (0–3). Sections of paraffin embedded synovial tissue received immunohistochemical staining for CD3, CD20, CD68, CD68sland CD138 and these parameters were graded in a semiquantitative fashion (0–4). Spearman's rho was used to correlate scores at each time point.

Results: At baseline, US power doppler (PD) was significantly correlated with histological markers of inflammation - CD3 ($r=0.43$, $p<0.05$), CD20 ($r=0.46$, $p<0.01$), CD68 ($r=0.37$, $p<0.05$), CD68sl ($r=0.46$, $p<0.01$) and CD138 ($r=0.61$, $p<0.001$), and with inflammatory markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) ($r=0.4$, $p<0.05$). After 6 months of therapy, most of these correlations were still present, most notably with CD68sl ($p<0.05$). Interestingly, we also found that a fall in US PD in response to treatment at 6 months is associated with a fall in CD68sl ($r=0.50$, $p<0.005$) and a fall in DAS28 ($r=0.40$, $p<0.05$).

Conclusion: US PD has long been recognised as an accurate reflection of disease activity in inflammatory arthritis. Our results have shown that US PD also reflects synovial inflammation at a histopathological level. The association of US PD, CD68sl and DAS28 supports the current opinion that Power Doppler US is a biomarker for treatment response and reflects both clinical and histological markers of disease activity in patients with RA.

Disclosure: N. Ng, None; **S. Kelly**, None; **F. Humby**, None; **M. DiCicco**, None; **V. Rocher**, None; **R. Hands**, None; **M. Bombardieri**, None; **C. Pitzalis**, None.

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First Step in the Development of an Ultrasound Joint Inflammation Score for Rheumatoid Arthritis: A Data Driven Approach. Anna-Birgitte Aga[1], Hilde Berner Hammer[1], Inge C. Olsen[1], Till Uhlig[1], Tore K. Kvien[1], Désirée van der Heijde[2], Elisabeth Lie[1], Espen A. Haavardsholm[1] and the Arctic study Group[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: The use of ultrasonography (US) in rheumatoid arthritis (RA) is rapidly increasing. Currently, there is no consensus regarding which joints and tendons should be systematically assessed. Validity, including comprehensiveness, and responsiveness must be weighted against feasibility. Our objectives were to develop candidate sets for assessment of US joint inflammation through a data driven approach using data from early RA patients, and then perform initial validation in an established RA cohort.

Methods: Between January 2010 and June 2013 patients (pts) were included in one of two cohorts: Early RA (DMARD-naïve pts with RA of <2 yrs symptom duration fulfilling 2010 ACR/EULAR classification criteria), and established RA (pts starting or switching biologic DMARDs). An extensive US examination was performed by experienced sonographers using a validated grey-scale (GSUS) and power Doppler (PDUS) semi-quantitative scoring system with scores 0–3 for GSUS and PDUS in each of the following 36 joints and 4 tendons: MCP 1–5, PIP 2–3, radiocarpal, distal radioulnar, intercarpal, elbow, knee, talocrural, MTP 1–5, extensor carpi ulnaris and tibialis posterior tendons, bilaterally. An US atlas was used as reference[1]. We performed principal component factor analyses (PCA) in the early RA US data to identify joint groups with high internal correlation, and selected candidate joint/tendon sets based on these analyses. We assessed the loss of information compared to the full score by R^2 from linear regression analysis. Finally, the candidate sets were validated in the established RA cohort.

Results: A total of 439 patients were included, 227 with early and 212 with established RA; 62% vs. 77% anti-CCP pos, mean(SD) age 51(14) vs. 52(13) yrs, DAS28 4.7(1.2) vs. 4.7(1.4), median(25–75 percentile) 28-SJC 6(3–11) vs. 5(2–10), disease duration 0.5(0.2–0.9) vs. 8(3–15) yrs, mean(95% CI) 36-joint GSUS score 23(21–25) vs. 28(25–30) ($p=0.003$), 36-joint PDUS score 11(10–12) vs. 13(11–15) ($p=0.20$). Nearly 17,000 individual joints/tendons were assessed. We identified 9 groups based on PCA in the early RA data, presented in table 1. Comparisons between the candidate sets and the total GSUS and PDUS scores in the early RA cohort as well as validation in the established RA cohort are presented in table 2.

Conclusion: We used a data driven approach to develop candidate sets of joints/tendons to be assessed by GS and PD US, and the resulting reduced scores retained most of the information from the total score of 40 joints/tendons. Unilateral reduced scores explained 78% to 85% of the total score, while bilateral reduced scores explained 89% to 93% of the total score. The candidate scores performed equally well in a validation cohort of established RA. Our results show that a reduced US assessment may efficiently contribute to disease assessment in RA. Further validation in longitudinal RA cohorts and data on responsiveness are needed.

[1]Hammer HB et al. ARD 2011

Table 1: 9 joint/tendon groups with correlating scores based on principal component factor analysis of the GSUS and PDUS scores in early RA

Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9

MTP 2	Radiocarpal	MCP 2	PIP 2	Elbow	Tib.post. tendon	MTP 1	Ext.carpi ulnaris tendon	MCP 1
MTP 3	Intercarpal	MCP 3	PIP 3					
MTP 4	Radioulnar	MCP 4						
MTP 5		MCP 5						

Table 2: Comparison of candidate joint/tendon sets for GSUS and PDUS assessment and the full 40-joint/tendon score in the early and established RA cohorts

Modality	Candidate set of US joint inflammation	Side	Number of joints/tendons	Early RA	Established RA
				Fraction of information in total score explained[3]	Fraction of information in total score explained[3]
GSUS	A[1]	Right	9	0.79	0.79
		Left	9	0.83	0.81
		Bilateral	18	0.89	0.91
	B[2]	Right	11	0.85	0.85
		Left	11	0.85	0.86
		Bilateral	22	0.93	0.94
PDUS	A[1]	Right	9	0.78	0.78
		Left	9	0.78	0.81
		Bilateral	18	0.89	0.91
	B[2]	Right	11	0.83	0.85
		Left	11	0.81	0.84
		Bilateral	22	0.92	0.95

[1]MCP 1, MCP 2, PIP 3, radiocarpal, elbow, MTP 1, MTP 2, and extensor carpi ulnaris and tibialis posterior tendons
[2]Same as candidate set A with addition of MCP 5 and MTP 5
[3]Linear regression analysis with the total US score as dependent variable and the sum score of the candidate sets as independent variable
GSUS = gray-scale ultrasonography. PDUS = power Doppler ultrasonography.

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How Long Does Sonographic Joint Activity Continue in Clinically Remittive Joints of Patients with Rheumatoid Arthritis? Miriam Gärtner, Farideh Alasthi, Gabriela Supp, Peter Mandl, Josef Smolen and Daniel Aletaha. Medical University of Vienna, Vienna, Austria.

Background/Purpose: Ultrasound (US) assessment was shown to be a sensitive tool for the evaluation of inflammatory joint activity in patients with rheumatoid arthritis (RA). Synovial effusion and hypertrophy are evaluated by gray scale (GS), while hypervascularisation, can be measured using power Doppler (PD) signals. Both types of signals are highly sensitive, and may persist even in clinical inactivity. It is conceivable that such subclinical US signals may resolve if clinical inactivity of the respective joint is sustained, but this has not yet been shown during long-term follow-up.

It was the objective of this study to evaluate the persistence of subclinical US signals in previously clinically active joints, which have reached a state of continuous clinical inactivity.

Methods: We performed US imaging of 22 joints of the hands of RA patients, including GS and PD, each graded on a four point scale (0=no, 1=mild, 2=moderate, 3=marked). All joints with no activity by clinical assessment at the same time of the US examination were selected, and we identified the last time point of clinical joint activity (swelling, tenderness, or both). The time between the last clinical joint activity and the current sonographic assessment in that joint was determined and persistence of subclinical US activity was estimated for all patients and all joints using time-to-event analysis.

Results: A total of 90 RA patients with 1980 assessed joints were included in this study: 67.1% (1329) of the joints were positive on GS and 20.7% (410) showed PD signals. The mean±SD number of joints showing signs of sonographic activity was: 15±5 for GS, 5±3.8 for PD.

The median (IQR) time between the last visit exhibiting clinical activity in a single joint and the US assessment in the same joint was 3.6 (1.2;6.3) for joints with PD signals, and 3.5 (1.3;5.6) years for joints with GS signals.

If GS signals were ≥2 we found a significantly shorter time to the last visit with clinical activity compared to joints with GS=1 (median[IQR] 2.6[0.6;2.6] vs. 3.9[1.9;6.6]; p<0.001); for PD signals we saw the same trend (median [IQR] of 2.4[0.5;5.3] for PD≥2 vs. 4.3[1.0;6.2] for PD=1; p=0.066). In joints showing both highly positive GS and PD signals (both≥2), the time to the last clinical activity was even shorter, with a median of 1.4 years. (Figure 1)

Conclusion: We conclude that subclinical joint activity is long lasting in RA joints in clinical remission, but resolves over time. The latter is indicated by a shorter period from last clinical activity for strong signals (PD≥2, GS≥2) as compared to weak signals (PD≤1, GS≤1).

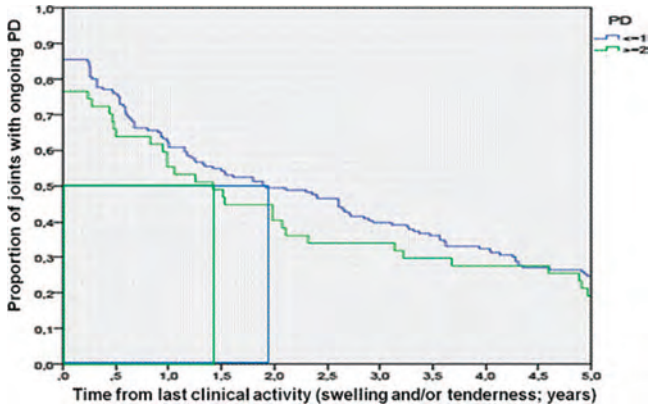

Figure 1: Kaplan Meier curve for subclinical sonographic activity in joints showing GS ≥ 2 and PD signals. GS=grey scale, PD= power Doppler

Disclosure: M. Gärtner, None; **F. Alasthi**, None; **G. Supp**, None; **P. Mandl**, None; **J. Smolen**, None; **D. Aletaha**, None.

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Ultrasonographic Tenosynovitis Score Is Responsive to Biologic Treatment in Patients with Rheumatoid Arthritis. Hilde B. Hammer and Tore K. Kvien. Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: Ultrasound (US) is sensitive for detecting tenosynovitis in patients with rheumatoid arthritis (RA), where the synovitis can be assessed by grey scale (GS) and the increased vascularization by power Doppler (PD). The extensor carpi radialis (ECU) tendon in the wrist and the tibialis posterior (TP) tendon in the ankle are frequently involved in RA patients, and the tenosynovitis can be scored by use of a semi-quantitative (0–3) scoring system. The objective of the present study was to assess the involvement of ECU and TP tendons in patients with established RA as well as to explore the change in US scores of these tendons during treatment with biologic disease-modifying anti-rheumatic drugs (bDMARDs).

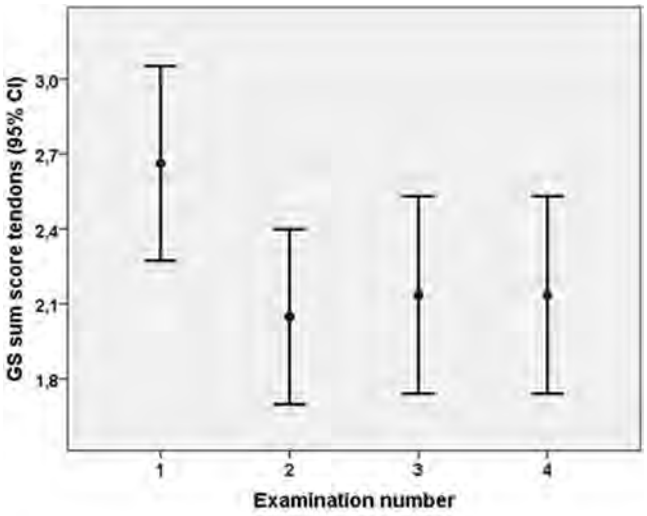
Methods: A total of 181 RA patients (83% women, mean (SD) age 51 (13) years, disease duration 11 (9) years, 77 % positive for anti-CCP) were examined when they started bDMARD (infliximab 10%, etanercept 43%, adalimumab 8%, golimumab 5%, certolizumab pegol 5%, rituximab 19%, abatacept 4% and tocilizumab 6%). All were examined at baseline and after 1, 2 and 3 months with US (GS and PD of ECU and TP tendons bilaterally, all assessments performed by one sonographer (HBH) with Siemens Acuson Antares, Excellence version, using a 5–13 MHz probe with an optimized pre-setting of the machine for all examinations), laboratory and clinical assessments. The changes from baseline were assessed by use of paired samples T-test.

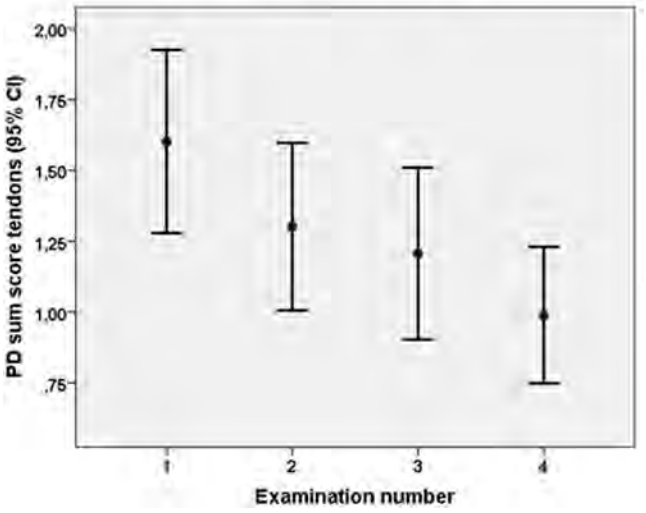
Results: Tenosynovitis was found in a high number of tendons at baseline (table). The mean (SD) sum score of the four tendons was 2.7 (2.7) for GS and 1.6 (2.2) for PD, including 26% of the patients with no GS inflammation and 51% with no PD activity in any tendon. Mean (SD) baseline values for the clinical examinations were: ESR 28.6 (21.7), CRP 14.2 (20.6) and DAS28 4.6 (1.5). Both sum scores GS and PD decreased significantly from baseline to 1 month (p<0.001 and p=0.013, respectively), and both showed highly significant reduction after 3 months (p<0.001) (figure). Also ESR, CRP and DAS28 decreased already after 1 month (p<0.001 for all), as well as after 3 months (p<0.001 for all).

Conclusion: A large number of ECU and TP tendons were inflamed at baseline, and the sum scores of both GS and PD fell significantly already after 1 month. Since tenosynovitis in ECU and TP tendons are common in RA patients and responsive to change during bDMARD treatment, US of these tendons should be considered as candidates for inclusion in future US scores of RA patients.

	ECU tendons		TP tendons	
	Grey scale (percentage involvement)	Power Doppler (percentage involvement)	Grey scale (percentage involvement)	Power Doppler (percentage involvement)
Score 0	57	76	64	76
Score 1	21	11	15	9

Score 2	17	11	14	11
Score 3	5	2	7	4





Disclosure: H. B. Hammer, None; **T. K. Kvien**, None.

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Ultrasound-Detected Tenosynovitis Independently Associates with Flare in Patients with Rheumatoid Arthritis in Clinical Remission. Emanuela Bellis[1], Greta Carrara[2], Carlo Alberto Scirè[2], Alessandra Bortoluzzi[3], Alberto Batticciotto[4], Antonella Adinolfi[5], Giovanni Cagnotto[6], Marta Caprioli[7], Marco Canzoni[8], Francesco Cavatorta[9], Fulvia Ceccarelli[10], Orazio De Lucia[11], Valentina Di Sabatino[12], Antonella Draghessi[13], Georgios Filippou[12], Ilaria Farina[3], Maria Cristina Focherini[14], Paola Frallonardo[15], Alessandra Gabba[16], Angelica Gattamelata[10], Marwin Gutierrez[13], Luca Idolazzi[17], Filippo Luccioli[18], Pierluigi Macchioni[19], Marco Massarotti[20], Claudio Mastaglio[21], Luana Menza[21], Giulia Mirabelli[18], Maurizio Muratore[22], Simone Parisi[23], Valentina Picerno[12], Matteo Piga[24], Roberta Ramonda[25], Bernd Raffeiner[15], Daniela Rossi[26], Paola Rossini[27], Garifallia Sakellariou[28], Crescenzio Scioscia[29], Carlo Venditti[30], Annamaria Iagnocco[10] and Marco Matucci-Cerinic[31] [1]Ospedale Mauriziano, Turin, Italy, [2]Italian Society for Rheumatology, Milan, Italy, [3]A.O.U. S.Anna di Cona, Ferrara, Italy, [4]L.Sacco University Hospital, Milan, Italy, [5]Policlinico le Scotte, Siena, Italy, [6]IRCCS Policlinico San Matteo, Pavia, Italy, [7]Istituto di Cura Città di Pavia, Pavia, Italy, [8]A.O. Sant'Andrea, Rome, Italy, [9]A.O.U.P. Santa Chiara, Trento, Italy, [10]Sapienza University of Rome, Rome, Italy, [11]Orthopedic Institute Gaetano Pini, Milano, Italy, [12]University of Siena, Siena, Italy, [13]Università Politecnica delle Marche, Jesi, Italy, [14]Ospedale Infermi, Rimini, Italy, [15]University of Padova, Padova, Italy, [16]A.O.U. di Cagliari, Cagliari, Italy, [17]Ospedale Civile Maggiore, Verona, Italy, [18]University of Perugia, Perugia, Italy, [19]Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [20]Istituto Clinico Humanitas, Rozzano, Italy, [21]Moriggia-Pelascini, Gravedona, Italy, [22]Department of Rheumatology, Hospital Galateo, San Cesario di Lecce, Italy, [23]A.O. Città della Salute e della Scienza di Torino, Turin, Italy, [24]Unit and Chair of Rheumatology, University Hospital of Cagliari, Cagliari, Italy, [25]University of Padua, Padova, Italy, [26]University of Turin, Turin, Italy, [27]P.O. "Destra Secchia", Pieve di Coriano, Italy, [28]Rheumatology and Translational Immunology Research Laboratories (LaRIT), Division of Rheumatology, IRCCS Policlinico S.Matteo Foundation/University of Pavia, Pavia, Italy, [29]University of Bari, Bari, Italy, [30]A.O. Rummo, Benevento, Italy, [31]University of Florence, Florence, Italy.

Background/Purpose: Clinical remission is now an achievable goal in patients with rheumatoid arthritis (RA). Much has been done in order to better understand and define the concept of remission; in the field of ultrasonography (US) some studies have focused on joint synovitis and its significance in terms of prognosis. In the literature, data on the prevalence of tenosynovitis in patients in clinical remission are scarce and its clinical and prognostic significance has not been studied yet. The objective of this study is to assess whether the US tenosynovitis is associated with a decreased risk of flare.

Methods: Sonographic Tenosynovitis Assessment in RheumaToid arthritis patiEnts in Remission (STARTER) is a multicentre cohort study promoted by the Italian Society for Rheumatology (SIR) that includes 26 rheumatology centres recruited across Italy between Oct 2013 and Jun 2014. Ultrasonographers were trained and selected by an inter-reader reliability exercise against a reference standard using static images, setting to 0.7 one ad hoc weighted kappa as entry criterion. Only high level US machines and high frequency probes were allowed. Patients with RA and clinical remission (DAS28 or SDAI or CDAI) were eligible. All patients underwent full clinical evaluation and US examination (synovitis (-S) and tenosynovitis (-T). A 0–3 semiquantitaive score of Grey Scale (GS-) and Power Doppler (PD-) was calculated for wrists, metacarpophalangeal, interphalageal joints and extensor and flexor tendon sheets. Flare was assessed using the flare questionnaire score ranging from 0 (no flare) to 10 (definite flare) [1], dichotomized at the median value (=3). The cross-sectional relationship between presence of GS-T/-S, PD-T/-S were evaluated by logistic models, and presented as odds ratios (OR) and 95%CI, both crude and adjusted for pre-specified confounders.

Results: A total of 408 RA patients in clinical remission were included in the analyses: 103(25.4%) men, mean(SD) age 56.4(13.5), median(IQR) disease duration 7.1(3.7–13.5) years, median(IQR) remission duration 12 (8–28) months, RF positive 249/360 (69.2%), mean(SD) DAS28 2.1 (0.8), median(IQR) HAQ 0.125(0–0.375), on DMARDs 300 (73.5%), on biologics 161 (39.5%), on glucocorticoids 170 (43.8%).

GS-T was present in 198/373 (53.1%) patients, PD-T in 88/372 (23.7%), while GS-S was present in 270/368 (73.4%) patients and PD-S in 171/372 (46.5%). The association between US variables and flare is reported in the Table.

Outcome: flare questionnaire >3	Crude OR (95%CI)	Adjusted* OR (95%CI)
Grey Scale Tenosynovitis	1.05 (0.69, 1.58)	1.09 (0.68, 1.75)
Power Doppler Tenosynovitis	**2.11 (1.29, 3.45)**	**2.29 (1.29, 4.07)**
Grey Scale Synovitis	1.09 (0.68, 1.74)	0.88 (0.50, 1.56)
Power Doppler Synovitis	**1.60 (1.05, 2.43)**	1.48 (0.91, 2.40)

age, sex, disease duration, remission duration, musculoskeletal comorbidities, RF, ACPA, DMARDs, biologics, glucocorticoids (oral and injections), NSAIDs.

Using absence of PD-T and PD-S as reference, PD-S alone showed an adjusted OR(95%CI) of 1.45(0.82, 2.58), PD-T alone 3.84(1.33, 11.08) and both PD-S and PD-T 2.55(1.27, 5.10).

Conclusion: Power Dopper tenosynovitis is independently associated with patient reported flare more strongly than synovial indexes. US-tenosynovitis is new promising feature to identify patients in remission at higher risk of flare.

[1]. Berthelot JM et al. Ann Rheum Dis 2012;71:1110–1116.

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A Diagnostic Protocol for Giant Cell Arteritis (GCA) Using Ultrasound Assessment. Jennifer Piper[1], Ana Sofia Serafim[1], Cristina Ponte[1], Surjeet Singh[2], Bhaskar Dasgupta[3], Wolfgang A. Schmidt[4], Eugene McNally[5], Andreas P. Diamantopoulos[6], Andrew Hutchings[7] and Raashid Luqmani[8]. [1]University of Oxford, Oxford, United Kingdom, [2]Sciences, Oxford, England, [3]Southend University Hospital, Essex, United Kingdom, [4]Immanuel Krankenhaus, Berlin, Germany, [5]Oxford University, Oxford, United Kingdom, [6]Hospital of Southern Norway Trust, Kristiansand, Norway, [7]London School of Hygiene and Tropical Medicine, London, United Kingdom, [8]Oxford NIHR Musculoskeletal Biomedical Research Unit, Oxford, United Kingdom.

Background/Purpose: Ultrasound (US) has not yet superseded temporal artery biopsy as a diagnostic test. This may reflect poor consistency of the scanning technique, due to the lack of a standardised scanning protocol. We have developed a standardised protocol which was implemented in a prospective study of 857 participants: 439 healthy controls and 418 patients with suspected GCA (Temporal Artery Biopsy versus Ultrasound, TABUL). We assessed each patient for evidence of typical ultrasound features of GCA: the presence of a halo surrounding the vessel wall, stenosis or occlusion of the vessel.

Methods: A detailed scanning protocol was developed for all cases and controls. We recorded the presence or absence of ultrasound features of GCA in each segment of each temporal artery (common, parietal, frontal proximal and frontal distal) and both axillary arteries. Sonographers were asked to acquire video and static images for each patient to ensure accuracy of findings. The sonographer measured and documented: halo diameter (based on a normal range of up to 0.3 mm for the temporal artery and up to 1.0 mm in the axillary artery) and length; pulse Doppler measurements prior to and within a stenosis (confirmed if the highest maximum systolic velocity was over twice the lowest maximum systolic velocity) and arterial occlusion. Each study site sonographer was required to be proficient in the protocol by scanning at least 10 healthy controls, passing an online test showing normal and abnormal scans (pass mark >75%) and scanning a patient with ultrasound evidence of active GCA.

Results: The US scanning protocol was started by 33 sites, with only 22 sites completing the training in 6.7 months [range 0.2 – 16.4 months]. A total of 439 controls were scanned across 31 sites (1 sonographer covered 3 sites). The online test was passed by 39 sonographers (multiple sonographers at some sites) with an average of 2 attempts [range 1–4]); 22 sonographers successfully scanned an active GCA patient, validated by the expert panel. The longest delay in completing the training was due to difficulty in recruiting a patient with active GCA (hot case), which was necessary for each site prior to it joining the main study. Common issues encountered were a lack of time away from clinical duties and locating a new suspected GCA case for the hot case assessment.

We have created a bank of 857 sets of consistently recorded US images of temporal and axillary arteries from 418 patients with suspected GCA and 439 healthy controls. Expert review of the first 263 suspected patients has confirmed positive US findings of GCA in 100 patients and no US evidence in 163 cases.

Conclusion: Quality and accuracy are imperative for the clinical use of ultrasound data in the diagnosis of GCA. We have developed an effective training program and scanning protocol which ensures consistency and proficiency. The methodology can be adapted and extended to allow for additional artery assessment, including carotid, vertebral and subclavian arteries, extending the value of a structured approach. We recommend the TABUL study scanning protocol as the standard approach for diagnosis of GCA using ultrasound.

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ACR Concurrent Abstract Session
Muscle Biology, Myositis and Myopathies
Sunday, November 16, 2014, 4:30 PM–6:00 PM

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The Selective Sphingosine-1- Phosphate Receptor 1/5 Modulator Siponimod (BAF312) Shows Beneficial Effects in Patients with Active, Treatment Refractory Polymyositis and Dermatomyositis: A Phase IIa Proof-of-Concept, Double-Blind, Randomized Trial. Katalin Danko[1], Jiri Vencovsky[2], Ingrid E. Lundberg[3], Anthony A Amato[4], Chester V. Oddis[5], Maria Molnar[6], Antonette Mallari Moher[7], Laurence Colin[8], Florian Muellershausen[9], David Lee[9] and Peter Gergely[9]. [1]University of Debrecen, Hungary, Debrecen, Hungary, [2]Charles University, Prague, Czech Republic, [3]Rheumatology Unit, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, [4]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [5]University of Pittsburgh, Pittsburgh, PA, [6]Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary, [7]Novartis Institutes for Biomedical Research (former emplyee), Basel, Switzerland, [8]Novartis Pharma, Basel, Switzerland, [9]Novartis Institutes for Biomedical Research, Basel, Switzerland.

Background/Purpose: Polymyositis and dermatomyositis (PM/DM) comprise a heterogeneous group of chronic inflammatory muscle diseases where infiltration of lymphocytes in the skeletal muscle plays a key pathogenic role. BAF312 (siponimod), an oral sphingosine-1-phosphate (S1P) receptor 1/5 modulator may be efficacious in inflammatory myopathies by inhibiting lymphocyte trafficking from secondary lymphoid organs to the muscle. A randomized, double–blind, placebo-controlled, multi-centric, partial cross-over Phase IIa Proof of Concept study was conducted to evaluate the safety, tolerability and efficacy of BAF312 in patients with PM/DM.

Methods: Eighteen patients with clinically active PM/DM who had responded inadequately to conventional treatment were randomized to receive 10 mg BAF312 or matching placebo (1:1) once daily for 12 weeks. The 10 mg dose was reached by a dose up-titration regimen over 10 days to minimize bradycardia, a common adverse effect of the S1P1 receptor modulator class. Following the placebo-controlled Period 1, all patients received 10 mg BAF312 for an additional 12 weeks in Period 2. No immunosuppressives but oral corticosteroids at a stable dose (max. 20 mg prednisone/day) were allowed as concomitant medication. Key outcomes were safety and efficacy as assessed by the responder rate according to the Definition of Improvement by the IMACS (International Myositis Assessment Study) group. Clinical response was defined as an improvement in the IMACS core set measure of myositis disease global activity by greater than 30% and an improvement in manual muscle testing (MMT8) by 1 –15 %; or an improvement in MMT8 by greater than 15% and in myositis disease global activity by greater than 10%; and in either case, with no more than 2 IMACS measures worsening by 25%.

For safety, in addition to routine assessments, cardiac monitoring for the first 10 days, pulmonary function testing, ocular coherence tomography were performed. Peripheral absolute lymphocyte counts were measured to monitor the pharmacodynamic (PD) effect of BAF312.

Results: Eighteen patients were enrolled into this trial and 16 patients received BAF312 either in Period 1 and/or Period 2. Overall, BAF312 was safe and well tolerated with no significant bradycardia observed. Four serious adverse events occurred in three patients, all in the Placebo group. Fourteen patients were evaluable for the efficacy analysis. The observed responder rates at week 12 were 4/7 (57%) for BAF312 and 1/7 (14%) for placebo using the IMACS definition of improvement. A Bayesian analysis of the IMACS responder status at week 12 yielded a probability of 0.96 that BAF312 is superior to Placebo. The PD effect of BAF312 (i.e. decrease in absolute lymphocyte count) was confirmed in all subjects receiving BAF312, with a mean decrease by >75% after 4 weeks of treatment.

Conclusion: Considering disease heterogeneity and low sample size firm conclusions should not be drawn, but further investigations of BAF312 as a new treatment modality for patients with refractory PM/DM are warranted.

Although disease heterogeneity and low sample size prevent definite conclusions, further investigations of BAF312 as a new treatment modality for patients with refractory PM/DM are warranted.

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Bioluminescent Imaging of Histidyl-Transfer RNA Synthetase-Induced Myositis Reveals Early-Phase Involvement of NF-Kb-Mediated Inflammation. Nicholas A. Young[1], Lai-Chu Wu[1], Michael Bruss[1], Wael N. Jarjour[1] and Dana P. Ascherman[2]. [1]The Ohio State University Wexner Medical Center, Columbus, OH, [2]Miami VAMC, Miami, FL.

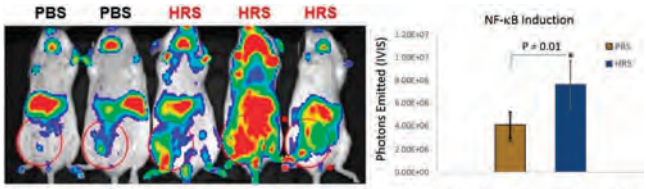
Background/Purpose: The idiopathic inflammatory myopathies represent a group of autoimmune diseases that target muscle as well as

extra-muscular organs, leading to significant morbidity and mortality. Among the most common specific autoantibodies associated with these disorders is Anti-histidyl-tRNA synthetase (HRS; Jo-1), which defines a subgroup of patients with clinical features. In order to further advance targeted therapies, we have modified a previously established model of HRS-induced myositis to highlight the potential role of NF-kB activation in early stages of disease.

Methods: BALB/C-Tg(NFkB-RE-luc)-Xen mice, which contain a firefly luciferase cDNA reporter gene under the regulation of 3 kB responsive binding sites, were injected intra-muscularly with 50 ml of recombinant murine HRS (5 mg/ml) affinity purified following amplification in a bacterial expression system. Inflammation was determined by measuring whole-body bioluminescent signals using the Xenogen *in vivo* imaging system (IVIS 200). The emitted photons from injected muscle were quantitated for each mouse at time zero and at 2 and 4 weeks. At 5 weeks post-HRS injection, mice were sacrificed; sections of injected as well as non-injected muscle tissue were then paraffin embedded and stained by H&E for histological analysis.

Results: NFkB-RE-luc mice inoculated with recombinant HRS developed a robust inflammatory response at the 2 week time point. This statistically significant inflammatory response measured by IVIS photon quantification was most pronounced at the site of injection, but did extend beyond this area in some mice (see figure). NF-kB activation subsided after 4 weeks, with residual bioluminescent signals approaching those induced by injection with PBS alone. Despite this apparent reduction in NF-kB activity, however, histologic analysis of HRS-injected muscle tissue revealed significant endomysial inflammatory infiltrates at these later time points.

Conclusion: This novel application of NF-kB-regulated luciferase mice establishes a system that may facilitate therapeutic drug development for myositis through longitudinal analysis of candidate NF-kB inhibitors in different strains expressing the NF-kB-luciferase transgene. However, because our results suggest that NF-kB-mediated signaling pathways primarily impact early stages of disease in this model system, alternative therapeutic targets must be sought for more temporally advanced disease; thus underscoring the need for phase-specific treatment in idiopathic inflammatory myopathy.



NF-κB activation is induced in histidyl-tRNA synthetase (HRS)-stimulated myositis. Transgenic mice expressing a luciferase reporter gene under the control of NF-κB responsive elements were injected intra-muscularly with PBS (n = 4) or recombinant HRS (n = 5). (left) After 14 days, bioluminescent signals in the injected muscle (red circles) were measured in the *in vivo* imaging system (IVIS). (right) The emitted photons were quantitated using IVIS software (±SD).

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A Consensus Hybrid Definition Using a Conjoint Analysis Is the Proposed As Response Criteria for Minimal and Moderate Improvement for Adult Polymyositis and Dermatomyositis Clincal Trials. Rohit Aggarwal[1], Lisa G. Rider[2], Nicolino Ruperto[3], Nastaran Bayat[2], Brian Erman[4], Brian M. Feldman[5], Adam M. Huber[6], Chester V. Oddis[1], Ingrid E. Lundberg[7], Anthony A. Amato, MD[8], Robert G. Cooper, MD, FRCP[9], Hector Chinoy[10], Maryam Dastmalchi[11], David Fiorentino[12], David Isenberg[13], James D. Katz[14], Andrew L. Mammen[15], Marianne de Visser[16], Steven R. Ytterberg[17], Katalin Danko[18], Luca Villa[19], Mariangela Rinaldi[19], Howard Rockette[1], Peter A. Lachenbruch[20], Frederick W. Miller[2] and Jiri Vencovsky, MD, DSc[21]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD, [3]Istituto Giannina Gaslini, Genoa, Italy, [4]Social and Scientific Systems, Inc., Durham, NC, [5]The Hospital for Sick Children, Toronto, ON, [6]IWK Health Centre, Halifax, NS, [7]Rheumatology Unit, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, [8]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [9]University of Liverpool, Liverpool, United Kingdom, [10]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, [11]Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [12]Stanford University, Redwood City, CA, [13]Arthritis Research UK Centre for Adolescent Rheumatology, University College London, London, United Kingdom, [14]NIH, Bethesda, MD, [15]Johns Hopkins University, Baltimore, MD, [16]Academic Medical Centre, Amsterdam, Netherlands, [17]Mayo Clinic, Rochester, MN, [18]University of Debrecen, Hungary, Debrecen, Hungary, [19]IRCCS Istituto G. Gaslini, Genova, Italy, [20]NIEHS, NIH, Bethesda, MD, [21]Charles University, Prague, Czech Republic.

Background/Purpose: To develop consensus on definitions of improvement (DOIs) for minimal and moderate improvement (and draft preliminary criteria for major improvement) in adult dermatomyositis (DM) and polymyositis (PM) for therapeutic trials.

Methods: Patient profiles from natural history and/trial data were rated by myositis experts. Consensus (≥70%) was reached in 91%; 157 rated with minimal, 72 moderate and 12 major improvement. Conjoint analysis was performed on forced-choice surveys (using 1000Minds software) that were administered to myositis experts. Candidate DOIs based on changes in IMACS core set measures (CSMs) were generated for minimal, moderate and major improvement: A) 23 previously-published DOIs; B) 408 new DOIs (called "Base") using expert survey and variations of published DOIs; C) 56 DOIs derived from logistic regression; D) 6 DOIs derived from a Conjoint Analysis survey that yielded scores with different levels of improvement in different CSMs; E) 8 DOIs drafted by combining changes in each CSM with respective Conjoint Analysis weights; and F) 194 DOIs drafted by applying weights from Conjoint Analysis to the base DOIs. Relative and absolute percentage change DOIs were tested for minimal, moderate and major improvement. The consensus-rated patient profiles were then used to: a) validate DOIs (including definitions A, B, D, E, F) for their sensitivity, specificity, kappa, odds ratio, and area under the curve (AUC); and b) develop logistic regression DOIs (definition C using 2/3rd of data) and then internal validation (using 1/3rd data). High performing DOIs were externally validated using Rituximab in Myositis (RIM) trial data (N=152 DM/PM), followed by a consensus meeting using nominal group technique (NGT). The 17 highest performing candidate DOIs with AUC ≥ 0.90 in profile data and with good validation (AUC > 0.70) in RIM, some from each category A-F, were discussed for their performance characteristics and clinical face validity at a consensus conference.

Results: A final ranking of the top DOIs from the adult working group yielded 92% consensus (among 12 adult PM/DM experts) for a Conjoint Analysis hybrid DOI using relative % change in CSMs with different cutpoints for minimal, moderate and major improvement. NGT discussion with the adult and pediatric working groups yielded consensus (91% agreement) in use of a different Conjoint Analysis hybrid DOI (Table 1) for both adult DM/PM and JDM clinical trials using absolute % change with different cutpoints for minimal, moderate and major improvement.

Conclusion: A Conjoint Analysis-driven hybrid DOI with a continuous score of improvement based on absolute % change in CSMs with different cut points for minimal, moderate and major improvement (prelim) was selected by a data and consensus-driven process as a final DOI to be used for clinical trials in adult DM/PM. Criteria for major improvement is considered preliminary.

Table 1. *Final Myositis Response Criteria Model*

1000 Minds Model (absolute % change)	
Core Set Measure	**Improvement score for each level of CSM**
MD Global Absolute % Change	
Up to <=5%	0
>5% up to <=15%	7.5
>15% up to <=25%	15
>25% up to <=40%	17.5
>40%	20
Patient Global/Parent Global Absolute % Change	
Up to <=5%	0
>5% up to <=15%	2.5
>15% up to <=25%	5
>25% up to <=40%	7.5
>40%	10
MMT/CMAS Absolute % Change	
Up to <=2%	0
>2% up to <=10%	10
>10% up to <=20%	20

>20% up to <=30%	27.5
>30%	32.5
HAQ/CHAQ Absolute % Change	
Up to <=5%	0
>5% up to <=15%	5
>15% up to <=25%	7.5
>25% up to <=40%	7.5
>40%	10
Muscle Enzyme/CHQ-PF50 Absolute % Change	
Up to <=5%	0
>5% up to <=15%	2.5
>15% up to <=25%	5
>25% up to <=40%	7.5
>40%	7.5
Extra Muscular VAS/DAS Absolute % Change	
Up to <=5%	0
>5% up to <=15%	7.5
>15% up to <=25%	12.5
>25% up to <=40%	15
>40%	20

Total Improvement Score is sum of score achieved in each CSM
Total improvement score >= cut points determines Minimal, Moderate and Major Improvement

Profile	Improvement Category	Cut point on total improvement score
Adult	Minimal	>=20
	Moderate	>=40
	Major (prelim)	>=60

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Long Term Outcomes of Patients with Moderate Creatine Kinase (CK) Elevation Seen in a Rheumatology Clinic. Lyudmila Kirillova[1], Abraham Tacang[1], Andrea Berger[2], Thomas M. Harrington[1] and Androniki Bili[1]. [1]Geisinger Health System, Danville, PA, [2]Center for Health Research, Geisinger Health System, Danville, PA.

Background/Purpose: Asymptomatic or mildly symptomatic patients with moderate creatine kinase (CK) elevation are commonly referred to rheumatologists. In patients without a clearly established diagnosis, the significance of the CK elevation and long term outcomes are unclear and there is lack of data to help rheumatologists to counsel these patients. The purpose of this study was to examine the outcomes of patients with moderate CK elevation of unclear etiology and identify possible predictors of CK normalization and symptom resolution.

Methods: Retrospective chart review of asymptomatic or mildly symptomatic patients with moderate (250–1000 U/L) CK elevation who were referred to a rheumatologist for that reason, in a tertiary health system. Patients with known inflammatory myopathy, elevated troponin, cardiovascular disease, epilepsy or rhabdomyolysis were excluded. Patients with an established diagnosis within the first two visits with the rheumatologist were also excluded. Comparisons between groups were tested using two-sample t-tests, Wilcoxon rank sum tests, or Kruskal-Wallis tests, and Pearson's chi-square or Fishers exact tests, as appropriate.

Results: 62 patients were included of which 67.7% were male, 95.2% Caucasian, with median CK 368 U/L at baseline, median highest CK 602 U/L and median follow up of 7 years (interquartile range 5 to 8 years). At the end of the observation period, 2 patients (3.2%) were diagnosed with inflammatory myopathy, 36 patients (58.1%) were thought to have elevated CK due to medications (mostly cholesterol lowering medications), 5 patients (8.1%) were classified as "other" (race, exercise) causes and for 19 (30.6%) patients there was no established cause for the elevated CK. There were no differences between the outcome groups regarding demographics, median CK or symptoms at baseline. In 27 patients (43.5%) CK normalized at follow-up. Patients with normalized CK were older (median age 66 vs. to 56 years, p= 0.03) and had lower CK levels (median CK 306 vs. to 403 U/L, p= 0.009) at baseline compared to patients whose CK remained elevated. Of the 56 patients with symptoms at baseline 28 (50%) became symptom-free at follow up; absence of muscle weakness was associated with resolution of the symptoms in follow-up (92.3% vs. 67.9%, p = 0.026). In the 36 patients with CK elevation due to medications, CK normalized in 19 (52.8%) and symptoms subsided in 20 (55.6%) patients at follow-up. In the 19 patients with CK elevation of unknown etiology, CK normalized in 6 (31.6%) and symptoms subsided also in 6 (31.6%) patients at follow-up.

Conclusion: In patients with asymptomatic or mildly symptomatic moderate CK elevation, the main etiology is lipid lowering medicines but in a substantial proportion the etiology remains unclear. In older patients and patients with lower CK at baseline it is more likely that CK normalizes in follow-up; patients without weakness as the main symptom at baseline were more likely to become asymptomatic at follow-up. These are encouraging findings that can help rheumatologists counsel these patients on their long term prognosis.

Disclosure: L. Kirillova, None; **A. Tacang**, None; **A. Berger**, None; **T. M. Harrington**, None; **A. Bili**, None.

914

A Predictive Model of Disease Outcome in Rituximab-Treated Myositis Patients Using Clinical Features, Autoantibodies, and Serum Biomarkers. Jeannette Olazagasti[1], Cynthia S. Crowson[1], Molly S. Hein[1], Consuelo Lopez de Padilla[1], Rohit Aggarwal[2], Chester V. Oddis[2] and Ann M. Reed[1]. [1]Mayo Clinic, Rochester, MN, [2]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Develop predictive models of early (8 week) and late (24 week) disease outcomes using clinical features, autoantibodies, and serum biomarkers in patients with refractory myositis treated with rituximab.

Methods: In the Rituximab in Myositis (RIM) trial, all subjects (76 with adult dermatomyositis, 76 with adult polymyositis and 48 with juvenile dermatomyositis) received rituximab (2 doses on consecutive weeks) with half the patients receiving drug at baseline and half receiving drug 8 weeks later. Using start of treatment as baseline, serum samples (n=177) were analyzed at baseline and after 8 and 24 weeks after rituximab. Potential predictors included the following baseline factors: clinical features, serum muscle enzymes, interferon gene score, autoantibodies (anti-synthetase n=28, TIF1-g n=19, Mi-2 n=25, SRP n=21, NXP2 n=18, non-myositis associated n=24, undefined autoantibody n=9), and cytokines/chemokines measured by multiplexed sandwich immunoassays (Meso Scale Discovery) (type-1 IFN-inducible [IP-10, I-TAC, MCP1], Th1 [IFNγ, TNFα, IL2], Th2 [IL4, IL5, IL10, IL12, IL13], Th17 [IL6, IL17, IL1β] and regulatory cytokines [IL10, TNFa, MIP-1α, MIP-1β]). Our primary definition of response to treatment was based on absolute change from baseline to 8 weeks and 24 weeks in physician global visual analog scale (VAS), muscle VAS, and extramuscular VAS. Multivariable linear regression models were developed using stepwise variable selection methods.

Results: Preliminary models were built with good predictive ability both for change in physician global assessment and muscle disease activity at 24 weeks (R-square=0.41 and 0.40, respectively). The model for change in physician global assessment included the following baseline clinical and lab features: muscle disease activity, physician global assessment, and I-TAC (Table). The model for change in muscle disease activity included baseline physician global assessment, skeletal disease activity, I-TAC and IFNγ. Similarly, a predictive model was built with excellent predictive ability (R-square=0.67) for change in extramuscular disease activity at 24 weeks. This model included the following baseline clinical and lab features: constitutional, skeletal and extramuscular disease activity by VAS, and MIP-1β and Mi-2. We also built models from baseline to 8 weeks but their predictive ability was inferior compared to those for 24 weeks (R-square<0.3).

Conclusion: Changes in disease activity over time following treatment with rituximab in patients with refractory myositis can be predicted. These models could be clinically useful to optimize treatment selection in these patients.

Outcomes ->	Change in Physician Global VAS		Change in Muscle VAS		Change in Extramuscular VAS	
Predictors (baseline)	**Coefficient**	**P-value**	**Coefficient**	**P-value**	**Coefficient**	**P-value**
Physician Global Assessment	−0.80	0.0007	−0.33	0.002	—	—

Muscle Disease Activity	0.51	0.0008	—	—	—	—
Extramuscular Global Assessment	—	—	—	—	0.60	0.0002
Skeletal Disease Activity	—	—	0.38	0.02	0.26	0.04
Constitutional Disease Activity	—	—	—	—	0.23	0.02
Mi-2	—	—	—	—	−15.47	0.002
I-TAC	−0.01	0.025	−0.02	0.01	—	—
IFNγ	—	—	−0.35	0.01	—	—
MIP-1β	—	—	—	—	0.008	<0.0001

Disclosure: J. Olazagasti, None; **C. S. Crowson**, None; **M. S. Hein**, None; **C. Lopez de Padilla**, None; **R. Aggarwal**, Questcor, 2, Questcor, 5; **C. V. Oddis**, Novartis Pharmaceutical Corporation, 5; **A. M. Reed**, None.

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Increased Risk of Myocardial Infarction in Dermatomyositis and Polymyositis: A General Population-Based Cohort Study. Kateryna Vostretsova[1], Erin Carruthers[2], Eric C. Sayre[2], John Esdaile[2] and J Antonio Avina-Zubieta[3]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada, Richmond, BC, [3]University of British Columbia, Department of Experimental Medicine, Vancouver, BC.

Background/Purpose: Patients with polymyositis (PM) and dermatomyositis (DM) may have an increased risk of myocardial infarction (MI), similar to other connective tissue diseases. However, no relevant data are scarce to date. We estimated the future risk and time trends of **newly recorded cases of MI** among **individuals with incident PM/DM (**1996–2010**)** compared to controls using physician-billing data from the province of British Columbia (~4.4 million).

Methods: Our data include all visits to health professionals and all hospital admissions, investigations (1990–2010) and all dispensed medications (1995–2010) for all individuals. We conducted a retrospective matched cohort study. Ten controls matched by birth year, sex and calendar year were randomly selected from the general population for each case. **Outcome**: Newly recorded MI events during follow up from hospitalization (ICD-9CM 410 or ICD-10 code: I21). In addition, we defined death from MI based on the death certificate diagnostic codes, including out of hospital deaths (ICD-10 code: I21). We calculated incidence rate ratios (IRR) overall and stratified by disease duration. We calculated hazard ratios (HR) and 95% confidence intervals (95% CI) adjusting for relevant confounders. Sensitivity analyses were conducted to assess for unmeasured confounders.

Results: Among 431 with PM (59% female, mean age 59.9 years y) and 352 with DM (65% female, mean age 55.7 yeas) the corresponding incidence rate ratio (IRRs)for MI were 8.14 (95% CI; 4.62–13.99) and 3.80 (95% CI; 1.89–7.09) respectively (**see table)**. Overall, the highest IRRs for MI were observed in the first year after PM diagnosis (IRR= 12.65, 95% CI: 5.11–31.65) as well as DM diagnosis (IRR= 6.32, 95% CI; 1.66–21.03). The risk of MI remained statistically significant in the fully adjusted models (hazard ratios= 3.78 (95% CI 2.05–6.95 and 6.54 (95% CI; 2.73–15.67), respectively) **(see table).** Our results remained statistically significant after adjusting for the potential impact of an unmeasured confounder.

Conclusion: The results of this large truly general population-based study indicates an increased risk of MI in people with PM (four fold) and DM (seven-fold) particularly in the first year after diagnosis, suggesting that inflammation plays a key role in the pathogenesis of MI. Our results support the need for increased monitoring for cardiovascular disease and risk modification to prevent this potentially fatal complication in patients with DM and PM.

	DM n = 352	**Non-DM n = 3,522**
MI events, N	**13**	**51**
Incidence Rate/1000 Person-Years	12.55	3.30
Age-,sex-, and entry time-matched IRRs (95% CI)	3.80 (1.89–7.09)	1.0
<1 year of disease duration	6.32 (1.66–21.01)	1.0
<2 years of disease duration	5.75 (2.14–14.06)	1.0
<3 years of disease duration	5.18 (2.10–11.70)	1.0
<4 years of disease duration	4.62 (2.09–9.44)	1.0
<5 years of disease duration	4.99 (2.42–9.68)	1.0
Multivariable RR (95% CI)*	6.54 (2.73–15.67)	1.0
	PM n = 431	**Non-PM n = 4,497**
MI events, N	29	93
Incidence Rate/1000 Person-Years	22.52	4.74
Age-,sex-, and entry time-matched RRs (95% CI)	4.74 (3.01–7.26)	1.0
<1 year of disease duration	12.65 (5.11–31.65)	1.0
<2 years of disease duration	6.13 (3.06–11.76)	1.0
<3 years of disease duration	5.33 (2.89–9.44)	1.0
<4 years of disease duration	5.55 (3.29–9.09)	1.0
<5 years of disease duration	5.56 (3.38–8.89)	1.0
Multivariable HR (95% CI)*	3.78 (2.05–6.95)	1.0

* Adjusting for healthcare utilization, medications use (glucocorticoids, hormone replacement therapy (HRT), contraceptives, COX-2 inhibitors, non-steroidal anti-inflammatory drugs), cardiovascular medications (antihypertensives, cardiac glycosides, diuretics, antiarrhythmic, nitrates and anticoagulants), fibrates and statins. In addition, the modified Charlson's co-morbidity index for administrative data was calculated in the year before the index date.

Disclosure: K. Vostretsova, None; **E. Carruthers**, None; **E. C. Sayre**, None; **J. Esdaile**, None; **J. A. Avina-Zubieta**, None.

ACR Concurrent Abstract Session
Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis: Clinical Osteoporosis: Treatment and Safety
Sunday, November 16, 2014, 4:30 PM–6:00 PM

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Effects of 2 Years of Treatment with Romosozumab Followed By 1 Year of Denosumab or Placebo in Postmenopausal Women with Low Bone Mineral Density. MR McClung[1], A Chines[2], JP Brown[3], A Diez-Perez[4], H Resch[5], J Caminis[6], MA Bolognese[7], S Goemaere[8], HG Bone[9], JR Zanchetta[10], J Maddox[2], O Rosen[2], S Bray[11] and A Grauer[2]. [1]Oregon Osteoporosis Center, Portland, OR, [2]Amgen Inc., Thousand Oaks, CA, [3]Laval University and CHU de Québec Research Centre, Quebec City, QC, [4]Autonomous University of Spain, Barcelona, Spain, [5]St. Vincent Hospital, Vienna, Austria, [6]UCB, Raleigh, NC, [7]Bethesda Health Research Center, Bethesda, MD, [8]Ghent University Hospital, Ghent, Belgium, [9]Michigan Bone and Mineral Clinic, Detroit, MI, [10]Instituto de Investigaciones Metabólicas, Buenos Aires, Argentina, [11]Amgen Ltd., Cambridge, United Kingdom.

Background/Purpose: We previously reported that 1 year of treatment with the sclerostin antibody romosozumab (Romo) was associated with increased bone mineral density (BMD) and bone formation and with decreased bone resorption in postmenopausal women with low BMD (McClung MR et al., *N Engl J Med* 2014;370:412–20). Here, we report the results of 2 years of treatment with Romo, followed by 1 year of denosumab (DMAb) or placebo.

Methods: This phase 2 study enrolled 419 postmenopausal women age 55 to 85 years with a lumbar spine, total hip, or femoral neck T-score ≤–2.0 and ≥–3.5. For the results described here, women received 1 of 5 regimens of Romo (70 mg QM, 140 mg QM, 210 mg QM, 140 mg Q3M, 210 mg Q3M; data for the 210 mg QM group are shown in the figure) or placebo for 2 years. At the end of 2 years, eligible subjects entered a 1-year extension phase and were re-randomized 1:1 within their original treatment group to placebo or DMAb 60 mg Q6M. Only women who entered the extension were included in these analyses.

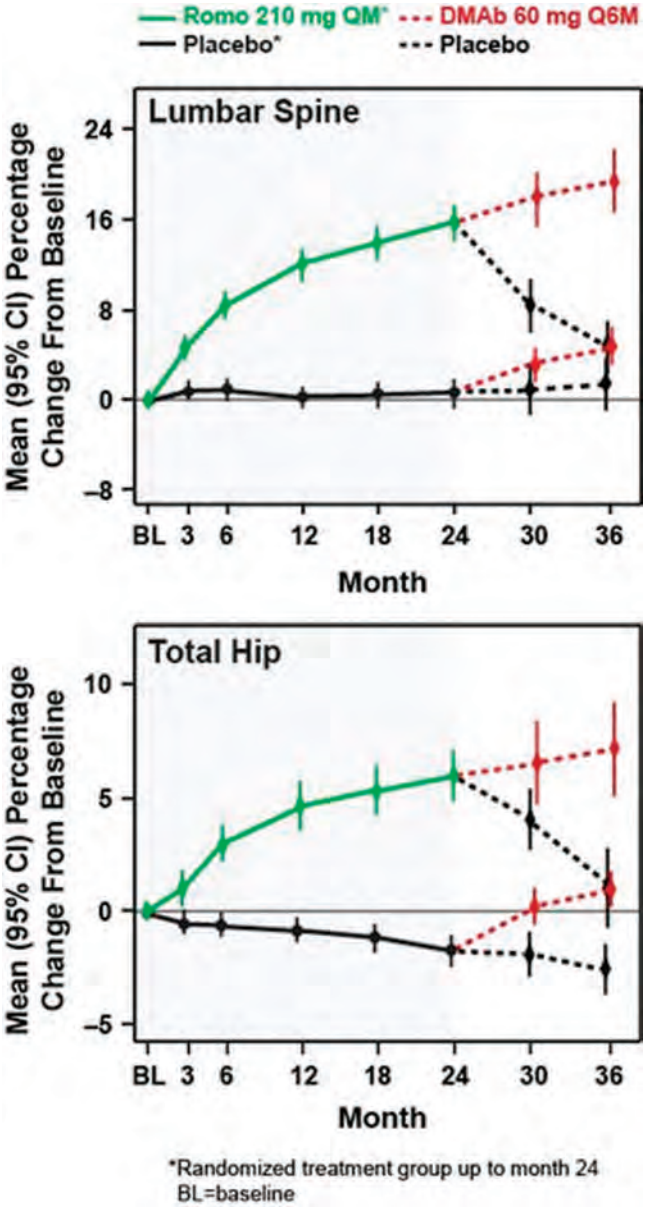
Results: Romo led to rapid and marked increases in lumbar spine and total hip BMD during year 1 and continued increases through year 2. The largest gains were observed with Romo 210 mg QM, with BMD increases of 15.7% (lumbar spine) and 6.0% (total hip) (Figure). Women receiving Romo 210 mg QM who transitioned to DMAb continued to accrue BMD at a rate similar to that in the second year of Romo; in those who transitioned to placebo, BMD returned toward pretreatment levels.

Romo induced rapid stimulation of bone formation (P1NP) and decreased bone resorption (CTX). Increases in P1NP were transitory, returning toward baseline within 6 to 12 months and remaining below baseline through year 2. CTX remained below baseline through year 2. In subjects receiving Romo 210 mg QM who transitioned to DMAb, P1NP and CTX decreased; for those who transitioned to placebo, P1NP gradually returned to pretreatment levels, while CTX initially increased above baseline and gradually returned toward baseline.

Adverse events were balanced between the placebo and Romo groups during the first 2 years of the study (with the exception of injection site reactions, most reported as mild) and in the placebo and DMAb groups during year 3.

Conclusion: Romo led to rapid and marked increases in lumbar spine and total hip BMD over 2 years, which continued with DMAb and resolved after

transition to placebo. These data suggest that the treatment effects observed with Romo are further augmented by follow-on treatments like DMAb.



Disclosure: M. McClung, Amgen Inc., Merck, 2, Amgen Inc., Lilly, Merck, 5; **A. Chines**, Amgen Inc., 1, Amgen Inc., 3; **J. Brown**, Actavis, Amgen Inc., Eli Lilly, Merck, Novartis, 2, Amgen Inc., Eli Lilly, 5, Amgen Inc., Eli Lilly, 8; **A. Diez-Perez**, Active Life Scientific, 1, Amgen Inc., 2, Lilly, Amgen Inc., 5, Lilly, Amgen Inc., GSK, Novartis, ViiV, 8; **H. Resch**, None; **J. Caminis**, UCB Inc., 1, UCB Inc., 3; **M. Bolognese**, Amgen Inc., Regeneron, Lilly, 2, Amgen Inc., 8; **S. Goemaere**, Amgen Inc., MSD, Novartis, 2, Amgen Inc., UCB, Eli Lilly, MSD, Novartis, 5, Amgen Inc., Eli Lilly, MSD, Novartis, Servier, Rottapharma, Willpharma, Takeda, 8; **H. Bone**, Amgen Inc., Merck, Novartis, NPS, 2, Amgen Inc., Merck, Novartis, Tarsa, Noven, 5; **J. Zanchetta**, Amgen Inc., Eli Lilly, MSD, GSK, 5, Amgen Inc., MSD, Radius Inc., 2; **J. Maddox**, Amgen Inc., 1, Amgen Inc., 3; **O. Rosen**, Amgen Inc., 1, Amgen Inc., 3; **S. Bray**, Amgen Inc., 1, Amgen Inc., 3; **A. Grauer**, Amgen Inc., 1, Amgen Inc., 3.

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Evaluation of Invasive Oral Procedures and Events in Women with Postmenopausal Osteoporosis Treated with Denosumab. Results from the Pivotal Phase 3 Fracture Study Extension Nelson B. Watts[1], John T. Grbic[2], Michael McClung[3], Socrates Papapoulos[4], David Kendler[5], Christence S. Teglbjaerg[6], Lawrence O'Connor[7], Rachel B. Wagman[7], Eric Ng[7], Nadia S. Daizadeh[7] and Pei-Ran Ho[7]. [1]Mercy Health Osteoporosis and Bone Health Services, Cincinnati, OH, [2]Columbia University, New York, NY, [3]Oregon Osteoporosis Center, Portland, OR, [4]Leiden University Medical Center, Leiden, Netherlands, [5]University of British Columbia, Vancouver, BC, [6]Center for Clinical and Basic Research, Ballerup, Denmark, [7]Amgen Inc., Thousand Oaks, CA.

Background/Purpose: Osteonecrosis of the jaw (ONJ) is a rare but serious adverse event of some antiresorptive therapies, including denosumab (DMAb), and invasive oral procedures and events (OPEs) are suggested to be an important risk factor (Ruggiero, *J Oral Maxillofac Surg* 2009). The incidence of positively adjudicated ONJ in the DMAb bone loss clinical program is rare (between ≥ 1 and < 10 per 10,000). In this study, we assessed the occurrence of invasive OPEs through Year 5 of the ongoing, 7-year FREEDOM Extension (EXT) trial.

Methods: In FREEDOM, women were randomized to receive DMAb 60 mg SC or placebo every 6 months for 3 years. Those who missed ≤ 1 dose of investigational product and completed the Year-3 visit were eligible for the open-label FREEDOM EXT; women in the EXT long-term group (N = 2343) received DMAb in FREEDOM and EXT, and women in the EXT cross-over group (N = 2207) received placebo in FREEDOM and DMAb in EXT. Women who reached the EXT Year-3 visit were asked to chronicle their history of invasive OPEs (eg, dental implants, tooth extraction, natural tooth loss, or scaling or root planing [extensive subgingival cleaning]) during the EXT. Every 6 months thereafter, women were asked to document their oral health history since the last visit. Jaw surgery information was collected starting from month 30 of the EXT.

Results: The majority of women (78%) participated in the survey. Over 5 years of the EXT, 42.4% of these women reported an invasive OPE; the incidence of the 5 individual OPEs reported was similar between groups (Table). ONJ incidence was 0.4% (7/1500 subjects) in women reporting invasive OPEs and 0.05% (1/2036 subjects) in women reporting no invasive OPEs. The actual number of invasive OPEs may be underestimated due to limited capture of OPEs in medical charts and due to subjects' recall bias of events that occurred in the first 3 years of the EXT. During the EXT (Years 1–5), the exposure-adjusted incidence of ONJ was 4.2 per 10,000 patient-years. Of the 8 ONJ cases, 6 have resolved, 1 is ongoing and continues to be followed, and the final outcome of 1 is unknown, as consent was withdrawn.

Conclusion: While invasive OPEs were common in this group of DMAb-treated women with postmenopausal osteoporosis, ONJ incidence was low. Invasive OPEs will continue to be queried prospectively in the EXT to characterize the long-term background rate.

Table: Summary of Invasive Oral Procedures and Events

	FREEDOM Extension Years 1–5		
	Long-term (N = 1827)	Cross-over (N = 1709)	All (N = 3536)
Age at EXT baseline in years, mean (SD)	74.4 (4.7)	74.2 (4.8)	74.3 (4.8)
Any invasive oral procedure or event, n (%)	763 (41.8)	737 (43.1)	1500 (42.4)
Scaling or root planing	500 (27.4)	481 (28.1)	981 (27.7)
Tooth extraction	387 (21.2)	354 (20.7)	741 (21.0)
Dental implant	88 (4.8)	79 (4.6)	167 (4.7)
Natural tooth loss	59 (3.2)	57 (3.3)	116 (3.3)
Jaw surgery	11 (0.6)	9 (0.5)	20 (0.6)

N = Number of subjects who received ≥ 1 dose of investigational product in FREEDOM Extension and responded to ≥ 1 ora event questionnaire related to FREEDOM Extension. n = Number of subjects with ≥ 1 invasive oral procedure or event.

Disclosure: N. B. Watts, OsteoDynamics, 1, AbbVie, Amarin, Amgen Inc., Bristol-Meyers Squibb, Corcept, Endo, Imagepace, Janssen, Lilly, Merck, Novartis, Noven, Pfizer/Wyeth, Radius, Sanofi-aventis, 5, Merck, NPS, 2, Amgen Inc., Merck, 9; **J. T. Grbic**, Dentsply Inc. (Dental Implant Division), 2; **M. McClung**, Amgen Inc., Merck, 2, Amgen Inc., Lilly, Merck, 5; **S. Papapoulos**, Amgen Inc, Merck & Co, Novartis, Axsome, Gador, 5, Board member International Osteoporosis Foundation, 6, Amgen Inc., GSK, Novartis, Roche, 8; **D. Kendler**, Astra Zeneca, Eli Lilly, Merck, Novartis, Amgen Inc., Pfizer, Astalis, 2, Eli Lilly, Merck, Amgen Inc., Pfizer, 5, Eli Lilly, Amgen Inc., Pfizer, GSK, 8; **C. S. Teglbjaerg**, None; **L. O'Connor**, Amgen Inc., 1, Amgen Inc., 3; **R. B. Wagman**, Amgen Inc., 1, Amgen Inc., 3; **E. Ng**, Amgen Inc., 1, Amgen Inc., 3; **N. S. Daizadeh**, Amgen Inc., 1, Amgen Inc., 3; **P. R. Ho**, Amgen Inc., 1, Amgen Inc., 3.

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Findings from Denosumab (Prolia®) Postmarketing Safety Surveillance for Serious Infections. W. Golden[1], D. B. Crittenden[1], M. Uhart[1], R. B. Wagman[1], C. Stehman-Breen[1], S. Papapoulos[2] and N. B. Watts[3]. [1]Amgen Inc., Thousand Oaks, CA, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Mercy Health Osteoporosis and Bone Health Services, Cincinnati, OH.

Background/Purpose: Prolia has marketing authorization in the EU, US, Canada, Japan, and over 40 countries or administrative districts worldwide for the treatment of postmenopausal women with osteoporosis at high/increased risk for fracture. As part of pharmacovigilance activities, Amgen Global Safety (AGS) continually assesses postmarketing adverse events reported by health care providers, patients, and other sources. Spontaneous adverse event reports, while often with insufficient information, are the cornerstone of safety surveillance programs and help detect rare and serious adverse drug reactions. Here we characterize the Prolia postmarketing experience for serious infections, including opportunistic infections.

Methods: A cumulative analysis of all non-clinical trial postmarketing serious infection reports (defined as those leading to ER visit or hospitalization) for Prolia in the AGS Database was conducted as of May 10, 2014 from solicited and spontaneous sources. Using postmarketing exposure estimates, we calculated overall reporting rates over time as well as cumulative rates for several serious infection subtypes, including opportunistic infections. Each infection subtype includes ≥ 1 related MedDRA Preferred Terms (PTs).

Results: Cumulatively through May 10, 2014, the total estimated postmarketing Prolia exposure was 1,963,794 patient-years (p-ys). There were 1,232 postmarketing reports of serious infection. The top 5 most frequently reported PTs were pneumonia (236), urinary tract infection (166), cellulitis (145), diverticulitis (59), and sepsis (59). Time to onset after the first dose of Prolia (reported for 305 cases) was highly variable, ranging from 1 to 916 days (mean 156, median 82.5). Among the 7 reported cases of endocarditis, only 2 were confirmed by echocardiography; both cases had confounding factors. The reporting rate of overall serious infection has decreased over time since product registration (first reporting period in 2010: 153 cases/100,000 p-ys; current reporting period in 2014: 57 cases/100,000 p-ys). Cumulative reporting rates of serious infection subtypes were low (Table) and below the background rates estimated from insurance claims data. Few cases of opportunistic infections were reported and included herpes zoster (32 cases; 1.6 cases/100,000 p-ys), unspecified fungal infections (10 cases; 0.5 cases/100,000 p-ys), and mycobacterium tuberculosis (5 cases; 0.3 cases/100,000 p-ys).

Conclusion: Recognizing the limitations of postmarketing safety data, these data suggest that reporting rates of serious infections decreased over time, and rates of events reported are lower than estimated background rates. The benefit/risk profile for Prolia remains favorable. Ongoing safety surveillance continues through clinical studies and pharmacovigilance activities.

Table. Cumulative Reporting Rates of Serious Infection Subtypes

Serious Infection Subtypes*	Reports (n)	Reporting Rate (per 100,000 p-ys)
Pneumonia	256	13.0
Urinary tract infection/cystitis	235	12.0
Cellulitis	149	7.6
Sepsis	95	4.8
Diverticulitis	59	3.0
Endocarditis	7	0.4

*Each serious infection subtype includes ≥ 1 related MedDRA Preferred Terms.

Disclosure: W. Golden, Amgen Inc., 1, Amgen Inc., 3; **D. Crittenden**, Amgen Inc., 1, Amgen Inc., 3; **M. Uhart**, Amgen Inc., 1, Amgen Inc., 3; **R. Wagman**, Amgen Inc., 1, Amgen Inc., 3; **C. Stehman-Breen**, Amgen Inc., 1, Amgen Inc., 3; **S. Papapoulos**, Amgen Inc, Merck Co, Novartis, Axsome, Gador, 5, International Osteoporosis Foundation, 6, Amgen Inc., GSK, Novartis, Roche, 8; **N. Watts**, OsteoDynamics, 1, OsteoDynamics, 4, OsteoDynamics, 6, AbbVie, Amarin, Amgen Inc., Bristol-Meyers Squibb, Corcept, Endo, Imagepace, Janseen, Lilly, Merck, Novartis, Noven, Pfizer/Wyeth, Radius, sanofi-aventis, 5, Merck, NPS, 2.

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Glucocorticoid Exposure and Fracture Risk in a Large Cohort of Commercially-Insured Rheumatoid Arthritis Patients Under Age 65. Akhila Balasubramanian[1], Sally Wade[2], Robert A Adler[3], Celia Fang (Lin)[4], Michael Maricic[5], Cynthia O'Malley[1], Kenneth G. Saag[6] and Jeffrey R. Curtis[6]. [1]Amgen, Inc., Thousand Oaks, CA, [2]Wade Outcomes Research and Consulting, Salt Lake City, UT, [3]Hunter Holmes McGuire VA Medical Center, Richmond, VA, [4]Amgen, Thousand Oaks, CA, [5]Catalina Pointe Rheumatology, Tucson, AZ, [6]The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Systemic glucocorticoid use can increase fracture risk, although dose-specific effects are not well understood, especially in younger adults. Underlying diseases (e.g., rheumatoid arthritis [RA]) can confound these associations. This study evaluated the impact of glucocorticoid exposure on risk of fragility fracture in RA patients.

Methods: The 42,034 study patients identified in the MarketScan® claims database were newly treated for RA (index date) between 1/1/2005 and 12/31/2011, aged 18–64 years at index, had benefits coverage for ≥12 months pre-index, and no pre-index cancer. Patients with pre-index glucocorticoid use were glucocorticoid-free for ≥ 12 months prior to their first glucocorticoid pharmacy claim, and had continuous benefits coverage from first glucocorticoid claim to index date. Glucocorticoid use (any; cumulative, peak, and average daily dose; cumulative days exposed; days of continuous exposure; days since most recent exposure) was assessed for each patient-day and censored at the earliest of post-index fragility fracture, cancer diagnosis, or end of follow-up. Exposures were converted to prednisone equivalents and cumulative measures included pre-index use. Patient demographics at index and pre-index clinical characteristics were assessed. Incidence rates per 1,000 person-years for post-index fragility fracture were stratified by glucocorticoid exposure. Cox's proportional hazards models estimated age- and sex-adjusted fracture risk by exposure level.

Results: Patients averaged 738 (standard deviation [SD] 615) post-index follow-up days. Most patients (82%) had glucocorticoid exposure during the study (43% with cumulative dose < 675 mgs; 73% had peak dose ≥ 15 mg/day). Exposed and unexposed patients were demographically similar (74% female; mean age 49.4 [10.7] and 49.8 [10.2] years); 1% had pre-index fracture. Fragility fracture incidence rates (95% confidence intervals) were 5.1 (4.6, 5.6) and 16.8 (11.4, 24.0) at daily doses of 0 mg/day and ≥ 15 mg/day, respectively, and 4.8 (3.8, 6.0) and 13.7 (10.6, 17.4) at cumulative doses of 0 mg and ≥ 5400 mgs, respectively. Among patients ever-exposed to glucocorticoids, fracture risk was significantly elevated at cumulative dose ≥ 2700 mg and daily dose ≥ 15 mg/day (Table). Following glucocorticoid discontinuation, fracture risk (adjusted for age, sex, and cumulative dose) was 32% lower at 60–181 days since last exposure versus current exposure. Analyses restricted to patients younger than 50 years also showed highest fracture risk at highest exposures.

Conclusion: In this large, relatively young cohort of RA patients, fracture risk increased by 2- to 3-fold at high levels of daily and cumulative glucocorticoid dose, and began to decline within months of glucocorticoid discontinuation.

Table: Risk of Post-Index Fragility Fracture among Rheumatoid Arthritis Patients Ever-Exposed to Systemic Glucocorticosteroids

		Hazard Ratio	95% C.I.	P-Value
Sex	Male (n=31,104)	ref		
		1.71	(1.33, 2.20)	<.0001
	Female (n=10,930)			
Age (years)	18 to 39 (n=7,230)	ref		
	40 to 44 (n=4,360)	1.81	(0.99, 3.31)	0.0524
	45 to 49 (n=6,168)	2.45	(1.44, 4.17)	0.0009
	50 to 54 (n=7,995)	2.94	(1.78, 4.86)	<.0001
	55 to 59 (n=8,736)	3.86	(2.37, 6.29)	<.0001
	60 to 64 (n=7,545)	5.57	(3.43, 9.04)	<.0001
Cumulative dose (mg)*†	> 0 to <675	ref		
	675 to <1350	1.07	(0.80, 1.44)	0.6504
	1350 to <2700	1.00	(0.74, 1.36)	0.9854
	2700 to <5400	1.41	(1.03, 1.93)	0.0317
	≥ 5400	2.34	(1.68, 3.26)	<.0001
Average daily dose (mg/day)*	0‡	ref		
	0 to <5	1.43	(0.92, 2.23)	0.1091
	5 to <7.5	1.00	(0.64, 1.55)	0.9891
	7.5 to <15	1.21	(0.82, 1.80)	0.3439
	≥ 15	2.67	(1.78, 3.99)	<.0001

*Exposure metrics were quantified on a person-time basis so patient numbers are not available.
†As the analysis represented in this table was restricted to patients ever-exposed to systemic glucocorticosteroids, all cumulative dose values are greater than zero.
‡Average daily dose would have a value of zero during unexposed periods for this ever-exposed population.

Disclosure: A. Balasubramanian, Amgen, 3, Amgen, 1; **S. Wade**, Amgen, 5; **R. A. Adler**, Amgen, 9; **C. Fang (Lin)**, Amgen, 1, Amgen, 3; **M. Maricic**, Amgen, 2; **C. O'Malley**, Amgen, 1, Amgen, 3; **K. G. Saag**, Amgen, 5; **J. R. Curtis**, Amgen, 5.

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Randomized Controlled Trial to Assess the Safety and Efficacy of Odanacatib in the Treatment of Men with Osteoporosis. Eric Orwoll[1], Silvano Adami[2], Neil Binkley[3], Roland Chapurlat[4], Bente Langdahl[5], Steven Doleckyj[6], Hilde Giezek[7], Boyd Scott[8] and Arthur Santora[8]. [1]Oregon Health and Science University, Portland, OR, [2]Rheumatology Department, University of Verona, Verona, Italy, [3]University of Wisconsin, Madison, WI, [4]Hopital Edouard Herriot, Lyon, France, [5]Aarhus University Hospital, Aarhus, Denmark, [6]Merck & Co., Inc., Whitehouse Station, NJ, [7]MSD Belgium, Brussels, Belgium, [8]Merck Sharp & Dohme Corp., Whitehouse Station, NJ.

Background/Purpose: Osteoporosis in men is an important clinical problem, associated with significant morbidity, mortality and societal expense. Men with osteoporosis represent between 20 and 25% of all osteoporotic patients and men are at greater risk of death following a hip fracture. Odanacatib (ODN), a selective inhibitor of cathepsin K, is currently being investigated as a treatment for osteoporosis. In a Phase II study in postmenopausal women, treatment with ODN 50mg once-weekly resulted in increases in bone mineral density (BMD) vs. baseline at the lumbar spine (LS) (11.9%) and total hip (TH) (8.5%) over 5 years. In this 2-yr Phase III study safety and efficacy of ODN in the treatment of men with osteoporosis was investigated.

Methods: This was a double-blind, randomized; placebo controlled 24-month trial. Men ≥40 and ≤95 years of age with idiopathic osteoporosis or osteoporosis due to hypogonadism were enrolled. Inclusion criteria included a LS or hip (TH, femoral neck (FN) or trochanter) T-score of ≤−2.5 to ≥−4.0 without prior vertebral fracture or ≤−1.5 to ≥−4.0 with one prior vertebral fracture. Participants were randomized (1:1) to 50mg ODN or PBO orally once-weekly, and all received vitamin D_3(5600IU/week) and calcium supplements (total intake including food of ~1200mg daily). The primary outcomes were the effect of ODN versus PBO on LS BMD assessed by DXA versus PBO at 24 months and safety and tolerability. Secondary outcomes included changes in BMD at the TH, FN, trochanter sites, and bone turnover markers (u-NTx, S-CTx, s-PINP and s-BSAP).

Results: A total of 292 men were randomized and received at least one dose of study medication. The average age was 68.8 years, and 5.8% had total testosterone levels below 250ng/dL. BMD increases from baseline at 24 months in the ODN group at the LS and all 3 hip sites (TH, FN and trochanter) were 6.9%, 1.9%, 1.7% and 2.8% respectively, and all were greater vs. PBO (LS, TH and trochanter $p<0.01$; FN $p=0.008$). ODN significantly decreased (vs. PBO) the bone resorption markers u-NTx/Cr and s-CTx (68% and 77%, both $p<0.001$) and also decreased bone formation markers, s-PINP and s-BSAP (16% and 8%, $p=0.001$ and $p=0.019$ respectively) compared to PBO at 24-months. The between group decrease of bone formation markers was maximal at 3 months, after which levels returned towards baseline by 24 months. The adverse events and overall safety profile were similar between ODN and PBO.

Conclusion: In this study, ODN increased spine and hip BMD in osteoporotic men. Changes in bone turnover markers suggest that ODN treatment decreases bone resorption while producing relatively small decreases in bone formation by the end of the study. ODN is a promising potential therapy for the treatment of osteoporosis in men.

Disclosure: E. Orwoll, Merck Human Health, 2; **S. Adami**, Amgen, Eli-Lilly, Abiogen, Roche, Merck, 5; **N. Binkley**, Merck Pharmaceuticals, 2, Merck Human Health, 5; **R. Chapurlat**, None; **B. Langdahl**, Merck, Amgen, Lilly, 5, Amgen, Lilly, Merck, 2, Merck, Amgen, Lilly, 8; **S. Doleckyj**, Merck Human Health, 1, Merck Human Health, 3; **H. Giezek**, Merck Pharmaceuticals, 1, Merck Human Health, 3; **B. Scott**, Merck Pharmaceuticals, 1, Merck Pharmaceuticals, 3; **A. Santora**, Merck Human Health, 1, Merck Pharmaceuticals, 3.

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Comparison of Infection Rates in Patients Receiving Denosumab, Denosumab and Biologics and Biologics Alone in a Suburban Rheumatology Clinic. Sajina Prabhakaran[1] and Charles Pritchard[2]. [1]Drexel University College of Medicine, Philadelphia, PA, [2]Drexel University College of Medicine, Willow Grove, PA.

Background/Purpose: Biologics including rituximab, abatacept and belimumab increase the risk of infection in patients. Denosumab, a RANK-ligand inhibitor used in the treatment of osteoporosis may theoretically make patients more susceptible to infections. RANK is a member of the tumor necrosis factor receptor (TNFR) superfamily so inhibition may cause immunosuppression. One pivotal trial showed an increase in cellulitis and erysipelas in patients on denosumab. We used a retrospective chart review of a patients in a sole specialty rheumatology practice to evaluate the infection rates and hospitalizations of patients on the combination of biologics with denosumab, biologic agents alone, and denosumab alone.

Methods: We reviewed the charts of 136 patients, 50 patients who received biologics only, 50 patients who received denosumab alone and 36 patients who received both simultaneously over the past 4 years. Biologics studied included infliximab, tocilizumab, rituximab, belimumab, abatacept, adalimumab, and golimumab. The primary end-point was to determine if there was a greater risk of infection, hospitalization, complication or discontinuation of biologic and/ or denosumab in the combined group versus the biologic alone. Percentage of incidence was calculated for each group and Chi-square and Fisher's Exact tests were used for analysis. Relative risks were calculated to compare infection risks between groups.

Results: There was no difference found in the risk of infection between the groups that received both biologic and denosumab compared to biologic alone, RR = 1.24, 95%, CI: 0.76 –2.04. There were statistically significant increases in the risk of infection in the groups that received both biologic and denosumab compared to the group that received denosumab; RR=7.87, 95% CI: 2.49–24.9 and biologic alone compared to denosumab, RR=6.33, 95% CI 2 – 20.1. Hospitalization rates were higher in the combination group compared to the denosumab (19.4% vs 12%, $p=0.038$). Statistically significant increases in the risk of infection with increased duration of exposure to biologics ($p<0.001$) were also noted.

Conclusion: We did not find an increased risk of infection with the combination of denosumab and a biologic compared to a biologic alone. The rates of infection and hospitalization of patients in the combination group were not significantly different between biologic medications.Secondary characteristics also did not affect the compared rates of infection.The duration of exposure to denosumab did not affect the infection rate. There did not seem to be any increased risk of infection in patients on combination non biologic DMARDs and denosumab. In summary this retrospective small study from a sole specialty rheumatology practice did not show a statistical increased risk of infection combining a biologic with denosumab vs a biologic. Hence it appears to be relatively safe to combine denosumab with a biologic agent.

Disclosure: S. Prabhakaran, None; **C. Pritchard**, Genetech, Abbvie, 6.

ACR Concurrent Abstract Session
Pain: Basic and Clinical Aspects I
Sunday, November 16, 2014, 4:30 PM–6:00 PM

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A Potential Role for TLR4 Activation in Osteoarthritis Associated Pain. Rachel E. Miller[1], Shingo Ishihara[1], Phuong Tran[1], Richard J. Miller[2] and Anne-Marie Malfait[1]. [1]Rush University Medical Center, Chicago, IL, [2]Northwestern University, Chicago, IL.

Background/Purpose: Damage associated molecular patterns (DAMPs) result from cellular stress and extracellular matrix breakdown. They may contribute to osteoarthritis (OA) pathogenesis by promoting synovitis and cartilage degradation, via activation of pattern recognition receptors (PRR) on chondrocytes and synovial cells. We hypothesized that DAMPs play a direct role in OA pain through activation of dorsal root ganglia (DRG) neurons. We investigated the effects of three OA-associated DAMPs, S100A8, S100A4, and α2-macroglobulin (α2M) on cultured DRG cells.

Methods: DRG neurons (L3-L5) were isolated from adult C57BL/6 mice (wild type, *Tlr4* null or *Tlr2* null) and cultured prior to (1) MCP-1 stimulation or (2) Ca^{2+} mobilization assays. For stimulation assays, cultures were treated overnight with S100A8 (1 μg/mL), S100A4 (1 μg/mL) or α2M (50–100 μg/mL) and supernatants collected for MCP-1 ELISA. The proalgesic chemokine MCP-1 is a key mediator of pain in murine experimental OA. For Ca^{2+} mobilization assays, cultures were loaded with a Ca^{2+}indicator dye and responses to S100A8 (1 μg/mL) or α2M (50 μg/mL) were recorded. Further, destabilization of the medial meniscus (DMM) or sham surgery was performed in 10-week old male C57BL/6 mice. Mice were euthanized 8 or 16 weeks later and L3-L5 DRG were harvested for culture, with or without the selective TLR4 antagonist, TAK242 (Tocris, 1 μM). After 96 hrs, supernatants were analyzed for MCP-1 levels via ELISA.

Results: Stimulation of DRG cultures with α2M resulted in a concentration-dependent increase of MCP-1 production, where 100μg/ml α2M caused a 10-fold increase compared to unstimulated cells ($p<0.0001$). These effects are similar to those observed with IL-1. S100A8 was an equally potent inducer of MCP-1 ($p<0.0001$ compared to control), whereas S100A4 did not stimulate MCP-1 expression.

Responses to α2M or S100A8 were unaltered in DRG cultures of *Tlr2* null mice. In contrast, DRG cells from *Tlr4* null mice did not produce MCP-1 in response to α2M, whereas the response to S100A8 was 50% suppressed, suggesting that the effects of α2M are mediated through TLR4 whereas S100A8 may use other receptors as well. This was confirmed using a selective TLR4 inhibitor in wild type (wt) DRG cultures.

8 and 16 weeks after DMM, unstimulated DRG cells produced increased amounts of MCP-1 compared to naïve and sham. Addition of TAK242 to the culture medium significantly reduced MCP-1 levels produced by DMM DRG

cells, suggesting that TLR4 contributes to MCP-1 production observed after DMM surgery.

Since DRG cultures contain glial cells in addition to sensory neurons, we studied direct effects of α2M and S100A8 on neurons through assessing Ca^{2+}-mobilization responses. On average, 8% of wt DRG neurons responded to S100A8 and 23% responded to α2M, suggesting that DRG neurons can express excitatory receptors for these DAMPs. In *Tlr4*null DRG, 6% of all neurons responded to S100A8 and none responded to α2M.

Conclusion: These studies suggest a potential role for DAMPs in DRG activation, which may contribute to OA pain. TLR4 plays an important role in these effects but other receptors may also be involved. Our results suggest that PRR may be a novel therapeutic target in OA associated pain.

Disclosure: R. E. Miller, None; **S. Ishihara**, None; **P. Tran**, None; **R. J. Miller**, None; **A. M. Malfait**, None.

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Phenotypes of Osteoarthritis-Related Knee Pain and Their Transitions over Time: The Osteoarthritis Initiative. Na Lu[1], Tuhina Neogi[1], K. Douglas Gross[1], Jingbo Niu[1], Hyon Choi[2] and Yuqing Zhang[1]. [1]Boston University School of Medicine, Boston, MA, [2]Harvard Medical School, Boston, MA.

Background/Purpose: The WOMAC questionnaire is one of most commonly used instruments to assess knee pain in persons with or at risk of knee osteoarthritis (OA). However, the summary score of the WOMAC pain subscale fails to distinguish pain experienced during activity from pain felt at rest. Yet these two symptomatic profiles may represent distinct phenotypes. If recognizable patterns of pain are, in fact, distinguishable as unique groupings of the individual WOMAC item responses, then their delineation could valuably inform distinct underlying mechanisms and the subsequent development of phenotype-specific treatments for OA-related knee pain.

Methods: The Osteoarthritis Initiative (OAI) cohort consists of adults ≥ 45 years of age that have or are at risk for knee OA. The WOMAC pain subscale was administered at baseline and each annual follow-up visit. Using a latent class model (SAS software PROC LTA), we identified distinct pain phenotypes based on participants' responses to each of the 5 WOMAC pain questions. The resultant pain phenotypes each consist of subjects with homogenous responses to the 5 WOMAC pain questions. We then examined the baseline characteristics of these pain phenotypes and estimated the transition probability of each pain phenotype to another over 24 months follow-up.

Results: Among 3,985 participants (7,906 knees) who had a WOMAC pain score available during the first 3 follow-up visits, we identified 5 distinct knee pain phenotypes at baseline: 1) No/minimal pain (No-Pain: 55.0%); 2) Mild pain during activity only (Mild-P-A: 20.0%); 3) Moderate pain during activity only (Mod-P-A: 12.3%); 4) Mild pain both during activity and at rest (Mild-P-A-R: 7.1%); and 5) Moderate pain both during activity and at rest (Mod-P-A-R: 5.8%). Age at baseline was similar across the 5 pain phenotypes; however women, higher BMI, higher depressive symptoms, and K/L score ≥3 tended to be higher among subjects with pain both during activity and at rest than pain during activity only. During follow-up, a majority of knees' pain phenotypes remain stable; ~11% of knees with No-Pain at baseline later developed Mild-P-A, ~20% of knees with Mild-P-A transitioned to the No-Pain group, and ~15% of knees with Mild-P-A transitioned to Mod-P-A. Among knees with Mild-P-A-R, ~43% improved to either No-Pain (~32%) or Mild-P-A (~11%). Among knees with Mod-P-A-R, ~26% had their pain improved to Mod-P-A, while the probability of transitioning to either No-Pain (9.5%) or Mild-P-A (7.2%) was small.

Conclusion: We identified 5 distinct knee pain phenotypes based on responses to the WOMAC pain questionnaire. While the pain phenotypes remained stable in the majority of knees over time, there was substantial transitioning both to better and worse pain phenotypes. These findings may have implications for identification of pain phenotype-specific risk factors and development of treatment for distinct pain phenotypes.

Table 1. Baseline Characteristics of Pain Phenotypes and Time 1 Status (Rows) to Time 2 Status (columns) Phenotype Transition Probabilities(%)

	TIME 1 STATUS				
	No.Pain	**Mild-P-A**	**Mod-P-A**	**Mild-P-A-R**	**Mod-P-A-R**
Age (Mean ± SD)	61.5 ± 9.2	61.2 ± 9.0	60.9 ± 9.0	60.6 ± 9.1	60.4 ± 8.9
Female (%)	56.2	54.9	61.9	63.7	69.0
BMI (Mean ± SD)	27.8 ± 4.5	28.7 ± 4.7	29.8 ± 4.9	28.6 ± 4.7	31.5 ± 5.5
CES-D (Mean ± SD)	5.4 ± 6.1	6.1 ± 5.9	8.4 ± 7.3	6.5 ± 6.7	11.2 ± 9.6
Kellgren-Lawrence (KL) Grade (%)					
0–1	67.5	49.8	39.0	51.7	27.3
2	22.7	29.8	29.9	28.2	35.5
3–4	9.8	20.4	31.1	20.1	37.3
TIME 2 STATUS					
No. Pain	82.6	19.5	7.7	32.0	9.5
Mild-P-A	11.3	62.2	20.8	10.8	7.2
Mod-P-A	1.5	14.4	57.2	4.1	26.1
Mild-P-A-R	3.9	2.5	1.5	48.9	5.8
Mod-P-A-R	0.8	1.4	5.8	4.2	51.5

Disclosure: N. Lu, None; **T. Neogi**, None; **K. D. Gross**, None; **J. Niu**, None; **H. Choi**, Takeda, 5, AstraZeneca, 5; **Y. Zhang**, None.

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Characteristics of Pain Flares in Knee Osteoarthritis. Susan L. Murphy[1], Angela K. Lyden[1], Arnold Gammaitoni[2], David A. Williams[3], Daniel J. Clauw[1], J. Ryan Scott[1] and Kristine Phillips[1]. [1]University of Michigan, Ann Arbor, MI, [2]Zogenix, Inc, San Diego, CA, [3]Univ of MI Hlth System-Lobby M, Ann Arbor, MI.

Background/Purpose: For inclusion in osteoarthritis clinical trials, participants often need to have a pain 'flare', usually defined as a pain increase over a period of time prior to study entry. Outside of clinical trial settings, there is no consensus regarding what constitutes a pain flare. The purpose of this study was to examine how individuals with knee osteoarthritis experience pain flares and their impact on daily living.

Methods: 45 participants (64 + 10 years; 55% female) with knee osteoarthritis underwent a baseline clinic visit as part of a larger pharmaceutical trial. At this visit, symptom measures were collected and participants were trained in procedures to collect data using a wrist-worn accelerometer in a 7-day home monitoring period. Participants wore the Actiwatch-Score and entered ratings of pain severity (0–10 scale) eight times per day. They were also asked to provide information at the end of each day in a logbook. Participants were asked to provide a definition of a pain flare and used that definition to indicate in the logbook if they experienced a pain flare that day and what they were doing when it occurred. Pain variability was calculated as the standard deviation of the pain ratings over the 7 day period. We hypothesized that pain flares and pain variability would be strongly related.

Results: When asked to define 'pain flare', descriptors of 'sharp' and 'increase in pain' were used by 30% and 21% of the sample respectively. Other descriptors included 'intense/severe', 'electrical' and various descriptors (e.g., twinge, stabbing, pulsation). Pain flares were most often described to be of short duration. During the home monitoring period, 77% of the sample experienced at least one pain flare and the mean was 2.2 + 2.0. Pain flares were most strongly associated with their worst daily pain (r =.51), followed by weekly average pain severity (r =.42), pain interference on the Brief Pain Inventory (r=.39), and WOMAC pain scale (r=.37). When asked to describe what they were doing when a pain flare occurred, participants most frequently mentioned activity-related causes (stair climbing, walking, shopping), while very few mentioned stiffness due to inactivity or being awakened by night pain. Pain flares were not significantly associated with pain variability (r =.12) or with neuropathic pain as measured by the PainDetect (r=.09); however PainDetect was most strongly correlated with WOMAC Pain (r=0.60), WOMAC Physical Function (r=0.57), and BPI severity (r=0.60).

Conclusion: Pain flares occurred frequently over a week for people with osteoarthritis, were of short duration, and were most often experienced during activities. Interestingly, pain flares were not associated with pain variability. Although pain flares and pain variability may be activity-related, WOMAC subscales, which asked about pain or function during activities, were most strongly associated with a neuropathic component to pain. These findings provide further insight into the pain experience for people with knee osteoarthritis. Pain flares appear to be characterized by researchers and individuals with knee osteoarthritis in a variety of ways suggesting the need for additional research in this area.

Disclosure: S. L. Murphy, None; **A. K. Lyden**, None; **A. Gammaitoni**, Zars Research, 3; **D. A. Williams**, Pfizer, Inc, 2; **D. J. Clauw**, None; **J. R. Scott**, None; **K. Phillips**, None.

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Cortical Reorganization after Duloxetine Treatment-Related Pain Decrease in Knee Osteoarthritis. Pascal Tetreault, Marwan Baliki, Etienne Vachon-Presseau, Renita Evonne Yeasted, Thomas J. Schnitzer and A. Vania Apkarian. Northwestern University, Chicago, IL.

Background/Purpose: Structural brain properties of patients coping with chronic painful conditions are becoming better understood but knowledge on how pain treatment affects these properties is still sparse. Assessment of cortical modifications during chronic pain evolution now permits identifying regions critically involved in painful pathologies. In this study, we evaluate structural brain reorganization of knee osteoarthritic (OA) patients after four months treatment with duloxetine (DLX) or placebo (P).

Methods: OA patients (n=40) meeting standard inclusion/exclusion criteria with pain ≥ 5 on 11 point NRS scale were randomized to DLX (60 mg) or placebo. Pain measurements were made at week 0, 2, 3, 6 and 16 and anatomic MRI scans done at baseline and at end of treatment (week 16). The total gray matter volume of the brain was obtained using SIENAX tool from FSL and cortical gray matter density (GMD) changes were evaluated using a voxel based morphometry approach (FSL-VBM). To evaluate structural brain properties, longitudinal contrast was made by using a two-way repeated measure ANOVA design.

Results: Patients were categorized as responders (≥ 20% pain decrease from baseline) and nonresponders in both DLX and placebo groups. The total gray matter volume showed an interaction of time*treatment*response ($F=16.69$, $p < 0.001$). Following treatment, DLX responders had a borderline significant volume increase ($p=0.07$); in contrast, placebo responders had a significant volume decrease ($p < 0.05$). Whole-brain voxel-wise VBM contrast (before – after treatment) revealed that DLX-treated patients underwent modification in GMD in the left precentral gyrus, left middle frontal gyrus and bilateral ACC (figure 1A). Interestingly, when patients positively responded to their treatment, independent of compound received, difference in GMD was observed only in the left precentral gyrus (figure 1B). In addition, regions in the left middle frontopolar (figure 1C) and inferior temporal gyri showed GMD changes when DLX induced pain relief. We thus show that some cortical regions presenting GMD reorganization were shared among all 4 groups studied, suggesting that a proportion of gray matter structural modification may be naturally occurring in time while other regional changes are directly related to treatment received.

Conclusion: Understanding how pharmacological treatment affects structural brain properties is important to assess drug efficacy and its potential deleterious effects. We herein show that pharmacological treatment of OA pain is affecting cortical reorganization in a way that is dependent on treatment, response and the interaction of both.

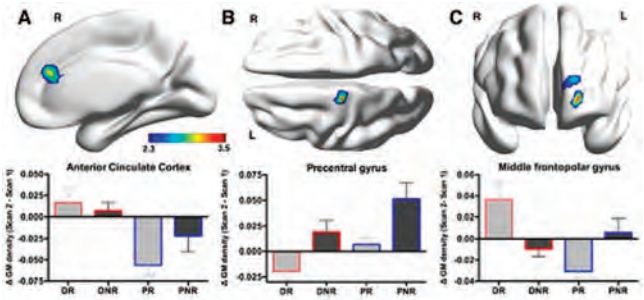

Figure 1. Treatment received, pain decrease and their interaction induce unique gray matter reorganization. Two-way repeated measure ANOVA revealed that **A)** DLX and P induce opposite GM modification in bilateral ACC. **B)** Response to the treatment is affecting cortical changes in a region in the left precentral gyrus (primary motor cortex) and **C)** Prefrontal cortex undergoes high GM reorganization for DLX-patients that show pain decrease. DR/NR=DLX responders/nonresponders, PR/NR=P responders/nonresponders

Disclosure: P. Tetreault, None; **M. Baliki**, None; **E. Vachon-Presseau**, None; **R. E. Yeasted**, None; **T. J. Schnitzer**, None; **A. V. Apkarian**, None.

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Does a Family History of Total Knee Replacement for Knee Osteoarthritis Influence Knee Pain and Structural Progression? a Prospective Longitudinal Cohort Study. Feng Pan[1], Hussain Khan[1], Changhai Ding[1], Tania Winzenberg[1], Johanne Martel-Pelletier[2], Jean-Pierre Pelletier[2], Flavia Cicuttini[3] and Graeme Jones[1]. [1]Menzies Research Institute Tasmania, University of Tasmania, Hobart,7000, Australia, [2]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, [3]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia.

Background/Purpose: Genetic factors appear to play an important role in the pathogenesis of both knee pain and radiographic osteoarthritis (OA) based on cross-sectional studies but there are limited studies on the role of genetic mechanisms in the development of these factors over time. The aims of this study were to describe whether offspring having at least one parent with a total knee replacement for severe primary knee OA have an increased risk of worsening knee pain and knee structural progression over 8 to 10 years as compared to randomly selected controls with no family history of knee OA.

Methods: A total of 219 participants (mean age 48 years, range 29 to 61) with 115 offspring and 104 controls participated in this study. Knee pain was respectively assessed using a simple knee pain questionnaire at baseline and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at 2 years and 10 years. T1 or T2-weighted fat saturated magnetic resonance imaging of the right knee was performed to assess knee cartilage defects, bone marrow lesions (BMLs), meniscal extrusion and tears.

Results: Compared with controls, the prevalence of knee pain for offspring was higher at baseline (45% versus 20%, $P < 0.001$, assessed as yes/no), similar at 2 years (56% versus 54%, $P = 0.764$, WOMAC >0) and much higher at 10 years (74% versus 54%, $P = 0.002$, WOMAC >0). Over 8 years, offspring more frequently had an increase in knee pain (66% versus 41% ≥1 point increase, $P = 0.003$) and in all subscales apart from walking (all $P < 0.05$). In addition, they also had a greater increase in cartilage defect score (1.03 versus 0.52, $P = 0.007$), meniscal extrusion score (0.28 versus 0.10, $P = 0.027$), and meniscal tear score (0.40 versus 0.10, $P = 0.012$) in the medial tibiofemoral compartment. No significant difference in BML change was observed. In multivariable analysis, after adjustment for confounders and these structural factors, offspring still had an elevated risk of worsening knee pain (OR = 2.22, 95%CI = 1.17 to 4.22), as well as each subscale apart for walking and standing (OR = 2.01 to 3.36, all $P < 0.05$).

Conclusion: Offspring with family history of knee OA have an increased risk of worsening knee pain and progression of knee cartilage and meniscal pathology but not bony structural changes suggesting that genetic factors may be independently involved in the pathogenesis of knee pain and facets of structural progression. Intriguingly, the change in knee pain was independent of structural factors suggesting this effect is mediated by factors outside the knee.

Disclosure: F. Pan, None; **H. Khan**, None; **C. Ding**, None; **T. Winzenberg**, None; **J. Martel-Pelletier**, None; **J. P. Pelletier**, None; **F. Cicuttini**, None; **G. Jones**, None.

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Urate Crystal Induced Inflammation and Joint Pain Are Reduced in Transient Receptor Potential Ankyrin 1 (TRPA1) Deficient Mice – a New Potential Role for TRPA1 in Gout. Lauri J Moilanen, Mari Hämäläinen, Lauri Lehtimäki, Riina Nieminen and Eeva Moilanen. The Immunopharmacology Research Group, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland.

Background/Purpose: In the gout, monosodium urate (MSU) crystals deposit intra-articularly and cause painful arthritis. In the present study we tested the hypothesis that Transient Receptor Potential Ankyrin 1 (TRPA1), an ion channel mediating nociceptive signals and neurogenic inflammation, is involved in MSU crystal-induced responses in gout by utilizing three experimental murine models.

Methods: The effects of pharmacological selective inhibition (HC-030031) and genetic depletion of TRPA1 were studied in MSU crystal-induced inflammation and pain by using 1) spontaneous weight-bearing test to assess MSU crystal-induced joint pain, 2) subcutaneous air-pouch model resembling joint inflammation to measure MSU crystal-induced cytokine production and inflammatory cell accumulation, and 3) MSU crystal -induced paw edema to assess acute vascular inflammatory responses and swelling.

Results: Intra-articularly injected MSU crystals provoked spontaneous weight shift off the affected limb in wild type but not in TRPA1 knock-out mice referring to alleviated joint pain in TRPA1 deficient animals. MSU crystal-induced cell infiltration and accumulation of cytokines MCP-1, IL-6, IL-1beta, MPO, MIP-1alpha and MIP-2 in subcutaneous air-pouch was attenuated in TRPA1 deficient mice and in mice treated with the TRPA1 inhibitor HC-030031 as compared to control animals. Further, HC-030031 treated and TRPA1 deficient mice developed tempered inflammatory edema when MSU crystals were injected into the paw.

Conclusion: TRPA1 mediates MSU crystal-induced inflammation and pain in experimental models introducing TRPA1 as a potential mediator and a drug target in gout flare.

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ACR Concurrent Abstract Session
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Juvenile Idiopathic Arthritis
Sunday, November 16, 2014, 4:30 PM–6:00 PM

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A Multinational Study of the Epidemiology, Treatment and Outcome of Childhood Arthritis Preliminary Data from 6,940 Patients. Alessandro Consolaro[1], Amita Aggarwal[2], Troels Herlin[3], Olga Vougiouka[4], Rubén Burgos-Vargas[5], Ilonka Orban[6], Nahid Shafaie[7], Maria Trachana[8], Lidia Rutkowska-Sak[9], Ingrida Rumba-Rozenfelde[10], Dimitrina Mihaylova[11], Alberto Martini[1] and Angelo Ravelli[12]. [1]Istituto Giannina Gaslini, Genova, Italy, [2]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India, [3]Aarhus University Hospital, Aarhus, Denmark, [4]P. A. Kyriakou Childrens Hospital of Athens University, Athens, Greece, [5]Hospital General de Mexico, Universidad Nacional Autonoma de Mexico, Mexico City, Mexico, [6]National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [7]Tehran University of Medical Sciences, Tehran, Iran, [8]Aristotle University, Thessaloniki, Greece, [9]Institute of Rheumatology, Warsaw, Poland, [10]University of Latvia, Riga, Latvia, [11]University Children Hospital, Sofia, Bulgaria, [12]Istituto Giannina Gaslini and University of Genova, Genova, Italy.

Background/Purpose: The epidemiology of juvenile idiopathic arthritis (JIA) is known to be variable worldwide and the therapeutic approach to JIA is not standardized. Moreover, the availability of the novel and costly biologic medications is not uniform throughout the world, with possible significant impact on disease prognosis. The EPOCA study is aimed to obtain information on the frequency of JIA subtypes in different geographic areas, the therapeutic approaches adopted, and the disease status of children with JIA currently followed worldwide.

Methods: So far, 124 centers in 55 countries have agreed to participate in the study. Participation in the study was proposed to the pediatric rheumatology center of all countries belonging to the Pediatric Rheumatology International Trials Organization (PRINTO), and to several centers in the US and Canada. Each centre was asked to enroll 100 consecutive JIA patients or, if less than 100, all consecutive patients seen within 6 months. Each patient received a retrospective and cross-sectional assessment. Parent- and child-reported outcomes were recorded through the administration of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR). Participating countries were grouped into 6 geographic areas.

Results: Currently, 6,940 patients from 41 countries have been entered in the web database. Comparison of data from the different geographic areas is presented in the table.

	Africa N = 79	Asia N = 726	Eastern Europe N = 2171	Latin America N = 795	North America N = 243	Western Europe N = 2845
JIA onset age, yrs, median (IQR)	5.7 (2.8; 10)	5.9 (2.9; 9.5)	6.3 (2.8; 10.4)	6.6 (3.5; 10.3)	7.5 (3.2; 11)	4 (2; 8.7)
Systemic arthritis, N (%)	11 (13.9)	174 (24)	165 (7.6)	143 (18)	16 (4.9)	202 (7.1)
Oligoarthritis, N (%)	25 (31.6)	256 (35.3)	958 (44.1)	247 (31.1)	103 (31.8)	1398 (49.1)
Enthesitis related arthritis, N (%)	3 (3.8)	92 (12.7)	248 (11.4)	74 (9.3)	35 (10.8)	253 (8.9)
Uveitis, N (%)	4 (5.1)	40 (5.5)	232 (10.7)	51 (6.4)	38 (11.7)	495 (17.4)
JADAS10, median (IQR)	5 (1.5; 10)	3.5 (0.5; 10)	5 (1; 10.6)	3.5 (0; 10.8)	2 (0; 5.5)	2 (0; 6.3)
Inactive disease, N (%)	13 (16.5)	237 (32.6)	454 (20.9)	268 (33.7)	114 (35.2)	1070 (37.6)
JADI articular > 0, N (%)	27 (34.2)	136 (18.7)	531 (24.5)	257 (32.3)	60 (18.5)	352 (12.4)
Treated with biologics, N (%)	27 (34.2)	134 (18.5)	637 (29.3)	273 (34.3)	178 (54.9)	1067 (37.5)

Conclusion: Patients seen in Western Europe have a younger age at onset and a greater prevalence of uveitis. Systemic arthritis is more common in Asian patients, whereas enthesitis related arthritis is less frequent in African patients. Children from Africa and Eastern Europe have a higher level of disease activity and a lower frequency of inactive disease, and African and Latin American patients have a greater prevalence of articular damage. Biologic medication are administered more frequently in North America and less commonly in Asia.

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Antibiotic Exposure and the Development of Juvenile Idiopathic Arthritis: A Population-Based Case-Control Study. Daniel B. Horton[1], Frank I. Scott IV[2], Kevin Haynes[1], Mary E. Putt[1], Carlos D. Rose[3], James D. Lewis[1] and Brian L. Strom[4]. [1]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [2]Division of Gastroenterology, Hospital of the University of Pennsylvania, Philadelphia, PA, [3]Division of Rheumatology, Nemours A.I. duPont Hospital for Children, Thomas Jefferson University, Wilmington, DE, [4]Rutgers Biomedical and Health Sciences, Newark, NJ.

Background/Purpose: Dysregulation of the human microbiome has been implicated in the development of several autoimmune diseases, including rheumatoid arthritis and inflammatory bowel disease (IBD). Moreover, antibiotic exposure has been linked with the development of IBD in children. This study aimed to determine whether early antibiotic exposure increases the risk of incident juvenile idiopathic arthritis (JIA) in a general pediatric population.

Methods: A nested case-control study was conducted using The Health Improvement Network, a United Kingdom population-based medical records database with comprehensive diagnostic and outpatient prescription data. Children with incident JIA diagnosed before age 16 were identified by validated diagnostic codes (positive predictive value 86%). Age- and sex-matched control subjects were randomly selected with incidence density sampling in a 10:1 ratio from general practices taking care of at least 1 child diagnosed with JIA. Eligible subjects needed to be registered within 3 months of their birthdate. Individuals with prior IBD, immunodeficiency, autoimmune connective tissue disease, or vasculitis were excluded. The association between antibiotic prescriptions and JIA diagnosis was determined by conditional logistic regression.

Results: There were 153 children diagnosed with JIA in the study population (table 1). Any antibiotic exposure was associated with an increased risk of developing JIA after adjusting for confounders (adjusted OR 2.6, 95% CI 1.5,4.6) (table 2). This risk increased with the number of prescriptions in a dose-dependent manner. These results did not significantly change when adjusting for the number or type of infections. Age of exposure did not significantly modify this association. The relationship between antibiotics and incident JIA was similar across different antibiotic classes, although use of non-bacterial antimicrobial agents (e.g., antifungal, antiviral) was not associated with JIA. In sensitivity analyses excluding data up to 12 months before the index date, the association between antibiotics and incident JIA did not substantively change.

Conclusion: Antibiotic exposure was associated with an increased incidence of JIA in a dose-dependent fashion in a large pediatric population. This study implicates a role for antibiotic exposure in disease pathogenesis, perhaps mediated through alteration in the microbiome.

Table 1 Subject characteristics

	Cases n = 153	Controls n = 1530	Total n = 1683	p value
Female	96 (63)	960 (63)	1056 (63)	1.00
Age category	107 (70)	1070 (70)	1177 (70)	1.00
1-5 years	36 (23)	360 (23)	396 (23)	
6-10 years	10 (7)	100 (7)	110 (7)	
11-15 years				
Low socioeconomic status	23 (15)	216 (14)	239 (14)	0.65
Personal autoimmune disease	5 (3)	2 (0.1)	7 (0.4)	<0.001
Psoriasis	3 (2)	2 (0.1)	5 (0.3)	
Type 1 diabetes	1 (0.7)	0	1 (<0.1)	
Thyroid disease	1 (0.7)	0	1 (<0.1)	
Uveitis	1 (0.7)	0	1 (<0.1)	
Hospitalization	44 (29)	195 (13)	239 (14)	<0.001
Any infection	142 (93)	1313 (86)	1455 (86)	0.02
Upper respiratory	125 (82)	1138 (74)	1263 (75)	
Lower respiratory	37 (24)	394 (26)	431 (26)	
Gastrointestinal	30 (20)	253 (17)	283 (17)	
Skin and soft tissue	35 (23)	296 (19)	331 (20)	
Urinary tract	7 (5)	63 (4)	70 (4)	
Bone and joint	0	0	0	
Other	83 (54)	865 (57)	948 (56)	
Total infections, median (IQR)	3 (1,4)	2 (1,4)	2 (1,4)	<0.001
Any antibiotic exposure	134 (88)	1157 (76)	1291 (77)	<0.001
Antianaerobic	127 (83)	1109 (72)	1236 (73)	0.004

Not antianaerobic	65 (42)	475 (31)	540 (32)	0.002
Number of antibiotic courses received	19 (12)			
Unexposed	40 (26)	373 (24)	392 (23)	
1-2 courses	46 (30)	500 (33)	540 (32)	
3-5 courses	48 (31)	345 (23)	391 (23)	
More than 5 courses		312 (20)	360 (21)	
*Other antimicrobial exposure, any	45 (29)	405 (26)	450 (27)	0.43
Maternal autoimmune disease	21 (14)	116 (8)	137 (8)	0.02
Prenatal antibiotic exposure	47 (31)	512 (33)	559 (33)	0.51

Legend. IQR interquartile range. All statistics are expressed as n (%) unless otherwise stated. All p values were obtained from univariable conditional logistic regression models.
*Other antimicrobial agents, including antifungal, antiviral, and antimycobacterial drugs.

Table 2 Multivariable models

Exposure associated with JIA	Odds ratio	95% CI	p value
Any antibiotic	2.6	1.5,4.6	0.001
Any antibiotic, by dose category			
Unexposed (reference)	2.0	1.1,3.7	0.03
1–2 courses	3.1	1.6,5.8	<0.001
3–5 courses	3.8	1.9,7.3	<0.001
More than 5 courses			

Legend. Final models adjusted for matching, personal autoimmune disease (any), hospitalization, and maternal autoimmune disease (any).

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An Exploratory Analysis of Predictors of Response from 12-Weeks of Canakinumab Therapy in Patients with Active Systemic Juvenile Idiopathic Arthritis. Hermine I. Brunner[1], Nicola Ruperto[2], Isabelle Koné-Paut[2], Bo Magnusson[2], Seza Ozen[2], Flavio Sztajnbok[2], Jordi Anton[2], Judith Barash[2], Reinhard Berner[2], Fabrizia Corona[2], Karine Lheritier[3], Corine Gaillez[3], Alberto Martini[2] and Daniel Lovell[1]. [1]PRCSG, Cincinnati, OH, [2]PRINTO-Istituto Gaslini, Genova, Italy, [3]Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: Systemic juvenile idiopathic arthritis (SJIA), an interleukin-1β (IL-1β)-mediated autoinflammatory disease, is characterized by recurrent flares of active disease. Canakinumab (CAN), a selective, human, anti- interleukin-1β monoclonal antibody, has been shown to be efficacious in the treatment of SJIA (Ruperto et al. N Engl J Med 2012). The present study aimed to explore baseline demographics and clinical characteristics that are most predictive of response to CAN in CAN-naïve SJIA patients during the initial 12 weeks of therapy.

Methods: Data from 3 trials were pooled for this analysis. CAN-naïve patients (pts; n=178) aged 2–19 years with active SJIA were enrolled and received sc CAN 4 mg/kg/month; Predictors of response (according to aACR* 30, 70, and Inactive Disease [ID]) at Days (D) 15, 29, 57 and 85 were explored using univariate and multivariate logistic regression analyses. The candidate predictors (categorical variables) of CAN-response considered were: Age group, Gender, Prior NSAIDs (no/yes), Prior MTX (no/yes), Steroids (0, >0 – ≤0.4; > 0.4 mg/kg/day), Number of Active Joints (≤10, 11-≤20, >20) and Joints with Limitation of Motion (≤10, 11-≤20, >20), CRP (elevated/normal) at baseline and at D15. All candidate predictors with p<0.1 in univariate analyses were included in the multivariate analysis. *ACR response plus absence of fever.

Results: By Week 2 there was substantial clinical benefit with 102 pts (57%) and 36 pts (20%) achieving aACR70 and ID, respectively; by Week 12, 108 pts (61%) had aACR70 and 50 pts (28%) ID. The multivariate analysis indicated that normal CRP at D15 is the only predictor significant (all p<0.05) for ID at all time-points (Table).

Table: Inactive Disease - Multivariate logistic regression analysis on 12-week data

	Odds Ratio (95% CI)			
Variable*	**Day 15**	**Day 29**	**Day 57**	**Day 85**
CRP at Day 15 (elevated vs normal)	**0.20 (0.07, 0.55)**	**0.14 (0.04, 0.41)**	**0.26 (0.10, 0.66)**	**0.31 (0.12, 0.82)**
Number of active joints (11-≤20 vs. ≤10)	0.22 (0.03, 1.66)	0.55 (0.09, 3.41)	**0.17 (0.031, 0.97)**	0.37 (0.06, 2.10)
Number of active joints (≤10 vs. >20)	2.56 (0.12, 55.39)	1.53 (0.06, 37.44)	**16.10 (1.00, 258.12)**	25.41 (1.60, 404.61)
Prior NSAID treatment (no vs. yes)	2.01 (0.71, 5.71)	**9.33 (2.44, 35.68)**	**3.10 (1.03, 9.31)**	**5.31 (1.66, 17.05)**
Steroid Level (0 vs. >0.4 mg/kg/day)	5.48 (0.97, 31.01)	**8.89 (1.26, 62.64)**	2.98 (0.51, 17.46)	**11.16 (1.72, 72.34)**
Steroid Level (>0.4 vs >0-≤0.4 mg/kg/day)	0.32 (0.08, 1.29)	0.41 (0.09, 1.82)	0.81 (0.25, 2.60)	**0.13 (0.03, 0.57)**
Prior MTX treatment (no vs. yes)	1.94 (0.75, 5.00)	2.78 (0.93, 8.33)	**2.79 (1.04, 7.51)**	1.77 (0.65, 4.83)
Prior anti-TNFs treatment (no vs. yes)	1.83 (0.52, 6.49)	3.62 (0.77, 17.00)	2.01 (0.63, 6.38)	**3.64 (1.04, 12.77)**

Values in bold are significant; *Significant in at least one time point

Conclusion: This exploratory analysis suggests that canakinumab-naïve patients with normal CRP (i.e. ≤10 mg/l) at Day 15, lower baseline steroid doses, low number of active joints, no prior NSAID use are most likely to achieve inactive disease up to 12 weeks.

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Response to Canakinumab Treatment Is Maintained in Systemic Juvenile Idiopathic Arthritis Patients. N.M. Wulffraat[1], N. Ruperto[2], H.I. Brunner[3], S. Oliveira[2], Y. Uziel[2], K. Nistala[2], R. Cimaz[2], M. Ferrandiz[2], B. Flato[2], M.L. Gamir[2], I. Koné-Paut[2], C. Gaillez[4], K. Lheritier[4], K. Abrams[5], A. Martini[2] and D.J. Lovell[3]. [1]UMC Utrecht, Utrecht, Netherlands, [2]PRINTO-Istituto Gaslini, Genova, Italy, [3]PRCSG, Cincinnati, OH, [4]Novartis Pharma AG, Basel, Switzerland, [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Background/Purpose: Canakinumab, a selective, human, anti-interleukin (IL) −1β monoclonal antibody, is approved for the treatment of systemic juvenile idiopathic arthritis (SJIA) patients (≥ 2 years old). SJIA is an IL-1β-mediated autoinflammatory disease, which is characterized by recurrent flares of active disease. Canakinumab treatment in patients with SJIA, allows for successful steroid dose reduction/discontinuation and reduces risk to experience a flare. [1] We evaluated the maintenance of efficacy with continued canakinumab treatment in SJIA patients during the blinded randomized treatment withdrawal part of a large phase III trial.

Methods: Patients 2–19 yrs of age with active SJIA who had responded to open-label canakinumab treatment 4mg/kg/4wks sc, maintained a minimum adapted ACR Pediatric criteria [aACR] 30 for up to 32 weeks, and were steroid-free or had successfully reduced systemic steroids to a minimum dose, were randomized to either continue canakinumab or receive placebo until 37 flare events occurred. [1] Patients were considered to have completed the study if they entered clinical remission on medication (CRM), i.e. achieved 24 consecutive weeks of clinical inactive disease (CID). [2] A survival analysis of the time to worsening in aACR level, after randomization for the canakinumab and placebo groups was performed. Time to worsening is the time to fail to maintain at least the same level of aACR response seen at randomization. The change in the proportion in each group of those with CID was also evaluated.

Results: 100 pts were randomized to a canakinumab (n=50) or a placebo (n=50) group, of whom 26 (53%) and 27 (54%), respectively, had CID at the start of the randomization part. In the first 2 months, probability of maintaining aACR response was similar for both treatment groups. Thereafter, the probability of maintaining aACR response was greater in the canakinumab vs placebo groups. The median time to worsening in aACR level for patients in the placebo group was 141 days (95% CI: 85, 281), and could not be calculated for canakinumab as <50% of canakinumab group had a worsening in their aACR level by the end of this phase. The median duration of exposure

for the canakinumab group was 221.5 days (range: 8–617 days). There was a statistically significant relative risk reduction of 51% for the canakinumab vs placebo group to experience a worsening in aACR level (HR= 0.49; 95% CI: 0.27, 0.90; p=0.0131). CID was achieved by 31 (62.0%) vs 17 (34.0%) patients in canakinumab vs placebo at their last visit (OR= 3.4; 95% CI: 1.5, 8.0; p=0.0020) and CRM was reached by 20 (40%) canakinumab and 2 (4%) placebo patients by the end of the study.

Conclusion: A greater proportion of SJIA patients who continued canakinumab treatment maintained/improved their aACR response, achieved CID and CRM than pts who discontinued canakinumab by being switched to placebo, demonstrating maintenance of efficacy with continued canakinumab treatment over time.

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1. Ruperto N, et al. *N Engl J Med* 2012;367(25):2396–406.
2. Wallace CA, et al. *J Rheumatol* 2004;31(11):2290–4.

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MRP8/14 Serum Level As Predictor of Response to Starting and Stopping Anti-TNF Treatment in Non-Systemic Juvenile Idiopathic Arthritis. Janneke Anink[1], Marieke H. Otten[1], Lisette W.A. van Suijlekom-Smit[1], Marion A.J. Van Rossum[2], Koert M. Dolman[3], Esther P.A. Hoppenreijs[4], Rebecca ten Cate[5], Simona Ursu[6], Lucy R Wedderburn[7], Gerd Horneff[8], Thomas Vogl[9], Dirk Föll[10], Johannes Roth[9] and Dirk Holzinger[11]. [1]Erasmus MC Sophia Children's Hospital, Rotterdam, Netherlands, [2]Emma Kinderziekenhuis Academic Medical Center, Amsterdam, Netherlands, [3]St. Lucas Andreas Hospital and Reade Institute, Amsterdam, Netherlands, [4]Radboud University Medical Center, Nijmegen, Netherlands, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Arthritis Research UK Centre for Adolescent Rheumatology at University College London, Great Ormond Street Hospital and UCLH, University College London, London, United Kingdom, [7]Arthritis Research UK Centre for Adolescent Rheumatology, University College London, London, United Kingdom, [8]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [9]Institute of Immunology University of Muenster, Muenster, Germany, [10]University Children's Hospital Muenster, Muenster, Germany, [11]University Hospital Muenster, Muenster, Germany.

Background/Purpose: Biological therapy has dramatically improved the treatment of patients with JIA. However, there is still a group of patients that shows a lack of clinical response to this treatment. Furthermore, when patients do respond to treatment with etanercept, it is unclear when they can discontinue this treatment. The use of robust predictive markers of response to identify individuals who are likely to respond to anti-TNF treatment (etanercept or adalimumab) and who are able to stop etanercept may provide guidance in optimizing treatment strategies. Our objective was to test the ability of baseline MRP8/14 serum levels to differentiate between responders and non-responders to anti-TNF treatment and to correlate longitudinal follow-up of this marker in response to treatment. A second objective was to test the ability of MRP8/14 to distinguish between patients who are likely to flare after discontinuing etanercept.

Methods: Samples were collected from 89 JIA patients (13 polyarthritis rheumatoid factor (RF) positive, 33 polyarthritis RF negative, 24 extended oligoarthritis, 5 persistent oligoarthritis, 4 enthesitis related arthritis, 10 psoriatic arthritis) included in the Dutch Arthritis and Biologics in Children Register, the German Registry for Biologics in Paediatric Rheumatology and Great Ormond Street Hospital for Children London treated with TNF blockers. The patients were categorized into responders (ACRpedi≥50 and/or inactive disease according to the Wallace) and non-responders (ACRpedi<50). Serum concentrations of MRP8/14 complexes were measured by ELISA at start of biologic treatment and if available also within 6 months after start of treatment. A flare was defined as having at least three of the following: VAS physician or patient ≥ 20 mm, ≥ 2 active joints, any worsening on the CHAQ and ≥30% worsening on ESR or limited joints. Non-parametric tests were used for analyses.

Results: Before initiation of etanercept treatment, responders (n=71) showed significantly higher levels of MRP8/14 serum complexes compared to non-responders (n=18) (p=0.004, median in responders: 1490 ng/ml (IQR 1020–3323 ng/ml), median in non-responders: 788 ng/ml (IQR 442–1233 ng/ml)). No significant correlation was found between baseline MRP8/14 and JADAS10 disease activity. In non-responders MRP8/14 levels did not significantly change after initiation of treatment whereas levels decreased in responders (p<0.001). Change in JADAS10 disease activity was significantly correlated to change in MRP8/14 levels (Spearman's rho: 0.4, p=0.03). Samples were available from 28 patients at the time of discontinuation of etanercept. Patients who flared within 6 months after the discontinuation of etanercept had higher MRP levels at discontinuation than patients who did not flare (p= 0.031, median 1025 ng/ml (IQR 588–1288 ng/ml) vs. 505 ng/ml (IQR 346–778 ng/ml)).

Conclusion: High levels of baseline serum MRP8/14 have prognostic value in predicting a subgroup of JIA patients who will respond well to anti-TNF treatment. Decrease of MRP8/14 after initiation of treatment is associated with response to treatment. High MRP8/14 serum levels at time of discontinuation of etanercept are associated with a higher chance to flare.

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A Multi-Center, Double-Blind, Randomized-Withdrawal Trial of Subcutaneous Golimumab in Pediatric Patients with Active Polyarticular Course Juvenile Idiopathic Arthritis Despite Methotrexate Therapy: Week 48 Results. Hermine I. Brunner[1], Nicolino Ruperto[2], N Tzaribachev[3], Gerd Horneff[4], Carine Wouters[5], Violeta Vladislava Panaviene[2], Vyacheslav Chasnyk[6], Carlos Abud-Mendoza[7], Ruben Cuttica[8], Andreas Reiff[9], M Maldonado-Velázquez[1], Nadina Rubio-Pérez[10], Rik Joos[11], V Keltsev[12], Evgeny Nasonov[13], Daniel Kingsbury[14], M Bandeira[15], Earl Silverman[16], F Weller-Heinemann[10], A van Royen-Kerkhof[17], Alan M. Mendelsohn[18], Lilianne Kim[18], Daniel Lovell[19] and A Martini[20]. [1]PRCSG, Cincinnati, OH, [2]Istituto Giannina Gaslini, Genoa, Italy, [3]PRINTO & PRCSG, Bramstedt, Germany, [4]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [5]University Hosp Gasthuisberg, Leuven, Belgium, [6]Novartis Pharma, Saint-Peterburg, Russia, [7]Hospital Central & Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico, [8]Hospital de Ninos Pedro de Elizalde, Capital Federal, Argentina, [9]Children's Hospital of Los Angeles, Los Angeles, CA, [10]PRINTO, Genoa, Italy, [11]UZ Gent, Gent, Belgium, [12]Paediatric Rheumatology International Trials Organisation–IRCCS [PRINTO], Genoa, Italy, [13]State Institute of Rheumatology of RAMS, Moscow, Russia, [14]Randall Children's Hospital at Legacy Emanuel, Portland, OR, [15]Hospital Infantil Pequeno Príncipe, Curitiba, Brazil, [16]Hosp for Sick Children, Toronto, ON, [17]Department of Pediatric Immunology & Rheumatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands, [18]Janssen Research & Development, LLC., Spring House, PA, [19]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati, Cincinnati, OH, [20]Istituto Gaslini-PRINTO, Genova, Italy.

Background/Purpose: To assess efficacy and safety of SC golimumab (GLM) in polyarticular pediatric juvenile idiopathic arthritis pts (aged 2 to <18 yrs) with active arthritis despite MTX for ≥3months.

Methods: In GO-KIDS, a 3-part randomized double-blind, PBO-controlled, withdrawal trial in pts with active JIA with a polyarticular course (≥5 active joints) and disease duration of ≥ 6 months despite current MTX (10–30 mg/m^2/wk).In Part 1(wk0–12), all pts received open-label (OL) 30 mg/m^2 GLM SC(max 50mg) q4wks with stable MTX dose. At wk16, pts with ACR JIA 30 response entered Part 2 (wk16–48).In Part 2, pts were randomized to continue GLM or switch to PBO q4wks. Upon Part 2 completion at wk48 or ACR JIA flare in Part 2, pts received OL GLM in Part 3. Primary endpoint was proportion of ACR JIA 30 responders at wk16 without a JIA flare in Part 2 using wk16 as baseline measurement. Secondary outcomes were ACR JIA 30/50/70/90 response rates and inactive disease rates at wk16 and wk48 by group and safety.

Results: 173 pts (Caucasian 87.9%, 75.7% females; age [median/range] 12 yrs/2–17 yrs) with moderately active disease were enrolled (Table1); 19 (11%) were d/c in Part 1 (lack of efficacy n=14, AE n=4, withdrawal of consent n=1). In Part 1, 151 of 173 (87.3%) achieved an ACR JIA 30 response and 36.1% inactive disease status (Table2). In Part 2, 154 pts were randomized (PBO n=76; continued GLM n=78). The trial did not meet primary endpoint, as at the end of Part 2 groups did not differ in flare rates [PBO-grp vs. GLM-grp: 52.6% vs. 59.0%, p=0.41) nor were there differences for major secondary endpoints (Table2). Nonetheless, sustained JIA improvement was maintained in both groups (PBO, GLM) relative to wk 0 (Table1 and 2). Through wk48, AEs, serious AE (SAE), and serious infections were reported in 87.9%, 13.3%, and 2.9% of all randomized pts, respectively. Most common SAE was JIA exacerbation. No deaths, active TB or malignancies were reported. Proportion of pts with ≥ 1 injection site reaction was 8.1%. None of the reactions were serious, severe, or led to GLM d/c.

Conclusion: Children with active polyarticular JIA demonstrated rapid response to GLM during16 wks of OL treatment, resulting in inactive disease in 36% of the pts after 3 injections of OL GLM during part 1. The lack of differences in flare rates between GLM and PBO arms during the double-blinded part of the study among OL GLM responders needs further evaluation. Safety profile was acceptable and injections well tolerated.

Table 1

Values are medians (interquartile range)	At Baseline (All enrolled patients n=173)	At wk16 (All randomized patients prior to randomization, n=154)	At wk48	
			PBO + MTX (n=76)	GLM + MTX (n=78)
Physicians global assessment of disease activity	5.40 (3.90; 7.00)	0.50 (0.10; 1.30)	0.30 (0.00; 1.00)	0.30 (0.00; 1.30)
Patient/parent global assessment of well-being	4.50 (2.80; 6.10)	0.90 (0.30, 2.30)	0.60 (0.20; 1.65)	0.45 (0.10; 1.70)
Number of active joints	12.0 (8.0; 18.0)	1.0 (0.0; 3.0)	1.0 (0.0; 3.0)	0.0 (0.0; 2.0)
Number of joints with limited range of motion	8.0 (6.0; 15.0)	1.0 (0.0, 4.0)	0.5 (0.00; 4.0)	1.0 (0.0; 3.0)
Physical function by CHAQ	0.94 (0.38; 1.50)	0.25 (0.00; 0.75)	0.13 (0.00; 0.63)	0.00 (0.00; 0.63)
ESR (mm/hr)	16.00 (8.00; 28.00)	9.00 (5.00; 19.00)	9.50 (5.00; 16.50)	10.00 (5.00; 19.00)
Methotrexate (mg/wk)	15 (5.00; 30.00)	15 (5.00; 30.00)	15 (5.00; 30.00)	15 (5.00; 30.00)

Table 2: ACR JIA response and flare rates

PART 1 [WK 0–16]			
Percentage of ACR JIA responders at end of Part 1 [WK 16] (n =173)	JIA ACR 30	87.3% (151)	
	JIA ACR 50	79.2% (137)	
	JIA ACR 70	65.9% (114)	
	JIA ACR 90	36.4% (63)	
	Inactive disease	36.1% (62)	
PART 2 [WK 16- 48]			
Percentage of ACR JIA 30 responders without flare in Part 2 (n = 154)	PBO + MTX (n=76)	52.6% (40)	P=0.41
	GLM + MTX (n=78)	59.0% (46)	
Percentage of ACR JIA responders at WK48 (vs. wk0) by treatment in Part 2* [PBO +MTX /GLM +MTX]	JIA ACR 30	95.9%/89.0%	
	JIA ACR 50	91.8%/86.3%	
	JIA ACR 70	78.1%/78.1%	
	JIA ACR 90	53.4%/56.2%	
Inactive disease [PBO +MTX/GLM +MTX]	PBO + MTX (n=76)	27.6% (21)	
	GLM + MTX (n=78)	39.7% (31)	
Clinical remission [PBO +MTX/ GLM +MTX]	PBO + MTX (n=76)	11.8% (9)	
	GLM + MTX (n=78)	12.8% (10)	

Pts experiencing flares/those considered treatment failures due to protocol violations are considered ACR non-responders from the flare failure visit to wk48
*Observed data

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Animal Models I
Sunday, November 16, 2014, 4:30 PM–6:00 PM

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Amelioration of Inflammatory Arthritis By Anti-TNF Therapy Is Associated with Restoration of Lymphatic Contraction. Echoe M. Bouta[1], Igor Kuzin[2], Karen de Mesy-Bentley[1], Ronald Wood[3], Homaira Rahimi[4], Rui-Cheng Ji[5], Christopher T. Ritchlin[3], Andrea Bottaro[2], Lianping Xing[1] and Edward M. Schwarz[1]. [1]University of Rochester, Rochester, NY, [2]Cooper Medical School, Camden, NJ, [3]University of Rochester Medical Center, Rochester, NY, [4]University of Rochester/Golisano Children's Hospit, Rochester, NY, [5]Oita University, Oita, Japan.

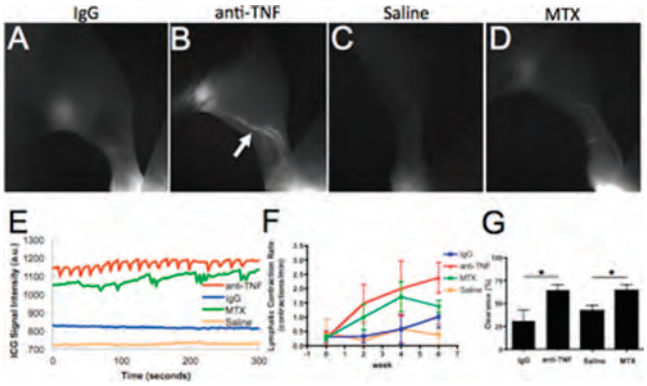
Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with episodic flares. In tumor necrosis factor transgenic (TNF-Tg) mice, a model of inflammatory-erosive arthritis, the popliteal lymph node (PLN) enlarges during the pre-arthritic "expanding" phase, and then "collapses" with adjacent knee flare associated with the loss of the intrinsic lymphatic pulse. Thus, a critical question is whether loss of the lymphatic pulse can be recovered by standard RA therapies.

Methods: We tested the hypothesis that anti-TNF vs. irrelevant IgG (IgG); and methotrexate (MTX) vs. saline treatment ameliorates knee synovitis adjacent to collapsed PLN in TNF-Tg mice by restoring the lymphatic pulse using contrast enhancement MRI (CE-MRI), ultrasound, near infrared indocyanine green (NIR-ICG) imaging, transmission electron microscopy (TEM) and flow cytometry.

Results: Anti-TNF treatment significantly decreased normalized synovial volume compared to IgG (0.87±0.21 vs. 1.52±0.16; p<0.05), measured by CE-MRI. This decrease correlated with a lower power Doppler volume within the joint, a measure of inflammation, in both anti-TNF and MTX treated mice compared to placebo treated (0.04±0.01 vs. 0.20±0.03 mm^3 and 0.05±0.01 vs. 0.18±0.08 mm^3, respectively; p<0.05). Lymphatic pulse rate and clearance were measured via NIR-ICG imaging (Figure). As predicted, anti-TNF significantly increased the lymphatic pulse vs. IgG (2.63±0.68 vs. 0.99±0.36 pulses/min), and MTX also induced an increase vs. saline (1.38±0.21 vs. 0.38±0.38 pulses/min), although this effect was weaker than anti-TNF. Consistently, footpad clearance of ICG was higher in anti-TNF and MTX treated mice vs. placebos (64.53±6.08 vs. 30.84±12.26 and 64.54±6.20 vs. 42.49±5.69, respectively; p<0.05). To gain insight into the mechanism of lymphatic pulse restoration, TEM was performed on the lymphatic vessels. We found that placebo treated mice showed damaged lymphatic endothelial cells (LECs) and smooth muscle cells (LSMCs), while anti-TNF treated mice showed intact LECs and LSMCs apical to fibrotic tissue, suggestive of tissue repair. Interestingly, anti-TNF treatment resulted in a significant ~4-fold increase in monocyte numbers normalized to placebo vs. MTX (3.77±0.77 vs. 1.08±0.19 cells per PLN; p<0.05), via flow cytometry. We previously reported monocytes trafficking in afferent lymphatic vessels. Thus, these findings indicate increased transit of monocytes to the PLN from the inflamed joint.

Conclusion: These NIR-ICG, CE-MRI and flow cytometry results

demonstrate that anti-TNF increases lymphatic transport to a greater extent than MTX. Furthermore, our data suggest that the primary mechanism for monocyte (type 1 synoviocyte) removal from inflamed joints following anti-TNF treatment is through restoration of lymphatic pulse and cellular egress.



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Targeting Glycolysis in Rheumatoid Arthritis. Monica Guma[1], Alessia Lodi[2], Ajit Divakaruni[1], Anne Murphy[1], Stefano Tiziani[2] and Gary S. Firestein[3]. [1]University of California, San Diego, La Jolla, CA, [2]University of Texas at Austin, Austin, TX, [3]University of California at San Diego School of Medicine, La Jolla, CA.

Background/Purpose: Many of the signaling pathways activated in inflammation have a profound effect on cell metabolism. However, little is known about metabolome in rheumatoid arthritis (RA), particularly in fibroblast-like synoviocytes (FLS). The shift from ATP generation through oxidative phosphorylation to glycolysis has been implicated not only in tumor cells growth but also in immune cell function upon activation. To determine the role of glycolysis in arthritis, we examined glucose metabolism in FLS and evaluated whether this pathway could play a role in inflammation and joint damage.

Methods: The glucose profile of FLS cells was determined by ^{1}H-MRS. Analysis of FLS oxygen consumption/extracellular acidification after LPS stimulation used Seahorse technology. FLS function using the glycolysis inhibitor 2-Deoxy-D-glucose (2-DG) in medium and platelet derived growth factor (PDGF) stimulated cells was evaluated by measuring 1) migration of cultured FLS monolayers (scratch assay); 2) proliferation using an MTT assay; and 3) protein expression by ELISA. For arthritis experiments, mice were injected with K/BxN sera on day 0. The glycolysis inhibitor bromopyruvate (BrPa; 5mg/kg) was injected daily i.p. beginning on day 0 after serum administration. Clinical arthritis scores were serially assessed. Joint histology was evaluated using a semiquantitative scoring system.

Results: One-dimensional ^{1}H MRS spectra of aqueous extracts revealed 39.8±5.2% higher intracellular lactate accumulation in RA FLS compared with osteoarthritis (OA) FLS ($p<0.01$) indicating increased glycolytic rate. Of interest, FLS also displayed an unusual mitochondrial response, decreasing mitochondrial respiration (pmol O_2/min) and increasing extracellular acidification (mpH/min) by 49.6±10.2% and 44±8.6% respectively after LPS stimulation. Glycolysis regulated key FLS functions that might contribute to cartilage damage in RA. For example, glycolysis inhibition with 2-DG (10 mM) reduced MMP3 and IL-6 secretion by 68±5.2% and 75±4.3%, respectively ($p<0.01$). Proliferation was reduced by 79±7.2% and migration by 63±15% ($p<0.05$). Finally, glycolysis inhibition by BrPa significantly decreased arthritis severity. Day 8 scores were 11.6±1.5 and 2±0.6 ($P<0.01$) for vehicle and BrPa-treated mice, respectively. Joint histology scores for vehicle and BrPa-treated mice for inflammation were 2.3±1.1 and 0.25±0.35 ($p<0.01$), bone erosion scores were 1.8±1.2 and 0.12±0.35 ($p<0.01$), and cartilage damage scores were 2.1±0.83 and 0.88±0.35 ($p<0.01$), respectively.

Conclusion: The metabolic profile in RA FLS suggests that glucose metabolism is abnormal and has shifted to ATP generation through oxidative phosphorylation to glycolysis. Blocking this pathway with a glycolysis inhibitor suppressed inflammatory arthritis in mice as well as the aggressive behavior of cultured RA FLS, including proliferation, cytokine secretion and cell migration. These data suggest that glycolysis inhibition may be disease modifying by directly modulating synoviocyte mediated functions and could be an effective strategy for arthritis.

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Active Invasion of Periodontal Bacteria into Synovial Joint Exacerbates Collagen-Induced Arthritis in Disease-Prone B10 Riii Mice. Sasanka Chukkapalli[1], Mercedes Rivera-Kweh[1], Irina Velsko[1], Indraneel Bhattacharyya[1], S. John Calise[2], Edward Chan[1], Minoru Satoh[3] and Lakshmyya Kesavalu[1]. [1]College of Dentistry, University of Florida, Gainesville, FL, [2]University of Florida, Gainesville, FL, [3]Univ. Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan.

Background/Purpose: Periodontitis (PD) is a chronic immunoinflammatory disease caused by complex subgingival periodontal bacteria. Rheumatoid Arthritis (RA) and PD both are chronic inflammatory disorders characterized by deregulation of the host inflammatory response. Both disease share risk factors and have pathological pathways in common, resulting in soft and hard tissue destruction of synovium and periodontium, respectively. In this study, we utilize an established murine PD model induced by chronic polybacterial infection of three major human periodontal bacterial pathogens: *P. gingivalis, T. denticola*, and *T. forsythia.* Our study was designed to examine whether the induction of PD enhance arthritis in the collagen-induced arthritis (CIA) mouse model.

Methods: CIA-prone major histocompatibility congenic B10 RIII mice were used in the study. These were divided into four groups (n=10 each). Group I mice were infected orally with a polybacterial mixture of *P. gingivalis, T. denticola, T. forsythia* for 24 weeks. Mice in group II were also orally infected with a polybacterial mixture followed by administration of collagen II (CII) emulsified in complete Freund's adjuvant (CFA) and boosted with CII in incomplete Freund's adjuvant (IFA) to induce arthritis. Group III mice were sham-infected controls. Group IV mice were administered CII emulsified in CFA and IFA as collagen control. After 24 weeks of infection, mice were examined for development of PD as well as for RA clinical signs; systemic spread of the infection, matrix metalloproteinase 3 (MMP3) levels, cytokine expression, anti-CCP (cyclic citrullinated peptide) antibodies, and autoimmune signaling molecules. Further, the tissue sections from mouse ankle joints and paws were evaluated for the presence of periodontal bacteria by fluorescence *in situ* hybridization (FISH).

Results: Group I and II showed oral colonization/infection with all 3 bacteria (100%), higher levels of anti-bacteria IgG antibodies ($P < 0.0005$) and greater significant alveolar bone resorption ($P < 0.0005$) than the sham-infected (Group III) and collagen control mice (Group IV). Group II mice showed exacerbated clinical signs of arthritis (10/10), systemic spread of periodontal bacteria, and significant serum MMP3 levels ($P < 0.05$) compared to Group IV. *In vivo* tomographic imaging of infected+collagen treated mice using MMP3 fluorescent probe showed intense MMP3 activity (fluorescence intensity=12) in arthritic lesions (4/4) compared to collagen control mice (fluorescence intensity=5). Histopathology of infected+collagen treated mouse ankle joints showed higher levels of characteristic inflammatory cellular infiltration, destruction of articular cartilage, pannus formation, and bone distortion (6/6) compared to collagen control mice. FISH showed the presence of *P. gingivalis* in the ankle joints of infected+collagen treated mice.

Conclusion: This is the first study to examine a causal relationship between PD and RA using two established disease models in mice. This study provides direct evidence for a causal association between major periodontal pathogens/PD and increased severity in induced arthritis.

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A Unique Role for IL-18 Receptor-α in Monocyte Migration in RA and K/BxN Serum Transfer Arthritis. W. Alexander Stinson[1], Phillip L. Campbell[1], Jeffrey Ruth[1], Gautam Edhayan[1], Ray A. Ohara[1], Nicholas Lepore[1], Alisa E. Koch[2], David A. Fox[1] and M. Asif Amin[1]. [1]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [2]Department of Veteran's Affairs and University of Michigan, Ann Arbor, MI.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by monocyte (MN) recruitment. Proinflammatory cytokines and their corresponding receptors play an important role in the progression of RA by increasing MN infiltration. Soluble IL-18 receptor-α (IL-18Rα) is highly expressed in RA synovial fluids (SFs), synovial tissues (STs), ST fibroblasts, and CD4+ T cells. In this study, we determined the contribution of IL-18Rα in the pathogenesis of RA.

Methods: Western blotting was performed to examine IL-18Rα expression on tumor necrosis factor-α (TNF-α) stimulated MNs. We performed MN chemotaxis in modified Boyden chambers to determine the role of IL-18Rα in MN migration *in vitro*. To examine MN homing in the context of RA, we employed an RA ST-severe combined immunodeficient (SCID) mouse chimera using RA SFs with or without IL-18Rα neutralizing antibody. We harvested RA ST after 48 hours and examined tissue sections by immunofluorescence. K/BxN serum transfer arthritis was performed in IL-18Rα null and wild type (wt) mice to determine the role of the IL-18Rα in arthritis and MN recruitment. Cytokine levels were determined by enzyme linked immunosorbent assays (ELISAs) in ankle homogenates of IL-18Rα null and wt mice.

Results: TNF-α stimulated normal human MNs showed a marked increase of IL-18Rα expression. After finding increased expression in IL-18Rα, we determined its role in MN migration. IL-18Rα partially mediates TNF-α and RA SF-induced MN migration, as anti-human IL-18Rα antibody significantly inhibited TNF-α and RA SF mediated MN migration *in vitro* ($p<0.05$). We further investigated the importance of IL-18Rα to MN migration in human RA by using the RA-SCID mouse chimera. RA SF injected into the chimeric human ST resulted in MN recruitment to the ST, which was decreased in the presence of mouse anti-human IL-18Rα, suggesting that IL-18Rα is essential in RA SF-stimulated MN migration *in vivo*. We determined the contribution of IL-18Rα in inflammatory arthritis by performing K/BxN serum transfer arthritis. IL-18Rα null mice were resistant to K/BxN arthritis, showing a significant decrease in ankle circumference compared to wt mice ($p<0.05$). Mouse ankles harvested on day 9 of maximal arthritis showed a significant decrease in MN migration in IL-18Rα null mouse joint sections compared to wt mice, as determined by staining for F4/80, a MN/macrophage marker. To determine the mechanism of decreased MN ingress and defective arthritis in IL-18Rα null mice, ELISAs were performed for proinflammatory cytokines using mouse ankle homogenates. We found a >3 fold decrease in IL-1β levels in IL-18Rα null mouse ankles compared to wt mouse ankles ($p<0.05$), suggesting that the IL-18Rα is critical in inflammatory cytokine expression.

Conclusion: These studies suggest that IL-18Rα is inducible in MNs and plays an important role in MN migration *in vitro* and *in vivo*. IL-18Rα null mice have impaired MN recruitment and arthritis development in part due to decreased IL-1β. These results provide strong evidence that the IL-18Rα plays an important role in MN ingress in RA and in a rodent model of inflammatory arthritis and may be a novel therapeutic target for RA.

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C1q Is Mandatory for Disease Development in Experimental Arthritis and Expression of Its Receptors Correlates with Disease Activity in Patients. Matthieu Ribon[1], Julie Mussard[1], Roxane Herve[1], Marina Botto[2], Marie-Christophe Boissier[3] and Patrice Decker[1]. [1]INSERM UMR 1125, Li2P, University Paris 13, Sorbonne Paris Cité and Rheumatology Department, Avicenne Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Bobigny, France, [2]Imperial College, London, United Kingdom, [3]INSERM UMR 1125, Li2P, University Paris 13, Sorbonne Paris Cité, Bobigny, France.

Background/Purpose: The complement system is a major effector mechanism of innate and adaptive immunity. It is activated in rheumatoid arthritis (RA) patients but the pathway involved remains unclear. RA is associated with the production of autoantibodies with some of them, anti-citrullinated protein antibodies, representing a diagnosis and even a prognosis marker. Antibodies are known to activate the complement system via the classical pathway in a C1q-dependent manner. But some models suggest C1q-independent pathways in arthritis. Therefore, we have investigated whether C1q is necessary for disease development in a mouse model of RA based on (auto)immunization and we have analyzed C1q receptor expression in patients.

Methods: Disease development was studied in the collagen-induced arthritis (CIA) mouse model. The impact of C1q was evaluated by comparing wild-type (WT) mice and C1q-knockout (KO) true littermates. Arthritis was followed by clinical score evaluation. Inflammation and bone destruction were estimated by histology. Anti-collagen antibody, C3a and blood cytokine levels were measured by ELISA and Luminex. B/T lymphocytes and neutrophils were analyzed by flow cytometry. Osteoclastogenesis was analyzed by culturing bone marrow cells with M-CSF/RANKL and then counting TRAP-positive multinucleated cells by microscopy. In addition, whole blood cells from healthy donors and RA patients were used to estimate their C1q binding capacity ex vivo by flow cytometry.

Results: C1q is absolutely required for arthritis development as C1q-KO mice did not develop clinical signs of arthritis in contrast to WT mice. Both WT and KO mice developed anti-collagen antibodies and particularly similar levels of pathogenic IgG2a anti-collagen antibodies. Moreover, neither inflammation nor joint destruction was observed in C1q-KO mice. Importantly, the level of complement activation, estimated by C3a production, was similar in WT and C1q-KO mice. Surprisingly, no statistical difference was observed between WT and KO mice regarding the percentage or the activation of lymphocytes and neutrophils in the blood, spleen and lymph nodes. As a recent study suggested that C1q might influence osteoclastogenesis in vitro, we have shown that C1q deficiency does not alter development of osteoclasts from CIA mice. The impact of C1q on cytokine secretion in vivo is currently being analyzed. In RA patients, we have shown that the percentage of neutrophils able to bind C1q is significantly and positively correlated with the disease activity estimated by the DAS28.

Conclusion: C1q-KO mice are protected from arthritis development and thus C1q plays a key role in the CIA model. Although the complement system is activated, the classical pathway cannot be compensated by the alternative/lectin pathways in this model. Our results strongly differ from those reported in the serum-transfer model where C1q is not necessary for disease development, suggesting that C1q might be involved at different steps, maybe before antibodies are produced, for example in the response to DAMPs. In patients, the expression of total C1q receptors by neutrophils reflects disease activity, supporting the potential role of C1q in RA.

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Prenatal Methyl-Rich Diet Decreases Inflammation in Collagen Induced Arthritis. Sanjay Garg[1], Dipak R. Patel[2] and Raymond Yung[2]. [1]University of Michigan, Ann Arbor, MI, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI.

Background/Purpose: Early-life nutrition can have a profound effect on late-life disease development. Most current studies focus on macro-nutrition (calorie, carbohydrate, fat, and protein), and much less is known about the role that early life micro-nutrition plays in diseases of adults. One notable exception is that prenatal folic acid supplementation dramatically decreases the incidence of spina bifida and other neural tube defects. In mouse models, supplementing 'methyl donors' in the diet of pregnant mice (dams) affects the incidence of diabetes and obesity in their offspring. These changes have been attributed to changes in the DNA methylation status of selected genes.

Previously, we have demonstrated that feeding dams a prenatal diet supplemented with methyl donors (MDS) during mating and pregnancy decreases the levels of selected CD4+ T cell pro-inflammatory chemokines and cytokines in F1 mice by changing the DNA methylation pattern of those genes. $CD4^+$ T cells are critical in arthritis pathogenesis, and many of the pro-inflammatory cytokines and chemokines required for arthritis development are regulated by DNA methylation. Recent studies have shown that RA is characterized by a perturbed extracellular redox environment. Based on our preliminary data, we hypothesize that the prenatal MDS diet will decrease inflammation in the collagen-induced arthritis (CIA) model of RA by modulating redox metabolites and $CD4^+$ T cell function.

Methods: Female DBA/J mice received either a control diet or MDS diet during pregnancy and lactation. Pups borne to these mice (F1 Control or F1 MDS) were maintained on those diets after birth and until they were weaned at 4 weeks. After weaning, all mice were fed a standard (NIH 31) diet. Arthritis was then induced, and paw swelling was measured. Cytokines and redox metabolites were measured in the serum at specified time points, and mice were sacrificed for in vitro analysis of CD4+ T cell function.

Results: Both F1-MDS and F1-Control mice developed arthritis 30 days after collagen injection, and the mean arthritis score was decreased by at least 2 points at day 45 after injection ($p<0.05$). At 55 days after injection, $CD4^+$ T cells from F1-MDS mice expressed decreased levels of TNF-α ($p=0.04$), IL-17 ($p=0.04$), and IL-6 ($p=0.02$) protein. Levels of the chemokine CCR7 were also decreased

in $CD4^+$ T cells from F1-MDS mice ($p=0.02$). The serum redox potential in CIA mice is more oxidizing (−77 mV) than in non-CIA mice (−83 mV) ($p<0.01$). After CIA induction, the redox potential was maintained at a more homeostatic level (−85 mV) in F1-MDS mice, and the redox potential was more oxidizing (−77 mV) in F1-Control mice ($p<0.01$).

Conclusion: The pre-natal MDS diet decreases disease severity, as measured by paw swelling in the CIA model of RA. The diet caused decreases in serum levels of pro-inflammatory cytokines and expression of pro-inflammatory genes in CD4+ T cells. Many of these genes are methylation sensitive. These results demonstrate that a pre-natal diet enriched in methyl donors can decrease disease severity in a mouse model of RA.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects II: Remission and De-escalation of Therapy
Sunday, November 16, 2014, 4:30 PM–6:00 PM

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Reducing Therapy in Rheumatoid Arthritis Patients in Ongoing Remission. Judith Haschka[1], Jürgen Rech[1], Matthias Englbrecht[1], Stephanie Finzel[1], Michaela Reiser[1], Axel J. Hueber[1], Arnd Kleyer[1], Hans-Peter Tony[2], Martin Fleck[3], Karin Manger[4], Wolfgang Ochs[5], Jörg Wendler[6], Hanns-Martin Lorenz[7], Hubert Nüßlein[8], Rieke Alten[9], Winfried Demary[10] and Georg Schett[1]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]University Hospital Würzburg, Würzburg, Germany, [3]Asklepios Medical Center Bad Abbach, Bad Abbach, Germany, [4]Rheumatology Practice Bamberg, Bamberg, Germany, [5]Rheumatology Practice Bayreuth, Bayreuth, Germany, [6]Rheumatology Practice Erlangen, Erlangen, Germany, [7]University of Heidelberg, Heidelberg, Germany, [8]Rheumatology Practice Nuremberg, Nuremberg, Germany, [9]Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany, [10]Rheumatolgy Practice Hildesheim, Hildesheim, Germany.

Background/Purpose: Due to improved therapeutic management a steadily increasing number of rheumatoid arthritis (RA) patients reach stable remission of disease. Data on withdrawal of medication after sustained remission are limited, though it is important for economic and safety reasons. The RETRO study represents a real-life study addressing different strategies of reduction of DMARD therapy in RA patients in disease remission. The aim of the study was to evaluate the possibility of tapering and even discontinuation of DMARD therapy in RA patients in stable long-lasting remission and to determine predictors for recurrence of disease.

Methods: RETRO is a phase 3, multicenter, randomized, controlled, open, prospective, parallel-group trial (EudraCT Number: 2009–015740–42). Patients, fulfilling the ACR/EULAR2010 criteria for RA with disease history of ≥12 months, were enrolled into the study if they were in clinical remission (DAS28-ESR < 2.6) at stable dose of DMARDs for more than 6 months. Patients on ≥1 conventional and/or biological DMARDs were included and randomized into three trial arms: Arm 1 (control group) was continuing full-dose conventional and/or biological DMARD treatment for 12 months; arm 2 was reducing the dose of all conventional and/or biological DMARD treatment by 50% for 12 months and arm 3 was reducing the dose of all conventional and/or biological DMARD treatment by 50% for 6 months before entirely stopping DMARD. In case of recurrence of disease (DAS >2.6) the original therapy was restarted.

Results: 101 patients (61.4% females, 60% ACPA positive, 63% RF positive; 37.6% biologic therapy, 80.2% MTX, 7.9% other DMARDs) finished the one year endpoint: 38 patients in arm 1 (age 55.8±13.9y, disease duration 6.8±5.9y, remission 20.9±16.7mo), 36 patients in arm 2 (age 54.1±13.1y, disease duration 8.6±7.7y, remission 14.5±12.7mo) and 27 patients in arm 3 (age 54.8±12.3y, disease duration 5.6±7.0y, remission 17.6±19.5mo). Of 101 patients, 66.3% were still in remission at 12 mo. Trial arms 2 (38.9%, $\chi^2(1)=5.0$, $p=0.036$) and 3 (51.9%, $\chi^2(1)=9.6$, $p=0.003$) significantly differed from the control group (15.8% flare rate) with more patients flaring in reduction arms. However, there was no significant difference between the two reduction arms ($\chi^2(1)=1.1$, $p=0.443$). A multivariate logistic regression identified ACPA positivity (Wald $\chi^2=4.5$, $p=0.03$) and treatment reduction compared to the control group (arm2: Wald $\chi^2=6.6$, $p=0.01$, arm3: Wald $\chi^2=8.8$, $p=0.003$) as predictors for subsequent flares. Sex, disease duration, remission duration, age, RF, biologic DMARD and remission depth (defined by fulfilling Boolean remission criteria yes/no) failed to predict recurrence of disease in this study.

Conclusion: This study is a prospective real life treatment strategy study investigating the effect of reduction and discontinuation of DMARD therapy in RA patients in stable remission. Interestingly neither remission depth, nor disease duration at baseline or biological DMARD therapy predicted the recurrence of disease. Presence of ACPA but not RF was the only predictor for recurrence of disease. The data indicate that treatment reduction and even discontinuation is feasible in a subset of RA patients in stable remission.

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Biologic De-Escalation in Rheumatoid Arthritis: Cost Savings and Clinical Success. Tarun S. Sharma[1], Lyudmila Kirillova[2], Andrea Berger[3] and Eric D. Newman[2]. [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Health System, Danville, PA, [3]Center for Health Research, Geisinger Health System, Danville, PA.

Background/Purpose: Economic considerations and clinical risks of prolonged biologic use in Rheumatoid Arthritis (RA) have emerged as concerns. In this study, we measured the clinical outcomes and cost savings of biologic de-escalation in patients with well-controlled RA.

Methods: We reviewed the electronic health records of all RA patients treated with a biologic medication from 01/01/13 to 12/31/13 (n= 940) and evaluated biologic de-escalation (decreased dose, frequency, or discontinuation). Baseline demographics were recorded for all patients. Successful de-escalation was defined as a de-escalation where the dose of biologic on 12/31/13 was lower than the pre-de-escalation dose and the efficacy was maintained until 12/31/13. Flare was defined as addition or increase in dose of steroid or Disease Modifying Anti-Rheumatic Drug or a switch in the biologic medication. We compared the de-escalated and non-de-escalated groups, the outcomes of de-escalation, and financial benefits of de-escalation. Predictors of successful de-escalation were evaluated using two-sample t or Wilcoxon rank sum tests for continuous variables and Pearson's chi-square or Fisher's exact tests for categorical variables.

Results: Of the 940 RA patients treated with biologics, 87 (9.3%) underwent biologic de-escalation. Successful de-escalation was achieved in 74 RA patients (85.1%) at the end of the study period. Using the CDAI (Clinical Disease Activity Index) to define disease activity, the de-escalated patients had a median duration of 501.5 days in low disease activity or remission prior to a de-escalation attempt. There was no significant difference in the baseline characteristics between the de-escalated and non-de-escalated patients, except the de-escalated patients were more likely to be RF positive (83.1% vs. 67.7%, $p=0.015$). Results of a univariate analysis showed that the successfully de-escalated patients were more likely to be on their biologic for ≥2 years prior to de-escalation (70.3% vs. 38.5%, $p=0.054$, marginal significance). The unsuccessful group was more likely to have a RA flare during the observational period (53.8% vs. 6.8%, $p<0.001$).

Cost Analysis of successful de-escalations revealed savings of $719,702 and projected annualized savings of $1,256,886 if the successfully de-escalated patients remained at their latest biologic dose for 1 year.

Conclusion: This is the largest observational study analyzing clinical outcomes and cost savings of biologic de-escalation in RA. In our cohort of 940 RA patients on a biologic in the year 2013, 85% of the de-escalations were successful. The only predictor of successful de-escalation was biologic use ≥ 2 years prior to de-escalation. Significant cost savings from biologic de-escalation were achieved. Biologic de-escalation in RA is a sound methodology for improving value of care delivery - maintaining clinical disease control while reducing cost.

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ACR/EULAR Remission in RA patients in Clinical Practice - Does Substitution of Patient Global with Pain Score Change Remission Rates? Data from the Danish Danbio Registry. Merete Lund Hetland. The Danish Rheumatologic Database (DANBIO), Glostrup Hospital., Copenhagen, Denmark.

Background/Purpose: Modern treatment strategy in RA aims at remission. In 2011, new ACR/EULAR remission criteria were published for patients with RA. Of four Boolean criteria, one is a patient-reported outcome:

The patient's global score (PATGL), which reflects how much the disease affects the patient's life at the present. It has been criticized that patient's pain score (PAIN) is not included, since pain is the single largest problem for patients with RA. Our aim was to investigate how such a modification of the remission criteria, replacing PATGL with PAIN, would impact achievement of remission in patients treated in routine care.

Methods: The DANBIO registry is a nationwide, Danish database that is used by all public hospital departments of rheumatology and many rheumatologists in private practice. Patients are followed prospectively and PATGL.PAIN, as well as doctor's global (DOCGL) and FATIGUE scores are collected routinely at all visits. For the present study, the latest visit for each patient was selected.

Results: A total of 16,154 patients with RA were included (age: 65 years (55–73) (median(25–75%)), disease duration: 8 years (3–16), 28.4% men, 86.5% IgM-RF positive, 25.0%/75.0% treated with biologics/sDMARD, HAQ: 0.625(0.125–1.375), DAS28CRP: 2.5 (1.8–3.4)).

16.5% of the patients fulfilled the Boolean criteria for remission (SJC≤1, TJC≤1, CRP≤10mg/L, and PATGL ≤10mm). PATGL and PAIN were closely correlated (Spearman's rho=0.86, p<0.0001).

If PATGL was substituted by PAIN, the remission rate was largely similar: 18.0%, but 5% (680/13,485 pts) changed status from no remission to remission, and 16.7% (446/2,669 pts) from remission to no remission.

If PATGL was substituted by FATIGUE, the remission rate was 13.2% (with 3% of patients (400/13,178) changing status from no remission to remission, and 36% of patients (946/2627) from remission to no remission.

If PATGL≤10 mm was substituted by PATGL≤20mm, the remission rate increased to 25.7%.

If PATGL was substituted by DOCGL, the remission rate increased to 45.4%, and 35.6% of patients (4,598/12,928) changed from no remission to remission, and 5.3% (138/2584) from remission to no remission.

Conclusion: In >15,000 RA patients treated in routine care in a treat-to-target setting, 16.5% fulfilled the 2011 ACR/EULAR Boolean remission criteria at their latest visit. Substitution of patient's global with pain score only changed the remission rate marginally. In accordance with this, the two scores were highly correlated. In contrast, substituting patient's global with doctor's global score almost tripled the fraction of patients in remission. The finding underscores the importance of inclusion of patient-reported outcomes in the remission criteria, but PATGLO and PAIN seemed to capture largely the same patients as being in remission.

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Improvements in the Proportion of Patients Achieving DAS, CDAI, and SDAI Remission By Omitting the Patient Global Assessment (PtGA): an Analysis from a Prospective, Observational Registry. Philip Baer[1], WG Bensen[2], Carter Thorne[3], Boulos Haraoui[4], Denis Choquette[5], Regan Arendse[6], John Kelsall[7], Maqbool Sheriff[8], John S. Sampalis[9], Emmanouil Rampakakis[9], Francois Nantel[10], May Shawi[10], Allen J Lehman[10], Susan Otawa[10] and Edward Keystone[11]. [1]Private Practice, Scarborough, ON, [2]St Josephs Hospital and McMaster University, Hamilton, ON, [3]Southlake Regional Health Centre, Newmarket, ON, [4]University of Montreal Hospital Centre, Montreal, QC, [5]Institut de rhumatologie de Montréal (IRM), Montréal, QC, [6]University of Saskatchewan, Saskatoon, SK, [7]The Mary Pack Arthritis Centre, Vancouver, BC, [8]Nanaimo Regional General Hospital, Nanaimo, BC, [9]JSS Medical Research, Montreal, QC, [10]Janssen Inc., Toronto, ON, [11]Mount Sinai Hospital, University of Toronto, Toronto, ON.

Background/Purpose: PtGA is included in the formula of all disease activity indices despite the fact that it may not accurately reflect RA disease activity, but rather reflect symptoms related to fibromyalgia (FM), low back pain, osteoarthritis, depression or other conditions. A high disease activity score based on FM could mislead the physician to overestimate disease activity of RA patients and thereby to initiate therapy not indicated. (1) We previously assessed the impact of the PtGA on the ability to achieve Boolean ACR/EULAR remission state. (2) The aim of this analysis was to assess the proportion of patients failing to achieve DAS, CDAI and SDAI remission based on a real-world, routine clinical care setting in Canada, and the implications of constructing new disease activity indices omitting the PtGA.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with IFX or GLM. In this analysis, RA patients treated with infliximab from 2002–2014 or with golimumab from 2010–2014 were included. Modified versions of DAS28 (mDAS28), CDAI (mCDAI), and SDAI (mSDAI) were calculated by omitting PtGA from the formulas. Correlation of the standard and modified versions of each index was assessed with the Pearson's correlation coefficient. In the absence of validated thresholds for remission and LDA for the modified versions, the standard definitions were considered as the gold standard and ROC curve analysis was used to identify new thresholds for the modified versions. Cross-tabulations with the Chi-square test were used to assess the agreement between the standard and modified definitions of remission and LDA.

Results: One thousand nineteen RA patients with a mean (SD) age of 56.1 years (13.5) and disease duration of 8.5 years (9.1) were included in the analysis.

A strong correlation was observed between the standard and modified versions of DAS28 (r=0.98; P<0.001), CDAI (r=0.99; P<0.001), and SDAI (r=0.99; P<0.001). Based on ROC analysis the new thresholds for remission and LDA were: mDAS28 (remission=2.6, LDA=3.1), mCDAI (remission=2.5, LDA=10.5), mSDAI (remission=3.3, LDA=10.9). Cross-tabulation of the standard and modified thresholds showed that an additional 10.1%, 10.6%, and 17.8% of non-remission cases for DAS28, CDAI and SDAI, respectively, would be classified as remission with the modified definitions. Similarly, an additional 11.5%, 21.2%, and 20.6% of non-LDA cases for DAS28, CDAI and SDAI, respectively, would be classified as LDA.

Conclusion: The results of this analysis have shown that PtGA could account for up to 10% of non-remission cases and up to 20% of non-LDA cases as measured by DAS, CDAI and SDAI. Further analyses are required to identify the determinants of patient global assessment.

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Predict the Chance of Remission for Your RA Patient in Real Life. Till Uhlig[1], Vibeke Norvang[1], Elisabeth Lie[1], Erik Rødevand[2], Knut Mikkelsen[3], Åse S. Lexberg[4], Synøve Kalstad[5] and Tore K. Kvien[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]St. Olavs Hospital, Trondheim, Norway, [3]Revmatismesykehuset, Lillehammer, Norway, [4]Vestre Viken Hospital, Drammen, Norway, [5]University Hospital of Northern Norway, Tromsø, Norway.

Background/Purpose: Clinical remission (REM) is the treatment target in rheumatoid arthritis (RA), and there are several composite REM criteria available. Knowledge on how disease duration affects REM in daily clinical practice, and whether predictors of REM depend on the method for assessment of REM, is limited.

Objective: To study the rates of REM after 3 and 6 months with DMARD treatment applying different criteria, and to study predictors of REM after 6 months.

Methods: Data from 4992 patients in the NOR-DMARD study, representing real life rheumatology practice, were analysed. All patients started with a synthetic or biological DMARD and had 6-month follow-up data available,. Mean (SD) age was 54.6 (14.9) yrs, disease duration was 8.5 (7.9) yrs, 73.2% were females. Disease duration (mean 7.9 [9.6] yrs) was grouped into: <0.5 yrs (n=1329), >0.5–1 yr (n=321), >1–5 yrs (n=992), >5–10 yrs (n=750), and >10 yrs (n=1532).

The applied definitions for clinical REM were Disease Activity Score28 (DAS28) <2.6, Simplified Disease Activity Index (SDAI) <3.3, Clinical Disease Activity Index (CDAI) <2.8, Routine Assessment of Patient Index Data (RAPID3, range 0–10) <1, and the Boolean ACR/EULAR REM definition (BOOL) <1, with additional BOOL for practical use (BOOLP) <1.

Results: Overall REM rates (%) after 3 (6) months were for DAS28 22.5 (26.0)%, CDAI 10.3 (12.6)%, SDAI 9.8 (11.8)%, RAPID3 20.3 (21.3)%, BOOL 8.7 (10.1)%, and BOOLP 10.3 (12.2)%. Both at 3 and 6 months REM rates were highest for disease duration <0.5 yr for all six composite definitions (ANOVA all <0.001), varying from BOOL 12.5% (3 mths) to DAS28 34.3% (6 mths), with lower rates and minor changes across higher disease duration groups.

The table shows odds ratios (*p<0.05 **p<0.01 ***p<0.001) for achieving 6-month REM in separate logistic regression models for each remission definition, adjusting always for age, respective baseline disease activity as well as other covariates (the latter were included in the multivariable model if p<0.10).

	DAS28	SDAI	CDAI	RAPID3	BOOL	BOOLP
Female	0.63***	0.76*	0.73*	1.00	0.81	0.85
High education	1.52***	1.34*	1.27	1.49***	1.44**	1.34*
Employed			1.31*	1.22		
Erosive disease	0.70**	0.78	0.71*		0.75*	
Dis duration						
<0.5 yrs (Ref)	1	1	1	1	1	1
>0.5–1 yr	0.69	0.60*	0.50*	0.74	0.47**	0.54*
>1–5 yrs	0.49***	0.59**	0.62	0.62**	0.63*	0.56**
>5–10 yrs	0.58**	0.55**	0.54**	0.57***	0.55**	0.52**
>10 yrs	0.50***	0.46***	0.51***	0.50***	0.62*	0.53***
Current smoking	0.64***	0.67**	0.67**		0.70*	0.72*
Treatment Non-MTX (Ref.)	1	1	1	1	1	1
- MTX mono	1.01	1.30	1.41*	1.03	1.12	1.19
- bDMARD	1.78***	2.74***	2.78***	1.43**	2.01***	2.01***
MHAQ	0.80	0.52***	0.59**	0.54***	0.60**	0.54***
Fatigue VAS	0.99*	0.99***	0.99***	0.99***	0.99***	0.99***
Invest global VAS	1.01*				1.01	1.01

Conclusion: In clinical practice REM within 6 months of start/change of therapy was most frequently achieved if baseline disease duration is <6 months. REM at 6 months is further independently predicted by use of biologic DMARDs, lower age, higher education, non-smoking, absence of erosions, lower baseline disease activity, lower fatigue score, and better physical function. These real life findings inform clinicians on optimal patient treatment, including the need for very early use of DMARDs.

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Disease Remission Reduces Risk of Heart Failure in Rheumatoid Arthritis Patients Independent of Treatment Strategy. Thomas Schau[1], Michael Gottwald[2], Christian Butter[1] and Michael Zaenker[2]. [1]Cardiology Dept., Immanuel Klinikum Bernau Heart Center Brandenburg, Bernau, Germany, [2]Immanuel Klinikum Bernau, Rheumatology Center Northern Brandenburg, Bernau, Germany.

Background/Purpose: Risk of heart failure (HF) is increased in patients with RA, however there is great variance in reported prevalence rates due to different diagnostic standards and underestimation of diastolic HF. Besides traditional risk factors, systemic inflammation and persistent RA-activity are thought to be independent contributors to increased HF risk. This study was to determine influence of RA-activity on prevalence of HF in a community-based RA-cohort compared to age- and gender-matched controls by using the European Society of Cardiology (ESC) diagnostic guidelines.

Methods: A prospective, cross-sectional study including 157 consecutively recruited RA-patients from our outpatient clinic during a 3 months period. Inclusion criteria were written consent and diagnosis of RA fulfilling ACR/EULAR-criteria. Blinded to any health information, an age- and gender-matched control group (n=77) was recruited from a district office and veterans of our hospital staff. Data were obtained using standardized questionnaire, clinical investigation, lab tests including NT-proBNP (Roche), and echocardiography containing tissue doppler and strain imaging.

Results: The RA and control cohorts were comparable in age (mean (SD) 61 years (±13) vs. 59(±12) and gender distribution (67% vs. 69% females). In RA, median HAQ was 1.1 (Interquartile range (IQR) 0.8–2.0), median DAS28 was 2.8 (IQR 2.0–3.4), with remission (DAS28<2.6) in 45%, low disease activity (DAS28 2.6–3.2) in 25% and higher disease activity (DAS28 >3.2) in 30% of the patients. Prevalence of HF was significantly higher in RA vs. controls (38(24%) vs. 5(6%), p<0.001). Of all diagnosed HF, only 2 RA patients showed reduced ejection fraction. Comparing RA and control group, traditional risk factors were not significantly different except mean BMI (29±5 vs. 27±4, p<0.001) and prevalence of hypertension (59% vs. 40%, p=0.019). No significant differences were found for diabetes, chronic kidney disease, hyperlipidaemia. Subgroup analysis revealed 37% prevalence of HF in patients with DAS28 >3.2 (RR 5.7, p<0.001 compared to controls), 30% in patients with DAS28 2.6–3.2 (RR 4.6, p=0.0015) and 13% in patients with DAS28-remission (RR 1.95, p=0.264). In multivariate analysis adjusted for age and gender, remaining risk factors for HF in RA were DAS28≥2.6 (OR 3.4, 95%CI 1.3–9.8), RA-duration >10years (OR 2.6, 95%CI 1.2–5.8), CRP median >10mg/l (OR 4.8, 95%CI 1.1–21), and ESR >16mm/h (OR 5.4, 95%CI 2.1–16). We found no influence of treatment type.

Conclusion: Compared to age and gender matched controls, prevalence of mostly diastolic HF was found 4–6fold increased in active RA but only 2fold increased in states of disease remission. We conclude that optimal control of RA and awareness for diastolic HF more than type of treatment are crucial for adequately addressing cardiovascular risk in RA patients.

Disclosure: T. Schau, None; **M. Gottwald**, None; **C. Butter**, None; **M. Zaenker**, None.

ACR Concurrent Abstract Session

Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy II: Novel Therapies in Rheumatoid Arthritis - Early in Development

Sunday, November 16, 2014, 4:30 PM–6:00 PM

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Phase 1 Study of Immunotherapy Using Autoantigen-Loaded Dendritic Cells in Patients with Anti-Citrullinated Peptide Antigen Positive Rheumatoid Arthritis. Young Bin Joo[1], Jun-Eui Park[2], Chan-Bum Choi[3], Jeongim Choi[1], Jin-ah Jang[2], Minkyu Heo[2], Hak-yeop Kim[2], Hye-Soon Lee[1], Yong-Soo Bae[4] and Sang-Cheol Bae[5]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]JW CreaGene Research Institute, JWCreaGene Inc., Seongnam-si, South Korea, [3]Hanyang University Hospital for Rheumatic Diseases, Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [4]Sungkyunkwan University, Suwon, South Korea, [5]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea.

Background/Purpose: To date, no dendritic cell (DC) immunotherapy has been shown to give a benefit in patients with rheumatoid arthritis (RA). In this prospective phase I study, we evaluated the safety and clinical efficacy of autologous tolerogenic dendritic cell (DC) administration (CreaVax-RA) in patients with RA.

Methods: Twelve RA patients (six for low dose vaccination, 0.5×10^7 cells/injection and remaining six for high dose vaccination, 1.5×10^7 cells/injection) were administrated five times at 2 to 4 week intervals subcutaneously (around inguinal lymph nodes) with each CreaVax-RA, autologous semi-mature DCs pulsed with recombinant PAD4, RA33, citrullinated-filaggrin (cit-FLG) and vimentin antigens. Safety and clinical benefits together with associated immune responses were evaluated as primary and secondary outcomes, respectively, at 14 and 24 weeks after first administration. The major clinical outcomes were assessed by European League Against Rheumatism (EULAR) response.

Results: Among a total of 12 adverse events (AEs) in eight patients, 11 events (91.7%) were restricted in patients treated with low dose (0.5×10^7 cells/inj) while 1 event in patients with high dose (1.5×10^7 cells/inj). All of the AEs were grade 1 or 2 without over grade 3 AE. In ELISPOT assay, the number of IFN-γ-secreting T cells decreased in 91.7% (n = 11/12). The level of antigen-specific autoantibodies significantly decreased in 55.6% (n=5/9) among the autoantibody-positive patients against more than one autoantigen ($p < 0.001$). The percentage of patients who achieved a good-to-moderate EULAR response ranged over 58.3% (n = 7/12) at 14 weeks after initial administration. The response rate was much higher in high dose group than in low dose group (83.3% vs 33.3%, respectively). The patients without any autoantibodies showed no clinical efficacy.

Conclusion: DC administration (CreaVax-RA) was safe and well tolerated in patients with RA in the present phase I study. Preliminary, but clinical outcomes were in good agreement with doses and immune responses. These phase I results warrant further clinical study of high dose CreaVax-RA (1.5×10^7/inj) in patients with RA.

Trial registration: CRiS KCT0000035

Clinical Research Information Service [Internet]; Osong (Chungchengbuk-do): Korea Centers for Disease Control and Prevention Ministry of Health and Welfare (Republic of Korea); 2010;KCT0000035; A phase I, open label, dose ranging study to evaluate the safety and tolerance of CreaVax-RA in active rheumatoid arthritis patients with usual DMARDs; 2010/09/14;[1 screen]. Available at: http://cris.nih.go.kr/cris/en/search/search_result_st01.jsp?seq=1645

Disclosure: Y. B. Joo, None; **J. E. Park**, JW CREAGENE, 3; **C. B. Choi**, None; **J. Choi**, None; **J. A. Jang**, JW CREAGENE, 3; **M. Heo**, JW CREAGENE, 3; **H. Y. Kim**, JW CREAGENE, 3; **H. S. Lee**, None; **Y. S. Bae**, JW CREAGENE, 1, JW CREAGENE, 3; **S. C. Bae**, None.

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Efficacy and Safety of NNC01140006, an Anti-IL-21 Monoclonal Antibody, in Patients with Active Rheumatoid Arthritis. Juan D. Cañete[1], Piotr Leszczynski[2], Rikke Riisbro[3] and Klaus S. Frederiksen[3]. [1]Hospital Clínic of Barcelona, Barcelona, Spain, [2]Department of Rheumatology and Rehabilitation, Poznan Medical University, Poznan, Poland, [3]Novo Nordisk A/S, Søborg, Denmark.

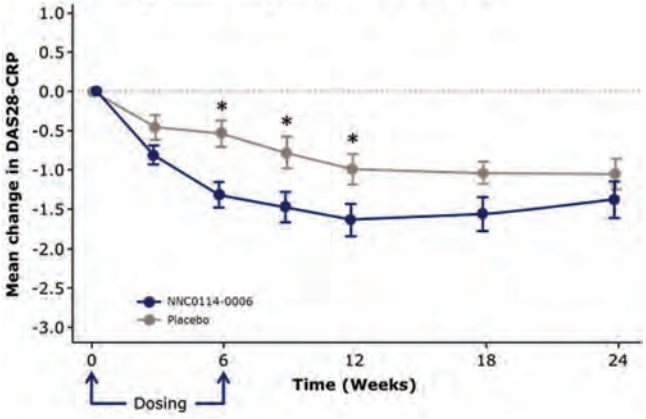
Background/Purpose: A phase 2, randomised, double-blind, placebo-controlled, parallel-group trial was conducted to evaluate the efficacy and safety of NNC0114-0006 in patients with active rheumatoid arthritis (RA) on background methotrexate (MTX) therapy.

Methods: Patients (N=62; 82% female) with RA (mean duration 6.9 years; 77% RF positive; 82% anti-CCP positive; mean DAS28-CRP 5.7) and on MTX (mean duration 3.9 years; mean dose 14.3 mg/week) were enrolled. Patients were randomised to i.v. NNC0114-0006 (12 mg/kg; n=41) or placebo (n=21); two doses given 6 weeks apart. The primary endpoint was change in DAS28-CRP from baseline to Week 12. ACR 20/50/70 and EULAR response at Week 12, adverse events (AEs), changes in laboratory safety measurements, antibodies against NNC0114–0006 (ADAs) and pharmacodynamic (PD) parameters were also evaluated.

Results: There were no significant differences between treatment groups with respect to baseline. Four patients in the NNC0114-0006 group withdrew (3 withdrew informed consent, 1 was lost to follow-up). A significant improvement in mean DAS28-CRP was observed with NNC0114-0006 versus placebo at Week 12 (–0.65, p=0.04; Fig. 1), due largely to reductions in swollen and tender joint counts. The reduction in DAS28-CRP at week 12 was supported by improved disease activity in terms of ACR20/50/70 and EULAR response, although these endpoints did not reach statistical significance. An expected increase in total (both free and antibody-bound) IL-21 levels after treatment with NNC0114-0006 was observed. While no change in absolute B cell numbers was observed at Week 1, about one third of patients treated with NNC0114-0006 had increased percentages of plasma cells, plasmablasts and short-lived plasmablasts, with decreased percentages of naïve B cells. They also showed increased transcript levels of Ig-Lambda light chain (IGLV7–43) and other plasma-cell signature genes in whole blood analysis. However, the DAS28-CRP response in these patients was comparable to placebo and those who did not exhibit this B cell alteration. Nevertheless, following treatment, DAS28-CRP and ACR-N outcomes appear to be related to baseline CTX-I – a marker of bone resorption – but not baseline DAS28-CRP. In NNC0114-0006-treated patients, 43 AEs were observed in 22/41 (54%) patients, while 24 AEs occurred in 11/21 (52%) placebo patients. Four serious AEs occurred in 3 placebo patients. A higher number of patients reported infections (24% vs 10%) and skin disorders (12% vs 5%) in the NNC0114-0006 group versus placebo. No treatment-related ADAs were detected. No clinically significant changes were observed in laboratory safety parameters.

Conclusion: Treatment with NNC0114-0006 significantly improved DAS28-CRP versus placebo at Week 12. Changes in B cell subsets detected at Week 1 may be due to altered distribution of homing of plasma cells/plasmablasts. No safety concerns were identified.

Fig 1. Mean change in DAS28-CRP over time



*P<0.05. Error bars represent standard error of the mean.

Disclosure: J. D. Cañete, Novo Nordisk, Pfizer, Celgene, Schering Plough-MSD, Janssen-Cilag, Merck Sharpe & Dohme, Bristol-Myers Squibb, and Abbott, 5; **P. Leszczynski**, Roche, Merck Sharp & Dohme, UCB, AbbVie, Novo Nordisk, Pfizer, Samsung Bioepis, GlaxoSmithKline, Eli Lilly, Bristol-Myers Squibb, Amgen, Janssen, and Novartis, 5; **R. Riisbro**, Novo Nordisk, 3; **K. S. Frederiksen**, Novo Nordisk, 3.

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A Phase 2b, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose-Finding, Multi-Center Study to Evaluate the Safety and Efficacy of ASP015K in Moderate to Severe Rheumatoid Arthritis Subjects Who Have Had an Inadequate Response to Methotrexate. Alan J. Kivitz[1], Anna Zubrzycka-Sienkiewicz[2], Sergio R. Gutierrez-Ureña[3], Jeffrey Poiley[4], Rita Kristy[5], Kathyjo Shay[5] and Jay P. Garg[5]. [1]Altoona Center for Clinical Research, Duncansville, PA, [2]ARS Rheumatica sp. Zo.o, Reumatika, Warszawa, Poland, [3]Hospital Civil de Guadalajara FAA, CUCS UdG, Guadalajara, Mexico, [4]Arthritis Associates, Orlando, FL, [5]Astellas Pharma Global Development, Northbrook, IL.

Background/Purpose: ASP015K is a novel oral Janus kinase (JAK) inhibitor in development for the treatment of rheumatoid arthritis (RA). ASP015K inhibits JAK 1/3 with relative selectivity over JAK2 and can be dosed once daily (QD). This study evaluated the efficacy, safety and dose response of ASP015K QD in patients (pts) with moderate to severe rheumatoid arthritis (RA) with an inadequate response to methotrexate (MTX) (Clinical Trials Registration: NCT01554696).

Methods: In a 12-week, double-blind, placebo (PBO)-controlled study, pts 18 years or older who met ACR criteria for RA, were on MTX ≥ 90 days, and had active RA (CRP ≥ 0.8 mg/dL or ESR ≥ 28 mm/hr and ≥ 6 tender/swollen joints on a stable dose of MTX) were randomized 1:1:1:1:1 to ASP015K 25 mg, 50 mg, 100 mg, 150 mg or PBO, stratified by prior anti-TNF use and geographic region. Pts continued stable MTX therapy during the study. The primary endpoint was ACR20 response at week 12.

Results: 378 pts (83% female; mean age 53 years) were randomized and dosed. 43% of subjects were enrolled in Europe, 39% in U.S., and 18% in Latin America. 26% had used a TNF-inhibitor. Mean baseline values: tender joint count 23.0 (of 68), swollen joint count 13.6 (of 66), CRP 1.17 mg/dL, ESR 39.86 mm/hr, DAS28-CRP 5.54, and DAS28-ESR 6.36. Concomitant MTX dose was similar among groups. Dose-response on ACR20 was not shown. Numerically greater ACR20 responses than PBO were seen in the ASP015K 50 mg and 150 mg groups, with statistical significance shown in the 50 mg group. A statistically significant dose response was demonstrated in change in DAS28-CRP and DAS28-ESR, with effects seen as early as week 1. Pre-specified analyses by geographic region showed significant responses in ACR20 in the ASP015K 100 mg and 150 mg dose groups as compared to PBO in Europe but not in the other regions (Table). The incidence of adverse events (AEs) was similar between combined ASP015K groups and PBO (47.7% vs 47.2%). The most frequently reported AEs in the combined ASP015K groups vs PBO were headache (2.9% vs 1.4%) and hypercholesterolemia (2.0% vs 1.4%). The overall incidence of infections and serious adverse events (SAEs) were similar between ASP015K and placebo (18.3% vs 26.4% and 1.0% vs 0%, respectively). No meaningful differences in absolute neutrophil and lymphocyte counts and hemoglobin were seen between ASP015K and PBO. The safety profile was comparable among the ASP015K dose groups, although more AEs leading to study drug discontinuation and all 3 SAEs occurred in the 100 mg and 150 mg groups.

Conclusion: In this study of active RA subjects with an inadequate response to MTX, ASP015K did not demonstrate a dose-response on the primary endpoint of ACR20, with differential placebo response rates seen by region. Significant effects on inflammatory markers and DAS28 were shown, warranting further evaluation. ASP015K was well tolerated with no meaningful differences in safety measures from placebo noted.

	Placebo (n=72)	ASP015K 25 mg (n=66)	ASP015K 50 mg (n=78)	ASP015K 100 mg (n=84)	ASP015K 150 mg (n=78)
Primary endpoint					
ACR20,n (%) [1]	32 (44.4)	29 (43.9)	48 (61.5)*	39 (46.4)	45 (57.7)
Secondary endpoints					
ACR50, n (%)	19 (26.4)	12 (18.2)	26 (33.3)	28 (33.3)	29 (37.2)
ACR70, n (%)	8 (11.1)	6 (9.1)	12 (15.4)	14 (16.7)	15 (19.2)
Change from baseline in DAS28-CRP (LS mean)	−1.38	−1.35	−1.84*	−1.64	−2.01**
Key exploratory endpoints					
Change from baseline in DAS28-ESR (LS mean)	−1.60	−1.62	−2.13*	−1.96	−2.37**
Change from baseline in CRP (LS mean)	0.13	−0.11	−0.47***	−0.28*	−0.50***
Change from baseline in ESR (LS mean)	−4.89	−9.17	−12.83**	−14.06***	−16.68***

Change from baseline in HAQ-DI (LS mean)	−0.26	−0.28	−0.36	−0.37	−0.39
ACR20 response by region					
North America (n=147)	14/28 (50.0)	13/24 (54.2)	21/34 (61.8)	10/28 (35.7)	20/33 (60.6)
Europe (n=163)	9/32 (28.1)	8/29 (27.6)	16/31 (51.6)	21/39 (53.8)*	18/32 (56.3)*
Latin America (n=68)	9/12 (75.0)	8/13 (61.5)	11/13 (84.6)	8/17 (47.1)	7/13 (53.8)

*p < 0.05; **p < 0.01; ***p < 0.001 vs PBO [1] Dose response, p=0.201
LS Mean: Least squares mean

Disclosure: A. J. Kivitz, None; **A. Zubrzycka-Sienkiewicz**, Astellas, paid by ICON CRO, 9, Janssen, 9, Roche, UCB, Sanofi, 9, Merck, 9; **S. R. Gutierrez-Ureña**, None; **J. Poiley**, None; **R. Kristy**, Astellas, 3; **K. Shay**, Astellas, 3; **J. P. Garg**, Astellas, 3.

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Safety and Efficacy of CF101 in Rheumatoid Arthritis Patients: A Phase II Study. Rumen M. Stoilov[1], Rodina N. Licheva[2], Mariyana K. Mihaylova[3], Tatiana Reitblat[4], Emil A. Dimitrov[1], Krasimira M. Shimbova[1], Girish Bhatia[5], Amit Pispati[6], Alexandra Gurman- Balbir[7], B R Bagaria[5], Boytcho A. Oparanov[2], Sari Fishman[8], Zivit Harpaz[8], Motti Farbstein[8], Shira Cohen[8], Michael H. Silverman[8] and Pnina Fishman[8]. [1]Multiprofile Hospital for Active Treatment "Sv. Ivan Rilski" - EAD, Clinic of Rheumatology, Sofia, Bulgaria, [2]Diagnostic Consulting Center, Rheumatology office, Sofia, Bulgaria, [3]3Diagnostic Consulting Center, Rheumatology office, Sofia, Bulgaria, [4]Barzilai Medical Center,, Ashkelon, Israel, [5]Malpani Multispeciality Hospital, mumbai, India, [6]Bhatia Hospital Medical Research Society, mumbai, India, [7]Rambam Medical Center, Haifa, Israel, [8]CanFite Biopharma Ltd, Petah Tikva, Israel.

Background/Purpose: CF101, is a highly selective A_3 adenosine receptor (A_3AR) agonist, demonstrated safety and anti-inflammatory effect in Phase 2 clinical studies of rheumatoid arthritis (RA) and Psoriasis. A_3AR has been defined as a biological predictive marker, based on a significant correlation found in a former Phase II study, between its over-expression at baseline and positive patients' response to CF101 treatment.

Methods: This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to assess the efficacy and safety of CF101 1mg, administered orally twice daily to patients with active RA for 12 weeks. Primary efficacy endpoint was ACR 20 response at week 12, with all-cause dropouts considered as non-responders, in the Intent-To-Treat (ITT) population. Secondary efficacy included: ACR 20/50/70 by visit, ITT, using non-responder imputation.

Seventy nine patients were enrolled for the study based on inclusion criteria of A_3AR > from 1.5 units and were randomized for two groups receiving CF101 1 mg (n = 42), or Placebo (n = 37).

Results: CF101 achieved ACR20 of 48.6%, statistically significantly higher than in the Placebo group (25.0%) at week 12 (P=0.0352). CF101 showed superiority in ACR50 and ACR70 values vs. placebo although not statistically significant, most probably due to the low number of patients. Interestingly, ACR20, ACR 50 and ACR 70 response rate at week 12 in patients with no prior systemic therapy, i.e., naïve patients were significantly higher compared to the response of the whole patient population treated with CF101.

The proportion of patients experiencing any adverse event (AE) was similar for both groups (16.7% for the CF101 group and 16.2% for the Placebo group). Two AEs, RA and rash, were considered possibly related to CF101. The majority of AEs were considered to be mild.

Conclusion: CF101 was very well tolerated and reached the primary endpoint in the current study demonstrating clear evidence of efficacy as a monotherapy for 12 weeks in patients with active RA.

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Multiple Mechanisms of Tolerance Characterize the Immune Response to Autologous Modified Dendritic Cells Exposed to Citrullinated Peptides in Patients with Rheumatoid Arthritis. Soi-Cheng Law[1], Hendrik Nel[2], Ahmed Mehdi[2], Kim-Anh Le Cao[2] and Ranjeny Thomas[1]. [1]Univ of Queensland, Brisbane, Australia, [2]University of Queensland, Brisbane, Australia.

Background/Purpose: We carried out a phase I clinical trial of tolerising autologous peripheral blood DCs exposed to 4 citrullinated self-peptides ("Rheumavax") in 29 HLA-DR shared epitope (SE)+ anti-citrullinated peptide antibody+ DMARD-treated rheumatoid arthritis (RA) patients, of whom 18 received Rheumavax. This study aimed to evaluate immune biomarkers of treatment and of clinical response to Rheumavax.

Methods: Frozen peripheral blood mononuclear cells (PBMC) were analysed for T cell, B cell, monocyte and DC subsets by flow cytometry (FACS) at baseline, 6 days, 4, 8, 12 and 24 weeks after Rheumavax, and Luminex and ELISA assays were used to measure 108 serum analytes. PBMC were stimulated ex vivo for 5 days with each of the delivered citrullinated peptides, or with control citrullinated aggrecan peptide or tetanus toxoid antigens. Proliferation and cytokine production were measured. To identify relevant markers of change, we used sparse partial least squares linear multivariate approach, multilinear regression, ANOVA and t tests.

Results: Median disease duration of recruited patients was 2 years. At baseline, 9 of 18 patients assigned to Rheumavax had an incomplete response to DMARDs with a swollen joint count (SJC) of at least 1; 9 had minimal disease activity. One month after Rheumavax, SJC of patients with active disease at baseline reduced by a mean of 5 joints and SJC of those with inactive disease did not change. Immune effects of Rheumavax were first expected 6 days after administration. Using a multiple linear regression to model the effect of changes in PB cells at day 6 on clinical response, we found that reduction in the proportions of CD25+CD127+ activated CD4+ T cells and CD14loCD16- monocytes, and increased proportions of CD25-CD127+CD4+ naive cells, CD56+CD16+ NK cells and Foxp3+CD127loCD25hi Treg cells predicted the reduction in SJC 1 month after Rheumavax with R^2 of 0.85 (p=0.0001). Relative to controls, treated patients had an increased proportion of PB CD25+CD127-CD4+ induced (i)Treg from 6 days until 8 weeks after Rheumavax. Specific increase in IL-10 production in response to delivered cit-peptides occurred ex vivo in 4 patients, increased iTreg in 8 patients and an increase in IL-10 and iTreg in 4 patients post-Rheumavax treatment. Reduction in 12 pro-inflammatory cytokines, chemokines and metabolic factors in serum discriminated the 1 month response in Rheumavax treated and untreated patients. Consistent with their clinical and inflammatory improvement, treated patients had an increased proliferative response to tetanus toxoid ex vivo within 6 days of Rheumavax.

Conclusion: These data suggest that autologous tolerising DCs exposed to citrullinated peptides improved disease control in RA patients with prior partial response to DMARDs through reduction in circulating activated T cells and dendritic cell precursors, induction of Treg and lytic NK cells, and suppression of systemic inflammation, thereby restoring regulatory balance and immune function.

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Safety, Tolerability, and Functional Activity of ABT-122, a Dual TNF- and IL-17A–Targeted DVD-Ig™, Following Single-Dose Administration in Healthy Subjects. Heikki Mansikka[1], Melanie Ruzek[2], Margaret Hugunin[2], Alexander Ivanov[2], Alyssa Brito[2], Anca Clabbers[2], Carolyn Cuff[2], Chung-Ming Hsieh[2], Martin Okun[1], Renee Heuser[1], David Carter[1], Barbara Hendrickson[1], Dipak Pisal[1], Sandra Goss[1], Jia Liu[1], Charles Locke[1], Nasser Khan[1] and Robert Padley[1]. [1]AbbVie, Inc, North Chicago, IL, [2]AbbVie, Inc, Worcester, MA.

Background/Purpose: Several lines of evidence indicate that greater clinical efficacy and protection of joints may be possible in patients with RA by neutralizing TNF and IL-17 concurrently, compared with neutralizing either alone. ABT-122 is a novel Dual Variable Domain immunoglobulin (DVD-Ig™) protein incorporating two sets of selective binding domains, with one pair targeting TNF and one pair targeting IL-17A. The safety, tolerability, and dual functionality of ABT-122 was investigated in a single ascending dose study in healthy subjects.

Methods: This was a first-in-human, double-blind, placebo-controlled study with single dose ABT-122 administration by intravenous (IV) or subcutaneous (SC) route in 64 healthy volunteers. Each ABT-122 dose was evaluated in a group of 8 subjects, 6 receiving active drug and 2 receiving placebo. Groups 1 through 5 received ABT-122 at 0.1, 0.3, 1, 3, and 10 mg/kg IV, respectively, and Groups 6 through 8 received 0.3, 1, and 3 mg/kg SC, respectively.

Dual binding capacity of ABT-122 for IL-17 and TNF in vitro was determined by sequential binding of human TNF and IL-17 to ABT-122 by surface plasmon resonance (SPR). Functional activity of recombinant ABT-

122 or of serum from subjects receiving ABT-122 was determined using an in vitro assay of inhibition of TNF- and IL-17–induced IL-6 production by human fibroblast-like synoviocytes (FLS), derived from RA patients.

Results: Following IV or SC administration there was no significant difference in the adverse event (AE) profile between subjects receiving ABT-122 or placebo. There were no serious AEs or premature discontinuations due to AEs reported in this study. No subject had an infusion reaction, systemic hypersensitivity reaction or an injection site reaction. No clinically relevant changes in laboratory parameters, vital signs, or ECG parameters occurred. All AEs were mild or moderate in intensity. The most frequently reported adverse event was upper respiratory infection for both subjects given ABT-122 or placebo.

ABT-122 simultaneously bound a similar amount of TNF per ABT-122 molecule independent of the occupancy of the IL-17 binding sites and vice versa by SPR. ABT-122 in the functional assay fully inhibited IL-6 release from FLS stimulated by the combination of TNF and IL-17, whereas individual monoclonal antibodies only partially blocked the IL-6 production. Serum from subjects receiving ABT-122 demonstrated comparable potency (IC_{50} and IC_{90}) to that defined by ABT-122 in the assay and was consistent across dose groups. Full neutralization was time- and dose-dependent through 21 days, and up to 10mg/kg, respectively.

Conclusion: These data demonstrate that ABT-122 can simultaneously bind and neutralize TNF and IL-17 in vitro and functional levels of dual TNF and IL-17 inhibition with ABT-122 are maintained for up to three weeks after a single dose in healthy subjects. ABT-122 demonstrated an acceptable safety profile following single dose administration up to 3 mg/kg SC and 10 mg/kg IV. These study results support continued development of ABT-122 for immune mediated inflammatory diseases.

Disclosure: H. Mansikka, AbbVie, 3, AbbVie, 1; **M. Ruzek**, AbbVie, 3, AbbVie, 1; **M. Hugunin**, AbbVie, Inc, 3, AbbVie, Inc, 1; **A. Ivanov**, AbbVie, Inc, 3, AbbVie, Inc, 1; **A. Brito**, AbbVie, Inc, 3, AbbVie, Inc, 1; **A. Clabbers**, AbbVie, Inc, 3, AbbVie, Inc, 1; **C. Cuff**, AbbVie, 3, AbbVie, 1; **C. M. Hsieh**, AbbVie, Inc, 3, AbbVie, Inc, 1; **M. Okun**, AbbVie, Inc, 3, AbbVie, Inc, 1; **R. Heuser**, AbbVie, Inc, 3, AbbVie, Inc, 1; **D. Carter**, AbbVie, Inc, 3, AbbVie, Inc, 1; **B. Hendrickson**, AbbVie, Inc, 3, AbbVie, Inc, 1; **D. Pisal**, AbbVie, Inc, 3, AbbVie, Inc, 1; **S. Goss**, AbbVie, Inc, 3, AbbVie, Inc, 1; **J. Liu**, AbbVie, Inc, 3, AbbVie, Inc, 1; **C. Locke**, AbbVie, Inc, 3, AbbVie, Inc, 1; **N. Khan**, AbbVie, Inc, 3, AbbVie, Inc, 1; **R. Padley**, AbbVie, 3, AbbVie, 1.

ACR Concurrent Abstract Session
Spondyloarthropathies and Psoriatic Arthritis II - Novel Treatments Psoriatic Arthritis
Sunday, November 16, 2014, 4:30 PM–6:00 PM

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A Phase IIb, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Multicenter Study to Evaluate the Efficacy and Safety of Clazakizumab, an Anti-IL-6 Monoclonal Antibody, in Adults with Active Psoriatic Arthritis. Philip Mease[1], A B Gottlieb[2], A Berman[3], E Drescher[4], J Xing[5], S Banerjee[5] and R Wong[5]. [1]Swedish Medical Center and University of Washington, Seattle, WA, [2]Tufts Medical Center and Tufts University School of Medicine, Boston, MA, [3]Centro Médico Privado de Reumatología, Tucuman, Argentina, [4]Csolnoky Ferenc Hospital, Veszprém, Hungary, [5]Bristol-Myers Squibb, Princeton, NJ.

Background/Purpose: New treatment options for psoriatic arthritis (PsA) are needed and interleukin-6 (IL-6), a cytokine with a central role in chronic inflammation, is a potential therapeutic target. This Phase IIb study evaluated the efficacy of 3 doses of SC clazakizumab (CLZ) – a potent, selective antibody to the IL-6 cytokine – with or without MTX versus placebo (PBO) in patients (pts) with PsA.

Methods: Pts with PsA according to the Classification Criteria for Psoriatic Arthritis (CASPAR) and active disease, who had an inadequate response to NSAIDs and/or DMARDs, were randomized to 1 of 4 treatment arms: CLZ 25, 100, or 200 mg, or PBO, with or without MTX, every 4 wks for 24 wks. The primary endpoint was ACR20 response rate at Wk 16. Additional secondary endpoints evaluated at Wk 24 include ACR20/50/70 and Psoriasis Area and Severity Index 75 (PASI75) response rates; changes in HAQ-DI and DAS28 (CRP); and dactylitis and enthesitis scores. All pts who discontinued or received rescue treatment prior to Wk 16 were imputed as non-responders at the Wk 16 analysis and all subsequent visits.

Results: A total of 165 pts were treated and analyzed. Baseline characteristics were balanced, including use of background MTX in ~70% of pts, except mean body weight (approximately 8 kg lower in PBO and CLZ 25 mg arms) and disease duration (3–5 yrs less in CLZ 100 and 200 mg arms). The study primary endpoint was met, with ACR20 response rates significantly higher in the CLZ 100 mg arm vs PBO (52.4 vs 29.3%, p=0.039) and numerically higher in the CLZ 25 and 200 mg arms (46.3 [p=0.101] and 39.0% [p=0.178], respectively) at Wk 16. The table shows secondary endpoints. ACR20/50/70 response rates were higher than PBO for all CLZ treatment arms at Wk 24, but no clear dose response was seen. Mean decreases from baseline to Wk 24 in DAS28 (CRP), HAQ-DI, the number of dactylitic digits and Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis score were greater in all CLZ treatment arms compared with PBO. PASI75 response rates were 12.2% in the PBO arm and between 12.2 and 28.6% in the CLZ arms at Wk 24. Through Wk 24, the rates of serious adverse events (SAEs) were similar across PBO, CLZ 25 and CLZ 100 mg arms (4.9, 4.9 and 4.8%, respectively) and higher for the CLZ 200 mg arm (9.8%), which was associated with more discontinuations. No serious infections, tuberculosis, malignancies, gastrointestinal perforations or unusual SAEs, were observed during the study period. Consistent with IL-6 blockade, non-clinically significant liver enzyme elevations and reductions in platelet and neutrophil counts were observed in the 3 CLZ treatment arms.

Week 24 results	PBO (n=41)	CLZ 25 mg (n=41)	CLZ 100 mg (n=42)	CLZ 200 mg (n=41)
ACR20, % (95% CI)	34.1 (19.6, 48.7)	56.1 (40.9, 71.3)	57.1 (42.2, 72.1)	39.0 (24.1, 54.0)
ACR50, % (95% CI)	14.6 (3.8, 25.5)	34.1 (19.6, 48.7)	35.7 (21.2, 50.2)	24.4 (11.2, 37.5)
ACR70, % (95% CI)	4.9 (0.6, 16.5)	19.5 (7.4, 31.6)	23.8 (10.9, 36.7)	12.2 (2.2, 22.2)
DAS28 (CRP), mean CFB (95% CI) % CFB*	−0.93 (−1.31, −0.55) −18.6	−2.26 (−2.65, −1.88) −43.7	−2.25 (−2.62, −1.87) −43.9	−2.16 (−2.55, −1.76) −44.3
HAQ-DI, mean CFB (95% CI) % CFB*	−0.26 (−0.43, −0.09) −19.0	−0.46 (−0.63, −0.29) −31.7	−0.43 (−0.59, −0.26) −32.1	−0.34 (−0.52, −0.17) −25.0
SPARCC, mean CFB (95% CI) % CFB*	−1.3 (−2.4, −0.3) −22.8	−3.6 (−4.6, −2.6) −72.0	−2.7 (−3.7, −1.7) −60.0	−2.5 (−3.7, −1.4) −59.5
LEI, mean CFB (95% CI) % CFB*	−1.1 (−1.5, −0.7) −44.0	−1.3 (−1.6, −0.9) −72.2	−1.4 (−1.8, −1.1) −77.8	−1.1 (−1.5, −0.7) −61.1
Mean no. dactylitic digits in pts with dactylitis at baseline (SD) % CFB*	2.5 (3.78) +4.2	1.4 (2.1) −51.7	0.2 (0.4) −90.0	0.8 (1.53) −68.0
PASI75, % (95% CI)	12.2 (2.2, 22.2)	19.5 (7.4, 31.6)	28.6 (14.9, 42.2)	12.2 (2.2, 22.2)

CFB=change from baseline; LEI=Leeds Enthesitis Index *Calculated based on mean values at baseline and Week 24.

Conclusion: Clazakizumab is effective in controlling clinical features of PsA such as arthritis, enthesitis and dactylitis, with modest skin benefits. The safety profile was acceptable and consistent with IL-6 blockade. This is the first demonstration of a beneficial effect of targeting IL-6 in PsA and further studies are warranted.

Disclosure: P. Mease, AbbVie, Amgen, Biogen Idec, Bristol-Myers Squibb, Celgene, Crescendo, Genentech, Jansses, Lilly, Merck, Novartis, Pfizer, UCB, Vertex, 2, AbbVie, Amgen, Biogen Idec, Bristol-Myers Squibb, Celgene, Covagen, Crescendo, Genentech, Jansses, Lilly, Merck, Novartis, Pfizer, UCB, Vertex, 5, AbbVie, Amgen, Biogen Idec, Bristol-Myers Squibb, Crescendo, Genentech, Jansses, Lilly, Pfizer, UCB, 8; **A. B. Gottlieb**, Amgen, Astellas, Akros, Centocor (Janssen), Celgene, Bristol-Myers Squibb, Beiersdorf, Abbott Labs (AbbVie), Teva, Actelion, UCB, Novo Nordisk, Novartis, Dermipsor, Incyte, Pfizer, Canfite, Lilly, Coronado, Vertex, Karyopharm, CSL Behring Biotherapies for, 5, Centocor (Janssen), Amgen, Abbott (Abbvie), Novartis, Celgene, Pfizer, Lilly, Coronado, Levia, Merck, 2; **A. Berman**, None; **E. Drescher**, None; **J. Xing**, Bristol-Myers Squibb, 3; **S. Banerjee**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **R. Wong**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3.

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Secukinumab, a Human Anti–Interleukin-17A Monoclonal Antibody, Improves Active Psoriatic Arthritis and Inhibits Radiographic Progression: Efficacy and Safety Data from a Phase 3 Randomized, Multicenter, Double-Blind, Placebo-Controlled Study. Philip Mease[1], Iain B. McInnes[2], Bruce Kirkham[3], Arthur Kavanaugh[4], Proton Rahman[5], Désirée van der Heijde[6], Robert Landewé[7], Peter Nash[8], Luminita Pricop[9], Jiacheng Yuan[9], Hanno Richards[10] and Shephard Mpofu[10]. [1]Swedish Medical Center and University of Washington, Seattle, WA, [2]University of Glasgow, Glasgow, United Kingdom, [3]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [4]UCSD School of Medicine, La Jolla, CA, [5]Memorial University of Newfoundland, St. John's, NF, [6]Leiden University Medical Center, Leiden, Netherlands, [7]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [8]University of Queensland, Brisbane, Australia, [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [10]Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: Secukinumab has demonstrated significant and rapid efficacy in the treatment of psoriasis in two phase 3 studies. We present the first randomized, multicenter, double-blind, placebo (PBO)-controlled phase 3 study to assess the efficacy and safety of secukinumab in patients (pts) with PsA (FUTURE 1; NCT01392326).

Methods: 606 adults with active, moderate to severe PsA were randomized to secukinumab or PBO. Pts on secukinumab received 10 mg/kg i.v. loading dose at baseline, Week (Wk) 2 and Wk 4, then either 75 mg s.c. (10

IV→75 SC) or 150 mg s.c. (10 IV→150 SC) every 4 wks from Wk 8. PBO was given on the same schedules. Patients naïve to anti-TNF therapy (~70%) and those intolerant of or inadequate responders to anti-TNF therapy (TNF-IR; ~30%), were stratified across groups. Statistical analyses for the primary and multiple secondary endpoints used non-responder imputation (binary variables), mixed-effects repeated measures model (continuous variables), and linear extrapolation (radiographic data), following a pre-defined hierarchical hypothesis testing strategy to adjust for multiplicity.

Results: Demographics and baseline characteristics were balanced between groups. Both 10 IV→75 SC and 10 IV→150 SC demonstrated significantly higher ACR20 responses vs. PBO at Wk 24 (50.5% and 50.0% vs. 17.3%, respectively; $P< 0.0001$ vs. PBO). All pre-specified secondary endpoints, including dactylitis, enthesitis, SF36-PCS, HAQ-DI, DAS28-CRP, ACR50, PASI 75, PASI 90, and mTSS score were achieved by Wk 24 and reached statistical significance; active dose separated from PBO as early as Wk 1 for ACR20, DAS28-CRP, and HAQ-DI. Drug exposure levels were similar in the secukinumab groups up to the primary endpoint due to i.v. loading. Improvements in all primary and secondary endpoints were sustained through Wk 52. At Wk 52, ACR 20/50/70 responses, using an observed analysis, were 66.9%, 38.4% and 25.6% for 10 IV→75 SC and 69.5%, 50.0% and 28.2% for 10 IV→150 SC. In both TNF-naïve and TNF-IR groups, secukinumab demonstrated superiority at Wk 24 in ACR20/50/70, PASI 75/90, HAQ-DI, SF36-PCS, dactylitis and enthesitis at both doses and the effect was maintained through Wk 52. Secukinumab significantly inhibited radiographic structural joint damage at Wk 24 vs. PBO. AEs at Wk 16: 60.4% (10 IV→75 SC), 64.9% (10 IV→150 SC) and 58.4% (PBO); non-fatal SAE rates: 2.5%, 4.5% and 5.0%, respectively. Mean, median, and maximum exposures: 438.5, 456.0 and 721 days; AE/non-fatal SAE rates: 78.1%/8.6% and 82.4%/12.9% in pts who received secukinumab 75 mg s.c. or 150 mg s.c., respectively, at any point in the study.

Table Summary of selected 24-week efficacy results

Week 24 Data	Secukinumab 10 mg/kg IV → 75 mg SC	Secukinumab 10 mg/kg IV → 150 mg SC	PBO
ACR20 (% responders)	50.5*	50.0*	17.3
ACR50 (% responders)	30.7*	34.7*	7.4
ACR70 (% responders)	16.8*	18.8*	2.0
DAS28-CRP (mean change from BL) Overall (n=606)	–1.67*	–1.62*	–0.77
[a]Dactylitis (presence of, %) Overall (n=324)	43.3*	51.9*	84.5
[a]Enthesitis (presence of, %) Overall (n=372)	51.2*	54.0*	87.2

*P <0.0001 vs. PBO; [a]Data from pts with dactylitis (n = 324) and enthesitis (n = 372) at baseline. ACR, American College of Rheumatology response criteria; BL, baseline; DAS28-CRP, Disease Activity Score 28 using C-reactive protein; IV, intravenous; pts, patients; SC, subcutaneous

Conclusion: In this first phase 3 trial to evaluate highly selective IL-17A inhibition in pts with PsA, secukinumab provided rapid, clinically significant and sustained improvements in signs and symptoms, and inhibited joint structural damage. Secukinumab was well tolerated through 52 wks.

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Secukinumab, a Monoclonal Antibody to Interleukin-17A, Provides Significant and Sustained Inhibition of Joint Structural Damage in Active Psoriatic Arthritis Regardless of Prior TNF Inhibitors or Concomitant Methotrexate: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study.

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Background/Purpose: Approximately two-thirds of patients (pts) with psoriatic arthritis (PsA) experience progressive joint damage associated with varying degrees of disability. Here we present the 1-year effect of IL-17A inhibition with secukinumab on radiographic progression in pts with active PsA enrolled in a 2-year, multicenter, randomized, double-blind, placebo (PBO)-controlled, phase 3 trial (FUTURE 1; NCT01392326).

Methods: 606 adults with moderate to severe PsA were randomized to PBO or one of two secukinumab treatment arms: secukinumab 10 mg/kg i.v. followed by 75 mg s.c. (10 IV→75 SC) or 150 mg s.c. (10 IV→150 SC). All pts were assessed for joint response at Week (Wk) 16 (based on ≥ 20% improvement in tender and swollen joint counts). PBO-treated pts were re-randomized to secukinumab 75 or 150 mg s.c. at Wk 16 (non-responders) or Wk 24 (responders). The van der Heijde total modified Sharp scores (mTSS), and erosion and joint space narrowing (JSN) scores were determined at baseline, Wks 16/24 (depending on response) and Wk 52. The effect of secukinumab on radiographic progression from baseline to Wk 24 was evaluated using a non-parametric ANCOVA model, with linear extrapolation for pts who had x-ray assessments at Wk 16. Exploratory analyses assessed the proportion of pts with no structural progression (defined as change from baseline in mTSS ≤ 0.5) and maintenance of this effect over time.

Results: The changes from baseline in mTSS, erosion and JSN scores demonstrated that secukinumab-treated pts had significantly less progression from baseline to Wk 24 compared with PBO-treated pts, regardless of whether pts had received prior therapy with a TNF inhibitor, were on secukinumab monotherapy, or were receiving concomitant methotrexate (MTX; Table). Inhibition of joint structural damage was sustained with secukinumab through Wk 52. Analysis of PBO pts who switched to secukinumab showed a greater mean change from baseline in mTSS for the PBO group from baseline to Wk 24 (mean increase of 0.48) vs. the period from Wk 24 to Wk 52 when pts had been switched to secukinumab (mean decrease of –0.03), providing additional support for efficacy. Analyses of pts who had x-rays at both Wk 16/24 and 52 showed that the proportion of pts who experienced no progression from randomization to Wk 24 vs. the period from Wk 24 to Wk 52 was consistently high in the secukinumab groups: 92.3% vs. 85.8%, respectively, for 10 IV→75 SC and 82.3% vs. 85.7% for 10 IV→150 SC. In pts initially randomized to PBO, 75.7% had no progression from randomization to Wk 24 and this increased to 86.8% for the period from Wk 24 to Wk 52 following active treatment with secukinumab ($P<$ 0.05).

Table

Radiographic progression at Week 24 by treatment group

Week 24 (Mean change from baseline)	Secukinumab 10 mg/kg IV → 75 mg SC n = 202	Secukinumab 10 mg/kg IV → 150 mg SC n = 202	PBO n = 202
mTSS	0.02[†]	0.13[†]	0.57
Erosion score	0.08[†]	0.04[‡]	0.35
JSN score	–0.06[†]	0.10	0.23

TNF-naïve/IR	n = 142/n = 60	n = 143/n = 59	n = 143/n = 59
mTSS	–0.06†/0.21	0.15/0.10†	0.57/0.58
Erosion score	0/0.25	0.02/0.08‡	0.29/0.50
JSN score	–0.06†/–0.05	0.13/0.02	0.28/0.09
Concomitant MTX use, yes/no	**n = 122/n = 80**	**n = 121/n = 81**	**n = 125/n = 77**
mTSS	–0.07†/0.14	0.14/0.12	0.57/0.58
Erosion score	0.01†/0.17	0.04†/0.02	0.34/0.37
JSN score	–0.08/–0.03	0.10/0.10	0.24/0.21

†P <0.05 vs. placebo; ‡P <0.01 vs. placebo
JSN, joint space narrowing; mTSS, modified total Sharp score; MTX, methotrexate; TNF-naïve/IR, tumor necrosis factor inhibitor naïve/inadequate responder
P-values based on a non-parametric ANCOVA model.

Conclusion: In patients with active PsA, secukinumab significantly inhibited radiographic progression at 24 wks regardless of prior TNF inhibitor therapy status or concomitant MTX administration; inhibition was sustained through Wk 52.

Disclosure: D. van der Heijde, Consulting fees from AbbVie, Amgen, AstraZeneca, Augurex, BMS, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Vertex., 5, Director of Imaging Rheumatology bv, 9, Rsearch grants from AbbVie, Amgen, AstraZeneca, Augurex, BMS, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB, Vertex., 2; **R. B. M. Landewé**, Consulting fees from Abbott/AbbVie, Ablynx, Amgen, Astra-Zeneca, Bristol-Myers Squibb, Centocor, GlaxoSmithKline, Novartis, Merck, Pfizer, Roche, Schering-Plough, UCB, and Wyeth, 5, Research grants: Abbott, Amgen, Centocor, Novartis, Pfizer, Roche, Schering-Plough, UCB, and Wyeth, 2, Speaker fees: Abbott, Amgen, Bristol-Myers Squibb, Centocor, Merck, Pfizer, Roche, Schering-Plough, UCB, and Wyeth, 8, Director of Rheumatology Consultancy BV, which is a registered company under Dutch law, 9, Participation in advisory boards: Abbott/AbbVie, Ablynx, Amgen, Astra-Zeneca, Bristol-Myers Squibb, Centocor, GlaxoSmithKline, Novartis, Merck, Pfizer, Roche, Schering-Plough, UCB, Wyeth., 9; **P. Mease**, Research grants from AbbVie, Amgen, Biogen Idec, BMS, Celgene, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, and Vertex, 2, Consulting fees from AbbVie, Amgen, Biogen Idec, BMS, Celgene, Covagen, Crescendo, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, and Vertex, 5, Speakers' bureau for AbbVie, Amgen, Biogen Idec, BMS, Crescendo, Janssen, Lilly, Pfizer, and UCB, 8; **I. B. McInnes**, Consulting fees from Novartis, Amgen, Janssen, BMS, Pfizer, UCB, Abbvie, Celgene and Lilly, 5; **P. G. Conaghan**, Consulting fees from AbbVie, Janssen, Novartis, Pfizer and Roche, 5, Speakers' bureau for Abbvie, Merck, Pfizer, Roche and UCB, 8; **L. Pricop**, Novartis stock, 1, Employee of Novartis, 3; **G. Ligozio**, Novartis stock, 1, Employee of Novartis, 3; **H. Richards**, Employee of Novartis, 3; **S. Mpofu**, Novartis stock, 1, Employee of Novartis, 3.

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Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients with Psoriatic Arthritis: Pharmacodynamic Results of a Phase 3, Randomized, Controlled Trial. Peter Schafer[1], Peng Chen[2], Lorraine Fang[2], Andrew Wang[2] and Rajesh Chopra[1]. [1]Celgene Corporation, Summit, NJ, [2]Celgene Corporation, Warren, NJ.

Background/Purpose: Apremilast (APR) is a phosphodiesterase 4 inhibitor that helps regulate the immune response that causes inflammation and skin disease associated with psoriatic arthritis (PsA). PALACE 1 compared the efficacy and safety of APR with placebo in patients with active PsA despite prior conventional DMARDs and/or biologics. In this phase 3 trial, APR demonstrated significant efficacy, including improvement in signs and symptoms and physical function related to PsA, and demonstrated maintenance of response through Week 52. This exploratory analysis evaluated the pharmacodynamic effects of APR on plasma biomarkers associated with inflammation in a subset of patients.

Methods: Patients were randomized (1:1:1) to receive placebo, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline DMARD use (yes/no). Peripheral blood plasma samples were collected from consenting patients at baseline and at Weeks 4, 16, 24, and 40 for analysis in a multiplexed cytometric bead array assay measuring 47 proteins (Human Inflammation MAP, Myriad RBM, Austin, TX). The statistical analysis identified significant differences ($P<0.05$; rank ANCOVA) in the percent change from baseline among the treatment groups. Logistic regression analyses assessed the association between the percent change of the biomarkers and the achievement of an ACR20 clinical response.

Results: The biomarker subset included 150 patients (placebo: n=51; APR20: n=51; APR30: n=48). Subjects in the biomarker subset had demographics and disease characteristics comparable with those of the full analysis set, with the exception of prior exposure to a biologic DMARD such as a TNF blocker, which was higher in the biomarker subset (48.8%) than in the full analysis set (23.6%). In the APR20 and APR30 treatment arms, there were significantly lower percent changes from baseline, compared with placebo, for the following markers: at Week 4, interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), and macrophage inflammatory protein beta (MIP-1β); at Week 16, IL-8, TNF-α, IL-6, and ferritin; and at Week 24, IL-8, TNF-α, IL-6, MIP-1β, MCP-1, and ferritin. Logistic regression analyses indicated that clinical responses correlated with the percent changes in TNF-α in the APR20 and APR30 treatment groups. A significant increase in von Willebrand Factor (vWF) was observed at Weeks 16 and 24 (although all vWF values remained within the normal range [<120 μg/mL] and returned to baseline levels by Week 40). After 40 weeks of APR30 treatment, there were significant decreases in IL-17, IL-23, IL-6, and ferritin from baseline levels, and significant increases in IL-10 and IL-1 receptor antagonist from baseline levels.

Conclusion: Treatment with APR for 4 to 24 weeks was associated with significant reductions in circulating levels of IL-8, TNF-α, IL-6, MIP-1β, MCP-1, and ferritin, representing components of pro-inflammatory innate Th1 immunity. After 40 weeks, there was significant inhibition of IL-6, IL-23, and IL-17 on APR30 treatment, suggesting that long-term APR therapy inhibits components of the systemic Th17 immune response in patients with PsA.

Disclosure: P. Schafer, Celgene Corporation, 3; **P. Chen**, Celgene Corporation, 3; **L. Fang**, Celgene Corporation, 3; **A. Wang**, Celgene Corporation, 3; **R. Chopra**, Celgene Corporation, 3.

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Real-World Validation of the Minimal Disease Activity Index in Psoriatic Arthritis: An Analysis from the Prospective, Observational, Biological Treatment Registry Across Canada. Proton Rahman[1], Saeed Shaikh[2], Michael Starr[3], William Bensen[4], Denis Choquette[5], Wojciech Olszynski[6], Maqbool Sheriff[7], Michel Zummer[8], Emmanouil Rampakakis[9], John S. Sampalis[9], Allen J Lehman[10], Susan Otawa[10], Francois Nantel[10], Vincent Letourneau[10] and May Shawi[10]. [1]Memorial University of Newfoundland, St. John's, NF, [2]McMaster University, Hamilton, ON, [3]Montreal General Hospital, Montreal, QC, [4]Division of Rheumatology, McMaster University, Hamilton, ON, [5]Notre Dame Hospital, Montreal, QC, [6]University of Saskatchewan, Saskatoon, SK, [7]Nanaimo Regional General Hospital, Nanaimo, BC, [8]Université de Montréal, Montreal, QC, [9]JSS Medical Research, Montreal, QC, [10]Janssen Inc., Toronto, ON.

Background/Purpose: A definition of minimal disease activity (MDA) in PsA was derived from the opinion of 60 PsA experts including fulfillment of ≥5 of the 7 following criteria: tender joint count (TJC) ≤1, swollen joint count (SJC) ≤1, PASI ≤1 or body surface area ≤3%, pain (VAS) ≤15, patient global disease activity (PtGA) (VAS) ≤20, HAQ ≤0.5, and tender entheseal points ≤1 (1). The aim of this analysis was to describe the rate of MDA achievement over time and to assess the association between MDA achievement and DAS28 remission in PsA patients treated with anti-TNF in a routine clinical practice setting.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis (RA), ankylosing spondylitis (AS), or PsA with infliximab or golimumab as first biologics or after having been treated with a biologic for <6 months. Data from PsA patients treated with infliximab (enrolled in 2005–2013) or golimumab (enrolled in 2010–2013) who had available MDA information at baseline, 6 months, and/or 12 months were included. Improvement in patient parameters over time was assessed for statistical significance with the paired-samples t-test. Agreement between MDA and remission as defined by the DAS28 (<2.6) criteria was assessed with the sensitivity, specificity, as well as the positive (PPV) and negative (NPV) predictive value

Results: A total of 123 PsA patients with mean (SD) age of 50.5 (10.5) yrs and mean (SD) duration since diagnosis of 6.1 (7.3) yrs were included in this analysis, providing information from 340 assessments. At the time of enrollment in the registry, mean (SD) patient parameters were: DAS28 =4.2 (1.5), PASI =2.7 (4.8), SJC28 =4.1 (3.5), TJC28 =6.1 (5.6), morning stiffness =45.4 (43.0) min, health assessment questionnaire (HAQ-DI) =1.09 (0.65), physician global assessment of disease activity (MDGA) =5.3 (2.1), patient global assessment of disease activity (PtGA) =49.3 (27.3) mm, and pain =46.5 (25.2) mm. By 6 mos of treatment, statistically significant (P<0.05) improvements were observed in all clinical and patient outcome parameters studied, which were sustained or further enhanced over 12 months of treatment.

The proportion of patients with MDA significantly increased from 12.3% at baseline to 45.0% after 6 months of treatment (P<0.001), and 41.9% at 12 mos (P=0.021). Similarly, DAS28 remission was observed in 15.9%, 47.8% and 45.1% of patients at baseline, 6 mos, and 12 mos, respectively. Using DAS28 as reference standard, sensitivity was 69.8%, specificity 93.0%, NPV 88.2%, and PPV 80.4%.

Conclusion: MDA has high discriminatory power for remission as defined by the DAS28 criteria, while being more rigorous than DAS28. Furthermore, treatment with anti-TNF is effective in inducing MDA in 45% of patients as early as 6 mos from treatment initiation.

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Long-Term Evaluation of NT-Probnp Levels in Ankylosing Spondylitis Patients Under TNF Blockers: A Marker of Persistent Disease Activity?

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Background/Purpose: N-terminal pro-brain natriuretic peptide (NT-proBNP) is a strong marker of cardiovascular risk with recent evidence that short-term inflammation control reduces its levels in ankylosing spondylitis (AS) patients under TNF blockers. There are no data regarding long-term NT-proBNP assessment in AS patients using TNF blockers. Therefore, we evaluated longitudinally NT-proBNP in AS patients pre- and post-long-term TNF blockage therapy and its possible association with sustained disease activity.

Methods: Forty-eight consecutive AS patients (NY criteria) without previous/current cardiovascular disease or systolic myocardial dysfunction in echocardiography, who were eligible to anti-TNF therapy, were prospectively enrolled. All patients received TNF blockers (infliximab, adalimumab or etanercept) and they were evaluated for circulating NT-proBNP levels, clinical and laboratory parameters of disease activity including BASDAI, ASDAS, ESR and CRP, traditional cardiovascular risk factors including blood pressure, body mass index, waist circumference and treatment data at baseline (BL), 12 (12M) and 24 months-after (24M). Statistical analysis included: ANOVA test or Friedman test to observe differences at BL, 12M and 24M evaluations; Mann-Whitney test or t-test to observe differences between patients with inactive/moderate active and high/very high disease activity at 24M; and multivariable linear regression analysis. All analyses used significance level of 0.05.

Results: At BL, all patients had active AS. NT-proBNP levels had a median (IQR) of 23.5(8–53.7) pg/ml and 6.2% had high levels without any evidence of cardiac systolic dysfucntion. Multiple linear regression analysis revealed that this peptide, at BL, was independently correlated with ESR (p=0.003) and pulse pressure (p=0.025). Longitudinal evaluation after 12M and 24M showed that all disease parameters improved (p<0.05) and NT-proBNP levels significantly reduced [19(5–38) pg/mL and 14(5–35) pg/mL respectively, p=0.011]. Of note, NT-proBNP levels were higher in patients with persistent high/very high disease activity (ASDAS-CRP >2.1) at 24M (p<0.001) compared to inactive/ moderate active disease patients (ASDAS-CRP<2.1) at same time. Reinforcing this finding, this difference between these groups was present also at BL (p=0.024) and 12M (p=0.03). Further comparison of BL parameters of patients that persists with ASDAS-CRP >2.1 at 24M identified that these patients are older (44.6±12.7 vs. 35±9.9 years-old, p=0.007), more often female (53.3% vs. 21.2%, p=0.043) and they have higher body mass index (29±5.0 vs. 25.7±4.7 kg/m2, p=0.028), BASDAI (6.6±2.4 vs.5.1±1.9, p=0.02) and ASDAS-ESR (3.9±1.0 vs.3.1±0.9, p=0.006) at BL. Multivariate analysis did not show any independent factor related to higher ASDAS-CRP at 24M.

Conclusion: The novel finding of sustained higher long-term NT-proBNP levels in AS patients with persistent high/very high disease activity during anti-TNF therapy and without systolic alteration suggest that this parameter may reflect longitudinal inflammatory status. (ClinicalTrials.govnumber: NCT01072058).

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ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Lupus Nephritis

Sunday, November 16, 2014, 4:30 PM–6:00 PM

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The 10-Year Followup of Nephritis Trial Comparing Azathioprine and Mycophenolate Mofetil for Longterm Immunosuppression of Lupus Nephritis.

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Background/Purpose: Very longterm data are rarely reported in lupus nephritis (LN) trials, despite their pivotal importance to detect late poor renal outcomers and to identify early prognostic markers. Here we report the 10-year followup of the MAINTAIN Nephritis Trial, a randomized European-based open trial comparing azathioprine (AZA) and mycophenolate mofetil (MMF) as maintenance therapy of proliferative LN.

Methods: 105 patients suffering from Class IV or V LN were randomly assigned to receive AZA or MMF after induction therapy with glucocorticoids and intravenous (IV) cyclophosphamide (CY) (Euro-Lupus protocol; 6 × 500mg fortnightly). The primary endpoint was time to renal flare. After a mean followup of 48 months, we reported that 25 and 19% of patients experienced a renal flare in the AZA and MMF group, respectively (NS) (Houssiau *et al*., ARD 2010). In March 2014, we collected the 10-year data. Survival curves were drawn according to Kaplan-Meier method and statistically tested by logrank test. Other statistical methods were used as appropriate.

Results: Five patients died (3 MMF, 2 AZA), of whom 2 (1 MMF, 1 AZA) had reached ESRD. Two additional MMF patients developed ESRD. Out of the 105 patients, 41 suffered from at least one renal flare, without difference between the two groups (22 AZA, 19 MMF). Proteinuric and nephritic flares were equally distributed between groups. Time to renal flare (all, proteinuric and nephritic) did not differ (p=0.77; p=0.39; p=0.50). Out of the 100 living patients, 13 were lost-to-followup. For the 87 remaining patients, the mean (±SD) followup was 115 (±17) months. Additional IVCY was prescribed in only 17% of the patients, somewhat more frequently in the AZA group, although the difference was not statistically significant (p=0.2). Further use of MMF in the AZA group and further use of AZA in the MMF group occurred in 33 and 26% of the patients, respectively. Patients were classified as good or poor longterm renal outcomers if their creatinine at last followup was ≤120% (n=83) or >120% (n=21) of baseline value, respectively. Interestingly, while their baseline 24-h proteinuria did not differ, patients with good longterm renal outcome had a much lower 24-h proteinuria at 3, 6 and 12 months compared to patients with poor outcome (p<0.0001 by ANOVA). Results were similar if different definitions of poor longterm renal outcome were used (eGFR below 60ml/min/1.72m^{2}BSA, creatinine ≥1.0mg/dl or ≥1.4mg/dl). The positive predictive value of a uP/C ratio <0.5mg/mg at 3, 6 and 12 months for a good longterm renal outcome was excellent (89, 90 and 92%, respectively). By contrast, the negative predictive value was low (21, 29 and 32%, respectively), since many patients without an early proteinuria drop also achieved a good longterm renal outcome.

Conclusion: The longterm followup data of the MAINTAIN Nephritis Trial do not indicate that MMF is superior to AZA for renal flare prevention in a Caucasian population suffering from proliferative LN. Moreover, we

confirm the excellent positive predictive value of an early proteinuria drop for longterm renal outcome.

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Discoid Lupus Onset and Decrease Risk of Renal Disease in Patients with Systemic Lupus Erythematosus: Data from a Large Latin American Cohort. Guillermo J. Pons-Estel[1], Gaobin Bao[2], Bernado Pons-Estel[3], Daniel Wojdyla[4], Veronica Saurit[5], Alejandro J. Alvarellos[6], Francisco Caeiro[7], Emilia I. Sato[8], Enrique R. Soriano[9], Lilian Tereza Costallat[10], Oscar Neira[11], Antonio A. Iglesias-Gamarra[12], Gil Reyes Llerena[13], Mario Cardiel[14], Eduardo M. Acevedo-Vásquez[15], Rosa Chacon[16] and Cristina M. Drenkard[2]. [1]Department of Autoimmune Diseases, Institut Clìnic de Medicina i Dermatologia, Hospital Clìnic, Barcelona, Spain, [2]Emory University, Atlanta, GA, [3]Hospital Provincial de Rosario, Rosario, Argentina, [4]Universidad Nacional de Rosario, Argentina, Rosario, Argentina, [5]Hospital Privado de Córdoba, Córdoba, Argentina, [6]Hospital Privado Córdoba, Córdoba, Argentina, [7]Hospital Privado Centro Médico de Córdoba, Cordoba, Argentina, [8]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil, [9]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [10]Unicamp, Campinas, Brazil, [11]Univ of Chile Hosp Salvador, Santiago, Chile, [12]Professor-Universidad Nacional de Colombia, Bogota, Colombia, [13]Centro de Investigaciones Médico Quirúrgicas (CIMEQ), La Habana, Cuba, [14]Secretaría de Salud de Michoacán, Morelia, Mexico, [15]Hospital Nacional "Guillermo Almenara Irigoyen", Lima, Peru, [16]Hospital Universitario, Centro Nacional de Enfermedades Reumáticas and Hospital de Clínicas Caracas, Caracas, Venezuela.

Background/Purpose: Early data derived from small selected samples suggest that discoid lupus erythematosus (DLE) is negatively associated with renal involvement in patients with SLE. Recent findings from two large transversal studies are controversial, and the prognosis value of DLE on renal disease remains unclear. We used a longitudinal design to examine whether DLE onset protects against the development of LN in patients with systemic lupus erythematosus SLE from a large multiethnic Latin-American cohort.

Methods: We studied SLE patients enrolled in GLADEL, an inception longitudinal cohort from 34 centers in 9 Latin American countries. The main predictor was DLE onset, which was defined as physician-documented DLE that occurred before the diagnosis of SLE. The outcome was time from the diagnosis of SLE to LN during the followup. LN was defined by clinical or histological documentation of lupus glomerulonephritis or renal insufficiency secondary to LN. Kaplan-Meier analysis and Cox proportional hazard models were used to examine the association between DLE onset and time to LN.

Results: We examined 891 GLADEL SLE patients at risk (91% females and 56% non-Caucasians). The mean age at SLE diagnosis and mean duration of follow-up were 30.8 years (SD 12.6) and 4.3 years (SD 2.3), respectively. Overall, 56 patients had DLE onset, and 329 developed LN during the followup. Among the LN group, only 10 (3.0%) had DLE onset, compared to 46 (8.2%) in the group that remained free of LN ($p<0.0023$). The cumulative proportion of LN at 1- and 5-year since SLE diagnosis was 12% and 24%, respectively in the DLE onset group, compared to 23% and 42% in those without DLE ($p<0.0019$) (Figure). Table 1 shows that DLE onset was negatively associated with time-to-LN after controlling for potential confounders. The final predictive model shows that the hazard ratio (HR) of LN in patients with DLE onset was 0.47 (95% CI 0.23–0.96) after controlling sociodemographic factors and disease severity at diagnosis.

Conclusion: Our data from the largest Latin-American SLE cohort indicate that the presence of DLE before the diagnosis of SLE protects against further LN, independently of other contributing factors such as age, ethnicity and SLE severity. These findings have relevant prognosis implications to SLE patients and their clinicians. Further studies are warranted to unravel the biological and environmental pathways implicated in the protective role of DLE against renal disease in patients with SLE.

Figure. Cumulative Proportion of Lupus Nephritis by Discoid Lupus Onset in Patients with SLE

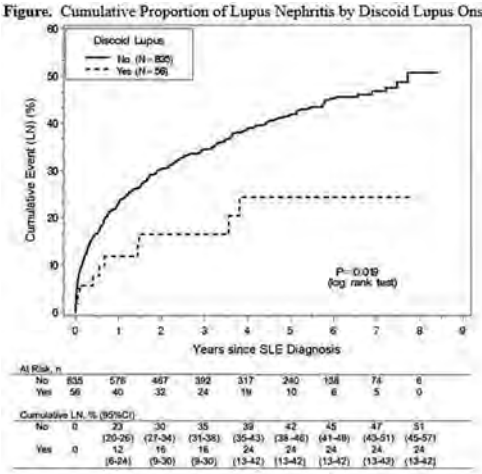

Table 1. Association of Onset Discoid Lupus with Time to Lupus Nephritis. Cox Proportional Models

Parameter	Model 1 DLE + Demographics		Model 2 DLE + Treatment		Model 3 DLE + Disease severity		Predictive Model	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Discoid lupus	0.42 (0.21-0.85)	0.015	0.47 (0.25-0.89)	0.019	0.53 (0.28-0.99)	0.047	0.47 (0.23-0.96)	0.038
Sociodemographics at diagnosis								
Age at diagnosis (5-year ↑)	0.92 (0.87-0.97)	0.0012					0.92 (0.87-0.97)	0.0020
Gender (female)	0.79 (0.55-1.14)	0.21						
Ethnicity (non-Caucasian)	1.57 (1.24-1.98)	0.0002					1.47 (1.14-1.90)	0.0032
Delay at diagnosis (6- month ↑)	0.99 (0.97-1.01)	0.33						
Education (3-year ↑)	0.96 (0.87-1.06)	0.41					0.90 (0.82-0.99)	0.026
Uninsured or underinsured	0.84 (0.67-1.05)	0.13						
Low socio-economic status	1.24 (0.95-1.63)	0.12						
Treatment prior to diagnosis								
Antimalarial drugs			0.75 (0.50-1.13)	0.17				
Immunosuppressant drugs			0.69 (0.28-1.69)	0.42				
Glucocorticoid, pulse			1.80 (0.80-4.08)	0.16				
Glucocorticoid, oral (≥60 mg/day)			1.08 (0.65-1.79)	0.77				
Disease severity at diagnosis								
SLEDAI (1-unit ↑)					1.03 (1.01-1.05)	0.0079	1.02 (1.00-1.04)	0.040
SDI (1-unit ↑)					1.18 (1.06-1.32)	0.0034	1.19 (1.05-1.34)	0.0047

Abbreviations: DLE=discoid lupus erythematosus; HR=hazard ratio; SLEDAI=Systemic Lupus Erythematosus Disease Activity Index; SDI= SLICC Damage Index

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Allogeneic Mesenchymal Stem Cell Transplantation for Lupus Nephritis Patients Refractory to Conventional Therapy. Dandan Wang, Huayong Zhang, Xuebing Feng and Lingyun Sun. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

Background/Purpose: Allogeneic mesenchymal stem cell transplantation (MSCT) has been shown to be clinically efficacious in the treatment of various autoimmune diseases. Here we analyzed the role of allogeneic MSCT to induce renal remission in patients with active and refractory lupus nephritis (LN).

Methods: This is an open-label and single-center clinical trial conducted from 2007 to 2010 in which 81 Chinese patients with active and refractory lupus nephritis were enrolled. Allogeneic bone marrow- or umbilical cord-derived mesenchymal stem cells (MSCs) were administered intravenously at the dose of one million cells per kilogram of bodyweight. All patients were

then monitored over the course of 12 months with periodic follow-up visits to evaluate renal remission, as well as possible adverse events. The primary outcome was complete renal remission (CR) and partial remission (PR) at each follow-up, as well as renal flares. The secondary outcome included renal activity score, total disease activity score, renal function and serologic index.

Results: During the 12-month follow-up, the overall rate of survival was 95% (77/81). Totally 60.5% (49/81) patients achieved renal remission during 12-month visit by MSCT. Eleven of 49 (22.4%) patients experienced renal flare by the end of 12 months after a previous remission. Renal activity evaluated by BILAG scores significantly declined after MSCT (mean±SD, from 4.48±2.60 at baseline to 1.09±0.83 at 12-month), in parallel with the obvious amelioration of renal function. Glomerular filtration rate (GFR) improved significantly 12 months after MSCT (mean±SD, from 58.55±19.16 mL/min to 69.51±27.93 mL/min). Total disease activity evaluated by SLEDAI scores also decreased after treatment (mean±SD, from 13.11±4.20 at baseline to 5.48±2.77 at 12 month). Additionally, the doses of concomitant prednisone and immunosuppressive drugs were tapered. No transplantation-related adverse event was observed.

Conclusion: Allogeneic MSCT resulted in renal remission for active LN patients within 12 months visit, confirming its use as a potential therapy for refractory LN.

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Outcome of Lupus Nephritis and Impact on Health Related Quality of Life: Results from an International, Prospective, Inception Cohort Study. John G. Hanly for the Systemic Lupus International Collaborating Clinics[1], Aidan O'Keeffe[2], Li Su[3], Murray B. Urowitz[4], Juanita Romero-Diaz[5], Caroline Gordon[6], Sang-Cheol Bae[7], Sasha R Bernatsky[8], Ann E. Clarke[9], Daniel J. Wallace[10], Joan T. Merrill[11], David A. Isenberg[12], Anisur Rahman[13], Ellen M. Ginzler[14], Paul Fortin[15], Dafna D. Gladman[4], Jorge Sanchez-Guerrero[16], Michelle A. Petri[17], Ian Bruce[18], Mary Anne Dooley[19], Rosalind Ramsey-Goldman[20], Cynthia Aranow[21], Graciela S. Alarcon[22], Barri Fessler[22], Kristjan Steinsson[23], Ola Nived[24], Gunnar Sturfelt[24], Susan Manzi[25], Munther A. Khamashta[26], Ronald F. van Vollenhoven[27], Asad Zoma[28], Manuel Ramos-Casals[29], Guillermo Ruiz-Irastorza[30], S. Sam Lim[31], Thomas Stoll[32], Murat Inanc[33], Kenneth C. Kalunian[34], Diane L. Kamen[35], Peter Maddison[36], Christine A. Peschken[37], Søren Jacobsen[38], Anca Askanase[39], Jill P. Buyon[40], Chris Theriault[41], Kara Thompson[41] and Vernon Farewell[3]. [1]Dalhousie University and Capital Health, Nova Scotia, Canada, Halifax, NS, [2]MRC Biostatistics Unit, Institute of Public Heath, Cambridge, United Kingdom, [3]MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Cambridge, United Kingdom, [4]University of Toronto, Toronto Western Hospital, Toronto, ON, [5]Instituto Nacional de Ciencias Médicas y Nutricion, Mexico city, Mexico, [6]Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, [7]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [8]Division of Rheumatology and Clinical Epidemiology, McGill University, Montreal, Quebec, QC, [9]Division of Rheumatology, University of Calgary, Alberta, Calgary, AB, [10]Cedars-Sinai/David Geffen School of Medicine at UCLA, Los Angeles, CA, [11]Department of Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [12]Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom, [13]University College London, London, United Kingdom, [14]SUNY-Downstate Medical Center, Brooklyn, NY, [15]Division of Rheumatology, Centre Hospitalier Universitaire de Quebec et Universite Laval, Quebec, QC, [16]Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital and University of Toronto, Toronto, ON, [17]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [18]Arthritis Research UK Epidemiology Unit, Institution of Inflammation and Repair, University of Manchester, NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [19]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, [20]Northwestern University and Feinberg School of Medicine, Chicago, IL, [21]Feinstein Institute for Medical Research, Mahasset, NY, [22]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [23]Center for Rheumatology Research, Landspitali University Hospital, Reykjavik, Iceland, [24]Department of Rheumatology, University Hospital Lund, Lund, Sweden, [25]Division of Rheumatology, University of Pittsburgh School of Medicine, Pittsburgh, PA, [26]Lupus Research Unit, The Rayne Institute, St Thomas Hospital, Kings College London School of Medicine, London, United Kingdom, [27]Unit for clinical therapy research (ClinTrid), Karolinska Institute, Stockholm, Sweden, [28]Lanarkshire Centre for Rheumatology, Hairmyres Hospital, East Kilbride, United Kingdom, [29]Josep Font Autoimmune Diseases Laboratory, IDIBAPS, Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Spain, [30]Autoimmune Diseases Research Unit, Department of Internal Medicine, BioCruces Health Research Institute, Hospital Universitario Cruces, University of the Basque Country, Barakaldo, Spain, [31]Emory University School of Medicine, Division of Rheumatology, Atlanta, GA, [32]Kantonsspital Geissbergstr, Schaffhausen, Switzerland, [33]Division of Rheumatology, Department of Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey, [34]UCSD School of Medicine, La Jolla, CA, [35]Medical University of South Carolina, Charleston, SC, [36]Ysbyty Gwynedd Bangor, North Wales, United Kingdom, [37]University of Manitoba, Winnipeg, MB, [38]Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [39]Columbia University Medical Center, New York, NY, [40]New York University School of Medicine, New York, NY, [41]Department of Medicine, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, NS.

Background/Purpose: Improved immunosuppressive therapies have changed the treatment of lupus nephritis (LN) over the past decade. We examined the outcome of LN with current standard of care in an inception cohort of SLE patients.

Methods: An observational study of new onset SLE was performed by an international network of 32 centers. Patients were evaluated at enrollment and annually. LN was identified as "renal disorder" (ACR classification criterion) and/or biopsy confirmation. Data included medications, estimated glomerular filtration rate (eGFR) and proteinuria (ePrU), end-stage renal disease (ESRD), SLE disease activity index-2000 (SLEDAI-2K) and Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index (SDI). GFR states were defined: state 1 (eGFR: >60 ml/min); state 2 (eGFR: 30–60 mL/min); and state 3 (eGFR: <30 ml/min). Similarly, PrU states were defined: state 1 (ePrU: <0.25 gr/day); state 2 (ePrU: 0.25–3.0 gr/day); and state 3 (ePrU: >3.0 gr/day). HRQoL was determined by SF-36 subscale, mental (MCS) and physical (PCS) component summary scores. Statistical analyses included analysis of variance or equivalent t-tests, Chi-squared test, regression and Kaplan-Meier curves.

Results: Of 1,827 SLE patients, 89% were female, 49.2% Caucasian with mean±SD age 35.1±13.3 years. At enrollment, mean SLE duration was 0.5±0.3 years, SLEDAI-2K was 5.4±5.4, SDI was 0.3±0.7. The mean follow-up was 4.6±3.4 years. LN occurred in 700/1,827 (38.3%) patients: 566 (31%) at enrollment and 134 (7.3%) during follow-up. It was more common in Hispanics (49.3%), African ancestry (39.9%) and Asians (36.8%) compared to Caucasians (20.3%) ($p<0.001$). Renal biopsies from 395 (56.4%) patients revealed ISN classes (%): I: 9 (2.4), II: 36 (9.5), III: 101 (26.8), IV: 163 (43.2), V: 121 (32.1) and VI: 3 (0.8); 21 and 34 biopsies had class III/V and IV/V respectively. At presentation, impaired renal function (eGFR <60 ml/min) occurred in 12.9% and proteinuria (ePrU of >0.25 gr/day) in 55.1% of patients with LN. Medications in LN patients were corticosteroids 651/700 (93%), antimalarials 517/700 (73.9%) and immunosuppressive (cyclophosphamide, azathioprine, mycophenolate mofetil) drugs in 614/700 (87.7%). At final follow-up 113/685 (16.5%) patients with LN had impaired renal function and 417/671 (62.1%) had proteinuria. Following LN the estimated 10 year incidence of ESRD was 10.1% (95%CI: (6.6%, 13.6%)) and there was a higher risk of death (HR=2.98, 95%CI (1.48, 5.99), $p=0.002$). Patients with eGFR <30 ml/min at diagnosis had lower SF-36 PCS scores ($p<0.01$) and lower Physical function, Physical role and Bodily pain scores. Over time, patients with abnormal eGFR and ePrU had lower SF-36 MCS ($p \leq 0.02$) scores compared to patients with normal values.

Conclusion: LN occurred in 38.3% of SLE patients, frequently as the initial presentation, in a large multi-ethnic inception cohort. Despite current standard of care, nephritis was associated with ESRD and death, and renal insufficiency was linked to lower HRQoL. New strategies are required to improve outcomes of lupus nephritis.

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A Systematic Review and Network Meta-Analysis of the Risk of Serious Infections with Immunosuppressives for Lupus Nephritis. Jasvinder Singh[1], Alomgir Hossain[2], Ahmed Kotb[2] and George Wells[3]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Ottawa, Ottawa, ON, [3]University of Ottawa Heart Institute, Ottawa, ON.

Background/Purpose: To compare the risk of serious infections of immunosuppressive medications used for the treatment of lupus nephritis.

Methods: We performed an up to date systematic review and network meta-analysis (NMA) by performing an updated search for randomized trails of immunosuppressive medications for lupus nephritis up to September 2013 with the help of Cochrane and ACR librarians. We updated the data from the systematic review for the 2012 ACR lupus nephritis treatment recommendations and the published Cochrane Review on lupus nephritis. We abstracted data related to infections from these trials. Bayesian network meta-analyses (NMA) were conducted. A binomial likelihood model, which allows for the use of multi-arm trials was used. Informed priors were assigned for basic parameters and odds ratios, as well as risk ratios and risk differences, and 95% credible intervals were modeled using Markov chain Monte Carlo methods. Brooks-Gelman-Rubin plots were used to assess model convergence. Model fit was examined using the deviance information criterion (DIC) and the residual deviance. The degree of inconsistency was assessed by comparing statistics for the deviance and deviance information criterion in fitted consistency and inconsistency models. In further sensitivity analyses, fixed effects models and models using vague priors were also conducted.

Results: 31 RCTs with 2, 442 patients provided data. There were twenty-five 2-arm, five 3-arm and one 4-arm trial. We found that tacrolimus was associated with significantly lower risk of serious infections compared to prednisone, cyclophosphamide, mycophenolate mofetil and azathioprine with a risk approximately one-third (**Table 1**). We also found that MMF-AZA (MMF followed by AZA) was associated with significantly lower risk of serious infections as compared to low dose CYC, high dose CYC or high dose prednisone, although this was based on fewer data (**Table 1**). Other differences between immunosuppressives did not reach statistical significance.

Conclusion: Tacrolimus and MMF-AZA combination were associated with lower risk of serious infections serious infections compared to other treatment options for lupus nephritis. These numbers can help patients make informed decisions about treatment options for lupus nephritis.

Table 1 Comparison of various drugs for the risk of infections in patients with lupus nephritis showing statistically significant results

Treatment	Reference	Odds Ratio (95% Credible Interval [CrI])	Relative Risk (95% CrI)	Risk Difference % (95% CrI)
TAC	PRED	0.30 (0.10, 0.86)	0.34 (0.11, 0.88)	−8.97 (−15.82, −1.46)
TAC	CYC	0.34 (0.13,0.87)	0.38 (0.14, 0.88)	−7.47 (−13.89, −1.26)
TAC	MMF	0.35 (0.14,0.82)	0.38 (0.16, 0.84)	−7.23 (−15.34, −1.53)
TAC	AZA	0.28 (0.09,0.81)	0.32 (0.11, 0.83)	−9.61 (−20.74, −1.73)
MMF-AZA	CYC LD	0.09 (0.01,0.80)	0.12 (0.01, 0.83)	−17.42 (−42.84, −2.08)
MMF-AZA	PRED HD	0.03 (0.00,0.59)	0.06 (0.01, 0.64)	−37.87 (−82.60, −3.54)
MMF-AZA	CYC HD	0.07 (0.01,0.56)	0.09 (0.01, 0.62)	−22.74 (−46.47, −6.14)

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Reduction in Proteinuria and Normalization of C4 Complement Levels Predict Response to Treatment of Lupus Nephritis with Low-Dose Pulse Cyclophosphamide and Abatacept. Sarah Goglin[1], David Wofsy[1], Miriam G. Cisternas[2] and Maria Dall'era[1]. [1]University of California, San Francisco, San Francisco, CA, [2]MGC Data Services, Carlsbad, CA.

Background/Purpose: The response to treatment of lupus nephritis is unpredictable. There is a need to identify clinical and biochemical characteristics that can predict treatment outcome in lupus nephritis. To do this, we utilized data from the Abatacept and Cyclophosphamide Combination: Efficacy and Safety Study (ACCESS) to identify predictors of renal response at 6 months in patients with lupus nephritis.

Methods: 134 subjects with class III or IV lupus nephritis were randomized to low-dose intravenous cyclophosphamide (IVC) or low-dose IVC with abatacept. Renal response was assessed at 24 weeks. Complete renal response (CR) was defined as: urine protein-to-creatinine ratio (UPCR) <0.5; serum creatinine (Cr) normal, or if abnormal, within 25% of baseline; and adherence to steroid taper regimen. Partial renal response (PR) was defined as: $>50\%$ improvement in UPCR; with the same parameters for serum Cr and steroid taper as CR. For the purposes of this analysis, we defined renal response as a composite of CR and PR. We identified possible predictors of renal response, including baseline demographic, clinical, laboratory, and histologic characteristics, as well as clinical and laboratory data obtained within the first 3 months of therapy. We calculated univariate odds ratios (ORs) and 95% confidence intervals (CIs) for renal response for each putative predictor, in the sample as a whole and within each treatment arm. We then conducted a multivariable logistic regression analysis, including all significant predictors (defined as $p<0.05$) from the univariate regressions.

Results: Reduction in proteinuria by at least 25% by week 12 was the strongest predictor of CR or PR at week 24 (OR 8.1; $p<0.05$). Normalization of C4 and normalization of C3 and C4 by week 12 were also predictive of renal response at week 24 (ORs 4.5 and 4.6 respectively; $p<0.05$). Reduction in proteinuria by at least 25% and normalization of C4 remained significant independent predictors in the multivariate analysis (ORs 13.3 and 3.6 respectively; $p<0.05$). This was independent of the treatment arm. None of the baseline characteristics was predictive of renal response.

Conclusion: This study demonstrates that a reduction of at least 25% in proteinuria at 3 months and normalization of C4 levels at 3 months independently predict renal response to therapy with low-dose IVC, with or without abatacept, at 6 months in patients with lupus nephritis. This supports previous findings from the Aspreva Lupus Management Study (ALMS), although reduction in proteinuria was a stronger predictor in this analysis. In contrast to the ALMS analysis, we did not find that time since lupus nephritis diagnosis or baseline eGFR were predictors of renal response. Future studies should address these and other, novel biomarkers so that we can more accurately predict which patients will respond well to treatment.

	Complete and Partial Responders	
Characteristic	Univariate model OR (95% CI)	Multivariate model OR (95% CI)
≥25% reduction in proteinuria from baseline		
No	–	–
Yes	8.1 (2.8–23.7)	13.3 (2.3–75.7)
Normalization of C3		
No	–	
Yes	2.2 (0.8–5.8)	
Normalization of C4		
No	–	–
Yes	4.5 (1.4–14.1)	3.6 (1.0–12.9)
Normalization of C3 and C4		
No	–	
Yes	4.6 (1.1–18.3)	
Normalization of anti-dsDNA antibody		
No	–	
Yes	0.7 (0.3–2.0)	

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ACR Concurrent Abstract Session
Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics I
Sunday, November 16, 2014, 4:30 PM–6:00 PM

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Skin Collagen Synthesis Rates Distinguish Between Early and Late Diffuse Scleroderma Patients. Claire Emson[1], Martin Decaris[1], Michelle Gatmaitan[1], Flora Luo[1], Dan Holochwost[1], Simplicia FloraCruz[1], Thomas Angel[1], Kelvin Li[1], Marc Hellerstein[1], Fredrick M. Wigley[2], Scott Turner[1] and Francesco Boin[2]. [1]KineMed Inc., Emeryville, CA, [2]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: The synthesis and degradation of extracellular matrix (ECM), particularly collagen, is one of the central mechanisms perturbed in scleroderma (SSc). Understanding the kinetics of this process can be of great value to define disease activity during the course of SSc and to develop better tools to assess with precision response to therapeutic interventions.

Methods: Using a stable isotope (deuterium) labeling method and a new kinetic proteomic approach designed to enrich for ECM, we assessed the turnover of collagen in the skin of SSc subjects. Moreover, we pursued the extraction of different collagen pools based on their solubility to measure kinetics of collagen subtypes and other matrix molecules. Three subpopulations were studied: limited (n=6), diffuse early-active (n=5) and diffuse late-stage SSc (n=6). Subjects were given heavy water for 3 weeks prior to a skin biopsy. Protein, lipid and cell kinetics were measured and correlated to gene array and histology from adjacent biopsies.

Results: Total collagen synthesis rates (% new collagen after 3 weeks of labeling) were significantly higher in late-stage diffuse SSc subjects (5.052%±1.953) compared to early-active (1.986%±0.8226; p=0.0031) or normal subjects (2.237%±0.6365; p=0.0031) demonstrating that fibrotic tissue in these subjects undergoes active remodeling. The microarray data showed that the higher collagen synthesis detected in late diffused patients is significantly associated with the expression of genes involved with fibrosis and cell cycle. When compared to total collagen synthesis rates, kinetic analysis of individual collagen pools revealed that the guanidine soluble collagen (corresponding to recently synthetized uncross-linked collagen and immature matrix) represented a greater proportion of the total collagen pool in the late diffuse subjects that have more established fibrosis.

Conclusion: This study shows that cutaneous fibrosis in late-stage SSc is not a static hypodynamic scarring but rather undergoes active remodeling with a pool of newly synthesized, uncross-linked collagen. These data emphasize that the biological processes and pathogenetic networks driving SSc skin involvement likely change over time with the different stages of the disease.

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Blockade of TLR4 Signaling By TAK242 Ameliorates Experimental Organ Fibrosis. Swati Bhattacharyya[1], Wenxia Wang[1], Zenshiro Tamaki[1], Yasuhiro Tsukimi[2], Masashi Yamasaki[2] and John Varga[3]. [1]Northwestern University, Feinberg School of Medicine, Chicago, IL, [2]Takeda Pharmaceutical Company Limited, Kanagawa, Japan, [3]Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Our recent studies implicate innate immune signaling through Toll like receptor 4 (TLR4) in scleroderma pathogenesis. Aberrant production and accumulation of the endogenous TLR4 ligand Fn-EDA drives TLR4-dependent persistent fibroblast activation and progressive fibrogenesis in scleroderma. The goal of these studies is to evaluate the antifibrotic potential of pharmacological TLR4 blockade in organ fibrosis.

Methods: For this study, we used TLR4 intracellular signaling inhibitor TAK242. The effect of TAK242 was investigated in normal dermal fibroblasts activated with TLR4 ligands or scleroderma fibroblasts by Western blot analysis, immunofluorescence and real-time qPCR; and in 3-D organotypic human skin equivalents reconstituted with scleroderma fibroblasts. The effect of TLR4 inhibition by TAK242 was examined *in vivo* by local subcutaneous injection of bleomycin (BLM) to induce dermal and pulmonary fibrosis in 6- to 8-week-old female mice (C57BL/6J).

Results: TAK242 treatment ameliorated dermal and pulmonary fibrosis and reduced the expression of pro-inflammatory and pro-fibrotic mediators in the skin of BLM-treated mice compared to vehicle-treated wildtype control mice. Importantly, TAK242 induced the regression of pre-established organ fibrosis. In vitro, TAK242 abrogated TLR4-induced stimulation of collagen synthesis and myofibroblasts differentiation in explanted normal skin fibroblasts, and in constitutively active scleroderma fibroblast populating 3D skin equivalents. The antifibrotic effects of TAK242 were accompanied by reduced activation of TLR4 signaling.

Conclusion: Our results provide evidence that specific TLR4 inhibitor TAK242 attenuates organ fibrogenesis both *in vitro* and *in vivo*. These findings identify TAK242 as a potential novel strategy for breaking the cycle of progressive fibrosis in scleroderma and other fibrotic diseases.

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Adiponectin Is an Endogenous Anti-Fibrotic and Target in Systemic Sclerosis: Novel Link Between Fibrosis and Metabolism. Feng Fang[1], Roberta G. Marangoni[1], Xingchun Zhou[2], Wen Hong[2], Boping Ye[2], Asano Yoshihide[3], Shinichi Sato[3], Yuri Masui[3], Chengning Zhang[1], Katja Lakota[1], Jun Wei[1], Monique E. Hinchcliff[1], Philipp Scherer[4], Laszlo Otvos[5] and John Varga[6]. [1]Northwestern University, Feinberg School of Medicine, Chicago, IL, [2]China Pharmaceutical University, Nanjing, China, [3]University of Tokyo, Tokyo, Japan, [4]University of Texas Southwestern Medical Center, Dallas, TX, [5]Temple University, Philadelphia, PA, [6]Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Systemic sclerosis (SSc) skin fibrosis is associated with attenuated cutaneous adipose tissue and adipogenic gene expression. Levels of the adipose-derived cytokine adiponectin (APN) and its receptors, are both reduced in SSc, and inversely correlated with extent of skin involvement. We investigated the role of APN in pathogenesis of skin fibrosis in mice with genetic APN gain- and loss-of-function, and determined the effects, mechanism and therapeutic potential of APN-derived synthetic peptides on the fibrotic process in vitro and in vivo.

Methods: Fibrotic responses were examined in human and mouse fibroblasts, skin organ cultures and 3D skin equivalents. Novel APN-derived peptides targeting APN receptors were designed and synthesized. Genetic and pharmacological manipulation of APN signaling was evaluated in mouse models of scleroderma.

Results: Mice lacking APN developed exaggerated cutaneous fibrosis and intradermal adipose loss upon bleomycin challenge. In contrast, ΔGly-APN mutant mice that have ~2-fold elevated levels of circulating APN were protected from fibrosis, and showed preferential expansion of intradermal adipose tissue. To directly evaluate the role of APN signaling in SSc fibrosis, recombinant APN, as well as synthetic APN-derived peptides were used. APN treatment of skin fibroblasts resulted in suppression of collagen synthesis, myofibroblast transformation and other fibrotic responses that were mediated via the energy-sensing enzyme AMP kinase. Synthetic APN-derived peptides targeting the APN receptors abrogated fibrotic responses in explanted fibroblasts, skin organ cultures and in 3D human skin equivalents. Daily treatment of mice with APN-derived peptides induced potent activation of AMP kinase in target organs in the absence of toxicity. Significantly, peptide treatment prevented, as well as reversed, bleomycin-induced cutaneous fibrosis.

Conclusion: We identified an important homeostatic role for the adipocyte-derived cytokine APN in negative regulation of collagen deposition and myofibroblast accumulation, highlighting a novel link between metabolism and skin fibrosis. Restoring impaired APN signaling in SSc (scleroderma) using synthetic APN-derived peptides might therefore represent a pharmacological approach to fibrosis therapy.

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Mir-145 Protects Against Skin Fibrosis *in Vivo* by targeting TGF-β Signaling. Serena Vettori[1], Christian Beyer[2], Matthias Brock[1], Naoki Iwamoto[1], Britta Maurer[1], Michelle Trenkmann[1], Astrid Jüngel[1], Renate E. Gay[1], Maurizio Calcagni[3], Gabriele Valentini[4], Steffen Gay[1], Joerg H. W. Distler[2] and Oliver Distler[1]. [1]Zurich University Hospital, Zurich, Switzerland, [2]Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Division of Plastic Surgery and Hand Surgery, University Hospital Zurich, Zurich, Switzerland, [4]Second University of Naples, Napoli, Italy.

Background/Purpose: *In vitro*, miR-145 exerts anti-fibrotic effects in systemic sclerosis (SSc) by downregulating TGF-β signaling. In turn, ectopic TGF-β downregulates miR-145 thereby optimizing TGF-β signaling pathways. In this study, we aimed to investigate whether therapeutic application of miR-145 could prevent fibrosis *via* regulation of TGF-β *in vivo*.

Methods: We used miR-145$^{-/-}$ (n=7–8), and mouse models of dermal fibrosis induced by either bleomycin (n = 6) or by adenoviral overexpression

of constitutively active TGF-β receptor type I (n = 3). MiR-145$^{-/-}$ mice and wild type controls were also treated with intradermal bleomycin, while a subset of bleomycin-induced dermal fibrosis mice were simultaneously treated with intradermal injections of a synthetic miR-145 designed for *in vivo* transfection. Dermal thickness, myofibroblast count (α-SMA staining on paraffin-embedded skin sections), and collagen content (hydroxyproline assay), were analyzed as outcomes of skin fibrosis. The expression of miR-145 and of miR-145 targets, TGFBR2 and SMAD3, was analyzed in mice treated with the synthetic miR-145 and in the mouse model of skin fibrosis induced by the constitutive activation of TGF-β receptor type I by real-time PCR.

Results: We found that miR-145$^{-/-}$ mice were more sensitive to the effects of bleomycin than wild type controls, as shown by a stronger increase of dermal thickness (2.04 versus 1.7 fold), α-SMA count (4.4 versus 3), and collagen content (1.82 versus 1.34; all $p < 0.01$). According to the anti-fibrotic effects shown by miR-145 *in vitro*, we expected to counteract bleomycin effects in C57BL/6 mice by the simultaneous administration of synthetic miR-145. Indeed, all explored outcomes improved in these mice, as compared to controls injected with a synthetic miR-scrambled: dermal thickness reduced from 1.7 to 1.27 fold, α-SMA count from 3.7 to 1.9, collagen content from 3.6 to 2.9; all $p < 0.01$. MiR-145 expression in mice injected with the synthetic miR-145 increased by 37 fold ($p < 0.01$) confirming the efficiency of the *in vivo* transfection. Accordingly, the downregulation of the previously identified direct miR-145 targets, TGFBR2 and SMAD3, by 0.21 and 0.10 fold ($p < 0.05$) supports the hypothesis that the anti-fibrotic effects of miR-145 are mediated by the downregulation of these TGF-β signaling components. Finally, in mice overexpressing constitutively active TGF-β receptor type I, miR-145 was strongly down-regulated by 0.55 fold in fibrotic skin as compared to mock-transfected controls, confirming the existence of a regulatory feedback loop between miR-145 and TGF-β *in vivo* and further proofing the relevance of the miR-145/TGF-β interaction *in vivo*.

Conclusion: Here we show for the first time that the therapeutic application of miR-145 protects against skin fibrosis *in vivo*, thus opening the road to new therapeutic targeted approaches to SSc and other fibrotic disorders. We also confirm on the *in vivo* level, that the anti-fibrotic effects of miR-145 are mediated by the downregulation of the TGF-β signaling components TGFBR2 and SMAD3, and that the abnormal miR-145 expression that is observed in SSc is dependent, at least in part, on activation of TGF-β.

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Priming of WNT Signalling during Fibrosis Is Mediated By TGF-β Induced Axin-2 Downregulation. Justin Gillespie[1], Emma C. Derrett-Smith[2], Michael McDermott[1], Paul Emery[3], Christopher P Denton[2] and Francesco Del Galdo[3]. [1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [2]UCL Medical School Royal Free Campus, London, United Kingdom, [3]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Background/Purpose: Systemic Sclerosis (SSc) is characterized by autoimmune activation, vasculopathy and tissue fibrosis. Recently, activation of the Wnt/β-catenin signaling pathway in SSc fibroblasts has been linked to the pathogenesis of SSc. However, the relative role of crosstalk between TGF-β and Wnt Pathways in SSc is still to be determined. Here we have aimed to evaluate the Wnt pathway in SSc fibroblasts and the effects of TGF-β on canonical Wnt signalling.

Methods: Dermal fibroblasts from 3 early diffuse cutaneous (dc)-SSc patients and 3 healthy controls (HC) were stimulated with recombinant human (rh)TGF-β and/or rhWnt-3a. mRNA stability was investigated using actimomycin D. mRNA levels were quantified by qRT-PCR and protein expression was measured by western blotting or immunohistochemistry. Canonical Wnt signaling was evaluated by TOPFlash luciferase reporter activity. *In- vivo*expression studies were performed on TGF-β-RII DeltaK transgenic mice, which have constitutive activation of the TGF-β pathway in fibroblasts, and wild-type littermates.

Results: In basal conditions, SSc fibroblasts did not show any increase in TOPFlash reporter activity compared to HC. On the contrary, the expression of *Axin2*, a Wnt target gene and negative regulator of the Wnt pathway, was reduced at both mRNA (58%; $P<0.01$) and protein levels. Indeed, SSc fibroblasts had an increased response to rhWnt-3a compared to HC fibroblasts (11.6 fold increase in TOPFlash activity and 2.5 fold in *Axin-2*mRNA vs. 4.2 and 1.8 fold, respectively, in HC). TGF-β treatment of HC fibroblasts decreased Axin-2 expression to levels similar to SSc fibroblasts, both at mRNA (38.7%; [$p<0.001$]) and protein levels. This effect was associated with a 3.7 fold increase in mRNA decay. Concordantly, TGF-β-RII DeltaK transgenic mice displayed a reduced expression of Axin-2 in the dermis. Similar to SSc, pretreatment of HC fibroblasts with TGF-β increased their responsiveness to Wnt-3a (16.1 vs. 7.7 fold increase in TOPFlash activity; $P<0.01$). Depletion of Axin-2 by siRNA was sufficient to mimic the effect of TGF-β pretreatment ($P<0.05$). Accordingly, XAV939-mediated Axin-2 stabilization ablated the Wnt-3a-induced canonical hyperactivation in 'TGF-β primed' fibroblasts.

Conclusion: TGF-β stimulation primes dermal fibroblasts to increase their responsiveness to Wnt ligand-induced canonical signaling. TGF-β mediates the downregualtion of Axin-2, which is required for canonical Wnt signaling hyperactivation in dermal fibroblasts. Our data suggest that the increased Wnt signaling observed in SSc is a consequence of TGF-β signaling and therefore targeting of the TGF-β pathway may also help to resolve the aberrant Wnt signaling observed in SSc.

Disclosure: J. Gillespie, None; **E. C. Derrett-Smith**, None; **M. McDermott**, None; **P. Emery**, None; **C. P. Denton**, None; **F. Del Galdo**, None.

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Caspase-8 Prevents Lung Fibrosis in a Murine SSc-like Disease Model By Preventing Macrophage Differentiation. Alexander Misharin[1], Carla M. Cuda[2], Luisa Morales-Nebreda[3], Gokhan Mutlu[1], GR Scott Budinger[3] and Harris R. Perlman[2]. [1]Northwestern University, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Northwestern University, Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Pulmonary fibrosis has emerged as the leading cause of death in patients with Systemic Sclerosis (SSc). Currently available therapies are only marginally effective in treating this devastating complication and even patients who respond to therapy are left with significant respiratory morbidity. Alternatively activated M2 macrophages have been demonstrated to be the key players in development of pulmonary fibrosis. Caspase-8 is a cysteine-aspartic acid protease was originally identified as a key initiator of the apoptotic death receptor pathway and was later found to suppress programmed necrotic cell death (necroptosis) by inhibiting the receptor-interacting serine/threonine kinase 1/3 (RIPK1/3). We have previously shown that mice deficient in caspase-8 specifically in macrophages and DCs have markedly less lung fibrosis than their littermate controls following intratracheal treatment with either bleomycin or an adenovirus encoding an active form of TGF-β. We now examined specific mechanisms, responsible for this protection.

Methods: Mice lacking caspase-8 specifically in DCs or macrophages were generated ($Cre^{CD11c}Casp8^{flox/flox}$ and $Cre^{LysM}Casp8^{flox/flox}$) and examined using the bleomycin and adenoviral TGF-β models of lung fibrosis. Flow cytometric analysis was used to characterize macrophages and DC. Luminex-based QuantiGene assay was used to determine gene expression profiles and polarization of FACS-sorted macrophages.

Results: We found that in the wild type mice, monocytes, recruited into the lung from the bone marrow after instillation of bleomycin, transition through the interstitial macrophage phase into alveolar macrophages, which are virtually indistinguishable from tissue-resident alveolar macrophages. However, unlike the tissue-resident macrophages, which do not exhibit profibrotic M2 phenotype, these bone marrow-derived alveolar macrophages were M2-polarized. Mice, deficient for caspase-8 in macrophages had similar number of interstitial macrophages to WT mice, but were lacking profibrotic M2 bone marrow-derived alveolar macrophages. Moreover, expression *Pparg*, *Tgm2*, *Shpk* and *Mertk*, which are important for mature alveolar macrophage phenotype, was decreased in Caspase-8-deficient bone marrow-derived alveolar macrophages.

Conclusion: Our data identified bone marrow-derived alveolar macrophages and not interstitial macrophages or tissue-resident alveolar macrophages as key players and perspective target for pulmonary fibrosis in patients

with scleroderma. Moreover, these data reveals a novel role for Caspase-8 in macrophage differentiation and polarization.

Disclosure: A. Misharin, None; **C. M. Cuda**, None; **L. Morales-Nebreda**, None; **G. Mutlu**, None; **G. S. Budinger**, None; **H. R. Perlman**, None.

ACR/ARHP Combined Session

ACR/ARHP Combined Abstract Session: Epidemiology and Public Health

Sunday, November 16, 2014, 4:30 PM–6:00 PM

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Risk of Developing Antiphospholipid Syndrome Following Infection: A Systematic Review and Meta-Analysis of Observational Studies. Noha Abdel-Wahab[1], Maria A. Lopez-Olivo[1], Saurabh Talathi[2] and Maria E. Suarez-Almazor[1]. [1]The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]The University of Texas Health Science Center at Houston, School of Public Health, Houston, TX.

Background/Purpose: Infection has been increasingly reported in the literature as an environmental trigger inducing the development of anti-phospholipid antibodies or antiphospholipid syndrome in genetically predisposed individuals. We conducted a systematic review and meta-analysis of observational studies to evaluate the risk of developing positive antiphospholipid (aPL) antibodies following infection compared to controls and determine whether these antibodies are associated with any clinical consequences.

Methods: We conducted a literature search using Medline, EMBASE, Web of Science, and the Cochrane CENTRAL databases with no language restriction to identify observational studies reporting on patients who develop positive aPL antibodies after infection from inception up to October 2013. Two independent reviewers assessed the studies for inclusion and for quality, and extracted relevant data. We extracted data on the related infection, profile and prevalence of aPL antibody, and patient clinical outcomes. We performed a meta-analysis and estimated relative risks (RR) with 95% confidence intervals (CI) of developing antibodies after an infection compared to controls

Results: From 2,257 unique citations, 320 publications met our inclusion criteria; from these, we selected 216 studies with controls to estimate risk. The most commonly reported infections were viral and bacterial. Compared to controls, patients with an infection were 10.9 times more likely to develop positive IgG anticardiolipin (aCL) antibodies after the infection (95% confidence Intervals (CI) 5.6–21.2). The highest risk ratio (RR) was observed after infection with tuberculosis (47.5; 95% CI 3.0–753.8), Q fever (44.0; 95% CI 2.8–702.5), and Hepatitis C virus infection (21.4; 95% CI 3.6–127.1). After an infection with Epstein Bar virus individuals were 33 times more likely to develop positive IgM aCL (95%CI 1.9–586.2) compared to controls. The RRs for developing lupus anticoagulant or and anti-β2 glycoprotein-I (GPI) antibodies were 2.4 (95% CI 1.3–4.5), and 2.3 (95%CI 1.2–4.4), respectively. For studies without controls (104), the pooled incidence of positive IgG aCL after infection was 36% (95% CI 27%-45%). The highest incidence was found in individuals with human immunodeficiency virus (HIV) (51%; 95% CI 38%-63%). Development of clinical manifestations of aPL syndrome was reported in 52.3% of the included studies. The most common manifestations were thromboembolic events or pregnancy related complications, occurring in 23.1% of individuals.

Conclusion: Various viral and bacterial infections can frequently induce the development of aPL antibodies, and can cause thromboembolic manifestations fulfilling the diagnosis of APS.

Disclosure: N. Abdel-Wahab, None; **M. A. Lopez-Olivo**, None; **S. Talathi**, None; **M. E. Suarez-Almazor**, None.

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The Long-Term Efficacy of an Anti-Pneumococcal Polysaccharide Vaccine (PPSV23, Pneumovax) Among Autoimmune Inflammatory Rheumatic Patients. Adi Broyde[1], Uri Arad[2], Noa Madar-Balakinski[2], Daphna Paran[3], Ilana Kaufman[4], Ira Litinsky[5], David Levartovsky[6], Irena Wigler[2], Dan Caspi[7] and Ori Elkayam[8]. [1]Tel Aviv medical center, Tel Aviv, Israel, [2]Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [3]Tel-Aviv Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel, [4]Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel-aviv, Israel, [5]Tel Aviv Sourasky Medical Ctr, Tel-Aviv University, Tel Aviv, Israel, [6]Department of rheumatology. Tel Aviv Medical Center, Tel Aviv, Israel, [7]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [8]Tel-Aviv Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

Background/Purpose: Vaccination with Pneumovax is recommended for adult patients with auto-immune inflammatory rheumatic diseases (AIIRD). Re-vaccination is recommended after 5 years in this population although reports on the long term efficacy of the vaccine are scarce.The objective of this study was to estimate the long term efficacy of anti-pneumococcal vaccine (PNEUMOVAX) using the surrogate marker of humoral response in patients with AIIRD on immune-suppressing therapy and the effect of clinical and demographic factors as well as treatment on the long term efficacy of the vaccine.

Methods: One hundred and forty five consecutive AIIRD patients (rheumatoid arthritis (RA) (48.5%), psoriatic arthritis (PsA) (22.3%), ankylosing spondylitis (AS) (21/5%), and IBD associated arthritis) (2.3%), (mean age 54.6, 61/5% women) treated with biologic therapy (TNF α or Il-6 receptor inhibitors) or Methotrexate (MTX) participated in this study. Data including the day of vaccination, demographic, clinical charasteristics and treatment was collected. Blood samples were drawn from each patient and tested for anti-pnemococcal antibody level

Results: 67.7% had received PNEUMOVAX, with a mean time from vaccination of 45 months. Treatment included TNF α inhibitors (73.9%), Il-6 receptor inhibitors (13.1%), or MTX without a biological treatment. (13%). The uptake of vaccination was significantly higher in the elderly population (>65 y). Vaccinated patients had significantly higher antibody levels compared with unvaccinated patients. After 10 years, we did not observe a decrease in the antibody levels. The use of MTX was associated with significant lower antibody levels whereas biologics – both TNF α blockers and tocilizumab-and low dose steroids showed not such tendency.

Conclusion: The long term efficacy of Pneumovax vaccination seems to be preserved among AIIRD patients for at least 10 years and its long term effect is not affected by the use of biologics while MTX might slightly impair it.. The actual recommendation for revaccination after 5 years should be reconsidered.

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Racial, Gender and Geographic Differences in Systemic Lupus Erythematous and Lupus Nephritis Mortality Rates in the Unites States, 1968–2010. Eric Y Yen[1], Magda Shaheen[2], Jennifer MP Woo[1], Deborah K. McCurdy[1] and Ram Raj Singh[3]. [1]UCLA Division of Pediatric Rheumatology, Los Angeles, CA, [2]Charles R. Drew University of Medicine and Science, Los Angeles, CA, [3]UCLA Division of Rheumatology, Los Angeles, CA.

Title: Racial, Gender and Geographic Differences in Systemic Lupus Erythematous and Lupus Nephritis Mortality Rates in the Unites States, 1968–2010

Background/Purpose: Many epidemiologic studies of systemic lupus erythematosus (SLE) mortality in the United States (US) utilize patient registries that are regional and may not be applicable to the general population. Our approach is to analyze comprehensive mortality data in the US over the past 43 years. We aimed to determine the variation of SLE and lupus nephritis (LN) mortality by race, gender, and geographic location.

Methods: Using county-level national mortality data from the National Center for Health Statistics from the period of 1968–2010 divided into 3 cohorts based on International Classification of Diseases periods for version 8 (1968–1978), 9 (1979–1998) and 10 (1999–2010), we estimated age-adjusted morality rates (AMR) per 100,000 persons and stratified results by gender, race, and geographic locations. We selected cases where the underlying cause of death was SLE (734.1, 710.0, M32) and further identified LN cases to include glomerular disease and renal failure.

Results: Of the 93,245,807 death records reviewed, we identified 46,786 cases of SLE. AMR-SLE were 3–5-fold higher in females than in males: 0.628 (95% CI 0.613–0.644), 0.748 (95% CI 0.737–0.759), and 0.700 (95% CI 0.688–0.712) among females; and 0.162 (95% CI 0.154–0.170), 0.176 (95% CI 0.170–0.182) and 0.134 (95% CI 0.128–0.140) among males for the periods of 1968–1978, 1979–1998, and 1999–2010 respectively. Intriguingly, while the AMR-SLE decreased among white males (from 0.149 in 1968–1978 to 0.107 in 1999–2010, $p<0.0001$) and remained stable among white females (0.496 to 0.499, $p=0.7$) over the last 43 years, it increased among black females and males (1.601 to 1.959 in females, $p<0.0001$; and 0.270 to 0.335 in males, $p=0.004$). Thus, black females had ~6-fold higher AMR-SLE than black males and ~10–18-fold higher than white males. To test whether differences in LN, a severe common manifestation of SLE, contributed to these differences, we analyzed mortality trends among 3,307 deaths (1999–2010) ascribed to LN. Black females had the highest AMR-LN at 0.473 (95% CI 0.445–0.501), which was ~5-fold higher than AMR-LN in black males and white females and 36-fold higher than in white males. Analyses of regional differences in AMR-LN showed even more dramatic racial trends, with black females living in the South census region with the highest AMR-LN of 0.507 (95% CI 0.468–0.547) and white males living in the Northeast census region with the lowest AMR-LN of 0.006, a 85-fold difference. While no regional differences in AMR-LN were observed for black males, AMR-LN was higher in the South than in the Northeast for white males, white females, and black females.

Conclusion: Overall SLE mortality has not substantially decreased from the 1968–1978 to the 1999–2010 periods, except in white males. In fact, SLE mortality has increased ~1.2-fold in blacks. Black females experience up to 18-fold higher mortality than white males. Increased deaths ascribed to LN in black females, particularly in southern states, might account for the profound racial differences in SLE outcome.

Disclosure: E. Y. Yen, None; **M. Shaheen**, None; **J. M. Woo**, None; **D. K. McCurdy**, None; **R. R. Singh**, None.

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Relation of Pelvic Drop during Walking to Risk of Incident Medial Knee Osteoarthritis: The Multicenter Osteoarthritis Study. K. Douglas Gross[1], Emily K. Quinn[2], Michael C. Nevitt[3], James C. Torner[4], Cora E. Lewis[5] and David T. Felson[1]. [1]Boston University School of Medicine, Boston, MA, [2]Boston University, Boston, MA, [3]UCSF (University of California, San Francisco), San Francisco, CA, [4]University of Iowa, Iowa City, Iowa City, IA, [5]The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: During walking, the contralateral pelvis tends to drop as the weight bearing limb enters midstance. If excessive, pelvic drop (PD) can result in increased loading of the medial knee. We previously reported an increased prevalence of medial knee OA in persons with greater PD, but while some rehabilitation strategies target reduction of PD in hopes of preventing knee OA onset, it is not yet known whether PD is actually a cause or a consequence of medial knee disease. The purpose of this longitudinal case-control study was to assess the causal relation of PD to 2-year risk of incident medial knee OA. We also determined the effect of trunk lean on this relationship.

Methods: The Multicenter Osteoarthritis Study (MOST) consists of middle aged and older adults living in Iowa or Alabama that have or are at risk of knee OA. Among knees with no medial OA at the 60-month exam, readers identified incident cases at 84 months as having Kellgren & Lawrence grade ≥ 2 with medial $>$ lateral joint space narrowing (0–3 scale) on fixed flexion knee x-ray (kappa > 0.80). Two control knees per case were randomly selected (1 per subject), and cases and controls underwent video assessment of PD during walking at the 60-month visit. Using synchronized frontal and sagittal cameras (60 Hz) and surface markers on the anterior superior iliac spines (ASISs), a physical therapist measured mean PD and mean trunk lean during the midstance phase of a mid-trial step over two self-paced walking trials. PD was measured as the frontal angle between the horizontal and a line joining left and right ASIS markers (ICC= 0.93), while trunk lean was measured as the frontal angle between the horizontal and a line joining left and right acromion processes (ICC= 0.98). Quartiles of PD were formed using the sex-specific distribution among cases, and logistic regression estimated the relative odds of incident medial knee OA in each quartile while controlling for covariates. Analysis was repeated within strata of ipsilateral ($\leq -0.1°$), neutral (0.0° to 6.4°), and contralateral ($\geq 6.5°$) trunk lean.

Results: 199 subjects contributed 64 case and 135 control knees. Mean +/− sd age, BMI, and walking speed was 66.8 +/− 8.3 yrs, 29.4 +/− 5.0 kg/m^2, and 1.18 +/− 0.17 m/sec, respectively. 60.3% were female, 85.4% were white, and 48.2% were seen in Alabama. Mean +/− sd PD was slightly greater in women, but comparable among case and control knees (2.5° +/− 2.6° vs. 2.3° +/− 2.8°, p= 0.66). Relative odds of incident medial knee OA did not change across PD quartiles (p trend = 0.89), and trunk lean did not modify the results (p = 0.92).

Conclusion: These findings do not confirm a longitudinal association between pelvic drop during walking and 2-year risk of incident medial knee OA. Previous reports of a cross-sectional association could indicate that pelvic drop is a frequent consequence of existing medial knee OA rather than an antecedent cause of incident knee disease.

Table. Relative Odds of Incident Medial Knee OA in Categories of Increasing Pelvic Drop During Walking

Pelvic Drop During Walking (sex-specific case-based quartiles)	Cases N = 64 n (%)	Controls N = 135 n (%)	Adj* Odds Ratio (95% CI)
Least Pelvic Drop (−3.9°, 1.0° men; −6.5°, 1.1° women)	15 (34.1%)	29 (65.9%)	1.0 (Reference)
2nd (1.1°, 1.9° men; 1.2°, 2.7° women)	16 (30.2%)	37 (69.8%)	0.8 (0.3, 1.9)
3rd (2.0°, 3.4° men; 2.8°, 3.9° women)	17 (33.3%)	34 (66.7%)	1.0 (0.4, 2.4)
Most Pelvic Drop (3.5°, 9.4° men; 4.0°, 10.2° women)	16 (31.4%)	35 (68.6%)	1.0 (0.4, 2.4)

* Adjusted for age, sex, BMI, race, clinic site, and walking velocity.

Disclosure: K. D. Gross, None; **E. K. Quinn**, None; **M. C. Nevitt**, None; **J. C. Torner**, None; **C. E. Lewis**, None; **D. T. Felson**, None.

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Obesity Paradox in Osteoarthritis Progression – What Effects Are We Measuring? Qiong Louie-Gao[1], Hyon K Choi[1], David T. Felson[2], Tuhina Neogi[1], Uyen Sa D.T. Nguyen[1], Na Lu[1] and Yuqing Zhang[1]. [1]Boston University School of Medicine, Boston, MA, [2]University of Manchester, Manchester, United Kingdom.

Background/Purpose: While obesity is a well-established risk factor for incident knee osteoarthritis (OA), it has a null association with OA progression. Among various potential explanations for such a paradox, one is a lack of precision in the research question. While investigators are interested in the total effect of BMI on OA progression among OA patients, most studies have instead measured a direct effect of BMI in the general population (Figure). This is because in these studies, data on BMI were assessed prior to OA diagnosis, or BMI measured after OA diagnosis has remained mostly unchanged compared with that prior to OA incidence. We have demonstrated this potential mechanism underlying the paradoxical findings of BMI in OA progression by decomposing its effect components (Figure) using mediation analyses.

Methods: Knee radiographs were taken at baseline and each annual follow-up visit, and severity of knee radiographic OA was assessed using Kellgren/Lawrence (KL) criteria among participants in the Osteoarthritis Initiative. We identified subjects who had no OA on either knee at baseline (i.e., KL <2) and used KL scores measured at 24-month and 36-month visits to assess radiographic OA progression. Baseline BMI was categorized as: <25, 25 –29.9 (i.e., overweight), and ≥ 30 kg/m^2 (i.e., obese). We first assessed the total effect of BMI on KL grade worsening at Month 36 (Figure). We then decomposed the effect into the indirect effect of BMI (i.e., the pathway through its effect on KL grade at Month 24) and the direct effect (i.e., the pathway not through its effect on KL grade at Month 24) (Figure), using marginal structural model mediation analyses. All analyses were adjusted for age, sex, knee injury, and education.

Results: Of 1930 subjects without knee OA on either knee (56% women, mean age 59 years) at baseline, 186 knees developed OA (e.g., 144 with KL=2, 41 with KL=3, and 1 with total knee replacement therapy) over 36 months. Compared with those with BMI <25, overweight and obese subjects had a 1.40 (95% CI: 1.13–1.73) and 1.95-fold (1.54–2.46) increased risk of KL grade worsening, respectively, after adjusting for potential confounders. Conditioning on the KL grade at Month 24, the indirect effects of being overweight and obese on OA progression were 1.38 (95% CI: 1.35–1.42) and 1.80 (1.75–1.86), respectively; however, the corresponding direct effects were 1.02 (0.81–1.29) and 1.10 (0.86–1.41), indicating that the effect of BMI on OA progression at Month 36 is entirely through its effect on OA progression at Month 24.

Conclusion: Our findings demonstrate that the paradoxical findings of BMI on the risk of OA incidence and OA progression are due to a mismatch between an intended total effect of BMI on OA and its direct effect in the

general population. To obtain the intended total effect of BMI on OA progression, one could use the change in BMI after OA diagnosis as an exposure for the outcome of OA progression.

Figure

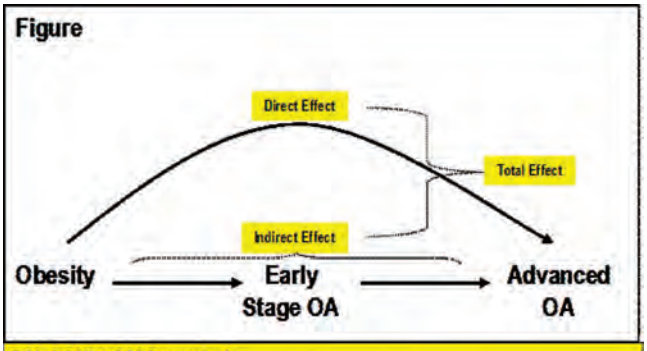

Table 1. BMI and OA Progression*

BMI	Baseline	Month 24	Month 36	Total effect	Direct effect	Indirect effect
< 25	1362	13(0.95%)	35(2.57%)	1.00	1.00	1.00
25-29.9	1540	54(3.51%)	81(5.26%)	1.40(1.13,1.73)	1.02(0.81,1.29)	1.38(1.35,1.42)
≥ 30	958	52(5.43%)	70(7.31%)	1.95(1.54,2.46)	1.10(0.86,1.41)	1.80(1.75,1.86)

*Adjusted for age, sex, knee injury, and education

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Chronic Pain Predicts Reduced Physical Activity in a Large Population Cohort Study. Kathryn Remmes Martin, Marcus Beasley, Gary J. Macfarlane and Daniel Whibley. University of Aberdeen, Aberdeen, United Kingdom.

Background/Purpose: Chronic musculoskeletal pain (CP) is associated with reduced levels of physical activity (PA), however few studies have examined the prospective nature of CP on PA at the population level. The aim of this study is to examine whether CP independently predicts a reduction in PA.

Methods: Data are from the UK Biobank, a large prospective cohort designed to support investigation of risk factors for major diseases of middle and old age. More than 500,000 men and women aged 40–69 were recruited between 2006–2010 (baseline); approximately 20,000 repeat assessments were conducted between 2012–2013 (follow-up). Participants answered questions on health and lifestyle by touch-screen questionnaire. CP is defined as self-reported pain lasting at least three months either all over the body or related to the neck or shoulder, back, abdomen, hip or knee, as well as facial pain or headache. Questions on PA and sedentary behaviour were asked using a modified short-form of the International Physical Activity Questionnaire at baseline and follow-up. PA was categorized as low, moderate or high according to frequency/duration of moderate and vigorous activity; PA change was calculated and dichotomized into same or improved activity category or worsened activity category. Hours spent watching TV and in non-work computer use were combined to estimate time in sedentary behaviour. Descriptive, linear and logistic regression analyses were conducted on 14,391 men and women with complete data on a priori covariates (age, gender, ethnicity, highest educational attainment, work status at follow-up, change in BMI status, baseline self-rated health, self-reported depression at follow-up and time-to-follow-up).

Results: Mean length of follow-up was 4 years (range 2.1–6.5). 5,567 participants (39%) had CP at baseline. Of those without CP at baseline, 20% (n=1,793) had developed it at follow-up. At baseline, fewer individuals with CP were categorized with moderate or high levels of PA (χ^2=12.5, p=0.002). Overall, the majority of participants maintained the same PA category, while 21% had an improved activity classification and 20% had a worsened activity classification. Individuals with CP at baseline were more likely to deteriorate in activity status, than those without, who were more likely to stay the same or improve activity status (χ^2=9.2, p=0.002). This relationship remained in multivariate logistic regression after adjustment for covariates, with baseline CP predicting a negative change in PA category (OR: 1.13; 95% CI: 1.04–1.23). Individuals with CP spent more time in sedentary behaviour than those without CP (B=0.07, 95% CI: 0.01–0.13) in linear regression analysis adjusted for covariates and baseline sedentary behaviour.

Conclusion: CP predicts a negative change in PA over an average four-year follow-up period. Given the prevalence and persistence of CP, attention should be given to supporting and encouraging physical activity so as to prevent deterioration of PA levels and the spiral of pain-related inactivity within middle-age and early old age adults with CP.

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ARHP Concurrent Abstract Session
Osteoarthritis
Sunday, November 16, 2014, 4:30 PM–6:00 PM

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Measurement Properties of the Health Assessment Questionnaire Disability Index (HAQ-DI) in Patients with Generalized Osteoarthritis (GOA). Nienke Cuperus[1], Elien A.M. Mahler[1], Thea Vliet Vlieland[2], Thomas Hoogeboom[3] and Cornelia H.M. van den Ende[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]CAPHRI school for public health and primary care, CCTR centre for Care Technology Research, Maastricht University, Maastricht, Netherlands.

Background/Purpose: The involvement of multiple joints is common in osteoarthritis (OA), often referred to as generalized OA (GOA). Individuals with GOA typically suffer from limitations of both upper and lower extremity function. However, existing instruments measuring functional limitations in OA focus on a specific localization; limiting their use in GOA. We hypothesized the Health Assessment Questionnaire Disability Index (HAQ-DI), originally developed for inflammatory arthritis, to be appropriate to measure functional limitations in GOA. Therefore we evaluated the measurement properties (content validity, construct validity and reliability) of the HAQ-DI in patients with GOA.

Methods: Data were used from a randomized clinical trial comparing the effectiveness of two multidisciplinary treatment program for patients with GOA. 137 patients completed a standardized set of questionnaires before and directly after treatment. The measurement properties of the HAQ-DI were assessed according the Consensus Based Standards for the Selection of health Status Measurement Instruments Checklist. Floor and ceiling effects for each HAQ-DI category at baseline were considered present if >15% of patients scored the worst (3) or best (0) possible score. For the content validity, 17 health professionals experienced with GOA were asked to judge the relevance of each HAQ-DI item. Construct validity was assessed by computing associations (Pearson r) between HAQ-DI scores and scores on other clinical (un)related measures. Reliability was assessed by Cronbach's alpha and intra-class correlation coefficient (ICC). The minimal important change (MIC) score was calculated using an anchor based method.

Results: Of 137 patients (mean age 60(SD 8) years; (85%) female), 93% reported to have complaints in both the upper and lower extremities. Floor and ceiling effects were present: 20%-30% of patients reported the best possible score on the HAQ-DI categories eating, dressing and gripping; 16% reported the worst possible score on the category hygiene. The content validity was questionable since according to the health professionals the HAQ-DI encompasses 9 (out of 20) activities that are not relevant or too easy to perform for GOA patients. Construct validity was rated positive given the moderate to strong associations with related constructs and weak associations with unrelated constructs. Cronbach's alpha was 0.90, confirming internal consistency and the ICC was 0.81, reflecting good reliability. The MIC was 0.25 points and the smallest detectable change was 0.60 indicating that important changes cannot be distinguished from measurement error in individuals.

Conclusion: The HAQ-DI showed a good construct validity and reliability to measure functional limitations in patients with GOA. Given the unsatisfactory content validity, we recommend an update of the HAQ-DI items when using the HAQ-DI in future clinical practice and research focusing on functional limitations in GOA. This update might also be worthwhile for RA and all other rheumatic diseases.

Disclosure: N. Cuperus, None; **E. A. M. Mahler**, None; **T. Vliet Vlieland**, None; **T. Hoogeboom**, None; **C. H. M. van den Ende**, None.

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Randomized Clinical Trial of a Patient and Provider Intervention for Managing Osteoarthritis in Veterans. Kelli D. Allen[1], Hayden B. Bosworth[2], Amy Jeffreys[1], Cynthia Coffman[2], Santanu Datta[2], Jennifer McDuffie[3], Eugene Oddone[2], Jennifer Strauss[3] and William S. Yancy Jr.[3]. [1]Durham VA Medical Center, Durham, NC, [2]Durham VA Medical Center and Duke University Medical Center, Durham, NC, [3]Duke University Medical Center, Durham, NC.

Background/Purpose: Adequate management of osteoarthritis (OA) requires both medical and behavioral strategies. However, some recommended therapies are under-utilized in clinical settings, and there is low use of behavioral strategies among patients. Consequently, interventions at the provider and patient levels both have potential for improving outcomes. The objective of this trial was to examine the effectiveness of a combined patient + provider intervention for managing OA in a primary care setting.

Methods: 300 patients with diagnoses of hip and / or knee OA at the VA Medical Center in Durham, NC (mean age = 61, SD = 11; 91% male; 50% non-white) were randomized to a combined patient + provider intervention for managing OA versus usual care. The 12-month, telephone-based patient intervention focused on weight management, physical activity and cognitive behavioral pain management. The provider intervention involved delivery of patient-specific recommendations for OA treatments (based on multiple sets of published guidelines and including non-pharmacological treatments such as physical therapy), delivered in the electronic medical record. The primary outcome was the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC), including the overall score (range: 0–96) and pain and function subscales. Secondary outcomes were objective physical function (Short Physical Performance Battery; SPPB, range: 0–20), weekly hours of any exercise and moderate or greater intensity exercise (Community Healthy Activities Model Program For Seniors or CHAMPS questionnaire) and depressive symptoms (Patient Health Questionnaire; PHQ-8, range: 0–24). Linear mixed models (LMM) were used to assess the difference in improvement in outcomes between the intervention and usual care groups, adjusting for clustering within physicians.

Results: At 12-month follow-up, WOMAC scores were 4.2 points lower in the intervention group vs. usual care [95% confidence interval (CI) = −7.2, −1.1; p=0.008], indicating improvement in symptoms and function. The WOMAC function subscale was 3.4 points lower in the intervention group compared to usual care [95% CI = −5.7, −1.0; p=0.005], but there was no significant difference in WOMAC pain subscale scores between groups (p=0.12). SPPB scores were 0.6 points higher in the intervention group than the usual care group [95% CI = 0.1, 1.2; p=0.02], indicating improvement in function. Weekly hours of exercise were also higher in the intervention group relative to the usual care group at 12-month follow-up: any exercise = 3.7 hours [95% CI = 1.5, 5.8; p=0.001] and moderate or greater intensity exercise = 1.6 hours [95% CI = 0.3, 2.9; p=0.02]. There was no significant difference between groups in PHQ-8 scores.

Conclusion: This combined patient and provider intervention improved physical function (self-reported and objectively assessed) and physical activity levels in patients with hip and knee OA. The telephone-based patient intervention is relatively low-cost and could be disseminated widely, and the provider intervention could be integrated in an automated manner within electronic medical record systems.

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Socioeconomic Status Measures Are Associated with Increasing Pain, Stiffness and Physical Function Among Individuals with Knee and Hip Osteoarthritis. Rebecca Cleveland[1], Jordan B. Renner[2], Joanne M. Jordan[3] and Leigh F. Callahan[4]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]University of North Carolina Department of Radiology, Chapel Hill, NC, [3]University of North Carolina Dept of Epidemiology, Chapel Hill, NC, [4]University of North Carolina, Chapel Hill, NC.

Background/Purpose: The determinants of disability progression (DP) among those with knee and/or hip osteoarthritis (OA) are not well known. Our aim was to explore whether socioeconomic status (SES) measures were associated with DP at follow-up (FU) in the Johnston County Osteoarthritis Project (JoCo OA).

Methods: Analyses were carried out among individuals with radiographic knee and/or hip OA (rOA) aged ≥45 years who participated in TIME 1 (T1; 1999–2004), which included those who entered the cohort during the original study enrollment who returned for their first follow-up, and new enrolls recruited for cohort enrichment. Follow-up was assessed at TIME 2 (T2 FU; 2006–2010). DP was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) which includes Pain, Stiffness and Physical Function Subscales. DP was defined as an increase from T1 to T2 FU of ≥10 in the WOMAC total score, or any increase in a subscale score. SES measures were education (no high school diploma [<HS] vs HS diploma or more [≥HS]), occupation (non-professional vs professional) and block group poverty (≥20% vs <20%). Odds ratios (OR) and 95% confidence intervals (CI) for associations between SES and DP were estimated using logistic regression simultaneously adjusting for other SES measures plus age, gender, hip and/or knee injury, BMI and smoking.

Results: There were 796 individuals with knee and/or hip rOA from T1 who returned at T2 FU. The mean age was 64.6 years, 66.3% were female, 30.7% African American, and mean BMI was 31.8 kg/m^2. At T2 FU, there was increased disability in 26.8% of individuals with knee rOA and 21.8% of individuals with hip rOA. Analyses including all individuals with knee and/or hip rOA showed that individuals with <HS education were more likely to have developed disability by T2 FU (OR=1.96, 95% CI=1.28–3.00) when compared with those ≥HS education (Table 1). Slightly stronger associations were seen when evaluating the effect of education among those with only knee rOA, where those with <HS education had nearly a three-fold increase in odds of having an ≥10 point increase in WOMAC score at T2 FU (OR=2.86, 95% CI=1.45–5.67). Among those with only hip rOA, having a non-professional occupation was associated with an increase in WOMAC disability, an association that narrowly missed statistical significance (OR=1.96, 95% CI=0.98–3.91). Across individual subscales, education was consistently associated with all subscales among those with only knee rOA, and occupation was associated with subscales among those with only hip rOA.

Conclusion: We report that individuals with lower education and non-professional occupation were more likely to have DP from T1 to T2 FU, associations that remained after adjustment for other SES measures. Our results suggest that SES may have an influence on DP, findings which may help clinicians in develop personalized OA management programs for individuals with low SES measures.

Table 1 Adjusted[†] odds ratios (OR) and 95% confidence intervals (CI) for the association between SES measures and WOMAC score increase between the first and second follow-up

	Knee and/or Hip rOA OR (95% CI)[‡] n=796	Only Hip rOA OR (95% CI)[µ] n=289	Only Knee rOA OR (95% CI)[¥] n=317
WOMAC Total Increase ≥10			
<HS Education[€]	**1.96 (1.28–3.00)**	1.59 (0.75–3.37)	**2.86 (1.45–5.67)**
Non-Professional Occupation[¶]	1.10 (0.74–1.64)	1.96 (0.98–3.91)	0.80 (0.43–1.51)
Block Group Poverty >20%[?]	1.07 (0.74–1.55)	1.26 (0.66–2.39)	1.02 (0.56–1.83)
WOMAC Stiffness Increase			
<HS Education[€]	1.30 (0.85–1.97)	0.81 (0.37–1.78)	**2.18 (1.13–4.20)**
Non-Professional Occupation[¶]	0.99 (0.68–1.45)	**2.03 (1.03–4.01)**	0.59 (0.32–1.07)
Block Group Poverty >20%[?]	0.87 (0.61–1.25)	0.97 (0.51–1.85)	0.93 (0.53–1.64)
WOMAC Pain Increase			
<HS Education[€]	**1.50 (1.01–2.21)**	1.34 (0.67–2.67)	**2.09 (1.11–3.96)**
Non-Professional Occupation[¶]	1.08 (0.76–1.53)	**1.86 (1.01–3.43)**	0.71 (0.40–1.24)
Block Group Poverty >20%[?]	0.90 (0.64–1.25)	1.12 (0.63–1.97)	0.72 (0.42–1.24)
WOMAC Physical Function Increase			
<HS Education[€]	**1.50 (1.02–2.20)**	1.00 (0.50–1.98)	**2.65 (1.40–5.00)**
Non-Professional Occupation[¶]	1.13 (0.80–1.60)	**1.90 (1.04–3.47)**	0.72 (0.41–1.26)
Block Group Poverty >20%[?]	0.83 (0.60–1.15)	0.69 (0.39–1.23)	1.05 (0.61–1.80)

[†]Mutually adjusted for education, occupation, poverty
[‡]Additionally adjusted for age, gender, hip & knee injury, BMI and smoking
[µ]Additionally adjusted for age, gender, hip injury, BMI and smoking
[¥]Additionally adjusted for age, gender, knee injury, BMI and smoking
[€]Comparing <HS education vs. ≥HS education
[¶]Comparing non-professional occupation vs. professional occupation
[?]Comparing block group poverty ≥20% vs. <20%

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Genome-Wide Association Study for Severe Radiographic Knee Osteoarthritis. Youfang Liu[1], Michelle Yau[2], Laura Yerges-Armstrong[3], Braxton Mitchell[3], Rebecca D. Jackson[4], Marc C. Hochberg[3], Shad Smith[1], William Maixner[1], Luda Diatchenko[5] and Joanne M. Jordan[6]. [1]University of North

Carolina, Chapel Hill, NC, [2]University of Maryland, Baltimore, MD, [3]University of Maryland School of Medicine, Baltimore, MD, [4]The Ohio State University, Columbus, OH, [5]McGill University, Montreal, QC, [6]University of North Carolina Dept of Epidemiology, Chapel Hill, NC.

Background/Purpose: Knee osteoarthritis (OA) is a heritable common joint disorder. In previously reported genetic studies, cases were usually defined with a radiographic Kellgren and Lawrence (K/L) grade ≥2. Since more severe knee OA is more likely to have greater medical and public health impact, we searched for genetic variations associated with severe radiographic knee OA (rKOA) of K/L grade 3 or 4.

Methods: Caucasian participants with knee radiographic grade from the Johnston County Osteoarthritis Project (JoCo) were included in this analysis. Cases were defined as the subjects with KL grade ≥3 in at least one knee, while the controls were defined as the subjects with KL grades = 0 in both knees. Genome wide genotyping was completed using the Illumina Infinium 1M-Duo array and imputed into 2.5M using HapMap II Caucasian as the reference data. Genome-wide association analysis was performed using logistic regression with adjustment for age and sex, with and without additional adjustment for BMI.

Results: Of 672 participants [64% women, mean age = 64.2 (SD=10.6), mean BMI = 30.3(SD=6.4)], 353 were cases and 319 were controls. Although no SNPs reached genome-wide significant p-values at 5E-8, we identified two SNPs with p-values less than E-06 in the model without BMI adjustment (table). After BMI adjustment, associations were attenuated but still statistically significant (table). Both SNPs, rs11196174 and rs11196175, are located in the TCF7L2 gene which encodes a T-cell specific transcription factor participating in the Wnt signaling pathway, which has been shown to be related to OA.

Conclusion: Two SNPs, rs11196174 and rs11196175, located in the TCF7L2 gene were associated with severe rKOA, supporting the possibility that the pathogenesis of severe rKOA may be through the Wnt signaling pathway. Further studies will need to validate this finding in other populations.

							W/O BMI adjustment		With BMI adjustment	
SNP	Gene	A1	A2	Freq1	Chr	Position	Beta	P-value	Beta	P-value
rs11196174	TCF7L2	A	G	0.69	10	114724086	0.82	5.4E-07	0.70	9.2e-05
rs11196175	TCF7L2	C	T	0.31	10	114726604	−0.81	3.9E-07	−0.71	6.0e-05

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Annual Medical Care Expenditures Among US Adults with Osteoarthritis, 2008–2011. Miriam G. Cisternas[1], Louise Murphy[2], David J. Pasta[3], Daniel H. Solomon[4] and Charles G. Helmick[2]. [1]MGC Data Services, Carlsbad, CA, [2]Centers for Disease Control and Prevention, Atlanta, GA, [3]DMA Corporation, Palo Alto, CA, [4]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: As the US population ages, concerns continue to grow about the cost of medical treatment for osteoarthritis (OA). We estimated all-cause medical care expenditures and OA-attributable expenditures among US adults with OA age ≥ 18 years.

Methods: We identified adults with OA in the 2008–2011 Medical Expenditure Panel Survey (MEPS). Adults were defined as having OA if (1) ICD-9-CM 715 was present, or (2) ICD-9-CM 716 or 719 was present along with self-reported doctor-diagnosed arthritis that excluded rheumatoid arthritis. We estimated annual national total (aggregate) and mean per-person all-cause and OA-attributable expenditures overall and for four expenditure categories: ambulatory care (office-based and hospital outpatient); inpatient care; prescriptions; and other (emergency room visits, home health care, vision aids, dental visits, and medical devices). OA-attributable expenditures were calculated using multi-stage regression models that adjusted for demographics (age, sex, race, Hispanic ethnicity, and education), health insurance coverage (any private, public only, or none), and 9 costly comorbid conditions. The increment was our estimate of expenditures that would be expected if those with OA did not have the condition by applying the parameter estimates from the models of those without OA to the data from those with OA. Estimates are in 2011 US dollars.

Results: National total all-cause medical care expenditures among the 30.8 million adults reporting OA were $328.2 billion; mean per-person expenditures among US adults with OA were $10,654, compared to $4,884 for all adults. Across expenditure categories, all-cause mean per-person expenditures were: ambulatory care ($3,354), inpatient ($3,320), prescriptions ($2,546), and other ($1,434). National OA-attributable expenditures totaled $62.1 billion (mean per person=$2,017) and accounted for 6% ($62.1 billion/$1,122.0 billion) of all medical expenditures for US adults. Mean per-person OA-attributable expenditures followed the same order as all-cause expenditures: ambulatory care ($754), inpatient ($544), prescriptions ($348), and other ($185).

Conclusion: Mean per-person all-cause medical expenditures were more than double for adults with OA compared to the entire adult population. Total annual national medical expenditures attributable to OA were $62.1 billion, accounting for 6% of medical expenditures for US adults. The increasing prevalence of obesity and continued aging of the population suggest that medical expenditures for treating OA will increase in the future. Underused interventions such as weight management, physical activity, and self-management education may mitigate its adverse effects on symptoms and function.

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The Effect of Compression Gloves in Hand Osteoarthritis: A Pre-Post-Test Trial. Alison Hammond[1], Yeliz Prior[1], Vivienne Jones[1], Mary Dooley[2], Yvonne Hough[3] and Angela Jacklin[4]. [1]University of Salford, Greater Manchester, United Kingdom, [2]Southport & Formby District Hospital, Southport, United Kingdom, [3]St Helens Hospital, St Helens, United Kingdom, [4]Stepping Hill Hospital, Stockport, United Kingdom.

Background/Purpose: Compression gloves are used in Hand Osteoarthritis (HOA) to reduce pain (day and/or night), stiffness and improve hand function. A systematic review identified only two trials (sample sizes n= 2 and 5), with inconclusive results [1]. The commonest compression gloves provided in the UK are Isotoner gloves. The aim was to evaluate effects of compression gloves on hand pain, stiffness and function.

Methods: A pre-post-test trial was conducted. Participants were recruited from 10 Rheumatology Occupational Therapy (OT) departments; had a doctor diagnosis of HOA and no steroid injections or new/changed medication within the previous 4 weeks. Assessments at 0 and 4 weeks included: hand pain on activity and at night, hand stiffness (all 0–10 numeric rating scales: none to very severe); Measure of Activity Performance of the Hand [MAP-HAND, 2]; Grip Ability Test [GAT, 3]; and composite finger flexion to distal wrist crease (CFF). OT assessors were trained in standardised hand assessment procedures. Assessor inter-rater reliability (ICC,10) was good: CFF (0.76–0.93); GAT (0.98) [4]. All participants received Isotoner ¾ finger gloves. Data were analysed using paired t-tests and effect sizes calculated using eta-squared (values of 0.14+ = large effect, 5).

Results: 30 people with HOA participated: 28 women, 2 men); average age = 61.23(SD 8.35) years; time since diagnosis 4.71(SD 6.47)years. (Right hand data presented below).

Mean(SD)	0 weeks	4 weeks	p	Effect size
Hand pain on activity	7.30 (1.61)	6.22 (1.99)	0.008	0.24
Hand pain at night	6.56 (2.10)	4.19 (2.20)	0.000	0.45
Hand stiffness	7.22 (1.74)	5.85 (2.14)	0.01	0.44
MAP-HAND	25.33 (7.08)	24.03 (7.87)	0.14	0.07
GAT	40.05 (12.04)	33.14 (13.10)	0.000	0.50
CFF Index (cms)	6.84 (2.17)	6.44 (2.33)	0.05	0.14
CFF Middle (cms)	5.72 (2.23)	5.29 (2.25)	0.03	0.17

Conclusion: This study demonstrates, for the first time, that compression gloves used by people with HOA led to significant improvements in: pain during the day and night, stiffness, hand function and finger motion, with moderate to large effect sizes. A limitation was the lack of a control group meaning we cannot be certain benefits were due to compression gloves. A randomised controlled trial needs to be conducted, including longer follow-up.

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2. Paulsen et al (2010) J Rehabil Med 42:636–644;
3. Dellhag & Bjelle (1995) J Rheumatol 22:1559–65;
4. Hammond et al (2014) Rheumatology 53(suppl 1):i124;
5. Cohen (1988) Statistical power for the Behavioural Sciences (Ehlrbaum).

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Identification of Potential SERUM Autoantibody Biomarkers in Rheumatic Diseases Using a New Generation of Protein Arrays. Lucia Lourido[1], Juan Fernandez-Tajes[1], Valentina Calamia[1], Carolina Fernandez-Costa[1], Beatriz Rocha[1], Patricia Fernandez-Puente[1], Jesus Mateos[1], Carlos Fernandez-Lopez[1], Natividad Oreiro-Villar[1], Manuel Fuentes[2], Francisco J. Blanco Garcia[1] and Cristina Ruiz-Romero[1]. [1]Grupo de Proteomica-PBR2-ProteoRed/ISCIII-Servicio de Reumatologia. Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC). As Xubias, 15006., A Coruña, Spain, [2]Centro de Investigación del Cáncer/IBMCC (USAL/CIC), IBSAL, Departamento de Medicina, Unidad de Proteomica Servicio general de Citometría, Universidad de Salamanca, Salamanca, SPAIN., Salamanca, Spain.

Background/Purpose: Osteoarthritis (OA) is characterized by the loss of structural components from the extracelullar matrix (ECM) of articular cartilage. The progressive release of proteins from the tissue and an abnormal metabolic activity can be specifically detected by the immune system, leading to a humoral immune response producing immunoglobulins against these proteins (autoantibodies). Autoantibodies are stable circulating proteins, easily measurable in serum, and may be the signature before clinical manifestations of the disease. Protein microarrays have emerged providing a tool for the identification of disease immunosignatures. The aim of this study was to detect the presence of autoantibodies in OA serum samples and compare these results with those obtained from healthy (CTRL) and rheumatoid arthritis (RA) sera using nucleic acid programmable protein arrays (NAPPA).

Methods: Antibodies were detected using NAPPA constructed as previously described by Ramachandran *et al*. 2008, containing 80 sequence-verified full-length human genes obtained from the Center for Personalized Diagnostics at the Arizona State University (www.dnasu.org) and selected by their possible relevance in OA disease. Once the 80 different proteins were displayed by *in situ* protein expression system, NAPPA arrays were incubated in optimized conditions with 20 OA, 20 RA and 18 CTRL serum samples. The autoantibodies were detected using an antibody against human IgGs fluorescently labelled. Array images were obtained and processed by Genepix4000B and GenePix Software 6.0. For data analysis, normalization across all the arrays was performed.

Results: Significantly ($p<0.05$) 4 different autoantibodies against four different proteins have been observed to be higher in OA compared to CTRL samples. Of note, 2 of these proteins are related to the metabolism of ECM (CHST14, PCOLCE); the others are associated to cell adhesion (CD44) and bone mineralization (LEP). We also observed that IL6 autoantibody levels distinguish RA and CTRL samples. Most interestingly, this approach allowed the differential classification of RA and OA patients by the detection of 3 specific autoantibodies against proteins involved in cell proliferation (IGFBP4, IGFBP6); and bone mineralization processes (LEP) whose levels are increased in OA compared to RA, one of these proteins (LEP) also distinguishing between CTRL and OA subjects.

Conclusion: We have identified the presence of specific autoantibodies in OA allowing to characterize differential autoantibody profiles between OA and CTRL patients and most interestingly, between OA and RA patients. These autoantibodies released to the serum might have a biomarker value to more accurate diagnosis and prognosis of OA patients in clinical routine.

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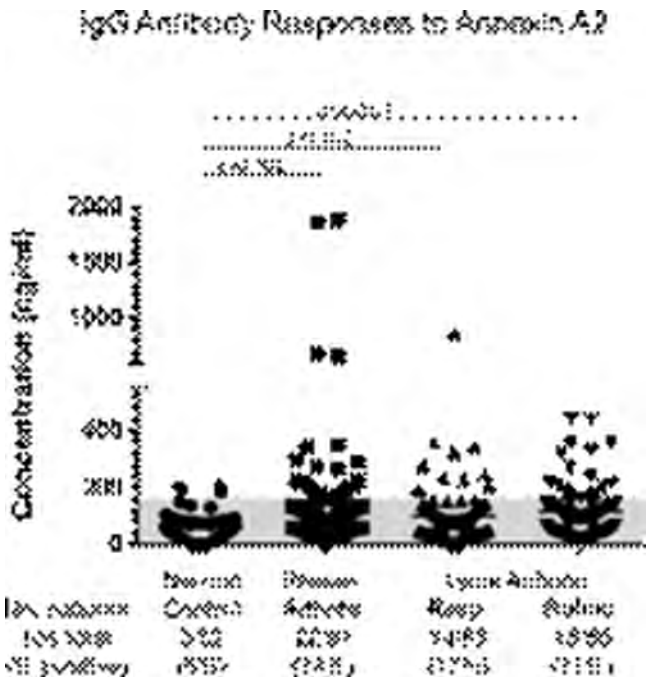
Identification of Annexin A2 As an Autoantigen in Rheumatoid Arthritis and in Lyme Arthritis. Annalisa Pianta[1], Elise E. Drouin[1], Sheila Arvikar[2], Catherine E. Costello[3] and Allen C. Steere[1]. [1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Massachusetts General Hospital, Boston, MA, [3]Boston University School of Medicine, Boston, MA.

Background/Purpose: Disease-associated HLA-DR molecules are the greatest genetic risk factor for rheumatoid arthritis (RA) and for antibiotic-refractory Lyme arthritis (LA). We have developed a novel approach to identify disease-relevant HLA-DR-presented peptides in synovial tissue using discovery-based proteomics and translational research. Using this approach, we previously identified endothelial cell growth factor (ECGF) as the first autoantigen known to be a target of T and B cell responses in antibiotic-refractory or antibiotic-responsive LA, but not in RA. In this study, we continued to characterize the repertoire of naturally presented HLA-DR peptides in synovial tissue in patients with RA or LA.

Methods: HLA-DR-presented peptides were eluted from synovia, identified by tandem mass spectrometry, synthesized, and tested for reactivity with the matching patient's PBMC. Immunoreactive peptides or their source proteins were then tested for T cell reactivity by IFN-g ELISpot assay or for antibody responses by ELISA. All RA patients met the 2010 ACR/EULAR criteria for RA and the LA patients met the CDC criteria for Lyme disease.



Results: In one RA patient who lacked positive tests for rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA), 1 of 86 non-redundant HLA-DR-presented peptides identified from her synovial tissue induced her PBMC to secrete IFN-g. The peptide was derived from the protein annexin A2 and others had shown that ~10% of RA patients make autoantibodies against this self-protein. We tested serum samples from our cohort of RA patients for anti-annexin A2 autoantibodies, and for comparison, from healthy control subjects or from patients with antibiotic-responsive or antibiotic-refractory LA. In our RA cohort, sera from 24% of 91 patients had antibody responses to annexin A2 that were >3SD above the mean value in healthy control subjects (Figure). Surprisingly, about 20% of the patients with antibiotic-responsive or antibiotic-refractory LA also had antibody reactivity with this autoantigen. In annexin A2-positive RA patients, the magnitude of antibody responses to ACPA or RF were less than in annexin A2-negative patients. Studies to look for linked T and B cell responses to annexin A2 are currently in progress in both the RA and LA cohorts.

Conclusion: We confirm that annexin A2, a phospholipid-binding protein that protects damaged endothelial cells, is a potential autoantigen in a subgroup of patients with RA. Moreover, we report for the first time that this protein may serve as an autoantigen in a subgroup of patients with LA. As with reactivity to ECGF, autoantibody responses to annexin A2 in Lyme disease seem to occur as a part of the immune response to the infection, whereas additional factors, such as immune dysregulation, are required for refractory arthritis.

Disclosure: A. Pianta, None; **E. E. Drouin**, None; **S. Arvikar**, None; **C. E. Costello**, None; **A. C. Steere**, ACR, NIH, Foundation, 2.

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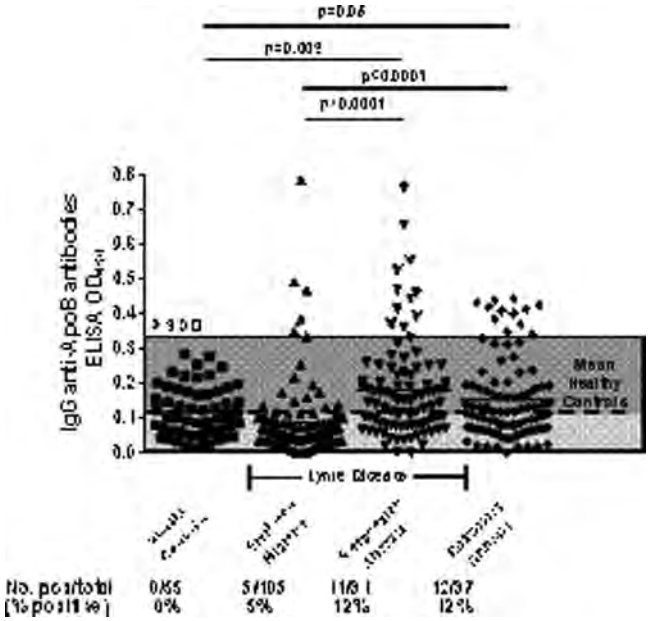
Apolipoprotein B Is a Target of T and B Cell Responses in a Subgroup of Patients with Lyme Disease. Jameson T. Crowley[1], Elise E. Drouin[1], Qi Wang[2], Gail McHugh[3], Catherine E. Costello[2] and Allen C. Steere[1]. [1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Massachusetts General Hospital, Boston, MA.

Background/Purpose: *Borrelia burgdorferi*-induced autoimmunity in affected joints has been hypothesized to be a contributing factor to antibiotic-refractory Lyme arthritis (ARLA). Our prior study, which combined proteomics and translational research, identified endothelial cell growth factor (ECGF) as the first known target of T and B cell responses in ~20% of patients with antibiotic-refractory or antibiotic-responsive arthritis and in ~10% of patients with erythema migrans (EM), the initial skin lesion of the disorder. Using this same approach, we identified apolipoprotein B (ApoB) as another novel autoantigen in Lyme disease.

Methods: HLA-DR presented self-peptides were isolated from ALRA patients' synovia, identified by tandem mass spectrometry, synthesized, and tested for reactivity with the matching patient's PBMC using an IFN-γ ELISpot assay. Immunoreactive peptides and their full-length source proteins were then tested for T and B cell reactivity using large numbers of patient and control cells and sera. Samples from patients with antibiotic-responsive arthritis were seen prior to antibiotic therapy, when the infection was still active, whereas those from patients with antibiotic-refractory arthritis were collected after antibiotics, during the presumed autoimmune phase of the illness. Antibody responses were quantified by ELISA.



Results: From the synovial tissue of one ALRA patient, 141 non-redundant HLA-DR-presented self-peptides were identified and tested. One peptide derived from ApoB caused significant secretion of IFN-γ by ELISpot. Additional testing of 25 patients showed ~10–30% patients with early or late manifestations of Lyme disease had T cell responses to ApoB.

To look for linked T and B cell responses, patients' serum samples were also tested for anti-ApoB IgG antibodies. By definition, none of the 55 healthy control subjects had a positive response (defined as >3 SD above the mean value in these subjects) (Figure). In comparison, 5% of patients with EM and 12% each of patients with responsive or refractory arthritis had positive responses for anti-ApoB IgG autoantibodies. Compared with the EM group, the values were significantly higher in both arthritis groups ($P<0.0001$), particularly in those with responsive arthritis, a group still actively infected.

Conclusion: We report for the first time that ApoB is a target of T and B cell responses in a subset of patients with Lyme disease. Although the molecular mechanisms are not yet known, *B. burgdorferi*, an organism with sequences for >100 lipoproteins and multiple membrane glycolipids containing cholesterol, may contribute directly to the development of this autoimmune response. As with reactivity to ECGF, autoantibody responses to ApoB seem to occur as part of the immune response to the infection, whereas additional factors, such as immune dysregulation, are also required for refractory arthritis.

Disclosure: J. T. Crowley, None; **E. E. Drouin**, None; **Q. Wang**, None; **G. McHugh**, None; **C. E. Costello**, None; **A. C. Steere**, ACR, NIH, Foundation, 2.

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Labial Salivary Gland Antibody-Secreting Cell Specificity and Characteristics in Sjögren's Patients. Kristi A. Koelsch[1], Jacen Maier-Moore[2], Kenneth Smith[3], Christopher Lessard[3], Astrid Rasmussen[3], Biji Kurien[3], Umesh Deshmukh[3], A. Darise Farris[3], Judith A. James[3], Kathy L. Moser Sivils[3], R. Hal Scofield[4] and Mark Coggeshall[3]. [1]Oklahoma Medical Research Foundation, Okalahoma City, OK, [2]University of Texas at El Paso, El Paso, TX, [3]Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]US Department of Veterans Affairs Medical Center, Oklahoma City, OK.

Background/Purpose: Studies were approved by the OMRF and the University of Oklahoma Health Sciences Center Institutional Review Boards. Samples and data were obtained from 9 subjects following written, informed consent and evaluated in the OMRF Sjögren's Research Clinic. Four subjects met American/European combined and American College of Rheumatology criteria for SS. One of these also met the American College of Rheumatology criteria for SLE. Five subjects that did not meet disease criteria served as sicca controls. ASCs were isolated from labial SGs by single-cell-sorting for hmAb production. hmAbs were produced by the OMRF Human Monoclonal Antibody Core. Serum Ab and hmAb profiles of patients and controls were evaluated by various assays to determine specificities including ELISA, immunofluorescence ANA and *Crithidia luciliae* testing, INNO-LIA™ and BioPlex2200™, and double immunodiffusion (sera only) assays.

Methods: Studies were approved by the OMRF and the University of Oklahoma Health Sciences Center Institutional Review Boards. Samples and data were obtained from 9 subjects following written, informed consent and evaluated in the OMRF Sjögren's Research Clinic. Four subjects met American/European combined and American College of Rheumatology criteria for SS. One of these also met the American College of Rheumatology criteria for SLE. Five subjects that did not meet disease criteria served as sicca controls. ASCs were isolated from labial SGs by single-cell-sorting for hmAb production. hmAbs were produced by the OMRF Human Monoclonal Antibody Core. Serum Ab and hmAb profiles of patients and controls were evaluated by various assays to determine specificities including ELISA, immunofluorescence ANA and *Crithidia luciliae* testing, INNO-LIA™ and BioPlex2200™, and double immunodiffusion (sera only) assays.

Results: From the 72 hmAbs analyzed to date (52/patient; 20/control), we found diverse antigen specificities, with hmAbs from SS patients more often binding self-antigens. While 56% of the hmAbs from SS patients bound Ro and/or La, only 19% from sicca controls did ($p = 0.001$). We found hmAbs from SS patients to be more often polyreactive (binding more than one antigen) than the controls (29% vs. 12%, respectively). In addition, 3 hmAbs were reactive to the bacterial antigen, peptidoglycan (PGN) (patient = 2, control = 1). The anti-PGN hmAbs also bound common self-antigens. We found correlation between patient serum and SG hmAbs specificities.

Conclusion: In this ongoing study, we show correlations between glandular and serum antibody specificities, demonstrate that ASCs other than anti-Ro or anti-La are present in SS salivary glands and produce Ab *in situ*. Furthermore, we observed that the SGs are representative of the systemic immune response and that glandular ASC specificities were consistent with co-morbid disease presentation. We have also identified SG derived hmAbs that have cross-reactivity to bacterial- and self-antigens, supporting the theory of an infection-triggering event that leads to development of disease. Finally, these are the first fully human, antigen-specific monoclonal antibodies produced from SS salivary gland ASCs and therefore, may have clinical or diagnostic importance.

Disclosure: K. A. Koelsch, None; **J. Maier-Moore**, None; **K. Smith**, None; **C. Lessard**, None; **A. Rasmussen**, None; **B. Kurien**, None; **U. Deshmukh**, None; **A. D.**

Farris, None; **J. A. James**, None; **K. L. Moser Sivils**, None; **R. H. Scofield**, None; **M. Coggeshall**, None.

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Integrated Comprehensive Analysis of Immune Cell Subsets and Serum Protein Profile Identifies the Role of Pre-Germinal Center B Cells in Sjogren's Syndrome Pathogenesis. Yoshiaki Kassai[1], Katsuya Suzuki[2], Rimpei Morita[3], Maiko Takiguchi[1], Rina Kurisu[1], Takahiro Miyazaki[1], Akihiko Yoshimura[3] and Tsutomu Takeuchi[2]. [1]Takeda Pharmaceutical Company Limited, Kanagawa, Japan, [2]Keio University School of Medicine, Tokyo, Japan, [3]Department of Microbiology and Immunology, Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Whole blood flow cytometric analysis and serum protein profiling were commonly utilized to characterize disease-specific alterations in a wide variety of autoimmune diseases. However, precise mechanisms underlying their pathophysiological conditions were still obscure because each experimental approach was carried out independently and not well integrated. Therefore, we performed comprehensive flow cytometric analysis by multi-colored staining in combination with serum protein profile to fully understand pathophysiological aspects in rheumatoid arthritis (RA) and primary Sjogren's syndrome (pSS).

Methods: Heparinized peripheral blood was collected from untreated RA patients (N = 51), pSS patients (N = 60), and healthy controls (N = 36). Fresh whole blood was immediately stained with fluorescent-labeled antibodies and analyzed with 3-laser, 8-color FACS equipment. Over a thousand of serum protein profile were also obtained with aptamer technology from SomaLogic, Inc. Serum immunoglobulin concentrations were evaluated by ELISA and gene expression levels were analyzed using quantitative real-time PCR.

Results: Among over 40 immune cell subsets we investigated, surface IgD+ CD38++ B cells, called pre-germinal center B (pre-GC B), were significantly increased in both RA and pSS patients. Interestingly, serum IgG but not IgM and IgA was positively correlated with the number of pre-GC B cells in pSS but not RA, suggesting their distinct role in pSS pathogenesis. Consistent with this, GC-related serum proteins such as PD-L2, SLAMF2, and CD30 ligand were significantly elevated and correlated with pre-GC B in pSS but not RA. Furthermore, pre-GC B cells isolated from pSS patients exhibited higher GC-related gene expressions including *XBP1* and *BACH2* than those from healthy controls.

Conclusion: Our findings suggest possible role of pre-GC B in pSS pathogenesis through IgG production and germinal center formation. By integrating multiple comprehensive analyses, we identified a novel immune cell phenotype, indicating this strategy as a useful tool to highly impact on better understanding of autoimmune diseases.

Disclosure: Y. Kassai, Takeda Pharmaceutical Company Limited, 3; **K. Suzuki**, None; **R. Morita**, None; **M. Takiguchi**, Takeda Pharmaceutical Company Limited, 3; **R. Kurisu**, Takeda Pharmaceutical Company Limited, 3; **T. Miyazaki**, Takeda Pharmaceutical Company Limited, 3; **A. Yoshimura**, None; **T. Takeuchi**, Abbott Japan Co., Ltd., Astellas Pharma, Bristol–Myers K.K., Chugai Pharmaceutical Co, Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Sanofi–Aventis K.K., Santen Pharmaceutica, 2, Abbott Japan Co., Ltd., Bristol–Myers K.K., Chugai Pharmaceutical Co,. Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., Astellas Pharma, Daiichi Sankyo Co.,Ltd., 8, Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., Asahi Kasei Medical K.K., Abbvie GK, Daiichi Sankyo Co.,Ltd., 5.

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Novel Auto-Antigen in Aortic Aneurysms of Large Vessel Vasculitis. Ritu Chakravarti[1], Karishma Gupta[2], Jaclyn Scholtz[3], Edward Soltesz[4], Eric Roselli[4], Gosta Pettersson[4], Lars Svensson[4], Douglas Johnston[4], Belinda Willard[4], Michifumi Yamashita[5], Thomas Daly[6] and Gary S. Hoffman[7]. [1]Assistant Prof/ Project Staff, Cleveland, OH, [2]Technician, Cleveland, OH, [3]Student, Cleveland Clinic, cleveland, OH, [4]Cleveland Clinic Foundation, Cleveland, OH, [5]Resident, Cleveland, OH, [6]Director,, Cleveland, OH, [7]Center for Vasculitis Care and Research, Cleveland Clinic Foundation, Cleveland, OH.

Background/Purpose: Large Vessel Vasculitides (LVV) are a group of autoimmune diseases characterized by injury and anatomic modifications of large vessels that may include the aorta and its branch vessels. Disease etiology is unknown. Using samples from aorta root, ascending aorta and aorta arch surgical specimens, we sought to identify antigen targets within affected vessel walls in patients with LVV, including giant cell arteritis (GCA), Takayasu's arteritis (TA) and isolated focal aortitis (IFA).

Methods: Thoracic aorta aneurysm specimens and autologous blood were acquired from consenting consecutive patients in whom aorta reconstruction procedures were indicated. Aorta tissues from patients with both LVV and age-, race- and gender-matched patients with non-inflammatory aneurysms, were lysed and resolved on SDS-polyacrylamide gels. Sera from study groups were used to probe antigen-antibody reactivity on western blots followed by MS analysis to identify antigen. Additional sera samples tested included sera from diseases including medium to small vessel vasculitis, sepsis etc.

Results: We found that patients with LVV (n=17) produce antibodies to 14-3-3 proteins in the aortic wall, whereas patients with non-inflammatory matrix disorders (n=17) rarely do so. Most of the sera from other immune diseases were also negative. Anti-14-3-3 antibody production was demonstrated in all 3 forms of LVV. In each, sera contained autoantibody that was sufficient to immunoprecipitate 14-3-3 protein(s) from the aortic lysates. Antibodies to 14-3-3 were not found in sera of additional controls. Three out of seven known isoforms of 14-3-3 were found to be upregulated in LVV aortas. Most 14-3-3 Ag was found to co-localize within granulomas, chronic inflammatory cells and smooth muscle cells in LVV.

Conclusion: This study is the first to utilize sterile, snap frozen tissue from aortic reconstruction surgeries in an attempt to identify autoantigens in LVV. 14-3-3 protein(s) appears to be a novel auto-antigen in aortic aneurysms caused by LVV. The precise role of these antibodies and 14-3-3 proteins in LVV etiology and pathogenesis deserves further study.

Disclosure: R. Chakravarti, None; **K. Gupta**, None; **J. Scholtz**, None; **E. Soltesz**, None; **E. Roselli**, None; **G. Pettersson**, None; **L. Svensson**, None; **D. Johnston**, None; **B. Willard**, None; **M. Yamashita**, None; **T. Daly**, None; **G. S. Hoffman**, None.

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Serum CXCL13 As a Biomarker of Disease Activity and Severity in Rheumatoid Arthritis: Comparison with Acute Phase Reactants and the Autoantibody Profile. Antonio Manzo, Serena Bugatti, Barbara Vitolo, Francesca Benaglio, Elisa Binda, Martina Scarabelli, Roberto Caporali and Carlomaurizio Montecurcco. Rheumatology and Translational Immunology Research Laboratories (LaRIT), Division of Rheumatology, IRCCS Policlinico S.Matteo Foundation/University of Pavia, Pavia, Italy.

Background/Purpose: The B cell chemoattractant CXCL13 has recently emerged as a new candidate biomarker of disease activity capable of identifying patients with persistent synovitis and worst radiographic outcomes in early rheumatoid arthritis (RA). However, whether CXCL13 reflects underlying disease processes or simply represents another non-specific marker of inflammation is currently unknown. The current study aimed at analysing the clinico-pathologic significance of serum CXCL13 in comparison to routine laboratory markers of disease activity and severity in patients with RA.

Methods: Baseline serum levels of CXCL13 were measured by colorimetric ELISA in 205 consecutive early untreated RA patients with disease duration <12 months (median 3 months, IQR 2–5.5). Disease activity was assessed by a comprehensive set of subjective, semi-objective and objective clinical features. Changes in CXCL13 levels were evaluated in 87 patients after 2 months of treatment with methotrexate and low-dose prednisone. An additional study population of 60 RA patients (n=22 with disease duration <12 months) in whom paired serum and synovial samples were collected on the same day was used to assess the pathologic correlates of circulating CXCL13.

Results: In cross-sectional analyses at baseline, CXCL13 was moderately correlated with the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (rho 0.35 and 0.36 respectively, $p<0.001$). Similarly to acute phase reactants, CXCL13 correlated with overall disease activity as measured by the DAS28, in particular with physician-derived measures, as well as with ultrasonographic scores for Gray Scale and power Doppler signals. In contrast to ESR and CRP, no correlation was found with patient-derived measures and functional status. Although increased CXCL13 levels were found in ACPA(+) patients, high CXCL13 and ACPA were not synonymous. CXCL13 levels in the 3rd tertile (>100 pg/ml) were found in 27.9% of ACPA(-) patients, and, in turn, 53.4% of ACPA(+) patients had CXCL13 <100 pg/ml. Similar results were observed for RF. After 2 months of treatment, CXCL13 levels were not significantly changed from baseline, as opposite to the significant reduction observed for acute phase reactants (standardised response mean 0.04, 0.52 and 0.66 for CXCL13, ESR and CRP respectively). In paired serum and tissue samples, circulating CXCL13 was

significantly correlated with synovial CXCL13 protein (rho 0.30, p=0.04) and mRNA (rho 0.56, p=0.02) expression. Similarly to ESR and CRP, serum CXCL13 was related to synovial inflammatory features such as the degree of sublining macrophage infiltration (rho 0.34, p=0.01). Serum CXCL13, but not acute phase reactants, showed further correlation with the presence and density of large B cell aggregates (rho 0.28, p=0.03), expression levels of the B cell enzyme activation induced cytidine deaminase (AID) (rho 0.4, p=0.046), and the receptor activator of nuclear factor κB ligand (RANKL)/ osteoprotegerin (OPG) ratio (rho 0.72, p<0.01).

Conclusion: Serum CXCL13 in RA reflects an immunologically active and potentially persistent pattern of synovial inflammation beyond the levels of conventional inflammatory markers and the ACPA status.

Disclosure: A. Manzo, None; **S. Bugatti**, None; **B. Vitolo**, None; **F. Benaglio**, None; **E. Binda**, None; **M. Scarabelli**, None; **R. Caporali**, None; **C. Montecucco**, None.

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Fcgamma Receptor IIb Facilitates Rapid Internalisation of Rituximab (type 1 anti-CD20 antibody) in B Cells from Patients with RA and SLE and Contributes to Less Efficient B Cell Lysis Than Type 2 Anti-CD20 Antibodies, *in Vitro*. Venkat Reddy[1], Geraldine Cambridge[2], David A. Isenberg[2], Mark Cragg[3] and Maria J. Leandro[2]. [1]Centre for Rheumatology Research, Division of Medicine, University College London, London, United Kingdom, [2]Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom, [3]Southampton University, Southampton, United Kingdom.

Background/Purpose: Incomplete B-cell depletion using rituximab (RTX) is associated with poor clinical response in some individuals with RA and SLE, in particular. However, the precise mechanisms of resistance to depletion with RTX (type1 anti-CD20 monoclonal antibodies, mAbs) are poorly understood. Improving depletion may augment clinical response. Newer mAbs such as GA101 (type2) are more potent than RTX at deleting malignant B cells.

Methods: We included 5 healthy controls (HC), 15 patients with RA and 16 with SLE. An *in vitro* autologous whole blood depletion assay was used to compare BHH2 (type2, glycosylated GA101) with RTX (type1) and B cell lysing potential of mAbs was defined as cytotoxicity index (CTI). Briefly, 100μl of heparinised blood was incubated with either RTX, BHH2 or without antibody, at a concentration of 1μg/ml at 37oC, 5% CO2for 24hours. Samples were analysed by flow cytometry for CD45+ lymphocytes, CD3+ Tcells and CD19+ Bcells. The CTI was calculated using the formula:CTI of mAb=100-[(number of B:Tcells in sample without mAb-number of B:Tcells with mAb)/number of B:T cells in sample without mAb) × 100]. Surface fluorescence quenching assay using isolated B cells was performed to assess for the internalisation of mAbs. Paired "t' test or Mann-Whitney U test was used to compare groups, as appropriate.

Results: *Whole Blood Depletion:* BHH2 (type2 mAb) was significantly more efficient than RTX (type1 mAb) at lysing B cells, *in vitro*, in all groups. The mean±SD CTI of BHH2 vs RTX in HC was 65±13 vs 45±24(p=0.04); in RA, 61±12 vs 28±18 (p<0.0001); and in SLE, 38±17 vs 13±10 (p<0.0001). Thus, a hierarchy of B cell susceptibility to lysis by RTX was noted with HC > RA >SLE. BHH2 lyses the RA cells as well as controls - i.e. it fully overcomes the defect in RA whereas it doesn't in SLE.

Internalisation: We performed a surface fluorescence-quenching assay at 6 and 24 hours. At both time points, a significantly greater % of BHH2 was accessible on surface when compared with RTX, in all groups. The mean±SD % surface accessible mAbs, after 6 hours of incubation for BHH2 vs RTX was 72±6 vs 57±11, 68±8 vs 57±12(p<0.005) and 71±10 vs 63±12(p<0.005) whereas after 24 hours of incubation it was 47±15 vs 28±12, 45±25 vs 36±15 and 59±9 vs 42±14(p<0.005 for all), for HC, RA and SLE, respectively. Prior incubation with AT10 (a mAb directed against Fcgamma receptor II, CD32) significantly reduced internalisation of type1 mAbs to a greater extent than type 2 mAbs, a mean reduction of 12% vs 4%, respectively (p<0.005). Further, a significant variability was noted between patients in the extent to which internalisation of RTX, but not BHH2, was reduced by AT10.

Conclusion: Type 2 anti-CD20 antibodies are more efficient than type1 (rituximab) at lysing B cells from patients with RA and SLE. B cells from patients with SLE may be less susceptible to lysis *in vitro* by rituximab when compared with B cells from patients with RA and healthy individuals. Fcgamma receptor IIb facilitates rapid internalisation of rituximab, but not type2 mAbs, by B cells from patients with RA and SLE, which may contribute to its inferior ability to lyse B cells. This study provides a mechanistic basis for considering type2 mAbs for clinical use in RA and SLE.

Disclosure: V. Reddy, None; **G. Cambridge**, None; **D. A. Isenberg**, None; **M. Cragg**, None; **M. J. Leandro**, None.

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The Alternative CD20 Transcript Variant Is Not a Factor for Resistance to Rituximab in Patients with Rheumatoid Arthritis. Cecile Gamonet[1], Marina Deschamps[2], Sandrine Marion[3], Philippe Saas[4], Gilles Chioccha[3], Christophe Ferrand[4] and Eric Toussirot[5]. [1]Etablissement Français du Sang / Université de Franche Comté, Besançon, France, [2]INSERM UMR1098 / Etablissement Français du Sang/ Université de Franche Comté, Besançon, France, [3]Université Versailles Saint Quentin, Montigny le Bretonneux, France, [4]INSERM UMR1098, Besançon, France, [5]Rheumatology Department, Univesity Hospital, besancon, France.

Background/Purpose: the identification of predictive factors for the response, or alternatively factors for resistance to biological agents is a relevant goal in the management of patients with rheumatoid arthritis (RA). Rituximab (RTX) is a chimeric monoclonal antibody directed against the membrane CD20 protein expressed by B cells. Predictive factors for good response to RTX therapy in RA have been previously determined, and included presence of rheumatoid factors and anti -CCP antibodies. A spliced mRNA transcript of CD20 (D393-CD20) has been observed in tumoral B cells from patients with lymphoma and leukaemia (1). This transcript is coding for a non-anchored membrane protein and its expression may be associated with resistance to RTX in patients with haematological malignancies.

Objectives: we previously reported that this alternative D393-CD20 transcript is not expressed in B cells and synovial tissue from patients with RA. In this study, we aim to determine whether D393-CD20 is expressed by circulating B cells from patients with RA who are refractory to RTX and whether it could be a factor for non-response to this treatment.

Methods: selected patients were from the SMART study (2). We included those who did not respond to RTX treatment (EULAR response). 24 RA patients (21 F, age [mean ± SD]: 57.6 ± 11.2 years; disease duration: 8.7 ± 6.7 years, positive rheumatoid factors: 13/24; positive anti- CCP antibodies: 13/24) were evaluated. All the patients had concomitant MTX and low corticosteroids (< 10 mg/j; 21/24). CD20 mRNA expression study was performed using RT-PCR assay allowing to discriminate full length CD20 (membrane CD20) from D393-CD20 transcripts. A more sensitive RT-PCR assay, using a specific primer spanning the splice fusion area was then used to detect specifically only the D393-CD20 transcript. This analysis was performed on peripheral blood B cells from patients with RA.

Results: RA patients had high disease activity at baseline (DAS28: 5.8 ± 0.8). Disease activity remained elevated after one course of RTX 1000 mg × 2 (DAS 28 at week 24: 5.5 ± 0.8). Among all the 24 RA samples, although full length CD20 expression was always detected, we were unable to detect D393-CD20, even with the more sensitive RT-PCR assay permitting to identify the spliced transcript form. We did not identify a subgroup of patients who display positive D393-CD20.

Conclusion: the present study showed that, on the contrary of leukemic or lymphoma B cells, RA B-cells from RA patients who did not respond to RTX do not express D393-CD20. This result, together with our previous data (lack of expression of this alternative transcript in cross-sectional analysis of RTX-naïve RA patients and in synovial tissue from RA patients) indicate that D393-CD20 may only be a molecular marker of malignancies rather than a factor predictive to RTX responses in auto-immune diseases like RA.

1- Henry C *et al*., Blood, 2010;115:2420–9
2- Mariette X, Ann Rheum Dis, 2013 May 30 [Epub ahead of print]

Disclosure: C. Gamonet, None; **M. Deschamps**, None; **S. Marion**, None; **P. Saas**, None; **G. Chioccha**, None; **C. Ferrand**, None; **E. Toussirot**, None.

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Differential Antigen-Presenting B-Cell Phenotype from Synovial Microenvironment of Rheumatoid Arthritis and Psoriatic Arthritis Patients. Estefania Armas-Gonzalez[1], Ana Diaz-Martin[1], María Jesús Dominguez-Luis[2], Maria Teresa Arce-Franco[1], Ada Herrera-Garcia[1], Vanesa

Hernandez[1], Alicia Usategui[3], Jose L. Pablos[4], Juan D. Cañete[5], Sagrario Bustabad[1] and Federico Díaz-González[1]. [1]Hospital Universitario de Canarias, La Laguna. Tenerife, Spain, [2]Center of Biomedical Research of the Canary Islands, University of La Laguna, Tenerife, Spain, [3]Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain, [4]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [5]Hospital Clínic of Barcelona, Barcelona, Spain.

Background/Purpose: The systemic depletion of B cells induced by mabthera, a monoclonal antibody against human CD20, has shown to be an effective therapy for controlling disease activity in rheumatoid arthritis (RA), but not in psoriatic arthritis (PsA) patients. This strongly suggests that B cells play a different role of in the pathogenesis of these diseases. It has been suggested that B cells participate in the pathogenesis of chronic synovitis through several mechanisms, including T-cell activation by acting as antigen-presenting cells.

Objective: To study the potential differences in antigen-presenting phenotypes of B cells present in the synovial microenvironment of RA and PsA patients.

Methods: The surface expression levels of CD27, CD23, class II molecules (HLA-DP, -DQ and -DR), CD40 and CD86 were assessed by double- or triple-staining flow cytometry on CD20+ cells from peripheral blood (PB) and synovial fluid (SF) of 13 RA and 15 PsA patients. Flow cytometry analysis data are presented as relative mean fluorescence intensity with respect to cells in PB, which was considered 100%. The expression of interferon-induced protein IFIT-4, which is involved in the differentiation of monocytes into dendritic cells, was assessed by quantitative RT-PCR in negatively immunoselected CD19+ B cells from SF and PB of RA patients.

Results: Analyzing all patients included in this study, the percentage of mononuclear CD20+ cells in SF (2.24±0.37%) was significantly lower than in PB (8.59±1.26%, $p<0.01$). When these data were compared in RA versus PsA patients, the percentages of CD20+ cells in PB and SF were similar in both range and tendency. B cells from SF of RA and PsA patients showed an activated phenotype (down-regulation of CD23) and seem to have had in contact with the antigen (up-regulation of CD27). Flow cytometry analyses showed an increased expression of HLA-DR and -DQ in CD20+ cells from SF compared to those from PB, in both RA (277.84±65.66; 262.20±108.81) and PsA (267.86±88.53; 311.08±116,65) patients. HLA-DP was also elevated in rheumatoid SF B cells (1009.48±335.70), although conversely, a significantly lower expression of this class II molecule was observed in SF from PsA patients (46.38±19.73). Surface expression of CD86 was higher in SF than in PB B cells from both pathologies (RA: 629.79±172.24; PsA: 326.46±138.77). CD40 expression was significantly lower in SF compared to PB in B cells from RA patients (66.31±12.21); however, this was not the case in PsA patients (243.76±71.18). Interestingly, CD20 surface expression was 35% lower in B cells (CD19+, CD138-) from SF with respect to PB in RA patients. Finally, qRT-PCR showed approximately a 5-fold increase in IFIT-4 mRNA content in B cells from SF compared to PB in RA patients.

Conclusion: These data show that B cells in the synovial microenvironment of RA and PsA patients show a differential phenotype respect to molecules involved in antigen presentation and co-stimulation, which suggest that B cells play a different role in the pathogenesis of these two pathologies. This could have implications for the understanding of the dissimilar clinical response to B cell-depleting treatment observed in RA and PsA.

Disclosure: E. Armas-Gonzalez, None; **A. Diaz-Martin**, None; **M. J. Dominguez-Luis**, None; **M. T. Arce-Franco**, None; **A. Herrera-Garcia**, None; **V. Hernandez**, None; **A. Usategui**, None; **J. L. Pablos**, None; **J. D. Cañete**, None; **S. Bustabad**, None; **F. Díaz-González**, None.

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Anti-Citrullinated Proteins Antibodies Promote Synovial Fibroblast Migration in Rheumatoid Arthritis. Meng Sun[1], Vijay Joshua[1], Aase Haj Hensvold[1], Sergiu-Bogdan Catrina[2], Lars Klareskog[3], Vivianne Malmström[4], Heidi Wähämaa[1] and Anca I Catrina[1]. [1]Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [2]Molecular Medicine and Surgery, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden, [3]Karolinska Institute, Stockholm, Sweden, [4]Rheumatology Unit, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: The presence of anti-citrullinated proteins antibodies (ACPAs) in RA is associated with aggressive disease phenotype and bone destruction. As synovial fibroblasts (SFs) are considered key players of both synovial inflammation and bone destruction in rheumatoid arthritis (RA), we studied the effect of ACPAs on fibroblasts migration.

Methods: Human dermal fibroblasts (HDFs) were obtained from PromoCell. SFs were isolated from synovial tissue of RA patients (RASFs) by enzymatic digestion. ACPA positive and negative IgGs were separated from plasma of RA patients and monoclonal anti-citrullinated antibodies were generated from RA synovial fluid by single B-cells[1]. Migration scratch assays were performed using either RASFs or HDFs to test the effect of ACPAs, anti-citrullinated monoclonal antibodies and appropriate negative controls. The effect of a phosphatidyl inositol-3-kinase (PI3K) inhibitor (wortmannin) and a focal adhesion kinase (FAK) inhibitor (PF-573228) was tested. Light microscopy images were taken at baseline and after 6 hours incubation and analyzed using NIH ImageJ to calculate migration index. Cytotoxicity and proliferation assays were done in parallel with migration assays.

Results: ACPAs but not control IgGs induced a 3.9±0.5 (mean±SD) fold increase in HDFs and a 2.6±0.5 (mean±SD) fold increase in RASFs migration ($p<0.05$). PI3K but not FAK inhibition almost completely abolished ACPAs effects, with minimal fold migration increase of 1.4±0.4 (mean±SD). No difference in either cytotoxicity or proliferation rate were observed between different treatments. One out of three different anti-citrullinated monoclonal antibodies displayed similar mig.

Conclusion: We describe a novel effect of ACPAs, providing a link between synovial fibroblasts and the adaptive immune system. We further suggest that different fine specificities of ACPAs might have distinct impact on disease pathogenesis.

1. Amara, K. et al. Monoclonal IgG antibodies generated from joint-derived B cells of RA patients have a strong bias toward citrullinated autoantigen recognition. *J Exp Med* **210**, 445–55 (2013).

Disclosure: M. Sun, None; **V. Joshua**, None; **A. H. Hensvold**, None; **S. B. Catrina**, None; **L. Klareskog**, None; **V. Malmström**, None; **H. Wähämaa**, None; **A. I. Catrina**, None.

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IL-7 Modulates B Cell Immunoglobulin Isotype Production and Increases B Cell Activating Factor of the Tumor Necrosis Factor Family (BAFF) in Synovial Fibroblasts from Osteoarthritis (OA) and Rheumatoid Arthritis (RA) Patients. Georg Pongratz, Stephan Kuhn, Madlen Melzer, Torsten Lowin and Rainer Strraub. University Hospital Regensburg, Regensburg, Germany.

Background/Purpose: Interleukin(IL)-7 is increased in synovial fluid from rheumatoid arthritis (RA) patients as compared to osteoarthritis (OA) patients and has been attributed a proinflammatory role, especially due to its well established influence on T cells. However, B cells and synovial fibroblasts (SFs) also possess functional IL-7 receptors and stimulation of IL-7 receptors on B cells increases disease severity in collagen-induced arthritis. However, the mechanisms involved in this proinflammatory effect are not known. We therefore wanted to further characterize the effect of IL-7 on B cell antibody production and on the production of B cell activating factor of the tumor necrosis factor family (BAFF) and IL-6 in synovial fibroblasts (SFs).

Methods: Naive splenic mouse B cells were cultured in the presence of different activating stimuli (LPS, anti-IgM, anti-CD40, anti-CD40 + IL-4, antiCD40 + IFN-γ) in the absence or presence of IL-7 added at different timepoints (with the initial stimulus or three days after start of culture) and different concentrations (0.1, 1.0, 10 ng/ml). Levels of antibody isotypes (IgA, IgM, IgG1, IgG2a, IgG2b, IgG3, IgE) and light chains (lambda, kappa) were determined in supernatant by ELISA after 5 days. SFs were isolated from OA (n=15) and RA (n=7) knee joints and cultured in the presence or absence of IFN-γ at different concentrations (0.1, 0.5, 1.0, 5.0, 10, 50 ng/ml) to induce BAFF and IL-6 in the absence or presence of different concentrations of IL-7 (0.01, 0.1, 1.0, 10 ng/ml). BAFF and IL-6 were determined in culture supernatants by ELISA.

Results: IL-7 shows a differential effect on B cell antibody production, depending on the co-stimulus used and the isotype analysed. Most prominent effects were observed when IL-7 was present from the beginning of B cell culture. IL-7 increased IgG2a ($p=0.038$), IgG3 ($p<0.001$), and lambda light chains ($p=0.024$) and decreased kappa light chains ($p<0.001$) in the presence of concomitant stimulation with IL-4 and anti-CD40. IL-7 further increased LPS-induced IgG3 ($p<0.001$) and IgE ($p<0.001$). IL-7 alone was able to induce IgE in B cells to some extent without any additional stimulus ($p<0.001$). IFN-induced BAFF was increased by IL-7 in a concentration dependent manner in RA ($p<0.001$) but not OA SFs ($p=0.078$). However,

under hypoxic conditions (O2 2%) both, RA ($p<0.001$) and OA ($p=0.008$) SFs increased IFN-induced BAFF production in the presence of IL-7 in a concentration dependent manner. In contrast, IFN-induced IL-6 was not altered in SFs in the presence of IL-7.

Conclusion: Effects of IL-7 on the B cell compartment in arthritis can be direct by modulation of isotype production or indirect by increasing BAFF production in SFs. Therefore, IL-7 not only plays a role in modulating T cells but also modulates B cell function in arhtritis and therefore might be a valuable drug target.

Disclosure: G. Pongratz, None; **S. Kuhn**, None; **M. Melzer**, None; **T. Lowin**, None; **R. Straub**, None.

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Rheumatoid Arthritis Patients Have Alterations in Inherently Autoreactive 9G4+ B-Cell Subpopulations in Peripheral Blood. Rita A. Moura[1], Maria J. Leandro[2], Venkat Reddy[1], João E. Fonseca[3] and Geraldine Cambridge[2]. [1]Centre for Rheumatology Research, Division of Medicine, University College London, London, United Kingdom, [2]Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom, [3]Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal.

Background/Purpose: B-cells utilizing the VH-region immunoglobulin gene VH4–34 produce natural autoreactive antibodies. The rat monoclonal antibody 9G4 recognizes B-cells with VH4–34-encoded B-cell receptors (9G4+ B-cells) and also secreted immunoglobulins. In healthy individuals, 9G4+ B-cells present in splenic marginal zones and tonsils are excluded from germinal centre (GC) reactions, whereas in autoimmune diseases such as systemic lupus erythematosus, 9G4+ B-cells expand in the post-GC memory compartment, suggesting defective 9G4+ B-cell censoring mechanisms. In rheumatoid arthritis (RA) patients, the distribution of tonsil 9G4+ B-cells is similar to healthy individuals, but only limited phenotypic analyses have examined 9G4+ B-cells in peripheral blood. The aim of this work was to perform an extensive phenotype characterization of 9G4+ B-cell subpopulations in peripheral blood in RA patients and healthy controls (HC).

Methods: Blood samples were collected from established RA patients ($n=12$) and age and sex-matched HC ($n=15$). Peripheral blood mononuclear cells were isolated by density gradient centrifugation and 9G4+ B-cells (gated in CD19+ B-cells) were characterized by flow cytometry. 9G4+ B-cell subpopulations were defined using combinations of IgD, CD27 and CD38. The expression of CD5, CD24, IgM, BAFF-R and CXCR5 was analyzed in total 9G4+ B-cells. Statistical analysis was performed with Mann-Whitney test.

Results: The frequency of total 9G4+ B-cells in circulation was similar between RA patients and HC (median values: 3.83% and 4.68%, respectively). We found that RA patients had a higher frequency of 9G4+IgD-CD27- B-cells than HC ($p=0.04$). No significant differences were found in other 9G4+ subpopulations based on IgD/CD27 classification, although there was a tendency for higher levels of 9G4+ switched memory B-cells (IgD-CD27+). RA patients also had significantly lower levels of 9G4+ transitional B-cells (IgD+CD38+++) ($p=0.004$) and 9G4+ plasmablasts (IgD-CD27+++CD38+++) ($p=0.004$) and increased frequencies of 9G4+ naïve B-cells (IgD+38++) ($p=0.04$) when compared to HC. A tendency for higher levels of 9G4+ post-GC memory B-cells (IgD-CD38+) was also observed in RA patients. Furthermore, BAFF-R expression was significantly increased in 9G4+ B-cells from RA patients (both frequency and mean fluorescence intensity values) compared to HC ($p=0.04$ and $p=0.006$, respectively). There was a significant decrease in levels of 9G4+CD5+ B-cells ($p=0.004$) in RA patients, but no other significant differences were found in 9G4+ B-cells expressing CD24, IgM and CXCR5.

Conclusion: RA patients have alterations in the frequency of 9G4+ B-cell subpopulations when compared to healthy individuals. The significant reduction in the frequency of 9G4+ transitional and 9G4+CD5+B-cells and the increased levels of 9G4+ naïve B-cells suggests a more rapid maturation of 9G4+ B-cells in RA patients following entry into the peripheral pool. This could be influenced by the antigen specificity of the B-cell receptor. Furthermore, the increased BAFF-R expression by 9G4+ B-cells observed in RA patients might support an increased survival mechanism for these already inherently autoreactive B-cells.

Disclosure: R. A. Moura, None; **M. J. Leandro**, None; **V. Reddy**, None; **J. E. Fonseca**, None; **G. Cambridge**, None.

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Memory B Cell Subtype Modulation in Patients with Rheumatoid Arthritis. Zafar Mahmood[1], Marc Schmalzing[1], Thomas Dörner[2] and Hans-Peter Tony[1]. [1]University of Würzburg, Würzburg, Germany, [2]Charité Universitätmedizin Berlin and DRFZ, Berlin, Germany.

Background/Purpose: Memory B cells have been shown to play important roles in the pathogenesis of rheumatoid arthritis (RA). With the advent of B cell targeted therapies the modulation of memory B cells seems to be a prime target. Human peripheral memory B cells can be classified into three major subtypes by the phenotypic expression of CD27 and IgD: CD27+IgD+ preswitch, CD27+IgD- postswitch and CD27-IgD- double negative (DN) memory B cells. We aimed in this study to analyze different subsets of memory B cells in patients with RA under cytokine inhibition.

Methods: Memory B cell subsets were phenotypically analyzed for activation (expressions of CD95 and ki-67) and their isotype profile using 10 color flow cytometry at baseline, week 12 and week 24 during cytokine inhibition. Single B cell PCR approach was used to study isotypes specific Ig-receptors. Mann-Whitney U test was used for statistical analysis by using GraphPad Prism 5.

Results: Surface and intracellular staining of memory B cell subsets showed a significantly higher percentage of CD95 and ki-67 expression in RA ($n=60$) compared to healthy donors ($n=20$). During cytokine (IL-6 or TNF-α) inhibition, both CD95 and ki-67 expression was significantly reduced at week 12 and 24 in all 3 types of memory B cells. RA patients showed a significant relative expansion of DN IgD-/CD27- B cells with a mixture of IgA, IgG and IgM expression dominated by the IgG phenotype. During IL-6 receptor inhibition, IgA+ DN B cells decreased significantly from 25.1 (8.0–54.2) percent median (range) to 19.0 (4.8–51.1) at week 12 ($P= 0.0016$) and 20.5 (4.6–33.8) at week 24 ($P=0.0008$) respectively without any remarkable change in relative IgG+ and IgM+ B DN B cells. In the postswitch compartment, IgA+ and IgG+ postswitch B cells were not influenced during IL-6R inhibition. Isotype specific analysis of rearranged Ig-R sequences from DN B cells revealed that mutational frequencies were highest in IgA+ B cells followed by IgG+ and IgM+, respectively. During IL-6R inhibition, significantly reduced mutational frequencies in Ig-receptors of all DN isotypes at week 12, 24 and 1year ($p<0.0001$) were observed. Accordingly hotspot motif targeting was also decreased whereas CDR3 length increased during therapy.

Conclusion: Our study suggests that all three major memory B cell subsets are activated in RA which can be significantly reduced by IL-6R and TNF-α inhibition in vivo. DN B cells are expanded in RA and IL-6R inhibition resulted in a reduction of particularly IgA+ DN B cells. IL-6 inhibition leads to a reduced mutational frequency and hot spot targeting in IgA, IgG as well IgM DN Ig receptors. The results are in accordance with a specific effect on DN memory B cells by in vivo IL-6 receptor inhibition.

Disclosure: Z. Mahmood, None; **M. Schmalzing**, None; **T. Dörner**, None; **H. P. Tony**, None.

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Explore Translational Pharmacokinetics/Pharmacodynamics Response/ Efficacy Relationship of a Novel Bruton's Tyrosine Kinase Inhibitor in Rat Collagen-Induced Arthritis Model. Jie Zhang-Hoover[1], Erica Leccese[1], Kalyan Chakravarthy[1], Ian Knemeyer[1], Jos Lommerse[1], Marianne Spatz[1], Francois Gervais[2], Raquel Sevilla[1], Jian Liu[3], Ronald Kim[3], Sachin Lohani[3], Kevin Matthew Maloney[3], Joseph Kozlowski[3] and Alexandra Hicks[1]. [1]Merck Research Laboratories, Boston, MA, [2]Merck & Co., Boston, MA, [3]Merck Research Laboratories, Rahway, NJ.

Background/Purpose: Abnormal B cell activation is an essential part of autoimmune inflammation. B cell depletion is proven to be an efficacious treatment in patients as well as in preclinical rodent rheumatoid arthritis models. Bruton's Tyrosine Kinase (BTK) is downstream of B cell receptor and critical in B-cell development and activation, making it a potential therapeutic target for autoimmune inflammatory diseases. Here we evaluated a novel and selective small molecule BTK inhibitor in disease mechanism and pharmacokinetics (PK)/pharmacodynamics (PD) models to understand the level and duration of compound exposure on activation biomarker PD effect that leads to efficacy.

Methods: Female Lewis rats were treated with the BTK inhibitor (3, 10, 30, 100 mg/kg PO QD) prophylactically starting from the day of immunization in the rat collagen induced arthritis (CIA) model. Disease severity was evaluated in life by measuring paw thickness and

clinical scores and terminal by micro-CT imaging of ankle and knee joints for bone erosion. The effect of the BTK inhibitor on B cells was evaluated by ex vivo whole blood B cell CD86 PK/PD assay. Blood was collected from rats at 0, 0.5, 4, 8, and 24 hours after compound dosing. B cells were stimulated in vitro in whole blood by crosslinking of BCR with dextran conjugated anti-IgD. Activation biomarker CD86 expression on B cells was quantified by flow cytometry. Rat plasma compound concentrations were determined by protein precipitation followed by liquid chromatography – tandem mass spectrometry. A PK/PD-CIA model was built linking the effect of compound exposure with CD86 biomarker expression in the ex vivo whole blood assay and paw inflammation in the rat CIA. PK was best described using a zero-order dissolvation linked with a first-order absorption compartment and a concentration dependent elimination rate. For CD86 expression a direct-effect model was used. Paw inflammation in the rat CIA modeling was performed based on the assumption that the biomarker PD effect drove the disease inhibition.

Results: The BTK inhibitor showed an exposure-dependent suppression of joint inflammation in the rat CIA model with an EAUC50 of 56 uM.h, and blocking of CD86 upregulation in ex vivo whole blood B cell biomarker activation assay (IC50= 918 nM). Micro-CT imaging revealed reduced bone erosion in both ankle and knee joints by the inhibitor, and the bone effect correlated well with the reduction on joint inflammation. The integrated PK/PD-CIA model was used to simulate the full range of target engagement by the inhibitor as measured by the CD86 assay. A good correlation between average CD86 inhibition over a 24 hour time period and the paw thickness inhibition in the rat CIA model was found. An average of 60% CD86 suppression led to a 90% suppression of disease development in the rat CIA model.

Conclusion: The selective and novel BTK inhibitor is efficacious in the rat CIA model. Pharmacological evaluation of compounds in disease mechanism and target pathway relevant PK/PD and efficacy models can provide valuable data in building a translational PK/PD/efficacy platform from preclinical *in vitro* and *in vivo* models to human diseases in drug discovery.

Disclosure: J. Zhang-Hoover, Merck Pharmaceuticals, 3; **E. Leccese**, Merck Pharmaceuticals, 3; **K. Chakravarthy**, Merck Pharmaceuticals, 3; **I. Knemeyer**, Merck Pharmaceuticals, 3; **J. Lommerse**, Merck Pharmaceuticals, 3; **M. Spatz**, Merck Pharmaceuticals, 3; **F. Gervais**, Merck Pharmaceuticals, 3; **R. Sevilla**, Merck Pharmaceuticals, 3; **J. Liu**, Merck Pharmaceuticals, 3; **R. Kim**, Merck Pharmaceuticals, 3; **S. Lohani**, Merck Pharmaceuticals, 3; **K. M. Maloney**, Merck Pharmaceuticals, 3; **J. Kozlowski**, Merck Pharmaceuticals, 3; **A. Hicks**, Merck Pharmaceuticals, 3.

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β2 Adrenoceptor Signal Is Augmented in B Cells in the Course of Arthritis to Increase IL-10. Georg Pongratz, Clemens Wiest, Madlen Melzer and Rainer Strraub. University Hospital Regensburg, Regensburg, Germany.

Background/Purpose: Splenic B cells from collagen-induced arthritis (CIA) mice react to a β2-adrenoceptor (AR) stimulus with increased IL-10 production and adoptive transfer of these cells decreases disease activity. However, B cells from unimmunized mice do not adequately increase IL-10. Therefore, we test the hypothesis that sensitivity to catecholamines changes during CIA. Furthermore, we wanted to test if human peripheral blood B cells from osteoarthritis (OA) and rheumatoid arthritis (RA) patients also increase IL-10 following a β2-adrenergic stimulus.

Methods: FACS to determine AR pathway related proteins (β2-adrenoceptor, G-protein coupled receptor kinase (GRK) 2, phophorylated and unphosphorylated mitogen activated protein kinase p38, and cAMP responsive element binding protein (CREB)) in B cells at different timepoints during CIA. Unstimulated splenic B cells and B cells stimulated with terbutalin, a β2-AR agonist, were used. Human B cells were isolated from peripheral blood of patients with OA or RA and stimulated under different conditions with and without terbutalin. IL-10 protein level was determined by ELISA after 5 days of culture.

Results: In the course of CIA the percentage of β2-AR+ B cells increased and stayed above baseline (ANOVA $p<0.05$). In contrast, the mean fluorescence intensity (MFI) as measure for the number of receptors per cell remained unchanged. MFI for GRK2 decreased and stayed low from day 6 p.i. (ANOVA $p<0.0001$). The relative increase in phosphorylation of p38 (ANOVA $p<0.001$) and CREB (ANOVA $p<0.001$) following a β2-AR stimulus was augmented starting at day 18 p.i. with a maximum response at day 55 p.i. in the late phase of CIA. In human B cells, similar mechanisms are in place, because β2-AR stimulation of RA, but not OA B cells increased IL-10.

Conclusion: The current data show, that B cells become more sensitive to β2-AR stimuli in the course of CIA, possibly due to a decrease in GRK2 and increase in the percentage of β2-AR expressing splenic B cells. Increased catecholamine sensitivity might support B cell and IL-10 mediated anti-inflammatory mechanisms primarily in the late phase of CIA. A similar mechanism is observed in human peripheral B cells and might be used to improve treatment of autoimmune arthritis.

Disclosure: G. Pongratz, None; **C. Wiest**, None; **M. Melzer**, None; **R. Straub**, None.

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Microrna-155 As an Epigenetic Regulator of B-Cell Activation in Rheumatoid Arthritis: In Vivo and in Vitro Evidences. Stefano Alivernini[1], Barbara Tolusso[1], Silvia Canestri[1], Luca Petricca[1], Clara Di Mario[2], Elisa Gremese[1] and Gianfranco Ferraccioli[1]. [1]Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy, [2]Division of Pathology, Catholic University of the Sacred Heart, Rome, Italy.

Background/Purpose: MicroRNAs (miRs) are a novel class of post-transcriptional regulators. miR-155 was shown to be a regulator of B cell biology in haematological diseases as well as in myeloid cells in Rheumatoid Arthritis (RA). The regulation of the transcription factor PU.1 by miR-155 is required for the production of high-affinity IgG1 antibodies. The aim of this study was to investigate the expression of miR-155 in B cells of RA patients and its association with synovial inflammation.

Methods: 31 RA patients underwent ultrasound guided synovial tissue (ST) biopsy. ST samples were categorized through Hematoxiline and Eosine staining as diffuse or aggregate pattern. B cells from peripheral blood (PB) and matched synovial fluid (SF) of RA patients (n=19) and PB of healthy controls (HC) (n=10) were isolated by CD19+ microbeads (Mylteni). B-cell subsets were determined by Flow-Cytometry using IgD/CD27 classification and ZAP70 intracellular expression was assessed. IL-6 and BAFF levels in PB and SF were measured by ELISA. miR-155 expression was determined by qPCR on B cells from PB and SF and on ST of osteoarthritis (OA) (n=3), diffuse RA (n=5) and aggregate RA (n=5) patients. Finally, B cells from PB of HC (n=5) were isolated by CD19+ microbeads and cultured in RPMI with or without IL-6 (30 ng/ml), BAFF (20 ng/ml), IL-6+BAFF. Cells were collected after 24h, 48h and 72h to assess miR-155 and PU.1 expression by qPCR.

Results: 14(45,2%) RA patients showed an aggregate synovial pattern in ST. RA patients with an aggregate synovial pattern were more likely anti-CCP positive compared to RA patients with diffuse pattern ($p=0.05$). Moreover, anti-CCP plasma levels directly correlates with the synovial aggregate grade ($r=0.38$; $p=0.01$). IL-6 and BAFF levels were higher in SF than in PB of RA patients regardless to the synovial pattern ($p=0.001$ for both). CD19+/IgD-CD27- and CD19+/ZAP70+ cells were over-represented in PB of RA patients with an aggregate pattern ($p=0.05$ and $p=0.04$) compared to RA patients with a diffuse pattern. Moreover, anti-CCP+ RA patients showed higher percentages of CD19+/IgD-CD27- and CD19+/ZAP70+ in the PB ($p=0.01$ for both) compared to anti-CCP- RA patients. miR-155 was over-expressed in PB B-cells compared to HC ($p=0.0002$). miR-155 was over-expressed in SF B-cells compared to matched PB B-cells ($p=0.05$) in RA patients. Moreover, anti-CCP+ RA showed higher miR-155 expression in PB B-cells compared to anti-CCP- RA patients ($p=0.02$) and HC ($p=0.001$). miR-155 was over-expressed in ST of aggregate RA compared to diffuse RA ($p=0.03$) and OA ($p=0.03$) patients respectively. Finally, IL-6 and BAFF in vitro stimulation of healthy B-cells induced an overexpression of miR-155 after 72h of incubation ($p=0.04$ and $p=0.03$). Consistently PU.1 was down-regulated after in vitro stimulation ($p=0.01$ and $p=0.03$).

Conclusion: This study indicates that miR-155 is over-expressed in B-cells of RA patients and is associated to anti-CCP positivity and to an aggregate synovial pattern. IL-6 and BAFF, that are over-expressed in the SF environment, induce in vitro an over-expression of miR-155 in B-cells. Thus, miR-155 may represent a key regulator of B-cells in RA patients with an activated memory phenotype.

Disclosure: S. Alivernini, None; **B. Tolusso**, None; **S. Canestri**, None; **L. Petricca**, None; **C. Di Mario**, None; **E. Gremese**, None; **G. Ferraccioli**, None.

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Pathogenic Role of CXC Chemokine receptor 3-Positive B Cells in Bone Destruction of Rheumatoid Arthritis. Yuri Hirosaki, Hiroaki Niiro, Shunichiro Ota, Naoko Ueki, Hirofumi Tsuzuki, Kumiko Noda, Siamak Jabbarzadeh-Tabrizi, Hiroki Mitoma, Yojiro Arinobu, Mitsuteru Akahoshi, Hiroshi Tsukamoto and Koichi Akarshi. Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan.

Background/Purpose: B cells can function as potent effector cells by production of autoantibody, immune complex formation and inflammatory cytokines. Clinical efficacy of B-cell depletion therapy underscores a pathogenic role of B cells in autoimmune diseases such as rheumatoid arthritis (RA). A recent study suggests that infiltrating B cells in the joints of RA express RANKL, which plays a key role in osteoclastogenesis and inflammatory bone loss. In the RA joints, abundant accumulation of B cells expressing chemokine receptor CXCR3 was also noted, however the role of these cells in bone destruction of RA remains to be established. In this study, we have sought to elucidate the relationship of RANKL- and CXCR3-expressing B cells and their role in osteoclast differentiation.

Methods: Levels of RANKL/CXCR3 mRNA and protein in B cells from peripheral blood of normal subjects and RA patients were evaluated using quantitative RT-PCR and flow cytometry, respectively. Highly-pure B cell subsets were isolated using cell sorter. To validate the functional significance of osteoclast differentiation, B cells were co-cultured with osteoclast precursor cells and the formation of tartrate-resistant acid phosphatase (TRAP)-positive cells were assessed thereafter.

Results: Without stimuli, freshly-isolated B cells only marginally expressed RANKL mRNA and protein. Combined stimulation of B cells with B-cell receptor (BCR) and CD40, mimicked as chronic inflammation stimuli, however, significantly induced RANKL expression. Among B cell subsets, switched-memory (CD27+IgD-) B cells, a normal counterpart of pathogenic B cells in the joints, expressed RANKL at the highest levels. Upon the same stimulation, the levels of joint-homing receptor CXCR3 increased from 30 to 80%, representing the state of activation, but not plasma cell differentiation. Switched-memory B cells of RA patients expressed higher levels of CD80/CD86 than that of healthy control. In addition, highly-activated switched-memory B cells expressing CD80/CD86 double-positive B cells from RA patients expressed RANKL and CXCR3 at higher levels than those from normal subjects. Consistent with these findings, these subsets induced osteoclast formation as assessed by TRAP staining compared with other B cell subsets.

Conclusion: Our current findings shed the light on a pathogenic role of switched-memory B cells in bone damage associated with RA via production of RANKL, and regulation of CXCR3-expressing B cells may provide a novel strategy for the treatment for this devastating disease.

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ACR/ARHP Poster Session B

Biology and Pathology of Bone and Joint: Cartilage, Synovium and Osteoarthritis

Monday, November 17, 2014, 8:30 AM–4:00 PM

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Fibroblast-like Synoviocytes Inhibit Wnt Signaling Pathway By Secreting Dockcop-1. Satoshi Yamasaki and Eiji Sugiyrama. Hiroshima University Hospital, Hiroshima, Japan.

Background/Purpose: There is evidence of osteoclast activation in the inflamed joints of patients with rheumatoid arthritis (RA). Studies that focus on osteoblasts are not sufficient to illustrate the cell functioning in an RA joint. Osteoblast differentiation is regulated by complex environmental stimuli. Among them, Wnt family proteins are thought to promote osteoblast differentiation via stabilization of β-catenin and activation of TCF transcription. It is now known that the Wnt pathway is blocked with several soluble proteins such as Dockcop-1 (DKK-1) or Sclerostin (SOST). Fibroblast-like synoviocyte (FLS) is a unique articular resident cell and is a therapeutic target for RA, because the cell is believed to play a role in the joint destruction observed in this disease. In this study, we aimed to determine if FLS has an inhibitory effect on Wnt signaling.

Methods: FLS derived from RA patients (Articular Engineering, USA) was cultured in Dulbecco's modified Eagle's medium with 10% fetal bovine serum. Supernatants were collected from the FLS culture for 24 hours, with or without TNF-α (100 ng/ml, Millipore). The supernatants were added to U2OS culture after the transfection of TCF reporter plasmid, which contains Wnt/β-catenin responsive consensus sequence (Millipore), by using lipofectamine 2000 to monitor the activity of Wnt3a responsive promoter. Wnt3a (R&D) or lithium chloride (LiCl) was used to activate the Wnt signaling pathway. Anti DKK-1 antibodies were used to neutralize DKK-1 in uupernatants from the FLS. The DKK-1 productions from FLS were measured by ELISA after treatment with TNF-α (100 ng/mL), IL-6 (100 ng/mL) with soluble IL-6 receptor (100 ng/mL), or IL-17A (100 ng/mL) for 24 hours.

Results: Wnt3a (200 ng/mL) or LiCl (50 mM) clearly increased the luciferase activity, which was effectively suppressed by the addition of supernatants from the FLS culture. The supernatant from FLS treated with TNF-α exhibited a greater inhibitory effect on luciferase activity induced by Wnt3a or LiCl. The inhibitory effects were blocked by anti DKK-1 neutralizing antibodies. DKK-1 was detectable in the FLS culture medium by ELISA, and the concentrations of DKK-1 were higher in the FLS culture medium supplemented with TNF-α, but not with IL-6 or IL-17, compared to the control.

Conclusion: Our data suggests that FLS inhibits osteogenesis by inhibiting osteoblast differentiation, which is achieved by inhibition of the Wnt signaling pathway. DKK-1, an antagonist for Wnt signaling, is one of the soluble factors that might contribute to the inhibition of the Wnt signaling pathway by FLS. The inflammatory milieu may enhance the Wnt signal inhibition by FLS because TNF-α facilitates the secretion of DKK-1 from FLS. Detailed research is required for the clinical application of DKK-1 blockade in promoting bone regeneration in an inflamed joint of a patient with RA.

Disclosure: S. Yamasaki, None; **E. Sugiyama**, None.

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Global Transcriptome Analysis in Osteoarthritic Cartilage Reveals Significant Differential Gene Expression and Associations with Histologic Disease Progression. Matlock A. Jeffries[1], Madison Donica[1], Anand Annan[1], Michael Stevenson[1], Mary Beth Humphrey[1], Judith A. James[2] and Amr H. Sawalha[3]. [1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]University of Michigan, Ann Arbor, MI.

Background/Purpose: Osteoarthritis (OA) is the leading cause of chronic disability affecting 40% of individuals over the age of 70 and costing $128 billion annually in the US alone. Little is known regarding changes in gene expression that occur regionally within these affected joints. Herein, we perform RNA-seq analysis of eroded and intact cartilage from human OA, and correlate transcript levels with histopathologic disease severity.

Methods: Six femoral heads were obtained at the time of hip arthroplasty for primary OA. Articular cartilage tissue samples were dissected from grossly affected and grossly normal areas of the same joints, flash frozen in liquid nitrogen, and RNA was extracted. A portion of these samples were also histologically examined for OA severity using modified Mankin scoring. Following confirmation of RNA quality (RIN value $\geq$6), samples were sequenced with the Illumina TruSeq system on a MiSeq sequencer. Raw data were analyzed and mapped using the GeneSifter software package. Genes with GeneSifter quality score $<$1.0 were excluded. For categorical analysis, EdgeR $p \leq 0.01$ with Benjamini-Hochberg $q \leq 0.1$ and expression ratios ≤ 0.83 or ≥ 1.2 between affected and normal tissues were considered significant. For correlations with histologic score, Pearson's $r > 0.75$ or < -0.75 with $p \leq 0.05$ were considered significant. Gene ontology and pathway analysis was performed using the Ingenuity IPA platform.

Results: Categorical analysis identified 43 overexpressed and 313 underexpressed genes in eroded compared to intact cartilage. Both under- and overexpressed genes were overrepresented in the fibroblastic growth factor (FGF) signaling pathway ($p=0.004$). *FGFR2* demonstrated an eroded to intact cartilage expression ratio of 0.46, was highly inversely correlated with OA histologic score severity ($r=0.92$), and is known to be hypermethylated in eroded OA cartilage. The WNT pathway genes, *WNT11* (ratio 0.27) and *WNT9A* (ratio 0.45), and the STAT3 pathway was also overrepresented, including both under- and overexpressed genes ($p=0.001$). A top predicted upstream regulator in differentially expressed genes was mir-9 ($p=0.005$), known to be associated with metalloproteinase production. Further, we

identified 176 genes positively and 1591 genes inversely correlated with histopathologic score. Among these, the NFAT pathway was highly overrepresented, including both positively and inversely correlated genes (24, p=0.002). The RIG-I innate immunity pathway was also overrepresented among inversely correlated genes (p=0.008), as were several genes related to chromatin remodeling (overall p=0.009: HDAC1, r=−0.89, MECP2 r=−0.78, RBBP4 r=−0.82, SAP130 r=−0.81, SIN3A r=−0.80).

Conclusion: Using RNA-seq we detected significant changes in gene expression in eroded compared to intact OA cartilage, as well as expression changes correlated with histologic disease progression in OA. Our data strongly suggest involvement of several signaling pathways, many of which are potential therapeutic targets for OA. This work reinforces the heterogeneity of the disease process and provides novel insights into OA pathogenesis.

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1003

Proteomic Analysis of Connexin 43 Reveals Novel Interactors Related to Osteoarthritis. Raquel Gago-Fuentes[1], Patricia Fernández-Puente[2], Paula Carpintero-Fernández[1], Jesus Mateos[2], Maria Dolores Mayan[1] and Francisco Javier Blanco[2]. [1]Cartilage Biology Research Group, Rheumatology Division, INIBIC-Hospital Universitario A Coruña, A Coruña, Spain, [2]Rheumatology Division, CIBER-BBN/ISCIII, INIBIC-Hospital Universitario A Coruña, A Coruña, Spain.

Background/Purpose: We have previously reported that articular chondrocytes in tissue contain long cytoplasmic arms that physically connect two distant cells. Cell-to-cell communication occurs through connexin channels termed Gap Junction (GJ) channels, which achieve direct cellular communication by allowing the intercellular exchange of ions, small RNAs, nutrients and second messengers. The Cx43 protein is overexpressed in several human diseases and inflammation processes and in articular cartilage from patients with osteoarthritis (OA). An increase in the level of Cx43 is known to alter gene expression, cell signalling, growth and cell proliferation. The interaction of proteins with the C-terminal tail of connexin 43 (Cx43) directly modulates GJ-dependent and -independent functions. Here, we describe the isolation of Cx43 complexes using mild extraction conditions and immunoaffinity purification.

Methods: Cx43 complexes were extracted from human primary articular chondrocytes isolated from healthy donors and patients with OA. The proteomic content of the native complexes was determined using LC-MS/MS, and protein associations with Cx43 were validated using western blot and immunolocalisation experiments.

Results: We identified >100 Cx43-associated proteins including previously uncharacterised proteins related to nucleolar functions, RNA transport and translation. We also identified several proteins involved in human diseases, cartilage structure and OA as novel functional Cx43 interactors, which emphasised the importance of Cx43 in the normal physiology and structural and functional integrity of chondrocytes and articular cartilage. Gene Ontology (GO) terms of the proteins identified in the OA samples showed an enrichment of Cx43-interactors related to cell adhesion, calmodulin binding, the nucleolus and the cytoskeleton in OA samples compared with healthy samples. However, the mitochondrial proteins SOD2 and ATP5J2 were identified only in samples from healthy donors.

Conclusion: The identification of Cx43 interactors will provide clues to the functions of Cx43 in human cells and its roles in the development of several diseases, including OA.

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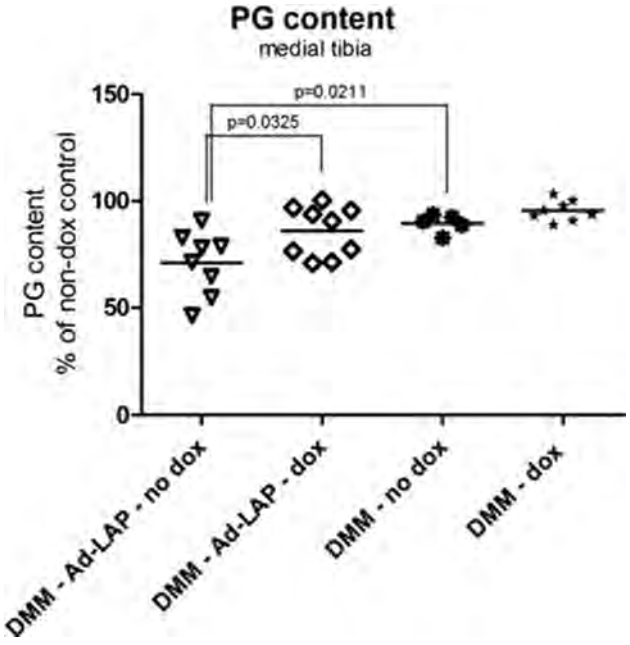
Elevated Levels of BMP2 Compensate for Loss of TGF-Beta in Articular Cartilage during Experimental Osteoarthritis. Esmeralda Blaney Davidson[1], Arjan van Caam[1], Arjen Blom[2], Elly Vitters[2], Miranda Bennink[1], Wim van den Berg[2], Fons van de Loo[1] and Peter van der Kraan[2]. [1]Radboud university medical center, Nijmegen, Netherlands, [2]Radboud University Medical Center, Nijmegen, Netherlands.

Background/Purpose: We have demonstrated that TGF-beta signaling via Smad2/3 is drastically reduced in articular cartilage (AC) with age and loss of Smad2/3-signaling predisposed AC for OA. We additionally showed that TGF-beta inhibition reduces the proteoglycan (PG) content in AC. During OA BMP2 is elevated in chondrocytes surrounding AC lesions. However, the effect of this BMP2 on AC is unclear. Therefore, we investigated whether elevated BMP-2 could counteract the loss of TGF-beta signaling during OA.

Methods: We made a unique transgenic mouse expressing human BMP2 under control of the Col2a1 promoter only when exposed to doxycycline (Col2a1-rtTA-BMP2). Functionality was tested on mRNA from AC, spleen and liver 72 hours after exposure to doxycycline- or standard diet (hBMP2 expression). We induced OA (DMM-model) while treating them with doxycycline- versus standard diet. To study the effect of losing TGF-beta activity, we intra-articularly injected an adenovirus overexpressing TGF-beta-inhibitor LAP (Ad-LAP). Four weeks after DMM induction knee joints were isolated for histology. OA was scored based on cartilage damage (adapted OARSI score, 0–30) and PG-content was measured with digital image analysis of Safranin O stainingin AC of the medial tibia.

Results: Doxycycline treatment clearly elevated hBMP2 mRNA in AC, but not in spleen and liver thereby confirming functionality of the transgenic mice. Doxycycline exposure in Col2a1-rtTA-BMP2 up to 8 weeks did not result in alterations in healthy AC. DMM induced a clear increase in OA-score (average of all DMM groups of 16.9 versus 2.5 in non-DMM), but this was not affected by elevated chondrocyte-specific BMP2. TGF-beta inhibition with LAP did not affect the OA-score either. However, TGF-beta inhibition during DMM significantly reduced the PG-content compared to DMM alone (18%). BMP2 did not affect the PG-content during DMM (figure). Nevertheless, the PG-depletion by inhibition of TGF-beta during DMM could significantly and nearly completely be counteracted by elevated chondrocyte-specific BMP2.



Conclusion: Our data show that in healthy AC and AC affected by OA in young animals BMP2 did not have detectible effects. However, when TGF-beta signaling was lost, a phenomenon occurring in aged individuals, this resulted in decreased levels of PG-content in AC during OA. In this setting, BMP2 compensated this PG loss. Therefore the elevated levels of BMP2 near OA lesions could be a reparative response of the AC, compensating age-related loss of TGF-beta signaling.

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Histone Lysine Demethylase KDM6A Mediates Joint Destruction in Osteoarthritic Knees By Epigenetic Disturbance of SOX9 Promoter and Histone H3K27. Feng-Sheng Wang, Pe-Chin Chuang, Yi-Chih Sun, Yu-Shan Chen and Jih-Yangr Ko. Kaohsiung Chang Gung Memorial Hospital, Taiwan, Kaohsiung, Taiwan.

Background/Purpose: Intensive articular cartilage deterioration and synovial fibrosis in joints are prominently pathogenic features of osteoarthritic (OA) knees. Epigenetic reactions in joint microenvironments are linked to the incidence

of OA knees. Histone lysine demethylase KDM6A is an emerging epigenetic regulator cntributing to tissue development and remodeling. This study was undertaken to investigate the biological roles of KDM6A in joint integrity of OA knees and decipher the epigenetic actions of KDM6A on methylation statuses of master cartilage regulator SOX9 promoter and histone 3 lysine 27 (H3K27) and metabolism of cartilage and synovial matrices in OA knee joints.

Methods: Mice with collagenase-induced OA knees were weekly administered with KDM6A inhibitor GSK-J4 or vehicle for 12 weeks. Gait profiles, fluorescence probe 2-deoxyglucose uptake by inflammatory tissues, and subchondral bone microstructures were analyzed using Catwalk, near infrared fluorescence in vivo imaging and μCT. Quantitative RT-PCR, immunoblotting, methylation-specific PCR, and chromatin immunoprecipitation were performed to quantify mRNA, protein expression, methylation statuses and enrichments of SOX9 promoter and H3K27.

Results: Articular cartilage damage and synovial fibrosis were in conjunction with increased expression of KDM6A, KDM6B and decreased levels of SOX9 and methylated H3K27 in OA knee joints. Administration with KDM6A inhibitor GSK-J4 alleviated the deleterious effects of OA on gait characteristics (maximum contact intensity, area and print area of paws) and joint inflammation. It also improved subchondral bone microarchitecture (trabecular volume, thickness, number and cortical porosity) and bone mineral density of affected joints. Inhibition of KDM6A attenuated the adverse effects of OA on chondrogenic matrix expression, morphology and OARSI scores of articular cartilage, as well as mitigated nucleated cell infiltration, hypervascularization and fibrotic matrix accumulation in synovial compartments. Loss of KDM6A signaling restored methylation of CpG islands in SOX9 promoter and alleviated the OA-mediated inhibition of SOX9 mRNA transcription and protein levels. Treatment with KDM6A inhibitor also increased H3K27 methylation that reduced the enrichment of H3K27 to proximal promoter region of fibrogenic transcription factor AP-1 and profibrotic gene expression in injured joint tissues.

Conclusion: KDM6A induces SOX9 promoter and H3K27 hypomethylation that deregulates SOX9 and AP-1 actions on articular cartilage integrity and synovium homeostasis in the pathogenesis of OA knees. Inhibition of KDM6A ameliorates the OA-mediated epigenetic dysfucntion in cartilage and synovium, thereby protects aganist excessive joint remodeling. This study sheds emerging lights on epigenetic modulation of joint integrity in OA knees and highlights that pharmaceutical modulation of KDM6A actions has therapeutic potentials for preventing against OA-induced joint damage.

Disclosure: F. S. Wang, None; **P. C. Chuang**, None; **Y. C. Sun**, None; **Y. S. Chen**, None; **J. Y. Ko**, None.

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Interleukin-4 As Promising, Anti-Inflammatory Transgene for Gene Therapeutic Application in Joint Diseases. Annemarie Lang[1], Johannes Neuhaus[2], Moritz Pfeiffenberger[3], Erik Schroeder[4], Frank Buttgereit[4], Michael F. G. Schmidt[3] and Timo Gaber[5]. [1]Berlin-Brandenburg School of Regenerative Therapies (BSRT), Berlin, Germany, [2]Research Center of Medical Technology and Biotechnology, Bad Langensalza, Germany, [3]Institute of Immunology, Freie Universität Berlin, Berlin, Germany, [4]Charité University Medicine, Berlin, Germany, [5]Berlin-Brandenburg Center of Regenerative Therapies (BCRT), Berlin, Germany.

Background/Purpose: Interleukin- 4 (IL-4), a Th2-cell released immunomodulatory factor, has potent chondroprotective and anti-inflammatory properties able to inhibit the synthesis of IL-1β and TNFα, and to reduce the inflammation-induced mediators of cartilage breakdown (e.g.: NO, PGE2, MMPs). To optimize cartilage transplants for the application in patients with cartilage defects as a result of osteoarthritis (OA) or rheumatoid arthritis (RA) we developed a vector for the transgenic expression of IL-4 in chondrocytes under the "smart" control of the inflammation-activated cyclooxygenase- 2 promoter (pCox-2) which is inactive under non-inflammatory conditions. For effective translation to the clinic we use the horse as naturally occurring model since the disease in this species parallels the human form of OA.

Methods: The non-viral transfection of equine chondrocytes was optimized by comparing a range of different reagents as well as by different vector designs using the co-expression of the reporter gene GFP by flow cytometry. For further investigations, we used vectors containing Cox-2 and IL-4 in combination or alone. After transfection cells were stimulated using 100ng/ml Il-1β to mimic inflammation. Induction of Il-4 was validated on mRNA level and protein level by quantitative PCR, ELISA and Western Blot. To confirm the functional activity of transgenic IL-4 as well as simulation of inflammation we additionally analyzed Cox-2, IL-1β, IL-6, IL-8, MMP-3, MMP-9 and MMP-13 on mRNA level by quantitative PCR.

Results: The transfection efficiency was increased up to 44% by delivering a vector without IRES and using Turbofect (Fermentas). A plasmid vector including IL-4 as therapeutic gene under the control of pCox-2 was proven to be functional since it induced the production of high levels of IL-4 in cell culture supernatants and cell lysates. Furthermore, in the same cultures IL-1β IL-1β, IL-6, IL-8, MMP-3, MMP-9 and MMP-13 expression was significantly decreased whenever IL-4 was expressed.

Conclusion: Our study shows the promising impact of new generation gene therapy where the therapeutic transgenic target IL-4 will only be expressed if inflammatory mediators are present. IL-4 demonstrated chondroprotective and anti-catabolic potential *in vitro*. Translation into clinical practice: cartilage transplants containing autologous cells with the inflammation sensitive plasmid could exert therapeutic effects when placed close to the defective joint area. We are presently focusing on the application of the new plasmids in a 3D-*in-vitro*-OA-model including viral gene delivery systems. Eventually, *in vivo* studies and clinical trials are needed to substantiate the promising potential of our therapy concept.

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Markedly Increased Mesenchymal Stem Cell Activity in MRI Bone Marrow Lesions Compared with Non-Involved Bone in Osteoarthritic Hips. T Mark Campbell[1], Frederique Ponchel[2], Alexandro Gomez[3], Richard J. Hodgson[2], Dennis McGonagle[4], Philip G. Conaghan[5] and Elena Jones[3]. [1]The Ottawa Hospital Rehabilitation Centre, Ottawa, ON, [2]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [3]1Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR, Leeds, United Kingdom, [4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [5]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, Leeds, United Kingdom.

Background/Purpose: Multipotent mesenchymal stem cells (MSCs) are critical for bone and cartilage repair but the role of such cells *in vivo* in hip OA is poorly defined. Subchondral bone changes depicted as bone marrow lesions (BMLs) on MRI are intimately linked to joint remodelling and OA structural deterioration, suggesting potential aberrant MSC responses within such tissue. We hypothesised that deficiencies in native *in vivo* $CD45^-CD271^+$ MSC numbers and/or function contributed to BML pathophysiology and investigated BML and non-BML hip subchondral bone for numerical, topographic and *in vitro* functional differences.

Methods: Twenty femoral heads were obtained during total hip arthroplasty from subjects with primary hip OA that fulfilled the ACR criteria for hip OA. *Ex vivo 3T* MRI identified BML and non-BML regions from excised hips; one half was enzymatically treated to extract cells and the other half EDTA-decalcified to quantify trabecular bone area and cartilage thickness. Digital imaging was performed on 15 paired excisions using 92 manually defined morphologically homogenous regions containing cartilage and 188 regions containing only bone. The MSC frequency relative to total live cells was established using flow cytometry for the $CD45^-CD271^+$ phenotype. A colony forming unit-fibroblast (CFU-F) assay determined the number of MSCs per million cells. *In vitro* tri-lineage MSC differentiation assessed functional capacity of expanded $CD271^+$ cells. MSC topography was examined using anti-CD271 IHC.

Results: Regions with a normal appearance of cartilage were closely associated with non-BML excisions ($p=0.01$) compared to BML where most of the surface was damaged. Trabecular bone area was increased in BML regions ($p=0.001$). In 18/20 subjects, the proportion of native $CD45^-CD271^+$ MSC phenotype cells was higher in BMLs (Figure 1A, median 3.5-fold difference; $p<0.001$). This was confirmed using CFU-F assays (Figure 1B, 12/14 subjects, median 3.5-fold; $p=0.013$). Small differences were detected in MSC proliferation and mineralization capacities but not in their phenotype ($\diamond$95% $CD73^+CD90^+$). We observed abundant $CD271^+$ MSCs surrounding subchondral blood vessels near the cement line underlying cartilage lesions and in regions surrounding subchondral cysts, suggesting an accumulation and/or local proliferative MSC response to tissue injury (Figure 1C).

Conclusion: BMLs of OA femoral heads contain a higher proportion of MSCs with similar *in vitro* functional capacity compared to neighbouring

non-BML regions. Topographically, MSCs appear to be abundant in areas of active osteochondral repair and neo-angiogenesis. Despite this abundance, the *in vivo* MSC response is likely to be inadequate in the face of abnormal joint biomechanical stressing. These data advocate that, given their abundance, *in vivo* MSC repair-capacity optimization may be a target for future OA treatments.

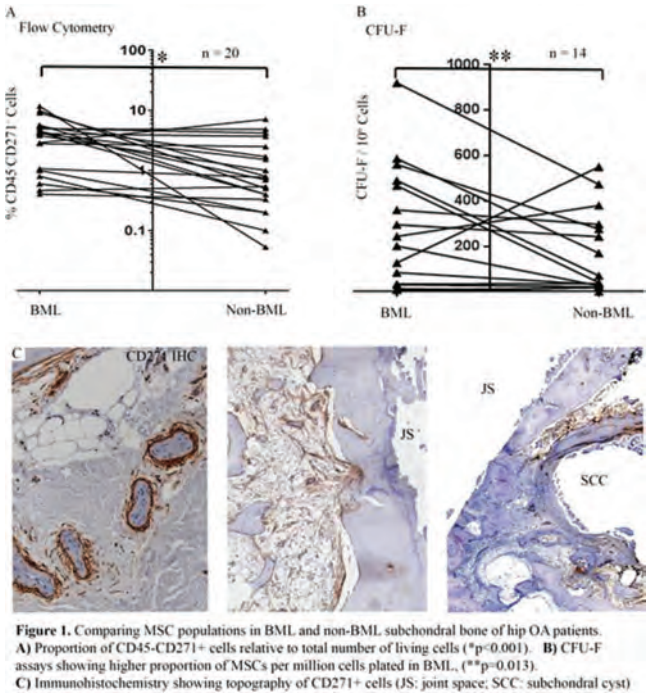

Figure 1. Comparing MSC populations in BML and non-BML subchondral bone of hip OA patients. **A)** Proportion of CD45-CD271+ cells relative to total number of living cells (*p<0.001). **B)** CFU-F assays showing higher proportion of MSCs per million cells plated in BML, (**p=0.013). **C)** Immunohistochemistry showing topography of CD271+ cells (JS: joint space; SCC: subchondral cyst)

Disclosure: T. M. Campbell, None; **F. Ponchel**, None; **A. Gomez**, None; **R. J. Hodgson**, None; **D. McGonagle**, None; **P. G. Conaghan**, None; **E. Jones**, None.

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Autophagy Activation Protects from Mitochondrial Dysfunction in Human Chondrocytes. Beatriz Carames[1], Paloma López de Figueroa[2], Martin Lotz[3] and Francisco J. Blanco[4]. [1]Cartilage Biology Group. Rheumatology Division, INIBIC–A Coruña, SPAIN, A Coruña, Spain, [2]Cartilage Biology group. Rheumatology Division, INIBIC-A Coruña, Spain, A Coruña, Spain,[3] The Scripps Research Institute, La Jolla, USA, La Jolla, CA, [4]Rheumatology Division, INIBIC-A Coruña, Spain, A Coruña, Spain.

Background/Purpose: Autophagy, is a key pathway of cellular homeostasis for removing damaged macromolecules and organelles, including mitochondria. Recent studies indicate that autophagy activation is defective in aging and osteoarthritis (OA), contributing to the cell death and tissue damage. In addition, there is increasing evidence that mitochondrial dysfunction plays an important role in OA pathogenesis. *The objective of this study is to determine whether activation of autophagy protects from mitochondrial dysfunction in human chondrocytes.*

Methods: Human chondrocytes were treated with Oligomycin (10 μg/ml), a mitochondrial respiratory chain (MRC) inhibitor of complex V. Mitochondrial function and cell death were evaluated by Flow Cytometry, Fluorescence Microscopy. Autophagy activation was analyzed by determination of LC3-II, a main marker of autophagy activation by Immunofluorescence and Western Blot. To investigate whether autophagy protects from mitochondrial dysfunction, autophagy was induced by mammalian target of rapamycin complex 1 (mTORC1) selective inhibitor Rapamycin (Rapa, 10 μM) and the dual mTORC1 and mTORC2 inhibitor Torin 1 (50 nM). Genetic deletion of Atg5 (siAtg5), a essential autophagy marker for autophagosome formation, was employed to evaluate the role of autophagy in mitochondrial dysfunction.

Results: Mitochondrial dysfunction was induced by treatment with Oligomycin, which significantly decreased mitochondrial membrane potential ($\Delta\Psi$m) (Oligo: 41.74 $\pm$ 7.59, expressed as % vs control; *.p $<$ 0.01). This was associated with increased intracellular ROS production (25.7 % vs. control; *p $<$ 0.001 compared to control condition) and mitochondrial superoxide generation (29.61 % vs. control; *p $<$ 0.001 compared to control condition). Furthermore, increased cell death by apoptosis was observed (Control: 11.35 $\pm$ 1.735; Oligo: 25.37 $\pm$ 6.767, *p$<$0.05 vs. control). Autophagy activation determined by LC3-II was increased at short incubation times, perhaps acting as an early response to stress and then decrease in a time dependent manner. To evaluate whether autophagy regulates mitochondrial dysfunction, chondrocytes were pretreated with Rapa and Torin 1 and then treated with Oligomycin. The results show an increase in LC3 expression compared to MRC inhibitor alone. Furthermore, autophagy inducers Rapa and Torin1 increased $\Delta\Psi$m (Rapa: 125.8 $\pm$ 20.74; Rapa $\pm$ Oligo: 108.5 $\pm$ 55.03 and Torin 1: 90.34 $\pm$ 9.17; Torin 1+Oligo: 98.19 $\pm$ 16.81; *p$<$0.05), decreased ROS production and reduced cell death (*p$<$0.05), suggesting a protective effect of autophagy activation on pharmacologically induced mitochondrial dysfunction. Importanly, blocking autophagy by siAtg5 showed a significant dysfunctional changes in the $\Delta\Psi$m and ROS production (*p$<$0.05), indicating the essential role of autophagy in mitocondrial function.

Conclusion: Our data highlight the role of autophagy as a critical protective mechanism against mitochondrial dysfunction. Pharmacological interventions that enhance autophagy may have chondroprotective activity in cartilage degenerative processes such as OA.

Disclosure: B. Carames, None; **P. López de Figueroa**, None; **M. Lotz**, None; **F. J. Blanco**, None.

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Regeneration of Articular Cartilage in Situ with Bone Marrow-Derived Mesenchymal Stem Cells. Cong-Qiu Chu[1], Xiaowei Zhang[2], Yuan K. Chou[2], Shili Wu[3], Camilo Avenano[3], Tom Caldwell[3], Brian Maniaci[3] and Yong Zhu[3]. [1]Oregon Health & Science Univ, Portland, OR, [2]Oregon Health & Science University, Portland, OR, [3]VivoScript, Inc, Costa Mesa, CA.

Background/Purpose: Regeneration of hyaline cartilage has been an attractive approach to cartilage repair and therapy of osteoarthritis (OA), but remains to be a challenge. SOX9 is a transcription factor belonging to the Sox (Sry-type HMG box) gene family and has been identified as a "master regulator" of chondrogenesis. We reported previously that a super positively charged cell penetrating SOX9 fusion protein (scSOX9) can induce bone marrow-derived mesenchymal stem cells (MSC) to differentiate into chondrocytes *in vitro*. Here we investigated the *in vivo* use of scSOX9 to promote hyaline cartilage regeneration *in situ* in combination with microfracture for articular cartilage repair in a rabbit model.

Methods: scSOX9) was generated by fusing SOX9 with a super positively charged green fluorescence protein. A 4 mm in diameter, full-thickness cartilage defect was created at the right femoral trochlear groove in New Zealand female rabbits. Microfracture was performed using a 0.9 mm Kirschner wire tapped into the subchondral bone to a depth of approximately 3 mm. Three microfracture holes were created within each full-thickness chondral defect in a triangular configuration. scSOX9 was administered at the site of mcrofracture via a bilayer collagen membrane. Cartilage repair was assessed at 8 weeks by gross morphology, histology and analysis of matrix component and was quantified using International Cartilage Repair Society (ICRS) macroscopic scale and ICRS Visual Histological Assessment Scale (ICRS-VHAS). High scores indicate high quality of repaired cartilage.

Results: After creation of cartilage defect, rabbits were divided into 4 groups (n=4 in each group) for treatment: Group 1, un-treated, Group 2, microfracture only, Group 3, microfracture plus scMyoD (a control protein for scSOX9) and Group 4, microfracture plus scSOX9. As shown in Table 1, microfracture plus scSOX9 significantly improved cartilage repair with nearly 100% defect area being covered with repaired tissue compared with 78% in Group 3, 80% in Group 2 and 18% in Group 1 respectively. Compared with all other groups, morphologically microfracture plus scSOX9 induced hyaline like cartilage which was well integrated with native cartilage and the repaired tissue showed highest intensity of Safranin O staining, indicating the highest density of proteoglycan.

Table 1. ICRS Macroscopic Scores and ICRS Visual Histological Assessment Scale

	ICRS Macroscopic Score	P value*	ICRS VHAS	P value*
Group 1	2.5 $\pm$ 0.5	$<$0.001	3 $\pm$ 1.5	$<$0.001
Group 2	7 $\pm$ 2.1	$<$0.05	14 $\pm$ 0.5	$<$0.005
Group 3	5 $\pm$ 2.3	$<$0.01	6 $\pm$ 3.2	$<$0.01
Group 4	12 $\pm$ 1.2		17 $\pm$ 1.5	

*p value indicated comparison of Group 4 with other groups.

Conclusion: This short term *in vivo* study demonstrated that when administered at the site of microfracture, scSOX9 was able to induce

reparative tissue with features of hyaline cartilage and significantly improved the outcome of cartilage repair by microfracture. These data suggest combination of microfracture with scSOX9 has great potential being translated into a therapy for cartilage repair and therapy for OA.

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Catecholaminergic-to-Cholinergic Transition of Sympathetic Nerve Fibers in Arthritis and in a Co-Culture System of Sympathetic Ganglia in Vitro. Hubert Stangl[1], Hans Robert Springorum[2], Dominique Muschter[2], Susanne Graessel[2] and Rainer Straub[1]. [1]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, University Hospital Regensburg, Regensburg, Germany, [2]Division of Experimental Orthopedic Surgery, University Hospital Regensburg, Regensburg, Germany.

Background/Purpose: Sympathetic nerve fibers play an important role in bone and tissue homeostasis of joints. However sympathetic nerve fibers are able to switch their phenotype and respective neurotransmitter machinery from sympathetic to cholinergic. This transition was shown in developing sweat glands, in the periosteum and in failing heart tissue. This is crucial since strong anti-inflammatory effects have been described for the α7nicotinic acetylcholine receptor as well as for the cholinergic co-transmitter vasoactive intestinal peptide (VIP). We studied connective tissue obtained from the knee and finger joints of osteoarthritis (OA) and rheumatoid arthritis (RA) patients and tested possible transition requirements in an in-vitro model with murine sympathetic ganglia.

Methods: Knee synovial tissue samples obtained from 44 OA and 21 RA patients and connective as well as bone tissue samples from interphalangeal finger joints obtained from seven OA and five RA patients were stained for tyrosine hydroxylase (TH, noradrenergic fibers), vesicular acetylcholine transporter (VAChT, cholinergic fibers) and VIP (cholinergic fibers). Sympathetic ganglia were obtained from newborn C57Bl/6 mice and double-stained for TH and VAChT after a co-culture period of two days with osteoclast progenitors attained from the femoral and tibial bone marrow from adult healthy and arthritic mice. Supernatants from osteoclast progenitors were tested for possible transition factors. Whole RNA isolated from the respective osteoclast progenitors was screened via microarray analysis in order to identify possible candidate transition factors.

Results: In connective tissue sections from human finger joints, VAChT but not VIP positive cholinergic nerve fibers were more present in OA than in RA patients. In knee synovial tissue no significant difference in the appearance of cholinergic (VAChT and VIP) nerve fibers was found. The ratio of VAChT/TH immunoreactivity of sympathetic ganglia in coculture with osteoclast progenitors from healthy mice was elevated compared to experiments with osteoclast progenitors from arthritic mice. Leukemia inhibitory factor (LIF), a known transition factor from the glycoprotein 130 cytokine family, is present in low concentrations in supernatants from osteoclast progenitor cells but did not induce transition. Microarray analysis showed an upregulation of several candidate molecules (biglycan, fibronectin, LIF, periostin, tenascin-C, tensin-1, TIMP-1) in the transcriptome of osteoclast progenitors from healthy mice compared to arthritic ($n=3$ vs. 3, mean fold chance >2.0, $p<0.01$).

Conclusion: In humans and mice, catecholaminergic-to-cholinergic transition is possible in less inflamed tissue of the joint but not in highly inflamed arthritic tissue.

Disclosure: H. Stangl, None; **H. R. Springorum**, None; **D. Muschter**, None; **S. Graessel**, None; **R. Straub**, None.

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Fibroblast Growth Factor-2 and Its Receptor Antagonists in Osteoarthritis. Elina Nummenmaa, Mari Hamalainen, Teemu Moilanen, Katriina Vuolteenaho and Eeva Moilarnen. The Immunopharmacology Research Group, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland.

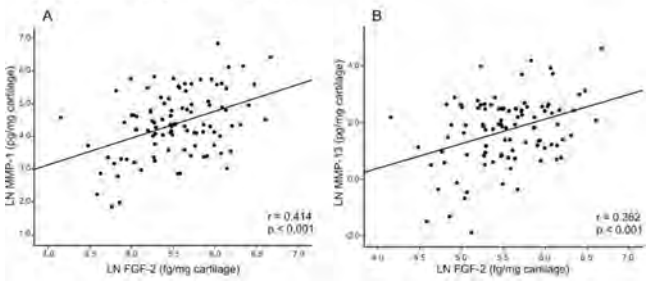
Background/Purpose: The fibroblast growth factor (FGF) family represents an interesting group of molecules which are involved in the regulation of connective tissue development and metabolism. FGF-18 has promising effects also in articular cartilage whereas FGF-2 seems to signal through different cellular receptors and its role in osteoarthritis (OA) remains unknown in many aspects. In the present study we investigated the presence and effects of FGF-2 in OA joints by assessing the associations of FGF-2 with cartilage degrading matrix metalloproteinase (MMP) enzymes and with the synthesis of the major cartilage matrix components aggrecan and collagen as well as by investigating the effects of FGF receptor antagonists.

Methods: Synovial fluid and cartilage samples were obtained from 97 OA patients undergoing total knee replacement surgery (60 females and 37 males, BMI 30.9 ± 0.6 kg/m^2, age 69.8 ± 1.0 years; mean $\pm$ SEM). FGF-2 concentrations in the synovial fluid and cartilage culture medium were measured by immunoassay. The effects of FGF-2 and its receptor antagonists on the production of MMP-1, MMP-13, aggrecan and collagen II were investigated in cultures of primary human OA chondrocytes. The study was approved by the Ethics Committee of Tampere University Hospital, Tampere, Finland and it was carried out in accordance with the Declaration of Helsinki. The patients gave their written informed consent, and their diagnosis was confirmed to fulfill the ACR classification criteria for osteoarthritis.

Results: FGF-2 was present in OA synovial fluid and released into the culture media from cartilage samples obtained from OA patients. Interestingly, FGF-2 concentrations correlated positively with the concentrations of MMP-1 ($r = 0.414$, $p < 0.001$) and MMP-13 ($r = 0.362$, $p < 0.001$) (Fig. 1) in the cultures of OA cartilage. Further, FGF-2 up-regulated the production of MMP-1 and MMP-13, and down-regulated the expression of aggrecan and collagen II, in human OA chondrocyte cultures. More importantly, FGF receptor antagonists AZD4547 and NVP-BGJ398 (10–300nM) down-regulated the production of MMP-1 and MMP-13 and up-regulated the expression of aggrecan and collagen II in a concentration dependent manner, and not only in the presence but also in the absence of exogenous FGF-2.

Conclusion: The present results suggest that, in contrast to its growth factor like effects in some other conditions, FGF-2 induces catabolic and anti-anabolic effects in osteoarthritis. Moreover, FGF-receptor antagonists showed promising beneficial effects on the balance of catabolic and anabolic mediators within OA cartilage.

Figure 1. Levels of FGF-2 released by human OA cartilage correlated positively with the levels of MMP-1 (A) and MMP-13 (B)



Disclosure: E. Nummenmaa, None; **M. Hamalainen**, None; **T. Moilanen**, None; **K. Vuolteenaho**, None; **E. Moilanen**, None.

1012

Role of High Glucose Environment on Chondrocyte Activation and Characterization of Diabetic Osteoarthritic Cartilage: Toward Pathophysiological Delineation of Diabetes Mellitus-Related Osteoarthritis. Marie-Charlotte Laiguillon[1], Alice Courties[2], Xavier Houard[1], Martine Auclair[1], Alain Sautet[3], Bruno Fève[1], Jacqueline Capeau[1], Francis Berenbaum[2] and Jérémie Sellam[2]. [1]Sorbonne Universités, UPMC Univ Paris 06, UMRS 938 and Inflammation-Immunopathology-Biotherapy Department (DHU i2B), Paris, France, [2]AP-HP, Saint-Antoine Hospital, Rheumatology Department and DHU i2B, Paris, France, [3]AP-HP, Saint-Antoine Hospital, Orthopaedic Surgery Department, Paris, France.

Background/Purpose: Recent epidemiological studies have suggested an association between type 2 diabetes/hyperglycemia and osteoarthritis (OA) but experimental evidences are lacking (1). We aimed i) to decipher *in vitro* the impact of a high glucose environment on chondrocyte activation ii) to compare the production of pro-inflammatory mediators by OA cartilage explants derived from diabetic (db) or non-db patients.

Methods: Primary cultures of chondrocytes from new-born mice were stimulated for 24h and 72h with/without IL-1β (5 ng/mL) under a normal (5.5 mM) or a high (25 mM) glucose environment. Glucose uptake by cells was

analyzed by incorporation of radioactive 2-deoxyglucose. Osmotic stress was assessed by adding mannitol. Gene expression and release of pro-inflammatory mediators (IL-6, COX2/PGE_2) were analyzed by RT-qPCR, ELISA and EIA, respectively. Oxidative stress was assessed by the measurement of reactive oxygen species (ROS) by fluorescent DCFDA and production of NO by Griess reaction. To address the role of high glucose and oxidative stress on chondrocyte activation, cells were pretreated with cytochalasin B (1 μM), a glucose transporter inhibitor, or treated with a specific inhibitor of the polyol pathway (Epalrestat, 10 μM), a specific mitochondrial antioxidant (Mitotempo, 50 μM) or a NO synthase inhibitor (L-NAME, 5 mM). *Ex vivo*, pro-inflammatory mediators (IL-6, PGE_2) release in 24h-conditioned media of IL-1b- stimulated OA cartilage from db and non-db patients was measured by ELISA/EIA.

Results : *In vitro*, at 72h, the expression and release of IL-6 and COX2/PGE_2 were dramatically increased in the presence of IL-1β in high glucose as compared to normal glucose concentration by 5.6- and 3- [IL-6 mRNA and protein, respectively], 8- [Cox2] and 3.6-fold [PGE_2]) (n=5, p=0.03 for all analyzes). Glucose uptake was also transiently increased by IL-1β at 72h (n=3). Mannitol experiments ruled out the hypothesis of an osmotic stress due to high glucose (n=3). High glucose environment under IL-1β stress increased ROS and NO production (2.1- and 1.9-fold, respectively; n=5, p=0.04 and p=0.03). Cytochalasin B significantly decreased the induction of IL-6 mRNA (−40%; n=6, p=0.02). L-NAME significantly decreased the release of IL-6 and PGE_2 (−40% and -78%, respectively; n=5, p=0.04) as did Epalrestat (−49% for mRNA IL-6 and -55% for COX2; n=3), and as did Mitotempo (IL-6: -69% and COX2: -90%; n=2).

Conclusion : High glucose exposure sensitizes chondrocytes to IL-1b activation *via* increased glucose uptake, oxidative stress and polyol metabolic pathway leading to a sustained chondrocytic pro-inflammatory phenotype. Such results are in accordance with an increased sensitivity to inflammatory stress of OA cartilage of db patients. These results strengthen the hypothesis that diabetes could be a trigger for the initiation and/or the severity of OA.

Reference:
Schett G et al. Diabetes Care. 2013

Disclosure: M. C. Laiguillon, None; **A. Courties**, None; **X. Houard**, None; **M. Auclair**, None; **A. Sautet**, None; **B. Fève**, None; **J. Capeau**, None; **F. Berenbaum**, None; **J. Sellam**, None.

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Mitochondrial Function Is Impaired in Human Knee Osteoarthritic (OA) Chondrocytes and Improved By Pharmacologic AMPK Activation Via SIRT1 and PGC-1α.

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Background/Purpose: Chondrocyte mitochondrial abnormalities have been identified in OA, and have the potential to mediate disease progression by promoting oxidative stress and inflammation-driven cartilage matrix catabolism. AMPK (AMP-activated protein kinase) and the NAD^+-dependent protein deacetylase SIRT1 are cellular energy bio-sensors recently implicated in cartilage tissue homeostasis. In chondrocytes, AMPK promotes expression of PGC-1α, a master regulator of mitochondrial biogenesis. SIRT1 also regulates PGC-1α through deacetylation, and AMPK can regulate SIRT1 activity. Hence, we tested the hypothesis that pharmacologic activation of AMPK improves mitochondrial function via SIRT1 and PGC-1α in human knee OA chondrocytes.

Methods: We studied cultured human knee chondrocytes from both normal and OA donors (passage 1) with and without the selective AMPK pharmacological activator A-769662, or overexpression of SIRT1 or PGC-1α via transfection. Phosphorylation and expression of AMPKa, expression of SIRT1, PGC-1α, acetylation status of PGC-1a, expression of mitochondrial transcriptional factor A (TFAM, a direct regulator of mitochondrial DNA replication and transcription), nuclear respiratory factor 1 and 2 (NRF1 and NRF2, stimulating transcription of TFAM), and oxidative phosphorylation (OXPHOS) were examined by Western blot analyses. Mitochondrial DNA copy number was determined by the ratio of cytochrome C oxidase I or II (*COX I* or *COX II*, mitochondrial-encoded gene) and 18S rRNA (nuclear gene) by quantitative PCR. Mitochondrial mass was assessed by Mitotracker Green FM staining. Oxygen consumption and intracellular ATP were measured.

Results: In comparison with normal chondrocytes, human OA chondrocytes (grade III and IV) exhibited reduced oxygen consumption (P=0.03), decreased intracellular ATP level (P=0.019), and less mitochondrial biogenesis indicated by decreased mitochondrial DNA content (P=0.001) and mitochondrial mass, decreased expression of NRF1, NRF2 and TFAM, as well as decreased expression of respiratory complexes I, II and III. These differences were linked to reduced phosphorylation of AMPKα and expression of SIRT1 and PGC-1α, and increased acetylated PGC-1α in OA chondrocytes. Stimulation of human OA chondrocytes with A-769662 increased phosphorylation of AMPKα and expression of SIRT1 and PGC-1α, and decreased acetylation of PGC-1α. A-769662 also increased oxygen consumption (p=0.003), intracellular ATP level (p=0.015), and mitochondrial biogenesis. Overexpression of SIRT1 or PGC-1α in chondrocytes also induced increased mitochondrial biogenesis.

Conclusion: Both mitochondrial oxidative phosphorylation and mitochondrial biogenesis are impaired in human knee OA chondrocytes. AMPK activation improved the observed impairments of mitochondria in OA chondrocytes, and did so via SIRT1 and PGC-1α.These findings provide a novel molecular mechanism by which pharmacologic activation of AMPK has translational potential to inhibit progression of cartilage degradation in OA via restoration of chondrocyte mitochondrial biogenesis and function.

Disclosure: R. Bryan, None; **Y. Wang**, None; **X. Zhao**, None; **M. Lotz**, None; **R. Terkeltaub**, None.

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Harpagide, a Low Molecular Weight Natural Product, Suppresses IL-1â-Induced IL-6 Expression By Blocking the Activation of p38 MAPK and Transcription Factors CEBPâ and AP-1 in Primary Human Osteoarthritis Chondrocytes.

Abdul Haseeb[1] and Tariq Haqqi[2]. [1]Northeast Ohio Medical University (NEOMED), Rootstown, OH, [2]Northeast Ohio Medical University, Rootstown, OH.

Background/Purpose: There is growing evidence that shows the involvement of IL-6 in cartilage degradation during OA. Significant correlation between IL-6 levels in serum as well as synovial fluid and OA severity has been reported. IL-6 stimulates the expression of MMP-13 and inhibits the expression of type II collagen. Harpagide is a low molecular weight compound isolated from the secondary roots of *Harpagophytum procumbens (Hp)*. In the present study we used an *in vitro* model of inflammation in OA to investigated the therapeutic potential of Harpagide in OA.

Methods: Primary human chondrocytes were isolated from the non-affected cartilage obtained from OA patients who underwent total knee arthroplasty. Human OA chondrocytes were cultured and pre-treated with Harpagide (500 μM) and then cultured with and without IL-1β (5 ng/ml). Chondrocyte viability was assayed using Trypan blue exclusion assay. Secreted levels of IL-6 in the culture supernatants were quantified by ELISA. Total protein levels and phosphorylation levels of CEBPβ and AP-1 in human OA chondrocytes were measured by Western blot analysis using specific antibodies. Nuclear extracts were prepared and used to study the effect on the nuclear localization and activation of NF-κB, CEBPβ and AP-1 in OA chondrocytes by Western blotting and DNA binding activity. IL-6 mRNA levels were quantified using the TaqMan assays. Data were derived using Origin 6.1 software and $P<0.05$ was considered significant.

Results: Harpagide had no effect on OA chondrocyte viability *in vitro*.Treatment of primary human OA chondrocytes with IL-1β markedly stimulated the mRNA expression of IL-6 and protein secretion in the culture supernatants which was inhibited significantly (p<0.05) by pre-treatment with Harpagide. Harpagide did not inhibit the IL-1b-induced degradation of IκB and the activation of NF-κB but suppressed the IL-1β-triggered nuclear localization and activation of CEBPβ and AP-1 in human OA chondrocytes. There was a significant decrease in IL-1β-induced phosphorylation of CEBPβ, c-Fos and ATF-2 by Harpagide which also inhibited the IL-1β-induced enhancement in cytoplasmic levels of total c-FOS protein in OA chondrocytes. While there was a significant decrease in the nuclear levels of CEBPβ and c-Fos, there was no effect of pre-treatment of the cells with Harpagide on nuclear levels of NF-kB-p-65. Activation of p38 MAPK, which phosphorylates CEBPβ, ATF-2 and c-Fos resulting in their activation was significantly inhibited by Harpagide in human OA chondrocytes. Two small molecule inhibitors of p38MAPK (SB203580 and SB202190) also significantly inhibited the IL-1b-induced activation of p38-MAPK and the expression and secretion of IL-6 in human OA chondrocytes.

Conclusion: Taken together, the data presented here suggests that Harpagide may have a significant chondroprotective and OA suppressive effect by inhibiting the expression and production of IL-6. Importantly, we

also identify a novel mechanism of IL-6 suppression which bypasses the activation of NF-*kB*.These data provide strong evidence with mechanistic details in support of the possible use of Harpagide as a therapeutic choice to prevent/retard the progression of OA.

Background/Purpose
Methods
Results
Conclusion

Disclosure: A. Haseeb, None; **T. Haqqi**, None.

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Mir-9/MCPIP1 Axis Mediated Regulation of IL-6 Expression in Osteoarthritis Chondrocytes. Tariq Haqqi[1], Abdul Haseeb[2] and Mohammad Shahidul Makki[2]. [1]Northeast Ohio Medical University, Rootstown, OH, [2]Northeast Ohio Medical University (NEOMED), Rootstown, OH.

Background/Purpose: Post-transcriptional regulation of cytokine expression is important for maintaining tissue integrity. MCPIP1 was identified as a novel protein, which destabilizes inflammatory cytokines mRNAs via their 3' UTR. IL-6 has recently gained attention because of its high levels in synovial fluid in Osteoarthritis (OA) and ability to induce high levels of MMP-13 in OA. In the present study we determined whether MCPIP1 regulates IL-6 expression and evaluated the role of miR-9/MCPIP1 axis in the regulation of IL-6 in human OA chondrocytes.

Methods: Human chondrocytes were prepared from OA cartilage by the enzymatic digestion. TaqMan assays were used for gene expression analysis using RNA isolated from cultured primary chondrocytes or from damaged or smooth regions of OA cartilage or RNA immunoprecipitation (RIP). RNA fluorescent *in-situ* hybridization (ISH) for *IL-6* and *MCPIP1* expression was performed using RNAScope. Transfection was done using Amaxa kit. Knockdown experiments were performed using Trisilencer-27 human siRNA. For RIP, lysates from IL-1b-stimulated chondrocytes were incubated overnight with anti-MCPIP1 antibody or with isotype control IgG followed by RNA purification.

Results: *MCPIP1* expression was low in damaged cartilage compared to smooth cartilage while the expression of IL-6 was high in damaged cartilage and low in smooth cartilage, suggesting that lower expression of MCPIP1 may be contributing to the excessive expression of IL-6 in OA. Expression of miR-9 predicted by TargetscanS to bind the seed sequence in MCPIP1 mRNA was high in damaged cartilage compared to smooth cartilage and was also upregulated by IL-1b in OA chondrocytes. Over expression of miR-9 mimic or inhibitor in OA chondrocytes altered the expression of MCPIP1 and IL-6. IL-1b-mediated induction of IL-6 was initially low in OA chondrocytes but was significantly accelerated 8 h post-stimulation. On the other hand, expression of MCPIP1 was high initially in IL-1b-stimulated OA chondrocytes but started to decline 8 h post-stimulation. Overexpression of wild type MCPIP1, but not of mutant MCPIP1, in OA chondrocytes reduced the expression of *IL-6* mRNA and protein significantly ($p<0.05$). Importantly siRNA-mediated knockdown of MCPIP1 elevated the *IL-6* mRNA expression in OA chondrocytes. TaqMan analysis of the immunoprecipitated mRNAs showed that anti-MCPIP1 antibody pulled down larger amount of *IL-6* mRNA than control IgG antibody did thus demonstrating the binding of MCPIP1 with IL-6 mRNA in OA chondrocytes.

Conclusion s: In this study for the first time expression of *MCPIP1* and miR-9 in human OA cartilage and chondrocytes is shown. The data also demonstrate miR-9/MCPIP1/IL-6 interactions and provide evidence of miR-9/MCPIP1 axis as an important regulator of IL-6 expression in OA.

Background/Purpose
Methods
Results
Conclusion

Disclosure: T. Haqqi, None; **A. Haseeb**, None; **M. Shahidul Makki**, None.

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Reduced Expression of Circadian Rhythm Genes in Human Osteoarthritis Cartilage: NR1D1 Suppression Alters Chondrocyte Response to IL-1β Stimulation. Ryuichiro Akagi[1], Kathleen M. Fisch[1], Oscar Alvarez-Garcia[1], Takeshi Teramura[1], Yuta Muramatsu[1], Masahiko Saito[2], Takahisa Sasho[3], Andrew I. Su[1] and Martin K. Lotz[1]. [1]The Scripps Research Institute, La Jolla, CA, [2]Toho University Sakura Medical Center, Sakura, Japan, [3]Chiba University School of Medicine, Chiba, Japan.

Background/Purpose: NR1D1 is a negative regulator of BMAL1, a core clock gene that regulate circadian rhythmicity. Involvement of NR1D1 in inflammatory process has been reported, but data regarding its function in articular cartilage is limited. Since IL-1β induced inflammation is one of the key factors that disturb cartilage homeostasis and lead to cartilage degradation, we examined the function of NR1D1 in articular cartilage in relation to IL-1β stimulation.

Methods: RNA was extracted from human cartilage tissues harvested from normal and osteoarthritis (OA) knees (n=15 each), and expression levels of NR1D1 and BMAL1 mRNA were assessed by quantitative PCR. NR1D1 protein expression was confirmed by immunohistochemistry in normal and OA human cartilage, as well as in normal knees and knees with surgically induced OA of mice. To examine the circadian rhythmicity of gene expression in cultured chondrocytes isolated from normal human cartilage, chondrocytes were synchronized by dexamethasone and harvested at 4-hour intervals up to 48 hours for RNA and protein extraction. Chondrocytes were then treated with small interfering RNA (siRNA) for NR1D1 or BMAL1, followed by IL-1β stimulation to test the effect of knock down on response to IL-1β.

Results: Both NR1D1 and BMAL1 mRNA levels were significantly reduced in OA cartilage, compared to normal cartilage. NR1D1 protein was predominantly expressed in the superficial and upper-mid zone of normal cartilage, both in human and in mouse knees. The protein expression was reduced in OA cartilage, although high expression was observed in cluster cells. In surgically induced mice OA, NR1D1 protein expression was significantly reduced before cartilage loss occurred. In cultured human chondrocytes, a clear circadian rhythmicity was observed for NR1D1 and BMAL1 mRNA levels. NR1D1 expression was at its lowest level at T12 and T36, whereas highest expression was observed at T24 and T48. The expression pattern of BMAL1 displayed the reversed pattern. Treatment with siRNA significantly suppressed levels of both genes at all time points, but the rhythmic expression pattern was preserved. Increase in BMAL1 expression was observed at T24 and T48 after knocking down NR1D1, and decreased NR1D1 levels were observed at all time points after knocking down BMAL1. IL-1β treatment significantly induced IL6, COX2, iNOS, MMP13 and ADAMTS4. NR1D1 knock down further increased the expression levels of iNOS, MMP13 and ADAMTS4, while by contrast the IL-1 induction of IL6 and COX2 was blunted. Genome-wide sequencing of RNA from chondrocytes treated with NR1D1 siRNA identified 330 genes that were significantly different and this affected predominantly TGFβ signaling pathway and protein processing in endoplasmic reticulum (ER), as well as ER stress response.

Conclusion: NR1D1 and BMAL1 expression are reduced in OA cartilage. NR1D1 and BMAL1 present circadian rhythmicity in cultured chondrocytes with an opposite phase, indicating a bidirectional regulation between the two genes. Reduced expression of NR1D1 in chondrocyte leads to altered response to IL-1β stimulation, affects TGFβ signaling and ER function, thus suggesting an important role of NR1D1 in cartilage homeostasis.

Disclosure: R. Akagi, None; **K. M. Fisch**, None; **O. Alvarez-Garcia**, None; **T. Teramura**, None; **Y. Muramatsu**, None; **M. Saito**, None; **T. Sasho**, None; **A. I. Su**, None; **M. K. Lotz**, None.

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BMP9-Induced pSmad1/5/8 Signaling and Chondrocyte Hypertrophy Are Effectively Inhibited By TGFβ1. Arjan van Caam, Esmeralda Blaney Davidson, Ellen W. van Geffen, Wim B. van den Berg and Peter M. van der Krraan. Radboud university medical center, Nijmegen, Netherlands.

Background/Purpose: Osteoarthritis is characterized by degradation of articular cartilage. TGFβ-superfamily signaling via Smad phosphorylation (pSmad) plays a crucial role in cartilage maintenance. Two distinct pSmad pathways exist: pSmad1/5/8 and pSmad2/3. pSmad2/3 induces matrix formation and protects cartilage against deleterious processes like chondrocyte hypertrophy and IL1-signalling. In contrast, pSmad1/5/8 is linked to chondrocyte hypertrophy and expression of the main cartilage degrading enzyme: MMP13. Recently a very potent pSmad1/5/8 inducing ligand has been identified: BMP9. BMP9 is produced by the liver and circulates in high levels. Over 60% of all BMP activity in serum can be attributed to BMP9, showing

the abundance of this BMP. In this study we investigated the effect of this potent pSmad1/5/8 inducing ligand, BMP9, on chondrocyte phenotype. Furthermore, because of pSmad2/3's importance in chondrocyte homeostasis, we studied the interaction between BMP9-signaling and TGFβ1-induced pSmad2/3 signaling.

Methods: In this study, primary bovine chondrocytes were used. BMP9-induced Smad phosphorylation was detected after 1 h and 2 h using Western Blot. Subsequently, BMP9-induced gene expression was measured up to 24 h using real time qPCR. Biological activity of pSmad2/3 was measured using the (CAGA)12-luc reporter assay, which produces luciferase in response to pSmad3. Cellular hypertrophy was investigated by culturing chondrocytes 1 week in the presence of growth factors and analyzing gene expression of hypertrophy markers.

Results: In primary bovine chondrocytes, BMP9 stimulation in doses upwards of 50 pg/ml induced pSmad1/5/8, which was reflected in expression of the Smad1/5/8 response gene bId1. Remarkably, BMP9 doses of 1 ng/ml and higher also induced pSmad2, but, expression of the pSmad3 response gene bSerpine1 was not induced. Co-stimulation of chondrocytes with BMP9 and a low dose TGFβ1 (0.1 ng/ml) reduced BMP9-induced pSmad1/5/8 and, surprisingly, enhanced TGFβ1-induced pSmad2. After 24 hours, this interaction was reflected in mRNA levels, as co-stimulation increased expression of the pSmad2/3 responsive genes: bSerpine1, bTgfb1 and bSmad7 and decreased expression of bId1. Furthermore, BMP9 also synergistically enhanced biological activity of TGFβ1 in the CAGA12Luc reporter assay. The uniqueness of this synergy between BMP9 and TGFβ1 was illustrated by co-stimulation of chondrocytes with TGFβ1 and two other BMPs important in chondrocyte biology: BMP2 and BMP7, which showed that both these BMPs do not synergize with TGFβ1 on Smad2/3p. As a more long term effect, BMP9 induced chondrocyte hypertrophy after one week of stimulation, as indicated by upregulation of Alkaline phosphatase and Col10a1, however addition of 0.1 ng/ml of TGFβ1 inhibited this BMP9-induced hypertrophy.

Conclusion: Our results show that BMP9 potently induces pSmad1/5/8 and its downstream gene expression in chondrocytes. In long term culture this results in induction of chondrocyte hypertrophy. However TGFβ1 can potently inhibit this hypertrophy. Possibly, this runs via the observed but yet unexplained pSmad2/3 enhancing interaction between both growth factors, which is unique for BMP9 compared to BMP2 or BMP7.

Disclosure: A. van Caam, None; **E. Blaney Davidson**, None; **E. W. van Geffen**, None; **W. B. van den Berg**, None; **P. M. van der Kraan**, None.

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Monolayer Culture Induced the Expression of Zyxin-Related Protein 1 (ZRP-1), $\alpha_v\beta_3$integrin Complex and Leptin in Human Articular Chondrocytes. Edith Charlier[1], Olivier Malaise[1], Mustapha Zeddou[2], Sophie Neuville[1], Gaël Cobraiville[1], Philippe Gillet[3], William Kurth[3], Dominique de Seny[1], Biserka Relic[1] and Michel G. Malaise[1]. [1]GIGA Research - University of Liège - CHU of Liège, Liège, Belgium, [2]Department of Biology, Faculty of Sciences, University Mohamed I, Oujda, Morocco, [3]Orthopedic Surgery Unit-CHU of Liège, Liège, Belgium.

Background/Purpose: During Osteoarthritis (OA), chondrocytes loose their initial anabolic properties, undergoing morphological and biochemical modifications similar to those encountered during chondrocyte dedifferentiation. However, the molecular mechanisms underlying this process are poorly known. In order to understand the morphological changes, we interested in the expression of two molecules involved in actin cytoskeletal organization, namely Zyxin-related protein 1 (ZRP-1) and in regulation of cell interaction with the extracellular matrix (ECM), meaning the integrin complex $\alpha_v\beta_3$. Concerning the biochemical changes, we followed the expression of leptin, an OA-related adipokine, during chondrocytes dedifferentiation. We next assessed pathways potentially involved in its production, namely TGFβ and Wnt/β-catenin, since they are both involved in chondrocytes phenotype maintenance and OA development.

Methods: Human articular cartilage was obtained from macroscopically preserved areas within OA hip after prosthetic surgery. Isolated chondrocytes were cultured in monolayer during 14 days sothat dedifferentiation happen, shifting from round (day1) to fibroblastic-like (day 14) shape. Classical dedifferentiation and hypertrophic markers were assed by qRT PCR, ELISA or western blotting. ZRP-1 was detected by western blotting and $\alpha_v\beta_3$complex was vizualized by immunohistochemistry using LM609 antibody. Components of TGFβ and Wnt/β-catenin were detected by western blotting and involvement of these pathways in leptin production was investigated by stable lentiviral silencing of Smad1 and β-catenin.

Results: Chondrocytes monolayer culture induced typical *Sox9* and *COLIIA1* gene expression lost, as well as *COLIA1*, Runx-2 and MMP-13 gain. We found that ZRP-1 and $\alpha_v\beta_3$ complex expression came with dedifferentiation. Similarly, leptin was absent in primary chondrocytes whereas present in dedifferentiated chondrocytes, and significantly more under prednisolone. ALK1/ALK5 ratio was shifted during dedifferentiation, from high ALK5 and p-Smad2 expression in primary chondrocytes to high endoglin, ALK1 and p-Smad1/5 expression in dedifferentiated counterpart. Moreover, inactive GSK3β and correspondant active β-catenin were found in dedifferentiated chondrocytes, whereas absent from primary cells. Smad1 and β-catenin stable lentiviral silencing led to a significative decrease in leptin production by dedifferentiated chondrocytes.

Conclusion: ZRP-1, $\alpha_v\beta_3$ integrin complex, leptin expression and its associated signaling might represent novel markers for chondrocyte loss of primary phenotype.

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Targeting the Bone-Driven Metabolic OA Phenotype By a Novel Dual Amylin Calcitonin Receptor Agonist, KBP-056. Ditte Reker, Sara Toftegaard Hjuler, Kim Andreassen, Morten Asser Karsdal, Kim Henriksen and Anner C. Bay-jensen.Nordic Bioscience, Biomarkers and Research, Herlev, Denmark.

Background/Purpose: Osteoarthritis (OA) may be segregated into different disease phenotypes based on disease drivers; cartilage damage, joint inflammation or subchondral bone remodelling. Each phenotype may require targeted treatments. Patients with a bone-driven OA may particularly benefit from a treatment with anti-resorptive and chondro-protective properties. Salmon calcitonin (sCT), a hormone acting through CT and amylin receptors, have in multiple preclinical models been demonstrated to improve bone homeostasis and attenuate joint destruction, in part through the anti-resorptive property. In addition, sCT have recently been shown to have a positive effect on obesity and diabetes, which may benefit certain OA subjects. Several Dual Amylin Calcitonin Receptor Agonists (DACRAs) were characterized through a larger screening program; KBP-056 was found to be particular interesting for OA, by showing higher potency for the receptors than sCT. The objective of this study was to investigate the *in vivo* effect of KBP-056 on bone and cartilage turnover, as well as metabolic health.

Methods: Male Sprague Dawley rats (Taconic, Ry, Denmark) were given HFD for 10 weeks before they were treated with defined doses of KBP-056 (0.625, 1.25, 2.5, 5, 10 ug/Kg) or vehicle as subcutaneous injections. Blood was collected from overnight fasted rats immediately at baseline, 3 and 24 hours after first treatment. Rats were treated for 8 weeks. Body weight was recorded weekly. Biomarkers of bone and cartilage degradation were assessed in the blood using the ELISAs CTX-I (bone resorption) and CTX-II (cartilage degradation). CTX-I and -II were reported as fold of baseline levels, as means with standard error of mean (SEM) and compared using two-way ANOVA assuming normal distribution. Significance levels; *P $<$ 0.05, **P $<$ 0.01, ***P $<$ 0.001. In addition, a similar study was performed using ovariectomy (OVX)-meniscectomy (MNX) Sprague Dawley rats.

Results: Serum levels of both CTX-I and -II decrease significantly 3 hours after treatment with KBP-056, even at the lowest dose tested ($P<0.05$, fig. 1). Moreover, a dose-dependent response by CTX-I still remained 24 hours after treatment, suggesting increased potency. KBP-056 caused a 19% vehicle-corrected weight reduction for two highest doses at the end of the experiment. A similar weight reducing effect was observed in OVX-MNX rats.

Conclusion: The data presented here clearly indicate a protective effect of KBP-056 on both bone and cartilage *in vivo*, when evaluated by biochemical markers. Furthermore, KBP-056 has demonstrated positive effects on metabolic health (cause a weight decrease), and may therefore represent a possible treatment opportunity for bone-driven OA, with an unhealthy phenotype (e.g. high BMI). Many further studies are needed to match the optimal treatment opportunity with the right OA patient for a personalized health care approach for OA.

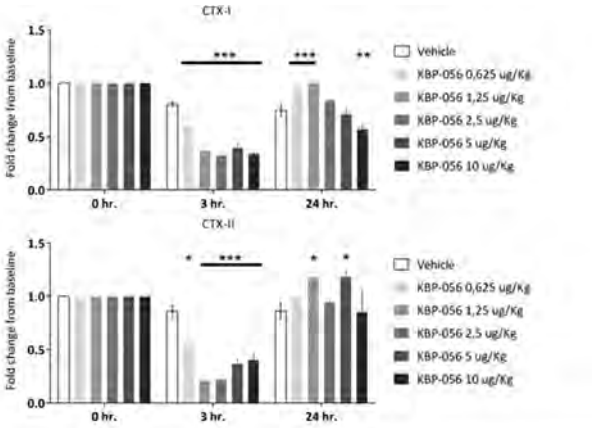

Figure 1. Acute CTX-I and -II response to KBP-056. High-fat diet Sprague-Dawley rats were subjected to a single subcutaneous injection with indicated treatments, and tail blood was collected at indicated timepoints. CTX-I and -II values of each rat were normalized to its baseline value (0 hr.). Values are means ± SEM of 5 replicate rats. Two-way ANOVA was used to compare each bar with its respective vehicle. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Disclosure: D. Reker, Nordic Bioscience Diagnostic, 3; **S. T. Hjuler**, Nordic Bioscience Diagnostic, 3; **K. Andreassen**, Nordic Bioscience Diagnostic, 3; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 3, AbbVie Inc., 5; **K. Henriksen**, Nordic Bioscience Biomarkers and Reasearch, 3; **A. C. Bay-jensen**, Nordic Bioscience Holding A/S, 1, Nordic Bioscience Diagnostic, 3.

1020

Changes in Peripheral Blood Immune Cell Composition in Osteoarthritis. Agata Burska[1], Mark Campbel[2], Rafi Raja[2], Dylan White[1], Paul Emery[3], Philip G. Conaghan[4] and Frederique Ponchel[1]. [1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, Translational Research in Immune Mediated Inflammatory Diseases, the University of Leeds, Leeds, United Kingdom, [2]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds., Leeds, United Kingdom, [3]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, Leeds, United Kingdom.

Background/Purpose: Healthy ageing and the occurrence of the common age-related disease osteoarthritis (OA) result from varying degrees of interaction between many determinants (genetic, lifestyle). Immunosenescence and inflammageing are features of the ageing immune system. Age-related abnormalities (loss of T-cell reactivity, development of autoantibodies, activation of inflammatory mechanisms) may be synergising with structural defects of the musculoskeletal system aiding the development of OA. We aimed to determine if abnormalities of blood immune cell composition are associated with OA, beyond the defects already associated with age.

Methods: Blood samples were collected from 120 healthy controls (age range 18–69) to establish variations associated with age and 120 OA (age range 49–80). We examined loss or acquisition of age-related changes in blood composition. 8-colours flowcytometry was performed to establish the frequencies of: CD4/CD8, B, NK-cells. Naïve and regulatory T and B-cell were subsequently analysed and cells with an abnormal phenotype identified in Rheumatoid arthritis is direct relation with inflammation (IRC phenotype).

Results: Flowcytometry was performed on all 240 samples (only 20 HC and 45 OA were analysed for B-cells) and demonstrated, as expected, very little change in lineage representation associated with age in health with: no change for NK, CD4, and B-cells, weak decline in CD8 (rho=−0.300, p=0.019) and increase in NKT (rho=0.315, p=0.012). In contrast phenotyping T and B-cells showed clear age-related changes with reduction of naïve CD4 T-cell (rho=0.817, p<0.0001). Regulatory T-cells increased (rho=0.401, p<0.0001) whereas B-reg reduced (rho= -0.658, p=0.002). IRC were not related to age.

In OA differences were observed. NK, CD4 and B cells were not related to age but in OA, NK cells were positively correlated (rho=0.350, p<0.0001), CD4 (rho=−0.318, P=0.001) and B-cells (rho=−0.260, p=0.006) negatively. The NKT correlation with age was maintained in OA (rho=0.296, p=0.002) but the CD8 relationship was lost. Naïve CD4 cells appeared to be particularly affected (see Figure 1 showing % of several subsets) with considerable increase in frequency. Treg were reduced in most patients irrespective of age. B-cell subsets were not particularly affected although the age-relationship for B-reg was lost. IRC were not increased with the exception of ~20 patients.

Conclusion: This analysis of the immune cell composition of the blood of OA patients suggests that immune dysfunction is present in OA above what is directly related to ageing. Immuno-senescence and inflammageing (as suggested by the increased frequency of IRC in some OA patents) may therefore play a role in OA in addition to their implication in healthy ageing.

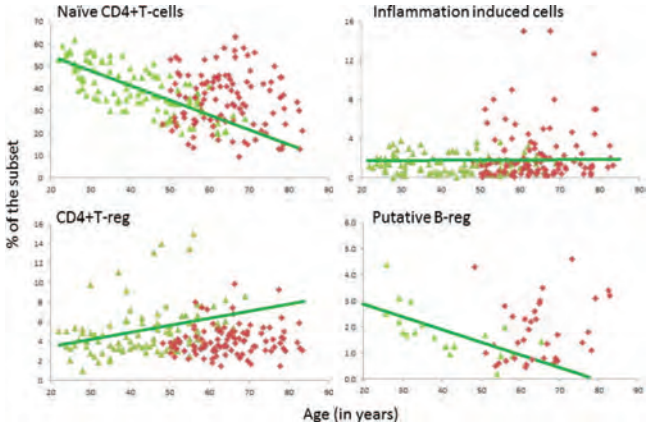

Figure 1. Cell subsets % in OA and HC (HC-green triangles, OA red diamonds)

Disclosure: A. Burska, None; **M. Campbel**, None; **R. Raja**, None; **D. White**, None; **P. Emery**, None; **P. G. Conaghan**, None; **F. Ponchel**, None.

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Transthyretin and Amyloid in Cartilage Aging and Osteoarthritis. Yukio Akasaki[1], Oscar Alvarez-Garcia[1], Natalia Reixach[1], Joel Buxbaum[1], Yukihide Iwamoto[2] and Martin K. Lotz[1]. [1]The Scripps Research Institute, La Jolla, CA, [2]Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Background/Purpose: Deposition of amyloid is a common aging-associated phenomenon and a key factor in the pathogenesis of several aging-related diseases. Osteoarthritis is the most prevalent joint disease and aging is its major risk factor. Although amyloid deposits appear to be a prevalent in OA-affected joints, their composition and effects on cell and tissue function are unknown. Transthyretin (TTR) is an amyloidogenic protein. Point mutations in the TTR gene cause of familial amyloidotic polyneuropathy and cardiomyopathy. Wild-type TTR can also assemble into amyloid deposits and this may be facilitated by oxidation, or the presence of sulfated glycosaminoglycans. This study addressed TTR deposition in aging and OA-affected knee cartilage and effects of TTR on chondrocyte function.

Methods: Amyloid deposition in normal and OA human knee cartilage was determined by Congo-red staining and polarized light microscopy. TTR in cartilage and synovial fluid was analyzed by immunohistochemistry and western blotting. TTR gene expression in chondrocytes was studied by quantitative PCR and RNA sequencing. Effects of wild type and mutant TTR were studied in normal human chondrocyte cultures with measurements of cell viability and OA-related gene expression.

Results: There was no amyloid deposition in young normal cartilage. In contrast, 58% (7/12) of aged normal cartilage and 100% (12/12) of OA cartilage samples had Congo red staining. TTR was detectable in all OA and a majority of aged but not in young normal cartilage and predominantly located at the cartilage surfaces. TTR is not produced by chondrocytes at substantial levels and synovial fluid levels are similar in normal and OA affected knees. In chondrocytes, TTR induces cell death, the expression of proinflammatory cytokines and extracellular matrix degrading enzymes. This was observed for the amyloidogenic but not for the non-amyloidogenic TTR mutant. Effects of TTR on cell viability and gene expression are mediated by activation of TLR4 signaling and MAP kinases.

Conclusion: These findings are the first to suggest that TTR amyloid deposition may not represent an inconsequential aging-related phenomenon but contribute to cell and extracellular matrix damage in articular cartilage.

Disclosure: Y. Akasaki, None; **O. Alvarez-Garcia**, None; **N. Reixach**, None; **J. Buxbaum**, None; **Y. Iwamoto**, None; **M. K. Lotz**, None.

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Fibroblast-like Synovial Cells and Monocytes Team up in the Organization and the Dynamic Modelling of the Synovial Tissue. Ruth Byrne, Karolina von Dalwigk, Thomas Karonitsch, Gunter Steiner, Johannes Holinka, Reinhard Windhager, Josef Smolen, Hans Peter Kiener and Clemens Scheinecrker. Medical University of Vienna, Vienna, Austria.

Background/Purpose: The synovial lining tissue consists of fibroblast-like synoviocytes (FLS) and monocyte-derived macrophage-like synoviocytes (MLS) within a self-built meshwork of dense extracellular matrix (ECM) components. FLS are thought to direct ECM synthesis, assembly and degradation. Whether this requires their cognitive interaction with MLS and whether FLS themselves or the ECM network serve as guiding structures for MLS migration is incompletely understood. This tempted us to study the dynamics of synovial tissue modelling under steady state and inflammatory conditions using a three-dimensional in-vitro model of the synovial tissue.

Methods: Human FLS were prepared from synovial tissues obtained as discarded specimens following joint arthroplasty. CD14+ monocytes (Mo) were isolated from peripheral blood. FLS and Mo were labeled with fluorescent membrane dyes and cultured in spherical extracellular matrix micromasses with an average size of 1.5 mm for up to two weeks. Second harmonic generation (SHG) was used for the visualization of collagen fibers. For stimulation experiments, micromasses were cultured in medium containing 10 ng/ml of tumor necrosis factor (TNF). Cell migration was monitored in individual micromasses by real-time confocal/multi-photon microscopy.

Results: The formation of a FLS network was observed within 3–7 days and coincided with the detection of collagen fibers that colocalized with FLS. The majority of Mo was found to be in close contact with the FLS network with low tendency for migration. A minor fraction of Mo displayed a directed cell movement with an impressive maximum speed of up to 15 mcm/min. Rapid Mo migration occurred in intimate contact with FLS but did not necessarily follow FLS network boundaries. In addition, we observed the formation of Mo cell clusters that co-localized with collagen fibers in the absence of FLS. The addition of TNF i) increased the frequency and size of Mo cell clusters and ii) prolonged the overall mobility of Mo.

Conclusion: The 3D synovial tissue culture system allows for monitoring and analyzing the dynamics of synovial lining modelling. Both, FLS and Mo appear to cooperate in the organization of the synovial lining tissue with subtle migration patterns of Mo in relation to the organized synovial lining architecture. Ongoing experiments address molecular mechanism(s) of Mo – FLS interaction in order to identify potential targets for future therapeutic intervention in arthritis.

Disclosure: R. Byrne, None; **K. von Dalwigk**, None; **T. Karonitsch**, None; **G. Steiner**, None; **J. Holinka**, None; **R. Windhager**, None; **J. Smolen**, None; **H. P. Kiener**, None; **C. Scheinecker**, None.

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Chronic PTHrP Treatment Promotes Hypertrophic Differentiation and Inflammatory Gene Expression in Chondrocytes. Bin Wrang. Center for Translational Medicine, Department of Medicine, Thomas Jefferson University Medical College, Philadelphia, PA.

Background/Purpose: Parathyroid hormone-related protein (PTHrP) binds to the type 1 PTH receptor (PTH1R), a member of the superfamily of G protein-coupled receptors (GPCRs). Activation of PTH1R by PTHrP has been widely documented to maintain cartilage homeostasis. However, PTHrP also acts as a cytokine-like peptide and mediates multi-organ inflammation. PTHrP content is higher in osteoarthritis (OA) synovial fluid. Changes in PTHrP expression in a rabbit OA model indicate PTHrP involvement in late rather than early pathogenic events. Blockade of PTHrP prevents articular cartilage destruction in streptococcal cell wall-induced arthritis. Emerging data show that GPCRs play important roles in inflammation through Ga12/13-mediated NF-kappa B/cyclooxygenase 2 (*COX2*) signaling pathway. In present studies.the effects of chronic PTHrP treatment on hypertrophic differentiation and inflammatory gene expression in chondrocytes were investigated.

Methods: Mouse chondrogenic cells (ATDC5), which express PTH1R during their differentiation, were used to examine hypertrophic differentiation and inflammatory gene expression in response to chronic PTHrP treatment. ATDC5 differentiation was induced by addition of ITS (10 μg/ml insulin, 10 μg/ml transferrin, and 10 ng/ml sodium selenite) into the cell culture medium after cell confluence. The mRNA expression for hypertrophic differentiation and inflammatory genes was detected by quantitative real-time PCR. PTH1R activation was determined by measuring [^{3}H]-adenine incorporation for cAMP accumulation.

Results: The cartilage nodules in cultures of ATDC5 cells were formed by day 30 after ITS treatment. PTHrP (10 nM) initially inhibited ITS-induced expression of type 10 collagen a1 (Col10a1) and matrix metalloproteinase 13 (MMP13) (hypertrophic differentiation markers). However, the prolonged and sustained PTHrP increased Col10a1 and MMP13 expression in the late stage of differentiation (hypertrophic cells). Chronic PTHrP treatment enhanced the mRNA expression of *COX2*, but inhibited adenylyl cyclase activity in the late stage of differentiated chondrocytes.

Conclusion: These data suggest that chronic PTHrP treatment promotes a specific switch of PTH1R signaling from Gas to Ga12/13 to induce hypertrophic differentiation and increase inflammatory gene expression. Locally produced PTHrP in OA synovial fluid may have a pathogenic role in diseased cartilage.

Disclosure: B. Wang, None;

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Racial Differences in Biochemical Knee Cartilage Composition Between African American and Caucasian American Women with MR-Based T2 Relaxation Time Measurements – Data from the Osteoarthritis Initiative. Martin Kretzschmar[1], Ursula Heilmeier[2], Aihong Yu[3], Gabby B. Joseph[4], Felix Liu[5], Hans Liebl[3], Charles E. McChulloch[3], Michael C. Nevitt[6], Nancy E. Lane[7] and Thomas M Link[2]. [1]University of California, San Francisco, San Francisco, CA, [2]Musculoskeletal Quantitative Imaging Research, UCSF, San Francisco, CA, [3]University of California San Francisco, San Francisco, CA, [4]University of California San Francisco, San FRancisco, CA, [5]University of California at San Francisco, San Francisco, CA, [6]UCSF (University of California, San Francisco), San Francisco, CA, [7]Center for Musculoskeletal Health, UC Davis School of Medicine, Sacramento, CA.

Background/Purpose: To determine whether knee cartilage composition differs between African-American and matched Caucasian-American women at risk for Osteoarthritis (OA) using in-vivo 3T MRI T2 relaxation time measurements.

Methods: Right knee 3 Tesla MRI studies of 200 subjects (100 African-American women, 100 Caucasian-American were selected from the Osteoarthritis Initiative Cohort and closely matched for age, BMI, Kellgren-Lawrence Scores (KL≤1), subcohort and clinical site. Knee cartilage was segmented and T2 maps were generated in five compartments (patella (PAT), medial and lateral femur (MF/LF), medial and lateral tibia (MT/LT)). Mean T2 relaxation time values per compartment and per whole joint cartilage were generated and analyzed spatially via laminar and grey-level-co-occurrence-matrix texture methods. Presence and severity of cartilage lesions per compartment were graded using a modified whole-organ magnetic resonance imaging score (WORMS). Statistical analysis employed paired t- and McNemar testing.

Results: Although African-American and matched Caucasian-Americans did not differ in their WORMS cartilage lesion score ($p=0.970$), African American women showed significantly lower mean T2 values than Caucasian-Americans in the whole knee cartilage ($p<0.001$), and in the subcompartments (LF: $p=0.001$, MF: $p<0.001$, LT: $p=0.019$, MT: $p=0.001$) and particularly in the superficial cartilage layer (whole cartilage: $p<0.001$, LF: $p<0.001$, MF: $p<0.001$, LT: $p=0.003$, MT: $p<0.001$). T2 texture parameters were also significantly lower in the whole joint cartilage of African-American women than in Caucasian-Americans (variance: $p=0.001$; contrast: $p=0.018$). In analyses limited to matched pairs with no cartilage lesions in a given compartment, T2 values remained significantly lower in African-Americans.

Conclusion: Using T2 relaxation time as a biomarker for the cartilage collagen network, our findings suggest racial differences in the biochemical knee cartilage composition between African-American and Caucasian-American women.

Disclosure: M. Kretzschmar, None; **U. Heilmeier**, None; **A. Yu**, None; **G. B. Joseph**, None; **F. Liu**, None; **H. Liebl**, None; **C. E. McChulloch**, None; **M. C. Nevitt**, None; **N. E. Lane**, None; **T. M. Link**, None.

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Leptin Production By Osteoarthritis Synovial Fibroblasts: Stimulation By Glucocorticoids and Mineralocorticoids through the Glucocorticoid Receptor and GILZ (Glucocorticoid-Induced Leucine Zipper) Protein. Olivier Malaise, Biserka Relic, Sophie Neuville, Edith Charlier, Dominique de Seny and Michel G. Malarise. GIGA Research - University of Liège - CHU of Liège, Liège, Belgium.

Background/Purpose: Osteoarthritis (OA) is a metabolic disorder for which leptin is playing a catabolic role on cartilage. In mice, obesity due to impaired leptin did not cause OA. *In vitro*, we have previously shown that OA synovial fibroblasts (SF) produced leptin, hypothesizing that they were also able to contribute to intra-articular levels of leptin. The glucocorticoid prednisolone strongly induced leptin and leptin receptor (Ob-R), suggesting a deleterious involvement in the metabolic component of OA.

Aldosterone, a mineralocorticoid, is found in OA synovial fluid and is involved in systemic metabolic regulation. First, we will study the mineralocorticoid's influence on leptin and Ob-R expressions, and determine whether leptin and Ob-R are glucocorticoid receptor (GR) or mineralocorticoid receptor (MR) dependent.

Glucocorticoid-Induced Leucine Zipper (GILZ) protein, induced by glucocorticoids, is an anti-inflammatory mediator in inflammatory models. Links with leptin are unknown, but GILZ's overexpression decreases adipogenic and enhances osteogenic differentiation, two processes associated to leptin. We will study GILZ's involvement in leptin expression.

Methods: Human SF were isolated from OA patients during knee surgery and treated with glucocorticoid (prednisolone), mineralocorticoid (aldosterone), GR agonist (Compound A, CpdA), GR antagonist (mifepristone), MR antagonists (eplerenone, spironolactone), TNF-α and TGF-β. SF were transfected with shRNA lentiviruses for GILZ and GR silencing. ELISA measured leptin and IL-6. Ob-R, GR, GILZ and GAPDH were analyzed by Western Blot.

Results:

(1) Prednisolone and aldosterone induced leptin and Ob-R through GR but not MR: mifeprisotone (GR antagonist), but not eplerenone or spironolactone (MR antagonists), reduced both prednisolone- and aldosterone-induced leptin and Ob-R. GR silencing with shRNA confirmed these results.

(2) GILZ was induced by prednisolone and aldosterone. Similarly to leptin, stimulations with GR or MR antagonists and GR silencing showed that both leptin and Ob-R inductions were GR-dependent: leptin and GILZ shared similar modulations. Moreover, CpdA and TGF-β, that did not induce GILZ in OA SF, did not induce leptin.

(3) GILZ was involved in prednisolone- and aldosterone-induced leptin and Ob-R, with a significant dose-response decrease when GILZ was down-regulated by shRNA.

(4) GILZ inhibition with shRNA did not modify the anti-inflammatory properties of prednisolone, with an unchanged endogenous or TNF-α-induced IL-6 reduction opposite to the control.

Conclusion:

(1) Both mineralocorticoids and glucocorticoids induced leptin and Ob-R in OA SF, suggesting a deleterious involvement of both corticosteroids in the metabolic component of OA. Synovial tissue could represent a new target for mineralocorticoids.

(2) Mechanistically, we propose a new role for GILZ in OA, with an involvement in corticosteroids-induced leptin and Ob-R. By contrast, GILZ did not seem significantly involved in the anti-inflammatory action of glucocorticoids in OA SF.

Disclosure: O. Malaise, None; **B. Relic**, None; **S. Neuville**, None; **E. Charlier**, None; **D. de Seny**, None; **M. G. Malaise**, None.

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Monosodium Urate Monohydrate Crystals Induces the Expression of Ihh and MMP-13 in ATDC5 Cells: Implications in Osteoarthritis (OA) Development. Melissa Ramirez, Josh Potvin, Diana Ramirez and Anthony M. Reginrato. The Warren Alpert School of Medicine at Brown University, Providence, RI.

Background/Purpose: Cartilage damage is often observed in affected joints with advance gout[1]. Musculoskeletal ultrasound studies have highlighted the close relationship between monosodium urate (MSU) crystals and articular cartilage in patients with gout. The "double contour sign" is an hyperechoic band over the superficial layers of the articular cartilage that highlights the close relationship between MSU and cartilage[2]. The interaction between MSU crystal and chondrocyte may contribute to cartilage damage in gout[3]. The objective of this study was to investigate the effect of increasing concentrations of MSU crystals on chondrocyte function and differentiation.

Methods: Primary chondrogenic cell line (ATDC5) were cultured in a 1:1 mixture of DMEM/F12 medium containing 10% FBS, Insulin-Transferrin-Selenium and incubated with increasing concentrations of endotoxin-free MSU crystals at increasing concentrations (0.01, 0.025, 0.05 and 0.1 mg/ml) for 4, 7, and 14 days respectively. Purification of total cellular RNA for real time PCR was prepared from ATDC5 at different time points. Real-time quantitative PCR was performed on specific extracellular matrix genes, transcription factors and metalloproteinases. Alcian-blue and Alizarin red S staining was performed at selected time point of ATDC5 cells exposed to different MSU concentration.

Results: MSU crystals have a negative effect in the function and differentiation of ATDC5 chondrogenic cell lines. The ability of chondrocyte to produce matrix protein assessed by relative mRNA expression of aggrecan and type II collagen was reduced in chondrocytes following culture with MSU crystals and correlated with Alcian-blue staining. The expression of of chondrogenic gene expression was found to correlate with Runx 2. The expression of Ihh, and MMP-13 was increased and confirmed by western blotting (1-way ANOVA $p<0.05$). Furthermore, the expression of degradative enzymes such as Adamts4 and Adamts5 was also increased contributing to the cartilage degradative process.

Conclusion: Long-term culture of MSU crystals with chondrogenic cell line ATDC5 impairs the function and differentiation of chondrocytes. MSU crystals stimulate gene expression of Ihh and MMP-13 contributing to the development of osteoarthritis.

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Disclosure: M. Ramirez, None; **J. Potvin**, None; **D. Ramirez**, None; **A. M. Reginato**, None.

ACR/ARHP Poster Session B

Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis

Monday, November 17, 2014, 8:30 AM–4:00 PM

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Hematopoietic Cell Kinase (HCK) As a Novel Regulator of Fibroblast-like Synoviocyte Function in RA. Ying Wang[1], Deepa Hammaker[2], David L. Boyle[3], Toshio Yoshizawa[4] and Gary S. Firestein[3]. [1]UCSD, La Jolla, CA, [2]University of California San Diego, La Jolla, CA, [3]University of California at San Diego School of Medicine, La Jolla, CA, [4]Ono Pharmaceutical Co., Ltd., Osaka, Japan.

Background/Purpose: Fibroblast-like synoviocytes (FLS) are key mediators of inflammation and joint damage in rheumatoid arthritis (RA) through the production of cytokines and matrix metalloproteinases (MMPs) as well as invasion into extracellular matrix. The search for potential kinases that target FLS for RA led to hematopoietic cell kinase (HCK) as a candidate target. HCK is a member of the Src tyrosine kinases and is primarily expressed by myeloid cells. HCK deficiency reduces the migration of M-CSF- and RANKL-induced murine bone marrow mononuclear cells in vitro, indicating that it might play a role in cell migration. However, its expression in mesenchymal cells is not defined, and nothing is known about HCK function in synoviocytes. To determine if HCK is a potential therapeutic target in RA, we evaluated HCK expression and function in RA FLS. These studies show that HCK is an inducible gene in RA FLS that regulates key pathogenic functions, thus allowing an inhibitor to target its effects primarily at sites of inflammation.

Methods: FLS were obtained from RA and osteoarthritis (OA) patients undergoing joint replacement surgery and used from passage 3 through 9. Three separate cell lines were studied for each experiment. To study HCK expression in FLS, RA and OA FLS were serum starved and treated with medium, IL-1β (2ng/ml) or TNF (50ng/ml) for various times. mRNA levels

were determined by qPCR. For functional studies, we used a novel selective small molecule HCK inhibitor, with an IC50 of approximately 7nM. IL-6 and MMP expression were measured by qPCR. MTT assays were performed to determine PDGF-induced proliferation. Apoptosis was induced by H2O2 stimulation and MTT assay. For cell migration, scratch assays were performed on PDGF-stimulated FLS monolayers. The data were analyzed using student's t test and one way ANOVA.

Results: HCK mRNA levels were very low under basal conditions in cultured FLS. IL-1 and TNF increased HCK expression, with maximal introduction at 24 hr by 734- and 65-fold, respectively. TNF-induced IL-6 expression was decreased by 39% in cells treated with 1 μM of the HCK inhibitor ($p = 0.025$). MMP3 expression was also inhibited by $50\pm15\%$ ($p = 0.03$) and $41\pm12\%$ ($p = 0.026$) after the stimulation with IL-1β and TNF, respectively. The small molecule HCK inhibitor (1 μM) significantly reduced PDGF-induced FLS growth by $93\pm32\%$ on day 3 ($n=3$ RA FLS, $p = 0.001$), and $81\pm19\%$ on day 7 ($p = 0.001$). The compound had no effect on H2O2-induced apoptosis, suggesting that the effect on cell growth was due to decreased proliferation rather than increased cell death. HCK inhibition impaired PDGF-induced migration by $83\pm31\%$ ($p = 0.04$).

Conclusion: HCK expressed was induced by IL-1β and TNF in RA FLS. HCK blockade decreased cytokine production, MMP production, proliferation, and cell migration in FLS. Because the gene is minimally expressed in resting cells, its main effect would be in cells at the site of inflammation. Therefore, HCK could be a promising therapeutic target for RA that can regulate pathogenic behavior in a site and event specific manner.

Disclosure: Y. Wang, None; **D. Hammaker**, None; **D. L. Boyle**, None; **T. Yoshizawa**, Ono Pharmaceutical Co., Ltd., 3; **G. S. Firestein**, None.

1028

ADAM-10 Plays Monocyte Migration and Adhesion in Rheumatoid Arthritis Synovial Fibroblasts. Takeo Isozaki[1], Sho Ishii[2], Shinichiro Nishimi[2], Airi Maeoka[2], Mayu Saito[2], Nao Oguro[2], Shinya Seki[2], Yoko Miura[2], Yusuke Miwa[2], Koei Oh[3], Yoichi Toyoshima[3], Masanori Nakamura[3], Katsunori Inagaki[3] and Tsuyoshi Kasama[2]. [1]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [2]Showa University School of Med, Shinagawa-ku Tokyo, Japan, [3]Showa University School of Med, Tokyo, Japan.

Background/Purpose: :A disintegrin and metalloprotease family proteins (ADAMs) have been reported to be involved in a number of inflammatory conditions. We previously reported that ADAM-10 mediated rheumatoid arthritis (RA) angiogenesis. In this study, we examine the expression of ADAM-10 in RA biological fluids and the role it plays in monocyte migration, cell adhesion, and proliferation.

Methods: ADAM-10 expression was determined in serum and synovial fluids (SFs) from normal (NL) subjects, osteoarthritis (OA) patients and RA patients using enzyme linked immunosorbent assay (ELISA). To determine expression of ADAM-10 on RA synovial fibroblasts, immunofluorescence was performed. To examine the role of ADAM-10 in RA synovial fluids (SFs), we performed THP-1 (human acute monocytic leukemia cell line) chemotaxis. To block the expression of ADAM-10, RA synovial fibroblasts were transfected with siRNA against ADAM-10. In order to determine that ADAM-10 mediates monocyte adhesion, ADAM-10 siRNA transfected RA synovial fibroblast adhesion assay was performed. To determine if ADAM-10 played a role in cell proliferation in the RA synovium, ADAM-10 siRNA-transfected RA synovial fibroblast proliferation assays were performed.

Results: The expression of ADAM-10 in RA serum was significantly higher compared to NL serum [mean $\pm$ SE; 450 $\pm$ 44 pg/ml ($n=90$) and 85 $\pm$ 33 pg/ml ($n=34$), respectively] and was correlated with a disease activity score of 28. ADAM-10 concentration in RA SFs was significantly elevated compared with that in OA SFs [(727 $\pm$ 144 pg/ml ($n=10$) and 255 $\pm$ 42 pg/ml ($n=7$), respectively]. ADAM-10 was expressed on RA synovial tissue lining cells and synovial fibroblasts. ADAM-10-depleted RA SFs showed a 56 $\pm$ 9% ($n=5$ patients) decrease in THP-1 migratory activity compared to sham-depleted controls. Adhesion of THP-1 to ADAM-10 siRNA-transfected RA synovial fibroblasts in response to tumor necrosis factor (TNF)-α was significantly decreased compared with control siRNA-transfected RA synovial fibroblasts. Finally, RA synovial fibroblasts transfected with ADAM-10 siRNA showed less proliferation in response to TNF-α at 2.5 ng/ml for 48 hours.

Conclusion: These data indicate that ADAM-10 plays a role in monocyte migration in RA and suggest that targeting ADAM-10 may provide a method by which to decrease inflammation and potentially treat other inflammatory diseases.

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Anandamide and Related Eicosanoids Decrease the Production of Pro-Inflammatory Cytokines in Synovial Fibroblasts By a COX-2 Dependent Mechanism: Involvement of Calcium and TRP Channels. Torsten Lowin[1], Tanja Späth[2], Angelika Graeber[1] and Rainer Straub[3]. [1]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, University Hospital of Regensburg, Regensburg, Germany, [2]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, Regensburg, Germany, [3]University Hospital Regensburg, Regensburg, Germany.

Background/Purpose: Endocannabinoids are immunomodulatory lipid compounds that act on cannabinoid receptors type 1 and 2 but also on transient receptor potential (TRP) channels. Their action is terminated by FAAH, one major enzyme responsible for endocannabinoid degradation. COX-2, however, also degrades endocannabinoids, and products from this reaction are pro-inflammatory. This study studied a potential mode of action for the anti-inflammatory effects of endocannabinoids in synovial fibroblasts from RA and OA donors. Furthermore it is investigated how pro-inflammatory cytokines alter the responsiveness of synovial fibroblasts to (endo)cannabinoid ligands.

Methods: MMP-3 and cytokines were detected by ELISA. ERK 1/2, p38, CREB and cjun phosphorylation was assessed by proteome profiler analysis and cell-based ELISA. Cannabinoid receptors 1 and 2, TRPA1, TRPV1, and COX-2 were detected by western blotting and cell-based ELISA. The XCELLigence system was used to determine EC50 values for CB_1/CB_2/TRPV1/TRPA1 with/without cytokine stimulation.

Results: The endocannabinoid arachidonylethanolamide (anandamide, AEA) and related eicosanoids palmitoylethanolamide (PEA), oleoylethanolamide (OEA) and N-arachidonylglycine (NAGly) reduced TNF induced production of IL-6, IL-8 and MMP-3. The effects of AEA, PEA and OEA were significantly enhanced by addition of the COX-2 inhibitor nimesulide but not by FAAH inhibiton. The effects of all compounds tested were not inhibited by CB_1 or CB_2 antagonism but were blocked by TRPV1 and TRPA1 antagonists in RASFs and OASFs. In the case of AEA, COX-2 inhibition reversed the effects of TRPA1 antagonism. Quantification of CB_1, CB_2, COX-2, TRPV1 and TRPA1 revealed a significant stimulatory influence of pro-inflammatory cytokines and hypoxia on observed protein levels. Furthermore, high AEA concentrations ($>1\mu$M) induced cell death only when combined with the intracellular calcium chelating agent BAPTA-AM. Analysis of intracellular signaling pathways revealed an inhibitory effect of AEA on p38 and ERK1/2 phosphorylation after TNF stimulation.

Conclusion: Under hypoxic conditions, Endocannabinoids promote an anti-inflammatory phenotype in RASFs and OASFs by activating/desensitizing TRPV1 and TRPA1. As a consequence, MAP kinase signaling is reduced as demonstrated after AEA treatment. Furthermore, COX-2 and FAAH inhibition are necessary to fully exploit the therapeutic potential of endocannabinoids. This might be important in RA where low oxygen and abundant cytokine expression up-regulate COX-2 in the joint. In addition, pro-inflammatory cytokines increase the efficacy of endocannabinoids due to upregulation of target receptors.

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ABT-122, a Novel Dual Variable Domain (DVD)-Ig™, Targeting TNF and IL-17, Inhibits Peripheral Blood Mononuclear Cell Production of GM-CSF and Decreases Lymphocyte Expression of CXCR4 in Healthy Subjects. Melanie Ruzek[1], Donna Conlon[1], Heikki Mansikka[2], Robert Padley[2] and Carolyn Cuff[1]. [1]AbbVie, Inc, Worcester, MA, [2]AbbVie, Inc, North Chicago, IL.

Background/Purpose: TNF and IL-17 contribute to the pathogenesis of several inflammatory disorders and are known to synergistically induce chemokines and cytokines, including chemokine (C-X-C motif) ligands 1 (CXCL1), 5 (CXCL5), and 8 (CXCL8), chemokine (C-C motif) ligand 2 (CCL2), IL-1b, IL-6, G-CSF, and GM-CSF. In addition, the CXCL12 chemokine receptor, CXCR4, is reported to be coordinately regulated by TNF and IL-17. As these factors play a role in the pathogenesis of several

autoimmune diseases, greater clinical responses in patients may be possible with dual neutralization of TNF and IL-17. ABT-122 is novel DVD-Ig™ molecule targeting both human TNF and IL-17 cytokines and is currently in clinical trials. The aim of this study was to determine the biologic response to ABT-122 in healthy volunteers based on known activities of TNF and/or IL-17 in humans.

Methods: Twenty-four healthy subjects were administered a single dose of ABT-122 (1.5 mg/kg subcutaneously) in a Phase I trial. PBMCs were collected prior to ABT-122 administration at baseline and at days 7, 15, 36, and 57 post dosing and cryopreserved. Thawed PBMCs were either analyzed directly by flow cytometry for chemokine receptors CXCR1, CXCR4, and CXCR5, or stimulated with LPS. Supernatants from the LPS cultures were analyzed by multiplex analysis (MAPx, Millipore EMD) for CXCL8, CXCL1, CXCL5, CCL2, IL-1b, IL-6, IL-10, G-CSF, and GM-CSF.

Results: A single dose of ABT-122 administered to healthy volunteers resulted in 4-fold lower production of GM-CSF through day 57 compared with baseline from LPS-stimulated PBMCs. CXCR4 expression also decreased on B cells, T cells, and monocytes at day 7 compared with baseline with average reductions of 54%, 41%, and 20%, respectively. Decreases in CXCR4 on B cells persisted to day 15 (24%) and day 36 (18%). As GM-CSF and CXCR4 are reported to be synergistically regulated by IL-17 and TNF, these results suggest dual neutralization by ABT-122. Consistent with known activities of anti-TNF agents in RA patients, there were 2.5-fold elevations in the anti-inflammatory cytokine IL-10 and significant 9–12% increases in CXCR5 expression on T cells following administration of ABT-122. Other chemokine/cytokine responses to LPS stimulation and expression of CXCR1 were unchanged after ABT-122.

Conclusion: The changes observed in expression of GM-CSF and CXCR4 in healthy subjects with dual neutralization of TNF and IL-17, demonstrate pharmacodynamic activity of ABT-122 DVD-Ig™ protein consistent with the known combinatorial activities of TNF and IL-17. Notably, the effects of ABT-122 on these analytes were demonstrated in healthy volunteers, thus these changes likely reflect modulation of the in vivo homeostatic activities of TNF and IL-17 in the absence of disease. These data further support the rationale that ABT-122 can be used to evaluate the therapeutic potential of dual IL-17 and TNF blockade in patients with disorders driven by these two cytokines.

Disclosure: M. Ruzek, AbbVie, 3, AbbVie, 1; **D. Conlon**, AbbVie, 3, AbbVie, 1; **H. Mansikka**, AbbVie, 3, AbbVie, 1; **R. Padley**, AbbVie, 3, AbbVie, 1; **C. Cuff**, AbbVie, 3, AbbVie, 1.

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Induction of Pro-Apoptotic Noxa Expression By Ursolic Acid Sensitizes Rheumatoid Arthritis Synovial Fibroblasts to Apoptosis: A Role of Mir-181a. Salahuddin Ahmed[1], Laura Walsh[2], Anil Singh[1], Maria Beamer[2], Kuladeep Sudini[2] and Douglas Leaman[2]. [1]Washington State University, Spokane, WA, [2]University of Toledo, Toledo, OH.

Background/Purpose: In rheumatoid arthritis (RA), the paucity of pro-apoptotic protein expression may significantly contribute to the resistance of synovial fibroblasts (FLS) to apoptosis. In the present study, we evaluated if inducing the expression of pro-apoptotic protein Noxa in RA-FLS using a potent anti-inflammatory pentacyclic triterpenoid uroslic acid (UA) triggers apoptosis and studied the underlying mechanism.

Methods: Effects of UA (2.5–10 μM) on human RA-FLS morphology and cell viability were determined by microscopy and a colorimetric MTT/SRB cell viability assays. Mechanism of UA's activity was modulated experimentally by using the siRNA or plasmid overexpression approaches. Epigenetic regulation of Noxa by microRNA-181a (mir-181a) was studied using the microarray and qRT-PCR methods. Apoptosis was measured by the cleavage of caspase-3 and poly-ADP-ribose polymerase (PARP). Western blotting was used to evaluate the apoptosis signaling mediators, Noxa, and Mcl-1 expression.

Results: UA (2.5–20 μM) decreased the cell viability of RA-FLS in a dose-dependent manner. Importantly, UA (10 μM) selectively induced Noxa expression within 3 h to ~2–3 fold in RA-FLS ($p<0.05$; $n=4$). Induction of Noxa led to the consequent downregulation of Mcl-1 expression and apoptosis by 24 h of UA treatment ($p<0.05$; $n=3$). The inhibition of Mcl-1 expression by UA resulted in the sensitization of RA-FLS to TRAIL-induced PARP cleavage and apoptosis. Overexpression of Noxa using a plasmid vector targeting Noxa was effective in making RA-FLS susceptible to apoptosis. Using a siRNA method to block Noxa expression, we found that the RA-FLS apoptosis-inducing activity of UA was significantly blocked suggesting that UA induced apoptosis in RA-FLS primarily through Noxa upregulation. Confirmatory studies using WT and Noxa−/− BMK cells showed that UA efficiently induced apoptosis in WT cells but had no effect in Noxa−/− counterparts ($p<0.01$; two independent experiments). Interestingly, transfection of stably expressing Noxa in Noxa−/− BMK cells restored the apoptosis inducing capability of UA. MicroRNA array analysis showed a significant decrease in RA-FLS mir-181a expression, a miRNA known to facilitate apoptosis, by ~30% as compared to the normal FLS ($p<0.05$). We also found that UA (5–10 μM) was capable of inducing mir-181a expression in RA-FLS as compared to the non-stimulated samples suggesting that UA-induced Noxa expression and consequent apoptosis in RA-FLS may be mediated epigenetically via upregulation of mir-181a.

Conclusion: Our novel findings indicate that inducing Noxa expression by UA in RA-FLS effectively induces apoptosis and this effect is partly mediated through mir-181a. Thus, developing therapeutic strategies that can selectively upregulate Noxa and/or modulate mir-181a to induce apoptosis in RA-FLS may have potential therapeutic application for the treatment of RA.

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Neutralization of IL-17 Ameliorated Kidney Pathology Associated with Immune-Complex Mediated Autoimmune Glomerulonephritis. Partha Biswas[1], Kritika Ramani[1], Kelly Maers[1], Anna Huppler[2] and Sarah L. Gaffen[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Immune complex mediated autoimmune glomerulonephritis (AGN) is an often-fatal clinical manifestation of systemic lupus erythematosus. In recent years, pro-inflammatory cytokines in the nephritic kidney appear to contribute to the pathogenesis of AGN. The inflammatory cytokine network that drives renal pathology is poorly understood. IL-17, the signature cytokine of T-helper 17 (Th17) cells, which promotes autoimmune pathology in a variety of settings, is beginning to be identified in kidney diseases as well. However, the role of IL-17 and the consequence of blocking IL-17 in the pathogenesis of AGN have not been elucidated.

Methods: We took advantage of a prototypic mouse model of AGN, where glomerular injury is induced by generating an autoimmune response against rabbit anti-mouse glomerular basement membrane serum. In this model, development of AGN is an inevitable consequence of glomerular injury induced by immune-complex deposition, recapitulating many features of lupus nephritis. Accordingly, wild type (WT) and IL-17 receptorA$^{-/-}$ (IL-17RA$^{-/-}$) mice were subjected to AGN and evaluated for the development of kidney pathology over a period of 14 days. We also test the therapeutic efficacy of neutralizing IL-17 in AGN induced WT mice.

Results: We showed that IL-17RA signaling is critical for the development of renal pathology. Despite normal systemic autoantibody response and glomerular immune-complex deposition, IL-17RA$^{-/-}$mice exhibit diminished influx of inflammatory cells and kidney specific expression of IL-17 target genes correlating with disease resistance in AGN. IL-17 enhanced the production of pro-inflammatory cytokines and chemokines from tubular epithelial cells. Finally, we were able to show that neutralization of IL-17 ameliorated renal pathology in wild type mice following AGN.

Conclusion: These results clearly demonstrated that IL-17RA signaling significantly contributes to renal tissue injury in experimental AGN. Additionally, it also suggested that blocking IL-17-IL-17R signaling may be a promising therapeutic strategy for the treatment of AGN associated with SLE, which may have ramifications in other autoinflammatory kidney disorders.

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Stat3 Promotes IL-10 Expression in SLE T Cells through *Trans*-activation and Chromatin Remodeling. Christian Hedrich[1], Thomas Rauen[2], Sokratis Apostolidis[3], Alexandros P. Grammatikos[4], Noe Rodriguez Rodriguez[4], Christina Ioannidis[3], Vasileios C. Kyttaris[4], José C. Crispin[4] and George C. Tsokos[5]. [1]Children's Hospital, Dresden, Germany, [2]BIDMC, Harvard Medical School, Boston, MA, [3]BIDMC, Boston, MA, [4]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [5]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA.

Background/Purpose: IL-10 is an immune-regulatory cytokine that is expressed by a wide range of cells and tissues. It plays a central role in the

regulation of the innate and adaptive immune system. IL-10 is elevated in the serum and tissues of patients with the autoimmune disorder systemic lupus erythematosus (SLE). SLE is characterized by autoantibody production, immune complex formation, and altered cytokine expression. Because IL-10 exhibits B cell-promoting effects, it has been suggested as a contributor to autoantibody production and tissue damage in SLE. In this study, we aimed to determine molecular events governing T cell-derived IL-10 expression in health and disease.

Methods: To achieve this, we forced the expression of the transcription factors Stat3 or Stat5, or inhibited them through siRNAs or chemical inhibitors in human T cells. Furthermore, *IL10* reporter constructs have been utilized to determine the relative contribution of Stat3/5 on specific regulatory elements in the *IL10* proximal promoter and an intronic enhancer. The influence of two major epigenetic events, DNA methylation and histone acetylation, on IL-10 expression has been determined using MeDIP or ChIP assays. Furthermore, we determined potential interactions between Stat transcription factors and the transcriptional co-regulator p300, using transfection systems, siRNA and chemical inhibition strategies, and proximity ligation assays.

Results: We link reduced DNA methylation of *IL10* regulatory regions with increased recruitment of Stat transcription factors. IL-10 is regulated by both Stat3 and Stat5 through their differential recruitment to the *IL10* promoter (Stat3) and an intronic enhancer (Stat5). Stat3 and Stat5 *trans*-activate regulatory elements and induce epigenetic remodeling of *IL10* through their interaction with the histone acetyltransferase p300. Of note, in T cells from SLE patients, activation of Stat3 is increased, resulting in enhanced recruitment to regulatory regions and competitive replacement of Stat5 at the intronic enhancer, subsequently promoting IL-10 expression.

Conclusion: Understanding the molecular events governing cytokine expression will provide new treatment options in autoimmune disorders, including SLE. The observation that altered Stat3 activation enhances IL-10 expression in T cells offers a potential target in the search for novel biomarkers and treatment options in SLE.

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Therapeutic Potential of Targeting Sialic Acid Modified Receptors in Osteoarthritis. Maria Dolores Mayan[1], Paula Carpintero-Fernández[1], Raquel Gago-Fuentes[1], Marta Varela-Eirin[1], Gary S. Goldberg[2] and Francisco Javier Blanco[1]. [1]Cartilage Biology Research Group, Rheumatology Division, INIBIC-Hospital Universitario A Coruña, A Coruña, Spain, [2]Department of Molecular Biology, School of Osteopathic Medicine, Stratford, NJ.

Background/Purpose: Glycosylated proteins are essential components of the extracellular matrix (ECM) of cartilage and contribute to the maintenance of its function. A shift from a-2,6- to a-2,3-linked sialic acids of glycoproteins modifies the binding ability of proteins to substrates influencing cellular anchoring and affecting signal transduction. Intriguingly, the predominance of a-2,3-sialylation of chondrocytes glycoproteins was associated with the pathophysiology of rheumatic diseases including rheumatoid arthritis (RA) and osteoarthritis (OA). A highly O-glycolysated protein with $\alpha-2,3$-sialic acid, involved in the induction of inflammation and tissue repair, is the transmembrane mucin receptor named Podoplanin (PDPN). The present study aimed to assess the effect of specifically targets a-2–3-sialic acid residues with a lectin-based drug (MASL) on chodrocyte dedifferentiation and cartilage breakdown processes.

Methods: For immunofluorescence and immunohistochemistry assays, in situ cartilage was fixed and frozen immediately using Tissue-Tek O.C.T. and isopentanol in liquid nitrogen. Primary cells in monolayer culture were fixed with formaldehyde for optical microscopy assays. 4mm cartilage punches were prepared from cartilage explants that were cut in the operating room immediately after surgery and cultured in DMEM with 0.1% FCS. Chondrocytes were isolated from articular cartilage and cultured in DMEM with 15% FCS. Cell viability was evaluated by the colorimetric MTT assay. Cell adhesion and grown was assess with fibrinogen-coated well plates and Wound Healing Assay Kit. Reactive oxygen species levels were measured by DCFH-DA and by Flow Cytometry. RNA was isolated with TRIZOL® Reagent and analyzed by Real-Time RT-PCR.

Results: The treatment of chondrocytes with 400 and 720 nM of MASL did not affect cell viability, adhesion or growth. To mimic pathological conditions, cells and cartilage explants were treated with 5 μg/ml oligomycin. Treatment of chondrocytes with oligomycin did not affect cell viability but increased ROS levels over 10 fold and MMP3, IL-6 and COX2 mRNA levels over 3–10 folds. The treatment of cells with MASL effectively protected chondrocytes from ROS production when incubated in the presence of oligomycin. Moreover, oligomycin induced the expression of inflammatory cytokines including IL-6 and COX2, and this induction was reverted by treatment with nanomolar concentrations of MASL. 5 μg/ml of oligomycin for 7 days decreased safranin uptake and disrupted the ECM structure of cartilage punches as evidenced by ulceration increasing lacunae space. However, the presence of 400 nM of MASL prevented the cartilage destruction and inhibited COX2 and MMP3 induction by oligomycin treatment. Immunohistochemistry assays revealed that OA cartilage contained significantly higher levels of PDPN protein in comparison with cartilage from healthy donors.

Conclusion: This study demonstrates that physiologically relevant concentrations of MASL protect chondrocytes from detrimental effects of ROS, inflammatory cytokines and MMPs and preserve chondrocyte phenotype and articular cartilage structure under pathological conditions.

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TNF-á Modulates the Expression of Circadian Clock Genes Via Calcium Signaling in Rheumatoid Synovial Cells. Kohsuke Yoshida[1], Nao Shibanuma[2], Teppei Hashimoto[3], Yoshiko Kawasaki[3], Naonori Hashimoto[1], Ayako Nakai[1], Kenta Kaneshiro[1], Koji Tateishi[4], Natsuko Nakagawa[4] and Akira Hashiramoto[3]. [1]Faculty of Health Sciences, Kobe University School of Medicine, Kobe, Japan, [2]Department of Orthopaedic Surgery, Kobe Kaisei Hospital, Kobe, Japan, [3]Department of Rheumatology, Kobe Kaisei Hospital, Kobe, Japan, [4]Department of Orthopaedic Surgery, Konan-Kakogawa Hospital, Kakogawa, Japan.

Background/Purpose: The mammalian clock genes including *Clock* (circadian locomotor output cycles kaput), *Bmal1* (brain and muscle Arnt-like protein 1), *Per* (Period) and *Cry* (Cryptochrome) regulate the circadian rhythm. We previously showed that arthritis was significantly accelerated in *Cry* knockout mice due to the activation of TNF-α (tumor necrosis factor a) transcription, and TNF-α inhibited the expression of *Per2* gene via D-box binding protein, such as *Dbp* (D site of albumin promoter binding protein), in rheumatoid synovial cells. Since the effect of TNF-α on expression of *Dbp* gene has been reported to be dependent on intra-cellular calcium signaling, we tried to elucidate the contribution of the calcium signaling on TNF-α-induced *Per2* inhibition in rheumatoid synovial cells.

Methods: Primary cultured rheumatoid synovial cells were synchronized upon incubation with 50% horse serum for 2 hours. Cells were treated with an intra-cellular [Ca^{2+}] chelator BAPTA-AM (25μg/mL) or a calcineurin inhibitor FK-506 (Tacrolimus; 0.25 to 25 μg/mL) for 60 min, and then stimulated with or without TNF-α (10 ng/mL) for 24 hours. Total RNA was extracted from synovial cells, and mRNA expression of D-box binding protein genes, including *Dbp*, *Hlf* (hepatic leukemia factor), *Tef* (thyrotroph embryonic factor) and *E4BP4* (E4-binding protein 4), were analyzed by real-time PCR. The viability of the synovial cells was determined using Cell Counting Kit-8.

Results: The mRNA expression of *Per2* was inhibited upon incubation with TNF-α in rheumatoid synovial cells, which was cancelled by BAPTA-AM treatment ($P < 0.05$), but not FK-506, suggesting that *Per2* inhibition by TNF-α could be induced via calcium signaling. Since *Dbp*, *Hlf*, *Tef* and *E4bp4* genes could transactivate and suppress the expression of *Per2* gene, respectively, we next examined the effect of BAPTA-AM on expression of these genes. As well as the result of *Per2*, the inhibition of *Dbp*, *Hlf* and *Tef* mRNA expression upon incubation with TNF-α were cancelled by BAPTA-AM treatment ($P < 0.05$). However, BAPTA-AM treatment did not affect the increase of *E4bp4* expression by TNF-α. In addition, the viability of the synovial cells was increased by stimulation with TNF-α, and this was reversed by treatment with BAPTA-AM ($P < 0.01$).

Conclusion: In rheumatoid synovial cells, TNF-α modulates the expression of *Dbp*, *Hlf*, *Tef* genes and then inhibits *Per2* gene via calcium signaling. Since *Per2* knockout mice exhibit increased resistance to apoptosis in thymocytes, our results suggest a novel role of TNF-α in the relationship between clock gene expression via calcium signaling and the anti-apoptotic character of rheumatoid synovial cells.

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Synergism Between GM-CSF and IL-17 Causes Enhanced Joint Pathology Via the Production of IL-6 and IL-23. Annemarie E.M. van Nieuwenhuijze[1], Debbie M. Roeleveld[1], Birgitte Walgreen[1], Miranda Bennink[1], Monique M. Helsen[1], Liduine van den Bersselaar[1], Ian P. Wicks[2], Wim B. van den Berg[1], Fons A. van de Loo[1] and Marije I. Koenders[1]. [1]Radboud university medical center, Nijmegen, Netherlands, [2]The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia.

Background/Purpose: T helper-17 (Th17) cells are important mediators of inflammatory diseases, and are the main pathogenic cell type in many animal models of autoimmunity. Recent studies highlight a surprising role for T-cell derived granulocyte-macrophage colony stimulating factor (GM-CSF) in the pathogenicity of Th17 cells. We examined the mechanism by which interleukin 17 (IL-17) and GM-CSF contribute to cartilage- and bone damage of synovial joints during experimental arthritis, and investigated their potential additive and synergistic effects to provide a rationale for combination therapy in auto-inflammatory conditions.

Methods: Collagen-induced arthritis (CIA) was elicited in DBA/1J mice. Neutralizing antibodies to IL-17 and/or GM-CSF were administered after onset of disease for 14 days. Arthritis progression was followed by macroscopic scoring of the paws (maximum score of 12 per mouse). In addition, the effect of local over-expression of IL-17 and/or GM-CSF was studied by adenoviral transfection in naïve knee joints. Joint pathology was studied by X-ray and histology, and Luminex and QPCR were performed to determine cytokine en chemokine expression.

Results: Combined therapeutic treatment of mice early after the onset of CIA ameliorated disease progression. Macroscopic joint inflammation was significantly reduced, from a total score of 5.6 ± 0.4 for mice treated with isotype control antibodies to 2 ± 0.6 for mice treated with combination therapy. Treatment with anti-IL-17 or anti-GM-CSF alone resulted in scores of 3.4 ± 0.5 and 3.5 ± 0.4, respectively. Simultaneous blocking of GM-CSF and IL-17 was also the most effective treatment in the prevention of radiological bone damage and histological cartilage destruction.

To provide further insight in local additive or synergistic effects of IL-17 and GM-CSF, overexpression of IL-17, GM-CSF or the combination was achieved with adenoviral vectors. Inflammatory infiltrate and cartilage- and bone damage developed in all groups from day 1 after adenoviral transfer, with the most severe effect observed in the combination group. On day 7, partial destruction of joint architecture was apparent in knee joints after combined overexpression of IL-17 and GM-CSF. Overexpression of GM-CSF alone induced IL-1β, which production was elevated by IL-17. Interestingly, overexpression of IL-17 alone caused a clear increase in synovial IL-6 production (179 ± 63pg/ml), which was dramatically enhanced in the co-presence of GM-CSF ($1{,}9\pm0{,}4$ng/ml). In addition, a strong synergistic effect of combined overexpression was seen on the Th17 differentiation factor IL-23.

Conclusion: Our results demonstrate that the combined presence of IL-17 and GM-CSF causes aggravated joint damage through synergistic effects on inflammatory mediators in the synovial joints. In view of the moderate success of therapeutic IL-17 or GM-CSF blockade in rheumatoid arthritis, combined inhibition of IL-17 and GM-CSF might be an interesting alternative option for RA patients that do not fully respond to inhibition of the separate cytokines.

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Anti-MDA5 Antibody Associated Myositis Compared to DM Patient: A Distinct Muscular Pattern Associated with a shared IFN Signature. Yves Allenbach[1], Gaelle Leroux[2], Aude Rigolet[3], Baptiste Hervier[4], Nicolas Limal[5], Peter Hufnagl[6], Norman Zerbe[6], Thierry Maisonobe[7], Alain Meyer[8], Yurdagul Uzunhan[9], Kuberaka Mariampillai[10], Romain Gherardi[11], Serge Herson[10], Olivier Benveniste[1] and Werner Stenzel[6]. [1]Sorbonne Universités, University Pierre et Marie-Curie-Paris 6, INSERM, Paris, France, [2]DHU 2iB Internal Medicine Referal Center for Autoimmune diseases Pitie Hospital, Paris, France, [3]Assistance Publique - Hôpitaux de Paris, Pitié-Salpêtrière University Hospital, Paris, France, [4]Assistance Publique - Hôpitaux de Paris, Pitié-Salpêtrière University Hospital, PARIS, France, [5]Hôpital Henri Mondor, APHP, Creteil, France, [6]Charite Hospital, Berlin, Germany, [7]Pitie-Salpetriere Hospital, Paris, France, [8]University Hospital of Strasbourg, Strasbourg, France, [9]APHP Avicenne Hospital, Bobigny, France, [10]Assistance Publique - Hôpitaux de Paris, Pitié-Salpêtrière University, Paris, France, [11]APHP Henri Mondor Hospital, Creteil, France.

Background/Purpose: Anti-MDA5 auto-antibodies are thought to be specifically associated with dermatomyositis (DM). Nevertheless anti-MDA5 auto-antibody positive patients ($MDA5^+$ DM) predominantly suffer from extra-muscular involvement with severe interstitial lung disease, and arthritis. Further, skin lesions may be atypical with skin ulcers and mechanics' hands. Importantly, clinical signs of myopathy are rather mild or absent and morphology and immunology of skeletal muscle tissue has not been studied yet. Thus, the previously described characteristic 'IFN signature' in classical DM may not be found in $MDA5^+$ DM patients. We aim to describe the histological pattern of the skeletal muscle and the intrinsic immune response $MDA5^+$ DM patients.

Methods: Muscle specimens were subjected to conventional staining and immunohistochemical analysis to describe muscle fibers, vessel morphology and inflammatory features. Morphometry of vessels was performed using imageJ software on digitally completely scanned slides and by electron microscopy. A panel of six interferon stimulated genes (ISGs) (*OAS1, OAS3, ISG15, MX1, RIG1 and MDA5*), involved in the IFN immune response were tested by quantitative PCR in muscle biopsie (results expressed as normalized fold change relative to a normal muscle). The median fold change of the six ISGs, was used to create an IFN score. **Results:** are compared to anti-MDA5 auto-antibody negative DM patients (based on ENMC criteria). Serum level of IFN-α was tested using a bioassay.

Results: In $MDA5^+$ DM patients ($n=9$) the mean MRC-score (five score) of the weakest muscular group was 4.5 ± 0.5 and CK levels were 498 ± 809 IU/l. Muscle biopsies ($n=10$) were analyzed compared to $MDA5^-$ DM patients ($n=7$). Histological analysis showed that anti-$MDA5^+$ patients did not present the classical feature of perifascicular fiber atrophy. Inflammation was focal in the perimysium and mainly perivascular but significantly less intense as it is shown by density scores of $CD45^+$ leukocytes (35.8 ± 28 vs. 5.9 ± 7.6 cells/mm^2, $p<0.05$). MHC-class I staining was also less intense and more focal compared to $MDA5^-$ DM patients who harboured a diffuse staining pattern with a perifascicular re-inforcement. $MDA5^+$ DM patients did not show signs of capillary loss since the capillary density was 279.9 ± 17.7/mm^2 vs. 340.9 ± 16.5/mm^2 ($p=0.05$) in $MDA5^-$ DM patients. In the same line the frequency of enlarged capillaries (diameter $>10\mu$m) was decreased $5.8\pm1.1\%$ vs. $13.9\pm2.5\%$. Tubulo-reticular formations were observed in only 50% of $MDA5^+$ patients, but in all cDM patients. In $MDA5^+$ DM patients a strong up-regulation of ISGs expression was observed with RQ values ranging from 74.5 ± 17.2 for *RIG* to 1107 ± 406 for *ISG15* even though, the IFN score was less increased than in controls (139.5 vs 634; $p=0.005$). Finally IFN-α serum levels were increased in all active $MDA5^+$DM patients ($n=2$).

Conclusion: These results show that myositis in patients with anti-MDA5 Ab positivity shows a distinct morphological pattern compared to $MDA5^-$ DM patients, but is associated with an IFN signature as well, underlining the importance of this pathway in the pathogenesis of both entities.

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Macrophage-Fibroblast Crosstalk Pathways Amplify RA Joint Pathology. Laura T. Donlin, Jennifer Ding and Lionel B. Ivashrkiv. Hospital for Special Surgery, New York, NY.

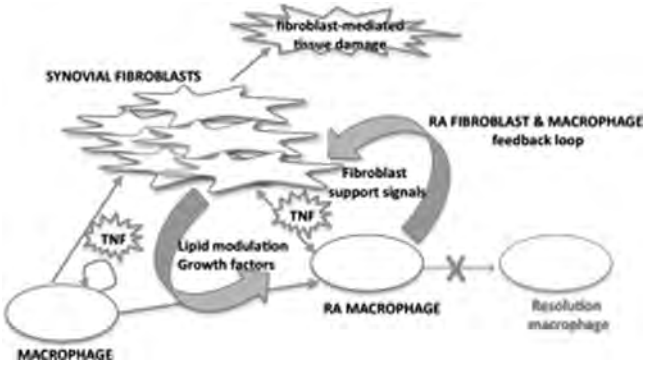
Background/Purpose: Macrophages and synovial fibroblasts represent key cellular drivers of RA. The goal of this study was to define how the complex cellular programs of macrophages and fibroblasts crossregulate within an inflammatory setting and potentially perpetuate pathologic responses. Previously, we have shown that soluble synovial fibroblast products

suppress the macrophage TNF-induced Type I Interferon response. Here through a next-gen sequencing transcriptome analysis, we describe on a global scale how the macrophage TNF-a response is reshaped by synovial fibroblast factors, ultimately converting classic anti-inflammatory/resolution pathways into programs that feedback to support fibroblast growth and function. Furthermore, macrophages isolated directly from RA synovium indeed activate a subset of these gene expression networks, suggesting these macrophage-fibroblast crosstalk pathways represent novel therapeutic targets.

Methods: Human blood derived macrophages and human RA synovial fibroblasts were co-cultured in transwell plates and treated with TNF for 2 days. The transcriptomes of both cell types were analyzed by RNA sequencing (RNAseq). Pathway analysis programs identified macrophage responses specifically controlled by synovial fibroblasts, as well as identified candidate soluble crosstalk mediators. Cellular STAT3 activity was monitored by Western blot detection of phospho-STAT3 levels and by qPCR analysis of STAT3-dependent genes, while the soluble mediators responsible for inducing differential STAT3 responses were confirmed with neutralizing antibodies in the culture media.

Results: Synovial fibroblasts modified specific programs within the macrophage inflammatory response, impacting 30% of TNF-regulated genes. Pathway analysis demonstrated fibroblast factors largely transformed macrophage lipid programs and induced growth factor responses, including genes known to promote wound healing activities and growth of fibroblasts. Interestingly, while TNF-a alone induced an anti-inflammatory STAT3 response, TNF-a combined with fibroblast factors blocked this resolution response and instead diverted STAT3 activity towards mitogenic and metabolic pathways. Furthermore, initial analysis of synovial macrophages isolated directly from RA synovium revealed a subset of the crosstalk pathways identified in the in co-culture system including specific growth factor responses.

Conclusion: We propose the combination of inflammatory and fibroblast-derived factors found in the RA synovium drive macrophages into an unresolving novel macrophage phenotype that in part functions to feedback and support synovial fibroblast pathologic activity.



Disclosure: L. T. Donlin, None; **J. Ding**, None; **L. B. Ivashkiv**, None.

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Interleukin-20 Is Triggered By TLR Ligands and Associates with Rheumatoid Arthritis Disease Activity. Ladislav Senolt[1], Klara Prajzlerova[1], Hana Hulejova[2], David Veigl[3], Karel Pavelka[1] and Jiri Vencovsky[1]. [1]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [2]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Prague, Czech Republic, [3]1st Orthopaedic Clinic, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovial inflammation and subsequent joint damage with systemic manifestations. Interleukin-20 (IL-20) has been previously identified as a pro-inflammatory cytokine that may be implicated in the pathogenesis of chronic inflammatory diseases, particularly RA (1). Recently, phase 2a trial (2) demonstrated that treatment with anti-IL-20 monoclonal antibody significantly reduced disease activity in seropositive patients with RA. Therefore, the aim of the current study was to characterize the role of IL-20 in patients with RA.

Methods: The levels of serum and synovial fluid IL-20 were measured by ELISA assay in 34 patients with RA (25 female) and 35 patients with OA (19 female). Disease activity was assessed based on the Disease Activity Score of 28 joints (DAS28). The expression of IL-20 in synovial tissue samples from patients with RA (n=5) and OA (n=7) were determined by immunohistochemistry. Secretion of IL-20 was analysed in human peripheral blood mononuclear cells (PBMCs) isolated from blood of patients with RA (n=8).

Results: The expression of IL-20 was significantly up-regulated in RA compared with OA synovial tissue, particularly in the lining (2.6±0.65 vs 0.93±0.19; p=0.003) as well as in the inflammatory infiltrates of the sublining layer (2.2±0.57 vs 0.37±0.36; p=0.005). The levels of IL-20 in synovial fluid were significantly higher in patients with RA compared to those with OA (86.3±87.5 vs 41.9±43.3 pg/ml; p=0.01). IL-20 production from PBMCs was induced by Poly I:C (TLR-3 ligand) (p<0.0001) and LPS (TLR-4 ligand) (p=0.0008), but not with pro-inflammatory cytokines such as TNFα (p=0.99) or IL-1 (p=0.74).

In contrast to local sites of inflammation, serum levels of IL-20 in RA patients were comparable to those in OA patients (41.7 ± 48.7 vs 32.3 ± 45.4 pg/ml; p=NS), and significantly correlated with DAS28 (r=0.581; p=0.001) and anti-CCP levels (r=0.362; p=0.045). When adjusted for anti-CCP levels, correlation with DAS28 remained still significant (r=0.540; p=0.002). Similarly, the levels of IL-20 in synovial fluid correlated with RA disease activity. In addition, the levels of IL-20 in synovial fluid were significantly higher in anti-CCP positive compared to anti-CCP negative patients with RA (122.3±104.1 and 45.9±35.8 pg/ml; p=0.008); this difference was however not paralleled by serum IL-20 levels (51±48.6 and 31.1±48.2 pg/ml; p=0.24).

Conclusion: Our data show that IL-20 is independently associated with RA disease activity and may be triggered by TLR ligands at local sites of inflammation. Association between IL-20 and anti-CCP levels may, at least partially, explain disease activity improvement after the treatment with anti-IL-20 monoclonal antibody in seropositive RA patients.

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1040

Dysregulated Serum Interleukin 16 Concentration Associated with Clinical Disease Activity in Patients with Rheumatoid Arthritis Is Efficiently Corrected By Immunological Intervention. Atsuko Murota[1], Katsuya Suzuki[1], Yoshiaki Kassai[2], Takahiro Miyazaki[3], Rimpei Morita[4], Akihiko Yoshimura[4] and Tsutomu Takeuchi[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Takeda Pharmaceutical Company, Fujisawa, Japan, [3]Takeda Pharmaceutical Company Limited, Kanagawa, Japan, [4]Department of Microbiology and Immunology, Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: IL-16 is a chemoattractant factor that evokes massive infiltration of mononuclear cells in the synovial tissue in patients (pts) with rheumatoid arthritis (RA). IL-16 concentrations are elevated in RA synovial fluid and also sera. However, the effect of current pharmacological intervention on this key cytokine and its association with clinical outcome are not fully understood. The purpose of this study was to clarify the effects of various treatments on IL-16 and the role in RA pts.

Methods: The study enrolled consecutive RA pts who met the 1987 or 2010 RA classification criteria, as well as pts with primary Sjogren's syndrome (pSS) and healthy controls (HC). Serum IL-16 and other proteins' concentrations in these groups were measured by quantitative proteomics assay using nucleic acid aptamers. Levels of IL-16 in RA pts were measured at baseline and 12 weeks after treatment with MTX or three different biologics (infliximab (IFX), tocilizumab (TCZ), and abatacept (ABT)) by conventional ELISA. In biologics therapy, pts who started with MTX at baseline or whose MTX dosage was increased during the 12 weeks were excluded. Correlations between IL-16 concentrations and clinical parameters were statistically analyzed.

Results: Serum IL-16 concentration was significantly increased in pts with untreated active RA (n=28) compared to the HC (n=30, p<0.0001) and pSS (n=30, p<0.0001) groups. IL-16 was a positively and most correlated cytokine with serum MMP-3 (R=0.70, P=3.5E-05) in pts with untreated RA, but only weakly and negatively correlated with MMP-3 in pts with pSS (R=−0.31, p=0.095). IL-16 was significantly decreased during treatment for RA for 12 weeks in all 86 RA pts (Figure). On stratification, IL-16 was decreased in the MTX- (n=31), TCZ- (n=17) and ABT-treated (n=16)

groups, but did not change in the IFX-treated group (n=22). Regarding clinical disease activity, the decrease in IL-16 was positively associated with DAS28-CRP in the MTX (R=0.48, p=0.007), ABT (R=0.60, p=0.01), TCZ (R=0.52, p=0.06) groups. Furthermore, the decrease in IL-16 was positively correlated with a decrease in serum CRP in the MTX (R=0.48, p=0.007) and ABT (R=0.54, p=0.03) groups, which indicates a stronger association with CRP in the composite measure, except for the TCZ group. MMP-3 in the MTX, IFX and TCZ groups was also significantly decreased at 12 weeks. In contrast, the decrease in IL-16 with treatment was not correlated with that of MMP-3, unlike the case with untreated RA at baseline.

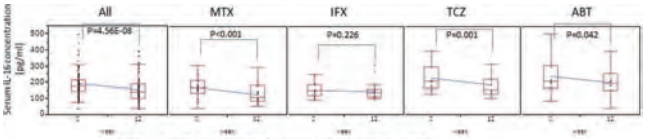

Figure. Serum IL-16 concentrations at baseline and 12 weeks.
MTX: methotrexate, IFX: infliximab, TCZ: tocilizumab, ABT: abatacept

Conclusion: Treatment with MTX, TCZ and ABT for active RA ameliorated the dysregulation of serum IL-16. This correction was correlated with decreases of clinical disease activity and CRP, except for TCZ, but not correlated with MMP-3. The directional change in serum IL-16 with different interventions, especially with TCZ, may indicate the need to revise molecular abnormalities in RA.

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Imaging the Role of Chemoattractants in Inflammatory Arthritis. Yoshishige Miyabe, Thomas T. Murooka, Chie Miyabe, Nancy Kim, Thorsten R. Mempel and Andrew D. Lusrter. Massachusetts General Hospital, Charlestown, MA.

Background/Purpose: Inflammatory arthritis, including rheumatoid arthritis, is characterized by neutrophil recruitment into the diseased joint. Our previous studies and the work of others have demonstrated important roles for several neutrophil chemoattractant receptors, including the leukotriene B4 receptor, BLT1, the chemokine receptors CCR1 and CXCR2, and the complement receptor C5aR in a murine model of immune-complex mediated arthritis. However, the precise role for each chemoattractant in the process of neutrophil recruitment into the inflamed joint remains unclear.

Methods: Multiphoton intravital microscopy (MP-IVM) was used to study the migratory behavior of wild-type and chemoattractant receptor-deficient leukocytes in the joint in the K/BxN serum transfer model of inflammatory arthritis. LysM-GFP mice in which endogenous neutrophils and macrophages express GFP were also used in these studies. Following the transfer of arthritogenic serum, MP-IVM was performed to analyze neutrophil migratory behavior in the joint on day 1 (early phase of arthritis) and day 7 (established arthritis). We also analyzed the ability of WT and chemoattractant receptor-deficient neutrophils to enter the joint in short term adoptive transfer homing assays on days 1 and 7 following arthritogenic serum transfer using MP-IVM.

Results: Analysis of neutrophil migratory behavior revealed that the number of neutrophils adhering to blood vessels of the joint and subsequently infiltrating into the inflamed joint was markedly increased on day 7 following arthritogenic serum transfer in WT LysM-GFP mice, compared to day 1 following serum transfer and compared to control untreated WT LysM-GFP mice. In short term homing assays, both WT and BLT1-deficient neutrophils rolled along the joint vessels of WT and BLT1-deficient mice and on day 1 following serum transfer but did not adhere or enter the joint. In contrast, adoptive transfer of WT and BLT1-deficient neutrophils on day 7 following serum transfer into WT mice revealed that the number of BLT1-deficient neutrophils that adhered to and subsequently migrated into the joint was dramatically reduced compared to WT neutrophils. Furthermore, neither WT nor BLT1-deficient neutrophils entered the joints of BLT1-deficent host mice on days 1 or 7 following serum transfer.

Conclusion: BLT1 plays an important role in both the adhesion and transmigration of neutrophil across blood vesseles of the joint during immune complex induced arthritis.

Disclosure: Y. Miyabe, None; **T. T. Murooka**, None; **C. Miyabe**, None; **N. Kim**, None; **T. R. Mempel**, None; **A. D. Luster**, None.

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IL-1β and TNF-α Promote Monocyte Viability through the Induction of GM-CSF Expression By Rheumatoid Arthritis Synovial Fibroblasts. Christelle Darrieutort-Laffite, Marie Astrid Boutet, Mathias Chatelais, Regis Brion, Frederic Blanchard, Dominique Heymann and Benoit Le Groff. INSERM, UMR 957, Nantes, France.

Background/Purpose: Macrophages and synovial fibroblasts (SF) are two major cells implicated in the pathogenesis of rheumatoid arthritis (RA). They can interact in the synovial micro-environment to drive inflammation and bone destruction. The aim of our work was to investigate the effects of SF on monocyte viability and differentiation and to determine which factors were implicated in these effects.

Methods: SF were isolated from synovial tissue of 9 RA patients and CD14+ cells were magnetically isolated from healthy donors by MACS technology. SF conditioned media were collected after 24 hours of culture with or without TNF-α or IL-1β. After 3 days of culture with RA SF conditioned media, monocyte survival was assessed using a WST-1 viability test. To study the involvement of M-CSF, IL-34 and GM-CSF, their expression was quantified in RA SF by qPCR, in RA synovial fluids by ELISA assay, and specific blocking antibodies were used in monocyte cultures. Macrophages polarization after culture with RA SF conditioned media was studied by flow cytometry. The cell surface markers analyzed were CD14, CD16, CD64 (M1), CD200R (M2a) and CD163 (M2c). A non-parametric test (Kruskall Wallis) was used to perform statistical analyzes.

Results: SF conditioned media significantly increased monocyte viability compared to cells cultured in medium alone ($p<0.001$). This effect was stronger when using conditioned media from IL-1β or TNF-α pre-stimulated SF. Monocyte viability was significantly increased compared to M-CSF (+29% ($p=0.05$) and +52% ($p=0.004$) for TNF-α and IL-1-β media respectively). M-CSF and IL-34 blocking antibodies, alone and in combination, had no effect on monocyte viability induced by SF conditioned media. In contrast, blocking GM-CSF resulted in a significant decrease in monocyte viability by 30% when added to the stimulated SF conditioned media ($p<0.001$). The expression of GM-CSF by RA SF was stimulated by TNF-α and IL-1β and GM-CSF levels in the synovial fluids were correlated with those of these two cytokines. Finally, studying the cell surface markers, we found no regulation of M1/M2 polarization when monocytes were differentiated in the presence of SF conditioned media.

Conclusion: SF conditioned media increased monocyte viability with a greater effect observed when SF were pre-stimulated with IL-1β or TNF-α and this effect was GM-CSF-dependent. However, cells cultured in the presence of conditioned media did not express specific M1 or M2 markers.

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Identification of Putative Biomarkers and Molecular Mechanisms Associated with Adverse Tissue Reactions to Metal-on-Metal and Modular Neck Hip Implants. Ed Purdue, Gabrielle Wilner, Kritti Kolatat, Geoffrey H. Westrich, Friedrich Boettner, Seth Jerabek and Steven R. Goldrring. Hospital for Special Surgery, New York, NY.

Background/Purpose: Total hip replacement (THR) is a highly successful treatment for degenerative arthritis, alleviating pain and restoring joint function in the vast majority of patients. However, inflammatory reactions to polyethylene wear debris resulting in destruction of bone (osteolysis) can lead to implant loosening and revision surgery. To avoid the adverse effects of polyethylene wear products, metal-on-metal bearings were introduced. Recent studies, however, have revealed an alarming rate of early revision surgery related to the development of adverse local tissue reactions (ALTR)

characterized by extensive and rapid necrosis of soft tissue surrounding implants with metal-on-metal (MoM) or dual modular neck (DMN) designs. We have used chemokine/cytokine profiling of synovial fluid and serum and gene expression analysis of peri-implant tissue to identify biomarkers for early detection and to gain insights into the pathogenesis of ALTR.

Methods: Synovial fluid and serum was collected from ALTR and osteolysis patients at revision surgery, and cell-free aliquots were prepared and immediately frozen. Antibody arrays were used to identify selected chemokines and cytokines, and results confirmed by ELISA. For gene expression profiling, total RNA was prepared from peri-implant tissue using Trizol. RNA integrity was verified using an Agilent Bioanalyzer, and then subjected to microarray analysis (Affymetrix U133 2.0). Results: were verified using real time PCR.

Results: Synovial fluid from ALTR patients demonstrated elevated levels of several chemokines and cytokines compared to those seen in osteolysis patients, including the interferon gamma inducible chemokines MIG/CXCL-9 and IP-10/CXCL10. Levels of these factors were generally higher in the DMN ALTR patients than the MoM ALTR patients. More modest elevations of these chemokines were found in ALTR serum samples. Microarray analysis revealed a unique ALTR gene expression profile that was absent in arrays prepared from peri-implant tissues from patients with osteolysis. Pathway analysis identified a unique chemokine/interferon signature that mirrored the protein profile of synovial fluid.

Table 1 Mean (Standard Deviation) levels of selected proteins in the synovial fluid and serum (in pg/ml). p-values are for comparison to the osteolysis group.

	Protein	Osteolysis	ALTR–DMN	p-value (DMN)	ALTR–MOM	p-value (MoM)
Synovial Fluid	MIG	1,320 (1,901)	178,442 (120,107)	8.46 E-6	68,609 (68,867)	2.52 E-3
	IP-10	1,880 (4,304)	100,137 (78,158)	9.32 E-5	32,829 (30,575)	2.00 E-3
	IL-6	497 (786)	28,583 (28,481)	1.53 E-3	16,102 (21,768)	2.10 E-2
	IL-8	8,621 (12,820)	64,172 (58,125)	2.21 E-3	54,338 (41,930)	1.32 E-3
Serum	MIG	273 (163)	592 (315)	1.68 E-3	456 (279)	0.036
	IP-10	17.4 (9.8)	25.7 (29.5)	0.31	32.9 (31.0)	0.074

Conclusion: Expression profiling of peri-implant tissues from ALTR patients reveals a unique chemokine/cytokine gene signature. The corresponding gene products are detectible in synovial fluid and serum, indicating their potential utility as biomarkers for early diagnosis and monitoring of patients at risk for ALTR. In addition, pathway analysis reveals up-regulation of genes involved in lymphocyte trafficking and activation, providing insights into disease pathogenesis and importantly identifies potential therapeutic targets to prevent this devastating complication.

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Novel Compound Cytokine Release Inhibitory Drug 3 (CRID3) Inhibits the NLRP3 Inflammasome in Rheumatoid Arthritis. Trudy McGarry[1], Mary Connolly[1], Rebecca C. Coll[2], Avril A. B. Robertson[3], Matthew A. Cooper[3], Luke A. O'Neill[2], Douglas J. Veale[1] and Ursula Fearon[1]. [1]Translational Rheumatology Research Group, Dublin, Ireland, [2]School of Biochemistry and Immunology, Dublin, Ireland, [3]The University of Queensland, Brisbane, Australia.

Background/Purpose: The NLRP3 inflammasome is a multi-protein complex activated in response to environmental pathogens. This results in caspase-1-dependant cleavage of pro-IL-1β and IL-18 to their active and mature form, induction of which leads to a variety of biological effects associated with infection, inflammation and autoimmunity. Cytokine Release Inhibitory Drug 3 (CRID3) is a novel inhibitory molecule thought to be active in the NLRP3 pathway. In this study, we examined the effects of Toll-like Receptor 2 on inflammasome activation and cytokine secretion. Furthermore, the role of CRID3 on the NLRP3 pathway in the RA joint was examined.

Methods: Rheumatoid Arthritis *ex vivo* synovial tissue biopsies were cultured in the presence or absence of synthetic Toll-like Receptor 2 agonist Pam3CSK4 (1 μg/mL). Expression of inflammasome component NLRP3 in addition to the pro and mature/active forms of IL-1β and IL-18 were assessed by Taqman PCR and ELISA. TLR-2-induced pro-inflammatory cytokine secretion (IL-6, IL-8, TNFα) was also assessed by ELISA. RA synovial biopsies were incubated in the presence or absence of CRID3 (100 nM), a novel inhibitory compound which is thought to act on or closely to NLRP3. Expression of NLRP3, IL-1β and IL-18 expression was analysed by Taqman PCR and ELISA. The effect of CRID3 on *ex vivo* pro-inflammatory cytokine secretion (IL-6, IL-8, TNFα) was also determined by ELISA.

Results: TLR2 stimulation significantly induced transcript levels of NLRP3 and pro IL-1β and IL-18 in RA *ex vivo* synovial tissue biopsies, a model which maintains cell-cell contact, preserves the synovial architecture and closely reflects the *in vivo* environment. Additionally, protein expression of IL-1β and IL-18 was increased in comparison to basal control. Pam3CSK4 significantly increased secretion of pro-inflammatory cytokines IL-6, IL-8 and TNFα. Incubation of synovial biopsies with CRID3 resulted in a decrease of pro IL1β, which was mirrored by a decrease in active IL-1β and NLRP3 expression. Spontaneous release of IL-6, IL-8 and TNFα were also reduced following CRID3 treatment.

Conclusion: TLR2 signalling induces NLRP3 activation in the RA joint, resulting in the secretion of inflammasome related cytokines IL-1β and IL-18. Additionally, we show for the first time that CRID3 is a novel compound which inhibits inflammasome activity in RA, and subsequent induction of pro-inflammatory pathways.

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Tertiary Lymphoid Organ Developmental Program: Diversgent Paradigm of Lymphoid Organogenesis. Saba Nayar[1], Bridget Glaysher[2], Joana Campos[1], Jorge Caamano[1], David Withers[1], Kai Toellner[1], Sanjiv Luther[3], Mark Coles[4], Christopher Buckley[5] and Francesca Barone[1]. [1]University of Birmingham, Birmingham, United Kingdom, [2]University of York, york, United Kingdom, [3]Losanne University, Epalinges, Switzerland, [4]University of York, York, United Kingdom, [5]The University of Birmingham, Birmingham, United Kingdom.

Background/Purpose: Tertiary lymphoid organs (TLOs) represent the histological hallmark of many immune-mediated inflammatory diseases. TLOs are characterized by a functional leukocyte aggregation and network of lymphoid-like stromal cells (LLSc). LLSc express lymphoid chemokines (CXCL13, CCL19, and CCL21), survival factors (BAFF and IL-7), lymphoid markers and adhesion molecules (gp38, RANKL, ICAM-1 and VCAM-1) that locally support lymphocytes survival and organization in ectopic sites areas.

Methods: We have used a combination of in vitro and in vivo approaches in two models of TLO formation to address the dynamic of stromal cell activation within TLOs.

Results: and Conclusion: We demonstrated that the acquisition of this lymphoid phenotype by the non-activated resident stroma requires a multistep process, fundamentally different from that responsible of secondary lymphoid organ formation. We showed that early, during TLO formation, IL-4Rα engagement via IL-13 on quiescent tissue-resident fibroblasts induces LLSc priming and mediates the up-regulation of gp38 and lymphoid-associated adhesion molecules. Expansion of this activated lymphoid stroma requires IL-22/IL-22R mediated signaling. Lack of IL-22 or its receptor induces defective LLS proliferation, abrogation of CXCL13 expression and TLO involution. Finally we demonstrated that, similarly to secondary lymphoid organ, stabilization of the stroma to a functional lymphoid phenotype requires lymphocyte infiltration and lymphotoxin beta expression. This work highlights critical differences between the embryonic program responsible for SLO formation and the inflammatory development of TLOs and unveils novel potential targets for TLO targeting.

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Modulatory Effect of Adiponectin on Apoptosis and Proliferation of Synovial Fibroblasts from Rheumatoid Arthritis Patients. Wei Yu[1], Wenfeng Tan[2] and Miaojia Zhang[3]. [1]The First Affiliated Hospital of Nanjing Medical University, nanjing, China, [2]the First Affiliated Hospital of Nanjing Medical University, Nanjing, CHINA., Nanjing, China, [3]the first affliated hospital with nanjing medical univercity, nanjing, China.

Background/Purpose: We previously reported that adiponectin (AD) is highly expressed in the inflammatory joint of rheumatoid arthritis (RA)

patients and closely correlated with progressive bone erosion, but the mechanism remained largely unclear. Synovial fibroblasts from RA patients (RASFs) have been suggested a unique characteristic of resistance to apoptosis that contributes to synovial hyerplasia, synovitis and bone erosion in RA. In this study, we tested the role of AD on apoptosis and proliferation in primary RASFs.

Methods:RASFs was treated with PBS in the absence and presence of AD (0.1, 1 or 10 μg/ml) for 24 h to 72 h and the frequencies of apoptosis cells were measured by flow cytometry. CCK-8 and direct microscopic count were used to analyze the proliferation of RASFs after stimulated with AD. Real-time PCR was used to test the expression of Bcl-2, Bax, p53, CDK4, PCNA, IL-6, IL-8 and MMP-3 mRNA in RASFs. Western blot was used to test the protein expression of Bcl-2 and Bax and activation of signal transduction pathways.

Results: The frequencies of apoptosis cells were significant decreased in RASFs after AD stimulation. AD could promote proliferation of RASFs compared with untreated it. A markedly increased CDK4 and PCNA mRNA expression and a decreased level of p53 mRNA were observed in RASFs after treated with AD. The levels of IL-6, IL-8 and MMP-3 expression also obviously increased in RASFs upon AD stimulation. Western blot indicated that AD could rapidly triggered p-Akt and p-ERK activity and then induced Bcl-2, but decreased Bax expression in RASFs.

Conclusion: Our findings indicate that AD could affect apoptosis and proliferation of RASFs via Akt and ERK pathway, suggesting a critical role of AD on disease progression in RA.

Disclosure: W. Yu, None; **W. Tan**, None; **M. Zhang**, None.

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Type I and II Interferon Signatures in Sjogren's Syndrome: Contributions in Distinct Clinical Phenotypes and Sjogren's Related Lymphomagenesis. Adrianos Nezos[1], Fotini Gravani[2], Efstathia K. Kapsogeorgou[3], Michael Voulgarelis[1], Haralampos M. Moutsopoulos[1], Mary K. Crow[4] and Clio Mavragani[1]. [1]School of Medicine, University of Athens, Athens, Greece, [2]General Hospital of Athens 'G.Gennimatas', Athens, Greece, [3]School of Medicine, National University of Athens, Greece, Athens, Greece, [4]Hospital for Special Surgery, New York, NY.

Background/Purpose: Both type I and II interferons (IFNs) have been implicated in the pathogenesis of Sjogren's syndrome (SS). We aimed to explore the contribution of type I and II IFN signatures in the generation of distinct SS clinical phenotypes including non-Hodgkin's lymphoma (NHL) development, a major SS complication.

Methods: Peripheral blood from SS patients (n=31), SS patients complicated by lymphoma (SSL, n=13) and healthy donors (HD, n=30) were subjected to real-time polymerase chain reaction for 3 interferon inducible genes (IFIGs) preferentially induced by type I IFN, 2 IFIGs preferentially induced by IFNγ as well as for IFNα and IFNγ genes. The same analysis was performed in minor salivary gland tissues (MSG) derived from 31 SS patients, 10 SSL patients and 17 sicca controls (SC).

Results: In peripheral blood and MSG tissues, overexpression of both type I and type II IFIGs was observed in SS patients versus HC and SC, respectively, with a predominance of type I IFN signature in peripheral blood and a type II IFN signature in MSG tissues. SS patients with salivary gland enlargement, lymphopenia, anti-Ro/SSA antibodies and hypergammaglobulinemia exhibited higher type I IFN scores in peripheral blood compared to their counterparts without those features. Hypergammaglobulinemia was also associated with increased type II IFN scores in peripheral blood. In MSG tissues derived from SSL patients we observed lower IFNα, but higher IFNγ and type II IFIG transcripts compared to both SS and SC. In ROC curve analysis, IFNγ/IFNα ratio in MSG tissues showed the best discrimination for lymphoma development, with an area under the curve of 0.88 (95% CI:0.72–1.00, p-value: 0.001).

Conclusion: Discrete expression patterns of type I and II IFN signatures might be related to distinct clinical SS features and SS related lymphomagenesis.

Disclosure: A. Nezos, None; **F. Gravani**, None; **E. K. Kapsogeorgou**, None; **M. Voulgarelis**, None; **H. M. Moutsopoulos**, None; **M. K. Crow**, None; **C. Mavragani**, None.

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Oncostatin M Suppresses Activation of IL-17/Th17 Via Suppressor of Cytokine signaling3 (SOCS3) Regulation in CD4+ T Cells. Young Ok Jung[1], seon Yeong Lee[2], Sung Yeon Lee[3], Mi-La Cho[2] and Hea-Jin Son[4]. [1]Hallym University Kangnam Sacred Heart Hospital, Seoul, South Korea, [2]Catholic University of Korea, Seoul, South Korea, [3]Hallym University Sacred Heart Hospital, Gyeonggi-do, South Korea, [4]Rheumatism Research Center, Catholic Institutes of Medical Science, The Catholic University of Korea, Seoul, South Korea.

Background/Purpose: Oncostatin M (OSM) is a pleiotropic cytokine that belongs to the interleukin(IL)-6 group of cytokines. High level of OSM were detected in synoviums of rheumatoid arthritis (RA) patients but its exact role in arthritis perpetuation has not been elucidated. We evaluated the role of OSM in T helper 17(Th17) cell differentiation, the most important cells in arthritis development.

Methods: Collagen-induced arthritis (CIA) was induced in DBA/1J mice. IL-2 immune complex(IC) were injected intraperitoneally three times at 2days intervals before 1st immunization. Severity of arthritis was assessed by clinical scoring of arthritis. CD4+ T cells were isolated by MACS and incubated in Th17 differentiation condition with and without OSM. The levels of cytokines were measured using ELISA. To analyze intracellular cytokine were analyed by FACS. Subpopulations of T cells of spleens were assessed by confocal microscopy. The mRNA levels of OSM and signaling molecules were determined by RT-PCR and real time PCR. The protein levels were assessed by Western blot. Suppressor of cytokine signaling3 (SOCS3) small interfering RNA(siRNA) was transfected by using the Amaxa 4D-nucleofector X unit (Lonxa, Cologne, Germany).

Results: IL-2IC treatment reduced the clinical arthritis score and OSM and SOCS were increased in spleens of IL-21C treated mice. We observed that OSM suppressed Th17 cell differentiation and the levels of IL-17 and IL-21 were decreased in dose dependent manner in vitro. OSM time dependently increase the level of STAT3, STAT5 and SOCS3 in mRNA and protein levels. STA21, the STAT3 inhibitor abrogated the suppressive effect of OSM on Th17 differentiation. SOCS3 siRNA also abrogated the suppressive effect of OSM.

Conclusion: OSM was up-regulated spleens of IL-2IC treated mice. OSM suppressed the Th17cell differentiation and the inhibitory effects of OSM on Th17 cells were via SCOS3 regulation.

Disclosure: Y. O. Jung, None; **S. Y. Lee**, None; **S. Y. Lee**, None; **M. L. Cho**, None; **H. J. Son**, None.

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Bioactive TGF-β Is Present on Bovine Milk-Derived Exosomes: Consequences for Patients? Bartijn C.H. Pieters, Onno J. Arntz, Mathijs G.A. Broeren, Arjan van Caam, Peter M. van der Kraan, Marieke de Vries and Fons A.J. van de rLoo. Radboud university medical center, Nijmegen, Netherlands.

Background/Purpose: Development of rheumatoid arthritis (RA) is associated with different genetic and environmental factors. We postulate that cow milk could be such an environmental trigger and a recent prospective study of Lu *et al.* (Arthritis Care Res 2014;66(6):802–9) suggests that frequent milk consumption is associated with reduced OA progression in women. Human breast milk contains many components to promote development of neonatal immune competence, such as cytokines, antibodies and immune cells. More recently, exosomes were identified in both bovine and human breast milk. Exosomes are small vesicles recently rediscovered as an important part of intercellular communication. Milk exosomes are known to carry immunoregulatory microRNAs and cytokines, thereby enhancing the antimicrobial defense in newborns. It is however unknown whether exosomes are present in commercial milk and whether they are bioactive.

Methods: By differential ultracentrifugation, followed by ExoQuick isolation, we isolated exosomes from commercial milk. NanoSight analysis was performed to estimate vesicles size (Ø120nm) and concentration (approx.10^{10} exosomes per ml). The expression of milk-derived mRNA and miRNA was confirmed by RT-qPCR. Exosomes were acidified at a gastrointestinal pH2 to test their stability. Cellular uptake of PKH-67 labeled exosomes was analyzed by confocal microscopy and flow cytometry. TGFβ levels were measured with a CAGA-fLuc reporter construct. Naïve T cells were cultured for 5 days with an inflammatory cocktail in the presence of milk exosomes, to induce Th17 differentiation. RORγT and IL-17 expression levels were determined by RT-qPCR.

Results: We found clear levels of messenger- and miRNAs (e.g. miR-let-7a, 124a) in cow milk exosomes. Sucrose gradient followed by electron microscopy revealed an exosome-like morphology. We showed cellular uptake of exosomes *in vitro* by murine macrophages, splenic antigen presenting cells and non-phagocytic fibroblasts. To test the stability of these vesicles, we used a luciferase reporter assay to measure *in vitro* NFκB-activation. Acidification, up to gastric acid level kept the exosomes intact, and did not alter the inhibitory effect they had on NFκB-activation. Active TGFβ was detected using CAGA-fluc reporter cells and blocked by addition of anti-TGFβ1,2,3 antibodies. More importantly, incubation of naïve T cells with milk exosomes in the presence of an inflammatory cytokine cocktail induced significant Th17 differentiation.

Conclusion: We clearly showed that commercial milk contains stable exosomes, which are resistant to acidification. These vesicles can facilitate Th17 differentiation and could therefore play an important role in autoimmune diseases, such as rheumatoid arthritis. To our knowledge, this is the first study to show that commercial milk contains immunoregulatory exosomes with active TGFβ. Our data suggest that bovine milk-derived exosomes, carrying immunoregulatory cargo, could remain intact in the gastrointestinal tract and therefore reach the circulation. This warrants further research to determine their biological effect in both healthy individuals and patients with autoimmune diseases.

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A Role for Purinergic Receptor Signalling in Basic Calcium Phosphate Crystal-Induced Inflammation. Clare C. Cunningham[1], Emma M. Corr[1], Geraldine M. McCarthy[2] and Aisling Dunne[1]. [1]Trinity College Dublin, Dublin 2, Ireland, [2]Mater Misericordiae University Hospital, Dublin 7, Ireland.

Background/Purpose: Basic calcium phosphate (BCP) crystals are uniquely associated with osteoarthritis (OA). They are found in the majority of affected joints and closely correlate with the extent of joint destruction, suggesting a pathogenic role in driving disease. They have been shown to induce pro-inflammatory cytokine production and activate synovial fibroblasts (SF) and articular chondrocytes, resulting in increased cell proliferation and matrix metalloprotease expression. These combined processes eventually lead to an imbalance in anabolic versus catabolic mediators of cartilage turnover and ultimately to extracellular matrix degradation. At the molecular level, BCP crystals were shown to activate protein kinase C, ERK1/2, MAP kinase and NF-κB in SF. Recent studies have demonstrated that both mechanical stress and activation of purinergic receptors drives the release of nucleotides such as ATP and UTP from osteocytes which then activate signalling pathways that can negatively impact bone remodelling. It has also been proposed that particulate matter such as alum and monosodium urate (MSU) crystals drive interleukin-1 production via ATP release and purinergic signalling. Furthermore, it has been reported that the P2Y6 receptor and its downstream signalling molecule phospholipase C (PLC) mediate the inflammatory responses induced by MSU crystals. In this study, we sought **1)** to determine whether BCP crystals induce the release of ATP from murine macrophages and **2)** to investigate the role of purinergic signalling in BCP-induced inflammation in order to identify novel targets for the treatment of BCP-related arthropathies, such as OA.

Methods: Murine macrophages were stimulated with BCP crystals over the course of 5 hours, and ATP release was measured using the ATPlite luminescence assay system. BCP crystals are known to drive IL-1β production in vitro. Therefore in order to investigate the role of purinergic receptors in BCP-induced cell activation, murine macrophages were primed with lipopolysaccharide, a toll-like receptor agonist prior to treatment with the broad-spectrum P2 receptor inhibitor oATP, the P2Y6-specific inhibitor MRS2578, or the PLC inhibitor U73122. Alternatively, siRNA was used to knock down the expression of P2Y6. The cells were then stimulated with BCP crystals and IL-1β production was quantified by enzyme linked immunosorbent assay (ELISA).

Results: We have found that physiological concentrations of BCP crystals (50μg/ml) induced the release of approximately 100 nM ATP by murine macrophages, a concentration sufficient to activate purinergic receptors. Inhibition of the P2Y6 receptor or PLC dose-dependently reduced IL-1β production following BCP stimulation, with full abrogation observed with the top dose of each inhibitor. Furthermore a 40% knockdown of the P2Y6 receptor led to an equal reduction in BCP-induced IL-1β production.

Conclusion: Based on these studies we propose that nucleotides released from BCP-activated cells act in an autocrine or paracrine manner via purinergic receptors to enhance BCP-induced inflammation. Released nucleotides may also act on neighbouring osteoblasts/osteoclasts to impact on bone remodelling.

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ACR/ARHP Poster Session B
Epidemiology and Public Health (ACR): Rheumatoid Arthritis and Systemic Lupus Erythematosus Outcomes
Monday, November 17, 2014, 8:30 AM–4:00 PM

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Rates of Renal Remission with Immunosuppressives in Lupus Nephritis: A Systematic Review and Network Meta-Analysis. Jasvinder Singh[1], Ahmed Kotb[2], Alomgir Hossain[2], Amy Mudano[3] and George Wells[4]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Ottawa, Ottawa, ON, [3]The University of Alabama at Birmingham, Birmingham, AL, [4]University of Ottawa Heart Institute, Ottawa, ON.

Background/Purpose: To compare renal remission rates with immunosuppressives by performing a systematic review and network meta-analyses (NMA) of RCTs of lupus nephritis.

Methods: We performed a systematic review and NMA of randomized trials of patients with lupus nephritis, who were treated with immunosuppressant alone or in combination with other immunosuppressant or biologics (such as rituximab or belimumab) compared with another immunosuppressant with/without biologic or placebo. We compared the rates of complete renal remission or partial renal remission. Complete renal remission was usually defined as return to normal serum creatinine, urine protein $\leq$0.5 g/d, and inactive urinary sediment ($\leq$5 white blood cells per high-power field and $\leq$5 red blood cells per high-power field, and a reading of lower than 2+ on dipstick and absence of red cell casts). Partial remission was variably defined in the studies, with the most common definition of improvements in urinary parameters between 25–50%. Bayesian NMA were conducted. A binomial likelihood model, which allows for the use of multi-arm trials was used. Informed priors were assigned for basic parameters and odds ratios, as well as risk ratios and risk differences, and 95% credible intervals were modeled using Markov chain Monte Carlo methods. Brooks-Gelman-Rubin plots were used to assess model convergence. Model fit was examined using the deviance information criterion (DIC) and the residual deviance. The degree of inconsistency was assessed by comparing statistics for the deviance and deviance information criterion in fitted consistency and inconsistency models. In further sensitivity analyses, fixed effects models and models using vague priors were also conducted.

Results: 39 RCTs with 2,730 patients provided data; 35 were 2-arm RCTs and 4 were 3-arm RCTs. Comparisons showed that cyclophosphamide (CYC), mycophenolate mofetil (MMF), tacrolimus (TAC), cyclosporine (CSA) and MMF+TAC were superior to prednisone alone in achieving renal remission (**Table 1**). Compared to MMF, CYC HD and PRED were less likely to lead to renal remission. Compared to AZA, TAC and MMF+TAC were superior. MMF+TAC was superior to MMF-AZA, CYC-AZA, CYC HD, CYC LD MMF+RTX and LEF in leading to renal remission.

Conclusion: Our NMA compared the ability of immunosuppressive medications and combinations to lead to remission (complete and/or partial) in RCTs of patients with lupus nephritis. Comparative effectiveness of medications is now available to assist treatment decision-making, with the caveats of trial heterogeneity and indirect comparisons.

Table 1 Comparison of various drugs for the renal remission (complete or partial) in patients with lupus nephritis showing statistically significant results

Treatment	Reference	Odds Ratio (95% Credible Interval [CrI])	Relative Risk (95% CrI)	Risk Difference % (95% CrI)
CYC	PRED	2.31 (1.30, 4.22)	1.58 (1.16, 2.23)	20.17 (6.34, 34.07)
MMF		3.12 (1.57, 6.53)	1.79 (1.28, 2.57)	27.31 (10.94, 43.19)
TAC		2.42 (1.10, 5.70)	1.61 (1.06, 2.42)	21.30 (2.18, 40.50)
CSA		5.74 (2.02, 17.24)	2.14 (1.44, 3.15)	40.06 (17.03, 57.38)
MMF+TAC		27.98 (4.96, 199.00)	2.65 (1.91, 3.88)	57.83 (36.83, 70.77)
CYC LD	CYC	0.29 (0.10, 0.78)	0.48 (0.20, 0.89)	−27.97 (−45.30, −6.08)
PRED HD		0.10 (0.02, 0.37)	0.20 (0.05, 0.57)	−43.03 (−57.32, −23.28)
CYC HD		0.51 (0.26, 0.93)	0.70 (0.43, 0.97)	−16.13 (−31.07, −1.68)
MMF+TAC		12.05 (2.41, 77.92)	1.66 (1.32, 2.22)	37.05 (18.88, 51.83)
CYC LD	MMF	0.22 (0.07, 0.56)	0.43 (0.18, 0.78)	−34.64 (−52.98, −13.94)
PRED HD		0.07 (0.02, 0.28)	0.17 (0.04, 0.51)	−49.95 (−66.00, −29.11)

MMF+TAC		9.01 (1.66, 59.84)	1.48 (1.14, 2.00)	30.01 (9.85, 47.21)
TAC	AZA	1.41(0.69,3.00)	1.17 (0.83,1.70)	8.25(−8.84,25.97)
PRED HD		0.13 (0.03, 0.53)	0.23 (0.06, 0.68)	−35.66 (−53.97, −13.53)
MMF+TAC		16.26 (2.87, 115.10)	1.92 (1.37, 3.00)	44.39 (21.99, 62.90)
MMF+TAC	TAC	11.48 (2.04, 79.76)	1.63 (1.20, 2.45)	35.83 (13.57, 55.76)
PLASMA	CSA	0.19 (0.04, 0.88)	0.50 (0.19, 0.96)	−37.43 (−66.07, −2.86)
CYC LD		0.12 (0.03, 0.45)	0.36 (0.14, 0.71)	−47.26 (−70.23, −18.60)
PRED HD		0.04 (0.01, 0.20)	0.15 (0.04, 0.45)	−62.69 (−81.20, −35.30)
CYC HD		0.21 (0.06, 0.63)	0.52 (0.29, 0.82)	−35.63 (−57.84, −11.18)
MMF+TAC	PLASMA	26.12 (3.20, 251.20)	2.51 (1.36, 6.41)	55.26 (22.09, 79.93)
MMF+TAC	CYC LD	41.94 (6.24, 350.20)	3.46 (1.76, 9.19)	65.20 (37.15, 84.18)
CYC HD	PRED HD	5.26 (1.38, 19.97)	3.55 (1.24, 12.49)	26.44 (6.39, 44.36)
LEF HD		6.86 (1.17, 43.02)	4.04 (1.12, 16.45)	32.60 (2.50, 65.59)
MMF+TAC		126.80 (14.94, 1266.00)	8.54 (2.76, 35.22)	81.06 (54.12, 93.36)
MMF+RTX		11.14 (2.15, 64.45)	5.16 (1.61, 21.04)	44.52 (14.61, 71.13)
MMF+TAC	CYC HD	23.82 (4.25, 172.00)	2.37 (1.57, 4.35)	53.32 (30.63, 72.30)
MMF+TAC	LEF HD	18.21 (2.20, 180.10)	2.03 (1.17, 5.75)	46.59 (12.63, 77.20)
MMF+TAC	CYC−AZA	26.24 (2.75, 286.40)	2.50 (1.22, 8.94)	54.99 (15.47, 83.42)
MMF+TAC	MMF−AZA	29.26 (2.21, 449.80)	2.69 (1.13, 15.55)	57.31 (10.56, 88.09)
MMF+RTX	MMF+TAC	0.09 (0.01, 0.64)	0.62 (0.32, 0.92)	−34.81 (−63.87, −7.03)

CYC HD = 500–1000 mg/m^2 qmon × 6 mons; CYC LD = 500–1000 mg/m^2 qmon × 3 mons; PRED HD = 1000mg/m^{2}qd × 3mons then qmon for 1 year; PRED = 20–60 mg qd × 1–3 mons then 10–20 mg qd
MMF+TAC= MMF plus TAC; MMF+RTX = MMF plus RTX; CYC-AZA = CYC followed by AZA; MMF-AZA = MMF followed by AZA

Disclosure: J. Singh, Savient, 2, Takeda, 2, Degeneron, 5, Allergan, 5; **A. Kotb**, None; **A. Hossain**, None; **A. Mudano**, None; **G. Wells**, Novartis, Bristol- Myers Squibb, and Abbott, 5, Bristol-Myers Squibb, 2, Abbott Immunology Pharmaceuticals, 8, he is a member of the executive of OMERACT and of the Scientific Committee for the Ontario Biologics Research Initiative, 9.

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Time Trends in Comorbidities Among Patients with Rheumatoid Arthritis Compared to the General Population. Cynthia S. Crowson, John M. Davis III, Brittny T. Major, Eric L. Matteson, Terry M. Therneau and Sherine E. Gabrriel. Mayo Clinic, Rochester, MN.

Background/Purpose: Rheumatoid arthritis (RA) related comorbidities are major determinants of morbidity and mortality. Little is known regarding the trends in these conditions. The purpose of our study was to examine whether the risk of comorbidities in RA patients has changed in recent years.

Methods: A population-based inception cohort of RA subjects who fulfilled 1987 ACR criteria for RA in 1980–2007 and a comparison cohort of subjects without RA of similar age and sex were assembled and followed until death, migration, or 7-1-2012. The presence of Charlson comorbidities (i.e., myocardial infarction, heart failure [HF], peripheral vascular disease [PVD], cerebrovascular disease, dementia, chronic obstructive pulmonary disease [COPD], ulcer, liver disease, diabetes mellitus, chronic kidney disease [CKD], and cancer) was ascertained by medical record review. Chi-square tests were used to assess trends in comorbidities present at baseline (i.e., RA incidence/index date) according to time period (1980–84 vs. 1995–2007) in each cohort. Cumulative incidence adjusted for competing risk of death was used to assess the risk of developing comorbidities during follow-up.

Results: The study included 813 RA patients and 813 non-RA subjects. Age and sex were similar in both cohorts and both time periods (mean age 56 [SD 16] years, 69% women). More patients with incident RA in the 1995–2007 time period had ≥1 Charlson comorbidity at baseline than those in the 1980–1994 time period (56% vs 44%; $p<0.001$). However, this trend was similar in the non-RA cohort (50% vs. 38%; $p<0.001$). Comorbidities that increased over time included cancer, CKD, COPD and liver disease in both cohorts, PVD and cerebrovascular disease in RA and HF in non-RA. However, among those with no comorbidities at baseline, the cumulative incidence of ≥1 Charlson comorbidity by 10 years later was lower among those with incident RA in the 1995–2007 time period than the 1980–1994 time period (22% vs. 27%; $p=0.008$), with similar findings for non-RA (17% vs. 25%; $p=0.03$). Considering both prevalent and incident comorbidities, there was no significant change over time in the cumulative incidence of ≥1 comorbidity at 10 years in the RA (76% in 1995–2007 vs. 71% in 1980–1994; $p=0.11$) or non-RA cohorts (67% in 1995–2007 vs. 64% in 1980–1994; $p=0.07$).

Conclusion: Although the prevalence of comorbidities at baseline was higher in more recent years in both the RA and non-RA cohorts, the rate of occurrence of new comorbidities has declined over time. This may indicate earlier recognition and improved management of comorbidities both in the RA and in the general population.

Disclosure: C. S. Crowson, None; **J. M. Davis III**, None; **B. T. Major**, None; **E. L. Matteson**, None; **T. M. Therneau**, None; **S. E. Gabriel**, None.

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Co-Morbidity Is Associated with Disease Severity in Early Rheumatoid Arthritis. Christopher Sparks[1], Aleena Abdullah[1], Steven Zhao[2], Cristina Estrach[2] and Nicola Goodson[1]. [1]University of Liverpool, Liverpool, United Kingdom, [2]University Hospital Aintree, Liverpool, United Kingdom.

Background/Purpose: Co-morbidity has been shown to increase length of hospital stay and mortality in hospitalised patients. However, in early rheumatoid arthritis (eRA) co-morbidity may confound treatment response and affect disease severity measures (disease activity scores (DAS28) and health assessment questionnaire (HAQ)).

The study aims were to assess:

1) Whether self reported comorbidity correlates with baseline DAS28 & HAQ in an eRA cohort?

2) Does co-morbidity burden predict DAS28 remission and HAQ after 1yr of treatment?

Methods: At time of eRA diagnosis, patients completed a modified validated self-reported 14 item comorbidity questionnaire (1). Each co-morbidity item scores 1 point (maximum score 14). Use of treatment or associated impairment contributes to a weighted co-morbidity score (Maximum score 36). The number of comorbidity items were divided into 3 categories: low≤1, medium=2, & and high ≥3. Correlation between co-morbidity number and weighted score and DAS28 and modified mHAQ were assessed at baseline using Spearman's rank correlation.

Logistic regression (adjusting for age, gender, smoking, obesity, & seropositive status) were used to explore whether baseline co-morbidity:1) number & 2) weighted score, predicted 1yr DAS28 remission & high HAQ (defined as >1).

Results: 147 eRA patients, with symptom duration less than 12 months, mean age 58.1yrs & 67% female, had complete baseline and 1yr data. All were treated with synthetic DMARDS following a treat to target regime.

At baseline, comorbid disease was reported by 107 (72.8%) with median number of 1 [IQR 0, 3] comorbid conditions in addition to RA. The median weighted co-morbidity score was 2 [IQR 0, 3]. Patients reporting ≥2 co-morbidities had higher prevalence of high HAQ>1 and DAS28> 5.1. Modest correlation was observed between the number of co-morbidities and 1)DAS28- rho 0.23, ($p<0.05$) and 2)HAQ- rho 0.31($p<0.01$).

After 1 year, 77 (52.4%) achieved DAS28 1. Reporting 2 or more co-morbidities was associated with reduced rates of DAS28 remission and high HAQ score at 1 year (table 1). Increasing numbers of co-morbidity and use of the co-morbidity weighted scores did not increase the strength of association.

Table1:- Predictors of disease severity after 1 year

Comorbidity		n	DAS28<2.6 ORadj (95%CI)	1 year HAQ >1 ORadj (95%CI)
Number	0–1 (ref)	90	1.0	1.0
	2	23	0.35 (0.13, 0.94)	2.16 (0.63, 7.31)
	>=3	34	0.46 (0.19, 1.56)	5.16 (1.64, 16.24)
Weighted	0–1 (ref)	58	1.0	1.0
	2–3	44	1.31 (0.57, 3.03)	2.48 (0.79, 7.77)
	>=4	45	0.30 (0.12, 0.74)	4.11 (1.26, 13.3)

Conclusion: Self reported comorbid disease burden predicts disease activity and level of disability in an eRA cohort after 1 year of treatment. Weighting co-morbidity for severity and function do not increase the strength of association with 1 year outcomes in early RA. Adjusting for the confounding effects of co-morbidity is important when assessing response to treatment. Use of self reported co-morbidity questionnaires appear to be an acceptable method of quantifying co-morbidity in routine rheumatology outpatient departments.

1) Sangha O, et al. The Self-Administered comorbidity questionnaire:A New Method to Assess Comorbidity for Clinical and Health Services Research. Arthritis Rheum 2003;49:156–63.

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Rheumatoid Factor, Not ACPA, Is Associated with Disease Activity in Rheumatoid Arthritis. Daniel Aletaha[1], Farideh Alasti[1] and Josef S. Smolen[2]. [1]Medical University of Vienna, Vienna, Austria, [2]PsAID taskforce, EULAR, Zurich, Switzerland.

Background/Purpose: To investigate the associations of rheumatoid factor (RF) and autoantibodies against citrullinated proteins (ACPA) with rheumatoid arthritis (RA) disease activity.

Methods: We analyzed the association of RF and ACPA on individual and composite measures of disease activity at baseline in four recent randomized controlled clinical trials (RCT) using stratified and matched analyses. Data included one RCT in early RA patients on rituximab, RTX; three on golimumab, GOL, in early and established populations.

Results: A total of 2118 patients were analyzed in the four studies. In both, the RTX and the pooled GOL cohorts, RF+ patients, regardless of ACPA status, had the highest levels of baseline disease activity, while ACPA+ patients had similar or lower disease activity than ACPA- patients, regardless of RF status (See Figure, using Simplified Disease Activity Index, SDAI).

When patients from the RTX trial were matched for the levels of ACPA, as well as for age, gender, and duration of RA (n=29), SDAI levels were 49.3±14.5 in the presence of high positive RF, and 42.3±12.7 in patients who were RF negative; this was the opposite for ACPA in patients matched for RF levels and the same covariates: high positive ACPA: 45.8±14.8; ACPA negative: 53.1±16.5 (p=0.025). These trends were supported in the respective analyses in the pooled GOL trials (RF high vs. neg.: SDAI of 36.8 vs. 33.1; ACPA high vs. neg.: 37.0 vs. 39.5), although the difference did not reach statistical significance.

Conclusion: The data suggest that the presence of RF rather than ACPA is related to higher disease activity. When matched for RF levels, ACPA had little influence on disease activity, if at all, with the tendency towards lower disease activity for ACPA+ patients.

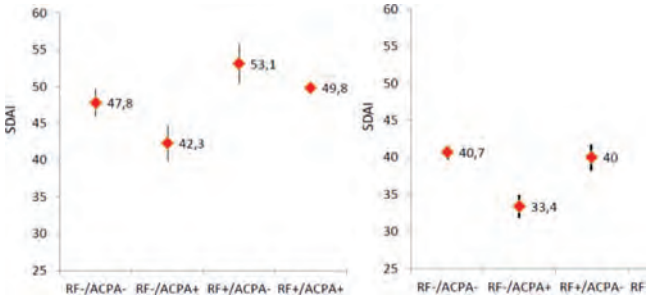

Figure. Simplified Disease Activity Index at baseline of the rituximab trial (left panel) or the pooled golimumab trials (right panel) by groups of RF/ACPA status.

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Identifying Flare in Rheumatoid Arthritis (RA): Performance of the Flare-Assessment in RA (FLARE) Questionnaire in a US Population. Elena Myasoedova[1], Cynthia S. Crowson[1], Bruno Fautrel[2], Francis Guillemin[3], Eric L. Matteson[1] and Sherine E. Gabriel[1]. [1]Mayo Clinic, Rochester, MN, [2]UPMC GRC08, Paris 06 University, Pitié Salpétrière Hospital, Paris, France, [3]Nancy University Hospital, Nancy, France.

Background/Purpose: Flare is an important aspect of rheumatoid arthritis (RA) patients' disease experience with a crucial impact on quality of life and well-being. The flare-assessment in RA (FLARE) questionnaire was developed for the detection of flares based on the joint symptoms and systemic impact of RA disease over the most recent 3 months. We aimed to assess the performance of FLARE questionnaire in relation to clinical and laboratory measures of RA disease activity/severity in RA patients.

Methods: Patients with RA (age≥18 yrs; 1987 ACR criteria) participating in an ongoing population-based cohort study completed FLARE, Bristol Rheumatoid Arthritis Fatigue (BRAF) questionnaires and Health Assessment Questionnaire (HAQ) with visual analogue scale for pain (VAS pain) on 100mm scale during a study visit (2012–2014), and submitted a blood sample for C-reactive protein (CRP) and Interleukin-6 (IL6) assessment. Retrospective medical records review was performed to collect prior history of flares (as per OMERACT 9 definition), as well as physician clinical assessment (PCA) and patient global assessment (PGA) of RA disease activity on 100mm scale for the most recent clinical visit prior to the study visit. The previously validated RA medical Records-Based Index of Severity (RARBIS) and Claims-based Index of RA Severity (CIRAS) were used to estimate RA severity based on the recent year of data on RA disease characteristics and medications. Pearson's correlation was used to examine relationships between the variables.

Results: The study included 160 RA patients (mean age 62.6 years; 74% female; mean RA duration 14.7 yrs). The mean standard deviation (SD) of the overall FLARE score was 2.47 (2.54) on 0–10 scale; 1.82 (2.43) for systemic subscale; 3.26 (3.08) for joint subscale. Mean (SD) CRP was 4.15 (5.8) mg/L; IL6 3.48 (5.52) pg/ml; HAQ 0.64 (0.62); VAS pain 28.6 (24.6). FLARE score overall and both subscales were statistically significantly correlated with BRAF, HAQ, VAS pain, IL6 and PGA, but not PCA (Table). CRP was significantly correlated with overall FLARE score and systemic, but not joint subscale. There was a statistically significant correlation of FLARE overall and its joint subscale with RARBIS, but not CIRAS. No significant correlation of FLARE was found with any history of prior flare. In a subset of patients (n=28) who had a clinical visit within 3 months of the study visit, being in a flare at that visit correlated with FLARE overall (r=0.41, p=0.03) and joint subscale (p=0.51, p=0.006), but not systemic subscale (r=0.26, p=0.18).

Conclusion: The FLARE score is highly correlated with other measures of RA patients' self-report, i.e. BRAF, HAQ, VAS pain and PGA; with systemic inflammatory markers, RARBIS and flare at the most recent visit. Our findings suggest that FLARE questionnaire may be a reliable tool for RA flare detection reflecting clinical and laboratory aspects of RA disease activity.

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Factors Associated with Impairment on Quality of Life in Early or Established RA Patients. Dam Kim[1], Yoon-Kyoung Sung[1], Soo-Kyung Cho[1], Soyoung Won[1], Minkyung Han[1], So-Young Bang[2], Hoon-Suk Cha[3], Chan-Bum Choi[1], Jung-Yoon Choe[4], Won Tae Chung[5], Seung-Jae Hong[6], Jae-Bum Jun[7], Young Ok Jung[8], Jinseok Kim[9], Seong-Kyu Kim[4], Tae-Hwan Kim[7], Tae-Jong Kim[10], Eunmi Koh[3], Choong Ki Lee[11], Hye-Soon Lee[7], Joo-Hyun Lee[12], Jaejoon Lee[13], Jisoo Lee[14], Sang-Heon Lee[15], Shin-Seok Lee[16], Sung Won Lee[17], Seung-Cheol Shim[18], Dae-Hyun Yoo[7], Wan-Hee Yoo[19], Bo Young Yoon[20] and Sang-Cheol Bae[1]. [1]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [2]Hanyang University Guri Hospital, Guri, South Korea, [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [4]Catholic University of Daegu School of Medicine, Daegu, South Korea, [5]Dong-A University Hospital, Busan, South Korea, [6]Kyung Hee University, Seoul, South Korea, [7]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [8]Hallym University Kangnam Sacred Heart Hospital, Seoul, South Korea, [9]Jeju National University Hospital, Jeju, South Korea, [10]Chonnam Nat'l University Medical School&Hospital, Gwangju, South Korea, [11]Yeungnam University, Daegu, South Korea, [12]Ilsan Paik Hospital, Inje University, Goyang, South Korea, [13]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [14]Ewha Womans University School of Medicine, Seoul, South Korea, [15]Konkuk University Hospital, Seoul, South Korea, [16]Chonnam National University Med School, Gwangju, South Korea, [17]Dong-A university,Busan, South Korea, Pusan, South Korea, [18]Chungnam National University Hospital, Daejeon, South Korea, [19]Chonbuk National University School of Medicine, Jeonju, South Korea, [20]Inje University Ilsan Paik Hospital, Goyang, South Korea.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disabling disease with significant impact on the quality of life (QOL) of patients. Since clinical features are different in RA patients according to the disease course, various factors might be influence on the low QOL depending on the phase of the disease. We aimed to explore the associating factors for impairment on quality of life in either early RA or established RA patients.

Methods: A total of 5,361 RA patients in the KORean Observational study Network for Arthritis (KORONA) were included in this study. The EuroQol-5 dimension (EQ-5D) is a widely used generic QOL instrument, and it allows for negative utility values, which correspond to health states worse than death. We defined the worst QOL as EQ-5D score < 0, a state worse than death. We classified RA patients according to their disease duration: early RA patients (n=714) as patients whose disease duration was less than 1 year and patients with longer disease duration formed the established RA patients (n=4,647). The distribution of EQ-5D in both groups of early and established RA patients were compared, and the possible determinants for negative EQ-5D score in each group were explored using the logistic regression analyses.

Results: The average EQ-5D score was not different between early and established RA patients (0.69±0.26 vs. 0.68±0.27, p=0.19), and the proportions of the negative EQ-5D score were comparable in both groups.

(4.9% vs. 4.6%, p=0.76). The most important determinant for worst QOL in early RA patients was high functional disability (OR 17.3, CI 6.0–50.2). In addition, sleep disturbance (OR 1.02, CI 1.01–1.04) and fatigue (OR 1.04, CI 1.01–1.07) were another factors for worst QOL in early RA patients. In established RA patients, though the odds ratio was lower than early RA patients, high functional disability (OR 10.0, CI 7.1–14.3), sleep disturbance (OR 1.01, CI 1.00–1.01) and fatigue (OR 1.03, CI 1.02–1.04) were still associated with impairment on QOL. In addition, higher disease activity (OR 1.28, CI 1.08–1.51) increased risk for worst QOL but regular exercise (OR 0.66, CI 0.43–0.99) showed protective effect in established RA patients.

Conclusion: The functional disability, sleep disturbance and high fatigue level were significantly associated with the impairment on QOL in both early and established RA patients, while high disease activity had significant effects on the worst QOL only in patients with established RA. Regular exercise might have a protective effect against the impairment on QOL in established RA patients.

Table 1. Determinants of health state worse than death (EQ-5D<0) in early and established RA patients.

°°	Early RA (n=714)	Established RA (n=4,647)
Age	1.00 (0.95–1.06)	1.01 (0.99–1.03)
Female	0.70 (0.15–3.16)	0.63 (0.30–1.33)
Education		
Middle school or less	1.08 (0.31–3.76)	1.25 (0.77–2.05)
High school or more	1.0 (ref)	1.0 (ref)
Income ($X10^3$ won)		
<2,000	2.83 (0.27–30.08)	1.46 (0.57–3.73)
2,000°Â, <5,000	2.52 (0.23–27.63)	1.58 (0.61–4.07)
°Ã5,000	1.0 (ref)	1.0 (ref)
Regular exercise, n(%)	1.41 (0.44–4.47)	0.66 (0.43–0.99)
Operation history due to RA, n(%)	0.63 (0.06–6.24)	0.81 (0.52–1.26)
Fracture history, n(%)	1.08 (0.32–3.65)	0.88 (0.57–1.38)
Sleep VAS(cm, mean±SD)	1.02 (1.01–1.04)	1.01 (1.00–1.01)
Fatigue VAS(cm, mean±SD)	1.04 (1.01–1.07)	1.03 (1.02–1.04)
DAS28-ESR	0.74 (0.46–1.20)	1.28 (1.08–1.51)
HAQ-DI	17.29 (5.96–50.15)	10.02 (7.05–14.25)
Comorbidities	0.64 (0.21–1.93)	1.21 (0.79–1.87)

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Work-Related Behavior and Experiences in Patients with Rheumatoid Arthritis.

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Background/Purpose: Work-related behavior and experiences are discussed to be either risk factors or resources for individual‘s health. Diseases and related changing working conditions and/or experiences might have additional effects. The objective of the study was to describe work-related attitudes and to examine their relationship to clinical data and health in patients (pts) with rheumatoid arthritis (RA).

Methods: Self-reported (outcome) questionnaires were applied to RA pts and controls (c) not suffering from rheumatic diseases, both groups were capable for work. The ’AVEM’ questionnaire assesses eleven health relevant dimensions via 66 items and thus determines the personal attitude towards work, see Table 1. The dimensions (d) are attributable to three areas: work engagement (d 1–5), resistance to stress (again d 5; 6–8) and emotions accompanying occupation (d 9–11). Pts self-reported clinical data. Ethics committee approval had been obtained.

Results: 267 pts (85.0% female (f)) and 177 c (90.3% f) contributed data. Pts’ mean age was 47.7±10.0 (c 42.8±9.8) years, mean disease duration 9.0±8.0 years, and the mean HAQ 1.1±0.5 (c 0.4±0.1). 85.5% of the pts self-reported at least one comorbidity (range 0–8, c 45.2%, range 0–4). In pts 81.7% received at least one immunosuppressive medication (range 0–6), 43.8% steroids ≤7.5mg, 9.0% steroids >7.5mg and 61.4% NSAIDS.

AVEM scales are depicted in Table 1, RA pts scored significantly different to c in six dimensions. Pts scored similar to c in work engagement scales and resignation tendencies, but showed less capability for emotional distancing, lower balance and mental stability, lower satisfaction with work & life and lower experiences of social support. OR indicate whether pts of the T- group (see table 1) have an increased risk for lower self-rated health status compared to T+.

Table 1 AVEM dimensions in c and RA pts, *mean±standarddeviation (SD), T+ and T- Percentage of pts deviating > 1 SD from mean of c, + Wilcoxon test, # Fisher’s exact test

AVEM dimensions	c*	RA*	p-value+	T+	T−	OR	p-value#
1. Subjective significance of work	15.2 ± 5.0	16.0 ± 5.0	p>0.05	17.4	15.1	0.86	p>0.05
2. Professional ambition	16.5 ± 5.0	16.2 ± 4.9	p>0.05	12.8	16.7	2.42	p>0.05
3. Tendency to exert	17.9 ± 5.1	18.7 ± 5.2	p>0.05	17.7	14.2	0.48	p>0.05
4. Striving for perfection	21.8 ± 4.5	21.6 ± 4.5	p>0.05	12.3	15.0	0.42	p>0.05
5. Emotional distancing	20.6 ± 5.0	19.0 ± 5.1	0.0019	9.3	26.7	3.08	0.0295
6. Resignation tendencies	15.4 ± 4.2	16.0 ± 5.2	p>0.05	24.3	20.0	0.52	p>0.05
7. Offensive coping with problems	22.0 ± 3.3	20.7 ± 3.6	0.0003	9.6	30.4	2.23	p>0.05
8. Balance and mental stability	20.3 ± 4.3	19.2 ± 4.6	0.0194	12.4	28.3	3.73	0.0044
9. Satisfaction with work	22.4 ± 4.1	20.9 ± 4.5	0.0008	8.6	31.2	2.34	p>0.05
10. Satisfaction with life	22.9 ± 3.9	20.4 ± 4.4	0.0000	7.7	30.4	9.21	0.0000
11. Experience of social support	23.5 ± 4.3	22.5 ± 4.5	0.0266	11.2	24.4	2.74	0.0367

Conclusion: This is the first study applying AVEM to RA pts. Results detected domains that are potentially modifiable and should be considered in clinical management. Resistance to stress and emotional issues should be predominantly targeted. Further study analyzes will address correlations to other study parameters and confounding factors. Thus, appropriate strategies that promote healthy personal attitudes and equip pts with adequate supporting coping skills that prepare them for the challenges at their daily work might and should be developed.

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Levels of Fatigue Are Dependent on Country of Residence in Rheumatoid Arthritis: An Analysis Among 3920 Patients from 17 Countries.

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Background/Purpose: For patients with rheumatoid arthritis (RA), fatigue is an important aspect of disease which impacts quality of life. However the complex relationship between fatigue and either disease-related or external factors remains unclear. Country of residence as a surrogate for a variety of cultural, economic and linguistic aspects might play a role, but this has never been formally explored. The aim of the study was to investigate how country of residence influences level of fatigue in addition to socio-demographic and objective disease- characteristics.

Methods: Data from a multi-national study were used (COMORA). Fatigue was measured using 0–10 VAS scale. A multivariable linear regression model (outcome fatigue) was computed using manual forward selection. Contribution of socio-demographic factors (age, gender, education, marital status, work status), comorbidities (Wolfe-Michaud index), smoking status, clinical disease characteristics (tender and swollen joints (TJC, SJC), erosions in hands or feet (yes/no), erythrocyte sedimentation rate) and medication (all type of DMARDs, steroids and NSAIDs) was tested. Country of residence was added using the country with the highest level of fatigue (Netherlands) as reference. In a second step, sensitivity analyses were

developed replacing country of residence by country specific variables including gross domestic product (GPD), human development index (HDI), a climate indicator (latitude) and income inequality (gini index).

Results: 3920 patients from 17 countries (range: 30 to 411, mean age 56 years (SD 13), 82% female) were included. Mean fatigue across countries was 4.13 (SD 2.8). 32.8% of all patients had fatigue scores >5. In multi-variable regression, female gender (βf=1=0.70, CI 0.49/0.91) and a higher comorbidity score (β=0.32, CI 0.24/0.39) were associated with higher fatigue. TJC and SJC had limited influence on fatigue with higher contribution of TJC (βTJC=0.14, CI 0.12/0.16 and βSJC=0.05, CI 0.02/0.08). When adding individual countries, the contribution was significant and increased the overall model fit (Δ R2=0.08). Country differences in fatigue varied between -3.9 for Venezuela vs Netherlands (NL) and -0.6 (Italy vs NL) after adjustment for individual factors. When country was replaced by GDP, HDI, latitude or gini index, only GPD and HDI index contributed significantly. The overall model improvement was lower compared to country (R2 GDP=0.14, R2 HDI=0.18, R2 country=0.20). Interactions were not significant.

Conclusion: While individual demographics and objective clinical measures of disease have only a small influence on the experience of fatigue, the country of residence adds substantially. Economic and development status of the country only explain small parts of the variation among countries. More research is needed to identify these unknown aspects of RA related fatigue, e.g. cultural (attitudes, believes), linguistic or work related factors might play a role.

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Patients with RA from Wealthier Countries Perform Better on Clinical Disease Activity Measures, but Tend to Show Worse Person Reported Outcomes. Polina Putrik[1], Sofia Ramiro[2], Andras Keszei[3], Ihsane Hmamouchi[4], Maxime Dougados[5], Monika Hifinger[6], Laure Gossec[7] and Annelies Boonen[1]. [1]Maastricht University Medical Center, Maastricht, Netherlands, [2]Amsterdam Rheumatology Center, University of Amsterdam & Hospital Garcia de Orta, Almada, Portugal, Amsterdam, Netherlands, [3]Uniklinik RWTH Aachen University, Aachen, Germany, [4]Mohamed V Souissi University, Rabat, Morocco, [5]Paris Descartes University, Paris, France, [6]University Hospital Maastricht, Maastricht, Netherlands, [7]Pierre et Marie Curie University, Paris, France.

Background/Purpose: Inequalities in health between low and high income countries are often reported, but it is not known whether clinical disease activity measures ("objective") and person reported outcomes ("subjective") follow the same patterns in patients with rheumatoid arthritis (RA). The objective of this study was to investigate the patterns in RA health outcomes ("objective" vs "subjective" outcomes) across countries with different level of socio-economic development.

Methods: Data from a cross-sectional multinational (17 countries) study COMORA was used. Contribution of gross domestic product (GDP) to clinical disease activity measures (DAS28, total joint count (TJC), swollen joint count (SJC), and erythrocyte sedimentation rate (ESR)) and person reported outcomes (Patient global assessment (PatGA) (0–10), fatigue (0–10), Physician global assessment (PhysGA) (0–10) and function assessed with health assessment questionnaire (HAQ) (0–3)) was explored. All models were adjusted for potentially relevant confounders, including age, gender, education and comorbidities (Wolfe-Michaud index). Models were computed with and without adjustment for current RA medication (steroids, NSAIDs and DMARDs). Additionally, models with person reported outcomes were adjusted for the presence of erosive disease, TJC, SJC, and ESR. GDP was dichotomized in low and high GDP countries (with a cut-off of 20,000 international dollars per capita (adjusted to purchasing power parity), which by data inspection was the one that discriminated best both groups).

Results: A total of 3920 RA patients from 17 countries (range 30–411) were included in COMORA (mean age 56 y.o. (SD13), 82% females). DAS28 varied between 5.3 (Egypt) and 2.6 (Netherlands), HAQ ranged between 0.7 (Taiwan) and 1.5 (Netherlands). Venezuela had the lowest average score on fatigue (1.7) and Netherlands scored on average highest on fatigue (5.0). In models adjusted for medication, low GDP countries had on average 0.94 higher DAS28, 2.84 and 1.85 higher scores on TJC and SJC, respectively, and 11.50 higher ESR compared to high GDP countries. At the same time, patients from low GDP societies had a 0.41 and 0.21 lower score on patient and physician global assessment, respectively and 0.96 lower score on fatigue compared to high GDP countries. HAQ was 0.14 higher in countries with low GDP (Table 1).

Table 1. Association between clinical disease activity measures and person reported outcomes with GDP

	Clinical disease activity measures				Person reported outcomes			
	DAS28	TJC	SJC	ESR	PatGA	Fatigue	PhyGA	HAQ
GDP (low vs. high) (Adjusted model,including medication)	0.94*	2.84*	1.85*	11.5*	−0.41*	−0.96*	−0.21*	0.14*
GDP (low vs. high) (Adjusted model, excluding medication)	0.97*	2.92*	1.75*	11.8*	−0.44*	−1.01*	−0.25*	0.11*

*p<0.05

Conclusion: Patients from countries with lower socio-economic welfare score worse on clinical measures of disease activity (DAS28 and its components), however, tend to score better on person reported outcomes (patient global assessment and fatigue) for the same level of objective disease activity. Cultural factors that may play a role in reporting of subjective outcomes should be further explored.

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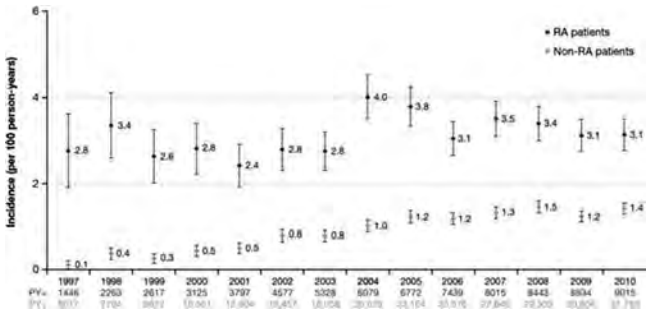
Musculoskeletal Surgeries and Procedures in Patients with RA: Results from a UK Retrospective Study. H Cawston[1], F Bourhis[1], T Le[2] and E Alemao[3]. [1]OptumInsight, Nanterre, France, [2]Bristol-Myers Squibb, Hopewell, NJ, [3]Bristol-Myers Squibb, Princeton, NJ.

Background/Purpose: Musculoskeletal surgeries and procedures substantially improve the quality of life of patients with RA, but represent an important burden in terms of medical costs. The aim of this study was to assess whether recent advances in RA treatment had an impact on long-term surgery rates in the UK.

Methods: A retrospective cohort study was conducted from 1997 to 2010, using Clinical Practice Research Database General Practice Online Data (GOLD) and Hospital Episode Statistics (HES) data. RA population was defined as all patients presenting with one or more RA read code after 01/01/1988 (index code), with no RA or juvenile RA codes before the RA index code. Patients were required to have a minimum of 12 months of data before the first RA code and to have no psoriatic arthritis-related codes over the entire period. Date of onset of disease was defined as date of first RA-related code. RA patients were matched 4:1 to non-RA patients based on their year of entry in the GOLD database, cardiovascular (CV) risk category (NCEP classification), CV treatment status, and a risk score measuring the probability of having RA. The index code of non-RA patients was defined as the date of observation closest to the index code of their matched RA patient. Surgeries such as total joint arthroplasties (TJA), non-TJA, TJA-associated procedures, as well as other orthopedic procedures were identified in HES and GOLD databases using operating procedure codes and read codes. Incidence rates (IRs) were estimated over the study period and by time since diagnosis in both cohorts. Time-to-first-surgery curves in all RA patients as well as stratified by terciles of CRP measured at diagnosis were based on Kaplan–Meier (KM) estimates. **Results:** Overall, 14,181 patients with RA were identified and matched to 49,935 non-RA patients. IRs in RA patients, relatively constant up to 2003, sharply increased in 2004 (IR=4.0/100 person-years; 95% CI: 3.5, 4.3) before a steady decrease was observed up to 2006 (3.1 [2.8, 3.5]). This trend was driven by TJAs, for which an IR of 2.7 (2.3, 3.0) was observed in 2010. Majority of TJAs involved the knee (43.5%) and hip (40.2%). However, IRs of all surgeries increased from 0.1 (0.0, 0.2) to 1.4 (1.3, 1.6) from 1997 to 2010 in non-RA patients. Based on the KM analysis, the probabilities of having a surgery at 3, 5 and 10 years were 5.5%, 8.6% and 17.3%, respectively. Patients in the higher tercile of CRP at diagnosis were at higher risk of first surgery than the two lower terciles (log-rank test between three groups: p=0.0007).

Conclusion: Decrease in the IRs of musculoskeletal surgeries in 2005/2006 could be attributed to greater availability of biologic therapies. However, these rates have not decreased in recent years, suggesting there is an unmet need for more effective therapies. CRP levels at diagnosis were associated with higher risk of surgeries, suggesting that therapies reducing CRP may be effective to further lower surgical rates.



Disclosure: H. Cawston, OptumInsight, 3, Bristol-Myers Squibb, 5; **F. Bourhis**, None; **T. Le**, BMS, 3; **E. Alemao**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3.

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How Does Rheumatoid Arthritis Disease Activity Affect Development of Upper Cervical Lesions? a Retrospective Study of Cervical Spine X-Rays Combined with a Cohort Study in Rheumatoid Arthritis Patients.

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Background/Purpose: It is believed that 40% to 80% of patients with rheumatoid arthritis (RA) have cervical spine lesions. In particular, atlanto-axial subluxation (AAS) and vertical subluxation (VS) are clinically important. However, little is known about how disease activity and other factors are involved in their development. The aim of this study is to identify risk factors for upper cervical lesions in RA patients.

Methods: IORRA is a prospective observational cohort study of Japanese patients with RA established in 2000 at the Institute of Rheumatology, Tokyo Women's Medical University. Approximately 5,000 patients with RA are involved in each phase of the biannual survey. In our department, when RA patients schedule surgery, dynamic X-rays of the cervical spine are conventionally taken to assess instabilities in case tracheal intubation for general anesthesia is required. In this study, we evaluated these X-rays and investigated their relevance to the integrated data in the IORRA cohort study. Inclusion criteria were: (1) scheduled surgery in our department from 1 April 2010 to 31 March 2013, and (2) registration into the IORRA cohort study within 2 years from onset of RA. Fifty-seven patients were selected, with the following characteristics: women, 49 (85.9%); median onset age, 56 years; disease duration, 8.5 years; and DAS28, 4.3. Cervical X-rays were measured two times by one board-certified orthopedic surgeon and mean values were generally used. To assess AAS, the atlantodental interval (ADI) was measured, and for VS, the Redlund-Johnell method (R-J) was adopted. AAS was defined as ADI≧3mm; VS was defined as 34mm≦R-J in males, 29mm≦R-J in females. For statistical analysis, regression analysis was used for ADI and R-J, and logistic regression analysis was used for AAS and VS.

Results: Median ADI was 2.8mm, and R-J was 34mm. Twenty-seven patients had AAS (48.2%) and twelve had VS (21.4%). No significant correlation between ADI and R-J was observed ($\rho = -0.025$, $p = 0.8$). By univariate regression analysis, gender ($p = 0.004$), height ($p < 0.0001$), body weight ($p = 0.03$), total methotrexate dose ($p = 0.002$), and DAS28 maximum value ($p = 0.001$) and integrated value ($p = 0.003$) during the IORRA enrollment period were significantly relevant to R-J. Multivariate regression analysis revealed height ($\beta = 0.59$, 95%CI: 0.011–0.25, $p < 0.0001$) and maximum DAS28 ($\beta = -0.27$, 95%CI: -2.4- to -0.33, $p = 0.011$) to be significantly associated with R-J. No factors were significantly associated with ADI. By univariate logistic regression analysis, maximum DAS28 (OR=2.4, 95%CI: 1.3–5.2, $p = 0.01$) was significantly associated with VS. Total duration of biological drug use (OR=1.2, 95%CI: 1.0–1.6, $p = 0.04$) was also significantly associated with AAS, but this involved development and was not thought to be causal.

Conclusion: Higher RA disease activity appears to be a significant risk factor for VS development and severity, regardless of integrated value of disease activities. We suggest that RA disease activity should be tightly controlled to prevent development of upper cervical lesions, particularly VS.

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Impact of Obesity on 1 Year Outcomes: Results from the Meteor Foundation International Rheumatoid Arthritis Cohort.

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Background/Purpose: Increased adiposity is associated with increased production of pro-inflammatory adipokines and raised inflammatory markers. As a result, standard disease activity scores (DAS) may be greater in obese rheumatoid arthritis (RA) patients, with important implications for their treatment in modern target based regimens. There is limited longitudinal evidence assessing the impact of obesity on DAS. We sought to investigate the influence of obesity on 1 year outcomes in a large international RA cohort.

Methods: Patients with a clinical diagnosis of RA with complete 6 and 12 month follow up from the METEOR Foundation International RA database were identified. The cohort was divided into early RA (eRA, disease duration <12 months) and established RA subgroups (disease duration ≥12 months). Patient demographics, DAS28, Health Assessment Questionnaire (HAQ) score and BMI were collected from the first recorded visit on the database. The cohorts were stratified into 4 categories by BMI: 1) Underweight <18.5, 2) Normal 18.5–24.9, 3) Overweight 25–29.9 and 4) Obese ≥30. Outcomes of interest were: good EULAR response (DAS28), low disease activity (DAS28 <3.2) and DAS28 remission (DAS28 <2.6) at follow up. Associations between BMI category and outcome measures at follow up (6 and 12 months) were explored using multivariate logistic regression analysis for both the eRA and established RA cohorts, adjusting for age, gender and smoking status.

Results: 1,525 patients with complete data were identified. Mean age was 53.2 (SD 13.2) and 78.8% were female. The eRA and established RA subgroups contained 641 and 884 patients respectively, with a similar distribution of BMI categories seen in both groups (mean BMI 26.8 (SD 5.6) and 26.8 (SD 5.07) respectively).

At baseline median DAS28 scores for each BMI category were similar to those described for this cohort previously.[1]Logistic regression analysis found no associations between overweight or obese BMI categories and clinical outcomes at 6 or 12 month follow up in the eRA subgroup. However, underweight patients had a lower probability of achieving low disease activity at 6 and 12 months (OR 0.24 (95%CI 0.07, 0.85) and OR 0.14 (95%CI 0.03, 0.62) respectively).

Analysis of the established RA subgroup identified obese patients to be significantly less likely to exhibit low disease activity at 6 and 12 month follow up, or disease remission at 12 months follow up (Table 1).

Table 1: Multivariate adjusted offs ratio (95% Confidence Intervals) for association between disease activity and BMI category for the established RA cohort.

Variable	Underweight (n=12)	Normal (r) (n=359)	Overweight (n=313)	Obese (n=200)
Good Response 6 months	0.42 (0.05, 3.37)	1.0	0.90 (0.60, 1.35)	0.59 (0.36, 0.97)
DAS28 <3.2 at 6 months	1.23 (0.38, 3.99)	1.0	0.83 (0.60, 1.13)	0.55 (0.39, 0.80)
DAS28 <2.6 at 6 months	0.62 (0.16, 2.38)	1.0	0.84 (0.60, 1.16)	0.48 (0.32, 0.72)
Good Response 12 months	0.39 (0.05, 3.15)	1.0	0.80 (0.54, 1.20)	0.97 (0.63, 1.52)
DAS28 <3.2 at 12 months	1.89 (0.55, 6.48)	1.0	1.12 (0.82, 1.53)	0.77 (0.54, 1.10)
DAS28 <2.6 at 12 months	0.97 (0.28, 3.38)	1.0	0.86 (0.62, 1.20)	0.62 (0.42, 0.92)

Conclusion: Obese patients with RA appear to respond to treatment, and achieve treatment goals within the first year following diagnosis. Outside of this period, obese patients are less likely to reach low disease activity or disease remission. These findings may have important implications for treatment objectives in modern target based regimens.

References

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Management of Hyperlipidemia Among Patients with Rheumatoid Arthritis in the Primary Care Setting. Kashif Jafri[1], Lynne Taylor[1], Nehal N. Mehta[1], Melissa Nezamzadeh[1], Joshua Baker[2] and Alexis Ogdie[1]. [1]University of Pennsylvania, Philadelphia, PA, [2]University of Pennsylvania and Philadelphia VAMC, Philadelphia, PA.

Background/Purpose: Rheumatoid arthritis has been associated with an increased risk of cardiovascular morbidity and mortality. It is unclear, however, whether this knowledge has translated into improved screening and management of traditional cardiovascular risk factors such as hyperlipidemia in the primary care setting. The objectives of this study included 1) To determine the prevalence of screening for hyperlipidemia in patients with rheumatoid arthritis (RA) that are followed by primary care physicians; 2) To examine whether current Adult Treatment Panel (ATP) III guidelines for the initiation of lipid-lowering therapy are being followed in patients with RA, and 3) to assess whether proposed modifications to cardiovascular risk calculations change the percentage of RA patients with an indication for therapy.

Methods: A retrospective cohort study was performed among patients with RA in an academic medical center medical record database in the United States between 2005–2010. A validation study prior to initiation of the study demonstrated a positive predictive value of 96.7% for accurate capture of patients with RA using ICD-9 codes. Descriptive statistics were used to report the prevalence of screening and use of lipid-lowering therapy (LLT) among those with an indication for LLT. Factors associated with not receiving lipid screening were examined using logistic regression models. Finally, indication for and receipt of therapy were assessed following application of the European Union League Against Rheumatism (EULAR) recommended multiplier to the Framingham risk score.

Results: Among 1418 patients with RA followed by primary care physicians, lipid screening was ordered for 780 (55%) within the 3-year follow-up period. Patients under the age of 50 were significantly less likely to be screened whereas patients with diabetes, hypertension, chronic kidney disease, and obesity were more likely to be screened (**Table**). Of those with lipid results (N=419), 50 (12%) patients had an indication for LLT based on the ATP III guidelines. Among the 50 patients with an indication for LLT, 38 (76%) received therapy. Applying the EULAR multiplier only changed the indication for LLT in two patients.

Conclusion: Although patients with RA have an increased risk for cardiovascular disease, they are often not receiving optimal management of traditional cardiovascular risk factors, such as screening for hyperlipidemia. Nevertheless, once hyperlipidemia has been identified, most patients received the appropriate lipid-lowering therapy. The EULAR multiplier does not seem to have a measurable impact on clinical care, and new methods for assessing cardiovascular risk among patients with RA are needed.

Table. Logistic regression models for non-receipt of screening*

		Univariable OR (95%CI)	Final Multivariable Model* OR (95%CI)
Age (<50)		1.74 (1.38–2.19)	1.65 (1.30–2.10)
Sex (F)		1.08 (0.81–1.43)	
Race	Caucasian	Ref	
	Black or African American	0.76 (0.61–0.95)	
	Asian	1.26 (0.60–2.64)	
	Other or unknown	1.60 (1.04–2.48)	
Hypertension		0.30 (0.21–0.42)	0.40 (0.28–0.57)
Hyperlipidemia Diagnosis		0.17 (0.10–0.31)	
Diabetes mellitus		0.41 (0.31–0.53)	0.47 (0.36–0.63)
Obesity		0.37 (0.25–0.56)	0.44 (0.28–0.68)
Peripheral Arterial Disease		0.13 (0.02–1.06)	
Tobacco use (n=564)	Current smoker vs non-smoker or past-smoker	1.50 (1.00–2.23)	

Note that odds ratios (OR) refer to NOT receiving screening. For example, age <50 is associated with an increased risk of NOT receiving screening by a factor of 1.95. *c=0.65 for the association between predicted probabilities and observed responses for the final multivariable model.

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Unique Profile of Cardiovascular Risk Factors in Rheumatoid Arthritis High-Risk Populations with Insufficient Risk Control. Ulf Müller-Ladner[1], Stefan Kleinert[2], Klaus Krüger[3], Bianca Wittig[4] and Rolf Hecker[4]. [1]Kerckhoff-Klinik GmbH, Abt. Rheumatologie und klinische Immunologie, Bad Nauheim, Germany, [2]Praxisgemeinschaft Rheumatologie-Nephrologie, Rheumatologische Schwerpunktpraxis, Erlangen, Germany, [3]Praxiszentrum St. Bonifatius, München, Germany, [4]Abbvie Deutschland GmbH & Co. KG, Wiesbaden, Germany.

Background/Purpose: More than 50% of premature deaths in patients with rheumatoid arthritis (RA) are due to cardiovascular disease (CVD). Both the cumulative burden of inflammation and the increased prevalence of conventional CVD risk factors contribute to this increase in CVD. CVD risk screening and management is therefore mandatory.[1]

Methods: A cross-sectional study was conducted to screen RA patients for CVD risk factors at rheumatology outpatient centers in Germany. Age, gender, smoking habits, blood pressure, and lipid levels were assessed, as well as medications, comorbidities, DAS28, CVD, and standard laboratory parameters. Using these parameters, a subset of patients was assigned to 3 high-risk CVD subgroups: patients with manifest CVD, patients with diabetes mellitus (DM; type 1 or 2), and, as the CVD mortality risk is a function of age, patients ≥70 years of age. Achievement of target values for CVD risk factors adopted from the European Society of Cardiology (ESC) and European League Against Rheumatism (EULAR) recommendations were compared within these groups.[1,2] Descriptive data analysis was performed without adjusting for confounders. The RA population without those risks was used as a comparator group and stratified into risk categories by the mSCORE model.[2]

Results: The comparator population included 866 patients with RA. High-risk subgroups included 146 RA patients with existing CVD, 111 RA patients with DM (28 aged ≥70 years) and 114 RA patients aged ≥70 years but without DM or CVD. 49% of the CVD patients had a previous myocardial infarction or stroke, 62% had coronary heart disease (CHD), and 22% had previous arterial occlusion events. Recommended target values for CVD risk factors were not achieved by a substantial number of patients even in the high risk populations. Depending on the subgroup, 40%–45% of the patients achieved low disease activity or DAS remission, 41%–63% reached the respective blood pressure target, and 0%–28% reached the low-density lipoprotein (LDL) cholesterol target (Table 1). Lipid target values were rarely achieved in high-risk populations. Only a minor fraction of patients received statin therapy; there was no difference in glucocorticoid use between the high-risk and comparator populations. 65% of the investigators stated that the EULAR recommendations for the management of CVD risk in RA influenced their diagnostic and therapeutic concept.

Conclusion: Target values for CVD risk factors are rarely achieved in high-risk RA patients in routine outpatient settings, reflecting the insufficient management of CVD risk.

References

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Demographics, CVD Risk Factors, and Target Values

	CVD (n = 146)	DM (n = 111)	Age ≥70 (n = 114)	RA comparator (n = 866)
Mean age, years	64.7	63.3	73.9	55.5
Gender, % of women	48.6	63.1	69.3	73.9
RF and/or ACPA positive, %	76	71.2	78.1	74.6
Mean disease duration, years	10.8	8.9	12	9.2
Mean BMI, kg/m^2	28.5	29.5	26.1	27.0
Smokers, %	21.2	19.8	4.4	26.8
Mean DAS28	3.5	3.5	3.3	3.3
DAS28 <3.2 (%)	39.7	43.2	44.8	43.9
Mean systolic blood pressure, mmHg	134	136.7	138.9	132.4
Blood pressure target achieved, %	63	41.4	47.4	56.8
Mean LDL-c, mg/dL	128.9	126.9	135	137.7
LDL-c target achieved, %	4.3	20.7	-	-
mSCORE* ≤5%	NA	NA	23.8	27.7
mSCORE* >5%	NA	NA	11.9	9.7
mSCORE* ≥10%	NA	NA	0	0
Cholesterol: HDL-c ratio	3.64	3.57	3.38	3.69
Anti-hypertensive therapy				
Combination therapy, %	42.4	34.6	41.5	10.5
Monotherapy, %	43.1	58	46.2	18.9
Actual statin therapy, %	19.5	7.2	9.6	3.3
Actual corticosteroid use, %	63	60.4	61.4	59.8
Corticosteroid >5 mg/day, %	46.7	52.2	52.9	46.9
Corticosteroid use, median duration, months	46.5	43	54	43
NSAID use, %	31.5	30.6	27.2	33.0

*Modified SCORE [2] adapted by introducing a 1.5 multiplication factor when the patient two of three criteria: Disease duration >10 years, RF or anti-CCP positivity, presence of certain extra-articular manifestations. Calculation for older patients was performed using the highest age category available (65 years). RF = Rheumatoid factor; ACPA = Anti-citrullinated protein antibodies; BMI = Body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NSAID = non-steroidal anti-inflammatory drug

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Characteristics of Rheumatoid Arthritis Patients with and without Cardiovascular Diseases - Data from the Ontario Best Practice Research Initiative (OBRI). Kangping Cui[1], Binu Jacob[2], Janet E. Pope[3], Jessica Widdifield[4], Xiuying Li[2], Bindee Kuriya[5], Pooneh Akhavan[6] and Claire Bombardier[5]. [1]University Health Network/Toronto General Hospital Research Institute, Toronto, ON, [2]University Health Network, Toronto General Research Institute, Toronto, ON, [3]Schulich School of Medicine and Dentistry, Western University, London, ON, [4]Institute for Clinical Evaluative Science, Toronto, ON, [5]University of Toronto, Toronto, ON, [6]Mount Sinai Hospital/ University of Toronto, Toronto, ON.

Background/Purpose: Cardiovascular disease (CVD) is a major comorbidity and the leading cause of death among patients with rheumatoid arthritis (RA). The aim of this study was to compare the characteristics and patterns of medication use in RA patients with and without CVD.

Methods: Descriptive analyses were performed using physician and patient-reported data collected from the Ontario Best Practice Research Initiative (OBRI), a clinical registry of RA patients followed in routine care. CVD was defined as the presence of coronary artery disease (CAD), congestive heart failure (CHF), hypertension (HTN), arrhythmia, stroke, transient ischemic attack (TIA), and/or other heart disorders upon entering the registry (baseline). Patient demographics, clinical characteristics, socioeconomic status and treatment regimens were compared between patients with and without CVD at baseline using Chi-square and t-tests. Generalized linear regression models were used to estimate means for disease activity and functional status scores, adjusting for age, sex, smoking history, and socioeconomic factors.

Results: Among 2305 RA patients, 725 (31.5%) had CVD at baseline. Of those who had CVD, 562 (77.5%) had HTN, 68 (9.4%) had CAD, 21(2.9%) had arrhythmia, 10 (1.4%) had CHF, 9 (1.2%) had TIA, 5 (0.7%) had stroke, and 108 (14.9%) had other heart disorders. Patients with CVD were older (64.5 ± 10.1 vs. 54.2 ± 12.9 yrs, $p<0.0001$), and had longer RA disease duration (9.3 ± 10.7 vs. 8.3 ± 9.1yrs, $p<0.0001$). Male sex, low education and income, lack of private insurance, and smoking were also associated with the presence of CVD.

Positive rheumatoid factor (71.0% vs. 75.1%, $p<0.05$) was less prevalent in CVD patients. After adjusting for age, sex, income, education, insurance status, and smoking history, there were no significant differences in disease duration but CVD patients maintained higher disease activity (see table), measured by DAS28, CDAI, RADAI, tender joint count-28 (TJC), and erythrocyte sedimentation rate (ESR). Functional status measured by HAQ was worse in CVD patients. Extra-articular features (24.7% vs. 16.0%, $p<0.05$) were higher among CVD patients. CVD patients were less frequently treated with biologics (19.5% vs. 24.0%, $p<0.05$) and NSAIDS (34.9% vs. 48.6%, $p<0.05$) but did not differ in disease-modifying agents (DMARDs) and steroids usage compared with non-CVD patients.

Conclusion: RA patients with CVD have worse disease activity, more extra-articular features, and lower utilization of biologics and NSAIDS. The latter may be due to CVD risk with NSAIDs, but the lower utilization of biologics may require further investigation. Clarification on the CVD status of HTN patients is ongoing.

Disease Activity and Functional Status comparing RA patients with and without CVD

Disease Activity and Functional Status Measures	CVD (N = 725) Adjusted Mean*	SE**	Non-CVD (N = 1580) Adjusted Mean*	SE**	P-value*
DAS28-ESR	4.6	0.06	4.4	0.04	0.007
CDAI	23.0	0.56	21.3	0.38	0.014
SDAI	24.7	0.64	23.6	0.44	0.178
RADAI	4.3	0.09	3.9	0.06	0.001
SJC	6.2	0.20	5.8	0.13	0.110
TJC	7.0	0.26	6.2	0.17	0.014
ESR	27.1	0.92	24.8	0.61	0.044
CRP	13.8	0.92	13.1	0.63	0.575
HAQ	1.3	0.03	1.2	0.02	<0.001

* Adjusted for age, gender, income, education, insurance status and smoking history
** Standard errors are reported

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Factors Associated with Recording of Rheumatoid Arthritis on Death Certificate. Emily Molina[1], Jose Felix Restrepo[2], Inmaculada Del Rincon[1], Daniel Battafarano[3] and Agustin Escalante[2]. [1]University of Texas Health Science Center, San Antonio, TX, [2]University of Texas Health Science Center at San Antonio, San Antonio, TX, [3]San Antonio Military Medical Center, JBSA - Ft Sam Houston, TX.

Factors Associated with Recording of Rheumatoid Arthritis on Death Certificates

Background/Purpose: Death certificates can be used to study mortality due to a particular disease. However, rheumatoid arthritis (RA) often remains unreported in death certificates. We sought to determine to what extent RA is underreported and what demographic and clinical characteristics could predict mention of RA in the death certificate.

Methods: Between 1996 and 2009, we recruited 1,328 patients with RA that met the American College of Rheumatology criteria. Patients were followed prospectively. A rheumatologist assessed clinical characteristics of RA at each evaluation, including number of tender, swollen and deformed joints, presence of rheumatoid nodules, as well as Steinbroker classification and Charlson comorbidity index. Joint damage was determined by Sharp score, using hand radiographs taken from the most recent visit prior to death. Deaths were identified through family members, friends, neighbors, other physicians, obituaries and public death databases. We obtained state-issued death certificates and mapped causes of death to ICD9 codes. Standard bivariate analyses were conducted comparing patients with and without RA on the death certificate. A multivariable logistic regression model was performed to determine what variables were associated with recording RA.

Results: By December 2013, 323 deaths had occurred during 8,326 person-years of observation, for a mortality rate of 3.8 per 100 person-years [95% confidence interval (CI) (3.4, 4.3)]. Of the 308 death certificates we received, 61 (19.8%) mentioned RA on the death certificate. Only two of them recorded RA as the immediate cause of death. Bivariate analysis revealed that a greater number of deformities (mean ±SD = 17.6±9.0 vs. 14.4±9.4; $P=0.016$), higher Sharp score (mean ±SD = 192±132 vs. 138±112; $P=0.010$) and lower socioeconomic status (mean ±SD = 42.4±21 vs. 48.3±19; $P=0.041$) were each associated with recording RA on the death certificate. Place of death, presence of rheumatoid nodules, having health insurance or an autopsy were not associated with recording RA. Multivariable analyses revealed that an increased number of deformed joints [odds ratio (95% confidence interval) = 1.04 (1.00, 1.07); $P=0.04$], less comorbidity [OR (95%CI) = 0.87 (0.76, 0.99); $P=0.048$] and having a certified physician sign the certificate [OR (95%CI) = 3.56 (1.16, 10.8); $P=0.026$] were associated with listing RA on the death certificate.

Conclusion: In this RA cohort, a diagnosis of RA was not listed in the death certificate in 80% of patients who died. Patients with fewer comorbidities and more joint deformities were more likely to have RA reported. Studies that rely on death certificates may underestimate the mortality of RA and be biased toward patients with more severe RA and less comorbidities.

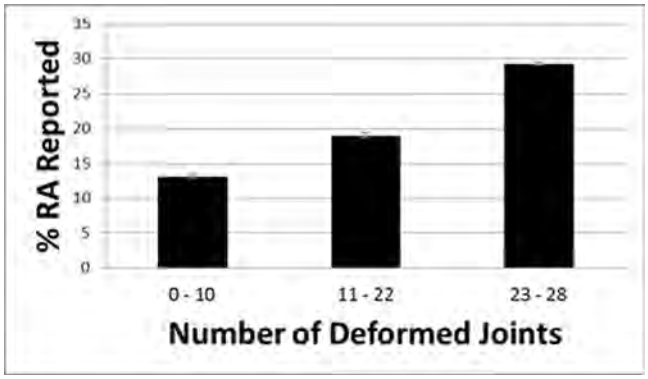


Figure 1. Percent death certificates reporting RA according to the number of deformed joints.

Disclosure: E. Molina, None; **J. F. Restrepo**, None; **I. Del Rincon**, None; **D. Battafarano**, None; **A. Escalante**, None.

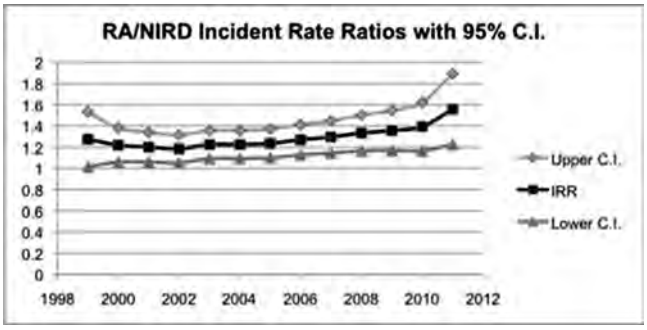
1067

Mortality Trends in Rheumatoid Arthritis during the Biologic Era, 1998 to 2011. Bryant R. England[1], Harlan Sayles[2], Ted R. Mikuls[2] and Kaleb Michaud[3]. [1]University of Nebraska Medical Center, Omaha, NE, [2]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [3]National Data Bank for Rheumatic Diseases, Wichita, KS.

Background/Purpose: Rheumatoid arthritis (RA) has consistently been associated with increased mortality risk, a risk that appears to be linked with greater disease activity. Although there have been substantial recent improvements in treatment, particularly with the availability of biologic treatments, it is unknown whether these advances have translated into improved RA-related survival. The purpose of this study was to describe and compare the trends in mortality in patients with RA and non-inflammatory rheumatic diseases (NIRD) from 1998 to 2011.

Methods: Patients were enrolled in a longitudinal study and open cohort of US rheumatologist diagnosed rheumatic diseases. Patients with RA and NIRD (osteoarthritis, back pain, tendonitis; excluding fibromyalgia) were followed from 1998 through 2011. Death records were obtained through the US National Death Index. Standardized mortality ratios (SMR) were calculated each year adjusting for age, sex, race, and calendar year. To account for possible participation bias, the RA group was compared to another enrolled group (NIRD) known to have an SMR close to or slightly lower than 1. Incidence rate ratios (IRR) comparing RA and NIRD groups and 95% confidence intervals were calculated each year controlling for age, sex, smoking status, disease duration, and comorbidity.

Results: In the RA group, 3,604 deaths occurred over 145,510 person-years. In the NIRD group, 965 deaths occurred over 40,003 person-years. SMR increased abruptly in the first three years in both groups. Annual SMRs were consistently higher for patients with RA (median 1.44, range 0.42 – 1.78) than for those with NIRD (median 0.88, range 0.09 – 1.35). Following multivariate adjustment, RA-related mortality risk remained significantly higher than NIRD mortality risk, a relative risk that remained constant throughout the observation period (IRR mean 1.29, range 1.18 – 1.56) (Figure).



Conclusion: Despite important advances in treatment that have accompanied the availability of biologics, there has been no meaningful improvement in RA-related mortality over this time period. As a result, there has been no narrowing of the 'mortality gap' separating RA patients from patients with NIRD. Though caution is warranted in interpretation, it appears that this gap may actually be widening. To determine whether this trend continues will require additional follow-up.

Disclosure: B. R. England, None; **H. Sayles**, None; **T. R. Mikuls**, None; **K. Michaud**, None.

1068

Smoking-Related Mortality in Rheumatoid Arthritis: A Retrospective Cohort Study Using Electronic Medical Records. Rebecca M Joseph[1], Mohammad Movahedi[2] and Deborah PM Symmons[2]. [1]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, Manchester, United Kingdom, [2]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Smoking is a known risk factor for rheumatoid arthritis (RA) and there is evidence suggesting that many patients with RA continue to smoke. The proportion of patients with RA who smoke is therefore higher than the general population. Smoking is associated with several serious adverse events and so is likely to reduce life expectancy. The aim of this study was to examine the influence of smoking status on all-cause mortality in patients with RA.

Methods: Incident cases of RA were identified from a large UK primary care database using a validated algorithm. Patients were followed from their first code for RA until death, leaving their general practice or the last data collection date within the study window of March 1991 to January 2014. Read codes, codes for smoking cessation therapy and additional clinical information were used to define smoking status at baseline and as a time-varying exposure during follow-up. Smoking status was classified as non-, current or former. Date of death was available in the database. The Cox regression model was used to compare mortality rates between smoking categories, adjusting for gender and diagnosis date (pre/post January 2000). Age, cardiovascular disease (CVD), diabetes, depression, use of immunosuppressive DMARDs, any code for painkillers in the past 6 months and any code for respiratory infections, oral steroids, cardiovascular medication and antidepressants in the past year were included in the model as time-varying covariates. As the effect of smoking status was not constant over time, the interaction between smoking status and year of follow-up was also included in the model.

Results: 13154 adult RA patients were identified, of whom 12431 (94.5%) had a baseline smoking status recorded and were included in the analysis. 68.9% were female and the median age was 60.8 years (IQR 50.2, 71.0). At baseline, all covariates differed significantly between the smoking categories. Former smokers had the highest prevalence of CVD, diabetes, and respiratory infection whilst current smokers had the highest prevalence of depression. The total follow-up time was 75467 person-years and there were 1719 deaths, giving a crude mortality rate of 22.8 per 1000 person years. The crude mortality rate for smoking status at baseline was 19.8, 25.6 and 24.8 per 1000 person years for non-, current and former smokers respectively. In the adjusted models, using time-varying smoking status, the risk of mortality for current smokers was nearly 80% greater than that of non-smokers (hazard ratio 1.79 (95% CI 1.46, 2.20) (Table).

Current smoking status	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
current (vs. non-smoker)	1.21 (1.06, 1.37)	1.79 (1.46, 2.20)
former (vs. non-smoker)	1.54 (1.38, 1.71)	0.96 (0.80, 1.16)
current (vs. former)	0.79 (0.70, 0.89)	1.86 (1.53, 2.27)

Conclusion: Current smoking significantly increases the risk of death at any time after RA diagnosis compared to both non- and former smokers. Adjusted risk of death is similar for former smokers and non-smokers. Stopping smoking prior to the development of associated comorbidities may therefore help to reduce the risk of smoking-related mortality.

Disclosure: R. M. Joseph, None; **M. Movahedi**, None; **D. P. Symmons**, None.

1069

Impact of Rheumatoid Arthritis on the Mortality of Patients Who Develop Cancer: A Population-Based Study. Pratibha Nayak, Ruili Luo, Linda Elting and Maria E. Suarez-Almarzor. The University of Texas, MD Anderson Cancer Center, Houston, TX.

Background/Purpose: Comorbidity among cancer patients imposes additional risks for premature mortality. The specific effect of rheumatoid arthritis (RA) on survival among cancer patients is unknown. Our objective was to examine survival among cancer patients diagnosed with RA compared to patients without RA.

Methods: Patients diagnosed with colorectal, breast, prostate or non-small cell lung cancer between years 2001 to 2010 were identified from the Texas Cancer Registry and Medicare-linked databases, which includes all beneficiaries in Texas 65 years and older who develop cancer. Patients were divided into 3 groups on the basis of previous Medicare claims for RA (International Classification of Diseases, ICD-9 code 714): (i) those who had no hospital or outpatient Medicare RA (No RA); (ii) those who had at least one claim related to RA (1-RA), and those who had at least 2 - claims related to RA that occurred a minimum of 6 months apart (2-RA). The overall survival and 95% confidence intervals (95% CIs) were estimated for each of the cancer types (colorectal, breast, prostate and non-small cell lung), and compared between RA and no RA groups. Cox proportional hazards regression models were used to control for demographic factors, cancer stage, and other comorbid conditions. Comorbidity was evaluated using the Charlson's comorbidity index.

Results: The overall analytical sample consisted of 126,241 cancer patients, with a mean age of 75 years (breast 31,545; prostate 38,858;

colorectal 27,784; non-small cell lung 28,054). About 1.7% (n=2,095) had 1-RA claim and 1.1% (n=1,397) 2-RA claims. After adjusting for covariates, the hazard ratios for patients in the 2-RA group were 1.42 (95% CI, 1.20–1.68) for those with breast cancer, and 1.45 (95% CI, 1.16–1.80) among those with prostate cancer. Increased mortality risk was observed among patients with colorectal cancer 1.17 (95% CI, 0.996–1.36) with 2-RA to those without RA, however this was not statistical significant (p value, 0.056). No differences in survival were observed between patients with or without RA and non-small cell lung cancer, and survival in patients with this tumor was much shorter than for the other 3 cancers.

Conclusion: A 40% increase in mortality was found among patients with breast or prostate cancer who also had RA, compared to those without RA. Additional research is needed to determine whether the observed increases mortality risk is related to comorbid burden, or differential utilization of cancer or rheumatoid therapies in patients with both diseases.

Disclosure: P. Nayak, None; **R. Luo**, None; **L. Elting**, None; **M. E. Suarez-Almazor**, None.

1070

Mortality Risk in Patients with Rheumatoid Arthritis Who Develop Non–Hodgkin's Lymphoma. Pratibha Nayak[1], Zaki Abou Zahr[2], Ruili Luo[1], Linda Elting[1] and Maria E. Suarez-Almazor[1]. [1]The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]Baylor College of Medicine, Houston, TX.

Background/Purpose: Patients with rheumatoid arthritis (RA) have greater risk of non-Hodgkin lymphoma (NHL) than the general population. A previous two-center study suggested that the rates of progression and relapse of patients with NHL and antecedent RA were better than those of patients with NHL alone, but that the overall risk of mortality was increased. The objective of this study was to conduct a population-based study of Medicare beneficiaries to compare the survival of patients with NHL and prior RA with that of patients with NHL alone.

Methods: We used for this study population-based data that links patients with cancer in the State of Texas (Texas Cancer Registry) with Medicare data in beneficiaries 65 years and older. The datafile has a case capture of over 95%. We included all Medicare-linked cases in the registry diagnosed with NHL (B cell, T cell, or not otherwise specified/unknown lineage) between 2001 and 2010. We classified each patient into one of three groups based on RA Medicare claims during the year prior to cancer diagnosis (International Classification of Diseases ICD 9, code 714): (i) 1-RA (having least one RA claim), (ii) 2-RA (having at least 2 hospital or outpatient claims, 6 or more months apart), and (iii) no-RA (having no claims related to RA). Cox proportional hazards regression models were used to compare overall survival among groups. Covariates included demographic variables, stage at diagnosis and comorbidity burden estimated using the Charlson's comorbidity index.

Results: 8,858 NHL patients were included, of whom 2.5% (n=226) had 1-RA claim and 2.3% (n=203) had 2-RA claims. Overall median survival for the cohort was close to 4 years. The hazard ratio (HR) for patients in the 1-RA group was 1.14 (95% CI, 0.95–1.37), and that for the 2-RA group was 1.04 (95% CI, 0.85–1.27), compared to that of patients without RA after controlling for demographics, and stage. The risk did not significantly change after including comorbidity in the models: 1-RA group HR=1.13, 95% CI, 0.94–1.36, and 2-RA group HR=1.04, 95% CI, 0.85–1.26. Comorbidity was an independent factor significantly associated with mortality such that having one additional comorbidity increased risk by 20% HR=1.20, (95% CI, 1.12–1.29), and having 3 or more comorbidities increased risk by more than 2 fold, HR=2.31 (95% CI, 2.01–2.43).

Conclusion: Having antecedent RA does not confer an independent mortality risk in NHL Medicare beneficiaries. However, patients with RA and NHL with other comorbidities can have decreased survival. Additional research should evaluate the risk associated with specific comorbid conditions, and whether this potential detrimental effect is from disease burden or differential use of cancer therapies.

Disclosure: P. Nayak, None; **Z. Abou Zahr**, None; **R. Luo**, None; **L. Elting**, None; **M. E. Suarez-Almazor**, None.

1071

What Is the Impact of Chronic Systemic Inflammation Such As Rheumatoid Arthritis on Mortality Following Cancer? Julia Simard[1], Sara Ekberg[2], Anna Johansson[3] and Johan Askling[4]. [1]Stanford School of Medicine, Stanford, CA, [2]Karolinska Institutet, Stockholm, Sweden, [3]Karolinska Institutet, stockholm, Sweden, [4]Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden.

Background/Purpose: Emerging evidence links inflammation and immune-competence to cancer progression and outcome. The few studies addressing cancer survival in the context of systemic inflammation, such as rheumatoid arthritis (RA), have reported reduced survival without accounting for the underlying mortality risk in RA. Whether this increased mortality is a cancer-associated phenomenon, an effect of the decreased lifespan in RA, or a combination of both is unknown.

Methods: Using Swedish register data (2001–2009), we performed a cohort study of individuals with RA (N=34930), matched to general population comparators (N=169740), including cancers (N=12676) and deaths (n=14291). We restricted to adults with no history of malignancy between 40 and 84 years old at start of study. Using multivariable adjusted stratified Cox models we first estimated the overall association between RA and death for those with and without cancer during follow-up using age as the underlying timescale., and then stratified by cancer stage. We then estimated the effect of RA versus non-RA by cancer stage restricting to individuals with an incident cancer during follow-up. We also investigated how the RA effect varied by time since cancer diagnosis (0–2 years, 2–5 years, >5 years since diagnosis) These analyses looked at all-cause mortality for all cancers and specific sites (lung, colorectal, female breast, prostate, malignant melanoma, and lymphoma).

Results: In the absence of cancer, RA was associated with a doubled mortality rate (HR=2.1, 95%CI 2.0–2.2). In the presence of cancer, the effect of RA on mortality was lower (HR=1.2, 95%CI 1.1–1.3), but only for advanced stage cancers. For stages I and II the relative effect of RA on mortality was doubled (HR=2.0 and HR=2.1, respectively). These associations remained across time since cancer diagnosis, and were reasonably similar across sites.

Conclusion: Our results offer limited evidence that RA would potentiate the effect of cancer on the risk of death, at least not in cancers diagnosed at advanced stage. Instead, much of the increase in mortality in RA patients diagnosed with cancer seems to reside with effects of RA independently of the cancer.

Table 1. Hazard ratios of all-cause death as a function of RA, cancer, and cancer stage

Cancer	Stage at cancer diagnosis	HR (95% CI) comparing patients with vs. without RA
No	–	2.1 (2.0, 2.2)
Yes	All	1.2 (1.1, 1.3)
No	–	2.1 (2.0, 2.2)
Yes	Stage I	2.0 (1.5, 2.8)
Yes	Stage II	2.1 (1.4, 2.9)
Yes	Stage III	1.6 (1.3, 2.0)
Yes	Stage IV	0.9 (0.7, 1.0)
Yes	Missing	1.2 (1.1, 1.4)

Stratified Cox models stratified on cancer or cancer stage, and adjusted for age (as underlying timescale), birth year, sex, civil status, region of residence, education, history of chronic obstructive pulmonary disease, history of diabetes, history of ischemic heart disease, and history of cerebrovascular disease.

Table 2 Hazard ratios for RA vs. non-RA among individuals diagnosed with any cancer, stratified by time since cancer diagnosis and stage at cancer diagnosis.

		Time since cancer diagnosis		
	All years	*0–2 years*	*2–5 years*	*>5 years*
All stages	1.3 (1.2, 1.4)	1.3 (1.2, 1.4)	1.3 (1.1, 1.6)	1.8 (1.2, 2.7)
Stage I	2.3 (1.7, 3.2)	2.5 (1.7, 3.7)	2.1 (1.2, 3.5)	2.8 (0.7, 11.6)
Stage II	2.5 (1.6, 3.1)	2.3 (1.5, 3.6)	1.8 (0.9, 3.5)	5.0 (1.1, 22.6)
Stage III	1.4 (1.2, 1.8)	1.4 (1.2, 1.8)	1.6 (0.9, 2.9)	*
Stage IV	1.0 (0.8, 1.2)	1.0 (0.9, 1.3)	0.5 (0.3, 1.1)	4.3 (0.7, 25.8)
Missing	1.3 (1.2, 1.4)	1.3 (1.1, 1.4)	1.3 (1.1, 1.6)	1.5 (0.9, 2.5)

The stratified Cox model is stratified by cancer status or stage, and adjusted for time since diagnosis (as underlying timescale) and age at cancer diagnosis, sex, civil status, geographic region, education, and history of comorbid conditions. Presented as HR and 95% confidence intervals.
*unestimable

Disclosure: J. Simard, None; **S. Ekberg**, None; **A. Johansson**, None; **J. Askling**, None.

1072

Sex Ratio of Offspring Born to Women with Lupus and Rheumatoid Arthritis. Elizabeth V. Arkema[1], Johan Askling[2], Jane Salmon[3] and Julia F. Simard[4]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Hospital for Special Surgery, New York, NY, [4]Stanford School of Medicine, Stanford, CA.

Background/Purpose: Women with SLE are at increased risk for pregnancy complications and specific autoantibodies may result in preferential loss of female offspring. Studies on the male to female (M:F) sex ratio of births in the SLE population have been contradictory. We used a large national population-based cohort of patients with SLE to determine whether the M:F ratio of births to mothers with SLE is different than the general population as well as a population of women with rheumatoid arthritis (RA) to estimate the ratio in another chronic inflammatory disease.

Methods: SLE was defined as ≥2 visits in inpatient or outpatient care (National Patient Register (NPR); 1969–2011) listing an SLE ICD code with ≥1 SLE-coded visit to a specialist. A sample of general population comparators was identified from the Total Population Register. Women with a delivery were identified from the Swedish Medical Birth Register (1973–2011). We used modified Poisson regression with robust sandwich estimators to calculate the risk ratio (RR) for having a male offspring associated with an SLE diagnosis adjusted for age, year and maternal country of birth. Our primary analysis was restricted to first singleton births only. In secondary analyses, we examined all births and restricted to live births only. We also examined antiphospholipid syndrome (APS) history in the SLE population using any ICD10 code before or at delivery, restricted to ≥1997 when the code was available. Lastly, we calculated the M:F ratio of offspring born to women with ≥2 RA-coded visits in the NPR with ≥1 visit to a specialist before delivery.

Results: We identified 604 women with SLE before their first delivery and 1289 singleton deliveries total to women with prevalent SLE. Maternal SLE at delivery had a lower proportion of male offspring compared to the general population. The RR for male offspring associated with SLE was 0.95 (95%CI 0.88, 1.04) for first births and 0.96 (95%CI 0.90, 1.01) for all singleton births (Table). RRs did not change with adjustment by age, year or country of birth. Results were similar among live births only and including multiples. Women with both APS and SLE had a lower odds of having a male child compared to the general population. We identified 1136 women with prevalent RA at first delivery and 2674 singleton deliveries total. The M:F ratio in RA was not significantly different than the general population (first birth RR=0.96 (95%CI 0.91, 1.02), all births OR=0.99 (95%CI 0.95, 1.03)).

Conclusion: We observed a lower proportion of male offspring born to women with prevalent SLE at delivery compared to the general population, which was not statistically significant. We observed a significantly lower odds of male offspring born to women with SLE and APS when all births were considered. In this large study using similar techniques to identify patients as that of a group in Canada, we did not confirm their findings of a male dominance in offspring.

Table 1: Maternal characteristics and M:F sex ratio among deliveries in Sweden, 1973-2011, comparing mothers with SLE at delivery to mothers from the general population restricted to singleton births

	First births			All births		
	Prevalent SLE at delivery		*General Population*	*Prevalent SLE at delivery*		*General Population*
N	604		18,226	1,289		45,185
Male baby, N (%)	293 (48.5)		9,303 (51.0)	631 (49.0)		23,204 (51.4)
M:F ratio	0.94		1.04	0.96		1.06
Mother born in Sweden, N (%)	542 (89.7)		16,314 (89.5)	1,145 (88.8)		39,927 (88.4)
Mother's age, mean (SD)	28.7 (4.6)†		26.5 (5.1)	30.4 (4.8)†		28.8 (5.3)
Stillbirth*, N (%)	7 (1.2)†		75 (0.41)	12 (0.93)†		173 (0.4)
Male baby, of live births, N (%)	290 (48.6)		9,265 (51.0)	627 (49.1)		23,113 (51.4)
RR¥ (95%CI)	0.95 (0.88, 1.04)		1.0 (ref)	0.96 (0.90, 1.01)		1.0 (ref)
Births 1997-2011℄	***SLE and APS+***	***SLE and APS−***		***SLE and APS+***	***SLE and APS−***	
RR (95%CI)	0.80 (0.50, 1.25)	0.96 (0.86, 1.08)	1.0 (ref)	0.69 (0.51, 0.94)	0.97 (0.90, 1.05)	1.0 (ref)

* fetal death before delivery or during delivery
† significant at alpha=0.05, chi-square test for proportions, 2-sided t-test for means
¥ RR for having a male offspring associated with a maternal SLE diagnosis
℄ Presenting RR and 95% CI, restricted to 1997 onwards to account for ICD10 coding of APS.

Table 1: Risk of high-grade cervical dysplasia or cervical cancer among women with SLE who initiated immunosuppressive drugs* versus hydroxychloroquine in a propensity score-matched analysis**

Disclosure: E. V. Arkema, None; **J. Askling**, None; **J. Salmon**, None; **J. F. Simard**, None.

1073

Prescription Medication Trends in Medicaid-Enrolled Pregnant Women with Rheumatoid Arthritis, Psoriasis, and Systemic Lupus Erythematosus.

Rishi Desai[1], Krista Huybrechts[2], Brian Bateman[2], Helen Mogun[2], Sonia Hernandez-diaz[3] and Seoyoung C. Kim[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Harvard School of Public Health, Boston, MA.

Background/Purpose: Little is known about the trends of medication use in pregnant women with autoimmune disorders. The objective of the current study was to examine the prevalence and trends of oral steroids and immunomodulatory drug use in pregnant women with rheumatoid arthritis (RA), psoriasis, and systemic lupus erythematosus (SLE).

Methods: A cohort of pregnant women with RA, psoriasis, or SLE was identified using data from the Medicaid Analytical eXtract for the period of 2000–2007. The following 3 classes of medications were identified using prescription dispensing data for these patients; 1) oral steroids, 2) non-biologic disease modifying anti-rheumatic drugs (nbDMARDs), and 3) biologic DMARDs. The proportion of women with RA, psoriasis, and SLE exposed to these medications in the following time-windows were reported, 1) 3 months pre-last menstrual period (LMP), 2) first trimester, 3) second trimester, and 4) third trimester. Trends in the use were also evaluated by calendar year.

Results: A total of 1,734 pregnant women with RA, 2,932 with psoriasis and 2,392 with SLE enrolled in Medicaid from 46 states and Washington, DC were identified. During the 3 months pre-LMP, 16.8% of women with RA used oral steroids, 11.9% used nbDMARDs, and 4.3% used biologics. During pregnancy, the use of steroids showed modest reduction in women with RA compared to 3 months pre-LMP use **(Figure)**. However, the use of nbDMARDs showed a marked reduction during the 1st, 2nd and 3rd trimesters with 7.8%, 2.9%, and 2.6% of women with RA using these agents during these periods, respectively. Similarly, the use of biologics in women with RA also decreased during pregnancy. In women with psoriasis, 6.3% used oral steroids, 0.8% used nbDMARDs, and 1.4% used biologics during the 3 months pre-LMP period. During pregnancy, use decreased for all the three classes of medications. In women with SLE, 16.7% used oral steroids, 14.9% used nbDMARDs, and 0.6% used biologics during the 3 months pre-LMP. Use of steroids was increased moderately during pregnancy compared to 3 months pre-LMP use, but a lower proportion of women used non-biologic and biologics during pregnancy in the SLE cohort. No meaningful time trends were observed in use of these three classes of medications during pregnancy between 2000 and 2007.

Conclusion: We observed reduced use of non-biologic and biologics in women with RA, psoriasis, and SLE during pregnancy compared to before pregnancy. This reduced use may be due to lowered disease activity during pregnancy or fetal safety concerns related to the use of these agents. Oral steroids were the most commonly used therapy in all three populations at all the stages of pregnancy. Given this high use, future research evaluating the safety of steroids in pregnancy is warranted.

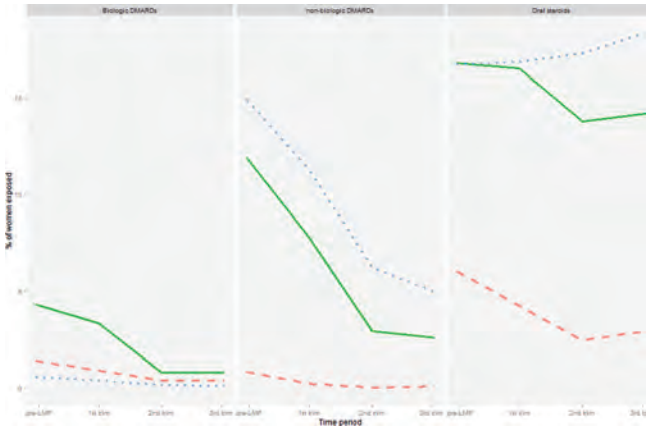


Figure: Trends in use of oral steroids, non-biologic and biologic DMARDs at different stages of pregnancy in women with RA, psoriasis, and SLE

Disclosure: R. Desai, Biogen Idec, 1; **K. Huybrechts**, None; **B. Bateman**, None; **H. Mogun**, None; **S. Hernandez-diaz**, Novartis, GSK, AstraZeneca, 5; **S. C. Kim**, Pfizer Inc, 2.

1074

A Meta-Analysis of the Risk of Venous Thromboembolism in Inflammatory Rheumatic Diseases.

Jason J. Lee[1] and Janet E. Pope[2]. [1]University of Western Ontario, London, ON, [2]St Joseph Health Care, London, ON.

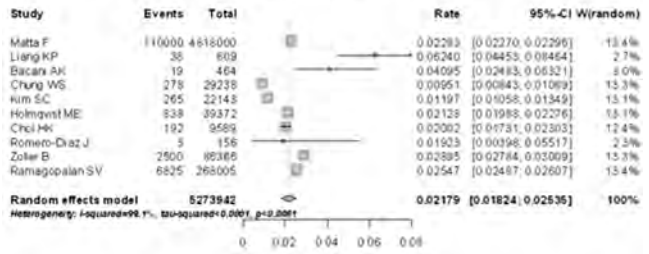
Background/Purpose: We performed a meta-analysis investigating the risk of developing deep vein thrombosis (DVT) and/or pulmonary embolisms (PE) in patients with inflammatory arthritis, vasculitis, and connective tissue diseases (CTD) [SLE, Sjogren's syndrome, inflammatory myositis and systemic sclerosis (SSc)].

Methods: PubMed, Embase, Cochrane Databases, and Medline were searched identifying full text English publications in adults related to rheumatologic inflammatory diseases and VTE. Data regarding rates of DVTs and PEs were extracted. Using random effects models, pooled estimates for VTE in individual and pooled diseases compared with matched populations where possible. Studies were excluded if VTEs were in the setting of pregnancy, postoperative outcomes or solely antiphospholipid antibody syndrome.

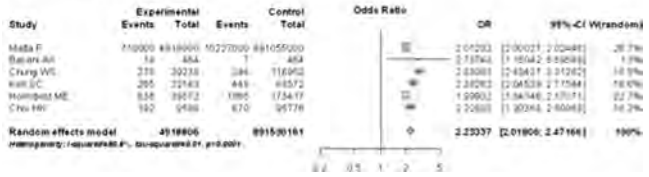
Results: Most of the 3,929 studies were excluded due to lack of rate or incidence of VTE. Twenty studies remained for analysis. Eight studies of RA identified 5,273,942 patients and 891,530,181 controls with a cumulative incidence of 2.18% (95% CI: 1.82–2.54%) and an odds ratio of 2.23 (95% CI: 2.02–2.47) compared to age and sex, matched population. Six studies included 36,582 SLE patients with a cumulative incidence of 8.24% (95% CI: 6.27–10.22%); three Sjogren's syndrome studies (N=16,180) demonstrated a VTE cumulative incidence of 2.62% (95% CI: 2.15–3.10%); four studies of inflammatory myositis (N=8,245) yielded a VTE cumulative incidence of 4.03% (95% CI: 2.38–5.67%), SSc and ANCA vasculitis rates (3 studies each) were 3.82% and 8.51% respectively. The figure shows VTEs in RA as an example.

Conclusion: Inflammatory rheumatologic diseases studied were all associated with high rates of VTEs, more nearly three times higher than the general population. Identification of those at risk is important. We cannot determine from these studies what the risk is when inflammation is effectively treated.

(a) Cumulative Incidence of VTEs in patients with RA



(b) Cumulative Incidence of VTEs in RA compared to matched control population presented as Odds Ratio



Disclosure: J. J. Lee, None; **J. E. Pope**, None.

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Risk of High-Grade Cervical Dysplasia and Cervical Cancer in Women with Systemic Lupus Erythematosus on Immunosuppressive Drugs. Candace H. Feldman, Jun Liu, Sarah Feldman, Daniel H. Solomon and Seoyoung C. Kim. Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Human papillomavirus (HPV) is the most common sexually transmitted disease in the US and the main cause of high-grade cervical dysplasia and cervical cancer. Prior studies suggest an increased risk of cervical cancer in women with systemic lupus erythematosus (SLE), however the relationship with immunosuppressive drugs (ISDs) is not well studied. We compared the risk of high-grade cervical dysplasia and cervical cancer among women with SLE receiving hydroxychloroquine (HCQ) to those on ISDs in a nationwide database. We hypothesized that the risk of cervical dysplasia and cervical cancer would be increased among ISD users.

Methods: We utilized US commercial insurance claims data (2001–2012) to conduct a cohort study to examine the incidence rates (IR) of high-grade cervical dysplasia or cervical cancer in women who initiated ISDs or HCQ for SLE. The index date was defined as the dispensing date of the first ISD or HCQ after ≥2 diagnoses of SLE (ICD-9 code 710.0). We required patients to have ≥365 days of continuous enrollment prior to the index date without use of ISDs or HCQ. We assessed baseline covariates during this period. We defined the outcome, high-grade cervical dysplasia or cervical cancer, using a validated claims-based algorithm with a positive predictive value of ≥81%. We also determined the number of gynecologic visits and procedures during follow-up. To control for potential confounders including age, comorbidities, HPV vaccination, corticosteroid use, additional medications, and healthcare utilization, initiators of ISDs were matched to HCQ initiators using propensity scores with a 1:1 ratio.

Results: Among 2,451 propensity score-matched pairs of women with SLE, the median age was 46 years, the mean follow-up was 1.15 (SD 1.38) years, and the overall follow-up was 5,622 person-years. The IR of high-grade cervical dysplasia or cervical cancer per 1,000 person-years was 4.70 in ISD initiators and 1.89 in HCQ initiators (**Table**). There were 14 cases of high-grade cervical dysplasia or cervical cancer in the ISD group and 5 cases in the HCQ group for a hazard ratio of 2.47 (95% CI: 0.89–6.85). The number of outpatient gynecologic visits (Rate ratio [RR] 0.93, 95% CI: 0.81–1.07) and gynecologic procedures (RR 1.13, 95% CI: 0.98–1.44) was not significantly different between the two groups.

Conclusion: Among women with SLE, initiation of ISDs may be associated with a greater, albeit not statistically significant risk of high-grade cervical dysplasia or cervical cancer compared to HCQ alone. Given the rare nature of cervical cancer and the prolonged latency period, further studies with extended follow-up are needed to confirm this finding.

Table 1. Risk of high-grade cervical dysplasia or cervical cancer among women with SLE who initiated immunosuppressive drugs* versus hydroxychloroquine in a propensity score-matched analysis**

	Immunosuppressive drugs* (N=2,451)				Hydroxychloroquine (N=2,451)			
	Event	Person-years	IR+ (95%CI)	HR (95% CI)	Event	Person-years	IR+ (95%CI)	HR (95% CI)
High-grade cervical dysplasia or cervical cancer	14	2,976	4.70 (2.78–7.94)	2.47 (0.89–6.85)	5	2,646	1.89 (0.79–4.54)	Ref.

*Immunosuppressive drugs include: methotrexate, azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, tacrolimus, abatacept, rituximab and belimumab
**The propensity score model includes age, sex, calendar year, comorbidities, HPV vaccination, being sexually active, sexually transmitted diseases, other comorbidities, medication use including oral contraceptives and corticosteroids, Pap test, HPV DNA test, and other health care utilization factors
+IR is per 1,000 person-years

Disclosure: C. H. Feldman, None; **J. Liu**, None; **S. Feldman**, None; **D. H. Solomon**, Pfizer Inc, 2, Amgen, 2, Lilly, 2, Corrona, 2, UpToDate, 7; **S. C. Kim**, Pfizer Inc, 2.

1076

U.S. Geographic Trends in the Distribution and Treatment Practices of Juvenile Systemic Lupus Erythematosus: An Analysis of the Childhood Arthritis and Rheumatology Research Alliance Registry. Jennifer M.P. Woo[1], Ornella J. Rullo[1], Deborah K. McCurdy[2] and The CARRA Registry Investigators[3]. [1]University of California, Los Angeles, Los Angeles, CA, [2]UCLA Division of Pediatric Rheumatology, Los Angeles, CA, [3]Childhood Arthritis and Rheumatology Research Alliance, Durham, NC.

Background/Purpose: The treatment of juvenile systemic lupus erythematosus (jSLE) often requires complex medication regimens in order to address the different disease manifestations. Despite the limited number of medications approved for the treatment of jSLE, standardized treatment protocols have been slow to emerge. Identification of regional and temporal variations in medication usage in jSLE can help to establish more unified treatment practices.

Methods: Demographic and clinical data were collected for jSLE patients (diagnosis <18 years of age) enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry between 2009 and 2012. Individuals identified as being diagnosed and starting treatment prior to 2007 (Cohort 1; C1; n = 285) or as being diagnosed and treated between 2007 and 2012 (Cohort 2; C2; n = 284) were used to evaluate temporal changes in treatment practices by region. Regions were identified based on U.S. Census definitions and inclusion in a region was determined by the U.S. Census 3-digit zip code tabulation area (ZCTA) prefix of the area in which the patient resided at the time of symptom onset.

Results: Of the 925 jSLE enrolled in the CARRA Registry by July 2012, 809 (87%) had geographic data available and were included in the spatial analysis. This cohort was further separated based on year of diagnosis and duration of jSLE treatment, resulting in groups C1 and C2. Although the population distribution of jSLE varied among U.S. Census regions, C1 and C2 population sizes within a region were similar. Both demonstrated comparable female-to-male ratios (~3–4:1), ACR criteria counts, and ACR functional scores at worst disease (Table 1).

At symptom onset, approximately 90% of CARRA Registry patients lived in ZCTAs within 50 miles of a CARRA Registry pediatric rheumatology center. Glucocorticoid, non-biologic, biologic, and NSAID use in jSLE varied by region, however, comparison of C1 and C2 suggests an overall decrease in steroid and NSAID use and an increase in use of biologic and non-biologic

medications (Fig 1). Furthermore, C2 jSLE required significantly fewer medications compared to C1 (4.4 vs 5.7, respectively; $p<0.01$).

Conclusion: The heterogeneous nature of jSLE and regional variation in medication usage may have impacted the development of standardized treatment practices. Importantly, however, the overall number of required medications, glucocorticoids and NSAIDs in particular, has decreased across the U.S. Subsequently, regional and temporal variations may reflect the recent trend towards the standardization of medication practices in jSLE.

Table 1. Demographics and characteristics of spatial analysis cohort and temporal cohorts

	Spatial Analysis Cohort	Cohort 1 (Diagnosis & treatment prior to 2007)	Cohort 2 (Diagnosis & treatment 2007–2012)
n (% of enrolled CARRA jSLE; N = 925)	809 (87)	246 (27)	260 (28)
Female-to-Male ratio	644:165 (3.9:1)	185:61 (3.0:1)	211:49 (4.3:1)
Age of disease onset (years); mean	12.4	10.7*	13.3*
Disease duration prior to diagnosis (years); mean	0.56	0.53	0.51
ACR criteria count; mean	4.1	4.1	4.1
ACR functional class at greatest disease†; mean	2.3	2.4	2.3
Medication count; mean	5.0	5.7*	4.4*
Medication count excluding glucocorticoids; mean	4.0	4.6*	3.1*
Health insurance (%)	94.7	95.5	93.1
Household income; median	25–49K	25–49K	25–49K

*Values compared between C1 and C2; $p < 0.01$.
†ACR functional class is a physician scored measure of disease morbidity; scaled from 1 to 4 with 1 representing "completely able to perform usual activities" to 4 representing "Limited in ability to perform usual self-care activities"

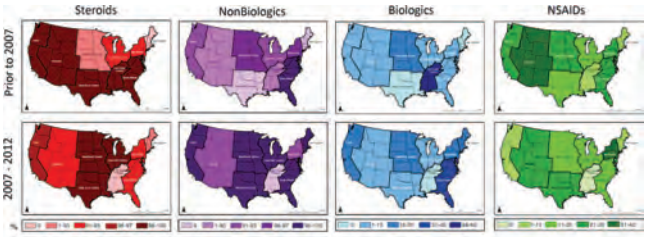

Figure 1. Trends in therapeutic use by U.S. Census region before and after 2007.
*Gradient represents percent ranges of medication use (% = Number of jSLE receiving medication by region/region population of CARRA Registry jSLE).

Disclosure: J. M. P. Woo, None; **O. J. Rullo**, None; **D. K. McCurdy**, None; **T. CARRA Registry Investigators**, None.

1077

A Real-World Characterization of US Patients with "Moderate-to-Severe" Systemic Lupus Erythematosus. Vibeke Strand[1], Jennifer Johnson[2], Carl Vandeloo[3], Catrinel Galateanu[3] and Steve Lobosco[2]. [1]Biopharmaceutical Consultant, Portola Valley, CA, [2]Adelphi Real World Ltd., Macclesfield, United Kingdom, [3]UCB Pharma, Brussels, Belgium.

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic, inflammatory disease which can impact on patients' Health-Related Quality of Life (HRQoL). This analysis was designed to characterize US SLE patients classified by physicians as having "moderate-to-severe" disease, and to assess their burden of disease compared with those with "mild" disease severity.

Methods: Data were extracted from the multi-sponsor Adelphi 2013 Lupus Disease-Specific Program, a multinational survey of clinical practice. US physicians completed Patient Record Forms (PRFs); disease severity was based on physician assessments. Patients self-reported data including EQ-5D and Work Productivity and Activity Impairment Index for SLE (WPAI-Lupus), which were included in Patient Self-Completion Records (PSCs).

Results: PRFs and PSCs were collected from 97 rheumatologists. Of 498 patients, disease severity was classified as "mild" in 355 (71%), and "moderate-to-severe" in 139 (28%) (severity was not specified in 4 patients [1%]). Physician assessment of disease severity was predominantly based on affected organs/symptoms (considered most important by 37% and 40% of rheumatologists, respectively). Only 11% reported test results/clinical assessments as a determinant of SLE severity, with no single disease activity index widely used in clinical practice; 68% rheumatologists reported using their own systematic assessment. Physician assessment of disease severity and control of disease activity were imperfectly correlated: disease activity was controlled in 54% of patients with "moderate-to-severe" disease severity, and partially controlled or uncontrolled in 29% of patients with "mild" disease severity. "Moderate-to-severe" patients initially presented with greater disease severity and organ involvement (13% had skin-only SLE at diagnosis), and more flares per 12 month period (Table), than "mild" patients. Compared to "mild" severity, "moderate-to-severe" SLE severity was associated with a greater impact on HRQoL, which was comparable to rheumatic conditions including rheumatoid arthritis and psoriatic arthritis (Table). Fewer "moderate-to-severe" patients were employed, and a higher proportion required care providers (Table). For both "mild" and "moderate-to-severe" patients, obesity was one of the most common associated comorbidities; the proportion of "moderate-to-severe" patients affected was over double that of "mild" patients (Table).

Conclusion: "Moderate-to-severe" SLE severity was associated with a greater burden of disease than patients with "mild" severity. Data show that disease severity is not consistently assessed in US clinical practice and is a multifaceted concept, imperfectly correlated with control of disease activity. Thus, there is a need for a simple, universal tool to accurately assess SLE disease activity, as well as severity, to inform physician and patient decisions regarding treatment.

Table: Characteristics of patients with "Mild" and "Moderate-to-severe" SLE disease severity

	"Mild" patients n = 355	"Moderate-to-severe" patients n = 139
Demographics		
Age at first consultation, mean years	34.1	29.1
Gender, n (%) female	312 (88)	132 (95)
Severity at diagnosis, n (%)		
Mild	129 (36)	23 (17)
Moderate	172 (49)	78 (56)
Severe	52 (15)	37 (27)
Employment status, n (%)		
Full time	181 (51)	50 (37)
Employed (full/part/self)	214 (60)	61 (41)
Unemployed	33 (9)	31 (23)
Patients with care provider, n (%)	8 (2)	12 (9)
Clinical status		
Flared in the last 12 months, n (%)	76 (21)	85 (61)
Number of flares in last 12 months, [a] mean	2.1	3.0
In remission, n (%)	181 (51)	4 (3)
Most common associated comorbidities	Obesity (10%); Hypertension (9%); Osteoporosis (8%)	Hypertension (24%); Obesity (24%); Respiratory condition (11%)
Level of disease control[b]†		
Controlled	71%	54%
Partially controlled	21%	31%
Uncontrolled/flaring	8%	15%
SLE clinical manifestations at diagnosis		
Skin only, n (%)	48 (14)	17 (13)
Skin and joints, n (%)	148 (44)	62 (47)
Joints only, n (%)	78 (23)	28 (22)
Kidney,[c] n (%)	64 (19)	24 (18)
Health-Related Quality of Life		
EQ-5D,[d] mean (SD)	0.87 (0.14)	0.68 (0.23)
EQ-5D VAS, mean (SD)	78.83 (17.48)	56.78 (26.78)*
WPAI,[e] mean % impairment (SD)	13.55 (18.76)	34.50 (27.34)**

[a]Of patients who have flared in last 12 months [b]Based on physician assessment; [c]With or without other manifestations [d]−0.594–1.000 where higher scores indicate better health state; [e]0–100 where higher scores indicate greater impairment
† p value significant to <0.05
*Moderate/severe rheumatoid arthritis (RA) EQ-5D Visual Analogue Score (VAS): 61.6, moderate/severe psoriatic arthritis (PsA) EQ-5D VAS: 62.2
**Moderate/severe RA WPAI: 13.5, moderate/severe PsA WPAI: 43.2

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Work-Related Behavior and Experiences in Patients with Systemic Lupus Erythematosus. Jutta G. Richter[1], Ralph Brinks[2], Thomas Muth[1], Tobias Koch[1], Peter Angerer[1] and Matthias Schneider[1]. [1]Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany, [2]Heinrich-Heine-University Duesseldorf, Düsseldorf, Germany.

Background/Purpose: Work-related behavior and experiences are discussed to be either risk factors or resources for individual's health. Diseases and related changing working conditions and/or experiences might have additional effects. The objective of the study was to describe work-related attitudes and to examine their relationship to

clinical data and health in patients (pts) with systemic lupus erythematosus (SLE).

Methods: Self-reported (outcome) questionnaires including clinical data were applied to SLE pts and controls (c) not suffering from rheumatic diseases, both groups were capable for work. The 'AVEM' questionnaire assesses eleven health relevant dimensions via 66 items and thus determines the personal attitudes towards work, see Table 1. The dimensions (d) are attributable to three areas: work engagement (d 1–5), resistance to stress (again d 5; 6–8) and the emotions accompanying occupation (d 9–11). Ethics committee approval had been obtained.

Results: 252 pts (95.6% female (f)) and 177 c (90.3% f) contributed data. Patients' mean age was 40.1±9.4 (c 42.8±9.8) years, mean disease duration 10.5±7.3 years, mean HAQ 0.8±0.4 (c 0.4±0.1). 86.0% reported at least one comorbidity (range 1–10, c 45.2%, range 0–4). 77.4% received at least one immunosuppressive medication (range 0–3). 40.5% were on steroids <7.5mg, 16.3% on steroids >7.5mg, 32.1% took NSAIDS.

AVEM scales are depicted in Table 1, SLE pts scored significantly different to c in eight dimensions. Pts showed higher scores for 4 of 5 work engagement scales, less capability for emotional distancing, higher resignation tendencies, lower satisfaction with life and lower experiences of social support. OR indicate whether pts of the T- group (see table 1) have an increased risk for lower self-rated health status compared to T+.

Table 1. AVEM dimensions in c and SLE, *mean±standarddeviation, T+ and T- Percentage of pts deviating > 1 SD from mean of c, + Wilcoxon test, # Fisher's exact test

AVEM dimensions	c*	SLE*	p-value+	T+	T−	OR	p-value#
1. Subjective significance of work	15.2 ± 5.0	16.5 ± 5.2	0.0080	19.8	14.0	0.70	p>0.05
2. Professional ambition	16.5 ± 5.0	17.5 ± 5.6	p>0.05	23.0	16.7	1.07	p>0.05
3. Tendency to exert	17.9 ± 5.1	19.8 ± 5.3	0.0004	28.0	9.6	0.12	0.0002
4. Striving for perfection	21.8 ± 4.5	22.7 ± 4.2	0.0448	21.7	13.8	0.30	0.0135
5. Emotional distancing	20.6 ± 5.0	18.7 ± 5.3	0.0007	8.3	27.7	4.37	0.0099
6. Resignation tendencies	15.4 ± 4.2	16.9 ± 4.9	0.0023	29.2	10.6	0.42	p>0.05
7. Offensive coping with problems	22.0 ± 3.3	21.0 ± 3.7	0.0098	10.5	23.8	1.69	p>0.05
8. Balance and mental stability	20.3 ± 4.3	18.6 ± 4.9	0.0006	12.2	32.8	2.06	p>0.05
9. Satisfaction with work	22.4 ± 4.1	21.6 ± 4.4	p>0.05	13.8	24.3	3.54	0.0084
10. Satisfaction with life	22.9 ± 3.9	20.3 ± 4.5	0.0000	8.4	30.3	9.93	0.0001
11. Experience of social support	23.5 ± 4.3	22.2 ± 4.7	0.0069	12.7	27.9	4.80	0.0014

Conclusion: This is the first study applying AVEM to SLE pts. Results detected domains that are potentially modifiable and should be considered in clinical management. Pts work engagement, resistance to stress and emotional issues should be predominantly targeted. Further study analyzes will address correlations to other study parameters and confounding factors. Thus, appropriate strategies that promote healthy personal attitudes and equip pts with adequate supporting coping skills that prepare them for the challenges at their daily work might and should be developed.

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Disclosure: J. G. Richter, None; **R. Brinks**, None; **T. Muth**, None; **T. Koch**, None; **P. Angerer**, None; **M. Schneider**, None.

1079

Prevalence of Cardiac Arrhythmias in Systemic Lupus Erythematosus. Gihyun Myung, Lindsy J. Forbess, Mariko L. Ishimori, Sumeet Chugh, Daniel Wallace and Michael H. Weisrman. Cedars-Sinai Medical Center, Los Angeles, CA.

Background/Purpose: Cardiovascular disease is a major cause of death among systemic lupus erythematosus (SLE) patients. Although the prevalence of atrial fibrillation (0.5–1%) and QT prolongation (7%) is well studied in the general population, little is known regarding arrhythmias in SLE. The aim of this project is to determine the prevalence of arrhythmias in a SLE population.

Methods: We retrospectively reviewed electrocardiograms (ECGs) of SLE patients seen in inpatient, outpatient and emergency department settings over a 10-year time frame at a single academic center. Abnormal ECG findings were confirmed by an electrophysiologist. ECGs were categorized as abnormal if arrhythmias or QT prolongation (QTc ≥460ms for women; ≥450ms for men) were present. Sinus bradycardia, 1st degree AV block, and sinus tachycardia were not considered arrhythmias but were recorded. Arrhythmias were also ascertained through review of ICD9 codes for the subset of SLE patients with available ECGs.

Results: Of 1,139 SLE patients, 235 had available ECGs. 160 were white (68%), 33 black (14%), 27 Asian (12%), and 15 Hispanic (6%). 217 were female (92%), 18 (8%) male, and the average age was 52 ± 15 (average ± SD). Through ECG review, 6% had tachyarrhythmias (3% with atrial fibrillation) and 17% had QT prolongation (Table 1). None had bradyarrhythmias. Through ICD9 code examination, more had tachyarrthythmias (15%), including atrial fibrillation (9%), compared with direct ECG review. 35 of 53 abnormal ECGs (66%) were obtained in the inpatient setting, 11 (21%) in the outpatient setting, and 7 (13%) in the emergency department. The most common ECG indication was chest pain (12% of abnormal and 16% of normal ECGs).

Conclusion: Sinus tachycardia was the most common ECG finding among our SLE patients. Compared to the general population, our SLE patients had a higher prevalence of atrial fibrillation and QT prolongation. This is likely an underestimation of the true arrhythmia prevalence, given that review of ICD9 codes revealed an even higher rate of tachyarrhythmias compared to direct ECG review. As QT prolongation was common in our SLE patients, it is important to be vigilant about drug interactions and the electrophysiologic effects of various medications, such as antibiotics, in these patients. Further prospective study of arrhythmias, their outcomes, and underlying causative factors (such as medication use and disease severity) in SLE patients is warranted.

Table 1. Prevalence of Arrhythmias in SLE patients after Review of ECGs and ICD9 codes

	Type of Review, N (%)	
Arrhythmia	ECG, N=235	ICD9 Code, N=235
Tachyarrhythmia	13 (6)	35 (15)
Atrial fibrillation	7 (3)	21 (9)
Atrial flutter	2 (1)	6 (3)
Atrial tachycardia	2 (1)	8 (3)
Supraventricular tachycardia	2 (1)	3 (1)
Paroxysmal ventricular tachycardia	0 (0)	8 (3)
QT Prolongation	40 (17)	4 (2)
Sinus Tachycardia	42 (18)	Not Available
Sinus Bradycardia	34 (14)	Not Available
1st Degree AV Block	6 (3)	3 (1)

Disclosure: G. Myung, None; **L. J. Forbess**, None; **M. L. Ishimori**, None; **S. Chugh**, None; **D. Wallace**, None; **M. H. Weisman**, None.

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Stroke Risks Among U.S. Medicaid Recipients with Systemic Lupus Erythematosus, 2000–2006: Racial and Ethnic Variation. Medha Barbhaiya[1], Jose A. Gomez-Puerta[2], Hongshu Guan[1], Daniel H. Solomon[1], Joanne M. Foody[3], Graciela S. Alarcon[4] and Karen H. Costenbader[1]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, Boston, MA, [3]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, [4]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: SLE patients are at increased stroke risk, but racial/ethnic variation in risk has not been examined in a population-based study. We examined risks by race/ethnicity among SLE patients in Medicaid, the US medical insurance program for the poor. We investigated whether differential loss to follow-up and variation in mortality between racial/ethnic groups influenced Cox regression model estimates.

Methods: From the Medicaid Analytic eXtract (MAX) 2000–2006, containing all billing claims for patients from 47 U.S. states and Washington D.C., we identified patients 18–65 with prevalent SLE (≥3 SLE ICD-9 codes of 710.0, >30 days apart) and/or lupus nephritis (additional >2 codes for nephritis, renal insufficiency or failure). The index date was the date when SLE or lupus nephritis definition was met. We extracted age, sex, US region, calendar year, zip code area-based socioeconomic status (SES). Baseline comorbidities and SLE-specific risk index (Ward M, *J Rheum*, 2000) were from ICD-9 and CPT codes until index date. Within inpatient claims, ICD-9 codes identified fatal and non-fatal, ischemic and hemorrhagic strokes (PPV 83%, Andrade SE, *Pharmacoepi Drug Saf*, 2012). Stroke incidence rates (IR) per 1,000 person-years with 95% CIs were calculated for each racial/ethnic group. Multivariable-adjusted Cox regression models calculated cause-specific hazard ratios (HRcs) for stroke from index date through end of follow-up, censoring for death or loss to Medicaid follow-up, adjusting for covariates (**Table**). We also used Fine and Gray proportional hazards models

to calculate subdistribution HRs (HRsd), accounting for competing risks of death and loss to follow-up, adjusting for the same covariates.

Results: Of 42,221 SLE patients, 39,320 (93%) were female and 6,467 (15%) had lupus nephritis. Mean age at baseline was 38.13 (SD 12.29); 38% lived in the South, 23% in the West, 20% in the Northeast and 20% in the Midwest. Blacks represented 40%, Whites 38%, Hispanics 15%, Asian 5%, and Native Americans 2%. IRs were 10.02 (95% CI 9.44–10.64) per 1,000 person-years for all SLE patients, and 17.03 (95%CI 15.11–19.20) per 1,000 person-years for all lupus nephritis patients. After multivariable adjustment, Blacks had higher stroke risks (HRcs 1.31) than Whites. (**Table**) This risk remained similarly elevated in competing risks models (multivariable HRsd 1.36). Among lupus nephritis patients, stroke risks among Blacks vs. Whites were also high (multivariable HRsd 1.57). Stroke risks among other racial/ethnic groups did not significantly differ from those in White patients.

Conclusion: Among US Medicaid SLE and lupus nephritis patients, stroke IRs were high. After adjusting for sociodemographic and clinical factors, Blacks compared to Whites with SLE had 36% increased risks and those with lupus nephritis had 57% increased risks. Accounting for competing risks did not substantially affect these estimates.

Table Incidence Rates and Adjusted Subdistribution Hazard Ratios for Stroke Hospitalization among Medicaid patients with SLE in the US, from 2000-2006, by Race and Ethnicity

Race/Ethnicity	Total individuals	Number of events	Person-years	IR* (95% CI)	Multivariable-Adjusted Proportional Hazards HRcs (95% CI)¥	HRsd (95% CI)¥
White	16,219	352	40,204	8.76 (7.89–9.72)	1.0 (Ref)	1.0 (Ref)
Black	16,956	538	42,091	12.78 (11.74–13.91)	**1.32 (1.18–1.48)**	1.36 (1.17–1.59)
Asian	1,880	41	5,525	7.42 (5.46–10.08)	1.14 (0.87–1.50)	1.26 (0.89–1.80)
Hispanic	6,489	114	16,495	6.91 (5.75–8.30)	1.01 (0.85–1.20)	0.95 (0.75–1.20)
Native American	677	17	1,653	10.29 (6.40–16.55)	1.32 (0.90–1.93)	1.38 (0.82–2.33)

*IR=Incidence rate, events per 1,000 person-years.
¥HRcs=Cause-specific hazard ratio from Cox proportional hazards model; HRsd=Sub-distribution hazard ratio from Fine and Gray proportional hazards competing risks model. Multivariable models adjusted for age, sex, U.S. region of residence, calendar year, area-based SES, and baseline comorbidities (including history of angina, coronary artery bypass graft, coronary atherosclerosis, percutaneous coronary intervention, hypertension, smoking, obesity) and SLE-specific risk adjustment index.

Disclosure: M. Barbhaiya, None; **J. A. Gomez-Puerta**, None; **H. Guan**, None; **D. H. Solomon**, None; **J. M. Foody**, None; **G. S. Alarcon**, None; **K. H. Costenbader**, None.

1081

Prediction of Mortality Risk Related to Cerebrovascular Accidents in Patients with Systemic Lupus Erythematosus (SLE) vs Anti-Phospho-Lipid-Antibody (aPL) syndrome. Khushboo Sheth[1], Tapan Mehta[1], Sonam Puri[1], Ronak Soni[2] and Kathan Mehta[3]. [1]University of Connecticut, Farmington, CT, Farmington, CT, [2]Government Medical College, Surat, India, [3]University of Pittsburgh Medical Center, Pittsburgh, PA, Pittsburgh, PA.

Background/Purpose: It is well-established that patients with co-existent Systemic Lupus Erythematosus (SLE) and Anti-Phospho-Lipid-Antibody (aPL) syndrome are at increased risk of cerebrovascular accidents (CVA). Many studies have described that incidence of stroke is significantly higher in SLE and aPL syndrome; However, both these conditions may overlap. Hence, in this nation-wide study, after controlling the potential confounders we studied the individual impact of either condition (SLE and aPL syndrome) on mortality related to CVA.

Methods: We queried the Healthcare Cost and Utilization Project's (HCUP) Nationwide Inpatient Sample (NIS) between 2004 and 2010 and separated the hospitalizations due to or with stroke using ICD 9 diagnostic codes previously established by HCUP. Among this population, we examined the patients with SLE and patients with aPL syndrome and compared their risk of mortality to the all stroke population using the logistic regression model. The model was controlled for confounders which included age, sex, atrial fibrillation, chronic kidney disease, diabetes mellitus, rheumatoid arthritis, chronic rheumatic heart disease and diseases of endocardium. Using SAS 9.2, survey procedures were used to identify multivariate predictors of stroke.

Results: A total of 1,799,560 (weighted N= 8,874,475) who were hospitalized with stroke were available for analysis out of which 6,890 (weighted N= 33,882) had SLE and 13,769 (weighted N=68,069) had aPL syndrome. On univariate analysis, patients with SLE had 4.43%mortality as compared to 4.35% in patients without SLE ($p = 0.47$); and patients with aPL syndrome had 11.37% mortality as compared to 4.3% in patients without aPL syndrome ($p<0.001$). After controlling for confounders mentioned above, com-morbid SLE had no impact on in-hospital mortality (Odds Ratio (OR)=0.93, Confidence Interval (CI)=0.81–1.06, $p = 0.2888$). Whereas, co-morbid aPL syndrome was associated with significantly increased risk of in-hospital mortality (OR= 2.77, CI=2.59–2.97, $p < 0.0001$), in patients with stroke.

Table 1: Multivariable predictors of mortality in the study population for stroke (N=1,799,560)

Variables	Model OR with 95% CI	P value
Age	1.017 (1.015–1.019)	<0.0001
Female Gender	1.065 (1.046–1.084)	<0.0001
Race(African American vs Caucasian)	1.122 (1.088–1.157)	<0.0001
CCI	1.213 (1.203–1.223)	<0.0001
Systemic Lupus Erythematosus	0.929 (0.810–1.065)	0.2888
Antiphosholipidantibody syndrome	2.772 (2.590–2.968)	<0.0001
Chronic Kidney Disease	2.064 (1.998–2.132)	<0.0001
Atrial fibrillation	1.921 (1.878–1.964)	<0.0001
Diseases of endocardium	0.791 (0.764–0.819)	<0.0001
Rheumatic heart disease	0.762 (0.720–0.806)	<0.0001
Rheumatoid Arthritis	0.718 (0.665–0.776)	<0.0001
Scleroderma	1.284 (0.999–1.650)	0.0508
Diabetes Mellitus	0.580 (0.566–0.594)	<0.0001
Teaching Hospital Status	1.175 (1.116–1.237)	<0.0001

*CCI = Charlson Co-morbidity Index.

Conclusion: Though SLE and aPL Syndrome overlap significantly, we found in our analysis that after controlling the significant confounders, SLE alone is not an independent risk factor for increasing mortality risk among the CVA population. Whereas, aPL Syndrome is an independant predictor of increased risk of mortality in patients with CVA.

Disclosure: K. Sheth, None; **T. Mehta**, None; **S. Puri**, None; **R. Soni**, None; **K. Mehta**, None.

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Risk of Intra Cranial Hemorrhage among Patients with Anti-Phospho-Lipid-Antibody (aPL) syndrome vs Systemic Lupus Erythematosus (SLE) in Stroke Population: A Nationwide Analysis. Tapan Mehta[1], Khushboo Sheth[1], Ronak Soni[2], Sonam Puri[1] and Kathan Mehta[3]. [1]University of Connecticut, Farmington, CT, Farmington, CT, [2]Government Medical College, Surat, India, [3]University of Pittsburgh Medical Center, Pittsburgh, PA, Pittsburgh, PA.

Background/Purpose: Central nervous system involvement is common in Systemic Lupus Erythematosus (SLE) and was first described in 1873. Though ischemic involvement is more common than Intra-Cerebral Hemorrhage (ICH) in SLE, hemorrhagic involvement is more life threatening and disabling. Several studies have shown that SLE patients with ICH present with higher frequency of Anti-Phospho-Lipid-Antibody (aPL) syndrome. In our study we tried to investigate if SLE or aPL syndrome independently predicts risk of ICH in CVA.

Methods: We queried the Healthcare Cost and Utilization Project's (HCUP) Nationwide Inpatient Sample (NIS) between 2004 and 2010 and separated the hospitalizations due to or with stroke using ICD 9 diagnostic codes previously established by HCUP. Among this population, we examined the patients with SLE and patients with aPL syndrome and compared their risk of ICH to the all stroke population using the logistic regression model. The model was controlled for confounders which included age, sex, atrial fibrillation, chronic kidney disease, diabetes mellitus, rheumatoid arthritis, chronic rheumatic heart disease and diseases of endocardium. Using SAS 9.2, survey procedures were used to identify multivariate predictors of stroke.

Results: A total of 1,799,560 (weighted N= 8,874,475) who were hospitalized with stroke were available for analysis out of which 6,890 (weighted N= 33,882) had SLE and 13,769 (weighted N=68,069) had aPL syndrome. On univariate analysis, among patients with SLE 1.41% developed ICH as compared to 1.29% in patients without SLE ($p = 0.06$); and among patients with aPL syndrome 3.5% developed ICH as compared to 1.28% in patients without aPL syndrome ($p<0.001$). After controlling for confounders mentioned above, co-morbid SLE was associated with decreased risk of having ICH (Odds Ratio (OR)= 0.68, Confidence Interval (CI)=0.53–0.89, $p < 0.0039$) in patients with stroke. Whereas, co-morbid aPL was associated with increased risk of having ICH (OR= 1.93, CI=1.72–2.17, $p<0.0001$), in patients with stroke.

Table 1: Multivariable predictors of ICH in the study population for stroke (N= 1,799,560)

Variables	Model OR with 95% CI	P value

Age	0.984 (0.982–0.985)	<0.0001
Female Gender	1.039 (1.001–1.079)	0.0434
Race(African American vs Caucasian)	1.154 (1.083–1.229)	<0.0001
CCI	1.097 (1.081–1.113)	<0.0001
Systemic Lupus Erythematosus	0.683 (0.528–0.885)	0.0039
Antiphosholipidantibody syndrome	1.932 (1.716–2.176)	<0.0001
Chronic Kidney Disease	0.909 (0.864–0.955)	0.0002
Atrial fibrillation	1.583 (1.512–1.658)	<0.0001
Diseases of endocardium	0.706 (0.658–0.757)	<0.0001
Rheumatic heart disease	0.857 (0.774–0.948)	0.0028
Rheumatoid Arthritis	0.778 (0.679–0.891)	0.0003
Scleroderma	0.744 (0.428–1.294)	0.2951
Diabetes Mellitus	0.631 (0.606–0.656)	<0.0001
Teaching Hospital Status	2.252 (2.024–2.507)	<0.0001

*CCI = Charlson Co-morbidity Index.

Conclusion: In addition to the understanding of increased risk of CVA in SLE and aPL Syndrome patients, further understanding of the nature of the cerebrovascular disease can influence treatment strategies. Our study showed that SLE patients are at decreased risk of hemorrhagic stroke in comparison to general stroke population. However, aPL Syndrome patients are at increased risk of hemorrhagic stroke in comparison to general stroke population. This suggests that aPL component of the disease spectrum predisposes the patients to ICH.

Disclosure: T. Mehta, None; **K. Sheth**, None; **R. Soni**, None; **S. Puri**, None; **K. Mehta**, None.

ACR/ARHP Poster Session B
Epidemiology and Public Health (ARHP)
Monday, November 17, 2014, 8:30 AM–4:00 PM

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The Relation of Step Length to MRI Features of Osteoarthritis in the Patellofemoral Joint: The MOST Study. Joshua Stefanik[1], K. Douglas Gross[2], David T. Felson[2], Jingbo Niu[1], Daniel K. White[2], Ali Guermazi[2], Frank Roemer[3], C.E. Lewis[4], Neil A. Segal[5], Michael Nevitt[6] and Cara Lewis[1]. [1]Boston University, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Klinikum Augsburg, Augsburg, Germany, [4]University of Alabama at Birmingham, Birmingham City, AL, [5]University of Iowa, Iowa City, IA, [6]UCSF, San Francisco, CA.

Background/Purpose: Patellofemoral joint (PFJ) osteoarthritis (OA) is a common source of pain and there is little evidence for rehabilitation treatment. Gait retraining treatments are effective in reducing pain in younger individuals with patellofemoral pain. Compared to self-selected step length, increased step length is related to increased PFJ stress. If step length affects PFJ stress, then individuals with a longer step length may be at increased risk of PFJ disease. The purpose of this study was to investigate the relation of step length to prevalent/worsening structural damage in the PFJ.

Methods: The Multicenter Osteoarthritis (MOST) Study is a NIH-funded cohort study of 3,026 individuals with or at risk for knee OA. Participants had MRI of their knee and two musculoskeletal radiologists assessed cartilage morphology and bone marrow lesions (BMLs) in the PFJ at the 60 and 84-month study visit. Spatial-temporal gait parameters were collected using the Gaitrite system at the 60-month visit. Step length was measured as the distance from heel center of footprint to heel center of previous footprint from the other foot. Step length was divided into quintiles and we determined the relation of step length to **prevalent** full-thickness cartilage loss and BMLs in PFJ subregions using logistic regression with generalized estimating equations, adjusting for age, sex, BMI and leg length (measured from long limb films from center of femoral head to center of talus). Because knee pain from structural damage could cause a person to shorten their step length and reduce PFJ stress, in order to examine causal effects of step length, we determined the relation of step length to **incident** cartilage loss and BMLs from 60 to 84-months in PFJ subregions without any cartilage loss or BMLs at 60-months. In secondary analyses we normalized step length by leg length and and also removed knees with frequent knee pain at 60 months.

Results: 4212 patellar and anterior femur subregions from 1132 knees were included. The mean age and BMI at the 60-month visit were 66.9 (±7.5) years and 29.6 (±4.7) kg/m^2, respectively, and 62% were female. While subregions in knees with the longest step length had the lowest *prevalence* of full-thickness cartilage loss, there was no association when adjusting for potential confounding variables. There was no association between step length and *incident* PFJ cartilage loss. Compared to subregions in knees with short step length, those with the longest step length were associated with 0.72 (0.52, 0.98) times the odds of *prevalent* BMLs in the PFJ (Table). There was no association between step length and *incident* BMLs. Similar results were seen in the secondary analysis.

Conclusion: Cartilage loss and BMLs were most common in knees with short step length but there was no relation of step length to worsening of cartilage or BMLs longitudinally. Individuals may shorten their step length to reduce PFJ stress.

Relation of step length quintiles to *prevalent* full-thickness cartilage loss and BMLs in subregions of the PFJ

	Full-thickness cartilage loss (n= 4212 subregions)			BMLs (n=4212 subregions)		
Step Length	**Prevalence**	**Crude OR**	**Adjusted OR***	**Prevalence**	**Crude OR**	**Adjusted OR***
Quintile 5 (Long Step)	100/844 (11.9%)	0.61 (0.43, 0.88)	0.94 (0.61, 1.4)	181/844 (21.5%)	0.66 (0.50, 0.87)	0.72 (0.52, 0.98)
Quintile 4	98/840 (11.7%)	0.60 (0.42, 0.86)	0.80 (0.56, 1.1)	186/840 (22.1%)	0.69 (0.53, 0.90)	0.71 (0.54, 0.95)
Quintile 3	123/844 (14.6%)	0.78 (0.56, 1.1)	0.90 (0.63, 1.3)	225/844 (26.7%)	0.88 (0.68, 1.1)	0.87 (0.66, 1.1)
Quintile 2	109/844 (12.9%)	0.68 (0.48, 0.96)	0.74 (0.52, 1.1)	254/844 (30.1%)	1.0 (0.81, 1.3)	1.0 (0.80, 1.3)
Quintile 1 (Short Step)	151/840 (18.0%)	1.0 (Reference)	1.0 (Reference)	245/840 (29.2%)	1.0 (Reference)	1.0 (Reference)
		p trend= 0.007	p trend=0.8		p trend <0.0001	p trend= 0.006

Relation of step length quintiles to *incident* any cartilage loss and any BMLs from 60 to 84 months in subregions of the PFJ

	Cartilage loss (n= 2499 subregions)			BMLs (n=2977 subregions)		
Step Length	**Prevalence**	**Crude OR**	**Adjusted OR***	**Prevalence**	**Crude OR**	**Adjusted OR***
Quintile 5 (Long Step)	26/554 (4.7%)	0.93 (0.51, 1.7)	0.87 (0.44, 1.7)	30/622 (4.8%)	0.89 (0.52, 1.5)	1.2 (0.66, 2.3)
Quintile 4	31/526 (5.9%)	1.2 (0.65, 2.2)	1.1 (0.61, 2.1)	42/604 (7.0%)	1.3 (0.80, 2.1)	1.6 (0.94, 2.8)
Quintile 3	21/481 (4.4%)	0.87 (0.46, 1.6)	0.82 (0.44, 1.5)	27/594 (4.6%)	0.84 (0.49, 1.4)	0.93 (0.54, 1.6)
Quintile 2	27/491 (5.5%)	1.1 (0.60, 2.0)	1.1 (0.58, 1.9)	35/582 (6.0%)	1.1 (0.67, 1.9)	1.2 (0.71, 2.0)
Quintile 1 (Short Step)	22/447 (4.9%)	1.0 (Reference)	1.0 (Reference)	31/575 (5.4%)	1.0 (Reference)	1.0 (Reference)
		p trend=0.9	p trend=0.8		p trend=0.9	p trend= 0.3

*Adjusted for age, sex, bmi, leg length

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1084

Obesity Is a Risk Factor for Depression in Systemic Lupus Erythematosus (SLE). Patricia P. Katz[1], Stephanie Rush[2], Laura Trupin[2], Jennifer Barton[2], Gabriela Schmajuk[2], Jinoos Yazdany[2], Chris Tonner[2] and Mary Margaretten[2]. [1]University of California, San Francisco, CA, [2]University of California, San Francisco, San Francisco, CA.

Background/Purpose: General population studies have found significant relationships between obesity and depression, including identifying obesity as a risk factor for onset of depression. In SLE, rates of depression are high, and depression can be a neuropsychiatric manifestation of SLE. The role of obesity as an independent risk factor for depression in SLE has not been studied. In this analysis, we examine the risk of depression onset for obese and non-obese women with SLE.

Methods: Analyses use data from the Lupus Outcomes Study (2004–2014) obtained through annual structured telephone interviews. All participants have physician-confirmed SLE. Depressive symptoms were measured with the Center for Epidemiologic Studies Depression scale (CESD). Possible and probable depression were estimated using validated SLE-specific cut-points (20 and 24, respectively). Body mass index (BMI) was calculated from self-reported height and weight, and obesity was defined using a validated SLE-specific BMI cut-point of ≥26.8. (A sensitivity analysis also examined the standard BMI obesity cut-point of 30.) Cox proportional hazard models were used to estimate the risk of becoming depressed associated with obesity at baseline. Models were calculated for both possible and probable depression. Multivariate analyses adjusted for age, race (white non-Hispanic vs. other), baseline disease activity (Systemic Lupus Activity Questionnaire, SLAQ), current smoking, prednisone use, and baseline functioning (SF-36 Physical Component Score). Only women were included in the analysis because the number of men was relatively small. Women who had BMI <18.5 or who met the depression criterion at baseline were excluded from analysis.

Results: Data from 718 women were available for analysis, of whom 32 had BMI<18.5. At baseline, 211 met the criterion for possible depression (CESD ≥ 20) and 171 for probable depression (CESD ≥ 24), leaving 471 and 515 in the analyses for possible and probable depression, respectively. BMIs ranged from 18.6 — 54.9. Mean follow-up time was 9 years (range 2–11 years). In the analysis for possible depression, 31.6% of those who were not obese became depressed, compared to 48.1% of those who were obese (table). The adjusted HR (95% CI) for possible depression associated with obesity was 1.56 (1.15, 2.11). In the analysis of probable depression, 25.9% of those not obese became depressed compared to 42.6% of those who were

obese. The adjusted HR (95% CI) for probable depression was 1.69 (1.23, 2.30). Using the standard BMI cut-point for obesity yielded similar results.

Conclusion: Obesity appears to be a risk factor for development of depression among women with SLE, even after controlling for disease activity and other relevant factors. This is a clinically important finding, as obesity is modifiable, and reducing obesity is likely to lead to additional health benefits such as reduced cardiovascular disease.

Risk of depression onset associated with obesity* among women with SLE

	Possible depression (CESD ≥20)	Probable depression (CESD ≥24)
Total n for analysis	471	515
Obese at baseline	38.9%	39.2%
Became depressed		
Not obese	31.6% (91)	25.9% (81)
Obese	48.1% (88)	42.6% (86)
Multivariate HR (95% CI) for obesity†	1.56 (1.15, 2.11)	1.69 (1.23, 2.30)

Women who met criteria for depression at baseline were excluded.
* Obesity defined as BMI ≥ 26.8.
† HR = Hazard ratio. Multivariate model adjusted for age race, baseline disease activity (SLAQ), smoking, and baseline physical functioning.

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1085

Trajectories and Predictors of Physical Activity over Two Years in Rheumatoid Arthritis. Ingrid Demmelmaier[1], Alyssa B. Dufour[2], Birgitta Nordgren[1] and Christina H. Opava[1]. [1]Karolinska Institutet, Huddinge, Sweden, [2]Hebrew SeniorLife & Boston Univ, Boston, MA.

Background/Purpose: Although physical activity is crucial for managing symptoms and comorbidities in rheumatoid arthritis (RA), the majority of the RA population does not reach recommended health-enhancing physical activity levels. Longitudinal studies are scarce and more knowledge is needed about predictors of different patterns of physical activity over time in large RA samples. The aim was to, within a large well-defined sample of persons with rheumatoid arthritis, identify and describe groups demonstrating different trajectories of physical activity over two years and to identify baseline predictors for being in each specific group.

Methods: This longitudinal study used data from the Swedish Quality Registries and a questionnaire covering sociodemographic, disease-related, psychosocial and physical activity variables. Physical activity was assessed by the International Physical Activity Questionnaire as total weekly hours of vigorously intense activity, moderately intense activity and walking. A total of 2752 participants responding to at least two out of three questionnaires at baseline, 12 months and 24 months were aged 18–75 years, diagnosed with RA according to the ACR criteria and independent in daily living (Stanford Health Assessment Questionnaire ≥ 2.0). K-means cluster analysis was used to identify three trajectories of hours of weekly physical activity. Multinomial logistic regression was used to identify predictors of trajectory membership. Multiple imputation was used to impute missing data in potential predictors, which included sociodemographic, disease-related, psychosocial and physical activity variables.

Results: We identified three patterns of physical activity: The "Stable High" group performed on average 25 hours of physical activity per week (n=272), the "Decreasing" group went from 22 to eight hours per week (n=564) and the "Stable Low" performed three hours of physical activity per week (n=1916). Predictors of being in the "Stable High" group versus the other two groups were male gender and already established health-enhancing physical activity at baseline. Increased age predicted being in the "Decreasing" group versus the other two groups. Predictors of being in the "Stable Low" group versus the other two groups were female gender, more activity limitation, lower self-efficacy for exercise and not having established health-enhancing physical activity at baseline. For detailed results, see Table 1.

Conclusion: The results indicate that physical activity levels are still low in the RA population. Different trajectories of physical activity over time exist and are possible to identify, with each trajectory being associated with a unique set of predictors. Modifiable predictors to improve physical activity include activity limitation and self-efficacy for exercise.

Table 1 Baseline predictors of being in the Stable High (n = 272), Decreasing (n = 564) and Stable Low (n = 1916) physical activity groups. Odds ratios (OR) with 95% confidence intervals (CI)

Baseline predictors	Stable High vs Stable Low OR (95% CI)	Stable High vs Decreasing OR (95% CI)	Decreasing vs Stable Low OR (95% CI)
Gender: Women vs men	0.50 (0.37–0.67)	0.70 (0.51–0.98)	0.71 (0.57–0.89)
Age, years:			
35–54 vs 18–34			2.18 (1.10–4.31)
>55 vs 18–34		0.34 (0.14–0.81)	2.70 (1.38–5.28)
Activity limitation, HAQ:			
>1.0 vs 0	0.58 (0.35–0.96)		0.41 (0.28–0.60)
Self-efficacy for exercise, ESES:			
middle vs lowest tertile	1.49 (1.04–2.15)		
highest vs lowest tertile	1.77 (1.22–2.56)		1.54 (1.19–2.00)
Social support for exercise from friends, SSEB:			
middle vs lowest tertile		0.61 (0.37–0.99)	
Maintained health-enhancing physical activity, ESAI:			
Yes vs no	2.9 (2.03–4.15)	1.53 (1.03–2.26)	1.90 (1.41–2.58)

HAQ = Stanford Health Assessment Questionnaire, ESES = Exercise Self-Efficacy Scale, SSEB = Social Support for Exercise Behaviors, ESAI = Exercise Stage Assessment Instrument

Disclosure: I. Demmelmaier, None; **A. B. Dufour**, None; **B. Nordgren**, None; **C. H. Opava**, None.

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The Effect of Foot Pain on Mobility Disability in Older Adults: The Framingham Foot Study. Alyssa B. Dufour[1], Patricia P. Katz[2], Yvonne M. Golightly[3], Arunima Awale[4] and Marian T. Hannan[5]. [1]Hebrew SeniorLife, Harvard Medical School & Beth Israel Deaconess Medical Center, Boston, MA, [2]University of California, San Francisco, San Francisco, CA, [3]University of North Carolina Dept of Epidemiology, Chapel Hill, NC, [4]Hebrew SeniorLife, Boston, MA, [5]Institute for Aging Research, Hebrew SeniorLife, Dept. of Medicine Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Background/Purpose: While lower extremity function is thought to affect mobility, little is known of the influence of foot structure or function upon mobility limitations. We evaluated the associations of foot structure and foot function with mobility limitations in community-dwelling older men and women.

Methods: Framingham Foot Study participants (2002–2008) with performance measures of mobility limitations were included in this cross-sectional analysis. Mobility limitations was assessed using the Short Physical Performance Battery (SPPB), a composite of 3 timed performance tests (4-meter walk (s), chair stands (s), and balance test) with each test scored on a scale of 0 to 4 (total score range 0–12, higher score = better function). Previously, SPPB scores have predicted physical limitations, disability and mortality. We dichotomized SPPB as 1–9 to indicate mobility limitations and 10–12 as good mobility. We also examined quartiles of chair stand and walk time. Foot function while walking (pronated, supinated, normal) and weight-bearing arch structure (low, high, normal arch) were defined using a Tekscan matscan pressure system. Age, sex, body mass index (BMI; <30, ≥ 30 kg/m^2), current smoker (y/n) and depression (CES-D scale) were also obtained. Sex-specific multivariate logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the association between foot structure and function with mobility limitations, adjusting for factors above.

Results: In 556 men and 700 women, average age was 70 yrs ($\pm$10.8) and BMI was 28 ($\pm$5.2). 16% had mobility limitations, 30% had high arched and 27% had low arched foot structure; 33% had pronated and 27% had supinated foot function. Foot function was not associated with mobility limitations. In women only, low arched foot structure was associated with increased odds of mobility limitations (SPPB; OR=2.27, p=0.005) after adjustment (Table). No associations were seen between foot structure or function and chair stand time (ORs= 0.8–1.1, all p>0.4). In quartiles of walk time, men in the 3rd quartile, compared to the lowest (fastest), were less likely to have a high arch foot structure (OR=0.53) and supinated foot function (OR=0.51). Women with a low arched foot were less likely to be in the 4th quartile (slowest walkers) compared to the fastest walkers and women with a pronated foot function were more likely to be in the 3rd quartile of walking speed compared to the fastest walkers.

Conclusion: Specific components of foot structure and function were associated with mobility limitations in our study, albeit with inconsistent patterns between men and women. Given these results, future work might examine specific regions of foot pressures and time-integral measures in order to drill down to biomechanical mechanisms.

Table. Odds Ratios and 95% Confidence Intervals for the Association* between SPPB and Quartiles of Measured Walk Time with Foot Structure and Foot Function in Men and Women of the Framingham Foot Study.

				Men	Women
SPPB (1–9 versus 10–12)	Foot Structure	High Arch		0.59 (0.31, 1.12)	0.783 (0.45, 1.37)
		Low Arch		0.87 (0.47, 1.61)	2.265 (1.28, 4.03)
	Foot Function	Over-Supinated		1.63 (0.86, 3.09)	0.772 (0.47, 1.28)
		Over-Pronated		0.77 (0.42, 1.42)	0.826 (0.43, 1.57)
Measured Walk	Foot Structure	High Arch	Q2 (3.85–4.53) vs. Q1 (2–3.84)	0.73 (0.42, 1.29)	0.926 (0.52, 1.67)
			Q3 (4.54–5.16) vs. Q1 (2–3.84)	0.53 (0.29, 0.94)	1.103 (0.61, 2.00)
			Q4 (5.18–16.88) Vs. Q1 (2–3.84)	0.61 (0.34, 1.12)	1.745 (0.99, 3.08)
		Low Arch	Q2 (3.85–4.53) vs. Q1 (2–3.84)	0.98 (0.54, 1.77)	0.628 (0.38, 1.03)
			Q3 (4.54–5.16) vs. Q1 (2–3.84)	0.77 (0.42, 1.39)	1.084 (0.67, 1.76)
			Q4 (5.18–16.88) vs. Q1 (2–3.84)	0.88 (0.48, 1.59)	0.474 (0.27, 0.83)
	Foot Function	Supinated	Q2 (3.85–4.53) vs. Q1 (2–3.84)	0.81 (0.47, 1.37)	1.678 (0.95, 2.95)
			Q3 (4.54–5.16) vs. Q1 (2–3.84)	0.51 (0.29, 0.89)	1.188 (0.65, 2.17)
			Q4 (5.18–16.88) vs. Q1 (2–3.84)	0.73 (0.42, 1.29)	1.091 (0.59, 2.00)
		Pronated	Q2 (3.85–4.53) vs. Q1 (2–3.84)	0.61 (0.32, 1.16)	1.374 (0.84, 2.25)
			Q3 (4.54–5.16) vs. Q1 (2–3.84)	0.73 (0.40, 1.35)	1.94 (1.20, 3.15)
			Q4 (5.18–16.88) vs. Q1 (2–3.84)	0.93 (0.50, 1.76)	1.285 (0.78, 2.11)

*Adjusted for age, BMI, CES-D score, current smoking

Disclosure: A. B. Dufour, None; **P. P. Katz**, None; **Y. M. Golightly**, None; **A. Awale**, None; **M. T. Hannan**, None.

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The Prevalence of Knee Arthritis and Associated Self-Reported Limitation of Activity in Chinese Populations. Xu Tang Sr., Ke TAO, Qiang LIU, Xu WU, Zheng Ming Cao and Jian Hao rLin. Arthritis Institute, People's Hospital, Peking University, Beijing, China.

Background/Purpose: To estimate the prevalence of knee arthritis and assess the association between knee arthritis and self-reported limitation of activity in Chinese Populations.

Methods: Populations: China Health and Retirement Longitudinal Study (CHARLS) is a population-based longitudinal survey among Chinese retired populations. Persons age ≥45 years and their spouse were interviewed in 450 randomly selected communities among China during 2011–2012.

Questionnaire and physical examination: The questionnaire and physical examination were used in this survey. Trained health professionals went door to door to administer the survey questionnaires and physical examination. We applied the information of "gender, age, living area, height, weight, self-reported knee pain and diagnosis of arthritis/rheumatism by a physician in the past" for the advanced analysis of knee arthritis prevalence. "Does the respondents have any difficulty in running or jogging about 1 km?/ walking 1 km?/ walking 100 meters?/ getting up from a chair?/ climbing upstairs?/ kneeling?" was employed for self-reported limitation assess.

Knee arthritis definition: We defined knee arthritis as "if one reported had knee pain and had a diagnosis of arthritis/rheumatism by a physician in the past".

Statistical analysis: The prevalence of knee arthritis by population groups was calculated, and the association between knee arthritis and the self-reported limitation of activity was assessed. Logistic regression analysis was used for statistical analysis.

Results: In 17708 participants (men: 47.9% vs women: 52.1%), the overall prevalence of knee arthritis was 9.1%, with women 1.9 times higher than men (95% CI 1.70–2.17, P<0.01). The prevalence of knee arthritis in the rural areas was approximately twice as much as urban regions in China (95% CI 0.46–0.60, P<0.01). The current knee arthritis structure of Chinese residents had been separated by a geographic structure (Qinling Mountains-Huaihe River Line) into two clusters: the South and North, and populations in South China had knee arthritis around 1.5 times the number of those in North China (95% CI 1.36–1.73, P<0.01). Along with the growth of the age and BMI (body mass index), the percentages of knee arthritis climbed gradually (P<0.01). Considering "running/walking distance, getting up from a chair, climbing upstairs or kneeling", subjects with knee arthritis had more difficulty in self-reported limitation (P<0.01).

Conclusion: The prevalence of knee arthritis in China is moderate, with women, populations in the rural area and geographic structure (South China) all the influencing factors of morbidity. It also indicates that growth of age and BMI contributes to the increase of knee arthritis rate and knee arthritis and self-reported limitation of activity demonstrates great association. This study provides a fundamental demographic profile for prevalence of knee arthritis and better to understand the knee arthritis and associated self-reported limitation of activity in Chinese populations.

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Socioeconomic Disparities in Health Outcomes Among Individuals with, or at Risk for, Osteoarthritis from the United States: Data from the Osteoarthritis Initiative. Antoine A. Baldassari[1], Todd Schwartz[1], Rebecca J. Cleveland[1], Joanne M. Jordan[2] and Leigh F. Callahan[3]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]University of North Carolina Dept of Epidemiology, Chapel Hill, NC, [3]University of North Carolina, Chapel Hill, NC.

Background/Purpose: Socioeconomic disparities in health outcomes among people with osteoarthritis are well documented, with some key limitations: existing studies limit their analyses to few outcome variables at a time and often evaluate socioeconomic status (SES) as a dichotomous exposure. As a result, there remains substantial uncertainty regarding the extent and nature of those health inequities. The data from the Osteoarthritis Initiative (OAI) allow us to comprehensively assess socioeconomic disparities in health outcomes within a large group of individuals at risk for or diagnosed with knee osteoarthritis.

Methods: This study includes 4081 OAI participants with full data on demographics, SES and health behaviors. Health outcomes included SF-12 measures of physical (PCS) and mental (MCS) health, the Center for Epidemiological Studies Depression scale (CESD), Western Ontario and McMaster Universities Arthritis Index (WOMAC) subscales for disability, pain and stiffness, Knee Injury and Osteoarthritis Outcome Scores (KOOS) for function and quality of life, and the amount of time needed to complete 20m and 400m walks. Our analyses focused on baseline measurements and used ordinary least squares regressions to evaluate the associations of health indicators with categories of family income and education, included separately and then simultaneously. All analyses were adjusted for race, sex and age, and standard errors were clustered by study site. Linear trends were assessed across income and education categories using linear contrasts.

Results: 58% of sample respondents were women, 18% self-identified as African-Americans, and the mean age was 61 years. Participants had an average BMI of 29kg/m^2, and nearly half (45%) ever smoked. 30% of all sample participants held a graduate degree and 24% reported family earnings over $100,000/year. There were graded associations of education and income with each of the health outcome measures, adjusted for age, race and sex (Table 1), with the exception that individuals who only partially attended graduate school experienced worse self-reported health than those with a college degree but no postgraduate schooling. Further adjustments for pack-years smoked, body mass index, alcohol use, comorbidities, marital status, current employment and study site did not substantially change the associations, while education and income remained independently associated with health outcomes when simultaneously included in models (Data not shown).

Conclusion: The health of OAI participants varied strongly according to their SES, in a gradient pattern of worsening health with lower levels of income and education. This may be the most comprehensive study of the health socioeconomic gradient in a population with OA or at risk for OA. Differences were not explained by health behaviors, and further studies should explore pathways related to the patterns described herein.

Table 1: Differences in adjusted means (from reference)[1] for the associations of education and income with health outcome measures in the Osteoarthritis Initiative (N=4081), in separate ordinary least squares regression models adjusted for age, race, and sex

	SF-12			WOMAC[1]			KOOS		Walk t (s)	
	PCS[2]	MCS[3]	CESD	Pain	Disability	Stiffness	Function	QOL[4]	20m	400m
Income										
<$10K-25K	−11.02‡	−7.76‡	9.12‡	3.82‡	12.71‡	1.28‡	−18.83‡	−15.94‡	2.51‡	38.84‡
$10K-25K	−4.79‡	−4.45‡	5.27‡	1.57‡	5.04‡	0.57‡	−8.87‡	−7.17‡	1.62‡	28.29‡
$25K-50K	−3.37‡	−2.59‡	2.93‡	1.01‡	3.07‡	0.45‡	−6.54‡	−4.74‡	0.92‡	17.61‡
$50K-100K	−1.19†	−1.07†	1.28‡	0.29*	0.92*	0.19†	−2.65*	−2.07*	0.30†	7.21†
linear trend (p)[6]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Education										
< High-school	−7.24‡	−7.13‡	8.14‡	3.10‡	9.14‡	0.88‡	−12.24‡	−10.23‡	2.74‡	44.53‡
High-school	−3.58‡	−1.92‡	3.26‡	1.90‡	5.38‡	0.65‡	−11.32‡	−6.81‡	0.97‡	17.58‡
Some college	−3.42‡	−1.29‡	1.87‡	1.50‡	4.82‡	0.58‡	−8.73‡	−6.48‡	0.78‡	13.37‡
College	−0.66	−0.36	0.56*	0.32*	0.9	0.15*	−1.99	−0.84	0.23	5.61*
Some grad. school	−1.73†	−0.65	1.31†	0.79‡	2.44‡	0.24*	−5.01†	−4.22†	0.04	2.85
linear trend (p)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.005	<0.001	<0.001	<0.001

[1] Referent categories are: ≥$100,000 (income) and graduate school (education).
[2] WOMAC scores are highest of both knees.
[3] PCS: physical component summary.
[4] MCS: mental component summary.
[5] QOL: Quality of life.
[6] Linear trend evaluated using linear contrasts.
*: p<0.05, †: p<0.01, ‡: p<0.001
Standard errors account for clustering by study site.

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Trajectories of Disability over Time Among Patients with Systemic Sclerosis. Sarah D. Mills[1], Rina S. Fox[1], Shadi Gholizadeh[1], Scott C. Roesch[1], Murray Baron[2], Marie Hudson[3], Russell Steele[3], Brett D. Thombs[3] and Vanessa L. Malcarne[4]. [1]SDSU/UCSD Joint Doctoral Program in Clinical Psychology, San Diego, CA, [2]McGill University, Montreal, QC, [3]Jewish General Hospital, Montreal, QC, [4]San Diego State University, San Diego, CA.

Background/Purpose: Systemic Sclerosis (SSc) is often associated with disability, which worsens over time. However, there is considerable heterogeneity in the rate of patients' disability progression. The aim of the present study was to identify homogenous subpopulations of SSc patients with distinct trajectories of change in disability over a three-year period.

Methods: The sample included patients with limited and diffuse SSc (N = 1,125) participating in the Canadian Scleroderma Research Group Registry. As part of the Registry, patients are scheduled for annual follow-up visits. Patients with and without follow-up visits were included to account for potentially informative patient drop out. Growth mixture modeling (GMM) with robust maximum likelihood estimation was completed to identify groups of patients with distinct trajectories of disability over a three-year period, as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI; range: 0 (no disability) – 3 (severe disability)). Multinomial logistic regression was used to identify baseline sociodemographic and clinical variables that predicted membership in the latent growth trajectory classes.

Results: Considering fit indices (AIC, sBIC, BLRT) and substantive interpretation (class proportions, entropy), the GMM analysis identified three distinct groups of patients based on their disability trajectories. Class 1 was comprised of 53.4% of the total sample, and Classes 2 and 3 were comprised of 35.3%, and 11.2% of the total sample, respectively. Based on trajectories of HAQ-DI scores the groups were named: Minimal Disability-Increasing (Class 1; baseline HAQ-DI:. 27), Moderate Disability-Stable (Class 2; baseline HAQ-DI: 1.20), and Severe Disability-Stable (Class 3; baseline HAQ-DI: 2.04). In Class 1, HAQ-DI scores increased by. 12 over three years. Patients in Class 3 had more finger ulcers, more breathing problems, and more gastrointestinal problems than patients in Class 2 or Class 1. In addition, patients in Class 3 were of older age, had shorter disease duration, and were more likely to be female and have diffuse disease than patients in Class 1. Patients in Class 2, when compared to Class 1, had more finger ulcers, breathing problems, and severe Raynaud's phenomenon, and were more likely to be older, female, and have diffuse disease.

Conclusion: Disability trajectories are not uniform across patients with SSc. Overall, patients with low baseline disability scores and disability progression had fewer finger ulcers, breathing problems, and gastrointestinal problems, less severe Raynaud's phenomenon, were of younger age, male, had longer disease duration, and limited disease in comparison to the moderate and severe disability groups. The moderate and severe disability groups did not report significant disability progression, suggesting that for at least some patients with SSc, disability may reach a peak and then remain stable overtime.

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Association of Objectively Measured Physical Activity and Metabolic Syndrome Among Adults with Osteoarthritis in the United States. Shao-Hsien Liu[1], Charles Eaton[2] and Kate Lapane[3]. [1]Clinical and Population Health Research Program, Graduate School of Biomedical Science, University of Massachusetts Medical School, Worcester, MA, [2]Departments of Family Medicine and Epidemiology, Warren Alpert Medical School, School of Public Health, Brown University, Providence, RI, [3]Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Metabolic syndrome increases the risk of osteoarthritis (OA). The accumulation of components of the metabolic syndrome is associated with a gradual increase in the risk of development and progression of knee OA. Physical activity may be a viable strategy to decrease the prevalence of metabolic syndrome. Studies examining physical activity among persons with OA are limited by self-reported data and the definitions are varied. The purpose of this study is to investigate the association between objectively-measured physical activity and metabolic syndrome among a nationally representative sample of adults with OA.

Methods: Using cross-sectional data from the 2003–2006 National Health and Nutrition Examination Survey, we identified 385 adults with OA who had physical activity measured with the Actigraph AM-7164 accelerometer worn over the right hip on an elasticized belt. Accelerometers provide a reliable and sensitive measure for the duration and intensity of bodily movement. As such, the activity counts derived from accelerometers were used to differentiate overall physical activity levels: 1) sedentary (>100 counts/min); 2) light physical activity (100 to 759 counts/min; 3) lifestyle (760 to 2019 counts/min); and 4) moderate to vigorous activity (≥2020 counts/min). Metabolic syndrome was defined using the National Cholesterol Education Program Adult Treatment Panel III standards. Logistic regression models estimated the relationship of quartile of daily minutes for each activity type to odds of metabolic syndrome adjusted for confounders and weighted for the complex survey design.

Results: Metabolic syndrome was present in 48.0% and of those, 11.2% met the physical activity guidelines of 150 minutes per week of moderate/vigorous activity. The proportion of sedentary time of total wear time, daily duration in light, lifestyle, or moderate to vigorous physical activity was associated with cluster components of metabolic syndrome. Relative to the lowest quartile of light activity, those in the highest quartile had reduced odds of metabolic syndrome (adjusted odds ratio (aOR) >296.3 versus ≤212.3 minutes/day : 0.43; 95% Confidence Interval (CI): 0.23 to 0.83; aOR 256.1–296.3 versus ≤212.3 minutes/day : 0.77; 95% CI: 0.30 to 1.97;aOR 212.4–256.0 versus ≤212.3 minutes/day : 1.43; 95% CI: 0.88 to 2.31; p-value for linear trend = 0.01).

Conclusion: Increased light physical activity was inversely associated with prevalence of metabolic syndrome among adults with OA. Effective interventions to encourage individuals with OA to increase light activity during daily living are warranted.

Disclosure: S. H. Liu, None; **C. Eaton**, None; **K. Lapane**, None.

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Skeletal Muscle Fat and Its Association with Physical Function and Physical Activity in Adults with Rheumatoid Arthritis. Samannaaz S. Khoja[1], Bret Goodpaster[2] and Sara R. Piva[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Sandford Burnham Medical Research Institute, Lake Nona in Orlando, FL.

Background/Purpose: Systemic inflammation in RA not only affects joints, but also body composition. People with RA tend to have lower lean body mass and higher body fat compared to healthy persons. Fat is also present inside the muscle, but little is known about how these fat depots are affected in RA, and their role in physical function. Skeletal muscle fat can potentially interfere with muscle fiber function and metabolic activity, and thus can be hypothesized to affect physical function. The aim of this study was to explore the association of skeletal muscle fat with outcomes of physical function and physical activity in persons with RA.

Methods: This was a cross-sectional, secondary analysis of baseline data from a study in adults diagnosed with RA as per the ACR criteria. Skeletal

muscle fat was quantified as the average muscle attenuation (MA) of the mid-thigh region, and was obtained through bilateral computed tomography (CT) imaging. MA values range from 0 to 100 Hounsfield units; higher values represent greater muscle density and thus, lower fat content. Physical function measures consisted of quadriceps maximum isometric strength, single leg balance time (up to 30 seconds), and the number of seconds taken to perform functional tasks such as chair rise (five times), ascend one flight of stairs, and walk four meters. Physical activity was captured with the SenseWear Armband, and time spent in moderate level activities (≥ 3 metabolic equivalent-MET) over 7 days was calculated. Bivariate correlations were used to test the associations of mid-thigh MA with physical function and physical activity. Separate hierarchical regression models were used to assess the contribution of mid-thigh MA to each physical function and physical activity measure after controlling for body mass index (BMI), quadriceps strength and quadriceps area.

Results: Study sample consisted of 60 subjects with RA, of which 82% were female, with average age and BMI of 59 ± 10 years and 31.2 ± 7.2 kg/m^2, respectively. Average RA duration was 15 ± 10 years and disease activity levels were moderate (mean DAS-28 score 4 ± 1.3). MA was inversely correlated with time to ascend one flight of stairs, and walk four meters; and directly correlated with time spent in physical activity (≥ 3 MET), and single leg stance. After adjusting for BMI, quadriceps strength and area, MA continued to contribute significantly to the variability in stair climb time, single leg balance time and physical activity time ≥ 3 MET (Table).

Conclusion: Higher skeletal muscle fat predicts lower physical function and physical activity. The contribution is above and beyond that of body size, and muscle strength and area. The mechanism by which skeletal muscle fat affects physical function is not clear, and perhaps muscle properties beyond its size and torque production need to be considered and investigated in future studies.

Table. Correlations between Muscle Attenuation, Physical Function and Physical Activity Outcomes

Outcome Variables	Correlations with MA (Spearman's rho)	Contribution of MA after adjusting for BMI, quadriceps strength and quadriceps area		
		β-coefficient	R^2 change	p-value
Quadriceps Isometric strength, *Newton-meters*	**.454***	–	–	–
Chair rise time, *sec*	−.244	.083	.005	.594
Stair climb time, *sec*	−.576*	.262	.044	.031*
4-meter walk time, *sec*	−.445*	.191	.023	.200
Single Leg Balance Time-Right, *sec*	.409*	.493	.154	.002*
Single Leg Balance time-Left, sec	.455*	.459	.130	.002*
Time spent in Physical Activity ≥ 3 METs, *min*	.578*	.533	.180	.000*

Disclosure: S. S. Khoja, None; **B. Goodpaster**, None; **S. R. Piva**, None.

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Does Arthritis Status Predict Starting or Stopping Work over a 2-Year Period? Kristina A. Theis[1], Miriam Cisternas[2] and Louise Murphy[1]. [1]Centers for Disease Control and Prevention, Atlanta, GA, [2]MGC Data Services, San Diego, CA.

Background/Purpose: Employment is linked to prosperity, identity, and the ability to contribute to society. Lower employment is well documented among adults with arthritis, but less is known about trajectories of stopping or starting work and subgroups particularly at risk for not working. Our purpose was to describe longitudinal patterns in work stopping and starting among three groups of U.S. adults ≥18 years: 1) those with no arthritis (arthritis$^-$), those with arthritis but no arthritis-attributable work limitation (AAWL-), and those with arthritis and AAWL (AAWL+).

Methods: We analyzed data for those in the 2009 National Health Interview Survey (an ongoing nationally representative survey of the U.S. civilian, noninstitutionalized population) Sample Adult Core who were subsequently followed for 5 rounds in the 2010–2011 Medical Expenditures Panel Survey (n=24,870; response rate=57.2%). AAWL+ was "yes" to: "Do arthritis or joint symptoms now affect whether you work, the type of work you do, or the amount of work you do?" Among those working in 2009, we examined baseline characteristics (sociodemographic [age, sex, race/ethnicity, education], chronic health condition, and job) and estimated risk of **stopping work** with hazard ratios (HR) and 95% confidence intervals (CIs) using unadjusted and multivariable adjusted models for the 3 groups; among those not working in 2009, we used the same methods to examine **starting work**.

Results: At baseline, the proportion working was substantially lower among those with AAWL+ (28.6%; 95% CI=26.1–31.1) compared with AAWL- (47.3%; 45.1–49.4) and arthritis$^-$ (66.9%; 66.0–67.8). A significantly higher proportion with AAWL+ (24.2%; 21.7–26.5) had not finished high school compared with AAWL- (13.6%; 12.3–14.8) and arthritis$^-$ (14.2%; 13.5–15.0), and more of those with AAWL+ (39.5%; 37.0–42.0) had high functional limitations compared with AAWL- (8.5%; 7.6–9.4) or arthritis$^-$ (2.1%; 1.8–2.3). Multivariable adjusted HRs for ***stopping*** work (referent: arthritis$^-$) were 1.1 (0.8–1.6) for AAWL- and 2.0 (1.4–3.1) for AAWL+ (unadjusted HRs were virtually identical). Multivariable adjusted HRs (referent: arthritis$^-$) for ***starting*** work were 1.1 (0.7–1.7) for AAWL- and 0.5 (0.3–0.9) for AAWL+; unadjusted HRs were 0.4 [0.2–0.6] for AAWL- and 0.3 [0.2–0.6] for AAWL+.

Conclusion: Over two years of follow-up, the presence of AAWL+ was a substantial and significant risk factor for stopping work (HR = 2.0) and not starting work (HR=0.5), even after adjusting for baseline differences, including characteristics (e.g., low educational attainment) associated with not working. Those with AAWL- followed the same pattern as those with arthritis$^-$. For starting work, adjustment attenuated arthritis effects only among AAWL-, whereas AAWL+ consistently identifies a unique group of individuals at risk for increased work loss and reduced work entry over time. Identification of AAWL+ may be a useful indicator for offering clinical, public health, job accommodation, and other interventions to retain and gain employment.

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ACR/ARHP Poster Session B
Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes: Clinical Focus
Monday, November 17, 2014, 8:30 AM–4:00 PM

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Female Sexual Function in Fibromyalgia. Maria Julieta Gamba[1], Claudia Uña[1], Alicia Igel[1], Fernando Eraña[1], Maritza Vidal[1], Gimena Gómez[2], Griselda Redondo[1], Maria Celina de la Vega[1], Estella Chiuzzi[1], Augusto Martin Riopedrer Sr.[1], Maria Ines de la Barrera[1], Norma Villa[1], Dario Mata[1], Alba Russo[1] and Osvaldo Daniel Messina[1]. [1]HOSPITAL ARGERICH, BUENOS AIRES, Argentina, [2]Hospital Argerich, Buenos Aires, Argentina.

Background/Purpose: Fibromyalgia (FM) is a common condition in young and middle-aged women, which is mainly characterized by diffuse chronic pain and is associated with other manifestations such as fatigue, unrefreshing sleep, stiffness, anxiety and depresión[1]. Recent studies have evaluated that chronic pain syndrome and related manifestations could have a negative impact on sexual function of these patients, as well as psychophysical abuse history could act as potential triggers of FM. **OBJECTIVE:** Assess sexual function in women with FM and correlate with tender points count, clinical severity, anxiety, depression, chronic fatigue and history of physical and psychological violence.

Methods: A case-control study. Between 03/01/12 and 06/30/12 were included consecutively: women >18 years diagnosed with FM according to ACR criteria '90, and healthy controls >18 years, without history of violence. We excluded patients with other causes of chronic pain disorders and psychotic disorders. We recorded: sociodemographic data, education, employment and menopausal status and sexual function by **Female Sexual Function Index**[2] (FSFI: self-administered questionnaire that assesses six domains). In the FM group tender points count, duration of disease, medication, psychological care, presence of chronic fatigue (by **Fukuda Criteria**), clinical severity **(FIQ-Spanish version)**, depression **(HADS)**, and history of physical or psychological violence **(Screening Questionnaire of Violence)**[3] were assessed. We used Chi^{2}test, Student t test and Mann-Whitney test, and Spearman correlation coefficient (significant $p \leq 0.05$).

Results: We included 52 patients in the FM group and 52 in the control group. Median age: 50 ± 9.2 and 47 ± 10 years, respectively. FM Group: Medium evolution time: 60 months, mean pain points: 15 ± 3, FIQ median: 67.8 (28–86). 73.1% received medication for FM and 44.2% demanded psychological care. Patients with FM showed <level education ($p = 0.001$) and <work activity level ($p < 0.001$). 56% had chronic fatigue, 35% depression and 75% had a history of personal violence. The most common link with the aggressor was, the current partner in cases of psychological violence (28.1%) and former partners for physical violence (31.25%).We found significant impaired sexual function vs controls (median FSFI total: 17.2 (1.2–33.3) vs. 29.4 (1.2–36), $p < 0.001$) and the difference persists analyzing each domain of the FSFI. Having violence history generated a tendency to

lower values of FSFI (no statistical significance). No correlation was found between values of FSFI and the other analyzed variables

Conclusion: Our patients with FM had impaired sexual function compared to control group. Physical and psychological violence were frequent but weren't related with sexuality function.

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Work Productivity and Healthcare Utilization in Patients with Fibromyalgia and Comorbid Depression Taking Antidepressant Medication. Jaren Landen[1], Claire Burbridge[2], Elizabeth Masters[3], Pritha Bhadra Brown[3], Joseph Scavone[1], Birol Emir[3], Richard Vissing[4], Andrew Clair[3] and Lynne Pauer[1]. [1]Pfizer Inc, Groton, CT, [2]Pfizer Ltd, Walton Oaks, United Kingdom, [3]Pfizer Inc, New York, NY, [4]Pfizer Inc, Louisville, KY.

Background/Purpose: Patients with fibromyalgia (FM) experience pain, sleep disruption, fatigue, and other symptoms that limit activity, impacting work productivity and increasing healthcare utilization. Here, we describe the burden of FM on work productivity and healthcare utilization in patients with FM taking antidepressant medication for their comorbid depression.

Methods: Patients from 38 centers in the United States, Europe (Italy, Spain), and Canada were enrolled in a phase 3 study of pregabalin efficacy and safety (NCT01432236). Patients with FM aged ≥18 years were taking a stable dose of a single selective serotonin reuptake inhibitor or serotonin/norepinephrine reuptake inhibitor for their comorbid depression for ≥2 months prior to randomization. FM-related work productivity and healthcare utilization were assessed at randomization. Work productivity over the preceding 7 days was measured using the Work Productivity and Activity Impairment:Fibromyalgia Symptoms (WPAI:FMS) questionnaire, a self-reported measure of FM-related absenteeism (work time missed), presenteeism (impairment while working), overall work impairment (absenteeism plus presenteeism), and activity impairment (impairment of regular activities other than work). Absenteeism, presenteeism, and overall work impairment were measured for employed individuals only. Each score is expressed as a percentage, higher scores indicating less productivity and greater impairment. Healthcare utilization related to FM in the preceding 3 months was measured using a self-reported Healthcare Utilization Assessment questionnaire that captured: number of healthcare professional (HCP) visits, hospitalizations, and emergency room (ER) visits; use of physical treatments and supplements; time other people spent providing help with activities of daily living without receiving payment; and out of pocket expenses for physical treatments, supplements, prescription and non-prescription medications, and professional services to assist with activities of daily living.

Results: 193 patients were evaluated at randomization. FM-related work productivity scores (mean ± SD) in the preceding 7 days were: absenteeism 15.2 ± 25.4% (n = 86), presenteeism 54.0 ± 21.5% (n = 83), overall work impairment 58.0 ± 23.4% (n = 82), and activity impairment 65.0 ± 18.8% (n = 193). In the preceding 3 months, the total number (mean ± SD) of HCP visits related to FM was 5.0 ± 6.6. There were no hospitalizations but 12 (6.2%) patients visited the ER. 67 (34.7%) and 61 (31.6%) patients used physical treatments and supplements, respectively. The number of hours (mean ± SD) other people spent providing help without payment was 50.4 ± 98.1. In patients who incurred out of pocket expenses in the preceding 3 months, total (mean [range]) expenditure was $US 307.12 (0–5,300; n = 110), EUR 410.43 (0–2,485; n = 49), and $CAN 211.26 (0–1,000; n = 19).

Conclusion: FM affects work productivity and regular activities other than work in patients with FM taking antidepressant medication for their comorbid depression. In these patients, FM is associated with substantial healthcare utilization, and generates considerable out of pocket expenses.

Disclosure: J. Landen, Pfizer Inc, 3, Pfizer Inc, 1; **C. Burbridge**, Pfizer Inc, 3, Pfizer Inc, 1; **E. Masters**, Pfizer Inc, 3, Pfizer Inc, 1; **P. Bhadra Brown**, Pfizer Inc, 3, Pfizer Inc, 1; **J. Scavone**, Pfizer Inc., 1, Pfizer Inc., 3; **B. Emir**, Pfizer Inc., 1, Pfizer Inc., 3; **R. Vissing**, Pfizer Inc, 3, Pfizer Inc, 1; **A. Clair**, Pfizer Inc, 3, Pfizer Inc, 1; **L. Pauer**, Pfizer Inc., 1, Pfizer Inc., 3.

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Treatment of Fibromyalgia with Neurostimulation: A Randomized, Double-Blinded, Sham-Controlled Trial. R. Michael Gendreau[1], Donald Deering[2], Judith Gendreau[3] and Jeffrey Hargrove[1]. [1]Cerephex Corporation, Los Altos, CA, [2]St. Joseph Mercy Oakland, Pontiac, MI, [3]Gendreau Consulting, LLC, Poway, CA.

Background/Purpose: NeuroPoint is a medical device designed to provide noninvasive brain stimulation using a proprietary approach to deliver very low energy levels to deep brain structures. NeuroPoint provides a therapy referred to as "reduced impedance noninvasive cortical electrostimulation" (RINCE). An initial feasibility study of 77 patients diagnosed with fibromyalgia (FM) was conducted between 2006 and 2008. The current pilot study was designed to further evaluate the safety and efficacy of RINCE therapy in the treatment of FM.

Methods: A total of 46 patients selected using the ACR 1990 FM criteria were enrolled in a single site, 12-week, double-blind, sham-controlled trial. Patients were randomized (1:1:1) to receive 24, 16 or 0 RINCE stimulations over a 12 week period. Due to an additional, unintended 60 Hz stimulation signal that was originally present in the system, 8 of 15 patients randomized to 0 treatments (Sham) received a form of stimulation. The final disposition was:

Group/	# Treatments	# Patients
A	24	15
B	16	16
C	0	7

Outcome measures included a 24-hour and 7-day recall pain VAS, Fibromyalgia Impact Questionnaire (FIQ-R), Patient Global Impression of Change (PGIC), and assessment of sleep, mood and neurocognitive changes.

Results: Completion rates were excellent with 45 of 46 patients completing all 12 weeks of scheduled treatments. At the 3 month landmark endpoint, patients treated with 24 RINCE stimulations were statistically improved on VAS pain relative to the sham group (MMRM LS Mean change from baseline −31.8 vs −8.3 mm, p=0.009). Pain responder analyses, defining a responder as 50% improvement from baseline, also favored RINCE but did not reach statistical significance due to small numbers (5 of 15 vs 1 of 7, p=NS). Likewise, PGIC responder analyses where a responder is defined as "Much Improved" and "Very Much Improved", also favored RINCE (8 of 15 vs 1 of 7, NS). Additional outcome measures generally favored RINCE as well: 7 day pain recall (VAS MMRM LS Mean contrast −22.9, p=0.013); FIQ-R total score (−24.5 vs −13.6, p=0.11); Neurocognitive functioning—MASQ improvement: −8.64 vs +2.43 (p=0.083); MCS cognition: −8.37 vs +0.09 (p=0.10); MCS mental clutter: −12.90 vs +0.44 (p=0.005). In addition, the Beck Depression Inventory and a modified Jenkins sleep questionnaire both numerically favored RINCE, but did not achieve statistical significance. Consistent with classification as a "non-significant risk" device, the adverse event profile of RINCE was very encouraging. The most common adverse event reported as potentially related to therapy was headache, reported by 3 patients out of 39 who received some form of stimulation therapy (8%). All other event reports were at rates of no more than 2 patients (5%), and were consistent with the underlying fibromyalgia.

Conclusion: Despite the very small control group of 7 patients, the benefit/ risk ratio of RINCE therapy with NeuroPoint appears highly favorable. This pilot study encouraged the sponsor to initiate a large, well powered pivotal trial in fibromyalgia.

Disclosure: R. M. Gendreau, Cerephex Corporation, 3; **D. Deering**, Cerephex Corporation, 5; **J. Gendreau**, Cerehex Corporation, 5; **J. Hargrove**, Cerephex Corporation, 3.

1096

Fibromyalgia Patients Who Have More Symptoms at Their Initial Office Visit Tend to Have a Worse Clinical Course. Robert S. Katz[1], Ben J. Small[2], Alexandra Small[3] and Hannah Bond[4]. [1]Rush Medical College, Chicago, IL, [2]MacNeal Hospital, Berwyn, IL, [3]University of Illinois College of Medicine, Chicago, IL, [4]Rheumatology Associates, Chicago, IL.

Background/Purpose: Patients with the fibromyalgia syndrome (FMS) experience pain, insomnia, fatigue, and memory/concentration problems. But

some fibromyalgia patients also have many additional somatic symptoms. We surveyed our patients with fibromyalgia to determine if those patients with many physical symptoms, in addition to the core FMS complaints, tended to have more challenging clinical courses, a poor response to treatment and more disabling limitations.

Methods: Patients from a rheumatology office practice were studied. We reviewed the charts of fibromyalgia patients and counted the number of symptoms from a list of 92 medical complaints as part of a form provided by the American College of Rheumatology. The total number of symptoms was recorded from the patient's initial visit. We then compared the number of symptoms to the patient's most recent office visit, a patient update form which includes patient recorded visual analog scales for health status in general, pain, fatigue, concentration, sleep, and also a HAQ activity questionnaire.

Results: 66 patients in this study met the 2010 ACR criteria for FMS, the number of symptoms varied from 6 to 55, with a mean number of symptoms 21.5. We found a relationship between the number of somatic symptoms and the patient's status with regard to pain, fatigue and overall health and HAQ scores. Those patients with 19 or more symptoms tended to have worse ability to perform activities and higher levels of pain and fatigue. (See table.)

Number of Symptoms	Mean HAQ	Mean Pan VAS	Mean Fatigue VAS	General Health Status VAS
less than 19 symptoms	2.18	5.11	5.04	4.79
19 or more symptoms	4.42	7.11	7.13	6.66

Conclusion: FMS **p**atients with many somatic symptoms tend to have a worse course with higher levels of pain, fatigue, insomnia, and fibrofog as well as higher HAQ scores,, indicating diminished physical functioning. FMS patients with a somatoform clinical picture tend to have a more challenging clinical course.

Disclosure: R. S. Katz, None; **B. J. Small**, None; **A. Small**, None; **H. Bond**, None.

1097

Can We Help Identify Learning Disabilities in Fibromyalgia Patients? Robert S. Katz[1], Lauren Kwan[2] and Jessica L. Polyak[2]. [1]Rush Medical College, Chicago, IL, [2]Rheumatology Associates, Chicago, IL.

Background/Purpose: A previous study (ArthRheum;S10:956) has shown that Fibromyalgia syndrome (FMS) patients may have learning disabilities. Experts in the field have identified seven types of learning disabilities. We queried FMS patients about the types of learning disabilities they might have.

Methods: 111 patients meeting the 2010 ACR criteria for Fibromyalgia, followed in a rheumatology office practice, were asked to fill out a questionnaire listing multiple questions and problems relating to learning disabilities. Based on responses, tentative classifications of specific learning disabilities were made from the following classifications: dyslexia, dysgraphia, dyscalculia, central auditory processing disorder, non-verbal learning disorder, visual processing disorder, and aphasia/dysphasia/global aphasia.

Results: According to FMS patients responses to a questionnaire, possible categories of learning disabilities were: 48.6% central auditory processing disorder; 36.9% dysphasia/global aphasia disorder; 34.2% visual processing disorder; 35.1% dyscalculia; 29.7% dysgraphia; 26.1% dyslexia; and 25.2% non verbal learning disorder.

Conclusion: Although a tentative diagnosis of a learning disability needs to be confirmed by a learning disability expert, these findings suggest that fibromyalgia patients may have multiple types of learning disabilities. The most common learning disability was central auditory processing disorder, an auditory disability causing difficulty processing verbal information and interpreting speech. It is possible that learning disability specialists could help FMS patients improve their performance at school and work.

Disclosure: R. S. Katz, None; **L. Kwan**, None; **J. L. Polyak**, None.

1098

Clinical Efficacy of the High-Concentration Capsaicin Patch for the Treatment of Carpal Tunnel Syndrome. Olga Sleglova[1] and Marek Hakl[2]. [1]Institute of Rheumatology, Prague, Prague, Czech Republic, [2]Pain Department Faculty Hospital Saint Anna, Brno, Brno, Czech Republic.

Background/Purpose: Carpal tunnel syndrome (CTS) is a clinical syndrome manifested by signs and symptoms of irritation of the median nerve at the level of the carpal tunnel in the wrist. CTS is the most frequent pressure neuropathy. The conservative treatments for chronic neuropathic pain that currently exist are only moderately effectively. Oral pharmaceuticals for neuropathic pain have significant side effects, and treatment efficacy tends to be modest. The use of topical analgesics allows direct application of medications to the area of pain. Capsaicin causes a brief initial sensitization followed by a prolonged desensitization of the local pain nerves. This occurs through stimulation of the transient receptor potential vanilloid-1 (TRPV1) expressing pain nerve fibers. Capsaicin dermal is an adhesive patch containing a high concentration (8 %) of synthetic capsaicin. It has not been studied yet in patients with CTS.

Methods: The patients with clinically and electrophysiologically confirmed CTS, indicated for the treatment of highly concentrated capsaicin 8% patch due to neuropathic pain, were included in the study. The aim of the study was to determine the proportion of patients who achieve at least a 30% reduction in pain intensity on the Numeric Pain Rating Scale (NPRS) compared with baseline. There were also observed absolute and percentage decline in the scale of NPRS and prior and concomitant medications. Patients were monitored in four visits - before treatment of capsaicin patch and after 3, 6 and 12 months of application. On all visits were evaluated clinical status, monitored the intensity of pain and quality of life. The intensity of pain was evaluated using a range of intensity of pain – NPRS. Quality of life was assessed using the EQ-5D questionnaire.

Results: Altogether, 30 patients (four male) with symptomatic CTS were included in this study between April 2012 and April 2014. Capsaicin dermal patch reduced NPRS scores from baseline 6.3 points to 4.3 points after 3 months treatment ($p < 0.001$). 71 % of patients experienced at least a 30% reduction of pain intensity measured with NPRS score, 64 % of patients had at least a 50% reduction of pain intensity. The quality of life assessed by EQ-5D questionnaire improved significantly from 0.51 to 0.69 (three months after patch administration, $p < 0.001$). The consumption of concomitant medication decreased from 81% of patients at baseline to 52% after 3 months. Pain intensity decreased and EQ-5D questionnaire improved significantly gradually during the visits after 6 and 12 months. NPRS scores decreased after 12 months to 3.4 points. Capsaicin dermal patch was well tolerated. The most common adverse events were transient, mostly mild, application reaction in 8% of patients.

Conclusion: Capsaicin in the form of 8% dermal patch is a new treatment for peripheral neuropathic pain in patients with CTS. This study showed a high therapeutic efficacy, excellent tolerability and a significant improvement in quality of life, persisting for 12 months after administration.

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Disclosure: O. Sleglova, None; **M. Hakl**, None.

1099

Which Stresses Bother Fibromyalgia Patients Most? Robert S. Katz[1], Alexandra Small[2] and Jessica L. Polyak[3]. [1]Rush Medical College, Chicago, IL, [2]University of Illinois College of Medicine, Chicago, IL, [3]Rheumatology Associates, Chicago, IL.

Background/Purpose: Fibromyalgia patients identify stress as a factor in aggravating their pain and other symptoms. We administered a questionnaire to fibromyalgia patients to try to identify a difference between various kinds of stress and the effect on fibromyalgia symptoms.

Methods: Patients in a fibromyalgia office practice completed a questionnaire including various types of stresses: family, financial, job, health issues, marital, other. All patients met the 2010 ACR criteria for the diagnosis of fibromyalgia.

Results: 91 patients responded regarding which stresses affect their fibromyalgia the greatest.

As expected, concern regarding health issues was the greatest stress, (6.64), followed by family stress (5.81), job stress (5.55), money stress (4.69), and marital stress (4.01).

Conclusion: Stress is reported by many fibromyalgia patients as aggravating their symptoms. Aside from health related concerns, family and job stress had the highest visual analog scale ratings as to the impact on fibromyalgia pain and related symptoms. Sometimes the rheumatologist or nurse needs to act as a psychotherapist, allowing the patient to ventilate and to discuss symptoms, but also areas of stress. Understanding the impact of

various stresses on fibromyalgia symptoms may assist clinicians in dealing with patients who have fibromyalgia.

Disclosure: R. S. Katz, None; **A. Small**, None; **J. L. Polyak**, None.

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System Review: The Most Common Symptoms of Fibromyalgia Patients Other Than Pain, Fatigue, Insomnia, and Cognitive Dysfunction. Robert S. Katz[1] and Jessica L. Polyak[2]. [1]Rush Medical College, Chicago, IL, [2]Rheumatology Associates, Chicago, IL.

Background/Purpose: Fibromyalgia patients are somatically sensitive. The frequently complain of symptoms other than the core ones used for the diagnosis- pain, fatigue, poor sleep and cognitive problems. We queried fibromyalgia patients as to which symptoms they commonly experienced.

Methods: We administered a questionnaire to fibromyalgia patients meeting the 2010 ACR criteria. Included was a checklist of symptoms called System Review, from the American College of Rheumatology, copyright 1999.

Results: 82 fibromyalgia patients completed the questionnaire. The most frequent symptoms reported other than pain, fatigue, poor sleep and cognitive changes were headaches 39 patients (47.6%), dry eyes 37 patients (45.1%), dry mouth 37 patients (45.1%), easy bruising 27 patients (32.9%), anxiety 25 patients (30.5%), ringing in the ears 21 patients (25.6%), dizziness 21 patients (25.6%), night sweats 21 patients (25.6%), weight gain 20 patients (24.4%), and constipation 20 patients (24.4%). Aside from these top 10 symptoms, also commonly reported were double or blurred vision 19 patients (23.2%), rash 19 patients (23.2%), color changes in hands/feet 19 patients (23.2%), runny nose 18 patients (22.0%), nausea 18 patients (22.0%), mouth sores 17 patients (20.7%), shortness of breath 17 patients (20.7%), and depression 17 patients (20.7%).

Conclusion: Fibromyalgia patients commonly have symptoms other than pain and fatigue. Non-rheumatologists, who see patients with fibromyalgia with some of the symptoms listed above, such as tinnitus, dizziness, blurred vision, mouth sores, shortness of breath, etc., may not think to link them to fibromyalgia, but they are common in this illness.

Disclosure: R. S. Katz, None; **J. L. Polyak**, None.

1101

Numbness and Tingling: Neurological Symptoms in Fibromyalgia. Robert S. Kratz. Rush Medical College, Chicago, IL.

Background/Purpose: Fibromyalgia patients may present with localized or diffuse paresthesias. Some patients have are concerned about the possible diagnosis of multiple sclerosis and other neurological disorders. Neurologists are hesitant to use the term fibromyalgia in patients with paresthesias.

Methods: We administered a questionnaire to office patients who met the 2010 ACR criteria for the diagnosis of fibromyalgia. Included were questions on presence and location of paresthesias. Location: right arm.left arm, right leg, left leg, right side of body, left side of body, right side of face, left side of face, whole body. If numbness and tingling were present, were the symptoms constant, intermittent, frequent?

Results: 95 patients with fibromyalgia completed the questionnaire. 53 of the 95 patients (55.7) answered positively to the question "Do you have numbness and tingling?" The mean age of the patients was 51.9 years; 83F and 12M.

The paresthesia's were considered to be diffuse (more than 2 areas of the body) in 21 patients (22.1%) and limited in 32 patients (33.6%).

Patients responded that the paresthesia's were constant in 21 patients (22.1%), intermittent in 42 patients (44.2%). 28 patients responded that numbness and tingling was frequent (29.4%).

Conclusion: 22.1% of this sample of fibromyalgia patients, taken from a rheumatology office practice, complained of diffuse paresthesias. Neurologists and Primary Care Physicians need to be aware that paresthesia's are common in fibromyalgia.

Disclosure: R. S. Katz, None.

1102

Anxiety in Fibromyalgia Patients. Robert S. Katz[1] and Frank Leavitt[2]. [1]Rush Medical College, Chicago, IL, [2]Rush University Medical Center, Chicago, IL.

Background/Purpose: In fibromyalgia (FMS), it is normal to expect people burdened with the uncertainty of unresolvable medical issues to face a certain amount of anxiety. A high number of medical and anxiety symptoms are seen in FMS; however, the normal reaction hypothesis may not fully explain the linkage. Another possibility is that anxiety levels differ in FMS relative to other medical conditions and may even promote the progression of medical symptoms. The purpose of this study is to determine if anxiety in FMS differs from other rheumatic disorders after adjusting for illness intensity.

Methods: The study was comprised of 191 patients seen in a rheumatologic practice. Of these, 79 had FMS and 112 had Non-FMS rheumatic disease. Diagnosis was based on ACR criteria. The two samples were closely matched on age (FMS: 51.2 ± 12.0 vs. 51.9± 15.9); the FMS sample had slightly less education (FMS: 14.8 ± 2.1 vs. 15.5 ± 2.0). The 0.7 year difference between means was significant ($p < 0.05$).

Patients were administered the 9-item Anxiety scale of the Profile of Mood States, and the Symptom Review section of the 1999 American College of Rheumatology Patient Forms. On the Anxiety scale, participants rated the anxiety variables listed in Table 1 on a 5 point scale, with 0= not at all and 4 = extremely. The anxiety score is the sum of the ratings. The system review is a symptom checklist covering 13 organ systems. Illness intensity is the number of symptoms endorsed as significantly affecting the individual.

Results: The mean anxiety levels of patients on the 9 items are shown in Table 1. FMS patients scored higher on 8 of the 9 anxiety items. As a whole, anxiety was significantly higher in FMS patients (12.7 ± 9.4 vs. 7.7 ±6.3; $p<0.001$). The score of 7.7 in the non-FMS group is in the normal range of healthy individuals (normative mean: 8.2±6.0). Illness intensity was also significantly higher in FMS participants (16.7± 11.8 vs. 8.7± 8.5: $p <0.001$). An analysis of covariance was used to subtract by statistics the effects of a higher number of medical symptoms on anxiety. Difference in anxiety remained significant after the affects of the number of medical symptoms endorsed was removed ($p<0.01$).

Conclusion: Results of the analysis of covariance essentially eliminates the greater number of medical problems in FMS as an explanation for the higher level of anxiety in FMS. With symptom intensity eliminated, the results could be read as suggesting that patients with FMS are more anxiety prone than other rheumatic disease patients.

However, more needs to be *learned about the source of higher anxiety in FMS, since competing explanations are present. For example, the argument could be made* that unexplained malfunctions of the body could in and of themselves be catalysts for excessive worry and higher levels of anxiety. Undoubtedly patients with FMS have a greater number of medically unexplained problems.

Disclosure: R. S. Katz, None; **F. Leavitt**, None.

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Analgesic and Anti-Hyperalgesic Effects of Deep Dry Needling Therapy in Fibromyalgia Patients. B. Casanueva[1], P. Rivas[2], R. López-Mejías[3], F. Genre[3], J. Llorca[4] and M. A. González-Gay[3]. [1]Rheumatologist. Rheumatology Service at the Specialist Clinic of Cantabria, Santander, Spain, [2]Physical Therapist. Specialist Clinic of Cantabria, Santander, Spain, [3]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, [4]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain.

Background/Purpose: Patients with fibromyalgia (FM) complain of widespread chronic pain from deep tissues including muscles. Previous research highlights the relevance of impulse input from deep tissues for clinical FM pain. Deep dry needle stimulation is an invasive treatment modality used in the management of musculoskeletal pain. Its efficacy has been confirmed in the management of myofascial trigger points, acute and chronic low back pain, and chronic whiplash. To determine if blocking abnormal impulse input with deep dry needling stimulation of tender point may decrease hyperalgesia and clinical pain in FM patients.

Methods: 120 patients that fulfilled the ACR 1990 criteria for FM were enrolled into a prospective controlled study of 12 week. Patients were randomly split into two groups: The control group (CG), 56 women and 4 men, who continued their treatment, and the deep dry needling group (DNG), 54 women and 6 men, who apart from continuing their medical treatment, also underwent weekly one-hour session of deep dry needling over 18 FM tender points for a 6-week-period. Study variables included pressure hyperalgesia as well as clinical pain. Patients were assessed at the start (at week 0), at the end of the 6-week intervention period (end of intervention), and were

again evaluated 6 week later (at week 12 after the onset of the study). Study questionnaires and protocol were approved by the Ethical Committee of the regional health authority. All statistical analyses were performed with de software Stata 12/SE (Stata Corporation, College Station, TX, US). P values < 0.05 were considered significant.

Results: 60 patients were randomly assigned to the CG and 60 to the DNG. A total of 100 (83.3%) patients completed the study: 50 (83.3%) in the CG and 50 (83.3%) in the DNG. The mean ± SD age of participants was 53.5 ± 11.1 years, and the average reported in Fibromyalgia Impact Questionnaire (FIQ) was 73.1. At the beginning of the program (week 0), there were only significant differences between groups in age (56.2 in DNG versus 50.8 in the CG, p: 0.01) and McGill Pain Questionnaire (MPQ) (39.1 in DNG versus 42.4 in the CG, p: 0.03). At the end of the intervention (week 6), DNG showed reduction in the FIQ (p: 0.02), VAS of pain (p: 0.002), pain of SF-36 (p: 0.0007), MPQ (p: 0.02), Pain Catastrophizing Scale (PCS) (p: 0.02), activity engagement of Chronic Pain Assessment Questionnaire (CPAQ) (p: 0.008), pain intensity of Brief Pain Inventory (BPI) (p: 0.03), pain interference of BPI (p: 0.01), myalgic score (p: 0.0005), number of tender points (p: 0.0004), and pressure pain threshold (p: 0.002). Six weeks after the end of the treatment, DNG still showed significant differences in the FIQ (p: 0.03), VAS of pain (p: 0.01), pain of SF-36 (p: 0.01), MPQ (p: 0.02), PCS (p: 0.03), activity engagement of CPAQ ($p = 0.01$), pain intensity of BPI (p: 0.04), pain interference of BPI (p: 0.01), number of tender points (p: 0.0008), myalgic score (p: 0.00001) and pressure pain threshold (p: 0.0004).

Conclusion: These results suggest that deep dry needling of tender points can reliably reduce clinical FM pain, and that peripheral input is required for the maintenance of mechanical hyperalgesia of these patients.

Disclosure: B. Casanueva, None; **P. Rivas**, None; **R. López-Mejías**, None; **F. Genre**, None; **J. Llorca**, None; **M. González-Gay**, None.

1104

Utility of the 2010 ACR Diagnostic Criteria for Fibromyalgia for Pediatric Patients with Juvenile Fibromyalgia. Tracy Ting[1], Kimberly Barnett[2], Anne Lynch-Jordan[2] and Susmita Kashikar-Zuck[2]. [1]Cincinnati Children's Hosp, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background/Purpose: Juvenile Fibromyalgia (JFM) is a chronic condition characterized by widespread musculoskeletal pain, fatigue, poor sleep and significant morbidity. Currently, a classification of JFM is based upon one of two published criteria – the 1990 American College of Rheumatology (ACR) criteria for adult fibromyalgia (FM) or the 1985 Yunus and Masi pediatric criteria. Both require a manual tender point examination that is controversial, not routinely or consistently applied by clinicians, and may be influenced by patient anxiety about the procedure. The newer 2010 ACR criteria allows for the use of a validated tool that excludes the use of the tender point exam and includes a clear scoring algorithm for consistency in screening and diagnosis of FM. However, these criteria were developed for adult FM patients and it is not clear whether they can be applied in pediatric populations. The aim of this study was to examine the utility of the new 2010 ACR criteria for pediatric patients with JFM in comparison to the ACR 1990 and Yunus and Masi classification criteria.

Methods: Participants were patients (ages 11–17) with primary JFM diagnosed by a rheumatologist or pain physician ($N=44$, $M_{age}=15.02$) and age and gender matched controls (MC) with localized pain conditions, e.g., abdominal pain, headaches, limb pain ($N=44$, $M_{age}=15.05$). Physicians completed a form indicating which set of criteria they used to make a JFM diagnosis (ACR 1990 or Yunus and Masi). The ACR 2010 Widespread Pain Index (WPI), regarding which body locations were painful and Symptom Severity (SS) checklist of associated somatic symptoms were administered by a trained assessor. Total scores for the WPI and SS tools were computed and the ACR 2010 algorithm was used to determine diagnosis of JFM. Also, t-tests were conducted to compare the two groups on number of pain locations and number of symptoms endorsed.

Results: The Yunus and Masi criteria were used the most often (93.2% of the time) by physicians to classify JFM and the ACR 1990 criteria were used far less (6.8%). When the 2010 criteria were applied, 83.7% of patients diagnosed with active JFM by their primary rheumatologist met the ACR 2010 criteria. However, approximately 11.4% of controls with localized pain were also classified as having JFM. JFM participants reported significantly more pain locations and associated symptoms than MC ($p<.01$).

Conclusion: Preliminary results indicate that the 2010 adult FM ACR Criteria may be a useful tool to screen for JFM in an adolescent population with JFM. The WPI and SS tools that comprise the 2010 criteria are brief and easy to administer and the tender point is not required. Therefore, the ACR 2010 criteria allow for more widespread application and potentially earlier identification of JFM in pediatric practices. However, confirmation of the clinical diagnosis by a specialty trained physician is still recommended. Further validation studies with larger samples to test the sensitivity and specificity of the measure are needed.

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1105

The Effectiveness of Mirror Therapy in Patients with Adhesive Capsulitis. Mehmet Cetin Baskaya[1], Cem Ercalik[2], Ozlem Kir Karatas[1] and Tiraje Tuncer[1]. [1]Akdeniz University School of Medicine, Antalya, Turkey, [2]Sisli Etfal Hospital, Istanbul, Turkey.

Background/Purpose: To investigate the efficacy of mirror therapy (MT) combined with conventional physical therapy on shoulder range of motion (ROM), pain and quality of life in the patients with adhesive capsulitis.

Methods: Thirty patients who had painful and limited 1/3 of shoulder ROM for 2 –12 months and were diagnosed as adhesive capsulitis included in this randomised single blind controlled trial(RCT). Patients who had neurological disorders, cervical radiculopathy, rotator cuff ruptures, calcific tendinitis/bursitis, tumoral lesions, humerus fracture, history of intraarticular injections within 3 months, and previous physical therapy programme within 6 months were excluded. Patiens were randomised into two groups: 15 patients (12 female, 3 male, mean age 59.8±10.6) randomised as mirror group and 15 patients (9 female, 6 male, mean age 54.4±7.6) as control group. 10 session of physical therapy programme (TENS, infrared, ultrasound, codman exercises, shoulder ROM and streching exercises and home programme for 20 minutes twice a day) was applied both groups. After each physical therapy session, mirror therapy group performed ROM exercises(flexion, abduction, internal and external rotation for 30 times once a day) while watching unaffected shoulder movements with reflected side of the mirror. Control group performed active ROM exercises (flexion, abduction, internal and external rotation for 30 times once a day) with non- reflected side of the mirror (The mirror has been placed midline of the patient's body while exercises were performed). Patients were evaluated for pain (VAS with shoulder movement), function(UCLA), quality of life (SF-36) and active - passive ROM with goniometer before and after treatment.

Results: There was no significant difference between the groups according to age and disease duration. After treatment, pain in the mirror group was found significantly less than the control group ($p<0,05$). Shoulder function scores were significantly higher than the control group ($p<0,05$). Post-treatment measurements of active flexion, active abduction, passive flexion, passive abduction in the mirror group significantly were better than the control group ($p<0,05$). Physical functioning, physical and emotional role functioning and pain parameters of SF-36 were found better in mirror therapy group than the control group after the treatment. When we compared each group before and after treatment, we found that statistically significant reduction in shoulder pain and statistically significant improvements in shoulder function, active-passive ROM measurements and quality of life after treatment.

Conclusion: Mirror therapy combined with physical thearapy programme seems to be an effective treatment to reduce pain and to improve shoulder function, shoulder ROM and quality of life in the patients with adhesive capsulitis. In our opinion, mirror therapy which is a cheap, easy appliable and reliable method should be added to standart physical therapy programme in adhesive capsulitis.

Disclosure: M. C. Baskaya, None; **C. Ercalik**, None; **O. Kir Karatas**, None; **T. Tuncer**, None.

1106

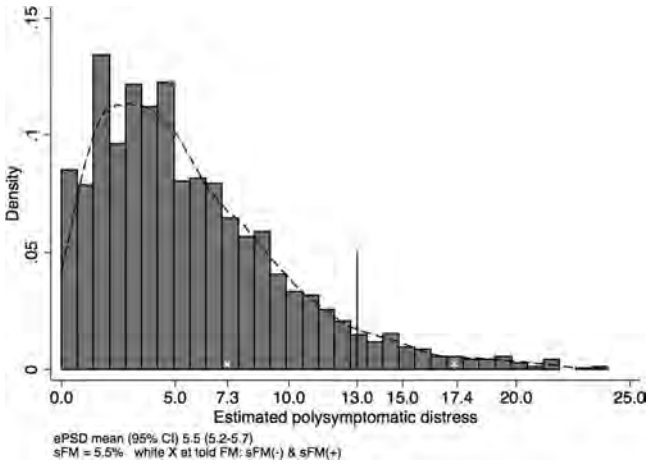
Most Patients Diagnosed with Fibromyalgia By Physicians Do Not Have Fibromyalgia: The 2012 National Health Interview Survey Fibromyalgia Study. Brian Walitt[1], Richard Nahin[2], Robert S. Katz[3], Martin J. Bergman[4] and Frederick Wolfe[5]. [1]MedStar Health, Washington, DC, [2]National Institutes of Health, Bethedsa, MD, [3]Rush Medical College, Chicago, IL, [4]Taylor Hospital, Ridley Park, PA, [5]National Data Bank for Rheumatic Diseases, Wichita, KS.

Background/Purpose: Although criteria exist for fibromyalgia (FM) diagnosis, little is known about how FM diagnosis is applied and understood by physicians and patients in the US population. The 2012 National Health Interview Survey (NHIS) is the largest US population-based health survey. We examined the relation between self-reported physician FM diagnosis, polysymptomatic distress (PSD), demographics and selected symptoms captured in the NHIS.

Methods: The NHIS asked participants about receiving a FM diagnosis from a physician along with questions about joint pain and somatic symptoms. We developed NHIS FM/PSD definitions by administering germane NHIS questions and the modified 2010 ACR criteria to 415 consecutive rheumatology patients in 2 clinics. After applying these definitions to the NHIS, we estimated a PSD score (ePSD) and set a surrogate FM diagnosis (sFM) at ePSD $\geq$ 13. Because of differences in questions and administration between the ACR criteria and the NHIS, the current data should be considered approximate.

Results: The ePSD distribution in the NHIS is shown in Figure 1. Using population derived survey weights in a sample of 2,680 participants, 4.8% reported being told they had FM (FM+); 5.6% met the criteria for sFM (sFM+).Table 1 shows the subjects stratified by told FM and sFM status. Of FM (+) subjects, 83.0% were sFM (-). Subjects that were FM (+) but sFM (-) were similar to the non-FM population but with modest increases in ePSD, not working, and lifetime depression (Table 1). In addition, they were generally white (82.1%) and female (91.0%). FM (-) but sFM (+) subjects were less often white (69.1%) or female (66.8%). Women were more likely to report being told they had FM (odds ratio 9.6) but not as likely to meet sFM criteria (odds ratio 2.1).

Conclusion: More than 80% of subjects in NHIS who report being told by physicians they have FM do not satisfy sFM criteria. Among these subjects, more are female and non-minorities than in those satisfying sFM criteria. In addition, FM (+) individuals are generally indistinguishable from the non-FM population (FM -), but are less likely to be employed and more likely to report functional limitations and a lifetime history of depression. The cause for over-diagnosis is likely multi-factorial, but may include physician misdiagnosis, access to health care, personal beliefs, and socio-cultural ideas about FM engendered by academic and industry messaging. Regardless, our current medical approach to FM/PSD results in 3.9% of minimally symptomatic Americans reporting themselves labeled as "sick". These results have important public health implications.



Group	Category %	Mean ePSD score	% White	% Female	% High School graduate	% Not working	% Functional limitations	% Lifetime depression
Not told FM, Not sFM	93.3	4.7	75.8	51.6	75.8	47.1	63.4	21.9
Told FM, Not sFM	3.9	7.3	82.1	91.0	82.1	73.5	73.7	42.1
Not told FM, +sFM	1.9	15.7	69.1	66.8	69.1	73.7	91.7	63.2
Told FM, +sFM	0.8	17.4	89.6	83.0	89.6	78.4	100.0	58.2

Disclosure: B. Walitt, None; **R. Nahin**, None; **R. S. Katz**, None; **M. J. Bergman**, None; **F. Wolfe**, None.

1107

A Strong Association Between Memory Loss and Word Finding Difficulties in Fibromyalgia. Robert S. Katz[1] and Frank Leavitt[2]. [1]Rush Medical College, Chicago, IL, [2]Rush University Medical Center, Chicago, IL.

Background/Purpose: A core feature of fibromyalgia (FMS) is cognitive dysfunction. The predominant clinical manifestations is memory loss; however impaired word retrieval frequently referred to as word finding difficulty sometimes unfolds in the clinical situation as the central patient focus. The purpose of this study is to build a more precise picture of cognitive dysfunction in FMS by examining the linkage between memory loss and word finding deficits and its relation to the severity of cognitive dysfunction.

Methods: Participants were 191 patients seen in a rheumatologic practice. Of these, 79 had FMS and 112 had Non-FMS rheumatic disease. Diagnosis was based on ACR criteria. The two samples were closely matched on age (FMS: 51.2 $\pm$ 12.0 vs. 51.9$\pm$ 15.9); the FMS sample had slightly less education (FMS: 14.8 $\pm$ 2.1 vs. 15.5 $\pm$ 2.0). The 0.7 year mean difference was significant ($p < 0.05$). Data on memory loss and word finding difficulty were collected by questionnaire. Data on 8 cognitive skills and 8 aspects of mental clarity were derived from the Mental Clutter Scale that was filled out by each participant.

Results: Compared to Non-FMS patients, patients with FMS were more likely to report memory loss (69.6%) [55 of 79] to (25.0%) [28 of 112] $p<0.001$ and word finding difficulties (69.6%) [55 of 79] to (23.2%) [26 of 112] p.<001. Within the FMS sample, 89.1% [49 of 55) of those with memory loss reported word finding difficulty, whereas 67.9% [19 of 28] of those in the Non-FMS with memory loss reported word finding difficulty ($p<0.001$). In respect to total samples, memory loss and word finding difficulty were coupled in 62.0% [49 of 79] of the FMS sample and in 17.0% [19 of 112] of the Non-FMS sample ($p<0.001$).

Results: of cognitive functioning as assessed by the 16 item Mental Clutter Scale show that cognitive difficulties are substantially skewed toward patients with FMS (Table 1). Compared to Non-FMS, those with FMS endorse a higher level of disturbance on the 8 of the 8 cognitive skills, and on 7 of the 8 aspects of mental clarity.

Conclusion: Cognitive difficulty varies widely depending upon the type of rheumatic disease. Patient with FMS appear to carry a considerably higher risk for memory loss and word finding difficulties than individuals with other rheumatic disease. The memory loss-FMS relationship is well established and has played a central role in cognitive studies to date; whereas the role of word finding difficulty has been largely unappreciated.

Memory loss and word finding difficulties co-occur in FMS to an unusual degree. Cases in which these cognitive difficulties are coupled to the experience of multiple concurrent cognitive difficulties and greater mental fog as reflected by a high level of disturbance in 7 aspects of mental clarity.

At this stage, it is unclear why the cognitive picture is worse when memory loss and word finding difficulties co-occur in FMS or what mechanisms bind them together.

Table 1. Comparison of Rheumatic Patients With (FMS) and Without (Non-FMS) Fibromyalgia Who Endorse Both Memory Loss and Word Finding Difficulties on the Cognitive and Mental Clarity Subscales of the Mental Clutter Scale.

	Fibromyalgia (n = 49)	Non-Fibromyalgia (n = 19)
Concentration*	6.4 $\pm$ 2.6	4.5 $\pm$ 2.0**
Memory	6.5 $\pm$ 2.2	4.6 $\pm$ 2.2**
Staying Focused	6.2 $\pm$ 2.3	4.7 $\pm$ 2.5**
Multitasking	6.3 $\pm$ 2.5	4.5 $\pm$ 3.1**
Expressing Yourself	5.6 $\pm$ 3.0	4.0 $\pm$ 2.1*
Thinking Clearly	5.7 $\pm$ 2.2	4.2 $\pm$ 2.4*
Perceptual Clarity	5.3 $\pm$ 2.3	4.0 $\pm$ 2.5*
Mental Speed	6.2 $\pm$ 2.3	4.6 $\pm$ 2.4*
Spaciness‡	5.4 $\pm$ 2.9	3.4 $\pm$ 2.2*
Looking at life through a haze	4.7 $\pm$ 3.0	2.9 $\pm$ 2.4*
Confusion	4.3 $\pm$ 2.8	3.5 $\pm$ 2.5
Cluttered thinking	5.5 $\pm$ 2.7	3.9 $\pm$ 3.1*
Fogginess	5.7 $\pm$ 2.7	2.9 $\pm$ 2.3*
Rushing thoughts	5.2 $\pm$ 3.1	3.5 $\pm$ 2.9*
Fuzzy headedness	4.9 $\pm$ 2.7	2.8 $\pm$ 2.3**
Information overload	5.9 $\pm$ 2.9	4.1 $\pm$ 3.1*

[a] Start of 8 Cognitive items
[b] Start of 8 Mental Clarity
*p<0.05, **p<0.01, ***p<0.001

Disclosure: R. S. Katz, None; **F. Leavitt**, None.

1108

Understanding Baseline Clinical Characteristics May be of Use in Considering the Response to Pregabalin in FM Patients with Comorbid Depression. Lynne Pauer[1], Jaren Landen[1], Pritha Bhadra Brown[2], Joseph Scavone[1], Richard Vissing[3] and Andrew Clair[2]. [1]Pfizer Inc, Groton, CT, [2]Pfizer Inc, New York, NY, [3]Pfizer Inc, Louisville, KY.

Background/Purpose: In a prior study in fibromyalgia (FM) patients taking an antidepressant for their comorbid depression, pregabalin (PGB) significantly reduced pain severity (treatment difference compared with placebo [95% CI], –0.61 [–0.91 to –0.31]). However, the effect of patients' baseline clinical characteristics on the treatment response to pregabalin has not previously been examined.

Methods: In the randomized, placebo (PBO)-controlled, 2-way crossover study, patients with FM aged ≥18 years taking a single antidepressant for their comorbid depression were randomized 1:1 to PGB (300 or 450 mg/d)/PBO or PBO/PGB. Treatment was for two 6-week periods, separated by a 2-week taper/washout. Antidepressant medication (SSRI or SNRI) was continued throughout the study. Endpoint mean pain scores (by 11-point numeric rating scale) were pooled from the two treatment periods. In this analysis, the effect of the following baseline clinical characteristics on endpoint mean pain scores was examined: pain severity (moderate, pain score of 4 to ≤7; severe, 7 to 10); depression diagnosis (major depressive disorder [MDD] or depression not otherwise specified [NOS]); prior or no prior opioid use; and Hospital Anxiety and Depression Scale-Anxiety (HADS-A) or -Depression (HADS-D) score (0–21 scale). Variables were analysed as fixed factors in a linear mixed effects model including sequence, period, and treatment as fixed factors, and subject within sequence and within subject error as random factors.

Results: A total of 193 patients were included in the analysis; 181 received ≥1 dose of PGB and 177 PBO. Mean age was 50.1 years and 93.3% of patients were female. Mean (median) pain, HADS-A, and HADS-D scores at baseline were 6.7 (6.9) 8.3 (8.0), and 8.0 (8.0), respectively. Endpoint mean pain scores were significantly lower ($P < 0.05$) with PGB compared with PBO (treatment difference, 95% CI) irrespective of patients having: moderate (–0.62, –1.06 to –0.17; n = 104) or severe (–0.53, –0.93 to –0.14; n = 89) pain; diagnosis of MDD (–0.73, –1.22 to –0.24; n = 84) or depression NOS (–0.54, –0.94 to –0.13; n = 101); prior (–0.70, –1.35 to –0.05; n = 44) or no prior opioid use (–0.53, –0.88 to –0.19; n = 149); HADS-A score <8 (–0.55, –1.08 to –0.02; n = 86) or ≥8 (–0.67, –1.04 to –0.31; n = 107); or HADS-D score <8 (–0.93, –1.44 to –0.42; n = 85). However, while there was a trend towards improvement with pregabalin in patients with HADS-D score ≥8, this was not significant (–0.31, –0.67 to 0.06; $P = 0.098$; n = 108).

Conclusion: In patients with FM taking an antidepressant for comorbid depression, pregabalin significantly improved mean pain scores irrespective of baseline pain severity, depression diagnosis, prior opioid use, or HADS-A score. This study has important clinical implications in that pregabalin improved pain in FM patients with a wide range of baseline clinical characteristics.

Disclosure: L. Pauer, Pfizer Inc., 1, Pfizer Inc., 3; **J. Landen**, Pfizer Inc, 3, Pfizer Inc, 1; **P. Bhadra Brown**, Pfizer Inc, 3, Pfizer Inc, 1; **J. Scavone**, Pfizer Inc., 1, Pfizer Inc., 3; **R. Vissing**, Pfizer Inc, 3, Pfizer Inc, 1; **A. Clair**, Pfizer Inc, 3, Pfizer Inc, 1.

1109

Impact of Age on Symptom Severity and Disease Management at Fibromyalgia Diagnosis. Emmanouil Rampakakis[1], Mary-Ann Fitzcharles[2], Peter A. Ste-Marie[2], John S. Sampalis[1] and Yoram Shir[2]. [1]JSS Medical Research, Montreal, QC, [2]McGill University Health Centre, Montreal, QC.

Background/Purpose: Population studies indicate that older persons experience more pain generally. Fibromyalgia (FM) affects persons of all ages, with previous studies on the impact of age on symptom severity reporting conflicting findings. Jiao et al. reported worse symptoms for younger patients[1], whereas Cronan et al. reported that increasing age was associated with reduced FM symptomatology.[2] The aim of this analysis was to describe the association between age at FM diagnosis and patient and clinical characteristics among Canadian patients in routine clinical care.

Methods: A cohort of FM patients prospectively followed at a tertiary care multidisciplinary clinic was included in the analysis. Demographic and disease severity measures included: pain visual analog scale (VAS), patient global assessment (PGA), Health Assessment Questionnaire (HAQ), Pain Disability Index (PDI), Pain Catastrophizing Scale (PCS), FIQ, MPQ, anxiety and depression by Arthritis Impact Measurement Scale (AIMS). General linear models and logistic regression were used to assess the association between age and, continuous or categorical, respectively, patient or disease parameters at baseline.

Results: The cohort comprised 248 patients with a mean ± SD age 47.89 ± 10.34 years, disease duration 10.84 ± 9.80 years, and 91.13% female. Baseline values were: pain VAS 6.52 ± 2.29, PGA 6.58 ± 2.23, FIQ 66.97 ± 16.82, HAQ 1.19 ± 0.61, MPQ 40.82 ± 15.22, PDI 37.69 ± 14.44, PCS 29.39 ± 12.17, AIMS anxiety 6.34 ± 1.84, AIMS depression 4.91 ± 1.84, with a mean medication count of 2.38 ± 1.67 per patient.

Increased age was associated with significantly ($P<0.001$) longer pain duration ($B=0.34$; i.e. increased duration of pain by 0.34 years for each additional year of age) and lower odds of having allodynia ($OR=0.97$; $P=0.037$). Furthermore, increased functional disability was observed in older patients as evidenced by the higher HAQ scores ($B=0.01$; $P=0.007$). However, no significant association was observed with pain severity, PDI, PCS, PGA, FIQ, MPQ, anxiety and depression. Older patients were more likely to be treated with tranquilizers ($OR=1.03$; $P=0.039$), with a statistical trend towards more analgesics ($OR=1.03$; $P=0.096$) but less antidepressant use ($OR=0.98$; $P=0.091$). No significant differences were observed for other treatments, cigarette smoking, or substance abuse.

Conclusion: Although older age at baseline was associated with significantly longer duration of pain, no significant differences in disease parameters were observed based on age; the only exception being HAQ which was worse among older patients. Patient management differed based on age without, however, reaching statistical significance. Further study is necessary to establish whether response to treatment is associated with age.

References

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Disclosure: E. Rampakakis, None; **M. A. Fitzcharles**, None; **P. A. Ste-Marie**, None; **J. S. Sampalis**, None; **Y. Shir**, None.

1110

The Comparative Efficacy of Kinesio Taping and Local Injection Therapy in Patients with Subacromial Impingement Syndrome. Hamit Goksu[1], Pinar Borman[2] and Figen Tuncay[3]. [1]Ankara Training and Research Hospital, Ankara, Turkey, [2]University of Hacettepe Faculty of Medicine, Ankara, Turkey, [3]Ahi Evran University, Kirsehir, Turkey.

Background/Purpose: The aim of this study was to compare the therapeutic effects of kinesio taping (KT) and local subacromial injection in patients with subacromial impingement syndrome (SIS) with regard to pain, range of motion (ROM) and disability.

Methods: Sixty-one patients with subacromial impingement syndrome were enrolled into the study. Demographic and clinical characteristics including age, sex, duration of disease were recorded. The patients were randomized into two treatment groups receiving either a single corticosteroid and local anesthetic (LA) injection, or kinesio taping performed three times by intervals of 3 day. Visual analog scale (VAS) was used to assess pain intensity, shoulder abduction, flexion and rotation range of motion (ROM) degrees were recorded and Shoulder Pain and Disability Index (SPADI) was performed to evaluate functional disability, before treatment, at the first and fourth weeks after therapies. Both groups were educated for home exercise programme.

Results: Forty-eight female and 13 male patients (mean age, 42.4+6.48 years; mean disease duration, 2.35+0.79 months) were included in the study. There were no differences between the groups regarding demographic variables on entry to the study. Pain, functional outcome measures were determined to have improved significantly in both groups at the end of therapies at first and fourth weeks, but these improvements were more significant in the injection group than in kinesio taping group. The improvements in pain at rest, shoulder abduction degrees, and SPADI scores at first and fourth weeks were statistically higher in injection group than in kinesio taping group.

Conclusion: We imply that single dose subacromial injection and three times of kinesio taping by 3 day intervals have favorable effects on pain and functional status in the early period (up to one month) of subacromial impingment syndrome. Although the improvement in pain intensity at rest, abduction ROM measures and disability were better with local injection, KT may be an alternative non-invasive method for patients suffering from subacromial impingement syndrome in the early period.

Disclosure: H. Goksu, None; **P. Borman**, None; **F. Tuncay**, None.

1111

The Effect of High Intensity Laser Therapy in the Management of Myofascial Pain Syndrome of the Trapezius: A Double Blind, Placebo-Controlled Study. Umit Dundar, Utku Turkmen, Hasan Toktas, Ozlem Solak and Alper Ulasli. Afyon Kocatepe University, Faculty of Medicine, Afyonkarahisar, Turkey.

Background/Purpose: Myofascial pain syndrome (MPS) of the trapezius muscle is one of the main causes of neck pain**.** In this randomized, double blinded study, we planned to evaluate the effects of high-intensity laser therapy (HILT) in female patients with chronic MPS of the trapezius muscle**.**

Methods: The female patients with the diagnosis of MPS of the trapezius muscle, were enrolled in the study and assigned to two groups**.** HILT group (group1) was treated with HILT and exercise. Sham therapy group (group2) received placebo HILT and exercise**.** The patients were assessed for pain, cervical active range of motion, disability and quality of life**.** Evaluations were performed before treatment (week 0) and after treatment (week 4 and week 12).

Results: Both groups showed significant improvement for all parameters at week 4 and week 12. However, comparison of the percentage changes of parameters both at week 4 and week 12 relative to pretreatment values showed that improvement in pain scores, neck disability index and physical functioning, role limitations due to physical functioning, bodily pain, general health perceptions, social functioning and role limitations due to emotional problems subparts of SF-36 were better in HILT group.

Conclusion: As a result, it is concluded that HILT is an effective therapeutic method in the treatment of patients with chronic MPS of the trapezius muscle**.**

Key words: Myofascial pain syndrome**,** high-intensity laser therapy**,** exercise**,** pain, disability, quality of life**.**

Disclosure: U. Dundar, None; **U. Turkmen**, None; **H. Toktas**, None; **O. Solak**, None; **A. Ulasli**, None.

1112

Cognitive Symptoms in Fibromyalgia Patients Compared with Rheumatoid Arthritis Patients. Robert S. Katz[1], Ben J Small[2], Alexandra Small[3] and Susan Shott[4]. [1]Rush Medical College, Chicago, IL, [2]MacNeal Hospital, Berwyn, IL, [3]University of Illinois College of Medicine, Chicago, IL, [4]Rush University Medical Center, Chicago, IL.

Background/Purpose: Many fibromyalgia symdrome (FMS) patients report impaired mental function (fibrofog.) We compared FMS and RA patients with respect to symptoms of impaired cognition.

Methods: 211 office patients with either FMS (150; 130 women and 20 men; mean age 51±12) and RA (61; 45 women and 16 men; mean age 55±15) completed a questionnaire about symptoms of impaired mental function, rated as 1 = never, 2 = occasionally, 3 = sometimes, 4 = mostly, and 5 = always. The two-sided Mann-Whitney test was done to compare FMS and RA patients with respect to these ratings, using a 0.05 significance level.

Results: Compared to RA patients, FMS patients had significantly worse ratings for inability to recall known words (1.9 ± 1.0 vs. 1.4 ± 0.6, p = 0.001), inability to write an idea down (1.5 ± 1.0 vs. 1.2 ± 0.4, p = 0.017), mistaking numbers that look similar (1.5 ± 0.8 vs. 1.2 ± 0.4, p = 0.034), inability to retain patterns when adding, subtracting, multiplying, or dividing (1.6 ± 1.0 vs. 1.2 ± 0.6, p = 0.02), distraction by background noises (2.3 ± 1.3 vs. 1.7 ± 1.0, p = 0.002), difficulty following directions (1.9 ± 1.1 vs. 1.4 ± 0.6, p = 0.005), trouble following conversations (1.7 ± 0.9 vs. 1.3 ± 0.6, p = 0.006), becoming disruptive in conversations (1.4 ± 0.8 vs. 1.2 ± 0.5, p = 0.027), misremembering spelling of familiar words (1.7 ± 0.9 vs. 1.4 ± 0.7, p = 0.009), losing place while reading (2.0 ± 1.1 vs. 1.6 ± 0.8, p = 0.03), difficulty expressing thoughts verbally (2.0 ± 1.1 vs. 1.5 ± 0.8, p = 0.001), poor reading comprehension (1.9 ± 1.1 vs. 1.4 ± 0.8, p = 0.003), frustration when speaking (1.8 ± 1.1 vs. 1.3 ± 0.6, p = 0.003), and difficulty concentrating (2.5 ± 1.2 vs. 1.8 + 1.0, p < 0.001).

Conclusion: FMS patients had median ratings for cognitive function that were significantly worse than patients with RA. FMS patients report significantly more symptoms of impaired concentration and mental fog. Fibrofog is a troubling problem for many fibromyalgia patients.

Disclosure: R. S. Katz, None; **B. J. Small**, None; **A. Small**, None; **S. Shott**, None.

1113

Mayor Trocanter Painful Syndrome. Treatment with Hyaluronic Acid Versus Triamcinolone Acetonide Injections. A Comparative Study. Asuncion Acostar Sr.[1], Arturo Rodriguez de la Serna[2], Berta Magallares[2] and Gary Sterba Sr.[3].[1]Hospital Santa Creu i Sant Pau, Barcelona, Spain, [2]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [3]rheumatologist, miami, FL.

Background/Purpose: Painful syndrome of the mayor trochanter (MTPS). The treatment includes intra-bursal injections with cortico-steroids.Steroids. Estimate the efficacy of the treatment with hyaluronic acid injections in comparison to injections with triamcinolone acetonide in a follow up time of 1,3 and 6 months.

Methods: Random double blind clinical study. The patients were recruited of the consult injection clinic of the rheumatic diseases. Inclusion: MTPS confirmed by physical exam/ Pain that persist at least 1 month in spite of treatment/Fulfillment of the informed content. Exclusion: coxo-femoral intra-articular pathology. The more symptomatic side was evaluated. First group intrabursal injection 40 mg of triamcinolone acetonide.Second group intra-bursal injection 60 mg of hyaluronic acid depot. Technique: spinal syringe 22 g in a maximal pain point. Non steroidal anti-inflammatory was not permitted and paracetamol was permitted. Variables: Analog visual scale espontaneous pain and pain upon palpation at baseline, 1, 3 and 6 months. Likert scale of interference of pain in activities at baseline, Likert scale of pain resolution and treatment satisfaction at baseline, 1, 3 and 6 months. Statistical Analysis age, pain VAS palpation: average and standard deviation. Sex and Likert scales: frequency and percentage. Chi-square/fisher exact test: category variables. T student test for independent data. To analyze the progression in the VAS:ANOVA. A non-inferiority analysis:treatment with hyaluronic acid is non inferior that the treatment with triamcinolone acetonide. SPSS 18.

Results: 52 patients, 2 arms: 4 lost in the triamcinolone acetonide group. 1 lost in the group with hyaluronic acid. Final sample 22pts triamcinolone acetonide group, 25 hyaluronic acid group. F/M:87.2/12.8%. VAS on palpation (was less than one point and considered irrelevant) in any case better results (barely) in the group with hyaluronic acid than in the group with triamcinolone acetonide. No statistically significant differences in the interference of pain in the activities at baseline. Analysis of the variance: the progression of spontaneous pain VAS 1, 3 and 6 for the group effect P=0,756, The interaction effect P=0,433. Time effect P<0,001 (both therapies reduce pain). Analysis of the progression of pain to VAS palpation. The group effect P=0,241. The interaction effect P=0,639. Time effect P<0,001 (Both therapies reduce pain). Non-inferiority analysis: The treatment with hyaluronic acid is non inferior to the treatment with triamcinolone acetonide. No secondary adverse effect.

Conclusion: MTPS treatment with hyaluronic acid injections is not inferior to the treatment with triamcinolone acetonide injections at 6 month. In specific cases like in diabetic patients or where corticosteroid have been unsuccessful or are contraindicated, hyaluronic acid injections is a therapeutic alternative.

Disclosure: A. Acosta Sr., None; **A. Rodriguez de la Serna**, None; **B. Magallares**, None; **G. Sterba Sr.**, None.

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Clinical Effectiveness of Exercise and Corticosteroid Injection for Subacromial Impingement Syndrome: A Randomised Controlled Trial. Edward Roddy[1], Reuben Ogollah[1], Irena Zwierska[1], Praveen Datta[2], Alison Hall[1], Elaine Hay[1], Sue Jackson[2], Martyn Lewis[1], Julie Shufflebotham[3], Kay Stevenson[2], Danielle van der Windt[1], Julie Young[1] and Nadine Foster[1]. [1]Keele University, Keele, United Kingdom, [2]University Hospital of North Staffordshire, Stoke-on-Trent, United Kingdom, [3]Staffordshire and Stoke-on-Trent Partnership Trust, Stoke-on-Trent, United Kingdom.

Background/Purpose: Subacromial impingement syndrome (SIS) is the most common cause of shoulder pain. It is commonly managed by exercise and corticosteroid injection yet how these are best-delivered is uncertain. The SUPPORT trial investigated whether better outcomes in pain and function are achieved with (1) physiotherapist-led individualised, supervised and progressed exercise rather than a standardised advice and exercise leaflet, and (2) ultrasound (US)-guided subacromial corticosteroid injection rather than unguided injection.

Methods: Study design was a 2×2 factorial randomised controlled trial. Adults with SIS were recruited from community musculoskeletal services and randomised equally to one of four treatment groups: (1) US-guided steroid

injection and physiotherapist-led exercise, (2) US-guided steroid injection and an exercise leaflet, (3) unguided steroid injection and physiotherapist-led exercise, or (4) unguided steroid injection and an exercise leaflet. Outcomes were collected at 6 weeks, 6 months and 12 months by postal questionnaire. The primary outcome measure was the Shoulder Pain and Disability Index (SPADI), compared at 6 weeks for the injection interventions and 6 months for the exercise interventions. Secondary outcomes included SPADI pain and disability subscales, current shoulder pain intensity, patient's global impression of change, and pain self-efficacy. 250 participants were required to detect a small-moderate effect size (0.4) in SPADI for the two main comparisons. Analysis was by intention-to-treat.

Results: 256 participants were recruited (48% male, mean age 54 years), 64 to each treatment group. Response rates for the primary outcome were 94% at 6 weeks, 88% at 6 months and 80% at 12 months.

Greater mean improvement in total SPADI score was seen with physiotherapist-led exercise than with the exercise leaflet at 6 months and 12 months: 3.02 (95%CI −3.00, 9.03) at 6 weeks, 9.48 (95%CI 3.30, 15.65) at 6 months, and 6.64 (95%CI 0.33, 12.96) at 12 months. Physiotherapist-led exercise led to greater mean improvement in SPADI pain subscale at 6 and 12 months, and in SPADI disability subscale at 6 months but not at 12 months. At 12 months, the physiotherapist-led exercise group showed a greater reduction in current shoulder pain intensity, stronger self-efficacy beliefs and more frequent patient reporting of being much or completely better.

Within-group improvement in total SPADI was seen in both injection groups but there were no significant between-group differences at any time-point: 2.99 (95%CI −3.03, 9.00) at 6 weeks, 3.38 (95%CI −2.79, 9.56) at 6 months, and −1.50 (95%CI −7.82, 4.82) at 12 months. There were no differences in secondary outcome measures between the injection groups at any time-point.

There was no significant interaction effect of combined US-guided injection and physiotherapist-led exercise at the primary endpoints of 6 weeks and 6 months.

Conclusion: Physiotherapist-led exercise in patients with SIS leads to greater improvements in pain and function than providing a standardised advice and exercise leaflet. Ultrasound-guidance confers no additional benefit over unguided corticosteroid injection.

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1115

The Effects of Mulligan's Mobilization with Movement Techniques in Patients with Lateral Epicondylitis. Aycan Cakmak[1], Elcin Dereli[1] and Dilsad Sindel[2]. [1]Istanbul Bilgi University, School of Health Sciences, Istanbul, Turkey, [2]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey.

Background/Purpose: The aim of this study was to investigate the effects of Mulligan's mobilization with movement (MWM) technique in the management of pain and improvement of functional status in patients with lateral epicondylitis (LE).

Methods: A total of 40 patients with LE were randomly assigned to two groups. The MWM group (n=20) was treated with MWM technique, exercise and cold therapy. The patients in control group (n=20) received only exercise and cold therapy. The physical therapy sessions were applied in our clinics five times a week for two weeks (total number: 10). All physical therapy sessions were supervised by the same investigator. We used the Visual Analogue Scale (VAS) to assess the intensity of pain. Moreover, the intensity of pain and functional disability were evaluated by the Patient-rated Tennis Elbow Evaluation (PRTEE) Questionnaire. Both dynamometer and pinchmeter were used to assess muscle strength of the hand. Muscle strength of elbow and wrist were evaluated by the manual muscle testing method. All outcome measures were conducted at baseline and repeated immediately after treatment (post-treatment), and at 1- and 3-month follow-up assessments. To compare the difference between two groups, we used the Mann-Whitney U test (α=0.05).

Results: There was a significant decrease in VAS scores during activity scores in MWM group at post-treatment (p=0.001), 1-month (p<0.001) and 3-month (p=0.040) assessments compared with the control group. Moreover, there was a significant decrease in VAS scores at night in MWM group (p=0.024) and significant increase in pain-free grip strength (p=0.002) at post-treatment assessment compared with the control group. The PRTEE-Pain Subscale scores decreased significantly in MWM group at post-treatment (p<0.001), 1-month (p<0.001) and 3-month (p=0.001) assessments compared with the control group. For all other outcome measures, there was no statistically significant difference between the two groups at all assessment intervals (p>0.05).

Conclusion: Mulligan's MWM techniques may be effective in reducing pain and improving in grip strength in patients with LE.

Disclosure: A. Cakmak, None; **E. Dereli**, None; **D. Sindel**, None.

1116

Mindfulness Is Associated with Sleep Quality Among Patients with Fibromyalgia. Yuan Zhang[1], Lori Lyn Price[2], Nani Morgan[3], Lucas Morgan[4] and Chenchen Wang[2]. [1]University of Massachusetts Lowell, Lowell, MA, [2]Tufts Medical Center, Boston, MA, [3]University of Hawaii, Honolulu, HI, [4]University of Massachusetts, Honolulu, HI.

Background/Purpose: Mindfulness is the ability to observe, describe, or be aware of present moment experiences without judgment or reactivity. Previous literature suggests that mindfulness-based interventions may be effective in reducing chronic pain and depression experienced among patients with fibromyalgia. Additionally, fibromyalgia patients commonly experience sleep disturbance, which at least partially attributes to chronic pain and depression. Therefore, we hypothesize that mindfulness could be associated with fibromyalgia patients' sleep quality, and the effect may be explained through reducing symptoms of chronic pain and depression.

Methods: We conducted a secondary analysis of baseline data from a randomized controlled trial comparing Tai Chi and aerobic exercise among patients with fibromyalgia. Patients completed the Five Facet Mindfulness Questionnaire (FFMQ), a 39-item, self-report questionnaire; scores ranging 39–195, with higher scores representing higher levels of mindfulness. Participants also completed the Beck Depression Inventory Second Edition (BDI-II), PROMIS Pain Interference, PROMIS Sleep Disturbance, and Pittsburgh Sleep Quality Index (PSQI). Pearson correlations were run to examine the associations of mindfulness with sleep quality and disturbance, chronic pain, and depression. Multivariate linear regressions were run to examine the predicting effect of mindfulness on sleep quality and disturbance. Chronic pain and depression were then separately introduced into the regressions to test their potential mediating effects.

Results: This study included 160 fibromyalgia patients with an average age of 51.9 years, primarily female (92%). Patients reporting higher levels of mindfulness tended to report better sleep quality (r=−0.25, p<0.01) and less sleep disturbance (r=−0.27, p<0.01), as well as lower chronic pain (r=−0.36, p<0.01), and less depression (r=−0.57, p<0.01)). Patients reporting higher levels of chronic pain or depression tended to report worse sleep quality (r=0.42 & r=0.43, p<0.01) and more sleep disturbance (r=0.42 & r=0.32, p<0.01). The linear regression modeling reported that mindfulness significantly predicted sleep quality and disturbance (Table 1). The association between mindfulness and sleep quality/disturbance was partially mediated through chronic pain and depression (Table 1).

Conclusion: Mindfulness may be associated with fibromyalgia patients' sleep quality, and the effect could possibly be explained through affecting the symptoms of chronic pain and depression. Longitudinal studies are needed to further evaluate whether improvement in mindfulness are associated with improvement in sleep quality of fibromyalgia patients.

Table 1. Linear Regression Models for the Predicting Effect of Mindfulness on Sleep Quality/Disturbance and the Mediating Effect of Chronic Pain and Depression

	Sleep quality (PSQI)			Sleep Disturbance (PROMIS)		
Independent variables	**Model 1**	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
FFMQ	−0.045**	−0.022	−0.007	−0.086**	−0.047	−0.055
PROMIS pain	–	0.225**	–	–	0.423**	–
BDI-II	–	–	0.118**	–	–	0.099
Age	−0.044	−0.014	−0.017	−0.109*	−0.057	−0.091
Female	0	0	0	0	0	0
Male	−1.391	−1.224	−0.995	−2.815	−1.46	−2.399
White	0	0	0	0	0	0
Black	−0.722	−0.271	−0.608	−1.482	−0.865	−1.499
Others	−2.293**	−2.162**	−2.077*	−4.651**	−4.651**	−4.560**
Education	−0.199	−0.146	−0.115	0.16	0.247	0.246

Note: *p<0.05; **p<0.01. Model 1 explains the predicting effect of mindfulness on sleep quality/disturbance, with adjustment of age, gender, race, and education. Model 2 explains the partial mediating effect of chronic pain on the association between mindfulness and sleep quality/disturbance. Model 3 explains the partial mediating effect of depression on the association between mindfulness and sleep quality/disturbance.

Disclosure: Y. Zhang, None; **L. L. Price**, None; **N. Morgan**, None; **L. Morgan**, None; **C. Wang**, None.

1117

Fibromyalgia Patients Taking Opioids Have Low Self-Efficacy and High Pain Catastrophizing but No Reduction in Pain or Improvement in Activity. Joseph Adu[1], Cecilia P. Chung[1], Li Alemo Munters[1], Leon Darghosian[1], Rebecca Spitz[2], Dana Dailey[2], Barbara Rakel[2], Kathleen Sluka[2] and Leslie J. Crofford[1]. [1]Vanderbilt University, Nashville, TN, [2]University of Iowa, Iowa City, IA.

Background/Purpose: Fibromyalgia (FM) is a chronic disease of unknown etiology characterized by diffuse pain leading to fatigue, unrefreshing sleep and mood disturbances. The Fibromyalgia Activity Study with Tens (FAST) is a randomized controlled multicenter trial designed to evaluate the efficacy of Transcutaneous Electrical Nerve Stimulation (TENS) for FM. We have found that at baseline, approximately 40% of patients enrolled in FAST have been prescribed chronic opioids. Data supporting opioid efficacy for FM is lacking and they are not recommended by professional societies. The purpose of this study is to compare the baseline characteristics of FAST participants who are taking opioids to those who are not.

Methods: Patients screened for FAST (n = 44) wore ActiGraph wGT3X-BT accelerometers for 7 days prior to each visit and were evaluated by pre-randomization baseline data. These included the Demographic Health History questionnaire, the Fibromyalgia Impact Questionnaire-Revised (FIQR), the Short-form-36 Health Survey (SF-36), the Brief Pain Inventory (BPI), the Pain Self-Efficacy Questionnaire (PSEQ), the Pain Catastrophizing Scale (PCS), and others. These results were compared between patients separated into a non-opioid vs. opioid classifications (n = 25 vs. n = 19). These data were analyzed using two-sample Wilcoxon rank-sum (Mann-Whitney) test and Fisher's exact test with significance set at $P \leq 0.05$.

Results: There were no significant differences between the two groups in terms of age, sex, race, education, income level, marital status, years diagnosed with FM, smoking history, and activity level as measured by actigraphy. FIQR scores, the main disease activity measure for FAST, between non-opioid and opioid users (median: 55.6; IQR: 49.5–63.6 vs. 53.1; 47.9–75.6; $P = 0.17$), and the SF-36, a quality of life measure, did not differ across domains except for General Health, which was lower in opioid patients (median: 38.9; IQR: 34.2–43.7 vs. 33.2; 26.1–38.9; $P = 0.05$). Patients in the opioid group had significantly lower ratings on the PSEQ (median: 25.5; IQR: 14.0–34.0 vs. 37.0; 25.5–49.5), which assesses patients' confidence to accomplish specific tasks despite concurrent pain ($P = 0.01$). In addition, PCS total scores, which measure negative thoughts experienced during pain, were significantly higher in the opioid group (median: 22.0; IQR: 13.0–35.0 vs. 10.5; 6.0–23.0; $P = 0.02$), although pain severity was not significantly different based on BPI.

Conclusion: These data suggest an association between opioid use, pain catastrophizing and low levels of pain self-efficacy. The reasons for these associations are not clear, but it is possible that patients with these characteristics are more likely to be prescribed opioids. There is no evidence that patients on opioids have improved disease activity or better health outcomes than those not on opioids.

Disclosure: J. Adu, None; **C. P. Chung**, None; **L. Alemo Munters**, None; **L. Darghosian**, None; **R. Spitz**, None; **D. Dailey**, None; **B. Rakel**, None; **K. Sluka**, None; **L. J. Crofford**, None.

1118

Olecranon Bursitis Is Often Hemorrhagic and Responds to Steroid Injections. Kyriakos A. Kirou and Naveed Chaudrhry. Hospital for Special Surgery, New York, NY.

Background/Purpose: Olecranon bursitis is a common presentation to an outpatient rheumatology practice. The differential diagnosis includes crystalline bursitis (gout and pseudogout), inflammatory bursitis due to systemic arthritis such as rheumatoid arthritis, infectious, and hemorrhagic. We have observed a larger than expected percentage of hemorrhagic olecranon bursitis in our practice and wanted to report our experience with this entity and its management.

Methods: We systematically looked for the ICD9 diagnosis code 726.33 in our academic rheumatology outpatient practice from 2011–2014. We recorded the patents demographic information, as well as clinical examination findings, bursa fluid analysis, and response to glucocorticoid injections. We defined inflammatory cases when the tissues around the swelling were erythematous and hot and the synovial fluid was inflammatory (>2,000 WBC with predominance of PMN). Non-inflammatory cases were defined when none of the above were present. A bursitis was defined as infectious when a culture was positive and possibly infectious when culture was negative but there were no crystals in the fluid. Hemorrhagic bursitis was identified when the bursa fluid had the appearance of pure blood. A bursa was defined as large when its diameter was >5 cm (larger than golf ball), intermediate when its diameter was 2.5–5 cm and small when its diameter was <2.5 cm.

Results: We identified 9 patients. Of those, 6 were non inflammatory in appearance. All of them proved to be hemorrhagic and negative for infection on culture. The remaining 3 were inflammatory, but no crystals were identified in the fluid under polarizing microscopy. The fluid was yellow opaque in 2 of those cases and in one case there was only 1 drop of blood which was hemorrhagic in appearance. The 6 hemorrhagic cases were injected with depomedrol 40 mg and five had a dramatic response within few days-few weeks. We had no follow up in 1 patient. Of 3 inflammatory cases, one had a documented infection with MSSA, another one responded well to antibiotics, and another was lost to follow up. Of note, all of our patients were males with an average age of 54 (range: 32–72), relatively high BMI (average 30.5 with range: 21–45). Of the 6 hemorrhagic cases, 4 were large and 2 intermediate in size. Two of the inflammatory cases were small and one large. One out of 6 hemorrhagic bursa patients was on warfarin and another on dabigatran.

Conclusion: Hemorrhagic bursitis is not uncommon and should be suspected when there is no inflammation on examination. Middle age men, especially those with higher BMIs, and perhaps those on anticoagulation appeared to be at higher risk for this entity. Our experience suggests that an injection with glucocorticoids is an effective treatment strategy and leads to resolution or marked improvement within few days-few weeks.

Disclosure: K. A. Kirou, None; **N. Chaudhry**, None.

1119

Comparison High Intensity Laser Therapy and Wrist Splint in the Treatment of Lateral Epicondylitis. Ekrem Akkurt[1], Halim Yilmaz[1], Ali Salli[2], Selman Parlak[3], Gulten Karaca[1] and Sami Kucuksen[4]. [1]MD, Konya, Turkey, [2]MD, Konya, Turkey, [3]MD, Konya, Turkey, [4]MD, Konya, Turkey.

Background/Purpose: Lateral epicondylitis (LA), also known as tennis elbow, is a quite common disease with a prevalence of 1.7% and mostly seen between 3rd and 6th decade of life.

Methods: 67 elbows diagnosed with lateral epicondylitis were divided randomly into two groups as HILT (33,9 and as wrist splint (34). 33 wrists were treated for 5 sessions weekly for two weeks. The remaining elbows, 34, were recommended to wear wrist splints for 6 subsequent weeks. The aim of this study is to compare the efficacy of HILT and wrist splint treatment. Patients were evaluated before and in 6th week of post treatment period using visual analogue scale for pain (VAS) during activity and resting, Disabilities of the Arm, Shoulder and Hand (DASH) Score, hand grip strength test (HGST), and Short Form 36 (SF-36).

Results: Out of the 60 patients, 14 male and 46 female with a mean age of 46,28 ± 9,44. The pretreatment and 6th week scores of the HILT patients were as follows: VAS activity 8,33±1,97, 6,03±2.35 VAS resting 5,75±3,27, 2,72±2.41, DASH 53.40±22, 38.33±17.10, HGST 15.49±9.95, 21,52±13,18, SF 36 physical component 35.35±17,72, 66,74±15,75, and SF 36 mental component 46,43±17.31, 62,16±17,93 and of the wrist splint group as the following: VAS activity 7,77±2,34, 6,14±3,20, VAS resting 4,67±3,10, 2,79±3.01, DASH 44,68±16,03, 30.49±17.52, HGST 17,19±7,66, 20,81±8,11, SF 36 physical component 36,70±15,13, 50,42±18,93, and SF 36 mental component 38,62±15,57, 52,33±18,72.

The VAS activity, resting, DASH, HGST, SF36 physical, and SF36 mental component scores of both groups revealed significant improvements on comparing their pretreatment and 6th week score. Except the SF physical component scores, none of these variables were statistically significant when the HILT and wrist splint groups were compared. The statistical difference was in favor of the HILT group.

Conclusion: The findings of the present study suggest that both HILT and wrist splints are reliable, safe, and effective treatment options in LE patients. Although HILT has been determined to be more effective in increasing functional capacity, both groups revealed almost equally positive outcomes, in the short and long term considering pain, functional status and quality of life.

Disclosure: E. Akkurt, None; **H. Yilmaz**, None; **A. Salli**, None; **S. Parlak**, None; **G. Karaca**, None; **S. Kucuksen**, None.

1120

The Relationship Between Tender Points and Disease Severity in Patients with Fibromyalgia. Oya Ozdemir[1] and Fitnat Dincer[2]. [1]Hacettepe University Faculty of Medicine, Ankara, Turkey, [2]Hacettepe University, Faculty of Medicine, Ankara, Turkey.

Background/Purpose: The aim of this study was to investigate the relationship between tender point examination and disease severity in patients with a diagnosis of fibromyalgia according to the 1990 American College of Rheumatology criteria.

Methods: Sixty three consecutive female patients, with a mean age of 43.8±10.5 years, were included to the study. Digital palpation of tender points was performed by the same physician (OO), after then total tender point count (TPC) and myalgic score (rated as 0=no pain, 1=mild pain, 2=a verbal exclamation of pain, 3=withdrawal or flinching) were calculated. In order to assess the disease severity, Fibromyalgia Impact Questionnaire (FIQ) was used.

Results: The median duration of symptoms was 3.0 years (range, 0.5–20). The mean of total TPC and myalgic score were 14.7±2.5 and 25.3±8.0, respectively. The mean of FIQ total score was found to be 63,2±15.9. Both TPC and myalgic score do not correlate with the patients' age and symptom duration. We have found no statistically significant correlation between total TPC and FIQ (p=0.070). However, there was a positive correlation between total myalgic score and FIQ (p=0.035, r=0,267).

Conclusion: As an indicator of disease severity, calculating the total myalgic score appears to be more informative than the TPC in female patients with fibromyalgia.

Disclosure: O. Ozdemir, None; **F. Dincer**, None.

ACR/ARHP Poster Session B
Genetics, Genomics and Proteomics II
Monday, November 17, 2014, 8:30 AM–4:00 PM

1121

The mtDNA Haplogroups Influence the DNA Methylome of Articular Chondrocytes. Ignacio Rego-Perez[1], Juan Fernández-Tajes[1], Mercedes Fernandez Moreno[1], Angel Soto-Hermida[1], María Eugenia Vázquez-Mosquera[1], Estefanía Cortés-Pereira[1], Maria Tamayo[2], Sara Relaño-Fernandez[1], Alejandro Mosquera[2], Natividad Oreiro-Villar[1], Carlos Fernandez-Lopez[1], Jose Luis Fernandez[2] and Francisco J. Blanco Garcia[1]. [1]Servicio de Reumatología. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC), A Coruña, Spain, [2]Departamento de Genética. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC), A Coruña, Spain.

Background/Purpose: Mitochondria and DNA methylation play a main role in the development of Osteoarthritis. The aim of this work is to analyze the influence of the mitochondrial background on the DNA methylome of articular chondrocytes.

Methods: DNA methylation profiling was performed using the Infinium HumanMethylation27 beadchip. Previously, cartilage isolated DNA from 41 cartilage samples (13 from haplogorup J and 20 from haplogroup H) was bisulfite-modified using EZ DNA methylation kit and hybridized according to the manufacturerxs instructions. DNA methylation M-values were obtained and further compared between haplogroups using ANOVA and adjusting for cofounder effects of age, gender and disease status. Bonferroni post-hoc analysis was performed for analysing haplogroup pairwise differences. Enrichment in biological process and molecular function was tested by means of IPA (Ingenuity Pathway Analysis) software (Qiagen). All statistical analyses were conducted in R software.

Results: ANOVA analysis showed a total of 1926 CpG probes with a p-value under 0.05 (Figure 1); bonferroni post-hoc analysis allowed us to identify 538 significant probes (adjusted p-value < 0.05) between haplogroup H and haplogroup J; of these, 451 were more methylated in J and 87 were less methylated in J in relation to the most common haplogroup H.

A CpG site in the promoter region of fucosidase, alpha-L-1 (FUCA1) gene was the most differentially methylated probe between H and J groups, being the most methylated in haplogroup J; on the contrary, a CpG site located in the promoter region of homeobox D3 (HOXD3) gene, the second most differentially methylated probe between H and J groups, was the less methylated in haplogroup J, compared with the most common haplogroup H.

Among the most significant altered canonical pathways obtained with IPA software, those involving apoptosis signalling (p=0.013) and inflammatory response (p=0.0048) stand out. Besides, an enrichment of several pathways involved in TGF-β signalling (p=0.0107), iNOS signalling (p=0.0011), BMP signalling (p=0.0044), Protein kinase A signalling (p=0.0071), MAPK signalling (p=0.016) or PI3K signalling (p=0.0074) were also revealed. It is noteworthy that, to a greater or lesser extent, these pathways are involved in the OA process.

Conclusion: The mitochondrial genetic background seems to modify the nuclear epigenome of articular chondrocytes. Some of the altered pathways, mainly enhanced in carriers of the haplogroup H, have been previously described to be involved in the etiology of OA. The role played by the mtDNA haplogroups on Spanish patients with OA could be mediated by this particular epigenetic profile.

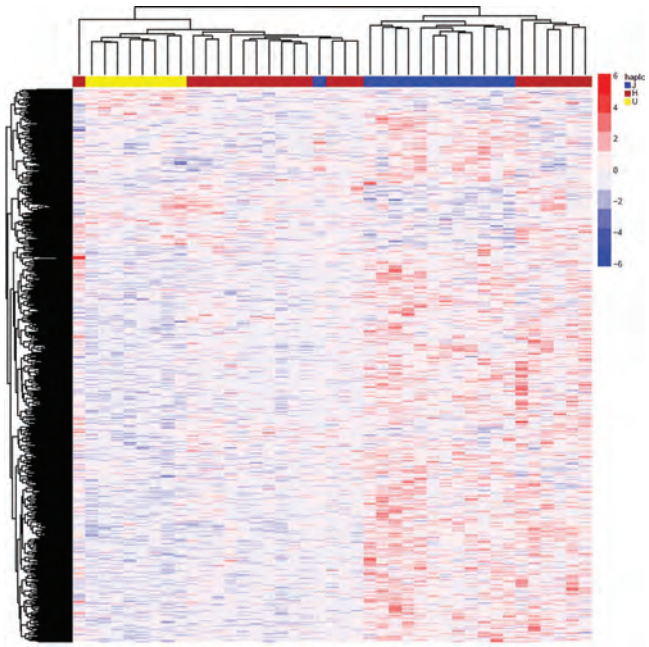

Figure 1. Heatmap showing the differential DNA methylome related to the mtDNA haplogroups

Disclosure: I. Rego-Perez, None; **J. Fernández-Tajes**, None; **M. Fernandez Moreno**, None; **A. Soto-Hermida**, None; **M. E. Vázquez-Mosquera**, None; **E. Cortés-Pereira**, None; **M. Tamayo**, None; **S. Relaño-Fernandez**, None; **A. Mosquera**, None; **N. Oreiro-Villar**, None; **C. Fernandez-Lopez**, None; **J. L. Fernandez**, None; **F. J. Blanco Garcia**, None.

1122

Transmitocondrial Cybrids: A Tool to Study the Role of mtDNA Haplogroups in OA Pathogenesis. Mercedes Fernandez Moreno[1], Tamara Hermida-Gómez[2], Angel Soto-Hermida[1], Juan Fernández-Tajes[1], María Eugenia Vázquez-Mosquera[1], Estefanía Cortés-Pereira[1], Sara Relaño-Fernandez[1], Natividad Oreiro-Villar[1], Carlos Fernandez-Lopez[1], Esther Gallardo-Perez[3], Rafael Garesse[3], Ignacio Rego-Perez[1] and Francisco J. Blanco Garcia[1]. [1]Servicio de Reumatología. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC), A Coruña, Spain, [2]Grupo de Bioingeniería Tisular y Terapia Celular (CBTTC-CHUAC). CIBER-BBN/ISCIII. Servicio de Reumatología. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de Coruña (CHUAC). SERGAS. Universidade de A Coruña, A Coruña, Spain, [3]Departamento de Bioquímica, Instituto de Investigaciones Biomédicas, Madrid, Spain.

Background/Purpose: Mitochondria play an important role in the OA pathogenesis. mtDNA haplogroup J is significantly associated with a lower risk of OA in northwest Spanish populations. Transmitochondrial cybrids,

that carry the same nuclear background and different mitochondrial variants, are optimal cellular model to study mitochondrial biology and function. This cellular model excludes variations from the nuclear genome in the cellular activity. The aim of this work is to test the real role of mtDNA haplogroups in cellular activity, using cybrids with mtDNA haplogroup H and J and analyzing several parameters implicated in the OA process.

Methods: Cybrids were developed using the 143B.TK$^-$ rho-0 cell line and platelets from healthy (without OA) and OA donors with mtDNA haplogroups H and J. The metabolic status was evaluated by measuring both lactic acid production and glucose consumption. The respiration was evaluated with a high resolution respirometry (Oroboros). The ATP levels were obtained by luciferase reaction. The expression levels of genes implicated in inflammation (COX-2 and iNOS), Metalloproteinases (MMP-1, 3 and 13) and MnSOD, were evaluated by RT-PCR. The ROS production and percentage of apoptotic cells were measured by Flow Cytometry (mean fluorescence intensity).

Results: Cybrids carrying the mtDNA haplogroup J show higher lactic acid production (62.22 mg/ml and 52.71 mg/ml; $p<0.05$) and 20% higher of glucose consumption than H cybrids, therefore being more efficient using glucose vie glycolysis, In addition, J cybrids show lower levels of ATP (0.027nmol ATP/mg protein) than H (0.033nmol ATP/mg protein), and higher values of oxygen consumption (36.92 nmmol/ml for J cybrids and 9.97 nmmol/ml for H cybrids). H cybrids had significantly higher levels of total ROS (203.30 for H cybrids and 131.26 for J) and mitochondrial ROS (47.36 and 36.87 respectively). MnSOD expression in basal conditions was higher in cybrids H than J (2-fold) and IL-1β stimulation (5 ng/ml 24 hours) showed 2-fold increase of MnSOD in J cybrids compared to H. The analysis of inflammatory process showed that the basal expression levels of COX-2 and iNOS were higher in H than in J (H expressed 4-fold COX-2 than J; iNOS was 1.5-fold). Basal expression of MMP-1, 3 and 13 was higher in cybrids H than J. The percentage of cell in spontaneous apoptosis was similar between cybrids H (3.76%) and J (5.78%). The use of staurosporine (0.2μM, 2 hours) to induce apoptosis showed a 7-fold increase of apoptosis in H cybrids.

Experiments performed in OA cybrids confirm the metabolic differences between H cybrids and J cybrids, as well as the higher susceptibility of H cybrids than to undergo apoptosis.

Conclusion: H and J cybrids have different metabolic behavior (J are more glycolysis dependent than H). Cybrids J have a lower ATP production, lower inflammatory response and produce less reactive species of oxygen. Cybrids J are less susceptible to undergo apoptosis. All these results offer a real rationale for why haplogroup J is associated with lower risk of OA.

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Impact of Genes Modulating Serum Low-Density Lipoprotein Cholesterol Levels on Progression of Joint Destruction in Japanese Patients with Rheumatoid Arthritis. Shinji Yoshida[1], Katsunori Ikari[1], Koichiro Yano[1], Yoshiaki Toyama[2], Atsuo Taniguchi[3], Hisashi Yamanaka[1] and Shigeki Momohara[3]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]Department of Orthopaedic Surgery, Keio University School of Medicine, Tokyo, Japan, [3]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) have a higher prevalence of dyslipidemia than healthy individuals. Since RA is a chronic inflammatory disease, an inflammatory response may be partly involved in the pathogenesis of dyslipidemia. Recently, low-density lipoprotein (LDL) cholesterolemia has been reported to be a risk factor for radiographic progression of joint destruction. Several genetic risk loci for progression of joint destruction have been identified so far. However, the genetic predisposition factors have not yet been elucidated. The purpose of this study was to evaluate impact of genetic variants modulating serum LDL cholesterol (LDL-C) levels on progression of joint destruction in Japanese patients with RA.

Methods: This study included 1,005 Japanese patients with RA for whom Sharp/van der Heijde scores (SHS) of hands were available at a disease duration of 5 years. DNA samples of the subjects were obtained from the Institute of Rheumatology Rheumatoid Arthritis cohort study (IORRA) DNA collection. All of the patients who donated DNA samples consented to participate in this study as approved by the Tokyo Women's Medical University Genome Ethics Committee, and satisfied the American College of Rheumatology 1987 revised criteria for the classification of RA. Thirteen single nucleotide polymorphisms (SNPs) in the 8 loci influencing serum LDL-C concentrations in the Japanese population were selected and genotyped in the DNA samples: rs611917, in *SORT1*; rs693, rs7575840, and rs515135, in *APOB*; rs3846662, in *HMGCR*; rs662799, in *BUD13-APOA1-APOA5*; rs838867, in *SCARB1*; rs1532624, and rs2303790, in *CETP*; rs688, and rs1433099, in *LDLR*; rs429358, and rs7412, in *APOE-C1*. Multivariate linear regression analyses were performed to examine the association of each SNP with radiographic progression of joint destruction in the first 5 years after onset of RA, calculated as SHS of hands at the 5-year disease duration. Adjustments were made for gender, age of onset, anti-citrullinated peptide status, and year of disease onset. All SHS were log-transformed to obtain a normal distribution.

Results: Multivariate linear regression analyses revealed that the minor allele of rs662799 in *BUD13-APOA1-APOA5* was associated with progression of joint destruction in the recessive model ($P=0.04$). However, the association could not reach the level of the significance after Bonferroni correction for multiple comparisons. The other SNPs showed no association (Table 1).

Conclusion: We could not confirm the association between genes modulating serum LDL-C levels and progression of joint destruction in Japanese patients with RA. Our results indicated that rs662799 in *BUD13-APOA1-APOA5* might be a risk factor for progression of joint destruction, but further studies would be required to confirm the association.

Table 1 Multivariate linear regression analyses of each SNP associated with progression of joint destruction

Gene	SNP	Allele (minor/major)	MAF	Risk allele	Tested model	β	*P* value
SORT1	rs611917	G/A	0.07	A	additive	−0.01	0.79
					dominant	0.02	0.65
					recessive	−0.01	0.69
APOB	rs693	A/G	0.04		Aadditive	0.02	0.6
					dominant	0.02	0.52
					recessive	−0.04	0.36
	rs7575840	T/G	0.08	T	additive	0.03	0.37
					dominant	0.03	0.39
					recessive	0.01	0.65
rs515135	T/C	0.1	T		additive	0.02	0.57
					dominant	0.02	0.59
					recessive	0.01	0.77
HMGCR	rs3846662	A/G	0.48	G	additive	0	0.93
					dominant	0.02	0.59
					recessive	−0.01	0.71
BUD13-APOA1-APOA5	rs662799	G/A	0.34	G	additive	0.05	0.14
					dominant	0.07	0.04
					recessive	0	0.95
SCARB1	rs838867	G/A	0.46	A	additive	0.03	0.32
					dominant	−0.01	0.88
					recessive	0.05	0.1
CETP	rs1532624	T/G	0.3	G	additive	−0.01	0.86
					dominant	0	0.96
					recessive	−0.01	0.8
	rs2303790	G/A	0.03	A	additive	−0.04	0.23
					dominant	0.02	0.43
					recessive	−0.05	0.16
LDLR	rs688	T/C	0.12	T	additive	−0.06	0.05
					dominant	−0.06	0.08
					recessive	−0.04	0.16
	rs1433099	T/C	0.29	C	additive	−0.03	0.4
					dominant	−0.05	0.11
					recessive	−0.01	0.85
APOE-C1	rs429358	C/T	0.1	C	additive	−0.03	0.3
					dominant	−0.03	0.36
					recessive	−0.02	0.43
	rs7412	T/C	0.04	T	additive	0.03	0.33
					dominant	−0.03	0.14
					recessive	0.04	0.17

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Genome-Wide Profiling of DNA from Cartilage Reveals Regions Differently Methylated in Osteoarthritis Patients. Guangju Zhai[1], Ming Liu[2], Yuhua Zhang[1], Patricia E. Harper[1], Erfan Aref-Eshghi[2], Glynn Martin[3], Andrew Furey[3], Roger Green[1], Guang Sun[4] and Proton Rahman[5]. [1]Discipline of Genetics, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NF, [2]Memorial University, St. John's, NF, [3]Department of Surgery, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NF, [4]Discipline of Medicine, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NF, [5]Memorial University of Newfoundland, St. John's, NF.

Background/Purpose: Osteoarthritis (OA) represents the most common form of arthritis and has substantial clinical and economic impact. Evidence supports that DNA methylation plays a significant role in OA. The aim of the study was to identify differentially methylated loci for OA using an epigenome-wide association approach.

Methods: Cartilage samples were collected from 14 patients who underwent total hip joint replacement due to primary OA and 16 hip fracture patients who do not have evidence of hip OA. DNA was extracted from the cartilage samples and methylation profiling was performed using the Illumina Infinium HumanMethylation 450k chip, which measures about 480,000 different CpG sites covering 96% of RefSeq genes. It provides comprehensive gene region coverage, targeting multiple sites including the promoter, 5' UTR, 1st exon, gene body and 3' UTR. The methylation level at each CpG site was measured by β values varying from 0 (no methylation) to 1 (100% methylation).

Results: We found 18 individual CpG sites significantly associated with OA, with a mean difference in methylation level of >10% and a p value < 10^{-4}. Six of them were hypermethylated and 12 were hypomethylated in OA patients. Nine of them are located within genes and other 9 are intergenic. Two genes – COL8A1 and CDKN2C have been reported recently using the same approach as ours and the other 16 CpG sites are novel. ATG7 involving in autophagic pathway and CLCN7 causing osteopetrosis are novel promising candidates for OA.

Conclusion: We confirmed the recently reported association of COL8A1 and CDKN2C methylation with OA and identified 16 novel DNA methylation loci for OA, providing new insight into the pathogenesis of OA. Confirmation study with large sample size is underway.

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The Mitochondrial Genome Influences the Risk of Incident Knee OA. DATA from the Osteoarthritis Initiative. Angel Soto-Hermida[1], Ignacio Rego-Pérez[1], Juan Fernández-Tajes[1], Mercedes Fernandez Moreno[1], María Eugenia Vázquez-Mosquera[1], Estefanía Cortés-Pereira[1], Sonia Pértega-Díaz[2], Natividad Oreiro-Villar[1], Carlos Fernandez-Lopez[1] and Francisco J. Blanco Garcia[1]. [1]Servicio de Reumatología. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC), A Coruña, Spain, [2]Unidad de Epidemiología Clínica y Bioestadística. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC), A Coruña, Spain.

Background/Purpose: Previous studies by our group showed a significant influence of the mtDNA haplogroups on both radiographic progression and cartilage integrity of knee OA patients from the Osteoarthritis Initiative (OAI). The aim of this study is to analyze the influence of the mitochondrial variants on the risk of incident knee OA in patients with pre-radiographic OA of the OAI.

Methods: We assessed the mtDNA haplogroups in 2374 Caucasian samples of the OAI to analyze their influence on incident knee OA. Incidence of knee OA was defined as a KL score <2 at baseline and a KL≥2 at 4 years follow-up of the same knee. We also included individuals with unilateral KOA, since they were at risk of developing incident OA at the other knee. Statistical analyses included chi-square contingency tables and logistic regression models considering age, gender, body mass index (BMI), contralateral knee OA and mtDNA variants as variables of interest. Further, the area under the receiving operative characteristic (ROC) curve (AUC) of the model was also calculated.

Results: After 4 years of follow-up, a total of 214 patients developed incident knee OA, meanwhile 1323 did not. The rest of patients (n=837) had a KL score≥2 at baseline in both knees, therefore did not meet the selection criteria and were subsequently excluded from further analyses. Patients belonging to mtDNA cluster HV were significantly overrepresented in the incident knee OA group (OR=1.395; CI=1.044–1.8636; p=0.024) meanwhile patients in cluster TJ were less represented in the incident group (OR=0.692; CI=0.466–1.026;p=0.065). The logistic regression model showed that female gender (p<0.001), higher BMI (p<0.001) and contralateral knee OA (p<0.001) were risk factors to develop incident OA; additionally, OA patients in cluster HV were at higher risk for incident knee OA than patients in cluster TJ (p=0.016). The AUC of this regression model was 0.707

Conclusion: The mitochondrial genome contributes to the development of incident knee OA. The assignment of the mtDNA haplogroups could be used as complementary genetic biomarkers to predict the risk of incident knee OA.

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Quantitative Proteomics (iTRAQ) Reveals Putative Biomarkers in Pre-Radiological Osteoarthritis. Jesús Mateos[1], Alejandra Pintor-Iglesias[1], Patricia Fernandez-Puente[2], Sara Relaño[3], Ignacio Rego-Perez[4], Carlos Fernández-López[5], Natividad Oreiro[6], Cristina Ruiz-Romero[7] and Francisco J. Blanco Garcia[4]. [1]Grupo de Proteomica-PBR2-ProteoRed/ISCIII Servicio de Reumatologia. Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC). As Xubias, 15006. A Coruña, Spain, A Coruña, Spain, [2]Grupo de Proteomica-PBR2-ProteoRed/ISCIII Servicio de Reumatologia. Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC). As Xubias, 15006. A Coruña, Spain, A Coruna, Spain, [3]Grupo de Genomica. RIER/ISCIII; Servicio de Reumatologia. Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC). As Xubias, 15006. A Coruña, Spain., A Coruña, Spain, [4]Servicio de Reumatología. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC), A Coruña, Spain, [5]INIBIC-Hospital Universitario A Coruña. Rheumatology Division. Genomic Group, A Coruña, Spain, [6]INIBIC-Complejo Hospitalario Universitario A Coruña (CHUAC), La Coruña, Spain, [7]Grupo de Proteomica-PBR2-ProteoRed/ISCIII Servicio de Reumatologia. Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC). As Xubias, 15006 A Coruña, Spain, A Coruña, Spain.

Background/Purpose: In this study we have identified proteins differentially abundant in the serum of Osteoarthritis (OA) patients comparing four different progressive pathological grades using mass spectrometry and iTRAQ technique for relative quantification. Our final aim is to establish a panel of biomarkers useful to predict the pathology in pre-radiological stages (early Osteoarthritis biomarkers), but also for its handling and the developing of trials of treatment in radiological stages (late Osteoarthritis biomarkers).

Methods: 15 individual samples for each condition (OA Grade 0, pre-radiological stage Grade I, and radiological stage grades II-III and IV) were pooled in three groups with the aim of reducing the contribution of individual extreme values. After enrichment in the low-abundant protein fraction, the pooled samples were subjected to in-solution digestion, followed by iTRAQ labelling following manufacturer instructions and Reverse Phase peptide separation in a LC system (Agilent 1200). Fractions were again separated in a nanoLC system (Tempo, Eksigent) automatically deposited on a MALDI plate and analyzed by MSMS in a 4800 MALDI-TOF/TOF system (ABSciex). Relative quantitative analysis was done using ProteinPilot software (ABSciex) and modulated proteins were analyzed with String 9.0 software.

Results: We have detected two big sets of serum proteins modulated in the early pre-radiological OA process. Serum levels of apolipoproteins are altered when comparing Grade I vs. Grade 0. Specifically, apolipoprotein E and apolipoprotein B-100, that mediates the binding, internalization, and catabolism of lipoprotein particles are accumulated in Grade I samples. Furthermore, up to six components of the complement, a group of proteins involved in immune response and inflammation are decreased in serum in early OA grades. Among them, complement component 5 -C5-, that have been recently identified as key player of the OA process, is much less abundant in any OA grade in comparison to Grade 0. Proteins previously described as putative biomarkers by our group and others, like histidine-rich

glycoprotein, gelsolin and decorin, are also modulated in our study, but at later radiological stages -Grade II/III and Grade IV *vs.* Grade I and Grade 0-.

Conclusion: Our results indicate that early pathological grades of the OA process are linked to an imbalance in the metabolism and, specifically, in the lipid metabolism. Altered serum levels of apo-lipoproteins could be used, in combination with other 'dry' biomarkers, as an indicator for early OA process and to detect the pathology in pre-radiological stages. Furthermore, the lower serum levels in the OA grades detected for the complement component 5 -C5-, strongly support recent *in vivo* data indicating that a decrease of this protein is linked to the development of the disease.

Table 1: Summary of the results

Main proteins modulated in pre-radiological OA Grade I vs. OA Grade 0 (Healthy controls)	*Ratio GI/G0*	*p-value*	*Main proteins modulated in late OA Grade IV vs. pre-radiological OA Grade I*	*Ratio GIV/GI*	*p-value*
Apolipoprotein E	2.25	0.02	Zinc-alpha-2-glycoprotein	5.43	0
Apolipoprotein B-100	2.0137	0.0001	Histidine-rich glycoprotein	4.1305	0
Apolipoprotein A-IV	1.9953	0.0046	Beta-2-glycoprotein 1	4.529	0.0084
Complement C5	0.3532	0.0001	Gelsolin	1.24	0
Complement C1s	0.413	0.0006	Decorin	0.20	0.04
Complement C2	0.2466	0.0014	Protein S100-A9	0.2399	0.0353

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Mass Spectrometry Imaging Revealed Potential Lipid Chondrogenic Biomarkers for Cell-Based Therapy in Cartilage. Beatriz Rocha[1], Berta Cillero-Pastor[2], Gert Eijkel[2], Valentina Calamia[1], Lucia Lourido[1], Carolina Fernández-Costa[1], Patricia Fernandez-Puente[1], Jesus Mateos[1], Cristina Ruiz-Romero[1], Ron MA Heeren[2] and Francisco J. Blanco Garcia[1]. [1]Grupo de Proteomica-PBR2-ProteoRed/ISCIII-Servicio de Reumatologia. Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC). As Xubias, 15006., A Coruña, Spain, [2]AMOLF, Amsterdam, Netherlands.

Background/Purpose: Recent studies highlight the importance of lipid metabolism in the modulation of chondrogenesis. Specifically, the positive chondrogenic effect of acid ceramidase, which is necessary to maintain the metabolic balance of several bioactive lipids, during the chondrogenesis of mesenchymal stem cells (MSCs) has been demonstrated. Therefore, knowledge on the distribution and modulation of lipids during chondrogenesis could be highly valuable to improve MSC-based cartilage therapies by the discovery of new chondrogenic markers. In this work, mass spectrometry imaging (MSI) has been employed to characterize the spatial distribution of lipids in human bone marrow MSCs (hBMSCs) during the first steps of their chondrogenic differentiation.

Methods: hBMSCs micromasses obtained from 3 osteoarthritic donors and collected at day 2 and 14 of chondrogenesis were gelatin-embedded and cryo-sectioned into thin sections for MSI. Samples were then sprayed with matrix and analyzed by matrix-assisted laser desorption ionization (MALDI)-MSI to obtain the lipid profiles. Statistical methods such as PCA and discriminant analysis were used for data interpretation. Lipid images were generated with Biomap software. Data were confirmed by Real-Time PCR analyses.

Results: Analysis of hBMSCs micromasses at days 2 and 14 of chondrogenesis by MALDI-MSI led to the identification of 20 different intact lipid species, including fatty acids, sphingolipids and phospholipids (Table 1). Among the lipid classes identified, we found phosphatidylcholines and sphingomyelins levels decreased during chondrogenic differentiation (Figure 1). These data suggest that hBMSCs mobilize the SMs in order to produce secondary metabolites such as sphingosine-1-phosphate and ceramides that are necessary for their differentiation towards chondrocytes. In addition, a clear up-regulation of 4.74-fold was found for sphingosine kinase 1 ($p<0.05$) at day 14 when compared to day 2, supporting the low expression of SMs intact species at day 14 of chondrogenesis.

Conclusion: The data compiled herein are undoubtedly useful for a better understanding of the molecular processes that occur during the differentiation of these cells towards cartilage-like tissues. In addition, the differential lipid profiles described in our study might serve as useful differentiation markers for the development of cell-based therapies for cartilage repair. In fact, the loss of SM during chondrogenesis might be used as a novel chondrogenic marker.

TABLE 1 Lipid profiles of hBMSCs undergoing chondrogenesis after MALDI-MSI analysis.

m/z peak	Lipid assignment	Condition
303.2	Arachidonic acid	Day 14
327.2	Docosahexaenoic acid	Day 14
723.5	SM (d18:1/16:1)	Day 2
725.5	SM (d18:1/16:0)	Day 2
729.5	SM (d18:1/18:1)	Day 2
739.5	PC (16:0/18:1-N(CH_3)$_3$)	Day 2
750.5	PE (18:0/20:4)	Day 14
767.5	SM (d18:1/19:0)	Day 2
778.5	ST (d18:1/16:0)	Day 14
790.5	PC (18:0/18:0)	Day 2
794.5	PE (18:0/22:4)	Day 14
798.5	PC (16:0/18:1)	Day 2
800.5	PC (34:0)	Day 2
819.5	PG (18:1/22:6)	Day 14
824.5	PC (36:2)	Day 2
826.6	PC (18:0/18:1)	Day 2
832.5	PC (18:4/20:0)	Day 2
853.6	SM (d18:1/24:0)	Day 2
883.6	PI (18:1/20:4)	Day 14
943.5	PI (18:0/20:4)	Day 14

PC: phosphatidylcholine, SM: sphingomyelin, PE: phosphatidylethanolamine, ST: sulfatide, PG: phosphatidylglycerol and PI: phosphatidylinositol.

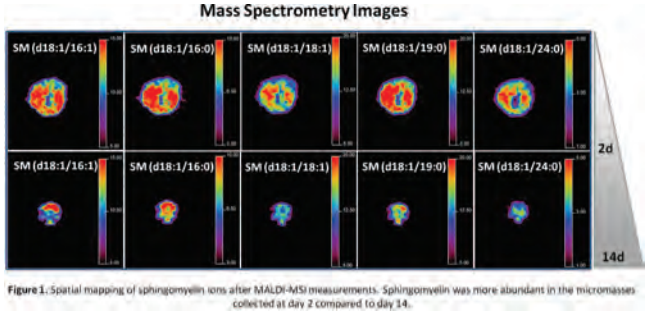

Figure 1. Spatial mapping of sphingomyelin ions after MALDI-MSI measurements. Sphingomyelin was more abundant in the micromasses collected at day 2 compared to day 14.

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Regulation of PIWIL4 By Histone Modifications in Rheumatoid Arthritis. Lenka Pleštilová[1], Niharika Gaur[1], Mária Filková[2], Borbala Aradi-Vegh[1], Ladislav Senolt[3], Adrian Ciurea[1], Renate E. Gay[4], Jiri Vencovsky[3], Michel Neidhart[5], Steffen Gay[5] and Astrid Juengel[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich Schlieren, Switzerland, [2]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [3]Institute of Rheumatology and Clinic of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [4]Zurich University Hospital, Zurich, Switzerland, [5]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: Analog to miRNAs that bind to argonaute proteins to suppress gene expression, a new group of non-coding RNAs piwi-interacting RNAs (piRNAs, 26–31 nt) build complexes with the argonaute-family members "P-element induced wimpy testis" (PIWI)-like proteins to repress retrotransposons in germ cells. In somatic cells a high expression of the PIWIL proteins was associated with cancer.

The aim of our study was to analyse the expression and regulation of PIWIL proteins in synovial cells and in peripheral blood mononuclear cells (PBMC) from patients with rheumatoid arthritis (RA) focusing on the regulation of PIWIL4 by histone methylation and acetylation.

Methods: Expression of PIWIL mRNA was analysed by TaqMan RealTime-PCR and normalised to HPRT1 in synovial fibroblasts (SF) and synovial tissues (ST) from RA and osteoarthritis (OA) patients (n=5 each). PIWIL4 protein expression was analysed by Western blot.

RASF and OASF (n=5–12) were stimulated or not for 24 hours with Poly(I:C) (10ug/ml), LPS (100ng/ml) or TNFα (10ng/ml) in combination with IL1β (1ng/ml). RASF (n=3–6) were treated or not with the DNA methylation inhibitor 5-Azacytidine (5-AZA, 1uM, 7 days), the histone deacetylase inhibitor Trichostatin A (TSA, 1uM, 24h), the histone methylation inhibitor 3-Deazaneplanocin A (DZNep, 2.5uM, 48h) or with the methyl donor Betaine (50mM, 14 days).

After silencing PIWIL4 we assessed proliferation by cell counting. We analysed expression of PIWIL4 mRNA in PBMC isolated from patients with RA, systemic lupus erythematosus (SLE), axial spondyloarthritis (axSpA) and from healthy controls (HC, n=6–12 each).

Results: PIWIL2, 3 and 4 but not PIWIL1 could be detected in both RA and OASF without significant changes (RA/OA mean dCt=3.87/2.83, 9.50/12.32, 2.63/3.21). A high expression of PIWIL4 was also found in ST of patients with RA and OA (mean dCt=3.59/2.91).

Levels of PIWIL4 mRNA were further enhanced by Poly(I:C) in both RASF and OASF 2.9-fold (p=0.003)/3.4-fold (p=0.013); LPS 2.1-fold (p=0.026)/2.6-fold (p=0.025) and TNFα in combination with IL1β 1.9-fold (p=0.003)/1.7-fold (p=0.007). However, on the protein level no induction of PIWIL4 expression could be detected.

Treatment of RASF with 5-AZA did not regulate PIWIL4 expression, treatment with TSA down-regulated PIWIL4 mRNA to 0.4-fold (p=0.003); DZNep to 0.7-fold (p=0.026) and Betaine treatment caused 1.4-fold induction of PIWIL4 mRNA (p=0.043).

PIWIL4 silencing in RASF significantly decreased mRNA expression of the histone deacetylase HDAC1 (to 0.6-fold, p=0.0003), but not HDAC2 or HDAC3. Furthermore PIWIL4 silencing decreased cell proliferation in RASF stimulated with TNFα and IL1β by 30% (p=0.034).

In PBMC of patients with RA the expression of PIWIL4 was higher than in HC (mean dCt=2.18 vs. 2.64, $p<0.05$), but lower than in patients with SLE (mean dCt=1.42, $p<0.001$). There was no difference between RA and axSpA patients (mean dCt=2.30).

Conclusion: We have demonstrated that PIWIL4 expression is regulated by inflammatory cytokines and epigenetic modifications with functional consequences on proliferation suggesting a role of PIWIL4 in the activation of synovial fibroblasts in RA.

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***FCGR2A* Polymorphism and Response to Anti-TNF Treatment in Rheumatoid Arthritis.**

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Background/Purpose: TNF-α inhibitors have significantly improved the prognosis of patients with Rheumatoid Arthritis (RA). Despite this, approximately 30% of patients fail to achieve a satisfactory clinical response. One of the main challenges of personalized medicine in RA is being able to predict those patients that have an increased likelihood of not responding to anti-TNF therapies so that such patients can be selected for other biological therapies. Recently, evidence for a specific association of the non synonymous SNP in *FCGR2A* with infliximab response has been reported. The aim of our study was to replicate this genetic association in an independent cohort of patients with RA.

Methods: A total of 348 RA patients treated with TNF-alpha inhibitors (i.e. Infliximab n=126, Adalimumab n=95, Etanercept n=127) were genotyped for *FCGRA* H131R polymorphism (i.e. rs1801274). Response to anti-TNF therapies was measured at 12–14 weeks of therapy using the EULAR response criteria. Association of clinical and epidemiological variables to treatment response was analyzed using linear model regression. Good and moderate responders were merged in a single responder group and association analyses were performed using logistic regression.

Results: The clinical characteristics of the RA patient cohorts according to anti-TNF treatment are shown in Table 1. We found a significant association ($P=0.05$) between smoking status (actual and past smokers vs non-smokers) and response to anti-TNF agents. No other clinical or epidemiological variable showed an association to treatment response. We found a significant association of *FCGR2A* SNP rs1801274 with treatment response in Adalimumab-treated patients ($P=0.01$, OR (95%CI) = 0.32(0.18–0.83)) but not in Infliximab ($P=0.3$) or Etanercept-treated patients ($P=0.82$). Including smoking status as a covariate of rs1801274 association with treatment response showed no evidence of confounding ($P_{FCGR2A} = 0.01$).

Conclusion: We have found, for the first time a specific association of *FCGR2A* with the response to Adalimumab in RA at 3 months of therapy. The lack of validation of the previous specific association of *FCGR2A* with Infliximab could be due to the low effect size of the genetic association or to differences between patient cohorts. Finally, we have also found a positive association with smoking and the response to anti-TNF agents.

Table 1 Epidemiological and Clinical Features of the Study Cohort

Feature	All (n=348)	Infliximab (n=126)	Adalimumab (n=95)	Etanercept (n=127)
Female N (%)	287 (82)	107 (85)	76 (80)	104 (82)
Age at diagnsosis Mean (SD), years	44 +/− 13	43 +/− 11	45 +/− 12	42 +/− 13
Disease duration Mean (SD), years	10 +/− 8	10 +/− 7	10 +/− 9	11 +/− 9
RF (+) N (%)	270 (78)	96 (76)	72 (77)	102 (80)
ACPA (+) N (%)	261 (78)	87 (73)	79 (86)	95 (77)
Smokers N (%)	148 (43)	52 (42)	43 (45)	43 (46)
DAS28 Mean (SD)				
Baseline	5.55 +/− 1.12	5.64 +/− 1.11	5.29 +/− 1.04	5.66 +/− 1.16
12 weeks	3.94 +/− 1.43	4.26 +/− 1.41	3.54 +/− 1.19	3.92 +/− 1.53
EULAR response (%)				
Responder (Good + Moderate)	261 (75%)	88 (70%)	76 (80%)	97 (76%)
Non responder	87 (25%)	38 (30%)	19 (20%)	30 (24%)

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***IRF8* Gene Contributes to Disease Susceptibility and Interacts with *NF-KB* By Modulating Interferon Signature in Patients with Systemic Sclerosis.**

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Background/Purpose: Systemic Sclerosis (SSc) is a polygenic autoimmune disease (AID) characterized by fibroblast dysregulation. It shares some genetic bases with other AIDs, as evidenced by autoimmune gene pleiotropism. Fibroblast dysregulation can be also observed in Primary Biliary Cirrhosis (PBC), another polygenic AID, which can be associated with SSc in the so called Reynold's Syndrome. The present study was undertaken to investigate whether single nucleotide polymorphisms (SNPs) identified by a large GWAS in PBC might contribute to SSc susceptibility by a cross-disease approach.

Methods: Sixteen PBC susceptibility SNPs were genotyped in a total of 1,616 SSc patients and 3,621 healthy controls all of whom were of European Caucasian origin.

Results: We observed an association between *PLCL2* rs1372072 (OR=1.23 [95% CI 1.12–1.33] $P_{adj}=7.22\times10^{-5}$, *NF-kB* rs7665090 OR=1.16 [95% CI 1.06–1.25], $P_{adj}=0.01$, and *IRF8* rs11117432, OR=0.75 [95% CI 0.67–0.86], $P_{adj}=2.50\times10^{-4}$ with SSc susceptibility. We subsequently queried associations according to the main subtypes and found that

rs1372072 and rs11117432 were associated with the limited cutaneous subgroup (P_{adj}=0.001 and P_{adj}=0.003, respectively) and that rs7665090 was conversely associated with the diffuse cutaneous subset (P_{adj}=0.007). We then looked for genotype – phenotype correlations by measuring mRNA expression of PBMC, obtained from patients (n=39) and controls (n=24), and observed that the *IRF8* protective allele was associated with decreased IFIT1 expression reflecting type 1 interferon signature. We investigated gene interactions between the 3 associated SNPs that revealed an epistatic interaction between *NF-kB* and *IRF8* SNPs (OR=0.56 [95% CI 0.00–0.74], $P=4\times10^{-4}$). Interestingly, we observed that the effects of *IRF8* and *NF-kB* were only observed in patients carrying the susceptibility allele from both genes.

Conclusion. By a cross disease approach querying pleiotropic genes, we identified 2 new susceptibility genes for SSc and confirmed *IRF8* locus. We also identified functional effects of *IRF8* variant affecting interferon signature and that an interaction between *IRF8* and *NF-kB* genes might play a role in SSc susceptibility.

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Identification of Genetic Variants Associated with Response to Adalimumab Plus Methotrexate in Patients with Early Rheumatoid Arthritis. Alla Skapenko[1], Hendrik Schulze-Koops[1], Viswanath Devanarayan[2], Kenneth Idler[3], Feng Hong[4], Josef S. Smolen[5], Arthur Kavanaugh[6], Hartmut Kupper[7] and Jeffrey F. Waring[3]. [1]University of Munich, Munich, Germany, [2]AbbVie Bioresearch Center, Worcester, MA, [3]AbbVie Inc., North Chicago, IL, [4]AbbVie Bioresearch Center, Worchester, MA, [5]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [6]University of California San Diego, La Jolla, CA, [7]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany.

Background/Purpose: For patients with rheumatoid arthritis (RA) who fail to attain remission or low disease activity after 6 months of methotrexate (MTX) treatment, TNF inhibitors should be considered for patients with a high risk of aggressive disease. The objective was to identify genetic variants associated with response to adalimumab (ADA)+MTX in patients with early RA.

Methods: OPTIMA was a 78-week, multicenter, randomized, double-period, double-blind study in which patients were randomized 1:1 to combination therapy with ADA+MTX or MTX alone for the first study period of 26 weeks. Enrolled patients were invited to participate in a genetic sub-study and asked to provide written, informed consent. 384 variants in genes previously shown to be associated with RA or treatment response were assayed using the Illumina BeadXpress GoldenGate Assay. Changes in the 28-joint disease activity score (DAS28) from baseline to 26 weeks and the total Sharp score (TSS) following 26 weeks of treatment were assessed for association with allele status using genotypic tests.

Results: A total of 413 patients randomized to ADA+MTX were included in the genetic sub-study. Three SNPs within the APOH gene were significantly associated with a response to ADA+MTX (Table). APOH (b2-GPI) has been shown to stimulate macrophages and to produce TNF-a in a TLR4-dependent manner, and some studies have suggested that RA patients display increased levels of autoantibodies against b2-GPI. Additionally, eight SNPs within the MAP2K6 gene, which has been shown to be activated in RA, were significantly associated with a response to ADA+MTX. Other SNPs within genes that have been associated with RA susceptibility or treatment response to TNF-a inhibitors, such as ABCB1, IL21, and STAT4, also showed an association with ADA+MTX treatment. For some genes, such as APOH and MAP2K6, multiple SNPs were identified, suggesting that haplotype analysis could identify stronger associations. In addition, SNPs within TRAF6/RAG1, APOH, and CDK6 were also associated with a change in TSS (DTSS ≥0.5).

Table. SNPs Significantly Associated with Treatment Response to ADA+MTX

Gene	SNP	Additive AA vs Ab vs bb (p-value)	Additive AA vs Ab vs bb False Discovery Rate (q-value)	Dominant Major AA vs Ab + bb (p-value)	Dominant Major AA vs Ab + bb False Discovery Rate (q-value)	Dominant Minor AA + Ab vs bb (p-value)	Dominant Minor AA + Ab vs bb False Discovery Rate (q-value)
ABCB1	rs3789244	NS	NS	0.040	0.58	NS	NS
ABCB1	rs7787082	NS	NS	0.046	0.61	NS	NS
APOH	rs4581	<0.001	0.14	<0.001	0.03	NS	NS
APOH	rs8178835	<0.001	0.14	<0.001	0.03	NS	NS
APOH	rs7212060	0.007	0.24	0.002	0.14	NS	NS
MAP2K6	rs11656130	NS	NS	NS	NS	0.022	0.55
MAP2K6	rs817543	0.006	0.23	0.003	0.14	0.031	0.55
MAP2K6	rs817546	NS	NS	NS	NS	0.031	0.55
MAP2K6	rs2716225	NS	NS	NS	NS	0.037	0.55
MAP2K6	rs707247	0.010	0.30	0.003	0.14	NS	NS
MAP2K6	rs11869348	0.015	0.42	0.004	0.17	NS	NS
MAP2K6	rs817565	0.032	0.51	0.015	0.39	NS	NS
MAP2K6	rs2716191	0.041	0.51	0.015	0.39	NS	NS
STAT4	rs7572482	NS	NS	0.026	0.52	NS	NS
STAT4	rs12327969	0.023	0.49	NS	NS	NS	NS

NS, not significant.

Conclusion: Genetic polymorphisms in genes such as ABCB1, APOH, MAP2K6, and STAT4 were shown to associate with ADA+MTX response in the OPTIMA study. These results may prove useful for the development of future diagnostic tests or personalized therapeutics for combination therapy treatment with ADA+MTX.

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A Novel Epigenetic Mark, Histone H1 Fucosylation, Orchestrates Macrophage Differentiation and Plasticity By Remodeling the Enhancer Landscape in Rheumatoid Arthritis. Jun Li[1], Keith Giles[2], Parastoo Azadi[3], Mayumi Ishihara[3], PingAr Yang[1], Qi Wu[1], Bao Luo[1], David M. Spalding[4], James A Mobley[5], S. Louis Bridgesr Jr.[1], Hui-Chen Hsu[1] and John D. Mountz[1].[1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Stem cell Institute, Birmingham, AL, [3]University of Georgia, Complex Carbohydrate Research Center, Athens, GA, [4]University of Alabama at Birmingham, Division of Clinical Immunology & Rheumatology, Birmingham, AL, [5]University of Alabama at Birmingham, Comprehensive Cancer Center Mass Spectrometry/Proteomics Facility, Birmingham, AL.

Background/Purpose: There is an imbalance of inflammatory M1 vs. anti-inflammatory M2 macrophages (MΦs) in rheumatoid arthritis (RA). The epigenetic codes underlying this M1 dominating pathogenesis in RA have not been well established. Our studies have demonstrated that terminal fucosylation, adding a fucose to the glycan termini by fucosyltransferases is a hallmark of M1 MΦs. A terminal fucosylation inhibitor, 2-Deoxy-D-galactose (2-D-gal), precluded the differentiation of M1 MΦ and skewed them to an M2 phenotype, resulting in suppression of collage II-induced arthritis. The purpose of the study is to investigate how terminal fucosylation regulates MΦ plasticity by modulating the epigenetic landscape.

Methods: Mouse bone marrow derived M1 and M2 MΦs were differentiated by GM-CSF and M-CSF respectively. Ulex Europaeus Agglutinin I [UEA 1, recognizing terminal Fucα(1–2)Gal] pull down coupled to liquid chromatography mass spectrometry (LCMS) was performed to identify the fucosylated proteins in M1 MΦs. Histone H1 was purified from mouse M1 MΦs by using high salt/acid extraction and SDS-PAGE. N-linked glycans on histone H1 was released by in gel PNGase F digestion, followed by permethylation and analyzed by MALDI/TOF-MS and NSI-FT-MS. MS/MS and MS3rd were further carried out to sequence the fucose moieties. Chromatin immunoprecipitations (ChIPs) were performed using anti-H3K4me1 and H3K27ac, followed by next generation sequencing (illumina HiSeq 2500). ChIP-Seq data were aligned to build version mm9 of mouse genome using Bowtie, and regions of enrichment were identified by the MACS peak-finding algorithm. A *p* value threshold of enrichment of $1\times10^{-9}$was used.

Results: Decreased chromatin condensation was observed in M1 compared to M2 macrophages by chromatin staining, which is reversed by 2-D-gal. This suggested that histone H1, a chromatin packing regulator, might be the fucosylated target. Indeed, MS analysis revealed that H1 (Q value 117.5), but not H2A, H2B, H3 and H4 (Q value 15.2, 6.1, 5.1 and 0), is the key protein that is highly fucosylated in M1 MΦs. Terminal fucose moieties and 23 distinct N-glycans were further identified on histone H1 from mouse M1 MΦs by MS analysis. ChIP-seq revealed that active enhancers, characterized by the co-enrichment of H3K4me1 and H3K27ac, exhibited a significantly higher activity at the M1 signature gene loci (including *Irf5, Tnf, Il12, Ifng,* and *H2 loci*) in M1 compared to M2 MΦs. Importantly, inhibition of H1 fucosylation in M1 MΦs by 2-D-gal dramatically reduced the enhancer activity at these loci to a level that is comparable to or even lower than that of M2 macrophages; On the other hand, 2-D-gal promoted the enhance

activity at the M2 signature gene loci, including *Arg1*, in M1 MΦs. Gene transcription was verified by illumina WG-6 gene array.

Conclusion: Histone H1 fucosylation is a novel chromatin mark. It regulates macrophage subset plasticity and determines their identities by dynamically interacting with histone H3 and modulating the enhancer activity at the M1and M2 signature gene loci. These processes can be reversed by the fucosylation inhibitor, which is a potential biologic agent that acts at the epigenetic level to reshape the inflammatory MΦs and reestablish immune homeostasis in RA.

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Genetic Variants Influencing Joint Damage in Mexican Americans and European Americans with Rheumatoid Arthritis. Rector Arya[1], del Rincon Inmaculada[1], Vidya S Farook[2], Jose Felix Restrepo[1], Deidre A Winnier[1], Marcel J Fourcaudot[1], Daniel Battafarano[3], Satish Kumar[2], Marcio AA de Almeida[2], Joanne E Curran[2], Christopher P Jenkinson[1], John Blangero[2], Ravindranath Duggirala[2] and Agustin Escalante[1]. [1]University of Texas Health Science Center at San Antonio, San Antonio, TX, [2]Texas Biomedical Research Institute, San Antonio, TX, [3]San Antonio Military Medical Center, JBSA - Ft Sam Houston, TX.

Background/Purpose: Joint damage in rheumatoid arthritis (RA) has been shown to be heritable, but knowledge on specific genetic determinants of joint damage in RA is limited. We have used the ImmunoChip array to examine whether genetic variants with relevance to susceptibility to multiple autoimmune diseases including RA, influence variation in joint damage in Mexican Americans (MA) and European Americans (EA) with RA.

Methods: We recruited 720 MA and 424 EA patients with RA from public, private, military and VA rheumatology clinics. Joint damage was quantified using a radiograph of both hands and wrists, scored for erosions and joint-space narrowing using Sharp's technique. The Sharp scores were transformed using inverse normalization to approximate a normal distribution for the subsequent association analyses. To identify ethnic outliers, principal components (PCs) were derived using EIGENSTRAT principal component analysis. We conducted association analyses with the transformed Sharp score as a quantitative trait and single nucleotide polymorphism (SNP) genotypic (i.e., autosomal SNPs) data obtained from the Immunochip in both MA and EA samples using the program PLINK. We used the linear regression additive genetic model which included covariates age, sex, and the first two principal components (PC1 and PC2) to adjust for potential population stratification influences.

Results: After excluding SNPs due to the following reasons: stringent quality control, admixture and cryptic relationship inference analyses, and SNPs with minor allele frequency below 1%, our Sharp score association analyses involved 127,563 and 128,387 autosomal SNPs in MA and EA, respectively. Both phenotypic and genotypic data were available for 666 MAs and 407 EAs. In MAs, the 15 SNPs with the strongest association with joint damage were located in chromosomes 1, 5, 9, 17 and 22 with p-values ranging from $p < 1 \times 10^{-5}$ to $p \leq 1 \times 10^{-6}$ including the best associated SNP rs7216796 ($\beta \pm SE = -0.25 \pm 0.05$, $p = 6.23 \times 10^{-6}$ within the *MAP3K14* gene on chromosome 17. In EAs, there were 28 SNPs from chromosomes 1, 4, 6, 9, and 21 with strong p-values ranging from $p < 1 \times 10^{-5}$ to $p \leq 1 \times 10^{-6}$, showing associations with joint damage. The best associated SNP was rs59902911 ($\beta \pm SE = 0.86 \pm 0.17$, $p = 1.01 \times 10^{-6}$) in the *CARD9* gene on chromosome 9. Aside from the above population-specific association signals, we also found evidence for several loci influencing joint damage in both MAs and EAs. However, none of the association signals found in our study reached the Bonferroni-adjusted significance level.

Conclusion: We identified novel loci that influence variation in joint damage on chromosomes 17 (*MAP3K14*) and 9 (*CARD9*) strongly associated with joint damage in MAs and EAs with RA, respectively. We also found several ethnic-specific and shared loci showing suggestive associations with joint damage in MAs and EAs. These novel findings, observed in MAs and EAs, may provide new insights into the genetic architecture of joint damage in RA.

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Role of NOD2 Pathway in Sarcoidosis Cases with Characteristics of Blau Syndrome. Gerard Dumancas[1], Indra Adrianto[1], Albert M. Levin[2], Michael C. Iannuzzi[3], Benjamin A. Rybicki[2] and Courtney Montgomery[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Henry Ford Health System, Detroit, MI, [3]SUNY Upstate Medical University, Syracuse, NY.

Background/Purpose: Blau syndrome (BS) is a rare autosomal dominant, autoinflammatory syndrome characterized by the clinical triad symptoms of symmetric arthritis, dermatitis, and granulomatous recurrent uveitis, similar to that of early onset sarcoidosis. The phenotype of the disease has proven to be more complex than initially thought but most commonly involve cutaneous and arthritis manifestations. Eye disease is rarely the presenting symptom but significant visual impairment has been observed in 46% of patients. Polymorphisms in the nucleotide oligomerization domain 2 *(NOD2)* are known to be associated with susceptibility to BS, Crohn's disease and sarcoidosis. Studies have shown that dysregulation of *NOD2* signaling is involved in the pathogenesis of a variety of inflammatory disorders and has been implicated in the development of autoimmune disease, allergy, and asthma. As such, the goal of our study was to investigate the involvement of the *NOD2* pathway genes by selecting sarcoidosis cases that presented with disease similar to BS in African Americans (AAs) and European Americans (EAs).

Methods: Our AA case-case analysis comprised 51 AA sarcoidosis cases with positive skin and bone/joint involvement (~35.3% also have eye involvement), and 255 AA sarcoidosis cases without any skin and bone/joint involvement. Our EA case-case analysis consisted of 27 EA sarcoidosis cases with positive skin and bone/joint involvement (~14.8% have eye involvement), and 135 EA sarcoidosis cases without any skin and bone/joint involvement. Genotyping was performed at the Oklahoma Medical Research Foundation (OMRF) using the Illumina HumanOmni1-Quad array and imputed using IMPUTE2/gtool. Quality control included removal of SNPs with call rate $< 80\%$ and Hardy-Weinberg proportion tests $P < 0.001$. We evaluated 5,362 SNPs in AAs and 2,639 SNPs in EAs from 30 genes within the *NOD2* pathway. Single-marker association test was performed using EMMAX adjusted for sex as a covariate.

Results: We observed novel significant associations in a *TAB1* variant in AAs (rs35506409) and *TAB2* variants (rs111447766, rs111576955, rs76778446, and rs79995379) in EAs passing Bonferroni thresholds ($P < 3.46 \times 10^{-5}$ in AAs; $P < 1.12 \times 10^{-4}$ in EAs). *TAB1* is involved in kinase activator activity while *TAB2* is involved in polyubiquitin binding molecular functions. Cursory analysis using BioGPS of these genes confirmed their high expression in retina, CD4+ T cells, and CD8+ T cells of human tissues. Previous studies have shown that TAB1 has been found to play a role in skin homeostasis, wound repair, and oncogenesis. Further, both *TAB1* and *TAB2* genes have been found to be redundantly involved in lipopolysaccharide-induced *TAK1* activation in macrophages, and that deletion of either *TAB1* or *TAB2* results in macrophage death.

Conclusion: Our genetic study of the key players in the *NOD2* pathway identified novel genetic associations in *TAB1* in AAs and *TAB2* in EAs. These findings will give insight into the genetic etiology of BS in adult sarcoidosis cases among AAs and EAs.

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Genes Involved in Cartilage Synthesis and Risk to Knee Osteoarthritis. Abhishek Mishra Sr., Rajeshwar Srivastava II, Divya Sanghi III, Ajai Singh IV and Devendra Parmarr V. King George's Medical University,, Lucknow, India.

Background/Purpose: Osteoarthritis (OA), characterized by gradual loss of articular cartilage in the joint, is a leading cause of disability among the elderly people. Though the etiology and pathogenesis of OA is obscure. Several studies have suggested that OA is not only related with aging, calcium and vitamin D deficiency; OA risk is also associated with several genetic susceptibility loci. The aim of this study to elucidate the genetic background of osteoarthritis.

Methods: In a case-control study; 500 cases with knee osteoarthritis (KOA) and an equal number of age matched healthy controls were included. Cases were diagnosed using the ACR guidelines for KOA. Blood were drawn for DNA, RNA and lymphocyte isolation. PCR-RFLP method, TaqMan

assay were carried out to identify the SNPs. Total RNA isolated from whole blood of healthy controls and patients suffering from KOA were analyzed for ESR- α, CALM-1 and GDF-5 mRNA by quantitative reverse transcriptase-PCR. ESR- α, CALM-1 and GDF-5 protein level were detected by western blot analysis in control and cases from peripheral blood lymphocytes. The haplotype analyses were carried out using Haploview software. All statistical analysis was performed with the SPSS software.

Results: The variant genotype of ESR- α, CALM-1 and GDF-5 genes were found to be present at relatively higher frequency in cases than the controls. Risk increased in cases that carried combination of variant genotypes of ESR α (Btg-AA) and GDF-5 (TT); CALM-1 (ApeKI-TG) and GDF-5 (TT); CALM-1(ApeKI-TG) and ESR α (Btg-AA) resulting in 4–6 fold elevated risk to KOA. The haplotype C-G-G and T-G-G of ESR- α gene reduced the risk to OA. In contrast the haplotype T-G-C containing variant of all three polymorphism of CALM-1 gene was over represented in the cases, increasing the risk to 3 fold. A significant association of this variant genotype was also found with clinical scores of KOA (VAS, WOMAC). RT-PCR data revealed that mRNA expression of GDF-5, ESR-α and CALM-1 in OA patients downregulate significantly 0.3, 0.64 and 0.48 -fold in blood when compared with the controls respectively. Protein Expression of GDF-5 was significantly decreased 0.24-fold in cases. Similar to that observed in GDF-5, westernblot analysis revealed that expression of ESR-α and CALM-1 proteins were also found to be decreased in lymphocyte.

Conclusion: This study demonstrate that polymorphism in genes involved in the development, maintenance and repair of bone and cartilage such as GDF-5, CALM-1and ESR- α modify the susceptibility to knee OA. Several fold higher risk was found in cases carrying haplotype of variant alleles of CALM-1 gene. Likewise, several folds increase in risk in individuals with variant genotype of GDF-5 with ESR- α (BtgI) or CALM-1 and ESR- α (BtgI) or CALM-1 and GDF-5 have further demonstrated that the importance of gene-gene interection in the development of knee OA. In addition, our data of gene expression by q-PCR and protein expression by western blotting of GDF-5, CALM-1 and ESR-α also suggest the relevance of these genes in pathophysiology of OA patients.

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Transcriptional Heterogeneity of the *SLC2A9* Gene Encoding the GLUT9 Urate Transporter. David B. Mount[1], Tony R. Merriman[2], Eli A. Stahl[3], Hyon K Choi[4] and Asim Mandal[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]University of Otago, Dunedin, New Zealand, [3]Mt Sinai School of Medicine, New York City, NY, [4]Boston University School of Medicine, Boston, MA.

Background/Purpose: Variation in *SLC2A9*, which encodes the urate transporter GLUT9, is the major *single* genetic determinant of serum uric acid (SUA); however, the causal variant(s) within *SLC2A9* have not been identified. Two distinct N-terminal isoforms, GLUT9a, (540 residues) and GLUT9b (511 residues), are generated by alternative 5' ends. Our aim was to characterize the 5' end of *SLC2A9*to further understanding of how variation in this gene affects SUA.

Methods: 5' untranslated region (UTR) exons, alternative splicing, and transcriptional start sites were identified by database mining, 5'-RACE PCR, and RT-PCR. GLUT9 cDNA expression constructs were characterized by ^{14}C-urate uptakes in *Xenopus*oocytes. Promoter analysis utilized the dual luciferase system.

Results: Seven novel 5' UTR exons were identified, with substantial alternative splicing; in GLUT9b only exon 2, containing the start codon, is spared from alternative splicing. Alternative splicing that deletes coding exons 3 +/− 4 was also identified, in both GLUT9a and GLUT9b transcripts. Exon 3 is a cassette exon encoding most of transmembrane domain 1 (TM1) and part of the first, glycosylated extracellular loop. Surprisingly, GLUT9b constructs with deletion of exon 3 were functional (GLUT9b-delta3), generating urate uptakes that were 10-fold higher than that of control *Xenopus*oocytes. Western blotting indicated that GLUT9b-delta3 protein is not glycosylated, presumably due to altered topology of the first extracellular, glycosylated loop.

A single GLUT9a transcriptional start site was identified, flanking exon 1a. Luciferase constructs for this promoter were highly active in multiple cell lines, with a minimal promoter construct of ~200 bp. Four GLUT9b start sites were identified, including one ~35 kb 5' of exon 1b flanking a novel 5' UTR exon. Only 2 out of 4 GLUT9b promoters were functional, with substantially lower activity than the GLUT9a promoter.

Using the publically available Atherosclersis Risk in Communities Study dataset a major urate-increasing haplotype (freq=0.50) was identified spanning the promoter elements, in addition to two related urate-lowering haplotypes (freq=0.21) with the remaining haplotypes not significantly associated with urate levels.

Conclusion: There is substantial transcriptional heterogeneity in SLC2A9, with seven new 5' UTR exons and at least four transcriptional initiation sites. Alternative splicing that removes exon 3 generates functional GLUT9 urate transporters, despite removal of TM1. The single GLUT9a promoter is strongly active in luciferase assays, whereas only 2 out of 4 GLUT9b promoters are weakly active. Relating these effects to genetic control of urate will increase understanding of the molecular basis of renal uric acid secretion.

Disclosure: D. B. Mount, None; **T. R. Merriman**, None; **E. A. Stahl**, None; **H. K. Choi**, None; **A. Mandal**, None.

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Multiway Transcriptomic Analysis of Monocyte-Derived Dendritic Cells Discriminates Effects of Disease and of HLA-B27 in Spondyloarthritis. Emmanuel Chaplais[1], Alice Talpin[2], Félicie Costantino[1], Clémence Desjardin[1], Nelly Bonilla[2], Ariane Leboime[3], Roula Said Nahal[4], Franck Letourneur[2], Jacques Sébastien[2], Gilles Chiocchia[5], Maxime Breban[1] and Henri-Jean Garchon[1]. [1]INSERM U987, Faculté des Sciences de la Santé Simone Veil, Montigny-le-Bretonneux, France, [2]INSERM U1016, Cochin Institute, Paris, France, [3]Rheumatology Division, Ambroise-Paré Hospital AP-HP, Boulogne-Billancourt, France, [4]Service de Rhumatologie, Hopital Ambroise Pare, Boulogne-Billancourt, France, [5]INSERM U987, UFR des Sciences de la Santé, Montigny-le-Bretonneux, France.

Background/Purpose: Spondyloarthritis (SpA) etiology is largely multifactorial with a genetic component dominated by the long-known strong association with the HLA-B27 allele. This allele, however, is not sufficient for the disease to occur. Whereas dendritic cells are believed to play a key role in SpA pathogenesis, the precise mechanisms underlying disease development and particularly the role of HLA-B27 remain poorly understood. To shed light on the genes involved, we carried out a transcriptome analysis of dendritic cells from patients and healthy controls, also accounting for HLA-B27.

Methods: Transcriptomic profiles of monocyte-derived dendritic cells (MD-DCs) were obtained from 23 HLA-B27+ SpA patients, and from 44 controls (23 HLA-B27+ and 21 HLA-B27-). MD-DCs were stimulated or not with endotoxin for 6 or 24 hrs. We used the Affymetrix Human Gene 1.0 ST platform. Analysis of differentially expressed (DE) genes was conducted with LIMMA considering both the disease and the HLA-B27 status (p-value $<$ 5%), followed by quantitative gene set enrichment analyses (quSAGE) and functional pathway annotation.

Results: We performed three comparisons to identify DE genes related to HLA-B27 or SpA status, thus generating three lists: A, including 800 DE genes between HLA-B27+ SpA patients and HLA-B27- healthy controls; B, including 673 DE genes between HLA-B27+ controls and HLA-B27- controls; and C, including 466 DE genes between HLA-B27+ patients and HLA-B27+ controls. Subtracting A–B left 656 genes, of which 68 are in list C, thus yielding a robust list of genes affected by SpA and filtering out irrelevant genes affected by HLA-B27. The most significantly DE gene was procollagen C-endopeptidase enhancer 2 (PCOLCE2), which was overexpressed in patients compared to both HLA-B27- (Fold Change = 2.35, P = 9×10-4) and HLA-B27+ (FC = 3.57, P = 2.7×10-6) controls. This gene codes for an enhancer of bone morphogenic protein-1 (BMP1) that facilitates the cleavage of procollagen and apolipoproteins. QuSAGE and functional annotation revealed that DE genes and gene sets associated with SpA were mainly related to lipid biosynthesis, autophagy, and ribosomal units.

Conclusion: Our study identified a list of MD-DC genes and functions that differ between SpA and controls after controlling for HLA-B27 and involve major pathways, including lipid synthesis, autophagy and ribosomal function. The most striking DE gene, PCOLCE2 is known to interact physically with BMP1, an enzyme that is implicated in ossification and cartilage formation. BMP1 loss-of-function mutations can cause osteogenesis imperfecta. Thus, it is conceivable that a mechanism of gain-of-function of BMP1 signalling pathway could be implicated in the SpA pathogenic process.

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Vasoactive Intestinal Peptide (VIP) Genetic Variants Determine VIP Serum Levels and Could be Used As a Prognosis Biomarker. Amalia Lamana[1], Iria Valino-Seoane[2], Luis Rodriguez-Rodriguez[3], Javier Leceta[2], Yasmina Juarranz[2], Ana M. Ortiz Garcia[1], Carmen Martinez-Mora[4], Benjamín Fernández-Gutiérrez[3], Isidoro González-Alvaro[5], Rosa P Gomariz[2] and Rosario Garcia-Vicuña[5]. [1]Hospital Universitario de La Princesa. IIS Princesa, Madrid, Spain, [2]School of Biology. Universidad Complutense de Madrid, Madrid, Spain, [3]Instituto de Investigación Sanitaria San Carlos (IdISSC), Madrid, Spain, [4]School of Medicine. Universidad Complutense de Madrid, Madrid, Spain, [5]Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain.

Background/Purpose: VIP has shown immunoregulatory properties in assays performed with human or murine cells. VIP has demonstrated a therapeutic effect in a murine model of collagen-induced arthritis. We recently reported that low VIP serum levels (sVIP) were associated to a worse clinical course in patients with early arthritis despite receiving a more intense treatment.

Purpose: determine whether genetic variants of VIP lead to variations in sVIP.

Methods: Princesa Early Arthritis Register Longitudinal (PEARL) study includes patients with early arthritis in which demographic, clinical, laboratory, therapeutic and radiological data are collected for 5 years follow-up (baseline, 6, 12, 24 and 60 months). Biological samples are obtained at each visit. sVIP had been measured in a previous study (Martinez et al. 2014). 11 patients with the highest and 9 patients with the lowest sVIP were selected for sequencing of VIP gene. Primers were designed to produce overlapping amplicons covering the promoter, exons and introns. We used BigDyeDirect sequencing Kit and performed capillary electrophoresis on a 3500xL Genetic Analyzer (Applied Biosystems [AB]). 16 single nucleotide polymorphisms (SNPs) were differentially expressed in patient groups with extreme sVIP. Rs3823082, rs35643203, rs71575932, rs7755568 and rs688136 were selected for validation (trend statistical significance [$p<0.2$] in population $n=20$). **Results** were validated in 457 patients (80% female, median age 54 [interquartile range 42–66], 60% RA, 40% undifferentiated arthritis) from PEARL study through RT-PCR and specific Taqman probes (AB). Fisher's exact test was applied to determine the significance level in the distribution of genotypes between patients with low and high sVIP. Kruskal-Wallis test was used to assess potential differences in sVIP between SNPs genotypes. To determine the effect of SNPs on disease activity, cumulative DMARD treatment and radiological progression, we fitted 3 multivariate analysis using generalized estimating equations for repeated measures. Statistical analysis was performed using Stata 12.1 for Windows.

Results: In the whole population, the minor allele frequency was 23.2% for rs3823082, 6.5% for rs35643203, 7.5% for rs71575932, 6.8% for rs7755568 and 34% for rs688136. Patients with at least one minor allele for rs35643203, rs71575932 or rs7755568 ($p=0.015$; being these SNPs in linkage disequilibrium) and those carrying the TT genotype of rs3823082 ($p=0.07$) showed significantly lower sVIP, and these genotypes showed an additive effect ($p=0.003$). Patients homozygous for the minor allele of rs688136 showed a slight trend to higher sVIP ($p=0.27$). Patients carrying one minor allele for rs35643203 and being homozygous for the T allele of rs3823082 displayed higher DAS28 along the follow-up if they were ACPA negative ($p=0.07$), required more intensive DMARD treatment ($p=0.028$) and showed higher radiological progression ($p=0.007$). Patients with CC genotype of rs688136 showed a trend to lower disease activity ($p=0.17$).

Conclusion: In our PEARL population genetic variants of VIP associated with low serum levels of this peptide may be a biomarker of severe disease in EA patients.

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***TACR1* rs3771863 Single Nucleotide Polymorphism Is a Genetic Risk Factor for *Sicca* Syndrome in Fibromyalgia Patients.** L. Rodriguez-Rodriguez[1], Jose Ramon Lamas[2], Juan A Jover[1], Sara Baena[1], Antonio Collado[3], Javier Rivera[4] and B. Fernández-Gutiérrez[1]. [1]Instituto de Investigación Sanitaria San Carlos (IdISSC), Madrid, Spain, [2]Hospital Clinico San Carlos, Madrid, Spain, [3]Hospital Clínic de Barcelona, Barcelona, Spain, [4]Instituto Provincial de Rehabilitación, Madrid, Spain.

Background/Purpose: Fibromyalgia (FM) is a condition characterized by chronic widespread pain associated to multiple symptoms, including fatigue, sleep disturbances, cognitive dysfunction, and depressive episodes. In recent years, many candidate gene association studies have been designed and carried out to identify the genes associated with FM. However, the study of the genetic factors associated to disease severity or to the presence of coexisting comorbidities, and therefore, potentially useful as predictors of disease outcome, is a relatively unexplored field. The aim of the study was to analyze in FM patients the genetic risk factors involved in the presence of syndromes and symptoms associated with this disease, and/or severity.

Methods: We included Spanish Caucasian patients diagnosed with FM according to 1990 ACR criteria. Fist, we used a discovery cohort (DC) of 564 patients, recruited from 15 centers throughout the Spanish geography. Subsequently, we used a replication cohort (RC) of 397 patients from the DNA Bank for Genetic Research in FM and Chronic Fatigue Syndrome of the FF Foundation and from the National DNA Bank (Salamanca, Spain). In the DC we studied the association between 320 single nucleotide polymorphisms (SNPs), located in 22 loci, and the presence of symptoms and syndromes associated with FM (depression, headache, sleep disorders, myofascial syndrome, irritable bowel syndrome, chronic fatigue, vertiginous syndrome, chronic cystitis, and sicca syndrome) and disease severity, using the FIQ (Fibromyalgia Impact Questionnaire) and the HADS (Hospital Anxiety and Depression Scale). In the RC, we studied those SNPs and those variables that were associated in the discovery cohort. As the dependent variables were dichotomous or continuous, linear or logistic regressions were performed, respectively, to study the genetic association, using an additive model of effects. The odds ratio (OR), with 95% confidence intervals [95% CIs], was used to assess the strength of association between genotypes and the main dichotomous variables. Analyses were adjusted for sex and time from the onset of pain symptoms. P values were adjusted for the number of main variables and a cutoff of 0.05 was established to select those SNPs to replicate in the RC. DC and RC results were pooled using meta-analysis techniques. P value was corrected considering the number of linkage disequilibrium blocks in which the analyzed SNPs were included.

Results: In the DC, we observed 10 SNPs with an adjusted p-value lower that 0.05: rs4760750, rs4760816, rs2171363 (associated to sleep disturbances), rs174696, rs10171225, rs3771863 (associated to sicca syndrome), rs2422148, rs2216307 (associated to vertigo), and rs12654778, rs10434128 (associated to HADS depression). After replication in the RC and pooling the results from both cohorts, only the rs3771863 variant, from the *TACR1* gene, showed a significant association with a lower risk of sicca syndrome (adjusted OR 0.56 [95% CI 0.42 – 0.76], $p = 0.00022$).

Conclusion: *TACR1* gene could play a role in the development of sicca syndrome in FM patients.

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Association of Polymorphisms on *OPG*, *RANK* and *RANKL* with ACPA Presence and Erosions: Results of a Meta-Analysis on 1570 Rheumatoid Arthritis Patients from 3 French Cohorts. Adeline Ruyssen Witrand[1], Sara Scaramuzzino[2], Delphine Nigon[1], Cédric Lukas[3], Yannick Allanore[4], Olivier Vittecoq[5], Thierry Schaeverbeke[6], Jacques Morel[7], Jean Sibilia[8], Anne Cambon-Thomsen[2], Alain G. Cantagrel[9], Philippe Dieude[10] and Arnaud Constantin[1]. [1]CHU Purpan - Hôpital Pierre-Paul Riquet, Toulouse, France, [2]University Paul Sabatier, Toulouse, France, [3]Hopital Lapeyronie, Montpellier, France, [4]Department of Rheumatology, University Paris Descartes and Cochin Hospital, Paris, France, [5]Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France, [6]Bordeaux University Hospital, Bordeaux, France, [7]Hôpital Lapeyronie, Montpellier, France, [8]University Hospital of Strasbourg, Strasbourg, France, [9]Centre Hospitalier Universitaire de Toulouse, Toulouse, France, [10]Hopital Bichat Claude Bernard, Paris, France.

Background/Purpose: Rheumatoid Arthritis (RA) is a multifactorial complex disease characterized by the presence of anti-citrullinated peptides antibodies (ACPA) and joints erosions. The mechanisms of bone erosions in RA are mediated by the RANK-RANKL-Osteoprotegerin (OPG) system. Some single nucleotide polymorphisms (SNPs) on *RANK*, *RANKL* and *OPG* genes have been previously associated with RA susceptibility. The aim of this study was to assess the association between 1 SNP on *RANK* (rs8086340), 3 SNPs on *RANKL* (rs7984870, rs7325635, rs1054016) and 1 SNP on *OPG*(rs2073618) and ACPA presence or joint erosions.

Methods: *Patients:* the study was based on 3 French cohorts: ESPOIR cohort ($n=632$ early RA patients, 76% of females, mean age: 50 years,

ACPA+: 49%, presence of erosions in 36,6%), RMP cohort (n=249 early RA patients, 75% of females, mean age: 50 years, ACPA+: 73%, presence of erosions in 39%) and FRAGC-PRI cohort (n=689 long-standing RA patients, 76% of females, mean age: 61 years, ACPA+: 62%, presence of erosions in 68%). *Genotyping:* the 5 SNPs located on *RANK, RANKL* and *OPG* were genotyped by Kbiosciences (GB). *Statistical analysis:* The proportion of patients with ACPA presence or presence of erosions were compared according to the allele carriage of each SNP by a Chi square test for each cohort separately. A meta-analysis on the 3 cohorts assessing the risk of ACPA presence or the risk of erosions according to the allele carriage of each SNP was performed using Mantel-Haenszel method.

Results: were expressed as Odds ratios (OR) and 95% confidence intervals (95%CI). Correction for multiple tests was performed using Bonferroni method (significance set at p=0.005).

Results: After meta-analysis performed on the 3 cohorts, 1 SNP located on *RANKL* had a protective effect against ACPA presence after Bonferroni correction: G allele of rs7325635 carriage: OR=0.63 [0.47–0.86], p=0.003, whereas the 2 other SNPs were not significantly associated with ACPA presence when Bonferroni correction was applied (G allele of rs1054016 carriage: OR=0.67 [95%CI: 0.49–0.91], p=0.01, G allele carriage of rs7984870: OR=0.71 [0.54–0.93], p=0.01). Furthermore, the SNP located on RANK had also a protective effect on ACPA presence: C allele of rs8086340: OR=0.64 [0.50–0.81], p=0,0003. However, these SNPs were not significantly associated with the risk of erosions. The SNP located on *OPG* was significantly associated with a protection against erosions after Bonferroni correction: G allele carriage of rs2073618: OR=0.68 [0.52–0.88], p=0.004.

Conclusion: This meta-analysis performed on 3 French cohorts identified 1 SNP located on *RANKL*, 1 SNP located on *RANK* associated with protection against ACPA presence and 1 SNP located on *OPG* associated with protection against erosions in RA.

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ACR/ARHP Poster Session B
Health Services Research

Monday, November 17, 2014, 8:30 AM–4:00 PM

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Comparisons of Quality of Life, Resource Use and Physical Functioning in RA Patients Classified As High, Moderate or Low Risk for Rapid Radiographic Progression. E Alemao[1], S Joo[2], P Allison[3], M Al[4], M Rutten-van Molken[4], S Banerjee[1], C Iannaccone[5], M Frits[5], N Shadick[5], M Weinblatt[5] and KP Liao[5]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]Bristol-Myers Squibb, Hopewell, NJ, [3]University of Pennsylvania, Philadelphia, PA, [4]Erasmus University, Rotterdam, Netherlands, [5]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: We developed and validated a prognostic model to identify subjects with elevated risk of rapid radiographic progression (RRP). The objective of this study was to compare differences in quality of life (QoL), resource use and clinical outcomes at 12 months in patients classified with high, moderate and low baseline risk of RRP by the prognostic model.

Methods: In a longitudinal cohort of RA patients with clinical and radiographic data in an outpatient setting, we applied the prognostic model to calculate the baseline probability of RRP. Variables to determine the probability of RRP in the prognostic model included seropositivity, body weight, disease duration, DAS28 (CRP) and total Sharp score. Based on the calculated probability of RRP, patients were categorized into low risk (probability 0 to 0.25), moderate risk (0.25 to 0.75) and high risk (>0.75) of RRP. The categorization was based on visual inspection of probability plots. QoL outcome measured by EQ5D, healthcare resource use (nursing home visits, home healthcare visits, surgeries, durable medical equipment use, hospitalization and ER visits) and clinical outcome of physical functioning measured by mHAQ at 12 months were compared by baseline RRP risk groups of low, moderate and high using analysis of variance for continuous variables and Chi-square test for categorical variables.

Results: In the RA cohort, 942 (72.6%) patients had adequate data to calculate RRP. Of these, 414 (43.9%) were classified as low, 477 (50.6%) as medium and 51 (5.4%) as high risk of RRP at baseline. Patients in the low-risk group when compared with those in the moderate- and high-risk groups tended to be younger, have a lower number of swollen or tender joints (mean [SD] 9.4 yrs [11.5], 19.8 [14.2], 33.1 [12.9], respectively), and less likely to be treated with a biologic DMARD. Patients in the low- versus high-risk groups had higher QoL, lower resource use and higher physical functioning at 12 months (Table).

Table: QoL, Resource Use and Physical Functioning at 12 Months in Patients at Low, Moderate and High Baseline Risk of RRP

Outcomes	Low Risk of RRP	Moderate Risk of RRP	High Risk of RRP
EQ5D, mean (SD)**	0.83 (0.14)	0.79 (0.15)	0.72 (0.19)
ER visits, % of pts*	23.4	25.1	38.2
Nursing home visits, % of pts*	2.4	2.7	14.6
Home healthcare visits, % of pts*	4.8	13.5	36.0
Surgeries, % of pts*	15.4	25.4	38.2
DME use, % of pts*	21.0	33.2	58.4
Hospital visits, % of pts*	13.3	20.4	37.1
mHAQ, mean (SD)**	0.39 (0.42)	0.65 (0.50)	0.72 (0.19)

*p<0.05 based on Chi-square test; **p<0.05 based on analysis of variance.

Conclusion: Patients categorized as having high risk of future RRP at baseline (compared with moderate and low risk of RRP) had worse outcomes at 12 months for QoL, resource utilization and physical functioning. These findings suggest that therapies are needed to improve QoL and resource utilization in these high-risk patients.

Disclosure: E. Alemao, BMS, 3, BMS, 1; **S. Joo**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **P. Allison**, None; **M. Al**, None; **M. Rutten-van Molken**, None; **S. Banerjee**, BMS, 1, BMS, 3; **C. Iannaccone**, None; **M. Frits**, None; **N. Shadick**, AbbVie, Amgen, Genentech, 2, BMS, UCB, Crescendo Biosciences, 9; **M. Weinblatt**, BMS, Crescendo Bioscience, UCB, Abbvie, Roche, Janssen, 5, BMS, Crescendo Bioscience, UCB, 2; **K. Liao**, None.

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Healthcare Costs Associated with Serious Infections Among Biologic-Naïve Rheumatoid Arthritis Patients Initiating First-Line Biologic Treatment. S Johnston[1], S Kelly[2], A Nadkarni[2], K Wilson[1], B Limone[1] and M Hochberg[3]. [1]Truven Health Analytics, Bethesda, MD, [2]Bristol-Myers Squibb, Plainsboro, NJ, [3]University of Maryland School of Medicine, Baltimore, MD.

Background/Purpose: The risk of serious infections can vary across biologics. For example, in the 2-year AMPLE trial, serious infections occurred in 3.8% of SC abatacept-treated patients and 5.8% of adalimumab-treated patients. In the 1-year ATTEST trial, serious infections occurred in 1.9% of IV abatacept-treated patients and 8.5% of infliximab-treated patients. Little is known about the healthcare costs associated with serious infections. This study quantified real-world healthcare costs associated with serious infections among biologic-naïve RA patients initiating first-line biologic treatment. **Results** were used to estimate serious infection costs in a hypothetical cohort of RA patients treated with abatacept, adalimumab or infliximab based on data from AMPLE and ATTEST.

Methods: Retrospective, observational cohort study based on US administrative claims data. Study patients initiated first-line biologic treatment (abatacept, adalimumab, etanercept, certolizumab, golimumab, or infliximab) between January 1 2008 and September 1 2012 (initiation=index), were aged ≥18 years, had continuous insurance enrollment for 12 months before (baseline) and 12–24 months after (follow-up) the index date, had no baseline biologic treatment, and had ≥2 baseline medical claims with an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis code for RA (714.0x). Published algorithms and medical coders were consulted in compiling a list of ICD-9-CM diagnosis codes for serious infections. Patients were identified as having experienced a serious infection if they incurred a hospitalization with a primary diagnosis indicative of a serious infection. The cost of serious infections, measured during follow-up, included the cost of the serious infection hospitalization, follow-up outpatient medical claims with diagnoses of the same serious infection, and anti-infective medications.

Results: The samples included 19,412 patients with 1 year of follow-up and 11,699 patients with 2 years of follow-up: in both samples, mean age was 53 years and 77% were female. Over the 1-year and 2-year follow-ups, 3.4% (n=669) and 6.2% (n=720) of patients experienced a serious infection, respectively. The most common serious infection was pneumonia. The total mean (median) cost of serious infections per patient experiencing a serious infection was $19,072 ($10,439) in the 1-year and $21,021 ($11,306) in the

2-year groups. Applying the serious infection cost estimate to the 2-year AMPLE and 1-year ATTEST trial findings in a hypothetical cohort of 1000 biologic-naïve patients, the 2-year expected cost of serious infections per 1000 biologic-naïve patients would be $798,811 for SC abatacept (3.8%*$21,021*1000) and $1,219,237 for adalimumab; and the 1-year cost would be $362,371 for IV abatacept and $1,697,420 for infliximab.

Conclusion: In this pharmacoeconomic study of biologic-naïve RA patients initiating biologic treatment, serious infections were associated with substantial healthcare costs over 1- and 2-year periods. Biologic treatments that are associated with lower infection risk may confer important cost savings related to serious infections.

Disclosure: S. Johnston, Truven Health Analytics, 3; **S. Kelly**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **A. Nadkarni**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **K. Wilson**, Truven Health Analytics, 3; **B. Limone**, None; **M. Hochberg**, Bristol-Myers Squibb, Eli Lilly, EMD Serono, Genentech/Roche, Novartis Pharma, Pfizer, UCB, 5, NIH, 2.

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Preferences of Biologic Treatment Characteristics Among Rheumatoid Arthritis Patients Who Are Current Biologic Therapy Users. David M. Kern[1], Angela E. Williams[2], Ozgur Tunceli[1], Bingcao Wu[1], Judy Stephenson[1], Laura Horne[3] and Alfred Sackeyfio[4]. [1]HealthCore, Inc., Wilmington, DE, [2]MedImmune, LLC, Cambridge, United Kingdom, [3]AstraZeneca, Wilmington, DE, [4]AstraZeneca, Manchester, United Kingdom.

Background/Purpose: To identify the most and least important characteristics of rheumatoid arthritis (RA) treatment according to patients currently on biologic therapy.

Methods: From the HealthCore Integrated Research Environment, RA patients (ICD-9-CM: 714.0x) ≥18 years old with ≥1 claim for a biologic therapy between 5/1/2012 and 7/31/2013 were identified. All eligible patients were targeted to complete a survey measuring their quality of life, RA treatment history, treatment satisfaction, and treatment preferences, among other measures. The Maximum Difference Scaling Instrument (MaxDiff) was used to determine what characteristics of RA treatments (e.g., efficacy; side effects; costs; how, when, and where the medication is administered) were most and least important to the patients. A MaxDiff score <100 denotes characteristics that are less important to the patient, while a score >100 signifies characteristics of higher importance.

Results: There were 9,802 patients meeting all study criteria, of which 219 completed a patient survey. Survey patients were 56 years old on average, 82% were female, 89% were white, and 51% had at least a 4-year college degree. 29% of patients were currently taking etanercept, while the next most common treatments were adalimumab (22%), infliximab (17%), and abatacept (12%).

The MaxDiff results identified that the 3 most important characteristics of RA treatment were related to the efficacy of the treatment: 'Keeps my disease from getting worse' (MaxDiff score = 209), 'Improves my physical abilities' (199), and 'Reduces Pain' (195). 'Potential side effects' (117) and 'How long treatment effects last' (102) were neither relatively important or unimportant to the patients surveyed, while 'How quickly (within a few weeks)' treatment works (70) and 'Personal costs' (67) were seen as less important. The least important characteristics were those that identified the 'how', 'when', and 'where' of treatment administration: 'How treatment is given (oral, injection, IV, etc.)' (15), 'How often treatment must be taken' (13), and 'Where treatment is given (home, doctor's office, hospital, etc.)' (13). Results were consistent across groups based on their current biologic therapy.

A separate question found that 75% of patients would like to take their medication at home if it were possible; however, the MaxDiff results show that relative to efficacy this is not a priority for patients. Additionally, when asked why patients stopped taking prior biologic therapy the statement 'I didn't feel that the drug was working' was cited as a major reason 66% of the time, more than any other reason. 'I don't like needles' and 'I don't like infusions' were cited as major reasons for stopping therapy just 1% and 3% of the time, respectively; while the cost of treatment and side effects were a major reason 12% and 21% of the time, respectively.

Conclusion: The effectiveness of RA treatment is the most important attribute according to patients currently treated with biologic therapy, while administration characteristics were seen as relatively unimportant. Reducing symptoms, improving physical abilities, and slowing disease progression should be considered as primary outcomes in studies comparing RA treatments.

Disclosure: D. M. Kern, Healthcore, Inc., 3; **A. E. Williams**, MedImmune, 3; **O. Tunceli**, Healthcore, Inc., 3; **B. Wu**, HealthCore, Inc., 3; **J. Stephenson**, HealthCore, Inc., 3; **L. Horne**, AstraZeneca, 1, AstraZeneca, 3; **A. Sackeyfio**, AstraZeneca, 3.

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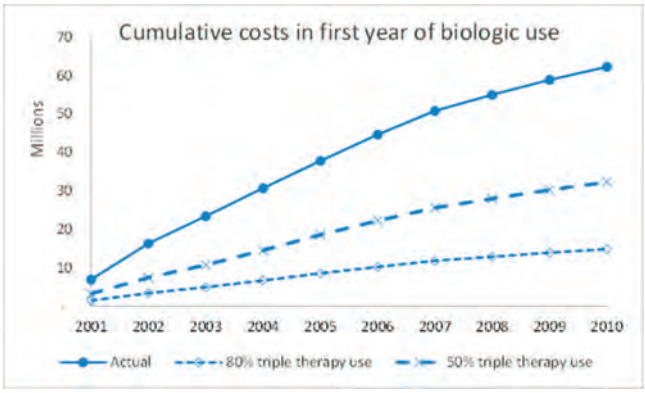
Economic Implications for Policies Regarding Triple Therapy Use in Patients with Rheumatoid Arthritis. Nick Bansback[1], Diane V. Lacaille[2], Daphne Guh[3], Kamran Shojania[1] and Aslam H. Anis[3]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada/University of British Columbia, Richmond, BC, [3]Centre for Health Evaluation and Outcome Sciences, Vancouver, BC.

Background/Purpose: Recent randomized controlled trials in rheumatoid arthritis (RA) patients have determined that a strategy of first adding the two Disease Modifying Anti-Rheumatic Drugs (DMARDs) sulfasalazine and hydroxychloroquine to methotrexate (a combination known as Triple Therapy) is neither inferior nor less safe than first adding anti-TNF drugs in patients with active disease despite methotrexate. The implication is that inexpensive triple therapy should be initiated prior to expensive biologic therapy. In this study we examine historical biologic and Triple Therapy use in British Columbia (BC), Canada over the past 10 years. We sought to estimate the potential savings in expenditures if Triple Therapy use had been more prevalent, and project potential future cost-savings.

Methods: We examined a population-based cohort of all BC patients with a rheumatologist diagnosis of RA identified from administrative data. We selected prevalent RA cases who used a biologic for the first time between 2001 and 2010 and examined their prior DMARD history from prescription billing data. For each year, we calculated the proportion of patients that had used Triple Therapy, the average drug prices, and the average duration patients remain on Triple Therapy. Since not all patients can use Triple Therapy, we conducted a series of scenarios which estimated the cost that would have been saved if a higher proportion of patients had used Triple Therapy.

Results: In total, we examined 2726 RA patients who started their first biologic over the time period. Triple therapy use prior to biologic therapy has increased over time, from 15.2% in 2001 to 24.4% in 2010. The average duration patients remained on triple therapy was 1.13 years. Of the $62million spent on patients first year of biologics, a scenario where 80% of patients would have received triple therapy instead would have resulted in cost savings to BC of $47.3 million over the 10 year period (figure 1). Assuming similar patterns of triple therapy use across Canada, projections suggest future cost-savings of over $12 million per year if triple therapy is used in 80% of patients prior to biologic use. Various sensitivity analyses are performed.

Conclusion: Higher utilization of Triple Therapy will require a willingness for rheumatologists to prescribe it, and a willingness for patients to use it. With the benefit of hindsight, higher use of Triple Therapy prior to biologic initiation would have released a substantial amount of pharmaceutical spending to alternative treatments. Importantly, with less than 25% of patients currently receiving triple therapy prior to a biologic, there is still a considerable potential for future savings. Strategies such as academic detailing and patient decision aids may be good investments if they can change treatment choices.



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Evaluation of Biologic Treatment Patterns, Clinical Outcomes, and Healthcare Resource Utilization Post-Tumor Necrosis Factor Inhibitor Discontinuation in Rheumatoid Arthritis. J. Harnett[1], D. Wiederkehr[1], R. Gerber[2], D. Gruben[2], A. Koenig[3] and J. Bourret[3]. [1]Pfizer Inc, New York, NY, [2]Pfizer Inc, Groton, CT, [3]Pfizer Inc, Collegeville, PA.

Background/Purpose: For rheumatoid arthritis (RA) patients (pts) with inadequate response to a TNF inhibitor (TNFi), limited evidence exists from observational studies and indirect comparisons of randomized trials to support switching to a nonTNFi vs another TNFi. These exploratory analyses evaluate clinical outcomes and healthcare resource use (HCRU) after switching from a TNFi to another TNFi or nonTNFi biologic across 2 de-identified real world data sources.

Methods: Pts (≥18 years) with ≥2 outpatient or 1 inpatient visit for RA (ICD-9: 714.xx) and (1) HCP-reported TNFi discontinuation and switch to a biologic or conventional DMARD (cDMARD) within 180 days in Humedica EHR database (1/07-7/13) or (2) switched from TNFi to another biologic (or 1 pt to tofacitinib) in Truven Marketscan® claims database (2010–2013) were included. Pts had continuous enrollment/follow-up ≥6 months (mo) before and ≥12 (claims) or 18 (EHR) mo after discontinuation. EHR cohort was followed for 18-mo all-cause HCRU and change in patient-reported pain scores (0–10 on provider-determined scales; ≥30 days pre-/post-switch). Claims cohort was evaluated for subsequent biologic switching and RA-related HCRU costs. Multivariable analyses evaluated the impact of switching to a TNFi vs nonTNFi on RA-related costs.

Results: Of 2799 pts who discontinued a TNFi (47% etanercept, 28% adalimumab, 21% infliximab, 4% other) in the EHR cohort, reasons were lack of efficacy (14%), AE/other clinical reason (16%), cost (6%), or unknown (65%). Following discontinuation, 21% switched to another biologic (67% TNFi) and 11% to cDMARD. In the claims cohort, 68% switched to another TNFi, of whom 43% switched again vs 28% of those first switched to a nonTNFi biologic. Among EHR pts with pre-/post-switch pain scores, TNFi (n=58), nonTNFi biologic (n=19), or cDMARD (n=55) switchers had mean (standard deviation [SD]) pain reductions of 0.72 (3.12), 1.11 (2.87), and 0.42 (3.88), respectively. Office visits comprised the largest HCRU category in the 18 mo after switching; mean (SD) number: 42.7 (34.5), 57.6 (47.3), and 38.4 (33.3) for TNFi, nonTNFi, or cDMARD switchers, respectively. Nearly half (n=7.2) the difference in office visits with TNFi vs nonTNFi was associated with biologic administration procedures. Unadjusted mean (SD) RA-related costs were $27544 ($21100) for TNFi vs $44742 ($30743) for nonTNFi switchers. Including biologic administrations without RA diagnosis (TNFi, $389; nonTNFi, $1126), most (79%) of the mean cost differences were attributed to outpatient visits, followed by prescriptions (18%). Biologic administration visits accounted for 89% of outpatient cost differences. NonTNFi therapy was associated with 32% higher total RA-related costs in adjusted analyses ($p<0.0001$).

Conclusion: NonTNFi switchers were less likely to switch again and had greater pain reduction vs TNFi switchers (in a small subset). NonTNFi switchers had higher all-cause HCRU and RA-related costs, largely due to in-office administration. NonTNFi therapies that do not require in-office administration may reduce switching and costs. Disease outcomes and financial consequences of clinical decision-making warrant future prospective structured research.

Disclosure: J. Harnett, Pfizer Inc, 1, Pfizer Inc, 3; **D. Wiederkehr**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Gerber**, Pfizer Inc, 1, Pfizer Inc, 3; **D. Gruben**, Pfizer Inc, 1, Pfizer Inc, 3; **A. Koenig**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Bourret**, Pfizer Inc, 1, Pfizer Inc, 3.

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Cost-Effectiveness of Adalimumab for Rheumatoid Arthritis in Germany. Christian Gissel[1], Georg Götz[1], Holger Repp[1] and Uwe Lange[2]. [1]Justus-Liebig-University Giessen, Giessen, Germany, [2]Justus-Liebig-University Giessen, Kerckhoff-Clinic, Bad Nauheim, Germany.

Background/Purpose: In Germany, Rheumatoid Arthritis (RA) can be treated with TNF-α inhibitors after the failure of conventional disease-modifying antirheumatic drugs like Methotrexate. The clinical use of TNF-α inhibitors grew from 2 % of treated RA patients in 2000 to 20 % in 2008. In 2012, Adalimumab was the most popular TNF-α inhibitor and the best selling drug in the German statutory health insurance system with net expenditure of € 581 mn. We aim to analyze the determinants of cost-effectiveness of Adalimumab and Methotrexate combination therapy for the treatment of RA in Germany.

Methods: We set up an individual patient sampling lifetime model to simulate 10,000 hypothetical patients. Health benefits are recorded in terms of quality-adjusted life years (QALYs). Quality of life is derived from patients' Health Assessment Questionnaire (HAQ) scores. Initially, patients can achieve one of three responses according to American College of Rheumatology (ACR) criteria or fail the therapy. Each ACR response is associated with an initial improvement in functional status. In each cycle, treatment might be discontinued due to loss of efficacy or adverse events. The patient is then switched to the next available treatment or palliative care. In the Adalimumab simulation arm, we add Adalimumab and Methotrexate combination therapy to the treatment algorithm after failure of both Methotrexate monotherapy and conventional triple therapy. Extensive sensitivity analysis investigates the effects of baseline age and functional status, cost and health effects discounting, methods for estimating quality of life and time horizon.

Results: In the base case, patients gain 7.07 QALYs with conventional synthetic therapy and 9.92 QALYs if Adalimumab combination therapy is added to the treatment algorithm. The incremental cost-utility ratio (ICUR) is € 24,492 based on German list prices. If mandatory rebates and taxes are deducted for international comparison, the ICUR is only € 17,277. Adalimumab combination therapy lowers indirect costs from € 162,698 to € 134,363. From a societal perspective, the ICUR based on total costs is € 14,550 (€ 7,335 after deducting taxes and rebates). Sensitivity analyses shows that Adalimumab combination therapy becomes a dominant treatment option for younger baseline populations, i.e. Adalimumab is both more effective and less expensive for baseline age 30 due to savings in indirect costs. The biggest increase in ICURs can be seen if the simulation period is limited. If the maximum simulation period is limited to 10 years, ICURs double compared to a lifetime perspective.

Conclusion: Cost-effectiveness of Adalimumab combination therapy in Germany compares favorably to analyses in other countries. Our lifetime simulation model shows that a sufficiently long simulation horizon is necessary to capture the complete range of possible outcomes and the associated longterm benefits of biological treatment. If a lifetime perspective is chosen, the most important determinant of cost-effectiveness is savings in indirect costs. Adalimumab combination therapy is most cost-effective for societies with high indirect costs like Germany.

Disclosure: C. Gissel, None; **G. Götz**, None; **H. Repp**, None; **U. Lange**, None.

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Economic Implications of Flares Among Patients with Early Rheumatoid Arthritis (RA). James Signorovitch[1], Keith Betts[1], Vishvas Garg[2] and Yanjun Bao[2]. [1]Analysis Group, Inc., Boston, MA, [2]AbbVie Inc., North Chicago, IL.

Background/Purpose: Government mandated dose tapering and withdrawal of biologic treatments for RA after achievement of sustained disease control is currently observed in Taiwan, the Netherlands, Denmark and the Czech Republic, among other countries. A recent systematic review reported that flares of RA signs and symptoms are associated with the withdrawal of biologics.[1] This study quantifies the direct, indirect, and total costs associated flares among early RA patients (pts) withdrawing biologics after achieving low disease activity (LDA).

Methods: Pts from the OPTIMA trial[2] who were re-randomized to methotrexate (MTX) monotherapy in Period II after achieving LDA on adalimumab plus MTX combination therapy at week 26 (re-randomization baseline [RBL]) were included (N = 102). Two definitions of flare were proposed: i) Change at visit week [VW] from RBL in Disease Activity Score (DAS) 28 >0.6 and DAS 28 >3.2, and, ii) Change in Health Assessment Questionnaire (HAQ) >0.22 and HAQ ≥0.5 in pts with HAQ <0.5 at RBL. Pts who met the definitions at any VW were considered as having flares. HAQ scores were assessed i) at VW of flare for pts who had flares and ii) at the last VW for pts who had no flares. Average annual direct medical and indirect costs were calculated based on the mapping between HAQ scores and published 2005 German costs.[3] Costs were inflated to 2012 values and differences in average annual costs were assessed between pts with and without flares. **Results** were converted to currencies in the Netherlands, Denmark, Taiwan, and the Czech Republic using standard currency conversions.

Results: Among pts who discontinue biologics after achieving LDA, 34% (35/102) experience flares according to the DAS definition, and 25% (19/76) experience flares according to the HAQ definition. Both the average annual medical cost and indirect cost for pts with flares were higher compared to those for pts without flares across all four countries regardless of which flare definition is used (Table 1). The incremental cost of flares based on the DAS28 and HAQ flare definitions were € 7,163 and € 10,190 for Germany/

Netherlands, DKK 53,483 and DKK 76,081 for Denmark, TWD 301,385 and TWD 428,729 for Taiwan, and 196,498 Kč and 279,525 Kč for the Czech Republic, respectively.

Conclusion: Flares after biologic withdrawal in early RA patients who achieved LDA are found to be costly based on the HAQ-costs mapping as published. Real world direct assessment of the consequences of biologic withdrawal is recommended to further the understanding of this practice.

Table 1: Direct, Indirect and Total costs for RA patients with disease flares

Country	DAS Change > 0.6 and DAS > 3.2		HAQ Change > 0.22 and HAQ >=0.5 for HAQ< 0.5 at baseline	
	DAS Flare	Non-DAS Flare	HAQ Flare	Non-HAQ Flare
Number of patients	37	65	19	57
Germany/ Netherlands				
Direct cost	€ 2,706	€ 1,558	€ 2,999	€ 1,105
Indirect cost	€ 14,826	€ 8,810	€ 15,308	€ 7,011
Total cost	€ 17,531	€ 10,368	€ 18,307	€ 8,117
Denmark				
Direct cost	DKK 20,202	DKK 11,631	DKK 22,389	DKK 8,249
Indirect cost	DKK 110,684	DKK 65,771	DKK 114,282	DKK 52,341
Total cost	DKK 130,886	DKK 77,403	DKK 136,671	DKK 60,590
Taiwan				
Direct cost	TWD 113,840	TWD 65,544	TWD 126,166	TWD 46,487
Indirect cost	TWD 623,720	TWD 370,631	TWD 643,998	TWD 294,948
Total cost	TWD 737,560	TWD 436,175	TWD 770,164	TWD 341,435
Czech Republic				
Direct cost	74,222 Kč	42,734 Kč	82,258 Kč	30,309 Kč
Indirect cost	406,656 Kč	241,646 Kč	419,877 Kč	192,302 Kč
Total cost	480,878 Kč	284,379 Kč	502,135 Kč	222,610 Kč

1. Yoshida et al. *Annals of the rheumatic diseases* (2013).
2. Kavanaugh et al. *Annals of the* rheumatic diseases (2012).
3. Schädlich et al. *Pharmacoeconomics* (2005).

Disclosure: J. Signorovitch, Analysis Group, Inc., 3; **K. Betts**, Analysis Group, Inc., 3; **V. Garg**, AbbVie, 1, AbbVie, 3; **Y. Bao**, AbbVie, 1, AbbVie, 3.

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Evaluation of a Methodological Approach to Determine Timing of Rheumatoid Arthritis Disease Onset Using Administrative Claims Data.

Jie Zhang[1], Fenglong Xie[2], Lang Chen[2], Jeffrey D. Greenberg[3] and Jeffrey R. Curtis[2]. [1]Univ. of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]New York University School of Medicine, New York, NY.

Background/Purpose: The identification of patients with recent-onset rheumatoid arthritis (RA) is often desirable to create inception cohorts of patients. We evaluated an approach to identify the timing of RA onset using administrative claims data from public (Medicare) and commercial health plans.

Methods: The study sample consisted of RA patients participating in Corrona, a large North American RA registry, linked to administrative medical and pharmacy claims data from Medicare (2006 to 2011) or a U.S. commercial health plan (2005–2012). We estimated year of RA onset in the claims data using several algorithms that were based on the following factors: 1) different ICD-9 diagnosis code for RA (e.g. 714.0, 714.2, and 714.81. vs. 714.X, code from physician visit claim vs. any claim); and 2) length of observable time in the health plan (>1 vs. > 2 years) preceding the first diagnosis code for RA, with exclusions for use of any disease modifying anti-rheumatic drugs. We compared the estimated year of RA onset using the claims-based algorithms to that recorded by rheumatologists in the Corrona registry (gold standard). We reported accuracy as a positive predictive value (PPV), calculated if the year of RA onset from the claims data agreed (+- 1 year) with that documented in Corrona. We conducted a subgroup analysis limited to patients whose disease duration was 2 years or less at their first Corrona rheumatologist visit to improve the reliability of disease onset ascertainment by reducing recall bias and misclassification of the gold standard.

Results: In the main analysis, using ICD-9 codes 714.0, 714.2, 714.81 from a physician visit, the PPVs for accurately classifying year of RA onset ranged from 62% to 68%. When ICD-9 codes 714.x from any type of claim were used, PPVs were higher, ranging from 67% to 100%. In subgroup analysis of patients with more recently diagnosed RA, PPVs were much higher, ranging from 91–100%.

Conclusion: Claims-based algorithms can be used with high validity to identify patients with recent onset RA. Additional research will focus on reasons and opportunities to reduce misclassification of disease onset.

Table: PPVs of claims-based algorithms to identify recent onset RA compared to gold standard of rheumatologist report

Claims-Based Algorithm	Look Back Period	Medicare		Commercial Health Plan	
		Total N	PPV	Total N	PPV
All Patients					
714.0, 714.2, 714.21 on physician claim	>=365 days	144	62%	21	67%
	>=730 days	84	68%	12	67%
714.xx from any claim	>=365 days	182	67%	34	71%
	>=730 days	93	77%	12	100%
Patients with year of RA diagnosis within 2 years from time of physician ascertainment*					
714.0, 714.2, 714.21 on physician claim	>=365 days	120	91%	24	100%
	>=730 days	80	91%	15	100%
714.xx from any claim	>=365 days	139	94%	22	91%
	>=730 days	73	92%	15	93%

*The purpose of the subgroup analysis is to identify patients whose year of onset is less likely to be biased due to recalling events occurred a long time ago

Disclosure: J. Zhang, None; **F. Xie**, None; **L. Chen**, None; **J. D. Greenberg**, Corrona, LLC., 1, Corrona, LLC., 3, AstraZeneca, Celgene, Novartis and Pfizer, 5; **J. R. Curtis**, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

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Novel Adherence Measures for Infusible Therapeutic Agents in Rheumatoid Arthritis.

Roxanne Meyer[1], Michael Ingham[2], Joseph Tkacz[3], Brenna Brady[3] and Charles Ruetsch[4]. [1]Janssen Scientific Affairs, Horsham, PA, [2]Janssen Services, LLC, Horsham, PA, [3]Health Analytics, LLC, Columbia, MD, [4]Health Analytics LLC, Columbia, MD.

Background/Purpose: Adherence is under consideration for quality reporting in a number of disease states. Published data on adherence of biologics reveal a wide range of calculation methods. Biologics administered via infusion do not lend themselves to the typical measures of adherence, such as the medication possession ratio (MPR) or proportion of days covered (PDC). The purpose of this study was to investigate a number of newly constructed proxies for medication adherence across two of the more commonly prescribed infusible biologic agents: infliximab (IFX) and abatacept (ABA).

Methods: Using the Optum™ Clinformatics™ database of insured individuals, IFX (n = 417) and ABA (n = 431) members who were continuously eligible for benefits one-year post-induction were selected for adherence analyses. New measures of medication adherence were designed for calculation over the maintenance phase of treatment (Table 1). For both IFX and ABA, the fourth dose constitutes the beginning of maintenance. Maintenance infusions are recommended every eight weeks for IFX and every four weeks for ABA. The total study measurement period was one year, beginning with the induction infusion, though only maintenance infusions were subjected to adherence measures. As a reference, mean maintenance intervals were also calculated for both groups.

TABLE 1. New Measures of Medication Adherence

Adherence Measure	Abbreviation	Definition
Patients w/Refill Gap ≥ 20%:	PtRG ≥ 20%	total number of patients who show at least one refill gap ≥ 20% based on labeling guidelines for maintenance treatment
Cumulative Amount of Time w/Refill Gap ≥ 20%:	CATRG ≥ 20%	summation of all refill gaps days ≥ 20% based on the days supply value
Cumulative Time Off Treatment:	CToTx	summation of all infusion interval gaps > 0 days
Days of Uninterrupted Use:	DoUU	length of time from index date to the first refill gap ≥ 10% based on the days supply value
Observed Vs. Expected Re-Fill Ratio:	OvERR	actual infusions in measurement period/expected infusions in measurement period
Repeated Observations of Under-Use:	ROoUU	total number of refill gaps ≥ 10% based on the days supply value

Variance in Time Between Re-Fill beyond expected interval	ViTBR	all infusion interval gaps categorized as either 0–7 days, 8–14 days, 15–21 days, >21 days
Persistence/Time to Discontinuation:	PT:D	Number of days between index date and the appearance of a gap in treatment ≥ 90 days + recommended number of days in a maintenance interval (or until the end of measurement year)

Results: Mean maintenance intervals approximated recommended guidelines. IFX patients had a mean observed infusion interval (MOII) of 53 days (recommended 56 days) while ABA patients demonstrated a MOII of 33 days (recommended 28 days). ABA patients had a significantly greater amount of CToTx than IFX patients (78.56 vs 61.08 days), and a significantly shorter number of DoUU (164 vs 286 days). ABA patients had a significantly lower OvERR than IFX patients (0.73 vs 0.97), and were over 3 times as likely as IFX patients to show a PtRG ≥ 20% (68.4% vs 20.63). The ROoUU was more than 4 times higher for ABA than IFX patients (1.91 vs 0.42), while the CATRG≥20% was also higher for ABA patients (32.23 days) compared to IFX patients (20.63 days). Finally, the ViTBR for 0–7 days was lower for ABA patients than IFX patients (88.2% vs 93.2%). All measured adherence outcomes were significantly different between groups ($p < 0.001$).

Conclusion: This study piloted a number of measures designed to assess infusion adherence. Results indicated more favorable adherence outcomes for IFX-treated patients compared to ABA patients. Substantial differences may result from assumptions made regarding days' supply and calculation methods for adherence when using medical claims. Quality reporting should include all details for days' supply assumptions and calculation methods. Future studies should examine the relationship between these new measures of adherence and more clinically relevant endpoints and/or cost outcomes to determine if they possess any predictive utility.

Disclosure: R. Meyer, Janssen Scientific Affairs, LLC, 3; **M. Ingham**, Janssen Scientific Affairs, LLC, 3; **J. Tkacz**, Janssen Scientific Affairs, LLC, 5; **B. Brady**, Janssen Scientific Affairs, LLC., 5; **C. Ruetsch**, Janssen Scientific Affairs, LLC, 5.

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Marked Differences in Euro-Qol-5-Dimensions Preference Sets Based on Hypothetical or Experience Based Valuation. Anna Cooper, Johan A. Karlsson and Anders Gürlfe. Lund University, Faculty of Medicine, Lund, Sweden.

Background/Purpose: Health related quality of life (HRQoL) can be expressed as utility, a value anchored at 0 (death) and 1 (perfect health, forming the basis for health economic evaluations. Utilities are determined by means of a generic instrument such as Euro-QoL-5-Dimensions (EQ-5D), a questionnaire rating mobility, self-care, usual activities, pain/discomfort and anxiety/depression on a 3-level scale. Each set of responses made by the individual constitutes a "health state", which is translated into a utility score by means of a a preference set (weights) from a reference population. Many preference sets are available based on hypothetical valuations (ratings of health states described), and the use of different weights may result in varying utility scores for the same "health state". Recently, Swedish (SE) weights were developed using experience based valuations (rating onexs own health), and we intended to compare these to the standard, hypothetically-derived UK weights.

Methods: Demographics, core set variables, EQ-5D and a PASS question (present state considered acceptable by patient) from patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or spondarthritis (SpA), including ankylosing spondylitis in southern Sweden, treated with biologics, were entered into a database. EQ-5D utility employing UK and SE weights were calculated for those with complete baseline data (n=360), and the cut-off for utility PASS was determined by ROC-curves.

Results: Baseline characteristics are shown in Table 1 and PASS cut-offs in Table 2.

Conclusion: PASS does not vary appreciably between arthritis diagnoses or over time. As expected, SE utilities (experience based) are higher than UK (hypothetical). This holds true both for baseline utilities and PASS cut-off values. This difference must be accounted for in health economic evaluations and when comparing studies using different EQ-5D preference sets.

Table 1. Baseline characeristics

	Entire cohort		RA		SpA		PsA	
n	360		230		80		50	
Age (years)	54.3	(41.8–63.5)	59.9	(47.9–65.7)	43.7	(34.0–53.5)	49.7	(42.8–55.5)
Women (%)	66.4		74.3		50		56	
Disease duration (years) (n=358)	8.6	(3.2–17.2)	8.9	(3.9–17.7)	7.8	2.1	8.6	(2.1–12.9)
Previous DMARDs (n=349)	2	(1–4)	3	(2–4)	1	(0–2)	1	(1–3)
Ongoing DMARDs (n=355)	1	(0–1)	1	(0–1)	0	(0–1)	1	(0–1)
Previous biologics (%)	38.1		43		23.8		38	
EQ5D-UK (n=360)	0.55	(0.06–0.69)	0.52	(0.02–0.73)	0.62	(0.09–0.69)	0.62	(0.08–0.69)
EQ5D-SE (n=360)	0.71	(0.61–0.83)	0.71	(0.59–0.83)	0.71	(0.62–0.80)	0.712	(0.61–0.81)

Median (IQR) for continuous variables, % for categorical values.
RA, Rheumatoid Arthritis; SpA, Spondylarthritis; PsA, Psoriatic Arthritis; DMARDs, Disease–Modifying Anti–Rheumatic Drugs; BL, Baseline.
EQ5D, EuroQoL-5-Dimension; SE, Swedish; UK, United Kingdom.

Table 2. Patient acceptable symptom state cut-off points in RA, SpA and PsA

	Baseline		Followup	
Measure	**PASS**	**Sens/Spec**	**PASS**	**Sens/Spec**
RA	n=230		n=218	
EQ5D-UK	0.66	72/79	0.69	72/79
EQ5D-SE	0.78	76/80	0.78	78/81
SpA	n=80		n=78	
EQ5D-UK	0.69	73/78	0.78	68/85
EQ5D-SE	0.78	64/80	0.85	84/85
PsA	n=50		n=49	
EQ5D-UK				
EQ5D-SE	0.69	56/81	0.69	72/79
	0.79	56/81	0.8	72/79

Followup: 2.5-25 months. Sensitivity/Specificity stated in %.
All results have a significance of p <0.05 unless stated otherwise.
ROC, Receiver Operating Characteristic; Sens/Spec, Sensitivity/Specificity; EQ5D, EuroQoL-5-Dimension; SE, Swedish; UK, United Kingdom.

Disclosure: A. Cooper, None; **J. A. Karlsson**, None; **A. Gülfe**, None.

1151

Barriers and Facilitators of a Career in Research Among Rheumatologists in the United States. Alexis Ogdie[1], Sheila Angeles-Han[2], Una Makris[3], Amanda Nelson[4], Ami Shah[5], Yihui Jiang[1], J. Michelle Kahlenberg[6], Eyal Muscal[7], Flavia V. Castelino[8], Amit Golding[9] and Alfred Kim[10]. [1]University of Pennsylvania, Philadelphia, PA, [2]Emory University School of Medicine, Atlanta, GA, [3]Dallas VA Medical Ctr, Dallas, TX, [4]University of North Carolina at Chapel Hill, Chapel Hill, NC, [5]John Hopkins University, Baltimore, MD, [6]University of Michigan, Ann Arbor, MI, [7]Texas Children's Hospital, Houston, TX, [8]Massachusetts General Hospital, Boston, MA, [9]Baltimore VA and University of Maryland School of Medicine, Baltimore, MD, [10]Washington Univ School of Med, Saint Louis, MO.

Background/Purpose: Development of young rheumatology investigators is critical to the future of rheumatology. Beyond funding, the specific barriers to maintaining a career in rheumatology research remain unclear. The objective of this study was to determine the perceived barriers and facilitators to a career in rheumatology research.

Methods: A web-based survey was conducted among the domestic ACR membership from Jan-Mar 2014. Inclusion criteria were current or previous fellowship in rheumatology, ACR membership, and an available email address. Non-rheumatologist members were excluded. The instrument was developed by the Early Career Investigator subcommittee using a Delphi method to identify and distill facilitators and barriers to a career in research for inclusion in the survey. The survey also assessed demographics, research participation, and free text response for ways in which the ACR could support young investigators. After excluding incomplete surveys and duplicates, demographics were summarized. The chi-squared test was used to assess differences in rating of barriers and facilitators by category of respondents (e.g., young investigators, mentors, fellows, and R01 recipients). Free text comments were analyzed by content analysis using NVivo software.

Results: Among 5,448 ACR domestic members, 502 responses were obtained (9.2% response rate). After exclusions (38 incomplete, 2 duplicates, 32 non-rheumatologists), 430 responses were analyzed. Demographics and types of research represented are shown in the **Table.** The most highly ranked barrier and facilitator of a career in research was funding. Other common barriers were clinical workload, insufficient protected time, lower salary, and lack of institutional research infrastructure. Current fellows were more likely to report difficulty establishing a niche as an important barrier (34% vs 22%, p=0.04) and mentors were significantly less likely to report personal finances as an important barrier (21% vs 39%, p=0.004). Facilitators included protected research time, outstanding mentors, institutional

support, as well as personal skills or traits such as hard work, resilience, initiative, persistence and passion for the job. Personal skills were significantly more often cited by recipients of an R01 than other groups (71% vs 49%, p=0.001). Evaluation of free text comments revealed few additional themes including gender issues and lack of flexibility to allow part-time work to care for children.

Conclusion: To our knowledge, this is the first study to examine barriers and facilitators to a career in rheumatology research from the perspectives of young investigators, established investigators, mentors, and fellows. Knowledge of such barriers and facilitators may assist in designing interventions to support young investigators during vulnerable points in their career.

Table. Demographics of Survey Participants (N=430)

Current Position	Adult Rheumatologist	309 (72%)
	Pediatric Rheumatologist	62 (14%)
	Adult Fellow	42 (10%)
	Pediatric Fellow	17 (4%)
Place of Employment	Academic Medical Center	306 (71%)
	Clinical Practice	97 (23%)
	Industry	20 (5%)
	Government	3 (1%)
	Retired	4 (1%)
Academic Appointment	Instructor (or equivalent Junior Faculty)	34 (8%)
	Assistant Professor	102 (24%)
	Associate Professor	58 (13%)
	Professor	89 (21%)
	Other (or no academic appointment)	147 (34%)
Year Completed Fellowship	Median (IQR)	2005 (1987–2012)
	1960-1969	6 (1%)
	1970-1979	27 (6%)
	1980-1989	73 (17%)
	1990-1999	51 (12%)
	2000-2009	98 (23%)
	2010-2016	131 (30%)
	Missing	*6 (1%)*
Female Sex	N (%)	241 (56%)
Medical School in the US	N (%)	318 (74%)
Underrepresented Minority*	N (%)	28 (7%)
Effort** median (IQR)	Clinical	50% (20–75%)
	Research	15% (2–70%)
	Teaching	5% (4–10%)
	Administrative	5% (0–11%)
Successful Funding	Foundation fellowship/post-doc award	92 (21%)
	Foundation career development award	99 (23%)
	NIH Loan Repayment Program	24 (6%)
	NIH K-series or VA career development award	76 (18%)
	NIH R01	59 (14%)
	Other NIH awards	71 (17%)
	Other grants	141 (33%)
Current Researcher	Total	171 (40%)
	Young Investigator	88 (20%)
	Mentor†	76 (18%)
	Research effort ≥50%	134 (31%)
	Research effort ≥70%	100 (23%)
Type of Research‡	Clinical	88 (51%)
	Epidemiology/Health Services	18 (11%)
	Translational	99 (58%)
	Basic Science	53 (31%)

All percentages are of the total N=430. *An "under-represented minority within rheumatology" was defined as Black, Hispanic, or Native American (that is, American Indians, Alaska Natives, and Native Hawaiians
**Effort estimates exclude fellows.
†Mentor refers specifically to a mentor of a young investigator
‡Among those currently engaged in research (N=171), participants were allowed to select more than one answer so the total adds to greater than 100%. Abbreviations: NIH = National Institutes of Health

Disclosure: A. Ogdie, None; **S. Angeles-Han**, None; **U. Makris**, None; **Nelson**, None; **A. Shah**, None; **Y. Jiang**, None; **J. M. Kahlenberg**, None; **E. Muscal**, None; **F. V. Castelino**, None; **A. Golding**, None; **A. Kim**, Pfizer Inc, 5, Amgen, 5, Janssen Pharmaceutica Product, L.P., 5, Kypha, Inc., 2.

1152

Euroqol-5-Dimensions Utility Gain in Rheumatoid Arthritis, Treated with Abatacept, Rituximab, Tocilizumab or Tumor Necrosis Factor Inhibitors. Anders Gülfe[1], Johan A. Karlsson[1] and Lars-Erik Kristensen[2]. [1]Lund University, Faculty of Medicine, Lund, Sweden, [2]Lund University, Faculty of Medicine, Malmö, Sweden.

Background/Purpose: We have earlier demonstrated that EuroQoL-5-Dimensions (EQ-5D) utility improves rapidly after commencement of tumor necrosis factor inhibition (TNFi) in rheumatoid arthritis (RA) and other arthritides, and that it is fairly stable for up to 7 years in those remaining on therapy(1). The development of utility over time in RA treated with other biologics is not well known.

Methods: Demographics, core set data, EQ-5D and data on drug treatment for patients with established RA on biologics from southern Sweden were retrieved from an observational database. Diagnosis was as by the treating rheumatologist, and has been shown to comply with 1987 ACR criteria in >95% of cases. Time frame was Jan 2006 – March 2014. EQ-5D utilities based on the British weights were computed and means and plotted over time.

Results: There were 2418 patients treated with Abatacept (ABA), Rituximab (RTX), Tocilizumab (TOZ) or tumor necrosis factor inhibitors (TNFi) with utilities at treatment start (Table 1). Patients lacking baseline EQ-5D (n=913) did not differ appreciably from the main cohort (data not shown). TNFi patients had shorter disease duration and fewer previous DMARDs than patients on ABA, RTX or TOC, as these drugs were seldom started in bio-naïve patients. EQ-5D utility development over time is shown in Figure 1.

Conclusion: Despite starting at very low mean utilities, patients receiving ABA and TOC display rapid utility gains similar to TNFi although at a lower level, reflecting more longstanding and treatment resistant disease. As compared to the other biologics, the utility gain after commencement of RTX therapy starts at a level similar to TNFi (perhaps more bio-naïve patients with recent malignancy or other contraindications to TNFi) but is more gradual. Such differences may influence the area under the curve and thus accumulation of quality-adjusted life years. The continuing improvement observed in all groups may partly reflect a selection of patients responding and thus adhering to therapy.

Reference:

1. Gülfe A, Kristensen LE, Saxne T, Jacobsson LT, Petersson IF, Geborek P. Ann Rheum Dis. 2010 Feb;69(2):352–7.

Table 1. Baseline characteristics by therapy. Values are mean(SD) unless stated otherwise.

	Abatacept	Rituximab	Tocilizumab	TNFi
n	100	230	121	1967
Age, years	59.0 (12.1)	60.2 (12.3)	57.9 (13.5)	56.6 (13.6)
Female, n (%)	82 (80.4)	166 (72.2)	98 (80.3)	1520 (77.3)
Disease duration	15.9 (8.6)	15.5 (11.4)	18.6 (11.7)	12.2 (11.7)
Baseline HAQ	1.46 (0.61)	1.35 (0.67)	1.43 (0.64)	1.18 (0.64)
Baseline DAS28	5.50 (1.41)	5.04 (1.57)	5.68 (1.34)	5.10 (1.37)
Number of previous DMARDs*	5.9 (3.2)	5.3 (2.8)	5.2 (2.8)	3.0 (1.9)
Number of ongoing DMARDs**	0.7 (1.0)	0.8 (0.6)	0.7 (0.6)	0.8 (0.6)
Steroids, yes/no, n(%)	66 (64.7)	156 (67.8)	82 (67.2)	1164 (59.2)

TNFi, tumor necrosis factor inhibitors; DMARD, disease modifying antirheumatic drug; HAQ. Health assessment questionnaire.
*including biologics
**excluding ongoing biologic

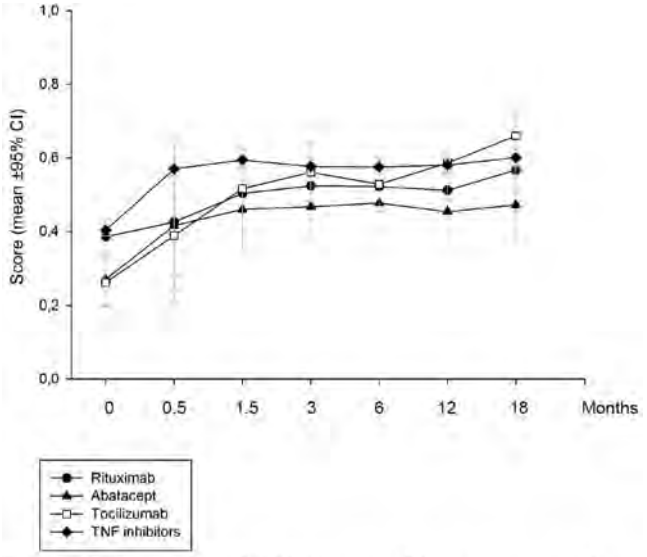

Figure 1. EQ-5D utility (mean, 95% CI) development for RA patients remaining on therapy.

Disclosure: A. Gülfe, None; **J. A. Karlsson**, None; **L. E. Kristensen**, Abbvie, Pfizer, UCB, BMS, Roche, MSD, 5.

1153

Area of Residence and Socio-Economic Factors Significantly Affect Access to Biological Therapy for Rheumatoid Arthritis Patients in Romania. Catalin Codreanu[1], Corina Mogosan[2], Ruxandra Ionescu[3], Ioan Ancuta[4], Magda Parvu[5] and Simona Rednic[6]. [1]'Dr. Ion Stoia' Clinical Center of Rheumatic Diseases, Bucharest, Romania, [2]'Dr. Ion Stoia' Clinical Center of Rheumatic Diseases, Bucharest, Romania, [3]Sfanta Maria Clinical Hospital, UMF Carol Davila, Bucharest, Romania, [4]"Dr. I. Cantacuzino" Hospital, Bucharest, Romania, [5]Colentina Clinical Hospital, Bucuresti, Romania, [6]University of Medicine and Pharmacy, Cluj-Napoca, Romania.

Background/Purpose: Clinical trials have proven the efficacy of biological therapy for rheumatoid arthritis (RA) worldwide. However, high costs have set boundaries to their use, especially in developing countries. Whereas in Europe, there are countries without any biological reimbursed, other countries have a more liberal prescription, regardless of the RA duration and previous therapy. To be eligible for biologics, in Romania, patients with active RA must be non-responders to at least two synthetic DMARDs; up to date four biological products are reimbursed: infliximab, etanercept, adalimumab, rituximab. The aim of the study is to evaluate patient's accessibility to biological therapy on a national scale (41 counties and Bucharest, i.e. the capital) and the correlation with socio-economical indicators for each region.

Methods: Observational study carried out in 41 counties and Bucharest. Data was gathered from the Romanian Registry of Rheumatic Diseases, while the socio-economic indicators were extracted from the yearbook of the National Institute for Statistics (EUROSTAT).

Results: The sample enrolled data of 4507 RA patients (4267 being treated with biologics and 240 being eligible for biologics). The mean age was 56.69 yrs (+−12.07), 85.24% women, 67.80% live in urban residences, with a mean RA duration of 12 yrs. 80.20% (n=3614) of patients had access to biologics in their county of residence, whereas 19.80% (n=893) of patients were treated elsewhere. The group treated outside of their county of residence come from areas with high deficit of physicians (1.67 physicians/1000 inhabitants, compared to 3.24 physicians/1000 inhabitants, for the group treated locally) and with a decreased welfare (GDP/inhabitant: 6634.83 €, compared to 4891.02 €, $p<0.001$). The total number of rheumatologists working in a county varies from none (7 counties do not have any rheumatologist) to 75 (in Bucharest). There is a positive correlation between areas with better living conditions and the number of local working rheumatologists ($r=0.54$, $p<0.01$). Patients living in urban areas (70.20%) have significantly greater access to biologics in their county of residence compared to patients living in rural environments (29.7%), most of them being forced to travel in order to be taken into care by a rheumatologist. The patients' age does not impact on their access to biological therapy. On a national scale, the majority of RA patients who are treated outside their county of residence chose the capital, Bucharest: 53.73% [805/1498] of patients treated in Bucharest came from a different geographical area.

Conclusion: In Romania, the accessibility of RA patients to biological therapy greatly varies according to the socio-economic situation of their county of residence. Living in an area with a low socio-economic status significantly decreases the patients' chances of getting treated with biologics compared to other national counties, even when therapeutic protocols are equal and equitable.

Disclosure: C. Codreanu, None; **C. Mogosan**, None; **R. Ionescu**, None; **I. Ancuta**, None; **M. Parvu**, None; **S. Rednic**, None.

1154

Increasing Discrepancies Between Physician Assessment of Disease Activity and Patient Global Health in Germany Between 2000 and 2012. Dörte Huscher[1], Katinka Albrecht[2], Katja Thiele[2], Sascha Bischoff[2], Andreas Krause[3], Susanna Späthling-Mestekemper[4], Siegfried Wassenberg[5] and Angela Zink[1]. [1]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, [2]German Rheumatism Research Centre, Berlin, Germany, [3]Immanuel Krankenhaus Berlin, Berlin, Germany, [4]Praxis für Innere Medizin/Rheumatologie, München, Germany, [5]Fachkrankenhaus, Ratingen, Germany.

Background/Purpose: We have seen remarkable achievements in disease control (DAS28) in rheumatoid arthritis in the past decade. They were, however, not accompanied to the same degree by improvements in patient reported outcomes. To evaluate whether the relationship between patient global health and physician assessment of disease activity, both measured on numerical rating scales 0–10, has changed in the last decade and if these changes differ between diagnoses or depend on sex, age, disease duration or education.

Methods: Patients recorded in the National Database of the German Collaborative Arthritis Centres between 2000 and 2012 for whom both physician and patient assessments were available were evaluated. The percentages of patients assessing their global health worse than the physician rated disease activity were analysed for rheumatoid arthritis (RA, on average n≈6,554 each year), ankylosing spondylitis (AS, n≈1,079), psoriatic arthritis (PsA, n≈1,191), systemic lupus erythematodes (SLE, n≈800) and polymyalgia rheumatica (PMR, n≈489) with regard to sex, age, disease duration and education.

Results: In 2000, patient ratings were on average 0.9–1.6 scores worse than physician ratings. These differences further increased by 0.4–1.2 score units until 2012. In 2000, patient ratings at least one score worse than physician ratings were found in 62–65% of patients with RA, AS, PsA and PMR, and in 53% of patients with SLE. We saw an increase in poorer patient ratings by 12–16% for all diagnoses but AS (+7%) between 2000 and 2012. Male patients showed a stronger increase in discrepant ratings over time. Patients aged up to 40 had a higher agreement between physicians and patients than older patients. Poorer patient ratings were more frequent in patients with longer disease duration and lower education. The higher rates with both increasing age and disease duration are probably also reflecting the burden of co-morbid conditions. When analysing by logistic regression which parameters predict a poorer patient than physician rating, calendar year played a significant role in all diagnosis groups after adjusting for sex, age, disease duration and education.

Conclusion: The discrepancies between patient and physician ratings have increased over the past decade for various diagnoses. In addition to a rising importance of quality of life in public perception in recent years, in times of almost universal internet access this might also reflect the better informed patient with higher expectations. These changes should be taken into account when comparing patient reported outcomes over long periods. In general, our findings underline the need to consider carefully the patient view when assessing treatment outcomes.

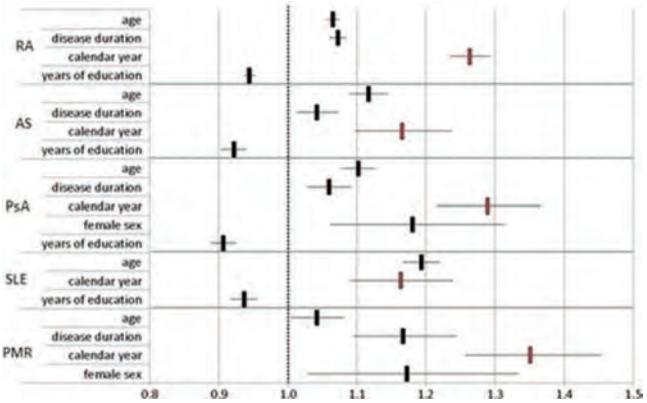

Figure 1: Predictors of a poorer patient than physician rating (odds ratios with 95% confidence interval); age, disease duration and calendar year in 5-years steps

Disclosure: D. Huscher, None; **K. Albrecht**, None; **K. Thiele**, None; **S. Bischoff**, None; **A. Krause**, None; **S. Späthling-Mestekemper**, None; **S. Wassenberg**, None; **A. Zink**, None.

1155

Economic Impact of Frequent Gout Flares in a Managed Care Setting. Robert Jackson[1], Aki Shiozawa[1], Erin Buysman[2], Aylin Altan[2], Stephanie Korrer[2] and Hyon K Choi[3]. [1]Takeda Pharmaceuticals International, Inc, Deerfield, IL, [2]Optum, Eden Prairie, MN, [3]Boston University School of Medicine, Boston, MA.

Background/Purpose: Gout is the most common inflammatory arthritis in the US. For most patients, excruciatingly painful gout attacks ("flares") are the major clinical burden of the disease. The goal of this study was to assess the association of flare frequency with economic outcomes including all-cause and gout-related health care costs to better understand the economic benefit of reducing flare frequency.

Methods: This cohort study used administrative claims data from a large US health plan of commercially insured and Medicare Advantage enrollees. Patients were identified based on medical and pharmacy claims for gout between January 2009 and April 2012. The 12 months prior to the index gout

claim was used to assess baseline confounders. Gout flares were assessed in the 12 months following the index gout claim based on diagnoses for gout or joint pain followed within 7 days by claims for NSAIDs, colchicine, corticosteroids, or joint aspiration/drainage. Flare frequency, gout treatments, and all-cause and gout-related health care costs were assessed in the 12 months following the index gout claim. Patient characteristics and economic outcomes were compared between patients with infrequent flares (0–1 flares in the 12-month follow-up period) to those with 2 flares or ≥3 flares. Generalized linear models were used to adjust for potential confounders.

Results: Our study included 102,703 patients; 89,201 had 0–1 flares, 9714 had 2 flares, and 3788 had ≥3 flares. Demographic and baseline characteristics did not appear to be meaningfully different among these groups (Table). After adjusting for potential confounders, patients with 2 or ≥3 flares had significantly higher mean all-cause and gout-related total health care costs compared to those with 0–1 flares. Adjusted all-cause costs were $11,786, $12,625, and $15,328 in those with 0–1, 2, and ≥3 gout flares, respectively ($p=0.012$ comparing 0–1 flares to 2 flares; $p<0.001$ comparing 0–1 flares to ≥3 flares). Adjusted gout-related costs were $1,804, $3,014, and $4,363, in those with 0–1, 2, and ≥3 gout flares, respectively ($p<0.001$ comparing 0–1 flares to 2 or ≥3 flares).

Conclusion: The economic implications of frequent gout flares are significant, particularly when comparing patients with infrequent flares (0–1 flares per year) to those with 2 or ≥3 flares. Gout-related costs were 67% higher in those with 2 flares and nearly 150% higher in those with ≥3 flares compared to those with infrequent flares. This suggests significant cost benefit to a disease management plan with a goal of reducing flare frequency to fewer than 2 per year. Future research should consider costs beyond those related to health care utilization and include costs from other sources such as missed work and loss of worker productivity.

Table. Demographics and Baseline Patient Characteristics by Flare Frequency

	0-1 Flares	2 Flares	≥3 Flares
N	89,201	9714	3788
Age (years), mean (sd)	58.3 (13.9)	56.6 (13.8)	57.0 (13.9)
Gender (male), n (%)	68,704 (77.0)	7729 (79.6)	3005 (79.3)
Insurance Type, n (%)			
Commercial	68,595 (76.9)	7533 (77.5)	2875 (75.9)
Medicare Advantage	20,606 (23.1)	2181 (22.5)	913 (24.1)
Race/Ethnicity, n (%)			
White	64,389 (72.2)	6781 (69.8)	2576 (68.0)
Black	11,938 (13.4)	1592 (16.4)	679 (17.9)
Hispanic/Asian/Other	9185 (10.3)	993 (10.2)	380 (10.0)
Unknown	3689 (4.1)	348 (3.6)	153 (4.0)
Net Worth, n (%)			
<$250,000	37,416 (41.9)	4539 (46.7)	1815 (47.9)
≥$250,000	43,425 (48.7)	4299 (44.3)	1595 (42.1)
Unknown	8360 (9.4)	876 (9.0)	378 (10.0)
Quan-Charlson comorbidity index, mean (sd)	0.60 (1.15)	0.59 (1.13)	0.71 (1.23)
Renal Impairment, n (%)	18,025 (20.2)	2061 (21.2)	888 (23.4)
Diabetes, n (%)	26,071 (29.2)	2613 (26.9)	1005 (26.5)
Cardiovascular Conditions, n (%)	68,005 (76.2)	7082 (72.9)	2872 (75.8)
Baseline Health Care Utilization			
Inpatient Visits, n (%)	9758 (10.9)	975 (10.0)	440 (11.6)
Emergency Room Visits, n (%)	23,358 (26.2)	2693 (27.7)	1213 (32.0)
Count of Ambulatory Visits per Patient, mean (sd)	12.8 (14.1)	12.7 (13.9)	15.0 (15.2)
Baseline Serum Uric Acid Level, mean (sd)*	7.36 (1.96)	8.31 (1.77)	8.70 (1.88)

* Based on 12,741, 1358, and 542 patients, respectively, who had serum uric acid results available

Disclosure: R. Jackson, Takeda Pharmaceuticals International, Inc., 3; **A. Shiozawa**, Takeda Pharmaceuticals International, Inc., 3; **E. Buysman**, Takeda Pharmaceuticals International, Inc, 9; **A. Altan**, Takeda Pharmaceuticals International, Inc., 9; **S. Korrer**, Takeda Pharmaceuticals International, Inc, 9; **H. K. Choi**, Takeda Pharmaceuticals International, Inc;, 5, AstraZeneca, 5.

1156

Satisfaction with Rural Rheumatology Telehealth Service. Katherine Poulsen[1], Lynden Roberts[2], Catherine Millen[3], Umayal Lakshman[3] and Petra Buttner[4]. [1]Queensland Health, Brisbane, Australia, [2]James Cook University, Melbourne, Australia, [3]Queensland Health, Mount Isa, Australia, [4]James Cook University, Townsville, Australia.

Background/Purpose: To assess patient satisfaction with the rheumatology telemedicine service provided to a rural town in northern Australia.

Methods: A prospective, questionnaire-based exploratory study of patients seen in Mount Isa rheumatology telemedicine clinics during 2012 was done. Control groups included patients travelling over 3 hours to be seen face-to-face in Townsville, and patients seen face-to-face in Mount Isa. A 5-point Likert scale was used to explore themes of communication, confidentiality, physical examination, rapport, medication safety and access.

Results: This study evaluated 107 rheumatology outpatients (49 telemedicine, 46 face-to-face Townsville, 12 face-to-face Mount Isa). Patients seen in Mount Isa travelled a median of 3km for telemedicine and 5km for face-to-face appointments. The face-to-face Townsville control group travelled a median of 354km. New patients comprised 14% of consultations. Satisfaction with themes related to quality-of-care was high with over 90% selecting 'agree' or 'strongly agree' to these questions. Comparing models of care, there were no significant differences in the rates of those selecting 'strongly agree' across questions, apart from a single question related to rapport which favoured the Mount Isa face-to-face model ($p=0.018$). When asked whether they would rather travel to Townsville than participate in a telemedicine consultation, 63% of patients selected 'disagree' (17%) or 'strongly disagree' (46%).

Conclusion: These results suggest that patients are satisfied with a rheumatology telemedicine service, and may prefer this alternative to extensive travelling. Evaluation in other settings is recommended before generalizing this finding.

Disclosure: K. Poulsen, None; **L. Roberts**, None; **C. Millen**, None; **U. Lakshman**, None; **P. Buttner**, None.

1157

Delay in Diagnosis from Onset of Symptoms By More Than One Year in 31% of Patients with Different Rheumatic Diseases in Australia. Isabel Castrejón[1], Kathryn A. Gibson[2] and Theodore Pincus[1]. [1]Rush University Medical Center, Chicago, IL, [2]Liverpool Hospital, Liverpool, Australia.

Background/Purpose: Early treatment is regarded as critical for optimal clinical outcomes in patients with inflammatory rheumatic diseases. However, delayed diagnosis is recognized in many rheumatic diseases. We studied possible delay in diagnosis in routine care in a rheumatology teaching hospital in 2013, using a simple 1-page form completed by the rheumatologist.

Methods: All patients seen in the study setting complete a multidimensional health assessment questionnaire (MDHAQ) at each visit in the waiting area before seeing the rheumatologist. The rheumatologist completes a complementary doctor form (RHEUMDOC). RHEUMDOC includes entry of 3 possible rheumatic diagnoses, queried for year of onset of symptoms and year of diagnosis. For this study, patients were classified into 4 groups according to diagnosis: rheumatoid arthritis (RA), osteoarthritis (OA), other inflammatory diseases (INF), and other non-inflammatory diseases (NON); differences between groups were compared using Wilcoxon rank sum tests.

Results: Among 211 patients seen between February and December 2013, 145 (69%) reported establishment of a diagnosis within one year, including 81% with RA, 55% with OA, 70% with other INF, and 57% with other NON (Table). The delay in RA was significantly less than in OA ($p=0.0046$). Nonetheless, 10% of RA patients received a diagnosis 1–5 years, and 8% >5 years, after symptom onset. Among all patients, 13% of RA patients received a diagnosis 1–5 years after onset of symptoms, and 18% after more than 5 years after onset of symptoms.

		Number of patients in each group according to interval from onset of symptoms to diagnosis		
Diagnosis	Number of patients	<1 year N (%)	1–5 years N (%)	>5 years N (%)
RA	59	48 (81%)	6 (10%)	5 (8%)
OA	45	25 (55%)	10 (22%)	10 (22%)
Other INF	86	60 (70%)	8 (9%)	18 (21%)
Other Non-INF	21	12 (57%)	4 (19%)	5 (24%)
Total	211	145 (69%)	28 (13%)	38 (18%)

Conclusion: A delay from onset of symptoms to definitive diagnosis remains an important problem in rheumatic diseases. Delay in diagnosis more than 1 year is more common in patients with diseases other than RA, but remains in more than 30% of all patients and 19% of RA patients. Identification of specific contributors to this delay could inform education of both patients and physicians regarding the importance of early diagnosis and treatment, and health policy resources to facilitate timely management of rheumatic diseases.

Disclosure: I. Castrejón, None; **K. A. Gibson**, None; **T. Pincus**, None.

1158

A Patient Survey Study of Zoledronic Acid Utilization and Factors Associated with Persistence. Deborah T. Gold[1], Stuart L. Silverman[2], Benjamin J. Chastek[3], Lung-I Cheng[4], Alyssa Goolsby Hunter[3], John C. White[3], Damon Van Voorhis[3] and Bradley S. Stolshek[4]. [1]Duke University Medical Center, Durham, NC, [2]OMC Clinical Research Center, Beverly Hills, CA, [3]Optum Life Sciences, Eden Prairie, MN, [4]Amgen, Inc., Thousand Oaks, CA.

Background/Purpose: Persistence with osteoporosis therapies is associated with clinical outcomes. The goal of this study is to examine patient-reported persistence with zoledronic acid, a once-yearly bisphosphonate infusion, and to assess the factors associated with non-persistence with zoledronic acid therapy.

Methods: A cross-sectional study of patients affiliated with a large US health plan was conducted via a mailed survey. The Optum Research Database was used to identify female patients receiving a zoledronic acid infusion (index date) 13–19 months prior to the November 2013 survey administration. Patients were required to be age 50 or older at index date with continuous enrollment in medical and pharmacy benefits and an osteoporosis diagnosis in the 6 months prior to the index date. Patients who received the index infusion in a long-term care institution or had a diagnosis of Paget's disease or cancer during the 6-month pre-index period were excluded. Data collection included a pilot-tested patient survey to assess patient clinical and demographic characteristics, experiences associated with index zoledronic acid therapy (e.g., side effects and barriers to treatment), knowledge of osteoporosis and zoledronic acid therapy, attitudes toward medication, and availability of support for disease and therapy management. Mailed survey administration followed the Dillman tailored design method. Survey data were collected from November 2013 to January 2014. The chi-squared test was used to examine the differences in survey responses between patients who did and did not receive a follow-up infusion.

Results: Of the 391 surveys sent to patients identified for the survey, 111 returned the survey (response rate = 32.0%). The mean (SD) age of the respondents was 62.2 (7.4). Among the respondents, 55 (49.6%) reported having received their follow-up zoledronic acid infusion in the previous 6 months. The differences in demographic characteristics were not statistically significant between those who did and did not receive a follow-up infusion. Those who received a follow-up infusion were more likely to report having had a discussion with the physician regarding the need to return for additional infusions compared with those who did not return (98.2% vs. 83.9%; p=0.016). Patients who scheduled a follow-up appointment to receive another dose at the time of the initial infusion (n=27) were more likely to receive a follow-up infusion (74.1%) than those who did not schedule (43.6%) (p=0.006). Similarly, patients who reported having been contacted by the physician's office about scheduling their next infusion (n=61) were more likely to receive a follow-up infusion (60.7%) than those who were not contacted (36.7%) (p=0.013).

Conclusion: Results from the survey study show that half of the patients on zoledronic acid therapy for osteoporosis reported receiving a follow-up infusion 13 to 19 months after the index infusion. Higher follow-up infusion rates were seen among patients who discussed the need to return for additional infusions with their physicians, scheduled a follow-up appointment for a follow-up infusion at the time of the index infusion, or received contact from the physician's office about scheduling their next infusion.

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Long-Term Quality of Life, Productivity Impairment, Disease Severity and Health Care Costs in Relation to Functional Impairment in Ankylosing Spondylitis Patients in the Czech Republic. Liliana Sedova[1], Monika Urbanova[2], Jiri Stolfa[3], David Suchy[4], Andrea Smrzova[5], Tomas Mlcoch[6], Jiri Klimes[7] and Tomas Dolezal[7]. [1]Institute of Rheumatology, Prague, Czech Republic, [2]Institute of Rheumatology Prague, Prague, Czech Republic, [3]Charles University Prague, Prague, Czech Republic, [4]University hospital Plzen, Plzen, Czech Republic, [5]University hospital Olomouc, Olomouc, Czech Republic, [6]Institute of Health Economics and Technology Assessment, Prague, Dominica, [7]Charles University, Prague, Czech Republic.

Background/Purpose: To describe the quality-of-life (QoL), productivity impairment, clinical indicators and health care costs in relationship to functional status described by Bath Ankylosing Spondylitis Functional Index (BASFI) in ankylosing spondylitis (AS) patients in three-year follow-up. These are follow-up results; the first visit was presented in ACR 2013.

Methods: This is a prospective multicenter non-interventional observational study with AS patients in 4 specialized centers for treatment of rheumatic diseases in the Czech Republic. A three-year follow-up with 6 months period between each time point observation is ongoing. The data presented here comes from the first visit and three subsequent visits (i.e. time 0, 6, 12 and 18 months). The demographic, clinical, QoL and productivity data were directly collected from patients. Health care consumption was assessed retrospectively reviewing individual patient's medical record. Clinical data were described by ASDAS-CRP, QoL measured by EuroQol questionnaire (EQ-5D), work impairment by Work Productivity and Activity Impairment (WPAI) with respect to BASFI categories. Patients were stratified according to their BASFI into 10 categories. Within health care consumption directly related to AS, we focus on medication, out-patient & in-patient care, complement, examination and out-of pocket expenses. Health care expenditures are presented as average yearly costs per patient. Patients were analyzed as the whole cohort and specifically by the presence of biologic treatment.

Results: 291 patients with AS were registered at the first visit, 218 on biological drugs, mean age was 44.3 years, mean time from diagnoses was 13.6 years, 26.1% were female. With higher functional impairment, described by BASFI, there is a trend in age increase, increase in time from diagnosis, percentage of work impairment and also decrease in percentage of work-active patients. There is also deterioration in clinical impairment (ASDAS-CRP) and QoL observed with higher BASFI. See the results in table 1 & 2; values presented as mean, n.a.-not applicable.

Conclusion: Patients with worse functional impairment revealed more significant impairment of their QoL, work productivity and revealed also worse clinical outcomes and higher costs (in non-biologic treated patients). There is a trend of decreasing number of work active patients who are not on biologics. For patients not treated with biologics, BASFI is a very good cost predictor.

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Table 1: Initial visit of AS patients

Patients on biologic drugs

BASFI category	BASFI	No.	Age	Time from Dx (years)	% women	Costs (EUR)	% of work active	% WPAI	ASDAS-CRP	EQ-5D
0–1>	0.4	52	38.0	9.8	31%	12,074	88%	6%	1.2	0.894
1–2>	1.5	42	40.8	11.9	21%	11,157	81%	21%	1.6	0.780
2–3>	2.5	35	46.2	15.3	14%	12,069	74%	27%	2.1	0.722
3–4>	3.4	29	44.6	15.1	24%	10,960	66%	27%	2.2	0.670
4–5>	4.4	23	44.5	14.9	22%	12,315	57%	40%	2.1	0.651
5–6>	5.4	20	44.8	17.9	20%	11,151	50%	41%	2.5	0.624
6–7>	6.5	7	46.4	7.1	29%	13,408	57%	23%	7.1	0.613
7–8>	7.5	2	66.5	27.0	0%	7,100	50%	70%	2.8	0.623
8–9>	8.5	6	51.0	15.5	0%	14,294	33%	40%	3.0	0.583
9–10>	9.2	2	50.5	18.5	50%	11,309	50%	95%	3.4	0.429
Mean/total	2.8	218	43.0	13.4	22%	11,740	72%	22%	2.0	0.740

Patients without biologic drugs

BASFI category	BASFI	No.	Age	Time from Dx (years)	% women	Costs (EUR)	% of work active	% WPAI	ASDAS-CRP	EQ-5D
0–1>	0.4	15	40.6	9.5	40%	174	80%	26%	1.9	0.838
1–2>	1.6	9	45.2	8.2	44%	327	89%	37%	2.4	0.746
2–3>	2.4	8	45.8	7.6	50%	221	63%	16%	2.5	0.682
3–4>	3.6	8	49.0	16.6	63%	354	75%	36%	2.5	0.614
4–5>	4.4	8	49.9	16.6	38%	290	50%	28%	2.9	0.583
5–6>	5.4	10	54.9	18.5	20%	645	70%	53%	3.3	0.603
6–7>	6.3	3	52.7	18.7	33%	348	67%	35%	3.0	0.608
7–8>	7.4	6	52.0	20.0	17%	665	50%	51%	2.9	0.530
8–9>	8.6	6	52.5	23.0	17%	1,593	0%	n.a.	8.4	0.392
9–10>	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Mean/total	3.7	73	48.0	14.3	37%	459	64%	34%	3.1	0.653

Whole patient cohort

BASFI category	BASFI	No.	Age	Time from Dx (years)	% women	Costs (EUR)	% of work active	% WPAI	ASDAS-CRP	EQ-5D
Mean/total	3.0	291	44.3	13.6	26%	8,910	70%	25%	2.3	0.718

Table 2: Follow-up observations

	1st visit			2nd visit			3rd visit			4th visit		
Mean/total	Bio	w/o Bio	Whole	Bio	w/o Bio	Whole	Bio	w/o Bio	Whole	Bio	w/o Bio	Whole
BASFI	2.8	3.7	3.0	2.7	4.3	2.9	2.5	4.0	2.7	2.7	n.a.	2.8
No. (% of work active)	218 (72%)	73 (64%)	291 (70%)	185 (72%)	23 (65%)	208 (71%)	152 (75%)	22 (59%)	174 (73%)	64 (70%)	n.a.	66 (70%)
% WPAI	22%	34%	25%	19%	26%	19%	21%	23%	21%	23%	n.a.	23%
ASDAS-CRP	2.0	3.1	2.3	1.8	2.6	1.9	1.8	2.6	1.9	1.8	n.a.	1.8
EQ-5D	0.740	0.653	0.718	0.738	0.667	0.730	0.744	0.638	0.731	0.726	n.a.	0.723

Bio – patients on biologic treatment; w/o - patients without biologic treatment; Whole – Whole cohort of patients

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1160

Annual Real-Practice Costs of Biologics for 200 Cases with Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis Treated By *Tight Control* and *Treat to Target* Strategy Permitting Dose Reduction. Bernd Raffeiner[1], Costantino Botsios[2], Michele Ragazzi[3] and Ernesto De Menis[4]. [1]Rheumatology-General Hospital Bolzano, Bolzano, Italy, [2]Rheumatology-Hospital San Valentino Montebelluna, Montebelluna, Italy, [3]Pharmacy-Hospital San Valentino Montebelluna, Montebelluna, Italy, [4]Internal Medicine-Hospital San Valentino Montebelluna, Montebelluna, Italy.

Background/Purpose: To investigate annually real-practice costs of biologic therapy for rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) cohort treated by *tight control* and *treat to target* strategy permitting dose reduction in Italian local health centre.

Methods: 200 Italian patients in treatment with biologic therapy including all five TNFα inhibitors (adalimumab, ADA; certolizumab, CER; etanercept, ETA; golimumab, GOL; infliximab, IFX), abatacept (ABA), tocilizumab (TCZ) and anakinra (ANK) adhering to local health centre Asolo, in northeast of Italy counting population of 250.000 people, were investigated. ABA and TCZ were used as second and third biologic line. 127 were affected from RA, 39 from PsA and 34 from AS. All patients were controlled every 3 months for low disease activity or remission following EULAR criteria (DAS 28-CRP $<$ 2.6 or ASDAS $<$ 1.3). After achieving sustained remission for at least 12 months doses of biologics were reduced and maintained when activity permitted it. Real-practice costs were supplied by payment bureau of local health centre for the year 2013. Costs for eventual concomitant DMARDS, NSAIDs, steroids and other pain killers were excluded. Periods of treatment stops because of justified or unjustified causes were included.

Results: Clinical remission by *tight control* and *treat to target* strategy was achieved in 81 RA (63.7%), 26 PsA (66.6%) and 22 AS (64.7%) patients. Dose reduction was very frequent for RA (49.6%), PsA (69%) and AS (44%); and significantly more frequent in patients treated with ETA (69.6%) than ADA (30.2%). Dose reduction was infrequent for the other biologics and beyond first biologic line. Total annual costs of biologics for the year 2013 were € 1.463.470, mean costs per patient per year were € 7.317. Mean annual costs per patient per year were € 5.736 for ETA, € 6.511 for CER, € 6.876 for ANK, € 7.867 for IFX, € 8.485 for TCZ, € 8.563 for GOL, € 9.285 for ADA and € 9.404 for ABA.

Conclusion: a) Clinical remission was achieved by *tight control* and *treat to target* strategy in high number of patients with RA, PsA and AS; b) Dose reduction was very frequent in real-practice conditions; c) This was especially possible during ETA and first line biologic treatment; d) Permitting dose reduction importantly decreased expected annual costs for biologics in real-practice conditions.

Disclosure: B. Raffeiner, None; **C. Botsios**, None; **M. Ragazzi**, None; **E. De Menis**, None.

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The Price of a Positive Test: Is It Worth the Cost? Lara H. Huber, Kristen Morella, Natasha M. Ruth and Murray H. Parsso. Medical University of South Carolina, Charleston, SC.

Background/Purpose: The ACR Choosing Wisely Campaign top 5 lists highlight the appropriate use of autoantibody testing, thereby reducing unnecessary spending. Positive antinuclear antibodies (ANA) are one of the most common reasons for referral to pediatric rheumatology clinics. The prevalence of positive ANAs in the pediatric population ranges from 3 – 36%. ANAs are useful when used for confirmation of a suspected diagnosis and for risk stratification of a known diagnosis, but ANAs are often inappropriately used to screen for autoimmunity resulting in positive tests with unclear clinical significance. We hypothesize that a large amount of health care dollars are spent on laboratory and radiographic tests related to a positive ANA and that general pediatricians are more likely to order an ANA than pediatric rheumatologists when confronted with the same clinical scenario.

Methods: We conducted a retrospective chart review of new patients referred for a positive ANA to the pediatric rheumatology clinic at our institution from July 1, 2010 through June 30, 2011. We recorded findings from the history and physical examination, any studies ordered prior to and at the time of the rheumatology visit, and the final diagnosis. The history, physical examination, and baseline laboratories were reviewed by 2 pediatric rheumatologists, 3 pediatric hospitalists, and 2 ambulatory pediatricians blinded to the final diagnosis, ANA titer, and other studies. The reviewers indicated whether they would have ordered an ANA. A list of gross charges for the studies was obtained from the laboratory and department of radiology at our institution.

Results: Seventy-five patients were identified. The total charges equaled $195,402 with a mean of $2,605 per patient. Only 5 patients had a primary rheumatologic disease. Two patients had lupus, 2 had JIA, and 1 had UCTD. Hypermobility was the most common diagnosis, and 24% of patients had a negative ANA on repeat testing. There was a significant difference in the total charges per patient based on the final diagnosis (primary rheumatologic disease vs. other diagnosis, $p = 0.0499$). The interrater reliability between all 7 reviewers was fair with an intraclass correlation coefficient of 0.303; it was moderate between rheumatologists with a kappa statistic of 0.478. There was not a significant difference between the number of ANAs ordered by the 3 groups. The responses for the patients with a rheumatologic disease were analyzed. The rheumatologists agreed on ordering an ANA for all these patients, but there was disagreement among the general pediatricians.

Conclusion: ANAs are useful when used appropriately, but they generate large amounts of unnecessary spending if used inappropriately. Most patients with a positive ANA did not have an autoimmune disease bringing into question the necessity of the initial ANA test. When comparing the utilization of ANAs between pediatric rheumatologists and general pediatricians, there was not a significant difference in the number of tests ordered; however, the rheumatologists more accurately identified patients with a rheumatologic disease.

Disclosure: L. H. Huber, None; **K. Morella**, None; **N. M. Ruth**, None; **M. H. Passo**, None.

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Patterns of Use of Long-Term (> 5 Years) Oral Bisphophonate Prescription Among Primary Care Providers and Rheumatologists for the Treatment of Osteopenia and Osteoporosis in a Veteran Population. Mathilde Pioro[1], Stephanie Ogorzaly[2] and Maya Mattar[3]. [1]Cleveland Veterans Affairs Medical Center, Cleveland, OH, [2]Cleveland Veterans' Affairs Medical Center, Cleveland, OH, [3]University Hospitals Case Medical Center, Cleveland, OH.

Background/Purpose: Osteoporosis is a widely prevalent but underrecognized condition. Oral bisphosphonates are considered first-line treatment of osteoporosis in men and women however long term use is associated with potential adverse effects. In patients taking bisphosphonates for at least 5 years, it is generally recommended that the need for continued bisphophonate therapy be reevaluated and a drug holiday be considered.

Methods: We conducted a computerized retrospective cohort study of all veterans, male and female $>$ 50 years of age at the Cleveland VA Medical Center receiving a prescription for an oral bisphosphonate for greater than 5 years. Medication compliance was determined by a medication possession ratio (MPR) greater than 0.8 over 5 years (MPR= total number of days supplied/total number of days since first fill). We excluded patients receiving bisphosphonates for Paget's disease or an indication other than osteoporosis/osteopenia (ICD9 codes 733.00, 733.90,733.01, 733.02). We identified whether prescribers were rheumatologists or primary care providers. We reviewed laboratory testing for serum 25 (OH) D3 at any time during bisphosphonate therapy, and VA pharmacy prescriptions for Calcium and Vitamin D supplementation. Chart review of clinical notes and radiology reports was performed to determine if baseline and follow-up bone mineral densitometry (BMD) were obtained and documented.

Results: 100 patients met inclusion criteria, 78 male and 22 female, mean age 76 years (range 50–96). The diagnosis was osteoporosis in 54%, osteopenia in 21%, and not documented in 23%. The most commonly prescribed bisphosphonate was alendronate (71%). The duration of bisphosphonate therapy ranged from 5 to 14 years (mean 8 years).

	Prescription of oral bisphosphonate by rheumatologist		Prescription of oral bisphosphonate by primary care provider	
Number of patients (total N=100)	n=5	%	n=95	%
Documentation of BMD at initiation of bisphosphonate	4	80	44	46.3
Documentation of follow-up BMD	5	100	37	38.9
Glomerular filtration rate $<$ 30 ml/min	0	0	3	3.2
Serum level of 25(OH)D3	5	100	60	63.1
Active order for Calcium	5	100	71	74.7
Active order for Vitamin D	5	100	72	75.7

Conclusion: The large majority (95%) of patients on long-term bisphophonate therapy in this veteran population were managed by PCPs rather than

rheumatologists (5%). In comparison to patients managed by rheumatologists, patients managed by PCPs had low frequency of BMD documentation at initiation of therapy and in follow-up, suboptimal measurement of serum 25(OH)D3, and suboptimal Calcium and vitamin D supplementation. Our study was limited by possible use of non-VA Calcium and Vitamin D supplementation, and possible use of non-VA BMDs in patients living in areas distant from the medical center. Future studies should be directed to educational outreach to PCPs and use of computerized clinical reminders at the time of prescription renewal.

Disclosure: M. Pioro, None; **S. Ogorzaly**, None; **M. Mattar**, None.

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Predictors of Cholesterol and Lifestyle Discussions in Rheumatoid Arthritis Visits: Impact of Perceived RA Control and Comparison with Other Prevention Topics. Christie M. Bartels[1], Joanna Wong[2], Heather Johnson[1], Katya Voelker[3] and Maureen Smith[1]. [1]University of Wisconsin School of Medicine and Public Health, Madison, WI, [2]Tufts University School of Medicine, Boston, MA, [3]Univ of Wisconsin School of Medicine and Public Health, Madison, AA.

Background/Purpose: Experts recommend discussing modifiable cardiovascular disease (CVD) risk factors in RA visits. We examined the predictors of discussions about cholesterol and or lifestyle (weight, diet, exercise) in RA visits among patients eligible for improved cholesterol control, and compared them to other prevention topics: vaccination, bone health. We hypothesized that cholesterol/lifestyle discussions would depend on perceived RA control at a given visit.

Methods: Electronic health records were used to identify RA patients with uncontrolled cholesterol who received primary and rheumatology care in a health system with 3 rheumatology clinics (2004–2011). Those with diabetes, CVD, chronic kidney disease with low density lipoprotein (LDL) cholesterol >100 mg/dL and without such conditions whose LDL exceeded 130 mg/dL had visit notes reviewed by trained abstractors until LDL control or censoring for loss of continuity, death, or end of data. "RA control" was defined as stated by a rheumatologist in the visit note. We used logistic regression to calculate the odds ratios (OR) and 95% confidence intervals reflecting RA control as a predictor of cholesterol/lifestyle or other prevention discussions after controlling for sociodemographics, comorbidity (ACG score), and clinic.

Results: 1785 abstracted RA visits showed a mean age 60 years, 84% female, 93% white, 10% smokers, and mean BMI was 30.2 (SD 7.3). Prevalent CVD was noted in 18%, diabetes 15%. Overall 37% of visits reported controlled RA, and 31% discussed either cholesterol or lifestyle (13% cholesterol). As hypothesized, perceived RA control at a visit increased the odds of cholesterol/lifestyle discussion at that visit (OR 1.54, 1.21–1.98; Table 1). Other predictors of cholesterol/lifestyle discussions included single marital status, Medicaid, higher ACG score and hyperlipidemia codes or medications. In contrast, black race, non-English language, tobacco use, obesity and chronic kidney disease (CKD) predicted lower odds of such discussions. RA control was not predictive of vaccine or bone health discussions which showed less variation. Obese patients had lower odds of any prevention discussions. Clinic effects were significant for cholesterol and vaccine discussions but not bone health (data not shown). Limitations of our study include a visit note level analysis, which may not reflect care over several visits or without documentation, and use of subjective "RA control" definitions, although this may reflect usual care.

Conclusion: Perceived RA control predicted higher odds of cholesterol/lifestyle discussions, but not vaccine or bone health discussions. Concerning low discussion rates in at-risk patients with tobacco use, obesity, chronic kidney disease, and black race and clinic variation call for improved quality guidelines and systematic practices to address modifiable CVD risk factors in RA visits.

TABLE 1. Predictors of cholesterol & lifestyle discussions vs. other prevention topics in RA visits

	Cholesterol/Lifestyle Discussions n=547	Vaccine Discussions n=127	Bone Health Discussions n=651
	OR	OR	OR
RA Control	1.54*	1.55	1.1
Age Categories	*ns*	*ns*	0.41*(<60)*
Female	1.01	0.71	3.43*
Race: Black (White ref)	0.38*	0.25	0.07
Other race/ethnicity	2.95*	0.83	0.55
Non-English	0.12*	~	5.96*
Single (Married ref)	1.71*	0.87	0.46*
Divorced/widowed	0.93	0.57	0.85
Medicaid (Never ref)	2.27*	1.89	0.92
Tobacco User (Never ref)	0.6*	3.16*	1.03
Former User	0.89	2.18*	0.71*
BMI Overwt (≤25 ref)	0.99	0.78	0.96
BMI Obese	0.66*	0.35*	0.68*
ACG 2nd Quart (1st ref)	1.01	1.44	2.5
3rd Quartile	1.41*	1.59	1.75
Highest Quartile	1.47*	1.03	2.6
Cardiovascular disease	0.82	0.64	2.32
Chronic kidney/ESRD	0.38*	0.53	0.95
Diabetes mellitus	1.17	1.63	0.74
Hyperlipidemia	2.08*	0.69	0.73

** Indicates significant OR and 95% CI; ~ Indicates omitted for colinearity*

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Inequity: Level of Education Is Associated with Access to Biologic Dmards Even in a Country with Highly Developed Social Welfare (Norway). Polina Putrik[1], Sofia Ramiro[2], Elisabeth Lie[3], Andras Keszei[4], Desirée van der Heijde[5], Robert Landewé[6], Tore K. Kvien[3], Till Uhlig[3] and Annelies Boonen[1]. [1]Maastricht University Medical Center, Maastricht, Netherlands, [2]Amsterdam Rheumatology Center, University of Amsterdam & Hospital Garcia de Orta, Almada, Portugal, Amsterdam, Netherlands, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Uniklinik RWTH Aachen University, Aachen, Germany, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: Biologic DMARDs (bDMARDs) have greatly improved the outcome of rheumatoid arthritis (RA). Investigating possible inequities in access to bDMARDs across socio-economic factors is important, and such analyses could provide clinicians and healthcare decision makers with useful information. The objective of the study was to explore whether there are differences in initiation rates of a first bDMARD across age, gender and educational status among RA patients.

Methods: Data from the Norwegian NOR-DMARD study (collected between 2000–2012) was used. Only patients who were DMARD naïve at entrance into the study were included in the analyses. The first prescription of any bDMARD was the event of interest. In order to assess impact of education, age and gender on time to first bDMARD, two Cox regression models were built using a manual forward step-wise modelling strategy. Models were adjusted for potential clinical confounders (DAS28, erosive disease, physician global assessment, HAQ, rheumatoid factor, disease duration, and comorbidities) and year of baseline visit. The first model included baseline predictors; the second was a time-varying model accounting for clinical information of all other visits between study inclusion and either start of bDMARD or censoring. Interactions between education and either year of baseline visit or age were tested.

Results: In total, 2005 patients were included (mean age at baseline 55 yrs, 68% females), and 368 patients received a bDMARD in the time of the period of observation (mean time to bDMARD 2.6 yrs). In both models, the socio-economic factors age and education were significant predictors of time-till-prescription (prescription of a first bDMARD), with lower hazard ratios (HR) for lower education and older age (Table). Education and age consistently and significantly contributed to the access to first bDMARD. Effect of lower education was more pronounced in later years (HR low vs. high education= 0.17 and 0.34 in patients who entered the cohort in 2008–2011, in time-varying and baseline models, respectively).

	Time-varying Cox regression model	Baseline predictors Cox regression model
	Hazard ratio [95% CI]	
High education (ref.)	1	1
Medium education	0.71* [0.52; 0.96]	0.77 [0.57; 1.05]
Low education	0.75* [0.57; 0.99]	0.67* [0.52; 0.87]
Gender (female vs male)	0.84 [0.65; 1.03]	0.99 [0.77; 1.27]
Age, years	0.97* [0.96; 0.98]	0.97* [0.96; 0.98]
Comorbidities	0.90 [0.78; 1.03]	0.92 [0.80; 1.06]
DAS28 (per unit)	1.62* [1.45; 1.81]	1.20* [1.08; 1.33]
Erosive disease (at baseline)	2.12* [1.67; 2.69]	**
Physician global assessment (0-100)	1.03* [1.03; 1.04]	**
Disease duration (>1 year vs. ≤ 1 year)	0.19* [0.11; 0.33]	**
HAQ (0–3, per unit)	**	1.42* [1.10; 1.84]
Rheumatoid factor (yes vs. no)	**	1.30* [1.02; 1.64]
Year of baseline visit	1	1
2000–2003 (ref.)	2.06* [1.55; 2.75]	1.49* [1.14; 1.96]

2004–2007	5.13* [3.52; 7.46]	3.04* [2.17; 4.26]
2008–2011		

*p<0.05, ** not included in the final model

Conclusion: Well-educated and younger patients apparently have potentially decisive advantages with regard to access to expensive treatments, even a country with highly developed welfare like Norway. A stronger effect of education in later years might be explained by changes in prescription practice and social trends towards longer education, pointing at increasing health gaps between education groups. Findings are relevant as the impact of age and education on access might result in avoidable adverse impact on health.

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1165

Evaluation of Symptom Control Among Treated Gout Patients in the United States, United Kingdom, and Germany. Robert Morlock[1], Chris Storgard[1], Vernon F. Schabert[2], Augustina Ogbonnaya[2], Pierre Chevalier[3], Dionne Hines[2] and Sulabha Ramachandran[4]. [1]Ardea Biosciences, San Diego, CA, [2]IMS Health, Alexandria, VA, [3]IMS Health, Vilvoorde, Belgium, [4]AstraZeneca, Wilmington, DE.

Background/Purpose: Gout affects approximately 1–4% of the population in developed Western countries. The hallmark signs of gout are elevated serum uric acid (SUA) level, episodes of painful inflammatory arthritis (flares), and tophi. Despite treatment with urate lowering therapies (ULT), e.g., xanthine oxidase inhibitors, a significant proportion of patients continue to have elevated SUA, recurrent flares, or tophi. This study aimed to estimate the rate of gout control among ULT treated established gout patients in the United States (US), United Kingdom (UK), and Germany (DE).

Methods: A longitudinal panel study was conducted using IMS' PharMetrics Plus database linked with outpatient laboratory results (US), Disease Analyzer (DE) databases, and the Clinical Practice Research Datalink-Hospital Episode Statistics (UK) from Jan 1, 2009 to Dec 31, 2011. Patients were required to have evidence of established gout (treated with ULT or eligible for ULT based on American College of Rheumatology guidelines) between Jan 1, 2009 and Dec 31, 2009; aged ≥18 years on index date (Jan 1, 2010); and have SUA results for outcome assessment at continuous follow-up in their respective databases throughout the observation period. ULT treatment was defined as having ≥60 days' supply of consecutive therapy any time during the baseline period (calendar year 2010). Gout symptom control was defined as SUA <6 mg/dL, ≤1 flare, and no tophi, and was measured at any time during the outcome assessment period (calendar year 2011).

Results: A total of 1,765 (US), 3,594 (UK), and 17,486 (DE) patients met the patient selection criteria and the ULT treatment definition in the respective databases. The mean (SD) age of the patients was 54.5 (9.6), 64.6 (12.3), and 69.2 (11.0) years in the US, UK, and DE, respectively. Most patients were male (US: 89.2%; UK: 85.6%; DE: 70.3%). Of the comorbidities evaluated at baseline, hypertension and hyperlipidemia were the most common in the US (64.9% and 54.8%, respectively) and DE (73.8% and 54.0%, respectively), while hyperlipidemia (51.6%) was the most common in the UK. Overall, 40.9%, 49.6%, and 41.1% of patients treated with ULT in the US, UK, and DE, respectively, achieved gout symptom control. When baseline ULT treatment was evaluated among controlled and uncontrolled patients, allopurinol was the predominant treatment in all 3 countries (US: N=1,575; UK: N=3,466; DE: N=16,684). Of those treated with allopurinol in the respective databases, 43.6% (US), 51.2% (UK), and 41.5% (DE) were controlled patients. Fewer patients were treated with febuxostat (US: N=76; UK: N=15; DE: N=61); and of those treated with febuxostat in the respective databases, 39.5% (US), 33.3% (UK), and 36.1% (DE) were controlled patients.

Conclusion: Overall, less than half of patients treated with ULT achieved gout symptom control, with the vast majority of patients in this study treated with allopurinol. New treatment options might be needed to improve outcomes/gout control for some patients. Further investigation is also necessary to understand factors that impact gout symptom control among treated patients.

Disclosure: R. Morlock, Ardea Biosciences, Inc., 1, Ardea Biosciences, Inc., 3; **C. Storgard**, Ardea Biosciences, Inc., 1, Ardea Biosciences, Inc., 3; **V. F. Schabert**, IMS Health, 3; **A. Ogbonnaya**, IMS Health, 3; **P. Chevalier**, IMS Health, 3; **D. Hines**, IMS Health, 3; **S. Ramachandran**, AstraZeneca, 1, AstraZeneca, 3.

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5 Year Budget Impact Analysis of Biosimilar Infliximab for the Treatment of Rheumatoid Arthritis in UK, Italy, France and Germany. JiSeon Kim[1], JungAn Hong[1] and Alex Kudrin[2]. [1]CELLTRION HEALTHCARE, INCHEON, South Korea, [2]CELLTRION, Inc., Incheon, South Korea.

Background/Purpose: Biosimilar infliximab has been approved by EMA based on comparable quality, safety and efficacy profile to infliximab for the management of inflammatory autoimmune disorders including rheumatoid arthritis (RA), ankylosing spondylitis (AS), Crohn's disease, ulcerative colitis (UC), psoriatic arthritis (PsA), and psoriasis. Recent studies have shown considerable potential savings through the use of biosimilars for the investigated classes of biological drugs, for instance, the first generation biosimilar filgrastim which decreased the treatment cost by its introduction in oncology field.

Methods: We aimed to evaluate the budget impact of the introduction of biosimilar infliximab in treatment of Rheumatoid arthritis from the payer and the patient perspectives by using an Excel based budget-impact model over a five-year time horizon. The model calculated patients eligible for infliximab treatment based on the total population, annual population growth rate and prevalence of RA in 4 major EU countries; UK, Italy, France, and Germany. The acquisition cost of comparator infliximab was assumed not to change after the introduction of biosimilar mAb. The price of the biosimilar infliximab is currently unknown, therefore three different discount scenarios (10%, 20%, and 30%) were applied to evaluate the budget impact. Market uptake growth rate was also varied in each of the scenarios at 20%, 30%, and 40%, respectively. The market share was assumed to be 25% in the first year in all scenarios.

Results: The total budget saving for the 10% price discount scenario for all four countries for 2015, 2016, 2017, 2018, and 2019 was € 12,880,000, € 15,450,000, € 18,560,000, € 22,260,000, and € 26,710,000, respectively. The total budget saving for the 20% price discount scenario for 2015, 2016, 2017, 2018, and 2019 was €25,750,000, €33,490,000, €43,550,000, € 56,610,000, and € 73,600,000, respectively. The total budget saving for the 30% price discount scenario for 2015, 2016, 2017, 2018, and 2019 was € 38,630,000, € 64,630,000, € 75,740,000 €106,050,000, and € 148,470,000, respectively. The total budget saving over the five year period (2015 –2019) for all four countries was € 95,860,000, €233,000,000, and € 433,520,000 for the 10%, 20%, and 30% price discount scenarios, respectively.

Conclusion: The introduction of the biosimilar infliximab as a treatment option for patients with Rheumatoid arthritis could achieve substantial cost savings. In the scenarios tested, the total 5 year saving across UK, Italy, France and Germnay ranged from € 96 million to € 433 million.

Disclosure: J. Kim, None; **J. Hong**, None; **A. Kudrin**, None.

1167

A Description and Comparison of Treatments for Low Back Pain in the United States. Elizabeth G. Salt, Yevgeniya Gokun, Anna Kerr and Jeffery Talbrert. University of Kentucky, Lexington, KY.

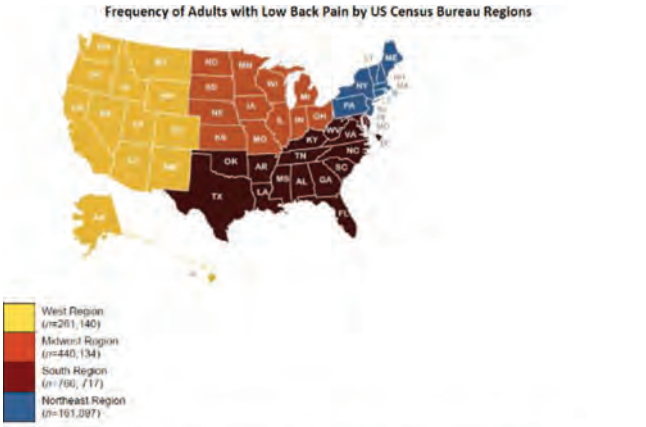
Background/Purpose: Low back pain (LBP) affects 67% to 84% of persons residing in industrialized countries, and is a significant source of lost productivity, disability, and increased health care costs (treatment costs estimated at $90 billion). Both pharmacologic (i.e., opioids-"fair" evidence to support use) and non-pharmacologic (i.e., exercise therapy-"good" evidence) treatments are recommended for LBP management. Because the prevalence of LBP and opioids use (p=.0014) differs between the U.S. Census Regions, we compared the treatments used for LBP and their related costs between regions.

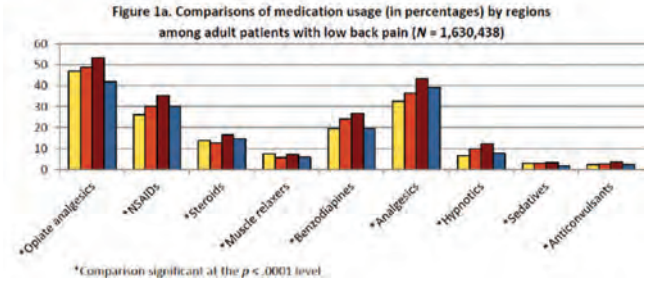
Methods: De-identified patient health claims data from persons with LBP (ICD-9 codes-724.2 [lumbago]) along with treatments received (CPT codes-97001 [physical therapy {PT}]) and medication records was extracted from a large commercially insured dataset (January 1, 2007-December 31, 2009) (N=1,630,438). After using descriptive statistics to describe the sample and the frequency of received LBP treatments, we used Pearson's Chi-Squared Test of Independence to compare therapy and medication usages among the different regions.

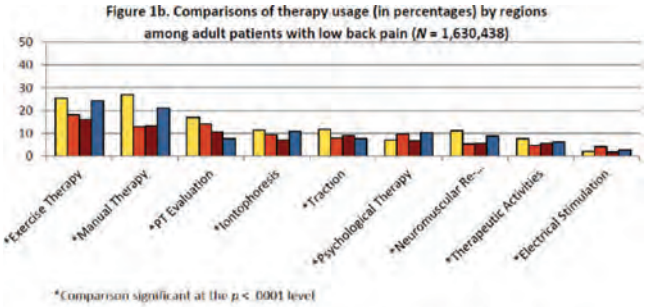
Results: An opioid was used by 49.8% (n=812,479) of this sample while nonpharmacologic therapies were rarely used (8%-psychological therapies; 19%-exercise therapies; 12%-PT). Opioids had the lowest standardized cost ($16);

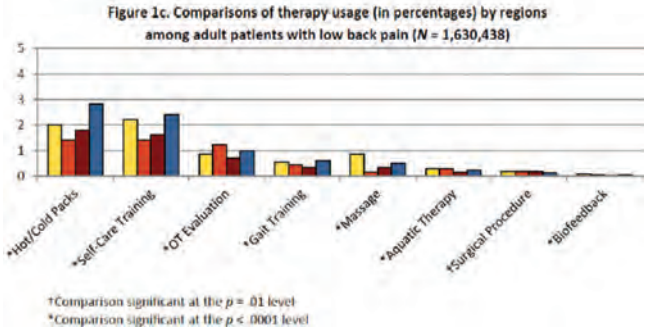
anti-convulsants (n=49,073) had the highest standardized cost ($452). The median costs for non-pharmacologic treatments are variable ($5,526-surgical procedures vs. $40-hot/cold packs). We found significant differences in the medications and therapies used in the U.S. Census Regions ($p <$ .0001; Figure 1).

Conclusion: There is a lack of adherence to treatment recommendations for LBP and significant differences in the receipt of various LBP treatments per U.S. Census Region. Further research is needed to explore this discrepancy.









Disclosure: E. G. Salt, None; **Y. Gokun**, None; **A. Kerr**, None; **J. Talbert**, None.

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Usng an Advanced Clinician Practitioner in Arthritis Care Trained Physiotherapist and a Standardized Electronic Medical Record Triage Assessment Tool to Detect Inflammatory Arthritis and Initiate Dmards Earlier in a Community Rheumatology Office Setting. Vandana Ahluwalia[1] and Tiffany Larsen[2]. [1]William Osler Health Center, Brampton, ON, [2]Headwaters Health Care Centre, Orangeville, ON.

Background/Purpose: An experienced Advanced Clinician Practitioner in Arthritis Care (ACPAC) trained physiotherapist with advanced directives using a standardized Electronic Medical Record (EMR) triage tool conducted a 15 minute assessment on patients with suspected inflammatory arthritis. We evaluated the time from referral to the initiation of Disease Modifying Antirheumatic Drug (DMARD) therapy in those patients who had been triaged and confirmed to have inflammatory arthritis (IA).

Methods: Patients were referred by local primary care physicians to a solo community rheumatology practice. The rheumatologist triaged the paper referrals, and those with suspected inflammatory arthritis were selected to be initially seen by the ACPAC physiotherapist (ACPAC triage model). Patients in whom the physiotherapist suspected inflammatory arthritis were given a workup with laboratory and x-ray testing as per advanced directives. These patients were then booked as priority to see the rheumatologist. The average number of days from referral to the initiation of DMARDs was determined for those patients confirmed to have a diagnosis of IA. A retrospective chart review using the rheumatologists EMR was conducted on new referrals that were seen solely by the rheumatologist (Traditional triage model) and suspected to have IA. The time from referral to the initiation of DMARDs was determined was also determined for this group.

Results: One hundred and twenty-one patients were triaged by the ACPAC physiotherapist prior to the assessment by the rheumatologist. Forty eight patients (40%) were diagnosed with IA and 31 patients were started on a DMARD. Twenty-nine patients (93.5%) were started on a DMARD at the first Rheumatology visit, and two patients (6.5%) were started on a DMARD on the second Rheumatology visit. The average number of days from referral to Rheumatology visit for patients with IA was 73 days. The average number of days from the referral to initiation of DMARDs was 75 days. We compared these findings to patients from a retrospective chart review using the Traditional Triage Model. One hundred and ten charts were retrospectively reviewed on patients with suspected IA. There were 53 patients (48%) diagnosed with IA and forty-three patients were started on a DMARD. Fifteen patients (35%) started on a DMARD at the first Rheumatology visit, and 28 patients (65%) started on a DMARD at the second Rheumatology visit. In this group, the average number of days from referral to Rheumatology visit was 84 days. The average number of days from the referral to the initiation of DMARDs was 125 days.

Conclusion: The utilization of an ACPAC trained physiotherapist with advanced directives to triage suspected inflammatory arthritis referrals prior to a Rheumatology assessment resulted in an earlier initiation of DMARDs with the majority of patients starting a DMARD at the first Rheumatology visit. This approach may serve as a model for other settings in which there is a need for health human resources in musculoskeletal care.

Disclosure: V. Ahluwalia, None; **T. Larsen**, None.

ACR/ARHP Poster Session B
Imaging of Rheumatic Diseases: Magnetic Resonance Imaging
Monday, November 17, 2014, 8:30 AM–4:00 PM

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Hippocampal Atrophy Is Associated with Anti-NR2 Antibodies in Patients with Systemic Lupus Erythematosus and Primary Sjögren's Syndrome. Maria B Lauvsnes[1], Mona K Beyer[2], Jan T Kvaløy[1], Ole J Greve[1], Simone Appenzeller[3], Erna Harboe[1], Anne B Tjensvoll[1], Lasse G Gøransson[1] and Roald Omdal[1]. [1]Stavanger University Hospital, Stavanger, Norway, [2]Oslo University Hospital, National Hospital, Oslo, Norway, [3]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: Antibodies against the NR2 subtype of the NMDA-receptor (anti-NR2 antibodies) are detected in patients with systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (SS). It is known from murine lupus models that these antibodies can cause hippocampal atrophy and cognitive impairment when they gain access to the brain. Reduced hippocampal volumes have been described in both SLE and primary SS patients; but a link between anti-NR2 antibodies and hippocampal atrophy has never been described in humans until now.

Methods: A population-based cohort of 50 SLE (all fulfilling the ACR criteria) and 50 primary SS patients (all fulfilling the AECG criteria) were clinically examined and cerebral MRI scanning performed. Anti-NR2 antibodies were measured in cerebrospinal fluid (CSF). We applied the SPM8 software and compared hippocampal volumes between patients with and without anti-NR2 antibodies.

Results: 16 % of the SLE patients and 12 % of the primary SS patients had anti-NR2 antibodies in CSF. Patients with anti-NR2 antibodies had less grey matter in their hippocampi compared to patients without these antibodies. There were no differences in grey matter volumes in other areas of the brain. Hippocampal grey matter volumes did not differ between the two total groups of SLE and primary SS patients, and there were no statistical significant interactions between groups and anti-NR2 antibodies. No effect on hippocampal volumes were found for presence of anti-phospholipid antibodies, disease duration, or present use of corticosteroids.

Conclusion: Less hippocampal grey matter is observed in SLE and primary SS patients with anti-NR2 antibodies compared to those without these antibodies. This indicates that anti-NR2 antibodies may cause neuronal death in humans, as previously demonstrated in mice with autoimmune disease.

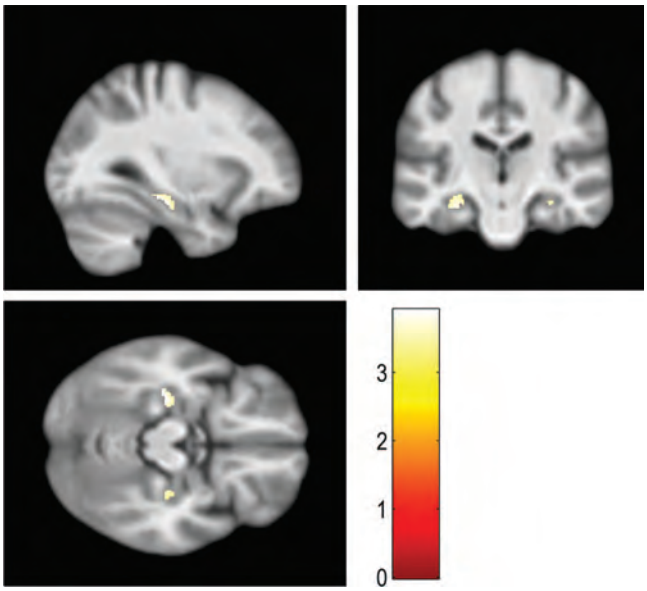

Figure 1: Clusters of voxels with GM loss in patients with anti-NR2 antibodies ($p < 0.05$, FWE corrected). The cluster color represents the statistical significance of GM decrease according to the gradation of the color bar.

Disclosure: M. B. Lauvsnes, None; **M. K. Beyer**, None; **J. T. Kvaløy**, None; **O. J. Greve**, None; **S. Appenzeller**, None; **E. Harboe**, None; **A. B. Tjensvoll**, None; **L. G. Gøransson**, None; **R. Omdal**, None.

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Neurological Complications during Anti-TNF Therapy: A Prospective Imaging and Electrophysiological Study. Evripidis Kaltsonoudis[1], Anastasia Zikou[2], Paraskevi V. Voulgari[3], Spyridon Konitsiotis[4], Maria Argyropoulou[5] and Alexandros A. Drosos[6]. [1]Rheumatologist, Ioannina, Greece, [2]Lecturer of Radiology, Ioannina, Greece, [3]Associate Professor of Rheumatology, Ioannina, Greece, [4]Associate Professor of Neurology, Ioannina, Greece, [5]Professor of Radiology, Ioannina, Greece, [6]Professor of Medicine/Rheumatology, Ioannina, Greece.

Background/Purpose: The aim was to investigate the frequency of neurological adverse events in patients with rheumatoid arthritis (RA) and spondylarthropathies (SpA) treated with tumor necrosis factor (TNF) α antagonists.

Methods: Seventy-seven patients eligible for anti-TNFα therapy were evaluated. There were 36 patients with RA, 41 with SpA (24 psoriatic arthritis [PsA] and 17 with ankylosing spondylitis [AS]). All patients had a complete physical and neurological examination. Brain and cervical spine magnetic resonance imaging (MRI) and neurophysiological tests were performed in all patients before the initiation of anti-TNFα therapy and after a mean of 18 months or when clinical symptoms and signs indicated a neurological disease. Exclusion criteria included hypertension, diabetes mellitus, dyslipidemia, heart arrhythmias, atherothrombotic events, vitamin 12 and iron deficiency, head and neck trauma and neurological surgeries.

Results: Two patients did not receive anti-TNFα therapy because brain MRIs at baseline revealed lesions compatible with demyelinating diseases. Thus, 75 patients received anti-TNFα (38 infliximab, 19 adalimumab and 18 etanercept). Three patients developed neurological adverse events. A 35-year-old man with PsA after 8 months of infliximab therapy presented with paresis of the left facial nerve and brain MRI showed demyelinating lesions. Infliximab was discontinued and he was treated with pulses of corticosteroids recovering completely after two months. The second patient was a 45-year-old woman with RA who after 6 months of adalimumab therapy presented with optic neuritis. The third patient was a 50-year-old woman with AS, whom after 25 months of infliximab therapy, presented with tingling and numbness of the lower extremities and neurophysiological tests revealed peripheral neuropathy. In both patients anti-TNF were discontinued and they improved without treatment after 2 months. The rest of our patients showed no symptoms and MRIs showed no abnormalities.

Conclusion: Neurological adverse events after anti-TNFα therapy were observed in our patient. The estimated rate of neurological complications is 4% (3/75). Brain MRI and neurophysiological tests are essential tools to discriminate neurological diseases.

Disclosure: E. Kaltsonoudis, None; **A. Zikou**, None; **P. V. Voulgari**, None; **S. Konitsiotis**, None; **M. Argyropoulou**, None; **A. A. Drosos**, None.

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Diffusion–weighted Magnetic Resonance Imaging (MRI) of Wrist and Hands in Patients with Rheumatoid arthritis –reproducibility and Correlation with Conventional MRI. Misbah Khurram[1], Jakob M. Møller[1], Mikkel Østergaard[2], Henrik Thomsen[1], Bo Jannik Ejbjerg[3], Merete Lund Hetland[4] and Signe Møller-Bisgaard[3]. [1]Department of Radiology, Copenhagen University Hospital Herlev, Copenhagen, Denmark, [2]Copenhagen Center for Arthritis Research, Copenhagen University Hospital at Glostrup, Glostrup, Denmark, [3]Department of Rheumatology, Slagelse Hospital, Slagelse, Denmark, [4]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup Hospital, Glostrup, Denmark.

Background/Purpose: The aim of this study was to investigate the performance of diffusion-weighted imaging (DWI) in detecting high signal intensity areas (HSIA), as potential signs of bone inflammation, in wrist and metacarpophalangeal (MCP) joints of rheumatoid arthritis (RA) patients, in comparison with short tau inversion recovery (STIR) MRI images.

Methods: 26 patients with RA in clinical remission underwent MRI including DWI (with apparent diffusion coefficient (ADC) maps), T1-weighted (T1w) and STIR images. 13 were rescanned after 4 months. STIR scans were scored for bone marrow edema (BME) according to Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging scoring system (RAMRIS) and DWI scans were scored for absence (0) or presence (1) of HSIA in bone marrow. STIR and DWI images were reviewed separately by one reader and ADC values were calculated in each of 21 bones in the wrist and MCP joints. For calculation of ADC, regions of interest (ROIs) were drawn, which covered the maximal possible subcortical bone areas, including both areas with high and with normal signal, avoiding erosions (method A). Furthermore, in DWI positive areas, ROIs were also placed within the HSIA (method B). ADC values were divided into 4 groups based on STIR and DWI scores as seen in the table below and nonparametric tests were used to compare groups. The reproducibility of the scores was analyzed by kappa (k) values, intra-class correlation coefficient (ICC), and smallest detectable difference (SDD) and change (SDC).

Results: STIR showed more positive lesions (132 HSIA (=bone marrow edema)) than DWI (50 HSIA) ($p<0.001$ Fisher's exact test). Mean ADC of "STIR-only" (STIR+/DWI-) positive lesions ($318\pm172\times10^{-3}mm^2/s$ was significantly lower than lesions, where both STIR and DWI were positive (STIR+/DWI+; $894\pm486\times10^{-3}mm^2/s$) ($p<0.001$; Mann-Whitney U test). ADC-values increased with increasing STIR scores (see table).The median ADC, in DWI positive areas, with method A ($759.5\times10^{-3}mm^2/s$) was slightly lower than the median ADC with method B ($846\times10^{-3}mm^2/s$) (p-value 0.048; Wilcoxon signed rank test). There was no statistically significant difference between baseline and 4 months follow-up scans in any parameters ($p=0.9$, 0.8 and 0.2 for STIR, DWI and ADC respectively; Wilcoxon signed rank test).The intraobserver agreement was good to excellent using STIR ($k=0.80$) and DWI ($k=0.76$), respectively (baseline). The intraobserver ICC of ADC measurements was 0.85. Intraobserver SDD of ADC at baseline was $60\times10^{-3}mm^2/s$, whereas intraobserver SDC between baseline and 4 months follow up was $108\times10^{-3}mm^2/s$.

Conclusion: DWI, including ADC measurements, in bones of patients with RA were highly reproducible and may partially reflect BME on STIR MRI. Further studies are needed to investigate if the method is useful for monitoring treatment response and/or predicting disease progression.

Table: ADC values stratified by STIR and DWI assessments

	Number of ROIs	Mean (SD)	Median (IQR)	Range	Mann-Whitney U test: P values		
					STIR+/DWI−	STIR−/DWI+	STIR−/DWI−
STIR+/DWI+	47	894(486)	790(589–1114)	203–2315	<0.001	0.533	<0.001
STIR+/DWI−	86	318(172)	303(216–397)	95–1071		<0.001	0.004
STIR−/DWI+	3	684(94)	666	600–786			0.003
STIR−/DWI−	364	258(111)	235(178–317)	67–705			
Only DWI+ area ADC (method B ROI)	50	957(424)	846(662–1119)	286–2315			
					Mann-Whitney U test: p value		
					STIR 1	STIR 2	STIR 3
STIR 0	367	262(117)	237(180–317)	67–786	>0.001	>0.001	>0.001
STIR 1	98	392(280)	315(218–479)	95–1588		0.002	>0.001
STIR 2	17	690(401)	618(390–898)	203–1813			0.045
STIR 3	17	1074(603)	1007(680–1410)	227–2315			

STIR+/− and DWI+/−: High intensity signal detected/not detected on STIR and diffusion-weighted MRI sequences, respectively; STIR 0,1,2,3: Scores of bone marrow edema on STIR sequence by using RAMRIS system; ROIs: regions of interest; SD: standard deviation; IQR: interquartile range.

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Assessing the Validity and Reliability of a Novel MRI Semi-Automated Algorithm for Quantifying Bone Loss in the Hand. Matthew Jessome[1], Isabel Rodrigues[1], Michael Tomizza[1], Joshua Barbosa[1], Melissa XP. Koh[1], Karen Beattie[2], William G. Bensen[2], Raja Bobba[2], Alfred Cividino[2], Patrick D. Emond[2], Karen Finlay[3], Chris Gordon[2], Lawrence Hart[2], George Ioannidis[2], Erik Jurriaans[3], Maggie Larche[2], Arthur Lau[2], Naveen Parasu[3], Ruben Tavares[2], Stephen Tytus[2], Hao Wu[1] and Jonathan D. Adachi[2]. [1]McMaster University, Hamilton, ON, [2]St Joseph's Healthcare Hamilton, Hamilton, ON, [3]Hamilton Health Sciences, Hamilton, ON.

Background/Purpose: Efficient and accurate evaluation of erosive damage to the MCP joints in RA patients is desirable in both clinical trials and clinical practice. The novel software *Early Erosions in Rheumatoid Arthritis* (EERA) hybridizes region growing and level-set segmentation algorithms, and can be used by a novice reader to semi-automatically quantify bone erosion volumes of the MCP joints captured by MRI. The objectives of this study were firstly to compare EERA to the Outcome Measures in Rheumatology Clinical Trials RA MRI score (RAMRIS), which is an established tool for evaluating erosive damage, and secondly to assess the inter- and intra-rater reliability of EERA.

Methods: Magnetic resonance images were acquired of both hands of 71 RA patients from a single rheumatology clinic at baseline and 2 years follow-up using a 1T magnet, 100mm cylindrical transmit and receive coil, and a 3D spoiled gradient echo sequence. Images were randomly distributed to 4 blinded musculoskeletal radiologists trained in RAMRIS. RAMRIS erosion scores for the 2nd through 5th MCP joints of both hands were evaluated and summed. A separate reader trained in EERA, but otherwise inexperienced with conventional quantification techniques, used EERA to evaluate and sum the volume of bone loss (in mm^3) of the 2nd through 5th MCP joints of these same images. To assess reliability, a random subset of 20 images was evaluated by 2 additional novice readers similarly trained in EERA. All 3 readers scored these 20 images a second time after 72 hours. Spearman's correlations were calculated to compare EERA and RAMRIS cross-sectionally and longitudinally, and intra-class correlation coefficients, ICC (2,1) with 95% confidence intervals (CI) were used to assess EERA reliability.

Results: Of the 71 participants [female: 78%, Caucasian: 72%, age: mean (standard deviation) 56.5 (12.8)yr, DAS28-ESR: 4.39 (1.42), symptom duration: 5.5 (5.7)yr], 52 (73%) were imaged at 2 years follow-up. EERA detected erosions in 43 (61%) participants, whereas RAMRIS detected erosions in 65 (92%) participants. The mean baseline erosion volume per participant was 63.4mm^3 (129.7mm^3), and mean baseline RAMRIS erosion score per participant was 10.8 (10.9). A Spearman's rho=0.450 ($p<0.001$) showed moderate correlation between EERA erosion volumes and RAMRIS erosion scores at baseline, with similar correlation at 2 years follow-up (rho=0.496, $p<0.001$). The 2 year mean change in EERA erosion volume was 1.2mm^3, and volume changes did not correlate significantly with 2 year RAMRIS erosion score changes ($p=0.505$). EERA reliability was excellent between all 3 raters, with an inter-rater reliability ICC of 0.945 (95% CI 0.887 to 0.959). Intra-rater reliability ICCs of 0.993 (95% CI 0.982 to 0.997), 0.979 (95% CI 0.949 to 0.992), and 0.933 (95% CI 0.834 to 0.973) were achieved for each reader.

Conclusion: EERA erosion volumes evaluated by a novice reader exhibited moderate correlation with RAMRIS erosion scores evaluated by trained radiologists. The excellent reliability of EERA suggests that it may have practical utility in a clinical setting, and future assessment of responsiveness is warranted.

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Magnetic Resonance Imaging of Inflammatory Severity and Cartilage Damage of Finger Joints in Rheumatoid Arthritis. Dr. Philipp Sewerin[1], Dr. Christoph Schleich[2], Anja Mueller-Lutz[1], Prof. Dr. Benedikt Ostendorf[1], Christian Rubbert[1], Dr. Christian Buchbender[1], Prof. Dr. Matthias Schneider[2], Prof. Dr. Gerald Antoch[1] and Dr. Falk Miese[1]. [1]Univ. Duesseldorf, Düsseldorf, Germany, [2]Univ. Duesseldorf, Duesseldorf, Germany.

Background/Purpose: To assess the association of inflammation severity and cartilage damage measured by delayed gadolinium-enhanced magnetic resonance imaging of the cartilage (dGEMRIC) of metacarpophalangeal (MCP) joints in patients with rheumatoid arthritis (RA).

Methods: 43 patients with RA according to ACR/EULAR classification criteria [age 52.9 ± 14.5 years, range: 18 – 77 years; disease duration 2.9 ± 4.9 years, range: <0.5 – 19 years; Disease Activity Score of 28 joints (DAS28) 3.7 ± 1.5] were included in this study. All study participants received 3T MRI scans of the metacarpophalangeal joints of the second and third finger. Cartilage composition was assessed with dGEMRIC. The severity of synovitis was scored according to the RAMRIS synovitis subscore (range: 0–3) by two readers in consensus. In the cases with identical synovitis subscores in MCP 2 and 3, two radiologists decided in consensus on the joint with more severe synovitis and the joint with less severe synovitis. To test the association of inflammation severity and cartilage damage and in order to eliminate inter-patient confounders, each patient's MCP 2 and 3 were dichotomized into the joint with more severe synovitis versus the joint with less severe synovitis for a paired Wilcoxon test of dGEMRIC value. The study was approved by the local ethics committee and written informed consent was obtained from all patients prior to the MR examination.

Results: dGEMRIC value of MCP with more severe synovitis was 369 msec ± 137, dGEMRIC value of MCP with less severe synovitis was 421 msec ± 129. RAMRIS synovitis subscore of the joint with more severe synovitis was 2.51 (range: 1–3), synovitis subscore of the joint with less severe synovitis was 1.86 (range: 0–3). There was a significant difference of dGEMRIC value (median of difference: 47.12, CI [16.6; 62.76]) between the dichotomized MCPs ($p = 0.0001$). There was a significant correlation between dGEMRIC value and RAMRIS synovitis grading of the joint with more severe synovitis ($r = 0.5$; $p < 0.05$) and the joint with less severe synovitis ($r = 0.33$; $p < 0.05$).

Conclusion: Our data concur with the concept that synovitis severity is associated with cartilage damage. The local inflammatory status on a joint level correlated significantly with the extent of cartilage degradation.

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Evaluating MRI-Detected Tenosynovitis of the Hand and Wrist in Early Arthritis. W.P. Nieuwenhuis, A. Krabben, W. Stomp, T. W. J. Huizinga, D. M. van der Heijde, J.L Bloem, M. Reijnierse and A.H.M. van der Helm-van rMil. Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Magnetic resonance imaging (MRI) is a sensitive method to detect local inflammation in rheumatoid arthritis (RA), visualizing synovitis, bone marrow edema and tenosynovitis. The prevalence of MRI-detected tenosynovitis and the diagnostic value in early arthritis are unclear. This study aimed to identify the frequency of MRI-detected tenosynovitis at the metacarpophalangeal (MCP) and wrist joints in early arthritis and the association with RA and severity features within RA.

Methods: 178 early arthritis patients underwent unilateral 1.5T extremity-MRI at baseline. The MCP and wrist-joints were scored using the RA MRI scoring (RAMRIS) system extended with Haavardsholms tenosynovitis score. 69 patients fulfilled the 2010 RA classification criteria during the first year and were compared with the other patients. Within RA-patients com-

parisons were made for anti-citrullinated-peptide-antibody (ACPA) positivity and for radiographic progression during year-1.

Results: 65% of all patients had MRI-detected tenosynovitis. RA-patients had tenosynovitis more often than non-RA patients (75% versus 59%, p=0.023). The flexor tendons at MCP-5, the extensor tendons at MCP-2 and MCP-4 and extensor compartment-I of the wrist were more frequently affected in RA than in other diagnoses (odds ratio's 2.8 (95% confidence interval (CI) 1.2–7.0), 9.1 (95% CI 1.9–42.8), 14.2 (95% CI 1.7–115.9), 4.0 (95% CI 1.4–11.1) respectively). These associations were independent of local MRI-detected synovitis. Specificities were all ≥82%. Within RA, tenosynovitis-scores were not associated with ACPA-positivity or radiographic progression.

Conclusion: MRI-detected tenosynovitis is common in early arthritis. The flexor tendons at MCP-5, the extensor tendons at MCP-2 and MCP-4 and the first extensor compartment of the wrist are more often affected in RA, independent of local synovitis.

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Association of Hand MRI Findings with the Level of Plasma Cytokines in Patients with Newly Diagnosed Rheumatoid Arthritis. Yasushi Kondo, Yuko Kaneko, Hiroaki Sugiura, Shunsuke Matsumoto, Naoshi Nishina, Masataka Kuwana, Masahiro Jinzaki and Tsutomu Takeurchi. Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Magnetic resonance imaging (MRI) is a very useful modality that can directly visualize both inflammatory and structural changes of affected joints in patients with rheumatoid arthritis (RA). On another front, cytokines have pleiotropic and strong effector functions in inflammatory response and play an important role in pathogenesis of RA joints. However, it is still unclear MRI findings can reflect dynamic features of cytokines in RA.The aim of this study is to examine the association with hand MRI findings scored using Outcome Measures in Rheumatology (OMERACT) RA MRI scoring (RAMRIS) system and plasma cytokine levels in patients with RA.

Methods: In total of 98 newly diagnosed, untreated consecutive RA patients in our cohort (SAKURA study) were included. MRI of dominant wrist and finger joints were evaluated for synovitis, osteitis, tenosynovitis, JSN and bone erosions according to the latest OMERACT RAMRIS. MR images were assessed by 2 experienced radiologists independently, and the mean of their scores were used in the analysis. Ten cytokines including IL-6, VEGF, IL-1β, TNF-α, IL-8, GM-CSF, IFN-γ, IL-10, IL-12p70 and IL-2 in patients' plasma were measured by electrochemiluminescence assay. Clinical and laboratory data were collected from their charts. The associations between RAMRIS scores and cytokine levels were examined by Spearman's Rank Correlation Coefficient. The agreement of the two MRI readers was tested intraclass correlation coefficient (ICC).

Results: Seventy-seven (80.2 %) patients were female, 69 (71.9%) were positive for anti-CCP, and the median age and symptom duration were 59 years and 3.5 months, respectively. Mean disease activities score (DAS) 28 was 4.80. The median scores of RAMRIS were 5.75 for synovitis, 5.00 for osteitis, 4.00 for bone erosion, 2.50 for tenosynovitis and 1.00 for JSN. The ICCs of these scores were approximately 0.90 for all. RAMRIS synovitis and tenosynovitis scores were significantly correlated with DAS28, pain, global and evaluator Visual Analog Scale and Health Assessment Questionnaire-Disability Index. While RAMRIS synovitis, osteitis and tenosynovitis scores significantly correlated with plasma IL-6 ρ=0.410, p<0.001; ρ=0.381, p<0.001; ρ=0.337, p=0.001, repectively) and VEGF (ρ=0.296, p=0.003,; ρ=0.323, p=0.001; ρ=0.268, p=0.008, respctively), RAMRIS osteitis and bone erosion scores were significantly correlated with plasma IL-1β (ρ=0.221, p<0.031; ρ=0392, p<0.001). TNF and the other cytokines were not correlated with any RAMRIS score although IL-8 tended to correlate with osteitis score. In patients with anti-CCP antibody positive the correlations between RAMRIS synovitis and plasma levels of IL-6 and VEGF were more significant.

Conclusion: In newly diagnosed RA patients, synovial, bone and tendon inflammatory changes of hand MRI may reflect the high level of plasma IL-6 and VEGF, and plasma IL-1β may be associated with MRI bone involvements.

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Feasibility and Clinical Implication of Radiocarpal Cartilage $T_{1\rho}$ MR Imaging in Rheumatoid Arthritis. Valentina Pedoia[1], Favian Su[1], Andrew J. Burghardt[1], Jonathan Graft[2], John B. Imboden[2], Mary Nakamura[3], Ursula Heilmeier[1], Thomas M Link[1] and Xiaojuan Li[1]. [1]Musculoskeletal Quantitative Imaging Research, UCSF, San Francisco, CA, [2]Division of Rheumatology, UCSF, San Francisco, CA, [3]SFVAMC/UCSF, San Francisco, CA.

Background/Purpose: Rheumatoid arthritic (RA) disease progression and anti-rheumatic treatment efficacy have traditionally been monitored by evaluation of radiographs. However, MRI has emerged as a more sensitive tool to depict synovial and articular inflammatory changes in early and low disease activity that are not radiographically evident. In particular, $T_{1\rho}$ MRI allows the detection of early-stage cartilage damage[1]. There are no prior reports of using $T_{1\rho}$ to evaluate cartilage composition changes in the wrist of RA patients. In this study we assessed the feasibility of wrist cartilage $T_{1\rho}$ mapping in RA patients and the association of $T_{1\rho}$ values with RA MRI scoring (RAMRIS).

Methods: The wrists of 5 RA patients (55.2 ± 13.3 yrs.,4 fem., DASCRP28: 3.72 ± 2.26, RA) and two healthy subjects (27 ± 4 yrs., 1 fem.) were scanned on a 3T MR scanner (GE, Healthcare) using the standard imaging protocol recommended by the OMERACT group and a coronal $T_{1\rho}$ (time of spin-lock = 0/10/20/50 ms; spin-lock frequency = 500Hz, resolution $0.21\times0.21\times3$ mm)^2. For both volunteers, scan/re-scan data were acquired after repositioning. Radiocarpal joint cartilage was segmented semi-automatically in the lunate, scaphoid and radius. Lunate, scaphoid and radius bones were automatically segmented using active contours initialized by the cartilage segmentations. The individual bone masks were used to perform piecewise rigid registration between the 4 echo images. Reliability measurements were computed as coefficients of variation (CV). MRI wrist images were scored using the OMERACT RA MRI Scoring (RAMRIS) system[3]. Joint space narrowing (JSN), bone erosion and bone marrow edema-like lesion (BMEL) scores were correlated with $T_{1\rho}$.

Results: The mean scan/re-scan $T_{1\rho}$ CVs were 1.48%, 3.60% and 5.62% for the lunate, scaphoid and radial cartilage. The overall CV was 3.59%. In Tab. 1, the mean cartilage $T_{1\rho}$ values and MRI scores are reported. Strong linear correlations were found between the overall $T_{1\rho}$ values and both BMEL (R^2 = 0.87, p<0.01) and erosion scores (R^2 = 0.95, p<0.01). Fig. 1 shows FSE T2 IDEAL sequence and the corresponding $T_{1\rho}$ map of representative RA cases with high $T_{1\rho}$ (43.2 ms) and low $T_{1\rho}$ (36.9 ms).

Conclusion: We demonstrated excellent in vivo reproducibility of MRI $T_{1\rho}$ quantification in wrist cartilage. Despite the small sample size, the results obtained demonstrate the feasibility of using $T_{1\rho}$ to study the progression of cartilage damage and response to therapy in the wrist of RA patients.

References

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Table 1: Mean wrist cartilage $T_{1\rho}$ values and corresponding MRI RAMRIS scores in 5 subjects with RA.

Subjects	Tlp (ms)				MRI Scoring			
	Lunate	Scaphoid	Radius	Global	BMEL	Bone Erosion	JSN	DASCRP28
1	33.10	41.79	38.18	37.45	1	0	0	1.21
2	37.82	49.07	42.77	43.22	18	17	4	4.28
3	32.57	40.36	44.46	39.13	7	8	0	5.49
4	30.91	35.06	44.81	36.93	3	3	2	1.5
5	34.00	43.56	43.14	40.23	8	6	1	6.13
Mean	33.68	41.97	42.67	39.39	7.40	6.80	1.40	3.72
SD	2.57	5.08	2.65	2.51	6.58	6.46	1.67	2.26

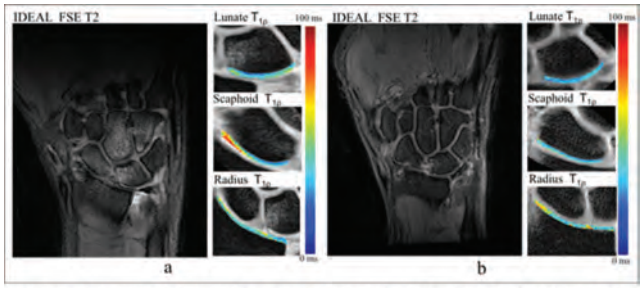

Figure 1: Comparison between IDEAL FSE T2 image and cartilage $T_{1\rho}$ maps for subjects with (a) high $T_{1\rho}$ (Subject 2) and (b) low $T_{1\rho}$ values (Subject 4).

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Evaluation of a Simplified Version of the Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) Comprising 5 Joints (RAMRIS5). Dr. Philipp Sewerin[1], Dr. Christoph Schleich[2], Dr. Christian Buchbender[1], Dr. Falk Miese[1], Dr. Ralph Brinks[3], Prof. Dr. Matthias Schneider[2], Prof. Dr. Gerald Antoch[1] and Prof. Dr. Benedikt Ostendorf[1]. [1]Univ. Duesseldorf, Düsseldorf, Germany, [2]Univ. Duesseldorf, Duesseldorf, Germany, [3]Univ Duesseldorf, Düsseldorf, Germany.

Background/Purpose: Semi-quantitative measurement of inflammatory pathologies of the hand in magnetic resonance images (MRI) is a mandatory, but time-consuming task for MRI controlled studies in Rheumatoid Arthritis (RA). The objective of this study was to evaluate a simplified version of the Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) reduced to five joints of the hand (RAMRIS5).

Methods: 94 patients with rheumatoid arthritis (62 female; age 59 ±12 years, range 25 – 83 years; disease duration 60 ± 90 months (median: 22 months, first quartile: 7 months, third quartile: 66 months) from the REMISSION PLUS study cohort who had complete files on C-reactive protein (CRP) levels and Disease Activity Score of 28 joints (DAS28) and complete MRI of the clinical dominant hand at baseline and after one year under anti-rheumatic therapy (follow-up time 12.5 ± 1.1 months) in a dedicated extremity MRI scanner at 0.2T were included in this retrospective study. MR images were scored according the RAMRIS criteria by two readers in consensus. Spearman correlations of the RAMRIS sum-score, subscores for RAMRIS of the metacarpophalangeal joints (RAMRISMCP), wrist (RAMRISWrist) and a reduced score comprising the MCP 2 and 3, capitate bone, triquetral bone, distal ulna were assessed. Additionally, Spearman correlations of MRI scores, CRP levels and DAS28 were calculated.

Results: There was a strong correlation between RAMRIS5 and the RAMRIS sum-score for all patients ($r = 0.87$, $p < 0.001$) at baseline and follow up ($r = 0.87$, $p < 0.001$). Among the subscores there was a significant correlation between RAMRIS5 and RAMRISMCP (baseline: $r = 0.66$, $p < 0.001$; follow-up: $r = 0.74$, $p < 0.001$) as well as between RAMRIS5 and RAMRISwrist (baseline: $r = 0.72$, $p < 0.001$, follow-up: $r = 0.69$, $p < 0.001$) at baseline and follow up. The correlation between RAMRIS5 and CRP (baseline: $r = 0.21$, $p < 0.05$; follow-up: $r = 0.03$, $p = 0.76$) or DAS28 (baseline: $r = 0.17$, $p = 0.11$; follow-up: 0.31, $p < 0.01$) were weak, similarly as observed for conventional RAMRIS (for CRP baseline: $r = 0.29$, $p < 0.01$; follow-up: $r = 0.10$, $p = 0.34$; for DAS28 baseline: $r = 0.20$, $p = 0.05$; follow-up: $r = 0.32$, $p < 0.01$).

Conclusion: RAMRIS5, a modified shorter RAMRIS score based on five joints of the hand is a viable tool for semi-quantitative assessment and monitoring of joint damage in RA. This abbreviated score might reduce the time needed for image analysis in MRI-controlled studies in RA and facilitate the use of MRI in studies on therapy response assessment in RA.

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Novel Quantification of MRI Provides a More Sensitive Outcome Measure Than Ramris. Michael A. Bowes[1], Gwenael Guillard[1], Eleanor Gill[1], Graham R. Vincent[1], Elizabeth Hensor[2], Jane E. Freeston[3], Edward M. Vital[3], P. Bird[4], Paul Emery[3] and Philip G. Conaghan[5]. [1]Imorphics Ltd, Manchester, United Kingdom, [2]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [3]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds., United Kingdom, Leeds, United Kingdom, [4]Combined Rheumatology Practice, Sydney, Australia, [5]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, Leeds, United Kingdom.

Background/Purpose: There is increasing need for sensitive, objective outcome measures in rheumatoid arthritis (RA). MRI is more sensitive than clinical examination and X-rays, using a semi-quantitative score (OMERACT RAMRIS). The objective was to use statistical shape models (SSMs) to identify RA pathology, and compare rates of change with RAMRIS in a RA population treated with a biologic therapy.

Methods: MR images of the hand were acquired from 45 established, active (mean (SD) DAS28 = 5.4(1.1), seropositive) RA patients who received a single cycle of rituximab at 0 months in an open label study. DAS28 improved by mean (SD) 1.7(1.4). Subjects were imaged at 0,3,6,9 & 12 months. Hand bones were segmented using SSMs; resulting bone surfaces were used to quantify erosion and oedema (inside bone), synovitis and 3D joint space width (3DJSW, outside bone). RAMRIS scoring was performed by a single experienced reader blinded to time point. Multilevel linear regression analysis was used to model changes over time. Quantitative values were adjusted for differences in scale using total bone area at baseline. Observations were nested within patients; random slopes for time were included. Non-linear changes were modelled with polynomial terms. Likelihood ratio (LR) tests were used to compare nested models. Accuracy of automated segmentation was examined using point-to-surface distance between automated and manually segmented bone surfaces.

Results: Quantitative synovitis decreased over time; the extent of the change varied between patients (Table 1). By contrast, there was no change over time in RAMRIS synovitis. There was no change in quantitative or RAMRIS erosion and no inter-patient variation. In some patients there was evidence of cubic change in quantitative oedema; with relatively rapid change between 0 and 3m. There was no evidence of changes in RAMRIS oedema. There was strong evidence of change over time for 3DJSW (LR test chi-square=22.0, $p<0.001$), though the result was complex, with the most responsive patient showing increase in joint space width, while others showed a decrease. Mean accuracy of automatically generated bone surfaces was 0.2 mm (Table 2); 90th percentile 0.44 mm.

Conclusion: Fully automatic quantitative analysis of RAMRIS measures is now practical, and showed change for synovitis and oedema where RAMRIS did not. 3DJSW is a novel measure that needs careful interpretation as it includes more than one type of change. Quantitative analysis depends upon accurate and automatic identification of all hand bones; these results show excellent accuracy of around 1/3 pixel.

Table 1: Change in quantitative and RAMRIS measures

Quantitative RA MRI feature (ln-transformed)	Synovitis	Erosions	Oedema
Change: per month	−2.70 (−4.82, −0.58), p=0.013	0.07 (−0.99, 1.13), p=0.898	2.79 (−1.19, 6.76), p=0.169
Change: per month squared	n/a	n/a	0.06 (−0.43, 0.55), p=0.810
Change: per month cubed	n/a	n/a	−0.12 (−0.26, 0.01), p=0.073
LR test for change model*	chi-sq=21.9, p<0.001	chi-sq=0.0, p=0.992	chi-sq=19.3, p=0.004
Pseudo-R^2 for time	0.34	0.00	0.43
RAMRIS (sqrt transformed)			
Change: per month	−0.87 (−2.84, 1.11), p=0.388	0.23 (−1.14, 1.59), p=0.746	−0.75 (−2.42, 0.92), p=0.378
LR test for change model*	chi-sq=2.2, p=0.331	chi-sq=8.7, p=0.068	chi-sq=0.78, p=0.679
Pseudo-R^2 for time	0.08	0.00	0.01

chi-sq = Chi-square; ln = natural logarithm; LR = likelihood ratio test; sqrt = square root
* Random slopes model compared to unconditional means model

Table 2: Accuracy of automated search

Bone	Mean point-to-surface distance (mm)	90% point-to-surface distance (mm)
Capitate	0.15	0.33
Hamate	0.14	0.31
Lunate	0.19	0.42
M2_dist	0.22	0.48
M2_prox	0.21	0.50
M3_dist	0.21	0.48
M3_prox	0.18	0.42
M4_dist	0.19	0.41
M4_prox	0.14	0.31
M5_dist	0.17	0.36
M5_prox	0.19	0.46
P2_prox	0.27	0.61
P3_prox	0.24	0.54
P4_prox	0.19	0.42
P5_prox	0.20	0.46
Radius	0.24	0.54
Scaphoid	0.21	0.47
Trapezium	0.18	0.40
Trapezoid	0.14	0.31
Triquetrum	0.18	0.39
Ulna	0.26	0.56
	0.20	0.44

Voxel size was 0.47 × 0.47 × 0.45 mm. Note mean accuracy is typically around 1/3 of a voxel, and 90th percentile is still typically sub-voxel

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GSK, 8, NIHR clinician scientist fellowship, 2; **P. Bird**, Abbvie, 8, Pfizer Inc, 8, Roche Pharmaceuticals, 8, Celgene, 8, Janssen Pharmaceutica Product, L.P., 8, UCB, 8; **P. Emery**, AbbVie, Bristol-Myers Squibb (BMS), MSD, Novartis, Pfizer Inc, Roche, and UCB Pharma, 2, AbbVie, Bristol-Myers Squibb (BMS), MSD, Novartis, Pfizer Inc, Roche, and UCB Pharma, 5; **P. G. Conaghan**, Abbvie, 8, Merck Human Health, 8, Novartis Pharmaceutical Corporation, 8, Pfizer Inc, 8, Roche Pharmaceuticals, 8, UCB, 8.

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Efficacy of Tocilizumab in Patients with Rheumatoid Arthritis: Sequential Evaluation Using Whole-Body Magnetic Resonance Imaging. Michihito Kono[1], Shinsuke Yasuda[1], Kazumasa Ohmura[1], Tomoko Fukui[1], Sanae Shimamura[1], Ikuma Nakagawa[1], Atsushi Noguchi[1], Haruki Shida[1], Toshiyuki Watanabe[1], Yuka Shimizu[1], Takashi Kurita[1], Kenji Oku[1], Toshiyuki Bohgaki[1], Olga Amengual[1], Tetsuya Horita[1], Keita Sakamoto[1], Tamotsu Kamishima[2] and Tatsuya Atsumi[1]. [1]Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]Faculty of Health Science, Sapporo, Japan.

Background/Purpose: Magnetic Resonance Imaging (MRI) has been established as a useful modality to evaluate synovitis, bone edema, and bone erosion in patients with rheumatoid arthritis (RA). Most of previous MRI studies in RA, however, have focused their evaluation only on finger, wrist, or knee joints. In daily clinical practice for RA, we use whole-body MRI technique to validate effect of anti-rheumatic drugs. The purpose of this study was to clarify the efficacy of tocilizumab (TCZ) in patients with RA using this technique.

Methods: A total of 21 consecutive RA patients on TCZ in our department between 2008 and 2014 were included in this retrospective study. Contrast whole-body MRI (1.5T) was performed before and one year after the initiation of TCZ. MR images were assessed by one experienced radiologist without any clinical information. Hand joints were evaluated according to RA MRI score (RAMRIS) and the other joints (atlantoaxial, shoulder, hip, and knee joints) were scored in the modified RAMRIS for this study.

Results: Mean age was 54.7 years old and mean duration of the disease 2.7 years. Of the subjects, 67% were on methotrexate and 24% had a history of other biologics agents. Mean DAS28-ESR at baseline was 5.04. After one year, clinical remission was obtained in 76%, 57% and 57% by DAS28-ESR, CDAI and SDAI, respectively. TCZ treatment led to improvement (Figure) in whole-body synovitis score ($p < 0.01$, paired t-test) from baseline (mean ± S.D; 32.6 ± 15.2) to one year (22.2 ± 11.0), as well as in whole-body bone edema score ($p < 0.01$, Wilcoxon signed-rank test) from baseline (median [range]; 11 [1–45]) to one year (3 [0–15]). Whole-body MRI-bone-erosion-score was improved in six patients and deteriorated in 11 patients. Whole-body synovitis score ($p = 0.03$, t-test) was identified as one of the poor prognostic factors for development of whole-body MRI-bone-erosion. Changes in RAMRIS synovitis score of hands did not correlate with those in modified RAMRIS synovitis score of other joints in whole-body MRI ($r = 0.34$, $p = 0.13$), as in the cases of bone edema score ($r = 0.01$, $p = 0.96$) and of MRI-bone-erosion-score ($r = -0.13$, $p = 0.57$).

Conclusion: TCZ exhibited significant efficacy and improvement in synovitis and bone edema. Changes in synovitis, bone edema, or erosion detected by hand MRI did not correlate with those of other joints in whole-body MRI. Whole-body MRI may be a potent tool to evaluate the inflammation and structural damage of the joints in RA independent of traditional hand MRI.

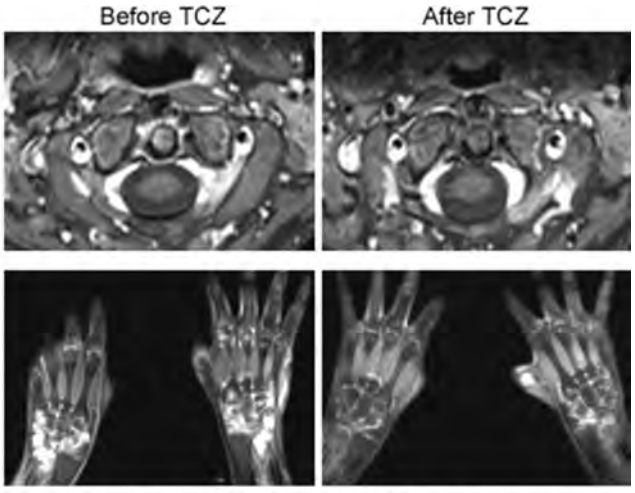

Figure. Contrast-enhanced fat-suppressed T1-weighted images of atlantoaxial joint and hands before and one year after TCZ.

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Dynamic Magnetic Resonance Imaging in the Assessment of the Response to Certolizumab Pegol in Rheumatoid Arthritis Patients: Results from a Phase IIIb Randomized Study. Mikkel Østergaard[1], Mette Bjørndal Axelsen[1], Lennart T.H. Jacobsson[2], Christopher Schaufelberger[2], Michael Sejer Hansen[3], Johannes W.J. Bijlsma[4], Anna Dudek[5], Maria Rell-Bakalarska[6], Fabienne Staelens[7], Robert Haake[8], Britt Sundman-Engberg[9] and Henning Bliddal[10]. [1]Copenhagen Center for Arthritis Research, Copenhagen University Hospital at Glostrup, Glostrup, Denmark, [2]Department of Rheumatology and Inflammation Research, Institute of Medicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [3]Department of Rheumatology, Gentofte Hospital, Copenhagen, Denmark, [4]University Medical Center Utrecht, Utrecht, Netherlands, [5]Medica Pro Familia, Warsaw, Poland, [6]Rheuma Medicus, Warsaw, Poland, [7]UCB Pharma, Brussels, Belgium, [8]UCB Pharma, Raleigh, NC, [9]UCB Pharma, Stockholm, Sweden, [10]The Parker Institute, Department of Rheumatology, Frederiksberg, Denmark.

Background/Purpose: Magnetic resonance imaging (MRI) can detect early joint inflammation with high sensitivity, without use of radiation. The MARVELOUS study (NCT01235598), using the OMERACT RA MRI scoring system (RAMRIS), previously established 16 weeks (wks) as the earliest time point at which certolizumab pegol (CZP) had a statistically significant reduction on synovitis and bone edema.[1] To further evaluate efficacy of CZP on synovitis, dynamic contrast-enhanced MRI (DCE-MRI) parameters were examined on proximal interphalangeal (PIP) joints 2–5 (PIP 2–5), metacarpophalangeal (MCP) joints 2–5 (MCP 2–5), and PIP 2–5 and MCP 2–5 joints combined (PIP+MCP 2–5).

Methods: A total of 41 patients (pts) with active RA despite DMARD therapy and ≤1 biological therapy were randomized 2:1 to CZP, or 2 wks placebo followed by CZP (PBO-CZP). 40 were treated (27 CZP, 13 PBO-CZP), 36 completed Wk16 (24 CZP, 12 PBO-CZP). The approved CZP dose was administered: CZP loading dose 400mg every 2 wks (Q2W) Wks 0–4 for CZP pts or Wks 2–6 for PBO-CZP, followed by CZP 200mg Q2W to Wk16. The DCE-MRI parameters Initial Rate of Enhancement (IRE), Maximum Enhancement (ME; % increase compared to pre-contrast) and Number of voxels with Plateau and Washout Pattern (Nvox) were used to quantify contrast-enhanced MRIs. Data were analyzed using Dynamika software (Image Analysis, UK) by an experienced reader blinded to time, pt identity and treatment group who manually performed precise outlining of regions of interest at each joint for all 6 acquired time points (Wks 0, 1, 2, 4, 8, 16). Each DCE-MRI parameter was analyzed for PIP 2–5, MCP 2–5, and PIP+MCP 2–5. Intrareader variability (intraclass correlation coefficients [ICCs]) was assessed.

Results: There were statistically significant changes from baseline at Wk16 in the CZP group for PIP 2–5 in median IRE (−0.009; p=0.024) and median ME (−0.33; p=0.021), and for MCP 2–5 and PIP+MCP 2–5 in median Nvox (−235.0; p=0.025 and -421.5; p=0.015, respectively). Changes at Wk8 were not statistically significant, precluding earlier timepoint testing (Table 1). For PBO-CZP vs CZP comparisons at Wks 1 and 2, 3 of the 9 (ME for MCP 2–5 and PIP+MCP 2–5, Nvox for MCP 2–5) had nominal p-values <0.05 at Wk1. However, no nominal p-values were <0.05 at Wk2. The complete set of results is displayed in Table 2. All parameters had very good intrareader reliability (ICC>0.90).

Conclusion: Statistically significant improvements in dynamic MRI variables were observed at Wk16 following initiation of CZP therapy, despite small sample size. Dynamic MRI results were consistent with primary analysis (RAMRIS scoring).[1] Thus, both conventional MRI RAMRIS and DCE-MRI criteria confirmed efficacy of CZP in reducing joint inflammation in RA pts.

Reference

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Table 1: Change from baseline in dynamic MRI parameters in the CZP group (n = 27)

Outcome, median (95% CI)	Week 1	Week 2	Week 4	Week 8	Week 16
Change from baseline in ME					
PIP 2–5	−0.23 (−0.86, 0.01)	0.01 (−0.26, 0.20)	−0.05 (−0.22, 0.15)	0.06 (−0.20, 0.72) NS	**−0.33** (−0.78, −0.02) **p = 0.021**

MCP 2–5	−0.17 (−0.36, −0.06)	−0.07 (−0.28, 0.02)	−0.06 (−0.17, 0.13)	−0.06 (−0.15, 0.07)	−0.01 (−0.16, 0.29) NS
PIP + MCP 2–5	−0.14 (−0.26, −0.03)	−0.05 (−0.22, 0.04)	−0.10 (−0.22, 0.02)	−0.04 (−0.13, 0.06)	−0.07 (−0.20, 0.14) NS
Change from baseline in IRE					
PIP 2–5	−0.005 (−0.012, 0.001)	0.002 (−0.004, 0.006)	−0.003 (−0.008, 0.002)	0.000 (−0.006, 0.006) NS	**−0.009** (−0.019, −0.002) **p = 0.024**
MCP 2–5	−0.003 (−0.007, 0.001)	−0.003 (−0.007, 0.001)	−0.002 (−0.004, 0.002)	−0.002 (−0.005, 0.003)	−0.001 (−0.006, 0.005) NS
PIP + MCP 2–5	−0.003 (−0.006, 0.000)	−0.003 (−0.007, 0.002)	−0.004 (−0.008, 0.000)	−0.002 (−0.006, 0.003)	−0.004 (−0.012, 0.003) NS
Change from baseline in Nvox					
PIP 2–5	−47.0 (−436.5, 134.0)	28.3 (−79.0, 179.5)	−38.0 (−229.0, 112.5)	21.0 (−127.0, 160.0)	−136.5 (−535.5, 8.5) NS
MCP 2–5	−146.5 (−630.5, 30.0)	16.5 (−278.0, 117.0)	1.0 (−202.0, 70.0)	−17.0 (−375.0, 147.5) NS	**−235.0** (−879.0, 23.5) **p = 0.025**
PIP + MCP 2–5	−153.5 (−984.5, 83.5)	64.5 (−307.0, 245.5)	−50.0 (−344.5, 49.0)	−14.5 (−265.0, 216.5) NS	**−421.5** (−1542.5, −47.0) **p = 0.015**

ME: Maximum enhancement (% increase on post-contrast image compared to pre-contrast image); Nvox: Number of voxels with Plateau and Washout pattern; IRE: Initial rate of enhancement (% increase per second); PIP 2–5: Proximal interphalangeal joints 2 to 5; MCP 2–5: Metacarpophalangeal joints 2 to 5; PIP + MCP 2–5: PIP 2–5 and MCP 2–5 joints combined; NS: Not-significant; once a non-significant result was obtained no further testing was allowed.

Table 2: Difference in change from baseline in dynamic MRI parameters

Outcome, median (95% CI) [unadjusted p-value] [a,b]	Week 1	Week 2
Difference in CFB in ME (CZP vs PBO-CZP)		
PIP 2–5	−0.17 (−0.63, 0.17) [0.336]	0.07 (−0.13, 0.31) [0.460]
MCP 2–5	−0.25 (−0.53, −0.09) [0.004]	−0.09 (−0.32, 0.02) [0.127]
PIP + MCP 2–5	−0.23 (−0.49, −0.06) [0.013]	−0.12 (−0.33, 0.01) [0.077]
Difference in CFB in IRE (CZP vs PBO-CZP)		
PIP 2–5	−0.002 (−0.008, 0.006) [0.617]	0.004 (−0.001, 0.011) [0.138]
MCP 2–5	−0.005 (−0.010, 0.001) [0.113]	−0.002 (−0.009, 0.003) [0.441]
PIP + MCP 2–5	−0.004 (−0.010, 0.001) [0.172]	−0.003 (−0.010, 0.003) [0.331]
Difference in CFB in Nvox (CZP vs PBO-CZP)		
PIP 2–5	−8.0 (−231.0, 241.0) [0.928]	80.0 (−39.0, 304.0) [0.179]
MCP 2–5	−328.5 (−877.0, −4.0) [0.037]	101.0 (−114.0, 314.0) [0.393]
PIP + MCP 2–5	−266.5 (−1155.0, 171.0) [0.242]	261.0 (−19.0, 547.0) [0.087]

[a] PBO-CZP: n = 11 (Wk1), n = 12 (Wk2) for all dMRI parameters and joint sets. CZP: n = 26 (Wk1), n = 26 (Wk2) for all dMRI parameters for MCP 2–5 and PIP + MCP 2–5; n = 26 (Wk1), n = 24 (Wk2) for PIP. [b] p-value from Wilcoxon Rank-Sum Test.
CFB: Change from Baseline; ME: Maximum enhancement (% increase on post-contrast image compared to pre-contrast image); Nvox: Number of voxels with Plateau and Washout pattern; IRE: Initial rate of enhancement (% increase per second); PIP 2–5: Proximal interphalangeal joints 2 to 5; MCP 2–5: Metacarpophalangeal joints 2 to 5; PIP + MCP 2–5: PIP 2–5 and MCP 2–5 joints combined

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Effects of Tofacitinib on Bone Marrow Edema, Synovitis, and Erosive Damage in Methotrexate-Naïve Patients with Early Active Rheumatoid Arthritis (Duration ≤2 Years): Results of an Exploratory Phase 2 MRI Study.

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Background/Purpose: Inflammation of the synovium and in particular the bone marrow, as assessed by magnetic resonance imaging (MRI), have been identified as prognostic indicators of structural joint damage in patients (pts) with rheumatoid arthritis (RA).[1] Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA. Inhibition of structural damage has been shown using conventional radiography in pts receiving tofacitinib for moderate to severe RA.[2] Here we explore the effects of tofacitinib, with or without methotrexate (MTX), on tissue inflammation and progression of structural damage in early RA using highly-sensitive MRI endpoints.

Methods: This was an exploratory, Phase 2, randomized, double-blind, parallel group, multicenter study (NCT01164579) in MTX-naïve adult pts with early active RA (duration ≤2 years) and evidence of clinical synovitis in an index wrist or metacarpophalangeal (MCP) joint. Pts were randomized 1:1:1 to receive tofacitinib 10 mg twice daily (BID) + MTX, tofacitinib 10 mg BID + placebo (PBO), or MTX + PBO, for 1 year. MTX was titrated, if tolerated, from 10 mg once weekly for the first month to 20 mg weekly by Month 2. Change in synovitis, bone marrow edema (BME), and erosions were assessed in the wrist and MCP joints using OMERACT RAMRIS. Co-primary endpoints: change from baseline (BL) in synovitis at Month (M) 3, and change from BL in BME at M6. Evaluable pts were assessed using a mixed effect model for repeated measures to evaluate endpoints (statistical significance at 10% [2-sided] level). Scoring was performed by one centralized reader blinded to time point and treatment.

Results: Of 109 pts randomized and treated (Table 1), most were female and Caucasian. Disease duration was consistent with early RA (Table 1). Mean age, disease activity, and RAMRIS were similar across treatment groups at BL (Table 1). More pts from the tofacitinib + MTX and tofacitinib + PBO groups completed the study (n=28, n=27, respectively) vs the MTX + PBO group (n=21). Synovitis improvements were observed in all groups; while improvements were numerically greater in both tofacitinib groups vs MTX + PBO, statistically significant differences were not consistently observed across assessment time points. Mean BME improvements were statistically greater in both tofacitinib groups vs MTX + PBO at M6 (primary), M3 and M12. Significantly less erosive damage was seen in both tofacitinib groups vs MTX + PBO at M6 and M12.

Conclusion: These results provide evidence of a reduction in tissue inflammation using assessments identified as positive prognostic factors for radiographic joint damage. The greater magnitude of improvement in BME and inhibition of erosive damage measured by MRI is consistent with the established effect of tofacitinib on inhibiting radiographic structural damage.

References:

1. Palosaari K, et al. Rheumatology (Oxford) 2006; 45: 1542–8.
2. Lee EB, et al. N Engl J Med 2014;370: 2377–86.

Table 1 Baseline characteristics, MRI endpoints (OMERACT RAMRIS), and safety overview

	Tofacitinib 10 mg BID + MTX (N = 36)	Tofacitinib 10 mg BID + PBO (N = 36)	MTX + PBO (N = 37)
Age, mean (SD)	47.8 (12.3)	50.8 (12.8)	47.8 (11.6)
Race, n (%)			
White	21 (58.3)	19 (52.8)	20 (54.1)
Black	0 (0)	1 (2.8)	0 (0)
Other	15 (41.7)	16 (44.4)	17 (45.9)
Mean duration of disease, years (range)	0.8 (0.1–2.2)	0.8 (0.1–8.5)	0.6 (0.1–1.9)
Baseline DAS28-4 (ESR), mean (SD)	6.25 (0.94)	6.50 (0.75)	6.44 (0.78)
Baseline synovitis score, mean (SD)	5.81 (3.82)	5.69 (3.53)	5.30 (3.93)
Baseline bone marrow edema score, mean (SD)	1.89 (3.74)	2.58 (3.74)	2.22 (5.12)
Baseline erosion score, mean (SD)	9.42 (10.82)	7.47 (7.55)	12.19 (14.85)
Change from baseline in OMERACT RAMRIS synovitis score, LS mean (SE), evaluable set			
Month 3[a] (Primary)	−0.80 (0.41)	−0.69 (0.40)	−0.17 (0.40)
Month 6[b]	−1.22 (0.40)	−1.29 (0.41)*	−0.28 (0.42)
Month 12[c]	−2.26 (0.41)*	−1.16 (0.43)	−0.66 (0.46)
Change from baseline in OMERACT RAMRIS bone marrow edema score, LS mean (SE), evaluable set			
Month 3[a]	−0.77 (0.42)*	−0.86 (0.41)*	0.47 (0.41)
Month 6[b] (Primary)	−1.26 (0.41)**	−1.45 (0.42)**	0.29 (0.42)
Month 12[c]	−1.52 (0.42)***	−1.70 (0.43)***	0.59 (0.46)
Change from baseline in OMERACT RAMRIS erosion score, LS mean (SE), evaluable set			
Month 3[a]	−0.12 (0.25)	0.36 (0.24)	0.44 (0.25)
Month 6[b]	−0.06 (0.25)*	−0.02 (0.25)*	0.65 (0.25)
Month 12[c]	−0.11 (0.25)***	−0.08 (0.25)***	1.18 (0.26)
Safety events, n (%)			
Patients with AEs (any cause)	25 (69.4)	31 (86.1)	30 (81.1)

Serious AEs	2 (5.6)	1 (2.8)	2 (5.4)
Severe AEs	4 (11.1%)	4 (11.1%)	1 (2.7%)

Evaluable set includes pts who were randomized, received ≥1 dose of study medication, and had endpoint values at both baseline and the time point assessed
[a]N = 30 (tofacitinib + MTX); N = 32 (tofacitinib + PBO); N = 31 (MTX + PBO); [b]N = 33 (tofacitinib + MTX); N = 29 (tofacitinib + PBO); N = 28 (MTX + PBO); [c]N = 29 (tofacitinib + MTX); N = 26 (tofacitinib + PBO); N = 21 (MTX + PBO)
Mixed effect model for repeated measures: *p<0.1; **p<0.01; ***p<0.001 vs MTX + PBO
AE, adverse event; BID, twice daily; CI, confidence interval; DAS28, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate; LS, least squares; PBO, placebo; MRI, magnetic resonance imaging; MTX, methotrexate; OMERACT RAMRIS, outcome measures in rheumatology clinical trials rheumatoid arthritis magnetic resonance imaging score; SAE, serious adverse event; SD, standard deviation; SE, standard error

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Do Patients with Active RA Also Have Inflamed Atherosclerotic Plaques on PET-MRI? Sarah Skeoch[1], Heather Williams[1], Penny Cristanacce[1], Jacqueline James[2], Paul Hockings[3], Yvonne Alexander[4], John Waterton[1] and Ian N. Bruce[5]. [1]University of Manchester, Manchester, United Kingdom, [2]Central Manchester University Hospitals Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom, [3]Chalmers University of Technology, Gottenburg, Sweden, [4]Manchester Metropolitan University, Manchester, United Kingdom, [5]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Inflammation plays a key role in the progression and destabilisation of atherosclerotic plaque in the general population. In RA, inflammation is thought to accelerate atherosclerosis and may lead to a more unstable plaque phenotype. ^{18F}-Fludeoxyglucose PET-CT (FDG-PET-CT) is a nuclear imaging technique which can be used to quantify carotid plaque inflammation. Histology studies have shown that FDG-uptake correlates with macrophage content of plaque and it has been used to identify vulnerable lesions and evaluate the effects of statins. We hypothesised that patients with active arthritis would have carotid plaque inflammation on FDG-PET and that plaque inflammation would correlate with the degree of disease activity using the DAS-28 score.

Methods: Patients with active arthritis (DAS-28>3.2), who had evidence of carotid plaque on ultrasound, were invited to have MRI then an FDG-PET-CT scan of the carotid arteries. Those on statins, or those with a history of cancer or recent infection, were excluded.

Following MRI scans performed on a 3 Tesla scanner, patients subsequently attended for a PET-CT within 2 weeks. FDG tracer was injected after a 6 hour fast. The scan was performed 2 hours after injection. Patients were positioned in a specialist head support to mimic MRI position. Mandible to sternal notch distance was also measured to ensure similar positioning during the 2 scans.

T1-weighted sequences from the MRI and PET-CT images were co-registered, then a region of interest (ROI) was drawn round the plaque. FDG uptake in the ROI was measured by a physicist, blinded to clinical information. The tissue activity was divided by the injected activity per kilo to give a maximum standardised uptake value (SUV^{max}). Descriptive and non-parametric statistical analyses were performed.

Results: 12 patients underwent MRI and FDG-PET-CT, 8 of whom were female. The median (IQR) age and disease duration was 59.5 (56.5, 64.5) and 11 (5.5, 25) years, respectively. The median DAS-28 score was 4.52 (4.32, 5.13) and 10 patients were rheumatoid factor and/or ACPA positive. No patients had a history of arterial disease, 2 had hypertension, 1 had dyslipidaemia and 2 were smokers.

The median plaque thickness was 2.5 (2.3, 2.8) mm and all had less than 70% stenosis. All subjects had plaque inflammation on PET-MRI, median (range) SUV^{max} was 2.14 (1.46, 6.11). An example of a PET-MRI can be seen in figure 1. There was no significant correlation with SUV^{max} and DAS28 or erythrocyte sedimentation rate ($r=0.126$, $p=0.70$ and $r=-0.15$, $p=0.63$ respectively).

Conclusion: Plaque inflammation was demonstrated in all subjects, despite the cohort having no history of cardiovascular disease and relatively small lesions. Larger longitudinal studies are required to further investigate the relationship between disease activity and plaque inflammation and to study the effects of inflammation on plaque progression.

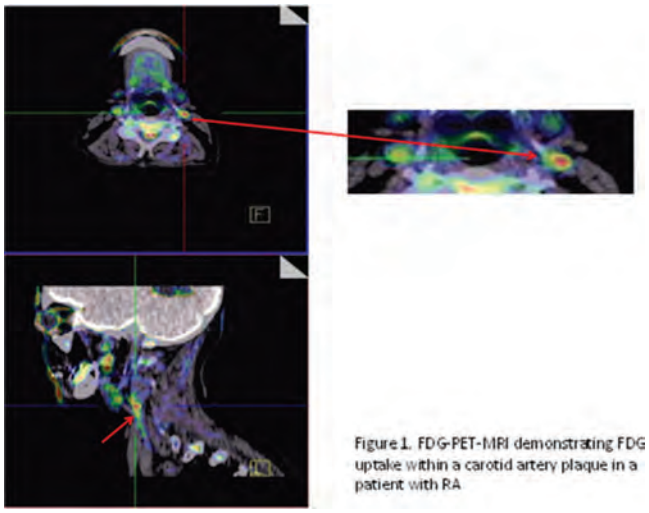

Figure 1. FDG-PET-MRI demonstrating FDG uptake within a carotid artery plaque in a patient with RA

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Validation of the Omeract Psoriatic Arthritis Magnetic Resonance Imaging Score for the Hand and Foot in a Randomized Placebo-Controlled Trial. Daniel Malm[1], P. Bird[2], Frédérique Gandjbakhch[3], Philip Mease[4], Pernille Bøyesen[5], Mikkel Østergaard[6], Charles G. Peterfy[7] and Philip G. Conaghan[8]. [1]Copenhagen University Hospital at Glostrup, Glostrup, Denmark, [2]Combined Rheumatology Practice, Sydney, Australia, [3]Groupe Hospitalier Pitie Salpetriere, Paris, France, [4]Swedish Medical Center and University of Washington, Seattle, WA, [5]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [6]Copenhagen Center for Arthritis Research, Copenhagen University Hospital at Glostrup, Glostrup, Denmark, [7]Spire Sciences LLC, Boca Raton, FL, [8]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, Leeds, United Kingdom.

Background/Purpose: The joint involvement in psoriatic arthritis (PsA) is heterogeneous, and inflammation is seen in both axial and peripheral joints, including the small joints of the hands and feet. The quickly evolving treatment options increase the requirements for developing efficient measures for assessing the treatment response. MRI can visualize the inflammatory components of PsA as well as features reflecting bone damage. The objective of this randomized controlled trial (RCT) was to assess the course during treatment, reliability and responsiveness to change of the Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) in hand and foot.

Methods: Forty PsA patients randomized to either placebo or abatacept in an RCT had MRI of either a single hand (n=20; all MCP, PIP and DIP joints) or foot (n=20; all MTP joints and the 1st interphalangeal joint) at baseline and after 6 months. Axial, T1-weighted, pre-contrast images, axial and coronal 3D post-contrast fat suppressed images, coronal and sagittal fat suppressed T2-weighted images and coronal short-tau inversion recovery (STIR) images were acquired. Images were scored blindedly, twice, by 3 readers according to the OMERACT PsAMRIS (synovitis, tenosynovitis, periarticular inflammation, bone oedema, bone erosion and bone proliferation). Change over time was assessed using Wilcoxon signed-rank test. Smallest detectable change (SDC) and intraclass correlation coefficient (ICC) were used for assessment of intrareader (single measure; SmICC) and interreader (average measure; AvmICC) reliability.

Results: Inflammatory features improved numerically but non-significantly in the abatacept group but not the placebo group (table 1). Baseline intrareader intraclass correlation coefficients (ICC) for all features were good (≥0.50) to very good (≥0.80) for all or some readers in hand and

foot. Baseline interreader ICC was good (ICC 0.72–0.96) for all features, except periarticular inflammation and bone proliferation in the hand and tenosynovitis in the foot (ICC 0.25–0.44). Intra- and interreader ICC for change scores varied. SDC was overall low (table 2). Guyatt's responsiveness index (GRI) was high for inflammatory features in the hand and metatarsophalangeal joints of the foot (GRI 0.67–3.13) (bone oedema not calculable). Minimal change and low prevalence may explain low ICC and GRI for bone damage.

Conclusion: PsAMRIS showed overall good intrareader agreement in the hand and foot and the inflammatory features were responsive to change, suggesting that PsAMRIS is a valid tool for MRI assessment of hands and feet in PsA clinical trials.

Table 1

	Total scores, mean (range)			
HAND	**Placebo**		**Abatacept**	
PsAMRIS features (Range of total score)	**Baseline**	**Change**	**Baseline**	**Change**
Synovitis (0–42)	7.2 (6.0 to 9.1)	−0.2 (−0.2 to −0.2)	7.1 (5.6 to 9.1)	−1.3 (−3.1 to 0.0)
Flexor tenosynovitis (0–42)	3.1 (2.1 to 4.8)	0.1 (−0.4 to 0.6)	3.7 (2.8 to 4.2)	−1.4 (−2.2 to −0.5)
Periarticular inflammation (0–28)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	1.5 (0.5 to 3.3)	−0.8 (−1.8 to −0.2)
Bone oedema (0–84)	0.3 (0.1 to 0.7)	0.0 (0.0 to 0.0)	1.9 (1.1 to 2.8)	−0.5 (−0.7 to −0.4)
Bone erosion (0–280)	0.9 (0.7 to 1.1)	−0.1 (−0.4 to 0.0)	2.5 (1.8 to 2.9)	0.0 (0.0 to 0.0)
Bone proliferation (0–14)	0.2 (0.0 to 0.3)	0.0 (−0.1 to 0.0)	0.5 (0.1 to 0.8)	0.0 (−0.1 to 0.0)
	Total scores			
HAND	**Placebo**		**Abatacept**	
PsAMRIS features (Range of total score)	**Baseline**	**Change**	**Baseline**	**Change**
Synovitis (0–18)	2.6 (1.8 to 3.3)	0.4 (0.0 to 0.8)	5.4 (4.8 to 6.1)	−1.2 (−1.3 to −1.1)
Flexor tenosynovitis (0–18)	0.4 (0.1 to 0.7)	0.6 (0.3 to 0.8)	1.0 (0.5 to 1.7)	−0.1 (−0.7 to 0.6)
Periarticular inflammation (0–12)	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.2)	1.5 (0.3 to 2.1)	−0.3 (−0.4 to −0.1)
Bone oedema (0–36)	0.7 (0.3 to 0.9)	0.0 (0.0 to 0.0)	2.9 (2.5 to 3.1)	−0.5 (−0.9 to −0.1)
Bone erosion (0–120)	1.3 (0.9 to 1.5)	0.0 (−0.1 to 0.0)	3.3 (2.3 to 5.0)	0.0 (−0.1 to 0.1)
Bone proliferation (0–6)	0.5 (0.2 to 0.8)	0.0 (−0.1 to 0.0)	0.2 (0.1 to 0.3)	0.0 (0.0 to 0.0)

Table 2

HAND	**Intrareader**			**Interreader**		
PsAMRIS features	**Baseline SmICC Range reader 1 to 3**	**Change SmICC Range reader 1 to 3**	**Change SDC Range reader 1 to 3**	**Baseline AvmICC**	**Change AvmICC**	**Change SDC**
Synovitis	0.30 to 0.75	0.06 to 0.66	1.7 to 5.5	0.72	0.41	2.9
Flexor tenosynovitis	0.69 to 0.89	0.78 to 0.88	2.2 to 2.6	0.92	0.87	1.9
Periarticular inflammation	0.74 to 1.00	0.22 to 0.85	0.4 to 5.8	0.37	0.12	1.8
Bone marrow oedema	0.60 to 0.95	−0.06 to 0.72	1.5 to 2.9	0.84	0.81	0.8
Bone erosion	0.67 to 0.94	−0.06 to 0.04	0.0 to 1.4	0.90	0.23	0.4
Bone proliferation	0.00 to 0.75	NA/0.00	0.0 to 0.3	0.25	0.06	0.2
FOOT	**Intrareader**			**Interreader**		
PsAMRIS features	**Baseline SmICC Range reader 1 to 3**	**Change SmICC Range reader 1 to 3**	**Change SDC Range reader 1 to 3**	**Baseline AvmICC**	**Change AvmICC**	**Change SDC**
Synovitis	0.70 to 0.77	0.19 to 0.90	1.7 to 2.9	0.90	0.72	1.7
Flexor tenosynovitis	0.42 to 0.74	0.42 to 0.79	0.8 to 2.4	0.44	0.40	1.6
Periarticular inflammation	0.14 to 0.60	0.00 to 0.38	0.6 to 2.5	0.76	0.77	0.8
Bone marrow oedema	0.70 to 0.96	−0.04 to 0.38	2.3 to 4.0	0.96	0.75	1.0
Bone erosion	0.75 to 0.97	−0.02 to 0.75	0.3 to 1.6	0.73	0.30	0.7
Bone proliferation	−0.15 to 0.59	NA/0.00	0.0 to 0.3	0.50	0.07	0.1

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Subclinical Inflammation in Psoriatic Patients with No History of Psoriatic Arthritis: An Assessment By Magnetic Resonance Imaging. David Simon[1], Francesca Faustini[1], Matthias Englbrecht[1], Arnd Kleyer[1], Roland Kocijan[2], Judith Haschka[1], Sebastian Kraus[1], Axel J. Hueber[1], Michael Sticherling[1], Georg Schett[1] and Jürgen Rech[1]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]St. Vincent Hospital, Vienna, Austria.

Background/Purpose: Six to 39% of patients with cutaneous psoriasis (PSO) can develop psoriatic arthritis (PsA). The transition from skin disease to joint involvement is only partially characterized. Advanced imaging can depict signs of subclinical joint involvement. The present study analyzes the prevalence of hand-MRI signs of inflammation in PSO patients without clinical history of synovitis, dactylitis and enthesitis and no positive CASPAR criteria at any time, but evidence of bone proliferative changes on high resolution peripheral computed tomography (HR-pQCT) of the dominant hand.

Methods: PSO patients underwent HR-pQCT (Scanco Medical, Switzerland) and 1.5T MRI (Siemens, Germany) of the dominant hand. HR-pQCT focused on the metacarpophalangeal (MCP) joints 2 and 3. Imaging analysis searched for erosions and new bone formation (bony spurs) with a periarticular location. MRI of the whole hand was conducted to detect osteitis, synovitis, tenosynovitis of the flexor tendon, periarticular inflammation at the MCP, PIP and DIP regions of the 2nd to 5th finger, according to the definitions of key pathologies provided for the PsAMRIS scoring system. Patients participated after signing informed consent. The study was conducted upon approval by the local ethic committee and the National Radiation Safety Agency (BfS).

Results: Images were acquired from 55 PSO patients (36.4% female) of mean age 49.5±11.5 y, mean disease duration 15.2±15.4 y and mean PASI score of 6.2±8.0. The most prevalent subtype was psoriasis vulgaris (73%), while nail psoriasis was present in 51 % and scalp involvement in 29%. On HR-pQCT erosions were found in 29% of patients, while all showed new bone formation. On MRI, 26 patients (47%) showed at list one of the mentioned signs of MRI detectable inflammation. In detail, osteitis was found in 6 patients (11%), while synovitis in 21 (38%); tenosynovitis and periarticular inflammation were detected each in 2 patients (4%). In the total sample, partial correlations (controlling for the influence of age and disease duration) between periarticular bone changes observed on HRp-QCT and osteitis as well as synovitis on MRI did not show any significant relations.

Conclusion: MRI signs of inflammation can be found in patients with cutaneous psoriasis without a history of arthritis. No evident relation seems to link these signs to bony changes observed on HR-pQCT. Longitudinal assessment of inflammation might provide deeper insight into the relationship between inflammation and changes in bone microstructure before the onset of clinical signs of arthritis.

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Feature of Fatty Deposition in Sacroiliac Joints in Ankylosing Spondylitis Patients Seen By MRI. Zaiying Hu[1], Qing Lv[2], Xiaohong Wang[1], Zetao Liao[3], Zhiming Lin[3] and Jieruo Gu[3]. [1]Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, [2]the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, [3]The Affiliated Third Hospital of Sun Yat-san University, Rheumatology, Guangzhou, China.

Background/Purpose: Fatty deposition (FD) is often seen in ankylosing spondylitis (AS) patients in the sacroiliac joints (SIJs). Magnetic Resonance Imaging (MRI) is a useful equipment to detect FD. The feature of FD of AS patients is seldom reported. We planned to investigate the feature of FD in SIJs in AS patients seen by MRI that may help in diagnosing.

Methods: This was a retrospective study. MR images of SIJs of 353 AS patients and 224 non-spondyloarthritis (SpA) patients were read by a radiologist and a rheumatologist without knowing the history of patients. FD were recorded and compared between two groups.

Results: Totally 1154 SIJs were studied and FD were recorded in 611 (52.95%) of them. FD was significantly more often to be seen in AS group than in non-SpA group (71.95% vs. 22.99%, $p<0.01$). There was no difference of positive FD rate between the left SIJs and the right SIJs either in AS group (left vs. right = 70.82% vs. 73.9%, $p>0.05$) or non-SpA group (24.11% vs. 21.88%, $p>0.05$). FD was more frequently seen in the upper half than the lower half SIJs in AS group (79.89% vs. 64.02%, $p<0.01$). The ilium bones were with more FD than the sacrum bones in AS group (83.85% vs. 60.06%, $p<0.01$). The rate of FD was of no difference between the upper and the lower half SIJs or between the ilium and sacrum bones in non-SpA group (both $p>0.05$). In AS group, the rate of FD was of no difference between patients under 25 years old (n=191) and over 45 years old (n=25) (70.68% vs. 76%, p=0.58). In non-SpA group, the rate of FD was significantly higher in patients over 45 years old (n=58) than under 25 years old (n=54) (53.45% vs. 7.41%, $p<0.01$).

Conclusion: Our study found that fatty deposition was much more often to be seen in AS patients than non-SpA subjects. FD appeared more in the upper half and ilium bones and did not depend much on age in AS patients.

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Prevalence of MRI Spinal Lesions Typical for Axial Spondyloarthritis in Patients with Inflammatory Back Pain. Manouk de Hooge[1], Jean-Baptiste Pialat[2], Antoine Feydy[3], Monique Reijnierse[1], Pascal Claudepierre[4], Alain Saraux[5], Maxime Dougados[3] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Hôpital Edouard Herriot, Lyon, France, [3]Descartes University, Cochin Hospital, Paris, France, [4]Henri Mondor Teaching Hospital, Creteil, France, [5]CHU de la Cavale Blanche, Brest Cedex, France.

Background/Purpose: A cut-off value of ≥3 inflammatory lesions was suggested by the ASAS/OMERACT group, as positive MRI of the spine (MRI-spine). Moreover, fatty lesions on MRI-spine are associated with axial Spondyloarthritis (axSpA). In this study the aim was to determine the prevalence of inflammatory (BME) and fatty lesions on MRI-spine in patients (pts) with and without axSpA.

Methods: Pts aged 18–50 with inflammatory back pain (≥3 months, [2]3 years) from 25 participating centers in France were included in the DESIR-cohort (n=708). All available baseline MRIs were independently scored by 2 well-calibrated readers, blinded to any other data. In case of disagreement, an experienced radiologist served as adjudicator. BME and fatty lesions typical for axSpA were scored when visible on ≥2 consecutive slices. Prevalence of MRI lesions was calculated based on several cut-offs and lesions were considered present if 2/3 readers agreed.

Results: All pts with symptom onset <45 yrs with MRI-spine (n=549) were included in the analyses. Pts fulfilling the ASAS criteria could either fulfill both arms, only the imaging arm or only the clinical arm. The first 2 groups were subdivided; pts with radiographic sacroiliitis (mNY+) & sacroiliitis on MRI (MRI+), pts with mNY+ & no sacroiliitis on MRI (MRI-), pts without radiographic sacroiliitis (mNY-) & MRI+. BME lesions occur in all different subgroups of the ASAS criteria and in pts without axSpA (table). The prevalence in no SpA group (which can be seen as false positives) is only 6.1%. With a cut-off ≥2 BME lesions false positives drop below 5% while the prevalence in the ASAS axSpA groups is still reasonable. Especially prevalence in pts with mNY+ & MRI+ is very high; 61.9% (both arms positive) and 43.8% (imaging arm only positive). Fatty lesions are seen slightly less often seen in all patient groups. However the same trend is seen as with BME lesions; Even with cut-off ≥1 the prevalence in no SpA group is low (5.5%), with cut-off ≥2 false positives drop below 5% and again pts with mNY+ & MRI+ have the highest percentage of spinal fatty lesions.

Conclusion: In a low percentage of pts without axSpA BME and fatty lesions is found indicating that spinal BME and fatty lesions are specific for patients with axSpA. These lesions are especially prevalent in pts with sacroiliitis on imaging. In this cohort, a cut-off ≥2 or ≥3 BME lesions and similarly ≥2 or ≥3 fatty lesions discriminate best between pts with and without axSpA.

	ASAS axSpA							
	Both arms positive:			Imaging arm only positive:			Clinical arm positive	No SpA
	mNY+, MRI+ N=63	mNY+, MRI− N=24	mNY−, MRI+ N=48	mNY+, MRI+ N=16	mNY+, MRI− N=15	mNY-, MRI+ N=53	N=166	N=164
BME ≥1	42 (66.7%)	14 (58.3%)	14 (29.2%)	7 (43.8%)	3 (20.0%)	7 (13.2%)	28 (16.9%)	10 (6.1%)
BME ≥2	39 (61.9%)	10 (41.7%)	10 (20.8%)	7 (43.8%)	2 (13.3%)	2 (3.8%)	22 (13.3%)	7 (4.3%)
BME ≥3	32 (50.8%)	7 (29.2%)	6 (12.5%)	5 (31.3%)	1 (6.7%)	1 (1.9%)	12 (7.2%)	4 (2.4%)
Fat ≥1	25 (39.7%)	6 (25.0%)	7 (14.6%)	5 (31.3%)	2 (13.3%)	6 (11.3%)	17 (10.2%)	9 (5.5%)
Fat ≥2	22 (34.9%)	6 (25.0%)	4 (8.3%)	3 (18.8%)	1 (6.7%)	5 (9.4%)	11 (6.6%)	7 (4.3%)
Fat ≥3	20 (31.7%)	5 (20.8%)	2 (4.2%)	2 (12.5%)	1 (6.7%)	4 (7.5%)	6 (3.6%)	6 (3.7%)

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Scoring of Spinal Lesions Compatible with Axial Spondyloarthritis on MRI in Clinical Practice By Local Radiologist or Rheumatologist in Desir; Comparison with Central Reading. Manouk de Hooge[1], Jean-Baptiste Pialat[2], Monique Reijnierse[1], Désirée van der Heijde[1], Pascal Claudepierre[3], Alain Saraux[4], Maxime Dougados[5] and Antoine Feydy[5]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Hôpital Edouard Herriot, Lyon, France, [3]Henri Mondor Teaching Hospital, Creteil, France, [4]CHU Brest and EA 2216, UBO, Brest, France, [5]Descartes University, Cochin Hospital, Paris, France.

Background/Purpose: In clinical practice radiologists and rheumatologists assess whether lesions compatible with axial SpondyloArthritis (axSpA) are present on spinal MRI. The objective was to compare the results of local readings (LocR) to centralized reading (CentR) as external standard of BME and structural lesions on MRI-spine, in patients (pts) with inflammatory back pain (IBP).

Methods: Pts aged 18–50 with recent IBP (≥3 months, [2]3 years) from 25 participating centers in France were included in the DESIR-cohort (n=708). All available baseline MRIs-spine were scored on BME and structural lesions as present, absent or doubtful by the local radiologist/rheumatologist who might have access to clinical data. In addition, 2 well-calibrated centralized readers independently scored the same MRIs for BME lesions and structural lesions (fatty lesions, erosions and (bridging) syndesmophytes). In case the centralized readers disagreed, an experienced radiologist served as adjudicator. Agreement between CentR and LocR was calculated excluding the cases assessed as doubtful by LocR (kappa κ).

Results: BME/structural lesions were in 492/492 pts scored by a radiologist, 206/205 by a rheumatologist and in 32/32 pts by both. The k agreement between LocR and CentR was 0.27 for BME lesions and 0.13 for structural lesions. For radiologists, $\kappa=0.36$ for BME, and $\kappa=0.15$ for structural lesions. For rheumatologists $\kappa=0.006$ for BME and $\kappa=0.12$ for structural lesions.

Overall, local specialists are highly overrating positive findings: 42.3% and 85.7% of the positive MRIs for BME are scored negative by the central read (radiologists and rheumatologist respectively). Similarly findings for structural lesions: 48.4% and 70% of MRIs positive for structural lesions are scored normal by central reading.

Conclusion: Both local radiologists, but especially rheumatologists overrate the presence of BME lesions and structural lesions on MRI of the spine compared to trained central readers. These results do not even take doubtful cases into account.

BME lesions		LocR (rheumatologist)		
		Positive	Negative	Doubt
CentR	Positive	4	20	21
	Negative	24	126	11
		LocR (radiologist)		
		Positive	Negative	Doubt
	Positive	30	29	58
	Negative	41	304	30

Structural lesions		LocR (rheumatologist)		
		Positive	Negative	Doubt
CentR	Positive	6	26	7
	Negative	14	146	6
		LocR (radiologist)		
		Positive	Negative	Doubt
	Positive	16	87	21
	Negative	15	338	15

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Reproducibility of Magnetic Resonance Imaging Diffusion Weighted Imaging in Axial Spondyloarthritis Patients and Healthy Subjects. Jakob M. Møller[1], Inge Juul Sorensen[2], Mikkel Ostergaard[3], Henrik Thomsen[1], Ole Rintek Madsen[4] and Susanne Juhl Pedersen[3]. [1]Department of Radiology, Copenhagen University Hospital Herlev, Copenhagen, Denmark, [2]Copenhagen University Hospital at Glostrup, Glostrup, Denmark, [3]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [4]Copenhagen University Hospital at Gentofte, Copenhagen, Denmark.

Background/Purpose: Diffusion weighted imaging (DWI) is a magnetic resonance imaging (MRI) technique where the image contrast is dependent on the diffusion of the extracellular free water molecules. DWI is widely used in oncology imaging, but only few papers address DWI in spondyloarthritis (SpA). From DWI the apparent diffusion coefficient (ADC) can be calculated and hence the diffusion in a region of interest (ROI) can be quantified. The water diffusion reflects the cellularity and thus it may be used as a quantification of inflammatory cells. The aim of the study was to measure the reproducibility of DWI in SpA patients and healthy subjects.

Methods: 25 SpA patients (13 females, mean age 36.1 years (SD 9.6); 12 males, mean age 42.3 (SD10.8) and 24 healthy subjects (13 females, mean age 42.7 (SD 13.2); 11 males, mean age 45.3 (SD 7.5)) were MRI examined at 1.5T two times with a mean interval of 6.8 days (SD 0.9). A 5mm (gap 1.2mm) sagittal single-shot echo-planar imaging DW sequence with four b values (0;50;500;800) and a resolution of 2mm × 1.65mm was performed on Th6 to L5. ADC maps were calculated based on all b values. The MRIs were anonymized and read in random order without information on time point and clinical data. On ADC maps 50mm^2 circular ROIs were placed in each vertebral corner just inside cortex. ADC was measured on the sagittal slice in the middle of the spine and on the adjacent slice to the right and left to the middle. ADCs from the four ROIs were pooled. Another ROI was placed in the right and left pedicle and in the spinous process from L1 to L5. The inter-reader variability was measured by intra-class correlation coefficient (ICC). Intra-reader variability was measured by a second reading of the examinations at time point (TP) 2.

Results: Overall ICC of the vertebral bodies between TP1 and TP2 was 0.80 (95% CI: 0.77–0.83). At TP1, ICC between the right and middle slice was 0.89 (95% CI: 0.87–0.90) and between left and middle slice 0.89 (95% CI: 0.87–0.90). Intra-reader reliability was 0.94 (95% CI: 0.93–0.95). For the right pedicle ICC was 0.44 (95% CI: 0.33–0.54), for the left pedicle 0.49 (95% CI: 0.39–0.58), for the spinous processes 0.20 (95% CI: 0.07–0.32). Table 1 provides ICCs for each vertebral body.

Table 1. Inter-reader and intra-reader ICCs for each vertebral body.

	Inter-reader Reliability	Intra-reader Reliability		Inter-reader Reliability	Intra-reader Reliability
T6	0.64 (0.39–0.80)	0.83 (0.70–0.90)	T12	0.76 (0.60–0.86)	0.96 (0.93–0.98)
T7	0.58 (0.33–0.75)	0.92 (0.86–0.96)	L1	0.85 (0.75–0.91)	0.97 (0.94–0.98)
T8	0.39 (0.11–0.62)	0.75 (0.59–0.85)	L2	0.91 (0.84–0.95)	0.97 (0.95–0.98)
T9	0.57 (0.32–0.75)	0.94 (0.89–0.97)	L3	0.91 (0.84–0.94)	0.99 (0.98–0.99)
T10	0.49 (0.23–0.69)	0.95 (0.91–0.97)	L4	0.81 (0.67–0.89)	0.98 (0.96–0.99)
T11	0.77 (0.55–0.89)	0.98 (0.94–0.99)	L5	0.79 (0.65–0.88)	0.96 (0.93–0.98)

Table 1: ICC (95% CI) measurements per vertebral body.

Conclusion: MR DWI is overall a reproducible imaging sequence performed in the sagittal plane. The reproducibility is better in the lumbar spine compared to lower thoracic spine. Pedicles and spinous proceses are not reliably imaged by DWI.

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Disclosure: J. M. Møller, None; **I. J. Sorensen**, None; **M. Ostergaard**, None; **H. Thomsen**, None; **O. R. Madsen**, None; **S. J. Pedersen**, AbbVie, 2.

1189

Conventional Magnetic Resonance Imaging (MR) and Hybrid 18F-Fluoride Positron Emission Tomography MRI (18F-F- PET/MRI) of the Spine and the Sacroiliac Joints – a Detailed Description of Pathologic Signals in Patients with Active Ankylosing Spondylitis. Xenofon Baraliakos[1], Dr. Christian Buchbender[2], Prof. Dr. Benedikt Ostendorf[2], Verena Ruhlmann[3], P. Heusch[4], F. Miese[4], K. Beiderwellen[5], Matthias Schneider[6], G. Antoch[7] and Jürgen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Univ. Duesseldorf, Düsseldorf, Germany, [3]Univ Duisburg-Essen, Medical Faculty, Duisburg, Germany, [4]Univ Duisburg-Essen, Medical Faculty, Essen, Germany, [5]Univ Dusseldorf, Medical Faculty, Duesseldorf, Germany, [6]MNR-Klinik, Düsseldorf, Germany, [7]Univ Dusseldorf, Medical Faculty, Dusseldorf, Germany.

Background/Purpose: PET is a nuclear imaging technique that depicts functional processes within the body based on gamma rays. The biologically active molecule used for PET is the bone-seeking agent ^{18}F labeled Fluoride (^{18}F-F). The concentrations of tracer reflect tissue metabolic activity of regional bone perfusion and bone remodeling. We tested the performance of integrated 18F-Fluoride positron emission tomography and magnetic resonance imaging (PET/MRI) of the whole spine and the sacroiliac joints and compared bone marrow edema (BME) and structural (fat deposition, FD) and metabolic findings (18F-F) in patients with active ankylosing spondylitis (AS).

Methods: 13 AS patients (6 male, 7 female, mean age 37.8±11.4 years, all BASDAI>4, no anti-TNF treatment) underwent a 3-Tesla MRI and integrated PET/MRI 40 minutes after injection of a mean dose 157 MBq of 18F-Fluoride of their whole spine and the SIJs. Two readers scored all images independently and the lesions where both readers showed agreement were considered for analysis. Inflammatory activity (bone marrow edema, BME), structural lesions (fat deposition) and focal 18F-Fluoride uptake were recorded on the level of a vertebral quadrant (VQ) or SIJ-quadrant (SQ), where one VQ and SQ consisted by 4 VQs (superior anterior and posterior and inferior anterior and posterior).

Results: Acquisition of whole-spine 18F-F PET/MRI including the SIJ was successful in all patients. There was excellent agreement in the reading of the two readers. For the SIJ, a total of 104 SQs could be analyzed by MRI and PET/MRI and 44.2% showed BME, while FD 42.3% and 18F-F in 46.2% SQs. BMD without FD was found in 60.9%, the majority with concomitant 18F-F. In comparison, FD alone without BME was found in 59.1% SQs and in those, parallel 18F-F was seen in only 7.7% SQs. The combination of BMD/FD was found in 17.3% SQs and in those, parallel 18F-F uptake was seen 72.2% SQs. For the spine, a total of 1,196 VQs could be analyzed and 9.9% showed BME, while FD was found in 18.2% and 18F-F 5.4% VQs. BME without FD was found in 41.5% and in those, parallel 18F-F was seen in 14.3% VQs. In comparison, FD without BME was found in 68.3% VQs and in those, 18F-F was 8.7% VQs. Finally, the combination BME/FD was found in 5.8% VQs and in those, 18F-F uptake 40.6%. The highest mean SUVmax per lesion was found in both the SIJ (28.1 ±13.5) and the spine (25.7 ±21.1) in in SQs or VQs with a combination of BME and FD.

Conclusion: In this first study on hybrid 18F-F-PET/MRI of active AS patients we show that rather BME than chronic changes is associated with osteoblastic activity. The combination of BME and FD showed the highest 18F-F uptake, confirming our previous finding that this is the strongest predictor of future syndesmophyte formation.

Disclosure: X. Baraliakos, None; **D. C. Buchbender**, None; **P. D. B. Ostendorf**, None; **V. Ruhlmann**, None; **P. Heusch**, None; **F. Miese**, None; **K. Beiderwellen**, None; **M. Schneider**, None; **G. Antoch**, None; **J. Braun**, None.

1190

Osteoarthritis-like Changes Are Present in the Tibia and Femur 1 Year Following ACL Reconstruction. Valentina Pedoia[1], Drew A. Lansdown[2], Musa Zaid[1], Charles McCulloch[3], C. Benjamin Ma[2] and Xiaojuan Li[1]. [1]Musculoskeletal Quantitative Imaging Research, UCSF, San Francisco, CA, [2]Department of Orthopedic Surgery, UCSF, San Francisco, CA, [3]Department of Epidemiology and Biostatistics, San Francisco, CA.

Background/Purpose: Statistical Shape Modeling (SSM) is a promising tool that has the ability to characterize complex shapes in a brief feature vector. The application of SSM in 2D imaging is widely used, though 3D MRI application is still a challenge. Injury of the anterior cruciate ligament (ACL) is a high risk factor for developing post-traumatic osteoarthritis (OA). The aim of this study is to analyze the longitudinal shape changes of the tibia and femur in patients with ACL injuries using a novel MR-based SSM algorithm. We hypothesized that distinct shape changes are present one year following ACL injury.

Methods: Bilateral knees were scanned using a 3T MRI scanner (GE Healthcare) for 15 patients (29.3 ± 4.2 yrs, 5 female) with ACL injuries prior to surgical reconstruction, and at 6 and 12 months after reconstruction. 10

controls (30.5 ± 5.2 yrs, 3 female) with no history of knee injuries underwent MR imaging at baseline and 12 months later. The imaging protocol included sagittal T_2 fast spin-echo (FSE) images with TR/TE = 4000/49.3 ms, resolution 0.39×0.39×1.5 mm, slice spacing of 1.5 mm. The SSM is extracted individually from the segmentation of tibia and femur. Each principal component analysis (PCA)'s mode of the model describes a different aspect of the bone shape. Starting from the mean mode's vector we can return to the space domain after the perturbation of a single mode. This method allows for the identification of the specific shape feature that is described in each mode. The first 20 modes were analyzed. The difference in mode values between baseline, 6-month, and 12-month follow-up were compared to the changes in the control knees from baseline to 12 months. Unpaired t-tests were used to compare longitudinal changes in ACL-injured and control knees, with significance set at alpha less than 0.05.

Results: The variation in Mode 10 for the tibia from baseline to 12 months is significantly different between injured (19.46 ± 28.83) patients and controls (−11.68 ± 22.18). The change in Mode 10 in the injured group occurs primarily in the second 6 months, as the variation between 6 and 12 month is 18.17± 33.31, which is significantly different as well. The variation of the same mode in the first 6 months is not significantly different (1.29 ± 22.18). A decrease of this mode is related with an expansion and elevation of the lateral tibial plateau.

The variation in Mode 12 for the femur from baseline to 6 months and 12 months is significantly different between injured patients (6 months: 15.28 ± 28.67, 12 month 21.67 ± 21.86) and controls (−4.85 ± 17.79). The change Mode 12 in the injured group occurs primarily in the first 6 months. A decrease of the mode value is related to a flattening of the lateral femoral condyle, and to an increase of the height in the intercondylar notch.

Conclusion: In this study the longitudinal shape changes in the femur and tibia in ACL patient was analyzed. The observed expansion and elevation of the lateral tibial plateau is similar to previously observed radiographic changes in patients with OA. Significant differences are also observed in the shape of the lateral femoral condyle following ACL injury. This novel methodology may lead to the development of imaging biomarkers for post-traumatic OA.

Disclosure: V. Pedoia, None; **D. A. Lansdown**, None; **M. Zaid**, None; **C. McCulloch**, None; **C. B. Ma**, None; **X. Li**, None.

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The Kimriss Bone Marrow Lesion Score in Patients with Osteoarthritis of the Knee Correlates with WOMAC Pain Status Using Target-Lesion Based Scoring Methodology; Data from the Osteoarthritis Initiative. David McDougall, Jacob Jaremko, RG Lambert and Walter P. Maksymowrych. University of Alberta, Edmonton, AB.

Background/Purpose: Inflammatory components of osteoarthritis including bone marrow lesions (BML) may be a target for therapy. Limited literature quantifies the relation of these markers on MRI with respect to pain and dysfunction in hip osteoarthritis. We sought to correlate the extent of BML using a validated scoring methodology, the Knee Inflammation MRI Scoring System (KIMRISS), with a validated pain score, WOMAC, in patients with hip osteoarthritis. In KIMRISS a score of 0 (no BML) or 1 (BML present) is assigned to each region of bone in each slice using a customized grid overlay with regions each approximately 1 cm × 1 cm in size; a higher KIMRISS BML sum score directly represents a larger volume of BML.

Methods: Data for these analyses are from the OAI public use data set(s). MRI scans at enrolment and 1 year follow-up were evaluated in 80 patients for BML score by two readers using KIMRISS methodology. The WOMAC pain score was available for each patient at the same time points. We assessed association of BML status and change scores with WOMAC pain status and change scores using correlation (Pearson chi square) and by multivariate regression adjusted for age, sex, Kellgren-Lawrence grade, and baseline scores for WOMAC pain.

Results: The volume of BML correlated highly with both WOMAC pain score (chi-square 0.86 $p < 0.0001$) and change in WOMAC pain score between enrolment and 1 year (chi-square 0.84 $p < 0.0001$)

Conclusion: KIMRISS BML score correlates highly with pain in patients with hip osteoarthritis, and was highly responsive to change. KIMRISS offers an alternative approach for scoring bone marrow lesions in knee osteoarthritis that is designed to be easily learned and can potentially be automated in future.

Disclosure: D. McDougall, None; **J. Jaremko**, None; **R. Lambert**, None; **W. P. Maksymowych**, None.

1192

Erosions Detected By Magnet Resonance Imaging in Patients with Juvenile Idiopathic Arthritis (JIA) Are True Erosions As Visualized By Computed Tomography. Stephanie Finzel[1], Georg A. Schett[1] and Nikolay Tzaribachev[2]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Pediatric Rheumatology, Bad Bramstedt, Germany.

Background/Purpose: Chronic arthritis occurs relatively frequent in childhood. Patients with polyarticular disease might have a destructive disease course and thus a worse outcome. In adult rheumatology MRI is known to detect erosions in early stages. In children little is known about changes in bone structure during the course of JIA and thus erosions detected by MRI are discussed controversially. (1–3)

To test, whether MRI erosions in patients with chronic arthritis are true erosions as detected by conventional computed tomography (CT).

Methods: Six children (all female) with a median age of 14 years, 4 with polyarthritis, 1 – psoriatic arthritis and 1 with systemic sclerosis were identified as having both MRI and CT of the same wrist during retrospective chart review. The median disease duration was 4 years. All patients with treated with sq methotrexate and NSAR.

A descriptive statistical approach was chosen due to the relatively low number of patients.

Results: Overall 55 surfaces were evaluated both in MRI and CT; in MRI 9 erosions were detected by MRI and 19 by CT. In MRI erosions were localized in the Os capitatum and hamatum, whereas in CT erosions were found in all carpal bones despite the scaphoid as well as in the 2nd through 4th proximal metacarpal bone. Of the 9 erosions detected in MRI, 5 were confirmed as being true bone erosions in CT and 4 MRI erosions were detected as vessel channels in CT. Widths in MRI varied from 1.50–3.50mm, and depths from 2.00–4.00mm. In CT widths ranged from 0.57–3.07mm, and depths from 0.95–3.24mm. Due to contrast agent artifacts, no physiological vessel channels could be detected, whereas in CT 254 vessel channels were found. Visualization of os pisiforme was difficult in MRI because of soft tissue and signal of immature bone.

Conclusion: Erosions in the bone of patients with chronic arthritis vizualised by MRI relate to pathological cortical defects as detected by conventional CT. Our findings suggest that these pathological CT-alterations represent either premature or manifest bone erosions identical to those in adult bone. Given the irradiation dose of conventional CT, future imaging studies are needed in order to evaluate the significance of novel CT-techniques with lower irradiation load such as HR-pQCT for use in juvenile chronic arthritis.

Disclosure: S. Finzel, None; **G. A. Schett**, Abbott, Celgene Corporation, Roche, and UCB, 2, Abbott, Celgene Corporation, Roche, and UCB, 5; **N. Tzaribachev**, None.

1193

Diagnostic value of Contrast-Enhanced MR-Angiography in diagnosing large Vessel Vasculitis. Sabine Adler, Marco Sprecher, Harald Bonel, Thorsten Klink and Peter M. Villirger. University Hospital Bern, Bern, Switzerland.

Background/Purpose: Diagnosis of large-vessel vasculitis (LVV) remains difficult despite clinical and serological signs and symptoms. Detection by histology might be unavailable in exclusive thoracic or abdominal involvement. PET-scans rarely are ready to be used in every-day practice and CT-scans might miss vascular affections. The value of easily accessible, contrast-enhanced MR-angiographies has only rarely been described.

Methods: Between 2005 and 2012 we investigated 76 patients (44 females, 32 males, aged 18–82 years, mean age 64.5 years) with clinical and serological suspicion of LVV by contrast-enhanced MR-angiography (MRA). Gadolinium was used as contrast-medium. Twenty-nine patients underwent both thoracic and abdominal MRA, 32 patients had thoracic and 15 patients abdominal MRA only. Additional histologies of the temporal arteries were performed in 22 patients. MRAs were independently reviewed by two radiologists. Correlations were measured for clinical, serological, histological and radiological parameters.

Results: LVV was diagnosed by MRA in 20/76 patients with 13/20 being abdominal and 7/20 thoracical vasculitides. Out of those, nine patients showed both thoracical and abominal LVV. Interobserver agreement regarding LVV correlated in all but one patient. Diagnoses other than LVV were fibrosis in 36/76 patients, vascular stenosis in 2/76 and arterial dissection in another 2/76 patients. The remaining 10/76 patients showed no vascular abnormalities. In 7/22 biopsied patients, histology was positive for temporal arteritis; 2 out of those 7 patients had additional LVV. Neither erythrocyte

sedimentation rate (ESR) nor C-reactive protein (CRP) showed significant differences regarding patients with or without LVV.

Conclusion: Occult LVV can be detected by MRA despite negative serological and/or histological parameters. MRA enables distinguished diagnosis and therefore initiation of tailored immunosuppression in LVV and allows for follow-up investigations in order to control therapeutic success.

Disclosure: S. Adler, None; **M. Sprecher**, None; **H. Bonel**, None; **T. Klink**, None; **P. M. Villiger**, None.

ACR/ARHP Poster Session B
Innate Immunity and Rheumatic Disease: Signaling Mechanisms
Monday, November 17, 2014, 8:30 AM–4:00 PM

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Cofilin-1 Is a ROS Sensor in Regulating the NLRP3 Inflammasome. Yong Hwan Park, Daniel L. Kastner and Jae Jin Crhae. National Human Genome Research Institute, Bethesda, MD.

Background/Purpose: NLRP3 (NOD-like receptor family, pyrin domain containing 3) has a pivotal role in nucleating inflammasome, cytoplasmic multiprotein complexes that mediate the maturation of the proinflammatory cytokines interleukin-1β (IL-1b) by activating caspase-1. Mutations in the gene encoding NLRP3 cause a series of autoinflammatory disease, cryopyrin-associated periodic syndromes (CAPS). It has been reported that generation of reactive oxygen species (ROS) is one of the major NLRP3 inflammasome activating factor. However, the molecular mechanism of relationship between change of cellular redox state and NLRP3 inflammasome activation has not been elucidated. Here we show that cofilin-1, a redox sensitive actin binding protein, is involved in NLRP3 inflammasome activation.

Methods: Mouse bone marrow derived macrophages (BMDMs) were obtained by differentiating bone marrow progenitors from tibial and femoral bone with M-CSF for 7 days. Inflammasome activation experiments were performed in two stages, initial LPS priming for 3 h and then inflammasome activation for 30 to 50 min by replacing the medium with RPMI 1640 medium supplemented with activators (ATP or nigericin). Inflammasome activation was analyzed by Western blotting of secreted interleukin-1b (IL-1b). The lysates from BMDMs or PT67 cells transiently transfected with expression constructs for the wild-type (WT) or various deleted forms of NLRP3 were immunoprecipitated with anti-cofilin-1 antibody.

Results: When the NLRP3 inflammasome is activated, not only activated IL-1b but also inflammasome components, such as ASC and caspase-1 are secreted. We found that cofilin-1 is also secreted along with IL-1b from the LPS-primed BMDMs when the cells are treated with ATP, a NLRP3 inflammasome activator. In addition, knockdown of *cofilin-1* reduces inflammasome activation in response to ATP, which suggests that cofilin-1 has an important role for the activation of the NLRP3 inflammasome. Cofilin-1 directly interacts to the nucleotide-binding domain (NBD) of NLRP3 protein. However, when the cells are stimulated with the NLRP3 inflammasome activators, ATP or nigericin, cofilin-1 is oxidized and dissociated from NLRP3. Indeed, the interaction of cofilin-1 with NLRP3 is increased significantly when the oxidation sites of cofilin-1 are substituted from cysteine to alanine. Finally, we found that NLRP3 inflammasome activation is attenuated when WT cofilin-1 is replaced with the oxidation-resistant mutant cofilin-1.

Conclusion: Taken together, these results suggest that cofilin-1 is a key component in regulating the activation of the NLRP3 inflammasome in response to ROS. Furthermore, since cofilin-1 is an actin binding protein that depolymerizes and severs actin filaments, and is able to translocate into mitochondria during oxidative stress condition, our finding about the interaction of cofilin-1 with NLRP3 provides an important molecular mechanism for the mitochondrial localization of the NLRP3 inflammasome.

Disclosure: Y. H. Park, None; **D. L. Kastner**, None; **J. J. Chae**, None.

1195

Activation of the nlrp3 Inflammasome By an Endogenous TLR2 Ligand in Rheumatoid Arthritis. Mary Connolly, Trudy McGarry, Monika Biniecka, Douglas J. Veale and Ursula Fearron. Translational Rheumatology Research Group, Dublin, Ireland.

Background/Purpose: The inflammasome is a large multiprotein complex which plays a key role in innate immunity by mediating the production of pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18. The most characterised inflammasome is nlrp3, activation of which results in numerous biological effects associated with infection, inflammation and autoimmune processes. While the inflammasome has traditionally been thought to regulate infection and inflammation, impaired mitochondrial metabolism may mediate this process. In this study we examined the interplay between the inflammasome and mitochondrial function following TLR2 activation.

Methods: Mitochondrial mutagenesis was assessed by Random Mutation Capture Assay. Reactive oxygen species were measured by cellular detection assay. Primary RASFC and whole ex vivo synovial tissue were stimulated with a TLR2 agonist, PAMCSK, in the presence of absence of N-Acetyl Cysteine (NAC). IL-1β and IL-18 expression was examined by PCR. Nlrp3 expression was assessed by real-time PCR and western blot. To establish whether A-SAA activates TLR, human embryonic kidney (HEK) -TLR2 or -TLR4 cells were cultured in the presence of A-SAA and NFκB luciferase activity was examined. In parallel, the effect of A-SAA on RASFC function was examined in the presence of a specific neutralising anti-TLR2 mAb (1μg/ml) and matched IgG isotype control Ab (1μg/ml). RASFC proliferation, adhesion, chemokine expression, migration and invasion were assessed by proliferation assays, flow cytometry, Taqman PCR, ELISA, wound repair and transwell assays.

Results: PAM3CYSK4 significantly induced mitochondrial mutagenesis and reactive oxygen species in RA synovial explants cultures and fibroblasts ($p<0.05$). TLR2 activation increased transcript levels of inflammasome and pro-inflammatory mediators including IL-1, IL-18 and nlrp3. Furthermore, activation of TLR2 induced IL-6, IL-8, IL-1, IL-18 at a protein level, effects which were significantly inhibited in presence of NAC, an ROS inhibitor (all $p<0.05$). Additionally, we demonstrated that A-SAA is an endogenous TLR2 ligand since it induced TLR2 mediated NF-κB lucifearse activity ($p<0.05$), with no effect observed for NFκB in HEK-TLR4 cells. A-SAA significantly induced NLRP3 mRNA and protein expression. In parallel, A-SAA induced RASFC proliferation, ICAM-1 expression, invasion and migration, all of which were significantly inhibited in the presence of anti-TLR2 (all $p<0.05$), further confirming its role as an endogenous TLR2 ligand.

Conclusion: TLR2 induces mitochondrial dysfunction which plays a key role in the regulation of downstream inflammasome activation. TLR2-induced pro-inflammatory effects in RA may be mediated by endogenous secretion of A-SAA from the synovium at the site of inflammation.

Disclosure: M. Connolly, None; **T. McGarry**, None; **M. Biniecka**, None; **D. J. Veale**, Abbvie, 2, MSD, 2, Pfizer Inc, 2, Roche, 2, Pfizer, 5, Roche, 5, Abbott, 8, MSD, 8, Pfizer, 8, Roche, 8; **U. Fearon**, None.

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Inflammation Develops in a Toll-like Receptor 9-Independent Manner in Experimental Arthritis and Rheumatoid Arthritis. Julie Mussard[1], Matthieu Ribon[1], Gaelle Clavel[2], Marie-Christophe Boissier[3] and Patrice Decker[1]. [1]INSERM UMR 1125, Li2P, University Paris 13, Sorbonne Paris Cité and Rheumatology Department, Avicenne Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Bobigny, France, [2]Fondation Ophtalmologique A. De Rothschild, Paris cedex 19, France, [3]INSERM UMR 1125, Li2P, University Paris 13, Sorbonne Paris Cité, Bobigny, France.

Background/Purpose: Rheumatoid arthritis (RA) is an inflammatory disease of unknown etiology. Toll-like receptor (TLR) 9 recognizes pathogen-derived DNA and even self DNA under certain circumstances. Interestingly, environmental factors and especially bacterial infections have been suggested to favor RA development. In addition, TLR9 might also recognize damage-associated molecular patterns (DAMP) in RA. Since the involvement of TLR9 in RA remains unclear, we have investigated whether TLR9 is necessary for disease development in a mouse model of RA and we have analyzed TLR9 expression in samples from patients and controls.

Methods: Disease development was followed in the collagen-induced arthritis (CIA) mouse model. The impact of TLR9 was evaluated by comparing wild-type (WT) mice and TLR9-knockout (KO) true littermates. Arthritis was followed by clinical score evaluation. Inflammation and bone destruction were estimated by histology. Anti-collagen antibody, C3a and blood cytokine levels were measured by ELISA and Luminex. B and T lymphocytes as well as neutrophils were analyzed by flow cytometry. Osteoclastogenesis was analyzed by culturing bone marrow cells with M-CSF and RANKL and then counting TRAP-positive multinucleated cells by microscopy. Moreover, TLR9 expression was analyzed ex vivo by flow cytometry on whole blood from healthy donors and RA patients.

Results: We clearly show for the first time that TLR9 is not crucial in inflammatory arthritis. Indeed, TLR9 is not required for arthritis development in CIA as TLR9-KO mice strongly developed clinical arthritis. Accordingly, WT and KO mice produced similar levels of anti-collagen antibodies. As a control, we verified that WT and KO mice responded to complete Freund's adjuvant. Moreover, inflammation and joint destruction were observed in both WT and TLR9-KO mice and at a similar level. In agreement with those observations, no statistically significant difference was noted between WT and KO mice regarding the percentage or the activation of lymphocytes and neutrophils in the blood, spleen and lymph nodes. Osteoclastogenesis and complement activation (the latter being estimated by C3a production) are similar in WT and TLR9-KO CIA mice. Importantly, TLR7 does not compensate TLR9 deficiency in vivo as there is no TLR7 over-expression in TLR9-deficeint mice. The impact of TLR9 on cytokine secretion in vivo is currently being analyzed. In human samples, we have shown that leukocytes from healthy donors and RA patients express endosomal and cell surface TLR9 at the same extent and accordingly TLR9 expression is not correlated with disease activity in patients.

Conclusion: This is the first demonstration that TLR9-KO mice clearly develop arthritis. Immune cells from RA patients do not over-express TLR9 in comparison to healthy donors. Our results thus suggest that TLR9 does not play a crucial role in inflammatory arthritis development in the CIA model and that there is no intrinsic abnormal TLR9 expression in RA patients. This also suggests that TLR9 is not strongly involved in the recognition of DAMP in RA.

Disclosure: J. Mussard, None; **M. Ribon**, None; **G. Clavel**, None; **M. C. Boissier**, None; **P. Decker**, None.

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Febuxostat Inhibits Monosodium Urate Crystal-Induced IL-1beta Secretion and Cell Death Via ROS- and Intracellular ATP-Dependent Pathways. Johji Nomura[1], Nathalie Busso[2], Mizuho Tamura[1], Tsunefumi Kobayashi[1] and Alexander So[2]. [1]Teijin Pharma Limited, Tokyo, Japan, [2]Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland.

Background/Purpose: In gout, monosodium urate (MSU) crystals trigger acute inflammation. MSU has been reported to activate NLRP3 inflammasome via ROS-dependent pathways, which result in IL-1beta secretion and cell death. To date, we have shown that febuxostat, a potent inhibitor of xanthine oxidoreductase (XOR), inhibits crystal-induced IL-1beta secretion and cell death in activated macrophages. In this study, we examined its inhibitory mechanisms. **Methods:** Bone marrow-derived macrophages were primed, incubated with febuxostat and stimulated with MSU. IL-1beta in the supernatant, intracellular ATP, mitochondrial ROS and membrane potential were analyzed. **Results:** MSU treatment resulted in the production of mitochondrial ROS as well as IL-1beta secretion, and led to decreased intracellular ATP (iATP) levels and depolarization of mitochondrial membrane potential. All these intracellular mechanisms were inhibited by febuxostat. Accordingly, Mito-TEMPO, a mitochondria-targeted antioxidant, inhibited IL-1beta secretion by decreasing mitochondrial ROS production; in addition, artificially decreased iATP induced IL-1beta secretion and depolarization of membrane potential in activated macrophages. **Conclusion:** These results suggested that MSU induces IL-1beta and cell death via two pathways: 1) mitochondrial ROS formation, 2) iATP reduction and mitochondrial dysfunction. Both pathways can be inhibited by febuxostat, suggesting that XOR inhibition not only decreases uric acid level in the blood but also suppresses crystal-induced inflammation.

Disclosure: J. Nomura, Teijin Pharma Limited, 3; **N. Busso**, None; **M. Tamura**, Teijin Phama Limited, 3; **T. Kobayashi**, Teijin Pharma Limited, 3; **A. So**, None.

1198

Prolactin Is Locally Produced in the Synovium of Patients with Inflammatory Arthritic Diseases and Promotes Macrophage Activation. Man Wai Tang[1], Samuel Garcia[2], Danielle M. Gerlag[2], Kris A. Reedquist[3] and Paul P. Tak[4]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [3]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [4]University of Cambridge, Cambridge & GlaxoSmithKline, UK, Stevenage, United Kingdom.

Background/Purpose: The sex hormone prolactin (PRL) has immunomodulatory properties, can be produced by immune cells, and elevated PRL serum levels have been reported in rheumatoid arthritis (RA) patients. Here we examined synovial expression of PRL and PRL receptor (PRLR) in patients with inflammatory arthritis, their expression in polarized macrophages from patients and healthy donors, and the effects of PRL on macrophage activation.

Methods: PRL levels in paired synovial fluid (SF) and peripheral blood of RA (n=19), psoriatic arthritis (PsA, n=13) and gout (n=11) patients were measured using an immunofluorescent metric assay. PRL mRNA expression was measured in synovial tissue (ST) of RA (n=25), PsA (n=11) and gout (n=12) patients, and in macrophages differentiated in RA, PsA, spondyloarthritis (SpA) and gout SF by qPCR. PRLR protein expression was determined in ST of RA (n=19), PsA (n=15) and osteoarthritis (OA, n=9) patients by immunohistochemistry and detected in specific cell types by immunofluorescence. IL-6 production by IFN-y and IL-10 -differentiated macrophages following stimulation with CD40L or TNF in the absence or presence of PRL was measured by ELISA.

Results: PRL protein levels were similar in serum and SF of RA, PsA and gout patients, as was mRNA expression in RA, PsA and gout ST. Of interest, PRL mRNA expression significantly correlated with clinical disease parameters in PsA (DAS28, R=0.729, P=0.017) and RA (ESR, R=0.424, P=0.049). PRL expression was also detected in monocyte-derived macrophages from RA patients, and significantly higher ($P \leq 0.01$) in healthy donor macrophages differentiated in pooled SF of RA and PsA compared to SpA and gout SF. In RA SF-differentiated macrophages PRL production was increased by CD40L or IgG stimulation but not LPS or TNFα.

Median (IQR) PRLR expression was significantly higher ($P<0.05$) in RA [0.06 (0.00–0.33)] and PsA [0.18 (0.00–1.67)] ST compared to OA [0.00 (0.00–0.02)], and there was no significant difference in PRLR expression between (pre/postmenopausal) females and males, independently of disease. PRLR expression was mainly colocalized with $CD68^+$ macrophages and vWF^+ endothelial cells. In vitro, PRLR was prominently expressed in IFN-y and IL-10 polarized monocyte-derived macrophages compared to macrophages polarized in GM-CSF, M-CSF or RA SF. In these macrophages, PRL stimulation significantly enhanced IL-6 production in response to TNFα or CD40L.

Conclusion: Our results provide the first evidence that PRL is produced locally in the synovium of patients with inflammatory arthritis, and contributes to the activation of macrophages in the presence of other inflammatory stimuli.

Disclosure: M. W. Tang, None; **S. Garcia**, None; **D. M. Gerlag**, GlaxoSmithKline, 3; **K. A. Reedquist**, None; **P. P. Tak**, GlaxoSmithKline, 3.

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Alarmins S100A8/S100A9 Aggravate Osteophyte Formation in Experimental Osteoarthritis and Predict Osteophyte Progression in EARLY Human Osteoarthritis in the Dutch Check Cohort. Rik Schelbergen[1], Wouter de Munter[1], Martijn van den Bosch[1], Floris Lafeber[2], Annet Sloetjes[1], Thomas Vogl[3], Johannes Roth[3], Peter M. van der Kraan[1], Arjen B. Blom[1], Wim B van den Berg[1] and Peter L. van Lent[1]. [1]Radboud university medical center, Nijmegen, Netherlands, [2]University Medical Center Utrecht, Utrecht, Netherlands, [3]Institute of Immunology University of Muenster, Muenster, Germany.

Background/Purpose: The main pathological feature of osteoarthritis (OA) is degradation of the articular cartilage. Other important hallmarks include subclinical inflammation of the synovium and ectopic formation of new bone and cartilage at the ligaments or joint margins, termed osteophytes. Alarmins S100A8 and S100A9 are major products of activated macrophages regulating cartilage damage and synovial activation during murine and human osteoarthritis (1) (OA).

In the current study we investigated whether S100A8 and S100A9 are involved in osteophyte formation during experimental OA and if S100A8/A9 predicts osteophyte progression in early human OA.

Methods: OA was elicited in S100A9 −/− and wild-type C57Bl/6 mice in two experimental models that differ in degree of synovial activation. Osteophyte size, S100A8, S100A9 and VDIPEN expression was measured on histology. Chondrogenesis was induced in murine mesenchymal stem cells (MSCs) in the presence of S100A8. Levels of S100A8/A9 were determined in plasma of early symptomatic OA patients of the CHECK cohort study and osteophyte size measured at baseline and after 2 and 5 years.

Results: S100A8 and S100A9 protein levels in the synovial lining and serum coincide with osteophyte development in collagenase-induced OA

(CIOA), in which synovial activation is high. Osteophyte size was drastically reduced in S100A9 −/− mice on day 21 and 42 of CIOA, in the medial collateral ligaments (58% and 93% reduction) and at medial femur and tibia (62% and 67% reduction). In contrast, osteophyte size was not reduced in S100A9 −/− mice during destabilized medial meniscus OA, in which synovial activation is scant. One explanation for the reduced osteophyte size in S100A9−/− mice may be a direct effect of S100-proteins on chondrogenesis. During *in vitro* chondrogenesis using murine MSCs, S100A8 caused a marked increase in MMP-3 mRNA and VDIPEN expression (as measure for MMP activity) as well as a strongly altered morphology, indicating increased remodeling allowing for larger osteophytes. Interestingly, early symptomatic OA patients of the CHECK study with osteophyte progression after two and five years had significantly elevated S100A8/A9 plasma levels at baseline, while CRP, COMP and ESR were not higher.

Conclusion: S100A8/A9 aggravate osteophyte formation in experimental OA with high synovial activation and may be used to predict osteophyte formation in early human OA.

Reference:

(1) van Lent PL et al. Arthritis and rheumatism. 2012; 64(5):1466–1476.

Disclosure: R. Schelbergen, None; **W. de Munter**, None; **M. van den Bosch**, None; **F. Lafeber**, None; **A. Sloetjes**, None; **T. Vogl**, None; **J. Roth**, None; **P. M. van der Kraan**, None; **A. B. Blom**, None; **W. B. van den Berg**, None; **P. L. van Lent**, None.

1200

Plasma Levels of Pattern Recognition Molecules of the Lectin Pathway Are Altered in SLE Patients. Anne Troldborg[1], Steffen Thiel[1], Magdalena Janina Laska[1], Bent Deleuran[2], Jens Christian Jensenius[1] and Kristian Stengaard-Pedersen[2]. [1]Aarhus University, Aarhus, Denmark, [2]Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease where the Complement System plays a key role in the pathogenesis. The objective of this pilot study was to measure the levels of the pattern recognition molecules of the Lectin Pathway: mannan binding lectin (MBL), collectin-L1 (CL-L1), and the three ficolins in plasma of patients with SLE and compare the plasma levels to a group of age and gender matched healthy controls. Further, we analyzed for associations between the plasma levels and SLE disease activity score and characteristic SLE manifestations.

Methods: Plasma was obtained from a cross-sectional cohort of 58 SLE patients. We collected prospectively demographic and clinical data including ACR classification criteria and SLE disease activity index score (SLEDAI). For comparison, blood samples were collected from 65 age and gender matched healthy blood donors. Plasma levels of MBL, CL-L1, M-ficolin (Ficolin-1) and H-ficolin (Ficolin-3) were measured using Time Resolved Immuno-Flourometric Assay (TRIFMA) developed at our own lab. Plasma levels of L-ficolin (Ficolin-2) were measured by ELISA (Hycult Biotech , the Netherlands). Mann-Whitney test were used for comparison of plasma levels of the proteins in patients and controls and Spearman correlation analysis was used for correlation analysis. p values < 0.05 were considered statistically significant.

Results:

RESULTS	SLE Patients (n=58) Mean plasma conc. ng/ml (SD)	Healthy Controls (n=65) Mean plasma conc. ng/ml (SD)	Difference between means ng/ml (SD)	Mann-Whitney P value
MBL	1003 (±821)	1137 (±1157)	219,5 ± 183,5	0,5204
CL-L1	771 (±145)	937 (±191)	165,5 ± 30,84	<0,0001
M-ficolin	356 (±231)	564 (±266)	214,1 ± 46,96	<0,0001
L-ficolin	2649 (±1031)	2554 (±998)	94,97 (±192,5)	0,6116
H-ficolin	23998 (±10397)	16387 (±4927)	7611 (±1450)	<0,0001

Mean plasma levels of CL-L1 and M-ficolin were significantly lower and H-ficolin significantly higher in patients with SLE compared to healthy controls ($p<0.0001$). A statistical significant difference between plasma levels of H-ficolin in SLE patients with lymphopenia compared to the non-lymphopenic patients was found ($p=0.0434$). A relatively higher level of CL-L1 in the subgroup of SLE patients with discoid rash was statistically significant ($p=0.0364$). Otherwise, analysis showed no statistically significant association between characteristic disease manifestations or SLEDAI score on one side and plasma level of MBL, CL-L1, M-ficolin, L-ficolin and H-ficolin on the other hand.

Conclusion: The plasma concentrations of several of the pattern recognition molecules of the Lectin Pathway were significantly altered in a cross-sectional co-hort of SLE-patients showing low levels of CL-L1 and M-ficolin and high levels of H-ficolin. In the subgroup of patients with lymphopenia, this manifestation was associated with a high level of H-ficolin. The association with a key element of the clinical picture, lymphopenia, may indicate a pathogenic role of Ficolin-3 in SLE.

A limitation of the study is small SLE subgroups.

Disclosure: A. Troldborg, None; **S. Thiel**, None; **M. J. Laska**, None; **B. Deleuran**, None; **J. C. Jensenius**, None; **K. Stengaard-Pedersen**, None.

1201

Hypoxia Modulates Peptidyl Arginine Deiminase 4 Activity and Neutrophil Extracellular Trap Formation. Akif A. Khawaja[1], Charis Pericleous[1], Luke W. Thomas[2], Margaret Ashcroft[2], Joanna C. Porter[3] and Ian Giles[1]. [1]Centre for Rheumatology, University College London, London, United Kingdom, [2]Centre for Cell Signalling and Molecular Genetics, University College London, London, United Kingdom, [3]Centre for Inflammation and Tissue Repair, University College London, London, United Kingdom.

Background/Purpose: RA is an autoimmune rheumatic disease characterised by ACPA, endothelial dysfunction, platelet activation, synovial hyperplasia and hypoxia in affected joints. ACPA recognise citrullinated proteins, generated by the activity of peptidyl arginine deiminase (PAD)-2/4, however the source of these autoantigens is unknown. Neutrophil extracellular traps (NETs) play a critical role in the innate immune response and have been identified in serum and synovial fluid of patients with RA. NETs require PAD-4 for their generation and are also a source of citrullinated proteins. NET formation is enhanced by integrin engagement, interactions with activated platelets, and other stimuli but the effects of hypoxia upon their generation are unknown. Therefore, we hypothesise that hypoxia modulates the cellular interactions leading to enhanced NETosis and the externalisation of citrullinated autoantigens in RA.

Methods: Human umbilical cord endothelial cells (HUVEC) were grown in hypoxia (1% oxygen, equivalent to 7.6 mmHg) to mimic conditions found in the RA joint or normoxia (21% oxygen, 159.6 mmHg) in the presence or absence of TNF-α or lipopolysaccharide (LPS). Expression of PAD-4 and citrullinated histone H3, a PAD-4 target, were measured by western blot, and levels of surface adhesion molecules, intercellular adhesion molecule (ICAM)-1, ICAM-2, vascular cell adhesion molecule (VCAM)-1 and E selectin, were measured by FACs. Neutrophils were isolated from whole blood donated by healthy volunteers. Cell adhesion assays were performed in which binding of 2',7'-bis-(2-carboxyethyl)-5-(and-6)-carboxyfluorescein, acetoxymethyl ester (BCECF-AM) labelled neutrophils to HUVEC monolayers was measured using a fluorescent plate reader. A capture ELISA was established and validated to compare NET release between experimental conditions.

Results: Culture of HUVEC under hypoxia increased PAD-4 expression by 13.5% (1.2 fold) with levels of citrullinated histone H3 elevated by 1415.3% (15 fold). Hypoxia modulated both basal expression of ICAM-1, ICAM-2, VCAM-1 and E selectin as well as on stimulation with TNF-α or LPS. Hypoxia also increased neutrophil adhesion to HUVEC monolayers from 3+/−3.1% to 47+/−12.0% of total cells added ($p=0.0002$). NET formation of phorbol 12-myristate 13-acetate (PMA)-stimulated neutrophils was elevated under hypoxia compared to unstimulated controls (49.6% vs. 58.4%, $p<0.01$). Co-culture experiments demonstrated enhanced NETosis of PMA-stimulated neutrophils cultured with HUVEC compared to neutrophils cultured alone under normoxia ($p<0.05$).

Conclusion: We have shown that hypoxia modulates: PAD-4 expression; citrullination of histone H3; adhesion molecule expression in HUVEC; neutrophil adherence to HUVEC monolayers; and NET release. Furthermore, co-culture of neutrophils with HUVEC under normoxia elevates NET production on stimulation. Given that these processes are all relevant to the pathogenesis of citrullinated antigens in RA, further experiments are currently underway to dissect the modulatory effects of hypoxia on NETosis and investigate the effects of ACPA positive RA-IgG upon these cellular conditions.

Disclosure: A. A. Khawaja, None; **C. Pericleous**, None; **L. W. Thomas**, None; **M. Ashcroft**, None; **J. C. Porter**, None; **I. Giles**, None.

1202

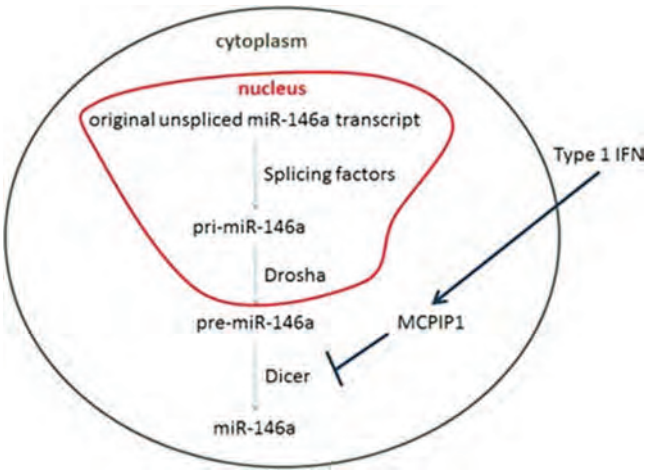
Type I Interferon Promotes Inflammatory Cytokine Production By Inhibiting Mir-146a Maturation in SLE. Bo Qu[1], Jianchang Cao[2], Feifei Zhang[2] and Nan Shen[2]. [1]Shanghai Institute of Rheumatology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, Shanghai, China, [2]Institute of Health Sciences, Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS) & Shanghai Jiao Tong University School of Medicine (SJTUSM), Shanghai, China, Shanghai, China.

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by the uncontrolled inflammation along with over produced inflammatory cytokines, among which type I interferon (IFN) is recognized as a crucial pathogenic factor. The expression of miR-146a, which plays a key role in negatively controlling both the innate and adaptive immune responses, is reduced in the peripheral blood cells of SLE patients and accounts for the overactivated inflammatory responses in SLE. However, the mechanism of the reduction of miR-146a is still not fully understood. Not only are miRNAs regulated at the transcriptional level, their biogenesis consists of complex posttranscriptional processing that is affected by many factors, some of which are indicated to be associated with autoimmune diseases and can even be regulated by IFN. In this study, we tested whether the key pathogenic cytokine of SLE, type I IFN, is responsible for the dysregulation of miR-146a through regulating its posttranscriptional processing.

Methods: Gene expression was measured with RT-qPCR, northern blotting, or western blotting. MCPIP1 expression was knocked down in THP1 cells with a lentivirus encoding a short hairpin RNA targeting MCPIP1. Gene expression data for IFN-inducible genes, MCPIP1, and miR-146a in the peripheral blood cells of SLE patients was used in the correlation analysis.

Results: The pretreatment of THP1 cells with type I IFN attenuated the induction of miR-146a by LPS. Further investigation revealed that this phenomenon happened at the posttranscriptional level, along with downregulated pre-miR-146a, but not pri-miR-146a or its original unspliced transcript. We then demonstrated that the expression of MCPIP1, which is reported to limit miR-146a maturation by antagonizing the function of DICER1, was enhanced by type I IFN. Knocking down the expression of MCPIP1 abolished the inhibition of miR-146a and alleviated the enhancement of the expression of inflammatory cytokines by type I IFN. Finally, we demonstrated that MCPIP1 expression was elevated in the peripheral blood cells of SLE patients and its expression correlated positively with the IFN score and negatively with the level of miR-146a.

Conclusion: Our data suggest that elevated type I IFN inhibits the maturation of miR-146a and contributes to the reduction of miR-146a via MCPIP1 in SLE patients, providing new insights into the mechanisms by which the overproduction of type I IFN in SLE patients amplifies inflammation and even destroys immune tolerance. This knowledge may lead to more-specific therapeutic approaches, targeting downstream effectors of type I IFN. Our findings also indicate that the posttranscriptional regulation of miRNA maturation may be involved in the pathogenic process of SLE and may account for the dysregulated inflammatory gene expression in this disease.



Disclosure: B. Qu, None; **J. Cao**, None; **F. Zhang**, None; **N. Shen**, None.

1203

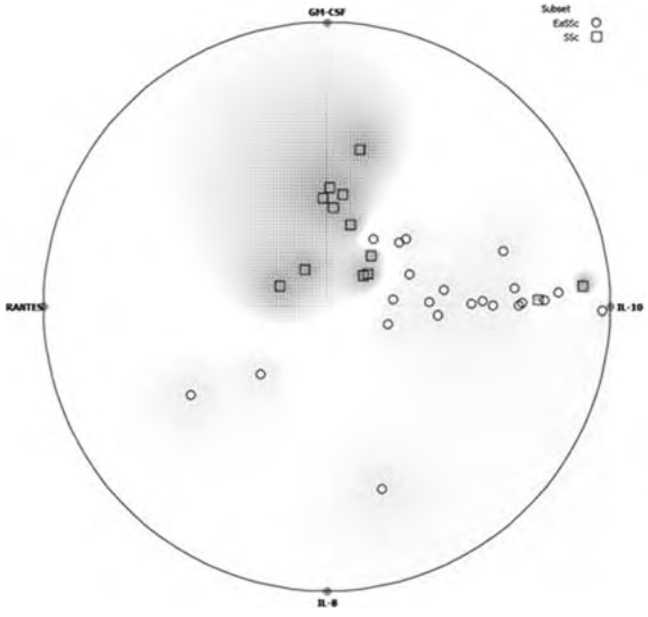
NK/NKT Cells from Early and Definite Systemic Sclerosis Patients Show Different Immunological Responses after IL-2 Stimulation. Marta Cossu[1], Lenny van Bon[1], Stefan Nierkens[2], Alessandro Santaniello[3], Lorenzo Beretta[4] and Timothy Radstake[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]University Medical Centre Utrecht, Utrecht, Netherlands, [3]Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy, [4]Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy.

Background/Purpose: The innate immune system may be implicated in the fibrotic processes of systemic sclerosis (SSc); to date little has been done to unravel the immunological events that take place in earlySSc (EaSSc) and definite SSc patients prior to the onset of fibrosis. To this end, we evaluated the response of CD56+ cells (NK/NKT) cells to different stimuli with the potential to trigger immune responses in the early phases of the disease before the onset of fibrosis.

Methods: CD56+ NK/NKT cells were isolated from 22 EaSSc (LeRoy and Medger criteria, e.g. Raynaud phenomenon (RP) + either SSc-specific nailfold videocapillaropic changes and/or SSc-specific autoantibodies and no other manifestations of SSc) and from 13 definite SSc patients (ACR/EULAR 2013 criteria) without evidence of fibrotic features. Cells were stimulated for 24 hours with Toll-Like receptor (TLR) agonists (Pam3CSK4, Poly(I:C), R848) and human recombinant IL-2 and IFNα. Levels of IFNγ, TNFa, IL-6, IL-10, IL-4, IL-13, IL-17, IL-22, IL-8, GM-CSF, RANTES, MIP-1a were measured in cell-free supernatants using a validated multiplex immunoassay based on Luminex technology. Differences in analytes concentrations between groups were tested via the Mann-Withney's test. We then used the radial coordinate visualization method (Radviz™), a projection-based visualization technique, to represent high dimensional data into the orthogonal space to provide an interpretation of the joint effect of cellular responses on the disease status. The best projection is chosen and validated via the VizRank method.

Results: No single analyte could differentiate NK/NKT responses between groups. Joint-effect analysis via VizRank sorted out meaningful results for NK/NKT-products after IL-2 stimulation. The best Radviz™ representation considering 4 simultaneous attributes is represented in the Graph. This projection had an accuracy to correctly classify patients on the basis of GM-CSF, RANTES, IL-10 and IL-8 levels equal to 82.9%. When these molecules are jointly considered, the decision boundary between EaSSc and definite SSc patients is clearly marked; most definite SSc lie close to the GM-CSF and far from IL-8 anchor points (e.g have higher GM-CSF levels and low IL-8 levels); on the other hand, most EaSSc patients lie far from the RANTES and close to the IL-10 anchor points (e.g. have low RANTES and high IL-10 levels).

Conclusion: We showed that NK/NKT cells from EaSSc and definite SSc patients present distinct immunological patterns after stimulation with IL-2 and that these patterns accurately differentiate these groups of patients.



Disclosure: M. Cossu, None; **L. van Bon**, None; **S. Nierkens**, None; **A. Santaniello**, None; **L. Beretta**, None; **T. Radstake**, None.

1204

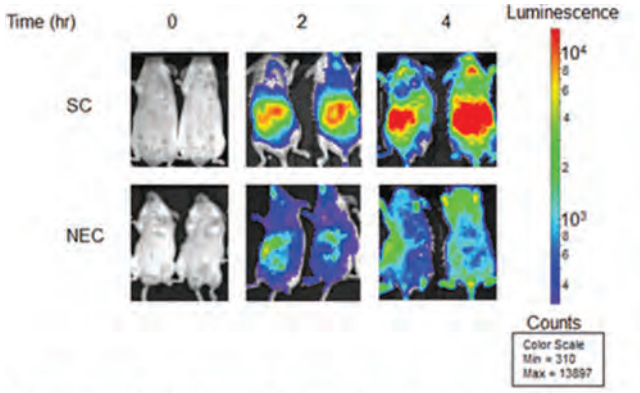
Oral Administration of Nano-Emulsion Curcumin in Mice Suppresses Inflammatory-Induced NFkB Signaling and Macrophage Migration. Nicholas A. Young[1], Michael Bruss[1], Mark Gardner[1], William Willis[1], Xiaokui Mo[1], Giancarlo Valiente[1], Yu Cao[2], Zhongfa Liu[2], Lai-Chu Wu[1] and Wael N. Jarjour[1]. [1]The Ohio State University Wexner Medical Center, Columbus, OH, [2]The Ohio State University Wexner Medical Center, columbus, OH.

Background/Purpose: The major obstacles to successful use of curcumin as an anti-inflammatory agent are its low solubility in water and rapid metabolism, which both translate to poor systemic bioavailability. To protect against metabolism and to enhance accessibility systemically, we have previously reported a novel formulation of nano-emulsified curcumin (NEC) that increases relative bioavailability by over 10-fold. In this study, we validated the bioactivity of NEC *in vivo* and characterized the associated mechanisms of immunosuppression.

Methods: Since curcumin has been shown to inhibit NFkB activation, we used BALB/C-Tg(NFkB-RE-luc)-Xen mice, which contain a firefly luciferase reporter gene under the control of kB responsive elements. Mice were treated with identical concentrations of curcumin in aqueous suspension (SC) or NEC by oral gavage and subsequently challenged with LPS. Acute systemic inflammation was measured and quantitated on the Xenogen *in vivo* imaging system (IVIS 200). Whole blood was collected for flow cytometry and serum was analyzed by ELISA. Acute peritonitis was induced in BALB/C mice by thioglycollate injection with and without NEC administration by oral gavage; peritoneal lavages were isolated for flow cytometry. Scratch assays to measure cell migration were performed on a human cells.

Results: Treatment with NEC significantly reduced LPS-induced inflammation relative to SC, as measured by IVIS detection of NFkB activity. Flow cytometry of peripheral blood indicated that circulating monocytes were reduced with administration of NEC and levels of LPS receptors TLR4 and RAGE were down-regulated on the surface of cells. Induction of monocyte chemoattractant protein (MCP)-1 secretion by LPS stimulation was significantly reduced with NEC administration. While macrophage recruitment was significantly reduced with NEC administration in thioglycollate-induced peritonitis, levels of T-cells and B-cells were not affected. Scratch assays to measure *in vitro* cell migration showed that curcumin significantly inhibited responses in both THP-1 cells and primary human macrophages.

Conclusion: In this study, we establish a novel system to screen and validate curcumin-derived drugs for longitudinal analysis *in vivo*. Furthermore, our results validate NEC as a candidate for future therapeutic studies and demonstrate that curcumin can suppress inflammation by selectively inhibiting macrophage migration via NFkB and MCP-1 inhibition.



LPS-induced NFκB reporter gene expression is suppressed with nano-emulsion curcumin (NEC) in mice when compared to equivalent concentration of suspension curcumin (SC). Transgenic BALB/C-Tg(NFκB-RE-luc)-Xen mice were treated with NEC or SC by oral gavage prior to LPS injection and imaged 0 h, 2 h, and 4 h. Representative whole body bioluminescent images are shown.

Disclosure: N. A. Young, None; **M. Bruss**, None; **M. Gardner**, None; **W. Willis**, None; **X. Mo**, None; **G. Valiente**, None; **Y. Cao**, None; **Z. Liu**, None; **L. C. Wu**, None; **W. N. Jarjour**, None.

1205

Expression of Lectin-like Transcript 1, the Ligand for CD161, in Rheumatoid Arthritis. Paulina Chalan[1], Johan Bijzet[2], Minke G. Huitema[1], Bart-Jan Kroesen[1], Elisabeth Brouwer[1] and Annemieke M.H. Boots[1]. [1]University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [2]University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: Precursor Th17 lineage cells expressing CD161 are implicated in rheumatoid arthritis (RA) pathogenesis. CD4+CD161+ T cells were found to accumulate in RA synovial fluid (SF) and tissue (ST) where they may acquire a non-classical T-helper 1 phenotype. The endogenous ligand for CD161 is lectin-like transcript 1 (LLT1). Previously, the LLT1-CD161 interaction was reported to co-stimulate T cell effector functions and to enhance IFN-γ production. This prompted us to investigate whether LLT1 is upregulated in arthritic joints. To that end we investigated the presence and identity of LLT1-expressing cells in RA synovial fluid and synovial tissue.

Methods: Paired samples of peripheral blood (PB) and SF mononuclear cells (n=14) and digested ST cells (n=4) from late-stage rheumatoid arthritis patients were analyzed for LLT1 expression by flow cytometry. Cell suspensions were stained with fluorochrome labeled anti-human LLT1, CCR2, CD14, HLA-DR, CD1a, CD16, CD163, CD1c, CD141, CD62L, CD86, CD303. Cells were analyzed using an LSR II flow cytometer and data analysis was performed with Kaluza® analysis software. Paraffin-embedded ST sections (n=6) were used for the immunohistochemical detection of LLT1. To further characterize LLT1 expressing cells, consecutive tissue sections were stained with the antibodies recognizing macrophage marker CD68, T cell marker CD3 and B cell marker CD20.

Results: In rheumatoid arthritis SF LLT1 expression was found upregulated in a subset of monocytes with a more differentiated, mature phenotype. In RA ST, LLT1-expressing cells were detected in the lining layer, sublining layer and in areas with lymphoid infiltrates. The LLT1 staining pattern overlapped with the CD68 (macrophages) staining pattern. Flow cytometric analysis of digested ST confirmed that LLT1 is expressed on CD68+ cells.

Conclusion: This is the first study showing that surface-expressed LLT1 is present in arthritic joints in RA. The finding of LLT1 expression by macrophages in synovial tissue suggests potential crosstalk with CD161+ T-cells. Ligation of CD161-LLT1 on CD4 T cells and macrophages respectively, may contribute to modulation of their function at the level of the joint.

Disclosure: P. Chalan, None; **J. Bijzet**, None; **M. G. Huitema**, None; **B. J. Kroesen**, None; **E. Brouwer**, None; **A. M. H. Boots**, None.

1206

Low Dose Colchicine Anti-Inflammatory Effects Are Transduced By AMP-Activated Protein Kinase (AMPK). Ru Bryan[1], Robert Terkeltaub[2] and Yun Wang[3]. [1]VA Medical Center/University of California San Diego, San Diego, CA, [2]VA Medical Ctr/University of California San Diego, San Diego, CA, [3]VA Medical Ctr/UCSD, San Diego, CA.

Background/Purpose: AMPK is a master metabolic energy regulator, whose tissue activity drops in response to nutritional excesses, alcohol consumption, and in obesity, metabolic syndrome and diabetes, and high levels of soluble urate. In addition to its anti-inflammatory effects, AMPK activity promotes microtubule stabilization. Therefore, we tested the effects of AMPK activation on urate crystal-induced inflammatory responses, and the hypothesis that AMPK activation transduces the capacity of the microtubule stabilizing agent colchicine to limit gout-like inflammation.

Methods: We studied bone marrow derived macrophages (BMDMs) from AMPKα1 knockout (KO) and wild type (WT) mice, and human monocytic THP-1 cells, and assessed a low concentration (10 nM) of colchicine achieved by "low dose regimens" for both prophylaxis and treatment of gout in humans. We examined expression and phosphorylation (activation) of AMPKa and of LKB1, the major upstream activating kinase for AMPK. We also assessed negative regulators of AMPKα phosphorylation (phosphatases 2A and 2C), and parameters of NLRP3 inflammasome activation and of macrophage inflammatory M1 to anti-inflammatory M2 polarization (iNOS, arginase, respectively). We studied acute MSU crystal-induced inflammation *in vivo*in subcutaneous air pouches.

Results: Colchicine (10 nM) increased AMPKα and LKB1 phosphorylation in cultured macrophage lineage cells, but phosphatases 2A and 2C were unchanged. Colchicine (10 nM) enhanced protein expression of total AMPKα translationally in BMDMs. Furthermore, colchicine (10 nM) promoted

macrophage polarization toward anti-inflammatory M2 phenotype by increasing ratio of arginase (M2-like) to iNOS (M1-like) mRNA expression. Colchicine partially but significantly inhibited caspase-1 cleavage and IL-1β maturation, as well as release of IL-1β and CXCL1 in response to MSU crystals in WT but not AMPKα1 KO BMDMs. Hence, manifold anti-inflammatory effects of colchicine were AMPK-dependent. Last, acute gout-like inflammation (neutrophil infiltration) were attenuated by pharmacologic AMPK activation in WT ($p<0.01$ compare to non-treated mice, 95% CI of difference: -5.9 to -0.9), but were enhanced in AMPKα1 KO mice ($p<0.001$ compared to WT mice, 95% CI of difference: 1.6 to 5.6) *in vivo*.

Conclusion: AMPK transduced multiple low dose colchicine anti-inflammatory effects *in vitro*, including promotion of M2 macrophage polarization, inhibition of NLRP3 inflammasome activation and reduction of IL-1β and CXCL1 release. Moreover, AMPKα1 knockout significantly enhanced model acute gout-like inflammation. Our results reveal a novel molecular mechanism of action for colchicine, and suggest that decreased AMPK activation triggered by certain nutritional excesses and co-morbidities may heighten the inflammatory potential of deposits of urate crystals. Hence, colchicine, and other pharmacologic AMPK activators currently in the clinic for other conditions (methotrexate, salicylates, high dose aspirin, metformin), may have the potential to enhance efficacy of anti-inflammatory prophylaxis and treatment of gouty inflammation.

Disclosure: R. Bryan, None; **R. Terkeltaub**, Astar Zeneca, Takeda, Relburn, Abbvie, BioMarin, Quest, 5; **Y. Wang**, None.

1207

Novel Role of Liver X Receptor Alpha (LXRα) in the Attenuation of TLR Signalling: Implications in Congenital Heart Block. Susmita Bagchi[1], Mark Halushka[2], Robert M. Clancy[1] and Jill P. Buyon[1]. [1]New York University School of Medicine, New York, NY, [2]John Hopkins Pathology, Baltimore, MD.

Background/Purpose: Anti-SSA/Ro associated congenital heart block provides a unique opportunity to examine the effector arm of immunity and define the molecular mechanisms that link maternal antibodies and the inflammatory cellular response. Based on an agnostic survey of transcripts from macrophages stimulated by immune complexes (IC) containing anti-Ro, 60kD Ro, and ssRNA-hY3, risk and protective genes were recently compiled. Two highly significant candidates in the injury spectrum, one enhancing - interleukin 6 (*IL6)*, and one attenuating - liver X receptor alpha (*NR1H3 or* LXRα), which has been shown to decrease NFkB-induced expression, were identified. Accordingly, this study was initiated to determine the potential functional significance of these candidates; specifically, whether LXRα expression influences TLR7/8 ligation and downstream NF-kB–dependent cytokine release underlying both overt inflammation and the transition to established fibrosis.

Methods: The approach included both in vitro and in vivo studies. The former employed TLR7/8 stimulated human macrophage cells (THP1) and peripheral blood macrophages in the presence and absence of a LXRα ligand, and the latter used immunohistochemistry of autopsy tissue from the heart of a fetus dying with CHB and an age matched control.

Results: As expected, exposure of THP-1 cells and isolated macrophages to a LXRα ligand, GW3965 (10 μM), resulted in the upregulation of its receptor LXRα mRNA (10 ± 1.25 vs 1, $N=4$). In addition, LXRα expression was likewise increased in hY3-transfected macrophages (14 ± 6.1 vs 1), confirming results obtained by the previous microarray data (gene name *NR1H3*). Increased protein expression of LXRα following either GW3965 or hY3 alone was confirmed using anti-LXRα antibodies in immunofluorescence and permeabilized FACS (whole cells, digitonin treated, respectively). To identify whether an increase of LXRα expression might alter proinflammatory hY3-induced transcripts, macrophages were simultaneously treated with hY3 and GW3965. As expected, hY3 treatment increased IL-6 mRNA expression compared to untreated cells or those treated with GW3965 alone (transcript normalized to GAPDH, 2.04, 1.03 and 0.83, respectively). In a cotreatment approach, we addressed whether the provision of ligand and upregulation of its receptor would impact the hY3-stimulated expression of IL-6. There was a 65% reduction in IL6 transcripts in macrophages treated with hY3 and GW3965 compared to hY3 alone ($N=2$) suggesting that ligand binding to receptor (but not increase of receptor alone) is a sufficient stimulus to trigger a sustained anti-inflammatory response. Immunohistochemistry of a heart from a fetus dying with CHB revealed focal expression of LXRα in proximity to the AV nodal region in areas containing calcified myocytes. In contrast, as assessed in the control heart, healthy myocytes did not express LXRα.

Conclusion: These data support the novel identification of a link between TLR7 activation and expression of a potential anti-inflammatory checkpoint, LXRα. In vitro and in vivo approaches suggest that LXRα may represent a thwarted attempt to forestall a smoldering hY3-driven inflammatory milieu.

Disclosure: S. Bagchi, None; **M. Halushka**, None; **R. M. Clancy**, None; **J. P. Buyon**, None.

1208

Cholesterol Loading Induces Neutrophil Extracellular Traps, and Atorvastatin Attenuates This Effect. Ming-Lin Liu[1], Muhammad Bashir[2], Kevin Williams[3] and Victoria Werth[2]. [1]University of Pennsylvania, Philadelphia, PA, [2]Philadelphia V.A. Hospital, Philadelphia, PA, [3]Temple University School of Medicine, Philadelphia, PA.

Background/Purpose: Neutrophils are the most common white blood cell, but their role in autoimmune and cardiovascular diseases has been underestimated. As part of host defense, neutrophils release granule proteins and chromatin DNA into the extracellular space to form neutrophil extracellular traps (NETs). Recent studies reported the presence of NETs in atherosclerotic lesions, and NETs promote thrombosis. Moreover, pharmacological inhibition of NET formation through peptidyl-arginine deiminase blockade can reduce atherosclerosis and arterial thrombosis in mice. Hypercholesterolemia is the underlying cause of atherosclerotic cardiovascular disease. Nevertheless, the effects of cholesterol loading on NET formation and the relevant cellular mechanisms have not been investigated.

Methods: Primary neutrophils were isolated from healthy donors by sequential centrifugation with Histopaque 1077 and 1119. Cultured human HL-60 cells were differentiated into neutrophil-like cells with 1.2% DMSO. Cholesterol was delivered to primary and HL-60 neutrophils as a water-soluble complex with meythl-β-cyclodextrin (MCD, Chol/MCD), which is widely used to modify the cholesterol content of cultured cells without potentially confounding effects from receptor engagement. Cells were fixed and then stained with Sytox Green, which indicates exposed nucleic acids. Formation of NETs was assessed with a fluorescence microplate reader and by fluorescence microscopy. To study the effects of atorvastatin on NET formation, selected plates were pretreated with this agent before exposure to Chol/MCD.

Results: We found that Chol/MCD loading could induce NET formation in a time- and dose-dependent manner in primary neutrophils [4491 ± 60 RFUs (relative fluorescent units) for control without Chol/MCD, 6553 ± 206 RFUs with 12.5 μg/ml Chol/MCD, and 9297 ± 223 RFUs with 25 μg/ml Chol/MCD, mean$\pm$SEM, $P<0.001$ by ANOVA], and in HL-60 neutrophils, detected with a fluorescence microplate reader. Both findings were confirmed by examination of the NET structure with fluorescent microscopy. Importantly, pretreatment of neutrophils with low or lower dose (10 or 25 μM), but not high dose (75 μM), atorvastatin, significantly attenuated cholesterol-induced NETosis in vitro.

Conclusion: Our studies indicated that cholesterol loading can induce neutrophil extracellular trap formation in vitro. Low-dose atorvastatin can attenuate cholesterol-induced NETosis. Our preliminary results indicate a potential role of hypercholesterolemia in NET formation and a potential beneficial role for statins.

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1209

Anti-Scavenger Receptor Autoantibodies Disrupted Marginal Zone Macrophage Integrity Via *Bruton's Tyrosine Kinase*. Hao Li[1], Qi Wu[1], PingAr Yang[1], Zheng Wang[1], Jun Li[1], Bao Luo[1], Jeffrey C. Edberg[1], Hui-Chen Hsu[1], John D. Mountz[1] and Robert P. Kimberly on behalf of PROFILE investigators[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Ibrutinib, a Btk kinase activity inhibitor, is a novel inhibitor under development for autoimmune disease therapy. We have shown that Btk was significantly upregulated in spleen MΦs of lupus prone BXD2 mice that spontaneously develop high titers of autoantibodies (auto-Abs). As loss of control on Btk expression in myeloid cells has been implicated previously to cause mislocation and loss of marginal zone macrophages (MZMs), a critical apoptotic bleb clearance barrier, in the spleen, the purpose of the present study is to determine a possible pathogenic

role of autoAbs to disrupt MZM integrity throught upregulating Btk activity in MZMs. The implication of these results in human systemic lupus erythematosus (SLE) was further studied.

Methods: Purified polyreactive monoclonal antibodies isolated from the spleen of BXD2 mice were screened for their reactivity to MZM specific scavenger-receptors including MZRCO and SR-A. AutoAbs that are either reactive or non-reactive to anti-MARCO/anti-SR-A were individually administered to recipient B6 mice to evaluate the pathogenic effects on MZMs. Confocal microscope analysis and FACS analysis were carried out to quantitate the percentage of MZMs in the spleen and evaluate the expression of phospho-Btk (pBtk). ELISA was carried out to determine the autoAb titers.

Results: In BXD2 mice, elevated anti-MARCO/anti-SR-A autoAbs in the sera correlated with the loss of MZMs in the spleens. Different purified monoclonal autoAbs were administrated into normal B6 mice. Disruption of MZMs was only observed when recipient mice were administered with polyreactive autoAbs that exhibit high reactivity to both MARCO and SR-A. In these mice, there was gradual induction of *pBtk* in the MZMs. Increased pBtk was also observed in MZMs of BXD2, and this induction can be efficiently blocked via early global inhibition of endogenous apoptosis using a pan-caspase inhibitor, z-VAD. Delivery of Ibrutinib either systemically or via an Ibrutinib-*l*iposome strategy to target MZM specifically, prevented MZM loss and attenuated autoantibodies mediated glomerulonephritis in autoAb administrated B6 or BXD2 mice. Surprisingly, anti-MARCO/anti-SR-A autoantibody administration also induced the reduction of MZMs in the spleen of $Fc\gamma r^{-/-}$ or $C3^{-/-}$mice, suggesting that autoAb mediated MZM loss is not related to either antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). In SLE patients, higher serologic levels of anti-MARCO autoAb titers exhibited significant positive correlation with the development of end-stage-renal disease (ESRD). Loss of MZMs was also identified in SLE patient spleens.

Conclusion: The present study suggests a novel autoAb-mediated systemic autoimmune disease mechanism based on the induction of pBtk in MZMs to break a critical barrier that is crucial to clear apoptotic debris in the spleen. The present study further suggests the potential to develop anti-MARCO/anti-SR-A into a novel biomarker for apoptosis clearance defects and development of ESRD in human SLE.

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1210

The Role of the Transcription Factor cAMP Responsive Element Binding Protein 1 in Lipopolysaccharide-Induced Tolerance. Kerstin Klein[1], Renate E. Gay[2], Christoph Kolling[3], Lih-Ling Lin[4], Steffen Gay[1] and Caroline Ospelt[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Zurich University Hospital, Zurich, Switzerland, [3]Schulthess Clinic, Zurich, Switzerland, [4]Inflammation and Remodeling Research Unit, Pfizer, Cambridge, MA.

Background/Purpose: In macrophages, repeated stimulation of Toll-like receptor (TLR) 4 leads to adaptation of signaling pathways and epigenetic modifications resulting in a tolerant state of the cell which protects inflamed tissues from damage. We have recently shown that in contrast to macrophages, rheumatoid arthritis synovial fibroblasts (RASF) lack these protective mechanisms and keep on secreting inflammatory cytokines and matrix degrading metalloproteinases also after repeated stimulation with LPS. The objective was to investigate mechanisms behind tolerizable and non-tolerizable effects in RASF.

Methods: RASF were treated with LPS (100 ng/ml). 24h after the initial stimulation, cells were re-stimulated with LPS (10 ng/ml) for another 24h. The expression levels of IL6, IL8, CXCL10, matrix metalloproteinases (MMP) 1 and MMP3, as well as RIG1 and OAS1 were analyzed by quantitative Real-time PCR or ELISA. Nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) promoter activities in RASF (n=4) were evaluated by Dual-Luciferase reporter assays after repeated stimulation with LPS. RASF (n=8) were transfected with siRNAs targeting cAMP responsive element binding protein 1 (CREB1) or scrambled siRNAs as control prior to stimulation with LPS (100 ng/ml, 24h). Activation of CREB1 after repeated LPS stimulation was analyzed in nuclear extracts (n=2) using p-CREB1 antibodies.

Results: RASF (n=10) maintained their production of IL6 after repeated TLR4 stimulation (single stimulation: 13.2 ± 5.8 ng/ml, double stimulation: 12.4 ± 7.1 ng/ml). A lack of tolerizable effects of RASF was also found for MMP1 and MMP3, whereas the interferon-responsive genes OAS1, RIG1, MDA5 and CXCL10 were tolerizable. RASF (n=5) secreted 531 ± 385 pg/ml CXCL10 after a single LPS stimulation and 111 ± 97 pg/ml CXCL10 after double stimulation ($p<0.05$). Reporter gene activities for NF-κB and AP-1 were similar in single and double stimulated RASF, excluding potential differences in the activation of these transcription factors as underlying mechanisms for tolerizable/non-tolerizable effects in RASF. Silencing of CREB1 reduced the LPS-induced expression levels of the tolerizable genes CXCL10 (x-fold: ctrl 54.8 ± 64.9; siCREB1 34.5 ± 42.9; $p<0.05$), OAS1 (x-fold: ctrl 24.0 ± 21.1; siCREB1 15.6 ± 15.2, $p<0.05$) and RIG1 (x-fold: ctrl 14.8 ± 12.1; siCREB1 10.1 ± 8.6, $p<0.05$), whereas LPS-induced expression levels of the non-tolerizable genes IL6, IL8, MMP1 and MMP3 were not affected. Similar effects of CREB1 silencing were obtained when secreted protein levels of LPS-induced CXCL10, IL6, IL8, MMP1 and MMP3 where measured. The phosphorylation of CREB1 was not changed by LPS double compared to single stimulation indicating that CREB1 activation was not impaired by double stimulation.

Conclusion: The expression of tolerizable genes in RASF is dependent on the transcription factor CREB1. Based on the fact that CREB1 activation is not altered by repeated LPS stimulation, epigenetic modifications on target gene promoters that effect the recruitment of CREB1 to promoters are likely to contribute to tolerization effects seen in RASF.

Disclosure: K. Klein, IMI-BT Cure, IAR Epalinges, 2; **R. E. Gay**, IMI-BT Cure, IAR Epalinges, euroTEAM, 2; **C. Kolling**, None; **L. L. Lin**, Pfizer Inc, 3; **S. Gay**, IMI-BT Cure, IAR Epalinges, euroTEAM, 2; **C. Ospelt**, IMI-BT Cure, IAR Epalinges, euroTEAM, 2.

1211

Gene Expression Profile in Muscle Tissue before and after Immunosuppressive Treatment in Patients with Myositis. Joan Raouf[1], Ingela M. Loell[2], Yi-Wen Chen[3], Rongye Shi[4], Inger Nennesmo[5], Helene Alexanderson[6], Maryam Dastmalchi[7], Marina Korotkova[8], Kanneboyina Nagaraju[9] and Ingrid E. Lundberg[10]. [1]Rheumatology Unit, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, [2]Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [3]Research Center for Genetic Medicine, Children's National Medical Center, Washington DC, USA., Washington DC, DC, [4]Childrens National Medical Center, Research Center for Genetic Medicine, Washington DC, USA, Washington DC, WA, [5]Institution for Laboratory Medicine (LABMED), Karolinska Universitetssjukhuset Huddinge, Stockholm, Sweden, Stockholm, Sweden, [6]Karolinska Institutet, Department of medicine, Rheumatology Unit, Karolinska Universitetssjukhuset Solna, Stockholm, Sweden, Stockholm, Sweden, [7]Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, [8]Rheumatology Unit, Department of Medicine, Karolinska University Hospital in Solna, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, [9]Children's National Medical Center, Washington DC, DC, [10]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Autoimmune muscle diseases such as polymyositis (PM) and dermatomyositis (DM) are characterized by infiltration of inflammatory cells, production of cytokines and chemokines, as well as the expression of major histocompatibility complex (MHC) class I on skeletal muscle fibers. Patients are conventionally treated with high doses of glucocorticoids in combination with additional immunosuppressive drugs. Nevertheless, many patients have persisting muscle weakness even after prolonged treatment.

Objectives: To investigate the effect of conventional immunosuppressive treatment on gene expression profiling in skeletal muscle biopsies from patients with PM and DM, taken before and after treatment in order to develop further understanding of molecular mechanisms that might contribute to the persisting compromised function.

Methods: Biopsies (*vastus lateralis muscle)* from six newly diagnosed, untreated patients with PM (n=2) or DM (n=4) before and after a median of 8.5 months of immunosuppressive treatment were examined by gene expression microarray analysis. Functional associations were analyzed by using Ingenuity Pathway Analysis. Tissue sections from corresponding biopsies were evaluated for MHC class I molecule expression, inflammatory infiltrates, and signs of fiber regeneration/degeneration. Selected genes that displayed changes in expression were validated by western blot (WB).

Results: Evaluation of the biopsies taken after a median of 8.5 months of treatment showed MHC class I staining in muscle fibers, presence of CD3 positive cells (low in general with few positive cells scattered throughout the tissue) and CD68 positive cells (frequent but also ranging from scattered

mononuclear cells to infiltrates). By microarray analyses alterations were observed in the overall gene expression in muscle tissue. As expected most of the genes related to immune response such as interferon (IFN) pathway and inflammasome (e.g. AIM-2 and Caspase-1) were down-regulated. In addition alterations were seen in the expression of genes involved in muscle tissue remodeling suggesting protein breakdown as well as muscle regeneration (e.g. by up-regulation of the FKBP5 gene which encodes the protein important in basic cellular processes involving protein folding/trafficking). Validation of changes in gene expression by WB confirmed changes in protein expression; AIM-2 ($p=0.044$) and Caspase-1 ($p=0.035$) were significantly down-regulated, while FKBP5 ($p=0.020$) was up-regulated after chronic glucocorticoid treatment.

Conclusion: Together, these data indicate that during conventional immunosuppressive treatment of myositis patients transcriptional modifications in genes involved in muscle tissue inflammation and remodelling are taking place and their changes could be validated by changes in protein expression. The alteration indicate that besides the beneficial down-regulation of inflammatory pathways there are signs of protein breakdown which may have a negative consequence in muscle repair and may contribute to a defect recovery of muscle strength that may be seen in patients with PM/DM despite immunosuppressive treatment.

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1212

Behcets Disease in Females Due to Mutation in NEMO, the NF-Kb Essential Modulator. Alex Wessel[1], Spiros Vonortas[2], Jevgenia Zilberman-Rudenko[3], Richard Siegel[4] and Eric Hanson[5]. [1]NIH, Bethseda, MD, [2]NIH, NIAMS, Bethesda, MD, [3]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [4]NIAMS, NIH, Bethesda, MD, [5]National Institute of Health, Bethesda, MD.

Background/Purpose: Behçet's disease (BD) is a chronic multi-system inflammatory disorder associated clinically with oral and genital ulceration, uveitis, erythema nodosum, and other inflammatory disease. The cause of BD is unknown. A current hypothesis is that an autoinflammatory reaction in individuals with a permissive genotype may arise due to altered cellular signal transduction events and hence altered immune cell function. This reaction may be triggered in these individuals due to infectious agents or microbes not generally considered pathogenic. The family of NF-kB transcription factors are activated in various signaling pathways involved in microbial sensing, immunity, and inflammatory disease. Previously, a case of familial Behcets was described in two females harboring a mutation in the C-termial Zinc finger domain of NEMO, the NF-kB essential modulator, a key regulator of NF-kB activation.

Methods: We evaluated female patients diagnosed with Behcets disease who harbor mutation in the NEMO C-terminus, in addition to those with mutation affecting another ubiquitin binding domain. Patient mononuclear cells in addition to patient-mutation-reconstituted NF-kB reporter T cell lines were stimulated with TNF, Toll-like Receptor (TLR) ligands Flagellin and LPS, in addition to anti-CD3/CD28, and PMA/Ionomycin. Gene expression, cytokine production and biochemical assays including co-immunoprecipitation of endogenous proteins implicated in the regulation of NF-kB activation were performed to characterize signaling and cellular responses.

Results: Mutation leading to premature truncation of the C-terminal Zinc finger in females is associated with a BD phenotype. NF-kB activation by reporter assay in cells harboring the patient mutation reveals enhanced NF-kB activation in response to TNF and TLR5 stimulation compared to the response seen in cells harboring other NEMO mutation not associated with BD. Cytokine production by capture assay indicates LPS induced IL-1b, TNF and GMCSF were approximately 2-fold increased compared to unrelated control, whereas other cytokine responses were normal or reduced. Co-immunoprecipitation studies following cell stimulation with TNF reveal impaired stabilization of the NF-kB negative regulator A20 at the receptor in cells harboring the patient mutation.

Conclusion: These results illustrate that single gene defects may lead to phenotypes observed in complex genetic disease. Molecular characterization of the altered signaling resulting from NEMO mutation may yield important insights into more common rheumatic disease such as BD.

Disclosure: A. Wessel, None; **S. Vonortas**, None; **J. Zilberman-Rudenko**, None; **R. Siegel**, None; **E. Hanson**, None.

1213

Absence of Hormone Responsive Estrogen Receptor Alpha Reduces the Activation of Plasmacytoid Dendritic Cells in Lupus Prone Mice. Jennifer L. Scott[1], Melissa A. Cunningham[1], Osama S. Naga[1], Jackie G. Eudaly[1], Jena R. Wirth[2] and Gary S. Gilkeson[1]. [1]Medical University of South Carolina, Charleston, SC, [2]MUSC, Charleston, SC.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that affects women at a 9 to 1 ratio compared to men. To further understand mechanisms underlying the female predominance our laboratory is investigating the role of estrogen receptor alpha (ERα) in SLE disease development. In lupus-prone mice, absence of hormone responsive ERα increased survival and decreased glomerulonephritis despite no effect on autoantibody production or renal immune complex deposition. To explain this protective effect, we hypothesized ERα deficiency impacts innate immune responses and in particular plasmacytoid dendritic cell (pDC) function. Our previous work showed ERα deficiency reduced the bone marrow derived dendritic cell (DC) toll-like receptor (TLR) mediated type I Interferon response. To determine the significance of the reduced dendritic cell interferon response in disease development we investigated the impact of ERα deficiency on spleen pDC activation state *ex vivo* in pre-disease lupus-prone mice.

Methods: We measured the number, maturation state, and activation state of pDCs *ex vivo* from the spleens of pre-disease (12 to 14 week old) WT and hormone responsive ERα deficient female lupus-prone mice (NZM2410) using flow cytometry. pDCs were identified as singlets, live, $CD11b^{-}B220^{+}SiglecH^{+}$. Activation markers measured included MHC class lI, CD40, and pDC-TREM. Ly49Q expression was used as the marker to identify fully mature pDCs. We also measured activation of the bone marrow derived pDCs, sorted as live, $CD11b^{-}$, $B220^{+}$, and $CD11c^{+}$, after TLR 9 stimulation *in vitro*.

Results: ERα deficiency reduced the activation state of spleen pDCs from pre-disease lupus-prone mice. The frequency of spleen pDCs expressing the activation markers MHC class II and pDC-TREM was reduced by ERα deficiency ($n=20$, $p=0.002$, $p=0.06$). This finding was specific to lupus-prone prone mice. We did not detect any alteration in the frequency of activated pDCs between WT and ERα deficient age and sex matched C57BL/6 mice. To determine if the reduced frequency of activated pDCs was the result of ERα deficiency mediated alterations in pDC maturation or Toll-like receptor (TLR) responsiveness, we measured pDC maturation state *ex vivo* and TLR responsiveness *in vitro* in pDCs from WT and ERα deficient lupus-prone mice. ERα deficiency did not affect the maturation state of spleen pDCs, as measured by Ly49Q expression. However, ERα deficiency reduced TLR 9 mediated activation of bone marrow derived pDCs. After stimulation with TLR 9 ligand, a greater frequency of pDCs from WT mice expressed MHC class II and pDC-TREM compared to ERα deficient pDCs ($n=8$, $p=0.002$, $p=0.002$).

Conclusion: Our findings suggest the absence of hormone responsive ERα reduces *in vivo* pDC activation state by impairing pDC responsiveness to TLR ligands in lupus-prone mice. These findings may explain the protective role of hormone responsive ERα deficiency in SLE.

Disclosure: J. L. Scott, None; **M. A. Cunningham**, None; **O. S. Naga**, None; **J. G. Eudaly**, None; **J. R. Wirth**, None; **G. S. Gilkeson**, None.XXzar110141211XX

ACR/ARHP Poster Session B
Metabolic and Crystal Arthropathies: Mechanisms of Disease
Monday, November 17, 2014, 8:30 AM–4:00 PM

1214

Oxidative Stress from Use of Allopurinol - Is There a Reason for Patients with Gout to Take Vitamin C? Lisa K. Stamp[1], Peter T. Chapman[2], John L. O'Donnell[3], Irada Khalilova[1], Rufus Turner[1] and Anthony Kettle[1]. [1]University of Otago, Christchurch, Christchurch, New Zealand, [2]Christchurch Hospital, Christchurch, New Zealand, [3]Canterbury Health Laboratories, Christchurch, New Zealand.

Background/Purpose: During acute gout attacks neutrophils are activated and release a number of pro-inflammatory cytokines and enzymes. One of these enzymes is myeloperoxidase (MPO), which we have previously shown to be elevated in the circulation of patients with acute gout. Furthermore, MPO was associated with increased oxidation of urate as demonstrated by the increased concentration of allantoin in the plasma of these patients. Thus, oxidative stress is a feature of acute attacks of gout. Allopurinol is the most commonly used urate

lowering therapy. It is rapidly metabolised by aldehyde oxidase to oxypurinol as well as superoxide and hydrogen peroxide. Oxypurinol exerts most of its inhibitory effects on xanthine oxidoreductase. In our previous work, allopurinol use was also associated with an increase in allantoin, indicating that it increases oxidative stress. The aim of this study was to determine the effects of allopurinol on plasma ascorbate (vitamin C), because its levels are sensitive to oxidative stress.

Methods: Patients with gout and a serum urate >0.36mmol/L were recruited. Twenty patients already receiving allopurinol were randomised to either increase the dose of allopurinol or commence vitamin C 500mg/d. Twenty patients not receiving urate lowering therapy were randomised to either start allopurinol or vitamin C 500mg/d. Plasma ascorbate, allantoin, myeloperoxidase, oxypurinol and serum urate were measured at day 0 and week 8.

Results: As expected at day 0, the 20 patients receiving allopurinol had significantly lower serum urate compared to those not on allopurinol (0.44 vs 0.54 mM $p<0.001$). Use of allopurinol was also associated with significantly lower plasma ascorbate levels (38.8 vs 56.7 μM $p=0.03$) and higher MPO levels (29.4 vs 18.0 μM $p<0.001$) at day 0. There was a non-significant increase in serum allantoin.

In the 10 patients who commenced allopurinol there was a significant reduction between day 0 and week 8 in serum urate (0.57 vs 0.41 mM $p=0.0003$) and plasma ascorbate (54.2 vs 28.1 μM $p=0.003$) and an increase in plasma allantoin (2.6 vs 3.0 μM $p=0.04$). Plasma MPO was not affected by allopurinol. There was a significant negative correlation between plasma oxypurinol and plasma ascorbate concentrations ($r=-0.54$, $p<0.0004$). For the 10 patients who stayed on their original dose of allopurinol, supplementation with vitamin C increased plasma vitamin C (48.4 vs 68.1 μM $p=0.01$) but had no effect on either urate or allantoin levels.

Conclusion: These results suggest that allopurinol promotes oxidative stress thereby depleting plasma ascorbate. Supplementation with vitamin C can increase plasma ascorbate in patients on allopurinol. The clinical significance of oxidative stress and low plasma ascorbate remains to be determined but our results indicate there may be a reason other than urate lowering for patients with gout to take vitamin C.

Disclosure: L. K. Stamp, Astra Zenec, 5, Abbvie, 9, PHARMAC, 6; **P. T. Chapman**, None; **J. L. O'Donnell**, None; **I. Khalilova**, None; **R. Turner**, None; **A. Kettle**, None.

1215

Circulating Mediators of Bone Remodeling in Patients with Tophaceous Gout. Ashika Chhana[1], Opetaia Aati[1], Gregory Gamble[1], Karen E. Callon[1], Anthony Doyle[1], Mark Roger[2], Fiona M. McQueen[1], Anne Horne[1], Ian R. Reid[1], Jillian Cornish[1] and Nicola Dalbeth[1]. [1]University of Auckland, Auckland, New Zealand, [2]Auckland District Health Board, Auckland, New Zealand.

Background/Purpose: Disordered bone remodeling has been implicated in the development of bone erosion in tophaceous gout. The function of bone cells in the skeleton is regulated by a number of factors, including soluble mediators that influence osteoclast and osteoblast function. The aim of this study was to determine the relationship between bone erosion and circulating mediators of bone remodeling in people with tophaceous gout.

Methods: One hundred patients with tophaceous gout were prospectively recruited from rheumatology outpatient clinics. Bone erosion at articular sites was assessed by two readers in conventional computed tomography (CT) scans of the feet using a validated semi-quantitative erosion score, and in plain radiographs (XR) of the hands and feet using a modification of the Sharp-van der Heijde score. Readers were blinded to all clinical details, including laboratory results. Hip, spine and total body bone mineral density (BMD) was also measured. The following soluble mediators of bone remodeling were measured in serum by ELISA: osteoprotegerin (OPG, a soluble decoy receptor for RANKL), sclerostin (an osteocyte-derived Wnt inhibitor), dickkopf-1 (DKK-1, a Wnt inhibitor), and fibroblast growth factor-23 (FGF-23, an osteocyte-derived regulator of phosphorous and vitamin D).

Results: CT bone erosion scores positively correlated with circulating OPG concentrations ($r=0.22$, $p=0.03$), and negatively correlated with sclerostin concentrations ($r=-0.29$, $p=0.003$). Similar correlations were observed for XR erosion scores for OPG ($r=0.30$, $p=0.002$), and sclerostin ($r=-0.21$, $p=0.04$). Neck of femur BMD negatively correlated with OPG concentrations ($r=-0.34$, $p=0.001$), and positively correlated with sclerostin concentrations ($r=0.24$, $p=0.02$). Similar relationships were observed for total body BMD. No relationship was observed between bone erosion scores or BMD, and DKK-1 or FGF-23 concentrations. In linear regression analysis, OPG and sclerostin were independently associated with CT erosion score ($p=0.005$ for OPG and $p=0.003$ for sclerostin, R^2 for model 0.16, $p<0.0001$). Similarly, OPG and sclerostin were independently associated with neck of femur BMD ($p=0.002$ for OPG and $p=0.04$ for sclerostin, $R^2$for model 0.13, $p=0.001$). These relationships persisted after adjusting for eGFR.

Conclusion: In people with tophaceous gout, circulating OPG and sclerostin levels are independently associated with both central and peripheral bone loss. The direction of the associations does not support a direct role for bone-remodeling factors in pathogenesis of bone erosion, but may reflect compensatory or repair mechanisms to maintain bone homeostasis at both central and peripheral sites.

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1216

The Relationship Between Serum Homocysteine, Uric Acid and Renal Function in Chronic Gouty Patients: 2 Year Follow-up Results. Eun-Hye Park, Sang Tae Choi and Jung-Soo Srong. Chung-Ang University College of Medicine, Seoul, South Korea.

Background/Purpose: Hyperhomocysteinemia is one of the important factors for the endothelial cell damage and also a risk factor for cardiovascular events. Gout is known to be associated with cardiovascular disease (CVD) as well. Although both hyperhomocysteinemia and gout are related to CVD, the only few cases about serum homocysteine (Hcy) in gouty patients have been reported. In this study, we investigated the associations between serum Hcy level and the other parameters including serum uric acid level, renal function, and cholesterol profiles in chronic gouty patients with longitudinal follow-up data.

Methods: Ninety-one male patients with chronic gout and 97 age-matched healthy male controls were included in this study, and the average age of each was 51.19 $\pm$ 15.08 and 51.57 $\pm$ 17.01 years old, respectively. Among them, 33 patients with gout and 39 healthy controls underwent follow-up tests for Hcy levels with 24.00 $\pm$ 9.12 months on average. Serum Hcy levels were measured by a competitive immunoassay using direct chemiluminescent. The estimated glomurular filtration rate (eGFR) was calculated using modification of diet in renal disease equation, and then chronic kidney disease (CKD) was defined as an eGFR below 60 ml/min/1.73m^2.

Results: In the serum uric acid level, there was no significant difference between chronic gouty patients and controls (6.15 $\pm$ 2.23 mg/dL vs 5.82 $\pm$ 1.22 mg/dL, $p = 0.214$). In contrast, gouty patients showed significantly higher levels in serum Hcy than those in controls (13.96 $\pm$ 4.05 μmol/L vs 12.67 $\pm$ 3.51 μmol/L, $p = 0.022$). In patients with chronic gout, serum Hcy level was negatively correlated with eGFR (γ= -0.413, $p < 0.001$), while it was uncorrelated with serum uric acid levels or cholesterol profiles. Serum Hcy levels were not different between the groups treated with allopurinol and with benzbromarone. When we observed the follow-up results in chronic gouty group, the change of serum Hcy level was positively correlated with the change of serum creatinine level ($\gamma = 0.560$, $p < 0.001$), and negatively correlated with the change of eGFR ($\gamma = -0.556$, $p < 0.001$). However the change of serum Hcy level was uncorrelated with the changes of uric acid level or the lipid profiles. The chronic gouty patients with CKD showed significantly higher serum Hcy level than those without CKD (17.45 $\pm$ 4.68 μmol/L vs 13.15 $\pm$ 3.46 μmol/L, $p < 0.001$), and the follow-up result also showed similar tendency (19.12 $\pm$ 4.29 μmol/L vs 15.69 $\pm$ 5.73 μmol/L, $p = 0.059$). In multiple linear analyses, serum Hcy level was affected by eGFR (β = -0.385, $p< 0.001$), however, was not affected by the serum uric acid level.

Conclusion: Serum Hcy level was elevated in chronic gouty patients than in controls. The change of serum Hcy level was negatively correlated with the change of eGFR. Hyperhomocysteinemia in chronic gouty patients was related with decreased renal function, and was not with serum uric acid or lipid profiles.

Disclosure: E. H. Park, None; **S. T. Choi**, None; **J. S. Song**, None.

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The Random Urine Uric Acid to Creatinine Ratio As a Predictor of 24-Hour Urine Uric Acid Excretion in Gout Patients. Sang Tae Choi, Jung-Soo Song and Eun-Hye Prark. Chung-Ang University College of Medicine, Seoul, South Korea.

Background/Purpose: Gout is an inflammatory disease resulted from an increased body pool of uric acid. The measurement of 24-hour uric acid excretion is important to evaluate the disease status as well as to select the

kind of uric acid lowering agents. However, 24-hour urine collection is inconvenient, and frequently unreliable due to errors in collection. The average person excretes approximately 1 g/day creatinine, and thus a lot of studies showed that the random urine protein to creatinine ratio was well correlated with 24-hour urine protein excretion rate. In this study, we investigated the utility of the random urine uric acid to creatinine ratio for predicting 24-hour urine uric acid excretion in gouty patients.

Methods: The cross-sectional study included 37 gouty patients without any use of uric acid lowering agents. The average age was 47.7 ± 17.7 years old and 34 out of 37 were male patients. 24-hour urine collections of the patients were conducted to the evaluate uric acid excretion and renal function. Random urine uric acid and creatinine specimens were obtained from all participants at the day when 24-hour urine collection was conducted. The creatinine clearance (CCr) was measured from the 24-hour urine collected sample, and chronic kidney disease was defined as the CCr levels below 60 ml/min/1.73m^2.

Results: The mean of 24-hour uric acid excretion was 602.4 ± 236.0 mg, and those of serum uric acid levels and CCr values were 7.31 ± 1.31 mg/dl and 100.9 ± 33.2 ml/min/1.73m^2, respectively. Random urine uric acid to creatinine ratio was closely correlated with the absolute and log transformed 24-hour urine uric acid excretions ($\gamma = 0.450$, $p = 0.005$;$\gamma = 0.474$, $p = 0.003$, respectively). In the linear regression analysis, the amount of absolute 24-hour urine uric acid excretion was estimated by 0.812 × (random urine uric acid to creatinine ratio) + 290.466 ($R^2 = 0.450$, $p = 0.005$). The correlation between random urine uric acid to creatinine ratio and 24-hour urine uric acid excretion was also found in the patients with chronic kidney disease ($\gamma = 0.900$, $p = 0.037$).

Conclusion: Random urine uric acid to creatinine ratio showed positive correlation with the absolute and log transformed 24-hour urine uric acid excretions. The random urine uric acid to creatinine ratio would be a good predictor of 24-hour urine uric acid excretion in gouty patients.

Disclosure: S. T. Choi, None; **J. S. Song**, None; **E. H. Park**, None.

1218

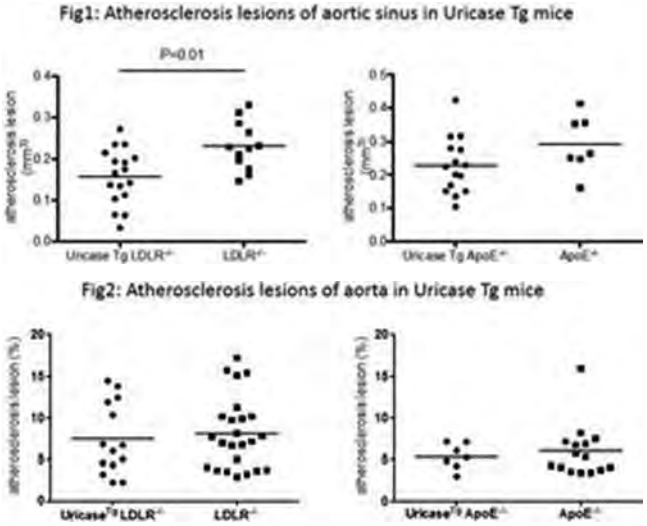
The Reduction of Serum Uric Acid Level Might Prevent Atherosclerosis in Mice. Yoshitaka Kimura[1], Tamiko Yanagida[2], Akiko Onda[2], Hajime Kono[2], Maki Takayama[2], Kurumi Asako[2], Akiko Okamoto[2], Hirotoshi Kikuchi[2] and Toshihiro Nanki[3]. [1]The University of Tokyo, Tokyo, Japan, [2]Teikyo University School of Medicine, Tokyo, Japan, [3]Teikyo University, Tokyo, Japan.

Background/Purpose: Excess amount of uric acid in human body causes acute inflammation, gout. In addition, uric acid is identified as a danger signal and is implicated in playing roles in chronic inflammatory processes. Recently several retrospective studies have reported that serum uric acid might be one of the independent risk factors of atherosclerosis. However there has been no prospective study showing the association of serum uric acid level and atherosclerosis. It's not still clear whether uric acid progresses atherosclerosis. Using the transgenic mice expressed uricase, an uric acid hydrolytic enzyme, we investigated the reduction of serum uric acid level could prevent atherosclerosis in mice.

Methods: We prepared uricase transgenic mice based in C57BL/6 mice. They expressed the urcase secreted to extracellular space and their serum uric acid level were decreased. We bred Uricase^{Tg} mice with LDL receptor deficient or apolipoprotein E deficient mice to develop LDLR$^{-/-}$Uricase^{Tg} mice or ApoE$^{-/-}$Uricase^{Tg} mice, respectively. LDLR$^{-/-}$Uricase^{Tg} mice, ApoE$^{-/-}$Uricase^{Tg} mice and control mice (LDLR$^{-/-}$ mice and ApoE$^{-/-}$ mice) at 6 weeks of age received high-fat diet for 16 weeks. Then their hearts and aortas were removed at 22 weeks of age. Aortic sinuses of these mice were fixed and sliced into 8 micrometer. We measured atherosclerosis area of each slice and computed volume of lesions of aortic sinus. Aortas of these mice were stained with oil red O and measured area of atherosclerosis lesions. We calculated ratio of the lesion area to whole aortic area.

Results: The volumes of atherosclerosis lesions in aortic sinuses of LDLR$^{-/-}$Uricase^{Tg} (0.158±0.016 mm^3) [n=17] were smaller than that of LDLR$^{-/-}$ (0.231±0.017 mm^3) [n=12] [p=0.0049]. There were no significant differences between ApoE$^{-/-}$Uricase^{Tg} (0.227±0.022 mm^3) [n=15] and ApoE$^{-/-}$ (0.292±0.032 mm^3) [n=7] [p=0.11]. The ratio of area of atherosclerosis in aorta was 7.4±1.2 % in LDLR$^{-/-}$Uricase^{Tg} [n=14], 8.1±0.9% in LDLR$^{-/-}$[n=24], 6.0±0.8% in ApoE$^{-/-}$Uricase^{Tg} [n=15] and 5.3±0.6% in ApoE$^{-/-}$ [n=7]. There were little differences between each group (LDLR$^{-/-}$Uricase^{Tg} vs LDLR$^{-/-}$Uricase^{Tg} [p=0.63], ApoE$^{-/-}$Uricase^{Tg} vs ApoE$^{-/-}$ [p=0.63]).

Conclusion: Although there was a discrepancy between atherosclerosis prone strains, the results showed that the reduction of serum uric acid level by expressing secretable uriase may inhibit the progression of atherosclerosis.



Disclosure: Y. Kimura, None; **T. Yanagida**, None; **A. Onda**, None; **H. Kono**, None; **M. Takayama**, None; **K. Asako**, None; **A. Okamoto**, None; **H. Kikuchi**, None; **T. Nanki**, None.

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Lack of Gene-Diuretic Interactions on Risk of Incident Gout: The Nurses' Health Study and Health Professionals Follow-up Study. Ying Bao[1], Tony R. Merriman[2], Gary Curhan[3], Eli A. Stahl[4], David B. Mount[1], Robert M. Plenge[1], Peter Kraft[5] and Hyon K Choi[6]. [1]Brigham and Women's Hospital, Boston, MA, [2]University of Otago, Dunedin, New Zealand, [3]Harvard Medical School, Boston, MA, [4]Mt Sinai School of Medicine, New York City, NY, [5]Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, MA, [6]Boston University School of Medicine, Boston, MA.

Background/Purpose: Diuretics, particularly thiazide and loop diuretics, increase the risk of gout, likely through urate transporters (e.g., OAT4) and volume depletion promoting urate reabsorption. As the prevalence of hypertension is remarkably high in gout patients (74% in the US general population), diuretic use is commonly encountered in gout care as a first line anti-hypertensive agent. A recent analysis based on 108 self-reported incident cases of gout in the Atherosclerosis Risk in Communities (ARIC) Study has reported that diuretic-induced gout occurs only among those with a genetic predisposition to hyperuricemia (*Ann Rheum Dis* 2013). If confirmed, those genes could potentially be used to predict gout from diuretic use, a first line agent for hypertension and congestive heart failure.

Methods: We examined the potential interaction between urate genes and diuretic use in relation to the risk of incident gout in 6788 women from the Nurses' Health Study (NHS) and 4012 men from the Health Professionals Follow-up Study (HPFS). Two genetic risk scores (GRS) were created from common urate SNPs for eight previously known genes (GRS8, used by the ARIC study above) as well as for 29 genes (GRS29, a new score incorporating additional novel genes). We ascertained incident gout cases using the American College of Rheumatology survey criteria. We used Cox proportional hazards models for associations and interactions of interest.

Results: Our study included 310 and 674 confirmed cases of incident gout in the NHS and HPFS cohorts, respectively. In the NHS, compared with no thiazide or loop diuretic use, their use was associated with a multivariate RR of 1.97 (95% CI 1.32 to 2.93) among those with a GRS8 below the median and 2.33 (95% CI 1.73 to 3.13) for those with a GRS8 above the median (p for interaction = 0.21) (**Table 1**). The corresponding RRs according to GRS29 categories were 1.89 (95% CI 1.28 to 2.79) for below the median and 2.39 (95% CI 1.77 to 3.24) for above the median (p for interaction = 0.33). Similarly, two previously purported genes, SLC2A9 (GLUT9) and SLC22A11 (OAT4), showed no significant interactions (p for interactions > 0.05). Corresponding analyses in the HPFS showed no significant interactions (**Table 1**) (all p values for interaction > 0.28). Further, the lack of interaction persisted in our analyses when limited to those with hypertension in both cohorts, except for SLC22A11

among women, which showed a significant interaction but in the opposite direction to that in the recent ARIC study.

Conclusion: These prospective studies based on a large number of incident cases of confirmed gout indicate that individuals with a genetic predisposition for hyperuricemia are not at an increased risk of developing diuretic-induced gout as compared with those without such a predisposition. These findings do not support the potential utility of these genes to assess gout risk in relation to diuretic use.

Table 1 Relative Risk for Incident Gout According to Diuretic Use and Genetic Urate Score Based on 8 Urate SNPs (GRS8) and 29 Urate SNPSs (GRS29)

	NHS					HPFS				
GRS8	Below median		Above median		P for interaction	Below median		Above median		P for interaction
Thiazide or loop diuretic use	No	Yes	No	Yes		No	Yes	No	Yes	
No. of Cases	73	53	120	108		229	38	404	56	
Person-Years	78216	13386	79389	12936		37835	1673	37533	1836	
Age adjusted	1.00	3.89 (2.69, 5.62)	1.00	4.81 (3.67, 6.31)	0.22	1.00	4.57 (3.08, 6.76)	1.00	3.10 (2.29, 4.20)	0.25
MV adjusted	1.00	1.97 (1.32, 2.93)	1.00	2.33 (1.73, 3.13)	0.21	1.00	2.19 (1.41, 3.40)	1.00	1.69 (1.20, 2.37)	0.28
GRS29	Below median		Above median		P for interaction	Below median		Above median		P for interaction
Thiazide or loop diuretic use	No	Yes	No	Yes		No	Yes	No	Yes	
No. of Cases	73	57	120	104		218	35	415	59	
Person-Years	78292	13585	79313	12737		37698	1705	37670	1805	
Age adjusted	1.00	4.04 (2.82, 5.79)	1.00	4.79 (3.65, 6.30)	0.38	1.00	4.19 (2.81, 6.23)	1.00	3.46 (2.56, 4.68)	0.48
MV adjusted	1.00	1.89 (1.28, 2.79)	1.00	2.39 (1.77, 3.24)	0.33	1.00	2.19 (1.40, 3.42)	1.00	1.88 (1.34, 2.63)	0.38

Adjusted for age, BMI, menopause (NHS), use of hormone therapy (NHS), history of hypertension, systolic and diastolic blood pressure, alcohol, total energy intake, and intake of sugar-sweetened soft drinks, meat, seafood, and dairy products.

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Higher Inflammatory Response in Elderly Patients during Gout Attack.

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Background/Purpose: Clinical experiences suggest that gout attacks in elderly patients are accompanied by stronger systemic inflammatory response including fever, higher C-reactive protein (CRP) and erythrocyte sediment ratio (ESR) as compared those in younger patients. As such, it is often difficult to differentiate them from septic arthritis, leading to frequent use of empiric antibiotics and unnecessary diagnostic and therapeutic joint surgery. To define whether gout attacks are accompanied by stronger systemic inflammatory response with age.

Methods: In this retrospective study, medical records of patients who were evaluated for a possible gout attack between January 2000 and April 2014 were examined. The presence of fever (>37.8°Æ), levels of C-reactive protein (CRP) and erythrocyte sediment ratio (ESR) on attack were compared between young (<50 years), middle aged (50- 65 years) and elderly patients (>65 years).

Results: Gout attacks were observed in 188 patients with 34 young, 54 middle aged and 100 elderly patients. Baseline characteristics of three groups differed; elderly patients had more comorbidities including diabetes mellitus ($p<0.001$), hypertension ($p<0.001$), coronary artery disease ($p=0.015$), cerebrovascular accident ($p<0.001$), and cancer ($p=0.031$) as compared other groups. The elderly patients had a low body mass index (BMI) (24.60 ± 4.65, 24.55 ± 3.30, 23.27 ± 3.12, $p=0.041$ by ANOVA) and longer disease duration (2.76 ± 5.16, 4.20 ± 6.13, 6.58 ± 9.23 years, $p=0.028$ by ANOVA).

Fever was more often present in the elderly patients (17.6% in young vs. 29.6% in middle aged vs. 50.0% in elderly, $p=0.001$ by chi-square test). Although numbers of involved joints during attacks did not differ between groups ($p=0.656$), CRP and ESR levels during gout attack increased significantly with age (Figure 1).

Conclusion: Since gout attacks in elderly patients are accompanied by stronger systemic inflammatory response, often resembling sepsis or septic arthritis, it is crucial to correctly diagnose them as gout so that unnecessary invasive diagnostics including joint lavage and prolonged antibiotic treatment can be avoided.

Key words: gout, age, elderly, fever

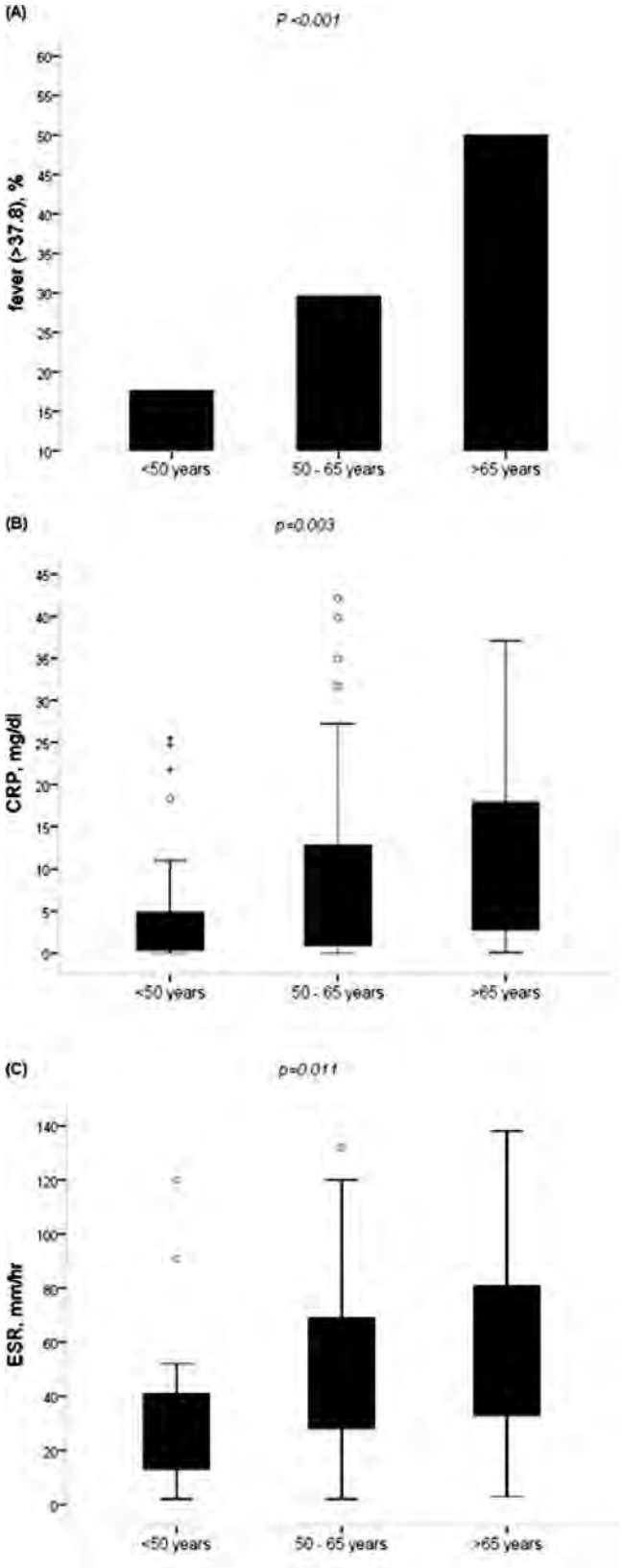

Figure 1. Differences in characteristics on gout attack among young (<50 years), middle aged (50 - 65 years) and elderly patients (>65 years). (A) Percentage of patient with fever (>37.8) (B) C-reactive protein (CRP) (C) Erythrocyte sedimentation ratio (ESR) were significantly higher in the elderly group.

Disclosure: J. A. Yang, None; **J. H. Lee**, None; **E. Y. Lee**, None; **E. B. Lee**, None; **Y. W. Song**, None; **J. K. Park**, None.

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Serum Uric Acid As an Independent Risk Factor on Progression of Chronic Kidney Disease in Gout Patients with Uric Acid Lowering Agent. Young Hyup Lim[1], Eun-Jung Park[1], Seulkee Lee[2], Hemin Jeong[3], Hyungjin Kim[4], Jinseok Kim[1], Jaejoon Lee[3], Hoon-Suk Cha[5] and Eun-Mi Koh[5]. [1]Department of Medicine, Jeju National University Hospital, Jeju University School of Medicine, Republic of Korea, Jeju, South Korea, [2]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, Seoul, South Korea, [3]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [4]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, Seul, South Korea, [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

Background/Purpose: Hyperuricemia is particularly common in patients with chronic kidney disease (CKD). Its role, however, as a risk factor for renal outcomes of CKD is debated. This aim of study was to evaluate long-term effect of serum uric acid (SUA) level on progression of CKD in gout patients with uric acid lowering treatment.

Methods: All patients who had a first visit for gout with CKD at Samsung Medical Center between 1995 and 2003, and follow-up until December 2012 or expired during follow-up period were included and retrospective analyzed. CKD was defined as an estimated glomerular filtration rate (GFR) of < 60 mL/min/1.73m^2 via MDRD Study equation more than 3 months. All serum creatinine and matched SUA taken during follow-up period were analyzed by using Mixed effect model to determine the effect of SUA level on renal outcome.

Results: One-hundred eleven gout patients with CKD were observed. The mean age of the patients at diagnosis of gout was 51.3 and mean follow-up duration was 13 years. Baseline eGFR and serum creatinine were 47.7 mL/min/1.73m^2 and 1.62 mg/dL, respectively. Maintaining the SUA below 6 mg/dL showed protective effect on serum creatinine and eGFR compared with SUA more than 6 mg/dL ($p < 0.0001$ and $p = 0.02$, respectively). Mixed effect model demonstrated that the protective effect on renal outcome with maintaining the SUA below 6 mg/dL was statistically significant after adjusting baseline age, follow-up time, hypertension, diabetes mellitus, history of cardiovascular disease, obesity, and intrinsic renal disease ($p < 0.0001$). Hypertension, diabetes mellitus and follow-up time were independently associated with progression of chronic kidney disease ($p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively). In particular, for every 1 mg/dL increase of the SUA, serum creatinine revealed to be increased 0.02 mg/dL when the SUA is more than 6 mg/dL ($p < 0.0001$).

Conclusion: Our long term follow-up data demonstrated the SUA level was associated with progression of CKD in gout patients. Maintaining of SUA level below 6 mg/dL would be essential to protect renal function in gout patients with CKD.

Disclosure: Y. H. Lim, None; **E. J. Park**, None; **S. Lee**, None; **H. Jeong**, None; **H. Kim**, None; **J. Kim**, None; **J. Lee**, None; **H. S. Cha**, None; **E. M. Koh**, None.

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Suppressive Effect of Butyrate on Monosodium Urate (MSU) Crystal-Induced IL-1 beta Production Is Mediated Via Inhibition of Class I Histone Deacetylases. Maartje Cleophas[1], Tania Crisan[2], Heidi Lemmers[3], Helga Toenhake-Dijkstra[2], Gianluca Fossati[4], Tim Jansen[2], Charles Dinarello[5], Mihai Netea[2] and Leo Joosten[2]. [1]Radboud Unversity Medical Center, Nijmegen, Netherlands, [2]Radboud University Medical Center, Nijmegen, Netherlands, [3]Radboud Univeristy Medical Center, Nijmegen, Netherlands, [4]Italfarmaco, Cinisello Balsamo, Italy, [5]University of Colorado, Denver, CO.

Background/Purpose: Gouty arthritis is triggered by endogenously formed monosodium urate (MSU) crystals. MSU crystals alone are unable to induce cytokine production and therefore a second stimulus is needed to induce the release of active interleukin (IL)-1β, the dominant cytokine in acute gout. Toll-like receptor (TLR) ligands such as LPS or saturated free fatty acids (FFA) can provide such a second signal and stimulate transcription of pro-IL-1β. In contrast to FFA, which can act as second signal for MSU-mediated cytokine production, the short-chain fatty acid butyrate has many anti-inflammatory effects. One of the possible mechanisms involved is inhibition of histone deacetylases (HDACs). Here, we explored the effects of butyrate on MSU/FFA-induced cytokine production and its inhibition of several specific HDACs.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from healthy donors or gouty arthritis patients and stimulated for 24 hours with MSU and palmitic acid (C16.0) in the presence or absence of butyrate or the synthetic HDAC inhibitors. Cytokine responses were measured with specific ELISAs and quantitative PCR. Effects on HDAC activity were measured with a fluorimetric cellular assay kit.

Results: Butyrate decreased C16.0/MSU-induced production of IL-1b, IL-6, and IL-8, as well as the transcription of IL-1b mRNA. Similar results were obtained when PBMCs isolated from gout patients were exposed to butyrate and C16.0/MSU. Butyrate selectively inhibited class I HDACs, but the strongest inhibition was found for HDAC8. However, the selective HDAC8 inhibitor ITF-A did not decrease ex-vivo C16.0/MSU-induced IL-1b production. The pan HDAC inhibitor Panobinostat and the HDAC inhibitor ITF-B significantly decreased C16.0/MSU-induced IL-1b production. Interestingly, the dose-response curves of butyrate and ITF-B are very different between PBMC's stimulated with C16.0/MSU or with LPS.

Conclusion: Butyrate and ITF-B have in common that they both inhibit class I HDACs and potently inhibit C16.0/MSU-induced IL-1b production. ITF-B also inhibits HDAC10 and -11, but the effect on C16.0/MSU- and LPS-induced IL-1b production is strikingly similar to that of butyrate. Therefore we conclude that the effect of butyrate on C16.0/MSU-induced cytokine production is mediated through class I HDAC inhibition. In contrast to the high concentrations of butyrate needed for cytokine suppression, synthetic HDAC inhibitors show potent anti-inflammatory effects at low concentrations. These novel HDAC inhibitors could be effective in the treatment of acute gout. Moreover, the use of specific HDAC inhibitors could even improve the efficacy and reduce any potential adverse effects.

Disclosure: M. Cleophas, None; **T. Crisan**, None; **H. Lemmers**, None; **H. Toenhake-Dijkstra**, None; **G. Fossati**, None; **T. Jansen**, Abbvie, 2, UCB, 2, Abbvie, 5, AstraZeneca, 5, UMS, 5, Janssen Pharmaceutica Product, L.P., 5, Menarini, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, Abbvie, 8; **C. Dinarello**, None; **M. Netea**, None; **L. Joosten**, None.

1223

Enhancement of Proinflammatory Cytokine Production By Uric Acid in Human Cells Via Down Regulation of IL-1Ra. Tania Crisan[1], Maartje Cleophas[2], Heidi Lemmers[3], Helga Toenhake-Dijkstra[1], Mihai Netea[1], Tim Jansen[1] and Leo Joosten[1]. [1]Radboud University Medical Center, Nijmegen, Netherlands, [2]Radboud Unversity Medical Center, Nijmegen, Netherlands, [3]Radboud Univeristy Medical Center, Nijmegen, Netherlands.

Background/Purpose: Gout is an autoinflammatory disease characterized by the deposition of monosodium urate (MSU) crystals in the joints of hyperuricaemic patients and subsequent attacks of severe gouty arthritis. Major lines of research investigating the proinflammatory effects of uric acid have been mainly focusing on MSU crystal-induced processes that come into role once uric acid reaches supersaturation. However, some indications exist that uric acid can directly have pro-inflammatory effects. In this study we investigate the effects of high uric acid exposure on the cytokine production of primary human immune cells upon stimulation with MSU crystals and synergizing agents.

Methods: Peripheral blood mononuclear cells (PBMCs) were harvested from gout patients and healthy volunteers. Cells were pre-treated with uric acid, allantoin or left untreated for 24h and then subjected to 24h stimulation with TLR2 or TLR4 ligands in the presence or absence of MSU. Cytokine production was assessed using specific sandwich ELISA kits. mRNA levels were measured using quantitative real-time PCR.

Results: MSU crystals stimulation alone did not induce detectable levels of IL-1β or IL-6 neither in patients nor in controls, however, synergy was present between MSU and Pam3Cys or LPS. Of high importance, higher levels of IL-1β and IL-6 were seen in patients compared to controls. An enhanced pro-inflammatory cytokine production was also observed when cells were specifically pretreated with uric acid, together with a significant down regulation of IL-1Ra but not IL-10. This observation correlated with mRNA levels for these cytokines observed in uric acid pre-treated cells.

Conclusion: In this study we propose a mechanism in which high uric acid concentrations might influence inflammatory responses by facilitating IL-1β production in immune cells. We show that a mechanism for the amplification of IL-1β consists in downregulation of IL-1Ra production that has the role of counterbalancing IL-1β auto-induction loop. As a consequence, patients having hyperuricaemia could be at risk of exhibiting increased vulnerability upon encounter of acute inflammatory stimuli and this might induce enhanced states of inflammation.

Disclosure: T. Crisan, None; **M. Cleophas**, None; **H. Lemmers**, None; **H. Toenhake-Dijkstra**, None; **M. Netea**, None; **T. Jansen**, Abbvie, 2, UCB, 2, Abbvie, 5, AstraZeneca, 5, UMS, 5, Janssen Pharmaceutica Product, L.P., 5, Menarini, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, Abbvie, 8; **L. Joosten**, None.

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Pegloticase for Tophus Debulking: Comparison of Dual Energy Computerized Tomography (DECT), Musculoskeletal Ultrasound (MSK-US) and Topographic Caliper Measurement for Assessing Debulking Rate. Dodji Modjinou[1], Elaine Karis[2], Soterios Gyftopoulos[3], Jonathan Samuels[4], Robert T. Keenan[5], Daisy Bang[6], Kristen Lee[4], Svetlana Krasnokutsky-Samuels[6], Daria B. Crittenden[7] and Michael H. Pillinger[7]. [1]NYU/HJD, New York, NY, [2]pending, pending, NY, [3]NYU Langone Medical Center/NYU Hospital for Joint Diseases, New York, NY, [4]NYU Langone Medical Center, New York, NY, [5]Duke University, Durham, NC, [6]NYU School of Medicine, New York, NY, [7]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Pegloticase is approved for lowering serum urate (sUA) in chronic refractory tophaceous gout (CRTG), but the rate of tophus resolution is not well defined, in part owing to limitations of measurement techniques. DECT permits 3-dimensional reconstruction and volumetric assessment of tophi, but comparisons between DECT and other imaging modalities are limited. We conducted an n-of-1 pilot study comparing DECT, MSK-US and surface caliper measurement to assess the rate of tophus debulking during pegloticase treatment.

Methods: A 32-year old male with a 10 year history of CRTG underwent a 13-infusion, twice-monthly course of pegloticase 8 mg, with sUA assessment prior to each infusion. Monthly caliper measurements of 3 index tophi, photographs and MSK-US imaging (gray scale, 18 mHz probe) every 3 months, as well as DECT and X-Rays (pre-/post-treatment) of the hands and feet were performed and compared.

Results: 8 tophi were noted on physical exam of the hands and feet, with 3 selected as index tophi. Whereas physical exam identified 4 tophi on the right hand, DECT revealed 15; whereas X-ray identified a single erosive lesion in the right hand, DECT identified 4 more in the feet. Pegloticase persistently lowered the patient's sUA to <0.5 mg/dL. Caliper measurements at the start and end of treatment revealed 73, 60, & 63% reductions of the index tophi, while MSK-US showed 29, 80, and 41% reductions of the same tophi, respectively. In contrast, DECT revealed 100% resolution of all 3 index tophi, and resolution/improvement of all other tophi identified. Initial DECT images revealed a composite tophus volume of 2,170 mm^3 on the right hand and 900mm^3 on the left; each decreased to 130 $mm^3$by study completion. On caliper measurement, the size of the index tophi fluctuated over time despite overall reduction. On MSK-US, some individual tophi appeared to "soften" and expand initially, followed by overall size reduction.

Conclusion: Pegloticase rapidly reduced all tophi assessed. While all assessment modalities were informative, correlation between them was poor, probably relating to the fact that calipers and MSK-US measure tophus area in non-congruent, perpendicular planes, whereas DECT measures volume. As previously reported, DECT identified occult urate deposition not visible on physical exam. Interestingly, tophi may fluctuate in size, even transiently increasing, during the process of resolution, revealed on ultrasound as tophus "softening" and loss of structure. Moreover, DECT imaging indicated that some urate deposits fully resolved even as their visible/palpable lesions persisted, possibly because of persistence of soft tissue swelling and/or fibrosis. We conclude that urate resorption begins early in the course of pegloticase therapy, but may be hard to recognize because of fluctuating volumes. While all imaging modalities have value, DECT is superior for identifying total (including occult) urate deposition, assessing absolute volume of deposits, and confirming urate resolution, even when soft tissue swelling persists. DECT may therefore be particularly valuable for determining the end point of pegloticase therapy.

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ACR/ARHP Poster Session B
Miscellaneous Rheumatic and Inflammatory Diseases
Monday, November 17, 2014, 8:30 AM–4:00 PM

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Clinical Presentation and Cytokine Production Abnormalities in a Cohort of Patients Carrying NLRP12 GENE Variants. Antonella Insalaco[1], Luigi Raganelli[2], Manuela Pardeo[2], Virginia Messia[2], Denise Pires Marafon Jr.[2], Francesca Romana Lepri[2], Elisa Pisaneschi[2], Claudia Bracaglia[1], Valeria Gerloni[3], Rebecca Nicolai[2], Elisabetta Cortis[4], Fabrizio De Benedetti Sr.[1] and Giusi Prencipe[1]. [1]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, [2]Ospedale Pediatrico Bambino Gesù, IRCCS, Roma, Italy, [3]Istituto Ortopedico Gaetano Pini, Milano, Italy, [4]Santa Maria della Stella Hospital, Orvieto, Italy.

Background/Purpose: The NLRP12 related autoinflammatory disorder (NLRP12-RD) is a rare autosomal dominant disease, caused by mutations in the NLRP12 gene.Clinical manifestations are extremely heterogeneous. We describe clinical features and inflammatory response of a cohort of patients carrying different NLRP12 variants, some of which not yet described as being associated with NLRP12-RD.

Methods: Twelve caucasian patients(6 males)carrying NLRP12 variants were identified. Blood samples obtained from 9/12 NLRP12 patients and from 7 active Juvenile idiopathic arthritis(JIA) patients were stimulated ex vivo with 1 mg/ml of Zymosan for 22h. Whole blood RNA analysis was also performed, using a human immune array(TaqMan® Human Immune Array from Applied Biosystems),containing 92 genes typically involved in the immune response.

Results: The median age at symptoms onset was 11,4 months(IQR 4,6–35,2)and the median of disease duration was 6,8 years(IQR 4,1–11). Sequencing of NLRP12 gene in the 12 patients revealed 5 heterozygous mutations:F402L(n=6),G448A(n=1),H304Y(n=1),R1030G(n=1) and G39V(n=1). Two patients were homozygous for NLRP12 variants:F402L and G39V. In 6/12 variants of NLRP3 were also found:Q703K(n=4) and V198M(n=2). All patients had symptoms consistent with a recurrent inflammatory syndrome:11/12 presented recurrent episodes of skin lesions,11/12 arthralgia,10/12 recurrent fever episodes,8/12 arthritis,10/12 headache,11/12 fatigue,5/12 conjunctivitis,7/12 recurrent abdominal pain and lymphadenopathy,5/12 oral aphthosis,4/12 thoracic pain and 2/12 sensorineural deafness. During the attacks 5/12 patients showed increased acute phase reactants. In 5/12 patients anakinra was administered because of the severity of phenotype and the persistence of elevated acute phase reactants. In 2 of these 5 patients lack of efficacy led withdrawal of anakinra and introduction of tocilizumab with good response. In vitro cytokine release studies, performed in 9 patients, showed that the production of IL-6 and TNF-α was significantly higher in patients carrying the NLRP12 variants compared to patients with JIA (IL-6:2841$\pm$1682 ng/ml and 1496$\pm$982.4 ng/ml versus 498.8$\pm$338.7 ng/ml and 226.6$\pm$111.8 ng/ml respectively;p=0.0002 and p=0.007)and even higher in homozygous patients;no significant difference in IL-1β production was found(2134 $\pm$ 1026 ng/ml versus 1527$\pm$930.3 ng/ml, p=0.29). Whole blood RNA samples collected from 5 NLRP12 patients were compared to 6 whole blood RNA samples collected from healthy controls comparable for age. At basal level, we did not find significant differences in the expression of 92 genes evaluated.

Conclusion: Our data in vitro and in vivo suggest that these NLRP12 variants are pathogenic. The role played by the concomitant presence of the NLRP3 variants remains to be clarified, though an effect in modifying the disease phenotype cannot be excluded. Our data also confirm the clinical and functional heterogeneity of NLRP12 related disorder, a condition often misunderstood. Furthermore, although the small number of patients treated, our data suggest that inhibition of IL-6 may be effective in NLRP12-related disorder.

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1226

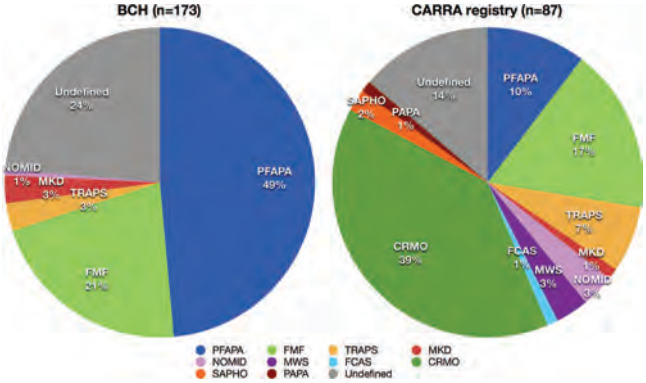
Studying Patients with Autoinflammatory Diseases: The Past, Present, and a Perspective for the Future. Jonathan S. Hausmann[1], Catherine Biggs[2], Donald P. Goldsmith[3] and Fatma Dedeoglu[4]. [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Boston Children's Hospital, Boston, MA, [3]St Christopher's Hospital for Children/Drexel College of Medicine, Philadelphia, PA, [4]on behalf of CARRAnet Investigators, Palo Alto, CA.

Background/Purpose: Autoinflammatory diseases (AIDs) are uncommon disorders characterized by recurrent episodes of systemic and organ-specific inflammation. Because of their rarity, finding large numbers of patients to study has been challenging. This project will compare the results of a retrospective chart review of patients with AIDs at a single academic medical center, with those of participants within the Childhood Arthritis and

Rheumatology Research Alliance (CARRA) Registry, a multicenter observational pediatric rheumatic disease registry in North America.

Methods: Patients with a clinical or genetic diagnosis of AID were included in this study. A retrospective chart review was conducted at Boston Children's Hospital (BCH) from 2002–2012. Charts were identified by keywords and billing codes related to AIDs and recurrent fevers. We also conducted a cross-sectional study of children with AIDs enrolled in the CARRA registry from May 2011 to December 2013.

Results: At BCH,173 subjects with AIDs were identified. In the CARRA registry, of 9,523 subjects enrolled, 87 patients were classified as having AIDs. The frequency of diagnoses are found in Figure 1.



Conclusion: Using the traditional methodology of a single-center retrospective chart review, we described the patients with AIDs seen at BCH, and estimated the frequency of various AIDs within this population. This research required little cost and relatively little time. Limitations included incomplete documentation in some cases, and the variety of AIDs identified was limited.

The CARRA registry, on the other hand, was a modern, multicenter effort that allowed enrollment of patients from multiple sites at a faster rate, and with a greater variety of diagnoses. However, this registry required significant financial investments in technology and operational costs. The fact that PFAPA, the most common pediatric AID, represented a minority of subjects within the CARRA registry suggests that physicians enrolled a select number of patients, possibly due to the time required for the consent, enrollment, and data-uploading processes.

Integration of registries into the patient's electronic health records will potentially minimize the current barriers to research. In addition, we believe that online patient communities can also contribute valuable information. In future studies, we plan to empower and engage patients with AIDs through social media to collaborate in the design and implementation of research studies. Our efforts could exponentially expand the number of patients available to participate in research, and help our understanding of these complex disorders.

Disclosure: J. S. Hausmann, None; **C. Biggs**, None; **D. P. Goldsmith**, None; **F. Dedeoglu**, None.

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Cryopyrinopathy with a Myeloid-Specific *NLRP3* Mutation. Patrycja Hoffmann[1], Qing Zhou[2], Amanda Ombrello[2], Anne Jones[2], Beverly Barham[2], Ivona Aksentijevich[1] and Daniel L. Kastner[1]. [1]National Human Genome Research Institute, Bethesda, MD, [2]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD.

Background/Purpose: To identify the cause of disease in an adult patient who presented with recurrent fevers and urticaria which responded to IL-1 inhibition with anakinra. She was negative for *NLRP3* mutations based on conventional sequencing.

Methods: A 52 year-old perimenopausal pediatrician presented to the NIH with new-onset episodes of urticarial rash, fever, chills, fatigue, arthralgia, and myalgia. A skin biopsy revealed neutrophilic infiltrates. She recalled a similar urticarial rash as a child, which resolved at puberty. Prior treatments included colchicine, prednisone, IVIG, antihistamines, H2 blockers, high dose aspirin, and hydroxychloroquine, without significant benefit. The patient was started on anakinra 100 mg daily, and eventually increased to 300 mg daily. Frequency and duration of flares and diagnostic biomarkers, including CRP, ESR, and WBC, were recorded before starting anakinra and for eleven years afterwards. Whole-exome sequencing, targeted deep resequencing of *NLRP3* in peripheral blood and buccal cells, and mutational screening in subcloned amplicons from skin fibroblasts, buccal cells, and flow-sorted monocytes, granulocytes, T lymphocytes, and B lymphocytes, was performed to interrogate the possibility of somatic mutations in *NLRP3*.

Results: Prior to starting anakinra, flares occurred every 2–3 days lasting less than 24 hours. A stress-induced erythematous rash was the predominant symptom during flares, along with constitutional symptoms, arthralgia, and myalgia. During flares the CRP was elevated at 16.5 mg/L, and the WBC was slightly elevated at 9.860 K/uL. After starting anakinra, there was immediate resolution of rash, constitutional symptoms and normalization of inflammatory markers. WBC also normalized at 5.060 K/uL. Whole- exome sequencing identified a previously reported CAPS-associated mutation, p.Tyr570Cys, with a mutant allele ratio of 15% in whole blood. Targeted deep sequencing of *NLRP3* in blood and buccal cells demonstrated similar levels of mosaicism, but only in the peripheral blood. We then analyzed 192 colonies each from subcloned amplicons derived from monocytes, granulocytes, T lymphocytes, B lymphocytes, fibroblasts, and buccal cells. This confirmed the presence of the mosaic mutation at a ratio similar to the exome data in monocytes and granulocytes but not in lymphocytes, cultured fibroblasts, or buccal cells.

Conclusion: To our knowledge this abstract represents the first report documenting lineage-specific *NLRP3* mosaicism, established by subcloning amplicons from six different cell types. The patient's initial presentation of urticarial rash before puberty and reoccurrence during menopause along with constitutional symptoms, arthralgia and myalgia was not classic for Muckle-Wells syndrome, however the clinical presentation was suggestive of a cryopyronpathy. The molecular demonstration of lineage-specific *NLRP3* mosaicism, taken together with the clinical response to anakinra, confirm the diagnosis of cryopyrinopathy, and underscore the emerging role of massively-parallel sequencing in clinical diagnosis.

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Involvement of the IFN-Õ Pathway in a Patient with Candle Syndrome Carrying a Novel Variant of PSMB8 Gene. Antonella Insalaco[1], Giusi Prencipe[1], Manuela Pardeo[2], Virginia Messia[2], Andrea Masotti[2], Cristina de Min[3], Claudia Bracaglia[1], Rebecca Nicolai[2], Ivan Caiello[1] and Fabrizio De Benedetti Sr.[1]. [1]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, [2]Ospedale Pediatrico Bambino Gesù, IRCCS, Roma, Italy, [3]Novimmmune S.A., Plan-Les-Ouates, Geneva, Switzerland.

Background/Purpose: Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome is a newly described autoinflammatory disease. We describe clinical phenotype and cytokine profile of our patient.

Methods: A 10 years-old young girl presented at 10 months of age with recurrent fever, hepatosplenomegaly and nodular erythematous skin lesions; she progressively developed lypodistrophy, arthralgia, arthritis and edema of eyelids. Skin biopsy showed features of lobular panniculitis. Laboratory tests showed persistent elevated acute phase reactants with anemia, recurrent leucopenia, thrombocytopenia and hypogammglobulinemia. Immunological and cytogenetic studies performed on bone marrow were normal. Subsequently, the patient developed nephrotic syndrome. Renal biopsy revealed a minimal change glomerulopathy responsive to high-dose glucocorticoid. Response to hydroxychlorochine, colchicine, cyclosporine-A, and anakinra was unsatisfactory. Complete sequencing of TNFRSF1A and MVK genes showed no mutations. Analysis of the PSMB8 (proteasome subunit β type 8) gene revealed the presence of c.220A>T p.(T74S) variant in heterozygotic status that has never been reported before. In order to assess the dysregulated inflammatory response, we evaluated the cytokine profile in patient's sera using the Luminex multiplexing assay. Whole blood RNA analysis was also performed using a human immune array (TaqMan® Human Immune Array from Applied Biosystems), containing 92 genes typically involved in the immune response.

Results: Serum samples (n=4) were collected during the last two years. We found high levels of IFNγ (mean $\pm$ S.D.: 115.3 pg/ml $\pm$ 64.21), of IFNγ inducible protein 10 (IP-10, also called CXCL10) (1641$\pm$ 892.5 pg/ml) and of IFNγ inducible protein 9 (IP-9, also called CXCL11) (582.9$\pm$ 335.6 pg/ml) and especially of CXCL9, also known as monokine induced by γ-interferon (MIG) (18161$\pm$ 6405 pg/ml), compared to healthy controls or pediatric patients with sJIA during active disease. Two whole blood RNA samples collected from our Candle patient were compared to 6 whole blood RNA samples collected from healthy controls comparable for age. We obtained results consistent with those obtained by serum cytokine measurement: IFNγ, CXCL10 and CXCL11 mRNA expression were significantly increased compared to healthy controls (1.88, 32.7 and 4.1 fold higher

respectively). We also found that the expression of the HLA-DRB1, a gene whose expression is known to be induced by IFNγ, was markedly upregulated (> 100.000 fold increase) compared to healthy controls.

Conclusion: we describe a typical CANDLE clinical phenotype in the absence of biallelic mutations of PSMB8 gene. The presence of high levels of IFNγ and of IFNγ related chemokines points to a major pathogenic role of the IFNγ pathway, which appears to be similar to what has been recently reported in CANDLE (Liu et al). The pathogenic role of the variant T74S remains to be elucidated:a potential role is suggested by its presence in a patient with a classical phenotype and with a dysregulation of the IFNγ pathway, taking also into account that this variant is close to the know pathogenic mutation T75M.

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Is NOD2-Associated Autoinflammatory Disease Remotely Related to Familial Mediterranean Fever or Continuum of It? Min Shen, Bo Shen and Qingping Yao Cleveland Clinic, Cleveland, OH.

Background/Purpose: NOD2-associated autoinflammatory disease (NAID) is a newly described autoinflammatory disease characterized by periodic fever, dermatitis, polyarthritis, gastrointestinal and sicca symptoms. It is genotypically associated with NOD2. Its clinical phenotype may superficially resemble familial Mediterranean fever (FMF). We report a case series to illustrate the similarities and differences between these two autoinflammatory diseases.

Methods: Three patients with NAID or FMF were cared for by the authors between 2012 and 2014, and their phenotypes and genotypes were retrospectively studied. Genetic testing for MEFV and NOD2 mutations was performed.

Results: The clinical phenotypes and genotypes of these patients are summarized (Table). Patient 1 presented with recurrent fever, abdominal pain/diarrhea, chest pain, and arthralgia since the age of 5 years. Her symptoms responded well to colchicine, and FMF was diagnosed in the presence of heterozygous K695R. Patient 2 is the niece of patient 1 and presented with symptoms since the age of 17 years and shared the similar phenotypes with her aunt except the presence of recurrent erythematous patches of the skin and longer lasting gastrointestinal symptoms. FMF was suspected, but she had a transiently mild response to colchicine. Genetic testing identified the NOD2 mutations IVS8+158 and R702W and negative MEFV. NAID was diagnosed with a complete response to oral sulfasalazine. Patient 3 is a man and presented with recurrent fever and abdominal pain/diarrhea since the age of 17 years, with mild response to colchicine. Genetic testing identified heterozygous M694V in the MEFV and NOD2 mutation IVS8+158.

Conclusion: Both NAID and FMF appear similar phenotypically, but they are distinct. The symptoms can last longer than 3 days, and spongiotic dermatitis is common in NAID, whereas erysipelas-like erythema with sparse infiltrate on the lower extremities is a feature of FMF. NAID does not respond to colchicine. Both MEFV and NOD2 genes are located on chromosome 16 and share similar gene structures. This case study suggests that these two diseases could be remotely related.

Disclosure: M. Shen, None; **B. Shen**, None; **Q. Yao**, None.

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Efficacy of Interleukin-1 Targeting Drugs in Familial Mediterranean Fever Patients. Pinar Cetin[1], Ismail Sari[1], Betul Sozeri[2], Ozlem Cam[2], Merih Birlik[1], Fatos Onen[1], Nurullah Akkoc[1] and Servet Akar[1]. [1]Dokuz Eylul University School of Medicine, Izmir, Turkey, [2]Ege University School of Medicine, Izmir, Turkey.

Background/Purpose: Familial Mediterranean fever (FMF) is an autosomal-recessive autoinflammatory disorder characterized by recurrent episodes of fever accompanied by sterile peritonitis. The most devastating complication of FMF is the development of secondary amyloidosis which has a potential risk for developing end stage renal disease. However cholchicine is the most effective treatment regimen in FMF patients, 5–10% of patients are refractory. However, there are several drugs being tested in this group of patients. The most promising group of drugs appears to be the anti-IL-1 therapies. The objective of this study is to demonstrate the efficacy of anakinra and canakinumab in FMF patients who followed up in our outpatient clinics.

Methods: In this study we included 20 cholchicine resistant FMF patients (16 adults and 4 children) diagnosed according to the Tel–Hashomer or Sheba Medical Center criteria, who are receiving anti-IL-1 treatments (anakinra n= 12 or canakinumab n= 8). A retrospective review of medical records of anti-IL-1 recipients was performed. The main clinical characteristics of these patients and their genotypes for MEFV gene and the evolution after anti-IL-1 were recorded laboratory response was evaluated with erythrocyte sedimentaion rate(ESR) and C-reactive protein (CRP).

Results: The median age of patients was 23 (14–50), the median disease duration was 16 years (4–46) and the median follow up time in clinic was 12 years (1–26). 16 were homozygous for the M694V mutation. Attacks per month and year were significantly decreased after anti IL-1 theraphy $p < 0.05$ (Table 1). The median follow-up of the anakinra and canakinumab patients were 14 (4–36) and 18 (4–25) months respectively ($p = 0.51$). All patients were also receiving background colchicine with a median dose of 1.5 mg. there is a trend towers a decreasing dose of colchicine after anti-IL-1. Acute phase responses were aslo significantly decreased after IL-1 treatments ($p < 0.05$, Table 1). Besides the effectiveness on acute attacks we also noted significant decreases in proteinuria in patients with amyloidosis (9 gr to 3.7 gr/day in the adult and 25.6 mg/m^2/hour to 12 mg/m^2/hour in the pediatric patient). In a median 16 months of follow-up there were only one serious adverse event (pneumonia) in a patient receiving anakinra therapy However, after antibiotic treatment we resumed treatment in this patient.

Conclusion: In this study we revealed that 95% of our colchicine-resistant patients responded to the anti-IL-1 targeting agents. These drugs tolerated well and only one patient had serious adverse events during the 16 months of follow-up. We also noted significant ameloration of proteinuria in amyloidosis patients. IL-1 receptor antagonists anakinra and canakunimab seem to be safe and effective treatment options in colchicine-refractory FMF patients.

Table 3: Number of attacks and acute phase protein levels before and after anti-IL-1 treatment

	Attacks/mo (Before treatment)	Attacks/mo (After treatment)	*p*	Attacks/year (Before treatment)	Attacks/year (After treatment)	*p*
Anti-IL-1 (n:20)	1.5 (1–4)	0 (0–3)	<0.0001	15 (5–50)	0.5 (0–24)	0.001
Anakinra (n:12)	2.5 (1–4)	0 (0–3)	0.003	30 (12–50)	2 (0–24)	0.018
Canakunimab (n:8)	1 (1–2)	0	0.007	10 (2–20)	1 (0–2)	0.018
	CRP mg/l (Before treatment)	**CRP mg/l (After treatment)**	***p***	**ESR mm/h (Before treatment)**	**ESR mm/h (After treatment)**	***p***
Anti-IL-1 (n:20)	52.5 (5–195)	4.5 (0.6–53)	<0.0001	41 (8–110)	12 (5–100)	<0.0001
Anakinra (n:12)	43.3 (5–195)	5 (0.7–53)	0.003	42 (8–110)	14 (5–100)	0.004
Canakunimab (n:8)	52.5 (5.4–140)	3.7 (0.6–7)	0.001	37 (14–57)	11 (6–55)	0.001

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Evidence Based Recommendations for Genetic Diagnosis of Familial Mediterranean Fever. Gabriella Giancane[1], Nienke ter Haar[2], Nico Wulffraat[3], Bas Vastert[2], Karyl Barron[4], Veronique Hentgen[5], Tilmann Kallinich[6], Huri Ozdogan[7], Jordi Anton[8], Paul Brogan[9], Luca Cantarini[10], Joost Frenkel[2], Caroline Galeotti[11], Marco Gattorno[12], Gilles Grateau[13], Michael Hofer[14], Isabelle Kone-Paut[11], J B. Kuemmerle-Deschner[15], Helen Lachmann[16], Anna Simon[17], Brian Feldman[18], Yosef Uziel[19] and Seza Ozen[20]. [1]UMC, Utrecht, Netherlands, Utrecht, Netherlands, [2]University Medical Center Utrecht, Utrecht, Netherlands, [3]Wilhelmina Children's Hospital/UMC Utrecht, Utrecht, Netherlands, [4]NIH, Bethesda, MD, [5]Versailles Hospital, Le Chesnay Cedex, France, [6]Charite, University Medicine Berlin, Berlin, Germany, [7]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [8]Pediatric Rheumatology Unit. Hospital Sant Joan de Déu. Universitat de Barcelona, Barcelona, Spain, [9]Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [10]University of Siena, Siena, Italy, [11]Bicêtre Hospital, University of Paris SUD, Paris, France, [12]Istituto Giannina Gaslini, Genova, Italy, [13]Hopital Tenon, Paris, France, [14]Centre Multisite Romand de Rhumatologie Pediatrique, Lausanne, Switzerland, [15]University Hospital Tuebingen, Tuebingen, Germany, [16]University College London Medical School, London, United Kingdom, [17]Radboudumc, Nijmegen, Netherlands, [18]The Hospital for Sick Children, Toronto, ON, [19]Tel-Aviv University, Sackler School of Medicine, Tel-Aviv, Israel, [20]Deptartment. of Pediatric Rheumatology, Hacettepe University, Ankara, Turkey.

Background/Purpose: Familial Mediterranean Fever (FMF) is a disease that starts in childhood and can lead to significant morbidity. In 2013, an initiative called SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) has been launched for children and young adults with rheumatic diseases. For FMF, attention was focused on genetics. The aim of the SHARE recommendations in FMF is to provide a diagnostic tool for inexperienced pediatric rheumatologists to cope with FMF in their clinical practice. This is possible through a correct interpretation of the diagnostic value of *MEFV*mutations in predicting FMF phenotype.

Methods: An expert committee was instituted, consisting of pediatric rheumatologists, and search terms for the systematic literature review were defined. Two independent experts scored articles for validity and level of evidence. Recommendations derived from the literature were evaluated by an online survey. Those with less than 80% agreement during the online survey were reformulated. Subsequently, all recommendations were discussed at a consensus meeting using the nominal group technique. Recommendations were accepted if more than 80% agreement was reached.

Results: The literature search yielded 3386 articles, of which 25 considered relevant and therefore scored for validity and level of evidence. 17 articles were scored valid and used in the formulation of the recommendations. 8 recommendations were finally accepted with 100% agreement after the consensus meeting (Table 1). Topics covered for diagnosis were: clinical versus genetic diagnosis of FMF; genotype-phenotype correlation; genotype-age at onset correlation; silent carriers and risk for amyloidosis; role of the specialist in FMF diagnosis.

Conclusion: The SHARE initiative provides recommendations for the diagnosis of FMF and thereby facilitates improvement and uniformity of care.

FMF Recommendations

1. FMF is a clinical diagnosis, which can be supported but not excluded by genetic testing.
2. Consider patients homozygotes for M694V at risk of developing, with very high probability, a severe phenotype.
3. FMF patients carrying two of the common mutated alleles (homozygotes or compound heterozygotes), especially for M694V mutation or mutations in the position 680 to 694 on exon 10, must be considered at risk of having a more severe disease than those carrying only one mutated allele (heterozygotes).
4. The E148Q variant is common, of unknown pathogenic significance and as the only MEFV variant does not support the diagnosis of FMF.
5. Patients homozygous for M694V mutation are at risk for an early onset disease.
6. Individuals, homozygous for M694V, who are not reporting symptoms, should be evaluated and followed closely in order to consider therapy.
7. For individuals with two pathogenic mutations for FMF who don't report symptoms, if there are risk factors for AA amyloidosis (such as country of origin, family history and persistently elevated inflammatory markers) treatment and close follow-up should be considered.
8. Consultation with an autoinflammatory disease specialist may be helpful, in order to aid in the indication and interpretation of the genetic testing and diagnosis.

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Canakinumab Therapy in Patients with Familial Mediterranean Fever. Serdal Ugurlu, Emire Seyahi, Gulen Hatemi, Aysa Hacioglu, Fatma Nihan Akkoc and Huri Ozdogan. Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey.

Background/Purpose: According to a recent pilot study Canakinumab reduced the frequency of attacks in 9 patients with Familial Mediterranean Fever (FMF) resistant to colchicine with no apparent side effects(1). We present our experience with Canakinumab in FMF patients resistant or intolerant to colchicine.

Methods: The charts of the patients with FMF who were on Canacinumab were evaluated retrospectively with regard to response and safety.

Results: There were 30 patients with FMF (16 F/14 M) receiving canakinumab for various indications. Here we report 28 (15 F/13 M) who had at least 3 injections. Six patients had concomitant diseases such as psoriasis (1), ankylosing spondylitis (3), polyarteritis nodosa (1), ankylosing spondylitis and polyarteritis nodosa (1). The indications for canakinumab (150mg/mo) were insufficient response to colchicine in 15 (>1 attack/month), amyloidosis in 6, injection site reaction to anakinra in 5, oligospermia in one and myopathy in one patient, both being adverse effects of colchicine. The mean age of the patients was 34,67 ± 13,45 years, the disease duration was 16,75 ± 9,42 years, the mean injection number was 7,00 ± 3,62 and the mean duration of canakinumab therapy was 10,98 ± 6,06 months. Twenty of the patients had no attacks after canakinumab, six patients' attack frequency was reduced more than %50 while two patient's attack frequency did not change. In 6 cases with FMF amyloidosis, proteinuria decreased in 2 (from 15020 mg/dl to 910 mg/dl, and from 6135 mg/dl to 4610 mg/dl), increased in 2 (from 1700mg/dl to 4700mg/dl and from 5001 mg/dl to 7061 mg/dl), and did not change in the other 2. Eleven of the 24 patients with severe myalgia and calf pain unresponsive to colchicine treatment, improved significantly on canakinumab. According to patient global assessment the mean score decresed from 7,9 ± 2,6 to 2.1 ± 2.9 ($p<0.001$). Canacinumab was stopped because of remission (no attacks at least for 3 months) in 5 and for pregnancy demand in one. The treatment was also stopped in the patient with oligospermia after being fertile, and he is without attacks for 5 months. Attacks recurred after 4, 6, 12 months from discontinuation of the therapy in 3 patients, and 3 patients are attack-free for 5, 6 and 13 months till now. None of the patients had injection site reactions. The patient with psoriasis reported a flare in psoriatic plaques, which responded to local treatment. Therapy was discontinued temporarily in one patient who developed mild leucopenia, which did not recur on a 2-monthly regimen. Treatment was switched to another biological agent in 2 patients with amyloidosis because of increasing proteinuria. One other patient with amyloidosis whose proteinuria was stable, developed lichen planus lesions and the treatment had to be stopped. One patient had pnomonia, also he is attack-free for three months untill last dose.

Conclusion: Canacinumab is effective in controlling the attacks in patients with inadequate response to colchicine. In a selected group of FMF patients, Canacunimab may serve as a treatment alternative with a favorable side effect profile. For better understanding the drug's efficacy and safety in the long term there is a need for controlled trials.

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Tocilizumab (TCZ) in the Treatment of AA Amyloidosis in Patients with Familial Mediterranean Fever. Huri Ozdogan, Serdal Ugurlu, Aysa Hacioglu, Yasaman Adibnia and Vedat Hamuryudan. Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey.

Background/Purpose: AA amyloidosis is the major long-term complication of various chronic inflammatory diseases like rheumatoid arthritis, ankylosing spondylitis, FMF and other autoinflammatory syndromes. Treatment of the underlying disease decreases the frequency of this complication however if it develops there is no established treatment of AA amyloidosis. Recently there are few reports pointing out that tocilizumab (TCZ), an anti IL-6 agent may be effective in controlling resistant AA amyloidosis.

We aim to demonstrate our data on the effect of TCZ in patients with AA amyloidosis secondary to FMF.

Methods: The follow-up data of FMF patients with histologically proven AA amyloidosis, treated with TCZ (8 mg/kg per month) is evaluated by assessing the changes in creatinine, creatine clearance, the amount of 24-hour urine protein, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values measured before and throughout the treatment period. Adverse and side effects of the treatment were closely monitored.

Results: TCZ was given to 13 patients (8 female, 5male) with AA amyloidosis secondary to FMF who were also on Colchicine (2.28 mg± 0.48 mg/day). Two patients had coexisting ankylosing spondylitis, one had systemic lupus erythematosus and one other had Crohn's disease. The mean age was 36.46±9.96 years, while the mean disease duration of FMF was

23.15±7.65 years and of amyloidosis was 4.52±4.98 years. The mean follow-up period on TCZ treatment was 8.76 ± 5.59 months. The mean creatinine levels decreased from 1.21±0.93 mg/dl to 1.05 ± 0.65 mg/dl (p = 0.001), mean creatine clearance increased from 102.34±53.95 ml/min to 109.08±60.23 ml/min (p <0.001). Renal function was impaired in 3 of the 13 patients which improved significantly on TCZ therapy (serum creatinine from a mean of 2.64±0.57 mg/dl to 1.97±0.46 mg/dl, p=0.018; creatinin clearence from a mean of 36.2±4.51 to 45.3±5.55ml/min, p=0.005). The median of 24-hour urinary protein excretion for the whole group was reduced from 3038.5 mg/dl (IQR 1827–7061) to 1155mg/d (IQR 802–4707) (p=0.013). A significant decrease in acute phase reactants was also recorded. The mean level of CRP was reduced from 19.43 ±18.75 mg/l to 3.87±4.8 mg/dl (p=0.004) as the mean ESR was reduced from 45.41±26.68 mm/h to 27.63 ± 29.25 mm/h (<0.001).

Twelve of the patients did not experience any FMF attack under TCZ treatment. In one patient TCZ was switched to canakinumab because of an increase in the frequency of attacks associated with erysipelas-like erythema and no decrease in proteinuria. One other patient with FMF and AS had 2 attacks of acute sacroiliitis during the follow-up. Increased blood pressure (220/120 mm Hg) was noted 5 days after the single infusion in one patient who was an illicit user of synthetic cannabinoid. TCZ was stopped in one other patient with underlying SLE and APLS who developed ishemic chest pain after the 12th infusion.

Conclusion: TCZ improves the acute phase response and the renal function impaired by amyloidosis secondary to FMF. Among this patient group TCZ treatment is well tolerated and not associated with serious side effects. Further studies are warrented to test the efficacy and safety of TCZ in AA amyloidosis secondary to FMF as well as other inflammatory conditions.

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Periodic Fever Syndromes in an Academic Medical Center. Mark Cervinski[1] and Daniel Albert[2]. [1]Dartmouth Hitchcock Medical Center, Lebanon, NH, [2]The Dartmouth Institute for Health Policy and Clinical Practice, lebanon, NH.

Background/Purpose: Most published clinical data on this rapidly evolving group of diseases are from highly specialized centers and do not reflect what is commonly seen in academic rheumatology practices. This retrospective case series examines the breadth and phenotypic variation seen in our medical center over the last two years.

Methods: Case acquisition was acheived by three methods: review of ICD 9 code for periodic fever (277.31 -Famillial Mediterranean Fever); laboratory test requests for periodic fever genetic screening; and, clinic records.

Results: 30 cases were obtained. The age range was 2m to 54 years old. 13 were female, 17 male. All but 3 were seen by a rheumatologist. Of the rheumatology patients 1 was cared for by an adult only rheumatologist and 1 by a rheumologist who predominantly cares for adult patients and the remainder (25) by a rheumatologist who cares for children (DA). 11 patients had the periodic fever, apthous stomatitis, pharyngitis, adenopathy syndrome (PFAPA) and all responded to abortive therapy with prednisone 1–2mg/kg at the onset of symptoms. 9 patients had an unknown syndrome predominantly abdominal pain and fever with a negative screen for common mutations associated with Familial Mediterrean Fever and other periodic fever syndromes (GeneDX). 5 patients with the Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) were diverse ranging from asymptomatic relatives to classical presentiations including fever, abdominal pain, myalgias, arthritis and conjunctivitis. Only one of TRAPS patients received Entanercept and had a partial response but developed systemic lupus when given infliximab.Two of the three Familial Mediterranean patients responded to colchicine. The single patient with Hyper IgD Syndrome (HIDS) did not respond to either prednisone or anakinra. One child is a compound heterozygote with a mutation in the CIAS1 gene and the MEFV gene. This patient presented with urticaria, abdominal pain, and fever reflecting an overlap syndrome as did one of the othe FMF patients.

Conclusion: Patients with Periodic Fever Syndromes have a variable clinical presentation and response to therapy and are predominantly cared for by rheumatologists. Familiarity with these disorders is essential for trainees and practicing rheumatologists. Expertise in pediatric rheumatology is useful to distinguish these patients from those with systemic juvenile rheumatoid arthritis and to appropriately treat this population that predominantly present in childhood.

Disclosure: M. Cervinski, None; **D. Albert**, None.

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Recovery of Renal Function after Corticosteroid Therapy for IgG4-Related Kidney Disease. Takako Saeki[1], Mitsuhiro Kawano[2], Ichiro Mizushima[2], Motohisa Yamamoto[3], Yoshifumi Ubara[4], Hitoshi Nakashima[5], Yoko Wada[6], Tomoyuki Ito[1], Hajime Yamazaki[1], Ichiei Narita[6] and Takao Saito[5]. [1]Nagaoka Red Cross Hospital, Nagaoka, Japan, [2]Kanazawa University Hospital, Kanazawa, Japan, [3]Sapporo Medical University School of Medicine, Sapporo, Japan, [4]Toranomon Hospital, Tokyo, Japan, [5]Fukuoka University, Fukuoka, Japan, [6]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.

Background/Purpose: In our earlier study of IgG4-related kidney disease (IgG4-RKD), we found that renal dysfunction, which was mostly attributable to IgG4-related tubulointerstitial nephritis, was significantly improved at 1 month after the start of corticosteroid therapy, but reached a plateau thereafter, and renal atrophy developed in many patients (Saeki, et al. Kidney Int 2013). Little is known about the appropriate initial corticosteroid dose for induction therapy or the long-term renal outcome in IgG4-RKD with renal dysfunction.

Methods: This retrospective cohort analysis evaluated the recovery of renal function during the initial 1 month of corticosteroid therapy, and the long-term course of renal function after treatment, in 41 patients with confirmed IgG4-RKD in whom the eGFR before corticosteroid treatment had been less than 60 ml/min. The patients were collected from 16 collaborating institutions in Japan between 2004 and 2013, and divided into two groups (group L, initial prednisolone dose <0.6 mg/kg/day; group H, >0.6 mg/kg/day).

Results: Among the patients, 88% were male, and the mean age at the time of diagnosis of renal disease was 66.6±9.3 years. Renal pathology data were available for 38 of the 41 patients, and all of them had the tubulointerstitial features characteristic of IgG4-RKD. One patient with renal failure in group L showed no recovery of renal function and maintenance hemodialysis became necessary within 1 month after the start of treatment. Except for this patient, eGFR data at 1 month after treatment were available for 31 patients (group L 17; group H 14). The initial prednisolone dose was 0.47±0.12 mg/kg daily in group L and 0.84±0.16 mg/kg daily in group H, being significantly lower (P<0.001) in the former. There was no significant inter-group difference in patient age, sex or pretreatment eGFR. In both groups, the pretreatment eGFR was significantly improved at 1 month after the start of corticosteroid therapy [30.5±15.7 to 41.8±14.9 ml/min in group L (p<0.05) and 32.7±13.8 to 46.6±17.0 mi/min in group H (p<0.05)], and the degree of improvement showed no significant inter-group difference. Fifteen of the 41 patients were followed up for over 36 months (39 – 210 months, median 56 months), and all of them had been maintained on low-dose prednisolone (5.1 ± 2.1 mg daily) at the last review. No patient showed progression to end-stage renal disease, and there was no significant difference in eGFR at the last review (45.1 ±11.3 ml/min) in comparison to that at 1 month after the start of treatment (42.5 ±12.8 ml/min).

Conclusion: In IgG4-RKD, prednisolone 0.5 mg/kg daily is sufficient for induction therapy, and the recovery of renal function during the first month of this treatment can be maintained for a long period on low-dose corticosteroid maintenance therapy.

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IgG4 Immunostaining Is Common but Not Specific in Orbitbal Inflammatory Diseases. James T. Rosenbaum[1], Amanda Wong[2], Patrick Stauffer[2], Megan Troxell[3], Donald Houghton[2], Dongseok Choi[3], Christine Harrington[2], David Wilson[2], Hans Grossniklaus[4], Roger Dailey[2], John Ng[2], Eric Steele[2], Patrick Yeatts[5], Peter Dolman[6], Valerie White[6], Craig Czyz[7], Jill Foster[7], Deepak Edward[8], Hind Alkatan[8], Don Kikkawa[9], Bobby Korn[9], Dinesh Selva[10], Gerald Harris[11], Michael Kazim[12], Payal Patel[12] and Stephen R. Planck[2]. [1]OHSU, Portland, OR, [2]Oregon Health & Science University,

Portland, OR, [3]Oregon Health and Science University, Portland, OR, [4]Emory University, Atlanta, GA, [5]Wake Forest University, Winston-Salem, NC, [6]University of British Columbia, Vancouver, BC, [7]Ohio State Univeristy, Columbus, OH, [8]King Khaled Eye Hospital, Riyadh, Saudi Arabia, [9]University of California, San Diego, San Diego, CA, [10]Royal Adelaide Hospital, Adelaide, Australia, [11]Medical College of Wisconsin, Milwaukee, WI, [12]Columbia University, New York City, NY.

Background/Purpose: IgG4-related disease is an emerging clinical entity which frequently involves tissue within the orbit. In order to appreciate the implications of IgG4 immunostaining, we analyzed gene expression and the prevalence of IgG4- immunostaining among subjects with orbital inflammatory diseases.

Methods: We organized an international consortium to collect orbital biopsies from 109 subjects including 22 with no known orbital disease, 42 with nonspecific orbital inflammatory disease (NSOI), 27 with thyroid eye disease (TED), 12 with sarcoidosis, and 6 with granulomatosis with polyangiitis (GPA). Lacrimal gland and anterior orbit adipose tissue biopsies were immunostained for IgG4 or IgG secreting plasma cells. RNA transcripts were quantified by Affymetrix microarrays.

Results: None of the healthy controls or subjects with TED had substantial IgG4 staining. Among the 63 others, the prevalence of significant IgG4-immunostaining ranged from 11 to 39% depending on the definition for significant. IgG4 staining was detectable in the majority of tissues from subjects with GPA and less commonly in tissue from subjects with sarcoidosis or NSOI. The detection of IgG4+ cells correlated with inflammation in the lacrimal gland based on histology. Subjects with NSOI and IgG4 staining did not have multisystem disease. IgG4 staining tissue expressed an increase in transcripts associated with inflammation, especially B cell-related genes. Functional annotation analysis confirmed this.

Conclusion: IgG4+ plasma cells are common in orbital tissue from patients with sarcoidosis, GPA, or NSOI and do not consistently indicate a multisystem disease. Even using the low threshold of 10 IgG4+ cells/high powered field, IgG4 staining correlates with increased inflammation in the lacrimal gland based on histology and gene expression.

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Retroperitoneal Fibrosis and IgG4 Disease: Response to Immunosuppressive Therapy - a Single Centre Retrospective Study. Shirish Sangle[1], Pamela Lutalo[2], Louise Nel[3], James Pattison[3], Tim OBrien[4] and David P. D'Cruz[1]. [1]Louise Coote Lupus Unit, Guy's and St Thomas' Hospital, London, United Kingdom, [2]King's College London School of Medicine, London, United Kingdom, [3]Guy's and St Thomas' Hospital NHS Foundation Trust, London, United Kingdom, [4]Guy's and St Thomas' Hospital NHS Trust, London, United Kingdom.

Background/Purpose: A retrospective observational study of patients with IgG4 related disease and retroperitoneal fibrosis.

Methods: Retroperitoneal fibrosis (RPF) is a rare chronic inflammatory condition which may be associated with IgG4 disease. Thirty nine patients diagnosed with idiopathic RPF were retrospectively analysed at Guy's and St Thomas' Hospitals, London, England. All patients' data regarding clinical presentation, markers of inflammation, immunoglobulin subsets, autoantibody profiles, imaging and histopathology was collected. Comprehensive Diagnostic Criteria (CDC) for the diagnosis of IgG4 disease was applied to all patients.

Results: The study included 24 Caucasian, 9 African and 6 Asian patients. There were 19 female and 20 male patients. The median age of the patients was 54 years (range 38 – 80). The majority presented with ureteric obstruction (n=18) and 12 of these patients had renal failure. Clinical features included periaortitis (n=8), periaortic masses (n=6), left kidney atrophy (n=1), atheroma (n=1), lung cavitations (n=1), polymyalgia rheumatica (n=1), 1 patient had RPF diagnosed after a positive PET scan, 1 patient had RPF and a malignancy, and 1 patient developed RPF after methysurgide.

Laboratory markers of inflammation were significantly elevated in IgG4 related RPF. The median ESR was 28 (5 – 91) mm per hour and CRP was 26 (6 – 200) mg/l. The mean ESR=56mm/hr (S.D 28) in IgG4RPF was higher versus non-IgG4 RPF mean ESR=29mm/hr (S.D 27) [p=0.008]. IgG4 RPF, mean CRP=51mg/l (S.D 39) versus non-IgG4 RPF, mean CRP=31 mg/l (S.D 29) [p=0.04]. Immunoglobulin IgG subclass analysis showed higher IgG4 levels in IgG4 RPF, mean IgG4=0.96g/l (S.D 0.8) compared to non-IgG4 RPF, mean IgG4=0.44g/l (S.D 0.3) [p=0.05]. There were no statistically significant differences between IgG3, IgG2 and IgG1 levels in the IgG4 RPF and non-IgG4 RPF patients. Seven patients had elevated IgG4 levels. Thirty seven patients had biopsies, 7 had confirmed diagnosis and 4 had a probable diagnosis of IgG4 RPF based on IgG4 plasma cells and fibrosis in biopsy specimens. None of the patients diagnosed with IgG4 RPF had positive serology for ANA, dsDNA, ENA or ANCA. Seventeen patients had FDG-PET-CT scans of which 12 showed active inflammation, 5 with IgG4 RPF had positive scans. Therapeutic interventions included corticosteroids (n=28), immunosuppressants: azathioprine, methotrexate, ureteric stents (n=12), ureterolysis (n=4), and nephrectomy (n=2). Median corticosteroid dose was 20 mgs (0 - 40)/day. The median ESR 11 (3–63) mm/hour and CRP was 6 (5–70) mg/l improved after treatment. The median IgG4 levels dropped from 7.44 to 0.37 gm/l. Four patients had post therapy FDG-PET-CT scans and 3 (1 with IgG4 RPF) had reduced activity. Clinical improvement was reported in 72% of the patients (n=28), 1 patient deteriorated but declined Rituximab. Fifteen patients had a confirmed diagnosis of IgG4 disease based on CDC criteria.

Conclusion: IgG4 disease may be considered in patients with retroperitoneal fibrosis and periaortic lesions. FDG-CT-PET imaging is useful diagnostically and response to corticosteroids and immunosuppressant therapy is favourable.

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Proportion of Peripheral Plasmacytoid Dendritic Cells and Plasmablasts Reflects Disease Activity in IgG4-related Disease. Mitsuhiro Akiyama[1], Katsuya Suzuki[1], Yoshiaki Kassai[2], Takahiro Miyazaki[2], Rimpei Morita[3], Akihiko Yoshimura[3] and Tsutomu Takeuchi[4]. [1]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [2]Takeda Pharmaceutical Company Limited, Kanagawa, Japan, [3]Department of Microbiology and Immunology, Keio University School of Medicine, Tokyo, Japan, [4]Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a recently recognized fibro-inflammatory disease with multi-organ system involvement. Affected patients frequently have a history of bronchial asthma and allergic rhinitis. The reported pathogenesis of IgG4-RD describes the clear involvement of excessive Th2 cells and regulatory immune reaction in addition to plasma cells 1). However, peripheral immune cell phenotype, which reflects disease status, has not been comprehensively evaluated. Our aim was to definitively determine peripheral blood cell abnormalities and their correlation with disease activity in patients with IgG4-RD.

Methods: Peripheral blood samples were obtained from active untreated IgG4-RD patients (n=11) and healthy controls (n=16). Comprehensive immunophenotyping assay with information on activation status was done by multi-color flow cytometry, and the proportion of peripheral blood mononuclear cells (PBMCs), including T cells (naïve/memory, Th1/2/17, Treg, and Tfh), B cells (naïve/memory, plasmablast, Breg), monocytes (classical, intermediate, non-classical) and dendritic cells (myeloid, plasmacytoid), and their activity status were precisely defined. Disease activity was measured using the IgG4-RD responder index (RI). Statistical analysis was done using the Mann-Whitney U test and Spearman rank correlation coefficient test.

Results: The proportion of plasmablasts (CD19+CD20−CD27+CD38+), memory Th2 cells (CD3+CD4+CXCR3-CCR6-CD45RA-), Tregs (CD3+CD4+CD25+CD127low), Tfh (CD3+CD4+CXCR5+), and mDCs (CD3-CD19-CD14-HLA-DR+CD1c+CD303-) in peripheral blood was significantly increased in IgG4-RD patients compared with HC, whereas the proportion of pDCs (CD3-CD19-CD14-HLA-DR+CD1c-CD303+) was significantly decreased. Interestingly, the proportion of pDCs in total DCs was negatively correlated with IgG4-RD RI (r=−0.778, p=0.005) while the proportion of plasmablasts in CD19+cells was positively correlated with RI (r=0.701, p=0.016). Further, the increased proportion of plasmablasts was positively correlated with serum IgG4 level (r=0.718, p=0.013)

while the decreased proportion of pDCs tended to be negatively correlated with the number of affected organs ($r=-0.518$, $p=0.061$).

Conclusion: Our comprehensive analysis identified distinct proportional changes in PBMCs in IgG4-RD. In particular, the decrease in pDCs and increase in plasmablasts were strongly linked with disease activity. These combined measurements are expected to be clinically useful surrogate cell markers. This newly identified decrease in circulating pDCs may be involved in the pathogenesis in IgG4-RD via the recently described role in the enhancement of Th2 response 2).

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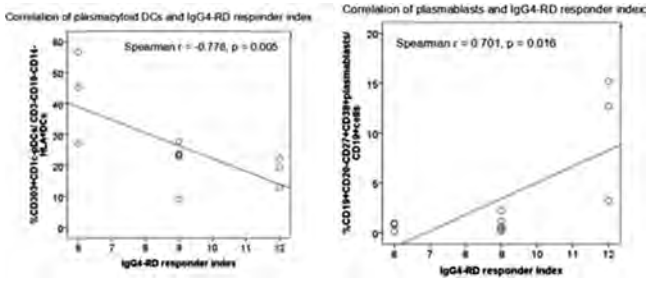

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Is Lymphocytic Sialadenitis IgG4-Related? Nathalie Shehwaro[1], Murielle Hourseau[1], Thomas Papo[2] and Karim Sacre[3]. [1]University Paris-7, APHP, Bichat Hospital, Paris, France, [2]Bichat Hospital, Paris, Paris, France, [3]University Paris-7, INSERM U699, APHP, Bichat Hospital, Paris, France.

Background/Purpose: To assess the prevalence of IgG4-related disease among patients with lymphocytic sialadenitis on labial salivary gland biopsy.

Methods: All labial salivary gland biopsies (LSGB) performed in a French University Hospital Center over a one-year period (2012) were retrospectively screened. IgG4 immunostaining was performed on all LSGB showing lymphocytic sialadenitis defined by a Chisholm score ≥3. Histopathological criteria for IgG4-related disease according to international criteria and final diagnosis associated with lymphocytic sialadenitis were analyzed in all cases.

Results: Three hundred and fifty patients had a labial salivary gland biopsy (LSGB). Among them, 79 (23%) had a lymphocytic sialadenitis. Mean age was of 55.5±15.7 years old. Female/Male Sex ratio was 3.2/1. LSGB was performed because of sicca symptoms in most cases (48/79, 60.8%). Only one (1/79, 1.3%) LSGB showed histopathological features of IgG4-related disease in a patient who otherwise displayed obvious extra-salivary features of IgG4-related disease. Overall, the diagnoses associated with lymphocytic sialadenitis were Sjögren's syndrome (29/79, 36.7%), other autoimmune disorders (besides Sjogren's syndrome) (17/79, 21.5%), idiopathic pulmonary fibrosis (5/79, 6.3%), sarcoïdosis (3/79, 3.8%), B-cell hemopathy (3/79, 3.8%), hepatitis C infection (2/79, 2.5%), unclassified arthritis (1/79, 1.3%), idiopathic uveitis (1/79, 1.3%), multiple sclerosis (1/79, 1.3%) and tuberculosis (1/79, 1.3%). In 15 cases (19%), no diagnosis could be obtained despite extensive work-up. Of note, IgG4 staining was negative in all patients with unexplained lymphocytic sialadenitis.

Conclusion: The prevalence of IgG4-related disease among patients with lymphocytic sialadenitis on LSGB is very low. Systematic IgG4 immunostaining has no diagnostic value in patients with lymphocytic sialadenitis. On the other hand, lip biopsy, by being simple and safe, can be useful for a definite diagnosis when IgG4-related disease is suspected.

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Efficacy of Anakinra in Refractory Adult-Onset Still′s Disease: Multicenter Study of 41 Patients. Leyre Riancho-Zarrabeitia[1], Ricardo Blanco[1], Alejandro Olivé[2], Anne Riveros-Frutos[2], Santos Castañeda[3], Maria Luisa Velloso Feijoo[4], Javier Narváez[5], Inmaculada Jiménez-Moleón[6], Olga Maiz-Alonso[7], Maria Carmen Ordóñez[8], José Antonio Bernal[9], M. Victoria Hernández[10], Alberto Sifuentes Giraldo[11], Catalina Gomez Arango[12], Eva Galindez-Agirregoikoa[12], Vera Ortiz-Santamaría[13], Jordi del Blanco[14], Juan Ramón De Dios[15], Mireia Moreno[16], Jordi Fiter[17], Marina de los Riscos[18], Patricia Carreira[18], María José Rodríguez Valls Sr.[19], Francisco Ortiz-Sanjuán[1], Trinitario Pina Murcia[20], Montserrat Santos-Gómez[1] and Miguel A González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [2]Hospital Universitario Germans Trias i Pujol, Badalona, Spain, [3]Hospital Universitario de La Princesa, IISP, Madrid, Spain, [4]H Valme, Sevilla, Spain, [5]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, [6]Hospital San Cecilio, Granada, Spain, [7]HU Donostia, San Sebastián, Spain, [8]Hospital Regional Universitario Carlos Haya., Málaga, Spain, [9]HGU. Alicante., Alicante, Spain, [10]Hospital Clinic, Barcelona, Barcelona, Spain, [11]HU Ramón y Cajal, Madrid, Spain, [12]Hospital Universitario Basurto, Bilbao, Spain, [13]Hospital General. Granollers., Granollers, Spain, [14]H Sant Jaume, Calella, Spain, [15]HU Álava, Vitoria, Spain, [16]University Hospital Parc Taulí, Sabadell, Spain, [17]HU Son Espases. Palma de Mallorca., Palma de Mallorca, Spain, [18]Hospital Universitario 12 de Octubre, Madrid, Spain, [19]Rheumatolgy Unit. Hospital Jerez, Jerez, Spain, [20]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain.

Background/Purpose: Adult-onset Still's disease (AOSD) is frequently refractory to standard therapy. Anakinra (ANK), an interleukin-1 (IL-1) receptor antagonist, has demonstrated efficacy in single cases or in small series of AOSD. We assessed the efficacy of ANK in a large series of AOSD patients.

Methods: Multicenter retrospective open-label study of 41 patients with AOSD from 19 hospitals. ANK was used due to lack of efficacy to standard synthetic immunosuppressive drugs and some cases also due to lack of adequate response to at least 1 biologic agent.

Results: 41 Patients (26 women/15 men) had a mean age of 34.4±14 years and a median [interquartile range- IQR] AOSD duration of 2.2 [1–24] years before ANK onset.

Besides oral steroids, patients had previously received the following drugs: Methotrexate (32 patients), Leflunomide (7), Etanercept (10), Infliximab (9) and Adalimumab (6). ANK standard dose was 100 mg/sc/day.

At ANK onset, the most frequent clinical manifestations were joint manifestations (n=36), fever (n=32) and cutaneous manifestations (n=24). Abnormality of laboratory parameters was generally observed at that time: high C reactive protein (CRP) (n=37), high erythrocyte sedimentation rate (ESR) (n=32), leukocytosis (n=27) or anemia (n=23). ANK yielded rapid and maintained clinical and laboratory improvement (TABLE). After one year of ANK therapy, joint manifestations had decreased from 87.8% to 29.6%, fever from 78% to 7.4%, cutaneous manifestations from 58.5% to 3.7%, anemia from 56.1% to 0%, hepatomegaly and/or splenomegaly from 31.7% to 3.7% and lymphadenopathy from 26.8% to 0%. Also, a dramatic reduction of laboratory markers of inflammation including CRP, ESR and ferritin was achieved. The median [IQR] dose of prednisone was also reduced from 20 [0–100] mg/day at ANK onset to 2.5 [0–40] at 12 months. After a median [IQR] follow-up of 15.5 [1–206] months, the most important side effects were cutaneous rash (n=8), mild leukopenia (n=3), myopathy with elevation of muscle enzymes (n=1), respiratory infection by *Pseudomonas Aeruginosa* and gluteal abscess (n=1), herpes zoster (n=1), phalanx osteomyelitis (n=1) and urinary tract infection (n=2).

Conclusion: ANK is associated with rapid and maintained clinical and laboratory improvement, even in cases that are refractory to other biologic agents. However, joint manifestations seem to be more refractory than systemic manifestations.

Table

	Baseline N=41	Month 1 N=41	Month 3 N=37	Month 6 N=32	Month 12 N=27
Patients with joint manifestations, %	87.8	48.7	34.1	28.1	29.6
Patients with fever, %	78	17.1	10.8	0	7.4
Patients with cutaneous manifestations, %	58.5	9.8	10.8	0	3.7

Leukocytosis/mm3, mean ± StD	15120.7 ± 7752.3	8100.5 ± 3655.1	7807.6 ± 3001.7	7843.9 ± 2297	7842.9 ± 2702.6
ESR (mm/1st hour), median [IQR]	60.5 [1–137]	16.5 [1–95]	16 [1–120]	8 [1–75]	6 [1–104]
CRP (mg/dL), median [IQR]	8.9 [0.1–37.7]	1.1 [0–14]	0.6 [0–31.5]	0.5 [0–17]	0.3 [0–22]
Prednisone dosage, median [IQR]	20 [0–100]	15 [0–100]	8.75 [0–60]	5 [0–15]	2.5 [0–40]

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1241

Efficacy of Tocilizumab Therapy in Korean Patients with Adults Onset Still's Disease: Multicenter Retrospective Study of 20 Cases. Jin Ju Kim[1], Joo Hyun Lee[2], Chang-Nam Son[3], Hyoun-Ah Kim[4], Kwang-Hoon Lee[5], Sang Tae Choi[6], Eun Young Lee[7], Ki Chul Shin[7], Hoon-Suk Cha[8] and Dae-Hyun Yoo[1]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Ilsan Paik Hospital, Inje University, Goyang, South Korea, [3]Keimyung University School of Medicine, Daegu, South Korea, [4]Ajou University School of Medicine, Suwan, South Korea, [5]Dongguk University Ilsan Hospital, Goyang, South Korea, [6]Chung-Ang University College of Medicine, Seoul, South Korea, [7]Seoul National University College of Medicine, Seoul, South Korea, [8]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

Background/Purpose: Adult onset Still's disease (AOSD) is a rare inflammatory disorder of unknown etiology. Refractory cases to conventional therapy require biologic agents. Although IL-1 targeting therapy is very effective, but tocilizumab (TCZ), an anti-interleukin-6 receptor monoclonal antibody may be an effective agent especially in the countries where anti-IL-1 therapy is not easily available. In this study, we assessed the efficacy of TCZ in multicenter retrospective fashion.

Methods: We retrospectively collected clinical data of AOSD patients who were treated with in Korea. The response to TCZ was defined as decreased modified Pouchot's score more than 2 score with decreased acute phase reactants compared to initial treatment of TCZ at least two consecutive months.

Results: Patients (15 women/5 men) had a mean age of 42.5± 18.8 years and the age of diagnosis was 37.3 ±21.2years old. The mean disease duration before TCZ treatment was 40.7 ± 33.6 months. Ten patients (52.6%) had polycyclic systemic pattern and 9 patient had chronic articular pattern, but 1 patient was no classified due to short disease duration.

Immune modulating agents before TCZ therapy were as follows: methotrexate (n=18), leflunomide (n=12), cyclosporine (n=9), azathioprine (n=8) and hydroxychloroquine (n=7). Biologic agents before TCZ therapy were etanercept (n=7), infliximab (n=4), adalimumab (n=3), abatacept (n=2) and anakinra (n=1). At TCZ onset, the most frequent clinical manifestations were: joint manifestations (80.0%), rash (50.0%), myalgia (35.0%), fever (25.0%) and sore throat (25.0%) (Table 1). The baseline laboratory parameters such as leukocytosis, ESR, CRP and serum ferritin showed high level (Table 1). The mean dose of TCZ was 7.8 mg/kg (4–8 mg/kg) per 4 weeks and mean duration of TCZ administration was 7.9 ± 6.7 months. The 90.0% of patients showed clinical and laboratory improvement after TCZ therapy (Table 1). The median dose of prednisolone was also significantly reduced from17.1± 10.1 mg/day at TCZ onset to 7.5 ± 3.9 mg/day at 12months (Table 1).

The 35% of patients had side effects during TCZ treatment as follows: leukopenia (n=2), hypertension (n=2), alopecia (n=2), pneumonia (n=1). Four patients (20%) relapsed after 5.0 ± 3.6 months of discontinuation of TCZ.

Conclusion: TCZ was effective in Korean AOSD patients refractory to conventional therapy and/or other biologic agents. Larger and prospective study is needed for further investigation.

Table 1. Change of clinical manifestations and laboratory parameters before and after TCZ treatment

	Baseline (N=20)	After 6 months (N=12)	After 12 months (N=7)
Fever (n, %)	5, 25.0	0, 0	1, 14.3
Sore throat (n, %)	5, 25.0	1, 8.3	0, 0
Rash* (n, %)	10, 50.0	1, 8.3	0, 0
Itching (n, %)	5, 25.0	1, 8.3	0, 0
Myalgia* (n, %)	7, 35.0	0, 8.3	0, 0
Arthralgia/arthritis* (n, %)	16, 80.0	5, 66.7	1, 14.3
Lymphadenopathy (n, %)	1, 5.0	0, 0	0, 0
Splenomegaly (n, %)	0, 0	0, 0	0, 0
Serositis (n, %)	1, 5.0	0, 0	0, 0
Modified Pouchot's Score, mean ± SD	3.1 ± 1.7	1.3 ± 1.3	1.4 ± 1.0
Leukocytosis, mean ± SD	12697.5 ± 5193.4	11130.8 ± 6221.7	11547.1 ± 6935.3
ESR (mm/hour), mean ± SD**	63.6 ± 28.0	10.3 ± 15.8	14.0 ± 23.3
CRP (mg/dL), mean ± SD*	4.4 ± 3.6	1.0 ± 2.2	2.3 ± 2.9
Ferritin (ng/mL), mean ± SD	1657.8 ± 2222.6	558.4 ± 1113.4	165.2 ± 130.4
Prednisolone dose (mg/day), mean ± SD*	17.1 ± 10.1	7.1 ± 5.1	7.5 ± 3.9

*P < 0.05, ** P < 0.001

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Switching Biologic Agents in Refractory Adult-Onset Still's Disease: Efficacy and Safety in a Cohort of 20 Patients at a Single Referral Center. Giulio Cavalli[1], Stefano Franchini[1], Corrado Campochiaro[1], Elena Baldissera[2], Lorenzo Dagna[3] and Maria Grazia Sabbadini[3]. [1]Vita-Salute San Raffaele University, Milan, Italy, [2]Clinical immunopathology and advanced medical therapeutics, San Raffaele Scientific Institute, Milan, Italy, [3]Vita-Salute San Raffaele University, Milano, Italy.

Background/Purpose: No data is available on the long-term clinical outcome of Adult-Onset Still's Disease (AOSD) patients treated with biological drugs, nor on the efficacy and safety of switching biologics in the management of refractory cases. We aimed to evaluate the efficacy and safety of switching biological agents in a large, monocentric cohort of 20 patients with refractory AOSD.

Methods: Twenty Italian AOSD patients treated with biological agents were followed-up at our Institution for at least 24 months. For each case we retrospectively evaluated the disease course, the efficacy of treatment, and the potential adverse effects. Efficacy was evaluated as "Complete response" (CR: absence of articular and systemic manifestations, normalization of inflammatory indexes, >50% reduction in the corticosteroid dosage); "Partial response" (PR: clinical improvement without normalization of inflammatory markers, nor >50% reduction in the dose of steroids); or "Treatment failure" (TF: persistence/worsening of disease manifestations, persistent elevation of inflammatory markers, or need for an increased dose of corticosteroids despite 2 months of treatment).

Results: The median duration of follow-up was 5 years. In 12 patients a single biological drug induced a clinical response. Five patients were switched to a different biologic because of lack of efficacy. In 3 patients, a third biologic was necessary to achieve disease control. Biologics eventually determined a clinical response in all patients. Anakinra was used in all 20 patients; etanercept, tocilizumab and adalimumab was used in 6, 4, and 1 patient, respectively. Sixteen patients responded to anakinra (80%; CR 70%; PR 10%). Four patients (20%) did not respond to anakinra, and of these three responded to tocilizumab, and one responded to adalimumab. Etanercept was used unsuccessfully in six patients. Patients with systemic manifestations showed better responses than patients with chronic articular disease ($p<0.05$). Overall, biologic agents determined a significant reduction in the dose of the associated therapy with corticosteroids ($p<0.0001$) and DMARDs ($p<0.05$). Three patients experienced herpes zoster reactivation.

Conclusion: Biological agents represent a pivotal therapeutic resource for AOSD patients refractory to conventional treatment. Although the biologic drug of choice may prove ineffective, switching between biologics ultimately resulted in a clinical response in all patients without significant adverse effects, hence the importance of pursuing a tailored treatment approach. Although IL-1 blockade with anakinra represents the mainstay of treatment, IL-6 blockade may be more effective in patients with chronic articular involvement. Both anakinra and tocilizumab were more effective than TNF-α blockers. Patients with SD are more likely to respond favorably to biologics than patients with CAD. Different pathogenic mechanisms underlying SD and

CAD, or the development of irreversible articular damage in CAD, may account for the differences in response to treatment.

References:
Al-Homood IA. Biologic treatments for adult-onset Still's disease. Rheumatology 2013.

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1243

Macrophage Activation Syndrome Complicating Adult Onset Still's Disease - Single Center Experience and Literature Review. Aleksander Lenert and Qingping Yao. Cleveland Clinic, Cleveland, OH.

Background/Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a life threatening complication typically associated with hematologic malignancies and infections. HLH, also referred to as macrophage activation syndrome (MAS), has been recognized to complicate adult onset Still's disease (AOSD) and systemic lupus erythematosus. Due to paucity of reported cases, there is no clear consensus concerning treatment recommendations and outcomes.

Methods: We performed a retrospective study of 5 patients with MAS complicating AOSD at the Cleveland Clinic over the past 7 years. All 5 patients underwent bone marrow biopsy. We also reviewed a total of 77 cases from various published reports and identified 49 cases with definitive evidence of MAS and with complete data. Our cohort and the historical data were compared and analyzed.

Results: We identified 5 cases (4 female, 1 male) for our cohort that satisfy both criteria for AOSD and MAS, with 3 cases simultaneously presenting with MAS and AOSD. Mean age at diagnosis of MAS was 35.8 years and mean follow-up was 14.4 months. All patients had fever, arthralgias, typical rash, and leukocytosis, with lymphadenopathy in 3/5 and sore throat in 2/5 consistent with AOSD. These patients also had MAS, with lung involvement in 2/5, renal insufficiency in 2/5 and shock in 1/5. There was significant hepatic dysfunction in all, but only 1/5 had hepatomegaly. One patient had superimposed histoplasmosis. All patients had bi-cytopenia. Besides systemic glucocorticoids, 4/5 patients received Anakinra and 2 of the patients received combination treatment with Cyclosporine. All 5 patients survived with a mean follow-up of 14.4 $\pm$ 15 months. We also reviewed 49 cases (34 female, 15 male) for the literature cohort. Mean age at diagnosis of MAS was 39.9 years and mean follow-up was 17.2 months. Compared with the historical data, the levels of ferritin and hepatic dysfunction were similarly higher, and triglycerides were less elevated in our cohort, while fibrinogen was normal in both. Soluble IL-2 receptor level was significantly higher as well.

Conclusion: MAS can be a serious complication of AOSD and may coexist with its onset. In conjunction with literature, this study of a relatively largest case series suggests that treatment with a triple combination of an IL-1 receptor antagonist, a calcineurin inhibitor and systemic glucocorticoids may have favorable outcomes.

Disclosure: A. Lenert, None; **Q. Yao**, None.

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The Prevalence of Malignancy in Adult-Onset Still's Disease. Rupal Chavda[1], Melissa R. Bussey[2], Rodney Tehrani[1] and Rochella A. Ostrowski[1]. [1]Loyola University Medical Center, Maywood, IL, [2]Division of Rheumatology, Loyola University Medical Center, Maywood, IL.

Background/Purpose: Adult-onset Still's disease (AOSD) is a systemic inflammatory disease of unknown etiology. It is characterized by high fever, evanescent salmon-colored rash, sore throat, liver dysfunction, lymphadenopathy, hepato-splenomegaly, arthritis, and leukocytosis. Although most inflammatory disorders have a known risk of malignancy there is a lack of published data regarding the risk of malignancy in AOSD. There are multiple case reports suggesting the presence of AOSD or an AOSD-like syndrome in the setting of various solid tumors (breast, lung, renal and thyroid cancer) and hematological malignancies (leukemia and lymphoma). To date, there are no published studies of the relationship between AOSD and cancer. We conducted a retrospective observational study to identify an association between AOSD and malignancy.

Methods: A chart review was performed of patients 18 years of age and older who were diagnosed with AOSD based on Yamaguchi criteria between January 1, 2006 and June 30, 2013 at Loyola University Medical Center. Patients with known infection, pre-existing malignancy, or other rheumatic disorders at the time of diagnosis of AOSD were excluded. Patient charts were reviewed for a subsequent diagnosis of cancer.

Results: From January 2006 to June 2013 twenty-one cases of AOSD were identified. Of these cases, eight fulfilled Yamaguchi criteria for definite AOSD while one was diagnosed with probable AOSD (Table 1). The median age was 38 years (range 18–63 years) and median follow up was 25 months (1-72 months). One patient was subsequently diagnosed with Hodgkin's lymphoma at 7 months follow up. Another patient was diagnosed with non-small cell lung cancer (NSCLC) at 3 months follow up and then acute myeloid leukemia (AML) at 19 months follow up.

Conclusion: In our case series of 9 patients followed over a median period of 25 months, we noted 1 case of Hodgkin's lymphoma, 1 case of AML and 1 case of NSCLC. The National Cancer Institute reports the incidence of Hodgkin's lymphoma as 2.7 per 100,000 and the incidence of leukemia as 13.0 per 100,000 per year. The incidence reported for all lung cancers is 49.2–66.8 per 100,000 per year. The observed incidence of Hodgkin's lymphoma, AML and NSCLCA in our case series is many times higher. Although the association between AOSD and malignancy has been rarely reported, careful screening for malignancy in patients diagnosed with AOSD may be warranted. Additional studies of association between AOSD and malignancy are needed to further explore the relationship between these diagnoses.

Table 1. Cases of Definite and Probable Adult Onset Still's Disease

Case	Age	Sex	Criteria Met	Ferritin (ng/mL)	ALT/AST (IU/L)	WBC (K/UL)	Malignancy
1	34	F	F,S, R, A, T, L	>10,000	131/90	17.5	None
2	38	F	F,R, A, L	2229	12/21	16.4	None
3	57	M	F,A, T, L	2279	209/356	17.4	None
4	54	F	F,R, A	58	19/22	10.2	None
5	23	F	F,S,R,LN, A, T, L	3507	59/87	11.7	None
6	63	F	F,R, A,LN, T, L	5228	194/200	15.7	NSCLC, AML
7	56	F	F, S, R, A,LN, T, L	8405	41/57	21.0	None
8	21	F	F,R,HSM, A, T, L	>10,000	127/108	27.0	None
9	18	M	F, LN, A, L	1147	30/26	13.0	Hodgkin's Lymphoma

F = fever, S = sore throat, R = maculopapular rash, LN = Lymphadenopathy, HSM = hepatosplenomegaly, A = arthritis, T = transaminase elevation, L = leukocytosis. Ferritin normal range: 22–322 ng/mL for males, 10–291 ng/mL for females; AST normal range: 10–40 IU/L, ALT normal range: 15–45 IU/L, WBC normal range (3.5–10.5 K/UL). NSCLC = Nonsmall cell lung cancer. AML = Acute Myeloid Leukemia

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1245

Long Term Outcome of Infliximab in Severe and Refractory Systemic Sarcoidosis: Report of 16 Cases. Catherine Chapelon[1], David Saadoun[1], Lucie Biard[2], Matthieu Resche-Rigon[3], Baptiste Hervier[4], Nathalie Costedoat-Chalumeau[5], Aurélie Drier[6], Jean-Marc Léger[7] and Patrice Cacoub[8]. [1]DHU 2iB Internal Medicine Referal Center for Autoimmune diseases Pitie Hospital, Paris, France, [2]Hôpital St Louis, Biostatistics, Paris, France, [3]Hopital Saint-Louis, Paris, France, [4]Assistance Publique - Hôpitaux de Paris, Pitié-Salpêtrière University Hospital, PARIS, France, [5]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [6]Hôpital Pitié-Salpêtrière, Neuroradiology, Paris, France, [7]Hôpital Pitié-Salpêtrière, Neurology, Paris, France, [8]Groupe Hospitalier Pitié Salpétrière, Service de Médecine Interne, DHU i2B, Paris, France.

Background/Purpose: Infliximab (IFX) appears to be effective in refractory sarcoidosis. However, data are lacking regarding its efficacy in severe sarcoidosis (i.e. with cardiac and/or neurological involvement).

Methods: Retrospective single-center study including 16 unselected consecutive patients with biopsy proven, severe, and resistant sarcoidosis, who were treated by infliximab (3 or 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks) between 2005 and 2013.

Results: Following IFX therapy we observed an improvement in 92% of cases, with a marked decrease of the severity score [median score 6 (3–12) vs. 2 (1–8), $p<0.0001$] and trend toward steroid sparing effect [12.5 (0–40) vs. 8.5 mg/d (0–30), $p=0.11$] between baseline and the end of follow-up, respectively. Regarding the index organ response, we observed a remission of cardiac and central nervous system involvements in 4 out of 4 and 11 out 12 cases, respectively. Thirty-eight percent of patients experienced a relapse. After a median follow-up of 57 months (2 to 91), we observed 7 (44%) infectious complications, 1 paradoxical cutaneous granuloma and 1 leucoen-

cephalopathy. Infectious complications were mostly observed in male [6/7 (86%), p=0.06], with a longer duration of steroids (108 vs. 39 months, p= 0.11) and immunosuppressant use prior IFX (42 vs. 24 months, p = 0.08) compared to their negative counterpart, respectively.

Conclusion: IFX was efficient in severe and refractory sarcoidosis. Infectious complications were frequent and occurred mainly in male patients with longer duration of steroids and immunosuppressant use prior IFX.

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Assessment of Protective Factors of Bone Mineral Density in a New Orleans Sarcoidosis Population. McCall Walker[1], Harmanjot K. Grewal[2], Adam Janot[3], Mary Yu[4], Sophia Cenac[5], Matthew R. Lammi[6] and Lesley Ann Saketkoo[4]. [1]LSUHSC School of Medicine, New Orleans, LA, [2]Louisiana State University Health Sciences Center, New Orleans, LA, [3]Virginia Commonwealth University –Medical College of Virginia, Charlottesville, VA, [4]Louisiana State University Health Sciences Center, New Orleans, LA, [5]Louisiana State University Health Science Center, New Orleans, LA, [6]Louisiana State University Health Sciences Center, Pulmonary and Critical Medicine, New Orleans, LA.

Background/Purpose: Sarcoidosis often involves pathological dysregulation of dependent factors of bone metabolism, e.g. calcitriol/calcium, and administration of high dose glucocorticoids (GCs) leading to low bone mineral density (LBMD). Traditional risk factors for LBMD include advancing age, female sex, low body mass index (BMI), smoking, white race and GCs. LBMD in sarcoidosis is presumed but not yet described.

Methods: A retrospective chart review of biopsy-diagnosed patients with sarcoidosis for > 1 year extracted and compared variables of prevalence, age (at chart review), sex, race, smoking status and designation of LBMD defined as osteopenia or osteoporosis with a T-score of ≤ -1 on DXA. Calculations were performed by non-parametric analyses using Fisher's exact for categorical data and Mann Whitney tests for continuous variables.

Results: 269 charts were reviewed and 109 had documentation of biopsy. Of these 109, 61 patients (86.9% Black) had documentation of DXA, 38 (62.3%) with LBMD (30 with osteopenia and 8 with osteoporosis). Although patients with BMI ≥ 30 had a significantly lower incidence of LBMD vs. those with BMI <30, LBMD incidence exceeded reported in CDC data for overweight subjects. No differences (table) were seen in incident LBMD in patients age ≥ vs < 65, in ever vs never smokers (no significant age difference between groups), nor in males vs females (despite females being significantly older than males with median 54 and 48 respectively).

Table 1. Comparison of Factors Influencing Bone Mineral Density within a New Orleans Sarcoidosis Population

	Low BMD	Normal BMD	Odds Ratio	p Value
% ≥65 Years Old	26% (10/38)	9% (2/23)	3.75 (95% CI 0.74 to 18.96)	0.11
% Male	13% (5/38)	26% (6/23)	0.43 (95% CI 0.11 to 1.61)	0.30
% BMI ≥30	18% (7/38)	52% (12/23)	0.21 (95% CI 0.06 to 0.66)	0.01
% Smoker	32% (12/37)	55% (12/22)	0.40 (95% CI 0.14 to 1.19)	0.11

Conclusion: Factors protective against LBMD in the general population were not demonstrated in this retrospective sarcoidosis predominantly black cohort. A lower risk of LBMD was not conferred by age < 65, male gender, or non-smoking status. While BMI appeared to confer protection, the prevalence in obese sarcoidosis patients supersedes that in CDC reported data. These trends suggest an abnormal signal of incident LBMD in this population differing from the general population. Lack of uniformity of documentation inherent in retrospective methods limits the assessment of important associative and causative influences such as duration and dose of GCs, biomarkers of bone metabolism (e.g. calcium, calcitriol, etc) and fracture risk which will be examined in our prospective sarcoid registry. Nevertheless these findings are important and support increased vigilance in GC use and perhaps consideration to initiate GC sparing agents earlier in the disease course, as well as routine DXA screening in sarcoidosis.

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The Prevalence of Sacroiliitis and Spondyloarthritis in Patients with Sarcoidosis. Senol Kobak[1], Fidan Sever[2], Ozlem Ince[2] and Mehmet Orman[3]. [1]SIFA UNIVERSITY, Izmir, Turkey, [2]Sifa University, Izmir, Turkey, [3]Associated Professor, Izmir, Turkey.

Background/Purpose: Sarcoidosis is a chronic granulomatous disease, which can involve different organs and systems. Coexistence of sarcoidosis and spondyloarthritis has been reported in numerous case reports. **Purpose:** To determine the prevalance of sacroiliitis and spondyloarthritis in patients previously diagnosed with sarcoidosis, and to investigate any possible relation with clinical findings.

Methods: Forty-two patients with sarcoidosis were enrolled in the study. Any signs and symptoms in regard to spondyloarthritis (i.e. existence of inflammatory back pain, gluteal pain, uveitis, enthesitis, dactylitis, inflammatory bowel disease, psoriasis) were questioned in details and biochemical tests were evaluated. Sacroiliac joint imaging and lateral heel imaging were performed in all patients. The existence of active sacroiliitis was confirmed by magnetic resonance imaging of sacroiliac joint with short time inversion recovery (STIR) method.

Results: Sacroiliitis was found in 6 of the 42 (14.3%) sarcoidosis patients and all of these patients were female. The average age of the patients with sacroiliitis was 55 years, while the average duration of the disease was 17.8 months. Common features of the disease in these six patients were inflammatory back pain as the major clinical complaint, stage 2 sacroiliitis as revealed by radiological staging and the negativity of HLA B-27 test.These six patients with sacroiliitis were diagnosed as spondyloarthritis according to the criteria of ASAS and of ESSG.

Conclusion: We found spondyloarthritis in patients with sarcoidosis at a higher percentage rate than in the general population (1–1.9%). Controlled trials involving large series of patients are required for the confirmation of the data.

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Serologic and Clinical Overlap Between Sarcoidosis and the Rheumatic Autoimmume Diseases. Sabrina Qazi and Marie Claire Maroun. Wayne State University, Detroit, MI.

Background/Purpose: Sarcoidosis is a systemic inflammatory disorder of unknown etiology, characterized pathologically by noncaseating epithelioid cell granulomas, primarily affecting the lungs, the eye, the skin, and the lymphatics. Musculoskeletal manifestations and the immunologic profile in sarcoidosis may mimick those seen in the rheumatic autoimmune diseases. Hyperglobulinemia and autoantibodies including rheumatoid factor [RF] and anti-nuclear antibodies [ANA] have been reported. Citrullination is a post-translational modification of proteins, in which the amino acid arginine is enzymatically converted to citrulline. Citrullinated peptides can be found at the site of chronic inflammation and, in the appropriate genetic setting, can elicit an autoimmune response. Anti-cyclic citrullinated peptide antibodies [ACPA] are thought to be a new and more specific marker than RFs in rheumatoid arthritis [RA] and have been added to the new RA classification criteria. The occurrence of ACPA in sarcoidosis has not previously been described.

Objectives: The aim of this study was to investigate the serologic profile, in particular the serum RFs, ANAs and ACPA in patients with sarcoidosis attending the rheumatology and/or pulmonary clinics.

Methods: We retrospectively reviewed the charts of 73 patients with the diagnosis of sarcoidosis and recorded the clinical manifestations and the immunological profile including ANA, RF, and ACPA.

Results: Forty one percent of patients with sarcoidosis [30/73] had a positive ANA, with titers ranging from weakly positive [1/40] to high positive [1/1280]. RF and ACPA were not available on all patients. RF was found in 22 % of patients [13/59] while ACPA was found positive at moderately elevated titers in 8% of patients [2/24] in the absence of RA. One patient with RA with positive CCP was excluded from the analysis. One patient had Sjogren syndrome and one had systemic lupus erythemathosus. In addition, 22% of the patients had sarcoid arthropathy.

Conclusion: ANAs, RFs and ACPA were found in sarcoidosis patients at titers within the range found in the rheumatic ADs. ACPA was present in 8% of sarcoidosis patients in the absence of RA. We suggest that investigation of the autoantibody signatures responsible for the serologic overlap between sarcoidosis and the rheumatic ADs, especially ACPA may be of great interest

since, since inflammation is central in the immune-pathogenesis of sarcoidosis.

Disclosure: S. Qazi, None; **M. C. Maroun**, None.

1249

Efficacy of Tocilizumab in Patients with Uveitis Refractory to Other Biologic Drugs: A Multicenter Study on 31 Cases. Leyre Riancho-Zarrabeitia[1], Vanesa Calvo-Río[1], Ricardo Blanco[1], Inmaculada Calvo[2], Emma Beltrán-Catalán[3], Alfredo Adan[4], Marina Mesquida[4], Maria Victoria Hernández[5], Marisa Hernández[3], Antonio Atanes-Sandoval[6], Luis Francisco Linares Ferrando[7], Olga Maiz Alonso[8], Ana Blanco[8], Beatriz Bravo[9], Gisela Díaz-Cordovés[10], Trinitario Pina[1], Montserrat Santos-Gómez[1] and Miguel A González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [2]Hospital La Fe. Valencia. Spain, Valencia, Spain, [3]Hospital General Universitario de Valencia. Spain, Valencia, Spain, [4]Hospital Clinic. Barcelona. Spain, Barcelona, Spain, [5]Hospital Clínic of Barcelona. IDIBAPS. University of Barcelona, Barcelona, Spain, [6]Rheumatology Division. C. Hospitalario Universitario A Coruña, A Coruña, Spain, [7]Hospital Virgen de la Arrixaca. Murcia. Spain, Murcia, Spain, [8]Hospital Universitario de Donostia. San Sebastián. Spain, San Sebastián, Spain, [9]Hospital Virgen de las Nieves. Granada, Granada, Spain, [10]Hospital Regional Universitario (Carlos Haya). Málaga. Spain., Málaga, Spain.

Background/Purpose: To evaluate the clinical response and safety of Tocilizumab (TCZ) in a series of patients with non-infectious uveitis refractory to other biologic drugs.

Methods: Multicenter study of patients studied in the Uveitis Units of 14 hospitals from Spain. All patients had experienced inadequate response to at least one biologic agent. Intraocular inflammation, macular thickness, visual acuity, steroid sparing effect and immunosuppression load score were the outcome variables. Comparisons were made between baseline and 1st week, 1st month, 6th month and 1st year.

Results: We studied 31 patients/58 affected eyes (7 men/24 women) with a mean age of 31.7±17.2 years (range 8–70). Uveitis was bilateral (n=27 cases) or unilateral (n=4). The pattern of ocular involvement was anterior uveitis (n=11 cases), panuveitis (n=6), posterior (n=4), intermediate (n=3), panuveitis+ retinal vasculitis (n=3), retinal vasculitis without uveitis (n=2) and panuveitis+retinal vasculitis+papillitis (n=1). Uveitis was acute (n=1), chronic (n=26) or recurrent (n=4).

The main underlying diseases were: Juvenile Idiopathic Arthritis (n=13), Behçet disease (n=5), idiopathic uveitis (n=5), Birdshot retinopathy (n=3), idiopathic retinal vasculitis (n=2), spondyloarthritis (n=2) and rheumatoid arthritis (n=1).

Besides oral steroids and before TCZ onset they had received: intraocular corticosteroids (n=21), intravenous. methylprednisolone pulses (n=9), methotrexate (n=25), cyclosporine A (n=20), azathioprine (n=3), other synthetic immunosuppressive drugs (n=9), adalimumab (n=25), infliximab (n=12), etanercept (n=7), abatacept (n=6), rituximab (n=2), golimumab (n=2) and anakinra (n=1). TCZ was started because of inefficacy (n=28) and/or toxicity (n=3) to other biologics. TCZ was used as monotherapy (n=10) or in combination with methotrexate (n=12), leflunomide (n=4), cyclosporine A (n=4) and mycophenolate (n=1). After one year of TCZ therapy all the following variable improved statistically ($p<0.05$) **(TABLE): a)** mean best corrected visual acuity (from 0.46±0.3 at baseline to 0.58±0.3); **b)** anterior chamber cells and vitreous inflammation (from 58% and 60% of eyes, to 15.3% and 34%, respectively); **c)** cystoid macular edema (OCT>300 μm) (from 66.6% to 21%); **d)** the mean OCT (from 389.1±197.2 to 261.8±46.1 μm); and **e)** the median [IQR] dose of prednisone (from 30 [10–90] to 5 [0–5] mg/day). A non-statistically reduction in the mean of the immunosuppression load score (from 6.3±5.1 to 4.2±3.3, p=0.6) was also observed.

After a mean follow-up of 13.4±9.5 months the more important side-effects observed were bullous impetigo (n=1), mild thrombocytopenia (n=1), pneumonia (n=1) and infusional reaction (n=1).

Conclusion: Our results indicate that TCZ is an effective and safe therapy for patients with non-infectious uveitis refractory to other biologic agents.

Table.

	Basal Patients (n) active eyes (%)	1 week active eyes (%)	1 month active eyes (%)	6 months active eyes (%)	1 year active eyes (%)
Anterior chamber cells	21 58%	46.66%*	21.7%*	17.6%*	15.3%*
Vitritis	20 60%	59%*	37.7%*	29%*	34%*
Choroiditis	10 29.2%	24.4%*	8.8%*	3%*	0%*
Retinitis	7 23.9%	11.9%*	14.3%	3.2%*	0%*
Retinal vasculitis	17 48.1%	46.9%*	27.1%*	14.7%*	14.8%*
Macular thickness ≥300 microns	15 66.6%	53.8%*	41.6%*	27%*	21%*

*p<0.05 compare with baseline

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1250

Golimumab As an Alternative Therapy in Patients with Uveitis Refractory to Other Anti-TNFα Drugs. Multicenter Study of 29 Cases. Montserrat Santos-Gómez[1], Francisco Ortiz-Sanjuán[1], Ricardo Blanco[1], Joaquín Cañal Villanueva[1], Alfredo Adan[2], Marina Mesquida[2], M. Victoria Hernández[3], Esteban Rubio Romero[4], Angel M. Garcia-Aparicio[5], Antonio Atanes[6], Ignacio Torre Salaberri[7], Félix Francisco[8], Cruz Fernández- Espartero[9], Natalia Palmou[10], Vanesa Calvo-Río[1], Javier Loricera[1], Juan Ventosa[1], Trinitario Pina Murcia[11], Leyre Riancho-Zarrabeitia[1] and Miguel A. González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [2]Hospital Clinic. Barcelona. Spain, Barcelona, Spain, [3]Hospital Clinic, Barcelona, Barcelona, Spain, [4]Hospital Universitario Virgen del Rocío. Sevilla. Spain, Sevilla, Spain, [5]Virgen de la Salud Hospital, Toledo, Spain, [6]HUCA. La coruña. Spain, La Coruña, Spain, [7]Hospital Universitario de Basurto. Bilbao. Spain, Bilbao, Spain, [8]Hospital Doctor Negrín. Las Palmas de Gran Canaria. Spain, Las Palmas de Gran Canaria, Spain, [9]Hospital Universitario de Móstoles. Madrid. Spain, Madrid, Spain, [10]Complejo Hospitalario Universitario de Albacete. Spain, Albacete, Spain, [11]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain.

Background/Purpose: To evaluate the clinical response and safety of golimumab (GLM) in a series of patients with non-infectious uveitis refractory to other anti-TNFα drugs.

Methods: Multicenter study of 29 patients with uveitis that was refractory to previous standard synthetic immunosuppressive drugs and at least 1 anti-TNFα drug. GLM was given at the standard dose of 50 mg/sc/month. The main outcome measures were degree of anterior and posterior chamber inflammation, visual acuity, and macular thickness.

Results: A total of 29 patients (44 affected eyes) (21 men/8 women) with a mean age of 34.6±9.5 years (range 11–48) were studied. Uveitis was bilateral (n=15 cases) or unilateral (n=14). The pattern of ocular involvement was anterior uveitis (n=19), panuveitis (n=6) and intermediate, anterior+intermediate, anterior+posterior and intermediate+posterior (one case each). Uveitis was acute (n=1), chronic (n=16) or recurrent (n=12).The underlying diseases were spondyloarthritis (n=9), psoriatic arthritis (n=5), juvenile idiopathic arthritis (n=4), Behçet disease (n=4), sarcoidosis (n=3), uveitis associated with HLA-B27 and ulcerative colitis (n=1), undifferentiated arthritis (n=1), pars planitis (n=1) and Vogt-Koyanagi-Harada (n=1).

Besides oral steroids and before GLM onset they had received: intraocular corticosteroids (n=11), intravenous pulses of methylprednisolone (n=6), methotrexate (n=23), cyclosporine A (n=6), azathioprine (n=7), adalimumab (n=17), infliximab (n=15), abatacept (n=2) and certolizumab (n=1). GLM was started because inefficacy (n=27) and/or toxicity (n=2) to other biologics. GLM was used as monotherapy (n=11) or in combination with methotrexate (n=10), azathioprine (n=4), leflunomide (n=2), and mycophenolate (n=2).

After one year of GLM therapy all the following variables improved significantly ($p<0.05$)**(TABLE): a)** The mean best corrected visual acuity (from 0.68±0.3 at baseline to 0.75±0.3); **b)** anterior chamber and vitreous inflammation (from 62.7% and 40.4% of eyes, to 12.5% and 0% respectively); **c)** Cystoid Macular Edema (OCT>300 μm), (from 50% to 0%), **d)** the mean OCT (from 318.9±76 to 244.2±43.2 μm); and **d)** the mean dose of prednisone (from 24±20.1 to 7.7±7.6 mg/day). After a mean follow-up of 13.1±8.5 (range 2–30) months the most important side-effects observed were Injection site erythema (n=3) and herpes zoster (n=1).

Conclusion: Our results suggest that GLM may be an effective and safe treatment for patients with uveitis refractory to other anti-TNFα drugs.

Table

	Basal active patients, N active eyes (%)	1 week active eyes (%)	1 month active eyes (%)	3 months active eyes (%)	6 months active eyes (%)	1 year active eyes (%)
Anterior chamber cells	22 62.7%	55.5%*	30.6%*	23.25%*	7.3%*	9.7%*
Vitritis	12 40.4%	29.7%*	21.9%*	10.5%*	2.7%*	0%*
Choroiditis	2 2.12%	2.12%	0%	0%	0%	0%
Retinitis	1 1.96%	1.96%*	0%*	0%*	0%*	0%*
Retinal vasculitis	3 5.88%	5.88%*	4.1%*	0%*	0%*	0%*
Macular thickness ≥ 300 microns	8 50%	45.4%*	22.7%*	25%*	20%*	0%*

*$p<0.05$ compare with baseline

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Efficacy of Certolizumab in Patients with Refractory Uveitis to Other Biologic Therapy. Study of 7 Cases. Montserrat Santos-Gómez[1], Victor Llorens[2], Marina Mesquida[2], Ricardo Blanco[1], Vanesa Calvo-Río[1], Olga Maíz[3], Ana Blanco[3], Maite Sainz de la Maza[2], Alfredo Adan[2], Leyre Riancho-Zarrabeitia[1] and Miguel A. González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [2]Hospital Clinic. Barcelona. Spain, Barcelona, Spain, [3]Hospital Universitario de Donostia. San Sebastián. Spain, San Sebastián, Spain.

Background/Purpose: Anti-TNF-α therapy may be useful in cases of uveitis refractory to standard synthetic immunosuppressive drugs. Infliximab (IFX) and adalimumab (ADA) are the biologic agents more frequently used. To our knowledge information on Certolizumab Pegol (CZP) in patients with uveitis is scarce. Due to this, we assessed the efficacy of CZP in a series of patients with uveitis refractory to other anti-TNF-α drugs.

Methods: Study from 3 tertiary referral centers that included patients with uveitis that had been refractory to previous standard synthetic immunosuppressive and at least 1 anti-TNF-α drug. For the inclusion in the assessment a follow-up of at least 6 months was required.

Outcome was measured according to SUN criteria (Jabs et al. 2005) for anterior chamber inflammation (0 to 4+) and scale (0 to 4+) for vitreous haze (Bloch-Michel 1997). Best corrected visual acuity (BCVA) was measured by Snellen charts and converted to logarithm (LogMAR) (Jabs 2005). Macular thickness was defined by OCT.

Results: We studied 7 patients (14 affected eyes) (4 men/3 women) with a mean age of 42.4±8.8 years. The main underlying diseases were: Behçet disease (3 cases), idiopathic retinal vasculitis (1 case), ankylosing spondylitis (1 case), psoriatic arthritis and Crohn's disease (1 case) and relapsing polychondritis (1 case). All patients suffered from long-lasting chronic-relapsing ocular inflammation with a median evolution time until CZP onset of 108 (range 68–302) months.

The 1st biological drug was IFX. It was changed to ADA because of serious adverse events (n=3) or loss of efficacy (n=4). However, ADA was withdrawn in all these cases because of inefficacy (n=6) or lupus-like reaction (n=1)]. Afterward, 3 patients were switched to golimumab (GLM) and 1 to etanercept (ETN) **(TABLE).** Due to inefficacy, all 7 patients were switched to CZP that was administered at the standard dose (induction dose of 400 mg q2w for 4 weeks followed by 200mg q2 w for maintenance). After a mean follow-up of 10.4±4.8 months since CZP onset, 5 (71.4%) patients achieved remission and 4 of them could withdraw oral prednisone. Mean logMAR visual acuity improved significantly from 0.41±0.48 at baseline to 0.34±0.45 at first month ($p=0.03$) and remained stable since then. Macular edema was present in 4 eyes (3 patients) at baseline. The mean OCT decreased from 328.3±96.5 microns at baseline to 303.1±81.8 at final visit ($p=0.099$). CZP was well tolerated in all cases and no adverse event was observed during follow-up.

Conclusion: CZP can be an alternative to other anti-TNF-α agents in patients with refractory uveitis.

Table

case	sex/age	anatomical pattern	etiology	previous non-biologic immunosuppressive drugs	previous biologic immunosuppressive
1	M/34	panuveitis	Behçet disease	CyA	IFX, ADA, GLM
2	M/38	panuveitis	Ankylosing spondylitis	CyA, MTX	IFX, ADA, GLM
3	F/33	anterior uveitis	Psoriatic arthritis & Crohn's disease	CyA, AZA	IFX, ADA
4	F/51	panuveitis	Behçet disease	CyA, AZA, MTX	IFX, ADA
5	F/37	posterior uveitis	Idiopathic retinal vasculitis	AZA, MTX	IFX, ADA
6	M/53	anterior uveitis + scleritis	Relapsing polychondritis	MTX	IFX, ADA, ETN
7	M/51	panuveitis	Behçet disease	CyA, AZA, MTX	IFX, ADA, GLM

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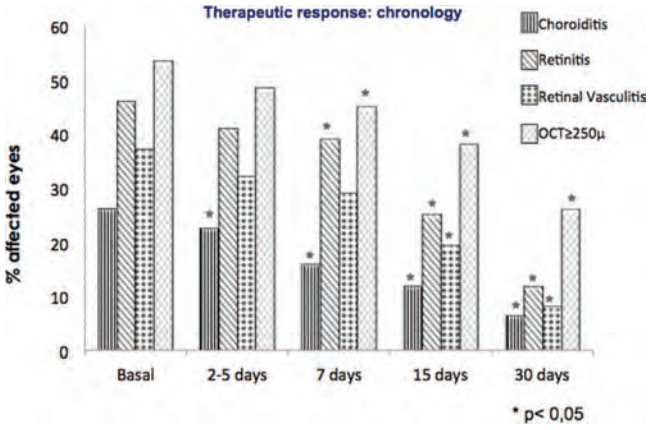
Intravenous Methylprednisolone Pulse Therapy in Severe Inflammatory Eye Disease. A Multicenter Study. Montserrat Santos-Gómez[1], Emma Beltrán[2], Vanesa Calvo-Río[1], Ricardo Blanco[1], Norberto Ortego[3], Jose L. García Serrano[3], Lucía Martínez Costa[3], Alejandro Fonollosa[4], Marisa Hernández[2], Elia Valls[5], Félix Francisco[6], Miguel A. Reyes[6], Ignacio Torre Salaberri[7], Olga Maíz[8], Ana Blanco[8], Santiago Muñoz-Fernández[9], M. Mar Esteban[9], Esperanza Pato[10], Manuel Díaz-Llopis[11], Roberto Gallego[11], Miguel Cordero[12], Francisco Ortiz-Sanjuán[1], Joaquín Cañal Villanueva[1], Leyre Riancho-Zarrabeitia[1] and Miguel A González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [2]Hospital General Universitario de Valencia. Spain, Valencia, Spain, [3]Hospital Universitario San Cecilio. Granada. Spain, Granada, Spain, [4]Hospital de Cruces. Bilbao. Spain, Bilbao, Spain, [5]Hospital Dr. Peset. Valencia. Spain, Valencia, Spain, [6]Hospital Doctor Negrín. Las Palmas de Gran Canaria. Spain, Las Palmas de Gran Canaria, Spain, [7]Hospital Universitario de Basurto. Bilbao. Spain, Bilbao, Spain, [8]Hospital Universitario de Donostia. San Sebastián. Spain, San Sebastián, Spain, [9]Hospital Infanta Sofía. San Sebastián de los Reyes. Spain, Madrid, Spain, [10]Hospital Clínico San Carlos. Madrid. Spain, Madrid, Spain, [11]Hospital Universitario La Fe. Valencia. Spain, Valencia, Spain, [12]Hospital de León. Spain, León, Spain.

Background/Purpose: Treatment with high-dose intravenous methylprednisolone (IVMP) pulse therapy has proved to be effective in different inflammatory conditions. Since severe ocular inflammation can lead to rapid and irreversible structural and functional eye damage, we aimed to assess the efficacy of IVMP pulse therapy as a remission induction therapy in patients with severe ocular inflammation.

Methods: Multicenter study of patients with severe ocular inflammation attended at 11 Uveitis Units from Spain. All patients were treated with IVMP pulse therapy for 2–5 consecutive days. MP dose ranged from 0.25 to 1 gram per day. Patients were evaluated at baseline and on days 2–5, 7, 15 and 30 after treatment with IVMP.

Results: 104 patients (59 women/45 men; mean age of 42.27±14.42 years [range 8–76 years]) with severe ocular inflammation were included in the study. The most frequent underlying conditions were: idiopathic uveitis (n=21), Vogt-Koyanagi-Harada (n=26), Behçet disease (n=19), spondyloarthritis (n=4), Sjögren syndrome (n=2), psoriatic arthritis (n=2) and multiple Sclerosis (n=2). All the patients had active and severe intraocular inflammation at baseline. The inflammatory ocular patterns were: panuveitis (n=61), posterior uveitis (n=35), anterior uveitis (n=3), scleritis (n=3) and intermediate uveitis (n=2). Bilateral ocular involvement was observed in 65 patients (62.5 %). Following IVMP pulse therapy inflammation in the anterior chamber, vitritis and visual acuity experienced rapid and statistically significant improvement. It was already seen 2 days after the onset of IVMP therapy. However, improvement of retinal vasculitis, choroiditis/chorioretinitis and macular edema was achieved more gradually, reaching statistical significance from the first week. Optical coherence tomography (OCT) showed a macular thickening ($>250\mu$) in 90 eyes at baseline, with normalization in 30 % of the affected eyes at day 15 and in 50 % of the affected eyes at day 30 ($p<0.05$). IVMP pulse therapy was well tolerated without remarkable side effects.

Conclusion: Treatment with IVMP pulse therapy decreases rapidly the ocular inflammation, leading to an improvement of all the ophthalmological measurements without important side effects.



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Anakinra – a Promising New Therapy for Idiopathic Recurrent Pericarditis. Sonia Jain[1], Charat Thongprayoon[2], Raul Espinosa[1], Sharonne Hayes[1], Kyle Klarich[1], Kevin Moder[3], Nandan Anavekar[1], Jae Oh[1] and Eric L. Matteson[4]. [1]Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, [2]Mayo clinic, Rochester, MN, [3]Division of Rheumatology, Mayo Clinic, Rochester, MN, [4]Mayo Clinic, Rochester, MN.

Background/Purpose: Idiopathic recurrent pericarditis (IRP) is a debilitating condition that can be recalcitrant to conventional therapy. Some patients develop steroid dependency with the attendant risks of systemic side effects and increased future recurrence. Anakinra is a recombinant human interleukin-1 receptor antagonist that reduces systemic inflammatory responses. The aim of this study was to evaluate the therapeutic role of anakinra in a series of adult patients with IRP refractory to conventional therapy.

Methods: We retrospectively studied consenting patients with treatment refractory IRP who received anakinra, between January 2009 and November 2013. None of the patients had an identified systemic inflammatory rheumatic disease. The primary end points were symptom resolution and steroid discontinuation.

Results: Nine patients were followed for a median of 16.8 (IQR 1.3–24) months. Study subjects were predominantly female (7 [78%]) with a median age of 53 (IQR 38 – 58) years. All 9 patients had failed maximum tolerated doses of NSAIDs, colchicine and prednisone (median dose 20 mg [IQR 15 – 22.5]). Additionally, 2 patients (22%) were on hydroxychloroquine, 2 (22%) on azathioprine and 1 (11%) on methotrexate. Primary symptom was chest pain in 9 (100%), with concurrent dyspnea in 5 (56%) patients. Symptom duration prior to anakinra initiation was 24 (IQR 13 – 71) months. Indication for anakinra was steroid sparing agent in 7 (78%) and symptom control in 2 (22%) patients. The dosage was 100 mg once daily via subcutaneous injection. Baseline left ventricular ejection fraction was 62% (IQR 59% - 67%). Echocardiographic findings include pericardial effusion in 3 (33%), pericardial thickening in 6 (67%), and constrictive physiology in 4 (44%). Pericardial enhancement on cardiac MRI was seen in 7 (78%) patients. All 9 patients (100%) had prompt symptom improvement with complete resolution in 8 (89%) and partial resolution in 1 (11%) patient. At last follow up, all (100%) patients had discontinued NSAIDs and colchicine, 5 (56%) patients discontinued and 4 (44%) had reduced prednisone dosage. 4 out of 5 patients (80%) discontinued concomitant immunsuppressive agents. 1 patient remained on low dose hydroxychloroquine. All patients remained on anakinra at the end of follow up. The only reported side effect was transient injection site reaction in 4 (44%) patients. In 2 (22%) patients, attempted anakinra weaning was unsuccessful due to symptoms flare after 6 weeks.

Conclusion: Anakinra is an effective alternative agent for the management of steroid dependent IRP. It can provide remarkable symptomatic amelioration, avoid steroid dependency, and is associated with minimal side effects.

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Anakinra for the Management of Resistant Idiopathic Recurrent Pericarditis in Adults. Dimitrios Vassilopoulos[1], Panagiotis Vasileiou[1], Christos Koutsianas[1], Katerina Antonatou[2], Christina Tsalapaki[1], Dimitrios Pectasides[1] and George Lazaros[2]. [1]University of Athens Medical School, Athens, Greece, [2]Hippokration General Hospital, Athens, Greece.

Background/Purpose: Recurrent idiopathic pericarditis is currently considered as an auto-inflammatory disorder which is frequently either resistant to standard therapy (with NSAIDs, colchicine or corticosteroids-CS) or requires long term treatment with high doses of CS. Interleukin-1 (IL-1) inhibition has shown encouraging results in pediatric cases and a few adult cases. The aim of our study was to explore the efficacy and safety of anakinra in adult patients with recurrent idiopathic pericarditis.

Methods: In this open label study, ten patients with idiopathic recurrent pericarditis were included. All were resistant and/or intolerant to previous treatment with aspirin and/or NSAIDs, colchicine and CS while two (20%) had failed azathioprine therapy. Patients were initially treated with daily subcutaneous injections of anakinra (100 mg) with gradual tapering of the administered dose. Recurrences as well as adverse events were recorded in all patients during the follow-up period (24 $\pm$ 16 months).

Results: Among the 10 patients included (5 females/5 males, mean age = 42 $\pm$ 18 years, mean disease duration=37 $\pm$ 22 months), the mean number of recurrences despite standard therapy was 8 $\pm$ 3.7 while the baseline mean daily dose of prednisolone was 14.1 $\pm$ 7.9 mg. All patients treated with anakinra demonstrated a rapid clinical response with resolution of symptoms and normalization of CRP (mean time=5.9 $\pm$ 2.3 days). All patients receiving CS at baseline (n=8) were able to gradually discontinue them (mean time to discontinuation = 53 $\pm$ 44 days). Among 7 patients who discontinued anakinra, 5 (70%) relapsed after a mean time of 18 $\pm$ 9 days; in 4/5, anakinra was restarted leading again to clinical remission while one was successfully treated with NSAIDs and colchicine. One patient discontinued therapy due to transient elevation of aminotransferases while 6 (60%) demonstrated mild skin reactions at the injection site.

Conclusion: Our study shows that IL-1 inhibition with anakinra is a highly efficacious, safe and steroid-sparing strategy for treatment-resistant recurrent idiopathic pericarditis in adults. Further studies are needed to clarify the appropriate dose and duration of therapy in these patients.

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ACR/ARHP Poster Session B
Muscle Biology, Myositis and Myopathies: Myositis Autoantibodies and Disease Phenotype
Monday, November 17, 2014, 8:30 AM–4:00 PM

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Pathogenic Role of Tyrosyl–Transfer RNA Synthetase in Anti-Synthetase Syndrome. Yuko Okamoto[1], Yasuhiro Katsumata[1], Yasushi Kawaguchi[1], Manabu Kawamoto[1], Ken Iwaki[2], Miki Miyanokoshi[2], Keisuke Wakasugi[2], Koji Tahara[3], Kaori Ito[3], Hiroaki Hattori[3], Takahisa Gono[1], Masanori Hanaoka[1], Tomoaki Higuchi[1], Hidenaga Kawasumi[1] and Hisashi Yamanaka[4]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]The University of Tokyo, Tokyo, Japan, [3]BML, Saitama, Japan, [4]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Autoantibodies directed against the aminoacyl transfer RNA (tRNA) synthetases are associated with myositis, arthritis, Raynaud's phenomenon, mechanic's hands, fever, and interstitial lung disease, clinically referred to as anti–synthetase syndrome. Targoff and his colleagues reported a case with an autoantibody to tyrosyl–tRNA synthetase (TyrRS) with features of anti–synthetase syndrome at the 2005 ACR meeting. At the 2013 ACR meeting, we reported three more patients with anti–TyrRS autoantibodies in the setting of anti–synthetase syndrome using other assays than previously reported methods: enzyme–linked immunosorbent assay, Western blot, and immunoprecipitation assay. In addition, one of the authors of this abstract reported that TyrRS can be split into two fragments with distinct chemotactic activities: an interleukin-8 (IL-8)–like cytokine, and an

endothelial-monocyte-activating polypeptide II (EMAP II)–like cytokine (*Science*. 1999). We aimed to further elucidate the pathogenic role of TyrRS in anti–synthetase syndrome.

Methods: Previously defined anti–TyrRS antibody–positive patients with features of anti–synthetase syndrome were the study subjects. Anti–TyrRS antibody–positive and control sera were tested for the ability to inhibit TyrRS aminoacylation by preincubation of the enzyme source with the sera. Recombinant human TyrRS and histidyl–tRNA synthetase (HisRS; Jo–1) proteins were generated. Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized whole blood of an anti–TyrRS or an anti–HisRS antibody–positive patient by density gradient centrifugation. Then, PBMCs were cultured and stimulated with TyrRS, HisRS, or phytohemagglutinin (PHA). Antigen–specific cell proliferation was analyzed using tetrazolium salt as a chromogenic indicator for nicotinamide adenine dinucleotide (NADH). Immunohistochemical analyses were performed to determine if the corresponding chemokine receptors were upregulated in frozen muscle tissue from an anti-TyrRS antibody–positive patient using primary mouse anti–human mAbs and peroxidase-conjugated anti–mouse IgG Fab'.

Results: Anti–TyrRS sera significantly inhibited the *in vitro* enzymatic function of TyrRS (aminoacylation of $tRNA^{Tyr}$) compared with normal control serum. In the cell proliferation assay using PBMCs from an anti–TyrRS patient, the O.D. values of the TyrRS–stimulated cells were significantly higher than in those of the unstimulated cells and HisRS–stimulated cells. Immunohistochemical analyses demonstrated that C–C chemokine receptor type 1 (CCR1) and type 2 (CCR2) which are the receptor of IL–8, and type 3 (CCR3) which is the receptor of EMAP II, were expressed in degenerating muscle fibers, vascular endothelial cells, and infiltrating mononuclear cells in muscle tissue from an anti–TyrRS antibody–positive patient.

Conclusion: This study showed that the anti–TyrRS sera can function as an enzyme inhibitor. TyrRS may also play some pathogenic roles in anti–synthetase syndrome by recruiting leukocytes to inflammatory cites and eliciting adaptive immune responses.

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Clinical and Temporal Characterization of Anti-Jo-1 Positive Anti-Synthetase Syndrome: Preliminary Results of an International Multicentre Study.

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Background/Purpose: Anti Jo-1 antibodies are the main marker of the antisynthetase syndrome (As), a connective tissue disease chiefly characterized by arthritis (A), myositis (M) and interstitial lung disease (I). These manifestations may occur concomitantly but incomplete clinical pictures have been described. Aim of this study is to further characterize clinical presentation and course of anti Jo-1 positive As

Methods: Data from multicentre, multinational series of patients diagnosed with anti Jo-1 positive As were retrospectively collected and analyzed. Anti Jo-1 antibodies were tested in all cases by commercially available ELISA techniques.

Results: 146 patients were included (Table 1). Median follow up was 91 months (IQR 40.25–153.75). At the onset, a complete clinical picture (AMI) was present in 26 patients (18%). Seventy-two patients (49%) had monosymptomatic presentation (A 36, 24.5%; M 20, 14%; I 16, 11%), 19 AM (13.5%), 19 MI (13.5%) and 10 AI (7%). Arthritis was the most frequent feature at the onset, the only detectable in 24.5% of patients. Many patients meet the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA). Rheumatoid factor, anti citrullinated peptide antibodies and RA typical radiographic erosions were not a rare finding. Time from clinical onset to diagnosis was longer in incomplete forms ($p<0.001$). During the follow up, 69 patients (57.5%) developed additional features (median time to progression: 17 months, IQR 7.5–43.5). Progression rate was significantly higher in patients with single feature onset (57/72) with respect to those with two features (12/48) ($p<0.001$). At the last follow-up, 69 patients (47%) had AMI, 23 (15.5%) AM, 23 (15.5%) MI, 16 (11%) AI, 8 (5.5%) I, 4 (3%) A and 3 (2%) M. Twenty-five patients (17.5%) died, 7 (5%) due to As progression. First line treatment was based on corticosteroids (140 patients, 96%) and immunosuppressants (112, 77%; hydroxychloroquine, HCQ, 30; methotrexate, MTX, 24; IV cyclophosphamide, CYC, 20; cyclosporine, Cys, 20; azathioprine, AZA, 17; mycophenolate mofetil, MMF, 4; tacrolimus, TC, 3; other not listed). Globally, MTX was prescribed in 58 patients (40%, 22 withdrawn for side effects/ineffectiveness), Cys in 47 (32%, 10), AZA 36 (24.5%, 21), CYC 34 (23%, 23), HCQ 34 (23%, 21), MMF in 17 (11.5%, in 5), TC in 9 (6%, 5)

Conclusion: The diagnosis of anti Jo1 positive As may be delayed in incomplete forms, which are the vast majority at presentation. Joint involvement may be very similar to RA, adding further challenges to differential diagnosis. Clinical picture evolution is common in patients presenting with incomplete forms and it may occur even after several years from disease onset. Treatment appears heterogeneous and with high drop-out rates in both first and second line. This suggests the need of better strategies supported by specific recommendations.

DISEASE ONSET						LAST FOLLOW UP			
p	Incomplete forms	Complete forms	All patients	Patients characteristics		All patients	Complete forms	Incomplete forms	p
\	120 (82)	26 (18)	146 (100)	Patients number (%)		146	69 (47)	77 (53)	\
*0.9327	51 (40.5-65.5)	52 (45-62)	51 (42-64)	Age (years; median, IQR)		\	\	\	\
* <0.0001	9 (2-34)	2 (1-6)	6 (2-20)	Diagnostic delay (months;median, IQR)	Disease duration (months;median, IQR)	91 (48.25-153.75)	105 (60-171.25)	71 (37.5-131.25)	0.1174*
0.8743	36/84	8/18	44/102	Males/females (number)		44/102	22/47	22/55	0.0925
\	63 (43)	26 (18)	89 (61)	Arthritis (number,%)		112 (77)	69 (47)	43 (29.5)	\
0.9188	45 (31)	19 (13)	64 (44)	RA-like (number,%)		76 (52)	47 (32)	29 (20)	0.8936
	18 (12.5)	7 (5)	25 (17.5)	Non RA-like (number,%)		36 (24.5)	22 (15)	14	
0.8636	22 (15)	5 (3.5)	27 (18.5)	RF positivity (number,%)		31 (21.5)	18 (12.5)	13 (9)	0.2481
0.9429	6 (4)	2 (1.5)	8 (5.5)	ACPA positivity (number,%)		9 (6)	6 (4)	3 (2)	0.3902
0.8005	19 (13)	3 (2)	22 (15)	Patients with erosive arthritis (number,%)		24 (16)	16 (11)	8 (5.5)	0.629
\	80 (41)	26 (18)	86 (59)	Myositis (number,%)		119 (81)	69	50 (34)	\
0.6041	42 (29)	16 (11)	58 (40)	Classic (number,%)		77 (53)	44 (30)	33 (22.5)	0.7183
	18 (12.5)	10 (7)	28 (19)	Hypomyopathic (number, %)		42 (29)	25 (17.5)	15 (10)	
\	44 (30)	26 (18)	70 (48)	Interstitial lung disease (number,%)		117 (80)	69 (47.5)	48 (33)	\
0.5913	23 (16)	11 (7.5)	34 (23)	Acute (number,%)		44 (30)	22 (15)	22(15)	0.247
	12 (8)	7 (5)	19 (13)	Chronic (number, %)		41 (28)	25 (17.5)	16 (11)	
	9 (6)	8 (5.5)	17 (11.5)	Asymptomatic (number, %)		32 (22)	22 (15)	10 (7)	
0.2648	52 (36)	15 (10)	67 (46)	Anti-Ro positivity (number, %)		67 (46)	33 (22.5)	34 (23)	0.781
0.3819	33 (22.5)	10 (7)	43 (29.5)	Fever (number, %)		53 (36)	26 (18)	27 (18.5)	0.8762
0.8044	24 (16.5)	7 (5)	31 (21)	Mechanic's hands (number, %)		42 (29)	21 (14.5)	21 (14.5)	0.8117
0.2490	30 (20.5)	10 (7)	40 (27.5)	Raynaud's phenomenon (number, %)		55 (37.5)	31 (21)	24 (16)	0.127

Table 1: main characteristics of anti Jo-1 patients at disease onset and at last follow up. IQR: interquartile range. RA: Rheumatoid arthritis. RF: rheumatoid factor. ACPA: anti-cyclic citrullinate peptide. * Independent Sample T test (if equal variances) or Welch-test (if unequal variances). Others: Chi-square test . % are expressed in number with respect to all patients enroled

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A New Multianalyte Assay for Detection of Dermatomyositis-Specific Autoantibodies Undetectable By Commercially Available Immunoassays. Masataka Kuwana, Yuka Okazaki and Tsutomu Takeuchi. Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: The disease expression of dermatomyositis (DM) is highly variable among patients, ranging form those with severe muscle weakness in the absence of internal organ involvement to those with clinically amyopathic DM (CADM) complicating fatal rapidly progressive interstitial lung disease. A series of serum autoantibodies have been identified in DM patients, and are useful in diagnosis as well as disease subsetting. These are antibodies to aminoacyl tRNA synthetase (ARS), including Jo-1, EJ, OJ, PL-7, PL-12, and KS, Mi-2, melanoma differentiation-associated gene 5 (MDA5), transcription intermediary factor-1 (TIF1)-γ, NXP2, SAE, and Ku. These antibodies are detectable by immunorecipitation (IP) assays for RNA and protein components, which require a complicated procedure with cultured human cell lines and a radioisotope. Recently, a novel enzyme-immunoassay (MESACUP anti-ARS test; MBL) has been developed for detection of 5 different anti-ARS specificities together (Jo-1, EJ, PL-7, PL-12, and KS), and a multianalyte line-blot assay that detects Mi-2, Ku, PM-Scl, Jo-1, SRP, PL-7, PL-12, EJ, OJ (Myositis Profile 3 EUROLINE, EUROIMMUN) is commercially available. However, many DM-specific antibodies are still undetectable by these convenient assays. In this study, we have developed a new multianalyte assay for detection of DM-specific antibodies undetectable by current commercial assays, using a principle of IP combined with immunoblots (IB).

Methods: We enrolled 116 patients with DM, including 52 with CADM, who were diagnosed at our institution between 2000 and 2013. DM-specific antibodies were first identified using IP assays and the MESACUP anti-ARS test. Patients' sera negative by the MESACUP test were further applied to a multianalyte IP/IB assay, in which native autoantigens were isolated by IP technique, followed by IB probed with a mixture of monoclonal or polyclonal antibodies specific to Mi-2 (240kDa), TIF1γ (155kDa), OJ (150kDa), NXP2 (145kDa), MDA5 (140kDa), SAE (90kDa), and Ku (80kDa). Identification of individual antibodies was based on the molecular sizes of the immunoreactive bands. In some sera, DM-specific specificities were also measured by the EUROLINE.

Results: DM-specific antibodies were detected in 101 (87%) patients by IP assays. These included MDA5 in 26, Jo-1 in 14, TIF1γ in 14, EJ in 10, PL-7 in 7, PL-12 in 7, OJ in 6, NXP2 in 6, Mi-2 in 4, Ku in 3, SAE in 2, and U1RNP in 2). The MESACUP anti-ARS test was positive in 38 (33%) patients who were completely matched to those positive for Jo-1, EJ, PL-7, or PL-12 by IP assays. When 78 sera negative by the MESACUP test were further subjected to the multianalyte IP/IB assay, results obtained by IP assays and the IP/IB assay were identical in terms of Mi-2, TIF1γ, OJ, NXP2, MDA5, SAE, and Ku (sensitivity and specificity 100%). We also applied 51 sera positive for Mi-2, Ku, Jo-1, PL-7, PL-12, EJ, or OJ to the Euroline, resulting in a false-negative result in all 6 anti-OJ-positive sera and a false-positive result of Ku in 3 sera.

Conclusion: Multianalyte IP/IB assay is a convenient and reliable method useful for detection of a full panel of DM-specific autoantibodies when it is combined with the commercial MESACUP test.

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Enzyme-Linked Immunosorbent Assays for Detection of Anti-Transcriptional Intermediary Factor-1 Gamma and Anti-Mi-2 Autoantibodies in Dermatomyositis: Utility and Crossreactivity. Manabu Fujimoto[1], Akihiro Murakami[2], Shunsuke Kurei[2], Akiko Kuwajima[3], Yasuhiro Fujisawa[1], Atsushi Kawakami[4], Michiaki Mishima[5], Shinji Sato[6], Mariko Seishima[7], Takafumi Suda[8], Tsuneyo Mimori[9], Kazuhiko Takehara[10] and Masataka Kuwana[11]. [1]Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [2]Medical & Biological Laboratories Co., Ltd, Nagaya, Japan, [3]Medical & Biological Laboratories Co.,Ltd., Nagoya, Japan, [4]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [5]Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan, Kyoto, Japan, [6]Tokai University School of Medicine, Isehara, Japan, [7]Gifu University Graduate School of Medicine, Gifu, Japan, [8]Hamamatsu University School of Medicine, Hamamatsu, Japan, [9]Kyoto Univ Grad Schl of Med, Kyoto, Japan, [10]Kanazawa University, Kanazawa, Japan, [11]Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Anti-transcriptional intermediary factor 1 (TIF-1) and anti-Mi-2 antibodies (Abs) are myositis-specific autoantibodies (MSA) selectively detected in dernatomyositis (DM) patients. Anti-TIF-1 Ab is frequently found in juvenile DM and cancer-associated adult DM. Anti-Mi-2 Ab is predominantly detected in patients with classic DM with favorable prognosis. TIF-1 and Mi-2 proteins share similar molecular structures and amino acid sequences, suggesting a potential crossreactivity. In this study, we have established enzyme-linked immunosorbent assays (ELISAs) for anti-Mi-2 and anti-TIF-1γ Abs, and have assessed their utility and crossreactivity.

Methods: Serum samples were obtained from 242 patients with idiopathic inflammatory myopathy (IIM) who were followed up at 8 medical centers across Japan. IIM patients included 104 with classic DM, 68 with clinically amyopathic DM (CADM) and 70 with polymyositis. Serum samples from 190 patients with other connective tissue diseases (CTDs) including 45 with rheumatoid arthritis, 67 with systemic lupus erythematosus, 43 with systemic sclerosis, 20 with mixed connective tissue disease, 8 with Sjögren's syndrome, and 7 with others, and 123 healthy individuals were also assessed.

Full-length TIF-1γ and Mi-2β proteins were produced by a baculovirus expression system. Purified proteins were respectively coated on ELISA plates, on which serum antibody levels were examined. To assess the crossreactivity, partial-length Mi-2β proteins with or without mutations were produced and processed similarly, before subjected to ELISA.

Results: Cutoff levels for anti-TIF-1γ and anti-Mi-2 ELISAs were calculated using Receiver Operating Characteristic analysis based on the results from the gold standard IP assay of 242 IIM samples. When compared with IP assay, anti-TIF-1γ ELISA showed 100% sensitivity and 100% specificity, while anti-Mi-2 ELISA showed 100% sensitivity and 99.6% specificity.

Anti-TIF-1γ Ab was positive in 30 (28.8%) with classic DM and 4 (5.9%) with CADM, whereas 14 (13.5%) with classic DM, but none with CADM, were positive for anti-Mi-2 Ab. Anti-TIF-1γ and anti-Mi-2 Abs were both positive in 2 (1.1%) with CTDs other than IIM, respectively. Of 30 anti-TIF-1γ positive DM patients, 23 (67.6%) and 5 (14.7%) had malignancy and interstitial lung disease (ILD), respectively. By contrast, 3 (21.4%) had malignancy in 14 anti-Mi-2 positive DM patients, but none had ILD. Both Abs were negative in normal subjects.

Although no samples positive for anti-Mi-2 Ab exceeded the cutoff level of anti-TIF-1γ Ab, they showed substantially higher levels than those negative for anti-TIF-1γ Ab. ELISA analyses after absorption with various truncated Mi-2 proteins with and without inserted mutations identified that anti-Mi-2 Ab weakly crossreacted with the 896–903 amino acid sequence (ggdllcce) within a Plant Homeo domain of TIF-1γ protein, due to the sequence homology with Mi-2β protein (458–465, ggellccd).

Conclusion: The current study demonstrates the utility of newly established ELISAs for anti-TIF-1γ and anti-Mi-2 Abs, which can serve as easier detection systems for routine testing. Developing these ELISAs needs attention to crossreactivity of anti-Mi-2 Ab with TIF1 antigen.

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A Multi-Center Study for Validation of a New Assay for Anti-Melanoma Differentiation-Associated Gene 5 (MDA5) Autoantibody. Shinji Sato[1], Akihiro Murakami[2], Akiko Kuwajima[3], Kazuhiko Takehara[4], Tsuneyo Mimori[5], Atsushi Kawakami[6], Michiaki Mishima[7], Takafumi Suda[8], Mariko Seishima[9], Manabu Fujimoto[10] and Masataka Kuwana[11]. [1]Tokai University School of Medicine, Isehara, Japan, [2]Medical & Biological Laboratories Co., Ltd, Nagaya, Japan, [3]Medical & Biological Laboratories Co.,Ltd., Nagoya, Japan, [4]Kanazawa University, Kanazawa, Japan, [5]Kyoto Univ Grad Schl of Med, Kyoto, Japan, [6]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [7]Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan, Kyoto, Japan, [8]Hamamatsu University School of Medicine, Hamamatsu, Japan, [9]Gifu University Graduate School of Medicine, Gifu, Japan, [10]Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [11]Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Anti-Melanoma Differentiation-Associated Gene 5 (MDA5) antibody is found specifically in patients with dermatomyositis (DM). This autoantibody is associated with clinically amyopathic DM (CADM) and rapidly progressive interstitial lung disease (RP-ILD) especially in eastern Asian population. An association between anti-MDA5 antibody titer measured by in-house enzyme-linked immunosorbent assay (ELISA) and disease activity has been also reported. Recently, we have established an ELISA system for detection of anti-MDA5 antibody for clinical practice use.

Objectives: To verify utility of our anti-MDA5 ELISA in a multi-center study.

Methods: Sera and clinical information were obtained from 432 patients with connective tissue disease (CTD) and 154 with Idiopathic interstitial pneumonia (IIP), who were followed at 8 participating hospitals. CTD patients included 104 with classic DM, 68 with CADM, 70 with polymyositis (PM), 43 with systemic sclerosis, 67 with systemic lupus erythematosus, 45 with rheumatoid arthritis, 20 with mixed connective tissue disease, 8 with Sjögren syndrome, and 7 with other CTD. IIP was defined as interstitial lung disease of unknown cause, in which patients did not fulfill classification criteria for any specific CTD or vasculitis. A healthy control included 123 volunteers. Anti-MDA5 ELISA utilized a recombinant protein encompassing the entire amino acid sequence of MDA5, which was expressed and purified using a baculovirus expression system. Antibody levels were shown in an index, which was calculated by optical density (OD) at 450 nm according to the following formula: (sample OD – blank OD/positive reference OD – blank OD) $\times$ 100. Immunoprecipitation (IP) assay was also conducted in patients with PM/DM (including classic DM, CADM, and PM). Comparisons between two groups were made using the chi-square test.

Results: Of 242 PM/DM samples, 10 (9.6%) with classic DM and 46 (67.6%) with CADM were positive for anti-MDA5 antibody by the gold standard IP assay. When a cutoff of the anti-MDA5 ELISA was set at 32 index based on receiver operating characteristics curve analysis in comparison with results of IP assay, analytical sensitivity and specificity of the ELISA were 98.2% and 100%, respectively. The ELISA showed an extremely high specificity, since anti-MDA5 antibody was detected in none of the patients with other CTD (including PM), those with IIP, or healthy controls. RP-ILD was more frequently found in classic DM/CADM patients with anti-MDA5 than in those without (83.6% versus 14.5%, $P < 0.001$).

Conclusion: This multi-center study has confirmed that a newly established ELISA for anti-MDA5 antibody is as efficient as the IP assay. This system enables easier and wider use in the detection of anti-MDA5 antibody in patients suspected to have DM and/or RP-ILD.

Disclosure: S. Sato, Holding a patent on anti-MDA5 antibody-measuring kit, 7; **A. Murakami**, employee of Medical & Biological Laboratories Co., Ltd., 3; **A. Kuwajima**, employee of Medical & Biological Laboratories Co., Ltd., 3; **K. Takehara**, None; **T. Mimori**, None; **A. Kawakami**, None; **M. Mishima**, None; **T. Suda**, None; **M. Seishima**, None; **M. Fujimoto**, None; **M. Kuwana**, Holding a patent on anti- MDA5 antibody-measuring kit., 7.

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The Early Use of Cyclosporine Is Beneficial for Long-Term Prognosis in Patients of Polymyositis/Dermatomyositis-Associated Interstitial Lung Disease with Anti- Synthetase Antibodies. Yuji Hosono[1], Ran Nakashima[2], Yoshitaka Imura[2], Naoichiro Yukawa[2], Hajime Yoshifuji[2], Takaki Nojima[3], Koichiro Ohmura[2] and Tsuneyo Mimori[2]. [1]Graduate School of Medicine, Kyoto University, Kyoto, Japan, [2]Kyoto University Graduate School of Medicine, Kyoto, Japan, [3]Hiroshima University Hospital, Hiroshima, Japan.

Background/Purpose: Interstitial lung disesases (ILD) is the most common cause of mortality in polymyosotis (PM) and dermatomyositis (DM). Cyclosporine had been reported to improve clinical outocome in some patients with PM/DM and associated ILD. However, the efficiencies and longterm prognosis depending on the time of administration are still unclear. Here, we intended to investigate the benefits of early use of cyclosporine in PM/DM-associated ILD with antibodies (Ab) against aminoacyl-tRNA synthetase.

Methods: Clinical data and serum samples were collected from 144 adult Japanese patients with PM/DM who visited our department from January 2005 to December 2013. Patients who were treated with cyclosporine within 3 months from the initial treatment with high dose glucocorticoids were defined as early use group. Myositis-specific Abs (MSAs) were screened using the RNA immunoprecipitation assay. Kaplan-Meier survival analysis was applied to compare overall mortality rates.

Results: Sixty eight patients (33 with PM and 35 with DM) were positive for anti- synthetase Ab positive (25 anti-Jo-1, 14 anti-PL-7, 13 anti-EJ, 7 anti-PL-12, 5 anti-OJ, and 4 anti-KS). Among them, 64 patients (94%) had ILD. Among PM/DM associated ILD patients, 11 (17%, 6 with PM and 5 with DM) were cyclosporine early use group. Twenty-one (32%, 7 with PM and 14 with DM) were treated after more than 3 month from initial treatment and 32 (50%, 18 with PM and 14 with DM) were not treated with cyclosporine. The 15-year survival rate of early use group was significantly higher than that of delayed use of cyclosporine and non-combination with cyclosporine groups ($P<0.05$ by log-rank test). Three of 11 (27%) of early use group did not show any exacerbation of ILD after the treatment, while none of delayed group ($P<0.05$). There were no significant differences in age, sex, duration of diseases, rates of each anti-synthetase Ab, and requirement of intravenous cyclophosphamide pulse therapy among each group. One of 2 in early use group needed no longer home oxygen therapy within first year from the initial treatment, whereas none of other groups.

Conclusion: Our study showed significant survival benefits of cyclosporine use at early stage in PM/DM-associated ILD with anti- synthetase Ab. The introduction of combination therapy with cyclosporine and high dose glucocorticoids at early stage for ILD in PM/DM patients should be strongly recommended.

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1261

Pulmonary Arterial Hypertension in Patients with Anti-PM-Scl Antibody. Hiromichi Tamaki, Colin O'Rourke and Soumya Chatterjee. Cleveland Clinic, Cleveland, OH.

Background/Purpose: Patients with anti-PM-Scl antibody (PM-Scl) can present with several different phenotypes: polymyositis (PM), dermatomyositis (DM), systemic sclerosis (SSc), scleromyositis, or sclero-dermatomyositis. Pulmonary arterial hypertension (PAH) may be a disease manifestation of patients with PM-Scl but the association has not been rigorously examined and the association between its clinical manifestations and PAH is not clear, especially with PAH confirmed on right heart catheterization (RHC).

The association of PAH in systemic sclerosis is well established. Recent discoveries of effective medications to treat PAH, especially in patients with SSc have been encouraging and have important implications for other "autoimmune rheumatic disease"-associated PAH. It is not clear whether similar recommendations should apply to patients with PM-Scl.

Methods: All patients screened for PM-Scl between October 1999 and April 2014 were evaluated through our electronic medical record (EMR) system and patients with positive PM-Scl were identified. The patients' demographics, rheumatologic diagnoses (PM, DM, SSc, scleromyositis, or sclero-dermatomyositis), co-existing auto-antibodies, RHC variables, skin manifestations related with dermatomyositis, and presence of CT defined interstitial lung disease (ILD) were extracted from their EMR retrospectively. The primary outcome of this study was to compare the prevalence of RHC-confirmed PAH among patients with PM-Scl to that in the general population and also to that in SSc. The secondary outcomes were to explore possible predictors of PAH among these patients including presenting phenotypes or co-existing auto-antibodies.

Results: PM-Scl was detected in 42 patients; 32 (76.2%) were female. Mean age at diagnosis of their rheumatologic condition was 45.1 years and that of PM-Scl detection was 51 years. Five patients had RHC proven PAH [11.9% (95% confident interval 4.0% - 25.6%)], of whom 2 had moderate (mean pulmonary artery pressure (PAP) 41–55 mmHg) and 3 had mild PAH (mean PAP 25–40 mmHg). Compared to a previously documented prevalence of PAH in the general population of 0.0015%, this study found a significantly higher rate of PAH in patients with PM-Scl (1). However, the rate (11.9%) did not differ significantly from a previously documented prevalence of PAH in SSc patients (7.8%) (2). Of all PM-Scl positive patients 27 had ILD, of whom 4 also had PAH. There was a significant association between phenotype and PAH ($P=0.003$). In our cohort, all patients with PAH were associated with either DM or sclero-dermatomyositis phenotypes. There was no significant association of co-existing autoantibodies in these PAH patients.

Conclusion: Patients with PM-Scl have a higher prevalence of PAH than that in the general population, and should be screened for it at baseline and periodically thereafter. In our cohort PAH was seen in those presenting with a clinical phenotype of DM or sclero-dermatomyositis.

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Disclosure: H. Tamaki, None; **C. O'Rourke**, None; **S. Chatterjee**, United Therapeutics, 2.

1262

Mechanisms of Muscular Necrosis in Auto-Immune Myopathies Associated with Anti-Signal Recognition Particle and Anti-3-Hydroxy-3-Methylglutaryl-Coenzyme a Reductase Antibodies: Pathogenic Role of Auto-Antibodies. Yves Allenbach[1], Aude Rigolet[2], Bruno Eymard[3], Tanya Stojkovic[3], Anthony. Behin[3], Pascal Laforet[3], Peter Hufnagl[4], Norman Zerbe[4], Thierry Maisonobe[5], Kuberaka Mariampillai[3], Serge Herson[3], Olivier Benveniste[1] and Werner Stenzel[4]. [1]Sorbonne Universités, University Pierre et Marie-Curie-Paris 6, INSERM, Paris, France, [2]Assistance Publique - Hôpitaux de Paris, Pitié-Salpêtrière University Hospital, Paris, France, [3]Assistance Publique - Hôpitaux de Paris, Pitié-Salpêtrière University, Paris, France, [4]Charite Hospital, Berlin, Germany, [5]Pitie-Salpetriere Hospital, Paris, France.

Background/Purpose: Necrotizing auto-immune myopathies (NAM) are a group of acquired idiopathic inflammatory myopathies characterized by severe muscle weakness and no or mild extra-muscular involvement. Definition of NAM is based on morphological features including fiber necrosis with no or few inflammation. Anti-SRP and anti-HMGCR auto-antibodies are specifically associated with NAM. However, to date data concerning histological features of anti-SRP or anti-HMGCR auto-antibody positive NAM patients (SRP^+ or $HMGCR^+$ NAM) are rare and mechanisms involved in fiber necrosis are totally unknown. We aim to describe the histological pattern of the skeletal muscle of a large series of SRP^+ or $HMGCR^+$NAM patients and to analyze mechanisms involved in muscle necrosis.

Methods: Fiber necrosis was detected on combined dystrophin stain and eosin counterstaining. Fiber necrosis were manually counted and normal fibers were automatically counted using imageJ software on digitally completely scanned slides. For immunohistochemical analysis, cell density was measured. **Results** are compare to a myositis group of anti-Jo-1 auto-antibody positive patients. A panel of immune mediators was tested by quantitative PCR in muscle biopsies (expressed as normalized fold change relative to normal muscle).

Results: The percentage of fiber necrosis is higher ($3.2\pm2.5\%$) in SRP^+ NAM patients ($n=22$) compared to $1.6\pm1.5\%$ in $HMGCR^+$ NAM patients ($n=19$) ($p=0.02$) and $1.6\pm2.5\%$ in Jo-1+ patients ($n=17$) ($p=0.007$). Amount of necrosis is not different in $HMGCR^+$ NAM patients vs. $Jo1^+$ patients but $80.7\pm6.7\%$ of necrosis occurs in perifasciuclar region in Jo-1^+ patients ($25.3\pm2.8\%$ in NAM; $p<0.001$). T cells and $CD8^+$ T cells densities are higher in Jo-1^+ patients (33.2 ± 7.9 cells/mm^2 and 22.3 ± 24.6 cells/mm^2) compared to NAM patients (10.2 ± 2.3 and 4.1 ± 6.0 cells/mm^2; $p=0.001$) but 17.7% of NAM patients harbored significant T cells infiltrates (>20 cells/mm^2). A diffuse MHC-I expression was observed in 22.7% of NAM patient vs. 87% in Jo1+ patients ($p<0.001$). In NAM patients T cells, $CD8^+$ T cell densities are correlated with amount of necrosis ($r=0.5$ and $r=0.4$; $p<0.01$) and an up-regulation of *IFN-γ* gene expression is observed in NAM patients (SRP^+ ($n=7$) and $HMGCR^+$($n=7$)).

On the other hand, a Th-2 immune polarization is observed in SRP^+ ($n=7$) and $HMGCR^+$ ($n=7$) NAM patients attested by the up-regulation of *STAT6*expression (11.5 ± 5.1). In the same line 95.2% of NAM patients harbor complement membrane attack complex (C5b-9) deposits with $13.8\pm16.1\%$ of muscle fibers decorated by C5b-9. Sarcolemmal C1q and IgG deposits are observed in all tested NAM patients ($n=3$).

Conclusion: SRP^+ and $HMGCR^+$ NAM patients present mostly a NAM pattern with a randomly distributed necrosis (contrary to Jo-1^+ patients) more pronounced in SRP^+ patients. Nevertheless a subgroup of patients presents inflammatory infiltrates which could be involved partly in muscular necrosis. In addition the Th-2 immune response with signs of classical complement pathway activation suggests the pathogenic role of auto-antibodies.

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Evidence for the Involvement of NK Cells in Antisynthetase Syndrome. Baptiste Hervier[1], Yves Allenbach[2], Mikael Perez[3], Hervé Devilliers[4], Fleur Cohen-Aubart[5], Zahir Amoura[6], Werner Stenzel[7], Isabelle Cremer[3], Olivier Benveniste[2] and Vincent Vieillard[1]. [1]INSERM UMR-S 1135, UPMC, Paris, France, [2]Sorbonne Universités, University Pierre et Marie-Curie-Paris 6, INSERM, Paris, France, [3]INSERM & UPMC, Paris, France, [4]CHU de Dijon, Dijon, France, [5]Pitié-Salpêtrière Hospital, APHP, Paris, France, [6]Pitié-Salpêtrière Hospital (AP-HP), Paris, France, [7]Charite Hospital, Berlin, Germany.

Background/Purpose: Antisynthetase syndrome (aSS) is characterized by the association of interstitial lung disease and myositis with anti-tRNA-synthetase autoantibodies. Its pathogenesis remains unknown, especially regarding the involvement of innate immune cells, including natural killer (NK) cells. Here, we describe the first phenotypic and functional characterization of NK cells in this context.

Methods: A total of 20 patients with inactive and active aSS were included (women/men =9, median age =50 years), and compared to 20 healthy controls. Freshly isolated NK cell phenotype was performed by Flow cytometry. Polyfunctionality assays were performed to measure degranulation and intracellular production of TNFa and IFNg, spontaneously or after stimulation by interleukin(IL)-12 and IL18, in the presence of K562 target cells. The presence and the localization of NK cells in primary human specimens of lung ($n=3$) and muscle ($n=3$) target tissue were studied by immunohistochemistry, using anti-NKp46 monoclonal antibody.

Results: NK cells from inactive patients showed normal phenotype, whereas active aSS revealed a differentiated NK cell profile, as indicated by a increased level of CD57 ($p=0.09$) and ILT2 ($p=0.016$) associated with decreased CD161 ($p=0.052$) and NKp30 ($p=0.009$), compared to healthy donors. This is consistent with the inability of circulating NK cells of active aSS patients to produce IFNγ ($p=0.0017$) after IL12 plus IL18 stimulation, compared to healthy controls. More importantly, our in-depth analysis reveals that NKp30 down-modulation strongly correlated with the loss of NK cell functions (Spearman coefficient $r=0.57$, $p=0.009$), and could be a surrogate marker of aSS activity. Histological studies reveal for the first time the presence of small numbers of NK cells in the muscles, as well as a massive infiltration of NK cells inside the lungs of aSS patients.

Conclusion: Taken as a whole, NK cell phenotypic and polyfunctional changes as well as infiltration of target tissue argue for an involvement of NK cells in aSS pathogenesis.

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Analysis of Clinical Manifestations and Myositis-Specific Autoantibodies Associated with Severity of Physical Dysfunction after Treatment for Polymyositis and Dermatomyositis. Hidenaga Kawasumi[1], Takahisa Gono[1], Yasushi Kawaguchi[1], Yasuhiro Katsumata[1], Hisae Ichida[1], Akiko Tochimoto[1], Masanori Hanaoka[1], Yuko Okamoto[1], Sayuri Kataoka[1] and Hisashi Yamanaka[2]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Half of all polymyositis (PM)/dermatomyositis (DM) patients suffer from muscle weakness after initial treatment. Therefore, many patients with PM/DM have trouble with daily living even after disease activity has been adequately controlled. However, details regarding the clinical factors that are associated with the disability of physical function after treatment in PM/DM remain unclear. The aim of our study was to clarify the clinical manifestations and myositis-specific autoantibodies (MSA) that are associated with the severity of physical dysfunction after treatments in PM/DM.

Methods: In the present study, Seventy seven patients who were diagnosed with PM, DM or clinically amyopathic DM (CADM) were retrospectively enrolled. They were admitted to our hospital from December 1991 to February 2013 because of initial treatment for PM/DM/CADM. Diagnoses were made based on the criteria of Bohan and Peter or those of Sontheimer. We obtained clinical data from their medical records, including age of disease onset, gender, and disease duration. We also obtained laboratory data prior to initial treatment, such as CK, LD, antinuclear

antibodies and MSA, the content of treatment, and the presence of relapse. We evaluated the physical dysfunction of each patient after treatment from August to October 2013 using the Japanese version of the Health Assessment Questionnaire Disability Index (J-HAQ-DI). We retrospectively analyzed the clinical data prior to the initial treatment as predictors for the severity of physical dysfunction after treatment.

Results: Of the 77 patients with PM/DM/CADM, the median age of disease onset was 46 years old, and 79% of the patients were female. The numbers of PM, DM, and CADM cases were 40, 30, and 7, respectively. Anti-a*minoacyl*-tRNA synthetase antibody (anti-ARS), anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5), and anti-signal recognition particle antibody (anti-SRP) were identified in 25, 7, and 9 patients, respectively. Anti-Mi-2, anti-TIF1-γ, and anti-NXP-2 were also identified in a few patients. The median dose of prednisolone (PSL) at the initial treatment was 50 mg/day. The median of J-HAQ-DI score after treatment was 0.125 (range 0–2.75). In a multivariate analysis, the age of disease onset (t value=4.72, $p<0.0001$), female status (t=2.80, $p<0.01$), and the initial doses of PSL (t=1.83, $p=0.073$) were associated with the severity of the J-HAQ-DI score after treatment. The serum levels of CK prior to treatment, the presence of mPSL pulse therapy, and the relapse of the diseases were not associated with the severity of the J-HAQ-DI scores after treatment. From the viewpoint of MSA, anti-SRP positivity was associated with more severe physical dysfunction after treatment than other MSAs. However, anti-MDA-5-positivity was associated with better physical function after treatment than other MSAs.

Conclusion: The age of disease onset, gender, and the initial dose of PSL were significant factors associated with the severity of physical dysfunction after treatment in PM/DM. The clarification of MSA is useful for predicting the prognosis of physical function after treatment in PM/DM.

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Diabetes and Atorvastatin Are Potential Risk Factors for Statin-Associated Myopathy with Autoantibodies Against 3-Hydroxy-3-Methylglutaryl-Coenzyme a Reductase. Pari Basharat[1], Arash Lahouti H.[1], Andrew L. Mammen[1], Iago Pinal-Fernandez[1], Tanmayee Bichile[2], Thomas E. Lloyd[3], Sonye K. Danoff[1], Livia Casciola-Rosen[2] and Lisa Christopher-Stine[1]. [1]Johns Hopkins University, Baltimore, MD, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Johns Hopkins, Baltimore, MD.

Background/Purpose: The idiopathic inflammatory myopathies (IIM) comprise a group of autoimmune disorders that target skeletal muscle. Some IIM cases may be associated with an autoantibody against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), especially in statin exposed patients. The purpose of our study was to characterize the disease course, prevalence of comorbidities and detailed statin history in HMGCR antibody positive (HMGCR +) IIM patients, as compared to statin exposed HMGCR antibody negative (HMGCR -) IIM patients. We also aimed to distinguish differences between statin exposed vs statin naive HMGCR + patients.

Methods: From 5/1/02 to 1/31/14, 1687 suspected myopathy patients evaluated at the Johns Hopkins Myositis Center were enrolled in a longitudinal study. Serum and DNA samples were available for 1083 patients. Patients were included in our analysis if they met Bohan and Peter (B and P) criteria for definite/probable polymyositis or dermatomyositis. HMGCR autoantibodies were tested for via immunoprecipitation and ELISA. Patients in the comparator group were selected from the large cohort of myositis patients if they were HMGCR-, fulfilled the aforementioned B and P criteria, and had a documented statin history including exact statin name, dose, and start/stop dates. We performed a retrospective chart review from time of first clinic visit until 01/31/2014 or last clinical encounter.

Results: There were 77 HMGCR+ patients, 19 statin naïve. Data was compared between 58 statin exposed HMGCR+ IIM patients and 39 statin exposed HMGCR- IIM patients. HMGCR+ patients were slightly older (mean age 59.9 vs 55; p=0.013) but otherwise had similar baseline characteristics. HMGCR+ patients had higher mean creatine kinase (CK) values ($p<0.001$), and greater hip flexor weakness at presentation (p=0.002) and over time. Distal weakness was more prevalent in HMGCR– patients (p=0.023). IVIG (p=0.036) and Rituximab (p=0.018) were used more in HMGCR+ patients. More HMGCR– patients had interstitial lung disease (ILD) (p=0.003). There was no difference in the prevalence of dysphagia. HMGCR+ patients had a higher prevalence of non-steroid induced type II diabetes (p=0.002). There was a higher prevalence of cancers in the HMGCR+ group (10 patients), although not statistically significant (p=0.775). More patients in the HMGCR+ group were exposed to atorvastatin ($p<0.001$). Adjusted for HMGCR antibody status, multiple regression showed no significant association between individual statins and measures of CK and proximal weakness. HMGCR- patients exposed to statins > 1 year had slightly increased arm abduction weakness at presentation. Statin naïve HMGCR+ patients were significantly younger than statin exposed HMGCR+ patients and received less Rituximab and IVIG, although results for IVIG were not statistically significant. Four statin naïve HMGCR+ patients had a history of cancer.

Conclusion: Compared to statin exposed HMGCR- patients, statin exposed HMGCR+ patients had a higher prevalence of type II diabetes, a high number of cancers, increased exposure to atorvastatin prior to symptom onset, less prevalence of ILD, and greater treatment with IVIG and Rituximab.

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Anti-MDA5 Is Associated with Rapidly-Progressive Interstitial Lung Disease and Poor Survival in U.S. Patients with Amyopathic and Myopathic Dermatomyositis. Siamak Moghadam-Kia[1], Chester V. Oddis[1], Shinji Sato[2], Masataka Kuwana[3] and Rohit Aggarwal[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Tokai University School of Medicine, Isehara, Japan, [3]Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Clinically amyopathic dermatomyositis (CADM) is a subset of dermatomyositis (DM) presenting with the characteristic rash(es) of DM without objective muscle weakness. Asian studies report that anti-MDA5 autoantibody (autoAb) in CADM is associated with interstitial lung disease (ILD), particularly rapidly-progressive ILD (RPILD). These associations have not been established in U.S. myositis patients. The goals of our study were to determine the association of anti-MDA5 autoAb with ILD, RPILD and survival in U.S. patients with CADM and DM.

Methods: A cohort of CADM patients were matched (gender and age) 1:1 with classic DM controls. CADM was defined by a DM rash without objective muscle weakness for at least 6 months after rash onset with no or minimal abnormalities of serum muscle enzymes, electromyography or muscle biopsy. We collected clinical, laboratory, radiographic and survival data on the CADM and DM cohorts. Anti-MDA5 autoAb was measured by serum ELISA on both groups. ILD was defined by fibrosis on imaging studies and RPILD by the acute onset and rapid worsening of dyspnea or severe radiographic ILD/fibrosis within 3 months from the onset of respiratory symptoms. Kaplan-Meier and Cox proportional hazard model was used for survival analysis. Chi-square test and Student's t-test was used for other associations.

Results: We identified 61 CADM patients and 61 age and gender matched DM controls. There were 62% and 64% females, 92% and 87% Caucasians, with a mean (SD) age of 48.2 (16.9) and 44.8 (17.6) in the DM and CADM cohorts, respectively. Anti-MDA5 frequency was similar in CADM (13.1% [8/61]) and DM (13.1% [8/61]) as was ILD (CADM: 31.1% [19/61], DM: 26.2% [16/61]) or RPILD (CADM: 8.2% [5/61], DM: 5% [3/61]), p = NS]. Anti-MDA5 positivity was significantly associated with ILD as 50% (8/16) of MDA-5+ subjects had ILD vs. 25.5% (27/106) of MDA-5- subjects (p=0.043). Anti-MDA5 was strongly associated with RPILD ($p<0.001$). Among 8 anti-MDA5+ patients with ILD, 7 had RPILD leading to early death in 5; whereas, only one MDA5- patient had RPILD (1/106). Anti-MDA5 positivity was significantly associated with poor survival (Figure 1, p=0.007), but the presence of ILD or CADM was not predictive of survival. RPILD had a very poor prognosis with hazard ratio (HR) of 28 (CI: 9–86, $p<0.001$). Multivariate analysis suggested that anti-MDA5 positivity predicted survival (HR [C.I.] = 7 [2–23], p=0.001) even after controlling for diagnosis (CADM vs. DM), age at diagnosis, gender, ethnicity, smoking, and ILD (p=0.002).

Conclusion: CADM is not associated with anti-MDA5 or ILD in U.S. DM patients. Anti-MDA5 has a similar frequency in CADM and DM and is significantly associated with ILD, RPILD, and poor survival in U.S. DM patients.

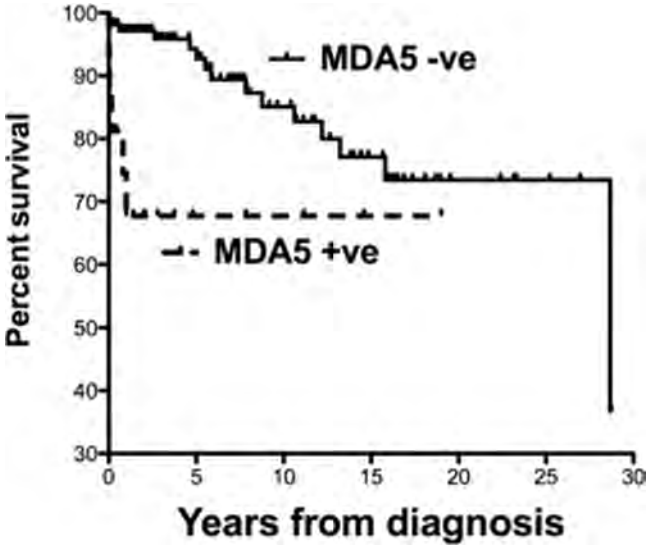

Figure 1. Kaplan-Meier survival curve for anti-MDA5 positive and negative patients (p-value=0.007).

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Are Anti-SRP Auto-Antibodies Specific for Myositis? Samantha Rodriguez-Muguruza, Ines Lozano, Jaume Coll, Maria Lourdes Mateo, Susana Holgado, Eva Martínez-Cácerez and Alejandro Olivé Marqués. Hospital Universitari Germans Trias i Pujol, Barcelona, Spain.

Background/Purpose: Myositis-specific auto-antibodies (Ab) include those directed against aminoacyl-tRNA synthetases (ARS), signal recognition particle (SRP) and nuclear helicase Mi-2. Anti-SRP Ab are among the most abundant and best characterized myositis-specific Ab. Patients diagnosed with myositis associated with anti-SRP Ab are mainly associated with aggressive disease and poor prognosis and are refractory to glucocorticoids/To determine the clinical features, serological features and long-term prognosis among patients with anti-SRP Ab.

Methods: We retrospectively analyzed 8 patients with positive anti-SRP Ab, detected between 2000 and 2013 in our hospital (Tertiary, referral: 850,000 inhabitants). Medical records of patients with polymyositis (PM) or dermatomyositis according to the Bohan and Peter criteria, and patients with anti-cytoplasmic Ab, were reviewed regardless of diagnosis. Past and current status were assessed from hospital records. A post-questionnaire, personal interview and electromyography (EMG) test were performed in patients without myositis. Anti-nuclear Ab and anti-tissue Ab (AMA, LC, LKM) were tested at diagnosis by indirect immunofluorescence on Hep-2000 cells (Immunoconcepts®) and in-house tissue, respectively. Myositis-specific Ab: anti-ARS (Jo-1, PL7, PL12) and anti-SRP were tested by immunoblot (Orgentec®). In addition, levels of creatine kinase (CK) were measured by turbidimetry (Roche®).

Results: Patients with anti-SRP Ab were 6 Caucasians and 2 north-African women, mean age 63 years; three (37.5%) had PM (1 associated with systemic sclerosis). At diagnosis, muscle weakness was severe in 2 patients (defined as < 3 of manual muscle strength testing), associated with dysphagia and respiratory muscle involvement. Season of onset of muscle weakness: 2 in spring and 1 in winter. All 3 patients were treated with glucocorticoids; 2 required immunosuppressive agents (methotrexate, azathioprine, rituximab or intravenous immunoglobulin). Histological study of biceps brachii showed histological changes consistent with necrotising myopathy with scarce inflammatory cells. Five (62.5%) patients showed no features of myositis after a follow-up of 6 months to 3.5 years; 4 had a normal EMG and normal CK levels. Their diagnoses were: rheumatoid arthritis, Sjögren′s syndrome, autoimmune hepatitis, and primary biliary cirrhosis (pure and associated with systemic sclerosis). There were no deaths or history of malignancy among the 8 anti-SRP patients.

Race/Age (years)	Diagnosis	Treatment	EMG	CK U/L (maximum)	Other Ab
North african/36	Autoimmune hepatitis	Azathioprine	N/A	40	Ro52, La
White/65	Primary biliary cirrhosis, sarcoidosis	Ursobilane	Normal	42	M2
White/69	Primary biliary cirrhosis, systemic sclerosis	Ursobilane	Normal	72	M2, Cep B
White/83	Rheumatoid arthritis	Azathioprine, prednisone	Normal	37	Anti-CCP antibodies, ANA Homogenous Pattern 1/640
White/74	Sjogren′s Syndrome	No	Normal	41	Ro 52, Ro 60, La
North african/46	PM	Methotrexate, azathioprine, prednisone, Ig, Rituximab	Polymyositis	3000	Ro 52, La
White/80	PM	Methotrexate, prednisone	Polymyositis	2339	No
White/58	PM, systemic sclerosis	Prednisone	Polymyositis	1100	Ro52, SP100

N/A not available.

Conclusion: Although anti-SRP remains a specific Ab for PM, it is occasionally detected in patients with other rheumatic diseases and autoimmune hepatitis in the absence of myositis.

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Study of Autoantibodies in a cohort of Mexican patients with idiopathic inflammatory myopathies. Yelitza Gonzalez-Bello[1], Miguel Angel Ortiz-Villalvazo[2], Ignacio Garcia-Valladares[1], Gabriel Medrano-Ramírez[3], José E. Navarro-Zarza[4], Lilia Andrade-Ortega[5], Arnulfo Nava-Zavala[1], Gerardo Orozco-Barocio[1], Marco Maradiaga-Ceceña[6], Marvin Fritzler[7] and Ignacio Garcia-De La Torre[8]. [1]Hospital General de Occidente, Zapopan, Jal., Mexico, [2]Hospital Civil de Guadalajara, Guadalajara, Jal., Mexico, [3]Hospital General de Mexico de la Secretaría de Salud, Mexico City, Mexico, [4]Hospital General de Chilpancingo, Chilpancingo, Gro., Mexico, [5]CMN 20 Noviembre ISSSTE, Mexico City, Mexico, [6]Hospital General de Culiacan de la Secretaría de Salud, Culiacan, Sin., Mexico, [7]University of Calgary, Calgary, AB, [8]Universidad de Guadalajara, Guadalajara, Jal., Mexico.

Background/Purpose: Idiopathic inflammatory myopathies (IIM) are a group of autoimmune disorders characterized by muscle inflammation, progressive weakness with a combination of clinical, electromyography and laboratory findings, which includes the expression of autoantibodies. In the last few years there has been an increasing interest to study IIM in different geographic populations. The objective of the study was to identify ANA, the myositis specific antibodies (MSA) and the myositis associated antibodies (MAA) in a cohort of Mexican IIM patients.

Methods: Serum samples from 77 IIM patients were collected from five participating centers in Mexico. ANA were detected by indirect immunofluorescence (IIF) on HEp-2 cells (Antibodies Inc., Davis, CA., USA). MSA and MAA were tested by two different methods: Luminex ENA (FIDIS: Thera-Diag, Paris, France) kit (ALBIA), and EUROLine Autoimmune Inflammatory Myopathies 15 Analyte kit (Euroimmun, Luebeck, Germany, line immunoassay).

Results: Of the 77 IIM patients, 55 (71%) had dermatomyositis (DM), 13 (17%) polymyositis (PM) and 9 (12%) juvenile dermatomyositis (JDM). The mean age was 40 years (6–69 years), 67 (87%) were female. The frequency of ANA by IIF was 81%, the most common IIF patterns were homogeneous and speckled representing close to 60%, the second most common pattern was cytoplasmic speckled 13% and then nucleolar 10%, 37% had the highest end point titer of 1:5,120.

By LIA the frequency of MSA was: Mi-2β (40.2%), Jo-1 (18.1%), SRP (5.2%), PL-12 and Mi-2α (3.9%), Anti-PL-7 (2.6%), Anti-EJ (1.3%) and Anti-OJ (0%). The most frequent MAA tested by LIA was PM/Scl-75 (12.9%), followed by Ku and TIF-1-gamma (9%), and MDA-5 (7.8%); with less than 4% attributed to PM/Scl-100, NXP-2 and SAE-1. Ro52/TRIM21 (16.9%) was detected by FIDIS ALBIA. Of the 16.9% of positive Ro52/TRIM21 patients, 30% were also positive for Jo-1 (LIA), and 54% for Mi-2β (LIA).

Conclusion: This is the first study of MSA and MAA in a cohort of Mexican IIM patients from 5 different centers. We observed a high prevalence of IIF ANA (81%) which is consistent with some previous reports. Homogeneous and speckled pattern represented approximately

60% of the ANA and the second most common pattern was cytoplasmic and nucleolar (13 and 10%, respectively). Regarding the analysis of the MSA and MAA we found an increased prevalence of anti-Mi2 antibodies (32.5%) an autoantibody typically associated with DM which was even higher frequency (~40%) when the two α and β isoforms of anti-Mi2 were analyzed. This is in contrast to many other geographic studies were anti-synthetase antibodies tend to be the most common IIM autoantibody. The most common MAA antibody was anti-Ro52/TRIM21, an autoantibody that has been associated with pulmonary fibrosis and polyautoimmunity. It is worth noting that up to 46% of the positive Ro52/TRIM21 patients did not share any MSA or MAA which may indicate that it is an independent marker in IIM sera.

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Epidemiology and Characteristics of Antisynthetase Syndrome in the African Descent Population of Martinique. Christophe Deligny[1], Maryvonne Dueymes[2], Serge Arfi[1], José Zécler[2], Maia Forgues[3], Véronique Dehlinger[4], Michel DeBandt[5], Lauren Brunier-Agot[5], Remi Bellance[5], Isabelle Lamaury[6], Nadege Cordel[6], Nicolas Baillet[7], Gilbert. Cadelis[8], Georges Jean Baptiste[9] and Katlyne Polomat[5]. [1]Centre hospitalier Universitaire de Fort de France, Fort de France, Martinique, [2]Centre Hospitalier Universitaire de Fort de France, Fort de France, Martinique, [3]Centre Hospitalier Andre Rosemon, Cayenne, French Guiana, [4]Centre Hospitalier universitaire de Fort de France, Fort De France - Martinique, Martinique, [5]Centre Hospitalier universitaire de Fort de France, Fort de France, Martinique, [6]Centre Hospitalier universitaire de Guadeloupe, Pointe à Pitre, Guadeloupe, [7]Centre Hospitalier de la Basse Terre, Basse Terre, Guadeloupe, [8]Cnetre Hospitalier Universitaire de Guadeloupe, Pointe à Pitre, Guadeloupe, [9]Centre Hospitalier Universitaire de Fort de France, Fort de France, Guadeloupe.

Background/Purpose: There is no population based epidemiologic studies of antisynthetase syndrome (ASS). We described characteristics and epidemiology of this disease in Martinique, populated by an African descent population.

Methods: Incidence was calculated including incident cases prospectively identified from 2006 to 2013 by 3 sources in Martinique: (1) competence center for rare systemic autoimmune diseases, (2) national referral center for rare neuromuscular disorders, (3) the only respiratory medicine department, all located in the academic hospital of Fort de France. We included to describe biological and clinical characteristics, more patients from the rheumatology, internal medicine and respiratory medicine units of the 2 others French American regions (Guadeloupe and French Guiana). Inclusion criteria were: presence of one of the antisynthetase antibodies associated to muscular, rheumatologic involvement or interstitial lung disease.

Results: In the 3 regions, 41 patients (all of African descent) were found (31 from Martinique, 6 from Guadeloupe and 5 from French Guiana): 31 females, 10 males. The mean age at diagnosis was 44.1 yo (range: 25–82). Three patients were lost to follow up (none in Martinique) and 5 deceased (2.06 dead/100 patients-year). The mean follow up time was 72.3 months. Fifty one percent had anti-Jo1 antibody, 44% anti-PL12, 5% anti-PL7. Initially, the clinical picture was: 15% and 57% muscular ($p< 0.05$), 60 and 38% pulmonary ($p>0.05$), 50 and 23.8% rheumatologic ($p> 0.05$) for anti-PL7/PL12 and anti-Jo1 respectively. Cumulative characteristics in 41 patients showed: Interstitial lung disease 82.9% (PL7/12: 90%, Jo1: 76.2%; $p> 0.05$), arthritis 63.4% (PL7/12: 65%, Jo1: 62.9%; $p>0.05$), mechanic hands 51.2% (PL7/12: 36.8%, Jo1: 71.4%, $p>0.05$), fever 51.2% (PL7/12: 60%, Jo1: 42.9%; $p>0.05$). Clinical myopathy was found for 43.9% (PL7/12: 25%, Jo1: 61.9%; $p< 0.05$) and 56.1% were considered as amyopathic (34.1%; PL7/12: 45%, Jo1: 23.8%) or clinically amyopathic (22%; PL7/12: 30%, Jo1: 14.3%). Main histologic patterns at the chest CT scan were: non specific interstitial pneumonia (52.9%), usual interstitial pneumonia (23.5%), cryptogenic organizing pneumonia (5.9%), diffuse alveolar damage (3%). Myocarditis was present in 3 patients. Associated diseases were: rheumatoid arthritis (5), Juvenile idiopathic arthritis (1), systemic sclerosis (1), antiphospholipid syndrome (1), Evans syndrome (3). Pulmonary hypertension was found in 4 patients and responsible for 3 of the 5 deaths. Eighteen patients were considered as incident cases in Martinique during the 2006–2013 period, allowing a mean annual incidence of $5.3/10^6$ (PL7-12: 2.5; Jo1: 3.1). In December 31, 2013, the prevalence of ASS in Martinique was $67.5/10^6$(PL7/12: 30; Jo1: 37.5).

Conclusion: We provide the first population based epidemiology of ASS, moreover in an African origin population. We confirm the elevated proportion with anti-PL7/12 close to anti-Jo1 in our black patients from the French West Indies. This initial clinical profile, frequently mimicking infectious pneumonia with fever and high blood c reactive proteine level without clinical myopathy, can explain difficulties in the diagnosis.

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Distinctive Muscle Histopathological Features of Anti-Synthetase Syndrome. Baptiste Hervier[1], Yves Allenbach[2], Lenaig Mescam-Mancini[3], Thierry Maisonobe[4], Werner Stenzel[5], Aude Rigolet[6] and Olivier Benveniste[2]. [1]Pitié-Salpêtrière Hospital, APHP, Paris, France, [2]Sorbonne Universités, University Pierre et Marie-Curie-Paris 6, INSERM, Paris, France, [3]University hospital, Grenoble, France, [4]Pitie-Salpetriere Hospital, Paris, France, [5]Charite Hospital, Berlin, Germany, [6]Assistance Publique - Hôpitaux de Paris, Pitié-Salpêtrière University Hospital, Paris, France.

Background/Purpose: As supported by recent studies, anti-histidyl tRNA synthetase (anti-Jo1) antibodies are specific for clinico-biological features and outcomes. Though, anti-Jo1 synthetase syndrome is a clinical distinct entity among idiopathic inflammatory myopathies and among other anti-synthetase syndromes, its pathological features are poorly described.

Methods: This study was performed to define the histological characteristics of the associated myopathy, as well as to immunophenotype the inflammatory infiltrates, in a series of 53 anti-Jo1-positive patients with antisynthetase syndrome.

Results: Myopathic changes in myofibers were observed with predominant perifascicular topography: these changes included a characteristic peripheral necrosis (66%), or atrophy (45%). A perimysial fragmentation, seen with a trichrome coloration or with histoenzymological stain for alkaline phosphatases was commonly noted (90%). C5b9 membrane-attack-complex staining showed a sarcolemmal perifascicular expression in 57% of the biopsies. Human-leucocyte antigen class-I (HLA I) expression was enhanced at the periphery of the fascicles in 60% of the cases. A perimysial inflammatory infiltrate was present in 90 %, extending to endomysium in 83 %.

Conclusion: This largest study to date is highlighting that anti-Jo1 synthetase syndrome is a distinct histological entity within the spectrum of myositis, with a particular perifascicular necrotizing involvement, associated with a perimysial fragmentation, and a striking membrane-attack-complex perifascicular sarcolemmal expression.

Disclosure: B. Hervier, None; **Y. Allenbach**, None; **L. Mescam-Mancini**, None; **T. Maisonobe**, None; **W. Stenzel**, None; **A. Rigolet**, None; **O. Benveniste**, None.

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Myocarditis in Antisynthetase Syndrome. Céline Dieval[1], Olivier Benveniste[2], Christophe Deligny[3], Alain Meyer[4], Guillaume Lefevre[5], Yoland Schoindre[6], Aude Rigolet[7] and Baptiste Hervier[8]. [1]Rochefort Hospital, Rochefort, France, [2]Sorbonne Universités, University Pierre et Marie-Curie-Paris 6, INSERM, Paris, France, [3]CHU Fort de France, Fort de France, France, [4]University Hospital of Strasbourg, Strasbourg, France, [5]CHRU Lille, Lille, France, [6]DHU 2iB Internal Medicine Referal Center for Autoimmune diseases Pitie Hospital, PARIS, France, [7]Assistance Publique - Hôpitaux de Paris, Pitié-Salpêtrière University Hospital, Paris, France, [8]Pitié-Salpêtrière Hospital, APHP, Paris, France.

Background/Purpose: Antisynthetase syndrome (aSS) corresponds to an overlapping inflammatory myopathy identified by different myositis specific autoantibodies (directed against tRNA-synthetases). Myocardial involvement in this condition is poorly described.

Methods: From a 342 aSS patient registry, nine cases of myocarditis were identified on the basis of an unexplained increased in cardiac troponin I levels associated with either suggestive cardiac magnetic resonance imaging (MRI) findings, normal coronary artery explorations, and/or positive endomyocardial biopsy.

Results: The prevalence of myocarditis in aSS is 2.6% (n=9) and was not linked to any autoantibody specificity: anti-Jo1 (n=5), anti-PL7 (n=3) and anti-PL12 (n=1). Myocarditis was an inaugural presentation in 44% of the

cases and was asymptomatic (n=1) or revealed by an acute (n=4) or subacute (n=4) cardiac failure. Of note, myocarditis was always associated with an active myositis. When performed (n=8), cardiac MRI revealed a late hypersignal in the T_1-images in 87% of the cases (n=7). Four patients (44%) required intensive care. Seven patients (78%) received dedicated cardiotropic drugs. Steroids and at least one immunosuppressive drug were given in all cases. After a median follow-up of 23 months (range 2–51), six (67%) patients recovered whereas three (33%) developed chronic cardiac insufficiency. No patient died.

Conclusion: The prevalence of myocarditis in aSS is similar to that reported in other inflammatory myopathies. Although it has a relatively good prognosis, myocarditis is a severe condition and should be carrefully explored in active aSS patients.

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Myositis-Specific and Myositis Associated Autoantibodies in Indian Patients with Inflammatory Myositis. Puja Srivastava, Ramnath Misra, Able Lawrence, Amita Aggarwal and Vikas Agarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: Recently, idiopathic inflammatory myositis (IIM) has been categorised into distinct subsets based on myositis specific autoantibodies (MSA) and myositis associated autoantibodies (MAA). However, there is little data on prevalence of these autoantibodies from Indian subcontinent. Hence, we studied the prevalence and clinical associations of MSAs and MAAs in Indian patients with IIM.

Methods: Clinical data and sera were collected from patients with IIM (November 2012-May 2014). Sera were analysed for antibodies against SRP, Mi2, Jo1, PL 7, PL 12, EJ, OJ, Ro 52, Ku, Pm-Scl75 and PM-Scl 100, using line immunoblot assay (Euroimmune).

Results: During 18 months there were 124 patients with IIM. ANA positivity was found in 84 (68.9%). The distribution of different autoantibodies in different subset is given below:

Parameter	DM	PM	CTD assoc. IIM	JDM	Total
Number	**55**	**25**	**22**	**22**	**124**
Female: Male	40:15	24:1	22:0	11:11	97:27
Mean age	34.4	35.2	34.4	10.1	30.4
Mean disease duration	8.3+11.2	11.4+16.7	7.6+7	20.6+25.1	10.9
Myosits specific antibodies (number positive)					
Mi2	21	2	1	2	26
SRP	3	1	1	1	6
Anti-Jo1	3	6	0	5	14
Other Anti-synthetase	7	3	2	3	15
Myositis associated antibodies (number positive)					
Ro52	14	11	15	5	45
Ku	7	1	2	3	13
PM-Scl 100	1	1	2	1	5
PM-Scl 75	3	4	3	3	13
All antibody negative					
	13	**5**	**5**	**10**	**33**

Thirty eight (30.6%) patients had two autoantibodies and 7(5.6%) patients had 3 autoantibodies.

Anti-Jo1 showed positive association(r= 0.31) while anti-Mi2 showed negative association (r= −0.26) with anti-Ro52 antibody. Anti-Mi2 antibodies were strongly associated with adult DM ($p< 0.0001$) as well as it was associated with decreased risk for ILD (p=0.001) and increased risk for pharyngeal weakness (p=0.006). ILD and mechanics hands were strongly associated, both with anti-Jo1and anti-synthetase antibodies ($p<0.0001$). Four of the six patients with anti-SRP antibody had poor response to multiple drugs.

Conclusion: Higher prevalence of anti-Mi2 is probably related to higher proportion of patients with DM. We found absence of ILD in patients with anti-Mi2 antibody suggesting that it may protect against ILD. In Indian population also anti-synthetase antibodies are associated with ILD and anti-SRP with poor response to treatment.

Disclosure: P. Srivastava, None; **R. Misra**, None; **A. Lawrence**, None; **A. Aggarwal**, None; **V. Agarwal**, None.

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Assessment of the Effect of Rituximab in the Treatment of Interstitial Lung Disease associated with the Antisynthetase Syndrome. Tracy Doyle[1], Juan Osorio[2], Eduarda Nilo DeMagaldi[3], Rachna Madan[4], Fernanda Cabral[5], Ivan Rosas[2] and Paul Dellaripa[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Harvard Medical School, Boston, MA, [4]Brigham and women's Hospital, Boston, MA, [5]Brigham and women's Hospital, boston, MA.

Background/purpose: To assess clinical outcomes including pulmonary function and radiographic imaging in patients with ILD and the antisynthetase syndrome who were treated with Rituxan (RTX).

Methods: We retrospectively identified all patients at one institution with the antisynthetase syndrome who presented with ILD and were treated with RTX. Data regarding demographics, serologic status, muscle disease, concomitant steroid use, pulmonary function testing and chest CT scans were assessed before and after the use of RTX. Serial assessments with PFTs were performed using standardized methods. Two radiologists independently evaluated axial chest CT scans using a standardized scoring system (Oda et al. Respiratory Research 2014, 15:10) and made a subjective assessment of the type of ILD pattern at 0 and 6 months and the scores of the two radiologists were averaged.

Results: 12 patients were identified who were treated with RTX for the anti-synthetase syndrome. Anti-synthetase antibodies were identified in all patients (5 PL-12, 4 Jo-1, 3 PL-7). 11 patients (92%) were females and the mean age was 54. Three patients (25%) had been smokers. The diagnosis of antisynthetase syndrome followed the diagnosis of ILD in 8 patients (67%) by a mean of 4.5 years. 7 of the patients had myositis. In 9 cases (75%), the principal indication for use of RTX was recurrent or progressive ILD due to failure of other agents. Mean time to initiation of RTX after identification of ILD was 5.4 years. One patient discontinued RTX in this time due to anaphylaxis. One patient proceeded to lung transplant, and 2 patients had serious gastrointestinal complications requiring surgery but subsequently resumed RTX.

Comparing pre and post RTX PFTs at 3–12 months for the 10 patients with adequate follow-up, FVC% and TLC% were stable or improved in 70% and 80% of subjects, and DLCO% increased in 38% [Table 1]. The average individual change was 12%, 13%, and −6%, respectively. CT score was stable or improved in 83% of subjects where followup CT was available. Eight CTs were consistent with non specific interstitial pneumonia (NSIP) and 2 had components of both cryptogenic organizing pneumonia (COP) and NSIP. Steroid dose decreased in 88% of subjects with an average decrease in dose of 6mg.

Conclusions: Use of RTX was well tolerated in the majority of patients who had ILD and the anti-synthetase syndrome. Stability or improvement in pulmonary function or CT imaging was seen in most patients. RTX may play a therapeutic role in patients with ILD associated with the antisynthetase syndrome and further clinical investigation is warranted.

Table 1: Comparison of pre and post RTX pulmonary function test measurements, CT scan score at 0 and 6 months, and prednisone dose (mg/d) with individual values and % change

	FEV1%	FVC%	TLC%	DLCO%	CT Score	Prednisone Dose
Average Pre-RTX	55.3	55.6	42.3	39.8	171.9	19 mg
Average Post-RTX	62.3	62.6	63.5	45.9	162.7	12 mg
Subjects Stable or Improved	9/10 (90%)	7/10 (70%)	4/5 (80%)	3/8 (38%)	5/6 (83%)	7/8 (88%)
Average Individual Δ	15%	12%	13%	−6%	−8%	−37%
Subject/Follow-up	FEV1% (% Δ)	FVC% (% Δ)	TLC% (% Δ)	DLCO% (% Δ)	CT Score (% Δ)	Prednisone Dose (mg)
Subject 1	94	95	–	87	117.5	5
6 months	97 (+3%)	95 (0%)	80	96 (+10%)	117.5 (0%)	5
Subject 2	61	65	62	40	125.1	20
12 months	72 (+18%)	76 (+17%)	74 (+19%)	56 (+40%)	138.3 (+11%)	10
Subject 3	37	41	–	40	–	30
6 months	39 (+5%)	39 (−5%)	–	26 (−35%)	–	2.5
Subject 4	54	63	53	36	237.4	40
6 months	56 (+4%)	59 (−6%)	51 (−4%)	26 (−28%)	216.6 (−9%)	30
Subject 5	56	50	40	39	192.4	15
12 months	63 (+13%)	56 (+12%)	49 (+23%)	37 (−5%)	192.4 (0%)	5
Subject 6	47	44	43	39	223.2	20
12 months	43 (−9%)	42 (−5%)	–	28 (−28%)	186.6 (−16%)	40
Subject 7	48	47	–	–	181.6	20
12 months	86 (+79%)	88 (+87%)	71	56	124.85 (−31%)	10
Subject 8	50	45	–	–	250	20
12 months*	54 (+8%)	49 (+9%)	–	–	–	–

Subject 9	53	58	74	50	139.15	5
6 months	53 (0%)	58 (0%)	86 (+16%)	52 (+4%)	–	5
Subject 10	53	48	45	27	158.7	15
3 months	55 (+4%)	51 (+6%)	49 (+9%)	26 (−4%)	–	–

*baseline PFT data on subject 8 obtained after RTX administration.

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ACR/ARHP Poster Session B
Osteoarthritis - Clinical Aspects: Epidemiology and Pathogenesis
Monday, November 17, 2014, 8:30 AM–4:00 PM

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Patients with Osteoarthritis Do NOT Have Increased Risk of Cardiovascular Disease in Ullensaker Community in Norway. Silvia Rollefstad[1], Ingvild Eeg[1], Ida K. Haugen[1], Inge C. Olsen[1], Nina Østerås[1], Barbara Christensen[1], Hilde Berner Hammer[1], Lars Nordsletten[2], Bård Natvig[3], Tore K. Kvien[1] and Anne Grete Semb[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Oslo University Hospital, Oslo, Norway, [3]Oslo University, Oslo, Norway.

Background/Purpose: Controversies exist regarding whether patients with osteoarthritis (OA) have an increased risk of cardiovascular (CV) disease. Our aim was to evaluate the CV risk in a population-based OA cohort.

Methods: The **M**usculoskeletal pain in Ullensaker **ST**udy (**MUST**) is a cross-sectional investigation comprising a thorough clinical examination, recording of CV risk factors in addition to radiographic evaluation of hands, hips and knees of persons with self-reported OA (The MUST-Heart study). Of the 604 persons examined, 438 fulfilled the ACR classification criteria for OA in the hand, knee and/or hip joints. The study population was divided into: 1) generalized OA, defined as bilateral hand OA or involvement of > 3 out of 6 sites (bilateral hand/hip/knee); 2) focal OA; or 3) non-OA. CV risk was calculated by the SCORE algorithm for persons without CV disease, not using lipid lowering and/or antihypertensive medication (OA n=200 and non-OA n=87). An estimated CV risk < 5% for a fatal myocardial infarction coming 10 years is defined as low to medium risk, while > 5% is the cut off for initiation of CV preventive pharmacotherapy. Comparisons between groups were done by using independent samples T-test, Mann Whitney-U and χ^2.

Results: The median CV risk for patients with OA [1.40 (IQR 0.65, 2.92)] was significantly higher compared to non-OA [0.99 (IQR 0.52, 1.92)] (p=0.02). The difference in the CV risk was related to higher age (p <0.001), but not to total cholesterol (p=0.07), systolic blood pressure (p=0.13) or to the OA diagnosis. Only 17/200 (8.5%) of the OA patients and 3/87 (3.4%) of the non-OA persons had a CV risk > 5% (p=0.12) (Table). The presence of established CV disease was comparable for those with (n=72/438, 16.8%) and without OA (n=34/166, 21.1%) (p=0.23). Dividing the OA group into focal and generalized OA, did not reveal any further differences regarding estimated CV risk or CV disease compared with non-OA. Inflammatory biomarkers (erythrocyte sedimentation rate and C-reactive protein) were in the normal range for the whole study population, with no difference between OA and non-OA (p=0.30 and 0.10, respectively) (Fig 1a&b).

Conclusion: Inhabitants with OA in a Norwegian municipality had an overall low risk of CV disease and did not have higher prevalence of established CV disease compared to non-OA.

Figure 1a

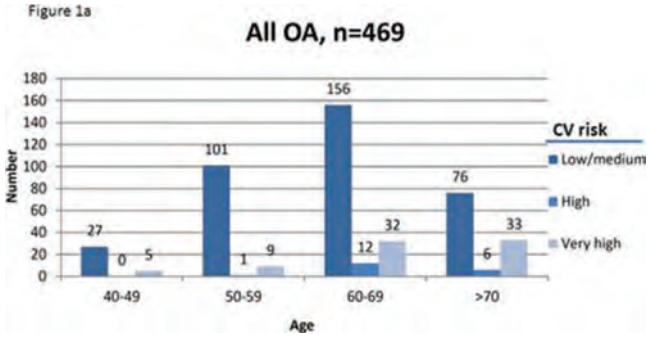

Figure 1b

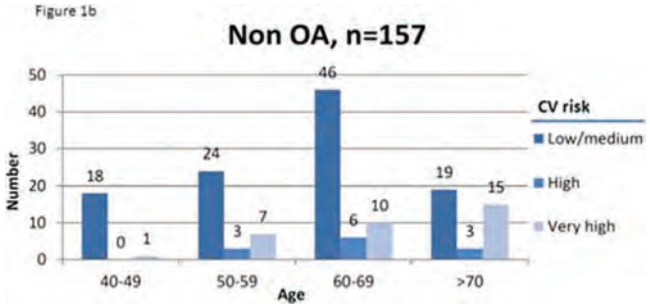

Table. Patient characteristics

	OA	Non-OA	P-value
Number	469	157	–
Cardiovascular disease n (%)	77 (16.4)	33 (21.0)	0.22
Hypertension n (%)	269 (57.4)	93 (59.2)	0.72
Smoking n (%)	71 (15.1)	21 (13.4)	0.59
Male n (%)	126 (26.9)	66 (42.0)	<0.001
Age mean + SD	64.1 + 8.6	63.3 + 9.3	0.27
Systolic blood pressure mean + SD	136.2 + 17.4	134.4 + 16.1	0.25
Total cholesterol mean + SD	5.90 + 1.15	5.60 + 1.18	0.01
HDL-c mean + SD	1.58 + 0.48	1.62 + 0.48	0.28

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Association Between Cardiometabolic Disorders and Hand Osteoarthritis Severity: A Cross-Sectional and Longitudinal Study. Alice Courties[1], Jérémie Sellam[1], Francis Berenbaum[1], Emmanuel Maheu[1], Yoann Barthe[2], Fabrice Carrat[2] and Christian Cadet[3]. [1]AP-HP, Saint-Antoine Hospital, Rheumatology Department and DHU i2B, Paris, France, [2]Saint-Antoine Hospital, Inserm UMRS_1136, UPMC Univ Paris 06, AP-HP, Paris, France, [3]Private office, Paris, France.

Background/Purpose: Obesity and metabolic disorders increase the risk of hand osteoarthritis (HOA)**.** This study aimed to determine i) clinical and radiographic features associated with HOA symptoms and structural severity ii) factors associated with HOA progression.

Methods: This is an ancillary study from an international 3-year, randomized, placebo-controlled phase III trial designed to evaluate strontium ranelate on the X-ray progression of knee OA (SEKOIA trial). A clinical assessment at baseline and at 3 years was performed. Hand radiographs were scored by 2 reproducible readers (ICCs >0.8) for Kellgren-Lawrence (KL) and Verbruggen anatomical phase (Verb) scores. We included subjects with radiographic HOA defined by at least 2 joints with KL≥2. Symptoms were assessed using the overall Australian/Canadian (AUSCAN) score (normalized at 300) and the criterion hand pain and Functional index for HOA (FIHOA) ≥5. Radiographic HOA severity at baseline was assessed by global KL and Verb scorings. The longitudinal analysis was performed on the placebo group only to avoid potential biases due to a treatment effect. The clinical and radiographic progressions were defined as the changes of AUSCAN, KL or Verb scores between baseline and endpoint. Baseline age, gender, body mass index (BMI), clinical features and cardio-metabolic parameters were included in a multivariate linear or logistic regression model.

Results: At baseline, 869 subjects (72 % women) with mean ± SD age of 64 ± 7 years and BMI 29.6 ±4.7 kg/m^2 had radiographic HOA. Multivariate analyses indicated that AUSCAN level was associated with menopause (p<0.0005), depression (p<0.01), a history of ischemic cardiopathy (p<0.05) and radiographic severity (p<0.0005) (**Table**). A similar association was found for "FIHOA ≥ 5 and pain" criterion (p<0.05 for all analyses). Accumulation of metabolic factors (hypertension, dyslipidemia, diabetes mellitus and obesity (BMI ≥30 kg/m^2) was associated with the AUSCAN score (β=5.5 [0.3;10.9]; p<0.05). Radiographic severity was associated with age, obesity, menopause as well as knee KL grade after adjustment on confounders (Table). Similar associations were found for Verb score (p<0.05 for all

analyzes). 307 HOA patients from the placebo group were followed for a mean duration of 31.5 ± 8.5 months. Obesity independently predicted Verb score variation (β=−1.3 [−2.2;−0.45]; p<0.01). Baseline KL score was the main factor associated with radiographic progression (KL or Verb). Baseline AUSCAN score was the main factor associated with subsequent clinical progression (β=−0.39 [−0.05;−0.03]; p<0.0001).

Conclusion: In HOA, obesity and ischemic cardiopathy are associated with structural damages and symptoms respectively. Such results further delineate the metabolic OA phenotype.

Table. Factors associated with baseline HOA symptoms and radiographic severity. NT: not tested, NS: not significant

	Corrected AUSCAN score		Hand KL score	
Average (± SD)	95.4 ± 79.9		21.4 ± 13.1	
	β (95% CI)	p-value	β (95% CI)	p-value
Age	−0.18 (−0.95–0.59)	0.64	0.46 (0.34–0.58)	<0.0001
Gender				
Male	Ref		Ref	
Female with menopause	27 (10.57–43.44)	0.001	2.79 (0.12–5.47)	0.04
Female without menopause	27.11 (14.37–39.86)	<0.0001	3.65 (1.69–5.61)	0.0003
BMI (kg/m^2)				
BMI <30	Ref		Ref	
BMI ≥30	0.973 (−9.6–11.59)	0.36	1.94 (0.22–3.67)	0.02
Ischemic cardiopathy	24.4 (5.67–43.23)	0.01	NS	
Depression	30.91 (13.07–48.75)	0.0007		
Knee KL Score	NT		1.77 (0.03–3.51)	0.04
Verbruggen score	1.259 (0.91–1.61)	<0.0001	NT	
KL score	1.42 (1–1.84)	<0.0001		
Number of joints with KL ≥2	3.48 (2.33–4.64)	<0.0001		
Number of Erosive joints	9.646 (6.53–12.76)	<0.0001		

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Hyperglycemia and Risk of Osteoarthritis. Mona Walimbe[1], Ann V. Schwartz[1], Irina Tolstykh[1], Charles E. McCulloch[1], David T. Felson[2], Cora E. Lewis[3], Neil A. Segal[4], Michael C. Nevitt[1] and Nancy E. Lane[5]. [1]UCSF (University of California, San Francisco), San Francisco, CA, [2]Boston University School of Medicine, Boston, MA, [3]The University of Alabama at Birmingham, Birmingham, AL, [4]University of Iowa, Iowa City, IA, [5]Center for Musculoskeletal Health, UC Davis School of Medicine, Sacramento, CA.

Background/Purpose: Osteoarthritis (OA) is reported to be more prevalent in individuals with diabetes mellitus (DM). Potential etiologies include advanced glycation endproducts, which reduce cartilage integrity, and obesity which increases the mechanical load on the knee. We further explored the relationship of abnormal glucose metabolism and incident knee OA in a community based cohort with 84 months of follow up.

Methods: The Multicenter Osteoarthritis Study Group (MOST) is an NIH-funded longitudinal study of risk factors for knee OA in people age 50–79 years, with or at high risk of knee OA. Subjects were eligible for this ancillary study if they did not have RKOA at baseline (Kellgren and Lawrence (KL) grade <2 bilaterally). Subjects were excluded if they lacked follow up knee radiographs or if their baseline blood sample was not available. A random sample diverse in baseline body mass index (BMI) of 1000 subjects (out of 1280 eligible subjects) was selected. Fasting glucose (Unical DxC 800 Auto-analyser (Beckman Coulter, Fullerton, CA, USA) and free insulin (Luminex Milliplex Analyzer Model XYP 100/200 S, Austin, Texas) levels at baseline were measured on all subjects. Subjects were categorized as DM based on any of the following: self-report DM, use of anti-diabetic medications or a fasting glucose at baseline of > 126 mg/dL. The outcome was the cumulative incidence of RKOA between baseline and the 84-month follow-up visit, defined by either a KL grade > 2 or total knee replacement. Knee-level pooled binary regression analysis was performed in men and women separately. GEE (to account for within-subject correlation) was used to obtain risk ratios (95% CI) for incidence of RKOA predicted by: fasting glucose, insulin resistance (measured by homeostatic model assessment - insulin resistance (HOMA-IR)) and diabetes status. Subjects who were taking insulin were excluded from models in which insulin resistance was analyzed.

Results: Among the 1000 subjects (mean age 61+/−7.8 years, 58% women, mean BMI at baseline 29.1+/−4.9 kg/m^2), there were 107 subjects with DM. DM subjects were more likely to be male, non-white and have higher BMI. Over the 84 months of follow-up, incidence of RKOA did not differ between diabetics compared to non-diabetics. In men, both elevated fasting glucose and HOMA-IR were associated with an increased risk of incident RKOA, but this effect did not persist after adjustment for BMI. In women, HOMA-IR levels were associated with a decreased risk of incident RKOA after adjustment for BMI. (Table)

Conclusion: DM at baseline was not associated with incident RKOA in this cohort. However, insulin resistance in women may be protective against the development of RKOA once the effect of high BMI is accounted for. This finding needs to be replicated in additional studies.

Table: Risk Ratio for Incident Knee Osteoarthritis, stratified by sex

	WOMEN 580 subjects/1160 knees/278 events Risk Ratio (95% CI) and p-values		MEN 420 subjects/840 knees/137 events Risk Ratio (95% CI) and p values	
Baseline Predictor	**Unadjusted Model**	**BMI-Adjusted Model[a]**	**Unadjusted Model**	**BMI-Adjusted Model[a]**
Fasting glucose (per 1SD)	1.09 (0.96–1.23) 0.2	0.93 (0.81–1.07) 0.3	**1.21 (1.04–1.42) 0.01**	1.04 (0.88–1.23) 0.7
HOMA-IR (per 1SD)	1.05 (0.93–1.19) 0.4	**0.81 (0.71–0.93) <0.01**	**1.26 (1.05–1.51) 0.01**	1.03 (0.84–1.27) 0.8
Diabetes	0.92 (0.59–1.45) 0.7	0.63 (0.38–1.06) 0.08	1.49 (0.96–2.30) 0.08	1.10 (0.69–1.75) 0.7

[a]Adjusted for age, race, clinic site, visit, and body mass index.

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Retinal Arteriolar Narrowing and Incidence of Knee Replacement for Osteoarthritis: A Prospective Cohort Study. Sultana Monira Hussain[1], Yuanyuan Wang[1], Jonathan E Shaw[2], Dianna J Magliano[2], Tien Yin Wong[3], Anita Wluka[1], Stephen Graves[4], Robyn J Tapp[5] and Flavia Cicuttini[1]. [1]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia, [2]Baker IDI Heart and Diabetes Institute, Melbourne, Australia, [3]Singapore Eye Research Institute, Singapore, Singapore, [4]Australian Orthopaedic Association National Joint Replacement Registry, Adelaide, Australia, [5]The University of Melbourne, Melbourne, Australia.

Background/Purpose: Epidemiological studies suggest that macrovascular disease is involved in the pathogenesis of osteoarthritis (OA) possibly through reduced nutrition to the joint. However, the role of the microcirculation in the pathogenesis of OA remains unclear. The retinal vasculature provides a unique window to assess the microcirculation noninvasively and directly. This study examined the association between retinal vascular caliber and incidence of knee replacement for OA.

Methods: 1,838 participants of the Australian Diabetes, Obesity and Lifestyle Study - a population-based, national prospective cohort study, had retinal vascular caliber measured in 1999–2000 using a nonmydriatic digital fundus camera and a validated computer-based program. Participants were aged >40 years at joint replacement data collection commencement. The incidence of knee replacement for OA during 2002–2011 was determined by linking cohort records to the Australian Orthopaedic Association National Joint Replacement Registry. Cox proportional hazard regression models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the incidence of knee replacement due to OA associated with retinal vascular caliber, with age as the time scale. Follow-up for joint replacement (calculation of person-time) began 1 January 2002, and ended at the date of first knee replacement for OA or date of censoring. Retinal vascular caliber was standardized so that HR represents the effect of a one-standard-deviation difference in caliber. Retinal vascular caliber was also categorized into tertiles based on the analysis sample. The widest tertile was used as the referent category. Each analysis was adjusted for sex and body mass index (BMI), and further adjusted for physical activity, HbA1c, and cardiovascular risk factors (systolic blood pressure, total cholesterol and microalbuminuria).

Results: 77 participants underwent knee replacement for OA. At baseline, these participants had narrower retinal arteriolar calibre than those who did not need knee replacement (166.1±24.8μm vs. 174.3±24.5μm, p=0.004). Narrower retinal arteriolar caliber was associated with an increased risk of knee replacement (HR 1.25, 95%CI 1.00–1.56, per 1 standard deviation decrease in retinal arteri-

olar caliber); and participants with arteriolar caliber in the narrower two-thirds of the cohort had twice the risk of knee replacement compared with those in the widest one-third (HR 2.00, 95%CI 1.07–3.74, p=0.03) after adjustment for sex, BMI, physical activity and HbA1c. Further adjustment for the cardiovascular risk factors did not change the associations. There was no association for retinal venular caliber.

Conclusion: Persons with narrower retinal arteriolar caliber had a higher risk of knee replacement for OA, suggesting a role of microvascular disease in the pathogenesis of knee OA.

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Association of Low Birth Weight and Preterm Birth with the Incidence of Knee and Hip Arthroplasty for Osteoarthritis. Sultana Monira Hussain[1], Yuanyuan Wang[1], Anita Wluka[1], Jonathan E Shaw[2], Dianna J Magliano[2], Stephen Graves[3] and Flavia Cicuttini[1]. [1]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia, [2]Baker IDI Heart and Diabetes Institute, Melbourne, Australia, [3]Australian Orthopaedic Association National Joint Replacement Registry, Adelaide, Australia.

Background/Purpose: Low birth weight and preterm birth have been associated with adverse adult outcomes including hypertension, insulin resistance, cardiovascular disease and reduced bone mass. It is unknown whether low birth weight and preterm birth affect the risk of osteoarthritis (OA). This study aims to examine whether low birth weight and preterm birth were associated with the incidence of knee and hip arthroplasty for OA.

Methods: 3,604 participants of the Australian Diabetes, Obesity and Lifestyle Study - a population-based, national prospective cohort study who reported their birth weight and history of preterm birth and were aged more than 40 years at the commencement of arthroplasty data collection. The incidence of knee or hip arthroplasty for OA during 2002–2011 was determined by linking cohort records to the Australian Orthopaedic Association National Joint Replacement Registry. Cox proportional hazard regression models were used to estimate the hazard ratios (HR) and 95% confidence interval (CI) for knee or hip arthroplasty due to OA associated with low birth weight and preterm birth. Follow-up for arthroplasty (i.e. calculation of person-time) began in January 1, 2002, and ended at the date of first arthroplasty for OA or date of censoring. Each analysis was adjusted for age, sex, and body mass index (BMI), in model 1, as these are established risk factors for arthroplasty for OA. In model 2, the analyses were further adjusted for hypertension, diabetes, smoking status and physical activity. To test whether associations of low birth weight and preterm birth with arthroplasty risk were modified by obesity (BMI $\geq$ 30 kg/m^2) and sex, interactions were fitted, and tested using the likelihood ratio test.

Results: One hundred and sixteen participants underwent knee arthroplasty and 75 underwent hip arthroplasty for OA. Low birth weight (yes vs. no, HR 2.04, 95% CI 1.11–3.75, p=0.02) and preterm birth (yes vs. no, HR 2.50, 95% CI 1.29–4.87, p=0.007) were associated with increased incidence of hip arthroplasty independent of age, sex, BMI, education level, hypertension, diabetes, smoking and physical activity. No significant association was observed for knee arthroplasty.

Conclusion: Although these findings will need to be confirmed, they suggest that individuals born with low birth weight or preterm are at increased risk of hip arthroplasty for OA in adult life. The underlying mechanisms warrant further investigation.

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Pre-Operative Musculoskeletal Comorbidities Limit Improvement in Functional Outcomes and Hip Pain in Total Hip Arthroplasty Patients. Scott Pascal, David Ayers, Wenjun Li, Leslie Harrold, Jeroan Allison and Patricia D. Franklin. University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Identifying clinical factors predictive of total hip arthroplasty (THA) outcomes is valuable for clinicians and patients to make a data-driven surgical decision. While factors such as age, weight, and medical comorbidities have been shown to affect post-operative pain and/or functional gains following THA, musculoskeletal comorbidities have not been investigated. We evaluated whether lumbar pain and pain in the knees and non-operative hip joints predict poorer 6 month pain relief and functional gain.

Methods: Data were collected from 2,848 patients enrolled in FORCE-TJR, a national prospective cohort of patients who underwent a primary unilateral total hip replacement due to osteoarthritis. Data including patient demographics, medical comorbidities, emotional health (SF/MCS), low back pain (Oswestry), pain in both hips and knees (HOOS/KOOS pain score), and pre-operative and post-operative function (SF/PCS) were collected pre-operatively and six months post-operatively. Post-THA pain relief and functional gain were analyzed using descriptive statistics as well as linear mixed regression models, in relation to musculoskeletal comorbid conditions and traditional patient and clinical factors.

Results: This cohort was 59% female, with a mean age of 65.4 years and mean BMI of 28.9 (kg/m$\hat{2}$). Out of the 2,848 patients, 992 (34.8%) reported moderate to severe low back pain pre-operatively. In addition, 264 (9.3%) reported moderate to severe pain in at least two non-operative hip or knee joints. After adjusting for gender, age, BMI, emotional health and medical co-morbidities, moderate to severe pre-THA back pain and pain in one or more non-operative hip or knees was significantly correlated (p<0.001) with a smaller improvement in hip pain and function after THA. Additionally, the greater the number of nonsurgical hip and knee joints with pain pre-operatively, the stronger the negative effect on pre-to-6 month post-THA gain in pain and function outcomes.

Conclusion: The presence of low back pain and pain in non-operative hip and knee joints has a significant negative impact on post-THA pain relief and functional outcome. In addition to traditionally reported clinical factors (i.e. age, weight and medical co-morbidities) the burden of musculoskeletal co-morbidity is an important consideration in predicting post-THA gains.

Table 1. Predictors of pre-to-6 month post-THA change in HOOS ADL/Function Score

	Coefficient
Baseline Characteristics	
Age	−0.136***
BMI	−0.109*
Female	0.326
pre SF36 MCS	0.190***
Baseline Hip Function	
pre HOOS ADL	−0.886***
pre HOOS Pain	
Basline Medical Co-Morbidities	
pre MCCOM =1	−1.068
pre MCCOM =2	−3.219**
Pre MCCOM=>3	−4.453**
Baseline Low Back Pain	
Pre OSW LB Pain = Mild	−1.207
Pre OSW LB Pain = Moderate	−2.709***
Pre OSW LB Pain = Severe	−3.737***
Other hip or knee joints with pain	
Pre Pain HK Joint = 1	−2.571***
Pre Pain HK Joint = 2	−5.866***
Pre Pain HK Joint = 3	−7.422***
Constant	86.19***

*p<0.05, **p<0.01, ***p<0.001.

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Relationship of Buckling and Knee Injury to Pain Exacerbation in Knee Osteoarthritis: A Web-Based Case-Crossover Stud. Isabelle Zobel[1], Tahereh Erfani[2], Kim Bennell[3], Joanna Makovey[2], Ben Metcalf[3], Jian Sheng Chen[4], Lyn March[2], Yuqing Zhang[5], Felix Eckstein[6] and David J. Hunter[2]. [1]Institute of Bone and Joint Research, Kolling

Institute, University of Sydney, St Leonards, Australia, [2]Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, Australia, [3]University of Melbourne, Melbourne, Australia, [4]University of Sydney Institute of Bone and Joint Research, St Leonards, Australia, [5]Boston University School of Medicine, Boston, MA, [6]Paracelsus Medical University, Salzburg, Austria.

Background/Purpose: Knee osteoarthritis (OA) pain is neither constant nor stable and exacerbations of pain are disabling. We examined whether knee injury and buckling (giving way) are triggers for exacerbation of pain, also defined as flare, in persons with symptomatic knee OA.

Methods: We conducted a web-based case-crossover study with all data collected via the Internet. Participants with painful radiographic knee OA were recruited and followed at 10-day intervals for 3 months (control periods). Participants were instructed to additionally record knee pain exacerbations during the 3 months interval. Pain exacerbation was defined as an increase of ***20mm from baseline on*** VAS knee pain score (VAS 0–100). Information about triggers occurring during ***"control periods***" (without pain exacerbation) and ***"hazard periods"*** (immediately preceding the pain exacerbation) was collected. We collected data on potential triggers by asking for acute knee injuries in the previous seven days. Similarly we asked about knee buckling events, defined as giving way in the previous two days (i.e., date of pain exacerbation for hazard period, and date of data assessment for control periods). The relationship of knee injury and buckling to the risk of pain exacerbation was examined using conditional logistic regression models.

Results: Of the 297 participants (women: 61%, mean age: 62 years, mean BMI: 29.3 kg/m^2) recruited, 157 (53%) had both hazard and control periods and were included in the data analysis. Sustaining a knee injury increased the likelihood of experiencing a pain flare (odds ratio (OR) 10.2; 95% CI 5.4, 19.3) compared to no injury (Table). An event of knee buckling increased the likelihood of experiencing a pain exacerbation (OR 4.0; 95% CI 2.6, 6.2) compared to no buckling and the risk increased with a greater number of buckling events (for ≥ 6 buckling events, OR 20.1; 95%CI 3.7, 110).

Table. Association of knee injury and risk of knee pain exacerbation

Knee injury	Case periods	Control periods	Odds ratio (95%CI)
No	329	820	
Yes	71	31	10.2 (5.4, 19.3)
Association of knee buckling and risk of knee pain exacerbation.			
No	259	743	1.0 (referent)
Yes	141	108	4.0 (2.59, 6.18)
Number of episodes			
1	64	54	3.5 (2.0, 6.0)
2–5	66	50	4.1 (2.4, 7.0)
≥6	11	4	20.1 (3.7, 110)

Conclusion: Knee injury and buckling are associated with knee pain exacerbation. Reducing the likelihood of knee injury and buckling through avoidance of particular activities and/or appropriate rehabilitation programs may decrease the risk of pain exacerbation.

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Knee Pain and a Prior Injury Are Associated with Increased Risk of a New Knee Injury: Data from the Osteoarthritis Initiative.

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Background/Purpose: A knee injury increases the risk for early-onset osteoarthritis (OA) and accelerated knee OA progression but little is known about risk factors for injuries among adults. Knee pain and a history of knee injury may be key risk factors because both can lead to altered joint biomechanics. Therefore, we explored if knee pain or a history of knee injury was associated with a knee injury in the subsequent 12 months.

Methods: We conducted longitudinal knee-based analyses among participants in the Osteoarthritis Initiative, a longitudinal observational study. We included both knees of all participants who attended baseline and had at least one follow-up visit with complete data. Our first set of exposures were knee pain (frequency and severity) at baseline, 12-month, 24-month, and 36-month visits. We defined frequent knee pain as pain on most days of a month in past 12 months. Knee pain severity was based on the WOMAC pain subscale, which we dichotomized as no-to-little pain (0 to 2) or knee pain (≥ 3). Another exposure was a history of injury, which we defined as a self-reported injury at any time prior to baseline, 12-month, 24-month, or 36-month visits. The outcome was self-reported knee injury during the past year at 12-month, 24-month, 36-month, and 48-month OAI visits. We conducted secondary analyses based on the bilateral absence or presence of knee OA at baseline, which we defined as Kellgren-Lawrence Grade ≥ 2. We evaluated the association between knee pain or history of injury (in both knees) and a new knee injury within 12 months of the exposure by performing repeated measures random intercept models to adjust for correlations within person observations over time and between knees. Analyses were adjusted for sex, age and body mass index at each visit.

Results: The baseline characteristics of the samples are presented in Table 1. In our primary analyses, individuals who reported frequent knee pain or an injury in either knee were more likely to experience a new knee injury in the following 12 months (Table 2) than individuals without frequent knee pain or prior injury. These findings were supported when we evaluated knee pain severity and in our secondary analyses. The only exception was that a history of a contralateral knee injury was not related with a new knee injury among those without radiographic OA at baseline.

Conclusion: Knee pain and a history of injury are associated with new knee injuries in the following 12 months. This may identify a group of people at higher risk for accelerated knee OA. It may be beneficial for individuals with knee pain or a history of injury to participate in injury prevention programs.

Table 1. Descriptive Baseline Characteristics of the Study Samples in Primary and Secondary Analyses

	Full OAI Cohort (n = 4,435)	ROA at Baseline (n = 1,443)	No ROA at Baseline (n = 1,863)
Age (years, mean (sd))	61.2 (9.2)	63.0 (8.8)	59.2 (9.0)
Body mass index (kg/m^2, mean (sd))	28.6 (4.8)	30.2 (5.0)	27.2 (4.5)
Females (n (%))	2591 (58.4%)	905 (62.7%)	1095 (58.8%)
Frequent right knee pain (n (%))	1639 (37.0%)	683 (47.3%)	543 (29.2%)
WOMAC right knee pain score > 2 (n (%))	1567 (35.3%)	687 (47.6%)	498 (26.7%)
Frequent left knee pain (n (%))	1582 (35.7%)	658 (45.6%)	537 (28.9%)
WOMAC left knee pain score > 2 (n (%))	1349 (30.4%)	609 (42.2%)	412 (22.1%)

Note. ROA = radiographic osteoarthritis.

Table 2. Frequent Knee Pain and History of Injury Predict a New Knee Injury within 12 Months

	Frequency of Injuries/ Total Observations	Adjusted Odds Ratio for Injury
Full Osteoarthritis Initiative (4,435 participants, 875 injuries)		
No Frequent Knee Pain	422/21312 (2.0%)	Reference
Frequent Knee Pain	453/10118 (4.5%)	**1.84 (1.57, 2.16)**
No Frequent Contralateral Knee Pain	502/21311 (2.4%)	Reference
Frequent Contralateral Knee Pain	373/10119 (3.7%)	1.02 (0.87, 1.20)
No History of Knee Injury	443/22275 (2.0%)	Reference
History of Knee Injury	432/9155 (4.7%)	**1.81 (1.56, 2.09)**
No History of Contralateral Knee Injury	518/22275 (2.3%)	Reference
History of Contralateral Knee Injury	357/9155 (3.9%)	**1.43 (1.23, 1.66)**
Bilateral ROA at Baseline (1,443 participants, 345 injuries)		
No Frequent Knee Pain	128/5480 (2.3%)	Reference
Frequent Knee Pain	217/4265 (5.1%)	**1.76 (1.36, 2.28)**
No Frequent Contralateral Knee Pain	153/5479 (2.8%)	Reference
Frequent Contralateral Knee Pain	192/4266 (4.5%)	1.08 (0.84, 1.39)
No History of Knee Injury	156/6365 (2.5%)	Reference

History of Knee Injury	189/3380 (5.6%)	**1.69 (1.33, 2.15)**
No History of Contralateral Knee Injury	172/6365 (2.7%)	Reference
History of Contralateral Knee Injury	173/3380 (5.1%)	**1.65 (1.30, 2.10)**
No ROA at Baseline (1,863 participants, 280 injuries)		
No Frequent Knee Pain	173/10215 (1.7%)	Reference
Frequent Knee Pain	107/3257 (3.3%)	**1.75 (1.30, 2.34)**
No Frequent Contralateral Knee Pain	199/10216 (2.0%)	Reference
Frequent Contralateral Knee Pain	81/3256 (2.5%)	0.90 (0.66, 1.23)
No History of Knee Injury	166/10298 (1.6%)	Reference
History of Knee Injury	114/3174 (3.6%)	**1.82 (1.39, 2.38)**
No History of Contralateral Knee Injury	201/10299 (2.0%)	Reference
History of Contralateral Knee Injury	79/3173 (2.5%)	1.08 (0.81, 1.44)

Note: In addition to the variables indicated above each model was adjusted for sex, age, and body mass index at each visit. Bold = significant odds ratios.

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Systemic Pain Modulation Is Related to Body Perception in People with Knee Osteoarthritis. Jennifer Stevens-Lapsley[1] and Andrew Kittelson[2]. [1]UCD Physical Therapy Program, Aurora, CO, [2]University of Colorado Denver, Aurora, CO.

Background/Purpose: Cortically mediated changes in body perception have been linked to a variety of chronic pain conditions, including knee osteoarthritis (OA). However, associations between body perception and pain neurophysiology have yet to be examined, and the role of body perception in the etiology or mechanisms of chronic pain remains largely unknown. Therefore, the purpose of this study was to assess measures of cortical body representation in a population of people with knee OA, to determine the relationship with physiological measures of pain sensitivity and systemic pain modulation.

Methods: Forty-six people with knee OA (68% female, average age = 65.0 ± 8.5 years) were assessed in this cross-sectional study. Measures of body perception included an assessment of motor imagery performance (via a right-left lower extremity recognition task), an assessment of tactile acuity (two-point discrimination threshold) at the knee joint, and an assessment of knee size perception. To assess perception of knee size, a single photograph for each participant, capturing both of the participant's lower extremities. This photograph was then digitally manipulated to make either the right or left knee appear larger or smaller than reality. An array of images containing several of these manipulations (ranging from 85% to 115% of the original size) was displayed to the participant, who was instructed to select the most accurate representation. The relative size of the more painful knee was selected for analysis. Pain sensitivity was assessed by measuring pressure pain threshold (PPT) at the medial knee joint. Conditioned pain modulation (CPM), via a cold pressor paradigm, was performed at the forearm to assess endogenous analgesic pathways. Bivariate Pearson correlation coefficients were then determined between measures of cortical body representation and measures of pain neurophysiology.

Results: Although motor imagery performance and tactile acuity appeared weakly related to each other ($r=-0.24$, $p=0.08$), no significant associations were found between either of these measures and any measure of pain neurophysiology. Perception of knee size was not related to PPT but was significantly associated with CPM, such that participants with higher capacity for descending analgesia tended to overestimate the size of the more painful knee ($r=0.56$, $p=<0.0001$).

Conclusion: For the first time, this study provides evidence linking a specific measure of pain neurophysiology to body perception. Descending analgesia may affect a person's overall perception of the knee joint, with potential functional sequelae deserving of further study. Alternatively, abnormalities in knee perception may contribute to diminished capacity for endongenous pain inhibition, thereby exacerbating pain. Regardless of the direction of the relationship, a relatively simple assessment of knee size perception could allow clinicians to identify people with deficits in systemic pain modulation who may require alternative treatment approaches.

Disclosure: J. Stevens-Lapsley, None; **A. Kittelson**, None.

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Sensitivity to Change of Patient Preference Outcome Measures for Pain in Trials of Patients with Knee Osteoarthritis. Matthew J. Parkes, Michael J. Callaghan, Terence W. O'Neill and David T. Felson. University of Manchester, Manchester, United Kingdom.

Background/Purpose: A variety of pain and function instruments are often measured in osteoarthritis (OA) clinical trials. Instruments with maximal sensitivity to change are preferred as the primary measure in trials. Shown to be sensitive to change in rheumatoid arthritis, patient preference instruments, in which a patient nominates a painful activity to track, have not been tested in OA trials. Ideally, to compare the sensitivity to change of outcome measures, trials with a positive result need to be studied. We compared the sensitivity to change of pain and function self-report outcomes in 2 OA trials that reported statistically significant improvements in pain/functional status outcomes.

Methods: We used data from a controlled trial of a knee brace (BRACE; n = 126) and an uncontrolled trial of intraarticular steroid injection (TASK; n = 120). For both trials, eligible subjects had to meet ACR criteria for knee OA and have significant knee pain. In addition to completing KOOS and WOMAC questionnaires, and questions about overall knee pain, subjects were asked to nominate an activity that commonly caused them knee pain, and to rate pain during that activity throughout the trial. Standardised response means (SRMs) were generated for multiple time points in both trials, in the active treatment group alone, and comparing treatment to control, where possible. Additionally, we tested correlations between the study outcomes and an anchor variable: a 5-point likert scale of patient-perceived change in pain, using ordinal regression to determine the odds of an improvement in pain for a 1 SD increase in each pain outcome.

Results: Both trials reported a positive effect of the intervention on pain and function. Pain on nominated activity visual analogue score (VAS) produced SRMs that were at least as high as other pain outcomes, and usually higher (table 1). Sensitivity to change of the other outcomes was less consistent. Patient perceived improvement in pain was more strongly associated with pain on nominated activity than the other pain or function outcomes (table 2).

Conclusion: Pain on nominated activity may be an extremely sensitive outcome for OA trials, and appears more strongly associated with perceived pain improvement than other currently used outcome measures.

Table 1: Standardised Response Means (SRMs) for the TASK and BRACE Trials

Outcome	BRACE Study - 6 week active vs. control treatment difference: SRMs	BRACE Study - 6 week active treatment only: SRMs	BRACE Study - 12 week active treatment only: SRMs	TASK Study - Change at 1 week after intra-articular steroid: SRMs
Pain on nominated activity VAS	−0.31	−0.85	−0.95	−1.13
Pain in last week VAS	−0.25	−0.86	−0.73	−1.07
Global pain VAS	–	–	–	−0.51
KOOS pain subscale	−0.16	−0.53	−0.73	−1.12
KOOS symptom subscale	−0.20	−0.62	−0.61	−0.94
KOOS activities of daily living subscale	−0.12	−0.54	−0.77	−1.04
WOMAC pain subscale	−0.13	−0.47	−0.63	−1.06
WOMAC stiffness subscale	−0.19	−0.53	−0.51	−1.17
WOMAC function subscale	−0.12	−0.54	−0.77	−1.04

Table 2: Association between Different Pain Outcomes and Patient Perceived Improvement in Pain. Odds Ratios Indicate Odds of Improvement in Patient Perceived Pain, for a 1 SD Improvement in the Outcomes Listed

Outcome	BRACE Study - 6 week change, all persons pooled	BRACE Study - 12 week change, all persons pooled	TASK Study - Change at 1 week follow-up
Pain on nominated activity VAS	2.09	2.57	6.12
Pain in last week VAS	1.94	2.15	4.45
Global pain VAS	–	–	2.36
KOOS pain subscale	1.63	1.79	1.87
KOOS symptom subscale	1.64	1.62	1.88
KOOS activities of daily living subscale	1.67	1.70	1.86
WOMAC pain subscale	1.60	1.71	1.84

WOMAC stiffness subscale	1.57	1.56	1.79
WOMAC function subscale	1.67	1.70	1.86

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Prevalence of Risk Factors for Gastrointestinal Side Effects of Drugs for the Treatment of Pain in Rheumatic Diseases and the Provision of Gastroprotective Treatment – Results of a Large Non-Intervention Study. Gustavo Citera[1], Edgardo Smecuol[2], Alberto Millán[3], Manuel Robles[4] and Ruben Mantilla[5]. [1]Universidad de Buenos Aires, Buenos Aires, Argentina, [2]Hospital Municipal de Gastroenterología, Buenos Aires, Argentina, [3]Hospital Universitario de Caracas, Caracas, Venezuela, [4]Centro Médico Toluca, Toluca, Mexico, [5]Clínica de Artritis y Rehabilitación (CAYRE), Bogota, Colombia.

Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are the long established first-line treatment for the management of pain associated with rheumatic diseases but carry a risk of gastrointestinal (GI) disturbance. The recognized GI risk factors are age >60 years; concomitant use of acetylsalicylic acid (ASA), oral corticosteroids or anticoagulants; previous history of ulcer, bleeding, or dyspepsia; and use of two NSAIDs or high dose of one NSAID. Evidence-based guidelines recommend the concomitant use of gastroprotective agents (GPAs) in NSAID users with one or more risk factors. Current evidence suggests that a significant proportion of patients at risk for GI events do not receive a GPA.

Methods: The RATIONAL study was conducted in Asia, Russia and Latin America and had an observational, multicenter, cross-sectional design to evaluate the prevalence of GI risk factors in patients with osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis (AS). The single study visit was part of standard practice. Patients were aged >21 years with a documented diagnosis of RA (ACR/EULAR 2010 criteria), OA (ACR 1991 criteria) or AS (New York 1984 criteria or ESSG 2002 criteria) and had taken at least one dose of NSAIDs in the 15 days before enrolment. Information collected included NSAID treatment over the year preceding the study visit, GPA use, and occurrence of any of a defined range of GI events.

Results: The distribution of rheumatic disorders in the 5373 patients was OA 2996 (55.8%), RA 1882 (35.0%), AS 283 (5.3%), and a combination of these 212 (3.9%). One or more GI risk factors were present in 87.7% of patients. The prevalence of individual risk factors and treatment with GPAs is shown in the Table 1. GPA use in patients aged ≥60 years or concomitantly using anticoagulants was close to the study average (57.9%). A modest numerical increase from this mean value was observed in patients taking concomitant ASA (63.8%) or high doses of an NSAID (64.1%). A greater numerical increase in this percentage was seen for all of the other risk factors with values of 96.6% and 93.3% for those with histories of GI complications and GI ulcer, respectively. There was a strong preference for using proton pump inhibitors as the class of GPA and the most commonly used individual treatment was omeprazole (36.4% of total patients).

Table 1: Prevalence of risk factors

	Risk factor present		Receiving a GPA	
Risk factor	n	%	n	%
Any risk factor	4711	87.70	3112	57.9
Age ≥60 years	2627	48.89	1534	58.4
Concomitant ASA	564	10.64	360	63.8
Concomitant corticosteroids	1202	22.37	850	70.7
Concomitant anticoagulants	87	1.64	53	60.9
History of complicated ulcer	45	2.08	42	93.3
History of GI complications	405	7.50	28	96.6
History of dyspepsia	569	26.34	501	88.0
High dose NSAID	1206	22.45	773	64.1
More than one NSAID	21	0.39	15	71.4

Conclusion: Risk factors that appeared to influence the provision of treatment with a GPA were those related to a previous history of GI-related symptoms or events and concomitant use of corticosteroids. Most of the other risk factors appeared to have little influence on the prescription of a GPA. Although 87.8% of the study population had one or more GI risk factors, only 57.9% received any form of GPA. Age does not appear to be recognized as a risk factor for GI symptoms and GPAs are under prescribed. **Study identifier [NCT01577563]**

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The Natural Course of Physical Function in People with Symptomatic Knee Osteoarthritis: Data from the Osteoarthritis Initiative. Britt Elin Øiestad[1], Daniel White[2], Ross Booton[3], Jingbo Niu[3], Yuqing Zhang[4], James C. Torner[5], Cora E. Lewis[6], Michael C. Nevitt[7], Michael P. Lavalley[3] and David T. Felson[4]. [1]Oslo University Hospital, 0407 Oslo, Norway, [2]Boston Univ School of Med, Boston, MA, [3]Boston University, Boston, MA, [4]Boston University School of Medicine, Boston, MA, [5]University of Iowa, Iowa City, Iowa City, IA, [6]The University of Alabama at Birmingham, Birmingham, AL, [7]UCSF (University of California, San Francisco), San Francisco, CA.

Background/Purpose: Longitudinal studies of people with knee osteoarthritis (OA) have reported stable or improved physical function, contrary to the progressive degenerative nature of OA. The early improvement may be from regression to the mean, because subjects enroll when they are in pain. Limitations to current studies are exclusion of subjects with missing data, and of total knee replacements (TKRs). Little is known when including imputation of missing values and pre-TKR physical function data. The aim of this study was to describe physical function over 7 years among subjects with symptomatic knee OA before and after imputation of missing values, and inclusion of pre-TKR physical function values.

Methods: Participants from the Osteoarthritis Initiative (OAI) with symptomatic knee OA at baseline were included, excluding those with hip replacement, those that died, and with TKR at baseline. We defined symptomatic knee OA when at least one knee showed Kellgren and Lawrence grade >1 by x-ray and pain on most days the last month. WOMAC physical function (pf) (0–68) was assessed annually over 7 years in clinic visits. We set the post-TKR values to missing. For all, missing WOMAC-pf values were imputed using the multiple imputation method. For the TKR group, time from the last clinic visit prior to TKR was regressed on WOMAC-pf using a fitted LOESS curve. Then, new predicted WOMAC-pf values were assigned to the existing pre-TKR values, to provide values close to the actual time of the TKR. Mixed effect models were used to compare original WOMAC-pf values against adjusted values (after imputation and prediction of pre-TKR values) (grey vs. red lines in the figure).

Results: Of 4344 eligible people in OAI, 1065 (24.5%) had symptomatic knee OA at baseline (age: 61.3±8.9 years, women: 58.4%, BMI: 30.3±5.0). There were 163 unilateral and 45 bilateral TKRs (19.5%). There was no significant difference in WOMAC-pf between original values and adjusted values, although incorporating data on missing and predicted pre-TKR values left WOMAC-pf worse on average (figure, red and grey lines), and created a larger sample followed over time than original analyses in which pre-TKR and missing values were excluded.

Conclusion: Physical function over time is sensitive to missing values when excluding people who go through TKR and missing clinic visits. Including imputation of missing visit and adjusted pre-TKR values better depicts physical function in persons with symptomatic OA, and permits the evaluation of function in many persons left out of current studies.

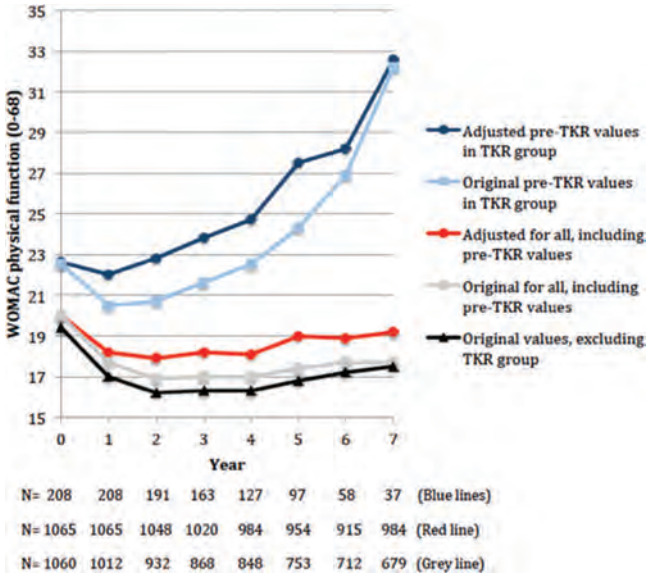

Figure. WOMAC physical function over 7 years among people with symptomatic knee osteoarthritis.

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Patient Perspective of the Main Health Concerns and Needs of Living with Hand Osteoarthritis. Mariko L. Ishimori[1], Geraldine Racaza[1], Mellissa Withers[2] and Michael Weisman[1]. [1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]UCLA, Los Angeles, CA.

Background/Purpose: Hand OA (HOA) is associated with substantial pain, joint stiffness, functional impairment and disability, and cosmetic concerns. Data regarding patients' perspective on living with these consequences is limited. We aimed to explore the experiences of HOA patients of different phenotypes and explored their perspectives in the symptom, function and aesthetics domains.

Methods: Unrelated patients ≥ 45 years of age with clinical and radiographic idiopathic HOA (distal interphalangeal (DIP) and/or carpalmetacarpal (CMC) joints) from our registry were recruited and consented for a 45-minute, face-to-face semi-structured interview by a trained medical anthropologist to assess symptom, function and aesthetics domains. Interviews were audiotaped and interviewer notes and tapes were reviewed using a content analysis approach.

Results: 14 (11 women and 3 men) patients were interviewed. 10 of 14 were ≥ 60 years with a median age of 70 years. 5 had erosive disease, of whom 3 also had CMC involvement, 3 had CMC only disease, 6 had non erosive HOA, of whom 4 had CMC disease as well.

Most participants (13 of 14) had dull, aching pain (median score=6 out of 10 with 0=none and 10=maximum possible) and stiffness. Many described different adaptations to address pain, discussed their fears of future disease progression and their reluctance to medication for HOA, and accepted pain as part of the aging process. The participants claimed the worst part of having HOA was decreased functionality and potential loss of independence (median score=5). They discussed how HOA limited daily activities, hobbies, and work, leading to frustration. Those with HOA in multiple joint areas reported the most limitations; those with DIP joint involvement reported worse function vs. those with CMC only disease. Whether it was erosive or non-erosive did not make much difference.

Participants rated how much the appearance of their hands affected them (median score=2). Most related HOA to aging However, of those bothered by their appearance (all female), they reported being very troubled.

Important issues of concern to the patients also emerged and were discussed openly – coping strategies, self-reliance and personal strength, lessons learned, and worry and fears for the future, given this chronic illness. They also commonly articulated their desire to receive more counseling and information, including non-medical healing approaches, from their rheumatologists.

Conclusion: Patients with more joint area involvement suffered the most functional loss. IP involvement led to more severe functional limitations compared to CMC OA but erosive disease did not compound functional disability. Patients experienced frustration over functionality loss and potential loss of future independence since many either experienced or anticipated living alone. Other areas of concern not traditionally assessed or considered by physicians, including coping, lessons learned from the disease, fears for the future, and desire for non-drug approaches were identified. Understanding the impact of HOA on patient perception may identify new opportunities for targeted intervention outside of traditional methods.

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Older Adults with Osteoarthritis Do Not Have an Increased Risk of Cognitive Impairment. Bansari Gujar[1], Ann Gruber-Baldini[1], Mona Baumgarten[1], William Hawkes[1], Michael C. Nevitt[2], Kristine Yaffe[2], Tamara Harris[3] and Marc C. Hochberg[1]. [1]University of Maryland School of Medicine, Baltimore, MD, [2]UCSF (University of California, San Francisco), San Francisco, CA, [3]National Institute on Aging, National Institutes of Health, Bethesda, MD.

Background/Purpose: A prior study showed an association between osteoarthritis (OA) and increased mortality from dementia. Recent preclinical studies suggest a possible association between OA and the development of dementia. The objective of this analysis was to determine if older adults with OA have a higher risk of cognitive impairment (CI).

Methods: We used data from the Health Aging and Body Composition (HABC) study, a multicenter prospective cohort study of community dwelling adults, ages 70–79, to determine if participants with OA at baseline (self-reported OA or OA defined by HABC prevalent disease algorithm) have an increased risk of developing CI. CI was defined as a Modified Mini-Mental State examination (3MS) score<80. Participants with 3MS scores of <80 at baseline were excluded. Baseline and year 3, 5, 8, and 10 scores were analyzed.

Results: There were 2577 participants with 3MS scores of >=80 at baseline (n=1277 with OA, n=1300 without OA)**.** The OA group had more women (54% vs 44%, p<0.001), higher baseline CES-Depression scores (4.9 SD 5.4 vs 4.2, SD4.9, p=0.003) and hypertension (46% vs 40%, p=0.028).There was no significant difference in development of CI after 9 years amongst those with OA (n=165, 12.9%) versus without OA (n=197, 15.1%). $\chi^2(1, n= 2577) = 2.66$, $p > 0.10$. The results of the multiple variable logistic regression analysis (adjusted for age, race, education and gender) suggest a protective effect that did not reach statistical significance (odds ratio= 0.8; 95% CI 0.6–1.0; P-value = 0.10). There was no significant association between baseline OA and the development of CI at the 3, 5, 8 and 10 year time points. No differences were found upon sensitivity analysis using race and education adjusted cut-points for 3MS scores.

Conclusion: These results do not support the hypothesis that there is a causal association between OA and CI.

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Classification of Osteoarthritis Phenotypes By Metabolomics Analysis. Weidong Zhang[1], Sergei Likhodii[2], Yuhua Zhang[1], Erfan Aref-Eshghi[1], Patricia E. Harper[1], Edward Randell[2], Roger Green[1], Glynn Martin[3], Andrew Furey[3], Guang Sun[4], Proton Rahman[5] and Guangju Zhai[1]. [1]Discipline of Genetics, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NF, [2]Department of Laboratory Medicine, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NF, [3]Department of Surgery, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NF, [4]Discipline of Medicine, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NF, [5]Memorial University of Newfoundland, St. John's, NF.

Background/Purpose: Osteoarthritis (OA) is a group of heterogeneous conditions consisting of different subgroups or phenotypes that continuously evolve, eventually leading to common clinical manifestations. Identifying OA subphenotypes and uncovering their different mechanisms of pathogenesis is of fundamental importance for the development of appropriate therapies and diagnostic tools. The aim of the study was to identify metabolic markers that can classify OA patients into subgroups.

Methods: A case-only study design was utilized in this study. Patients undergoing total hip/knee joint replacements due to primary OA were recruited and their synovial fluid samples were collected during their joint surgeries. Metabolic profiling was performed on the synovial fluid samples by the targeted metabolomics approach using the Biocrates AbsoluteIDQ p180 kit. Various analytic methods including principal component analysis (PCA), hierarchical clustering (HCL) method, and partial least squares discriminant analysis (PLS-DA) were utilized to identify metabolic markers for classifying subgroups of OA patients. Potential confounders such as age, sex, body mass index (BMI), and comorbidities were considered in the analysis.

Results: A total of 80 OA patients were included in the study. 38 were males and 42 were females with an average age of 65.2 ± 8.7 years. Two distinct patient groups, A and B, were clearly identified. Patients in group A had significant higher concentration on 39 acylcarnitines in their synovial fluids than the patients in group B. Patients in group B were further subdivided into five subgroups, i.e., B1-1, B1-2-1, B1-2-2, B2-1 and B2-2. The corresponding metabolites that contribute to the grouping were 14 amino acids, 24 glycerophospholipids, 12 acylcarnitines and 1 biogenic amine. The grouping was not associated with any known confounders including age, sex, BMI, and comorbidities. The possible biological processes involved in these clusters are carnitine, lipid, and collagen metabolism, respectively.

Conclusion: The study demonstrated that OA consists of metabolically distinct subgroups. Identification of these distinct subgroups will help to unravel the pathogenesis and develop targeted therapies for OA.

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Knee Osteoarthritis Progression Is Predictable By Genetic Polymorphisms. Results from a Multicenter Association Study. Francisco J Blanco[1], Ingrid Möller[2], Nerea Bartolome[3], Marta Artieda[3], Diego Tejedor[3], Antonio Martínez[4], Eulàlia Montell[5], Helena Martínez[5], Marta Herrero[5] and Josep Vergés[5]. [1]INIBIC-Hospital Universitario A Coruña, A Coruña, Spain, [2]Instituto Poal de Reumatología., Barcelona, Spain, [3]Progenika Biopharma, a Grifols Company, Derio, Bizkaia, Spain, [4]Progenika, a Grifols Company, Derio, Bizkaia, Spain, [5]Pharmascience Division, Bioiberica S.A., Barcelona, Spain.

Background/Purpose: Single Nucleotide Polymorphisms (SNPs) are inherited genetic variations that can predispose or protect individuals against clinical events. Osteoarthritis (OA) has a multifactorial etiology with a strong genetic component. Genetic factors influence not only knee OA onset, but also disease progression. The aim of the Arthrotest study was to develop a genetic prognostic tool to predict radiologic progression towards severe disease in primary knee OA (KOA) patients.

Methods: Cross-sectional, retrospective, multicentric, association study with Spanish KOA patients. 595 patients from 31 sites were selected. Inclusion criteria: Caucasian patients aged ≥40 years at the time of diagnosis of primary KOA (according to the ACR criteria), for whom two anteroposterior X-rays were available, one corresponding to the time of OA diagnosis with Kellgren-Lawrence grade 2 or 3 and the other to the end of the follow-up period. Patients who progressed to KL score 4 or were referred for total knee replacement in ≤ 8 years since the diagnosis were classified as progressors to severe disease. A unique expert viewer measured radiologic progression from all X-rays. A candidate gene study analyzing 774 SNPs was conducted. SNP genotyping was performed with Illumina Golden gate technology or KASPar chemistry. Clinical variables of the initial stages of the disease (gender, BMI, age at diagnosis, OA in the contralateral knee and OA in other joints) were registered as potential predictors. Univariate analysis was done to identify associations between the baseline clinical variables or SNPs and KOA progression. SNPs and clinical variables with an association of $p<0.05$ were included on the multivariate analysis using forward logistic regression.

Results: 282 patients fulfilled DNA and X-ray quality control criteria (220 in the exploratory cohort and 62 in the replication cohort). The univariate association analysis showed that one of the clinical variables and 23 SNPs were significantly associated to KOA severe progression in the exploratory cohort ($p<0.05$). The predictive accuracy of the clinical variable was limited, as indicated by the area under the ROC curve (AUC=0.66). Combining only genetic variables, a predictive model with a good accuracy (AUC=0.78) was obtained. When genetic variables were added to the clinical model (full model) the prediction of KOA progression was improved and the AUC increased to 0.82. The predictive ability for KOA progression of the full model was confirmed on the replication cohort (two-sample Z-test $p=0.190$). The full final model developed combines the clinical variable age at KOA diagnosis and 8 SNPs (rs2073508, rs10845493, rs2206593, rs10519263, rs874692, rs7342880, rs12009 and rs780094 – located in GCKR2 gene -). Interestingly, a new association between GCKR2 gene (previously shown to be associated with elevated diabetes type II risk) and OA was first found in this study.

Conclusion: Genetic polymorphisms predict radiologic progression more precisely than clinical variables. An accurate prognostic tool to predict primary KOA progression has been developed based on genetic and clinical information from OA patients.

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Relationships Between Inflammation, Disease Severity and Synovial Fluid Calcium Crystals Detected By Scanning Electronic Microscopy in Early Osteoarthritis. Paola Frallonardo[1], Francesca Oliviero[1], Luca Peruzzo[2], Leonardo Tauro[1], Anna Scanu[1], Mariagrazia Lorenzin[1], Augusta Ortolan[1], Leonardo Punzi[1] and Roberta Ramonda[1]. [1]University of Padova, Padova, Italy, [2]Institute for Geosciences and Earth Resources IGG-CNR, Padova, Italy.

Background/Purpose: The presence of calcium crystals (CC) in synovial fluid (SF) of osteoarthritis (OA) is a well known and frequent feature (1). However, their role in the pathogenesis of OA is still unclear and matter of discussion, in particular as regard the local inflammation (2). The objective of the study was to evaluate the presence of the most common CC, calcium pyrophosphate (dehydrate) (CPP) and basic calcium phosphate (BCP), in SF of the symptomatic knee OA (KOA, particularly in early disease stage (<1year) and to investigate their association with local infiammation, disease activityand severity.We performed an ultrasensitive analysis of SF crystals using the scanning electron microscopy (SEM) and the routinary method by compensated polarized ligth microscopy (CPLM) and alizarin red staining.

Methods: Seventy-four (48 F, mean age 64.85±9.33 yrs, range 50–89 yrs) consecutive outpatients attending theRheumatology Unit, University of Padova with symptomatic KOA (according to the American College of Rheumatology criteria) underwent knee arthrocentesis. After optical and CPLM, the SF was analysed by SEM. Total white blood cell (WBC) count was performed and a cut-off of total WBC was established in $< 1000/mm^3$. Patients' medical history, clinical features (WOMAC, Lequense and VAS) X-ray findings (Kellgren & Lawrence), ultrasound and power Doppler (PD) signal values were also assessed.

Results: CPP crystals were identified in 32.4% by CPLM and in 31.1% by SEM. Alizarin was positive in 36.5% of the samples. BCP were found in 13.5% by SEM. CPP and BCP crystals were simultaneously positive in 8.1% of the samples by SEM.

The study population was divided into three groups depending on disease duration (group A <1 yr; group B 1–5 yrs; group C > 5 yrs). The SF volume ($p=0.0008$) was significantly different in the group A with respect to B and C groups. The SF WBC was higher during the early stages of disease (group A), although not significant, with respect to B and C groups. Moreover, the presence of CC in group A correlated significantly with SF WBC ($p=0.048$) and % of PMN ($p=0.033$) with respect to those without CC in the same group.

PD resulted positive in 43.24% of all the patients, 62.5% of these were CC+ according to SEM ($p<0.0001$).

Conclusion: The presence of CC in SF, also when detected in early OA stages, was associated with a higher degree of local inflammation, so suggesting that they may play a role of in eliciting an inflammatory reaction, which may be crucial in OA pathogenesis.

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Synovitis Characteristics and Associated Intra-Articular Pathology in a Cohort of Patients Undergoing Meniscectomy for Meniscal Tear. Marta Favero[1], Giovanni Trisolino[2], Antonello Lazzaro[3], Mary B. Goldring[4], Steven R. Goldring[5], Elisa Assirelli[6], Claudio Iacobellis[7], Augusto Cigolotti[8], Assunta Pozzuoli[3], Ambrogio Fassina[8], Ermanno Martucci[2], Leonardo Punzi[9], Andrea Facchini[6] and Eleonora Olivotto[6]. [1]Rheumatology Unit, Padova, Italy, [2]Reconstructive Hip and Knee Joint Surgery, Bologna, Italy, [3]Orthopaedic Clinic, Padova, Italy, [4]Tissue Engineering Repair and Regeneration Program, Hospital for Special Surgery and Weill Cornell Medical College, New York, NY, [5]Hospital for Special Surgery, New York, NY, [6]Laboratory of Immunorheumatology and Tissue Regeneration/RAMSES, Bologna, Italy, [7]UOC of Orthopaedic and Traumatology, Padova, Italy, [8]Surgical Pathology and Cytopathology Unit, Department of Medicine, University of Padova, Italy, Padova, Italy, [9]University of Padova, Padova, Italy.

Background/Purpose: Previous epidemiologic studies have established that there is a strong relationship between meniscal tear and the risk for subsequent development of osteoarthritis (OA). Though not normally considered a classical inflammatory arthropathy, OA is often associated with low-grade synovitis. In patients with OA, synovial inflammation is one factor associated with risk of progression of structural joint deterioration and symptoms. The aims of the study were to characterize the synovial features in patients undergoing partial meniscectomy for meniscal tear.

Methods: The study was conducted in the context of a three-year project funded by the Italian Ministry of Health (Ricerca Finalizzata - Giovani Ricercatori - project code: GR-2010-2317593), which maintains extensive records of preclinical, intraoperative and post-operative data so far for 58 patients who have undergone meniscectomy for both degenerative and traumatic meniscal tear. Synovial biopsies were collected in suprapatellar area during arthroscopic surgery and processed for histology. Synovial features of

inflammation were assessed using an histological synovial scoring based on perivascular mononuclear cell infiltration as follows: grade 0=none, grade 1=mild (0–1 perivascular aggregates per low-power field); grade 2=moderate (>1 perivascular aggregate per low power field with or without focal interstitial infiltration); grade 3=marked aggregates (both perivascular and interstitial) (Scanzello CR, Arthritis Rheum. 2011). The following clinical data were collected: age, sex, BMI, date of injury and time to surgery, pre-operative VAS and KOOS, 3–6 months KOOS and meniscal tear characteristics and/or cartilage pathology. Cartilage damage was assessed intra-operatively using the Outerbridge scoring system.

Results: In the series of 58 patients, males were predominant (72%) with median ages of 43.6 and 50 years, respectively. Meniscal tear were traumatic in 50% of patients. KOOS at 3–6 months after meniscectomy statistically improved compared with the baseline ($p<0.0001$). No association was observed between traumatic or degenerative meniscal tear and age, BMI, KOOS, frequency of cartilage defects or macroscopic synovitis score. Of 26 suprapatellar synovial biopsies H&E stained: 15 exhibited mild synovial inflammation, 7 moderate, 1 marked. Cartilage defects were observed in 48 patients (82,7%). 35 patients had multiple cartilage defects, while 13 exhibited only a single focal chondral lesion. Outerbridge scores were distributed as follows: grade I (7 patients), grade II (13 patients), grade III (16 patients) and grade IV (12 patients). The grade of cartilage defects correlated with synovial inflammation assessed by histological scoring ($r=0{,}500$; $p=0{,}009$) and both patients age and BMI.

Conclusion: In our study, we observed an high percentage of low-grade synovitis (88%), and/or cartilage defects (82,7%) in patients undergoing partial meniscectomy for meniscal tear. Microscopic synovial inflammation correlate with the grade of cartilage defect confirming that synovitis play a role in the progression of the disease.

Disclosure: M. Favero, None; **G. Trisolino**, None; **A. Lazzaro**, None; **M. B. Goldring**, None; **S. R. Goldring**, None; **E. Assirelli**, None; **C. Iacobellis**, None; **A. Cigolotti**, None; **A. Pozzuoli**, None; **A. Fassina**, None; **E. Martucci**, None; **L. Punzi**, None; **A. Facchini**, None; **E. Olivotto**, None.

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Identification of an Inflammation-Driven Phenotype of Osteoarthritis By Quantification of Synovial Inflammation *Ex Vivo* and in Serum from Patients.

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Background/Purpose: Osteoarthritis (OA) is a multifaceted degenerative joint disease, where inflammation of the synovial membrane leads to accelerated joint destruction, resulting in elevated release of matrix metalloproteinase (MMP)-mediated type I and III collagen degradation fragments, C1M and C3M. The aim of the study was to investigate if C1M and C3M were associated with joint inflammation in OA, by i) measuring the release of the biomarkers in response to pro-inflammatory factors in an *ex vivo* human OA synovial explant model and ii) investigate the level of the biomarkers in patients in association with radiographic and inflammatory knee OA.

Methods: *Synovial membrane explants (SME);* Synovial membrane from 4 OA patients undergoing total knee replacement at Gentofte Hospital, Denmark, were cultured as SMEs (30±2mg) for 3 weeks with media alone (w/o), 10 ng/mL TNFα, IL-1β or TGFβ-2, or metabolic inactivated. Supernatant was collected 3 times a week and stored at -20°C. In-house neo-epitope biomarkers; C1M, C3M, and active MMP-3 were assessed by ELISA. MMP-2 and -9 were detected by gelatin zymography. *Knee OA cohort:* A cross-sectional study including 332 subjects with knee pain; 52% women, mean age: 65 (8.4) years; BMI: 28 (4.4). Patients were divided into 4 groups based on Kellgren-Lawrence (KL) score Mild; KL 0, (n=12), Moderate: KL 1+2 (n=202); Severe: KL 3+4 (n=57); and Terminal OA (n=61). The degree of inflammation was evaluated by VAS pain and level of hsCRP. C1M and C3M were measured in serum. The study was approved by The Ethical Committee of Northern Jutland.

Results: *SME:* C1M and C3M were increased (10 and 100-fold, respectively) at day 7 in response to TNFα compared to w/o (C1M: $p<0.05$, C3M: $p<0.0001$). IL-1β showed similar pattern. TGFβ-2 did not affect C1M or C3M. Activated MMP-9 and activated MMP-3 ($p<0.0001$) was increased in SMEs treated with IL-1β or TNFα throughout the study for SMEs, while activation of MMP-2 was not affected. *Knee OA cohort*: Serum C1M were significant elevated in the Terminal group compared to the Moderate ($p<0.0001$) and Severe OA ($p<0.01$) groups, but no significant difference in serum C3M. Patients with inflammatory OA (high hsCRP and pain) had a higher level of C1M and C3M as compared to non-inflammatory patients (table). There was no difference in KL between the two groups.

Conclusion: In OA patients with the same KL score, C1M and C3M were significantly higher in those with an inflammation-driven phenotype. C1M and C3M were released from the SMEs upon treatment with the pro-inflammatory cytokines IL-1β and TNFα, but not TGFβ-2, which indicates that C1M and C3M are direct measures of synovial turnover and inflammation. This was supported by the detection of active MMP-3 and -9, which act down-stream of the cytokines and up-stream of the biomarkers. These biomarkers may be part of the identification of the important and possibly treatable inflammation-driven OA phenotype.

Table

	Non-inflammatory OA		Inflammatory OA		
	Mean	*95%-CI*	*Mean*	*95%-CI*	*P value*
KL	2.3	2.2–2.5	2.3	1.7–2.8	ns
C1M, ng/mL	49.0	46.8–51.2	94.2	69.3–119	p<0.0001
C3M, ng/mL	17.7	16.9–18.4	26.2	21.6–30.9	P<0.01

Disclosure: C. F. Kjelgaard-Petersen, None; **A. S. Siebuhr**, Nordic Bioscience A/S, 3; **K. K. Petersen**, None; **L. Arendt-Nielsen**, None; **T. Eskehave**, CCBR-Synarc, 3; **H. C. Hoeck**, CCBR-Synarc, 3; **O. Simonsen**, None; **T. Christiansen**, None; **L. L. Egsgaard**, None; **M. A. Karsdal**, Nordic Bioscience Holding, 1, Nordic Bioscience Diagnostic, 3; **A. C. Bay-jensen**, Nordic Bioscience Holding A/S, 1, Nordic Bioscience Diagnostic, 3.

ACR/ARHP Poster Session B
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Pediatric Lupus, Scleroderma and Myositis
Monday, November 17, 2014, 8:30 AM–4:00 PM

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Gender Differences in the Lupus Nephritis Biomarkers in Children.

Khalid Abulaban[1], Hermine Brunner[2], Michael Bennett[1], Shannen L. Nelson[1], Jun Ying[3] and Prasad Devarajan[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]University of Cincinnati, Cincinnati, OH.

Background/Purpose: Lupus nephritis (LN) is frequently associated with a poor long-term prognosis. The non-invasive traditional measures of LN (LN-TM) currently used to monitor LN have limited responsiveness to change. Though the discovered and initially validated promising LN biomarkers (i.e. the LN-Panel) accurately reflect LN activity & chronicity as seen on kidney biopsy, and can forecast LN flares, however, there remains an important unknown in regards whether the LN-Panel biomarkers are influenced in their levels by patient gender. The objective of this study is to assess the gender and age specific differences in the levels of the LN-Panel biomarkers and to establish normative values of the combinatorial biomarkers in healthy children.

Methods: Urine concentrations of the LN biomarkers Neutrophil gelatinase associated lipocalin (NGAL), Monocyte chemoattractant protein-1 (MCP1), Ceruloplasmin (CP), Alpha1-acid glycoprotein (AGP), Transferrin (TF)and Lipocalin-like prostaglandin-D Synthase (LPDGS) were measured by nephelometry or ELISA in select male and female pediatric LN patients. All the biomarkers were logarithmically transformed and standardized to urinary creatinine concentration. Student t test was used to compare means of the LN panel biomarkers between female and male active LN patients. A fixed effect model was used to compare means after adjusting for differences in clinical measures of LN activity using the Renal SLEDAI domain scores. P value of <0.05 was considered statistically significant.

Results: In a sample of 64 females and 12 males with childhood LN, the means of urinary MCP-1 was significantly elevated in females compared to males (table 1). Also the means of urinary LPGDS was significantly elevated

in 27 female patients who had histological feature of Epimembranous deposits compared to 6 males (table2). There were also significant gender differences in select LN Panel biomarkers when looking at the activity and chronicity of LN on kidney biopsy (see Table 3).

Conclusion: This study supports that there are gender differences in select LN-Panel markers. Also these differences can be seen with certain type of underlying histological features of LN.

Table 1: Gender related differences in LN-Panel with LN adjusted for differences in clinical measures of LN activity using the Renal SLEDAI domain scores

*Type of Biomarker**	*Biomarker*	*Female (n=64)*	*Male (n=12)*	*P-value*
Select LN-Panel Biomarkers	***NGAL***	3.50 ± 1.18	2.83 ± 1.68	0.097
	MCP1	**0.00 ± 1.10**	**−0.95 ± 0.89**	**0.013**
	CP	8.91 ± 1.47	8.42 ± 1.24	0.299
	ACG	10.60 ± 1.41	10.34 ± 1.52	0.584
	TF	1.83 ± 1.43	1.36 ± 1.19	0.328
	LPGDS	−0.59 ± 0.90	−1.10 ± 1.23	0.103
Traditional LN Measures	**BP(syst)**	129.03 ± 21.58	138.17 ± 23.60	0.189
	BP(diast)	80.66 ± 15.03	81.25 ± 15.98	0.901
	Serum BUN	2.84 ± 0.65	2.80 ± 0.83	0.852
	Serum creatinine	−0.06 ± 0.53	0.16 ± 0.67	0.197
	Urine prot/crea ratio	0.83 ± 1.10	0.38 ± 1.34	0.217
	Complement C3	4.15 ± 0.50	4.14 ± 0.46	0.956
	Complement C4	2.43 ± 0.72	2.54 ± 0.57	0.642

*Values are mean ± SD of LOG transformed in serum & urine biomarkers; the LN-Panel markers are all standardized by urine creatinine.

Table 2: Some LN Panel biomarkers differ with histological features by gender

	Epimembranous deposits					
	Absent			**Present**		
Biomarker	**Female (N=37)**	**Male (N=6)**	**p-value**	**Female (N=27)**	**Male (N=6)**	**p-value**
NGAL	3.51 ± 1.25	3.19 ± 1.81	0.574	3.48 ± 1.10	2.46 ± 1.62	0.081
MCP-1	0.02 ± 1.11	−0.97 ± 0.81	0.093	−0.03 ± 1.12	−0.94 ± 1.02	0.077
CP	8.70 ± 1.66	8.33 ± 1.63	0.600	9.20 ± 1.13	8.49 ± 0.96	0.275
ACG	10.43 ± 1.32	10.17 ± 1.67	0.703	10.82 ± 1.52	10.49 ± 1.53	0.606
TF	1.59 ± 1.51	1.40 ± 0.85	0.801	2.15 ± 1.27	1.33 ± 1.46	0.201
LPGDS	−0.74 ± 0.98	−0.87 ± 1.22	0.777	**−0.37 ± 0.74**	**−1.29 ± 1.32**	**0.035**

Table 3: Some LN Panel biomarkers show gender differences with the activity and chronicity of LN on kidney biopsy.

	Active kidney inflammation: Biopsy NIH-Activity Score (range 0–24)						*Kidney damage: Biospy NIH-Chronicity Score (0–12)*					
	NIH-AI score <7			**NIH-AI score ≥7**			**NIH-CI <4**			**>=4 (or w. Chronicity)**		
LN-Panel	**Female (N=53)**	**Male (N=11)**	**p-**	**Female (N=11)**	**Male (N=1)**	**p**	**Female (N=55)**	**Male (N=10)**	**p**	**Female (N=9)**	**Male (N=2)**	**p**
NGAL	3.41 ± 1.22	2.89 ± 1.75	0.22	*3.92 ± 0.90*	*2.11 ± 0.00*	*0.17*	**3.49 ± 1.09**	**2.61 ± 1.72**	**0.04**	3.55 ± 1.73	3.89 ± 1.32	0.73
MCP-1	**−0.20 ± 1.05**	**−0.95 ± 0.89**	***0.03***	0.89 ± 0.84	N/A	N/A	**−0.08 ± 1.02**	**−1.17 ± 0.84**	**0.01**	0.34 ± 1.41	−0.07 ± 0.46	0.62
CP	8.66 ± 1.43	8.43 ± 1.31	0.61	10.09 ± 1.05	8.32 ± 0.00	0.22	8.97 ± 1.35	8.30 ± 1.34	0.20	8.53 ± 2.13	8.95 ± 0.56	0.71
ACG	10.39 ± 1.40	10.27 ± 1.59	0.81	11.60 ± 0.99	11.01 ± 0.00	0.69	10.60 ± 1.44	10.20 ± 1.41	0.44	10.57 ± 1.29	10.98 ± 2.52	0.72
TF	1.57 ± 1.38	1.43 ± 1.25	0.75	*2.96 ± 1.10*	*0.74 ± 0.00*	*0.11*	1.81 ± 1.38	1.24 ± 1.23	0.29	1.96 ± 1.81	1.83 ± 1.27	0.90
LPGDS	−0.64 ± 0.91	−1.10 ± 1.29	0.16	−0.31 ± 0.83	−1.07 ± 0.0	0.45	***−0.59 ± 0.88***	***−1.29 ± 1.29***	***0.04***	−0.53 ± 1.05	−0.24 ± 0.13	0.69

Disclosure: K. Abulaban, None; **H. Brunner**, None; **M. Bennett**, None; **S. L. Nelson**, None; **J. Ying**, None; **P. Devarajan**, None.

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Childhood-Onset Systemic Lupus Erythematosus: Short-Term Treatment Response Rates in Proliferative Lupus Nephritis. Andrea Human[1], Simon Yu Tian[2], Earl D. Silverman[3] and Deborah M. Levy[1]. [1]The Hospital for Sick Children and University of Toronto, Toronto, ON, [2]The Hospital for Sick Children, Institute of Medical Science, University of Toronto, Toronto, ON, [3]The Hospital for Sick Children, Toronto, ON.

Background/Purpose: Proliferative Lupus Nephritis (PLN) occurs in up to 50% of patients with childhood-onset systemic lupus erythematosus (cSLE). PLN is a significant source of morbidity and can lead to end-stage renal disease. Our objectives were to examine rates of complete and partial response to treatment in the first year in a large multiethnic cohort using non-cyclophosphamide induction strategies.

Methods: A single-centre retrospective cohort study at the Hospital for Sick Children examined partial and complete response rates at 6 and 12 months following the diagnosis of biopsy-proven PLN (WHO Class III or IV) in cSLE patients. Patients with PLN and concomitant Class V lupus nephritis were included. Urine protein/creatinine ratio (uPCR) and serum creatinine (Cr) were used as core renal parameters. Urinary sediment was not included due to lack of available data. Criteria for complete (CR) and partial response (PR) were adapted from the American College of Rheumatology consensus guidelines, and from the outcome measures defined in Wofsy et al (Table 1). All data were collected prospectively on standardized clinic forms and maintained in a clinical database. Demographic, clinical, pathologic and laboratory data were analyzed. As therapeutic options have evolved over the past 30 years, results were stratified into two treatment eras, the 1st era when prednisone and azathioprine (aza) were routinely used in the first year, and the 2nd era when prednisone and mycophenolate mofetil (MMF) were more commonly used.

Table 1: Renal Response Definitions

Complete Response	For patients with abnormal Cr, - Normalization of Cr For patients with normal Cr, - Maintenance of a normal Cr within 50% of baseline value uPCR <25g/mol
Partial Response	For patients with abnormal Cr, - Normalization of Cr OR 50% improvement in Cr For patients with normal Cr, - Maintenance of a normal Cr within 50% of baseline value For patients with uPCR >300 (nephrotic range) at baseline, - Reduction in uPCR to <300 For patients with uPCR ≤300 - Reduction in uPCR by 50% to final uPCR<100 OR normalization of uPCR <25g/mol

Results: 155 patients had biopsy-proven PLN between 1983–2013. Mean age at PLN diagnosis was 12.6±3.4 years old, and 80% were female. The cohort's ethnic heritage was 38% Asian, 28% Caucasian, 19% Black, and 15% other. 47 (30%) patients had class III, 85 (55%) had class IV, 5 (3.2%) had III/V, and 11 (7.1%) had class IV/V. 34 (22%) patients developed acute renal failure. Other phenotypic features included malar rash (71%), arthritis (74%), fever (65%), and photosensitivity (28%). At baseline, mean C3 was 0.72, and mean C4 was 0.11. Overall, 61% had CR and 15% had PR at 6 months, while 68% had CR and 7.5% had PR at 12 months (see Table 2 for complete results). We found that the rate of CR at 6 and 12 months was significantly higher in Era 1 (aza) than in Era 2 (MMF).

Table 2: Response rates

	Overall (1983–2012) (N=150)	**ERA 1 (1983–2002) (N=86)**	**ERA 2 (2003–2012) (N=64)**	**p-value**
Complete response @ 6 mo (N, %)	92 (61)	59 (69)	33 (52)	0.04
Complete response @ 12 mo	101 (68) (n=149)	64 (76)	37 (59) (n=63)	0.04
Partial response @ 6 mo	23 (15)	10 (12)	13 (20)	0.17
Partial response @ 12 mo	12 (7.5) (n=149)	4 (4.6)	8 (13) (n=63)	0.13

Conclusion: The majority of patients showed a complete response to treatment at 6 months, with 68% of patients demonstrating complete response by one year. Partial response rates at both 6 and 12 months were comparatively lower. Interestingly, CR rates at 6 and 12 months were higher in the aza-prednisone era as compared to the MMF-prednisone era.

Disclosure: A. Human, None; **S. Y. Tian**, None; **E. D. Silverman**, None; **D. M. Levy**, None.

1296

Pulse- Pediatric Update on Lupus in South Africa: Epidemiology and Management. Laura Lewandowski[1], Laura Schanberg[1], Nathan Thielman[2] and Christiaan Scott[3]. [1]Duke University Medical Center, Durham, NC, [2]Duke Hubert Yeargan Center for Global Health, Durham, NC, [3]Red Cross War Memorial Children's Hospital, Cape Town, South Africa.

Background/Purpose: In developed nations, SLE is more common and severe in people of African extraction than in Caucasians; however, the epidemiology of SLE in Africa is largely undetermined. Historically, the incidence of SLE in Africa was presumed to be low, but recent studies challenge this theory. In general, children present with higher disease activity, require more therapy, and accrue more organ damage than adult-onset patients. Although African children with SLE may be at high risk for poor outcomes, little research has investigated this population. We have initiated the first prospective study of this high risk pediatric SLE (pSLE) population. Here, we

report the initial findings of the South African pSLE patients (PULSE cohort).

Methods: We conducted a retrospective chart review of pediatric and adult rheumatology and nephrology patients seen at 2 centers in Cape Town, South Africa from 1988–2014 meeting American College of Rheumatology criteria for pSLE. Patient age, gender, race, and presenting features were recorded for the PULSE cohort and compared to previously described pSLE cohorts in South Africa and worldwide.

Results: Initial review of patients yielded 68 patients (age 12.2; 83% female). The racial distribution was 65% colored, 26% black, 3% white, and 3% Asian/Indian. A much larger proportion of patients in our cohort are of colored or black race compared to a previously published South African cohort. Most patients presented with severe lupus nephritis (LN) (renal biopsy performed in 49%)). Of patients with LN, 83% presented with ISN class IV or higher. Pediatric LN cohorts from developed nations report 6–7% progressing to end stage renal disease (ESRD), and reports from developing nations report 8–12%. Within the cohort, 13% went on to develop ESRD requiring transplant, strikingly higher than previously reported cohorts. Our cohort had severe disease at diagnosis (mean SLEDAI 20.4), compared to previously reported pSLE cohorts (SLEDAI 4-13). Also, the PULSE cohort had end organ damage with 63% of the cohort having a SLICC score >0 (mean SLICC 1.9), compared to only 23% in a previously reported US cohort of 221 pSLE patients.

Table 1. Demographic Information

	PULSE cohort South Africa 2014 n=68	Faller cohort (South Africa, 2005) n=36	APPLE cohort (USA, 2010) N=221
Average age (years)	12	11.5	15.7
Median Age (years)	12.2	Not reported	15.5
% Female	83	61	83
% Colored	65	14	Not reported
% Black	26	38	27 (African Am)
% Indian/Asian	3	1	13
% White	3	42	51

Table 2. International Society of Nephrology/ Renal Pathology Society 2003 Classification of Lupus Nephritis

Class of Lupus Nephritis	PULSE cohort South Africa 2014 N=32	Toronto Cohort N=43
I Minimal Change	0 (0%)	0 (0%)
II Mesangial	3 (9%)	10 (23%)
III Focal Proliferative	2 (6%)	11 (26%)
IV Diffuse Proliferative	17 (53%)	17 (40%)
V Membranous	7 (21%)	5 (11%)
VI Advanced Sclerosis	3 (9%)	Not Reported

Conclusion: The PULSE cohort is the largest registry of pSLE patients in Africa to date. Preliminary findings show these children present with high disease activity and progress to end organ damage at higher rates than pSLE cohorts in developed nations.

Disclosure: L. Lewandowski, None; **L. Schanberg**, None; **N. Thielman**, None; **C. Scott**, None.

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Safety and Efficacy of Rituximab in Pediatric Lupus and Other Rheumatic Diseases. Ajay Tambralli[1], Timothy Beukelman[2], Randy Q. Cron[2] and Matthew L. Stoll[2]. [1]University of Rochester, Rochester, NY, [2]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Rituximab (RTX) is a chimeric monoclonal antibody that specifically targets CD20 positive B cells and is used successfully for a variety of pediatric rheumatologic conditions. One pediatric autoimmune disease for which RTX has gained particular interest is systemic lupus erythematosus (SLE). Herein, we report on the safety and effectiveness of use of RTX in 104 subjects with a variety of pediatric autoimmune diseases, with a focus on SLE.

Methods: This was a retrospective study of children treated by 1 or more pediatric rheumatologists at Children's of Alabama (CoA) with at least 1 course (2 doses of 750 mg/m^2, maximum of one gram, 2 weeks apart) of RTX between August 1, 2007 and April 1, 2014. To evaluate effectiveness, we documented for all patients the MD Global assessment of disease activity and corticosteroid dosage at baseline (just prior to RTX) and at 12 months of follow-up. For SLE patients, we additionally documented complement levels, ESR, CBC, creatinine, albumin, urine protein, and anti-DNA levels. For safety outcomes, we documented infusion reactions and severe adverse events. Comparisons were performed with the Student's t-test.

Results: 104 children were included in the study. The single most common diagnosis was SLE (n = 50), and the next most common diagnosis was dermatomyositis (n=11). In total, 464 RTX infusions were administered during the study period. A total of 251.4 person-years of follow-up was available (median 2.4 years; range 1 month – 6.4 years.) Among patients with one-year follow-up data available, mean daily corticosteroid dose decreased from 29.8 ± 25.7 mg to 8.7 ± 13.1 mg (n = 98; $p < 0.001$) and mean MD global assessment of disease activity decreased from 34.4 ± 19.2 to 15.7 ± 12.3 (n = 88; $p < 0.001$). Among SLE patients with data available at 12 months of follow-up, significant improvements were observed in corticosteroid dosage and MD global assessment of disease activity, as well as in multiple SLE-associated markers of disease activity (Table.) Overall, RTX was well-tolerated. There were no infusion reactions requiring emergent intervention. The incidence of hospitalized infections among the cohort as a whole (83.5/1,000 person-years) and among the 50 SLE patients (92.2/1,000 person-years) is similar to previous studies of children with SLE treated with cyclophosphamide. One patient died after transition to adult care.

Conclusion: RTX can be safely administered to children with a variety of rheumatic conditions and appears to contribute to decreased disease activity and steroid burden.

Table. Effectiveness data among 48 SLE patients with at least 12 months of follow-up

Variable	Baseline	12 months	p-value, Student's t-test
Corticosteroid dose (n = 48)	31.7 ± 23.4	8.8 ± 12.1	<0.001
C3 (n = 29)	70.4 ± 39.8	115 ± 41.8	<0.001
C4 (n = 29)	11.6 ± 11.5	25.6 ± 15.9	<0.001
ESR (n = 47)	57.4 ± 37.7	37.2 ± 28.4	0.005
Hemoglobin (n = 48)	10.9 ± 1.6	12.0 ± 1.4	<0.001
Creatinine (n = 48)	1.0 ± 2.0	0.84 ± 1.1	0.143
Albumin (n = 48)	3.7 ± 0.76	4.2 ± 0.51	<0.001
Urine pr : cr (n = 40)	0.96 ± 2.0	0.75 ± 1.8	0.548
dsDNA (n = 37)	860 ± 3300	85 ± 301	0.128
Physician global (n = 41)	35.2 ± 19.2	14.3 ± 12.1	<0.001

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Macrophage Activation Macrophage Activation Syndrome: A Severe and Frequent Manifestation of Acute Pancreatitis in Childhood-Onset Compared to Adult Systemic Lupus Erythematosus Patients. Natali W. Spelling[1], Carini I. Otsuzi[1], Diego L. Barros[1], Mariana A. da Silva[1], Rosa M. R. Pereira[1], Lucia M. A. Campos[1], Eduardo F. Borba[1], Eloisa Bonfá[1] and Clovis A Silva[2]. [1]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: Acute pancreatitis (AP) is a rare and severe manifestation of childhood-onset systemic lupus erythematosus (cSLE) and adult SLE (aSLE) patients. Macrophage activation syndrome (MAS) is reported in lupus patients, however the comparisons of specific clinical and laboratorial features of MAS in cSLE and aSLE populations with AP were not performed. Therefore, the aim of this study was to analyze in a large population of cSLE and aSLE patients the rare group of AP and MAS.

Methods: A retrospective study included 362 cSLE and 1,830 aSLE patients followed in the same University Hospital. AP was defined according to the presence of abdominal pain or vomiting associated with an increase of pancreatic enzymes (3X) and/or pancreatic radiological abnormalities. MAS was diagnosed according to preliminary diagnostic guidelines, requiring the presence of at least one clinical and two laboratorial criteria. Bone marrow aspirate to assess macrophage hemophagocytosis was evaluated when available. Demographic data, clinical features, SLEDAI-2K, SLICC/ACR-DI and treatment were also assessed.

Results: A higher frequency of AP was observed in cSLE compared to aSLE [12/362 (3.3%) vs. 20/1830 (1.1%), p=0.003], with similar AP duration [22(6–60) vs. 15(4–90) days, p=0.534]. MAS was significantly higher in the former group (85% vs. 30%, p=0.003) and four of them had

macrophage hemophagocytosis. cSLE patients had higher SLEDAI-2K at AP diagnosis [22(8–41) vs. 10(0–40), p=0.007], fever (p=0.002), anti-dsDNA antibodies (p=0.002) and death by MAS complication (31% vs. 0%, p=0.017) than aSLE. No differences were evidenced in glucocorticoid use in both groups (p=0.394). Further analysis of MAS patients showed that the median of ferritin [1804(28–24,511) vs. 409(25–4,282) ng/ml, p=0.041], aspartate aminotransferase (AST) [121(23–1,156) vs. 30(13–1,446) U/L, p=0.018] and triglyceride [285 (163–526) vs. 172(61–357) mg/dL, p=0.005] were significantly higher in AP patients with MAS compared those without this complication. Fever (94% vs. 38%, p=0.001), leucopenia (82% vs. 19%, p=0.0001), thrombocytopenia (65% vs. 19%, p=0.013), hypertriglyceridemia (87% vs. 42%, p=0.037) and hyperferritinemia (93% vs. 37%, p=0.011) were also more frequently observed in AP patients with *versus* without MAS. Of note, acute infections were alike in both groups (p=0.438).

Conclusion: This study provides novel data demonstrating that MAS occur in the majority of cSLE with AP with a higher mortality compared to aSLE. In addition, we identified in AP patients, a cluster of MAS clinical and laboratorial parameters more associated with this complication.

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A Cross-Sectional Study of Mental Health Symptoms and Mental Health Care in Pediatric SLE/MCTD Patients and Their Peers. Andrea Knight[1], Michelle Vickery[1], Pamela Weiss[1], Knashawn Morales[2] and Ron Keren[2]. [1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Mental health problems are prevalent in pediatric systemic lupus erythematosus (SLE). We aimed to compare the rates of mental health problems and mental health services use for children and adolescents with SLE and mixed connective tissue disease (MCTD) to healthy peers and those with other chronic disease.

Methods: In a cross-sectional analysis, 40 children and adolescents with SLE/MCTD were matched according to sex and age with 40 healthy and 40 type 1 diabetic controls. Subjects were consecutively recruited and consented at outpatient clinic visits. We screened for symptoms of depression, suicidal ideation and anxiety using the Patient Health Questionnaire 9 (PHQ-9) and the Screen for Child Anxiety Related Disorders (SCARED), respectively. We also assessed for use of mental health services in the previous 12 months by parent report. We used matched pair analysis to compare the rate of mental health symptoms, and the Fisher's exact test to compare rates of mental health services use among the groups.

Results: Mental health symptoms were prevalent in all groups with 33% (13) of SLE/MCTD, 30% (12) of healthy controls and 43% (17) of diabetic controls screening positive for any symptom. Compared to the 10% prevalence of depression symptoms in the healthy controls, there was a trend towards higher prevalence in the SLE/MCTD group at 23% (RR=2.3, 95%CI 0.8–6.6) and statistically higher prevalence in the diabetes group at 30% (RR=2.5, 95%CI 1.2–5.3). Compared to the 5% prevalence of suicidal ideation in the healthy controls, there was a trend towards higher prevalence in the SLE/MCTD group at 18% (RR=3.5, 95%CI 0.7–16.8) and in the diabetes group at 18% (RR=2.5, 95%CI 0.9–7.3), but these were not statistically significant. There was no difference in depression and suicidal symptoms between the SLE/MCTD and diabetes groups. Anxiety was prevalent among all groups, but there was no difference between the groups. In those with any symptom, previous mental health care had been obtained in none (0/12) of the healthy controls, 23 % (3/13) of the SLE/MCTD and 53% (9/17) of the diabetes groups. Compared to healthy controls, the diabetes group had a statistically significant higher rate of mental health care in those with symptoms (p=0.003), but there was no difference for the SLE/MCTD group (p=0.12). There was no statistically significant difference in mental health care rates between SLE/MCTD and diabetic patients with symptoms (p=0.14).

Conclusion: Mental health symptoms were common in pediatric SLE/MCTD patients and their peers, but there was a trend towards more frequent depression and suicidal ideation in the SLE/MCTD and diabetes groups, implicating chronic disease as a risk factor for these symptoms. The majority of those with symptoms had no previous mental health care, although those with diabetes had a significantly higher rate of mental health care compared to healthy peers. Further study of the risk factors for mental health problems in chronic illness and factors affecting mental health care may improve overall care for pediatric SLE/MCTD patients.

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Subclinical Right Ventricle Systolic Dysfunction By Two-Dimensional Speckle-Tracking Echocardiography in Childhood-Onset Systemic Lupus Erythematosus Patients. Gabriela N Leal[1], Kellen F Silva[1], Camila M. P. França[1], Alessandro C. Lianza[2], José L. Andrade[1], Lucia M. A. Campos[1], Eloisa Bonfa[1] and Clovis A Silva[3]. [1]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [2]University of São Paulo, Sao Paulo, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: Evaluation of right ventricle (RV) systolic function by standard echocardiogram remains a challenge because of the complex geometry of this chamber. Recently, two-dimensional Speckle-tracking derived strain (2DST) was proven to have a better accuracy in detecting subtle RV dysfunction in children with congenital heart diseases, however this new technique was not systematically studied in childhood-onset SLE patients. Therefore, the aim of this study was to evaluate strain imaging by 2DST in cSLE patients and healthy controls and possible association of RV dysfunction with demographic data, clinical manifestations, laboratory and treatment.

Methods: A cross-sectional study was conducted at our Pediatric Rheumatology Unit from September 2012 to September 2013. Exclusion criteria were heart failure, congenital heart disease, pericardial effusion, history of infectious myocarditis or pulmonary obstructive diseases and poor quality echocardiographic imaging. Thirty-five cSLE patients and 33 healthy volunteers were submitted to standard echocardiogram, and 2DST. Conventional parameters included: RV diastolic diameter (RVDD), tricuspid annular plane systolic excursion (TAPSE), tricuspid annular systolic wave velocity (S), Tei index and the presence of pulmonary hypertension (velocity of tricuspid regurgitation jet>2.5m/s). 2DST analyzed global systolic longitudinal strain and strain rate of RV. Demographic data, clinical features, SLEDAI-2K, SLICC/ACR-DI and treatment were also assessed.

Results: The median current age was similar in cSLE patients and controls (14.75 vs. 14.88 years, p=0.62). Standard echocardiogram analysis revealed that cSLE patients had a significant increase RVDD (14.65±3.68 mm/m^2 vs. 12.31±2.43 mm/m^2, p=0.031) and Tei index compared to controls [0.49 (0.3–0.96) vs. 0.32 (0.22–0.45), p<0.0001]. They also had reduced S wave velocity [0.13 (0.09–0.2) vs. 0.16 (0.13–0.23)m/s, p<0.0001] and TAPSE (1.84±0.26 vs. 2.59±0.41cm, p<0.0001). Four patients had mild pulmonary hypertension. Further evaluation of function by 2DST showed that RV longitudinal peak systolic strain was significantly reduced in cSLE (−24.5±5.09 vs. −27.62±3.02%, p=0.003). The same finding was observed with the exclusion of four patients with mild pulmonary hypertension (−24.62 ± 4.87 vs. −27.62 ± 3.02, 0.0041, p=0.0041). RV longitudinal peak systolic strain was positively correlated with TAPSE (r=+0.49, p=0.0027) and negatively correlated with Tei index (r=-0.34, p=0.04) in cSLE patients. Further analysis of cSLE patients revealed higher frequencies of neuropsychiatric manifestations (39% vs. 0%, p=0.007) and antiphospholipid antibodies (55% vs. 18%, p=0.035) in those with reduced strain (≤ −23.7%) compared to high strain values (>−23.7%). No differences were evidenced in demographic data, disease activity/damage and treatments (p>0.05).

Conclusion: This is the first study to identify, using a more accurate methodology, subclinical RV systolic dysfunction in cSLE patients. The novel association of asymptomatic cardiac dysfunction with neuropsychiatric manifestations and antiphospholipid antibodies may suggest a common underlying mechanism.

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Trabecular Bone Impairment Assessed By HR-pQCT in Juvenile-Onset Systemic Lupus Erythematous with Vertebral Fractures. Juliane Paupitz, Glauce Lima, Valéria Caparbo, Henrique Fuller, Eloisa Bonfa and Rosa M R Pereira. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: The three-dimensional evaluation of bone by HR-pQCT has the advantage to provide assessment to not only bone density, but also to a noninvasive evaluation of bone structure and bone strength. Information about changes in bone microarchitecture in juvenile-onset SLE (JoSLE) with and without fractures is lacking and they may improve future strategies of therapy and prediction of fracture risk in these patients. The objective of this study was, therefore, to analyze bone microarchitecture in JoSLE with and without vertebral fractures(VF).

Methods: Twelve consecutive JoSLE female patients with VF according to Vertebral fracture assessment (VFA) by dual-energy X-ray absorptiometry (DXA) were selected and compared to 44 female JoSLE patients without VF. Demographic, anthropometric, clinical and laboratory data were recorded by interview and electronic chart review. Bone microarchitecture was evaluated by High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT) at the distal radius.

Results: Patients with and without VF had comparable age (18.0±2.73 vs. 18.5±3.35 years, p=0.0636), BMI (23.03±4.39 vs. 23.15±3.45 kg/m^2, p=0.927), disease duration (58.25 ± 45.03 vs. 71.39 ± 48.57 months, p=0.403), SLEDAI (4.14±4.04 vs. 4.73±5.92, p=0.744), CG cumulative dose (8602.71±8484.15 vs. 6291.54±6737.18 mg, p=0.454), current GC dose (16.04±14.44 vs. 15.97±19.75 mg/day, p=0.990), maximum GC dose (34.17±26.53 vs. 29.20±31.35 mg/day, p=0.466) and 25-hydroxyvitamin D (22.25 ± 6.93 vs. 23.38 ± 6.90 ng/ml, p=0.610). In spite of these comparable parameters, Table 1 illustrates significant differences in HR-pQCT in distal radius findings in the two groups of patients analyzed. Patients with vertebral fractures had reduced density parameters, particularly related to D100 (p=0.011) and D trab (p=0.024), suggesting a predominant trabecular bone involvement. Structural evaluation in patients with VF revealed a significant reduction in BV/TV (p=0.023) and Tb.Th (p=0.033), both parameters associated with trabecular organization. Finally, a significant decrease in apparent modulus was observed in patients with VF (p=0.018) indicating a bone strength impairment of VF group.

Table 1: Density and Structural parameters of distal radius assessed HR-pQCT in JoSLE patients with and without vertebral fractures

HR-pQCT	Vertebral Fractures (n=12)	No Vertebral Fractures (n=44)	*P*
Density Parameters			
D 100, mg HA/ccm	**229.45 ± 42.09**	**275.93 ± 56.87**	**0.011***
D trab, mg HA/ccm	**136.96 ± 30.84**	**163.17 ± 35.45**	**0.024***
D comp, mg HA/ccm	**742.83 ± 87.41**	**787.67 ± 105.88**	**0.122**
Structural Parameters			
BV/TV	**0.114 ± 0.03**	**0.136 ± 0.03**	**0.023***
Tb.N, 1/mm	**1.986 ± 0.31**	**2.123 ± 0.28**	**0.165**
Tb.Th, mm	**0.057 ± 0.01**	**0.064 ± 0.01**	**0.033***
Th.Sp, mm	**0.461 ± 0.11**	**0.416 ± 0.07**	**0.129**
Ct.Th, mm	**0.428 ± 0.17**	**0.520 ± 0.22**	**0.189**
Biomechanical Properties			
Stiffness, *k*N/mm	**61599.99 ± 34636.81**	**61814.79 ± 13493.61**	**0.071**
Estimated Failure Load, N	**3196.70 ± 2345.13**	**3005.52 ± 619.73**	**0.059**
Apparent Modulus, N/mm^2	**1236.36 ± 334.85**	**1523.70 ± 367.14**	**0.018***

D100=average bone density; Dtrab=trabecular bone density; Dcomp=compact bone density; HA=hydroxyapatite; BV/TV=trabecular bone volume to tissue volume; Tb.N=trabecular number; Tb.Th=trabecular thickness; Tb.Sp=trabecular separation; Ct.Th=cortical thickness

Conclusion: The novel identification by a non-invasive technique (HRpQCT) that JoSLE patients with vertebral fractures have trabecular bone alterations with a significant reduction in bone strength opens a new perspective to define in future prospective studies the utility of this method for fracture prediction in this disease.

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The Psychological Impact on Health-Related Quality of Life in Childhood-Onset Lupus. Jordan T. Jones, Natoshia Cunningham, Jennifer L. Huggins, Susmita Kashikar-Zuck and Hermine I. Brunner. Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background/Purpose: Childhood-onset lupus (cSLE) is a chronic autoimmune disease and its effect on health-related quality of life (HRQoL) has not been fully established, but, disease activity alone does not solely account for the impact on HRQoL. Gaps in the literature exist around the impact of potentially modifiable factors (pain, sleep, fatigue, pain coping, mood, anxiety) in relation to HRQoL. Disease activity measures are often unrelated to psychological factors associated with cSLE. Chronic disease and its related psychological factors can impair participation in developmentally appropriate activities in adolescents, leading to chronically poor HRQoL. *Objectives* of this study were to evaluate psychological factors in patients with cSLE and the degree of HRQoL impairment in cSLE due to psychological factors commonly associated with chronic diseases.

Methods: As part of an ongoing study, a population-based cohort of cSLE patients (n= 20; 8 – 18 years) followed at Cincinnati Children's Hospital were asked to complete brief measures of *pain* (Pain visual analog scale[Pain VAS]), *sleep* (Adolescent Sleep Wake Scale), *fatigue* (PedsQL Multidimensional Fatigue Scale), *pain coping* (Pain Coping Efficacy questionnaire, Pain Catastrophizing questionnaire), *mood* (Children's Depression Inventory [CDI1]), *anxiety* (Screen for Child Anxiety Related Disorders [SCARED]), and *HRQoL* (PedsQL Generic Core scale and Rheumatology Module). Measures of disease activity (Systemic Lupus Erythematosus Disease Activity Index [SLEDAI], and physician completed visual analog scale of cSLE disease activity [MD Global, 0–10; 0=inactive]) were also obtained.

Results: Subjects were 90% female with mean age of 15.5 years (SD 1.5) and mean SLEDAI score of 7.8 (SD 6.1). Of the subjects, 60% had fatigue and more than minimal pain (Pain VAS ≥ 3), and 40% reported often feeling rested the next morning. Also, 25% had clinically significant anxiety symptoms (SCARED ≥ 25), and 30% had mild-to-moderate depressive symptoms (CDI1 ≥ 10). The average HRQoL score for cSLE patients was well below the reported healthy mean, and the presence of fatigue, anxiety, and decreased mood correlated highly with HRQoL (Pearson's r > 0.70). Conversely, none of the HRQoL measures correlated with SLEDAI score or MD global (r< 0.25; see **Table 1**). Regression demonstrated HRQoL was most impacted by fatigue (p <0.05) when evaluating all factors concurrently.

Conclusion: cSLE is often associated with decreased HRQoL, despite comprehensive treatment provided at a tertiary pediatric rheumatology center. Our data suggests that psychological aspects of health (pain, mood, fatigue and anxiety) contribute substantially to diminished HRQoL in cSLE patients, whereas, measures of cSLE activity are not related to HRQoL outcomes. Psychological factors, and especially fatigue, need to be addressed to achieve optimal health outcomes with cSLE.

Table 1: Pearson Correlation Coefficients

	HRQoL Measures		Psychological Variables						
Pearson Correlations	PedsQL GC	Peds QL RM	Fatigue	Anxiety	Mood	Sleep	Pain	Pain Coping	Pain Catastrophizing
PedsQL GC	1	0.89**	0.86**	−0.75**	−0.76**	0.65**	−0.51*	0.08	−0.56*
Peds QL RM	0.89**	1	0.86**	−0.71**	−0.78**	0.62**	−0.52*	0.01	−0.56*
Fatigue	0.86**	0.86**	1	−0.73**	−0.81**	0.62**	−0.55*	0.23	−0.63**
Anxiety	−0.75**	−0.71**	−0.73**	1	0.89**	−0.55*	0.36	0.09	0.54*
Mood	−0.76**	−0.78**	−0.81**	0.89**	1	−0.64**	0.32	0.06	0.52*
Sleep	0.65**	0.62**	0.62**	−0.55*	−0.64**	1	−0.15	−0.28	−0.35
Pain	−0.51*	−0.52*	−0.55*	0.36	0.32	−0.15	1	−0.21	0.34
Pain Coping	0.08	0.01	0.23	0.09	0.06	−0.28	−0.21	1	−0.27
Pain Catastrophizing	−0.56*	−0.56*	−0.63**	0.54*	0.52*	−0.35	0.34	−0.27	1
SLEDAI	0.06	0.14	−0.04	−0.04	−0.09	0.12	0.15	0.22	0.08
MD Global	−0.08	−0.06	−0.20	−0.04	0.11	−0.04	0.23	0.12	0.11

*Denotes p-value <0.05.
** Denotes p-value < 0.01.

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Accuracy of Laboratory Measures and Clinical Renal Activity Indices for Reflecting Biopsy-Proven Lupus Nephritis (LN) Activity. Khalid Abulaban[1], Stacy P. Ardoin[2], Marisa Klein-Gitelman[3], Kelly A. Rouster-Stevens[4], Michael Bennett[1], Lori B. Tucker[5], Kasha Wiley[6], Shannen Nelson[7], Karen Onel[8], Nora G. Singer[9], B Anne Eberhard[10], Kathleen M. O'Neil[11], Elizabeth B. Brooks[12], Lawrence K. Jung[13], Lisa F. Imundo[14], Tracey Wright[15], David Witte[16], Jun Ying[17], Prasad Devarajan[1] and Hermine I. Brunner[7]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Ohio State University College of Medicine, Columbus, OH, [3]Anne & Robert H Lurie Childrens Hospital of Chicago, Chicago, IL, [4]Emory University School of Medicine, Atlanta, GA, [5]BC Children's Hospital and University of British Columbia, Vancouver, BC, [6]Cincinnati Children's Hospital Medical Center, c, OH, [7]Cincinnati Children's Hospital Medical Center, Cincinnati,

OH, [8]University of Chicago Hospitals, Chicago, IL, [9]Division of Rheumatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH, [10]Cohen Children's Medical Center, Lake Success, NY, [11]Riley Hospital for Children, Indianapolis, IN, [12]Case Medical Center, Cleveland, OH, [13]Children's National Medical Center, Washington, DC, [14]Columbia University Medical Center, New York, NY, [15]UT Southwestern Medical Center, Dallas, TX, [16]Cincinnati Children's Hospital, Cincinnati, OH, [17]University of Cincinnati, Cincinnati, OH.

Background/Purpose: LN is common in childhood-onset Systemic Lupus Erythematosus (cSLE). Kidney biopsies are impractical to assess the course of LN given their invasiveness and cost. Therefore, traditional laboratory measures [GFR, complement levels, anti-dsDNA antibodies, serum creatinine and urinary protein/creatinine ratio] are used and several clinical indices [Systemic Lupus International Collaborating Clinics Renal Activity Score (SLICC-RAS), renal domain score of the BILAG (BILAG-R) and SLEDAI (SLEDAI-R)] have been developed: The objective of this study was to validate these traditional non-invasive measures of LN activity in cSLE, using histological activity & severity of LN as criterion standard.

Methods: The traditional laboratory measures were measured in 83 children with LN at time of the kidney biopsy. The biopsy specimens were rated by a single nephropathologist for LN severity as per International Societies for Nephrology & Renal Pathology (ISN/RPS) class, the NIH glomerular activity Index (GLAI; range 0-24) and the tubulointerstitial activity index (TIAI, range 0–21). For the statistical analysis, LN severity is categorized as Class I/II vs. III/IV vs. V; GLAI score ($\leq$10 vs. $>$10), or TIAI score ($\leq$5 vs. $>$5) in fixed effect models and logistical models, respectively.

Results: Of the 83 kidney biopsies, 12%, 60% and 28%, of the patients had class I/II, III/IV and V, respectively. The median scores of the GLAI and TIAI are summarized (Table 1). SLEDAI-R and SLICC-RAS, but not BILAG-R was positively associated to the ISN/RPS classification (Table 2). In particular, higher SLEDAI-R and serum creatinine level and lower GFR level was found in patients with LN inflammatory activity (GLAI $>$ 10 or TIAI $>$5). Similar patterns were also noticed in patients with ISN/RPR Class III/IV being compared against those with ISN/RPR Class V.

Conclusion: Of the currently used measures to assess LN in routine daily practice, the SLEDAI-R and the GFR appears to best reflect inflammatory LN activity in both the glomerulus and the interstitium of pediatric populations.

Table 1. Summary of GLAI, TIAI and ISNPR CLASS in cSLE Cohort

Score	Stat Type	Statistics
GLAI score	Median (range)	6 (0, 22)
	Freq (%) of score$>$10	27/71 (38.0%)
TIAI score	Median (range)	4 (0, 11)
	Freq (%) % of score$>$5	14/55 (25.5%)
ISNPR CLASS	I/II	10 (12.05%)
	III/IV	50 (60.24%)
	V	23 (27.71%)

Table 2. Traditional LN measures validated by LN biopsy

Traditional LN measure	ISNRP Class I/II	ISNRP Class III/IV	ISNRP Class V	GLAI Score $\leq$ 10	GLAI Score $>$ 10	AITI Score $\leq$ 5	AITI Score $>$ 5
SLEDAI-R*	6.80 (3.75, 9.85)	10.20 (8.84, 11.56)#	6.78 (4.77, 8.79)	7.45 (6.06, 8.84)	11.93 (10.15, 13.70)‡	8.20 (6.75, 9.64)	11.43 (8.96, 13.90)‡
BILAG-R*	10.10 (8.26, 11.94)	11.20 (10.38, 12.02)	9.86 (8.62, 11.11)	10.37 (9.52, 11.23)	11.56 (10.48, 12.63)	10.93 (10.02, 11.83)	10.86 (9.33, 12.38)
SLICC-RAS*	3.11 (0.45, 6.67)	6.96 (5.42, 8.50)	5.83 (3.32, 8.35)	4.38 (2.75, 6.02)	7.58 (5.57, 9.58)	5.20 (3.47, 6.92)	5.92 (2.86, 8.98)
Protein/ Cr ratio*	1.89 (0.79, 4.56)	1.93 (1.35, 2.75)	3.05 (1.77, 5.25)	1.79 (1.20, 2.67)	2.85 (1.74, 4.67)	1.98 (1.31, 2.97)	2.67 (1.31, 5.42)
Urine Random Protein*	177 (31, 1,030)	246 (139, 434)	278 (48, 1,612)	186 (102, 339)	424 (206, 871)	185 (107, 321)	542 (221, 1,327)
GFR*	111 (79, 158)	84 (72, 98)	133 (105, 168)†	115 (97, 136)	76 (61, 93)‡	108. (94, 125)	70 (55, 88)‡
Serum Cr*	0.56 (0.41, 0.76)	0.90 (0.78, 1.03)#	0.60 (0.49, 0.73)	0.63 (0.55, 0.74)	0.99 (0.82, 1.20)‡	0.66 (0.58, 0.76)	1.06 (0.85, 1.33)‡
C3 level*	55.65 (38.31, 80.84)	47.77 (40.28, 56.64)	73.12 (56.51, 94.60)†	64.28 (53.79, 76.82)	41.94 (33.44, 52.60)‡	53.31 (43.72, 65.01)	52.35 (37.43, 73.22)
C3 (Low)**	40.00%	27.08%	57.14%†	47.62%	15.38%†	30.00%	28.57%
C4 level*	7.42 (4.77, 11.54)	7.17 (5.86, 8.78)	12.29 (9.06, 16.66)†	9.95 (7.92, 12.50)	6.35 (4.80, 8.41)‡	7.63 (6.04, 9.64)	7.67 (5.17, 11.39)
C4 (Low)**	20.00%	12.24%	52.38%†	30.95%	14.81%	25.00%	21.43%
DSDNA (Positive)**	0.00%	10.64%	36.84%†	16.67%	8.00%	11.43%	9.09%

*: Values in the cells are mean (95% CI).
**: Values in the cells are %.
#: The ISNRP Class=III/IV group is different from other two groups.
†: The ISNRP Class=V group is different from the III/IV group.
‡: The GLAI Score $>$ 10 (or AITI $>$5) group is different from the GLAI Score $\leq$ 10 (or TIAI Score $\leq$ 5) group.

Disclosure: K. Abulaban, None; **S. P. Ardoin**, None; **M. Klein-Gitelman**, None; **K. A. Rouster-Stevens**, None; **M. Bennett**, None; **L. B. Tucker**, None; **K. Wiley**, None; **S. Nelson**, None; **K. Onel**, None; **N. G. Singer**, None; **B. A. Eberhard**, None; **K. M. O'Neil**, None; **E. B. Brooks**, None; **L. K. Jung**, None; **L. F. Imundo**, None; **T. Wright**, None; **D. Witte**, None; **J. Ying**, None; **P. Devarajan**, None; **H. I. Brunner**, TMA and NIEHS, 9.

1304

Development of an Index to Non-Invasively Quantify Lupus Nephritis Chronicity in Children. Khalid Abulaban[1], Michael Bennett[1], Marisa Klein-Gitelman[2], Stacy P. Ardoin[3], Kelly A. Rouster-Stevens[4], Lori B. Tucker[5], Kasha Wiley[6], Shannen Nelson[7], Karen Onel[8], Nora G. Singer[9], Kathleen M. O'Neil[10], B Anne Eberhard[11], Lawrence K. Jung[12], Lisa F. Imundo[13], Tracey Wright[14], David Witte[15], Jun Ying[16], Prasad Devarajan[1] and Hermine I. Brunner[7]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Anne & Robert H Lurie Childrens Hospital of Chicago, Chicago, IL, [3]Ohio State University College of Medicine, Columbus, OH, [4]Emory University School of Medicine, Atlanta, GA, [5]BC Children's Hospital and University of British Columbia, Vancouver, BC, [6]Cincinnati Children's Hospital Medical Center, c, OH, [7]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [8]University of Chicago Hospitals, Chicago, IL, [9]Division of Rheumatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH, [10]Riley Hospital for Children, Indianapolis, IN, [11]Cohen Children's Medical Center, Lake Success, NY, [12]Children's National Medical Center, Washington, DC, [13]Columbia University Medical Center, New York, NY, [14]UT Southwestern Medical Center, Dallas, TX, [15]Cincinnati Children's Hospital, Cincinnati, OH, [16]University of Cincinnati, Cincinnati, OH.

Background/Purpose: The current gold standard for assessing chronic changes in Lupus Nephritis (LN) is a kidney biopsy interpreted using the International Societies for Nephrology & Renal Pathology (ISN/RPS) Classification. However, kidney biopsies are invasive, costly and unsuited for close surveillance of LN. The objective of this study was to develop a non-invasive Index to measure LN chronicity or damage, considering both traditional measures of LN (LN-TM) and recently discovered renal biomarkers (RBM).

Methods: In this ongoing prospective study, 70 children with LN were studied at the time of the kidney biopsy for the LN-TM [GFR, anti-dsDNA antibodies, urinary protein/creatinine ratio] and the urine concentrations of the RBM (see Table 1) were measured. Histological findings were rated by a single nephropathologist who provided the NIH chronicity index (NIH CI; range 0–12) which served as the Criterion Standard. Prior to statistical analysis, RBM levels were normalized by urine creatinine and logarithmically transformed. NIH-CI scores ranged from 0 to 12. LN damage was categorized as low (NIH-CI $<$3) or moderate (NIH-CI $>$3). LN-TM and the RBM that showed significance in univariate logistic analysis at a p-value$<$0.20 were considered in exploratory stepwise multivariate logistical regression models as candidate predictors, using the NIH CI as dependent variable (outcome) to assess the combinatorial character of the candidate predictors.

Results: The means and percentages of the values of the LN-TM and RBM levels are summarized (Table1). Based on multivariate logistical regression modeling levels of TGFB, NGAL and GFR (or serum creatinine) but not protein excretion (urinary protein/creatinine ratio) were found to be combinatorial biomarkers of LN damage. Results on the RBM liver-type fatty acid binding protein (LFABP), Kidney Injury Molecule-1 (KIM1) and the receiver operating characteristic curve analyses will be presented.

Conclusion: NGAL, TGBF and GFR are good potential components for Children a Lupus Nephritis Index for Damage (C-LID) to non-invasively measure chronic histological changes in LN in the glomeruli, interstitium and tubules. Further studies with larger numbers of patients are required for further evaluation and confirmation of our finding.

Table 1. Comparisons of LN biomarkers between NIH CI Groups

LN biomarkers	NIH CI Score $<$ 3	NIH CI Score $\geq$ 3	p
Protein/ Cr ratio*	1.85 (1.32, 2.59)	3.73 (1.94, 7.18)	0.065
GFR*	***104.39 (90.12, 120.91)***	***72.00 (54.34, 95.40)***	***0.025***
Serum Cr*	0.71 (0.62, 0.81)	1.04 (0.80, 1.35)	0.012
NGAL	***0.33 (0.21, 0.53)***	***0.83 (0.33, 2.08)***	***0.089***
CP	175 (102, 301)	302 (104, 876)	0.377
MCP1	11.37 (7.22, 17.90)	10.86 (4.45, 26.49)	0.930
AGP	929 (416, 2,075)	395 (102, 1,534)	0.298
TGFB*†	***0.69 (0.49, 0.96)***	***3.37 (1.41, 8.06)***	***0.005***
ADI	0.17 (0.07, 0.42)	0.29 (0.05, 1.64)	0.591
HEPCIDIN	0.62 (0.33, 1.17)	0.47 (0.14, 1.56)	0.695
LPGDS	3.76 (2.30, 6.15)	3.92 (1.49, 10.30)	0.942

TF	0.12 (0.07, 0.18)	0.17 (0.07, 0.43)	0.470
VDBP	6.20 (2.94, 13.06)	4.98 (1.15, 21.54)	0.796
HPX	26.57 (15.11, 46.72)	20.24 (7.12, 57.57)	0.657

*: Values in the cells are mean (95% CI).
**: Values in the cells are %.
†: N=16, too small sample size for Step 2 analysis.
NGAL: neutrophil gelatinase associated lipocalin, **MCP1**: monocyte chemoattractant protein-1, **CP**: ceruloplasmin**, AGP:** alpha1-acid glycoprotein, **TF:** transferrin**, LPDGS:** lipocalin-like prostaglandin-D Synthase, **ADI:** adiponectin, **HPX:** hemopexin, **TGFB:** TGF-beta, **VDBP:** vitamin D binding protein.

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1305

Adiposity and Adipokines Are Associated with Insulin Resistance in Pediatric Systemic Lupus Erythematosus. Leandra Uribe Woolnaugh[1], Tracey Wright[1] and Gloria Vega[2]. [1]Children's Medical Center, Dallas, TX, [2]UTSouthwestern Medical Center, Dallas, TX.

Background/Purpose: Traditional risk factors for cardiovascular disease do not fully account for the increase in atherosclerosis in SLE. Insulin resistance (IR) and other metabolic derangements are considered a harbinger of cardiovascular disease Specific factors related to SLE including immune dysregulation and chronic inflammation are also important and may, in part, be mediated by adipocytokines. The relationship between body composition and cardiometabolic risk factors is not well characterized in children with chronic illness including pediatric SLE. The study's objective was to evaluate the association of body composition measures, inflammation, and insulin resistance a cohort of pediatric SLE.

Methods: This cross sectional study examined metabolic parameters, including adiponectin, leptin and hsCRP, and body composition, using dual x-ray absorptiometry to measure whole body lean and fat mass, in 33 children with SLE and 27 healthy controls. All SLE subjects met ACR criteria for diagnosis. Sex- specific BMI z scores (BMIZ), fat mass index (FMIZ) and lean mass index z scores (LMIZ) relative to age were calculated using national reference data. Multi-variable linear regression was used to determine the relationship of IR and SLE and predictors of IR within the SLE subjects.

Results: FMIZ (0.5 vs −0.6; p=0.001) was significantly greater in SLE, with no difference in LMIZ. High sensitivity-c reactive protein (hs-CRP) (4.4 vs 1.1; p=0.04), homeostasis model assessment of insulin resistance (HOMA-IR) (6.4 vs 3.5; p=0.006), measured leptin (40.8 vs 12.9; p=0.0001), and leptin/kg of body fat (1.5 vs 0.7; p<0.001) were significantly greater in SLE. While there was no difference in measured adiponectin, the adiponectin/leptin ratio was greater in controls compared to SLE (2.7 vs 1.1; p=0.03). After adjustment for age, gender, ethnicity and tanner stage, hs-CRP (β=3.9 (1.3–6.4); p=0.004) was significantly associated with IR in SLE. FMIZ (β=1.1 (0.2–2.1); p=0.02), was the significant body composition measure, and leptin/kg of body fat (β=2.3 (0.2–4.4); p=0.03), the most significant metabolic parameter, associated with IR in SLE. Cumulative prednisone dose was not associated with IR.

Conclusion: In this cohort, SLE subjects demonstrated cardiometabolic risk factors with elevated leptin and leptin/kg of body fat and decreased adiponectin/leptin ratio. IR was more common in SLE with adiposity, leptin, and inflammation as the crucial determinants of this association. Further studies are needed to evaluate the use of adipocytokines as biomarkers of cardiovascular disease in this vulnerable population.

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1306

Outcome of Lupus Nephritis in Children Less Than 12 Years Old from North-India. Anju Gupta, Bonnie Abujam, Deepti Suri, Amit Rawat and Surjit Singh. Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Background/Purpose: Studies on lupus nephritis in young children below 12 years of age from developing countries are limited. This study looks at long-term outcome in North-Indian children.

Methods: This was a single-center retrospective study from a University referral hospital that provides subsidized treatment. Children seen in the center during the last 25 years were included if they had been diagnosed with systemic lupus erythematosus (as per the ACR 1997 criteria) and lupus nephritis (proteinuria >500mg/day or hematuria (>5RBC/HPF) or any cellular cast) before their 12thbirthday. Initial presentation, laboratory data and treatment received was obtained from the file. Renal biopsy data was classified as per the WHO classification. The primary endpoint was survival with functioning kidneys (absence of death or ESRD). Patients were followed up till January 2012. Kaplan-Meier analysis was used for survival and log-rank test was used to compare different classes. *Definitions used:* Chronic kidney disease = elevated serum creatinine (>1.5mg/dl) for atleast 3 months. End-stage renal disease = need for renal replacement therapy > 3 months.

Results: This study included 72 children (F: M 3.2:1). The mean± SD age at onset of lupus was 9.3±2.4 years and the duration of disease before presentation was 9.2±12.6 months. Majority of the children (76%) had nephritis at presentation. Renal biopsy was done in 54 children. The histological class was class II in 9, class III in 1, class IV in 35 and class V in 7. Biopsy was not done in the remaining 18 patients due to poor general condition in 7, ongoing anticoagulation in 5, thrombocytopenia, uncontrolled hypertension and refusal by caregivers in 2 children each. The most common induction treatment was monthy pulses of cyclophosphamide (6–12 pulses) followed by maintenance with azathioprine or quarterly pulses of cyclophosphamide. At 1 year of follow up, 11 (15%) children had died (all in 1st admission), 11 (15%) were lost to follow up, 36 (50%) were in complete remission and 5 each (6.9%) were in partial remission and active disease. Data for 4 children at 1 year could not be retrieved. Another 11 (15%) children died after the 1st year. The common causes of mortality was infection, disease activity and renal failure. (Table 1). The mean duration of follow up was 4 ± 4.4 years (0.2–20 years) with a total follow up of 287 patient years. Survival with functioning kidneys was seen in 71% at 3 years, 68% at 5 years and 60% at 10 years. There was no difference in survival among various histological classes.

Conclusion: We found a majority of young children presented with lupus nephritis. There was a high mortality at initial presentation. The long term outcome is still much lower as compared to those from the developed nations. Majority of deaths occur in the initial presentation due to infections, severe disease activity and renal failure.

Table 1: Causes of death

	Total	Initial visit	Later
Septicemia	7	7	0
Severe disease activity	3	3	–
End stage renal disease	4	–	4
Disseminated kochs with shunt malfunction	2	–	2
Pulmonary thromboembolism	2	–	2
Hypertensive Intracranial bleed	1	–	1
Myocarditis with left ventricular failure	1	1	–
Unknown cause (died at home)	2	–	2
Total	22 (30)	11	11

Disclosure: A. Gupta, None; **B. Abujam**, None; **D. Suri**, None; **A. Rawat**, None; **S. Singh**, None.

1307

Monitoring of Mid-Interval Plasma Levels of Mycophenolic Acid in Pediatric Lupus Nephritis Patients. Joyce S Hui-Yuen[1], Kristi Truong[2], Liza Mariel Bermudez-Santiago[1], Amy J. Starr[3], Andrew Eichenfield[4], Lisa F. Imundo[3] and Anca Askanase[3]. [1]Morgan Stanley Children's Hospital of New York Presbyterian, Columbia University Medical Center, New York, NY, [2]St John's University, Queens, NY, [3]Columbia University Medical Center, New York, NY, [4]Children's Hosp of New York, New York, NY.

Background/Purpose: Mycophenolate mofetil (MMF) is often used to treat lupus nephritis (LN) and extra-renal lupus in children with SLE. Plasma levels of mycophenolic acid (MPA) are used in clinical practice to determine absorption of MMF and compliance. However, data are equivocal in the use of plasma MPA levels as a measure of efficacy or a predictor of prognosis in pediatric LN patients. This study was initiated to evaluate the use of MPA levels in routine care of children with LN.

Methods: This is a retrospective study of pediatric LN patients treated with MMF. Data were collected on demographic and disease characteristics, concomitant medications, and treatment outcomes. Complete renal remission (CR) was defined as proteinuria <500mg/24h, and no other clinical manifestations of renal disease. Mid-interval MPA plasma levels were drawn

during routine follow-up. Calculated steady-state concentrations can predict plasma MPA levels at peak, trough, or any time during the dosing interval. Steady-state levels of MPA were calculated using basic pharmacokinetics and compared to routine mid-interval plasma MPA levels. Student t-tests were used when appropriate.

Results: We describe 17 patients with pediatric lupus nephritis treated with MMF that have plasma MPA levels available from our cohort. The mean duration of SLE was 5 years, and LN was 3.3 years. Ten LN patients were in CR at the time of this study, 5 had mixed proliferative/membranous nephritis and 5 had proliferative disease alone. All 7 patients not in CR had some component of membranous LN. MMF was dosed at 600mg/m^2/dose for all patients. The mean dose of corticosteroids was 23.75mg prednisone equivalent/day in patients in CR compared with 62.5mg prednisone equivalent/day in patients with persistent disease (p=0.06). The mean mid-interval levels of MPA were 1.69 ug/ml (range <0.5 to 8 ug/ml) in patients in CR and 2.04 ug/ml (range <0.5 to 6 ug/ml) in patients with persistent active disease (p=NS). Of note, 3 patients in each group had undetectable MPA levels. Based on dose, the calculated mid-interval steady-state level was 13.62 ± 3.67 mg*h/L and did not reflect the observed mid-interval levels.

Conclusion: This is the first study to investigate the correlation between mid-interval levels of MPA and predicted steady-state serum levels in patients with lupus nephritis. Our data suggest a large inter-individual variability but also clearly raise concerns about compliance with MMF regimens and emphasize the need to more precisely monitor MPA levels with peak, trough, and area-under-the-curve, as well as the need to discuss with patients and families the reason(s) for non-compliance.

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1308

Antinucleosome Antibodies As Potential Diagnostic and Prognostic Biomarkers in Childhood Onset Systemic Lupus Erythematosus. Thaschawee Arkachaisri, Joo Guan Yeo, Justin Hung Tiong Tan, Sook Fun Hoh, Lena Das and Jing Yao Leong. KK Women's and Children's Hospital, Singapore, Singapore.

Background/Purpose: The role of antinucleosome antibodies (ANuA) in the immunopathogenesis of SLE is evident. ANuA was shown to be a good, if not better than anti-dsDNA antibody, diagnostic and prognostic biomarkers in adult SLE pts of different ethnicities. Such evidence is scarce in childhood onset SLE (cSLE). We aim to explore the role of ANuA as potential diagnostic and prognostic biomarker in our ASEAN cohort.

Methods: 68 cSLE pts (onset < 18) were recruited and 55 pts with 180 pt-visits with complete clinical data/blood samples were studied. Disease activity (DA) indices: SLEDAI-2K, SLAM and BILAG were recorded. Anti-dsDNA, ANuA (H1-stripped) and anti-C1q were measured by ELISA. Pts were evaluated at 1–3 mo intervals depending on DA. Pts were grouped into 3 DA groups: no activity (ID), minimal DA (MD) = mild DA with no treatment change or DA with improvement from previous visit and active DA (AD) = new case or flare or persistent DA/refractory to treatment. 72 JIA, 6 JDM, 5 MCTD/UCTD, 11 vasculitides, 5 ANA-positive and 17 other inflammatory conditions composed 116 controls (female 45%, median age (IQR) 13.6 (10.3–16.6)). Descriptive statistics were used to describe data. Mann-Whitney/Kruskal-Wallis tests were used to compare data and Spearman's rho for correlation studies.

Results: 55 cSLE (84% female) with median age of 15.9 (14.4–18.2) and median disease duration of 54.7 (29.4–76.2) mo were included. Majority were Chinese and Malay (38%, 33%). Hematologic disorder (98%), arthritis (58%), malar rash (47%) and renal disease (44%) were among most common manifestations. All cSLE had positive ANA at onset. The median (IQR) of SLEDAI-2K, SLAM and BILAG for each disease activity groups were as follows: ID-2.0 (0.0–2.0), 1.0 (0.0–3.0), 1.0 (0.0–1.0); MD-4.0 (3.0–8.0), 3.0 (2.0–4.0), 2.0 (2.0–4.0) and AD-8.0 (4.0–12.0), 6.0 (3.0–9.0), 5.0 (3.0–12.0). ANuA titers among cSLE disease groups and controls were shown in Figure 1. Diagnostic property and correlation studies were shown in Table 1. ANuA level did not fluctuate with renal DA (p=0.601) or associated with the presence of nephritis (p=0.58), so did anti-dsDNA Ab (p=0.587). ANuA showed good and reasonable diagnostic properties, moderate – strong correlations with laboratory parameters but rather weak correlation with DA indices.

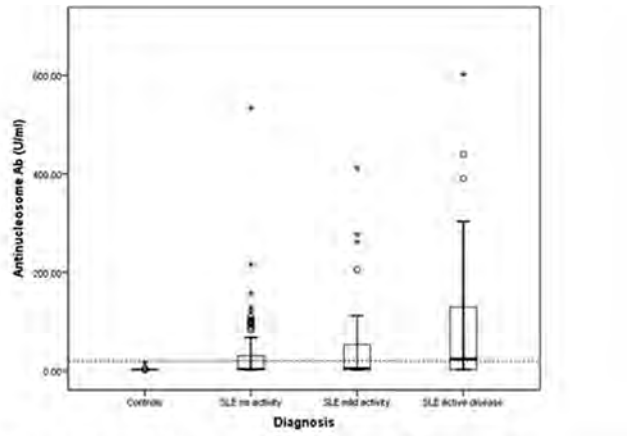

Figure 1 Antinucleosome antibody level distribution among disease group, normal < 20 U/ml
p-value: cSLE vs. Controls (p < 0.001); ; cSLE no activity vs. controls (p<0.001); cSLE min activity vs. active disease (p=0.002); cSLE no activity vs. min activity (p=0.983); cSLE min activity vs. active disease (p=0.073)

Table 1.

Antinucleosome antibodies (ANuA) as diagnostic biomarkers*

Properties	%	95% confidence interval
Sensitivity	66.67	46.04–83.48
Specificity	100.00	96.87–100.00
+ Likelihood ratio (+LR)	NA as specificity 100.00%, very large	
− Likelihood ratio (−LR)	0.33	0.20–0.57
+ Predictive value (+PPV)	100.00	81.47–100.00
− Predictive value (−PPV)	92.80	86.77–96.65
Diagnostic odd ratio (DOR)	NA as specificity 100.00%, very large	

Antinucleosome antibodies (ANuA) in cSLE and controls

Parameters	cSLE (n=180)δ	Controls (n=116)
ANuA titers (nil < 20 U/ml)		
No activity (n=106) ‡	3.57 (2.01–30.63)	
Minimal activity (n=23) ‡	5.47 (1.83–53.48)	1.79 (1.59–1.99)
Active disease activity (n=51) ‡	24.14 (2.57–129.64)	
ANuA and	Correlation coefficients (*rho*)	p value
ESR	0.461	<0.001
CRP	0.140	0.065
C3	−0.581	<0.001
C4	−0.479	<0.001
Anti-dsDNA	0.865	<0.001
Anti C1q Ab	0.558	<0.001
SLEDAI	0.338	<0.001
SLAM	0.188	0.012
BILAG	0.074	0.324

*Controls n=116, cSLE n=27 (20 active disease + 7 newly diagnosed).
‡Minimal activity = mild activity with no therapeutic intervention or activity with improvement from previous visit.
Active disease activity = New case or flare or persistent activity/refractory to treatment
δpatient-visits.

Conclusion: ANuA has a good diagnostic property with high specificity and high PPV suggesting that it could be a compliment biomarker in cSLE diagnosis. The levels fluctuated with DA with moderate - strong correlation with lab parameters despite weak correlation with clinical index, for which a larger validation study is needed.

Disclosure: T. Arkachaisri, None; **J. G. Yeo**, None; **J. H. T. Tan**, None; **S. F. Hoh**, None; **L. Das**, None; **J. Y. Leong**, None.

1309

Does Anti-C1q Antibody Have Diagnostic and Prognostic Roles in Childhood – Onset Systemic Lupus Erythematosus? Thaschawee Arkachaisri, Joo Guan Yeo, Justin Hung Tiong Tan, Sook Fun Hoh, Lena Das and Jing Yao Leong. KK Women's and Children's Hospital, Singapore, Singapore.

Background/Purpose: Biomarkers proven to be effective in aSLE patients may not directly apply to cSLE unless validation is done. Existing

evidences have shown immunopathogenic roles of C1q and anti-C1q antibody (aC1qA) in SLE both in vitro and in vivo. The latter are strongly associated with the development of lupus nephritis especially in aSLE but evidences of its role in cSLE are rare. We aim to explore the role of aC1qA in our Southeast Asian cSLE cohort in regard to its diagnostic and prognostic properties as our proof-of-concept study.

Methods: Sixty-eight cSLE patients were recruited and 55 patients with 180 patient-visits with complete clinical data/blood samples were studied. Disease activity indices including SLEDAI-2K, SLAM and BILAG were recorded. Anti-dsDNA, antinucleosome Abs (ANuA, H1-stripped) and aC1qA were measured by ELISA. Patients were evaluated at 1–3 mo intervals depending on their disease severity. Patients were grouped into 3 disease activity groups: no activity (ID), minimal activity (MD) = mild activity with no therapeutic intervention or activity with improvement from previous visit and active disease activity (AD) = new case or flare or persistent activity/ refractory to treatment. 72 JIA, 6 JDM, 5 MCTD/UCTD, 11 vasculitides, 5 ANA-positive and 17 other inflammatory conditions composed 116 controls (female 45%, median age (IQR) 13.6 (10.3–16.6) years). Descriptive statistics were used to describe data. Mann-Whitney/Kruskal-Wallis tests were used to compare data and Spearman's rho for correlation studies.

Results: 55 cSLE (84% female) with median age of 15.9 (14.4–18.2) yrs and median disease duration of 54.7 (29.4–76.2) mo were included. Majority were Chinese and Malay (38% and 33%). Hematologic disease (98%), arthritis (58%), malar rash (47%) and renal disease (44%) were among most common manifestations. All patients had ANA positivity at onset. Fig 1 shows significant differences in AC1qA levels between controls vs. cSLE and among disease activity groups ($p < 0.001$). Table 1 reveals strong diagnostic properties of aC1qA. aC1qA was also associated with the presence of nephritis ($p=0.034$). Correlation analysis showed moderate to good correlations with ESR, C3, C4, anti-dsDNA and ANuA and SLEDAI.

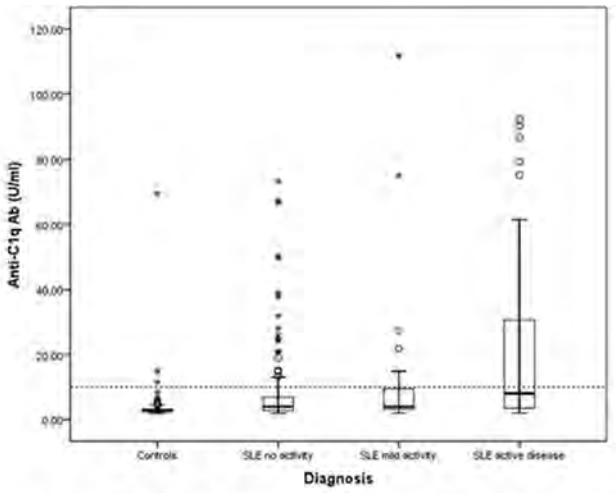

Figure 1 Anti-C1q antibody level distribution among disease group, normal < 10 U/ml. p-value: cSLE vs. Controls ($p < 0.001$); cSLE no activity vs. controls ($p<0.001$); cSLE min activity vs. active disease ($p=0.158$); cSLE no activity vs. min activity ($p=0.456$); cSLE min activity vs. active disease ($p=0.001$).

Table 1.

Anti-C1q antibody as diagnostic biomarker*

Properties	%	95% confidence interval
Sensitivity	48.15	28.67–68.05
Specificity	97.41	92.63–99.46
+ Likelihood ratio	18.62	5.70–60.80
− Likelihood ratio	0.53	0.37–0.77
+ Predictive value	81.25	54.35–95.95
− Predictive value	88.98	82.20–93.84
Diagnostic odd ratio (DOR)	35.13	

Anti-C1q antibody (aC1q) in cSLE and Controls

Parameters	cSLE (n=180)δ	Controls (n=116)
aC1q titers (nil < 10 U/ml)		
No activity (n=106)**	4.03 (2.78–6.97)	2.81 (2.46–3.27)
Minimal activity (n=23)**	4.01 (3.25–9.50)	
Active disease activity (n=51)**	8.05 (3.53–30.85)	

aC1q and	Correlation coefficients (*rho*)	p value
ESR	0.321	<0.001
CRP	0.011	0.886
C3	−0.573	<0.001
C4	−0.486	<0.001
Anti-dsDNA Ab	0.596	<0.001
Antinucleosome Ab	0.558	<0.001
SLEDAI	0.473	<0.001
SLAM	0.276	<0.001
BILAG	0.235	0.002

*Controls n=116, cSLE n=27 (20 active disease + 7 newly diagnosed).
**Minimal activity = mild activity with no therapeutic intervention or activity with improvement from previous visit.
Active disease activity = New case or flare or persistent activity/ refractory to treatment.
†Median (IQR).
δpatient-visits.

Conclusion: Our initial findings showed a strong diagnostic and possible, prognostic properties of aC1qA in our cSLE cohort. The presence of aC1qA was associated with lupus nephritis and its levels seem to fluctuate with global, if not only renal disease activity. A longer term and prospective study is needed to validate these initial findings in our region.

Disclosure: T. Arkachaisri, None; **J. G. Yeo**, None; **J. H. T. Tan**, None; **S. F. Hoh**, None; **L. Das**, None; **J. Y. Leong**, None.

1310

Predicting Macrophage Activation Syndrome in Pediatric Systemic Lupus Erythematosus Patients at Diagnosis. Maya Gerstein[1], Roberto Ezequiel Borgia[1], Brian Feldman[1], Deborah M. Levy[2], Sharon Sukhdeo[3], Susanne M. Benseler[4], Lawrence W.K. Ng[1], Mohamed Abdelhaleem[1], Earl D. Silverman[1] and Linda T Hiraki[1]. [1]The Hospital for Sick Children, Toronto, ON, [2]The Hospital for Sick Children and University of Toronto, Toronto, ON, [3]The Hospital For Sick Children, Toronto, ON, [4]Alberta Children's Hospital, University of Calgary, Calgary, AB.

Background/Purpose: It can be difficult to differentiate macrophage activation syndrome (MAS) from active pediatric systemic lupus erythematosus (pSLE). However, this differentiation is in determining correct treatment decisions. The purpose of this study is to generate a decision tree for the recognition of MAS in newly diagnosed pSLE and test the performance of these proposed criteria in an independent pSLE cohort.

Methods: A retrospective cohort study of consecutive patients requiring admission to SickKids Hospital with newly diagnosed, active pSLE between January 2002 and July 2007 (training cohort) was performed. All patients met ≥4 /11 ACR criteria. Data collection on: 1) Clinical features including fever, CNS dysfunction, splenomegaly, hepatomegaly and hemorrhage; 2) laboratory parameters; CBC, ESR, CRP, C3, C4, ferritin, AST, ALT, LDH, albumin, bilirubin, triglycerides, LDL, HDL, urea, creatinine, sodium, coagulation parameters including INR, PTT, fibrinogen and D-Dimer, and soluble IL-2 receptor (sIL-2R) and CD163. Patients were assigned to one of 2 cohorts exclusively (MAS/non-MAS). Putative predictor variables were compared between cohorts. A decision tree analysis for diagnosis of MAS in pSLE was constructed using recursive partitioning, and decision rules were subsequently applied to an independent cohort of newly diagnosed, active pSLE diagnosed and admitted to SickKids between July 2007 and July 2013 (testing cohort) to determine the sensitivity and specificity of the proposed criteria

Results: The training cohort consisted of 56 pSLE patients: 9 (16%) diagnosed with MAS and 47 non-MAS patients. Splenomegaly was more common in the non-MAS cohort, with no other differences in clinical characteristics between cohorts. Of all the available laboratory data, ALT ≥ 45 units/L, neutrophils $< 1.65 \times 10^3/mm^3$ and ferritin ≥ 836 μg/L identified 55% of the patients with MAS ($R^2 = 0.75$) with 100% specificity. The testing cohort consisted of 9 (20%) MAS and 32 non-MAS pSLE patients. The proposed thresholds for ALT, neutrophil count and ferritin demonstrated a sensitivity of 67% and specificity of 94% in discriminating MAS from nonMAS patients.

Conclusion: None of the clinical features differentiated pSLE patients with and without MAS. Using all laboratory data proposed to be elevated in MAS and decision tree analysis demonstrated that ALT, neutrophil count and ferritin had excellent specificity and adequate sensitivity for distinguishing MAS from active SLE at diagnosis in the both the testing and validation

cohorts. This is a first step in improved recognition of MAS among pSLE patients. Future analyses are planned to further refine methods in distinguishing these two groups.

Disclosure: M. Gerstein, None; **R. E. Borgia**, None; **B. Feldman**, None; **D. M. Levy**, None; **S. Sukhdeo**, None; **S. M. Benseler**, None; **L. W. K. Ng**, None; **M. Abdelhaleem**, None; **E. D. Silverman**, None; **L. T. Hiraki**, None.

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Lupus Nephritis in Mexican Children. María del Rocío Maldonado-Velázquez, Enrique Faugier, Fernando Garcia-Rodriguez, Paola Lara, Angel Flores, Javier Tomala-Haz and Diego Salinas-Encinas. Hospital Infantil de Mexico Federico Gomez, Mexico City, Mexico.

Background/Purpose: Incidence and disease pattern of childhood-onset systemic lupus erythematosus (SLE) is reported to differ among ethnic groups. Lupus nephritis (LN) strongly affects the outcome in children with LES systemic lupus erythematosus (SLE). There are lack of data on the clinical course, long-term outcome and predictors of disease progression in mexican children. This study reports the results and outcomes of a cohort of Mexican patients with LN.

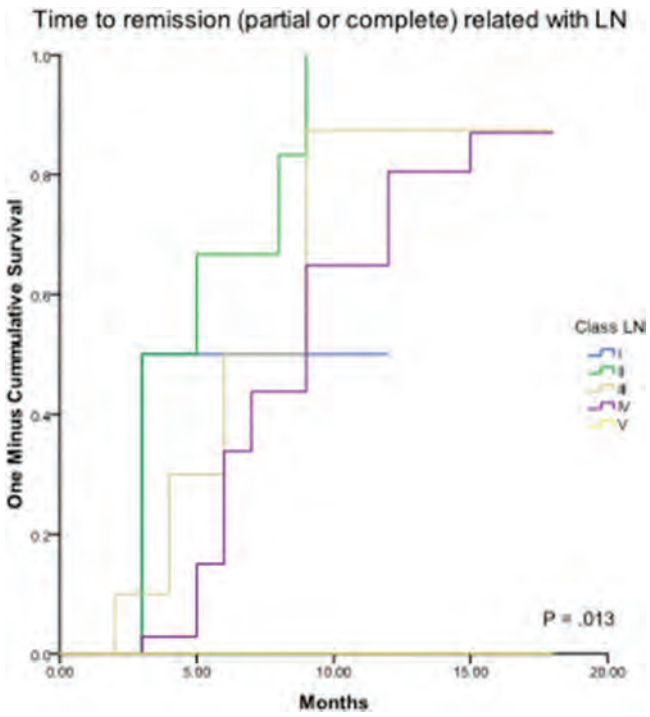
Methods: To describe lupus nefritis pattern and follow-up of a cohort of 61 Mexican children with SLE in the Hospital Infantil de Mexico Federico Gomez during a 18-month period in 2013–2014. Descriptive data, parametric, non parametric statistics and Kaplan-Meier graphs was used to analyze disease remission.

Results: The mean age at diagnosis was 12.4 years (SD = 2.6), most of them was female (85%) and 51 (83%) presented nephritis at the time of LES diagnosis. The mean plasma creatinine was 0. 8 (SD 0.4) and 24 (39%) patients presented with nephritic syndrome. Renal function was reported with a median proteinuria 41 mg/m2TBS/h (0 - 735) and 53 (86.9%) presented with positive urinary sediment. Complement was diminished in the most of the patients. Class IV LN was the most prevalent (62%).

Treatment was based on cyclophpsphamide IV pulses alone or combined with oral either azathioprine or MMF. The patients completed a mean follow-up of 8 months, 26 (42.6%) patients were in complete remission and 15 (24.6%) were in partial remission. Two patients needs to move to rituximab treatment.

Mean time to remission (either complete or partial) was 9 months (SD 0.6) and the best outcome was related with class II LN (Figure, P =.013).

Conclusion: The current study provides outcome data on a mexican pediatric population with LN and underlines the importance of prescribing appropriate induction treatment to all children, also we identify that class II LN presents the best outcome in our patients.



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Features, Treatment and Outcome of Macrophage Activation Syndrome in Pediatric Systemic Lupus Erythematosus. Roberto Ezequiel Borgia[1], Maya Gerstein[1], Deborah M. Levy[2], Earl D. Silverman[1] and Linda T Hiraki[1]. [1]The Hospital for Sick Children, Toronto, ON, [2]The Hospital for Sick Children and University of Toronto, Toronto, ON.

Background/Purpose: Macrophage activation syndrome (MAS) is a life-threatening inflammatory complication of pediatric systemic lupus erythematosus (pSLE). There are few reports of the presentation, treatment and outcome of MAS in pSLE. Our objective is to describe the presentation and treatment of pSLE-MAS patients seen at a single tertiary centre.

Methods: Our retrospective review included all patients seen at the Hospital for Sick Children, Toronto, diagnosed with pSLE (≥ 4/11 ACR classification criteria) and MAS (by Pediatric Reumatologist expert opinion) between January 2002 and December 2012. We collected data on: 1) Demographics: Sex, ethnicity, age of diagnoses; 2) MAS clinical features (fever, hepatosplenomegaly, lymphadenopathy, hemorrhages, CNS involvement); 3) SLE ACR classification criteria; 3) Additional laboratory, pathological and genetic parameters including autoantibodies and bone marrow aspiration (BMA); 4) Treatment; 5) Frequency of hospitalization, PICU admission and death.

Results: We identified 34 patients diagnosed with pSLE and MAS. The majority were female (70%). The most common SLE features were malar rash, arthritis and anti-dsDNA antibodies (Table). Mean age at SLE diagnosis was 13.4 years (SD: 3.0), the average interval between SLE and MAS diagnosis was 1.5 months (SD: 0.54), with the majority (76%) of patients diagnosed with MAS concomitantly with their SLE diagnosis. 4 patients had documented concomitant infections: 2 bacterial, 1 EBV and 1 HSV1.

All patients had fever (Table). 6/23 patients (26%) who underwent BMA demonstrated hemophagocytosis. Targeted gene sequencing of HLH genes perforin and syntaxin 11 was performed in 5 patients with the only abnormality a silent heterozygous polymorphism in perforin coding region detected in one patient. All patients were treated with corticosteroids with the majority (59%) receiving IV pulse of methylprednisolone (average 3 pulses/patient). Concomitant medications: IVIG in 59%, calcineurin inhibitor in 32%, and etoposide in 6%. All the patients required hospital admission, 6 required PICU admission and there were no deaths from MAS.

Conclusion: To our knowledge this is the largest cohort of patients with diagnosis of MAS in pSLE reported in a single center. We observed that MAS is most likely to develop concomitantly with pSLE diagnosis. The majority of the patients were successfully treated with corticosteroids and IVIG with complete recovery in all.

Table: Clinical and Laboratory characteristics:

Clinical Features of MAS n (%)		*SLE ACR Classification Criteria n (%)*	
Fever	34 (100)	Malar rash	27 (79)
Hemorrhages	9 (26)	Arthritis	18 (52)
CNS dysfunction	9 (26)	Ulcers	16 (47)
Lymphadenopathy	8 (23)	Nephritis	13 (38)
Hepatomegaly	6 (17)	Serositis	10 (29)
Splenomegaly	6 (17)	CNS disease	10 (29)
		Photosensitivity	6 (17)
MAS Laboratory Parameters mean (+/− SD)		*Autoantibodies n (%)*	
WBC (mm3)	2.56 (1.87)	ANA	33 (97)
Neutrophils (mm3)	1.32 (1.01)		
HGB (g/L)	95 (16.04)	anti-ds DNA	28 (82)
PLT (mm3)	134,000 (79.94)		
AST (units/L)	249 (301)	anti-RNP	16 (47)
ALT (units/L)	161 (259)		
LDH (IU/L)	2,728 (2,655)	anti-Ro	15 (44)
Ferritin (μg/L)	6,310 (11,091)		
Fibrinogen (g/L)	2,86 (1,04)	anti-SM	14 (41)
aPTT	37 (8)		
D-Dimer (ng/mL)	1,923 (5,709)	anticardiolipin	14 (41)
Triglycerides (mmol/L)	2,78 (1,19)		
Sodium (mmol/L)	135 (4,61)	anti-La	5 (14)

ERS (mm)	69 (38)		
sIL-R2 (UI/ml) in 4 patients	2,561 (2,986)	LAC	3 (9)

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Comorbidity Patterns in Children with Juvenile Idiopathic Arthritis and Systemic Lupus Erythematosus: The Childhood Arthritis and Rheumatology Research Alliance Registry. Marc D. Natter[1], Mei-Sing Ong[2], Kenneth D. Mandl[1], Laura Schanberg[3], Yukiko Kimura[4], Norman Ilowite[5] and the CARRA Registry Investigators. [1]Children's Hospital Boston, Boston, MA, [2]University of New South Wales, Sydney, Australia, [3]Duke University, Durham, NC, [4]Hackensack Univ Medical Ctr, Hackensack, NJ, [5]Children's Hospital Montefiore, Bronx, NY.

Background/Purpose: Knowledge of co-occurring disease processes (comorbidities) is important for understanding disease pathogenesis, refining disease classifications, developing appropriate screening and prevention strategies, and determining overall burden of disease. We analyze prevalence and patterns of comorbidities in children with JIA and SLE in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry.

Methods: We analyzed cross-sectional data from the CARRA Registry across 60 sites between 2010 and 2013. Patterns of comorbidities in children with JIA and SLE were assessed. Network analysis of disease co-occurrence was carried out to identify clusters of comorbidities that are likely to present in the same individual.

Comorbidities were present and captured (1 or more) for subjects in the registry according to disease type:

JIA: uveitis, fibromyalgia, sarcoid, autism, autoimmune hepatitis, autoimmune thyroiditis, celiac disease, cerebral palsy, congenital heart disease, cystic fibrosis, type 1 diabetes (T1D), type 2 diabetes (T2D), malignancy, immunodeficiency, asthma, Down syndrome, demyelinating disorder, seizure, pulmonary hypertension, psoriasis, IBD, interstitial lung disease.

SLE: chronic vasculitis, autoinflammatory disease, uveitis, fibromyalgia, sarcoid, autism, autoimmune hepatitis, autoimmune thyroiditis, celiac disease, cerebral palsy, congenital heart disease, cystic fibrosis, T1D, T2D, malignancy, immunodeficiency, asthma, Down syndrome, demyelinating disorder, coronary heart disease.

Results: 6,150 children with JIA and 1,067 children with SLE were enrolled in the CARRA registry. 20.5% of JIA and 11.5% of SLE patients had at least 1 comorbidity (Table 1). Multiple co-occurring co-morbidities were individually much less common (0.6% or less), including in known associations (e.g. JIA with Down's syndrome and hypothyroidism or congenital heart disease).

Conclusion: The prevalence of comorbidities in children with JIA and SLE in the CARRA Registry is in accordance with ranges reported in other studies. We analyzed multiple co-occurring co-morbidities, including a network clustering analyses, which showed established and potential associations that are candidates for further evaluation in larger, population-based data sets.

Table 1. Number of comorbidities in JIA and SLE patients

	Frequency (%)	
Number of Comorbiditics	**JIA* (n=6,150)**	**SLE # (n = 1,067)**
1	1153 (18.7)	118 (11.1)
2	95 (1.5)	3 (0.3)
3	8 (0.1)	1 (0.1)
4	4 (0.1)	
At least one	1258 (20.5)	120 (11.5)

*Comorbidities considered included: uveitis, fibromyalgia, sarcoid, autism, autoimmune hepatitis, autoimmune thyroiditis, celiac disease, cerebral palsy, congenital heart disease, cystic fibrosis, type 1 diabetes, type 2 diabetes, malignancy, immunodeficiency, asthma, Down syndrome, demyelinating disorder, seizure, pulmonary hyertension, psoriasis, inflammatory bowel disease, interstitial lung disease.
Comorbidities considered included: chronic vasculitis, autoinflammatory disease, uveitis, fibromyalgia, sarcoid, autism, autoimmune hepatitis, autoimmune thyroiditis, celiac disease, cerebral palsy, congenital heart disease, cystic fibrosis, type 1 diabetes, type 2 diabetes, malignancy, immunodeficiency, asthma, Down syndrome, demyclinating disorder, coronary heart disease.

Table 2. Summary of comorbidity patterns

Table 2a. Comorbidities in children with JIA (n=6,150)

Comorbidities	Frequency (%)	
	Including other comorbidities	**Excluding other comorbidities**
Co-occurring autoimmune disease	1181 (19.2)	1083 (17.6)
Uveitis	713 (11.6)	653 (10.6)
Psoriasis	324 (5.3)	267 (4.3)
Asthma	105 (1.7)	84 (13.7)
Inflammatory bowel disease	58 (0.9)	47 (0.8)
Thyroiditis	19 (0.3)	8 (0.1)
Type 1 diabetes	18 (0.3)	9 (0.1)
Scleroderma	11 (0.2)	10 (0.6)
Interstitial lung disease	9 (0.1)	4 (0.07)
Celiac disease	7 (0.1)	5 (0.08)
Chronic vasculitis	5 (0.08)	3 (0.05)
Autoimmune hepatitis	2 (0.03)	1 (0.02)
Co-occurring non-autoimmune disease	103 (1.7)	62 (1.0)
Juvenile fibromyalgia	36 (0.6)	21 (0.3)
Autism	17 (0.3)	13 (0.2)
Seizure	16 (0.3)	9 (0.1)
Down's syndrome	12 (0.2)	6 (0.1)
Congenital heart disease	10 (0.2)	5 (0.08)
Pulmonary hypertension	8 (0.1)	0
Type 2 diabetes	7 (0.1)	4 (0.07)
Malignancy	4 (0.07)	2 (0.03)
Immunodeficiency	1 (0.02)	0
Cystic fibrosis	1 (0.02)	1 (0.02)
Cerebral palsy	1 (0.02)	1 (0.02)
Comorbidity couplets		
Uveitis, psoriasis	34 (0.6)	34 (0.6)
Asthma, psoriasis	10 (0.2)	7 (0.1)
Uveitis, asthma	5 (0.08)	5 (0.08)
Uveitis, IBD	5 (0.08)	5 (0.08)
Psoriasis, IBD	4 (0.07)	4 (0.07)
Fibromyalgia, psoriasis	4 (0.07)	2 (0.03)
Thyroiditis, Down's syndrome	4 (0.07)	2 (0.03)
Thyroiditis, type 1 diabetes	3 (0.05)	3 (0.05)
Uveitis, pulmonary hypertension	3 (0.05)	3 (0.05)
Uveitis, fibromyalgia	3 (0.05)	2 (0.03)
Uveitis, seizure	3 (0.05)	2 (0.03)
Chronic vasculitis, fibromyalgia	3 (0.05)	1 (0.02)
Chronic vasculitis, psoriasis	3 (0.05)	1 (0.02)
Fibromyalgia, asthma	3 (0.05)	1 (0.02)
Thyroiditis, congenital heart disease	2 (0.03)	0
Congenital heart disease, Down's syndrome	2 (0.03)	0
Type 1 diabetes, seizure	2 (0.03)	2 (0.03)
Type 2 diabetes, asthma	2 (0.03)	2 (0.03)
Uveitis, autism	2 (0.03)	2 (0.03)
Autism, asthma	1 (0.02)	1 (0.02)
Celiac, IBD	1 (0.02)	1 (0.02)
Celiac, type 1 diabetes	1 (0.02)	1 (0.02)
Fibromyalgia, IBD	1 (0.02)	1 (0.02)
Fibromyalgia, malignancy	1 (0.02)	1 (0.02)
Fibromyalgia, type 2 diabetes	1 (0.02)	1 (0.02)
Fibromyalgia, thyroiditis	1 (0.02)	1 (0.02)
Immunodeficiency , asthma	1 (0.02)	1 (0.02)
Pulmonary hypertension, Down's syndrome	1 (0.02)	1 (0.02)
Pulmonary hypertension, interstitial lung disease	1 (0.02)	1 (0.02)
Scleroderma, asthma	1 (0.02)	1 (0.02)
Seizure, psoriasis	1 (0.02)	1 (0.02)
Type 1 diabetes, Down's syndrome	1 (0.02)	1 (0.02)
Thyroiditis, psoriasis	1 (0.02)	1 (0.02)
Uveitis, congenital heart disease	1 (0.02)	1 (0.02)
Uveitis, interstitial lung disease	1 (0.02)	1 (0.02)
Uveitis, thyroiditis	1 (0.02)	1 (0.02)
Congenital heart disease, seizure	1 (0.02)	0
Autism, congenital heart disease	1 (0.02)	0
Autism, seizure	1 (0.02)	0
Type 1 diabetes, asthma	1 (0.02)	0
Type 1 diabetes, psoriasis	1 (0.02)	0
Fibromyalgia, seizure	1 (0.02)	0
Comorbidity triplets		
Fibromyalgia, asthma, psoriasis	2 (0.03)	2 (0.03)
Thyroiditis, congenital heart disease, Down's syndrome	2 (0.03)	2 (0.03)
Autism, congenital heart disease, seizure	1 (0.02)	1 (0.02)
Fibromyalgia, type 1 diabetes, malignancy	1 (0.02)	1 (0.02)
Type 1 diabetes, asthma, psoriasis	1 (0.02)	1 (0.02)
Uveitis, fibromyalgia, seizure	1 (0.02)	1 (0.02)
Comorbidity quadruplets		
Uveitis, pulmonary hypertension, psoriasis, interstitial lung disease	3 (0.05)	3 (0.05)
Autoimmune hepatitis, thyroiditis, congenital heart disease, psoriasis	1 (0.02)	1 (0.02)
Co-occurring autoimmune disease	111 (10.4)	107 (10.0)
Chronic vasculitis	79 (7.4)	77 (7.2)
Asthma	17 (1.6)	16 (1.5)
Thyroiditis	11 (1.0)	9 (0.8)
Celiac	2 (0.2)	2 (0.2)
Type 1 diabetes	2 (0.2)	1 (0.1)
Uveitis	1 (0.1)	1 (0.1)
Autoinflammatory disease	1 (0.1)	1 (0.1)
Co-occurring non-autoimmune disease	14 (1.3)	11 (1.0)
Juvenile fibromyalgia	6 (0.6)	5 (0.5)
Autism	2 (0.2)	1 (0.1)
Congenital heart disease	2 (0.2)	1 (0.1)
Coronary heart disease	2 (0.2)	2 (0.2)
Type 2 diabetes	2 (0.2)	2 (0.2)
Comorbidity couplets		
Chronic vasculitis, fibromyalgia	1 (0.1)	1 (0.1)
Chronic vasculitis, thyroiditis	1 (0.1)	1 (0.1)
Autism, Asthma	1 (0.1)	1 (0.1)
Thyroiditis, congenital heart disease	1 (0.1)	1 (0.1)
Thyroiditis, type 1 diabetes	1 (0.1)	1 (0.1)
Congenital heart disease, type 1 diabetes	1 (0.1)	1 (0.1)
Comorbidity triplets		
Thyroiditis, congenital heart disease, type 1 diabetes	1 (0.1)	1 (0.1)

Figure 1. Comorbidity network depicting the inter-relationships among comorbidities. Each node represents a comorbidity, and the size of a node is proportional to the prevalence of a comorbidity. A link between two nodes denotes disease-pair co-occurrence, and the width of a link is proportional to the prevalence of co-occurrence.

Figure 1a. Comorbidity network in children with JIA. Two comorbidity clusters were identified: (1) uveitis, fibromyalgia, psoriasis, asthma, IBD, T2D, malignancy, immunodeficiency, chronic vasculitis, and scleroderma; (2) thyroiditis, seizure, congenital heart disease, T1D, autism, pulmonary hypertension, celiac disease, Down's syndrome, and interstitial lung disease.

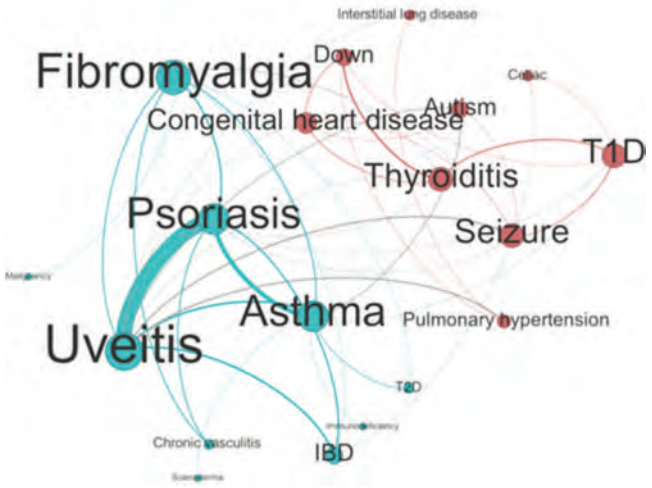
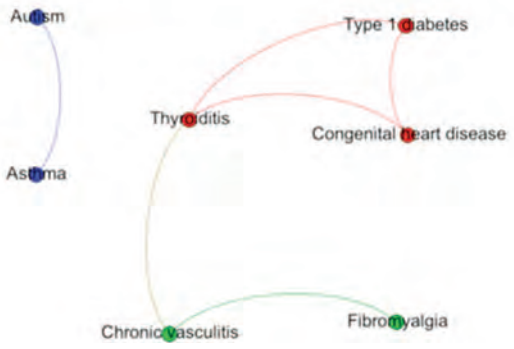


Figure 1b. SLE comorbidity network. Three comorbidity clusters were identified: (1) autism, asthma; (2) thyroiditis, T1D, congenital heart disease; (3) chronic vasculitis, fibromyalgia.



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Comparison of the Utility and Validity of Three Scoring Tools to Detect Skin Disease in Patients with Juvenile Dermatomyositis.

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Background/Purpose: Juvenile dermatomyositis (JDM) is a rare condition affecting 3 children/million/year. Muscle and skin involvement are key features. The muscle symptoms are frequently the main initial focus: formal measures (Childhood Myositis Assessment Scale - CMAS and Manual Muscle Test - MMT8) exist to routinely and accurately assess this component of the disease. However the involvement of skin, and its assessment, is a vital aspect. The abbreviated Cutaneous Assessment Tool (CAT) encompassing active skin disease and skin damage, Disease Activity Score (DAS) and Myositis Intention to Treat Activity Index (MITAX), both with skin components, have all been suggested to measure skin disease in JDM; however the optimal tool is unknown. The aim was to compare 3 tools for assessment of skin disease in JDM and correlate them with the physician's 10cm skin visual analogue scale (physician's skin VAS) to define which tool best assesses skin disease.

Methods: Patients recruited to the UK JDM Cohort & Biomarker Study who fulfil Bohan-Peter criteria for JDM were included. Each patient was assessed for skin disease using the CAT, DAS, MITAX and an overall physician's skin VAS. Markers of muscle disease (CMAS, MMT8, CK U/L), inflammatory markers (CRP mg/L and ESR mm/hr) and overall physician's global score were also recorded. Spearman's correlations (rs) were used to correlate categorical and continuous variables and a relationship >0.75 was considered strong. A p-value <0.05 was considered significant.

Results: Between 2012 and 2014, 67 JDM patients were assessed. 59.7% were female. The mean (±SD) age of the patients was 9.86 ±3.37 years, with mean age at diagnosis 6.59 ±3.42 years and mean disease duration of 3.26 ±3.08 years. The skin section of the DAS had the strongest correlation with the physician's skin VAS (Table 1). The skin section of the MITAX and the CAT activity scores were significantly correlated with the physician's skin VAS. DAS skin, MITAX skin and CAT Activity scores were all negatively correlated with CMAS and MMT8 scores; no significant correlations were noted with the CK. DAS skin scores were significantly correlated with both the CRP and ESR, while the MITAX skin was significantly correlated only with the ESR, and CAT Activity only with the CRP.

Table 1. Spearman's correlation between items shown as r_s and corresponding p value

	Skin VAS n=67	CMAS n=67	MMT8 n=67	CK n=52	CRP n=55	ESR n=54
DAS skin	r_s 0.795 p<0.001	r_s −0.443 p<0.001	r_s −0.424 p<0.001	r_s 0.176 p 0.212	r_s 0.280 p 0.039	r_s 0.311 p 0.022
MITAX skin	r_s 0.594 p<0.001	r_s −0.404 p 0.001	r_s −0.453 p<0.001	r_s 0.177 p 0.210	r_s 0.208 p 0.127	r_s 0.281 p 0.040
CAT Activity	r_s 0.623 p<0.001	r_s −0.471 p<0.001	r_s −0.428 p<0.001	r_s 0.157 p 0.267	r_s 0.300 p 0.026	r_s 0.164 p 0.235

Conclusion: These data demonstrate the potential application of using a skin assessment tool to evaluate and monitor skin involvement in JDM patients. It also demonstrates that the DAS skin section appears to be the best of the tools using the physician's skin VAS as the gold standard. The DAS skin tool was concise, quick to use and easy to score.

Disclosure: R. Campanilho-Marques, None; **B. Almeida**, None; **K. Arnold**, None; **K. Nistala**, None; **C. A Pilkington**, None; **L. R. Wedderburn**, None.

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Cross-Sectional Evaluation of Hydroxychloroquine (HCQ) Therapy in Children with Juvenile Dermatomyositis (JDM) Enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry.

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Background/Purpose: Hydroxychloroquine is an antimalarial agent commonly used in the treatment of rheumatologic diseases. Data on the use of HCQ in JDM is limited, primarily based on anecdotal experience and two small, retrospective reviews. As a result, there is no current consensus on the utility of HCQ in the management of JDM. Our objective was to investigate the use of HCQ in JDM using a large, national, multi-center registry.

Methods: Subjects meeting Bohan and Peter criteria for definite or probable JDM were enrolled into the CARRA registry between 2010 and 2013. Cross sectional analysis of data regarding demographics, disease characteristics, measures of disease activity, diagnostic assessments, medications and long term complications were examined. Bivariate analysis was performed evaluating the use of HCQ with clinical variables of interest. Variables with biologic relevance or statistically significant associations (p<0.25) were selected for inclusion into a multivariate logistic regression model examining independent predictors of HCQ use.

Results: Baseline information was available for 604 patients. Information on HCQ treatment was available for 565 patients (93.5%). 295 (52.2%) patients had current or prior treatment with HCQ and 270 (47.8%) patients had never been treated with HCQ. In bivariate analysis, an association was found between the use of HCQ and age at first rheumatology visit (p=0.02), disease duration (p<0.001), abnormal CHAQ (p=0.001), symmetric proximal muscle weakness (p=0.002), large joint arthritis (p=0.002), malar erythema (p=0.04) and calcinosis (p=0.012). In multivariate analysis,

patients with symmetrical proximal muscle weakness or an abnormal CHAQ score were less likely to be on HCQ therapy; whereas patients with any rash (malar erythema, Gottron's sign, heliotrope rash, V-sign or shawl sign), calcinosis or arthritis had a higher likelihood to be on current or prior HCQ therapy (Table 1).

Table 1. Multivariable model using logistic regression predicting use of HCQ (n=496)

	Odds ratio [95% Confidence interval]	p-value
Symmetrical muscle weakness	0.46 [0.28–0.74]	0.002
Abnormal CHAQ	0.66 [0.44–0.99]	0.044
Calcinosis	1.93 [1.08–3.45]	0.027
Rash	1.65 [1.11–2.46]	0.014
Arthritis	1.56 [1.05–2.31]	0.027

Conclusion: The CARRA registry represents one of the largest ongoing multi-center JDM registries. This data aids our understanding of which clinical characteristics may predict HCQ use in JDM. Prior evidence in other rheumatologic conditions suggests that HCQ improves arthritis and skin manifestations. As expected, patients with these characteristics were more likely to be on HCQ. Patients with muscle weakness and abnormal CHAQ were less likely to be on HCQ. We speculate these patients had a more severe disease course and likely treated with aggressive immunosuppression. Due to the design of this study as a cross-sectional analysis, we are unable to determine the causal association of these results. Further longitudinal data is needed to examine the benefits of HCQ in these patients.

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A Hybrid Conjoint Analysis Model Is Proposed As the Definition of Minimal, Moderate and Major Clinical Improvement in Juvenile Dermatomyositis Clinical Trials.

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Background/Purpose: Preliminary definitions of improvement (DOIs) for juvenile dermatomyositis (JDM) combining IMACS or PRINTO core set activity measures (CSMs) have been used as a responder index in clinical trials. However, these DOIs defined only minimal clinical improvement and are in need of further validation.

Methods: Using natural history study data, JDM experts rated patient profiles containing IMACS or PRINTO CSMs and achieved consensus (≥ 70% agreement) in 98% (247 minimal, 174 moderate and 84 major improvement). Conjoint analysis was performed on forced-choice surveys (by using 1000Minds software) administered to myositis experts. Candidate DOIs based on changes in core set measures (CSMs) were generated as follows: A) 23 published DOIs were retested; B) 436 DOIs developed using expert survey and variations of published DOIs; C) 56 DOIs derived from logistic regression analysis; D) 6 DOIs derived from a conjoint analysis survey that yielded scores with different levels of improvement in different CSMs; E) 8 DOIs drafted by combining changes in each CSM with respective conjoint analysis weights; and F) 194 DOIs drafted by applying weights from conjoint analysis to the base DOIs. Relative and absolute % change DOIs were tested. The consensus patient profiles were then used to test DOIs for their validity, including sensitivity, specificity, kappa, OR and area under the curve (AUC). High performing DOIs were externally validated using Rituximab in Myositis (RIM) trial data (N=48) and PRINTO JDM (n=139) trials.

Results: The 14 highest performing candidate DOIs with AUC ≥ 0.90 in profile data for minimal, moderate and major improvement, and comparable results in the RIM trial, were discussed among 12 JDM experts for their performance characteristics and clinical face validity at a consensus conference using Nominal Group Technique (NGT). Many DOIs had significant discriminant validity in the PRINTO trial. A final ranking of the pediatric experts' top DOIs yielded 92% consensus for a conjoint analysis hybrid model DOI using absolute % change in CSMs with different cut points for minimal, moderate and major improvement (Table 1). NGT discussion with the pediatric and adult working groups yielded consensus (91% agreement) in use of this hybrid DOI for adult DM/PM and JDM.

Conclusion: A conjoint analysis-driven hybrid definition with a continuous score of improvement based on absolute % change in CSMs with different cut points for minimal, moderate and major improvement was selected by a data- and consensus-driven process as a final DOI to be used for JDM and adult DM/PM clinical trials. ACR and EULAR funding support was received for this project, and their approval will be sought for these as new criteria for clinical response.

Table 1

Conjoint Analysis Model (absolute % change)	
Core Set Measure	**Improvement score for each level of CSM**
MD Global Absolute % Change	
Up to <=5%	0
>5% up to <=15%	7.5
>15% up to <=25%	15
>25% up to <=40%	17.5
>40%	20
Parent Global/Patient Global Absolute % Change	
Up to <=5%	0
>5% up to <=15%	2.5
>15% up to <=25%	5
>25% up to <=40%	7.5
>40%	10
MMT/CMAS Absolute % Change	
Up to <=2%	0
>2% up to <=10%	10
>10% up to <=20%	20
>20% up to <=30%	27.5
>30%	32.5
CHAQ/HAQ Absolute % Change	
Up to <=5%	0
>5% up to <=15%	5
>15% up to <=25%	7.5
>25% up to <=40%	7.5
>40%	10
Muscle Enzyme/CHQ-PF50 Absolute % Change	
Up to <=5%	0
>5% up to <=15%	2.5
>15% up to <=25%	5
>25% up to <=40%	7.5
>40%	7.5
Extra Muscular VAS/DAS Absolute % Change	
Up to <=5%	0
>5% up to <=15%	7.5
>15% up to <=25%	12.5
>25% up to <=40%	15
>40%	20
Total Improvement Score is sum of score achieved in each CSM	
Total improvement score ≥ cut points determines Minimal, Moderate and Major Improvement	
For JDM using PRINTO or IMACS CSMs	**Improvement Category** / **Cut point on Total Improvement Score**
	Minimal ≥30
	Moderate ≥45
	Major ≥70

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Anti-p155/140 Autoantibodies and Selected Features at Illness Onset Are Associated with a Chronic Course of Illness in the Juvenile Idiopathic Inflammatory Myopathies. G. Esther A. Habers[1], Adam M. Huber[2], Gulnara Mamyrova[3], Ira Targoff[4], Chantal Boonacker[5], Marco van Brussel[1], Frederick W. Miller[6], Lisa G. Rider[6] and Annet van Royen-Kerkhof[7]. [1]Child Development and Exercise Center, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands, [2]IWK Health Centre, Halifax, NS, [3]George Washington University, Washington, DC, [4]Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands, [6]Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD, [7]University Medical Centre Utrecht - Wilhelmina Children's Hospital, Utrecht, Netherlands.

Background/Purpose: Three types of disease courses can be distinguished in patients with juvenile idiopathic inflammatory myopathies (JIIM), namely monocyclic (M), polycyclic (P), and chronic (C). This study explored the association of demographics, clinical onset features and myositis autoantibodies with disease course in a large JIIM cohort.

Methods: In the present study, we included 365 patients with JIIM (295 dermato-, 28 poly-, and 42 overlap myositis) which were enrolled into IRB-approved studies in the US and Canada and had a disease duration >2 years from diagnosis. Blood samples and physician questionnaires with demographics and clinical onset features were obtained. Myositis autoantibodies were determined by immunoprecipitation and blotting methods. Follow-up was performed through medical record review. The disease course classification was: M - no active disease and off medication within 2 years of diagnosis (n=88); P - disease recurrence after definite remission (n=86); and C - persistent disease or continuation of medication for >2 years (n=191). Parameters with $p<0.10$ in univariate analysis were analyzed by multinomial logistic regression.

Results: Factors significant only in univariate analysis were cuticular overgrowth (M < P and C), V- and/or shawl-sign rash (M and P < C), contractures (P < C and M), photosensitivity (M < C), dyspnea at rest (P < C), palpitations and/or syncope (M and C < P), geoclimactic zone, and anti-Ro autoantibodies (M < C). Abnormal aldolase was more frequent in P compared to M and C, but not included in multivariable analysis due to missing values. Two different multinomial logistic regression analyses with non-overlapping parameters were performed (see Table 1 for results). Myositis -specific and -associated autoantibodies were more frequent in P and C than in M, with the anti-p155/140 autoantibody as the most significant ($p<0.0001$). Documented infections within 6 months prior to illness onset were also more frequent in the P and C compared to M. P had less early illness signs and symptoms (=lower clinical symptom score) compared to M and C. A more severe illness onset was present in C compared to M and P. Compared to M, mucous membrane involvement was less frequent in C and distal weakness was less frequent in P and C. Weight loss was more frequent in C compared to P.

Conclusion: Myositis -specific and -associated autoantibodies (especially the anti-p155/140 autoantibodies) and selected features at illness onset were associated with a chronic course of illness in patients with JIIM. These findings suggest that certain predictors of poor prognoses can be identified that might influence treatment options at illness onset.

Table 1. Results of 2 separate multinomial logistic regression analyses.

		OR (95% CI)		
Significant parameters	**p**	**P vs. M**	**C vs. M**	**C vs. P**
Significant parameters from analysis 1				
Any myositis specific autoantibodies	<0.0001	2.7 (1.3 to 5.7) #	4.0 (2.1 to 7.6) #	NS
Any myositis associated autoantibodies	<0.01	3.8 (1.2 to 11.9) †	4.3 (1.6 to 12.0) #	NS
Any infection 6 months prior to illness onset	<0.01	5.1 (2.0 to 12.7) #	2.4 (1.0 to 5.8) †	0.5 (0.2 to 1.0) †
Clinical symptom score $	0.01	0.02 (0.0–0.8) †	NS	81 (4 to 1686) #
Significant parameters from analysis 2				
Anti-p155/140 autoantibodies	<0.0001	3.5 (1.2 to 10.1) †	7.1 (2.7 to 19.0) #	2.1 (0.9–4.5) *
Severity of illness at onset	<0.01	NS	3.3 (1.5 to 7.3) #	2.2 (1.0 to 4.9) *
Mucous membrane involvement	0.02	NS	0.3 (0.1 to 0.7) #	NS
Distal weakness	0.04	0.4 (0.2 to 0.8) †	0.5 (0.2 to 1.0) *	NS
Weight loss	0.03	NS	NS	3.1 (1.3 to 7.6) †

Data was adjusted for date of diagnosis and for the significant parameters in the analysis.
*p≤0.10.
†p≤0.05.
#p≤0.01.
$ Odds ratio: per 0.01 increase in clinical symptom score.

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Illness Onset Features and Misdiagnosis in Juvenile Idiopathic Inflammatory Myopathies (JIIM) Differ Among Clinical and Autoantibody (Ab) Subgroups. Gulnara Mamyrova[1], Lan Wu[2], Adam Huber[3], Ira N. Targoff[4], Frederick W. Miller[2] and Lisa G. Rider[2]. [1]George Washington University, Washington, DC, [2]Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD, [3]IWK Health Centre, Halifax, NS, [4]Veterans Affairs Medical Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Background/Purpose: To evaluate features of JIIM clinical and Ab subgroups at illness onset.

Methods: Physician-completed questionnaires illness onset features were reviewed in 465 JIIM pts (381 juvenile dermatomyositis [JDM], 33 polymyositis, [JPM], and 51 JIIM associated with other autoimmune diseases [JCTM]) meeting probable or definite Bohan and Peter criteria. Myositis Abs were tested by standard immunopreciptation and blotting methods. Univariate analysis was performed using GraphPad Prism 5.0.

Results: The first weakness was proximal in all clinical and Ab subgroups (86–90%). Gottron's papules were most often the first rash in JDM and JCTM (48% and 47%), followed by heliotrope (45% and 29%), and malar rash (30% and 14%). Gottron's papules were also the first rash in 57% of pts with anti-p155/140, 50% of anti-Mi2, 40% of anti-MJ and 32% of pts with anti-ARS Abs ($P < 0.04$). Heliotrope was most often the first rash in pts with anti-MJ (52%) and anti-ARS (47%). Both Gottron's papules and heliotrope were present at diagnosis in 72% of JDM and 58% of JCTM pts. Gottron's papules or heliotrope alone were seen in 18% and 9% of JDM pts at diagnosis, yet 1.7% of JDM patients did not have either rash at diagnosis. 81% of pts with anti-p155/140 Abs had both Gottron's and heliotrope at diagnosis. Rash before weakness was seen in 54% of JDM and 74% of JCTM pts. Weakness before rash was seen in 23% of JDM and 14% of JCTM pts; 23% of JDM and 12% of JCTM pts developed rash and weakness simultaneously. Rash before weakness was observed in 73% of pts with anti-p155/140, 67% of anti-Mi2, 39% of anti-MJ, and 39% of anti-ARS Ab pts ($P <0.04$). Weakness before rash was observed in 33% of anti-ARS, 31% of anti-MJ, 17% of anti-Mi2 and 12% of anti-p155/140 pts ($P < 0.02$). All JIIM pts had a median delay to diagnosis of 4.1 mo and JCTM pts had delay of 7.1 mo ($P < 0.03$); pts with anti-p155/140 had a median delay of 4.8 mo, anti-ARS 6.6 mo, and anti-SRP Abs 2.0 mo between first symptom and diagnosis. The median time between rash and diagnosis was 2.5 mo in JDM, 6.1 mo in JCTM, 4.0 mo in anti-p155/140 and 1 mo in anti-ARS Ab groups ($P < 0.007$). Twenty-three percent of JIIM pts had one and 5.7% had ≥ 2 misdiagnoses. Common misdiagnoses included infections (9.6%), other autoimmune diseases (4.6%), musculoskeletal (2.4%) and dermatologic conditions (17.6%), neurologic diseases (1.5%), and psychologic disorders (0.7%). JPM and pts with anti-SRP Abs were often misdiagnosed with hepatitis (15.2–28.6%) and neurologic conditions (9.1%) including Guillain-Barre (3–14%). Pts with JDM and JCTM, including those with p155/140 and MJ Abs, were often misdiagnosed with other skin conditions (11–21%), including eczema (11–21%).

Conclusion: JIIM clinical and Ab groups vary in their type of rash and weakness and misdiagnosis at illness onset. Most present with rash before weakness, and with Gottron's papules first. Better recognition of these varied presentations of illness should enhance recognition of JIIM phenotypes and help decrease delay in diagnosis and therapy.

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Safety of Rituximab in Treating Pediatric Rheumatologic Disease. Arunima Agarwal[1], Anusha Ramanathan[2] and Rhina Castillo[3]. [1]Children's Hospital of Los Angeles, Los Angeles, CA, [2]Children's Hospital Los Angeles, Los Angeles, CA, [3]Childrens Hospital Los Angeles, Los Angeles, CA.

Background/Purpose: Rituximab is a chimeric human/murine monoclonal antibody directed against the B cell specific antigen CD20. There is growing evidence that suggests Rituximab may also influence T cell immu-

nity and thus predispose patients to opportunistic infections by this mechanism as well. Rituximab use, both as monotherapy and in combination with other immunosuppressants, is increasing in the pediatric population. Data regarding infection associated with Rituximab is limited and inconsistent. The most concerning side effect is the development of progressive multifocal leukoencephalopathy (PML), a fatal condition which has been reported rarely with Rituximab use. This study seeks to report adverse events associated with Rituximab use in the pediatric rheumatologic population.

Methods: A retrospective chart review of 20 pediatric patients with rheumatologic disease followed at Children's Hospital Los Angeles between January 2007 and April 2014 was conducted. All patients received Rituximab and incidence of infection was assessed for a follow-up period of 6 months to 7 years following first Rituximab course.

Results: The majority of patients were female (55%) and Hispanic (70%), with 3 African American, 2 Caucasian and 1 Asian patient. The most common diagnoses were lupus (35%), dermatomyositis (30%), or overlap syndrome (20%). Sixty percent of patients received only one course of Rituximab and most (65%) received high dose glucocorticoids concurrently with their first course of Rituximab. Other immunosuppressants included methotrexate (55%), cyclophosphamide (CYC) (15%, with an average cumulative dose of 6g/m2), and anti-TNF therapy (15%). One patient each was on concurrent therapy with cyclosporine or azathioprine. There were 15 total infections in 9 patients during a mean follow up of 16.2 months (range 6 to 45 months) occurring on average 4.5 months (range 1 to 19 months) following Rituximab. Two infections (bacterial pneumonia and cellulitis) requiring hospitalization occurred in one patient who had received CYC as well. The remainder of infections were minor, 11 required outpatient antibiotics and 2 self-resolved. The majority of infections (87%) occurred in patients with lupus or an overlap syndrome. Only 1 patient developed prolonged hypogammaglobulinemia requiring supplemental IVIG. There were no cases of infusion related adverse events or PML in this cohort.

Conclusion: Overall the occurrence of significant adverse events following Rituximab was low in this pediatric cohort. Serious infections may be increased in those receiving combination therapy with CYC. Larger studies are needed to determine the attributable risk for infection from Rituximab alone versus that associated with underlying diagnosis or combination therapy. However, our results suggest that Rituximab use is safe and well-tolerated in a variety of pediatric rheumatologic conditions.

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Analysis of Risk Factors for Thrombosis in Pediatric Patients with Systemic Lupus Erythematosus. Kyla D. Driest[1], Mollie S. Sturm[2], Sarah H. O'Brien[2], Charles H. Spencer[3] and Stacy P. Ardoin[4]. [1]OSU Pediatrics, Nationwide Children's Hospital, Columbus, OH, [2]Nationwide Children's Hospital, Columbus, OH, [3]Nationwide Childrens Hospital, Columbus, OH, [4]Ohio State University College of Medicine, Columbus, OH.

Background/Purpose: Patients with systemic lupus erythematosus (SLE) have a higher thrombotic risk compared to the general population, and arterial and venous thromboses impart substantial morbidity and mortality. Few studies have focused on thrombotic risk within the pediatric SLE (pSLE) population. We sought to better characterize the risk factors for thrombosis in patients with pSLE utilizing the Childhood Arthritis & Rheumatology Research Alliance (CARRA) registry.

Methods: The CARRA registry contains 979 patients with pSLE. Pediatric SLE patients with a history of thrombosis were compared to those with no history of thrombosis. A history for thrombosis was defined as any patient within the SLE registry who had a history of arterial or venous thrombotic event as reported by the treating pediatric rheumatologist. For continuous variables, the Wilcoxon Mann-Whitney test was used to compare groups. In the case of categorical variables, univariate logistical regression was used to calculate odds ratios (OR). Patients with missing outcome data were excluded from analysis. Statistical Analysis System software 9.3 (SAS Institute Inc., Cary, NC, USA) was used to perform statistical analysis.

Results: Of the 979 patients in the registry, 974 had data recorded for thrombosis and were included in the analysis. The majority of these patients were female (82.4%), non-Hispanic (72.8%) and white (44.7%). Of the 974 patients, 24 (2.5%) had history of arterial thrombosis and 35 (3.6%) of venous thrombosis. Odds ratios for thrombosis were calculated for gender, ethnicity, BMI, race, Raynaud's phenomenon, vasculitis, avascular necrosis (AVN), renal disease, positive antiphospholipid antibody (APLA), thrombocytopenia, and hydroxychloroquine use. Utilizing a p value of < 0.05 as significant, the odds ratios of having a thrombotic event were significantly higher in patients with vasculitis [3.11, 95% CI: (1.60, 6.01)], history of AVN [3.08, 95% CI: (1.24, 7.67)], or APLA [3.03, 95% CI: (1.45, 6.36)]. Odds ratios for other variables were not statistically significant.

Conclusion: Our study of 974 patients with pSLE including 59 with a history of thrombotic event suggests that pSLE patients with a history of vasculitis, positive APLA, and AVN are at a greater risk for thrombotic events than those without. Odds ratios for gender, race, ethnicity, hydroxychloroquine use, renal disease, history of Raynaud's phenomenon, and thrombocytopenia were not found to be statistically significant within this subset of patients.

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A Pilot Study to Evaluate the Feasibility of Conducting Juvenile Localized Scleroderma Comparative Effectiveness Treatment Studies. Suzanne C. Li[1], Kathryn S. Torok[2], Mara L Becker[3], Fatma Dedeoglu[4], Polly J. Ferguson[5], Robert C. Fuhlbrigge[6], Gloria C. Higgins[7], Sandy D. Hong[8], Maria F. Ibarra[3], Ronald M. Laxer[9], Thomas G. Mason II[10], Elena Pope[11], Marilynn G. Punaro[12], C. Egla Rabinovich[13], Katie G. Stewart[12] and Brian Feldman[11]. [1]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [2]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [3]Children's Mercy Hospital, Kansas City, MO, [4]Boston Children's Hospital, Boston, MA, [5]University of Iowa Carver College of Medicine, Iowa City, IA, [6]Brigham and Women's Hospital, Boston, MA, [7]Nationwide Childrens Hosp, Columbus, OH, [8]U of Iowa Children's Hosp, Iowa City, IA, [9]The Hospital for Sick Children, University of Toronto, Toronto, ON, [10]Mayo Clinic Rochester, Rochester, MN, [11]The Hospital for Sick Children, Toronto, ON, [12]Texas Scottish Rite Hospital, Dallas, TX, [13]Duke Univ Med Ctr, Durham, NC.

Background/Purpose: Juvenile localized scleroderma (jLS) often causes severe morbidity in the developing child, including growth defects and disfigurement. Optimal therapy is not known. The LS Children's Arthritis and Rheumatology Research Alliance (CARRA) subgroup has been working towards improving long-term outcome for these patients. Towards this end, we have developed standardized treatment regimens based upon best available evidence and consensus methodology (consensus treatment plans, CTPs), and clinical tools to use in comparative effectiveness treatment studies. We are currently conducting a pilot study to evaluate the feasibility of conducting jLS comparative effectiveness treatment studies. Additional analyses will include evaluating performance characteristics of developed tools.

Methods: Fifteen physicians from 10 CARRA centers have been conducting a prospective observational cohort study of jLS subjects initiating systemic immunosuppressive treatment. Inclusion criteria include diagnosis of jLS by pediatric rheumatologist or dermatologist, and presence of active disease according to delineated activity criteria generated by the group. Exclusion criteria include treatment with methotrexate (MTX) within prior 3 months or corticosteroids (CS) within prior 2 weeks. Subjects were treated with one of three MTX-based CTPs (MTX alone, MTX with intravenous CS (IV CS), or MTX with oral CS), determined by treating physician, and evaluated at 6 visits over 1 year. At the start of the study, a workshop meeting was held to standardize evaluation.

Results: The target enrollment (50 subjects) was reached. All sites enrolled subjects, with enrollment taking approximately 23 months to complete following study initiation at the first site. Subjects were enrolled in all 3 CTPs, with half enrolled in MTX + IV CS CTP. Over 40% of subjects deviated from their initial treatment regimen, with persistent activity a frequent reason. Over 80% of subjects agreed to participate in the optional sample collection and banking sub study.

Study Subject Features	
Gender	35 Females (73%)
Age at study entry, median (range)	12.7 yr (3 – 21 yr)
Race	43 White
	1 Black
	2 Asian
	2 unknown
Ethnicity	39 non-Hispanic: 9 Hispanics
Treatment Regimen	12 (25.5%)
MTX alone	24 (51%)
MTX+intravenous CS	11 (23%)
MTX + oral CS	

Number who deviated from starting CTP among subjects who completed at least 2 study visits	15/34 (44%)
Agreed to participate in sample collection	38/46 (82%)
Completed 1 year of study visits	13 (26%)
Dropped out from study	2 (4%)

Conclusion: This is the first study to explore the feasibility of conducting comparative effectiveness treatment studies in jLS. We achieved our target enrollment of 50 subjects, with subjects enrolled in all 3 standardized treatment regimens. Biological samples have been collected from the majority of subjects, which will enable future translational studies. This study will enable us to evaluate and refine clinical tools needed for treatment studies based upon study data, and identify issues related to conducting jLS treatment studies. Further analyses of these data once completed will also include clinical effectiveness and tolerability of the 3 different treatment regimens in LS subjects.

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Cardiopulmonary Involvement in Juvenile Systemic Sclerosis: Development of Recommendations for Screening and Investigation. Ivan Foeldvari[1], Clare Pain[2], Tamás Constantin[3], Eileen Baildam[4], Christian Beyer[5], Michael Blakley[6], Dana Nemkova[7] and Clarissa A Pilkington[8]. [1]Department of Pediatric Rheumatology, Hamburger Zentrum für Kinder und Jugendrheumatologie, Hamburg, Germany, [2]University Children′s Hospital, Liverpool, United Kingdom, [3]University Childrens Hospital, Budapest, Hungary, [4]Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [5]Pediatric Cardiology, Hamburg, Germany, [6]Indiana University School of Medicine and Riley Hospital for Children at IU Health, Indianapolis, IN, [7]Pedaitric Rheumatology, Prague, Czech Republic, [8]Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom.

Background/Purpose: There are currently no agreed recommendations on how to investigate children for cardiopulmonary involvement in Juvenile Systemic Sclerosis (JSSc). The aim of screening is to detect disease early to facilitate early aggressive therapy and improve outcomes. Cardiopulmonary involvement is the leading cause of death in JSSc and cardiopulmonary involvement at diagnosis incurs a worse outcome (1). Most deaths occur early in the disease course (1, 2).

Objectives: To develop recommendations for investigation of cardiopulmonary in JSSc, based on paediatric evidence and where this was lacking, consensus expert agreement.

Methods: Members of the PRES Scleroderma Working Group were invited to participate; additionally a paediatric cardiologist were invited. A nominal group technique was used. 75% consensus was defined as agreement.

Results: Table 1 shows the recommendations for screening for cardiopulmonary and GI involvement at baseline and at defined time points from diagnosis. Other recommendations agreed by the group which are relevant at any stage in the disease course are as follows:

1. If there are any concerns or signs of pulmonary hypertension then right heart catheterisation should be undertaken.

2. Any child with exertional chest pain or abnormality on 24hr ECG should undergo exercise ECG (if old enough to comply).

3. Those with worsening PFTS or clinical deterioration should have HRCT thorax repeated sooner (particularly, FVC <70% or DLCO <80% or drop in values by 20% of baseline).

Recommendations are based on low grade evidence and in the most part from expert consensus opinion with extrapolation from adult studies

Table 1. Recommendations for screening for cardiopulmonary and GI involvement in JSSc at baseline and follow-up (75% consensus defined as agreement)

Cardiopulmonary	**Baseline**	
	All patients should undergo:	
	- BP	
	- 12 lead ECG	
	- 24 hour ECG	
	- ECHO with Doppler	
	- Cardiac MRI with gadolinium	
	- HRCT thorax	
	- PFT with DLCO	
	- 6MWT	
	Follow-up screening (for first 5 years from diagnosis)*	
	6 monthly	12 lead ECG
		ECHO with doppler
		6MWT
		PFT with DLCO
	Annual	24hr ECG
	At 3 years	Repeat HRCT

Conclusion: JSSc has a significant mortality particularly early on in the disease course. The objective of an aggressive screening program is to identify cardiopulmonary and GI involvement at a stage which may be amenable to treatment. The recommendations developed by this group aim to standardise care and improve outcomes in this rare disease.

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Gastrointestinal Involvement in Juvenile Systemic Sclerosis: Development of Recommendations for Screening and Investigation. Ivan Foeldvari[1], Clare Pain[2], Tamás Constantin[3], Eileen Baildam[4], Henning Lenhartz[5], Michael Blakley[6], Dana Nemkova[7] and Clarissa A Pilkington[8]. [1]Department of Pediatric Rheumatology, Hamburger Zentrum für Kinder und Jugendrheumatologie, Hamburg, Germany, [2]University Children′s Hospital, Liverpool, United Kingdom, [3]University Childrens Hospital, Budapest, Hungary, [4]Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [5]Wilhelmstift, Hamburg, Germany, [6]Indiana University School of Medicine and Riley Hospital for Children at IU Health, Indianapolis, IN, [7]Pedaitric Rheumatology, Prague, Czech Republic, [8]Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom.

Background/Purpose: There are currently no agreed recommendations on how to investigate children for gastrointestinal (GI) involvement in Juvenile Systemic Sclerosis (JSSc). The aim of screening is to detect disease early to facilitate early aggressive therapy and improve outcomes. GI involvement at diagnosis incurs a worse outcome (1). Most deaths occur early in the disease course (1, 2).

Objectives: To develop recommendations for investigation of GI involvement in JSSc, based on paediatric evidence and where this was lacking, consensus expert agreement.

Methods: Members of the PRES Scleroderma Working Group were invited to participate; additionally a paediatric cardiologist and paediatric gastroenterologist were invited. A nominal group technique was used. 75% consensus was defined as agreement.

Results: Table 1 shows the recommendations for screening for GI involvement at baseline and at defined time points from diagnosis. Other recommendations agreed by the group which are relevant at any stage in the disease course are as follows:

1. Oesophageal dilatation should be assessed on any HRCT thorax performed.

2. If any concerns regarding bleeding such as chronic anaemia, consider upper GI endoscopy.

3. Any patient with nausea, vomiting, abdominal pain, bloating, diarrhoea or poor weight gain should undergo a hydrogen breath test for bacterial overgrowth.

4. Consider dietetic or gastroenterology review to assess nutritional intake and status.

5. Any patient with significant persistent GI symptoms including poor weight gain should be referred to a paediatric gastroenterologist.

Table 1. Recommendations for screening for GI involvement in JSSc at baseline and follow-up (75% consensus defined as agreement)

Gastrointestinal	**Baseline**	
	All patients should have a barium swallow to assess for dysmotility or stricture and 24 hour pH monitoring for GORD and progress to upper GI endoscopy if any abnormality detected	
	Follow-up	
	Every 3 years or sooner if worsening lung involvement and/or worsening GI symptoms	Upper GI endoscopy Barium swallow 24 hours pH monitoring

*screening guidelines are based on asymptomatic patients. However, children may need more frequent monitoring depending on clinical status and abnormalities detected on previous.

Conclusion: JSSc has a significant mortality particularly early on in the disease course. The objective of an aggressive screening program is to identify GI involvement at a stage which may be amenable to treatment. The recommendations developed by this group aim to standardise care and improve outcomes in this rare disease.

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Predictors of Disease Relapse in Juvenile Localized Scleroderma. Kathryn S. Torok[1], Katherine Kurzinski[2] and Christina Kelsey[3]. [1]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [3]University of Pittsburgh/UPMC, Pittsburgh, PA.

Background/Purpose: Localized scleroderma (LS) is an autoimmune disease characterized by inflammation of the skin and underlying tissue leading tissue damage including atrophy, dyspigmentation, and fibrosis. More recent literature supports childhood-onset LS as a chronic relapsing condition which may cause significant physical and psychological disability into adulthood. Often, initial control of the disease is obtained using systemic therapy regimens including methotrexate (MTX) combined with a corticosteroid (CS). For unknown reasons, patients may exhibit a relapse of LS activity following a period of disease remission. This study was designed to evaluate the clinical characteristics of patients exhibiting LS flares after an initial disease response (inactive disease) to a standardized MTX and CS regimen with the goal of identifying predictors of LS activity relapse.

Methods: Pediatric-onset LS patients at a single scleroderma center with at least 2 years of follow-up and three or more clinical visits were included in the analysis. Clinical data, including patient demographics, laboratory parameters, and treatment regimens were evaluated. Flare of LS was defined as a relapse of disease activity from inactive disease, as determined by the modified Localized Scleroderma Severity Index (mLoSSI) and the Physician Global Assessment of Disease Activity. Chi-square and Fisher's Exact test were used to compare rates of categorical variables, and independent sample t-tests were used to compare continuous variables between groups ($\alpha < 0.05$).

Results: Seventy-seven patients were followed for greater than two years and 35 patients (46%) were found to experience LS flare after an initial response to MTX and CS. Demographic and laboratory data are summarized in Table 1. Patients that flared were significantly older at age of onset and were more likely to be ANA positive. Unexpectedly, flare patients were less likely to have an extracutaneous manifestation (ECM).

Table 1. Patient characteristics

	Flare (n=35)	No Flare (n=42)	p-value
Gender, n (%)			
Female	26 (74)	28 (62)	0.23
LS Subtype, n (%)			
Circumscribed Superficial	10 (29)	11 (26)	1
Circumscribed Deep	4 (11)	4 (10)	1
Generalized Morphea	6 (17)	4 (10)	0.5
Linear Trunk/Limb	20 (57)	22 (52)	0.81
Linear Face	3 (9)	9 (21)	0.21
Mixed Morphea	6 (17)	6 (14)	0.76
Pansclerotic Morphea	—	2 (4.5)	0.76
Eosinophilic Fasciitis	—	1 (2)	1
Age Onset (years), mean (SD)	**10.0 (3.9)**	**6.7 (3.7)**	**<0.001**
Time Onset to Diagnosis (mos), mean (SD)	13.8 (18.5)	22.4 (31.4)	0.16
Follow-up Duration (years), mean (SD)	4.3 (2.0)	4.9 (2.8)	0.34
Laboratory Evaluation, n (%)*			
ANA Positive	**18/30 (60)**	**8/33 (24)**	**<0.01**
ssDNA Positive	13/32 (41)	18/39 (46)	0.81
AHA Positive	9/31 (29)	17/39 (44)	0.23
CPK Elevated	10/34 (29)	8/37 (22)	0.59
Aldolase Elevated	13/32 (41)	9/34 (27)	0.21
Extracutaneous Manifestation (ECM), n (%)			
At least 1 ECM	**10 (28)**	**23 (55)**	**0.02**
Joint Contractures	8 (23)	15 (35)	0.22
Arthritis	2 (5.7)	1 (2.4)	. . .
Dental	. . .	4 (9.5)	. . .
Uveitis	. . .	1 (2.4)	. . .
Limb length discrepancy	1 (2.9)	4 (9.5)	0.37
Limb circumference difference	6 (17)	8 (19)	0.83

*Laboratory parameters not obtained for all patients.

Conclusion: Our assessment of a cohort of LS patients has shown older age at onset of disease and ANA positivity to be potential risk factors for reactivation of disease. ANA positivity may reflect a higher propensity for immune system reactivity after disease remission, and older onset might indicate that the immune system is more developed, hindering a sustained the effect of treatment. Surprisingly, the presence of joint contractures and other accepted measures of LS severity do not seem to represent an inherent risk of flare after disease remission. A possible explanation may be closer patient follow-up and adherence to medication regimen given physician's judgment of more severe disease when an ECM is present. We suggest that these risk factors, ANA positivity and older age of onset, serve as indicators for more extensive treatment or follow-up to avoid disease flare in at-risk LS patients.

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Single Hub and Access Point for Pediatric Rheumatology in Europe (SHARE): Evidence Based Recommendations for Diagnosis and Treatment of Juvenile Localized Scleroderma and Juvenile Systemic Sclerosis. Bas Vastert[1], Roberta Culpo[2], Jordi Anton[3], Tadej Avcin[4], Eileen Baildam[5], Christina Boros[6], Tamás Constantin[7], Jeff Chaitow[8], Pavla Dolezalova[9], Ozgur Kasapcopur[10], Sheila Oliveira[11], Clarissa Pilkington[12], Annet van Royen-Kerkhof[13], Ricardo A. G. Russo[14], Claudia Saad-Magalhaes[15], Natasa Toplak[16], Angelo Ravelli[17], Nico Wulffraat[18], Ivan Foeldvari[19] and Francesco Zulian[2]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]University of Padua, Padua, Italy, [3]Pediatric Rheumatology Unit. Hospital Sant Joan de Déu. Universitat de Barcelona, Barcelona, Spain, [4]University Children′s Hospital, Ljubjana, Slovenia, [5]Alder Hey Children's Foundation NHS Trust, Liverpool, United Kingdom, [6]University of Adelaide, Adelaide, Australia, [7]University Childrens Hospital, Budapest, Hungary, [8]The Children's Hospital Westmead, Sydney, Australia, [9]Charles University, Prague, Czech Republic, [10]University Cerrahpasa Faculty of Medicine, Istanbul, Turkey, [11]Universidade F Rio De Janeiro, Rio De Janeiro, Brazil, [12]Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [13]University Medical Centre Utrecht - Wilhelmina Children's Hospital, Utrecht, Netherlands, [14]Hospital de Pediatria Garrahan, Buenos Aires, Argentina, [15]Faculdade de Medicina de Botucatu, Botucatu, Brazil, [16]University Medical Center, Ljubliana, Slovenia, [17]Istituto Giannina Gaslini and University of Genova, Genova, Italy, [18]Wilhelmina Children's Hospital/ UMC Utrecht, Utrecht, Netherlands, [19]Department of Pediatric Rheumatology, Hamburger Zentrum für Kinder und Jugendrheumatologie, Hamburg, Germany.

Background/Purpose: Juvenile Localized Scleroderma (JLS) and Juvenile Systemic Sclerosis (JSSc) form a group of rare pediatric diseases that can lead to significant morbidity. Evidence-based guidelines are sparse and management is mostly based on physician's experience. In 2012, a European initiative called SHARE (Single Hub and Access point for pediatric Rheumatology in Europe) was launched to optimize and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases. Purpose: to provide evidence based recommendations for diagnosis and treatment of Juvenile Scleroderma.

Methods: Evidence based recommendations were developed using the European League Against Rheumatism (EULAR) standard operating procedure. An expert committee was instituted, consisting of pediatric rheumatologists and experts in Juvenile Scleroderma. The expert committee defined search terms for the systematic literature review. Two independent experts scored articles for validity and level of evidence. Recommendations derived from the literature were evaluated by an online survey. Those with less than 80% agreement during the online survey were reformulated. Subsequently, all

recommendations were discussed at a consensus meeting using the nominal group technique. Recommendations were accepted if more than 80% agreement was reached.

Results: The literature search yielded 1550 articles for JLS and 8562 for JSSc, of which 52 and 37, respectively (25 for diagnosis and 27 for treatment of JLS, 21 for diagnosis and 16 for treatment of JSSc) were considered relevant and therefore scored for validity and level of evidence. 42 articles (15 for diagnosis and 14 for treatment of JLS, 6 for diagnosis and 7 for treatment of JSSc) were scored valid and used in the formulation of the recommendations. Eleven recommendations for diagnosis and 7 for treatment were suggested in the online survey on JLS. Ten recommendations for diagnosis and 6 for treatment were accepted with more than 80% agreement after the consensus meeting. Six recommendations for diagnosis and 5 for treatment were suggested in the online survey on JSSc. Six recommendations for diagnosis and 4 for treatment were accepted with more than 80% agreement after the consensus meeting. Topics covered for diagnosis and for treatment are showed in *Table 1*.

JLS

DIAGNOSIS		TREATMENT	
Disease activity assessment and response to therapy	*Clinical scores*	Topical treatment	*Medium-dose UVA1 phototherapy*
	Thermography		*Imiquimod*
	Ultrasounds	Systemic treatment	*Corticosteroids*
Disease severity and damage assessment	*Clinical scores*		*Metotrexate*
Extra-cutaneous involvement (articular, musculoskeletal, neurological, ophtalmological, dental, maxillo-facial)	*Clinical assessment*		*Mychophenolate mofetil*
	Musculoskeletal MRI		
	Brain MRI		

JSSc

DIAGNOSIS		TREATMENT	
Disease severity and damage assessment	*Clinical scores*	Skin and lung involvement	*Mychophenolate mofetil*
Skin involvement	*Clinical scores*	Vascular involvement	*Bosentan*
Lung involvement	*Pulmonary function tests*	Progressive and refractory disease	*Autologous stem-cell transplantation*
	Serological markers		
Raynaud's phenomenon	*Capillaroscopy*	Ineffective treatments	*D-penicillamine*

Conclusion: The SHARE initiative provides recommendations for diagnosis and treatment for Juvenile Scleroderma and thereby facilitates improvement and uniformity of care throughout Europe.

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Transition of Care and Long-Term Outcomes of Juvenile Systemic Sclerosis during Adulthood: Results from a French Single-Center Case-Control Study. Francois-Xavier Mauvais[1], Brigitte Bader-Meunier[2], Alice Berezne[3], Guillaume Bussone[4], Christine Bodemer[5], Loïc Guillevin[6], Pierre Quartier[2] and Luc Mouthon[6]. [1]INSERM U1151 / CNRS 8253, PARIS, France, [2]IMAGINE Institute, Hôpital Necker-Enfants Malades, Assistance Publique Hôpitaux de Paris, Université Paris-Descartes, Paris, France, [3]Paris Descartes University, Internal Medicine department, Cochin Hospital, Paris, France, [4]Hopital Cochin, Paris, France, [5]Hôpital Necker-Enfants Malades, Paris, France, [6]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France.

Background/Purpose: To describe the transition of care from Pediatric to an adult Internal Medicine department and long-term outcomes of patients with juvenile-onset SSc.

Methods: Twenty patients with SSc diagnosed before the age of 17 and previously followed in Pediatric departments were included. The control group comprised 60 patients randomly selected from all patients with a SSc diagnosed after 18 years old, matching by sex and disease duration.

Results: In the juvenile-onset group, 16/20 (80%) patients were female and 11/20 (55%) presented a diffuse SSc. Mean age for diagnosis was 11.9 years (5.1–15.9). One patient had anti-centromere, 4/20 (20%) anti-Scl70 and 1/20 (5%) anti-U1RNP autoantibodies.

While juvenile-onset patients had a significantly higher incidence of calcinosis (9/20 (45%) vs 12/60 (20%); $p=0.04$), they had a lower incidence of interstitial lung disease (4/20 (20%) vs 32/60 (53.3%); $p=0.01$) compared to the adult-onset group.

At the time of last follow-up, mean disease duration was 14.2 ± 13.1 years. Survival rate was lower among the juvenile-onset group but this difference was not significant (17/20 (85%) vs 57/60 (95%); $p=0.16$). Bowel involvement had a significantly higher incidence (11/20 (55%) vs 6/60 (10%); $p<0.001$) in the juvenile-onset group as well as calcinosis (13/20 (65%) vs 15/20 (25%); $p<0.02$) compared to the adult-onset group. Juvenile-onset patients had received significantly more steroids $>$ 15mg/d (11/20 (55%) vs 7/60 (11.7%); $p<0.001$) and methotrexate (10/20 (50%) vs 8/60 (13.3%); $p=0.002$). No significant difference could be observed regarding biological parameters between the two groups.

Only one patient in the juvenile-onset group had a major impact on quality of life, with a significant delay in his education and a depressive syndrome. Factors associated with a poor prognosis in juvenile-onset SSc were lung fibrosis and pericarditis.

Conclusion: At the time of transition of care to adult structures, patients with juvenile-onset SSc present with important musculoskeletal damages and lower incidence of lung involvement than patients with adult-onset SSc.

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Decreased CD3-CD16CD56+ Natural Killer Cell Counts Are Associated with Disease Activity in Children with Orbital Myositis. Melissa R. Bussey[1], Gabrielle A. Morgan[2], Maria C. Amoruso[2], Bahram Rahmani[3] and Lauren M. Pachman[4]. [1]Division of Rheumatology, Loyola University Medical Center, Maywood, IL, [2]Stanley Manne Children's Research Institute, affiliated with Ann & Robert H. Lurie Children's Hospital of Chicago, Cure JM Myositis Center, Chicago, IL, [3]Department of Ophthalmology, Northwestern University Feinberg School of Medicine, Chicago, IL, [4]Division of Pediatric Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Orbital myositis (OM), an inflammatory disease affecting the extra-ocular muscles, typically presents in the third decade. It more commonly affects females and is extremely rare in children. Pediatric orbital inflammatory disorders account for 6–17% of the total orbital inflammatory disorders and OM specifically makes up about 8% of pediatric orbital inflammatory disease. Because of the rarity of pediatric OM, many questions remain unanswered and specific laboratory markers of disease activity have not yet been identified, often resulting in a protracted course. The objective of this study is to describe the course of OM in children and to identify potential reliable indicators of disease activity.

Methods: After obtaining IRB approval, a retrospective review was performed of all patients with a diagnosis of OM presenting between 2006 and 2012 to the Cure-JM Program of Excellence of The Ann and Robert H. Lurie Children's Hospital of Chicago. Duration of untreated disease (DUD) was defined as time, in months, from onset of first symptoms to the date of the first medication. Data for muscle enzymes, neopterin, and absolute level of CD3-CD56/16+ natural killer cells (NK) via flow cytometry were determined using standard methods in the Diagnostic Immunology Laboratory. In addition, frozen sera were tested for immunoglobulin G 4 (IgG4) levels.

Results: Of the 4 cases, 2 were female and all were Caucasian; the mean age of onset of the first symptom was 14.4 ± 1.2 years, and the mean DUD was 0.28 ± 0.26 months. One child was seen after diagnosis, treatment, and resolution of disease. At diagnosis/first visit of the 3 active children, muscle enzymes were tested and the means are as follows ($n=3$ except where noted): CPK: 97.3 ± 44.2, aldolase: 8.5 ± 2.8 ($n=2$), ALT: 13 ± 2.8 ($n=2$), AST: 21.3 ± 2.9, LDH: 176 ± 52.4. Their mean WBC was 10.4 ± 1.3 ($n=2$), mean ESR 6 ± 4, mean neopterin: 6.3 ± 0.14 ($n=2$); mean Von Willebrand Factor Antigen: 133 ± 14.1 ($n=2$). The mean for IgG4 was 87.7 ± 66 (normal range=8–89 mg/dl). The mean NK was 96.7 ± 28.7 at diagnosis/first visit of the 3 active subjects (lower limit of normal =138) which increased to normal range 163 ± 57.2 with resolution of active disease. Computed tomography studies with contrast document involvement of left superior oblique, right superior oblique, left medial rectus, left lateral rectus, and right lateral rectus muscles in the 4 children. Only 1 child had multiple orbital muscles involved concomitantly. Treatment was initiated with high dose intermittent pulse methylprednisolone supplemented by daily oral prednisone (0.5 mg/kg) on non-IV day as well as methotrexate ($n=2$) and other steroid-sparing agents. Three of the 4 children returned to normal baseline after treatment completion. The fourth child was followed in another part of the country.

Conclusion: OM does occur in children and disease activity was not associated with creatine kinase, aldolase, neopterin, sedimentation rate, or C reactive protein values, which typically remained within normal range. In contrast, initially decreased absolute NK trended toward normal ranges as the inflammation improved. We speculate that this lymphocyte subset may contribute to the inflammatory myopathy.

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Modulation of Natural IgM-Autoantibodies to Oxidative Stress-Related Neo-Epitopes on Apoptotic Cells in Newborns of Mothers with Anti-Ro Autoimmunity. Caroline Grönwall[1], Robert M. Clancy[1], Lelise Getu[1], Don L. Siegel[2], Joanne Reed[1], Jill P. Buyon[1] and Gregg J. Silverman[1]. [1]New York University School of Medicine, New York, NY, [2]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA.

Background/Purpose: At birth, the human immune system expresses substantial circulating levels of polymeric IgM that include autoantibodies to oxidation-associated epitopes on apoptotic cells. This study addressed whether the neonatal IgM-repertoire may be affected by exposure to anti-Ro/La IgG-autoantibodies of maternal origin, which in some offspring leads to development of neonatal lupus.

Methods: Levels of IgM-specificities were compared in 43 healthy adults, and in umbilical cord blood (CB) from 31 unaffected newborns of non-autoimmune mothers and 103 newborns of mothers from the Research Registry for Neonatal Lupus. All mothers enrolled in the Registry have IgG anti-Ro (Ro60 and/or Ro52). In this cohort, 56 fetuses developed cardiac neonatal lupus, 4 neonates had rash, while 40 were clinically unaffected. Sandwich ELISA used phosphorylcholine (PC16)-BSA, malondialdehyde (MDA)-BSA or Ro60, with anti-IgM detection.

Results: IgM-antibodies to oxidation-associated MDA-determinants were relatively more highly represented in control newborns compared to adults (IgM anti-MDA/total IgM 7.2±3.6 CB vs 1.0±0.6 adults) while the ratio IgM anti-PC/total IgM was lower (2.7±1.7 vs 10.7±5.6, $p<0.0001$). CB levels of IgM anti-MDA directly correlated with IgM binding to apoptotic cells. In neonates exposed to IgG anti-Ro, total IgM and IgM anti-Ro60 were significantly elevated compared to control neonates (41±39 RU/ml vs 27±18, $p=0.008$; 218±203 RU/ml vs 129±115 RU/ml, $p=0.003$, respectively). Similarly, the ratio of IgM anti-Ro60 was higher in these newborns compared to controls (8.6±9.6 vs 5.0±2.8, $p=0.001$). No correlation between IgM and IgG anti-Ro60 or RF IgM in CB could be detected. In contrast, the proportion of IgM anti-MDA was significantly lower in CB from neonates exposed to IgG anti-Ro60 mothers compared to controls (4.8±4.7 vs 7.2±3.6, $p=0.004$). Neither the development of heart block, nor the disease status of the mothers, was associated with differences in neonatal IgM levels.

Conclusion: These findings document the relative dominance in the neonate of specificities of IgM-autoantibodies to oxidation-associated neo-determinants associated with protective properties in other settings. These data suggest that early immune development of the natural IgM-repertoire may become imprinted by maternally transferred anti-Ro60 IgG-autoantibodies.

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Comparison of Clinical and Serological Features of Childhood Sjögren Syndrome Based on the Presence or Absence of Parotitis. Jay Mehta[1], Namrata Singh[2] and Scott Lieberman[3]. [1]Children's Hospital at Montefiore/Albert Einstein College of Medicine, Bronx, NY, [2]University of Iowa, Iowa City, IA, [3]University of Iowa Children's Hospital, Iowa City, IA.

Background/Purpose: Sjögren syndrome is a complex autoimmune disease that affects lacrimal and salivary glands with the potential to cause damage to other organs. Diagnosis of childhood Sjögren syndrome (cSS) is currently based on expert opinion due to the lack of child-specific diagnostic criteria. Children do not typically present with sicca symptoms characteristic of adult Sjögren syndrome. While they most commonly present with recurrent parotitis, some children present with other organ involvement in the absence of parotitis. The goal of this study was to compare clinical and serological profiles of cSS patients presenting with or without parotitis as a first step towards defining cSS diagnostic criteria.

Methods: We reviewed cSS cases from a single center as well as those in the published English literature with individual patient data. We collected available data on sicca symptoms, serologies (ANA, anti-SSA/B, RF), lacrimal and salivary gland function, imaging, and histopathology as well as extraglandular clinical features. For analyses of laboratory, serologic, imaging, pathology, and functional data, cases were excluded if specific data were not explicitly reported.

Results: We reviewed 26 cases of cSS diagnosed and followed at The Children's Hospital of Philadelphia and 196 cases in the literature that contained information on individual children. Parotitis status was clearly indicated for 162 cases which were considered further. Parotitis was a main feature in presentation in 131 (81%) cases. Comparing the cases with parotitis ($n=131$) to those without ($n=31$), there were no differences in sex (78% and 87% female, respectively, $P=0.448$) or positive serologies: 87% and 90% ANA+, respectively ($P=0.768$), 72% and 61% RF+ ($P=0.405$), 86% and 90% SSA+ ($P=0.761$), 69% and 64% SSB+ ($P=0.649$). 53% of children had sicca symptoms regardless of parotitis status ($P=1$). Among extraglandular features, children without parotitis developed more joint symptoms (58% vs. 33%, $P=0.012$), CNS symptoms (32% vs. 7%, $P=0.0003$), Raynaud Phenomenon (16% vs. 5%, $P=0.048$), and renal tubular acidosis (16% vs. 4%, $P=0.032$). Non-significant extraglandular features included fever, rash, lymphadenopathy, fatigue, other renal manifestations, myositis, vaginal dryness, serositis, and transaminitis.

Conclusion: While the majority of childhood Sjögren syndrome (cSS) patients have parotitis, a significant percentage do not. Those who do not differ in their clinical features, with a significantly higher incidence of joint symptoms, RP, renal tubular acidosis, neuromyelitis optica, and all CNS manifestations. A large majority of all cSS patients have positive ANA and/or anti-SSA/B, and the serologic profiles do not significantly differ based on parotitis status. Thus, testing for ANA and anti-SSA/B is warranted in the diagnostic workup of any child suspected of having Sjögren syndrome, especially in patients who do not present with parotitis. Given the selection bias inherent in this approach, development of cSS-specific diagnostic criteria are needed for future prospective studies to better characterize the prognosis and optimal therapies for this potentially devastating disease.

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ACR/ARHP Poster Session B
Pediatrics (ARHP)
Monday, November 17, 2014, 8:30 AM–4:00 PM

1330

The Efficacy of a Multidisciplinary Intervention Strategy for the Treatment of Benign Joint Hypermobility Syndrome (BJHS) in Childhood. a Randomised, Single Centre Parallel Group Trial. Peter Bale[1], Vicky Easton[2], Holly Bacon[2], Emma Jerman[3], Kate Armon[2] and Alex J Macgregor[2]. [1]University of East Anglia, Norwich, United Kingdom, [2]Norfolk and Norwich University Hospital, Norwich, United Kingdom, [3]Occupational Therapist, Norwich, United Kingdom.

Background/Purpose: Joint hypermobility is common in childhood and can be associated with musculoskeletal pain and dysfunction. Current management is delivered by a multidisciplinary team but evidence of efficacy is limited. This clinical trial aimed to determine whether a structured multidisciplinary intervention resulted in improved clinical outcomes compared with standard care.

Methods: A prospective randomised, single centre parallel group trial comparing an 8-week individualised multidisciplinary intervention programme with current standard management (advice and a physiotherapy appointment). Children and young people (CYP) were assessed for pain, function, coordination and strength at baseline, 3 and 12 months.

Results: 119 CYP, aged 5 to 16 years, with symptomatic hypermobility were randomised to receive targeted multidisciplinary intervention (I) ($n=59$) or standard management (S) ($n=60$). Of these, 105 were followed to 12-months. There was a significant improvement in child and parent reported pain, coordination and strength. However, no added benefit could be shown from the intervention (Table 1). The number of CYP showing significant pain reduction (>=40%) was 27 (50.0%) (I) vs 21 (41.1%) (S). Those pain free at 12 months were 29 (56.9%) (I) vs 20 (45.5%) (S). The response was independent of the degree of hypermobility.

Conclusion: This is the first RCT to compare a structured multidisciplinary intervention with standard care in symptomatic childhood hypermobility. The study demonstrates significant improvement among subjects but no additional benefit from targeted intervention. The findings emphasise the benefit of information and physiotherapy, but highlight the difficulty in demonstrating subtle benefit from specific interventions without better tools for case definition and outcomes assessment.

Table 1. The rate of change in primary and secondary outcomes over 12 month follow-up period, this data includes analysis from multilevel modelling

Outcome variable	Baseline score (SD)	Rate of change over 12 months (95% CI)			
		Intervention group		Control group	
Child pain assessment (Wong-Baker Faces pain scale), (0–5, zero is the best) n=103	2.31 (1.55)	−1.42	(−1.78 to −1.06)	−1.31	(−1.75 to −0.85)
Parent observed pain assessment (0–100 VAS, zero is the best) n=105	35.90 (26.46)	−6.09	(12.90 to 0.73)	−6.22	(−13.62 to 1.18)
Child health assessment questionnaire (CHAQ) (0–3, zero is the best) n=104	0.82 (0.63)	+0.02	(−0.12 to 0.16)	−0.03	(−0.13 to 0.64)
Child health 9 dimensional utility (CHU9D) (0–1, zero is the worst) n=104	0.85 (0.11)	+0.02	(−0.01 to 0.04)	+0.002	(−0.02 to 0.03)
Movement assessment battery for children (M-ABC) (0–100, zero is the worst) n =104	34.56 (28.61)	+2.60	(−2.92 to 8.11)	+8.51	(3.17 to 13.86)
Grip Strength (Dynamometer) n= 104	57.29 (28.30)	+4.55	(0.16 to 8.94)	+6.75	(2.85 to 10.66)

Disclosure: P. Bale, None; **V. Easton**, None; **H. Bacon**, None; **E. Jerman**, None; **K. Armon**, None; **A. J. Macgregor**, None.

1331

Factors Associated with Pain in Children with Hypermobility - a Pilot Study. Susan Maillard[1], Clarissa Pilkington[1], Richard Howard[1], Christine Liossi[1] and Suellen Walker[2]. [1]Great Ormond Street Hospital NHS Foundation Trust for Children, London, United Kingdom, [2]Great Ormond Street Hospital NHS Foundation Trust for Children, London, United Kingdom.

Background/Purpose: To explore the relationships between the degree of musculoskeletal pain, pain associated with disability and quality of life and how they are affected by having hypermobile joints.

It is now recognised that the symptoms that are common in young people with hypermobile joints are not necessarily linked to the range of movement presented and that the variation between young people has a very biopsychosocial complexity to it.

Methods: Young people aged between 8–14 were recruited from the paediatric rheumatology based Non-Inflammatory Musculoskeletal Pain Clinic at Great Ormond Street Hospital over a 12 month period. They were assessed using biomechanical measures (muscle strength and degree of hypermobility), sensory processing using Quantitative Sensory Testing and psychological measures of anxiety, depression and pain coping styles using validated questions. Full Ethics approval was granted.

Results: 30 children were recruited (18 female: 12 male); mean age 11.08 with 77% being Caucasian. The mean Beighton score was 6.79/9. All patients reported pain mainly affecting lower limbs with an average score of 49/100 VAS. Degree of hypermobility did not have any impact. Reduced muscle strength was associated with increased pain and reduced quality of life. Other measures were compared to the norms for healthy children. Children with hypermobility appeared to demonstrate increased depression, negative mood, anhedonia and increased anxiety. They demonstrated reduced quality of life specifically with school, emotional well being, physical health and psychosocially. The subjects also had reduced sensitivity to touch including hot and cold.

Conclusion: The pain experienced by children with hypermobile joints is complex and includes biomechanical, sensory, psychological and social factors. This pilot study is planned to be expanded into a multi-centred project depending upon funding.

Disclosure: S. Maillard, None; **C. Pilkington**, None; **R. Howard**, None; **C. Liossi**, None; **S. Walker**, None.

1332

From Social Support to Information Sharing, How Are Persons with Rheumatoid Arthritis Using Disease-Specific Facebook Communities? a Content Analysis. Cheryl Crow and Kristin Jones. Samuel Merritt University, Oakland, CA.

Background/Purpose: High perceived social support is associated with better quality of life and lower rates of depression for persons with rheumatoid arthritis (Minnock, et al 2003 and Zyrianova, et al, 2006), yet pain, fatigue and the invisible nature of the disease can lead to social isolation. Disease-specific Facebook communities have become thriving, accessible platforms for information sharing and social support. However, little is understood about the content of patient engagement on this medium.

Methods: The 4 largest patient-driven Facebook community pages devoted to rheumatoid arthritis were identified. Text from 10 sequential "wall posts" from May-June 2013 by members each community and ensuing discussion posts were thematically coded and aggregated into a database. Multiple codes were allowed for each post. Members self-identified as persons with rheumatoid arthritis, loved ones, caregivers, or did not specify. Providing advice, sharing a personal story and providing support were predominant themes. Content coded as "providing advice" and "personal story" was further categorized based on areas of occupation according to the Occupational Therapy Practice Framework. Patient-provider interactions were coded under "Health Management and Maintenance" and then further sub-categorized to be of relevance to rheumatology professionals.

Results: 1066 posts were thematically coded. In 73% of posts, information was provided (44% of which involved a personal story, 29% of which involved advice). In 20% of posts, support was provided. Instrumental activities of daily living (such as home, medical and financial management) were the most frequently discussed topics. Health management was the most frequently discussed instrumental activity of daily living (which included pain management, medication management, nutrition and fitness, and patient-provider interactions).

Conclusion: Participants primarily use rheumatoid arthritis-specific Facebook pages to share stories, advice and support about health management and maintenance. While this medium allows for many potential positive effects such as increased social support and the sharing of effective daily living strategies, potential drawbacks include frequent medical advice given by individuals with unknown qualifications. It would behoove healthcare professionals to understand and address the role of this medium in social participation for their clients.

Disclosure: C. Crow, None; **K. Jones**, None.

1333

Bridging the Social Support Needs Gap for African American Women with Systemic Lupus Erythematosus through the Chronic Disease Self-Management Program. Charmayne M. Dunlop-Thomas[1], Hannah Cooper[2], Terrika Barham[1] and Cristina M. Drenkard[1]. [1]Emory University, Atlanta, GA, [2]Emory Unversity, Atlanta, GA.

Background/Purpose: Social support is instrumental in the mental and physical well-being of people with systemic lupus erythematosus (SLE). Research has demonstrated that strengthening social ties can potentially reduce the negative influences of biology, genetics and environment. For instance, positive social integration has been found to be associated with both reduced mortality and improved health outcomes in people with SLE. This study assessed the social support needs among a socioeconomically disadvantaged cohort of African American women with SLE and investigated the ways in which a low-cost high-impact chronic disease self-management program (CDSMP) met these needs.

Methods: Participants were validated SLE patients receiving care at a lupus clinic at a public hospital. Qualitative data were gathered via focus groups with 27 of the 45 participants who completed the CDSMP, and with one-on-one interviews with two CDSMP leaders. The purport of focus groups and interviews was to gain insight into the acceptability of the CDSMP and the relevance and usefulness of its components. In addition, we surveyed

participants regarding the number of close relatives and friends, and CDSMP satisfaction.

Thematic analysis methods were used to analyze qualitative data; codes were developed using the data and the study's theoretical framework, including Cohen's definitions of social relationships and resources. Descriptive statistics were used to analyze survey data. Data sources and methodologies were triangulated.

Results: Six key themes emerged that depicted the types of social support needs: mental health (stress, depression, coping), personal empowerment (motivation), person-centered (care, "self-love"), interpersonal relationships, communication, and physical health (exercise, nutrition, pain management, stress). Survey data showed an average CDSMP satisfaction score of 4.8 (range 4 [agree] to 5 [strongly agree]). The most frequent memorable program opportunities were learning, personal support, and interpersonal interactions, respectively. There was no significant change in the numbers of close relatives and friends before and after the program. The emotion- and problem-focused channels of the CDSMP offered the supportive resources to satisfy participant needs. The data and methodological triangulation demonstrated a consistency across data sources and approaches.

Conclusion: This qualitative study provided a greater understanding of the role of social support among African American women with SLE and the ways in which the CDSMP might help develop, enhance and utilize supportive resources. Healthy social relationships were found to have significant impact in SLE women's ability to cope with stress and self-manage this disease. The influences of stress were revealed in both the mental health and physical health themes. The CDSMP offered the resources needed to enhance resilience, healthy behaviors, and overall well-being.

Disclosure: C. M. Dunlop-Thomas, NIH, 2, GlaxoSmithKline, 2; **H. Cooper**, None; **T. Barham**, None; **C. M. Drenkard**, NIH, 2, GlaxoSmithKline, 2.

1334

Social Support and Suicidal Ideation in Systemic Lupus Erythematosus: Georgians Organized Against Lupus Cohort. Charmayne M. Dunlop-Thomas[1], Gaobin Bao[1], S. Sam Lim[2] and Cristina M. Drenkard[1]. [1]Emory University, Atlanta, GA, [2]Emory University School of Medicine, Division of Rheumatology, Atlanta, GA.

Background/Purpose: Social support (SS) is instrumental in the mental and physical well-being of people with systemic lupus erythematosus (SLE). Moreover, SS contributes to overall health by providing a buffer from the adverse effects of stress. This is especially salient for people with SLE who may experience a wide-range of physical and psychological disease stressors. These stressors combined with other risk factors can contribute to suicidal ideation (SI). We examined the impact of perceived social support on suicidal ideation in SLE patients from the Georgians Organized Against Lupus (GOAL) Cohort.

Methods: We examined cross-sectional data from the GOAL Cohort, a large population-based cohort of validated SLE patients from metropolitan Atlanta, Georgia. GOAL participants responded to a variety of validated self-administered tools on health outcomes. The Systemic Lupus Activity Questionnaire assessed disease activity. The Patient Health Questionnaire-9 assessed depression severity, including the presence and duration of SI during the preceding two weeks. The emotional support question from the Behavioral Risk Factor Surveillance System assessed the perceived adequateness of SS received. Those who responded positively for SI were further contacted, provided with depression management resources, and probed for current SS resources. Logistic regression was used to examine the factors associated with SI.

Results: Of 600 SLE participants studied (93.3% women, mean age 48.8 [SD 12.8], 78.3% Black, mean disease duration 16 years [SD 9.6], and 68% uninsured), the average PHQ-9 score was 7.8 (SD 6.2), indicating mild to moderate depression. SI was present in 67 (11%) of GOAL participants. Significant differences were found in SS received, disease activity and poverty level between participants with and without SI.

Among the 67 with SI, only 23.4% reported visiting a psychologist, psychiatrist, or mental health counselor during the past 12 months. Thirty-one with SI were contacted. Many depended on family, friends or support groups (35%), or pastors, counselors, or physicians (25%) for SS. Moreover, 40% reported having no SS resource.

Conclusion: In a population-based cohort with large numbers of minorities and uninsured, depression was highly prevalent, with a significant proportion contemplating suicide. After controlling for other risk factors, such as socio-demographics and disease status, those with perceived inadequate social support, living in poverty, or with greater disease activity were at higher risk for SI. Further development and recognition of SS resources to which SLE patients can be referred are warranted, especially in socioeconomically disadvantaged communities.

Factors Associated with Suicidal Ideation in SLE

	Univariable		Multivariable	
Characteristics	**Odds Ratio**	**P Value**	**Odds Ratio**	**P Value**
Adequate Social Support*	0.17 (0.09–0.31)	<0.0001	**0.19 (0.10–0.38)**	**<0.0001**
Age at Diagnosis (5-year increase)	1.01 (0.91–1.12)	0.81	1.07 (0.92–1.24)	0.40
Disease Duration (1-year increase)	0.98 (0.95–1.01)	0.19	0.99 (0.96–1.03)	0.75
Education (3-year increase)	0.85 (0.66–1.11)	0.23	1.37 (0.98–1.91)	0.066
Gender (female)	1.14 (0.39–3.31)	0.81	0.54 (0.17–1.78)	0.32
Race (Black)	0.77 (0.40–1.48)	0.43	1.28 (0.54–3.02)	0.57
Married or living with a partner	0.76 (0.45–1.30)	0.32	0.98 (0.50–1.93)	0.96
Above Poverty Level	0.26 (0.15–0.46)	<0.0001	**0.27 (0.12–0.62)**	**0.0020**
Insurance Type (Ref: Private)				
No Insurance	3.61 (1.54–8.47)	0.0032	1.58 (0.53–4.73)	0.44
Medicare	2.42 (1.15–5.08)	0.019	1.36 (0.55–3.41)	0.67
Medicaid	2.87 (1.37–6.00)	0.0051	1.03 (0.36–2.95)	0.56
Disease Activity Score (SLAQ score; 5-unit decrease)	0.61 (0.52–0.71)	<0.0001	**0.62 (0.51–0.75)**	**<0.0001**
Organ damage (Ref: SA-BILD = 0)				
Mild damage (SA-BILD =1 or 2)	1.38 (0.65–2.89)	0.40	0.65 (0.26–1.58)	0.52
Severe damage (SA-BILD ≥ 3)	1.78 (0.87–3.68)	0.12	0.64 (0.25–1.64)	0.53

*Adequate Social Support defined if SS was reported as always or usually received when needed. Inadequate Social Support defined if SS was reported as never, rarely or sometimes received when needed. Abbreviations: SLAQ – Systemic Lupus Activity Questionnaire; SA-BILD – Self-administered-Brief Index of Lupus Damage.

Disclosure: C. M. Dunlop-Thomas, NIH, 2, GlaxoSmithKline, 2; **G. Bao**, GlaxoSmithKline, 2; **S. S. Lim**, NIH, 2, GlaxoSmithKline, 2, Emory University, 3; **C. M. Drenkard**, NIH, 2, GlaxoSmithKline, 2.

1335

Early Birds Versus Night Owls: Morning/Evening Preference and Its Association with Sleep Problems, Fatigue, and Emotional Well-Being Among RA Patients. Alyssa Wohlfahrt[1], Jing Cui[2], Michelle A. Frits[1], Christine K. Iannaccone[1], Jonathan S. Coblyn[1], Michael E. Weinblatt[1], Nancy A. Shadick[3] and Yvonne C. Lee[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Womens Hospital, Boston, MA, [3]Brigham and Women's Hospital/Harvard University, Cambridge, MA.

Background/Purpose: Over 60% of rheumatoid arthritis (RA) patients report sleep problems. Previous studies suggest that chronotype (the preferred time of day when individuals are active and alert), sleep problems, pain and emotional well-being are intimately linked. In the normal population, evening chronotype (preference for activity in the evenings) is associated with poor sleep, pain, and depression. This study examines the association between chronotypes and measures of sleep, pain and emotional well-being among RA patients with sleep problems.

Methods: Cross-sectional data were analyzed from 191 RA patients who participated in a substudy on sleep and morning/evening preference, within a large RA registry. Inclusion criteria included RA patients with sleep problems (Medical Outcomes Study (MOS) Sleep Problems Index II score > 35). Between March and June 2012, subjects were mailed the Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ). The Multidimensional Health Assessment Questionnaire (MDHAQ), the 5-item Mental Health Index (MHI-5) and the MOS Sleep Scale were completed during the subjects' annual study visit. Multivariable linear regression models, adjusted for age, sex, serology, and disease activity (DAS28-CRP), were used to determine the association between chronotype and sleep problems, pain and emotional well-being. Scores for morning and intermediate chronotypes were compared to scores for evening chronotypes.

Results: Mean age was 61.0 ± 11.3 years. 162 (84.8%) were female. Mean DAS28-CRP was 2.90 ± 1.29. 43 (22.5%) exhibited a morning preference. 67 (35.1%) exhibited an evening preference, and 81 (42.4%) were intermediate chronotypes. Evening chronotypes reported significantly longer sleep duration (6.8 hours vs. 6.1 hours, $p = 0.01$) than intermediate chronotypes (Table). Although not statistically significant, evening chronotypes reported the lowest sleep adequacy scores (34.5 vs. 37.1 for intermediate and 41.9 for morning chronotypes) and the highest somnolence scores (34.4 vs. 31.8 for intermediate and 28.9 for morning chronotypes). Evening chronotypes also had the lowest mean scores on the MHI-5 (69.3 vs. 71.6 for

intermediate and 77.3 for morning chronotypes). Both morning and evening chronotypes had similar scores on the MOS Sleep Disturbance Scale (45.0 versus 45.8), MDHAQ Fatigue Scale (53.6 vs. 53.0) and MDHAQ Pain Scale (40.6 vs. 37.5).

Conclusion: In contrast to the general population, RA patients with an evening preference did not report worse emotional health or higher pain and fatigue, compared to intermediate or morning chronotypes. RA patients with evening chronotypes did report sleeping more hours than subjects with morning or intermediate chronotypes, despite similar sleep adequacy scores. Additional studies are needed to determine whether morning/evening preference can be used to identify subgroups of RA patients at increased risk for sleep problems. Table. Adjusted mean values for sleep, fatigue, pain and emotional well-being among RA patients with clinically significant sleep problems.

Clinical Characteristic	Morning* (N = 43)	Intermediate* (N = 81)	Evening 71.6 (p=0.51)
Sleep Quantity (hours)	6.4 (p=0.26)	6.1 (p=0.01)	6.8
Sleep Adequacy (0-100 scale, higher = better sleep adequacy)	41.9 (p=0.11)	37.1 (p=0.49)	34.5
Somnolence Scale (0-100 scale, higher = more somnolence)	28.9 (p=0.25)	31.8 (p=0.51)	34.4
Sleep Disturbance Scale (0-100 scale, higher = more disturbance)	45.0 (p=0.86)	48.5 (p=0.52)	45.8
MDHAQ Fatigue Scale (0-100 scale, higher = more fatigue)	53.6 (p=0.93)	52.2 (p=0.87)	53.0
MDHAQ Pain Scale (0-100 scale, higher = more pain)	40.6 (p=0.60)	39.7 (p=0.65)	37.5
Mental Health Index - 5 (0-100 scale, higher = better emotional well-being)	77.3 (p=0.07)	71.6 (p=0.51)	69.3

*P values are for comparison between morning chronotypes and evening chronotypes and the comparison between intermediate chronotypes and evening chronotypes.

Disclosure: A. Wohlfahrt, None; **J. Cui**, None; **M. A. Frits**, None; **C. K. Iannaccone**, None; **J. S. Coblyn**, CVS caremark, 5; **M. E. Weinblatt**, UCB, 2, Bristol-Myers Squibb, 2, Crescendo, 2, UCB, 5, Bristol-Myers Squibb, 5, Crescendo, 5; **N. A. Shadick**, Crescendo Bioscience, 2, Amgen, 2, UCB, 2, Abbvie, 2, Bristol Myers Squibb, 2, Genentech, 2; **Y. C. Lee**, Forest Research Institute, 2, Merck Pharmaceuticals, 1, Cubist Pharmaceuticals, 1, Perrigo, 1, Express Scripts, 1.

1336

Associations of Physical and Mental Factors with Outcome Expectations for Exercise in a Clinical Trial. Shaoyu Chang, Lori Lyn Price, Jeffrey Driban, William F. Harvey and Chenchen Wrang. Tufts Medical Center, Boston, MA.

Background/Purpose: In exercise intervention trials, higher outcome expectancy can predict stronger adherence. Such expectancy is known to be associated with gender, age, marital status, physical and mental health, and self-efficacy. However, it remains unclear whether specific disease conditions may help discriminate high expectancy individuals from those with moderate expectancy when screening participants for clinical trials. This study aimed to explore whether physical and mental health factors are associated with outcome expectations for exercise among patients with knee osteoarthritis (KOA) participating a large clinical trial.

Methods: We conducted a secondary analysis of baseline data from a randomized clinical trial comparing physical therapy and Tai Chi among individuals with KOA defined by the American College of Rheumatology criteria. We assessed expectancy for exercise with a 9-item Outcome Expectations for Exercise (OES) questionnaire, which utilizes a 5-point scale where a higher value indicates stronger expectation for a positive outcome. Participants reported the degree of pain and physical function through the WOMAC questionnaire. They also reported their confidence in coping with chronic pain through the Chronic Pain Self-Efficacy Scale (CPSS). A single reader scored radiographs for KL grades. We assessed participants' mental status with the Beck II scale and PROMIS anxiety inventory.

OES was analyzed as a binary variable (<4 versus ≥ 4). The physical and psychological parameters were analyzed as tertiles. Separate logistic regression models were performed to evaluate the relationship between OES and each of the physical and psychological parameters, controlled for age, gender, and BMI. Statistical significance was set at $p<0.05$.

Results: The 282 participants in the trial were 69% female; 51% white and 35% African American; aged 59.7±10.4 years (mean ± SD); and 51% with a low KL score (0–2), 22% with a moderate KL score (3), and 27% with a high KL score (4). Table 1 shows the odds ratio of higher OES for the six physical and psychological parameters after adjustment for age, gender, and BMI. We found that Beck II score and self-efficacy were significantly associated with OES.

Conclusion: The participants with worse depression symptoms and lower confidence in coping chronic pain tended to have lower outcome expectations. We observed trends that more severe self-reported symptoms and worse radiographic KOA severity were associated with higher outcome expectancy, although the statistical tests failed to reach significance. Such relationship may be confirmed by a larger sample size. Our results showed that in the clinical trials settings, high outcome expectancy populations may be identified through physical and psychological measurements, though further research is needed to determine their predictive ability.

Table 1. Odds ratios for high outcome expectations (OES ≥4) by physical and psychological parameters

Variable	Tertile	OR (95% CI)	Global p-value	p-value
WOMAC Pain	Best	Reference	0.2328	
	Middle	1.57 (0.78, 3.14)		0.2037
	Worst	1.83 (0.88, 3.80)		0.1042
WOMAC Function	Best	Reference	0.9788	
	Middle	1.00 (0.50, 2.01)		0.9998
	Worst	0.94 (0.46, 1.92)		0.8581
BECK II	Best	Reference	0.0462	
	Middle	0.57 (0.30, 1.10)		0.0920
	Worst	0.43 (0.22, 0.85)		0.0147
ANXIETY	Best	Reference	0.3908	
	Middle	1.52 (0.80, 2.90)		0.2044
	Worst	1.46 (0.75, 2.85)		0.2649
Kellgren-Lawrence (KL) (collapsed)	0-2	Reference	0.1469	
	3	1.62 (0.87, 3.00)		0.6807
	4	2.01 (0.89, 4.56)		0.2416
Self Efficacy	Worst	Reference	0.0464	
	Middle	1.83 (0.97, 3.45)		0.0605
	Best	2.22 (1.14, 4.34)		0.0193

Disclosure: S. Chang, None; **L. L. Price**, None; **J. Driban**, None; **W. F. Harvey**, None; **C. Wang**, None.

1337

Mindfulness Is Associated with Symptom Severity and Pain Impact in Patients with Fibromyalgia. Emily Wolcott[1], William F. Harvey[1], Lori Lyn Price[1], Jeffrey B. Driban[1], Nani Morgan[2], Lucas Morgan[1] and Chenchen Wang[1]. [1]Tufts Medical Center, Boston, MA, [2]University of Hawaii, Honolulu, HI.

Background/Purpose: Mindfulness is attention to and awareness of present experiences (e.g. physical sensations, emotions, thoughts) in a nonjudgmental way. Initial evidence suggests that increased mindfulness may be associated with less pain intensity and catastrophizing among some people with chronic pain. However, this has not been confirmed among people with fibromyalgia. We evaluated whether greater mindfulness is associated with less pain and severity of associated symptoms in people with fibromyalgia.

Methods: We performed a secondary analysis of baseline data from a randomized clinical trial comparing Tai Chi to aerobic exercise in fibromyalgia patients as defined by the ACR criteria. At their baseline evaluation, subjects completed the Five Facet Mindfulness Questionnaire (FFMQ), a 39-item, self-report questionnaire that measures five facets of mindfulness: observing, describing, acting with awareness, non-judging, and non-reacting to inner experience. Higher scores in each facet indicate higher levels of mindfulness. Subjects also completed validated symptom measures including the PROMIS Pain Impact Short Form (PROMIS pain), Symptom Severity Scale, and the revised Fibromyalgia Impact Questionnaire (FIQR).We calculated Pearson's correlation coefficients to assess associations between mindfulness and measures of fibromyalgia pain impact and symptom severity. We determined an overall mindfulness score by calculating a mean of the five facets for each participant. We also completed a multivariate regression analysis to control for age, gender, body mass index, and education.

Results: Our analysis included data from rounds 1–4 (160 participants) with a mean age of 51.9 (SD=12.2) years; 92% women, mean BMI 29.5 kg/m^2, and 83% completed at least some college. Higher global mindfulness scores were associated with lower symptom severity and pain intensity as measured by the PROMIS Pain, Symptom Severity, and FIQR (see table). These relationships were also significant for most of the sub-facets of mindfulness with the exceptions of observing and non-reacting. Mindfulness

remained independently associated with PROMIS pain, Symptom Severity, and FIQR after adjusting for confounders.

Conclusion: Our results suggest that greater mindfulness is associated with less pain impact and severity of associated symptoms in people with fibromyalgia. Thus, mindfulness-based interventions may have the potential to improve the way those with fibromyalgia relate to their symptoms, by increasing non-judgmental acceptance of their experience, resulting in a reduction of their perception of pain intensity. Longitudinal studies are in progress to assess whether the cultivation of mindfulness alters the severity and prevalence of associated symptoms and experience of pain in people with fibromyalgia amongst those with other chronic pain disorders.

Table 1: Association between the Facets of Mindfulness and Measures of Symptom Severity and Pain Impact

	Correlations with Fibromyalgia Pain Impact and Severity		
FFMQ Variable (range; m±sd)	**PROMIS Pain r (p-value)**	**Symptom Severity r (p-value)**	**FIQR r (p-value)**
FFMQ-Overall Mindfulness (16.8-36;26.2±4.3)	−.36 (<.0001)	−0.32 (<.001)	−0.25 (<.001)
FFMQ-Observing (15–40; 29.8±5.7)	−0.09 (0.25)	−0.03 (0.75)	0.01 (0.95)
FFMQ-Describing (13–40; 27±6.2)	−0.32 (<.001)	−0.20 (0.014)	−0.18 (0.02)
FFMQ-Acting with Awareness (8-38;24.5±7.1)	−0.28 (<.001)	−0.37 (<.001)	−0.24 (<.001)
FFMQ-Non-judging (9–40; 27.0±7.6)	−0.31 (<.001)	−0.33 (<.001)	−0.30 (<.001)
FFMQ-Non-reacting (9–35; 21.5±4.9)	−0.27 (<.001)	−0.16 (0.05)	−0.14 (0.08)

Note: FFMQ = Five Facet Mindfulness Questionnaire, PROMIS = PROMIS Pain Impact Short Form, FIQR = revised Fibromyalgia Impact Questionnaire.

Disclosure: E. Wolcott, None; **W. F. Harvey**, None; **L. L. Price**, None; **J. B. Driban**, None; **N. Morgan**, None; **L. Morgan**, None; **C. Wang**, None.

1338

Correlates of Body Image Dissatisfaction in Patients with Limited and Diffuse Systemic Sclerosis. Rina S. Fox[1], Sarah D. Mills[1], Shadi Gholizadeh[1], Erin L. Merz[1], Scott C. Roesch[2], Philip J. Clements[3], Suzanne Kafaja[3], Dinesh Khanna[4], Daniel E. Furst[3] and Vanessa L. Malcarne[2]. [1]SDSU/UCSD Joint Doctoral Program in Clinical Psychology, San Diego, CA, [2]San Diego State University, San Diego, CA, [3]University of California, Los Angeles, Department of Medicine, Los Angeles, CA, [4]University of Michigan Health System, Ann Arbor, MI.

Background/Purpose: Little research has evaluated body image dissatisfaction (BID) in Systemic Sclerosis (SSc). What has been conducted shows that BID is common and associated with worse psychosocial functioning. Additionally, age, upper-body telangiectasias, fingertip-to-palm distance, and facial skin involvement have been shown to be associated with Dissatisfaction with Appearance and Social Discomfort, two components of BID. However, it remains unclear if these factors relate to BID in the same way across disease classification (i.e., limited versus diffuse disease). Because limited and diffuse patients may have very different physical disease manifestations, the current study aimed to determine if sociodemographic and medical correlates of BID differed for patients with limited versus diffuse SSc, and identify which variables related to the two components of BID for each disease classification.

Methods: Participants were adults participating in the UCLA Scleroderma Quality of Life Study with rheumatologist-diagnosed limited (n = 101) or diffuse (n = 82) SSc. The Brief-Satisfaction with Appearance Scale (Brief-SWAP), which is comprised of two subscales measuring Dissatisfaction with Appearance and Social Discomfort, evaluated BID. The present analysis 1) examined if the relationships of sociodemographic (i.e., age, gender, race, education, and marital status) and medical (i.e., disease duration, presence of telangiectasis, presence of hyper/hypo-pigmentation, and facial, hand/finger, forearm, and leg/foot skin involvement) variables to the Brief-SWAP subscales were equivalent for limited and diffuse SSc, and 2) identified which of these variables were associated with each of the two Brief-SWAP subscales. Structural Equation Modeling evaluated both of these research questions. Both statistical and practical indicators of model fit were considered.

Results: There were similarities and differences in how sociodemographic and medical variables related to BID for limited versus diffuse SSc (S-Bχ^2 [143] = 181.42, p =. 02; RMSEA =. 06, CFI =. 91, SRMR =. 06). Greater Dissatisfaction with Appearance was associated with younger age (b = -.02, SD =. 01) and being unmarried (b = -.64, SE =. 30) for limited patients, and with younger age (b = -.02, SE =. 01) and increased finger/hand skin involvement (b =. 69, SE =. 15) for diffuse patients (ps <. 05). Greater Social Discomfort was associated with younger age (b = -.02, SE =. 01) and being unmarried (b = -.46, SE =. 22) for both subtypes (ps <. 05).

Conclusion: Both sociodemographic (i.e., age, marital status) and medical (i.e., finger/hand skin involvement) variables were related to BID. This is consistent with prior research and underscores the complex nature of BID in SSc. The present analysis suggests that young, unmarried patients may be at greatest risk for BID across disease subtypes. However, these factors may be more important for patients with limited disease, and finger/hand skin involvement may also be important for patients with diffuse disease. These findings can inform development of optimal, targeted interventions to diminish BID in SSc.

Disclosure: R. S. Fox, Rheumatology Research Foundation, 2; **S. D. Mills**, None; **S. Gholizadeh**, None; **E. L. Merz**, None; **S. C. Roesch**, None; **P. J. Clements**, None; **S. Kafaja**, None; **D. Khanna**, Actelion, Bayer, Biogen-Idec, BMS, DIGNA, Genentech/Roche, Gilead, InterMune, Merck, Sanofi-Aventis, United Therapeutics, 5, Patient Health Organization, 6, Scleroderma Foundation, 6; **D. E. Furst**, Abbott, Actelion, Amgen, BMS, Janssen, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB, 5; **V. L. Malcarne**, None.

1339

Is Psychological Status Related to Symptom Experience in Behçet's Syndrome? Robert Moots[1] and Sophie Campbell[2]. [1]University of Liverpool, Liverpool, United Kingdom, [2]Aintree University Hospital, Liverpool, United Kingdom.

Background/Purpose: Little is known about the impact of Behçet's Syndrome (BS) within the UK. The recent establishment of National Centres of Excellence now allows a systematic and holistic investigation of both physical and psychological effects of BS. This study investigates the relationship between disease characteristics and psychological status reported by attendees at one Centre.

Methods: Psychological questionnaires measuring depression, anxiety, pain, fatigue and condition intrusion were sent to all patients with a diagnosis of BS and attending a Behçet's Centre of Excellence (N=106). Associations between psychological scores and responses from the Behçet's Disease Activity Index (BDAI), a subjective measure of BS symptoms, were analysed using Spearman's correlation.

Results: Response rate was 51%. A high proportion of patients scored above the clinical cut off for depression (88.9%) and anxiety (74.1%). High levels of pain, fatigue and condition intrusion were also recorded. Female patients reported higher scores on all measures. On average, 4 out of 12 active BS symptoms were reported.

Overall, whilst psychological scores and BDAI responses indicated statistically significant positive correlations, associations were only moderate or low.

Surprisingly of the 12 BS symptoms measured by the BDAI, headache, arthralgia, arthritis, nausea, diarrhoea and erythema were significantly associated with higher psychological scores with no association between psychological scores and mouth ulcers, genital ulcers or skin pustules. Certain symptoms domains were not reported to be present by the majority of patients, notably eye, nervous system or major vessel problems, reflecting the spectrum of disease observed in the UK.

Table 1. Summary of results

Psychological Measure	Spearman's rho[a] (p-value)	Headache[b]	Skin Pustule[b]	Arthralgia[b]	Mouth Ulcer[b]	Genital Ulcer[b]	Arthritis[b]	Nausea[b]	Diarrhoea[b]	Erythema[b]
PHQ 9	0.426 (0.002)	0.017	0.581	**0.004**	0.759	0.993	**0.011**	**0.003**	0.051	0.135
GAD 7	0.305 (0.027)	0.373	0.505	**0.017**	0.412	0.709	0.271	0.061	0.075	**0.021**
MAF Total	0.374 (0.006)	0.198	0.739	**0.017**	0.138	0.624	**0.026**	**0.009**	0.371	**0.024**
BPI severity	0.556 (<0.001)	**0.012**	0.352	**0.003**	0.316	0.127	0.098	**<0.001**	**0.033**	**<0.001**
BPI interference	0.481 (<0.001)	**0.041**	0.161	**0.030**	0.299	0.277	**0.036**	**<0.001**	**0.015**	**0.034**
WSAS Total	0.428 (0.001)	0.060	0.914	**0.037**	0.060	0.900	**0.008**	**<0.001**	0.305	**0.021**

1. Rank correlation coefficient for the association between BDAI Total Score and psychological scores.
2. Mann-Whitney U test.

Conclusion: Whilst high levels of psychological morbidities were present within this UK BS cohort, psychological status was not strongly associated with BS symptoms. Surprisingly, many symptoms typically associated with BS and usually considered to be most debilitating (e.g. mouth and genital ulcers or eye problems), were not associated with increased psychological scores, whereas symptoms generally though to be less significant (eg headache, nausea, pain, diarrhoea) were more closely associated with poorer psychological status.

Disclosure: R. Moots, None; **S. Campbell**, None.

1340

Choosing Subserologies Wisely: An Opportunity for Rheumatologic Healthcare Resource Savings. David Bulbin[1], Alicia Meadows[1], Sandi Kelsey[1], Harold Harrison[1] and Alfred E. Denio[2]. [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Health System, Danville, PA.

Background/Purpose: In March 2013, the American College of Rheumatology published its Top 5 List of Things Physicians and Patients Should Question as part of the American Board of Internal Medicine's Choosing Wisely campaign. First on the list was "Don't test ANA subserologies without a positive ANA and clinical suspicion of immune-mediated disease." Previously, we examined positive subserologies when the ANA was negative, and were surprised to find that rheumatologists were frequently ordering subserologies when the ANA was negative. The present study was undertaken to elucidate the extent of this ordering pattern and understand the providers' rationales. The ultimate goal is to develop a quality improvement program to support cost effective utilization of subserologies.

Methods: We conducted a retrospective study of the Geisinger Health System that includes 2198 providers; 342 in primary care and 14 in rheumatology. We looked at the incidence of subserologies ordered simultaneously with an ELISA ANA when the ANA result was normal. Data from 2011–2012 was collected via the Sunquest lab system and EPIC electronic health record. Subserologies included were ELISA dsDNA, Anti-Smith/RNP, SSA/SSB, SCL70 and JO1 antibodies. Since anti-Smith/RNP, SCL70, and dsDNA should be negative when the ANA screen is negative, those testing instances represent unnecessary utilization. A six question survey was sent to providers who ordered ANA negative subserologies more than twice in an attempt to determine the providers' ordering rationale and to ascertain if they had quality improvement educational preferences. Finally, a cost analysis was done totaling the allowed reimbursement of unnecessary subserology tests based on the Medicare fee schedule.

Results: 22596 ANA tests were ordered from 2011–2012. 2246 ANA's were ordered at the same time as subserologies when all tests were negative (9.4%). 32.8% were ordered by Rheumatologists.

Out of 440 unique ordering providers, 183 ordered testing more than twice. 130 were sent the survey and 47 completed it. The primary reasons for ordering ANA's in conjunction with subserologies were an unclear diagnosis based on history and physical (16) and patient convenience (7). Providers were asked about opportunities for quality improvement. 10 preferred monetary incentives, 18 were interested in educational materials, 28 favored reflex testing, and 10 would want training through the EHR.

In our cost analysis we found that, excluding SSA/SSB and Jo-1, the estimated total cost of subserologies ordered with a negative ANA from 2011–2012 was $39,091.

Conclusion: In the Geisinger Integrated Health System, Rheumatologists frequently did not choose subserologies wisely. No specialty was immune from ordering ANA's and subserologies simultaneously. Responding physicians were most receptive to educational materials and reflex testing to help eliminate superfluous subserologies. If reflex testing had been available in 2011–2012, Geisinger would have saved close to $40,000 in unnecessary tests. We will be implementing an ANA/reflex subserology option combined with directed provider education about ordering patterns to improve utilization.

Disclosure: D. Bulbin, None; **A. Meadows**, None; **S. Kelsey**, None; **H. Harrison**, None; **A. E. Denio**, None.

1341

Choosing Not so Wisely: The Tale of Antinuclear Antibody Testing. Tejas Sheth[1] and David Alcid[2]. [1]Albert Einstein College of Medicine / Yeshiva University, Bronx, NY, [2]Drexel University College of Medicine / St Peter's University Hospital, New Brunswick, NJ.

Background/Purpose: Choosing Wisely campaign aims to promote evidence based care that is truly necessary and not duplicative. ACR has furnished guidelines for use of ANA and ANA subserologies (ANAS)[1]: First, repeat testing of ANA is not indicated in patients with established diagnosis of SLE. Second, ANAS should not be ordered along with initial ANA testing. Third, ANA should not be used as a screening test in patients with nonspecific symptoms. The study objective was to identify occasions where ANA testing does not reflect high-value, cost-conscious care.

Methods: All patients having ANA test done at St Peter's Hospital lab from 4/1/2012 to 3/31/2014 were included. Retrospective chart review was done for demographics, indication of testing and outcomes. Inferential analysis and logistic regression were done by SAS 9.0.

Results: Total 851 patient encounters were found with mean age of 46.9 years and M:F ratio of 1:3.3. In 91 encounters, ANA testing was done despite a history of SLE. In 223 encounters, ANAS were ordered along with initial ANA. Of 223 ANAS ordered, only 15 were positive; all of which had positive ANA results. Female patients (OR 2.92, 95% CI 1.86–4.59) and those with history of autoimmune disease (AID) (OR 6.76, 95% CI 4.37–10.44) were more likely to have a positive ANA result. Patients with history of AID (OR 7.87, 95% CI 1.72–35.95) and those with a positive ANA results ($p<0.001$) were more likely to have positive ANAS. Age (OR 0.99, 95% CI 0.98–1.01) and location of patient ($p=0.48$) did not show association with ANA results. ANA testing ordered in family medicine, pediatrics and gastroenterology were more likely to have negative results (OR 2.61, 2.3 and 5.04 respectively) as compared to rheumatology. Follow up visits were available in 587 encounters; on 12 occasions (2.07%) a positive ANA result translated in a change in management.

Conclusion: A significant amount of clinically done ANA testing does not reflect high value care and is associated with significant economic burden (>150,000 USD/yr).

Reference

1. Yazdany J et al. Arthritis care & research 2013;65:329–39.

Table 1: ANA testing behavior of different specialties in patients with history of SLE

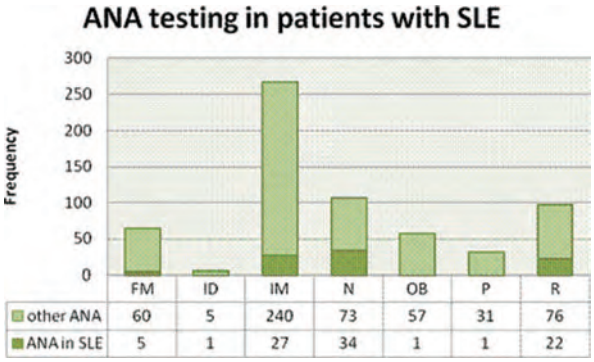


Table 2: ANAS testing behavior of different specialties along with initial ANA testing

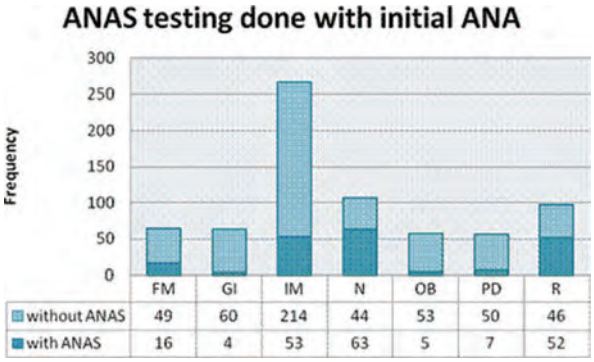


Table 3: Clinical situations where ANA testing does not reflect high-value care

Not choosing wisely	Frequency (n=851)	Specialty ordering majority of testing
ANA testing done in patients with established diagnosis of SLE	91 (10.7%)	Nephrology, Internal Medicine, Rheumatology
ANAS ordered along with initial ANA testing	223 (26.2%)	Nephrology, Internal Medicine, Rheumatology
ANA ordered for fatigue, malaise and other non-specific symptoms	264 (31.02%)	Internal Medicine, Family Medicine

Disclosure: T. Sheth, None; **D.** Alcid, None.

1342

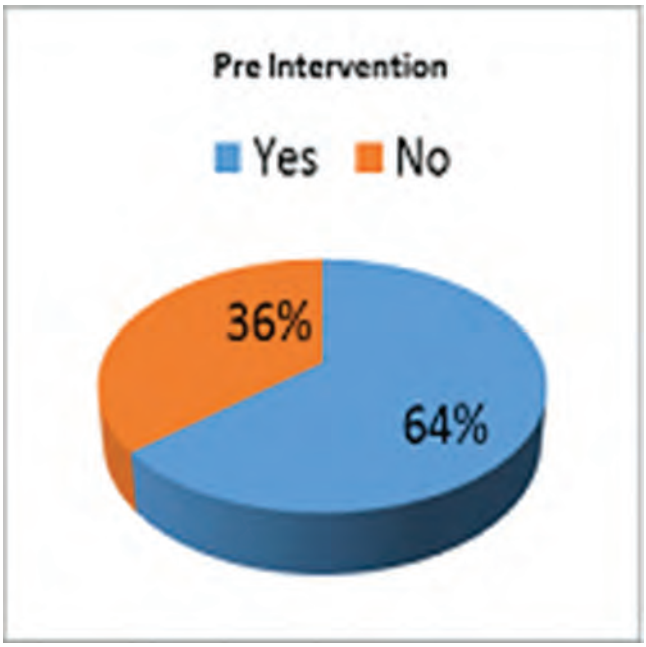
Improving Serologic Testing for Antiphospholipid Antibodies in Patients with Systemic Lupus Erythematosus. Arshad Mustafa[1], Kara Prescott[2], Una Makris[2] and E. Blair Solow[3]. [1]UT Southwestern Medical Center at Dallas, Dallas, TX, [2]Dallas VA Medical Ctr, Dallas, TX, [3]UT Southwestern Medical Center, Dallas, TX.

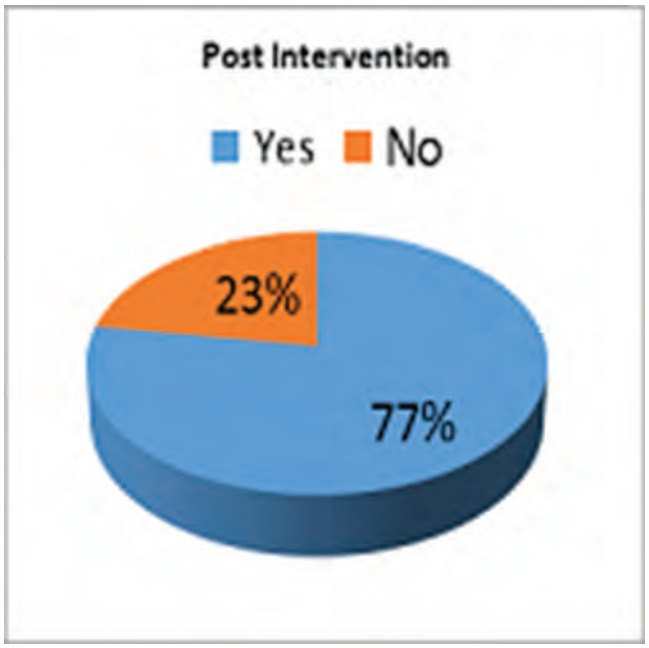
Background/Purpose: Antiphospholipid antibodies (APL) in patients with Systemic Lupus Erythematosus (SLE) are common. Persistent positivity is known to increase the risk of thrombosis and pregnancy morbidity and predicts early damage in patients with SLE. Testing for APL is part of the American College of Rheumatology (ACR) and the Systemic Lupus International Collaborating Clinics (SLICC) immunologic criteria for SLE. The purpose of the Quality Improvement (QI) project was to determine the percentage of SLE patients in whom APL were checked before and after intervention at the Parkland Rheumatology Clinic—the largest urban safety net hospital in Dallas, Texas.

Methods: Initially, 150 Parkland Rheumatology charts with an International Classification of Disease (ICD)-9 code of 710.0 were selected at random and reviewed for the presence of APL (lupus anticoagulant, anticardiolipin, and beta 2 glycoprotein I). Patients who met the ACR or SLICC classification criteria were included. APL testing done before July 2012 was recorded. Charts with ≥ 2 APL were counted as "Yes" and < 2 APL were counted as "No". The intervention consisted of a 6 month education period focusing on the impact of APL in SLE. This consisted of a series of case presentations and journal club by the fellows, guest speakers with expertise on Antiphospholipid Syndrome, and a QI related SLE-APL literature review. Verbal reminders were made to the providers on their clinic days. Subsequently, another 150 Parkland charts with an ICD-9 code of 710.0 were selected at random and reviewed for the presence of APL. Patients not seen in the clinic after July 2012 were excluded, as changes after intervention could not be applied to these patient's charts. Fisher's exact test was used to investigate the change in APL testing in SLE patients before and after the intervention.

Results: Pre-intervention data showed that in 95 (64%) charts APL were checked, and in 54 (36%) charts APL were not measured. Post-intervention, in 93 (77%) charts, APL were checked and in 27 (23%) charts APL were not measured, see Figure. The intervention was significant for a change in APL testing in SLE patients by the providers ($p = 0.02$).

Conclusion: Routine APL testing in patients with SLE is often overlooked. It is important to identify APL in SLE patients for diagnostic, therapeutic and prognostic purposes. In this QI project provider education significantly improved the testing for APL in patients with SLE. Future interventions include ongoing education strategies and creating rheumatology template notes with smartphrases in the electronic medical record.





Disclosure: A. Mustafa, None; **K. Prescott**, None; **U. Makris**, None; **E. B. Solow**, None.

1343

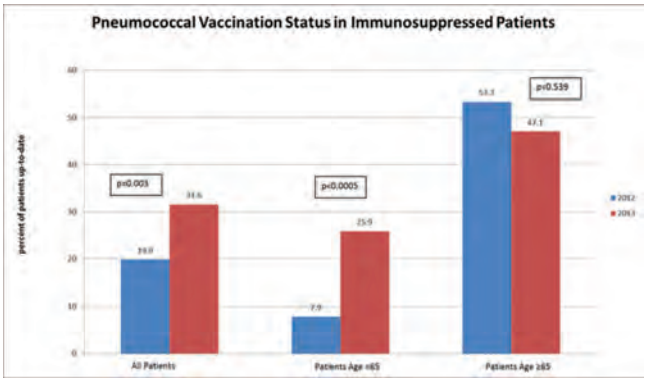
A Quality Improvement Initiative to Improve Pneumococcal Vaccination Rates in Immunosuppressed Patients. Melissa Bussey[1] and Rochella A. Ostrowski[2]. [1]Division of Rheumatology, Loyola University Medical Center, Maywood, IL, [2]Loyola University Medical Center, Maywood, IL.

Background/Purpose: Patients with autoimmune diseases are at increased risk of complicated infections, and immunomodulating treatment regimens further enhance this risk. Many of these infections, including influenza, invasive pneumococcal disease, herpes zoster, and human papillomavirus, are vaccine preventable. The Centers for Disease Control (CDC), American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) recommend pneumococcal vaccination for patients who are immunosuppressed. Despite these clear recommendations, studies have shown pneumococcal vaccination rates ranging from only 19–54% in immunosuppressed populations. The aim of this study was to evaluate the effect of an educational intervention and distribution of a pocket vaccination guide on pneumococcal vaccination rates in an academic rheumatology practice.

Methods: Six attending rheumatologists in an academic setting were selected to receive the intervention in the form of an oral PowerPoint presentation and a pocket-sized guide containing CDC guidelines for vaccination, ACR recommendations regarding the use of vaccines in patients with rheumatoid arthritis, and the most recent recommendations for the pneumococcal vaccine including indications for the pneumococcal conjugate vaccine (PCV13). The rates of immunosuppressed patients being up-to-date with pneumococcal vaccination were assessed pre- and post-intervention over a one month time period (August 2012 and August 2013). Up-to-date vaccination status was defined as any one vaccine dose over age 65, any one dose in the last 5 years, or any 2 prior doses 5 years apart. Only patients age 18 and older on immunosuppressive therapy who were being seen on a follow up basis were included. Patients receiving rituximab were excluded as it is thought to decrease vaccine efficacy. Chi-square test and logistic regression were used to analyze the data (STATA 11.0).

Results: Among all providers, 171 immunosuppressed patients were seen in the pre-intervention time period and 190 in the post-intervention time period. 19.9% of eligible immunosuppressed patients were up-to-date with their pneumococcal vaccination pre-intervention as compared to 31.6% post-intervention ($p=0.003$) with an odds ratio of 1.85 (95% CI 1.11–3.01)[Table 1]. This increase remained significant when adjusting for site of clinic and provider. Among patients less than 65 years old, up-to-date vaccination status increased from 7.9% pre-intervention to 25.9% post-intervention ($p<0.0005$). Vaccination practices varied widely among providers.

Conclusion: A QI strategy involving an educational session along with distribution of a pocket-sized vaccination guide significantly increased the rate of being up-to-date with pneumococcal vaccination among immunosuppressed patients in our academic rheumatology practice.



Disclosure: M. Bussey, None; **R. A. Ostrowski**, None.

1344

Electronic Medical Record-Based Best Practice Alert Used By Clinical Staff Improved Pneumococcal Vaccination and Documentation Among Immunosuppressed Rheumatoid Arthritis Patients. Heena Sheth, Larry W. Moreland, Hilary J. Peterson and Rohit Aggarrwal. University of Pittsburgh, Pittsburgh, PA.

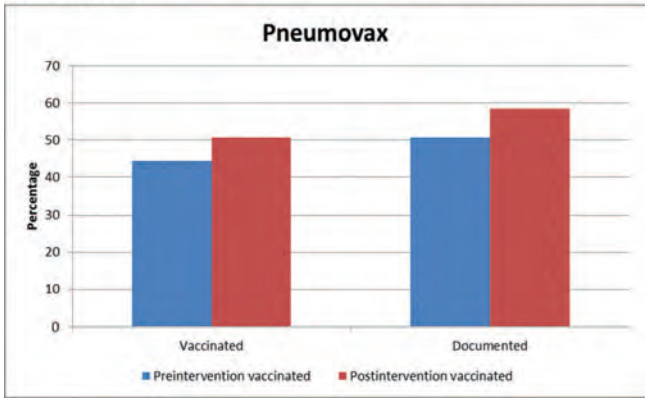
Background/Purpose: The Centers for Disease Control and American College of Rheumatology guidelines recommend pneumococcal vaccination for all immunosuppressed patients, specifically those taking disease modifying antirheumatic drugs (DMARDs) or biologic agents. Despite these guidelines, the rates of pneumococcal vaccination are very low in RA patients. The aim of this study was to improve the rate of administration and documentation of pneumococcal vaccine in rheumatoid arthritis (RA) patients taking DMARDs and biologic agents at rheumatology outpatient clinics.

Methods: An automated electronic medical record (EMR)-based best practice alert (BPA) intervention was designed to be used by clinical staff and to provide user-friendly interface to remind, document and order pneumococcal vaccine for eligible patients. EMR determined the eligibility of the patients at the time of rooming by medical assistant (MA) or nurse, and the BPA appeared for eligible patients. MA confirmed eligibility, documented prior vaccination or patient refusals and ordered the vaccine using the BPA if the patient agreed. Physicians reviewed and verified orders, and the patient either received the vaccination or a written prescription based on clinic/patient preferences. If the patient was unsure, the BPA was passed on to the physician for further discussion. The process continues at each visit until patient is vaccinated or documentation occurs. The study was designed as a pre- and post-intervention comparison. Clinical staff and physicians were educated on the guidelines and intervention. Patient education about vaccination was performed during clinic visit, and educational material was also provided. Eligibility for pneumococcal vaccine was all RA patients on immunosuppressant medications (DMARDs or biologics) who have not completed pneumococcal vaccination. Vaccination and documentation rates for the pre-intervention period (July 2012-June 2013) were compared with post-intervention period rates (2/17/2014 – 5/17/2014) using chi square test.

Results: 3285 and 1949 patients were analyzed for baseline and intervention data, respectively. Demographic characteristics were similar in both groups. Vaccination and documentation rates increased significantly from 44.4% and 51.4% in pre-intervention phase to 50.8 % and 58.4%, respectively within 3 months of intervention phase ($p<0.0001$). Approximately 3% of patients refused vaccination, and for 4% of patients, physicians noted deferral during both study phases.

Conclusion: Pneumonia vaccination administration rates in immunosuppressed patients with RA are low. Implementation of an automated EMR and clinical staff-based BPA intervention significantly improved vaccination rates without the need for considerable physician input. The project is ongoing and will become standard of practice in our rheumatology clinics.

Figure 1. Pre- and post-intervention rates of pneumococcal vaccination and documentation in our rheumatology clinics.



Disclosure: H. Sheth, None; **L. W. Moreland**, Pfizer Inc, 9; **H. J. Peterson**, None; **R. Aggarwal**, Questcor, 2, Pfizer Inc, 2, NIEHS-NIH, 2, Questcor, 5, aTyr Pharma, 5.

1345

Improving Pneumococcal Immunization Rates for Patients on Immunosuppressant Medications at an Academic Rheumatology Clinic. Lauren Dudley, Stephen Liu, Krista Merrihew, Jocelyn Verrill and Lin Brrown. Dartmouth-Hitchcock Medical Center, Lebanon, NH.

Background/Purpose: Patients with rheumatologic diseases are frequently placed on immunosuppressant medications which increase their risk of developing *Streptococcus pneumoniae* infections. The Advisory Committee on Immunization Practices recommends that all immunosuppressed adults receive the 13-valent pneumococcal conjugate vaccine (PCV-13) followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV-23) but many specialty clinics lack processes of care that facilitate immunization. The objective of this study was to improve pneumococcal immunization rates for patients on immunosuppressant medications in the adult rheumatology clinic.

Methods: Immunization rates for PCV-13 and PPSV-23 were defined as the proportion of visits in which patients were up to date on their immunization. Data obtained from the electronic health record from May 2011 to April 2014 was analyzed using statistical process control methods. Rates over time were tracked using p-charts. Semi-structured interviews were performed with clinic staff to map the processes for immunization and create cause-and-effect diagrams. Interventions consisted of staff and provider education, a standardized process for obtaining immunization histories and a standing order permitting clinical support staff to order and administer immunizations via a protocol.

Results: At baseline, there was no standardized process for assessing immunization histories or providing immunizations in the clinic. Barriers included provider knowledge gaps, uncertainty regarding whether specialists or primary care providers should immunize, missing immunization records, lack of reminders and lack of time. The interventions resulted in statistically significant increases in the PCV-13 immunization rate from 3.0% to 33.3% (p-value < 0.001) and the PPSV-23 immunization rate from 58.1% to 64.9% (p-value < 0.001).

Conclusion: Rheumatologists place many patients on immunosuppressant medications rendering them high risk for infection yet many clinics have not incorporated immunizations into their standard processes. Standing orders combined with education should be considered as a potential intervention.

Figure 1. Up-to-date immunization rate for the 13-valent pneumococcal conjugate vaccine (PCV-13) at Dartmouth-Hitchcock Medical Center Adult Rheumatology Clinic.

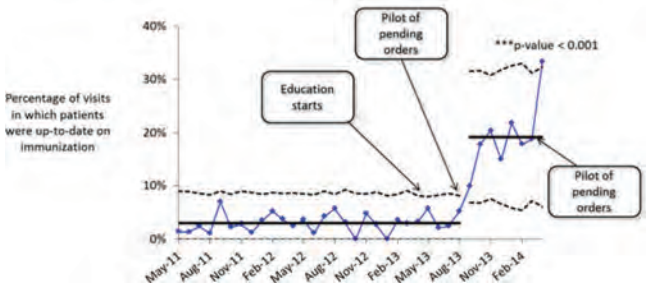
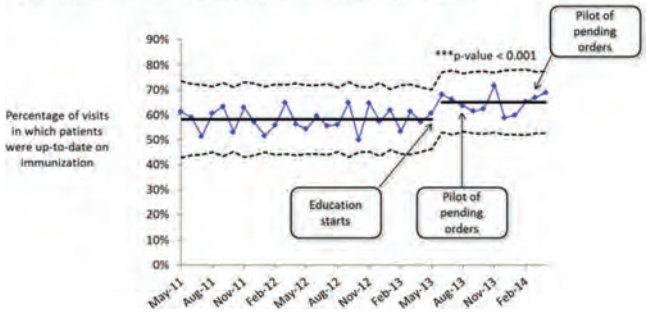


Figure 2. Up-to-date immunization rate for the 23-valent pneumococcal polysaccharide vaccine (PPSV-23) at Dartmouth-Hitchcock Medical Center Adult Rheumatology Clinic.



Disclosure: L. Dudley, None; **S. Liu**, None; **K. Merrihew**, None; **J. Verrill**, None; **L. Brown**, None.

1346

Leveraging Electronic Health Records to Improve Vaccination Rates for Patients with Rheumatoid Arthritis. David W Baker, Tiffany Brown, Ji Young Lee, Diana S Sandler, David T Liss, Amanda Ozanich, Elizabeth Harsha Strong, Alpa Patel and Eric M. Ruderrman. Northwestern University, Chicago, IL.

Background/Purpose: Vaccination rates among patients with rheumatoid arthritis (RA) remain low. Improving these rates is important, as RA patients are inherently immunocompromised and frequently treated with immunosuppressives. To address this, we implemented a multifaceted, system-level intervention to improve pneumococcal (PVX) and zoster (ZVX) vaccination rates among patients with RA that was designed to make clinicians aware of their low vaccination rates, improve processes at the point of care (i.e., during a visit), and use panel-management strategies to contact patients between visits.

Methods: This study was conducted at an academic medical center in Chicago, IL. The study cohort included all adults seen in the faculty practice plan's rheumatology clinic with a diagnosis of RA. Our intervention had 3 main components: (1) clinicians received quarterly performance reports of the PVX and ZVX rates for their RA patients, generated from EHR data; (2) EHR clinical decision support best practice alerts (BPAs), designed to alert clinicians and facilitate PVX and ZVX administration at the point of care, and; (3) outreach to patients needing vaccination via mail or secure electronic messaging through the EHR patient portal, regardless of whether they had in-person clinic visits. Study BPAs allowed clinicians to either link to a standing order set for vaccination at the time of the visit, document why vaccination was inappropriate, or write a prescription for the patient to receive ZVX elsewhere. We assessed vaccination rates monthly from baseline in October 2013 through May 2014 using EHR data. For this interim analysis we assessed the statistical significance of differences in vaccination rates pre- and post-intervention.

Results: The study cohort included 1255 eligible patients. At baseline 293 (23.3%) had received PVX, and this increased to 524 (41.8%) at follow-up ($p<0.001$). An additional 11 (0.9%) patients had a documented medical exception for why PVX was not administered, and 53 (4.2%) had a documented refusal. At baseline, 35 (2.8%) patients had received ZVX, and at follow-up 63 (5.0%) patients had received ZVX at clinic or received a prescription to receive ZVX elsewhere ($p<0.01$). During follow-up, 99 (7.9%) patients had a documented medical exception and 44 (3.5%) had a documented patient exception (refusal or financial barrier) for ZVX.

Conclusion: Vaccination rates increased substantially following implementation of this multifaceted intervention. However, the rate of PVX remained much lower than rates we have achieved for PVX using similar interventions in a primary care clinic, and ZVX rates remained quite low. The reasons for these suboptimal vaccination rates are unclear, but could be due to rheumatologists' limited time to discuss prevention with patients or beliefs that vaccination is the responsibility of primary care providers. Alternatively, our results could be due to clinical confusion following the recent publication of new PVX recommendations, and uncertainty regarding ZVX administration in immunocompromised patients under age 60. Future research should seek to identify and overcome barriers to vaccination in this patient population.

Disclosure: D. W. Baker, None; **T. Brown**, None; **J. Y. Lee**, None; **D. S. Sandler**, None; **D. T. Liss**, None; **A. Ozanich**, None; **E. Harsha Strong**, None; **A. Patel**, None; **E. M. Ruderman**, Pfizer Inc, 5.

1347

Understanding Vaccination Rates Among Patients with Rheumatoid Arthritis. Diana S Sandler, Eric M. Ruderman, Tiffany Brown, Ji Young Lee, Amanda Ozanich, David T Liss and David W Barker. Northwestern University, Chicago, IL.

Background/Purpose: Vaccinations are important for patients with rheumatoid arthritis (RA) who may receive immunosuppressive therapies that increase their risk of infection. The Advisory Committee on Immunization Practices (ACIP) recommends all adults receive annual influenza vaccination (INFVX), patients with immunocompromising conditions such as RA receive pneumococcal vaccine (PVX), and adults age 60 and older receive zoster vaccine (ZVX). However, rates of these vaccinations among RA patients are suboptimal. Using data from electronic health record (EHR) among our RA patients in 2012, 41% of patients had ever received PVX, 19% had received INFVX during 2011–2012 season (this may be low due to incomplete EHR capture), and 2% had ever received ZVX. We conducted a telephone survey among RA patients to assess self-reported vaccination status and to understand patient vaccination behavior and attitudes.

Methods: We recruited randomly selected RA patients in an academic practice from July to September 2013. Eligible participants were identified by EHR query with diagnosis of RA, at least one rheumatology visit in each of the previous two years, were 18+ years of age, and listed English as preferred language. Chart review confirmed diagnosis of RA. The 10 minute survey included: (1) Patient self-reported receipt of INFVX, PVX, and ZVX; (2) Attitudes about these vaccines, reasons for unvaccinated status if applicable and; (3) Provider recommendations about these vaccines. For patients that reported ever receiving INFVX, we asked if they had been vaccinated during the previous year's flu season (2012–2013).

Results: Participants' (n=102) mean age was 57.8 (SD=14.5), 85.3% were female, 67.3% were white and 85.2% reported taking immunosuppressive medication. The vast majority of participants (90.2%) reported having *ever*received INFVX; 79.4% reported receipt of INFVX during the 2012–2013 flu season. Approximately half of participants (53.9%) reported receipt of PVX, and only a few (7.8%) reported receipt of ZVX. When participants, regardless of vaccination status, were asked "How important do you think it is get vaccinations to prevent infections?" 78.5% felt it was at least somewhat important to get vaccinations; 14.7% thought vaccines were not important at all. 74.5% of respondents reported being told they had an increased risk of infection, but only 63.7% recalled being told the importance of vaccines by providers. 96.1% participants reported that their provider had recommended INFVX, but only 16.7% reported that ZVX had been recommended. The most common reason patients gave for not receiving PVX and ZVX was that it had not been recommended to them.

Conclusion: Academic rheumatology patients with RA reported very high levels of INFVX, low rates of PVX, and very poor ZVX uptake. The majority of participants thought vaccinations are at least somewhat important and the most common reason for not receiving vaccination was lack of provider recommendation. Further research is needed to investigate system-level barriers to vaccination, including reasons for inadequate provider recommendations and the impact of evidence-based provider-level interventions on vaccination rates.

Disclosure: D. S. Sandler, None; **E. M. Ruderman**, Pfizer Inc, 5; **T. Brown**, None; **J. Y. Lee**, None; **A. Ozanich**, None; **D. T. Liss**, None; **D. W. Baker**, None.

1348

Improvement in Herpes Zoster Vaccination and Documentation for Rheumatoid Arthritis Patients Using Electronic Medical Record. Heena Sheth, Siamak Moghadam-Kia, Rayford June, Hilary J. Peterson, Davi Sa Leitao, Larry W. Moreland and Rohit Aggarwal. University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Despite increased risk of herpes zoster (HZ) in rheumatoid arthritis (RA) patients on immunosuppressive medication, American College of Rheumatology guidelines on HZ vaccination in RA and availability of HZ vaccine that decreases the risk of infection, the rates of vaccination against HZ in RA are very low. The aim of this study was to improve the rate of vaccination and e-record documentation of HZ vaccine in RA patients at high risk for HZ in rheumatology outpatient clinics.

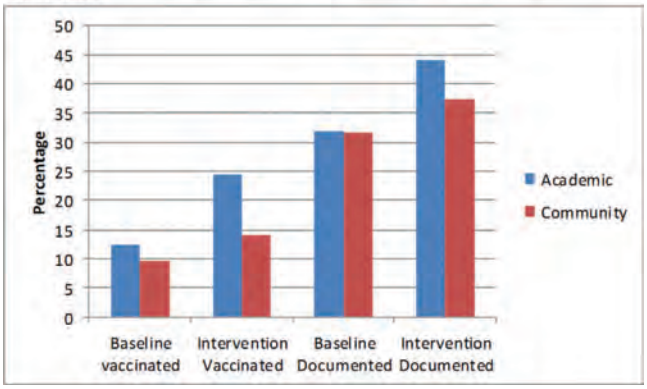
Methods: This study evaluated HZ vaccination and documentation for RA patients using pre- and post-intervention data. All RA patients aged ≥ 60 years were considered eligible for HZ vaccine if they were on or starting DMARDs or starting a biologic agent or steroid >20 mg

equivalent of prednisone >3 months. Clinical staff and physicians were educated in vaccine guidelines and planned intervention. Intervention was an electronic medical record (EMR)-based best practice alert (BPA), which is a user friendly system for ancillary staff and physician with integrated vaccine eligibility verification, documentation and vaccine order capability at the time of patient visit. The BPA appeared for eligible patients upon opening the EMR, prompting the medical assistant or nurse to document vaccination status and order HZ vaccine if the patient agreed. The physician subsequently reviewed and confirmed the order. BPA was passed to physician if a patient was unsure. The pre-intervention phase included all eligible RA patients who were seen at the Rheumatology Clinics between 7/1/2012 – 6/30/2013. The intervention phase data was collected for 3 months after implementation of BPA system. Reasons like patient refusal or physician deferral were also documented. The proportion of patients vaccinated and documented among all eligible patients pre- and post-intervention was compared using chi-square tests.

Results: 1846 RA patients were analyzed for pre-intervention (baseline) data (76% female, 90% white, mean age of 72 years) and 1267 patients for the post-intervention data (76% female, 82% white, mean age of 71 years). Overall vaccination rate increased from 9.9 to 15.7% p=0.001, and documentation rate increased from 30.1 to 44.8% p<0.0001. Academic clinic vaccination rate improved from 12.4 to 24.3% p=0.003, documentation rate from 32 to 44% p=0.04. Community clinic vaccination rate improved from 8.6 to 14.5% p=0.0008; and documentation rate increased from average 25.2 to 35.6% p=0.014 (Figure 1). There was 4.4% patient refusal while 15.7% patients had documented physician deferral. The process was automated using EMR and user-friendly interface for ordering and documentation of vaccination without much increase in physician burden.

Conclusion: EMR-based BPA at the time of patient encounter and physician education intervention resulted in significant increase in HZ vaccination and documentation rates in RA patients.

Figure 1. Rates of HZ vaccination and documentation in 2 academic and 10 community clinics before and after use of EMR-based BPA and education intervention.



Disclosure: H. Sheth, None; **S. Moghadam-Kia**, None; **R. June**, None; **H. J. Peterson**, None; **D. Sa Leitao**, None; **L. W. Moreland**, Pfizer Inc, 9; **R. Aggarwal**, Questcor, 2, Pfizer Inc, 2, NIEHS-NIH, 2, Questcor, 5, aTyr Pharma, 5.

1349

A Decision Support Tool to Improve Herpes Zoster Vaccination Rates Among Patients Starting Biologic Medications.

Sara Schoenfeld[1], Eli Miloslavsky[1], Weihong Yang[1], Naina Rastalsky[1], Mollie Carruthers[1], Zachary Wallace[1], Traci Powers[1], Marcy Bolster[2] and Deborah Collier[1]. [1]Massachusetts General Hospital, Boston, MA, [2]Massachusetts General Hospital/Harvard Medical School, Boston, MA.

Background/Purpose: Herpes zoster infection causes serious morbidity and mortality in immunocompromised patients. Vaccination reduces the risk of zoster infection by up to 40% among patients with autoimmune disease and is recommended for patients aged 60 or above before starting immunosuppressive treatment. We implemented an electronic medical record based zoster vaccine decision support tool to improve vaccination rates among patients prescribed but not yet started on biologic medications.

Methods: We incorporated a zoster vaccine screening tool into the mandatory prior authorization (PA) process required for prescribing biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs) across a multicenter rheumatology practice at a tertiary care academic medical center. The revised electronic PA form included a zoster section with decision support prompts to screen each patient's appropriateness for the vaccine and to facilitate referral for the vaccine.

Process and outcome measures were analyzed during a 9 month period. The process measure assessed whether physicians accurately completed the zoster section of the PA form. The outcome measure assessed whether patients actually received the zoster vaccine. As a comparison group we used zoster immunization data derived from chart reviews of 123 patients over age 60 prescribed biologic medications in the same rheumatology unit during the 12 month period before implementation of the zoster screening decision support tool.

Results: During the 9 month period following the intervention, 119 PA forms with the zoster section were filled out for patients starting a biologic medication. The form was filled out correctly in 114/119 cases (Figure 1a). Prior to implementation of the zoster section on the PA form, 86/123 patients over age 60 who were prescribed a biologic were eligible for the vaccine without a contraindication. Of these 86 patients, 25% received the vaccine (Figure 1b). After the intervention, 41 of 119 patients prescribed a biologic were age-appropriate for the zoster vaccine, of whom 29 had one of the pre-defined contraindications to receiving the vaccine. Of the 12 age-eligible patients without contraindications, 42% received the vaccine (Figure 1c).

Conclusion: Incorporating a zoster immunization decision support tool in an electronic PA form for biologic medications was a successful method of prompting physicians to screen patients requiring biologic DMARD therapy for the zoster vaccine. After the support tool was implemented, a greater percentage of age-appropriate patients without a contraindication received the vaccine. Vaccination rates could be further improved by addressing a number of barriers including cost and logistical vaccine administration hurdles as well as by considering zoster screening prior to initiating a nonbiologic DMARD or prednisone.

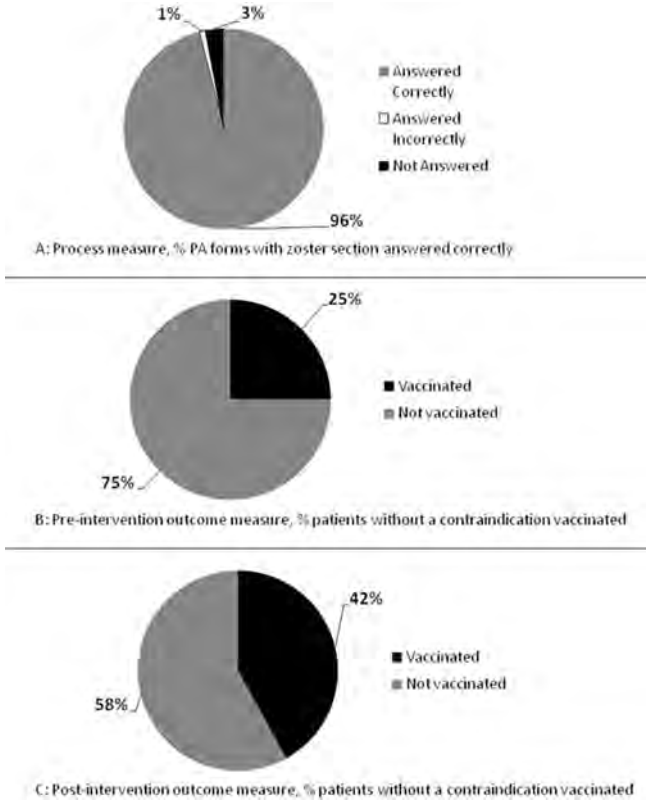


Figure 1. Zoster Screening Tool - Process and Outcome Measures

Disclosure: S. Schoenfeld, None; **E. Miloslavsky**, None; **W. Yang**, None; **N. Rastalsky**, None; **M. Carruthers**, None; **Z. Wallace**, None; **T. Powers**, None; **M. Bolster**, Johnson and Johnson, 1, Eli Lilly and Company, 2, ABIM Rheumatology Speciality Board, Chair, 6, ABIM Rheumatology Test Writing Committee, Chair, 6, ACR COTW, Chair, 6, ACR Board of Directors, 6, RRF Board of Directors, 6; **D. Collier**, None.

1350

Practice What You Preach? Suboptimal Guideline Adherence By Rheumatologists in Patients with Rheumatoid Arthritis. Nienke Lesuis[1], Ronald van Vollenhoven[2], Marlies Hulscher[3] and Alfons den Broeder[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]The Karolinska Institute, Stockholm, Sweden, [3]Radboud University Medical Centre, Nijmegen, Netherlands.

Background/Purpose: Tight control based treatment principles of rheumatoid arthritis (RA) are superior to usual care and therefore recommended in many (inter)national guidelines.[1–3] Unfortunately guideline adherence to these guidelines has often been shown to be suboptimal in clinical practice.[4,5] As this is mainly described in clinical trials and pre-defined cohorts, we aim to assess RA guideline adherence in daily practice. In addition, we will also explore potential determinants of guideline adherence.

Methods: In this retrospective, single-center observational study, all adult RA patients with a first outpatient clinic visit at the Sint Maartenskliniek (SMK) between September 2009 and March 2011 were included, either new RA patients or second opinions. Data from all visits in the first year of treatment were collected by manual chart revision. Afterwards, for every single visit guideline adherence to 7 indicators was assessed. The indicators were based on evidence-based national and local RA guideline recommendations (issued in 2009) and concerned diagnostic, therapeutic and follow-up decisions. To assess potential determinants of guideline adherence, all rheumatologists working at the SMK in March 2011 received a set of questionnaires about personality traits, propensity towards cognitive bias, thinking styles and knowledge about guideline content. Furthermore, demographic and disease characteristics of the patients were collected during the chart revision.

Results: A total of 994 patient visits for 137 RA patients were reviewed (mean age 59 years ± 14.1; 67% female; disease duration 4.9 years ± 8.5; 85% rheumatoid factor and/or anti-CCP positive). Guideline adherence varied between 21 and 72%, with referral to the physician assistant as worst scoring indicator and referral to a specialized nurse as best scoring one (see table 1). Both are routine measures implemented at our centre in order to facilitate frequent systematic follow-up. Patients and physician characteristics were analysed for relations with guideline adherence, preliminary analyses found two associations. In patients never seen by a rheumatologist before intervals between visits were more often correct and X-rays were more frequently made if more treatment options were available.

Table 1: Guideline adherence percentages

Indicator		Adherence percentages *[lowest – highest score rheumatologists]*
	Diagnostics	
1)	X-rays of hands, feet and thorax within the first three visits	54.7 [29.0–100.0]
	Treatment	
2)	Therapy change in case of moderate to high disease activity	65.6 [46.7–84.4]
3)	Prescription of conventional and biological DMARDs in agreement with the local preferential sequence	23 [0–50.0]
	Follow-up and shared care	
4)	Referral to a specialized nurse within the first three visits	71.5 [43.0–100.0]
5)	Referral to a physician assistant (PA) or nurse practitioner (NP) within the first year of treatment	21.2 [0–50.0]
6)	Regular outpatient clinic visits combined with a nurse visit for DAS28 assessment (clinimetric center)	35.5 [9.3–70.5]
7)	Correct intervals between regular outpatient clinic visits	21.3 [11.1–44.3]

Conclusion: Guideline adherence to the seven recommendations varied between 21 and 72%. This indicates that there is still room for improvement with regard to guideline adherence. Guideline adherence seems only marginally related to factors on patient- or clinician level. Therefore, adherence is more likely to be guided by a complex interplay of facilitators and barriers.

References:

[1]van Riel *et al.* Van Zuiden Communications 2009. [2]Singh *et al.* Arthritis Care Res 2012. [3]Peters *et al.* Ann Rheum Dis 2010. [4]van Hulst *et al.* Rheumatology 2010. [5]Vermeer *et al.* Arthritis Res Ther 2012.

Disclosure: N. Lesuis, None; **R. van Vollenhoven**, None; **M. Hulscher**, None; **A. den Broeder**, None.

1351

Assessment of ACR Endorsed Quality Indicators in Rheumatoid Arthritis Patients – a Quality Improvement Initiative. Puneet Bajaj, Erik Anderson, Siddharth Raghavan, Asha Patnaik and Heidi Ropprelt. Stony Brook University Medical Center, East Setauket, NY.

Background/Purpose: Quality assessments are being increasingly used for quality improvement, accountability, and performance based incentives. The current research regarding quality of care provided to rheumatoid arthritis (RA) patients, although limited, does identify gaps and variations in several domains of care.

The American College of Rheumatology (ACR) has endorsed seven RA quality indicators (QI), which we used to access the quality of care provided to RA patients at our institution.

Methods: A retrospective chart review was performed on patients identified by the ICD9 code for RA (714.0) entered by a Rheumatologist between 1/1/09 to 8/31/13. We excluded patients whose records were not available and those without a definitive diagnosis of RA.

Our clinic began consistently applying the Multi-Dimensional Health Assessment Questionnaire for assessment of disease activity and functional status in June 2009; therefore, we only included patients seen in our clinic between 1/1/2010 and 12/31/2012. We adhered to specifications for inclusion and exclusion criteria endorsed by the ACR regarding the seven RA QI. In addition, we excluded patients being considered for initial DMARD therapy or undergoing management for worsening disease, who were lost to follow-up. P-values were calculated using Chi-Squared Test.

Results: A total of 356 patients were included. 87.9% (N=58) of eligible patients had documentation of TB screening. Measurement of disease activity and functional status rose significantly each year from 2010 to 2012 (72.8 to 94%, $p < 0.0001$ and 70.8% to 93.3%, $p < 0.0001$ respectively). None of the patients had documentation of disease prognosis. Documentation of a glucocorticoid management plan was done in 60% (N=5) of the patients who required it. 48.9% (N=174) of patients either did not take glucocorticoids or received glucocorticoids but did not meet the criteria to require a management plan. 98.8% (N=328) of eligible patients were treated with a DMARD. 61% (N=215) of patients on a DMARD required intervention for increased disease activity, of which 100% received it.

Conclusion: The majority of patients had documentation of TB screening. Our assessment of disease activity and functional status improved significantly over time, likely due to increasing provider awareness of quality metrics. Although most patients were stratified and treated as per disease severity, their prognosis was not documented. Only a small percentage of our patients met the criteria requiring a glucocorticoid management plan, thus limiting our assessment of this quality indicator. Our clinic had excellent adherence to treatment with DMARDs, as well as managing worsening disease.

A limitation of our study was a lack of electronic medical records (EMR), which may have negatively impacted data collection. As a result, actual rates of adherence may have been higher than those measured.

Better adherence to guidelines and documentation is required, especially with regards to assessment and classification of disease prognosis, which could be achieved through provider education. In addition, an automated EMR reminder to obtain TB screening upon ordering a biologic treatment may further improve documentation of this QI.

Disclosure: P. Bajaj, None; **E. Anderson**, None; **S. Raghavan**, None; **A. Patnaik**, None; **H. Roppelt**, None.

1352

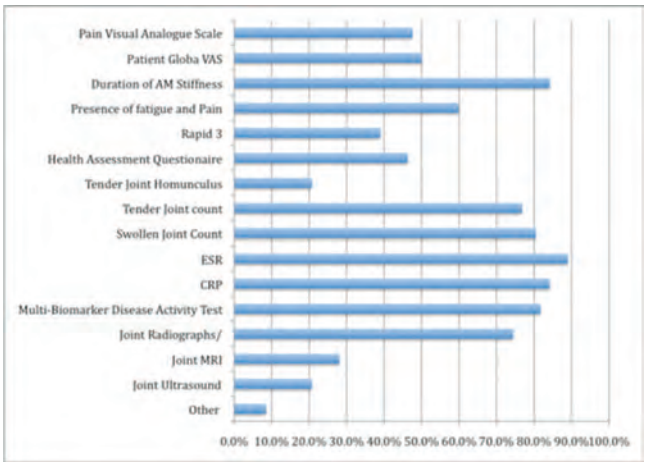
Rheumatoid Arthritis (RA) Disease Activity Assessment and Population Management Processes Used By Clinician Rheumatologists. Anne Winkler[1], James Mossell[2], Edmund MacLaughlin[3], Drew Johnson[4] and J. Timothy Harrington[5]. [1]Winkler Medical Practice LLC, Springfield, MO, [2]Arthritis & Osteo Center of South GA, Tifton, GA, [3]Edmund L. MacLaughlin LLC, Cambridge, MD, [4]Crescendo Bioscience, Inc., South San Francisco, CA, [5]Joiner Associates LLC, Madison, WI.

Background/Purpose: Timely disease activity assessment (DAA) and population management (PM) are known to reduce the burdens of chronic diseases**,** including RA. Currently, the measures and processes being used by clinician rheumatologists for managing RA are poorly documented. Our purpose is to survey DAA and PM processes across a cohort of clinician rheumatologists as a starting point for improving RA management and outcomes in these practices.

Methods: The Rheumatoid Arthritis Practice Performance (RAPP) Project is a voluntary collaboration of US clinician rheumatologists whose goal is to improve RA management, and to document our performance. Most invited to participate are multi-biomarker disease activity test users. To date, 97 physicians from 91 practices have attended quality improvement project kick-off meetings, and each has completed a baseline survey regarding their DAA and PM processes. Their aggregated responses are reported here.

Results: Participants represent all regions of the United States and differing practice environments: solo (33), single specialty (35), and multi-specialty group/integrated system practices (20). RA patients managed per rheumatologist derived from practice billing systems vary from 112 to 1800, self-reported patient visits/day from 12 to 80, and new patients/week from 0 to 32. Forty-six % have mid-level providers sharing in RA management, 91% have an electronic medical record (38 different brands), and 35% have any RA disease registry capability. DAAs used are highly variable, and often multiple. (Table 1) Composite DAA use varies from none (25%), to RAPID3 (39%), DAS28 (18%), CDAI (20%) and SDAI (2%). Disease activity documentation in medical records includes a non-numeric impression (active/controlled)(63%), 0–10 Physician Global (23%), composite score (11%), or other (3%).

Conclusion: 1. Practices vary in RA population size, office work flows, staffing, and DAAs utilized. 2. Use of composite disease activity measures is limited, with the majority documenting a binary, active/controlled clinical impression. 3. PM processes (analytic disease registries and team management) are used infrequently. 4. These results indicate opportunities to improve practice performance and RA disease outcomes in rheumatology practices.



Disclosure: A. Winkler, Novartis Pharmaceutical Corporation, 2, Janssen Pharmaceutica Product, L.P., 2, Pfizer Inc, 2, Janssen Pharmaceutica Product, L.P., 8, Crescendo Bioscience, 8, Abbott Immunology Pharmaceuticals, 8, Genentech and Biogen IDEC Inc., 8, Bristol-Myers Squibb, 8, GlaxoSmithKline, 8, Pfizer Inc, 8, Crescendo Bioscience, 5; **J. Mossell**, Crescendo Bioscience, 5, Genentech and Biogen IDEC Inc., 8, Amgen, 8, Abboie, 8, Iroko, 8, Takeda, 8, Crescendo Bioscience, 8, Paizer, 8; **E. MacLaughlin**, Crescendo Bioscience, 5; **D. Johnson**, Crescendo Bioscience, Inc., 3; **J. T. Harrington**, Joiner Associates LLC, Crescendo Bioscience, 5, Pfizer Inc, 5.

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Integrating Collection of Rheumatoid Arthritis Disease Activity and Physical Function Scores into an Academic Rheumatology Practice to Improve Quality of Care. Vladimir Chernitskiy[1], Andre DeVito[2], Naama Neeman[2], Niraj Sehgal[2], Jinoos Yazdany[1] and Andrew J. Gross[1]. [1]University of California, San Francisco, San Francisco, CA, [2]University of California San Francisco, San Francisco, CA.

Background/Purpose: The default design of our institutions' electronic health record (EHR)(Epic Systems) was not optimally structured to systematically collect quality metrics for rheumatic disease management such as disease activity and physical function measures. Our goal was to implement a Quality Improvement (QI) program for care of patients with RA that could easily be incorporated into routine clinical practice. By optimizing EHR technology to provide relevant and timely data analysis reports, we hypothesized that we would create reproducible, actionable population management solutions for providers caring for patients with RA.

Methods: With the assistance of information technology (IT) technicians at our institution, we created "documentation flowsheets" in our EHR with the following fields: Patient Global Activity score, Provider Global Activity Score, Tender Joint count, Swollen Joint count, and ESR. This allowed the automatic calculation of Clinical Disease Activity Index (CDAI) as well as DAS28-ESR. Providers and clinic staff collaborated to enter data into flowsheets for each RA patient visit. Provider could review scores in real time for individual patients and track scores over time in a flowsheet. Data was collected and analyzed on a monthly basis for individual providers as well as the entire practice and was disseminated to the Rheumatology faculty with full transparency.

Results: Over the first six months of data collection for this project we observed continuous improvement in all RA documentation metrics. There was steady improvement in documentation of disease activity measures. CDAI scores were documented in 80.9% of visits 6 months into this project, compared to 56.5% of visits at study initiation. Patient global assessment was documented in 85.4% of visits vs. 68.5% at baseline. DAS28-ESR scores were documented at a lower frequency, 40.4%, due to lack of availability of ESR results to physicians at the time of the patient visit, but rates improved compared to the start of the study (21.7%).

In the final month of data collection, among RA patients with documented disease activity, 54.1% had CDAI scores of $\leq$10.0 indicating low level of disease or remission, where as 19.4% had high levels of disease activity (CDAI $>$22). We could not determine if there was an overall improvement in RA disease activity level in our patients over the six months of data collection due to large variation in distributions of patient disease activity from month to month.

Conclusion: Effective implementation of an RA QI Program is challenging but achievable. In addition to technical tools and having the right personnel involved (e.g. physician champions, IT programmers and report writers, analysts and clinic manager and clinic support staff), successful implementation requires strong buy-in from providers. This can be accelerated by objective documentation and analysis to identify areas needing improvement, and then providing this feedback to providers. In the future we plan to assess whether systematic documentation of disease activity can lead to improved patient outcomes.

Disclosure: V. Chernitskiy, None; **A. DeVito**, None; **N. Neeman**, None; **N. Sehgal**, None; **J. Yazdany**, None; **A. J. Gross**, None.

1354

Improving the Measurement of Disease Activity for Patients with Rheumatoid Arthritis: Validation of an Electronic Version of the Routine Assessment of Patient Index Data (RAPID 3). Ruthie May Chua[1], John Mecchella[2] and Alicia Zbehlik[3]. [1]Dartmouth-Hitchcock Medical Center, Lebanon, NH, [2]Geisel School of Medicine at Dartmouth, Hanover, NH, [3]The Dartmouth Centers for Health and Aging, The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH.

Background/Purpose: Quantitative measures of disease activity are associated with improved outcomes for patients with rheumatoid arthritis (RA), but many rheumatologists continue to rely on non-quantitative assessments. The Dartmouth-Hitchcock Medical Center (DHMC) electronic health record (EHR) does not currently support patient-reported outcome measures (PROMs) to assess RA activity that can be searched and aggregated for patient care, research, or system-based quality improvement. The Routine Assessment of Patient Index Data 3 (RAPID 3) is a validated PROM which evaluates physical function, pain and global health. To integrate the RAPID 3 into routine clinical practice, an electronic version was built to allow patients to complete the RAPID3 through the EHR. Because we could not replicate the exact visual presentation of the RAPID 3 in the EHR, the aim of this study was to demonstrate equivalence between the electronic RAPID 3 and the validated paper version.

Methods: From March to June 2014, patients in the Rheumatology clinic age $\geq$ 18 years with seropositive or seronegative RA were identified. All participants were active users of the web-based patient portal of the EHR. The electronic RAPID 3 was sent via the patient portal to each participant 1 week prior to their appointment. Patients were notified electronically and by phone to complete the survey. The RAPID 3 paper version was administered on the day of their clinic visit. The first 50 patients to complete both versions were included. The EHR automatically calculates and interprets the disease activity score (scale 0–30: $>$12 high; 6.1–12 moderate; and 3.1–6 low; $\leq$3 remission). Paper surveys were scored manually. A paired *t*-test was used to compare samples with p values of $\leq$0.05 considered significant. The study was exempt from review by the Committee for the Protection of Human Subjects at Dartmouth College.

Results: Of the 50 patients included in the study, 33 (66%) were female and the average age was 58.8 years ($\pm$12.27). An average of 4.2

days passed between the assessments. The mean total RAPID 3 scores for the paper and EHR versions were 9.57(SD±6.45) and 9.75 (SD±6.46) respectively. There were no statistically significant differences between the mean total RAPID3 of the paper and electronic versions (p=0.46), or each component score (table 1).

Table 1. Comparison of paper and EHR versions of RAPID3.

	Mean (±Standard Deviation)		paired *t*-test p value
	Paper	EHR	
Physical Function	1.87 (1.91)	1.85 (1.83)	0.85
Dress yourself	0.40 (0.64)	0.42 (0.67)	0.36
Get in and out of bed	0.46 (0.61)	0.34 (0.59)	0.41
Lift full cup or glass to mouth	0.20 (0.53)	0.18 (0.56)	0.37
Walking outdoors on flat ground	0.40 (0.67)	0.40 (0.67)	0.50
Wash and dry your entire body	0.42 (0.64)	0.48 (0.68)	0.36
Bend down to pick up clothing from floor	0.48 (0.68)	0.50 (0.68)	0.50
Turn regular faucet on and off	0.20 (0.53)	0.20 (0.53)	0.50
Get in and out of a car, bus, train or airplane	0.54 (0.65)	0.50 (0.58)	0.23
Walk two miles or three kilometers, if you wish	1.20 (1.18)	1.20 (1.20)	0.46
Participate in recreational activities and sports	1.28 (1.03)	1.34 (1.08)	0.37
Pain Score	3.86 (2.64)	4.03 (2.65)	0.27
Patient Global Assessment	3.84 (2.75)	3.87 (2.80)	0.65
Total	**9.57 (6.45)**	**9.75 (6.46)**	**0.46**

Conclusion: There was no significant difference in responses between the electronic and paper versions. The electronic RAPID3 (built in an Epic system v2010) can and should be included in the care of all RA patients without interrupting clinic flow, and will facilitate research and systems-based practice improvement.

Disclosure: R. M. Chua, None; **J. Mecchella**, None; **A. Zbehlik**, None.

1355

Population Management of Rheumatoid Arthritis (RA) in Rheumatology Practices: A Quality Improvement Project. David Sikes[1], Gary Crump[2], Kathleen Thomas[3], Alex Bangs[4] and J. Timothy Harrington[5]. [1]Florida Medical Clinic PA, Zephyrhills, FL, [2]Rheumatology Associates - Louisville, Louisville, KY, [3]Community Rheumatology, Noblesville, IN, [4]Crescendo Bioscience, Inc, South San Francisco, CA, [5]Joiner Associates LLC, Madison, WI.

Background/Purpose: Population management (PM) is required for reducing the burdens of chronic diseases, including RA. PM depends on standardizing disease activity assessment (DAA) and coordinating care for the entire disease population, as well as for individuals within this context. Our purpose is to implement PM for RA within rheumatology practices by optimizing DAA to define controlled, low, moderate, and high disease activity cohorts; to focus resources on those patients with the highest needs; and to document our delivery of care and outcomes.

Methods: The Rheumatoid Arthritis Practice Performance (RAPP) Project is a rapidly growing voluntary collaboration of U.S. clinician rheumatologists (current N = 94) who manage more than 50,000 RA patients in total, based on ICD-9 diagnoses. Patients are being enrolled in an analytic RA disease population registry from practice billing records, and RAPP physicians are reporting their preferred disease activity measures, including CDAI, RAPID3, DAS28, SDAI, Physician Global Assessment, and/or a multi biomarker disease activity score. Monthly Population Reports are provided that include 1) patients registered (N) and % ever assessed, 2) % with controlled-low DAA within 7 months, 3) % with moderate-high DAA within 4 months, and 4) %'s with controlled, low, moderate, and high disease activity. Working lists are also provided of patients lacking timely DAA (Report numbers 1, 2, and 3), and those with high disease activity (number 4). Practices are managing their DAA care gaps and high disease activity cohorts, and implementing these population management processes through clinical process improvement projects.

Results: Aggregated data from the baseline Population Reports for the first 26 fully enrolled registries are included in this abstract using multi-biomarker assay results. Other encounter-based disease activity measures are being added currently. The total patients enrolled = 16,979 (Median = 594/physician). At least one DAA is documented for 58% of the total (Median/physician = 69%). Forty-seven % of the controlled-low disease activity cohort has been assessed within 7 months, as has 29% of the moderate-high disease activity cohort within 4 months. The population disease activity distribution includes 21% with controlled-low, 39% with moderate, and 40% with high RA disease activity.

Conclusion: 1. These PM capabilities identify care gaps in DAA and disease control that were not identified previously. 2. Timely DAA and tracking of population measures are known to support improved care and disease activity outcomes.

Disclosure: D. Sikes, Crescendo Bioscience, 5, Abbvie, 8; **G. Crump**, Caescendo Bioscience, 5, Abbvie, 8, Amgen, 8, BMS, 8, Celgene, 8, Janssen Pharmaceutica Product, L.P., 8, Takeda, 8, UCB, 8; **K. Thomas**, Crescendo Bioscience, 5, Takeda, 8, Crescendo Bioscience, 8, Abbvie, 8; **A. Bangs**, Crescendo Bioscience, Inc, 1, Crescendo Bioscience, Inc, 3; **J. T. Harrington**, Joiner Associates LLC, Crescendo Bioscience, 5, Pfizer Inc, 5.

1356

Collaboration Between a Third Party Payer and Community Rheumatologists to Create a Clinical Pathway for the Treatment of Rheumatoid Arthritis to Assure Proper Use of Biologics and Quality of Care. Alan K. Matsumoto[1], Herbert S. B. Baraf[1], Bruce Feinberg[2], Phil Miller[3] and Daniel Winn[3]. [1]Arthritis & Rheumatism Associates, PC, Wheaton, MD, [2]Cardinal Health, Dublin, OH, [3]CareFirst BlueCross, Baltimore, MD.

Background/Purpose: Use of biologic agents for the treatment of rheumatoid arthritis continues to grow rapidly, with the cost of these agents putting a significant strain on health care budgets. Although rheumatologists and third party payers share the goal of ensuring quality of care for RA patients, rheumatologists fear potential limitation of access to biologics due to cost while third party payers are concerned about the rising expenses associated with the use of these agents. New models of healthcare delivery stress the relationship of cost to quality and improved outcomes. This results in adversarial and inefficient procedures between physician and insurer. Treatment pathways have been suggested as a means to address these issues.

Methods: At the request of CareFirst/Blue Cross and Cardinal Health, we organized a committee of 12 community based rheumatologists to create a treatment pathway for RA patients based on published evidence and community standard of care. CareFirst did not participate in the specific details of the pathway in accordance of the belief that structure should be driven by community standards. Practices that reached 80 % compliance with the program were offered increased reimbursements to offset the cost of data collection and program compliance. Compliance was judged as follows. All patients insured by CareFirst with the RA ICD-9 code of 714.0 were required to be entered into the pathway. Patient visits were required at a minimum of every 3–6 month intervals with a Clinical Disease Activity Index (CDAI) measure recorded at each visit. The use of a non -biologic DMARD (methotrexate unless contraindicated) was mandated for 3 months prior to initiation of first biologic therapy. Indication and dosing of biologics were to be within the package insert guidelines but no specific biologic agent was preferred by the pathway. Site of infusion was required to be non-hospital based. Patients were not required to change biologics for ongoing disease activity, but biologics could not be initiated, switched or increased if the patient was in CDAI remission. Data was captured using a real time iPad based tool.

Results: Over the first 12 months, 80 physicians from 37 practices in the mid Atlantic were recruited and 1800 patients were entered into the pathway. Over 90% of patients were on compliant pathways and 74 % of practices reached compliance. Over 70% of patients were in remission or low disease activity by CDAI measurement. Biologic switches were infrequent. Within the program, site of infusion was more likely non-hospital based.

Conclusion: To our knowledge this is the first collaboration between rheumatologists and a third party payer to create a Rheumatoid Arthritis treatment pathway to assure proper biologic use and assess outcomes. We believe this is a powerful model to assess and improve cost and effectiveness of treatment strategies for rheumatoid arthritis.

Disclosure: A. K. Matsumoto, Cardinal Health, 5; **H. S. B. Baraf**, Cardinal Health, 5; **B. Feinberg**, Cardinal Health, 3; **P. Miller**, CareFirst BlueCross, 3; **D. Winn**, CareFirst BlueCross, 3.

1357

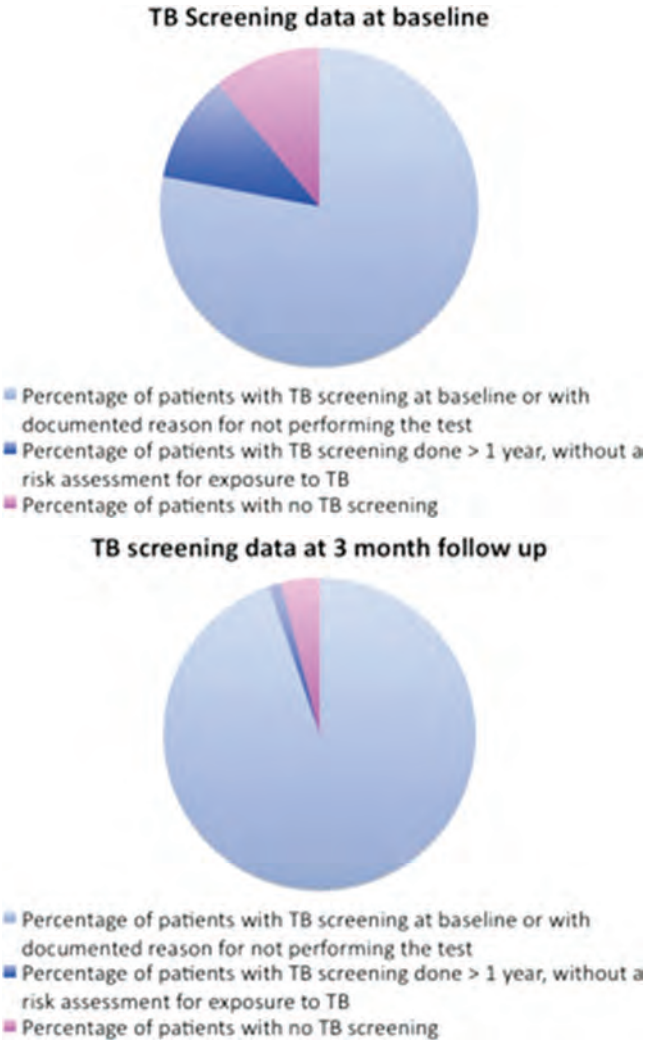
Improving Compliance for Tuberculosis Screening for Patients on Biologics in Rheumatology Clinics. Shraddha Jatwani, Rajani Rudrangi, Karan Jatwani, Vijaya Murthy, Rashmi Maganti, Rex McCallum and Emilio Gonzarlez. University of Texas Medical Branch, Galveston, TX.

Background/Purpose: Biologics are used commonly for patient with autoimmune diseases. These agents have ensured important efficacy advantages in the treatment of inflammatory rheumatic diseases. All biologics have been associated with risk of infections. The risk of serious infections has been reported to increase 1–2–1.8 times for patients on tumor necrosis factor inhibitors (TNFi) compared to patients on conventional agents. The risk of tuberculosis (TB) has been reported to increase manifold, up to 12 to 35 times. American College of Rheumatology (ACR) recommends that all patients on biologics should be screened for risk of latent TB infection (LTBI) either with tuberculin skin test (TST) or interferon-release assays (IGRAs), regardless of risk factors for LTBI.

With this Quality improvement exercise, we aim to improve compliance with TB screening in patients receiving biologics to a target of 90% over 3 months.

Methods: We generated an EMR query to review pre-intervention screening rates of patients on biologics from 3 university clinics over 6 months (July-December 2013). A list of 104 such patients was created. Chart review for these 104 patients was performed to determine adequacy of TB screening defined by presence of a documented TB screening, either PPD or Quantiferon gold TB test, within 1 year of last clinic visit. At baseline, TB screening had been performed in 78% of patients. To improve compliance, as an intervention, we conducted conferences with providers to educate them on the guidelines and our current performance. Nurses were educated through emails. Monthly email follow-up reminders were also sent to the providers and nurses. At 3 months a follow up chart review was conducted for 152 patients in the same three clinics, who had received prescriptions of biologics between March-June 2014 to determine effect of provider education on compliance with TB screening.

Results: Educational conferences and emails were well received by providers and nurses. At follow up after 3 months, the target was achieved in all clinics, with compliance rates for TB screening at 94.7% across board.



Conclusion: Developing methods to improve quality will become even more relevant in future. In this study, we demonstrated provider education makes a difference in implementation of guidelines for TB screening in patients receiving biologics. This was achieved in relatively short period of time. A similar strategy can be implemented in other subspecialty clinics like dermatology and gastroenterology where biologics are also being used.

Disclosure: S. Jatwani, None; **R. Rudrangi**, None; **K. Jatwani**, None; **V. Murthy**, None; **R. Maganti**, None; **R. McCallum**, None; **E. Gonzalez**, None.

1358

A Systematic Analysis of the Safety of Prescribing Anti-Rheumatic Immunosuppressive and Biologic Drugs in Pregnant Women.

Sonia Panchal[1], Julia Flint[2], Maud van de Venne[3], Madeline Piper[4], Alice Hurrel[2], Joel Cunningham[2], Mary Gayed[5], Karen Schreiber[6], Subha Anthanari[7], Mohamed Nisar[7], David Williams[2], Munther Khamashta[8], Caroline Gordon[5] and Ian Giles[2]. [1]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom, [2]University College London, London, United Kingdom, [3]North Bristol NHS Trust, Bristol, United Kingdom, [4]Ysbyty Ystrad Fawr, Aneurin Bevan Health Board Wales, Wales, United Kingdom, [5]The Medical School, University of Birmingham, Birmingham, United Kingdom, [6]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [7]Burton Hospitals NHS Foundation Trust, Burton-upon-Trent, United Kingdom, [8]Guy's and St Thomas' NSH Foundation Trust, London, United Kingdom.

Background/Purpose: The use of anti-rheumatic drugs in pregnancy is often complicated by concerns over their potential for adverse effects. Given that rheumatic diseases often affect women of childbearing age and may flare during pregnancy, the safety (or otherwise) of anti-rheumatic drugs and immunosuppressant's are of particular importance. Practice has relied on information based mainly on experimental and animal studies. Human data is limited to inadvertent exposure described in case reports/series and population registries. Previous systematic reviews have identified risks with various anti-rheumatic drugs and biologics. This systematic review is an update on the consensus papers on anti-rheumatic drugs, biological agents and reproduction published in 2006/8.

Methods: A systematic search from 2006–2013 of PubMed, Embase, Cochrane, Lactmed and the UK Tetarology Information Services was carried out using MESH and free terms for drug, rheumatic disease and pregnancy. Review articles and non-English language papers were excluded.

Results: The search strategy identified 352 papers with original pregnancy outcome data.

Table 1. illustrates pregnancy outcomes for the immunosuppressant and biologic therapies.

Table 1 Pregnancy outcomes for rheumatological drugs

Drug	No. of pregnancies exposed to drug	Live births related to exposed drug (min)*	Spontaneous 1st trimester loss (min)	Spontaneous 2nd/3rd trimester loss (min)	Major Malformations (min)§	Minor malformations (min)§	Level of evidence
Prednisolone	771	565	23	35	39	3	C
Methotrexate	12	10	2	0	4	5	D
Leflunomide	77	78	0	0	7	63#	D
Sulphasalazine	12	12	1	0	2	0	D
Azathioprine	320	269	32	7	12	5	C
HCQ	212	230	15	0	29	7	B
MMF	17	18	0	0	19	5	D
Ciclosporin	136	135	1	1	6	0	D
Cyclophosphamide	10	7	2	1	1	0	D
Adalimumab	122	110	6	1	5	1	D
Etanercept	19	16	1	1	1	0	D
Infliximab	130	120	11	2	1	2	D
Group aTNFi$^{\Delta}$	215	160	39	5	1	4	D
Abatacept	3	1	1	0	0	0	D
Certolizumab	10	12	0	0	0	0	D

$^{\Delta}$Combination antiTNFi (infliximab, etanercept, adalimumab, certolizumab)*Includes twin pregnancies. #No increased risk of minor malformations compared to control group §Major & minor malformations meet the EUROCAT criteria for congenital anomalies

Conclusion: Evidence from this systematic review supports the compatibility of hydroxychloroquine, azathioprine, sulphasalazine and steroids in pregnancy. Increasing evidence of compatibility was found from pregnancies exposed (mostly at conception or during the first trimester) to anti-TNF alpha drugs that do not show an appreciable increase in the number of spontaneous

miscarriages and congenital malformations. Further registry data is required for biologic drugs, before the safe use of these drugs can be advocated throughout pregnancy.

Disclosure: S. Panchal, None; **J. Flint**, None; **M. van de Venne**, None; **M. Piper**, None; **A. Hurrel**, None; **J. Cunningham**, None; **M. Gayed**, None; **K. Schreiber**, None; **S. Anthanari**, None; **M. Nisar**, None; **D. Williams**, None; **M. Khamashta**, None; **C. Gordon**, None; **I. Giles**, None.

1359

Care of Women with Rheumatological Conditions during Family Planning and Pregnancy. Megan E. B. Clowse[1], Munther Khamashta[2], Daphnee S. Pushparajah[3] and Eliza Chakravarty[4]. [1]Duke University Medical Center, Durham, NC, [2]The Rayne Institute, London, United Kingdom, [3]UCB Pharma, Brussels, Belgium, [4]OMRF, Oklahoma City, OK.

Background/Purpose: Rheumatological diseases often affect women of reproductive age and can impact pregnancy outcomes. There is a need to understand how patients (pts) are managed by their rheumatologists. We investigate the treatment pathway and care of women with rheumatological conditions who become pregnant.

Methods: Two online surveys, one in rheumatologists and one in pts, were undertaken. Surveys were conducted in the US, UK, Germany and Mexico. Rheumatologists were questioned on the last three pts who they have consulted whilst being pregnant or considering becoming pregnant. Rheumatologists were questioned on pts with rheumatoid arthritis (RA) and lupus. Pt survey included women with RA who had been pregnant in the past 2 years. Pts were questioned on their interactions with rheumatologists and obstetrics/gynaecology physicians (OBGYN).

Results: 30 rheumatologists completed the physician survey. 57 RA pts completed the pt survey. Rheumatologists were aware of the pt's intention to become pregnant in 70% of pts. When planning their pregnancy 44% of pts consulted with their rheumatologist and 51% with their OBGYN. On learning they were pregnant 33% of pts consulted with their rheumatologist and 61% with their OBGYN. For rheumatologists the majority of initial visits occurred prior to pregnancy (70%). During pregnancy rheumatologists saw 43% of pts once a month or more, 42% every trimester and 14% only once during pregnancy. 83% of pts reported that rheumatologists were very influential on how they managed their pregnancy. For OBGYN, this figure was 87%. The majority of pts rated the level of information reliability on managing disease from both rheumatologists and OBGYNs as very reliable. A treatment plan related to management of RA or pregnancy was initiated by rheumatologists for 56% of pts. 51% of pts reported they had a treatment plan in place prior to pregnancy. 60% of rheumatologists made treatment changes in anticipation of or during pregnancy. When considering treatment switches during pregnancy, rheumatologists increased steroid use and decreased biologic use (Table). For rheumatologists, the most common reason for switch was the pt requesting a change due to medication concerns (43%).

Conclusion: The involvement of rheumatologists in the management of women with rheumatological conditions who are planning to become or are pregnant is high, and they have substantial influence on how pts manage their pregnancy. The patients had a high level of interaction with both rheumatologists and OBGYN throughout the journey. This emphasizes the importance of cross-collaborative care and the sharing of information between specialists involved in the management of women with rheumatological conditions during family planning and pregnancy.

Table: Treatment switches in pregnant women

	Rheumatologists (N=30)	
	Before Switch	**After Switch**
Steroids	35%	43%
DMARDs	76%	35%
No treatment	0%	24%
NSAIDs	33%	13%
Other treatment	0%	13%
Anti-TNF biologic	28%	0%
Non-anti-TNF biologic	7%	2%

Response to question: Thinking about your last three patients who have consulted you whilst being pregnant or considering becoming pregnant, what treatment change did you make during pregnancy? Please indicate the product before and after the switch. If you stopped the treatment without switching the patient to another product, you don't need to indicate a product in the "after switch" column.

Disclosure: M. E. B. Clowse, UCB Pharma, 5; **M. Khamashta**, INOVA diagnostics,AstraZeneca,Medimmune,UCB, GSK, 5; **D. S. Pushparajah**, UCB Pharma, 3; **E. Chakravarty**, UCB, 5.

1360

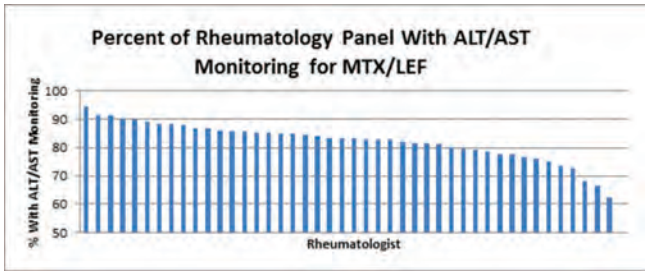
Monitoring Methotrexate and Leflunomide Treatment for Liver Toxicity: the Kaiser Permanente Experience. Robert Goldfien[1] and Lisa Herrinton[2]. [1]Kaiser Permanente, Richmond, CA, [2]Kaiser Permanente, Oakland, CA.

Background/Purpose: Methotrexate (MTX) and Leflunomide (LEF) are widely prescribed to treat rheumatologic and other diseases. Each has the potential to cause liver injury in some patients. Current guidelines recommend regular monitoring of either ALT or AST every 2–3 months even in patients on a stable, long-term dose. Adherence to monitoring guidelines has not been reported for a large, community-based population. As part of a quality improvement project, we assessed adherence to monitoring guidelines as well as practices used by rheumatologists to assure monitoring.

Methods: First, we queried the clinical databases of Kaiser Permanente Northern California to identify all patients who had received 2 or more prescriptions of MTX or LEF, with at least 1 prescription dispensed in the previous 6 months. Adherence to guidelines was defined as having a result for ALT or AST in the 90 days prior to data collection. Second, to assess knowledge of guidelines, as well as clinical prescribing and monitoring practices, we surveyed 40 rheumatologists.

Results: We identified 8,276 Internal Medicine patients on MTX/LEF. Among the rheumatologists, the rate of adherence ranged from 62.3 to 94.6% (weighted mean, 82.3%) (Figure). Survey of the rheumatologists (87.5% response) revealed that all were knowledgeable of guidelines, all prescribed ≤3 month supply of medication, 94% used standing laboratory orders, and 71% did not refill prescriptions in patients without an ALT or AST in the prior 3 months.

Conclusion: Despite use of an electronic health record, knowledge of monitoring guidelines, and efforts to assure adherence, we observed significant variation in monitoring liver toxicity in a community rheumatology practice. Our results underscore the need for more effective tools and workflows that integrate prescribing with monitoring. Such solutions, implemented at the system level, would have wide applicability for drugs used across a range of diseases and specialty areas.



Disclosure: R. Goldfien, None; **L. Herrinton**, Medimmune, 2.

1361

Rheumatologists' Attitudes on Cardiovascular Risk and Lipid Screening in Patients with Rheumatoid Arthritis at an Academic Medical Center. Ashwini Komarla and Alexis Ogrdie. University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Cardiovascular (CV) disease is a major cause of morbidity and mortality in the rheumatoid arthritis (RA) population. Thus, the recognition and management of cardiovascular risk factors in patients with RA is especially important. Despite increased awareness of this risk, recent data suggests that adherence to both primary and secondary prevention strategies is low in the RA population compared to other high risk groups (e.g. diabetics). The objective of this study was to assess rheumatologists' perceptions of screening for and treating hyperlipidemia (HLD) and CV risk factors in patients with RA to inform the development of quality improvement initiatives.

Methods: In this qualitative study, all University of Pennsylvania rheumatologists were contacted with an email link to an online survey. The survey, administered via REDCap, included 15 questions assessing attitudes towards lipid screening and CV risk in RA. Answers were deindentified. The

chi-squared test was used to examine the association between respondent characteristics and attitudes.

Results: Of 28 survey invitations, 24 (85.7%) were returned. All respondents felt there was either a high (N=14) or moderate (N=10) risk of CV disease in RA. Rheumatologists' perceptions of their practice are given in the Table. Seventeen (70.8%) respondents did not believe that primary care physicians (PCPs) are aware of the increased CV risk in RA. Eighteen (75%) believed that both rheumatologists and PCPs should screen for HLD in patients with RA; the remainder felt that PCPs are responsible. Female physicians were more likely to report that both rheumatologists and PCPs should be responsible for screening for HLD (p= 0.03). Nearly all respondents (87.5%) felt that PCPs should be responsible for treating HLD. When asked to rank the clinically most useful approach to estimating CV risk in RA among 3 options, 17 of 21 respondents ranked "CAD equivalent like diabetes mellitus" as their first choice. The most commonly mentioned barriers to screening were time (N=11), patient complexity (N=6), and forgetting or needing a prompt (N=4). An electronic health record (EHR) reminder was the most commonly mentioned idea for increasing HLD screening in rheumatology and primary care practices (N=11).

Conclusion: All respondents believed that there is at least a moderately increased risk of CV disease in RA. Most believed that PCPs are not aware of the increased risk, but the majority also believed that PCPs should be responsible for treating HLD. Quality improvement strategies to bridge this disconnect are needed. Several barriers to screening were identified. Respondents recommended using an EHR prompt to increase screening for HLD and improve recognition of CV risk.

Table. Rheumatologists' Perceptions of Their Own Practice

Question	Total Respondents - n (%)
Do you routinely check lipids in your patients with RA?	
Never	1 (4.2)
Almost Never	5 (20.8)
Sometimes	8 (33.3)
Most of the Time	9 (37.5)
Always	1 (4.2)
Do you routinely initiate treatment of hyperlipidemia in your patients with RA?	
Never	4 (16.7)
Almost Never	11 (45.8)
Sometimes	8 (33.3)
Most of the Time	1 (4.2)
Always	0
Do you regularly counsel your RA patients about the increased risk for cardiovascular disease?	
Never	1 (4.2)
Almost Never	1 (4.2)
Sometimes	6 (25.0)
Most of the Time	12 (50.0)
Always	4 (16.7)
How comfortable do you feel in counseling about diet and exercise in your patients with RA and hyperlipidemia?	
Not at all comfortable	1 (4.2)
Somewhat comfortable	6 (25.0)
Very comfortable	17 (70.8)
How comfortable do you feel initiating medication therapy for hyperlipidemia?	
Not at all comfortable	2 (8.3)
Somewhat comfortable	12 (50.0)
Very comfortable	10 (41.7)

Disclosure: A. Komarla, None; **A. Ogdie**, None.

ACR/ARHP Poster Session B
Rheumatoid Arthritis - Clinical Aspects: Comorbidities, Treatment Outcomes and Mortality
Monday, November 17, 2014, 8:30 AM–4:00 PM

1362

Impact of Rapid Attainment of Stringent Measures of Efficacy in Rheumatoid Arthritis on Patient-Reported Outcomes. EA Alemao[1], S Joo[2], S Banerjee[1], P Emery[3] and M Weinblatt[4]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]Bristol-Myers Squibb, Hopewell, NJ, [3]University of Leeds, Leeds, United Kingdom, [4]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Treatment guidelines in RA recommend that therapies aim to reach a target of remission or low disease activity (LDA) and that these targets should be reached in 3–6 months (mths). This timeframe is based on 'expert opinion' rather than empirical data. Our objective was to evaluate the benefits of rapid (within 3 mths) vs later attainment of stringent measures of efficacy (SME) such as ACR/EULAR remission criteria (SDAI ≤3.3, CDAI ≤2.8), LDA (DAS <2.6), and ACR70 on pt-reported outcomes (PROs) in pts with RA in a randomized controlled trial.

Methods: Data were analyzed from a Phase IIb study evaluating SC anti-IL-6 monoclonal antibody clazakizumab (CLZ) with or without MTX in pts with moderate-to-severe RA and inadequate response to MTX. Pts were randomized equally to CLZ 25, 100 or 200 mg with MTX every 4 wks; CLZ 100 or 200 mg monotherapy every 4 wks; MTX alone; or adalimumab with MTX every 2 wks. 'Rapid' attainment of SME (DAS28 [CRP] <2.6, ACR70, SDAI ≤3.3 and CDAI ≤2.8) was based on attaining SME within 3 mths. Pts attaining SME between 3 to 6 mths and after 6 mths were considered 'intermediate' and 'late' respectively. PROs evaluated during the 12-mth follow-up period included physical functioning using HAQ-DI, quality of life (QoL) using the Short Form-36 Health Survey (SF-36) (physical component summary [PCS] and mental component summary [MCS]), and pain and fatigue using visual analog scales. Mixed models were used to estimate both fixed and random effects of independent variables on the outcome measures.

Results: A total of 418 pts were included in the analysis; average age was 50.4 yrs and 83.5% were females. At 12 wks ('rapid' group), 33.3%, 22.7%, 12.2% and 11.2% had attained DAS28 (CRP) <2.6, ACR70, SDAI ≤3.3 and CDAI ≤2.8, respectively. Between 12 and 24 wks ('intermediate' group) these values were 17.5%, 16.0%, 12.4% and 12.7%, respectively; and after 24 wks ('late' group) they were 18.2%, 20.8%, 19.6% and 18.9%, respectively. Baseline characteristics between groups were similar. Pts who attained DAS28 (CRP) <2.6 or ACR70 early ('rapid' group) had significantly better HAQ, SF-36 PCS, pain and fatigue scores at Wk 48 than those who attained DAS28 (CRP) <2.6 or ACR70 later ('late' group); the mean differences (delta) between the 'rapid' vs 'late' group were higher than the thresholds for minimum clinically important differences for these outcomes. Directionally similar results were observed for those attaining SDAI ≤3.3 and CDAI ≤2.8 rapidly vs late, although the results did not meet statistical significance due to small numbers of pts. There was no consistent pattern in PROs between the 'rapid' vs 'intermediate' group (Table).

Outcome	D DAS28 (CRP) <2.6 'rapid' vs 'late'	p-value	D ACR70 'rapid' vs 'late'	p-value
HAQ	**–0.37**	**0.0085**	**–0.60**	**<0.0001**
SF-36 PCS	**3.5**	**0.0007**	**3.4**	**0.0011**
SF-36 MCS	2.2	0.1073	2.2	0.1261
Pain	**–16.4**	**<0.0001**	**–14.4**	**<0.0001**
Fatigue	**–15.5**	**<0.0001**	**–13.6**	**<0.0001**
	D **DAS28 (CRP) <2.6 'rapid' vs 'intermediate'**	**p-value**	D **ACR70 'rapid' vs 'intermediate'**	**p-value**
HAQ	0.02	0.8731	–0.10	0.4489
SF-36 PCS	0.5	0.6113	0.2	0.8336
SF-36 MCS	1.5	0.2963	–1.0	0.4942
Pain	**–6.8**	**0.0046**	–4.0	0.0939
Fatigue	**–6.6**	**0.0113**	–4.1	0.1192

Conclusion: Pts with rapid attainment of SME (including treatment guideline targets) tend to benefit more in the longer term in physical functioning, QoL, pain and fatigue than those attaining these measures much later; the findings are mixed for those attaining SME in the intermediate 3–6 mths time period.

Disclosure: E. Alemao, BMS, 1, BMS, 3; **S. Joo**, BMS, 3, BMS, 1; **S. Banerjee**, BMS, 1, BMS, 3; **P. Emery**, AbbVie, BMS, Merck, Pfizer, Roche, Takeda, 5, AbbVie, BMS, Merck, Pfizer, Roche, 2; **M. Weinblatt**, BMS, Crescendo Bioscience, UCB, Abbvie, Roche, Janssen, 5, BMS, Crescendo Bioscience, UCB, 2.

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Psychosocial Comorbidities Are Independently Associated with Subclinical Atherosclerosis in Rheumatoid Arthritis. Ying Liu[1], Moyses Szklo[2], Karina Davidson[1], Joan Bathon[3] and Jon Giles[1]. [1]Columbia University Medical Center, New York, NY, [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [3]Columbia University, New York, NY.

Background/Purpose: Rheumatoid arthritis (RA) is associated with higher rates of cardiovascular disease (CVD) and subclinical atherosclerosis as well as psychosocial comorbidities, which themselves are associated with CVD. We explored if psychosocial comorbidities differentially contribute to CVD risk in individuals with RA compared with non-RA controls.

Methods: Data were derived from a longitudinal cohort study of subclinical cardiovascular disease in RA and non-RA controls. Using validated scales, psychosocial comorbidities (depression, chronic life stressors, anxiety/anger, social support, discrimination/hassles) were assessed. Differences in the associations of psychosocial measures with measures of subclinical atherosclerosis [coronary artery calcium (CAC) assessed using computed tomography and carotid intimal-media thickness (IMT)/plaque assessed using ultrasound] were explored using multivariable regression models incorporating RA x psychosocial variable interaction terms. Models were adjusted for relevant unbalanced demographic variables, CVD risk factors, and markers of RA activity/inflammation.

Results: 195 RA patients [mean age=59 ± 9 years, 61% female; 87% Caucasian; median RA=9 years; mean DAS28=3.65 ± 1.1] were compared with 1073 controls. RA participants had a higher prevalence of psychosocial comorbidities (depression and personal health, job, and total stress) compared with controls. In RA, per-unit higher Spielberger trait anxiety scores and the presence of caregiver stress were associated with an increased adjusted odds of CAC>100 units (Table). Per-unit higher Spielberger trait anger scores and Center for Epidemiologic Studies Depression scores were also associated with an increased odds of CAC>100 after adjustment (Table), although these effects were diminished with adjustment for anxiety. All associations were preserved after adjusting for markers of inflammation (IL-6 and CRP) and were only observed in RA patients, but not controls (adjusted interaction term p-values 0.001–0.077). Having job stress was associated with an increased frequency of carotid plaque [adjusted OR=3.21 (p=0.019)], and increasing social support was associated with lower internal carotid IMT (adjusted p=0.024) in RA participants, but not in controls.

Conclusion: Depression, stress, anger/anxiety and social support may affect CVD risk, specifically in RA patients, by promoting atherosclerosis. Because the impact of these factors on atherogenesis may be accentuated in RA compared with the non-RA population, screening and treatment of psychosocial comorbidities may help reduce the known increased burden of CVD in RA.

Table. Adjusted Associations of Psychosocial Variables with Moderate to Severe Coronary Arterial Calcification (CAC>100) Among 195 RA Patients Compared with 1073 non-RA Controls

	Anger			Anxiety			CES-D			CES-D≥ 16 units			Caregiver Stress		
	OR	p-value	interaction p-value	OR	p-value	interaction p-value	OR	p-value	interaction p-value	OR	p-value	interaction p-value	OR	p-value	interaction p-value
RA	**1.15**	0.038	0.051	**1.12**	0.018	0.001	**1.06**	0.032	0.012	**3.41**	0.032	0.027	**2.86**	0.014	0.077
Control	**1.00**	0.87		**0.93**	0.001		**0.96**	0.22		**0.83**	0.55		**1.03**	0.86	

- *Odds ratios represent the average unit change in the frequency of CAC>100 per one unit higher psychosocial variable score.*
- *RA models adjusted for age, gender, body mass index, smoking, RA duration and prednisone history. Control models adjusted for age, gender, race/ethnicity, body mass index, hypertension, and smoking.*
- *Interaction p-values are from modeled RA x psychosocial variable interaction terms.*

Anger=Spielberger Trait Anger Scale; Anxiety=Spielberger Trait Anxiety Scale; CES-D=Center for Epidemiologic Studies Depression Scale; Caregiver Stress=Chronic Burden Scale

Disclosure: Y. Liu, None; **M. Szklo**, None; **K. Davidson**, None; **J. Bathon**, None; **J. Giles**, None.

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Accelerated Diastolic Dysfunction in Premenopausal Women with Rheumatoid Arthritis. Yune-Jung Park[1], JiHee Kim[2], Ki-Jo Kim[3], Wan-Uk Kim[4], Chul-Soo Cho[5], Kyung-Su Park[6] and Ki-Dong Yoo[2]. [1]St. Vincent's Hospital, The Catholic University of Korea, Suwon, South Korea, [2]Division of Cardiology, Department of Internal Medicine, St.Vincent's Hospital, The Catholic University of Korea, Suwon, Republic of Korea, Suwon, South Korea, [3]St. Vincent's Hospital, The Catholic University of Korea, Suwon, South Korea, [4]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [5]Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul, South Korea.

Background/Purpose: Disturbances of diastolic function precede systolic heart failure and, although clinically silent, represent the earliest sign of cardiac involvement. Diastolic dysfunction is associated with age, female, and hypertension. However, little is known about the age-specific incidence rates and risk factors for diastolic dysfunction in patients with rheumatoid arthritis (RA).

Methods: We used standard two-dimensional/Doppler echocardiography to screen for the presence of diastolic dysfunction in 61 patients with RA (mean [±SD] age, 48.1±7.9 years) and 107 healthy subjects (47.3±9.4 years). All participants were premenopausal women with no history of hypertension. Diastolic dysfunction was defined as impaired relaxation with or without increased filling pressures.

Results: The two groups were similar with respect to age (P=0.269). Patients with RA had significantly higher LV mass index, LV filling pressure, and lower E/A velocity than controls. All patients had preserved ejection fraction (EF ≥50%). Diastolic dysfunction was more common in patients with RA at 47% compared with 26% in the controls (P=0.004). Women with RA in the 30- to 49- year age group were over 3.5 times more likely to have diastolic dysfunction than those of similar age in the control group (OR=3.54; 95% CI 1.27 to 9.85). Among patients with RA, high CRP levels were independently associated with diastolic dysfunction even after adjustment for cardiovascular risk factors (P=0.009).

Conclusion: In premenopausal women with RA, diastolic dysfunction is much more common and the age at onset is reduced. Early screening of myocardial function may provide an opportunity for preventing future cardiovascular disease.

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1365

ARE Erosions a Disappearing Feature in Rheumatoid Arthritis (RA)? Joint Damage in Patients with EARLY RA at 10 YEARS after Diagnosis. Juha Asikainen[1], Kalevi Kaarela[2], Heidi Mäkinen[3], Hannu Kautiainen[4], Pekka Hannonen[5], Tuomas Rannio[6] and Tuulikki Sokka[1]. [1]Jyvaskyla Central Hospital, Jyväskylä, Finland, [2]Jyväskylä Central Hospital, Jyväskylä, Finland, [3]Tampere University Hospital, Tampere, Finland, [4]Medcare Oy, Äänekoski, Finland, [5]Jyväskylä Central Hospital, Jyvaskyla, Finland, [6]Kuopio University Hospital, Kuopio, Finland.

Background/Purpose: Treatment of rheumatoid arthritis (RA) has improved during the last decade. Also importance of regular monitoring has been emphasized. Our objective was to study the extent of radiographic joint damage in an early RA cohort at 10 years after diagnosis.

Methods: Our early RA cohort includes 990 patients from a single clinic with a clinical diagnosis of early RA in 1997 – 2004. Radiographs of hands and feet were taken at a 10 year follow-up visit and were analyzed according to the Larsen score (0–100) including MCP I-V, wrists, and MTP II-V. Patients were treated with the T2T strategy by a multidisciplinary care for 2 years with follow-up visits at 5 and 10 years.

Results: Baseline characteristics of 990 patients were: the mean (SD) age 57(16) years, 67% female, 61% seropositive (RF/CCP+ any time over 10 years) and median (IQR) duration of symptoms before diagnosis 6(3, 12) months; 657(66%) patients were available for a 10 year follow up. Reasons for non-attendance among 333 patients included death (52%), high age, multi-comorbidity or institutionalization (10%), moving from the area (12%); 8% declined, 4% were lost to follow-up and 14% miscellaneous reasons. Thus, radiographs were available in 657 patients (66% seropositive); serology of one patient was missing.

At 10 years, erosions were present in 48% (314/656) patients including 61%(266/435) seropositive and 22% (48/221) seronegative patients. Among seropositive patients, Larsen score was >=10% of theoretical maximum in 28%(121/435) patients, <10% of max in 33%(145/435) patients, and 39% (169/435) remained non/erosive; for seronegative patients the corresponding figures were 5%(11/221), 17%(37/221) and 78%(173/221), respectively. The mean (SD) and median (IQR) Larsen score in seropositive patients was 7.8 (11) and 4.0 (1.0, 10), and in seronegative patients 2.0 (4.0) and 0 (0. 3).

In seropositive patients, the 10-years Larsen score declined over time while in seronegative patients erosiveness remained low and stabile (figure).

Over 10 years, all patients had been taking csDMARDs, 83% had been taking systemic glucocortikoids, and 20% bDMARDs.

Conclusion: Larsen score remained low over 10 years and erosion rates decreased over time.

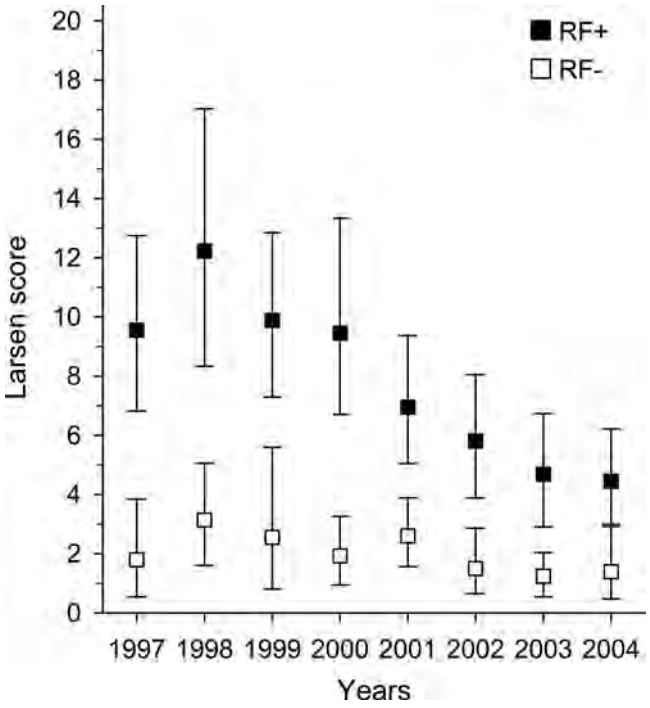

Figure. Larsen score (0–100) in seropositive and negative patients with early RA diagnosed 1997–2004 at 10 years after diagnosis. Mean with bootstrap type 95 per cent confidence intervals.

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Outcomes of Interstitial Lung Disease Associated with Rheumatoid Arthritis in High Volume Referral Centers. Megan Krause[1], Amish Dave[2], Cynthia S. Crowson[1], Arun K. Chandran[1], C. John Michet[1], Paul F. Dellaripa[2] and Eric L. Matteson[1]. [1]Mayo Clinic, Rochester, MN, [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

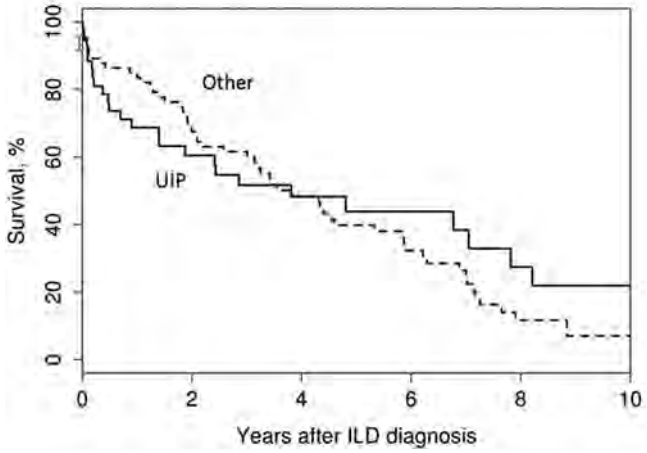
Background/Purpose: To describe the characteristics and morbidity and mortality impact of interstitial lung disease in rheumatoid arthritis (RA).

Methods: A retrospective review was performed at 2 high volume tertiary medical centers identifying patients with clinician determined RA associated interstitial lung disease (RA-ILD) in 1998–2012. Data regarding demographics and disease characteristics of RA, including serologic status and erosions, were collected. Features of pulmonary disease, including successive radiographic findings and pulmonary function test (PFT) results, were abstracted. Kaplan-Meier methods and Cox models were used to estimate survival rates and examine risk factors for mortality.

Results: A total of 119 patients were identified with RA-ILD (55% women; mean age at RA diagnosis 56.6 [range: 13.1–84.8] years; 63% former/current smokers; 75% rheumatoid factor positive). Cyclic citrullinated antibodies were tested in 92 (79%) and present in 71/92 (77%). Erosive disease was present in 32 patients (30%). The mean time from RA diagnosis to ILD diagnosis was 9.4 [−10.9–43.0] years. The mean follow-up time after ILD diagnosis was 3.5 [0.0–15.0] years. Over follow-up, 51 patients (44%) required supplemental oxygen. On repeat PFT, the mean percent predicted were 76.1% [40–148] for total lung capacity (TLC), 70.5% [32–141] for forced vital capacity (FVC), 70.0% [25–135], for forced vital capacity in one second (FEV1) and 51.9% [6–95] for diffusion capacity for carbon monoxide (DLCO). 33 patients died with cause of death attributed to pulmonary disease in 21%. One-year survival rate was 78% (95% confidence interval (CI) 71–86%) with 5 year survival only 41% (95% CI 32–52%**)**. The most common types of ILD were usual interstitial pneumonia (UIP; 44 [37%]) and nonspecific interstitial pneumonia (NSIP; 42 [35%]). Survival rates did not differ for those with UIP compared to those without (5 year survival rate 44% vs 40%; p=0.45; **Figure**). In patients with UIP compared to those without, the initial percent predicted DLCO (p=0.02) and the last available percent predicted TLC, FVC, FEV1, and DLCO were all significantly lower (p=0.003, 0.005, 0.02, 0.02, respectively). In patients without UIP, the first FEV1, both absolute volume and percent predicted, were associated with mortality (p=0.027 and p=0.007, respectively, adjusted for age and sex).

Conclusion: In this large cohort, ILD is an important complication of RA with a very high mortality rate in the first 5 years following diagnosis. The most common RA-ILD diagnoses were UIP and NSIP, and contrary to previously published data, there was no survival difference between these two groups. Earlier in disease, a lower diffusion capacity may identify UIP RA-ILD compared to non UIP RA-ILD. Further research is required to identify risk factors and biomarkers for this extraarticular manifestation of RA.

Figure. Kaplan-Meier Survival Curve for Patients with UIP (solid line) and without UIP (dashed line)



Disclosure: M. Krause, None; **A. Dave**, None; **C. S. Crowson**, None; **A. K. Chandran**, None; **C. J. Michet**, None; **P. F. Dellaripa**, None; **E. L. Matteson**, None.

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Cardiovascular Morbidity and Associated Risk Factors in Spanish Patients with Chronic Inflammatory Rheumatic Diseases Attending Rheumatology Clinics. Santos Castañeda[1], Maria Auxiliadora Martin[2], Carlos González-Juanatey[3], Javier Llorca[4], María Jesús García Yébenes[2], Sabina Pérez-Vicente[5], Jesús Sánchez Costa[2], Federico Diaz-Gonzalez[6], Miguel A. González-Gay[7] and CARMA Project Collaborative Group[2]. [1]Hospital Universitario de La Princesa, IISP, Madrid, Spain, [2]Sociedad Española de Reumatología, Madrid, Spain, [3]Hospital Universitario Lucus Augusti. Cardiology Division, Lugo, Spain, [4]School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), Santander, Spain, [5]Unidad de Investigación de la Sociedad Española de Reumatología, Madrid, Spain, [6]Servicio de Reumatologia.Hospital Universitario de Canarias, La Laguna, Spain, [7]Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain.

Background/Purpose: The prevalence of cardiovascular disease (CVD) in chronic inflammatory rheumatic diseases (CIRD) is higher than in the general population. Recent studies have emphasized that tight control of the disease leads to a reduction in the rate of CVD in patients with rheumatic diseases. However, the prevalence of CVD in patients with CIRD and low disease activity is not well established. Thus, the aim f this study was to establish the cardiovascular (CV) morbidity and associated risk factors for CV disease (CVD) in Spanish patients with chronic inflammatory rheumatic diseases (CIRD) with low disease activity and unexposed individuals attending rheumatology clinics.

Methods: Analysis of data from the baseline visit of a 10-year prospective study (CARdiovascular in rheuMAtology-CARMA-project) that includes a cohort of patients with CIRD [rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA)] and another cohort of matched individuals without CIRD attending outpatient rheumatology clinics from sixty-six hospitals in Spain. Prevalence of CV morbidity, CV risk factors and systematic coronary risk evaluation (SCORE) assessment were analyzed.

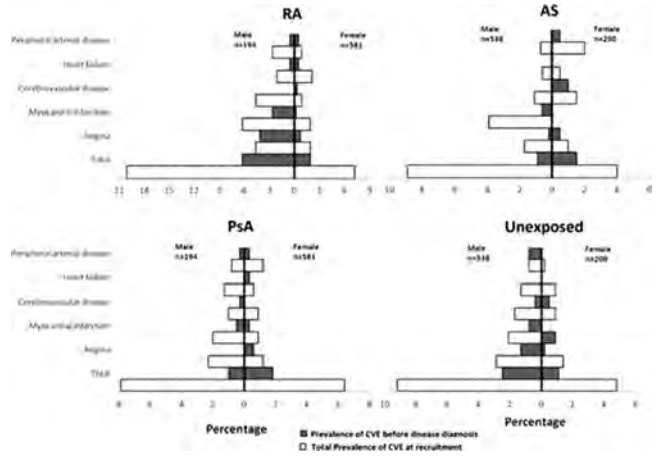
Results: 2,234 patients (775 RA, 738 AS and 721 PsA) and 677 unexposed subjects were included.

Patients had low disease activity at the time of recruitment. PsA patients had more commonly classic CV risk factors and metabolic syndrome features than did the remaining individuals.

Prevalence of CVD was higher in RA (10.5%) than in AS (7.6%), PsA (7.2%) and unexposed individuals (6.4%). A multivariate analysis adjusted for the presence of classic CV risk factors and disease duration revealed a

positive trend for CVD in RA (OR=1.58; 95%CI=0.90–2.76; p=0.10) and AS (OR=1.77; 95%CI=0.96–3.27; p=0.07). Disease duration in all CIRD groups and functional capacity (HAQ) in RA were associated with an increased risk of CVD (OR=2.15; 95%CI=1.29–3.56; p=0.003). Most patients had a moderate CV risk according to the SCORE charts.

Conclusion: Despite recent advances in the management of CIRD, incidence of CVD remains increased in Spanish subjects with CIRD attending outpatient rheumatology clinics. It is of particular relevance that almost half of them were receiving biological therapy and most patients had low disease activity at the time of assessment.



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Are Tender Joints Better Than Synovitis to Predict Structural Damage in Rheumatoid Arthritis? Peter Cheung[1], Karine Mari[2], Valerie Devauchelle[3], Jacques Bentin[4], Sandrine Jousse-Joulin[5], Maria-Antonietta d'Agostino[6], Gérard Chales[7], Isabelle Chary-Valckenaere[8], Fabien Etchepare[9], Philippe Gaudin[10], Xavier Mariette[11], Alain Saraux[12] and Maxime Dougados[13]. [1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [2]RCT, Lyon, France, [3]Brest university medical school, EA 2216, Lab Ex, INSERM, IGO, UBO and CHU de la Cavale Blanche,, Brest, France, [4]CHU-Brugmann, Brussels, Belgium, [5]CHU Brest, Brest, France, [6]Versailles-Saint Quentin en Yvelines University, Boulogne-Billancourt, France, [7]CHR - Hopital Sud, Rennes, France, [8]Nancy University Hospital, Nancy, France, [9]AP-HP, La Pitié-Salpétrière Hospital, Rheumatology Department, Paris-VI University, Paris, France, [10]Hopital Sud Grenoble, Echirolles, France, [11]Paris-Sud University, Paris, France, [12]CHU Brest and EA 2216, UBO, Brest, France, [13]Université Paris René Descartes and Hôpital Cochin, Paris, France.

Background/Purpose: Longitudinal studies indicate that synovitis can predict subsequent structural damage in rheumatoid arthritis (RA) but the clinical relevance of tenderness is unclear. The aim is to evaluate the predictive validity of tenderness for subsequent structural damage in RA, with synovitis as the comparator.

Methods: *Study design*: 2-year prospective study. *Patients*: Active RA (1987 ACR criteria) requiring anti-TNF. *Data collected*: For each patient, 32 joints were evaluated (2 wrists, 10 MCP, 10 PIP, 10 MTP) for tenderness and clinical synovitis, followed by blinded US assessment for synovitis in B-mode and Power Doppler (PDUS), at baseline and after 4 months of anti-TNF. X-rays of hands and feet were performed at baseline and 2 years. Radiographic progression: occurrence/worsening in structural damage (bone erosion/joint space narrowing) at 2 years compared to baseline. *Analysis*: The ability of baseline tenderness or synovitis to predict radiographic progression of the same joints at 2 years was compared using odds ratio, OR with 95% confidence interval, through generalized estimating equation adjusted for within patient correlation, age, gender, disease duration, baseline DAS28 and initial structural damage.

Results: Fifty-nine out of the 77 recruited patients had completed the 4 months of the study with radiographic evaluation at 2 years (female: 81%, age 56±12 years, rheumatoid factor positive: 73%). Radiographic progression was observed in 9% of the 1888 evaluated joints (16% of the 118 wrists, 7% of the 590 MCP, 8% of the 590 PIP, and 11% of the 590 MTP). Baseline tender joints were the least predictive for radiographic progression at 2 years (OR=1.53 [1.02; 2.29] p=0.04) when compared to synovitis (clinical OR=2.08 [1.39; 3.11] p<0.001 or PDUS OR=1.80 [1.20; 2.71] p=0.005 respectively) (Figure 1). Tender joints with presence of synovitis, was predictive of radiographic progression (OR=1.89 [1.25, 2.85] p=0.002) while non-tender joints with no synovitis was negatively predictive (OR=0.57 [0.39, 0.82] p=0.003) (Figure 2).

Conclusion: Clinical or US synovitis is more predictive than tenderness to predict subsequent structural progression. Co-existence of tenderness and synovitis at the level of an individual joint would suggest the need for either local/systemic treatment to prevent subsequent structural damage.

Figure 1. The predictive ability of baseline tenderness for radiographic progression at 2 years compared to synovitis

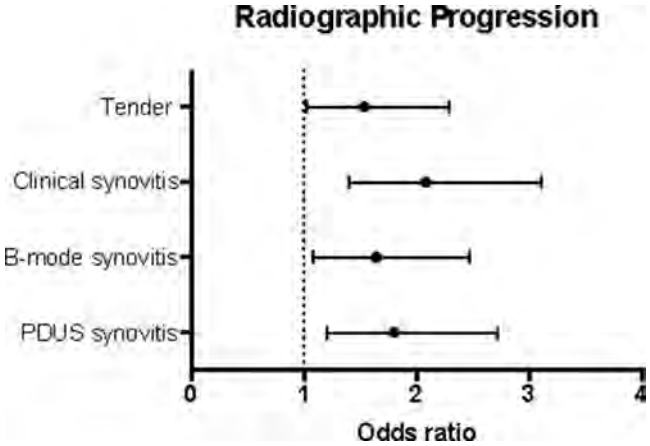
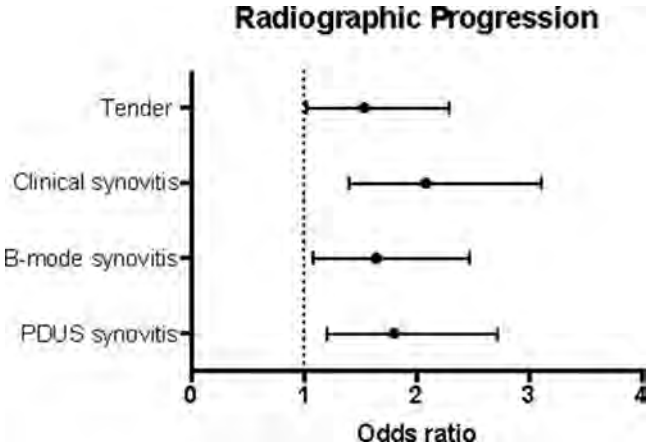


Figure 2. Predictive ability of tenderness with/without synovitis to predict radiographic progression



Disclosure: P. Cheung, None; **K. Mari**, None; **V. Devauchelle**, None; **J. Bentin**, None; **S. Jousse-Joulin**, None; **M. A. d'Agostino**, None; **G. Chales**, None; **I. Chary-Valckenaere**, None; **F. Etchepare**, None; **P. Gaudin**, None; **X. Mariette**, None; **A. Saraux**, None; **M. Dougados**, None.

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Predictors of Deterioration in Subjective Cognition: Results from a Rheumatoid Arthritis (RA) Observational Cohort Study. Christine K. Iannaccone[1], Jing Cui[2], Jonathan S. Coblyn[1], Michael Weinblatt[3] and Nancy A. Shadick[4]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Womens Hospital, Boston, MA, [3]Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [4]Brigham and Women's Hospital/Harvard University, Cambridge, MA.

Background/Purpose: Previous studies have suggested that RA confers an increased risk for worsened cognition later in life compared with the general population. Research in dementia has also indicated that the presence of subjective cognitive complaints may be a sensitive indicator of cognitive decline. Little is known about the inflammatory, psychological, and functional predictors of worsening subjective

cognitive complaints among patients with RA. Less is known about the relative contribution of how a change in these risk factors may affect an RA patient's perceived cognitive function.

Methods: We analyzed data from BRASS, a longitudinal RA cohort study. The data collection includes joint exams, serological analyses, and patient reported outcome measures collected annually from 2003–2014. Patients were asked to report the degree of their cognitive complaints concerning their memory, concentration, and word-finding difficulties (Table). In univariate analyses, we assessed known predictors for cognitive complaints (age, gender, ethnicity, education, CV Risk (Desai et al, 2012)) and computed variables that measured the past year's change (MDHAQ depression, MDHAQ fatigue, MDHAQ sleep, exercise level (METS), DAS28-CRP3, corticosteroid use) in relation to a worsening of cognitive complaints. Univariate factors ($p<0.10$), sociodemographic variables and the CV risk score were then entered into a multivariate backwards elimination mixed model to assess their impact on the degree of cognitive complaints.

Results: There were a total of 1126 subjects with at least two annual visits used in this analysis. Univariate analyses revealed that an increase in MDHAQ depression, fatigue, and corticosteroid use as well as a decrease in sleep quality and exercise level were associated with worsened cognitive complaints at follow-up. The multivariate mixed model that adjusted for sociodemographic variables and the CV risk score showed only that worsening MDHAQ depression, fatigue and increased corticosteroid use were associated with an increase in cognitive complaints one year later (Table). Neither a change in DAS28-CRP3 score nor exercise level impacted the degree of reported cognitive complaints.

Conclusion: Cognitive difficulties in RA are sensitive to a worsening of psychological factors such as depression but also to a change in corticosteroid use and fatigue. In this analysis disease activity measures do not appear to influence subjective cognitive complaints over time. Future studies of cognition difficulties in RA patients should focus on whether corticosteroid use and fatigue levels may be markers of subclinical disease activity that may drive patients to more likely reflect upon cognitive difficulties.

Clinical and Psychological factors predicting an increase is subjective cognitive complaints

Multivariate Mixed Model*	β coefficient	Standard Error	P-Value
Age (continuous)	−0.001	0.002	0.64
Sex (Female or not)	−0.100	0.059	0.09
CV Risk Score (0–9)	−0.004	0.013	0.76
Ethnicity (White or not)	0.072	0.094	0.44
Education (college and above or not)	0.049	0.046	0.28
Worsened MDHAQ Depression (−3, 3)	**0.290**	**0.047**	**<0.0001**
Worsened MDHAQ Fatigue (−100, 100)	**0.007**	**0.001**	**<0.0001**
Addition of corticosteroids	**0.149**	**0.070**	**0.03**

*Dependent variable (Δ Cognitive complaint -6, 6) higher equals increased cognitive complaints
Do you have any of the following symptoms NOW?
Poor Memory (Not at all, Sometimes, Often)
Poor Concentration (Not at all, Sometimes, Often)
Word-finding Difficulty (Not at all, Sometimes, Often)

Disclosure: C. K. Iannaccone, None; **J. Cui**, None; **J. S. Coblyn**, CVS caremark, 5; **M. Weinblatt**, BMS, UCB, Crescendo Bioscience, 2, Medimmune, AstraZeneca, Amgen, Abbvie, BMS, Crescendo Bioscience, Lilly, Pfizer, UCB, Roche, 5; **N. A. Shadick**, Crescendo Bioscience, 2, Amgen, 2, UCB, 2, Abbvie, 2, Bristol Myers Squibb, 2, Genentech, 2.

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The Association of Body Mass Index (BMI) and Radiographic Progression of Joint Disease in Rheumatoid Arthritis (RA). Christine K. Iannaccone[1], Jing Cui[2], K P Liao[1], Jonathan S. Coblyn[1], Michael Weinblatt[3] and Nancy A. Shadick[4]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Womens Hospital, Boston, MA, [3]Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [4]Brigham and Women's Hospital/Harvard University, Cambridge, MA.

Background/Purpose: Previous studies suggest that lower BMI is associated with progression of radiographic joint damage in RA but little is known about the biological role BMI plays in radiographic joint damage and research outcomes of the association have varied. Whether the association of BMI and radiographic joint damage may be mediated by disease activity variables is currently unknown. Using a cohort of RA patients, this study aims to examine the relationship between BMI and radiographic joint damage and disease activity.

Methods: We analyzed data from a longitudinal RA cohort study. The data collection included joint examinations, blood draws and patient reported outcome measures over 10 years. Hand and wrist radiographs were acquired at baseline and 2 years and scored by the van der Heijde-modified Sharp score method (vdHSs) (n=543). We created a dichotomous outcome variable for radiologic progression; defining patients with radiographic progression as having a change of ≥ 10 units in total vdHSs over two years. We conducted univariate analyses to assess predictors of radiographic joint damage progression that included age, gender, BMI group (underweight BMI $<20 kg/m^2$, normal BMI 20–24.9 kg/m^2, overweight BMI 25–29.9 kg/m^2, obese BMI $\geq 30 kg/m^2$ (Baker et al, 2011)), DAS28-CRP4, anti-TNF use and anti-CCP status. For our primary analysis, we constructed a multivariate logistic regression model to study the effect between BMI and radiographic progression.

Results: We studied 543 patients with a mean age (SD) of 57.6 (12.7) years and a mean disease duration of 14.4 (12.2) years. Eighty-three percent were female and 68.3% were anti-CCP+; 69 (12.7%) of the patients had progression of joint damage. In the univariate analysis, BMI (group), anti-CCP+, and DAS28-CRP4 were all associated with radiographic joint damage, but age, gender and anti-TNF use did not show any association. The multivariate logistic regression analyses showed that patients who were underweight or normal weight had a significantly increased odds (OR=4.85, 95%CI 1.76–9.05; OR=3.99, 95%CI 1.76–9.05) of having radiographic progression compared to patients who were obese. Having a higher DAS28-CRP4 score was associated with greater odds of having radiographic joint damage (Table).

Conclusion: We found that lower BMI was associated with radiographic joint damage progression in RA, independent of disease activity. Further work is necessary to understand the biological role BMI plays in radiographic joint damage progression, as well as the involvement of inflammation in the relationship between BMI and progression of joint disease in RA.

Association of BMI and radiologic progression of joint disease in RA

Multivariate Logistic Regression Model*	Odds Ratios	Confidence Intervals
BMI (underweight vs. Obese)	**4.85**	**1.34–17.53****
BMI (Normal vs. Obese)	**3.99**	**1.76–9.05**
BMI (Overweight vs. Obese)	1.65	0.68–4.02
DAS28-CRP4 (continuous)	**1.28**	**1.08–1.51**
Anti-CCP Positive	1.85	0.96–3.57

*adjusted for age and gender
**test for trend of BMI group and radiologic progression p=0.0006

Disclosure: C. K. Iannaccone, None; **J. Cui**, None; **K. P. Liao**, None; **J. S. Coblyn**, CVS caremark, 5; **M. Weinblatt**, BMS, UCB, Crescendo Bioscience, 2, Medimmune, AstraZeneca, Amgen, Abbvie, BMS, Crescendo Bioscience, Lilly, Pfizer, UCB, Roche, 5; **N. A. Shadick**, Crescendo Bioscience, 2, Amgen, 2, UCB, 2, Abbvie, 2, Bristol Myers Squibb, 2, Genentech, 2.

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Impact of Metabolic Syndrome (MetS) on Rheumatoid Arthritis Disease Activity. Federico Parra-Salcedo[1], Irazú Contreras-Yáñez[2], Daniel Elías-López[3], Carlos A. Aguilar-Salinas[3] and Virginia Pascual-Ramos[2]. [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, Mexico, [2]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [3]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán., Mexico City, Mexico.

Background/Purpose: The purpose of the study was to describe prevalence and components (c) of MetS in a cohort of early RA, to compare it with data from matched controls and to investigate MetS impact on disease activity.

Methods: The study population was a prospective cohort of early RA (95% satisfying 2010 ACR/EULAR criteria) initiated in 2004. At baseline, 2 months-apart for the first 2 years and thereafter at least six-months-apart, patients had complete medical evaluations that included height, weight and blood pressure, standardized rheumatic evaluations and assessments of

comorbidity and treatment; at 6 months fixed intervals, fasting serum glucose (GLU), triglycerides (TRG), HDL-Cholesterol (HDL) and acute reactant-phase were performed. Data from a local database of healthy controls randomly selected and matched were used.

MetS was defined according to 3 sets of criteria (ATP-III, AHA/NHLBI, IDF) and body mass index (BMI) ≥30 was used as a surrogate of the waist circumference criteria-c. Sustained remission (SR) was defined according to ACR/EULAR 2012 criteria and lasting ≥ 6 months.

The study was approved by the internal review board. Written informed consent was obtained.

Appropriated statistics was used. All statistical tests were 2-sided and evaluated at the 0.05 significance level.

Results: Up to March 2014, 162 patients were included in the cohort, of whom 160 had complete baseline data; they were more frequently middle-aged females (142 □S, [mean±SD] years of age: 38.1±12.8), RF+ (81.3%), ACCP+ (83.8%) and had high disease activity; comorbid conditions were present in 82 patients (51.3%). Patients were treated with conventional DMARDs.

Prevalence of MetS at the baseline evaluation varied (depending on the criteria applied) from 11.3% to 17.5% in RA patients and was similar to that in controls (vs. 13.8% to 18.8%). Distribution of MetS c varied from 64–100% for BMI-c, 93–96% for TRG-c, 94–96% for HDL-c, 21–22% for systolic blood pressure-c and from 28–54% for GLU-c.

During follow-up (69.2±36.8 months), 108 patients had at least ≥ 1 sustained remission state at (median) 14 months of study entry and remained in remission for 16 months; of them, 20.4% had MetS and no differences were seen between patients with/without MetS regarding remission related outcomes.

Up to last follow-up, 39 patients (34.5%) developed incidental MetS (out of 113 baseline MetS-free patients). Annual incidental rate decreased after the third year of follow-up. Patients who developed incidental MetS were older, more frequently menopause females, had higher BMI, had more cumulative disease activity and disability previous incidental MetS and developed more frequently erosive disease than their counterparts. In the Cox regression analysis, cumulative DAS28 (OR: 1.81, 95% CI: 1.346–2.433, p=0.000) and baseline BMI (OR: 1.131, 96% CI: 1.035–1.236, p=0.007) were the only predictors for incidental MetS (X^2=28.8%).

Conclusion: MetS prevalence in a cohort of early RA patients was similar to that from matched controls and varied from 11 to 18%. Cumulative disease activity and higher BMI were risk factors for incidental Mets. Disease activity control in RA patients may additionally impact comorbid conditions.

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Prevalence of Cardiovascular Disease in US Veterans with Rheumatoid Arthritis and Hepatitis C Infection.

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Background/Purpose: Chronic hepatitis C (HCV) and rheumatoid arthritis (RA) have both been associated with higher cardiovascular disease (CVD) in US veterans. Whether the presence of both conditions compounds the risk of CVD remains unknown. We compared the prevalence of CVD in RA patients with and without HCV.

Methods: In this cross-sectional study, 97 out of 1952 (5%) RA subjects were identified with HCV within the Veterans Affairs Rheumatoid Arthritis (VARA) registry by the presence of at least one diagnosis (ICD9) code for chronic HCV. This was validated by chart review in a subset of 28 RA patients, of which 25 (89%) were identified as HCV-antibody positive. At enrollment, the presence of cardiovascular disease (composite of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, stroke, heart failure, and peripheral vascular disease) was determined using previously validated algorithms based on ICD9 codes and Current Procedural Terminology codes. Step-wise multivariable logistic regression models assessed differences in the prevalence of CVD, adjusting for factors known to be associated with CVD in RA.

Results: At enrollment, HCV-positive RA patients were younger, were more likely to be African-American, were more likely to smoke, had a lower body mass index (BMI), and had shorter disease duration **(Table 1).** RA disease characteristics between the two groups were similar, though HCV-positive patients were less likely to be prescribed methotrexate and had higher disease activity scores. CVD was less prevalent in the HCV-positive RA patients [24 (25%) vs. 729 (39%)]. There was no difference noted in the prevalence of other comorbidities (type 2 diabetes, chronic kidney disease, or hypertension). LDL, HDL, and triglyceride levels were similar between groups **(Table 1)**. After adjusting for age, sex, race, smoking, BMI, comorbidities, disease duration, and RA therapies, the prevalence of CVD was lower in the HCV-positive RA group [OR 0.58 (0.33–0.99) p=0.05]. In multivariate regression logistic models performed in a subset of 942 subjects with available data and adjusting for DAS28 scores, these associations were no longer significant [OR 0.55 (0.28–1.09), p=0.09 (**Table 2**)], although the point estimate remained similar.

Conclusion: Patients with concomitant RA and chronic HCV appear to have a lower odds of prevalent CVD at enrollment compared to those with RA alone. It might be hypothesized that comorbid HCV infection modulates chronic systemic inflammation by altering known atherogenic pathways.

Table 1: Baseline Demographics

	HCV+RAN=97	HCV-RAN=1853	P value
Demographic data			
Age (yrs)	58.2 ± 7	63.9 ± 11.2	<0.001
Men, N (%)	94 (96.9)	1640 (90.4)	0.02
Caucasian, N (%)	59 (60.8)	1390 (75.3)	0.001
Current smoker, N (%)	46/97 (47.4)	461/1814 (25.4)	<0.001
BMI (kg/m^2)	27.3 (0.56)	28.5 (0.14)	0.04
Disease Duration (yrs)	8.4 (9.4)	10.9 (11.4)	0.03
RA disease Characteristics			
DAS28 (N=986)	4.7 (1.6)	4.02 (1.6)	0.003
RF	74/93 (80.0)	1260/1632 (77.2)	0.6
CCP	73/91 (80.2)	1241/1626 (76.3)	0.4
Erosions	44/79 (55.7)	727/1403 (51.8)	0.5
Medications			
Methotrexate, N (%)	21 (23.3)	852 (51.6)	<0.001
Prednisone, N (%)	42 (46.7)	625 (37.9)	0.06
Anti-TNFα, N (%)	23 (25.6)	321 (19.5)	0.1
Lipid panel			
LDL (N=1128)	102.5 ± 4.2	102.1 ± 1.05	0.93
HDL (N=1157)	46.5 ± 2,5	44.7 ± 0.47	0.39
Triglycerides (N=1133)	129.7 ± 9.6	141.3 ± 2.7	0.33
Comorbidities			
CKD, N (%)	3 (3.1)	127 (6.9)	0.15
DM, N (%)	25 (25.8)	530 (28.6)	0.55
COPD, N (%)	12 (12.4)	144 (7.8)	0.1
HTN, N (%)	68 (70.1)	1212 (65.4)	0.9
CAD, N (%)	17 (17.5)	564 (30.4)	0.01
CVD, N (%)	24 (24.7)	729 (39.3)	0.004

Abbreviations: BMI=Body Mass Index; CKD=Chronic Kidney Disease; DM=Diabetes Mellitus; COPD=Chronic Obstructive Pulmonary Disease; HTN=hypertension; CAD=Coronary Artery Disease; CVD=Cardiovascular Disease

Table 2: Prevalence of cardiovascular disease in Hepatitis C positive RA patients compared to RA controls

	OR (95% CI)	P value
Model 1 *(Observations 1905)*	0.70 (0.43–1.14)	0.16
Model 2 *(Observations 1561)*	0.58 (0.33–0.99)	0.05
Model 3 *(Observations 942)*	0.55 (0.28–1.09)	0.09

Model 1: adjusted for age, sex, race
Model 2: Model 1 + DM, HTN, BMI, current smoking, methotrexate use, prednisone use, anti-TNF therapy use, disease duration
Model 3: Model 2 + DAS28
Abbreviations: DM=Diabetes Mellitus; HTN=hypertension; BMI= Body Mass Index; CRP=c-reactive protein; DAS28=disease activity score

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Physical Function of Patients with RA Varies Importantly Across Countries, and These Differences Are Not Attributed to GDP: Results from Multi-National Study with 17 Countries. Polina Putrik[1], Sofia Ramiro[2], Andras Keszei[3], Ihsane Hmamouchi[4], Maxime Dougados[5], Till Uhlig[6], Tore K. Kvien[6] and Annelies Boonen[1]. [1]Maastricht University Medical Center, Maastricht, Netherlands, [2]Amsterdam Rheumatology Center, University of Amsterdam & Hospital Garcia de Orta, Almada, Portugal, Amsterdam, Netherlands, [3]Uniklinik RWTH Aachen University, Aachen, Germany, [4]Mohamed V Souissi University, Rabat, Morocco, [5]Paris Descartes University, Paris, France, [6]Diakonhjemmet Hospital, Oslo, Norway.

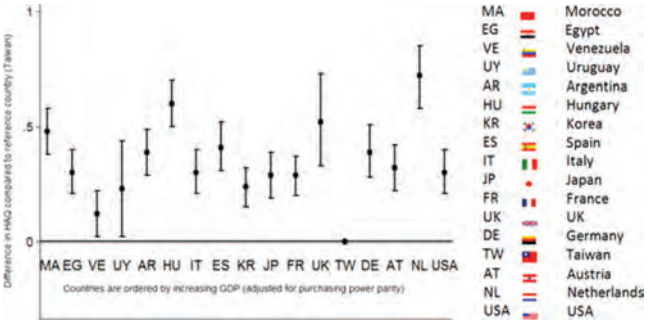
Background/Purpose: Physical function is an important outcome in RA and is essential for patients' quality of life. Is has not yet been sufficiently explored whether country level differences in reported function exist, and whether they interact with individual level factors. The objective of this study was to understand which individual or country level socio-economic factors contribute to functional status of RA patients.

Methods: Data from a cross-sectional multinational (17 countries) study (COMORA) was used. Contribution of age, gender, education, employment to function (as measured by the HAQ) were explored, adjusting for potential confounders. Adjusted differences (Bonferroni correction) between countries were tested. Taiwan was chosen as the reference (country with lowest mean HAQ). Further, country was replaced by gross domestic product (GDP) (low vs high GDP), and contribution of socio-economic welfare was investigated. Improvement in R-square of the two models that included either country or GPD was compared. Interactions between (1) education (2) age and (3) gender with country and GDP were tested.

Results: A total of 3920 RA patients from 17 countries (range 30 to 411) were included in COMORA. Mean age was 56 y.o. (SD13), 82% females, 35% and 39% had primary and secondary education, respectively. Mean HAQ was 1.0 (range 0.7 (Taiwan) – 1.5 (Morocco)). Gradients in HAQ across individual socio-economic factors were seen for education and gender but not age, after adjusting for individual disease characteristics and disfavouring low educated (β=0.16 vs high educated) and females (β=0.11 vs males). Final model was adjusted for comorbidities (Wolfe-Michaud index), total joint count, swollen joint count, erythrocyte sedimentation rate, and marital status. Country differences in HAQ varied from 0.11 (Venezuela) to 0.74 (Netherlands) compared to Taiwan, after adjustment for individual factors (Figure 1). Low GDP countries had 0.11 higher score on HAQ compared to high GDP countries. Contribution of country to R-square (model fit) was 0.05 and of GDP 0.01 (negligible). Interactions were either not statistically significant or not clinically relevant after stratification.

Conclusion: Among socio-economics factors, female gender and low education were independently associated with worse physical function after adjusting for individual disease characteristics. While substantial differences in HAQ exist between countries, socio-economic welfare did not explain these differences. Other cultural factors should be examined. Awareness of existing inequalities is a first step towards clinical and policy actions to reduce them.

Figure 1. Difference in HAQ score between countries, adjusted for confounders.



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A Comparison of the Risk for Cardiovascular Event in Patients with Rheumatoid Arthritis Treated with Biologic Disease Modifiers and Patients Treated with Methotrexate Only. Majed Khraishi[1] and Rana Aslanov[2]. [1]Nexus Clinical Research, St John's, NF, [2]Memorial University of Newfoundland, St.John's, NF.

Background/Purpose: We aimed to investigate whether the 10-year cardiovascular risk (CV) differs between patients with RA treated with Biologic Disease Modifiers (BDMARDs) and Methotrexate (MTX) and with MTX only.

Methods: Patients with RA receiving MTX and BDMARDs were prospectively followed-up from January 2011 to March 2014. Cardiovascular risk was assessed using the Framingham Risk Score (CCS 2009 Guidelines) and compared between cohorts. The presence of traditional CV risk factors was ascertained at the baseline and at every six months of observation up to 24 months.

Results: From 515 patients enrolled at the baseline, 15 patients dropped out of the study. Total 500 patients (75.2% females) with median age 57 years (Q1-Q3=50–65) were prospectively followed for at least 24 months. The mean (SD) age at RA diagnosis was 46.7 (13.5) years with the mean (SD) duration of RA symptoms 10.0 (8.6) years. Overall, females were significantly younger (p (95%CI)=0.016 (0.6–5.7)) while more males were obese (61.3% vs. 49.5%, p=0.023). Forty (8.0%) patients with documented MI and 12 (2.4%) patients with TIA/Stroke had their CV events prior to the study. Twelve patients (2.4%) experienced MI during the observation period with median age for males 68 years and for females 75 years. Significant differences in age, disease duration and activity indices were detected between cohorts. However, no significant changes were found in gender distribution, smoking status, and mean Atherogenic Index (AI) values. RA patients treated with MTX were older at the time of RA diagnosis and enrollment into the study but with significantly shorter duration of disease. 50.2% of patients were treated by Prednisone; 95.8% by MTX. 10-year CV risk was strongly correlated with Prednisone (r=0.122, p=0.006) and MTX only (r=0.178, p<0.001) therapy, and with total number of comorbidities in RA patients (r=0.569, p<0.001). Men had a significantly higher risk for CV event than women at the baseline and 24 months later.

	BASELINE		14.8 (9.0)	24-MONTH		
	MTX	BIO + MTX	P (95%CI)	MTX	BIO + MTX	P (95%CI)
CRP	7.0 (15.5)	14.7 (28.1)	<0.001 (−11.9-(−3.4))	5.5 (8.6)	8.4 (13.9)	0.009 (−5.1-(−0.7))
DAS28	3.1 (1.1)	4.0 (1.2)	<0.001 (−1.1-(−0.7))	2.8 (1.1)	3.4 (1.2)	<0.001 (−0.8-(−0.4))
CDAI	11.9 (9.4)	18.1 (10.0)	<0.001 (−8.0-(−4.5))	9.9 (7.4)	13.6 (9.7)	<0.001 (−5.2-(−2.0))
HAQ	0.7 (0.9)	1.1 (0.8)	<0.001 (−0.6-(−0.3))	0.6 (0.7)	1.0 (0.8)	<0.001 (−0.5-(−0.3))
TC	4.1 (1.9)	3.3 (2.6)	<0.001 (0.4–1.2))	3.8 (2.0)	3.5 (2.5)	0.107 (−0.1–0.7)
HDL-C	1.2 (0.7)	1.1 (1.2)	0.656 (−0.1–0.2)	1.2 (0.7)	1.2 (1.1)	0.703 (−0.2–0.1)
LDL-C	2.5 (1.3)	1.7 (1.4)	<0.001 (0.6–1.1)	2.2 (1.3)	1.2 (1.3)	<0.001 (0.8–1.2)
AI (TC/HDL-C)	3.7 (1.2)	3.6 (1.9)	0.408 (−0.2–0.5)	3.4 (1.1)	3.3 (1.4)	0.434 (−0.2–0.4)
10-year CV Risk	14.8 (9.0)	12.3 (99.3)	0.003 (0.9–4.2)	13.7 (8.6)	11.8 (8.9)	0.016 (0.4–3.5)

Conclusion: Our findings demonstrated significant difference in the 10-year cardiovascular risk at 24 months between the two treatment modalities. The combination of BDMARDs and MTX treatment modality seems to be more beneficial in the reducing patients' risk for CV events. Intensive treatment of chronic inflammation positively affects both patients' arthritis and their RA-dependent CV risk.

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Educational Level and Not Ethnicity an Important Determinant of Disease Progression in Patients with Rheumatoid Arthritis. Sharon Dowell[1], Gail S. Kerr[2], Yusuf Yazici[3], Christopher Swearingen[4], Mercedes Quinones[5], Luis R. Espinoza[6], Edward L. Treadwell[7], Theresa Lawrence-Ford[8], Yvonne Sherrer[9], Angelia Mosley-WIlliams[10], Ignacio Garcia-Valladares[11], Rodolfo Perez Alamino[12], Chunqiao Luo[13], Akgun Ince[14], Adrian Godoy[1] and John Amatruda[1]. [1]Howard University, Washington, DC, [2]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [3]New York University School of Medicine, New York, NY, [4]University of Arkansas, Little Rock, AR, [5]Howard University Hospital, Washington, DC, [6]LSU Medical Center, New Orleans, LA, [7]East Carolina University, Greenville, NC, [8]North Georgia Rheumatology Group, PC, Lawrenceville, GA, [9]Centre Rheum Immunol Arthritis, Fort Lauderdale, FL, [10]Detroit VAMC, Detroit, MI, [11]Hospital General de Occidente, Zapopan, Jal., Mexico, [12]LSUHSC, New Orleans, LA, [13]University of Arkansas for Medical Sciences, Little Rock, AR, [14]St. Louis University, St. Louis, MO.

Background/Purpose: Formal educational level is often used as a surrogate for socioeconomic status and in patients with rheumatoid arthritis (RA), low levels have been associated with greater morbidity and worse disease outcomes. Yet, the role of formal educational level and its impact on meaningful clinical response (MCR) in ethnic minorities with RA is unknown**.** We evaluated the correlation of educational level with meaningful clinical response in ethnic minorities with RA.

Methods: Ethnic Minority RA Consortium (EMRAC) patients with at least one follow up visit were assigned to three educational level categories: high school only (HS), high school with some college, and college graduates. Comparisons between educational categories of demographic (age, gender, race, tobacco use), RA disease status (RF, ACPA, nodules/erosions), and RA treatment (prednisone, DMARD, biologics [anti-TNF, other]) variables were performed between these groups. The frequency of MCR (DRAPID3 [−3.6]) at 3, 6, and 12 months was also evaluated between educational groups.

Results: EMRAC patients (n= 723) with approximately 10 months of follow-up were evaluated (Table 1.). HS patients were significantly older, with longer disease duration and follow-up than those with advanced educational levels. HS patients also had higher baseline RAPID3 scores ($p < 0.001$). Overall, few patients achieved MCR and there was no difference in the frequencies of MCR between education categories at 3, 6 and 12 months. However, in multivariate analyses adjusted for, age, ethnicity, disease duration, and baseline RAPID3 scores, of those who did not achieve MCR, there were more HS patients with significant disease progression (RAPID3 D+0.2) versus college (RAPID3 D-0.5) and college graduates (RAPID3D-0.6)($p = 0.02$).

Conclusion: Regardless of race or ethnicity, RA patients with low formal education levels are at risk of disease progression. In clinical practice, this category of patient needs to be identified early, and focused interventions such as self-efficacy and health literacy instituted in order to improve disease outcomes.

Table. 1

Clinical Characteristics of Educational Categories in EMRAC cohort

	< High School	High School - Some College	College Graduate	P
N	97	320	306	
# of Follow-ups	2.9 (2.5)	3.0 (2.6)	2.9 (2.6)	0.681
Follow-up Length(months)	11.8 (13.1)	9.1 (7.4)	8.8 (6.3)	**0.033**
Age (years)	63.1 (12.5)	56.4 (14.3)	49.5 (15.8)	**<0.001**
Female (N, %)	72 (75.8%)	258 (81.9%)	249 (81.6%)	0.382
Duration (years)	12.0 (11.8)	9.7 (9.1)	8.4 (9.2)	**0.016**
Race				**<0.001**
African-American	36 (47%)	118 (42%)	56 (24%)	
Caucasian	11 (14%)	99 (35%)	151 (63%)	
Hispanic	29 (39%)	65 (23%)	31 (13%)	
RAPID3	13.7 (7.3)	12.8 (7.2)	9.6 (7.0)	**<0.001**
Hx Smoking (N, %)	25 (33.8%)	91 (39.1%)	45 (21.2%)	**<0.001**
RF+ (N, %)	57 (70.4%)	152 (57.6%)	94 (39.7%)	**<0.001**
ACPA+ (N, %)	41 (50.6%)	99 (39.9%)	50 (21.1%)	**<0.001**
Hx Nodules (N, %)	5 (8.1%)	24 (11.9%)	10 (5.8%)	0.111
Hx Erosions (N, %)	22 (33.8%)	54 (25.2%)	36 (19.7%)	0.065
Prednisone (N, %)	38 (39.2%)	119 (37.2%)	79 (25.8%)	**0.003**
DMARD (N, %)	73 (75.3%)	234 (73.1%)	215 (70.3%)	0.560
Biologic (N, %)	28 (28.9%)	96 (30.0%)	119 (38.9%)	**0.036**
RAPID3 −3.6 (N, %)	27 (27.8%)	94 (29.4%)	84 (27.5%)	0.861
Response in 3M, (N, %)	9 (9.3%)	34 (10.6%)	32 (10.5%)	0.928
Response in 6M, (N, %)	14 (14.4%)	66 (20.6%)	56 (18.3%)	0.375
Response in 12M, (N, %)	19 (19.6%)	81 (25.3%)	76 (24.8%)	0.498
Average D RAPID3 Predicted from Model*	0.2 (3.3)	−0.5 (3.4)	−0.6 (3.2)	**0.020**

*Analysis of variance, adjusted for baseline RAPID3, age, race, disease duration

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Angiographic Pattern Among Rheumatoid Arthritis Patients Who Are Hospitalized Due to Acute Coronary Syndrome. Marie Holmqvist[1], Ängla Mantel[2], Tomas Jernberg[3], Stefan James[4], Solveig Wållberg-Jonsson[5] and Johan Askling[6]. [1]Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden, [2]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Solna, Sweden, [3]Department of medicine, Section of Cardiology, Karolinska University Hospital, Stockholm, Sweden, [4]3Department of Cardiology and Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden, [5]Institution of Public health and clinical medicine/ Rheumatology, University of Umeå, Umeå, Sweden, [6]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: We aimed at investigating and to compare the angiographic pattern of stenoses in patients with rheumatoid arthritis (RA) and general population comparators hospitalized due to acute coronary syndrome (ACS). This was done in a population which we have previously shown to be at increased risk for ACS, at increased risk of death following first event of ACS, and with more severe ACS events than the general population [1]. Our purpose was to investigate whether differences in angiographic findings could explain the more severe ACS phenotype.

Methods: Using nationwide Swedish registries, a cohort of individuals with established RA and general population individuals matched on sex, year of birth, area of residency and educational level were identified between 2006 and 2009. They were followed for a year to identify all cases hospitalized with a first time ACS and admitted to a coronary intensive care unit (CICU). For those with ACS who underwent angiography, the occurrence and extent of coronary stenoses were compared using logistic regression models. Analyses were stratified by diagnosis resulting in coronary angiography (non-ST-elevation myocardial infarction [NSTEMI], ST-elevation myocardial infarction [STEMI]), and adjusted for age and sex. The overall analyses were adjusted for age, sex, and diagnosis.

Results: 1135 RA patients and 3184 general population individuals were hospitalized with ACS during follow-up. Of those, 743 (65%) RA patients and 2203 (69%) general population comparators were admitted to a CICU within ±10 days of the event. 531 (71%) of those RA patients and 1683 (76%) of those general population comparators underwent angiography in conjunction with the ACS event. After adjusting for diagnosis resulting in angiography the adjusted OR for undergoing angiography was 0.84 (95% confidence interval [CI] 0.69, 1.02). Mean age at angiography was 70 years in both groups. 58 % of the RA patients and 53 % of the general population were women. STEMI was a more common indication for investigation in RA (45%) than in the general population (36%). RA patients were more likely to have three-vessel disease than the general population, even after adjusting for diagnosis, age, and sex, OR 1.53 (95% CI 1.04, 2.26). When stratified by indication, we noted an increased risk of having any stenosis, and for three-vessel disease for those with STEMI and for those with NSTEMI. All ORs are found in the table below.

Conclusion: RA patients with ACS seem to have more stenoses and a more unfavourable angiographic pattern than the general population with ACS. This, however, is seen regardless of indication for investigation and therefore does not seem to offer a ready explanation for the more severe presentation of ACS seen in RA.

Table. Odds ratios (OR) and 95% Confidence Intervals (CI) comparing findings on angiography in RA patients and general population comparators. Normal findings are used as reference group in all models.

	Overall OR (95% CI) Adjusted for age, sex, and diagnosis	NSTEMI OR (95% CI) Adjusted for age, sex	STEMI OR (95% CI) Adjusted for age, sex
Any stenosis	1.18 (0.88–1.59)	1.12 (0.80–1.56)	1.50 (0.79–2.85)
Any main stem	1.22 (0.76–1.96)	1.10 (0.63–1.93)	1.76 (0.67–4.61)
One vessel, not main stem	1.12 (0.81–1.55)	1.02 (0.70–1.49)	1.40 (0.72–2.72)
Two vessels, not main stem	1.12 (0.78–1.60)	0.99 (0.64–1.52)	1.65 (0.81–3.38)
Three vessels, not main stem	1.53 (1.04–2.26)	1.44 (0.91–2.28)	1.97 (0.92–4.24)

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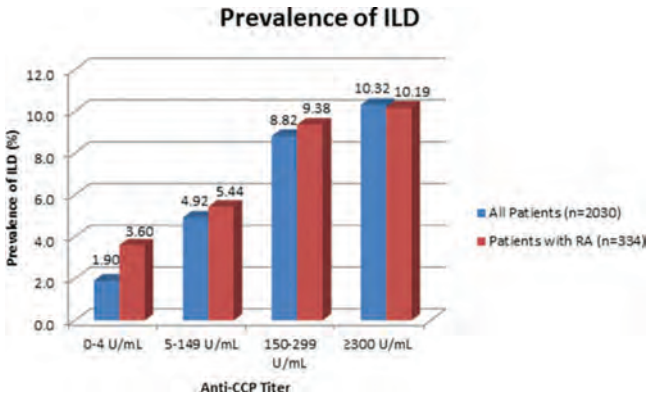
Anti-Citrullinated Peptide Antibody Titers and the Prevalence of Interstitial Lung Disease in Patients with and without Rheumatoid Arthritis. Chase Correia[1], Melissa R. Bussey[2], Brittany Panico[1], Rong Guo[1] and Rochella A. Ostrowski[3]. [1]Loyola University Medical Center, Chicago, IL, [2]Division of Rheumatology, Loyola University Medical Center, Maywood, IL, [3]Loyola University Medical Center, Maywood, IL.

Background/Purpose: Rheumatoid arthritis (RA) is a multisystem inflammatory disease characterized by a symmetric, destructive polyarthritis. Interstitial lung disease (ILD) is an extra-articular manifestation that occurs in 7.7% of RA patients and confers a poor prognosis. The anti-citrullinated peptide (anti-CCP) antibody has a specificity of greater than 90% for RA and is associated with worse articular outcomes. Four studies have evaluated the association between anti-CCP and ILD in RA patients with contradictory results. Furthermore, there are no published observations of an association between the extent of the anti-CCP titer elevation and the prevalence of ILD. The objective of this study is to determine whether the anti-CCP titer is associated with the prevalence of ILD in patients with and without RA.

Methods: A chart review was performed of all adult patients with anti-CCP testing between January 1, 2007 and December 31, 2012 at a single academic hospital. Patients were excluded if they had any of 12 other exposures or conditions known to cause ILD. Patients meeting inclusion criteria were divided into four groups based on anti-CCP titers: 0–4 U/mL (negative titer), 5–149 U/mL (low titer), 150–299 U/mL (moderate titer), and 300 U/mL or greater (high titer). Charts were reviewed to determine a diagnosis of RA by a rheumatologist or American College of Rheumatology (ACR) 2010 criteria, a diagnosis of ILD by imaging, relevant laboratory analysis, and treatment of RA. Fisher's exact test and logistic regression were used to compare the prevalence of ILD in the anti-CCP titer groups and to adjust for potential confounders.

Results: 2,030 patients met inclusion criteria, and 334 of these patients were diagnosed with RA by a rheumatologist or 2010 ACR criteria. Among all patients tested for anti-CCP, a progressively higher prevalence of ILD was associated with each anti-CCP titer group ($p<0.0001$) (Figure 1). However, the association was diminished when adjusting for age, C-reactive protein (CRP), tobacco use, and a diagnosis of RA (odds ratio: 1.18, 95% confidence interval: 0.78–1.78). In patients diagnosed with RA, there was a similar progression in the prevalence of ILD as anti-CCP titers increased, although this finding did not achieve statistical significance ($p=0.18$).

Conclusion: An increasing prevalence of ILD was observed in patients with higher levels of anti-CCP titers, regardless of a diagnosis of RA. However, additional factors, particularly age and disease activity represented by CRP, may influence these findings. To our knowledge, this is the first study to evaluate the relationship of increasing anti-CCP titers and ILD prevalence. Larger investigations are essential to better define the role of anti-CCP in the development of ILD and to determine whether higher anti-CCP titers further augment the risk of developing ILD.



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The Impact of Rheumatoid Arthritis Activity and Medications on Pregnancy Outcomes. Megan E. B. Clorwse. Duke University Medical Center, Durham, NC.

Background/Purpose: While rheumatoid arthritis (RA) has historically improved in pregnancy, recent studies suggest the improvement may not be dramatic now that we are able to control the disease better outside of pregnancy. TNF inhibitors are now routinely continued during pregnancy for women with inflammatory bowel disease (IBD) because active IBD is associated with pregnancy morbidity. The link between RA activity and pregnancy outcomes.however, is less clear. We sought to explore the role that RA activity and medications play in pregnancy outcomes.

Methods: Pregnancies in women with RA from a prospective registry were reviewed to determine the extent that RA activity and medications in the 1st and 2nd trimesters impacted pregnancy outcomes. Disease activity was divided into 2 levels based on the worst DAS-CRP3 and/or physician's global assessment in the first 24 weeks of pregnancy. Chi-square and non-parametric tests were used for univariate analysis. A general estimating equation was used in multivariate analysis to account for multiple pregnancies in some women.

Results: A total of 31 pregnancies in 25 women with RA or JIA were enrolled in the registry before 24 weeks gestation. Seven pregnancies were in women with JIA and 24 with adult-onset RA. Two ended with first trimester miscarriages; both in women with low RA activity without prednisone or TNF inhibitor exposure, but one took methotrexate in pregnancy. Of the remaining 29 pregnancies, 15 (51.7%) had RA that was either mild or in remission throughout the 1st and 2nd trimesters and 14 (48.3%) had RA that was moderately to severely active during this period. 6 of 29 (20.7%) live births had poor outcomes: 4 with preterm delivery, 1 with preeclampsia, and 1 with preterm preeclampsia.

The rate of Sulfasalazine (SSZ), hydroxychloroquine (HCQ), and TNF inhibitor use was not statistically different for women with low vs high RA activity. Women with high RA activity, however, were more likely to take prednisone (57.1% vs 13.3%, $p=0.02$).

Significantly more women with preterm birth and/or preeclampsia had moderate/severe RA in early pregnancy (see table). While not statistically significant, more pregnancies with poor outcomes were exposed to prednisone and fewer to TNF inhibitors early in pregnancy. SSZ and HCQ were not associated with pregnancy outcomes. Methotrexate was associated with preterm birth.

A logistic regression model demonstrated that lower RA activity and use of a TNF inhibitor in the 1st and 2nd trimesters were associated with term birth without preeclampsia. Taking prednisone in the first half of pregnancy did not appear to impact pregnancy outcomes.

Conclusion: In this era of treat-to-target management of RA, our paradigm for RA pregnancy management may need adjusting. By controlling RA activity with medications considered relatively safe in pregnancy, we may be able to improve both the pregnancy experience and pregnancy outcomes.

Table: RA activity and medications in the 1st and 2nd trimesters of pregnancy for live births:

	All Live Births	Full term delivery without preeclampsia	Preterm delivery and/or preeclampsia	p-value
Number of live births	29	23 (79.3%)	6 (20.7%)	
Moderate/severe RA	14 (45.2%)	8 (34.8%)	6 (100%)	0.006
Physician's Global Assessment	63.7 (22.6)	Mean 69.9 (SD 20.1) Range: 25–100	Mean 40 (SD 15.2) Range: 20–60	0.005
Any prednisone use	10 (34.5%)	6 (26.1%)	4 (66.7%)	0.143
Prednisone dose	9.5mg (5.37)	10mg (SD 6.89) Range: 2.5–20mg	8.75mg (SD 2.5) Range: 5-10mg	0.83
Sulfasalazine	7 (24.1%)	6 (26.1%)	1 (16.7%)	0.55
Hydroxychloroquine	13 (44.8%)	11 (47.8%)	2 (33.3%)	0.44
Methotrexate	2 (6.9%)	0	2 (33.3%)	0.037
TNF inhibitor use	9 (31.0%)	8 (34.8%) 5 continuous 3 started in pregnancy	1 (16.7%) 1 started in pregnancy	0.38

Disclosure: M. E. B. Clowse, UCB Pharma, 5.

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Studies on Ageing and the Severity of Radiographic Joint Damage in Rheumatoid Arthritis. L. Mangnus[1], H.W. van Steenbergen[1], E. Brouwer[2], E. Lindqvist[3], M. Reijnierse[1], P.K. Gregersen[4], S. M. Rantapää-Dahlqvist[5], D. M. van der Heijde[1] and A. H. M. van der Helm- van Mil[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [3]Lund University, Lund, Sweden, [4]The Feinstein Institute for Medical Research, Manhasset, NY, [5]Umeå University, Umeå, Sweden.

Background/Purpose: The Western population is getting older; consequently the proportion of elderly persons presenting with Rheumatoid Arthritis (RA) is increasing. We studied whether age is associated to the severity of RA at presentation and during the disease course, measured using radiographic joint damage.

Methods: Relationship between age and structural damage was studied in 7,232 radiographs of hands and feet of 1,879 RA-patients included in five European and North-American cohorts (Leiden EAC, Groningen, Lund, Umeå, Wichita). Within 702 early RA-patients included in the Leiden EAC between 1993–2006 associations between age and joint space narrowing (JSN) and erosions were evaluated separately; secondly mediation analyses were performed to explore whether the association of age with joint damage was mediated by symptom duration at diagnosis, swollen joint count (SJC), tender joint count (TJC), CRP or ACPA. Finally, 56 RA-patients included in the Leiden EAC between 2010–2012 underwent 1.5 Tesla MRI of the most symptomatic hand and foot at baseline and radiographs at baseline and after 1 year. The MRI-inflammation score (RAMRIS-synovitis plus bone marrow edema) was evaluated.

Results: In all cohorts, age at diagnosis was positively associated with more severe joint damage at baseline and during follow-up. A meta-analysis of these cohorts revealed that per year increase in age, patients had 2.6% (β1.026 $p<0.001$) more joint damage. Both JSN and erosion-scores correlated with age; pearson correlation coefficients were significantly stronger for erosion-scores than for JSN-scores (r 0.38 versus 0.29, $p=0.006$). Structural damage in PIP, CMC-1 and MTP-1 joints increased with age, however a similar increase was observed in wrist, MCP and MTP(2–5)-joints. Together this suggests that the association of joint damage with age cannot be totally explained by osteoarthritis. Age at diagnosis was associated with a shorter symptom duration (β0.99, $p= 0.011$), a lower odds on ACPA-positivity (OR 0.98 $p<0.001$) and was not associated with the SJC or TJC. Older age was positively associated with CRP (β1.016, $p<0.001$) but in a multivariate analysis including age and CRP, CRP was not associated with radiographic damage (β1.00, $p=0.14$). Therefore, symptom duration, ACPA and regular measures of inflammation did not mediate the association between age and joint damage. Finally, we questioned whether subclinical inflammation was a mediator. Age was significantly associated with the severity of MRI-detected inflammation when adjusted for CRP and SJC (β1.018, $p=0.027$). The effect size of the association between age and joint damage reduced after including MRI-inflammation in the analysis (from β1.032, $p=0.004$ to β1.025, $p=0.021$, adjusted for CRP and SJC), suggesting partial mediation.

Conclusion: RA-patients with a higher age at diagnosis had more severe joint damage at the time of diagnosis and during the disease course. This effect was partially explained by more severe subclinical joint inflammation at higher age. To what extend the remaining part of the effect is caused by disease-specific processes or is related to 'normal ageing' needs to be explored in further studies.

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Patient Global Impression of Change for Patient Reported Outcomes in Rheumatoid Arthritis: Impact of Comorbidities. Pankaj Bansal[1], Aneet Kaur[1], Horace Spencer[1] and Nasim A. Khan[2]. [1]University of Arkansas for Medical Sciences, Little Rock, AR, [2]University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR.

Background/Purpose: Understanding patient's perspective of minimally clinically important difference (MCID) in health (or disease) status is important to improve patient-centered clinical care and planning and interpretation of clinical trial results. The aim of this study was to estimate mean changes in patient reported outcomes (PROs) and a PRO-based composite index [Routine Assessment of Patient Index Data 3 (RAPID3)] and assess the impact of comorbidities on MCID in rheumatoid arthritis (RA) patients.

Methods: A retrospective study of RA patients receiving routine clinical care at a single academic center from 2009 to 2012 was conducted. Eligibility criteria were a board-certified Rheumatologist diagnosed RA and ≥ 2 Rheumatology clinic visits. A patient completed questionnaire is part of routine clinical practice and includes patient's global impression of change compared to their last Rheumatology clinic visit on a 5-point Linkert scale (much better, somewhat better, about the same, somewhat worse, much worse). Data on socio-demographics; RA characteristics; PROs [functional status by Multi-Dimensional Health Assessment Questionnaires (MDHAQ); pain, patient's global assessment (PTGL) by 21-point Numeric Rating Scale; RAPID3; and comorbidities were extracted in standardized manner from medical records. Comorbidity burden was quantified by a composite comorbidity score (range: 0–9) [1] and categorized as low (0–1), moderate (2–3) and high (>3). Random effects analysis of variance models were used to assess the association between change in disease characteristics and PGIC classification. Since each subject may have multiple observations in the data, a random effects term was included to account for the correlation among observations from the same subject.

Results: Data on 155 patients [125 (80.6%) females; 112 (72.3%) white; median (interquartile range, IQR) age of 58 (50–66) years; RA duration 6 (1.4–9.8) years; seropositive 76.5%] were available for analysis. 46 (29.7%), 64 (41.3%), and 45 (29%) patients had low, moderate and high comorbidity burden respectively. Table shows the estimated mean of the study measures. Negative values means improvement in scores compared to prior Rheumatology visits. For each PRO and RAPID3 there was strong interaction with comorbidity burden. In general patients with low comorbidity burden have higher threshold for change for MCID than those with moderate to high comorbidity burden (Table).

Conclusion: Comorbidities have strong influence on RA patient's assessment of change of their health status. Comorbidities need to be considered when interpreting MCID.

	Somewhat better	About the same	Somewhat worse
MDHAQ (0-10)*			
Low comorbidity burden	−0.51	0.09	2.45
Moderate comorbidity burden	−0.43	−0.36	0.73
High comorbidity burden	−0.79	−0.34	−0.31
Pain (0-10)*			
Low comorbidity burden	−1.82	0.64	1.95
Moderate comorbidity burden	−0.34	−0.43	0.87
High comorbidity burden	−0.35	−0.13	0.41
PTGL (0-10)*			
Low comorbidity burden	−0.51	0.09	2.45
Moderate comorbidity burden	−0.43	−0.36	0.73
High comorbidity burden	−0.79	−0.34	−0.31
RAPID3 (0-30)*			
Low comorbidity burden	−2.85	0.76	4.43
Moderate comorbidity burden	−1.81	−0.97	1.94
High comorbidity burden	−1.15	−0.62	0.24

* P value < 0.001 for interaction of the variable with comorbidity burden.

Disclosure: P. Bansal, None; **A. Kaur**, None; **H. Spencer**, None; **N. A. Khan**, None.

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Subaxial Cervical Spine Involvement in Symptomatic Rheumatoid Arthritis Patients: Comparison with Cervical Spondylosis. Helena Borrell[1], Javier Narváez[2], Jose Antonio Narvaez[3], Marta Serrallonga[4], Carmen Gomez Vaquero[1], Eugenia de Lama[1], Javier Hernandez Gañan[3] and Joan Miquel Nolla[1]. [1]Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, [3]Hospital Universitari de Bellvitge - IDIBELL, Barcelona, Spain, [4]Institut de Diagnostic per la Imatge (IDI), Centre Bellvitge, Barcelona, Spain.

Background/Purpose: To investigate the frequency, location, nature, and clinical significance of subaxial involvement (below C1-C2) in a series of patients with rheumatoid arthritis (RA) and symptomatic involvement of the cervical spine.

Methods: Forty-one patients with RA were studied with cervical spine MRI. A comparative study of the incidence of the different types of subaxial lesions was also performed with respect to 41 age- and sex-matched patients with symptomatic cervical spondylosis.

Results: Stenosis of the spinal canal was found at the subaxial level in 85% of RA patients, and at the atlantoaxial level in 44%. The comparative study with cervical spondylosis revealed significant differences in the type and frequency of subaxial lesions (Table 1). In RA patients, subaxial stenosis seems to be the consequence of both the inflammatory activity of the disease (multilevel vertebral subluxations, inflammatory involvement of cervical spine ligaments, interapophyseal synovitis, bone marrow edema involving the vertebral plates and the interapophyseal joints, spinous process damage, and acquired vertebral blocks) and mechanical-degenerative changes (discopathy and ligamentum flavum hypertrophy).

Unconditional logistic regression analysis was used to identify MRI parameters of subaxial spine involvement associated with the development of

neurological dysfunction (Ranawat class II or III). Evidence of alterations in the signal intensity of the spinal cord was the only independent risk factor found for the development of neurological dysfunction (p=.01; OR=11.43), increasing the risk 11-fold. There was a trend toward statistical significance for spinal cord compression (p=.06; OR=3.95). The presence of stenosis of the subaxial spinal canal without evidence of cord compression did not achieve statistical significance (p=.17). These data suggest that neurological manifestations correlate poorly with MRI findings at this level.

Table 1. Frequency of subaxial lesions in patients with RA and Spondylosis.

	RA patients N = 41	Spondylosis N = 41	p value
Stenosis of the subaxial canal	85%	27%	0.0000003
Spinal cord compression	34%	0%	0.0001
Alteration in signal intensity of the spinal cord	27%	0%	0.0003
Bone marrow edema involving the vertebral plates and the interapophyseal joints	27%	2%	0.003
Inflammatory involvement of cervical spine ligaments (interspinal ligaments and/or ligamentum nuchae)	32%	0%	0.0002
Interapophyseal or facet joint synovitis	17%	0%	0.012
Synovitis of the uncovertebral joints	0%	0%	–
Spinous process damage (sharpening, erosions, sclerosis or fusion)	7%	0%	NS
Pannus formation	0%	0%	–
Discopathy (disk bulging or disruption and/or herniation)	90%	98%	NS
Ligamentum flavum hypertrophy	66%	22%	0.0001
Degenerative spinal osteophytosis	71%	78%	NS
Vertebral subluxation	24%	5%	0.026
Vertebral ankylosis	24%	2%	0.007
Sclerosis and/or hypertrophy of the interapophyseal joints	0%	49%	0.000001
Sclerosis and/or hypertrophy of the uncovertebral joints	0%	17%	0.0012

NS = not significant.

Conclusion: Subaxial stenosis seems to be the consequence of both the inflammatory process and mechanical-degenerative changes. Despite its frequency, it was not usually related to the occurrence of myelopathy symptoms, not even in cases with MRI evidence of spinal cord compression. These data seem to indicate a notable behavioral adaptation of this segment.

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The Longitudinal Course of Fatigue in Rheumatoid Arthritis – Results from the Norfolk Arthritis Register. Katie L Druce[1], Gareth T Jones[1], Gary J. Macfarlane[1], Suzanne M. Verstappen[2] and Neil Basu[1]. [1]University of Aberdeen, Aberdeen, United Kingdom, [2]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Fatigue is common and burdensome in Rheumatoid Arthritis (RA). Though RA fatigue progression varies significantly between individuals, to date, published analyses have only considered average changes in fatigue. The aim of the current study was to determine if it is possible to distinguish participants who follow distinct trajectories of fatigue reporting over time and thus potentially inform to whom specific management should be targeted.

Methods: Participants from the Norfolk Arthritis Register (NOAR), a long-term inflammatory polyarthritis (IP) inception cohort, who met 1987 ACR RA criteria reported levels of fatigue (0–100mm visual analogue scale (VAS)) at recruitment and annually thereafter for four years. Among those with clinically relevant fatigue at recruitment (VAS≥20mm), changes in fatigue were calculated over the four years of follow-up; clinically significant improvements were defined as ≥10mm. Latent fatigue trajectory groups were determined using sex-stratified group-based trajectory modelling. Baseline variables (demographic, clinical and patient-reported) were compared between identified groups using descriptive statistics (p<0.05 considered significant).

Results: In 338 participants (30.2% male), there were only small average improvements in fatigue from recruitment to one (6.0mm, SD 26.9) and four years later (5.5mm, 29.3), yet improvements were clinically significant for 45.2% and 56.0% of participants at these follow-ups, respectively. The best fitting models revealed two fatigue trajectories in men (improved, and moderate-high), and three trajectories in women (as the male group, plus an additional 'High' trajectory (Figure 1)).

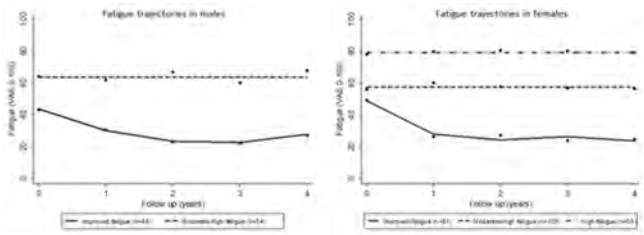

Figure 1. Fatigue trajectories in males (left) and females (right).

To determine the characteristics of those likely to benefit from fatigue-specific interventions, baseline variables were compared between those who improved and all other participants ('non-improved'). In both sexes, non-improvers reported significantly poorer scores for disability, pain, fatigue and sleep problems, at baseline. Female non-improvers were significantly younger, reported more disease activity and use of antidepressants and NSAIDs. Whereas, in males, the use of analgesics at recruitment was greater among non-improvers; as was the proportion of patients unable to work due to illness.

Conclusion: Among a group of patients who, on average, show only small improvements in fatigue, significant variation in fatigue progression exists. At presentation, it is possible to identify and characterise sub-groups of patients who do not improve. Such patients are most likely to require early and targeted interventions, to alleviate fatigue.

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Disease Characteristics and RA Development in Undifferentiated Arthritis: A 2-Year Follow-up Study of 413 Patients with Arthritis of Less Than 16 Weeks Duration. Gina Hetland Brinkmann[1], Ellen Sauar Norli[1], Tore K. Kvien[1], Anne Julsrud Haugen[2], Lars Grøvle[2], Halvor Nygaard[3], Cathrine Thunem[4], Maria Dahl Mjaavatten[1] and Elisabeth Lie[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Østfold Hospital Trust, Fredrikstad, Norway, [3]Lillehammer Hospital of Rheumatic Diseases, Lillehammer, Norway, [4]Telemark Hospital, Skien, Norway.

Background/Purpose: Correct identification of the subset of patients with undifferentiated arthritis (UA) who will develop rheumatoid arthritis (RA) is important to enable initiation of appropriate treatment. Our objectives were to compare baseline characteristics and treatment of UA patients developing vs. not developing RA according to the 2010 ACR/EULAR RA classification criteria (UA-RA vs. UA-non RA) over a 2-year follow-up period, and to investigate the relationship between clinical RA diagnosis and fulfilment of the RA criteria in these patients.

Methods: Patients (18–75 years old) with ≥1 swollen joint of ≤16 weeks duration were from 2004 included in a multi-center longitudinal observational study and followed for 2 years with examinations at 0, 3, 6, 12 and 24 months. Patients with arthritis due to trauma, septic arthritis, crystal arthritis and osteoarthritis were excluded. Mann-Whitney U test, independent samples T test and chi-square test were used to compare baseline characteristics between UA-non-RA and UA-RA patients.

Results: 1119 patients were included during the period 2004–2010 (mean (SD) age 46(15) years, 55% females, median ((25, 75 perc) duration of joint swelling 34(13, 66) days). Patients with a clinical diagnosis of a rheumatic disease other than RA, and those without available anti-CCP/RF or follow-up data were excluded. Consequently, 663 patients were eligible for the current analyses, and 250 (37%) of these patients fulfilled the 2010 ACR/EULAR RA classification criteria at baseline. Among the remaining 413 patients, who were denoted UA, 27 patients (7%) were classified as RA during follow-up. 21/27 (78%) of these UA-RA patients fulfilled the criteria within the first 6 months. 58/386 patients (15%) of patients started DMARDs (3 patients started biologics for diagnosis of AS, RA and UA, respectively) vs. 16/27

(59%) in the UA-RA group (3 patients on biologics, all with clinical RA diagnosis) ($p<0.001$). In both groups approx. 2/3 of those started on DMARDs did so within the first 3 months and were mostly started on methotrexate. 22/386 (6%) of all the UA-non-RA were given a clinical diagnosis of RA during follow-up (19 of these patients were anti-CCP and RF negative).

Comparison of baseline characteristics between the UA-non-RA and UA-RA patients

		UA-non-RA (n=386)	UA-RA (n=27)	P-value
Age, mean (SD)		46.6 (14.8)	51.3 (13.8)	0.11
Female gender, n (%)		**207 (53.6)**	**20 (74.1)**	**0.039**
Duration of joint swelling, days, median (25, 75 perc.)		31 (10,66)	30 (14,60)	0.75
Body mass index, mean (SD)		25.9 (4.4)	26.2 (4.4)	0.707
Smoker ever, n (%)		214 (55.7)	21 (77.8)	0.09
RF and/or ACPA positive, n (%)		**15 (3.9)**	**10 (37.0)**	**<0.001**
Small joint involvement, n (%)		**168 (43.5)**	**12 (55.6)**	**0.049**
Shoulder involvement, n (%)		**5 (1.3)**	**4 (14.8)**	**0.001**
Ankle involvement, n (%)		**74 (19.2)**	**1 (3.7)**	**0.04**
ESR, mm/h, median (25,75 perc.)		18 (9,36)	23 (3,28)	0.42
CRP, mg/L median (25,75 perc)		10 (8,38)	8 (3,21)	0.96
68-SJC*, median (25,75 perc.)		**1 (1,3)**	**2 (1,6)**	**0.005**
28-TJC, median (25,75 perc.)		**1 (0,2)**	**2 (1,5)**	**<0.001**
Assessor global VAS, mean (SD)		**29.2 (16.7)**	**37.6 (18.3)**	**0.012**
Patient global VAS, mean (SD)		**50.6 (24.2)**	**62.4 (22.9)**	**0.015**
DAS 28, mean (SD)		**3.5 (1.0)**	**4.3 (1.0)**	**<0.001**
HAQ, mean (SD)		**0.69 (0.58)**	**1.17 (0.80)**	**<0.001**
Criteria points, median (25,75 perc.)		**2 (1,4)**	**4 (3,5)**	**<0.001**
Criteria points distribution	**5 points**	**n=21**	**n=11**	**<0.001**
	4 points	**n=80**	**n=7**	
	3 points	**n=83**	**n=6**	
	2 points	**n=73**	**n=0**	
	1 point	**n=99**	**n=2**	
	0 points	**n=30**	**n=1**	

***Standard 66-swollen joint count plus hips**

Conclusion: Among 413 patients with UA of ≤16 weeks duration only 7% fulfilled the 2010 RA classification criteria during 2 years of follow-up. Female gender, positive RF and/or ACPA, shoulder arthritis and number of involved joints were among the factors associated with RA development while ankle arthritis was more common in UA-non-RA patients. Some patients (mostly RF and/or ACPA negative) were given a clinical diagnosis of RA despite not fulfilling the criteria, but the proportion was low (6%).

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1384

Fibromyalgia and Its Effect on Treatment Response in Early Rheumatoid Arthritis Patients. Josefina Durán Santa Cruz[1], Bernard Combe[2], Jingbo Niu[1], Nathalie Rincheval[3], Cécile Gaujoux-Viala[4] and David T. Felson[1]. [1]Boston University School of Medicine, Boston, MA, [2]Hôpital Lapeyronie, Montpellier, France, [3]Institut Universitaire de Recherche Clinique, Montpellier, France, [4]EA 2415, Montpellier I University, Nîmes University Hospital, Rheumatology Department, Nîmes, France.

Background/Purpose: Fibromyalgia (FM) occurs commonly in patients with rheumatoid arthritis (RA) and its effect on treatment response is unknown. In this study we aimed to evaluate if patients with RA and concomitant FM have an impaired response to treatment measured by traditional activity scores.

Methods: Patients from the ESPOIR cohort were analyzed. This prospective cohort included 813 patients with early arthritis not initially receiving disease-modifying antirheumatic drugs (DMARDs). We defined FM at baseline using Pollard et al. (Rheumatology (Oxford) 2010;49:924–928) validated criteria of tender joint count at least 7 higher than swollen joint count (72% sensitivity and 98% using ACR 1990 FM criteria as gold standard). Among the 697 patients who met RA classification (either ACR 1987 or ACR/EULAR 2010) criteria, we studied two groups, one with and the other without FM. The following endpoints were compared at 6, 12 and 18 months using a mixed linear regression model: 28-joint Disease Activity Score (DAS28), Simple Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and the Health Assessment Questionnaire. In addition attainment of low disease activity (LDA) (DAS28<3.2) and remission (DAS28<2.6, SDAI<3.3, CDAI<2.8) at these timepoints were analyzed using a log binomial regression.

Results: At baseline, patients with FM (n=120) had a higher DAS28, SDAI, CDAI and HAQ than patients with isolated RA (n=548). While they started out higher, DAS28 and other disease activity scores improved to a similar extent as in the isolated RA group. However, scores remained consistently higher among FM patients. (see figure) Achievement of LDA and of remission was significantly less likely in subjects with FM and few would have met treat to target goals.

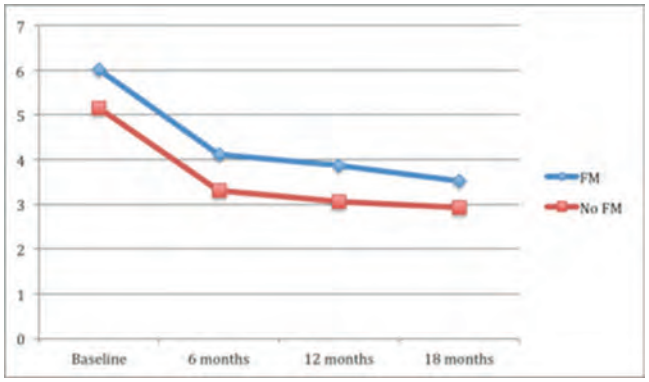
Conclusion: Patients with FM and RA have a similar response to treatment according to a decrease in indexes of disease activity but may miss the target of remission or low disease activity.

Table 1. Comparison of rheumatoid arthritis activity scores and radiologic scores over follow up according to the presence of fibromyalgia

	FM	No FM	Difference in scores	P value*
DAS 28	3.50	3.05	0.45	<0.0001
SDAI	16.09	11.54	4.55	<0.0001
CDAI	14.98	10.75	4.23	<0.0001
HAQ	0.63	0.45	0.17	0.0002
SJC	2.32	2.18	0.14	0.5476
TJC	5.64	3.27	2.37	0.0001
PtGH VAS	3.82	3.01	0.81	<0.0001
PhGH VAS	2.88	2.38	0.51	0.0044
CRP (mg/l)	0.75	0.84	0.09	0.4147
ESR (mm/h)	13.99	15.05	1.06	0.3602
SHARP	7.33	7.68	0.34	0.3125

*P values denote the overall significance of a linear regression adjusting for baseline score, gender, age and smoking status. HAQ: Health Assessment Questionnaire; SJC: swollen joint counts, TJC: tender joint counts PtGH: patient global health; PhGH: physician global health; VAS: visual analog scale; RF: rheumatoid factor; CCP: Anti-citrullinated protein antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

Figure 1. DAS28 score at different time points grouped by fibromyalgia presence



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What Discriminates Best Flares in Rheumatoid Arthritis (RA)? a Subanalysis of the Strass Treatment Tapering in RA Study. Agnès Danré[1], Bruno Fautrel[2], Toni Alfaiate[3], Thao Pham[4], Jacques Morel[5], Emmanuelle Dernis Labous[6], Philippe Gaudin[7], Olivier Brocq[8], Elisabeth Solau-Gervais[9], Jean-Marie Berthelot[10], Jean Charles Balblanc[11], Xavier Mariette[12], Florence Tubach[13] and Laure Gossec[14]. [1]La Pitié Salpêtrière, Paris, France, [2]Pitie Salpetriere Hospital, Paris, France, [3]APHP, Hospital Bichat, Paris, France, [4]Sainte Marguerite Hospital, Marseille, France, [5]Hôpital Lapeyronie, Montpellier, France, [6]Ch Du Mans, Le Mans, France, [7]Hopital Sud Grenoble, Echirolles, France, [8]Hospital of Princesse Grâce de Monaco, Monaco, France, [9]University Hospital of Poitiers, Poitiers, France, [10]CHU Nantes (Nantes University Hospital), Nantes, France, [11]Ch de Belfort, Belfort Cedex, France, [12]University Hospital, Le Kremlin Bicetre, Paris, France, [13]Universite Paris Diderot, Paris, France, [14]UPMC GRC08, Paris 06 University, Pitié Salpétrière Hospital, Paris, France.

Background/Purpose: Flares in rheumatoid arthritis (RA) are a patient-perceived increase of disease activity which might be particularly important to assess in the context of treatment tapering. However, there is little data on what patient-perceived flares really encompass. In a treatment tapering study, STRASS, patients were asked about flares, and many validated outcomes were collected.

The objective was to explore the discrimination properties of different validated outcomes for flares, by comparing these outcomes between visits where patients self-reported flares, and visits without flares, in the STRASS tapering study.

Methods: The STRASS study was a step-down randomized trial (ref). Patients had RA, were treated with adalimumab or etanercept for ≥12 months, and were in DAS 28-remission (DAS≤2.6) for ≥6 months. Patients were randomized to either the "spacing"(S) arm (where the TNF blocker was tapered gradually) or the "maintaining"(M) arm, over 18 months. Flares were evaluated through a patient-reported questionnaire every 3 months, asking: "Concerning the last 3 months, did you experience symptoms of a relapse of RA?". RA outcomes, including HAQ, patient global assessment, SF36, pain, tender joint count, swollen joint count, ESR and CRP were compared between visits with flares and visits without. Cohen's effect size was calculated for indicative purposes, without adjustment on these repeated measures. Effect size is considered high when above 0.8.

Results: In all, 137 patients were included in STRASS, 64 and 73 in the S and M arms respectively: age (mean±SD) 55±11 yrs, females 78%, RA duration 9±8 years. Over the 18 months of the study, the mean number of visits where the patient reported at least one flare (out of a possible total number of visits of 6 visits) was 1.87±1.74, with 2.44±1.68 visits with flares in the S arm, and 1.37 ±1.65 visits with flares in the M arm (p=0.0001). Overall, 55 patients (88.7%) in the S arm and 40 patients (55.6%) in the M arm reported flares at least once. Comparisons between visits at which patients reported flares, and visits without, showed statistically significant differences concerning all the outcomes, with effect sizes comprised between 0.27 [0.12–0.42] and 1.09 [0.94–1.25] (table). The highest effect sizes were observed for patient global assessment and SF36 PCS, and the lowest for ESR.

Conclusion: Patient-perceived flares are frequent during treatment tapering. Patient-reported outcomes discriminated better between visits with versus without flares, than physician measures or biology. More work is needed on the concept of flares.

Ref: Fautrel B et al. Arthritis Rheum 2013; 65: S1150.

Table:

	Visits with patient-reported flares. N=256	Visits without patient-reported flares. N=684	Indicative effect size [95% CI]
Patient global assessment 0–10	2.92 ± 2.41	1.11 ± 1.07	1.09 [0.94-1.25]
SF36 PCS	42.28 ± 8.86	49.70 ± 7.66	−0.91 [−1.13–−0.70]
Tender joint count	4.14 ± 5.73	0.97 ± 2.71	0.78 [0.63-0.94]
Swollen joint count	2.00 ± 3.12	0.41 ± 1.03	0.77 [0.62-0.92]
HAQ	0.67 ± 0.66	0.37 ± 0.53	0.56 [0.35-0.77]
SF36 MCS	43.77 ± 9.96	48.43 ± 10.05	−0.52 [−0.73–−0.30]
CRP, mg/l	5.73 ± 8.96	3.00 ± 3.68	0.44 [0.29-0.59]
ESR, mm	16.54 ± 15.40	13.21± 9.72	0.27 [0.12-0.42]

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Disease Flares during 10 Year Follow-up in Patients with Rheumatoid Arthritis Are Associated with Joint Damage Progression and Disability.

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Background/Purpose: Disease flares frequently occur in patients with rheumatoid arthritis (RA). It has been suggested that these may spontaneously remit, in which case targeted treatment including intensification at the time of a flare could entail overtreatment. We investigated the occurrence and outcomes of flares during long-term follow-up in early RA patients who were treated to target over 10 years.

Methods: In the BeSt study, which enrolled 508 patients, targeted treatment aimed at a disease activity score (DAS) ≤2.4. A flare was defined from the second year of follow-up onwards as a DAS >2.4 *and* an increase in DAS of ≥0.6 from the previous DAS, regardless of the height of the previous DAS, measured during 3-monthly visits. Of 480 patients sufficient follow-up data were available to apply this definition. Functional ability (health assessment questionnaire, HAQ) during a flare was compared to functional ability during the absence of a flare with a linear mixed model (LMM). Visual analogue scales (VAS) (increase of ≥20mm between two visits, yes/no) and radiographic progression (Sharp van der Heijde score; increase ≥0.5 during 1 year, yes/no) were analysed similarly with a generalized LMM.

Results: The incidence of flares was 7 – 11% per visit during year 2 to 4 of follow-up, and 4 – 6% per visit during the later years of follow-up. During year 2 to year 10, 321/480 patients (67%) experienced at least one flare with a median (interquartile range) frequency of 4 (2 – 8) times. At the time of a flare, functional ability decreased with a mean difference of 0.25 in HAQ (p<0.001). During a flare, the odds ratio (95% confidence interval) for an increase of ≥20mm in VAS compared to the previous visit was 8.8 (7.3 – 9.8), 9.6 (7.2 – 9.7) and 5.6 (4.8 – 6.6) for patient's assessment of disease activity, pain and morning stiffness, respectively, compared to the absence of a flare. The odds ratio for developing radiographic progression in a year a flare occurred was 1.7 (95% confidence interval 1.1 – 2.8), compared to a year without a flare. In patients without any flare during follow-up, median (IQR) radiographic progression from baseline to year 10 was 1.3 (0.0 – 3.1). The more flares occurred, the higher progression rates were observed: median (IQR) SHS progression was 2.3 (0.5 – 9.6), 3.0 (0.0 – 10.0) and 4.3 (0.5 – 20.1) in patients who experienced 1, 2 and ≥3 flares during follow-up, respectively (p=0.005). A similar dose response relation was shown for functioning; in patients without any flare during follow-up, median (IQR) HAQ was 0.0 (0.0 – 0.5) at year 10, and was 0.4 (0.0 – 0.9), 0.6 (0.1 – 0.9) and 0.8 (0.4 – 1.3) in patients with 0, 1, 2, or ≥3 flares during follow-up, respectively (p<0.001).

Conclusion: Disease flares in rheumatoid arthritis are associated with short term deterioration in functioning and pain as well as radiographic damage progression, and show a dose response relation with long term functional disability and joint damage. The incidence of flares was low, and with a treatment strategy targeted at DAS≤2.4, the frequency of flares further decreased over time. This suggests that the disease may become more indolent in the majority of patients.

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Radiographic Progression Differs Between Trajectory Clusters Defined By DAS28 Scores in Early Rheumatoid Arthritis.

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Background/Purpose: Group-based trajectory modeling defines clusters of individuals in observed data with similar disease trajectories. We have previously defined five distinct trajectories in early rheumatoid arthritis based on DAS28 scores. Our objective was to examine radiographic progression in these defined clusters.

Methods: Patients were assigned to mutually exclusive trajectories by their DAS28 scores over 24 months. Patients with baseline and follow-up radiographs (n=601) were included in this analysis and baseline demographics did not differ from the larger cohort (n=1,568). Radiographs were scored with the van der Heijde modification of the Sharp score (vdHSS). ANOVA with the Bonferroni correction was applied to test for mean differences in baseline and follow-up vdHSS between clusters. Paired t-tests were applied to

test differences in mean total vdHSS between baseline and last follow-up by cluster group. Pearson's chi-squared test was used to identify differences between clusters in the proportion of patients with vdHSS progression (≥3.5 units/year) and rapid progression (≥5 units/year).

Results: Clusters (Cl) were characterized as: Cl-1 (n=163, 27%) began in high disease activity and achieved remission; Cl-2 (n=121, 20%) began in moderate or low disease activity and achieved remission; Cl-3 (n=158, 26%) began in moderate disease activity and achieved low disease activity; Cl-4 (n=132, 22%) began in high disease activity and achieved moderate disease activity; and Cl-5 (n=27, 5%) began and remained in high disease activity. At 24 months, patients in Cl-5 were more frequently on biologics (35%) and steroids (38%) but were less frequently on methotrexate monotherapy (18%), despite earlier use of DMARD combination therapy (43% at 3 months) relative to other clusters. The overall mean baseline vdHSS score was 5.3 units (SD 8.4) with progression of 2.8 units annually (95%CI 2.4–3.2, p<0.001); 43% of the cohort had no change in radiographic scores in follow-up. Clusters differed in baseline and follow-up scores for joint space and total vdHSS but not erosions, with Cl-4 and Cl-5 experiencing the worst radiographic progression by 3.6 units annually (95%CI 2.5–4.6) and 4.4 units annually (95%CI 1.1–7.7) respectively (Table 1).

Table 1. Baseline and Mean Change in van der Heijde Sharp Scores over 24 months in Early Rheumatoid Arthritis, Overall and by Trajectory Cluster

	Erosion Score		Joint Space Score		Total vdHSS	
	Baseline	Change	Baseline	Change	Baseline	Change
	Mean (SD)	Difference (95%CI, p value)	Mean (SD)	Difference (95%CI, p value)	Mean (SD)	Difference (95%CI, p value)
OVERALL n=601	2.1 (3.8)	1.4 (1.2-1.7, p<0.001)	3.3 (6.1)	1.4 (1.1-1.6, p<0.001)	5.3 (8.4)	2.8 (2.4-3.2, p<0.001)
Cluster 1(HDA to REM) n=163	1.8 (4.2)	1.0 (0.6-1.4, p<0.001)	2.1 (3.9)	1.1 (0.7-1.6, p<0.001)	3.9 (6.8)	2.1 (1.4-2.9, p<0.001)
Cluster 2(LDA to REM) n=121	2.0 (3.4)	1.5 (1.0-2.0, p<0.001)	3.0 (4.7)	1.3 (0.9-1.7, p<0.001)	5.0 (6.7)	2.7 (2.0-3.5, p<0.001)
Cluster 3(MDA to LDA) n=158	2.2 (3.9)	1.5 (1.0-2.0, p<0.001)	3.7 (6.1)	1.1 (0.7-1.5, p<0.001)	5.9 (8.8)	2.6 (1.8-3.4, p<0.001)
Cluster 4(HDA to MDA) n=132	2.4 (3.6)	1.8 (1.2-3.1, p<0.001)	4.6 (8.8)	1.8 (1.2-2.3, p<0.001)	7.0 (11.0)	3.6 (2.5-4.6, p<0.001)
Cluster 5(HDA) n=27	1.2 (2.0)	1.7 (−0.1-3.6, p=0.065)	2.3 (4.7)	2.7 (0.9-4.5, p=0.0054)	3.5 (5.4)	4.4 (1.1-7.7, p=0.0107)

Legend: HDA high disease activity; REM remission; LDA low disease activity

Cl-4 and Cl-5 had the highest proportion of progressors (24 and 26% respectively) compared to the other clusters (range 14–19%) although not statistically significant (p=0.204) and Cl-5 was characterized by all patients being rapid progressors.

Conclusion: We have defined five clinical disease trajectories in early rheumatoid arthritis. The cluster defined by patients beginning and remaining in high disease activity have the lowest baseline radiographic scores but the highest propensity for radiographic progression despite aggressive therapy. This highlights the importance of defining patient prognosis at baseline and immediately optimizing therapy to prevent functional decline.

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Prevalence and Predictive Factors of Drug-Free and Sustained Remission in Patients with Early Arthritis. Margarita Landi[1], Christian A. Waimann[2], Gustavo Citera[3], O Cerda[4], Federico Ceccatto[5], Sergio Paira[6], Francisco Caeiro[7], Lucila Marino[8], M Mamani[8], Anastasia Secco[8], G Crespo[8], AC Alvarez[9], Maria Haye Salinas[7], A Alvarellos[10], Javier Rosa[11], Valeria Scaglioni[12], Enrique R. Soriano[13], Josefina Marcos[14], Mercedes García[14], A Salas[14], Alejandro Martinez[15], Rafael Chaparro del Moral[15], Oscar Luis Rillo[15], Horacio Berman[16], Alberto Berman[16], Francisco Colombres[16], Edson Veloso[17], Ricardo V. Juárez[18], Maria Elena Crespo[19], Ana Quinteros[20], M Leal[20], Gabriela Salvatierra[21], C Ledesma[21], Mónica P. Sacnun[22], R Quintana[23] and Marcelo Abdala[24]. [1]Instituto Rehabilitacion Psicofisica, Buenos Aires, Argentina, [2]Hospital Olavarria, Olavarria, Argentina, [3]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [4]Instituto de Rehabilitacion Psicofisica, Buenos Aires, Argentina, [5]Hospital Jose María Cullen, Santa Fé, Argentina, [6]Hospital Jose Maria Cullen, Santa Fe, Argentina, [7]Hospital Privado de Córdoba, Córdoba, Argentina, [8]Hospital Bernardino Rivadavia, Buenos Aires, Argentina, [9]Hospital Privado Centro Médico de, Córdoba, Argentina, [10]Hospital Privado Centro Medico De Córdoba, Cordoba, Argentina, [11]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [12]Rheumatology Unit, Internal Medical Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [13]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [14]HIGA San Martín, La Plata, Argentina, [15]Hospital General de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [16]Centro Medico Privado de Reumatologia, Tucumán, Argentina, [17]Sanatorio y Universidad Adventista Del Plata, Entre Rios, Argentina, [18]Hospital Señor del Milagro, Salta, Argentina, [19]Hospital Señor Del Milagro, Salta, Argentina, [20]Centro Integral de Reumatología, Tucumán, Argentina, [21]Instituto Provincial De Rehabilitación Integral, Stgo. del Estero, Argentina, [22]Hospital Provincial, Rosario, Argentina, [23]Hospital provincial, Rosario, Argentina, [24]Hospital Provincial del Centenario, Santa Fe, Argentina.

Background/Purpose: Early and sustained remission has become the ultimate goal in early arthritis patients. The aim of our study was to estimate the prevalence of clinical, sustained and drug free remission in patients with early arthritis, and to explore possible predictive factors of remission.

Methods: We included a cohort of DMARDs naïve patients with diagnosis of early rheumatoid arthritis (RA) or undifferentiated arthritis (UA) of less than 2 years of disease duration. Data was collected every 3 months, including sociodemographic characteristics, functional status, disease activity and medication. Remission was defined according to 2010 ACR/EULAR criteria. We selected four outcomes: Clinical Remission, Drug-Free Remission, steroids-Free Remission (Patients receiving DMARDs but not corticosteroids) and Sustained remission (patients who in the last follow up visit were still in remission). Time to outcome was assessed from date of baseline visit to the date of remission or last follow-up. Kaplan-Meier product limit method was used to estimate probability of each outcome. Patients were stratified according to initial and final diagnosis: UA-UA, UA-RA and RA-RA, respectively. Groups were compared with the log-rank statistic. Cox proportional hazards (PH) models were fit to determine possible predictors of remission including gender, age, disease duration, HAQ, DAS28, rheumatoid factor and baseline diagnosis.

Results: A total of 684 patients were included: UA-UA=125 (18%), UA-RA= 127 (19%) and RA-RA= 432 (63%). Mean follow-up was 21 ± 16 months (1228 patients-year). Baseline DAS28 and HAQ were 5.2 ± 1.3 and 1.2 ± 0.8, respectively. Mean age was 51 ± 15 years, 81% were female and 62% had positive rheumatoid factor. The mean disease duration was 7 ± 6 months. At baseline, 625 (98%) of patients were not in remission. During follow-up 36% achieved clinical remission at a median time of 12 months. Only 54% of these patients continued in sustained remission (median follow-up after first remission= 17 months). Steroids-free remission and Drug-free remission were achieved in 21% and 13%, respectively. The overall probability of remission per patients-year of follow-up were 0.29, 0.13, 0.07; for clinical, steroids-free and drug-free, respectively. There were no differences in rate of remission between different diagnosis groups. On multivariate analysis, male gender and baseline diagnosis of RA were associated with higher probability of remission (HR=1.70, p=0.001 and HR=1.43, p=0.03, respectively), while higher HAQ-score and longer disease duration were associated with lower probability of remission (HR=0.77, p=0.01 and HR=0.95, p=0.001; respectively).

Conclusion: In our cohort 36% of patients with early arthritis achieved clinical remission; however half of them relapse during follow-up. Only one in every ten patients reached drug free remission. A short disease duration, lower disability, male gender and initial diagnosis of RA were associated with higher probability of remission.

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Osteophytes Increase the Ambiguity of Clinical Evaluation of Joint Swelling in Rheumatoid Arthritis. Peter Mandl, Paul Studenic, Gabriela Supp, Tanja A. Stamm, Martina Sadlonova, Michaela Ernst, Stefanie Haider, Daniel Aletaha and Josef Smorlen. Medical University of Vienna, Vienna, Austria.

Background/Purpose: It is recommended that a joint be classified as clinically swollen if this swelling is beyond doubt. However in clinical practice the evaluation of joint swelling in patients with rheumatoid arthritis (RA) is often hindered by joint deformity, secondary osteoarthritis (OA) or adiposity. The aim of this study was to evaluate the ambiguity and reliability of clinical swollen joint assessment in patients with RA.

Methods: Clinical joint swelling was evaluated in 2 cohorts of consecutive RA patients with at least 1 swollen joint. In Cohort A (n=20) a conventional 28 swollen joint count (SJC) was performed on the same day by 2 independent, blinded examiners. In Cohort B (n=28) the same examiners performed a modified 28 SJC in which joints were graded as either definitely swollen, non-swollen or doubtfully swollen (defined as a joint where swelling can not be excluded or confirmed due to limited evaluation attributed to the physical characteristics of the joint). In addition a standard grey-scale (GS) and Power Doppler (PD) ultrasonographic evaluation (US) was performed by a sonographer blinded to clinical data in Cohort B patients. Presence/absence of GS synovitis, PD signal, erosion and osteophytes were recorded.

Results: A total of 1316 joints were clinically evaluated in 48 RA patients (89% women; mean(±): age: 59.4 (12.1) years, disease duration: 12.5 (8.1) years, SDAI: 10.74 (8.9)) in 2 cohorts. Eighty-five percent (24 out of 28) of patients in Cohort B had at least 1 doubtfully swollen joint, with a maximum number of 4 doubtful joints/patient. The top joints with doubtful swelling were the wrist, knee, MCP3 and MCP1 joint. Interobserver reliability, evaluated by intraclass correlation coefficient in Cohort A for the conventional SJC and in Cohort B for the modified SJC was 0.80 (95% confidence interval (95%CI) 0.77–0.83) and 0.83 (95%CI: 0.81–0.85) respectively. Agreement between the 2 examiners for definitely swollen and doubtfully swollen joints was 65% and 16% respectively. Doubtfully swollen joints were more often GS ($p<0.001$) and PD positive ($p<0.001$) as compared to non-swollen joints (80% vs. 54% and 26% vs. 12% respectively) and had more frequently osteophytes on US than either swollen ($p=0.021$) or non-swollen joints ($p=0.003$) (11% vs. 4.5/4.5% respectively). Erosions were more commonly detected in swollen joints than in doubtfully swollen or non-swollen joints (4.8% vs. 1.8/2.2%) (Table 1). No association was found between body mass index and the number of doubtfully swollen joints.

Conclusion: A modified SJC including doubtfully swollen joints is characterized by similar interobserver reliability as the conventional SJC. Agreement between 2 blinded examiners was low for the evaluation of doubtful swelling. Doubtfully swollen joints had significantly more osteophytes on US suggesting a relationship between ambiguity of swelling and secondary OA in patients with RA.

Table 1: Summary of logistic regression for the dichotomized outcomes (yes/no) grey scale (GS), Power doppler (PD), erosions, and osteophytes. Tested independent variables: doubtfully swollen joints (DSJ) versus either non-swollen joints (NSJ) or swollen joints (SJ); OR: odds ratio

	Regression coefficient	Standard error	p	95% Confidence Interval for Odds Ratio		
				Lower	OR	Upper
GS						
DSJ vs. NSJ	1.45	0.374	<0.001	2.05	4.26	8.87
DSJ vs. SJ	0.68	0.520	0.188	0.18	0.51	1.40
PD						
DSJ vs. NSJ	1.10	0.316	<0.001	1.62	3.02	5.61
DSJ vs. SJ	−1.48	0.368	<0.001	0.11	0.23	0.47
Erosions						
DSJ vs. NSJ	−0.19	1.047	0.859	0.11	0.83	6.47
DSJ vs. SJ	−0.93	1.131	0.410	0.043	0.39	3.62
Osteophytes						
DSJ vs. NSJ	1.07	0.357	0.003	1.45	2.92	5.89
DSJ vs. SJ	1.19	0.512	0.021	1.20	3.26	8.91

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Heterogeneity in Cardiovascular Risk Factors, Event Rates and RA Disease Characteristics Among Patients with Rheumatoid Arthritis Across 10 Countries - Implications for CV Risk Assessment. Atacc-RA Collaborative Grroup. University of Umeå, Umeå, Sweden.

Background/Purpose: Patients with rheumatoid arthritis (RA) have an increased risk of cardiovascular disease (CVD). CVD risk scores for the general population do not accurately predict CVD events in RA. Heterogeneity of traditional CV risk factors and RA characteristics across various countries may be associated with varying impacts on CVD events. We compared the impact of traditional CV risk factors and RA characteristics on CVD outcomes in RA patients from 10 countries.

Methods: RA cohorts from 13 rheumatology centers in UK.Norway, Netherlands, US, Sweden, Greece, South Africa, Spain, Canada and Mexico were compared. Data on CV risk factors and RA characteristics were collected at baseline for each cohort; CVD outcomes were collected prospectively using standardized definitions. Cox models with random effects for center were used to compare the impact of CV risk factors and RA characteristics on CVD events. Traditional CV risk factor effects were adjusted for age and sex; RA characteristic effects were adjusted for age, sex and CV risk factors.

Results: 5685 RA patients without prior CVD were included (mean age: 55 [SD: 14] years, 76% female). During a mean follow-up of 6.1 years (31155 person years), 476 patients developed CVD events. RA duration varied by center: 4 with early RA (<1 year), 7 established (mean 9–13 years) RA and 2 with both. Mean age varied from 37 to 61 years (younger in the early RA cohorts - $p<0.001$); females varied from 66% to 90% ($p<0.001$). 2 cohorts consisted of Hispanics, the rest Caucasians. CVD event rates varied across countries (range of 5 year CVD event rate: 0.8 – 7.5%) with the lowest observed in Norway and UK and the highest in South Africa, Netherlands, US-Mayo and Sweden. Age effects were fairly consistent (hazard ratios [HR] ranged from 1.6–1.8 per 10 year increase in age), but male sex varied from no effect to a doubled effect (HR=1.0–2.3). Varied effects were also seen for current smoking (HR=1.1–2.1), hypertension (HR=0.6–2.0), total cholesterol: high-density lipoprotein ratio (HR=0.9–1.2) and diabetes mellitus (HR=0.7–2.8). Effects were also varied for RA characteristics, including rheumatoid factor and/or anti-citrullinated protein antibody seropositivity (HR=0.7–1.4), disease activity score [DAS28] (HR=0.9–1.2) and RA disease duration (HR=0.7–1.1 per 10 years).

Conclusion: Major heterogeneity exists in CVD event rates and in the effects of traditional CV risk factors and RA characteristics on CVD outcomes among patients with RA across different countries. Generation of a CVD risk score that will be widely applicable for patients with RA must address this inherent heterogeneity. Efforts are underway to do this.

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Weight Loss and Risk of Death in Rheumatoid Arthritis. Joshua Baker[1], Erica Billig[1], Grant W. Cannon[2], Liron Caplan[3], Vikas Majithia[4] and Ted R. Mikuls[5]. [1]University of Pennsylvania, Philadelphia, PA, [2]Salt Lake City VA and University of Utah, Salt Lake City, UT, [3]Denver VA and Univ of Colorado School of Medicine, Aurora, CO, [4]University of Mississippi Medical Center, Jackson, MS, [5]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: Low body mass index (BMI) has been linked to greater mortality among patients with Rheumatoid Arthritis (RA). Weight loss has also been associated with a greater risk of death among the elderly. The purpose of this study was to determine if weight loss is a predictor of death in RA.

Methods: Our sample consists of 1634 subjects from the Veterans Affairs Rheumatoid Arthritis (VARA) Registry. Dates of death were identified through review of the VA Computerized Patient Record System. BMI was

extracted within 14 days of each visit and the change in BMI from the previous visit was determined. BMI category and weight change were considered time-varying. Weight loss at each visit was defined as a decrease in BMI of 1 kg/m^2 from the preceding visit. Rate of loss (per 1 year) was defined as the change BMI from the preceding visit divided by the preceding interval length. Potential confounding co-variables associated with mortality in this cohort were identified. Cox proportional hazard models were used to assess associations between time-variant and time-invariant predictors of survival including the change in BMI and the rate of decline in BMI from the preceding visit adjusting for age, gender, race, BMI, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, smoking, and current use of methotrexate, prednisone, and anti-Tumor Necrosis Factor (TNF-α) medications.

Results: Among 1634 subjects (280 deaths, 8102 patient-years, 17,057 unique observations), weight loss of 1 kg/m^2 of BMI occurred in 2,308 observation periods (13.5%). Weight loss over the preceding interval was associated with an increased risk of subsequent death [HR: 2.00 (1.54, 2.60) p<0.001] (Table 1). In a subset of 1520 subjects with available data (223 deaths, 6650 patient-years), weight loss remained associated with an increased risk of death after further adjusting for CRP [HR 1.78 (1.33, 2.38) p<0.001] (full model not shown). In similar models, a rate of weight loss of >1 kg/m^2 of BMI over a 6-month period was associated with a greater risk of death [HR: 1.74 (1.31, 2.32) p<0.001] while a slower rate of weight loss was not associated with an increased risk compared to those who did not lose weight [HR: 0.94 (0.70, 1.27) p=0.7].

Conclusion: Recent weight loss, particularly a loss of more than 1 kg/m^2 of BMI (approximately 3.1 kg on average) over a 6-month period, is an independent predictor of death in RA. Changing weight may be a marker of poor functional status, poor nutrition, ongoing inflammation, and/or underlying malignancy and may help risk-stratify patients for more aggressive interventions.

Table 1: Multivariable-adjusted risk of death among subjects with rheumatoid arthritis. (N=1634, Deaths=280, Person-Years=8,102)

	Risk of Death HR (95% CI)
Baseline Age	**1.06 (1.04, 1.07)‡**
Female	**0.47 (0.23, 0.95)***
White	1.10 (0.82, 1.49)
BMI Category	
BMI <20 kg/m^2	**2.89 (1.99, 4.21)‡**
BMI 20-25 kg/m^2	1 (reference)
BMI 25-30 kg/m^2	0.91 (0.67, 1.23)
BMI >30 kg/m^2	0.88 (0.61, 1.25)
Interval Weight Change	
< 1 kg/m^2 loss	1 (reference)
> 1 kg/m^2 loss	**2.00 (1.54, 2.60)‡**
Current Therapies	
Methotrexate Use	**0.59 (0.45, 0.76)‡**
Prednisone Use	**1.40 (1.10-1.80)***
TNF Use	0.73 (0.53, 1.01)
Baseline Comorbidities	
Diabetes	**1.42 (1.09, 1.84)†**
Cardiovascular Disease	**1.35 (1.05, 1.72)***
Chronic Kidney Disease	**1.89 (1.31, 2.73)‡**
COPD	**1.73 (1.26, 2.36)‡**
Active Smoking	**1.57 (1.16, 2.13)†**

*p<0.05; †p<0.01; cm<0.001.
Abbreviations: BMI= Body Mass Index; TNF= anti-Tumor Necrosis Factor Blocker Therapy; COPD= Chronic Obstructive Pulmonary Disease.

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Predictors of Long-Term Changes in Body Mass Index in Rheumatoid Arthritis. Joshua Baker[1], Grant W. Cannon[2], Said Ibrahim[3], Candace Haroldsen[4], Liron Caplan[5] and Ted R. Mikuls[6]. [1]Philadelphia VA Medical Center, Philadelphia, PA, [2]Salt Lake City VA and University of Utah, Salt Lake City, UT, [3]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, [4]University of Utah, Salt Lake City, UT, [5]Denver VA and Univ of Colorado School of Medicine, Aurora, CO, [6]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: Low body mass index (BMI) is a risk factor for poor long-term outcomes in rheumatoid arthritis (RA). Low BMI in RA has been speculated to reflect weight loss due to the greater resting energy expenditure among subjects with more active and severe RA. We determined predictors of change in BMI in RA, and specifically examined whether greater disease activity was associated with weight loss over time.

Methods: Subjects from the Veterans Affairs RA Registry (VARA) (n=1396) were studied. Information on inflammatory markers, presence of erosions, and smoking status were extracted from the VARA database. VARA participants without longitudinal data were excluded (n = 349) but were similar in age, gender, race, and enrollment BMI (data not shown). BMI was extracted from the vital signs package from VA electronic medical records within 14 days of each visit date. VA pharmacy records were queried to identify prescriptions for specific RA therapies within 1 month of each visit. Robust Generalized Estimating Equations (GEE) regression models determined independent associations between pre-hypothesized clinical variables and change in BMI (or odds of weight loss >1 kg/m^2) over the subsequent observation period. Variables were either time-varying (log-transformed C-Reactive Protein [lnCRP] and medication use) or time-invariant (baseline CCP seropositivity, erosive disease, and smoking status).

Results: Increasing age, current smoking, and the presence of erosions at baseline were associated with lower BMI (all p<0.001). On average, weight decreased over time [β: −0.017 (−0.029, −0.0052) p=0.005]. Higher ln(CRP), current smoking at baseline, greater baseline BMI, and older age were associated with greater reductions in BMI over the subsequent observation period (Table 1) (all p<0.01). Higher ln(CRP), current smoking, greater baseline BMI, and older age were also associated with a greater risk of weight loss over the subsequent observation period (Table 1) (all p<0.01). Methotrexate use was associated with a lower risk of weight loss (p=0.002). The use of prednisone and the use of anti-TNF therapies were not associated with change in BMI or the risk of weight loss.

Conclusion: Greater age, greater inflammatory activity, and current smoking are associated with weight loss in RA. The weight loss (and lack of weight gain) among subjects with inflammation may be due to the greater resting energy expenditure and catabolism seen with the active inflammatory process. While methotrexate was associated with a decreased risk of weight loss, there were no consistent associations between other RA medications and changes in weight.

Table 1: GEE in linear and logistic regression models evaluating independent predictors of the change in BMI and the risk of weight loss over the subsequent observation period.

	Change in BMI (kg/m^2) (N=1396; Obs= 10707)		Risk of Weight Loss (≥ 1 kg/m^2) (N=1396, Obs=10707)	
	β (95% CI)	P	OR (95% CI)	P Value
Age (per 1 year)	−0.0070 (−0.0090,−0.0051)	<0.001	1.01 (1.00,1.02)	0.001
Female Sex	0.040 (−0.028,0.11)	0.3	0.98 (0.80,1.20)	0.9
Caucasian	−0.013 (−0.055,0.030)	0.6	1.20 (1.04,1.38)	0.01
Baseline BMI (per 1 kg/m^2)	−0.0083 (−0.013,−0.0037)	<0.001	1.07 (1.06,1.08)	<0.001
Ln[CRP (mg/dL)]	−0.024 (−0.040,−0.0076)	0.004	1.12 (1.07,1.18)	<0.001
Prednisone	0.019 (−0.027,0.066)	0.4	1.04 (0.92,1.18)	0.3
Anti-TNF Therapy	0.032 (−0.013,0.078)	0.2	0.99 (0.88,1.11)	0.8
Methotrexate	0.016 (−0.025,0.057)	0.5	0.84 (0.74,0.94)	0.002
Baseline aCCP Positive	0.015 (−0.030,0.061)	0.5	1.07 (0.93,1.23)	0.3
Baseline Erosive Disease	−0.032 (−0.069,0.0048)	0.09	1.15 (0.99,1.27)	0.07
Baseline Smoker	−0.059 (−0.10,−0.017)	0.006	1.28 (1.11,1.47)	0.001

Abbreviations: Obs= Observations; CI= Confidence Interval; BMI= Body Mass Index; CRP= C-Reactive Protein; TNF= Tumor Necrosis Factor Inhibitor; CCP= Cyclic Citrullinated Peptide Ab.

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Periodontal Disease and Its Impact on Structural Joint Damage in a Rheumatoid Arthritis Peruvian Population. Rocio V. Gamboa-Cardenas, Manuel F. Ugarte-Gil, José Quiñones, Francisco Zevallos-Miranda, Fiorella Lazo, J. Mariano Cucho-Venegas, Risto A. Perich-Campos, Jose L. Alfaro-Lozano, Mariela Medina-Chinchon, Zoila Rodriguez-Bellido, Hugo Torrealva and Cesar A. Pastor-Asurrza. Hospital Guillermo Almenara, EsSalud, Lima, Peru.

Background/Purpose: Periodontal disease (PD) or periodontitis is currently considered an epigenetic determinant of both occurrence and severity of Rheumatoid Arthritis (RA). Common pathophysiological mechanisms like the migration of osteoclasts and secretion of pro-inflammatory cytokines, would occur in RA and PD but it has not been determined if the severity of

PD influence on joint damage (JD). The aim of the study was to demonstrate that a more severe PD is independently associated with a greater JD in RA patients.

Methods: A cross sectional study. RA was defined using the 1987 ACR criteria. Patients should not have other autoimmune disease and they were older than 18 years at time of diagnosis. We excluded patients with less than 4 teeth, serious or local ongoing infections, oral cancer or precancerous lesions; inpatients, pregnant, diabetic patients, severe Sjögren syndrome and local antibiotic or gingival hyperplasia associated drug users were also excluded. We applied a personal interview, physical examination, laboratory analysis and review of medical records to assess factors associated with JD. An assessment of periodontal attachment loss and panoramic dental X ray were done. To determine diagnosis and severity of PD the American Academy of Periodontology criteria were applied. Two categories were defined mild PD and moderate/severe PD. All dental assessments and radiographs were interpreted by three odolontologist blinded to JD. A blinded investigator to clinical RA and PD status determined JD scoring hands/feet radiographs according to Sharp VDH method. The association of PD severity and JD was determined using student's T test, after that a multivariable linear regression model adjusted for age, tobacco, gender, rheumatoid factor (RF), anticitrullinate protein antibody (ACPA), disease duration, socioeconomic status (SES) using Graffar scale, disease activity (DAS28CRP), functional status (MDHAQ) and quality of life (SF36) was performed to determined persistence of the associations. SPSSv21.0 statistical package was used.

Results: 213 patients were evaluated, 192 (90.1%) were women, mean (SD) age was 59.55 (12.59) years, disease duration was 15.14 (11.74) years, SES were more frequently medium / medium low (31.5% and 36.6% respectively); 79.3% were ACPA positive, mean ACPA title was 679.23 uM/L, mean DAS28PCR was 3.85 (1.24). 2.3% and 14.6% were current or past smokers. Erosion, joint space narrowing and total Sharp VDH scores were 41.25 (49.02), 64.65 (42.30) and 105.81 (88.44) respectively; 94 (44.1%) patients had mild PD and 119 (55.9%) patients had moderate/ severe PD. In multivariable analysis PD severity (adjusted for age, SES, tobacco, gender, RF, ACPA, disease duration, DAS28PCR, MDHAQ and SF36) was independently associated with a higher score join narrowing space (β:21.47, p =0.008) and total SharpVDH scores (β:17.78, p=0.029). Erosions and PD severity did not remain associated (β:18.17, p=0.085).

Conclusion: A more severe PD impacts on structural joint damage independently of other known associated factors. A routine periodontal evaluation and monitoring could be useful for better outcomes in RA patients.

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Low Vitamin D Level Is Not Associated with Increased Risk of Cardiovascular Disease in Rheumatoid Arthritis Patients. Tarun S. Sharma[1], Xiaoqin Tang[2], Deepak Vedamurthy[1], Jonida Cote[3] and Androniki Bili[3]. [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Center for Health Research, Danville, PA, [3]Geisinger Health System, Danville, PA.

Background/Purpose: Cardiovascular disease (CVD) is the leading cause of death in patients with Rheumatoid Arthritis (RA). Vitamin D deficiency is prevalent in RA and it has also been shown to be related to disease activity in some studies which is attributed to its immunomodulatory properties. There have been increasing reports of an inverse relationship between vitamin D levels and CVD risk in the general population but no studies in the RA population. The aim of this study was to evaluate the association between Vitamin D levels and CVD risk in RA.

Methods: A retrospective cohort of adult patients with RA (defined as ICD-9 714.0 twice by a rheumatologist) within a tertiary health system and with primary care physician within the health system from 1/1/2001 to 10/31/2013 was constructed (n=1459). Patients with prevalent diagnosis of CVD at the time of RA diagnosis (n=127) or those without available vitamin D levels (n=410) were excluded. Vitamin D level was analyzed as both a continuous and dichotomous variable with level <20 ng/ml defined as "deficient" and ≥20 ng/ml "sufficient" vitamin D level groups. Primary outcome was independent physician adjudicated incident CVD defined as a composite of CAD, stroke, transient ischemic attack or peripheral vascular disease. Data was censored for death or end of the study period and vitamin D levels closest to the censoring point were captured. Poisson regression models were used to calculate the relative risk (RR) for CVD between the deficient and sufficient vitamin D level groups. Cox regression models were used to calculate the hazard ratios (HR) for CVD between the two vitamin D groups. The models were adjusted for age, gender, BMI, smoking, RF and ACPA positivity, LDL, NSAID, corticosteroid, DMARD, statin and TNF inhibitor use. The study was designed to have an 80% power to detect a minimum HR for incident CVD of 2.5 between the two groups.

Results: 921 RA patients were included. Patients were 80.5% women, 96.9% Caucasian, with mean age of 58 years and BMI 30.4 kg/m^2. Median time from vitamin D level measurement to CVD events was 2.7 years. There were 128 patients in the deficient and 793 patients in the sufficient vitamin D level groups with mean vitamin D levels of 14.3 ng/ml and 36.8 ng/ml respectively. There were 88 incident CVD events with an Incidence Rate (IR) of 14.8/1000 patent years; of these events, 19 were in the deficient and 69 in the sufficient vitamin D groups with Incidence Rate Ratio (IRR) of 1.43 (0.84–2.43, p=0.19) for CVD between the groups. In the multivariate fully adjusted Cox model, the HR for incident CVD events was 1.30 (95% CI 0.78–2.15 p=0.32) between the two groups. When treating vitamin D as a continuous variable, the HR for incident CVD was 0.99 (95% CI 0.97–1.004, p=0.14) between the deficient and sufficient vitamin D level groups.

Conclusion: In this study, vitamin D level <20 vs. ≥20 ng/ml was not associated with increased risk of incident CVD in patients with RA. However, the study was powered to detect a minimum of double the risk between the vitamin D groups and may have missed an association of smaller magnitude.

Disclosure: T. S. Sharma, None; **X. Tang**, None; **D. Vedamurthy**, None; **J. Cote**, None; **A. Bili**, None.

1395

Disease Activity Is Associated with Insulin Resistance in Early Rheumatoid Arthritis. Androniki Bili[1], Debra Webb[2], Cynthia Matzko[2], Andrea Berger[3], Eric D. Newman[1], Thomas P. Olenginski[1], David M. Pugliese[4], Maria Butterwick[5], Lisa L. Schroeder[1], Thomas M. Harrington[1], Jonida Cote[1], Lyudmila Kirillova[1], Susan Mathew[1], Tarun Sharma[1], H. Lester Kirchner[1], Jon Giles[6] and Mary Chester M. Wasko[7]. [1]Geisinger Health System, Danville, PA, [2]Geisinger Medical Center, Danville, PA, [3]Center for Health Research, Geisinger Health System, Danville, PA, [4]Geisinger Health System, Wilkes-Barre, PA, [5]Geisinger Specialty Group, Wilkes-Barre, PA, [6]Columbia University Medical Center, New York, NY, [7]Temple University School of Medicine, Pittsburgh, PA.

Background/Purpose: Rheumatoid arthritis (RA) is a systemic disease that manifests mainly with articular symptoms, but the main cause of death is cardiovascular disease (CVD). Chronic inflammation is thought to contribute both directly to CVD as well as indirectly to cardiometabolic risk factors such as insulin resistance, atherogenic lipid profile and sarcopenic obesity, all features of chronic active RA. Data on the presence of these risk factors in newly diagnosed RA are scarce but need to be defined so that they can be addressed if present in early disease. The aim of the present study was to examine the association of disease activity with cardiometabolic risk factors in newly diagnosed RA.

Methods: Patients are participants in an ongoing study that compares the effect of a treat to target strategy vs. usual care on cardiometabolic comorbidities in RA. For the present study, baseline patient data were analyzed in a cross-sectional design. Participants had RA based on 2010 ACR classification criteria with symptoms < 2 years; were DMARD and biologic-naïve (except hydroxychloroquine); took corticosteroid equivalent of prednisone ≤10 mg daily; had clinical disease activity index >10, and did not have known diabetes. Disease activity was assessed by the disease activity score (DAS)28 and disability by the Modified Health Assessment Questionnaire (MHAQ). The primary outcome was insulin resistance as assessed by the 2 hour glucose tolerance test (GTT). Secondary outcomes were high density lipoprotein cholesterol (HDL-c) and body composition measurements by DXA (Hologic), including android/gynecoid ratio, appendicular lean mass (kg/m^2) and appendicular lean mass/height^2. The associations between DAS28 and MHAQ with the outcome variables were evaluated using linear regression analysis, both unadjusted and adjusted for age, gender and BMI. All outcome variables were analyzed as continuous. Pearson's partial correlation coefficient was used to estimate the strength of the associations.

Results: Of the 33 participants, 64% were female, with mean age 50 years, 70% RF positive, 53% ACPA positive, with median BMI 30.3 kg/m^2 and median DAS28 4.5. In the unadjusted model, DAS28 was positively associated with insulin resistance (p=0.01). In the adjusted model, the Pearson partial correlation was 0.3777 (p = 0.05). There was no association of the DAS28 with HDL or body composition measures. MHAQ was inversely associated with HDL (p= 0.05) in the unadjusted analysis but this

association lost significance in the adjusted model. There was no association of the MHAQ with insulin resistance or body composition measures. As expected, age and female gender were inversely associated with appendicular lean mass.

Conclusion: In early RA, higher disease activity was associated with increased insulin resistance, a risk factor for CVD. Our findings underscore the importance of addressing cardiometabolic comorbidities in early RA to minimize disease-related morbidity and mortality.

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1396

Assessment of Pulmonary Function in Rheumatoid Arthritis Patients Attending Rheumatology Clinics in Nairobi,Kenya. Irene Biomdo[1] and Omondi G. Oyoo[2]. [1]Ministry of Health,Kenya, Nairobi, Kenya, [2]University of Nairobi, Nairobi, Kenya.

Background/Purpose: Pulmonary involvement is frequent and among the most severe extra-articular manifestations of Rheumatoid arthritis (RA) ranking as the second cause of mortality in this patient population. Rheumatoid arthritis can affect the lung parenchyma, airways and pleura. Pulmonary complications are directly responsible for 10–20% of all mortality in RA patients. Spirometry is becoming increasingly available in Kenya and could be used in peripheral areas to screen and monitor for pulmonary function abnormalities in well characterized patient populations such as those with RA. Abnormalities detected by pulmonary function tests may precede symptoms by years and lead to early diagnosis of pulmonary fibrosis in rheumatoid arthritis and hence intervention.

Objective: To determine the prevalence of pulmonary function abnormalities in Rheumatoid arthritis patients attending Rheumatology Clinics in Nairobi.

Methods: Rheumatoid arthritis patients who fulfilled the study inclusion criteria were recruited. Sociodemographic characterictics and respiratory symptoms were assessed using Lung Tissue Research Consortium questionnaire (LTRC) and RA disease activity was established by Disease Activity Score (DAS28). Pulmonary function tests were then done using Spirolab 111 according to the American thoracic society recommendations.

Results: One hundred and sixty six RA patients were recruited; the male to female ratio was 1:9.3, with a median age of 47 years. The overall 6 month prevalence of pulmonary function abnormalities was 38.5% as measured by Spirometry and all our patients did not carry any prior pulmonary disease diagnosis. The predominant ventilatory defect was Obstructive pattern at 20.4%, followed by Restrictive pattern at 16.8% and least common being a mixed picture at 1.2%. Factors that were shown to be independently associated with pulmonary function abnormalities were age and RA disease activity. Respiratory symptoms that were predictive of PFTs abnormalities were cough, increased frequency of chest colds and illnesses and phlegm.

Conclusion: High prevalence of pulmonary function abnormalities was observed. Respiratory symptoms, older age and ongoing disease activity can identify patients in greatest need of further pulmonary evaluation.

Disclosure: I. Biomdo, None; **O. G. Oyoo**, None.

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Impact of Corticosteroid Use on Remission Sustainability and Infection Rates Among Rheumatoid Arthritis Patients in Remission While on Infliximab: Treatment Implications Based on a Real-World Canadian Population. Boulos Haraoui[1], Algis Jovaisas[2], William G. Bensen[3], Rafat Faraawi[4], John Kelsall[5], Sanjay Dixit[4], Jude Rodrigues[6], Maqbool Sheriff[7], Emmanouil Rampakakis[8], John S. Sampalis[8], Allen J Lehman[9], Susan Otawa[9], Francois Nantel[9] and May Shawi[9]. [1]Centre Hospitalier de l'Université de Montréal, Montréal, QC, [2]University of Ottawa, Ottawa, ON, [3]St. Joseph's Hospital and McMaster University, Hamilton, ON, [4]McMaster University, Hamilton, ON, [5]The Mary Pack Arthritis Centre, Vancouver, BC, [6]Clinical Research and Arthritis Centre, Windsor, ON, [7]Nanaimo Regional General Hospital, Nanaimo, BC, [8]JSS Medical Research, Montreal, QC, [9]Janssen Inc., Toronto, ON.

Background/Purpose: The Canadian Rheumatology Association[1] recommends that addition of corticosteroids (CS) should be considered only for the shortest period possible in rheumatoid arthritis (RA) patients treated with a traditional or biologic DMARD based on the patient's clinical status. The aim of this analysis was to examine the effect of chronic systemic CS treatment at different doses on the incidence of infections in RA patients treated with IFX in a real-life setting. The impact of CS use on the sustainability of remission was also assessed.

Methods: BioTRAC is an ongoing, Canadian, prospective, registry of rheumatology patients initiating treatment with IFX or golimumab as first biologics or after having been treated with a biologic for less than 6 mos. RA patients treated with IFX who were enrolled between 2002 and 2012 were included. Cox regression was used to examine the time-dependent association between systemic CS dose (no CS, ≤5 mg, >5 mg) and the incidence of first infection, while adjusting for possible confounders, and to assess the sustainability of remission.

Results: 838 RA patients were included in the analyses. Mean (SD) age of the patient cohort was 56.6 (13.5) yrs and mean (SD) duration since diagnosis was 10.5 (9.8) yrs. At initiation of treatment, 38.2% of patients were treated with a systemic CS. After a mean (SE) follow-up of 51.3 (1.7) mos, 310 infections were reported for 19.7% of patients (19.6 /100 PYs). Among these, the majority (90.0%) were non-serious infections. Multivariate survival analysis using Cox regression showed that, upon adjusting for enrolment period, age, disease duration, number of steroid administrations, and HAQ-DI, the hazard ratio (HR) (95%CI) for acquiring an infection was 2.48 (1.24–4.98) in patients treated with high dose (>5 mg) CS compared to patients not receiving CS. Treatment with low dose CS was also associated with an increased hazard for infection (HR (95%CI) = 2.12 (0.97–4.66)) which did not reach statistical significance. Consistent with previous studies, increased HAQ-DI (HR (95%CI) = 1.51 (1.15–1.92)) and disease duration (HR (95%CI) = 1.01 (1.00–1.03)) were also identified as significant predictors. CS use was continued in 15% of cases despite the achievement of remission (DAS28-CRP: 15.2%; CDAI: 15.7%). Survival analysis did not show a significant positive effect of steroid use on sustainability of remission [$HR_{DAS28\text{-}CRP}$ (95%CI) = 1.40 (0.95–2.06); HR_{CDAI}(95%CI) = 1.19 (0.75–1.88)].

Conclusion: Treatment with systemic CS was associated with an increased hazard ratio for acquiring an infection upon adjusting for possible confounders. Despite the achievement of remission, steroid use was continued in 15% of cases without having an impact on sustainability of remission. We show that treatment with systemic CS is an independent predictor of infection in patients treated with anti-TNF agents and suggest that the use of concomitant medications should be considered in the interpretation of safety data.

References: J Rheumatol 2012;39;1559–1582

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Spontaneous Regression of Methotrexate (MTX)-Related Lymphoproliferative Disorder Correlates with Lymphocyte Restoration after MTX Withdrawal. Shuntaro Saito[1], Yuko Kaneko[1], Katsuya Suzuki[1], Michihide Tokuhira[2] and Tsutomu Takeuchi[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Saitama Medical Center, Saitama Medical University., Saitama, Japan.

Background/Purpose: Lymphoproliferative disorder (LPD) is a rare complication with rheumatoid arthritis (RA) patients treated with methotrexate (MTX). It is known that not little proportion of these LPD shows spontaneous regression by MTX withdrawal without chemotherapy. This study is to identify factors by which the spontaneous regression of MTX-LPD can be predicted.

Methods: All 32 RA patients regarded as being complicated with MTX-LPDfrom 2007 to2013in our institution were studied. We analyzed the patients who had been observed after the withdrawal of MTX without chemotherapy. The comparisons of continuous values were examined by student t-test.

Results: Five patients were given chemotherapy after the diagnosis of MTX-LPD, so we analyzed the remaining 27 patients in this study. Baseline characteristics of 27 patients were following: median age, 65 years old,

female, 82%, duration of MTX administration, 7.5 years, RA duration, 11.9 years. In these patients, MTX was withdrawn without any additional treatment, and LPD was assessed during the follow up (median 5 weeks, range: 3–12 weeks). Seventeen patients were pathologically diagnosed as LPD and 10 were highly suspected of LPD with imaging tests. Spontaneous regression observed in 19 patients with 3 achieving complete remission (CR) and 16 partial remission (PR). Three patients were stable disease (SD) and 5 were progressive disease (PD).

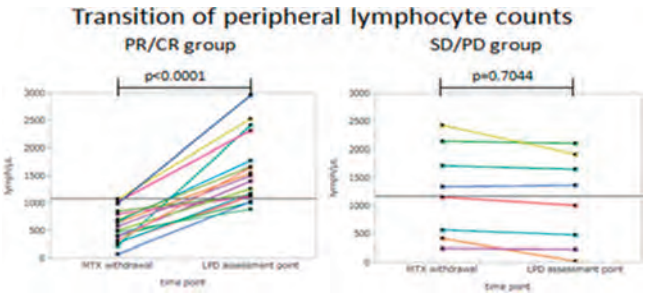
We focused on the time course changes in absolute number of lymphocytes at the MTX withdrawal and at the time of follow-up assessment. In CR/PR group, the number of lymphocytes were decreased at the MTX withdrawal (median 510/μL, range:87–1045), but restored at the time of follow-up assessment (median 1409/μL, 900–2969). In SD/PD group, the patients could be classified into 2 groups; 3 of low lymphocytes (median 426/μL, 255–578) and 5 of high lymphocytes (median 1725/μL, 1165–2438). However in both groups the lymphocyte counts did not change after follow up duration. Therefore, the ratio between the number of lymphocytes at the MTX withdrawal and at the time of follow-up assessment was significantly higher in PR/CR group than SD/PD group (3.73 vs 0.96, p=0.02). There was no significant difference of follow up duration between 2 groups (median 4 vs 5.5 weeks, p=0.46).

Same tendency were observed in histologically diagnosed 17 patients. The outcomes were 2 CR, 11 PR, and 4 PD, and lymphocytes ratios were 4.07 in CR/PR group and 0.65 in SD/PD group (p=0.04).

Of 17 histologically defined LPDs, 15 had information on Epstein Barr virus encoded small RNA (EBER). EBER positivity was relatively higher (9/11, 81%) in PR/CR group and lower (2/4,50%) in SD/PD group, but difference was not statistically significant (p=0.261).

Conclusion: Careful observation of the changes in the number of lymphocytes may predict the LPD spontaneous regression after the withdrawal of MTX.

Figure Transition of peripheral lymphocyte counts



Disclosure: S. Saito, None; **Y. Kaneko**, None; **K. Suzuki**, None; **M. Tokuhira**, None; **T. Takeuchi**, Abbott Japan Co., Ltd., Astellas Pharma, Bristol–Myers K.K., Chugai Pharmaceutical Co, Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Sanofi–Aventis K.K., Santen Pharmaceutica, 2, Abbott Japan Co., Ltd., Bristol–Myers K.K., Chugai Pharmaceutical Co,. Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., Astellas Pharma, Diaichi Sankyo Co.,Ltd., 8, Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., Asahi Kasei Medical K.K., Abbivie GK, Daiichi Sankyo Co.,Ltd., 5.

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Proteinase K-like Serine Protease PCSK9 Influence on the Dyslipidemia and Endothelial Dysfunction Observed in Rheumatoid Arthritis Patients.

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Background/Purpose: Proteinase K-like serine protease PCSK9 binds the low-density lipoprotein (LDL) receptor at the surface of hepatocytes, thereby preventing its recycling and enhancing its degradation in endosomes/lysosomes, resulting in reduced LDL-cholesterol clearance. Therefore, gain-of-function in PCSK9 lead to higher levels of LDL-cholesterol and increased risk of cardiovascular disease. The objective is to investigate how PCSK9, one of the molecules involved in the metabolism of LDL-cholesterol, is expressed in patients with rheumatoid arthritis (RA) and its potential relationship with the dyslipidemia and the endothelial dysfunction observed in these patients.

Methods: Plasma PCSK9 concentrations and brachial artery flow-mediated dilation (FMD) by ultrasound were measured in 115 patients with RA and 101 matched controls. A multivariable analysis adjusted for standard cardiovascular risk factors, disease activity and lipids, including LDL cholesterol, was performed to evaluate the relation of PCSK9 on RA dyslipidemia and endothelial dysfunction compared to controls.

Results: FMD was higher in controls when compared to RA patients (8.5 [95%CI 4.5–15.6] vs. 5.3 [0.0–9.2] mm, p=0.00). In the univariate analysis, RA patients tended to have lower levels of total cholesterol(p=0.08), LDL(p=0.18) and apolipoprotein A1(p=0.15), although statistical significance was not reached. PCSK9 levels were not different between patients and controls even adjusting for comorbidity or disease activity. PCSK9 tended to be correlated with LDL cholesterol in patients and controls, but statistical significance was not reached. Nevertheless PCSK9 was positively correlated with apolipoprotein B in RA patients (beta coef. 0.06 [0.02–0.09] x10 ng/ml, p=0.00) but not in controls. Disease activity score DAS28, both considering as continuous (766 [100–1432] ng/ml, p=0.03) or categorical -low, moderate, high and very high- (832 [82–1583] ng/ml, p=0.03) was correlated with PCSK9 levels. Therefore, higher DAS28 was associated with greater PCSK9 concentration. When RA patients were split in tertiles according to PCSK9 values we observed that patients which were more commonly included in the third tertile, showed the higher values of FMD. Therefore, in RA patients, as FMD increased we observed that the risk of having PCSK9 values included in the third tertile compared to that of being in the first tertile was statistically significant multiplied by OR 0.98 ([0.82–0.99],p=0.04). However, this association was not found in controls.

Conclusion: PCSK9 concentrations are associated with disease activity scores and endothelial dysfunction in RA patients. The role of PCSK9 in RA related dyslipidemia and cardiovascular risk needs further investigation.

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1400

Risk of Venous Thromboembolic Events in Patients with Rheumatoid Arthritis: A Meta-Analysis of Observational Studies.

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Background/Purpose: Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common vascular event after myocardial infarction and stroke. Several studies have investigated the risk of VTE among patients with rheumatoid arthritis (RA), a chronic and disabling disease associated with systemic inflammation. Our objective was to perform a meta-analysis of studies evaluating the risk of DVT and PE in patients with RA.

Methods: We systematically searched MEDLINE (1946–2013) and EMBASE (1974–2013) databases for studies that reported the risk of VTE in patients with RA. Our search strategy employed Medical Subject Headings (MeSH terms) together with keywords for unindexed concepts relating to the themes of RA and VTE. Eligibility criteria were: 1) original data from cohort or case-control studies; 2) pre-specified RA; 3) clearly defined VTE outcomes; 4) relative risk (RR), odds ratio (OR), or hazard ratio (HR), and corresponding 95% confidence intervals (CI); 5) sex- and age-matched comparison group; and 6) English language. We calculated weight-pooled summary estimates of RRs for VTE outcomes using the random effects model. The robustness of the results was evaluated using a jack-knife sensitivity analysis (i.e., removal of a single study from the baseline group of studies). All analyses were done using HePIMA software.

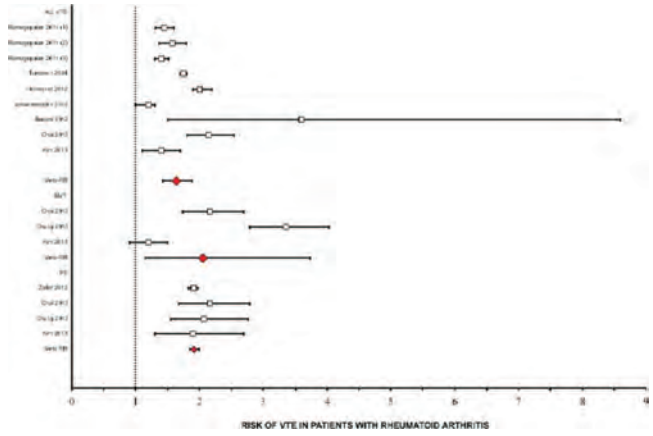
Results: Our search strategy yielded 86 articles, and we identified an additional 2 citations through a hand-search of relevant bibliographies. After applying the eligibility criteria, we identified 8 studies with a total of 479,452 RA patients for inclusion in the meta-analysis. We identified 7 cohort studies (of which one reported results for three separate cohorts) and 1 case-control

study. Overall, pooled estimates for VTE, DVT and PE were significantly increased (**Table 1 and Figure 1**). The estimates remained statistically significant in the jack-knife sensitivity analysis with the point estimates ranging from 1.58 to 1.72 and the corresponding 95% CIs >1 in all cases except for DVT.

Conclusion: The risk of new VTE events is increased in RA patients compared to age- and sex-matched controls. However, there exist a paucity of data on the risk of PE and DVT. These findings support increased vigilance of VTE complications and potential risk-factor intervention among RA patients.

Table 1. Pooled estimates on the risk of VTE events in Rheumatoid Arthritis

Events	No. of Studies	Pooled RR (95% CI)
VTE	8	1.64 (1.42,1.89)
DVT	3	2.06 (1.14,3.74)
PE	4	1.92 (1.85,1.99)



Disclosure: M. Avina, None; **S. Choi**, None; **S. Rai**, None; **H. K. Choi**, None; **M. De Vera**, None.

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Higher-Order Neuropsychological Deficits Are Frequent and Occur Early in RA and SLE: The Impact of Basic Processing Abilities on Psychological Well-Being. Giorgia Dimitraki[1], Georgia Ktistaki[1], Emmanouil Papastefanakis[1], Antonis Fanouriakis[2], Irini Gergiannaki[2], George Bertsias[2], Nikolaos Kougkas[2], Argyro Repa[2], Evangelos Karademas[1], Prodromos Sidiropoulos[2] and Panagiotis Simos[1]. [1]University of Crete, Rethymnon, Greece, [2]University of Crete, Heraklion, Greece.

Background/Purpose: Deficits in higher-order cognitive abilities (episodic memory, executive functions) have been reported in patients with chronic inflammatory disorders, albeit inconsistently. We investigated whether such deficits are associated with impairments in basic cognitive processes (short-term memory, visuomotor speed) and premorbid verbal intelligence, and their potential impact on psychological well-being in newly diagnosed rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

Methods: Patients with RA (N=84, age: 54.1±9.1 years, education: 9.1±4.1 years, DAS28: 3.9±1.4) or non-neuropsychiatric SLE (N=60, age: 43.8±9.7 years, education: 12.1±3.7 years, SLEDAI: 3.6±2.7), diagnosed within the last 3 years, were administered a battery of standardized tests of short-term memory (Digits Forward and Digits Reverse tasks), episodic memory (Auditory Verbal Learning Test [AVLT]), executive functions (Stroop Color-Word Naming, General Ability Measure for Adults [GAMA], Controlled Oral Word Association Test [COWAT], Trail Making Test [TMT] B), visuomotor processing speed (TMT A). Premorbid verbal capacity was estimated using the Peabody Picture Vocabulary Test (PPVT-R). Scores were evaluated against age- and education-adjusted Greek population norms. The Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of impaired mood.

Results: Compared to population norms, RA patients had significantly lower average scores on short term memory, immediate and delayed episodic recall, phonemic fluency, problem solving ability, visuomotor speed and set-shifting ability ($p<0.002$). SLE patients had significantly reduced performance on short-term memory, immediate and delayed episodic recall, visuomotor speed and set-shifting ability ($p<0.003$). Cognitive impairment (defined as performance ≥1.5 SD below the population mean on ≥3 indices) was found in 15.5% and 21.3% of RA and SLE patients respectively, and was not significantly affected by medical comorbidities or disease activity. Notably, impairments on higher-order cognitive abilities in patients were explained by deficits in verbal IQ, short-term memory and visuomotor speed. Both clinical variables (number of physical symptoms experienced, β-coefficient = 3.63, $p=0.002$) and processing speed ($\beta=2.59$, $p=0.035$) significantly contributed independently to the intensity of depression symptoms experienced by patients.

Conclusion: A wide range of cognitive domains was affected in a significant proportion of patients with newly diagnosed RA and SLE. Deficits in higher-order complex memory and executive tasks were largely due to impaired basic cognitive abilities and had an adverse impact on patients' psychological well-being. Emergence of cognitive defects early in the course of RA and SLE suggests common etiopathogenesis possibly linked to underlying disease processes (including inflammation) and/or administered treatments.

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1402

Parameters of Periodontitis Correlate with Anti-Citrullinated Protein Antibodies and *P. Gingivalis* Antibody Titers in Patients with Early or Chronic Rheumatoid Arthritis. Sheila L. Arvikar[1], Hatice Hasturk[2], Marcy B. Bolster[1], Deborah S. Collier[1], Alpdogan Kantarci[2] and Allen C. Steere[3]. [1]Massachusetts General Hospital, Boston, MA, [2]Forsyth Institute, Cambridge, MA, [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Emerging evidence suggests that periodontitis and periodontal pathogens, such as *Porphyromonas gingivalis* (*Pg*), may be an environmental trigger for rheumatoid arthritis (RA). We found that antibodies to *Pg* are increased in a subset of untreated early RA patients and correlate with anti-citrullinated protein antibodies (ACPA). As a next step, we are evaluating periodontal disease in our RA patients. We report here findings of periodontitis in the first 23 patients who have completed formal dental examinations.

Methods: 23 RA patients, 15 with new-onset disease and 8 with chronic RA, completed standardized dental examination performed by a single periodontist. All patients met the 2010 ACR/EULAR criteria for RA. 20 age- and gender-matched healthy subjects without periodontitis or RA were also enrolled. Dental parameters for assessment of periodontitis per the Centers for Disease Control criteria included pocket depth (PD), gingival margin, bleeding on probing (BOP) measured at 6 sites per tooth, and clinical attachment loss (CAL). Serum *Pg* IgG antibodies were measured by ELISA. The dental examiner was blinded to joint and laboratory findings.

Results: Typical of RA cohorts, the patients were predominantly female (87%) with median age of 48. The majority (61%) was seropositive for ACPA, 43% were positive for rheumatoid factor (RF), and they had a range of disease activity. None were current smokers, but 10 previously smoked. All but one patient received routine dental care with cleanings every 6 months.

Of the 23 patients, 10 (43%) had gingivitis, a precursor of periodontitis, 9 (39%) had periodontitis, and only 4 patients (17%) had healthy periodontal tissue. Compared with the 20 healthy subjects, the 23 RA patients had significantly increased pocket depth ($P<0.000001$), CAL ($P=0.001$), and BOP ($P=0.0001$). There were no differences in dental parameters between former vs. never smokers.

In the 23 patients, ACPA levels correlated directly with CAL ($P=0.03$), the most significant determinant of periodontal disease, and with BOP ($P=0.05$). In addition, dental parameters correlated with ESR values ($P=0.04$) and tended to correlate with RF ($P\leq0.09$) and disease activity (DAS-28-ESR, swollen and tender joint counts) ($P\leq0.1$).

Six of the 23 patients (26%) had elevated serum *Pg* IgG antibodies. All 6 patients with positive *Pg* antibodies had periodontitis, while no patient with gingivitis or normal periodontal tissue had elevated *Pg* antibodies ($P<0.001$). Finally, *Pg* antibodies strongly correlated with all dental parameters including pocket depth ($P<0.0001$), BOP ($P=0.003$), and CAL ($P=0.02$).

Conclusion: Most of our patients with early and chronic RA had gingivitis or periodontitis on formal examination, although they received regular dental care. Parameters of periodontitis correlated significantly with ACPA, supporting a role for periodontal disease in RA pathogenesis. As *Pg* antibodies correlate strongly with periodontitis, these may be useful biomarkers in screening for periodontal disease in RA patients. Finally, periodontitis

tended to correlate with RA disease activity, supporting a role for periodontal disease evaluation and treatment in a subset of RA patients.

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1403

Psychosocial Impact of Rheumatoid Arthritis Patients on Their Family Members. Sang Wan Chung[1], Ji Ae Yang[2], Eun Ha Kang[1], Yun Jong Lee[1] and You Jung Ha[1]. [1]Division of Rheumatology, Department of Internal Medicine,Seoul National University Bundang Hospital, Seongnam, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory arthritis that can cause pain and functional disability, and RA patients have a higher risk of psychiatric disorders, especially depression. However, disability and socioeconomic burden of RA patients can also contribute to psychosocial wellbeing of their family members. To date, several studies have been conducted for evaluation of the burden of caregivers in chronic disease such as stroke and dementia, however, the burden of family members of RA patients has not been evaluated. In this study, we conducted a population-based analysis to examine the psychosocial characteristics of family members of RA patients in comparison with the general population and to evaluate the psychosocial impact of RA patients on their family members.

Methods: From the Fifth Korea National Health and Nutrition Examination Surveys (KNHANES V) (2010–2012) dataset, we identified 452 RA patients and then selected family members of these patients who were aged 20 years or older (n=515). The control group was sampled from members of families without RA patient with matching for sex and age (n=1,545).

We compared the psychosocial characteristics between family members of RA patients and control group. Also, serial conditional logistic regression models were performed to evaluate the association of psychosocial impact with the presence of RA patient after adjustment of covariants.

Results: The mean age was 51.9 ± 18.8 years and sixty percent were male in our study population. Family members of RA patients were more employed (63.6% vs. 60.2%, $p = 0.037$), and had higher household income ($p = 0.037$) compared with sex and age-matched control subjects. No significant differences were observed in comorbidities between two groups.

Family members of RA patients had a significantly higher level of stress (29% vs. 24.3%, $p = 0.046$), history of depression (17.3% vs. 11.9%, $p = 0.004$). The presence of a RA patient in the family showed significant association with history of depression (odds ratio, 1.60; 95% confidence interval, 1.19 to 2.16; $p = 0.002$), after adjustment for household income, education level, and employment status.

Conclusion: Family members of RA patients have higher level of stress and they are more susceptible to depression. Our findings suggest that physicians or rheumatologists who treat RA patients should pay more attention to psychosocial burden of their family members.

Table 3. Multivariate (adjusted) analyses of factors influencing psychosocial status of the study population

Parameter	Level of stress			History of depression		
	OR	95% CI	p-value	OR	95% CI	p-value
Presence of RA patients						
No	1.00			1.00		
Yes	1.27	0.10–1.61	0.055	1.60	1.19–2.16	0.002
Household income						
Highest	1.00			1.00		
Higher intermediate	0.96	0.72–1.29	0.803	1.02	0.68–1.53	0.919
Lower intermediate	1.07	0.79–1.44	0.673	1.30	0.87–1.95	0.196
Lower	1.15	0.82–1.62	0.418	1.64	1.07–2.50	0.022
Education						
College	1.00			1.00		
High	0.90	0.69–1.18	0.453	1.46	0.97–2.19	0.068
Middle	0.69	0.48–1.01	0.055	1.25	0.77–2.04	0.368
Primary	0.70	0.51–0.96	0.026	1.46	0.97–2.19	0.068
Employment status						
Unemployed	1.00			1.00		
Employed	0.81	0.64–1.03	0.813	1.34	1.00–1.78	0.048

OR, odds ratio; CI, confidence interval

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1404

Presence and Significance of Anti-CCP Antibody in Patients with Interstitial Lung Disease with and without Clinically Apparent Rheumatoid Arthritis. Muhammad Imran[1], Shanley O'brien[2], Mark Hamblin[2] and Mehrdad Maz[1]. [1]University of Kansas Medical Center, Kansas City, KS, [2]Kansas University Medical Center, Kansas city, MO.

Background/Purpose: Interstitial lung disease (ILD) can be idiopathic or associated with underlying etiologies including rheumatoid arthritis (RA). The purpose of this study is to determine the presence and significance of anti-CCP (and RF) in patients with ILD, whether or not they meet the diagnostic criteria for RA; supporting the notion that ILD as an extra articular manifestation of RA can develop prior to articular symptoms and that anti-CCP antibodies can be a prognostic marker for development of ILD in RA.

Methods: This is a retrospective chart review of 160 patients with ILD to identify and compare patients without articular manifestations whom had CCP antibodies (with or without RF) to those who met the diagnostic criteria for RA. The data was abstracted from patients seen at the University of Kansas Medical Center Pulmonary ILD Clinic between January 2008 to June 2014. Each subject had serologic studies, pulmonary function testing (PFT), and thoracic computed tomography scan as part of the routine clinical evaluation.

Results: Of the 160 patients, RF and/or anti-CCP were measured in 125 patients (78%). Of these 125 patients, 55 patients (44%) who had ILD along with positive RF and/or anti-CCP were identified. Of these 55 patients, only 4 patients who had ILD and anti-CCP positivity (median 94.7, range 36–138) did not have articular manifestations of RA, 3 of whom were male and one was female. The 3 male patients had a mean age of 65 at the time of diagnosis of ILD and only one had a history of smoking. The female patient was a 53 y/o cocaine abuser who also had a p-ANCA titer at 1:1280, MPO >8, and PR3 (0.4). One female patient died within 6 years of diagnosis of ILD and never developed articular manifestations of RA; the remaining 3 patients have not developed articular symptoms of RA yet. Nine patients with ILD had a positive RF but negative anti-CCP without articular findings of RA. Majority of these patients were female, and most were former cigarette smokers. However, 6 of these 9 patients had elevated ANA (> 1:640) without features of a connective tissue disease. Among patients with ILD and RA, a positive anti-CCP antibody (28 patients) had a strong association with ILD ($x^2 = 8.526$, $p=0.0035$). Of these patients who had PFTs, 73% (30 of 41) already had moderate to severe restrictive lung disease or a severe impairment in diffusing capacity at the time of initial pulmonary evaluation.

Conclusion: Our data indicates that the majority of patients with ILD and positive RF and/or anti CCP antibody in the ILD Clinic met the diagnostic criteria for RA. Consistent with other reports, there was a strong association with presence of anti-CCP antibody and development of interstitial lung disease. These findings highlight the prognostic value of anti-CCP antibody in patients with RA who may be at increased risk of developing ILD. Hence, it is reasonable for CCP positive RA patients to undergo routine screening and surveillance for early detection and management of ILD at the time of diagnosis and thereafter. Further investigation and prospective studies are needed to fully assess the implications of a positive anti-CCP and RF in patients with ILD without articular manifestations of RA.

Disclosure: M. Imran, None; **S. O'brien**, None; **M. Hamblin**, None; **M. Maz**, None.

1405

Five-Year Changes in Myocardial Structure and Function in Patients with Rheumatoid Arthritis. John M. Davis III[1], Grace Lin[1], Jae Oh[2], Cynthia S. Crowson[1], Terry M. Therneau[1], Eric L. Matteson[1] and Sherine E. Gabriel[1]. [1]Mayo Clinic, Rochester, MN, [2]Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN.

Background/Purpose: Patients with rheumatoid arthritis (RA) suffer an increased risk of heart failure not explained by traditional cardiovascular risk factors. Previously, we have shown that these patients have a high prevalence of abnormal left ventricular (LV) diastolic dysfunction and altered ventricular

geometry. The objective of this study was to evaluate longitudinal changes in LV structure and function in patients with RA.

Methods: A prospective longitudinal study of patients with RA from our community population-based inception cohort was performed. RA was defined according to the 1987 classification criteria. Patients were seen at study baseline (2007 – 2009) and approximately 5 years later (2012 – 2014). For each participant, a registered diagnostic cardiac sonographer performed pulse wave and tissue Doppler echocardiography according to a standardized research protocol. LV diastolic function parameters were analyzed according to guidelines and criteria of the American Society of Echocardiography. Medical records were reviewed to ascertain demographics, cardiovascular risk factors, and RA disease characteristics. Changes in the echo parameters between baseline and 5 years were tested using paired t-tests.

Results: A total of 137 patients to date have been studied at the 5-year time point. The mean age was 58.4 years, disease duration 9.6 years, and 76% were female. The E/e' ratio increased from 8.7 to 10.9 ($p<0.001$), consistent with increasing filling pressures of the left ventricle (Table). The left atrial volume index increased from 25.6 to 34.3 ($p<0.001$). The LV mass index and relative wall thickness decreased over time. On average, there was no biologically relevant change in the ejection fraction over time.

Measurement	Baseline Mean (SD)	5 Years Mean (SD)	Mean Difference	P-value
LV ejection fraction, %	62.0 (5.8)	61.2 (4.6)	−0.8 (6.3)	0.13
E velocity, m/s	0.69 (0.17)	0.7 (0.17)	0.01 (0.17)	0.53
A velocity, m/s	0.43 (0.1)	0.71 (0.21)	0.28 (0.25)	<0.001
Tissue Doppler e', m/s	0.08 (0.02)	0.07 (0.02)	−0.02 (0.02)	<0.001
E/A ratio	1.7 (0.4)	1.1 (0.4)	−0.6 (0.6)	<0.001
E/e' ratio	8.7 (2.9)	10.9 (3.9)	2.2 (3.4)	<0.001
Left atrial volume index, mL/m^2	25.6 (5.4)	34.3 (8.7)	8.6 (7.9)	<0.001
LV mass index, gm/m^2	80.7 (14.9)	77.3 (18.4)	−3.4 (17.5)	0.06
Relative wall thickness	0.40 (0.07)	0.36 (0.07)	−0.04 (0.08)	<0.001

Conclusion: In this sample of patients with RA, clinically significant worsening in cardiac structure and function occurred during 5 years of follow-up, including progression of diastolic dysfunction. Additionally, decline in the LV mass index was observed, which contrasts the expected increased LV mass associated with diastolic dysfunction (hypertrophy). Future work is necessary to compare these findings to age-related changes in the general population in order to better understand the significance of the results with respect to the risk of future heart failure.

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1406

Comorbidity in Rheumatoid Arthritis. It Is Feasible to Record Concomitant Medical Conditions and Multi-Morbidity in Observational Research Studies. Can This be Extended to Routine Clinical Settings? Elena Nikiphorou[1], Sam Norton[2] and Adam Young[3]. [1]University of Hertfordshire, Hatfield, United Kingdom, [2]King's College London, London, United Kingdom, [3]ERAS, St Albans City Hospital, St Albans, United Kingdom.

Background/Purpose: Comorbidity in RA can delay diagnosis and influence treatment decisions. It is known to affect RA outcomes, and can confound data analysis. Most RA observational cohort studies have used either the generic and weighted Charlson Comorbidity Index (CCI), one of few validated tools but complicated and designed for medical inpatient settings, or non-standardised but simple comorbidity counts. We have previously reported on the feasibility of the latter and its value in assessing impact of comorbidity on survival and function [ref]. There is currently no standardised, uncomplicated and validated instrument for recording and collecting comorbidity data which is relevant to contemporary and routine rheumatology practice. Is it feasible to measure comorbidity in daily rheumatology practice? The purpose of the study is to evaluate the feasibility of a simple method based on ICD10 systems (chapters) to measure comorbidity in RA.

Methods: Clinicians involved in a UK inception observational cohort study of RA (the Early RA Study, ERAS, n=1465, median follow up 10yrs) completed a simple and specific outcome form at regular intervals which included indicating the presence or not of the main ICD10 systems (n=15), with space to add details as free text (completed in 91%).

Results: More than 90% of all comorbidities reported covered 10 systems in order of frequency – Non Cardiac Vascular (to comply with WHO classification), Cardiovascular, Endocrine, Gastro Intestinal & Hepatic, Respiratory, Psychiatric, Malignancies, Renal, Dermatology, Opthalmology. As musculoskeletal and extra articular RA conditions would be managed within the specialty, these were identified and remained as a separate group and not part of this analysis. 75% of all individual comorbidities recorded in the ICD10 systems included only 20 specific medical conditions, and the most common 2–3 specific conditions in each ICD10 system made up most (70–80%) of each system. For the other less common systems, there was a wider range of individual conditions of roughly equal frequencies. At least one comorbidity at baseline, 3, 5 & 10yr follow up was present in 21%, 40%, 50% and 78% respectively based on a simple numeric score, compared to weighted CCI of 11%, 27%, 36%, 52%. Mean scores were 0.21, 0.53, 0.72, 1.08 and 0.13, 0.4, 0.55, 0.86 respectively, with modest correlations since they measure different aspects: Spearman's rho of around 0.72. Kappa statistics were 19.3, 25.1, 24.6, 22.9 respectively. Multiple morbidity can be measured from ICD10 (>1 major condition) and was present in <1%, 11%, 17% & 29% at baseline, 3, 5, 10yrs.

Conclusion: This study has shown the feasibility of collecting comorbidity data in a relatively simple way using standard definitions, and its value in identifying multi-morbidity. It is this latter group with complex disease that requires prompt identification, multiple speciality input and coordination of patient care routine clinical settings.

Ref: Norton S et al. A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome. Rheumatology (Oxford) 2013;52(1): 99–110

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1407

Low HAQ and Pain Predict Patient Perceived Remission in Rheumatoid Arthritis Patients Receiving MTX or Anti-TNF-Alpha Treatment. Paul Studenic[1], Josef S. Smolen[2] and Daniel Aletaha[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria.

Background/Purpose: The induction of remission is the primary target of RA therapy. Failing to achieve the patient global estimate of disease activity criterion (PGA<=1cm) has been shown to be the primary cause hindering patients to be classified as being in remission. Here, we aimed to determine factors that predict achieving the PGA criterion of remission in RA patients in usual clinical care.

Methods: We selected patients from a longitudinal RA database, who started MTX monotherapy or TNFi treatment in combination with MTX or leflunomide and had at least 6 months of follow-up. In univariate analysis, we tested core-set variables to identify candidate predictors of patient perceived remission (PGA≤1cm), which we then subjected to multivariate logistic regression analysis for the outcome: PGA≤1cm.

Results: Data of 172 patients receiving MTX (82% female, 65% rheumatoid factor positive, mean SDAI: 18.5±12.3) and of 112 patients on TNFi (82% female, 62% rheumatoid factor positive, mean SDAI: 19.7±13.3) were used for analysis. After 6 month of treatment 70% of those receiving MTX and 55% of the TNFi group were in a state of remission or low disease activity, based on the SDAI. Forty-seven percent of MTX and 34% of TNFi patients evaluated their PGA as being ≤1cm. Seventy-four percent of MTX and 58% of TNFi treated patients who had PGA≤1cm had also an evaluator global assessment of ≤1cm. The overlap of patient perceived remission and remission by SDAI was 49% in the MTX group and 46% in the TNFi group.

Univariate analyses in MTX treated patients showed an association of pain, HAQ scores, and TJC with the outcome PGA≤1cm. In the multivariate logistic regression model, the odds ratio (OR) was 0.46 for baseline HAQ (**Table**) and 0.98 for pain as predictors for achieving remission after 6 months of treatment. Higher HAQ and pain scores therefore lead to a lower odds for achieving PGA ≤1cm.

Patients with an improvement in HAQ within the first 3 month have a 3.5 (CI: 1–13) times higher odds to achieve PGA≤1cm after 6 months of treatment than patients who report a worsening in HAQ, which corresponds to a probability of 23% versus 8% to achieve PGA≤1cm.

In patients receiving TNFi-therapy, baseline HAQ (OR: 0.31) and pain (OR: 0.98) were shown to be predictive, i.e. a patient with a baseline HAQ of

1.25 or a pain score of 50mm has a 20% probability of achieving PGA remission, whereas a baseline HAQ of 0.5 or a pain score of 20mm coincides with a 40% probability.

Table: Summary of the multivariate logistic regression model for the outcome PGA≤1cm

		Regression coefficient	Standard error	p	95% Confidence Interval for Odds Ratio		
					Lower	OR	Upper
MTX	**Baseline HAQ**	−0.77	0.36	0.034	0.23	0.46	0.94
	Baseline pain	−0.02	0.01	0.026	0.96	0.98	1.00
	Constant	0.18	0.35	0.611		1.19	
TNFi	**Baseline pain**	−0.03	0.01	0.022	0.95	0.98	0.99
	Baseline HAQ	−1.16	0.41	0.004	0.14	0.31	0.70
	Constant	0.87	0.41	0.036		2.39	

Conclusion: We demonstrated here that patients with poor function or high pain levels are likely to fail patient reported remission, as shown here for the patient global variable, which is part of the established remission criteria. These findings were independent of the treatment regimen. Improvement in function enhances the chances for achieving patient perceived remission after 6 months of DMARD treatment.

Disclosure: P. Studenic, None; **J. S. Smolen**, None; **D. Aletaha**, None.

1408

Inflammatory Biomarkers, Sleep Quantity and Sleep Quality in Rheumatoid Arthritis. Alexander Fine[1], Michelle A. Frits[2], Jing Cui[3], Christine K. Iannaccone[2], Jonathan S. Coblyn[2], Michael E. Weinblatt[2], Nancy A. Shadick[4] and Yvonne C. Lee[2]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Brigham and Womens Hospital, Boston, MA, [4]Brigham and Women's Hospital/Harvard University, Cambridge, MA.

Background/Purpose: Sleep problems affect over 60% of rheumatoid arthritis (RA) patients. However, little is known about the association between sleep problems and inflammatory pathways in RA. In the general population, studies have shown that sleep problems are associated with elevations in inflammatory biomarkers, notably CRP and the inflammatory cytokines, TNF-a and IL-6. The goal of this study was to examine the cross-sectional association between biomarkers associated with RA disease activity and sleep quantity and quality in patients with RA.

Methods: 208 patients in a RA registry were enrolled in a substudy on sleep and psychosocial distress. All subjects completed the Medical Outcomes Study (MOS) Sleep Scale. Of these 208 patients, 189 also had 12 biomarkers of disease activity (EGF, VEGF-A, leptin, IL-6, SAA, CRP, VCAM-1, MMP-1, MMP-3, TNFRI, YKL-40 and resistin) measured using a quantitative multiplex immunoassay. Biomarkers with non-normal distributions were transformed. The primary independent variables were the individual biomarkers and a composite disease activity score, calculated according to a validated algorithm. The primary dependent variables were sleep quantity (in hours) and sleep quality, measured by the MOS Sleep Problems Index II (0–100 scale with 100 indicating greater sleep problems). Linear regression models were used to examine the association between biomarkers and sleep quantity and quality, adjusted for age, sex, RA disease duration and RF or anti-CCP seropositivity. To elucidate the impact of TNF inhibitors on this association, secondary analyses were performed including an indicator variable for TNF inhibitor use. Using the Bonferroni correction for multiple comparisons, the threshold for significance was set at $p < 0.002$.

Results: The study population (N = 189) included 85.2% women. The average age was 58.2 ± 11.2 years. The average DAS28-CRP was 2.95 ± 1.29. 17.5% were taking corticosteroids. 59.8% were taking non-biologic disease-modifying anti rheumatic drugs, and 54.0% were taking TNF inhibitors. 61.9% were either RF or anti-CCP positive. After adjustment for multiple comparisons, neither the composite disease activity score nor the individual biomarkers of disease activity were significantly associated with sleep quantity or the MOS Sleep Problems Index II (Table). Similarly, neither the composite disease activity score nor the individual biomarkers were significantly associated with sleep quantity or the MOS Sleep Problems Index II in secondary analyses including TNF inhibitor use as an indicator variable.

Conclusion: Contrary to previous studies in the general population, no associations were observed between inflammatory biomarkers and measures of sleep quantity and quality in this cross-sectional study of established RA patients. These findings suggest that RA disease activity may not be the primary driver of sleep problems in RA.

Table. Adjusted associations between biomarkers of RA disease activity and sleep quantity and sleep quality, measured using the Medical Outcomes Study Sleep Scale.*

Biomarkers	Sleep Quantity(n=174)		Sleep Quality(n=176)	
	b	*P*	b	*P*
Composite score	0.01	0.42	−0.04	0.68
ln CRP	−0.05	0.48	−0.55	0.61
ln TNFRI	0.13	0.72	0.92	0.86
ln IL-6	0.15	0.13	−0.87	0.54
ln EGF	−0.25	0.16	1.33	0.62
ln VEGF-A	−0.31	0.07	3.14	0.21
ln Leptin	−0.13	0.18	2.54	0.07
ln SAA	0.05	0.57	−0.93	0.44
ln VCAM-1	0.75	0.05	−0.07	0.99
ln MMP-1	−0.18	0.20	3.83	0.06
ln MMP-3	−0.02	0.91	−1.62	0.48
ln YKL-40	0.09	0.56	0.87	0.68
ln Resistin	−0.18	0.46	6.28	0.08

* All results are from multivariable linear regression models adjusted for age, sex, RA disease duration and seropositivity.

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1409

Pregnancy Outcomes after Exposure to Certolizumab Pegol: Updated Results from Safety Surveillance. Megan E. B. Clowse[1], Douglas C. Wolf[2], Frauke Förger[3], John J. Cush[4], Amanda Golembesky[5], Laura Shaughnessy[5], Dirk De Cuyper[6], Kristel Luijtens[6], Sarah Abbas[7] and Uma Mahadevan[8]. [1]Duke University Medical Center, Durham, NC, [2]Atlanta Gastroenterology Associates, Atlanta, GA, [3]Inselspital, University of Bern, Bern, Switzerland, [4]Baylor Research Institute and Baylor University Medical Center, Dallas, TX, [5]UCB Pharma, Raleigh, NC, [6]UCB Pharma, Brussels, Belgium, [7]UCB Pharma, Paris, France, [8]UCSF Medical Center, San Francisco, CA.

Background/Purpose: Certolizumab pegol (CZP) is a PEGylated Fc-free anti-TNF approved for the treatment of RA, CD, psoriatic arthritis (PsA) and ankylosing spondylitis (AS). The objective was to provide an updated analysis of pregnancy outcomes in rheumatic patients (pts) after CZP exposure, with a focus on RA pregnancies, from clinical trial and spontaneous post-marketing reports. Concomitant medications and disease activity are also reported from clinical trials.

Methods: The UCB Pharma global safety database was searched for all medically confirmed cases of pregnancy through 28 March 2013. The number of live births, spontaneous miscarriages and elective terminations for neonates exposed to CZP (maternal/paternal exposure) was examined. Congenital abnormalities, neonatal deaths, maternal demographics, disease activity and concomitant medications were also investigated.

Results: 309 CZP-exposed pregnancies were reported: 285 maternal exposure, 24 paternal. For maternal exposure pregnancies, the most common underlying maternal conditions were CD (190/285) and RA (52/285), with the remaining 43/285 for other indications (including AS and PsA). Pregnancy outcomes were available for 190 of 285 pregnancies: 42 in women with RA, 124 in CD and 24 in other rheumatic indications. Pregnancy outcomes, where reported, are shown in Table 1. Maternal disease activity in women with RA are shown in

Table 2. Common concomitant medications in all pregnancies are shown in Table 3. 5 congenital anomalies were reported, in 4 neonates, among all maternal exposure live births (n=132): vesicoureteric reflux; congenital morbus hirschsprung disease and club foot; right aortic arch with aberrant left subclavian artery; mild unilateral hydronephrosis on antenatal ultrasound (healthy at birth). None were considered related to CZP by the treating physicians. A single neonatal death was reported after maternal exposure in one of a set of twins with gestation <26 weeks.

Conclusion: Updated analysis of pregnancy outcomes after exposure to CZP supports previous reports[1] suggesting no apparent impact of maternal CZP exposure on pregnancy outcomes. Additional prospective data are required to better evaluate the safety of CZP in pregnancy and the role of concomitant medications and disease activity.

References 1. Clowse M. Arthritis Rheum 2012;64(S10):702

Table 1: Pregnancy outcomes and characteristics for all maternal exposure pregnancies with known outcomes, with focus on the subgroup of women with RA

	RA Subgroup (n = 42)	All Pregnancies [a] (N = 190)
Pregnancy outcome, n (%)		
Number with available data	42	190
Live birth	26 (61.9%)	132 (69.5%)
Spontaneous abortion	9 (21.4%)	36 (18.9%)
Elective termination	7 (16.7%)	22 (11.6%)
Maternal age at delivery [b] (years)		
Number with available data	21	101
Mean (SD)	31.2 (5.74)	30.5 (5.10)
Median	30.7	29.8
Min, Max	21.5, 40.1	21.5, 42.9
Gestational age at outcome [c] (weeks)		
Number with available data	22	77
Mean (SD)	37.9 (1.99)	38.3 (1.97)
Median	38.1	39.0
Min, Max	33.7, 41.0	32.0, 41.7
Prematurity [c]		
Number with available data	24	86
<32 weeks	0 (0.0%)	1 (1.2%)
32–36 weeks	4 (16.7%)	10 (11.6%)
≥37 weeks	20 (83.3%)	75 (87.2%)
Birth weight [d] (grams)		
Number with available data	16	62
Mean (SD)	3168.7 (523.89)	3194.3 (447.84)
Median	3080.0	3215.0
Min, max	2500.0, 4535.9	2100.0, 4535.9
Low birth weight [d]		
Number with available data	16	62
1500–2499 grams	0 (0.0%)	2 (3.2%)
≥2500 grams	16 (100.0%)	60 (96.8%)

[a] Pts with all indications, including CD, RA, axial spondyloarthritis (axSpA) and PsA; [b] Analyses restricted to live births; [c] Analyses restricted to singleton live births; [d] Analyses restricted to singleton, term, live births.

Table 2: Maternal disease activity for pregnancies from clinical trial reports (RA subgroup only)

	Live Birth (n = 7)	Spontaneous Abortion (n = 4)	Elective Termination (n = 3)	Total (N = 14)
DAS28 (ESR) at baseline (RA study entry)				
Mean (SD)	6.39 (0.79)	6.14 (0.68)	6.64 (0.92)	6.37 (0.75)
Median	6.18	6.09	6.56	6.15
Min, Max	5.1, 7.3	5.4, 7.0	5.8, 7.6	5.1, 7.6
DAS28 (ESR) at visit prior to pregnancy report				
Mean (SD)	3.51 (1.65)	2.43 (1.44)	4.41 (1.05)	3.39 (1.56)
Median	2.67	1.93	4.18	2.86
Min, Max	2.2, 6.3	1.3, 4.5	3.5, 5.6	1.3, 6.3
DAS28 (ESR) change from baseline				
Mean (SD)	−2.88 (1.59)	−3.71 (1.62)	−2.23 (0.76)	−2.98 (1.47)
Median	−2.99	−4.02	−2.05	−3.03
Min, Max	−4.7, −0.6	−5.2, −1.6	−3.1, −1.6	−5.2, −0.6

Table 3: Concomitant medications at time of pregnancy report for all pregnancies from clinical trials

Concomitant Medication, n (%) [a] WHO Drug Dictionary	Live Birth (n = 31)	Spontaneous Abortion (n = 11)	Elective Termination (n = 15)	Outcome Unknown (n = 8)	Total (N = 65)
Any concomitant medications	29 (93.5%)	11 (100.0%)	15 (100.0%)	7 (87.5%)	62 (95.4%)
Antihypertensive	2 (6.5%)	1 (9.1%)	0	0	3 (4.6%)
Anti-inflammatory/Antirheumatic	9 (29.0%)	4 (36.4%)	7 (46.7%)	1 (12.5%)	21 (32.3%)
NSAIDs	7 (22.6%)	4 (36.4%)	6 (40.0%)	2 (25.0%)	19 (29.2%)
Oral Corticosteroids	12 (38.7%)	4 (36.4%)	6 (40.0%)	3 (37.5)	25 (38.5%)
Azathioprine/Mercaptopurine (6-MP)	11 (35.5%)	2 (18.2%)	1 (6.7%)	1 (12.5%)	15 (23.1%)
Mesalazine/Sulfasalazine	12 (38.7%)	3 (27.3%)	5 (33.3%)	2 (25.0%)	22 (33.8%)
Methotrexate (MTX)	5 (16.1%)	6 (54.5%)	2 (13.3%)	0	13 (20.0%)
Folic acid	6 (19.4%)	7 (63.6%)	1 (6.7%)	3 (37.5%)	17 (26.2%)

[a] Concomitant medications are defined as any medication taken at the time of the pregnancy report study visit.

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Low Rates of Cardiovascular Risk Factor Modification Among High-Risk Rheumatoid Arthritis Patients: Barrier to Cardiovascular Prevention Strategies?

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Background/Purpose: Despite higher risk of cardiovascular disease (CVD) in rheumatoid arthritis (RA), systematic cardiovascular (CV) prevention strategies are lacking. Recent guidelines for CV risk modification rely on documentation of traditional risk factors to estimate 10-year CV risk scores. Our primary objective was to quantify, by utilizing electronic medical records (EMR), the frequency of CV risk factors in a prospective longitudinal RA cohort, as well as use of CV medications, including statins, angiotensin-converting enzyme inhibitors (ACE-i), or angiotensin-receptor blockers (ARB). We also sought to determine the rates of CV risk factors and CV medication use in the subset of RA patients with 2 or more 'high risk' disease features, i.e., seropositivity for rheumatoid factor or anti-cyclic citrullinated peptide, disease duration >10 years, or severe extra-articular manifestations (ExRA).

Methods: Utilizing the EMR, we identified presence of hypertension (HTN), hyperlipidemia (HL), diabetes mellitus (DM), family history, and personal history of CVD, as defined by ICD-9 codes, as well as body mass index (BMI) >30 kg/m^2 (obesity), uncontrolled HTN (blood pressure [BP] ≥150/90 mm Hg for those aged ≥60 years; and BP ≥140/90 mm Hg for those aged <60 years), and current/ever smoking status. We defined use of any statin, ACE-I, or ARB if listed on EMR's medications. Severe ExRA was defined by ICD-9 codes for pericarditis, pleuritis, Felty's syndrome, vasculitis, neuropathy, scleritis/episcleritis, or glomerulonephritis. Merging EMR data with ongoing prospective RA Comparative Effectiveness Research (RACER) database, frequencies were calculated for each of the CV risk factors and medications in a subset of active RACER subjects from enrollment up to October 2013.

Results: A total of 934 active RACER subjects were identified among 1039 enrolled. Table 1 shows prevalence of CV risk factors. Only 14.7% were taking any statin, 26.3% any ACE-i, and 14.1% any ARB. Out of 675 subjects with complete data, 317 (47.0%) had at least 2 'high-risk' RA disease features that increase their estimated 10-year CV risk score. Of this subgroup, 259 (81.7%) had one or more CV risk factors, yet only 57 (18.0%) were treated with any statin, and 138 (43.5%) were treated with any ACE-i or ARB.

Conclusion: Among RA patients with available EMR data for traditional CV risk factors, a majority had modifiable obesity, HL and HTN (including uncontrolled). Yet, only a minority were treated with statins, ACE-I, or ARB. These data suggest that CV risk factor management is suboptimal in RA patients, even in the subgroup of RA patients with 'high-risk' disease features. The low rates of CV risk factor modification are potential barriers to optimizing CV preventive strategies in RA. Future studies are needed to improve work flows using EMR for CV risk factor documentation and to help modify them in this high-risk population.

Table 1: Prevalence of CV Risk Factors Reported in EMR in RACER Cohort. Analysis of 934 active RACER patients (out of 1039 patients) from enrollment up to October 2013

	Present	Absent	Data Missing
HTN*	505 (54.1%)	428 (45.9%)	1
Uncontrolled HTN	705 (76.6%)	216 (23.5%)	13
HL	480 (51.5%)	453 (48.6%)	1
DM[a]	158 (16.9%)	775 (83.1%)	1
Family Hx HD[ı]	11 (1.2%)	922 (98.8%)	1
Personal Hx CVD**	161 (17.3%)	772 (82.7%)	1
BMI			237
BMI ^{2}30 kg/m^2	211 (30.3%)	N/A	
BMI >30 kg/m^2	486 (69.7%)	N/A	
Smoking history[¤]			1
Current/Ever smokers	457 (48.9%)		
Never smokers	341 (36.5%)		
Unknown	135 (14.5%)		

ICD codes: *401.0-401.9; 272.0-272.9; [a]250.00-250.83; [ı]V17.49; **V12.50, 429.0-429.9, 410.0-410.9, 414.00-414.19, 414.2-414.9; [¤]305.1, V15.82, or self reported in RACER annually
CV = cardiovascular; EMR = electronic medical record; RACER = Rheumatoid Arthritis Comparative Effectiveness Research; HTN = hypertension; HL = hyperlipidemia; DM = diabetes mellitus; Hx = history; HD = heart disease; CVD = cardiovascular disease; BMI = body mass index. Percentages are calculated based on those with available data.

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Psychological Distress over Time in Early Rheumatoid Arthritis: Results from a Longitudinal Study in an Early Arthritis Cohort. Bernard Combe[1], Nathalie Rincheval[2], René-Marc Flipo[3], Philipe M. Goupille[4], Jean-Pierre Daurès[2] and JP Boulenger[5]. [1]Hôpital Lapeyronie, Montpellier, France, [2]Institut Universitaire de Recherche Clinique, Montpellier, France, [3]Hopital R Salengro CHRU, Lille CEDEX, France, [4]Hopital Trousseau, Tours, France, [5]La Colombiere Hospital, Montpellier, France.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic disease with frequent psychological comorbidities, of which depression and anxiety are 2 common manifestations. We aimed to identify predictive factors of psychological distress in a large prospective cohort of very early RA patients.

Methods: ESPOIR (Etude et Suivi des POlyarthrites Indifférenciées Récentes) is a multicentre, longitudinal and prospective cohort study of patients with early arthritis (< 6-month disease duration). The study sample comprised 641 patients with very early RA according to the 2010 ACR/EULAR RA criteria from the ESPOIR cohort. Psychological distress was assessed over 3 years by the Mental Health Inventory 5 questionnaire, at different timepoints (baseline, 6, 12, 18, 24 and 36 months). Logistic regression with a Generalized Estimating Equation (GEE) model was used to analyse the association of disease variables and risk of psychological distress.

Results: At baseline, 46.9% of RA patients were screened as positive for psychological distress. Over 3 years, psychological distress decreased significantly, with a prevalence of 25.8% at 36 months. The Health Assessment Questionnaire–Disability Index (HAQ-DI) score was the most important factor predicting psychological distress over 3 years (odds ratio 1.81 [95% confidence interval 1.13–2.91] to 3.66 [2.07–6.45]). On GEE analysis, other significant variables predicting psychological distress included female sex (p= 0.0117), low educational level (p=0.0047), family income (p= 0.0138 or 0.0385) and occupation of employee according to national classification of socio-professional categories (p= 0.0096). Low (< median) patient and physician global assessment of disease activity or DAS28-CRP ≤ 3.2 were protective for risk of psychological distress. Finally, risk of psychological distress was increased during the first year after diagnosis (OR 1.31 [1.04–1.72] to 1.95 [1.44–2.84]. Baseline biological and radiological variables and treatment regimen were not associated with distress.

Conclusion: Psychological distress in very early RA is frequent and the HAQ-DI score is a predictor of depression and anxiety in these patients. Psychological evaluation in patients with early RA is important for further individual psychiatric diagnosis and management.

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Sarcopenia and Its Impact on Disability in Rheumatoid Arthritis, a Pilot Study. Meltem Alkan Melikoglu[1] and Kazim Senel[2]. [1]Ataturk University Faculty of Medicine, Erzurum, Turkey, [2]Ataturk University Medical School, Erzurum, Turkey.

Background/Purpose: Rheumatoid arthritis (RA) is associated with increased morbidity and mortality due to several metabolic deteriorations one of which is sarcopenia. The aim of this cross-sectional pilot study was to investigate sarcopenia in patients with RA and to evaluate its relation to the disability assessment.

Methods: Forty female patients with RA and age-gender and body mass index (BMI) matched 40 healthy controls were included. Demographic data, pain, morning stiffness duration, disease activity score (DAS28), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and the Health Assessment Questionnaire (HAQ) were evaluated. Body compositions were assessed with whole body dual energy X-ray absorptiometry. We compared the appendicular appendicular skeletal muscle mass (ASM) and skeletal muscle mass index (SMI) of patients to their healthy matches. Also possible correlations between SMI and the disease characteristics and HAQ score were investigated. The independent samples t test and the Pearson's correlation test were used to evaluate the data.

Results: The mean age of the patients and controls were 48,29 ±8,34 and 46.21±6.90 years, respectively. The BMI values, percentages of obese, overweigth and healthy weight subjects were similar in patient and control groups. However, ASM and SMI calculations were found to be significantly lower in patients with RA than those in controls (p<0,05). The percentage of sarcopenia was significantly higher in patients with RA than that in their age-gender and BMI similar healthy matches (20% and 7%; respectively; p<0,05). Although there were no significant correlation between SMI and age, disease duration, morning stiffness, pain, DAS28 levels and laboratory investigations, a significant negative correlation was determined between SMI and HAQ score in patients with RA (p<0,05).

Conclusion: We demontrated lower SMI values and higher sarcopenia ratios in patients with RA than their age-gender and BMI similar healthy matches. Also, independetly from other disease characteristics, the inverse correlation between SMI and HAQ scores found in our study may contribute the understanding of the impact of the process on the disability of the patients.

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The Prevalence of Renal Impairment in Patients with Rheumatoid Arthritis. Marion Coudercr Sr.[1], Martin Soubrier[2], Bruno Pereira[3], Aurelien Tiple[4], Melanie Gilson[5], Bruno Fautrel[6], Sophie Pouplin[7], Emmanuelle Dernis Labous[8], Laure Gossec[9], Cécile Gaujoux-Viala[10] and Maxime Dougados[11]. [1]Chu G.Montpied, Clermont Ferrand, France, [2]CHU G.-Montpied,

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Background/Purpose: To assess the prevalence and associations of renal dysfunction in patients with rheumatoid arthritis (RA).

Methods: COMEDRA is a French nationwide cross-sectional multicentre study on comorbidities in RA. Renal function was assessed from the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation. RA characteristics, risk factors for renal dysfunction (cardiovascular risk factors, medications) were collected in all participants.

Results: 931 of the 970 recruited patients, were analysed (female gender: 79.6%, age: 57.8 years, disease duration: 11.1 years, DAS28-erythrocyte sedimentation rate: 3.1). About 9 % of patients had an eGFR<60 ml/min/1.73m^2 and 9.9% of the patients had proteinuria (defined by positive dipstick testing). In the univariate analysis, age ($p<0.001$), the presence of hypertension ($p<0.001$), systolic blood pressure ($p=0.03$), and Framingham Risk score ($p<0.001$) were associated with an eGFR<60ml/min/1.73m^2. Renal dysfunction was not associated with gender ($p=0.35$), disease duration ($p=0.91$), disease activity (as assessed by DAS28-ESR: $p=0.14$), NSAID use ($p=0.77$), disease severity (erosions [$p=0.9$], joint replacement [$p=0.6$]) or RA medications ($p=0.14$). Two multivariate analysis models were constructed: Model A, without the Framingham risk score which showed that age (OR: 1.05; 95%CI [1.03–1.09]) and hypertension (OR: 2.5, 95%CI [1.5–4.3]); were predictive of an eGFR <60 ml/ min/1,73m^2; Model B, which showed that the Framingham risk score was predictive of low eGFR (OR 1.06, 95%CI [1.03–1.09]).

Conclusion: Renal impairment is relatively common in RA and is associated with cardiovascular risk factors such as age, hypertension and the Framingham risk score but not with disease activity or severity.

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Investigation of the Association Between Gastroesophageal Reflux Disease and Clinical Factors in Patients with Rheumatoid Arthritis. Katsushi Ishii[1], Yuichi Mochida[1], Yuki Ozawa[1], Naoto Mitsugi[1] and Tomoyuki Saito[2]. [1]Yokohama City University Medical Center, Yokohama, Japan, [2]Yokohama City University School of Medicine, Yokohama, Japan.

Background/Purpose: Gastroesophageal reflux disease (GERD) is caused by the abnormal reflux of the gastric contents into the esophagus. Many risk factors are considered as a cause of GERD. Nonsteroidal anti-inflammatory drugs (NSAIDs) consumption is regard as one cause of the development of GERD; but, there are few reports regarding the relationship between NSAIDs consumption and the development of GERD. NSAIDs are commonly used to control pain, inflammation related to patients with rheumatoid arthritis (RA). Therefore, the prevalence of GERD in RA may be high because of high rate of NSAIDs consumption. However, there are few reports regarding as the development of GERD in RA. The purpose of this study was to examine the prevalence of GERD in RA. We also investigate the association between GERD and clinical factors in RA.

Methods: We investigated 378 outpatients with RA (70 males, 308 females). Three rheumatologist of orthopaedic surgery examined all patients. The presence or absence of GERD was evaluated by using GerdQ questionnaire. It is well known that GerdQ can be used to diagnose GERD with an accuracy similar to that of the gastroenterologist. When heartburn or acid regurgitation symptoms are observed more than once a week, the patients are diagnosed with GERD. The correlation between GERD and clinical factors such as age, sex, height, weight, BMI, disease duration, DAS28/DAS28-CRP/SDAI, Pt-VAS, and medication drugs (NSAIDs, steroid, bisphosphonate, and gatroprotective agents) were analyzed.

Results: The GERD symptoms were observed in 96 of these 378 patients (25.4%). SDAI and patient's VAS were significantly higher in the GERD positive group than in the GERD negative group ($p<0.05$). DAS28 and DAS28-CRP were higher in the GERD positive group than in the GERD negative group, but these differences did not reach statistical significances. There was no statistical correlation between the presence or absence of GERD symptoms and the presence or absence of taking NSAIDs, steroid, and bisphosphonate.

Conclusion: The prevalence of GERD in RA (25.4%) was higher than that in the Japanese healthy population (7.6–10.6%). The prevalence of GERD in RA was high and associated with Pt-VAS. Therefore, we should pay attention to the complication of GERD when the evaluation of disease activity of RA.

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Differential Gender Impact in the Quality of Life of Patients with Rheumatoid Arthritis. Comprehensive Study Including Clinical, Comorbidity and Psicho-Social Variables. Elena Aurrecoechea[1], Jaime Calvo-Alen[2], Graciela S. Alarcon[3], Gerald McGwin[4], Maria Luisa Diez Lizuain[5] and Javier Llorca[6]. [1]Hospital Sierrallana. Torrelavega, Torrelavega, Spain, [2]Hospital de Sierrallana. Torrelavega. Spain, Torrelavega, Spain, [3]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [4]Rheumatologist, Birmingham, AL, [5]MD, Torrelavega, Spain, [6]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain.

Background/Purpose: To evaluate whether gender portends a differential impact in the outcome of RA in terms of quality of life (QOL) and which type of variables may cause such effect.

Methods: Seventy female and 70 male RA unselected patients followed in our division were cross-sectionally evaluated according to a pre-established protocol. It includes: medical history review, standardized measurements of disease severity (biological parameters, DAS28 activity index, HAQ index, modified Sharp-van der Heidje scoring method) as well as specific tools to assess comprehensively different psychological and disease related behavior and coping aspects (The Beck Depression Scale, The ISEL questionnaire for social support, The illness behavior abnormalities using the Illness Behavior Questionnaire (IBQ),The Rheumatology Attitude Index, and the level of disease with the Self-efficacy Questionnaire). QOL was assessed by the SF-36 questionnaire. Univariate and multivariate analyses were performed to examine the different contribution of these variables in both genders in the final outcome of the disease assessed in terms of QOL.

Results: Both groups were homogeneous regarding to age at diagnosis (49.92+13.43 vs 52.94+13.63; $p=0.189$), disease duration (2472.48+2236.46 vs2441.62+2220.26 days; $p=0.93$), disease activity by DAS28 (3.81+1.49 vs 3.5+ 1.43, $p=0.21$), functional impairment by HAQ (0.89+ 2.61 vs 0.22+0.96, $p=0.04$) or radiologic damage by SVH score (24.6+48.4 vs men 22.1+ 27.7; $p= 0.71$). Regarding to comorbidity, men had a higher prevalence of ischemic heart disease (1.43% vs 11% $p=0.029$), chronic pulmonary obstructive disease, COPD (2.86% vs17.14% $p=0.005$), and conversely women had higher prevalence of osteoporosis (18.57% vs 5.71, $p=0.02$ and received more frequently anti-resortive therapy (15.71% vs 5.71%, $p=0.056$). Regarding to psychological variables, women presented significant higher scores in the Beck scale (10.78+7.52 vs 7.83+ 6.85, $p=0.016$) and numerically worse IBQ results (11.91+6.07 vs 10.55+ 5.88, $p=0.181$); not finding differences in the rest of studied physochological and behavioral variables. A greater impairment in the physical functioning (PF) subscale of SF36 was observed among female patients (57.78 + 22.11 vs 67.30 + 22.75; $p=0.01$). In the different models of multivariate analyses performed, Beck Scale ($p=0.000$), and the presence of osteoporosis ($p=0.000$) remained independently associated with the SF36 results.

Conclusion: Female RA patients have lower levels of quality of life than their male counterparts. Psychological variables as a higher level of depressive symptoms and, maybe, a worse disease related behavior as well as a higher incidence of osteoporosis plays a major role in this result, rather than pure biological disease related variables. This fact should be taken into account in the management of these patients.

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1416

Analysis of Cardiac Involvement in Patients with Amyloid a (AA) Amyloidosis Due to Rheumatoidarthritis. Daisuke Kobayashi[1], Satoshi Ito[1], Satoru Kodama[1], Akira Murasawa[1], Ichiei Narita[2] and Kiyoshi Nakazono[1]. [1]Niigata Rheumatic Center, Shibata, Japan, [2]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.

Background/Purpose: Rheumatoid arthritis (RA) is one of the major causes of amyloid A (AA) amyloidosis. The major organs affected are the kidneys and gastrointestinal (GI) tract. Although cardiac amyloidosis is the principal cause of death in patients with amyloid L amyloidosis, significant cardiac involvement in AA amyloidosis is thought to be rare. On the other hand, the survival rate of hemodialysis patients with AA amyloidosis associated with RA has been shown to be low, and our previous study revealed that cardiac failure accounted for more than half of the mortality in these patients. The purpose of this analysis was to clarify the cardiac involvement and its clinical significance in patients with RA-associated AA amyloidosis.

Methods: Twenty-seven RA patients (4 males, 23 females) with AA amyloidosis who were followed up at Niigata Rheumatic Center between April 2007 and March 2014 were enrolled. Each patient fulfilled the 1987 American College of Rheumatology criteria for RA. All patients had undergone GI tract biopsies, and had been confirmed to have reactive AA amyloidosis by pathological examination. The patients' background data and echocardiographic features were analyzed retrospectively. Differences were assessed by Mann-Whitney U test*, Fisher's exact test#, and log rank test**, and differences at $p < 0.05$ were considered statistically significant.

Results: The median age was 71 [range, 48–89] yr, the period between the onset of RA and echocardiographic examination was 20 [2–41] yr, and the period between the onset of AA amyloidosis and echocardiographic examination was 1007 [20–6458] day. Echocardiography showed that the left ventricular (LV) posterior wall thickness was 11.0 [7.4–17.0] mm, with an interventricular septal thickness of 10.5 [5.5–14.2] mm, and an ejection fraction (EF) of 72.1% [32.3–85.4%]. Thirteen patients with LV wall thickness exceeded 11.0 mm were assigned to a LV hypertrophy (LVH) group, and their clinical features were compared with a normal group (n=14). Fatalities in the LVH group vs normal group were 7 vs 0 at two year after echocardiography and 9 vs 2 at the last observation. Kaplan-Meier survival curves showed a significant association with reduced survival in the LVH group (p=0.039**). There were no significant differences between the LVH group and the normal group at the baseline in terms of patient age (p=0.512*), duration of RA (p=0.627*), serum albumin level (p=0.92*), estimated glomerular filtration rate (eGFR) (p=0.094*), disease activity score in 28 Joints based on erythrocyte sedimentation rate (p=0.19*), modified Health Assessment Questionnaire score (p=0.77*), and echocardiogram EF (p=0.21*). Patients in the LVH group had a higher systolic blood pressure (133 [116–160] vs 120.5 [110–142] mmHg, p=0.039*), in spite of higher usage of antihypertensive agents (12 vs 3, respectively, $p<0.001$#). Although the LVH group appeared to have a lower eGFR, there was no significant difference in survival rate between the patients whose eGFR was under 45 ml/min/1.73 m^2 (n=12) and the others (n=15) (p=0.52**).

Conclusion: Thickening of the LV wall is a notable cardiac feature of patients with AA amyloidosis and is strongly suspected to contribute to their poor prognosis.

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1417

Red Cell Distribution Width: A Measure for Cardiovascular Risk in Rheumatoid Arthritis Patients? Sobia Hassan[1], Maria Antonelli[2] and Stanley P Ballou[3]. [1]Case Western Reserve University, MetroHealth Medical Center, Cleveland, OH, [2]Case Western Reserve University School of Medicine at MetroHealth Medical Center, Cleveland, OH, [3]MetroHealth Medical Center / Case Western Reserve University, Cleveland, OH.

Background/Purpose: Red cell distribution width (RDW) is a measure of the variation in red blood cell size reported on the automated complete blood count. Although traditionally used to differentiate between causes of anemia, elevated RDW has recently been found to predict cardiovascular (CVS) risk and outcome in patients with and without heart disease. RDW may be a marker for the inflammation that drives CVS risk.

Supporting an inflammatory link, RDW has been shown to correlate with disease activity and inflammatory markers in conditions such as Bechet's, inflammatory bowel disease, rheumatoid arthritis (RA) and systemic lupus erythematosus.

RA is a chronic inflammatory condition with an increased risk of CVS disease. We hypothesized that RA patients with elevated RDW levels would experience greater burden of myocardial infarction (MI).

Methods: Utilizing a secure cloud based platform, Explorys, we searched de-identified patient data from multiple US healthcare systems between the years 1999 to 2014. Patients with a diagnosis of RA were identified by CCP and/or RF positivity. To exclude the influence of anemia only patients with Hb>12 mg/dl were included. Patients were stratified into a high (≥15.6 %) RDW group if they ever had an RDW > 15.6% and a low RDW group (<13.5% and excluding any patient with prior episode of RDW 15.6%). The proportion of patients with a diagnosis of MI in each RDW group was collected.

For comparison, patients were divided into a high and low CRP group (≥ 2.5 and ≤ 0.8 mg/dl) and a high and low ESR group (≥50 and ≤30 mm/hr) and MI data was collected.

Statistical comparison between high and low laboratory test groups was performed with chi square and odds ratios were calculated.

Results:

Table 1: Proportion of patients with RA who have had MI

	N with MI/Total N (%)	N with MI/Total N (%)	*p*-value
RDW	High RDW (>15.6%) 1410/11250 (11)	Low RDW (<13.5%) 1320/21990 (6)	<.0001
ESR	High ESR (>50mm/hr) 710/5480 (13)	Low ESR (<30mm/hr) 1120/22490 (5)	<.0001
CRP	High CRP (>2.5 mg/dL) 630/5380 (10)	Low CRP (<0.8mg/dL) 580/11700 (5)	<.0001

The total cohort of patients with RA from the database was 35 890; of which 2 810 had an MI.

The proportion of RA patients with MI was significantly increased in the high compared to low RDW, ESR and CRP groups (results depicted in Table 1).

The odds of MI was more likely in the high verses low RDW (OR 2.1, 95% CI 1.9 to 2.3), ESR (OR 2.6, 95 % CI 2.4–2.9) and CRP (OR 2.4, 95% CI 2.1 to 2.7) groups.

Conclusion: In keeping with previous findings in RA patients, elevated levels of ESR and CRP were associated with increased risk of MI. Elevated levels of RDW in RA patients also appear to indicate an increased risk of MI. RDW is a widely available laboratory parameter that may be useful as a measure for CVS risk in RA.

We propose that in addition to elevated ESR and CRP, elevated RDW levels in RA patients should prompt physicians to aggressively screen and treat their patients for modifiable CVS risk factors, in addition to treating RA inflammation.

Disclosure: S. Hassan, None; **M. Antonelli**, None; **S. P. Ballou**, None.

1418

Prevalence of Vitamin D Deficiency in Rheumatoid Arthritis (RA). Stella Cecchetti[1], Martin Soubrier[2], Pilar Galan[3], Bruno Pereira[4], Gael Mouterde[5] and Maxime Dougados[6]. [1]CHU Gabriel Montpied, 63000, France, [2]CHU G.-Montpied, Clermont-Ferrand, France, [3]Université Paris 13, Sorbonne Paris Cité, Paris Cité, France, [4]Clinical research department, Clermont-Ferrand, France, [5]Hopital Lapeyronie, Montpellier, France, [6]RAID working group for EULAR, Zurich, Switzerland.

Background/Purpose: Serum levels of vitamin D (VitD) are usually inversely correlated with RA activity. However, the prevalence of VitD deficiency does not appear to differ from that of the general population. Hypertension (HT) and low levels of HDL-cholesterol (HDL-c) –two cardio-

vascular (CV) risk factors with an increased prevalence in RA – are inversely correlated with VitD levels. The objectives were to determine the prevalence of VitD deficiency in RA patients versus a control population, and detect correlations between VitD levels and RA disease activity and/or characteristics, and between VitD levels and CV risk factors.

Methods: The COMEDRA study evaluated the impact of a visit with a nurse on the management of comorbidities in RA patients. VitD and lipids assays were performed in all patients. Controls were from the SU.VI.MAX cohort and were matched for gender, age, latitude and season during which samples were taken for assay. VitD deficiency was defined as VitD<10 ng/ml and VitD insufficiency as VitD between 10 and 29.9 ng/ml (VDI).

Results: 894 patients (79.3% women) with an average disease duration of 11.2 years [6.3 – 19.1] were analyzed. RA was erosive in 73.3% of patients and 83.9% had positive RF or anti-CCP antibodies. The DAS28-ESR was 3.0 ± 1.3. 630 patients (70.4%) were treated with biologic therapy and 341 (38.1%) received glucocorticoids (5.5 ± 5.7 mg/day). BMI was 25.1 ± 4.8. SBP was 124.9 ± 16.5 mmHg, and DBP 75.6 ± 11.4 mmHg. Total cholesterol was 2.2 ± 0.5 g/l, LDL-c was 1.3 ± 0.4 g/l, HDL-c was 0.7 ± 0.2 g/l. 147 patients (16.4%) were smokers and 52 (5.8%) were diabetic. VitD levels were in the normal range in 362 patients (40.5%), whereas 501 patients (56.0%) had VitD insufficiency and 31 (3.5%) had VitD deficiency. Comparison of 861 RA patients with 861 matched controls revealed that the RA patients had a lower prevalence of VitD insufficiency (RA: 480 (55.8%) vs. controls: 508 (59%); p=0.04) and of VitD deficiency (RA: 31 (3.6%) vs. controls: 45 (5.23%); p=0.04).

Among RA patients, males had a higher frequency of VitD insufficiency (117 (63.3%) vs.: 384 (54.2%); p=0.04) and VitD deficiency (8 (4.3%) vs.23 (3.2%); p=0.04 in males vs females respectively). There was no difference according to latitude, but the prevalence of VitD insufficiency and VitD deficiency were higher in springtime. Univariate analysis found an inverse correlation between VitD levels and RA activity defined by DAS28-CRP (p=0.02), SDAI (p=0.05) and CDAI (p=0.05), but only a trend for DAS28-ESR (p=0.08). No correlation was found with antibody status or with treatments. VitD levels were inversely correlated with BMI (p<0.001) but not with blood pressure, total-c, LDL-c, HDL-c or diabetes.

Conclusion: This study confirms that VitD is inversely correlated with RA activity and BMI but not with other CV risk factors. The prevalence of VitD deficiency was lower than in the control population, which could be explained by the fact that RA patients more frequently received VitD supplementation.

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1419

Rituximab Use in Patients with Rheumatoid Arthritis-Associated Interstitial Lung Disease and Other Connective Tissue Disease-Associated Interstitial Lung Disease: A Single Center Experience.

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Background/Purpose: Small series have suggested that rituximab (RTX) may be effective as rescue-therapy for connective tissue disease-associated interstitial lung disease (CTD-ILD). We sought to describe our center's experience of the outpatient use of RTX in patients with a diverse spectrum of CTD-ILD.

Methods: We identified all patients with CTD-ILD who (1) received at least one cycle of RTX as an outpatient between January 2008 and May 2014, (2) had at least one thoracic HRCT scan, and (3) pulmonary function testing pre- and post-initial RTX treatment. We extracted data from the medical record for the following: demographics, concurrent immunosuppressive medications, pulmonary function and thoracic imaging, RTX-associated side effects, infection history, and discontinuation rate. We analyzed the % predicted forced vital capacity (FVC%) closest to pre- (mean 131.8±204.6 days) and post-initial RTX administration (mean 121.7±97.2 days). T-tests were used for continuous variables analysis and Fisher's exact test was used for contingency table analysis.

Results: The cohort comprised 24 subjects with a diverse spectrum of CTD-ILD.

Table 1: Clinical characteristics

	All patients (n=24)	RA patients (n=15)
Age, years (mean±SD)	61.3±10.4	62.9±10.3
Female, n (%)	15 (62.5)	10 (66.7)
Race, n (%)		
White	21 (87.5)	14 (93.3)
Afro-American	2 (8.3)	1 (6.7)
Asian	1 (4.2)	0 (0.0)
Past smokers, n (%)	8 (33.3)	5 (33.3)
Current smokers, n (%)	1 (4.2)	1 (4.2)
Pack-year (mean±SD)	27.1±9.5	29.7±6.8
Expired, n (%)	1 (4.2)	0 (0.0)
Diagnosis, n (%)		
RA	15 (62.5)	15 (100.0)
Idiopathic inflammatory myositis (IIM)	3 (12.5)	
IIM+RA	2 (8.3)	
Systemic sclerosis	3 (12.5)	
Suggestive CTD-ILD	1 (4.2)	
Rheumatic disease duration, years (mean±SD)	9.5±9.1	11.6±10.0
ILD duration, years (mean±SD)	3.0±2.8	2.5±2.1
RTX regimen		
RA protocol	22	14
Vasculitis protocol	2	1
Concurrent corticosteroid-sparing agent, n (%)		
Mycophenolate mofetil	8 (33.3)	3 (20.0)
Methotrexate	4 (16.7)	4 (26.7)
Leflunomide	1 (4.2)	1 (6.7)
Azathioprine	1 (4.2)	1 (6.7)
Intravenous immunoglobulin	1 (4.2)	0 (0.0)
Cyclophosphamide	1 (4.2)	0 (0.0)
Thoracic HRCT patterns, n (%)		
NSIP	11 (45.8)	7 (46.7)
NSIP+OP	5 (20.8)	1 (6.7)
NSIP+UIP	1 (4.1)	1 (6.7)
UIP	4 (16.7)	4 (26.7)
LIP	1 (4.1)	1 (6.7)
Unclassifiable diffuse lung disease	2 (8.3)	1 (6.7)

There was no change in mean FVC% pre- and post-initial RTX cycle (71.3±18.6 vs. 71.6±17.9, p=0.87). Post-RTX, in 9 subjects (38%) FVC% improved (4 by >10%), and in 15 subjects (63%) FVC% declined (3 by >10%). In the 15 subjects with RA, FVC% was unchanged (70.4±20.2 vs. 74.5±19.7, p=0.18). Post-RTX, in 9 RA subjects (60%) FVC% improved (4 by >10%), and in 6 subjects (40%) FVC% declined (1 by >10%). In those without RA (n=9), FVC% declined significantly (72.7±15.4 vs. 66.8±12.8, p=0.015; 3 by >10%).

Pre- and post-RTX change in FVC% were 4.2±17.4 in RA vs. −8.6±7.2 in non-RA (p=0.025). RA subjects were also more likely to have improved FVC% (p=0.0068).

Sixteen (67%) subjects were on a concomitant corticosteroid-sparing medication. Thirteen (54%) were on prednisone at RTX initiation (mean dosage 10.2±16.2 mg) and 9 (38%) remained on prednisone at 6 months post-RTX (mean dosage 5.6±11.0 mg) (p=0.27).

Five infectious episodes (2 upper respiratory tract infections, 2 lower respiratory tract infections and 1 disseminated Herpes Zoster infection) occurred in 5 different subjects within 6 months post-initial RTX cycle. An additional 11 infectious episodes (mostly upper or lower respiratory tract infections) occurred in 5 of 12 subjects that received more than 1 RTX cycle (mean observation period of 35.6±19.3 months and 66 RTX cycles).

Conclusion: Treatment of RA-ILD and other forms of CTD-ILD with RTX was associated with variable effects on pulmonary physiology and our series suggests a possible beneficial role for RTX in RA-ILD. RTX treatment was associated with modest corticosteroid sparing effects and a sizeable number of post-infusion infections. RTX warrants prospective study to better assess its role in managing RA-ILD and other CTD-ILD.

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1420

Non-Use of Glucocorticoid and Osteoarthritis Absence As Predictors of Clinical Remission in AR. Salvador Loredo-Alanís[1], David Vega-Morales[2], Mario Garza-Elizondo[1], Mario Garcia-Pompermayer[3], Roberto Negrete-López[1], Daniel Treviño-Montes[1] and Diana Flores-Alvarado[2]. [1]Servicio de Reumatología, Departamento de Medicina Interna del Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Monterrey, Mexico, [2]Hospital Universitario UANL, Monterrey, Mexico, [3]Servicio de Reumatología, Departamento de Medicina Interna del Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Monterey, Mexico.

Background/Purpose: The clinical evaluation of Rheumatoid arthritis (RA) is accomplished with compound indexes allowing better clinical decision. Clinical remission nowadays is an attainable target in the management of RA patients. Clinical remission associated factors are under investigation.

Objetive: Determine which factors are associated with clinical remission by CDAI in a RA population (ACR/EULAR 2010).

Methods: From a rheumatologic diseases cohort in a University Hospital we made an observational, descriptive, retrospective and cross-sectional study of 361 patientes with RA. We analized variables such as demographics, rheumatoid factor, Anti-Cyclic Citrullinated Peptide antibodies, erythrocyte sedimentation rate, C-reactive protein, treatment, clinical activity, visual analog scale, comorbidities, extra-articular manifestations and temporality of RA. CDAI was calculated. Remission was defined with a CDAI score of 2.8.

Results: 361 patients were evaluated. Female sex was predominant (97.7%). Mean age was 51.4. Clinical remission was found in 40.2%. When patients with and without clinical remission were compared, we found significant differences in: non use of prednisone (p 0.0001), use of Non-steroidal anti-inflammatory drugs (NSAIDs) (p 0.012), use of tramadol (p 0.0001), absence of osteoarthritis (p 0.33) and BMI <25Kg/m2 (p 0.017). In multivariate analysis factors associated with reach clinical remission were: Non use of oral steroids (p 0.0001, OR 3.39 IC 2.05–5.63) and absence of osteoarthritis (p 0.025, OR 1.8, IC 1.007–3.048). It was found a negative association to reach clinical remission with use of NSAIDs (p 0.008, OR 0.292, IC 0.117–0.73) and use of tramadol (p 0.003, OR 0.107, IC 0.024–0.47).

Conclusion: According to our study the presence of OA in patients with RA is a factor that decreases the CDAI specificity for detecting clinical remission. This possibly related to the score given by the patient to the visual analog scale and the presence of painful joints secondary to OA, but not inflamed by RA activity. It is therefore important that clinicians consider these factors when evaluating clinical remission in RA.

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Preclinical Interstitial Lung Disease in Early Rheumatoid Arthritis. Javier Narváez[1], Alejandro Robles Perez[2], Maria Molina Molina[2] and Joan Miquel Nolla[2]. [1]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, [2]Hospital Universitario de Bellvitge, Barcelona, Spain.

Background/Purpose: Early detection and treatment of interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA) may ameliorate disease progression. The objective of the present study was to: *1)* study the frequency of asymptomatic preclinical ILD in early RA patients, in order to determine how early the lungs are affected in the disease and establish whether it is clinically advantageous to systematically screen asymptomatic patients for this complication; and *2)* study the potential association of anti-citrullinated peptide antibody (ACPA) positivity with RA-ILD.

Methods: Observational prospective study of a cohort of early RA patients (joint symptoms < 2 years) who did not present respiratory symptoms and were included in an ILD screening program via baseline chest radiograph and complete pulmonary function tests (PFT). In patients with lung abnormalities in the chest radiograph or any restriction or impaired diffusion, defined as < 80% of predicted forced vital capacity (FVC) and diffusing lung capacity for carbon monoxide (DLCO) respectively, the study was completed with a high-resolution computerized tomography scan (HRCT) of the chest.

Results: Forty patients (30 women) were included in the study, with PFR alterations detected in 18 (45%). All cases had a DLCO < 80% of predicted (mean 68%; range 43% to 78%), without significant reduction in the FVC values. The HRCT detected abnormalities in only 7 of these 18 patients: 1 radiographic pattern suggestive of non-specific interstitial pneumonia (NSIP); 1 radiographic pattern of respiratory bronchiolitis-associated interstitial lung disease (RB-ILD); the other 5 had bronchiectasis in the absence of fibrosis, emphysema or pulmonary nodules**.** In 11 patients with DLCO alterations, the HRCT was normal, and in none of these cases could the alteration be attributed to the presence of anemia.

A significant inverse correlation between ACPA levels and baseline DLCO was found. We also observed, a significant association between the severity of disease activity as measured by DAS28-CRP and baseline DLCO values.

Conclusion: Asymptomatic preclinical ILD, which is detectable by restrictive abnormalities in PFT (mainly, DLCO < 80% of predicted), is common (45%) among patients with early RA. PFT screening may be indicated for such patients since early detection of these alterations could change the course of the lung disease if risk factors (such as smoking or environmental exposures) are avoided, infections are prevented and drugs for RA treatment are selected that are less harmful to the lung. Our data also support a relationship between high ACPA levels and the occurrence of RA-ILD.

Disclosure: J. Narváez, None; **A. Robles Perez**, None; **M. Molina Molina**, None; **J. M. Nolla**, None.

1422

Demographic Differences in Health Related Information Technology Use Among Patients with Rheumatic Diseases. David Mackey[1], Aseem Bharat[1], Lang Chen[1], Ben Nowell[2], Liana Fraenkel[3], Peter J. Embi[4], Kenneth G. Saag[5], James Willig[1], Seth Ginsberg[2], Ruth McConnell[1] and Jeffrey R. Curtis[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Creaky Joints/Global Healthy Living Foundation, Upper Nyack, NY, [3]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT, [4]The Ohio State University, Columbus, OH, [5]The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Use of the Internet and mobile technologies can be a valuable resource for patients with rheumatic diseases who are seeking health-related information, allowing patients to track health longitudinally, and/or engage with similar patients or their clinicians. However, such technologies may have a limited penetrance among certain demographic groups defined by older age, non-Caucasian race, and lower education and income. We evaluated use and ownership of information technologies among patients in a rheumatology clinic to assess their use of these technologies, and assess any differences based on patients' characteristics.

Methods: Starting in 2014 (with ongoing recruitment), we approached adult patients from two rheumatology outpatient clinics at a large academic medical center to participate in a descriptive survey, administered either on paper or electronically (iPad tablet) according to patient preference. The survey included questions derived from the Pew Internet Survey regarding 1) ownership of a smartphone; 2) use of the Internet for health-related information in the last 12 months; and 3) willingness to electronically exchange medical information with their healthcare provider. Additional data included information about demographics and socioeconomic status. These three outcomes were examined according to various demographic and socioeconomic status (SES) categories.

Results: Among 195 patients approached to take the survey, 171 (87%) completed the survey, 24 (12%) refused, and 2 (1%) failed to complete it. Among complete responders, 82% were women, 75% were white, with median age 56 years, and 77% had at least some college education. The gender and race distribution was similar between respondents and those who refused.

Age older than 65, lower education, and lower income were associated with less smartphone ownership, less use of the Internet for health-related reasons, and a lower willingness to share electronic health information with their healthcare provider (Table). In contrast, sex and race were not strongly associated with these outcomes. However, even for patient groups with less access to or use of technologies for health reasons, more than 50% of patients reported ownership or willingness to use IT.

Conclusion: Based upon this sample of rheumatology patients, older age, lower education and lower household income were associated with less use of the Internet and information technology for health reasons. However, at least half of patients in these demographic and SES categories had access to these technologies. Given these results, it is reasonable to expect that technolgical solutions that address the health information needs of patients with rheumatic diseases can reach a broad patient population.

Table: Factors associated with Healthcare-related Internet use and Technology

	Total responders N=171	Owns a Smartphone	Accessed the Internet for a health-related search	Willing to exchange medical information electronically
Age				
< 40	33	91%~	79%*	79%*
40–55	49	92%~	82%*	82%*
55–65	43	71%~	86%*	57%*
>65	36	53%~	72%*	53%*
Gender				
F	140	79%	85%	70%
M	31	71%	84%	58%
Race				
Caucasian	129	78%	88%	69%
Non caucasian	42	76%	74%	64%
Education Level				
High School or less	39	59%*	72%*	49%*
Some college or higher	130	82%*	88%*	75%*
Annual household income:				
<$40,000	51	63%~	69%~	65%
>$40,000	101	88%~	94%~	75%

*= p-value =<0.05
~= p-value <0.0001

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Cardiovascular Risk Estimation in Rheumatoid Arthritis: What Is Missing in Traditional Risk Estimators? Gulsen Ozen, Murat Sunbul, Pamir Atagunduz, Haner Direskeneli, Kursat Tigen and Nevsun Inranc. Marmara University School of Medicine, Istanbul, Turkey.

Background/Purpose: Cardiovascular (CV) disease is one of the major causes of mortality in rheumatoid arthritis (RA). Although the CV risk in RA is well-recognized, detection of high risk patients and prevention of CV disease are still major challenges. We aimed to determine which CV risk estimation index is better in RA patients and to determine the factors that may improve CV risk estimation in RA.

Methods: Two-hundred and ten consecutive RA patients without history of CV disease or diabetes mellitus were assessed. Systematic Coronary Risk Evaluation (SCORE), 2013 American College of Cardiology/American Heart Association (ACC/AHA) 10-year atherosclerotic CV disease risk (ASCVD), QRisk II indices and their modified versions (mSCORE, mASCVD, mQRisk II) according to EULAR recommendations were calculated. All patients were evaluated with carotid ultrasonography (US). Carotid intima-media thickness (cIMT) > 0.90 mm and/or carotid plaques were used as the gold standard test for subclinical atherosclerosis and high CV risk (US+). Retrospectively, along with disease characteristics, DAS28 scores, ESR and CRP values of each visit during the entire follow-up of RA patients were recorded and average DAS28, ESR and CRP were calculated.

Results: The study cohort consisted of 210 RA patients (F/M= 169/41, mean age 52.5±11.4) with a mean disease duration of 11.1±7.0 years. The EULAR multiplier factor was used in 95 (45.2%) patients. The mean mSCORE was 1.6±2.5%, mASCVD risk was 5.8±7.1%.and mQRisk II was 9.8±9.6%. Eleven (5.2%), 61 (29%) and 80 (38.1%) patients were defined as having high CV risk (mSCORE≥5%, mASCVD≥7.5%, mQRiskII≥10%) according to mSCORE, mASCVD and mQRisk II, respectively. Concerning US results, 50 (23.8%) patients had either cIMT> 0.90 mm or carotid plaques. The mASCVD and mQRisk II indices better identified US+ patients, that 29 (58%) and 30 (60%) of the US+ patients were in high risk group according to mASCVD and mQRisk II, respectively. Whereas only 8 (16%) of the US+ patients were in high risk group according to mSCORE ($P<0.0001$). However mASCVD and mQRisk II still failed to identify 42% and 40% of US+ patients. When traditional risk factors and disease characteristics of US+ and US- patients were compared, it was found that US+ patients were older at diagnosis, had higher average DAS28 scores, average ESR and CRP levels. Impaired fasting glucose was also higher in US+ patients along with similar rates of biologic treatment, steroids and NSAIDs (Table 1).

Conclusion: EULAR recommendation for CV risk assessment, SCORE, seems inadequate even after modification according to RA characteristics. On the other hand QRisk II and ACC/AHA 10-year ASCVD risk indices are better in estimating CV risk in RA patients. However, still additional modifications, like age at disease onset, cumulative disease activity and inflammatory biomarkers are required to fully identify high-risk RA patients.

Table 1. Characteristics of US(+) and US(–) RA patients

	US(+) (n=50)	US(–) (n=160)	*P* Value
Female, n (%)	35 (70)	134 (83.8)	**0.032**
Age (years)	58.8 ± 8.3	50.5 ± 11.5	**<0.0001**
Age at diagnosis (years)	48.3 ± 8.8	39.3 ± 11.1	**<0.0001**
Disease duration (years)	10.5 ± 7.6	11.3 ± 6.9	**0.49**
RF and/or Anti-CCP positivity, n(%)	40 (80)	124 (77.5)	**0.70**
Extra-articular involvement, n (%)	10 (20)	45 (28.1)	**0.25**
Average DAS28 score¶	4.04 ± 1.1	3.59 ± 0.97	**0.007**
HDA visits/Total visits†	24.4 ± 26.9	15.6 ± 21.3	**0.018**
Average ESR (mm/h) ¶	32.5 ± 14.2	24.4 ± 12.0	**<0.0001**
Average CRP (mg/L) ¶	14.1 ± 12.2	8.9 ± 8.1	**0.001**
HAQ score	0.48 ± 0.49	0.58 ± 0.63	**0.31**
Hypertension, n (%)	19 (38)	53 (33.1)	**0.52**
Hyperlipidemia, n (%)ٱ	38 (76)	90 (56.2)	**0.012**
Impaired fasting glucose, n (%)‡	12 (24)	19 (11.9)	**0.035**
Ever-smoked, n (%)	22 (44)	42 (26.2)	**0.017**
Total cholesterol/HDL-cholesterol	4.0 ± 1.64	3.5 ± 1.09	**0.015**
mSCORE	2.8 ± 2.5	1.2 ± 2.4	**<0.0001**
mASCVD	8.9 ± 7.7	4.8 ± 6.6	**<0.0001**
mQRisk II	14.5 ± 10.8	8.3 ± 8.7	**<0.0001**
Current corticosteroid, n (%)	29 (58)	83 (51.9)	**0.44**
Biologic treatment (ever), n (%)	23 (46)	92 (57.5%)	**0.15**

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Bone Erosions in Patients with RA: Exploring the Impact of the Anatomy of Interest on the Relationship Between MRI and X-Ray Erosion Detection. Michael Tomizza[1], Isabel Rodrigues[1], Matthew Jessome[1], Joshua Barbosa[1], Karen Beattie[2], William G. Bensen[2], Raja Bobba[2], Alfred Cividino[2], Patrick D. Emond[2], Karen Finlay[3], Chris Gordon[2], Lawrence Hart[2], George Ioannidis[2], Erik Jurriaans[3], Melissa Koh[1], Maggie Larche[2], Arthur Lau[2], Naveen Parasu[3], Ruben Tavares[2], Stephen Tytus[2], Hao Wu[1] and Jonathan D. Adachi[1]. [1]McMaster University, Hamilton, ON, [2]St Joseph's Healthcare Hamilton, Hamilton, ON, [3]Hamilton Health Sciences, Hamilton, ON.

Background/Purpose: Detection of bone erosions in patients with RA is critical in clinical practice, with treatment initiation and effectiveness largely based on limiting erosive progression. While studies have compared the use of MRI and x-ray for the assessment of erosive damage, the potential influence of the anatomy of interest is not always considered. Given that the joints assessed by researchers and clinicians vary and may contribute to differences in the ability of MRI and x-ray to identify erosions, this study focused on describing the relationship between these two modalities while taking into account the anatomy of interest.

Methods: This was a cross-sectional study. For each participant, MRI scans of both hands (bilateral MCP 2–5 joints) and x-ray scans of the hands, wrists, and feet were acquired. A 1.0T MRI scanner with a 100-mm cylindrical coil was used and multiple sequences were obtained, including T1-weighted images for erosion detection. On x-ray, the conventional erosion definition was applied and three imaging projections were used: posteroanterior, oblique, and lateral. Four radiologists used the RA-MRI scoring system (RAMRIS) and the van der Heijde-modified Sharp scoring system (vdHSS) to semi-quantitatively evaluate the MRI and x-ray images, respectively. For statistical analysis, interval data (RAMRIS) and ordinal data (vdHSS) were classified by erosion presence (yes/no).

Results: A total of 488 joints from 122 hands of 65 RA patients were included in this analysis [median (interquartile range) age: 59.0 (49.0–66.0) years, sex: 83.1% female, ethnicity: 61% Caucasian, symptom duration: 4.3 (2.6–7.0) years, Rheumatoid Factor positivity: 70.8%, Disease Activity Score (DAS28): 4.5 (3.3–5.7), Clinical Disease Activity Index (CDAI): 62.3 (32.7–91.6)]. 331 individual MCP 2–5 joints were assessed as having erosions on MRI (67.8%), while 134 erosions were detected in the same joints on x-ray (27.5%). MCP 2–5 joints of the hand were also grouped together for analysis. Overall, 2.1-fold the MCP 2–5 joint sets with erosions on x-ray had erosions on MRI.

Per common joint imaged, 2.6- to 8.0-fold the erosions detected on x-ray were detected on MRI. At the patient level of analysis, bilateral MRI of the MCP 2–5 joints resulted in the detection of erosive disease in 1.1-fold the number detected on x-rays of the hands, wrists, and feet. Limiting MRI to the dominant MCP 2–5 joints, the proportion of patients with erosive disease was 66% of the frequency detected on x-rays of the hands, wrists, and feet; the same frequency detected on x-rays of the feet alone; and 1.3-fold the frequency detected on x-rays of the hands and wrists.

Conclusion: Practically, the results suggest that the relative performance of the two imaging modalities is highly dependent on the anatomy imaged. Technologically, the findings demonstrate the enhanced capacity of MRI to detect erosions per joint imaged. The ability of a single MRI scan of the dominant hand to identify more patients with erosive disease than x-rays of both hands and wrists emphasizes the clinical value of MRI as a tool for detecting and monitoring erosive damage in patients with RA.

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Screening Behavior and Prevalence of Hepatitis C Virus in Mexico. Cassandra Skinner-Taylor[1], Alejandro Erhard-Ramírez[1], David Vega-Morales[2], Jorge Esquivel-Valerio[1], Diana Flores-Alvarado[2], Daniel Treviño-Montes[1] and Ernesto Torres-López[3]. [1]Servicio de Reumatología, Departamento de Medicina Interna del Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Monterrey, Mexico, [2]Hospital Universitario UANL, Monterrey, Mexico, [3]Servicio de Inmunología del Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Monterrey, Mexico.

Background/Purpose: In some countries, the prevalence of Hepatitis C virus infection is high and sometimes the appropriate tests to detect it are not performed in a routine evaluation in patients with Rheumatoid arthritis (RA). Our aim was to study the hepatitis C virus infection prevalence in RA patients and to determine the clinical characteristics of the patients who were screened and to evaluate the behavior of the current screening.

Methods: Retrospective, Observational, non-comparative study. We reviewed all charts of RA patients seen between 2013 and 2014 in three settings. University Hospital (HU), Private Practice (PP), and Instituto Mexicano del Seguro Social (IMSS), all from Monterrey, Nuevo León, Mexico. We select cases that met the ACR 1987 and EULAR/ ACR 2010 criteria for RA. We look for laboratory tests including rheumatoid factor, anti CCP, the screening test for hepatitis C virus and liver function tests.

Results: Eight hundred and sixty-four patients were analyzed, 312 (36.1%) of HU, 380 (44%) of IMSS and 172 (19.9%) of PP. Females 92% (n = 792). Mean age 51.6 years (age range 17–89). Anti-TNF therapy were used in 172 patients (19.9%), and the rest used DMARDs (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide and chloroquine). Rheumatoid factor was positive in 63.7%. Anti CCP was positive in 69.8%. Only 197 patients(22.8%) were screened for hepatitis C. One hundred eighty-eight (95%) from PP. The main reason because they were being treated with anti-TNF agents (golimumab, adalimumab, certolizumab pegol and infliximab). In public practice, corresponding to HU, five patients were screened and at IMSS only four. There was only one positive patient (1/197) corresponding to 0.5% for the screened patients.

Conclusion: In countries where hepatitis C virus is not endemic, as in Mexico, routine screening for HCV does not seem a regular practice for the rheumatologists, the main reason for screening in private practice was that the population was mostly being treated with anti-TNF agents, in contrast to public practice where the mainstay of treatment were DMARDs.

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Periodontal disease and Clinical Activity of Rheumatoid Arthritis Patients. Daniel Xibille-Friedmann[1], Jose Ivan Martinez Rivera[2], Jaqueline Rodriguez Amado[3], Carolina Bustos Rivera Bahena[4], Marisol Sandoval Rios[5] and Jose Luis Montiel Hernandez[6]. [1]Hospital General de Cuernavaca, Cuernavaca, Mexico, [2]Instituto Nacional de Salud Publica, Cuernavaca, Mexico, [3]Centro de Investigación y Desarrollo en Ciencias de la Salud, Monterrey, Mexico, [4]Science Faculty, Cuernavaca, Mexico, [5]Faculty of Pharmacy, Cuernavaca, Mexico, [6]Cytokines and Autoimmunity Laboratory, Faculty of Pharmacy, Universidad Autónoma del Estado de Morelos, Cuernavaca, México, Cuernavaca, Mexico.

Background/Purpose: Although several studies have suggested the association between periodontitis, infection by *Porphyromona gingivalis*and Rheumatoid Arthritis disease activity, its relationship with periodontal disease, oral and plasma peptidyl-arginine deiminase (PAD) activity and citrullination of soluble blood proteins still remains poorly known.

Objective: To evaluate the relationship between periodontal disease, and clinical disease activity of Rheumatoid Arthritis (RA) patients.

Methods: RA patients included fulfilled the ACR/EULAR 2010 criteria, signed an informed consent form and were followed at the rheumatology clinic for one year. Patients were divided into 2 groups according to clinical activity. Patients with secondary Sjögrens disease were excluded. Patients having a DAS28 of less than 3.4 were considered as having low activity and above that number they were grouped as having high activity. Periodontal evaluation and oral and peripheral blood samples were obtained the same day as the clinical evaluation. PAD-activity was performed using a colorimetric assay employing BAEE (Sigma) as substrate and recombinant human PAD4 (Cayman Chem) as positive control. Citrullination was evaluated by Western Blot of immunoprecipitated saliva and blood fibrinogen, employing a polyclonal anti-citrulline antibody (Millipore). Plasma pro-inflammatory cytokines and aCCP levels were evaluated by ELISA. Descriptive statistics were employed to evaluate differences between groups and the Spearman correlation test was used to associate them with clinical parameters.

Results: 48 RA patients were divided into 2 groups: 33 presented high activity and 15 low activity; their mean age was 41.2 vs. 43 years of age, respectively, BMI was 26.8 vs. 27.2, and time since onset of disease 8.5 ± 10.9 vs. 5.44 ± 3.8 years, respectively; both groups' demographic characteristics showed no statistically significant differences. High disease activity patients had a significantly lower index of periodontitis (1.57 ± 1.06; $p < 0.02$), while low disease activity patients were associated with severe periodontitis (3.0 ± 1.23). Otherwise, high disease activity patients showed a mean decrease of 1.5 DAS28 units after one year of follow-up and treatment, while low disease activity RA patients showed a lower therapeutic response (a change of <0.5 DAS28 units). No relationship was seen with PAD activity.

Conclusion: High RA disease activity is negatively associated with severe periodontitis, although the same patients showed a higher therapeutic response after one year of follow up, in comparison to low disease activity RA patients.

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Low Prevalence of Sarcopenic Obesity in Rheumatoid Arthritis Patients with Moderate Clinical Activity. Nina Tello-Winniczuk[1], David Vega-Morales[2], Mario Garza-Elizondo[1], Dionicio Galarza-Delgado[1], Jorge Esquivel-Valerio[1], Octavio Ilizaliturri-Guerra[3] and Jorge Rodriguez-Olivo[1]. [1]Servicio de Reumatología, Departamento de Medicina Interna del Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Monterrey, Mexico, [2]Hospital Universitario UANL, Monterrey, Mexico, [3]Departamento de Medicina Interna del Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Monterrey, Mexico.

Background/Purpose: Rheumatoid arthritis is an inflammatory systemic disease that leads to body composition alterations. Objective: The aim of our study was to identify the prevalence of sarcopenia, obesity and sarcopenic obesity in our population.

Methods: We performed an observational, analytical study with 101 rheumatoid arthritis patients. Demographic, clinical and biochemical variables were recorded. Studies of body composition by dual X-ray absorciometry were performed. We took into account different definitions to determine body composition alterations (Table 1).

Results: Ninety-seven (96%) patients were female, the rest of baseline characteristics are shown in Table 2. The mean age of our patients was 50.5 years (SD 12.3). The mean body mass index was 29.29 kg/m^2 (5.4 SD). According to the World Health Organization classification of body mass index (BMI), 24 (23.8 %) patients had normal weight, 38 (37.6%) were overweight and 39 (38.6 %) some degree of obesity. According to the BMI adjusted for rheumatoid arthritis, 13 patients (12.9 %) were normal, 34 (33.7 %) overweight and 54 (53.5 %) obese. Ten patients had sarcopenia (9.9 %). Six patients (5.9 %) had sarcopenic obesity. Patients with obesity by dual X-ray absorciometry were 83 (82.2 %). Among clinical and paraclinical variables, the only significant association with sarcopenia was a higher score in the Health Assessment Questionnaire.

Conclusion: The most prevalent body composition alteration in RA patients, were obesity. Sarcopenic obesity had a low prevalence, contrary to previous reports.

TABLE 1. Patient Baseline Characteristics

Variable	
Age, mean, SD	50.4 ± 12.3
Gender Female/Male n, (%)	97 (96)/ 4 (4)
Time elapsed since diagnosis Mean, SD	9.8 ± 8.6
Rheumatoid factor +, n, (%)	61 (71.8)
Anti-CCP+, n (%)	31 (57.4)
DAS28, mean, SD	3.26 ± 1.29
HAQ, mean, SD	0.62 ± 0.68
DMARD, n (%)	97 (98)
Methotrexate, n (%)	85 (85.9)
Prednisone, n (%)	47 (47%)
Hypertension, n (%)	17 (18.2)
Dyslipidemia, n (%)	15 (15)
Type 2 Diabetes mellitus, n (%)	10 (10)
Hipothyroidism, n (%)	7 (7)

Table 2. Sarcopenia and Sarcopenic Obesity Prevalence according to different definitions.

	Definition	Sarcopenia n, (%)	Sarcopenic Obesity* n, (%)
1	Lean mass Index <%10 (9) (LMI < 13.3 kg/m^2)	10 (9.9)	6 (5.9)
2	Elkan et al (9) (LMI < 13.7 kg/m^2)	21 (21.6)	13 (13.4)
3	Cruz-Jentoft et al (14) (LMI a < 5.67 kg/m^2)***	21 (21.6)	6 (6)

*Sarcopenia + Fat mass index >25%, ***women, LMI = lean mass index, IMMa = appendicular lean mass index.

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Comparison of Application of the European Society Cardiology, Adult Treatment Panel III, and ACC/AHA Guidelines for Cardiovascular Disease Prevention in a French Cohort of Rheumatoid Arthritis. Martin Soubrier[1], Zuzana Tatar[2], Maxime Chevreau[3], Bruno Pereira[4], Laure Gossec[5], P Gaudin[6] and Maxime Dougados[7]. [1]COMEDRA trial group, Paris, France, [2]Centre Jean Perrin, Clermont Ferrand, France, [3]CHU Sud Hospital, Grenoble, France, [4]Clinical research department, Clermont-Ferrand, France, [5]Sorbonne Universités, UPMC Univ Paris 06, GRC-08, Institut Pierre Louis d'Epidémiologie et de Santé Publique, paris, France, [6]CHU Hôpital Sud, Grenoble, France, [7]RAID working group for EULAR, Zurich, Switzerland.

Background/Purpose: Cardiovascular risk (CVR) is increased in RA and should be evaluated annually. EULAR recommends using the SCORE equation to calculate risk, after applying a multiplier of 1.5 in patients with RA who meet two of the following three criteria: disease duration > 10 years, rheumatoid factor or anti-CCP antibody positivity, presence of extra-articular manifestations. European guidelines (ESC) recommend statin therapy for subjects with high or very high risk i.e when CVR calculated with the SCORE equation is ≥ 10% and LDL-cholesterol is ≥ 1.8 mmol/l, or when CVR is > 5% and < 10% and LDL-cholesterol is ≥ 2.5 mmol/l (1,2). Until now the Adult Treatment Panel -III (ATP-III) guidelines recommended the use of statin therapy for primary prevention on the basis of a combined assessment of LDL cholesterol and the 10-year risk of coronary heart disease as calculated with the use of the Framingham risk calculator. American recommendations (ACC/AHA) have recently changed and a new equation to assess overall CVR has been validated. Statin therapy is recommended for subjects aged 40–75 years when CVR is ≥ 7.5.

Assess the need for statin in an established RA cohort (COMEDRA study) according to ESC, ATP-III, and ACC/AHA guidelines with application of the multiplier proposed by EULAR, in patients aged 40 years or older without diabetes, overt cardiovascular disease (CVD) and statins.

Methods: COMEDRA is a multicentre French cohort study of comorbidities in patients with RA and a self-assessment of the disease. At inclusion, general characteristics (age, sex), duration of the disease and treatments for the RA, cardiovascular risk factors (hypertension, diabetes, smoking habit, total, HDL and LDL cholesterol, obesity), RA activity assessed using the DAS28VS, DAS28CRP, SDAI, CDAI, HAQ, ESR, CRP, RA antibodies were recorded for each patient.

Results: 970 patients were included. 612 patients (82.7% women) with established RA (mean disease duration 11.3 [6.5 – 19.8] years) were analyzed (Exclusion age (n = 49); Diabetes or overt CVD (n = 65), statins (n = 168), incomplete data (n = 76)). RA was erosive in 450 (74.3 %) and 484 (79.1%) had positive RF or anti-CCP antibodies. 431 patients (70.4%) were treated with a biologic and 217 (35.6%) received glucocorticoids (mean, 5.34 ± 5.59 mg/day). 90 (14.7%) patients had a family history of early onset CVD, 147 (24.0%) were treated for hypertension, 100 (16.3%) were smokers.

Treatment recommendations based on Different Guidelines

	ESC	*ATP-III*	*ACC/AHA*
Women (n = 506)			
Treatment recommended	*7 (1.4)*	*50 (9.9)*	*155 (30.6)*
Treatment considered	*241 (47.6)*	*57 (11.2)*	*292 (57.7)*
No treatment	*257 (50.8)*	*399 (78.9)*	*59 (11.7)*
Men (n = 106)			
Treatment recommended	*9 (8.5)*	*47 (44.3)*	*76 (71.7)*
Treatment considered	*80 (75.5)*	*21 (19.8)*	*29 (27.4)*
No treatment	*17 (16)*	*38 (35.8)*	*1 (0.9)*

Conclusion: In this RA patient's aged 40 years or older, proportion of individuals eligible for statins differed substantially among the guidelines.

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Systemic Inflammation in Alzheimer's Disease: Relevance to Patients with Rheumatoid Arthritis. M. Elaine Husni[1], Colin O'Rourke[2], Travis Moore[2] and Jagan Pillai[2]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]Cleveland Clinic, Cleveland, OH.

Background/Purpose: Alzheimer's disease (AD) dementia is the most common form of dementia affecting > 25 million people worldwide without known cure. Research regarding involvement of inflammatory component of Alzheimer's Disease (AD) has been well documented. A recent study via whole genome and exome DNA sequencing have provided evidence that coding mutations in the TREM2 gene are associated with a ~2.5–4 fold increased risk in developing AD. Notably TREM2 is only expressed within macrophages and dendritic cells in the periphery and within microglia within the brain and is involved in innate immunity, suggesting that alterations in neuroinflammation are directly linked to the development and progression of AD. Autoimmune diseases such as rheumatoid arthritis (RA) known to be a chronic systemic inflammatory disorder may thereby be important to see if the prevalence of these diseases makes a subsequent neurodegenerative diagnosis like AD more likely.

Our objective was to investigate whether the risk of Alzheimer's disease is increased in patient with rheumatoid arthritis in a large population cohort.

Methods: Our study consists of a large retrospective hospital based cohort from a network of north east Ohio health providers through Explorys database. Population was defined by a) subjects using medications used in RA and AD, b) ICD9 codes (714.0, 294.1, 331.0, 331.11, 331.19, 331.82, 331.83, 290.0, 290.43, 294.20 and 294.21) was used to understand the specific subtypes of dementia. Descriptive analysis was performed on individual cohorts. Statistical Analysis: Relative risk of use of AD medications among subjects using RA medications will be compared with a control cohort without these medications use, to determine the risk of AD medication use in each cohort.

Results: Overall number of subjects from our database was 2,592,280 (77% females). Number of subjects with RA medication + AD medications was 430. Subjects with either RA and/or FDA approved AD medications were 52,330. Subjects with RA but no AD medications was 37,650. In this cohort, 60% of treated RA subjects had an RA diagnosis based on ICD9 codes, but only 2.2 % subjects using AD medications had an AD or AD dementia diagnosis and 1.25% had a diagnosis of mild cogntive impairment based on ICD9 codes.

Relative risk of AD medication use among subjects using RA medications was 2.02 [1.83–2.22], P<0.001. This effect was noted to be most prominent in subjects less than 65 years old.

Conclusion: Our study supports that patients with RA could be associated with an increased risk of Alzheimer's Dementia and raises the possibility of shared risk factors that may not have been appreciated previously. Further study into this association would help develop guidelines to screen for cognitive impairment and elucidate novel therapeutic options in AD.

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IMPACT of Initiative to Control Cardiovascular Risk Factors in Collaboration with LOCAL Doctors in Patients with Rheumatoid Arthritis. Andrea Zacarias Crovato[1], Javier Narváez[2], Joan Miquel Nolla[3], Jesús Rodríguez-Moreno[1], Montserrat Jordana[1] and Carmen Gomez Vaquero[3]. [1]Hospital Universitari de Bellvitge, Barcelona, Spain, [2]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, [3]Hospital Universitario de Bellvitge, Barcelona, Spain.

Background/Purpose: Rheumatoid arthritis (RA) is associated with cardiovascular risk (CVR) with an increased prevalence of cardiovascular events and cardiovascular mortality than the general population. Good control of both, the disease activity and cardiovascular risk factors (CVRF), reduces morbidity and mortality associated with this increase in CVR. While control of disease activity is assumed by the rheumatologist, CVRF control could correspond to both the rheumatologist and the family doctor.

Objectives:To evaluate the impact of an initiative to control CVRF in collaboration with family doctors in patients with rheumatoid arthritis.

Methods: RA patients selected consecutively when they came to visit monitoring. For each patient, we collected CVRF (body mass index, smoking, blood pressure, serum glucose, total cholesterol, LDL cholesterol and triglycerides) and calculated the SCORE and the SCORE modified. The patient was informed of the need to correct their CVRF and handed a letter to your family doctor reported in which the importance of control of cardiovascular risk factors in patients with RA and were asked for their cooperation in controlling thereof. In addition, you specify the therapeutic objective to achieve respect to LDL cholesterol: 1.7 nmol / L (70 mg / dL) in patients with high CVR (SCOREm ≥ 5%) or suffered a cardiovascular event and 2.5 nmol / L (100mg/dL) in the rest. In the next view of control, there was whether there had been any intervention, and if he had achieved the therapeutic goal.

Results: We included 211 patients (171 (81%) women) with a mean age of 60 ± 12 years and a duration of RA of 13 ± 9 years. FR was 72% and 70% + PCC +. 70% of patients were treated with glucocorticoids, 86% and 32% FAME with biological treatment. For DAS28 criteria, 71% had low activity, 27%, moderate and 2%, high activity. On a visit home, 25% of patients were overweight, 17% smoked, 51% were hypertensive, 6% were hyperglycemic, 53% had a serum total cholesterol> 5.2 mmol / L (200 mg / dL), and 23% were hipertrigliceridémico. The 5% had no cardiovascular risk factors, 20% had one, 34% two, 28% three, and 13%, more than three. The goal LDL was 1.7 in 29% of patients. There were new diagnoses of CVRF in 100 patients (47%): 1 diabetes, 18 hypertension, 82 with elevated LDL cholesterol and 27 hypertriglyceridemia. The family physician changed the treatment in 2/12 diabetes, 30/84 HTA, 74/167 with elevated LDL cholesterol and 21/51 hypertriglyceridemia in which the change was indicated. The end result of the intervention was that between the two visits, the percentage of patients with CRF who had good control over it happened: a) in diabetes, from 48% to 44%, b) in hypertension, 25% to 73% c) elevation of LDL cholesterol from 10 to 17%, and d) in hypertriglyceridemia, 25% to 38%.

Conclusion: Through the intervention has been diagnosed at least a new CVRF not known in a high percentage of patients. The response of family physicians as measured by the change in drug regimen is considered insufficient. As a result, control of cardiovascular risk factors, and mainly of dyslipidemia is suboptimal.

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Influence of Radiographic Joint Damage in Mortality Risk in a Cohort of Rheumatoid Arthritis Patients: A 20 Years Survival Study. L. Rodriguez-Rodriguez[1], J. Ivorra-Cortes[2], Lydia Abasolo[1], Leticia Leon[1], Oscar Fontsere[3], B. Fernández-Gutiérrez[1] and Juan A Jover[1]. [1]Instituto de Investigación Sanitaria San Carlos (IdISSC), Madrid, Spain, [2]University Hospital la Fe, Valencia, Spain, [3]Hospital Clínico San Carlos, Madrid, Spain.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with increased mortality and reduced life expectancy compared with the general population. This mortality gap has increased in the last years since mortality rates for RA have remained constant throughout time while mortality rates for the general population have decline. Excess mortality has been associated with disease activity. Radiographic joint destruction reflects the cumulative burden of inflammation and it is conceived as an objective measure of RA severity. The aim of our study was to analyze the influence of radiological joint damage in the mortality rate in a cohort of RA patients.

Methods: We included 783 RA patients in a retrospective longitudinal study, from May 1993 to November 2013, attending the rheumatology outpatient clinic of the Hospital Clínico San Carlos (Madrid, Spain). Subjects were included at the moment of their first X-ray, until October 2012, and followed until patients' death, loss of follow up or November 2013. Clinical records were examined and demographic and clinical data was collected. Radiographic joint damage of hands and wrists was assessed with the Sharp vand-der-Heijde score [total (SHS), erosion (ES) and narrowing/(sub)luxation

(NSLS) components]. Survival techniques were applied to estimate the mortality rate (MR; expressed per 1000 patients-years with a 95% of Confidence Interval [95% CI]). Cox bivariate and multivariate regression models were conducted to examine risk factors for death. Interaction terms between radiological damage and rheumatoid factor (RF) positivity, and the elapsed time from RA onset to X-ray, were introduce in the models. Proportional hazard assumption was tested using Schoenfeld residuals and the scaled Schoenfeld residuals. Results: were expressed as hazard ratio (HR) and 95% CI.

Results: Most of the patients included were women (74%), with a median age of 61 years old (interquartile range [IQR]: 47–71), 67% were RF positive, and the median (IQR) elapsed time between RA symptoms onset and the X-ray was 2 (0–7) years. The median (range) followed up time per patient was 5 [0.4–20] years. 92 patients died during a follow up time of 4758 person-years. Mortality rate (MR) was 19 per 1000 patient-year [95% CI 16–24]. We observed in the bivariate analysis that older age, male sex, higher elapsed time from RA onset to X-ray, SHS, ES, NSLS, number of hospital admissions (used as a surrogate measure of comorbidity), basal Health Assessment Questionnaire, RF positivity, earlier RA onset (in calendar time), and no treatment with biological therapy, were associated with a higher MR. 3 multivariate models were constructed, using SHS, ES or NSLS as measures for joint destruction, and adjusted by the previous variables. In none of the models radiographic damage was associated with MR. However, we observed that the interaction between ES and RF positivity was significant ($p=0.001$): ES was associated with MR only in RF negative patients.

Conclusion: Erosive joint damage seems to be a risk factor for all cause mortality only among RF negative RA patients.

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Mortality Ratio of Rheumatoid Arthritis Under Biological Treatment. Umut Kalyoncu[1], Abdulsamet Erden[2], Hakan Babaoglu[2], Murat Torgutalp[2], Sadettin Kilickap[2], Omer Karadag[3], Sule Apras Bilgen[3], Ihsan Ertenli[1], Ali Akdogan[3] and Sedat Kiraz[3]. [1]Hacettepe University School of Medicine, Ankara, Turkey, [2]Hacettepe University, Faculty of Medicine, Ankara, Turkey, [3]Hacettepe University Faculty of Medicine, Ankara, Turkey.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease, which, in many patients, leads to a substantial disability and has a major effect on the quality of life. Patients with RA also have an increased mortality compared with the general population. Main causes of mortality in RA are cardivascular events and serious infections. The objective of this study was to evaluate mortaility ratio in patients with RA during biological treatment.

Methods: HUR-BIO (Hacettepe University Rheumatology Biologic Registry) is a single center biological registry since 2005 that include 815 RA patients under biological treatments. Data collected includes demographic data, co-morbidities, smoking, switch ratio, baseline and follow-up disease activity parameters (such as DAS28, CRP, ESR, global VAS, swollen joint count ad tender joint count). For all individuals in the study population, follow up time began at the first known use of etanercept, infliximab, or adalimumab. The outcome of interest was death from any cause, which was identified through linkage of the study population to the Turkish Cause of Death Register through May 31, 2014. Overall and anti-TNF biologic stratified incidence rates per 1000 person-years were calculated.

Results: HUR-BIO includes 815 RA patients (77,9% female). Mean age was 51 ± 13 years and mean disease duration was 11 ± 8 years. TNFi drug duration was $2,7\pm2,6$ years and 176 (21,5%) patients were used TNFÝ drugs more than 5 years. Positive ACPA and RF were 297/465 (63,9%) and 454/740 (61,3%), respectively. First biological drugs were etanercept 321 (39,4%), adalimumab 223 (27,4%) and infliximab 115 (14,1%), rituksimab 92 (11,3%), abatecept 43 (5,3%), golimumab 20 (2,5) and tocilizumab 1 (0,1%). TNFi switch was found in 262 (32,1%) patients. Among the 815 patients in our entire study population and during a total of 2,235 person-years of follow-up (mean 2,7 years; median 1,8 years), 21 patients died. The all-cause mortality rate was 9,4 per 1000 person-years. Five of 21 patients died in our hospital (3 patients were lung infection, 1 tuberculosis and 1 acute coronary syndrome). Mortality ratio was sligthly, not significantly, higher in male patients (%38,1 vs %21,4 $p=0.071$). There were certain difference in age ($60,1\pm10,9$ vs $51,1\pm13,1$, $p=0.004$), biological drug duration ($2,7\pm2,7$ vs $0,6\pm0,9$ years, $p<0.001$), baseline erytrocyte sedimentation rate (53 ± 18 vs 40 ± 25 mm/hour, $p=0.018$), positive RF (%89,5 vs %60,6, $p=0.039$) and level of RF (median 103 (0–2500) vs 44 (0–2710), $p=0.032$).

Conclusion: Crude mortality ratio in our biological database was comparable with literature, that between 5.3 to 16.8 (1–2). Crude mortality ratio of our patients is slightly higher than general population [9,3/1000 person-year vs 4,9/1000 person-year (3)]. Biological treatments seem like relatively safe drug in our database, however, we need biological naive RA cohort for certain conclusion.

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Clinical Characterization of Subclinical Rheumatoid Arthritis-Associated Interstitial Lung Disease. Masaomi Yamasraki. Shin-Yokohama Yamasaki Clinic, Yokohama, Japan.

Background/Purpose: Rheumatoid arthritis-associated interstitial lung disease (RA-ILD) is a common manifestation of rheumatoid lung disease. Subclinical RA-ILD is most commonly identified on HRCT imaging. In this study, we aimed to define the clinical characteristics of subclinical RA-ILD on HRCT, and to analyze long-term prognosis of subclinical RA-ILD.

Methods: 340 patients with RA were treated at our hospital and followed them up for three years or until development of symptomatic ILD. All patients were performed chest radiological examinations at the initial presentation. The HRCT findings which include (1) ground glass opacity.(2) air-space consolidation, linear opacity including (3) septal line and (4) non-septal line, (5) honeycomb lung, (6) traction bronchiectasis, (7)pleural irregularity, and (8)pleural effusion were scored as the CT scoring system. The extent of involvement of each abnormality was assessed independently for each of the three zones of each lung. The HRCT extent score was represented the sum of the score of each lung. HRCT parameters which included the extension score, ACPA and the clinical features at the initial presentation were retrospectively analyzed.

Results: 76 (22.3%) out of 340 RA patients had abnormal chest radiological findings which consist with ILD. 5 out of 76 patients had shortness of breath and showed a rapidly progressive ILD (6.6%). The rest of 71 (48women, 23men) had subclinical RA-ILD who were either asymptomatic or have symptoms and physiologic abnormalities that are as yet unrecognized as being due to RA-ILD. There was no difference in the positive rates of anti-CCP2 between subclinical RA-ILD and clinical evident RA-ILD. However there were no difference in the HRCT findings which included nonseptal linear attenuation, ground-glass attenuation and air space consolidation between subclinical RA-ILD group and clinical RA-ILD group, subclinical RA-ILD group showed less degree in honeycombing ($p=0.0003$) and focal ILD ($p=0.0061$). There have only two cases lead to clinically evident RA-ILD within 6 months. These two cases were treated with azathioprine and with MMF showed stable ILD on HRCT.

Conclusion: HRCT finding focused on honeycombing and the extension score at the initial presentation is a sensitive technique for detection of subclinical RA-ILD. This study suggest the progression of asymptomatic radiologic changes could lead to the development of clinical RA-ILD.

Disclosure: M. Yamasaki, None.

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The Longitudinal Association Between Inflammation and Blood Pressure in Rheumatoid Arthritis. Chih-Chin Liu[1], Daniel H. Solomon[2], Rishi Desai[2], Seoyoung C. Kim[2] and KP Liao[2]. [1]Rheumatology & Immunology, Brigham & Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Inflammation is hypothesized to have direct effects on arterial endothelial and vasomotor function, functions which regulate blood pressure (BP). While inflammation has been implicated in the development of elevated BP, few studies have examined BP longitudinally after diagnosis of an inflammatory disease. The objective of this study is to examine the longitudinal association between changes in levels of inflammation and changes in BP in patients with rheumatoid arthritis (RA).

Methods: We studied RA subjects classified using a validated electronic medical record (EMR) algorithm (positive predictive value 94%) linked with Medicare Claims Data (patients age>65 years) between 2006–2010. We extracted EMR data on age, gender, systolic BP (SBP), diastolic BP (DBP), erythrocyte sedimentation rates (ESR), smoking status (ever/never), and calendar year of measurements. We extracted RA treatment data from Medicare prescription data including non-steroidal anti-inflammatory drugs (NSAIDs), anti-hypertensive drugs and dates of claims. We studied all subjects with ≥2 concurrent BP and ESR measurements at separate visits at least one week apart. The baseline was defined as the 1st concurrent ESR and BP measurement 6 months after the 1st Medicare claims date. We examined the association between the change in ESR and change in SBP between baseline and follow-up using multiple linear regression models adjusted by age, gender and smoking status. We performed sensitivity analyses by including potential treatments received +/− 15 days of ESR measurements that may affect blood pressure individually into the models; the treatments included anti-TNF, NSAIDs, anti-hypertensive medications, and steroids.

Results: We identified 313 subjects with ≥2 instances with ESR and BP measured on the same date. The mean age was 69.2 years (SD 10.3), 83.7% female, and 57.6% ACPA positive. The mean SBP was 134.4(SD 18.8) mm/Hg, mean DBP was 75.7(SD 12) mm/Hg, and the mean ESR was 32 (SD 27.1) mm/hour. We observed an inverse association between change in ESR and SBP, where every 10mm/hour increase in ESR was associated with a 1.2mm/Hg lower in SBP, adjusted by age, gender and smoking status (**Table**). A similar relationship was found with DBP: each 10mm/hour increase in ESR was associated with a 0.43 mm/Hg lower DBP (95% CI −0.75, −0.01, p=0.009). The effect size of the association between change in ESR and change in BP was similar with the addition of indicator variables for anti-hypertensive treatments, anti-TNF, and NSAIDs into the model.

Conclusion: In a linked dataset containing clinical data from the EMR and detailed prescription data from Medicare, we observed that increases in ESR were associated with a modest reduction in blood pressure. These findings have potential implications for CV risk assessment in RA patients who commonly experience large fluctuations in inflammation.

Table. The association between change in ESR (per 10mm/hour) increase with change in systolic blood pressure (SBP), N=313.

Linear regression models for ΔESR and ΔSBP, adjusted by:	ΔSBP (mm/Hg) per 10mm/h Δ ESR	95% CI
Model 1: Age, gender, race, smoking	−1.22	−1.74, −0.71
Sensitivity analyses		
Model 2: Model 1 + anti-hypertensive	−1.21	−1.72, −0.70
Model 2+ anti-TNF	−1.19	−1.70, −0.70
Model 2+ NSAIDs	−1.21	−1.72, −0.70
Model 2+ Steroids	−1.21	−1.72, −0.70
Model 3: Model 1 + anti-hypertensive + anti-TNF + NSAIDs + steroids	−1.16	−1.67, −0.65

*All p-values <0.0001

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Changes in the Types and Prognoses of Infections Complicated in RA Patients during the Last 15 Years, in Japan.. Yoichiro Akiyama[1], Takeo Sato[1], Takamasa Murosaki[1], Katsuya Nagatani[1] and Seiji Minota[2]. [1]Jichi Medical University, Tochigi, Japan, [2]Jichi Medical University, Tochigi-Ken, Japan.

Background/Purpose: Infliximab was introduced in 2002 as the first biological DMARD (bDMARD) in Japan. Currently, 5 TNF inhibitors, tocilizumab, and abatacept are available. Tacrolimus and leflunomide were included as immunosuppressant and synthetic DMARD (sDMARD), and methotrexate (MTX) was approved up to 16 mg/week since 2011. We investigated the type and prognosis of infections in RA patients through the course of the evolution of DMARDs during the last 15 years in Japan.

Methods: We collected, retrospectively, the hospitalized cases of RA under the diagnosis of infections from 1999 to 2013. The diagnosis of infection was based clinically, when it was not confirmed microbiologically. The years between 1999 and 2013 were divided into 5, each consisting of 3 years. The clinical characteristics of the patients, type of infections, hospitalized durations, and mortality were summed up in each period, and their changes in these 5 periods were investigated.

Results: The numbers of hospitalized cases in the 5 periods from 1999 to 2013 were 40, 60, 87, 88, and 84, respectively. When compared between the 1st period of 1999 to 2001 and 5th period of 2011 to 2013, there was no difference in age (median 66.5 vs. 67 years), sex (female to male ratio, 2.6 vs. 2.8), and RA disease duration (median 11.5 vs. 11 years). Glucocorticoid was administered in over 80% of the patients in each period. When compared between the 1st and 5th periods, MTX-use increased from 37.5% to 50.0%, and 15.5% of the patients on MTX were administered over 8 mg/week in the last period. The frequency of bDMARDs-use was 5.0% and 38.1%, in the 1st and 5th period, respectively. Immunosuppressants were used in 10.0% and 16.7%, and sDMARDs other than MTX were used in 37.5% and 14.3% of the patients, in the 1st and 5th period, respectively. The respiratory system was most frequently infected in each period. The mortality in each period was 7.5%, 6.7%, 4.6%, 9.1%, and 7.0%, from 1st to 5th, respectively (p=0.48), and there was no difference in the hospitalized duration (p=0.33). Although there was no significant difference in the prognosis, the frequency of Pneumocystis jirovecii pneumonia (PCP), and the mortality thereof increased from 7.5% to 16.7%, and 33.3% to 80.0% between 1st and 5th period. By univariate analysis of all patients, the mortality was significantly associated with PCP (crude Odds ratio 12.04, p<0.01, 95% CI 4.84 to 29.97), concurrent interstitial pneumonia (crude Odds ratio 2.56, p=0.031, 95% CI 1.09 to 6.01), and glucocorticoid-use (crude Odds ratio 1.06, p=0.001, 95% CI 1.02 to 1.10). PCP was associated with MTX- (crude Odds ratio 3.78, p<0.01, 95% CI 1.74 to 8.20) and glucocorticoid-use (crude Odds ratio 1.05, p<0.01, 95% CI, 1.02 to 1.08). There was no association between bDMARDs-use and PCP (crude Odds ratio 1.74, p=0.17), or mortality (crude Odds ratio 0.78, p=0.67).

Conclusion: With the evolution of treatment in RA during the last 15 years, infections complicated in RA have changed. Although there was no difference in hospitalized durations or mortality, the frequency of PCP and death thereof have been increasing. Compared to Western countries, PCP is more prevalent in Japan, and early diagnosis and treatment are mandatory.

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Impact of Depression on Clinical and Social Outcomes in Patients with Rheumatoid Arthritis: Comparative Study in Germany and Brazil. Harriet Morf[1], Olga Malysheva[1], G da Rocha[2], Anna Beatriz Vargas[2] and Christoph G. Baerwald[1]. [1]University Hospital, Leipzig, Germany, [2]Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil.

Background/Purpose: Rheumatoid Arthritis (RA) can be associated with psychological disorders and especially depression. About 13 – 20 % of patients have clinical significant depression. It was shown (Dougados, 2014 COMORA Study) that depression in this group of patients has a high variability between countries (2 % Morocco – 33 % USA). However, it is still incompletely understood how RA could influence on perception of depression and its impact on quality of life in RA patients from different countries. The purpose of study was to characterise distribution of depression and its impact on pain and social status of patients with RA in different countries.

Methods: 100 RA patients from Germany (age 62,4 ± 12,3 years) and 91 RA patients from Brazil (age 56,3 ± 12,6 years), mean duration of disease in Germany was 14,3 ± 10,4 years and in Brazil 15,9 ± 10,2 years, could be included in this study. RA was diagnosed according to the ACR/EULAR Criteria 2010 and the following questionnaires were utilised: Beck depression inventory (BDI), painDETECT test (Freyn-

hagen R., et al., 2006), visual analogue scale for pain (VAS), SF - 36 and Health Assessment Questionnaire (HAQ-DI).

Results: About 20% RA patients in Brazil were diagnosed with associated depression. Furthermore 27,4 % of Brazilian patients had a subclinical depression. It is significant higher compare to RA patients in Germany (only 10%; $p = 0,039$). There is no difference between pain intensity in two groups of patients (VAS 4,7 ± 3,4 mm (Brazil) vs 3,6 ± 2.3 (Germany). However 61,5 % of Brazilian patients showed symptoms of neuropathic pain compare to 48.3 % of patients from Germany ($p = 0,001$). There are a correlation between pain and depression in both groups (Brazil: $r = 0,520$, $p < 0,001$; Germany: $r = 0,392$, $p < 0,001$). Furthermore, a significant difference was detected in psychological scales of quality of life between both groups of patients (46,6 ± 12,3 Brazil compare to 51,4 ± 11,4 Germany; $p = 0,002$). Interestingly, there was no difference between the activity of disease (DAS 28) between two groups of patients (3,4 ± 1,5, Brazil vs 3,3 ± 1,3, Germany). However Brazilian patients had more erosions (X-ray) compare to Germans group of patients ($p = 0,011$). Moreover it was significant difference between methods of therapy in both groups of patients. Only 5 % Brazilian patients had biologics compare to about 30% RA patients in Germany. There are correlation between the functional status of patients and pain (HAQ and pain: $r = 0,628$, $p < 0,001$), as well as the functional status and depression (HAQ and BDI: $r = 0,552$, $p < 0,01$). Concerning family status, more Brazilian patients were single compare to Germans patients ($p = 0,001$). In Brazil there was found an higher number of patients with children compare with Germans group (74,2 %; $p = 0,015$).

Conclusion: The study indicates that RA-related depression could contribute to diminished psychological well-being in RA patients and suggests the need for psychoeducational and management strategies that specifically target depression as part of RA management program. Future research should attempt to obtain a larger sample of male and younger RA patients to determine if there are significant gender and age differences in the impact of depression on outcomes of RA in different countries.

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Cholesterol Efflux Capacity of HDL and Coronary Atherosclerosis in Rheumatoid Arthritis. Michelle J. Ormseth[1], Patricia Yancey[1], Suguru Yamamoto[1], Annette M. Oeser[1], Tebeb Gebretsadik[1], Ayumi Shintani[1], MacRae F. Linton[1], Sergio Fazio[1], Sean Davies[1], L Jackson Roberts II[1], Kasey C. Vickers[1], Paolo Raggi[2], Valentina Kon[1] and C Michael Stein[1]. [1]Vanderbilt University, Nashville, TN, [2]Emory University, Atlanta, GA.

Background/Purpose: Cardiovascular (CV) risk is increased in patients with rheumatoid arthritis (RA), but not fully explained by traditional risk factors such as LDL and HDL cholesterol concentrations. The cholesterol efflux capacity of HDL may be a better CV risk predictor than HDL concentrations. We hypothesized that HDL's cholesterol efflux capacity is impaired and inversely associated with coronary atherosclerosis in patients with RA.

Methods: We measured the cholesterol efflux capacity of apolipoprotein B depleted serum and coronary artery calcium score in 134 patients with RA and 76 control subjects, frequency-matched for age, race and sex. The relationship between cholesterol efflux capacity and coronary artery calcium score and other clinical variables of interest was assessed in patients with RA.

Results: Cholesterol efflux capacity was similar among RA (median [IQR]: 34% removal [28, 41%]) and control subjects (35% removal [27%, 39%]) ($P=0.73$). In RA, increasing cholesterol efflux capacity was not significantly associated with decreased coronary calcium score ($OR=0.78$ (95% CI 0.51–1.19), $P=0.24$, adjusted for age, race and sex, Framingham risk score and presence of diabetes). Cholesterol efflux capacity was not significantly associated with RA disease activity score, C-reactive protein, urinary F_2-isoprostanes, or degree of insulin resistance in RA.

Conclusion: Cholesterol efflux capacity is not significantly altered in patients with relatively well-controlled RA nor is it significantly associated with coronary artery calcium score.

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Association Between Chronic Inflammatory Conditions and Anti Cyclic Citrullinated Peptide Antibodies in Patients with Early Rheumatoid Arthritis. Lucila Marino[1], Marta Mamani[1], Antonio Catalán Pellet[1], Fernando Dal Pra[2], Gustavo Citera[3], Margarita Landi[2], O Cerda[2], Alejandro Martinez[4], Rafael Chaparro del Moral[4], Oscar L. Rillo[4], Francisco Colombres[5], Alberto Berman[5], Horacio Berman[5], Josefina Marcos[6], Mercedes García[6], A Salas[6], Francisco Caeiro[7], AC Alvarez[8], Maria Haye Salinas[7], N Benzaquen[8], Enrique Soriano[9], Javier Rosa[10], Emanuel Bertiller[10], Federico Ceccato[11], Sergio O. Paira[11], Gabriela Salvatierra[12], C Ledesma[12], Ana Quinteros[13], M Leal[13], Maria Elena Crespo[14], V Juarez[14], Edson Veloso[15], Mónica P. Sacnun[16], R. Quintana[16], Marcelo Abdala[17] and Anastasia Secco[1]. [1]Hospital Bernardino Rivadavia, Buenos Aires, Argentina, [2]Instituto de Rehabilitacion Psicofisica, Buenos Aires, Argentina, [3]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [4]Hospital General de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [5]Centro Medico Privado de Reumatologia, Tucumán, Argentina, [6]HIGA San Martín, La Plata, Argentina, [7]Hospital Privado de Córdoba, Córdoba, Argentina, [8]Hospital Privado Centro Médico de, Córdoba, Argentina, [9]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [10]Hospital Italiano, Buenos Aires, Argentina, [11]Hospital Jose Maria Cullen, Santa Fe, Argentina, [12]Instituto Provincial De Rehabilitación Integral, Stgo. del Estero, Argentina, [13]Centro Integral de Reumatología, Tucumán, Argentina, [14]Hospital Señor Del Milagro, Salta, Argentina, [15]Sanatorio y Universidad Adventista Del Plata, Entre Rios, Argentina, [16]Hospital Provincial, Rosario, Argentina, [17]Hospital Provincial del Centenario, Santa Fe, Argentina.

Background/Purpose: Increased citrullination process and anti–CCP production are not restricted to rheumatoid arthritis (RA). Other inflammatory processes could develop citrullinated proteins which may contribute to the production of such antibodies. The aim of our study was to analyze whether patients with anti-CCP positive early rheumatoid arthritis have higher frequency of previous history of chronic inflammatory conditions than anti-CCP negative patients at the time of diagnosis.

Methods: We included patients with early RA according to ACR/ EULAR classification criteria, belonging to a prospective cohort of patients with early arthritis (<2 years of disease duration). Data from the first visit were collected. We studied the relationship between anti-CCP antibodies with the previous history of chronic inflammatory conditions (ischemic heart disease, peripheral vascular disease, ischemic or hemorrhagic stroke, hypertension, dyslipidemia, asthma, chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypothyroidism, tuberculosis, alcohol and smoking). The association between anti-CCP status and the presence of inflammatory processes were assessed using univariate and multivariate models.

Results: We included 557 patients with early rheumatoid arthritis. We found positive anti-CCP antibodies (≥ 25 UI/ ml) in 396 patients and negative anti-CCP antibodies in 161. There were no differences between anti-CCP negative and anti-CCP positive patients regarding to age (51 ± 14 vs 50 ± 14 years; $p= 0,76$) and female gender (83% vs 80%; $p=0,42$). When evaluating the association between anti-CCP positivity and presence of inflammatory conditions, patients with negative anti-CCP antibodies experienced significantly higher frequency of dyslipidemia (14% vs 5%; $p < 0,01$) and alcohol intake (7% vs 3%; $p= 0,03$). No association was found between anti-CCP status and ischemic heart disease, peripheral vascular disease, ischemic or hemorrhagic stroke, hypertension, chronic respiratory diseases including asthma and COPD, diabetes mellitus, hypothyroidism, tuberculosis and smoking. Multivariate logistic regression analysis with anti-CCP as dependent variable, showed that dyslipidemia [$OR=0,39$ (0,17- 0,89); $p=0,03$] and alcoholism [$OR= 0,29$ (0,15- 0,55); $p< 0,01$] were independently associated with negative anti-CCP antibodies.

Conclusion: In this cohort with early rheumatoid arthritis, we did not found higher frequency of previous chronic inflammatory conditions in patients with positive anti-CCP antibodies. Nevertheless, negative anti-CCP antibodies were significantly and independently associated with previous history of dyslipidemia and alcoholism.

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Miscarriage in Rheumatoid Arthritis – Association with Disease Characteristics and Medication Use. Jenny Brouwer, Joop SE Laven, Johanna MW Hazes and Radboud JEM Dolhrain. Erasmus MC University Medical Center Rotterdam, Rotterdam, Netherlands.

Background/Purpose: The chance of miscarriage is increased after the diagnosis of rheumatoid arthritis (RA). The association of miscarriage with RA disease activity or anti-rheumatic medication is unclear, mainly due to lack of prospective studies. Our aim was to study the associations of miscarriage with RA serology, disease activity and periconceptional medication use in women with RA.

Methods: In a nationwide prospective cohort on pregnancy in RA (PARA study, 2002–2010) women with RA according to the 1987 American College of Rheumatology (ACR) criteria were visited preconceptionally, during pregnancy and after delivery or miscarriage. General characteristics and medication use were recorded and disease activity (DAS28) was measured. We analyzed the data retrospectively by logistic regression with purposeful selection of covariates, with inclusion at a significance level of $p<0.20$.

Results: A total of 239 preconceptional visits resulted in 181 pregnancies in 164 women. We analyzed only the first included pregnancy for each woman. Thirty (18%) of 164 pregnancies resulted in a miscarriage.

There were significant differences between women with a miscarriage and women with an ongoing pregnancy in age (33.8 (3.9) vs 32.0 (3.8) years, $p=0.022$) and presence of ACPA (83% vs 60%, $p=0.032$). The preconceptional DAS28 was higher in women who had a miscarriage (4.0 (1.0) vs 3.6 (1.2), $p=0.087$) and more women who miscarried had used MTX in the past (83% vs 68%, $p=0.121$), though these differences were not significant. There were no significant differences in RF positivity (80% vs 69%, $p=0.41$), and use of NSAIDs (20% vs 31%, $p=0.27$) or sulfasalazine (27% vs 32%, $p=0.67$).

Logistic regression with the occurrence of miscarriage as dependent variable, showed a tendency towards a higher OR for increasing age, presence of ACPA, increasing DAS28 or past MTX use, though none of these variables reached significance (table 1).

Twenty-one (70%) of the women who miscarried became pregnant again, of whom 19 within one year after miscarriage. This resulted in a live birth in 19 women (90%). Four women decided to stop trying to conceive. Five women were lost to follow up.

Conclusion: The miscarriage rate in the PARA study is comparable to that in the general population. However, this might be biased by a healthy cohort effect found earlier in this study. Despite having miscarried, the majority of patients were pregnant again within one year. RA patients who had a miscarriage tended to be older, to have higher disease activity, to be ACPA positive and to have a past of MTX use. This indicates that miscarriages are more likely to occur in a subgroup of RA patients with more severe disease. Although the PARA study is a large prospective cohort on pregnancy in RA, the associations found did not reach statistical significance due to the relative low frequency of miscarriages in the study.

Table 1. Logistic regression for the occurrence of miscarriage in women with rheumatoid arthritis in the PARA study

Variable	OR	95% Confidence interval	p-value
Age - per year	1.11	0.99–1.24	0.081
Presence of ACPA	2.71	0.94–7.78	0.065
DAS28 - per point	1.35	0.92–1.97	0.124
MTX use in past	2.78	0.95–8.09	0.061

PARA = pregnancy induced amelioration of rheumatoid arthritis; ACPA = anti-citrullinated peptide antibody; DAS28 = disease activity score with a 28-joint count; MTX = methotrexate

Disclosure: J. Brouwer, None; **J. S. Laven**, None; **J. M. Hazes**, None; **R. J. Dolhain**, None.

1440

Asymptomatic Carotid Plaques in RA Patients Are Associated with Increased HDL Function. Silvia Rollefstad[1], Bente Halvorsen[2], Tonje Skarpengland[2], Sella Provan[1], Tore K. Kvien[3] and Anne Grete Semb[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Oslo University Hospital Rikshospitalet, Oslo, Norway, [3]PsAID taskforce, EULAR, Zurich, Switzerland.

Background/Purpose: Reverse cholesterol transport (RCT) is a major anti atherogenic function of high density lipoprotein cholesterol (HDL) and has been shown to be related to disease activity in patients with rheumatoid arthritis (RA).Our aim was to evaluate if atherosclerosis affects HDL function differently in RA patients compared to controls.

Methods: RA patients from the ORA register and the EURIDISS cohorts without cardiovascular (CV) disease and not using statins or biologic DMARDS were included. Healthy community controls were selected by Statistics Norway. RCT was measured as plasma induced 14C-cholesterol efflux from 14C-cholesterol loaded human THP1 macrophages as previously described. Apolipoprotein (Apo) A1 and paraoxonase-1 (PON-1) activity were measured.

Results: RA patients, 10 with and 10 without carotid plaques (CP), and 10 controls were age and gender matched (Table 1). Traditional CV risk factors were comparable in RA patients with and without CP and controls; smoking: $p=0.55$, systolic blood pressure: $p=0.77$, total cholesterol: $p=0.48$, LDL-c $p=0.31$, HDL-c: $p= 0.89$, triglycerides: $p=0.85$. None had diabetes. Untraditional biomarkers of CV disease such as CRP and ESR were also comparable across the 3 groups; $p=0.53$, $p=0.86$ and $p=0.45$, respectively. RA disease factors as disease duration, rheumatoid factor, anti-CCP and DAS-28 were comparable between RA patients with and without CP ($p=0.81$, $p=0.34$, $p=0.34$ and $p=0.94$). Efflux capacity was significantly increased in RA patients with CP compared both to controls without CP ($p=0.03$) and controls with CP ($p=0.01$)(Table 2). Likewise, both ApoA1 and PON-1 activity were increased in RA patients with CP compared to controls ($p=0.02$ and $p=0.05$, respectively). Further, APOA1 and PON-1 activity were comparable between RA patients without CP and controls ($p=0.58$ and $p=0.69$, respectively).

Conclusion: The cholesterol efflux capacity was increased in RA patients with early atherosclerosis compared to controls, independent of HDL level and CRP. Our findings indicate an association between atherosclerosis and upgraded HDL function in patients with RA having low disease activity, possibly as a compensatory mechanism to the atherosclerotic process. This study is hypothesis generating and larger studies are warranted to verify these findings.

Table 1 Patient characteristics

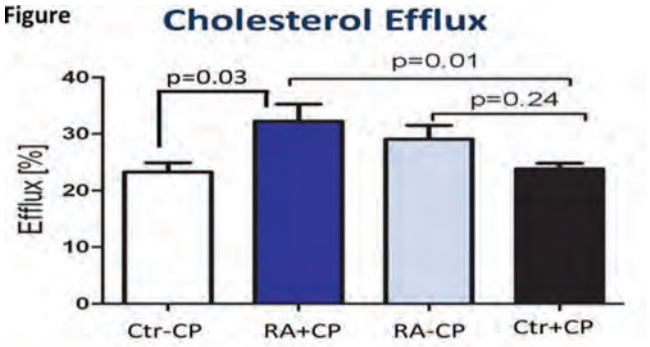
	RA with Carotid Plaque n=10	RA without Carotid Plaque n=10	Controls n=10	p-value
Age median (IQR)	65.2 (53.7, 68.1)	59.1 (54.3, 62.2)	56.6 (51.1, 61.4)	0.09*
Sex male/female n (%)	3/7 (30.0/70.0)	2/8 (20.0/80.0)	5/5 (50.0/50.0)	0.35
Disease duration median (IQR)	16.0 ± 2.1	16.2 ± 1.5	–	0.81
CV risk factors				
Smoke n (%)	3 (30.0)	1 (11.1)	3 (30.0)	0.55
BMI mean ± SD	26.1 ± 3.5	26.3 ± 4.0	27.5 ± 5.4	0.73
TC (mmol/L) mean ± SD	6.10 ± 0.67	5.74 ± 0.97	6.09 ± 0.44	0.48
HDL-c (mmol/L) mean ± SD	1.84 ± 0.48	1.73 ± 0.55	1.80 ± 0.47	0.89
TG (mmol/L) median (IQR)	1.08 (0.68, 1.43)	1.11 (0.80, 1.49)	0.98 (0.72, 1.49)	0.85**
LDL-c (mmol/L) mean ± SD	4.04 ± 0.91	3.46 ± 0.90	3.51 ± 0.09	0.31
BP systolic (mmHg) mean ± SD	131.5 ± 17.1	131.6 ± 16.8	136.8 ± 21.1	0.77
BP diastolic (mmHg) mean ± SD	81.2 ± 8.4	79.9 ± 8.3	82.4 ± 12.9	0.86
ProBNP	11.9 ± 9.2	10.4 ± 9.4	8.1 ± 7.6	0.45**
Co morbidities n (%)				
HT	6 (60.0)	3 (30.0)	6 (60.0)	0.30
Diabetes	0 (0.0)	0 (0.0)	0 (0.0)	–
Biomarkers mean ± SD				
ESR (mm/h)	10.90 ± 9.77	11.90 ± 9.05	9.57 ± 4.79	0.86
CRP (mg/L) median (IQR)	3.5 (1.0, 6.5)	2.0 (1.0, 6.3)	2.0 (1.0, 3.0)	0.53**
RA disease factors				
DAS-28 median (IQR)	2.1 ± 0.9	2.1 ± 1.2	–	0.94
Reumatoid factor positiv n (%)	5 (62.5)	3 (37.5)	–	0.34
Anti-CCP positiv n (%)	5 (62.5)	3 (37.5)	–	0.34

Table 2 HDL function

HDL mean ± SD	RA with CP	RA without CP	Controls	RA with CP vs. CTR p-value	RA without CP vs. CTR p-value
Efflux, g/l (%)	32.24 ± 7.40	29.05 ± 6.04	23.24 ± 4.11	0.03	0.08
ApoA1, g/L	8.74 ± 1.39	7.98 ± 1.70	7.30 ± 0.96	0.02	0.58
ApoA2, g/L	2.16 ± 0.52	1.86 ± 0.57	1.77 ± 0.41	0.08	0.29
PON-1, U/ml)	0.19 ± 0.05	0.14 ± 0.06	0.15 ± 0.04	0.05	0.69

RA patients had HDL with sign. higher APOA 1 and PON-1 compared to control subjects

Figure



Efflux capacity was significantly increased in RA patients with CP compared to controls with CP (p=0.01) and without CP (p=0.03)

Disclosure: S. Rollefstad, None; **B. Halvorsen**, None; **T. Skarpengland**, None; **S. Provan**, None; **T. K. Kvien**, None; **A. G. Semb**, None.

1441

Accelerated Aging in DMARD and Treatment Naive Early Rheumatoid Arthritis Patients Measured By a Stem Cell Assay Is Associated with Increased LDL and Is Linked to Impaired Cardiopulmonary Function. Torkell Ellingsen[1], Henriette Jørgensen[2], Dino Demirovic[2], Lone Deibjerg[3], Frank Andersen[3], Agnete Hedemann-Andersen[3], Brian Bridal Løgstrup[3] and Suresh Rattan[2]. [1]Diagnostic Centre Region, Hospital Silkeborg Denmark, Odense, Denmark, [2]Laboratory of Cellular Ageing, Institute of Molecular Biology and Genetics, Århus University, Århus, Denmark, [3]Diagnostic Centre Region, Hospital Silkeborg Denmark, Silkeborg, Denmark.

Background/Purpose: The cardiovascular comorbidity seen in early treatment naive rheumatoid arthritis (RA) can be considered as an aspect of "accelerated aging".

Methods: We investigated cell migration and proliferation of human cells *in vitro* in a so-called wound healing assay, using telomerase-immortalized mesenchymal stem cells (hTERT-MSC)[1]. Confluent monolayers of hTERT-MSC were mechanically "wounded" creating a fixed size scratch and then allowed to "heal" in the presence of culture medium containing 5% serum from RA-patients (n=30) or healthy subjects (n=25) for 3 days. We examine the effect of serum from RA-patients and controls on hTERT-M and to correlate these *in vitro* measures to standardized measures of cardiopulmonary parameters assessing global longitudinal systolic strain (GLS) by speckle tracking echocardiography[2], coronary calcium score (Agaston score) by coronary computer tomography (CT COR), diffusing capacity of the lungs for carbon monoxide (DLCO), LDL, C-reactive protein (CRP), fasting Insulin (fIns) levels and whole body fat percent by whole body DXA-scan. The assay was performed on serum from 30 treatment-naive RA patients (mean age 56 yr; range 27–73) and 24 healthy controls (age 44 yr; range 24–64).RA patients and controls were free of medication at the time of serum sampling (the RA patients received methotrexate treatment at year one). Disease activity was scored by the use of the Danish national DANBIO registry using standard assessments. CCP titers, LDL and fIns were evaluated by standardized techniques before treatment was initiated.

Results: We found "accelerated aging" measured as decreased wound healing *in vitro* by mean 53% (range 20–100%) in RA patients compared to healthy controls ($p<0.0001$). One year of national guideline DMARD treatment improved the "*in vitro* decreased wound healing" to mean 60% although not significant ($p=0.068$). We found "decreased wound healing *in vitro*" to be associated with increased LDL levels ($p=0.02$; $r=0.43$) in univariate analysis (no association to GLS, Agaston calcium score, DLCO (mmol/min/kPa/L), total fat %, fIns and CRP (p-values in the range 0.31–0.79). We also found a significant difference in GLS in patients with high values of anti-CCP (titers ≥ 340) compared to patients with normal titers and anti-CCP titers CCP titers. Anti-CCP larger than 7 and below 340 $p=0.02$ (DLCO mean 88%) and if anti340 $p=0.004$ (DLCO mean 82%) in anti-CCP negative patients mean DLCO% 102%.

Conclusion: We observed a significant decreased "wound healing *in vitro*" using hTERT-MSC assay in early RA. The "decreased *in vitro* wound healing" was significantly associated with increased LDL. Further we found a significant association between increased anti-CCP titers and initial increased cardiac function and decreased pulmonary function.

References:

[1] Demirovic, D. and Rattan, S.I.S. *Biogerontology, 12: 437–444, 2011*

[2] Løgstrup BB et al: In Press. American Journal of Cardiovascular Disease.

Disclosure: T. Ellingsen, None; **H. Jørgensen**, None; **D. Demirovic**, None; **L. Deibjerg**, None; **F. Andersen**, None; **A. Hedemann-Andersen**, None; **B. B. Løgstrup**, None; **S. Rattan**, None.

1442

The 2013 ACC/AHA Cardiovascular Risk Prediction Model and Coronary Atherosclerosis in Patients with Rheumatoid Arthritis. Vivian K. Kawai[1], Cecilia P. Chung[1], Joseph F. Solus[1], Annette Oeser[1], Paolo Raggi[2] and C. Michael Stein[1]. [1]Vanderbilt University, Nashville, TN, [2]University of Alberta, Edmonton, AB.

Background/Purpose: Patients with rheumatoid arthritis (RA) have increased risk of atherosclerotic cardiovascular (CV) disease that is underestimated by the Framingham risk score (FRS). We hypothesized that the new 2013 ACC/AHA 10-year risk score could better identify patients with RA with high coronary artery calcification (CAC) scores, and consequently elevated CV risk, compared to the FRS and the Reynolds risk score (RRS).

Methods: We calculated the 10-year FRS, RRS and ACC/AHA risk score in 98 RA patients aged between 40 and 75 years who would be eligible for risk stratification using the ACC/AHA score and assigned them to either elevated or low risk categories. We identified patients categorized as having elevated CV risk based on the presence of high CAC scores using the thresholds defined by Goff et al. (≥ 300 Agatston units or ≥ 75th percentile) and compared the ability of the three risk scores to correctly categorize these patients with high CAC as having elevated cardiovascular risk. We used receiver operator characteristic (ROC) curves (or c-statistics) to compare the ability of the three risk scores to identify patients with high CAC.

Results: All three risk scores were higher in patients with high CAC than those without (all P values <0.05). The FRS (32% vs. 16%, P=0.055) and RRS (32% vs. 13%, P=0.018) both assigned more patients with high CAC than low CAC into the elevated risk category. The ACC/AHA risk score assigned more patients with high CAC into the elevated risk category (41%) and also assigned 28% of patients without high CAC into the elevated risk category so that the proportion patients with and without high CAC assigned to the elevated CV risk category was not significantly different (P=0.190). The c-statistics (95% C.I.) for the FRS, RRS and ACC/AHA risk score predicting the presence of high CAC were 0.65 (0.53–0.76), 0.66 (0.55–0.77), and 0.65 (0.53–0.76), respectively.

Table: Cardiovascular risk estimates in patients with rheumatoid arthritis with and without high coronary artery calcium

10-year cardiovascular risk scores		CAC<300 agatston units or CAC <75th percentile (n=64)	CAC≥300 Agatston units or CAC≥75th percentile (n=34)	P values
Framingham risk score	Low risk category	54 (84)	23 (68)	0.055
	Elevated risk category	10 (16)	11 (32)	
Reynolds risk score	Low risk category	56 (87)	23 (68)	0.018
	Elevated risk category	8 (13)	11 (32)	
ACC/AHA risk score	Low risk category	46 (72)	20 (59)	0.190
	Elevated risk category	18 (28)	14 (41)	

Conclusion: The new ACC/AHA 10-year risk score, despite classifying more patients with high CAC into the elevated risk category than the FRS and RRS, assigned almost 60% of patients with elevated risk as determined by a high CAC score into the low CV risk category. Modifications of standard CV risk prediction models used in the general population may not improve risk prediction in patients with RA.

Disclosure: V. K. Kawai, NIH, 2; **C. P. Chung**, NIH, 2; **J. F. Solus**, None; **A. Oeser**, None; **P. Raggi**, None; **C. M. Stein**, NIH, 2.

1443

Increased Occurence of Carotid and Femoral Plaques, but Not Increased Arterial Stiffness of Hypertrophy, in Classical Risk Factor-Free Patients with Rheumatoid Arthritis. Aikaterini I. Arida[1], Evaggelia Zampeli[1], George Konstantonis[1], Kalliopi Fragkiadaki[1], George D. Kitas[2], Athanasios D. Protogerou[1] and Petros P. Sfikakis[1]. [1]First Department of Propedeutic Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece, [2]The Dudley Group of Hospitals NHS Foundation Trust, Dudley, and Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom.

Background/Purpose: Several lines of evidence indicate that classical cardiovascular disease (CVD) risk factors, such as arterial hypertension, diabetes mellitus, smoking and dyslipidemia, are significantly increased in rheumatoid arthritis (RA), which, in turn, is associated with 1.5- to 2-fold increased prevalence of CVD. The exact contribution of the RA disease *per se* in this association, in terms of systemic inflammation, drugs, disease-related genetics and/or other factors, remains under study. We aimed to test the hypothesis that RA *per se* in patients free of classical CVD risk factors is associated with accelerated subclinical arterial disease.

Methods: Consecutive patients with RA (n=267) were comprehensively studied by ultrasound for, a) subclinical atheromatosis, assessed by the presence of carotid artery and/or femoral artery plaques, b) stiffness of common carotid artery and aortic stiffness by pulse wave velocity, and, c) hypertrophy of common carotid artery assessed by intimal-medial thickness and cross sectional area (calculated adjacent to plaques, when plaques were present). Of all patients, we identified those who were CVD-free, non-smokers, without hypertension, diabetes and dyslipidemia (only 18%). Of them, 41 (aged 49+13 years, 36 women, median disease duration of 7 years, range 3–19 years) were compared to 41 healthy non-smokers, without hypertension, diabetes and dyslipidemia who were effectively matched 1:1 for age and gender and studied in parallel.

Results: Patients had more than 2-fold higher prevalence of carotid and/or femoral atheromatic plaques than healthy controls (29% vs. 12%, p=0.05). All patients with plaques had an acceptable functional status of class I or II. Moreover, body mass index, as well as family history of CVD, was similar between patients with plaques and their matched controls. Multi-arterial subclinical atheromatosis, defined as plaque presence at more than 1 of 8 arterial sites evaluated, was by far more prevalent in RA patients than controls (22% vs. 2%, p=0.007). Notably, plaque burden in the subgroup of RA patients with less than 5 years of disease duration was comparable to their matched controls. Either arterial stiffness or hypertrophy, however, was not significantly increased compared to controls, even in patients with long-standing RA.

Conclusion: These data directly show, independently of the classical CVD risk factors, an acceleration of atheromatosis in RA, but not of arterial stiffness or hypertrophy. This phenomenon is not evidenced during the first 5 years after disease onset and seems to be chronic inflammation-dependent. Also, the dissociation between atheromatosis and arterial stiffness in this selected population suggests a minimal, if any, effect of chronic inflammation in arterial remodeling and arterial stiffness. Studies testing whether early and effective RA clinical disease control prevents the development of arterial damage in the long-term are ongoing.

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ACR/ARHP Poster Session B
Clinical Practice/Patient Care (ARHP)
Monday, November 17, 2014, 8:30 AM–4:00 PM

1444

The Vocational Experiences of Young People with Juvenile Idiopathic Arthritis and the Role of the Multidisciplinary Team Supporting Positive Employment Outcomes. Helen Hanson[1], Ruth Hart[2], Alison Jordan[3], Rachel Tattersall[4], Ben Thompson[1] and Helen E. Foster[2]. [1]Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, [2]Newcastle University, Newcastle upon Tyne, United Kingdom, [3]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom, [4]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom.

Background/Purpose: Recent decades have seen marked changes in the management of juvenile idiopathic arthritis (JIA), with improved clinical outcomes for many patients. However, unemployment rates for adults with JIA remain high compared to peers, highlighting the need to address vocational issues as an integral part of transitional care.

The aims of this study were to explore i) experiences and expectations of employment amongst young people with JIA ii) the actual and potential role of the multidisciplinary team in promoting positive employment outcomes.

Methods: We interviewed 13 young people with JIA (median age 22y, range 16–31y) and nine health professionals from three tertiary rheumatology services. A focus group for young people with JIA was held in each of the three centres. Qualitative techniques were used to analyse the transcripts.

Results: Three related themes associated with vocational experience emerged from our data analysis, i) JIA has made education and employment more challenging for all the young people in our sample, ii) young people often disclose only minimal information about their condition to educators or employers, iii) all the young people have experienced emotional challenges associated with having JIA and learning to manage these emotions would appear to contribute to vocational success. Young people from one recruiting centre have met peers with JIA at social events and many associate this with gains in both practical coping skills and emotional wellbeing.

Data relating to vocational expectations suggests two important issues. Firstly, many young people have low expectations of employers' willingness to support employees with health conditions and secondly, few are well informed about their legal rights.

Each tertiary rheumatology service includes nurses, doctors and occupational therapists, while access to other professionals varies. We identified three themes concerning perceived barriers to maintaining and improving vocational support, namely i) staff need appropriate knowledge and skills to address vocational issues (currently training or team discussions about vocation appear to be rare), ii) all staff find it challenging to provide holistic care within short appointments, with some describing a lack of attention to vocational issues, iii) dialogue with educators or employers can improve support for struggling individuals but happens less for young people compared to under 16s.

Conclusion: Young people with JIA have a significant need for vocational support from health professionals. Specifically, our work suggests that these young people would benefit from accessible information on: talking about arthritis; anti-discrimination legislation; and local support services. Many would value emotional support, which may include opportunities to meet peers.

The generic nature of vocational challenge lends itself to cross-specialty approaches to addressing training needs and facilitating dialogue with educators and employers. Further work is indicated to improve information resources, explore the needs of educators and employers and develop appropriate and cost-effective interventions.

Disclosure: H. Hanson, Pfizer Inc, 2; **R. Hart**, None; **A. Jordan**, None; **R. Tattersall**, Pfizer Inc, 5; **B. Thompson**, None; **H. E. Foster**, None.

1445

Improving Osteoarthritis Outcomes Utilizing a Multidisciplinary Model of Care; Experience in a Diverse Multicultural Urban Teaching Hospital. Caroline Jones[1], Laurence A. Rubin[2], Angelo Papachristos[3], Elaine Harniman[3] and Jann Patrick Ong[4]. [1]St. Michael's Hospital, Aurora, ON, [2]St. Michael Hospital, Toronto, ON, [3]St Michael's Hospital, Toronto, ON, [4]University of Toronto, Toronto, ON.

Background/Purpose: In 2008, a multidisciplinary osteoarthritis (MOA) clinic was established at St. Michael's Hospital (SMH), a tertiary care academic teaching facility, serving a diverse social, economic and cultural urban population in Toronto. The team (Rheumatologist, Advanced Practice Physiotherapists) designs a comprehensive treatment plan which consists of one or more of the following:

- patient education
- weight loss strategies which may include a referral to a dietition and possible bariatric surgery
- an exercise program
- prescription for an unloader brace, orthotics or wedges
- intrarticular corticosteroid or hyaluronic acid injection
- discussion about referral for joint replacement surgery

All patients complete two questionnaires at each visit:

1) Multi-Dimensional Health Assessment Questionnaire (MDHAQ).

2) Western Ontario and McMaster Universities Arthritis Index (WOMAC).

The purpose of this continuous qualitative improvement project is to evaluate the outcomes of patients who attend the OA clinic. The research question is: How much change occurs in a patient's functional scores from the initial assessment to the three month follow up visit after a treatment intervention has occurred?

Methods: This study is a retrospective observational cohort. Patients with knee, hip, or other joint OA visiting the OA clinic from January 2009 to Dec 2011 were included in the study. Patients visiting for other reasons such as rheumatoid arthritis or bursitis were not included in analysis. A chart review of patients with baseline information and 3-month follow-up (+/− 3 weeks) were used for analysis, which includes WOMAC and MDHAQ questionnaires for both visits. Subsequent visits are on "as needed" basis, although data from those visits are still recorded and used in some of the analysis. Unfortunately, given the nature of the population and the study, no control population was available.

Results:

- Most patients attended the clinic for symptomatic knee OA.
- Approximately 1/3 of the patients were recommended for surgery consult.

There was baseline and follow-up data that was analyzed for patients with knee OA (group 1) and a subset (group 2) with moderate to severe baseline pain.

Group 1: statistically significant improvements in function (WOMAC $p = 0.0061$) and fatigue (MDHAQ $p = 0.0372$) but not pain (WOMAC $p = 0.656$ and MDHAQ $p = 0.3137$) were observed.

Group 2: the results were similar, with the exception of the change in pain, which was statistically significant as measured by the MDHAQ ($p = 0.0004$) but not the WOMAC ($p = 0.5059$).

A change in WOMAC stiffness was higher for group 2 ($p = 0.07$), but the change in duration of stiffness was similar in both groups ($p = 0.0513$ and $p = 0.0608$).

Other trends observed were:

(i) Patients with a knee effusion tended to respond better to cortisone injections,
(ii) Patients less than 40 years old respond better to treatment
(iii) Patients with neutral knee alignment did better.

Conclusion: These results reflect actual clinical situations, and validate a multidisciplinary approach to OA management. The results support a multidisciplinary approach utilizing a coordinated assessment by both rheumatologist and advanced physiotherapy practitioners in a one stop shop model to substantially improve overall OA management.

Disclosure: C. Jones, None; **L. A. Rubin**, None; **A. Papachristos**, None; **E. Harniman**, None; **J. P. Ong**, None.

1446

Utility of Ultrasound in the Nuffield Orthopaedic Centre Emergency Rheumatology Clinic: Survey of Clinical Effectiveness. Kuljeet Bhamra, Catherine Swales, Matthew Seymour, Catherine McClinton and Peter C. Tayrlor. University of Oxford, Oxford, United Kingdom.

Background/Purpose: The aim of the survey was to evaluate the impact of clinic-based musculoskeletal ultrasonography (MSUS) on diagnosis and management of cases seen in the Nuffield Orthopaedic Hospital emergency rheumatology clinic.

Methods: MSUS was performed on a selected population of cases, which included new patients with diagnostic uncertainty and challenging follow-up patients requiring assessment of disease activity/severity. The service was provided by a consultant rheumatologist trained and experienced in MSUS; the scans were performed during the emergency clinic appointment. Clinician evaluating patient requested MSUS for confirmation of diagnosis or in cases of diagnostic uncertainty. All scans were performed on a GE Logiq E9 using a linear transducer, recording grey-scale and power Doppler findings. Data from all patients who had undergone scans during October 2011- November 2012 was reviewed for demographics, suspected or existing diagnosis of inflammatory arthritis, clinical presentation, clinical findings and management outcome as a direct result of MSUS.

Results: There were 62 patients studied (25 men, 38 women); their mean age was 57.17 years (range 30–88). A set joint scan was performed in all patients consisting of 10 MCP and PIP joints, radiocarpal joint and ulnar styloid.

The new patient group consisted of 34 patients; all had been referred for inflammatory arthritis. Of these, at ultrasound 17 (50%) had osteophytes, 16 (47%) had grey-scale synovitis, with 15 (44%) power Doppler. In one, (3%) no abnormality was detected. This resulted in change in final diagnosis in 22 (65%) new patients and a confirmed diagnosis of active inflammatory arthritis in 12 (35%) patients. Overall, management of new patients directly influenced by ultrasound scan resulted in the discharge of 50% of patients. Of the 17/34 new patients who had a confirmed diagnosis of inflammatory arthritis, 14 (82%) started combination disease modifying anti rheumatic agents at first visit.

There were 28 patients in the follow-up group who were referred for diagnostic uncertainty. Rheumatoid arthritis, psoriatic arthritis, connective tissue disease accounted for the majority, with 17 (61%), 5 (18%), 4 (14%) and 3 (11%) patients, respectively. The impact of MSUS on the follow-up group influenced change in treatment in 13/28 (47%) of patients. Specifically, all RA patients underwent scanning for disease assessment. In 15/17 (88%) patients, treatment escalation was directly influenced by MSUS findings; co-existing pathology was detected in 3/17 (18%) which included findings of gout and osteoarthritis. Ultrasound remission was identified in 5/17 (30%) with 2/17 (12%) were started on neuromodulators for pain management.

Conclusion: This data shows the positive impact of MSUS in the rheumatology clinic, specifically highlighting multiple benefits in daily practice of reduced visits, discharge at first encounter, immediate management decisions. Our survey shows the importance of integrating MSUS service in a one-stop clinic.

Disclosure: K. Bhamra, None; **C. Swales**, None; **M. Seymour**, None; **C. McClinton**, None; **P. C. Taylor**, None.

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Implementing American College of Rheumatology (ACR) Quality Indicators for Rheumatoid Arthritis (RA) in the United Arab Emirates (UAE). Hannah Beermann, Joyce Daoud and Humeira Badrsha. Dr. Humeira Badsha Medical Centre, Dubai, United Arab Emirates.

Background/Purpose: Prior to the establishment of RA standards set by the ACR, a widespread discrepancy was formed between practices, which were treating patients with RA with different levels of care. Thus, in order to regulate quality, the ACR implemented the following quality indicators worldwide: tuberculosis screening prior to biological disease modifying drugs (DMARDs), periodic assessment of disease activity, functional status assessment, assessment and classification of disease prognosis, glucocorticoid management, treatment with DMARDs, and follow up treatment with DMARDs.

The aim of our study was to audit our management of RA patients, and assess whether the before mentioned quality indicators were being implemented in our practice and whether this was reflected in better RA disease control.

Methods: Data was collected on 182 consecutive RA patients in the UAE meeting ACR criteria for RA, and measuring the care we provide with the expected standard of quality outlined.

Results: 100% of patients received a tuberculosis screening prior to being prescribed biological DMARDS (16% of the 181 total); TB tests were not applicable to patients receiving any other type of treatment for RA. 98% of patients had a periodic assessment of disease activity (DAS Score) at least once over a twelve-month span. All 100% of patients were subject to a functional status assessment by HAQ at least once during their treatment. However, no patients were provided with a disease prognosis, or prediction of how their disease may progress positively or negatively. Similarly, no patients were provided with documentation of a glucocorticoid management plan correlating with the improvement or change their disease activity (however, no patients were prescribed 10 mg of Prednisone daily for any period of time). 100% of patients were being treated with disease modifying treatments (DMARD), unless contraindicated, and 100% of patients were followed up with as treatment progressed to ensure the medication continued to be effective, and dosage adjustments made based on DAS Score. 53% of our patients were in low disease activity as defined as a DAS28 score < 3.2.

Conclusion: The majority (53%) of patients in our practice had achieved RA disease activity DAS 28 targets of <3.2, which may be a reflection that the practice is strong in upholding most of the tenets of quality with almost 100% compliance with six of the seven ACR quality indicators. There are still areas for improvement such as documenting a yearly disease prognosis and ensuring a written glucocorticoid management plan, assuming the patient is being treated with a glucocorticoid greater than 10 mg of prednisolone daily. We feel that there is correlation between achieving treatment targets and

adherence to ACR quality guidelines but this will need to be studied in larger cohorts in the region.

Disclosure: H. Beermann, None; **J. Daoud**, None; **H. Badsha**, None.

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A Questionnaire Assessment of Knowledge about Methotrexate of Patients with Rheumatoid Arthritis. Françoise Fayet[1], Carine Savel[1], Malory Rodere[2], Bruno Pereira[3], Dihya Abdi[1], Marion Coudercr Sr. [4], Sylvain Mathieu[5], Anne Tournadre[6], Sandrine Malochet-Guinamand[6], Martin Soubrier[7] and Jean Jacques Dubost[8].[1]CHU Gabriel-Montpied, Clermont-ferrand, France, [2]CHU Gabriel-Montpied, Clermont-Ferrand, France, [3]Clinical research department, Clermont-Ferrand, France, [4]Chu G.Montpied, Clermont Ferrand, France, [5]Hopital Gabriel Montpied, Clermont Ferrand, France, [6]Rheumatology CHU Gabriel Montpied, Clermont-Ferrand, France, [7]COMEDRA trial group, Paris, France, [8]CHU G.-Montpied, Clermont-Ferrand, France.

Background/Purpose: Methotrexate is the reference treatment for rheumatoid arthritis (RA). It has potentially serious side effects which can be prevented by an improvement in patient's information.

The aim is to assess the knowledge of patients suffering from RA about their methotrexate treatment with a questionnaire.

Methods: A questionnaire containing 21 closed questions and 2 situation studies about the medication (mechanism of action, method of administration, therapeutic interactions, side effects, monitoring and implications on lifestyle) was given to all RA patients treated with methotrexate who consulted between March and September 2013 in the rheumatology department of Clermont-Ferrand Hospital.

Results: 183 patients were recruited, including 143 women (79%), with a mean age of 60 years +/−13.5 and a median RA duration of 12 years (IQR : 7–20). Methotrexate has been initiated for a mean of 8 years (IQR: 5–13). Methotrexate was identified as a DMARD by 78% of participants. The weekly administration method was well known (97%) and 67% said that the folic acid was to reduce the toxicity of treatment. Only 21% knew that trimethoprim was contraindicated. Half of the patients knew about the haematological risks and 36% about the risks of hypersensitivity pneumonia. The frequency of laboratory assessments was known (80%) but 54% thought that the only purpose of these tests was to assess the RA activity. Only 13% of men (n=38) knew that contraception was essential compared to 90% of women of child-bearing age (n=20), 75% reported that alcohol consumption should be reduced. In multivariate analysis, a low knowledge score correlated significantly, with age and low educational status. Scores were independent of sex, duration of treatment or of the RA.

Conclusion: Patients' knowledge about methotrexate, particularly about the interaction with trimethoprim, risk of hypersensitive pneumonia and need for men to use a couple contraception should be increased by the treatment education programme instruments, especially in the elderly and the lower socio-educational status population.

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Combined Intra-Articular Corticosteroid and Exercise in Patients with Knee Osteoarthritis: A Randomised Trial. Marius Henriksen[1], Robin Christensen[1], Louise Klokker[1], Cecilie Bartholdy[1], Karen Ellegaard[1], Mikael Boesen[2], Robert Riis[1], Else Bartels[1] and Henning Bliddal[1]. [1]The Parker Institute, Copenhagen, Denmark, [2]Department of Radiology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, Frederiskberg, Denmark.

Background/Purpose: Combined non-pharmacological and pharmacological treatment is recommended as optimal management of knee osteoarthritis (OA). However, the two treatment approaches have mostly been investigated separately. We aimed to assess the efficacy of combined intra-articular corticosteroid injection and exercise compared to placebo injection and exercise in patients with knee OA.

Methods: This randomized, double blinded, placebo-controlled trial running over 26 weeks was designed as a superiority trial comparing the efficacy of a single intra-articular corticosteroid injection (1 mL of 40 mg/mL methylprednisolone dissolved in 4 mL 10 mg/mL Lidocaine) plus exercise, with a single placebo injection (1 mL isotonic saline mixed with 4 mL 10 mg/mL Lidocaine) plus exercise. Participants with clinical and radiographic knee OA were randomly allocated (1:1) to either corticosteroid (Steroid Group) or saline (Placebo Group) injection. Two weeks after injections, all participants started a 12 week supervised exercise program with 3 weekly sessions. Outcomes were assessed at baseline, week 2 (exercise start), week 14 (end of exercise), and week 26 (follow-up). The primary outcome was the mean change in KOOS pain subscale at week 14. Analyses were done on the intention-to-treat (ITT) population (all randomized participants). Missing data were replaced using multiple imputation. A repeated measures mixed model was used to analyze the primary outcome; week, treatment, and week x treatment were included as fixed effects, adjusting for the baseline value.

Results: A total of 263 patients were screened and 100 patients were randomized to receive either Steroid (n=50) or Placebo (n=50). Of these, 93 completed the week 14 assessment and 89 completed the 26 weeks trial. There were no group differences in the proportions completing. Mean age was 63.4 (SD 9.3) years, 61% were women. The mean exercise attendance rate was 79% (SD 15); no group difference. The mean (SD) KOOS pain score at randomization was 53.3 (11.4) and 55.2 (16.0) in the Steroid and Placebo groups, respectively. The mean (SEM) change in pain at week 14 was 13.6 (1.8) and 14.8 (1.8) in the Steroid and Placebo Groups, respectively, corresponding to a mean difference of 1.2 units (95% CI -3.8 to 6.2; P=0.64). These results were robust in sensitivity analyses using baseline observation carried-forward imputation and no imputation. There were no group differences at week 2, 14, and 26 in any of the 5 KOOS subscales and the 95% confidence intervals of the group differences did not exceed the suggested minimal clinical important difference of 8–10 KOOS points.

Conclusion: These results show comparable efficacy of intra-articular corticosteroid and placebo when combined with exercise for pain relief in knee OA.

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Spironolactone As a Novel DMARD in Rheumatoid Arthritis. Inderjeet Verma[1], Pawan Krishan[2] and Ashit Syngle[3]. [1]Punjabi University Patiala, India, Chandigarh, India, [2]Punjabi University Patiala, India, Patiala, India, [3]Healing Touch City Clinic, Fortis Multispeciality Hospital, Chandigarh, India.

Background/Purpose: Synthetic disease-modifying antirheumatic drugs (DMARDs) though effective have limitations often requiring use of expensive parenteral biologic DMARDs in Rheumatoid Arthritis (RA). Hence there is a need for safe, efficacious economical therapies for management of disease and its co-morbidities. Anticytokine therapy with Biologic DMARDs is efficacious but has limitations. Given the TNF inhibiting potential of spironolactone (SPIR)[1–2], We therefore investigated the anti-inflammatory effects of SPIR in RA patients in a randomized, placebo-controlled, open label study.

Methods: We organized a 24-week study on 70 patients (36 in SPIR and 34 in placebo arm) with active RA. They were randomized to oral SPIR (2 mg/kg/day) or placebo for 24 weeks as an adjunct to existing stable DMARD regimen. Therapy results were evaluated by ESR, CRP, Disease Activity Score in 28 joints (DAS28), simple disease activity index (SDAI), ACR response criteria and pro-inflammatory cytokines (TNF-α, IL-6 and IL-1). Flow mediated dilatation (FMD) was assessed by AngioDefender™ and carotid intima media thickness (CIMT) of brachial artery. Endothelial progenitor cells (EPCs) ($CD34^+/CD133^+$) were quantified by flow cytometry. Quality of life was assessed using HAQ-DI.

Results: At 24 weeks; ESR, CRP, DAS-28 and SDAI significantly ($p<0{\cdot}05$) improved in SPIR group compared with placebo (Table 1). At 24 weeks, more patients in the 2 mg/kg/day SPIR group than in the placebo group had an ACR20 response 47.5% (n=16) versus 25% (n=8). ACR50 response rates were 23% (n=8) and 6.2 % (n=2), respectively, in the SPIR and placebo groups, and ACR70 rates were 11.7% (n=4) and 2.9% (n=1). At 24weeks, TNF-α, IL-6 and IL-1 improved significantly in SPIR compared with placebo (Table 1). With SPIR treatment the mean value of the FMD improved from 6.5 to 8.9 ($p<0{\cdot}001$) and with placebo from 7.56 to 7.7 ($p=0{\cdot}12$). SPIR significantly improved EPC population (p=0.008) compared with placebo (p=0.305) after treatment. After 24 weeks, CIMT was significantly improved in SPIR (p=0.03) compared with placebo (p=0.30) (Table 1). At 24 weeks, HAQ disability index score was significantly improved in SPIR compared to placebo group (table 1). Two patients in the SPIR and 1

patient experienced adverse events or discontinued treatment because of adverse events.

Conclusion: These results suggest that SPIR is a powerful anti-inflammatory agent that significantly reduces inflammatory biomarkers and disease severity and improves physical function in RA. It also improves endothelial dysfunction, EPC population and CIMT indicating its beneficial effects on the enhanced cardiovascular risk of RA. SPIR could therefore possibly be used as an adjunct therapy with DMARDs in patients with RA.

Disclosure: I. Verma, None; **P. Krishan**, None; **A. Syngle**, None.

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Use of Analgesics in Patients with Knee and/or Hip Osteoarthritis: Results from the Amsterdam Osteoarthritis Cohort. Joyce van Tunen[1], Marike van der Leeden[1], Martin van der Esch[1], Leo D. Roorda[1], Willem F. Lems[2] and Joost Dekker[3]. [1]Amsterdam Rehabilitation Research Center | Reade, Amsterdam, the Netherlands, Amsterdam, Netherlands, [2]Jan van Breemen Research Institute | Reade, Amsterdam, the Netherlands, Amsterdam, Netherlands, [3]VU University Medical Center, Amsterdam, Netherlands.

Background/Purpose: Use of analgesics is recommended by international guidelines to reduce pain complaints related to knee and/or hip osteoarthritis. Underuse of analgesics might be substantial in patients with knee and/or hip osteoarthritis due to poor implementation of guidelines. Factors associated with analgesic use are not assessed systematically, although knowledge of the use of analgesics will improve the prescription of analgesics. Therefore, the first aim of this study was to describe the use of analgesics in patients with knee and/or hip osteoarthritis, referred to an outpatient center for rehabilitation and rheumatology in the Netherlands. The second aim was to determine factors that are associated with analgesic use in this population.

Methods: Data from 497 patients with knee and/or hip osteoarthritis according to clinical ACR criteria from the Amsterdam Osteoarthritis cohort were used. Self-reported analgesic use was measured. Independent factors included predisposing (e.g. demographic and social characteristics), enabling (the ability to use care resources, e.g. referring physician) and disease-related (the most immediate cause for analgesic use) factors. Logistic regression analysis was performed to analyze the association between analgesic use and the independent factors.

Results: The mean±SD age of patients was 61,6±9,0 year and 72% were woman. Total scores on pain, stiffness and activity limitations on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) were 43,5±18,1. Analgesic use was reported in 53% of the patients; 37% used acetaminophen, 21% used non-selective non-steroidal anti-inflammatory drugs (NSAIDs), 3% used coxibs and 8% used opioids. Both monotherapy or combinations of analgesics were used. Univariate logistic regression analysis showed that high scores on pain, stiffness and activity limitations on the WOMAC were associated with analgesic use. In addition, gender (women), being overweight or obese, having bilateral knee symptoms, higher levels of psychological distress and a higher amount of comorbidities were associated with analgesic use. Higher levels of psychological distress were associated with the use of acetaminophen. Preliminary results of multivariate logistic regression analysis showed that a higher score on the subscale pain of the WOMAC was associated with analgesic use.

Conclusion: Half of patients with knee and/or hip osteoarthritis referred to an outpatient center for rehabilitation and rheumatology used analgesics. More pain was associated with use of analgesics, suggesting that the analgesics used are not sufficiently effective in reducing symptoms. This may indicate that more effective strategies of pain management need to be implemented.

Disclosure: J. van Tunen, None; **M. van der Leeden**, None; **M. van der Esch**, None; **L. D. Roorda**, None; **W. F. Lems**, None; **J. Dekker**, None.

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Timing of Decisions to Adjust Disease Modifying Anti-Rheumatic Drug (DMARD) Therapy for Rheumatoid Arthritis (RA) Patients with Active Disease in a Usual Practice Setting. Yomei Shaw[1], Chung-Chou H. Chang[2], Marc C. Levesque[2], Julie M. Donohue[1], Kaleb Michaud[3] and Mark S. Roberts[1]. [1]University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, [2]University of Pittsburgh Department of Medicine, Pittsburgh, PA, [3]National Data Bank for Rheumatic Diseases, Wichita, KS.

Background/Purpose: Current guidelines recommend that rheumatoid arthritis (RA) patients with poor response to their current regimen of disease modifying anti-rheumatic drugs (DMARDs) have therapy adjusted until reaching low disease activity or remission. We examined factors associated with timing of decisions to adjust DMARD therapy for RA patients with active disease and how the timing of decisions impacts resolution of active disease.

Methods: Data came from the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Research (RACER) registry, which captures subjects' disease activity status (DAS28-CRP) and medications at clinic visits.

We conducted survival analyses on time to DMARD therapy adjustment and time to resolution of active disease for RACER subjects with active disease. A Cox proportional hazards model was used to assess the impact of covariates on the survival times. For both analyses, followup begins when the subject is first known to have active disease (DAS28-CRP>3.2) and ends with the event of interest (DMARD therapy adjustment or resolution of active disease). For the analysis of time to therapy adjustment, we excluded patients who adjusted therapy at t=0 and those who exited active disease before adjusting therapy, and the model included covariates for age, gender, African-American race, comorbidities, duration of RA, and current use of a biologic therapy. For the analysis of time to resolution of active disease, the model included the same covariates plus an indicator for time to therapy adjustment.

Results: We identified 562 subjects with active disease at a first timepoint and a followup DAS28-CRP measurement.

The analysis for time to therapy adjustment included 177 subjects (117 therapy augmentations observed). 364 subjects were excluded because they adjusted DMARD therapy at t=0 (n=196) or because they exited active disease status before adjusting therapy (n=162). The median time to therapy adjustment was 203 days. Age over 75 and longer duration of RA were significantly associated with longer times to therapy adjustment.

The analysis for time to resolution of active disease included 530 subjects (383 achieved DAS28-CRP ≤ 3.2). The median time to resolution of active disease was 257 days. African-American race and duration of RA >1 year were associated with longer times to resolution of active disease. (See **Table 1**)

Conclusion: Among those with persistent active disease (n=394), 60% adjusted DMARD therapy within 90 days; however 50% of subjects took longer than 257 days to achieve DAS28-CRP ≤ 3.2. We found that age ≥ 75 and longer duration of RA were associated with longer times to DMARD therapy adjustment, while African-American race and duration of RA > 1 year were associated with poorer disease outcomes. Future studies should further examine how these factors affect treatment choices as well as long term health outcomes.

Table 1 Rheumatoid arthritis patient characteristics associated with time to therapy adjustment/resolution of active disease

Parameter	Cox regression 1 Outcome: Time to DMARD therapy adjustment[+] N=177, 117 events, 60 censored[#] (33.9% censored)		Cox regression 2 Outcome: Time to resolution of active disease N=530, 383 events, 147 censored[#] (27.7% censored)	
	Hazard ratio	P-value	Hazard ratio	P-value
Age at baseline ≥ 75	0.480	0.092	1.200	0.276
Male	0.938	0.785	1.193	0.162
Charlson group 2:1*	1.200	0.408	1.024	0.837
Charlson group 3:1*	0.788	0.447	0.913	0.592
African-American	1.000	0.999	0.625	0.011
Using biologic at baseline	0.830	0.341	0.992	0.938
Disease duration at baseline	0.981	0.014	–	–
Disease duration <1 yr at baseline	–	–	1.574	0.026
Adjusted therapy in ≤90 days	–	–	1.057	0.597

[+]DMARD therapy adjustment is defined as adding, switching or increasing dose of biologic or nonbiologic DMARD therapies.
[#]Subjects who had not achieved the outcome (adjusted DMARD therapy or exited active disease) by the end of followup were marked as censored.
*Subjects were classified according to Deyo-Charlson comorbidity index (group 1: index of 1; group 2: index of 2–3; group 3: index ≥ 4).

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Gastrointestinal Risk Factors and Treatment Patterns of Rheumatoid Arthritis Versus Osteoarthritis Patients in Korea. Eun Young Lee[1], Sang Heon Lee[2], Hyo-Jin Kim[3] and Korea RA/OA OR Grroup. [1]Seoul National University College of Medicine, Seoul, South Korea, [2]Konkuk University Hospital, Seoul, South Korea, [3]Pfizer Tower, 1–11, Hoehyun-Dong 3-Ga, Jung-Gu, Seoul, South Korea.

Background/Purpose: Little is known about local data of the gastrointestinal risk faocts (GI) and treatment pattenrs in rheumatoid arthritis (RA) and osteoarthritis (OA) patients. This study aimed to investigate and compare the GI risk factors and treatment patterns of RA and OA patients in real clinical practice of Korea.

Methods: This was a nationwide, cross-sectional and observational study of patients taking non-steroidal anti-inflammatory drugs (NSAID, either non-selective or selective COX-2 inhibitor (COX2i)) from 20 hospitals between December 2012 and September 2013. Total 1,896 patients who were ≥20 years old (RA:981 OA:915) and were taking NSAID at least 1 month were enrolled. Data were collected through medical chart review and patients survey. The GI risk factors included NSAID duration (≥3 months), high-dose of NSIAD use, drinking, smoking, comorbid disease, aspirin use, anticoagulant(warfarin) use, steroid use, Helicobacter pylori infection, experience of GI event (i.e. GI bleeding or ulcer). The treatment patterns were identified as non-selective NSAID (ns-NSAID) or COX2i with/without gastroprotective agents respectively.

Results: In RA, proportion of patients taking NSAID≥3 months, smoker and steroid users were higher than in OA patients ($p<.0001$). In OA, proportion of patients who have comorbid disease and take aspirin were higher than in RA patients ($p<.0001$). The rest of the GI risk factors were present as a similar proportion in both groups. The percentage of treatment with COX2i (RA:54.3% vs OA:44.2%, $p<.001$) and gastroprotective agents (RA:83.0% vs OA:78.3%, $p=.009$) in RA patients was higher than that in OA patients. In older aged patients (age≥60) in both groups, there was tendency to get more treatment of COX2i (RA: 60.9%, OA:50.2%) compared to ns-NSAID. Interestingly, as patients get more numbers of GI risk factors, there seemed to get more proportions of ns-NSAIDs users in both RA and OA patients.

Conclusion: The proportion of GI risk factors found in OA patients was comparable to that in RA patients. There was a tendency to show preferential ns-NSAID treatment pattern rather than COX2i especially in the presence of multiple GI risk factors in arthritis patients.

Disclosure: E. Y. Lee, None; **S. H. Lee**, None; **H. J. Kim**, None.

ACR/ARHP Poster Session B
Rheumatoid Arthritis - Human Etiology and Pathogenesis
Monday, November 17, 2014, 8:30 AM–4:00 PM

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Quantitative and Qualitative Tracking of Expanded CD4$^+$ T Cell Clones in Rheumatoid Arthritis Patients. Kazuyoshi Ishigaki[1], Hirofumi Shoda[1], Yuta Kochi[2], Tetsurou Yasui[1], Yuho Kadono[1], Sakae Tanaka[1], Keishi Fujio[1] and Kazuhiko Yamamoto[1]. [1]The University of Tokyo, Tokyo, Japan, [2]RIKEN, Yokohama, Japan.

Background/Purpose: The purpose of this study is to elucidate the characteristics of expanded CD4$^+$ T cell clones (ECs) in peripheral blood and synovium of rheumatoid arthritis (RA) patients by T cell receptor (TCR) repertoire and single cell transcriptome analysis.

Methods: We obtained peripheral blood from 5 RA patients and 5 control subjects. We performed TCR repertoire analysis by combination of single cell and next-generation sequencer (NGS) in CD4$^+$ T cells. We also performed single cell RNA-Seq and real time PCR analysis of ECs and non-expanded clones (NECs). Similarly, CD4$^+$ T cells from synovium were analyzed in 1 patient.

Results: We detected significantly higher frequency of ECs in peripheral blood of 4 RA patients compared with controls both in naïve and memory subset of CD4$^+$ T cells. Within memory CD4$^+$ T cells of peripheral blood, non-Th1/Th17/Tfh subset (negative for CXCR3, CCR6 and CXCR5) contained majority of expanded clones in PBMC of 3 RA patients and synovium-infiltrating clones in 1 RA patient. Gene expression analysis of the mostly expanded CD4$^+$ T cell clones in synovium of 1 RA patient and peripheral blood of 2 RA patients revealed up-regulation of GZMB, TBX21 and CD5 and down-regulation of CD28 compared with NECs. The tracking of gene expression profile of one unique EC in peripheral blood showed down-regulation of CXCR4 and CCR5 compared with that of the identical clone in synovium of the same patient.

Conclusion: ECs were more frequently observed in non-Th1/Th17/Tfh subset in peripheral blood and had gene expression profiles consistent with senescent CD4$^+$ T cells in both of peripheral blood and synovium. Given that there are no reliable markers of clonal expansion, single cell transcriptome analysis is the only method to investigate gene expression profiles of expanded clones. Combined with the robustness of NGS TCR repertoire analysis, our approach should be a rational strategy to characterize ECs and might be able to identify pathogenic clones in RA.

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Ex Vivo-Expanded, but Not in Vitro-Induced, Human Regulatory T Cells Are Suitable for Cell Therapy in Rheumatological Autoimmune Diseases Thanks to Stable FOXP3 Demethylation. Maura Rossetti[1], Roberto Spreafico[1], Maryam Moshref[2], Jorg van Loosdregt[3] and Salvatore Albani[1]. [1]Singapore Health Services Pte Ltd, Duke-NUS Graduate Medical School, Translational Research Unit, Sanford-Burnham Medical Research Institute, Singapore, Singapore, [2]Translational Research Unit, Sanford-Burnham Medical Research Institute, La Jolla, CA, [3]Translational Research Unit, Sanford-Burnham Medical Research Institute, San Diego, CA.

Background/Purpose: Treg cell therapy is a promising approach for transplant rejection and severe autoimmunity. Unfortunately, sufficient Treg numbers can be obtained only upon *in vitro*culture. Functional stability of human expanded (e)Treg and induced (i)Tregs has not been thoroughly addressed for all proposed protocols, hindering clinical translation. We undertook a systematic comparison of eTreg and iTregs to recommend the most suitable protocol for clinical implementation, and then tested its effectiveness and feasibility in autoimmune rheumatological settings with cells from rheumatoid arthritis (RA) patients.

Methods: eTregs were expanded with rapamycin (rapa), while iTregs were induced from naive T cells in the presence of TGF-β with either all-trans retinoic acid (ATRA) or rapa. *FOXP3* expression and demethylation, regulatory molecular signature and suppressive function were evaluated after a first round of differentiation and a secondary restimulation deprived of differentiation factors.

Results: Regardless of the protocol, iTregs acquired suppressive functions and FOXP3 expression, but lost them upon withdrawal of differentiation factors. In contrast, rapa eTregs maintained their regulatory properties and retained *FOXP3* upon restimulation. Demethylation, but not expression, of FOXP3 predicted Treg functional stability upon secondary TCR engagement in the absence of stabilizing factors. Importantly, Treg expansion with rapa from RA patients produced functionally stable and suppressive Tregs with yields comparable to healthy donors.

Conclusion: Our data indicate *ex vivo* Treg expansion with rapa as the protocol of choice for clinical application in rheumatological settings, with assessment of *FOXP3* demethylation as a necessary quality control step.

Disclosure: M. Rossetti, None; **R. Spreafico**, None; **M. Moshref**, None; **J. van Loosdregt**, None; **S. Albani**, None.

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Foxp3+ Regulatory T Cells in Peripheral Blood and Synovial Fluid of Patients with RA: A Comparative Phenotypic Analysis. Jun Saegusa[1], Fumichika Matsuki[1], Yasushi Miura[2], Goichi Kageyama[1], Seiji Kawano[1], Shunichi Kumagai[3] and Akio Morinobu[1]. [1]Kobe University Graduate School of Medicine, Kobe, Japan, [2]Kobe University Graduate School of Health Sciences, Kobe, Japan, [3]Shinko Hospital, Kobe, Japan.

Background/Purpose: Human regulatory T (Treg) cells play an indispensable role for the maintenance of self tolerance and immune homeostasis. Numerous studies dealt with Treg population in peripheral blood from RA patients (RAPB) with various conclusions regarding the frequency of circulating Treg cells. Most studies reported decreased or normal proportions of Treg cells, whereas some other groups reported an increase. On the other hand, the frequency of Treg cells in synovial fluid from RA patients (RASF) has been reported to be significantly higher than that in RAPB. In addition, Treg cells in RASF have been shown to have impaired suppressive function compared to those in RAPB. However, the cause of impaired function of Treg cells in RASF is unknown. A recent study has demonstrated that human Treg cells can be separated into three functionally unique subpopulations: CD45RA+Foxp3^{low} naïve Treg cells; CD45RA-Foxp3^{high} effector Treg cells, both of which have suppressive functions, and non-suppressive cytokine-secreting CD45RA-Foxp3^{low}non-Treg cells. The purpose of this study is to determine the characteristics of Foxp3+ Treg cells in RAPB and RASF.

Methods: Synovial fluid and peripheral blood CD4+ T cells from RA patients were classified into different subsets based on the expression of CD45RA, CCR7, CD27, and CD28. The frequency of IFN-γ-, IL-17-, or TNF-α-producing cells, and of Foxp3- or RANKL-positive cells in each subset was analyzed by eight-color flow cytometry. CD4+Foxp3+ cells were further classified into three functionally distinct subsets based on the expression of CD45RA and Foxp3.

Results: The frequency of CD45RA−Foxp3^{high} effector Treg cells was significantly decreased in the peripheral blood CD4+ T cells from RA patients, compared to those from healthy controls. As a result of the decrease of effector Treg cells, more than half of the Foxp3+ Treg cells (60.5 ± 9.5%) were the CD45RA−Foxp3^{low} non-Treg cells in RAPB. Furthermore, the frequency of CD45RA−Foxp3^{high} effector Treg cells in the CD27+CD28+ central memory (T_{CM}) subset was significantly decreased in RA patients. In addition, the percentage of CD45RA+Foxp3^{low} naïve Treg cells was negatively correlated with DAS28-CRP. In RASF, the frequency of Foxp3+ cells in the CD27+CD28+ effector memory (T_{EM}) population was significantly increased in RASF, compared to that in RAPB. Most of the Foxp3+ cells in RASF were CD45RA-Foxp3^{low} non-Treg cells (81.7 ± 10.4%), and the frequency of non-Treg cells in RASF was significantly increased compared to that in RAPB. Furthermore, the non-Treg cells in CD27+CD28+ T_{EM} subset was significantly increased in RASF (RASF; 5.9 ± 4.0%, RAPB; 0.7 ± 0.5%). Collectively, increase in Foxp3+ cells in RASF was due to increased number of non-Treg cells which exist in CD27+CD28+ T_{EM} subset.

Conclusion: The decreased proportion of CD45RA−Foxp3^{high} effector Treg cells and the increased proportion of CD45RA-Foxp3^{low} non-Treg cells may have critical roles in the pathogenesis of RA.

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Stem Cell Growth Factor Expression in Rheumatoid Arthritis. Youn Jung Woo[1], Young Ae Baik[1], Yong-Beom Park[1], Soo-Kon Lee[1], William H. Robinson[2] and Jason Jungsik Song[1]. [1]Yonsei University College of Medicine, Seoul, South Korea, [2]Stanford University School of Medicine, Stanford, CA.

Background/Purpose: Stem cell growth factor (SCGF) is a member of the C-type lectin superfamily, encoded by gene *CLEC11A*. SCGF is not related to stem cell factor (a ligand for the receptor-type protein-tyrosine kinase KIT) although the two proteins can be confused due to similarity in name. SCGF has been recently discovered as a growth factor of hematopoietic precursor cells in the bone marrow. However, the role of SCGF in inflammation has not been investigated. Because various growth factors such as M-CSF (macrophage colony stimulating factor) have been shown to be involved in RA pathogenesis by promoting the survival and activity of inflammatory cells, we investigated SCGF expression using samples derived from RA patients and controls.

Methods: SCGF level is measured using sandwich ELISA methods with synovial fluid and serum derived from RA patients and controls. SCGF expression in synovial tissue is evaluated by immunohistochemistry using anti-SCGF antibody. SCGF localization in synovial tissue is evaluated with confocal microscopy using anti-SCGF antibody and anti-von Willebrand Factor (vWF) antibody (a marker for endothelial cells). SCGF expression in endothelial cells is evaluated using HUVEC cell and EAhy.926 cells by quantitative PCR and immunocytostaining.

Results: SCGF levels in RA synovial fluid (n=25) were significantly elevated compared to SCGF levels in osteoarthritis synovial fluid (n=25) (RA 9.4±1.6 vs OA 4.6±0.9 ng/ml, $p<0.01$). However there was no difference in SCGF levels in serum from RA patients and healthy controls. Immunohistochemical analyses demonstrated that SCGF is highly expressed in the endothelium of synovial tissues derived from RA patients. Confocal microscopy demonstrated SCGF positive cells are colocalized with vWF positive cells. Immunocytostaining with anti-SCGF antibody detected SCGF from various types of endothelial cells, such as HUVECs and EA.hy926 cells. LPS increased *CLEC11A* mRNA in EA.hy926 cells.

Conclusion: These results suggest that SCGF expression is associated with rheumatoid arthritis. SCGF is locally produced by endothelial cells in RA synovial tissue. Inflammation promotes SCGF expression in endothelial cells. SCGF might be involved in immune cell survival and differentiation in peripheral inflammatory tissue. Studies are underway to investigate the pro-inflammatory role of SCGF in RA.

Disclosure: Y. J. Woo, None; **Y. A. Baik**, None; **Y. B. Park**, None; **S. K. Lee**, None; **W. H. Robinson**, None; **J. J. Song**, None.

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Functional Phenotype of Synovial Monocytes Modulating Inflammatory T-Cell Response in Rheumatoid Arthritis. Seong-Wook Kang[1], Seung-Cheol Shim[1], Jinhyun Kim[1], In-Seol Yoo[1], Su-Jin Yoo[1], Seung-Taek Song[1], Bo-Ruem Yoon[2] and Won-Woo Lee[2]. [1]Chungnam National University School of Medicine, Daejeon, South Korea, [2]Seoul National University College of Medicine, Seoul, South Korea.

Background/Purpose: Monocytes function as crucial innate effectors during inflammation. Human monocytes can be divided into three distinct subsets based on CD14 and CD16 expression. Accumulating evidences suggest that three monocyte subsets have distinct functions in inflammatory responses. Here we investigated the characteristics of monocytes in synovial fluid (SF) of rheumatoid arthritis (RA) patients.

Methods: Monocytes and T cells were separated from the peripheral blood (PB) and SF obtained from patients with RA and analyzed by using flow cytometry. For global transcriptome analysis of pathogenic monocytes in RA, we performed a microarray analysis of SF and PB monocytes from the same RA patients and PB monocytes of healthy control (HC).

Results: CD16 expression on CD14^{++} monocytes in the SF was significantly increased compared with that in the PB of RA patients and HC. Microarray data showed that 3,134 genes were differentially expressed in SF monocytes compared with PB monocytes from RA and HC. Among the genes, CD80 and CD276 expression were significantly elevated on SF monocytes, while PB monocytes of RA and HC did not express both of them without stimulation. CD80 and CD276 belong to the B7 family, which plays a checkpoint role for modulating T-cell responses. To explore how SF monocytes gain unique properties, PB monocytes were stimulated with various cytokines and TLR ligands. TGF-β is a potent inducer of CD16 expression on CD14^{++} monocytes, whereas expressions of CD80 and CD276 were markedly elevated by IFN-γ and GM-CSF, respectively. *In vitro* assay, SF monocytes were found to significantly promote Th17 and Th1 responses, compared with PB monocytes of RA patients.

Conclusion: Our findings suggest the possible role for cytokine milieu of the synovial fluid in giving unique features to SF monocytes and their cardinal roles in affecting inflammatory T-cell response in RA.

Disclosure: S. W. Kang, None; **S. C. Shim**, None; **J. Kim**, None; **I. S. Yoo**, None; **S. J. Yoo**, None; **S. T. Song**, None; **B. R. Yoon**, None; **W. W. Lee**, None.

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IL-22 Secreted By NKp44+NK Cells Promote the Proliferation of Synovium in Patients with Rheumatoid Arthritis By Activation of STAT3. Junqing Zhu[1], Juan Li[1] and Xiaoguang Chen[2]. [1]Nanfang Hospital, College of Traditional Chinese Medicine, Southern Medical University, Guangzhou, China, [2]School of Public Health and Tropical Medicine, Southern Medical University, Guangzhou, China.

Background/Purpose: Although CD3-CD56+NKp44+ natural Killer cells (NKp44+NK cells) have been linked to autoimmune diseases including inflammatory bowel disease, ankylosing spondylitis, and primary Sjogren's syndrome, the expansion and role of those cells in rheumatoid arthritis (RA) remain less defined. Here, we investigate the proportion of NKp44+NK cells in RA patients and examine whether those cells play a role in the pathogenesis of RA.

Methods: The frequency of NKp44+NK cells using flow cytometric analysis in peripheral blood (PB) or synovial fluid (SF) and their association with disease activity were examined in RA patients and controls. The expansion of those cells in RA and OA synovial tissues was also detected by dual-labeling immunofluorescence. And then, the concentration of IL -22 secreted by NKp44+NK cells was examined by Enzyme-linked immunosorbent assay. Eventually, the proliferation of fibroblast-like synoviocytes (FLS) and detection of IL-22-dependent signal pathway were examined by methyl thiazolyl tetrazolium and western blot analysis respectively after the treatment of NKp44+NK cells culture supernatant, IL-22 antagonist, recombinant human (rh) IL-22, or a selective signalling pathways inhibitor (AG490).

Results: When compared with controls, NKp44+NK cells significantly expanded in RA PB (3.1±2.4% vs 0.5±0.8%; $p<0.001$) and SF (7.1±4.2% vs 0.9±1.2%; $p<0.001$), which were correlated positively with disease activity scroe in 28 joints and clinical disease activity index ($p<0.001$). Those cells also highly expressed in RA synovial tissues, but were not detected in

OA synovial tissues. It provided a source of IL-22 with high concentrations (5826.5±284.2pg/ml). Further, NKp44+NK cells culture supernatant promoted the proliferation of FLS which was blocked by IL-22 antagonist. Treated with rhIL-22, the proliferation and phosphorylation-STAT3 on RA-FLS increased in a dose dependent manner and time dependent manner respectively, the progress of which could be blocked by AG490.

Conclusion: The present study clarifies the expansion of NKp44+NK cells in the PB and SF of RA patients, especially in the synovial tissues of RA for the first time. STAT3 is an essential pathway in mediating the effects of IL-22 secreted by NKp44+NK cells on the proliferation of synovium in patients with RA.

Disclosure: J. Zhu, None; **J. Li**, None; **X. Chen**, None.

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Midkine, a Growth Factor, May Play a Pathophysiological Role in Patients with Rheumatoid Arthritis. Emiko Shindo, Tomoko Hasunuma, Shotaro Masuoka, Mai Kawazoe, Hiroshi Sato, Natsuki Fujio, Kotaro Shikano, Makoto Kaburaki, Sei Muraoka, Nahoko Tanaka, Kaichi Kaneko, Tatsuhiro Yamamoto, Kenji Takagi, Natsuko Kusunoki and Shinichi Karwai. School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan.

Background/Purpose: Midkine (MK) is known as a heparin-binding growth factor. Recent studies revealed that MK has various functions such as cell proliferation, differentiation, and apoptosis in various cells. Its pathological role is noted in various diseases, especially in solid tumor, such as Wilms tumor, liver cell cancer, and neuroblastoma. High level of serum MK is reported in these cancer patients who have poor prognosis. On the other hand, we reported in the last ACR meeting that high level of serum MK is correlates poor prognosis in patients with systemic vasculitis. In this study, we measured serum level of MK in patients with RA and compared with that in healthy controls. We also analyzed relationships between MK level and several clinical parameters to clarify the pathophysiological role of MK in RA. Moreover, expression of MK protein and mRNA were examined in RA synovial tissue and/or RA synovial fibroblasts (RSFs).

Methods: Serum samples were obtained from 146 RA patients (female: male = 121:25, average age ± SD: 61.0 ± 1.2 y.o.) and 85 healthy controls (female:male = 83:8, 63.2 ± 1.3 y.o.). MK concentration was measured by Human Midkine ELISA kit using a monoclonal antibody against MK (Cellmid, Merborne, Australia). Clinical parameters for RA, such as serum CRP, ESR, rheumatoid factor (RF), MMP-3, DAS28-ESR, patient and doctor VAS, HAQ, and Sharp score were also examined. Statistical analysis was conducted by StatFlex v6.0. Immunohistochemical analysis was performed using RA synovial tissue, which wasobtained at the total knee replacement surgery. Cultured RSFs separated from RA synovial tissue were stimulated with interleukin 1β (IL-1β), tumor necrosis factor-α (TNFα) or dexamethasone for 18 hours, then culture medium was collected for measuring MK protein and mRNA was extracted from RSFs. RT-PCR of MK was performed by standard methods.

Results: Serum MK level was significantly increased in RA patients compared with that of healthy controls (average value ± SD; 157.4±13.7 and 69.64±3.0 pg/mL, respectively) by Mann-Whitney U test ($P < 0.0001$). ESR, RF, MMP-3, DAS28-ESR, patient VAS, doctor VAS, and HAQ, Sharp score were correlated with MK values by univariate analysis. Multiple linear regression analysis showed that MK level was positively correlated with CRP and RF ($P = 0.00012$ and $P < 0.000001$, respectively), but not with MMP-3, DAS28-ESR, HAQ, and Sharp score. Immunohistochemical analysis showed that MK was stained in lining layer of RA synovial tissues. MK mRNA in RSFs and MK protein in the culture medium of RSFs were detectable, however, their expression levels were not changed by addition of IL-1β, TNFα or dexamethasone.

Conclusion: In this study, MK was significantly increased in serum of RA patients, and its level was correlated with several clinical markers of RA. In addition, MK protein and mRNA were detected in RA synovial lining layer and/or cultured RSFs. It might be possible that MK has a pathophysiological role in RA development.

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Quantitave Analysis of Cadherin-11 and Beta-Catenin Signaling during Proliferation of Rheumatoid Arthritis-Derived Synovial Fibroblast Cells. Ryosuke Yoshioka, Yasuhiro Kita, Asako Nagahira, Atsushi Manno, Naoyuki Makita, Urara Tomita and Masao Murakrawa. Asubio Pharma Co., Ltd., Kobe, Japan.

Background/Purpose: Cadherin-11 (CDH11) is a cadherin adhesion molecule that anchors b-catenin, and is involved with various functions of synovial fibroblast cells (SFCs) during the development of rheumatoid arthritis (RA). However, the functional mechanism of CDH11 during RA-SFC proliferation is unclear. The aim of our study was to clarify the involvement of CDH11 and b-catenin signaling during human RA-SFC proliferation.

Methods: In order to investigate the involvement of CDH11 and b-catenin to proliferation, BrdU incorporation assay with each siRNA treatment was carried out. The effect of knockdown was determined by western blotting and immunohistochemistry. The values of E_{max} and EC_{50} in proliferation were caluculated by regression analysis with GraphPad Prism.

Results: Using CDH11 specific siRNAs, there were a 42% reduction in IL-1b-induced human RA-SFC proliferation and a 64% reduction in b-catenin protein levels. When b-catenin specific siRNAs were applied, there was a 63% reduction in IL-1b-induced RA-SFC proliferation. The EC_{50}values for IL-1b during RA-SFC proliferation via CDH11-mediated b-catenin-dependent, total b-catenin-dependent, and b-catenin-independent signaling were 0.0015, 0.016, and 0.18 ng/mL, respectively. Blocking homophilic CDH11 ligation with a CDH11 neutralizing antibody did not decrease IL-1b-induced RA-SFC proliferation.

Conclusion: CDH11-mediated b-catenin signaling was 42% involved in IL-1b-induced human RA-SFC proliferation and had the highest susceptibility to IL-1b. The mode of action for CDH11 during the cell proliferation was likely associated with a pool of b-catenin protein. In contrast to IL-1b, CDH11 and b-catenin were not involved in TNF-a-induced RA-SFC proliferation.

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Cadherin-11 mRNA Expression in the Peripheral Blood of Rheumatoid Arthritis Patients As a Marker of Active Polyarthritis. Petros P. Sfikakis[1], Panagiotis F. Christopoulos[2], Aristeidis G. Vaiopoulos[2], Kalliopi Fragkiadaki[1], Christina Katsiari[3], Violetta Kapsimali[4], George Lallas[1], Panayiotis Panayiotidis[4], Pinelopi Korkopoulou[5] and Michael Koutsilieris[2]. [1]First Department of Propedeutic Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece, [2]Department of Physiology, Athens University Medical School, Athens, Greece, [3]School of Health Sciences, University of Thessaly, Larissa, Greece, [4]Department of Microbiology, Athens University Medical School, Athens, Greece, [5]Department of Pathology, Athens University Medical School, Athens, Greece.

Background/Purpose: Human rheumatoid arthritis synovial fibroblasts (RASF) implanted subcutaneously in immunodeficient mice trans-migrate through the vasculature and drive the progression from oligo- to poly-articular disease. On the other hand, RASFs overexpress the mesenchymal cadherin-11, an adhesion molecule involved in tumor invasion and metastasis and cadherin-11 therapeutics prevent and reduce experimental arthritis. We tested the hypothesis that aberrant expression of cadherin-11, deriving from possibly circulating RASFs with pathogenic potential, can be identified in the peripheral blood of patients with active RA.

Methods: Cadherin-11 mRNA was quantified by real-time reverse transcription-PCR in peripheral blood (3ml) from 100 consecutive RA patients (15 studied serially) and 70 healthy controls. Western blotting and flow cytometry were performed in synovial fluid and peripheral blood using an anti-cadherin-11 antibody that decorated RASFs in synovial tissue's immunohistochemistry.

Results: Cadherin-11 mRNA was detected in 69.2% of moderately or severely active disease, versus 31.8% of patients with low disease activity or clinical remission ($p=0.001$), versus 17.1 % of healthy controls ($p<0.0001$). Repeated measurements after 2–4 months confirmed these findings. Disease duration was significantly longer in cadherin-11 positive versus negative patients, whereas rheumatoid factor, ESR, CRP levels and treatment modalities were comparable. Notably, among patients with established RA (disease duration longer than one year) cadherin-11 mRNA was detectable in 88.4% of those with active polyarthritis (5 or more tender and swollen joints at the

time of sampling) versus 48.3% in those with oligo- or monoarthtitis ($p<0.0001$). Western blotting experiments were not sensitive enough to reveal cadherin-11 expression at the protein level in either synovial fluid or peripheral blood samples. However, rare cells expressing surface cadherin-11, together, or not, with the pan-hematopoietic marker CD45 were consistently present in RA-derived synovial fluid. Such rare cells were also identified in peripheral blood from 5/6 versus 1/6 patients with established or early, respectively, poly-articular RA.

Conclusion: Cadherin-11 mRNA transcripts in the peripheral blood may serve as the first biomarker of active polyarthritis in established RA. Rare circulating cells expressing surface cadherin-11 in patients with RA could possibly represent macrophages and RASFs; the latter could enter the circulation as the synovium transforms into an hyperplastic, invasive tissue with new vessel formation. Taken together, these data further identify cadherin-11 as a potential therapeutic target in RA.

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Dickkopf-1 Perpetuated Synovial Fibroblast Activation and Synovial Angiogenesis in Rheumatoid Arthritis. Li Zheng, Fanlei Hu, Yingni Li, Lianjie Shi, Xiaoxu Ma, Xuewu Zhang and Zhanguo Li. Peking University People's Hospital, Beijing, China.

Background/Purpose. Dkk-1, a master regulator of joint remodeling, is elevated and leads to bone resorption in patients with RA. This study aimed to investigate the contribution of Dkk-1 to synovial inflammation and synovial fibroblasts-mediated angiogenesis in RA.

Methods: Dkk-1 concentration in synovial fluids from RA and osteoarthritis (OA) patients was evaluated by ELISA. The expression of Dkk-1 in RA synovial fibroblasts (RASF) and OASF was compared by real-time PCR and ELISA. RASF were stimulated with different pro-inflammatory factors and the expression of Dkk-1 was determined by real-time PCR and ELISA. The expression of angiogenic factors (MCP-1, SDF-1, VEGF, ADAM-10 and CD147), pro-inflammatory cytokines (TNF-α, IL-6, IL-8 and IL-1β), and MMPs (MMP-1, MMP-3 and MMP-9) in RASF was determined by real-time PCR when DKK-1 was knocked down or overexpressed. Meanwhile, the levels of MCP-1, IL-6, IL-8, and MMP-3 in the cell culture supernatants were determined by ELISA. The effects of Dkk-1 on the MAPK signaling pathway was evaluated by Western blot when it was silenced. Matrigel tube formation assay was employed to reveal the direct and indirect effect of Dkk-1 on synovial angiogenesis.

Results: Levels of Dkk-1 in synovial fluids and synovial fibroblasts were elevated in RA patients. The secretion of Dkk-1 was accelerated by various pro-inflammatory cytokines in RASF, including TNF-α,IL-6,IL-17,INF-$\gamma$and IL-1β. Dkk-1 stimulated the production of potent angiogenic factors, pro-inflammatory cytokines, and MMPs in RASF, while silencing Dkk-1 expression suppressed such factor expression. Silencing Dkk-1 in RASF dampened its mediated capillary tube organization both in direct and indirect manners, accompanied with restrained ERK, JNK, and p38 signaling pathway activation.

Conclusion: Dkk-1 exacerbated synovial fibroblasts-mediated inflammation, cartilage erosion, and angiogenesis in RA. Targeting Dkk-1 might provide novel therapeutic strategy for overcoming the persistent disease.

Disclosure: L. Zheng, None; **F. Hu**, None; **Y. Li**, None; **L. Shi**, None; **X. Ma**, None; **X. Zhang**, None; **Z. Li**, None.

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Numbers of Circulating CD4 Positive CD28null T Cells Are Increased in Patients with Rheumatoid Arthritis and Are Associated with Rheumatoid Factor Positivity but Not Subclinical Cardiovascular Disease. Sarah Skeoch[1], John Waterton[2], Yvonne Alexander[3] and Ian N. Bruce[4]. [1]Arthritis Research UK Centre for Epidemiology and NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom, [2]University of Manchester, Manchester, United Kingdom, [3]Manchester Metropolitan University, Manchester, United Kingdom, [4]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: CD4+ T cells which lack CD28 co-expression (CD28null cells) account for less than 2.5% of CD4+ T cells in healthy individuals. These cells are pro-inflammatory, resistant to apoptosis and have cytolytic properties. Increased circulating numbers are found in some RA patients and their presence is associated with extra-articular disease. In unstable angina patients, CD28null cells are independently associated with recurrent cardiac events and are thought to promote atherosclerotic plaque rupture. The aims of the current study were to quantify CD28null cells in RA patients and to investigate the association with RA disease characteristics and subclinical cardiovascular disease.

Methods: RA patients with active arthritis, who were not taking a statin, were recruited to a prospective observational study. Clinical and serological evaluation of RA disease characteristics was undertaken including extra-articular involvement, the disease activity 28 score (DAS-28) and the health assessment questionnaire (HAQ). Presence of carotid plaque was evaluated using B-mode doppler ultrasound. Plaque was defined as 2 out of 3: intimal medial thickness$>$1.5mm, luminal protrusion, increased wall echogenicity.

CD28null cells were quantified using flow cytometry. In brief, fluorescently labelled CD45, CD28 and CD4 antibodies were added to whole blood. Following red cell lysis, flow cytometry was used to measure the proportion of CD45+CD4+ lymphocytes which lacked CD28 expression. Presence of an expanded CD28null cell population was defined as $>$2.5% of CD45+CD4+ T cells lacking CD28 expression. Descriptive and non-parametric statistics were used to analyse the data.

Results: 91 RA patients were included in the study and 68 (74.2%) were female. Median (IQR) age and disease duration was 56(48, 62) and 9(4, 19) years respectively. 64 patients (70.3%) were rheumatoid factor positive and 74 patients (81.3%) were ACPA positive. 1 patient had a history of clinical cardiovascular disease.

Expanded CD28null cell populations were found in 28 patients (30.8%). Presence of CD28 null cells were associated with rheumatoid factor positivity ($p=0.02$) but not with ACPA positivity. No association was found with age, disease activity, HAQ, biologic use, extra-articular disease or with carotid plaque.

Conclusion: The current study confirms that this abnormal T cell subset is expanded in a significant proportion of RA patients. There was no association between CD28null cells and carotid plaque but these cells may contribute to plaque destabilisation and rupture rather than plaque development. Prospective evaluation of cardiovascular outcomes in this population is underway.

Disclosure: S. Skeoch, None; **J. Waterton**, None; **Y. Alexander**, None; **I. N. Bruce**, None.

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Follicular Helper T Cells Control Autoimmunity through IL-21/IL-21 Receptor Interaction in RA Patients. Shikha Singla[1], Minzi Chen[2], Jerry Poundsr Jr.[2], Omar Khan[2], Jerald M. Zakem[2], Kismet Collins[2], Tamika Webb-Detiege[2], William E. Davis[2], Robert Quinet[2] and Xin Zhang[2]. [1]Ochner Medical Center, New Orleans, LA, [2]Ochsner Medical Center, New Orleans, LA.

Background/Purpose: Rheumatoid Arthritis (RA) is an autoimmune disease characterized by chronic inflammation of the synovium, causing progressive joint destruction and reduction in quality of life for patients. Auto-antibodies in RA patients appear prior to the onset of clinic disease, and are responsible for disease progression. Our previous study showed that follicular helper T (Tfh) cells are increased in peripheral blood of RA patients and correlate with anti-citrullinated protein antibodies (ACPAs) production and disease activity score (DAS-28). IL-21 is the signature cytokine produced by Tfh cells. Through its receptor (IL-21R), IL-21 induces B cell differentiation into antibody producing plasma cells, and also promotes T cell differentiation in an autocrine manner. To dissect the role of IL-21 and IL-21R in RA, we examined the IL-21 and IL-21R expression on different subsets of B cells and T cells in RA patients and healthy donors, and determined their correlation with autoantibody level and disease activity.

Methods: Peripheral blood was collected from 50 subjects (25 RA patients meeting 2010 ACR/EULAR RA classification criteria and 25 age/gender matched healthy donors). Tonsils were surgically derived from non-RA donors and used as positive controls. Clinical disease activity was assessed using DAS-28 score. RA patients were divided into four groups based on DAS-28 score ranging from remisson, low, moderate and high disease activity. Serum laboratory measurements including Rheumatoid factor (RF), ACPA, Erythrocyte sedimentation rate (ESR) and C Reactive Protein (CRP) levels were obtained. IL-21 and IL-21R expression on T cell subsets (Tfh, Th1, and Th2 cells) and B cell subsets (naïve B cell, memory B cell, and pre-plasmablast) in peripheral blood and tonsils (naïve B cells, memory B cells, germinal center B cells, and plasma cells) were determined

via flow cytometry. Pearson correlation coefficient was determined in the analysis of correlation between IL-21R expression and clinic parameters.

Results: $ICOS^+CXCR5^+$ Tfh cells were identified in peripheral blood of RA patients. These circulating Tfh cells are the dominant T cell subset producing IL-21. We found that Tfh cells were significantly elevated in RA patients with moderate/high disease activity ($P<0.05$). IL-21R was expressed on naïve B cells, germinal center B cells, and plasma cells in tonsillar lymphoid follicles. As compared to healthy donors, the level of IL-21R expression on naïve B cells, pre-plasma cells, and T cells was significantly elevated in peripheral blood of RA patients and correlated with disease activity.

Conclusion: RA patients with moderate/high disease activity have elevated levels of IL-21 expression on Tfh cells and IL-21R expression on B cell subsets, similar to that seen in tonsillar lymphoid follicles. Our results indicate that IL-21/IL-21R pathway is involved in RA pathogenesis. Interruption of IL-21/IL-21R interaction may be a potential therapeutic target for RA patients.

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Patients with Active Rheumatoid Arthritis Display an Expanded Population of GM-CSF Expressing Peripheral B Cells. Sofia Adamidi, Anastasia Makris, Christos Koutsianas, Christina Tsalapaki, Emilia Hadziyannis and Dimitrios Vassilopourlos. University of Athens Medical School, Athens, Greece.

Background/Purpose: GM-CSF has been implicated in rheumatoid arthritis (RA) pathogenesis and is being investigated as a novel therapeutic target. B cells secreting GM-CSF have been recently reported to participate in innate immune responses in animal models. The aim of our study was to determine the expression of GM-CSF secreting peripheral B cells in RA patients.

Methods: 23 patients with RA (fulfilling the 2010 ACR/EULAR RA Classification Criteria), 11 disease controls (psoriatic arthritis n=4, osteoarthritis n=3, ANCA-associated vasculitides n=2, Sjögren's syndrome n = 1, giant cell aortitis n=1) and 10 healthy controls were included in the study. Peripheral blood mononuclear cells (PBMC) were stimulated overnight with Phorbol Myristate Acetate (PMA) and ionomycin in the presence of Brefeldin. Cells were then stained with specific antibodies against surface CD19 and intracellular GM-CSF (BioLegend). Positive cells were quantified by flow cytometry (Partec) and compared between the different groups.

Results: 23 RA patients with moderate to high disease activity not receiving anti-rheumatic drugs (females/males=19/4, DAS28-CRP=5.53 ± 0.84, median disease duration=14 months, RF and/or anti-CCP+=52%) were studied. The % of peripheral B cells (CD19+) was similar between the RA and the 2 control groups (6.9 ± 3.9% vs. 6.3 ± 3.5% vs.8.4 ± 1.9%, p=NS). We detected an expanded population of peripheral CD19GM-CSF + cells in RA patients (4.4 ± 2.6%) compared to disease (1.1 ± 1.5%, p=0.0002) and healthy (0.2 ± 0.2%, p=0.00000002) controls while there was no difference between disease and healthy controls (p=0.512). Similarly, we did not observe any difference between seropositive (RF and/or anti-CCP+, 4 ± 2.6%) and seronegative (4.8 ± 2.5%, p=0.347) patients. GM-CSF+ B cell expression did not correlate with RA disease activity measured by DAS28 (p=0.926, Spearman correlation).

Conclusion: Our study shows for the first time an expanded population of peripheral B cells expressing GM-CSF among patients with active RA compared to patients with other inflammatory or non-inflammatory rheumatic diseases and healthy controls. The functional significance of this cell population remains to be determined.

Disclosure: S. Adamidi, None; **A. Makris**, None; **C. Koutsianas**, None; **C. Tsalapaki**, None; **E. Hadziyannis**, None; **D. Vassilopoulos**, None.

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Do G-CSF and Neutrophils Contribute to the Pathophysiology of Rheumatoid Arthritis? Gabrielle Goldberg[1], Simon Chatfield[2], Jane Murphy[1], Ee Shan Pang[1], Yunshun Chen[1], Gordon Smyth[1], Milica Ng[3], Michael Wilson[3], Clare O'Neill[2], Samantha Busfield[3], Arna Andrews[3] and Ian P. Wicks[2]. [1]Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, [2]The Royal Melbourne Hospital, Melbourne, Australia, [3]CSL Limited, Melbourne, Australia.

Background/Purpose: Rheumatoid arthritis (RA) is characterised by a persistent, but poorly understood interplay between innate and adaptive immunity. Neutrophils are the predominant cell type in inflamed RA synovial fluid (SF). Granulocyte colony-stimulating factor (G-CSF) is a key regulator of neutrophil production, function and survival.

Methods: In this study peripheral blood (PB) neutrophil phenotype and function were analysed according to disease activity (DAS28 scores and other clinical parameters) in RA patients (n=50–60).

Results: We found significant correlations between disease activity and PB neutrophil percentage ($r=0.26$, $p\leq0.05$), as well as between neutrophil activation state (CD62L, CD11b) and the expression of receptors for factors regulating neutrophil production and function. For example, CD62L vs G-CSF-R ($r=0.58$, $p\leq0.0001$); CD62L vs CD35 ($r=-0.37$, $p\leq0.01$); CD62L vs CXCR2 ($r=0.42$, $p\leq0.01$); CD62L vs CXCR1 ($r=0.46$, $p\leq0.001$). To further explore the role of neutrophils and G-CSF in RA, transcriptional profiling using RNASeq was performed comparing: PB neutrophils isolated from healthy donors (HD) and RA patients (n=5); neutrophils isolated from paired PB and SF samples of RA patients (n=3); neutrophils or white blood cells from HDs stimulated with G-CSF *in vitro* (n=4). 194 genes were differentially expressed (DE) in RA neutrophils ($logFC\geq1$; adjusted $p\leq0.05$) when compared to HDs. Over 50 of those genes were also differentially expressed when neutrophils were stimulated with G-CSF *in vitro*. There were 1724 DE genes ($logFC\geq1$; adjusted $p\leq0.05$) when comparing PB and SF neutrophils from RA patients. Bioinformatic interrogation using Ingenuity Pathway Analysis software demonstrated that G-CSF was a likely regulator ($p=9.83\times10^{-21}$) of these differences.

Conclusion: These data provide evidence that neutrophils and G-CSF contribute to the pathogenesis of RA. G-CSF may therefore represent a potential therapeutic target in the treatment of RA and other inflammatory diseases where there is a pathogenic contribution from neutrophils.

Disclosure: G. Goldberg, CSL Limited, 2; **S. Chatfield**, None; **J. Murphy**, None; **E. S. Pang**, None; **Y. Chen**, None; **G. Smyth**, None; **M. Ng**, CSL Limited, 3; **M. Wilson**, CSL Limited, 3; **C. O'Neill**, None; **S. Busfield**, CSL Limited, 3; **A. Andrews**, CSL Limited, 3; **I. P. Wicks**, CSL Limited, 2.

1468

Mechanism of Effectiveness of IL-6 Blockade for Reduction of SAA Production and Amyloid a Deposition in AA Amyloidosis Patients with RA. Kazuyuki Yoshizraki. Osaka University, Osaka, Japan.

Background/Purpose: AA amyloidosis is a serious complication of chronic inflammatory and infectious diseases resulting from the deposition of amyloid A protein. Serum amyloid A (SAA).a precursor molecule of AA protein produced in hepatocyte, is deposited in various organs as amyloid fibril during the development of AA amyloidosis. Proinflammatory cytokines, especially IL-6, play a key role in SAA production.

Methods:

1. The expression of SAA mRNA in hepatoma-derived cells treated by cytokines (IL-6, IL-1, TNF-a) with or without their inhibitors was examined by quantitative real-time PCR. Luciferase assay, EMSA and Chip assay were also used for analysis of SAA transcription mechanism
2. Clinical effects of IL-6 blockade on amyloidosis-related parameters including serum SAA, urinal protein and RA disease activity were evaluated in AA amyloidosis patients with RA. Scores of amyloid deposits in gastro-duodenal mucosal biopsy specimens were examined by histopathological staining and protein quantitative ELISA.

Results:

1. Our results proved that IL-6 plays a critical role in cytokine-driven SAA expression through STAT3 activation. TNF-a/IL-1 complementally contributes to the synergistic induction of the triple-cytokines-induced SAA gene through NF-kB activation. We further found that a novel STAT3 non-consensus TFBS at the immediate downstream of the NF-κB RE in the SAA1 promoter region that is required for NF-κB p65 and STAT3 to activate SAA1 transcription. In addition, the synergistic induction of SAA expression by cytokines combination was completely inhibited by tocilizumab but not by TNF-a or IL-1 inhibitor.
2. 23 AA amyloidosis with RA patients treated with tocilizumab showed significant improvements in disease activity, and reductions in serum SAA and urinal protein levels, and these effects were more pronounced in the tocilizumab group than in the TNF-a inhibitors group at 12 months after initiation of the treatment. Meanwhile, histological scores of AA deposition observed in gastroduodental biopsy specimens treated with tocilizumab showed significantly decrease in the area and concentration of amyloid deposits after the treatment.

Conclusion: Although activated NF-kB by IL-1 and TNF-a is also involved hepcidin production during inflammation, IL-6-activated STAT3 plays a key role in SAA regulation. Our clinical results with IL-6 blockage therapy suggest that the pathogenic cascade causing AA amyloidosis started from SAA induction by IL-6, so that IL-6 blockage constitute a promising molecular targeting therapy for AA amyloidosis.

Disclosure: K. Yoshizaki, Chugai Pamaceuicl Co., 1.

1469

Methotrexate Treatment Reduces Serum IL-6 Level By Decreasing a CD14brightCD16+ Intermediate Non-Classical Subset of Monocytes in RA Patients. Masako Tsukamoto[1], Keiko Yoshimoto[1], Noriyuki Seta[2], Katsuya Suzuki[1] and Tsutomu Takeuchi[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Keio university, Tokyo, Japan.

Background/Purpose: It is well known that circulating monocytes are the source of inflammatory cytokines, such as IL-6 and TNFα and newly divided into three subsets based on the expression levels of CD14 and CD16. We have previously reported that plasma IL-6 level was decreased in RA patients with clinically significant improvement after MTX treatment, but a detail mechanism is not clearly clarified. The purpose of this study is to investigate the association between three subsets of monocytes and change of serum cytokine repertoire after MTX treatment.

Methods: 33 RA patients fulfilled the 2010 ACR/EULAR RA Classification Criteria and 15 healthy donors (HD) were enrolled in this study. The patients had never been received a treatment with DMARDs or biological agents and had moderate disease activity or more (DAS28-ESR $\geq$ 3.2). Peripheral blood samples and clinical records of the patients were obtained at the time of 0 and 12 weeks after MTX treatment. Peripheral blood samples were also obtained HD. The expression levels of CD14 and CD16 on monocytes and serum levels of cytokines were measured by flow cytometric (FACS) analysis and multiplex electrochemiluminescence assays on the Meso Scale Discovery SECTOR Imager 2400 platform®, respectively. A decrease in DAS28-ESR of 1.2 or more was defined as a clinically significant improvement after MTX treatment.

Results: The mean DAS28-ESR score of the patients was 4.8 $\pm$ 0.8. There was no significant difference in clinical backgrounds between RA patients with and without improvement. Serum levels of IL-6, IL-8 and IL-10 at baseline were significantly higher in RA patients compared with HD. Only IL-6 significantly decreased in RA patients with improvement after MTX treatment. FACS analysis revealed that the proportion of CD14brightCD16+ monocytes was significantly decreased in RA patients at baseline (13.9 $\pm$ 6.9%) compared with HD (7.3 $\pm$ 2.1%) ($p<0.01$). After MTX therapy, the proportion of CD14brightCD16+ monocytes was significantly decreased (14.0 $\pm$ 6.5% vs 9.3 $\pm$ 5.0%, $p<0.01$) in RA patients with improvement, but not in those without ($p=0.3$). Moreover, the proportion of CD14brightCD16+ monocytes were significantly and positively correlated with serum IL-6 level and DAS28-ESR ($p=0.01$ and $p<0.01$) in RA patients.

Conclusion: These results indicate that CD14brightCD16+ intermediate non-classical monocytes possibly play an important role in the pathogenesis of RA by producing IL-6 and the curative effect of MTX may be demonstrated through the reduction of CD14brightCD16+ monocytes in peripheral blood.

Disclosure: M. Tsukamoto, None; **K. Yoshimoto**, None; **N. Seta**, None; **K. Suzuki**, None; **T. Takeuchi**, Abbott Japan Co., Ltd., Astellas Pharma, Bristol–Myers K.K., Chugai Pharmaceutical Co, Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Sanofi–Aventis K.K., Santen Pharmaceutica, 2, Abbott Japan Co., Ltd., Bristol–Myers K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., Astellas Pharma, Daiichi Sankyo Co., Ltd., 8, Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., Asahi Kasei Medical K.K., Abbvie GK, Daiichi Sankyo Co., Ltd., 5.

1470

Malondialdehyde-Acetaldehyde Adducts (MAA) and Anti-Malondialdehyde-Acetaldehyde Antibody in Rheumatoid Arthritis. Geoffrey Thiele[1], Michael J. Duryee[2], Daniel Anderson[1], Lynell W. Klassen[1], Stephen Mohring[2], Kathleen Young[2], Dathe Benissan-Messan[2], Harlan Sayles[1], Jeremy Sokolove[3], William H. Robinson[4], James O' Dell[1], Anthony Nicholas[5] and Ted R. Mikuls[1]. [1]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [2]University of Nebraska Medical Center, Omaha, NE, [3]VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA, [4]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [5]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Products of oxidative stress, MAA adducts are highly immunogenic and have been associated with tolerance loss. To examine their potential role in disease-related inflammation, we investigated the presence of MAA adducts and circulating anti-MAA antibody in RA and their relationship with citrullinated proteins and anti-citrullinated protein antibody (ACPA).

Methods: Synovial tissues from RA and OA patients were examined for the presence of MAA-modified and citrullinated proteins. Anti-MAA antibody isotypes were measured in RA cases ($n = 1720$) and healthy controls ($n = 80$) by ELISA. Antigen-specific ACPA was measured in RA cases using a multiplex antigen array. Anti-MAA antibody isotype (IgG, IgM, and IgA) concentrations were compared in a subset of cases ($n = 80$) and controls ($n = 80$), matched based on age, gender, race, and smoking status. Associations of anti-MAA antibody isotypes with disease characteristics, including ACPA, were examined in all RA cases.

Results: MAA-adducted and citrullinated proteins were detected and shown to co-localize in RA synovial tissues (Fig. 1). In contrast, MAA adducts were present in negligible quantity while citrullinated proteins were absent in OA synovial tissue. All anti-MAA antibody isotypes were markedly increased in RA cases vs. controls ($p < 0.001$). Among RA cases, anti-MAA antibody isotypes were associated with anti-CCP antibody and RF positivity ($p < 0.001$) in addition to select measures of disease activity. Higher anti-MAA antibody concentrations were associated with a higher number of antigen-specific ACPA analytes positive in high titer ($p < 0.001$) and a higher ACPA score ($p < 0.001$), defined as the sum of normalized fluorescent values divided by the number of analytes examined (Fig. 2). Associations of anti-MAA antibody isotypes with ACPA score and the number of analytes positive were independent of other covariates.

Conclusion: This is the first study to show that MAA adduct formation is increased in RA and appears to result in robust antibody responses that are strongly associated with ACPA. These results support speculation that MAA adduct formation may be a co-factor that drives tolerance loss resulting in the autoimmune responses characteristic of RA.

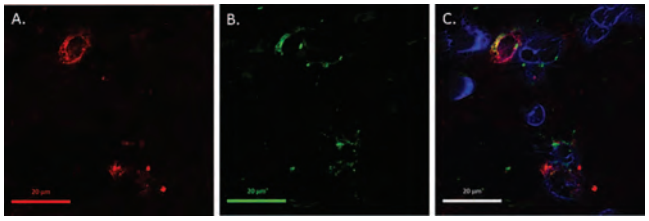

Fig. 1: Immunohistochemical staining of RA synovial tissue demonstrated the presence of: a) citrullinated proteins, b) MAA, and c) co-localization of citrullinated proteins and MAA adducts.

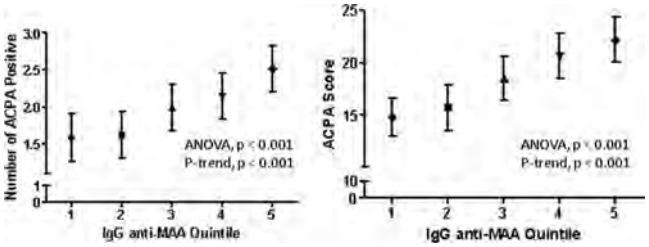

Fig. 2: Number of ACPA analytes positive (left) and total ACPA score (right) based on the quintile of circulating IgG anti-MAA antibody; similar results observed for IgA and IgM anti-MAA isotypes (data not shown).

Disclosure: G. Thiele, None; **M. J. Duryee**, None; **D. Anderson**, None; **L. W. Klassen**, None; **S. Mohring**, None; **K. Young**, None; **D. Benissan-Messan**, None; **H. Sayles**, None; **J. Sokolove**, None; **W. H. Robinson**, Atreca, Inc., 5; **J. O' Dell**, None; **A. Nicholas**, None; **T. R. Mikuls**, None.

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TNFα Influences the Status of B and T Cells By Acting on BCR and TCR Pathways *Via* RasGRP1 and RasGRP3 Proteins. Marie-Laure Golinski[1], Martine Hiron[2], Céline Derambure[2], Clément Guillou[1], Manuel Fréret[2], Olivier Boyer[3], Olivier Vittecoq[4] and Thierry Lequerré[5]. [1]Inserm 905 & Institute for Biomedical Research, University of Rouen, Rouen, France, [2]Inserm 905 & Institute for Biomedical Research, University of Rouen, Rouen, France, Rouen, France, [3]INSERM U905, University of Rouen, Rouen, France, [4]Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France, [5]Chu De Rouen, Rouen, France.

Background/Purpose: Rheumatoid arthritis (RA) is the most common inflammatory arthritis. B and T cells play a key role in the RA pathophysiology. RasGRP is a member of the CDC25 family of Ras guanyl nucleotide exchange factors. RasGRP1 is expressed in T and B cells whereas RasGRP3 is only expressed in B cells. In previous studies, we have shown that *RasGRP3 gene*expression level significantly decreased in peripheral blood mononuclear cells from RA patients responders to adalimumab and etanercept (anti-TNFa drugs), leading to the question of TNFα involvement in RasGRP1 and RasGRP3 pathways. To study TNFα effects on RasGRP1 and RasGRP3 expression levels *in vitro*.

Methods: We measured, by qRT-PCR and western-blot, RasGRP1 and RasGRP3 expression levels in B and T cells isolated from buffy coat. In each condition, cells were cultured with or without TNFα for 24 or 48 hours. C*ell proliferation was evaluated* by [^{3}H] *thymidine* incorporation. To investigate the TNFα implication on signaling pathways, MAPK and apoptosis protein arrays were used.

Results: In B cells, TNFα induced an increase of *RasGRP1* and *RasGRP3* gene expression levels without effect on B cells proliferation and BCR pathway phosphorylations, but apoptotic pathways were inhibited. In T cells, TNFα increased *RasGRP1* gene expression level but RasGRP1 protein expression level decreased, inhibiting T cell proliferation and TCR pathway phosphorylations.

Conclusion: This study suggests a link, never described previously, between RasGRP1 or RasGRP3 and the TNFa' effects on T and B cells. While the response to anti-TNFα treatments in RA patients modulates RasGRP3 gene expression, TNFα inhibits RasGRP1 protein expression leading to TCR pathway inhibition, in vitro, in pathophysiological condition. The better understanding of TNFα effects on RasGRP proteins could permit a better understanding of the mechanisms of action of TNFα blocking agents on T and B cells.

Disclosure: M. L. Golinski, None; **M. Hiron**, None; **C. Derambure**, None; **C. Guillou**, None; **M. Fréret**, None; **O. Boyer**, None; **O. Vittecoq**, None; **T. Lequerré**, None.

1472

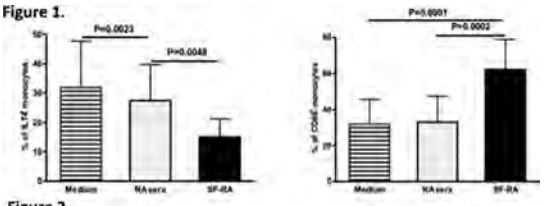
Synovial Fluid from Rheumatoid Arthritis Patients Modulates the Immunophenotype and Viability of Monocytes. Maria Sole Chimenti, Alberto Bergamini, Eleonora Baffari, Eleonora Ballanti, Alessia Musto, Paola Conigliaro and Roberto Perricrone. Department of "Medicina dei Sistemi", University of Rome "Tor Vergata", Rome, Italy.

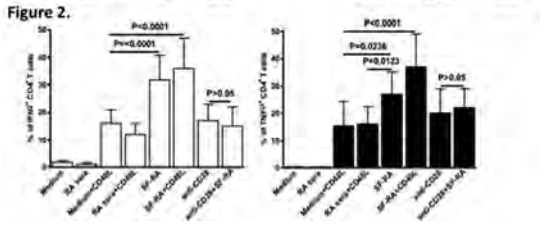
Background/Purpose: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by infiltration of the synovium by inflammatory cells that destroys the cartilage and the bone adjacent to the joint. The thickened synovium, called pannus, causes swelling of the joint with excess of synovial fluid (SF) production. A large number of proteins involved in inflammation and immune response have been identified in SF from RA patients (SF-RA). The aim of this study was to determine the effects of synovial fluids (SF) from RA patients (SF-RA) on surface phenotype, co-stimulatory activity, viability and cytokine production of monocytes, as a model for the interaction between SF and synovial tissue macrophages in RA.

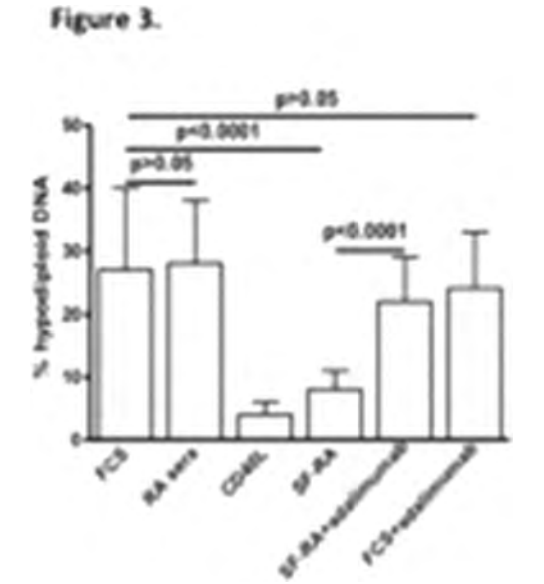
Methods: Purified monocytes from healthy donors were incubated with individual specimens of SF-RA obtained from twelve RA patients with active knee arthritis and then analyzed by flow cytometry for ILT4 and CD86 expression, co-stimulation ability, rate of spontaneous apoptosis and TNFα, IL-1β and IL-10 production. Comparative analysis was carried out with serum from RA patients and medium alone.

Results: Downmodulation of ILT4 and upmodulation of CD86 expression (Figure 1), together with increased ability to co-stimulate $CD4^+$ T cells for IFNγ and TNFα production, was observed in monocytes incubated with SF-RA (SF-RA monocytes) compared with control cells, even under condition of activation by CD40L (Figure 2). A reduction of spontaneous apoptosis was observed in SF-RA monocytes compared to control cells. Adalimumab increased the rate of SF-RA monocytes apoptosis, whereas no significant influence of adalimumab was detected in control monocytes. The TNFα and IL1β response, but not that of IL-10, to LPS was greater in SF-RA monocytes compared with control cells (Figure 3).

Conclusion: Our findings suggest that soluble factors present in SF-RA could function as so-called damage-associated molecular patterns and contribute to increase the effectiveness intra-articular of the immune response and inflammation by increasing monocyte numbers and pro-inflammatory activity.







Disclosure: M. S. Chimenti, None; **A. Bergamini**, None; **E. Baffari**, None; **E. Ballanti**, None; **A. Musto**, None; **P. Conigliaro**, None; **R. Perricone**, None.

1473

Manocept-Cy3 Localizes CD206 + Macrophages in Synovial Tissue and Fluid from Rheumatoid Arthritis Patients Differentially Compared to Controls. Nicholas A. Young[1], Larry Schlesinger[2], Thomas J. Rosol[3], Fred Cope[4] and Wael N. Jarjour[1]. [1]The Ohio State University Wexner Medical Center, Columbus, OH, [2]The Ohio State University College of Medicine, Columbus, OH, [3]The Ohio State University College of Veterinary Medicine, Columbus, OH, [4]Navidea Biopharmaceuticals, Dublin, OH.

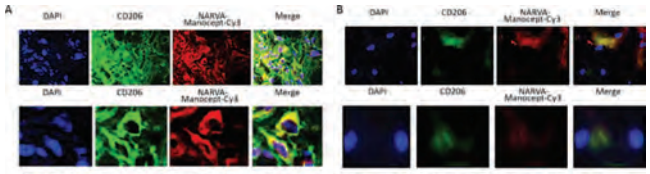
Background/Purpose: Early identification of rheumatoid arthritis (RA) would allow aggressive treatment with disease modifying rheumatic drugs and provide a system to monitor patient responses. Therefore, we developed a fluorescent agent (manocept-Cy3) that targets C-type lectin mannose receptor (CD206) to provide a diagnostic imaging tool for RA. This receptor is expressed on macrophages, which contribute to RA pathology and are strongly implicated in autoimmunity. Manocept-Cy3 follows work that was done in developing Technicium 99m Tilmanocept (Lymphoseek), which is currently used in lymph node mapping of breast cancer patients. The aim of this study was to determine if this agent could also detect these cells in synovial compartments of RA patients; thus providing the foundation to study its potential as an imaging biomarker in RA.

Methods: Rheumatoid arthritis and osteoarthritis (OA) patients, and healthy volunteers were recruited through approved institutional review board protocols. Synovial fluid was isolated and analyzed by flow cytometry. Synovial tissue was flash-frozen at the time of collection for immunohistochemical analysis and fluorescent imaging by microscopy. Tissue was incubated with DAPI nuclear stain, manocept-Cy3, and/or anti-CD206 antibody. Slides were digitally scanned for image analysis to quantitate

manocept-Cy3+ staining. To demonstrate the specificity, samples were stained with an isotype-matched control antibody for CD206 or pre-incubated with 10X unlabeled ("cold") manocept.

Results: Fluorescence microscopy showed that manocept-Cy3+/CD206+ cells were present at high levels in the synovial compartment of RA. These signals were co-localized along cellular membranes, and manocept-Cy3+ staining was statistically significant when compared to OA patients and healthy controls, as measured by digital image analysis. Flow cytometry demonstrated similar levels of CD68, CD206, and manocept-Cy3 in synovial fluid samples. No fluorescent signal was observed in RA synovial tissue incubated with CD206 isotype-matched antibody or with "cold" manocept incubation prior to manocept-Cy3 staining.

Conclusion: The identification of an imaging biomarker that is both sensitive and specific for the RA inflammatory process is critical in the diagnosis of patients with early joint symptoms and in monitoring therapeutic responses. Our results suggest that CD206-targeted manocept is a viable candidate to pursue clinically as an imaging biomarker for RA.



CD206$^+$/NAVRA-Manocept-Cy3$^+$ cells are detected in synovium of Rheumatoid arthritis patients. Synovial tissue was collected from patients with rheumatoid arthritis **(A)** or healthy controls **(B)** and flash-frozen for immunohistochemistry with anti-CD206 (green) antibody, NAVRA-Manocept-Cy3 (red), and DAPI nuclear label (blue). Enhanced image magnification is displayed in subsequent rows. Representative images are shown.

Disclosure: N. A. Young, None; **L. Schlesinger**, Navidea Biopharmaceuticals, 5; **T. J. Rosol**, Navidea Biopharmaceuticals, 5; **F. Cope**, Navidea Biopharmaceuticals, 4; **W. N. Jarjour**, Navidea Biopharmaceuticals, 5.

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Anti-Peptidyl Arginine Deiminase 4 Antibodies in African-Americans with Rheumatoid Arthritis and Radiographic Scores. Iris Navarro-Millan[1], Andrew Westfall[1], Erika Darrah[2], Antony Rosen[3], Ted R. Mikuls[4], Richard Reynolds[1], Maria I. Danila[1], Jeffrey R. Curtis[1] and S. Louis Bridgesr Jr. [1].[1]University of Alabama at Birmingham, Birmingham, AL, [2]The Johns Hopkins University, Division of Rheumatology, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]Veteran Affairs Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: The presence of serum autoantibodies to peptidyl arginine deiminase 4 (PAD4) have been associated with erosive rheumatoid arthritis (RA) in populations that were composed of predominantly Caucasian patients with RA but their role has not been studied in African-Americans with RA. We sought to determine the prevalence of serum anti-PAD4 antibodies in African-Americans with RA and if there was an increase in radiographic scores among those patients with anti-PAD4 antibodies (+anti-PAD4) compared to those that were negative for anti-PAD4 (-anti-PAD4).

Methods: Patients with RA included in the study were 193 participants in the Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis (CLEAR) Registry I and II. For this analysis we combined patients with early RA (CLEAR I) and established RA (CLEAR II). Descriptive statistics were used to determine the main characteristics of the cohort, the prevalence of anti-PAD4, the proportion of radiographic scores >0 among those that were +anti-PAD4 and those that were –anti-PAD4 and the distribution of radiographic scores. All the data for this study were analyzed cross-sectionally.

Results: The mean age was 55 years, mean disease duration was 8 years, 86% of the patients were female, 73% were positive for anti-cyclic citrullinated peptide (CCP). The prevalence of anti-PAD4 antibodies was 24% and 91% of the patients that were +anti-PAD4 were also positive for anti-CCP. There were 83% of the +anti-PAD4 patients that had radiographic scores >0 and 63% in the –anti-PAD4 had radiographic scores >0. The mean radiographic scores for the +anti-PAD4 and –anti-PAD4 patients were 52.8 (SD ± 69.7) and 31.0 (SD ± 59.8), respectively (p-value = 0.005).

Conclusion: In this cross-sectional analysis of African American RA patients, the prevalence of anti-PAD4 antibodies among African-American RA patients was similar to that reported in previous RA cohorts of predominantly Caucasian RA patients. African-American patients with +anti-PAD4 were more likely to have higher radiographic scores than those that were –anti-PAD4. Further analyses where the association of anti-PAD4 antibodies is used to determine radiographic progression among African-Americans with RA is warranted.

Disclosure: I. Navarro-Millan, None; **A. Westfall**, None; **E. Darrah**, None; **A. Rosen**, None; **T. R. Mikuls**, Genentech/Roche, 2; **R. Reynolds**, NIAMS-NIH, 2; **M. I. Danila**, NIAMS-NIH, 2; **J. R. Curtis**, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **S. L. Bridges Jr.**, None.

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***Porphyromonas Gingivalis* and Bone Turnover Biomarkers in Rheumatoid Arthritis.** Manpreet Sethi[1], Anand Dusad[1], Harlan Sayles[2], Geoffrey Thiele[2], Jeffrey Payne[3], Michael J. Duryee[1], Bart Hamilton[4] and Ted R. Mikuls[5]. [1]University of Nebraska Medical Center, Omaha, NE, [2]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [3]University of Nebraska Medical Center, Lincoln, NE, [4]University of Nebraska Medical Centre and Omaha VA Medical Center, Omaha, NE, [5]Veteran Affairs Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: Periodontitis (PD) associated with *P. gingivalis* has been implicated as a risk factor for rheumatoid arthritis (RA). We have previously demonstrated that RA patients with PD have more active and more severe disease, the latter reflected by the presence of more radiographic damage in the hands and wrists (Mikuls et al. *Arthritis Rheumatol* 2014). Moreover, we have shown that antigen-specific ACPA are overexpressed in those with PD, including ACPA implicated in osteoclastogenesis and bone damage that characterizes RA. The purpose of this study was to examine whether the presence of subgingival *P. gingivalis* was associated with increased bone turnover and to further explore the associations of bone turnover markers with RA-related autoantibody and joint damage.

Methods: RA patients (n=287) underwent a standardized full-mouth periodontal examination that included the collection of subgingival plaque samples with the presence of *P. gingivalis* identified using PCR. Hand/wrist radiographs were scored using a modified Sharp score. Patients were tested for RF, anti-CCP, and anti-cit-vimentin antibody. Serum bone turnover biomarkers were measured by ELISA and included BAP (MicroVue, an indicator of bone formation); TRAP5b (MicroVue) and cathepsin-K (CTPK; Biomedica), the latter two biomarkers of bone resorption. The Kruskal-Wallis test was used to examine associations of bone biomarkers with the presence of *P. gingivalis* or PD. Spearman rank correlations were used to assess associations between these biomarkers with RA clinical measures.

Results: RA patients with subgingival *P. gingivalis* had significantly higher serum concentrations of TRAP5b (<0.001) and CTPK (p=0.003) compared to those without *P. gingivalis* (Table). CTPK, but not TRAP5b was higher in those with PD vs. those without PD. There was no difference in BAP based on PD or *P. gingivalis* status. TRAP5b demonstrated modest but statistically significant associations with modified Sharp score ($r = 0.16$, $p = 0.01$), anti-CCP ($r = -0.26$, $p < 0.001$), and anti-cit-vimentin ($r = -0.14$, $p = 0.02$) while CTPK demonstrated associations with DAS-28-CRP ($r = 0.13$, $p = 0.03$), anti-CCP ($r = 0.17$, $p = 0.005$), anti-cit-vimentin ($r = 0.13$, $p = 0.03$), and RF ($r = 0.30$, $p < 0.001$).

Conclusion: Serum biomarkers of osteoclast mediated bone resorption, TRAP5b and CTPK, are elevated in RA patients harboring *P. gingivalis* infection and are associated with disease-related autoantibody and joint damage. These results suggest that previously reported links between PD with greater RA disease severity may be related at least in part to oral infection with *P. gingivalis* with detrimental effects on bone that appear to be mediated by the increased osteoclast activity.

Table: Mean (SD) of bone turnover markers in patients with RA (n=287) based on presence/absence of subgingival *P.* gingivalis or PD; p-values generated using Kruskal-Wallis test

	Subgingival *P. gingivalis* (PCR)			Periodontitis (PD)		
Measure	**Positive**	**Negative**	**p-value**	**Positive**	**Negative**	**p-value**
BAP	22.9 (8.0)	22.5 (8.4)	0.484	23.5 (8.0)	22.4 (8.2)	0.265
Trap5b	2.6 (2.0)	1.7 (1.3)	<0.001	2.1 (1.4)	2.4 (2.0)	0.790
CTPK	13.6 (59.5)	4.5 (10.3)	0.003	11.0 (46.9)	10.2 (49.6)	0.008

Disclosure: M. Sethi, None; **A. Dusad**, None; **H. Sayles**, None; **G. Thiele**, None; **J. Payne**, None; **M. J. Duryee**, None; **B. Hamilton**, None; **T. R. Mikuls**, None.

1476

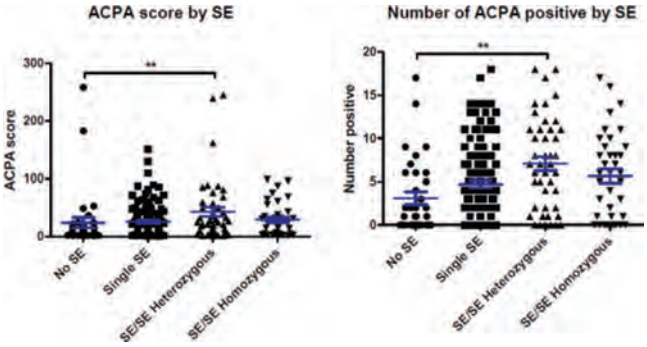
A Dose Response Relationship Between Shared Epitope and ACPA Level: But Not All SE Alleles Are Created Equal. Jeremy Sokolove[1], Lauren J. Lahey[1], Catriona Wagner[2], Irene Smolik[3], David B. Robinson[3], Elizabeth D. Ferucci[4], Marianna Newkirk[5], Marvin Fritzler[6], William H. Robinson[7] and Hani El-Gabalawy[3]. [1]VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA, [2]VA Palo Alto Healtlh Care System and Stanford University, Palo Alto, CA, [3]University of Manitoba, Winnipeg, MB, [4]Alaska Native Tribal Health Consortium, Anchorage, AK, [5]McGill University, Montreal, QC, [6]University of Calgary, Calgary, AB, [7]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA.

Background/Purpose: Indigenous North American populations have high prevalence of seropositive RA. The Cree/Ojibway population in Central Canada and the Alaska Native population have a high prevalence of SE alleles, specifically DRB1∗0404 and ∗1402. Presence of the SE with the non-SE allele∗0901, is associated with early RA onset and the presence of ACPA in unaffected relatives of RA patients. We examined the association of SE copy number as well as specific SE alleles with the depth and breadth and fine specificity of ACPA response.

Methods: RA patient subjects were classified as containing no copies of the SE (n=58), a single copy of the SE (SE/X, n=116), or two copies of the SE (SE/SE, n=58). We similarly stratified subjects with two copies as homozygous (n=36) or heterozygous (n=22). Using a multiplex ACPA antigen array, we evaluated the depth of the ACPA response using an ACPA score (sum of all normalized ACPA titers divided by number of epitopes) and the breadth of the ACPA response by defining the total number of ACPA positive. We used significance analysis of microarrays to compare ACPA subtypes between different SE alleles.

Results: Those with one copy of the shared epitope had more ACPA than those with no copies of the SE and those with two copies displayed more ACPA than those with one copy. Among those with two copies of the SE, the highest levels were observed among subjects heterozygous for two different SE alleles compared to those with no copies of the SE ($P<0.01$) and a trend toward higher levels in those with a single SE allele or homozogous for two copies of the same SE allele. Analysis of the predominant SE alleles within this population revealed a gradient of ACPA associations with *1402 positive patients demonstrating increased ACPA compared with all non-1402 patients and more than the *0404 population. ACPA specificities increased among the 1402 patients included several citrullinated fibrinogen epitopes and citrullinated enolase. Subjects with the *0901 allele alone (X/0901) demonstrated no increase in ACPA and no additional contribution 0901 was noted in heterozygotes expressing a single copy of the SE and *0901.

Conclusion: We observed a stepwise increase in depth and breadth of the ACPA response with increasing dose of SE, an effect primarily seen among those heterozygous for two different SE alleles. These observations support reports suggesting that a heterozygous SE allele combination is associated with RA severity. Moreover, the prominence of the *1402 SE allele as a strong risk factor for an expanded ACPA response is intriguing considering the proposed protective effect of serine residues present in positions 11 and 13 of this allele. Exploration of the peptide binding capacity of this MHC molecule will be important in understanding how it may shape the ACPA response.



Disclosure: J. Sokolove, None; **L. J. Lahey**, None; **C. Wagner**, None; **I. Smolik**, None; **D. B. Robinson**, None; **E. D. Ferucci**, None; **M. Newkirk**, None; **M. Fritzler**, None; **W. H. Robinson**, None; **H. El-Gabalawy**, None.

1477

Overweight and Obesity Are Associated with Reduced Risk of Rheumatoid Arthritis in Men, but Not in Women. Carl Turesson[1], Ulf Bergström[2], Mitra Pikwer[3], Jan-Åke Nilsson[2] and Lennart Jacobsson[2]. [1]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [2]Lund University, Malmö, Sweden, [3]Mälar Hospital, Eskilstuna, Sweden.

Background/Purpose: There are diverging results on the relation between body mass index (BMI) and risk of rheumatoid arthritis (RA). Several studies have reported different patterns in men and women. Our purpose was to investigate the impact of overweight and obesity on the risk of RA in a prospective study.

Methods: Between 1991 and 1996, 30447 subjects (12121 men; 18326 women) were included in a population based health survey. Height and weight were measured, and life style factors were assessed using a questionnaire. From this population, we identified individuals who developed RA after inclusion by linkage to 4 different RA registers. In a structured review of the medical records, patients were classified according to the 1987 American College of Rheumatology criteria for RA. Four controls for each validated case, matched for sex, year of birth and year of screening, who were alive and free of RA when the index person was diagnosed with RA, were selected from the health survey database. The impact of overweight or obesity (BMI > 25 kg/m^2) compared to normal BMI (18.5–25 kg/m^2) on the risk of RA was examined in conditional logistic regression models, stratified by sex.

Results: A total of 172 patients (36 men/136 women, mean age at RA diagnosis 63 years) were diagnosed with RA after inclusion in the health survey. The median time from inclusion to RA diagnosis was 5 years (range 1–13). A total of 51 % of cases and controls combined were overweight or obese. Being overweight or obese at inclusion in the health survey was associated with a reduced risk of subsequent development of RA in men [odds ratio (OR) 0.33; 95 % confidence interval (CI) 0.14–0.76], but not in women (OR 1.01; 95 % CI 0.65–1.54). Men who fulfilled the WHO definition for obesity (BMI >30 kg/m^2) had a significantly decreased risk of RA compared to those with normal BMI (OR 0.08; 95 % CI 0.01–0.67), and there was a similar trend for those with overweight (BMI 25–30 kg/m^2) (OR 0.42; 95 % CI 0.17–1.00). Smoking was a significant predictor of RA in both sexes, and negatively associated with overweight/obesity in men. The estimated impact of overweight/obesity on the risk of RA in men was similar in analyses adjusted for smoking (OR 0.37; 95 % CI 0.16–0.87) and analyses adjusted for smoking, level of education and alcohol use (OR 0.37; 95 % CI 0.13–1.04). In women, overweight/obesity had no effect on the risk of RA in multivariate analyses.

Conclusion: Being overweight or obese was associated with a reduced risk of future RA in men. This pattern did not appear to be explained bydifferences in smoking, education or alcohol use. There was no such association in women. Factors related to adipose tissue may contribute to mechanisms that are protective from RA in men.

Disclosure: C. Turesson, None; **U. Bergström**, None; **M. Pikwer**, None; **J. Nilsson**, None; **L. Jacobsson**, None.

ACR/ARHP Poster Session B
Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy: Novel therapies, Biosimilars, Strategies and Mechanisms in Rheumatoid Arthritis
Monday, November 17, 2014, 8:30 AM–4:00 PM

1478

Pharmacokinetics, Bioavailability and Safety of a Modified-Release Once-Daily Formulation of Tofacitinib in Healthy Volunteers. M. Lamba[1], R. Wang[1], T. Fletcher[2], C. Alvey[1], A. Hazra[1], J. Kushner[1], J. Larmann[1] and T. Stock[2]. [1]Pfizer Inc, Groton, CT, [2]Pfizer Inc, Collegeville, PA.

Background/Purpose: Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). The efficacy and safety of an immediate-release (IR) formulation of tofacitinib, dosed twice daily (BID), has been assessed in patients with active moderate to severe RA. A once daily (QD) posology of tofacitinib will enhance patient convenience, ease of use, and has the potential to optimize compliance.[1] To facilitate QD dosing, a novel modified-release (MR) formulation of tofacitinib at a dose of 11 mg has

been designed to achieve comparability of systemic exposure parameters vs IR 5 mg BID. The study aimed to determine equivalence for extent of exposure between the tofacitinib MR 11 mg vs IR formulation administered as two 5 mg tablets.

Methods: This was a randomized, open-label, 2-period, 2-sequence crossover study conducted in 26 healthy volunteers (HV). Following an overnight fast, HV were randomized to receive single doses of either MR 11 mg or IR 2 × 5 mg. Treatments were separated by a 72-hour (h) washout. Pharmacokinetic (PK) parameters were calculated using non-compartmental analyses (NCA). The primary endpoint was extent of tofacitinib exposure, measured as area under the concentration-time curve from time zero extrapolated to infinite time (AUC_{inf}). A mixed-effects model was used to generate adjusted geometric mean ratios (MR/IR) and 90% confidence intervals (CIs). The steady-state profiles of tofacitinib MR and IR were predicted using single-dose data from this study.

Results: All 26 HV completed the study and were included in the analyses. The study population had mean age of 33.6 years, mean body weight of 77.5 kg, and was 81% male. For the MR and IR formulations, geometric mean AUC_{inf} (ng*h/mL) was 297.5 and 286.3, respectively, resulting in an MR/IR ratio of 103.91% (90% CI 100.49%, 107.45%). Maximum plasma concentration adjusted for formulation ($C_{max,\ adj}$; ng/mL) was 40.75 and 44.10 for MR and IR, respectively, resulting in an MR/IR ratio of 92.40% (90% CI 84.99%, 100.45%). For both parameters, 90% CI values were wholly contained within the 80–125% interval. Mean terminal half-life was 5.71 h and 3.41 h for MR and IR formulations, respectively. The most common AEs were nausea, abdominal pain, back pain, and headache. Incidence of AEs was similar between treatment groups and no serious or severe AEs were reported. Predictions following steady-state dosing indicate similar AUC, peak concentration and minimum concentration values, and similar time above JAK1/3 half-maximal inhibitory concentration signaling thresholds between MR and IR formulations.

Conclusion: This study demonstrates the single dose equivalence of AUC_{inf} and $C_{max,\ adj}$ of the MR and IR formulations of tofacitinib. Single doses of both formulations were well tolerated. This novel MR formulation of tofacitinib facilitates an opportunity to enable QD dosing, while maintaining systemic drug concentrations similar to the IR formulation (administered BID). Multiple-dose studies will be conducted to confirm the steady-state PK profile predictions and demonstrate equivalence between formulations following steady-state dosing.

1. Coleman CI et al. J Manag Care Pharm 2012; 18: 527–39.

Disclosure: M. Lamba, Pfizer Inc, 1, Pfizer Inc, 3; **R. Wang**, Pfizer Inc, 1, Pfizer Inc, 3; **T. Fletcher**, Pfizer Inc, 1, Pfizer Inc, 3; **C. Alvey**, Pfizer Inc, 1, Pfizer Inc, 3; **A. Hazra**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Kushner**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Larmann**, Pfizer Inc, 1, Pfizer Inc, 3; **T. Stock**, Pfizer Inc, 1, Pfizer Inc, 3.

1479

Impact of Clinical Remission on Physical Function in Patients with Rheumatoid Arthritis Treated with ALX-0061: Post-Hoc Analysis of Phase I/II Data.

Katrien Van Beneden[1], Katrien Verschueren[1], Wouter Willems[1], Heidi Wouters[1], Joke D'Artois[1], Katelijne De Swert[1], Steven De Bruyn[1] and Gerhard Arold[2]. [1]Ablynx nv, Zwijnaarde, Belgium, [2]PRA International GmbH, Berlin, Germany.

Background/Purpose: ALX-0061 is a monovalent IL-6R targeting Nanobody, inhibiting signaling via soluble and membrane IL-6R. The safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of ALX-0061 was assessed in a Phase I/II study in patients (pts) with active rheumatoid arthritis (RA) on stable methotrexate (MTX) therapy (1).

Since remission is the recommended treatment target in the management of RA, the purpose of this post-hoc analysis was to assess induction and maintenance of remission during ALX-0061 treatment. In addition, the impact of disease remission on physical function following 24-week treatment with ALX-0061 was also assessed.

Methods: Data were obtained from the multi-center, randomized, double-blind, placebo (PBO) controlled, dose escalation, Phase I/II study (1). During the first 12 weeks (wks) of the multiple ascending dose period, 37 pts received PBO (n=6) or ALX-0061 IV (n=31) at 1 or 3 mg/kg Q4W, or 6 mg/kg Q8W. Patients received stable doses of MTX ranging from 10–25 mg/week. In the second 12 wks period, pts with insufficient EULAR response had the ALX-0061 dose increased or switched from PBO to ALX-0061. 24 pts continued on their originally-assigned ALX-0061 IV dose (8 pts in 1 mg/kg arm, 8 pts in 3 mg/kg arm, and 8 pts in 6 mg/kg arm), 4 pts changed their dosing regimen, and 3 pts switched from PBO to ALX-0061. This post-hoc analysis utilized data from pts whose originally assigned ALX-0061 dose remained unmodified. Clinical remission as defined by both DAS28 < 0.5 defining normal physical function. An improvement in HAQ score 0.25 was considered to be clinically meaningful.

Results: At week 24, 62.5% (15/24) of pts treated with ALX-0061 achieved DAS28<2.6 remission, while remission using the more stringent Boolean criteria was observed in 29.2% (7/24) of the pts. Looking at maintenance of remission between 12 and 24 wks, approximately one third, i.e. 37.5% and 29.2%, of pts treated with ALX-0061 remained in DAS28 remission during the last 3 (at wks 16, 20, and 24) and 4 (at wks 12, 16, 20, and 24) consecutive time points, respectively. Maintenance of remission based on the Boolean criteria was also observed, being 20.8 and 16.7% of the pts for up to the last 3 or 4 successive time points. At week 24, clinically meaningful improvement in HAQ was observed in 66.7% (16/24) of the pts treated with ALX-0061. Compared to pts not in remission, more pts in DAS28 remission at week 24 achieved normal physical function (86.7% vs. 22.2%). Moreover, normal physical function was observed in 100% (7/7) of pts in Boolean remission at week 24.

Conclusion: In this study in pts with established RA, ALX-0061 induced and maintained remission as assessed by both DAS28 and the more stringent Boolean remission definition. Control of disease activity was also important in regaining normal physical function, supporting treat-to-target management of RA as reflected in the EULAR recommendations.

Reference:

(1) Ann Rheum Dis 2013;72(Suppl3):64

Disclosure: K. Van Beneden, Ablynx nv, 3; **K. Verschueren**, Ablynx nv, 3; **W. Willems**, Ablynx nv, 3; **H. Wouters**, Ablynx nv, 3; **J. D'Artois**, Ablynx nv, 3; **K. De Swert**, Ablynx nv, 3; **S. De Bruyn**, Ablynx nv, 3; **G. Arold**, PRA, 3.

1480

Dose Selection of GLPG0634, a Selective JAK1 Inhibitor, for Rheumatoid Arthritis Phase 2B Studies: PK/PD and Exposure-DAS28 Modeling Approach.

Florence Namour[1], Chantal Tasset[2], Béatrice Vayssière[1], Gerben van 't Klooster[2], Paul Diderichsen[3] and Eugène Cox[4]. [1]Galapagos SASU, Romainville, France, [2]Galapagos NV, Mechelen, Belgium, [3]Quantitative Solution, Breda, Netherlands, [4]Quantitative Solutions, Breda, Netherlands.

Background/Purpose: GLPG0634 is an orally-available, selective Janus kinase 1 (JAK1) inhibitor. Selective inhibition of JAK1 may combine favorable safety and clinical efficacy profiles with rapid onset of action. GLPG0634 showed encouraging pharmacodynamics, safety and efficacy in early clinical studies treating RA patients for 4 weeks. Here the contribution of exposure-response (E-R) modelling and simulation to support GLPG0634 dose selection for Phase 2B studies is presented.

Methods: Population predicted and individual responses to treatment were investigated on the basis of simulated exposures to GLPG0634 and its main metabolite. Non-linear mixed-effects E-R models were built to describe the proportion of cells showing phosphorylation of STAT1 following activation with IL-6 in healthy subjects (JAK1 activity, PD response) and DAS28 improvement from baseline in RA patients treated for 4 weeks (clinical response). Continuous covariates were evaluated in the models as a power function while binary covariates were tested as factors. The pSTAT1 response over 24-h at steady state and the contribution of the active metabolite to the biomarker response, were predicted for a male with bodyweight of 75 kg. The DAS28 E-R model was used to predict the improvement of the clinical response following 12 weeks of GLPG0634 treatment. Simulations of both biomarker and clinical responses were investigated over a 30 to 300 mg daily dose range.

Results: The PK of GLPG0634 and its active metabolite were adequately described by an integrated model with two- and one-compartmental disposition, respectively. The observed pSTAT1 response was described by a sigmoidal E_{MAX} model, with EC_{50} values of 471 ng/mL and 1770 ng/mL for GLPG0634 and its metabolite, respectively. The steady state inhibition of pSTAT1 was predicted to be between 64.3% (pre-dose) and 91.9% (at C_{max}) following treatment with 200 mg GLPG0634 QD with no relevant increase in PD response at higher doses. Biomarker response over the dosing interval correlates with the time profiles of GLPG0634 and its metabolite. While inhibition is maximal at the peak of GLPG0634, the sustained inhibition correlated with the long lasting metabolite exposure. The observed DAS28 change from baseline was adequately described by a linear direct response model using the individual predicted metabolite exposure as a predictor of response. The population DAS28 change from baseline was predicted to be -2.2 and -2.6 at week 4 and 12 following 200 mg GLPG0634 QD with no further improvement in DAS28 response at higher

doses. No covariates were included in the models of biomarker or clinical response.

Conclusion: Current modeling and simulation on the basis of early clinical data support that both GLPG0634 and its main metabolite contribute to JAK1 inhibition, as reflected in pSTAT1 biomarker response. Simulations of the pharmacodynamics (pSTAT1) and efficacy (DAS28) show a dose-related response with a maximum efficacy achieved at a daily dose of 200 mg GLPG0634. No further gain is obtained at higher doses. The overall clinical response is in the range of that observed with registered biological DMARDS. A daily dose range from 50 to 200 mg is currently being tested in the DARWIN Phase 2B program.

Disclosure: F. Namour, GALAPAGOS, 3; **C. Tasset**, GALAPAGOS, 3; **B. Vayssière**, GALAPAGOS, 3; **G. van 't Klooster**, GALAPAGOS, 3; **P. Diderichsen**, QUANTITATIVE SOLUTIONS, 3; **E. Cox**, QUANTITATIVE SOLUTIONS, 3.

1481

Phase 1 and Phase 2 Data Confirm That GLPG0634, a Selective JAK1 Inhibitor, Has a Low Potential for Drug-Drug Interactions. Namour Florence[1], Desrivot Julie[1], Annegret Van der Aa[2], Chantal Tasset[2] and Gerben van 't Klooster[2]. [1]Galapagos, Romainville, France, [2]Galapagos NV, Mechelen, Belgium.

Background/Purpose: GLPG0634 is an orally-available, selective Janus kinase 1 (JAK1) inhibitor. Selective inhibition of JAK1 may combine improved safety and clinical efficacy profiles with a rapid onset of action. GLPG0634 showed encouraging safety and efficacy results in early clinical studies treating RA patients for 4 weeks. As RA patients can be on multiple medications, an understanding of the potential for drug-drug interaction was of interest.The exploration of potential drug-drug interactions *in vitro* and in humans is presented here.

Methods: Inhibition or induction of drug-metabolizing enzymes [CYP450, uridine glucuronyltransferases (UGT)] and key drug transporters (Pgp, BCRP, BSEP, OATs, OCTs, OATP1B1 and OATP1B3) were studied using human microsomes, cell systems or recombinant enzymes with reference substrates as suitable. An open-label study in healthy subjects was conducted to confirm the in vitro conclusion on interaction potential with CYP3A4 by evaluating the effects of GLPG0634 co-administration on a sensitive CYP3A4 substrate, midazolam. The oral pharmacokinetics of midazolam was assessed following a single dose of 2 mg prior to and after once daily dosing of 200 mg GLPG0634 for 7 days. Furthermore, the potential interaction with methotrexate, a drug commonly administered to RA patients and shown in vitro to be partially eliminated in urine by OCTs transporters was investigated during a clinical study in RA patients treated with up to 300 mg daily dose GLPG0634 for 4 weeks.

Results: *In vitro* studies showed that the GLPG0634 metabolism is not CYP450 dependent and is mediated by carboxylesterases (CES)with 70% of the metabolite produced by CES2. *In vitro*, GLPG0634 and its main metabolite do not induce CYP1A2, CYP2B6 and CYP3A4 at concentrations at least two-fold of the peak concentration (C_{max}) in patients administered a 200 mg daily dose of GLPG0634. The IC_{50} for inhibition of each of the CYPs tested and UGT1A1 and UGT2B7 is at least 7-fold above the C_{max} for GLPG0634 and its main metabolite. Drug transporters are not inhibited by GLPG0634 and its metabolite, except minor effects on OCT2. The IC_{50} for OCT2 inhibition are 2.6- and 6.2-fold over the C_{max} values of GLPG0634 and its metabolite, respectively, after a daily dose of 200 mg, while. In healthy subjects, there was no difference in the plasma midazolam pharmacokinetic profile with and without GLPG0634. Adjusted geometric ratios for midazolam plus GLPG0634 were 99.3% [87.6–112.5%] and 105.4% [94.8–117.3%] for C_{max} and AUC, respectively, well within the no effect boundary guidelines (80–125%). In RA patients, neither the C_{max}, nor AUC of methotrexate in plasma was influenced by the co-administration of GLPG0634, with mean values of 156–172 ng/mL and 568–680 ng.h/mL for C_{max} and AUC, respectively. GLPG0634 was safe and well tolerated.

Conclusion: The clinical data show a lack of relevant drug interactions by GLPG0634 with CYP3A4 substrates, either through inhibition or induction of CYP3A4 activity in humans, as well as with OCTs transporters via methotrexate elimination. All together the *in vitro* data on CYP450s, UGTs and key drug transporters, support that GLPG0634 can be co-administered with drugs usually administered to RA patients without dose adjustment.

Disclosure: N. Florence, Galapagos, 3; **D. Julie**, Galapagos, 3; **A. Van der Aa**, Galapagos, 3; **C. Tasset**, GALAPAGOS, 3; **G. van 't Klooster**, GALAPAGOS, 3.

1482

Response of Patient Reported Symptoms of Stiffness and Pain during the Day from Adding Low-Dose Delayed-Release (DR) Prednisone to Stable DMARD Therapy over 12 Weeks in Patients with Moderate Rheumatoid Arthritis (RA). Rieke Alten[1], Amy Y. Grahn[2], Patricia Rice[3], Robert Holt[4] and Frank Buttgereit[1]. [1]Charité University Medicine, Berlin, Germany, [2]Horizon Pharma, Inc., Deerfield, IL, [3]Premier Research, Naperville, IL, [4]University of Illinois-Chicago, Vernon Hill, IL.

Background/Purpose: RA patients experience stiffness which impacts their daily lives. Although this patient reported symptom was dropped from the RA classification criteria there is growing interest in understanding more about stiffness in RA. (1) Stiffness is described in temporal terms (morning, evening) and patients report difficulty distinguishing stiffness from pain and swelling. (1) The CAPRA-2 (C2) study previously demonstrated significant relative reductions in patient reported morning stiffness duration and severity with 5 mg daily DR prednisone as compared to placebo in RA patients receiving non-biologic DMARDs. (2) We report the 12 week relative change of reoccurrence of joint stiffness and pain during the day collected by patient diary to further characterize these symptoms. Previously a strong correlation between morning stiffness severity and morning pain was reported for C2. (3)

Methods: RA patients with moderate disease on non-biologic DMARDs previously randomized (2:1) to receive DR-prednisone or placebo were evaluated at baseline (BL), 2, 6, and 12 weeks for relative changes in patient reported outcomes listed in Table 1. Data on relative change from baseline to 12 weeks were analyzed for the modified-intent-to-treat population under observed-case and last observation carried forward (LOCF) conditions. Significance (least square means) and 95% confidence intervals were established based on the mean relative percent change from BL. Point biserial correlation of daily reoccurrence of joint stiffness (Y or N) and pain (100mm VAS) for all patients was performed.

Results: 350 moderate RA patients mean age 57, 58% female, mean duration of RA 8 years, 94% naïve to prednisone. 231 received 5 mg DR prednisone and 119 received placebo, all on stable DMARDs. There was a statistically significant reduction in reoccurrence of joint stiffness during the day over the 12 weeks; pain decreased for all patients with no difference in treatment groups (Table 1). Patient global assessment, SF-36 physical function and analgesic use showed significance between treatment groups. There was moderate correlation of reoccurrence of joint stiffness and pain ($r = 0.47$).

Conclusion: Adding DR prednisone to the treatment of RA patients on non-biologic DMARDs produced statistically significant reduction in reoccurrence of joint stiffness during the day, improvements in patient global assessment and SF-36 physical function and a decrease in analgesic use over 12 weeks. Correlation was shown regardless of treatment between reoccurrence of joint stiffness and pain during the day further supporting the strong patient relationship of symptoms of stiffness and pain reported previously.(3)

References:

(1) Orbai, et al. Ann Rheum Dis 2014;73(2):S261–262.
(2) Buttgereit, et al. Ann Rheum Dis 2013;72:204–210.
(3) Buttgereit, et al. Arthritis Rheum2012;64(10):S544–545.

Table 1. Results of CAPRA-2 Patient Reported Outcomes Over 12 Weeks

Patient Reported Outcome	DMARD + DR Prednisone (N = 231)	DMARD + Placebo (N = 119)	Difference 95% (CI)	*P* value
Joint stiffness reoccurrence (diary; Y/N: % change in days with stiffness reoccurrence during the day)*	−27.0	−7.1	−19.9 (−37.7, −2.1)	0.03
Pain during the day (diary; 100 mm VAS)	−25.5	−31.7	6.14 (−37.8, 50.1)	0.78
Patient Global Assessment (Visit)	−17.8	7.49	−25.3 (−44.6, −5.9)	0.01
SF-36 Physical Functioning (Visit)	33.9	13.6	20.33 (2.33, 38.3)	0.03
SF-36 Mental Health (Visit)	14.3	9.16	5.10 (−1.71, 11.9)	0.14
Daily Analgesic Use (diary; %)+	−18.7	1.9	−20.6 (−37.3, −4.0)	0.02

LOCF median, relative % change from BL (95% CI), Least Square Means (LSM)
LSMs are from an ANCOVA with baseline value, treatment, and geographic region as factors
*Reoccurrence of stiffness during the day is the percentage of days with stiffness reoccurrence over last 7 days prior to visit day (including day of visit). If more than 4 assessments are missing then reoccurrence isset to missing.
+% days with additional analgesics use

Disclosure: R. Alten, Horizon Pharma, Inc, 5; **A. Y. Grahn**, Horizon Pharma, Inc, 3; **P. Rice**, Horizon Pharma, Inc, 5; **R. Holt**, Horizon Pharma, Inc, 5; **F. Buttgereit**, Horizon Pharma, Inc, 5.

1483

Efficacy and Safety of Baricitinib in Japanese Rheumatoid Arthritis Patients during a 52 Week Extension Phase. Yoshiya Tanaka[1], Kahaku Emoto[2], Zhihong Cai[2], Douglas E. Schlichting[3], Terence Rooney[3] and William Macias[3]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Eli Lilly Japan K.K., Kobe, Japan, [3]Eli Lilly and Company, Indianapolis, IN.

Background/Purpose: Baricitinib (bari), an oral JAK1/JAK2 signaling inhibitor, was evaluated in a blinded phase 2b study for 12 weeks as a treatment for rheumatoid arthritis (RA) in Japanese patients (pts) on background methotrexate therapy[1]. Clinical efficacy (ACR20 response) was significantly greater for a combined 4- and 8-mg QD baricitinib group versus placebo (PBO) and safety signals were consistent with previous experience in non-Japanese pts[2]. Baricitinib's safety and efficacy during an additional 52 weeks of treatment in Japanese RA pts completing the12 week, PBO-controlled study are reported here.

Methods: Pts were randomized (double-blind) to receive PBO or 1-, 2-, 4- or 8-mg baricitinib QD for 12 weeks (Part A; N=145). At 12 weeks, pts receiving PBO or 1- or 2-mg baricitinib were randomized 1:1 to 4- or 8-mg bari QD for an additional 52 weeks (Part B). Pts receiving 4- or 8-mg baricitinib QD during Part A received the same doses in Part B. However, those receiving 8 mg in Part B were dose-reduced to 4 mg bari QD in a blinded fashion, upon approval of a protocol amendment. Pts and investigators remained blinded to Part B treatment assignment. Efficacy and safety were evaluated by ACR response, measures of low disease activity (LDA) and remission, adverse events (AEs), and discontinuation rates.

Results: Of 145 pts randomized in Part A, 141 entered Part B and received 4 mg (n=71) or at least one dose of 8 mg (n=70) baricitinib QD (Table). Rates of ACR20 responses at 64 weeks were 66% and 73% for the 4- and 8-mg baricitinib groups, respectively. LDA rates ranged from 48% to 65% and 53% to 70%, respectively, for 4- and 8-mg baricitinib groups. Remission rates ranged from 32% to 56% and 24% to 66% for 4- and 8-mg baricitinib groups, respectively. No deaths occurred during the study. Incidences of serious AEs (SAEs) were 11% and 17% for 4- and 8-mg baricitinib, respectively. Incidences of AEs leading to discontinuation were 21% and 17% for 4- and 8-mg groups. AE incidences leading to study drug interruption occurred for 25% of 4 mg and 43% of the 8 mg baricitinib groups. Treatment-emergent AEs (TEAEs) occurred in over 95% of all pts during Part B. For those pts with TEAEs 74% and 68% were rated as mild and 9% and 12% were rated as severe for the 4- and 8-mg baricitinib groups, respectively. Treatment-emergent (TE) infections occurred in 66% of pts in each group with 3% and 6% of pts experiencing a serious infection for the 4- and 8-mg groups, respectively.

Conclusion: In a single-blind 52 week extension of a phase 2b study in Japanese RA patients, efficacy rates observed at 12 weeks[1] were well maintained at 64 weeks for patients on either 4- or 8-mg baricitinib QD. Consistent with prior phase 2 data, the benefit: risk profile seen during 64 weeks of treatment in this study continues to support further development of baricitinib for treatment of RA.

1- Y Tanaka et al. Arthr Rheum. 2013;65(S10):S765.
2- P Taylor et al. Ann Rheum Dis. 2013;72(Suppl3):A65-A66.

Disease Improvement/Activity Measure at 64 Weeks* % (n)	Baricitinib 4 mg (N=71)	Baricitinib 8 mg (N=70)
ACR20	66% (47)	73% (51)
ACR50	54% (38)	61% (43)
ACR70	37% (26)	34% (24)
SDAI ≤ 11.0 LDA	59% (42)	66% (46)
SDAI ≤ 3.3 Remission	38% (27)	31% (22)
DAS28 ESR ≤3.2 LDA	48% (34)	53% (37)
DAS28 ESR < 2.6 Remission	32% (23)	33% (23)
DAS28 CRP ≤ 3.2 LDA	65% (46)	70% (49)
DAS28 CRP < 2.6 Remission	55% (39)	54% (38)
HAQ-DI ≤ 0.5 Remission	56% (40)	66% (46)
Boolean Remission	32% (23)	24%(17)
Safety Measures Occurring During Weeks 12 to 64 (Part B) % (n)		
Serious Adverse Event	11% (8)	17% (12)
Adverse Event (AE) leading to discontinuation	21% (15)	17% (12)
AE leading to study drug interruption	25% (18)	43% (30)
Treatment-emergent AEs (TEAEs)	92% (65)	99% (69)

*Non-responder imputation used to calculate all values so that all patients discontinuing study during Part B treated as non-responders.

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Discovery of ARN-4079 - a Potent, Orally Available Dual Target Inhibitor of Janus Kinase 3 (JAK3) and Interleukin-2 Inducible T-Cell Kinase (ITK) for Rheumatoid Arthritis. Hariprasad Vankayalapati[1], Venkatakrishnareddy Yerramreddy[1], Philip Bendele[2], Alison Bendele[3], Rueban Jacob Anicattu Issac[4], Ram Sudheer Adluri[4], Philip LoGrasso[5] and Joel M. Kremer[6]. [1]Arrien Pharmaceuticals, Salt Lake City, UT, [2]Bolder BioPATH, Inc., Boulder, CO, [3]Bolder BioPATH Inc., Boulder, CO, [4]GVK Biosciences Private Limited., Hyderabad, India, [5]The Scripps Research Institute, Jupiter, FL, [6]Albany Medical College and the Center for Rheumatology, Albany, NY.

Background/Purpose: The Non-receptor tyrosine kinases, JAK3 and ITK are key regulators of cytokine pathways and are important clinically validated targets, which offer the potential for developing targeted therapeutics in treating Rheumatoid Arthritis (RA) and other immunological, inflammatory and autoimmune diseases such as systemic lupus erythematosus, psoriasis, psoriatic arthritis, atherosclerosis, ulcerative colitis and crohns disease. Development of selective small-molecule inhibitors for both JAK3 and ITK is challenging due to the highly conserved ATP binding pocket within the Janus and TEC-kinase family members. Three variable amino acids within the ATP binding pocket of JAK3 and ITK were targeted and inhibitors were rationally designed by employing FIELDS platform. The FIELDS assisted in identifying fragments/scaffolds to a series of lead compounds, and SAR efforts lead to the discovery of the first-in-class irreversible dual JAK3 and ITK inhibitor ARN-4079 for the treatment of RA.

Methods: The JAK3 and ITK enzymatic inhibition and selectivity studies were performed at DiscoveRx. The cell-based profiling using SelectScreen was performed at Life Technologies. *In vivo*cytokine and CIA efficacy studies were conducted using BALB/c and DBA/1OlaHsd mouse models.

Results: Fragment-based discovery and lead optimization of a series of highly selective JAK3 and ITK inhibitors in tandem with control of physicochemical and ADME-Tox properties culminated in selecting clinically ready ARN-4079 from ~300 new chemical entities. ARN-4079 potently inhibited JAK3 and ITK activity with an IC_{50} = 5 nM, and 33 nM in biochemical kinase assay. The ScanKIENTIC Kds were estimated to be 2.5 and 23 nM. ARN-4079 exhibited over 100-fold cellular selectivity within the JAK family and potently inhibited IL-4 induced STAT6 phosphorylation with an IC_{50} = 70 nM. Its low mM inhibition in SelectScreen IL-6, IFN-γ, and EPO supported the JAK3 selectivity and inhibition of PLCγ1-mediated calcium release from $CD4^+$T cells (EC_{50} = 630 nM) *via* TCR engagement supports its ITK selectivity in cells. In a set of *in vivo* experiments, ARN-4079 potently inhibited IL-2, IL-4 and IFN-λ production in mice which are the key characteristics supporting its dual activity. Additionally, ARN-4079 was optimized to have many drug like characteristics in terms of solubility, cell permeation, and DMPK properties. ARN-4079 is an orally available entity (%F = 23), demonstrated efficacy 84% at 60 mg/kg which was equivalent to Tofacitinib in the mouse CIA model. PK studies indicated that, after oral dosing of ARN-4079 reached plasma levels (1080 ng/mL) that are higher or comparable to the therapeutic dose of Tofacitinib (627 ng/mL). Moreover, ARN-4079 showed no toxicity up to doses of 300 mg/kg in rats. On the basis of its strong *in vivo*efficacy and dose tolerability, ARN-4079 was selected for IND enabling studies.

Conclusion: ARN-4079 is a novel, potent, selective small molecule irreversible dual target inhibitor of JAK3 and ITK that has demonstrated dose linear pharmacokinetic, and *in vivo* efficacy in CIA models on par with Tofacitinib. Safety and IND studies are ongoing to develop ARN-4079 as a therapeutic agent for RA.

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Analysis of Patient-Reported Outcomes during Treatment with Mavrilimumab, a Human Monoclonal Antibody Targeting GM-CSFRá, in the Randomized Phase 2b Earth Explorer 1 Study. Joel M. Kremer[1], Gerd Burmester[2], Michael Weinblatt[3], Angela Williams[4], Niklas Karlsson[5], Alex Godwood[4] and David Close[4]. [1]Albany Medical College and the Center for Rheumatology, Albany, NY, [2]Charité University Medicine, Berlin, Germany, [3]Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [4]MedImmune Ltd, Cambridge, United Kingdom, [5]AstraZeneca, Molndal, Sweden.

Background/Purpose: Active RA significantly impairs health-related quality of life (HRQoL) and physical function of patients. Granulocyte-macrophage colony-stimulating factor (GM-CSF) plays a key role in macrophage activation and RA pathogenesis, including inflammatory and arthritic pain development. A prior Phase 2a study (EARTH; NCT01050998) in active RA showed that mavrilimumab produced clinically meaningful improvements across a variety of patient-reported outcomes (PROs). Here we assess the benefit experienced by patients in a 24-week Phase 2b study.

Methods: This randomized, placebo (PBO)-controlled, multicenter study (NCT01706926) evaluated the efficacy/safety of 3 subcutaneous mavrilimumab doses vs PBO every 2 weeks (Q2W) over 24 weeks. Patients with adult-onset RA (18–80 years; DAS28-CRP ≥3.2; ≥4 swollen joints; inadequate response to ≥1 DMARD; receiving methotrexate) were enrolled. Co-primary endpoints were changes in DAS28-CRP score (day 1 to week 12) and ACR20 response (week 24). PRO endpoints included changes from baseline and percent responders in patient assessments of pain, HRQoL (SF-36), physical function (HAQ-DI), and fatigue (FACIT–Fatigue). Patients could enter a long-term open-label rescue study from week 12 (not reported).

Results: In total, 326 patients (mean [SD] age 51.8 [11.1] years; female 86.5%) with a mean (SD) DAS-CRP of 5.8 (0.9) and DAS28-ESR of 6.6 (0.9) were randomized to 30, 100, or 150 mg mavrilimumab, or PBO (n=81, 85, 79 and 81, respectively). Both co-primary endpoints (DAS28-CRP at week 12; ACR20 at week 24) were met at all mavrilimumab doses. At weeks 12 and 24, mavrilimumab treatment groups showed improvements in PROs vs PBO (Table), with more than half of patients receiving mavrilimumab 150 mg having a clinically meaningful response. At this dose, significant improvements (p=0.017–p<0.001) were seen vs PBO across multiple PRO endpoints at weeks 12 and 24 (Table). Statistically significant improvements in pain were seen for mavrilimumab from week 1. Of mavrilimumab 30, 100, and 150 mg patients with a pain response at week 12, 72.2% (26/36), 69.2% (27/39), and 66.7% (28/42) maintained responses at week 24. HAQ-DI responses at week 12 were maintained at week 24 in 75.0% (33/44), 84.0% (42/50), and 78.8% (41/52) patients (mavrilimumab 30, 100 and 150 mg, respectively).

Table: PRO Endpoints Data at Weeks 12 and 24

	Week 12				Week 24[c]			
		Mavrilimumab				Mavrilimumab		
	PBO (n=81)	30 mg (n=81)	100 mg (n=85)	150 mg (n=79)	PBO (n=81)	30 mg (n=81)	100mg (n=85)	150 mg (n=79)
Pain								
Mean change from baseline	−8.11	−16.30	−19.15	−23.35	−15.20	−23.14	−23.31	−26.53
Mean difference from PBO (SE)	-	−8.19	−11.05	−15.24	–	−7.94	−8.11	−11.32
	(−)	(3.38)	(3.34)	(3.38)	(−)	(3.95)	(3.88)	(3.90)
p-value[a]	–	0.016	0.001	<0.001	-	0.045	0.037	0.004
Responders (MCID)[b], %	32.1	44.4	45.9	53.2	25.9	44.4	50.6	51.9
p-value[a]	–	0.107	0.070	0.008		–[d]	–[d]	–[d]
SF-36 physical component								
Mean change from baseline	2.84	4.29	5.13	6.24	3.21	5.44	6.55	7.58
Mean difference from PBO (SE)	–	1.45	2.29	3.40	–	2.23	3.34	4.38
	(−)	(1.08)	(1.06)	(1.08)	(−)	(1.43)	(1.40)	(1.41)
p-value[a]	–	0.178	0.032	0.002	–	0.120	0.018	0.002
Responders (MCID)[b], %	35.8	48.1	50.6	65.8	24.7	46.9	56.5	72.2
p-value[a]	–	0.112	0.056	<0.001		–[d]	–[d]	–[d]
HAQ-DI								
Mean change from baseline	−0.26	−0.27	−0.39	−0.47	−0.29	−0.37	−0.46	−0.55
Mean difference from PBO (SE)	–	−0.01	−0.13	−0.21	–	−0.08	−0.16	−0.26
	(−)	(0.08)	(0.08)	(0.08)	(−)	(0.11)	(0.11)	(0.11)
p-value[a]	–	0.871	0.099	0.010	–	0.479	0.124	0.017
Responders (MCID)[b], %	43.2	54.3	58.8	65.8	29.6	53.1	57.6	64.6
p-value[a]	–	0.158	0.045	0.004		–[d]	–[d]	–[d]
FACIT-Fatigue								
Mean change from baseline	3.61	4.59	5.07	6.84	4.53	5.72	6.80	8.45
Mean difference from PBO (SE)	–	0.98	1.46	3.23	–	1.18	2.27	3.92
	(−)	(1.37)	(1.35)	(1.37)	(−)	(1.61)	(1.57)	(1.58)
p-value[a]	–	0.476	0.280	0.019	–	0.463	0.151	0.014
Responders (MCID)[b], %	44.4	51.9	56.5	68.4	30.9	55.6	58.8	69.6
p-value[a]	–	0.346	0.122	0.003		–[d]	–[d]	–[d]

[a]Vs mean difference from PBO
[b]Responders were defined as: Pain=change from baseline ≤−20; HAQ-DI=change from baseline ≤−0.25; SF-36=change from baseline ≥3.8; FACIT-fatigue=change from baseline ≥3
[c]Mixed model for repeated measures used to handle missing data in analysis of mean change from baseline due to entry to open-label extension at week 12
[d]Week 24 response rates vs PBO not included due to high rates of rescue to open-label extension at week 12
FACIT, functional assessment of chronic illness therapy; HAQ-DI, health assessment questionnaire disability index; MCID, minimal clinically important difference; PBO, placebo; PRO, patient-reported outcome; SE, standard error; SF-36, short form-36

Conclusion: Targeting activated macrophages through inhibition of the GM-CSFRα pathway with mavrilimumab, especially at a dose of 150 mg Q2W, substantially and rapidly reduced RA disease activity. In turn, patients receiving mavrilimumab, vs PBO, reported significant and clinically meaningful sustained improvements in multiple PROs that reflect patients' pain, HRQoL, physical function and fatigue. The majority of mavrilimumab patients with improvement in pain and physical function at week 12 sustained these improvements to the end of the study at week 24.

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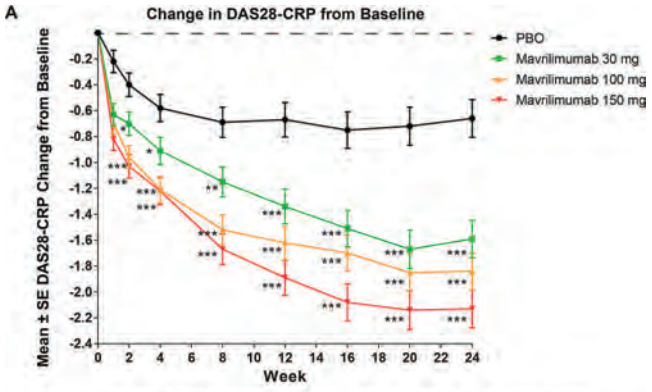
Rapid Onset of Clinical Benefit Is Associated with a Reduction in Validated Biomarkers of Disease in Patients with Rheumatoid Arthritis Treated with Mavrilimumab, a Human Monoclonal Antibody Targeting GM-CSFRá. Iain B. McInnes[1], Gerd Burmester[2], Joel M. Kremer[3], Pedro Miranda[4], Mariusz Korkosz[5], Jiri Vencovsky[6], Andrea Rubbert-Roth[7], Eduardo Mysler[8], David Close[9], Matthew A. Sleeman[9], Alex Godwood[9], Sara Sandbach[9], Patricia C. Ryan[10], Dominic Sinibaldi[10], Wendy White[10], Nadine A. Defranoux[11] and Michael Weinblatt[12]. [1]University of Glasgow, Glasgow, United Kingdom, [2]Charité - University Medicine Berlin, Berlin, Germany, [3]Albany Medical College and the Center for Rheumatology, Albany, NY, [4]Centro de Estudios Reumatologicos, Santiago, Chile, [5]Malopolskie Centrum Medyczne, Krakow, Poland, [6]Charles University Institute of Rheumatology, Prague, Czech Republic, [7]University of Cologne, koln, Germany, [8]OMI, Buenos Aires, Argentina, [9]MedImmune Ltd, Cambridge, United Kingdom, [10]MedImmune, Gaithersburg, MD, [11]Crescendo Bioscience Inc., South San Francisco, CA, [12]Brigham & Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Macrophages are pivotal to rheumatoid pathogenesis and their inflammatory products drive many of the signs and symptoms of disease. Mavrilimumab inhibits macrophage activation and survival via blockade of granulocyte-macrophage colony-stimulating factor receptor-α (GM-CSFRα) and has previously shown a rapid (2 week) and sustained clinical benefit in patients with RA. We present data from the EARTH EXPLORER 1 study examining speed of clinical response to mavrilimumab, and effect on the multi-biomarker disease activity (MBDA) score after week 1 (1 dose).

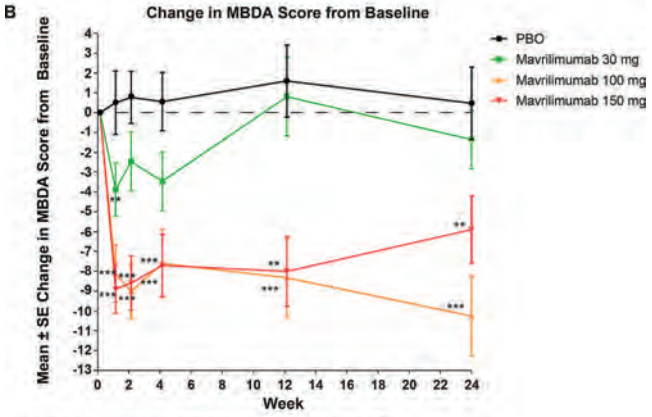
Methods: This was a Phase 2b, 24-week, randomized, double-blind, placebo (PBO)-controlled study (NCT01706926). Patients with adult-onset RA (18–80 years; DAS28-CRP >3.2; ≥4 swollen joints; inadequate response to ≥1 DMARD) received mavrilimumab (30, 100, or 150 mg) or PBO, administered subcutaneously every 2 weeks + methotrexate (7.5–25.0 mg/week). Efficacy assessments included DAS28-CRP, ACR responses, CRP, ESR, swollen joint count (SJC), tender joint count (TJC) and pain. MBDA score was calculated using the validated Vectra®DA algorithm, based on serum concentration of 12 biomarkers, to track the effect of mavrilimumab on disease over time. Additional assessments were conducted on MBDA biomarker components.

Results: Overall, 326 patients with mean (SD) DAS28-CRP 5.8 (0.9) were randomized to mavrilimumab (30, 100, or 150 mg) or PBO (n=81, 85, 79, and 81, respectively). At week 1 (first assessment), all mavrilimumab doses showed significant reductions from baseline in DAS28-CRP (p<0.001 vs PBO; Figure A), with treatment benefit increasing to week 12. Significant improvements for 150 mg vs PBO were seen at week 1 for CRP, ESR, SJC, TJC, and pain (Table). Effects of mavrilimumab 150 mg were near maximal vs PBO for CRP, ESR, and pain at week 1, and sustained (week 24). SJC and TJC for 150 mg improved from baseline (week 1) and continued to improve (week 12); this was sustained until week 24. Rapid onset of clinical benefit was paralleled with reduction in MBDA

score; 100 and 150 mg showed early (week 1) and sustained (week 24) significant changes in MBDA score vs PBO ($p<0.01$; Figure B), with greater decreases in DAS28-CRP responders vs non-responders (week 12). Approximately ≥50% decreases in serum IL-6, CRP, and serum amyloid-A protein levels were observed at week 1 and maintained during treatment.



*p<0.05, mavrilimumab vs PBO; **p<0.01, mavrilimumab vs PBO; ***p<0.001, mavrilimumab vs PBO
At week 1, all mavrilimumab treatment groups were statistically significant vs PBO (***p<0.001)
Mavrilimumab 150 mg difference (95% CI) from PBO: week 1 -0.60 (-0.84, -0.36); week 12 -1.22 (-1.59, -0.85)
PBO, placebo; SE, standard error



**p<0.01, mavrilimumab vs PBO; ***p<0.001, mavrilimumab vs PBO
MBDA, multi-biomarker disease activity; PBO, placebo; SE, standard error

Table: Clinical Efficacy and MBDA Score Results at First Assessment (Week 1, 1 Dose)

	PBO (n=81)	Mavrilimumab 30 mg (n=81)	Mavrilimumab 100 mg (n=85)	Mavrilimumab 150 mg (n=79)
DAS28-CRP response[a], n (%)	3 (3.7)	17 (21.0)	17 (20.0)	18 (22.8)
Difference from placebo, % (95% CI)	–	17.3 (7.5, 27.1)	16.3 (6.9, 25.7)	19.1 (9.0, 29.2)
p-value	–	0.001	0.001	>0.001
CRP				
Adjusted geometric mean, mg/L	5.08	4.58	2.58	2.80
Mean ratio to baseline	0.89	0.80	0.45	0.49
(95% CI[b])	–	(0.70, 1.17)	(0.39, 0.65)	(0.43, 0.71)
p-value[b]	–	0.424	>0.001	>0.001
ESR				
Mean ratio to baseline	0.97	0.79	0.80	0.74
(95% CI[b])	–	(0.71, 0.92)	(0.73, 0.94)	(0.67, 0.87)
p-value[b]	–	0.002	0.004	>0.001
SJC				
Mean change from baseline	−1.85	−3.57	−3.38	−5.20
(95% CI[c])	–	(−3.48, 0.06)	(−3.26, 0.22)	(−5.11, −1.58)
p-value[c]	–	0.058	0.087	>0.001
TJC				
Mean change from baseline	−2.55	−5.60	−3.96	−6.37
(95% CI[c])	–	(−5.53, −0.56)	(−3.85, 1.05)	(−6.30, −1.32)
p-value[c]	–	0.016	0.261	0.003
Pain				
Mean change from baseline	−1.58	−7.57	−6.14	−16.78
(95% CI[c])	–	(−11.41, −0.56)	(−9.92, 0.80)	(−20.64, −9.75)
p-value[c]	–	0.031	0.095	>0.001
MBDA score[d]				
Mean change from baseline (SEM)	0.51 (1.60)	−3.87 (1.33)	−8.12 (1.44)	−8.89 (1.23)
p-value[c]		0.0067	>0.001	>0.001

[a]Defined by EULAR response criteria as a DAS28-CRP decrease from baseline <1.2 (moderate response)
[b]Adjusted mean ratio mavrilimumab vs PBO
[c]Adjusted mean difference mavrilimumab vs PBO
[d]MBDA components: vascular cell adhesion molecule-1 (VCAM), epidermal growth factor (EGF), vascular endothelial growth factor-A (VEGF-A), interleukin-6 (IL-6), tumour-necrosis factor receptor-1 (TNF-R1), matrix metalloproteinase-1&3 (MMP 1&3), YKL-40, leptin, resistin, serum amyloid-A protein (SAA) and C-reactive protein (CRP)
CI, confidence interval; DAS28-CRP, disease activity score 28 C-reactive protein; ESR, erythrocyte sedimentation rate; MBDA, multi-biomarker disease activity; PBO, placebo; SEM, standard error of the mean;SJC, swollen joint count; TJC, tender joint count

Conclusion: By targeting activated macrophages via inhibition of GM-CSFRα, mavrilimumab substantially reduced patients' RA disease activity from first (week 1; 1 dose) to final assessment, evaluated by multiple clinical endpoints and biomarkers.

Disclosure: I. B. McInnes, MedImmune, 5, MedImmune, AstraZeneca, 5; **G. Burmester**, Medimmune, 5; **J. M. Kremer**, Corrona, 1, AbbVie, Amgen, Genentech, Lilly, Pfizer, 2, AbbVie, Amgen, Genentech, Lilly, Pfizer, BMS, 5, Corrona, 3; **P. Miranda**, Medimmune, 2; **M. Korkosz**, None; **J. Vencovsky**, None; **A. Rubbert-Roth**, None; **E. Mysler**, Medimmune, 2; **D. Close**, Medimmune, 3; **M. A. Sleeman**, AstraZeneca, 1, Medimmune, 3; **A. Godwood**, AstraZeneca, 1, Medimmune, 3; **S. Sandbach**, Medimmune, 3; **P. C. Ryan**, Medimmune/AstraZeneca, 1, Medimmune, 3; **D. Sinibaldi**, Medimmune, 1, Medimmune, 3; **W. White**, Medimmune, 3; **N. A. Defranoux**, Crescendo Bioscience, 1, Crescendo Bioscience, 3; **M. Weinblatt**, BMS, UCB, Crescendo Bioscience, 2, Medimmune, AstraZeneca, Amgen, AbbVie, BMS, UCB, Crescendo Bioscience, Lilley, Pfizer, Roche, 5.

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A Phase 1 Dose-Ranging Repeated-Dose Trial of Parenteral Staphylococcal Protein A (PRTX-100) in Patients with Active Rheumatoid Arthritis on Methotrexate or Leflunamide Therapy. Craig Wiesenhutter[1], Rakesh Patel[2], John Lavery[3], Nighat Tahir[4], Lydie Hazan[5], Alan Kivitz[6], Elizabeth Bretton[7] and Jeffrey Kaine[8]. [1]Coeur d'Alene Arthritis Clinic, Coeur d'Alene, ID, [2]PMG Research of Salisbury, Salisbury, NC, [3]Allen Arthritis and Allergy, Allen, TX, [4]Community Rheumatology of Anderson, Anderson, IN, [5]Axis Clinical Trials, Los Angeles, CA, [6]Altoona Center for Clinical Research, Duncansville, PA, [7]Albuquerque Clinical Trials, Albuquerque, NM, [8]Sarasota Arthritis Center, Sarasota, FL.

Background/Purpose: Staphylococcal protein A (SpA) binds with high affinity to the Fc region of human immunoglobulin G and also to the Fab framework region of immunoglobulin encoded from genes of the VH3 family. At intravenous doses up to 1.5 μg/kg weekly SpA was found to have an acceptable safety profile in a Phase I rheumatoid arthritis (RA) trial. The current Phase I study evaluates the safety and effect on RA disease activity of 6 months of SpA treatment.

Methods: This study enrolled 61 RA patients (pts) at 8 US centers. In Part 1 of the study, 41 pts received 5 weekly doses of either placebo, 1.5, 3, 6 or 12 μg/kg of SpA. Partial results from Part 1 have been reported previously [1]. In Part 2, pts received placebo or a fixed SpA dose of either 240 μg or 420 μg given as 5 weekly doses followed by 'maintenance' doses at weeks 8, 12, 16 and 20 (6 months' total treatment). Adverse events (AEs), pharmacokinetics, anti-SpA antibodies and disease activity (ACR20/50/70, DAS28-CRP, and CDAI [Clinical Disease Activity Index]) are being evaluated over the course of this ongoing study.

Results: Twenty pts were randomized in Part 2: 3 pts (240 μg), 12 pts (420 μg) and 5 pts (placebo). All AEs were Grade 1 or 2 in severity with the exception of 1 pt who experienced Grade 3 influenza (unrelated to treatment) and 1 pt with Grade 3 worsening of arthritis (related to treatment). 9 pts (45%) had related AEs, the most common being transient flare of musculoskeletal symptoms usually occurring 1–3 days post-infusion. In Parts 1 and 2 of the study, there were no deaths or serious AEs considered to be related to SpA. Nine of the 12 pts in the 420 μg SpA arm met per-protocol criteria for efficacy evaluation. For comparative purposes, the control group was pooled from the 15 placebo pts enrolled in Parts 1 and 2; 13 placebo pts met per-protocol criteria for efficacy evaluation. Of the 9 pts in Part 2 that received 420 μg SpA, 56% achieved ACR20 at day 113 vs. 31% of pts in the control group (see table). A similar pattern was seen with the

ACR50: on day 113, 33% of 9 SpA-treated pts attained an ACR50 vs. 8% of pts in the control group.

ACR20 Responders: 420 μg SpA vs. Placebo

	Study Day								
	1	**8**	**15**	**22**	**29**	**43**	**57**	**85**	**113**
SpA 420 μg (9 pts)	0%	0%	38%	63%	50%	33%	50%	56%	56%
Placebo (13 pts)	0%	11%	31%	23%	31%	25%	39%	39%	31%

CDAI data also indicated some reduction in disease activity, as 44% of 420 μg pts achieved a CDAI of ≤14 on 3 or more consecutive visits vs. 23% of pts in the control group. SpA and control pts had MDHAQ mean physical function scores of 3.57 and 3.59, respectively, at baseline. By day 85, the change from baseline was –1.17 and –0.59 for SpA and control pts, respectively. At day 113, the change from baseline was –1.38 vs. –0.6, respectively.

Conclusion:

- A 6-month regimen of 5 weekly infusions of SpA followed by 4 monthly 'maintenance' infusions had an acceptable safety profile in pts with RA. The most common AEs seemed to be associated with transient worsening of musculoskeletal symptoms.
- During a 6-month study period, SpA appeared to result in some reduction in disease activity. Some patients experienced improvements.

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1488

Clinical Efficacy of Add-on Iguratimod Therapy in Patients with Active Rheumatoid Arthritis Despite of Methotrexate ~a Multicenter Registry Study~. Yasuhide Kanayama[1], Toshihisa Kojima[2], Atsushi Kaneko[3], Yuji Hirano[4], Nobunori Takahashi[2], Shinya Hirabara[4] and Naoki Ishiguro[2]. [1]Toyota Kosei Hospital, Toyota, Japan, [2]Nagoya University Graduate School of Medicine, Nagoya, Japan, [3]Nagoya Medical Center, Nagoya, Japan, [4]Toyohashi Municipal Hospital, Toyohashi, Japan.

Background/Purpose: Iguratimod (IGU) is a small-molecule antirheumatic drug that was approved in Japan in September 2012. IGU suppressed tumor necrosis factor-alpha-induced production of interleukin (IL)-6, IL-8, and monocyte chemoattractant protein 1 via inhibition of nuclear factorkappa B activation in cultured human synovial cells and human acute monocytic leukemia cells. IGU also reduced immunoglobulin production by acting directly on human B lymphocytes without affecting B lymphocyte proliferation. Recently, an increased release of extracellular adenosine and a decreased production of lymphotoxins such as ammonia and superoxide have been shown to be involved in the anti-inflammatory mechanisms of methotrexate. Thus, the combination of MTX and IGU may have synergic efficacy for rheumatoid arthritis (RA) treatment. To evaluate the clinical efficacy of add-on IGU in patients with Japanese active RA who had shown inadequate responses to MTX therapy.

Methods: Patients with a diagnosis of RA according to the 2010 ACR/EULAR criteria who had been unresponsive to MTX therapy (DAS>3.2 or CDAI>10), and who had been prescribed add-on IGU from Tsurumai Biologics Communication Registry (TBCR) between November 2012 and August 2013 were enrolled. The final study cohort of 51 patients received continuous IGU therapy more than 24 weeks. We reviewed the methods about the improvement of CRP, MMP3, DAS28-ESR and CDAI which was an index of disease activity of RA using Wilcoxon signed-rank test and the rate of remission patients at Week24.

Results: The group of patients included 8 males and 43 females. The mean age was 63.6 ± 10.3 years old; the disease duration was 8.4 ± 9.7 years and the methotrexate dose was 9.6 ± 4.2 mg/week. Clinical findings related to RA were as follows: mean tender joint count, 4.5 ± 4.9; swollen joint count, 4.2 ± 3.9; patient's global assessment of disease activity, 41.5 ± 22.8mm; Physician's global assessment of disease activity, 40.0 ± 20.8mm; CRP, 2.0 ± 2.3 mg/dL; ESR, 42.9 ± 19.2 mm/h; MMP3, 249.7 ± 284.6 ng/ml; DAS28 (ESR), 4.67 ± 0.97; and CDAI, 16.9 ± 9.4. There were no patients who had received Biologics treatment. The mean CRP improved to 1.7 ± 2.2, 1.2 ± 2.0 and 1.1± 1.9 at Week 4, 12 and 24 ($p=0.064$, $p<0.001$, $p<0.001$), mean MMP3 improved to 223.7 ± 266.1, 161.7 ± 242.1 and 148.3 ± 244.4 at Week 4, 12 and 24 ($p=0.045$, $p<0.001$, $p<0.001$), the mean DAS28 improved to 4.26 ± 1.03, 3.44 ± 1.07 and 3.32± 1.28 at Week 4, 12 and 24 ($p<0.001$, $p<0.001$, $p < 0.001$) and the mean CDAI improved to 13.1 ± 8.2, 8.3 ± 6.5 and 7.9± 7.6 at Week 4, 12 and 24 ($p<0.001$, $p<0.001$, $p < 0.001$) significantly. At Week 24 the rate of patients who achieved remission were each 33.3% and 27.5% in DAS and CDAI criteria.

Conclusion: This study suggested that the new combination therapy of add-on IGU with MTX was effective in patients with active RA with inadequate response to MTX.

Disclosure: Y. Kanayama, Astellas Pharma, 8, Eisai, 8, Mitsubishi Tanabe Pharma Corporation, 8, AbbVie Inc, 8, Chugai, 8; **T. Kojima**, Takeda Pharma Corporation, Janssen Pharmaceutical, and Astellas Pharma Corporation., 2, Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Eisai Pharma Corporation, Abbvie, Bristol-Myers Squibb□ APfizer and Chugai Pharma Corporation, 8; **A. Kaneko**, Janssen Pharmaceutica Product, L.P., 8, Astellas Pharma, 8, Mitsubishi-Tanabe Pharma, 8, Chugai, 8, Eisai, 8, Abbott Immunology Pharmaceuticals, 8, Bristol-Myers Squibb, 8; **Y. Hirano**, AbbVie Inc.; Eisai Co. Ltd.; Mitsubishi Tanabe Pharma Corporation; Takeda Pharma Corporation; Pfizer Co. Ltd; Chugai Pharmaceutical Co. Ltd. and Bristol-Myers Squibb Co. Ltd., 8; **N. Takahashi**, Abbott Japan Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Co. Ltd, Chugai Pharmaceutical Co. Ltd., and Bristol-Myers Squibb Co. Ltd., 8; **S. Hirabara**, None; **N. Ishiguro**, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 5, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 8.

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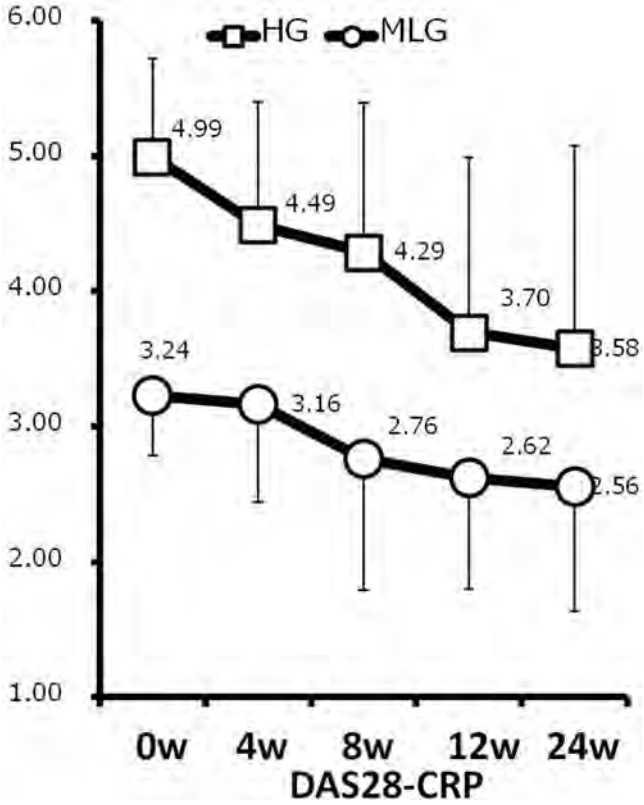
Influences of Disease Activity at the Initiation of Iguratimod, a Small Molecule Antirheumatic Drug, on Efficacy of Iguratimod in Patients with Rheumatoid Arthritis –a Multicenter Registry Study-. Yuji Hirano[1], Toshihisa Kojima[2], Yasuhide Kanayama[3], Shinya Hirabara[1], Nobunori Takahashi[2], Atsushi Kaneko[4] and Naoki Ishiguro[2]. [1]Toyohashi Municipal Hospital, Toyohashi, Japan, [2]Nagoya University Graduate School of Medicine, Nagoya, Japan, [3]Toyota Kosei Hospital, Toyota, Japan, [4]Nagoya Medical Center, Nagoya, Japan.

Background/Purpose: Iguratimod (IGU), known as T-614, is a small-molecule antirheumatic drug developed in Japan and used in Japanese clinical practice since June in 2012. IGU is known to inhibit nuclear factor-kappa B activation in cultured human synovial cells. Although biological agents (BIO) have good efficacy to treat rheumatoid arthritis (RA), they costs very much. IGU is not comparatively expensive and used as monotherapy or combination therapy with methotrexate (MTX). Data in clinical practice is lacking and necessary for the best use of IGU.This retrospective study investigated efficacy of IGU in RA patients with focus on disease activity at initiation of IGU using data from the Japanese multicenter registry.

Methods: 78 cases (62 female and 16 male) with RA from 9 institutes in Japan were included. These patients were divided into two groups (high disease activity group; HG and moderate and low disease activity group; MLG) using DAS28-CRP at initiation of IGU. 42 cases were included in HG and 36 cases were included in MLG. Patients' characteristics, time course of disease activity, drug retention rate at 24 weeks and change value in disease activity parameters from 0w to 24w were compared with each other.

Results: and Conclusion: Mean age was 68.3 years old in HG and 65.7 years old in MLG. Mean RA duration was 147 months in HG and 94 months in MLG. Although MTX use rate was low in HG compared with in MLG (52.4% vs. 63.9%), there was no significant difference between groups. The mean dose of MTX used was 4.7 mg/w in HG and 5.2 mg/w in MLG. The mean DAS28-CRP at 0, 4, 8, 12 and 24w was 4.99, 4.49, 4.29, 3.70 and 3.58 in HG and 3.24, 3.16, 2.76, 2.62 and 2.56 in MLG. DAS28-CRP was significantly decreased after 4w in HG and after 8w in MLG. Similar findings were observed in SDAI. Drug retention rates at 24w were 81.0% in HG and 86.1% in MLG (not significant). Delta DAS28-CRP from 0w to 24w was 1.4 in HG and 0.7 in MLG ($p=0.04$). Delta SDAI were 11.5 in HG and 4.3 in MLG ($p=0.02$). There were significant differences in delta tender joints counts, delta ESR between two groups and better improvement was seen in HG than MLG. More treatment options other than sufficient MTX and BIO are needed in RA patients with concomitant disease such as lung disease or renal dysfunction. High cost of BIO is another issue to inhibit improvement of signs and symptoms in RA patients. This study suggests that IGU is one of the options not only in RA patients with high disease activity treated with insufficient MTX.



Disclosure: Y. Hirano, Abbott Immunology Pharmaceuticals, 8, Mitsbishi-Tanabe Pharma, 8, Pfizer Inc, 8, Eisai, 8, Chugai, 8, Bristol-Myers Squibb, 8, Astellas Pharma, 8; **T. Kojima**, Takeda Pharma Corporation, Janssen Pharmaceutical, and Astellas Pharma Corporation., 2, Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Eisai Pharma Corporation, Abbvie, Bristol-Myers Squibb, Pfizer and Chugai Pharma Corporation, 8; **Y. Kanayama**, Astellas Pharma, 8, Eisai, 8; **S. Hirabara**, None; **N. Takahashi**, Abbott Japan Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Co. Ltd, Chugai Pharmaceutical Co. Ltd., and Bristol-Myers Squibb Co. Ltd., 8; **A. Kaneko**, Janssen Pharmaceutica Product, L.P., 8, Astellas Pharma, 8, Mitsubishi-Tanabe Pharma, 8, Chugai, 8, Eisai, 8, Abbott Immunology Pharmaceuticals, 8, Bristol-Myers Squibb, 8; **N. Ishiguro**, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 5, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 8.

1490

Can Tumor Necrosis Factor Inhibitors Protect Rheumatoid Arthritis Patients from Osteoporosis? Impact of Tumor Necrosis Factor Inhibitors on Bone Mineral Density and Bone Remodeling Markers. Anaïz Nutz[1], Yohan Duny[2], Thomas Barnetche[3], Jacques Morel[4], Bernard Combe[4] and Claire Daien[1]. [1]Hopital Lapeyronie, Montpellier, France, [2]INSERM, Montpellier, France, [3]Department of rheumatology, Bordeau, France, [4]Hôpital Lapeyronie, Montpellier, France.

Background/Purpose: Rheumatoid Arthritis (RA) is a chronic inflammatory disease characterized by joint and bone destruction. Loss of bone in RA is not only localized in joints but is also generalized. Tumor necrosis factor (TNF) alpha is involved in the pathogenesis of joint erosion and loss of bone. TNF alpha is also known to be an inhibitor of bone formation through Wnt pathway and RANKL/osteoprotegerin balance. The use of TNF alpha inhibitors (TNFi) has effect on focal bone erosions. This has led to the hypothesis that TNFi has a positive effect on bone mineral density. The aim of this study is to summarize the published data on the effect of TNFi on bone mineral density (BMD) and bone markers in RA by a systemic review of the literature and meta-analysis.

Methods: We searched Medline via PubMed, COCHRANE and EMBASE database for articles published up to April 2014 using Mesh terms ("Bone mineral density" (MeSH) OR "bone" (MeSH) OR "bone remodeling" (MeSH) AND "rheumatoid arthritis" AND ("infliximab" OR "adalimumab" OR "etanercept" OR "certolizumab" OR "golimumab" OR "anti-TNF"). To be selected a study need to be a controlled trial with a group treated by TNFi and a control group without treatment of interest or to have values before and after treatment by TNFi or value of variation under treatment of at least one variable among BMD at hip or lumbar spine, CTX-1, Bone Alkaline bone Phosphatase (BAP), osteocalcin (OC) and type 1 collagen amino-terminal propeptide (P1NP). Statistical analysis of pre and post-data was performed using Comprehensive meta-analysis software. The percentage heterogeneity in the study results was determined by the Cochran's Q-test and the I^2 values. A significant statistical threshold of 0.05 was used.

Results: The search retrieved 49 articles. 15 articles complied with inclusion criteria. Although heterogeneity was high, BMD at hip and lumbar spine stay unchanged after TNFi (6 studies for hip BMD including 386 patients and 7 studies for lumbar spine BMD including 443 patients) with a mean difference of 0.058 (−0.220 to 0.337, IC95%) for BMD at hip and of 0.154 (−0.110 to 0.418,IC95%) for BMD at lumbar spine. In controlled trials, no difference was found for BMD at hip or at lumbar spine (6 studies; 558 patients). Concerning bone remodeling markers, CTX level was statistically decreased in 2 studies and showed a trend of decrease in 4 other studies. OC level increased statistically in 4 studies and decreased no significally in a fifth one; P1NP level was increased significally in 1 study of 3 available whereas BAP level did not significally change in studies available (2 studies). BMD change were influenced by therapeutic response to TNFi in 2 studies, with a trend in a third one whereas no association was found in 3 other studies.

Conclusion: TNFi in RA seem to decrease bone resorption and to increase bone remodeling at biologic levels but do not have an effect on BMD. However, only few data with mid-term assessment are available with an important heterogeneity in terms of patients included, disease duration, comedications and follow up. Several long term trials are required to evaluate the exact effect of TNFi on bone mineral density in rheumatoid arthritis.

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1491

Discovery and Characterization of COVA322, a Clinical Stage Bispecific TNF/IL-17A Inhibitor for the Treatment of Inflammatory Diseases. Dragan Grabulovski, Michela Silacci, Wibke Lembke, Wenjuan Zha, Richard Woods, Roger Santimaria, Julian Bertschinger and Mathias Locrher. Covagen AG, Schlieren, Switzerland.

Background/Purpose: Biologics such as TNF inhibitors have revolutionized the treatment of inflammatory diseases including rheumatoid arthritis (RA), psoriasis and psoriatic arthritis. However, recent data suggest that full and long-lasting responses to TNF inhibitors are limited because of the activation of the pro-inflammatory T_H17/IL-17 pathway in patients. Therefore, an attractive avenue to achieve superior efficacy levels in inflammatory diseases represents the combined inhibition of TNF and IL-17A. We present here COVA322, a bispecific TNF/IL-17A inhibitor that is currently being tested in a Phase Ib/IIa study in psoriasis patients.

Methods: Using phage display technology we have isolated Fynomers inhibiting human IL-17A. Fynomers are small binding proteins (7 kDa) derived from the human Fyn SH3 domain which can be engineered to bind to essentially any target of interest with high affinity and specificity. After genetic fusion of the anti-IL-17A Fynomer to a commercially validated anti-TNF antibody the resulting bispecific molecule COVA322 was characterized for its stability, dual binding characteristics, and IL-17A and TNF inhibition properties, including the inhibition of human T cell derived cytokines.

Results: The fusion of the anti-IL-17A Fynomer to the fully human anti-TNF antibody did not alter the favorable biophysical properties of the antibody: COVA322 was monomeric and its stability was comparable to the stability of the unmodified antibody. Furthermore, COVA322 could be produced and purified with very high yields (3.3 g/L obtained from our 1000 L GMP run). Importantly, COVA322 inhibited TNF and IL-17A with picomolar inhibition potencies as shown in a variety of different cell assays. Moreover, we could show that COVA322 was able to inhibit human derived cytokines from different donors.

Conclusion: COVA322 is a unique bispecific TNF/IL-17A inhibitor with excellent biophysical properties. It is currently being tested in a first in man, single dose escalation, tolerability, safety, PK and efficacy Phase Ib/IIa study in psoriasis.

Disclosure: D. Grabulovski, Covagen AG, 1, Covagen AG, 3, Covagen AG, 4; **M. Silacci**, Covagen AG, 1, Covagen AG, 3; **W. Lembke**, Covagen AG, 3, Covagen AG,

1; **W. Zha**, Covagen AG, 1, Covagen AG, 3; **R. Woods**, Covagen AG, 1, Covagen AG, 3; **R. Santimaria**, Covagen AG, 3; **J. Bertschinger**, Covagen AG, 4, Covagen AG, 1, Covagen AG, 3; **M. Locher**, Covagen AG, 1, Covagen AG, 3.

1492

Safety and Tolerability of NNC01140006, an Anti-IL-21 Monoclonal Antibody, at Multiple s.c. Dose Levels in Patients with Rheumatoid Arthritis. Frank Wagner[1], Birte Skrumsager[2] and Sergey Fitilev[3]. [1]Charité Research Org GmbH, Berlin, Germany, [2]Novo Nordisk A/S, Søborg, Denmark, [3]Department of Clinical Pharmacology, Municipal Clinic #2, Moscow, Russia.

Background/Purpose: A phase 1, randomised, double-blind, placebo-controlled, dose-escalation trial was conducted to assess the safety and tolerability of the anti-IL-21-antibody NNC0114-0006, in patients with active moderate-to-severe rheumatoid arthritis (RA) on background methotrexate (MTX) monotherapy.

Methods: Patients (N=32; 84% female) with RA (mean duration 8.9 years; 72% RF positive; 63% anti-CCP positive; mean DAS28-CRP 5.4), who were on MTX (mean duration 4.7 years; mean dose 13 mg/week) were enrolled. Patients were randomised to NNC0114-0006 or placebo (3:1) for s.c. dosing every other week for 6 weeks (a total of four doses) at 0.05, 0.25, 1 or 4 mg/kg. Dose levels of NNC0114-0006 were escalated when 6 of 8 patients in a cohort completed the third dose. The primary endpoint was incidence of adverse events (AEs) from first administration until trial completion, 26 weeks later. Secondary endpoints were changes in laboratory measurements, antibodies against NNC0114-0006, and pharmacokinetic (PK) and pharmacodynamic (PD) parameters.

Results: There were no significant differences between the treatment groups with respect to baseline data. One patient in the 1 mg/kg NNC0114-0006 group withdrew informed consent after the second dose due to intensification of joint pain considered possibly related to the use of the trial product. Overall, 42 AEs were reported in 18 of 24 (75%) NNC0114-0006 patients, while 20 AEs were reported in 6 of 8 (75%) placebo patients. Two patients receiving 4 mg/kg NNC0114-0006 experienced serious adverse events, which were considered unlikely related to the use of the trial product. No severe or life-threatening events, or fatalities were observed. Two patients at the highest dose reported AEs related to infections, compared with only one patient in each of the other treatment groups, including placebo. No treatment-related anti-drug antibodies were detected during the course of the trial. No clinically significant changes from baseline levels were observed in laboratory safety parameters. From PK measurements, systemic exposure to NNC0114-0006 increased with increasing dose levels, as expected with a mean half-life of approximately 2.5 weeks. PD assessments demonstrated an expected increase in circulating levels of total (both free and antibody-bound) IL-21 after treatment with NNC0114-0006; however, large interpatient variability was observed. No significant changes were observed in RF, CRP and ESR, IL-21R expression on selected lymphocyte subsets, B cells, or gene expression by microarray from whole blood or fractionated blood.

Conclusion: No safety or tolerability concerns were identified following multiple-dose administration of up to 4 mg/kg NNC0114-0006, and no anti-drug antibodies were detected. NNC0114-0006 has a long terminal half-life (2–3 weeks) and s.c. bioavailability similar to that of other monoclonal antibodies. An increase in circulating levels of total IL-21 after treatment with NNC0114-0006 was observed, as expected. No changes in other PD parameters were observed with increasing doses of NNC0114-0006 compared with placebo.

Disclosure: F. Wagner, Novo Nordisk, 5; **B. Skrumsager**, Novo Nordisk, 3; **S. Fitilev**, Novo Nordisk, 5.

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A Phase 1 Study of FPA008, an Anti-Colony Stimulating Factor 1 Receptor (anti-CSF1R) Antibody in Healthy Volunteers and Subjects with Rheumatoid Arthritis (RA): Preliminary Results. Julie Hambleton[1], Lei Zhou[1], Seema Rogers[1], Sjoerd van Marle[2], Thijs van Iersel[2], James Zanghi[1], Emma Masteller[1], Kevin Baker[1] and Brian Wong[1]. [1]Five Prime Therapeutics, South San Francisco, CA, [2]PRA Health Sciences, Groningen, Netherlands.

Background/Purpose: Activation of CSF1R via IL34 or CSF1 results in activation, differentiation, and survival of monocytes, macrophages and osteoclasts. CSF1R activation produces inflammatory cytokines responsible for joint destruction, thus pathway inhibition may provide a therapeutic benefit to RA patients (pts). FPA008 is a humanized IgG4 anti-CSF1R antibody that blocks ligand binding and has preclinical activity in models of arthritis. This is a double-blind, randomized, placebo-controlled first-in-human trial designed in 3 parts to study safety, pharmacokinetics (PK) and pharmacodynamic (PD) biomarkers. In Parts 1 & 2, healthy volunteers received either one or two doses, respectively. Part 3 will be in RA pts, and clinical and radiographic efficacy parameters will also be explored.

Methods: In Part 1, 8 subjects were randomized (3:1) to receive a single intravenous infusion of FPA008 or placebo, per dose cohort of 0.2, 1, 3, or 10 mg/kg. In Part 2, 8 subjects were randomized (3:1) to receive 2 doses of FPA008 or placebo administered 14 days apart, at 1 or 3 mg/kg. Dose escalation decisions were based on the incidence of dose limiting toxicities (DLTs), plus attributed adverse events (AEs) beyond the DLT period. PK, bone turnover biomarkers, CSF1 and IL34 serum concentrations, and CD16+ monocytes were assessed. Part 3 consists of an open-label evaluation of 3 dose levels in RA pts whose disease is not responding to methotrexate. Three pts per dose level will receive 2 doses of FPA008 administered 14 days apart. Thereafter, 30 new pts will be randomized (2:2:1) to one of two dose levels of FPA008 or placebo, respectively.

Results: As of May 30, 2014, the first 5 cohorts in Parts 1 and 2 (up to 1 mg/kg, two doses) were completed through the DLT period. No DLTs were reported.

Frequently reported AEs were Grade 1 or 2 pruritus, headache and periorbital edema. Dosing in the 10 mg/kg cohort was associated with moderate periorbital edema, facial and finger swelling, and mild, transient blurred vision outside the DLT period. Dose-dependent elevations of CK and LDH were noted at 1 mg/kg and above; AST elevation occurred at 3 mg/kg and above; and mild ALT elevation occurred at 10 mg/kg in one subject. These elevations were not associated with clinical signs/symptoms or abnormalities in total bilirubin, CK isoenzymes or troponin, were reversible, and were expected due to FPA008-mediated inhibition of Kupffer cells responsible for removing these enzymes.

Non-linear PK was observed, with exposure increasing greater than dose proportionality from 0.2 to 3 mg/kg, suggesting target mediated clearance. Suppression of CD16+ monocytes, decreased bone turn-over biomarkers (CTx, Trap5), and dose-dependent increase in serum CSF1 and IL34 concentrations were observed.

Conclusion: FPA008 is well tolerated up to 3 mg/kg. Persistent AEs beyond the DLT period at 10 mg/kg coincide with the prolonged PK exposure. PD effects of full suppression of non-classical CD16+ monocytes and decrease of bone turnover biomarkers were noted at dose levels tested and may track with clinical benefit in RA pts. Updated data including preliminary data in RA pts will be presented.

Disclosure: J. Hambleton, Five Prime Therapeutics, 3, Five Prime Therapeutics, 1; **L. Zhou**, Five Prime Therapeutics, 5; **S. Rogers**, Five Prime Therapeutics, 3, Five Prime Therapeutics, 1; **S. van Marle**, None; **T. van Iersel**, PRA Health Sciences, 3; **J. Zanghi**, Five Prime Therapeutics, 3, Five Prime Therapeutics, 1; **E. Masteller**, Five Prime Therapeutics, 3, Five Prime Therapeutics, 1; **K. Baker**, Five Prime Therapeutics, 3, Five Prime Therapeutics, 1; **B. Wong**, Five Prime Therapeutics, 3, Five Prime Therapeutics, 1.

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Treatment of Rheumatoid Arthritis Patients with the JAK1-Selective Inhibitor GLPG0634 Reverses an Arthritis-Specific Blood Gene Signature to Healthy State. Mate Ongenaert[1], Sonia Dupont[2], Béatrice Vayssière[2], Reginald Brys[1], Luc Van Rompaey[1], Christel Menet[1] and René Galien[2]. [1]Galapagos NV, Mechelen, Belgium, [2]Galapagos SASU, Romainville, France.

Background/Purpose: The 4 Janus kinases (JAK1, JAK2, JAK3 and TYK2) are cytoplasmic tyrosine kinases that mediate intracellular signaling of cytokines (e.g. certain interleukins and interferons) and growth factors (e.g. erythropoietin). GLPG0634 is the first JAK inhibitor that displays a high JAK1 selectivity towards the 3 other JAK family members in functional assays. It showed a favorable safety and efficacy profile in two 4-week Phase 2a studies in rheumatoid arthritis (RA) patients. In order to further characterize GLPG0634, we compared the gene expression profile of circulating leukocytes of healthy volunteers and RA patients before and after 4 weeks of daily treatment with 200 mg of GLPG0634.

Methods: RA patients participated in the Phase 2a Proof of concept, a randomized, double-blind, placebo-controlled study enrolling 36 patients with insufficient response to MTX. They were orally treated with placebo or 200 mg QD GLPG0634 for 4 weeks. Blood was sampled in PAXgene tubes at pre-dose the first and the last days of treatment. Non-matched healthy

volunteers were also sampled in PAXgene tubes. mRNA was extracted, labeled and profiled using Affymetrix U219 micro-arrays. Data analysis was performed in R/BioConductor using linear regression models (limma).

Results: The leukocyte gene signature of 12 healthy subjects was first compared to the one obtained from 24 RA patients prior to placebo or GLPG0634 treatment. As expected, genes showing differential expression compared to healthy subjects allowed for definition of a disease signature. Four weeks of treatment with GLPG0634 (200 mg QD) impacted the signal levels for 3120 probes in RA patient samples (adjusted p-value < 0.05 and absolute log2-fold change > 1 compared to the same subjects at pre-dose), while the signal levels of only 78 probes were impacted to the same extent in the placebo group. Remarkably, the highly GLPG0634-impacted genes matched with the disease-effect genes and displayed an inverse regulation (Spearman $R = -0.85$), showing that administration of GLPG0634 at 200 mg QD led to the restoration of a healthy-like gene expression profile (treatment-effect genes). Pathway analysis performed for the affected gene sets suggests an impact on immune-inflammation systems.

Conclusion: Blood transcriptome analysis of healthy volunteers and patients recruited in the proof-of-concept study of GLPG0634 in RA identified a disease signature with many genes involved in RA-linked pathways. After 4 weeks of treatment with GLPG0634, transcriptome analysis showed that the compound was able to reverse strongly the disease effect, leading to a gene signature close to that of healthy volunteers. These data are in line with the good efficacy of the 200 mg QD administration of GLPG0634 in RA patients and further support the use of GLGP0634 in RA patients.

Disclosure: M. Ongenaert, Galapagos, 3, AbbVie, 9; **S. Dupont**, Galapagos, 3, AbbVie, 9; **B. Vayssière**, Galapagos, 3, AbbVie, 9; **R. Brys**, Galapagos, 3, AbbVie, 9; **L. Van Rompaey**, Galapagos, 3, AbbVie, 9; **C. Menet**, Galapagos, 3, AbbVie, 9; **R. Galien**, Galapagos, 3, AbbVie, 9.

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Preclinical and Clinical Phase I Profile of MK-8457, a Selective Spleen Tyrosine Kinase and Zeta-Chain-Associated Protein Kinase 70 Inhibitor, Developed for the Treatment of Rheumatoid Arthritis. Gene Marcantonio[1], Alan Bass[2], Gretchen Baltus[2], Judith Boice[1], Hongmin Chen[2], Michael Crackower[2], Jeroen Elassaiss-Schaap[3], Michael Ellis[2], Tomoko Freshwater[4], Francois Gervais[2], Jane Guo[2], Sammy Kim[2], Lily Moy[2], Alan Northrup[2], Jie Zhang-Hoover[2], Mathew Maddess[2], Richard Miller[2], Marcella Ruddy[2], Stella Vincent[2], Haoling Weng[1] and Hani Houshyar[2]. [1]Merck & Co., Whitehouse Station, NJ, [2]Merck & Co., Boston, MA, [3]Merck & Co., Oss, Netherlands, [4]Merck & Co., Rahway, NJ.

Background/Purpose: Spleen tyrosine kinase (SYK) is a potential target for treatment of several diseases including rheumatoid arthritis. SYK is a member of the Zeta-chain-associated protein kinase 70 (ZAP70) family of non-receptor protein kinases, critical in signaling downstream of Fc epsilon receptor I (FceRI) in mast cells and basophils, B-cell receptor (BCR) in B cells, and the collagen receptor in platelets. ZAP70, plays a predominant role in T-cell receptor (TCR) signaling in mature T cells. Here, we report the *in vitro*, *in vivo*, and early clinical characterization of a highly selective and potent dual SYK/ZAP70 inhibitor, MK-8457.

Methods: The *in vitro* characteristics of MK-8457 were evaluated in a series of biochemical and cellular assays. The *in vivo* characteristics of MK-8457 were evaluated in the rat adjuvant- and collagen-induced arthritis models. MK-8457 preclinical PK-PD-Efficacy relationship was established to select clinical doses required for efficacy in RA. Healthy volunteer clinical studies assessed the PK, PD, and safety of MK-8457 in single- and multiple-rising dose studies.

Results: MK-8457 is a potent, reversible ATP competitive inhibitor of SYK and ZAP70, displaying comparable cellular activity for these two kinases despite 40x enzymatic selectivity for SYK vs. ZAP70. Beyond ZAP70, out of 191 off-target kinases tested, MK-8457 inhibits only 3 kinases (TRKC, SRC, BLK) with IC_{50} values less than 100-fold above the SYK IC_{50}. *In vitro*, MK-8457 is a potent inhibitor of (1) FceRI-mediated anti-IgE induced degranulation in primary human mast cells (38 ± 20 nM) and human whole blood basophils (797 ± 365 nM), (2) BCR-mediated anti-IgM induced pBLNK activation in human RAMOS cells (35 ± 27 nM) and anti-CD79b induced CD69 upregulation in human whole blood B cells (1398 ± 505 nM), and (3) TCR-mediated anti-CD3 induced IL-2 production in Jurkat cells (84 ± 26 nM) and human whole blood phytohemagglutinin induced IL-2 production (1175 ± 362 nM). MK-8457 also inhibits collagen-induced platelet aggregation in human platelet rich plasma, with 20x reduced potency (19 ± 3 uM) as compared with the human whole blood basophil, B-cell, and T-cell assays. MK-8457 produces dose-dependent inhibition of adjuvant- and collagen-induced arthritis, as assessed by changes in paw thickness. Preclinical PK-PD-Efficacy modeling and simulations suggest that high level of SYK/ZAP70 inhibition (69%) is required to attain nearly full suppression of the CIA response. In healthy volunteers, MK-8457 is rapidly absorbed, shows increased exposure with dose, with a terminal half-life estimated to be 10–20 hours. MK-8457 was generally safe and well-tolerated in single dose up to 800 mg and multiple doses of 200 mg twice daily for up to 10 days. There was evidence of increased bleeding times at the T_{max} in single dose studies; however, there were no bleeding adverse events. The C_{max} for this effect in healthy volunteers is ~2x higher than observed at steady state for the highest dose (100 mg BID) tested in Phase II RA studies.

Conclusion: These data suggest that MK-8457 has the appropriate characteristics for assessment of the hypothesis that a selective SYK/ZAP70 inhibitor is efficacious in RA patients.

Disclosure: G. Marcantonio, Merck Pharmaceuticals, 3; **A. Bass**, Merck Pharmaceuticals, 3; **G. Baltus**, Merck Pharmaceuticals, 3; **J. Boice**, Merck Pharmaceuticals, 3; **H. Chen**, Merck Pharmaceuticals, 3; **M. Crackower**, Merck Pharmaceuticals, 3; **J. Elassaiss-Schaap**, Merck Pharmaceuticals, 3; **M. Ellis**, Merck Pharmaceuticals, 3; **T. Freshwater**, Merck Pharmaceuticals, 3; **F. Gervais**, Merck Pharmaceuticals, 3; **J. Guo**, Merck Pharmaceuticals, 3; **S. Kim**, Merck Pharmaceuticals, 3; **L. Moy**, Merck Pharmaceuticals, 3; **A. Northrup**, Merck Pharmaceuticals, 3; **J. Zhang-Hoover**, Merck Pharmaceuticals, 3; **M. Maddess**, Merck Pharmaceuticals, 3; **R. Miller**, Merck Pharmaceuticals, 3; **M. Ruddy**, Merck Pharmaceuticals, 3; **S. Vincent**, Merck Pharmaceuticals, 3; **H. Weng**, Employee of Merck Co., 3; **H. Houshyar**, Merck Pharmaceuticals, 3.

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Exposure-Response Analysis for Mavrilimumab Phase2b Study in RA Patients with Informative Dropout. Chi-Yuan Wu[1], Denise Jin[1], Alex Godwood[2], David Close[2], Lorin Roskos[3] and Bing Wang[1]. [1]Medimmune, Mountain View, CA, [2]MedImmune Ltd, Cambridge, United Kingdom, [3]Medimmune, Gaithersburg, MD.

Background/Purpose: Mavrilimumab is a recombinant human monoclonal antibody which neutralizes granulocyte-macrophage colony stimulating factor (GM-CSF) activity by selectively binding to the alpha subunit of its receptor (GM-CSFRα). A Phase 2b randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy and safety of mavrilimumab in subjects with at least moderately active rheumatoid arthritis (RA). Population modeling was performed to characterize the exposure-response relationship of mavrilimumab in RA patients.

Methods: In a Phase2b study, subjects with RA received subcutaneously administered placebo or mavrilimumab (30, 100 or 150 mg) once every other week for 24 weeks. The pharmacokinetic data was pooled and analyzed using a population approach. The binary ACR20 and ACR50 responses were modeled by logistic regression. A dropout hazard function was introduced to describe the voluntary patient withdrawals during the study period. Stochastic simulations based on the final PK-ACR20(50)-Dropout model were subsequently conducted for model evaluations and exposure-response relationship assessment.

Results: A mechanistic model incorporating the subcutaneous absorption, distribution, and parallel elimination pathways of mavrilimumab by the reticuloendothelium system and GM-CSFRα mediated internalization and intracellular degradation adequately described the observed PK profiles of mavrilimumab. The placebo effect and mavrilimumab treatment effect were integrated in the logit (log odds ratio) of ACR20 or ACR50. The treatment effect was described by an Emax model for ACR20, and by a linear relationship with mavrilimumab concentration for ACR50. The dropout hazard increased with time on study, and was significantly higher in ACR20 nonresponders than in responders. The protocol-permitted rollover of patients with inadequate ACR20 responses to an open-label extension study at any time after Week 12 substantially increased the dropout risk for nonresponders in placebo and two lower dose groups. There was no change in the dropout pattern for subjects receiving the 150 mg dose.

Conclusion: The pharmacokinetics of mavrilimumab, ACR20 and ACR50 responses in patients with moderate to severe RA were well described by a model incorporating mechanistic drug disposition, logistic regression for ACR20 or ACR50, and informative patient dropout. The population model facilitated the interpretation of Phase 2b outcome and the appropriate design of late-stage clinical trials for mavrilimumab.

Disclosure: C. Y. Wu, Medimmune, 3; **D. Jin**, Medimmune, 3; **A. Godwood**, AstraZeneca, 1, Medimmune, 3; **D. Close**, Medimmune, 3; **L. Roskos**, Medimmune, 3; **B. Wang**, Medimmune, 3.

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Efficacy and Safety of Iguratimod for Rheumatoid Arthritis. Tsuneo Kondo, Akiko Shibata, Ryota Sakai, Kentaro Chino, Ayumi Okuyama, Hirofumi Takei and Koichi Amrano. Saitama Medical Center, Saitama Medical University, Kawagoe, Japan.

Background/Purpose: Iguratimod is a new small-molecular drug for rheumatoid arthritis (RA), which was approved on June, 2012 in Japan. The agent inhibits the production of immunoglobulins and various inflammatory cytokines (interleukin-1, -6 and -8 and TNF), and exerts anabolic effects on bone metabolism by stimulating osteoblastic differentiation and inhibiting osteoclastogenesis in mice through inhibiting the nuclear transcription factor NF-κB, but not its inhibitor, IκBα. In addition this agent is very cheap (1.5$/25 mg tablet), so 50 mg/day iguratimod therapy costs only 3$/day. In this study, We evaluate the efficacy and safety of iguratimod for RA patients. In addition, We examine NK cell counts compared with tofacitinib to evaluate the mechanism of the safety.

Methods: 62 patients who were administered iguratimod at a dosage of 25mg qd during the first month, then 50mg qd thereafter, and followed up for 24 weeks were enrolled. Efficacy and safety were evaluated utilizing clinical and laboratory findings. We also monitor the NK cell counts in peripheral blood from 20 RA patients before and 12 weeks after the commencement of Iguratimod by flow cytometery analysis.

Results: The mean age was 61.6 years and 75.8% of patients were female. MTX was used in 46.8%, the average dose was 8.6±2.9 mg/week. LOCF analysis revealed that DAS28-ESR and SDAI decreased significantly from 4.49±1.33 to 3.09±1.12 and from 18.5±10.9 to 7.44±7.11 in 24 weeks respectively ($P<0.01$). Remission and LDA rate in SDAI were 30.4% and 47.8%. HAQ-DI score also decreased from 1.2±0.8 to 0.94±0.85. The difference between the efficacy of igurarimod with and without MTX was not significant. 29.0% of the patients discontinued iguratimod within 24 weeks. The reason of cessation consisted of adverse events (21.0%) and lack of efficacy (4.8%). Adverse events were digestive symptom (n=6), liver dysfunction (n=3), nasal hemorrhage (n=2) and so on. There's no severe adverse event. Peripheral NK cell counts in 12 weeks had not been changed significantly.

Conclusion: Iguratimod was well tolerable and may have a good cost effectiveness. So iguratimod be a new useful option as small molecule DMARDs for RA patients in a manner similar to tofacitinib.

Disclosure: T. Kondo, None; **A. Shibata**, None; **R. Sakai**, None; **K. Chino**, None; **A. Okuyama**, None; **H. Takei**, None; **K. Amano**, None.

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ALX-0061, an Anti-IL-6R Nanobody®for use in Rheumatoid Arthritis, Demonstrates a Different *in Vitro* Profile As Compared to Tocilizumab. Maarten Van Roy, Ariella Van De Sompel, Kristi De Smet, Jasper Jacobs, Tinneke Denayer and Hans Ulricrhts. Ablynx N.V., Zwijnaarde, Belgium.

Background/Purpose: Interleukin-6 (IL-6) is a pleiotropic cytokine inducing a wide range of biological activities via its receptor, which can either be soluble (sIL-6R) or membrane-bound (mIL-6R). In rheumatoid arthritis, blocking of IL-6R results in clinical benefit as demonstrated by the IL-6R inhibitor tocilizumab (TCZ). Signalling via the mIL-6R (classical pathway) is confined to selected cell types due to the restricted expression of mIL-6R. However, IL-6 can also activate cells through sIL-6R in a process known as trans-signalling. Unwanted pharmacology associated with IL-6 pathway inhibition has been linked to inhibition of mIL-6R. Preferential inhibition of sIL-6R could therefore provide higher therapeutic efficacy with a better safety profile compared to equivalent inhibition of both IL-6R forms (Waetzig & Rose-John, Expert Opin Ther Targets, 2012). Nanobodies are therapeutic proteins based on the smallest functional fragments of heavy chain-only antibodies, naturally occurring in the *Camelidae* family. ALX-0061 is a bispecific anti-IL-6R Nanobody engineered to have an extended half-life *in vivo* by targeting human serum albumin (HSA), in combination with strong target binding using a single anti-IL-6R building block. ALX-0061 was extensively characterised using *in vitro* systems: biological activity and affinity for both sIL-6R and mIL-6R were assessed and compared to TCZ.

Methods: Biological activity of ALX-0061 and TCZ was analysed in a cell-based assay for mIL-6R, ELISA-based neutralisation assays for sIL-6R, and cell-binding and cell-signalling (mIL-6R) experiments in whole blood from human donors using flow cytometry. The affinity of ALX-0061 for sIL-6R could not be accurately determined via surface plasmon resonance due to its very tight target binding. Consequently, the more sensitive Gyrolab™ platform was used to assess affinity for both receptors. The $K_D$for mIL-6R was determined after pre-incubation of mIL-6R-transfected cells with constant compound concentrations and subsequent quantification of free compound in the supernatant.

Results: Flow cytometry experiments demonstrated that ALX-0061 binds to mIL-6R expressed on peripheral blood leukocyte populations with expected pharmacology. ALX-0061 specifically neutralised sIL-6R with a 10-fold higher *in vitro* potency compared to TCZ, while the (apparent) affinity of ALX-0061 for sIL-6R (0.19 ± 0.08 pM) was about 2400-fold superior compared to TCZ (462 ± 138 pM). In the mIL-6R-driven cell-based assay, however, *in vitro*potencies were similar for ALX-0061 and TCZ, with the latter one showing avid binding due to its bivalency. In addition, TCZ showed a 3-fold higher affinity for mIL-6R (462 ± 138 pM) compared to sIL-6R (154 ± 16 pM), while the affinity of ALX-0061 was about 50-fold lower for mIL-6R compared to sIL-6R (9.1 ± 3.6 pM).

Conclusion: ALX-0061 demonstrates *in vitro* a preferential binding profile for sIL-6R with a lesser activity for mIL-6R, while TCZ has a higher preference for mIL-6R. Preferential inhibition of sIL-6R trans-signalling by ALX-0061 could provide improved therapeutic efficacy with a better safety profile compared to TCZ.

Disclosure: M. Van Roy, Ablynx N.V., 3; **A. Van De Sompel**, Ablynx N.V., 3; **K. De Smet**, Ablynx N.V., 3; **J. Jacobs**, Ablynx. V., 3; **T. Denayer**, Ablynx N.V., 3; **H. Ulrichts**, Ablynx N.V., 3.

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Characterization of ABT-494, a Second Generation Jak1 Selective Inhibitor. Candace Graff[1], Annette Schwartz[1], Jeffrey Voss[2], Neil Wishart[3], Lisa Olson[1], Jonathon George[3], Deborah Hyland[3] and Heidi Camp[4]. [1]AbbVie Inc, AbbVie Bioresearch Center, Worcester, MA, [2]AbbVie Pharmaceuticals, Worcester, MA, [3]Abbvie Pharmaceuticals, worcester, MA, [4]Abbvie, Winnetka, IL.

Background/Purpose: Jak kinase blockade can effectively manage rheumatoid arthritis (RA) and in some cases achieve remission. However, first generation Jak inhibitors have not met expectations due to dose-limiting tolerability and safety issues. ABT-494 is a second generation Jak inhibitor with high Jak1 selectivity thereby minimizing the potential for Jak2 and Jak3 related side effects. Here we describe preclinical and early clinical data that suggest ABT-494 has potential to address some of the current unmet medical needs of RA patients.

Methods: ABT-494 was engineered for increased selectivity for Jak1 using structural predictions indicating the potential for differential binding interactions outside the ATP-binding active site of Jak1 but not Jak2 or Jak3. ABT-494 efficacy and selectivity were tested in a battery of relevant cellular *and in vivo* pharmacology assays including bone marrow colony formation, adjuvant induced arthritis, erythropoietin (EPO) induced reticulocyte deployment and NK/NKT cell suppression. ABT-494 potency in a variety of complementary pharmacodynamic assays was also assessed at multiple oral dosages in healthy human subjects and patients with RA.

Results: ABT-494 is approximately 74 fold selective for Jak1 over Jak2 in cellular assays dependent on specific, relevant cytokines. The ability of ABT-494 and tofacitinib to inhibit Jak2/EPO signaling in these assays was consistent with their ability to inhibit bone marrow cell differentiation *in vitro*. Surprisingly, GMCSF (and IL3) signaling in TF1 cells were consistently more sensitive to inhibition than EPO signaling in UT7 cells indicating that Jak2 inhibition in some contexts may over-estimate inhibition of Jak2 via EPO signaling. Accordingly, in whole blood assays, ABT-494 was about 10X more potent against IL6 (Jak1) signaling than GMCSF (Jak2) driven signaling based on free drug concentrations. By contrast, tofacitinib under the same conditions was about 2X more potent. No changes in reticulocyte counts were observed in RA patients after 28 days of ABT-494 dosing.

ABT-494 and tofacitinib inhibited common gamma chain cytokine signaling (IL7, IL15 and IL21) in whole blood with similar potencies and *in vivo* were similarly potent in driving down NK cell counts in healthy rats. Consistent with its higher potency against IL6 signaling, ABT-494 had substantially greater potency in a rat arthritis model.

Conclusion: ABT-494 is a Jak1-selective inhibitor that demonstrates efficacy in rat arthritis models. Preliminary evidence suggests that compared to tofacitinib, ABT-494 may spare Jak2 and Jak3 dependent signaling. Taken together, these encouraging observations support further testing of ABT-494 in RA patients in Phase II randomized placebo controlled trials and indicate it may have increased potential to address patient needs over existing agents.

Disclosure: C. Graff, AbbVie Inc., 3; **A. Schwartz**, AbbVie Inc., 3; **J. Voss**, Abbvie, 3; **N. Wishart**, Abboie, 3; **L. Olson**, AbbVie Inc., 3; **J. George**, abbvie, 3; **D. Hyland**, abbvie, 3; **H. Camp**, Abbvie, 3.

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Preclinical and Clinical Characterization of MK-8457, a Selective Spleen Tyrosine Kinase and Zeta-Chain-Associated Protein Kinase 70 Inhibitor, in Normotensive and Hypertensive Cardiovascular Models. Hani Houshyar[1], Alan Bass[1], Judith Boice[2], Michael Ellis[1], Patrick Fanelli[3], Tomoko Freshwater[4], Jane Guo[1], Kimberly Hoagland[3], Janet Kerr[3], Alan Northrup[1], Mathew Maddess[1], Richard Miller[1], Marcella Ruddy[1], Stella Vincent[1], Jayanthi Wolf[3], Haoling Weng[2], Gloria Zingaro[3] and Gene Marcantonio[2]. [1]Merck & Co., Boston, MA, [2]Merck & Co., Whitehouse Station, NJ, [3]Merck & Co., West Point, PA, [4]Merck & Co., Rahway, NJ.

Background/Purpose: Spleen Tyrosine Kinase (SYK) and Zeta-chain-associated protein kinase 70 (ZAP70) are non-receptor protein kinases that bind phosophorylated receptor tyrosine-based activation motifs, critical in immune receptor signaling in multiple hematopoietic and non-hematopoietic cells, supporting potential utility of SYK/ZAP70 inhibitors in multiple indications including rheumatoid arthritis. While neither SYK nor ZAP70 are implicated in blood pressure (BP) regulation, the non-selective SYK/ZAP70 inhibitor, Fostamatinib, is associated with BP increases both preclinically and in patients. Fostamatinib's impact on BP has been attributed to off-target activity on vascular endothelial growth factor receptor 2 (VEGF-R2). Here, we report the *in vitro*, *in vivo*, and clinical profile of MK-8457 to demonstrate that a highly selective SYK/ZAP70 inhibitor does not affect BP.

Methods: The *in vitro* off-target activity of MK-8457 vs. Fostamatinib on VEGFR-2 was assessed in enzymatic as well as cellular assays. *In vivo*, the BP effects of MK-8457 were compared with Fostamatinib in conscious telemetered normotensive Wistar rats and Beagle dogs. In the clinic, MK-8457 was studied in a multi-center, randomized, double-blind, placebo controlled 2-period crossover ambulatory BP measurement (ABPM) trial in men and women with mild to moderate hypertension. This study in 29 subjects was powered to detect a 5 mmHg increase in BP, to rule out a Fostamatinib-like BP effect.

Results: In contrast to Fostamatinib, MK-8457 is devoid of off-target VEGFR2 activity in both enzymatic and cellular assays. Whereas Fostmatinib produces dose-dependent increases in BP in conscious telemetry instrumented rats, MK-8457 does not. Similarly, MK-8457 does not significantly affect BP in conscious telemetry instrumented dogs. In the ABPM study, MK-8457 was studied at a dose of 100 mg BID for 10 days, a dose projected to result in nearly complete 24 hour inhibition of SYK and ZAP70. At this dose, MK-8457 does not result in a statistically significant change in BP. The mean treatment difference (MK-8457-placebo) in 24 hr mean systolic and diastolic ABPM change from baseline was 2.02 and 1.57 mmHg, respectively.

Statistical Comparison of 24-Hour Change From Baseline in Ambulatory BP Parameters Following 10 days of Multiple dosing of MK-8457 or Matching Placebo in Hypertensive Patients

	MK-8457			Placebo			MK-8457 - Placebo	
Parameters	N	LS Mean†	95 % CI	N	LS Mean†	95 % CI	Mean Difference	90 % CI
Systolic blood pressure (mm Hg)	29	−0.47	(−2.60, 1.66)	28	−2.49	(−4.66, −0.31)	2.02	(−0.52, 4.56)
Diastolic blood pressure (mm Hg)	29	0.22	(−1.33, 1.78)	28	−1.35	(−2.93, 0.23)	1.57	(0.19, 2.96)

† Least square Mean using linear mixed effect model where the response was average 24-hour change from baseline for Day 10 and the model contained period, treatment as fixed effect and Day -1 baseline as a fixed continuous covariate and subject as a random effect.

Conclusion: These data illustrate that full SYK and ZAP70 inhibition with a selective inhibitor does not significantly impact BP preclinically or clinically in a sensitive population.

Disclosure: H. Houshyar, Merck Pharmaceuticals, 3; **A. Bass**, Merck Pharmaceuticals, 3; **J. Boice**, Merck Pharmaceuticals, 3; **M. Ellis**, Merck Pharmaceuticals, 3; **P. Fanelli**, Merck Pharmaceuticals, 3; **T. Freshwater**, Merck Pharmaceuticals, 3; **J. Guo**, Merck Pharmaceuticals, 3; **K. Hoagland**, Merck Pharmaceuticals, 3; **J. Kerr**, Merck Pharmaceuticals, 1; **A. Northrup**, Merck Pharmaceuticals, 3; **M. Maddess**, Merck Pharmaceuticals, 3; **R. Miller**, Merck Pharmaceuticals, 3; **M. Ruddy**, Merck Pharmaceuticals, 3; **S. Vincent**, Merck Pharmaceuticals, 3; **J. Wolf**, Merck Pharmaceuticals, 3; **H. Weng**, Employee of Merck Co., 3; **G. Zingaro**, Merck Pharmaceuticals, 3; **G. Marcantonio**, Merck Pharmaceuticals, 3.

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Immunogenicity Assessment of PF-06438179, a Potential Biosimilar to Infliximab, in Healthy Volunteers. Chandrasekhar Udata[1], Donghua Yin[1], Chun-hua Cai[2], Stephanie Salts[1], Steven Y. Hua[1], Muhammad I. Rehman[3] and Xu Meng[1]. [1]Pfizer Inc., San Diego, CA, [2]Pfizer Inc., Groton, CT, [3]Pfizer Inc., Cambridge, MA.

Background/Purpose: PF-06438179, a proposed biosimilar to infliximab, was evaluated for immunogenicity in a phase 1 pharmacokinetic (PK) similarity study.

Methods: In this double-blind trial (NCT01844804), 151 healthy volunteers aged 18–55 years were randomized 1:1:1 to 1 of 3 treatment groups, of which 146 received a single 10 mg/kg intravenous dose of PF-06438179 (n=49), infliximab sourced from the US (infliximab-US; n=49), or infliximab sourced from the EU (infliximab-EU; n=48). All subjects provided informed consent and were evaluated post dose for safety and immunogenicity over 12 weeks, and for PK over 8 weeks. Serum samples for detecting anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were collected at 0, 336, 672, 1008, 1344, and 2016 hours post dose. ADA samples were analyzed using 2 validated electrochemiluminescent immunoassays, 1 each to detect antibodies against PF-06438179 and reference drugs (infliximab-US or -EU). A tiered approach of screening, confirmation and titer quantitation was utilized. Samples were first tested for antibodies against the dosed product and confirmed ADA positive samples were then tested for ADA cross-reactivity using the alternate assay. ADA positive samples were also analyzed for NAb using a validated semi-quantitative cell-based assay against the dosed product and for NAb cross-reactivity using the alternative NAb assay.

Results: Samples for immunogenicity assessment were collected from all 146 subjects. No subjects tested positive for ADA at baseline. Six (16.2%), 14 (32.6%) and 11 (28.2%) subjects in the PF-06438179, infliximab-EU, and infliximab-US groups, respectively, had ≥1 ADA-positive sample through Day 85. Twenty-seven of the 31 subjects (6/6 in PF-06438179, 10/14 in infliximab-EU, and 11/11 in infliximab-US) that tested positive for ADA also tested positive for cross-reactivity by the alternative assay, suggesting that anti-drug antibodies were likely developed against epitopes shared among the study drugs. Of the 31 subjects who tested positive for ADA, 26 tested positive for NAb (5/6 in PF-06438179; 12/14 in infliximab-EU; 9/11 in infliximab-US). Overall safety profiles were similar across the 3 study drugs and no infusion related reactions were reported. The 3 study drugs demonstrated PK similarity, based on the 90% confidence intervals of the test-to-reference ratios for maximum observed serum concentration (C_{max}), area under the serum concentration-time profile from time 0 to the time of last quantifiable concentration (AUC_t), and area under the serum concentration-time profile from time 0 extrapolated to infinite time (AUC_{inf}) each falling within the standard bioequivalence region of 80–125%.

Conclusion: The 3 study drugs had comparable immunogenicity profiles with a somewhat lower incidence of ADA response in the PF-06438179 group. The majority of ADA-positive subjects also developed NAb. Overall, PF-06438179 demonstrated PK similarity and comparable safety and immunogenicity profiles to infliximab in healthy subjects. Further comparative assessment of immunogenicity for PF-06438179 will be carried out in a planned phase 3 trial in patients with rheumatoid arthritis.

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Disclosure: C. Udata, Pfizer Inc., 1, Pfizer Inc., 3; **D. Yin**, Pfizer Inc., 1, Pfizer Inc., 3; **C. H. Cai**, Pfizer Inc., 1, Pfizer Inc., 3; **S. Salts**, Pfizer Inc., 3; **S. Y. Hua**, Pfizer Inc., 1, Pfizer Inc., 3; **M. I. Rehman**, Pfizer Inc., 1, Pfizer Inc., 3; **X. Meng**, Pfizer Inc., 3.

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A Phase I Trial Comparing PF-05280586 (A Potential Biosimilar) and Rituximab in Subjects with Active Rheumatoid Arthritis. Jean-Claude P. Becker[1], Donghua Yin[2], Lisa Ann Melia[2], Ruifeng Li[3], Barry Gumbiner[2], Dolca Thomas[1], George Spencer-Green[3] and Xu Meng[2]. [1]Pfizer Inc., New York, NY, [2]Pfizer Inc., San Diego, CA, [3]Pfizer Inc., Cambridge, MA.

Background/Purpose: PF-05280586, a proposed biosimilar to rituximab, has the same primary amino acid sequence as rituximab with similar physicochemical and in vitro functional properties. This pharmacokinetic (PK) similarity study in subjects with active rheumatoid arthritis on a background of methotrexate who had an inadequate response to one or more TNF antagonist therapies (NCT01526057) also evaluated the clinical response and safety of PF-05280586, and rituximab sourced from the US (rituximab-US) and EU (rituximab-EU).

Methods: 220 subjects were randomized 1:1:1 to one course of IV PF-05280586, rituximab-US or rituximab-EU 1000 mg (with stable background regimen of methotrexate) on Days 1 and 15. Clinical response was assessed via Disease Activity Score in 28 joints-C-reactive protein (DAS28-CRP) and American College of Rheumatology (ACR) assessments. After Week 17, subjects could enroll in an extension study and receive additional courses of treatment.

Results: Baseline demographics were generally similar among the treatment arms. The primary endpoint of PK similarity among the three treatment arms was achieved. Measures of disease activity were numerically higher at baseline among patients randomized to rituximab-US (Table). Although not designed to demonstrate similarity for efficacy, mean DAS28-CRP (Figure), mean number of tender/painful joint counts, mean number of swollen joint counts, and mean high-sensitivity C reactive protein values decreased over time, and improvement in ACR20, ACR50, and ACR70 scores were seen in all groups. The safety profile was similar among treatment arms. A total of 10 subjects experienced SAEs (rituximab-US: 4; PF-05280586: 5; rituximab-EU: 1).

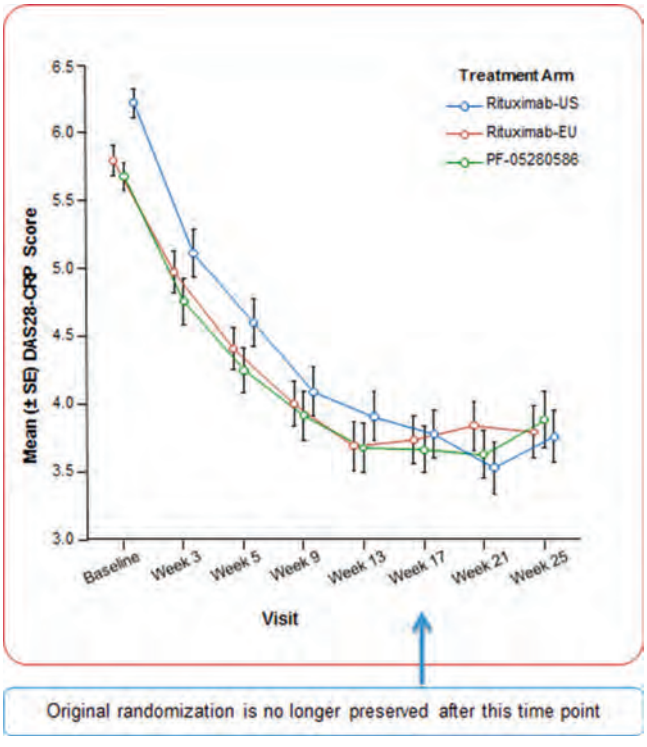
Conclusion: In this PK similarity study, a robust improvement in clinical response occurred with PF-05280586, rituximab-US, and rituximab-EU. All 3 treatments were generally well tolerated with a low incidence of treatment-related AEs. **Role of the Study Sponsor:** Study supported by Pfizer Inc.

Table. Baseline disease characteristics

Mean (SD)	Rituximab-US n=73	Rituximab-EU n=74	PF-05280586 n=73
Swollen joint count (28)	14.1 (5.92)	13.0 (6.53)	11.7 (5.36)
Tender/painful joint count (28)	18.1 (6.45)	14.9 (6.79)	14.6 (6.70)
Swollen joint count (66)	19.3 (8.73)	17.8 (10.56)	15.6 (8.91)
Tender/painful joint count (68)	30.4 (15.33)	23.3 (13.23)	22.9 (12.46)
HAQ-DI score	1.75 (0.62)	1.59 (0.54)	1.65 (0.57)
Serum hsCRP (mg/L)	18.17 (24.80)	14.80 (17.42)	12.70 (15.28)
DAS28-CRP	6.22 (0.89)	5.79 (0.95)	5.68 (0.86)

hsCRP=high-sensitivity C reactive protein; DAS28-CRP=Disease Activity Score in 28 joints - C-reactive protein; HAQ-DI=Health Assessment Questionnaire – Disability Index; SD=standard deviation

Figure. Mean (±SE) DAS28-CRP score over time



Disclosure: J. C. P. Becker, Pfizer Inc., 1, Pfizer Inc., 9; **D. Yin**, Pfizer Inc., 1, Pfizer Inc., 3; **L. A. Melia**, Pfizer Inc., 3; **R. Li**, Pfizer Inc., 1, Pfizer Inc., 3; **B. Gumbiner**, Pfizer Inc., 1, Pfizer Inc., 3; **D. Thomas**, Pfizer Inc., 1, Pfizer Inc., 3; **G. Spencer-Green**, Pfizer Inc., 3; **X. Meng**, Pfizer Inc., 3.

1503

Demonstration of Functional Similarity Comparing Adalimumab to Biosimilar Candidate ABP 501. Teresa Born[1], Jyoti Velayudhan[1], Yuh-fung Chen[2], Heather Thomas[1], Christina Pastula[1], Gwen Maher[2] and Ryan Brown[1]. [1]Amgen, Seattle, WA, [2]Amgen, Thousand Oaks, CA.

Background/Purpose: ABP 501 is being developed as a biosimilar to adalimumab, a recombinant monoclonal antibody that binds tumor necrosis factor alpha (TNF) thus inhibiting engagement of TNF receptors and initiation of consequent proinflammatory signaling. Although adalimumab and intended biosimilars share the same amino acid sequence, differences will likely exist in product quality attributes due to differences in proprietary expression systems, bioprocess and purification. Equivalence of product quality attributes, especially demonstration of comprehensive functional equivalence, is of primary importance during stepwise development of a biosimilar in order to provide confidence for similar clinical safety and efficacy in patients, including extrapolation to all indications of use.

Methods: The similarity assessment of biological activity included testing binding of ABP 501 and adalimumab to soluble TNF by surface plasmon resonance and to cell-surface expressed TNF (mbTNF) in a competitive imaging cytometry-based assay. The similarity assessment for F(ab)-mediated activity included blocking TNF-induced caspase activation, IL-8 secretion and cytotoxicity. Inhibition of TNF activity in healthy volunteer blood samples stimulated ex vivo was also compared. To assess Fc-mediated functions, binding to the neonatal Fc receptor (FcRn) was measured in a competitive cell-based assay and to FcγRIIIa (158V) by AlphaLISA™. To confirm similarity in Fc-mediated functions, antibody-dependent cell-mediated cytotoxicity (ADCC) was assessed using cells expressing mbTNF and NK92-M1 cells expressing FcγRIIIa (158V). Complement-dependent cytotoxicity (CDC) was also tested, using complement and cells expressing mbTNF. Data from up to three lots of each antibody were assessed in the described assays as part of the initial similarity assessment.

Results: Equilibrium binding affinity to TNF was similar between ABP 501 (48–52 pM) and adalimumab (48–53 pM). Binding to mbTNF was also similar between ABP 501 (100–106% relative binding) and adalimumab (100–111%). Relative potency in the caspase activation assay was similar between ABP 501 (103–107%) and adalimumab (100–110%). Dose response profiles and resulting EC50 values in the IL-8 secretion (192–294 pM for ABP 501 and 156–253 pM for adalimumab), cytotoxicity (390–457 pM for ABP 501 and 391–544 pM for adalimumab) and whole blood assays, measuring both MCP-1 and MIP-1 beta production, were also similar between ABP 501 and adalimumab.

Binding to FcRn was similar between ABP 501 (86–94%) and adalimumab (92–114%) as was binding to FcγRIIIa (158V) comparing ABP 501 (103–113%) to adalimumab (92–94%). The dose response profile for ADCC (101% relative cytotoxicity for ABP 501 and 107% for adalimumab) and CDC (97% relative cytotoxicity for ABP 501 and 93% for adalimumab) were also similar.

Conclusion: Results from an initial similarity assessment demonstrate that ABP 501 is functionally highly similar to adalimumab in multiple sensitive preclinical pharmacologic assays.

Disclosure: T. Born, Amgen, 3, Amgen, 1; **J. Velayudhan**, Amgen, 3, Amgen, 1; **Y. F. Chen**, Amgen, 1, Amgen, 3; **H. Thomas**, Amgen, 1, Amgen, 3; **C. Pastula**, Amgen, 1, Amgen, 3; **G. Maher**, Amgen, 1, Amgen, 3; **R. Brown**, Amgen, 1, Amgen, 3.

1504

Pharmacokinetic Equivalence of ABP 501 Relative to Adalimumab: Results from a Randomized, Single-Blind, Single-Dose, Parallel Group Study in Healthy Subjects. Primal P. Kaur[1], Vincent Chow[2], Nan Zhang[1], Mike Moxness[1] and Richard Markus[1]. [1]Amgen, Inc., Thousand Oaks, CA, [2]Amgen, Inc., Seattle, WA.

Background/Purpose: Adalimumab is a recombinant IgG1 monoclonal antibody that binds to TNFα blocking its interaction with p55 and p75 cell surface receptors. ABP 501 is being developed as a biosimilar candidate to adalimumab; it contains a fully human recombinant monoclonal antibody with the same amino acid sequence. Evidence from analytical comparisons indicates that ABP 501 is highly similar to adalimumab. This report describes the pharmacokinetics (PK) results of ABP 501 compared with adalimumab sourced from the United States (US).

Methods: This was a single-blind, single-dose, parallel-group study in healthy male and female subjects, 18 to 45 years of age with a body mass

index of 18 to 30 kg/m^2. Subjects were randomized to receive 40-mg subcutaneous (SC) injection of ABP 501 or adalimumab. The primary objective was demonstration of PK equivalence of ABP 501 relative to adalimumab based on area under the serum concentration-time curve from time 0 extrapolated to infinity (AUC_{inf}) and the maximum observed serum concentration (C_{max}). Pre-specified equivalence criterion for the primary PK parameters was the standard 90% confidence interval (CI) for geometric means (GM) ratio to be within 0.80 to 1.25. Secondary endpoints included the safety, tolerability, and immunogenicity.

Results: Pharmacokinetics: A total of 67 subjects received ABP 501 and 69 subjects received adalimumab. Following a single dose, the adjusted least square (LS) GM of C_{max} and AUC_{inf} for ABP 501 were 3.22 μg/mL and 2140 μg.h/mL. The adjusted LS GM of C_{max} and AUC_{inf} for adalimumab were 3.11 μg/mL and 1920 μg.h/mL. Ratios of adjusted LS GM (90% CIs) between ABP 501 and adalimumab for C_{max} and AUC_{inf} were 1.04 (0.96, 1.12) and 1.11 (1.00, 1.24). The 90% CIs of these ratios were fully contained within 0.80 to 1.25 interval, confirming PK equivalence between ABP 501 and adalimumab.

Safety: There were no deaths, treatment-related serious adverse events, or treatment-related adverse events leading to discontinuation from the study. The most frequently reported treatment-related AEs included headache, nausea, nasopharyngitis, and oropharyngeal pain.

Immunogenicity: No pre-existing anti-drug antibodies (ADA) were detected at baseline. In the ABP 501 treatment group, 36 (54%) subjects developed binding antibodies and 12 (18%) developed neutralizing antibodies. In the adalimumab treatment group, 38 (55%) subjects developed binding antibodies and 15 (22%) developed neutralizing antibodies.

Conclusion: Results of this phase 1 study demonstrated PK equivalence of ABP 501 following a single 40-mg SC injection relative to that after a 40-mg SC injection of adalimumab sourced from the US. Similar ADA rates were observed in healthy subjects.

Disclosure: P. P. Kaur, Amgen, 1, Amgen, 3; **V. Chow**, Amgen, 1, Amgen, 3; **N. Zhang**, Amgen, 3, Amgen, 3; **M. Moxness**, Amgen, 1, Amgen, 3; **R. Markus**, Amgen, 1, Amgen, 3.

1505

The Biosimilar Landscape: A Systematic Review of Its Current Status. Niti Goel and Kamali Charnce. Quintiles, Durham, NC.

Background/Purpose: In the last 5 years, the number of biosimilars in development for the treatment of immunologic diseases has increased as innovator etanercept (ETA), infliximab (IFX), adalimumab (ADA) and rituximab (RTX) near expiry of their original patents. Adequate clinical data may be achieved for a biosimilar with a single Phase (Ph) III study in a representative indication if the mode of action for the various proposed indications is similar. Disease prevalence, effect sizes for treatment response, regulatory and marketing considerations all may play a role in the indication(s) chosen for evaluation. In 2013, an IFX biosimilar, CT-P13, was the first mAb biosimilar approved in the EU on the basis of an extensive nonclinical and clinical comparative data package. Included clinical data demonstrated noninferiority to innovator IFX in just 2 indications, ankylosing spondylitis (AS) and rheumatoid arthritis (RA); approval was obtained for all pediatric and adult indications (8 in total) of innovator IFX. The US has yet to approve a biosimilar via the Public Health Service 351(k) pathway that is designated for biosimilar approval.

Methods: We performed a systematic review of ClinicalTrials.gov (CT.gov) to assess the evolution of the biosimilar trial landscape for immunologic indications. A cutoff date of 31 May 2014 was used to identify studies of biosimilars of innovator ETA, ADA, IFX and RTX, excluding oncologic studies for RTX.

Results: Overall, there were 14 unique biosimilars in development: 12 in Ph III and 2 in Ph I or I/II only; 4 each were ADA or ETA, 3 each, IFX or RTX. Thirty-one biosimilar studies were registered on CT.gov over the last 5 years, with none reported as being initiated prior to 2010. Fifteen (55%) were Ph III, double-blind, randomized controlled trials (DBRCT). Of these, 12 (80%) were or planned to be started in 2013 to 2014. Four DBRCT each evaluated ADA or IFX biosimilars (27% each); 5, ETA (33%); and 2, RTX (13%). Listed indications for the Ph III DBRCT were RA (10 studies, 67%), psoriasis (PsO; 4, 27%), and Crohn's disease (CD; 1, 7%). Only 3 biosimilars had Ph III DBRCT in $>$ 1 indication each: RA and PsO for both an ADA and ETA biosimilar, and RA and CD for CT-P13. PsO was used only for evaluation of ADA or ETA biosimilars. RA was used to also assess RTX biosimilars in Ph I, due to regulatory authorities not permitting RTX use in normal healthy volunteers. Only 7 of the Ph III DBRCT (47%) included US sites.

Conclusion: Biosimilar development has increased significantly in the last 5 years, with the majority of the Ph III studies having been or planned to be started from 2013 onward. Most biosimilars appear to be evaluating efficacy, safety and immunogenicity against the innovator in only 1 indication. The common use of RA and/or PsO as indications may reflect disease prevalence, effect sizes and actual innovator use for these indications in clinical practice. RTX biosimilar Ph I studies in RA may not translate into eventual development in RA for Ph III. Less than half of the Ph III studies involve US sites. It is unclear whether the development programs proposed will be adequate to achieve approval of a biosimilar mAb in the US for the treatment of rheumatic conditions as well as extrapolation to other indications approved for the innovator product.

Disclosure: N. Goel, Quintiles, 3; **K. Chance**, Quintiles, 3.

1506

Incidence of Adverse Events in Patients Treated with Intended Copies of Biologic Therapeutic Agents in Colombia and Mexico. Leonor A. Barile-Fabris[1], Fedra Irazoque-Palazuelos[2], Ramiro Hernández Vásquez[3], Sandra Carrillo Vazquez[4] and R. Gúzman[5]. [1]Hospital Especialidades CMN, Mexico City, Mexico, [2]Centro Médico Nacional '20 de Noviembre' ISSSTE, Mexico City, Mexico, [3]Hospital de Especialidades "Dr. Bernardo Sepúlveda Gutiérrez", Mexico, Mexico, [4]Hospital Angeles Lindavista, Mexico DF, Mexico, [5]IDEARG, SaludCoop, Bogotá, Colombia.

Background/Purpose: A biosimilar is a copy of an approved biologic therapeutic agent that has undergone rigorous evaluation to ensure that it is similar to the innovator in physicochemical characteristics, efficacy and safety. In many countries, there are biologic products available that have not undergone such evaluation and thus should be labeled "intended copy".[1] It is critical to examine the safety profile of these intended copies to ensure that patients receive the best medical care available. The purpose was to evaluate the incidence of adverse events reported by patients treated with intended copies of etanercept (Infinitam or Etanar) and rituximab (Kikuzubam).

Methods: These data are a compilation of observations from four hospitals in Mexico and Colombia. Patients with rheumatic diseases, e.g., rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, were treated with Infinitam/Etanar or Kikuzubam. Patients were followed from initiation of treatment till first experience of an adverse event. Based on the nature and severity of the adverse event, treatment was continued, interrupted, suspended, or discontinued as determined by the treating physician.

Results: A preliminary analysis was performed of 219 patients with various diagnoses treated with Infinitam/Etanar (14) or Kikuzubam (205) in the four hospitals. Among patients receiving treatment, 10 (4.6%) on Infinitam/Etanar and 101 (46.1%) on Kikuzubam experienced at least one treatment-related adverse event (AE). Of these, 86.7% were female, and the median age was 51.9 years (range: 22 – 93 years). The median duration of disease was 14.5 years (range: 1 – 67 years). Overall, although the majority of the AEs reported (98/118, 83.1%) were Grade 2 or less, there were several reports of Grade 3 (13/118; 11.0%) and Grade 4 (7/118; 5.9%) AEs; there were no Grade 5 AEs reported for any agent. The time to the first experience of an AE from initiation of intended copy therapy was ranged from 0 – 50 months with 38 (36.2%) patients experiencing AEs on the same day as the first treatment.

Conclusion: A significant percent (14.3%) of patients receiving Infinitam/Etanar or Kikuzubam, intended copies of etanercept and rituximab, respectively, experience Grade 3/4 AEs with a very short time to onset.

Reference

1. Dörner T. et al. *Ann Rheum Dis*2013;72:322.

Disclosure: L. A. Barile-Fabris, Abbvie, Pfizer, UCB, Roche, Janssen, 5, Abbvie, Pfizer, UCB, Roche, Janssen, 8; **F. Irazoque-Palazuelos**, Bristol-Myers Squibb, Janssen, Pfizer, and Roche, 2, Bristol-Myers Squibb, Janssen, Pfizer, and Roche, 5, Bristol-Myers Squibb, Janssen, Pfizer, and Roche, 8; **R. Hernández Vásquez**, Abbvie, Roche, UCB and BMS, 2, Abbvie, Roche, UCB and BMS, 8; **S. Carrillo Vazquez**, Pfizer, Roche, Bristol, 8, Janssen, Roche, Pfizer, Bristol, 5; **R. Gúzman**, None.

1507

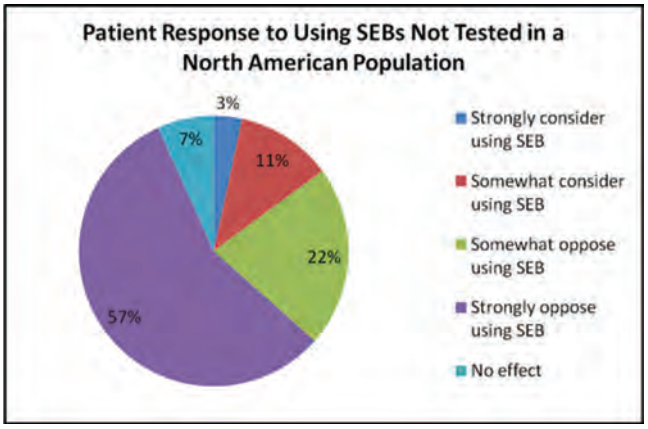
Patient Perspectives on the Introduction of Subsequent Entry Biologics in Canada. Suneet Sekhon[1], Raman Rai[1], Debbie McClory[2], Carolyn Whiskin[2], Melissa Deamude[2], Cynthia Mech[2], Lauri Vanstone[2], Alpesh Shah[3], Arthur N. Lau[1] and William Bensen[1]. [1]Division of Rheumatology, McMaster University, Hamilton, ON, [2]Rheumatology Health Team, Dr. Bensen's Rheumatology Clinic, Hamilton, ON, [3]MSc in Clinical Epidemiology, University of Western Ontario, London, ON.

Background/Purpose: Biologic medications have revolutionized the treatment of inflammatory arthritis. Subsequent entry biologics (SEBs) or biosimilars are medications that are similar but not identical to the innovator biologics. Despite a paucity of comparative trials, SEBs are poised to enter the Canadian market. They will be prescribed under the same drug name even though they are not identical. This may have implications for patients that are currently on biologic therapy. We conducted a survey of Canadian arthritis patients currently taking innovator biologics to understand their perspectives on SEBs and the possibility of being switched to them.

Methods: A survey consisting of 14 closed-ended and one open-ended question was administered sequentially to 208 patients at a biologic infusion clinic. In addition to demographic data, patients were asked about their understanding of SEBs, and after providing a definition were asked about factors that might influence them switching to an SEB. The survey results were analyzed using SAS version 9.3.

Results: Of the patients surveyed (n=208), mean age was 56 years, 67% were female, 56% of patients had an annual household income of less than $75, 000, and 63% had private drug insurance. The majority of patients had a diagnosis of rheumatoid arthritis (76%) and had been on their current biologic for 1–5 years (55%). Most preferred the subcutaneous route of administration (64%) versus intravenous. When asked about the definition of a SEB, 58% indicated they did not know, 26% chose correctly, and 16% chose incorrectly. When asked about their interest in using a SEB, 30% were neutral, 40% were somewhat or very interested, and 30% were somewhat or completely opposed to it. Potential lower cost of a SEB did not greatly influence this decision, though if an insurance company mandated use due to lower cost most opposed this (54%). The lack of testing in North American patients led to 79% of patients being somewhat or completely opposed to SEBs. Most patients were interested in continuing to use the innovator biologic if there was no further expense (70%) and felt their doctor's opinion would influence their decision (85%). Demographics, household income, diagnosis and type of current biologic therapy did not affect patient opinions.

Conclusion: Given the lack of efficacy and safety data for SEBs, there is understandable concern as these medications enter the biologic landscape. This survey identifies a lack of patient understanding of SEBs and highlights a need for further education. Patients are hesitant to use SEBs that are not tested in a North American population and would prefer to stay on innovator biologics if cost was not an issue. Patients value their doctors' opinions to help them make informed decisions about SEBs. Open dialogue is needed between patients, physicians, industry and regulatory bodies in order to safely introduce SEBs into practice.



Disclosure: S. Sekhon, None; **R. Rai**, None; **D. McClory**, None; **C. Whiskin**, None; **M. Deamude**, None; **C. Mech**, None; **L. Vanstone**, None; **A. Shah**, None; **A. N. Lau**, Amgen, Roche, 2, Amgen, Roche, 8, Amgen, Roche, 2; **W. Bensen**, Janssen Inc., 5.

1508

Impact of Anti-Drug Antibody on Efficacy and Safety over Week 24 in Both CT-P10 and Innovator Rituximab Treatment Groups. Dae-Hyun Yoo[1], Won Park[2], Slawomir Jeka[3], Fidencio Cons Molina[4], Pawel Hrycaj[5], Piotr Wiland[6], Wolfgang Spieler[7], Eun Young Lee[8], Francisco G. Medina-Rodriguez[9], Pavel Shesternya[10], Sebastiao Radominski[11], Dong Hyuk Sheen[12], Mie Jin Lim[2], Jung-Yoon Choe[13], Leysan Myasoutova[14], Taek Kwon[15], Sang Joon Lee[15], Seung-Cheol Shim[16] and Chang-Hee Suh[17]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Inha University Hospital, Incheon, South Korea, [3]Clinic of Rheumatology and Connective Tissue Diseases, Bydgoszcz, Poland, [4]Centro de Investigacion en Artritis y Osteoporosis, Mexicali, Mexico, [5]Poznan University of Medical Sciences, Poznan, Poland, [6]Medical University of Wroclaw, Wroclaw, Poland, [7]ZeFOR GmbH Zentrum für Forschung, Zerbst, Germany, [8]Seoul National University College of Medicine, Seoul, South Korea, [9]Centro de Investigación Farmacológica y Biotecnológica, Mexico City, Mexico, [10]Krasnoyarsk State Medical University, Krasnoyarsk, Russia, [11]Universidade Federal do Parana, Curitiba, Brazil, [12]Eulji University Hospital, Daejeon, South Korea, [13]Catholic University of Daegu School of Medicine, Daegu, South Korea, [14]Research Medical Complex Vashe Zdorovie, Kazan, Russia, [15]CELLTRION, Inc., Incheon, South Korea, [16]Chungnam National University Hospital, Daejeon, South Korea, [17]Ajou University Hospital, Suwon, South Korea.

Background/Purpose: CT-P10 is a biosimilar candidate for rituximab. Pharmacokinetic equivalence and similarity of clinical efficacy, safety and immunogenicity had been demonstrated between CT-P10 and Innovator Rituximab (RTX) groups[1]. The immunogenicity to the biologic monoclonal antibody may affect both patient's safety and therapeutic efficacy. Until now the presence of human anti-chimeric antibodies (HACA) to rituximab was known not to change the clinical efficacy and safety of rituximab.

The purpose of this analysis was to demonstrate the impact of anti-drug antibody (ADA) on efficacy and safety of CT-P10 and RTX in patients with rheumatoid arthritis (RA) over week 24.

Methods: A total of 154 RA patients were randomized 2:1 to receive 2 infusions (1000 mg, 2 week interval) of either CT-P10 (n=103) or RTX (n=51), and efficacy, safety and immunogenicity were assessed during the study. Electrochemilumencent (ECL) assay was used to assess immunogenicity in this study since this assay is about 10 times more sensitive than the enzyme-linked immuno sorbent assay (ELISA) which was used in the historical rituximab trials.

The impact of ADA on efficacy and safety in both treatment groups was evaluated at week 24, when drug concentration was low enough not to interfere with the analysis.

Results: The proportion of patients who developed ADA at week 24 was exactly same (17.6% each) in both CT-P10 and RTX treatment groups. Similar proportion of patients achieved ACR20 and the European League Against Rheumatism (EULAR-CRP and -ESR) responses after the CT-P10 and RTX treatment in both ADA (+) and (-) subgroups (Table 1). The interference of the ADA on the clinical response was not significant in both treatment groups.

The safety profiles of CT-P10 were generally comparable to those of RTX in both ADA (+) and (-) subgroups. The proportion of patients with adverse event (AE) were 55.6% and 49.4% for CT-P10-ADA (+) and (-) subgroups and 88.9% and 67.6% for RTX-ADA (+) and (-) subgroups, respectively. Serious AE was reported in 11.1% and 15.6% in the CT-P10-ADA (+) and (-) subgroups and 22.2% and 16.2% in the RTX-ADA (+) and (-) subgroups, respectively. The proportion of patients with AE due to infections and infusion related reactions was also similar between the treatment groups in ADA (+) and (-) subgroups.

Table 1. The Impact of ADA on Efficacy in Treatment Groups (%)

	CT-P10		RTX	
Clinical Response	**ADA (+)**	**ADA (−)**	**ADA (+)**	**ADA (−)**
ACR20	61.1	67.5	62.5	75.0
EULAR response (CRP)	66.7	85.7	75.0	85.7
EULAR response (ESR)	61.1	80.5	75.0	80.0

Note: No statistical difference in all comparisons between ADA subgroups or treatment groups ($p>0.05$). EULAR (CRP/ESR): the proportion of patients with moderate or good response

Conclusion: The development of ADA did not affect clinical response or safety profiles in RA patients treated with CT-P10 or RTX, and the magnitude of impact of ADA was similar in both treatment groups. These results

confirmed the comparability of CT-P10 to those of RTX in efficacy and safety over 24 weeks regardless of the immunogenic reaction.

Reference

1. Yoo DH, et al. Arthritis Rheum 2013;65(Suppl 10): S736

Disclosure: D. H. Yoo, CELLTRION, Inc., 5; **W. Park**, CELLTRION, Inc., 5; **S. Jeka**, CELLTRION, Inc., 2; **F. Cons Molina**, CELLTRION, Inc., 2; **P. Hrycaj**, CELLTRION, Inc., 2; **P. Wiland**, CELLTRION, Inc., 2; **W. Spieler**, CELLTRION, Inc., 2; **E. Y. Lee**, CELLTRION, Inc., 2; **F. G. Medina-Rodriguez**, CELLTRION, Inc., 2; **P. Shesternya**, CELLTRION, Inc., 2; **S. Radominski**, CELLTRION, Inc., 2; **D. H. Sheen**, CELLTRION, Inc., 2; **M. J. Lim**, CELLTRION, Inc., 2; **J. Y. Choe**, CELLTRION, Inc., 2; **L. Myasoutova**, CELLTRION, Inc., 2; **T. Kwon**, CELLTRION, Inc., 3; **S. J. Lee**, CELLTRION, Inc., 3; **S. C. Shim**, CELLTRION, Inc., 5; **C. H. Suh**, CELLTRION, Inc., 5.

1509

A Randomized, Double-Blind, Three-Arm, Parallel Group, Single-Dose Study to Compare the Pharmacokinetics, Safety, and Tolerability of Three Formulations of Infliximab (CT-P13, EU-sourced Infliximab and US-sourced Infliximab) in Healthy Volunteers. Dae-Hyun Yoo[1], Won Park[2], Seung-Cheol Shim[3], Chang-Hee Suh[4], Jihye Yun[5] and Tina Pyo[5]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Inha University Hospital, Incheon, South Korea, [3]Chungnam National University Hospital, Daejeon, South Korea, [4]Ajou University Hospital, Suwon, South Korea, [5]CELLTRION, Inc, Incheon, South Korea.

Background/Purpose: CT-P13 has been approved as the first biosimilar to innovator infliximab sourced from European Union (EU-INX) in Sep 2013. Even if it has been concluded as equivalent or comparable to EU-INX through pivotal studies and switching studies, it was questioned about the comparability between reference products with different origins[1,2,3,4].

This study was designed to demonstrate comparability among CT-P13, EU-INX and US-sourced infliximab (US-INX) in healthy volunteers and to examine whether three-biologic infliximab from the different manufacturing sources are comparable to each other primarily in pharmacokinetics (PK).

Methods: In this double blind, randomized, parallel group, single-dose study, a total of 213 healthy volunteers were randomized 1:1:1 to receive a single dose (5 mg/kg) of CT-P13, EU-INX or US-INX by intravenous infusion on Day 1 followed for 8 weeks. The primary endpoints were maximum serum concentration (C_{max}), area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_{last}) and area under the concentration-time curve from time zero to infinity (AUC_{inf}) of CT-P13, EU-INX and US-INX. A total of 11 serum blood samples were obtained for the primary PK analysis, and safety and tolerability were also evaluated up to 8 weeks. Similarity of systemic exposure (C_{max}, AUC_{last} and AUC_{inf}) was considered to be demonstrated if the 90% confidence interval (CI) for the ratio of geometric means was within the acceptance interval of 0.8 to 1.25 for the following comparisons: CT-P13 vs EU-INX, CT-P13 vs US-INX, and EU-INX vs US-INX.

Results: The baseline demographics for 213 subjects among 3 study groups were highly similar. The PK parameters in the study groups were highly similar (Table 1). The 90% CI for the ratios of C_{max}, AUC_{last} and AUC_{inf} were within the acceptance interval of 0.8 to 1.25 for the comparisons of CT-P13 to EU-INX, CT-P13 to US-INX and EU-INX to US-INX.

Adverse events (AEs) were similar between 3 study groups with AEs related to the study drug reported by 39.4%, 23.9%, and 42.3% of subjects in CT-P13, EU-INX and US-INX groups, respectively. The majority of AEs related to the study drug reported in the study groups was Grade 1, and there was only 1 AE reported as Grade 3 in US-INX group based on Common Terminology Criteria for Adverse Events. No serious AE related to the study drug was reported, and no AEs led to the withdrawal of a subject from the study. All AEs related to study drug were resolved by the end of the study.

Table 1. Pharmacokinetic Exposure Estimates (Mean ± SD)

Parameters (units)	CT-P13 (N=71)	EU-INX (N=71)	US-INX (N=71)
C_{max} (ug/mL)	127.6 ± 21.6	121.3 ± 19.7	119.9 ± 19.5
AUC_{last} (h*ug/mL)	31343.2 ± 7107.3	30669.0 ± 6020.5	31629.6 ± 5886.8
AUC_{inf} (h*ug/mL)	33212.3 ± 8326.1	32986.6 ± 7806.8	34363.6 ± 8004.2

Conclusion: Equivalence of PK in terms of C_{max}, AUC_{last} and AUC_{inf} was demonstrated and comparable safety profiles were observed in the comparisons of CT-P13 to EU-INX, CT-P13 to US-INX and EU-INX to US-INX in healthy volunteers.

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1510

Blockade of TLR5 Ligation Is a Novel Strategy for RA Therapy. Seung-jae Kim[1], Zhenlong Chen[1], Abdul Essani[1], Michael Volin[2], Suncica Volkov[1], William Swedler[1], Shiva Arami[1], Nadera J. Sweiss[1] and Shiva Shahrara[1]. [1]University of Illinois at Chicago, Chicago, IL, [2]Midwestern University, Downers Grove, IL.

Background/Purpose: TLR5 expression is highly elevated in RA and CIA lining and sublining macrophages and endothelial cells compared to non-arthritic controls. Additionally, expression of TLR5 in RA myeloid cells closely correlates with disease activity score, indicating that ligation of TLR5+ cells intensifies disease progression. Hence studies were conducted to determine whether dysregulation of TLR5 function can be utilized as a promising strategy for RA treatment.

Methods: CIA mice were treated with IgG or anti-TLR5 antibody on days 23, 27, 30, 34, 37, 41, 44 and 48 and mice were sacrificed on day 49 post induction. CIA joint inflammation and bone erosion were assessed by measuring ankle circumference as well as H&E and TRAP staining. Joint myeloid cell recruitment and their phenotype were evaluated by F480 and iNOS immunostaining. Proinflammatory factors secreted from CIA joint were quantified by ELISA in the IgG and anti-TLR5 antibody treated mice. Remodeling of mouse bone marrow progenitor cells into M1 macrophages was examined following flagellin treatment by real-time RT-PCR and FACS analysis.

Results: To uncover whether disruption of TLR5 ligation is a potential for RA therapy, CIA mice were treated with monoclonal anti-TLR5 antibody or IgG control. Results from these experiments demonstrate that CIA mice treated with anti-TLR5 antibody have markedly lower joint swelling starting on day 44 until day 48 post onset compared to the IgG group. Consistently, histological studies document that anti-TLR5 treatment was capable of reducing CIA synovial inflammation, joint lining thickness and bone erosion by 40% compared to the control mice. We next found that anti-TLR5 treatment impairs migration of circulating myeloid cells into the CIA joint. To better understand the mechanism by which blockade of TLR5 function relieves arthritis, joint myeloid cell phenotype was evaluated in CIA synovial tissues. Histological examination demonstrates that the frequency of iNOS+ M1 macrophages is 40% higher in the IgG treated CIA mice compared to anti-TLR5 group. Corroborating with this notion, M1 macrophage producing factors, IL-6 and CCL2, are significantly suppressed in the CIA joints following anti-TLR5 treatment compared to the control group. Confirming the findings *in vivo*, we established that flagellin ligation to TLR5 can transform naïve mouse myeloid cells into M1 macrophages. This differentiation process was assessed by transcription of TNF and IL-6 and frequency of CD80 staining which was dysregulated by blockade of TLR5. Moreover, we show that TRAP+ bone eroding osteoclasts are 30% higher in the control group compared to CIA joints treated with anti-TLR5. These findings are in agreement with our recent data, revealing that ligation of TLR5 plays a key role in osteoclast formation through a mechanism that is predominantly contingent on myeloid cells and their production of RANK and TNF-a.

Conclusion: We conclude that TLR5 ligation promotes joint myeloid cell infiltration and can further remodel the newly recruited myeloid cells into M1 macrophages or fully mature osteoclasts suggesting that blockade of TLR5 can be employed as a promising new therapeutic target in RA.

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1511

COVA322: A Clinical Stage Bispecific TNF/IL-17A Inhibitor for the Treatment of Inflammatory Diseases. Wibke Lembke, Bernd Schlereth, Julian Bertschinger, Dragan Grabulovski and Mathias Locrher. Covagen AG, Schlieren, Switzerland.

Background/Purpose: Biologic therapeutics such as TNF inhibitors have revolutionized the treatment of inflammatory diseases, including rheumatoid arthritis (RA), psoriasis and psoriatic arthritis. However, there is still a significant

unmet medical need in these indications. In RA for example, only about half of all patients achieve an ACR50 score and many become refractory to anti-TNF treatment after a few years. Several studies in preclinical mouse models of arthritis have demonstrated that simultaneous treatment with antibodies to TNF and IL-17 is significantly more efficacious than treatment with either antibody alone. We present here the non-clinical safety package of COVA322, a bispecific TNF/IL-17A inhibitor that is currently being tested in a Phase Ib/IIa study in psoriasis patients.

Methods: COVA322 was analyzed for its cross-reactivity in a GLP study with human and Cynomolgus tissues. In addition, a cytokine release study using human whole blood cells was performed. In Cynomolgus monkeys, COVA322 was tested in a single dose PK/dose range finding study and a GLP 4-week repeat-dose toxicity study at 5, 25 and 100mg/kg doses.

Results: COVA322 showed no unexpected tissue cross-reactivity and no indication for the potential to cause a cytokine release syndrome. COVA322 was well tolerated in single- and repeat-dose toxicity studies in Cynomolgus monkeys. In particular, no adverse effects on the cardiovascular-, respiratory- and central nervous system were observed. The toxicology package (no observed adverse effect level (NOAEL) = 100mg/kg) support the clinical starting dose as well as the anticipated clinical dose range.

Conclusion: COVA322 is a unique bispecific TNF/IL-17A inhibitor, which was well tolerated in non-clinical safety studies. The non-clinical data package supports the planned dose range for the currently ongoing first in man, single dose escalation, tolerability, safety, PK and efficacy Phase Ib/IIa study in psoriasis.

Disclosure: W. Lembke, Covagen AG, 3, Covagen AG, 1; **B. Schlereth**, Covagen AG, 3, Covagen AG, 1; **J. Bertschinger**, Covagen AG, 4, Covagen AG, 1, Covagen AG, 3; **D. Grabulovski**, Covagen AG, 1, Covagen AG, 3, Covagen AG, 4; **M. Locher**, Covagen AG, 1, Covagen AG, 3.

1512

Therapeutic Efficacy of a Novel Oral Small Molecule Macrophage Migration Inhibitory Factor [MIF] Inhibitor: A Promising Safe & Efficacious Treatment for Rheumatoid Arthritis. Anderson Gaweco[1], Samantha Palmer[1], Rambon Shamilov[1], Caroline Stremnitzer[1], Michael Fisher[1], Gregg Crichlow[1], William Windsor[1], Ellen M. Ginzler[2] and Jefferson Tilley[1]. [1]Innovimmune Biotherapeutics, Brooklyn, NY, [2]SUNY-Downstate Medical Center, Brooklyn, NY.

Background/Purpose: Macrophage migration inhibitory factor [MIF] is a cytokine secreted by activated T cells and macrophages that plays an important role in RA and autoimmune disease pathogenesis. MIF exerts its proinflammatory effects through its direct biological function and downstream signaling events following receptor engagement. The therapeutic utility in targeting MIF has been established, demonstrating preclinical efficacy in several RA and autoimmune disease models. Lead development efforts of several proprietary novel chemical scaffolds of the INV-88 portfolio of small molecule MIF inhibitors led to the identification of an INV-88 clinical compound candidate demonstrating potent *in vitro* pharmacological effects against proinflammatory effector cells and cytokines coupled with optimal druggable properties. To establish the preclinical Proof of Concept in RA prior to advancing to IND-enabling development, the *in vivo*treatment efficacy of INV-88 was assessed in the mouse CIA model.

Methods: Disease was induced in DBA1 mice according to a standard protocol. Prior mouse *in vivo*pharmacokinetic [PK] studies determined the optimal oral bioavailability and drug exposure of INV-88 enabling p.o. dosing in this study. To assess the preclinical efficacy in a mouse CIA model, INV-88 was administered orally for 7 days as a therapeutic treatment regimen following chicken collagen CII/CFA disease induction on day 0 and CII/IFA booster immunization on day 15 in DBA1 mice. Upon disease-onset, mice with a clinical arthritis score > 1 (Scale: 0–16) were randomized to receive 7-day dosing with INV-88 at 60 mg/kg (n=12) or comparator controls: Vehicle (n=11) or Dexamethasone [Dex] (n=9).

Results: Successful disease amelioration following INV-88 and Dex treatments was observed with statistically significant reduction of cumulative arthritis score of 3.72 +/− 0.36 [mean +/− SEM] ($p<0.05$) and 1.51 +/− 0.58 ($p<0.001$), respectively, in contrast to the vehicle group of 5.92 +/− 0.68. Significant rapid improvement in clinical disease scores in the INV-88 treated group was evident as early as arthritis day 2 ($p=0.041$) through end of study on arthritis day 7 ($p=0.036$). INV-88 was well tolerated and INV-88-treated mice were unremarkable with optimal body conditions.

Conclusion: The superior safety and therapeutic efficacy data following 7-day treatment of an orally bioavailable small molecule INV-88 MIF inhibitor provide the first compelling evidence ever reported of the preclinical utility of MIF inhibition and of a small molecule-based cytokine inhibitor. These profound findings support advancing INV-88 into further IND-enabling development and highlight the potential promise of INV-88 as a safe & efficacious novel RA DMARD treatment.

Disclosure: A. Gaweco, Innovimmune Biotherapeutics Holding, LLC, 3; **S. Palmer**, Innovimmune Biotherapeutics Holding, LLC, 3; **R. Shamilov**, Innovimmune Biotherapeutics Holding, LLC, 3; **C. Stremnitzer**, Innovimmune Biotherapeutics Holding, LLC, 3; **M. Fisher**, Innovimmune Biotherapeutics Holding, LLC, 3; **G. Crichlow**, Innovimmune Biotherapeutics Holding, LLC, 5; **W. Windsor**, Innovimmune Biotherapeutics Holding, LLC, 3; **E. M. Ginzler**, Innovimmune Biotherapeutics Holding, LLC, 5; **J. Tilley**, Innovimmune Biotherapeutics Holding, LLC, 3.

1513

Selection of Vagus Nerve Stimulation Parameters for a First-in-Human Study in Rheumatoid Arthritis: A Unique Translational Medicine Challenge. Frieda A. Koopman[1], Yaakov Levine[2], Mike Faltys[2], Ralph Zitnik[2] and Paul P. Tak[3]. [1]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [2]SetPoint Medical Corporation, Valencia, CA, [3]GlaxoSmithKline U.K. and Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: Cholinergic anti-inflammatory pathway (CAP) activation by electrical vagus nerve stimulation (VNS) is being studied in rheumatoid arthritis (RA) trials (NCT01552941). CAP signaling proceeds sequentially through vagus and splenic nerves to splenic acetylcholine-secreting T cells, which in turn signal adjacent macrophages to diminish cytokine secretion after proinflammatory stilmuli(1). VNS devices depolarize nerves by application of charge, modulated by varying output current (OC), pulse width (PW), and pulse frequency (F). Stimulation duration (D), and daily stimulation interval (SI) can also be varied. Optimally activating this complex neural-immune pathway created unique translational medicine challenges. Herein we report preclinical data guiding stimulation parameter selection for RA trials.

Methods: VNS stimulation parameter effect on cytokine production and tissue inflammation was studied in 5 models: 1) TNF production in rat systemic endotoxemia with VNS delivered by cervical vagus hook electrodes (HE); 2) morphometric measurement of ulceration in rat indomethacin-induced inflammatory enteritis using cervical vagus cuff electrodes (CE); 3) reduction in *in vitro* LPS-induced whole blood TNF release using VNS delivered chronically by implanted CE in normal canines; 4) improvement in endoscopic ulceration score after dextran sulfate sodium (DSS) colitis in rats using implanted CE; and 5) improvement in ankle swelling, joint histology and systemic cytokines in rat CIA using implanted CE.

Results: Selection of PW (200–250usec) and F (10Hz) was guided by prior clinical tolerability experience with VNS in epilepsy(2). OC titration experiments in rat endotoxemia/HE showed optimal CAP activation at 0.5–1.0mA, and was confirmed in canine CE. The implanted CE used in rodent experiments surrounded the entire carotid sheath rather than only the vagus, so correlation experiments in rat endotoxemia with CE vs. HE verified 3.0 mA as optimal OC for chronic rodent models using this peri-carotid CE. D variation experiments in rat endotoxemia/HE confirmed prior findings(3) that 60 seconds sufficiently activated the CAP. SI experiments in indomethacin enteritis also confirmed prior findings(3) that a 60 second stimulus caused anti-inflammatory effects persisting for at least 24 hours. Efficacy in rodent subacute DSS colitis and CIA using peri-carotid CE was achieved using 3.0mA OC, 10Hz F, 200usec PW, 60 second D, and once daily SI. For RA trials using peri-vagus CE these same parameters were selected with exception of targeted OC of >1.0mA and 250usec PW.

Conclusion: Preclinical pharmacokinetic-pharmacodynamic-efficacy relationships are typically used to understand dose-response and guide dose selection for drug trials. CAP activation involves complex interactions between neuronal cell depolarization and immune effector cell function, complicating study of analogous stimulation parameter-response relationships. These experiments show that despite these hurdles, rational optimization of therapy delivery with "bioelectronic medicines" can be achieved. 1. Science 2011; 334:98 2. Neurology 2002; 59:S31 3. Crit Care Med 2007; 35:2762

Disclosure: F. A. Koopman, None; **Y. Levine**, SetPoint Medical, 3, SetPoint Medical, 1; **M. Faltys**, SetPoint Medical, 1, SetPoint Medical, 3; **R. Zitnik**, SetPoint Medical, 3, SetPoint Medical, 1; **P. P. Tak**, SetPoint Medical, 2.

1514

An Analysis of in-Vitro Cytokine Inhibition Profiles of Tofacitinib and Other Janus Kinase Inhibitors at Clinically-Meaningful Concentrations.
M.E. Dowty, T.S. Lin, L. Wang, J. Jussif, B. Juba, L. Li, E. Moy and J.-B. Tellriez. Pfizer Worldwide R&D, Cambridge, MA.

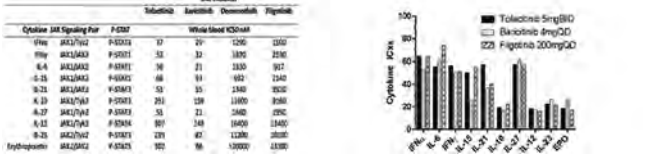
Background/Purpose: A number of Janus kinase (JAK) inhibitors are being actively investigated for treatment of rheumatoid arthritis (RA), including tofacitinib, baricitinib, filgotinib (GLPG0634), and decernotinib (VX-509). However, it is unclear how these drugs may differentiate from each other in the clinic based on their profiles of JAK-dependent cytokine inhibition. The aim of this work was to provide an integrated modelling approach using knowledge of both in-vitro whole cell JAK inhibition potencies and plasma pharmacokinetics to better understand profiles of cytokine inhibition for clinical JAK inhibitors in the context of clinically-meaningful doses.

Methods: IC50 values for IFNα, IFNγ, IL-6, IL-15, IL-21, IL-10, IL-27, IL-12, IL-23 and erythropoietin (EPO) signaling of tofacitinib, baricitinib, filgotinib, and decernotinib were measured in total lymphocytes, CD34+ cells (EPO) and CD3+ cells (IL-6) in human whole blood by a flow cytometry-based assay, quantifying the phosphorylation state of various STAT proteins. Human daily average plasma concentrations (C_{av}) were used as reported or predicted for tofacitinib (5 mg BID; 68 nM), baricitinib (4 mg QD; 32 nM), and filgotinib (200 mg QD; 527 nM). Confidence in the prediction of decernotinib pharmacokinetics was considered low because of high in-vitro metabolic instability and was not assessed further. Percent levels of cytokine inhibition ($IC_{xx}=100*C_{av}/(IC_{50}+C_{av})$) were determined at clinically-meaningful doses.

Results: Each JAK inhibitor showed a relatively similar profile of cytokine inhibition versus type I and II interferons (IFNα, IFNγ), the common γ-chain cytokines (IL-15, IL-21), and IL-6 and IL-27 (Figure 1). Each also showed some decrease in potency for IL-10, IL-12 and 23, and EPO. Comparing between JAK inhibitors, tofacitinib and baricitinib were overall more potent inhibitors than decernotinib and filgotinib. Clinical pharmacokinetics of tofacitinib, baricitinib, and filgotinib were available and used to further compare predicted cytokine profiles of inhibition in patients with RA. The profile of cytokine inhibition for each JAK inhibitor was in general similar at clinically-meaningful doses (Figure 1). While the pharmacokinetics were unavailable for decernotinib, the clinical dose ranges being explored are consistent with filgotinib which showed similar in-vitro inhibitory potencies.

Conclusion: These analyses illustrate the importance of studying a broad range of JAK pairing potencies and clinical concentrations when comparing JAK-inhibitor compounds. Calculated profiles of cytokine inhibition for a number of JAK inhibitors in RA are in general similar when efficacious doses are considered, suggesting limited differentiation of these JAK inhibitors based on JAK pharmacology. Ultimately, only robust clinical testing will determine whether there are clinical differences between JAK inhibitors.

Figure 1. In vitro whole blood JAK inhibitory potencies (left) and overall cytokine inhibition in the context of clinical concentrations (right) for various JAK inhibitors



Disclosure: M. E. Dowty, Pfizer Inc, 1, Pfizer Inc, 3; **T. S. Lin**, Pfizer Inc, 1, Pfizer Inc, 3; **L. Wang**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Jussif**, Pfizer Inc, 1, Pfizer Inc, 3; **B. Juba**, Pfizer Inc, 1, Pfizer Inc, 3; **L. Li**, Pfizer Inc, 1, Pfizer Inc, 3; **E. Moy**, Pfizer Inc, 1, Pfizer Inc, 3; **J. B. Telliez**, Pfizer Inc, 1, Pfizer Inc, 3.

1515

The Impact on Anti-Citrullinated Protein Antibody Isotypes and Epitope Fine Specificity in Patients with Early RA Treated with Abatacept and Methotrexate.
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Background/Purpose: Anti-citrullinated protein antibodies (ACPA) are a marker of RA and may contribute to disease progression.[1,2] ACPA analysis in patients offers the opportunity to estimate whether specific intervention during early disease may have an impact on the maturation of the ACPA response and a subsequent altering effect on the course of the disease process. Here we assessed the impact on ACPA isotypes and the number of specific epitopes recognized in patients with early RA from the AVERT study who were treated with abatacept (ABA) + methotrexate (MTX), ABA monotherapy or MTX alone.

Methods: Patients enrolled in AVERT had symptomatic synovitis in ≥2 joints for ≥8 weeks with an onset of symptoms ≤2 years, were anti-cyclic citrullinated peptide 2 positive and naïve to both MTX and biologic treatment.[3] ACPA isotype and the epitope analysis of 6 specificities were performed using custom ELISA assays and were measured in patient serum at baseline, and at Days 85 and 365.[1,2] Adjusted mean change from baseline was calculated using a longitudinal repeated measures model.

Results: Baseline means for the IgG isotype were 585.0 (ABA + MTX), 515.2 (ABA) and 575.5 (MTX) U/mL. IgM baseline means were 23,613 (ABA + MTX), 24,221 (ABA) and 28,377 (MTX) U/mL. Baseline means for the IgA isotype were 10,127 (ABA + MTX), 11,098 (ABA) and 12,335 (MTX) U/mL. Adjusted mean (+95% CI) unit changes in ACPA isotype from baseline to Days 85 and 365 are shown (Table). Of the 6 epitopes tested, the average baseline net numbers recognized were 2.6 (ABA + MTX), 2.69 (ABA) and 2.88 (MTX). Consistent with reductions in the ACPA isotypes, from baseline to Day 365, treatment with ABA + MTX reduced the average (+95% CI) net number of epitopes recognized by –0.82 (–1.03, –0.61) compared with –0.32 (–0.54, –0.10) for ABA alone or –0.42 (–0.64, –0.20) for MTX alone.

Table: Adjusted mean change from baseline (+95% CI) for ACPA isotypes (U/mL)

	Day 85			Day 365		
	IgG	IgM	IgA	IgG	IgM	IgA
ABA	−47.26 (−88.85, −5.66)	−3270 (−4898, −1642)	636.1 (−930.4, 2202)	−13.81 (−67.79, 40.17)	−356 (−3096, 2382)	3186 (843.2, 5529)
MTX	−22.94 (−63.66, 17.78)	−4604 (−6204, −3004)	−1794 (−3331, −256.6)	−30.07 (−84.51, 24.38)	−4591 (−7345, −1838)	−1914 (−4269, 440.1)
ABA + MTX	−70.58 (−110.9, −30.27)	−6392 (−7975, −4809)	−2434 (−3957, −910.8)	−135.6 (−178.4, −83.82)	−6363 (−8991, −3735)	−2230 (−4479, 19.30)

Conclusion: Baseline levels of each ACPA isotype and net number of epitopes recognized were comparable across the 3 treatment arms. Concentrations of all ACPA isotypes (IgM, IgA, IgG) were substantially reduced by abatacept + MTX therapy to a greater extent than by either MTX or abatacept alone. Abatacept + MTX also reduced the average number of epitopes recognized over 1 year of treatment more than either monotherapy arms. These results indicate that abatacept impacts the maturation of the ACPA response in patients with early RA, suggesting an alteration in the course of the autoimmune disease process. 1. Verpoort KN, et al. *Arthritis Rheum* 2006;**54:**3799–808. 2. van der Woude D, et al. *Ann Rheum Dis* 2010;**69:**1554–61. 3. Emery P, et al. *Ann Rheum Dis* 2014:**73**(Suppl 2):69.

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1516

TNF-Alpha Inhibitors Normalizes Melanocortin Receptor Subtype 2, 3 and 4 Expression in CD8+, CD14+ and CD19+ Leukocyte Subsets in Rheumatoid Arthritis.
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Background/Purpose: We examined Adalimumab′s effects on melanocortin receptor subtype (MC)1–5 gene expression in important leukocyte subsets in rheumatoid arthritis (RA). The melanocortin system is a neuroimmunomodulatory system with anti-inflammatory and tolerance inducing properties. It consists of MC1–5 and their ligands, the melanocortins: α-, β-, γ- melanocyte stimulating hormones (MSH) and ACTH. Especially CD4+T helper (Th) lymphocytes and $CD14^+$ monocytes express the genes of MC1, 2, 3 and 5. Binding of a melanocortin to its MC inhibits the nuclear translocation of transcription factor NFκB and thereby the synthesis of inflammatory mediators, such as TNFα, adhesionmolecules and NO. While the synthesis of the melanocortins is stimulated by TNFα, the MCs are upregulated by the melanocortins. Thus the melanocortin system is upregulated in inflammation. Adalimumab reduces circulating TNFα, and is therefore supposed to down-regulate melanocortin synthesis and MC expression.

Methods: Blood was drawn at pre-start and at 4 months of Adalimumab 40 mg every other week. Leukocyte subsets were isolated by magnetic beads coated with CD4, CD8, CD14 and CD19 mAB. RNA was extracted and RT-qPCR performed with primers and probes specific to MC1–5, TNFα, TGFβ and IL-10.

Results: 6 females and 1 male with RA according to ACR criteria were examined. Median age 48.0 ±7.2 yrs (SD), disease duration 21 ±71 months. 4 were treated with methotrexate 25 mg/w and 3 with leflunomid 20 mg/d. 3 patients took prednisolon, mean dose 6.67 mg/d. At start and 4 months′ therapy, CRP was 3.0 ±22.1 and 2.9 ±0.6mg/L (median ±SD), respectively, hemoglobin 8.4 ±1.5 and 8.6 ±0.4 mmol/L, DAS28 4.9 ±1.5 and 2.0 ±0.6. At 4 months none took prednisolon. Adalimumab significantly reduced MC2, 3 and 4 mRNA in $CD8^+$, $CD14^+$ and $CD19^+$ leukocyte subsets. In $CD4^+$ Th lymphocytes there was no uniform reaction. IL-10 was lowered in CD4+, and tended as TNFα to be so in CD14+ cells, TGFβ unchanged.

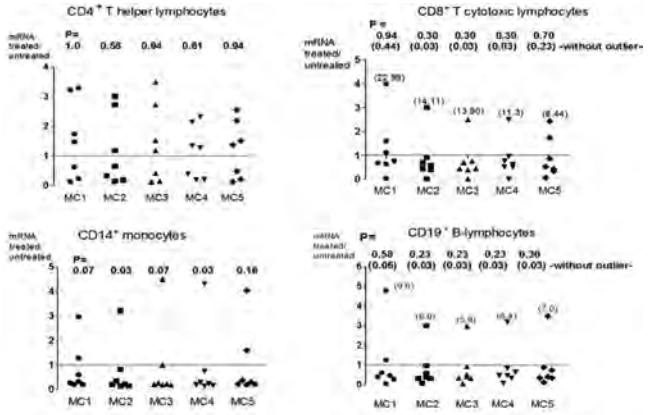

Figure. Quotes between MC1-5 mRNA measured by real-time RT-qPCR adjusted for housekeeping gene 18sRNA and with stimulated peripheral blood monocytes (PBMC) as reference in subtypes of leukocytes from 7 patients with rheumatoid arthritis, before and 4 months after start of adalimumab (Humira®) treatment. *Statistic*: Wilcoxon´s test for paired samples.

Conclusion: Here we show that Adalimumab down-regulates the MC2, 3 and 4 gene expression in the CD14+ monocytes in RA. Thus we have uncovered a new peripheral melanocortin signalling pathway through MC4 in monocytes. Monocytes are known to have an anti-inflammatory autocrin circuit based on the melanocortins, previously thought to operate solely through MC3 as shown in experimental gouty arthritis. Interestingly, our results show, that the MC1–5 gene expression of the $CD4^+$Th lymphocyte does not react uniformly to Adalimumab therapy. The $CD4^+$Th cell has a superior role in the immune reaction, as the central conductor of other cell types. Therefore, it is not surprising, that the powerful melanocortin system in just this very important cell type, seems to be controlled via several redundant mechanisms, interacting to exert fine tuning of the immune reaction.

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1517

Analysis of Gene Expression Fluctuation with Abatacept Highlights the Involvement of the Proteasome Pathway As a Mechanism of Action of Abatacept in Rheumatoid Arthritis. C Derambure[1], O Vittecoq[2], G Dzangue Tchoupou[1], Maria-Antonietta d'Agostino[3], P Gaudin[4], C Gaillez[5], M Le Bars[6] and T Lequerré[2]. [1]Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France, [2]Rouen University Hospital, Rouen, France, [3]AP-HP Ambroise Paré Hospital, Boulogne-Billancourt, France, [4]University Hospital Grenoble, Grenoble, France, [5]Formerly of Bristol-Myers Squibb, Rueil-Malmaison, France, [6]Bristol-Myers Squibb, Rueil-Malmaison, France.

Background/Purpose: Abatacept (ABA) is a biologic therapy targeting T cells, which play a major role in the pathophysiology of RA. Overall, 57.1% of patients reached LDA (DAS28 [CRP] ≤3.2) after 6 months of treatment with ABA and MTX in the open-label ABA Power Doppler Ultrasonography APPRAISE study, in patients with RA and inadequate MTX response.[1] The objective of this substudy was to explore gene expression fluctuations and to identify the main molecular mechanism modifications that occur in a subset of ABA-treated patients according to their treatment response.

Methods: In this substudy, 19 patients with active RA and inadequate MTX response were treated with approved doses of ABA and MTX. For this analysis, patients were categorized as ABA responders (R; DAS28 ≤3.2 [LDA]) (n=14) or non-responders (NR; DAS28 >3.2) (n=5) following 6 months of treatment. Whole blood was collected in Paxgene tubes for each patient at baseline and 6 months. RNAs were hybridized to a whole human genome 4 × 44K microarray Agilent slide to identify mRNA specifically dysregulated between baseline and 6 months in R and NR patients using GeneSpring GX software and a *t*-test with false discovery rate correction for multiple testing ($p<0.05$). Gene ontology (GO), pathways analysis (curated WikiPathways) and text mining via Natural Language processing were performed to identify the molecular mechanisms regulated by ABA in R and NR. Correlations between gene expression fluctuation and changes in DAS28 were assessed to identify the impact of ABA treatment on disease activity.

Results: After 6 months of treatment with ABA, no genes were significantly differentially expressed in NR patients, whereas 935 genes were significantly differentially expressed in R patients ($p<0.05$). Of these genes, 298 were down-regulated at 6 months and 637 were up-regulated compared with baseline. GO allowed us to identify GO terms enriched only in the list of the 637 up-regulated genes. All of these GO terms were relative to the mRNA process ($p<0.05$). Pathways analysis allowed us to identify 15 curated pathways significantly enriched in the 935 mRNAs dysregulated in R patients ($p<0.05$). The most significant pathways found to be in agreement with the GO analysis were Hs_mRNA_processing_WP411_45374 (p=0.002) and Hs_Proteasome_Degradation_WP183_45274 (p=0.001). Among the 935 genes identified, 7 up-regulated genes were significantly involved in the proteasome degradation pathway, including 65 proteins in humans. Six gene expression fluctuations (among 935) between baseline and 6 months were correlated with variation of DAS28: 3 positive and 3 negative correlations ($p<0.01$).

Conclusion: Comparison of gene expression fluctuations between R and NR to abatacept treatment highlighted 935 genes differentially expressed only in R in our cohort. As the proteasome is required for essential immune functions of activated CD4(+) T cells, and can be defined as a molecular target for suppression of deregulated and unwanted T-cell-mediated immune responses, this study suggests a new mechanism of action for abatacept in patients with LDA. Small sample size may be a limitation. 1. D'Agostino MA, et al. *Arthritis Rheum* 2012;**64**(Suppl):S352.

Disclosure: C. Derambure, None; **O. Vittecoq**, None; **G. Dzangue Tchoupou**, None; **M. A. d'Agostino**, Bristol-Myers Squibb, AbbVie, 8; **P. Gaudin**, None; **C. Gaillez**, Bristol-Myers Squibb, Novartis, 1, Novartis Pharma AG, 3; **M. Le Bars**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1; **T. Lequerré**, Bristol-Myers Squibb, 2.

1518

Disentangling the Effects of Tocilizumab on Neutrophil Survival and Function. Timo Gaber[1], Martin Hahne[2], Cindy Strehl[3], Paula Hoff[4], Yvonne Doerffel[4], Eugen Feist[4], Gerd Burmester[4] and Frank Buttgereit[4]. [1]Berlin-Brandenburg Center of Regenerative Therapies (BCRT), Berlin, Germany, [2]Berlin-Brandenburg School of Regenerative Therapies (BSRT), Berlin, Germany, [3]German Rheumatism Research Center (DRFZ), Berlin, Germany, [4]Charité University Medicine, Berlin, Germany.

Background/Purpose: The synovial tissue in rheumatoid arthritis (RA) represents a hypoxic environment with up-regulated pro-inflammatory cytokines and cellular infiltrates including neutrophils. Tocilizumab, a humanized IgG1 monoclonal antibody directed against the interleukin (IL) 6 receptor, is a potent biologic treatment for RA but the inhibition of the IL6 pathway may also cause unwanted effects such as a decrease in blood neutrophil counts and occasionally high grade neutropenia.

In order to understand both therapeutic and adverse effects of IL6 receptor inhibition, we analysed the effects of tocilizumab on survival, phagocytotic capacity and energy metabolism of neutrophils under normoxic versus hypoxic conditions.

Methods: Human neutrophils were purified, pre-treated with varying doses of tocilizumab and, for comparison, dexamethasone or vehicle and finally stimulated with lipopolysaccharide (LPS) or left unstimulated. Cells

were then incubated under normoxic (18% O_2) or hypoxic (1% O_2) conditions and subsequently analysed.

Results: Both neutrophil survival and energy availability were significantly decreased by tocilizumab in a dose-dependent manner in LPS stimulated cells, but to a greater extent under normoxia as compared to hypoxia. We also found LPS stimulated phagocytotic activity of neutrophils to be significantly higher under hypoxic versus normoxic conditions, but this difference was significantly reduced by tocilizumab.

Conclusion: Tocilizumab is known for both beneficial effects and a higher incidence of neutropenia (>1/100 bis 1/10) when treating RA patients. Our results suggest that both effects can at least in part be explained by a reduction in neutrophil survival and a dose-dependent inhibition of a hypoxia-induced phagocytic activity of infiltrating hypoxic neutrophils, mimicking conditions of the inflamed joint environment.

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1519

Implementation of an Acid Dissociation Procedure for Immunogenicity Detection in Patients Treated with ANTI-TNF Drugs. Francisca Llinares-Tello[1], Jose Rosas[2], José M. Senabre-Gallego[1], Gregorio Santos-Soler[1], Carlos Santos-Ramirez[3], Esteban Salas-Heredia[1], Xavier Barber[4], Juan Molina[1], Catalina Cano[1], Ana Pons[1] and Group Aire-MB[1]. [1]Hospital Marina Baixa, Villajoyosa, Spain, [2]Hospital Marina Baixa. Villajoyosa, Villajoyosa, Spain, [3]Hospital Marina Salud, Denia, Spain, [4]CIO, Elche, Spain.

Background/Purpose: To evaluate the application of an acid dissociation procedure in monitoring patients with subtherapeutic serum concentrations of infliximab (IFX), adalimumab (ADL) and etanercept (ETN), using an immunoassay commercialized (Promonitor®-ETN, Progenika Biopharma, S.A., a Grifols Company).

Methods: For 3 years 612 trough samples were analyzed of 247 patients with different rheumatic pathologies treated with IFX (44 patients, 94 samples), ADL (123 patients, 289 samples) and ETN (80 patients, 229 samples). With the standard technology, ADA was detected in 27, 15 and 0% of the patients treated with IFX, ADL and ETN respectively, coinciding always with a level of undetectable drug.

92 samples quantified with detectable but subtherapeutic drug levels at the standard treatment (31 samples of 25 patients with IFX<2 mg/L, 38 samples of 26 patients with ADL<3 mg/L and 23 samples of 18 patients with ETN<2 mg/L), were analyzed for ADA after submitting them to an acid pre-treatment. The protocol of acidification consisted of the incubation of the serum during 15 minutes with acetic acid 300 mM and later neutralization with Tris 1 M fitting to a final dilution 1/10.

Results: With the protocol of acid dissociation anti-ADL antibodies were detected in 46% of the patients with subtherapeutic levels of ADL, which were undetectable with the standard assay (18 samples, 12 patients, middle age: 55 years, 67% women, diagnoses: 8 ankylosing spondylitis (BASDAI: 4,8±1,5), 3 rheumatoid arthritis and 1 psoriasic arthritis (DAS28: 3,5±0,2). In 7 cases ADA's detection after acidificatión was produced already in the first request of monitoring at 6 months of initiated the treatment. In other 3 cases, ADA's positive after dissociation confirmed a previous positive with the standard assay. Initially the treatment was kept with ADL in 5 patients, which ended up by turning out to be positives with the standard technology between 2 and 6 months after the positive with dissociation. Finally, in all the patients a change of treatment was necessary for lack of clinical response, being chosen by another anti-TNF before ADA's evidence. ADL's maximum concentration in the samples with a positive result was of 1,8 mg/L and the title of detected antibodies ranged between 35 and 282 UA/mL. Anti-IFX not anti-ETN antibodies were not detected after the acidificación of the samples by subtherapeutic concentrations of these two drugs.

Conclusion:

1) The acid pre-treatment of the samples increases the sensibility of the test of detection of anti-drug antibodies breaking possible drug-antibody complexes.
2) The monitoring of immunogenicity in patients with subtherapeutic levels of ADL, following a protocol of acid dissociation, has allowed us to detect in a precocious way ADA's presence in these patients contributing to the optimization of the treatment.

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1520

Gene Expression Analyses of Abatacept- and Adalimumab-Treated Patients from the Ample Trial. S Bandyopadhyay[1], M Maldonado[1], M Schiff[2], ME Weinblatt[3], Roy Fleischmann[4] and SE Connolly[1]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]University of Colorado, Denver, CO, [3]Brigham and Women's Hospital, Boston, MA, [4]University of Texas Southwestern Medical Center, Dallas, TX.

Background/Purpose: The distinct mechanisms of action (MoA) of abatacept (ABA) and adalimumab (ADA) are expected to manifest in different transcriptional profiles in RA patients (pts). This post-hoc analysis assessed peripheral blood gene expression in RA pts from AMPLE treated with ABA or ADA, and the pharmacodynamic (PD) changes between baseline and month (Mth) 3 that correlate with the magnitude of clinical response.

Methods: The AMPLE study has been described elsewhere.[1] Peripheral blood mRNA was isolated from 566 pts at baseline and 3 mths. Whole genome transcriptional profiling used Affymetrix U219 chips, representing 18,567 genes. Differentially expressed genes from baseline to Mth 3 were identified for each treatment (fold-change >/< 0.2, adjusted p-value <0.05) using Bioconductor/LIMMA.[2] PD-response analysis was done by placing pts in non-overlapping groups based on their ACR response at Mth 3. From this, consensus-stabilized k-means clustering was used to reduce the data into the minimal number of PD clusters for ABA- and ADA-treated pts.[3] Genes within these clusters were analyzed by gene-set enrichment analysis (GSEA) to estimate the over-representation of molecular pathways.

Results: Pts treated with ABA had 236 genes significantly up-regulated by Mth 3, while ADA treatment had significant up-regulation of 634 genes (Figure). There was overlap on 221 of the genes up-regulated. Treatment with ABA resulted in the down-regulation of 179 genes, while treatment with ADA resulted in the down-regulation of 513 genes. The therapies overlapped on 172 genes. Across therapies, many genes were significantly regulated in one group but not the other (Figure, black dots). K-means clustering based on ACR response groups at Mth 3 resulted in 6 unique patterns of PD per treatment. GSEA identified 118 pathways enriched across the 6 ABA clusters and 119 pathways enriched in the 6 ADA clusters. Among the pathways showing PD response for both therapies were "NFAT in immune response", "inhibitory PD-1 signaling in T cells" and "T-cell subsets: cell surface markers".

Conclusion: ABA was more selective on modulating gene expression in RA pts, although there was overlap in genes impacted by both therapies. The treatment- and response-dependent clusters might reflect differences related to MoA leading to similar clinical outcomes. Further delineation of the pathways will elucidate how these two agents with unique mechanisms provide comparable efficacy with some differences in safety and tolerability.

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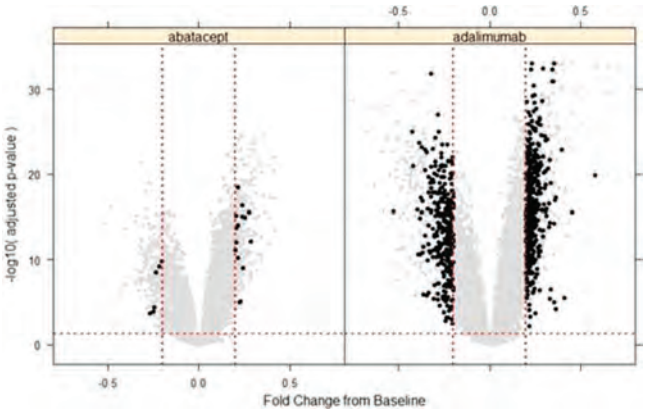

Disclosure: S. Bandyopadhyay, Bristol-Myers Squibb, 3; **M. Maldonado**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1; **M. Schiff**, Bristol-Myers Squibb, Abbvie, 5;

M. Weinblatt, BMS, Crescendo Bioscience, UCB, Abbvie, Roche, Janssen, 5, BMS, Crescendo Bioscience, UCB, 2; **R. Fleischmann**, AbbVie, Amgen, Astellas, Astra Zeneca, BMS, Celgene, Dynavax, Genzyme, Janssen, Eli Lilly, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, UCB, Xoma, 2, AbbVie, Amgen, Astra Zeneca, BMS, Celgene, Janssen, Eli Lilly, Pfizer, Roche, Sanofi-Aventis, UCB, 5; **S. Connolly**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3.

1521

Sustained Improvements in Magnetic Resonance Imaging Outcomes with Abatacept Following the Withdrawal of All Treatment in Patients with Early Rheumatoid Arthritis. C Peterfy[1], Gerd Burmester[2], Vivian P. Bykerk[3], B G Combe[4], J C DiCarlo[1], D E Furst[5], T W J Huizinga[6], C S Karyekar[7], D Wong[7], Philip G. Conaghan[8] and P Emery[9]. [1]Spire Sciences, Inc., Boca Raton, FL, [2]Charité – University Medicine Berlin, Berlin, Germany, [3]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [4]Hôpital Lapeyronie, Montpellier, France, [5]University of California at Los Angeles, Los Angeles, CA, [6]Leiden University Medical Center, Leiden, Netherlands, [7]Bristol-Myers Squibb, Princeton, NJ, [8]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [9]University of Leeds, Leeds, United Kingdom.

Background/Purpose: Biologic treatment can lead to improved clinical outcomes in early RA. In the Assessing Very Early Rheumatoid arthritis Treatment (AVERT) study, abatacept (ABA) + MTX achieved significantly higher rates of DAS-defined remission (DAS28 [CRP] <2.6) vs MTX alone at 12 mths of treatment; a small but significantly higher number of patients (pts) on ABA + MTX vs MTX alone sustained remission following the rapid withdrawal of all RA drugs.[1] To assess the progression of structural joint damage in pts with early RA in AVERT, MRI changes were evaluated after 12 mths on treatment and following the withdrawal of all RA medication in pts in DAS-defined remission or LDA.

Methods: Pts with DAS28 (CRP) ≥3.2, onset of symptoms ≤2 yrs, active synovitis in ≥2 joints, who were MTX-naïve and anti-cyclic citrullinated peptide (CCP2) positive were randomized to SC ABA 125 mg/wk + MTX, SC ABA 125 mg/wk monotherapy or MTX alone for 12 mths. All RA treatment was removed after 12 mths (ABA immediately and MTX and steroids tapered over 1 mth) in pts with DAS28 (CRP) >3.2. Gadolinium-enhanced MRI of the clinically worse hand/wrist was performed at baseline and at Mths 6, 12, 18 and 24. Adjusted mean changes from baseline in synovitis, osteitis and erosion were calculated at Mths 12 and 18 for pts with MRI assessments. In a *post hoc* analysis, adjusted mean changes from baseline in synovitis, osteitis and erosion MRI scores were compared in pts who had DAS28 (CRP) <2.6 at both Mths 12 and 18 (after withdrawal).

Results: Pts in the intent-to-treat population had early RA (mean symptom duration 0.56 yrs) with highly inflammatory disease (mean TJC 23.3, SJC 16.5, CRP 17.5 mg/dL), severe disease activity (mean DAS28 [CRP] 5.44 and HAQ-DI 1.42), poor prognostic factors (95.2% RF and anti-CCP2 double positive) and 31.9% were on steroids at baseline (mean dose 7.0 mg/day). Improvements in synovitis and osteitis were greater, and the progression of erosion was less, in the ABA + MTX arm vs MTX, both on treatment (Mth 12) and following all treatment withdrawal (Mth 18); benefits of ABA monotherapy on synovitis at Mths 12 and 18 and osteitis at Mth 12 were intermediate to those of ABA + MTX and MTX alone (Table 1). In pts with DAS28 (CRP) <2.6 at both Mths 12 and 18, MRI benefits were maintained from Mth 12 to Mth 18 (Table 2).

Table 1. Adjusted mean change from baseline in MRI scores (intent-to-treat population)

Adjusted mean change from baseline (95% CI)		ABA + MTX (n=119)	ABA monotherapy (n=116)	MTX (n=116)
Synovitis	Mth 12	−2.35 (232.89, −1.81)* n=91	−1.36 (231.91, −0.80) n=81	−0.68 (−1.24, −0.13) n=84
	Mth 18	−1.34 (232.18, −0.50) n=38	−1.19 (232.01, −0.31) n=35	−0.49 (231.45, 0.46) n=29
Osteitis	Mth 12	−2.58 (233.47, −1.69)* n=91	−1.37 (−2.27, −0.46) n=81	−0.68 (−1.59, 0.24) n=84
	Mth 18	−2.03 (−3.72, −0.34) n=38	0.45 (−1.31, 2.20) n=35	0.34 (−1.55, 2.24) n=29
Erosion	Mth 12	0.19 (−0.46, 0.84)* n=91	1.42 (0.76, 2.07) n=81	1.53 (0.86, 2.19) n=84
	Mth 18	0.13 (−0.74, 1.01)* n=38	1.85 (0.96, 2.74) n=35	2.00 (1.07, 2.93) n=29

*p<0.05 for treatment difference vs MTX (95% CI for the estimate of treatment difference did not cross 0)

Table 2. Adjusted mean change from baseline in MRI scores; *post hoc* analysis in pts with DAS28 (CRP) <2.6 at both Mths 12 and 18

Adjusted mean change from baseline (95% CI)		ABA + MTX (n=18)	ABA monotherapy (n=14)	MTX (n=9)
Synovitis	Mth 12	−1.95 (−2.82, −1.08) n=18	−2.43 (−3.38, −1.48) n=12	−1.25 (−2.62, 0.13) n=6
	Mth 18	−2.14 (−3.14, −1.15) n=16	−2.45 (−3.49, −1.41) n=13	−1.47 (−2.85, −0.10) n=8
Osteitis	Mth 12	−2.39 (−3.15, −1.63) n=18	−2.06 (−2.86, −1.26) n=12	−1.28 (−2.39, −0.16) n=6
	Mth 18	−2.37 (−3.10, −1.63) n=16	−2.23 (−2.98, −1.49) n=13	−1.46 (−2.48, −0.43) n=8
Erosion	Mth 12	0.18 (−0.79, 1.15) n=18	0.42 (−0.57, 1.42) n=12	1.21 (−0.16, 2.58) n=6
	Mth 18	0.09 (−0.93, 1.12) n=16	0.36 (−0.70, 1.41) n=13	1.25 (−0.18, 2.68) n=8

There were no significant treatment differences vs MTX

Conclusion: Abatacept reduced MRI-detected joint inflammation and joint damage in pts with early RA; these benefits may be maintained for at least 6 mths after treatment withdrawal in pts who are in remission or low disease activity, suggesting an alteration in the autoimmune process.

1. Emery P, et al. *Ann Rheum Dis* 2014;**73**(Suppl 2):69.

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1522

Impact of Sarilumab on Health Related Quality of Life (HRQoL), Fatigue, and Sleep in Rheumatoid Arthritis Patients at Week 24 - Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study. Vibeke Strand[1], George Joseph[2], Hubert van Hoogstraten[2], Chieh-I Chen[3], Chungpeng Fan[2], Paulo Carita[4], Neil Graham[3], Tanya Momtahen[2] and Mark C Genovese[5]. [1]Biopharmaceutical Consultant, Portola Valley, CA, [2]Sanofi, Bridgewater, NJ, [3]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [4]Sanofi, Chilly-Mazarin, France, [5]Stanford University Medical Center, Palo Alto, CA.

Background/Purpose: Sarilumab, a fully human monoclonal antibody directed against the IL-6 receptor, demonstrated efficacy in the phase 3 part of the RA-MOBILITY study (NCT01061736) in adults with active, moderate-to-severe RA with inadequate responses to methotrexate (MTX).[1] Most common TEAEs included infections and injection site reactions. A higher incidence of serious infections was observed with sarilumab. Lab abnormalities included decreases in neutrophils and increases in transaminases and lipids. This analysis focuses on the impact of sarilumab + MTX on HRQoL, fatigue, and sleep, all of which were pre-defined secondary endpoints at Week 24 among patients who had a patient reported outcome (PRO) measured at that time point. Overall work impairment due to RA was assessed at Week 12.

Methods: The intent-to-treat population included 1,197 patients who were randomized 1:1:1 to receive placebo + MTX, sarilumab 150 mg every two weeks (q2w) + MTX or 200 mg q2w + MTX. The Short Form-36 (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Sleep-Visual Analog Scale (Sleep-VAS) and Work Productivity and Activity Impairment (WPAI) questionnaires were assessed at baseline, Weeks 12 (WPAI only), 24 and 52.

Results: Statistically significant improvements versus placebo + MTX in SF-36 T-Scores for Physical Component Summary (PCS) and Mental Component Summary (MCS), all 8 domains of SF-36, FACIT-F and Sleep-VAS were reported by patients receiving sarilumab 150 mg + MTX and 200 mg + MTX at Week 24, which exceeded the minimum clinically important difference (MCID) in all SF-36 summary and domain scores (PCS and MCS: 2.5; 8 domains: 5.0), FACIT-F (3.0) and Sleep-VAS (4.1) scores in both active treatment groups (Table 1, Bolded). Improvements evident at Week 24 were sustained through Week 52. Statistically significant improvements in WPAI "% overall work impairment due to RA" scores were reported for 150 mg + MTX group at Week 12.

Conclusion: In this Phase 3 trial, patients with active RA receiving either dose of sarilumab q2w + MTX reported clinically meaningful change from baseline in all HRQoL and fatigue scores at Week 24, which were maintained through Week 52. Statistically significant benefit was also reported in sleep and "% overall work impairment due to RA" for sarilumab 150 mg q2w + MTX dose.

1. Genovese M et al. Abstr. EULAR14-SCIE-3001, EULAR 2014.

Table 1. HRQoL, Fatigue, WPAI-% overall work impairment due to RA, and Sleep-VAS at Baseline, Week 12 (for WPAI only), and Week 24

PRO	Placebo	Sarilumab 150 mg + MTX	Sarilumab 200 mg + MTX
SF-36 PCS			
Baseline mean	32.15	31.92	31.24
Mean change from baseline	**5.27**	**8.16**	**8.83**
LSM difference, 95% CI		2.860 (1.630, 4.091)	3.201 (1.978, 4.423)
p-value		<0.0001	<0.0001
SF-36 MCS			
Baseline mean	37.82	39.46	38.92
Mean change from baseline	3.98	**5.10**	**7.79**
LSM difference, 95% CI		1.808 (0.285, 3.331)	4.271 (2.761, 5.781)
p-value		0.0200	<0.0001
SF-36 PF			
Baseline mean	29.06	29.36	28.70
Mean change from baseline	4.97	**7.19**	**7.77**
LSM difference, 95% CI		2.357 (0.809, 3.906)	2.650 (1.106, 4.194)
p-value		0.0029	0.0008
SF-36 RP			
Baseline mean	31.93	32.37	32.03
Mean change from baseline	4.99	**7.10**	**7.92**
LSM difference, 95% CI		2.324 (0.952, 3.696)	2.991 (1.628, 4.354)
p-value		0.0009	<0.0001
SF-36 BP			
Baseline mean	33.13	33.20	32.65
Mean change from baseline	**6.59**	**10.75**	**12.02**
LSM difference, 95% CI		4.256 (2.864, 5.649)	5.193 (3.807, 6.580)
p-value		<0.0001	<0.0001
SF-36 GH			
Baseline mean	35.04	35.41	34.13
Mean change from baseline	3.83	**6.11**	**7.73**
LSM difference, 95% CI		2.473 (1.179, 3.767)	3.597 (2.312, 4.881)
p-value		0.0002	<0.0001
SF-36 VT			
Baseline mean	40.67	41.30	40.19
Mean change from baseline	**5.43**	**7.16**	**9.72**
LSM difference, 95% CI		2.073 (0.580, 3.566)	4.127 (2.647, 5.607)
p-value		0.0066	<0.0001
SF-36 SF			
Baseline mean	34.38	35.59	34.76
Mean change from baseline	4.50	**7.11**	**9.12**
LSM difference, 95% CI		3.270 (1.786, 4.754)	4.814 (3.340, 6.288)
p-value		<0.0001	<0.0001
SF-36 RE			
Baseline mean	30.70	31.41	31.49
Mean change from baseline	4.50	**6.21**	**7.70**
LSM difference, 95% CI		1.997 (0.236, 3.759)	3.548 (1.800, 5.297)
p-value		0.0263	<0.0001
SF-36 MH			
Baseline mean	37.07	39.15	37.59
Mean change from baseline	4.29	**5.10**	**7.77**
LSM difference, 95% CI		1.686 (0.147, 3.224)	3.694 (2.172, 5.215)
p-value		0.0318	<0.0001
FACIT-F			
Baseline mean	27.24	22.07	26.16
Mean change from baseline	**6.49**	**9.1**	**10.16**
LSM difference, 95% CI		2.817 (1.552, 4.083)	3.351 (2.092, 4.611)
p-value		<0.0001	<0.0001
WPAI- % overall work impairment due to RA			
Baseline mean	51.55	49.26	54.33
Mean change from baseline	−9.26	−17.84	−18.00
LSM difference, 95% CI		−9.606 (−17.144, −2.068)	−7.228 (−14.854, 0.397)
p-value		0.0127	0.0631
Sleep VAS			
Baseline mean	54.05	53.77	54.23
Mean change from baseline	**−16.89**	**−23.17**	**−23.07**
LSM difference, 95% CI		−6.778 (−10.734, −2.821)	−6.891 (−10.826, −2.955)
p-value		0.0008	0.0006

PCS=Physical Component Summary, LSM=Least Square Means, MCS=Mental Component Summary, PF=Physical Function, RP=Role Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role Emotional, MH=Mental Health & VAS=Visual Analog Scale

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Follow-up Data on the Rheumatoid Arthritis Comparison of Active Therapies Trial: Observational Cohort. Robert Lew[1], Denis Rybin[2], Keri Hannagan[1], Hongsheng Wu[3], Edward Keystone[4], Ted R. Mikuls[5] and James O' Dell[5]. [1]VA Boston Heathcare System, Boston, MA, [2]VA Boston Healthcare System, Boston, MA, [3]Wentworth Institute of Technology, Boston, MA, [4]Mount Sinai Hospital, Toronto, ON, [5]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: In this 48-week, double-blinded, non-inferiority trial, 353 methotrexate suboptimal-responders were randomized to two treatment strategies, either the addition of sulfasalazine and hydroxychloroquine (triple therapy [T]) or the addition of etanercept (E). Participants without marked improvement in DAS28 at 24 weeks switched to the alternate treatment, while maintaining the blind. This created 4 treatment subgroups: no switch (T-only, E-only), and switch (T-E, E-T). At 48 weeks treatment blind was broken. Follow-up data on major study outcomes from the observational sub-cohort of participants who consented to long term f/u is presented.

Methods: DAS28 scores, joint assessments, laboratory values, visual analog scale (VAS), HAQ, Health Utilities Index (HUI), EQ5D, and changes in therapy (grouped as either any conventional (DMARDs) or to any biologic were collected every 24 weeks up to week 120 or end of study. The last participants enrolled had minimal potential for follow-up, decreasing overall mean follow-up. We compared two follow-up groups: participants on E at 48 weeks (E-only and T-E) who then changed to a DMARD and participants on T at 48 weeks (T-only and E-T) who then changed to a biologic. Study measure results were compared by simple ANOVA at each follow-up time across the four treatment subgroups. The stability of measures over time within each subgroup was assessed by repeated measures ANOVA.

Results: Of the 353 participants, 289 with 48 week data agreed to extend follow-up. Treatment subgroups consisted of 106 T-only, 103 E-only, 42 T-E, and 38 E-T. Data were available on 213 (74%), 168 (58%), and 162 (56%) at 72, 96, and 120 week, respectively. For week 120, data available within the subgroups ranged from 46% to 59%. With respect to DAS28, the censoring patterns appeared completely at random (at each time the null hypothesis was not rejected). Measures of joint assessment, laboratory values, VAS, HAQ, HUI, and EQ5D were stable over time within subgroups. DAS28 scores and various component scores were slightly higher over time among switchers than non-switchers, but not significantly (NS). Within each subgroup no symptom or disability index rose significantly over time. 218 patients had follow-up data on medication use on or after 48 weeks. In this group at week 48, 90% of 101 patients who ended the study on T continued on DMARDs compared to 48% of the 117 patients who ended the study on E and continued on biologics. Of those who changed treatment at week 48, more changed from E to a DMARD than from T to a biologic (chi-square test $p<0.01$). After week 48 medication change rates remained similar in the two groups.

Conclusion: In this observational cohort, major study outcomes including DAS28 remained stable over time. Those patients who switched therapy at week 24 of the interventional trial had slightly higher DAS28 and component scores. Censoring from the treatment subgroups was similar to the overall cohort indicating that censoring was independent of treatment assignment. Of those with post-study medication data, there was a larger change to DMARDs than to biologics immediately after ending the study. The reasons for this are being explored.

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UCB, 5, Abbott Laboratories, Astrazeneca LP, Bristol-Myers Squibb Canada,F. Hoffmann-La Roche Inc., Janssen Inc., Pfizer Pharmaceuticals, UCB, Amgen, 8; **T. R. Mikuls**, Genentech/Roche, 2; **J. O' Dell**, Abbvie, Lilly, Antares, Medac, 5.

1524

Rituximab Done! What's Next in RA? Ulrich A. Walker[1], Veronika K. Jaeger[1], Katerina Chatzidionysiou[2], Merete Lund Hetland[3], Ellen Margrethe Hauge[4], Karel Pavelka[5], Dan C. Nordström[6], Helena Canhao[7], Matija Tomsic[8], Ronald van Vollenhoven[2] and Cem Gabay[9]. [1]Department of Rheumatology, University Hospital Basel, Basel, Switzerland, Basel, Switzerland, [2]Karolinska University Hospital, Stockholm, Sweden, Stockholm, Sweden, [3]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, Aarhus, Denmark, [4]DANBIO, Center for Rheumatology and Spine Diseases, Glostrup University Hospital, Glostrup, Denmark, Glostrup, Denmark, [5]Charles University, Prague, Czech Republic, Prague, Czech Republic, [6]ROB-FIN, Helsinki University Central Hospital, Helsinki, Finland, Helsinki, Finland, [7]Rheumatology Research Unit, Instituto de Medicina Molecular, Lisbon, Portugal on behalf of the Rheumatic Diseases Portugal Register, Lisbon, Portugal, [8]University Medical Centre Ljubljana, Ljubljana, Slovenia, Ljubljana, Slovenia, [9]University Hospitals of Geneva/SCQM Registry, Geneva, Switzerland, Geneva, Switzerland.

Background/Purpose: The optimal strategy to use biologics after rituximab (RTX) in RA is unknown. We therefore aimed to evaluate the effectiveness of different biologics after RTX treatment.

Methods: The CERRERA registry, a prospective, longitudinal, multinational database of RA patients (Pts) treated with RTX was analyzed with respect to the effectiveness of tumor necrosis factor alpha inhibitor (TNFi), abatacept (ABA) or tocilizumab (TCZ) as a new biologic after RTX. Pts were included, if they had stopped RTX no longer than 6 months prior to the new biologic, had a baseline (BL) visit within 21 days of commencement of the new biologic, and at least 1 follow up visit. BL characteristics were compared across biological classes and between TCZ mono and TCZ combination therapy (methotrexate (MTX) and/or leflunomide (LEF)).

Results: The inclusion criteria were met by 265 Pts. Demographic and disease characteristics did not differ across treatment groups (Table). Pts on TCZ had a significantly greater decline of DAS28(ESR) and CDAI, than Pts on TNFi or ABA after 6 months of treatment (Figure 1). This effect was also seen after adjusting for prednisone use and the number of previous biologics. DAS28 scores in Pts on TCZ were 1.0 (95% CI 0.2–1.7) and 1.8 (95% CI 1.1–2.6) lower than in Pts on TNFi or ABA, respectively. Similarly, the CDAI was 7.2 (95% CI 0–15) and 7.5 (95% CI 0–15) points lower in Pts on TCZ than on TNFi or ABA. Pts with TCZ more frequently had a good EULAR response than Pts with TNFi or ABA (66% vs 31% & 14%, $p<0.001$). Overall, Pts reported a lower HAQ after 6 months of treatment ($p<0.001$), though the decline did not differ between treatment groups.

When comparing TCZ mono with TCZ combination therapy, ΔDAS28 and ΔCDAI and EULAR response did not differ. The drug retention rates did not differ between all treatments (Figure 2).

Conclusion: In this observational cohort study, TCZ provided a better control of RA activity than ABA or TNFi in Pts who discontinued RTX. There was no difference in effectiveness between TCZ given as mono therapy and TCZ given in combination with non-biologic DMARDs.

Table Baseline characteristics by treatment groups in patients who had stopped RTX. Characteristics between TNFI, ABA and TCZ were compared by X^2, Fisher's exact, ANOVA or Kruskal Wallis tests as appropriate.

		Overall (n = 265)	TNFi (n = 89)	ABA (n = 90)	TCZ (n = 86)	TCZ Mono (n = 27)	TCZ Combination (n = 59)	P value
Females (%)		57.0	61.8	57.8	51.2	48.2	52.5	0.36
Age (years; mean, SD)		55.0 (12.2)	56.3 (12.3)	55.6 (12.0)	53.2 (12.2)	51.5 (12.9)	55.9 (12.1)	0.26
RA duration (years; median, IQR)		12.0 (7.0–17.2)	12.7 (5.0–19.0)	11.7 (8.0–17.5)	12.0 (7.0–17.0)	13.9 (8.3–17.2)	11.0 (7.0–16.0)	0.91
RF positive (%)		72.6	70.2	72.4	75.3	84.0	71.4	0.77
Anti-CCP positive (%)		73.6	68.4	78.8	74.3	80.0	72.0	0.61
Number of previous biologics (%)	1	11.4	13.5	17.62.8	4.6	2.0	0.08	
	2	25.6	29.7	21.6	23.4	40.9	18.4	
	3	32.9	32.4	29.7	36.6	31.8	38.8	
	≥4	30.1	24.3	31.1	35.2	22.7	40.8	
Prednisone use (%)		65.5	68.5	71.9	55.8	51.9	57.6	0.06
Prednisone dose (median, IQR)		7.0 (5.0–10.0)	6.3 (5.0–10.0)	7.5 (5.0–10.0)	5.0 (5.0–10.0)	5.0 (5.0–7.5)	5.0 (5.0–10.0)	0.50
Reason to stop RTX (%)	Ineffectiveness	78.2	80.0	80.0	74.7	73.9	75.0	0.65
	Other	21.8	20.0	20.0	25.3	26.1	25.0	
DAS-28 (ESR) (median, IQR)		5.7 (4.8–6.6)	5.7 (4.7–6.5)	5.6 (5.0–6.6)	5.9 (4.9–6.7)	6.0 (5.7–7.0)	5.7 (4.3–6.7)	0.97
CDAI (median, IQR)		25.1 (17.6–34.9)	21.1 (17.6–33.9)	27.2 (19.7–37.5)	24.9 (15.8–33.7)	29.6 (20.4–35.6)	23.5 (15.3–32.0)	0.41
HAQ (median, IQR)		1.4 (1.1–2.0)	1.4 (1.1–2.0)	1.6 (1.1–2.0)	1.4 (1.1–1.9)	1.9 (1.1–1.9)	1.4 (1.1–1.8)	0.76

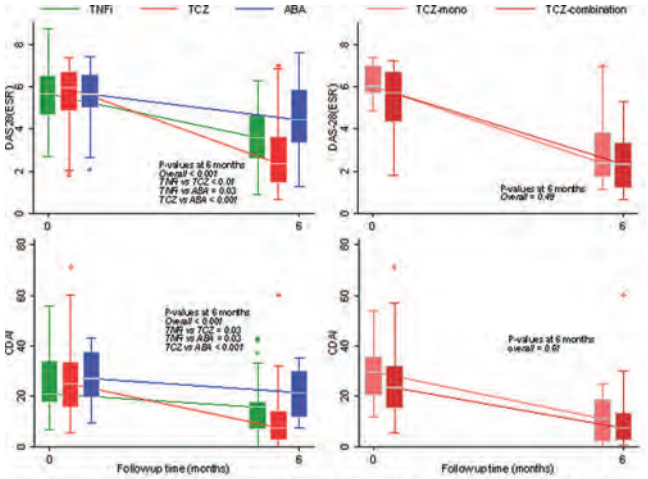

Figure 1 Decline of DAS28 (ESR) and CDAI after 6 months of treatment with TNFi, TCZ or ABA (left graphs). Comparison of outcomes under TCZ treatment with or without additional MTX or LEF. Boxes represent the 25th, 50th and 75th percentiles, whiskers define the lowest and highest data point within 1.5IQR.

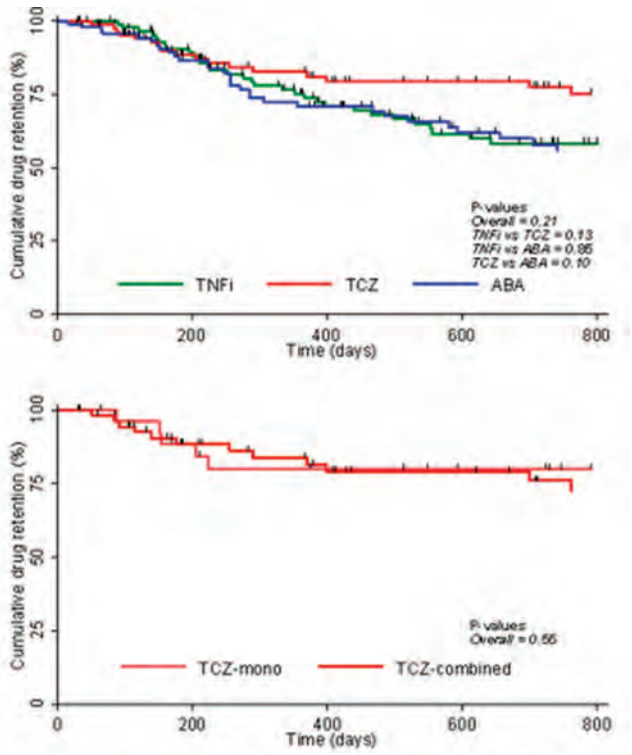

Figure 2 Kaplan Meier curves for the time to discontinuation for TNFi, TCZ or ABA and TCZ mono or TCZ combination therapy.

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Cumulative Clinical Response in Rheumatoid Arthritis Patients with Rituximab Repeated Courses after Failure to Tumor Necrosis Factor Inhibitors in Routine Clinical Practice. Catalin Codreanu[1], Ruxandra Ionescu[2], Ioan Ancuta[3], Corina Mogosan[4], Simona Rednic[5], Paulina Ciurea[6], Maria Suta[7], Magda Parvu[8], Andra Balanescu[2], Mihai Bojinca[3], Dan Nemes[9], Codrina Ancuta[10] and Elena Rezus[11]. [1]'Dr. Ion Stoia' Clinical Center of

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Background/Purpose: The concept of achieving tight control of rheumatoid arthritis (RA) and treating to target has been well established. It focuses on early diagnosis, aggressive treatment and regular monitoring, thus leading to positive outcomes in a significant number of patients with RA who achieve current treatment goals of low levels of disease activity (LDA) or clinical remission (REM).To observe and evaluate the treatment response (REM and LDA) to repeated courses of Rituximab (RTX) in patients with RA treated in current practice in Romania.

Methods: In this open-label, multicenter, prospective observational study (REPEAT), patients were treated with initial (2×1000 mg IV, at 2 weeks apart) and subsequent RTX courses. Clinical assessments, including 28-joint count disease activity score (DAS 28), were performed at baseline (before RTX initiation), and after each retreatment course at 6, 12, 18, 24, 30 and 36 months. Statistical analyses were carried out using STATA SE/11 software: Kruskal-Wallis test for disease activity stages across evaluations, Cuzicks' test for time trend along evaluations.

Results: 1087 patients with active RA and inadequate response to at least one TNF inhibitor, who received an initial RTX treatment were included. Their average age at entry was 56.2 ± 11.2 yrs (mean ± SD) and 86% were women. 929 patients (85.5%) had only one anti-TNF treatment, whereas 158 (14.5%) had more than one. Percentages of remission and LDA are presented below. The Kruskal-Wallis test between evaluations was used, $P<0.0001$, as well as Nptrend for trend across evaluations, $P < 0.0001$.

Time Evaluation after RTX (months)	REM % (pts/n)	LDA % (pts/n)	Treat to Target % (pts/n)
6	9,43 (100/1060)	13,40 (142/1060)	**22,83** (242/1060)
12	19,32 (187/968)	19,42 (188/968)	**38,74** (375/968)
18	31,48 (244/775)	29,81(231/775)	**61,29** (475/775)
24	41,54 (243/585)	31,28 (183/585)	**72,82** (426/585)
30	44,56 (172/386)	31,87 (123/386)	**76,43** (295/386)
36	51,83 (85/164)	30,49 (50/164)	**82,32** (135/164)

n = patients who completed RTX courses along evaluations

Conclusion: The data show continuous improvement of clinical response after each retreatment course with RTX. Each RTX course led to an increased and cumulative clinical response compared to the previous one, being in line with treat to target principle and EULAR/ACR recommendations.

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Sustained Clinical Efficacy after Multiple Courses of Rituximab in Rheumatoid Arthritis Patients with Inadequate Response to Tumor Necrosis Factor Inhibitors: 3-Year Data from Repeat. Catalin Codreanu[1], Ruxandra Ionescu[2], Ioan Ancuta[3], Corina Mogosan[4], Simona Rednic[5], Paulina Ciurea[6], Maria Suta[7], Magda Parvu[8], Andra Balanescu[2], Mihai Bojinca[3], Dan Nemes[9], Codrina Ancuta[10] and Elena Rezus[11]. [1]'Dr. Ion Stoia' Clinical Center of Rheumatic Diseases, Bucharest, Romania, [2]Sfanta Maria Clinical Hospital, UMF Carol Davila, Bucharest, Romania, [3]Carol Davila University of Medicine and Pharmacy & Cantacuzino Hospital, Bucharest, Romania, [4]'Dr. Ion Stoia' Clinical Center of Rheumatic Diseases, Bucharest, Romania, [5]University of Medicine and Pharmacy, Cluj-Napoca, Romania, [6]Clinical County Hospital,Craiova, Craiova, Romania, [7]Constanta Municipal Hospital, Constanta, Romania, [8]Colentina Clinical Hospital, Bucuresti, Romania, [9]"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania, [10]G.T.Popa Center for Biomedical Research, Iasi, Romania, [11]Recovering Clinical Hospital, Iasi, Romania.

Background/Purpose: Efficacy and safety of multiple courses of biologics used over extended periods of time in rheumatoid arthritis (RA) is still a medical debate. The purpose: to assess clinical efficacy of subsequent courses with Rituximab (RTX) in patients with active RA despite treatment with a TNF inhibitor in routine clinical practice in Romania.

Methods: Open-label, multicenter, prospective observational study started in 2010,using RTX every 6 months. Clinical efficacy included DAS-28, SDAI and CDAI at baseline and at 6, 12, 18, 24, 30 and 36 months. **Δ** DAS-28, **Δ** SDAI and **Δ** CDAI were calculated based on two consecutive evaluations. Statistical analyses: STATA SE/11.

Results: 1087 patients with active RA and inadequate response to at least one TNF inhibitor who received an initial RTX treatment were included. Their average age at entry was 56.2 ± 11.2 yrs (mean ± SD) and 86% were women. The mean values of disease activity scores steadily decreased after each retreatment indicating significant improvement.

Evaluation	DAS-28 (mean±SD)	SDAI (mean± SD)	CDAI (mean ±SD)
Baseline	5.57 ± 1.48 (n=1071)*	29.5±15.98 (n=1057)**	27.33 ± 15.07 (n=1071)
6 months	4.03 ± 1.13 (n=1060)	13.84 ± 9.33 (n=1041)	12.5 ± 8.82 (n=1060)
12 months	3.42 ± 0.96 (n=968)	9.16 ± 7.48 (n=938)	7.83 ± 6.69 (n=968)
18 months	3.02 ± 0.86 (n=775)	6.58 ± 5.63 (n=761)	5.45 ± 5.12 (n=775)
24 months	2.8 ± 0.76 (n=585)	5.43 ± 5.07 (n=574)	4.21 ± 4.22 (n=585)
30 months	2.69 ± 0.85 (n=386)	5.55 ± 5.49 (n=379)	4.15 ± 4.78 (n=386)
36 months	2.56 ± 0.83 (n=164)	5.27 ± 5.1 (n=159)	3.92 ± 4.2 (n=164)

*Patient's number (n) decreases in time because of the enrolment timeframe and represents the number of patients who reached each evaluation ** SDAI patient's /number is lower as CRP was not determined in all patients. Remission rate progressively increased after each retreatment course: 9.43% (100/1060 pts), 19.32% (187/968 pts), 31.48% (244/775 pts), 41.54% (243/585 pts), 44.56% (172/386 pts) and 51.83% (85/164 pts), whereas initial percentage of patients showing high disease activity (HDA) (66.2%=709/1071 pts) decreased to 18.02% (191/1060 pts), 4.44% (43/968 ps), 1.81% (14/775 pts), 0.68% (4/585 pts), 1.04% (4/386 pts) and 1.22% (2/164 pts) at 6, 12, 18, 24, 30 and 36 months, respectively. Similar trends were observed in SDAI and CDAI scores. All **Δ** DAS-28, **Δ** SDAI and **Δ** CDAI changes, as well as DAS-28 vs. SDAI and DAS-28 vs. CDAI comparisons were statistically significant ($p<0.0001$).

Conclusion: Our study showed a sustained improvement of clinical response after each retreatment course with RTX.

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Efficacy of Biologic Treatments in Early Active Rheumatoid Arthritis: An Indirect Comparison. Laura Sawyer[1], Stacey Chang[1], Alex Diamantopoulos[2] and Fred Dejonckheere[3]. [1]Symmetron Limited, London, United Kingdom, [2]Symmetron Limited, Herts, United Kingdom, [3]F. Hoffmann-La Roche, Basel, Switzerland.

Background/Purpose: To date, no head-to-head trials have been conducted comparing the efficacy of biologic treatments for early active rheumatoid arthritis (ERA). Here, we evaluated the effectiveness of tocilizumab (TCZ) compared with other traditional and biologic disease-modifying antirheumatic drugs (tDMARDs and bDMARDs), alone and in combination, in adult patients with moderate to severe ERA who have not been treated with methotrexate (MTX) or bDMARDs.

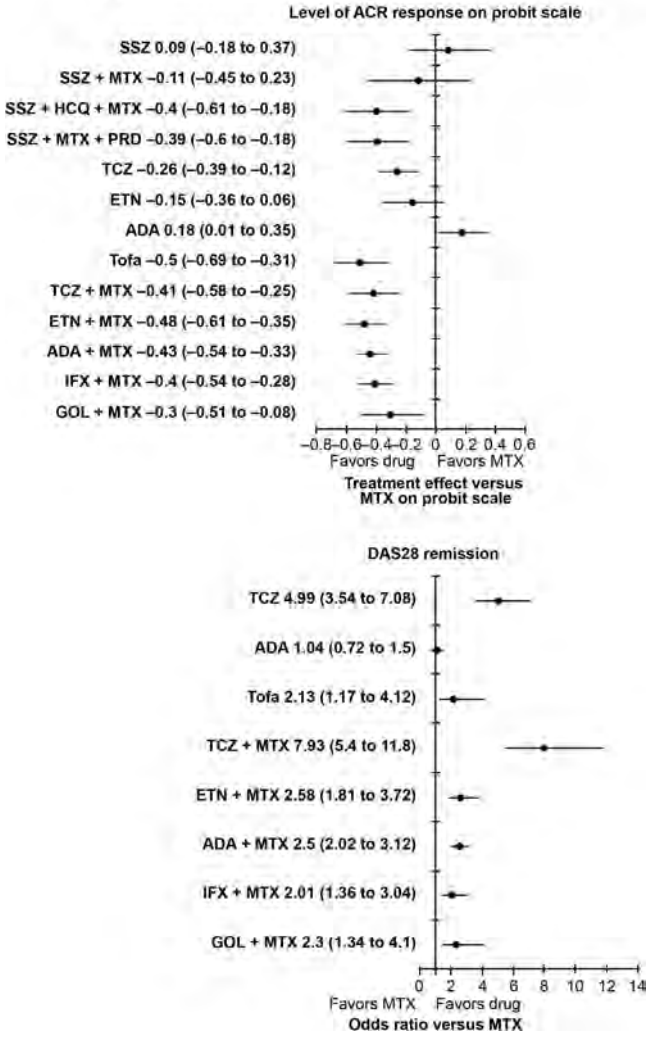
Methods: A literature review was undertaken to identify randomized controlled trials (RCTs) of tDMARDs and bDMARDs in patients with ERA (duration, <3 years) that reported efficacy outcomes, including the proportions of patients achieving American College of Rheumatology (ACR) scores of 20, 50, 70, and 90 and disease activity score (DAS28)–defined remission (DAS28 <2.6). Study data were pooled using Bayesian network meta-analysis techniques. For ACR response, data were analyzed using a fixed-effects (FE) ordered probit model, which makes efficient use of ordered categorical data and guarantees coherent prediction of multinomial response probabilities. For DAS remission, data were analyzed with an FE binomial logit model. The analysis included only results for treatments in licensed doses. Sensitivity analyses tested the effects of grouping treatments by class and broadening and narrowing inclusion criteria.

Results: We included 16 RCTs of tDMARDs (MTX, sulfasalazine [SSZ], hydroxychloroquine [HCQ]), bDMARDs (abatacept [ABT], adalimumab [ADA], etanercept [ETN], infliximab [IFX], golimumab [GOL], and TCZ), and tofacitinib (Tofa). Results indicate that all bDMARDs + MTX, triple tDMARD therapies, and TCZ and Tofa in monotherapy significantly increased response across all ACR categories versus MTX. (Figure). Probabilities of ACR response to bDMARDs + MTX were broadly similar, with no significant differences between agents. Probabilities of ACR response to

bDMARDs in monotherapy were more varied, with a trend toward higher values for Tofa and TCZ than for ETN or ADA. Only a subset of studies reported DAS remission. Results show that treatment with Tofa or any bDMARD (± MTX) except ADA alone improved the likelihood of DAS remission versus MTX. TCZ (± MTX) generated the highest probability of remission among bDMARD agents and was significantly more effective than all other bDMARDs (± MTX) and Tofa. Results across both outcomes were robust to alternative grouping of interventions and to change in the inclusion criteria.

Conclusion: Based on ACR response, the expected efficacy of bDMARDs + MTX, Tofa and TCZ monotherapy, and triple tDMARD therapy appears comparable in early RA. TCZ and Tofa in monotherapy are more effective than ADA alone and are likely to be more effective than ETN alone. TCZ ± MTX is expected to have the highest probability of generating DAS.

Figure. Median relative treatment effects vs MTX (95% credible interval). PRD, prednisone/prednisolone.



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Efficacy and Safety of MK-8457, a Novel SYK Inhibitor for the Treatment of Rheumatoid Arthritis in Two Randomized, Controlled, Phase 2 Studies.

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Background/Purpose: Novel, targeted small-molecular medications are needed in the treatment of rheumatoid arthritis (RA). MK-8457 is a novel inhibitor of spleen tyrosine kinase (SYK) and zeta-chain-associated protein kinase 70 (ZAP70) that is being investigated as an RA treatment.

Methods: Two Phase 2, multicenter, double-blind, placebo-controlled trials were conducted in RA subjects (≥ 18 years old). Study 1 was an adaptive study in subjects with active RA despite treatment with methotrexate (MTX) and included MRI; Study 2 included subjects with active RA and an inadequate response or intolerance to anti-TNF-α therapy. Subjects in both studies were randomized to MK-8457 100 mg BID + MTX or placebo + MTX for 24 weeks, this dose has 99% inhibition of basophil CD63 biomarker. The primary endpoints were the American College of Rheumatology 20 (ACR20) response at Week 12 in Study 1 and change from baseline in the Disease Activity Score 28 (DAS28) based on C-reactive protein (CRP) at Week 12 in Study 2. ACR 50 and ACR70 were also evaluated. Subjects were eligible to continue open-label safety extensions for up to 100 weeks upon completion of the initial 24-week treatment period. Safety was monitored by physical examination, vital signs, safety labs, and adverse event (AE) reporting.

Results: Both studies were discontinued early due to serious infections. At the time of study discontinuation, there were 82 subjects (mean age 55 years; 77% female; baseline mean $DAS28^{CRP}$ 5.98) randomized to MK-8457 (n=41) and placebo (n=41) in Study 1. In Study 2, 56 subjects (mean age 59 years; 77% female; baseline mean $DAS28^{CRP}$ 6.12) were randomized to MK-8457 (n=30) and placebo (n=26). Statistically significant efficacy improvement was observed with MK-8457 in Study 1 (MTX-IR), but not in Study 2 (TNF-IR) (Table). Study 1 also showed efficacy on osteitis and synovitis on MRI. At termination, Study 2 only had 31 subjects with Week 12 data; therefore, there was little power to assess efficacy endpoints. There were 27% (MK-8457) vs 10% (placebo) with non-infection gastrointestinal (GI) AEs in Study 1, and; 27% (MK-8457) vs 4% (placebo) with GI AEs in Study 2. In Studies 1 and 2, there were 6 serious respiratory infections (5 pneumonia and 1 bronchitis) and 1 serious case of enterocolitis; 1 subject with presumed opportunistic infection died during the Study 1 extension. The combined serious infection rate per 100 patient-years was 16.3. There were no significant changes in blood pressure in the MK-8547 treated groups.

Conclusion: MK-8457 improved efficacy in subjects with an inadequate response to MTX (Study 1), but not in subjects who failed anti-TNF-α therapy (Study 2), although Study 2 was limited to a small sample size. A high rate of serious infections was observed leading to the termination of both studies suggesting a potential increased infection risk with high degree of SYK and/or ZAP70 inhibition.

Table: Efficacy Endpoints at Week 12

	Study 1 (MTX-IR)		Study 2 (TNF-IR)	
	Placebo	MK-8457	Placebo	MK-8457
Key Endpoints				
ACR20 (%)†	24.4%; n=41	68.3%**; n=41	26.9%; n=26	26.7%; n=30
ACR50 (%)	4.9%; n=41	36.6%**; n=41	11.5%; n=26	20%; n=30
ACR70 (%)	4.9%; n=41	19.5%*; n=41	7.7%; n=26	13.3%; n=30
$DAS28^{CRP}$ ‡ (LS Mean [95% CI])	−0.87 (−1.23, −0.51); n=39	−1.98 (−2.34, −1.61)**; n=37	−1.31 (−2.01, −0.62); n=18	−1.83 (−2.58, −1.09); n=13
Mean (SD) 12-Week MRI Scores (Change from Baseline)				
Osteitis	2.12 (7.8); n=12	−3.29 (4.43)*; n=9	N/A	N/A
Synovitis	1.08 (3.02); n=12	−1.71 (2.54)*; n=9	N/A	N/A
Erosion	1.08 (2.29); n=12	0.03 (1.19); n=9	N/A	N/A

*p<0.05 vs. placebo; **p<0.001 vs. placebo †Primary endpoint (Study 1); ‡Primary endpoint (Study 2) N/A = Not applicable (MRI data not collected in Study 2)

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Evaluation of the Pharmacokinetics and Safety of the Interactions Between the Anti-Interleukin-6 Monoclonal Antibody Sirukumab and Cytochrome P450 Activities in Patients with Rheumatoid Arthritis. Dick de Vries, Yanli Zhuang, Stanley Marciniak, Zhenhua Xu, Dion Chen, Hugh M. Davis, Honghui Zhou and Francisco Lreon. Janssen Research & Development, LLC., Spring House, PA.

Background/Purpose: Interleukin 6 (IL-6) reduces the expression of cytochrome P450 (CYP) enzymes. The goal of the study was to evaluate: 1) the effect of sirukumab on the pharmacokinetics of probe substrates for CYP3A4, CYP2C9, CYP2C19, and CYP1A2 in patients with active rheumatoid arthritis (RA), a disease in which IL-6 is elevated; 2) the safety of a single subcutaneous high dose of sirukumab in RA patients.

Methods: This was an open-label, Phase 1 study in men and women 18–65 years of age, diagnosed with RA and with a screening CRP≥8.0 mg/L. Twelve patients, genotyped to exclude poor metabolizers of CYP2C9 and CYP2C19, were enrolled. Patients received oral "cocktail" administrations of CYP probe substrates (midazolam, warfarin, omeprazole and caffeine) at weeks -1, 1, 3, and 6 weeks relative to a single subcutaneous dose of 300 mg sirukumab. Serum sirukumab concentration and antibodies to sirukumab were analyzed. Safety was monitored through 7 weeks after sirukumab administration. Plasma levels of 4-β-hydroxycholesterol were measured.

Results: AUC_{inf} of each probe substrate before and after sirukumab treatment showed that exposure to midazolam, omeprazole and S-warfarin was reduced modestly (<50%) at 1, 3 and 6 weeks after sirukumab treatment. CRP decreased after sirukumab administration. Mean plasma levels of 4-β-hydroxycholesterol showed an increase of about 25% over time, but the ratio of 4-β-hydroxycholesterol to cholesterol did not change. All 12 patients reported at least one non-serious adverse event, the two most frequent ones being laboratory abnormalities and mild injection site reactions. No new safety findings were observed and no SAEs were reported.

Conclusion: Consistent with its intended suppression of IL-6 effects, treatment with sirukumab may reverse IL-6-mediated suppression of CYP3A4, CYP2C9 and CYP2C19 activities in RA patients. These results suggest the possibility of potential changes in the levels of certain CYP-metabolized medications in RA patients treated with sirukumab. Single high-dose sirukumab and probe cocktail administrations were well tolerated, without new safety findings.

Table 1: Mean (SD) values for AUC_{inf} of each probe substrate before and after sirukumab treatment

	Pre-sirukumab (n=12)	1 week after sirukumab (n=12)		3 weeks after sirukumab (n=12)		6 weeks after sirukumab (n=12)	
Probe Substrate	AUC_{inf} (ng*h/mL) Day 1	AUC_{inf} (ng*h/mL) Day 15	% change*	AUC_{inf} (ng*h/mL) Day 29	% change*	AUC_{inf} (ng*h/mL) Day 50	% change*
Midazolam	50.67 (24.29)	34.34 (13.89)	−30	32.63 (15.76)	−35	33.80 (15.39)	−33
Omeprazole	3720 (2623)	1937 (1372)	−45	2130 (1537)	−41	2152 (1369)	−37
S-warfarin	24248 (4359)	19816 (3126)	−18	19845 (3354)	−18	19476 (2824)	−19
Caffeine	13989 (10534)	15747 (10036)	20	19538 (15794)	34	17967 (13900)	28

*calculated based on geometric mean ratio

Disclosure: D. de Vries, Janssen Research and Development, LLC, 3; **Y. Zhuang**, Janssen Research and Development, LLC, 3; **S. Marciniak**, Janssen Research and Development, LLC, 3; **Z. Xu**, Janssen Research and Development, LLC, 3; **D. Chen**, Janssen Research and Development, LLC, 3; **H. M. Davis**, Janssen Research and Development, LLC, 3; **H. Zhou**, Janssen Research and Development, LLC., 3; **F. Leon**, Janssen Research and Development, LLC., 3.

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Autologous Tolerogenic Dendritic Cells for Rheumatoid and Inflammatory Arthritis. Gillian Bell, Amy E. Anderson, Julie Diboll, Rachel Harry, Elaine McColl, Anne Dickinson, Catharien Hilkens and John D Isaracs. NIHR Newcastle Biomedical Research Centre, Newcastle Hospitals Foundation Trust and Newcastle University, Newcastle upon Tyne, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease which results from a breakdown of immune tolerance. Despite their efficacy current RA therapeutics, including biologic and non-biologic DMARDs, generally require chronic administration with the associated risk of adverse effects. The concept of therapeutic tolerance states that it should be possible to reprogram unwanted immune responses, including autoimmunity, and reset the immune system to self-tolerance. Although the concept has been achieved in animal models of autoimmunity and transplantation it has not yet been convincingly demonstrated in humans. We have developed a potentially tolerogenic therapy, autologous tolerogenic dendritic cells (tolDC), and now report the results of a phase 1 safety trial in patients with inflammatory arthritis. The secondary objectives were to assess tolerability and feasibility; exploratory objectives include preliminary evidence of potential efficacy including biomarkers.

Methods: This was an ascending dose, randomised, controlled, unblinded phase I study. Participants had a chronic inflammatory arthritis (75% RA) with an actively inflamed knee joint. Background therapy was maintained throughout the trial. There were three dosing cohorts of 1 million, 3 million and 10 million tolDC; controls received saline washout only. Following screening, participants underwent leukapheresis and leukocytes were transferred to a GMP facility. CD14+ monocytes were positively selected and tolDC differentiated according to our published methods[1]. During differentiation tolDC were loaded with autologous synovial fluid as autoantigen. After 7 days tolDC were administered arthroscopically into the inflamed knee joint following saline washout. Synovial biopsies were taken arthroscopically at baseline and again 14 days later, when intra-articular glucocorticoid was administered for persistent inflammation. The primary endpoint of the study was the proportion of patients experiencing a flare of target knee joint inflammation within 5 days of tolDC administration (knee flare). Secondary endpoints were patient acceptability and the success rate of tolDC preparation.

Results: TolDC were successfully manufactured from 9 patients. The product marginally failed quality control in a tenth case. No knee flares were observed in patients or controls. In most participants there was residual inflammation at day 14 arthroscopy except for two patients in the 10 million tolDC cohort. There was one SAE (flare of RA on day 70, requiring hospital admission and subsequent pneumonia) and several AEs, most of which were deemed unrelated to therapy. Patient acceptability of the intervention was high.

Conclusion: We have peformed a phase 1 study of intra-articular tolDC in patients with inflammatory arthritis. The intervention appeared safe, feasible and acceptable to participants. We are currently planning tracking studies, to study the fate of administered cells, and biomarker analysis. [1]Harry RA, Anderson AE, **Isaacs JD**, Hilkens CM. Generation and characterisation of therapeutic tolerogenic dendritic cells for rheumatoid arthritis. **Ann Rheum Dis** 2010;69:2042–2050.

Disclosure: G. Bell, None; **A. E. Anderson**, None; **J. Diboll**, None; **R. Harry**, None; **E. McColl**, None; **A. Dickinson**, None; **C. Hilkens**, None; **J. D. Isaacs**, None.

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CUT-Off LEVEL of Adalimumab and Prevalence of Antibodies ANTI-Adalimumab in Patients with Ankylosing Spondylitis: Results from a LOCAL Registry. Jose Rosas[1], Francisca Llinares-Tello[2], José M. Senabre-Gallego[2], Carlos Santos-Ramirez[3], Esteban Salas-Heredia[2], Xavier Barber[4], Gregorio Santos-Soler[2], Juan Molina[2], Mario García-Carrasco[5], Ana Pons[2], Catalina Cano[2] and Group Aire-MB[2]. [1]Hospital Marina Baixa. Villajoyosa, Villajoyosa, Spain, [2]Hospital Marina Baixa, Villajoyosa, Spain, [3]Hospital Marina Salud, Denia, Spain, [4]CIO, Elche, Spain, [5]Universidad Autónoma de Puebla, Puebla, Mexico.

Background/Purpose: To evaluate the Cut-off level of adalimumab (ADL) and the prevalence of antibodies anti-adalimumab (anti-ADL-ab), in patients with psoriatic arthritis (PsA) and ankylosing spondylitis (AS).

Methods: We included 115 test of serum level of ADL and anti-ADL-Ab from 60 consecutives patients, on treatment with ADL at least 6 months, diagnosed of peripheral arthritis PsA (16 test in 10 patients), or AS (99 test in 50 patients). Clinical characteristics, clinical activity index (DAS28-ESR, SDAI, for peripheral PsA; BASDAI and ASDAS for AS, were recorded.

Serum levels of ADL and anti-ADL-Ab was evaluated by an ELISA kit: Promonitor®-ADL and Promonitor®-anti-ADL-Ab (Progenika Biopharma, S.A., a Grifols Company). Cut-off level for serum level of ADL was >0.004 U/mL and for anti-ADL-Ab was >3.5 U/mL. Serum samples were collected before injection of ADL, and stored frozen -80°C, until analysis.

Receiver operating characteristics (ROC) analysis was used to obtain a cut-off value for ADL trough levels between RA patients with low disease activity (DAS28 ≤ 3.2) versus those with moderate or high activity (DAS28 > 3.2), and for AS patients, between ASDAS ≤2.1 vs >2.1.

Results: We enrolled 60 patients, 56% were women, mean age 48±16 years. In 50 (84%) patients with AS, 99 test (86%) for ADL level and anti-ADL-Ab and in 10 patients (16%), diagnosed of PsA, 16 (14%) test was done.

For the whole patients: the average time of treatment was 9.5±9 years and the average time on treatment with ADL 1.7±1.4 years; in 38 (63%), ADL was the first biological drug administered; the mean BMI was 27 and the prevalence of anti-ADL-Ab was 30% (18 patients: 14 –28%- patients with AS and 4 –40%- of patients with PsA).

In patients with anti-ADL-Ab versus patients without ant-ADL-ab, we obtained significantly higher level of ADL (11.5±5.3 vs 0.12 ± 0.2; p<0.0001), less BASDAI response (2.7±1.8 vs 5.5±2.0; p<0.0001), less ASDAS level (1.8±0.6 vs 3.5±2.6; p=0.008) and less time on treatment with ADL (2.2±1.4 vs 0.8±0.4; p<0.0001). Although the 35% patients without anti-ADL-ab was treated with DMARDs and only 10% of patients with anti-ADL-ab, there was not statistical differences (p=0.2).. The cut-off level of ADL in patients with AS to achieve an ASDAS≤2.1 was 5.4 mg/L, with AUC of 82.9% (sensitivity: 91%; specificity: 75%).

Table 1. Characteristics in responders and non-responders patients in relation with ASDAS results

	Responders (n:42) ASDAS ≤ 2.1	Non-Responders (n:42) ASDAS ≤ 2.1	P
ADL level, mean ± SD	11.0 ± 4.4	1.7 ± 4.1	<0.001
Anti-ADL-ab (%)	2*	71	0.006
BASDAI, mean ± SD	2.5 ± 1.5	5.7 ± 1.8	<0.001
DMARD (%)	40	17	0.4
Time (years) on ADL, mean±SD	1.7±1.2	1.2±1	0,08

(*a patient with a detectable low level of ADL and the anti-ADL-ab was demonstrated using acid dissociation technique).

Conclusion: 1.Cut-off level of ADL in patients with AS to achieve an ASDAS≤2.1 was 5.4 mg/L. 2. Prevalence anti-ADL-Ab in AS was 28%. 3. Anti-ADL-ab is correlated significantly with lower level of ADL, BASDAI and ASDAI results and less time on treatment. 4. Patients responders have occasionally anti-ADL-ab, and significantly higher serum concentrations of ADL than non-responders.

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Efficacy of the Subcutaneous Formulation of Abatacept/Orencia in Rheumatoid Arthritis, a Single-Center Italian Experience. Rossella Reggia[1], Franco Franceschini[1], Angela Tincani[2] and Ilaria Cavazzana[1]. [1]AO Spedali Civili, Rheumatology and Clinical Immunology Unit, Brescia, Italy, [2]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy.

Background/Purpose: Abatacept is a selective T cell costimulation modulator indicated for moderately to severely active Rheumatoid Arthritis (RA). Since August 2013 is available in Italy the new subcutaneous (sc) formulation, that consists in a fixed dose of 125 mg of the drug, administered once weekly. Four clinical trials demonstrated an efficacy and a safety profile comparable to those obtained with the intravenous (iv) administration.

Aim of our work was to analyze the clinical response of a series of patients (pts) with RA treated with monthly iv infusion and than converted to the sc formulation.

Methods: We included 48 pts with RA, converted to the sc formulation of Abatacept from October 2013 to April 2014. We divided them into two groups, depending on their need to return to the iv administration for the appearance of a disease flare. The main clinical and serological features of the two groups were compared using the Chi-square, T-test or the Mann-Whitney test when appropriate.

Results: Pts converted to the sc formulation were the 48.5% of all cases receiving Abatacept therapy in our Unit. No pts received the iv "loading dose". Eleven pts (22.9%) returned to the iv administration due to a disease flare (mean DAS 28: 2.35 vs 3.85, p:0.005), after a mean of 7.3 injections (range 4–14). The remaining 38 (77.1%) continued with the sc formulation. The compared parameters between the two groups are summarized in Table 1.

In pts with arthritis flare, disease activity decreased again (mean DAS 28: 2.45 vs 3.85, p:0.009) after returning to the iv administration of the drug (after a mean of 38.2 days).

One patient discontinued the sc formulation for the onset of related side-effects (headache and nausea) not reported with the iv administration.

Conclusion: although the safety profile of the sc formulation of Abatacept seems to confirm the data previously obtained with the iv use of the drug, a high rate of our patients complained a reduced efficacy and needed the return to the traditional way of administration.

We failed to identify clear risk factors that may help toward the selection of pts to which propose the formulation switch. However, if an arthritic flare occurs, the return to the iv administration seems to ensure a good control of the disease again. Therefore, the efficacy of the molecule does not seem to be compromised by an eventual switch failure.

Tab.1 Comparison between the clinical and serological features of patients with and without the need to return to the intravenous administration of Abatacept after the switch to subcutaneous formulation

Analyzed features	Pts who maintained the sc formulation n=38 (77,5%)	Pts who returned to iv formulation n=11 (22,5%)	p:
Mean age (years)	58.8	55.1	ns
Positivity for Rheumatoid Factor (RF)	n:34; (92%)	n:10; (91%)	ns
Positivity for anti-citrullinated protein antibodies (ACPA)	n:21; (70%)	n:8; (80%)	ns
Mean disease duration (months)	140.3	125.1	ns
Previous iv therapy duration (months)	20.8	17	ns
Body Max Index (BMI)	24.2	26.1	ns
Smokers	n:4; (10.5%)	n:3; (30%)	ns
DMARDs in association	n:33; (89.5%)	n:10; (90%)	ns
Previous use of biological agents	n:25; (65.8%)	n:8; (72.7%)	ns
N' of different biological agents used in the past: mean; [SD]	1.7; [1.6]	1.7; [2.3]	ns
Abatacept as first biological agent	n:13; (34.2%)	n:3; (27.3%)	ns
Remission of the disease at sc therapy start	n:29; (76.3%)	n:6; (54.5%)	ns
DAS28 at sc therapy start: mean; [SD]	2.07; [1.07]	2.35; [0.98]	ns

iv: intravenous, sc: subcutaneous, DMARDs: disease-modifying antirheumatic drugs, SD: standard deviation, ns: not significant.

Disclosure: R. Reggia, None; **F. Franceschini**, None; **A. Tincani**, None; **I. Cavazzana**, None.

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Study of One Vial (400mg) per Body Infusion of Tocilizumab in Patients with Active Rheumatoid Arthritis. Hiroshi Uda, Koji Shigematsu and Osamu Sariki. Higashiosaka City General Hospital, Higashiosaka, Japan.

Background/Purpose: The treatment of active rheumatoid arthritis (RA) patients are usually started with synthetic disease modifying antirheumatic drugs (DMARDs), but when adequate response are not achieved, biologics DMARDs are introduced. Tocilizumab (TCZ) is one of useful biologics and the infusion dose of TCZ was settled at 8mg/kg. The residues of TCZ fluid were always discarded. The procedure of sucking and discharging of TCZ is troublesome and dispose of TCZ residue is uneconomical. The fixed dose injection become majority of biologics administration, but fixed dose of biologics infusion has not been attempted to date. The present study is carried out to clarify that one vial (400mg) of TCZ infusion per body (body weight >50kg) is effective in the patients with active RA.

Methods: The RA patients who showed inadequate response to synthetic and biologic DMARDs other than TCZ and whose body weight was between 50 to 100kg were enrolled in the present study. The patients discontinued biologics before starting TCZ, and one vial (400mg) per body infusion of tocilizumab every 4 weeks (OBOTO study) was added to synthetic DMARDs. The clinical assessments and blood tests were also carried out every 4 weeks. To the patients who did not achieve clinical remission by one vial (400mg) of TCZ, prednisolone (PSL) and/or methotrexate were added. The patients who achieved clinical remission in 12 months were estimated as responder and others were as non-responders. To the patients who achieved clinical remission, we tapered the dose of PSL and/or DMARDs. We followed up the patients at least for 5 years.

Results: Total of 106 patients was enrolled in the present study. Male and female were 25 and 81 respectively. Seventy-four patients achieved good response, 21 patients achieved moderate response and 11 patients were non-responders. DAS28 remission was achieved in 59 patients. The body weight of the patients enrolled was between 92 to 50 kg and the mean body

weight of responders and non-responders did not differ significantly. After the clinical remission was achieved, PSL and/or DMARDs were decreased. In five years, 12 patients were treated TCZ alone without any synthetic DMARDs or corticosteroids and kept the condition more than 4 years. The rest of responders received either or both PSL (1 to 7.5 mg/day) and MTX (2 to 8mg/week). To the patients who could not achieve clinical remission, dose escalation of TCZ was not attempted in the present study. Serious adverse events including tuberculosis or death were not found. The overall incidence of adverse events of one vial (400mg) of TCZ was less than those of 8mg/kg infusion.

Conclusion: We provide evidence that one vial (400mg) of TCZ infusion is effective in active RA patients whose body weight is over 50 kg. The finding of OBOTO study is quite useful for taking care of active RA patients both financially and technically.

Disclosure: H. Uda, None; **K. Shigematsu**, None; **O. Saiki**, None.

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Disease Severity and Treatment of Rheumatoid Arthritis: A Comparative Study Between Sudan and Sweden. Amir Elshafie[1], Abdalla D Elkhalifa[2], Thomas Weitoft[3], Musa Nur[4], Elnour Elagib[4], Mawahib Aledrissy[5], Sahwa Elbagir[6] and Johan Rönnelid[7]. [1]MD, MDpath, PhD, Uppsala, Sweden, [2]MD, Gävle, Sweden, [3]MD, PhD, Gävle, Sweden, [4]MD, FRCP, Khartoum, Sudan, [5]MD, MD internal Medicine, Khartoum, Sudan, [6]M, PhD student, Uppsala, Sweden, [7]Uppsala University, Uppsala, Sweden.

Background/Purpose: To perform a comparative study concerning clinical characteristics and treatment between Sudanese and Swedish RA outpatients.

Methods: A 286 Sudanese and 542 Swedish RA outpatients diagnosed according to 1987 ACR classification criteria were recruited between December 2008 and September 2010 and compared concerning clinical presentation, treatment and laboratory findings including IgM RF.

Results: Age at inclusion, disease duration and median age at disease onset were all significantly lower among the Sudanese patients ($p < 0.0001$). When stratified concerning age of inclusion, Swedish patients between 41–50 years had however a significantly lower age of onset, with a similar trend for all age groups above 30 years. Levels of ESR and number of affected joints were significantly higher among Sudanese RA patients. The proportion of IgM RF positivity was significantly lower among Sudanese RA patients ($p<0.0001$). Higher proportions of Sudanese RA patients were treated with methotrexate and DMARD combinations but none of them on biologics. Sudanese patient used lower doses of methotrexate and sulfasalazine ($p < 0.0001$) and higher doses of prednisolone ($p < 0.0001$) than Swedish patients. The female preponderance was more striking among Sudanese patients ($p < 0.0001$), although smoking was non-existent among the Sudanese female RA patients ($p<0.0001$).

Conclusion: Sudanese RA patients have significantly higher disease activity and are often IgM RF seronegative. Together with reports from Uganda and Cameroon our data indicate a cluster of highly active seronegative RA in central Africa.

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Use of Rituximab Compared to Anti-Tnf Agents As Second and Third Line Therapy in Patients with Rheumatoid Arthritis: A Report from the rhumadata® Clinical Database and registry. Denis Choquette[1], Jean-Pierre Raynauld[1], Jean Pierre Pelletier[1], Boulos Haraoui[1], Louis Bessette[2], Edith Villeneuve[1], Marie-Anaïs Rémillard[1], Isabelle Fortin[3], Diane Sauvageau[1] and Louis Coupal[1]. [1]Institut de rhumatologie de Montréal (IRM), Montréal, QC, [2]Centre d'ostéoporose et de rhumatologie de Québec (CORQ), Québec, QC, [3]Centre de rhumatologie de l'est du Québec (CREQ), Rimouski, QC.

Background/Purpose: The order of use of biologic agents after failing a TNF inhibitor is still a question for debate. Phase III trial data in TNF-IR patients show comparable efficacy results across biologic agents and limited head-to-head studies have been published. Prospective registries offer a unique opportunity to observe the effectiveness (combined evaluation of efficacy and safety profile over time) of these agents in a clinical setting. Our objective is to evaluate if patients with rheumatoid arthritis (RA) treated with rituximab (RIT) after failing a first or a second anti-TNF agents (TNF-IR) have a different drug retention rate than patients similarly prescribed anti-TNF agents (pooled adalimumab, etanercept or infliximab) and compare the treatment strategies of using RIT as second or third biologic treatment.

Methods: Data from TNF-IR RA patients prescribed adalimumab (ADA), etanercept (ETA), infliximab (INF) or rituximab (RIT) as second or third biologic agents on or after January 1st 2007 was extracted and subjects taking either ADA, ETA or INF were pooled to form the anti-TNF cohort. Baseline demographics included age, disease duration, HAQ-DI, fatigue and pain visual analog scale evaluations (VAS), TJC, SJC, DAS 28 ESR and SDAI. Five-year drug retention rates were estimated and compared using Kaplan-Meier survival estimates. Statistical analysis was performed using SAS version 9.3. RHUMADATA® is a clinical database and registry used in daily clinical practice at the IRM, CORQ and CREQ.

Results: The data from 226 RA patients were extracted, 153 and 73 having respectively failed a first and a second anti-TNF agent. No clinically significant differences in baseline variables were observed between treatment groups in second and third intention. The 5 year retention rates of second line RIT and anti-TNF use were 74% and 36% respectively (Log-rank $p=0.002$). In patients having failed two anti-TNF, subsequent use of RIT and anti-TNF agents respectively demonstrated 5 year retention rates of 48% and 24% (Log-rank $p=0.004$). Although numerically superior (74% vs 48%) second line use of RIT did not reach statistical difference when compared to third line usage.

Conclusion: As a second line agent, in TNF-IR patients, RIT demonstrates a better 5 year retention rate than anti-TNF agents. As third line therapy, RIT is also statistically superior to anti-TNF agents. Although no statistical difference was demonstrated between second and third line RIT use, it is evident that positioning RIT as second line offers a better long term outcome.

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Comparing Abatacept to Adalimumab, Etanercept and Infliximab As First Line Agents in Patients with Rheumatoid Arthritis. Experience from the Rhumadata® Clinical Database and Registry. Denis Choquette[1], Louis Bessette[2], Isabelle Fortin[3], Boulos Haraoui[1], Jean Pierre Pelletier[1], Jean-Pierre Raynauld[1], Marie-Anaïs Rémillard[1], Diane Sauvageau[1], Edith Villeneuve[1] and Louis Coupal[1]. [1]Institut de rhumatologie de Montréal (IRM), Montréal, QC, [2]Centre d'ostéoporose et de rhumatologie de Québec (CORQ), Québec, QC, [3]Centre de rhumatologie de l'est du Québec (CREQ), Rimouski, QC.

Background/Purpose: The order of use of biologic agents is still a question for debate. Phase III trial data in MTX-IR patients show comparable efficacy results across biologic agents and limited head-to-head studies have been published. Registries offer a unique opportunity to prospectively monitor the effectiveness of these agents in a clinical setting. We aim to assess if patients with rheumatoid arthritis (RA) treated with abatacept after failure of a first line agent (MTX-IR) have a different drug survival rate than patients similarly treated with adalimumab, etanercept or infliximab.

Methods: RA patients prescribed a first biologic agent after January 1st2007 were included in the present analysis. We extracted a cohort formed of all patients prescribed abatacept (ABA), adalimumab (ADA), etanercept (ETA) or infliximab (INF) as their first biologic agent. Baseline demographics for this cohort included age, disease duration, HAQ-DI, fatigue and pain visual analog scale evaluation (VAS), TJC, SJC, DAS 28 ESR and SDAI. Person-years of treatment were also compared across biologic agents. Statistical analysis was performed using SAS version 9.3. RHUMADATA® is a clinical database and registry used daily in clinical practice at the IRM, CORQ and CREQ.

Results: A total 340 patients were included in the cohort. No clinically significant differences in baseline characteristics were noted between treatment groups. The 5 year retention rate of ABA, ADA, ETA and INF post MTX failure were 64%, 40%, 49% and 42% without significant statistical differences (Log-Rank $p=0.29$).

Conclusion: Abatacept, adalimumab, etanercept and infliximab after MTX failure have similar 5-years retention rates.

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Squibb, 5, Janssen Pharmaceutica Product, L.P., 2, Janssen Pharmaceutica Product, L.P., 5, Pfizer Inc, 2, Pfizer Inc, 5, Roche Pharmaceuticals, 2, Roche Pharmaceuticals, 5, UCB, 2, UCB, 5; **J. P. Pelletier**, None; **J. P. Raynauld**, None; **M. A. Rémillard**, None; **D. Sauvageau**, None; **E. Villeneuve**, None; **L. Coupal**, None.

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Clinical Characteristics of RA Patients Newly Prescribed Tofacitinib Citrate (tofacitinib) in the United States after Food and Drug Administration Approval: Results from the Corrona US Rheumatoid Arthritis Registry. Arthur Kavanaugh[1], George W. Reed[2], Katherine C. Saunders[2], Andrew S. Koenig[3], Jamie Geier[4], Joel M. Kremer[5], Jeffrey D. Greenberg[6] and Clifton O. Bingham III[7]. [1]University of California San Diego, La Jolla, CA, [2]Corrona, LLC., Southborough, MA, [3]Pfizer, Inc., Collegeville, PA, [4]Pfizer, Inc., New York, NY, [5]Albany Medical College and the Center for Rheumatology, Albany, NY, [6]New York University School of Medicine, New York, NY, [7]Johns Hopkins University, Baltimore, MD.

Background/Purpose: To provide initial characterization of the patients prescribed tofacitinib during the early period after United States (US) Food and Drug Administration (FDA) approval (11/6/2012).

Methods: Rheumatoid Arthritis (RA) patients in the Corrona registry initiating tofacitinib through 3/1/2014 were identified. As a comparator, RA patients with no history of tofacitinib use initiating any biologic agent between 11/6/2012–3/1/2014 were also identified. Patient characteristics at the time of initiation are summarized and compared between groups. Continuous covariates are compared using a rank-sum test; categorical covariates are compared using a chi-square test.

Results: Over the study period, there were 299 RA patients newly prescribed tofacitinib and 2418 newly prescribed biologic disease modifying antirheumatic drugs (bDMARD) in the registry. Clinical characteristics are summarized in the **Table 1.** Tender and swollen joint counts and clinical disease activity index (CDAI) scores were similar for tofacitinib and bDMARD initiators, as were the distribution of CDAI scores (i.e. high/moderate/low disease activity and remission). However, tofacitinib initiators had significantly higher health assessment questionnaire (HAQ) scores. In addition, the mean disease duration was significantly longer for initiators of tofacitinib (13.9 yrs) versus bDMARDs (9.9 years, $p<0.001$). Tofacitinib initiators also had a higher median (IQR) number of prior biologic drugs [tofacitinib 3 (2–4) versus bDMARDs 1 (0–2)]. Use of monotherapy and combination DMARD therapies differed among tofacitinib versus bDMARD users ($p<0.001$), with monotherapy more commonly used for tofacitinib (43%) versus bDMARD (27%) users.

Conclusion: Analysis of this US-based cohort reflects prescriber patient selection decisions. The RA patients with long-standing severe disease and multiple prior biologics have tended to be the patients for whom tofacitinib has been initiated to date compared with those starting a bDMARD during the same time period, although prescribing is not limited to patients with moderate/high disease activity. Monotherapy and combination treatment strategies differed between tofacitinib versus bDMARD treated patients. These factors may impact assessment of the comparative effectiveness and safety of tofacitinib versus other RA therapies during longitudinal followup.

Table 1. Baseline characteristics

Characteristics	Tofacitinib	Biologic DMARDs	p-value*
Mean (SD)	**N = 299**	**N = 2418**	
Median (IQR)			
	Demographics		
Age (yrs)	56.9 (12.17)	57.14 (13)	0.68
	57 (50–65)	58 (49–66)	
Sex (% Female)	82.94%	79.88%	0.21
Race (% Caucasian)	92.54%	88.94%	0.06
	Disease characteristics		
Tender Joint Count	7.47 (7.47)	7.83 (7.48)	0.3
	5 (1–12)	6 (2–12)	
Swollen Joint Count	5.04 (5.04)	5.67 (5.66)	0.08
	4 (1–8)	4 (1–8)	
HAQ	1.2 (0.71)	1.04 (0.71)	<0.001
	1.25 (0.71–1.75)	1 (0.43–1.57)	
CDAI	20.88 (13.64)	21.97 (14.42)	0.31
	19 (9.6–30)	20 (11–30)	
CDAI Distribution, %			0.13
Remission	5.67%	5.85%	
Low	21.63%	16.07%	
Moderate	31.56%	34.67%	
High	41.13%	43.42%	
RA Disease duration	13.9 (10.25)	9.91 (9.47)	<0.001
	11 (6–20)	7 (3–14)	
	Medication history		
Number of previous biologics	3 (2–4)	1 (0–2)	<0.001
	0–9	0–6	
Concomitant DMARD use, %			<0.001
Monotherapy	43.19%	27.26%	
MTX	30.23%	43.62%	
MTX + other nbDMARD	7.31%	11.61%	
Other nbDMARD	19.27%	17.51%	

*P-value calculated using rank test for continuous variables and chi-square test for categorical variables. SD, standard deviation,; IQR, inter quartile range; HAQ, health assessment questionnaire; CDAI, Clinical Disease Activity Index; RA, rheumatoid arthritis; DMARD, Disease modifying anti-rheumatic drug; MTX, methotrexate; nbDMARD, non-biologic disease modifying anti-rheumatic drug

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Sustained Clinical Benefit with Multiple Courses of Rituximab in Second Line for All Rheumatoid Arthtritis Patients Irrespective to the Inhibitor of Tumour Necrosis Factor Previously Used. Ioan Ancuta[1], Ruxandra Ionescu[2], Catalin Codreanu[3], Andra Balanescu[2], Elena Rezus[4], Maria Suta[5], Paulina Ciurea[6], Mihaela Milicescu[7], Dan Nemes[8], Codrina Ancuta[9], Mihai Bojinca[1], Magda Parvu[10] and Horatiu Popoviciu[11]. [1]"Dr. I. Cantacuzino" Hospital, Bucharest, Romania, [2]Sfanta Maria Clinical Hospital, UMF Carol Davila, Bucharest, Romania, [3]'Dr. Ion Stoia' Clinical Center of Rheumatic Diseases, Bucharest, Romania, [4]Recovering Clinical Hospital, Iasi, Romania, [5]Constanta Municipal Hospital, Constanta, Romania, [6]Clinical County Hospital,Craiova, Craiova, Romania, [7]"Dr. I. Cantacuzino" Clinical Hospital, Bucharest, Romania, [8]"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania, [9]G. T.Popa Center for Biomedical Research, Iasi, Romania, [10]Colentina Clinical Hospital, Bucuresti, Romania, [11]Clinical County Hospital, Tg Mures, Romania.

Background/Purpose: In the last decade, biologic therapy changed dramatically treatment options for rheumatoid arthritis (RA). However, a significant number of patients failed to maintain the initial response to a TNF blocker. More information is needed regarding efficacy and safety of multiple courses of biologics administered over extended periods of time.To assess the clinical benefit of subsequent courses with Rituximab (RTX) in patients with moderate to severe active RA after the failure to different TNF inhibitors used in routine clinical practice in Romania.

Methods: REPEAT is an open-label, multicenter, prospective observational study started in 2010, patients were treated with RTX at each 6 months. Clinical efficacy was assessed at baseline and after each retreatment course at 6, 12, 18, 24, 30 and 36 months. Clinical assessments included disease activity (DAS-28), visual analogue scale (VAS) scores, Δ DAS-28 and Δ VAS. The previous anti-TNF treatments were; adalimumab (ADA), etanercept (ETA) and infliximab (INF). Statistical analyses: STATA SE 11.0 software, Comparison between all treatments and evaluations ANOVA and Kruskal-Wallis and Nptrend for trend across evaluations.

Results: A total of 1087 adult patients with active RA and inadequate response to at least one TNF inhibitor received initial RTX treatment. In our cohort, 929 (85.5%) patients had only one anti-TNF treatment (no switch); 210 (19.3%) patients received ADA, 318(29.3%) received ETA and 401 (36.9%) received INF and the rest of 158 (14.5%) had more than one. As a second TNF inhibitor, 59(5.42%) patients received ADA, 63 (5.79%) received ETA and 36 (3.31%) received INF. Median DAS-28 values for all patients (1087)and each groups ADA, ETA, INF as first TNF inhibitors were: *5.76; 6.05; 5.75; 5.66* at baseline, 3.98; 4.07; 4.11; 3.84 at 6 months, *3,43; 3.43;3.48; 3.33* at 12 months, *2.98; 3.00; 3.11; 2.89* at 18 months, *2.79; 2.72; 2.85; 2.75* at 24 months, *2.67; 2.55;* 2.65; 2.69 at 30 months and *2.57; 2.56; 2.41; 2.6* at 36 months. The median DAS28 values for the group (158) who received a second TNF inhibitor, *5.66; 3.955; 3;56; 2.91; 2.85; 2.71* and *2.57*

followed the same linear decrease across evaluations at baseline, 6;12;18; 24;30 and 36 months. ANOVA test between treatment and evaluations*P < 0.0001*, between previous treatment *P = 0.0014*.DAS-28 score has been improved for all groups of patients, independent from the TNF – inhibitor used as previous treatment. The VAS score was improved in the same manner, independent to previous treatment. ANOVA test between treatment and evaluations P < 0.0001, between evaluations *P < 0.0001*, test between previous treatment *P = 0.0003*.

Conclusion: In our study, Rituximab have demonstrated to be a reliable therapeutic option for all patients regardless the TNF inhibitor used in first line (adalimumab, etanercept or infliximab).

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Relation Between Number of Previous Anti TNF Agents and Clinical Response in Rheumatoid Arthritis Patients Treated with Rituximab. Daniela Opris, Diana Mazilu, Violeta Bojinca, Andreea Borangiu, Andra Balanescu, Denisa Predeteanu and Ruxandra Ionerscu. Sfanta Maria Clinical Hospital, UMF Carol Davila, Bucharest, Romania.

Background/Purpose: Debate is still ongoing regarding rituximab (RTX) as a first or second line biologic therapy. The objective of present study is to assess correlations between patient's characteristics, including previous treatments with drug level, clinical response and further evolution.

Methods: A group of 62 consecutive rheumatoid arthritis (RA) patients treated with RTX according to National Guideline (2 iv infusions of 1 g separated by 2 weeks, every 6 months) were followed for 2 years. All patients were previously diagnosed according to ACR 1987 or ACR/EULAR 2010 criteria. Demographic data, clinical (number of tender and swollen joints) and laboratory (ESR-erythrocyte sedimentation rate, CRP- C reactive protein, RF -rheumatoid factor, ACPA - anti cyclic citrullinated peptide) variables were collected at baseline and at each reevaluation. RA activity was evaluated in all patients by using DAS28 4v, Simplified Disease Activity Index (SDAI). All clinical evaluation was performed by two independent assessors. RTX drug level and anti drug antibodies were measured just before a new infusion using Progenika kits (Promonitor®-RTX, Promonitor®-anti-RTX). Patients were excluded if between baseline and next reevaluation had a change in their treatment regimen. The study was approved by local Ethics Committee and all patients gave written informed consent before inclusion. Statistical analysis was performed using SPSS statistical software, version 20.0.

Results: Mean rituximab treatment duration in the cohort was 41,79±27,76 months. All patients had Methotrexate associated. No antidrug atibodies were found. During evaluation period 25 patients (40.32%) had signs of inadequate response to treatment. At baseline, 9 (36%) of this patients had undetectable drug level. At that moment there was no difference between patients with detectable and undetectable drug level regarding DAS28 (3,65±1,12 vs 3,45±1,19, P=0.678) and SDAI (20±15,7 vs 21,7±29,6, P=0.845), nor in their treatment duration (48.8±53.4 vs 27.7±13.7, P=0.294). At follow-up, 6 months from dosing RTX, patients with detectable drug level had significantly lower DAS28 (mean DAS28 2,93±1,2 vs 3,27±1,47, P=0.01) and SDAI (mean 12,33±14,13 vs 14,83±20,51, P=0.033). Significantly higher number of patients with detectable rituximab level had anti citrulinated antibodies (P=0.021) and were rheumatoid factor positive (P=0.049). Number of previous anti TNF agents correlated to rituximab level (r=0.514, P=0.009). 62% of patients with detectable rituximab level were were non-responders to two or more anti TNF agents. All patients with undetectable drug level had only one anti TNF agent as previous biologic treatment.

Conclusion: Significant differences were found in clinical response in patients depending on the rituximab level and number of previous anti TNF agents used. RTX detectable drug level and 2 or more anti TNFs correlated with better clinical response at follow-up. This result support the actual guidelines for RA treatment regarding rituximab as a second line biologic agent.

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Treatment Patterns of Biologics Used in Rheumatoid Arthritis and Ankylosing Spondylitis in the US Veterans Population. Brian Sauer[1], Chia-Chen Teng[1], Tao He[1], Jianwei Leng[2], Chao-Chin Lu[1], Neel Shah[3], David J. Harrison[3], Derek Tang[3] and Grant W. Cannon[1]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]Salt Lake City VA and University of Utah, Salt Lake Citty, UT, [3]Amgen Inc., Thousand Oaks, CA.

Background/Purpose: Biologics used for rheumatoid arthritis (RA) and ankylosing spondylitis (AS), including tumor necrosis factor blockers, are a key area of focus for Veterans Affairs (VA) Pharmacy Benefits Programs. This study describes treatment patterns with etanercept (ETN), adalimumab (ADA), and infliximab (IFX) in US veterans with RA or AS during the first year of treatment.

Methods: National VA pharmacy, administrative, and clinical databases were used for this analysis. Eligibility criteria included ≥1 claim for ETN, ADA, or IFX from Jan 1, 2008 to Dec 31, 2011 preceded by at least 180 days of enrollment in the VA. The first drug and date that met this criterion was the index drug and date. Patients had to be ≥ 18 years of age on their index date; have ≥360 days of enrollment following their index date; and have ≥1 claim with an ICD-9-CM diagnosis of RA or AS prior to or within 30-days after their index date. Patients with a diagnosis of psoriatic arthritis, psoriasis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, non-Hodgkin's lymphoma, or chronic lymphocytic lymphoma, prior to or within 30-days of their index date; a claim for their index biologic prior to their index date; who used a biologic prior to its receiving approval for that condition; or who had implausible dosing (≥200% of the maximum labeled dose) were excluded.

Treatment patterns were classified based on whether or not patients were persistent on their index agent for the 360 days after their index date. Non-persistence was defined as a ≥45 day gap in days of supply on their index agent or a claim for a non-index biologic. Non-persistent patients were further categorized based on the first observed event after non-persistence: switching, a claim for a biologic other than their index biologic; restarting, another claim for their index biologic after the ≥45 day gap, or discontinued no subsequent claims for any biologic following the gap.

Results: ETN, ADA, and IFX were the index biologic for 2,109, 2,035, and 263 veterans with RA and 286, 422, and 46 veterans with AS. Approximately half of all patients with RA were persistent on therapy for the entire year; 49.3% of ETN, 51.4% of ADA, and 52.5% of IFX. Persistence in AS was lower (ETN, 42.0% and ADA, 40.0%), but higher with INF, 56.4%. In both RA and AS, switching rates were numerically higher in IFX users (RA: 18.6%; AS: 15.2%) compared with ETN (RA: 11.8%, AS: 10.1%) and ADA (RA: 10.3%, AS: 12.8%). Restarting was more common with ETN and ADA than INF in both RA and AS. Discontinuation rates were similar (11.9–14.0%) across agents in both RA and AS.

Conclusion: Overall, persistence during the first year of therapy for RA and AS was relatively low, 40.0–56.5%. Gaps in therapy occurred in 26.5–34.6% of patients taking self-injected agents, but only 15.5–16.3% of patients taking INF. More work is needed to understand the reasons for non-persistence in this population.

Diseases and Treatment Patterns		Etanercept		Adalimumab		Infliximab	
		%	95% CI	%	95% CI	%	95% CI
RA	All	N=2,109		N=2,035		N=263	
	Persistent	49.3%	47.2–51.4%	51.4%	49.2–53.6%	52.5%	46.4–58.5%
	Non-Persistent	50.7%	48.6–52.8%	48.6%	46.4–50.8%	47.5%	41.5–53.6%
	Discontinued Biologic Therapy	12.0%	10.7–13.4%	11.9%	10.5–13.3%	12.5%	8.5–16.6%
	Restart After a ≥45 day gap	26.9%	25.0–28.8%	26.4%	24.5–28.3%	16.3%	11.9–20.8%
	Switch Biologic Therapy	11.8%	10.4–13.1%	10.3%	9.0–11.6%	18.6%	13.9–23.3%
AS	All	286		N=422		N=46	
	Persistent	42.0%	36.2–47.7%	40.0%	35.4–44.7%	56.5%	42.2–70.8%
	Non-Persistent	58.0%	52.3–63.8%	60.0%	55.3–64.6%	43.5%	29.2–57.8%
	Discontinued Biologic Therapy	13.3%	9.4–17.2%	14.0%	10.7–17.3%	13.0%	3.3–22.8%
	Restart After a ≥45 day gap	34.6%	29.1–40.1%	33.2%	28.7–37.7%	15.2%	4.8–25.6%
	Switch Biologic Therapy	10.1%	6.6–13.6%	12.8%	9.6–16.0%	15.2%	4.8–25.6%

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Distinct Regulation of T Helper Cell Differentiation By Biologic DMARD Therapy in Rheumatoid Arthritis. Shingo Nakayamada, Satoshi Kubo, Maiko Yoshikawa, Naoki Yunoue, Yusuke Miyazaki, Kazuyoshi Saito and Yoshiya Tanraka. University of Occupational and Environmental Health, Japan, Kitakyushu, Japan.

Background/Purpose: In the pathogenesis of rheumatoid arthritis (RA), T helper cells can differentiate into functionally distinct subsets, leading to the persistent inflammation and immune abnormality associated with the interactive activation between T cells and B cells. However, little is known about pathological T cell subset targeted by biologic DMARD (bDMARD) therapy such as TNF inhibitor and CTLA4-Ig. We investigated association between the phenotype of $CD4^+$ T helper cells and $CD19^+CD20^+$ B cells and disease activity in patients with RA, and responsiveness to bDMARD treatment.

Methods: Peripheral blood mononuclear cells were obtained from 86 patients with bio-naïve RA and 24 healthy donors (HD). The study included 25 patients treated with TNF inhibitors such infliximab, etanercept and adalimumab, and 15 patients treated with CTLA-4 Ig (abatacept). The blood samples were taken at baseline and week 24 after treatment. The phenotype of T cells and B cells was defined based on comprehensive 8-color flow cytometric analysis for human immune system termed "the Human Immunology Project" by NIH and FOCIS. The results were correlated with the clinical disease activity including the titer of RF and ACPA, CRP, ESR, MMP-3 and simplified disease activity index (SDAI).

Results: The proportion of effector memory T cells was higher in RA compared with HD, whereas the proportions of $CD4^+CXCR3^+$ Th1 cells and $CD4^+CCR6^+$ Th17 cells were not different between RA and HD. The frequency of $CD4^+CXCR5^+ICOS^+$ activated Tfh cells was significantly increased and correlated with RF titer in patients with RA. For B cell subsets, the proportions of $CD19^+CD20^+CD27^-IgD^-$ effector B cells and $CD19^+CD20^-CD38^+$ plasmablasts closely correlated with CRP, ESR and MMP-3. TNF inhibitors and abatacept markedly improved the disease activity scores such as SDAI at 24 weeks post-treatment. Abatacept significantly decreased the proportions of effector memory T cells which consisted of activated Tfh and Th17 cells, and consequently the proportion of naïve T cells increased after abatacept therapy. By contrast, the proportion of naïve T cells has decreased after TNF inhibitors, but those of effector T cells mainly Th17 cell and $CD19^+CD20^+CD27^+IgD^+$ IgM memory B cells has inversely increased. The percentage of $CD4^+CCR4^+CD25^+CD127^{low}$ regulatory T cells significantly decreased after treatment with abatacept and TNF inhibitors.

Conclusion: These results imply that TNF blockade and CD28 costimulation blockade may alter contradictory changes of both T helper cell and B cell differentiation, *i.e.* abatacept decreases activated Tfh cells and Th17 cells whereas TNF inhibitor increases Th17 cells and memory B cells, even though both treatments improve the disease activity in patients with RA. Thus, abnormal regulation of T helper cell differentiation independent of inflammation may underlie in the pathogenesis of RA and needs to be borne in mind in the design of new therapeutic strategies for this disease.

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ACR/ARHP Poster Session B
Spondyloarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment
Monday, November 17, 2014, 8:30 AM–4:00 PM

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Predicting Successful Long-Term Treatment with Tumour Necrosis Factor-Alpha Inhibitors in Patients with Psoriatic Arthritis. Karen M. Fagerli[1], Kath D. Watson[2], Jonathon Packham[3], Deborah PM Symmons[4], Kimme L. Hyrich[5] and. On behalf of the BSRBR[6]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Arthritis Research UK Centre for Epidemiology, University of Manchester, Manchester, United Kingdom, [3]Institute of Science and Technology in Medicine, Keele, United Kingdom, [4]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [5]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, [6]British Society for Rheumatology, London, United Kingdom.

Background/Purpose: Short-term efficacy of tumour necrosis factor-alpha inhibitor (TNFi) therapy in patients with psoriatic arthritis (PsA) is well documented. In observational studies, effectiveness has mainly been explored in the short term (1–3 years) and predictors of improved short-term drug-survival include male gender, concomitant methotrexate (MTX) use, etanercept (ETN) use and high CRP. The aim of this analysis was to identify predictors of long-term (5 years) persistent treatment with TNFi in patients with PsA.

Methods: We included PsA patients registered with the British Society for Rheumatology Biologics Register starting a TNFi (recruited 2002–2006). Demographics, disease activity (joint counts, patient reported outcomes and inflammatory markers), disability, comorbidities and previous/current treatments were recorded at baseline. Follow-up (biannual for 3 years and then annually) includes changes in treatment, disease activity and adverse events. We identified patients who had continued their initial treatment for 5 years (allowing pauses < 90 days). Univariate logistic regression was used to identify factors associated with 5 years persitent therapy – covariates included age, disease duration, gender, number of previously used non-biologic DMARDs, comorbidity, TNFi-type, co-medication, steroid use, disease activity score (DAS) 28, erythrocyte sedimentation rate (ESR), patient global assessment, tender and swollen joints, current smoking and Health Assessment Questionnaire (HAQ). Age, gender and variables with p-value < 0.25 were included in a multivariate model and a backward section was performed to fit the final model.

Results: We included 666 patients starting TNFi (table). At 5 years, 312 (46.8%) patients were still on their initial treatment. Gender, disease duration, TNFi-type, comorbidity, tender joints, current smoking and HAQ were relevant predictors in univariate analysis ($p<0.25$). Concomitant MTX was not a predictor, neither in the whole cohort or when stratified by TNFi-type, but only 14 patients received infliximab (IFX) as monotherapy. Male gender, absence of baseline comorbidity and use of ETN or adalimumab (ADA) rather than IFX were independently associated with persistent treatment at 5 years (Table). HAQ, disease duration, tender joint count and current smoking were not significant predictors in the multivariate model.

Conclusion: Among this severe cohort of patients with PsA who initiated a TNFi prior to 2007, almost 50 percent were still on their initial treatment at 5 years. The only patient characteristics predicting this were gender and baseline comorbidity status which limits applicability to clinical practice. Concomitant MTX was not a significant predictor of long-term treatment persistence, suggesting an absence of a beneficiary effect across all TNFi therapies, opposed to that seen in rheumatoid arthritis.

Table Baseline variables and logistic regression predicting continued treatment at 5 years

		Univariate analysis	Final multivariate model	
	Baseline	**OR (95% CI)[e]**	**OR (95% CI)[e]**	**p-value**
Females (n(%))	352 (52.9)	0.54 (0.40–0.74)	0.55 (0.40–0.75)	<0.001
Age (years)	45.83 (11.05)[a]	1.01 (0.99–1.02)	1.01 (1.00–1.03)	0.052
Disease duration (years)	12.71 (8.75)[a]	1.02 (1.00–1.04)	–	–
Previously used DMARDs	3 (2–4)[b]	0.92 (0.74–1.14)	–	–
TNFi (n(%)) Etanercept	365 (54.8)	REF	REF	REF
Infiximab	196 (29.4)	0.52 (0.37–0.75)	0.55 (0.38–0.78)	0.001
Adalimumab	105 (15.8)	0.87 (0.53–1.34)	0.89 (0.57–1.39)	0.622
Current smoker (n(%))	111 (21.0)	0.62 (0.41–0.95)	–	–
Comorbidity[c] (n(%))	366 (54.9)	0.62 (0.46–0.85)	0.60 (0.44–0.84)	0.002
Co-medication (n(%)) None	190 (28.5)	REF	–	–
MTX[d]	396 (59.5)	0.87 (0.61–1.23)	–	–
Other	80 (12.0)	0.70 (0.41–1.19)	–	–
Baseline steroid use (n(%))	156 (23.4)	0.84 (0.59–1.21)	–	–
Global (0–100)	70.97 (20.99)[a]	1.00 (0.99–1.01)	–	–
DAS 28	6.05 (1.19)[a]	0.98 (0.85–1.11)	–	–
Tender joints (28 joint-count)	13 (7–19)[b]	0.98 (0.96–1.00)	–	–
Swollen joints (28 joint-count)	8 (4–12)[b]	1.00 (0.98–1.03)	–	–
ESR (mm/hr)	33 (18–57)[b]	1.00 (1.00–1.01)	–	–
HAQ (0–3)	1.88 (1.38–2.25)[b]	0.72 (0.57–0.92)	–	–
Reason for discontinuation				
Inefficacy (n(%))	125 (35.3)			
Adverse events (n(%))	102 (28.8)			
Other/missing (n(%))	127 (35.9)			

OR=Odds ratio [a]mean (standard deviation) [b]median (inter-quartile range) [c]≥1 of (previous or current) hypertension, angina, MI, stroke, epilepsy, asthma, chronic obstructive airway disease, peptic ulcer

disease, liver disease, renal disease, tuberculosis, demyelinating disease, diabetes, depression, cancer [d]alone or in combination with other DMARD [e]per unit increase (in continuous variables).

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Apremilast, an Oral Phosphodiesterase 4 Inhibitor, Is Associated with Long-Term (52-Week) Improvement in the Signs and Symptoms of Psoriatic Arthritis in DMARD-Naive Patients: Results from a Phase 3, Randomized, Controlled Trial. Alvin Wells[1], Adewale O. Adebajo[2], Jacob A. Aelion[3], Paul Bird[4], Alan Kivitz[5], Frédéric Lioté[6], Piercarlo Sarzi-Puttini[7], ChiaChi Hu[8], Randall M. Stevens[8] and Christopher J. Edwards[9]. [1]Rheumatology & Immunotherapy Center, Franklin, WI, [2]University of Sheffield, Sheffield, United Kingdom, [3]West Tennessee Research Institute, Jackson, TN, [4]Combined Rheumatology Practice, Kogarah, Australia, [5]Altoona Arthritis & Osteoporosis Center, Duncansville, PA, [6]Hôpital Lariboisière & University Paris Diderot, Paris, France, [7]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy, [8]Celgene Corporation, Warren, NJ, [9]University Hospital Southampton, Southampton, United Kingdom.

Background/Purpose: Apremilast (APR), an oral phosphodiesterase 4 inhibitor, helps regulate the immune response that causes inflammation and skin disease associated with psoriatic arthritis (PsA). PALACE 4 compared the efficacy and safety of APR with placebo in patients with active PsA who were DMARD-naive.

Methods: Patients were randomized (1:1:1) to placebo, APR 20 mg BID (APR20), or APR 30 mg BID (APR30). Patients whose swollen and tender joint counts (SJC and TJC) had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if they were initially randomized to placebo, or continued on their initial APR dose. At Week 24, all remaining placebo patients were re-randomized to APR20 or APR30. The analysis comprises data from Weeks 0 to 52.

Results: At baseline, median PsA duration among patients in the full analysis set, overall, was 1.1 years; median SJC was 9.0 and median TJC was 16.0. At Week 16, significantly greater proportions of patients receiving APR achieved modified American College of Rheumatology 20 (ACR20) response (primary endpoint) (placebo: 15.9%; APR20: 28.0% [$P=0.0062$]; APR30: 30.7% [$P=0.0010$]) and modified ACR50 response (placebo: 4.5%; APR20: 11.4% [$P=0.0173$]; and APR30: 11.4% [$P<0.0181$]). ACR70 response was observed in 1.1%, 4.0%, and 4.0% of patients receiving placebo, APR20, and APR30, respectively. Median percent change in SJC at Week 16 was significantly greater with APR compared with placebo (placebo: -16.7%; APR20: -50.0% [$P=0.0001$]; APR30: -42.9% [$P=0.0001$]). Median percent change in TJC at Week 16 was also significantly improved with APR30 compared with placebo (placebo: -8.3%; APR20: -29.5% [$P=0.0007$]; APR30: -33.3% [$P=0.0001$]). At Week 52, modified ACR20/ACR50/ACR70 response was achieved by 53.4%/27.1%/13.7% and 58.7%/31.9%/18.1% of patients continually treated with APR20 or APR30, respectively, from baseline. Among these patients, improvements in SJC/TJC were sustained over 52 weeks; at Week 52 median percent change in SJC/TJC was -89.4%/-67.1% (APR20) and -100.0%/-66.7% (APR30). Consistent results were demonstrated in patients randomized to placebo at baseline and re-randomized to APR20 or APR30 at Week 16 or 24 who completed Week 52 (Table). The most common adverse events (AEs) reported among patients receiving either APR dose during the placebo-controlled period were nausea (12.6%), diarrhea (9.4%), and headache (6.0%). The nature and severity of AEs did not change with long-term exposure through 52 weeks.

Conclusion: Over 52 weeks, APR demonstrated clinically meaningful, sustained improvements in the signs and symptoms of PsA in DMARD-naïve patients. APR demonstrated an acceptable safety profile and was generally well tolerated.

Table 1. Efficacy Outcomes at Week 52 in Patients Receiving APR From Baseline (Data as Observed)

	APR20 n = 132	APR30 n = 141
ACR20, n/m (%)	70/131 (53.4)	81/138 (58.7)
ACR50, n/m (%)	35/129 (27.1)	44/138 (31.9)
ACR70, n/m (%)	18/131 (13.7)	25/138 (18.1)
SJC (0–76)		
Baseline, median	9.0	8.0
Median % change	−89.4	−100.0
TJC (0–78)		
Baseline, median	17.0	15.0
Median % change	−67.1	−66.7

Note: The n reflects the number of patients who completed 52 weeks; actual number of patients available for each endpoint may vary. Baseline values presented were based on the patients who had data at Week 52. n/m = number of responders/number of patients with sufficient data for evaluation.

Disclosure: A. Wells, Celgene Corporation, 2; **A. O. Adebajo**, None; **J. A. Aelion**, Ardea, Astra Zeneca, Bristol-Myers Squibb, Celgene Corporation, Centocor, Galapagos, Genentech, GlaxoSmithKline, Human Genome Sciences, Janssen, Eli Lilly, Merck, Mesoblast, Novartis, Novo Nordisk, Pfizer Inc, Roche, UCB Biosciences, Sanofi-Aventis, Taked, 2, Ardea, Astra Zeneca, Bristol-Myers Squibb, Celgene Corporation, Centocor, Galapagos, Genentech, GlaxoSmithKline, Human Genome Sciences, Janssen, Eli Lilly, Merck, Mesoblast, Novartis, Novo Nordisk, Pfizer Inc, Roche, UCB Biosciences, Sanofi-Aventis, Taked, 5, AbbVie, Amgen, and UCB, 8; **P. Bird**, Celgene Corporation, 2; **A. Kivitz**, Amgen, Janssen, Eli Lilly, Novartis, Pfizer Inc, and UCB, 2, Amgen, Janssen, Eli Lilly, Novartis, Pfizer Inc, and UCB, 5, Pfizer Inc, 8; **F. Lioté**, Celgene Corporation, 2, Celgene Corporation, 5; **P. Sarzi-Puttini**, Abbvie, MSD, Roche, UCB and Alpha-Wassermann, 2; **C. Hu**, Celgene Corporation, 3, Celgene Corporation, 1; **R. M. Stevens**, Celgene Corporation, 1, Celgene Corporation, 3; **C. J. Edwards**, Celgene Corporation, Pfizer Inc, Roche, and Samsung, 2, Celgene Corporation, Pfizer Inc, Roche, and Samsung, 5, Abbott, Glaxo-SmithKline, Pfizer Inc, and Roche, 8.

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Economic and Comorbidity Burden Among Moderate-to-Severe Psoriasis Patients Comorbid with Psoriatic Arthritis. Steven R Feldman[1], Yang Zhao[2], Lizheng Shi[3], Jackie Lu[2] and MaryHelen Tran[2]. [1]Wake Forest University School of Medicine, Winston-Salem, NC, [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [3]Tulane University, New Orleans, LA.

Background/Purpose: Psoriasis (PsO) and psoriatic arthritis (PsA) are associated with substantial economic and comorbidity burdens. However, the burden among PsO patients comorbid with PsA has not been evaluated in the biologics era. This study aimed to compare the comorbidity burden, healthcare resource utilization, and costs between moderate-to-severe PsO patients comorbid with PsA and matched controls.

Methods: Adults (18–64 years) with ≥2 distinct PsO diagnoses (ICD-9-CM: 696.1) were identified in the OptumHealth Reporting and Insights claims database (01/2007–03/2012). Moderate-to-severe PsO patients were selected as those receiving ≥1 systemic or phototherapy during the 12-month study period following the index date (randomly selected date after the first PsO diagnosis); PsO patients comorbid with PsA (PsO+PsA cases) were further selected as those with ≥2 distinct PsA diagnoses (ICD-9-CM: 696.0) between 01/2007 and the index date or during the 12-month study period. Controls were free of PsO and PsA in the entire claims history and matched 1: 1 with PsO+PsA cases on age, gender, and geographic region. All patients had at least 12 months of continuous enrollment after the index date. Multivariate regression models were performed to examine the impact of PsO+PsA on comorbidities, medication use, and healthcare utilization and costs between cases and controls, adjusting for demographics, index year, insurance type, non-PsO/PsA related comorbidities. Adjusted cost differences between cases and controls were also estimated.

Results: A total of 1,230 matched pairs of PsO+PsA patients and controls were selected, with mean age 48.5 years and 52.1% of male. During the 12-month period, PsO+PsA patients had significantly higher disease burden in major PsO/PsA related comorbidities assessed than controls, with the top 4 most common being hypertension (35.8% vs. 23.5%), hyperlipidemia (34.6% vs. 28.5%), rheumatoid arthritis (16.6% vs. 0.7%) and diabetes (15.9% vs. 10.0%). Controlling for between-group differences, PsO+PsA patients had more number of prescription medications filled (IRR=2.3), and were more likely to have any inpatient admission (OR=1.6), emergency department (OR=1.3), and outpatient visit (OR=62.7) compared with controls (all $p<0.05$). Additionally, PsO+PsA patients incurred significantly higher total, pharmacy, and medical costs (adjusted annual costs differences: $23,160, $17,696 and $5,077 per patient, respectively, all $p<0.01$) than controls.

Conclusion: Compared with matched controls without PsO and PsA, moderate-to-severe PsO patients comorbid with PsA were more likely to have PsO/PsA-related comorbidities and incurred significantly higher healthcare utilization and costs.

Disclosure: S. R. Feldman, Causa Technologies, Medical Quality Enhancement Corp., 1, Causa Technologies, 4, Doak, Pfizer Inc., Pharmaderm, and SkinMedica, Inc., 9,

Abbott Labs, Amgen, Astellas, Centocor Ortho Biotech Inc., Dermatology Foundation, Galderma, Leo Pharma Inc., Pharmaderm, Sanofi-Aventis, Stiefel/GSK, and Taro, 8, Abbott Labs, Amgen, Astellas, Caremark, Celgene, Coria Laboratories, Galderma, Gerson Lehrman Group, Hanall Pharmaceutical Co. Ltd., Kikaku, Leo Pharma Inc., Medicis Pharmaceutical Corporation, Medscape, Merck & Co., Inc., Merz Pharmaceuticals, Novan, 5, Novartis Pharmarceutical Corporation, Peplin Inc., Pfizer Inc., Photomedex, Reader's Digest, Stiefel/GSK, Suncare Research, and US Department of Justice, 5, Abbott Labs, Amgen, Anacor Pharmaceuticals Inc., Astellas, Celgene, Centocor Ortho Biotech Inc., Galderma, Medicis Pharmaceutical Corporation, SkinMedica Inc., and Stiefel/GSK, 2, Informa Healthcare and Xlibris, 7, Acuderm, Advanced Tissue Sciences, Allergan, Aventis, Bristol-Myers Squibb, Combe, Curatek, Ferndale, Fujisawa, Hermal, Hoffman LaRoche, Galderma, Genderm, Glaxo Wellcome, Hill, Janssen, Mayrand, NeoStrata, Neutrogena, Novartis, Oclassen, Ortho, 9, Person & Covey, Proctor & Gamble, RJR Nabisco, Schering-Plough, Shelton, SmithKline, Stiefel, 3M, United Catalyst, Upjohn and Wolff Systems, 9; **Y. Zhao**, Novartis Pharmaceuticals Corporation, 3; **L. Shi**, Novartis Pharmaceuticals Corporation, 5; **J. Lu**, Novartis Pharmaceuticals Corporation, 9; **M. Tran**, Novartis Pharmaceuticals Corporation, 3.

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Better Performance of the Leeds and Sparcc Enthesitis Indices Compared to the Mases in Patients with Peripheral Spondyloarthritis during Treatment with Adalimumab. Philip Mease[1], Filip Van den Bosch[2], Joachim Sieper[3], Aileen L. Pangan[4], Nupun A. Varothai[4] and In-Ho Song[5]. [1]Swedish Medical Center and University of Washington, Seattle, WA, [2]Ghent University Hospital, Ghent, Belgium, [3]Charité Universitätsmedizin Berlin, Berlin, Germany, [4]AbbVie Inc., North Chicago, IL, [5]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany.

Background/Purpose: Peripheral spondyloarthritis (pSpA) is characterized by arthritis, enthesitis, and/or dactylitis. Enthesitis is considered a core outcome domain for SpA; however, there is no clear recommendation which of the available enthesitis tools should be used. The objective of this analysis was to evaluate the validity of different enthesitis indices in patients (pts) with non-psoriatic pSpA during treatment with adalimumab (ADA).

Methods: ABILITY-2 is a multicenter phase 3 study. Eligible pts were age ≥18 yrs, fulfilled ASAS pSpA criteria, and had active disease. Pts were randomized to ADA 40 mg every other week (wk) or placebo (PBO) for 12 wks followed by 144 wks of open-label ADA. 29 enthesitis sites based on Leeds (range 0–6) and SPARCC (Spondyloarthritis Research Consortium of Canada, 0–16) enthesitis indices, and the MASES (Maastricht Ankylosing Spondylitis Enthesitis Score, 0–13) were assessed during the study. Discriminatory capacity and sensitivity to change of enthesitis indices at wk 12 were calculated: mean differences from BL to wk 12 in ADA vs PBO-treated pts with corresponding 95% confidence limits, standardized mean differences, and Guyatt's effect sizes. Presence of enthesitis at each anatomical enthesitis site at BL and proportion of sites that show resolution or new onset enthesitis from BL to wk 12, ADA vs PBO, were analyzed.

Results: 165 pts (ADA 84/PBO 81) were randomized. At BL 143 (87%) had ≥1 enthesitis site. The Leeds and SPARCC enthesitis scores showed higher discriminatory ability and sensitivity to change compared to the MASES (Table). Individual enthesitis site analysis suggests that in the overall population the percent change from BL to wk 12 at the following sites may have higher discriminatory capacity to other more axial sites: Achilles tendon (ADA 52.8% vs PBO 13.5%), greater trochanter (42.6% vs 6.8%), lateral epicondyle humerus (63.9% vs 0%), and medial epicondyle humerus (51.2% vs 0%). Among enthesitis sites positive at BL, a greater proportion showed resolution at wk 12 among pts on ADA in the Achilles tendon (ADA 60.4% vs PBO 36.5%, $P=0.019$), medial epicondyle (73.2% vs 48.7%, $P=0.038$), and lateral epicondyle (80.6% vs 52.8%, $P=0.023$). Among sites negative at BL less new onset enthesitis was observed with ADA at the following sites: Achilles tendon (ADA 3.6% vs PBO 10.9%, $P=0.041$), lateral epicondyle (4.7% vs 15.1%, $P=0.006$), greater trochanter (3.4% vs 14.4%, $P=0.005$), quadriceps insertion patella (1.5% vs 7.0%, $P=0.034$), and medial condyle femoral (1.6% vs 9.2%, $P=0.009$).

Table. Enthesitis Index Mean Change (±SD) [95% CL] from Baseline to Week 12, SMD, and Guyatt's Effect Size*

	ADA	PBO	Mean Difference (ADA-PBO)	SMD	Guyatt's Effect Size
Leeds	−1.35 (±1.20) [−1.69, −1.02] n=51	−0.45 (±1.27) [−0.81, −0.09] n=51	−0.90 [−1.39, −0.42]	0.73	−1.07
SPARCC	−2.35 (±2.46) [−2.97, −1.73] n=63	−1.00 (±2.37)[−1.59, −0.41] n=65	−1.35 [−2.19, −0.51]	0.56	−0.99
MASES	−2.02 (±2.78) [−2.76, −1.28] n=57	−1.17 (±2.50) [−1.79, −0.55] n=65	−0.85 [−1.80, 0.10]	0.32	−0.81

*Among patients who had score ≥1 for that index. CL, confidence limit; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; SD, standard deviation; SMD, standardized mean difference; SPARCC, Spondyloarthritis Research Consortium of Canada.

Conclusion: In ABILITY-2, the LEEDS and SPARCC enthesitis indices showed better discriminatory capacity and sensitivity to change compared to the MASES during treatment with ADA in pSpA patients. Enthesitis sites showing higher discriminatory capacity are peripheral sites predominantly in the Leeds and SPARCC indices which may explain their better performance compared to the MASES, which has fewer peripheral sites.

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Risk of Non Melanoma Skin Cancer Among Medicare Psoriasis/Psoriasis Arthritis Patients. Huifeng Yun[1], K. L. Winthrop[2], Lang Chen[3], Wilson Smith[3], Benjamin Chan[2], Fenglong Xie[3], Allison Taylor[3], Ronac Mamtani[4], Frank I Scott[4], James D. Lewis[5] and Jeffrey R. Curtis[3]. [1]University of Alabama at Birmingham School of Public Health, Birmingham, AL, [2]Oregon Health and Science University, Portland, OR, [3]University of Alabama at Birmingham, Birmingham, AL, [4]University of Pennsylvania, Philadelphia, PA, [5]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Many systemic treatments for psoriatic arthritis and psoriasis (PsA/PsO) are immune-modulating, which may increase the risk of non-melanoma skin cancer (NMSC). However, the comparative risks of NMSC are unclear. This study aimed to determine if the risks of NMSC associated with biologic and non-biologic treatments for PsA/PsO differ in their NMSC risk.

Methods: Using data from 2006–2011 for 100% of patients with patients with PsA and PsO, we defined separate PsA and PsO cohorts based upon >=1rheumatologist visit for PsA or >= 1 dermatologist visit for PsO, followed by a prescription or administration of etanercept (ETA), adalimumab (ADA), ustekinumab (UST), methotrexate (MTX), cyclosporine (CIC) or ultraviolet light therapy (UV). Patients could be in both cohorts if they meet criteria for each cohort. We identified new treatment episodes, defined specific to each drug as no use of that therapy in the prior 6 month 'baseline' period. Eligible subjects were continuously enrolled in Medicare Parts A, B and D in baseline and throughout follow-up. Patients contributing treatment episodes with history of organ transplantation, infection with human immunodeficiency virus, advanced kidney (hemodialysis-dependent), severe liver disease, or cancer diagnoses were excluded. Follow up started from drug initiation date and ended at the earliest date of: NMSC, a 90 day gap in current exposure, death, loss of Medicare coverage or Dec 31, 2011. We identified NMSC using validated claims-based algorithm with a list of physician diagnosis (ICD9 713.x) and procedure codes and calculated the incidence rate (IR) of NMSC for each treatment. Using pairwise propensity scores (PS), we compared NMSC risks between different treatments during follow-up using Cox regression adjusting for PS quintile.

Results: We identified 10,261 PsA and 31,052 PsO new treatments episodes. For the PsA cohort, 50% of treatment-episode exposure time was in common with the PsO, and 20% of PsO exposure time was in common with PsA exposures. During follow up, patients in the PsA cohort experienced 51 (ADA), 11 (CIC), 31 (ETA), 117 (MTX), <11 (UV) NMSCs, and the PsO cohort experienced 130 (ADA), 106 (CIC), 122 (ETA), 394 (MTX), 273 (UV) NMSCs. The overall IR in PsA was 23.2/1000, ranging from a low of 14.0 (ETA) to a high of 48.9 (CIC). The overall IR in the PsO cohort was 36.3/1000, ranging from 22.4 (ETA) to 53.6 (CIC). After PS quintile adjustment, significant associations with NMSC were observed for ADA compared to ETA (PsA, Hazard ratio (HR): 1.58, 95% confidence interval (CI): 1.01–2.51; PsO, HR: 1.33 95% CI: 1.03–1.71), and ADA compared to MTX (PsA, HR: 1.69, 95% CI: 1.17–2.44; PsO, HR: 1.32, 95% CI: 1.07–1.64).

Conclusion: Among psoriatic arthritis and psoriasis patients enrolled in Medicare, adalimumab had higher rates for NMSC relative to comparator treatments.

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Endocrine Co-Morbidities in Patients with Psoriatic Arthritis: A Population-Based Study. Devy Zisman[1], Ron Ilan Ashkenazi[2], Haim Bitterman[3], Guy Shallom[4], Ilan Feldhamer[4], Idit Lavi[5], Sari Greenberg-Dotan[4] and Arnon-Dov Cohen[4]. [1]The Ruth and Bruce Rappaport Faculty of Medicine, Haifa, Israel, [2]Carmel Medical Center, Haifa, Israel, [3]Chief Physician's Office, Clalit Health Services, Haifa, Israel, [4]Chief Physician's Office, Clalit Health Services, Tel Aviv, Israel, [5]Department of Community Medicine and Epidemiology, Carmel Medical Center, Haifa, Israel.

Background/Purpose: Co-morbidities associated with psoriatic arthritis (PsA) include cardiovascular, ophthalmic and gastrointestinal diseases. The aim of the study was to investigate endocrine co-morbidities in patients with psoriatic arthritis.

Methods: A cross-sectional study was performed in the database of Clalit Health Services, the largest healthcare provider in Israel, between 2000 and 2013. Patients with a diagnosis of PsA were identified (study group). For each of these patients, ten patients matched for age and gender, without a history of psoriasis, rheumatoid arthritis or ankylosing spondylitis were enrolled in the study as a control group. The following morbidities were analyzed: hypo- and hyperthyroidism, hypo- and hyperparathyroidism, hyperprolactinemia, Cushing's disease, Addison's disease, diabetes insipidus, diabetes mellitus (DM), pituitary adenoma, acromegaly and osteoporosis. A t-test was used to compare continuous variables and a chi-square test was used for categorical variables. A univariable model and multivariable logistic regression models were used to assess the association between PsA and endocrine co-morbidities.

Results: The study included 3161 patients with PsA, 1474 males (46.6%) and 1687 (53.4%) females, with a mean age of 58.36 ±15.42 years, and 31610 controls. Comparative analyses demonstrated higher prevalence of hypothyroidism (12.7% vs. 8.6% $p<0.0001$), Cushing's disease (0.3% vs. 0.1% $p<0.0001$), osteoporosis (13.2% vs. 9.1% $p<0.001$) and DM (27.9% vs. 20.7% $p<0.0001$) in the PsA population compared to the control group, respectively. The prevalence of hyperthyroidism, hypo- and hyperparathyroidism, hyperprolactinemia, Addison's disease, diabetes insipidus, pituitary adenoma and acromegaly was not statistically different between the two groups. In multivariate regression analysis models, hypothyroidism after adjustment for age and gender (OR 1.61 95%CI 1.43–1.80), DM after adjustment for age, gender, smoking, obesity and steroids use (OR 1.30 95% CI 1.18–1.42), Cushing's disease after adjustment for age, gender and steroids use (OR=3.79 95% CI 1.64–8.77) and osteoporosis after adjustment for age, gender, steroids use and smoking (OR=1.50 95% CI 1.33–1.70) had a higher prevalence in PsA patients.

Conclusion: A high prevalence of hypothyroidism, osteoporosis, DM and Cushing's disease was found in this cohort of PsA patients. It is recommended that medical practitioners be aware of and look for these co-morbidities while taking care of PsA patients.

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Treatment Effect of Ustekinumab on Fatigue in Patients with Psoriatic Arthritis: Results from a Phase 3 Clinical Trial. Christopher T. Ritchlin[1], Proton Rahman[2], Lluís Puig Sanz[3], Alice B. Gottlieb[4], Arthur Kavanaugh[5], Iain B. McInnes[6], Shu Li[7], Yuhua Wang[7], Rita Ganguly[8], Alan M. Mendelsohn[7] and Chenglong Han[8]. [1]University of Rochester Medical Center, Rochester, NY, [2]Memorial University of Newfoundland, St. John's, NF, [3]Universitat Autònoma de Barcelona, Barcelona, Spain, [4]Tufts Medical Center, Boston, MA, [5]University of California San Diego, La Jolla, CA, [6]University of Glasgow, Glasgow, United Kingdom, [7]Janssen Research & Development, LLC., Spring House, PA, [8]Janssen Global Services, LLC., Malvern, PA.

Background/Purpose: To assess the treatment effect of ustekinumab on fatigue using data from PSUMMIT 2.

Methods: Adult patients with active psoriatic arthritis (PsA) despite DMARD (N=132) and/or previous treatment with biologics (N=180) were randomized to receive ustekinumab 45mg, 90mg, or placebo (PBO) at wks 0, 4, and q12wks thereafter through week 40. PBO-treated patients crossed over to receive ustekinumab 45mg at weeks 24, 28 and q12wks through week 40. Fatigue was measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue, 0–52) and the vitality scales of SF-36 health survey questionnaire (SF-36 VT, 0–100). High scores indicate low severity in fatigue. Clinically meaningful improvement was defined as ≥4 point increase in FACIT-Fatigue or ≥3 point increase in SF-36 VT score from baseline. Disease activity was measured by disease activity score using 28 joints (DAS28), and physical function was measured using Health Assessment Questionnaire (HAQ).

Results: At baseline, patients had a mean FACIT-Fatigue score of 25.8 and had a mean SF-36 VT score of 36.9, which was significantly below the values of the U.S. normal population (50), indicating severe fatigue. Both FACIT-Fatigue and SF-36 VT scores were significantly correlated with DAS28 ($r=0.42$, 0.38, respectively) and HAQ ($r=0.62$, 0.51, respectively) at baseline, and the improvements in FACIT-Fatigue and SF-36 VT scores were significantly correlated with improvement in DAS28 ($r=0.45$, 0.43, respectively) and improvement in HAQ scores ($r=0.43$, 0.41, respectively) at week 24. At week 24, patients who received ustekinumab achieved statistically significantly greater improvement in FACIT-Fatigue score (4.35 vs. 0.86, $p=0.002$) and in SF-36 VT score (3.87 vs. 0.67, $p=0.004$) compared with PBO. Compared to PBO, a greater proportion of ustekinumab-treated patients achieved a clinically meaningful improvement in FACIT-Fatigue (49% vs. 25.5%) or SF-36 VT (45% vs. 29.9%) (all $p<0.01$). No significant differences were observed between the ustekinumab 45 and 90mg groups. The treatment effect on fatigue was consistent across biologically-experienced and DMARD-experienced patients, and maintained through week 52. Patients who were randomized to PBO and switched to active treatment at week 24 achieved comparable improvement at week 52.

Conclusion: Ustekinumab therapy significantly reduces the symptom of fatigue in patients with active PsA. Clinically meaningful improvement in fatigue was observed within 3 doses of ustekinumab therapy.

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The Swedish Early Psoriatic Arhtritis (SWEPSA) Registry 5-Yeear Follow-up: Slow Radiographic Progression with Highest Scores in Male Feet and in Patients with Baseline X-Ray Abnormalities. Elke Theander[1], Tomas Husmark[2], Ulla Lindqvist[3], Per T Larsson[4], Annika Teleman[5], Gerd-Marie Alenius[6] and Mats Geijer[7]. [1]Skane University Hospital Malmö, Lund University, Malmö, Sweden, [2]Falu Hospital, Falun, Sweden, [3]Department of Medical Sciences, Rheumatology, University Hospital, Uppsala university, Uppsala, Sweden, [4]Department of Rheumatology, Karolinska University Hospital, Stockholm, Sweden, [5]Spenshult Rheumatological Hospital, Oskarström, Sweden, [6]Department of Public Health and Clinical Medicine, Rheumatology, Umeå University Hospital, Umeå, Sweden, [7]Skåne University Hospital, Lund, Center for Medical Imaging and Physiology, Lund, Sweden.

Background/Purpose: The aim of this study is to describe early X-ray findings in psoriatic arthritis (PsA) patients from the SwePsA registry using the Wassenberg score, evaluate progression of structural damage, analyze correlations to clinical disease parameters and identify predictors of progressive radiographic joint disease.

Methods: Out of 197 SwePsA patients followed for 5 years, 72 (38% of the women and 35% of the men) had radiographs of hands and feet performed

at the 5-year follow-up. According to the SwePsA protocol hand and feet radiographs should be performed in polyarticular disease or when these joints showed signs of inflammation at baseline, and repeated during follow-up. Reading (MG) in chronological order was centralized. Clinical data were collected according to the SwePsA protocol.

Results: Mean (SD) baseline age of the 43 women and 29 men was 48.7 (15.0) and 46.4 (14.5) years respectively. While in the total SwePsA cohort women had higher clinical disease activity (Theander et al, ARD 2014), in this sub-cohort mean baseline DAS28 / DAPSA were similar in women and men (3.94 / 22.27 and 3.73 / 21.63, respectively, ns). However, radiographic abnormalities were more pronounced in men:

Baseline x-rays: Total Wassenberg score was 0 (no abnormalities) in 55% of women and 46% of men. Scores over 10 were unusual and only found in one women and one man. Mean (SD) total scores for women and men at baseline were 1.38 (2.44) vs 3.05 (4.04) respectively, p=0.044, erosion scores 0.30 (0.88) vs 1.17 (2.27), p=0.025, proliferation scores 1.30 (1.99) vs 1.79 (2.41), p=0.35. Feet scores at baseline were 0.30 (0.74) vs 0.93 (1.69), p = 0.039.

5-year follow-up x-rays: Total score was 0 in 42% of women but only in 17% of men (p=0.018). Scores over 10 were now found in 7.2% of women and in 17% of men. Mean (SD) total scores for women and men were 3.37 (4.85) vs 7.79 (12.46), p=0.034, erosion scores 0.86 (1.68) vs 3.41 (8.20), p=0.051, proliferation scores 2.56 (3.49) vs 4.62 (4.92), p=0.041. Feet scores at 5-year follow-up were 0.84 (2.13) vs 2.35 (3.92), in women and men, p=0.028, hand scores 2.58 (3.74) vs 5.55 (8.53), p=0.047.

Baseline and 5-year scores were highly correlated (for total scores: Spearman rho 0.752, p=0.000). Baseline total score correlated with ESR (rho: 0.364, p=0.004) and 5-year score with swollen joint count (rho 0.310, p=0.016), higher BASDAI showed a trend to be associated with lower total score (rho -0.285, p= 0.058).

Male gender and higher total baseline score were the only predictors of radiographic abnormalities after 5 years: OR (male/female): 4.42 (95% CI: 0.35–8.49) p=0.034. Baseline total score: OR: 2.23 (1.80–2.65), p=0.000. Only the baseline Wassenberg score was an independent predictor of radiographic progression.

Disease activity, inflammatory markers, joint counts, delay before inclusion and smoking did not predict 5-year Wassenberg score. None of the 15 patients with the highest scores/progression had received TNF-blockers.

Conclusion: Radiographic progression in early PsA is slow in general, early prevalent in male feet and predicted by baseline radiographic findings. Thus scoring of hand **and** feet X-rays at baseline cannot be substituted by clinical signs, especially not in men.

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Prevalence of Enthesitis and Dactylitis, Impact on Disease Severity and Evolution over 12 Months in Psa Patients Treated with Anti-TNF in a Real-World Setting. Proton Rahman[1], Denis Choquette[2], William Bensen[3], Majed Khraishi[4], Saeed Shaikh[3], Regan Arendse[5], Isabelle Fortin[6], Andrew Chow[7], Maqbool Sheriff[8], Eliofotisti Psaradellis[9], John S. Sampalis[9], Susan Otawa[10], Francois Nantel[10], Allen J Lehman[10] and May Shawi[10]. [1]Memorial University of Newfoundland, St. John's, NF, [2]Notre Dame Hospital, Montreal, QC, [3]McMaster University, Hamilton, ON, [4]Nexus Clinical Research, St John's, NF, [5]University of Saskatchewan, Saskatoon, SK, [6]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, [7]Credit Valley Rheumatology, Mississauga, ON, [8]Nanaimo Regional General Hospital, Nanaimo, BC, [9]JSS Medical Research, Montreal, QC, [10]Janssen Inc., Toronto, ON.

Background/Purpose: Spondyloarthritis, including psoriatic arthritis (PsA), is characterized by inflammatory arthritis affecting axial and peripheral joints. It is commonly associated with extra-articular and peri-articular manifestations (PAMs) including dactylitis and enthesitis. The aim of this analysis was to evaluate the point prevalence of enthesitis and dactylitis at the time of anti-TNF initiation, their impact on disease severity, and their evolution over time in patients with active PsA treated in a routine clinical practice setting.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis (RA), ankylosing spondylitis (AS), or PsA with infliximab or golimumab as first biologics or after having been treated with a biologic for <6 months. In this analysis, 132 PsA patients enrolled between 2010 and 2013 were included. The time to no PAM (enthesitis/dactylitis) was assessed with the Kaplan-Meier (KM) estimator of the survival function.

Results: At baseline, mean (SD) age and disease duration were 49.1 (10.8) years and 5.8 (7.1) years, respectively. The mean (SD) DAS28 score was 4.0 (1.3). A total of 73 (55.3%) patients had enthesitis and/or dactylitis at baseline; 27 (20.5%) patients had enthesitis, 24 (18.2%) had dactylitis, 22 (16.7%) had both dactylitis and enthesitis, while 59 (44.7%) had none. Significant differences, in disease parameters were observed at baseline based on the presence of a PAM. Specifically, mean (SD) DAS28 was 4.6 (0.8) among patients with enthesitis, 3.9 (1.4) in patients with dactylitis, 4.3 (1.1) in patients with both, and 3.6 (1.4) in patients with none (P=0.023). Similarly, mean (SD) HAQ-DI was 1.5 (0.5), 1.1 (0.8), 1.0 (0.6), and 0.9 (0.6), respectively, in these patient subgroups (P=0.004). A statistical trend was observed for morning stiffness which was 36.7 (34.6), 65.7 (48.1), 54.5 (48.9), and 41.9 (42.3) min in patients with enthesitis, dactylitis, both, and none, respectively (P=0.067).

At 6 and 12 months of treatment, 29.1% and 30.4% of patients with available information, respectively, had enthesitis/dactylitis. Treatment with anti-TNF for 12 months resulted in a significant reduction in the prevalence of PAM (P=0.004). Specifically, among patients with enthesitis and/or dactylitis at baseline who had available data at 12 months, 61.1% did not present any manifestation after 12 months of treatment; while 27.3% of patients without enthesitis/dactylitis at baseline developed a new PAM. Survival analysis showed that, for patients with enthesitis/dactylitis at baseline, the KM-based mean time to no PAM was 9.8 months.

Conclusion: A high prevalence of enthesitis/dactylitis was observed at anti-TNF treatment initiation (55.3%). Patients with enthesitis, dactylitis or both had increased disease activity compared to patients without a PAM. Treatment with infliximab or golimumab for 12 months was associated with a significant reduction in PAMs with low incidence of new cases.

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Correlation of Individual HAQ Questions with Disease Activity Measures in Psoriatic Arthritis: Implications for Instrument Reduction. Denis Choquette[1], Carter Thorne[2], Majed Khraishi[3], Isabelle Fortin[4], Regan Arendse[5], Andrew Chow[6], John Kelsall[7], Milton Baker[8], Julie Vaillancourt[9], John S. Sampalis[9], Francois Nantel[10], Allen J Lehman[10], Susan Otawa[10] and May Shawi[10]. [1]Notre Dame Hospital, Montreal, QC, [2]Southlake Regional Health Centre, Newmarket, ON, [3]Nexus Clinical Research, St John's, NF, [4]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, [5]University of Saskatchewan, Saskatoon, SK, [6]Credit Valley Rheumatology, Mississauga, ON, [7]The Mary Pack Arthritis Centre, Vancouver, BC, [8]University of Victoria, Victoria, BC, [9]JSS Medical Research, Montreal, QC, [10]Janssen Inc., Toronto, ON.

Background/Purpose: The Health Assessment Questionnaire (HAQ) is commonly used for assessing patient-reported functional status and disease activity in psoriatic arthritis (PsA). However, it has been critiqued for being time-consuming, not easily scored and thus, not contributing to decisions in routine care (1,2). The aim of this analysis was to describe the correlation of individual HAQ questions with patient and physician reported measures used in PsA and to examine whether the instrument could be reduced to better reflect routine clinical practice.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with infliximab or golimumab as first biologics or after <6 months of biologic treatment. Data from PsA patients treated with infliximab or golimumab in 2006–2013 were used. The correlation of each HAQ question with patient and physician (pain, patient global assessment (PtGA), SJC28, TJC28 and physician global assessment (MDGA)) reported measures were described with the Pearson's correlation coefficient. The impact of each HAQ question on the need for help in each HAQ domain was assessed with logistic regression. Factor analysis was used to assess the variability due to each question in HAQ.

Results: A total of 183 PsA patients with 596 HAQ assessments were included. Individual HAQ questions correlated at different extents with each PsA measures (Table 1). All questions showed higher correlations with PtGA and pain compared to MDGA. Regarding patient reported outcomes, Ques-

tion 5A ("Wash / dry your entire body") showed the highest correlation, specifically with pain.

The majority of HAQ questions were significantly associated with the need for help within their corresponding ability category, with the exception of questions Q3B, Q3C, Q4B, Q5C and Q8B.

The results of factor analysis showed that 2 (Q1A and Q3B) out of the 20 HAQ questions accounted for 61.5% of its matrix variance, suggesting that the question on the ability to "dress, tie shoelaces and do buttons", as well as the question on the ability to "lift a full cup or glass" may be the main drivers of HAQ in PsA.

Conclusion: Variability exists in the correlation of individual HAQ questions with patient and physician reported PsA measures. Pain and PtGA are significantly associated with the various domains of HAQ, while clinical outcomes (SJC28 and TJC28) and MDGA are less important. Among PsA patients, the HAQ is driven by components related to dressing and grooming and to eating abilities, suggesting that PsA patients may be facing different challenges than RA patients. This may have implications from an occupational health perspective and in the design of a shorter self-report instrument more suitable for PsA patients.

Table 1. Correlation* between Individual HAQ Questions and PsA Outcome Measures

HAQ Questions	Pain	PtGA	SJC28	TJC28	MDGA
Dressing and Grooming (Q1 A/B)	0.57/0.42	0.53/0.37	0.35/0.28	0.39/0.35	0.46/0.33
Arising (Q2 A/B)	0.57/0.56	0.56/0.54	0.28/0.27	0.37/0.37	0.41/0.40
Eating (Q3 A/B/C)	0.41/0.69/0.43	0.35/0.32/0.41	0.32/0.24/0.31	0.35/0.28/0.37	0.31/0.26/0.37
Walking (Q4 A/B)	0.51/0.57	0.49/0.54	0.29/0.33	0.37/0.39	0.43/0.43
Hygiene (Q5 A/B/C)	0.67/0.48/0.53	0.45/0.44/0.48	0.27/0.18/0.25	0.34/0.34/0.32	0.37/0.32/0.31
Reach (Q6 A/B)	0.38/0.57	0.40/0.53	0.26/0.29	0.52/0.35	0.36/0.40
Grip (Q7 A/B/C)	0.34/0.43/0.54	0.33/0.39/0.30	0.28/0.28/0.27	0.37/0.35/0.39	0.29/0.35/0.27
Activities (Q8 A/B/C)	0.56/0.57/0.55	0.53/0.55/0.53	0.27/0.27	0.37/0.38/0.41	0.40/0.40/0.42
HAQ-DI score	***0.67***	***0.63***	***0.38***	***0.50***	***0.51***

** Levels of correlation are Weak: r <0.30; Moderate: r =0.30 - 0.39; Strong: r =0.40 - 0.69; and Very Strong: r ≥0.70.*

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Sustained Improvements in Workplace and Household Productivity and Social Participation with Certolizumab Pegol over 96 Weeks in Patients with Psoriatic Arthritis.

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Background/Purpose: Compared to the general population, patients (pts) with psoriatic arthritis (PsA) suffer greater amounts of disability and substantially lower employment rates.[1] The previous results from the RAPID-PsA study indicate significant improvements in work and household productivity and social participation with certolizumab pegol (CZP) vs placebo (PBO) up to Week (Wk) 24, which were maintained to Wk48.[2] The purpose of this report is to examine the long-term effect of CZP on workplace and household productivity in RAPID-PsA up to Wk96.

Methods: The ongoing RAPID-PsA trial (NCT01087788) is double-blind and PBO-controlled to Wk24, dose-blind to Wk48 and open-label to Wk216.[3] Pts had active PsA and had failed ≥1 DMARD. Pts originally randomized to CZP (200mg Q2W or 400mg Q4W, following 400mg loading dose [LD] at Wks 0, 2, 4) continued on their assigned dose in the OLE; PBO pts entering dose-blind phase were re-randomized to CZP LD followed by CZP 200mg Q2W or 400mg Q4W after Wk24 or, for non-responders, Wk16. The validated arthritis-specific Work Productivity Survey (WPS),[4] administered Q4W from baseline (BL), assessed the impact of PsA on workplace and household productivity in the randomized set (RS). WPS responses (LOCF imputation) in pts originally randomized to CZP groups are summarized descriptively over 96 wks.

Results: 409 pts were randomized, of which 273 were assigned to CZP 200mg Q2W or CZP 400mg Q4W. Of the pts randomized to CZP, 91% completed Wk24, 87% Wk48 and 80% Wk96; 60.1% and 61.5% were employed at BL in the CZP 200mg Q2W and CZP 400mg Q4W groups, respectively. At BL, pts randomized to CZP reported on average ~1 wk of paid work, ~2 wks of household duties, and mean 3.7 days of social activities affected over previous month. In employed pts in both CZP groups, decreases in absenteeism and presenteeism reported to Wk24 were continued up to Wk96 (Table). The initial improvements in household productivity and increased participation in social activities reported in both CZP groups over 24 wks were maintained up to Wk96 (Table).

Conclusion: The initial improvements with CZP in workplace and household productivity, and participation in social activities were sustained up to 96 wks, suggesting long-term productivity benefits of CZP treatment in PsA pts.

References

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Table 1. Workplace and household productivity over 96 wks in the RAPID-PsA trial (RS population; LOCF)

WPS responses		CZP 200mg Q2W n = 138 Mean	CZP 200mg Q2W n = 138 Median	CZP 400mg Q4W n = 135 Mean	CZP 400mg Q4W n = 135 Median
Productivity at workplace (employed patients)					
Work days missed due to arthritis per month [a]	BL	2.0	0.0	1.6	0.0
	Wk24	0.2	0.0	0.6	0.0
	Wk96	0.3	0.0	0.4	0.0
Days with work productivity reduced by ≥50% due to arthritis per month [a, b]	BL	5.2	0.0	5.1	0.0
	Wk24	1.3	0.0	2.1	0.0
	Wk96	0.7	0.0	1.5	0.0
Level of arthritis interference with work productivity (0–10 scale) [a, c]	BL	4.4	5.0	3.8	4.0
	Wk24	1.7	1.0	1.9	1.0
	Wk96	1.1	0.0	1.3	0.0
Household productivity and social participation (all patients)					
Household work days missed due to arthritis per month	BL	5.9	0.5	5.5	2.0
	Wk24	2.4	0.0	2.5	0.0
	Wk96	2.0	0.0	2.1	0.0
Household workdays with productivity reduced by ≥50% due to arthritis per month [b]	BL	7.1	4.5	7.1	5.0
	Wk24	2.9	0.0	3.5	0.0
	Wk96	2.2	0.0	2.3	0.0
Level of arthritis interference with household productivity (0–10 scale) [c]	BL	5.2	5.0	4.9	5.0
	Wk24	2.2	1.0	2.6	2.0
	Wk96	1.8	0.0	2.0	0.0
Days missed family/social/ leisure activities due to arthritis per month	BL	4.1	0.0	3.3	0.0
	Wk24	1.1	0.0	1.0	0.0
	Wk96	0.7	0.0	0.7	0.0

[a] Based only on employed pts at the specific visit; pts employed at BL (CZP 200mg Q2W/CZP 400mg Q4W): 83/83; [b] Does not include work days missed counted in the previous question; [c] 0–10 scale, 0 = no interference and 10 = complete interference.

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Disease Activity and Clinical Response Early in the Course of Treatment Predict Long-Term Outcomes in Psoriatic Arthritis Patients Treated with Certolizumab Pegol. Philip Mease[1], Roy Fleischmann[2], Owen Davies[3], Tommi Nurminen[4] and Désirée van der Heijde[5]. [1]Swedish Medical Center and University of Washington, Seattle, WA, [2]Metroplex Clinical Research Center, University of Texas, Dallas, TX, [3]UCB Pharma, Slough, United Kingdom, [4]UCB Pharma, Monheim, Germany, [5]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Early non-response to biologic therapy has been shown to be associated with a low probability of long-term response in rheumatoid arthritis[1] and psoriasis[2]. However, to date there is a shortage of data regarding early identification of non-responders in psoriatic arthritis (PsA). Such analyses may help avoid unnecessary exposure, increase cost-effectiveness and improve the chance of achieving long-term treatment goals. Here we aim to assess the association between disease activity (DA) and clinical response (CR) during the first 12 weeks (wks) of treatment, and attainment/lack of attainment of treatment targets at Wk48 in PsA patients (pts) receiving certolizumab pegol (CZP).

Methods: The relationship between DA state during the first 12 wks of treatment, and Minimal Disease Activity (minDA)3 or DAS28(CRP) <2.6 at Wk48 was assessed post hoc using data from the RAPID-PsA study (NCT01087788).4 DA state was defined using either DAS28(CRP) values: <2.6, 2.6–3.2, 3.2–5.1, >5.1; or PsARC response/non-response. Descriptive analyses are based on all pts randomized to CZP from Wk0. Pts that discontinued treatment during the first 12 wks were excluded from the analysis. For remaining pts, missing data were imputed using LOCF for DAS28 and PsARC, and NRI for minDA.

Results: A relationship between Wk2 DA state and Wk48 minDA was observed, with 68% (17/25) of pts with DAS28(CRP) <2.6 at Wk2 achieving Wk48 minDA, compared with 10% (5/52) of pts with Wk2 DAS28(CRP) >5.1. This trend was maintained at Wk12, by which point more pts had lower DA. 73% (57/78) of pts with Wk12 DAS28(CRP) <2.6 achieved Wk48 minDA, compared to 0% (0/26) of pts with Wk12 DAS28(CRP) >5.1 (Table A). When Wk48 DAS28(CRP) <2.6–a less stringent target that excludes enthesitis and skin manifestations - was used, a similar trend was observed, but more pts in each category achieved the target; however, still only 4% (1/26) of pts with Wk12 DAS28(CRP) >5.1 attained Wk48 DAS28(CRP) <2.6 (Table B). CR at Wk12 was also associated with likelihood of attaining minDA at Wk48: Of 153/256 (60%) CZP pts that achieved Wk12 DAS28(CRP) CR >1.2, 50% (76/153) achieved Wk48 minDA, compared to 32% (17/53) of pts with Wk12 DAS28(CRP) CR 0.6–1.2 and 12% (6/50) of Wk12 non-responders (DAS28[CRP] CR ≤0.6). PsARC response at Wk12 was also associated with Wk48 outcomes: 10.7% (6/56) of Wk12 PsARC non-responders achieved Wk48 minDA, compared to 47.7% (95/199) of Wk12 PsARC responders.

Conclusion: Using DA state and CR level at an early stage of CZP treatment, it was possible to identify PsA pts unlikely to achieve long-term treatment goals. This approach may enable physicians adopting a treat-to-target strategy to determine early on when to change therapy in pts not responding to CZP.

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Table:

A) Likelihood of achieving minDA at Wk48 based on DAS28(CRP) classification of DA at Baseline, Wk2, Wk8 and Wk12

Visit	DAS28(CRP) <2.6 n/N (%)	DAS28(CRP) 2.6–3.2 n/N (%)	DAS28(CRP) 3.2–5.1 n/N (%)	DAS28(CRP) >5.1 n/N (%)
Baseline	1/1 (100.0%)	2/6 (33.3%)	64/145 (44.1%)	32/120 (26.7%)
Week 2	17/25 (68.0%)	22/34 (64.7%)	55/159 (34.6%)	5/52 (9.6%)
Week 8	50/71 (70.4%)	23/38 (60.5%)	25/114 (21.9%)	1/39 (2.6%)
Week 12	57/78 (73.1%)	23/47 (48.9%)	19/105 (18.1%)	0/26

B) Likelihood of achieving DAS28(CRP) <2.6 at Wk48 based on DAS28(CRP) classification of DA at Baseline, Wk2, Wk8 and Wk12

Visit	DAS28(CRP) <2.6 n/N (%)	DAS28(CRP) 2.6–3.2 n/N (%)	DAS28(CRP) 3.2–5.1 n/N (%)	DAS28(CRP) >5.1 n/N (%)
Baseline	1/1 (100.0%)	3/6 (50.0%)	82/145 (56.6%)	38/120 (31.7%)
Week 2	22/25 (88.0%)	25/34 (73.5%)	68/159 (42.8%)	8/52 (15.4%)
Week 8	59/71 (83.1%)	24/38 (63.2%)	37/114 (32.5%)	3/39 (7.7%)
Week 12	66/78 (84.6%)	28/47 (59.6%)	28/105 (26.7%)	1/26 (3.8%)

Key to probability: Light grey: 10–20% Dark grey: 0–10%

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Early and Sustained Modified Psarc Response in Psoriatic Arthritis Patients Treated with Ustekinumab: Results from 2 Phase 3 Studies. Iain B. McInnes[1], Christopher T. Ritchlin[2], Proton Rahman[3], Lluís Puig Sanz[4], Alice B. Gottlieb[5], Shu Li[6], Michael Song[6], Bruce Randazzo[6], Yuhua Wang[6], Alan M. Mendelsohn[6] and Arthur Kavanaugh[7]. [1]University of Glasgow, Glasgow, United Kingdom, [2]University of Rochester Medical Center, Rochester, NY, [3]Memorial University of Newfoundland, St. John's, NF, [4]Universitat Autònoma de Barcelona, Barcelona, Spain, [5]Tufts Medical Center, Boston, MA, [6]Janssen Research & Development, LLC., Spring House, PA, [7]University of California San Diego, La Jolla, CA.

Background/Purpose: We have previously reported the efficacy and safety results of ustekinumab (UST), an IL-12/23 p40 inhibitor, in patients with active psoriatic arthritis (PsA) up to 2yrs of UST treatment from the PSUMMIT 1&II trials. Here, we describe the sustained effects of UST using the modified Psoriatic Arthritis Response Criteria (PsARC) response. Although not validated, the modified PsARC has been widely used in PsA clinical trials and clinical practice.

Methods: Adult PsA patients with active disease (≥5 SJC and ≥5 TJC; CRP≥0.3mg/dL [ULN 1.0 mg/dL]) despite DMARD and/or NSAID therapy (PSUMMIT 1, n=615; PSUMMIT 2, n=312 [of which 180 pts were previously treated with DMARD and/or NSAID, and prior anti-TNFα therapy]) were randomized to UST45mg, 90mg, or PBO at wks 0, 4, and q12wks, thereafter. PBO-treated pts were crossed over to UST45mg at wks24 and 28 followed by q12wk dosing. At wk16, patients with <5% improvement in TJC & SJC entered blinded early escape [EE] (PBO→UST45mg; UST45mg→90mg; 90mg→90mg). No concomitant DMARDs with the exception of MTX (approx 50% of patients in each study) were permitted. Patients were considered a responder using the modified PsARC if improvement was demonstrated in ≥ 2 (including≥1 of the joint criteria) of the following criteria and no deterioration was noted in the other criteria: ≥30% decrease in the swollen joint count, ≥30% decrease in the tender joint count, ≥20% improvement in the patient's overall assessment (VAS), and ≥20% improvement in the physician's overall assessment (VAS). The proportion of patients who were modified PSARC responders and ACR 20 non-responders at wk28 were assessed.

Results: Modified PSARC results are summarized in Table 1. Statistically significantly higher PSARC response rates were observed as early as wk4 for both UST groups vs PBO in the PSUMMIT 1 trial and statistically significantly higher responses were also observed at wks 8, 12 and 24 for both UST dose groups vs PBO in both trials. Responses in both UST dose groups continued to increase after wk24, reached a plateau at wk28 and were maintained through wk52. Patients who were initially randomized to PBO and crossed over to 45mg achieved similar responses to those originally randomized to UST. Higher PSARC responses were consistently observed at wk8–24 for both UST groups vs PBO regardless of baseline MTX status. The early onset of PSARC responses observed was consistent with early onset of ACR20 responses. UST was generally well-tolerated.

Conclusion: Significantly higher PSARC responses were observed as early as wk4–8 for both UST dose groups vs PBO. Improvements observed at wk24 continued to increase at wk28 and were sustained through wk52.

Table 1: Proportion of patients achieving modified PSARC response; randomized patients

	PSUMMIT 1 (TNF naïve)		
	PBO/PBO→45mg†	**UST45mg**	**UST90mg**
Pts randomized	206	205	204
wk4	27.5% (56/204)	37.1% (76/205)*	38.5% (77/200)*
wk8	33.2% (67/202)	51.2% (104/203)***	55.6% (110/198)***
wk12	37.1% (75/202)	59.9% (121/202)***	60.9% (120/197)***

wk24	37.4% (77/206)	56.1% (115/205)***	64.7% (132/204)***
wk28	68.6% (129/188)	67.3% (136/202)	76.1% (150/197)
wk52	75.5% (139/184)	73.2% (142/194)	74.6% (141/189)

PSUMMIT 2 (Mixed TNF naïve and experience)

Pts randomized	104	103	105
wk4	27.7% (28/101)	30.4% (31/102)	31.7% (33/104)
wk8	34.7% (34/98)	51.0% (52/102)*	52.0% (52/100)*
wk12	34.0%(33/97)	53.5% (54/101)**	53.5% (54/101)**
wk24	30.8% (32/104)	55.3% (57/103)***	51.4% (54/105)**
wk28	64.1% (50/78)	68.0% (68/100)	61.6% (61/99)
wk52	64.9% (50/77)	58.5% (55/94)	60.0% (57/95)

† Patients early escaped to UST at wk 16 or crossed-over to UST at wk 24 and patients who did not receive UST are excluded in the analyses after wk 24; *, **, *** indicate $p < 0.05, 0.01, 0.001$, respectively, vs PBO. No statistical tests for significance were performed after wk24.

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An Indirect Comparison and Cost per Responder Analysis of Adalimumab, Methotrexate (MTX) and Apremilast in the Treatment of MTX-naïve Psoriatic Arthritis (PsA) Patients. Vibeke Strand[1], Jenny Griffith[2], Keith Betts[3], Alan Friedman[2], James Signorovitch[3] and Arijit Ganguli[2]. [1]Stanford University, Palo Alto, CA, [2]AbbVie, Inc., North Chicago, IL, [3]Analysis Group, Inc., Boston, MA.

Background/Purpose: Apremilast (APR), a small molecule inhibitor of phospodiesterase 4 (PDE-4), was recently approved for treating PsA patients in the US. To date, there are no studies directly comparing APR to the current standard of care, MTX. This analysis compared the cost per responder for APR versus MTX and adalimumab (ADA) (a TNF inhibitor) from a US perspective.

Methods: A systematic literature review was performed to extract response rates from clinical trials of approved biologics, MTX, and APR. The selected clinical trials were required to be in the MTX-naïve PsA population and have a placebo arm. A subanalysis of the ADEPT trial, a phase 3 trial comparing ADA with placebo, was conducted among patients who did not receive MTX in the 3 month baseline period. Using Bayesian methods, a network meta-analysis was conducted to indirectly compare the efficacy outcomes between approved therapies for PsA at week 16. Based on the response outcomes relative to placebo, the number needed to treat (NNT) was calculated using the inverse of absolute risk reduction. Cost of treatment was defined as the cost of drug (wholesale acquisition cost) required to treat patients for 16 weeks per labelled dose and cost for placebo was assumed to be zero. The incremental cost per responder was calculated by multiplying the cost of treatment and NNT for each of the therapies.

Results: The MIPA[1] trial for MTX, PALACE 4[2] for APR and the ADEPT subpopulation for ADA were the only clinical trials that met inclusion criteria. ACR20 was the common clinical outcome among the trials and was reported at week 16 for both ADA in ADEPT and APR in PALACE4, while week 24 results were reported for MTX in MIPA. In the absence of week 16 efficacy data for MTX, efficacy at week 24 was assumed to be similar at week 16 for this analysis, conservatively. Upon analysis, the NNTs for MTX, APR and ADA were 8.31, 6.69 and 2.63, respectively, and the 16 weeks drug costs were $436, $6,844 and $10,010, respectively. The cost per ACR20 responder was $3,622 for MTX, $45,808 for APR and $26,316 for ADA.

Conclusion: Among MTX-naïve PsA patients, ADA had the lowest NNT compared with MTX and APR at week 16. Compared with MTX and ADA, APR had the highest cost per responder estimates among MTX-naïve PsA patients at week 16.

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	Median NNT	95% CrI	16-week incremental drug cost (2014 USD)	Cost Per Responder (2014 USD)
Core Model (Fixed effects)				
Adalimumab vs. Placebo	2.63	(1.76–5.15)	$10,010.44	$26,316
Apremilast vs. Placebo	6.69	(3.67–19.50)	$6,843.75	$45,808
Methotrexate vs. Placebo	8.31	(3.37–**)	$436.09	$3,622

**At the upper limit there is no incremental benefit

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Integrated Safety of Ustekinumab in Psoriatic Arthritis: 2 Year Follow-up from the Psoriatic Arthritis Clinical Development Program. Arthur Kavanaugh[1], Iain B. McInnes[2], Christopher T. Ritchlin[3], Proton Rahman[4], Lluís Puig Sanz[5], Alice B. Gottlieb[6], Michael Song[7], Bruce Randazzo[7], Shu Li[7], Yin You[7] and Alan M. Mendelsohn[7]. [1]University of California San Diego, La Jolla, CA, [2]University of Glasgow, Glasgow, United Kingdom, [3]University of Rochester Medical Center, Rochester, NY, [4]Memorial University of Newfoundland, St. John's, NF, [5]Universitat Autònoma de Barcelona, Barcelona, Spain, [6]Tufts Medical Center, Boston, MA, [7]Janssen Research & Development, LLC., Spring House, PA.

Background/Purpose: To report the safety of ustekinumab(UST) from the psoriatic arthritis (PsA)development program.

Methods: Safety data through up to 2yrs of follow-up were pooled from Ph3 for the analysis of overall safety endpoints. Data were pooled from Ph2(n=146) and Ph3 for AEs of interest**.** In Ph3, adult PsA pts (PSUMMIT I [n=615], PSUMMIT II [n=312]) with active disease (≥5 SJC and ≥5 TJC; CRP≥0.3mg/dL [ULN 1.0 mg/dL]) despite DMARD and/or NSAID or previously treated with DMARD and/or NSAID, and prior anti-TNFα therapy (PSUMMIT II only) were randomized to UST45mg, 90mg, or PBO at wks 0, 4, and q12wks; at wk16, pts with <5% improvement in SJC & TJC entered blinded EE (PBO→UST45mg; UST45mg→90mg; 90mg→90mg). PBO pts crossed over to UST45mg at wks24 and 28 and q12wk dosing. No concomitant DMARDs except MTX (approx 50% in each Ph3 study) were permitted. The PBO-controlled period was 12wks and 16wks for the Ph2 and Ph3 trials, respectively. AEs were reported as the number of events /100 pt-yrs of follow-up (PY). All pts who received ≥1 dose of treatment were included.

Results: 379 and 1018 pts were treated with PBO and UST, resp, for up to 2yrs(duration of follow-up: Ph2 36wks, PSUMMIT1 108wks, and PSUMMIT2 60wks) with 145 PY and 1403 PY overall for the PBO and UST grps, resp. At baseline, 96.8% were white, 52.2% male, mean age 47.6yrs(SD 11.8). Mean BMI was 30.9 kg/m^2(SD 7.1), mean PsA and PsO duration was 7.2 yrs(SD 7.7) and 15.8yrs (SD 12.6), resp. Safety outcomes are detailed in Table 1. Event rates of overall AEs, infections, and SAEs, were comparable among PBO and UST during the PBO-controlled period; rates remained comparable through 2yrs of follow-up. Rates of AEs leading to d/c were higher in PBO. Overall AE rates were not impacted by baseline MTX or prior anti-TNF usage. 1 squamous cell carcinoma (90mg), 1 serious infection (PBO) and 1 MI (PBO) were reported during PBO-controlled period. With up to 2yrs of follow-up, rate of infections was similar in 90mg vs 45mg grps; serious infections were numerically greater in the 90mg vs 45 mg grp(2.1/100PY [95% CI:1.1,3.5] vs 0.5/100PY [95% CI: 0.1,1.3], resp), and included 2 pts in the 90mg grp with multiple events(most were single events without apparent trend). 4 non-melanoma skin cancers (NMSC)(0.64/100PY) occurred in the 90mg grp and no NMSCs occurred in the 45mg grp. 3 malignancies(0.4/100PY), other than NMSC, occurred in 45mg grp and none in 90mg grp. Major adverse cardiovascular event(MACE) rates were low and

no dose effects were observed(1.15 vs 0.24 for 45mg and 90mg, resp). No cases of active TB or serious opportunistic infections, RPLS, demyelination, anaphylaxis or serum sickness-like reactions were reported.

Conclusion: Pooled safety data show that UST was well tolerated at both doses with up to 2yrs of follow-up without new safety signals. The safety profile of UST in the PsA clinical development program was generally comparable to that observed in the psoriasis population.

Table 1: Adverse Events Rates per 100 PY of Follow-up (95% CI)

	PBO-Controlled Period (16 weeks)			Through 2 years		
	PBO	UST 45mg	UST 90mg	PBO→45mg	UST 45mg	UST 90mg
[a]Overall AEs						
Pts treated (n)	309	308	308	269	308	308
Pt-yrs of follow-up	94	96	95	348	489	491
AEs	314.3 (279.5, 352.3)	333.5 (297.9, 372.2)	378.6 (340.5, 419.9)	134.0 (122.1, 146.7)	217.8 (205.0, 231.3)	202.0 (189.6, 215.0)
Infections	101.2 (81.9, 123.8)	84.7 (67.3, 105.3)	97.03 (78.2, 119.0)	45.4 (38.6, 53.1)	61.6 (54.8, 68.9)	66.4 (59.4, 74.1)
AEs leading to d/c	11.9 (5.9, 21.2)	3.2 (0.6,9.2)	4.2 (1.2, 10.9)	1.4 (0.5,3.4)	3.5(2.0, 5.6)	2.5 (1.3, 4.3)
Serious AE	11.7 (5.8, 21.0)	4.2 (1.1, 10.7)	8.4 (3.6, 16.6)	6.3 (4.0, 9.6)	8.2 (5.8, 11.1)	9.2 (6.7, 12.3)
Deaths	0	0	0	0	0	0
	PBO	UST 45mg	UST 90mg	PBO	UST 45mg	UST 90mg
[b]AEs of Interest						
Pts treated (n)	379	308	384	379	577	497
Pt-yrs of follow-up	110	96	113	145	773	631
Serious infxns	0.9 (0.0, 5.0)	0.0 (0.0, 3.1)	0.0 (0.0, 2.6)	0.7 (0.0, 3.8)	0.5 (0.1, 1.3)	2.1 (1.1, 3.5)
NMSC	0.0 (0.0,2.7)	0.0 (0.0, 3.1)	0.9 (0.0, 4.9)	0.0 (0.0, 2.0)	0.0 (0.0, 0.4)	0.6 (0.2, 1.6)
Other malignancies	0.0 (0.0, 2.7)	0.0 (0.0, 3.1)	0.0 (0.0, 2.6)	0.0 (0.0, 2.1)	0.4 (0.1, 1.1)	0.0 (0.0, 0.5)
MACE	0.9 (0.0, 5.0)	0.0 (0.0, 3.1)	0.0 (0.0, 2.6)	0.7 (0.0, 3.8)	1.0 (0.4, 2.0)	0.3 (0.0, 1.2)

[a]Overall AEs: Ph3 trials (PSUMMIT I&II); Analyzed by dose randomized. [b]AEs of interest: Ph2 and Ph3 trials (PSUMMIT I&II); [b] PBO EE and crossover pts were included in the UST 45mg column after EE at wk16 or crossover at wk24. Pts who were dose escalated from 45mg to 90mg were switched to the 90mg column following dose escalation.

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Clinical Response in Subjects with Psoriatic Arthritis Following One Year of Treatment with Brodalumab, an Anti-Interleukin-17 Receptor Antibody. Mark C Genovese[1], Philip Mease[2], Maria W. Greenwald[3], Christopher T. Ritchlin[4], A Beaulieu[5], Atul A. Deodhar[6], Richard Newmark[7], JingYuan Feng[8], Ngozi Erondu[9] and Ajay Nirula[7]. [1]Stanford University Medical Center, Palo Alto, CA, [2]Swedish Medical Center and University of Washington, Seattle, WA, [3]Desert Medical Advances, Palm Desert, CA, [4]University of Rochester Medical Center, Rochester, NY, [5]Centre de Rhumatologie, St-Louis, QC, [6]Oregon Health and Sciences University, Portland, OR, [7]Amgen, Thousand Oaks, CA, [8]Amgen Inc, Thousand Oaks, CA, [9]Amgen, Inc., Thousand Oaks, CA.

Background/Purpose: Interleukin-17 (IL-17) plays a role in the pathogenesis of psoriatic disease of both skin and joint. We sought to assess long-term efficacy and safety of brodalumab, a human anti-IL-17 receptor A monoclonal antibody, in patients with psoriatic arthritis (PsA) in an open-label extension (OLE) of a Phase 2 study (NCT01516957).

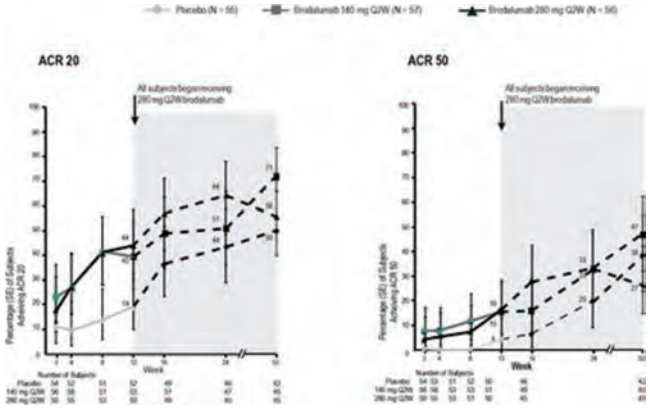
Methods: Adults with active PsA (Classification Criteria for Psoriatic Arthritis and ≥3 tender and ≥3 swollen joints) for ≥6 months were randomized to brodalumab (140 or 280 mg Q2W) or placebo. At week 12, subjects could enroll in an OLE; all subjects received 280 mg brodalumab. Outcomes based on available data up to week 52 from the ongoing study included American College of Rheumatology 20% response (ACR20), ACR50, changes in DAS 28, CDAI, and ACR response components. Safety was assessed by monitoring adverse events (AEs).

Results: The majority of enrolled subjects (113 brodalumab and 55 placebo) were female (64%), white (94%), and rheumatoid factor negative (92%). Mean age, weight, and duration of PsA at baseline were 52 years, 91 kg, and 9 years, respectively. 156 subjects entered the OLE (52 prior placebo, 53 prior 140 mg, 51 prior 280 mg).

ACR20 and ACR50 response rates (observed), which were higher in brodalumab arms than in placebo at week 12, continued to improve and were sustained through week 52 across all groups (Figure 1). Improvements in DAS 28, CDAI, and several ACR components, observed from baseline to week 12, continued through week 52.

During the OLE (through week 52), 142 subjects reported AEs; most frequently reported (≥5% of subjects in any treatment group) were nasopharyngitis, arthralgia, psoriatic arthropathy, upper respiratory tract infection, bronchitis, nausea, sinusitis, and oropharyngeal pain. Ten subjects reported serious adverse events during the OLE through week 52: including 1 case each of acute myocardial infarction, invasive ductal breast carcinoma, metastatic lung cancer, melanoma, pyelonephritis, and streptococcal septic arthritis. Exposure adjusted AE rates (per 100 subject years) were 706 (all brodalumab) and 757 (placebo). Exposure adjusted SAE rates were 11 (brodalumab) and 8 (placebo). No deaths, clinically significant neutropenia (≥ Grade 2), or mycobacterial/fungal/opportunistic infections were reported.

Conclusion: Brodalumab treatment was associated with significant clinical response with continued improvement from weeks 12 to 52.



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Evaluation of Extreme Enthesitis and/or Patient-Related Outcome Score As Potential Surrogates for Fibromyalgia and As Potential Confounding Factors of Anti-TNF Response. M Dougados[1], H Jones[2], A Szumski[2], I Logeart[3] and J Coindreau[4]. [1]Université Paris René Descartes and Hôpital Cochin, Paris, France, [2]Pfizer Inc., Collegeville, PA, [3]Pfizer, Paris, France, [4]Pfizer Inc., New York, NY.

Background/Purpose: Differentiating between pain related to spondyloarthritis (in particular polyenthesitis) and pain related to fibromyalgia can be challenging, both in daily practice and in clinical trials. Some rheumatologists believe an "extreme" enthesitis score and/or pain/Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score may reflect a "fibromyalgia" disease. Additionally, depression is frequently observed in fibromyalgia patients; thus, an "extreme" enthesitis and/or pain/BASDAI score may correlate with an elevated depression score. The purpose of this post-hoc analysis was to evaluate patients with spondyloarthritis in order to: 1) estimate the percentage of patients with such "extreme" scores; 2) evaluate the relationship between "extreme" scores and depression; 3) evaluate the effect

of baseline "extreme" scores on treatment outcome for etanercept and placebo.

Methods: Patients with non-radiographic axial spondyloarthritis participated in a randomized clinical trial and received double-blind etanercept 50 mg or placebo weekly. For this analysis, patients were divided into those who did vs. those who did not have extreme scores at baseline. Extreme baseline scores were defined as the highest quintile for enthesitis score (≥6), and/or scores ≥8 on 3 of 5 BASDAI items (morning stiffness duration was excluded). Depression was evaluated using the Hospital Anxiety and Depression Scale, depression subscale (HADS-D). Treatment outcome was the Assessment of SpondyloArthritis (ASAS) 40 response rate at week 12.

Results: Of the 213 patients at baseline, 35 (16%) met only enthesitis criteria, 31 (15%) met only BASDAI criteria, 12 (6%) met both criteria, and 135 (63%) met neither criteria. Patients with extreme enthesitis and/or BASDAI scores vs. those without were more likely to have moderate to severe depression at baseline: 20/68 (29%) vs. 10/118 (9%) of patients had HADS-D score >11 ($P<0.001$). For patients with vs. without extreme scores, no significant difference existed in week 12 ASAS40: etanercept 13/41 (32%) vs. 21/60 (35%); placebo 5/36 (14%) vs. 12/68 (18%).

Conclusion: Extreme enthesitis and/or BASDAI scores correlated with depression at baseline, but did not have an effect on week 12 ASAS40 in either the etanercept or placebo treatment group.

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Long Term Improvements in Physical Function Are Associated with Improvements in Dactylitis, Enthesitis, Tender and Swollen Joint Counts, and Psoriasis Skin Involvement: Results from a Phase 3 Study of Ustekinumab in Psoriatic Arthritis Patients. Arthur Kavanaugh[1], Lluís Puig Sanz[2], Alice B. Gottlieb[3], Christopher T. Ritchlin[4], Shu Li[5], Yin You[5], Alan M. Mendelsohn[5], Michael Song[5], Proton Rahman[6] and Iain B. McInnes[7]. [1]University of California San Diego, La Jolla, CA, [2]Universitat Autònoma de Barcelona, Barcelona, Spain, [3]Tufts Medical Center, Boston, MA, [4]University of Rochester Medical Center, Rochester, NY, [5]Janssen Research & Development, LLC., Spring House, PA, [6]Memorial University of Newfoundland, St. John's, NF, [7]University of Glasgow, Glasgow, United Kingdom.

Background/Purpose: To evaluate the association of improvements in tender and swollen joint counts (TJC, SJC), psoriasis skin involvement, and dactylitis/enthesitis (in patients affected at baseline) with improvement in physical function using data from the ustekinumab (UST) PSUMMIT 1 trial in psoriatic arthritis (PsA) pts.

Methods: Adult PsA pts (n=615) with active disease (≥5 SJC and ≥5 TJC;CRP≥0.3mg/dL) despite DMARD and/or NSAIDs were randomized to UST45mg, 90mg, or PBO at wks 0, 4, and q12wks. Pts treated with prior anti-TNF agents were excluded. Stable concomitant MTX was permitted but not mandated. At wk16, pts with <5% improvement in TJC and SJC entered blinded early escape (PBO→UST45mg; UST45mg→90mg; 90mg→90mg). PBO-treated patients subsequently crossed over to UST45mg at wk24. Pts received q12wks dosing to wk88, with final efficacy evaluation at wk100 and safety assessment at wk108. The percent change from baseline in enthesitis score, dactylitis score, TJC and SJC by HAQ responder status (response defined as achieving≥0.3 point improvement from baseline) was assessed at wks 52 and 100.The correlation between change from baseline in HAQ and percent change from baseline in TJC, SJC, enthesitis and dactylitis were also determined at wks 52 and 100.

Results: At baseline; mean(median) TJC and SJC values were 23.5(20.0) and 13.5(10.0), respectively. 441(71.7%) and 296(48.1%) patients had enthesitis or dactylits at baseline, respectively; 440(71.7%) patients had >3% BSA psoriasis skin involvement. Improvements in TJC, SJC, dactylitis and enthesitis, and PASI scores were generally greater in HAQ responders compared with HAQ non-responders at both wk52 and wk100(Table). Significant correlations were demonstrated between the HAQ change from baseline with percent change in outcomes parameters for all outcomes(Table) at wk52 and wk100. In addition, associations were observed at earlier time points at wk24/wk28 [TJC -0.39/-0.36; SJC -0.27/-0.20; enthesitis 0.30/0.28(all p<0.0001); dactylitis 0.19/0.18 (p=0.001/p=0.002); PASI -0.24/-0.10(p<0.0001/p=0.0397)].

Conclusion: Based on this post-hoc analysis of the PSUMMIT 1 population, improvements in physical function as measured by HAQ were associated with improvements in TJC, SJC, dactylitis and enthesitis, and these correlations were observed as early as week 24 and continued through week100. Improvement in skin disease was also associated with improvements in HAQ.

Table: Summary of percent change from baseline at wk52 and wk100 in HAQ responders; randomized patients at baseline [mean(median)]

HAQ response at wk52/wk100	PBO → 45 mg[a] (n=189) Responders	PBO → 45 mg[a] (n=189) Non-responders	UST 45mg (n=205) Responders	UST 45mg (n=205) Non-responders	UST 90mg (n=204) Responders	UST 90mg (n=204) Non-responders	Spearman Correl coeff	p-value
TJC	N=98	N=84	N=91	N=103	N=97	N=92	N=572	<0.001
Wk52	71.8 (78.4)	35.9 (38.7)	61.6 (75)	40.6 (48.7)	68.5 (77.8)	35.3 (42.9)	−0.329	<0.001
Wk100	N=89	N=88	N=85	N=90	N=91	N=84	N=534	
	76.6 (80.0)	29.1 (25.4)	74.6 (90.0)	37.3 (40.8)	76.7 (87.5)	33.4 (25.0)	−0.430	
SJC	N=98	N=84	N=91	N=103	N=97	N=92	N=572	<0.001
Wk52	73.4 (85.7)	42.1 (53.7)	69.0 (87.5)	52.5 (66.7)	70.4 (84.6)	46.2 (61.8)	−0.434	<0.001
Wk100	N=89	N=88	N=85	N=90	N=91	N=84	N=534	
	80.1 (83.3)	44.0 (54.8)	79.1 (92.3)	44.0 (48.5)	84.2 (93.3)	46.4 (58.6)	−0.500	
Entheses score (modified MASES index)*	N=68	N=54	N=69	N=65	N=71	N=71	N=405	<0.001
	−58.7 (−100.0)	−28.2 (−40.0)	−55.4 (−100.0)	−34.7 (−66.7)	−66.9 (−100.0)	−46.1 (−66.7)	0.286	<0.001
Wk52	N=58	N=60	N=60	N=59	N=65	N=65	N=374	
Wk100	−71.5 (−100.0)	−7.3 (−17.4)	−69.5 (−100.0)	−22.6 (−50.0)	−73.7 (−100.0)	−42.6 (−50.0)	0.370	
Dactylitis score**	N=53	N=31	N=46	N=51	N=49	N=42	N=277	0.002
Wk52	−76.6 (−100.0)	−55.5 (−78.6)	−48.8 (−100.0)	−59.7 (−100.0)	−56.4 (−100.0)	−53.7 (−75.0)	0.182	<0.001
Wk100	N=48	N=36	N=42	N=48	N=50	N=36	N=265	
	−81.1 (−100.0)	−43.8 (−88.9)	−75.6 (−100.0)	−67.5 (−100.0)	−85.6 (−100.0)	−18.8 (−83.4)	0.286	
PASI score***	N=74	N=56	N=63	N=71	N=74	N=66	N=404	0.0006
Wk52	80.1 (90.1)	71.5 (79.2)	82.6 (93.8)	64.2 (85.7)	77.1 (90.3)	74.0 (88.7)	−0.17	<0.0001
	N=63	N=58	N=62	N=57	N=67	N=59	N=366	
Wk100	71.4 (91.2)	68.5 (81.4)	84.7 (93.5)	60.3 (87.0)	84.9 (97.6)	69.8 (86.7)	−0.24	

[a]Patients who did not receive UST are excluded; *Randomized patients with enthesitis at baseline PBO→45mg n=128, 45mg n=142, 90mg n=154; **Randomized patients with dactylitis at baseline PBO→45mg n=87 45mg n=101, 90mg n=99; ***Randomized patients with ≥3% BSA psoriasis skin involvement at baseline PBO→45mg n=136 45mg n=145, 90mg n=149

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Rheumatoid Factor Status Is a Predictor of Osteoporosis in Patients with Psoriatic Arthritis. Frank Behrens[1], Michaela Koehm[2], Eva C. Scharbatke[3], Bianca Wittig[4], Marc Schmalzing[3], Holger Gnann[5], H M Lorenz[6], Diamant Thaci[7] and Harald Burkhardt[1]. [1]Goethe-University Frankfurt, Frankfurt, Germany, [2]Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Project Group Translational Medicine & Pharmacology TMP, Frankfurt/Main, Germany, [3]University of Würzburg, Würzburg, Germany, [4]Abbvie Deutschland GmbH & Co. KG, Wiesbaden, Germany, [5]Abteilung Biostatistik, GKM Gesellschaft für Therapieforschung mbH, München, Germany, [6]University Hospital Heidelberg, Heidelberg, Germany, [7]University Hospital Schleswig Holstein Campus Luebeck, Lübeck, Germany.

Background/Purpose: Osteoporosis is an important comorbidity in patients with rheumatic diseases, but risk factors for osteoporosis in Psoriatic Arthritis (PsA) patients have not been explored.

Methods: We evaluated baseline characteristics of active PsA patients enrolled in a German observational multicenter study with Adalimumab (ADA). Multiple logistic regression analyses were utilized to identify risk factors for osteoporosis. Risk factors were confirmed in a validation cohort.

Results: At baseline, 6.0% (N=88) of patients in the initial PsA cohort (N=1467) had osteoporosis as indicated by medical history. Logistic regression analyses (1194 patients with adequate data for modeling) found that age, systemic glucocorticoid use and rheumatoid factor (RF) seropositivity were significantly associated with osteoporosis. As the association between RF status and osteoporosis has not been previously described in PsA, we evaluated a second cohort of PsA patients (validation cohort; N = 1762) to determine whether this association could be verified. As in the initial cohort, positive RF status was associated with a >2-fold increase in the risk of osteoporosis in patients with PsA in the same range as use of glucocorticoids. The rate of osteoporosis was 5.4% (168/3102) in the total cohort and 12.1%

(35/290) in RF-positive patients. Analysis of typical PsA-features like confirmed nail involvement, enthesitis and dactylitis and active psoriasis suggests that it is unlikely that the RF-positive PsA patients were misdiagnosed RA-cases. The full set of predictors of osteoporosis of the full cohort (2956 patients with adequate data) is shown in Table 1. Negative predictors were male gender and higher functional (FFbH) scores.

Conclusion: RF seropositivity is an independent risk factor for osteoporosis in active PsA patients. Other variables that increase the risk of osteoporosis are steroid use, older age, longer disease duration, recent hospitalization, female gender, and worse functional status.

Variable	Range	Odds ratio*	95% CI	*P* value
Positive predictors				
Systemic glucocorticoid use	1 = yes, 0 = no	2.783	1.938–3.995	<0.0001
Rheumatoid factor	1 = yes, 0 = no	2.450	1.590–3.775	<0.0001
Age (yrs)	12–90	1.046	1.030–1.062	<0.0001
Duration of arthritis (yrs)	0 to 53	1.030	1.014–1.048	0.0004
Hospitalization in last 12 months	1 = yes, 0 = no	1.688	1.151–2.475	0.0074
Negative predictors				
Gender	1 = male, 0 = female	0.544	0.380–0.780	0.0009
FFbH	0–100	0.987	0.979–0.995	0.0012

*Odds ratio for one unit difference. For x units difference use the odds to the power of x. FFbH = Funktionsfragebogen Hannover patient function questionnaire (higher scores correspond to better function)

Disclosure: F. Behrens, AbbVie, 5, Chugai, 8, Chugai, 5, Roche Pharmaceuticals, 5, Janssen Pharmaceutica Product, L.P., 5; **M. Koehm**, AbbVie, 2, Pfizer Inc, 2; **E. C. Scharbatke**, AbbVie, 5, Chugai, 5, Roche Pharmaceuticals, 5; **B. Wittig**, AbbVie, 3; **M. Schmalzing**, AbbVie, 5, Roche Pharmaceuticals, 5, Actelion Pharmaceuticals US, 5, BMS, 5, Chugai, 5, UCB, 5, Pfizer Inc, 5; **H. Gnann**, AbbVie, 5; **H. M. Lorenz**, AbbVie, 5, Roche Pharmaceuticals, 5, Actelion Pharmaceuticals US, 5, Pfizer Inc, 5, BMS, 5, Chugai, 5, UCB, 5; **D. Thaci**, Abbvie, 5, Lilly, 5, Amgen, 5, Pfizer Inc, 5, MSD, 5, Novartis Pharmaceutical Corporation, 5, Biogen Idec, 5, Leo Pharma, 5; **H. Burkhardt**, Pfizer Inc, 2, Pfizer Inc, 5, AbbVie, 5, UCB, 5, BMS, 5, Chugai, 5.

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Apremilast, an Oral Phosphodiesterase 4 Inhibitor, and the Impact of Baseline Weight and BMI on ACR20 and HAQ-DI Response: Pooled Results from 3 Phase 3, Randomized, Controlled Trials. Georg A. Schett[1], Philip Mease[2], Dafna D. Gladman[3], Arthur Kavanaugh[4], Adewale O. Adebajo[5], Juan J. Gomez-Reino[6], Jurgen Wollenhaupt[7], Maurizio Cutolo[8], Eric Lespessailles[9], ChiaChi Hu[10], Randall M. Stevens[10], Christopher J. Edwards[11] and Charles A. Birbara[12]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]Swedish Medical Center and University of Washington, Seattle, WA, [3]University of Toronto, Toronto Western Hospital, Toronto, ON, [4]University of California San Diego, La Jolla, CA, [5]University of Sheffield, Sheffield, United Kingdom, [6]Hospital Clinico Universitario, Santiago, Spain, [7]Schoen-Klinik Hamburg-Eilbek Teaching Hospital of the University of Hamburg, Hamburg, Germany, [8]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, [9]University of Orléans, Orléans, France, [10]Celgene Corporation, Warren, NJ, [11]University Hospital Southampton, Southampton, United Kingdom, [12]University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Apremilast (APR) is a phosphodiesterase 4 inhibitor that helps to regulate the immune response that causes inflammation and skin disease associated with psoriatic arthritis (PsA). PALACE 1, 2, and 3 compared the efficacy and safety of APR with placebo in patients with active PsA despite prior disease-modifying antirheumatic drugs (DMARDs) and/or biologics, including biologic failures. We assessed the impact of baseline weight and body mass index (BMI) on clinical response to APR over 24 weeks in a pooled analysis.

Methods: Patients were randomized (1:1:1) to receive placebo, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline DMARD use (yes/no). Patients whose swollen and tender joint counts had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if they were initially randomized to placebo, or continued on their initial apremilast dose. At Week 24, all remaining placebo patients were re-randomized to APR20 or APR30.

Results: 1,493 patients were randomized, received ≥1 dose of study medication (placebo: n=496; APR20: n=500; APR30: n=497), and were comparable across treatment groups for demographics, disease characteristics, and prior/concurrent therapy. At baseline, mean (SD) weight was 85.7 (20.6) kg and mean (SD) BMI was 29.9 (6.5) kg/m^2. At Week 16, a significantly greater proportion of patients receiving APR20 or APR30 achieved a modified ACR20 response vs placebo (primary endpoint) in all 3 PALACE trials. APR30 was associated with significant improvements in Health Assessment Questionnaire-Disability Index (HAQ-DI) score vs placebo at Week 16 (key secondary endpoint) across all 3 trials. At Week 16, similar ACR20 response rates and improvements in HAQ-DI scores were observed across all weight and BMI ranges (Table). A favorable treatment effect for both APR treatment groups vs placebo was observed, irrespective of baseline body weight or BMI. Overall, the treatment effect was dose-dependent, with greater effects generally observed in APR30 patients over APR20 patients. These treatment effects were generally maintained at Week 24.

Conclusion: APR demonstrated a favorable treatment effect in patients with active PsA. Comparable improvements in the signs and symptoms of PsA and physical function were observed across a broad range of baseline weight and BMI values. Results suggest that no dose adjustment is required to account for baseline body weight or BMI.

	Placebo n = 496*	APR20 n = 500*	APR30 n = 497*
ACR20 Response at Week 16 (NRI)§, m/n‡ (%)			
Baseline weight (kg)			
<70, n = 336	22/107 (20.6)	34/108 (31.5)	44/121 (36.4)
70–<85, n = 454	31/151 (21.2)	43/150 (28.7)	53/153 (34.6)
85–<100, n = 391	22/129 (17.1)	39/133 (29.3)	48/129 (37.2)
≥100, n = 311	17/109 (15.6)	44/108 (40.7)	39/94 (41.5)
Baseline BMI (kg/m^2)			
<25, n = 339	24/112 (21.4)	38/111 (34.2)	41/116 (35.3)
25–<30, n = 496	24/152 (15.8)	48/174 (27.6)	66/170 (38.8)
30–<35, n = 351	28/125 (22.4)	44/113 (38.9)	39/113 (34.5)
35–<40, n = 198	10/66 (15.2)	15/63 (23.8)	25/69 (36.2)
≥40, n = 107	7/40 (17.5)	15/38 (39.5)	13/29 (44.8)
LS‖ Mean Change in HAQ-DI# at Week 16 (LOCF)¶			
Baseline weight (kg)			
<70, n = 324	−0.047	−0.128	−0.168
70–<85, n = 434	−0.134	−0.182	−0.239
85–<100, n = 383	−0.053	−0.122	−0.225
≥100, n = 297	−0.016	−0.224	−0.202
Baseline BMI (kg/m^2)			
<25, n = 330	−0.052	−0.164	−0.183
25–<30, n = 474	−0.092	−0.180	−0.237
30–<35, n = 343	−0.095	−0.135	−0.239
35–<40, n = 189	−0.014	−0.108	−0.168
≥40, n = 102	−0.031	−0.267	−0.165

*The n reflects the number of randomized patients.
§NRI = non-responder imputation. Patients who discontinued early prior to Week 16 and patients who did not have sufficient data for a definitive determination of response status at Week 16 were counted as non-responders. ‡m/n = number of responders/number of patients in the subgroup. Patients with a missing subgroup factor are not included.
‖LS = least-squares. #A negative change from baseline indicates improvement.
¶LOCF = last observation carried forward. Patients with a baseline value and at least 1 post-baseline value at or before Week 16 are included. Patients with a missing subgroup factor are not included.

Disclosure: G. A. Schett, Abbott, Celgene Corporation, Roche, and UCB, 2, Abbott, Celgene Corporation, Roche, and UCB, 5; **P. Mease**, Abbott, Amgen, Biogen Idec, Bristol-Myers Squibb, Genentech, Janssen, Eli Lilly, Pfizer Inc, UCB, Celgene Corporation, Novartis, and Roche, 2, Abbott, Amgen, Biogen Idec, Bristol-Myers Squibb, Genentech, Janssen, Eli Lilly, Pfizer Inc, UCBCelgene Corporation, Novartis, and Roche, 5, Abbott, Amgen, Biogen Idec, Bristol-Myers Squibb, Genentech, Janssen, Eli Lilly, Pfizer Inc, and UCB, 8; **D. D. Gladman**, AbbVie, Amgen, Bristol-Myers Squibb, Celgene Corporation, Janssen, Pfizer Inc, Novartis, and UCB, 2, AbbVie, Amgen, Bristol-Myers Squibb, Celgene Corporation, Janssen, Pfizer Inc, Novartis, and UCB, 5; **A. Kavanaugh**, Abbott, Amgen, Astra-Zeneca, Bristol-Myers Squibb, Celgene Corporation, Centocor-Janssen, Pfizer Inc, Roche, and UCB, 2; **A. O. Adebajo**, None; **J. J. Gomez-Reino**, Bristol-Myers Squibb, Pfizer Inc, Roche, Schering-Plough, and UCB SA, 9, Bristol-Myers Squibb, Roche, Schering-Plough, and Wyeth, 9, Roche and Schering-Plough, 2; **J. Wollenhaupt**, Abbott, Bristol-Myers Squibb, MSD, Pfizer Inc, and UCB, 2, Abbott, Bristol-Myers Squibb, MSD, Pfizer Inc, and UCB, 5; **M. Cutolo**, Actelion, Bristol-Myers Squibb, and Sanofi-Aventis, 2, Actelion, Bristol-Myers Squibb, and Sanofi-Aventis, 5; **E. Lespessailles**, Amgen, Eli Lilly, Novartis, and Servier, 2, Amgen, Eli Lilly, Novartis, and Servier, 8; **C. Hu**, Celgene Corporation, 3, Celgene Corporation, 1; **R. M. Stevens**, Celgene Corporation, 1, Celgene Corporation, 3; **C. J. Edwards**, Celgene Corporation, Pfizer Inc, Roche, and Samsung, 2, Celgene Corporation, Pfizer Inc, Roche, and Samsung, 5, Abbott, Glaxo-SmithKline, Pfizer Inc, and Roche, 8; **C. A. Birbara**, Amgen, Bristol-Myers Squibb, Incyte, Eli Lilly, Merck, and Pfizer Inc, 2.

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Psoriasis Longitudinal Assessment and Registry: Global Update upon Full Enrollment. Bruce Strober[1], Alan Menter[2], Craig Leonardi[3], Lyn Guenther[4], Kavitha Goyal[5], Wayne Langholff[6], Steve Calabro[5] and Steve Fakharzadeh[7]. [1]University of Connecticut Heatlh Center, Farmington, CT, [2]Baylor Research Institute, Dallas, TX, [3]Central Dermatology, St. Louis, MO, [4]The Guenther Dermatology Research Centre, London, ON, [5]Janssen Services, LLC, Horsham, PA, [6]Janssen Research and Development, LLC, Spring House, PA, [7]Janssen Services, LLC, Spring House, PA.

Background/Purpose: To report the baseline demographics and clinical characteristics of participants enrolled in the Psoriasis Longtitudinal Assessment and Registry (PSOLAR) study.

Methods: PSOLAR is a multicenter, prospective, longitudinal, observational study initiated by the FDA designed to follow psoriasis patients for 8 years in academic and community settings. Eligible patients are aged ≥18 years, have a diagnosis of psoriasis and are currently receiving or are candidates to receive systemic therapies for psoriasis. Demographics and medical/family history are collected at enrollment, including self-reported diagnosis of psoriatic arthritis. Evaluations at 6 month intervals include: adverse events, disease activity, quality of life, economic status, healthcare utilization and interval therapies.

Results: PSOLAR is fully enrolled, with sites in North America, Latin America, and Europe having recruited 12 095 patients as of 23 August 2013. Baseline characteristics at enrollment were as follows: mean age 48.6 years; median age 49.0 years; 13% were ≥65 years of age; 54.9% male; 82.9% white; mean body mass index (BMI) 30.9 (SD 7.2); and mean psoriasis duration 17.5 years (SD 13.5 years). Psoriatic arthritis was self-reported in 35.7% of patients and 96.9% of patients had plaque-type psoriasis. Mean and median historical peak psoriasis activity as measured by PGA were 3.11 and 3.0 respectively, and by BSA, 29.7% and 20.0% respectively.

Co-morbidities included cardiovascular disease in 38.3%, pulmonary disorders in 14.4%, psychiatric disorders in 20.7%, and endocrine disorders in 18.8%; 6.2% had a previous skin cancer. Infections requiring treatment in the 3 years preceding enrollment occurred in 24.5% of patients; 21.5% were bacterial. The mean body surface area (BSA) coverage was 12.1% (SD 17.5%) and mean physicians' global assessment (PGA) score 2 (SD 1.2).

Psoriasis medications (current and historical) included topicals (96.9%), phototherapy (54.5%), systemic steroids (23.4%), systemic agents [e.g. MTX, cyclosporine] (47.9%), and biologic agents (etanercept 40.3%, adalimumab 29.4%, ustekinumab 18.8%, infliximab 16.0%, and efalizumab 11.1%).

Conclusion: PSOLAR is fully enrolled with 12 095 patients with an accrual of 31 818 patient- years of followup as of August 23, 2013. Participation is global with the majority of patient representation from North America. Clinical features are as expected for a moderate to severe psoriasis population, including a 35.7% prevalence of self-reported psoriatic arthritis. Serious adverse events and adverse events of interest have been presented for the overall registry and future analyses will provide similar data with respect to various treatment groups represented in PSOLAR.

Disclosure: B. Strober, Janssen Scientific Affairs, LLC, 2; **A. Menter**, Janssen Scientific Affairs, LLC, 2; **C. Leonardi**, Janssen Scientific Affairs, LLC, 2; **L. Guenther**, Janssen Scientific Affairs, LLC, 2; **K. Goyal**, Janssen Scientific Affairs, LLC, 3; **W. Langholff**, Janssen Scientific Affairs, LLC, 3; **S. Calabro**, Janssen Scientific Affairs, LLC, 3; **S. Fakharzadeh**, Janssen Scientific Affairs, LLC, 3.

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Malignancies in the Psoriasis Longitudinal Assessment and Registry Study: Cumulative Experience. David Fiorentino[1], Mark Lebwohl[2], Vincent Ho[3], Richard Langley[4], Kavitha Goyal[5], Steve Fakharzadeh[6], Steve Calabro[5] and Wayne Langholff[7]. [1]Stanford University School of Medicine, Redwood City, CA, [2]Mount Sinai Medical Center, New York, NY, [3]University of British Columbia, Vancouver, BC, [4]Dalhousie University, Halifax, NS, [5]Janssen Services, LLC, Horsham, PA, [6]Janssen Services, LLC, Spring House, PA, [7]Janssen Research and Development, LLC, Spring House, PA.

Background/Purpose: To report the cumulative incidence of malignancies excluding non-melanoma skin cancers (NMSC) in the PSOLAR study.

Methods: PSOLAR is a multicenter, longitudinal, observational study evaluating long-term safety and clinical outcomes for patients eligible to receive treatment with biologics and/or conventional systemic agents for psoriasis (includes patients with self-reported psoriatic arthritis. The incidence of malignancies excluding NMSC (ie, basal/squamous cell carcinomas) in PSOLAR overall and by treatment groups is reported. Rates of malignancy are assessed using a definition of exposure based on whether patients had ever been exposed to a given therapy at any time prior to the event. In cases of exposure to >1 therapy, the rule for attribution of malignancy to a treatment group is ustekinumab first, infliximab/golimumab second, other biologics third (nearly all adalimumab or etanercept), or non-biologic therapy fourth, which is consistent with the pre-specified analytic plan.

Results: PSOLAR is fully enrolled and as of the August 23, 2013 data cut has 31, 818 cumulative patient-years of follow up with 12, 095 patients; 36% of those patients had self-reported psoriatic arthritis. Unadjusted cumulative rates of malignancy (excluding NMSC) overall and across treatment groups: overall 0.68 events per 100 patient years of observation (PYO) [95% CI: 0.59, 0.77; 215/31818], ustekinumab 0.51 per 100 PYO [95% CI: 0.37, 0.68; 45/8870 PYO], infliximab/golimumab (almost exclusively infliximab) 0.64 per 100 PYO [95% CI: 0.42, 0.93; 27/4205, other biologics (almost exclusively etanercept/adalimumab) 0.74 per 100 PYO [95% CI: 0.60, 0.91; 98/13167], and non-biologic therapy 0.81 per 100 PYO [95% CI: 0.59, 1.08; 45/5576]. The cumulative rates per 100 PY for the overall registry population for the most frequent specific malignancies were: breast cancer 0.13 [40], prostate cancer 0.09 [30], lung cancer 0.08 [26], and melanoma 0.07 [22]. Limitations: Rates have not been adjusted for demographic and clinical differences among treatment groups and are subject to attribution rules.

Conclusion: In the current evaluation, reflecting a median duration of 2.5 years of follow-up, cumulative unadjusted rates of malignancies in PSOLAR are comparable across treatment groups. The most frequently reported malignancies in the registry are comparable with the most frequently reported malignancies in the general population. Additional evaluation of malignancies with accruing longitudinal exposure will be informative.

Disclosure: D. Fiorentino, Janssen Scientific Affairs, LLC, 2; **M. Lebwohl**, Janssen Scientific Affairs, LLC, 2; **V. Ho**, Janssen Scientific Affairs, LLC, 2; **R. Langley**, Janssen Scientific Affairs, LLC, 2; **K. Goyal**, Janssen Scientific Affairs, LLC, 3; **S. Fakharzadeh**, Janssen Scientific Affairs, LLC, 3; **S. Calabro**, Janssen Scientific Affairs, LLC, 3; **W. Langholff**, Janssen Scientific Affairs, LLC, 3.

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Long-Term (104-Week) Safety Profile of Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients with Psoriatic Arthritis: Results from a Phase 3, Randomized, Controlled Trial and Open-Label Extension. Philip Mease[1], Adewale O. Adebajo[2], Dafna D. Gladman[3], Juan J. Gomez-Reino[4], Stephan Hall[5], Arthur Kavanaugh[6], Eric Lespessailles[7], Georg A. Schett[8], Kamal Shah[9], Randall M. Stevens[9], Lichen Teng[9] and Jürgen Wollenhaupt[10]. [1]Swedish Medical Center and University of Washington, Seattle, WA, [2]University of Sheffield, Sheffield, United Kingdom, [3]University of Toronto, Toronto Western Hospital, Toronto, ON, [4]Hospital Clinico Universitario, Santiago, Spain, [5]Cabrini Health and Monash University, Melbourne, Australia, [6]University of California San Diego, La Jolla, CA, [7]University of Orléans, Orléans, France, [8]University of Erlangen-Nuremberg, Erlangen, Germany, [9]Celgene Corporation, Warren, NJ, [10]Schön Klinik Hamburg Eilbek, Hamburg, Germany.

Background/Purpose: Apremilast (APR), a phosphodiesterase 4 inhibitor, helps regulate the immune response that causes inflammation and skin disease associated with psoriatic arthritis (PsA). PALACE 1, a phase 3 randomized trial with an open-label extension, compared the efficacy/safety of APR with placebo (PBO) in pts with active PsA despite prior conventional DMARDs and/or biologics.

Methods: Pts were randomized (1:1:1) to receive PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline DMARD use (yes/no). Pts whose swollen/tender joint counts had not improved ≥20% at Wk 16 were considered non-responders and were re-randomized (1:1) to APR20 or APR30 (PBO pts) or continued on their initial dose (APR pts). At Wk 24, all remaining PBO pts were re-randomized to APR20 or APR30. Double-blind APR treatment continued to Wk 52; pts could continue to receive APR during an open-label, long-term treatment phase. The analysis reports safety findings from the APR-exposure period (Wks 0 to ≤104).

Results: 504 pts were randomized and received ≥1 dose of study medication (PBO: n=168; APR20: n=168; APR30: n=168). A total of 490

(410.3 pt-years) and 344 (306.2 pt-years) pts received APR in the Wk 0 to ≤52 and Wk >52 to ≤104 APR-exposure periods, respectively. During the Wk >52 to ≤104 period, AEs occurring in ≥5% of APR-exposed pts were nasopharyngitis and URTI (Table). Most AEs were mild/moderate in severity between Wks >52 to ≤104 and in general, no increase was seen in the incidence or severity of AEs with longer term exposure. During the Wk >52 to ≤104 exposure period, diarrhea and nausea occurred at lower rates (1.7% and 1.2%, respectively) than in the Wk 0 to ≤52 period (15.3% and 12.4%, respectively). Serious AEs occurred in 6.4% (APR20) and 4.7% (APR30) over the Wk >52 to ≤104 APR-exposure period.Through Wk 104, serious infections were reported by 5 pts receiving APR during Wks 0 to ≤52 and 3 pts receiving APR during Wks >52 to ≤104; none were opportunistic infections. No cases of tuberculosis (new or reactivation) were reported with either APR dose. Discontinuations due to AEs occurred at a lower rate in the combined APR-exposure pts during the Wk >52 to ≤104 (1.5%) APR-exposure period than in Wks 0 to ≤52 (8.2%). Discontinuation rates due to diarrhea and nausea also decreased over the Wk >52 to ≤104 APR-exposure period. Marked laboratory abnormalities were generally infrequent and returned to baseline with continued treatment or were associated with a concurrent medical condition.

Conclusion: APR demonstrated an acceptable safety profile and was generally well tolerated for up to 104 wks, with no new safety concerns identified with long-term exposure. These data continue to support that specific laboratory monitoring is not needed with APR.

	APR-Exposure Period* Wks 0 to ≤52		APR-Exposure Period* Wks >52 to ≤104	
Patients, n (%)	**APR20 n=245**	**APR30 n=245**	**APR20 n=173**	**APR30 n=171**
≥1 AE	171 (69.8)	178 (72.7)	108 (62.4)	101 (59.1)
≥1 serious AE	14 (5.7)	21 (8.6)	11 (6.4)	8 (4.7)
≥1 serious infection	2 (0.8)	3 (1.2)	2 (1.2)	1 (0.6)
AE leading to drug withdrawal	17 (6.9)	23 (9.4)	2 (1.2)	3 (1.8)
Death	1 (0.4)$^{\mu}$	0 (0.0)	0 (0.0)	1 (0.6)‡
AEs in ≥5% of patients, any treatment group, n (%)				
Diarrhea	28 (11.4)	47 (19.2)	3 (1.7)	3 (1.8)
Nausea	24 (9.8)	37 (15.1)	3 (1.7)	1 (0.6)
Headache	22 (9.0)	24 (9.8)	6 (3.5)	8 (4.7)
URTI	20 (8.2)	15 (6.1)	15 (8.7)	8 (4.7)
Nasopharyngitis	18 (7.3)	16 (6.5)	7 (4.0)	12 (7.0)

*Includes all patients who received APR during the time interval relative to the start of APR. $^{\mu}$Multiorgan failure not suspected to be treatment related. ‡Patient died in a motor vehicle accident on study day 489 while receiving APR 30.

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Apremilast, an Oral Phosphodiesterase 4 Inhibitor, Is Associated with Improvement of Pain, Fatigue, and Disability in Patients with Psoriatic Arthritis: Results from 3 Phase 3, Randomized, Controlled Trials.

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Background/Purpose: Apremilast (APR) is an oral phosphodiesterase 4 inhibitor that helps regulate the immune response that causes inflammation and skin disease associated with psoriatic arthritis (PsA). The PALACE 1, 2, and 3 trials compared the efficacy and safety of APR with placebo in patients with active PsA despite prior conventional disease-modifying antirheumatic drugs (DMARDs) and/or biologics, including biologic failures.

Methods: Patients were randomized (1:1:1) to receive placebo, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline DMARD use (yes/no). Patients whose swollen and tender joint counts had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if they were initially randomized to placebo, or continued on their initial apremilast dose. At Week 24, all remaining placebo patients were re-randomized to APR20 or APR30. This analysis reports data over 52 weeks.

Results: In the pooled PALACE 1–3 population, a significantly greater proportion of patients receiving APR20 and APR30 achieved a modified ACR20 response vs placebo at Week 16 (placebo: 18.8%; APR20: 32.0% [$P<0.0001$]; APR30: 37.0% [$P<0.0001$]) (primary endpoint). At Week 16, significant improvements were observed with APR20 and APR30 (PALACE 1–3, pooled) for multiple patient-reported outcomes compared with placebo (placebo; APR20; and APR30, respectively): least-squares (LS) mean changes in Health Assessment Questionnaire-Disability Index (HAQ-DI) (−0.07; −0.16 [$P=0.0009$]; and −0.21 [$P<0.0001$]), pain visual analog scale (VAS) (−5.8; −10.7 [$P=0.0009$]; and −12.7 [$P<0.0001$]), 36-item Short-Form Health Survey version 2 (SF-36v2) physical component summary (PCS) (1.9; 3.3 [$P=0.0016$]; and 3.9 [$P<0.0001$]), and SF-36v2 Physical Functioning (PF) domain (1.3; 2.7 [$P=0.0057$]; and 3.6 [$P<0.0001$]) scores. APR30 also significantly improved the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score at Week 16 (1.1; 1.5 [$P=NS$]; and 3.5 [$P<0.0001$]). In patients initially randomized to APR who completed Week 52, improvements were sustained at Week 52 across the individual studies (Table). The most common adverse events reported for up to 24 weeks of APR treatment were diarrhea (12.2%), nausea (10.1%), and headache (8.0%) (PALACE 1–3; pooled). The safety profile of APR through 52 weeks was similar to that observed with APR for up to 24 weeks of treatment.

Conclusion: Among patients continuously treated with APR, sustained clinically meaningful improvements in patient-reported outcome measures of pain, physical function, and fatigue were observed through Week 52. APR demonstrated an acceptable safety profile and was generally well tolerated through 52 weeks.

Impact of APR on Parameters of Pain, Disability, and Fatigue at Week 52 (Data as Observed)

	PALACE 1		PALACE 2		PALACE 3	
Mean Change From Baseline	**APR20 n=124**	**APR30 n=130**	**APR20 n=125**	**APR30 n=114**	**APR20 n=120**	**APR30 n=126**
HAQ-DI (0–3)*	−0.37	−0.32	−0.19	−0.33	−0.33	−0.35
Pain VAS (0–100 mm)*	−17.8	−20.3	−13.5	−12.9	−14.9	−18.7
SF-36v2 PCS (0–100 mm)$^{\mu}$	7.8	6.5	5.1	6.4	6.3	5.9
SF-36v2 PF (0–00 mm)$^{\mu}$	7.0	5.7	4.1	5.0	5.7	5.9
FACIT-fatigue (0–52)$^{\mu}$	4.3	3.7	2.5	4.4	4.8	6.2

Note: The n reflects the number of patients who completed 52 weeks; actual number of patients available for each endpoint may vary. *Decrease indicates improvement. $^{\mu}$Increase indicates improvement.

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The Efficacy and Safety of Biological Disease Modifying Anti-Rheumatic Drugs and Apremilast in the Treatment of Psoriatic Arthritis: A Systematic Review and Meta-Analysis. Arthur N. Lau[1], Michael Zoratti[2], Alfred Cividino[1], William Bensen[1], Jonathan D. Adachi[1] and Christopher Edwards[3]. [1]Division of Rheumatology, McMaster University, Hamilton, ON, [2]Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, ON, [3]NIHR Wellcome Trust Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom.

Background/Purpose: Currently, there are a number of effective therapies for psoriatic arthritis (PsA). The objective of this systematic review was to assess the efficacy (PSARC, ACR 20/50/70 and PASI75 response) and adverse event profile (AEs) (any AEs, serious AEs, and infection rate) of using TNF inhibitors or new therapies including Ustekinumab and Apremilast to treat active PsA.

Methods: This review included all published/unpublished RCTs comparing biologics or Apremilast to placebo in PsA patients. Multiple mechanisms of action (MOA) were included: TNF inhibitor (Adalimumab, Certolizumab, Etanercept, Infliximab and Golimumab), IL12/23 inhibitor(Ustekinumab) and PDE4 inhibitor(Apremilast). The databases MEDLINE(n=245), EMBASE(n=1551) and CENTRAL(n=223) were searched. Conference abstracts from the ACR and American Academy of Dermatology (2009–13) were hand searched. Two reviewers independently screened titles/abstracts/full text for eligibility. Data extraction and risk of bias assessment were performed in duplicate using Cochrane's Risk of Bias Assessment.

Results: 18 studies (5433 participants) were included. Kappa for full text and risk of bias was 0.8545 and 0.9217 respectively. When the MOAs were pooled, the risk ratio (RR) for achieving PSARC, ACR20,50,70, and PASI75 at 12–16 and 24 weeks(wk) were all statistically significant. The likelihood of achieving the primary outcome ACR20 (12–16wk) had RR=2.74(95%CI=2.27–3.32) with significant heterogeneity (I^2= 65%) which was explained by *a priori* subgroup analysis (by MOA). When comparing the ACR20 (12–16wk) response by MOA, the RR was 3.99 (95%CI: 2.91–5.46), 2.03 (95%CI: 1.70–2.42) and 2.08 (95%CI: 1.66–2.59) respectively for the TNF, PDE4 and IL12/23 inhibitors. RR of achieving ACR20 response (24wk) by MOA is shown in figure1. Low heterogeneity (I^2<40%) was seen for the outcomes ACR50,70 at 12–16/24wk respectively, suggesting there may be comparable efficacy of each MOA class for these outcomes. There was no significant increase in risk for any AEs or severe AEs, except a mild increase in risk of infections at 24wk (RR=1.15, 95%CI= 1.00–1.32).

Conclusion: TNF inhibitors, Ustekinumab & Apremilast all appear to produce significant benefits on joint and skin disease for individuals with PsA. The safety profile, aside from a slight increased risk of infections, appears acceptable. When comparing the three MOAs, the TNF inhibitors appeared most effective in achieving an ACR20 response at 12–16wk. However, by 24wk there was no significant difference between TNF inhibition and Apremilast while a significant difference remained between TNF inhibition and Ustekinumab. Whilst head to head trials are needed to definitively draw such conclusions, incorporating additional RCTs in future analyses will provide greater power to characterize this relationship.

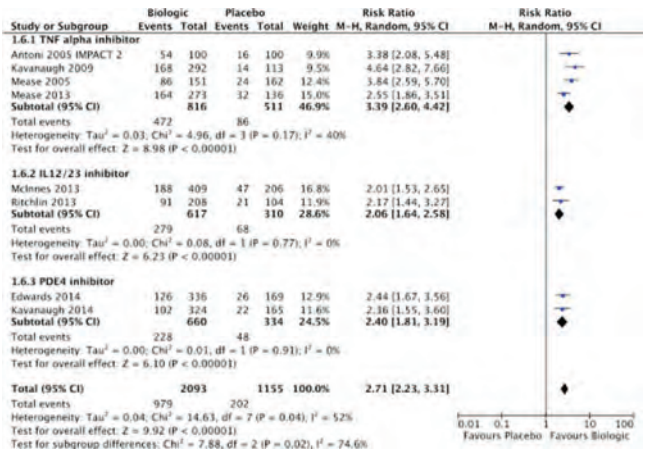

Fig1: RR for achieving ACR20 response (24wk) vs placebo by MOA

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The Spectrum of Autoimmune Ophthalmic Manifestations in Psoriatic Disease. Sergio Schwartzman[1], Anton Kolomeyer[2] and David Chu[3]. [1]Hospital for Special Surgery, New York, NY, [2]University of Pittsburgh, Pittsburgh, PA, [3]Rutgers, Newark, NJ.

Background/Purpose: Psoriatic disease is characterized by the presence of psoriasis with or without an association of extra-dermal manifestations. Inflammatory forms of arthritis are the most common concomitant findings in this continuum but not infrequently other organ systems manifest involvement. There is a dearth of primary literature on autoimmune ocular manifestations in patients with Psoriasis (Ps) and Psoriatic arthritis (PsA) although the prevalence of uveitis in PsA has been documented to be as high as 25.1%. [1]

The purpose of this study is to describe the pattern of ocular inflammation in patients with psoriatic disease.

Methods: Retrospective chart review of ocular manifestations in patients with Ps and PsA from two tertiary care centers in the United States specializing in autoimmune ophthalmic disease. Data was collected on age, gender, ethnicity, associated autoimmune disease, ocular manifestations, HLA Typing, systemic immunomodulating agents and ocular therapy

Results: 20 patients were identified with the following characteristics:

Age in years at Diagnosis of Ophthalmic Disease mean +/− SD	45.9 SD +/− 14.4
Male/Female	5/15
Race	1 Hispanic, 2 African Americans. 17 Caucasians
Psoriatic Disease	6 Ps, 14 PsA
Additional Systemic Illnesses	3 Sarcoid, 2 RA
Pattern of PsA	8 Oligoarticular, 2 Axial, 1 Polyarticular (not available in 3 pts)
Ophthalmic Illness	6 Anterior Uveitis, 3 Panuveitis 2 Scleritis, 1 Episcleritis, 3 Sclerouveitis, 2 PUK, 1 Vasculitis, 1 Multifocal Choroiditis
Systemic Therapy	Systemic and Local Steroids, Sulfasalzine, Methotrexate, Mycophenolate, Cyclosporin, Adalimumab, Infliximab, Certolizumab, Etanercept, Cytoxan, Rituximab
Number of Patients Requiring More than One Immunomodulatory Medication	11

Conclusion: The breadth and severity of ocular manifestations in patients with Ps and PsA is diverse. This is the largest cohort of patients with autoimmune ophthalmic manifestations and psoriatic disease described to date. There are several unique features of this cohort:

1. 30% of patients had only skin disease.
2. Although it appears that anterior uveitis is the most common autoimmune ocular manifestation of this group of diseases in this cohort of patients it tends to be chronic, differentiating this ocular manifestation from the pattern in Ankylosing Spondylitis.
3. 33% of patients had an overlap of two underlying systemic autoimmune diseases.
4. When ocular manifestations do occur in patients with psoriatic disease, they tend to be more severe and require more than one immunomodulatory therapy.
5. The most common pattern of PsA in patients with autoimmune ophthalmic disease is the oligoarticular form.

1.Zeboulon N, Dougados M, Gossec L. Prevalence and characteristics of uveitis in the spondyloarthropathies: a systematic literature review. Ann Rheum Dis. 2008; 67(7):955–9. Epub 2007/10/27. doi: ard.2007.075754

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Joint Damage Is Not Associated with Smoking Status in Patients with Psoriatic Arthritis. Hernán Maldonado-Ficco, Arane Thavaneswaran, Vinod Chandran and Dafna D. Gladrman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: The association between smoking and radiographic progression has been established in axial spondyloarthritides and rheumatoid arthritis (RA) but this association has not been established in psoriatic arthritis (PsA). The **aim** of this study was to determine the effects of cigarette smoking on clinical joint damage in patients with psoriatic arthritis.

Methods: From 1306 PsA patients followed prospectively between 1978 and 2014 as part of an observational cohort, a total of 1107 that started treatment after the first visit was included in the current study. We defined clinical damage as limitation of movement of more than 20% of the range that is not related to a joint effusion, the presence of flexion contractures, fused or flail joints, or evidence of surgery in a particular joint. We used clinical damage as it is assessed at each protocol visit and we have previously demonstrated that clinical joint damage in linked to radiological joint damage. We evaluated the smoking status at the baseline visit up until the first development of clinical joint damage. Smoking status was defined as 'non-smoker', 'past smoker' and 'current smoker'. Time to development of joint damage was assessed using a Cox Regression Analysis to determine the factors predictive of clinical damage, including age, sex, dactylitis and smoking status, joint counts, treatment and HLA B*27 status.

Results: Among the 1107 patients, 55.6% were males, with a mean age of 46 years, duration of psoriasis 17.4 years and the duration of PsA 8.4 years at baseline. 55.6% of the patients were non-smokers, 24.4% were past-smokers and 12.4% were current smokers. 7.9% of the patient had clinical joint damage and 26% had dactylitis at baseline. Males, HLA-B*27 positivity, higher age at diagnosis of PsA, clinical damage at baseline, dactylitis and swollen joints were associated with a higher probability of developing clinically damaged joints whereas current and past-smokers at baseline were associated with a lower probability of developing clinically damaged joints compared to non-smokers.

Conclusion: Unlike what occurs in RA and ankylosing spondylitis, the clinical damage in PsA was not associated with smoking status but was associated with disease-specific features.

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Persistence of Biologic Therapy in Psoriatic Disease: Results from the Psoriasis Longitudinal Assessment and Registry. Alan Menter[1], Kim Papp[2], Gerald G. Krueger[3], Matthias Augustin[4], Francisco Kerdel[5], Melinda Gooderham[6], Kavitha Goyal[7], Steve Fakharzadeh[8], Wayne Langholff[9], Jan Sermon[10], Steve Calabro[7] and David Pariser[11]. [1]Baylor Research Institute, Dallas, TX, [2]Probity Medical Research, Waterloo, ON, [3]University of Utah, Salt Lake City, UT, [4]University Clinics of Hamburg, Hamburg, Germany, [5]University of Miami, Miami, FL, [6]SKiN Centre for Dermatology, Peterborough, ON, [7]Janssen Services, LLC, Horsham, PA, [8]Janssen Services, LLC, Spring House, PA, [9]Janssen Research and Development, LLC, Spring House, PA, [10]Janssen-Cilag, Beerse, Belgium, [11]Eastern Virginia Medical School and Virginia Clinical Research, Inc, Norfolk, VA.

Background/Purpose: We evaluated persistency (treatment longevity) of biologics in patients (pts) with psoriasis (PsO), as well as with psoriatic arthritis (PsA) in the context of a large disease-based registry.

Methods: PSOLAR evaluates safety and clinical outcomes for PsO pts eligible to receive treatment with systemic agents. The study includes 36% pts (n=4317) with self-reported PsA. Duration of therapy was defined as time (in days) between first dose of biologic and the first of: 1) discontinuation 2) switch 3) registry withdrawal or 4) last database cutoff (August 23, 2013). Separate analyses were performed for: 1st line (bio-naïve; i.e. first biologic started on registry), 2nd line (second biologic started while on registry) and 3rdline usage (third biologic started while on registry) to reduce confounding associated with prior exposures for overall population and for subset with PsA. Baseline demographics and reasons for stop/switch were summarized. Persistence was assessed by Kaplan-Meier (KM) analysis for time to therapy stop/switch separately for ustekinumab (UST), infliximab (IFX), adalimumab (ADA), and etanercept (ETN). Cox proportional hazard regression was used to compare time to stop/switch of UST with time to stop/switch of other biologics for each cohort.

Results: The highest starts were attributed to UST (1833 pts) and ADA (1303) with lower starts for ETN (537) and IFX (327). Among UST starts, the proportions of 1st, 2nd and 3rd line usage were 20%, 31%, and 30%; ADA starts 31%, 48%, and 15%; ETN starts 54%, 29% and 13%; IFX starts 19%, 28% and 32%, respectively. Baseline clinical characteristics were generally comparable across biologics and cohorts, with some variability: prevalence of severe PsO was greater for UST and IFX vs ADA and ETN (higher BSA and higher proportions of pts with PGA score of 4 and 5). Fewer pts discontinued UST than IFX, ETN, and ADA in all 3 lines. Overall, median duration of therapy was generally longer for UST vs the 3 anti-TNF therapies. For first line starts, a better persistence was observed for UST based on statistically significant differences in time to stop/switch for each biologic vs UST (IFX vs UST: HR3.04; CI:1.66–5.57; p=0.0003; ADA vs UST: HR4.99; CI:3.39–7.35; p<0.0001; ETN vs UST: HR5.59; CI:3.77–8.29; p<0.0001). Similar results were observed for analysis of 2nd and 3rd line starts. In the subgroup with self-reported PsA, for first line starts, better persistence was observed with UST vs ETN (HR 2.53; CI 1.39–4.62; p=0.0024) but there were no significant differences vs IFX and ADA. UST had better persistence than all 3 anti-TNFs in the analyses of 2nd and 3rdline starts. Reasons for stop/switch were similar across biologics and cohorts (most frequent reason-lack of efficacy). Data were not adjusted for expected variability such as socioeconomic factors (eg, access to medication), setting of administration (self vs HCP office, e.g, UST was likely often administered in a HCP office which may affect persistency), and geographic region.

Conclusion: Persistence of UST therapy in psoriatic disease was significantly better than anti-TNF therapies in biologic- naïve and experienced PsO pts, with lower rates of stopping/switching and higher median days on therapy.

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Relationship Between Psoriatic Arthritis Severity, Duration, and Comorbidities. Stacy Tanner[1], Molly McFadden[2], Daniel Clegg[3] and Jessica Walsh[1]. [1]University of Utah, Salt Lake City, UT, [2]University of Utah, SLC, UT, [3]University of Utah Medical Ctr, Salt Lake City, UT.

Background/Purpose: People with psoriatic arthritis (PsA) have an increased risk for several comorbidities that negatively impact quality of life and survival. Defining the relationships between comorbidities and PsA characteristics may help identify subsets of PsA patients at high risk for comorbidities. The objective of this study was to determine if PsA severity or duration associated with the number of comorbidities.

Methods: This was a cross-sectional study of PsA participants in the Utah Psoriasis Initiative Arthritis Registry. Data were collected with questionnaires, interviews, and examinations between 1/22/2010 and 4/21/2014. Disease severity measures included a functional assessment [BASFI], a quality of life instrument [Psoriatic Arthritis Quality of Life (PsAQOL)], and disease activity measures, [68 tender joint count (TJC), 66 swollen joint count (SJC), BASDAI, Physician Global, Patient Global, and a cutaneous physician global assessment multiplied by the body surface area (PGAxBSA)]. To analyze PsA duration, a proportional odds logistic regression model was used to test for an association between PsA duration (<5 years, 5–15 years, and >15 years) and number of comorbidities (0, 1–2, or ≥3 comorbidities), after adjustment for age, gender, race, body mass index (BMI), TJC, and SJC. For severity assessments, a general linear model was used to test for differences in the mean score for each instrument after adjusting for age, gender, race, BMI, and PsA duration.

Results: PsA was diagnosed and phenotyped by a rheumatologist in 190 participants (Table 1). Compared to participants with PsA duration 15 years had higher mean numbers of comorbidities, but the difference was statistically significant only in the group with duration of 5–15 years (Table 2). The number of comorbidities was associated with BASFI (Table 3), but not with measures of quality of life or disease activity (data not shown).

Conclusion: Higher numbers of comorbidities may be associated with longer PsA duration and functional limitations as measured by BASFI. Anticipated analysis of a larger number of participants in a multi-center comorbidity project will provide a better understanding of the relationships between comorbidities, PsA duration, and PsA severity.

Table 1. Demographics, disease characteristics, and comorbidities (n=170-190)

	Number of participants (%) or mean (SD)		
PsA duration	**<5 years**	**5-15 years**	**15 years**
Number	76	55	58
Demographics			
Age, yrs	46.0 (12.3)	49.0 (14.0)	54.7 (12.8)
Female	43 (56.6)	27 (49.1)	30 (51.7)
Caucasian Race	71 (93.4)	54 (98.2)	55 (94.8)
BMI > 30	30.3 (8.7)	30.5 (8.8)	30.4 (8.9)
Disease severity			
BASFI	3.7 (2.6)	4.8 (2.7)	4.3 (2.7)
BASDAI	5.3 (2.2)	6.0 (2.4)	4.7 (2.1)
PsAQOL	7.0 (5.6)	11.1 (9.0)	6.6 (5.8)
Tender joint count	3.4 (4.3)	4.2 (5.3)	3.7 (6.0)
Swollen joint count	2.8 (3.3)	4.6 (7.3)	2.9 (5.5)
PGAxBSA	5.5 (10.0)	14.7 (52.2)	5.0 (13.1)
Physician Global	3.8 (1.5)	4.3 (1.9)	3.4 (1.8)
Comorbidities			
Number of comorbidities	1.8 (2.0)	2.7 (2.0)	2.6 (2.1)
Uveitis	2 (2.6)	0	4 (6.9)
Inflammatory Bowel Disease	0	2 (3.6)	5 (8.6)
Hypertension	18 (23.7)	25 (45.5)	21 (36.2)
Myocardial Infarction	2 (2.6)	1 (1.8)	1 (1.7)
Congestive Heart Failure	3 (3.9)	3 (5.5)	0
Angina	1 (1.3)	2 (3.6)	2 (3.4)
Stroke	3 (3.9)	2 (3.6)	2 (3.4)
Dyslipidemia	13 (17.1)	17 (30.9)	20 (34.5)
Chronic kidney disease	2 (2.6)	4 (7.3)	2 (3.4)
COPD/emphysema	1 (1.3)	0	3 (5.2)
Cancer	5 (6.6)	1 (1.8)	6 (10.3)
Diabetes	5 (6.6)	7 (12.7)	11 (19.0)
Osteoporosis/osteopenia	5 (6.6)	8 (14.5)	7 (12.1)
Seizure disorder	1 (1.3)	1 (1.8)	0
Multiple sclerosis	0	0	2 (3.4)
Restless leg syndrome	5 (6.6)	2(3.6)	7 (12.1)
Insomnia	6 (7.9)	10 (18.2)	7 (12.1)
Sleep apnea	12 (15.8)	11 (20.0)	14 (24.1)
Chronic heartburn/reflux	13 (17.1)	14 (25.5)	15 (25.9)
Thyroid disease	8 (10.5)	7 (12.7)	8 (13.8)
Hepatitis B	1 (1.3)	2 (3.6)	0
Hepatitis C	1 (1.3)	3 (5.5)	0
Depression	17 (22.4)	18 (32.7)	12 (20.7)

Table 2. Number of comorbidities and PsA duration (n=190)

Duration (years)	**n**	**Unadjusted OR (95% CI)**	**p value before adjustment**	**Adjusted* OR (95% CI)**	**p value after adjustment**
<5	76	Reference	Reference	Reference	Reference
5–15	55	2.54 (1.36–4.73)	0.003	2.63 (1.29–5.36)	0.008
>15	58	2.39 (1.30–4.42]	0.003	1.73 (0.86–3.48)	0.128

* Adjusted for age, gender, race, body mass index, tender joint count, & swollen joint count.

Table 3. Number of comorbidities and BASFI (n=170)

Number of comorbidities	**n**	**BASFI LS* mean (95% Confidence Limits)**	**p value (Compared to ≥5 comorbidities)**
0	47	2.33 (0.46–4.29)	0.04
1	34	2.51 (0.57–4.46)	0.10
2	31	2.18 (0.32–4.14)	0.03
3	27	3.84 (1.83–5.85)	0.99
4	21	4.20 (2.11–6.30)	1.00
≥5	29	4.26 (2.42–6.11)	Reference

LS = least squares.

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Musculoskeletal Complaints and Psoriatic Arthritis in Primary Care Patients with Psoriasis. M.C. Karreman[1], A.E.a.M. Weel[1], M. van der Ven[1], M. Vis[1], I. Tchetverikov[2], T.E.C. Nijsten[1], J.M.W. Hazes[1] and J.J. Luime[1]. [1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]Albert Schweitzer Hospital, Dordrecht, Netherlands.

Background/Purpose: Musculoskeletal complaints(MSC) account for about 10% of the General Practitioner (GP) consultations[1], in a small percentage the underlying disease is psoriatic arthritis (PsA). Evidence suggests that when a psoriasis patient visits the GP with MSCs, GP's don't always link the existing psoriasis with the MSC limiting early referral of PsA. This may be explained by the limited knowledge about the frequency of MSC and PsA in psoriasis patients in primary care.[2,3]

Our objective was to estimate the prevalence of MSC and PsA in primary care patients with psoriasis.

Methods: We conducted a cross-sectional study in adult primary care patients with psoriasis. Patients were identified from GP records by ICPC code S91 for psoriasis. Responding patients reporting pain in joints, entheses or the lower back were checked on eligibility by a telephone interview and invited for clinical evaluation. Ultrasonoghraphy (US) of the enthesis was performed if a patient had at least one tender enthesis (LEI/MASES) by an independent trained examiner. Patients were referred to a rheumatologist if clinical evaluation suggested the presence of arthritis or axial disease or ultrasonography of the enthesis showed positive Power Doppler(PD) signal. A PsA case was defined by opinion of the rheumatologist or fulfilling the CASPAR criteria with PD signal in an enthesis on US.

Results: 649 psoriasis (PsO) patients from 97 GPs were invited (Table 1). Of the 1722 responders (65.0 %), 890(51.7%) were willing to participate of which 672 (75.5%) reported MSC at the telephone interview (TI) and 527 were clinically evaluated. 145 out of the 672 patients dropped out between TI and the visit, mostly without giving any reason. The 832 patients that did not want to participate reported MSC in 19.7% (n=164) on the reply slip.

Among the 527 patients we found 54 new cases of PsA(10.2%): inflammatory arthritis (n=11), axial disease (n=3), enthesitis (n=37; confirmed by US) and a combination of symptoms(n=3). Another 62 existing PsA patients were identified. This led to a prevalence of 6.7% among PsO patients that responded (n=1722) and 4.4% among all invited PsO patients (n=2649) assuming no additional cases in the non-responders (Table 2).

Conclusion: Among psoriasis patients with musculoskeletal complaints in primary care (n=836) the prevalence of PsA is estimated to be 13.8% (95%CI 11.6%-16.2%), which would decrease to 4.4% (95% CI 3.7%-5.2%) among all PsO patients if no additional cases would be observed in the non-responders. Besides 54 of the 116 cases (46.6%) hadn't been diagnosed before our study, this indicates underdiagnosis of PsA in primary care.

Table 2. Prevalence of PsA

	Prevalence (n = 116)	**Prevalence new cases (n = 54)**
Overall (n = 2649)	4.4 (3.7–5.2)	2.0 (1.6–2.7)
Responders (n = 1722)	6.7 (5.6–8.0)	3.1 (2.4–4.1)
Psoriasis patients with MSC (n = 836)	13.8 (11.6–16.2)	6.5 (5.0–8.3)

Numbers presented in % (95%CI)

Table 1. Musculoskeletal complaints (MSC) in the study population

	All Patients n = 2649	**All Responders n = 1722**	**Eligible Participants n = 890**	**Evaluated Patients n = 527**
Female (%)	48.4	50.9	48.5	50.1
Age in yr; mean (sd)	55.4 (17.5)	59.4 (16.2)	57.4 (15.2)	55.8 (13.9)
MSC Unknown (n)		158	68	0
No MSC (n)		724	150	13
MSC - self reported (n)		840	672	514
More than 1 feature (n)			513	331
Only arthralgia (n)			98	161
Only tendon pain (n)			18	12
Only cLBP[#] (n)			43	10

[#] cLBP: chronic Low Back Pain (at least one episode/spell that lasted 3 months or longer, that started before the age of 45)

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1572

Apremilast, an Oral Phosphodiesterase 4 Inhibitor, Is Associated with Long-Term (52-Week) Improvements in Enthesitis and Dactylitis in Patients with Psoriatic Arthritis: Results from a Phase 3, Randomized, Controlled Trial. Christopher J. Edwards[1], Jacob A. Aelion[2], Adewale O. Adebajo[3], Alan Kivitz[4], Paul Bird[5], ChiaChi Hu[6], Randall M. Stevens[6] and Alvin Wells[7]. [1]University Hospital Southampton, Southampton, United Kingdom, [2]West Tennessee Research Institute, Jackson, TN, [3]University of Sheffield, Sheffield, United Kingdom, [4]Altoona Arthritis & Osteoporosis Center, Duncansville, PA, [5]Combined Rheumatology Practice, Kogarah, Australia, [6]Celgene Corporation, Warren, NJ, [7]Rheumatology & Immunotherapy Center, Franklin, WI.

Background/Purpose: Apremilast (APR) is a phosphodiesterase 4 inhibitor that helps regulate the immune response that causes inflammation and skin disease associated with psoriatic arthritis (PsA). PALACE 4 compared

the efficacy and safety of APR with placebo (PBO) in patients with active PsA who were DMARD-naïve. We evaluated the impact of APR treatment over 52 weeks on enthesitis and dactylitis among PALACE 4 patients.

Methods: Patients were randomized (1:1:1) to PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30). Patients whose swollen and tender joint counts had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if initially randomized to placebo, or continued on their initial apremilast dose. At Week 24, all remaining PBO patients were re-randomized to APR20 or APR30. The analysis comprises data from Weeks 0 to 52. Enthesitis was evaluated based on MASES (range 0–13), which indicates the number of painful entheses out of 13 entheses sites. The dactylitis count (range 0–20) is the number of digits (hands and feet) with dactylitis present; each digit is rated as 0 (no dactylitis) or 1 (dactylitis present).

Results: At Week 16, a significantly greater proportion of patients receiving APR20 or APR30 achieved the modified ACR20 response vs PBO (primary endpoint). In patients initially randomized to APR and with enthesitis (n=228) or dactylitis (n=173) at baseline, APR was associated with improvements in enthesitis and dactylitis over 52 weeks, as evidenced by reductions in MASES and dactylitis count. At Week 16, median percent changes in MASES were 0.0% (PBO), −20.0% (APR20; P=0.2948), and −50.0% (APR30; P=0.0008). In patients initially randomized to APR and completing 52 weeks, median percent changes in MASES were −66.7% (APR20) and −75% (APR30) (Table); 39.6% (APR20) and 45.9% (APR30) of patients achieved a score of 0, indicating no pain at any of the entheses assessed. Median percent changes in dactylitis count at Week 16 were −50.0% (PBO), −70.8% (APR20; P=0.0691), and −69.2% (APR30; P=0.1494). In patients initially randomized to APR and completing 52 weeks, both doses resulted in a median 100% decrease in the dactylitis count; a dactylitis count of 0 was achieved in 68.6% (APR20) and 68.8% (APR30) of patients. The most common adverse events reported during the PBO-controlled period were nausea (12.6%), diarrhea (9.4%), and headache (6.0%). The safety profile of APR for up to 52 weeks was similar to that observed with APR for up to 24 weeks of treatment (PBO-controlled period).

Conclusion: Among patients continuously treated with APR through 52 weeks, sustained improvements in both enthesitis and dactylitis were observed in patients with active PsA, who had enthesitis or dactylitis at baseline. APR demonstrated an acceptable safety profile and was generally well tolerated for up to 52 weeks.

Enthesitis and Dactylitis at Week 52 in Patients Receiving APR From Baseline

MASES*	APR20 n=91	APR30 n=85
Baseline, median	3.0	2.0
Median % change from baseline	−66.7	−75.0
Patients achieving score of 0, %	39.6	45.9
Dactylitis count$^{\mu}$	**n=70**	**n=64**
Baseline, median	2.0	2.5
Median % change from baseline	−100	−100
Patients achieving score of 0, %	68.6	68.8

The n represents the number of patients with a baseline value >0 and a value at Week 52. *MASES ranges from 0 to 13, with 0 indicating no pain at any assessed entheses and 13 indicating pain at all assessed entheses. $^{\mu}$Dactylitis count is the sum of all scores for each of the 20 digits, with each digit scored as 0=absence or 1=presence of dactylitis.

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1573

Norwegian Psoriatic Arthritis Patients Are More Obese Than Rheumatoid Arthritis and Axial Spondyloarthropathy Patients. Brigitte Michelsen[1], Andreas P. Diamantopoulos[1], Arthur Kavanaugh[2] and Glenn Haugeberg[3]. [1]Hospital of Southern Norway Trust, Kristiansand, Norway, [2]University of California San Diego, La Jolla, CA, [3]University of Agder, Kristiansand, Norway.

Background/Purpose: Higher rates of obesity in psoriatic arthritis (PsA) compared to rheumatoid arthritis (RA) have been described. Obesity, C-reactive protein (CRP) and inflammatory arthritides itself are known risk factors for cardiovascular disease. Obesity is also shown to affect response to therapy in patients with inflammatory arthritis. This study aimed to compare BMI in RA, PsA and ax-SpA and additionally to examine for possible correlation between BMI and CRP in these diseases.

Methods: All the RA, PsA and ax-SpA patients that visited the out-patient clinic during the year 2013 were included. The RA patients had a diagnosis verified by the treating rheumatologist, the PsA patients all fulfilled the ClASsifcation for Psoriatic ARthritis (CASPAR) criteria and the ax-SpA patients all fulfilled the ASAS classification criteria for ax-SpA. BMI was calculated as the patient's weight in kilograms divided by height in meters, squared. CRP was assessed by turbidimetry (mg/L). The unadjusted analyses of BMI and CRP were performed using analyses of variance (ANOVA) with post hoc tests (Tuckey HSD; homogeneity of variance). The adjusted analyses were performed by use of a General Linear Model with adjustments for age, sex, smoking, years of education, disease duration and multiple comparisons (Bonferroni). Correlation analysis of BMI and CRP was performed by use of Spearman's rho.

Results: A total of 1045 RA, 351 PsA and 314 ax-SpA patients were included. Respectively, mean (SD) age was 62.9 (13.9), 55.2 (12.3), 48.2 (12.8) years, mean disease duration 12.5 (10.6), 9.9 (8.0), 13.2 (11.7) years, mean years of education 11.5 (3.6), 12.4 (3.6), 12.9 (3.5) years, percentages currently smoking 20.7, 18.6, 23.6 % and percentage females 68.0, 49.0 and 34.1%. In both unadjusted and adjusted analyses the PsA patients had significantly higher mean BMI compared to the RA and ax-SpA patients. The male PsA patients had significantly higher BMI than the RA and the ax-SpA patients in the unadjusted analyses, but this difference was only significant for the PsA patients compared to the RA patients in the adjusted analyses. For females the PsA patients had significantly higher BMI than the RA and the ax-SpA patients both in the unadjusted and in the adjusted analyses. There was only a significant correlation between BMI and CRP for females (rho=0.18, p<0.001).

	RA (n=1045)		PsA (n=351)		Ax-SpA (n=314)		p	
Unadjusted analyses BMI (SE) (kg/m^2)	25.9 (0.2)		27.7 (0.2)		26.4 (0.3)		**<0.001^a** 0.259^b **0.002^c**	
	Males (n=334)	**Females (n=711)**	**Males (n=179)**	**Females (n=172)**	**Males (n=207)**	**Females (n=107)**	**Males**	**Females**
	26.8 (0.4)	25.5 (0.2)	28.1 (0.3)	27.2 (0.4)	26.8 (0.3)	25.7 (0.5)	**0.023^a** 0.992^b **0.034^c**	**<0.001^a** 0.885^b **0.018^c**
	RA (n=1045)		**PsA (n=351)**		**Ax-SpA (n=314)**		**p**	
Adjusted analyses BMI (SE) (kg/m^2)	25.9 (0.2)		27.4 (0.3)		26.1 (0.3)		**<0.001^a** 1.000^b **0.002^c**	
	Males (n=334)	**Females (n=711)**	**Males (n=179)**	**Females (n=172)**	**Males (n=207)**	**Females (n=107)**	**Males**	**Females**
	26.7 (0.3)	25.5 (0.2)	28.1 (0.4)	27.1 (0.4)	27.1 (0.4)	25.6 (0.5)	**0.037^a** 1.000^b 0.194^c	**<0.001^a** 1.000^b **0.031^c**

a: RA - PsA, **b:** RA – ax-SpA, **c:** PsA - ax-SpA.

Conclusion: In our population of patients with inflammatory arthritides, PsA patients were significantly more obese than RA and ax-SpA patients. These differences were more pronounced for female patients. A weak correlation between CRP and BMI was found, but only for females. Both CRP and obesity are independent cardiovascular risk factors. Given the increased risk of cardiovascular events in inflammatory arthritides, obesity represents a potentially important modifiable risk factor.

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1574

University Students with Psoriatic Nail Changes Have a Greater Number of Tender Enthesial Points Than Those with Normal Nails. A Eftal Yucel, Melih Pamukcu, Elif Durukan, Busra Tosun, Berk Batman, Omer Ozkan and Anil Korcak. Baskent University Faculty of Medicine, Ankara, Turkey.

Background/Purpose: Nail pitting is present in about 10% of healthy adults, and more than 50% of patients with psoriatic arthritis. We believe that the prevalence of spondyloarthritis, especially psoriatic arthritis is higher than published in literature. Most of those patients are undiagnosed or diagnosed with different diseases. Enthesitis is the primary pathology of spondyloarthritis particularly psoriatic arthritis. It was suggested that enthesitis was an autoinflammatory lesion linking nail and joint involvement in psoriatic disease. Additionally, subclinical enthesopathy was detected more frequently

in patients with psoriatic arthritis than those with psoriasis. We hypothesized that individuals with psoriatic nail changes would have a larger magnitude of enthesitis than those with normal nails. To support this hypothesis, we aimed to determine the association between psoriatic nail changes and enthesitis as well as the frequencies of both.

Methods: We examined the hand nails of university students for psoriatic nail changes, including pitting, leukonychia, longitudinal and horizontal ridging, pitting, subungal hyperkeratosis, onycholysis, splinter hemorrhages, red spot and oil drop. All students underwent manual palpation of 14 enthesial sites (quadriceps to patella, patella to tibia, Achilles, plantar fascia, medial epicondyle, lateral epicondyle, supraspinatus) that were described in the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. Additionally, tenderness of spinous processes of thoracic vertebrae and sacroiliac joints were recorded.

Results: Three hundred seventy-seven university students (240 female, 137 male) who are attending to the faculties of medicine (229 students) and of dentistry (148 students) were included in this study. Two hundred thirty two (61.6%) of 377 students had at least one psoriatic nail change. Less specific nail changes for psoriasis such as leukonychia, horizontal and longitudinal ridging were very common among the university students (Table 1). Pitting was observed in 52 (13.8%) students. Eighty-eight (23.3%) of 377 participants had at least one tender enthesial point. The most frequently affected enthesial site was supraspinatus insertion (Table 2). Students with pitting or any other psoriatic nail changes had a greater number of tender enthesial points than those with normal nails ($p=0.002$ and $p=0.006$, respectively).

Conclusion: Pitting was detected more frequently than published in the literature among university students and pitting or any other psoriatic nail changes correlated with tender enthesial points.

Table 1. Psoriatic nail changes in university students

Nail change	N (%)
Leukonychia	136 (36.1)
Horizontal ridging	62 (16.4)
Longitudinal ridging	58 (15.4)
Pitting	52 (13.8)
Subungal hyperkeratosis	19 (5.0)
Onycholysis	18 (4.8)
Splinter hemorrhages	6 (1.6)
Red spot	1 (0.3)
Oil drop	0 (0)

Table 2. Frequency of affected enthesial points in university students

Enthesial points	N (%)
Supraspinatus	55 (14.6)
Thoracic vertebrae	27 (7.2)
Sacroiliac joints	20 (5.3)
Lateral epicondyle	20 (5.3)
Medial epicondyle	18 (4.8)
Achilles	12 (3.2)
Quadriceps to patella	10 (2.7)
Patella to tibia	9 (2.4)
Plantar fascia	8 (2.1)

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1575

The Association Between Obesity and Disease Phenotype in Psoriatic Arthritis. Lihi Eder[1], Cheryl Rosen[2], Vinod Chandran[1] and Dafna D. Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Toronto, Toronto western Hospital, Toronto, ON.

Background/Purpose: Obesity is associated with an increased risk of developing psoriatic arthritis (PsA) in patients with psoriasis. This study aimed to assess whether obesity is associated with a distinct phenotype of PsA.

Methods: A cross-sectional analysis was performed among patients with early PsA (≤2 years from the diagnosis) from a large PsA clinic and compared them to patients with psoriasis alone (PsC). Patients with PsA met the CASPAR criteria. Patients with PsC were examined by a rheumatologist to exclude the presence of arthritis. The participants were assessed according to a standardized protocol. Demographic, clinical and radiographic information was retrieved from the clinic database. The primary predictor was Body Mass Index (BMI) at the first visit to the clinic that was classified to normal (BMI30). The association between BMI and clinical and radiographic outcomes was assessed using Cochran-Armitage and linear trend tests.

Results: A total of 305 early PsA and 498 PsC patients were analyzed. Higher BMI was associated with older age (years) at onset of PsA (Normal: 38 ± 14, Overweight: 44 ± 14, Obese: 47 ± 11, $p^{trend}<0.0001$) and psoriasis (Normal: 27 ± 17 years, Overweight: 29 ± 15, Obese: 33 ± 15, $p^{trend}=0.009$). A similar trend was observed in patients with psoriasis alone, higher BMI was associated with older age (years) at onset of psoriasis (Normal: 28 ± 16, Overweight: 39 ± 16, Obese: 32 ± 16, $p^{trend}=0.01$). In addition, a longer delay (years) from the onset of symptoms to the time of the diagnosis was found in overweight and obese patients (Normal: 2.8 ± 5.8, Overweight: 3.9 ± 10, Obese: 6 ± 9.4, $p=0.02$). No difference was observed in the pattern and severity of the skin, nail or joint manifestations across the three BMI groups. Patients with higher BMI were more likely to have new bone formation at the pelvic and heel entheses (each <0.001) however no difference was observed in the extent of radiographic erosive damage. The frequency of overweight and obesity was higher in PsA compared to psoriasis alone only among participants who were older than 40 years of age (Table 1) while no difference in BMI was observed among younger individuals.

Conclusion: Obesity may mark a distinct phenotype of PsA. Higher BMI is associated with older onset of PsA and psoriasis. This finding may suggest that obesity predisposes to late-onset psoriatic disease but has little role in the development of early onset disease.

The association between BMI and PsA vs. Psoriasis by age group

		BMI Category			
		Normal BMI<25	Overweight 25≥BMI>30	Obese BMI≥30	P value
Age ≤40	PsA(N=120)	45 (37.5%)	47 (39.2%)	28 (23.3%)	0.21
	PsC(N=184)	84 (45.7%)	63 (34.2%)	37 (20.1%)	
Age >40	PsA (n=185)	35 (18.9%)	64 (34.6%)	86 (46.5%)	0.0002
	PsC(N=314)	91 (29%)	129 (41.1%)	94 (29.9%)	

Disclosure: L. Eder, None; **C. Rosen**, None; **V. Chandran**, None; **D. D. Gladman**, None.

1576

Reversal of Damage in Psoriatic Arthritis. Amir Haddad[1], Ker-Ai Lee[2], Arane Thavaneswaran[1], Vinod Chandran[1], Richard J. Cook[2] and Dafna D. Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Waterloo, Waterloo, ON.

Background/Purpose: Psoriatic arthritis could lead to severe damage and disability. However, cases of improvement in joint damage over time have been reported in the literature. We aimed to determine the prevalence of damage reversal in a large cohort of patients with psoriatic arthritis and to identify predictors of this unique feature.

Methods: In a cohort of PsA patients established in 1978, radiographic assessments are made every two years with readings by at least 2 investigators. A consensus rating according the modified Steinbrocker scoring (mSS) method classifies each of 42 hand and foot joints on a 0–4 scale where grade 0=normal, 1= juxtaarticular osteopenia or soft tissue swelling, 2= erosion, 3= erosion and joint space narrowing and 4=total destruction. Reversal of damage was defined as a decrease in the total mSS confirmed on second reading. Disease characteristics of the study population were presented using descriptive statistics. A transitional multistate model was applied to investigate ratios of transition intensities in the Steinbrocker staging of each joint, with a working independence assumption used for joints within the same patient. A reversible Markov model was applied to investigate predictors for damage reversal and progression including age, sex, disease duration, the number of actively inflamed joints at baseline and treatment with MTX and biologics in the course of follow up.

Results: Of 537 PsA patients with baseline and at least 1 follow-up radiographs with all available data 56.2% were males, had a mean (SD) age of 43.7 (12.7) and disease duration of 7.0 (8.3) years. 32.4% and 66.9% were treated with DMARDs and biologics, respectively. 373 patients developed at least 1 damaged joint. 117/537 patients (21.8%) had evidence of reversal in damage in at least one joint. Of the20,307 assessed joints in 537 patients, 339 joints had improvement in damage, of whom the majority 213 out of 348 transitions were from mSS 2 to 1 and had an intensity score of 0.025 (0.022, 0.029) as apposed to the highest estimated progression rate of 0.061 (0.055, 0.067). 164 joint improvement occurred before treatment with biologics in 63

patients, of whom the majority 104/168 transitions were also from mSS 2 to 1. When analyzing the data on the 89,965 patient-joint assessments, treatment with biologics was a predictor for transition to a state of joint improvement (RR=2.25 (1.79,2.83) P 0.0001) and less for joint progression (RR=0.67 (0.61,0.74) P 0.0001).

Conclusion: A number of patients have reversal in damage (21.8%), which occurred in 1.7% of the assessed joints. Treatment with biologics is a predictor for joint improvement and less progression of damage. Transitions of joint improvement were observed also in patients not treated with biologics.

Disclosure: A. Haddad, None; **K. A. Lee**, None; **A. Thavaneswaran**, None; **V. Chandran**, None; **R. J. Cook**, None; **D. D. Gladman**, None.

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Value and Prediction of Minimal Disease Activity in Patients with Psoriatic Arthritis. Arthur Kavanaugh[1], Philip Mease[2], Laura C. Coates[3], Iain B. McInnes[4], Maja Hojnik[5], Alex Dorr[6], Ying Zhang[6], Benoit Guerette[6], Alan Friedman[6] and Dafna D. Gladman[7]. [1]University of California San Diego, La Jolla, CA, [2]Swedish Medical Center and University of Washington, Seattle, WA, [3]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [4]University of Glasgow, Glasgow, United Kingdom, [5]AbbVie, Ljubljana, Slovenia, [6]AbbVie, Inc., North Chicago, IL, [7]University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: The prediction of treatment outcomes based on early response could be useful in guiding decisions to adjust therapy. The objective was to determine if week (wk) 12 SJC and TJC, DAS28, CDAI and RAPID3 scores are predictive of achievement of a minimal disease activity (MDA) target at wk 24 in patients (pts) with Psoriatic Arthritis (PsA) and to evaluate patient-reported outcomes (PROs) associated with achieving MDA.

Methods: This post hoc analysis used pt data from ADEPT, a double blind randomized trial of adalimumab (ADA) versus placebo (PBO) in pts with moderate to severely active PsA and an inadequate response to NSAIDs. Pts who achieved MDA at wk 24 were termed as "achievers", while those who did not, were termed "non-achievers" (NAs). PROs studied in association with MDA were: quality of life by DLQI and SF-36 scores (total, physical and mental component summary scores (P/MCS)), and fatigue by FACIT scores. The following criteria at wk 12 were considered as possible predictors of achieving MDA at wk 24: tender joint count (TJC) of 28 and 78 joints and swollen joint count (SJC) of 28 and 76 joints, DAS28, CDAI and RAPID3. The likelihood of predicting achievement of wk 24 MDA was assessed by ROC-AUC analysis, negative and positive predictive values (N/PPV).

Results: At wk 24, 24/62 pts (38.7%) on ADA treatment, and 4/60 pts (6.7%) on PBO treatment achieved MDA. While radiographic progression was low, overall, in the ADEPT trial, achievers had no progression compared to mild progression in NAs, although this difference was not statistically significant (-0.31 ± 1.88 vs. 1.26 ± 5.93, $p= 0.201$). Achievers also had higher total SF-36 scores (81.6 ± 16.8 vs. 52.1 ± 21.2, $p<0.001$), SF-36 PCS (51.0 ± 7.2 vs. 35.0 ± 10.8, $p<0.001$) and FACIT scores (43.5 ± 10.6 vs. 30.5 ± 12.2, $p<0.05$). There was no difference in the SF-36 MCS and DLQI scores of achievers compared to that of NAs. MDA achievers had lower mean SJC 76, TJC 78, DAS28(CRP), RAPID3 and CDAI scores at wk 12 than NAs, and greater improvement from BL to wk 12 in mean SJC 76 and TJC 78 scores. Wk 12 DAS28, CDAI and RAPID3 all predicted wk 24 MDA with an AUC 0.94–0.96 (table); Wk 12 TJC was a slightly better predictor than wk 12 SJC, with 28 joint-counts having similar accuracy to 78 joint-counts. All of the criteria cut points, as determined by ROC analysis, had high NPV for wk 24 MDA (table).

Wk 12 criterion	Area under the Curve (CL)	ROC Threshold	PPV	NPV
TJC28	0.89 (0.83, 0.94)	1.00	0.60	0.95
TJC78	0.91 (0.86, 0.97)	3.00	0.61	0.96
SJC28	0.80 (0.72, 0.89)	3.00	0.46	0.98
SJC76	0.84 (0.76, 0.91)	4.00	0.46	0.94
DAS28 (CRP)	0.96 (0.92, 0.99)	2.84	0.75	0.97
CDAI	0.97 (0.94, 1.00)	10.00	0.80	0.97
RAPID3	0.95 (0.90, 1.00)	1.30	0.75	0.97

Conclusion: In pts with PsA, the achievement of MDA was associated with improvements in HRQoL, physical function and fatigue. Wk 12 composite scores such as CDAI or RAPID3 remission and DAS28(CRP) LDA, as well as SJC and TJC had good ability to predict the likelihood of achieving MDA at wk 24, with 28 joint counts being as informative as 78 joint counts in this analysis. These quick and convenient tools can be used to guide treatment decisions at an early timepoint.

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Abatacept Improves Synovitis As Assessed By Magnetic Resonance Imaging (MRI) in Psoriatic Arthritis - Preliminary Analysis from a Single Centre, Placebo-Controlled, Crossover Study. Agnes Szentpetery[1], Eric J. Heffernan[1], Muhammad Haroon[2], Phil Gallagher[1], Anne-Marie Baker[1], Martina Cooney[1] and Oliver FitzGerald[1]. [1]St. Vincent's University Hospital, Dublin, Ireland, [2]Cork University Hospital, Cork, Ireland.

Background/Purpose: Abatacept is a soluble, fully human fusion protein which selectively inhibits T-cell activation via the CD80/CD86:CD28 co-stimulation pathway and decreases serum levels of inflammatory cytokines and proteins implicated in the pathogenesis of psoriatic arthritis (PsA). Improvement in skin psoriasis has been shown with abatacept treatment previously with greatest reduction in PASI using 3 mg/kg dose. It has been proposed that 10 mg/kg of abatacept, the approved dose for rheumatoid arthritis may be an effective treatment choice for PsA.

The objectives of the study were (1) to study both skin and joint-related clinical outcomes prior to and 6 months after introducing abatacept treatment in PsA; (2) to investigate MRI changes of an inflamed knee joint over time in PsA patients on abatacept.

Methods: Biological treatment-naïve PsA patients fulfilling the CASPAR criteria with active disease for >3 months (>3 swollen and >3 tender joints) with clinical synovitis of a knee and the presence of a psoriatic skin lesion were enrolled to the study. Patients were randomised to receive abatacept 3mg/kg or placebo infusion on day 1, 15 and 29; thereafter abatacept 10mg/kg was administered every 28 days for 5 months. A stable dose of methotrexate (7.5–25 mgs/week) for >3 months prior to randomization was the only concomitant DMARD permitted in the study. Ga-enhanced MRI of the same involved knee was performed at baseline, 2 and 6 months and scored using the PsAMRIS method by one consultant radiologist. For the semi-quantitative method each knee was divided into 4 anatomical regions; medial (MED) and lateral (LAT) parapateller recesses, intercondylar notch (ICN) and suprapatellar pouch (SPP). A synovitis score ranging from 0 to 3 was assigned to each region and then added for a total synovitis score (MRS) ranging from 0 to 12 per knee.

Results: 15 patients (8 female/ 7 male) with mean age of 44.6 (±14.6) years were randomized by June 2014. Four (27%) patients were on methotrexate, the remainder did not receive any DMARDs during the study.

At baseline, mean DAS28-ESR was 4.9 ± 1 and DAS28-CRP was 4.7 ± 0.9. Median PASI, HAQ, PsAQol and DLQI were 3.8 (0–16.2), 1 (0–2.125), 10 (1–17) and 3 (0–27) respectively. Mean synovitis scores at MED, LAT, ICN and SPP regions were 2.07 (±0.9), 2.21 (±0.9), 1.4 (±0.8) and 1.85(±1) respectively at baseline, mean MRS was 7.6 (±3.4).

As per EULAR criteria 87.5 % of patients responded to the treatment at 6 months and 75% were good responders. Patients' TJC68, SJC68, duration of morning stiffness, global health score, DAS28-ESR, DAS28-CRP, HAQ and PsAQol reduced significantly at 6 months compared to baseline. Median MRS decreased over the study period and was significantly lower at 6 months compared to baseline ($p=0.016$).

Conclusion: Six months of abatacept treatment reduced synovitis scores as assessed by MRI. The results of our study suggest that 10 mg/kg of abatacept is a potent treatment option in PsA.

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Change in Weight from Baseline with Apremilast, an Oral Phosphodiesterase 4 Inhibitor: Pooled Results from 3 Phase 3, Randomized, Controlled Trials. Philip Mease[1], Dafna D. Gladman[2], Arthur Kavanaugh[3], Adewale O. Adebajo[4], Juan Gomez-Reino[5], Jurgen Wollenhaupt[6], Georg A. Schett[7], Kamal Shah[8], ChiaChi Hu[8], Randall M. Stevens[8], Christopher Edwards[9] and Charles A. Birbara[10]. [1]Swedish Medical Center, Seattle, WA, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, [3]University of California San Diego, La Jolla, CA, [4]University of Sheffield, Sheffield, United Kingdom, [5]Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [6]Schön-Klinik, Hamburg, Germany, [7]University of Erlangen-Nuremberg, Erlangen, Germany, [8]Celgene Corporation, Warren, NJ, [9]NIHR Wellcome Trust Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, [10]University of Massachusetts Medical School, Worcester, MA.

Background/Purpose: Apremilast (APR) is a PDE4 inhibitor that helps regulate the immune response. PALACE 1, 2, and 3 assessed the efficacy and safety of APR in pts with active psoriatic arthritis (PsA) despite prior DMARDs and/or biologics. We evaluated weight change from BL in PALACE 1, 2, and 3.

Methods: Pts were randomized (1:1:1) to PBO, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline DMARD use (yes/no). Patients whose swollen and tender joint counts had not improved by ≥20% at Wk 16 were considered non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if initially randomized to placebo, or continued on their initial apremilast dose. At Wk 24, all remaining PBO patients were re-randomized to APR20 or APR30. The pooled analysis comprises data for the PBO-controlled period (Wks 0 to 24) and the APR-exposure period (Wks 0 to ≥52) up to cutoff date, 3/1/2013.

Results: During the PBO-controlled period, 495 pts received PBO, 501 received APR20, and 497 received APR30. At cutoff, 720 pts had received APR20 and 721 had received APR30. At BL, mean/median weight was 86.4/84.0 (PBO), 86.1/84.0 (APR20), and 84.5/83.0 (APR30) kg. Weight decrease was spontaneously reported as an AE in a small proportion of pts during both the PBO-controlled (PBO: 0.4%; APR20: 1.0%; APR30: 1.4%) and APR exposure (APR20: 1.4%; APR30: 1.8%) periods. No pts in the PBO-controlled and 2/1,441 pts (APR20: 1; APR30: 1) in the APR-exposure period discontinued due to weight decrease. An additional analysis using observed weight measurements collected at selected visits assessed changes from BL weight. In the PBO-controlled period, most pts remained within 5% of their BL weight (PBO: 92.1%; APR20: 83.5%; APR30: 86.4%). A larger proportion of APR-treated pts experienced any weight loss (APR20: 57.9%; APR30: 56.8%) vs PBO (40.1%). Weight loss >5% was experienced by 3.9% (PBO), 12.7% (APR20), and 11.0% (APR30) (Table). At the end of the PBO-controlled period, mean/median weight change from BL was 0.09/0.0 (PBO), -1.16/-0.60 (APR20), and -0.96/-0.60 (APR30) kg. In the APR-exposure period (Wks 0 to ≥52), most pts remained within 5% of BL weight (APR20: 77.0%; APR30: 75.8%); 57.3% (APR20) and 57.1% (APR30) experienced weight loss. Weight loss did not lead to any overt medical sequelae or manifestations through the APR-exposure period. In an analysis to determine the relationship between weight loss and GI AEs, weight loss was not associated with diarrhea or nausea/vomiting.

Conclusion: APR was associated with a small rate of weight decrease reported as an AE. The incidence of observed weight loss was higher with APR vs PBO, although most pts remained within 5% of their BL weight. Observed weight loss did not appear to be dose-dependent and did not lead to overt clinical sequelae. No association between weight loss and incidence of other AEs, including GI AEs, was apparent.

% Change From BL to End of Period, n (%)	PBO-Controlled Period* Wks 0 to 24			APR-Exposure Period§ Wks 0 to ≥52	
	PBO n = 491 Pt-yrs = 168.1	APR20 n = 496 Pt-yrs = 211.6	APR30 n = 491 Pt-yrs = 209.5	APR20 n = 708 Pt-yrs = 677.7	APR30 n = 711 Pt-yrs = 687.2
<−5%	19 (3.9)	63 (12.7)	54 (11.0)	116 (16.4)	126 (17.7)
≥−5% to <0%	178 (36.3)	224 (45.2)	225 (45.8)	290 (41.0)	280 (39.4)
0%	67 (13.6)	45 (9.1)	57 (11.6)	51 (7.2)	53 (7.5)
>0% to ≤5%	207 (42.2)	145 (29.2)	142 (28.9)	204 (28.8)	206 (29.0)
>5%	20 (4.1)	19 (3.8)	13 (2.6)	47 (6.6)	46 (6.5)

*PBO-controlled period includes all data through Wk 16 for pts initially assigned to PBO who escaped, and data through Wk 24 for all other pts.
§Includes all pts who received ≥1 dose of APR, regardless of when APR was initiated, with all available data up to the cutoff of 3/1/2013.

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Gender Differences in Disease Activity Accounting for Inflammatory Biomarkers in a Psoriatic Arthritis Routine Care Cohort. Soumya M. Reddy[1], Jose U. Scher[1], Christopher Swearingen[2] and Yusuf Yazici[1]. [1]New York University School of Medicine, New York, NY, [2]University of Arkansas, Little Rock, AR.

Background/Purpose: Routine care cohorts can provide data about patient phenotypes, treatment choices and responses in the 'real world'. Studying the true impact of psoriatic arthritis (PsA) and the role of available treatment options for patients seen in routine clinical environment may help physicians care for these patients more effectively. The purpose of this study is to evaluate patient characteristics, disease activity, treatment choices and responses in a routine care psoriatic arthritis cohort in a university setting.

Methods: New York University PsA Cohort, established in 2005, as part of the Arthritis Registry Monitoring Database and has been following patients with PsA prospectively as part of routine care. Clinical data is collected through MDHAQ (for function, pain, patient global assessment, fatigue, patient self report joint counts, physician global assessment), and 28 tender and swollen joint counts. In addition, medication history, demographic data and selected laboratory tests are collected. We analyzed patient characteristics and medication use along with disease activity in our cohort.

Results: 497 patients were seen to date (48.5% female, mean age 49.6 yr, disease duration 11.9yr, years of education 16.4, White 64%, Black 1.6%, Hispanic 6.8%, Other 27.6%). No differences were noted between males and females. However, female patients with PsA had significantly worse function (2.0 vs 1.6, p=0.005), pain (4.9 vs 4.2, p=0.006), pt global (4.6 vs 3.7, p=0.001), RAPID 3 scores (11.6 vs 9.4, p=0.001), fatigue (4.6 vs 3.2, p<0.001), and pt reported joint counts by RADAI (9.9 vs 7.9, p=0.017) compared to males with the disease. After adjusting for age and education; pain, patient global scores, RAPID3 scores, and fatigue remained significant. No differences in ESR and duration of morning stiffness were noted. Although CRP levels were overall lower in females, the values were not statistically significant (4.6 vs 9.9, p=0.060). Differences in RAPID3 scores between females and males remained significant after adjusting for CRP and disease duration. (Table 1) No differences were noted in the proportion of patients treated with prednisone, DMARDs, biologics, or combination DMARD/Biologics among females and males.

Table 1: Differences in RAPID3 in Females and Males Adjusting for Disease Duration and CRP

	Female	Male	
RAPID3 adjusting for Duration	12.0 (0.6)	10.0 (0.5)	**0.011**
RAPID3 adjusting for CRP	11.8 (0.7)	9.9 (0.6)	**0.021**

Conclusion: In this routine care cohort of almost 500 PsA patients, females had worse disease activity compared to males, despite receiving the same type of medication. The differences persisted even after adjusting for disease duration and CRP levels. The reasons for this seemingly undertreatment among females needs further study.

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Inflammatory Back Pain in Psoriasis and Psoriatic Arthritis Is Suggestive of Undiagnosed Spondyloarthropathies. Majed Khraishi[1], Heather Jones[2] and Annette Szumski[2]. [1]Memorial University of Newfoundland, St. John's, NF, [2]Pfizer Inc., Collegeville, PA.

Background/Purpose: Patients with psoriasis (Ps) and/or psoriatic arthritis (PsA) may have clinical features suggestive of axial skeletal abnormalities and should be assessed for the presence of spondyloarthropathies (SpA). The purpose of this post-hoc analysis from 2 clinical trials is to assess the prevalence, demographic and disease characteristics of Ps patients with and without PsA with MRI evidence of sacroiliitis (SI) abnormalities or axial involvement. We also investigated how common screening questionnaires perform in detecting inflammatory back pain (IBP) that may be suggestive of other SpAs.

Methods: From the PRESTA trial, the medical history of patients with Ps and PsA were analyzed for axial involvement. From the PREPARE trial, patients with Ps who had baseline MRIs were analyzed and characteristics assessed between those with and without MRI evidence of SI abnormalities (SI +/–). Results of the PASQi and TOPAS questionnaires in the PREPARE trial were assessed for patient-reported IBP and compared with their respective patients' SI findings to determine possible trends in each IBP +/– and SI +/– group.

Results: In the PRESTA trial, 747 patients with Ps/PsA were evaluated and 41% (304/747) had axial involvement. Those with axial involvement had a longer duration of PsA, greater Ps-affected BSA, and higher PASI, DAS28, TJC, SJC, HAQ, EQ-5D scores than those without (Table 1). A total of 186 Ps patients with MRIs were analyzed in the PREPARE trial; 47% were SI+ who tended to be older with a lower Ps-affected BSA than those who were SI– (Table 1). Only 43% (38/88) of Ps patients who were SI+ were also diagnosed with PsA. IBP was evaluated in 128 patients from the PREPARE trial with the PASQi and ToPAS questionnaires of which 45% (57/128) were IBP+ and 33% (19/57) of those were also SI+. These patients tended to be older, have a higher Ps-affected BSA, and higher PASI compared to 38 patients who were IBP+/SI– (Table 2). 58% (41/71) of patients who were IBP– were SI+ and have the fewest number of females versus the 2 IBP+ groups. 47% (9/19) of Ps patients who were IBP+/SI+ did not have PsA.

Conclusion: Patients with spinal involvement tended to be older with longer disease duration. Patients with Ps, with or without a PsA diagnosis, may exhibit clinical features of SpAs. These findings suggest that patients should be evaluated carefully for the presence of entities such as non-radiographic axial SpA and radiologic evidence of SI regardless of PsA diagnosis or reported IBP. The PASQi and TOPAS questionnaires detected 1/3 of Ps/PsA patients who reported IBP were SI+ which may be useful in detecting the possibility of SpAs.

Table 1: Baseline characteristics for patients with and without SI and axial involvement in the PRESTA and PREPARE and clinical trials

	PRESTA[a]			PREPARE[b]		
	Axial involvement n=304	Non-axial involvement n=443	P-value[c]	SI+ n=88	SI– n=98	P-value[c]
Age, years	47.33 (11.1)	45.9 (11.6)	0.086	52.2 (11.7)	44.6 (13.1)	<0.001
Male gender, n (%)	197 (64.8)	275 (62.1)	0.487	59 (67.0)	54 (55.1)	0.101
Race			0.098			0.092
White	260 (85.5)	403 (91.0)		82 (93.2)	85 (86.7)	
Asian	21 (6.9)	22 (5.0)		4 (4.5)	12 (12.2)	
Other[d]	21 (6.9)	17 (3.8)		2 (2.3)	1 (1.0)	
BMI, kg/m^2	27.6 (5.1)	28.2 (5.6)	0.105	28.9 (4.9)	29.4 (6.1)	0.534
PsA diagnosis,[e] n (%)	–	–	–	38 (43.2)	37 (37.8)	0.764
Duration of PsA, years[f]	8.3 (7.7)	6.3 (3.6)	<0.001	9.4 (8.1)	9.4 (7.8)	0.976
Duration of Ps	19.7 (11.6)	18.3 (11.6)	0.102	19.3 (13.6)	17.7 (12.0)	0.376
Ps affected BSA, %	33.4 (24.6)	28.9 (20.2)	0.007	5.3 (8.3)	8.6 (12.7)	0.036
PASI	20.6 (11.1)	18.6 (9.6)	0.007	4.5 (5.8)	5.6 (5.7)	0.185
DAS28	4.6 (1.32)	4.3 (1.3)	0.008	–	–	–
TJC	21.1 (19.9)	18.0 (11.2)	0.018	–	–	–
SJC	12.2 (15.2)	9.9 (11.1)	0.019	–	–	–
HAQ	1.1 (0.7)	0.8 (0.7)	<0.001	–	–	–
EQ-5D	0.4 (0.3)	0.5 (0.3)	<0.001	–	–	–

All values mean (standard deviation) unless otherwise specified. [a]Axial/non-axial involvement determined by medical history. [b]SI abnormalities determined by MRI. [c]P-values for continuous values are calculated using ANOVA comparing means between groups; P-values for categorical values use the chi-square test. [d]Includes those with missing values. [e]Based on physical exam, medical history, and laboratory findings. [f]Based on medical history. BSA=body surface area; PASI=psoriasis area severity index; Ps=psoriasis; PsA=psoriatic arthritis; SI=sacroiliitis.

Table 2: Baseline characteristics for the presence/absence of IBP and/or SI abnormalities in the PREPARE study

	IBP+/SI+ (n=19)	IBP–/SI+ (n=41)	IBP+/SI– (n=38)	IBP–/SI– (n=30)	P-value[a]
Age, years	54.4 (10.4)	51.2 (12.9)	45.2 (11.9)	44.9 (12.5)	0.010
Male gender, n (%)	8 (42.1)	31 (75.6)	17 (44.7)	17 (56.7)	0.018
Race, n (%)					0.369
White	18 (94.7)	39 (95.1)	32 (84.2)	25 (83.3)	
Asian	1 (5.3)	2 (4.9)	5 (13.2)	5 (16.7)	
Other[b]	–	–	1 (2.6)	–	
BMI, kg/m^2	28.1 (4.9)	29.2 (5.1)	30.4 (6.4)	27.2 (5.2)	0.120
PsA diagnosis,[c] n (%)	10 (52.6)	16 (42.1)	10 (33.3)	15 (36.6)	0.723
Duration of PsA,[d] years	7.1 (5.9)	11.6 (6.8)	9.9 (7.2)	10.1 (9.9)	0.668
Duration of Ps	21.1 (13.7)	18.4 (13.8)	16.0 (11.0)	20.4 (12.2)	0.399
Ps affected BSA, %	7.5 (15.5)	4.9 (4.7)	6.3 (10.8)	10.0 (16.4)	0.341
PASI	5.9 (10.8)	4.4 (3.6)	4.2 (4.8)	6.1 (7.0)	0.492

All values mean (standard deviation) unless otherwise specified. IBP is based on inflammatory back pain obtained either from PASQi or ToPAS. Any SI abnormalities +/– determined by MRI. [a]P-values for continuous values are calculated using ANOVA comparing means between groups; P-values for categorical values use the chi-square test. [b]Includes those with missing values. [c]Based on physical exam, medical history, and laboratory findings. [d]Based on medical history. BMI=body mass index; PASI=psoriasis area severity index; Ps=psoriasis; PsA=psoriatic arthritis.

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Cumulative Inflammatory Burden Is Independently Associated with Increased Arterial Stiffness in Patients with Psoriatic Arthritis. Jiayun Shen[1], Qing Shang[1], Ying Ying Leung[2], Edmund Li[1], Tracy Y. Zhu[1] and Lai-Shan Tam[1]. [1]Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Hong Kong, Hong Kong, [2]Department of Rheumatology and Immunology, Singapore General Hospital, Singapore, Singapore.

Background/Purpose: Patients with psoriatic arthritis (PsA) are at increased risk of cardiovascular (CV) morbidity compared with the general population, probably as a result of chronic inflammation interacting with traditional CV risk factors. Two cross-sectional studies (n<30) had reported increased arterial stiffness in patients with PsA. However, these studies were unable to assess the effect of inflammation over time. In this study, we examined whether the cumulative inflammatory burden over time is associated with an increase in arterial stiffness in a prospective cohort of PsA patients.

Methods: 72 PsA patients were followed up for 6.6±0.17 years. Clinical and cardiovascular risk factors were assessed at baseline and last visit. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were measured at each clinic visit. Cumulative inflammatory burden was represented by the cumulative averages of repeated measures of ESR and CRP, which were calculated from the area under the curve divided by the follow up time. Arterial stiffness was measured at the last visit as brachial-ankle pulse wave velocity (PWV) by a dedicated tonometry system (Non-Invasive Vascular Profile Device VP-2000; Omron Healthcare, Bannockburn, Illinois, USA). The correlation among PWV and cumulative averages of ESR (ca-ESR) and CRP (ca-CRP), as well as baseline and last follow up clinical parameters and CV risk factors were explored.

Results: The median PWV at last follow up was 1463 (interquartile range: 1331–1676) cm/s. There was a significant correlation between PWV and ca-ESR (Spearman's rho: 0.390, p =0.001). PsA patients were divided into 2 groups based on whether their PWV value is ≥ (High PWV group) or st hr, p =0.005], There was also a trend suggestive of an increased ca-CRP in the High PWV group (p =0.087). The High PWV group were older, had a longer disease duration and a higher prevalence of having Framingham 10-year CV risk score (FRS) of 10% at baseline. The High PWV group also had a lower body mass index (BMI), higher systolic blood pressure (SBP) and damage joint count at PWV assessment. In the regression analysis, high ca-ESR (defined as ≥75th percentile: 37 mm/1st hr) was associated with a higher likelihood of being in the High PWV group [OR: 5.969 (95% confidence interval: 1.361–26.176), p =0.018, adjusted for baseline clinical parameters and CV risk factors; and 5.140 (1.162–22.734), p=0.031, adjusted for last visit parameters, respectively].

Conclusion: Cumulative inflammatory burden was associated with increased arterial stiffness in patients with PsA even after adjustment for CV risk factors, emphasizing the important role of chronic inflammation in accelerating the development of CV risks in PsA patients.

Table 1. Clinical features at baseline and last follow up in patients with high and low PWV group

	Baseline			Last follow up		
	Low PWV	High PWV	*p* value	Low PWV	High PWV	*p* value
Male gender	18 (50.0%)	18 (50.0%)	1.000			
Age (years)	43.6±10.0	55.6±10.1	<0.001			
PsA duration (years)	7.5±6.8	11.0±7.5	0.041			
BMI (kg/m^2)	25.7±4.0	24.6±3.3	0.184	25.7±3.6	23.9±3.1	0.028
Systolic BP	133±23	139±21	0.226	122±13	132±16	0.003
Framingham 10-year CVD risk > 10%	13 (39.4%)	23 (67.6%)	0.020	2 (5.6%)	8 (22.2%)	0.085
Damaged joint count	1 (0–3)	2 (0–6)	0.112	1 (0–4)	4 (1–8)	0.011

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Screening for Psa in Primary Care Psoriasis Patients with Musculoskeletal Complaints with PEST, PASE & Earp. M.C. Karreman[1], A.E.a.M. Weel[1], M. van der Ven[1], M. Vis[1], I. Tchetverikov[2], M. Wakkee[1], T.E.C. Nijsten[1], J.M.W. Hazes[1] and J.J. Luime[1]. [1]Erasmus University Medical Center, Rotterdam, Netherlands, [2]Albert Schweitzer Hospital, Dordrecht, Netherlands.

Background/Purpose: Psoriatic Arthritis (PsA) is a progressive inflammatory joint disease that can lead to severe joint damage. New treatment strategies can be very effective in early stages of the disease. This requires early recognition of the symptoms to be PsA. Several screening tools have been developed to enhance early recognition. However, most were developed in secondary care, while early recognition should ideally take place in primary care.

Our objective was to evaluate the screening performance of the PEST, PASE and EARP to identify psoriatic arthritis among primary care psoriasis patients with recurrent spells musculoskeletal complaints (MSC).

Methods: We conducted a cross-sectional study in adult primary care patients with psoriasis who reported recurrent spells MSC. Patients were selected by ICPC code S91 for psoriasis and the presence of recurrent spells of MSC (joints, enthesis or low back pain) was determined by telephone interview. Patients completed the PEST, PASE & EARP questionnaires before clinical evaluation by a trained research nurse. Assessments included PASI, LEI/MASES, 66/68-joint count and the presence of nail-psoriasis. If clinical evaluation suggested the presence of arthritis or axial disease, or ultrasound (US) evaluation showed Power Doppler signal in an enthesis, patients were referred to the rheumatologist.

A PsA case was defined by fulfilling the CASPAR criteria. Sensitivity and specificity were determined for the PEST and EARP cut off ≥3 and PASE cut off ≥44 as well as ≥47.

Results: 480 psoriasis patients participated with a mean±SD age of 55.9±13.9 years and 50.8% being male (Table 1). We found 54 new cases of PsA (10.2%). Among the cases the skin was slightly more affected and more tender joints were reported, while nails were affected evenly compared to the non-cases. The PEST had a true positive rate of 63.0% and a false positive rate of 30.0%, for the EARP this was 87.0% and 67.1%. The PASE had a true positive rate of 62.9% and a false positive rate of 45.6% at the cut off of ≥44 and 55.6% and 36.4% at the cut off of≥47 (Table 2).

Conclusion: Modest sensitivity was observed for the PEST and PASE with an acceptable false positive rate for the PEST, while the EARP had high true and false positive rate, which is undesirable for screening. The performance of all screening tools was lower than previously reported in secondary care settings.

Table 1 Characteristics of the study population (n=480)

	Non-Cases (n=426)	Cases (n=54)
Age mean (SD)	56.0 (14.0)	55.2 (12.4)
% Men	50.5	53.7
TJC median (IQR**)**	0 (0–3)	2.5 (0–7)*
SJC median (IQR**)**	–	0 (0–2)
PASI median (IQR**)**	2.2 (0.9–4)	3.1 (1.6–4.4)*
Nail abnormalities n (%)	64 (15.2)	8 (14.8)
EARP median (IQR**)**	3 (2–5)	5 (3–6)*
PEST median (IQR**)**	2 (1–3)	3 (2–4)*
PASE median (IQR**)**	41 (33–49)	48 (40–52)*

TJC=Tender Joint Count, SJC=Swollen Joint Count, PASI=Psoriasis Area Severity Index
*p<0.05

Table 2 Sensitivity & Specificity of Screening Tools for PsA among primary care psoriasis patients

	Cut off	Sensitivity (95% CI)	Specificity (95% CI)
PEST	≥3	63.0 (48.7–75.7)	70.0 (65.4–74.3)
EARP	≥3	87.0 (75.1–94.6)	32.9 (28.4–37.5)
PASE	≥44	63.0 (48.7–75.7)	54.5 (49.6–59.3)
	≥47	55.6 (41.4–69.1)	63.6 (58.8–68.2)

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Evaluation of the Patient Acceptable Symptom State in Patients with Psoriatic Arthritis. Pinar Cetin[1], Dilek Solmaz[2], Murat Keser[1], Ismail Sari[1], Merih Birlik[1], Nurullah Akkoc[1] and Fatos Onen[1]. [1]Dokuz Eylul University School of Medicine, Izmir, Turkey, [2]Namik Kemal University School of Medicine, Tekirdag, Turkey.

Background/Purpose: The Patient Acceptable Symptom State (PASS), a single-question outcome, has been defined as an absolute level of patient well-being, which was used in the evaluation of treatment efficacy in several rheumatologic diseases. We aimed to evaluate the acceptability, reliability and discriminant capacity of the PASS in patients with psoriatic arthritis (PsA).

Methods: This study included PsA patients who fulfilled the CASPAR criteria. Disease activity was assessed in the patients by using "Composite Psoriatic Disease Activity Index (CPDAI)", "Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)", "Patient Global" and "Disease Activity Score (DAS) 28". "Psoriasis Area Severity Index (PASI)" was used for the measurement of severity of *psoriasis* and high-sensitive C-reactive protein (hs-CRP) level was measured as laboratory parameter of disease activity. Other follow-up parameters such as "Bath Ankylosing Spondylitis Functional Index (BASFI)","Health Assessment Questionnaire (HAQ)" and "Ankylosing Spondylitis Quality of Life (ASQoL)" were also included in the study. PASS (+) and PASS (–) groups were compared for demographic features and disease severity parameters using Mann-Whitney U test. Stepwise logistic regression was used to assess contributors to PASS. PASS thresholds were estimated with receiver operating characteristic (ROC) curve analysis. Cut off levels targeting the 75th percentile of the cumulative distribution were also determined.

Results: There were 101 PsA patients (34 male, 67 female; mean age: 46.8 ± 11.5). Eighteen (17.8%) patients had predominantly axial disease, 52 (51.5%) had predominantly peripheral disease and 31 (30.7%) had mixed symptoms. Thirty-four (33.6%) of 101 patients were in PASS. The patients with an acceptable status had significantly lower mean CPDAI, BASDAI, DAS28-CRP, ASQoL and patient global scores than the others (Table 1). The significant contributor to PASS was BASDAI (r:−0,343 Exp(B): 0.71; p<0.001). PASS (+) 75th percentile thresholds were 4.3 for BASDAI (sensivity:70.6%, specificity: 64%) and 4.0 for CPDAI (sensivity:76.5%, specificity: 54%).

Conclusion: PASS can be considered as a method in determination of PSA disease activity in the future.

Table 1. Clinical and demographic feautures of the PASS (+) and PASS (–) PSA patients

	PASS (+) (n:34)	PASS (−) (n:67)	P
Age, mean ± SD	47.9 ± 12.3	46 ± 11.0	>0.05
Male, n; %	13, 38.2	21, 31.3	>0.05
Education (years), mean ± SD	9.1 ± 4.1	9.2 ± 4.0	>0.05
CPDAI, mean ± SD	2.9 ± 2.1	4.0 ± 2.5	0.012
BASDAI, mean ± SD	2.5 ± 2.2	4.5 ± 2.3	<0.001
DAS28 CRP, mean ± SD	2.2 ± 0.8	2.7 ± 1.1	0.044
PASI, mean ± SD	5.8 ± 7.4	6.7 ± 10.1	>0.05
hs CRP, mean ± SD	10.4 ± 13.1	10.2 ± 12.5	>0.05
BASFI, mean ± SD	1.9 ± 2.1	2.9 ± 2.7	>0.05
HAQ, mean ± SD	0.4 ± 0.5	0.8 ± 0.6	>0.05
ASQoL, mean± SD	5.7 ± 5.8	8.6 ± 5.7	0.012
Patient global, mean ± SD	2.85 ± 2.8	4.4 ± 2.8	0.011

Disclosure: P. Cetin, None; **D. Solmaz**, None; **M. Keser**, None; **I. Sari**, None; **M. Birlik**, None; **N. Akkoc**, None; **F. Onen**, None.

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Presence of Swollen and Tender Joints in Patients Fulfilling Minimal Disease Activity Criteria. Josefina Marin[1], Maria L. Acosta Felquer[2], Leandro Ferreyra-Garrot[1], Santiago Ruta[3], Javier Rosa[1] and Enrique R. Soriano[4]. [1]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Rheumatology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [4]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina.

Background/Purpose: Minimal disease activity (MDA) is a composite measure created for patients with psoriatic arthritis (PsA) that encompasses many clinically important aspects of PsA: arthritis, psoriasis, enthesitis, pain, patient-assessed global disease activity, and physical function. A patient is considered to be in MDA if fulfills 5/7 criteria. In theory, a patient could be in MDA, but still have several tender and/or swollen joints.Objectives:1) To evaluate the number of patients fulfilling MDA criteria that still have several tender/swollen joints, and 2) To analyze the components of MDA that contribute most to prevent patients achieving MDA.

Methods: Consecutive patients with PsA (CASPAR criteria) were included, and all components of MDA score were assessed by a single experienced Rheumatologist. Patients were classified as in MDA if they fulfilled 5/7 criteria (tender joint count (TJC; 0–68) $\leq$ 1; swollen joint count (SJC; 0–66) $\leq$ 1; PASI $\leq$ 1 or BSA $\leq$ 3%; patient pain score on a visual analog scale (VAS; 0–100) $\leq$ 15; patient global assessment of disease activity (PaGA; VAS; 0–100) $\leq$ 20 mm; Health Assessment Questionnaire (HAQ; 0–3) $\leq$ 0.5; and tender entheseal points (0–13) $\leq$ 1). Percentage of patients with >= 2 tender and/or swollen joints within patients in MDA was calculated. We also calculated the percentage of patients not fulfilling each one of the criteria for those patients with 4 out of 7 MDA criteria.

Results: 83 patients were included. Patient's characteristics according to MDA status are shown in the table. Among the 41 patients fulfilling MDA criteria, only one patient (2.4 %) showed more than 2 tender joints (3 tender joints), and two other patients showed >=2 swollen joints (one patient two and one patient three swollen joints). Altogether 7.4 % of patients, fulfilling MDA criteria presented a clinically significant number of tender/swollen joints.Among patients fulfilling MDA criteria, only 24 % fulfilled all 7 criteria, and 32 % and 43% fulfilled 6 and 5 criteria respectively. Of those patients not in MDA status, 17 (40.5 %) fulfilled 4/7 criteria. Among those patients, the criteria more often not fulfilled were: patient pain score VAS $\leq$ 15= 100 %; PaGA VAS $\leq$ 20 mm =76.5 %; and PASI $\leq$ 1 = 65 %. Only 29 %, 18 %, 6% and 6 % did not fulfilled tender joint count, HAQ, swollen joint count and entheseal tenderness criteria, respectively.

Characteristics	MDA (n=41)	No MDA (n=42)	P value
Male sex (%)	23 (56)	21 (50)	0.578
Mean age yrs (SD)	55.6 (13.6)	51.2(14.3)	0.1528
Median months disease duration (IQR)	36 (12–96)	31.5 (10–48)	0.3460
Mean pain VAS mm (SD)	17.5(20.1)	52.7 (20.1)	<0.0001
Mean Patient Global Activity VAS mm (SD)	14 (18.2)	47.2 (21.2)	<0.0001
Mean swollen joint count (SD)	0.3 (0.6)	2.7 (2.6)	<0.0001
Mean tender joint count (SD)	0.3 (0.6)	1.8 (2.6)	0.0003
Mean HAQ (SD)	0.15(0.37)	0.43 (0.51)	0.0047
Mean tender entheseal points (SD)	0.12 (0.33)	0.49 (0.87)	0.0121
Mean PASI (SD)	1.5 (2.2)	3.8 (4.8)	0.0074
Mean DAS28 (SD)	2.3 (0.71)	3.7 (1.1)	<0.0001
Mean CPDAI (SD)	2.1 (1)	4 (1.9)	<0.0001
Mean ESR (SD)	19.8 (14.2)	24.8 (19.5)	0.1737
Number with >=2 tender joint count (%)	1 (2.4)	27 (64.3)	<0.0001
Number with >=2 swollen joint count (%)	2 (4.9)	18 (43)	0.002

Conclusion: Although possible in theory, only a minority of patients fulfilling MDA criteria present a clinically significant number of tender and/or swollen joints. In patients that were close to fulfill MDA criteria patient's VAS scores (pain and disease activity) and PASI were the most frequent reasons to fall short to MDA status.

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Quantitative Proteomic Analysis of Synovial Fluid and Skin Identifies Putative Psoriatic Arthritis Biomarkers. Daniela Cretu[1], Kun Liang[2], Dafna D. Gladman[3], Eleftherios Diamandis[4] and Vinod Chandran[3]. [1]University of Toronto, Mount Sinai Hospital, Ontario, Canada, Toronto, ON, [2]University of Waterloo, Waterloo, ON, [3]University of Toronto, Toronto Western Hospital, Toronto, ON, [4]University of Toronto, Toronto, ON.

Background/Purpose: Psoriatic arthritis (PsA) is a unique form of arthritis occurring in 30% of psoriasis patients. There is a high prevalence of undiagnosed PsA in psoriasis patients; therefore identifying soluble biomarkers for PsA will help in screening psoriasis patients for appropriate referral to a rheumatologist. Potential PsA biomarkers likely originate in sites of inflammation, such as inflamed joints and skin, and subsequently enter systemic circulation. We hypothesize that quantitative proteomic analysis of synovial fluid (SF) and skin obtained from PsA patients, willgenerate a comprehensive list of proteins specific to PsA, facilitating the identification of potential PsA screening biomarkers.

Methods: SF was obtained from swollen knee joints of 10 PsA patients, and age/sex matched early osteoarthritis (OA) controls. Likewise, skin biopsies were obtained from involved and uninvolved skin of 10 PsA, and 10 age/sex matched psoriasis patients. Using strong cation exchange chromatography, followed by tandem mass spectrometry, we characterized the proteomes of pooled SF and pooled skin samples. Extracted ion current (XIC) intensities were used to calculate protein abundance ratios, and utilized to classify upregulated proteins. Selected reaction monitoring (SRM) assays were developed to quantify these potential PsA markers in individual patient samples. Identified markers were subsequently measured in serum samples from 33 PsA and 15 PsC patients, using commercially available or in-house developed enzyme-linked immunosorbent assays (ELISA).

Results: We quantified a total of 443 and 1922 proteins in SF and skin extracts, respectively, but only 17 proteins represented upregulated proteins in PsA SF, while 47 proteins were specifically elevated in PsA-derived skin. SRM validation confirmed that 12 and 8 proteins were indeed elevated in an independent set of PsA SF and involved PsA skin, respectively. Based on the fold change between PsA and controls, the associated P-values, and the cellular localization, we ranked the proteins, and selected the following putative markers for validation in the serum - S100A9, M2BP, CD5L, MMP3, CRP, EPO, POSTN, and ITGB5. Only ITGB5, (1.2$\pm$0.5 compared to 0.8$\pm$0.6; P=0.007), M2BP (553.0$\pm$150.9 compared to 453.0$\pm$115.0; P=0.027), EPO (19.6$\pm$12.3 compared to 13.7$\pm$12.2;P=0.035), and MMP3 (3.4$\pm$3.4 compared to 1.8$\pm$1.1; P=0.046) were significantly elevated in PsA serum compared to PsC.

Conclusion: Proteomic analysis of PsA SF and skin has identified 20 candidate biomarkers, and 4 of these have been confirmed in serum following a small-scale validation. In the future, these markers must be validated in a larger and independent sample cohort, in order to identify their clinical utility in PsA patients. Additionally, these proteins may also uncover aspects of PsA pathobiology that are currently unknown.

Disclosure: D. Cretu, None; **K. Liang**, None; **D. D. Gladman**, AbbVie Canada, 5; **E. Diamandis**, None; **V. Chandran**, AbbVie, 5.

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The Economic Impact of Psoriatic Arthritis in Toronto, Ontario. Dafna D. Gladman, Melissa Yu, Michal Bohdanowicz, Arane Thavaneswaran and Vinod Chandran. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: This study aimed to quantify the direct and indirect costs of psoriatic arthritis (PsA) at a single center in Toronto, Ontario and to assess whether these costs varied with respect to socioeconomic status.

Methods: Participants were identified from the Psoriatic Arthritis Clinic at Toronto Western Hospital in Toronto, Ontario. To be included in the study, patients fulfilled the Classification criteria for Psoriatic Arthritis (CASPAR) and attended the clinic for $\geq$ 1 year. Participants were excluded if they were <18 years old or if they were non-English speakers.

Consented participants completed a questionnaire that included healthcare utilization, out-of-pocket expenses, and productivity losses in the preceding 12 months. **Results** from this survey were supplemented with a chart review of participant's prescription medication in the past year, demographic information, socioeconomic characteristics, and disease severity measures.

Direct costs were estimated according to the Ontario Drug Benefit Formulary, Ontario Health Insurance Plan, or industry averages. Indirect costs were estimated from productivity losses due to sick days or early

retirement. Age, sex, education, marital status, employment status and household income were used as indicators of socioeconomic status. The relationship between cost of PsA and socioeconomic status was assessed using the Kruskal-Wallis test, with significance of $p < 0.05$.

Results: Of the 188 patients included in the study, the mean annual direct cost of PsA was $15,802 per patient, of which $5,499 and $10,219 accounted for non-pharmacologic and pharmacologic costs, respectively. Women, unemployed, and lower income patients had significantly higher non-pharmacologic costs, whereas patients under the age of 65 had significantly higher pharmacologic costs compared to their counterparts. Thirteen % of patients were unemployed due to psoriatic arthritis, with an average 3.3 years of lost employment.

Conclusion: This study showed that PsA generates a substantial economic burden for patients in Toronto, Ontario. This burden is composed of healthcare resource consumption as well as productivity loss due to early retirement. Furthermore, age, sex, employment status, and income are all significantly associated with the direct cost of PsA. Information from this study will help to estimate the cost-effectiveness of new PsA medications and to allocate healthcare resources more effectively to certain socioeconomic groups in need.

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Resistance Training in Patients with Psoriatic Arthritis Improves Function, Disease Activity and Quality of Life. Diego Roger Silva[1], Fabio Jennings[1], Emilia Moreira[1] and Jamil Natour[2]. [1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [2]Escola Paulista de Medicina/ Universidade Federal de São Paulo, São Paulo, Brazil.

Background/Purpose: Psoriatic arthritis (PSA) is a chronic inflammatory arthritis, defined as the association of inflammatory arthropathy and skin psoriasis. The literature is still very scarce with regard to non-pharmacological treatments for patients with PSA, specially physical exercise.

Objective: The aim of this study was to assess the effectiveness of resistance training in improving functional capacity, muscle strength, quality of life and disease activity in patients with PSA.

Methods: Forty-one patients aged between 18 and 65 years with diagnosis of psoriatic arthritis were selected to this study.,The patients were randomized into two groups: intervention group and control group. The intervention group (IG) underwent resistance exercise twice a week, for twelve weeks. The control group remained on the waiting list with the conventional drug therapy. The outcome measurements were: BASFI and HAQ-S for functional capacity, one maximum-repetition test (! RM) for strength (1RM), SF-36 questionnaire for general quality of life; and BASDAI and DAS-28 for disease activity. The evaluations were done by a blinded evaluator at baseline (T0), 6 weeks (T6) and 12 weeks (T12) after the beginning of the study.

Results: At baseline the groups were homogeneous regarding clinical and demographic characteristics. The IG significantly improved functional capacity measured by HAQ-S and disease activity measured by BASDAI, compared to CG, at week 12. Regarding quality of life, the IG improved the domains "pain" and "general health status" compared to CG. ($p < 0.05$). There was improvement in muscular strength in almost all exercises in IG, except in the exercise for biceps. In the CG, the improvement in strength was observed only on "crucifix" (bilateral) and "leg extension" (bilateral) exercises. However, there was statistical differences between groups only on exercise "leg extension" (right side) in favor of IG.

Conclusion: Resistance training is effective in improving physical capacity, disease activity and quality of life of patients with psoriatic arthritis. The clinical improvements were not coupled to significant changes in muscular strength.

Disclosure: D. R. Silva, None; **F. Jennings**, None; **E. Moreira**, None; **J. Natour**, None.

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Risk of Opportunistic Infection and Herpes Zoster Infection in a Psoriasis/Psoriatic Arthritis Cohort. Kevin L. Winthrop[1], Lang Chen[2], John Baddley[2], Allison Taylor[2], Benjamin Chan[3], Huifeng Yun[4], Sarah Siegel[1] and Jeffrey R. Curtis[5]. [1]Oregon Health & Science University, Portland, OR, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Oregon Health and Science University, Portland, OR, [4]University of Alabama at Birmingham School of Public Health, Birmingham, AL, [5]The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Psoriasis/Psoriatic arthritis (PsO/PsA) often requires treatment with systemic agents. Some of these agents are associated with infectious adverse events. Few studies have described the background incidence of opportunistic infections (OIs) or Herpes zoster (HZ) infections, in a cohort of PsO/PsA patients.

Methods: We used the US Medicare dataset from 2006–2011 to identify a large cohort of PsA and PsO patients. We defined PsA and PsO as those with >1 rheumatologist-diagnosis code for psoriatic arthritis (ICD 9 696.0) or >1 dermatologist-diagnosis code for psoriasis (ICD 9 696.1) respectively, followed by a prescription for etanercept (ETA), cyclosporine (CIC), ustekinumab (UST), adalimumab (ADA), methotrexate (MTX) or ultraviolet light (UV) therapy. Patients had at least 6 months of continuous Medicare enrollment prior to the first date of exposure to these therapies. We excluded patients with organ transplantation, human immunodeficiency virus infection, advanced kidney and liver disease, or cancer with a 183-day period prior to cohort inception. Pairwise propensity scores (PS) were calculated and used to control for potential differences between comparator treatments. We used validated-claims based algorithms to identify OIs and HZ events among exposure groups. Patient exposures were censored at time of serious infection, death, end of study, loss of coverage, or 90 days following end of treatment exposure whichever came first. For OIs and for HZ, we calculated crude incidence rates in all exposure groups, and used Cox-proportional hazard regression models to calculate hazard ratios for these outcomes between exposure groups while adjusting for PS quintile.

Results: We identified 10,261 PsA individuals and 31,052 PsO individuals. Of the PsA cohort, there were fewer than 11 OI infections yielding an overall incidence rate of 1.5 (95% CI: 0.7–3.0) per 1,000 py, while the PsO cohort also had fewer than 11 OI infections with an overall incidence rate of 1.5 (95% CI: 0.6–3.0) per 1,000 py. For HZ, there were 82 HZ infections in the PsA cohort yielding an overall incidence rate of 16.1 (95% CI: 12.8–20.0) per 1,000 py, with the incidence rate ranging from 13.5 (95% CI: 4.3, 41.7) per 1,000 py for the UV therapy group to 20.0 (95% CI: 13.3–30.2) per 1,000 py for the ETA group. Of the PsO cohort, there were fewer than 391 HF infections with an overall incidence rate of 13.0 (95% CI: 11.8, 14.4) per 1,000 py. The incidence rate ranged from 11.1 (95% CI: 7.4–16.7) per 1,000 py for the CIC group to 14.3 (95% CI: 2.2–16.7) per 1,000 py for the MTX group. Rates of HZ infection were similar by exposure groups, but were higher than rates found in rheumatoid arthritis patients of the same age. For both the PsA and PsO cohorts, there were no significant associations by treatment type for either OI or the HZ infection, even when compared to the UV therapy group.

Conclusion: Among Medicare enrollees with PsA or PsO, biologic treatments were not associated with an increased risk of either OIs or HZ compared to non-biologic treatment (e.g. UV light).

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Apremilast, an Oral Phosphodiesterase 4 Inhibitor, Is Associated with Long-Term (104-Week) Improvements in Patients with Psoriatic Arthritis: Results from a Phase 3, Randomized, Controlled Trial. Arthur Kavanaugh[1], Adewale O. Adebajo[2], Dafna D. Gladman[3], Juan J. Gomez-Reino[4], Stephan Hall[5], Eric Lespessailles[6], Philip Mease[7], Georg A. Schett[8], ChiaChi Hu[9], Randall M. Stevens[9] and Jürgen Wollenhaupt[10]. [1]University of California San Diego, La Jolla, CA, [2]University of Sheffield, Sheffield, United Kingdom, [3]University of Toronto, Toronto Western Hospital, Toronto, ON, [4]Hospital Clinico Universitario, Santiago, Spain, [5]Cabrini Health and Monash University, Melbourne, Australia, [6]University of Orléans, Orléans, France, [7]Swedish Medical Center and University of Washington, Seattle, WA, [8]University of Erlangen-Nuremberg, Erlangen, Germany, [9]Celgene Corporation, Warren, NJ, [10]Schön Klinik Hamburg Eilbek, Hamburg, Germany.

Background/Purpose: Apremilast (APR), an oral phosphodiesterase 4 inhibitor that may modify the immune response, has been shown effective in psoriatic arthritis (PsA). PALACE 1 compared the efficacy and safety of APR with placebo in patients with active PsA despite prior conventional DMARDs and/or biologics, including biologic failures.

Methods: Patients were randomized (1:1:1) to receive placebo, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline

DMARD use (yes/no). Patients whose swollen and tender joint counts (SJC and TJC) had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to APR20 or APR30 if they were initially randomized to placebo, or continued on their initial apremilast dose. At Week 24, all remaining placebo patients were re-randomized to APR20 or APR30. Double-blind APR treatment continued to Week 52; patients could continue to receive apremilast during an active treatment, long-term phase of up to 4 years, for a total follow-up of up to 5 years. Efficacy in patients randomized to apremilast at baseline and with evaluable data at Week 52 and Week 104 is described herein (analysis: as observed).

Results: 504 patients were randomized and received ≥1 dose of study medication (placebo: n=168; APR20: n=168; APR30: n=168). At Week 52, modified ACR20 response was achieved by 63.0% and 54.6% of patients continually treated with APR20 or APR30 from baseline, respectively. Among patients who were randomized to APR at baseline, 97 APR20 and 101 APR30 patients remained in the study and completed evaluations at Week 104. Approximately 80% of patients who completed year 1 were maintained on therapy at year 2. In patients receiving APR from baseline, improvements were sustained over 104 weeks for multiple endpoints (Table), including (1) modified ACR20/ACR50/ACR70 of 61.3%/29.8%/16.0% (APR20) and 66.3%/35.6%/19.8%, respectively (APR30); (2) median percent change in SJC/TJC of −88.9%/−80.5% (APR20) and −87.5%/−76.7% (APR30); (3) mean change in Health Assessment Questionnaire-Disability Index (HAQ-DI) of −0.33 (APR20) and −0.43 (APR30), and greater than 50% achieving minimal important differences ≥0.30; (4) mean change in 28-joint count Disease Activity Score (DAS-28) of −1.61 (APR20) and −1.83 (APR30); and (5) achievement of DAS <2.6 in 35.1% (APR20) and 38.6% (APR30) of patients. Consistent results were demonstrated in patients randomized to placebo at baseline and re-randomized to APR20 or APR30 at Week 16 or 24 who completed Week 104. No new safety signals were observed with treatment through 104 weeks.

Conclusion: Over 104 weeks, APR demonstrated sustained clinically meaningful improvements in the signs and symptoms of PsA, physical function, and associated skin symptoms. ACR 20 response at Week 104 was 66% for APR 30. APR continued to demonstrate an acceptable safety profile and was generally well tolerated.

Outcomes at Week 52 and Week 104 (Data as Observed)

	Week 52		Week 104	
	APR20 n = 120*	APR30 n= 132*	APR20 n= 97*	APR30 n= 101*
ACR20, n/m (%)	75/119 (63.0)	71/130 (54.6)	57/93 (61.3)	67/101 (66.3)
ACR50, n/m (%)	29/117 (24.8)	32/130 (24.6)	28/94 (29.8)	36/101 (35.6)
ACR70, n/m (%)	18/117 (15.4)	18/130 (13.8)	15/94 (16.0)	20/101 (19.8)
SJC, median % change	−78.8	−77.8	−88.9	−87.5
TJC, median % change	−69.2	−62.5	−80.5	−76.7
HAQ-DI (0–3), mean change	−0.37	−0.32	−0.33	−0.43
HAQ-DI MCID, ≥0.30§, n/m (%)	55/120 (45.8)	59/132 (44.7)	50/97 (51.5)	55/101 (54.5)
DAS-28 (CRP), mean change	−1.40	−1.31	−1.61	−1.83
DAS-28 (CRP), <2.6, n/m (%)	39/120 (32.5)	30/129 (23.3)	34/97 (35.1)	39/101 (38.6)
PASI-50, n/m (%)	28/53 (52.8)	41/68 (60.3)	22/41 (53.7)	29/53 (54.7)
PASI-75, n/m (%)	13/53 (24.5)	25/68 (36.8)	15/41 (36.6)	16/53 (30.2)

n/m = number of responders/number of patients with sufficient data for evaluation.
*The n reflects the number of patients who were randomized to APR 20 BID (APR 20) and APR 30 mg BID (APR30) at baseline and had data available at the specific time point; actual number of patients available for each endpoint may vary.
§Pre-specified MCID threshold, based on the literature (Mease PJ, et al. *Ann Rheum Dis.* 2004;63[Suppl 1]:391) at the time of protocol and analysis.

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Exploring the Association of Serum Paraoxonase and Arylesterase Activities with Cardiovascular Risk in Psoriasis and Psoriatic Arthritis.
M. Elaine Husni[1], Danielle Brennan[1], WH Wilson Tang[2] and Stanley Hazen[2]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]CCF, Cleveland, OH.

Background/Purpose: Psoriatic diseases are systemic inflammatory joint and skin disorders associated with increased cardiovascular (CV) morbidity. Paraoxonase (PON) and Arylesterase (ARYL) are antioxidant enzymatic proteins associated with High Density Lipoproteins (HDL). These levels have been associated with providing systemic protection against HDL and LDL lipid peroxidation and promoting the atheroprotective properties. Previously reports show PON/ARYL levels are significantly reduced in RA and SLE. While it is known that the risk for CV disease is elevated in patients with psoriatic disease relative to the general population, we believe this is the first report between serum PON/Aryl levels and risk of coronary heart disease (CHD) using Framingham risk score (FRS) in Psoriasis (PsO) and Psoriatic Arthritis (PsA) patients. We sought to compare the prevalence of FRS and the levels of related biomarkers in patients with PsO and PsA.

Methods: We performed a cross sectional study of 289 patients (age 49(+/−13.2), 51% males) with PsO and PsA from our Cardiometabolic Outcome Measures in Psoriatic Arthritis Study (COMPASS), a longitudinal cohort with a focus on cardiovascular health from 2011–2014. Baseline serum PON/ARYL levels were obtained from our cohort (N = 238, PsA 57%, PsO, 43%). The disease cohorts were each further subdivided into 3 groups based on their FRS; FRS <10% (low risk, PsA/PsO n=111/76), 10–20% (intermediate risk, PsA/PsO n=17/23) and FRS ≥ 20% (high risk group, PsA/PsO n=8/3), respectively. Analysis of variance (ANOVA) was used to compare mean serum levels across FRS categories (Kruskal-Wallis for comparison of medians). Odds ratios (OR) and 95% confidence interval from logistic regression were computed to show the association of PON/Aryl levels to increased CV risk (FRS ≥ 20%). P values < 0.05 are considered statistically significant.

Results: A statistically significant inverse relationship between the mean levels of serum Aryl activity (126.8 ± 29.0, 117.9 ± 37.3, 86.6 ± 19.4 μmol/min/mL, p = 0.001) and the levels of increasing CHD risk were found in PsA patients. A similarly strong inverse relationship between serum PON activity (median: 667.0, 544.0, 268.0 nmol/min/mL, P = 0.051) and increasing levels of CHD risk also existed in the PsA population. There was no significant relationship between both PON (p=0.45) and Aryl (p=0.19) compared to FRS in the PsO population.

Baseline PON and Aryl were significantly associated with FRS≥20% (natural-log transformed PON OR: 0.19 (0.05, 0.69), p=0.01; Aryl OR: 0.95 (0.92, 0.98), p=0.002). No significant associations with PON/Aryl and increased CV risk were found within the PsO population.

Conclusion: Exposure of increased burden of inflammation (PsA>PsO>controls) is associated with more severe CV risk in patients with PsA. This association may be mediated by novel biomarkers for dysfunctional HDL. The stronger relationship between FRS and PON/Aryl activity levels in the PsA patients is hypothesized to be due to the greater level of systemic inflammatory disease and oxidative stress. Given the early onset of PsA (before the age of 40), this test can potentially provide an incremental benefit to assess CV risk.

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Ability of Clinical Variables to Predict Radiographic Damage in Psoriatic Arthritis.
Vinod Chandran[1], Arane Thavaneswaran[1], Richard J. Cook[2] and Dafna D. Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Waterloo, Waterloo, ON.

Background/Purpose: Psoriatic Arthritis (PsA) is an inflammatory arthritis associated with psoriasis that leads to progressive joint damage. Biomarkers in addition to clinical features may help stratify patients with PsA at high risk of joint damage so that they may be aggressively treated. Our

purpose was to determine the predictive value of clinical features to predict joint damage in PsA.

Methods: The study was conducted in a large prospective cohort of patients with PsA who are assessed according to a standard protocol that includes detailed clinical evaluation every 6 months and radiographic evaluation every 2 years. Patients who had at least 2 radiographs were included in this study. Radiographic joint damage progression was defined as increase in the count of radiographically damaged joints between 1st and 2nd radiographic assessment in any of the following joints- wrists, MCP, PIP, DIP, MTPs and 1st IP of toes (total 42 joints). The following clinical variables at the time of first radiographic assessment were evaluated as predictors- age, sex, age at diagnosis of psoriasis and PsA, duration of psoriasis and PsA, PASI, active, swollen, clinically damaged and radiographically damaged joint count, dactylitis, presence of axial disease, ESR, SF-36, HAQ, NSAID, DMARD and biologic use at baseline, HLA-B*27 and HLA-C*6. Univariate followed by multivariate models were developed to determine association of clinical variables with radiographic damage progression. ROC curves were constructed using variables found to be significantly associated with radiographic progression.

Results: 656 (380 males) with a mean age of 43 years, age at onset of psoriasis 28 years and of PsA 37 years were included. At the time of the first radiograph these patients had 11active, 5 swollen, 9 clinically damage, 4 radiographically damaged joints. The ESR was 24 mm/hr and PASI score 5. 33% had dactylitis and 45% had evidence of axial disease. 17% were HLA-B*27 and 32% HLA-C*06 positive. Their SF-36 PCS was 36.5 and HAQ 0.8. In univariate analyses older age, age at diagnosis of psoriasis, duration of psoriasis and PsA, active, swollen, clinically damaged and radiographically damaged joint counts, dactylitis, axial arthritis, ESR, HAQ and treatment with DMARDs were associated with radiographic progression ($p<0.05$). The predictors independently associated with radiographic progression in a multivariate reduced model are shown in Table 1. The area under the curve of the ROC curves was 0.71.

Table 1: Predictors of radiographic damage progression in a multivariate reduced model

Predictors	OR (95% CI)	P value
Age (1 year increase)	1.01 (1.004, 1.02)	0.001
Active joint count	1.01 (1.001, 1.02)	0.04
Clinically damaged joint count	0.98 (0.97, 0.998)	0.03
Radiographically damage joint count	1.16 (1.14, 1.19)	<0.0001
Axial arthritis	1.19 (1.001, 1.42)	0.05
Dactylitis	1.49 (1.25, 1.78)	<0.0001

Conclusion: Clinical features have only a fair ability to discriminate patients who have radiographic joint damage progression in PsA. Therefore, identifying biomarkers that predict joint damage is an important research question.

Disclosure: V. Chandran, None; **A. Thavaneswaran**, None; **R. J. Cook**, None; **D. D. Gladman**, None.

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Neutrophil-Lymphocyte Ratio As a Marker of Disease Activity in Psoriatic Arthritis. Vinod Chandran, Arane Thavaneswaran and Dafna D. Gladman. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. There are few biomarkers for disease activity in PsA. Traditional acute phase reactants are elevated only in about 50% of patients with active PsA. Neutrophil-Lymphocyte Ratio (NLR) has been recently shown to be a marker of inflammation with prognostic value in inflammatory, cardiovascular and malignant diseases. We therefore evaluated NLR as a marker of disease activity in patients with PsA.

Methods: The study was conducted in a large PsA cohort were patients are seen accordingly to a standard protocol that includes clinical and laboratory assessment. Swollen joint count (SJC) and PASI score were used as measures of disease activity in PsA at baseline. NLR was calculated from the neutrophil and lymphocyte count obtained from a complete blood count done at the time of clinic assessment. Pearson correlation between NLR and disease activity markers (SJC, PASI) and traditional acute phase reactants [ESR, haemoglobin (Hb), platelet count] were investigated. The association between ESR, Hb, platelet count and NLR with SJC and PASI score was determined using univariate and multivariate linear regression. Since the NLR was not normally distributed, lognormal transformation was done.

Results: 1130 (631 males) with a mean age of 45 years, age at onset of psoriasis 29 years and of PsA 38 years were included. At the time of the first assessment these patients had 11 active, 5 swollen and 8 clinically damaged joints and the PASI score was 5.3. The mean ESR was 23 mm/hr, Hb 139 g/dL, platelet count 286,000/microL and NLR 3.2. The NLR significantly correlated with SJC ($r=0.12$, $p<0.0001$), PASI ($r=0.15$, $p<0.0001$), ESR ($r=0.24$, $p<0.0001$), Hb ($r=-0.18$, $p<0.0001$) and platelet count ($r=0.15$, $p<0.0001$). Multivariate linear regression analysis showed that NLR (β 0.16, $p = 0.04$) and ESR (β 0.11, $p = 0.003$) were independently associated with SJC. Similarly, multivariate linear regression analysis showed that NLR (β 0.41, $p = <0.0001$) and ESR (β 0.11, $p = 0.007$) were independently associated with PASI score.

Conclusion: NLR has a potential as a marker of disease activity in PsA independent of traditional acute phase reactants. Further evaluation to determine threshold of abnormal values in the context of psoriatic disease, as well as prognostic value in predicting joint damage and cardiovascular disease is required.

Disclosure: V. Chandran, None; **A. Thavaneswaran**, None; **D. D. Gladman**, None.

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Persistence of Low Disease Activity after Tumor Necrosis Factor Inhibitor Withdrawal in Patients with Psoriatic Arthritis. Doquyen H. Huynh[1], Carol J. Etzel[2], Vanessa Cox[3], Philip Mease[4] and Arthur Kavanaugh[5]. [1]UC San Diego School of Medicine, San Diego, CA, [2]Corrona, LLC., Southborough, MA, [3]CORRONA, Inc, Southborough, MA, [4]CORRONA, Seattle, WA, [5]UCSD School of Medicine, La Jolla, CA.

Background/Purpose: The increased use of tumor necrosis factor inhibitors (TNFi) has improved clinical outcomes for psoriatic arthritis (PsA) patients and made low disease activity (LDA) and remission viable treatment goals. Due to factors such as pharmacoeconomic considerations, concern for long term side effects, and patient preferences, there has been increasing interest in the possibility that TNFi may be discontinued by patients achieving remission or LDA, with maintenance of clinical benefit. The purpose of this study is to determine the duration of clinical benefit among PsA patients discontinuing TNFi while in LDA, and to identify patient characteristics and disease related factors that may be associated with prolonged clinical benefit.

Methods: An observational cohort study of PsA patients in the CORRONA registry who discontinued TNFi use after achieving LDA. LDA was defined as CDAI $\leq$ 10 and skin psoriasis physician global assessment $\leq$ 20/100. Patients were considered to have lost clinical benefit if: 1) increase in CDAI to $>$ 10; 2) increase in skin assessment to $>$20; or 3) increase in concomitant DMARD or prednisone doses or start of DMARD, prednisone, or biologic agents. Clinical data were collected at baseline (the time of TNFi discontinuation) and at loss of clinical benefit or the last clinic visit. Kaplan Meier analyses were used to estimate duration of clinical benefit. Both univariable and multivariable Cox proportional hazard analyses were used to evaluate characteristics associated with duration of benefit.

Results: Of 5945 PsA patients in CORRONA, 325 discontinued TNFi while in LDA and had follow up data available. Mean age was 52.6 years, mean BMI 30.1, mean duration of PsA 9.8 years, and 51.9% were female. 52.6% of patients discontinued their 1st TNFi, and 31.1% discontinued their 2nd TNFi. Mean duration of TNFi use was 1.5 years. 53.5% used TNFi as monotherapy, 42.2% used concomitant MTX; 29% took low dose prednisone. 146 patients lost clinical benefit, due to: increased CDAI (31.5%), initiation or increase in DMARD (32.2%), TNFi restart (6.8%), initiation or increase in prednisone (9.6%) or worsening skin disease (15.8%). The median time to loss of benefit was 29.2 months. 179 patients still had persistent benefit at their last clinic visit. Patients with higher disease activity at TNFi discontinuation had increased risk of losing clinical benefit (hazard ratios [HR] for: CDAI $>$ 3.2 vs $<$3.2 - HR 1.43 ($p = 0.032$), patient global assessment $>$ 5 vs $<$ 5/10 - HR 1.7 ($p= 0.007$), moderate vs low DAS - HR 1.65 ($p = 0.017$). Interestingly smokers had significantly higher risk for loss of benefit (HR vs non-smokers 1.76; $p= 0.027$) in both univariable and multivariable analysis. Number of TNFi used and overweight or obese status did not significantly affect loss of benefit.

Conclusion: PsA patients who achieve LDA on treatment may maintain clinical benefit after discontinuation of TNFi. Patients with higher disease activity at the time of discontinuation and smokers may have less success at stopping therapy.

Disclosure: D. H. Huynh, None; **C. J. Etzel**, Corrona, 3; **V. Cox**, Corrona, 3; **P. Mease**, Corrona, 9; **A. Kavanaugh**, None.

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Economic Evaluation of Sequencing Strategies in the Treatment of Psoriatic Arthritis in the United States. Thomas Tencer[1], Zoe Clancy[1], Helene Cawston[2], Sandrine Cure[3] and Frank Zhang[1]. [1]Celgene Corporation, Warren, NJ, [2]OptumInsight, Nanterre, France, [3]OptumInsight, Uxbridge, United Kingdom.

Background/Purpose: In the treatment of psoriatic arthritis (PsA), switching between alternative biologic treatments is common. A cost-effectiveness model was developed to assess the impact of placing apremilast, a new oral treatment, before biologics in PsA patients who had failed conventional disease-modifying antirheumatic drug therapy, from a U.S. payer perspective.

Methods: A lifetime Markov state transition cohort model was developed to compare 2 treatment sequences in the base-case: apremilast followed by adalimumab followed by etanercept vs. adalimumab followed by etanercept. Patients who failed etanercept were assumed to receive best supportive care (BSC) as the last line of treatment. Response to therapy was assessed using the Psoriatic Arthritis Response Criteria (PsARC) at the end of the clinical trial periods, ranging from 12 to 16 weeks depending on drug. Non-responders moved to the next line of therapy. A 16.5% annual dropout rate was assumed for each drug. Treatment efficacy inputs were obtained from a meta-analysis and trial results. Drug costs were sourced from 2013 Wholesale Acquisition Costs prices, and a 3% annual discount rate was applied to costs and quality-adjusted life-years (QALYs). Apremilast was assumed to be priced at a discount to biologics. Utilities were estimated from the Health Assessment Questionnaire and Psoriasis Area and Severity Index response using a previously published regression equation.

Results: The apremilast arm provided an additional 2.53 years with a PsARC response and an additional 0.78 QALYs. Total time spent on the biologics was reduced by 0.34 years and time spent in BSC was reduced by 2.85 years. Under base-case assumptions, placing apremilast before biologics was found to be the dominant strategy (costs reduced by $28,794). Sensitivity analyses indicated that several parameters (e.g., cost of BSC and baseline utility) influence the incremental cost-effectiveness ratio. Similar results were obtained with different biologic drugs in the sequence.

Conclusion: Placing apremilast before biologics is a cost-saving strategy in the treatment of PsA.

Disclosure: T. Tencer, Celgene Corporation, 3; **Z. Clancy**, Celgene Corporation, 3; **H. Cawston**, Celgene Corporation, 2, OptumInsight, 3; **S. Cure**, Celgene Corporation, 2, OptumInsight, 3; **F. Zhang**, Celgene Corporation, 3.

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Clinical Characteristics and Outcome of Golimumab Treatment Differs Between Bio-naïve and Patients Previously Exposed to Biologicals. Nationwide Results on Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS) and Other Spondylarthritidies (SpA). Saedis Saevarsdottir[1], Michele Santacatterina[2], Carl Turesson[3], Helena Forsblad[4], Lennart Jacobsson[4] and Staffan Lindblad[2]. [1]Rheumatology Unit, Department of Medicine, Karolinska institutet and Karolinska University Hospital, Stockholm, Sweden, [2]Karolinska Institutet, Stockholm, Sweden, [3]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [4]The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

Background/Purpose: Golimumab is a TNF inhibiting biological drug that was approved in Sweden in 2010 for the treatment of RA, PsA and AS. Our previous analyses have demonstrated similar drug adherence as for other TNF-inhibitors and better adherence in bio-naïve patients (Saevarsdottir S et al, ACR 2013). Given that, the aim of the current study in an updated dataset with longer follow-up time, was to investigate the differences in clinical characteristics and drug survival probability between golimumab treated patients that were bio-naïve compared to those previously exposed to biologicals, separately for patients with RA, PsA, AS as well as other SpA.

Methods: Data were retrieved for all patients initiating golimumab treatment in 2010–2013 from the nationwide SRQ register. A survival analysis (Kaplan Meier) was performed over 24 months with right censoring and log-rank test of equality across strata.

Results: Of 2106 patients initiating golimumab treatment during the study period, 849 (40%) had RA, 454 (22%) PsA, 303 (14%) AS, 242 (12%) SpA and 258 (12%) had other diagnoses. The proportions of women in RA/PsA/AS/SpA patient groups were 78%/50%/29%/55%, respectively; and their median age at baseline was 54/48/42/40 years. In patients with RA/PsA/AS/SpA, the proportions receiving golimumab as the first biological treatment were 48%/46%/42%/40%; and the proportions receiving concurrent disease-modifying anti-rheumatic drugs (DMARDs) were 76%/64%/32%/47%.

Several baseline characteristics differed between bio-naïve patients (0) and those previously exposed to biological treatment (1–2 or 3+ biologic drugs, see Table 1, parameters showing significant difference in each disease are mentioned below). Bio-naïve patients were less likely to have concurrent treatment with DMARDs (PsA, AS), prednisolone (all) and NSAID (all); and they reported lower HAQ (RA, PsA, SpA), DAS28 (RA, PsA), inflammatory markers (CRP/ESR: RA, SpA), VAS-global health (RA, PsA, SpA) and VAS-pain (RA) at baseline. Furthermore, bio-naïve were more likely to be male (RA, PsA), older (RA, PsA, AS) and with short disease duration (RA, AS, SpA).

The drug survival probability over 24 months was also higher in bio-naïve patients (RA, AS, trend for PsA but less so for SpA).

Conclusion: In this real-life nationwide cohort, patients starting golimumab as their first biologic were treated with co-medication to a lesser extent, but had more favorable prognostic factors, and better drug survival over two years compared to those previously treated with other biologics. Patterns were similar for the various rheumatologic diseases treated with golimumab. It is of major importance to take previous biologic exposure into account when evaluating new biologics in observational studies.

Table 1. Clinical characteristics of patients receiving golimumab treatment 2010–2013 in Sweden.*

Number of previous biologics	Reumatoid Artritis (RA)			Psoriatic Arthritis (PsA)			Ankylosing Spondylitis (AS)			Spondylarthritidies (SpA)		
	0	1–2	3+	0	1–2	3+	0	1–2	3+	0	1–2	3+
Number (N)	404	331	114	208	188	58	126	145	32	96	109	37
Baseline visit:												
Female (%)	74	82	86	41	52	78	27	31	25	55	59	46
p-value		*0.003*			*<0.001*			*0.7*			*0.4*	
Age (years)	57	54	52	50	47	44	43	43	37	39	41	40
p-value		*0.003*			*0.07*			*0.03*			*0.6*	
Disease duration (yrs)	2.9	4.8	6.9	6.1	7.0	6.9	12.5	15.1	7.8	6.3	6.7	13.1
p-value		*0.02*			*0.8*			*0.02*			*0.05*	
Concurrent treatment:												
Any DMARD (%)	76	76	79	62	64	67	17	42	47	41	46	65
p-value		*0.3*			*0.003*			*<0.001*			*0.1*	
prednisolone (%)	38	45	50	16	18	36	10	7	22	10	20	49
p-value		*0.03*			*0.002*			*0.03*			*<0.001*	
NSAID (%)	30	49	53	28	42	46	41	55	56	32	46	49
p-value		*<0.001*			*0.003*			*0.04*			*<0.001*	
HAQ (units)	1.0	1.0	1.4	0.8	1.0	1.0	0.6	0.9	0.9	0.8	0.8	1.0
p-value		*<0.001*			*0.003*			*0.1*			*0.04*	
DAS28 (units)	4.8	5.1	5.5	3.9	4.3	4.8	–	–	–	–	–	–
p-value		*<0.001*			*<0.001*			*NA*			*NA*	
CRP (mg/dL)	8	11	18	5	6	8	10	9	18	5	9	12
p-value		*<0.001*			*0.2*			*0.2*			*<0.001*	
ESR (mm/h)	19	23	30	1.	13	14	17	16	18	9	18	30
p-value		*<0.001*			*0.2*			*0.7*			*0.001*	
VAS-global (mm)	52	63	68	53	62	60	60	63	70	53	65	72
p-value		*<0.001*			*0.02*			*0.2*			*0.003*	
VAS-pain (mm)	52	60	70	55	62	58	61	65	67	54	67	70
p-value		*0.001*			*0.1*			*0.2*			*0.1*	
Drug survival probability at follow-up:**												
6 months (%)	81	77	65	85	77	72	85	80	71	81	78	63
12 months (%)	67	63	47	73	62	54	80	70	52	75	62	60
18 months (%)	63	56	40	63	57	45	68	63	47	67	54	54
24 months (%)	60	54	32	61	53	45	64	60	47	67	52	54
p-value		*<0.0001*			*0.08*			*0.04*			*0.2*	

*Values are presented as % or median, if not otherwise specified. P-values compare bionaive (0) to those with 1 or more biological treatments.
**Population at risk and % survival probability.

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Work Productivity Improvement Associated with Apremilast, an Oral Phosphodiesterase 4 Inhibitor, in Patients with Psoriatic Arthritis: Results of a Phase 3, Randomized, Controlled Trial. Frank Zhang[1], Thomas Tencer[1], Stan Li[1] and Vibeke Strand[2]. [1]Celgene Corporation, Warren, NJ, [2]Biopharmaceutical Consultant, Portola Valley, CA.

Background/Purpose: Apremilast (APR) is an oral phosphodiesterase 4 inhibitor that helps regulate the aberrant immune response that causes the joint symptoms, systemic inflammation, and skin disease associated with psoriatic arthritis (PsA). The Work Limitations Questionnaire (WLQ) measures the degree to which employed individuals are experiencing limitations on the job due to their health problems, as well as health-related productivity loss. The PALACE 1

study compared the efficacy and safety of APR with placebo in patients with active PsA despite prior or concurrent conventional disease-modifying anti-rheumatic drugs (DMARDs) and/or prior biologics. The objective of the current analysis was to assess the effect of APR on work productivity and work limitations of employed patients in the PALACE 1 study.

Methods: Patients were randomized (1:1:1) to receive placebo, APR 20 mg BID (APR20), or APR 30 mg BID (APR30) stratified by baseline DMARD use (yes/no). Treatment efficacy was assessed at Week 16 based on the intent-to-treat population. Employed patients completed the WLQ, a 25-item questionnaire that assesses the impact of chronic health conditions on work performance and productivity, at baseline and Week 16. Work limitations were categorized into 4 domains, which were then used to calculate the WLQ index: physical demands (PDS), mental demands (MDS), time management demands (TMS), output demands (ODS). Improvement in the WLQ index, and its 4 domains, is represented by a negative change from baseline. Improvement in work productivity is represented by a positive improvement in percentage of productivity loss.

Results: 504 patients were randomized (mean age: 50.4 years; 49.4%: male). Of these 261 who were both employed and completed at least 1 component of the WLQ were analyzed. At Week 16, APR20 and APR30, vs. placebo, were associated with a greater mean change from baseline in PDS (−5.58 and −6.24 vs. −2.14), MDS (−2.22 and −5.18 vs. 1.15), TMS (−4.03 and −8.76 vs. −4.25), and ODS (−5.92 and −10.3 vs. −1.34), resulting in a greater mean improvement in the WLQ index (−0.01 and −0.03 vs. 0.00), which corresponds to a higher median percent improvement of productivity loss (18.9% and 24.7% vs. −3.7%). Higher productivity improvements were also observed among APR20 and APR30 ACR20 responders at Week 16—PDS (−11.8 and −7.61), MDS (−8.56 and −11.0), TMS (−7.88 and −15.8), and ODS (−10.6 and −20.1), respectively—resulting in a higher mean improvement in the WLQ index (−0.03 and −0.05, respectively), which corresponds to a higher median percent improvement in work productivity (57.9% and 46.8%), respectively.

Conclusion: APR20 and APR30 increased work productivity and improved work limitations among patients active PsA who were not adequately controlled with prior or concurrent conventional DMARDs and/or prior biologics.

Disclosure: F. Zhang, Celgene Corporation, 3; **T. Tencer**, Celgene Corporation, 3; **S. Li**, Celgene Corporation, 3; **V. Strand**, Consultant for AbbVie, Afferent, Amgen, Biogen Idec, Bioventus, BMS, Carbylan, Celgene, Celltrion, CORRONA, Crescendo, Genentech/Roche, GSK, Hospira, Iroko, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi, SKK, Takeda, UCB, Vertex, 5.

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Serum Fetuin-a, Intercellular Adhesion Molecule -1 and Interleukin -18 Levels in Ankylosing Spondylitis and Psoriatic Arthritis. Hanna Przepiera-Bedzak[1], Katarzyna Fischer[2] and Marek Brzosko[1]. [1]Department of Rheumatology and Internal Diseases Pomeranian Medical University in Szczecin, Szczecin, Poland, [2]Independent Laboratory of Rheumatic Diagnostics, Pomeranian Medical University in Szczecin, Szczecin, Poland.

Background/Purpose: In recent years, increased incidences of metabolic disorders have been observed in patients with systemic inflammatory rheumatic diseases. Fetuin-A, Intercellular Adhesion Molecule -1(ICAM-1) and interleukin 18 (IL-18) have been implicated in the endothelial function and atherosclerosis. The aim of the study was to investigate serum levels of fetuin-A, ICAM-1and IL-18 in ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

Methods: We studied 123 patients and 20 controls. We recorded: age, sex, disease duration, treatment type, history of metabolic disorders, VAS, BASDAI, PASI, BMI, waist-hip ratio. Blood was collected for analysis of fetuin-A, ICAM-1, IL-18, IL-6, IL-23, VEGF and EGF by ELISA method. We assessed lipid profile, CRP and ESR. This work was supported by a grant from the National Science Centre in Poland (UMO-2011/03/B/NZ5/04192).

Results: A total of 59 AS (43,5 ± 12,5; 12F/47M) and 64 PsA (49,7 ± 12,9 years; 36 F/28 M) patients were studied. Serum fetuin-A, ICAM-1and IL-18, levels were significantly higher in patients compared to controls ($p<0,05$).

No differences were found in serum fetuin-A, ICAM-1 and IL-18 levels in AS and PsA patients.

Serum fetuin-A positively correlated with triglycerides (r=0,3; p=0,02) and VEGF (r=0,3; p=0,02) in AS and with IL-23 (r=0,2; p=0,05) and VEGF (r=0,3; p=0,04) in PsA patients.

Serum ICAM-1 positively correlated with IL-6 (r=0,3; p=0,007) and ESR (r=0,3; p=0,007) in AS and with IL-6 (r=0,2; p=0,05) in PsA patients.

Serum Il-18 positively correlated with CRP (r=0,25; p=0,05), cholesterol (r=0,4; p=0,01), triglycerides (r=0,4; p=0,04) and BASFI (r=0,3; p=0,02) in AS and with IL-6 (r=0,3; p=0,03) and VEGF (r=0,3; p=0,04) in PsA patients.

No differences were found in comparison of subjects to treatment type regarding to serum fetuin-A, ICAM-1 and IL-18 levels in AS and PsA patients.

Conclusion: Serum fetuin-A, ICAM-1, IL-18, levels were increased and correlated with disease activity in AS and PsA patients. Serum fetuin-A and IL-18 correlated with triglycerides in AS patients.

Disclosure: H. Przepiera-Bedzak, None; **K. Fischer**, None; **M. Brzosko**, None.

1599

Comparison of Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis Pregnancies: Disease Activity, Treatment, and Outcomes. Megan E. B. Clowse. Duke University Medical Center, Durham, NC.

Background/Purpose: While it has long been reported that rheumatoid arthritis (RA) improves with pregnancy, there is very limited information about ankylosing spondylitis (AS) or psoriatic arthritis (PsA). We sought to explore similarities and differences between disease activity and treatment in pregnancy.delivery, and the postpartum experience for women with RA, AS, and PsA.

Methods: The pregnancies in women with RA, juvenile inflammatory arthritis (JIA), AS, other spondyloarthropathies (Spondy), and PsA were collected through a prospective pregnancy registry collected at a single center. For analysis, pregnancies were divided into 3 groups by diagnosis: RA & JIA, AS & Spondy, and PsA. Medications, disease activity, and pregnancy complications were collected throughout pregnancy to a post-partum visit. The physician's global assessment (PGA) was used to compare disease activity between the diseases. Non-parametric statistical testing was used due to small sample sizes. A generalized estimating equation controlled for multiple pregnancies in some women.

Results: 62 pregnancies in 50 women were completed between January 2008 and May 2014. Of these, 37 were in women with RA (including 10 with JIA), 17 with AS/Spondy (including 11 with AS and 6 with other forms), and 8 with PsA (see table). Disease Activity: While the large majority of women with RA (96.5%) or AS/Spondy (80%) had either improved or stable disease activity over the course of pregnancy, 40% of women with PsA had increasing disease activity (p=0.02). Medications: Overall, 32.2% took no medications for arthritis in pregnancy, 8% took only prednisone, 21% took SSZ, HCQ, and/or a TNF inhibitor and prednisone, and 38.7% took SSZ, HCQ, and/or a TNF inhibitor without prednisone. About a third (35.5%) of all pregnancies received TNF-inhibitors. Medication use was similar across the diagnoses (see table)

Pregnancy Outcomes: Half of the pregnancies in women with PsA were complicated by preeclampsia and/or preterm birth, compared to 18.9% with RA and 5.9% with AS (p=0.046). Overall, prednisone exposure was associated with preterm birth and/or preeclampsia (38.9%) compared to those without prednisone exposure (11.4%, p=0.029).

Postpartum: Women with PsA continued to have more active disease than other women; AS/spondy patients improved following delivery. Breastfeeding: Far fewer women with PsA (14.3%) were breastfeeding at follow-up, compared to women with RA (76.9%) or AS/Spondy (80%, p=0.006).

Conclusion: It appears that the experience in pregnancy may be different for women with PsA compared to women with RA or AS/Spondy, with higher levels of disease activity as pregnancy progresses and following delivery, a higher rate of preterm birth and preeclampsia, and greater difficulties with breastfeeding. This small cohort demonstrates an urgency to study PsA in pregnancy.

	RA/JIA	AS/Spondy	PsA	p-values
Number of pregnancies	37	17	8	
Maternal age	32.8yrs (4.2)	32.1yrs (3.8)	33.6yrs (7.1)	
Race	73.0% Caucasian	94.1% Caucasian	87.5% Caucasian	
	16.2% African-American	0 AA	0 AA	0.14
Miscarriage	2 (5.4%)	1 (5.9%)	0	1.0
Preterm births	5 (14.3%)	1 (6.3%)	3 (37.5%)	0.153
Gestational Age at Delivery (only live births)	37.7 weeks (SD 2.9) Range 28.1–40.7	38.5 weeks (SD 2.5) Range 29.1–40.9	37.1 weeks (SD 3.5) Range 30.6–40.6	0.49
Preeclampsia	3 (9.1%)	0	3 (37.5%)	0.024
Preterm birth and/or preeclampsia	7 (18.9%)	1 (5.9%)	4 (50%)	0.046
Medications:				
Prednisone	14 (37.8%)	2 (11.8%)	2 (25%)	0.158
Prednisone dose	16.7mg (SD 14.3)	12.5mg (SD 10.6)	5mg	
TNF inhibitor	11 (28.7%)	9 (47.1%)	3 (37.5%)	0.477

Sulfasalazine	9 (24.3%)	2 (11.8%)	1 (12.5%)	0.582
Hydroxychloroquine	14 (37.8%)	2 (11.8%)	0	0.027
Methotrexate	3 (9.7%)	0	0	0.71
No medications for inflammatory arthritis	11 (29.7%)	6 (35.3%)	3 (37.5%)	0.79

Disclosure: M. E. B. Clowse, UCB Pharma, 5.

1600

Is There a Role for Inflammasome Activation in PsA Pathogenesis and Its Comorbidities? Rodolfo Perez Alamino[1], Raquel Cuchacovich[2], Arnold Zea[3] and Luis R. Espinoza[2]. [1]LSUHSC, New Orleans, LA, [2]LSU Medical Center, New Orleans, LA, [3]Stanley Scott Cancer Center, New Orleans, LA.

Background/Purpose: New data has emerged about the role of the inflammasome in psoriasis and psoriatic arthritis (PsA). The assembly of the inflammasome components in innate immune cells (monocytes) results in the rapid activation of Caspase-1, which cleaves pro-IL-1β and pro-IL-18 to generate active forms of these cytokines. We *hypothesized* that: "inflammasome activation occurs in monocytes, as a key element on the initiation and amplification of the innate immune response in PsA pathogenesis". Therefore, it was decided: 1) To determine whether inflammasome activation occurs in monocytes of PsA patients and, 2) To determine the relationship between inflammasome activation with disease activity and metabolic syndrome in these patients.

Methods: After informed consent, 13 PsA patients (CASPAR criteria) and 16 age-matched healthy individuals attending to the outpatient Rheumatology clinic were enrolled. Demographic, laboratory and clinical data was recorded. Disease activity was determined by DAS-28 score. Blood pressure, diabetes history, lipid profile and waist circumference data were included. Metabolic syndrome (MS) was defined following the International Diabetes Federation (IDF) criteria. Purified monocytes were plated and stimulated for 18 h with LPS (100ng/ml) in presence or absence of Caspase-1 inhibitor. CD14 and Caspase-1 expression was analyzed by flow cytometry. Cell lysates and supernatants were collected for determination of Caspase-1 and NLRP3 protein by Western blot and cytokine levels by ELISA, respectively. Student's *t*test and Mann-Whitney tests were used for statistical analysis.

Results: Sixty two percent (62%) of patients were females, mostly (77%) Caucasians. The mean age was 45.15 (SD 9.7) years and mean disease duration was 6.7 (SD 5.5) years. Ten patients presented with active disease, mean DAS28 3.25 (SD 1.2). Metabolic syndrome was present in 77% of patients.

The percentage of $CD14^+$/$Caspase1^+$was numerically higher in PBMC-monocytes from PsA patients compared to normal controls (33.5 $\pm$ 13 vs. 22.5 $\pm$ 11.3, respectively), although difference did not reach statistical significance ($p<0.1$). Caspase-1 expression was confirmed by Western blot. No differences were found regarding cytokine levels. Purified monocytes from PsA patients displayed a robust inflammatory response after LPS stimulation where Caspase-1, NLRP3, IL-1β and IL-18 were highly expressed. Neither Caspase-1 nor cytokine expression were associated with disease activity. In a subset of PsA patients with MS, there was a trend to higher IL-1β levels (19.4 $\pm$ 24.8 vs. 4.1 $\pm$ 6.6) ($p=0.08$).

Conclusion: In this pilot study, PsA patients showed an enhanced expression of inflammasome activation, although difference did not reach statistical significance. Further studies including a larger number of patients are needed to truly establish a role of inflammasome activation in PsA pathogenesis and associated comorbidities**.**

Disclosure: R. Perez Alamino, Genentech and Biogen IDEC Inc., 2, Pfizer, 2, Bristol-Myers Squibb, 2; **R. Cuchacovich**, None; **A. Zea**, None; **L. R. Espinoza**, None.

1601

Are There Gender Specific Differences in Patient Characteristics at Initiation of Biologic Treatment in Ankylosing Spondylitis and Psoriatic Arthritis? John Kelsall[1], William Bensen[2], Wojciech Olszynski[3], Niall Jones[4], Isabelle Fortin[5], Andrew Chow[6], Milton Baker[7], Saeed Shaikh[8], Denis Choquette[9], Emmanouil Rampakakis[10], John S. Sampalis[10], May Shawi[11], Francois Nantel[11], Susan Otawa[11] and Allen J Lehman[11]. [1]The Mary Pack Arthritis Centre, Vancouver, BC, [2]St Josephs Hospital and McMaster University, Hamilton, ON, [3]University of Saskatchewan, Saskatoon, SK, [4]University of Alberta, Edmonton, AB, [5]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, [6]McMaster University, Hamilton and Credit Valley Hospital, Mississauga, ON, [7]University of Victoria, Victoria, BC, [8]McMaster University, Hamilton, ON, [9]Institut de rhumatologie de Montréal (IRM), Montréal, QC, [10]JSS Medical Research, Montreal, QC, [11]Janssen Inc., Toronto, ON.

Background/Purpose: The prevalence of ankylosing spondylitis (AS) is 2–3 times higher in men compared to women whereas psoriatic arthritis (PsA) is generally considered a disease affecting both genders equally. Recent studies have suggested that clinical differences exist between men and women with the latter experiencing a higher burden of disease (1–4). This analysis examined gender-specific differences with respect to patient and disease parameters at initiation of the first anti-TNF agent (infliximab; IFX) for the treatment of AS and PsA in a Canadian routine clinical practice setting.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis (RA), ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with IFX or golimumab as first biologics or after having been treated with a biologic for <6 months. Patients with AS and PsA treated with IFX who were enrolled between 2005 and 2012 were included in this analysis.

Results: Among the 303 AS patients and 91 PsA patients, 189 (62.4%) and 49 (53.3%) were male, respectively. Mean age and disease duration at initiation of IFX treatment were comparable between genders (Table 1). Overall, disease parameters in AS patients were similar between genders with the exception of CRP which was significantly lower in female patients and HAQ-DI which was significantly higher (Table 1). Among PsA patients, females reported a significantly greater functional disability and showed a higher DAS28 compared to men.

Table 1: Patient Characteristics at Baseline by Gender

Parameter Mean (SD)/%	Male	Female	P-Value
AS	**n=189**	**n=114**	
Age: years	44.8 (12.2)	46.9 (10.8)	0.142
Disease duration: years	9.9 (10.3)	8.8 (9.4)	0.360
C-Reactive Protein (CRP): mg/L	20.9 (27.4)	14.3 (19.9)	*0.044*
Patient Global (PtGA): VAS mm	61.4 (26.8)	64.7 (23.4)	0.751
Physician Global (MDGA): NRS 0–10	6.5 (1.9)	6.7 (1.8)	0.635
Morning stiffness: min	73.5 (42.3)	75.2 (38.9)	0.736
HAQ-DI	1.16 (0.56)	1.32 (0.62)	*0.018*
ASDAS	3.8 (1.0)	3.7 (1.0)	0.238
BASDAI	6.3 (2.0)	6.7 (2.0)	0.101
BASFI	6.1 (2.4)	6.3 (2.3)	0.529
Prior biologic (<6 months)	7.4%	13.2%	0.099
Concomitant DMARD	28.6%	37.7%	0.098
Concomitant NSAID	78.4%	86.0%	0.098
PsA	**n=49**	**n=42**	
Age: years	48.6 (10.8)	48.9 (8.9)	0.862
Disease duration: years	6.9 (7.4)	6.8 (10.8)	0.980
C-Reactive Protein: mg/L	11.1 (14.4)	15.7 (23.8)	0.342
Patient Global: VAS mm	46.6 (27.0)	55.0 (28.9)	0.168
Physician Global: NRS 0–10	5.6 (2.0)	6.0 (2.3)	0.369
Pain: VAS mm	43.9 (25.6)	49.1 (26.1)	0.355
Morning stiffness: min	61.4 (48.1)	55.2 (42.2)	0.527
HAQ-DI	0.92 (0.58)	1.43 (0.66)	*<0.001*
TJC28	5.0 (5.0)	6.8 (5.4)	0.105
SJC28	3.9 (4.0)	4.0 (3.6)	0.939
PASI	4.2 (5.6)	2.4 (5.7)	0.188
DAS28	3.8 (1.6)	4.6 (1.5)	*0.036*
Prior biologic (<6 months)	23.8%	14.3%	0.245
Concomitant DMARD	71.4%	78.6%	0.434
Concomitant corticosteroid	11.9%	4.1%	0.163

Conclusion: Overall, some significant differences in disease parameters were observed between genders in AS and PsA at anti-TNF initiation. Female AS patients experience greater functional impairment compared to men. Female PsA patients, in addition to higher HAQ, also show greater disease activity as measured by DAS28. These results suggest that female patients appear to be receiving their first biologics at a higher level of disease activity. Whether this represents a gender bias in prescribing, or a gender based difference in the acceptance of biologic treatment, requires additional research.

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Disclosure: J. Kelsall, Janssen Inc., 5; **W. Bensen**, Janssen Inc, 5; **W. Olszynski**, Janssen Inc., 5; **N. Jones**, None; **I. Fortin**, Janssen Inc., 5; **A. Chow**, Janssen Inc., 5; **M. Baker**, Janssen Inc., 5; **S. Shaikh**, Janssen Inc., 5; **D. Choquette**, Notre-Dame Hospital,

Quebec, Canada, 3, AbbVie, 5, Amgen, 5, Celgene, 5, BMS Canada, 5, Janssen Pharmaceutica Product, L.P., 5, Pfizer Inc, 5; **E. Rampakakis**, None; **J. S. Sampalis**, None; **M. Shawi**, Janssen Inc., 3; **F. Nantel**, Janssen Inc., 3; **S. Otawa**, Janssen Inc., 3; **A. J. Lehman**, Janssen Inc., 3.

1602

Th9 Cells in Inflammatory Cascades of Autoimmune Arthritis. Siba Raychaudhuri[1], Anupam Mitra[2], Ananya Datta Mitra[2], Christine Abria[2] and Smriti K. Raychaudhuri[2]. [1]Univ California Davis/VA Sac, Davis, CA, [2]VA Sacramento Medical Center, Mather, CA.

Background/Purpose: Interleukin (IL)-9, a member of IL-2 cytokine family was recently attributed to a novel CD4 T cell subset termed Th9 cells in the murine system. It is secreted by naïve CD4+ T cells in response to TGF-β and IL-4. IL-9 can also be secreted by Th17 cells and itself induces Th17 cells to differentiate and regulate autoimmune and inflammatory diseases by enhancing their secretion of IL-17. These observations provoked us to elucidate the pathogenic role of IL-9 in autoimmune arthritis.

Methods: From peripheral blood and synovial fluid (SF) of psoriatic arthritis (PsA) (n = 8), rheumatoid arthritis (RA) (n = 10) and osteoarthritis (OA, n = 10) patients, mononuclear cells were obtained and magnetically sorted for CD3+ T cells. IL-9 levels in SF and serum were measured by enzyme linked immunosorbent assay (ELISA). Proliferative effect of human recombinant IL-9 (rIL-9) on CD3+ T cells of peripheral blood and SF was assessed by MTT (3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide, a yellow tetrazole) and CFSE dilution (Carboxyfluorescein succinimidyl ester) assays. The CD3+ cells from peripheral blood were activated with anti-CD3/CD28 cocktail.

Results: IL-9 levels were significantly elevated in SF and serum of PsA patient and RA patients as compared to SF and serum of OA (Figure 1). Further we demonstrated that activated synovial T cells of PsA and RA patients produced significantly more IL-9 than those of OA patients. In MTT and CFSE dilution assays, rIL-9 (MTT, OD: 0.642 ± 0.02) induced significant proliferation of CD3+ T cells of peripheral blood (Figure 2) and SF (Figure 3) derived from RA and PsA patients compared to media. Further, initial observations suggest that IL-9 receptor ab inhibits IL-9 induced proliferation of the activated SF derived T cells in inflammatory arthritis.

Conclusion: Our data showed that serum and SF of PsA and RA patients have higher concentration of IL-9 than matched OA controls. Moreover, rIL-9 induced marked proliferation of RA and PsA derived activated CD3+ T cells of SF from RA and PsA patients. Thus, IL-9 is likely to play a critical role in the inflammatory cascades of autoimmune arthritis. More importantly IL-9 provides a unique target to develop therapy for PsA patients where we do not have many options like in RA.

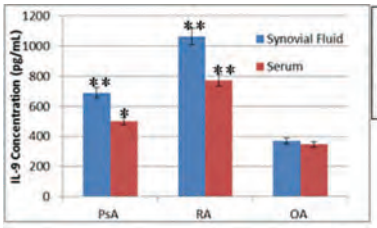


Figure 1: IL-9 in SF and serum of PsA and RA were elevated compared to OA patients (*=p<0.01, **=p<0.001, ANOVA, as compared to OA)

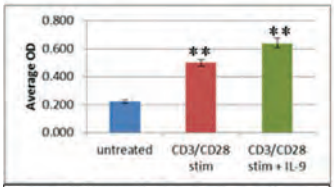


Figure 2: Human rIL-9 (10ng/ml) induced marked proliferation of activated CD3+ cells in serum of RA patients. (*=p<0.01, **=p<0.001, unpaired t-Test, as compared to untreated cells)

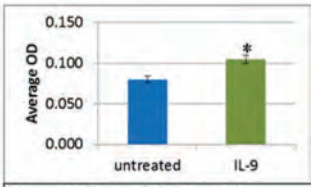


Figure 3: Human rIL-9 (10ng/ml) induced marked proliferation of CD3+ cells in SF of RA patients. (*=p<0.01, unpaired t-Test, as compared to untreated cells)

Disclosure: S. Raychaudhuri, None; **A. Mitra**, None; **A. Datta Mitra**, None; **C. Abria**, None; **S. K. Raychaudhuri**, None.

1603

Effect of Methotrexate on the Immunogenicity of TNF Inhibitors in Spondyloarthritis Patients. Alejandro Villalba[1], Chamaida Plasencia-Rodriguez[1], Diana Peiteado[1], Laura Nuño[2], Gema Bonilla[3], Alejandro Balsa[4], Emilio Martín-Mola[4] and Dora Pascual-Salcedo[5]. [1]Hospital La Paz - IdiPaz, Madrid, Spain, [2]Hospital La Paz-IdiPaz, Madrid, Spain, [3]Hospital La Paz, Madrid, Spain, [4]Hospital Universitario La Paz, Madrid, Spain, [5]La Paz University Hospital, Madrid, Spain.

Background/Purpose: The spondyloarthritis (SpA) patients treated under TNF inhibitors (TNFi) with detectable antidrug antibodies (ADA) often develop loss of efficacy. Concomitant therapy with methotrexate (MTX) appears to reduce the the immunogenicity of biological drugs. Our aim was to analyze if the use of combined therapy with MTX and TNFi can reduce the incidence of ADA and whether its effect is MTX dose dependent in SpA patients.

Methods: In this retrospective observational study, 162 SpA patients (including ankylosing spondylitis, Psoriatic SpA, SpA associated with *inflammatory bowel disease* and undifferentiated SpA) were included. The patients are treated with infliximab (Ifx) or adalimumab (Ada). The presence of ADA were measured at baseline and before each administration by ELISA to complete a follow up of 3 years. The patients were divided in two groups [MTX-15 (dose <15 mg/week) and MTX+15 (≥15 mg/week)] to study the influence of baseline MTX dose on immunogenicity. The statistical analysis was performed using SPSS 11.0.

Results: Eighty nine out of 162 (54,9%) patients were male. Eighty five out of 162 (52,5%) patients received Ifx and 77 out of 162 (47,5%) Ada. The mean duration of treatment was 13.38±9.19 years to Ifx and 12.71±10.46 years for Ada. Forty five patients received MTX weekly at baseline [25/85 (29.4%)in Ifx and 20/77 (26%)in Ada]. The mean dose of MTX was 15,9±4.76 mg/week. Twenty nine out of 162 (17,9%) patients developed ADA, and ADA presence was significantly higher in SpA patients on Ifx therapy [21/85(24.7%) in Ifx vs 8/77 (10.4%) in Ada, p=0.018)]. The presence of ADA was less frequent in SpA patients taking MTX [3/45 (6.7%) with MTX vs 26/117 (22,2%) without MTX, p=0.022]. No statistically differences were observed in the influence of baseline MTX dose on the ADA appearance (in Ifx: 2/18 (11,1%) in MTX+15 vs 1/9 (11,1%)in MTX-15, p=1,0; in Ada: 1/14 (7,4%) in MTX+15 vs 0/4 (0,0%)in MTX-15, p=1,0).

Conclusion: In this cohort of SpA patients treated with Ifx and Ada, the use of MTX has a preventive effect on the ADA development. However, the baseline MTX dose is not a determinant factor to get this effect. Further prospective studies are needed to confirm these data.

Disclosure: A. Villalba, None; **C. Plasencia-Rodriguez**, Pfizer Inc, 2; **D. Peiteado**, None; **L. Nuño**, None; **G. Bonilla**, None; **A. Balsa**, Pfizer Inc, 8, Amgen, 8; **E. Martín-Mola**, Pfizer Inc, 8, Abbie, 8, U.C.B., 8, Roche Pharmaceuticals, 8; **D. Pascual-Salcedo**, Pfizer Inc, 2.

ACR/ARHP Poster Session B
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis: Autoimmune Disease Transition, Disease Subsets and Prediction of Flares, Cytokines and Autoantibodies
Monday, November 17, 2014, 8:30 AM–4:00 PM

1604

IFN-γ (Th_1), IL4 (Th_2), and IL5 (Th_2) Are Elevated in Pre-Clinical SLE and Predict Transition to Classified Disease Prior to Appearance of Autoantibodies or Clinical Criteria. Rufei Lu[1], Melissa E. Munroe[2], Joel M. Guthridge[2], Krista M. Bean[2], Dustin Fife[2], John B. Harley[3], Judith A. James[2] and Michael P. Keith[4]. [1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Cincinnati Children's Hospital Medical Center; US Department of Veterans Affairs Medical Center, Cincinnati, OH, [4]Walter Reed National Military Medical Center, Bethesda, MD.

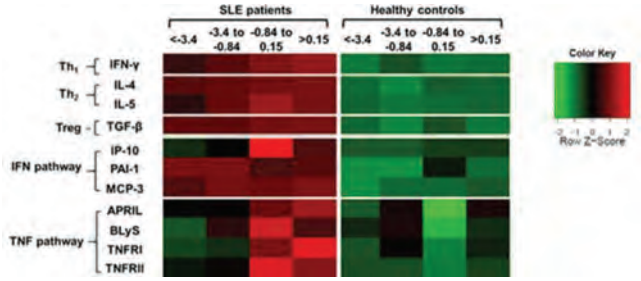
Background/Purpose: Systemic Lupus Erythematosus (SLE) is a clinically diverse autoimmune disease that often begins with a pre-disease period of autoantibody production and symptom accrual. Identifying reliable and biologically relevant predictors for future SLE onset could contribute to understanding disease pathogenesis, discovering disease-specific targetable pathways and facilitating prevention of this debilitating disorder.

Methods: To assess potential mechanistic pathways dysregulated early in lupus autoimmunity and to identify serum biomarkers that can accurately

forecast SLE development, we measured 13 autoantibodies and 34 circulating soluble mediators including cytokines, chemokines, and soluble receptors in serially collected serum samples from time points before and after meeting ACR classification in 55 individuals who subsequently developed SLE and 60 matched healthy controls.

Results: Elevated IL-4 (median, 13.9 vs 2.67 pg/mL), IL-5 (median, 51.14 vs 11.18 pg/mL), and IFN-γ levels (median, 9.12 vs 0.81 pg/mL) are present in subsequent SLE patient sera long before the disease classification (≥3.4 years) [compared to the healthy controls, $p<0.05$]. Path analysis shows that the elevation of IL-4 and IL-5 likely precede development of the majority of lupus specific autospecificities. Random forest modeling during the *preclinical period* identified IFN-γ (Th_1), IL-4 (Th_2), and IL-5 (Th_2) as reliable predictors of future SLE onset of SLE with only a 3.27% out of bag (OOB) prediction error. The best set of predictive biomarkers *at/after disease classification* includes IFN-γ, IL-4, IL-5 MCP-3, and TGF-β (3.68% OOB classification error).

Conclusion: These results suggest that dysfunctional Th_2 related pathways likely potentiate autoantibody production during the pre-clinical period and abnormal elevations in Th_1 cytokine levels exacerbate immune dysregulation. This longitudinal case-control retrospective study has not only provided a panel of SLE predictors to help develop prevention strategies, but strengthened the hypothesis that dysregulated Th_1 and Th_2 pathways are involved in early SLE pathogenesis.



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1605

Elevated Regulatory Mediators and Interferon Gamma Associated Responses, but Not Interferon Alpha, BLyS or IP-10, Accompany High-Titer Anti-Ro Autoantibodies in Asymptomatic Mothers of Children with Neonatal Lupus.

Peter M. Izmirly[1], Robert M. Clancy[1], Melissa Munroe[2], Sara Rasmussen[1], Amit Saxena[1], Jose U. Scher[1], Aikaterini Thanou[2], Stan Kamp[2], Joan T. Merrill[2], Jill P. Buyon[1] and Judith James[2]. [1]New York University School of Medicine, New York, NY, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Mothers of children with neonatal lupus offer a unique opportunity to study the drivers and consequences of autoantibody production in the absence of ongoing maternal inflammation/damage or concurrent immunotherapeutics since many of these women are clinically asymptomatic with high titer anti-Ro antibodies identified solely by disease in the child. This study was initiated to assess the contribution of soluble mediators in the innate, adaptive and effector arms of the immune system to the production of anti-Ro responses independent of other autoantibodies or established systemic lupus erythematosus (SLE), Sjogren's syndrome (SS) or rheumatoid arthritis (RA).

Methods: Soluble mediators (N= 32) were examined including cytokines, chemokines, and soluble receptors using validated multiplex bead-based (xMAP) or enzyme-linked immunosorbent assays in serum from 44 anti-Ro positive women within 5 years of a pregnancy complicated by either heart block (N=36) or skin rash (N=8). Autoantibodies were measured by Bio-Rad Bioplex ANA2200 and recombinant and native Ro60/52 proteins by ELISA. Antibodies to dsDNA, Sm, and RNP were all negative. Based on questionnaire, phone interview, and review of medical records, 18 mothers were completely asymptomatic, 8 had either photosensitivity or Raynauds, and 18 had a combination of mild complaints, including articular and cutaneous symptoms and did not fulfill SLE (ACR or SLICC), SS or RA criteria. Comparisons were made with sera obtained from 156 healthy controls and 94 SLE patients (30 = anti-Ro positive).

Results: Compared to healthy controls, asymptomatic/undifferentiated anti-Ro positive mothers had significant ($p<0.0001$) alterations in 21 of 32 tested mediators. These mothers had higher levels of IFN g and associated molecules (MIG, MIP-1a) ($p<0.0001$) than ANA negative healthy controls at levels that were comparable with SLE patients. However, levels of IFNa and associated molecules important in SLE (BLyS, IP-10) were much lower in anti-Ro positive mothers than SLE patients, and similar to healthy controls ($p<0.0001$). These anti-Ro positive mothers also had higher levels of Th17 (IL-17A, IL-21, IL-6), Th1 (IL-2, TNFa), Th2 (IL-4, IL-6), shed TNF receptors (TNFRI, TNFRII, sCD40L) and regulatory responses (IL-1RA) compared to healthy controls ($p<0.0001$). In addition, these anti-Ro positive mothers had dramatically higher levels of IL-1RA and TGFb compared to SLE patients including those with anti-Ro ($p<0.0001$). No significant differences in soluble mediator levels were noted between anti-Ro positive mothers who were completely asymptomatic and those with mild rheumatic symptoms.

Conclusion: High titer anti-Ro positive asymptomatic neonatal lupus mothers have dysregulated levels of soluble mediators across several inflammatory and immune pathways; however, BlyS and IP10, which appear temporally important in transition to clinical SLE, are not elevated. This cohort provides a unique opportunity to dissect critical pathways resulting in autoimmunity absent overt disease, thus guiding the development of targeted therapeutics for decreasing anti-Ro antibodies and risk of neonatal lupus, as well as providing insights into lupus pathogenesis.

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1606

Profiling a Broad Range of Autoantibodies in Healthy and Systemic Lupus Erythematosis Revealed Autoantibody Patterns Associated with Autoantibody Transition and Disease Activity.

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Background/Purpose: Autoantibodies targeting to nuclear antigens are serological hallmarks of SLE, however, the processing of autoantibody production during the transition from normal to autoimmunity and the pathogenicity of the autoantibodies related with the disease activities are still unclear.

Methods: In this study, we first measured the serum anti-nuclear antibody (ANA) in 2,353 healthy controls (HC) and 500 SLE patients by ELISA. We then screened the levels of IgG and IgM autoantibodies (autoAbs) targeting to a broad range of nuclear and non-nuclear antigens using proteomic microarrays bearing 95 autoantigens, in a cohort of 121 well defined SLE patients and the same number of matched HCs. For a subset of samples, we also measured the IgA subtype of AutoAbs using autoantigen arrays.

Results: ANA testing showed a positivity of 92.5% in SLE, in which 78% with high ANA titers (>40 AU) and 14.5% with moderate to low ANA (20–40 AU). About 25% of HCs also exhibited positive ANA among which 9% with high titer (>40 AU). Autoantigen array analysis revealed high prevalence of IgG autoAbs in SLE patients, the average number of positive IgG autoAbs in SLE were 28.5 and over 95% of SLE harbor more than 5 autoAbs, comparing with average of 3 IgG autoAbs with only 25% have more than 5 autoAbs in HCs ($p<0.05$). A group of 19 IgG autoAbs targeting to various nuclear antigens (dsDNA, chromatin, nucleosome, histone, Sm/RNP, PCNA, CENP-B, etc.) were identified to be significantly enriched in SLE patients by clustering analysis. The presence of IgG autoantibodies against DNA antigens (dsDNA, ssDNA, chromatin, nucleosome, histone) were most significantly associated with disease activity (SLEDAI) and lupus nephritis ($r=0.56$, $p<0.001$) in SLE. Among the normal populations, the young females (age 20–45) with high ANA (>20) tend to carry more IgG autoAbs than other groups, however, majority of the IgG autoAbs identified in HCs were those targeting to non-nuclear antigens, such as cell matrix (collagens, alpha-actinin, heparin sulfate, etc) and phospholipid proteins (cardiolipin). The ANA negative NCs showed low positivity for both IgG and IgM autoAbs, however, the ANA positive NC exhibited higher IgM specificities targeting to 33 non-nuclear and nuclear antigens whereas in SLE the IgM autoAb reaction were relatively lower. Interestingly we noticed a subgroup of SLE patients who have active disease (SLIDAI>10) with lupus nephritis exhibited strong positivity for both IgG and IgM autoantibodies again DNA-associated antigens (dsDNA, ssDNA, chromatin, nucleosome, histone). IgA autoabs were detected in 17 (out of 30) SLEs, preferentially targeting to RNA-associated antigens (Ro, La, Sm/RNP and Ribo phophoproteins).

Interestingly, 3 of the ANA- SLE who have no IgG autoAbs showed positive IgA autoantibodies.

Conclusion: Breach in immune tolerance in normal population was usually accompanied by production of autoantibodies against non-nuclear antigens and the transition from IgM to IgG autoAbs was an indication of increased pathogenicity of the autoantibodies. IgG autoantibodies against nuclear antigens especially DNA associated antigens were closely related with the disease activitity and renal damage in SLE.

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1607

B Cell and Neutrophil-Related Transcripts Predict and Characterize a Lupus Flare. Mikhail Olferiev[1], Kyriakos A. Kirou[2] and Mary K. Crow[2]. [1]HSS, New York, NY, [2]Hospital for Special Surgery, New York, NY.

Background/Purpose: Lupus flare reflects an increase of disease activity that is associated with significant morbidity and accumulation of tissue damage. Prediction and prevention of lupus flare is an important goal of lupus research and, ultimately, clinical management. Our aim was to identify perturbations in molecular and cellular mechanisms that precede and coincide with lupus flare.

Methods: PBMC samples, clinical and laboratory data were collected longitudinally from 19 patients meeting ACR criteria for SLE. From 2 to 8 visits/patient (total 90 data points) were analyzed. All patients experienced at least one SELENA-SLEDAI flare. Patients did not receive biologic agents during flare visits, but therapy was otherwise uncontrolled. Transcriptional profiles were obtained for each visit using Affymetrix HG U133Plus 2.0 GeneChips (by Novo Nordisk). SELENA-SLEDAI, BILAG and physician global assessments were compared to identify a point of maximum disease activity (flare). The flare point was set as day 0 for each patient over a 2 year interval. The remaining visits were arranged by time before or after flare. An mRNA profile for each transcript was established using the smoothing-splines mixed effect model (Berk M., 2012). All fitted models were classified by hierarchical clustering, and obtained clusters were studied using the gene-enrichment profiler database (Xavier lab; Benita Y. et al., 2010) and the DAVID v6.7 database to link functionally-related transcripts. The selected cell-specific or function-related genes were refitted and dynamic changes over one year intervals preceding and following flare were characterized.

Results: From 22190 transcripts, the models were successfully fit for 3189 transcripts. Clustering identified 9 major patterns over the observed time course. Most striking was the rise of B cell-related transcripts, including IRF4, SPIB, CD19, CD22, and CD79b, as early as 180 days before lupus flare. Subsequently, transcripts expressed in the myeloid lineage [mannose receptor (MRC1/CD206), CLEC10A/CD301, GPR137B] and those linked to lysosomal function [N-acetylgalactosaminidase (NAGA), acid phosphatase 2 (ACP2), scavenger receptor class B (SCARB2), and endolyn (CD164)] were decreased. B cell-related transcripts rapidly declined immediately prior to flare, while a distinct transcript cluster, including SIGLEC5/CD170, FPR1, IL1R2, SLC11A1, CR1, C1RL, emerged and coincided with flare. A tissue enrichment profiler identified those transcripts as highly expressed in blood neutrophils. The mean level of neutrophil-related transcripts correlated with SLEDAI and BILAG scores at time of flare ($R=0.49$ and $R=0.44$, respectively; $p<0.001$ for both).

Conclusion: Despite the clinical heterogeneity that characterizes flare in individual patients, a common sequence of molecular events was observed preceding and during lupus flares. Strikingly, changes in the B cell population were observed as early as 6 months before flare. Similarly, perturbations in myeloid lineage transcripts occurred prior to flare. An increase in neutrophil-related transcripts is an indicator of lupus flare and correlates with disease activity at time of flare.

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1608

Erythrocyte C4d and Antibodies to Anti-C1q Are Associated with Proteinuria in Lupus Nephritis. Jill P. Buyon[1], R. Ramsey-Goldman[2], Richard Furie[3], Chaim Putterman[4], Kenneth Kalunian[5], John Conklin[6], Tyler O'Malley[6], Derren Barken[6] and Thierry Dervieux[6]. [1]New York University School of Medicine, New York, NY, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, [3]North Shore-LIJ Health System, Great Neck, NY, [4]Albert Einstein College of Medicine, Bronx, NY, [5]UCSD School of Medicine, La Jolla, CA, [6]Exagen Diagnostics, Inc., Vista, CA.

Background/Purpose: Biomarkers of renal response in patients with systemic lupus erythematosus (SLE) may provide clues to pathogenesis and drive translation to treatment. This study was initiated to evaluate the association between renal activity and the changes in erythrocyte bound complement C4d product (EC4d), anti-C1q, anti-dsDNA antibodies and low complement.

Methods: The study enrolled 289 SLE patients (mean age 40 years, 92% females) meeting the 1982 ACR classification criteria. All patients were evaluated at one time point as part of a cross-sectional study and a subset of 34 patients (mean age 34 years, 94% female) were followed monthly for an average of 9 months. Among patients enrolled in the cross sectional study, the presence of proteinuria was defined by the renal domain on the SELENA-SLEDAI (increase >0.5 g thus implies active and not chronic proteinuria). For the longitudinal study, proteinuria was defined using the random protein to creatinine ratio (expressed as g/g). Complement protein levels (C3 and C4) were determined using immunoturbidimetry, antibodies to anti-C1q and anti-dsDNA were determined by ELISA and EC4d was determined using flow cytometry (expressed as mean fluorescence intensity [MFI]). Statistical analyses consisted of non-parametric tests, and Chi-square tests. Longitudinal changes in urine protein as a function of the change in the biomarkers were evaluated using generalized linear mixed models effects using random intercept and fixed slopes.

Results: Among 289 SLE, 12% presented with proteinuria at the time of the clinical assessment. Higher EC4d levels were observed in the SLE patients who presented with proteinuria compared to those who did not (median 21 MFI [Interquartile range, IQR: 15–29] vs 12 MFI [IQR: 7–22], $p<0.01$). Abnormal EC4d levels (>20 MFI) were found in 62% of patients with proteinuria compared to 27% of patients without ($p<0.001$). In contrast, the presence of the low complement component of the SELENA-SLEDAI domain was not significantly different between the groups (53% versus 36% $p=0.08$). Neither Anti-C1q nor anti-dsDNA antibodies differentiated between the two groups at baseline. Among the 34 SLE patients followed monthly, a decrease in EC4d levels to lower than 20 MFI was associated with a concomitant decrease of 0.7 g/g urine protein to creatinine ratio ($p=0.0018$) (**Table**). Similarly, the decrease in anti-C1q levels to lower than 80 units was accompanied by decreased proteinuria ($p=0.0015$). Normalization of low complement or loss of anti-dsDNA was non-significantly associated with proteinuria ($p>0.19$). In multivariate analysis both EC4d and anti-C1q were independently associated with proteinuria ($p<0.01$).

Conclusion: These data suggest that longitudinal changes in EC4d and anti-C1q levels track with changes in proteinuria. EC4d correlates more strongly with proteinuria than traditional measures of complement.

Table: Mixed model effect estimates

	Estimate (SEM) g/g	P value
EC4d≤20 MFI	−0.70±0.22	0.0018
Anti-C1q≤80 units	−1.12±0.35	0.0015
Normal Complement (C3/C4)	−0.33±0.24	0.19
Loss of Anti-dsDNA	+0.07±0.29	0.81

Disclosure: J. P. Buyon, Exagen, 2; **R. Ramsey-Goldman**, Exagen, 2; **R. Furie**, Exagen, 2; **C. Putterman**, Exagen, 2, Exagen, 5; **K. Kalunian**, Exagen, 2, Exagen, 5; **J. Conklin**, Exagen, 3; **T. O'Malley**, Exagen, 3; **D. Barken**, Exagen, 3; **T. Dervieux**, None.

1609

Dissection of the Type I Interferon Response in Systemic Lupus Erythematosus : Serum IFNα Is Elevated in Lupus Nephritis and Correlates with IFN Score; IFNβ Is Elevated in Mucocutaneous Disease. Julie Ducreux[1], Fabien Colaone[2], Séverine Nieuwland[1], Patrick Blanco[3], Thierry Defrance[4], Pierre Vandepapeliere[2], Géraldine Grouard-Vogel[2], Frédéric A. Houssiau[1] and Bernard R. Lauwerys[1]. [1]Université catholique de Louvain, Brussels, Belgium, [2]NEOVACS SA, Paris, France, [3]CHU Bordeaux, Bordeaux, France, [4]INSERM, Lyon, France.

Background/Purpose: Type I interferons play a role in the pathogenesis of systemic lupus erythematosus (SLE), but their mechanisms of action are still not fully understood. In this study, we measured serum concentrations of IFNα, IFNβ and IFNω in a cross-sectional cohort of SLE patients followed at a single center, and investigated whether they correlate with clinical or biological indices of disease activity. The link between serum IFNα and IFN

signature in SLE whole blood cells was further evaluated in a prospective set of samples from patients included in the IFNα kinoid study.

Methods: Sera from 178 patients with SLE were harvested during a visit at the Lupus Clinic, and stored at −80°. Serum IFNα, IFNβ and IFNω were measured by ELISA. BILAG scores, serum C3 and double-stranded DNA antibody titers were retrieved from the medical records. Active mucocutaneous disease was defined based on the presence of a mucocutaneous BILAG A, B or C. Because persistent hematuria results in a renal BILAG B score, only renal BILAG A was considered for the definition of active renal disease. Whole blood transcriptome (GeneChip HGU133Plus 2.0 chips) and serum IFNα concentrations were determined at day 0, 112 and 168 in an additional cohort of 28 patients (SLEDAI between 4 and 10) included in the IFNα kinoid trial. Statistical analyses (Mann-Whitney tests and Spearman correlations) were performed using Prism 5.0 software.

Results: 14 out of 178 patients had active renal disease, and 33 had active mucocutaneous disease. Ouf of them, 7 displayed both renal and mucocutaneous disease activity.

Serum IFNα and IFNβ, but not IFNω, were significantly higher in the presence of a renal BILAG A. However, when patients with simultaneous renal and mucocutaneous involvement were discarded, only serum IFNα remained significantly higher in the presence of active renal disease (median concentration 4.53 *versus* 0 pg/ml, $p < 0.0001$).

Similarly, serum IFNβ and IFNα, but not IFNω, were significantly higher in the presence of a mucocutaneous BILAG A, B and C. However, when patients with simultaneous mucocutaneous and renal involvement were discarded, only serum IFNβ remained significantly higher in the presence of active mucocutaneous disease.

There was a low, albeit significant correlation between serum IFNα and serum dsDNA titers or C3 concentrations. In the set of patients included in the IFNα kinoid trial, the IFN signature score displayed a strong and significant correlation with serum IFNα concentrations (Spearman $r = 0.54$, $p < 0.0001$).

Conclusion: Our data indicate for the first time that the type I interferon response in SLE is different according to the affected system. The IFN signature score observed in SLE whole blood cells is driven by IFNα. Increased IFNα in systemic and renal disease and IFNβ in mucocutaneous disease indicate that distinct pathogenic mechanisms are involved in these different manifestations of the disease.

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1610

New Autoantigens Associated with Lupus Nephritis. Sachiko Onishi[1], Yuki Tanaka[2], Tatsuhiko Miyazaki[3], Jun Ishizaki[1], Takuya Matsumoto[1], Endy Adnan[1], Hitoshi Yamasaki[1], Koichiro Suemori[1], Takafumi Okura[1], Masaki Yasukawa[1] and Hitoshi Hasegawa[1]. [1]Ehime University Graduate School of Medicine, Toon, Japan, [2]Ehime University, Toon, Japan, [3]Gifu University Hospital, Gifu, Japan.

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by the production of a variety of autoantibodies and is considered a prototype immune complex disease. Anti-dsDNA antibodies contribute to the pathogenesis of lupus nephritis (LN). However, since anti-dsDNA antibodies are not sufficient for the diagnosis, prognosis or evaluation of disease activity, other autoantibodies associated with LN need to be identified. Using an N-terminal biotinylated protein library (BPL) we screened for autoantigens reacting with LN patient sera and then further characterize these autoantigens.

Methods: We screened for autoantigens using the AlphaScreen method with the sera from 3 SLE patients with different disease complications; thrombocytopenia, nephritis or serositis. Antigens used for screening were created using the 2296 cDNA library from a wheat cell-free protein production system in the Ehime University Cell-Free Sciences and Technology Research Center. The proteins characteristic of nephritis were selected, and immunoprecipitation was performed using serum from patients with LN. Immunohistochemical staining of renal tissues was carried out with antibodies against proteins positive in the immunoprecipitation. The specificity of the identified autoantigens was analyzed by an enzyme-linked immunosorbent assay (ELISA) with serum from approximately 250 patients with various autoimmune diseases such as polymiositis/dermatomyositis, systemic sclerosis, and rheumatoid arthritis.

Results: We screened 66 proteins which reacted with LN patient sera at a high levels. Of these, ten proteins showed strong reaction specifically to SLE sera with immunoprecipitation. Immune complex deposition of these ten proteins was confirmed by immunohistochemical staining of renal biopsy tissue and autopsy renal tissue of LN. Clear deposition of 2 proteins, ribosomal RNA processing 8 (RRP8) and transition protein 1 (TNP1), was seen in some renal tissues. ELISA analysis showed that RRP8 and TNP1 reacted to the sera from some SLE patients but have little or no reaction with those from other autoimmune diseases. In addition, anti-RRP8 and anti-TNP1 antibodies were detected in 5 and 7 out of 11 LN patients, respectively.

Conclusion: The AlphaScreen method using BPL created by wheat germ cell-free protein synthesis proved to be useful for autoantibody screening. We have identified RRP8 and TNP1 as new LN autoantigens. RRP8 and TNP1 may play an important role in the pathogenesis of LN.

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1611

Modular Transcriptional Neutrophil Signature As Predictive of Nephritis and of Its Severity in SLE Patients. Noémie Jourde-Chiche Sr.[1], Stéphane Burtey[2], Nathalie Bardin[3], Elizabeth Whalen[4], Bertrand Gondouin[2], Scott Presnell[5], Bertrand Dussol[6], Gilles Kaplanski[7], Jean-Robert Harle[2], Yvon Berland[2], Virginia Pascual[8], Damien Chaussabel[4] and Laurent Chiche[9]. [1]Aix-Marseille Université - APHM, Marseille, France, [2]APHM, Marseille, France, [3]Hopital de la Conception, Marseille, France, [4]BRI, seattle, WA, [5]bri, seattle, WA, [6]AP Marseille, Marseille, France, [7]INSERM U608, Marseille, France, [8]Baylor University, Dallas, TX, [9]CHU Marseille, Marseille, France.

Background/Purpose: Lupus nephritis (LN) is a serious complication of SLE. Reliable biomarkers to assess and/or predict renal involvement in SLE patients are needed. The aim of this study was to better assess the link between blood transcriptional signatures and LN.

Methods: Consecutive SLE patients (ACR criteria) were followed-up prospectively. Blood samples were split in: group 1, samples collected at the time of a biopsy-proven LN with active lesions, either proliferative (class III or IV) or not (class II or V); group 2, patients sampled at the time of an extra-renal flare; group 3, patients sampled at their first clinically quiescent visit (no flare or treatment modification in the past 60 days and SLEDAI $\leq$4). Microarray data were generated using Illumina beadchips and analyzed using modular repertoire analyses. Modules with ^{3} 20% transcripts differentially expressed compared to matched healthy controls were considered active.

Results: In addition to the IFN-related modules (M1.2, M3.4 and M5.12), modular repertoire analysis in SLE patients revealed a strong upregulation of M5.15, a module of 24 transcripts annotated "neutrophil". There was no significant correlation between IFN modules and M5.15 activity. At the individual level, spearman correlations between modules and SLEDAI were significant for M5.12 ($r=0.25$, $p=0.03$), but not for M5.15 ($r=0.21$, $p=0.09$). M5.15, however, was the only module strongly associated with LN (Wilcox t-test $p=0.009$), although there was a trend for M5.12 ($p=0.099$). M5.15 was not associated with cutaneous, articular or hematological flares.

Group 1 comprised 24 patients, with proliferative ($n=14$) or non-proliferative ($n=10$) LN. Group 2 comprised 11 patients with an extra-renal flare. Group 3 comprised 34 patients, among whom 22 had a past history of LN. A neutrophil modular signature (M5.15 $\geq$ 20%) was observed in 16/24 (67%), 2/11 (18%) and 16/34 (47%) of patients respectively from group 1, 2 and 3 (Fisher's exact test $p=0.027$). In group 2, 1 patient with a neutrophil signature had a history of LN, the other subsequently had a LN flare (class III at M24). In group 3, 9/16 had a previous LN and 4/16 subsequently developed a LN flare (class IV at M18, M21 and M36; class V at M13).

M5.15 activity was neither correlated to age, gender or ethnicity, nor with the titer of anti-dsDNA ($p=0.7$). There was a strong correlation between daily corticosteroid dose and M5.15 ($r=0.45$, $p<0.0001$). M5.15 was not significantly correlated with 24h proteinuria or serum creatinine but was correlated with acute renal failure ($p=0.03$) and serum albumin ($r=-0.30$, $p=0.01$). In group 1, the median value of M5.15 in patients was significantly higher in patients with proliferative than non proliferative LN (66.7 vs 18.8 %, $p=0.04$). After initiation of treatment in patients with proliferative LN and $\geq$3 consecutive evaluation ($n=10$), a trend was observed between the decrease of M5.15 activity and remission at M6 ($p=0.13$).

Conclusion: Modular repertoire analysis demonstrates that neutrophil signature in SLE patients is correlated with the occurrence and severity of lupus nephritis and may help in the design of disease prognostic and/or activity biomarkers.

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1612

Deficient Repair of DNA Double-Strand Breaks and Increased Apoptosis in Patients with Lupus Nephritis. Vassilis Souliotis[1] and Petros P. Sfikakis[2]. [1]Institute of Biology, Medicinal Chemistry and Biotechnology, National Hellenic Research Foundation, Athens, Greece, Athens, Greece, [2]First Department of Propedeutic Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece.

Background/Purpose: Accumulation of apoptotic cells leads to excessive autoantigen presentation and autoantibody formation in autoimmunity, whereas mandatory to avoid apoptosis is the efficient repair of DNA double-strand breaks (DSBs). Herein, we tested the hypothesis that in patients with lupus nephritis, a severe complication of the prototypic systemic autoimmune disease, the DSBs repair is deficient and linked with increased apoptosis in peripheral blood mononuclear cells.

Methods: The intrinsic DNA damage and the DNA repair capacity using γH2Ax foci measurement by confocal microscopy and comet assay, as well as the induction of apoptosis following *ex vivo* treatment with genotoxic drugs (cisplatin, melphalan) were evaluated in peripheral blood mononuclear cells from lupus nephritis patients (n=6). Healthy individuals (n=10), age- and gender-matched to patients were served as controls.

Results: We found that the intrinsic DNA damage was significantly higher in lupus patients than in healthy volunteers ($p<0.01$). Particularly, using comet assay, lupus patients showed Olive Tail Moment values of 15.8+2.3 arbitrary units, while healthy controls only 3.0+1.4 units. Also, using confocal microscopy, the percentage of the γH2AX positive cells was 13.6+1.8 in lupus patients and 4.6+0.9 in healthy controls. Moreover, the genotoxic agent-induced apoptosis rates were significantly higher in lupus than in control cells ($p<0.01$). That is, melphalan dose as low as 9.9+4.8μg/ml was sufficient to induce detectable levels of apoptosis in lupus patients, while healthy controls required doses of 32.3+7.7μg/ml. The corresponding values for cisplatin treatment were 29.8+8.3μg/ml and 67.7+5.5μg/ml, respectively. Finally, following *ex vivo* treatment of mononuclear cells with a genotoxic agent, DSBs repair efficiency was inversely correlated with the apoptosis rates of these cells, being significantly lower in lupus than in control cells ($p<0.01$). That is, melphalan-induced DNA damage was removed with $t_{1/2}$=9.1+2.4h in healthy controls and 51.3+7.6h in lupus patients, with the corresponding values for cisplatin-induced damage being 4.2+1.5h and 25.4+5.9h, respectively. Results in lupus cells were not associated with individual disease activity level or treatment modalities at the time of study.

Conclusion: We demonstrated that circulating mononuclear cells from lupus nephritis patients are characterized by higher intrinsic DNA damage and profoundly reduced DSBs repair capacity. Since failure to repair DNA lesions such as DSBs leads to mutations, genomic instability and induction of apoptosis, these results suggest a novel mechanism by which deficient repair of DSBs may contribute to the induction of systemic autoimmunity.

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Circulating microRNAs As Candidate Biomarkers of Diagnosis in Systemic Lupus Erythematosus. Juyang Jung[1], Ja-Young Jeon[2], Bong-Sik Kim[2], Hyoun-Ah Kim[2] and Chang-Hee Suh[3]. [1]Ajou university of medical school, Suwon, South Korea, [2]Ajou University School of Medicine, Suwon, South Korea, [3]Ajou University School of Med, Suwon, South Korea.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by polyclonal B-cell activation and elevated production of pathogenic autoantibodies. MicroRNAs (miRNAs) are short, noncoding RNAs that regulate gene expression on the posttranslational level, which can be measured in the circulation, and are emerging as novel biomarkers in various diseases. However, a systematic analysis of circulating miRNAs in SLE patients has been rarely addressed. We attempted to identify circulating miRNAs associated with the susceptibility to SLE in Korean populations, and to elucidate their significance in clinical phenotypes of SLE.

Methods: Blood samples were collected from Korean SLE patients (n = 70) and normal controls (NC, n = 40) at the rheumatology clinic, Ajou University Hospital. The microRNA PCR arrays identified miRNAs differentially expressed in SLE patients and NC. For the microRNA PCR arrays, we isolated total RNA from plasma samples of 10 SLE patients and 10 NC. The RNAs were pooled in each sample group (n = 10) with an equal amount of RNAs. A miRNA expression profiling analysis was performed and compared between SLE patients and NC. To verify the microRNA PCR arrays results, we performed the quantitative real-time PCR in samples from SLE patients (n = 70) and NC (n = 40).

Results: Nine miRNAs were differentially expressed in plasma between SLE patients and NC by miRNA PCR array. The plasma expression level of hsa-miR-17-5p, hsa-miR-19a-3p, hsa-miR-21-5p, hsa-miR-25-3p, hsa-miR-92a-3p, hsa-miR-223-3p, and hsa-miR-30e-5p were up-regulated in the SLE patients compared to the NC. The plasma expression level of hsa-miR-26b-5p and hsa-miR-150-5p were down-regulated in the SLE patients compared to the NC. The hsa-miR-30e-5p, hsa-miR-92a-3p, and hsa-miR-223-3p were significantly up-regulated in plasma from patients with SLE by quantitative real-time PCR. Especially, the hsa-miR-223-3p was significantly associated with oral ulcer ($p<0.001$) and lupus anticoagulant ($p=0.031$).

Conclusion: Our data suggest that plasma hsa-miR-30e-5p, hsa-miR-92a-3p and hsa-miR-223-3p may be novel important promising biomarkers in the diagnosis of SLE. These novel and promising markers warrant validation in larger prospective studies.

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Functional Analysis of Interferon Responsiveness in PBMC from SLE Donors Identifies Subgroups with Higher and Lower Disease Activity. Rachael Hawtin[1], Wouter Korver[2], Erik Evensen[2], Diane Longo[2], Drew Hotson[2], Nikil Wale[2], Andy Conroy[2], Alessandra Cesano[2], Barbara Mittleman[2], Tsung Lin[3], Vikram R. Rao[4], Elena Peeva[3], Stephen Benoit[3], Martin Hodge[3], James D. Clark[3], Aaron R. Winkler[3] and Jean-Baptiste Telliez[3]. [1]Nodality Inc., South San Francisco, CA, [2]Nodality, Inc., South San Francisco, CA, [3]Pfizer Biotherapeutics Research and Development, Cambridge, MA, [4]Pfizer, Cambridge, MA.

Background/Purpose: Interferons (IFN) reportedly are central to SLE pathogenesis and increased expression of IFN regulated genes (the 'IFN signature') is associated with active disease. Clinical utility of the IFN signature is unclear, and refinement to define further patient subgroups may improve disease management. Toll-like receptor (TLR) activation leads to IFNα induction. To increase understanding of the role of IFNs in SLE pathobiology, and connectivity between IFN and TLR signaling, functional profiling of immune signaling downstream of IFNα, IFNγ and TLR modulators in peripheral blood mononuclear cells (PBMC) of SLE donors was performed and compared with signaling in healthy donors (HD).

Methods: Single Cell Network Profiling (SCNP) is a multiparametric flow cytometry based technology that enables simultaneous analysis of signaling networks in multiple immune cell subsets. PBMC from 60 SLE patients (meeting ACR criteria (2007), SELENA SLEDAI ≥6) and 59 HD were profiled by SCNP, interrogating IFN modulated JAK-STAT signaling and TLR modulated signaling relevant to SLE. CD4+/− CD45RA+/− T cells, CD20+ B cells, CD14+ monocytes and CD11b+ myeloid dendritic cells were profiled (see Table 1).

Table 1. Overview of nodes and cell subsets interrogated

Modulator	Intracellular Reads	Cell Subsets Analyzed
IFNα	p-STAT1, p-STAT3, p-STAT5	B cells, Monocytes, T cell subsets
IFNγ	p-STAT1, p-STAT3, p-STAT5	B cells, Monocytes, T cell subsets
Pam3CSK4 (TLR1/2)	p-ERK, p-p38, Ikb, p-c-Jun, p-CREB	Monocytes
LPS (TLR4)	p-ERK, p-p38, Ikb, p-c-Jun, p-CREB	Monocytes
R848 (TLR7/8)	p-ERK, p-p38, Ikb, p-c-Jun, p-CREB	B cells, Monocytes, mDCs
CpG-C (TLR9)	p-AKT, p-ERK, p-S6, IkB, p-STAT3	B cells

Results: IFNα and IFNγ modulated p-STAT1, -3 and -5 signaling was more heterogeneous in SLE vs HD. An SLE subgroup demonstrated low IFNα/high IFNγ signaling in lymphocytes and monocytes. Based on low IFNα->p-STAT5 /high IFNγ->p-STAT1 modulated signaling in B cells, the SLE-IFN subgroup was defined as outside the 95 percentile (z-score>+/−1.96) of HD, comprising 20 of 60 SLE samples.

The SLE-IFN subgroup was 9.4-fold more likely to be positive for anti-dsDNA antibodies (Fisher's exact test p-val<0.001), consistent with published data on the IFN signature and its link to disease activity, and

supporting the clinical relevance of this observation. Significant associations with ANA Ab positivity (p=0.04), report of a new rash (p=0.03) and age (p=0.04) were also identified. No significant associations with other clinical or demographic parameters were identified.

Strikingly, the members of the SLE-IFN subgroup displayed higher TLR7/8 modulated signaling in B cells (Wilcoxon test p=0.003–0.03, depending on the intracellular readout), and dendritic cells (p=0.03), but not in monocytes. Moreover, TLR9 signaling was lower in B cells (p=0.02), and TLR1/2 and TLR4 modulated signaling was lower in monocytes (p=0.003–0.01).

Conclusion: These data identify potential connectivity in immune signaling across cell subsets and signaling pathways that underlie disease pathobiology and further define SLE donor subgroups. Refinement of the IFN signature in SLE through SCNP may facilitate the clinical applicability of the signature to better inform patient stratification for treatment options.

Disclosure: R. Hawtin, Nodality Inc., 3; **W. Korver**, Nodality, Inc., 3; **E. Evensen**, Nodality, Inc., 3; **D. Longo**, Nodality, Inc, 3; **D. Hotson**, Nodality, Inc., 3; **N. Wale**, Nodality, Inc., 3; **A. Conroy**, Nodality, Inc., 3; **A. Cesano**, Nodality, Inc., 3; **B. Mittleman**, Nodality, Inc., 3; **T. Lin**, Pfizer Biotherapeutics Research and Development, 3; **V. R. Rao**, Pfizer Inc, 3; **E. Peeva**, Pfizer Biotherapeutics Research and Development, 3; **S. Benoit**, Pfizer Biotherapeutics Research and Development, 3; **M. Hodge**, Pfizer Biotherapeutics Research and Development, 3; **J. D. Clark**, Pfizer Biotherapeutics Research and Development, 3; **A. R. Winkler**, Pfizer Biotherapeutics Research and Development, 3; **J. B. Telliez**, Pfizer Biotherapeutics Research and Development, 3.

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MiR-127-3p As a Novel Regulator of Type I Interferon Signaling Pathway in SLE. Bo Qu, Xiao Han and Nan Shen. Institute of Health Sciences, Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS) & Shanghai Jiao Tong University School of Medicine (SJTUSM), Shanghai, China, Shanghai, China.

Background/Purpose: Type I interferon(IFN) is a critical pathogenic factor in Systemic Lupus Erythematosus(SLE) and its associated nephritis, as elevated IFN inducible genes have been found in the kidney tissues and deficiency of IFN receptor protects lupus mouse model from developing nephritis. Reduced miR-146a is in part the reason for uncontrolled IFN response in peripheral blood cells of SLE. However, we are not clear if there are abnormally expressed kidney miRNAs that are responsible for the overactivated IFN response in the renal tissue of SLE. Our previous miRNA profiling data showed that miR-127-3p was one of the most reduced miRNAs in renal biopsies of lupus nephritis patients, raising the question whether miR-127-3p plays a role in IFN signaling. In this study, we explored the regulatory function of miR-127-3p in IFN signaling and its therapeutic effects on SLE.

Methods: miR-127-3p was quantified by RT-qPCR. Interferon-stimulated response element(ISRE)-luciferase reporter assay and western blotting were used to investigate the function of miR-127-3p. Genes affected by miR-127-3p were identified by microarray. Antagomir(chemical modified miRNA inhibitors) was used to inhibit the function of miR-127-3p to validate its function. We administrated agomir(chemical modified miRNA mimics) into pristane induced lupus mouse model to investigate the in vivo function of miR-127-3p.

Results: To test its function in IFN signaling, we transfected miR-127-3p together with ISRE-luciferase reporter plasmids into Hela cells and then stimulated the cells with IFN. We found that miR-127-3p inhibited IFN mediated expression of the reporter gene. Consistently, miR-127-3p inhibited IFN induced phosphorylation of STAT1 and STAT2, which are two major upstream molecules that activate ISRE mediated gene expression. We further revealed that most of the IFN inducible genes were inhibited by miR-127-3p in Hela cells. In addition, in human primary renal mesangial cells, loss of function of miR-127-3p augmented IFN signaling including enhanced ISRE mediated reporter gene expression, stronger phosphorylation of STAT2 and elevated expression of IFN inducible genes. By Ribonucleoprotein Immuno-Precipitation assay, we identified JAK1, the upstream tyrosine kinase of STAT1 and STAT2, as the target of miR-127-3p. To elucidate the mechanism of reduced miR-127-3p, we screened several inflammatory factors and found that IFN inhibited miR-127-3p in renal cells. What's more, we injected IFN into the mice and found that IFN inhibited the expression of miR-127-3p in their kidneys. To test its therapeutic effects, we examined a short-term phenomenon, pulmonary hemorrhage(PH), in pristane induced lupus mouse model and found that administrating miR-127-3p alleviated PH and inhibited IFN inducible gene Mx1 in peripheral blood cells.

Conclusion: Our study shows renal miR-127-3p can inhibit IFN signaling, indicating a new mechanism of overactivated IFN response in the kidney of SLE. Preliminary in vivo data suggest miR-127-3p has therapeutic potential in SLE. Ongoing mouse model studies about the effects of miR-127-3p on lupus nephritis will give us more insights into its therapeutic value.

Disclosure: B. Qu, None; **X. Han**, None; **N. Shen**, None.

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Functional Profiling of PBMC from SLE Patients Versus Healthy Controls Identifies Subgroups with Disease-Associated Dysfunctional Signaling. Rachael Hawtin[1], Wouter Korver[2], Erik Evensen[2], Diane Longo[2], Drew Hotson[2], Nikil Wale[2], Andy Conroy[2], Alessandra Cesano[2], Barbara Mittleman[2], Shirley Tu[2], Matt Westfall[2], Tsung Lin[3], Vik Rao[3], Elena Peeva[3], Stephen Benoit[3], Martin Hodge[3], James D. Clark[3], Jean-Baptiste Telliez[3] and Aaron R. Winkler[3]. [1]Nodality Inc., South San Francisco, CA, [2]Nodality, Inc., South San Francisco, CA, [3]Pfizer Biotherapeutics Research and Development, Cambridge, MA.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a multisystem rheumatic disease with widely differing clinical manifestations and outcomes. Treatment is generally immunosuppressive, with no available biomarkers to inform therapeutic selection for a given patient or disease manifestation. Profiling the immune signaling pathways in PBMCs from patients with active SLE and healthy donors (HD) enables improved understanding of pathobiology and provides a basis for rational treatment decisions.

Methods: Single Cell Network Profiling (SCNP) is a multiparametric flow cytometry based technology that enables simultaneous quantitative analysis of signaling networks in multiple immune cell subsets. PBMC from 60 SLE patients meeting ACR (2007) criteria with SELENA-SLEDAI scores ≥6 were profiled by SCNP and compared to PBMC from 59 age, gender and race matched HD in the presence and absence of modulators of immune function (11 cytokines; 5 toll-like receptor (TLR) modulators and IL-1β; B cell-specific modulators CD40L and Anti-IgD, and PMA), across B (defined by IgD and CD27) and T (CD4/CD45RA) cell subsets, monocytes, and dendritic (HLA-DR, CD11b, CD123) cells, and evaluated through induced p-STATs, MAPK, PI3K and NFkB pathway readouts.

Results: SLE vs HD: SLE PBMC overall had a broader signaling range than HD, with median modulated signaling in B and T cells lower in SLE. Exceptions include IFNγ->p-STAT1 in B cells and CD45RA+CD4+ T cells, IL-2->p-STAT5 in CD45RA+CD4+ T cells, IL-4->p-STAT6 in T cell subsets, and IL-10->p-STAT1, −3 in T cell subsets. Modulation of p-STAT1 by IFNγ, IL-10 and IL-27, and IL-6->p-STAT3 was increased in SLE monocytes. TLR->p-ERK, but not NFkB signaling was increased in monocytes. SLE mDCs showed elevated TLR7/8 induced IkB degradation. Unmodulated levels of intracellular readouts and PMA induced signaling were similar between SLE and HD, suggesting that 1. Signaling differences are not the result of elevated unmodulated levels of signaling and 2. Overall signaling capacity is not compromised in SLE.

SLE donor subgroups: Distinct signaling profiles were identified based upon multivariate analysis of signaling within the SLE population. Not only was signaling quantitatively more broadly distributed in SLE vs HD, distinct subgroups were also observed (Table 1). Associations of dysfunctional signaling with donor demographics, including belimumab treatment will be presented.

Table 1. Subgroups of SLE patients based on modulated signaling outside the range for HD.

Modulator	Intracellular Readout	Cell Subset	SLE subgroup identified with higher/lower signaling compared to HD
IFNα	p-STAT1, -3, -5	B cells, monocytes, T cell subsets	Lower
IFNγ	p-STAT1, -3, -5	B cells, monocytes, T cell subsets	Higher
IL-4	p-STAT5	B cell subsets	Lower
IL-6	p-STAT5	T cell subsets	Lower
IL-7	p-STAT5	B cells	Higher
IL-10	p-STAT1	Monocytes	Higher
IL-10	p-STAT5	Monocytes	Lower
IL-21	p-STAT3	B cell subsets	Lower
CD40L	IkB, p-AKT, p-ERK, p-S6	B cells	Lower

Anti-IgD	p-AKT, p-S6	B cells	Lower
TLR7/8, TLR9	IkB, p-ERK	B cells	Lower
TLR1/2, TLR4, TLR7/8	IkB	Monocytes	Lower
TLR1/2, TLR4, TLR7/8	p-ERK	Monocytes	Higher
IL-1b	p-CREB, p-ERK, p-c-Jun	Monocytes	Higher
TLR7/8	IkB	mDCs	Higher

Conclusion: These SCNP data identify both modulator-specific, disease-associated dysfunctional signaling and SLE donor subgroups based upon cell subset specific immune signaling capacity. Ongoing analyses will inform on the clinical relevance of these observations to enable functional refinement of the spectrum of SLE and identification of novel targets for therapeutic intervention.

Disclosure: R. Hawtin, Nodality, Inc., 3; **W. Korver**, Nodality, Inc., 3; **E. Evensen**, Nodality, Inc., 3; **D. Longo**, Nodality, Inc, 3; **D. Hotson**, Nodality, Inc., 3; **N. Wale**, Nodality, Inc., 3; **A. Conroy**, Nodality, Inc., 3; **A. Cesano**, Nodality, Inc., 3; **B. Mittleman**, Nodality, Inc., 3; **S. Tu**, Nodality, Inc., 3; **M. Westfall**, Nodality, Inc., 3; **T. Lin**, Pfizer Biotherapeutics Research and Development, 3; **V. Rao**, Pfizer Biotherapeutics Research and Development, 3; **E. Peeva**, Pfizer Biotherapeutics Research and Development, 3; **S. Benoit**, Pfizer Biotherapeutics Research and Development, 3; **M. Hodge**, Pfizer Biotherapeutics Research and Development, 3; **J. D. Clark**, Pfizer Biotherapeutics Research and Development, 3; **J. B. Telliez**, Pfizer Biotherapeutics Research and Development, 3; **A. R. Winkler**, Pfizer Biotherapeutics Research and Development, 3.

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Single Cell Interferon Signatures in Lupus Patient Monocytes Reveal a Differential Impact of Interferon Signaling Between Monocyte Subtypes. Zhongbo Jin[1], Mark A. Jensen[1], Jessica M. Dorschner[1], Danielle Vsetecka[1], Shreyasee Amin[1], Ashima Makol[1], Floranne C. Ernste[2], Thomas Osborn[3], Kevin G. Moder[1], Vaidehi Chowdhary[1] and Timothy B. Niewold[1]. [1]Mayo Clinic, Rochester, MN, [2]Mayo Clinic Rochester, Rochester, MN, [3]Mayo Clinc, Rochester, MN.

Background/Purpose: Type I interferon (IFN) is a primary pathogenic factor in human systemic lupus erythematosus (SLE). IFN gene expression signatures have been observed in whole blood and mixed peripheral blood mononuclear cell populations in SLE, but the significance of this IFN signaling in immune cell subsets is still incompletely understood. We examined gene expression in individual SLE patient monocytes to explore the impact of increased IFN-induced transcription in single cells.

Methods: CD14++CD16- classical monocytes and CD14dimCD16+ non classical monocytes from SLE patients were purified by magnetic separation. The Fluidigm C1 System was used for single cell capture and target gene pre-amplification, and equal numbers of classical and non-classical monocytes were studied. rtPCR was used to quantify expression of 87 monocyte-related genes, 17 of which were IFN-induced genes. An individual cell IFN score was generated based upon the expression of the 17 IFN-induced genes.

Results: Monocytes from the same SLE patient blood sample demonstrated varying levels of IFN-induced gene expression. In classical monocytes, high IFN score correlated with CD32a, IL1B, and IL8 expression. In non-classical monocytes, high IFN score was correlated with a larger number of inflammatory mediators, including cytokines such as IL12, IL23, and IL15; the immune receptors CD36, CD32a, CD80, and TLR7; and inflammatory signaling genes such as RELA, STAT2, IRAK1, IRAK4, and MyD88. CD16 transcripts were detected in a small group of classical monocytes, despite a lack of surface CD16 expression, suggesting that these cells may be transitioning from classical to non-classical subgroup. In these cells, CD16 expression was positively correlated with IFN score ($p=0.019$).

Conclusion: This study revealed striking diversity in the IFN responses of individual monocytes, and supports the idea that IFN signaling has distinct effects upon classical and non-classical monocytes, as the IFN signature correlated with a diverse panel of inflammatory mediators in the non-classical subset. IFN may contribute to the transition from classical to non-classical subtype in SLE. Single cell studies can reveal effects of IFN on single immune cells and uncommon populations such as non-classical monocytes, which may be masked in whole blood or mixed cell populations.

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Suppression of IFN-α Production from Systemic Lupus Erythematosus Immune Complexes Via C1 Complex Enzymatic Properties. Jing Yao Leong[1], Joo Guan Yeo[1], Thaschawee Arkachaisri[1] and Jinhua Lu[2]. [1]KK Women's and Children's Hospital, Singapore, Singapore, [2]National University of Singapore, Singapore, Singapore.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disease associated with the development of auto-antibodies particularly against nuclear antigens. Previous studies have revealed the possible role of type I interferon, IFN-α, in disease pathogenesis. Notably the formation of immune complexes (auto-antibodies with auto-antigens) can result in the production of IFN-α via Fc receptor signaling. Hereditary homozygous deficiency in the complement protein, C1q has shown a high penetrance of 88–93% in afflicted individuals resulting in disease development. Remarkably it was shown in recent years that C1q has the capacity to suppress immune complex mediated IFN-α production. Considering that in vivo C1q functions as the sensory adaptor in the C1 complex, we compared C1 with C1q in modulating immune complex-mediated IFN-α production from peripheral blood mononuclear cells (PBMCs).

Methods: Serum samples were obtained from 15 SLE patients and assayed for the presence of auto-antibodies (anti-nucleosome) via ELISA. The monocytic U937 cell line was UV-irradiated and the apoptotic supernatant was harvested after 24 hours. The apoptotic supernatant was incubated with SLE sera to form immune complexes. The immune complexes were pre-treated with C1 complex or, as controls, C1q or PBS. Human PBMCs, isolated from healthy donors by Ficoll- Hypaque density centrifugation were treated with the immune complexes for 24 hours and IFN-α production was measured by ELISA.

Results: After screening 15 SLE patients for anti-nucleosome autoantibodies, 4 patients with disease activity (SLEDAI-2K $\geq$ 4) and high titer of anti-nucleosome (>60 R units/ml, where clinical cutoff $\geq$20 R units/ml) were selected. SLE sera were incubated with UV-irradiated U937 apoptotic supernatant to form SLE immune complexes. Human PBMCs were stimulated with SLE immune complexes and assayed for IFN-α production. Healthy control serum elicited 86.7 $\pm$ 8.0 R units/ml IFN-α (media control was 85.7 $\pm$ 3.5 R units/ml), whereas SLE patient A elicited 674.7 $\pm$ 244.3 R units/ml IFN-α, SLE patient B elicited 243.8 $\pm$ 37.0 R units/ml IFN-α ($p < 0.05$), SLE patient C elicited 1115.8$\pm$ 166.5 R units/ml IFN-α ($p < 0.05$), and SLE patient D elicited 142.6 $\pm$ 7.4 R units/ml IFN-α ($p < 0.05$). SLE patient C immune complexes were treated with C1, C1q or PBS and C1 and C1q showed a dose-dependent inhibition in IFN-α induction (853.2 $\pm$ 16.3, 701.1 $\pm$ 1.0, 508.4 $\pm$ 18.6 and 192.1 $\pm$ 16.4 R units/ml respectively) as compared to PBS-treated SLE immune complex (1362.3 $\pm$80.5 R units/ml). Furthermore, it was noted that, at equal molar concentration of C1 and C1q, C1-treated SLE immune complex suppressed immune complex-induced IFN-α production more effectively than C1q-treated immune complex.

Conclusion: C1 is the natural complex encompassing C1q and C1-treated SLE immune complexes exhibit suppressed IFN-α induction from human PBMCs. C1 appeared to be more potent than C1q in inhibiting immune complex-induced IFN-a production showing corporation among the complement classical pathway in providing enhanced protection against SLE pathogenesis as compared with C1q alone.

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Interferon Dysregulation in an Academic SLE Cohort Is Associated with Distinct Signaling Differences in Blood Neutrophils Versus PBMCs. David Drubin[1], Xiang Guo[2], Linglin Yang[2], Rong Zeng[2], Yuling Wu[2], Mustimbo EliPollard Roberts[2], Reynald Lescarbeau[1], Aaron Van Hooser[1], Michael Macoritto[1], Michelle A. Petri[3] and Wendy White[4]. [1]Selventa, Cambridge, MA, [2]MedImmune LLC, Gaithersburg, MD, [3]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [4]MedImmune, Gaithersburg, MD.

Background/Purpose: Interferons (IFNs) have long been implicated in the pathogenesis of systemic lupus erythematosus (SLE). However, the specific consequences of the IFN activity have not been defined. In this study, the biology associated with an IFN activity signature was assessed in SLE blood neutrophil and PBMC fractions.

Methods: RNA was collected from isolated blood PBMC and neutrophil fractions from a cohort of 46 SLE patients and 23 healthy

donors. The patients fulfilled both ACR and SLICC criteria for SLE and represented a clinical population with a SLEDAI range of 0–12 (median 2), with 63% treated with prednisone, a cytotoxic immunosuppressant, or both. Patients were grouped by positive or negative IFN activity by assessing 21 IFN-inducible genes in whole blood, and gene expression changes were determined by RNA sequencing. Gene expression differences were analyzed further to determine the most likely upstream mechanistic explanations for the data in each comparison. The significance of these mechanisms is based on the evaluation of two metrics: supporting gene change enrichment using a hypergeometric distribution, and directional consistency as assessed by a binomial distribution. Differential mechanisms between positive and negative IFN groups were examined in the context of those with inferred activity significantly different in SLE compared to healthy donors.

Results: This analysis identified mechanisms inferred to be distinctly active in positive vs. negative IFN neutrophils. Table 1 indicates the gene expression support for representative mechanisms where enrichment and directional consistency are both significant ($p<0.05$ vs healthy, $p<0.1$ Negative vs Positive) for the indicated comparisons. Positive IFN neutrophils exhibited distinctly active biology, including IFNG, mTOR and CCL5 consistent signaling. Additionally, mechanisms preferentially associated with IFN positive neutrophils including TLR signaling and IFNA, as well as many mechanisms in common and at similar levels with IFN negative neutrophils, were also active. TGFB1 and MAPK1 activation were distinct in negative IFN neutrophils. Mechanisms activated in PBMCs were very similar between the IFN groups, with most activated to similar extents.

Conclusion: Our analysis supports that in a patient population with low SLEDAI scores, the IFN activity signature in blood correlates with biological differences that predominate in neutrophils. The work permits better understanding of the impact of IFN signaling in SLE, by demonstrating different effects in neutrophil vs PBMC fractions in an academic cohort.

Table 1. Representative mechanism association with IFN activity in neutrophil and PBMC fractions

		Mechanism Direction and Gene Expression Change Evidence			
	Mechanism	IFN Pos vs Healthy N-2432 Gene changes P-939 Gene changes	IFN Neg vs Healthy N-325 Gene changes P-989 Gene changes	IFN Pos vs IFN Neg N-569 Gene changes P-61 Gene changes	Activation Behavior in IFN-Pos vs IFN-Neg
Representative Mechanisms in Neutrophils	TLR9	↑ (13 genes)	↑ (7 genes)	–	Equivalent Activation
	TNF	↑ (214 genes)	↑ (55 genes)	↑ (67 genes)	Higher in IFN-Pos
	TGFB1	–	↑ (38 genes)	↓ (47 genes)	Active only in IFN-Neg
	TLR4	↑ (106 genes)	↑ (34 genes)	↑ (44 genes)	Higher in IFN-Pos
	NFKB	↑ (108 genes)	↑ (33 genes)	↑ (43 genes)	Higher in IFN-Pos
	IL2	↑ (75 genes)	↑ (27 genes)	↑ (18 genes)	Higher in IFN-Pos
	IL6	↑ (94 genes)	↑ (26 genes)	↑ (28 genes)	Higher in IFN-Pos
	MAPK1	–	↑ (17 genes)	↓ (8 genes)	Active only in IFN-Neg
	IFNA Family	↑ (125 genes)	↑ (17 genes)	↑ (76 genes)	Higher in IFN-Pos
	CSF2	↑ (66 genes)	↑ (15 genes)	–	Equivalent Activation
	IFNG	↑ (174 genes)	–	↑ (86 genes)	Active only in IFN-Pos
	CCL5	↑ (11 genes)	–	↑ (4 genes)	Active only in IFN-Pos
	mTOR	↑ (77 genes)	–	↑ (25 genes)	Active only in IFN-Pos
	SPI1 (PU.1)	↑ (43 genes)	–	↑ (14 genes)	Active only in IFN-Pos
Representative Mechanisms in PBMCs	TLR4	↑ (100 genes)	↑ (99 genes)	↑ (11 genes)	Higher in IFN-Pos
	NFKB	↑ (103 genes)	↑ (99 genes)	↑ (11 genes)	Higher in IFN-Pos
	IL6	↑ (49 genes)	↑ (56 genes)	–	Equivalent Activation
	IL2	↑ (44 genes)	↑ (52 genes)	–	Equivalent Activation
	SPI1 (PU.1)	↑ (33 genes)	↑ (38 genes)	–	Equivalent Activation
	MAPK1	↑ (27 genes)	↑ (31 genes)	–	Equivalent Activation
	IL17A	↑ (22 genes)	↑ (28 genes)	–	Equivalent Activation
	TLR9	↑ (22 genes)	↑ (18 genes)	–	Equivalent Activation
	TNF	↑ (158 genes)	↑ (168 genes)	↑ (16 genes)	Higher in IFN-Pos
	CCL5	↑ (12 genes)	↑ (17 genes)	–	Equivalent Activation
	IFNG	↑ (153 genes)	↑ (138 genes)	↑ (31 genes)	Higher in IFN-Pos
	TGFB1	–	↑ (107 genes)	↓ (9 genes)	Active only in IFN-Neg
	IFNA Family	↑ (114 genes)	↑ (103 genes)	↑ (20) genes	Higher in IFN-Pos

Gene expression changes are defined by at least a 1.5 fold change with an FDR p-value of < 0.05 (N= Neutrophils, P= PBMCs, Pos=positive, Neg=negative). Arrows indicate downstream gene expression support for mechanism increase (↑), decrease (↓), or no signficant change (–) based the statistics in methods, followed by number of supporting gene expression changes.

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Antibody to Malondialdehyde-Acetaldehyde Adducts (MAA) As a Potential Biomarker of Inflammation in Systemic Lupus Erythrematosus (SLE).

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Background/Purpose: Studies have shown that malondialdehyde-acetaldehyde (MAA) is formed as a result of lipid peroxidation of cellular membranes and is capable of binding or adducting to various macromolecules. MAA-adducted macromolecules are cytotoxic, proinflammatory and result in a robust specific adaptive immune response to the MAA structure. Previous studies have shown serum anti-MAA antibodies present in inflammatory diseases including; atherosclerosis, aortic aneurysm, alcoholic liver disease, and recently rheumatoid arthritis. The purpose of this study was to examine the potential utility of anti-MAA antibody isotypes as biomarkers in systemic lupus erythematosus (SLE). We also explored whether anti-MAA antibody isotypes were associated with two novel biomarkers that we have recently demonstrated to be increased in SLE, neutrophil extracellular traps (NETs) and NOD27/NLRC5.

Methods: Eighty-eight SLE patients, all satisfying ACR classification criteria, and 92 controls were examined. Serum antibody levels were measured by enzyme-linked immunosorbent assay (ELISA) for levels of IgG, IgA, and IgM specific to the MAA epitope. Spearman correlation coefficients were used to examine associations of MAA isotypes with NETs and NOD27/NLRC5.

Results: MAA IgG concentration was significantly higher ($p=0.004$) in SLE patients ($M=488.7$ mg/L) compared to controls ($M=331.7$ mg/L) Figure 1. There was a strong trend ($p=0.064$) observed in MAA IgM concentrations between SLE samples ($M=769.7$ mg/L) and controls ($M=586.7$ mg/L). There was no difference observed between control and SLE groups for MAA IgA concentrations. Levels of MAA IgG demonstrated modest but statistically significant correlations with levels of NOD27/NLRC5 ($r=.256$, $p=0.0508$) and NB4 NET ($r=.213$, $p=0.048$) within the SLE group.

Conclusion: These data show that patients with SLE have significantly higher levels of MAA IgG and IgM compared to controls. In addition, MAA IgG concentrations were positively correlated with circulating levels of NB4 NETs and NOD27, consistent with the increased inflammatory burden that characterizes SLE. MAA has been shown to contribute to protein modifications eliciting strong immune responses and recruitment of proinflammatory cytokines. Whether MAA adduct formation and resulting immune responses mediate tolerance loss in SLE, as has been shown in other conditions, or other complications of SLE such as premature atherosclerosis warrants further investigation.

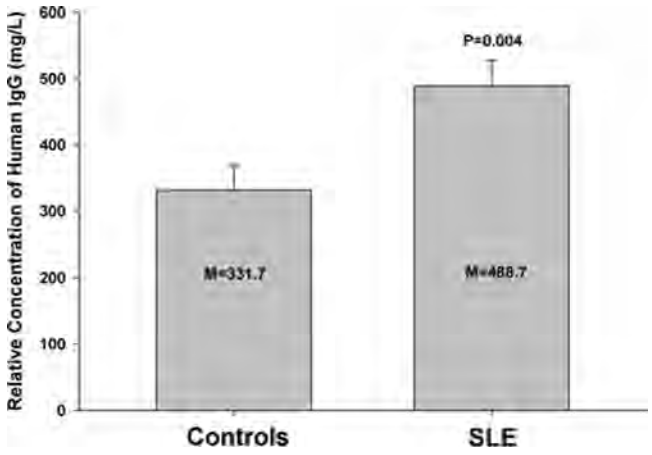

Figure 1. Serum samples were assayed by ELISA for the presence of IgG anti-MAA antibodies.

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A Shift Towards Trans-Signalling Explains Relatively Low CRP Despite an Active Interleukin-6 (IL-6)/IL-6-Receptor (IL-6R) System in SLE.
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Background/Purpose: IL-6 has been found increased in SLE, while CRP, which is directly stimulated by IL-6, usually remains low. We therefore analyzed the IL-6/ IL-6 R system in SLE.

Methods: Peripheral blood mononuclear cells (PBMC) of 41 SLE patients and 71 healthy individuals (HC) were prepared. CRP and disease activity (by ECLAM) were recorded. Serum IL-6 and sIL-6R were measured by ELISA. For determining the percentages of CD126 and CD130 positive cells, PBMC were directly stained with PE-labelled or control antibodies. For analyzing IL-6 induced Stat3 phosphorylation, PBMC were stimulated with rhIL-6 (250 ng/ml) for 15 min, fixed with formaldehyde (2%), permeabilized with methanol (80%), and stained with PE-labelled antibodies to phosphorylated Stat3 (pStat3) or control antibodies. For in vitro experiments on the influence on receptor expression, healthy PBMC were incubated for 24 hours with or without the addition of IL-6, IL-10, tumor necrosis factor (TNF), interferon-α (IFNα), or combinations of these cytokines. Stained cells were immediately analyzed on a Becton Dickinson FACSCalibur fluorocytometer, gating for lymphocytes. As a semiquantitative measure of pStat3 contents mean fluorescence intensity (mfi) was used.

Results: SLE serum IL-6 levels (median (range)) (3.6 (0.69–69.3) pg/ml) were significantly ($p<0.0001$) higher than those of HC (0.9 (0.12–10.5) pg/ml) and correlated with disease activity (Spearman $r= 0.41$, $p= 0.01$). CRP was slightly increased in SLE (1.8 (1.0–40.8) pg/ml vs 0.8 (0.3–4.8) pg/ml for HC, $p<0.0001$). The percentage of CD126+ lymphocytes (mean±SD) was decreased in SLE (48±16 % vs. 61±11% for HC $p<0.0001$). In line with reduced receptor expression, the IL-6 induced increase in pStat3 was significantly reduced in SLE (Δmfi 14.2 (−19.91–37.15) vs. HC (Δmfi 18.8 (−2.2–50.06), $p=0.004$). In a mirror image to the membrane receptor, soluble IL6 receptor (sIL-6R) serum levels were increased in SLE (42.1 (24.1–109.6) ng/ml as compared to (38.6 (16.4–80.5) ng/ml in HC, $p=0.05$). Moreover, sIL-6R was negatively correlated with the percentage of CD126+ lymphocytes (Spearman $r=-0.35$, $p=0.03$). In vitro stimulation assays showed that the reduction in CD126+ cells could be mimicked by combinations of IL-6 with either IFNα (−39± 13%) or TNF (−16± 6%).

Conclusion: In SLE, combinations of IFNα or TNF with IL-6, all of which are increased in response to immune complexes, apparently lead to shedding of the cellular IL-6 receptor CD126 and thus increase sIL-6R. This shifts the IL-6 system towards trans-signalling, directing the effects of the increased IL-6 away from conventional signalling, as responsible for increased CRP, and towards effects on cells carrying gp130 only.

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Th1 and Th2 Cytokines Are Associated with Cerebral Atrophy in Systemic Lupus Erythematosus.
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Background/Purpose: Cerebral atrophy has been described to occur in systemic lupus erythematosus (SLE) with variable frequency. The pathophysiology of central nervous system (CNS) involvement in SLE remains unclear. The proposed mechanisms that are likely due to the assault of several autoimmune system changes include circulating immune complexes, corticosteroid use, autoantibodies, and cytokine release. The aim of this study was to determine the prevalence of cerebral atrophy and to elucidate the possible role of sera Th1 (IL-12, IFN-γ,TNF-α) and Th2 (IL-4, 5,6 and 10) cytokines levels in SLE.

Methods: Consecutive SLE patients followed at the rheumatology unit of the State University of Campinas were enrolled in this study. The control group was consisted by age and sex matched healthy individuals. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. Mood and anxiety disorders were determined through Becks Depression and Becks Anxiety Inventory. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current drug exposures. Magnetic resonance imaging (MRI) scans were performed in a 3T Phillips® scanner using a standardized protocol. Sagittal T1 weighted images were used for semiautomatic volumetric measurements. Volumes smaller 2 standard deviation from the means of controls were considered abnormal. Total dose of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by data obtained by careful review of the medical charts. Sera samples were obtained from all participants in the absence of infections. Th1 (IL-12, IFN-γ,TNF-α) and Th2 (IL-4, 5,6 and 10) cytokines sera levels were measuredby ELISA using commercial kits. Data were compared by non-parametric tests.

Results: We included 146 SLE patients (138 women; mean age of 26.60±13.42 years; range 9–67) and 91 (86women; mean age of 27.82± 15.23 years; range 5–80) age and sex matched healthy controls. The median and range of cerebral volume in SLE patients was 1064.16cm^3(range 831.1–1449.24) cm^3, compared to healthy volunteers 1134.46 (range 880.01–1417.59) cm^3($p<0.001$). Cerebral atrophy was identified in 20 (13.69%) SLE patients and in none of controls ($p<0.001$). Significantly increased Th1 [IL-12 ($p<0.001$), IFN-γ ($p<0.001$), TNF-α ($p<0.001$)] and Th2 [IL-4 ($p=0.002$), IL-5 ($p<0.001$), IL-6 ($p=0.001$) and IL-10 ($p<0.001$)] levels were observed in SLE patients compared to controls. We observed an association between cerebral atrophy and IL-12 ($p=0.044$), IFN-γ ($p=0.017$) and IL-10 ($p=0.003$). We did not observe association between cerebral volume and corticosteroidsor any other clinical or laboratory manifestations.

Conclusion: IL-12, IFN-γ and IL-10 were associated with cerebral atrophy in SLE, suggesting immunological basis for global atrophy in SLE. Cytokines have been highlighted as potential contributory factors to cerebral atrophy in SLE.

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1623

Increased CD95 (Fas) Expression on Naive B Cells Is Associated with a Switch to Double Negative and Plasma Cells in the Peripheral Blood, and Correlates with Disease Activity in Systemic Lupus Erythematosus.
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Background/Purpose: systemic lupus erythematosus (SLE) is characterized by a break of tolerance to autoantigens, and polyclonal activation of B cells. We performed multicolor flow cytometry analyses of B cell subsets in SLE patients and controls, in order to increase our understanding of the B cell activation steps characteristic of the disease.

Methods: PBMC from 16 SLE patients and 5 controls were analyzed using the following flow cytometry markers : CD5, IgD, CD27, CD20, CD19, CD38, CD95 and intracellular survivin, and their control isotypes. The data were acquired using a BD FacsCantoII and analyzed using FlowJo software. Serum C3 concentrations were retrieved from the medical records of the patients.

Results: SLE patients had significantly less CD19+CD20+IgD+CD27- naive B cells compared to controls (40.5 ± 30.7 versus 70.4 ± 8.5 % of total B cells, $p = 0.048$). By contrast, proportions of CD19+CD20+IgD-CD27- double negative (11.6 ± 8.8 versus 4.2 ± 1.6 %, $p = 0.029$) and CD19+CD20-CD38+ plasma cells (11.5 ± 18,4 versus 1.5 ± 1.0 %, $p = 0.015$) were significantly higher in SLE patients compared to controls. Proportions of CD19+CD20+IgD-CD27+ conventional memory B cells were also higher in SLE patients, but the difference was not significant (24.5 ± 18.7 versus 11.9 ± 4.4 %, $p = 0.15$).

Percentage of CD95 (Fas) positive cells was significantly higher in SLE naive (24.5 ± 17,4 versus 2.4 ± 1.3 %, $p = 0.001$), but also in double negative B cells compared to controls. Almost all SLE and control plasma cells expressed CD95. Strikingly, expression of CD95 on naive B cells correlated negatively with the proportion of naive B cells themselves ($r = -0.50$, $p = 0.022$), and positively with the proportions of double negative ($r = 0.46$, $p = 0.034$) and plasma cells ($r = 0.57$, $p = 0.007$).

In all B cell subsets, expression of CD95 displayed a significant positive correlation with intracellular expression of survivin ($r = 0.63$, $p = 0.002$), a

cell proliferation and anti-apoptotic marker. Finally, we observed a significant negative correlation between both CD95 ($r = -0.53$, $p = 0.036$) or survivin ($r = -0.50$, $p = 0.048$) expression in naive B cells and serum C3.

Conclusion: CD95 expression on naive B cells is associated with a switch to double negative and plasma cells in the peripheral blood of SLE patients. The positive correlation between CD95 and survivin expression in SLE B cell subsets confirms that CD95 is a marker of B cell activation in SLE. Activation (CD95 and survivin expression) of naive B cells correlates with disease activity. Further studies on additional cross-sectional and longitudinal samples are ongoing.

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The Role of B Lymphocyte Stimulator in Monocyte Subpopulation Differentiation in SLE. Eoghan M. McCarthy[1], Joan Ní Gabhann[2], Siobhán Smith[2], Michele Doran[3], Gaye Cunnane[4], S. Donnelly[5], Donough Howard[1], Paul G. O'Connell[1], Caroline Jefferies[2] and Grainne M. Kearns[1]. [1]Beaumont Hospital, Dublin, Ireland, [2]Royal College of Surgeons in Ireland, Dublin, Ireland, [3]St. James's Hospital, Dublin, Ireland, [4]St James's Hospital and Trinity College Dublin, Dublin, Ireland, [5]Mater Misericordiae University Hospital, Dublin 7, Ireland.

Background/Purpose: Monocytes are increasingly recognised to play a key role in the pathogenesis of SLE. Different subpopulations of monocytes contribute to the disease through dysregulated pro and anti-inflammatory responses. B Lymphocyte Stimulator(BLyS) has been shown to promote disease activity in SLE however its effect on monocyte subpopulation differentiation has not previously been reported. This study sought to investigate the effect of BLyS on monocyte subpopulations in healthy controls and SLE patients.

Methods: 25 Patients with matched controls were recruited. CD 14+ monocyte subpopulations were analysed by Flow Cytometry using the following markers: M1 CD86+ HLA-DR+; M2a CD163+ CD206+; M2b CD86+ HLA-DR+ CD163+. qPCR was utilised to investigate gene expression for the subsets markers as follows: M1 CXCL10; M2a CCL17; M2b CCL1. Serum levels of cytokines were measured by ELISA. Differences between groups were examined using the Mann Whitney.

Results: Following stimulation with BLyS a significant increase in the pro-inflammatory M1 and anti-inflammatory M2a monocyte subpopulations was observed in healthy controls and SLE patients with a corresponding decrease in M2b levels.

Interestingly SLE patients demonstrated a trend toward increased M1 levels in both the resting state and following BLyS stimulation in comparison to controls. In keeping with this SLE patient M1 monocytes exhibited significantly enhanced HLA-DR MFI expression in the resting state and following stimulation compared to controls. Furthermore a significant increase in CD86 MFI was observed following BLyS stimulation in patients, a result not replicated in controls. No differences were observed between patients and controls with regard to the M2b subpopulation.

In keeping with the literature SLE patients exhibited significantly reduced basal M2a levels. Surprisingly however, following BLyS stimulation an increased percentage of M2a monocytes was observed in patients compared to healthy controls(12.7% v 8.3%) such that the fold change from baseline in M2a monocytes between patients and controls following BLyS stimulation was significantly different (3.6 v 1.4,p= 0.0096).

In support of this qPCR confirmed a significant increase in the M2a-associated gene CCL 17 in SLE patients following stimulation, a result not replicated in controls. No absolute differences were observed in expression for the M1-associated gene(CXCL10) and M2b-associated gene(CCL1).

Strikingly BLyS stimulation significantly increased the M1 subpopulation in SLE patients with evidence of immunological activity(dsDNA+ve), an observation not replicated in dsDNA –ve patients.

Finally determination of M1 and M2 subset associated cytokines by ELISA confirmed significantly enhanced levels of both CXCL10(M1) and CCL17(M2a) in the serum of SLE patients with a strong correlation seen between CXCL10 and both dsDNA levels and disease activity. CCL17 demonstrated modest correlation with disease activity.

Conclusion: Our study highlights a heterogenous response to BLyS stimulation in both healthy control and SLE patient monocytes. SLE patient monocytes appear to have enhanced pro and anti-inflammatory responses to BLyS a finding which warrants further investigation.

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Interferon Stimulates Transglutaminase Activity on Human Monocytes and Their Microparticles. Kimberly Carroll[1], Elizabeth Mitton-Fitzgerald[1], Brittany Bettendorf[2], Claudia Gohr[1], Mary E. Cronin[1] and Ann K. Rosenthal[1]. [1]Medical College of Wisconsin, Milwaukee, WI, [2]Medical College of Wisconsin, Wauwatosa, WI.

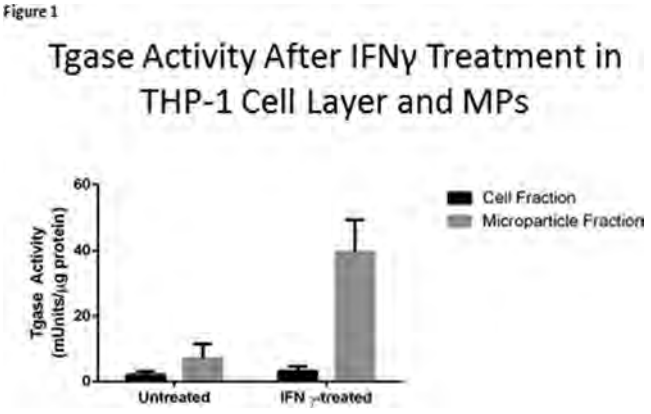
Background/Purpose: Microparticles (MPs) are circulating membrane-bound vesicles derived from blood and endothelial cells via a highly regulated process. They are immunomodulatory and have been implicated in autoimmunity and Systemic Lupus Erythematosus (SLE). We recently showed that MPs derived from SLE patients contain higher protein and activity levels of type II transglutaminase (Tgase). Tgases are protein crosslinking enzymes whose activity increases antigenicity of certain proteins. This enzyme family has been implicated in SLE pathogenesis, perhaps by stimulating autoantibody formation against such proteins as C3, which are major Tgase substrates. The cell source of MPs responsible for increased Tgase activity on SLE MPs is unknown. We explored the hypothesis that interferon, a key cytokine in SLE, could promote Tgase activity on human monocytes and their MPs.

Methods: MPs were isolated from non-adherent human monocyte THP-1 cells by differential centrifugation of conditioned media in cultures treated with or without 1000 U/ml interferon gamma or 10–1000 U/ml interferon alpha for 24– 72 hours. Tgase activity was measured on the MP sample and THP-1 cell layer using a standard radiometric assay. Tgase protein levels for type II Tgase and factor XIIIA were measured in cells and on MPs with Western blotting. Similar experiments were carried out with human umbilical vein endothelial cells (HUVECs) and Jurkat cells (human T lymphocytes).

Results: An increase in type II Tgase protein as evidenced by Western blotting was noted on the cell layer of interferon gamma treated THP-1 cells. This corresponded to a slight, 1.56 fold increase in Tgase specific activity after interferon gamma exposure at 72 hours ($p=0.18$). Interestingly, a dramatic increase in Tgase activity was observed on MPs from interferon gamma treated cells with specific activity increasing 5.61 fold ($p=0.02$) over control MPs (figure 1). There were no differences in protein levels of factor XIIIA nor were there increases in Tgase activity with thrombin treatment, which activates latent Factor XIIIA. HUVECs and Jurkat cells did not respond similarly. Interferon alpha did not increase Tgase activity on any of the cell types tested.

Conclusion: Interferon gamma specifically increases Tgase activity and type II Tgase protein levels on human monocytes and has marked stimulatory effects on Tgase activity on monocyte-derived MPs. Increased Tgase activity may contribute to autoantibody formation through post-translational modification of proteins, such as C3, and their location on MPs may be important. Tgase inhibitors ameliorate SLE in animal models. Our data lend additional support for Tgase inhibitors as potential therapies for SLE.

Figure 1



Disclosure: K. Carroll, None; **E. Mitton-Fitzgerald**, None; **B. Bettendorf**, None; **C. Gohr**, None; **M. E. Cronin**, None; **A. K. Rosenthal**, None.

1626

Autoantibodies Against High Mobility Group Box 1 (HMGB1) in Patients with SLE. Fleur Schaper, Gerda Horst, Daan van Beijeren Bergen en Henegouwen, Johan Bijzet, Karina de Leeuw, Alja Stel, Pieter C Limburg, Peter Heeringa and Johanna Westra. University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: High mobility group box 1 (HMGB1) is a damage-associated molecular pattern and can be divided in three separate domains: the A Box, B Box and the acidic tail. Box A by itself serves as a competitive antagonist for HMGB1 and inhibits HMGB1 activity. In an earlier study we showed that anti-HMGB1 antibodies are present in Systemic Lupus Erythematosus (SLE) patients and may play a role in the pathogenesis of the disease, but are not present in patients with systemic vasculitis. In this study we investigate the relation between anti-HMGB1 antibodies and disease activity, renal involvement, anti-dsDNA antibodies and medication use. We performed cross-sectional and longitudinal analyses.

Methods: Seventy-one SLE patients, 25 age and sex matched healthy controls (HC), and 15 disease control patients with incomplete lupus (fulfilled less than 4 of the ACR criteria), were included in this study. All 71 SLE patients were measured during quiescent or mild (SLEDAI ≤ 4) disease, and 28 were also measured during an exacerbation (SLEDAI ≥ 5). Furthermore, in a subgroup of patients (n=11) longitudinal levels of HMGB1 were determined over a period of three years. Serum levels of anti-HMGB1 IgG and IgM were measured using an in house ELISA. Epitope recognition was measured by ELISA against Box A and B IgG. Data are presented as arbitrary units (AU).

Results: Quiescent as well as active SLE patients showed a significant increase in anti-HMGB1 IgG compared to HC (median 236 vs 339 vs 46 AU respectively). Incomplete lupus patients also had an increased anti-HMGB1 level compared to HC ($p=0.03$), but lower compared to SLE patients (ns). Patients recognized both Box A and Box B epitopes of the molecule. Anti-HMGB1 IgM levels were not different in patients versus controls. We did find an association with disease activity, as there was a significant decrease in Box A recognition after exacerbation ($p=0.028$). No differences were found comparing active patients with renal involvement to patients without for anti-HMGB1 IgG, IgM, Box A and Box B. There was also no effect of immunosuppressive medication, including hydroxychloroquine, on anti-HMGB1 levels. Finally, longitudinal values of anti-HMGB1 IgG showed similar patterns compared to anti-dsDNA and might even increase shortly before an increase in anti-ds DNA levels are seen.

Conclusion: Anti-HMGB1 antibodies seem specific for SLE, as they were significantly increased compared to HC. Interestingly, also incomplete lupus patients showed already a minor increase of anti-HMGB1 antibodies. Antibodies directed to Box A decreased after an exacerbation, indicating a correlation with disease activity. Furthermore, longitudinally levels of anti-HMGB1 seemed to increase before an increase in anti-dsDNA levels occurred, which might indicate an interesting new biomarker in the follow-up of SLE patients.

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ACR/ARHP Poster Session B
Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Biomarker, Translational and Nephritis Studies
Monday, November 17, 2014, 8:30 AM–4:00 PM

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The Global Antiphospholipid Syndrome Score (GAPSS) Differentiates Between Transient Ischemic Attack and Stroke in Patients with Antiphospholipid Antibodies. Savino Sciascia[1], Giovanni Sanna[2], Veronica Murru[3], Dario Roccatello[4], Munther A. Khamashta[5] and Maria Laura Bertolaccini[3]. [1]Rayne Institute, St. Thomas Hospital, London, United Kingdom, [2]St. Thomas' Hospital, London, United Kingdom, [3]Lupus Research Unit, The Rayne Institute, Kings College London School of Medicine, London, United Kingdom, [4]UNIVERSITY OF TURIN (ITALY), TURIN, Italy, [5]Lupus Research Unit, The Rayne Institute, St Thomas Hospital, Kings College London School of Medicine, London, United Kingdom.

Background/Purpose: Arterial event are frequent in the antiphospholipid syndrome (APS) and stroke is a major clinical manifestation of syndrome. Recently, we conducted a study in a large cohort of Systemic Lupus Erythematosus (SLE) patients applying a risk score for APS clinical manifestations (Global APS Score or GAPSS), demonstrating that risk profile for APS can be successfully assessed. In this study, we aimed to evaluate the clinical usefulness of the GAPSS in differentiating between transient ischemic attack (TIA) and stroke in a cohort of patients tested positive for aPL who sufferedcerebrovascular events.

Methods: We included 40 consecutive SLE patients attending the Louise Coote Lupus Unit at St Thomas Hospital, London, all with a history of cerebravoscular events. Demographic, clinical and laboratory characteristics were collected. aPL profile included anticardiolipin antibodies (aCL), lupus anticoagulant (LA), anti β2 glycoprotein I antibody (anti-β2GPI), and antibodies to phosphatidylserine-prothrombin complex (aPS/PT). Cardiovascular risk factors were assessed following NICE guidelines (1). The GAPSS system was calculated for each patient (2,3).

Results: Nineteen patients (47.5%) had stroke, 16 (40%) a transient ischemic attack (TIA), defined as neurologic symptoms or signs lasting less than 24 hours by a neurologist. Five patients (12.5%) experienced both. Thirty patients (75%) fulfilled the current APS classification criteria. Higher values of GAPSS were seen in patients who experienced stroke (alone or in association with TIA) when compared to those with TIA alone (10.13 ± 3.3 [range 5–16] vs. 6.3 ± 4.6 [range 3–13], $p=0.033$). This observation was confirmed when compared patients who had a history of stroke alone with patients with TIA alone (9.95 ± 3.29 [range 5–16] vs. 6.3 ± 4.6 [range 3–13], $p=0.029$). Patients who experienced both stroke and TIA showed the highest GAPSS but the difference was only statistically significant when compared to those with TIA alone (10.8 ± 3.63 [range 7–16] vs. 6.3 ± 4.6 [range 3–13], $p=0.03$).

Conclusion: The GAPSS is a valid tool for risk stratification for ischemic manifestation in the setting of cerebrovascular events. This tool may help identifying a more "at risk" population in whom a tailored prophylaxis therapy might be beneficial.

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Disclosure: S. Sciascia, None; **G. Sanna**, None; **V. Murru**, None; **D. Roccatello**, None; **M. A. Khamashta**, None; **M. L. Bertolaccini**, None.

1628

Upregulation of Myxovirus Resistance Protein 1 in Patients with Neuropsychiatric Systemic Lupus Erythematosus. Yuka Shimizu, Shinsuke Yasuda, Takashi Kurita, Sanae Shimamura, Ikuma Nakagawa, Atsushi Noguchi, Haruki Shida, Toshiyuki Watanabe, Michihito Kono, Kenji Oku, Toshiyuki Bohgaki, Olga Amengual, Tetsuya Horita and Tatsuya Atsumi. Hokkaido University Graduate School of Medicine, Sapporo, Japan.

Background/Purpose: Nervous system disease is one of the most common manifestations in patients with systemic lupus erythematosus (SLE) that significantly affects morbidity and mortality. Due to the complexity of clinical presentation of neuropsychiatric lupus (NPSLE), there are no specific markers for the diagnosis or for the evaluation of disease activity. A link between type I interferon (IFN) and SLE has been established by a series of studies. Recent studies have shown up-regulated IFN-inducible genes in the peripheral blood of lupus patients, which is correlated with disease activity[1)]. We previously reported that gene expression levels of Mx1 (myxovirus resistance protein 1), one of the IFN-inducible genes, was increased in lupus peripheral T cells compared with healthy controls[2)]. But it has not been revealed how the overexpression of Mx1 affects specific organs in lupus patients. Based on the report detecting Mx protein in active lesions of brain tissues from patients with multiple sclerosis (MS)[3)], we hypothesized that Mx1 is one of the factors related to the pathogenesis or the biomarker of NPSLE.

Methods: This study comprised 20 patients with NPSLE, 9 patients with SLE who were not considered NPSLE (non-NPSLE), and 20 patients with other non-inflammatory neuropsychiatric diseases as a disease control group. We evaluated the level of Mx1 in serum and cerebrospinal fluid (CSF) by enzyme-linked immuno-sorbent assay (ELISA). There was no significant

difference in disease activity (SLEDAI) between those with NPSLE or without.

Results: The levels of Mx1 in serum and CSF were correlated in patients with SLE (R=0.36). The levels of Mx1 in CSF were higher than that of serum in both patients with NPSLE ($p<0.05$) and non-NPSLE ($p<0.05$). The levels of serum Mx1 were significantly higher in patients with NPSLE than in those with non-NPSLE and other non-inflammatory neuropsychiatric diseases ($p<0.01$, $p<0.001$, respectively, Figure). The levels of Mx1 in CSF were significantly higher in patients with NPSLE than in those with other non-inflammatory neuropsychiatric diseases ($p<0.001$).

Conclusion: The upregulation of Mx1 was significantly correlated with NPSLE, suggesting that serum Mx1 is one of the candidates of biomarker for NPSLE.

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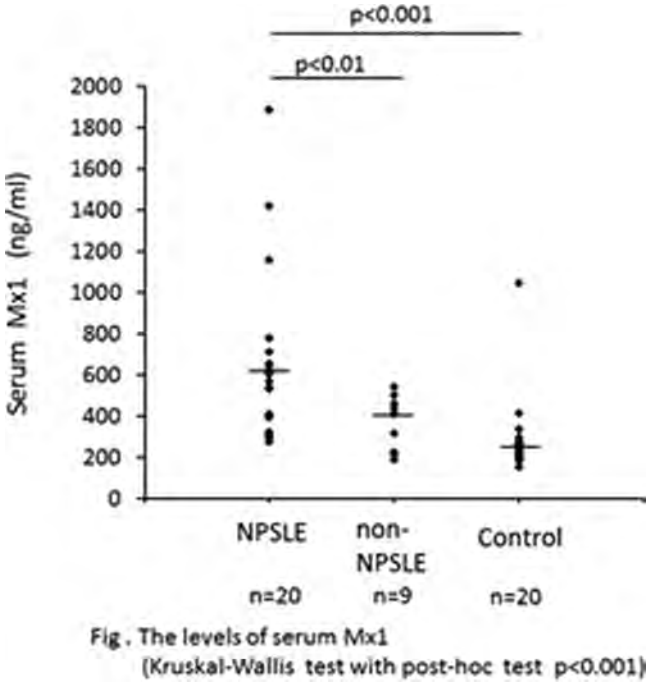

Fig. The levels of serum Mx1 (Kruskal-Wallis test with post-hoc test p<0.001)

Disclosure: Y. Shimizu, None; **S. Yasuda**, None; **T. Kurita**, None; **S. Shimamura**, None; **I. Nakagawa**, None; **A. Noguchi**, None; **H. Shida**, None; **T. Watanabe**, None; **M. Kono**, None; **K. Oku**, None; **T. Bohgaki**, None; **O. Amengual**, None; **T. Horita**, None; **T. Atsumi**, None.

1629

Added Value of the Determination of Anti-Ribosomal and Anti-Ku Antibodies for Diagnosis of Systemic Lupus Erythematosus. Johannes Schulte-Pelkum[1], Diana Carmona-Fernandes[2], Maria Jose Santos[2], Roger Albesa[1] and Michael Mahler[1]. [1]INOVA Diagnostics, San Diego, CA, [2]Faculty of Medicine, University of Lisbon, Lisbon, Portugal.

Background/Purpose: Anti-dsDNA antibodies (aab) are known as important serological marker to aid in the diagnosis of systemic lupus erythematosus (SLE) and are part of the ACR classification criteria. In addition, anti-ribosomal P (Rib-P) AAB are a specific diagnostic marker for SLE. Lately, anti-Ku AAB were also described to be present with a high prevalence in SLE patients. Here we describe the evaluation of new chemiluminescent immunoassays (CIA, QUANTA Flash®) for the detection of anti-Rib-P and anti-Ku AAB, and show that testing for these AAB might add value to the diagnosis of SLE.

Methods: Sera (125) from patients suffering from SLE and 280 control sera including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA) ancylosing spondylitis (AS) and healthy controls (HC) were tested using QUANTA Flash Ribosomal P, QUANTA Flash dsDNA, and QUANTA Flash Ku (prototype).

Results: 58/125 of the SLE Patients and 13/280 controls tested positive for antibodies against dsDNA corresponding to a sensitivity of 46.6% (95% CI of 37.4–55.5%) and a specificity of 95.4% (95% CI of 92.2–97.5%). 37/125 of the SLE patients and 14/280 controls tested positive for anti-Rib-P AAB corresponding to a sensitivity of 29.6% (95% CI: 21.8–38.4%) and a specificity of 95.0% (95% CI: 91.8–97.2%). In addition, 20/125 of the SLE patients and 5/280 controls sera tested positive for anti-Ku AAB corresponding to a sensitivity of 16.0% (95% CI: 10.1–23.6%) and a specificity of 98.2% (95% CI: 95.9–99.4 %). The reactivities against Rib-P and Ku show minimal overlap. Therefore, when combining the two markers, the sensitivity and specificity for SLE were 41.6% (95% CI: 32.9–50.8%) and 93.2% (95% CI: 89.6–95.9%), respectively. Table 1 part A shows a summary.

In the group of dsDNA negative samples anti-Ku (OR=8.1) and anti-Rib-P(OR=2.3) results could be used to discriminate SLE patients from controls. 16 /67 sera from SLE patients and 18/267 control sera had a positive test result for either anti-Rib-P or anti-Ku, thus discriminating SLE from controls with a specificity of 93.3% (95% CI 89.6–96.0%). Table 1 part B shows the individual and combined sensitivities, specificities and Odd ratios.

Table 1 Sensitivities, specificities and Odd ratios summarized (Part A: complete cohort, Part B: dsDNA negative sub cohort)

QUANTA Flash®	Sensitivity	95% CI	Specificity	95% CI	OR	95% CI
Part A: complete cohort (n=405)						
dsDNA	46.6%	37.4–55.5%	95.4%	92.2–97.5%	17.8	9.2–34.3
Rib-P	29.6%	21.8–38.4%	95.0%	91.8–97.2%	8.0	4.1–15.5
KU	16.0%	10.1–23.6%	98.2%	95.9–99.4%	10.5	3.8–28.6
either Rib-P or Ku	41.6%	32.9–50.8%	93.2%	89.6–95.9%	9.8	5.4–17.6
Part B: dsDNA negative sub cohort (n=334)						
Ku	13.4%	6.3–24.0%	98.1%	95.7–99.4%	8.1	2.6–25.2
Rib-P	10.4%	4.3–20.3%	95.1%	91.8–97.4%	2.3	0.9–6.0
either Rib-P or Ku	23.9%	14.3–35.9%	93.3%	89.6–96.0%	4.3	2.1–9.1

Conclusion: Our data confirm that anti-Rib-P and anti-Ku AAB represent potentially useful biomarkers to aid in the diagnosis of SLE. Interestingly, the reactivity against these two antigens shows only minimal overlap and thus, the combination of both markers showed high sensitivity and specificity for SLE. In addition, a significant portion of anti-dsDNA negative SLE patients were positive for anti-Rib-P or anti-Ku AAB. More studies will be needed to confirm this observation.

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1630

A Novel NMR Biomarker of Inflammation (GlycA) Is Elevated in Systemic Lupus Erythematosus. Cecilia P. Chung[1], Michelle J. Ormseth[1], Annette M. Oeser[1], Joseph F. Solus[1], Margery A. Connelly[2], James D. Otvos[3] and C. Michael Stein[1]. [1]Vanderbilt University, Nashville, TN, [2]LipoScience, Inc., Raleigh, NC, [3]LipoScience Inc., Raleigh, NC.

Background/Purpose: Nuclear magnetic resonance (NMR) spectra from samples analyzed for lipoproteins also contain a peak (termed GlycA) resulting from glycosylated proteins. GlycA is not only a novel marker of inflammation but was also associated with coronary heart disease in the MESA study. Little is known about GlycA in patients with systemic lupus erythematosus (SLE). Therefore, we tested the hypothesis that GlycA concentrations were elevated in patients with SLE and associated with other markers of inflammation.

Methods: We compared concentrations of GlycA in 116 patients with SLE and 83 control subjects, frequency-matched for age, sex, and race. GlycA was detected by NMR, as a signal from methyl group protons on the carbohydrate portions of glycosylated proteins. SLE disease activity index (SLEDAI) and the SLE Collaborating Clinics damage index (SLICC) were calculated. Acute phase reactants [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] were measured using standard methods by the hospital clinical laboratory and interleukin-6 (IL-6) using a Lincoplex ELISA assays.

Results: Patients with SLE had higher concentrations of GlycA [398 (350–445) μmol/L] than control subjects [338 (298–393) μmol/L, $p<0.001$]. In patients with SLE, concentrations of GlycA were significantly associated with ESR, CRP, IL-6, systolic and diastolic blood pressure. (Table)

Table: Association of GlycA with disease characteristics

	Rho	P
ESR	0.43	<0.001
CRP	0.59	<0.001
IL-6	0.27	0.003
Systolic blood pressure	0.23	0.01
Diastolic blood pressure	0.21	0.02
SLEDAI	0.15	0.11
SLICC Damage Index	0.02	0.83

Conclusion: Concentrations of GlycA are higher in patients with SLE than control subjects and are associated with markers of inflammation and blood pressure, but not with SLE disease activity/chronicity scores.

Disclosure: C. P. Chung, NIH, 2; **M. J. Ormseth**, None; **A. M. Oeser**, None; **J. F. Solus**, None; **M. A. Connelly**, LipoScience, Inc., 3; **J. D. Otvos**, LipoScience, Inc, 3; **C. M. Stein**, NIH, 2.

1631

Cell Bound Complement Activation Products and Their Relationship to Disease Activity and Quality of Life Measures in Systemic Lupus Erythematosus. Richard Furie[1], Jill P. Buyon[2], R. Ramsey-Goldman[3], Chaim Putterman[4], Kenneth Kalunian[5], Tyler O'Malley[6], John Conklin[6], Derren Barken[6] and Thierry Dervieux[6]. [1]North Shore-LIJ Health System, Great Neck, NY, [2]New York University School of Medicine, New York, NY, [3]Northwestern University Feinberg School of Medicine, Chicago, IL, [4]Albert Einstein College of Medicine, Bronx, NY, [5]UCSD School of Medicine, La Jolla, CA, [6]Exagen Diagnostics, Inc., Vista, CA.

Background/Purpose: To assess the association between cell bound complement activation products (CBCAPS) and measures of disease activity and quality of life in systemic lupus erythematosus (SLE).

Methods: SLE patients (1997 ACR classification criteria) with active disease as defined by an SLE disease activity 2000 index (SLEDAI 2K) ≥ 6 points or the presence of a 2004 British Isles Lupus Assessment Group (BILAG) index A or B score were eligible for enrollment. However, only those screened patients with elevated CBCAPS (e.g. erythrocyte C4d levels [EC4d] above 15 units) were permitted entry into the study. Clinical activity measures, consisting of a modified SLEDAI 2K (mSLEDAI 2K excludes complement and anti-dsDNA components) and a BILAG index score, and quality of life assessments (short-form 36 [SF-36]) were performed monthly for one year. Patients were also evaluated monthly for EC4d and erythrocyte C3d (EC3d), serum complement levels (C3/C4) and anti-dsDNA antibody concentrations at each visit. EC4d and EC3d levels were determined by flow cytometry, and the mean net fluorescence intensity (MFI) was log transformed for the analysis. Statistical analysis consisted of generalized linear mixed models with random intercept and fixed slopes.

Results: 33 patients (mean age 35 years; 94% female) were evaluated monthly for a total of 303 study visits (median 10 visits per patient, range 3–13). Anti-dsDNA positivity was observed in 61% and low complement levels in 70% of the cohort. The average (SEM) baseline EC4d and EC3d levels were 54.0±21.6 and 15.6±10.0 Net MFI, respectively, and decreased to 28.8±4.4 and 4.2±0.8 net MFI at the last visit. Similarly, the average mSLEDAI 2K and composite BILAG score (A=12, B=8, C=1 point) were 6.8±0.8 and 15.7±1.8 points at baseline, respectively, and decreased to 2.8±0.8 and 8.5±1.3 points, at the last visit. Mean SF-36 scores ranged from 42 (general health) to 68 (role emotional) at baseline. Generalized linear mixed models showed that the number of monthly follow up visits was significantly associated with clinical improvement (decreased mSLEDAI 2K and BILAG scores; increased SF36 scores). As presented in the Table, decreases in EC3d levels and increases in C4 levels were associated with reductions in mSLEDAI 2K and BILAG index scores, whereas increases in C3 levels were associated with reductions in mSLEDAI 2K only. The analysis also revealed that decreasing EC4d and EC3d levels were associated with improving quality of life ($p<0.05$) in 6/8 domains of the SF-36. Changes in C4 were not significantly associated with changes in quality of life measures. Increased C3 was associated with lower quality of life in 2/8 domains of the SF-36 (physical function and role physical).

Conclusion: Our data reveal that EC4d and EC3d levels are associated with changes in disease activity and quality of life measures in SLE.

Table Mixed model estimates

	EC4d Log Net MFI	EC3d Log Net MFI	C3 mg/dL	C4 mg/dL	Anti-dsDNA U/mL
Modified SLEDAI 2K	0.7±0.5	1.0±0.4	−0.03±0.01	−0.16±0.05	0.001±0.001
	p=0.167	p=0.009	p=0.014	p<0.001	p=0.201
BILAG Index Score	0.9±0.9	2.2±0.7	−0.04±0.03	−0.31±0.08	−0.001±0.002
	p=0.299	p=0.002	p=0.155	p<0.001	p=0.756
SF36 Physical Function	−0.7±2.3	−1.7±1.7	−0.22±0.07	0.08±0.21	0.003±0.004
	p=0.757	p=0.339	p=0.001	p=0.721	p=0.476
SF36 Role Physical	−5.7±2.2	−5.2±1.7	−0.15±0.07	−0.06±0.21	0.004±0.005
	p=0.011	p=0.003	p=0.028	p=0.786	p=0.412
SF36 Bodily pain	−6.6±2.8	−6.6±2.1	−0.16±0.08	0.18±0.27	−0.002±0.006
	p=0.018	p=0.002	p=0.052	p=0.492	p=0.713
SF36 General Health	−5.1±1.4	−3.2±1.1	−0.01±0.04	0.24±0.14	0.001±0.003
	p=<0.001	p=0.003	p=0.750	p=0.081	p=0.794
SF36 Vitality	−4.0±1.8	−5.0±1.4	−0.03±0.06	0.22±0.17	−0.001±0.004
	p=0.033	p=<0.001	p=0.532	p=0.197	p=0.828
SF36 Social Functioning	−6.6±2.4	−5.6±1.8	−0.06±0.07	0.22±0.23	0.005±0.005
	p=0.006	p=0.003	p=0.389	p=0.341	p=0.300
SF36 Role emotional	−2.7±2.4	−0.7±1.9	−0.12±0.07	−0.33±0.23	0.000±0.005
	p=0.264	p=0.726	p=0.089	p=0.140	p=0.928
SF36 Mental health	−6.1±1.7	−3.1±1.3	0.01±0.05	0.31±0.16	−0.001±0.003
	p<0.001	p=0.018	p=0.895	p=0.055	p=0.867

Disclosure: R. Furie, Exagen, 2; **J. P. Buyon**, Exagen, 2; **R. Ramsey-Goldman**, Exagen, 2; **C. Putterman**, Exagen, 2, Exagen, 5; **K. Kalunian**, Exagen, 2, Exagen, 5; **T. O'Malley**, Exagen, 3; **J. Conklin**, Exagen, 3; **D. Barken**, Exagen, 3; **T. Dervieux**, None.

1632

Is Liopxin A4 a Biomarker for Systemic Lupus Erythematosus? Manal Sedky Abdou[1], Dina Effat[2], Lamiaa Mansour[1], Mona mohsen Abdul Salam[1] and Noha abd El Baky[1]. [1]faculty of medicin, cairo university, cairo, Egypt, [2]faculty of medicin, cairo university, giza, Egypt.

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by autoantibody production and immune complex deposition which trigger both a local and systemic inflammatory response. The continuation of inflammation could be due to failure of the healing process resulting from insufficiency of the pro-resolution lipid mediators such as lipoxin A4 (LXA4) which might lead to progression and flares of lupus. Thus, we assessed the levels of serum and urinary LXA4 in SLE patients and in healthy controls, and correlated them with various clinical and laboratory data as well as renal biopsy and disease activity indices.

Methods: Forty female SLE patients, diagnosed according to the ACR revised criteria for SLE, were included in this study as well as forty healthy age & sex matched subjects who served as the control group. All patients were subjected to full history taking, clinical examination, assessment of disease activity (SLEDAI and renal SLEDAI), laboratory investigations including serum LXA4 and urinary LXA4/creatinine ratio using Enzyme Linked Immunosorbent Assay (ELISA) and renal biopsy. The SLE patients were divided into 2 groups: Group I: 20 patients without nephritis and Group II: 20 patients with nephritis. Statistical analysis was done using SPSS computer software package, version 15.0, 2006.

Results: Urinary LXA4/creatinine ratio levels were significantly higher in all SLE patients when compared to healthy controls ($p=0.037$). The median level of urinary LXA4/ creatinine ratio was lower in SLE patients with nephritis than those without nephritis (0.1, 0.3 ng/ml respectively), but this difference was not statistically significant ($p=0.11$). The urinary LXA4/ creatinine ratio levels were significantly lower in SLE patients with cardiovascular manifestations, as well as those with neuropsychiatric manifestations ($p=0.009$, 0.04 respectively).There was no significant statistical correlation between serum LXA4 and urinary LXA4/creatinine ratio ($r=0.065$, $p=0.7$). There was a positive significant correlation only between urinary LXA4 /creatinine ratio and ESR ($p=0.008$), but no significant correlation between serum LXA4 and urinary LXA4/creatinine ratio and other laboratory parameters including anti-ds DNA, C3 and C4. There was no significant statistical correlation between the level of serum LXA4 and urinary LXA4/creatinine ratio and activity scores (SLEDAI and renal SLEDAI) in all SLE patients. Also, there was no significant difference between WHO classes of Lupus nephritis in SLE patients as regards serum LXA4 and urinary LXA4/ creatinine ratio.

Conclusion: This is a novel study that showed that the urinary LXA4/ creatinine ratio levels were significantly lower in SLE patients with cardio-

vascular and those with neuropsychiatric manifestations, however, it was non significantly lower in patients with nephritis. This may suggest that insufficiency of LXA4 may be responsible for some of the systemic manifestations of SLE, making the disease progressive and more serious. Accordingly, LXA4 could be an inflammatory biomarker for systemic manifestations in SLE patients.

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1633

Galectin-3-Binding Protein Is Associated with Disease Activity, but Not with Atherosclerosis in SLE Patients. Susan Kay[1], Niels Heegaard[2] and Anne Voss[3]. [1]Rheumatology, Odense, Denmark, [2]Cinical Biochemistry and Pharmacology, Odense, Denmark, [3]Reumatology, Odense, Denmark.

Background/Purpose: Patients with systemic lupus erythematosus (SLE) have an increased risk of cardiovascular disease (CVD), which may be due to an increased prevalence of atherosclerosis. Atherosclerosis is recognized as being associated with chronic inflammation. SLE is characterized by activation of the innate immune system and an increased expression of type I interferon (IFN) leading to chronic inflammation. Galectin-3 binding protein(G3BP) is a putative marker of IFN activation and has recently been shown to be increased in plasma of SLE patients. The objective of this study was to quantify plasma G3BP and determine the association of G3BP and atherosclerosis in SLE.

Methods: In a population-based predominantly Caucasian cohort we recruited 80 SLE patients. Atherosclerotic burden was assessed by cardiac CT scan for coronary calcium score (CAC) and carotid duplex for carotid intima-media thickness (IMT) and plaque using the ARIC study plaque definition. The presence of atherosclerosis was defined by a CAC >0 and/or carotid plaque. A total of 38 patients were found to be negative for atherosclerosis and 42 patients were found to be positive. The concentration of galectin-3 binding protein (G3BP, 90k/Mac-2 BP) was determined in plasma samples by a commercially available sandwich-type enzyme-linked immunosorbent assay (eBioscience). Samples were diluted 1:100 and concentrations were determined by extrapolation to standard curves obtained with known concentrations of G3BP.

Results: Mean plasma galectin-3-binding protein in the entire study population was 59.54 ng/ml. Plasma galectin-3-binding protein did not significantly differ between SLE patients with atherosclerosis and without atherosclerosis. G3BP levels were significantly correlated with disease activity as expressed by SLEDAI ($P=0.02$).

Conclusion: The inflammatory marker galectin-3-binding protein is not significantly associated with atherosclerosis, but we confirm its association with disease activity in SLE patients.

Disclosure: S. Kay, None; **N. Heegaard**, None; **A. Voss**, None.

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Thrombophilia Associated with DFS70 Antibodies. Julien Marlet[1], Jean-Luc Charuel[1], Isabelle Martin-Toutain[1], Pascale Ghillani-Dalbin[1], Zahir Amoura[1], Annick Ankri[2] and Makoto Miyara[1]. [1]Pitié-Salpêtrière Hospital (AP-HP), Paris, France, [2]Groupe Hospitalier Pitié Salpétrière, service d'hématologie biologique, Paris, France.

Background/Purpose: The search for antinuclear antibodies (ANA) by indirect immunofluorescence (IIF) on Hep-2 cells is routinely performed as the first step for the biological diagnosis of systemic autoimmune diseases. Anti-DFS70 antibodies are a type of ANA defined by a nuclear dense fine speckled (DFS) IIF pattern, first described in 1994. It has also been reported that anti-DFS70 antibodies were the most frequent type of ANA found in healthy individuals. We therefore conducted a retrospective study on a large number of patients tested positive for anti-DFS70 antibodies.

Methods/Patients: The first group of patients, the anti-DFS+ group, included patients selected among those undergoing routine antinuclear antibodies testing (ANAs) at the Pitié-Salpêtrière hospital (Paris, France). Patient inclusion started on the 1st of July 2011 and ended on the 31st of July 2013. The criterion of inclusion was an ANA testing positive with a DFS pattern at titer higher or equal to 1:80. Anti-DFS70 antibodies were confirmed with QUANTA Flash DFS70 immunoassay (Inova diagnostics). 441 patients were included.

The second group of patients, the thrombosis group, included patients consulting in hematology at the Pitié-Salpêtrière hospital (Paris, France) who were screened for the first time for a factor V Leiden mutation, a test performed only in patients with a history of thrombosis. Patient inclusion started on the 1st of January 2013 and ended on the 31st of December 2013.

Clinical history of all patients was retrospectively analyzed by clinical chart review of medical records.

Results: The anti-DFS+ group included 441 patients. The prevalence of SARD among anti-DFS+ patients was low (18%, n=81) consistent with previous reports and the majority of them were followed up in internal medicine departments (82 %). Among them, 51 patients had SLE (11.6 %), 9 RA (2 %), 15 primary Sjogren syndrome (3.4 %) 3 inflammatory myositis (0.7 %) and 2 with mixed connective tissue diseases. Among the other patients, 17 patients had multiple sclerosis (3.9 %) and 16 thyroiditis (3.6 %).

Moreover, we observed an unexpectedly high prevalence of thrombotic events in the anti-DFS+ group (12 %, 54 patients).

We thus constituted a control thrombosis group with patients followed in a single tertiary center for thrombosis. All patients referred (n=67) for the first time to the center for thrombotic events were included. Interestingly, 10.4% of patients in the thrombosis group were positive for anti-DFS antibodies.

Prevalence of arterial thrombosis and venous thrombosis in the whole DFS+ population were respectively of 2.9 %, 6.1 % and prevalence of obstetric syndrome (fetal loss, HELLP or pre-eclampsia) in anti-DFS+ women was 6.3 %. One patient had both arterial and venous thrombosis, another had both arterial thrombosis and obstetric syndrome and four patients had both venous thrombosis and obstetric syndrome.

Conclusion: Presence of DFS70 antibodies on ANA testing may be associated with thrombophilia.

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1635

Association Between Carrying at Least One Apolipoprotein1 Variant Allele and Hypertension in Lupus Patients with Normal Renal Function. Ashira Blazer[1], H. Michael Belmont[1], Robert Clancy[2], Peter M. Izmirly[3] and Jill P. Buyon[3]. [1]NYU School of Medicine, New York, NY, [2]NYU Medical Center, New York, NY, [3]New York University School of Medicine, New York, NY.

Background/Purpose: The apolipoprotein1 (APOL1) gene encodes a 3 domain protein found both in serum and intracellularly in endothelial cells among other cell types. Variant APOL1 has undergone positive selection as the serum protein offers heterozygous advantage by promoting lysis of Trypanosoma Brucei conferring resistance to African Trypanosomiasis. Populations native to endemic regions carry this variant at high frequencies with 30% of African Americans (AA) heterozygous for the gene and 12% homozygous. The intracellular form of APOL1 is a cytokine mediated apoptosis factor. Recently homozygous status for APOL1 risk allele (RA) has been associated with non-diabetic end stage renal disease by multiple causes including Lupus Nephritis (LN). While the mechanism of disease progression has not yet been described, we postulate that aberrant apoptosis in the renal vasculature may lead to arterial dysfunction and renal injury.This study was undertaken to establish a relationship between carrying at least one APOL1 RA and known clinical indicators of renal vascular dysfunction in a sample of 34 AA lupus patients with average eGFR above 60 (calculated by the CKD Epi formula).

Methods: APOL1 G1 and G2 risk alleles were genotyped by PCR/DNA sequencing. All patients satisfied ACR criteria for SLE. The patients were distributed into 2 groups: those carrying 2 wild type (WT) alleles (WT/WT) and those with at least 1 RA (G1/WT, G2/WT, G1/G1, G2/G2, G1/G2). Charts were reviewed to assess clinical parameters including demographics, medical comorbidities, medications, vital signs, and laboratory values.

Results: There were 18 patients in the WT group and 16 in the risk variant (RV) group (G1/WT= 10pt; G2/WT=3pt; G2/G2= 1 pt; G1/G2= 2pt; G1/G1= 0pt). Subjects were AA (100%) and predominantly female (WT: 100%; RV: 81%). Hypertension was defined as diagnosis of HTN on chart review, taking at least 1 antihypertensive drug, or having BP over 140 systolic and/or 90 diastolic on at least 2 clinic visits. The APOL1 RA was strongly associated with HTN with 69% of the RV group meeting criteria for HTN compared to 22% of the WT group (odds ratio: 7.7; p value: 0.009). Subgroup analysis of 15 patients with biopsy proven LN showed a higher effect size (odds: ratio of 16; p value: 0.04). There was no significant difference in age, disease duration, disease activity, eGFR, proteinuria, or history of LN between the groups. Next the relationship between inflammation and APOL1 regulation was assessed. As a surrogate of mononuclear cells residing at

patient blood vessels and renal tissue and to evaluate the capacity of macrophages to serve as a source of APOL1, THP1 macrophages were stimulated with hY3 ssRNA and we found that APOL1 was a strongly upregulated transcript.

Conclusion: AA SLE patients carrying at least 1 APOL1 RA have an increased risk of HTN before onset of clinically significant renal disease potentially suggesting vascular dysfunction associated with this gene. Increased APOL1 transcription in the setting of inflammation may increase the gene effect in heterozygous carriers.

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1636

Disease Phenotype Is Associated with TH1, TH2 and TH17 Cytokines in Childhood-Onset Systemic Lupus Erythematosus. Karina Oliveira Peliçari[1], Mariana Postal[1], Renata Brabosa[2], Nailu A. Sinicato[1], Fernando Augusto Peres[1], Roberto Marini[1] and Simone Appenzeller[3]. [1]State University of Campinas, Campinas, Brazil, [2]Faculdade de Ciencias Medicas, Universidade Estadual de Campinas, Campinas, Germany, [3]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: Childhood-onset Systemic lupus erythematosus (cLES) is an autoimmune disease characterized by periods of activity and remission. There is a wide spectrum of manifestations, such as hematologic and immunologic, which are commonly found. The cytokine profile assists in the diagnosis, determination of disease activity and may predict future damage caused by the disease. To determine the serum levels of Th1 (IL-12 and TNF-α), Th2 (IL-6 and IL-10) and Th17 (IL-17) cytokines in cSLE and to evaluate their role in different disease phenotypes.

Methods: We included 53 consecutive cSLE patients [median age 21 years (range 13–28)] and 51 age and sex-matched healthy controls [median age 20 years (8–33)]. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. Mood and anxiety disorders were determined through Becks Depression and Becks Anxiety Inventory in all subjects. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index (SDI)] and current drug exposures. Th1 (IL-12 and TNF-α), Th2 (IL-6 and IL-10) and Th17 (IL-17) cytokines levels were measured by ELISA using commercial kits. Data were compared by non-parametric tests.

Results: Serum IL-6 ($p=0.002$), IL-10 ($p=0.028$), IL-17 ($p=0.009$) and TNF-α ($p=0.04$) levels were increased in cSLE patients when compared to healthy controls. TNF-α levels were significantly increased in patients with active disease (SLEDAI$\geq$3) ($p=0.004$). IL-6 ($p=0.006$) and TNF-α ($p=0.024$) levels were significantly increased in patients with nephritis and IL-10 levels were increased in patients with elevated ESR ($p=0.013$). We observed that IL-17 was associated with migraine ($p=0.040$) and IL-6 with thrombocytopenia ($p=0.022$) and low complement ($p=0.014$). IL-12 ($p=0.008$) and IL-17 ($p=0.005$) were associate with anxiety. No association between cytokine levels and SDI scores or medication was observed.

Conclusion: Cytokines play a central role in cSLE and may be responsible for different disease phenotype. TNF-α is associated with SLEDAI and may be a biomarker of disease activity, Th1 and Th2 responses may play a role in lupus nephritis and Th1 and Th17 may play a role in neuropsychiatric symptoms in cSLE. Longitudinal studies are needed to determine if these cytokines may be used as biomarkers in cSLE.

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1637

LACK of Association of ANTI CCP and Arthritis in SLE. Adrian Pablo Salas[1], Mariana Alejandra Pera[2], Pierina Sansinanea[2], Mercedes Argentina García[2], Valeria Arturi[2], Ana Carolina Costi[2], Claudia Elizabeth Pena[2], Adriana Testi[3], Josefina Marcos[4] and Ariel Vulcano[1]. [1]HIGA San Martin, La Plata, Argentina, [2]HIGA San Martín La Plata, La Plata, Argentina, [3]HIGA San Martin, La Plata - Buenos Ai, Argentina, [4]HIGA San Martín, La Plata, Argentina.

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by multiplicity of auto antibodies, many of them play an unknown role in disease pathogenesis. Anti cyclic citrulinated antibodies (aCCP Ab) predict the progression to rheumatoid arthritis in patients with recent onset arthritis, and are associated with erosive disease. Its utility in SLE has not been determined yet, but their positivity has been linked to arthritis, and presence of erosions in small retrospective studies. The aim of this study was to evaluate the prevalence of aCCP Ab in a cohort of patients with SLE and the possible association with clinical manifestations of disease.

Methods: the presence of third generation aCCP 3 Ab (ELISA) was evaluated in 100 consecutive, ambulatory patients with diagnosis of SLE 1997 ACR from January 2011 to June 2011, and medical records were reviewed retrospectively. The cumulative presence of photosensitivity, malar rash, alopecia, discoid lesions, Raynaud's phenomenon, arthritis, myositis, nephropathy, hemolytic anemia, lymphopenia, neutropenia, thrombocytopenia, serositis, myocarditis, pulmonary intersticiopathy, panniculitis, neuropsyquiatric lupus and antiphospholipid syndrome (APS) was evaluated. Categorical variables were compared by Fisher or Chi2 test 2 t.

Results: data of 83 patients was analyzed. aCCP Ab were positive in 15/83 cases (18%). Not significant association was found between a CCP Ab and any clinical manifestations, including the presence of arthritis: 13/15 (86.6%) in aCCP Ab positive group vs. 56/67 (83.6%) in the negative aCCP group. 28/83 (34%) patients developed lupus nephritis, none of them presented positive aCCP (OR: 0.00, p:0. 005, CI: 0.00–0.45).

Conclusion: The aCCP Ab was positive in only 18% of patients studied. No association was detected between the ACCP Ab and any clinical manifestation of SLE.Further prospective studies are needed to establish the role of this antibodies in SLE.

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1638

Anti-Dense Fine Speckled 70 Antibodies: Long-Term Followup Study of Clinical Associations in a US Laboratory Patient Population. Mark H. Wener[1] and Kathleen Hutchinson[2]. [1]University of Washington, Seattle, WA, [2]University of Washington, SEATTLE, WA.

Background/Purpose: The recently recognized nuclear dense fine speckled immunofluorescence (IF) ANA pattern is associated with antibodies to the dense fine speckled 70 (DFS70) antigen. Presence of antiDFS70 may identify populations with a low prevalence of autoimmune rheumatic disease. Long-term followup evaluation of the associations of antiDFS70 is limited.

Methods: Serum samples sent for ANA tests to our clinical laboratory were tested for ANA by a multiplex bead assay and HEp2 IF in 2011. Specimens with a positive IF ANA but negative for tested ANA subsets were identified. Randomly selected samples from that population were tested using a commercial anti-DFS70 ELISA and chart reviews were done on positive samples. Long-term followup based on chart review was performed in 2014.

Results: Long-term followup (at least 6 months, range 6 to 36 months) was available for 32 patients. No definitive autoimmune rheumatic disease was diagnosed in any patient. One patient was treated with hydroxychloroquine for possible undifferentiated connective tissue disease, in part because of the persistent positive ANA, arthralgias, and hearing problems felt most likely to be due to otosclerosis. One patient was diagnosed with celiac disease, one patient had idiopathic glomerulosclerosis with other features of autoimmune disease, and one patient had idiopathic pulmonary fibrosis requiring lung transplant. Two patients developed multiple sclerosis. Common clinical symptoms were arthralgias and/or myalgias (7/32) including 4 diagnosed with fibromyalgiaAsthma was found in 3 patients, irritable bowel syndrome in 3 patients, and headaches (including migraines) in 5. Two patients were diagnosed with depression. No chronic atopic dermatitis, cystitis or malignancy (diagnoses previously reported with antiDFS70) were found.

Conclusion: None of our subjects had an identified autoimmune rheumatic disease on long-term followup. From this U.S. population, although small, we provide additional support for the proposal that sera with only DFS70 antibodies may help identify patients who do not have a rheumatologic disease despite a positive ANA IF test.

Disclosure: M. H. Wener, Inova Diagnostics, Inc., 9; **K. Hutchinson**, None.

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Serum Anti-Müllerian Hormone Levels in SLE Patients. the Disease Severity and Cyclophosphamide Reduce the Ovarian Reserve. Gerardo Marino[1], Laura Messuti[1], Maria Rita Gigante[1], Angela Barini[2], Silvia Canestri[1], Antonella Barini[2], Barbara Tolusso[1], Elisa Gremese[1] and Gianfranco Ferraccioli[1]. [1]Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy, [2]Department of Laboratory Medicine, Institute of Biochemistry and Clinical Biochemistry, Catholic University of The Sacred Heart, Rome, Italy.

Background/Purpose: Systemic lupus erythematosus (SLE) predominantly affects women of childbearing age, can lead to severe organ involvement and may require prolonged immunosuppressive therapy. Anti-Müllerian Hormone is produced by the granulosa ovary cells and serum levels of Anti-Müllerian Hormone are used as a measure of ovarian reserve, reflecting the number of primary follicles. The aim of the study was to compare serum levels of AMH in a cohort of patients with SLE and healthy controls to assess whether the presence of the disease, the treatments used and/or other clinical parameters may affect the ovarian reserve.

Methods: 75 women with SLE of childbearing age, aged between 18 and 42 years and with regular menses, and 30 healthy controls age-matched (p=0.3) were evaluated. Anti-Müllerian Hormone levels were measured in peripheral blood samples (kit AMH Gen II ELISA, Beckman Coulter). Clinical and demographic characteristics, disease duration, pattern of organ involvement and previous and current therapies were collected at the time of sampling. 14 patients (18.7%) had been treated with cyclophosphamide (cumulative dose 8.3 ± 5.4 g), and of the remaining, 36 (48.0%) with other DMARDs (methotrexate, azathioprine, mycophenolate mofetil, cyclosporine) and 25 (33.3%) with anti-malarials only.

Results: Patients with SLE had a mean age of 30.2±6.3 years, a disease duration of 8.4±5.1 and 25 patients (33.3%) had a severe organ involvement (mainly renal and neurological, 14 were treated with cyclophosphamide, 11 with other DMARDs). Serum levels of AMH were comparable between patients and controls (4.3±3.3 vs 5.2±3.2 ng/ml, respectively, p=0.15). Considering patients on the basis of organ involvement, patients with major organ involvement had AMH levels (3.4±2.7 ng/ml) significantly lower than control subjects (p = 0.04); no difference was found between patients with minor organ involvement (AMH 4.7±3.4 ng/ml) and control subjects (p=0.45). Considering the treatments used, patients with major organ involvement treated with cyclophosphamide showed serum AMH levels lower than controls (3.3±4.0 ng/ml, p=0.04) and tendentially lower than patients not treated with cyclophosphamide (3.3±4.0 vs 4.5±3.0, p=0.09). There were no associations between the use of other DMARDs than cyclophosphamide and lower AMH levels in SLE patients compared to controls.

Conclusion: In the whole cohort of SLE patients, the ovarian reserve was overall comparable to that of healthy controls, whereas a reduction of the ovarian reserve was associated with the use of cyclophosphamide and the severity of the disease.

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1640

Cyclophosphamide Diminishes Plasmablasts and Transitional B Cells and Suppresses Autocrine Production of B Cell Activating Factor of Tumor Necrosis Factor Family (BAFF) in These Cells in Patients with Systemic Lupus Erythematosus. Yuko Okamoto[1], Yasuhiro Katsumata[1], Yasushi Kawaguchi[1], Manabu Kawamoto[1], Takahisa Gono[1], Masanori Hanaoka[1], Tomoaki Higuchi[1], Hidenaga Kawasumi[1] and Hisashi Yamanaka[2]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: B cell activating factor of tumor necrosis factor family (BAFF) is a positive regulator of B cell function and expressed in dendritic cells, monocytes/macrophages, and T cells. Clinical studies have demonstrated that BAFF is overexpressed in many patients with systemic lupus erythematosus (SLE). Furthermore, autocrine BAFF expression in B cells from SLE patients with high disease activity was reported. Although cyclophosphamide (CY) has remained the treatment of choice for major organ involvement in SLE, its precise therapeutic mechanism in SLE remains to be elucidated. At the 2010 ACR meeting, we reported CY predominantly and immediately suppresses activation and viability of plasmablasts *in vivo* and *in vitro*. In this study, we aimed to further clarify the precise effect of CY on human B cell subsets and BAFF expression on B cells in SLE.

Methods: We studied 10 consecutive patients with recent onset or flare of SLE in whom monthly intravenous CY and oral prednisolone were initiated, and 10 normal healthy controls (NHCs). Peripheral blood mononuclear cells (PBMCs) were isolated from heparinized whole blood of these subjects by density gradient centrifugation before and after CY initiation. Immunofluorescence staining of PBMCs for flow cytometric analyses was performed using anti–CD19, anti–CD27, anti–CD38, anti–IgD, anti–IgM, and anti–BAFF antibodies, which specifically recognizes membrane–bound BAFF and does not bind to shed soluble BAFF. Serum BAFF levels were measured by enzyme–linked immunosorbent assay (ELISA).

Results: The frequencies of plasmablasts ($CD19^+/CD27^{high}/CD38^{high}$), transitional B cells ($CD19^+/CD27^-/CD38^{high}$), and double negative memory B cells ($CD19^+/CD27^-/IgD^-$) were significantly higher in SLE patients than in NHCs, whereas the frequencies of memory B cells ($CD19^+/CD27^+$) were significantly lower in NHCs ($p < 0.01$ in all comparisons). $CD27^+$ memory B cells were further classified into $CD27^+IgD^+$ pre–switched memory B cells and $CD27^+IgD^-$ switched memory B cells. The frequencies of pre–switched and switched memory B cells were significantly lower in SLE patients than in NHCs ($p = 0.0003$ and 0.03, respectively). Two weeks after the initiation of CY, the frequencies of plasmablasts and transitional B cells in SLE patients significantly decreased ($p < 0.01$ in both comparisons), while the frequencies of pre–switched and switched memory B cells in SLE patients significantly increased ($p = 0.02$ and 0.002, respectively). The mean fluorescence intensity (MFI) of the membrane bound–BAFF on plasmablasts, memory B cells ($CD19^+/CD27^+$) and transitional B cells were significantly higher in SLE patients than in NHCs ($p = 0.002$, 0.02, and 0.007, respectively), and decreased significantly two weeks after the initiation of CY ($p = 0.004$, 0.01, and 0.01, respectively). Serum BAFF levels in SLE patients also significantly decreased with clinical amelioration following treatment ($p = 0.002$).

Conclusion: This study shows that administration of CY predominantly and immediately diminishes plasmablasts and transitional B cells, and the BAFF overexpression in these cells. These findings indicate that therapeutic effect of CY on SLE is at least partly exerted through this mechanism.

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Baseline Factors That Predict High BLyS Levels in Patients with Systemic Lupus Erythematosus (SLE) and High Disease Activity. David Roth[1], April Thompson[2], Tom Tang[2], Anne Hammer[2] and Charles T. Molta[1]. [1]GlaxoSmithKline, Philadelphia, PA, [2]GlaxoSmithKline, Research Triangle Park, NC.

Background/Purpose: Post hoc analyses from the BLISS trials demonstrated that patients with high baseline B-lymphocyte stimulator (BLyS) levels (≥2 ng/ml) had an increased risk of a clinically meaningful flare over 1 year.

Objectives: BLyS levels are not routinely collected in clinical practice; analyses were conducted to identify clinical variables that may predict high BLyS levels in patients with SLE high disease activity.

Methods: Data from BLISS-52 (NCT00424476) and BLISS-76 (NCT00410384) were pooled (GSK200619). High disease activity was defined as anti-dsDNA positive and low complement (low C3 and/or low C4). Those subjects with high disease activity and elevated BLyS levels (≥2 ng/ml) were examined. Univariate and stepwise logistic regression were employed to identify a subset of baseline factors (e.g. demographic, disease activity, laboratory, biomarker and SLE medication usage) predictive of high baseline BLyS levels. Only baseline factors at the 0.05 significance level entered the final logistic regression as covariates.

Results: A total of 243 out of 1664 (15%) subjects had high disease activity and high baseline BLyS levels (≥2 ng/ml). Most subjects were female (n=221, 91%); mean age was 34 (10.2 SD) years, and mean SELENA-SLEDAI score was 11.5 (4.39 SD). Significant baseline predictors of high baseline BLyS levels included positive anti-Smith (≥15 U/ml; $\chi2 = 10.96$, p<0.01), low C3 ($\chi2 = 7.85$, p<0.01), anti-dsDNA (>200 IU/ml; $\chi2 = 7.28$, p<0.01) and anti-dsDNA (80–200 IU/ml; $\chi2 = 3.57$, p=0.058), use of immunosuppressant medication ($\chi2 = 11.74$, p<0.01), proteinuria (≥0.5 g/24 h; $\chi2 = 10.48$, p<0.01) and elevated C-reactive protein (>3 mg/L; $\chi2 = 40.69$, p<0.01).

Conclusion: Positive anti-Smith, low C3, positive anti-dsDNA, immunosuppressant usage, proteinuria, and elevated C-reactive protein were predictors of high BLyS and may be useful clinical parameters in identifying SLE patients with high disease activity at risk of flare.

Disclosure: D. Roth, GlaxoSmithKline, 3, GlaxoSmithKline, 1; **A. Thompson**, GlaxoSmithKline, 3, GlaxoSmithKline, 1; **T. Tang**, GlaxoSmithKline, 3, GlaxoSmithKline, 1; **A. Hammer**, GlaxoSmithKline, 3, GlaxoSmithKline, 1; **C. T. Molta**, GlaxoSmithKline, 3, GlaxoSmithKline, 1.

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A Prospective Study of Vitamin D Effects on T Cells Phenotype in Patients with Systemic Lupus Erythematosus Treated with Different Regimens of Supplementation for Two Years. Silvia Piantoni, Laura Andreoli, Alessandra Zanola, Francesca Dall'Ara, Mirko Scarsi and Angela Tincani. Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy.

Background/Purpose: Vitamin D (VD) receptor is constitutively expressed on the membrane of multiple cells, including lymphocytes. Recent studies highlight that VD may have an action on T cells, inhibiting Th1 and Th17 response and enhancing Th2 and T regulatory (Treg) function.

After repeated antigenic presentation, T cells undergo different functional and phenotypical modifications, leading to the differentiation into highly experienced memory T cells (CD45RA+CCR7-). Similarly, the down-modulation of CD28 may lead to the expansion of the CD28- T cells, a subpopulation with peculiar effector activities (high γ-IFN production and cytotoxic function).

As the best of our knowledge, little is known about the effect of VD on CD28- T cell population and in the differentiation of memory T cells.

The aim of this study is to verify the effect of VD on the circulating levels of T cells in a cohort of SLE patients (pts).

Methods: 34 SLE pts were followed-up for 24 months. In the first year, 16 pts (group 1) were supplemented with an intensive regimen of colecalciferol (300.000UI for the first month and 50.000UI/monthly as maintenance), whereas 18 (group 2) were supplemented with a standard regimen (25.000UI monthly).

During the second year, patients switched to the other regimen.

Phenotypic analysis of peripheral T lymphocyte and the quantification of the intracytoplasmatic production of IL-4 and γ-IFN from peripheral blood mononuclear cells (PBMC) was evaluated by flow-cytometry.

Wilcoxon-signed rank test and Mann-Whitney test were used for the comparisons.

Results: At baseline, no significant difference emerged in VD levels and among main T cell subtypes in SLE pts, with the exception of CD8+CD28- T cells which were expanded in group 1 (group 1 vs. 2, 74.5 vs. 26.6 % of CD8+ T cells; $p<0.01$). These pts had a greater serological disease activity (group 1 vs. 2, antidsDNA= 16.6 vs. 4.1 UI/ml; $p=0.02$).

After 24 months, an increase of the absolute number of Treg cells (CD4+CD25highCD127low) was observed, independently from the regimen of supplementation. Over two years of treatment, a progressive increase in peripheral induced (CCR7-) Treg cells and in the total amount of CD4+CD45RA+CCR7- T cells was seen in both groups, whereas a gradual significant reduction of the CD8+CD28- T cells was observed only in group 2 (table 1–2).

In the group 1, PBMCs of 8 pts were evaluated for cytokines production at baseline and after 12 months of treatment: a reduction of γ-IFN/IL-4 (from 12.1 to 3.2; $p=0.01$) among CD8+ T cells was detected.

Conclusion: VD may promote the enhancement of peripheral induced Treg cells and the production of Th2 cytokines. Further studies will be necessary to understand the role of highly experienced memory T cells and of CD28- T cells. In our cohort, the expansion of CD8+CD28- T cells may reflect a greater serological activity in SLE pts.

CELL PHENOTYPE	GROUP 1					
	T0	T12	T24	p (T0-T12)	p (T12-T24)	p (T0-T24)
TREG CCR7- (% TREG)	29.8 (15.4-42.3)	33.8 (21.4-57.1)	49.0 (32.7-68.3)	0.02	0.02	<0.01
T CD4+CD45RA+CCR7- (cell/µl)	7.0 (2.5-13.0)	13.0 (3.4-34.5)	14.0 (5.3-36.8)	<0.01	ns	<0.01

Table 1: Data are expressed as median (range 10-90th percentile)

CELL PHENOTYPE	GROUP 2					
	T0	T12	T24	p (T0-T12)	p (T12-T24)	p (T0-T24)
TREG CCR7- (% TREG)	26.4 (17.5-43.1)	35.5 (19.8-61.5)	49.2 (26.7-62.6)	0.01	0.04	<0.01
T CD4+CD45RA+CCR7- (cell/µl)	7 (2.6-20.2)	18.2 (8.5-46.7)	16.0 (4.5-162.2)	<0.01	ns	<0.01
TCD8+CD28- (% CD8+)	26.6 (14.4-62.1)	19.2 (7.6-35.2)	8.5 (2.4-24)	0.04	0.02	<0.01

Table 2: Data are expressed as median (range 10-90th percentile)

Disclosure: S. Piantoni, None; **L. Andreoli**, None; **A. Zanola**, None; **F. Dall'Ara**, None; **M. Scarsi**, None; **A. Tincani**, None.

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Role of Inflammasome Activation in Systemic Lupus Erthematosus: Are Innate Immune Cells Activated? Rodolfo Perez Alamino[1], Raquel Cuchacovich[2], Arnold Zea[3] and Luis R. Espinoza[2]. [1]LSUHSC, New Orleans, LA, [2]LSU Medical Center, New Orleans, LA, [3]Stanley Scott Cancer Center, New Orleans, LA.

Background/Purpose: Systemic lupus erythematosus (SLE) presents with a wide spectrum of clinical and immunologic abnormalities. On the other hand, exciting data is emerging about the role of the inflammasome in autoimmune disorders. The assembly of the inflammasome components in innate immune cells (monocytes) results in the rapid activation of Caspase-1, which cleaves pro-IL-1β and pro-IL-18 to generate active forms of these cytokines. Because the precise etiology and the aberrant immune dysfunction in SLE are not completely understood, we hypothesized that: "inflammasome activation occurs in monocytes as a key element on the initiation and amplification of the innate immune response in SLE pathogenesis‹. Therefore, the aims of the present study were: 1) To determine whether inflammasome activation occurs in monocytes of SLE patients, and 2) To determine the relationship between inflammasome-related cytokines and disease activity in these patients.

Methods: After informed consent, 13 SLE patients and 13 age-matched healthy individuals attending the outpatient arthritis clinic were enrolled. Demographic, laboratory and clinical data were recorded. A score ≥ 6 (SELENA-SLEDAI) was defined as active disease. Purified monocytes were plated and stimulated for 18 h with LPS (100ng/ml) in the presence or absence of Caspase-1 inhibitor. CD14 and Caspase-1 expression was analyzed by flow cytometry. Cell lysates and supernatants were collected for determination of Caspase-1 and NRLP3 protein by Western blot and cytokine levels by ELISA, respectively. Student's t test and Mann-Whitney tests were used for statistical analysis. The study was approved by the LSU IRB committee.

Results: Ninety two percent (92%) of patients were females and 67% African-Americans. Mean age was 33.2 years and mean disease duration was 10 years. Six patients presented with active disease. Lupus nephritis was diagnosed in 3 patients. The percentage of CD14+/Caspase-1 was significantly higher ($p<0.01$) in PBMC-monocytes from SLE patients compared to normal controls (70.7 ± 11.1 vs 33.5 ± 13.0, respectively). These findings directly correlated with higher plasma levels of IL-1β (0.4 ± 0.28 vs 0.15 ± 0.24 pg/ml, $p<0.05$) and IL-18 (725.2 ± 215.4 vs 479.2 ± 125.2 pg/ml, 0.01). Caspase-1 expression was confirmed by Western blot. Purified monocytes from SLE patients displayed a robust inflammatory response after LPS stimulation where Caspase-1, NLRP3, IL-1β and IL-18 were highly expressed. The production of IL-18 was reduced by 3 fold when Caspase-1 inhibitor was added to the cultures. Plasma levels of IL-18 were significantly higher in SLE clinical patients with active disease ($p<0.05$). Neither Caspase-1 or IL-1β expression was associated with SLE clinical features and disease activity.

Conclusion: Innate immune cells in SLE patients exhibited enhanced inflammasome activation, characterized by high expression of Caspase-1, NLRP3, IL-1β and IL-18, and in-vitro suppression of IL-18 production by Caspase-1 inhibitor. These findings provide novel insights into the pathogenesis of SLE and potential new avenues to explore the development of newer therapeutic strategies in the management of the disease.

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Mycophenolic Acid and Ribavirin Induces Cytoplasmic Autoimmunogenic Rods and Rings Structures in Vivo. Gerson D Keppeke Sr.[1], Eunice Nunes[2], Maria Lucia Ferraz[3], Sandro F. Perazzio[1], Mônica Prado[1], Edward K.L. Chan[4] and Luis Eduardo C. Andrade[1]. [1]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil, [2]Universidade Federal de São Paulo, Sao Paulo, Brazil, [3]Universidade Federal de São Paulo, São Paulo, Brazil, [4]University of Florida, Gainesville, FL.

Background/Purpose: Autoantibodies to IMPDH2 occur in Hepatitis C patients receiving ribavirin (RBV) & interferon-α (IFN-α). Anti-IMPDH2 antibodies recognize "rods and rings" (RR) cytoplasmic structures in indirect immunofluorescence on HEp-2 cells (IIF-HEp-2). In vitro inhibition of

IMPDH2 by RBV or mycophenolic acid (MPA) induces RR formation. We investigate the in vivo formation of RR structures in patients and mice treated with RBV or MPA.

Methods: Sequentially retrieved RBV/IFN-α-treated HCV (n=108) and MPA-treated Systemic Lupus Erythematosus (SLE) patients (n=78) were tested for anti-RR autoantibodies. Peripheral blood mononuclear cells (PBMC) from 18 MPA-treated SLE and 17 RBV/IFN-α-treated HCV patients were analyzed for RR+ PBMC by double-labeling IIF with human anti-RR serum and rabbit anti-IMPDH2 IgG. Cryosections from 3 untreated and 3 RBV-treated (0.4 mg/day; 3 months) BALB/c mice were screened for RR.

Results: Forty-one (38%) HCV and none of the SLE patients presented anti-RR autoantibody ($p<0.0001$). In vivo RR formation in PBMC occurred in all RBV/IFN-α-treated HCV (28.2±15.2% RR+ cells) and MPA-treated SLE (22.3±15.1% RR+ cells) patients ($p=0.13$). The frequency of RR+ PBMC in HCV correlated with the duration of treatment ($r=0.55$; $p=0.01$). In SLE there was no correlation with duration of treatment ($r=-0.01$; $p=0.95$), time interval from last dose ingested prior to sample collection ($r=0.04$; $p=0.86$) and daily dose ($r=0.30$; $p=0.21$). RBV-treated mice showed widespread RR structures, with variable proportion of RR+ cells in the several tissues: spleen (21.5%), stomach (57.8%), liver (70.7%), kidney (38.8%), heart (13.3%), brain (56.2%), muscle (23.7%), skin (37.1%). Untreated mice showed RR only in spleen (16.3%) and pancreas (14.9%).

Conclusion: Ribavirin and MPA generate in vivo formation of IMPDH2-rich RR structures in PBMC from HCV and SLE patients, respectively. In addition, RBV-treated mice show widespread formation of RR with variable proportion of RR-positive cell across the several tissues. These findings support further studies for the investigation of the consequences of widespread RR formation in patients receiving chronic treatment with RBV or MPA, as well as the understanding of the role of in vivo RR structures on the generation of anti-IMPDH2 autoantibodies.

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Interferon Gene Signature Expression and Serological Differences in Japanese and Non-Japanese SLE Patients. Hitoshi Kohsaka[1], Kosuke Kotani[2], Tomonori Ishii[3], Tomoya Miyamura[4], Masato Okada[5], Toshihiko Aranishi[2], R. Maciuca[6], William P. Kennedy[6] and Junko Ohata[2]. [1]Tokyo Medical and Dental University (TMDU), Tokyo, Japan, [2]Chugai Pharmaceutical co., ltd, Tokyo, Japan, [3]Tohoku University, Sendai, Japan, [4]Department of Internal Medicine and Rheumatology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan, [5]St. Luke's International Hospital, Tokyo, Japan, [6]Genentech, Inc, South San Francisco, CA.

Background/Purpose: Elevated expression of interferon(IFN)-regulated genes in peripheral blood cells has been reported in systemic lupus erythematosus (SLE) patients and is known as the IFN signature. The IFN signature in SLE has been reported to be correlated with disease-related autoantibodies such as anti-dsDNA and anti-RNP and with disease activity. Differential expression of the IFN signature among SLE patients has been reported and may indicate that the patient subgroups categorized with IFN signature expression levels have distinct biological differences. We determined the IFN signature using a 3-gene surrogate for the expression of the IFN-regulated genes[1)] and serological biomarkers described below in Japanese SLE patients. We compared these results to reported values for non-Japanese SLE populations[2)].

Methods: Peripheral blood samples from healthy volunteers (HVs) and SLE patients were analyzed in Japanese and American/European[1)]populations. SLE patients with SELENA-SLEDAI (SS) score >6 and without active renal nephritis, CNS or hematological disease were eligible. Three IFN-regulated genes (EPSTI1, HERC5 and TYK1) were chosen to represent the overall IFN signature of IFN-regulated genes, and the standardized average values of PCR quanitified expression of the three genes are reported as the IFN signature metric (ISM) score. The titers of autoantibodies and serological markers (C3, C4, anti-dsDNA, anti-RNP, ANA, ENA and serum BAFF) were measured from the same patients.

Results: The mean of ISM scores in HVs were lower than in the SLE patients. The ISM score distribution range of HVs was higher in Japanese (n=20) than in non-Japanese (n=60); the ISM score at the 95 percentile of distribution was 1.7 and 1.0, respectively. The mean of ISM score of Japanese SLE patients (n=60, SS score 8.9±2.3) was 2.9±1.1, which is higher than in non-Japanese SLE patients (2.0±1.5) with similar disease activity(n=238, White n=76, Black n=34, Hispanic n=114, other n=14, SS score 9.8±3.3). ISM scores in non-Japanese patients showed correlations with anti-dsDNA titer, positive ENA, serum BAFF levels, hypocomplementemia and SS score. In contrast, ISM scores in Japanese patients were generally high as a whole population, and did not correlate with these findings. Although the frequency of anti-dsDNA antibody positive patients was comparable between the two populations, the median (IQR) titer was lower in Japanese [34 IU/mL (28–76)] than non-Japanese patients [53 IU/mL (14–193)[1)]]. Serum BAFF correlated with ISM scores in non-Japanese SLE patients but not in Japanese patients. The profiles in ISM and serological abnormality (SA) in two ethnic populations demonstrated a contrast; high ISM/ high SA or low ISM/ low SA in non-Japanese versus high ISM/ low SA in Japanese patients.

Conclusion: The differences in ISM and SA profiles between Japanese and non-Japanese SLE patients suggests that there are demographic differences in molecular pathophysiology of SLE. These differences may have implications for therapeutic interventions that target the innate and/or adaptive immune system.

1) submitted
2) Kalunian KC, et al. (submitted)

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Molecular, Cellular and Histopathologic Assessment of Baseline Characteristics of Sixteen Subjects with Discoid Lupus Erythematosus Prior to Treatment with AMG 811 (anti-IFNγ). Barbara Sullivan[1], Roberto Guzman[1], Christopher B. Russell[2], Greg Arnold[1], Michael Boedigheimer[1], Connie Ma[1], James Chung[1], Victoria P. Werth[3] and David A. Martin[2]. [1]Amgen, Thousand Oaks, CA, [2]Amgen, Seattle, WA, [3]Veteran Affairs Medical Center, Philadelphia, PA.

Background/Purpose: Discoid Lupus Erythematosus (DLE), the most common chronic cutaneous form seen in LE, includes inflammation leading to scarring, telangiectasias, atrophy, and/or dyspigmentation. Elevated levels of IFN-γ mRNA have been described in DLE skin biopsy specimens, and patients with DLE have an IFN transcriptional signature in both blood and skin. AMG 811 is a human monoclonal antibody that selectively targets and neutralizes human IFN-γ, and results from a randomized, placebo-controlled, crossover study in DLE subjects have been previously reported (NCT01164917; Werth et al, 2013). The primary results demonstrated acceptable safety and PK profiles without apparent clinical benefit. Evidence of a pharmacodynamic effect in the blood (e.g. inhibition of IFN-γ) was apparent; however, heterogeneity in skin samples prevented definitive conclusions about the effects of AMG 811 in diseased skin.

Methods: This multi-center clinical study included 16 subjects with DLE enrolled in a randomized, single-dose crossover study. DLE subjects required a history of skin biopsy consistent with the diagnosis of DLE (Gilliam and Sontheimer classification); a diagnosis of SLE (ACR criteria) was not required, however 14 of 16 subjects had both DLE and SLE. Microscopic histopathology was performed on punch biopsies obtained from discoid lesional and non-lesional areas, and the abundance of CD3+, CD4+, CD8+, CD68+ and Ki67+ cells were quantitated by laser scanning cytometry. Whole blood and skin RNA and serum proteins were analyzed by microarray and ELISA, respectively.

Results: The baseline CLASI activity and damage scores ranged from 10 to 34 and 6 to 35, respectively (maximum 70), reflecting heterogeneity in the anatomic location and severity of the DLE skin involvement in this cohort. A range of microscopic pathology findings was observed including acanthosis, keratinocyte apoptosis, inflammatory cell infiltrates and dermal mucinosis. As with psoriasis, there was a wide range of elevated numbers of CD3+, CD4+, CD8+ T cells, CD68+ macrophages and as well as Ki67+ proliferating cells in the lesional skin compared to non-lesional skin. The AMG 811 PD score, a microarray signature described previously, was significantly higher

in DLE lesional skin compared with non-lesional skin. Histopathology and RNA transcript analysis revealed substantial intra- and inter-subject heterogeneity between skin biopsies from DLE subjects as compared to published results from subjects with psoriasis. Pathway analysis of the transcriptome suggested differential activation of both the interferon and IL-17 pathways.

Conclusion: Discoid subjects in this small clinical study demonstrated a high level of clinical, histologic and molecular heterogeneity at baseline, creating hurdles for measuring response to therapy. Analysis of clinical and/or skin biomarkers may improve understanding of the heterogeneity within DLE, and may better enable subgroup selection for assessment of response to therapeutic treatments.

Disclosure: B. Sullivan, Amgen, 3, Amgen, 1; **R. Guzman**, Amgen, 3, Amgen, 1; **C. B. Russell**, Amgen, 3, Amgen, 1; **G. Arnold**, Amgen, 3, Amgen, 1; **M. Boedigheimer**, Amgen, 3, Amgen, 1; **C. Ma**, Amgen, 3, Amgen, 1; **J. Chung**, Amgen, 3, Amgen, 1; **V. P. Werth**, UV Therapeutics, 1, Amgen, Rigel, Janssen, Novartis, Invion, 2, Philadelphia VAMC and University of Pennsylvania, 3, Medimmune, Genentech, Novartis, Pfizer, Cephalon, UV Therapeutics, Rigel, Biogen, Lupus Foundation of America, Sanofi-Aventis, Stiefel, Merck, RPS, Idera, Canfield, Celgene, 5, Head MAB, International Pemphigus and Pemphigoid Foundation, 6, CLASI, CDASI, 7; **D. A. Martin**, Amgen, 3, Amgen, 1.

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Relationship Between Apom/S1P Levels and Atherosclerosis in Women with Systemic Lupus Erythematosus. Sonali Narain[1], Sylvain Galvani[2], Christina Christoffersen[3], Peiying Yang[4], Maureen A. McMahon[5], Timothy Hla[2] and Jane E. Salmon[1]. [1]Hospital for Special Surgery, New York, NY, [2]Weill Cornell College of Medicine, New York, NY, [3]University of Copenhagen, Copenhagen, Denmark, [4]University of Texas MD Anderson Cancer Center, Houston, TX, [5]UCLA David Geffen School of Medicine, Los Angeles, CA.

Background/Purpose: SLE patients are at risk for atherosclerotic cardiovascular disease (ASCVD). In some SLE patients, high density lipoprotein (HDL) has impaired vasoprotective effects, and this "proinflammatory" HDL (piHDL) is more prevalent in those with ASCVD. The protective effect of HDL in atherosclerosis is attributable, in part, to its ability to deliver to S1P to receptors on endothelial cells. Apolipoprotein M (ApoM) is a component of some HDLs and serves as a chaperone of sphingosine 1-phosphate (S1P), a critical mediator of vascular homeostasis. S1P interacts with its receptors on endothelial cells to prevent vascular injury and inflammation. We hypothesized that the ApoM/S1P axis is deregulated in SLE.

Methods: We performed a cross-sectional study to measure ApoM and S1P levels in SLE patients. Plasma samples were obtained from 52 SLE patients who were part of a University of California Los Angeles cohort followed for ASCVD and met at least four of eleven 1982 ACR SLE Classification Criteria (Table 1). Patients on statins or with renal failure (Cr $>$ 2.0) were excluded. Plasma lipid levels were measured using standard methods. Measurement of pro-inflammatory HDL was performed using a cell free LDL oxidation assay. ApoM was measured using a standardized ELISA and S1P levels by mass spectrometry. Statistics were performed using GraphPad Prism 6.0 and SPSS using appropriate non-parametric tests.

Results: Total plasma ApoM and S1P levels were significantly lower in the SLE patients compared to previously published levels in healthy controls (HC). Mean ApoM level was 0.75 $\pm$ 0.28 mmol/L in lupus patients versus 0.92 $\pm$ 0.32 mmol/L in HC ($p<0.0001$) and mean S1P level was 47.08 $\pm$ 17.08 ng/ml in lupus patients versus 221.7 $\pm$ 84.25 ng/ml in HC ($p=0.004$). There was a positive correlation between levels of ApoM and S1P ($r = 0.34$, $p=0.013$). ApoM levels negatively correlated with body mass index (BMI) ($r = -0.54$, $p<0.0001$) and SLE disease duration ($r = -0.33$, $p=0.017$). Level of S1P was negatively correlated with BMI ($r = -0.45$, $p=0.002$) and hs-CRP ($r = -0.46$, $p=0.008$). There was no statistically significant association of ApoM or S1P levels with piHDL status, plaque status, intimal medial thickness (IMT), smoking, age, hypertension, lipid levels, ethnicity or lifetime prednisone use. In a multivariate regression combining these variables, only BMI and disease duration was significantly associated with ApoM levels.

Conclusion: Although total plasma levels of ApoM and S1P in circulation appeared to be significantly lower in SLE patients, they were neither associated with cardiovascular risk factors nor established plaque or piHDL. Studies comparing ApoM/S1P levels in SLE patients with age and sex matched healthy controls and ApoM/S1P levels in lipid sub-fractions of SLE patients are ongoing. We postulate that levels of ApoM and S1P may be influenced by inflammation status of SLE patients as this has been previously reported in patients with sepsis.

Patient Demographics

Gender (F:M)	52:0
Age (yrs $\pm$ SD)	44.98 + 13.2
Carotid Plaque n, (%)	15 (28.9)
SLE Disease duration (yrs $\pm$ SD)	12.92 + 9.1
Total Cholesterol (mg/dl)	186.2 + 37.1
HDL (mg/dl)	60.23 + 19
BMI (baseline) kg/m^2 $\pm$ SD	26.98 + 5.8
Smoking n, (%)	12 (24.5)
Diabetes mellitus n, (%)	0 (0)
Hypertension n, (%)	15 (22.9)

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Urinary T Cells and Macrophages Strongly Reflect the Disease Activity, Kidney Function, and the Histopathologic Classification in Patients with Lupus Nephritis. Yoko Wada[1], Minoru Sakatsume[1], Masaaki Nakano[2] and Ichiei Narita[1]. [1]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [2]School of Health Sciences, Faculty of Medicine, Niigata University, Niigata, Japan.

Background/Purpose: Lupus nephritis (LN) is one of the common manifestations of systemic lupus erythematosus (SLE), and the occurrence of LN is considered to be a very important factor influencing the course of the disease. Although kidney biopsy is the gold standard for defining the histopathologic class of LN, it is invasive and sometimes associated with a risk of bleeding; furthermore, repeated biopsies are not always applicable in clinical practice. For this reason, some form of novel non-invasive examination would be useful for detecting renal flare-up in LN patients. We have already reported that, in patients with glomerulonephritis, T cells and macrophages appear in the urine when there are accompanying signs of active cellular infiltration such as cellular crescent formation and diffuse interstitial cell infiltration, but not when active inflammatory lesions are absent. In the present study, we assessed the utility of urinary immune cell analysis in patients with SLE by examining the correlation between the numbers of urinary inflammatory cells and disease activity, kidney function, and histopathological classification of lupus nephritis.

Methods: Sixty-four samples from 56 patients with SLE, who had been referred to Niigata University Hospital between 2004 and 2013, were recruited for this study. Flow-cytometric analysis of urinary inflammatory cells was performed for each sample. Numbers of urinary T cells or macrophages were determined by multiplying the number of viable cells in the gated mononuclear cell region in each sample by the percentage of urinary CD3-positive or CD14-positive cells in the population, respectively. The numbers of urinary CD3-positive cells (T cells) and CD14-positive cells (macrophages), laboratory markers, kidney function, and SLE disease activity index (SLEDAI) were examined in each subject and compared with reference to their urinalysis data. The data were also analyzed by Spearman's rank correlation coefficient and stepwise multiple regression analysis to determine the relationship with urinary T cells and macrophages. In 15 patients who underwent kidney biopsy simultaneously, the relationship between histopathologic classification and the number of urinary inflammatory cells was examined.

Results: The number of urinary CD3-positive cells was significantly elevated in patients with both proteinuria and abnormal urinary sedimentation, relative to patients with proteinuria alone or normal urinalysis data. The number of CD3-positive cells was positively correlated with serum Cr, abnormal urinary sedimentation, and SLEDAI, and negatively correlated with serum CH50, while the number of urinary CD14-positive cells was positively correlated with serum Cr, abnormal urinary sedimentation, 24-hour urinary protein excretion, and SLEDAI. Among the 15 patients who underwent kidney biopsy, 8 showing a significant increase in the total number of CD3-positive cells and CD14-positive cells ($\geq$120/ml urine) were diagnosed as ISN/RPS class III or IV, while the remaining 7 were diagnosed as ISN/RPS class V.

Conclusion: These results indicate the usefulness of urinary immune cell analysis for assessment of patients with SLE.

Disclosure: Y. Wada, None; **M. Sakatsume**, None; **M. Nakano**, None; **I. Narita**, None.

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High Specificity of Skin Immunoglobulin Deposits for diagnosing SLE in Patients with Lupus Nephritis. Marco Ulises Martinez-Martinez[1], Maria Daniela De Avila[2], Mario Perales[2], Lourdes Baranda[2], Susana Román Acosta[2], Jaime Antonio Borjas García[2] and Carlos Abud-Mendoza[1]. [1]Hospital Central & Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico, [2]Hospital Central y Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico.

Background/Purpose: Deposit of different classes of immunoglobulins is the main feature of lupus nephritis;[1] because of its high specificity, a patient is classified as having systemic lupus erythematosus (SLE) if he or she has antinuclear or anti-dsDNA antibodies and biopsy-proven nephritis.[2] Granular deposition of immunoglobulins at the dermoepidermal junction [lupus band (LB)] is distinctive of SLE, but its utility for SLE diagnosis is indefinite. The main objective was to evaluate concordance of immunoglobulin deposits between kidney and skin in patients with SLE. The secondary objective was to evaluate the accuracy of the LB as a diagnostic test for SLE in patients with lupus nephritis and controls with other non-SLE nephropathies.

Methods: All patients who required kidney biopsy in the last 10 months were invited to participate in the study. From all patients who signed informed consent, kidney and non-exposed-skin biopsies were taken at the same moment and were evaluated for immunoglobulins (IgG, IgM, IgA) and complement proteins (C1q and C3) deposits. A different evaluator assessed kidney and skin biopsies; nevertheless, to assess the technique's reliability, we obtained a weighted kappa of 0.89 (CI: 0.78–0.99) when they evaluated the same set of 20 images. Intensity of fluorescence for each biopsy specimen was graded from 0 to 4 + (negative=0, and positive= 1–4+).

Results: We included 25 patients with lupus nephritis and 28 controls (other nephropathies). In the 25 patients with lupus nephritis, IgG was positive in 23 (92%) in kidney and 13 (52%) of skin biopsies; IgA in 20 (80%) of kidney and 4 (16%) of skin biopsies; IgM 23 (92%) of kidney and 9 (36%) of skin biopsies; C3 in 24 (96%) of kidney and 3 (12%) of skin; C1q in 24 (96%) and 11 (44%) of skin biopsies. The table 1 shows the high sensitivity and specificity of kidney immunoglobulin deposits for diagnosing SLE and highlights the good specificity of C1q, IgA, and IgM deposits in the skin.

Table 1. Accuracy of immunoglobulin deposits in skin or kidney for diagnosing SLE

	Sensitivity	Specificity	PPV	NPV	LR (+)	LR (-)
IgG skin	0.52 (0.20–0.46)	0.86 (0.67–0.96)	0.76 (0.50–0.93)	0.67 (0.49–0.81)	3.64 (1.36–9.72)	0.56 (0.36–0.87)
IgG kidney	0.92 (0–74–0.99)	0.79 (0.59–0.92)	0.79 (0.60–0.92)	0.92 (0.73–0.99)	4.29 (2.09–8.81)	0.10 (0.03–0.39)
IgA skin	0.47 (0.33–0.61)	1 (0.82–1.0)	1 (0.28–1.0)	0.57 (0.42–0.71)	∞	0.84 (0.71–1.0)
IgA kidney	0.80 (0.59–0.93)	0.79 (0.59–0.92)	0.77 (0.56–0.91)	0.81 (0.62–0.94)	3.73 (1.79–7.79)	0.25 (0.11–0.57)
IgM skin	0.36 (0.18–0.57)	0.93 (0.76–0.99)	0.82 (0.48–0.98)	0.62 (0.46–0.76)	5.04 (1.20–21.15)	0.69 (0.50–0.94)
IgM kidney	0.92 (0–74–0.99)	0.54 (0.34–0.72)	0.64 (0.46–0.79)	0.88 (0.64–0.99)	1.98 (1.31–3.0)	0.15 (0.04–0.59)
C3 skin	0.12 (0.03–0.31)	0.93 (0.76–0.99)	0.60 (0.15–0.95)	0.54 (0.39–0.69)	1.68 (0.31–9.25)	0.95 (0.79–1.13)
C3 kidney	0.96 (0.80–1.0)	0.68 (0.48–0.84)	0.73 (0.54–0.87)	0.95 (0.75–1.0)	2.99 (1.73–5.15)	0.06 (0.01–0.41)
C1q skin	0.44 (0.24–0.65)	1 (0.82–1.0)	1 (0.62–1.0)	0.67 (0.50–0.80)	∞	0.56 (0.40–0.79)
C1q kidney	0.96 (0.80–1.0)	0.79 (0.59–0.92)	0.80 (0.61–0.92)	0.96 (0.78–1.0)	4.48 (2.19–9.15)	0.05 (0.01–0.35)

PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio, (+): positive, (−): negative.

Conclusion: Deposits of immunoglobulins are more common in kidney than skin. High specificity of LB justifies its use as a diagnostic tool for SLE; the high specificity of LB suggests its utility for SLE diagnosis.

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Prevalence and Prognostic Implications of IgG4 in Membranous Lupus Nephritis. David Herrera Van Oostdam, Marco Ulises Martinez-Martinez, Cuauhtémoc Oros-Ovalle, David Martínez-Galla, Gerardo Tonatiu Jaimes-Piñón, Natalia Alemán-Sánchez and Carlos Abud-Mendoza. Hospital Central & Facultad de Medicina, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico.

Background/Purpose: Patients with membranous lupus nephritis (MLN) have increased risk of thrombosis and different prognosis than other classes of lupus nephritis (LN). Previous studies demonstrated an association of idiopathic membranous nephropathy with IgG4+ against A2-phospholipase receptor. Scarce studies evaluate this fact in LN. To determine the prevalence of IgG4 deposits in renal biopsies of patients MLN (pure or combinations with proliferative LN). A secondary objective was to establish the prognosis of patients with IgG4 deposits.

Methods: Cross-sectional study. We included patients with LN class V or combination (classes V+III or V+IV) according to the 2004 ISN/RPS criteria. All patients with a kidney biopsy from January 1st 2008 to January 30th 2013 were included; all samples were stained with IgG4 using antibody anti-IgG4 (MRQ44, Cell Marque).

Results: We included 65 renal biopsies: 24 class IV+V, 23 class V, and 18 class III+V; 6/65 were IgG4 +. Patients with IgG4+ had a median age of 36 years (IQR 26yr), median of SLEDAI 8 (IQR 4) vs 12 in IgG4- (IQR 8; p 0.7). Patients with IgG4+ had median blood eosinophil count of 70 (IQR 171) vs IgG- 0 (IQR 30; p 0.03). IgG4 deposits were associated with plasmatic cell infiltration in renal biopsy (OR 42, IC 95% 2.4–228; p 0.03). All patients with IgG4+ had renal involvement as the first manifestation of SLE. Treatment: 28% of IgG4+ and 41% of IgG4- of patients received methylprednisolone pulses before renal biopsy, since their first manifestation was a rapidly progressive glomerulonephritis. Renal failure (GFR <60 ml/min) was similar in both groups (43% in IgG4+ and 42% in IgG4-). Fifty percent of patients with IgG4+ who required dialysis at baseline still continued this therapy at 12 months vs 8% of IgG4- patients.

Conclusion: The prevalence of IgG4 deposits in MLN was 10%. All patients who had MLN as their first SLE manifestation were IgG4 +. Patients with IgG4 +LN showed worse prognosis.

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Association of Glomerular Macrophage Phenotypes and Urine Soluble CD163 with Disease Activity in Human Lupus Nephritis. Naotake Tsuboi, Nobuhide Endo, Seiichi Matsuo and Shoichi Maruyama. Nagoya University Graduate School of Medicine, Nagoya, Japan.

Background/Purpose: In addition to the effector roles of classically activated macrophages for tissue injury, recent studies have shown that alternatively activated (M2) macrophages are involved in resolution of inflammation in animal models of kidney disease. But, clinical relevance of M2 macrophage in human disease is largely unknown. The current study aimed to evaluate renal accumulation of macrophage phenotypes in human lupus nephritis (LN) and significance of soluble form of CD163 (sCD163), a representative marker for M2 cells, for LN disease activity.

Methods: Plasma, urine and kidney biopsy samples were obtained from 74 patients with LN. Histological features were classified according to the ISN/RPS LN criteria. Immunohistochemical analyses using anti-human CD68, CD163 or CD204 antibodies were performed for identification of macrophage phenotypes. Concentrations sCD163 and MCP-1 in plasma and urine were measured by ELISA.

Results: Immunohistological analysis in LN glomeluli revealed more than 70% of $CD68^+$ macrophages was merged with $CD163^+$ cells and more than 90% of $CD163^+$ cells was merged with $CD68^+$ cells. However, $CD163^+$ cells appeared to be more than $CD68^+$ cells in interstitum, indicating the different origin of glomerular and interstitial $CD163^+$ macophages. The cell counts of glomerular $CD68^+$, $CD163^+$ or $CD204^+$ macrophages were increased in association with severity of biopsy active index (BAI) score in LN. Interstitial $CD68^+$, $CD163^+$ or $CD204^+$macrophage infiltration correlated with eGFR. Urine sCD163 level showed stronger correlation with the number of glomerular CD163 positive cell counts (r=0.501) and BAI score (r=0.644) than plasma sCD163 levels with both of the above (r=0.289 and r=0.295, respectively). Correlation of urine sCD163 with BAI was comparable to that of urine MCP-1 levels (r=0.592) and was much better than NGAL (r=0.174) in LN.

Conclusion: These results suggest that $CD163^+$ or $CD204^+$ macrophage is the dominant phenotype in kidneys of LN patients, and urine sCD163 level has a potential significance for estimation of disease activity in human LN.

Disclosure: N. Tsuboi, None; **N. Endo**, None; **S. Matsuo**, None; **S. Maruyama**, None.

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Biomarkers of Lupus Nephritis and Ethnic Disparities in Systemic Lupus Erythematosus. Adnan Kiani[1], Laurence S. Magder[2] and Michelle Petri[3]. [1]Johns Hopkins University, Baltimore, MD, [2]University of Maryland, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Lupus nephritis eventually occurs in 50% of Caucasian SLE patients and 75% of African-Americans. African Americans have a more severe presentation of SLE and more often progress to end stage renal disease (ESRD). We have found a number of serum and urine biomarkers that have been associated with lupus nephritis. Therefore, we compared Caucasians and African-Americans with respect to levels of these biomarkers.

Methods: Urinary tumor necrosis factor-like weak inducer of apoptosis (TWEAK), vascular cell adhesion molecule 1 (VCAM-1), monocyte chemoattractant protein 1 (MCP-1) and osteoprotegrin (OPG) were measured in a longitudinal cohort of SLE patients by ELISA (R&D). We analyzed the relationship between these potential urine biomarkers and Caucasian or African-American ethnicity.

Results: Urinary TWEAK levels were higher among Caucasians than African-Americans (p=.033). Urinary VCAM-1, MCP-1 and OPG levels were higher among African-Americans than Caucasians, but the results were not statistically significant (Table 1).

Table 1: Mean (SD) of Each Biomarker by Ethnicity

	TWEAK (p=.033)		VCAM-1(p=0.62)		MCP-1 (p=0.16)		OPG (p=0.21)	
	N	Mean log-Tweak (SD)	N	Mean log OPG (SD)	N	Mean (SD)	N	Mean (SD)
Caucasian	175	0.12 (0.10)	32	2.59 (0.96)	37	3.40 (2.00)	37	3.35 (2.44)
African-American	96	0.09 (0.09)	40	2.80 (0.85)	43	4.19 (1.77)	43	4.17 (1.94)

Conclusion: Systemic lupus erythematosus and lupus nephritis disproportionately affect racial/ethnic minorities. Renal outcome has not improved in African-Americans or in the South in United States. Our results show that not all urine biomarkers are worse in African-Americans. Surprisingly, urinary TWEAK was higher in Caucasians. The others, however, were higher in African-Americans. The identification of ethnicity-specific biomarkers of renal activity would allow ethnicity-specific regimens. Further larger studies are needed to corroborate our findings.

Disclosure: A. Kiani, None; **L. S. Magder**, None; **M. Petri**, None.

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Serum Cystatin C As a Biomarker for Clinical Practice in Patients with Lupus Nephritis. Hua Zhou, Di Lu, Hairong Tang and Lining Wang. The First Hospital of China Medical University, Shenyang, China.

Background/Purpose: Cystatin C has been developed as a novel biomarker of renal function in last decade and thought as more sensitive than serum creatinine (sCr). However, the clinical significance of serum cystatinC (sCysC) in lupus nephritis (LN) has been rarely reported. We aim to compare serum CysC with traditional indices of renal function and SLEDI in LN patients.

Methods: 75 patients with renal biopsy approved LN based on the ISN/ACR 2003 classification criteria were from The First Hospital of China Medical University since 2009 to 2014. sCysC (mg/L), sCr (umol/L), blood urea nitrogen (BUN, mmol/L), glomerular filtration rate (GFR, ml/min) measured by MDRD and EPI equation, serum albumin (sAlb, mg/L) and urinalysis including 24hr total protein (uTP, g/day), albumin (uAlb, g/L), and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) were measured before and 6 months after glucosteroid and cyclophosphamide(CTX) treatment. The correlation between sCysC and each traditional indicator were analyzed by Person and the difference of these indices before and after-treatment was analyzed by student ttest.

Results: sCysC showed closer correlation with traditional indices of renal impairment and SLE activity (Table1). sCysC also displayed a better statistical p value in the response to the treatment of glucosteroid and CTX than sCr and BUN (Table2).

Conclusion: The significance of sCysC should be more emphasized in clinical practice in LN patients. Prospective study needs to be contacted on the effect of early treatment giving based on the increase of sCysC but before sCr rise in large cohort of patients with lupus nephritis.

Table 1. Comparison of sCysC with SCr and BUN in correlation efficiency with disease activity of lupus nephritis

	eGFR(MDRD) r (p value)	eGFR(EPI) r (p value)	sAlb r (p value)	uTP/day r (p value)	uAlb r (p value)	SLEDAI r (p value)
sCysC	−0.73 (p<0.0001)	−0.84 (p<0.0001)	−0.37 (p<0.0001)	0.28 (p<0.0001)	0.40 (p<0.0001)	0.18 (p=0.0088)
sCr	−0.76 (p<0.0001)	−0.85 (p<0.0001)	−0.32 (p<0.0001)	0.21 (p=0.0026)	0.34 (p<0.0001)	0.15 (p=0.0280)
BUN	−0.66 (p<0.0001)	−0.73 (p<0.0001)	−0.23 (p<0.0001)	0.16 (p=0.0244)	0.23 (p=0.0042)	0.12 (p=0.0817)

Table 2. The changes of sCysC and traditional biomarkers before and after the treatment

	sCysC	sCr	BUN	eGFR(MDRD)	eGFR(EPI)	sAlb	uTP/day	uAlb	SLEDAI
Pre-treat	2.2 ± 0.3	123.3 ± 22.6	11.3 ± 2.2	84.8 ± 9.3	81.9 ± 8.1	25.5 ± 1.6	4.9 ± 0.6	4.8 ± 1.1	20.4 ± 1.4
Post-treat	1.6 ± 0.2	85.8 ± 14.6	8.4 ± 1.4	99.9 ± 7.6	96.4 ± 6.3	36.9 ± 1.3	2.5 ± 0.9	1.2 ± 4.5	7.3 ± 0.8
P value	P<0.0003	P = 0.0142	P = 0.1476	P = 0.0506	P = 0.0093	P<0.0001	P = 0.0079	P = 0.0401	P<0.0001

Disclosure: H. Zhou, None; **D. Lu**, None; **H. Tang**, None; **L. Wang**, None.

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Thrombotic Microangiopathy and Poor Renal Outcome in Lupus Patients Is Not Associated with Antiphospholipid Syndrome and/or Other Lupus Conventional Features. Gabriela Hernandez-Molina, Paola García-Trejo, Norma Uribe and Antonio R. Cabral. Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico.

Background/Purpose: To assess acute thrombotic microangiopathy (aTMA) and chronic vascular lesions (cTMA) in lupus nephropathy and to evaluate their association with extrarrenal lupus features, antiphospholipid (APS) clinical and/or serological criteria, low complement and renal survival.

Methods: We studied consecutive lupus patients (2008–2012) according to the following inclusion criteria: renal biopsy, at least two determinations of aCL (IgG-IgM), anti-b_2GP-I (IgG-IgM), lupus anticoagulant and ≥1 year of post-biopsy follow-up. We excluded patients with overlap syndromes, diabetes mellitus, uremic hemolytic syndrome, thrombotic thrombocytopenic purpura and malignant hypertension. A blinded nephropathologist evaluated all biopsies. aTMA was defined as a fibrin thombi in arterioles and glomeruli and cTMA as arterial fibrous intimal hyperplasia and/or organized thrombi and/or fibrous occlusion and/or subcapsular ischemic cortical atrophy. We retrospectively collected demographic and clinical data (lupus and APS features, immunosuppressors and anticoagulant use), hypocomplementenemia as well as renal survival assessed as chronic dialysis. We used X^2, t-student and U-Mann Whitney test, plotted survival curves and Cox regression analysis.

Results: We studied 90 lupus kidney biopsies from patients with disease duration at the time of the biopsy of 5.9 years and a median post-biopsy follow-up 2.4 of years (range 1–6.5). Eleven patients (12.2%) had cTMA and 3 (3%) aTMA. There were no differences in age, lupus duration, hypertension, immunosuppressors use, extra-renal lupus features (arthritis, vasculitis, serositis, hematologic, neurologic, Raynaud, cutaneous) and APS prevalence between patients with cTMA or without cTMA. We did not find any difference in the presence of low C3 (63% vs. 62%), low C4 (72% vs. 73%) nor in the frequency of aCL IgG (27% vs 30%), anti-β_2GP1 IgG (36% vs 46%), anti-β_2GP1 IgM (22% vs 40%) and AL (20% vs13%) among patients with and without cTMA, respectively. Patients with cTMA had less frequently aCL-IgM (27% vs 66%, p=0.02), a higher prevalence of chronic dyalisis (54.5% vs 24% p=0.06), a higher frequency of class IV nephropathy (100% vs 40%, p=0.01) also with a higher activity index (7.5 vs 2, p=0.03). At four years of follow-up, 28% of cTMA patients and 62% non-cTMA patients were free of dialysis (log Rank p=0.03). At the Cox analysis, cTMA was associated with chronic dialysis (RR 2.9, CI 95% 1.1–8.1, p=0.03).

Conclusion: cTMA confered a poor renal outcome. Unlike published studies, cTMA was not associated with lupus or antiphospholipid clinical or serological features. Other factors hitherto not studied are involved in the pathogenesis of this histopathological feature.

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Lupus Nephritis: Clinicopathological Correlation in 126 Biopsies. Milagros Ricse[1], Javier Narváez[2], Gloria Albert[1], Paula Estrada[1], Helena Borrell[1], Eugenia de Lama[1], Xavier Fulladosa[1], Manel Rubio Rivas[1], Olga Capdevila[1], Francesca Mitjavila[1], Xavier Juanola[3] and Joan Miquel Nolla[1]. [1]Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, [3]University Hospital Bellvitge, Barcelona, Spain.

Background/Purpose: To analyze the correlation between clinical and laboratory data and type of histological injury in a cohort of patients with lupus nephritis (LN).

Methods: The sample comprised 243 patients with SLE treated between 1980 and 2013 at a tertiary university hospital that does not attend pediatric populations. Patients were registered in a specific database. Patients diagnosed with LN classes 2–5 according to the WHO classification or the ISN/RPS classification (in use since 2004) were selected for analysis. In each case, the presence of arterial hypertension, renal insufficiency (RI), nephrotic syndrome (NS), hematuria, and cylindruria was assessed at the time of the biopsy; 24-h urine protein value was also recorded.

The specificity, sensitivity, PPV, NPV, LR +, LR-, and accuracy for each of the clinical and laboratory data in order to diagnose the different histological types of LN.

Results: The diagnoses were: **a)** *Class II Mesangial proliferative lupus nephritis*, 45 cases (35%); **b)** *Class III Focal lupus nephritis*, 16 (13%); **c)** *Class IV Diffuse lupus nephritis* 49 (39%), and d) *Class V Membranous lupus nephritis*, 16 (13%).

The mean levels of proteinuria were: a) class II; 1.62 g/24 h; b) class III: 1.53 g/24 h; c) class IV; 2.12 g/24 d) class V; 5.15 g/24 h. The only significant differences observed were between LN class V and the other histological types of LN. Five patients had proteinuria below 0.5 g/24 h (3 class II and 2 class IV) and 12 had proteinuria 0.5–1 g/24 (3 class II, 3 III, 4 IV and 2 class V).

The discriminative values of other clinical and laboratory data for the diagnosis of the different types of LN are shown in Table 1.

	Sensitivity	Specificity	PPV	NPV	LR+	LR−	Accuracy
CLASS II	–	–	–	–	–	–	–
Renal insufficiency	4%	83%	13%	61%	0.26	1.16	0.547
Arterial Hypertension	4%	78%	10%	59%	0.20	1.23	0.515
Nephrotic syndrome	18%	54%	18%	54%	0.39	1.51	0.412
Hematuria	69%	40%	39%	70%	1.14	0.79	0.500
Cylindruria	4%	81%	12%	61%	0.24	1.17	0.539
CLASS III	–	–	–	–	–	–	–
Renal insufficiency	6%	86%	6%	86%	0.46	1.09	0.761
Arterial Hypertension	6%	83%	5%	86%	0.36	1.13	0.730
Nephrotic syndrome	6%	60%	2%	81%	0.16	1.56	0.531
Hematuria	56%	35%	11%	85%	0.87	1.23	0.380
Cylindruria	13%	87%	13%	87%	0.98	1.00	0.777
CLASS IV	–	–	–	–	–	–	–
Renal insufficiency	20%	94%	67%	65%	3.14	0.85	0.650
Arterial Hypertension	35%	96%	85%	70%	8.90	0.68	0.722
Nephrotic syndrome	53%	75%	58%	72%	2.15	0.62	0.666
Hematuria	61%	35%	38%	59%	0.94	1.11	0.452
Cylindruria	22%	94%	69%	65%	3.46	0.83	0.658
CLASSV	–	–	–	–	–	–	–
Renal insufficiency	19%	88%	19%	88%	1.59	0.92	0.793
Arterial Hypertension	0%	82%	0%	85%	0.00	1.22	0.714
Nephrotic syndrome	63%	68%	22%	93%	1.96	0.55	0.674
Hematuria	63%	36%	13%	87%	0.98	1.03	0.396
Cylindruria	13%	87%	13%	87%	0.98	1.00	0.777

Parameters with a high LR + (greater than 3) and an acceptable diagnostic accuracy were the presence of RI, arterial hypertension and cylindruria in LN class IV. The presence of NS in classes IV and V also had a relatively high LR +. However, at the time of diagnosis or during follow-up, eight patients with LN class II had NS (excluding those patients with nephrotic-range proteinuria undergoing class transformation). Although uncommon, the presence of cylindruria was also observed in LN class II (one patient), class III (2) and type V (2).

In LN class II, none of the clinical and laboratory data had a LR- high enough (<0.5 to 0.3) to be a useful parameter to discard it.

Conclusion: In LN, only class IV and to a lesser extent class V present a good correlation between the clinical/ laboratory and histological data. In general, clinical/laboratory data cannot predict the type of histological lesion. In our experience, more than half of patients with mild proteinuria (below 1 g/24 h) presented advanced forms of LN (classes III, IV or V).

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Rate of Histological Transformation to Higher Grade Nephritis in Class II Mesangial Proliferative Lupus Glomerulonephritis. Andrea Zacarias[1], Javier Narváez[2], Gloria Albert[1], Milagros Ricse[1], Paula Estrada[1], Melany Pestaña[1], Chema Mora[1], Jesus Rodriguez Moreno[1], Xavier Fulladosa[1], Manel Rubio Rivas[1] and Joan Miquel Nolla[1]. [1]Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain.

Background/Purpose: Class II mesangial proliferative lupus nephritis has generally been considered a mild form of the condition, with a good response to glucocorticoid treatment. However, some recent studies have questioned this assumption after observing high rates of recurrence and histological transformation to more serious classes. Our aim was to analyse the baseline clinical features and clinical response at one year after treatment in patients with mesangial proliferative lupus nephritis (MPLN) identified at their first renal biopsy.

Methods: The sample comprised 243 patients with SLE treated between 1980 and 2013 at a tertiary university hospital that does not attend pediatric populations. Patients were registered in a specific database (ACHILLES Project). Patients with renal biopsy-confirmed MPLN according to the WHO classification (created in 1982 and modified in 1995, in use until 2004) or the ISN/RPS classification (in use since 2004) were selected for analysis. Data were collected ambispectively. Patients who presented remission (partial or complete) after completing induction therapy were considered "responders". "Non-responders" were those who presented "no response" (complete or partial absence of response of renal disease after completing induction therapy), class transformation or death due to lupus nephritis.

Results: Forty-five patients (36 women) were identified with a mean age (SD) at the time of diagnosis of nephritis of 39.5 (12.3) years. The median time between diagnosis of SLE and the development of nephritis was 33 months. Proteinuria above 0.5 g/24h was found in 42 (93%) patients, hematuria in 31 (69%), cylindruria in one (2%), mild renal insufficiency in two (4%), and hypocomplementemia in 22 (49%). Mean proteinuria was 1.62 (1.03) g/24 h.

Eight patients had nephrotic syndrome (17%) at the time of diagnosis or during follow-up, excluding patients with nephrotic range proteinuria undergoing class transformation. In the diagnostic biopsy, the mean activity index was 2.09 (1.6) and the chronicity index 0.5 (1.8).

All patients were treated with prednisone (dose 0.5 to 1 mg/kg/day). Thirty-three patients (73%) also received treatment with hydroxychloroquine.

At one year after biopsy, 30 (67%) patients achieved complete remission, seven (16%) partial remission and eight (17%) were non-responders. In six of the eight non-responders a second renal biopsy showed transformation to a higher grade of nephritis (class IV in three cases and class V in the other three), resulting in poor renal and poor overall outcome (one of these patients died at six months of follow-up due to SLE lupus activity in the context of transformation to class IV).

Conclusion: In our cohort of patients with MPLN, the rate of non-responders at one year following treatment reached 17%, and was associated with a high rate of transformation to higher grade nephritis. Our data highlight that renal biopsy should be repeated early in patients who fail to respond to glucocorticoid treatment in order to identify those who may require intense immunosuppressive therapy.

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Does Advanced Age Influence the Type of Renal Injury and the Prognosis of Lupus Nephritis? Eulalia Armengol[1], Javier Narváez[2], Helena Borrell[1], Sergi Heredia[1], Milagros Ricse[1], Eva Benavent[1], Alex Roset[1], Carmen Gomez Vaquero[1], Joan Torras[1], Francesca Mitjavila[1] and Joan Miquel Nolla[1]. [1]Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease that usually affects young people. Several reviews have shown that age may have an effect on the clinical expression of the disease and have suggested that in terms of its presentation and clinical course late-onset SLE is generally less severe. Although there is no unanimous agreement, most authors take late onset SLE to refer to disease occurring after

age 50. Our objetive was to examine whether advanced age influences the type of histological lesions and prognosis of lupus nephritis.

Methods: The sample comprised 243 patients with SLE treated between 1980 and 2013 at a tertiary university hospital that does not attend pediatric populations. Patients were registered in a specific database. Patients with lupus nephritis confirmed by renal biopsy and follow-up time of at least two years (n = 79) were selected for analysis. Patients were divided into two groups according to age: over 50 (n = 30) and under 50 (n = 49). "Responders" were defined as patients who presented remission (partial or complete) after completing induction therapy, and "non-responders" were patients in whom no improvement was observed in the analytical parameters, those with histological transformation, and those who died of causes related to nephritis.The Student t test was used to compare continuous variables between groups, or the Mann-Whitney test when variables were not normally distributed. To compare qualitative variables the chi-square or Fisher's exact test was used when the expected frequency was less than 5. The level of significance was set at $p < 0.05$.

Results: In the 79 patients (64 women), mean age at the time of diagnosis of nephritis was 45 years ± 14 (range 17–80) and mean time since onset of SLE was 15.9 months (range 0 – 456). In 81% (64/79) of cases, renal disease was present at the time of diagnosis or during the first year of follow-up. The mean SLEDAI score was 15 ± 7.6. The main results of the comparative study between age groups are shown in the following table:

	Age ≤ 50 years (N = 49)	Age > 50 years (N = 30)	*p*
Sex (male/female)	11/38	4/26	*0.268*
Evolution course of SLE in months (median)	2 (0–230)	1 (0–456)	*0.504*
Lupus nephritis Class II	7 *(14%)*	7 *(23%)*	*0.363*
Lupus nephritis Class III	10 *(20%)*	4 *(13%)*	*0.367*
Lupus nephritis Class IV-S	12 *(24.5%)*	5 *(17%)*	*0.349*
Lupus nephritis Class IV-G	13 *(26.5%)*	9 *(30%)*	*0.850*
Lupus nephritis Class V	7 *(14%)*	5 *(17%)*	*0.852*
Activity Index (mean ± SD)	7.8 ± 4.5	6 ± 4	*0.151*
Chronicity Index(mean ± SD)	1.5 ± 1.5	1.3 ± 1.9	*0.467*
Responders/No responders	40 *(82%)*/9 *(18%)*	24 *(80%)*/6 *(20%)*	*0.121*
Development of renal insufficiency	7 *(14.3%)*	3 *(10%)*	*0.114*

No significant differences were observed between age groups in either the type of renal injury or prognosis.

With regard to treatment, no differences were observed in the percentage of patients who were given hydroxychloroquine, corticosteroids or immunosuppressants, but the use of statins ($p = 0.038$) and ACE inhibitors ($p = 0.033$) was higher in the over 50s group.

Conclusion: Advanced age does not determine the type of histological lesion, nor does it appear to be a poor prognostic factor in lupus nephritis.

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Renal Thrombotic Microangiopathy in Systemic Lupus Erythematosus: Novel Risk Factors and Clinical Outcomes. Ana Barrera-Vargas[1], Rodrigo Rosado-Canto[2], Javier Merayo-Chalico[1], Jorge Alcocer-Varela[1] and Diana Gómez-Martín[1]. [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Instituto Nacional de Ciencias Médicas y Nutrición, Mexico City, Mexico.

Background/Purpose: Thrombotic microangiopathy (TMA) is characterized by microvascular occlusion, systemic or intrarenal platelet aggregation and mechanical injury to erythrocytes. It is a pathological endpoint that results from a disruption of the normal platelet–endothelial interface. TMA is one of the renal vascular lesions which can be found in systemic lupus erythematosus (SLE). The prevalence of renal TMA in SLE varies broadly between studies (8.1–24.3%), and there has been controversy regarding its prognostic value, as well as its association with antiphospholipid (APL) antibodies. The aim of this study was to evaluate risk factors and clinical outcomes for renal TMA in SLE patients.

Methods: A retrospective, single-center study was performed. Renal biopsies from 245 SLE patients between 2008 and January 2014 were studied. We included patients with renal TMA, as well as controls adjusted by glomerulonephritis class, glomerular filtration rate (GFR), activity and chronicity indexes, and follow-up time. The variables that were measured included: autoantibody profile; hypertension, disease activity, SLEDAI, C3 and C4 levels, leukocyte and lymphocyte count, treatment and GFR at the time of the biopsy; GFR, SLEDAI and treatment during follow-up. Differences between groups were analyzed by Student t test or Mann-Whitney U test. Association between variables was assessed by OR (95% CI). Multivariate analysis was performed by binary logistic regression model.

Results: Twenty-three patients with renal TMA and 21 controls were included. TMA prevalence was 9.38%. 90.9% of subjects were female; mean age was 26.04 years in the TMA group and 27.9 years in controls. Mean follow-up was 25.56±14.39 months. At the time of the biopsy, GFR (ml/min/1.73m^2) was 33.6±8.33 in the TMA group and 37.91±7.5 in controls; 56% of patients in the first group and 42.8% in the second required dialysis at that time. Two patients in the TMA group were diagnosed with thrombotic thrombocytopenic purpura (TTP); none of the others had clinical features suggestive of systemic TMA. Lymphopenia, platelet count, higher mean arterial pressure (MAP) and anti-Ro/SSA antibodies were associated with TMA. There was no association with APL syndrome or antibody positivity. There were no differences in SLEDAI score, GFR, end-stage renal disease (ESRD) or mortality between both groups throughout the follow-up period. At the end of follow-up, ESRD rates were 43.4% in the TMA group, and 42.8% in controls. After multivariate analysis, variables that remained significantly associated with renal TMA were: lymphopenia < 1000 cells/uL (OR 10.75, 95% CI 1.34–85.86, p=0.025), anti-Ro/SSA antibodies (OR 9.007, 1.49–54.11 95% CI, p=0.016), and MAP (OR 0.97, 95% CI 0.959–0.994, p=0.009).

Conclusion: Lymphopenia and anti-Ro/SSA positivity were independent risk factors for renal TMA in SLE patients. This association could be related to their potential role in endothelial dysfunction and damage. Outcomes were similar for patients with the same GFR and biopsy characteristics, regardless of the presence of TMA.

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The Clinical Relevance of a Repeat Biopsy in Lupus Nephritis (LN) Flares. Milagros Ricse[1], Javier Narváez[2], Gloria Albert[1], Paula Estrada[1], Sergi Heredia[1], Andrea Zacarias[1], Helena Borrell[1], Eulalia Armengol[1], Xavier Fulladosa[1], Joan Torras[1], Olga Capdevila[1], Francesca Mitjavila[1] and Joan Miquel Nolla[1]. [1]Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain.

Background/Purpose: Renal biopsy is the gold standard for assessing renal activity and hence guiding treatment. Whether a repeat renal biopsy is helpful during flares of LN remains unclear. In the present study, we retrospectively reviewed LN patients who had more than one renal biopsy, in the hope of finding the clinical advantage of repeat biopsy

Methods: The sample comprised 243 patients with systemic lupus erythematosus (SLE) treated between 1980 and 2013 at a tertiary university hospital that does not treat pediatric populations. The patients were registered in a specific database. From a total of 126 patients with LN, we selected those who underwent 2 renal biopsies for analysis. Renal biopsies were evaluated according to the WHO classification or the ISN/RPS classification (in use since 2004).

Results: We identified 28 SLE patients with LN for whom it was possible to compare reference and repeat biopsies. In total, 56 renal biopsies were considered. Overall, in 14 patients (50%), paired biopsies showed changes in the pathological pattern. Table 1 shows the pathological classification on repeat biopsy:

Reference biopsy	Repeat biopsy
Class II Mesangial LN N=9	**1 switched to Class I**
	2 no shift in pathological class
	6 switched to higher grade nephritis (Class IV: 3 cases, Class V: 3 cases)
Class III Focal LN N=4	**2 no shift in pathological class**
	2 switched to higher grade nephritis (Class IV: 1 case, Class V: 1 case)
Class IV Diffuse LN N= 13	**1 switched to Class II and 3 to Class III**
	9 no shift in pathological class
Class V Membranous LN N=2	**1 switched to Class IV**
	1 no shift in pathological class

In the subgroup of patients with Class II mesangial LN, the repeat biopsy showed a transformation to a higher grade of nephritis (Class IV or V) in 67% of the cases.

In contrast, in most patients (65%) with proliferative classes (III and IV), there was no shift in histological class on repeat biopsy. Of the 2 patients with Class V membranous LN, only 1 changed to a proliferative class. Clinically significant class switches during LN flares were more frequent in patients with non-proliferative lesions (Classes II and V) than those with proliferative lesions (classes III and IV) in their reference biopsy ($p<0.05$).

The mean renal activity index on first biopsy was 8.85 (SD: 4.43) and on repeat biopsy it was 7.26 (SD: 3.84) ($p = 0.315$). The mean chronicity index for the first biopsy was 1.95 (SD: 2.53) and for the repeat biopsy it was 2.52 (SD: 2.39) ($p<0.001$).

The pathological transition could not be predicted by any clinical characteristics. After the repeat biopsy, 10 (36%) of patients had a change of treatment regimen: 8 received an increase in immunosuppression; while in 2 cases immunosuppressive therapy was decreased or stopped.

Conclusion: Pathological conversion was highly prevalent (50%) in patients with LN. Overall, 66% of cases with class II mesangial LN in a reference biopsy showed transformation to a higher grade of nephritis (class IV or V) on repeat biopsy, so early repeat biopsy is advisable for this subgroup of patients. In contrast, in most patients (65%) with proliferative Classes (III and IV) in a reference biopsy, there was no shift in histological class on repeat biopsy.

Repeat biopsy might be helpful in guiding treatment, both to identify those patients for whom it is necessary to intensify immunosuppression therapy, and to avoid unnecessary increased immunosuppression therapy in others.

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A Systematic Review and Network Meta-Analysis of Cyclophosphamide and Mycophenolate Mofetil in Lupus Nephritis. Jasvinder Singh[1], Ahmed Kotb[2], Alomgir Hossain[2] and George A. Wells[3]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Ottawa, Ottawa, ON, [3]Univ of Ottawa Faculty of Med, Ottawa, ON.

Background/Purpose: Patients consider common side effects of medications prominently in treatment decision-making. To our knowledge, with the exception of a Cochrane review that analyzed data up to April 2012, limited or no information exists on comparisons of common, non-fatal side effects of immunosuppressive medications used for the treatment of lupus nephritis. Our objective was to perform an up to date systematic review and network meta-analysis (NMA) to compare harms/safety of cyclophosphamide (CYC) and mycophenolate mofetil (MMF) for the treatment of lupus nephritis.

Methods: Cochrane and ACR librarians performed an updated search for immunosuppressive medications for lupus nephritis up to September 2013 updating the data from the systematic review that formed the basis of the 2012 ACR lupus nephritis treatment recommendations and the published Cochrane Review. We abstracted safety data related to the following harms/adverse events (AEs): alopecia, nausea, ovarian failure, endocrine AEs, cytopenia and leucopenia. Bayesian network meta-analyses (NMA) were conducted. A binomial likelihood model, which allows for the use of multi-arm trials was used. Informed priors were assigned for basic parameters and odds ratios, as well as risk ratios and risk differences, and 95% credible intervals were modeled using Markov chain Monte Carlo methods. Brooks-Gelman-Rubin plots were used to assess model convergence. Model fit was examined using the deviance information criterion (DIC) and the residual deviance. The degree of inconsistency was assessed by comparing statistics for the deviance and deviance information criterion in fitted consistency and inconsistency models. In further sensitivity analyses, fixed effects models and models using vague priors were also conducted.

Results: Compared to MMF, CYC was associated with higher risk of alopecia by almost 4-fold, leucopenia by 3-fold and ovarian failure by 6-fold (**Table 1**). The higher risk of cytopenia with CYC almost reached statistical significance (**Table 1**). The risk of nausea and endocrine side effects did not differ significantly between CYC and MMF. Risk differences between CYC and MMF are provided in **Table 1**.

Conclusion: Our systematic review and meta-analysis identified several important differences between the harms of CYC and MMF in patients with lupus nephritis. These findings provide clinicians and patients with the magnitude of differences in these common side effects and can help patients with treatment decision-making.

Table 1: Comparison of cyclophosphamide (CYC) vs. mycophenolate mofetil (MMF)

Comparison	RR (95% CI)	Risk Difference (95% CI)
Alopecia, CYC vs. MMF	**3.69 (1.77, 6.86)**	**17.16 (4.79, 34.94)**
Nausea, MMF vs. CYC	0.37 (0.14, 1.10)	−2.32 (−10.86,0.27)
Endocrine AEs*, CYC vs. MMF	1.52 (0.70, 3.42)	2.04 (−1.72, 8.58)
Cytopenia, CYC vs. MMF	1.62 (0.99, 2.76)	8.58 (−0.13, 19.77)
Leucopenia, CYC vs. MMF	**2.82 (1.63, 4.64)**	**9.24 (3.48, 17.13)**
	Peto's odds ratio (95% CI)	
Ovarian failure, CYC vs. MMF	6.36 (2.59, 15.63)	–

*Diabetes and hyperglycemia; **significant odds ratios are in bold**

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1661

Are Repeat Renal Biopsies Important in Managing Lupus Nephritis Flares? Angela Pakozdi, Ravindra Rajakariar, Michael Sheaff and Dev Pyne. Barts Health NHS Trust, London, United Kingdom.

Background/Purpose: Lupus nephritis (LN) is the major cause of morbidity and mortality in patients with systemic lupus erythematosus. The role of repeat kidney biopsies (RB) to guide treatment or to predict outcome and prognosis has been controversial. In this retrospective study we focused on histological characteristics of RBs and aimed to identify any clinical variables useful to predict histological changes.

Methods: In a large single-centre cohort of 257 patients from 1988–2014 with biopsy proven LN, 58 (23%) had two or more biopsies (a total of 68 RBs). LN classes based on glomerular pathology were defined according to the ISN/RPS classification. Clinical and laboratory data were obtained from electronic records of patients.

Results: The median time between initial and RB was 33 months [IQR, 15–84]. Caucasians (n=8) had a lower RB rate of 16% compared to blacks (n=37, 33%; p=0.010). Indication for RB was worsening proteinuria (n=38, 71%; of which 23 had associated rising creatinine, 61%), rise in serum creatinine alone (n=6, 11%) and lack of treatment response (n=9, 17%) defined as <50% reduction in proteinuria. At time of RB, 25 (78%) had raised dsDNA, 33 (73%) had low complements. LN class transition occurred in 31 (48%), most commonly from class II or V to III or IV (n=11, 36%). 6 RB (6.8%) showed inactive lesions either due to FSGS or advanced sclerosing LN. 42 (65%) had a change in their treatment regime. Immunosuppression was more likely to be escalated in case of a class switch (87% vs. 38%, p=0.002). The histological transition could not be predicted by any serological or biochemical variables.

Conclusion: Over a 1/3 of our LN patients showed histological transition to a more aggressive class, based on which the majority (87%) had treatment escalation. Histological transition could not be predicted by clinical values. Hence, we conclude that RB remains an important tool to guide management of selected patients with LN, in particular those with initial class II or V who flare.

Disclosure: A. Pakozdi, None; **R. Rajakariar**, None; **M. Sheaff**, None; **D. Pyne**, None.

1662

Lupus Nephritis Patients Who Stopped Maintenance Immunosuppressive Therapy without Relapse. Robert S. Katz[1] and Lauren Kwan[2]. [1]Rush Medical College, Chicago, IL, [2]Rheumatology Associates, Chicago, IL.

Background/Purpose: The current guidelines from both the American College of Rheumatology and the American Society of Nephrology suggest initiating induction therapy for Class III and Class IV lupus nephritis with cyclophosphamide or mycophenolate mofetil and then starting maintenance therapy, generally mycophenolate mofetil or azathioprine. However, the duration of maintenance therapy is not specified in the guidelines. Many patients with lupus nephritis take these maintenance medications indefinitely.

Methods: We reviewed the charts of lupus nephritis patients in a rheumatology office practice whose biopsies showed Class III or Class IV lupus nephritis. All had been treated with mycophenolate mofetil or cyclo-

phosphamide and then switched to maintenance therapy. We describe the course of 6 patients who stopped their immunosuppressive maintenance therapy and 2 patients who never began maintenance immunosuppressive treatment.

Results: 6 patients stopped their maintenance immunosuppressive therapy for Class III or Class IV lupus nephritis. One patient with class III and one patient with class IV lupus nephritis never started it. All are still doing well without a renal or systemic disease flare up. The reasons these patients stopped the maintenance therapy included fertility and pregnancy concerns, doubt that continuing maintenance medicine was necessary, and lack of compliance.

Table 1.

Gender	Age	Renal Class	Maintenance Drug	Length on Maintenance Medication	Current time off Maintenance Medication	Current Outcome of Nephritis
F	58	III	Mycophenolate Mofetil	16 Months	2 1/2 years	Remission
F	45	III	Mycophenolate Mofetil	4 Months	4 months	Remission
F	31	III	Mycophenolate Mofetil	18 Months	3 years	Remission
F	27	III	No Maintenance	0	2 years	Mildly active
F	57	IV	No Maintenance	0	6 months	Remission
F	60	III	Azathioprine	1 year		Remission
F	47	III	Mycophenolate Mofetil	2 years	1 year	Remission
F	31	IV	Azathioprine	1 1/2 years	6 months	Remission

Conclusion: Previous studies have shown that patients with class III and IV lupus nephritis, who go into remission with induction therapy, with normalization of creatinine and a significant reduction of proteinuria, are likely to stay in remission. It is unknown whether they need indefinite maintenance therapy. The lupus patients described here were able to discontinue maintenance immunosuppressive therapy, or never began it, and are doing well without relapse of their nephritis. We did not find any Class III or IV lupus nephritis patients who flared after discontinuing immunosuppressive treatment in this small sample.

This study suggests that the duration of treatment with maintenance immunosuppressive therapy should be evaluated and guidelines amended to address the duration of maintenance medication based on patient responses to induction treatment.

Disclosure: R. S. Katz, None; **L. Kwan**, None.

1663

Influence of Ethnicity on Efficacy of Current Immunosuppressive Protocols in Proliferative Lupus Nephritis. Angela Pakozdi, Ravindra Rajakariar, Michael Sheaff and Dev Pyne. Barts Health NHS Trust, London, United Kingdom.

Background/Purpose: Lupus nephritis (LN) is a major complication of systemic lupus erythematous (SLE) and prevalence is estimated to be 50–60%. Recently, variable responses to induction regimes have been observed in different ethnic groups with Hispanics and Blacks tending to respond better to Mycophenolate Mofetil (MMF) than intravenous cyclophosphamide (CYC) (1). Limited data is available for Asians from the Indian Subcontinent. Our aim was to examine retrospectively the influence of ethnicity on LN outcome in our large single centre cohort of SLE patients.

Methods: We identified 119 SLE patients with biopsy proven LN diagnosed 1992–2013 from our electronic database. LN classes based on glomerular pathology were defined according to the ISN/RPS classification. Complete remission (CR) was defined as 24-hour proteinuria <0.5g. Clinical and laboratory data were obtained from patient records.

Results: Of 119 LN patients, 80 (67%) had proliferative LN (class III or IV, of which 21% had concomitant membranous, class V lesions). Among those, 16 were male (20%) and 64 female (80%). 35 were African black or Afro-Caribbean (44%), 28 were Asians from the Indian Subcontinent (35%), and 17 were Caucasians (21%). The median age was 27 years (IQR, 20–38) at SLE diagnosis and 31 years (IQR, 24–40) at LN diagnosis. There was no difference in baseline characteristics among ethnic groups, apart from increased frequencies of ENA antibodies in Blacks compared to Caucasians, specifically RNP (n=18, 54.5% vs. n=2, 11.8%; p=0.000) and Sm antibodies (n=13, 39% vs. n=1, 6%; p=0.002). The main induction regimes were CYC given either intravenously or orally (n=49, 61%; with a median 6-month cumulative dose of 6.3g, IQR, 3–9), or MMF (n=25, 31%; with target dose 3g/day). All patients had a tapering course of high dose corticosteroids. At 6 months, CR was achieved in 13 patients (46%) in the Asian subgroup, in 10 (31%) in the Black subgroup and in 8 (47%) in Caucasians. At 24 months, 16 Asians (67%), 14 Blacks (61%) and 10 Caucasians (83%) reached CR. At 6 months, MMF achieved a higher rate of CR in Blacks than CYC (n=7, 70% vs. n=3, 23%, respectively; p=0.024) and showed a trend in Asians (n=6, 75% vs. n=7, 41%, respectively; p=0.114). In contrast, in Caucasians, CR rate was similar in both treatment arms at 6 months (n=5, 56% in CYC vs. n=3, 50% in MMF, p=0.833). At month 24, there was a non-statistical trend for greater response to MMF than CYC in Asians and Blacks, but not in Caucasians. Up to date, 20 patients (25%) have developed end-stage kidney disease with the highest rate in Blacks (n=13, 37%). Severe infections tended to be more common in patients treated with CYC than MMF (n=7, 15% vs. n=2, 8%; p=0.642). CYC caused gonadal toxicity in 6 patients (14%).

Conclusion: Current ACR guidelines (2) recommend using MMF rather than CYC for LN class III/IV induction therapy in African Americans and Hispanics. Our retrospective study provides supportive evidence that MMF tends to achieve higher remission rates in Blacks, and is at least as effective as CYC in Caucasians and Asians from the Indian Subcontinent, with fewer adverse events.

1. Isenberg D, Rheumatology 2010;49:128–140
2. Hahn BH, Arthritis Care Res 2012;64(6):797–808

Disclosure: A. Pakozdi, None; **R. Rajakariar**, None; **M. Sheaff**, None; **D. Pyne**, None.

1664

Novel Risk Factors for Systemic Lupus Erythematosus (SLE) Flares in Patients with End-Stage Renal Disease: Is SLE in Patients with End-Stage Renal Disease a "sleeping beauty"? Jorge Alcocer-Varela[1], Mariana Quintanar[2], Javier Merayo-Chalico[1], Ana Barrera-Vargas[1] and Diana Gómez-Martín[1]. [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico.

Background/Purpose: Renal involvement in systemic lupus erythematosus (SLE) is frequent, and a high percentage of patients (~15%) develop end-stage renal disease (ESRD) even with optimal treatment. It is widely supposed that ESRD in these patients leads to an indefinite remission period. Currently, information about SLE activity in patients with renal replacement therapy is quite scant. The aim of this study was to identify risk factors for SLE flares in patients with ESRD.

Methods: A retrospective, case-control study was performed in a tertiary care center in Mexico City from 1993 to 2014. Cases (n=50) were patients with SLE diagnosis (at least 4 American College of Rheumatology criteria) who had any extra-renal flare (any increase in systemic lupus erythematosus activity index –SLEDAI- score that required the modification of immunosuppressive treatment) after at least three months of renal replacement therapy (RRT). Controls (n=50) were patients with SLE and ESRD but without any flares, studied during the same period of time as cases (±3 months). Association between variables was calculated by X^2 test and OR (95% CI). Multivariate analysis was performed by logistic regression. p values less than 0.05 were considered statistically significant.

Results: There was a higher percentage of men in the case group (24 vs 8%, p=0.029). At the time of the SLE flare, patients had required dialysis for a mean period of 23.1±3.6 months. There was no difference in the time period between SLE diagnosis and the beginning of dialysis in both groups (p=0.06). Variables previous to the exacerbation which had significant differences in the univariate analysis are showed in Table 1. Variables that remained significant after multivariate analysis were: history of fever secondary to SLE [OR 3.20 95%CI 1.02–10.04, p=0.046], history of hematologic activity [OR 4.02 95%CI 1.02–15.79, p=0.046], low C4 levels prior to the flare [OR 19.62 95%CI 3.72–103.3,p<0.001], anticardiolipin IgM positivity [OR 4.32 95% CI 1.07–17.43, p=0.040], presence of lupus anticoagulant [OR 9.38 95% CI 1.26–69.79, p=0.029], age at the beginning of renal replacement therapy [OR 0.92 95%CI 0.88–0.96, p<0.001], and adjusted SLEDAI score (excluding renal items) three months prior to exacerbation [OR 0.57 95%CI 0.37–0.87, p=0.010].

Conclusion: Our findings suggest that immunologic parameters, such as low C4 levels and antiphospholipid antibodies might play a key role in predisposing to flares in patients with SLE and ESRD. Moreover, patients who initiate RRT at older age and who have had persistent disease activity are at a higher risk for extrarenal flares during follow-up.

Table 1. Variables associated with development of (univariate analysis)

Prior to exacerbation	OR	95% CI	p value
History of different types of activity			
Hematologic	10.2	2.20–47.90	0.001
Hemolytic anemia	6.76	1.41–32.36	0.007
Persistent thrombocytopenia (<150,000/uL)	3.16	1.03–9.68	0.037
Persistent leukopenia (<3,000/uL)	10.28	2.20–47.90	0.001
Persistent lymphopenia (<1,000/uL)	2.97	1.30–9.68	0.009
Serositis	2.57	1.12–5.89	0.024
Previous Serology			
Lupus anticoagulant	6.76	1.41–32.36	0.007
Anticardiolipin IgM	2.95	1.14–7.64	0.023
Low C4 levels	4.93	1.98–12.26	<0.001
Previous Treatment (Three months)			
Azathioprine	13.82	1.71–111.72	0.002

Disclosure: J. Alcocer-Varela, None; **M. Quintanar**, None; **J. Merayo-Chalico**, None; **A. Barrera-Vargas**, None; **D. Gómez-Martín**, None.

1665

Efficacy Versus Safety of Prednisone in Lupus Nephritis Since 1988. Tanmayee Bichile[1], Laurence S Magder[2] and Michelle Petri[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, MD.

Background/Purpose: Morbidity and damage due to prednisone use in the treatment of SLE is recognized, but prednisone has been a requisite of lupus nephritis induction regimens. We examined, by calendar years, the prednisone exposure and urine protein in lupus nephritis patients in a large single-center cohort.

Methods: We identified 76 SLE patients who had: 1) biopsy-proven Class III or IV lupus nephritis 2) cohort visit prior to their biopsy with elevated urine protein (dip stick of 2+ to 4+) and at least 4 cohort visits in the year following their biopsy. For each patient, the average daily prednisone dose, urine dipstick, serum cholesterol, and systolic blood pressure in the year following the biopsy were calculated.

Results: The average daily dose of prednisone was lower in more recent years, but the average urine protein was better.

Table 1. Mean prednisone dose and urine dipstick scores in the year following renal biopsy, by calendar year and stratified by urine protein level prior to biopsy

Urine dipstick measure in the visit prior to biopsy	Year	Number of Patients	Average Daily Prednisone Dose in year following biopsy[1]	Average score on urine dipstick over the year following biopsy[2]
2	1988–1999	5	10.2	2.1
	2000–2005	10	20.9	1.6
	2006–2012	15	7.6	1.3
3–4	1988–1999	11	19.2	2.7
	2000–2005	24	17.1	2.2
	2006–2012	11	15.2	1.8

[1]P-value for differences between years with respect to mean daily dose of prednisone, adjusting for baseline dipstick equals 0.063.
[2]P-value for difference in mean urine dipstick score by year, adjusting for baseline dipstick score equals 0.047.

Prednisone use above 20mg daily (mean) had a major effect on total cholesterol, but not on systolic blood pressure (mean).

Table 2. Mean change (from pre-biopsy) in cholesterol and systolic blood pressure by average daily dose of prednisone in the year following biopsy

Average Daily Prednisone Dose	Sample Size	Mean change in Cholesterol	Mean change in systolic BP
0–9 mg/d	27	−2.3	−2.5
10–19 mg/d	28	−12.3	−5.7
20+	21	25.2	−0.4

Conclusion: Prednisone dose in Class III-IV lupus nephritis has been reduced in recent years, with no deleterious effect on urine protein (in fact there has been improved control of urine dipstick protein). The effect of prednisone on traditional risk factors was surprising. Patients receiving more than 20 mg/day of prednisone had a major increase in serum cholesterol. However, in those receiving 10–19 mg/d prednisone, there was a surprising decrease in both cholesterol and systolic blood pressure.

Disclosure: T. Bichile, None; **L. S. Magder**, None; **M. Petri**, None.

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The Relevance of Urinary Podocyte Number and Urinary Podocalyxin Level with Response to Treatment and 1 Year Renal Prognosis in Systemic Lupus Erythematosus. Hiroshi Kajiyama[1], Keiju Hiromura[2], Daisuke Ikuma[1], Hidekazu Ikeuchi[2], Hiroyuki Kurosawa[3], Yoshiaki Hirayama[3], Fumio Gondaira[3], Masanori Hara[4], Yoshihisa Nojima[2] and Toshihide Mimura[1]. [1]Saitama Medical University, Saitama, Japan, [2]Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan, [3]Denka Seiken Co. Ltd., Niigata, Japan, [4]Yoshida Hospital, Niigata, Japan.

Background/Purpose: Podocytes are glomerular visceral epithelial cells, whose number decrease due to death and/or detachment from capillary wall leads to severe proteinuria and end stage kidney disease. Podocalyxin (PCX) is one of the podocyte markers, and we reported in ACR meeting last year that two different urine PCX-related biomarkers, urine numbers of PCX-positive cells (podocytes, U-Pod) and urine levels of PCX (U-PCX) were higher in systemic lupus erythematosus (SLE) patients with kidney disease (KD) than those without KD. Purpose of this longitudinal study is to clarify the relevance of U-Pod and U-PCX with the response to treatment and renal prognosis.

Methods: U-Pod were determined by counting PCX-positive cells in sediments from urine samples. U-PCX were measured by sandwich ELISA, normalized to urine creatinine levels. Patients with proteinuria (defined as more than 0.2 urine protein/creatinine ratio, U-PCR) and/or renal failure (defined as estimated glomerular filtration rate, eGFR, less than 60 mL/min/1.73m^2) were defined as KD(+), and other patients were defined as KD(−). Patients were recruited between October 2010 and March 2013, 18 SLE-KD(+) patients (ISN/RPS Classification, IV: 5 patients, IV+V: 2 patients, V: 2 patients, biopsy was not performed in 9 patients), and 11 SLE-KD(−) patients. U-Pod, U-PCX, U-PCR and eGFR were obtained around the treatment start, and at 1, 3, 6 and 12 months (mo) after treatment. Correlation of cumulative U-Pods generated by the summations of U-Pods in first 6 months with one year change of eGFR was determined. Statistical analysis was done with Wilcoxon signed-rank test and Spearman correlation. $p<0.05$ was defined as statistical significance. Each value was described as median and interquartile range.

Results: In KD(−), U-Pod, U-PCX, and U-PCR were not significantly changed all through the year. In KD(+), U-PCR was significantly improved from 6 mo after treatment (before treatment 2.86 (0.91, 5.16), vs 1 mo 1.15 (0.42, 3.99) p=0.2366, vs 3 mo 0.41 (0.21, 3.80) p=0.0894, vs 6 mo 0.31 (0.11, 0.95) p=0.0004, vs 12 mo 0.22 (0.08, 0.72) p=0.0061). U-Pod significantly improved at 1 mo after treatment (before treatment 1.65 (0, 6.07), vs 1 mo 0.30 (0, 1.48) p=0.0084, vs 3 mo 0.30 (0, 0.60) p=0.0046, vs 6 mo 0 (0, 0.45) p=0.0037, vs 12 mo 0 (0, 0.25) cells/mL p=0.0039). Interestingly, U-PCX improvement delayed significantly, and was observed from 6 mo (before treatment 360.0 (160.0, 586.8), vs 1 mo 363.5 (185.5, 540.8) p=0.4204, vs 3 mo 294.0 (114.0, 422.5) p=0.072, vs 6 mo 154.9 (65.5, 251.5) p=0.0039, vs 12 mo 66.6 (41.5, 178.3) μg/gCr p=0.0008). One year changes of eGFR (subtracting 12 mo eGFR from pre-treatment eGFR) were −2.067 (−10.59, 16.00) mL/min./1.73m^2 in KD(+) and −20.61 (−35.75, 1.002) mL/min./1.73m^{2}in KD(−). There was no significant correlation of cumulative U-Pods with one year change of eGFR both in KD(+) and KD(−) (p=0.7228, and p=0.3831).

Conclusion: U-Pod significantly improves one month after treatment much faster than U-PCR and U-PCX, suggesting that U-Pod reflects acute inflammation, and that U-PCX is more relevant to filter dysfunction of podocyte. Cumulative podocyte loss may not affect decline of eGFR in one year in SLE.

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'probability of 3 and 6 Month Complete Response in Lupus Nephritis'. Homa Timlin[1], Michelle Petri[1] and Laurence S Magder[2]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, MD.

Background/Purpose: Lupus nephritis is a major cause of morbidity and mortality. The complete response rate is the most sensitive in detecting differences among therapeutic regimens. Mycophenolate mofetil has become the primary induction and maintenance therapy for lupus nephritis.

The purpose of this study was to assess the effect of MMF on the complete response after starting mycophenolate mofetil as initial therapy for

class III, IV or V in immunosuppressant naïve patients with lupus nephritis by using 5 criteria including BMS, ACR, LUNAR, ALMS, and ACCESS.

Methods: This is a retrospective study on 21 SLE patients who had begun mycophenolate mofetil shortly after a biopsy-confirmed diagnosis of lupus nephritis. They consisted of 18 females, 3 males, 9 African Americans, 8 Caucasians, and 4 other ethnicities. Ages ranged from 18 to 70 with a mean age of 37 (SD=15). There were 5 patients with class III, 9 with class IV, 4 with class III-V, 1 with class IV-V and 2 with class V lupus nephritis. At baseline, 76% had positive anti-dsDNA, 67% had low C3, 57% had low C4 and 71% had albumin below 3.5. The initial dose of mycophenolate mofetil was 1000mg twice daily. If no improvement, it was increased to 1500 mg twice daily after one month. The baseline urine protein to creatinine ratio ranged between 0.635 to 11.91grams, with only 1 patient being below 1 gram at baseline. Patients were on a renal sparing regimen (52%) and hydroxychloroquine (86%). Depending on the response index, complete response was defined, as reaching a urine protein to creatinine ratio of $<$ 0.2–0.5 grams, improvement in creatinine or estimated glomerular filtration rate of 10–25%, normalization of urinalysis and tapering dose of steroids.

Results: 52% of SLE patients reached 0.5 grams of proteinuria within 51 days of starting mycophenolate mofetil (95% confidence interval 29%–74%). 77% reached 0.5 grams or less within 260 days (95% confidence interval 57%–97%). The probability of response at 90 and 180 days is shown in the table for each response index.

Response Definition	Probability of response within 90 days	Probability of response within 180 days
BMS	14%	38%
ACR	23%	58%
LUNAR/ALMS/ACCESS	24%	31%

Conclusion: This study demonstrates that the majority of previously naive immunosuppressant patients can reach a complete response within 6 months after initiation of mycophenolate mofetil. Furthermore, the estimate of long term response was highest in the ACR criteria.

Disclosure: H. Timlin, None; **M. Petri**, None; **L. S. Magder**, None.

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Identifying Patient Perceptions of Medication Decision Making Barriers in Minorities with Lupus Nephritis. Jasvinder A Singh[1], Haiyan Qu[2], Jinoos Yazdany[3], W. Winn Chatham[2], Maria Dall'era[3] and Ricahrd Shewchuk[4]. [1]University of Alabama and VA Medical Center, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of California, San Francisco, San Francisco, CA, [4]University fo Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Studies suggest that adherence to medications for lupus nephritis is low. However, there are limited data available on the barriers that patients with lupus nephritis, encounter in their decisional processes involving immunosuppressive medications. Our objective was to identify a comprehensive array of patient-reported barriers (issues) and the relative difficulty these presented for racial/ethnic minority patients with lupus nephritis in their medication adherence decision-making process.

Methods: Barriers involved in the medication decision-making process were queried and then prioritized using a voting procedure during 8 Nominal Group Technique (NGT) meetings that were convened with participants who received treatment for lupus nephritis clinics at University of Alabama at Birmingham (UAB) and University of California at San Francisco (UCSF). The participants were asked "What sorts of things make it hard for people to decide to take the medicines that doctors prescribe for treating their lupus kidney disease?" We aggregated the prioritized responses from each NGT meeting by combining the same or very similar responses from different groups. The voting totals for the same or very similar responses were summed across groups.

Results: 51 patients with lupus nephritis participated in 8 NGT meetings: 26 African Americans (4 nominal groups), 13 Hispanic (2 nominal groups) and 12 Caucasian (2 nominal groups). Patients had a mean age of 40.6 years (SD=13.3), disease duration was 11.8 years (SD=8.3), 35.3% had education level of college and beyond. 55.8% needed help with reading health materials from a family member, indicating low health literacy. The participants generated 248 responses (range=19–37 responses/meeting). Across the 8 groups, about 41% of responses were endorsed by patients as relatively more important barriers than others in their decision making process (range=32–54% of endorsed/total). More agreement about the importance of barriers was observed among Caucasian and Hispanic patients (range=32–38% endorsed) than among African American patients (41–53% endorsed). Across the 8 groups, 33 barriers were endorsed as relatively more important than others in decision-making. Overall, participants allocated about 53% of the available votes from all groups as an endorsement of importance to just 7 barriers: potential for side effects, cost, doubts about efficacy, weight gain worries, fear of damage to other organs, potential for causing other conditions, and concerns about long-term risks.

Conclusion: We found general consistency of perceived barriers to medication use in lupus nephritis patients across all groups. NGT and its robustness as a patient-centered approach helped us generate objective, semi-quantitative information regarding factors that influence the decision making process in patients with lupus nephritis. An improved understanding of patient-perceived barriers to medication use will help us design interventions and educational materials for patients with lupus nephritis (e.g., decision aid).

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Validation of a Machine Learning Lupus Nephritis Decision Support Tool to Predict Complete Response to Therapy. Bethany Wolf[1], John Christian Spainhour[1], John Arthur[1], Michael Janech[1], Michelle Petri[2], Adnan Kiani[3] and Jim Oates[1]. [1]Medical University of South Carolina, Charleston, SC, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Johns Hopkins University, Baltimore, MD.

Background/Purpose: The American College of Rheumatology treatment guidelines for lupus nephritis (LN) recommend that induction therapy be changed when response to therapy has not occurred within six months. Response is not defined, and renal fibrosis can occur while waiting for this endpoint. Therefore, an early treatment decision support tool is needed. The goal of this project was to create and validate such a tool.

Methods: 140 patients with active LN were recruited within 12 months of renal biopsy and prospectively evaluated for one year after start of induction therapy. Patients came from two prospective cohorts (the Hopkins cohort and the Medical University of SC) and two randomized controlled trials (the Lupus Nephritis Assessment of Rituximab (LUNAR) and the abatacept lupus nephritis trial). Renal biopsy International Society of Pathology/Renal Pathology Society (ISN/RPS) class, demographics, serum complement, anti-double stranded DNA antibody (dsDNA), and creatinine values, and urine protein/creatinine (traditional biomarkers, per Dall'Era and Wofsy Arthritis Care & Research 2011;63(3):351–357) and novel biomarker values were determined at 0 & 3 months. Seventeen novel biomarkers measured (see table) were based on those in an initial discovery set of 52 candidate biomarkers that were significantly different between groups or that showed promise in the literature. Patients were randomly assigned to training (n=99) and external validation (n=41) sets, stratifying for ISN/RPS class. Baseline and three-month traditional and novel biomarker, ISN/RPS class, treatment regimen, age, sex, and race were used to train random forest models predictive of one-year complete response (CR) to therapy. External validation sets were used to determine the performance of the trained one-year CR model. The process of randomization into training and validation sets and model training/validation was repeated 1000 times, and the median model results were reported.

Results: Several individual biomarkers were different between the two groups ($P<0.001$). The resulting test of the LN Decision Support Tool (LNDST) demonstrated the clinically meaningful performance reported in Table I for both models, but the novel biomarker panel had superior specificity for cutpoints giving equal sensitivity.

Validation of performance for random forest models of complete response to therapy. Reported as median model from 1000 different training and validation sets

	Accuracy	ROC AUC	sensitivity	specificity	PPV	NPV
Traditional variables	0.72	0.70	0.95	0.30	0.50	0.76
Novel and traditional variables	0.76	0.76	0.95	0.50	0.62	0.82

Novel biomarkers studied: Cystatin C, N-acetyl-beta-D-glucosaminidase, neutrophil gelatinase associated lipocalin, osteoprotegerin, TNF-like weak inducer of apoptosis, eotaxin, granulocyte monocyte colony stimulation factor, interferon alpha2, interferon gamma, interleukin 1, 6, and 8, interleukin 2 receptor alpha, Interferon gamma-induced protein 10, macrophage inflammatory protein 1beta, monocyte chemotactic protein 1, and platelet derived growth factor

Conclusion: This study demonstrates the ability of the LNDST to predict CR. Implementation of LNDST may assist clinicians in following the ACR guidelines for treatment of LN.

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1670

Characterization of Patients with Lupus Nephritis Included in a Large Cohort from the Spanish Society of Rheumatology Registry of Patients with Systemic Lupus Erythematosus. María Galindo Izquierdo[1], Esther Rodriguez-Almaraz[1], Sabina Perez[2], José M. Pego-Reigosa[3], Jaime Calvo-Alen[4], Francisco Javier López-Longo[5], Iñigo Rúa-Figueroa[6], Alejandro Olivé[7], Víctor Martínez Taboada[8], Paloma Vela Casasempere[9], Mercedes Freire[10], Javier Narváez[11], Antonio Fernandez Nebro[12], Jose Rosas[13], Monica Ibanez Barcelo[14], Esther Uriarte[15], Eva Tomero[16], Antonio Zea[17], Maria Loreto Horcada[18], Vicente Torrente[19], Ivan Castellvi[20], Joan Calvet[21], Raúl Menor Almagro[22], Mª Angeles Aguirre[23], Enrique Raya[24], Elvira Diez Alvarez[25], Tomás Vázquez Rodríguez[26], Paloma García de la Peña[27], Atusa Movasat[28], José Luis Andreu[29], Patricia Richi[30], Carlos Marras Fernandez-Cid[31], Carlos Alberto Montilla Morales[32], Blanca Hernández-Cruz[33], José Luis Marenco de la Fuente[34], Marian Gantes[35], Eduardo Ucar[36], Juan J. Alegre[37], Javier Manero[38], Jesús Ibañez Ruán[39], Manuel Rodríguez-Gómez[40], Victor Quevedo[41], José Hernández Beiraín[42] and Lucía Silva Fernández[43]. [1]Department of Rheumatology. Hospital Universitario 12 de Octubre, Madrid, Spain, [2]Research Unit, Madrid, Spain, [3]Instituto de Investigación Biomédica de Vigo (IBIV), Vigo, Spain, [4]Sierrallana Hospital, Torrelavega, Spain, [5]Rheumatology, Hospital Gregorio Marañon, Madrid, Spain, [6]Hospital Doctor Negrin, Las Palmas de Gran Canaria, Spain, [7]Hospital Universitario Germans Trias i Pujol, Badalona, Spain, [8]Marqués de Valdecilla, Santander, Spain, [9]Hospital General de Alicante, Alicante, Spain, [10]Hospital Universitario Juan Canalejo, La Coruña, Spain, [11]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, [12]Hospital Regional Carlos Haya, Biomedical Research Institute of Malaga (IBIMA), Malaga, Spain, [13]Hospital Marina Baixa. Villajoyosa, Villajoyosa, Spain, [14]H. Son Llatzer, Palma de Mallorca, Spain, [15]Hospital de Donosti, San Sebastian, Spain, [16]Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [17]Hospital Universitario Ramon y Cajal, Madrid, Spain, [18]Complejo Hospitalario de Navarra, Pamplona, Spain, [19]Hospital Moisès Broggi, Barcelona, Spain, [20]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [21]Hospital Parc Taulí, Barcelona, Spain, [22]Hospital de Jerez, Jerez de la Frontera, Spain, [23]IMIBIC-Reina Sofia Hospital, Cordoba, Spain, [24]University Hospital San Cecilio, Granada, Spain, [25]Leon Hospital, Leon, Spain, [26]Hospital Lucus Augusti, Lugo, Spain, [27]Hospital Norte Sanchinarro, Madrid, Spain, [28]Hospital Príncipe de Asturias, Immune System Diseases/Rheumatology department, Alcalá de Henares, Madrid, Spain, [29]Rheumatology, Hospital Puerta de Hierro, Madrid, Spain, [30]Hospital Infanta Sofía, Madrid, Spain, [31]H. Arrixaca, Alicante, Spain, [32]Hospital Clínico Universitario de Salamanca, Salamanca, Spain, [33]University Hospital Virgen Macarena, Sevilla, Spain, [34]Hospital de Valme. Sevilla, Sevilla, Spain, [35]Hospital Universitario de Canarias, Tenerife, Spain, [36]Rheumatology, Bilbao, Spain, [37]Hospital Universitario Dr Peset, Valencia, Spain, [38]Ophthalmology and Rheumatology. Hospital Miguel Servet Zaragoza, Spain, Zaragoza, Spain, [39]Rheumatology, Vigo, Spain, [40]Complejo Hospitalario Universitario de Ourense, Ourense, Spain, [41]Hospital de Monforte, Lugo, Spain, [42]Hospital Insular de Gran Canaria, Las palmas Gran Canarias, Spain, [43]Hospital Universitario de Guadalajara, Guadalajara, Spain.

Background/Purpose: To describe the profile of patients included in RELESSER with histologically confirmed lupus nephritis (LN).

Methods: RELESSER is a multicentre cross-sectional study, with information retrospectively collected from the charts of patients with SLE followed up at participant rheumatology units. Globally, 359 variables including demographic and clinical data, activity, severity, comorbidities, treatments and mortality were recorded. The following renal data were included: WHO LN histological type, proteinuria, haematuria, leukocyturia, cellular casts and creatinine clearance, treatment response, recurrence, development of ESRD and/or the need for dialysis or renal transplantation. We performed a descriptive analysis by calculating means ± SD for numerical variables and frequencies for qualitative variables. Chi-square or t-Student tests were applied to analyse their relationship with LN. Odds ratio and confidence intervals were calculated by using simple logistic regression. Statistical significance was $p<0.05$.

Results: LN was confirmed in 1092 patients (31%). Most patients were female (86%), Caucasian (90%), and the mean age at disease onset was 33±14 years. Most patients developed LN in the first year after SLE diagnosis. Most had LN proliferative forms (70%), and there were only 16 cases of thrombotic microangiopathy (TMA). The risk of LN development was significantly lower among women ($p<0.001$), and higher as lower was the age of the disease onset and among hispanic ethnicity ($p<0.001$). Complete response to treatment was achieved in 68.3% of patients, whereas 17.9% remained with renal activity. A higher risk for persistence of renal activity was found with higher levels of baseline serum creatinine (1 vs 0.91, $p=0.004$) and proteinuria (2.76 vs 2.4, $p=0.006$). ESRD was clinically associated with positive a-dsDNA, low complement, pleuropericarditis, seizures (all $p<0.001$), and haemolytic anemia ($p=0.015$).TMA was a risk factor for ESRD, and the necessity of dialysis or renal transplantation (all $p<0.05$).ESRD was an independent mortality risk factor ($p<0.001$).326 recurrences were recorded, with a mean time to first recurrence of 47 months (0–28),regardless of histology.The lower was the serum creatinine and older was the age at LN onset, the lower was the recurrence risk.TMA was a risk factor for recurrence ($p=0.016$). Recurrences were related with persistent lupus activity and ESRD (both, $p<0.001$). During the follow up, the LN development associations are described in Table 1. LN was a poor prognostic factor associated with increased mortality risk OR 2.4 (1.81–3.22), $p<0.001$.

Table 1.

	OR (CI)
Malar rash	1.54 (1.33–1.78)**
Pleurisy	1.95 (1.66–2.29)**
Pericarditis	2.07 (1.73–2.50)**
Alveolar and interstitial lung disease:	1.73 (1.23–2.44)*
Alveolar hemorrhage	3.56 (1.77–7.19)**
Seizures	2.40 (1.84–3.13)**
Psychosis	1.88 (1.20–2.94)*
Haemolytic anemia	2.39 (1.89–3.03)**
Leukolymphopenia	1.38 (1.19–1.61)**
Thrombocytopenia	1.49 (1.26–1.76)**
a-dsDNA	4.77 (3.82–5.95)**
a-Sm	1.73 (1.45–2.05)**
Antiphospholipid syndrome:	1.57 (1.29–1.92)**
lupus anticoagulant	1.28 (1.06–1.55)*
arterial/venous thrombosis	1.84 (1.35–2.51)**/1.60 (1.27–2.01)**
Low complement levels	4.48 (3.53–5.68)**

*: $p<0.05$; **: $p<0.001$

Conclusion: LN, mainly proliferative forms, affects almost one third of patients with SLE, and is often associated with the occurrence of other severe lupus manifestations, being a poor prognostic factor. TMA and relapses are associated with worse outcome in renal function.

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Renal Relapses Are Common in Lupus Nephritis. Angela Pakozdi, Ravindra Rajakariar, Michael Sheaff and Dev Pyne. Barts Health NHS Trust, London, United Kingdom.

Background/Purpose: Renal relapses are part of the natural history of lupus nephritis (LN) and represent a significant challenge not only because they are associated with an increased risk of decline in renal function, but also there is a cumulative toxicity of immunosuppressive treatments. In this retrospective study, we aimed to review renal flare frequency and management in a large single centre cohort of adult LN patients.

Methods: Patients with biopsy proven LN were identified from our electronic database. LN classes based on glomerular pathology were defined according to the ISN/RPS classification. Clinical and laboratory data were obtained from electronic records of patients. Complete remission (CR) was

defined as proteinuria <0.5g/day, whilst partial remission (PR) was defined as >50% reduction in baseline proteinuria achieving <2g/day. We defined proteinuric flares as proteinuria >1g/day in patients with CR, and doubling of proteinuria in cases of PR.

Results: 104 (87%) of 119 SLE patients with biopsy proven LN achieved either CR (n=84, 81%) or PR (n=20, 19%). 34 (33%) had at least one flare (27 had preceding CR and 7 had PR); among those 8 had >2 flares (19%). 21 patients (64%) had class 3 or 4 LN, 7 (21%) class 5 LN, 4 (12%) class 2 LN and 1 (3%) focal segmental glomerulosclerosis. The median time between remission and relapse was 29 months (IQR, 16–66) in CR, and 13 months (IQR, 3–32) in PR (p=0.089). The maintenance immunosuppressive drug at time of flare was Mycophenolate Mofetil (MMF, n=13, 42%) or Azathioprine (AZA, n=10, 32%). 15 (48%) had Angiotensin blockers (ATB), and 22 (71%) were on low dose Corticosteroids (CS) (<10mg/day). Non-adherence to treatment at time of relapse was documented in 7 cases (22%). At the time of flare, the median proteinuria was 1.7g (IQR, 1.3–3.2) in CR, and 2.5g (IQR, 1.4–3.8) in PR. 14 (41%) had raised Creatinine, 14 had raised dsDNA (47%), 18 had low complements (56%) at flare. To treat relapse, 13 patients (45%) started a new immunosuppressive drug (Cyclophosphamide n=6, MMF n=5, Rituximab n=1 or AZA n=1), 3 (10%) had immunosuppressive drug dose escalation, 4 (14%) were treated with CS alone, and 6 (21%) were treated with ATB. After treatment, proteinuric outcome was available for 24 patients: 16 patients (67%) achieved CR, 6 (25%) reached PR, whilst 2 (8%) did not go into remission. 5 patients (15%) reached stage 5 chronic kidney disease after the flare.

Conclusion: LN renal flares are common. Our study shows that a third of LN patients develop at least one relapse after reaching remission, usually within 3 years. The length of time to flare tends to be shorter in cases of preceding PR than in CR. Lack of adherence to long term immunosuppression was identified as a significant factor in LN flare (22% cohort). Patients with LN in remission require close follow-up.

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Facilitating the Medication Decision-Making process—What Do Patients with Lupus Nephritis Say? Ricahrd Shewchuk[1], Haiyan Qu[2], W. Winn Chatham[2], Jinoos Yazdany[3], Maria Dall'era[3] and Jasvinder A Singh[4]. [1]University fo Alabama at Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of California, San Francisco, CA, [4]University of Alabama and VA Medical Center, Birmingham, AL.

Background/Purpose: Low medication adherence in lupus nephritis puts patients at risk for poor outcomes, but to our knowledge, relatively little is known about what patients perceive as facilitative factors in medication decisional processes. Our objective was to comprehensively identify factors that racial/ethnic minority patients with lupus perceive as facilitating decisions to take their lupus medications as prescribed.

Methods: We conducted 8 Nominal Group Technique (NGT) meetings with patients with lupus nephritis who received treatment from lupus clinics at University of Alabama at Birmingham (UAB) and University of California at San Francisco (UCSF). Patient perceptions of facilitators influencing the medication decision-making outcome were generated by asking the following question: "What sorts of things make it easier for people to decide to take the medications that doctors prescribe for treating their lupus kidney disease?" Patients in each NGT meeting prioritized a subset of facilitative factors in terms of importance using a voting procedure. To obtain an aggregated result, responses with the same or very similar wording generated by different groups were combined and the voting totals for all prioritized responses were summed across groups.

Results: 52 patients with lupus nephritis participated in 8 NGT meetings: 27 African Americans (4 nominal groups), 13 Hispanic (2 nominal groups) and 12 Caucasian (2 nominal groups). Mean age was 40.6 years (SD=13.3), disease duration was 11.8 years (SD=8.3), 34.6% had education level of college or greater, 55.8% needed help with reading health materials, indicating low health literacy. The participants generated 281 responses (range=26–42 responses/meeting). 36% of all responses were endorsed across all groups by patients as relatively more important than others in facilitating decisions to take prescribed medications (range=31–52% of endorsed facilitators/total). More variation in the level of agreement about the importance of specific facilitators was observed with African American patients (range 31–52%) than with Caucasian (32–37%) and Hispanic patients (31–34%). Overall, participants allocated about 57% of the available votes from all groups as an endorsement of perceived importance to 8 facilitators that can be briefly summarized as: demonstrated efficacy, longevity expectations, symptom relief, expectations for living a more normal life, family, cost and affordability, awareness of potential risks and benefits, and minimal side effects.

Conclusion: A general consistency of factors perceived to facilitate medication decision making by lupus nephritis patients was noted across ethnic/racial groups. Patient-identified facilitators of lupus medication adherence can inform the design of effective educational materials for patients with lupus nephritis.

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Disease Specific Quality of Life in Patients with Lupus Nephritis. Chi Chiu Mok[1], Sergio Toloza[2], Berna Goker[3], Ann E. Clarke[4], S. Navarra[5], Daniel J. Wallace[6], Michael H. Weisman[7] and Meenakshi Jolly[8]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Hospital San Juan Bautista, San Fernando del Valle de Catamarca, Argentina, [3]Gazi University School of Medicine, Ankara, Turkey, [4]University of Calgary, Calgary, AB, [5]University of Santo Tomas Hospital, Manila, Philippines, [6]Cedars-Sinai/David Geffen School of Medicine at UCLA, Los Angeles, CA, [7]Cedars-Sinai Medical Center, Los Angeles, CA, [8]Rush University Medical Center, Chicago, IL.

	ACR-LN			Active LN		
	No	Yes	P value	No	Yes	P value
Age (yrs)	42.8 (13.6)	40.3 (13.1)	0.002	41.1 (13.1)	37.9 (12.9)	0.01
PGA	0.6 (0.6)	0.7 (0.8)	0.04	0.5 (0.5)	1.5 (0.9)	<0.001
Total SLEDAI	3.0 (3.4)	4.0 (4.9)	0.01	2.2 (2.7)	9.4 (5.9)	
Total SDI	0.7 (1.2)	1.1 (1.8)	<0.001	1.2 (1.8)	1.1 (1.8)	0.96
Lupus Symptoms	75.4 (21.2)	76.5 (20.8)	0.32	78.4 (19.8)	70.3 (23.0)	<0.001
Medications	76.6 (26.5)	72.3 (25.7)	<0.001	73.7 (25.8)	67.9 (25.3)	0.01
Cognition	69.2 (27.3)	70.7 (24.9)	0.59	70.5 (25.0)	71.3 (24.6)	0.80
Procreation	88.4 (22.0)	84.5 (24.5)	<0.001	86.2 (23.5)	79.2 (27.1)	0.003
Physical Health	83.3 (21.9)	83.6 (22.1)	0.72	84.6 (21.1)	80.4 (24.8)	0.12
Emotional Health	64.0 (27.3)	63.3 (25.7)	0.50	65.0 (25.8)	58.2 (24.6)	0.005
Pain-Vitality	67.5 (26.3)	71.2 (24.2)	0.03	71.9 (24.5)	69.0 (23.2)	0.13
Body Image	79.0 (25.5)	80.0 (24.0)	0.91	81.3 (23.9)	75.6 (24.0)	0.002
Summary HRQOL	76.3 (17.1)	75.7 (16.6)	0.44	77.0 (16.3)	71.6 (16.8)	0.001
Desires-Goals	72.5 (25.7)	71.4 (25.4)	0.30	73.2 (24.8)	65.7 (26.6)	0.004
Social Support	65.7 (33.1)	67.6 (32.7)	0.30	66.1 (33.2)	72.4 (30.8)	0.06
Coping	65.0 (27.2)	64.9 (26.3)	0.87	63.8 (26.5)	68.5 (25.5)	0.08
Satisfaction with Treatment	64.0 (34.6)	64.1 (32.1)	0.54	60.5 (32.8)	75.7 (26.4)	<0.001
Summary Non HRQOL	66.8 (19.3)	66.9 (18.1)	0.94	65.8 (18.7)	70.3 (15.8)	0.02

Background/Purpose: Little is known about patient reported outcomes (PRO) in lupus nephritis (LN), and no studies using a disease targeted PRO tool have been undertaken thus far. Herein, we describe quality of life (QOL) among patients with LN using a valid and reliable disease targeted PRO measure (LupusPRO).

Methods: Cross sectional data obtained from patients with systemic lupus erythematosus (SLE) during psychometric evaluation studies of LupusPRO from various countries were compared between those: 1) with and without LN and 2) with active and inactive-LN." Data compared included demographics, disease characteristics, and LupusPRO constructs. Presence of LN was present if listed among the ACR classification criteria (ACR-LN), while presence of active LN was based on presence of urinary casts, hematuria, proteinuria or pyuria in the disease activity assessment (SELENA-SLEDAI) performed at the time of the study visit. LupusPRO has Health related QOL (HRQOL) and non-HRQOL constructs. HRQOL domains include lupus symptoms, cognition, medication, procreation, physical health, emotional health, pain-vitality and body image. Non-HRQOL domains include desires-goals, social support, coping and satisfaction with care. Non-parametric tests were used to make comparisons, and p values $\leq$ 0.05 were considered significant.

Results: There were 1,259 SLE patients; ninety-four percent were women and their mean (SD) age was 41.7 (13.5) yrs. Five-hundred and thirty-nine had ACR-LN. These patients were younger, had greater disease activity (PGA, Total SELENA-SLEDAI) and damage (SLICC/ACR) than those without LN. Summary HRQOL and non-HRQOL scores were similar in both groups; however, those with ACR-LN had significantly worse scores on medications and procreation domains, while those without ACR-LN had worse scores on Pain-Vitality domains (Table 1).

129/540 ACR-LN patients had active LN. Patients with active LN were younger, had significantly greater disease activity (PGA, Total SELENA-SLEDAI), worse HRQOL and non-HRQOL than patients with inactive LN.

Specific domains scores adversely affected among active LN patients were lupus symptoms, medications, procreation, emotional health, body image and desires-goals (Table 1). Satisfaction with care was significantly higher among patients with active LN as compared to inactive LN patients.

Conclusion: LN adversely affects several specific QOL domains and physicians need to be aware of these concerns.

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ACR/ARHP Poster Session B

Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics: Systemic Sclerosis, Diagnostic and Therapeutic Aspects

Monday, November 17, 2014, 8:30 AM–4:00 PM

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Long-Term Efficacy of Rituximab in Systemic Sclerosis. Javier Narváez[1], Juan Jose Alegre Sancho[2], Ivan Castellvi[3], Susana Herrera[2], Maria Molina Molina[4], Diego Castillo[3], Isabel de la Morena Barrio[2], Montserrat Robustillo Villarino[2], Angels Martínez Ferrer[2], Desamparados Ybañez García[2], Elia Valls Pascual[2], Josep Maria LLobet[3], Francisca Gil Latorre[2] and Joan Miquel Nolla[4]. [1]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, [2]Hospital Universitario Dr Peset, Valencia, Spain, [3]Hospital de Sant Pau, Barcelona, Spain, [4]Hospital Universitario de Bellvitge, Barcelona, Spain.

Background/Purpose: It has been proved in several studies with a small number of patients that Rituximab (RTX) can prevent worsening of interstitial lung disease (ILD) and improve skin fibrosis in patients with Systemic Sclerosis (SSc). Recently, a multicentre case-control study of the EUSTAR cohort has confirmed these favorable results *(Jordan S, et al. Ann Rheum Dis 2014 Jan 17 [Epub ahead of print]).* Moreover, RTX may be effective on calcinosis. However, little is known about its long-term effect. Our objective was to assess the efficacy of RTX on skin involvement, ILD and calcinosis in series of patients with refractory SSc.

Methods: Patients with refractory SSc treated with RTX *(off label use)* were recruited from 3 hospitals. At baseline, the following data were collected: gender, age, type and duration of the SSc, clinical features, modified Rodnan skin score (mRSS), HRCT, pulmonary function tests (PFTs), walking test, sPAP (measured by echo), previous and present treatments, and indication and dosage of RTX. Throughout the follow up, clinical changes, as well as changes in HRCT and PFTs, were registered. We also recorded the changes in the dosage of corticosteroids, number of RTX cycles, duration of treatment, and withdrawals. The package SPSS 17.0 was used for descriptive statistics, and quantitative variables were compared using the t-test for paired samples.

Results: Thirty SSc patients treated with RTX were included in the analysis. The majority were women (86.7%), with a mean age of 54 years, and a mean of 9.4 years of evolution of the disease. Subtypes: DSSc 50%, LSSc 37%, and Overlap syndromes 13.3%. The baseline mean mRSS was 15. Clinical features: ILD 80% (NSIP 67%), calcinosis 37%, pulmonary hypertension 10%, joint disease 49%. The baseline mean FVC, DLCO and TLC values were 70%, 47% and 73%, respectively.

The indication for RTX was: ILD (73.4%), arthritis (36.6%), calcinosis (33.3%) and severe skin involvement (19.7%). The most used previous treatments were cyclophosphamide(50%) and mycophenolate (46.6%). RTX was always used in a RA dosage, mainly in monotherapy (46.7%), or in association with mycophenolate (40%). When data were collected, patients had received a mean of 1.7 cycles (1–5) of RTX, with a dosing interval which ranged from 6 to 15 months, and a mean of 12.8 months (1–43) of treatment. The mean mRSS was significantly reduced at follow-up (17.2 ± 10.9 vs. 14 ± 9.8; $p=0.012$), without significant changes of the HRCT (76.9%) and/or PFTs in patients with ILD. The 40% of patients with calcinosis reported improvement. There was also a good response, in terms of TJC and SJC, in patients with arthritis ($p=0.024$ and 0.019, respectively). The dose of corticosteroids was significantly reduced (10.1 ± 8.8 vs. 5.3 ± 2.9 mg, $p=0.003$). Two patients with severe ILD died despite RTX, and there were 3 withdrawals for various reasons.

Conclusion: RTX is an effective long-term therapy in refractory SSc which can improve skin fibrosis, arthritis and calcinosis, and also prevent deterioration of ILD (stabilization of lung function).

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Regional Implantation of Adipose Tissue-Derived Cells Induces a Prompt Healing of Long-Lasting Indolent Digital Ulcers in Patients with Systemic Sclerosis. Nicoletta Del Papa[1], Gabriele Di Luca[2], Domenico Sambataro[1], Eleonora Zaccara[2], Wanda Maglione[2], Armando Gabrielli[3], Paolo Fraticelli[3], Gianluca Moroncini[3], Lorenzo Beretta[4], Alessandro Santaniello[5] and Claudio Vitali[6]. [1]Istituto G.Pini, Milan, Italy, [2]Osp. G. Pini, Milano, Italy, [3]Università Politecnica delle Marche, Ancona, Italy, [4]Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy, [5]Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy, [6]Istituto San Giuseppe, Lecco, Italy.

Background/Purpose: Fingertip digital ulcers (DUs) are a rather frequent and invalidating complication in the course of systemic sclerosis (SSc), often showing a very slow or null tendency to heal, and causing intense local pain. Furthermore, most of the commonly used systemic and local therapeutic procedures have demonstrated to be scarcely or totally inadequate to induce a rapid healing in the SSc-related DUs. Recently stem cell therapy has emerged as a new approach to accelerate wound healing, and some case reports have been published where local or regional transfer of bone marrow stem cells (BMSCs) was effective in improving or healing SSc-related ischemic lesions. Adipose-derived stem cells (ASCs) are considered another source of multipotent stem cells potentially able to induce angiogenesis and tissue repair.In the present study we have tentatively treated long lasting and poorly responsive to traditional therapy SSc-related DUs by the implantation of autologous adipose-tissue derived cells (ATDCs) fraction, that it know to contains both the ASCs and the stromal/vascular cell (SV) component.

Methods: Fifteen patients with SSc having a long lasting DU in only one fingertip, unresponsive to intensive systemic and local treatment, were enrolled into the study. The grafting procedure consisted in the injection, at the basis of the corresponding finger, of 0.5–1 ml of ATDCs fraction, separated by centrifugation of adipose tissue collected through liposuction from subcutaneous abdominal fat. Time to healing after the procedure was the primary end point of the study, while reduction of pain intensity (measured by visual analogue scale), and of analgesic consumption represented secondary end point. Furthermore, the after therapy variation of the number of capillaries, observed in the nailfold video-capillaroscopy (NVC) exam, and of the resistivity in the digit arteries, measured by high resolution echo-color doppler were also taken into account.

Results: A rather speed healing of the DUs was reached in all of the enrolled patients (mean time to healing 4.23 weeks; range 3–8 weeks). A significant reduction of pain intensity was observed after few weeks ($p<0.001$), while the number of capillaries was significantly increased at second (3 months) and third (6 months) NVC assessment ($p<0.0001$ in both cases, with respect to the basal examination). Finally, a significant after treatment reduction of digit artery resistivity was also recorded ($p<0.0001$).

Conclusion: Even with the limitations related to the small number of patients included, and to the open-label design of the study, the strongly favourable outcome we observed suggests that the local grafting with ATDC, containing both ASCs and SV fraction, could represent a promising option for the treatment of SSc-related DUs unresponsive to more consolidated therapies.

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1676

Physical Therapy for Systemic Sclerosis: Systematic Review and Meta-Analysis. Madhavi Peddi[1], Maria A. Lopez-Olivo[2], Prashanth Peddi[1], Gisela Espinosa Cuervo[3] and Maria E. Suarez-Almazor[2]. [1]The University of Tyler Texas, Tyler, TX, [2]The University of Texas, MD Anderson Cancer Center, Houston, TX, [3]Instituto Mexicano del Seguro Social, Mexico City, Mexico.

Background/Purpose: Physical therapy and rehabilitation are often recommended to improve function in patients with systemic sclerosis (SSc), but a systematic review of the evidence supporting these interventions has not

been performed. We conducted a systematic review to evaluate the efficacy of physical therapy alone or in combination with exercise in patients with SSC.

Methods: We searched electronic databases (MEDLINE, EMBASE, the Cochrane Collaboration library, and Web of Science) up to April, 2013. The reference lists from reviews were also searched. Two independent reviewers selected controlled trials (randomized or not) evaluating the efficacy of any physical therapy modality either alone or in combination with exercise in patients with SSc. Data was appraised and collected independently by two reviewers. Outcomes of interest were functional status, health-related quality of life, and hand mobility (measured by Health Assessment Questionnaire, Short Form-36 items, and Hand Mobility in Scleroderma, respectively). Meta-analysis was performed when data was available for 2 or more studies with the same outcome.

Results: Six studies with 221 patients were included. Five were randomized controlled trials and one was a controlled clinical trial. None of the studies were blinded; therefore, the risk of performance bias was judged to be high. All studies were conducted at single center in an outpatient setting. The weighted mean age of patients assigned to the treatment group was 57.6 years and 55.9 years for the control group. Disease duration was 9.0 years and 8.7 years, respectively. There were substantial variations in the interventions and duration of physical therapy across trials. Therapy modalities included connective tissue massage, Manual Lymphatic drainage, and Mc Mennell joint manipulation, among others. Patients treated with any modality of physical therapy had higher scores in functional status (mean difference, MD, −0.33; 95% CI −0.46, −0.19), physical component of health-related quality of life (MD 3.3; 95% CI 1.1, 5.5) and hand mobility (MD −0.22; 95% CI −0.37, −0.06) at 2 to12 weeks compared with standard of care. However, this improvement was not sustained for hand mobility, 12 weeks after stopping treatment (at 24 weeks) (MD −2.6; 95% CI −6.3, 1.0). No differences were observed by type of therapy modality.

Conclusion: Rehabilitation in patients with SSc improves functional status, ability to perform physical activities, and hand mobility 2 to12 weeks after therapy. However, loss of improvement in had mobility at 24 weeks suggests continuation of therapy is important to preserve the benefits of physical therapy.

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Association of Gastrointestinal Symptoms with Immunosuppressant Use in the Prospective Registry of Early Systemic Sclerosis Cohort. Tracy M. Frech[1], Maureen Murtaugh[2], Ami A. Shah[3], Jessica K. Gordon[4], Victoria K. Shanmugam[5], Robyn T. Domsic[6], Monique Hinchcliff[7], Faye N. Hant[8], Shervin Assassi[9], Virginia D. Steen[10] and Dinesh Khanna[11]. [1]Salt Lake City VAMC, Salt Lake, UT, [2]University of Utah School of Medicine, SLC, UT, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]Hospital for Special Surgery, New York, NY, [5]The George Washington University, Washington, DC, [6]University of Pittsburgh, Pittsburgh, PA, [7]Northwestern University Feinberg School of Medicine, Chicago, IL, [8]Medical Univ of South Carolina, Charleston, SC, [9]University of Texas Health Science Center at Houston, Houston, TX, [10]Georgetown University Medical Center, Washington, DC, [11]University of Michigan Health System, Ann Arbor, MI.

Background/Purpose: The Prospective Registry of Early Systemic Sclerosis (PRESS) is a multicenter incident cohort study of patients with early diffuse cutaneous systemic sclerosis (dcSSc; < 2 years duration). Gastrointestinal tract (GIT) symptoms are common in this patient population. The goal of this study was to analyze whether immunosuppressant choice differentially impacts GIT symptoms in early dcSSc.

Methods: There are currently 71 patients enrolled in the PRESS study at various centers in the United States. Data is collected longitudinally using REDCap, an NIH funded database including demographics, disease characteristics, physical exam data, and patient reported outcomes. PRESS patients who had both a complete gastrointestinal tract questionnaire (SCTC UCLA GIT 2.0) and immunosuppressant regimen recorded were included in this analysis. Statistical analysis was performed using SAS version 9.4. Fisher's exact was to examine associations between two categorical variables and unpaired t-test or Wilcoxin ranked sum was used for continuous variables. Significance was assigned at $p < 0.05$.

Results: A total of 37 PRESS patients had the presence or absence of an immunosuppressant at the baseline visit/ and a complete GIT 2.0 recorded. In this subgroup of PRESS patients, the most common immunosuppressant used was mycophenolate mofetil (n=17) followed by methotrexate (n=5) and cyclophosphamide (n=3). The mean age of this patient population was 52 years (12.8) and 24 were women. The average BMI was 25.2 (17.8–40.5). Fifteen patients reported > 5 kg of weight loss over the past year; 5 of those patients had > 20 kg of weight loss. In these 15 patients with weight loss there were significantly worse scores for total GIT 2.0 (p=0.03), soilage (p=0.01), social function (p=0.05) and emotional well-being (p=0.04).

There were no significant differences in the GIT 2.0 total and component scores between different immunosuppressive regimens (Table 1). No PRESS patients reported a complete absence of gastrointestinal tract symptoms.

Conclusion: Gastrointestinal symptoms captured by the GIT 2.0 are common in early dcSSc. In patients with weight loss, scores for soilage, social, and emotional well-being are significant aspects of GIT involvement. In the PRESS cohort specific immunosuppressant exposure was not a strong driver of GIT symptoms, however, further longitudinal study in this patient population is planned.

Table 1: PRESS patient immunosuppressant use and gastrointestinal symptoms captured as components of GIT 2.0 (mean, standard deviation)

	Cyclophosphamide		Mycophenolate Mofetil		Methotrexate	
	Yes N=3	No N=34	Yes N=17	No N=20	Yes N=5	No N=32
Reflux	0.94 0.5–1.38	0.58 0–2.63	0.44 0.-2.0	0.73 0–2.3	0.75 0–2.62	0.57 0–2.0
Bloating	0.94 1.5–2.5	0.74 0–2.5	0.72 0–2.25	0.88 0–2.5	0.95 0.25–2.0	0.78 0–2.5
Diarrhea	1.25 0.5–1.38	0.31 0–1.5	0.29 0–1.5	0.43 0–1.5	0.61 0–1.50	0.34 0–1.5
Social Function	0.42 0.–1.0	.29 0.–2.17	0.15 0–1.3	0.42 0–2.2	0.6 0–2.17	0.24 0–1.33
Soil	0.50 0–1.0	0.06 0–2.0	0	0.15 0–2.0	0.4 0–2.0	0.03 0–1
Emotional	0.23 0.23–0.56	0.24 0–1.88	0.20 0.-1.78	0.59 0–1.88	0.64 0–1.89	0.18 0–1.78
Constipation	0.5 0- 0.56	1.36 0–7.0	1.13 0–7	1.47 0–7.0	2.0 0–4.0	1.22 0–7.0
Total GIT 2.0	5.38 4.8–5.9	2.2 0–12.2	1.79 0.13–7.74	2.87 0–12.2	3.84 0.38–12.2	2.15 0–7.74

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1678

Initial Therapy with an Endothelin Receptor Antagonist Is Associated with Worse Outcomes in Patients with Systemic Sclerosis and Pulmonary Arterial Hypertension: Observations from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) Cohort. Matthew R. Lammi[1], Lesley Ann Saketkoo[1], Stephen C. Mathai[2], Robyn T. Domsic[3], Christine M. Bojanowski[4], Virginia D. Steen[5], Daniel E. Furst[6] and Pharos Investigators[5]. [1]LSU Scleroderma and Sarcoidosis Patient Care and Research Center, New Orleans, LA, [2]Johns Hopkins University, Baltimore, MD, [3]University of Pittsburgh, Pittsburgh, PA, [4]LSU Health Sciences Center, New Orleans, LA, [5]Georgetown University Medical Center, Washington, DC, [6]University of California, Los Angeles, Department of Medicine, Los Angeles, CA.

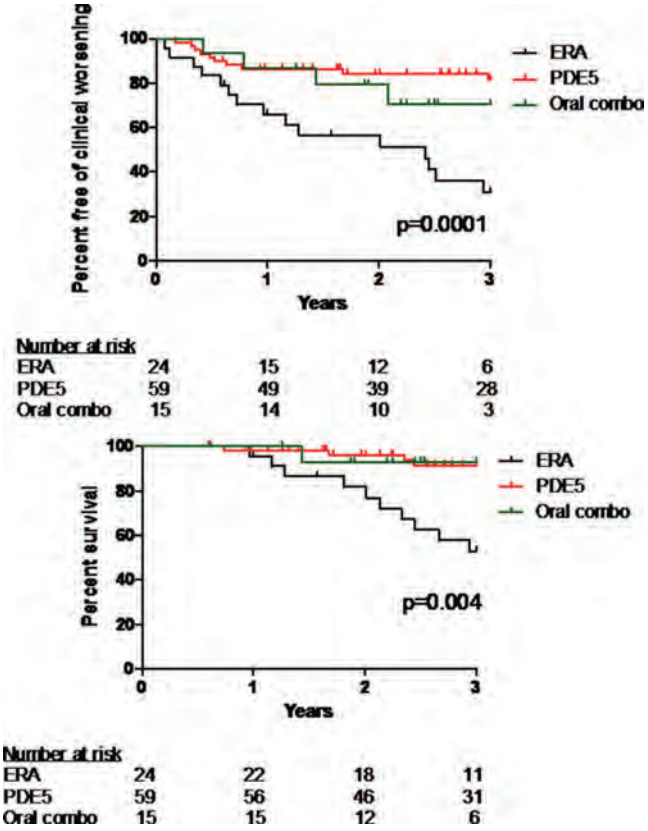
Background/Purpose: Pulmonary arterial hypertension (PAH) is a leading cause of mortality in systemic sclerosis (SSc). Although medications have improved their prognosis, optimal therapy remains undefined. The goal of this study was to compare time to clinical worsening (TTCW) and survival based on initial oral PAH therapy.

Methods: Using data from the PHAROS registry (a multicenter prospective observational study enrolling SSc patients with incident pulmonary hypertension), patients with group I PAH, 6 months of initial therapy with either an endothelin-receptor antagonist (ERA), phosphodiesterase-5 inhibitor (PDE5), or a combination of ERA/PDE5 were included. Patients treated initially with prostacyclins were excluded. The starting point for all analyses was the date of therapy initiation. Outcomes were survival and TTCW, defined as the first occurrence of death, PAH-related hospitalization, lung transplant, initiation of parenteral prostacyclin, or worsening symptoms.

Results: Ninety-eight patients (initial ERA=24, initial PDE5=59, initial ERA/PDE5=15) were included; no significant differences in baseline variables existed. TTCW was significantly worse in patients initially started on ERA compared to PDE5 or ERA/PDE5 (p=0.0001, Fig 1). Baseline factors

independently associated with shorter TTCW were initial ERA (HR 0.38, p=0.009), lower DLCO (HR 0.69 per 10% change, p=0.04), and higher PVR (HR 1.10 per Wood unit change, p=0.007). Three year survival was significantly worse in the initial ERA group (52.9%) compared to the PDE5 (91.5%) or ERA/PDE5 group (92.9%, p=0.004, Fig 2). The only baseline factor independently associated with risk for death in this cohort was initial ERA therapy (HR 0.22, p=0.004).

Conclusion: Compared to PDE5 or combination ERA/PDE5, initial therapy with an ERA in SSc-PAH patients was associated with a significantly worse TTCW and survival, even after adjustment for commonly accepted prognostic factors. Although these findings may be the result of unmeasured imbalances between groups, it is plausible that known ERA side effects such as fluid retention may have led to clinical worsening. Further study into the optimal initial oral therapy in patients with SSc-PAH is needed.



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A Double Blind Randomized Control Trial of Oral Tadalafil in Interstitial Lung Disease of Scleroderma. Jyoti Parida, Alok Nath, Zafar Neyaz and Vikas Agarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: We conducted a single center double-blind, randomized, placebo-controlled trial to determine the effects of oral Tadalafil on lung function and health-related symptoms in patients with scleroderma-related interstitial lung disease (ILD).

Methods: We enrolled 39 patients with scleroderma- related ILD patients who received oral Tadalafil 20 mg or matching placebo every alternate day for 6 months. The primary outcome measure was change in forced vital capacity (FVC, expressed as % of the predicted value) from baseline values and secondary outcome measures were change in Diffusion Lung Capacity for Carbon Monoxide (DLCO), Total Lung Capacity (TLC), Health Assessment Questionnaire (S HAQ), Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) and 6 min walk distance at the end of 6 months of treatment with Tadalafil in comparison to placebo group.

Results: Of 39 patients, 30 completed 6 months of treatment and were included in the analysis. At 6 month, although there was no statistically significant difference in change in FVC (% predicted) from baseline between the 2 groups, patients receiving Tadalafil had shown an improvement in mean (+SE) FVC of 1.82±2.08 whereas patients in placebo group had no change in mean FVC. Out of secondary outcome measures, the only significant difference between the 2 groups was found in patient global assessment scores which was significantly improved in Tadalafil group ($p<0.05$). There was a trend for improvement in TLC, breathing score in visual analogue scale (VAS) and physician global assessment score favoring Tadalafil although the difference between the 2 groups were not significant ($P>0.05$). There was no significant difference in adverse events between both groups.

Conclusion: Treatment with 6 month oral Tadalafil (20 mg alternate days) in patients with scleroderma-related ILD resulted in improvement in patient global assessment score. There was a trend for improvement for lung function, physician global assessment and VAS breathing scores. A larger multicentric study with sufficient power and high dose of Tadalafil may determine the efficacy of Tadalafil in ILD.

Table: Change in outcome measures from Baseline to 6 month in Tadalafil vs placebo group

Characteristics	Baseline	Value at 6 month	Difference
Tadalafil Group (n 17)			
FVC (%Predicted)	49.18 ± 3.81	51.0 ± 4.06	1.82 ± 2.08
TLC (%Predicted)#	75.70 ± 5.18	78.50 ± 7.42	2.8 ± 4.57
DLCO(%Predicted)#	36.30 ± 3.51	35.9 ± 4.95	−0.4 ± 2.24
Mahler Dyspnoea score			
Baseline Instrument	7.0 ± 2.58		
Transitional Dyspnoea score		2.47 ± 0.77	
VAS Breathing(mm)	54.12 ± 9.15	24.71 ± 6.99	−29.41 ± 8.03
Physician global	60.12 ± 5.14	33.41 ± 5.22	−26.70 ± 5.67
Patient global	73.41 ± 5.88	31.35 ± 5.83	−42.05 ± 6.40*
SF36 (physical)	37.2 ± 1.69	45.04 ± 1.71	7.81 ± 1.95
SF36(Mental)	37.02 ± 2.85	45.88 ± 2.88	8.85 ± 3.28
Skin thickness score	17.71 ± 2.11	15.94 ± 2.71	−1.76 ± 1.53
6 min walk test(meters)	426.69 ± 34.08	472.65 ± 22.83	47.06 ± 11.33
RVSP (mm Hg)	31.71 ± 2.67	29.59 ± 2.47	−2.11 ± 2.40
Placebo Group (n 13)			
FVC (%Predicted)	57.46 ± 2.37	57.46 ± 3.05	0 ± 2.41
TLC (%Predicted)	78 ± 3.92	75.29 ± 4.71	−2.71 ± 5.75
DLCO(%Predicted)	45.57 ± 3.92	45.71 ± 4.82	0.14 ± 6.97
Mahler Dyspnoea score			
Baseline Instrument	**7.77** ± 2.97		
Transitional Dyspnoea score		2.31 ± 0.90	
VAS Breathing(mm)	22.38 ± 8.28	12.31 ± 4.53	−10.07 ± 6.31
Physician global	45.31 ± 6.67	32.62 ± 8.77	−12.69 ± 4.78
Patient global	49.07 ± 7.51	32 ± 8.84	−17.07 ± 5.69
SF36 (physical)	43.03 ± 2.65	48.64 ± 2.29	5.61 ± 2.43
SF36(Mental)	39.83 ± 3.42	47.9 ± 2.73	8.06 ± 2.46
Skin thickness score	20.23 ± 2.21	17.08 ± 2.20	−3.15 ± 2.08
6 min walk test(meters)	419.23 ± 25.37	464.23 ± 26.29	45 ± 16.93
RVSP (mm Hg)	28.62 ± 2.12	27.77 ± 2.97	−0.84 ± 3.06

Plus-minus values are means±SD. *p <0.05 for comparison with placebo group.
#Paired data for DLCO and TLC were available and analyzed for only 10 and 7 patients in Tadalafil and placebo group respectively.

Disclosure: J. Parida, None; **A. Nath**, None; **Z. Neyaz**, None; **V. Agarwal**, None.

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An Indirect Comparisons Analysis of Medications Used for Treatment of Raynaud's Phenomenon. Sampath Manickam[1], Elie Donath[2], Sandeep Dayanand[3] and Jonathan Greer[4]. [1]University of Miami Palm Beach Internal Medicine, West Palm Beach, FL, [2]University of Miami Miller School of Medicine Palm Beach Regional Campus, Atlantis, FL, [3]University of Miami Palm Beach Internal medicine, West palm beach, FL, [4]Arthritis & Rheumatology Associates, Boynton Beach, FL.

Background/Purpose: There are several pharmacological treatments used for treatment of Raynaud's phenomenon: calcium channel blockers, endothelin receptor antagonists, phosphodiesterase-5 enzyme inhibitors. The treatments have shown varying efficacy for relieving the symptoms of raynaud's phenomenon. One of the main determinants of the medications used for treatment of Raynaud's phenomenon is cost. The objective of this research is to perform a comparison of several pharmacological treatments for

raynaud's phenomenon. The medications that were analyzed were: Bosentan, Vardenafil, Tadalifil, Sildenafil, Udenafil, MQX-503 (a topical nitro formulation), Amlodipine. The main outcomes that were analyzed were Raynaud phenomenon attack frequency (number of attacks per day) and Raynaud condition score (a scale of 1 to 10, with higher scores indicating more severe symptoms).

Methods: Studies were extracted from a computerized literature search of PubMed, MEDLINE and EMBASE of all relevant RCT's. 8 RCT's, including 491 patients, were identified. There were two outcomes of interest: Raynaud phenomenon attack frequency (number of attacks per day) and Raynaud condition score. There were several outcomes of interest for safety: headache, nausea, vomiting, dizziness. Studies were included if they provided data at 10 weeks. For each outcome, a fixed-effects meta-analysis was employed to compare each drug to placebo. A mixed-treatment comparisons analysis was then utilized to compare each of these drugs to one another indirectly. Calculation of the probability that each treatment is best was implemented using the Bayesian Markov chain Monte Carlo method.

Results: In terms of Raynaud phenomenon attack frequency at 10 weeks, patients taking Vardenafil only had a 0.01 reduced attack frequency when compared to Amlodipine. In terms of Raynaud phenomenon attack frequency at 10 weeks, patients taking MQX-503 only had a 0.44 reduced attack frequency both were compared to Amlodipine. In terms of Raynaud condition score at 10 weeks, patients taking Vardenafil had a reduced 0.13 reduced Raynaud condition score when compared to Amlodipine (95% CI −2.55 to 2.77). In terms of rank probability, Tadalifil had a 44% chance of being the option most likely to be associated with the lowest Raynaud condition score at 10 weeks. The degree of incoherence (measuring how closely the network fits together) was low for all outcomes.

Conclusion: There are many parameters that determine the selection of a medication in the treatment of Raynaud's phenomenon such as cost, side effects and tolerability. Our analysis attempts to compare various medications for Raynaud's phenomenon in a network meta-analysis. The goal was to compare Raynaud phenomenon attack frequency and Raynaud Condition score. Based on the above statistical analysis, Vardenafil and Tadalifil may be considered to be superior options to other medications for reducing Raynaud phenomenon attack frequency and Raynaud condition score at 10 weeks.

Disclosure: S. Manickam, None; **E. Donath**, None; **S. Dayanand**, None; **J. Greer**, None.

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Heart Transplantation in 6 Patients with Systemic Sclerosis and a Primary Cardiac Involvement. Alena Ikic[1], Emmanuel Chatelus[2], Eric Epailly[1], Hélène Kremer[1], Jean Sibilia[2], Jacques Gottenberg[1], Sabine Pattier[3], Erwan Flecher[4], Céline Goeminne[5] and Thierry Martin[1]. [1]Strasbourg University Hospital, Strasbourg, France, [2]University Hospital of Strasbourg, Strasbourg, France, [3]Nantes University Hospital, Nantes, France, [4]Rennes University Hospital, Rennes, France, [5]Lille University Hospital, Lille, France.

Background/Purpose: There is no specific treatment for primary cardiac involvement in SSc. Even if heart transplantation is an option, only 1 case have been reported[1]. The aim of the study was to collect data of patients with SSc and a primary cardiac involvement requiring a heart transplantation in order to establish the clinical course and expectable outcomes for this procedure.

Methods: Retrospective chart review of patients with SSc and a primary cardiac involvement requiring a heart graft in one of the major transplantation centers in France.

Results: A national survey allowed us to identify 6 patients fulfilling ACR/EULAR 2013 classification criteria for SSc. They had a history of primary cardiac involvement with an unequivocal indication for heart transplantation. 4/6 patients were women, 50% had lcSSc and 1 patient had an overlap with RA (Table 1). The median age at SSc diagnosis was 28 years and time to cardiac dysfunction diagnosis was 2.5 years. All patients had at least another systemic involvement, mostly gastrointestinal and/or musculoskeletal. Immunosuppressive treatment excluding corticosteroids has been prescribed to 3 patients.

In the year before transplantation, all patients were classified NYHA functional capacity III or IV and 5 of them required at least 1 hospitalisation. Median time from cardiac dysfunction diagnosis to transplantation was 4 years. The leading indication was heart failure requiring intravenous vasopressors except for 1 patient who was transplanted for recurrent ventricular arrhythmia. Cardiac pre-transplantation structural, functional and hemodynamic data are presented in Table 2.

The histopathology specimen of the explanted heart revealed myocardial fibrosis compatible with SSc primary cardiac involvement in all patients. Infectious complications occurred in 4 patients, 2 patients had ischemic lesions and 1 patient died from an unexplained graft failure. Median intensive care unit stay after the surgery was 22 days. During a median follow-up of 2.8 years, 4 patients had at least one acute cellular rejection, mainly of mild grade. Mild heart allograft vasculopathy occurred after a median of 2 years in 3 of 4 patients in whom coronary arteries were explored.

Conclusion: Symptomatic cardiac involvement in SSc has a bad prognosis. Heart transplantation is a relatively safe life-saving procedure in carefully chosen SSc patients with primary cardiac involvement manifesting with progressive dysfunction and/or arrhythmic complications.

Reference:

1. Martens E. Transplantation. 2012

Table 1: Patients' characteristics

Patient	Sex	SSc subset	Age at SSc diagnosis (years)	Antibody profile	SSc diagnosis to cardiac involvement (years)	Other systemic manifestations	Previous IS	Indication for heart transplantation	Post-op infectious complications	Post-op ischemic complications	Post-transplantation IS (ongoing)	Post-transplantation follow-up (years)	Acute rejection (number, intensity)	Time to allograft vasculopathy (years)	Vital status up to May 2014
1	F	DcSSc	15	Anti-Scl70+	5	Upper GI, arthritis, myositis	MMF, CS	Recurrent ventricular tachycardia	0	0	Tacrolimus, Everolimus	0,5	No	Alive	
2	F	DcSSc	12	ANA+	12	Upper + lower GI, arthritis, myositis	D-Pen	Global heart failure	5	Yes	MMF, Everolimus	3	1, severe	2	Alive
3	F	LcSSc	35	ANA+	2	Upper GI, arthritis, myositis	CS	Global heart failure	1	Yes	MMF, Tacrolimus	0,1	No		Deceased
4	H	LcSSc	46	ANA-	2	Upper GI	No	RV heart failure	1	0	MMF, CSA	10	2, mild	7	Alive
5	H	LcSSc	32	ANA-	3	Upper GI	No	Global heart failure	0	0	CSA, Everolimus	12	2, mild	10	Alive
6	F	RA overlap	24	ANA+, RF+, anti-CCP+	1	Arthritis	TCZ, MTX, CS	Global heart failure	1	0	MMF, CSA	2,5	1, mild	1	Alive
Median			28		2,5							2,75			

Table 2: Cardiac structural and hemodynamic values before transplantation

Patient	LVEF (%)	LV filling pressures	RV dysfunction	MRI - Gadolinium enhancement	mPAP (mmHg)	RAP (mmHg)	Wegde pressure (mmHg)	PVR (dyn x s x cm^{-5})	CI (L/min/m^2)
1	35	N	Yes	T1 Biventricular	7	5	5	56	1,70
2	25	↑	Yes		32	12	22	192	2,60
3	17	N	Yes	No	30	11	25	190	1,40
4	27		Yes		22	20	18	145	1,10
5	15		Yes	No	12	7	8	72	2,90
6	15	↑	Yes	No	20	1	10	149	3,23
Median	21				21	9	14	147	2,15

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Mycophenolate Mofetil Versus Azathioprine in Scleroderma-Associated Interstitial Lung Disease: Results from the Australian Scleroderma Cohort Study. Claire Owen[1], Gene Ngian[1], Kathleen Elford[1], Owen Moore[2], Mandy Nikpour[2], Wendy Stevens[2], Susanna Proudman[3], Janet Roddy[4], Jane Zochling[5], Catherine Hill[6], Peter Nash[7], Allan Sturgess[8] and Joanne Sahhar[1]. [1]Monash Health, Melbourne, Australia, [2]St Vincent's Hospital, Melbourne, Australia, [3]Royal Adelaide Hospital, Adelaide, Australia, [4]Royal Perth Hospital, Perth, Australia, [5]Menzies Research Institute Tasmania, Hobart, TAS, Australia, [6]Queen Elizabeth Hospital, Adelaide, Australia, [7]Sunshine Coast Rheumatology, Maroochydore, Australia, [8]The St George Hospital, Sydney, Australia.

Background/Purpose: Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is common and when progressive, associated with significant morbidity and mortality. Cyclophosphamide is frequently used as first line therapy but evidence is lacking for sustained benefit and toxicity remains a concern. Consequently, patients are often switched to azathioprine (AZA) for maintenance therapy.

We report the efficacy and tolerability of mycophenolate mofetil (MMF) in the management of SSc-ILD and compare this with AZA.

Methods: Patients in the Australian Scleroderma Cohort Study treated with at least 3 months of MMF or AZA for SSc-ILD confirmed on high resolution computed tomography were identified. Pulmonary function tests (absolute and percent predicted values) at 6-monthly intervals were retrieved. Stability was defined as $<10\%$ change in absolute forced vital capacity (FVC), whilst $\geq 10\%$ increase or decrease defined improvement or decline respectively.

The Wilcoxon sign-rank test was used to compare lung function at 12 months prior to commencement (T-1), baseline (T0), 12 months (T1) and 24 months (T2).

Results: 17 and 49 patients were treated with MMF or AZA for a mean of 3.7±1.4 and 3.8±3.1 years, respectively, with 66% of both groups previously treated with cyclophosphamide. Patients were treated with an average MMF dose of 1.57g/day and AZA of 100mg/day.

Mean age at commencement was 54.6±9.3 years for MMF and 52.9±12.9 years for AZA (p=0.23). Patients in both groups were predominantly female and Caucasian with long-standing disease (10.9±3.7 years for MMF vs. 12.7±7.3 years for AZA, p=0.28). Disease was diffuse in 65% of patients on MMF and 51% on AZA.

Median absolute FVC at T-1 for MMF treatment was 2.5L, declining to 2.3L at T0 (p=0.02). At T1 and T2, FVC was stable at 2.1L (p=0.63) and 2.1L (p=0.93). Median absolute diffusion capacity (DLCO) also demonstrated decline prior to treatment (12.2 to 9.8, p=0.03), with stability at T1 (10.4, p=0.83) and T2 (11.9, p=0.04). Stability or improvement was seen at T1 in 12/15 and T2 in 9/11 cases. Comparable efficacy was achieved with AZA (16/19 cases were stable or improved at T1 and 14/19 at T2).

Adverse events leading to discontinuation were less common in the MMF group (2/17 vs. 13/49). Gastrointestinal complications were the main cause for discontinuation in both groups.

Conclusion: In patients with SSc-ILD with declining pulmonary function, MMF treatment was associated with stability in FVC and DLCO comparable to AZA and was better tolerated, suggesting a potentially superior role as maintenance therapy.

Disclosure: C. Owen, None; **G. Ngian**, None; **K. Elford**, None; **O. Moore**, None; **M. Nikpour**, None; **W. Stevens**, None; **S. Proudman**, None; **J. Roddy**, None; **J. Zochling**, None; **C. Hill**, None; **P. Nash**, None; **A. Sturgess**, None; **J. Sahhar**, None.

1683

Botulinum Toxin-a for the Treatment of Severe Raynaud Phenomenon. Lucía Ruiz Gutiérrez[1], Ana Pérez Gómez[1], Nuria Valdeolivas Casillas[2], Henry Moruno Cruz[1], Eduardo Cuende Quintana[1], Ana Sánchez Atrio[1], Ana Turrión Nieves[1], Atusa Movasat[1], Cristina Bohórquez Heras[1], Fernando Albarrán Hernández[1], Maria Liz Romero Bogado[1], Susana Medina Montalvo[2] and Melchor Álvarez de Mon[1]. [1]Hospital Príncipe de Asturias, Immune System Diseases/Rheumatology department, Alcalá de Henares, Madrid, Spain, [2]Hospital Príncipe de Asturias, Dermatology department, Alcalá de Henares, Madrid, Spain.

Background/Purpose: Raynaud's phenomenon (RP) is characterized by transient episodes of vasoconstriction of the arteries and arterioles of the extremities in response to cold or emotional stimuli. Depending on the severity of the vascular insult, it can cause superficial ulceration or deep-tissue necrosis. Pharmacological treatments aim to enhance blood flow but their efficacy is not uniform.

Methods: We present a series of 7 patients with Raynaud's phenomenon with bad response to conventional pharmacological therapy that have been treated with local botulinum neurotoxin-A. Patients' characteristics are summarized in table 1. Exclusion criteria included botulinum toxin allergy, active infection at the site of injection, previous digital sympathectomy and pregnancy.

A cumulative total dose of 30–60 units of botulinum toxin was injected into the palmar aspect of the hand. Prior to infiltration, obstructive pathology was ruled out by Doppler ultrasound; also, a nailfold capillaroscopy test was performed before and after the infiltration. Variables such as the number of episodes per day, pain during the episodes, recuperation time, finger color and presence of digital ulceration or necrosis have been studied baseline, 30 minutes, one week and one month after the infiltration.

Results: 30 minutes after infiltration, three patients felt no improvement, two assessed slight improvement and two very important improvement. At the patients' one-week and thirty-days follow-up visits two patients did not perceive any change and four experienced great amelioration. Patients that did not register any change where those with fewer subjective clinical complaints and normal Doppler ultrasound and capillaroscopy tests.

The variable with the most remarkable response was pain, with important pain decrease in all of the cases. Three patients presented digit ulcers at baseline visit; ulceration healing was noted in all of them, two of them one week after the injection and the other one, one month after.

Three patients reported mild "weakness" after being injected and one reported slight thenar-eminence pain that lasted a few days. None of the patients suffered any systemic complications related to the toxin.

Conclusion: Botulinum toxin-A is a safe and effective therapeutic option for patients with severe Raynaud's phenomenon that have failed to conventional treatment.

Table 1

PATIENT	SEX	AGE	ASSOCIATED DIAGNOSIS	PREVIOUS MANAGEMENT
1	Female	52	CREST	- Calcium channel blockers - Prostacyclin Analogs
2	Female	51	CREST	- Calcium channel blockers
3	Female	41	CREST	- Calcium channel blockers
4	Female	35	CREST	- Calcium channel blockers - Prostacyclin Analogs - Pentoxifylline - Endothelin receptor antagonists
5	Female	41	MCTD	- Calcium channel blockers
6	Female	48	Reynolds syndrome	- Calcium channel blockers
7	Female	37	Primary RP	- Calcium channel blockers

CREST: Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia
MCTD: mixed connective tissue disease

Disclosure: L. Ruiz Gutiérrez, None; **A. Pérez Gómez**, None; **N. Valdeolivas Casillas**, None; **H. Moruno Cruz**, None; **E. Cuende Quintana**, None; **A. Sánchez Atrio**, None; **A. Turrión Nieves**, None; **A. Movasat**, None; **C. Bohórquez Heras**, None; **F. Albarrán Hernández**, None; **M. L. Romero Bogado**, None; **S. Medina Montalvo**, None; **M. Álvarez de Mon**, None.

1684

Treatment of Scleroderma Associated Lung Disease with Mycophenolate Mofetil: A Community-Based Study. Audrey Bearden[1], Kent Kwasind Huston[2] and Judy Foxworth[3]. [1]University of Missouri-Kansas City, Kansas City, MO, [2]The Center for Rheumatic Disease, Kansas City, MO, [3]The University of Missouri-Kansas City, Kansas City, MO.

Background/Purpose: Interstitial lung disease occurs in over 80% of patients with scleroderma. Cyclophosphamide is the only treatment proven to benefit scleroderma lung disease in a large randomized placebo-controlled trial. However, the clinical benefit is modest and potential adverse effects are a major concern. Mycophenolate mofetil (MMF) has been reported to stabilize scleroderma lung disease in case series from academic institutions. However, patient characteristics may vary from the academic to community setting and the relevance of these reports to the broader rheumatology community is uncertain. Our purpose is to analyze the effect of MMF in scleroderma lung disease from a community-based rheumatology clinic.

Methods: Patients who fulfilled the 2013 ACR/EULAR classification criteria for scleroderma were identified in a community-based rheumatology practice. All patients included had evidence of scleroderma lung disease and treatment with MMF. Exclusion criteria were patients treated for < 4months, >14 months between baseline data and initiation of MMF, or >24 months after initiation of MMF for follow-up data. Lung functions, CT scans, and clinical symptoms were analyzed at baseline and post treatment. A total of thirteen patients were identified who met the above criteria. A paired student t-test was performed to assess pre and post MMF treatment change in forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO).

Results: A total of 22 patients met inclusion criteria. Of these 22 patients, 1 was deceased from pulmonary arterial hypertension, 2 stopped treatment before follow-up due to severe diarrhea, and 6 did not have timely baseline or follow-up data. This left 13 patients for analysis who were treated an average of 10 months with MMF. There was no significant difference between baseline and post treatment values for FVC or DLCO (p=0.89, p =0.76, respectively). The mean % predicted FVC pre and post MMF was 72 and 72 respectively. The mean % predicted DLCO pre and post MMF was 66 and 67 respectively. There were only two individuals who experienced a significant decline in FVC from baseline to follow up as defined by national criteria (absolute change in FVC of 10%).Baseline and post treatment CT scans were also evaluated. Of the 13 patients, 9 had stable CT findings, 2 worsened, and 2 improved. Clinical symptoms of cough and dyspnea were all stable or improved on MMF therapy.

Conclusion: MMF appears effective in preventing progression of scleroderma lung disease in a community-based setting. Compared to historical controls, we would have expected worsening lung function in the absence of treatment as seen in the placebo arm of the Scleroderma Lung Study. Limitations to our study include the lack of a standard protocol for individual rheumatologists to record symptoms, clinical findings, or standard intervals for pulmonary function tests and CT scans. Also, pre and post treatment CT scans were not universally interpreted by the same radiologist. These limitations were expected given the nature of rheumatology practice outside of academic centers. Our study supports the use of MMF for scleroderma lung disease in the community-based setting.

Disclosure: A. Bearden, None; **K. K. Huston**, None; **J. Foxworth**, None.

1685

Effects of Mycophenolate Mofetil on Pulmonary Lung Function in Interstitial Lung Disease of Systemic Sclerosis. Michael Pham and W Leroy Griffing. Mayo Clinic Arizona, Scottsdale, AZ.

Background/Purpose: Interstitial lung disease remains a primary driver of morbidity and mortality in patients suffering from systemic sclerosis. Cyclophosphamide currently is the treatment with the most data and experience; however, toxicity and poor tolerance often limit its clinically modest usefulness. Mycophenolate mofetil (MMF) has received growing interest as an alternative agent. In this study, effects of MMF on pulmonary lung function in systemic sclerosis-associated interstitial lung disease were examined.

Methods: Twenty patient cases were retrospectively reviewed having met the American College of Rheumatology's criteria for systemic sclerosis. Interstitial lung disease was defined and characterized by high-resolution chest tomography. Cases were included if treatment was greater than 1 gram per day dosing of MMF for at least 6 months. Pulmonary function test results were collected prior to and following treatment initiation at 6 month intervals for a total 30-month monitoring time span.

Results: Six-to-twelve months prior to MMF initiation, mean predicted forced vital capacity (%FVC) was 74% ± 15.9% (mean ± SD) and declined to 71.3% ± 16.8% at treatment baseline. Following MMF initiation, the mean %FVC remained stable at 70.7% ± 12.9% and 71.2% ± 14.2% at the 6-to-12 and 12-to-18 month follow-up interval period, respectively. Mean rate of change in %FVC or *%FVC velocity* was −0.25% ± 0.93% per month prior to MMF treatment. Following MMF treatment, rates of decline reversed and %FVC velocity was +0.18% ± 0.62% per month at the 6-to-12 month follow-up interval – a statistically significant improvement (p=0.005). Mean predicted diffusion capacity of carbon monoxide (%DLCO) was 54.3% ± 14.4% prior to treatment. After MMF treatment, %DLCO improved to 56.1% ± 15.2% by the 6-to-12 month follow-up interval and to 57.4% ± 19.0% by the 12-to-18 month follow-up interval. These results are summarized in Figure 1 below.

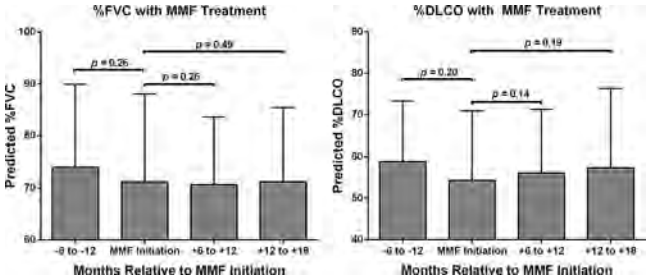

Figure 1

Conclusion: We report trends of stability with %FVC and trends of improvement with %DLCO over an 18-month period following MMF treatment. Our findings suggest mycophenolate mofetil is a promising alternative treatment for interstitial lung disease of systemic sclerosis. However, these observations were not statistically significant and further emphasize the need for a higher powered randomized clinical trial.

Disclosure: M. Pham, None; **W. L. Griffing**, None.

1686

DUAL Energy Computed Tomography for the Evaluation of Calcinosis in Systemic Sclerosis. Vivien Hsu[1], Mark Bramwit[2] and Naomi Schlesinger[3]. [1]RWJ Med Schl Scleroderma Prog, New Brunswick, NJ, [2]Robert Wood Johnson University Hospital, New Brunswick, NJ, [3]Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ.

Background/Purpose: To better characterize the soft tissue details of systemic sclerosis–related (SSc) calcinosis of the hands using dual-energy computer tomography (DECT). DECT is an imaging modality used similarly to study monosodium urate (MSU) deposition in gout (1).

Methods: Fourteen patients with symptomatic hand SSc-calcinosis had DECT imaging and their clinical characteristics reviewed.

Results: Eight of 14 patients had diffuse SSc and 6 also had rheumatoid arthritis (RA). Herein are 3 DECT images: *Image 1:* a caucasian male with lifelong calcinosis due to diffuse scleroderma, whose painful deposits drain intermittently. *Image 2:* a caucasian female with limited SSc and RA for 15 years, whose calcinosis was found by imaging. *Image 3:* an African-American female with diffuse scleroderma and RA for 10 years. Her calcinosis caused painful wrist swelling, but despite surgery, continues to accumulate.

On DECT imaging, calcinosis was most commonly found in the subcutaneous (SQ) fat pads of the fingertips and along tendon sheaths and muscle groups. Acro-osteolysis was present in most (93%) patients, 7 (50%) with calcinosis nearby. No MSU was identified. Our cohort also had pulmonary fibrosis (79%), ischemic digital ulcers (71%) and bowel (43%) complications.

Conclusion: SSc-calcinosis affects diffuse and limited SSc. We found DECT imaging better defined the soft tissue details and was useful in the evaluation of SSc-calcinosis.

References:

1. Choi K: Ann Rheum Dis 2009; 68 (10):1609.

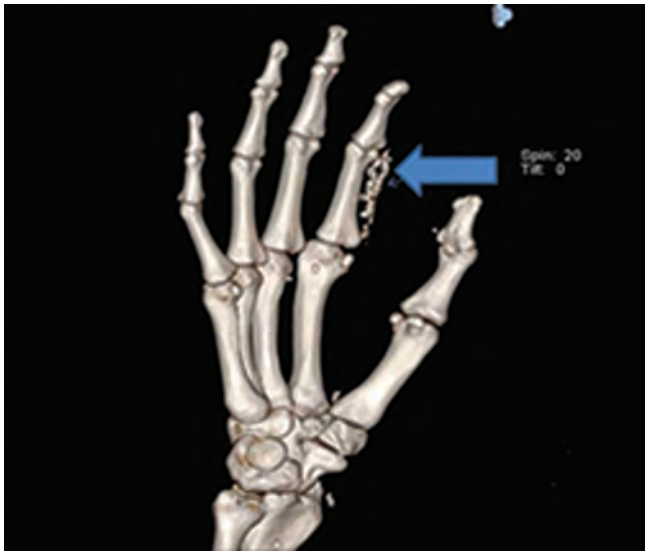

Image 1: 3D image shows acro-osteolysis of the 2nd and 3rd digits, extensive calcification in the SQ fat (volar) of the second digit (arrow), punctate deposits in the fat pad of thumb, lateral to the scaphoid bone, and between several MCP joints.

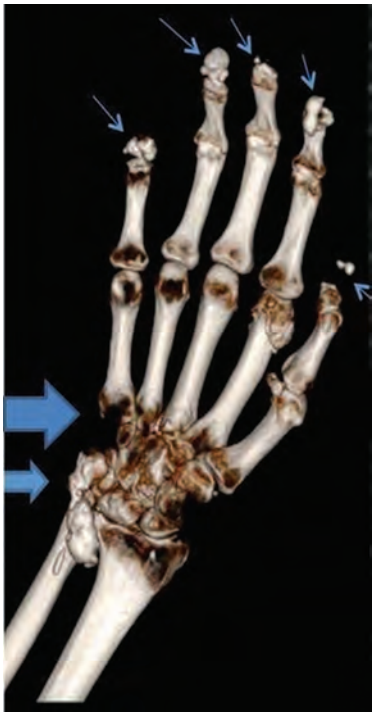

Image 2: Acro-osteolysis with associated calcinosis in the fat pads of all fingertips (small arrows); extensive calcification seen around the 1st and 2nd MCP and ulna (adjacent to the carpal tunnel) (medium arrow). The distal 5th phalanx is completely eroded (large arrow). The wrist deposits appear separate from the tendons.

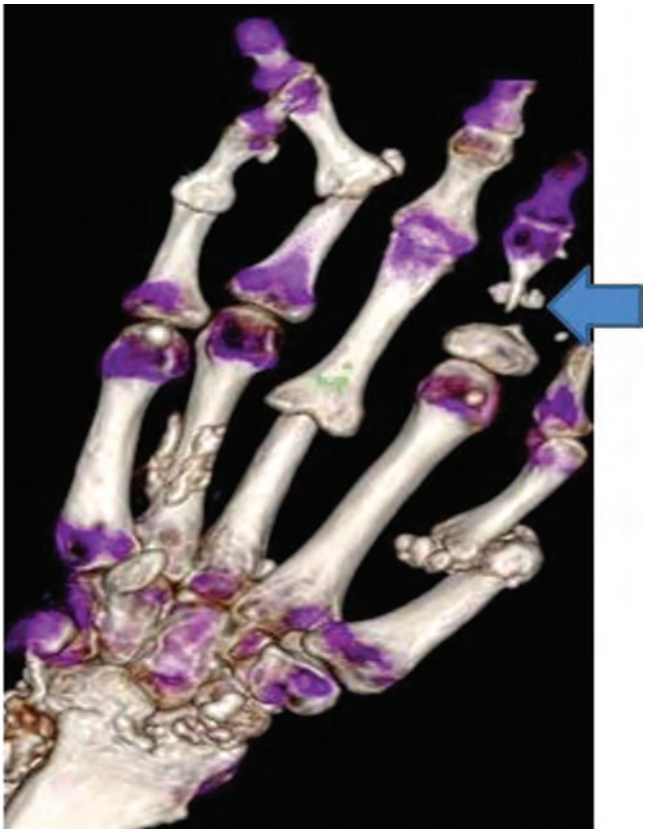

Image 3: Soft tissue calcifications seen throughout the fingers and wrist with marked destruction at the radio-carpal joint. The scaphoid may be partially collapsed. There is severe penciling with nearly complete bone resorption (large arrow) of mid portion of 2nd phalanx.

Disclosure: V. Hsu, None; **M. Bramwit**, None; **N. Schlesinger**, Novartis Pharmaceutical Corporation, 2, Takeda, 8, Sobi, 9, Astra Zeneca, 9.

1687

Key Role of Cardiac Biomarkers in the Assessment of Systemic Sclerosis: Contribution of High Sensitivity Cardiac Troponin. Jerome Avouac[1], Christophe Meune[2], Camille Gobeaux[3], Didier Borderie[3], Guillaume Lefevre[4], Andre Kahan[5] and Yannick Allanore[1]. [1]Paris Descartes University, Rheumatology A Department and INSERM U1016, Cochin Hospital, Paris, France, [2]Paris 13 University, University Hospital of Paris-Seine-Saint-Denis, Cardiology Department, Bobigny, France, [3]Paris Descartes University, Biochemistry A department, Cochin Hospital, Paris, France, [4]Clinical Chemistry and Hormonology Department, Tenon Hospital, paris, France, [5]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France.

Background/Purpose: Microangiopathy is a cardinal feature of systemic sclerosis (SSc), which plays a critical role in the development of primary myocardial involvement and pulmonary hypertension, two major causes of death in SSc. Our aim was to measure plasma concentrations of two cardiac biomarkers, high sensitive Cardiac troponin T (HS-cTnT), a marker of myocyte necrosis and/or ischemia, and N-terminal fragment of pro-BNP (NT-proBNP), a marker of cardiac strain, in two large cohorts of SSc patients and controls.

Methods: 161 SSc patients (135 women, 84%) with a mean ± SD age of 57±17 years were included and were compared to 213 healthy controls (170 women, 80%, mean ± SD age of 55±11 years).

Results: Among the SSc cohort, mean disease duration was 9±8 years, 65 patients (40%) had the diffuse cutaneous subset. HS-cTnT and NT-proBNP plasma levels were significantly increased in SSc patients versus controls ($p=0.0001$ and $p<0.0001$ respectively). SSc patients were more likely to have above the cut-off value concentrations of HS-cTnT (>14 ng/L) and NT-proBNP than controls (30/161 patients (19%) with HS-cTnT >14 ng/l vs. 4/213 controls (2%), $p<0.0001$; 17/161 patients (11%) with increased NT-proBNP levels vs. 8/213 controls (4%), $p=0.02$). Similar results were observed in the subgroup of patients free of any cardiovascular risk factors. Multivariate logistic regression analysis confirmed diabetes mellitus ($p=0.006$), high blood pressure ($p=0.02$), precapillary pulmonary hypertension (PH) ($p=0.04$), ESR >28 mm/H1 ($p=0.007$) and the diffuse cutaneous subset ($p=0.004$) as factors independently associated with HS-cTnT >14 ng/L. Increased NT-proBNP concentrations were only associated with the presence of precapillary PH ($p=0.0001$). The combination of increased HS-cTNT and NT-proBNP levels had the highest positive predictive value for the diagnosis of precapillary PH (67%) compared to HS-cTnT (20%) or NT-proBNP (35%) alone.

Conclusion: Plasma levels of HS-cTnT and NT-proBNP are increased in SSc patients. Associated factors with increased HS-cTnT include the diffuse cutaneous subset and precapillary PH, which reflect the severity of the disease. In addition, the combination of increased HS-cTnT and NT-proBNP plasma concentrations display higher positive predictive value for the diagnosis of precapillary PH than each marker alone. Given the prognostic significance of these biomarkers, they might be helpful to select the patients that justify further examinations in case of suspicion of cardiac complication.

Disclosure: J. Avouac, None; **C. Meune**, None; **C. Gobeaux**, None; **D. Borderie**, None; **G. Lefevre**, None; **A. Kahan**, None; **Y. Allanore**, None.

1688

Early Detection of Left Ventricular Morphological, Functional Abnormalities and Myocardial Characteristics in Systemic Sclerosis without Cardiac Symptoms Using Cardiac Magnetic Resonance Imaging: A Preliminary Report. Kaita Sugiyama[1], Hitomi Kobayashi[1], Yasuyuki Kobayashi[2], Yosuke Nagasawa[1], Natsumi Ikumi[1], Takamasa Nozaki[1], Hirotake Inomata[1], Hidetaka Shiraiwa[1], Hiromi Karasawa[1], Noboru Kitamura[1], Mitsuhiro Iwata[1], Yoshihiro Matsukawa[1] and Masami Takei[1]. [1]Nihon University School of Medicine, Tokyo, Japan, [2]St.Marianna University School of Medicine, Kawasaki, Japan.

Background/Purpose: Systemic sclerosis (SSc) is associated with an increased prevalence of cardiac involvement despite often being clinically silent. Cardiac involvement is a major factor in decreasing SSc survival rates because it is associated with a 70% 5-year mortality rate. Cardiac magnetic resonance imaging (CMR) is useful in SSc since it focuses on late gadolinium enhancement (LGE) abnormalities, ventricular morphology, and function. Our study aimed to comprehensively analyze CMR and investigate the association between CMR findings and brain natriuretic peptide (BNP) in SSc patients (pts) without cardiac symptoms.

Methods: Consecutive female pts with SSc without cardiac symptoms as well as healthy female controls were enrolled. SSc pts and control subjects with no history or clinical findings of systemic and pulmonary hypertension determined by echocardiography, coronary artery disease, valvular heart disease, atrial fibrillation, diabetes mellitus, and dyslipidemia underwent non-contrast or contrast CMR on a 1.5T scanner. Left ventricular (LV) function was measured using LV ejection fraction (EF), end-systolic volume (ESV), end-diastolic volume (EDV), stroke volume (SV), and cardiac output (CO). LV hypertrophy was measured by absolute LV mass (LVM) and LVM index (LVMI) determined by the LVM/body surface area. LGE was obtained to assess myocardial fibrosis. Myocardial inflammation was assessed with black blood T2-WI. Serum BNP concentrations were measured simultaneously in all participants.

Results: We compared 35 SSc pts (mean age, 55.9±7.1 years)—19 with diffuse type and 16 with limited type—with 20 healthy controls (mean age, 56.9±3.1 years). There were no significant differences in characteristics such as age, gender, and cardiovascular risk factors, between SSc and control group. Compared with the control group, the SSc group had a significant higher EDV with tendency toward a high LVMI. There was no difference in EF between the control and SSc groups. SSc with LGE was detected in 16 of 35 pts (46%). The main finding observed in 9 of these 16 (56%) pts was a linear pattern without coronary distribution. A patchy nodular enhancement pattern was observed in 7 pts (44%). LVMI and mass/EDV were significant higher in the LGE (+) group than in the LGE (−) group ($P>0.001$, $P=0.003$, respectively). T2-WI imaging showed myocardial inflammation in 6 of 35 pts (17%). The mean BNP level of the SSc group was significantly higher than that of the control group ($P=0.04$). The mean BNP level of the SSc with LGE group was significantly higher than that of the SSc without LGE group ($P=0.023$). BNP level was significantly correlated with LVMI and EF in the SSc group ($P=0.04$, $P=0.05$, respectively).

After adjustment for age, disease duration, and BNP, the SSc with LEG group did not have a modified association with LVMI.

Conclusion: SSc patients without cardiac symptoms have a high prevalence of cardiac abnormalities. SSc patients with LGE had abnormal morphology associated with LVMI and serum BNP even with a normal EF. Further studies are needed to determine whether CMR abnormalities affect prognosis or treatment strategy.

Disclosure: K. Sugiyama, None; **H. Kobayashi**, None; **Y. Kobayashi**, None; **Y. Nagasawa**, None; **N. Ikumi**, None; **T. Nozaki**, None; **H. Inomata**, None; **H. Shiraiwa**, None; **H. Karasawa**, None; **N. Kitamura**, None; **M. Iwata**, None; **Y. Matsukawa**, None; **M. Takei**, None.

1689

Microhaemorrages and Giant Capillaries in Nailfold Videocapillariscopies Are Able to Accurately Predict Disease Activity Level in Systemic Sclerosis. Domenico Sambataro[1], Nicoletta Del Papa[1], Gianluca Sambataro[2], Wanda Maglione[2], Eleonora Zaccara[2] and Claudio Vitali[3]. [1]Istituto G.Pini, Milan, Italy, [2]Osp. G. Pini, Milano, Italy, [3]Istituto San Giuseppe, Lecco, Italy.

Background/Purpose: Systemic Sclerosis (SSc) is a connective tissue disease characterized by Raynaud's phenomenon, skin fibrosis and involvement of internal organs such as lung, heart, bowel, and kidney. The microvascular involvement is considered an hallmark of disease. Nailfold Videocapillaroscopy (NVC) is a simple method able to identify the disease-related microvascular alterations in an easily accessible capillary bed and is commonly used for diagnosis and patients' sub-setting.

Aim of this study is to evaluate whether the number of micro-haemorrhages (MHE), micro-thrombosis (MT), giant capillaries (GC), and normal or dilated capillaries (Cs) in NVC could predict disease activity (DA) in SSc.

Methods: One hundred and seven patients (57 with limited cutaneous and 50 with diffuse cutaneous SSc, 10 males) meeting the 2013 ACR/EULAR classification criteria, were selected for this study. The European Scleroderma Study Group (ESSG) index was taken as gold standard for DA assessment. Score ≥ 3.5 and $=3$ were considered as indicative of highly and moderate DA, respectively. NVC was performed on 8 fingers (second to fifth of both hand) in the middle of nailfold taking 4 consecutive fields of 1 millimeter with a 200× magnification lens. The following NVC features were considered: total number of MHE/MT aligned in the same row on the cuticle (here called NEMO score); total number of GC (GC score); mean number of Cs observed in all NCV fields (Cs score).

Non-parametric tests were used to compare the NVC scores with the variables here taken into account. Receiver operating characteristic (ROC) curves were constructed by plotting sensitivity and specificity values of NVC scores in correctly classifying patient having or not an active disease phase. Logistic regression model was also tested to assess the contribution of the NVC scores in predicting the presence of DA.

Results: NEMO and GC scores were positively correlated with ESSG index ($R=0.65$, $p<0.0001$, and $R=0.47$, $p<0.0001$, respectively), whilst Cs score showed a negative correlation with that DA index ($R=-0.30$, $p<0.001$).

The area under the curve (AUC) of receiver operating characteristic (ROC) plots, obtained by NEMO score sensitivity and specificity values in classifying patients with ESSG index ≥ 3.5, was significantly higher than the corresponding AUC derived from either GC or Cs scores ($p<0.001$ and $p<0.0001$, respectively). A modified score, defined by the presence of given number of MHE/MT and GC, had a good performance in classifying active patients (ESSG index ≥ 3, sensitivity 95.1%, specificity 84.8%, accuracy 88.7%).

Conclusion: This newly proposed NCV scoring system, here named mNEMO score, seems to be a valid tool to predict DA level in SSc. In addition, it appears also feasible since it can be derived simply during an outpatient visit and in a rather short time.

It is, of course, evident that a patient with a positive mNEMO score should be addressed to a more careful clinical, instrumental, and serological evaluation to confirm the suspicion and define a more precise clinical profile.

Disclosure: D. Sambataro, None; **N. Del Papa**, None; **G. Sambataro**, None; **W. Maglione**, None; **E. Zaccara**, None; **C. Vitali**, None.

1690

Improvement of Digital Ulcerative Disease in Patients with Systemic Sclerosis Is Associated with Better Functional Prognosis. Patrick Carpentier[1], Catherine Lok-Charles[2], Pierre Clerson[3], Virginie Gressin[4], Eric Hachulla[5], Alice Berezne[6], Elizabeth Diot[7], Aurelie Khau VAN Kien[8], Patrick Jego[9], Christian Agard[10], Anne Bénédicte Duval Modeste[11], Agnès Sparsa[12], Eve Puzenat[13], Marie-Aleth Richard[14] and Luc Mouthon[15]. [1]La Tronche Hospital, Grenoble, France, [2]Amiens University Hospital, Amiens, France, [3]Orgametrie, Roubaix, France, [4]Actelion France, Paris, France, [5]National Scleroderma Centre, Lille CEDEX, France, [6]Paris Descartes University, Internal Medicine department, Cochin Hospital, Paris, France, [7]Department of Internal Medicine, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire de Tours, Tours, France, Tours, France, [8]Montpelier University Hospital, Department of Internal Medicine, Montpelier, France, [9]Rennes University Hospital, Rennes, France, [10]Nantes University Hospital, Nantes, France, [11]Rouen University Hospital - Clinical Dermatology, Rouen, France, [12]Dupuytren Regional University Hospital-, Limoges, France, [13]Besançon University Hospital, Besançon, France, [14]Marseille, Paris, France, [15]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France.

Background/Purpose: Ischemic digital ulcers (DU) represent a major complication of systemic sclerosis (SSc) leading to hand disability. We investigated the impact of controlling the ulcerative disease on hand disability and quality of life in SSc patients following one year of bosentan treatment.

Methods: ECLIPSE is a 2-year prospective, observational study. Patients with SSc who experienced at least one DU in previous year and received bosentan to prevent occurrence of new DU were included between October 2009 and March 2011.Demographical and clinical data were collected at inclusion and at 1 year, as well as disability scores (Cochin hand function scale (CHFS), health assessment questionnaire disability index (HAQ-DI)), pain score (Visual Analog Scale), and quality of life (SF-36). A controlled ulcerative disease was defined by healing of all DU present at inclusion and the absence of new ulcer between inclusion and one-year follow-up. Data are presented as means ± standard deviations.

Results: Follow-up data were available at one year for 120 patients out of the 190 included patients. Patients' characteristics were similar to those of the overall cohort. Mean age at inclusion and at SSc diagnosis were 54 ± 15 and 44 ± 15 years, respectively. SSc was diffuse in 42% of the cases. At inclusion, patients had been receiving bosentan for 15.6 ± 22.1 months. During the one-year follow-up, 46 (38%) patients experienced an episode of new DU and the incidence of the event was 0.6 event/patient-year [95% confidence interval: 0.44–0.81]. Nevertheless, the proportion of patients with at least one DU decreased from 61% to 22% and the number of DU per patient decreased from 1.4 ± 1.8 to 0.6 ± 1.6 ($p < 0.0001$). In parallel disability scores decreased from 29.4 ± 20.1 to 25.0 ± 20.2 ($p=0.005$) on the CHFS and from 0.96 ± 0.68 to 0.88 ± 0.73($p=0.04$) for the HAQ-DI; the pain score decreased from 4.3 ± 3.1 to 2.9 ± 2.8 ($p<0.0001$). Improvements in the physical and mental components of the SF-36 were non-significant except for bodily pain ($p=0.04$) and mental health ($p = 0.01$).

Patients with a controlled ulcerative disease ($n=58$) significantly improved CHFS ($p = 0.04$), HAQ-DI ($p = 0.04$), and physical component of the SF-36 ($p = 0.05$) compared with patients with an uncontrolled disease ($n=62$).

During the one-year follow-up, 21 (17%) patients discontinued bosentan for an adverse event including 5 patients presenting elevated aminotransferases

Conclusion: In patients with SSc receiving bosentan, a controlled ulcerative disease is associated with a significant attenuation of disability.

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Systemic Sclerosis Patients with Pulmonary Hypertension Have a Lower Change in End Tidal Carbon Dioxide Following Three Minutes of Step Exercise Than Systemic Sclerosis Patients without Pulmonary Hypertension: A Cross-Sectional Study. Elana J. Bernstein[1], Jessica K. Gordon[2], Robert F. Spiera[2], Wei-Ti Huang[2], Evelyn M. Horn[3] and Lisa A. Mandl[2]. [1]Columbia University College of Physicians & Surgeons, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]New York Presbyterian Hospital/Weill Cornell Medical College, New York, NY.

Background/Purpose: Pulmonary hypertension (PH) is a leading cause of death in patients with systemic sclerosis (SSc). Transthoracic echocardiogram and pulmonary function testing are standard noninvasive screening methods for PH. However, both are limited in their ability to distinguish between SSc patients with and without PH. The gold standard diagnostic test for PH is right heart catheterization (RHC), which although accurate, is expensive, invasive, and has associated risks. Finding an accurate, noninvasive technique to screen for PH in the SSc population is an important unmet need.

The submaximal heart and pulmonary evaluation (step test) is a standardized, noninvasive, submaximal stress test that consists of a 5.5 inch high step that patients step up and down on for 3 minutes. During the test, end tidal carbon dioxide, which is positively correlated with cardiac output and pulmonary blood flow and inversely correlated with the minute ventilation to carbon dioxide production ratio (V_E/V_{CO2}) and reflects the severity of PH, is monitored. Our primary aim was to determine whether SSc patients with PH would have a lower change in end tidal carbon dioxide (ΔP_{ETCO2}) from rest to end-exercise on the step test than SSc patients without PH. Our secondary aim was to determine whether SSc patients with PH would have a higher V_E/V_{CO2} than those without PH. We also examined differences in validated self-report questionnaires and biomarkers between SSc patients with and without PH. We hypothesized that SSc patients with PH would have a lower ΔP_{ETCO2} and higher V_E/V_{CO2} than SSc patients without PH.

Methods: This is a cross-sectional study of 27 patients with limited or diffuse cutaneous SSc who underwent an RHC within 24 months of study entry. All patients were administered the step test between May 2012 and August 2013. ΔP_{ETCO2} and V_E/V_{CO2} were compared between patients with and without PH, defined as a mean pulmonary artery pressure $\geq$ 25 mmHg on RHC. Differences in self-report data and biomarkers were also compared between groups. Statistical analysis was performed using Kruskal-Wallis, chi square, and Fisher exact tests, as appropriate.

Results: See Table 1 for patient characteristics. SSc patients with PH had a statistically significantly lower median ΔP_{ETCO2} than SSc patients without PH (−2.1 [−5.1 – +0.7] vs. 1.2 [−0.7 - +5.4], p=0.035) and a statistically significantly higher median V_E/V_{CO2} (53.4 [39–64.1] vs. 36.4 [31.9–41.1], p=0.035) than SSc patients without PH. There were no statistically significant differences in self-report data or biomarkers between groups (Table 1).

Conclusion: ΔP_{ETCO2} and V_E/V_{CO2} as measured by the step test are statistically significantly different between SSc patients with and without PH. Neither traditional self-report outcome measures nor biomarkers differed between groups. Further prospective studies are needed to evaluate the step test as a screening tool for PH in the SSc population.

Table 1: Patient Characteristics, Self-Report Questionnaire Scores, and Biomarker Levels

Patient Characteristics	PH (N = 18)	No PH (N = 9)	p-value
Age – yr	61.9 (52.9–69.2)	65.7 (56.4–70.3)	0.64
Female sex	13 (72%)	5 (56%)	0.39
White race	13 (72%)	7 (78%)	0.76
Limited cutaneous SSc	13 (72%)	6 (67%)	0.77
Disease duration – yr	17.5 (6.4–26.1)	11.5 (4.02–19.4)	0.22
Time between RHC and step test – months	9.9 (7.2–16.5)	12.5 (4.6–22.5)	0.64
Anti-centromere antibody positive	6/17 (35%)	3 (33%)	0.92
Anti-Scl-70 antibody positive	2/17 (12%)	4 (44%)	0.06
Anti-RNA polymerase III antibody positive	1/16 (6%)	0/7 (0%)	0.99
Raynaud's phenomenon	17 (94%)	9 (100%)	0.47
Digital ulcerations	10 (56%)	6 (67%)	0.58
Renal crisis	0 (0%)	0 (0%)	
Sclerodactyly	16 (89%)	8 (89%)	
Interstitial lung disease	10 (56%)	5 (56%)	
Gastroesophageal reflux disease	16 (89%)	9 (100%)	0.30
Calcinosis	7 (39%)	4 (44%)	0.78
Telangiectasias	13 (72%)	7 (78%)	0.76
Proximal lower extremity weakness	1 (6%)	0 (0%)	0.47
Arthritis	9 (50%)	5 (56%)	0.79
Tobacco use			0.41
Never	11 (61%)	4 (44%)	
Former	7 (39%)	5 (56%)	
Self-Report Questionnaires	**PH (N = 18)**	**No PH (N = 9)**	
Cambridge Pulmonary Hypertension Outcome Review			
Symptom Scale	8 (4–12)	6 (5–10)	0.90
Energy Subscale	4 (2–6)	5 (2–6)	0.68
Breathlessness Subscale	3.5 (1–4)	2 (2–4)	0.56
Mood Subscale	1 (0–2)	0 (0–2)	0.72
Functioning Scale	8.5 (6–15)	7 (5–11)	0.74
Quality of Life Scale	5 (2–8)	5 (2–7)	0.80
Scleroderma Health Assessment Questionnaire			
HAQ-DI component	0.88 (0.25–1.50)	0.75 (0.13–1.25)	0.74
Raynaud's phenomenon VAS	15 (0–40)	10 (2–35)	0.91
Digital tip ulceration VAS	0.5 (0–8)	1 (0–14)	0.67
Pulmonary symptom VAS	39.5 (10–52)	15 (11–50)	0.94
Gastrointestinal symptom VAS	12.5 (0–50)	12 (10–30)	0.80
Overall disease severity VAS	50 (21–68)	38 (27–56)	0.88
Borg Dyspnea Index	3 (1–4)	3 (2–4)	
Biomarkers	**PH (N = 18)**	**No PH (N = 9)**	
Vascular endothelial growth factor – pg/mL	346.4 (260.1–427.2) N = 17	265.2 (228.9–468.2)	0.55
Hypoxia-inducible factor 1α – units	23.62 (22.98–23.80) N = 17	23.29 (22.99–23.53)	0.40
Interleukin-6 – pg/mL	4.46 (3.72–10.54) N = 17	5.45 (3.19–6.3)	0.77
N-terminal pro brain natriuretic peptide – fmol/mL	1152.2 (503.7–2207.6) N = 17	566.6 (296.2–902.3)	0.08

Data presented as mean (SD), median (IQR), and frequency (percentage)
HAQ-DI = Health Assessment Questionnaire – Disability Index; VAS = Visual Analogue Scale

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The Additive Value of Nailfold Videocapillaroscopy Patterns to Disease-Specific Autoantibodies in Discrimination of Patients with Systemic Sclerosis at Risk for Severe Organ Involvement. I.M. Markusse, J. Meijs, B. de Boer, A. a. Schouffoer, N. Ajmone Marsan, L. J. M. Kroft, M. K. Ninaber, T. W. J. Huizinga and J.K. de Vries-Bouwstra. Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Severe nailfold videocapillaroscopy (NVC) patterns in patients with systemic sclerosis (SSc) are associated with a high risk of organ involvement. SSc-specific autoantibodies seem to be associated with different NVC scleroderma patterns. Whether the combination of autoantibodies and NVC pattern contributes to better discrimination of patients at risk for organ involvement remains unclear. The aim of this study is to explore the association between clinical phenotype and the combination of autoantibodies and NVC pattern, in order to compose individualized screening programs for organ involvement.

Methods: Data on NVC patterns and anti-centromere (ACA), anti-topoisomerase (anti-Scl70) and anti-ribonucleoprotein (anti-RNP) autoantibodies was investigated in 167 patients of the Leiden Systemic Sclerosis Cohort. The prevalence of autoantibodies and NVC scleroderma patterns (early, active, late) was described. Clinical phenotypes were evaluated for different combinations of autoantibodies and NVC pattern.

Results: 148/167 patients (89%) had a NVC scleroderma pattern: early in 16 patients (11%), active in 77 patients (52%), late in 55 patients (37%). Of these 148 patients, 82 (55%) were ACA+, 52 (35%) were anti-Scl-70+ and 17 (11%) were anti-RNP+. In 19 patients with a non-scleroderma NVC pattern, 11 (58%) were ACA+, 6 (32%) were anti-Scl-70+ and 2 (11%) were anti-RNP+.

Similar distributions of NVC patterns were found in ACA+ and ACA− patients (p=0.185), as also in anti-Scl-70+ and anti-Scl-70− patients (p=0.293). None of 17 anti-RNP+ patients had an early pattern, compared to 16/131 anti-RNP− patients (12%) (p=0.127). Overall, and probably due to small numbers, no significant difference in distribution of NVC patterns between anti-RNP+ and anti-RNP− patients was shown (p=0.178).

ACA+ patients with an early pattern tend to have less organ involvement than patients with an active or late pattern: less skin involvement, higher gas transfer for CO (DLCO), less vascular lesions (table). Early patterns in anti-Scl-70+ (n=3) and anti-RNP+ patients (n=0) were too rare to evaluate. In anti-Scl-70+ patients with a late pattern, more interstitial lung disease, lower DLCO, less vascular lesions and a higher NT-proBNP were seen, compared to an active pattern (table). Similar trends were seen in anti-RNP+ patients (table). ACA+, anti-Scl-70+ and anti-RNP+ patients with a late NVC pattern, seem to have more often a DLCO <70% of predicted and a higher NT-proBNP.

Conclusion: Early NVC patterns in ACA+ SSc patients seem to correlate with less severe organ involvement, while a late pattern in ACA+, anti-Scl-70+ or anti-RNP+ patients seems to correlate with more severe organ involvement. These data indicate that the combination of NVC pattern and antibodies can contribute to discrimination of SSc patients that need extensive organ screening.

Table: Clinical phenotypes stratified for systemic sclerosis specific autoantibodies and nailfold capillaroscopy pattern (anti-Scl-70+ patients and anti-RNP+ patients with an early pattern were left out because of low numbers, n=3 and n=0, respectively).

	ACA+			anti-Scl70+		anti-RNP+	
	Early	Active	Late	Active	Late	Active	Late
	n=12	n=43	n=27	n=27	n=22	n=8	n=9
Patient characteristics							
Age in years, mean (SD)	59 (15)	52 (14)	62 (12)	45 (14)	55 (13)	44 (7)	46 (14)
Female, n (%)	11 (92)	39 (91)	24 (89)	22 (82)	18 (82)	7 (88)	7 (78)
Skin							
SSc type, n (%)							
lcSSc	9 (75)	26 (61)	20 (74)	13 (48)	7 (32)	6 (75)	8 (89)
dcSSc	3 (25)	17 (40)	2 (7)	13 (48)	15 (68)	1 (13)	1 (11)
lSSc	0	0	5 (19)	1 (4)	0	1 (13)	0
mRSS, median (IQR)	2 (0.5–4)	2 (0–4)	4 (2–6)	4 (2–7)	7 (4–13)	2 (0.5–4)	4 (2–8)
Lung							
Interstitial lung disease, n (%)	1 (8)	14 (33)	6 (22)	20 (74)	20 (91)	4 (50)	6 (67)
DLCO % of predicted, mean (SD)	73 (10)	71 (18)	61 (13)	64 (17)	57 (14)	60 (12)	49 (9)
DLCO <70% of predicted, n (%)	3 (25)	20 (47)	17 (63)	16 (59)	18 (82)	5 (63)	9 (100)
Kidney							
eGFR, median (IQR)	71 (66–110)	96 (76–101)	82 (66–86)	92 (82–115)	91 (71–105)	98 (91–148)	103 (81–144)
eGFR ≤60 ml/min, n (%)	2 (17)	3 (7)	5 (19)	3 (11)	2 (9)	0	1 (11)
Vascular							
Digital ulcers, n (%)	2 (17)	14 (33)	13 (48)	7 (26)	10 (46)	2 (25)	5 (56)
Pitting scars, n (%)	1 (8)	16 (37)	15 (56)	8 (30)	14 (64)	4 (50)	9 (100)
Heart							
NT-proBNP, median (IQR)	93 (61–124)	68 (49–114)	159 (42–382)	60 (48–99)	83 (42–369)	147 (136–273)	197 (54–618)
Muscle							
CPK, mean (SD)	76 (61–143)	77 (53–106)	92 (66–105)	72 (54–181)	85 (63–132)	60 (40–83)	71 (54–125)
CPK >145 U/L, n (%)	3 (25)	1 (2)	1 (4)	8 (30)	5 (23)	0	1 (11)
Proximal muscle weakness, n	0	1	0	1	1	1	2

Note: 'Early', 'active' and 'late' refer to the systemic sclerosis specific nailfold capillaroscopy patterns.
ACA, anti-centromere; anti-Scl70, anti-topoisomerase; anti-RNP, anti-ribonucleoprotein; SD, standard deviation; SSc, systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; lSSc, limited cutaneous systemic sclerosis; mRSS, modified Rodnan skin score; IQR, interquartile range; DLCO, diffusion capacity of the lung for carbon monoxide; eGFR, estimated glomerular filtration rate, NT-proBNP, NT-pro-brain-natriuretic peptide; CPK, creatinine phosphokinase.

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Progressive Disease in Systemic Sclerosis after One Year of Follow-up; Results of a Standardized Multidisciplinary Health Care Program. Jessica Meijs, Anne Schouffoer, Nina Ajmone Marsan, Lucia Kroft, Maarten K. Ninaber, T.W.J. Huizinga and Jeska K. De Vries-Bouwstra. Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: The aim of this study is to evaluate disease course of systemic sclerosis (SSc) patients participating in a single centre multidisciplinary health-care program over one year of follow-up, and to evaluate which baseline variables discriminate patients with progressive disease.

Methods: Baseline characteristics and one year follow-up results from patients with diffuse cutaneous SSc (DcSSc), or limited (cutaneous) SSc (L(c)SSc) referred to the multidisciplinary health-care program were evaluated. Progressive disease was defined as: SSc-related decease, decrease of ≥10% of forced vital capacity (FVC), decrease of ≥15% of diffusing capacity for carbon monoxide (DLCO), decrease of ≥10% of body weight, decrease of ≥ 30% of estimated glomerular filtration rate, increase of ≥30% modified Rodnan Skin Score (mRSS) (with Δ ≥3) or ≥0.25 increase of Scleroderma Health Assessment Questionnaire. The number of patients with progressive disease was determined. Logistic regression analysis was used to determine the association between baseline characteristics and presence of progressive disease. Discriminative ability of the multivariable model was expressed as the area under the receiver operating characteristic (AUC) curve.

Results: Between April 2009 and January 2014 303 SSc patients were referred to the health-care program, of which 164 underwent re-evaluation after one year (mean 13.5, range 10–23 months). Sixty-six patients (38% of 172) had progressive disease, including 8 patients who died ≤18 months after first evaluation. Progressive disease was found in 27 (33%) patients with DcSSc, 32 (50%) with LcSSc, and seven (26%) with LSSc (Table 1). Type of skin involvement, mRSS and disease duration could not independently discriminate progressive patients. Multivariable analysis showed that friction rubs and proximal muscular weakness were most significantly associated with progressive disease, additional to type of SSc, age, gender, disease duration, autoantibody profile and use of immunosuppressive therapy. The multivariable model showed fair discrimination (AUC 0.718 [95% CI 0.636–0.800]).

Conclusion: Thirty-eight percent of SSc patients showed progressive disease after one year follow-up, with highest frequency of progression among patients with LcSSc. The strongest predictors of progressive disease were friction rubs and proximal muscular weakness; pattern of skin involvement and disease duration were not independently discriminative. These observations underline the relevance of strict follow-up in all SSc patients as well as the need for more effective treatment strategies.

Table 1. Progressive disease in SSc according to subtype of SSc

Progression, N (%)	Total	DcSSc	LcSSc	LSSc
	N=172*	N=81	N=64	N=27
SSc-related decease	8 (5)	3 (4)	4 (6)	1 (4)
≥ 10% decrease in body weight	9 (5)	5 (6)	2 (3)	2 (7)
≥ 30% increase with minimum of Δ3 in MRSS	21 (12)	10 (12)	10 (16)	1 (4)
≥ 30% decrease in eGFR	6 (3)	3 (4)	3 (5)	0 (0)
≥ 10% decrease in FVC	13 (8)	3 (4)	6 (9)	4 (15)
≥ 15% decrease in DLCO	12 (7)	5 (6)	6 (9)	1 (4)
≥ 0.25 increase in SHAQ	11 (6)	3 (4)	8 (13)	0 (0)
Total patients with progressive disease	66 (38)	27 (33)	32 (50)	7 (26)

*124 (72%) patients fulfilled the ACR/EULAR 2013 criteria at baseline evaluation
DcSSc: diffuse cutaneous systemic sclerosis; LcSSc: limited cutaneous systemic sclerosis; MRSS: modified Rodnan Skin Score; eGFR: estimated glomerular filtration rate; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; SHAQ: Scleroderma Health Assessment Questionnaire.

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a Feasibility Study of Subjective and Objective Assessment of Sublingual Abnormalities in Systemic Sclerosis. Tracy M. Frech[1], John Pauling[2], Maureen Murtaugh[3], Lee S. Shapiro[4], Bernard Choi[5], Ryan Farraro[5] and Robyn T. Domsic[6]. [1]Salt Lake City VAMC, Salt Lake, UT, [2]Royal National Hospital for Rheumatic Disease, Bath, United Kingdom, [3]University of Utah School of Medicine, SLC, UT, [4]The Center for Rheumatology, Albany, NY, [5]University of Irvine, Irvine, CA, [6]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Sublingual frenulum abnormalities are reported in systemic sclerosis (SSc), but the exact nature and clinical relevance of such abnormalities is unknown. Laser speckle contrast imaging (LSCI) is an emerging method for assessing tissue perfusion but has not been applied to the gastrointestinal tract (GIT) in SSc. We report a feasibility study evaluating clinical associations and inter-rater agreement using a novel scoring chart to assess sublingual abnormalities in SSc patients and healthy controls (HC). We also report preliminary findings and associations following objective assessment of sublingual perfusion using LSCI in SSc.

Methods: Ten patients fulfilling 2013 ACR/EULAR classification criteria for SSc and 8 HC were recruited from two different SSc clinics. SSc patients completed the GIT 2.0 questionnaire and baseline demographics were documented. A 0–2 Likert scale was used to assess sublingual frenulum thickness, frenulum length, mucosa pallor and the presence of sublingual and labial telangiectases. A composite index of scores for each domain was calculated for each subject. Photographs of the sublingual frenulum were obtained under standardised conditions to allow blinded assessment by 2 separate assessors of sublingual abnormalities without knowledge of GIT symptoms. Baseline perfusion (in arbitrary flux units [fu]) of the frenulum was assessed using LSCI in subjects with SSc.

Results: Each of the frenulum measures differed between HC and SSc (Mann-Whitney U, $p = 0.0003$). No HC had a composite score of greater than 2. Positive associations were identified between clinical frenulum assessment (rater 1), domains of GIT 2.0, disease duration and LSCI perfusion in SSc. Inter-rater agreement for individual domains of frenulum scoring chart and composite index revealed moderate agreement for assessment of frenulum (Table 1) with a weighted kappa for the total score is 0.53 (moderate agreement). When LSCI was applied to the frenulum, the perfusion index was 2308 fu (1810–3203). The perfusion index correlated negatively with disease duration, -0.64 ($p < 0.05$) and with social component of the GIT 2.0, -0.67 ($p = 0.05$).

Conclusion: This feasibility study confirms the presence of clinical sublingual abnormalities in SSc, which can be categorised using a simple scoring chart with moderate inter-rater agreement. Perfusion of the sublingual frenulum can be assessed by LSCI and may correlate with disease duration and GIT 2.0 self-report. Efforts to refine image capture and scoring shall be undertaken to improve blinded inter-rater agreement before embarking on a larger study exploring the significance of clinical and LSCI perfusion sublingual abnormalities in SSc.

Table 1: Frenulum Assessment

	Score			Inter-rater Agreement Cohen's Kappa (95% CI)		
Parameter	0	1	2	Rater 1 vs 2	Rater 1 vs 3	Rater 2 vs 3
Sublingual frenulum thickness	Normal	Intermediate thickening	Severe thickening	0.64 (0.28–1.0)	1.0 (1.0–1.0)	0.74 (0.40–1.0)
Sublingual frenulum length	Normal	Intermediate shortening	Severe Shortening	0.60 (0.28–0.64)	0.89 (0.68–1.0)	0.44 (.13–0.75)

Sublingual mucosa pallor	Normal	Intermediate pallor	Severe pallor	0.56 (0.11–0.99)	0.76 (0.47–1.0)	0.42 (0.06–0.77)
Buccal and labial telangiectases	None visible	1–6 visible	>7 visible	0.53 (0.28–0.79)	1.0 (1.0–1.0)	0.55 (0.11–0.99)
Total Score in 4 categories				0.53 (0.28–0.79)	1.0 (1.0–1.0)	0.62 (0.37–0.87)
0						
1–3						
3–5						
>5						

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Validation of Vesmeter As a Diagnostic Tool of Scleroderma. Yoshihiro Hishitani[1], Yoshihito Shima[2], Toshio Tanaka[2] and Atsushi Kumanogoh[2]. [1]Kinki Central Hospital, Itami, Japan, [2]Osaka University Graduate School of Medicine, Suita, Japan.

Background/Purpose: Objective method to evaluate the skin involvement in the patients with scleroderma has not been definitely established. We have developed Vesmeter, a computer-linked device to simultaneously quantify the skin characteristics such as viscosity, elasticity and softness, and have reported its usefulness to evaluate the skin characteristics of patients with scleroderma. Here, we validated Vesmeter as a diagnostic tool of scleroderma.

Methods: Using Vesmeter, we evaluated the skin characteristics of patients with scleroderma and healthy volunteers. 17 points of the body were evaluated, like modified Rodnan's skin score. First, we compared the skin characteristics of scleroderma patients with that of healthy volunteers matched by age and sex. Second, we conducted bivariate Receiver Operating Characteristic (ROC) analyses to examine which points and parameters are useful to diagnose scleroderma. Third, using whole data of healthy volunteers, we conducted logistic regression and ROC analysis to validate Vesmeter as a diagnostic tool of scleroderma.

Results: 39 patients with scleroderma and 413 healthy volunteers were included. Among the healthy volunteers, 78 people were selected at random, matching age and sex with patients as the control group for the first and second analyses. Regarding the background of the 2 groups, body weight of patients was lighter than controls. As the result of the comparison of skin characteristics, patients' skin were statistically harder and showed higher elasticity than control on both fingers, left hand, both forearms (Figure 1), both lower legs, and both feet. Viscosity of patients' skin were also statistically higher than control on both fingers, both hands, both forearms, face, chest, right femur, and right foot. As the result of bivariate ROC analyses, moderate accuracy to distinguish patients from control was recognized by softness of both fingers and both forearms, elasticity of right finger and both forearm, and viscosity of left finger, right hand, both forearms, and face. Based on this result, age, body weight, softness of both fingers and right forearm, elasticity of left forearm, and viscosity of face, left finger, right hand, and both forearms were selected variables for the next logistic regression and ROC analysis using whole data of 413 healthy volunteers. (One of softness and elasticity was used because of the multi-collinearity). This ROC analysis resulted in high accuracy (AUC = 0.92514, Sensitivity = 0.7949, Specificity = 0.9562) to diagnose scleroderma (Figure 2).

Conclusion: Vesmeter showed high accuracy to diagnose scleroderma.

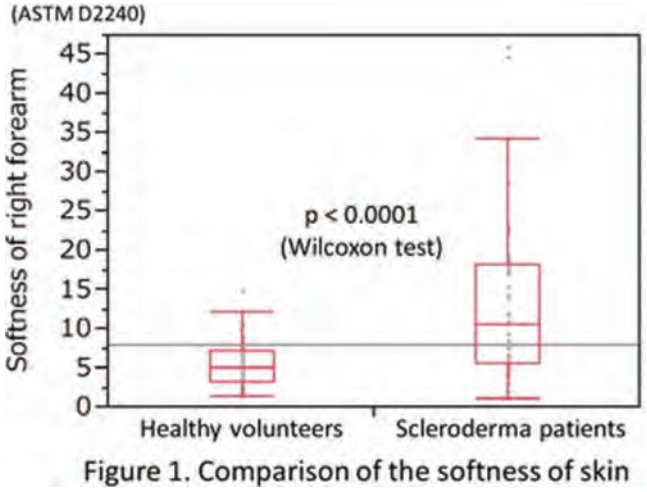

Figure 1. Comparison of the softness of skin

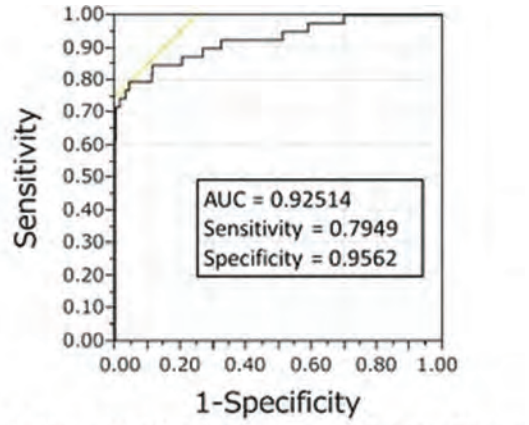

Figure 2. Vesmeter for the diagnosis of scleroderma

Disclosure: Y. Hishitani, None; **Y. Shima**, None; **T. Tanaka**, None; **A. Kumanogoh**, None.

1696

Left Atrial Area Measurement Is Useful for Evaluating Left Ventricular Diastolic Dysfunction Coexisting with Pulmonary Arterial Hypertension Associated with Systemic Sclerosis. Sumiaki Tanaka, Nobuhiro Sho, Tatsuo Nagai, Yoshiyuki Arinuma and Shunsei Hirohata. Kitasato University School of Medicine, Sagamihara, Japan.

Background/Purpose: Pulmonary arterial hypertension (PAH) is a crucial organ involvement affecting survival of patients with connective tissue disease (CTDs), such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD). Although some powerful PAH-specific drugs improve the survival of patients with idiopathic PAH, the prognosis of patients with PAH associated with SSc remains still poor. To explore the characteristics relevant to the poor survival of patients with PAH associated with SSc under treatment with PAH-specific drugs, we performed exploratory data analysis using echocardiogram (ECHO) in patients with PAH associated with CTDs.

Methods: We analyzed 1002 ECHO reports from 54 patients with PAH associated with CTDs, including 22 patients with SSc, and 33 patients with CTDs other than SSc (SLE:12, MCTD:16 and other CTDs: 5), who had been diagnosed as PAH based on right heart catheterization test and treated with PAH-specific drugs between April 2005 and March 2013 in our hospital. We selected systolic pulmonary arterial pressure (PAP), cardiac output (CO), and right atrial (RA) and left atrial (LA) areas which were traced at end-diastolic time on 4 chamber view as parameters. Comparison of these parameters between patients with PAH associated with SSc (PAH-SSc(+)) and patients with PAH associated with other CTDs (PAH-SSc(−)) was carried out using mixed effects model in which we set presence or absence of SSc, WHO-functional class (WHO-FC), and age at ECHO performed as fixed effects, and patient as a random effect. We also compared the serum levels of brain natriuretic peptide (BNP) between patients with PAH-SSc(+) and patients with PAH-SSc(−) with the same strategy. Representative value estimated by our model was displayed as mean (95% confidence interval) value adjusted for WHO-FC and age.

Results: PAH-specific drugs used for treatment of the patients, including bosentan, ambrisentan, sildenafil, tadalafil, epoprostenol, and beraprost (an oral prostacyclin analog that is only available in Japan). Mean of age and WHO-FC, which were substituted into our model to estimate the adjusted values, were 52.2 and 2, respectively. As shown in Table, systolic PAP was higher and RA area size was smaller in patients with PAH-SSc than in patients with PAH-SSc(−). By contrast, LA area size was significantly greater in patients with PAH-SSc(+) than in patients with PAH-SSc(−). Finally, serum level of BNP was higher in patients with PAH-SSc(+) than in patients with PAH-SSc(−) (log[BNP]: 1.906 (1.880 – 1.931), 1.839 (1.817 – 1.861),respectively, p=0.0002, n=2781).

Conclusion: The results demonstrate that greater LA area size and higher levels of BNP, indicating left ventricular diastolic dysfunction, coexists with PAH associated with SSc. Thus, the data emphasize the usefulness LA area size as well as RA area size for the appropriate management of patients with PAH-SSc using PAH-specific drugs.

Table 1. Parameters of ECHO in Patients with PAH-CTDs

values	PAH-SSc(+)	PAH-SSc(−)	p	n
systolic PAH (mmHg)	51.1 (49.2–52.8)	61.4 (60.0–63.0)	<0.0001	1002
CO (L/min)	5.13 (4.93–5.31)	4.90 (4.74–5.05)	0.0853	681
RA area size (cm2)	17.7 (16.4–19.0)	21.0 (20.0–21.9)	0.0002	381
LA area size (cm2)	19.6 (18.7–20.6)	18.2 (17.4–18.9)	0.0181	381

Means (95%CI) were estimated with mixed effects models (fixed effect: SSc, age, and WHO-FC(4), random effect: patient) and adjusted for age (52.2yo), and WHO-FC(2). p value was calculated for presence or absence of SSc.

Disclosure: S. Tanaka, None; **N. Sho**, None; **T. Nagai**, None; **Y. Arinuma**, None; **S. Hirohata**, None.

1697

High Frequency Skin Ultrasound Detects Subclinical Diffuse Dermal Involvement in Patients with Limited Cutaneous Systemic Sclerosis. Alberto Sulli, Barbara Ruaro, Carmen Pizzorni, Giorgia Ferrari, Elena Bernero, Sabrina Paolino and Maurizio Cutolo. Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy.

Background/Purpose: The modified Rodnan's skin score (mRSS) is the validated method to detect both severity and extension of skin involvement, and high frequency skin ultrasound (US) is a valid and reproducible technique to measure dermal thickness (DT) in patients with systemic sclerosis (SSc) (1–4). Skin involvement is critical for sub-classification of the disease into different subsets (5). The aim of the study was to detect by US possible subclinical skin involvement in limited cutaneous SSc (lcSSc) patients, in those skin areas apparently not affected on the basis of a normal mRSS.

Methods: Fifty lcSSc patients (ACR 2013 or LeRoy 2001 criteria) (mean disease duration 5±5 years) and fifty age-matched healthy subjects were analysed during clinical follow-up and after informed consent. Both mRSS and US were used to evaluate DT in the usual seventeen areas of the skin (cheeks, fingers, dorsum of hands, forearms, arms, chest, abdomen, thighs, legs, feet) of SSc patients. US was also performed in the same seventeen skin areas of healthy subjects, looking for DT differences in comparison with lcSSc patients. Nailfold videocapillaroscopy (NVC) was performed in lcSSc patients to identify the proper pattern of microangiopathy (Early, Active or Late) and calculate the microangiopathy evolution score (MES) (6–7).

Results: US detected significantly higher DT in lcSSc patients than in healthy subjects in all skin areas with exclusion of thighs ($p<0.0001$ for all). In particular, DT was significantly higher in lcSSc patients than in healthy subjects in four out of six skin areas where the mRSS was normal (=0) (arms, chest, and abdomen) in agreement with the diagnosis of lcSSc. At the level of the thighs DT was higher in lcSSc patients than in healthy subjects, but this was not statistical significant ($p=0.16$). As assessed by US, a positive correlation was found between DT and both progressive NVC patterns ($p<0.001$) and MES ($p=0.0015$).

Conclusion: This study strongly suggests that subclinical diffuse dermal involvement may be detectable by high frequency skin ultrasound already in lcSSc patients in almost 70% of skin areas where the mRSS was normal. This observation should be of relevance for future classification of SSc disease subsets, since patients with either lcSSc or diffuse cutaneous SSc often display similar organ/laboratory markers of involvement.

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Disclosure: A. Sulli, None; **B. Ruaro**, None; **C. Pizzorni**, None; **G. Ferrari**, None; **E. Bernero**, None; **S. Paolino**, None; **M. Cutolo**, None.

1698

Peripheral Blood Eosinophil Counts Increase in Patients with Systemic Sclerosis and Associated with Its Disease Severity. Tamao Nakashita[1], Shinji Motojima[1], Katsutoshi Ando[2] and Akira Dibatake[3]. [1]Kameda Medical Center, Kamogawa City, Japan, [2]Juntendo university, tokyo, Japan, [3]Kameda Medical Center, Kamogawa city, Japan.

Background/Purpose: Increased levels of serum pro-fibrotic cytokines such as IL-4 and IL-13 and plasma CXCL4 have been previously reported in patients with systemic sclerosis (SSc). These pro-fibrotic cytokines also play an important role for differentiation and migration of eosinophils and eosinophils themselves release pro-fbrotic cytokines such as IL-11 and TGF-beta. Accordingly, we hypothesized that eosinophils might contribute, at least partly, to fibrotic process of SSc.

Methods: We retrospectively reviewed the peripheral blood eosinophil counts (PB-EOS) in 70 untreated patients with SSc (diffuse 14, limited 56) and compared with those in other major connective tissue diseases including 126 patients with RA, 10 with PM/DM, 19 with primary Sjögren's syndrome (SjS), 20 with SLE and 8 with mixed connective tissue disease (MCTD). The diagnosis was made according to the criteria of ACR, except that criteria used for MCTD was that by Japan Ministry of Health, Labor and Welfare. All the patients were not on treatment by glucocorticoid and/or immunosuppressant. We also evaluated the association with disease severity of SSc, that is, the grade of interstitial lung disease (ILD) and skin sclerosis. The severity of ILD was graded into 4, grades 0 to grade 3, according to the extent of ILD on chest CT by the method of Gochuico et al. (Arch Intern Med 2008). Chest CT images were graded by 2 independent respirologists. The skin sclerosis was evaluated by modified Rodnan's skin score (mRodnan SS).

Results: The mean of coefficient of variance of PB-EOS in 8 patients was 0.32, suggesting that PB-EOS are considerably stable. The order of mean PB-EOS was as follows; diffuse-SSc (mean 312/mcL) > limited-SSc (210) > PM/DM (164) = RA (154) > pSJS (128) > MCTD (73) = SLE (57) (> indicates significantly different). ILD was observed in 39 % (27/70) of SSc patients, and the numbers of SSc patients with grade 0/1/2/3 were 43/15/9/3, respectively. PB-EOS positively correlated with ILD grade in SSc ($rs = 0.26$, $p < 0.02$), but not in RA ($rs = 0.02$) and other diseases. M-Rodnan SS also correlated with PB-EOS ($rs = 0.35$, $p = 0.003$) and ILD severity ($rs = 0.57$, $p < 0.0001$).

Conclusion: It was suggested that eosinophils contribute, at least in part, to fibrotic process in SSc and anti-eosinophil strategy might become a treatment option when such drugs become available. It is also suggested that the mechanism of ILD is somewhat different between SSc and RA. Authors have no COI.

Disclosure: T. Nakashita, None; **S. Motojima**, None; **K. Ando**, None; **A. Dibatake**, None.

1699

Endothelial and Platelet Microparticles As Potential Novel Biomarkers of Peripheral Microvascular Dysfunction in Systemic Sclerosis and Primary Raynaud's Phenomenon. John D. Pauling[1], Daniel Moreno-Martinez[2], Fiona Wilkinson[2], Ben Parker[3], Jacqueline A. Shipley[4], Darren Hart[4], Neil J McHugh[1] and Yvonne Alexander[2]. [1]Department of Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom, [2]Manchester Metropolitan University, Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [4]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom.

Background/Purpose: Microparticles (MPs) are membrane-bound vesicles derived from vascular and intravascular cells such as endothelial cells (EMPs) and platelets (PMPs). MPs form during cell activation or apoptosis and may directly contribute to disease pathogenesis. Circulating MPs have been found to be higher in systemic sclerosis (SSc) compared with healthy controls, however their precise functional role remains to be elucidated. The present study was undertaken to establish whether plasma MP levels differ between primary Raynaud's phenomenon (RP) and SSc and whether EMP and PMP levels correlate with dynamic assessment of digital microvascular function assessed using laser speckle contrast imaging (LSCI).

Methods: Patients with SSc (n=24, 22 with limited cutaneous SSc) and primary RP (n=16) not taking anti-platelet agents, NSAIDs or steroids were recruited to the study. Platelet-free plasma was obtained using citrated blood following a 2-step centrifugation regime. Digital perfusion at the volar aspect of the distal left middle finger was assessed using LSCI during a standardised local cold challenge (15°C for 60s). Digital perfusion was assessed at baseline, immediately following cold challenge (t0) and at 5 minute intervals during re-perfusion (t5, t10 and t15 respectively). Plasma levels of EMPs (AnnexinV+/CD31+/CD42b-) and PMPs (AnnexinV+/CD31+/CD42b+ or AnnexinV+/CD31-/CD42b+) were quantified using flow cytometry.

Results: Plasma levels of EMPs (161271/ml vs. 171318/ml) and PMPs (186348/ml vs. 246758/ml) did not differ between SSc and primary RP. Higher EMP levels were found in patients with SSc and a history of digital ulceration (DU) or digital pitting (DP) (median 198643/ml vs. 144840/ml, $p=0.03$). No additional associations between MP levels and disease characteristics were identified. Consistent positive correlations between MP levels and digital perfusion following cold challenge (but not at baseline) were

identified in SSc (Table). In contrast, there were consistent negative correlations between PMP (but not EMP) levels and digital perfusion at both baseline and following cold challenge in primary RP (Table).

Conclusion: This is the first study to explore the relationship between circulating MP levels and peripheral microvascular dysfunction in primary RP and SSc. Higher EMPs were associated with a history of DU/DP in SSc. Higher EMP and PMP levels, however, were associated with higher digital perfusion following local cold challenge in SSc. In contrast, higher PMP levels were associated with lower digital perfusion in primary RP. There was no association between EMP levels and digital perfusion in primary RP. Additional work is needed to explore factors leading to MP generation and their contribution to peripheral microvascular dysfunction in primary RP and SSc. MPs may have the potential to act as biomarkers of peripheral microvascular dysfunction/damage in primary RP and SSc.

Table

			Baseline	t0	t5	t10	t15
SSc	EMPs	Spearman's rho	0.05	0.42	0.42	0.46	0.46
		p value	0.821	0.044	0.043	0.026	0.025
	PMPs	Spearman's rho	0.377	0.047	0.009	0.006	0.001
		p value	0.19	0.42	0.52	0.54	0.64
Primary RP	EMPs	Spearman's rho	−0.34	−0.33	−0.13	−0.39	0.09
		p value	0.149	0.20	0.648	0.131	0.753
	PMPs	Spearman's rho	−0.52	−0.33	−0.69	−0.65	−0.49
		p value	0.041	0.232	0.003	0.006	0.057

Disclosure: J. D. Pauling, None; **D. Moreno-Martinez**, None; **F. Wilkinson**, None; **B. Parker**, None; **J. A. Shipley**, None; **D. Hart**, None; **N. J. McHugh**, None; **Y. Alexander**, None.

1700

Laser Speckle Contrast Analysis in the Follow-up of Digital Ulcers in Systemic Sclerosis Patients. Barbara Ruaro, Alberto Sulli, Teresa Cannavale, Marco Amedeo Cimmino, Carmen Pizzorni, Sabrina Paolino and Maurizio Cutolo. Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy.

Background/Purpose: Typical clinical aspects of systemic sclerosis (SSc) include microvascular damage and reduction of peripheral blood perfusion, resulting in increased incidence of digital ulcers (DUs) (1–2). Several studies report different methods to assess the severity of DUs but, to the best of our knowledge, ulcer blood perfusion was not assessed (3–5). This study investigates blood perfusion (BP) of DUs by laser speckle contrast analysis (LASCA), a non-contact technique, during treatment for ten days with local medications (6).

Methods: During their regular planned follow-up and systemic treatment, twenty SSc patients with DUs of recent onset (mean age 63±12 years, mean disease duration 7±6 years) were enrolled after informed consent. Local BP was studied in all patients by LASCA before starting local treatment (T0), both at the level of the dorsal and palmar aspect of the hands (6). Subsequently, regions of interest (ROIs) were created at the level of the fingertips, periungual, ulcer and periulcer areas and the perfusion values were reported as perfusion units (PU) (6). Hydrocolloid dressing was daily applied on ulcer area (7). After 10 days of treatment (T1) LASCA was repeated. Visual analogic scale for DU pain (VAS-pain) (score 0–10) was administered to patients before and after the treatment. The patients marked on the line from 0 ("no pain") to 10 ("worst imaginable pain") the intensity of DU pain that they felt (8). Statistical analysis was performed by non parametric tests.

Results: A statistically significant increase of BP was observed from T0 to T1 in the ROIs created at the level of the ulcer area (due to granulation tissue) (median 37 vs 57 PU, $p<0.0001$), as well as a significant decrease of BP was observed in the periulcer area (due to decreased inflammatory reaction) (median 108 vs 90 PU, $p<0.0001$). A positive correlation was observed between fingertip BP and periungual BP at both T0 ($r=0.66$, $p=0.02$) and T1 ($r=0.44$, $p=0.05$). There was a statistically significant decrease of VAS-pain scale during the ten days of treatment (median 9 vs 8; $p=0.001$).

Conclusion: LASCA seems to offer a quantifiable and safe method to evaluate local blood perfusion changes of the DU area during local treatment, and it most likely represents a reliable technique to monitor DU evolution in SSc patients.

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1701

Short-Term Effects of Iloprost on Micro-Vessels Hemodynamics in Systemic Sclerosis Patients Evaluated By Laser Doppler Flowmetry. Florenzo Iannone, Cinzia Rotondo, Mariangela Nivuori, Emanuela Praino, Laura Coladonato, Michele Covelli and Giovanni Lapadula. Rheumatology Unit, Bari, Italy.

Background/Purpose: Iloprost is a milestone in the treatment of Raynaud's Phenomenon (RP). However, it has transient hemodynamic effects due to a very short half-time, thereby a treatment protocol has been never validated and the interval time between infusions is empirical. We aimed at evaluating the short and medium term effects of Iloprost on blood flux, assessed by Laser Doppler (LD), in patients with RP associated to Systemic Sclerosis (SSc).

Methods: 19 SSc patients, aged 55.9±16 (mean ±SD) years with disease duration of 9.3±6 years, have undergone Iloprost infusions (50 ng at 1.5 ng/Kg/min) for 3 consecutive days. The LD flowmetry (Periflux System 5000, Perimed) was performed at baseline and after heating test (heat stimulus of 44 degree centigrade), and ischemic/occlusive test (200 mm/Hg pressure applied by air-bracelet on brachial artery for 3 min) before Iloprost (T0), at the end of 3 consecutive days of treatment (T1), at 24h (T2) and at 7 days (T3) after last administration of Iloprost. During occlusive test, LD evaluated the micro-vessels flux at rest (RF), flux at pick (PF), the percentage variation between RF and PF (RF/PF %), and recovering and hyperemic times before and after occlusion. During heating test, LD evaluated percentage variation between perfusion units before and after heating test (pre-postPUvar%). Comparisons between times were assessed by repeated measures ANOVA. The results are expressed as average of 4 fingers at each time. Statistic significance was set at $p<0.05$. During the study no variation of the baseline therapy was allowed.

Results: We observed a prompt improvement, even though transient, of LD parameters following Iloprost infusion. A statistically significant difference ($p<0.05$) (Tab.1) was found for RF/PF%, showing a time decreasing improvement. In particular the percentage difference comparing to T0 was: −10,26% at T1, −7,4% at T2, −7,8% at T3. For percentage variation between perfusion units before and after-heating test (pre-postPUvar%) a decreasing trend were observed, in particular the variation among times comparing to baseline is: +0.54 % at T1, −18.71% at T2, −19.37 % at T3).

TEST	LD Parameters	Baseline (T0)	End of infusion (T1)	24h after infusion (T2)	7 days after infusion (T3)	p value
OCCLUSION	Resting flux (RF)	86.7 ± 37,1	77.7 ± 45.5	80.2 ± 87	79.9 ± 39.46	0.821
	Flux at Peak (FP)	132.3 ± 51.1	118.8 ± 46.8	122.4 ± 45.9	121.9 ± 55.9	0.742
	% variation RF/PF	86.6 ± 37	77.7 ± 45	80.2 ± 35	79.8 ± 39	0.000
	Half hyperemic time	16.3 ± 23.9	14.5 ± 32.9	16.05 ± 19.7	15.1 ± 21.6	0.982
	Time at peak	162.1 ± 194.8	147.6 ± 246.1	147.9 ± 144.4	121.8 ± 139.6	0.795
HEATING	% variation pre and post	48.1 ± 28	48.36 ± 32	39.1 ± 21	38.7 ± 24	0.021

Conclusion: Microcirculation hemodynamic changes induced by Iloprost seem to run out within 24h after the last infusion, particularly when assessed by the occlusive test. Although the Iloprost treatment is an important tool in SSc associated RF, is yet necessary to define the suitable timing to obtain long-lasting benefit.

Disclosure: F. Iannone, None; **C. Rotondo**, None; **M. Nivuori**, None; **E. Praino**, None; **L. Coladonato**, None; **M. Covelli**, None; **G. Lapadula**, None.

1702

Antiphospholipid Antibodies in Systemic Sclerosis: Prevalence and Clinical Significance? Anjali Shetty[1], Suncica Volkov[1], Claudia Vergara[2] and William Swedler[1]. [1]University of Illinois at Chicago, Chicago, IL, [2]University of Illinois Chicago, Chicago, IL.

Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune disease characterized by collagen deposition and vascular changes of the skin

and internal organs, leading ultimately to fibrosis. Antiphospholipid (aPL) antibodies are immunoglobulins directed against negatively charged phospholipid-binding proteins mostly involved in blood coagulation. It has been suggested that aPL antibodies including anticardiolipin (aCL) and anti-beta-2-glycoprotein I (aβ2GPI) antibodies may play a role in the pathogenesis of SSc related vascular impairment. This study investigates the prevalence of antiphospholipid antibodies including aCL and aβ2GPI antibodies in patients with systemic sclerosis. We also evaluated a possible relationship between clinical findings in SSc including Raynaud's phenomenon, digital ulcers, and interstitial lung disease, and the presence of aCL/aβ2GPI antibodies.

Methods: A hundred patients who met the American College of Rheumatology classification criteria for systemic sclerosis were included in the study. There were ten men and ninety women with a median age of 58 years. Thirty-five percent had diffuse cutaneous SSc and 65 percent had limited cutaneous SSc. Assessment of organ involvement to detect systemic complications of SSc included presence of Rayanud's phenomenon, digital ulcers or pitting scars, and interstitial lung disease. Interstitial lung disease was characterized by pulmonary fibrosis seen on high-resolution computed tomography or chest radiography, or occurrence of "velcro" crackles on auscultation, not due to another cause such as congestive heart failure. Anticardiolipin IgG, IgM, and IgA and anti-beta-2-glycoprotein I IgG, IgM, and IgA antibodies were measured by enzyme-linked immunosorbent assay. Clinical associations were measured using conditional and simple logistic regression models.

Results: Twenty-seven percent of patients with systemic sclerosis were positive for either anticardiolipin or anti-beta-2-glycoprotein I (aβ2GPI) antibodies. A positive association was found between the presence of anticardiolipin antibody and interstitial lung disease (p=0.038). This association was maintained after adjusting for age, sex, and race (OR 2.765, 95% CI 1.038–7.368, p=0.0412). Anticardiolipin testing was not sensitive for predicting lung involvement with a sensitivity of 0.419, however, it had a high specificity at 0.789 for predicting lung involvement. There was no predictive value found for testing aCL and aβ2GPI antibodies with regards to Raynaud's phenomenon or digital ulcers.

Conclusion: Our study showed a positive association with aCL antibodies and interstitial lung disease in patients with systemic sclerosis. The use of aCL antibodies as a biomarker of pulmonary disease in SSc should be further explored.

Table 1. Association of positive anticardiolipin and anti-beta-2-glycoprotein I antibody testing with clinical features in SSc patients

	Raynauds phenomenon Odds ratios (95% confidence intervals)	*Digital Ulcers* Odds ratios (95% confidence intervals)	*Interstitial Lung Disease* Odds ratios (95% confidence intervals)
Anticardiolipin antibody	OR1.844 (0.175–19.427)	OR1.387 (0.522–3.688)	OR2.765 (1.038–7.368)
Anti-beta2-glycoprotein I antibody	OR0.629 (0.033–12.012)	OR3.427 (0.382–30.8)	OR0.845 (0.076–9.398)

Disclosure: A. Shetty, None; **S. Volkov**, None; **C. Vergara**, None; **W. Swedler**, None.

1703

An Association of Anti-PM/Scl Antibody Reactivity with Risk of Malignancy in Scleroderma. Cosimo Bruni[1], Ana Lages[2], Hitesh Patel[3], Jennifer Harvey[3], Voon H. Ong[4], Marco Matucci-Cerinic[1], Emma C. Derrett-Smith[4] and Christopher P Denton[4]. [1]University of Florence, Florence, Italy, [2]Affiliation servicio de Medicina Interna, Hospital De Braga, Braga, Portugal, [3]Department of Clinical Immunology, Royal Free Hospital, London, United Kingdom, [4]UCL Medical School Royal Free Campus, London, United Kingdom.

Association of anti-PM/Scl antibody with risk of malignancy in scleroderma.

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Background/Purpose: Anti-PM/Scl antibodies are heterogeneous autoantibodies in scleroderma (SSc) directed mainly against 75kDa and 100kDa human exosome components, associated with overlap syndromes. Published data suggest that up to 12.5% of SSc patients carry this seropositivity with associations with myositis, mild skin involvement, pulmonary fibrosis, articular involvement and calcinosis and a lower prevalence of pulmonary arterial hypertension and gastrointestinal involvement. In this study, we characterised the clinical and detailed serological phenotype of anti-PM/Scl positive SSc patients from a single centre cohort of 2200 patients and identified a cohort within this group with increased risk of malignancy.

Methods: Anti-PM/Scl positive SSc patients identified by indirect immunofluorescence pattern and confirmed on counter-immunoelectrophoresis were enrolled in the study. Demographics and clinical data on skin, internal organ involvement and history of malignancy were recorded.

Results: 70 anti-PmScl positive patients were identified (3.1% of cohort), with frequent lung, gastrointestinal and muscle involvement as described previously (table 1). 48 patients (68.6%) had antibodies targeting both PM/Scl 75 and 100; 6 (8.6%) PM/Scl 75 only and 16 (22.8%) PM/Scl 100 antibody only. There was a significant association between positivity for anti-PM/Scl 100 alone and malignancy (p=0.037) when compared to presence of both reactivities or reactivity to PM/Scl75 alone. 13 patients (18.6%) had developed a malignancy, 4 of these had onset within 36 months from SSc diagnosis and all were positive for anti-PM/Scl 100, combined with anti-PM/Scl75 in 7/13 (53.8%). The study population standardized incidence ratio (SIR) for cancer was 2.14 (CI 95%: 1.55–2.74), with higher values showed for male gender (SIR 3.10, CI 95%: 1.55–4.65) than female gender (SIR 1.95, CI 95%: 1.31–2.61). 7/13 were adenocarcinoma, mainly breast, 4/13 squamous cell and the remainder haematological malignancy.

Conclusion: The association of malignancy with PM/Scl reactivity in SSc is of interest in the context of recent studies describing a potential pathogenic role of anti-RNA polymerase III antibodies with malignant disease in SSc. This cohort is otherwise representative of others in terms of demographics and clinical characteristics and underlines the importance of close surveillance for concurrent malignancy in all SSc disease subphenotypes.

Table 1. Prevalence of clinical, instrumental and laboratory features in the study population

	Total PM-Scl population (n=70, 100%)		PM-Scl Patients with Cancer (n=13, 18.6%)		Cancer VS non cancer population – p value
Median Age	58.4 ± 14.0		60.9 ± 10,3		0.566
Female Sex	56	80.0%	9	69.2%	0.277
Median Age at SSc onset	44.1 ± 14.5		46.5 ± 9.9		0.365
Age at Cancer onset ± SD			55,2 ± 11.7		N.A.
Smoking history	32	45.7%	7	53.8%	0.486
LcSSc	47	67.1%	10	76.9%	0.740
DcSSc	20	28.6%	3	23.1%	
mRSS	4	(2–43)	11	(2–34)	0.204
Digital Ulcers	14	20.0%	5	38.5%	0.119
Calcinosis	27	38.6%	5	38.5%	>0.99
Gastrointestinal involvement	44	62.9%	9	69.2%	0.756
Pulmonary Hypertension	7	10.0%	2	15.4%	0.611
Myositis Overlap	43	61.4%	7	53.8%	0.545
Lung involvement	40	57.1%	7	53.8%	>0.99
Articular involvement	**27**	**38.6%**	**2**	**15.4%**	**0.067**
Renal involvement	4	5.7%	1	7.7%	0.569

Disclosure: C. Bruni, None; **A. Lages**, None; **H. Patel**, None; **J. Harvey**, None; **V. H. Ong**, Actelion Pharmaceuticals US, 8; **M. Matucci-Cerinic**, None; **E. C. Derrett-Smith**, None; **C. P. Denton**, None.

ACR/ARHP Poster Session B
Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics
Monday, November 17, 2014, 8:30 AM–4:00 PM

1704

CXCL4 Promotes Fibrosis By Increasing Expression of Extracellular Matrix Modifying Factors and By Facilitating Epithelial/Endothelial Mesenchymal Transition. W. Marut, A.J. Affandi, A. Limpers and T.R.D.J. Radstake. University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Systemic sclerosis (SSc) is a degenerative disorder, characterized by vascular abnormalities and immunological disturbances followed by excessive fibrosis in multiple organ systems. In a recent proteomic study we identified the chemokine - CXCL4 as a novel predictive biomarker for SSc[#]. Here we aim to elucidate the pathologic role of CXCL4 in SSc on fibroblasts and epithelial/endothelial cells.

Methods: The effect of CXCL4 was evaluated *ex vivo* on primary dermal fibroblasts, epithelial cells, and endothelial cells. Gene expression analysis

was performed using qPCR. Analysis of $CD44^{+}CD24^{-/low}$ expression in epithelial cells was measured using flow cytometry. The production of superoxide by mitochondria in fibroblasts was visualized by flow cytometry using the MitoSOX™ Red reagent. Hydrogen peroxide production by fibroblasts was measured by AmplexRed.

Results: After CXCL4 treatment, both, endothelial and epithelial cells acquired fibroblast-like, mesenchymal appearances, and showed upregulation of mesenchymal markers (such as N-cadherin, vimentin, and αSMA). Moreover, epithelial cells exposure to CXCL4 resulted in the acquisition of the $CD44^{high}/CD24^{low}$ antigen phenotype, which is associated with induction of an EMT (epithelial-mesenchymal transition). In human dermal fibroblasts, CXCL4 increased expression of collagen type I, and suppressed transcription factor Fli-1. Additionally, the levels of reactive oxygen species (ROS), such as superoxide anion and hydrogen peroxide, were increased upon stimulation with CXCL4.

Conclusion: Our results suggest that CXCL4 can directly promote the fibrotic process, by transition of fully differentiated epithelial and endothelial cells into activated myofibroblasts, a process called epithelial/endothelial mesenchymal transition (EMT/EndoMT). Moreover CXCL4 might indirectly drive fibrosis by inhibition of Fli-1 and induction of collagen type I expression in fibroblasts. Further, CXCL4 increases ROS production in fibroblasts, which additionally stimulate synthesis and deposition of extracellular matrix (ECM) and promote fibrosis. In accordance with high level of CXCL4 in the circulation and skin of SSc patients[#], we demonstrate novel mechanisms in which CXCL4 could contribute to SSc phenotype.

Reference:
#) Radstake T.R.D.J., *N Engl J Med.* 2014

Disclosure: W. Marut, None; **A. J. Affandi**, None; **A. Limpers**, None; **T. R. D. J. Radstake**, None.

1705

The Lectin Pathway of Complement – a Potential Role in the Pathogenesis and Disease Manifestations of Systemic Sclerosis. Michael Osthoff[1], Gene-Siew Ngian[2], Melinda Dean[3], Mandana Nikpour[4], Wendy Stevens[5], Susanna Proudman[6], Damon Eisen[2] and Joanne Sahhar[7]. [1]The University of Melbourne, Melbourne, Australia, [2]Royal Melbourne Hospital, Parkville, Australia, [3]Australian Red Cross Blood Service, Brisbane, Australia, [4]University of Melbourne, Fitzroy, Australia, [5]St. Vincent's Hospital, Fitzroy, Australia, [6]Royal Adelaide Hospital, Adelaide, Australia, [7]Monash Health, Melbourne, Australia.

Background/Purpose: Repetitive episodes of ischemia and reperfusion (I/R) are a cardinal feature of the pathogenesis of systemic sclerosis (SSc), which precedes tissue fibrosis. The complement system is a key mediator of tissue damage after I/R, primarily by activation of the lectin pathway. This study investigated whether serum levels and polymorphisms of mannose-binding lectin (MBL) and ficolin-2 (FCN2), two pattern recognition receptors of the lectin pathway, are associated with the predisposition to, and clinical features of SSc.

Methods: A case-control study was undertaken involving 90 patients with SSc according to the American College of Rheumatology (73/90) or the LeRoy and Medsger criteria (17/90) from a single SSc outpatient clinic and 90 age- and sex-matched blood donors. MBL and FCN2 levels and polymorphisms were measured in both groups, and in cases correlated with clinical data.

Results: MBL levels and genotypes were equally distributed in cases and controls while there were some significant differences in *FCN2* polymorphisms. Median MBL levels were higher in SSc cases with diffuse disease compared to controls (2.6 vs. 1.0 μg/ml, $p<0.001$).

In cases, higher MBL levels were associated with the presence of clinical findings associated with vascular dysfunction and local tissue damage (digital ulcers, calcinosis and pitting). Moreover, MBL levels were associated with fibrotic disease manifestations as evidenced by the presence of diffuse disease (median 2.6 vs. 0.8 μg/ml, $p=0.002$), the modified Rodnan skin score ($r=0.39$, $p<0.001$), and interstitial lung disease as measured by forced vital capacity ($r=-0.33$, $p=0.001$). Importantly, MBL levels also correlated with the SSc Health Assessment Questionnaire scores ($r=0.33$, $p=0.002$). Results for FCN2 levels were less striking. Phenotypic MBL results were largely confirmed by analysis of MBL polymorphisms. MBL levels were not associated with the presence of autoantibodies or hypocomplementemia.

Conclusion: Overall, predisposition to SSc was not influenced by the lectin pathway of complement in our matched case-control study. However, our preliminary data suggest that MBL, and to a lesser extent FCN2 may modulate disease manifestations of SSc, particularly in diffuse cutaneous disease.

Acknowledgments: Kathleen Elford, Scleroderma Nurse for her assistance in collection of data and samples. SSc patients were recruited from Monash Health as part of the Australian Scleroderma Cohort Study (ASCS), a longitudinal, prospective study of SSc patients.

Figure 1: Serum mannose-binding lectin levels in SSc cases and healthy controls. MBL levels were analysed in SSc cases overall and stratified according to skin involvement (limited cutaneous vs. diffuse cutaneous). Horizontal bars indicate median and 25-75 percentiles. Abbreviations: MBL, mannose-binding lectin. Lc SSc, limited cutaneous systemic sclerosis; Dc SSc, diffuse cutaneous systemic sclerosis.

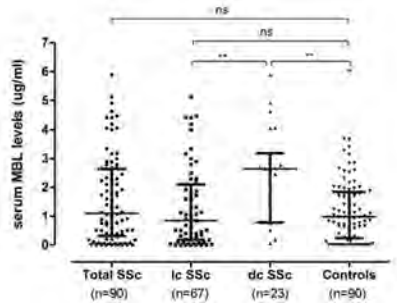
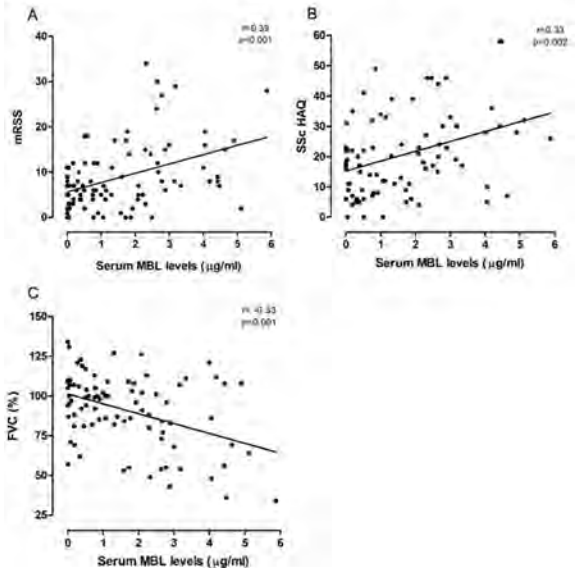


Figure 2. Correlation of serum MBL levels with activity and extent of disease in SSc cases. A. Correlation with extent of skin involvement as assessed by the modified Rodnan skin score (mRSS). B. Correlation with extent of functional disability as assessed by the Scleroderma Health Assessment Questionaire (SSc HAQ). C. Correlation with extent of pulmonary involvement as assessed by forced vital capacity (FVC, % predicted).



Disclosure: M. Osthoff, None; **G. S. Ngian**, None; **M. Dean**, None; **M. Nikpour**, None; **W. Stevens**, None; **S. Proudman**, None; **D. Eisen**, None; **J. Sahhar**, None.

1706

Prevention of SU5416-Induced Pulmonary Hypertension in a TGFβ Dependent Genetic Mouse Model of Scleroderma Using the Endothelin Receptor Antagonist Macitentan. Emma C. Derrett-Smith[1], Vincent Sobanski[2], Sarah Trinder[2], Adrian J Gilbane[2], Marc Iglarz[3], David J. Abraham[2], Alan M. Holmes[4] and Christopher P Denton[1]. [1]UCL Medical School Royal Free Campus, London, United Kingdom, [2]UCL Medical School, London, United Kingdom, [3]Actelion Pharmaceuticals Ltd., Allschwil, Switzerland, [4]UCL, London, United Kingdom.

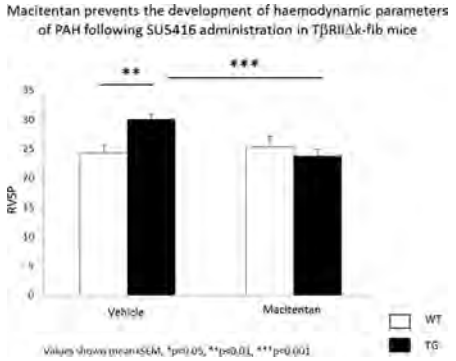
Background/Purpose: Pulmonary arterial hypertension (PAH) is an important complication of systemic sclerosis (SSc) that occurs in around 10% of cases. We have previously shown that a TGFbeta dependent transgenic mouse strain (TβRIIΔk-fib) is susceptible to organ based pathology relevant to SSc and that pulmonary endothelial injury is associated with development of PH with perturbed VEGF, BMP and endothelin signalling. In this study, we have prevented the development of PH in this mouse strain using macitentan, a potent endothelin receptor antagonist recently licensed to treat PAH in connective tissue disease based upon a significant effect on morbidity and mortality in PAH.

Methods: SU5416, a VEGF receptor inhibitor, was administered to all TβRIIΔk-fib transgenic (TG) mice and littermate wildtype (WT) animals to induce endothelial injury with subsequent endoluminal proliferation and PH in

transgenic mice only. Mice were treated with either 50mg/kg macitentan daily by oral gavage or vehicle alone (n=8 each group). The development of PH in each group was assessed by histology and immunohistochemistry of vessel architecture, *in vivo* haemodynamic studies and RV mass index measurements.

Results: Compared with WT littermates, after SU5416, all TG mice developed a prominent perivascular chronic inflammatory infiltrate and smooth muscle layer hypertrophy, as previously described. RV mass index was elevated in TG animals receiving vehicle compared to other groups (TG vehicle 0.29±0.007, TG macitentan 0.24±0.007, $p<0.05$). The increase in RV systolic pressure in TG animals treated with SU5416 was also abrogated by macitentan (figure 1) without any significant change in systemic arterial blood pressure in any group. Explanted TG lung fibroblasts showed an increase in proliferation and migration with upregulation of VEGF and TGFbeta signalling and downregulation of endothelin receptor A compared with WT littermates. There was obliterative pulmonary arteriolar occlusion in 21% of vessels in TG mice treated with vehicle. In contrast, no vessels in WT mice or TG mice treated with macitentan developed this histological change.

Conclusion: Macitentan prevents the development of histological and haemodynamic PH in this mouse model of SSc. These findings support a pivotal role for perturbed endothelin activity in a model that is induced by altered TGFbeta signalling and triggered by experimental VEGF inhibition. It underpins the value of this model as a platform for experimental therapeutic studies as well as providing insight into pathogenic mechanisms of disease.



Disclosure: E. C. Derrett-Smith, None; **V. Sobanski**, None; **S. Trinder**, None; **A. J. Gilbane**, None; **M. Iglarz**, Actelion Pharmaceuticals Ltd, 3; **D. J. Abraham**, None; **A. M. Holmes**, None; **C. P. Denton**, Actelion Pharmaceuticals Ltd, 2, Actelion Pharmaceuticals Ltd, 5.

1707

High Oxidative Stress in Fibrotic and Non-Fibrotic Skin of Patients with Systemic Sclerosis. Khalil I. Bourji[1], Alain Meyer[2], Emmanuel Chatelus[2], Erika Pigatto[1], François Singh[2], Bernard Geny[2], Leonardo Punzi[1], Jacques-Eric Gottenberg[2], Franco Cozzi[1] and Jean Sibilia[2]. [1]University Hospital of Padova, Padova, Italy, [2]University Hospital of Strasbourg, Strasbourg, France.

Background/Purpose: Systemic Sclerosis (SSc) is a chronic multisystemic connective tissue disease characterized by progressive fibrosis affecting skin and internal organs. Despite serious efforts to unveil pathogenic mechanisms of SSc, they are still unclear. High levels of Reactive Oxygen Species (ROS) in affected skin have been shown, but the role of oxidative stress remains controversial (1, 2, 3). In this study we assess ROS levels in non-fibrotic (NS) and fibrotic (FS) skin of patients with SSc and we compare them with those obtained from healthy controls (CS).

Patients and Methods: We enrolled 9 SSc patients fulfilling the EULAR/ACR classification criteria (4) and 7 healthy controls. Patients were 4 men and 5 women with mean age of 46±10 yrs. Controls were matched by sex and age. All patients were affected by diffuse cutaneous form of SSc and the ANA pattern anti-Scl70. Mean disease duration was 7.5±5 yrs. Skin involvement was evaluated by modified Rodnan Skin Score (mRSS). Skin samples (4mm punch biopsy) were taken from fibrotic skin (FS) and non-fibrotic skin (NS) of patients and from healthy controls (CS) as well. To detect ROS, specimens were analyzed immediately after sampling by electron paramagnetic resonance spectroscopy (5).

Results: ROS levels (expressed as median and range, unit of measurement was AU/mg) were 118.6×10^3 (52.4×10^3– 225.7×10^3) in FS, 89.6×10^3 (34.8×10^3– 163.1×10^3) in NS and 36.8×10^3 (17×10^3–65.1×10^3) in CS. ROS levels in Fibrotic (FS) and Non-fibrotic (NS) skin of SSc patients were significantly higher than in Healthy Control (CS) ($p=0.002$ and $p=0.009$, respectively). Although ROS levels in FS were raised in comparison to NS, this difference was not statistically significant ($p=0.24$). ROS levels of FS were correlated with DLCO ($r=-0.59$, $p=0.09$), VC ($r=-0.75$, $p=0.02$) and ESR ($r=0.70$, $p=0.03$). All other clinical and lab parameters showed no significant correlation.

Conclusion: Our results confirm the presence of high oxidative stress either in non-fibrotic skin (NS) or in fibrotic skin (FS) of SSc patients, but with higher tendency in the latter. Raised ROS levels in non-fibrotic skin (NS) of SSc patients might be a hint of early involvement in skin fibrogenesis. However, a longitudinal prospective study is necessary for such proof.

References

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Disclosure: K. I. Bourji, None; **A. Meyer**, None; **E. Chatelus**, None; **E. Pigatto**, None; **F. Singh**, None; **B. Geny**, None; **L. Punzi**, None; **J. E. Gottenberg**, None; **F. Cozzi**, None; **J. Sibilia**, None.

1708

The Pathogenic Role of Immune Complexes Containing Scleroderma-Specific Autoantibodies in the Inductor Phase of the Disease. Cecilia B. Chighizola[1], Elena Raschi[2], Laura Cesana[2], Silvana Zeni[3], Maria Orietta Borghi[4] and Pier Luigi Meroni[5]. [1]Istituto Auxologico Italiano, University of Milan, Cusano Milanino, Italy, [2]Istituto Auxologico Italiano, Milan, Italy, [3]Division of Rheumatology, Istituto G. Pini, Milano, Italy, [4]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [5]Division of Rheumatology, Istituto G. Pini, Milan, Italy.

Background/Purpose: Systemic sclerosis (SSc) is a chronic autoimmune condition characterized by excessive tissue fibrosis, microvascular alterations and immune dysfunction with the production of peculiar autoantibodies. These autoantibodies are highly specific for SSc diagnosis, and provide the most reliable tool to predict disease subset and the pattern of internal organ involvement. Despite such diagnostic and prognostic role, no evidence supporting the pathogenic potential of these autoantibodies has to date been raised.

Therefore the aim of this study is to evaluate for the first time the pathogenicity of immune complexes (IC) from scleroderma patients in the inductor phase of the disease, using skin fibroblasts from healthy controls as cellular in vitro model.

Methods: Fibroblasts have been isolated from skin biopsies obtained from healthy controls and then cultured in adequate conditions. IC have been purified from sera of scleroderma patients bearing different autoantibody specificities (antibodies against centromeric proteins [ACA], DNA topoisomerase I [ATA], RNA polymerase [ARA] and Th/To [anti-Th/To]) or of healthy controls using polyethylen glycol precipitation. Cell cultures have been incubated with pathologic and control IC and with cell activating agonists as TLR3 [Poly(I:C)] and TLR4 (LPS) ligands. Several parameters of fibroblast activation have been assessed in the different experimental conditions. In particular, mRNA levels of type I interferons (IFN-alpha and IFN-beta) have been investigated by real-Time PCR; ICAM-1 expression has been evaluated by cell-ELISA and the secretion of IL-6 and IL-8 in culture supernatants has been measured by commercial ELISA kits. Furthermore, the involvement of intracellular signaling pathways culminating with the activation of p38 MAPK, NFkB and JNK has been assessed by Western Blotting.

Results: Stimulation of normal skin fibroblasts with pathologic IC induced a significant increase in the gene expression levels of both IFN-alpha and IFN-beta; similar results have been observed in the presence of TLR agonists but not of control IC. In addition, the expression of ICAM-1 and the secretion of IL-6 and IL-8 were up-regulated by Poly(I:C), LPS and IC from scleroderma patients but not from healthy controls. Further, pathologic IC induced the activation of p38 MAPK, NFkB and JNK.

Conclusion: Our data provide the first demonstration of the pathogenic role of IC isolated from scleroderma patients with different autoantibody specificities in the inductor phase of SSc. Indeed, pathologic IC can interact with normal skin fibroblasts, inducing a pro-inflammatory phenotype mediated by p38 MAPK, NFkB and JNK. These evidences fit well with the diagnostic and prognostic role of scleroderma-specific autoantibodies, providing novel insights into SSc etiopathogenesis and potentially leading to new treatment strategies.

Disclosure: C. B. Chighizola, None; **E. Raschi**, None; **L. Cesana**, None; **S. Zeni**, None; **M. O. Borghi**, None; **P. L. Meroni**, None.

1709

Demonstration of Enhanced Hemodynamics with Topical Alprostadil Cream (RayVa®) Utilizing Laser Doppler Imaging in Primates. Susan Meier-Davis and Salma Debar. Apricus Biosciences, San Diego, CA.

Background/Purpose: Currently, there are no approved treatments in the United States for Raynaud's Phenomenon (RP). Prostanoids, i.e., prostacyclin (PGI2) and Alprostadil (PGE1); may be used to treat severe cases but have limited applicability for outpatient use due to intravenous administration. RayVa®or Alprostadil topical cream is being developed to treat the symptoms associated with Raynaud's Phenomenon (RP) secondary to scleroderma. In an ongoing Phase 2a study, topical administration of RayVa® to affected individuals is being assessed for changes in blood flow and temperature relative to treatment.

The active pharmaceutical ingredient in RayVa® is Alprostadil or the synthetic analog of the endogenous Prostaglandin E1 (PGE1). Owing to the proprietary penetration enhancer, dodecyl-2-N,N-dimethylaminopropionate hydrochloride (DDAIP-HCl), RayVa®is administered topically for a local delivery of alprostadil to the site of action without the need for systemic exposure.

This nonclinical study was conducted to demonstrate hemodynamics after local delivery utilizing Laser Doppler Imaging (LDI) and assessing varying dose levels of the alprostadil cream relative to placebo in non-human primates (NHP).

Methods: NHP were anesthetized and baseline blood flow recorded with LDI. Following baseline measurements, the animal's hands were placed in an ice-water bath for 2 minutes followed by application of placebo cream on one hand and one dose level of the alprostadil topical cream on the other hand. Both hands were imaged every 15 minutes from the end of the application until baseline blood flow was reached for a maximum of two hours.

The topical alprostadil cream consisted of 0.42% alprostadil and 2.5% DDAIP/HCl, administered at two alprostadil dose levels; 300 and 1000 micrograms. The placebo cream contained no alprostadil and 2.5% DDAIP-HCl.

Results: Alprostadil topical cream did not elicit clinical abnormalities in the majority of animals over the study duration. After cold-challenge, administration of the topical alprostadil cream induced a dose-responsive, statistically significant increase ($p<0.05$) in hemodynamic parameters relative to the placebo cream over the assessment period. The time-to-peak response was reached within 15 minutes after application and post-cold-challenge. The statistically significant increase in the hemodynamic response to the alprostadil cream was at least one hour in duration.

Conclusion: Topical alprostadil cream (RayVa®) induced a dose-responsive increase in hemodynamics relative to placebo utilizing LDI in NHP. Local application of the vasodilator may be a beneficial treatment for patients with restricted blood flow to distal extremities, as seen in Raynaud's Phenomenon. The observed hemodynamic changes support the RayVa® dose levels selected for an ongoing Phase 2a clinical trial assessing both blood flow and temperature changes in affected hands from individuals diagnosed with Raynaud's phenomenon secondary to scleroderma.

Disclosure: S. Meier-Davis, None; **S. Debar**, None.

1710

Endothelin-1 Is a Downstream Mediator of Profibrotic Effects by Transforming Growth Factor-β1 in Systemic Sclerosis Skin Fibroblasts. Tomoaki Higuchi[1], Yasushi Kawaguchi[1], Akiko Tochimoto[1], Yuko Ota[1], Yasuhiro Katsumata[1], Takahisa Gono[1], Masanori Hanaoka[1], Yuko Okamoto[1], Hidenaga Kawasumi[1] and Hisashi Yamanaka[2]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune connective tissue disorder characterized by excess collagen deposition, vascular changes and production of autoantibodies that affects multiple organs. Transforming growth factorβ1 (TGF-β1), that promotes collagen synthesis, extracellular matrix (ECM) remodeling and myofibroblast differentiation, is thought to play a key role in the pathogenesis of SSc. The vasoconstrictive peptide endothelin-1 (ET-1) is also known as potent fibrotic factors. ET-1 binds to two distinct subtype of G protein coupled receptors, ET receptor A (ETRA) and ET receptor B (ETRB). The fibrotic functions of each ET receptor remain unclear partly because the distribution and expression of ET receptors differs according to the disease situations, the respective organs or the cell types. The aim of our study was to examine the effects of TGF-β1 on the fibrogenic phenotype of SSc skin fibroblasts through ET-1 production and to clarify how the signal transduction through TGF-β1 is associated with upregulation of ET-1.

Methods: Human SSc skin fibroblasts (SSc fibroblasts) were obtained from 5 SSc patients. Recombinant TGF-β1, recombinant ET-1, SIS3 as an inhibitor of Smad3 phosphorylation, SP600125 as an inhibitor of c-JUN N-terminal kinase (JNK), BQ123 as a selective ETRA antagonist, BQ788 as a selective ETRB antagonist and bosentan as a dual ETRA/ETRB receptor antagonist were used in this study. SSc fibroblasts were incubated with TGF-β1 in the presence of SIS3 or SP600125. In addition, the effects of BQ123, BQ788 or bosentan were explored. The expression of ET-1, CTGF and type I collagen was evaluated using ELISA and real time RT-PCR. ETRA and ETRB expressions were assessed by immunohistochemistry and fluorescence activated cell sorting (FACS) analysis.

Results: Both ETRA and ETRB were expressed in SSc fibroblasts as detected by immunohistochemistry. TGF-β1 increased ET-1 in the levels of mRNA and protein and this increase in ET-1 was suppressed by either SIS3 or SP600125. Upregulation of *COL1A1* and *CTGF* by TGF-β1 were reduced by either ETRA or ETRB antagonist, and the effects were enhanced by dual ETRA/ETRB antagonist.

Conclusion: We herein revealed that TGF-β1 produced ET-1 through both Smad and JNK cascade and dual ETRA/ETRB antagonist contributed to diminishing COL1A1 and CTGF mRNA in fibroblasts. These findings suggest that the fibrogenic effects by TGF-b1 may in part be explained by the autocrine stimulation of ET-1. The dual ETRA/ETRB might be a novel therapeutic strategy for the SSc skin fibrosis.

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1711

The Relationship Between Vascular Biomarkers and Disease Characteristics in Systemic Sclerosis: Elevated MCP-1 Is Associated with Predominantly Fibrotic Manifestations. Yasemin Yalcinkaya[1], Suzan Cinar[1], Sevil Kamali[1], Lale Ocal[1], Gunnur Deniz[1] and Murat Inanc[2]. [1]Istanbul University, Istanbul, Turkey, [2]Division of Rheumatology, Department of Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey.

Background/Purpose: To determine the relationship between vascular biomarkers reflecting the vascular injury and organ involvement in systemic sclerosis (SSc).

Methods: Seventy-two SSc patients (66 female) fulfilling 2013 ACR/EULAR Criteria were evaluated. Serum samples of patients were collected for flow-cytometric analysis of CD40L, tPA, MCP-1, sE-selectin, IL-8, IL-6, VEGF, sP-selectin, TGF-β1 and VCAM levels (Bender MedSystems) in SSc patients and 20 healthy controls. **Results** were compared with Pearson chi-square / Fischer's and Mann Withney tests.

Results: The mean age of the patients was 44.9 and disease duration from the appearance of first non-Raynaud symptom was 3.2 ± 2.4 years. Of the patients 23 (32%) had diffuse and 49 (68%) limited cutaneous involvement, 15 (21%) were anti-centromere (+) and 34 (47%) were anti-Scl70 (+). In SSc patients, levels of tPA ($p=0.02$), MCP-1 ($p=0.001$), sE-selectin ($p=0.008$), TGF-β1 ($p=0.001$) were significantly higher, sP-selectin ($p=0.011$) and IL-8 ($p=0.001$) were lower than healthy controls (table-1).

Table-1: Vascular Biomarkers in Healthy Controls and Systemic Sclerosis

Biomarker Levels (mean ± SD)	Healthy Controls (n=20)	Systemic Sclerosis (n=72)
sCD40L (pg/ml)	24620 ± 13051	27847 ± 33315
tPA (pg/ml)	2415 ± 1279	4036 ± 6961*
MCP-1 (pg/ml)	907 ± 300	1302 ± 550**
sE-selectin (ng/ml)	205 ± 78	269 ± 106**
IL-8 (pg/ml)	49 ± 73**	22 ± 80
IL-6 (pg/ml)	0	0.6 ± 2.8
VEGF (pg/ml)	704 ± 363	776 ± 591
sP-selectin (ng/ml)	364 ± 137*	287 ± 86
TGF-β1 (pg/ml)	2421 ± 4785	8277 ± 8592**
VCAM (pg/ml)	3231 ± 1435	3945 ± 1754

**p<0.05, **p<0.01 When healthy controls and sytemic sclerosispatients were compared with Mann-Whitney test*

Levels of MCP-1 was elevated in patients with dcSSc, flexion contractures, FVC<80%, DLCO<80%, pulmonary fibrosis and high acute phase response ($p=0.002$, $p=0.005$, $p=0.045$, $p=0.005$, $p=0.036$, $p=0.006$, respectively), TGF-β1 in patients under immunosupressives ($p=0.001$), sE-selectin in patients with high acute phase response ($p=0.028$), sCD40L in patients with smoking habitus ($p=0.032$) and lcSSc ($p=0.011$) (table-2).

Table-2: Vascular Biomarkers between disease characteristics of Systemic Sclerosis Patients

		MCP-1 (pg/ml)	sCD40L (pg/ml)	sE-selectin (ng/ml)	TGF-β1 (pg/ml)
Skin Involvement -diffuse	+ (n=23)	*1586 ± 579***	18494 ± 20360	285 ± 107	9544 ± 8864
-limited	+ (n=49)	***1169 ± 486***	***32238 ± 37284****	262 ± 106	7683 ± 8489
Flexion Contractures	+ (n=12)	***1757 ± 646****	16768 ± 13118	279 ± 129	9068 ± 6873
	− (n=60)	*1211 ± 485*	30064 ± 35687	267 ± 102	8119 ± 8937
Low DLCO (<80%)	+ (n=28)	***1548 ± 654****	34841 ± 49690	274 ± 116	9832 ± 8785
	− (n=44)	*1145 ± 407*	23397 ± 15170	266 ± 100	7288 ± 8418
Low FVC (<80%)	+ (n=19)	***1537 ± 618****	23374 ± 21490	267 ± 104	10558 ± 8604
	− (n=53)	*1218 ± 503*	29452 ± 36683	270 ± 108	7460 ± 8520
Pulmonary Fibrosis	+ (n=18)	***1526 ± 558****	26309 ± 21268	287 ± 89	8831 ± 9385
	− (n=54)	*1228 ± 531*	28361 ± 36615	263 ± 111	8093 ± 8397
High Acute Phase Response	+ (n=30)	***1543 ± 621****	27581 ± 20414	***300 ± 95****	9219 ± 8522
	− (n=42)	*1137 ± 424*	28522 ± 40715	247 ± 110	7790 ± 8704
Smoking History	+ (n=32)	1233 ± 514	***36878 ± 45771***	281 ± 104	7627 ± 9047
	− (n=40)	1358 ± 576	20624 ± 15326	260 ± 108	8798 ± 8290
Immunosuppressives	+ (n=41)	1345 ± 547	24497 ± 19379	270 ± 110	***10981 ± 9057****
	− (n=31)	1246 ± 557	32279 ± 45720	268 ± 102	*4702 ± 6493*

*$p<0.05$, **$p<0.01$ When groups were compared with Mann-Whitney test*
MCP-1 and sE-selectin levels were correlated with disease activity (r=0.243, p=0.040 and r=0.303, p=0.010) (Valentini et al.)

Conclusion: MCP-1, t-PA, TGF-β1, sE-Selectin, sP-Selectin and IL-8 were differently regulated in SSc patients. MCP-1 was the prominently biomarker correlated with manifesatations related to fibrosis and may be a surrogate marker for fibrotic disease activity. Treatment and smoking may have an effect on cytokine profile. Vascular biomarkers can be used to predict the characteristics and severity of SSc warranting prospective studies.

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1712

Monocytic Angiotensin and Endothelin Receptor Imbalance Determines Secretion of the Profibrotic Chemokine Ligand CCL18. Judith Rademacher[1], Jeannine Guenther[2], Angela Kill[3], Elise Siegert[4] and Gabriela Riemekasten[5]. [1]Charité University Hospital and German Rheumatism Research Centre, a Leibniz Institute, Berlin, Germany, 10117 Berlin, Germany, [2]Charité University Hospital and German Rheumatism Research Centre, a Leibniz Institute, Berlin, Germany, Berlin, Germany, [3]Charité University Hospital, German Rheumatology Research Center, a Leibniz Institute, Berlin, Germany, [4]Charité – University Hospital, Berlin, Germany, [5]Charité University Hospital and German Rheumatism Research Centre, a Leibniz Institute, Berlin, Germany.

Background/Purpose: Circulating monocytes are progrenitor of extracellular matrix producing cells involved in fibrosis and show highest expression of angiotensin II (ATR) and endothelin receptors (ETR) compared to other peripheral blood mononuclear cell (PBMC) subsets(1, 2). Stimulating autoantibodies (aab) against AT_1R and ET_AR are elevated in patients with Systemic Sclerosis (SSc) and associated with mortality and the development of disease complications such as PAH, lung fibrosis and digital ulcers(3). SSc-IgG positive for Anti-AT_1R and Anti-ET_AR-aabs induces through the respective receptors the production of the profibrotic chemokine CCL18 in PBMCs(2).

We analysed whether effects of autoantibodies (aab) against angiotensinII receptor type 1 (AT_1R) and endothelin receptor type A (ET_AR) in patients with Systemic Sclerosis (SSc) might be influenced by expression of respective receptors and their functional counterparts AT_2R and ET_BR.

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Methods: AT_1R, AT_2R, ET_AR and ET_BR expression was measured on CD14+ monocytes of 29 SSc patients and 18 healthy donors by flow cytometry. PBMCs of 11 healthy donors were analyzed for receptor expression as well and in vitro stimulated with affinity purified IgG of SSc patients and normal controls. Afterwards, CCL18 concentration was measured in the supernatants by ELISA.

Results: Monocytes of SSc-patients presented higher expression of all 4 receptors compared to NC and an increased AT_1R/AT_2R ratio. ET_AR/ET_BR ratio was significantly reduced in patients with lung fibrosis and correlated negatively with the modified Rodnan Skin Score (Spearman rank correlation's coefficient $r=-0.49$, $p<0.01$).

PBMCs stimulated with SSc-IgG showed higher CCL18 concentration in supernatants than PBMCs stimulated with NC-IgG ($p<0.0001$). CCL18 induction by NC-IgG and SSc-IgG correlated with AT_1/AT_2 ratio (SSc-IgG: $r=0.72$, $p=0.03$, NC-IgG: $r=0.98$; $p<0.0001$) and negatively with ET_A/ET_B ratio (SSc-IgG: $r=-0.82$, $p=0.03$, NC-IgG: $r=-0.93$; $p=0.007$) of receptor positive monocytes.

Conclusion: Receptor expression might reflect systemic activation of the angiotensin and endothelin system in SSc. Since patients with lung fibrosis and high mRSS showed a reduced ET_AR/ET_BR ratio, imbalance of ATR and ETR may influence effects of aab in SSc and could serve as a marker for disease complications. High AT_1R/AT_2R but low ET_AR/ET_BR ratios on monocytes correspond to higher secretion of CCL18 suggesting a link between receptor expression and monocytic function.

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1713

Increased Number of $CD206^+$cells in Peripheral Blood and Skin of Systemic Sclerosis Patients. Stefano Soldano[1], Paola Contini[2], Renata Brizzolara[1], Paola Montagna[1], Barbara Villaggio[3], Alberto Sulli[4], Carmen Pizzorni[4], Sabrina Paolino[1], Bruno Seriolo[4] and Maurizio Cutolo[4]. [1]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy, [2]Division of Clinical Immunology, Department of Internal Medicine, University of Genova, Genova, Italy, [3]Research Laboratory of Nephrology, Department of Internal Medicine, University of Genova, Genova, Italy, [4]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy.

Background/Purpose: Systemic sclerosis (SSc) is characterised by microvascular damage, immune cell activation and fibrosis of the skin and internal organs. In SSc, the immune-inflammatory infiltrate is primarily made of macrophages and T cells (1). The alternatively activated macrophages (M2) are characterized by an increased expression of specific markers, primarily CD206 (macrophage mannose receptor-1) and macrophage scavenger receptors, and participate in the fibrotic process through the production of pro-fibrotic molecules (i.e. fibronectin, TGFβ) (2). The study investigated the presence of $CD206^+$cells in the peripheral blood and skin of SSc patients. The capability of SSc serum to induce the expression of CD206 in peripheral blood mononuclear cells (PBMCs) of healthy subjects was also investigated.

Methods: Eight SSc patients (mean age 65±7 years) who fulfilled the new criteria of EULAR/ACR (3) and five age matched healthy subjects (HS) were enrolled into the study, after signing of Informed Consent and local Ethical Committee approval. Peripheral blood from SSc patients and HS was analysed by flow cytometry (FC) to detect the presence of cells positive for CD206 and CD14 (a marker of monocyte/macrophage lineage). Skin biopsies were obtained from four of the enrolled SSc patients who were characterized by a "limited" cutaneous involvement (lSSc) and the five HS. The PBMCs obtained from the HS enrolled were plated into FlexPerm chamber slides (2×10^6cells/spot) and maintained for 12 hours in growth medium at 10% of fetal bovine serum in order to isolate the monocyte/macrophage cells. These monocyte/macrophage cells were stimulated for 48 hours with serum from SSc patients and the HS themselves. The expression of CD206 and CD68 (a macrophage marker) was evaluated by immunohistochemistry (IHC) on skin biopsies and by immunocytochemistry (ICC) on cultured human monocyte/macrophages derived from PBMCs.

Results: In the peripheral blood of SSc patients, the percentage of $CD206^+$cells was significantly higher than that of the HS ($p<0.01$). The FC confirmed that the $CD206^+$cells belong to the monocyte/macrophage lineage given the co-expression of CD14. In the skin of SSc patients, the $CD206^+$cells were detected in the immune-inflammatory infiltrate which is characterized by the presence of macrophages ($CD68^+$cells). Conversely, in the skin of HS no $CD206^+$cells were observed. ICC showed that SSc serum stimulated PBMCs-derived monocyte/macrophage cells to express CD206 and also induced these cells to express CD68 thus indicating their activation into macrophages. Conversely, serum from HS was unable to stimulate the expression of CD206 in these cells.

Conclusion: These preliminary results show the presence of $CD206^+$cells in both peripheral blood and skin of SSc patients. Moreover, the ability of SSc serum to induce the expression of this M2 macrophage marker in PBMCs-derived macrophages might support a possible involvement of this cell subset in the pathogenesis of SSc.

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1714

IL-6 Trans-Signalling Activates M2 Macrophage Polarisation and Mediates Fibrotic Response in Scleroderma. Rebecca Alade, Shiwen Xu, Korsa Khan, Angela Tam, Christopher P. Denton and Voon H. Ong. UCL Medical School Royal Free Campus, London, United Kingdom.

Background/Purpose: IL6 is a key mediator in activation of extracellular matrix (ECM) in scleroderma (SSc) fibroblasts and via its interplay with chemokines may modulate mononuclear cell recruitment and fibrosis. We have explored the role of IL6 in macrophage differentiation in SSc and its regulation of fibrotic response.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from patients with early stage diffuse cutaneous SSc (dcSSc) (n=12) and healthy controls (n=6) via Ficoll gradient centrifugation. Dermal fibroblasts were cultured from skin biopsies from healthy controls (n=4) and dcSSc (n=4). Flow cytometry was used to quantify M2 macrophages in PBMCs defined by $CD68^+CD163^+$ cells. A magnetic-activated cell sorting (MACS) based protocol was used to select $CD14^+$ cells. $CD14^+$Cells were stimulated for 7 days with M-CSF before further stimulation with M-CSF alone or IL6/sIL6R. Flow cytometry was then used to determine the effect of IL6 trans-signalling on macrophage polarisation. Control and dcSSc fibroblasts were stimulated with conditioned media(CM) from cultured M2 macrophages. Western blot analysis for Collagen type-1 (Col-1) and alpha smooth muscle actin (αSMA) were used to assess ECM protein levels induced by CM and the effect of CM on fibroblast contractile response was evaluated with collagen gel contraction assays.

Results: PMBCs were isolated from healthy controls (n=6) mean age (37 ± 13.8 months), and dcSSc patients (n=12), mean age (42.2 ±15.6 years) and disease duration (34.2 ±15.6 months). Flow cytometry of PBMCs demonstrated significantly higher proportion of circulating M2 macrophages (mean ± SEM %) in dcSSc patients compared to healthy controls (9.3±0.3% vs 1.4±1.2%, $p=0.0087$) respectively. There is no significant difference in the total number of $CD68^+$macrophages between the two groups. Stimulation of isolated macrophages with IL6/sIL6R polarised the M2 macrophage population by (4-fold, $p<0.02$) and (1.6-fold, $p<0.04$) in control and SSc macrophages respectively. Cultured fibroblasts treated with CM generated from SSc M2 macrophages led to increased synthesis of ECM proteins αSMA (3-fold, $p<0.04$) and Col-I (3.2-fold, $p<0.04$) compared with control macrophages in the presence of control fibroblasts. CM from SSc M2 macrophages induced contraction of control fibroblasts leading to (4mm±0.3,$p<0.05$) reduction in collagen gel diameter compared to control CM.

Conclusion: Our data indicate that M2 macrophage phenotype in early stage scleroderma may partly be polarised by IL-6 trans-signalling. This supports the critical role of distinct macrophage subpopulation in regulation of key fibrotic markers, myofibroblastic differentiation and contractile response in SSc. Elucidating these pathways may lead to better understanding of macrophage biology in disease pathogenesis and the potential for targeted specific subpopulation as emerging therapeutics in SSc.

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1715

Serum Levels of CD163/Tweak Predict Risk of Digital Ulcers in Patients with Systemic Sclerosis. Otylia M. Kowal-Bielecka[1], Marek Bielecki[2], Beata Trzcinska-Butkiewicz[3], Malgorzata Michalska-Jakubus[4], Marek Brzosko[3], Dorota Krasowska[4] and Krzysztof Kowal[5]. [1]Department of Rheumatology and Internal Medicine, Medical University in Bialystok, Bialystok, Poland, [2]Department of Orthopedics and Traumatology, Medical University of Bialystok, Bialystok, Poland, [3]Pomeranian Medical University, Szczecin, Poland, [4]Medical University of Lublin, Lublin, Poland, [5]Department of Allergology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland.

Background/Purpose: TNF-like weak inducer of apoptosis (TWEAK) regulates inflammation, angiogenesis and tissue remodeling. CD163 molecule, a scavenger receptor and marker of alternatively activated macrophages, modulates TWEAK activity through binding and internalization of TWEAK molecule. It has previously been shown that, in a crossectional study, high serum concentrations of soluble CD163 (sCD163) and high CD163/TWEAK ratio were associated with lack of digital ulcers (DU) in patients with systemic sclerosis (SSc) [1].

The aim of the present study was to investigate whether serum levels of soluble CD163 (sCD163), soluble TWEAK (sTWEAK), or sCD163/sTWEAK ratio can predict clinical course of DU in patients with (SSc).

Methods: 50 patients fulfilling the ACR/EULAR classification criteria of SSc who were followed for at least 1 year were included. Serum levels of sCD163 and sTWEAK were measured using commercially available ELISA kits. Digital ulcers were defined as painful area of loss of tissue on the volar surface of fingertips or around the nail distal to the proximal interphalangeal digital crease, present at the time of assessment. In addition, evaluation of SSc patients included assessment of disease subset (diffuse/limited SSc), modified Rodnan skin score, the presence of interstitial lung disease, pulmonary hypertension, results of pulmonary function tests, echo-Doppler, autoantibody testing (anticentromere antibodies, anti-Scl-70 antibodies) and erythrocyte sedimentation rate.

Results: At baseline DU were present in 18 patients. During follow-up DU healed in 12 SSc patients and persisted in the remaining 6. In addition, 5 patients without DU at baseline developed new DU during follow-up. Because of relatively low numbers, patients with recurrent/persistent DU and those with new DU were analyzed together (n=11). In the remaining 27 patients DU were not found at any visit.

There were no significant differences in baseline sCD163 levels between SSc patients in whom DU healed, those with persisted/new DU or those without DU at any visit. In contrast, baseline serum levels of sTWEAK were significantly higher in SSc patients who subsequently experienced healing of DU compared with SSc patients with DU at follow-up and with SSc patients who never had DU ($p<0.05$ for both comparisons). Accordingly, baseline sCD163/sTWEAK ratio was significantly lower in SSc patients with healed DU as compared with those with persisted/new DU at follow-up and with those who never had DU ($p<0.05$ for both comparisons).

In univariate analysis baseline DU, anticentromere antibodies (ACA) and sCD163/sTWEAK ratio were significantly associated with outcome of DU. In multivariate analysis including baseline DU, ACA and sCD163/sTWEAK ratio, baseline DUs were the strongest independent predictor of risk of DU at follow-up.

Conclusion: Our results suggest that CD163-TWEAK interactions might play a role in the development/healing of DU in SSc and indicate that sCD163/sTWEAK serum ratio is a potential biomarker of peripheral vascular disease in SSc.

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Disclosure: O. M. Kowal-Bielecka, Abbvie, Actelion, Pfizer, 8; **M. Bielecki**, None; **B. Trzcinska-Butkiewicz**, None; **M. Michalska-Jakubus**, None; **D. Brzosko**, None; **D. Krasowska**, None; **K. Kowal**, None.

1716

MHC Class I and Class II Genes Influence Systemic Sclerosis Susceptibility, Clinical Presentation and Autoantibody Profile in a Mexican Admixed Population. Tatiana Sofia Rodriguez-Reyna[1], Joaquin Zuniga[2], Julio Granados[3], Pamela Mercado Velazquez[4], Carlos Nunez Alvarez[4], Neng Yu[5], Sharon Alosco[5], Alfredo Cruz Lagunas[6] and Edmond Yunis[7]. [1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico, [2]Instituo Nacional de Enfermedades Respiratorias Ismael Cosio Villegas, Mexico, Mexico, [3]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubira, Mexico, Mexico, [4]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico, [5]American Red Cross Blood Services - Northeast Division, Dedham, MA, [6]Instituto Nacional de Enfermedades Respiratorias, Mexico, Mexico, [7]Dana Farber Cancer Institue, Boston, MA.

Background/Purpose: Systemic Sclerosis (SSc) exhibits great clinical and serologic variability in different populations. Herein we determined MHC class I and II alleles and extended haplotypes in a cohort of Mexican SSc patients to evaluate the contribution of these loci to SSc susceptibility, clinical and autoantibody profile, and to determine the prevalence of Amerindian, Caucasian and African haplotypes.

Methods: We included 159 SSc patients (ACR or LeRoy-Medsger criteria), with homogeneous ancestry (at least 3 generations). Patients were

classified in diffuse cutaneous (dcSSc) and limited cutaneous systemic sclerosis (lcSSc) based on the extent of their skin involvement. They were evaluated to determine presence and severity of organ involvement (Medsger's severity scale). Peripheral venous blood was obtained to test for ANA, SSc-associated antibodies and sequence based MHC class I and II typing. We included 234 healthy, ethnically matched individuals as controls. Admixture estimations and principal component analysis (PCA) were performed. IRB approval was obtained for this study, which was performed according to the Helsinki Declaration contents; informed consent was obtained for every participant. Differences were evaluated using Student's t test, X^2, Fisher exact test and Bonferroni when appropriate, p values <0.05 were considered significant.

Results: We found female predominance (98% vs 84%; p=0.004) and longer disease duration in lcSSc patients (13 vs 8 years; p=0.001); higher proportion of interstitial lung disease (44 vs 24%, p=0.01) and gastrointestinal involvement (73 vs 57%, p=0.03) in dcSSc patients. Anti-Topoisomerase I antibody predominated in dcSSc patients (p=0.0009), and anticentromere (ACA) in lcSSc patients (p=0.005). HLA allele analysis showed increased frequency of HLA-B*08:01 in SSc (gene frequency (gf) 4%) and in dcSSc (gf=4%) patients when compared to controls (gf=0.6%; p=0.01, OR 7.1, 95%CI 2–31; and p=0.004, OR 7.5, 95%CI 1.6–47, respectively); increased frequency of HLA-DRB1*11:04 in dcSSc patients (gf=7.8%) when compared to controls (gf=1.7%, p=0.01, OR 4.8, 95%CI 1.6-14-5); decreased frequency of HLA-DQB1*03:01 in SSc (gf=14.5%) and in lcSSc patients (gf=12.7%) when compared to controls (gf=24.7%, p=0.008, OR 0.5, 95%CI 0.3–0.7; and p=0.009, OR 0.4, 95%CI 0.2–0.7, respectively). Antibody analysis revealed association of HLA-DRB1*08:02 and HLA-DQB1*0402 alleles with anti-Topoisomerase I antibody (p=0.03, OR 2.2, 95%CI 1.2–4; and p=0.00001, OR 5.3, 95%CI 2.8–10, respectively), and HLA-DQB1*0302 was negatively associated to the presence of this autoantibody (p=0.04, OR 0.34, 95%CI 0.15–0.71). Admixture estimations using HLA-B showed significant increase in the percentage of Caucasian genes (33% in lcSSc vs 23% in dcSSc) and reduced percentage of African genes in lcSSc patients (13% vs 24% in dcSSc).

Conclusion: MHC Class I and II genes contribute to Systemic Sclerosis susceptibility, influence clinical presentation and autoantibody profile. Genetic admixture shows different components in dcSSc and lcSSc subsets and in controls.

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Endothelial to Mesenchymal Transition Contributes to the Development of Pulmonary Vasculopathy in Systemic Sclerosis PAH. Robert Good[1], Adrian Gilbane[2], Sarah Trinder[2], David Abraham[3], Christopher Denton[3] and Alan M. Holmes[2]. [1]UCL, LONDON, United Kingdom, [2]UCL, London, United Kingdom, [3]UCL Medical School, London, United Kingdom.

Background/Purpose: Vascular complications in Scleroderma (SSc) patients are associated with high mortality, particularly in patients who develop pulmonary arterial hypertension (SSc-PAH). Vascular complications, thought to arise from initial activation and dysfunction of the endothelium can lead to: elevated vascular leak, inflammation, mesenchymal hypertrophy by activation of resident smooth muscle cells and fibroblasts, and neointima formation. Recent studies suggest that as well as resident mesenchymal cells, endothelial cells can undergo endothelial-mesenchymal transition (EndoMT), and acquire a mesenchymal phenotype which may contribute to the expansion of the mesenchymal cell population. Here we sought to determine the prevalence of EndoMT in SSc-PAH patients and pre-clinical models of PAH, and assess the cellular effects on pulmonary artery endothelial cells (PAECs) functions.

Methods: Using lung tissue from SSc-PAH patients (n=3), healthy control (HC) donors (n=3), and from the hypoxia/SU5416 pre-clinical murine model of PAH (n=5), EndoMT was determined by immunofluorescence based on co-expression of vWF and αSMA. EndoMT was induced in human PAECs (n=3) *in vitro* by TNFα [5ng/ml], IL-1β [0.1ng/m;] and TGFβ [5ng/ml] in combination. Morphological changes were assessed by light microscopy and phalloidin staining. Western blotting and immunofluorescence was used to quantify: CD31, vWF, occludin, VE-cadherin, αSMA, calponin and collagen type 1 expression. Conditioned media was collected from PAECs, PAECs following treatment to initiate EndoMT and SSc-PAH and HC fibroblasts; levels of inflammatory secretion was quantified by MSD arrays. The capacity of homogenous EndoMT monolayers (n=6) and mixed cultures of 1:10 EndoMT:PAECs (n=6) cells to form exclusion barriers was assessed using trans-well permeability FITC-albumin assays.

Results: Co-localisation of vWF and αSMA was observed in ≤5% of pulmonary arteries from SSc-PAH patients and hypoxia/SU5416 mice. PAECs treated with TNFα, IL-1β and TGFβ exhibited significant changes in morphology, loss of endothelial markers and elevated expression of mesenchymal markers by day 6. There was a significant ($P<0.05$) increase in secretion of pro-inflammatory chemokines by EndoMT cells compared to PAECs including IL-6 [474±95 vs.12±6.6 pg/ml] and IL-8 [620±71 vs.28±6.5 pg/ml]. EndoMT cells alone or in mixed 1:10 ratio cultures with PAECs, exhibited a significant ($P>0.01$) 5-fold increase in permeability compared to PAECs alone. Consistent with this, EndoMT cells co-cultured with PAECs in a ratio of 1:10 led to 2.5-fold significant ($P>0.05$) increase in permeability.

Conclusion: The co-localisation of vWF and αSMA present in the pulmonary arteries of SSc-PAH patients and pre-clinical models of PAH, is indicative of EndoMT. We demonstrate EndoMT leads to a loss of normal PAEC morphology and an enhanced secretion of pro-inflammatory chemokines. Furthermore EndoMT cells failed to form integral biological barriers and contributed to enhanced permeability of PAEC barriers. Collectively our data suggests that EndoMT may contribute to the loss of normal endothelium function and the development of SSc-PAH.

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B Cell Subsets Homeostasis and Functional Properties Are Altered in a Murine Model of Systemic Sclerosis. Sébastien Sanges[1], Niloufar Kavian[2], Carine Hauspie[3], Carole Nicco[2], Thomas Guerrier[1], Virginie Dutoit-Lefèvre[1], Guillaume Lefèvre[4], Alexandra Forestier[5], Vincent Sobanski[4], Christelle Faveeuw[6], Myriam Labalette[3], Frédéric Batteux[2], David Launay[5] and Sylvain Dubucquoi[1]. [1]Université Lille Nord de France, Faculté de Médecine Henri Warembourg, Lille, Lille, France, [2]Université Paris Descartes, EA 1833, Hôpital Cochin, AP-HP, Paris, Paris, France, [3]Institut d'Immunologie, Centre de Biologie-Pathologie-Génétique, CHRU Lille, Lille, France, [4]Service de médecine interne, Centre National de Référence de la Sclérodermie Systémique, Hôpital Claude Huriez, CHRU Lille, Lille, France, [5]EA 2686, Lille, Lille, France, [6]Institut National de la Santé et de la Recherche Médicale Unité 547, Institut Pasteur de Lille, Institut Fédératif de Recherche 142, Université de Lille Nord de France, Lille, France.

Background/Purpose: Systemic sclerosis (SSc) is a multi-organ fibrotic disease associated with auto-immune abnormalities. Several clinical and experimental observations suggest that B cells are involved in the inflammatory and fibrotic processes responsible for the disease; but their exact role has yet to be precisely explored. In this work, we assessed the B cell homeostasis modifications in a murine model of SSc (HOCl mouse), both at a phenotypic and functional level, during the course of the disease.

Methods: Overall, 48 Balb/c mice underwent daily subcutaneous injection of hypochlorous acid (HOCl) or PBS, and were then sacrificed at day 21 (early, inflammatory stage) or day 42 (late, fibrotic stage) from the beginning of the protocol (n=12 in each of the 4 groups). Mouse spleens were retrieved and immediately dissected. The distribution of the splenic leucocyte populations (B cells, T CD4 and CD8 cells, macrophages) and B cell subsets (transitionnal, follicular, marginal zone, B1 and regulatory B cells) was analyzed by flow cytometry. The functional properties of B cells were evaluated by MACS- or FACS-sorting the different subsets, and measuring the secretion levels of 20 cytokines in culture supernatants, after stimulation by LPS and CD40L for 48h.

Results: The phenotypic analysis showed a B cell expansion in the HOCl mice at both stages of the disease. This expansion concerns mainly the transitional and B1a cells at the early stage; and mostly the mature forms (follicular and marginal zone) and B1b cells at the later stage. The regulatory $CD5^+$ $CD1d^{hi}$ B cells were also shown to expand at both times of the disease, but more importantly during the inflammatory stage.

At a functional level, the large screening of B cell secretion capacities identified 2 cytokines that were differently produced within the 4 groups: IL-6 and MIP-1α. Those 2 cytokines, that display pro-inflammatory and pro-fibrotic properties, were produced in more important levels in the supernatant of B cells culture from HOCl mice, at both stages of the disease. Within the B cell compartment, IL-6 was mainly secreted by the marginal zone (MZ) subset. Due to its potential regulatory effects, a special focus was also given

on IL-10 secretion. Levels of IL-10 in the supernatant of B cells appeared similar in the 4 groups.

Conclusion: To our knowledge, this study is the first to find evidence of B cell homeostasis alterations in murine model of SSc. It further implies a potential implication of B cells in the pathogenesis of this disease, either by secretion of cytokines (like IL-6 and MIP-1α) or by expansion of pathogenic subsets (such as marginal zone B cells). The exact role of the regulatory B cell subset, that may exert beneficial properties, needs further studying, as the expansion of the $CD5^+$ $CD1d^{hi}$ B cells in HOCl mice seems inconsistent with the similar secretion of IL-10 in the 4 groups. Nevertheless, in light of those results, the B cell appears to be a relevant target for therapy in SSc.

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Periostin May Promote Productin of Extracellular Matrix By Modulating TGF-β Signaling in Human Skin Fibroblasts. Yukie Yamaguchi[1], Noriko Koumitsu[1], Kazuhiko Arima[2], Kenji Izuhara[2] and Michiko Aihara[1]. [1]Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]Saga Medical School, Saga, Japan.

Background/Purpose: Systemic sclerosis (SSc) results in significant morbidity and mortality due to organ fibrosis characterized by increased deposition of extracellular matrix (ECM). Periostin is one of the matricellular proteins, a class of ECM-related molecules defined by their ability to modulate cell–matrix interactions. Recent studies revealed that periostin serves as a critical regulator of wound healing, epithelial mesenchymal transition, and fibrosis. We previously reported elevated serum periostin levels in SSc patients which correlated with severity of skin sclerosis. However, the pathogenic role of periostin in fibrosis has not been well elucidated. In this study, we further examined the role of periostin on transforming growth factor-β (TGF-β) signaling mediating fibrosis.

Methods: Periostin levels in skin and lung primary fibroblasts obtained from SSc patients were first determined. To enhance the function of periostin, we overexpressed periostin in human skin fibroblasts and examined protein levels of ECM proteins, α-smooth muscle actin (α-SMA), matrix metalloproteinases (MMPs) in the presence or absence of TGF-β by immunoblotting. Interaction of periostin with TGF-β receptors (TGF-βRI, TGF-βRII) was assessed by immunoprecipitation assay. Furthermore, effects of periostin to Smad proteins following TGF-β stimulation were also evaluated.

Results: Periostin was strongly expressed in skin and lung primary fibroblasts obtained from SSc patients compared with healthy subjects. Although single stimulation of recombinant periostin (rP) did not increase ECM protein levels, rP-treated fibroblasts and periostin overexpressed fibroblasts produced significant ECM proteins in the presence of TGF-β compared to respective control fibroblasts stimulated with TGF-β alone. Overexpression of periostin enhanced the induction of α-SMA in the presence of TGF-β and increased expression of MMP-1, which is reported to associate TGF-β activation. In addition, phosphorylation of Smad 2/3 by TGF-β was not affected by periostin, but a level of Smad 7, a TGF-β-inducible inhibitor of TGF-β signaling, was reduced in periostin expressed fibroblasts stimulated with TGF-β.

Conclusion: Periostin may contribute to fibrosis by enhancing TGF-β signaling via TGF-β activation and Smad 7 inhibition, which leads to further ECM deposition and periostin generation. Periostin may be a therapeutical target molecule mediating fibrosis.

Disclosure: Y. Yamaguchi, None; **N. Koumitsu**, None; **K. Arima**, None; **K. Izuhara**, None; **M. Aihara**, None.

1720

GATA6 Deficiency Activates UPR Pathways in Endothelial Cells during the Development of Pulmonary Arterial Hypertension. Rong Han[1], Rosanne Van Deuren[2], Stefania Lenna[1], Izabela Chrobak[1], Timothy Radstake[3], Carol Feghali-Bostwick[4] and Maria Trojanowska[1]. [1]Boston University, Boston, MA, [2]University Medical Center Nijmegen, Nijmegen, Netherlands, [3]University Medical Center Utrecht, Utrecht, Netherlands, [4]Medical University of South Carolina, Charleston, SC.

Background/Purpose: Pulmonary arterial hypertension (PAH) is a severe lung complication of systemic sclerosis (SSc), and accounts for a large proportion of SSc-related deaths. As a manifestation of the SSc vasculopathy in pulmonary arteries, PAH is characterized by endothelial dysfunction, inflammation, and vascular wall remodeling. The transcription factor GATA6 is produced at high level in the normal pulmonary vasculature, including endothelial cells and smooth muscle cells, but its level is markedly reduced in both SSc-PAH and idiopathic PAH (IPAH) lungs. Furthermore, genetically modified mice that lack Gata6 in endothelial cells develop PAH spontaneously, suggesting that downregulation of GATA6 is an early and key event that leads to endothelial dysfunction and the development of PAH (*Ghatnekar et al, 2013*). Given that various stimuli induce endothelial dysfunction through the unfolded protein response (UPR) and autophagy pathways, we aim to test the hypothesis that GATA6 deficiency induces ER stress and autophagy in endothelial cells during the process of PAH development.

Methods: Sections of lung specimens from SSc-PAH patients were stained for BiP and CHOP, two major players of UPR pathways, by immunohistochemistry. The level of these two proteins were similarly tested in the lungs of two mouse models of PAH: chronic hypoxia-induced, and endothelial conditional knockout of GATA6 (GATA6 CKO). Expression of UPR and autophagy pathway genes in the lungs of these mouse models was measured by quantitative RT-PCR. GATA6 expression was blocked by siRNA in human pulmonary endothelial cells (HPAECs) cultured *in vitro* and the expression of UPR pathway genes was measured by quantitative RT-PCR. BiP and CHOP protein levels were also determined by western.

Results: BiP and CHOP levels were low in lung sections from healthy human subjects, but increased dramatically in the lungs of patients with SSc-PAH. Similarly, these two proteins were more abundant in the lungs from the two mouse models of PAH than in the lungs of wild-type mice. Specifically, BiP and CHOP were found in endothelial cells and macrophages in both human and mouse PAH lungs. In addition to BiP and CHOP, other UPR pathway genes such as PERK, ATF6, and XBP1, and autophagy markers LC3B, ATG3, ATG5, and ATG12 were also upregulated in murine lung by chronic hypoxia or loss of GATA6 from endothelial cells, but hypoxia treatment of GATA6 CKO mice did not have any additive effect on the expression of these genes. Consistent with the above *in vivo* data, deleting GATA6 in HPAECs with siRNA increased ATF4 mRNA level and BiP and CHOP protein levels *in vitro*.

Conclusion: GATA6 deficiency disrupts endothelial homeostasis and triggers a stress response, including the activation of UPR and autophagy pathways. Chronic activation of these pathways in endothelial cells contributes to the development of PAH.

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1721

Investigating the SCF/c-Kit Pathway in Scleroderma Fibrosis. Bahja Ahmed Abdi, Oseme Etomi, Xu Shiwen, David Abraham, Christopher Denton and Richard J. Stratton. UCL Medical School, London, United Kingdom.

Background/Purpose: Stem cell factor (SCF) is a potential driving factor in the development of systemic sclerosis (SSc) and a possible therapeutic target. SCF is a cytokine which acts via c-Kit, a tyrosine kinase receptor, present on the surface of progenitor cells, mast cells and melanocytes. This relationship with mast cells potentially drives pruritus, an under-reported but significant problem in SSc, which can suggest disease activity. The greatly altered pigmentation seen in SSc may also reflect altered SCF/c-Kit signalling affecting melanocytes. Previous work from our laboratory has demonstrated increased levels of SCF and c-kit in SSc fibroblasts compared to healthy controls Our aim was to measure the activity of SCF/c-Kit pathway in Systemic sclerosis.

Methods: Blister fluid, tissue and plasma samples were harvested from healthy controls (HC) and SSc patients. The SCF and c-Kit protein levels in SSc and HC lung fibroblasts were determined by western blotting. SCF (soluble and membrane bound) and c-kit gene expression was measured using quantitative PCR (qPCR) from control and SSc lung fibroblasts and epidermal sheet. The levels of SCF and c-Kit in SSc and HC were assessed by ELISA. The expression of CD117 positive lung fibroblasts was analysed by FACS.

Results: The soluble SCF mRNA expression was enhanced in SSc lung fibroblast samples by qPCR compared to healthy controls (soluble transcript: 23 versus 10 copy number respectively $p=0.008$ and membrane bound: 1.1 versus 0.7 $p=$NS). C-kit was expressed at low levels in both SSc and HC

fibroblasts (0.31 versus 0.28 copy number, p=NS). Western blotting showed increased SCF protein levels in SSc lung fibroblasts compared to controls with relative density scan of 2.25 and 0.76 respectively (p=0.009) while the level of c-Kit protein expression was low in both SSc and control fibroblasts (0.16 vs 0.25) p=NS. Furthermore, measuring the epidermal sheet for SCF gene expression in SSc and HC showed that the soluble SCF isoform had 537 and 366 copy number respectively, while the membrane bound isoform showed gene copy numbers of 106 for SSc and 134 for HC. Using ELISA, SCF plasma levels were found to be lower in SSc patients (1272pg/ml) than the HC group (1425pg/ml) p=0.04, as were the plasma c-Kit levels (13ng/ml versus 16ng/ml respectively) p=0.028. Levels of SCF in conditioned media of cultured lung fibroblasts were higher in SSc (150ng/ml) vs HC (130ng/ml) p=0.002 but lower in blister fluid 1223pg/ml vs 1414 pg/ml respectively. C-Kit was undetectable in conditioned media and blister fluid. A subpopulation of CD117 positive cells was found in both SSc and HC lung fibroblasts (1.26% SSc cells, 2.3% HC).

Conclusion: We demonstrated that the full length soluble SCF mRNA is found at higher levels in the epidermis and in the lung fibroblasts of SSc subject and that SCF appears at slightly higher levels in SSc fibroblast conditioned media. However, when measured in plasma or blister fluid SCF was lower or unaltered in SSc when compared to controls. Cultured fibroblasts were heterogeneous and only a minority were positive for c-Kit. If SCF is important in SSc pathogenesis then it might be acting locally on a small subpopulation of c-Kit positive cells.

Disclosure: B. Ahmed Abdi, None; **O. Etomi**, None; **X. Shiwen**, None; **D. Abraham**, None; **C. Denton**, None; **R. J. Stratton**, None.

1722

TLR4 and TLR7 Are Required for Gadolinium Based Contrast Agent Induction of Dermal and Pulmonary Fibrosis in an Adenine-Induced Model of Chronic Renal Failure. Peter J. Wermuth and Sergio A. Jimenez. Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases and Scleroderma Center, Thomas Jefferson University, Philadelphia, PA.

Background/Purpose: Nephrogenic Systemic Fibrosis (NSF) is a generalized progressive fibrotic disorder that occurs in some patients with renal insufficiency exposed to various gadolinium based contrast agents (GdBCA). TLR4 and TLR7 signaling has been reported to be necessary for the *in vitro* establishment of a profibrotic phenotype by the GdBCA Omniscan in normal human macrophages. In this study, we examined the role of TLR4 and TLR7 in the development of NSF-like lesions *in vivo* in mice with renal failure induced by a high adenine diet following exposure to GdBCA by intratracheal instillation.

Methods: Chronic renal failure was induced in normal mice and in TLR4 and TLR7 knockout (TLR4 KO) and (TLR7 KO) mice by *ad libitum* feeding of a standard rodent diet supplemented with 3% adenine for 30 days. Two weekly doses of either the GdBCA Omniscan (100 μL of a 0.5 M solution, corresponding to a 0.05 mmol/kg dose) or an equal volume of normal saline were administered by intratracheal instillation to mice with either normal renal function or with adenine diet-induced chronic renal failure. Mice were sacrificed 56 days after the final instillation and tissues were isolated for analysis of the severity of tissue fibrosis by histological examination (hematoxyllin/eosin and Masson's trichrome stains) and by assays of collagen content employing a standard hydroxyproline assay of hydrolyzed tissue samples.

Results: Histopathology studies showed mononuclear cell infiltration and severe peribronchial fibrosis and moderate diffuse interstitial fibrosis in lungs isolated from adenine-fed control (C57BL6/J) mice instilled with Omniscan. In contrast, lungs from adenine-fed TLR4 KO or TLR7 KO mice maintained normal lung histology. Mice of all three strains with normal renal function instilled with Omniscan and mice with either normal or ablated renal function instilled with saline also demonstrated no fibrosis. Hydroxyproline content was increased ~3 fold in the lungs of Omniscan-instilled wild type mice with adenine diet-induced renal failure. In contrast, the lungs of Omniscan-instilled TLR4 KO and TLR7 KO mice with or without renal failure had normal hydroxyproline levels.

Conclusion: The present study demonstrates for the first time *in vivo* that the ability to induce significant tissue fibrosis and increased collagen deposition in mice with adenine induced renal failure exposed to the gadolinium contrast agent Omniscan requires signaling through TLR4 and TLR7. These results indicate that targeting of TLR signaling could be a valuable strategy to prevent or treat NSF and other TLR-mediated chemically-induced fibrotic disorders.

Disclosure: P. J. Wermuth, None; **S. A. Jimenez**, None.

1723

Identification of the Microbiome As a Potential Trigger of Systemic Sclerosis By Metagenomic RNA-Sequencing of Skin Biopsies. Michael Johnson[1], Zhenghui Li[1], Michelle Dimon[2], Tammara A. Wood[1], Robert Lafyatis[3], Sarah Arron[2] and Michael Whitfield[1]. [1]Geisel School of Medicine at Dartmouth, Hanover, NH, [2]University of California, San Francisco, San Francisco, CA, [3]Boston University, Boston, MA.

Background/Purpose: Systemic sclerosis (SSc) is a rare and poorly understood systemic autoimmune disease that results in skin fibrosis and severe internal organ involvement. There is a limited understanding of its pathophysiology and there are little data to indicate what may trigger the disease. Previous studies have suggested a variety of bacterial and viral pathogens as a trigger of systemic sclerosis (SSc), though neither a definitive pathogen nor a mechanism of pathogenesis has been established. Here we used RNA-seq to identify differences in the skin microbiome associated with SSc to test the hypothesis that an environmental microbiome component may be more strongly associated with SSc skin.

Methods: RNA-seq was performed on eight patients with early diffuse SSc and four controls, to a depth of 200 million reads per patient. All patients were diagnosed with diffuse systemic sclerosis (dSSc) and were not on immunosuppressive therapy at the time of biopsy. Each patient was assigned to their respective intrinsic gene expression subset: five patients mapped to the inflammatory subset, and three patients in the fibroproliferative subset; one patient classified in the inflammatory subset exhibited both inflammatory and fibroproliferative gene expression signatures. RNA-seq data were analyzed using Integrated Metagenomic Sequence Analysis (IMSA) to quantify non-human sequence reads in each sample, and compared to the NCBI taxonomic database to identify significantly enriched pathogens between groups. Differences in immunoreactivity of SSc and healthy controls were confirmed by Western blot and mass spectrometry using fungal lysates probed with human sera.

Results: Little difference in viral and bacterial read counts were found between SSc patients and healthy controls. However, a significant difference in the fungal mycobiomes of SSc and controls was evident for the read counts of *Rhodotorula glutinis*. Within SSc, the highest read counts were consistently found in patients classified in the inflammatory intrinsic subset ($p = 0.02$ vs. controls). Lower *R. glutinis* read counts were found in three fibroproliferative patients ($p = 0.15$ vs. controls); virtually no *R. glutinis* or other *Rhodotorula* sequence reads were present in controls. We were able to assemble the D1–D2 hypervariable region of the 28S ribosomal RNA (rRNA) of *R. glutinis* from each of the SSc samples. We observe differences in immunoreactivity to *R. glutinis* between SSc and healthy controls as determine by Western blot and mass spectrometry to autoantibody-bound proteins. Validation and expansion of these results are being performed by fungal Internal Transcribed Spacer (ITS) sequencing from SSc and control biopsies.

Conclusion: These results suggest the microbiome, and *R. glutinis* specifically, may be a trigger or potential modifier of the inflammatory response in SSc. We found *R. glutinis* to be most significantly associated with the inflammatory subset of SSc, extending our prior work. Anatomical and temporal differences in the abundance of this pathogen in the context of host genetics may be associated with differences in clinical presentation and molecular phenotypes.

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1724

Loss of IRF5 Ameliorates Tissue Fibrosis in a Murine Model of Systemic Sclerosis. Ryosuke Saigusa[1], Yoshihide Asano[1], Takashi Taniguchi[1], Yohei Ichimura[1], Takehiro Takahashi[1], Tetsuo Toyama[1], Ayumi Yoshizaki[1], Tadatsugu Taniguchi[2] and Shinichi Sato[1]. [1]University of Tokyo Graduate School of Medicine, Tokyo, Japan, [2]Institute of Industrial Science, University of Tokyo, Tokyo, Japan.

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disorder with clinical manifestations that result from fibrosis development, immune activation and vascular injuries. A genome-wide association study showed the involvement of genetic variants in the development of SSc. In particular, a single nucleotide polymorphism within the promoter region of interferon regulatory factor 5 (IRF5) was associated with an increase in SSc. This polymorphism results in a decrease in steady-state IRF5 transcript levels,

accompanied with longer survival and milder interstitial lung disease. In this study, we explore the function of IRF5 in the development of SSc utilizing a bleomycin (BLM)-induced SSc mouse model in mice deficient in IRF5 (*Irf5*$^{-/-}$mice).

Methods: Wild type (WT) and *Irf5*$^{-/-}$mice were induced to develop SSc following BLM treatment. Dermal thickness and fibrosis were measured by histological analyses. The quantity of the collagen-specific amino acid hydroxyproline was also measured. Immunohistochemistry and quantitative reverse transcription-PCR were conducted to evaluate the degree of inflammation and the expression of cytokines, growth factors, chemokines, and cell adhesion molecules.

Results: Dermal and pulmonary fibrosis in BLM-treated *Irf5*$^{-/-}$ mice was attenuated as compared to WT mice. Consistent with this, inflammatory cell infiltration induced by BLM treatment was suppressed in the mutant mice. Further, IRF5 deficiency modulated the expression of cell adhesion molecules toward the induction of Th1-skewed inflammation by BLM treatment, as represented by the lower expression of intercellular adhesion molecule-1 and glycosylation-dependent cell adhesion molecule-1 in the lesion skin and lung of *Irf5*$^{-/-}$ mice than in those of wild type mice. Finally, matrix metalloproteinase 13 mRNA and protein expression was higher in the skin and lung of the BLM-treated *Irf5*$^{-/-}$ mice.

Conclusion: With BLM treatment, *Irf5*$^{-/-}$ mice exhibited attenuated tissue fibrosis due to the alterations to fibroblasts, immune cells and cell adhesion molecules, indicating a pivotal contribution of IRF5 to pathological tissue fibrosis. As such, our results experimentally lend support to the notion that reduced IRF5 transcripts as a result of a nucleotide polymorphism in the IRF5 promoter region accounts for the attenuation of SSc manifestations.

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The SYK Inhibitor Fostamatinib Limits Tissue Damage and Fibrosis in a Bleomycin-Induced Scleroderma MOUSE MODEL. Omer Nuri Pamuk[1], Guray Can[1], Suleyman Ayvaz[1], Turan Karaca[1], Gulsum Pamuk[1], Selim Demirtas[1] and George C. Tsokos[2]. [1]Trakya University Medical Faculty, Edirne, Turkey, [2]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA.

Background/Purpose: The possible antifibrotic effects of various kinase inhibitors has been studied before in SSc. Spleen tyrosine kinase (Syk) is a protein tyrosine kinase which activates intracellular signal transduction pathways and has been claimed to be involved in the pathogenesis of systemic autoimmune diseases. We investigated the ability of a small drug Syk inhibitor, fostamatinib, to protect mice from bleomycin-induced SSc.

Methods: Four study groups of Balb/c mice were included in this study: control, bleomycin (administered subcutaneously to BALB/c mice for 21 days), bleomycin and fostamatinib (mice fed with chow containing a Syk inhibitor for 21 days) and fostamatinib alone groups. Skin and lung tissue specimens were obtained and evaluated histologically.

Results: Mice treated with bleomycin alone had significantly more skin thickness (416.1±6.1) compared to control (260.1±10.1) and fostamatinib (254.3±7.9) treated mice ($p<0.001$). Mice subjected to bleomycin and fed with fostamatinib-containing chow generated more (312.3±4.4) dermal thickness than control and fostamatinib-treated mice (p values <0.001) but, significantly less when compared to mice treated with bleomycin alone ($p<0.001$).Alveolar hemorrhage, edema, damage and leukocyte scores in the lungs of mice treated with bleomycin were significantly higher v compared to control or fostamatinib alone-treated mice (p values <0.001). At the end of the 21-day bleomycin administration, there was apparent prominent fibrosis which was reduced significantly in the group of mice which received in parallel fostamatinib. Following fostamatinib treatment, Syk, phospho-Syk, and TGF-β expression decreased in both skin and lung tissues

Conclusion: The Syk inhibitor fostamatinib prevented bleomycin-induced fibrosis and inflammation in the skin and the lung. The anti-fibrotic effect of fostamatinib is linked to reduced Syk phosphorylation and TGF-β expression. The Syk pathway appears as a potential molecular target for therapeutic intervention in SSc.

Disclosure: O. N. Pamuk, None; **G. Can**, None; **S. Ayvaz**, None; **T. Karaca**, None; **G. Pamuk**, None; **S. Demirtas**, None; **G. C. Tsokos**, None.

1726

Therapeutic Efficacy of Mesenchymal Stem Cells in Diffuse Murine Hypochlorite-Induced Systemic Sclerosis. Alexandre Maria[1], Claire Bony[1], Karine Toupet[1], Christian Jorgensen[2], Philippe Guilpain[3] and Daniele Noel[4]. [1]Inserm, Montpellier, France, [2]Clinical Immunology and Osteoarticular Diseases Therapeutic Unit, CHU Lapeyronie., Montpellier, France, [3]Department of Internal Medicine, Montpellier, France, [4]UM1, Montpellier, France.

Background/Purpose: Systemic sclerosis (SSc) is a rare intractable disease with unmet medical need and fibrosis-related mortality. Absence of efficient treatments has prompted to develop novel therapeutic strategies among which mesenchymal stem cells (MSCs) appear one of the most attractive options. Herein we provide the first preclinical study using MSCs in the relevant hypochlorite (HOCl)-induced murine model of diffuse SSc, recapitulating the main features of the disease: multivisceral fibrosis, vasculopathy, and autoimmunity.

Methods: Balb/c mice underwent six weeks of daily intradermal injections of HOCl leading to SSc-HOCl phenotype. Different doses of syngenic bone marrow-derived MSCs (2.5×10^5; 5×10^5 or 10^6cells) were infused in the tail vein of the mice, either the day before disease induction, or at day 21. Skin thickness was measured weekly, and samples of skin and lung were taken at euthanasia (d42) to assess by RT-qPCR the expression of collagens I and III, TGF-β1, alpha-smooth actin muscle (α-SMA), MMP-1 and -9, Tissue Inhibitor of MMP (TIMP1), Hepatocyte Growth Factor (HGF), VEGFA, IL-1β, TNF-α, IL-6, IL-10, Superoxide Dismutase (SOD2), and Heme Oxygenase (HMOX1). Anti-scl70 antibodies levels were measured in sera by ELISA.

Results: We first compared the effects of different doses of MSCs (2.5×10^5; 5×10^5 and 10^6) infused the day before disease induction, on clinical and biological parameters. When considering skin thickness in time, we observed a slower progression in MSC-treated mice, with the best results obtained with the lowest dose of 2.5×10^5 MSCs. At euthanasia, a lower expression of fibrotic markers (collagens I and III, TGF-β1, α-SMA) was observed in both skin and lung of treated mice, consistent with histological improvement and inversely proportional to the injected dose. Importantly, sera from treated mice exhibited lower levels of anti-scl70 autoantibodies and enhanced antioxidant capacity, confirming the systemic effect of MSCs. Of interest, MSC administration was also efficient when infused at d21 while disease is known to be established. We further provide evidence at a molecular level that in skin and lung tissues, MSCs exerted an anti-fibrotic role by normalizing extracellular matrix remodeling parameters (MMP-1 and -9, TIMP-1, HGF, VEGFA), as well as reducing pro-inflammatory cytokines (IL1β, TNF-α, IL-6, IL-10) and increasing antioxidant defenses (SOD2, HMOX1).

Conclusion: In conclusion, this preclinical study is the first to demonstrate the therapeutic efficacy of MSCs in SSc, acting through the modulation of inflammation, tissue remodeling and antioxidant defenses. The benefits observed in a curative approach are particularly promising in sight of clinical perspectives.

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1727

Poly(ADP-ribose) Polymerase-1 (PARP-1) Suppresses the Profibrotic Effects of Transforming Growth Factor â in Systemic Sclerosis. Yun Zhang. University Hospital Of Erlangen, Erlangen, Germany.

Background/Purpose: The enzyme poly(ADP-ribose) polymerase-1 (PARP-1) transfers negatively charged ADP-ribose units from the donor β-NAD onto various substrate proteins either as mono- or oligomeric moieties or as linear or branched poly (ADP-ribose) (PAR) chains. Those modifications can have pronounced regulatory effects on the half-life or the enzymatic activity of target proteins. Recent studies demonstrated that PARP-1 can poly(ADP-ribosyl)ates (PARylates) members of the Smad family of transcription factors. However, the role of PARP1 in the pathogenesis of SSc has not been investigated.

Methods: The expression of PARP1 in human skin and in experimental fibrosis was determined by qPCR and immunohistochemistry. TGFβ signalling was analysed by Smad reporter assays and target gene analysis after 1mM selective PARP1 inhibitor 3-Aminobenzamide (3AB). Bleomycin-induced skin fibrosis and Tsk-1 mice were used to

evaluate the effect of PARP deficiency and PARP inhibition (10mg/kg/d 3AB) *in vivo*.

Results: Decreased expression of PARP1 was detected by immunohistochemistry in skin sections of SSc patients.particularly in fibroblasts. Inhibition of PARylation by 3AB augmented the stimulatory effects of TGFβ on fibroblasts *in vitro*. PARP1 inhibition increased Smad dependent transcription in reporter assays and promoted the transcription of TGFβ/Smad target genes. Treatment with 3AB also stimulated the collagen release and fostered the expression of contractile proteins with increased expression of α-smooth muscle actin (α-SMA) and enhanced formation of stress fiber formation compared to fibroblasts stimulated with TGFβ alone. Inhibition of PARylation also exacerbated experimental fibrosis *in vivo*. Treatment with 3AB induced a more severe fibrotic response to bleomycin with increased dermal thickening by up to 103% ($p<0.0001$), hydroxyproline contents and myofibroblast counts compared to control mice ($p<0.0001$ and $p=0.0059$). Inhibition of PARylation also strongly exacerbated fibrosis in Tsk-1 mice. Meanwhile, after bleomycin injection, dermal thickening, hydroxyproline contents and myofibroblast counts of PARP1 knockout mice were increased by 85% ($p=0.0046$), 67% ($p=0.0098$) and 56% ($p=0.0043$) compared to wild-type mice.

Conclusion: We demonstrate that PARP1 negative regulates canonical TGFβ signalling. The down-regulation of PARP1 in SSc fibroblasts may thus directly contribute to hyperactive TGFβ signalling and to persistent fibroblast activation in SSc.

Disclosure: Y. Zhang, None.

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Bromodomain Inhibitor JQ1 Modulates Collagen Processing and Ameliorates Bleomycin Induced Dermal Fibrosis in Mice. Sarah Trinder[1], Mary Tarriela[2], Adrian Gilbane[1], Robert Good[3], Xu Shi-Wen[3], David Abraham[4] and Alan M. Holmes[1]. [1]UCL, London, United Kingdom, [2]Centre for Rheumatology and Connective Tissue Diseases, London, United Kingdom, [3]UCL, LONDON, United Kingdom, [4]UCL Medical School, London, United Kingdom.

Background/Purpose: Systemic sclerosis (SSc) is a complex pro-inflammatory scarring disease, characterised by elevated deposition of extracellular matrix (ECM) proteins, in particular collagen type I. The disease is heterogeneous affecting both the skin and visceral organs including kidney, lung and heart. The SSc fibroblast is a key cell which promotes a pro-inflammatory and fibrotic microenvironment that can lead to the loss of normal tissue architecture and organ function. The mechanisms that contribute to the formation and persistence of the SSc dermal fibroblast remain unclear. We have previously shown the epigenetic bromodomain and extra-terminal domain-containing proteins (Brd) which bind to acetylated histone residues, play a significant role in pulmonary fibrosis. Here we seek to explore the contribution of Brd proteins in the development of dermal fibrosis using a specific inhibitor of Brd proteins (Brd 2, 3, 4 and T), JQ1.

Methods: We investigated the dose-response of JQ1 on SSc and healthy control (HC) donor ($n\geq3$) dermal fibroblasts. We assessed the effects on collagen deposition and processing using the Scar-in-a-Jar *in vitro* fibrosis assay, by western blot and immuno-florescence microscopy for collagen type I ($n=4$). To determine the effect of JQ1 in a pre-clinical model of skin fibrosis, female C57BL/6 mice were given three weekly subcutaneous injections of 100μl sterile saline ($n\geq6$) or 0.1U/ml bleomycin ($n\geq6$) for 14 days and treated with 12mg/kg/day JQ1 ($n\geq6$) or vehicle ($n\geq6$). After 14 days histological analysis for fibrogenic proteins and ECM was performed on skin, and pro-inflammatory chemokines in sera assessed by ELISA.

Results: IL-6 and MCP-1 secretion by SSc and HC donor fibroblasts was significantly ($P<0.05$) inhibited in a dose dependent manner by JQ1. Consistent with this JQ1 attenuated SSc collagen deposition and processing ($P<0.05$). Assessment of JQ1 in a pre-clinical model of dermal fibrosis demonstrated a markedly attenuation of dermal thickening *in vivo*($P<0.05$). Consistent with this we observed significant reduction in fibrogenic markers including αSMA, and collagen expression in the skin ($P<0.05$). Furthermore secretion of the inflammatory marker, IL-6 was significantly attenuated ($P<0.05$).

Conclusion: We have assessed the functional effects of the Brd inhibitor, JQ1, on SSc dermal fibroblasts and the development of dermal fibrosis in a pre-clinical model of dermal fibrosis. We demonstrate that JQ1 markedly attenuated the excessive deposition and processing of collagen type I by SSc fibroblasts. In keeping with Brd proteins playing a pivotal role in the development and progression of dermal fibrosis, JQ1 significantly inhibited ECM deposition *in vivo*. Our data suggests a key role for Brd proteins in the persistence of the SSc dermal fibroblast phenotype.

Disclosure: S. Trinder, None; **M. Tarriela**, None; **A. Gilbane**, None; **R. Good**, None; **X. Shi-Wen**, None; **D. Abraham**, None; **A. M. Holmes**, None.

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Adenosine A2A Receptor (A2AR) Promotes Collagen Type 3 Expression Via β-Catenin Activation. Miguel Perez-Aso[1] and Bruce N. Cronstein[2]. [1]New York University, New York City, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: A2AR stimulation promotes collagen 1 and 3 (Col1 and Col3) synthesis, principal mediators of fibrosis and scarring. We have recently demonstrated that the A2AR is a fine-tune modulator of collagen balance that signals via PKA/EPAC2/AKT but is independent of Smad2/3 signaling. Wnt signaling is an important player in the progression of fibrosis, and other recent studies have suggested that cAMP and Wnt pathways converge. Since A2AR is Gs-linked and increases cAMP, we determined whether A2AR and Wnt signaling interact.

Methods: Primary human dermal fibroblasts (<5 passages) were stimulated by the A2AR-selective agent CGS21680 (1μM) and β-catenin, dephosphorylated β-catenin and β-catenin phospho-Ser552 levels were determined in cytosolic and nuclear fractions by Western Blot. Nuclear translocation of β-catenin was determined by confocal microscopy. β-catenin was knocked down by transfection with specific-siRNA or scrambled-siRNA and protein levels determined by Western Blot.

Results: Stimulation of A2AR rapidly (15 min) increases cellular β-catenin levels to 196±13% of control ($N=3$, $P<0.01$). Similarly CGS21680 stimulates de-phosphorylation of β-catenin (188±27% of control; $N=5$, $P<0.05$) and promotes β-catenin phosphorylation at Ser 552 (239±15% of control; $N=5$, $P<0.001$), the site of β-catenin activation by AKT. Furthermore, CGS21680 stimulates translocation of β-catenin to the nucleus, as confirmed by confocal microscopy and Western Blot. We next knocked down β-catenin (54±5% decrease in β-catenin siRNA *vs* scramble siRNA; $N=10$, $P<0.001$) and determined the effect of A2AR stimulation on collagen production. A2AR-stimulated increases in Col1 scramble-siRNA transfected cells (63±22% increase, $N=7$) which were unaffected by β-catenin knockdown (53±17% increase, $N=7$). In contrast, β-catenin knockdown abrogates A2AR-stimulated increments in Col3 synthesis by 73% (scramble-siRNA 66±14% increase of Col3 *vs* β-catenin-siRNA 18±16% increase of Col3; $P<0.05$, $N=8$).

Conclusion: Our results strongly indicate that A2AR stimulation activates both canonical and non-canonical Wnt pathways for increased Col3 synthesis, leading to dermal fibrosis and excessive scarring.

Disclosure: M. Perez-Aso, None; **B. N. Cronstein**, Canfite Pharma, 1, AstraZeneca, 2, Cellgene, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Reseach Foundation, 6, ACR, 6, Arthritis Foundation, 6.

1730

Identification of Novel Scleroderma –associated Antigens and Development of an Autoantibody Assay Panel Enabling Their Subsequent Validation. Hans-Dieter Zucht[1], Petra Budde[1], Peter Schulz-Knappe[1], Nicolas Hunzelmann[2], Karsten Conrad[3] and Prof. Dr. Matthias Schneider[4]. [1]Protagen AG, Dortmund, Germany, [2]University of Cologne, Cologne, Germany, [3]Technische Universität Dresden, Dresden, Germany, [4]Univ. Duesseldorf, Duesseldorf, Germany.

Background/Purpose: Scleroderma (systemic sclerosis or SSc) has a highly variable clinical presentation and course resulting in difficulties for disease management. When SSc is suspected, autoantibodies (AAB) are tested. The most frequently observed AABs, anti-topoisomerase I (anti-Scl70), anti-centromere (ACA) and anti-RNA polymerase III (ARA) are associated with different subtypes of SSc and with specific organ involvements and disease severity. Those biomarkers have recently been included in the new SSc classification criteria, but are only present in about 60–70% of SSc patients. Our aim is to identify additional highly frequent SSc-associated autoantigens using a high-throughput Luminex bead-based profiling platform as well as the development of a complementary ELISA-based autoantibody assay kit for enabling validation of the novel panel of SSc antigens to illustrate their clinical utility.

Methods: A systematic and undirected approach was undertaken to screen for autoantibodies in human serum samples of 100 individuals with SSc and related overlap syndromes using 7000 recombinant protein targets. Active and passive control groups comprised healthy controls and serum samples of other systemic autoimmune diseases including systemic lupus erythematosus (SLE), and early rheumatoid arthritis (RA). The frequency of autoantibodies for a particular antigen was determined by applying the mean value of the signal intensity of the healthy control cohort plus 2 standard deviations (SD) as a cut-off. Then, the frequency of 116 candidate antigens in 1100 healthy controls and 90 SSc samples was assessed using a connective tissue disease array. Afterwards, ELISAs were developed for 7 antigens with high frequency in SSc or higher frequency in SSc subtypes. The performance of ELISAs was analyzed in comparison with the Luminex multiplex system in additional 150 SSc samples.

Results: Sera of 100 SSc patients with limited or diffuse SSc or overlap syndromes were tested for established and novel autoantigens. 30% of SSc patients were previously tested negative for ACA and anti-Scl70. The frequency of established and novel autoantibodies in the test cohort ranged from 40% to 10% in descending order: CENPB: 40%, Scl70: 36%, TRIM21 (Ro52): 27%, antigen 1: 28%, antigen 2: 27%, antigen 3: 17%, antigen 4: 15%, antigen 5: 13%, antigen 6: 11% and antigen 7: 4%. While autoantibodies to antigens 1–4 were more frequently observed in limited SSc, autoantibodies to antigens 5–7 were more abundant in diffuse SSc. Autoantibody reactivity above the cut-off level was identified in 50% of the previously negative-tested SSc patients. ELISA and Luminex showed good qualitative agreement. The genes encoding for these proteins were found being enriched in pathways of histone modifications and chromatin remodeling suggesting their involvement in epigenetic processes.

Conclusion: Using a combination of Luminex bead-arrays for high-throughput autoantibody profiling and complementary ELISA development provides an alternative route to discover and verify novel SSc-associated autoantibodies. By measuring 7 antigens the number of autoantibody positive SSc patients increased from 68% to 84%.

Disclosure: H. D. Zucht, None; **P. Budde**, None; **P. Schulz-Knappe**, Protagen AG, 3; **N. Hunzelmann**, None; **K. Conrad**, None; **P. D. M. Schneider**, None.

1731

Translocation of IGFBP-5 to the Nucleus and Its Interaction with Nucleolin Do Not Dictate Its Fibrotic Effects. Yunyun Su and Carol Feghali-Bostwick. Medical University of South Carolina, Charleston, SC.

Background/Purpose: Insulin-like growth factor binding protein (IGFBP)-5 is one of six IGFBPs. IGFBP-5 is the most conserved member of the family. IGFBP-5 levels are increased in systemic sclerosis (SSc) skin and lung tissues. We previously reported that IGFBP-5 is a pro-fibrotic factor that induces extracellular matrix (ECM) production and deposition. IGFBP-5 promoted a fibrotic phenotype *in vitro* in primary human fibroblasts, *in vivo* in mouse lung and skin, and *ex vivo* in human skin. Since IGFBP-5 contains a nuclear localization signal (NLS) that facilitates its nuclear translocation, we sought to examine the role of nuclear translocation on the fibrotic activity of IGFBP-5 and identify IGFBP-5 binding partners relevant for its nuclear compartmentalization.

Methods: We generated functional wild type IGFBP-5 and IGFBP-5 with a mutated NLS. Abrogation of nuclear translocation in the NLS mutant was confirmed using immunofluorescence and immunoblotting of nuclear and cytoplasmic cellular extracts. The fibrotic activity of wild type and NLS-mutant IGFBP-5 was examined *in vitro* in primary human fibroblasts and *ex vivo* in human skin. We identified IGFBP-5 binding partners using immunoprecipitation and Mass Spectrometry. Binding of IGFBP-5 to its partner was validated using co-immunoprecipitation and immunoblotting. We examined the effect of the partner on IGFBP-5 localization and function via sequence-specific silencing in primary human fibroblasts.

Results: Our results show that IGFBP-5-induced ECM production *in vitro* in primary human fibroblasts is independent of its nuclear translocation as the NLS-mutant IGFBP-5 retained fibrotic activity. The NLS-mutant IGFBP-5 also induced fibrosis *ex vivo* in human skin maintained in organ culture, thus confirming and extending the *in vitro* findings. Nucleolin, a nucleolar protein that can serve as a nuclear receptor, was identified as an IGFBP-5 binding partner. Silencing nucleolin in primary human fibroblasts reduced IGFBP-5 translocation to the nucleus but did not block the ability of IGFBP-5 to induce ECM production and a fibrotic phenotype.

Conclusion: IGFBP-5 transport to nucleus requires an intact NLS and nucleolin. However, nuclear translocation is not necessary for IGFBP-5 fibrotic activity. Our data provide further insights into the mechanism mediating the fibrotic activity of IGFBP-5 and the role of nuclear compartmentalization in IGFBP-5-induced fibrosis.

Disclosure: Y. Su, None; **C. Feghali-Bostwick**, None.

1732

Attenuation of Sclerodermatous Graft Versus Host Disease (sclGVHD) in IL4RA Receptor-Deficient Mice. Katia Urso[1], Kelly Tsang[2], Robert Lafyatis[3] and Antonios O. Aliprantis[2]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Boston University School of Medicine, Boston, MA.

Background/Purpose: Scleroderma is a rare autoimmune disease characterized by the accumulation of fibrotic tissue in multiple organs including the skin, gut and lungs. To date, the cause of this disease has not been identified and specific treatments are unavailable. SclGVHD in mice recapitulates many scleroderma manifestations and can be used to determine potential therapeutic pathways. Previously, we identified activation of the Interleukin-13 (IL-13) cytokine pathway in the skin of both murine sclGVHD and a subset of scleroderma patients characterized by an "inflammatory" gene expression signature. We also showed that host mice lacking IL4RA, a functional subunit of IL-13 and IL-4 receptors, are protected from the cutaneous manifestations of sclGVHD. The purpose of this study is to define the mechanism that protects IL4RA-deficient mice from sclGVHD.

Methods: Splenocytes from B10.D2 mice were transferred into either BALB/c *Rag2*$^{-/-}$ or BALB/c *Rag2*$^{-/-}$*Il4ra*$^{-/-}$ hosts to induce sclGVHD. Seven days after cell transfer the skin was processed for histopathology and scored blindly for inflammation. Subcutaneous lymph-nodes (sLN) were isolated, collagenase digested and analyzed by flow cytometry. sLN cells were also stimulated in vitro for 5h with LPS, PMA and ionomycin to analyze IL-10 production by intracellular cytokine staining. mRNA was extracted from skin and sLN and subjected to qRT-PCR. Student's t-tests, with n=10–13 per group, were used to determine statistical significance.

Results: One week after cell transfer IL4RA-deficient mice lost significantly less weight than control sclGVHD mice (8.44% ± 4.25 of baseline body weight vs. 16.28% ± 3.68, $p<0.0001$) and displayed less skin inflammation as assessed by histopathologic score (1.50 ± 0.53 for BALB/c *Rag2*$^{-/-}$ and 0.80 ± 0.42 for BALB/c *Rag2*$^{-/-}$*Il4ra*$^{-/-}$, $p=0.0042$). Despite reduced skin inflammation, the sLNs of BALB/c *Rag2*$^{-/-}$*Il4ra*$^{-/-}$ mice showed significantly higher cellularity ($8.7 \pm 2.33 \times 10^6$ vs. $3.09 \pm 1.23 \times 10^6$, $p<0.0001$), with elevated numbers of T cells, B cells and myeloid CD11b$^+$Ly6C$^+$ cells compared to BALB/c *Rag2*$^{-/-}$ controls. Cells from these three populations also produced more IL10 than those isolated from control mice when stimulated ex vivo. In addition, among the CD4$^+$ T-cells, Il4RA-deficient hosts had a significantly higher frequency of Foxp3$^+$ regulatory T-cells (13.92% ± 1.95 vs. 6.82% ±1.40, $p<0.0001$). qRT-PCR analysis also revealed elevated *Il10* transcripts in the sLNs of BALB/c *Rag2*$^{-/-}$*Il4ra*$^{-/-}$ hosts ($p=0.0008$). In contrast, no differences were observed in transcript levels of chemokines important for the homing of immune cells to sLNs, including *ccl19* and *cxcl13*.

Conclusion: IL4RA promotes sclGVHD early in the disease course by promoting infiltration of immune cells into the skin and suppressing the expansion of regulatory T-cells and IL-10 expression. Surprisingly, the sLNs of mutant mice contained more adaptive and innate immune cells. Additional data are needed to understand if this accumulation of cells in sLN of IL4RA-deficient mice is due to a defect in the pathways that control apoptosis, proliferation or the migration of activated cells from the sLN to the skin.

Disclosure: K. Urso, None; **K. Tsang**, None; **R. Lafyatis**, None; **A. O. Aliprantis**, None.

ACR/ARHP Poster Session B
T cell Biology in Rheumatoid Arthritis and Other Arthritis
Monday, November 17, 2014, 8:30 AM–4:00 PM

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Immunomodulatory Effects of Dietary Non-Digestible Oligosaccharides in T Cell-Mediated Autoimmune Arthritis. Rebecca Rogier[1], Tom Ederveen[1], Anita Hartog[2], Birgitte Walgreen[1], Liduine van den Bersselaar[1], Monique M. Helsen[1], Paul Vos[2], Johan Garssen[3], Linette Willemsen[3], Wim B. van den Berg[1], Marije I. Koenders[1] and Shahla Abdollahi-Roodsaz[1]. [1]Radboud university medical center, Nijmegen, Netherlands, [2]Danone Nutricia Research, Utrecht, Netherlands, [3]Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands.

Background/Purpose: Accumulating evidence indicates the relevance of intestinal microbiota in shaping the immune response and supports its contribution to the development of autoimmune diseases. Prebiotic non-digestible oligosaccharides are known to selectively support growth of commensal Bifidobacteria and Lactobacilli and adjust the microbiota composition. The aim of this study was to assess the efficacy of microbiota modulation using non-digestible oligosaccharides as a therapeutic approach for T cell-dependent autoimmune arthritis.

Methods: IL-1 receptor antagonist (IL-1Ra) deficient mice spontaneously developing an autoimmune T cell- and interleukin (IL)-17- dependent arthritis were used for this study. We previously showed that spontaneous arthritis in IL-1Ra−/− mice depends on the presence of commensal microbiota, since germ-free mice develop less severe disease. To examine the feasibility of microbiota modulation as a therapeutic approach during established disease, IL-1Ra$^{-/-}$ mice which had already developed arthritis under conventional microbial status were orally fed a prebiotic diet containing 2.5% or 5% short-chain galacto- and long-chain fructooligosaccharides (scGos:lcFos, 9:1). Disease progression was monitored and intestinal and systemic T cell differentiation was studied.

Results: Oral treatment of arthritic IL-1Ra$^{-/-}$ mice with scGoslcFos significantly suppressed the progression of arthritis. Furthermore, dual-energy X-ray absorptiometry scanning revealed that a prebiotic diet containing scGoslcFos significantly improved bone mineral density and tended to increase bone mineral content in arthritic IL-1Ra$^{-/-}$mice.

Gene expression of T-bet and RORγt, the Th1 and Th17-related transcription factors, in lymph nodes draining the arthritic joints was significantly reduced in the group receiving the scGoslcFos diet. Flow cytometry analysis of the lymph nodes showed no effect on the percentages of Th1, Th17 and regulatory T cells (Tregs). However, the percentage of CD3$^+$CD4$^+$ IL-4 producing cells tended to be increased in the scGoslcFos treated group.

Interestingly, small intestine lamina propria of mice receiving scGoslcFos diet contained increased percentages of CD3$^+$CD4$^+$ FoxP3$^+$regulatory T cells. In addition, intestinal gene expression of the Treg-related transcription factor FoxP3 as well as anti-inflammatory cytokine IL-10 were increased with scGoslcFos. Accordingly, small intestine lamina propria lymphocytes of mice receiving the 5% scGoslcFos diet produced significant higher levels of IL-10 upon ex vivo stimulation with PMA and ionomycin. Production of IL-4 and IFNγ also tended to be increased, while production of TNFα, IL-6 and IL-17 was not affected by the prebiotic diet.

Conclusion: Our data suggest that scGoslcFos suppresses arthritis progression, potentially through induction of anti-inflammatory cytokines such as IL-10 and IL-4. Suppression of disease progression using dietary intervention with prebiotic scGoslcFos may be applicable as a therapeutic approach to suppress autoimmune arthritis.

Disclosure: R. Rogier, None; **T. Ederveen**, None; **A. Hartog**, None; **B. Walgreen**, None; **L. van den Bersselaar**, None; **M. M. Helsen**, None; **P. Vos**, None; **J. Garssen**, None; **L. Willemsen**, None; **W. B. van den Berg**, None; **M. I. Koenders**, None; **S. Abdollahi-Roodsaz**, None.

1734

IL-22 Plays a Significant Role in the Initiation and Augmentation of Th17-Dependent Experimental Arthritis. Debbie M. Roeleveld[1], Renoud Marijnissen[2], Rebecca Rogier[1], Birgitte Walgreen[1], Monique M. Helsen[1], Liduine van den Bersselaar[1], Shahla Abdollahi-Roodsaz[1], Wim B. van den Berg[1] and Marije I. Koenders[1]. [1]Radboud university medical center, Nijmegen, Netherlands, [2]Radboud University Medical Center, Nijmegen, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease that leads to progressive destruction of cartilage and bone. IL-22 and IL-22-producing T helper cells are elevated in RA patients, suggesting a role for this cytokine in the pathogenesis of this disease. Interestingly, IL-22 is a dual cytokine with both proinflammatory and anti-inflammatory properties, and therefore its exact role in RA pathology requires further investigation.

The aim of this study was to elucidate the role of IL-22 in the initiation and severity of a spontaneous model of experimental arthritis by using gene knockout mice and neutralizing antibodies for IL-22.

Methods: IL-1Ra-deficient mice develop spontaneous arthritis due to excess IL-1 signaling, and we previously demonstrated the importance of IL-17 and Th17 cells in this model (Koenders, Arthritis Rheum 2008). To investigate the role of IL-22 in this Th17-dependent arthritis model, we compared IL-1Ra$^{-/-}$ − IL-22$^{+/+}$ mice to mice lacking both IL-1Ra and IL-22. Paw joint swelling was scored weekly, and mice were sacrificed at the age of fifteen weeks. In addition, IL-1Ra-deficient mice were treated for 4 weeks with anti-IL-22 neutralizing antibodies administered after onset of arthritis to inhibit disease progression.

Results: Mice deficient for IL-1Ra and IL-22 showed reduced arthritis development, reaching a disease incidence of only 54% compared to an incidence of 93% in IL-1Ra$^{-/-}$ − IL-22$^{+/+}$ mice. In addition, macroscopically scored joint swelling (scale 0 to 4) of mice that did develop arthritis was significantly reduced from 1,83 for the IL-22$^{+/+}$ mice, to 1,27 for the IL-22-deficient mice. The reduction of inflammation was confirmed by histological analysis, that also showed protection against cartilage damage. Furthermore, significantly reduced bone damage was observed in IL-22 deficient mice as determined by X-ray analysis. Finally, IL-1Ra-deficient mice treated with anti-IL-22 antibodies after the clinical onset of arthritis showed reduced progression on inflammation and significant inhibition on bone erosion. This indicates that not only the onset but also the progression of arthritis in this Th17-driven arthritis model is dependent on IL-22.

Conclusion: These findings suggest that the Th17 cytokine IL-22 plays an important role both in the initiation and augmentation of Th17-dependent experimental arthritis, and might therefore be an interesting new target in RA treatment.

Disclosure: D. M. Roeleveld, None; **R. Marijnissen**, None; **R. Rogier**, None; **B. Walgreen**, None; **M. M. Helsen**, None; **L. van den Bersselaar**, None; **S. Abdollahi-Roodsaz**, None; **W. B. van den Berg**, None; **M. I. Koenders**, None.

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T–cell Tolerance Induction By the Glycosylated Type II Collagen Peptide-Based Vaccination in Murine Arthritis. Vilma Urbonaviciute[1], Changrong Ge[1], Bingze Xu[1], Susanne van den Berg[1], Balik Dzhambazov[2], Johan Bäcklund[1] and Rikard Holmdahl[1]. [1]Karolinska Institute, Stockholm, Sweden, [2]Plovdiv University, Plovdiv, Bulgaria.

Background/Purpose: Type II collagen (CII) has been suggested as a possible autoantigen in RA, since autoimmunity to CII is commonly detected in patients with RA. Also a RA-like disease, collagen-induced arthritis (CIA) can be induced in rodents expressing H-2Aq and H-2Ar MHC class II haplotypes after immunization with heterologous CII. Autoreactive T cells in both RA and CIA recognize the same immunodominant CII epitope 259–273, which binds both CIA-associated mouse H-2Aq and human RA-associated HLA-DRB1 MHC class II molecules. CII-reactive T cells from RA patients predominantly recognize the immunodominant CII 259–273 epitope when it is glycosylated at positions 264 and 270. Glycosylation of the lysine side chain at position 264 is of particular importance for CIA development as well as for tolerance induction to CII. It has been previously shown in our laboratory that administration of soluble MHC class II molecules in complex with the glycosylated CII peptide 259–273 (GalOK264/Aq) can prevent CIA development and ameliorate chronic relapsing disease, which can be relevant for patients with RA. However, the exact mechanism of tolerance induction by GalOK264/Aq complexes remains to be elucidated.

Methods: We established Vb12-transgenic mouse model, which have galactosylated CII epitope specific T cells and the corresponding clonotypic antibody to track them unambiguously. By immune-phenotyping of galactosylated CII epitope specific T cells we investigated the role of CII-reactive T cells in tolerance induced by vaccination with GalOK264/Aq complexes.

Vb12-tg mice were immunized with rat CII emulsified in CFA. 100 mg of GalOK264/Aq complexes or PBS were injected intravenously day 3 post-immunization. Day 10 post-immunization T cells from draining (inguinal) lymph nodes were either directly analyzed by FACS or restimulated in vitro with galactosylated CII peptide and the numbers of cytokine-expressing T cells were determined by FACS or ELISPOT and cytokine concentrations in cell culture supernatants were evaluated by ELISA.

Results: Injection of Vβ12 transgenic mice with GalOK264/Aq complexes leads to reduction in number of the galactosylated CII-specific T cells. Also the proportion of T cells expressing CD69, an early activation marker, within galactosylated CII specific T cell population, was reduced in vaccinated mice compared to PBS controls. Further phenotypic analysis of galactosylated CII-specific T cells revealed that vaccination with GalOK264/Aq of Vβ12 transgenic mice leads to an increased expression of the co-inhibitory molecules such as PD-1 and LAG3.

Furthermore, administration of Aq/gal-K264 complexes significantly attenuates Th1 and Th17 responses in galactosylated CII specific T cells both in and Vβ12-transgenic- and B6NQ mice.

Conclusion: Thus, vaccination with GalOK264/Aq complexes skews the CII specific T cell responses from activation and differentiation into effector cells toward antigen specific immune tolerance phenotype.

Disclosure: V. Urbonaviciute, None; **C. Ge**, None; **B. Xu**, None; **S. van den Berg**, None; **B. Dzhambazov**, None; **J. Bäcklund**, None; **R. Holmdahl**, None.

1736

Immune Related Adverse Events Associated with Anti-CTLA-4 Antibodies: Systematic Review and Meta-Analysis. Anne Bertrand, Marie Kostine, Thomas Barnetche and Thierry Schaeverbeke. Bordeaux University Hospital, Bordeaux, France.

Background/Purpose: CTLA-4 is a costimulatory molecule that downregulates T-cell activation and promotes an immunotolerance, well known by rheumatologist since the use of Abatacept. Targeting CTLA-4 is a recent strategic approach in cancer control: blocking CTLA-4 enhances an antitumor immunity by promoting T-cell activation and cytotoxic T-lymphocytes proliferation. This induction of a tolerance break against the tumor may be responsible for immune related adverse events (irAEs) in most responder patients, some of which concerning rheumatologists.

Objective

To assess the incidence and nature of irAEs in oncologic treatment with anti-CTLA-4 antibodies (Ipilimumab and Tremelimumab).

Methods: A systematic search of literature up to February 2014 was performed in MEDLINE, EMBASE and Cochrane databases to identify relevant articles. Reading and data extraction were performed independently by two readers. Pooled incidence was calculated using R software with the package meta. Heterogeneity was quantified using I^2.

Results: The literature search identified 491 articles and a manual search retrieved 4 other articles. Finally, 121 articles were full-text reviewed and 80 finally included in the study. 1265 patients from clinical trials were included for meta-analysis.

Anti-CTLA-4 antibodies were mainly given for melanoma, and in few studies for renal cell carcinoma, mesothelioma and pancreatic, gastric, oesophagal, colorectal, prostatic and bladder cancer.

Described irAEs consisted of skin lesions such as rash, pruritus and vitiligo, colitis, and less frequently inflammatory hepatitis, hypophysitis, thyroiditis and some rare events such as sarcoidosis, uveitis, Guillain-Barré syndrome, immune-mediated thrombocytopenia, auto immune inflammatory myopathy and polyarthritis.

The overall incidence of all-grade irAEs was 72% (CI95%: 61%–83%). The overall incidence of high-grade irAEs was 24% (CI95%: 18%–30%).

The risk of developing irAEs was dependent of dosage with incidence of all-grade irAEs being evaluated to 61% (CI95%: 56%–66%) for Ipilimumab 3mg/kg and 78,5% (CI95%: 65%–72%) for Ipilimumab 10 mg/kg.

Death due to irAEs occurred in less than 1% of patients (colic bowel perforation).

The median time of onset of irAEs was about nine weeks (IQR: 6–12) after the onset of treatment, corresponding with the first three cycles but varies according to the organ system involved.

Such immune activation could also be indicative for tumor-specific T-cell activation, and irAEs occurrence was associated with clinical response to CTLA-4 blocking: 61% of the patients presenting with irAEs experience a clinical remission (partial or complete), or at least a stabilisation of the cancer.

Conclusion: The price of potential long-term survival to metastatic tumors (such as melanoma) is atypical immune toxicity, reflecting the immune mechanism of action of anti-CTLA-4 antibodies. Rheumatologists will be involved in care of some irAEs such as arthralgia or polymyalgia rheumatica/giant cell arteritis, as recently published. A better knowledge of these irAEs and its management in a multidisciplinary approach will help to reduce morbidity and therapy interruptions.

Disclosure: A. Bertrand, None; **M. Kostine**, None; **T. Barnetche**, None; **T. Schaeverbeke**, None.

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Altered Phenotype and Function of Senescent Regulatory T Cells in Rheumatoid Arthritis. Johannes Fessler, Chrsitine Schwarz, Anja C. Ficjan, Rusmir Husic, Evelyne Höller, Angelika Lackner, Winfried B. Graninger and Christian Dejaco. Medical University Graz, Graz, Austria.

Background/Purpose: Immunosenescence accompanied by accumulation of senescent T cells is a hallmark feature in the pathogenesis of rheumatoid arthritis (RA). Here we characterize a novel senescent regulatory T cell (Tregs, $CD4^+CD28^-FoxP3^+$) subset in RA patients.

Methods: Prospective, cross-sectional study on 35 patients with RA [mean age 58 ($\pm$SD 9.5), 71.4% female, SDAI 8.15 ($\pm$1.2)] and 25 healthy controls [HC, mean age 56.4 ($\pm$6.7), 60% female]. We used flow cytometry to determine the prevalence of senescent $CD4^+CD28^-FoxP3^+$ T cells and to characterize their phenotype, proliferation, cytokine production and apoptosis. T cell receptor diversity was determined by RT-PCR. *In vitro* generation of senescent Tregs was performed in cell culture experiments using magnetic bead isolated $CD4^+CD25^+CD127^{low}$Tregs and stimulation with anti-CD3/CD28 beads, interleukin (IL) -2 with or without TNF-α (100ng/ml) for 14 days.

Results: Two percent [$\pm$2.8] of $CD4^+$ T cells were $CD28^-FoxP3^+$ in RA patients whereas this subset was almost absent in HC [0.6 ($\pm$0.8), p=0.077]. The number of $CD4^+CD28^+FoxP3^+$ Tregs was comparable in both groups [28.6 ($\pm$18.5) vs. 32.7 ($\pm$18), p=0.480]. *In vitro* assays showed that exposure of $CD4^+CD28^+$ Tregs to TNF-α led to a downregulation of CD28 and thus to the $CD28^-FoxP3^+$ phenotype.

Surface receptor expression analysis of $CD28^-FoxP3^+$ and $CD28^+FoxP3^+$ Tregs demonstrated that $CD28^-FoxP3^+$ cells expressed higher levels of the regulatory protein PD-1 [17.45% (0–36.4) vs. 5.45% (1.8–13.5), p=0.034], whereas CTLA-4 expression was similar in both subsets. Production of various cytokines including IL-2, IL-4, IL-10, IL-17, TNF-α and IFN-γ was increased in $CD28^-FoxP3^+$ compared to $CD28^+FoxP3^+$ Tregs [all p<0.05] whereas proliferation rate was lower than in the $CD28^+$ counterparts [50% (0–93.6) non proliferating cells vs. 4.6% (0–30.6), p=0.001]. In contrast, apoptosis induction was higher in $CD28^-FoxP3^+$ than in $CD28^-FoxP3^+$ Tregs [22.1% (0–30.8) vs. 4.4% (0–7.8), p<0.001]. TCR diversity was also reduced in $CD28^-FoxP3^+$ Tregs compared to their $CD28^+$ counterparts [median TCR diversity score: 84 (36–104) vs. 115 (109–125), p=0.037].

Conclusion: We discovered a novel T cell subset which combines both senescent as well as regulatory properties. This subset favors the proinflammatory milieu and shows altered phenotype and function compared to normal (non-senescent) Tregs.

Disclosure: J. Fessler, None; **C. Schwarz**, None; **A. C. Ficjan**, None; **R. Husic**, None; **E. Höller**, None; **A. Lackner**, None; **W. B. Graninger**, None; **C. Dejaco**, Pfizer, MSD, 2, Pfizer, MSD, Roche, UCB, BMS, AbbVie, 8.

1738

Prominent Role of CCR6+ T Helper Cells in the Pathogenesis of ACPA+ Patients with Early RA. Sandra M.J. Paulissen[1], Jan Piet van Hamburg[2], Nadine Davelaar[2], Heleen Vroman[2], Johanna MW Hazes[3], P.H.P. de Jong[4] and Erik Lubberts[2]. [1]Erasmus Medical Center, Rotterdam, Netherlands, [2]Erasmus MC, University Medical Center, Rotterdam, Netherlands, [3]Erasmus MC University Medical Center Rotterdam, Rotterdam, Netherlands, [4]Erasmus University Medical Center, Rotterdam, Netherlands.

Background/Purpose: Presence of serum anti-citrullinated protein antibodies (ACPAs) in patients with rheumatoid arthritis (RA) predicts worse disease course and a more erosive disease. In the pathogenesis of RA, inflammatory T cells play a central role. In this context, we recently found increased proportions of pathogenic peripheral CCR6+ memory T helper cells in patients with early RA compared to healthy individuals. However, it is unclear how T cell proportions are distributed between ACPA+ and ACPA- patients. Therefore alterations in peripheral T cell populations and their pathogenic potential were examined in ACPA+ and ACPA- patient groups.

Methods: A nested matched case control study was performed including n=27 ACPA+ and n=27 ACPA- patients with early RA. T cell profiles (Treg, Th1, Th2, Th17, Th22 and various less well classified populations) from these ACPA+ and ACPA- patients were generated based on chemokine receptor, cytokine and transcription factor expression. Differentially present T cell populations were isolated from peripheral blood and analyzed for their pathologic potential in a co-culture system with RA derived synovial fibroblasts (RASF).

Results: In comparison to ACPA- patients, ACPA+ patients have higher proportions of regulatory T cells (Treg) and CD4+ memory CCR6+ T cells. Since the CCR6+ T cell population is still a heterogeneous population, four

CCR6+ T cell subpopulations were distinguished by differential expression of CXCR3 and CCR4. All four CCR6+ subpopulations shared Th17 cell characteristics such as Rorγt and CCL20 expression, but IL-17A, IL-17F, IL-22 and IFN-γ expression differed greatly between these subpopulations. However, even the population with lowest expression of these cytokines showed high pathological potential as shown by stimulating IL-1β, IL-6, IL-8, COX-2 and MMP-3 expression upon co-culture with RASF. Indeed, despite dissimilar Th17 and Th1 characteristics between the CCR6+ subpopulations, all four showed highly increased pathological potential in co-culture compared to naive and T-helper-1 cells.

Conclusion: ACPA+ and ACPA- patients can be distinguished by the distribution of Treg and CCR6+ T helper cell subpopulations. These CCR6+ subpopulations exhibit dissimilar T-helper-17 and T-helper-1 characteristics, but all possess high pathological potential, including the population that has low IL-17A/F and IL-22 expression. These findings indicate a prominent role of CCR6+ T helper cells in the pathogenesis of ACPA+ patients with early RA and may contribute to the worse disease outcome in ACPA+ patients.

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1739

Immunomodulatory Properties of CD271+ and CD271- Synovial Mesenchymal Cells. Alicia Usategui[1], Manuel J. Del Rey[1], Regina Faré[1], Gabriel Criado[1], Vanessa Miranda[1], Juan D. Cañete[2] and Jose L. Pablos[1]. [1]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [2]Hospital Clínic of Barcelona, Barcelona, Spain.

Background/Purpose: Mesenchymal stem cells (MSC) have been isolated from synovium and represent a fraction of synovial fibroblast (SF) cultures. CD271+ is considered a MSC surface marker that is also present in a small fraction of primary cultures of SF. Bone marrow or synovial derived CD271+ cells have shown increased chondrogenic potential but their immunosuppressive properties have not been analyzed. We have analyzed the immunosuppressive potential of CD271+ compared to CD271- primary SF cultures from human osteoarthritic synovial tissues.

Methods: Osteoarthritic synovial membranes were obtained at knee joint replacement surgery (n=9). CD271+/− separation was carried out by magnetic sorting of passage 0 SF cultures and confirmed by flow cytometry. Multipotent differentiation capability of SF to adipocytes, chondroblasts and osteoclasts was studied using standard *in vitro* tissue culture-differentiating conditions and staining with oil red, alcian blue or alizarin red, respectively. Immunomodulatory properties of CD271+/− sorted cells were analyzed in co-cultures with T lymphocytes obtained from healthy donors (ratio 1:10), stimulated with anti-CD3/CD28 beads. T-cell proliferation was measured by CellVue dye dilution as detected by flow cytometry. T-cell cytokine production (IL-2, IL-10, IL-17 and IFN-γ) in supernatants was quantified by ELISA. Quantitative data were analyzed by Mann Whitney or one-sample t-test.

Results: Primary passage 0 OA SF cultures contained (11.27±7.25%) CD271+ cells. After sorting, both CD271+ and CD271- SF cultures contained multipotential MSC capacity to differentiate to adipocytes, chondroblasts and osteoclasts in specific differentiation media. Both types of cells significantly inhibited the proliferation of anti-CD3/CD28 stimulated T cells and there were no quantitative differences between CD271+ and CD271- cells (70.46±6.56% and 73.53±13.15% respectively compared to single T-cell parallel cultures where proliferation was set to 100%). Co-culture of SF and T lymphocytes induced a significant increase in IL-2, IL-10, IL-17 and IFN-γ production by T cells that was similar in CD271+ and CD271- cells.

Conclusion: These data confirm that SF cultures contain a CD271+ cell fraction. Both CD271+ and CD271- SF cultures showed multipotential and immunomodulatory properties previously described as characteristic of MSC. T-cell anti-proliferative effect and non-specific up-regulation of T-cell cytokine production were similar in CD271+ and CD271- SF.

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1740

Predicting the Evolution of Inflammatory Arthritis in ACPA-Positive Individuals: Can T-Cell Subsets Model Help? Laura Hunt[1], Agata Burska[2], Elizabeth M.A. Hensor[1], Jackie L. Nam[1], Frederique Ponchel[1] and Paul Emery[1]. [1]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [2]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds., Leeds, United Kingdom.

Background/Purpose: ACPA+ individuals with non-specific musculoskeletal symptoms are at high risk of developing rheumatoid arthritis (RA). We previously demonstrated dys-regulation of T-cell subsets with loss of naïve and regulatory T-cells (Treg) in early RA. The aim of the current study is to demonstrate the predictive value of T-cell subset analysis for progression towards inflammatory arthritis (IA) onset in ACPA+ individuals.

Methods: 82 ACPA+ individuals without clinical synovitis at recruitment were followed. 120 healthy controls provided a reference group. T-cell subset analyses were performed using 6-colour flowcytometry for naïve T-cells (CD4+CD45RB+CD45RA+CD62L+), Treg (CD4+CD25^{high}Foxp3+CD127^{low}) and inflammation related cells (IRC: CD4+CD45RB+CD45RA+CD62L-). We calculated one-sided 95% reference ranges for each subset (age-related for naïve and Treg) and classified values as normal or abnormal accordingly. Using Cox proportional hazards regression we created a risk score; each subset's coefficient rounded to nearest 0.5, multiplied by 2, then a total score for each person was calculated. Risk categories were then derived based on the proportions of patients progressing at each score level.

Results: In this cohort 40/82 (49%) developed IA within a median follow-up of 6.4 months (range 1–52 months). Cox regression analysis (Table 1) allowed categorisation into moderate and high risk. Within the high risk group 78% (18/23) progressed to IA in a median of 8 months compared to 37% (22/59) within the moderate group (Table 2; Figure 1).

Conclusion: T-cell dys-regulation in ACPA+ individuals with non-specific musculoskeletal pain may be useful in predicting progression to IA. Further modelling will be needed to quantify the added clinical utility of T-cell subsets in predicting progression to IA.

Table 1: Sensitivity and specificity of T-cell subset frequencies for progression to IA; results of multivariable Cox regression and risk scores for each subset

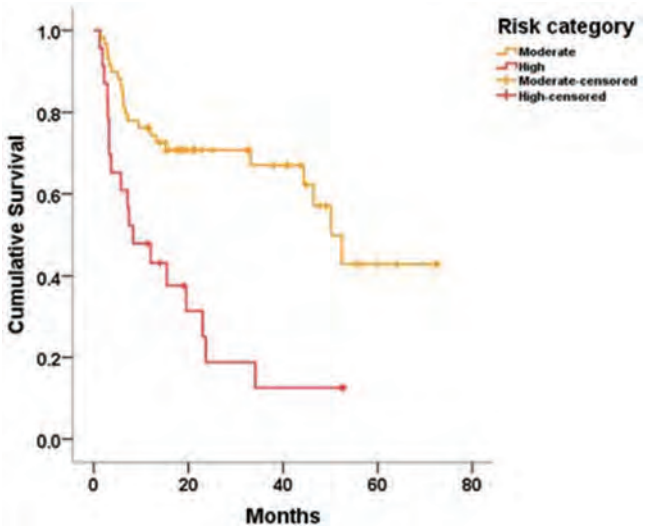
	Cut-off	Sensitivity	Specificity	HR (95% CI)	Coefficient: score
Naïve	<LLN for age	30.0 (18.1, 45.4)	83.3 (69.4, 91.7)	1.6 (0.8, 3.3)	0.5:1
IRC	>4.56	32.5 (20.1, 48.0)	90.5 (77.9, 96.2)	2.4 (1.2, 4.6)	0.9:2
Treg	< LLN for age	45.0 (30.7, 60.2)	73.8 (58.9, 84.7)	1.6 (0.8, 2.9)	0.4:1

LLN=lower limit of normal (one-sided age-related 95% reference range)

Table 2: Proportions of people progressing to IA according to T-cell risk score; risk categories derived

T-cell risk score	% progressed to IA (n/N)	Risk category	Median (95% CI) months to IA
0	31% (10/32)	Moderate	50 (41, 58)
1	44% (12/27)		
2	73% (11/15)	High	8 (1, 16)
3	86% (6/7)		
4	100% (1/1)		

Figure 1: Kaplan-Meier survival plot showing cumulative survival for people at moderate or high risk of progression to IA



Disclosure: L. Hunt, None; **A. Burska**, None; **E. M. A. Hensor**, None; **J. L. Nam**, None; **F. Ponchel**, None; **P. Emery**, None.

1741

Anti-TNFα Treatment Increases IL-17A+ and IL-22+ T Cells in Spondyloarthritis Regardless of Concomittant Gut Inflammation. Thomas Andersen[1], René Østgård[2], Bent Deleuran[2], Malene Hvid[1] and Henning Glerup[3]. [1]Aarhus University, Aarhus, Denmark, [2]Aarhus University Hospital, Aarhus, Denmark, [3]Regional Hospital of Silkeborg, Silkeborg, Denmark.

Background/Purpose: The pro-inflammatory Th17 associated cytokines IL-17A and IL-22 have been proposed as important mediators of the inflammation seen in spondyloarthritis (SpA) and inflammatory bowel disease (IBD). A strong link between the development of SpA and IBD has been established, with Th17 cells as presumed pivotal players in the co-development of these inflammatory diseases. The aim of this study was to investigate differences in Th17 expression between SpA patients with subclinical gut inflammation, and SpA patients without gut inflammation. Further, changes in Th17 levels with anti-TNFα-therapy was investigated.

Methods: Thirty SpA patients with high (>100 mg/kg, n=15) and with normal (<50 mg/kg, n=15) fCal, and 14 healthy controls (HC) were included in this study. Patients with known psoriasis or IBD at the time of enrollment were excluded. All patients were eligible for anti-TNFα treatment, which was initiated at the day of enrolment in the study continuing for 52 weeks. During treatment mean BASDAI changed from 60 + 66 at baseline to 15 + 21 at 52 weeks. At baseline patients were clinically examined and all had a capsular endoscopy done and fCal was measured. Peripheral blood mononuclear cells (PBMCs) were isolated at baseline and at week 12, 20 and 52. Multicolour flow cytometry was performed in order to evaluate percentage of IL-17A, IL-22 and IL-23R expressing CD45RO T cells. Further, PBMCs were analysed for the expression of the Th17 defining chemokine receptor 6 (CCR6) and the gut-homing integrin complex alfa4-beta7.

Results: Similar percentages of IL-17A, IL-22 and CCR6 expressing CD45RO T cells between SpA patients with high or low faecal calprotectin were observed. No difference in the gut homing potential of the IL-17A and IL-22 expressing T cells in either of the SpA groups evaluated as CD3+CD4+CD45RO+ lymphocytes double positive for alfa4 and beta7, was observed.

Since no differences in the two groups were observed, they were merged and further evaluated as one. Percentages of IL-17A+ 2.0% (1.4% - 2.4%), IL-22+ 2.9% (2.0% - 4.2%) and CCR6+ 20% (14.4% - 24.3%) CD45RO T cells at baseline was elevated compared to HCs IL-17A 1.16% (0.8%- 1.5%), IL-22 1.7% (1.0% - 2.3%) CCR6 9.5% (7.7% - 15.7%), respectively.

Despite major clinical improvement in the treatment period, the percentage of IL-17A+ CD45RO T cells increased to 3.1% (2.0% - 4.8%), IL-22+ CD45RO T cells increased to 3.8% (2.5%- 5.3%) and CCR6+ CD45RO T cells increased to 24.1% (18.7% - 27.1%) after 52 weeks of anti-TNFα therapy. No change in the percentage of alfa4/beta7+ or IL-23R+ CD45RO T cells was observed at any time-point.

Conclusion: Anti-TNFα therapy improved clinical disease activity of the SpA patients substantially. Surprisingly, underlying inflammatory activity, in the form of Th17/22 cells persisted, even 1 year after initiation of anti-TNFα therapy. The persistently elevated levels of Th17 cells could be involved in the on-going disease progression seen in SpA patients even with clinically low, and well-controlled disease activity.

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1742

Depletion of Reactive Oxygen Species Biases T Cells to Proinflammatory Cytokine Production in Rheumatoid Arthritis. Zhen Yang[1], Eric L. Matteson[2], Jorg J. Goronzy[1] and Cornelia M. Weyand[1]. [1]Stanford University School of Medicine, Stanford, CA, [2]Mayo Clinic, Rochester, MN.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease, genetically associated with polymorphisms in HLA class II molecules. CD4 cells produce proinflammatory cytokines and orchestrate multiple disease-relevant functions in the inflamed joint. How threshold settings in intracellular signaling cascades in such CD4 T cells affect arthritogenic functions is insufficiently understood.

Reactive oxygen species (ROS) are classically considered harmful as they can cause oxidative stress. However, they also have critical cytoprotective functions by modulating cellular signal transduction. Intracellular ROS derive from mitochondria as a byproduct of metabolic activity. Cells possess a complex machinery for ROS removal, with the principal cellular reductant NADPH deriving from the pentose phosphate pathway (PPP), where glucose-6-phosphate dehydrogenase (G6PD) functions as the rate-limiting enzyme.

Methods: Naive CD4 T cells from patients with seropositive RA and age-matched controls were isolated and their T cell receptors were cross-linked. The following parameters were measured in resting and poststimulation T cells: ROS production, cell cycle progression and apoptotic susceptibility; commitment to the Th1, Th17, Th2 and Treg lineage. Expression of G6PD transcripts was quantified by RT-PCR. To attenuate intracellular ROS levels, cells were treated with the SOD mimetic Tempol. Synovial membrane biopsies were typed for HLA-DRB1*04 by RT-PCR. Mitochondrial mass was quantified by measuring copy numbers of mitochondrial DNA.

Results: Intracellular ROS in RA T cells were consistently decreased below 70% of those in controls ($p=0.01$). The ROS loss in RA T cells was associated with faster cell cycle progression ($p<0.001$), increased apoptotic susceptibility ($p=0.01$) and premature conversion of the naïve to memory phenotype ($p=0.05$). Treating T cells with the ROS scavenger Tempol could mimic this differentiation defect. RA T cells were prone to differentiate into IFN-γ and IL-17-producing cells, whereas the frequencies of IL-4-producing and FoxP3-expressing cells were indistinguishable in RA and control cells. RA T cells had a reduced mitochondrial mass and their intracellular NADPH concentrations were increased ($p=0.04$). Further evidence for a more active PPP in RA T cells came from increased expression levels of G6PD ($p=0.03$). The reduction of mitochondrial mass was reproduced in synovial tissue biopsies, where HLA-DRB1*04+ patients expressed significantly reduced mitochondrial DNA ($p=0.05$).

Conclusion: Intracellular ROS levels in RA T cells are reduced, imposing reductive stress. ROS loss may result from reduced mitochondrial mass, but also from enhanced production of the reductant NADPH. ROS depletion fundamentally shifts the functional behavior of human T cells, enhancing their cell cycle progression and swaying their differentiation towards proinflammatory Th1 and Th17 cells. The data delineate a mechanistic connection between intracellular redox imbalance and athritogenic T cell functions, with the prospective of therapeutically influencing such T cell defects via restoration of ROS production.

Disclosure: Z. Yang, None; **E. L. Matteson**, None; **J. J. Goronzy**, None; **C. M. Weyand**, None.

1743

Antigen-Specificity Regulates Peripheral Homeostasis of Regulatory T Cells. Laura Su[1] and Mark Davis[2]. [1]University of Pennsylvania, Philadelphia, PA, [2]Stanford, Stanford, CA.

Background/Purpose: One key mechanism of peripheral tolerance involves regulatory T cells (Tregs). Tregs are best known for the expression of the transcription factor Foxp3 that drives many Treg-specific gene expressions. Defects in Foxp3 expression result in severe autoimmunity, but an increased numbers of Tregs can also be pathologic and contributes to the evasion of tumor surveillance. Thus, the appropriate balance between regulatory and effector T cells is essential to maintain self-tolerance while preserving effective immunity. How antigen-recognition impacts Treg homeostasis is not known. The goal of this study is to characterize the peripheral Treg repertoire in healthy people in order to establish the foundation for evaluating Treg homeostatic dysregulation in rheumatoid arthritis and other autoimmune diseases.

Methods: Antigen-specific T cells were identified directly *ex vivo* using peptide-MHC (pMHC) tetramers. We selected self-peptides from gp100, citrullinated fibrinogen (cit-Fib), or preproinsulin (PPins) for their relevance in vitiligo, rheumatoid arthritis, and type I diabetes. Three foreign antigens from the influenza virus (HA, PB1, and PA) were selected for comparison. Tetramer staining was performed using blood from de-identified healthy blood donors, followed by staining for CD25, CD45RO, Foxp3, and Ki67 expression. Tetramer tagged cells were magnetically enriched and analyzed by flow cytometry. We also compared the frequency of antigen-specific Foxp3+ cells in adult blood versus the cord blood.

Results: We show vastly different Foxp3 expression between self antigen-specific T cells versus flu-reactive T cells. On average, 10% of autoantigen-specific T cells express Foxp3, whereas less than 1% of flu-reactive T cells specific for HA are Foxp3+. This difference is likely due to antigen exposure, because many more HA-specific T cells express Foxp3 in cells from the cord blood. Moreover, the robustness of the T cell response also determines Foxp3 expression. We examined

three distinct flu-reactive T cell populations and found that the frequency of Foxp3+ cells is highest in the least abundant PA-specific T cells, followed by PB1-specific T cells, and lowest in the most highly expanded and memory dominant HA-specific T cells. In contrast, antigen exposure increases Treg frequency in self-reactive T cell populations, and this correlates with an increase in cellular proliferation.

Conclusion: These data demonstrate that peripheral homeostasis between Tregs and conventional T cells are regulated by antigen-specificity. Contextual differences in ligand exposures alter this balance and this has significant implications for autoimmunity.

Disclosure: L. Su, None; **M. Davis**, None.

1744

CD4+ T Cell Subpopulations in Blood and Synovial Fluid Defined By Differential Expression of Integrins. Deepak A. Rao[1], Adam Chicoine[2], Peter A. Nigrovic[3], Soumya Raychaudhuri[4], Michael B. Brenner[5] and ACR Authors 2014. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Brigham and Women's Hospital/Harvard University, Cambridge, MA, [4]Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [5]Brigham & Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: CD4+ T cells are important mediators of inflammation in rheumatoid arthritis; however, the specific CD4+ T cell populations most important in driving disease pathology remain unclear. CD4+ T cells are often divided into subsets based on effector functions (e.g. Th1, Th2, Th17). Here we describe an alternative strategy of defining T cell subpopulations in blood and synovial fluid based on differential expression of integrins and other migratory receptors that help cells localize to specific target tissues. Blockade of integrin-dependent migration is already employed clinically; therefore, understanding patterns of migratory receptor expression that allow infiltration into the joint and other target organs is of significant interest.

Methods: We developed multiparametric flow cytometry panels to characterize expression of integrins and other migratory receptors on blood and synovial fluid CD4+ T cells. Dimensional reduction was performed using Spanning tree Progression of Density normalized Events (SPADE) to identify CD4+ T cell subpopulations that express specific combinations of migratory receptors.

Results: More than half of circulating memory CD4+ T cells coordinately express α3, α5, and α6 integrins. α4 integrin is expressed on ~25–50% of circulating memory CD4+ T cells, but in a distinct pattern such that memory CD4+ T cells can be divided into 3 groups based on the differential expression of α4 and α6 integrin (α4+α6-, α4-α6+, α4+α6+). Both central memory and effector memory CD4+ T cell subsets contain these populations, while naïve T cells lack significant expression of either α chain. Interestingly, both CD4+CD25+CD127- regulatory T cells and CD4+ CLA+ 'skin-homing' cells fall predominantly within the α4-α6+ population. Both α4-α6+ and α4+α6+ cells co-express β1, while α4+α6- cells co-express β7 rather than β1. α4β7+ cells constitute ~10–20% of circulating memory CD4+ T cells; however, these cells are rare in inflammatory synovial fluid, in which almost all CD4+ T cells express β1. Small populations of circulating memory CD4+ cells also express α1, α2, αV, and αE integrins and CD146, with certain subsets substantially enriched in synovial fluid. SPADE analyses allowed for visual demonstration of cell subpopulations defined by migratory receptor expression.

Conclusion: Differential integrin expression identifies CD4+ T subpopulations in a manner non-redundant with traditional methods of classifying T cells. Specific integrin-defined memory CD4+ subpopulations are enriched in synovial fluid compared to blood, suggesting that certain integrins, in particular β1 integrins, may promote CD4+ T localization to the joint. Further characterization of integrin-defined T cell subpopulations that can infiltrate the joint may lend new insights into mechanisms of synovial inflammation.

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1745

Memory Stem T Cells Are Selectively Enriched in Patients with Rheumatoid Arthritis, Contract upon Anti-TNF Treatment, and May Provide a Long-Term Reservoir of Arthritogenic Lymphocytes. Nicoletta Cieri[1], Giacomo Oliveira[1], Raffaella Greco[2], Mattia Baldini[3], Elena Baldissera[3], Fabio Ciceri[2] and Chiara Bonini[1]. [1]Experimental Hematology Unit, San Raffaele Scientific Institute, Milan, Italy, [2]Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milan, Italy, [3]Clinical immunopathology and advanced medical therapeutics, San Raffaele Scientific Institute, Milan, Italy.

Background/Purpose: The T-cell memory compartment is multi-faceted and encompasses multiple subsets with divergent properties. In addition to central memory (T_{CM}) and effector memory (T_{EM}) cells, the spectrum of immunological memory has been recently extended with the identification of memory stem T cells (T_{SCM}). Gene expression profiling, corroborated by *in vitro* and *in vivo* experimental results, posits T_{SCM} upstream T_{CM} and T_{EM} in T-cell ontology (Gattinoni, Nat Med 2011; Cieri, Blood 2013). While self-renewing T_{SCM} would be highly desirable if bearing protective specificities, this very same cell subpopulation may also represent a foe when considering T-cell mediated pathologies. We hypothesized that, in these clinically relevant contexts, T_{SCM} may represent a reservoir of long-lived T cells with undesired and detrimental specificities responsible for disease perpetuation.

Methods: we characterized T_{SCM} dynamics in 15 patients with active rheumatoid arthritis (RA) and upon treatment with etanercept (median time from anti-TNF treatment onset: 3 months). T-cell subset composition and function was evaluated by 11-colors multiparametric flow cytometry.

Results: we found that T_{SCM} cells, defined as $CD45RA^+$-$CD62L^+CD95^+$, are significantly more represented in terms of frequencies and absolute counts in patients with active RA as compared to age- and sex-matched healthy controls. Of notice, the extent of T_{SCM} expansion correlated with disease severity (quantified by DAS28 score), suggesting an active role of T_{SCM} in disease pathophysiology. Functionally, expanded $CD4^+$ T_{SCM} displayed a preferential T_H17 polarization, known to have a fundamental pathogenic role in rheumatic synovitis, and thus further corroborating T_{SCM} lymphocytes as a potential novel player in RA pathogenesis and perpetuation. Importantly, TNF-a neutralization, upon etanercept administration, efficiently reduced the frequency and number of circulating T_{SCM} and restored T-cell homeostasis in responder patients. Prior to etanercept treatment, T_{SCM} lymphocytes expressed TNFR2 to significantly higher levels compared to the other T-cell subsets both in $CD4^+$ and $CD8^+$ compartments, suggesting that TNF-a might act as a costimulatory signal for T_{SCM} lymphocytes in the context of RA. Finally, ongoing experiments will elucidate whether T_{SCM} accumulation is due to the selective expansion of arthritogenic clones through the characterization of the TCR repertoire and antigen-specificities of T_{SCM} cells from RA patients.

Conclusion: Understanding the dynamic and quantitative aspects of T_{SCM} lymphocyte behavior in RA will have profound implications for devising strategies to counteract T-cell dysfunction in RA patients.

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1746

Involvement of IL-17-Producing MAIT Cells in the Pathogenesis of Rheumatoid Arthritis. Eri Hayashi, Asako Chiba, Mie Kitagaichi, Kurisu Tada, Ken Yamaji, Naoto Tamura, Yoshinari Takasaki and Sachiko Miyake. Juntendo University School of Medicine, Tokyo, Japan.

Background/Purpose: Mucosal-associated invariant T (MAIT) cells are a subset of innate-like lymphocytes which are restricted by the MHC-related molecule-1 (MR1) and express a semi-invariant TCRα chain: Vα7.2-Jα33 in humans and Vα19-Jα33 in mice. Previously, our group has reported that murine MAIT cells produced high levels of IL-17 and exacerbated arthritis by enhancing inflammatory responses by using animal models of arthritis. Recent studies have revealed that MAIT cells are abundant in humans. MAIT cells constitute about 5–10% of abT cells in peripheral blood and intestine, suggesting that MAIT cells may play important roles in human autoimmune diseases. In this study, we aimed to investigate whether MAIT cells are involved in the pathogenesis of rheumatoid arthritis (RA).

Methods: Peripheral blood mononuclear cells(PBMC) of RA patients and

age- and sex- matched healthy subjects were separated by Lymphoprep. PBMC were stained with anti-human monoclonal antibodies against CD3, γδTCR, Vα7.2TCR, and CD161, and MAIT cells were identified as $CD3^+\gamma\delta TCR^-V\alpha7.2TCR^+CD161^{high}$ cells by FACS. The expression of HLA-DR and CCR9 on MAIT cells and other T cell subsets were also assessed. PBMC (2×10^6 cells per well in 96-well culture plates) were stimulated with phorbol-myristate-acetate (50ng/ml) and ionomycin (500ng/ml) for 3 hours. Breferdin A was added in the last 2 hours of culture. After surface staining, cells were permeabilized by using BD Cytofix/Cytoperm Fixation/Permeabilization Solution Kit and intracellular cytokine staining for IL-17A, IFNγ, TNFα and IL-6 was performed. Cells were analyzed on FACS LSR Fortessa with Flowjo softwere.

Results: The percentages of MAIT cells were decreased in RA patients compared with healthy controls. The reduction in MAIT cell frequency was more enhanced in RA patients with active disease. There was a tendency of increased HLA-DR expression on MAIT cells from patients with lower MAIT cell frequencies. MAIT cells produced IL-17A, IFNγ, TNFα and IL-6 upon stimulation, and the frequency of IL-17A-producing MAIT cells was inversely correlated with that of MAIT cells in RA. However, there was no correlation with the frequencies of IFNγ-, TNFα- or IL-6- producing cells and that of MAIT cells. We also found the negative correlations in the frequency of a gut-homing chemokine receptor CCR9-positive MAIT cells with that of MAIT cells in RA.

Conclusion: We demonstrated that the frequency of MAIT cells was reduced in RA. The elevated expression of HLA-DR and IL-17 production by MAIT cells indicated the activated state of remaining MAIT cells in RA. The increase of CCR9-positive MAIT cells indicates the recruitment of gut MAIT cells to the peripheral blood in RA.

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1747 WITHDRAWN

1748

$CCR6^+CD4^+$ Cells Are Counterparts of Follicular T-Cells Supporting Autoantibody Production in Rheumatoid Arthritis. Karin ME Andersson[1], Dan Hu[2], Ron Cialic[2], Nicola Cavallini[3], Vijay K. Kuchroo[4], Malin Erlandsson[1], Howard Lee Weiner[2] and Maria Bokarewa[5]. [1]University of Gothenburg, Gothenburg, Sweden, [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]University of Göteborg, Göteborg, Sweden, [4]Brigham and Women's Hospital, Boston, MA, [5]University of Goteborg, Goteborg, Sweden.

Background/Purpose: CCR6 has been associated with rheumatoid arthritis (RA) in genome-wide association studies. CCR6 expression characterises Th17 cells recruited to inflamed joints of RA patients. The purpose of this study was to characterize gene transcription in the peripheral lymphocytes in RA patients.

Methods: $CCR6^+CD4^+$ cells were isolated from peripheral blood leukocytes of 14 RA patients and 6 healthy controls by magnetic beads. The isolated cells consisted of 85% $CCR6^+CXCR3^-$cells and had a viability of 94%. Cells were stimulated with PMA/ionomycine for 4h, supernatants were collected for cytokine analysis and cell pellets were used for gene expression analysis using nCounter Analysis System (NanoString Technologies).

Results: Transcription analysis showed that 140 genes had significant ($p<0.05$) ≥1.5-folds difference between $CCR6^+CD4^+$ cells of RA patients and healthy controls. As expected, RA patients $CCR6^+CD4^+$ cells were also $CCR5^-CXCR3^-$. Despite the intense immunosuppression with methotrexate and TNF-inhibitors, RA lymphocytes had had higher transcription of Th17 cytokines (IL17F, IL17A, IL22). Also Th17 (Rorc) and Th1 (Tbx21 and Egr-2) differentiation genes were enhanced, while other genes regulating IL-22 production (Ahr and NFAT1) were repressed. Genes controlling the formation of Th17(Beta) and Th17(23) subtypes were increased, and inhibitors of this formation were repressed. Transcription of IL23 receptor complex genes (IL23R, Jak2, *e.g.*) was up-regulated and production of IL23A and CCL20 was increased.

RA lymphocytes had a significant increase in the follicular T helper cell profile, characterized by the surface markers CXCR5 and ICOS, and the master transcription regulator Bcl-6. CXCR5 expression was combined with higher CCR6 and lower CXCR3. The enrichment of $CXCR5^+CCR6^+CXCR3^-$ phenotype was supported by expression of cytokine IL21. The cytokines activating the gp130-receptor family (IL31, IL35 and Lif), were increased. Interestingly, gp130-associated signalling in the CCR6+CD4+ cells was dampened by low IL27R, low STAT signal (reduced STAT1, STAT3, STAT4) and low transcriptional regulator AhR, suggesting that the gp130 activation occurs on a cell populations different from the studied, *e.g.* B-cells.

Conclusion: This study demonstrates that $CCR6^+CD4^+$ T cells of RA patients have features of proliferative, proinflammatory and IL17 producing cells controlled through TGFb and IL23 mediated signalling. $CCR6^+CD4^+$ T cells are a source of $CXCR5^+$ Tfh cells efficient producers of IL21 cytokine presumably stimulating autoantibody production in RA patients.

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1749

Molecular Mechanisms Underlying $1,25(OH)_2D_3$-Mediated Suppression of Th17 Cell Activity. Wendy Dankers[1], Jan Piet van Hamburg[1], Wida Razawy[1], Nadine Davelaar[1], Anne-Marie Mus[1], Patrick Asmawidjaja[1], Johannes van Leeuwen[1], Edgar Colin[2] and Erik Lubberts[1]. [1]Erasmus MC, University Medical Center, Rotterdam, Netherlands, [2]ZGT, Almelo, Netherlands.

Background/Purpose: Vitamin D has suppressive effects on autoimmune diseases, such as rheumatoid arthritis (RA). Within these diseases, Th17 cells play a crucial role in the processes underlying chronic inflammation. Currently, Th17 cells are of high interest in the development of novel therapeutics, such as the development of antibodies against IL-17A or specific small molecule inhibitors of RORγt, the Th17 cell associated transcription factor.

Previously we have shown that the active vitamin D metabolite $1,25(OH)_2D_3$is capable of directly inhibiting the polarization and pathogenic activity of Th17 cells. However the molecular mechanisms underlying this modulation of Th17 cell activity by vitamin D are currently unclear.

Methods: Therefore $CD4^+CD45RO^+$ (memory) and $CCR6^+$ memory T-helper cells were sorted from peripheral blood of patients with early RA and healthy volunteers. They were cultured under in the presence or absence of $1,25(OH)_2D_3$. The expression of cytokines and transcription factors of interest was analyzed using microarray based gene expression profiling, flow cytometry, ELISA and/or RT-PCR.

Results: In the presence of $1,25(OH)_2D_3$ the pro-inflammatory cytokines IL-17A, IL-17F and IL-22 were inhibited. Also the expression of Th17 signature genes like RORγt and IL-23R was reduced. On the other hand we find an increase in IL-4 and IL-10 expression.

Interestingly neutralization of IL-4 partly reversed the effect of $1,25(OH)_2D_3$ on the inhibition of IL-17A, IL22 and RORγt expression. In addition, the inhibition of IL-17F by $1,25(OH)_2D_3$ was almost completely absent when IL-4 was blocked.

In contrast to IL-4, IL-10 neutralization had limited effects in these cultures.

Because the effect of $1,25(OH)_2D_3$ is only partially dependent on IL-4, we examined factors that could play a role independent of IL-4. Gene expression profiling revealed that two transcription factors that are known to play a role in Th17 differentiation, EOMES and IRF8, are up regulated by $1,25(OH)_2D_3$. EOMES and IRF8 are direct regulators of RORγt expression. Blocking IL-4 does not affect this up regulation, indicating that EOMES and IRF8 might be important in the IL-4 independent regulating of Th17 polarization by $1,25(OH)_2D_3$.

Conclusion: From these findings, we conclude that $1,25(OH)_2D_3$ is a direct modulator of Th17 cell activity. This modulation is partly dependent on up regulation of IL-4. IL-4 independent mechanisms may include the down-regulation of RORγt expression via up regulation of IRF8 and EOMES.

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1750

The Effect of a Pro-Inflammatory Milieu on Tregalizumab (BT-061)-Induced Regulatory T-Cell Activity. Jan Kubach[1], Faiza Rharbaoui[2], Martin Koenig[2], Jörg Schüttrumpf[2], Silke Aigner[2], Benjamin Dälken[2] and Helmut Jonuleit[1]. [1]University of Mainz Medical Center, Mainz, Germany, [2]Biotest AG, Dreieich, Germany.

Background/Purpose: Regulatory T cells (Tregs) are essential for maintaining normal immune homeostasis. We have previously reported that tregalizumab is a humanized, non-depleting, CD4 agonistic antibody that selectively activates Tregs. The specific functionality of tregalizumab may originate from the recognition of a unique epitope on domain 2 of CD4 that is not recognized by other anti-CD4 monoclonal antibodies. Tregalizumab is in clinical development for the treatment of rheumatoid arthritis (RA). Currently, a Phase IIb trial -*TREAT 2b*- is in progress to further evaluate the efficacy and safety of tregalizumab and define the optimal dose in combination with methotrexate (MTX) in adults with RA and an inadequate response to MTX.

Recent data have shown that pro-inflammatory cytokines may have a profound negative effect on the suppressive properties of Tregs or on the responsiveness of effector cells to suppression. Serum cytokine levels for RA patients have been reported in the range of: IL 1β: 0–0.269 ng/mL; IL-6: 0–1.078 ng/mL; TNFα: 0.001–2.952 ng/mL (Meyer et al., 2010). Therefore, we performed *in vitro* studies to investigate the effects of pro-inflammatory cytokines on the ability of tregalizumab to activate Treg suppressive activity.

Methods: Allogenic effector T cells (Teffs) isolated from healthy volunteers were co-cultured with freshly isolated Tregs and APCs from a different blood donor (mixed lymphocyte reaction, MLR) in the presence of different concentrations of cytokines as previously described by Trinschek *et al.*(2013). Cell proliferation was measured by incorporation of radioactive thymidine. Suppression was derived by the ratio of the radioactive count obtained in the co-culture in presence of Treg versus no Treg. At least 3 independent experiments were performed at different days using cells isolated from different blood donors.

Results: In the absence of cytokine, activation of Tregs with tregalizumab resulted in strong suppression of Teff proliferation, on average at least 50% reduction of cell proliferation was measured with tregalizumab at 1 μg/mL. In presence of pro-inflammatory cytokines, little effects were observed. At the concentrations tested, corresponding to levels rarely measured in plasma from RA patients (up to 2000 ng/mL of IL-1β and 500 ng/mL of IL-6), neither IL-1β nor IL-6 inhibited tregalizumab-induced suppression of Teff proliferation. In case of TNFα, only the highest concentrations tested (50 and 100 ng/mL) had a marginal effect on tregalizumab-induced suppression.

Conclusion: In this *in vitro* study, activation of Tregs by tregalizumab and the suppression of Teffs was not notably inhibited by pro-inflammatory cytokines, only moderately by TNFα at very high concentration. This result gives further insights into the potential of tregalizumab to activate Tregs in the presence of systemic levels of pro-inflammatory cytokines that are elevated in autoimmune diseases such as RA. Further *in vitro* investigations are in progress to determine if the observed moderate effect of TNFα is the result of a reduction of Treg suppressive activity or an increased Teff-resistance to Treg suppression. In similar experimental conditions, effects of MTX or prednisolone will also be assessed.

Disclosure: J. Kubach, None; **F. Rharbaoui**, Biotest AG, 3; **M. Koenig**, Biotest AG, 3; **J. Schüttrumpf**, Biotest AG, 3; **S. Aigner**, Biotest AG, 3; **B. Dälken**, Biotest AG, 3; **H. Jonuleit**, Biotest AG, 2, Self, 9.

1751

CD4 Aptamer-RORγt shRNA Chimera Inhibits IL-17 Synthesis By Human CD4$^+$ T cells. Cong-Qiu Chu[1], Pingfang Song[2], Yuan K. Chou[2], Xiaowei Zhang[2], Roberto Meza-Romero[2], Kentaro Yomogida[2] and Gil Benedek[2]. [1]Oregon Health & Science Univ, Portland, OR, [2]Oregon Health & Science University, Portland, OR.

Background/Purpose: RNA interfering (RNAi)-mediated gene silencing holds great promise for manipulating T cells to study basic T cell biology and for developing potential T cell targeted therapeutics. However, efficient delivery of small interfering RNA (siRNA) specifically into primary T cells represents a major hurdle to the widely use of RNAi technology. We explored the use of single-stranded oligonucleotide aptamers as vehicle to deliver small hairpin RNA (shRNA) to target Th17 cells.

Methods: An RNA aptamer specifically binds to CD4 was previously selected and sequenced. siRNA to retinoic acid related orphan receptor (ROR)-γt was previously designed and tested. A cDNA encoding the CD4 aptamer and RORγt shRNA was constructed and the CD4 aptamer-RORγt shRNA (CD4-AshR-RORγt) chimera was generated using *in vitro* T7 RNA transcription. 2′-F-dCTP and 2′-F-dUTP were incorporated into CD4-AshR-RORγt for RNase resistance. CD4$^+$ human T lymphoma cells, Karpas 299 constitutively expressing RORγt were tested for CD4-AshR-RORγt internalization. Human CD4$^+$ T cells were polarized to Th17 cells for analysis of CD4-AshR-RORγt delivery efficiency and suppression of RORγt expression and IL-17 production.

Results: The CD4 aptamer and RORγt shRNA was transcribed to form a stable single chimeric aptamer-shRNA molecule, CD4-AshR-RORγt. CD4-AshR-RORγt was labeled with flurochrome Cy3 via Cy3-CTP incorporation during RNA transcription. CD4-AshR-RORγt was specifically uptaken by CD4$^+$ Karpas 299 cells and primary human CD4$^+$ T cells as visualized by confocal microscopy and flow cytometry. The RORγt shRNA moiety of CD4-AshR-RORγt chimera was cleaved and released by endoribonuclease Dicer. CD4-AshR-RORγt suppressed RORγt gene expression in Karpas 299 cells and CD4$^+$ T cells in a dose dependent manner, but did not affect Tbox21 gene expression. Furthermore, 50–70% IL-17A production by CD4$^+$ T cells was inhibited by CD4-AshR-RORγt, but not by mock-CD4-AshR-RORγt or CD4-AshR-scrambled sequence.

Conclusion: The present data in our study revealed that CD4 aptamer can serve as a delivery vehicle for shRNA that targets a specific gene in CD4$^+$ human T cells. CD4-AshR-RORγt specifically silenced the targeted RORγt gene expression and led to a marked decrease of Th17 differentiation and IL-17 production. CD4-AshR-RORγt can be evaluated for the development of a therapeutic agent in treatment of Th17 mediated inflammatory disorders.

Disclosure: C. Q. Chu, None; **P. Song**, None; **Y. K. Chou**, None; **X. Zhang**, None; **R. Meza-Romero**, None; **K. Yomogida**, None; **G. Benedek**, None.

1752

CD30 As a Target of Aptamers and Delivery Portal for Aptamer-shRNA to Block Th17 Cells. Cong-Qiu Chu[1], Pingfang Song[2], Yuan K. Chou[2] and Shao Tao[2]. [1]Oregon Health & Science Univ, Portland, OR, [2]Oregon Health & Science University, Portland, OR.

Background/Purpose: Aptamers are single-stranded 20 –100 nucleotides (RNA or DNA) that bind to molecular targets with high affinity and specificity due to their stable three dimensional shapes and were referred as "chemical antibodies". Aptamers are being investigated and developed as therapeutic agents and carriers for cell type specific delivery of drugs including small interfering RNA (siRNA). CD30 is expressed by activated Th17 cells a plays a critical role in Th17 cell differentiation.

Methods: Single stranded DNA (ssDNA) or RNA CD30 aptamers were synthesized. A chimera of RNA CD30 aptamer-small hairpin RNA (shRNA) against retinoic acid related orphan receptor (ROR)-γt (CD30-AshR-RORγt) was generated *in vitro* from a cDNA template by *in vitro* T7 RNA transcription. Human PBMC were stimulated with anti-CD3 and CD28 and polarized towards Th17 differentiation. CD30 aptamers or CD30-AshR-RORγt was incubated with the stimulated PBMC. ELISA and intracellular cytokine staining were used to quantify IL-17A production and Th17 cells.

Results: An ssDNA aptamer against CD30 was able to inhibit IL-17A production by anti-CD3/CD28 stimulated PBMCs in a dose dependent manner. The inhibitory effect of ssDNA CD30 aptamer was comparable to that by anti-CD30 antibody. CD30 RNA aptamer alone had a lesser inhibitory effect on IL-17A production but could enhance the effect of ssDNA CD30 aptamer. CD30-AshR-RORγt chimera was internalized by activated but not resting CD4$^+$ T cells. Compared with a CD30-AshR-scramble sequence, CD30-AshR-RORγt inhibited 60–70% of IL-17A production and IL-17A producing CD4$^+$ T cells.

Conclusion: CD30 Aptamers showed significant inhibitory effects on IL-17A production by human PBMCs. In addition being a target by CD30 aptamers, CD30 expressed by activated CD4$^+$ T cells can serve as a portal for aptamer mediated delivery of RNAi to target T cell genes. CD30 aptamers and CD30-AshR-RORγt chimera have the potential to be developed as a novel class of therapeutic agents to treat Th17 mediated inflammatory diseases.

Disclosure: C. Q. Chu, None; **P. Song**, None; **Y. K. Chou**, None; **S. Tao**, None.

1753

Human T-Cells Express RANKL in Response to Combination of ZAP-70, Calcineurin and Voltage-Gated K+-Channel Signaling Following Co-Ligation of the Adhesion Molecule CD2 and the T-Cell Receptor Complex. Bohdan P. Harvey and Zehra Kaymakcalan. AbbVie Bioresearch Center, Worcester, MA.

Background/Purpose: Human T lymphocytes promote osteolysis in rheumatic diseases through the production of the osteoclastogenic cytokine RANKL. We have previously demonstrated that RANKL secretion is

mediated by the simultaneous engagement of the lymphocyte function-associated antigen 2 (CD2) and T-cell receptor (TCR/CD3). However, the cell signaling events involved in its expression and release from T-cells are poorly understood. By using a variety of signaling mutants of Jurkat as well as chemical inhibitors to cell signaling factors, we sought to elucidate the role of the TCR signaling complex and that of ion channel-mediated signaling cascades in the induction of RANKL by CD2.

Methods: The human T-cell line Jurkat and several signaling mutant derivatives were exposed to various combinations of bead bound anti-CD3, CD2 and CD28 antibodies. Total soluble RANKL was determined by osteoprotegrin capture sandwich ELISA. A Jurkat clone with a stably integrated NFAT-luciferase reporter (NFAT-Luc) was used to assess the signaling events leading to NFAT activation, a known regulator of RANKL expression, in response to cross-linking of CD3, CD2 and CD28 for 4 hrs. Prior to being exposed to the bead-bound antibodies, these cells were treated with a panel of chemical inhibitors to a variety of signaling factors including kinases (PI3K, CaMKII, AKT and PKC), phosphatase (calcineurin), calmodulin (CaM), calcium (TRPC3) and potassium ion channels (Kv1.1, 1.2 and 1.5) at broad concentration ranges. Cytotoxicity was evaluated by CellTiter-Fluor®.

Results: Similar to primary human T lymphocytes, Jurkat cells secreted RANKL only in response to cross-linking of both CD2 and CD3. This process was dependent on ZAP70 signaling but was independent of the following components associated with TCR signaling: beta-chain of the TCR, CD45, and PLCgamma. Cross-linking of CD3 and CD28 failed to induce RANKL secretion in wild-type cells even though high levels of IL-2 were generated. A 2-fold higher level of NFAT-Luc activation was observed with CD2/CD3 co-ligation as compared to CD28/CD3 and from the panel of inhibitors, chlorpromazine HCl, an inhibitor of both calmodulin and K+-channel signaling, was more effective at blocking NFAT-Luc activation by CD2/CD3 co-ligation than that of CD28/CD3, suggesting that these signaling cascades contribute to RANKL expression regulated by NFAT in response to CD2. Additional inhibitors to either calcium or potassium signaling cascades (FK 506, a calcineurin inhibitor, and 4-aminopyridine, a Kv1.1 & 1.2 inhibitor, respectively) also blocked CD2/CD3-induced activation of the NFAT reporter without cytotoxicity; however, inhibition was not restricted to CD2 since CD28/CD3-induced signaling was also affected.

Conclusion: Our results demonstrate that T-cells secrete RANKL in a ZAP70-dependent manner and only require the co-ligation of CD3 and CD2 in the absence of the co-stimulatory receptor CD28. Furthermore, calcineurin and voltage-gated K+-channel signaling cascades were shown to induce the activation of NFAT in response to CD2/CD3 co-ligation, suggesting that these pathways may contribute to the expression RANKL in the inflamed RA synovium by T-cells.

Disclosure: B. P. Harvey, AbbVie Inc, 3, AbbVie Inc, 1; **Z. Kaymakcalan**, AbbVie Inc, 3, AbbVie Inc, 1.

ACR/ARHP Poster Session B
Vasculitis

Monday, November 17, 2014, 8:30 AM–4:00 PM

1754

Peripheral CD5$^+$ b-Cells in ANCA-Associated Vasculitis. Sebastian Unizony[1], Noha Lim[2], Vincent Carey[3], Deborah J. Phippard[2], Nadia Tchao[2], Eli M. Miloslavsky[1], Peter A. Merkel[4], Paul Monach[5], William St. Clair[6], Robert F. Spiera[7], Adam Asare[2], Philip Seo[8], Carol A. Langford[9], Gary S. Hoffman[10], Cees Kallenberg[11], Ulrich Specks[12] and John H. Stone[1]. [1]Massachusetts General Hospital, Boston, MA, [2]Immune Tolerance Network, Bethesda, MD, [3]Brigham and Women's Hospital, Boston, MA, [4]Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [5]Boston University, Boston, MA, [6]Duke University, Durham, NC, [7]Hospital for Special Surgery, New York, NY, [8]Johns Hopkins Vasculitis Center, Johns Hopkins University, Baltimore, MD, [9]Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, OH, [10]Cleveland Clinic Foundation, Cleveland, OH, [11]University of Groningen, Groningen, Netherlands, [12]Mayo Clinic, Rochester, MN.

Background/Purpose: We explored the utility of peripheral CD19$^+$ CD5$^+$ B-cells (CD5$^+$ B-cells) as biomarkers in ANCA-associated vasculitis (AAV).

Methods: CD5$^+$ B-cells were measured longitudinally by flow cytometry in patients randomized to rituximab (RTX, n = 99) or CYC followed by AZA (CYC/AZA, n = 98) for the treatment of AAV (RAVE trial). Number of CD5$^+$ B cells/mL and %CD5$^+$ B-cells within the total population of CD19$^+$ B-cells were determined. Outcomes assessed were disease activity, induction treatment failure, disease severity, relapse, and in the RTX arm, relapse-free survival according to %CD5$^+$ B-cells at B-cell *redetection* (10–68 CD19$^+$ B-cells/mL) and *reconstitution* (≥ 69 CD19$^+$ B-cells/mL) using %CD5$^+$ B-cells as dichotomous (>30% and ≤30% [1]) and categorical predictor. Repeated measure ANOVA, Wilcoxon, Fisher's, logrank and Cox PH tests were used.

Results: Median CD5$^+$ B-cell numbers and %CD5$^+$ B-cells were comparable between groups at baseline. After an initial decline, CD5$^+$ B-cell numbers increased in the RTX arm, but remained low in the CYC/AZA cohort. In both groups, %CD5$^+$ B-cells increased during remission induction and declined thereafter (**Fig 1**). %CD5$^+$ B-cells correlated inversely with disease activity in RTX-treated patients (baseline 12%, remission 28% and relapse 23%; $p < 0.05$), but not in CYC/AZA-treated patients (**Fig 2**). No significant association was observed between CD5$^+$ B-cells and induction failure or disease severity. Disease relapses were not preceded consistently by declines in %CD5$^+$ B-cells. Once B-cells returned in the RTX arm, %CD5$^+$ B-cells did not predict time to flare (**Fig 3**). The hazard ratio (HR) for relapse in patients with >30% CD5$^+$ B-cells (versus ≤30%) at B-cell *redetection* was 1.14 (95% CI 0.49–2.64; P = 0.75). The HR for relapse in patients with >30% CD5$^+$ B-cells (versus ≤30%) at B-cell *reconstitution*, was 0.9 (95% CI 0.31–2.55; P = 0.84). Division of patients by quartiles of %CD5$^+$ B-cells upon B-cell repopulation failed to show any trend in time to relapse following the order of the strata.

Conclusion: In patients with AAV treated with CYC or RTX CD5$^+$ B-cells do not predict treatment response, relapse or disease severity.

Fig 1

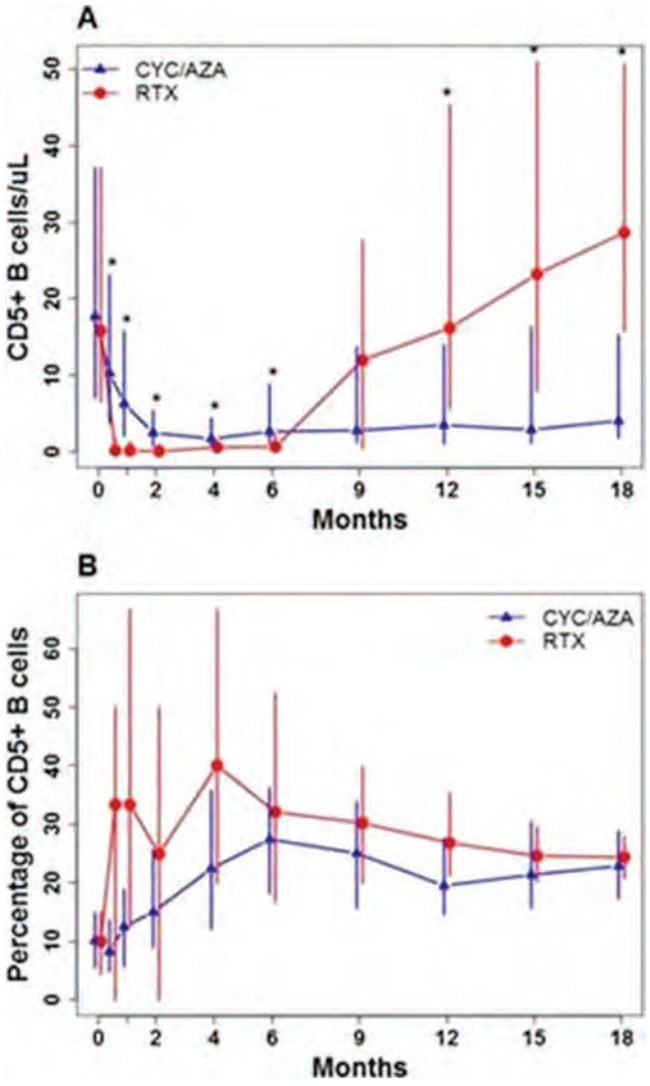
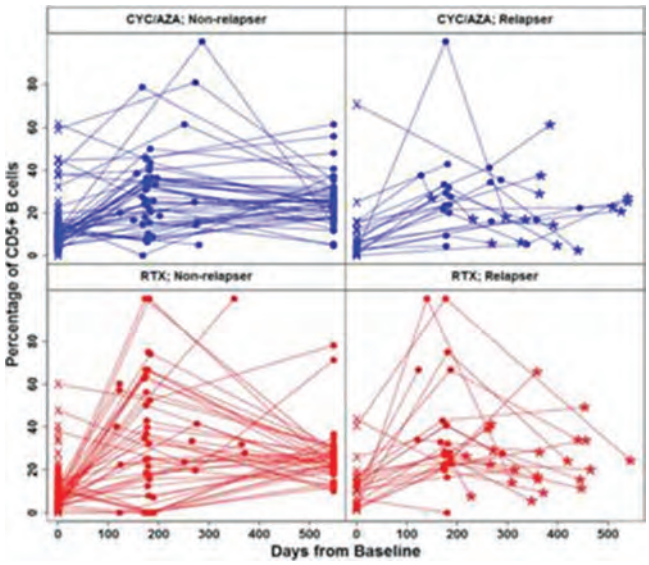
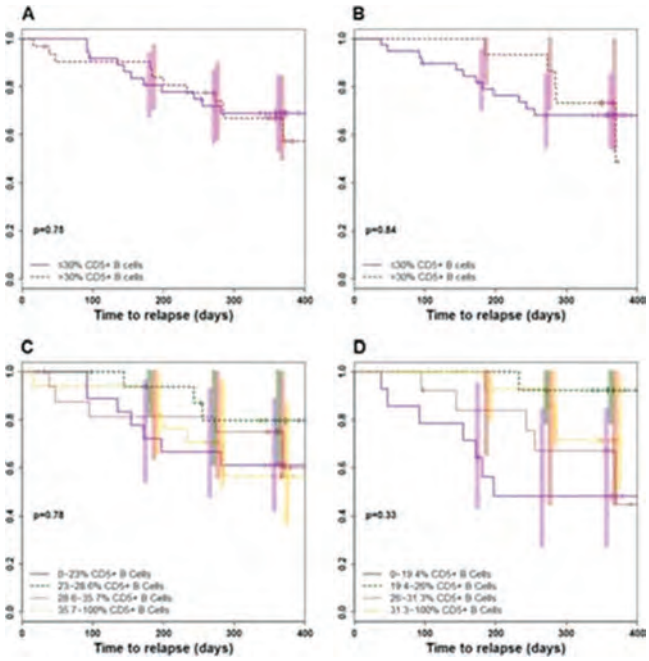


Fig 2



RTX n = 68 (22 relapsers); CYC/AZA n = 60 (16 relapsers); x = baseline; ● = remission; * = relapse

Fig 3



A/C redetection; B/D reconstitution

1 Bunch DO. CJASN 2013

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1755

Proteomic Analysis of ANCA Vasculitis Serum Reveals Broad Neutrophil Activation, Angiogenesis, and Selective Inflammatory Pathway Activation. Melissa Parker, David Gold, Koustubh Ranade and Ethan Grant. MedImmune, LLC, Gaithersburg, MD.

Background/Purpose: ANCA vasculitis is characterized by the presence of autoantibodies directed against MPO, PR3 and other neutrophil proteins. Binding of these autoantibodies to activated neutrophils is thought to be an important driver of the pathology underlying this disease. To date, investigation of serum biomarkers in this patient population have been limited. A more comprehensive approach to defining the biomarker profile would aid in our understanding of the mechanisms underlying the disease, may point to novel therapeutic targets, and would aid in the definition of biomarkers to monitor disease activity and therapeutic response.

Methods: ANCA vasculitis (n=46) and healthy control (n=30) donor serum samples were obtained from commercial sources. Vasculitis samples were derived from patients with positive c-ANCA or p-ANCA patterns by immunofluorescence analysis. Anti-PR3 and anti-MPO autoantibody levels were measured by ELISA to assess autoantibody status of the vasculitis samples. Proteomic profiling was performed using SOMAscan™ and multiplexed analysis on the Luminex® platform.

Results: Measurement of anti-MPO and anti-PR3 antibodies in the ANCA vasculitis sera indicated that approximately one-third of the samples had detectable levels of one or the other of these most common autoantibodies. Multiplexed proteomic analysis of control and vasculitis serum samples revealed elevated TNFα, GM-CSF, IL-7, eotaxin, MCP-1, CXCL1, sCD40L, IL-21, growth factors such as VEGF, EGF, and FGF-2 (see Table). Increased levels for these analytes were observed with both conventional Luminex® multiplex assay and with the SOMAscan™ analysis that measures levels of more than 1,200 protein analytes. No clear difference in levels of these biomarkers was apparent in patient samples with or without detectable antibodies against MPO or PR3. Further analysis of the SOMAscan™ data indicated a pattern of increased levels of proteins in several classes. Across vasculitis serum samples, we observed an elevation in levels of biomarkers associated with angiogenesis, select inflammatory mediators, platelet activation and markers of tissue remodeling/repair. Interestingly we also observed clear increases in the levels of several autoantigens associated with this disease – MPO, PR3, lactoferrin and moesin. This finding is consistent with heightened neutrophil activation, and in patients with autoantibodies against these proteins, may drive immune complex-mediated inflammation.

Table 1. Serum concentrations of select analytes measured by multiplex analysis (mean ± SD in pg/ml)

	Healthy control	ANCA vasculitis	*P*
sCD40L	145 ± 141	7252 ± 9070	0.0001
EGF	10 ± 15	233 ± 254	0.0001
VEGF	51 ± 69	262 ± 234	0.0001
CXCL1	189 ± 181	919 ± 764	0.0001
TGFα	2 ± 7	9 ± 9	0.0001
IL-21	2 ± 3	8 ± 15	0.01
Flt-3L	8 ± 18	28 ± 60	0.01
IL-17A	1 ± 1	3 ± 4	0.005
TNFα	7 ± 7	20 ± 16	0.01
IL-12p70	3 ± 14	8 ± 26	0.005
MCP-1	364 ± 285	830 ± 396	0.0001
FGF-2	18 ± 28	40 ± 48	0.0001
Eotaxin	56 ± 37	121 ± 73	0.0001
IL-7	4 ± 6	8 ± 6	0.0001
MIP-1β	27 ± 32	48 ± 38	0.0001
IFNγ	4 ± 7	6 ± 12	0.0005
GM-CSF	12 ± 16	16 ± 32	0.001

Conclusion: A deep analysis of the biomarker profile of ANCA vasculitis serum revealed upregulation of pathways related to angiogenesis, neutrophil and platelet activation, and tissue repair. These data provide a view more comprehensive than previously reported of the altered serum profile in ANCA vasculitis patients and highlight candidate biomarkers to track disease activity and therapeutic responses.

Disclosure: M. Parker, MedImmune, LLC, 3; **D. Gold**, MedImmune, LLC, 3, AstraZeneca, 1; **K. Ranade**, Medimmune, LLC, 3, AstraZeneca, 1; **E. Grant**, MedImmune, LLC, 3, AstraZeneca, 1.

1756

Molecular Diagnosis Reveals a Surprising Prevalence of Limited Gpa Among Patients with Orbital Inflammatory Diseases. James T. Rosenbaum[1], Dongseok Choi[2], Christine Harrington[3], Patrick Stauffer[3], David Wilson[3], Seema Gupta[3], Roger Dailey[3], John Ng[3], Eric Steele[3], Patrick Yeatts[4], Peter Dolman[5], Valerie White[5], Gerald Harris[6], Craig Czyz[7], Jill Foster[7], Deepak Edward[8], Hind Alkatan[8], Bobby Korn[9],Don Kikkawa[9], Dinesh Selva[10], Sander Dubovy[11], Chris Alabiad[11], David Tse[11], Michael Kazim[12], Payal Patel[12] and Stephen R. Planck[3]. [1]OHSU, Portland, OR, [2]Oregon Health and Science University, Portland, OR, [3]Oregon Health & Science University, Portland, OR, [4]Wake Forest University, Winston-Salem, NC, [5]University of British Columbia, Vancouver, BC, [6]Medical College of Wisconsin, Milwaukee, WI, [7]Ohio State Univeristy, Columbus, OH, [8]King Khaled Eye Hospital, Riyadh, Saudi Arabia, [9]University of California, San Diego, San Diego, CA, [10]Royal Adelaide Hospital, Adelaide, Australia, [11]University of Miami, Miami, FL, [12]Columbia University, New York City, NY.

Background/Purpose: Gene expression profiling provides diagnostic and therapeutic information in several malignancies, but its role in evaluating inflammatory disease is relatively untested. We hypothesized that gene expression profiling could provide diagnostic information for orbital inflammatory diseases which include thyroid eye disease (TED or T in Figure 1), sarcoidosis (S in figure), granulomatosis with polyangiitis (GPA or G in figure), or nonspecific orbital inflammation (NSOI (N in figure), previously known as pseudotumor).

Methods: Formalin-fixed orbital biopsies, 20 from healthy controls (C in Figure 1), 25 from subjects with NSOI, 25 from subjects with TED, 6 from subjects with GPA, and 7 from subjects with sarcoidosis were obtained by an international consortium, divided into discovery and validation sets, and analyzed with regard to histopathology and gene expression using microarray.

Results: Principal coordinate analysis (Figure 1), heat maps (Figure 2), and Venn diagrams showed distinct gene expression profiles for healthy controls and subjects with TED, GPA, or sarcoidosis. A statistical method called random forest based on 39 probe sets identified controls, GPA, or TED with an average accuracy of 76% ($p=0.02$ compared to random) while two expert pathologists had accuracies of 49% and 58% respectively (neither significant compared to random). Random forest analysis indicated that 52% of tissues from patients with nonspecific inflammation were consistent with a diagnosis of GPA.

Conclusion: Molecular diagnosis by gene expression profiling is more accurate than histopathology in differentiating forms of orbital inflammatory disease. Although NSOI is a heterogeneous collection of diseases, many patients with NSOI have a gene expression profile resembling GPA. A limited form of GPA affecting the orbit is far more common than previously realized. Molecular diagnosis should be tested for its ability to identify GPA affecting sinuses and nasal or subglottic mucosa.

Figure 1

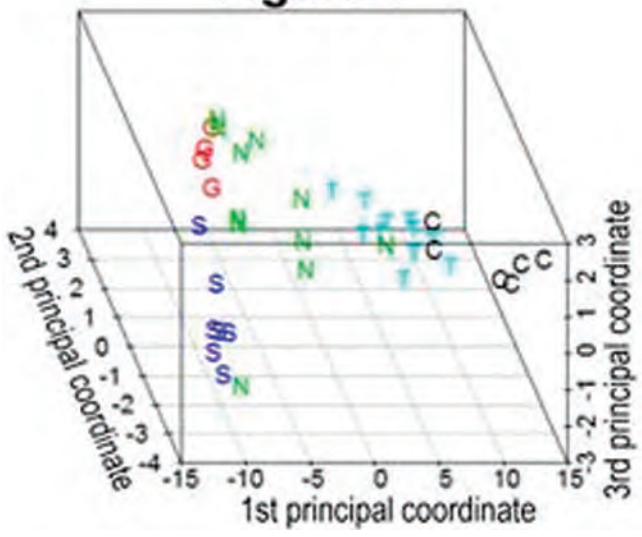
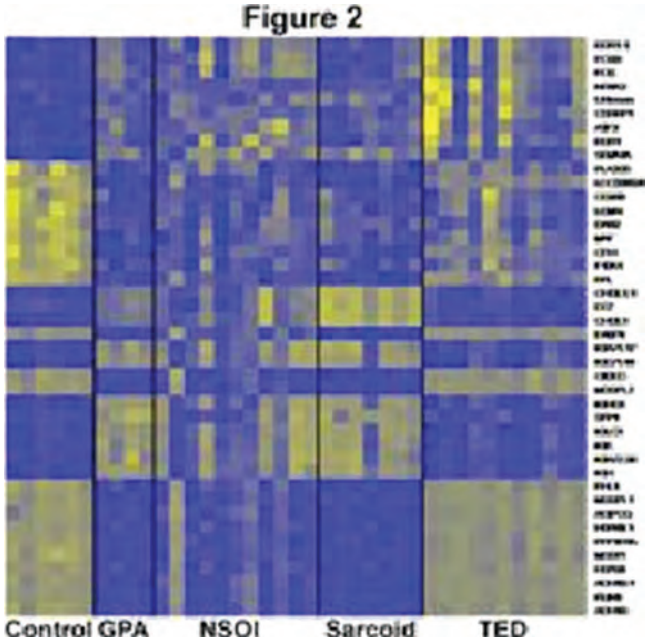


Figure 2



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1757

An Analysis of the Incidence and Characteristics of ANCA Positive Vasculitis before and after the Christchurch Earthquake. Ben McGettigan[1], John L. O'Donnell[1], Peter T. Chapman[2], Christopher Frampton[3] and Lisa K. Stamp[3]. [1]Canterbury Health Laboratories, Christchurch, New Zealand, [2]Christchurch Hospital, Christchurch, New Zealand, [3]University of Otago, Christchurch, Christchurch, New Zealand.

Background/Purpose: At 1251 on 22 February 2011 a magnitude 6.4 earthquake struck Christchurch killing up to 185 people and causing widespread damage to buildings in the city centre and surrounds. Multiple building collapses during the busy lunchtime period in Christchurch when the earthquake occurred will have resulted in significant environmental exposures. Prominent involvement of the upper and lower respiratory tracts suggests that inhaled antigens may have a role in pathogenesis of ANCA associated vasculitis. An increased incidence and severity of MPO positive vasculitis was observed after the Kobe earthquake in 1995. The aim of this study was to describe the incidence and characteristics of ANCA positive vasculitis before and after the 2011 Christchurch earthquake.

Methods: All ANCA tests reported by Christchurch pathology centres over a 2 year period prior to February 21 2010 (period 1) and the 2 year period after February 22 2011 (period 2) were extracted from laboratory information systems. Clinical notes from patients with positive MPO or PR3 antibodies were reviewed to confirm newly diagnosed vasculitis cases who resided within the Christchurch area. Demographic information and organ involvement was confirmed on all newly diagnosed cases and compared between periods using Fisher's exact and independent t-tests. Total Canterbury population was obtained from Statistics New Zealand.

Results: In period 1, 2592 total ANCA requests were processed; of these 37 (1.4%) were MPO positive and 100 (3.9%) were PR3 positive. 13/37 (35%) patients were subsequently confirmed to have newly diagnosed MPO positive vasculitis and 9/100 (9%) patients were confirmed to have PR3 positive vasculitis. In period 2, 2416 total ANCA requests were processed; of these 32 (1.3%) were MPO positive and 118 (4.9%) were PR3 positive. 7/32 (21.9%) patients were confirmed to have newly diagnosed MPO positive vasculitis and 11/118 (9.3%) newly diagnosed PR3 positive vasculitis. The rate of MPO vasculitis per 100,000 population was 3.45 in period 1 and 1.93 in period 2 (RR 1.8 95%CI 0.66–5.29). The rate of PR3 vasculitis per 100,000 population was 2.39 in period 1 and 3.03 in period 2 (RR 0.79 95%CI 0.29–2.09). In the post-earthquake period those with a new diagnosis of MPO

vasculitis were significantly younger than those diagnosed in the pre-earthquake period (Table1).

Conclusion: In contrast to a previous study we have shown no statistically significant difference in rate of newly diagnosed MPO or PR3 positive vasculitis after a major earthquake. A longer study period post-earthquake may be required. The earlier age of onset of MPO vasculitis post-earthquake is of interest and may relate to younger people being in the areas of greatest building collapse in the city center. Further information of location at the time of the earthquake will be required.

Table 1: Demographic and clinical characteristics pre (period 1) and post (period 2) the 2011 Christchurch earthquake

PR3 vasculitis	Period 1 (n=9)	Period 2 (n=11)	p value
Age years; mean (SEM)	63.0 (5.2)	68.7 (4.4)	0.41
% male	100%	63.6%	0.09
PR3 mean (SEM)	1224 (550)	934.8 (360.5)	0.66
Renal involvement	5 (55.6%)	4 (36.4%)	0.65
Respiratory involvement	8 (88.9%)	8 (72.7%)	0.59
MPO vasculitis	**Period 1 (n=13)**	**Period 2 (n=7)**	**p value**
Age years; mean (SEM)	71.3 (2.9)	58.4 (5.3)	0.03
% male	10/13 (77%)	5/7 (71.4%)	1
MPO mean (SEM)	623.7 (199.4)	462.3 (154.6)	0.59
Renal involvement	11/13 (84.6%)	5/7 (71.4%)	0.59
Respiratory involvement	6/13 (46.2%)	2/7 (28.6%)	0.64

Disclosure: B. McGettigan, None; **J. L. O'Donnell**, None; **P. T. Chapman**, None; **C. Frampton**, None; **L. K. Stamp**, Astra Zenec, 5, Abbvie, 9, PHARMAC, 6.

1758

Environmental Risk Factors for Granulomatous Polyangiitis (GPA): Southern Hemisphere Similar to Northern Hemisphere. Lisa K. Stamp[1], Peter T. Chapman[2], Richard A. Watts[3], Christopher Frampton[1] and John L. O'Donnell[4]. [1]University of Otago, Christchurch, Christchurch, New Zealand, [2]Christchurch Hospital, Christchurch, New Zealand, [3]Rheumatology Department Ipswich Hospital and University of East Anglia, Ipswich, United Kingdom, [4]Canterbury Health Laboratories, Christchurch, New Zealand.

Background/Purpose: GPA is a rare condition of unknown etiology. Prominent involvement of the upper and lower respiratory tracts suggests that inhaled antigens may trigger systemic immunopathogenic responses. Although no definite inhaled environmental factor has been identified farming and solvent exposure have been reported to be associated with GPA in Northern hemisphere studies. A latitudinal gradient has been observed in both Northern and Southern hemispheres with higher rates of disease in those areas closest to the North and South Poles. The aim of this study was to determine any environmental risk factors for GPA in Canterbury New Zealand (latitude 43°–44°S), with a particular focus on inhaled antigens.

Methods: A case-controlled study was undertaken. All GPA cases fulfilled ACR or CHCC criteria. Each case was age ± 10yrs and gender matched with four controls (2 osteoarthritis or fracture and 2 asthma or emphysema). A structured questionnaire to assess potential environmental agents was administered. Data was analyzed using conditional logistic regression to allow for the individual matching of cases and controls.

Results: 49 cases and 196 controls were recruited. 53% were male and 97.5% were New Zealand European. The mean ± SD age of the cases was 64.9 ± 12.4yrs and controls 59.5 ± 14.6yrs. In the 2 years prior to the first symptoms attributable to GPA 14.3% of cases and 18.6% of controls lived in a rural environment ($p=0.48$). Place of birth within New Zealand (whether North Island or South Island) had no influence on risk ($p=0.7$).

Any reported exposure to dust (specifically silicon and grain dust) increased the risk of GPA, OR 3.6 (1.5 – 8.3, $p=0.003$). GPA was associated with a higher intensity of exposure to silica ($p<0.001$), metals ($p=0.003$) and solvents ($p<0.001$).

Occupation as a farm worker was associated with GPA OR 3.43 (1.5 –7.5, $p=0.002$). In the year prior to the first symptoms attributable to GPA cases were significantly more likely to have lived on, worked on or visited a farm than controls OR 2.7 (1.3–5.9; $p=0.009$). There was no significant relationship between exposure to crops (OR 1.7; 0.8–3.6; $p=0.16$). However exposure to livestock was associated with an increase risk (OR 2.3; 1.1–5.0; $p=0.02$), specifically exposure to sheep (OR3.6; 1.6–7.7; $p=0.001$). GPA was also associated with more time spent in the garden (Cases 22.7 ± 4.1 hrs/month vs. controls 13.2 ± 2.0 hrs/month $p=0.04$). Specific gardening activities were associated with increased risk including digging (OR 3.2; 1.4–7.0; $p=0.003$), mowing (OR 2.7; 1.3–5.8; $p=0.008$) and planting (OR 2.6; 1.2–5.5; $p=0.013$).

Conclusion: Previous studies have identified a latitudinal gradient and a peak in GPA disease onset in the winter months. We have shown activities associated with exposure to inhaled antigens, in particular those related to farming or gardening activities may increase the risk of GPA. We have replicated findings from northern hemisphere studies identifying dust and solvent exposure as well as farm exposure as risk factors for the development of GPA.

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1759

Analysis of Employment, Work Disability and Quality of Life of Patients with ANCA-Associated Vasculitis. Lucas Benarous[1], Benjamin Terrier[1], Alice Berezne[2], Bertrand Dunogué[3], Hervé Laborde-Casterot[1], Pascal Cohen[4], Xavier Puéchal[4], Nathalie Costedoat-Chalumeau[4], Claire Le Jeunne[4], Dominique Choudat[1], Luc Mouthon[4] and Loïc Guillevin for the French Vasculitis Study Group[4]. [1]Cochin Hospital, Paris, France, [2]Paris Descartes University, Internal Medicine department, Cochin Hospital, Paris, France, [3]Hôpital Cochin, Paris, France, [4]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France.

Background/Purpose: Improved therapeutic strategies for ANCA-associated vasculitis (AAV) have transformed acute and life-threatening diseases into chronic ones responsible for marked morbidity that could impact employment, work disability and quality of life (QoL). The French EXPO-VAS inquiry aimed to analyze work, handicaps and QoL of AAV patients and identify their determinants.

Methods: Patients with AAV seen in our department were included in a cross-sectional study assessing employment, work disability and QoL. Specific and non-specific questionnaires, including SF-36, were sent to 531 AAV patients. QoL was compared to that of the general population, patients with end-stage renal disease (ESRD), and previously reported AAV patients from the EUVAS cohort. Clinical-biological data that could affect QoL were recorded, and their determinants analyzed.

Results: Questionnaires were completed by 198 patients (109 women (55%), mean age 59±14 years). Diagnoses were granulomatosis with polyangiitis for 132 (67%), eosinophilic granulomatosis with polyangiitis (EGPA) for 42 (21%) and microscopic polyangiitis for 24 (12%). Among 94 working-age (<60 years) patients, 57% had jobs, consistent with their qualifications for 81%; 77% were stably employed, with 67% working full-time. Concerning the impact of AAV, 23% of workers felt that their disease qualitatively limited the nature of their work, while 43% felt it limited the quantity of work they could do; 77% of patients did not benefit from any workstation adaptation; 50% thought their disease had hindered their careers and 43% that it had led to a salary reduction. 33% were not employed and not looking for work; and 9% were looking for a job. These results were comparable for the different vasculitides. QoL was significantly impaired for AAV patients compared to the general population ($P<0.0001$). In contrast, QoL of AAV patients was significantly better than that of ESRD patients. Finally, our AAV population's QoL was similar to that of the EUVAS cohort, except for our patients' physical functioning, which was better ($P<0.001$), and their mental health, which was more impaired ($P<0.001$). Physical health determinants for our population were an EGPA diagnosis, long disease duration and its neurological involvement, whereas mental health determinants were ear, nose & throat signs and cardiovascular involvement.

Conclusion: Our findings showed that AAV patients' QoL was impaired compared to the general population, mainly for patients with EGPA and long-standing disease. In contrast, normal employment seemed to be preserved.

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1760

United Kingdom & Ireland Vasculitis Registry – Cross-Sectional Data on the First 1085 Patients. Jan Sznajd[1], Alan D. Salama[2], David Jayne[3], Afzal Chaudhry[3], Michael Robson[4], Joe Rosa[1], Neil Basu[5], Sarah Moran[6], Michael Venning[7], Peter Lanyon[8], Asheesh Sharma[9], Mark A. Little[10], Richard Watts[11] and Raashid Luqmani[12]. [1]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [2]University College London, London, United Kingdom, [3]Addenbrookes Hospital University of Cambridge, Cambridge, United Kingdom, [4]King's College London, London, United Kingdom, [5]University of Aberdeen, Aberdeen, United Kingdom, [6]Cork University Hospital, Cork, United Kingdom, [7]Manchester Royal Infirmary, Manchester, United Kingdom, [8]Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom, [9]University Hospital Aintree Liverpool, Liverpool, United Kingdom, [10]Trinity College Dublin, Dublin, Ireland, [11]Ipswich Hospital NHS Trust, Ipswich, United Kingdom, [12]Oxford NIHR Musculoskeletal Biomedical Research Unit, Oxford, United Kingdom.

Background/Purpose: Clinical care and research into systemic vasculitis is hampered by its rarity and its presentation to a wide array of medical specialties. We aimed to establish a UK and Ireland registry of patients with different forms of vasculitis (UKIVAS) in order to amalgamate our clinical experience and provide comparative outcome data on a large cohort of patients from multiple centres. This will inform research (trials, immunogenetics, epidemiology), service planning and commissioning (particularly of expensive biologic agents).

Methods: We are recruiting patients with systemic vasculitis under regular care of a variety of specialists across the UK and Ireland. We developed web-based software to enable prospective collection and central storage of anonymised clinical data with local storage of patient identifiable information. The application was designed for use by each centre as the local clinical database and audit tool.

Results: To date, we have recruited 1085 patients from 18 centres. The median age at diagnosis was 55.8 years (IQR 40.9–66.0) with similar gender distribution; almost 90% were white Caucasians; 87% were prevalent cases at the time of recruitment. The majority had one of the anti-neutrophil cytoplasm antibody (ANCA) associated vasculitides: granulomatosis with polyangiitis (GPA) (42%), microscopic polyangiitis (MPA) (25%), or eosinophilic granulomatosis with polyangiitis (EGPA) (9%); the remainder were defined as giant cell arteritis (GCA) (5.6%), unclassified ANCA associated vasculitis (3.8%), anti-glomerular basement membrane disease (2.3%), Behcet's (2.3%), IgA vasculitis (2.3%), Takayasu's (1.2%), polyarteritis nodosa (1%) and other types of vasculitis (<1% each). Biopsies were performed in 755 (69.6%) patients; results were positive in 466/555 (84%) GPA and MPA (Vs. 54% EGPA and 52% GCA). The majority (82.1%) received oral corticosteroids and cyclophosphamide (56% overall, 68% in GPA/MPA) for induction. The most common maintenance treatment with corticosteroids was azathioprine (39.5%). The detailed characteristics of the whole cohort and the 3 largest groups are shown in Table 1.

Conclusion: We have established a web-based registry for systemic vasculitis which can be used for gathering data at a national level and potentially linked with other international databases. The clinical features and treatment regimens reflect the predominance of ANCA vasculitis with renal involvement, with relative under-representation of other types of vasculitis. The introduction of new non-renal centres, the opportunity to biobank samples and longitudinal observation of this cohort will support further development of this project and research in vasculitis. The UKIVAS registry will be a useful way of identifying patients who may wish to take part in future clinical trials.

Table 1. Selected characteristics of all vasculitis patients and the 3 largest groups recruited in UK and Ireland vasculitis (UKIVAS) registry.

		Total	GPA	MPA	EGPA
Demographics	Number of patients (% of total)	1085 (100)	453 (42)	269 (25)	99 (9)
	Female/male ratio	1.14	1.00	1.01	1.11
	Median age at diagnosis in years (IQR)	55.2 (40.0–65.7)	59.4 (47.0–67.4)	67.9 (53.9–76.6)	55,8 (48,2–65,2)
	Median duration of the disease in years (IQR)	4.0 (0.9–8.9)	5.5 (1.9–11.5)	2.2 (0.1–0.7)	4,9 (1,5–10,2)
Organ involvement	Kidney	56%	55%	86%	25%
	ENT	44%	74%	12%	67%
	Respiratory	42%	54%	32%	80%
	Mucocutaneous	25%	21%	15%	34%
	Ophthalmology	18%	27%	8%	6%
	Peripheral nervous system	13%	11%	10%	34%
	Central nervous system	9%	5%	3%	15%
	Abdominal	8%	6%	3%	16%
Poor outcomes	Death	1.7%	0.3%	1.2%	0.0%
	ESRD	6%	3%	13%	2%
	Transplanted (% of ESRD)	15%	0%	24%	50%
Biopsies	Performed	69.6%	72.8%	83.6%	44.4%
	Positive	80.0%	81.5%	87.6%	54.5%
ANCA	MPO	25.2%	10.2%	61.3%	32.3%
	PR3	39.0%	73.5%	21.9%	8.1%
	Negative	9.4%	5.3%	1.9%	25.3%
	Not tested	14.7%	3.8%	1.9%	21.2%
Induction treatment	Oral corticosteroids	82.1%	81.0%	84.0%	86.9%
	Pulsed IV corticosteroids	23.8%	27.6%	25.3%	22.2%
	Cyclophosphamide	56.0%	66.7%	70.3%	40.4%
	Plasma exchange	11.6%	11.5%	20.1%	2.0%
	Rituximab	13.4%	18.1%	9.3%	17.2%
	Mycophenolate mophetil	11.5%	10.8%	5.6%	23.2%
	Azathioprine	19.4%	20.3%	12.3%	27.3%
Maintenance treatment	Oral corticosteroids	70.5%	71.1%	65.4%	86.9%
	Cyclophosphamide	4.9%	6.2%	2.6%	5.1%
	Rituximab	9.9%	17.2%	3.7%	9.1%
	Mycophenolate mophetil	17.1%	17.2%	16.4%	29.3%
	Azathioprine	39.5%	46.6%	45.7%	38.4%
	Methotrexate	14.5%	19.2%	3.7%	11.1%

GPA - granulomatosis with polyangiitis, MPA - microscopic polyangiitis, EGPA - eosinophilic granulomatosis with polyangiitis,
ANCA - antineutrophil cytoplasmic antibodies, ESRD - end stage renal disease, ENT - ear/nose/throat

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Standardisation of Disease Assesment in Systemic Vasculitis: Use of a Novel Web-Based Software Training Application. Jan Sznajd[1], Joe Rosa[1], David Gray[1], Jennifer O'Donoghue[1], Joanna Robson[1], Surjeet Singh[1], Richard Philipson[2], Judith Brown[2], Thor Ostenfeld[2] and Raashid Luqmani[3]. [1]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom, [2]GlaxoSmithKline R&D, Brentford, United Kingdom, [3]Oxford NIHR Musculoskeletal Biomedical Research Unit, Oxford, United Kingdom.

Background/Purpose: The Birmingham Vasculitis Activity Score (BVAS) and Vasculitis Damage Index (VDI) are validated clinical assessment tools for the systemic vasculitides. However use of BVAS and VDI is limited, partly due to lack of training but also lack of perceived need. The increasing use of biological agents in vasculitis means that BVAS and VDI can provide quantifiable evaluation prior to treatment and be used to monitor response and outcome. We aimed to develop and test an online training tool for clinicians managing vasculitis patients and allow certification of clinical assessment in vasculitis. We present pilot data on the performance of this training package.

Methods: The training package (which consists of an introductory lecture, a manual plus 20 simple and 40 advanced vasculitis case scenarios selected from a large pool of cases) has been extensively used for clinical trials. Historically we have used paper cases; most recently 51 participants scored 3060 cases manually. We built an online customized interactive web-based application and tested it amongst a group of international physicians and research nurses specialized in vasculitis during 3 clinical trial investigators' meetings, and one educational meeting for UK rheumatology fellows. The overall pass mark for each set of cases was set at 85% and 75% agreement with gold standard for BVAS and VDI respectively (and at least 50% for each individual case). In case of failure to achieve the required mark, cases could be reset allowing reattempts. The application provided immediate formal evaluation on completion and detailed feedback on performance of each evaluated case. We analyzed the percentage agreement, number of attempts per case and time needed to complete the training by each observer, as well as their own feedback.

Results: Over the course of 4 events 3980 cases were scored online by 78 participants; 33.3% passed the advanced section on their first attempt. The number of reattempts per BVAS case decreased from 1.08 (1 in 14 cases

retaken) in the introductory set to 1.05 (1 in 21 cases retaken) in the advanced set, showing intra-training improvement. Median time to complete a case was 4.18 (IQR 2.50–6.67) minutes and there was a trend showing a decrease in time taken per case as the participants progressed through the cases. The average mark at completion was 92.3% (range 86.6–96.4) for BVAS and 92% (range 88.9–95.0) for VDI. Overall 100% completed the training and were awarded certification. 59.2% of participants agreed that the training should be mandatory for all doctors who treat vasculitis patients.

Conclusion: We have developed a web-based training package to enhance clinicians' ability to evaluate patients with systemic vasculitis, based on assessment of BVAS and VDI. This package is easy to use, feasible and acceptable to participants to facilitate their ability to manage patients with vasculitis, although its effectiveness needs to be validated in clinical setting. Currently we are expanding the number of cases based on clinical data from observational studies to allow for randomized case selection and retakes using different clinical scenarios.

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The Muscle Biopsy Is a Useful and Noninvasive Procedure in Diagnosing Systemic Vasculitis Affecting Small-to-Medium-Sized Vessels: A Prospective Evaluation. Takahiro Nunokawa, Takayasu Kise, Naoto Yokogawa, Kota Shimada and Shoji Sugii. Tokyo Metropolitan Tama Medical Center, Tokyo, Japan.

Background/Purpose: Histopathological confirmation is required for the diagnosis of systemic vasculitis. However, patients suspected of vasculitis often only have lesions with a low diagnostic yield for biopsies, such as ENT and lungs. In addition, the biopsy of an involved organ, especially the nerve and kidney, is an invasive procedure carrying the risk of significant complications. In contrast, a muscle biopsy is simple and minimally invasive. However, while the muscle biopsy combined with the nerve biopsy is effective for demonstrating vasculitic neuropathy, the utility of the muscle biopsy alone is uncertain. Herein we assess the accuracy and utility of the muscle biopsy in detecting small-vessel vasculitis (SVV), or medium-vessel vasculitis (MVV) in clinical practice.

Methods: Consecutive patients with suspected SVV or MVV seen at our hospital between 2012 and 2014 were prospectively studied. Patients for whom a skin or renal biopsy were indicated were excluded from this study because the skin biopsy is less invasive than the muscle biopsy while the renal biopsy can provide useful information about the severity and prognosis of the disease in addition to its diagnostic value. Muscle biopsies were performed in the bilateral vastus lateralis of the quadriceps femoris because of its hypervascularity unless the patient presented myalgia in the other muscles. Imaging studies of muscles were not routinely performed. The definition of a positive muscle biopsy was the presence of inflammatory infiltrates with fibrinoid necrosis in the vessels.

Results: Forty-seven patients underwent muscle biopsies. Diagnosis of SVV or MVV was made in 34 patients in the follow-up period lasting more than six months. An unrelated condition was diagnosed in ten patients while nothing could be diagnosed in three patients. Of the 34 patients in whom SVV or MVV was diagnosed, a positive muscle biopsy was obtained in 20 patients (15 with MPA, 3 with PN, and 2 with EGPA) while other findings led to the same diagnosis in 14 (7 with MPA, 3 with GPA, 3 with PN, 1 with rheumatoid vasculitis). The sensitivity of the muscle biopsy was 59%. Of the 12 patients presenting vasculitic neuropathy, muscle biopsies demonstrated vasculitis in nine patients, with 75% sensitivity. Myalgia was seen in ten (50%) vasculitis patients with positive biopsies and in two (14.3%) patients with negative biopsies ($p = 0.031$). There were no complications in the procedure except for delayed wound healing in one patient.

Conclusion: The muscle biopsy is a safe method which offers a high diagnostic yield in diagnosing SVV or MVV in the absence of indications for a skin or renal biopsy. Further, the muscle biopsy can be used in place of the nerve biopsy for diagnosing vasculitis in patients with vasculitic neuropathy.

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1763

Tobacco Differentially Affects the Clinical-Biological Phenotype of ANCA-Associated Vasculitides at Diagnosis. Lucas Benarous[1], Benjamin Terrier[1], Bertrand Dunogué[2], Pascal Cohen[3], Xavier Puéchal[3], Claire Le Jeunne[3], Luc Mouthon[3] and Loïc Guillevin for the French Vasculitis Study Group[3]. [1]Cochin Hospital, Paris, France, [2]Hôpital Cochin, Paris, France, [3]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France.

Background/Purpose: Occupational and non-occupational exposures may play a role in the occurrence of ANCA-associated vasculitides (AAV) and affect their initial clinical-biological phenotype. Among these potential exposures, tobacco use could represent a factor that could influence AAV characteristics at diagnosis. However, these effects could differ according to the type of AAV, since granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) involve different pathophysiological mechanisms.

Methods: AAV patients entered in the FVSG database with available information on previous and current smoking habits were analyzed. The clinical-biological phenotype at diagnosis was compared according to current tobacco use (current smokers) or not (including previous and never smokers).

Results: This analysis concerned 1165 patients (545 men and 620 women; mean age of 52.8±16.1 years). AAV diagnoses were: GPA for 583 (50%), MPA for 256 (22%) and EGPA for 326 (28%). Among them, 973 patients (84%) were never smokers, 116 (10%) were previous smokers and 76 (6%) were current smokers. Among GPA patients, current smokers (n=55), compared to non-current smokers (n=528) respectively, were younger (44.5±13.5 vs. 52.0±16.3, P=0.0001), more frequently men (64 vs. 48%, P=0.016) and had more frequent cutaneous involvement (50 vs. 32%, P=0.025), and tended to have more frequent arthralgias (67 vs. 54%, P=0.11) and less frequent constitutional symptoms (33 vs. 47%, P=0.08) and ear, nose & throat (ENT) involvement (73 vs. 83%, P=0.13). BVAS, PR3-ANCA–positivity and inflammatory parameters were similar for the 2 groups. Among EGPA patients, current smokers (n=15), compared to non-current smokers (n=311) respectively, were also younger (41.1±15.8 vs. 50.3±15.2, P=0.028) and had less frequent constitutional symptoms (29 vs. 62%, P=0.02), arthralgias (7 vs. 35%, P=0.04), renal involvement (0 vs. 26%, P=0.025) and MPO-ANCA–positivity (0 vs 30%, P=0.02). BVAS and inflammatory parameters were comparable for the 2 groups. Finally, analysis of MPA patients was impossible because only 6 (2%) were current smokers.

Conclusion: These results suggest that tobacco use could differentially affect GPA and EGPA clinical-biological phenotypes, while no conclusion can be drawn for MPA. Moreover, they support the role of environmental exposures in AAV development and its phenotype.

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Clinical and Other Differences Observed Between Cocaine Induced and Non-Cocaine Induced Anti-Neutrophil Cytoplasmic Antibody Positive Vasculitis. Santhi Penmetsa[1], N. Suzanne Emil[2], Joshua Duchesne[1], Wilmer Sibbitt Jr.[3], Arthur Bankhurst[4] and Roderick Fields[5]. [1]University of New Mexico Health sciences center, Albuquerque, NM, [2]Presbyterian Medical Group, Rio Rancho, NM, [3]University of New mexico health sciences center, Albuquerque, NM, [4]University of NM Med Ctr, Albuquerque, NM, [5]University of New Mexico health Sciences center, Albuquerque, NM.

Background/Purpose: Objective: To compare various factors including clinical manifestations, laboratory data and mortality in between two groups of patients with anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis: with cocaine use and without cocaine use. The goal of this study is to evaluate clinical differences and similarities between these two groups as there are no previous studies per literature review. This also may help clinicians to better understand these two disease processes and to further aid in diagnostic and management approaches.

Methods: Adult patients with a diagnosis of ANCA positive vasculitis between 2000 and 2012 were selected and a total 46 patients were included in this study of which 22 Patients were cocaine users (age range 26–61) and 24 patients (age range 17–80) with no history of cocaine use. Clinical manifestations, laboratory data, pertinent serology, skin biopsy and other diagnostic data were gathered and were analyzed in each category. Each of

these factors was compared between the Cocaine use and non-cocaine use group.

Results: Cocaine-associated ANCA positive vasculitis group had higher proportion of the patients with abnormal perinuclear ANCA (pANCA) (86% vs 66.7%, P=0.084), myeloperoxidase (MPO), (100% vs 66%), abnormal both MPO and proteinase 3 (PR3) antibodies (32% vs 4.2%, P=0.015) compared with non-cocaine use group. This group also has higher concentrations of anti- phospholipid antibodies (50% vs 4%) compared to non-cocaine use group. Skin lesions were significantly more frequent in cocaine use group (81.8% vs 33.3%, P=0.0009) with female sex preponderance for facial lesions. Pulmonary renal involvement and complications as well as mortality (12.5% vs none) were higher in non-cocaine use group compared to cocaine associated vasculitis group.

Conclusion: ANCA positive vasculitis, the cocaine-associated and non-cocaine associated have their own distinctive clinical, laboratory and other diagnostic characteristics as well as complications. It is important for clinicians to be aware of these differences in order to recognize cocaine-associated ANCA positive vasculitis in high-risk populations since management and long term prognosis differ. More studies are needed to evaluate the significance of the presence of the related antibodies in pathogenesis, follow up and management of ANCA positive vasculitis with immunosuppressive therapy in long term.

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Comparison of Clinical Characteristics of Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis By the Serotype Specificity to Myeloperoxidase and Proteinase-3. Takamasa Murosaki, Takeo Sato, Yoichiro Akiyama, Katsuya Nagatani and Seiji Minota. Jichi Medical University, Tochigi, Japan.

Background/Purpose: To correlate the clinical characteristics of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with myeloperoxidase (MPO)-ANCA and proteinase-3 (PR3)-ANCA, and to detect clinical characteristics of AAV in Japanese patients.

Methods: The clinical data of AAV patients from 2005 to 2014 were retrieved retrospectively. AAV patients were divided into three subgroups: MPO single positive-AAV (MPO-AAV), PR3 single positive-AAV (PR3-AAV), and double positive AAV. The clinical diagnosis was based on the European Medicines Agency Algorithm along with pathological findings. The clinical characteristics of AAV such as age, sex, organ involvement, treatment, and prognosis were evaluated and compared between MPO and PR3-ANCA.

Results: Among 165 patients positive for ANCA, 77 patients were diagnosed with MPO-AAV, 13 with PR3-AAV, 4 with double positive AAV, and 71 with non-AAV. The clinical diagnosis of MPO-AAV included microscopic polyangiitis (MPA) in 55, granulomatosis with polyangiitis (GPA) in 15, and eosinophilic granulomatosis with polyangiitis (EPGA) in 8. PR3-AAV included 10 GPA, 2 MPA, and 1 EGPA. All patients with double positive AAV were diagnosed with MPA. Patients PR3-AAV were younger than those with MPO-AAV (median age 70 vs. 55 years old, P=0.006). Involvement in the eyes (46.2% vs. 6.5%, P < 0.001), nose (53.8% vs.19.4%, P = 0.013), and ears (61.5% vs. 23.4%, P = 0.009) was higher in PR3-AAV. There was no difference in gender ratio or involvement in other organs between MPO and PR3-AAV. In both MPO and PR3-AAV, the respiratory system was most frequently involved (83.1% vs. 76.9%). The respiratory involvement in MPO and PR3-AAV included interstitial pneumonia (49.4% vs. 7.7%, P=0.004), nodular shadow (7.8% vs. 53.8%, P<0.001), alveolar hemorrhage (3.9% vs. 7.7%, P=0.47), and bronchitis (12.9% vs. 0%, P=0.191). All AAV patients except one with MPO-AAV were treated with glucocorticoid, and immunosuppressant was added as initial remission induction therapy in 20.8% and 46.2% of the patients with MPO- and PR3-AAV, respectively. In 58.4% and 23.0% of the patients with MPO- and PR3-AAV, respectively, glucocorticoid alone was sufficient for disease-activity suppression, however, in 20.8% and 30.8% of the patients with MPO- and PR3-AAV, respectively, additional immunosuppressant was required during the course. During 2 years, the relapse rate in the patients with PR3- was higher than that in those with MPO-AAV (log-rank test, P=0.046), and COX hazard analysis revealed that PR3-ANCA showed a higher relapse rate (hazard ratio 2.54, 95% CI 0.974–6.605, P=0.057). There was no difference in the survival between patients with MPO- and PR3-AAV (log-rank test, P=0.931).

Conclusion: Unlike AAV patients in Western countries, MPO-AAV was predominant in Japan. The clinical characteristics were different between MPO and PR3-AAV. The involvement of the respiratory system was most frequent in both AAVs. In contrast to Western countries, alveolar hemorrhage was rare in Japanese, and in half of MPO-AAV patients, glucocorticoid alone was sufficient. Higher relapse rate in PR3-AAV than in MPO-AAV was similar to reports from Western countries.

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Comparison of Clinicopathologically- and Serologically-Based Classification Systems for ANCA-Associated Vasculitis. Sebastian Unizony[1], Eli M. Miloslavsky[1], Miguel Villarreal[2], Peter A. Merkel[3], Paul Monach[4], E. William St. Claire[5], Cees Kallenberg[6], David Ikle[2], Robert F. Spiera[7], Nadia Tchao[8], Deborah J. Phippard[8], Linna Ding[9], Carol A. Langford[10], Philip Seo[11], Gary S. Hoffman[12], John H. Stone[1] and Ulrich Specks[13]. [1]Massachusetts General Hospital, Boston, MA, [2]Rho, Chapel Hill, NC, [3]Vasculitis Center, University of Pennsylvania, Philadelphia, PA, [4]Boston University, Boston, MA, [5]Duke University School of Medicine, Durham, NC, [6]University of Groningen, Groningen, Netherlands, [7]Hospital for Special Surgery, New York, NY, [8]Immune Tolerance Network, Bethesda, MD, [9]NIAID, Bethesda, MD, [10]Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, OH, [11]Johns Hopkins Vasculitis Center, Johns Hopkins University, Baltimore, MD, [12]Center for Vasculitis Care and Research, Cleveland Clinic Foundation, Cleveland, OH, [13]Mayo Clinic, Rochester, MN.

Background/Purpose: Genome-wide association studies suggest that PR3-ANCA-positive ANCA-associated vasculitis (AAV) is genetically distinct from MPO-ANCA AAV. We evaluated patients enrolled in the RAVE trial according to ANCA type (PR3- versus MPO-ANCA) as opposed to disease type (granulomatosis with polyangiitis [GPA] versus microscopic polyangiitis [MPA]) to explore whether either classification predicts clinical course and response to treatment.

Methods: The RAVE trial randomized 197 patients to receive rituximab (RTX) or CYC followed by AZA (CYC/AZA) for remission induction. Demographics, clinical features, response to induction treatment, and disease flares were analyzed according to ANCA type and AAV diagnosis. Chi square, Fisher and Mann-Whitney tests were used for univariate analyses. Logistic regression was used for multivariate analyses.

Results: ***Demographic characteristics and baseline organ system involvement:*** Considerable overlap existed between ANCA type and AAV diagnosis with regard to patient demographics and clinical phenotype (Table 1). Patients with GPA and PR3 were younger, more often male, and had more constitutional, ocular and ENT manifestations compared to those with MPA and MPO. Renal disease was more common among patients with MPA and MPO..

Response to treatment: PR3-positive patients achieved complete remission (CR) at 6 months more frequently when treated with RTX (65%) than CYC/AZA (48%) (p = 0.04) (Table 2). Findings were consistent after adjustments for age, sex and new versus relapsing disease. No significant association between CR at 6 months and treatment allocation was seen for MPO patients. When stratified by AAV diagnosis, the proportion of patients in CR at 6 months was not significantly different between treatment arms. The difference in response to treatment was no longer seen at 12 and 18 months, by which time the effects of RTX had waned.

Disease relapse: A higher percentage of PR3 and GPA patients had experienced flares at 12 and 18 months than did their MPO and MPA counterparts. There were no differences in time to first flare.

Conclusion: PR3-positive patients were more likely to achieve CR at 6 months if treated with RTX than with CYC/AZA. This observation requires confirmation in future studies but supports the concept that classifying patients according to ANCA type rather than AAV diagnosis may be highly relevant to the choice of remission induction therapy. Patient demographics, clinical features, and disease relapse were similar when patients were stratified by either AAV diagnosis or ANCA type.

Table 1. Baseline characteristics

	ANCA type			AAV type		
	MPO (n = 66)	PR3 (n = 131)	p-value	MPA (n = 48)	GPA (n = 147)	p-value
Age	59	49.6	<0.01	61	50	<0.01
Sex						
Male	24 (36%)	76 (58%)	<0.01	18 (37%)	80 (54%)	0.04

Female	42 (64%)	55 (42%)		30 (63%)	67 (46%)	
Organs involved						
General	35 (53%)	93 (71%)	0.01	21 (44%)	105 (71%)	<0.01
Cutaneous	13 (20%)	34 (26%)	0.33	8 (17%)	38 (26%)	0.19
Mucous membranes/ eyes	9 (14%)	42 (32%)	<0.01	5 (10%)	46 (31%)	<0.01
Ear, nose, throat	22 (33%)	92 (70%)	<0.01	8 (17%)	106 (72%)	<0.01
Pulmonary	30 (46%)	74 (57%)	0.14	20 (42%)	83 (57%)	0.08
Renal	52 (79%)	77 (59%)	<0.01	40 (83%)	89 (61%)	<0.01
Serum creatinine	1.7	1.3	<0.01	1.8	1.3	<0.01
Neurologic	18 (27%)	21 (16%)	0.06	9 (19%)	28 (19%)	0.97
BVAS/WG at baseline	8.1	8	0.87	7.3	8.2	0.09

Table 2. Treatment response

	PR3			MPO		
ANCA type	**RTX (n = 66)**	**CYC/AZA (n = 65)**	**p-value**	**RTX (n = 33)**	**CYC/AZA (n = 33)**	**p-value**
CR at 6 months, number (%)	43 (65%)	31 (48%)	0.04	20 (61%)	21 (64%)	0.80
CR at 12 months, number (%)	31 (47%)	21 (32%)	0.09	16 (49%)	17 (52%)	0.81
CR at 18 months, number (%)	24 (36%)	19 (20%)	0.39	15 (46%)	13 (39%)	0.62
AAV type	**GPA**			**MPA**		
	RTX (n = 73)	**CYC/AZA (n = 74)**	**p-value**	**RTX (n = 24)**	**CYC/AZA (n = 21)**	**p-value**
CR at 6 months, number (%)	46 (63%)	37 (50%)	0.11	16 (67%)	15 (63%)	0.76
CR at 12 months, number (%)	33 (45%)	27 (37%)	0.28	14 (58%)	11 (46%)	0.39
CR at 18 months, number (%)	27 (37%)	23 (31%)	0.45	12 (50%)	9 (38%)	0.38

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Granulomatosis with Polyangiitis (Wegener's) According to Geographic Origin and Ethnicity: Clinical-Biological Presentation and Outcome. Benjamin Terrier[1], Christophe Deligny[2], Xavier Puéchal[3], Pascal Godmer[4], Pierre Charles[5], Gilles Hayem[6], Bertrand Dunogué[7], Pascal Cohen[3], Serge Arfi[8], Luc Mouthon[3] and Loïc Guillevin for the French Vasculitis Study Group[3]. [1]Cochin Hospital, Paris, France, [2]CHU Fort de France, Fort de France, France, [3]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [4]Department of Internal Medicine, Centre Hospitalier Bretagne Atlantique de Vannes, Vannes, France, [5]Institut Mutualiste Montsouris, Paris, France, [6]Hopital Bichat, Paris Cedex 18, France, [7]Hôpital Cochin, Paris, France, [8]Centre hospitalier Universitaire de Fort de France, Fort de France, Martinique.

Background/Purpose: Granulomatosis with polyangiitis (Wegener's) (GPA) is an ANCA-associated vasculitis (AAV) predominantly affecting small-sized vessels, involving mainly the upper and lower respiratory tracts and kidneys. Cytoplasmic labeling by ANCA directed against proteinase-3 (PR3) is associated with >80% of the systemic GPA forms. GPA mainly affects white Europeans (Caucasians/Hispanic), with mean age at diagnosis of 52 years. Recent data revealed an AAV genetic component in European patients. Rarely, GPA may also affect non-Europeans. This study aimed to describe GPA clinical-biological presentation and outcome in black sub-Saharan Africans and Afro-Caribbeans.

Methods: Among 915 GPA patients included in the FVSG database, geographic origin and ethnicity were known for 761. Clinical-biological presentations and outcomes of white Europeans vs black sub-Saharans and Afro-Caribbeans were analyzed.

Results: Among the 761 patients with available geographic origin and ethnicity, 690 (91%) were white Europeans and 22 (2.9%) were sub-Saharans (n=8) or Afro-Caribbeans (French West Indies, n=14). While sex ratios were similar for the 2 populations, sub-Saharans and Afro-Caribbeans, compared to white Europeans, were younger at GPA diagnosis (41.7±14.7 vs 52.1±16.0; P<0.001), had more frequent chondritis (19 vs 6%; P<0.05), central nervous system involvement (18 vs 4.3%; P<0.05), severe granulomatous manifestations [eg retroorbital tumor (9.1 vs 0.9%; P<0.05), subglottic stenosis (19 vs 2.2; P<0.01) and pachymeningitis (13.6 vs 1.6%; P<0.01)]. In contrast, sub-Saharans and Afro-Caribbeans had less frequent fever (20 vs 51%; P<0.05), weight loss (25 vs 51%; P<0.05), kidney involvement (38 vs 59%; P=0.07), cardiovascular involvement (0 vs 15%; P=0.06) and peripheral neuropathy (4.5 vs 22%; P=0.06), and their serum creatinine levels (70 vs. 175 μmol/L; P<0.01) and BVAS (12.3±7.2 vs 19.6±9.1; P<0.01) were significantly lower. Finally, relapse-free survival tended to be shorter for sub-Saharans and Afro-Caribbeans (median survival 44.8 vs 59.8 months), without reaching the significance [HR 1.75 (0.92–4.80); P=0.08]. Overall survival was similar for the 2 populations.

Conclusion: Our findings indicated different GPA clinical presentations in white Europeans vs sub-Saharans and Afro-Caribbeans, with blacks having more frequent severe granulomatous manifestations and less frequent constitutional symptoms, renal involvement and peripheral neuropathy. Prognoses did not differ according to geographic origin.

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Cardiac Involvement in Granulomatosis with Polyangiitis: A Magnetic Resonance Imaging Study of 31 Consecutive Patients. Grégory Pugnet[1], Xavier Puéchal[1], Benjamin Terrier[1], Hervé Gouya[2], Andre Kahan[3], Paul Legmann[2], Loïc Guillevin[1] and Olivier Vignaux[4]. [1]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [2]AP-HP Cochin Hospital, Department of Radiology B, Paris, France, [3]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [4]Cochin University Hospital, Paris, France.

Background/Purpose: Cardiac manifestations in granulomatosis with polyangiitis (GPA) patients are usually considered to be rare but may be life-threatening. However specific cardiac involvement in GPA is probably underestimated during life because many of these cardiac disturbances are subclinical. Contrast-enhanced cardiac magnetic resonance imaging (CMRI) may be a sensitive tool to detect and analyze cardiac involvement in ANCA associated vasculitis. The objective of our study was to assess the prevalence and patterns of cardiac abnormalities detected by cardiac magnetic resonance imaging in patients with GPA.

Methods: Thirty-one consecutive patients with either new or relapsing GPA underwent CMRI to determine morphological, functional, perfusion at rest and delayed enhancement abnormalities.

Results: At least one abnormality on CMRI was observed in 19/31 patients (61.3%). Four patients (14.8%) had an impaired left ventricle (LV) ejection fraction with evidence of clinically cardiac failure in two of them. LV kinetic abnormalities were found in 11 patients (36.7%). Myocardial delayed contrast enhancement (DCE) was detected in 9/31 patients (29%), 6 of whom with cardiac manifestations. DCE was mainly nodular (n = 7/9). Myocardial early contrast enhancement was detected in 5 of the 31 patients (16.1%) and was always associated with DCE in the same territory. CMRI detected pericarditis in 7 patients (22.6%). GPA of less than 18 months duration as compared with GPA of longer duration had greater LV ejection fraction (P=0.008) and less CMRI abnormalities (P=0.04), DCE (P=0.19) or LV hypokinesia (P=0.04). Patients who presented with new-onset GPA had less CMRI abnormalities than patients who experienced a relapse (P= 0.02).

Conclusion: CMRI is an accurate technique for diagnosing heart involvement in GPA and for analyzing precisely its mechanisms including inflammatory, microvascular and fibrotic components. This unique noninvasive information may have important clinical implications in early and accurate assessment of cardiac lesions in GPA patients but also to detect cumulative non reversible damage. Moreover, it may have prognostic implications.

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Abdominal Visceral Adipose Tissue Measured By DXA As a Novel Surrogate Marker of Cardiovascular Risk in Primary Necrotizing Vasculitides. Bertrand Dunogué[1], Karine Briot[2], Sami Kolta[3], Alexis Regent[4], Pascal Cohen[5], Alice Berezne[6], Xavier Puéchal[5], Claire Le Jeunne[5], Luc Mouthon[5], Christian Roux[7], Loïc Guillevin for the French Vasculitis Study Group[5] and Benjamin Terrier[8]. [1]Hôpital Cochin, Paris, France, [2]Paris Descartes University, Paris, France, [3]Paris Descartes University, Cochin

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Background/Purpose: Studies have shown a strong prevalence of cardiovascular events among patients with primary necrotizing vasculitides. Recent studies indicate that visceral adipose tissue (VAT) is highly associated with insulin resistance and cardiovascular events. Dual energy X-ray absorptiometry (DXA) is a validated technique able to accurately determine cross-sectionally the mass of discreet fat deposits.

Objective. To assess the relevance of abdominal adipose tissue measurement as potential surrogate markers for cardiovascular risk in patients with primary necrotizing vasculitides.

Methods: Patients with ANCA-associated vasculitides (AAN) and polyarteritis nodosa (PAN) seen in our department were prospectively included in an ongoing cross-sectional study assessing cardio-vascular complications and other sequelae (OSTEOVAS cohort). Alongside the evaluation of usual clinical and extra-clinical features associated with increased cardiovascular risk, DXA was performed to evaluate body composition and abdominal adipose tissue (subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT).

Results: Sixty-five patients were analyzed (38 females, mean age 50±18 years, mean disease duration of 85±79 months). Diagnoses were granulomatosis with polyangiitis (GPA) in 33 patients, microscopic polyangiitis in 6, eosinophilic GPA in 18, and PAN in 8. Five (7.7%) patients had developed cardiovascular complications. The median daily dose of corticosteroid was 5 mg/day (0–80). High cardiovascular risk defined by the NCEP-ATPIII was found in 11 (16.9%) patients. Using univariate analysis, cumulated dose of corticosteroids ($p=0.038$), Vascular Damage Index (VDI) ($p=0.008$), and VAT/SAT ratio ($p=0.009$) were significantly associated with high cardiovascular risk. Using multivariate analysis, VAT/SAT ratio remained independently associated with high-risk status [OR 1.07 (1.03–1.12), $p=0.004$]. VAT/SAT ratio was also independently correlated with an increased Framingham cardiovascular risk score ($p<0.01$).

Among factors correlated with a higher VAT/SAT ratio, we identified male gender ($p<0.0001$), age ($r=+0.31$, $p=0.014$), cumulated corticosteroid dose ($r=+0.26$, $p=0.048$), VDI score ($r=+0.26$, $p=0.04$), Body Mass Index ($r=+0.35$, $p=0.006$), waist circumference ($r=+0.56$, $p<0.0001$), and elevated troponin levels at time of assessment ($r=+0.36$, $p=0.007$).

Conclusion: This is the first study showing a significant association between a high VAT/SAT ratio assessed by DXA and cardiovascular risk in patients with primary necrotizing vasculitides. Abdominal adipose tissue seems to be an accurate and independent surrogate marker of cardiovascular risk in these patients.

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Increased Risk of Chronic Obstructive Pulmonary Disease in Granulomatosis with Polyangiitis: A General Population-Based Study. Neda Amiri[1], Mohsen Sadatsafavi[1], Eric C. Sayre[2], John M. Esdaile[3] and J. Antonio Avina-Zubieta[2]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada, Richmond, BC, [3]University of British Columbia, Department of Medicine, Division of Rheumatology, Vancouver, BC.

Background/Purpose: Chronic obstructive pulmonary disease (COPD) is increasingly recognized as an inflammatory condition. We aimed to identify the risk of newly recorded COPD among patients with incident GPA cases compared to the control population using a combination of physician billing codes and hospitalization data covering the entire province of British Columbia, Canada.

Methods: Our data includes all health professionals and hospital visits covered by the comprehensive provincial medical services plan (1990–2010) and all dispensed medication (1996–2010), for all BC residents.

We conducted a retrospective matched cohort study among new cases with GPA meeting a pre-defined criteria as follows: **a)** diagnosis of GPA (ICD-9-CM 446.4) in adults on at least two visits within a two-year period between 1996 and 2010 by a non-rheumatologist physician; **b)** diagnosis of GPA on at least one visit by a rheumatologist or from hospitalization; **c)** absence of a prior GPA diagnosis between January 1990 and December 1995 (to ensure incident GPA cases). Ten controls matched by birth year, sex and calendar year of follow-up were selected from the general population. Incident COPD cases were identified using a validated algorithm (first ICD-9-CM: 491, 492, 496, 493.2, or ICD-10-CM J43 or J44) from hospitals or death certificates. We estimated incidence rate ratios (IRRs) by comparing GPA cases with age-, sex- and entry-time-matched comparison cohorts. Multivariable Cox-regression models adjusting for confounders were also used. Sensitivity analyses were conducted to assess for unmeasured confounders (e.g. smoking).

Results: Among 512 patients with incident GPA, (mean age 57.7, 54% female) 34 developed COPD. This translated to a 20.25 incident rate (IR) per 1000 person-years in the GPA cohort compared to 4.10 IR / 1000 person-years in the control population. The age-, sex- and entry-time matched RR was significantly increased in the GPA cohort (**See table**). The risk of developing COPD was the highest in the first year following diagnosis of GPA (17 fold). The results also remained statistically significant after adjusting for the potential impact of unmeasured confounders (adjusted RRs ranging between 5.03 and 5.58 in all sensitivity analyses).

Conclusion: To our knowledge, this is the first general population-based study that shows a six-fold increase in risk of COPD in patients with GPA. The highest incidence of COPD in the first year following diagnosis supports the role of immune mediated inflammation in the pathogenesis of COPD.

Table: Risk of Incident COPD according to GPA Status

	GPA n = 512	**Non-GPA** n = 5,798
COPD cases, N	34	100
Incidence Rate/1000 Person-Years	20.25	4.10
Age-, sex-, and entry time-matched IRRs (95% CI)	**4.94 (3.24–7.36)**	**1.0**
< 1 year of disease duration	16.93 (8.05–36.49)	1.0
< 2 years of disease duration	11.21 (5.93–21.03)	1.0
< 3 years of disease duration	7.72 (4.40–13.26)	1.0
< 4 years of disease duration	6.77 (4.00–11.17)	1.0
< 5 years of disease duration	5.64 (3.42–9.06)	1.0
> 5 years of disease duration	3.95 (1.59–8.60)	1.0
Multivariable RR (95% CI)	**5.59 (3.31–9.43)**	1.0
Male	5.20 (2.48–10.9)	1.0
Female	6.22 (2.90–13.33)	1.0

Disclosure: N. Amiri, None; **M. Sadatsafavi**, None; **E. C. Sayre**, None; **J. M. Esdaile**, None; **J. A. Avina-Zubieta**, None.

1771

Arterial Thrombotic Events in Systemic Vasculitis. Alexander Tsoukas[1], Sasha Bernatsky[1], Lawrence Joseph[2], David Buckeridge[2], Patrick Belisle[3] and Christian A. Pineau[1]. [1]McGill University Health Centre, Montreal, QC, [2]McGill University, Montreal, QC, [3]Research Institute of the McGill University Health Centre, Montreal, QC.

Background/Purpose: To estimate the incidence rate of clinically apparent arterial thrombotic events and associated comorbidities in patients with primary systemic vasculitis.

Methods: Using large-cohort administrative data from Quebec, Canada, we identified all patients with vasculitis, including those with polyarteritis nodosa and granulomatosis with polyangiitis. Incident myocardial infarctions and cerebrovascular events after the diagnosis of vasculitis were ascertained longitudinally via billing and hospitalization data and compared to rates of a general population comparator group. The incidences of comorbidities (DMII, dyslipidemia, and hypertension) were also collected.

Results: Among the 836 patients identified with vasculitis, the myocardial infarction event rate was substantially higher in younger patients, with rates up to 268.1 events per 10,000 pt years [95% CI 67.1–1070.2] in males aged 18–45 with polyarteritis nodosa, approximately 30 times that seen in the age- and sex-matched control group. The cerebrovascular event rate was also substantially higher, particularly in adults aged 45–65 regardless of vasculitis type. All patient groups with vasculitis had elevated incidences of diabetes, dyslipidemia and hypertension compared to the general population.

Conclusion: Atherothrombotic event rates were elevated in patients identified as having primary systemic vasculitis. While incident rates of cardiovascular comorbidities were also increased, the substantial elevation in

myocardial infarctions seen in young adults suggests a disease-specific component which requires further investigation.

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Venous Thromboembolic Events in Eosinophilic Granulomatosis with Polyangiitis (EGPA). Chiara Baldini[1], Francesco Ferro[1], Nicoletta Luciano[1], Antonio Tavoni[2], Francesca Sernissi[1], Daniela Martini[1], Sara L'Abbate[1], Marta Mosca[3] and Stefano Bombardieri[3]. [1]Rheumatology Unit, Pisa, Italy, [2]Immunoallergology Unit, Pisa, Italy, [3]Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: Previous studies have documented an increased risk of venous thromboembolic events in patients with antineutrophil cytoplasmic antibodies (ANCA) associated vasculitides (AAV) as compared to healthy subjects. However, only a limited number of studies have analyzed the prevalence of thrombosis in eosinophilic granulomatosis with polyangiitis (EGPA).Aim of the study was to determine the frequency of venous thromboembolic events (VTE) in a single center cohort of patients with EGPA and to describe its relation with disease clinical manifestations and activity.

Methods: Patients diagnosed with EGPA (1990 ACR classification criteria) from 1994 to 2014 were included in the study. Data were retrospectively retrieved from patients' charts, including gender, demographic data, cumulative clinical features, ANCA status and BVAS at the baseline. In patients with VTE (i.e deep venous thrombosis and/or pulmonary embolism), EGPA characteristics and disease activity at the time of VTE occurrence were also collected. Categorical variables were compared using Fisher's exact test; continuous variables were compared using Student's t-test. A 2-tailed value of $p < 0.05$ was taken to indicate statistical significance.

Results: The systematic search of our database identified 89 patients, among whom 51 were included in the study. Median (IQR) age at the EGPA diagnosis was 59 (41–62.2) years and their M:F sex ratio was 1.04. During a median (IQR) follow-up of 72.2 (14.8–135.2) months, 6/51 (11.8%) EGPA patients presented at least one VTE. One patient presented 4 recurrent thromboses despite anticoagulant therapy; overall, then, 9 VTE were recorded. Lower-limb deep venous thromboses (DVTs) were the most common VTE manifestations, representing the 89% (8/9) of all the VTE in our series. One patients developed also a pulmonary embolism, while another presented a cardiac intra-ventricular thrombus. Six (67%) VTE occurred within 6 months before the EGPA diagnosis. The patient with recurrent thromboses presented 2 DVTs before the EGPA diagnosis and 2 further DVTs within 15 months after the EGPA diagnosis. The patient with the pulmonary embolism, developed the VTE 13 years after EGPA diagnosis concomitantly with a femoral neck fracture. According to our analysis, factors associated with the occurrence of VTE were renal involvement ($p=0.01$), nephrotic range proteinuria >3 g/24 h ($p = 0.03$) and a FFS>1 ($p=0.03$). No differences were observed regarding theANCA status and the BVAS score at the diagnosis between the groups.

Conclusion: The results of this study confirm a higher risk of VTE in patients with EGPA. The pathogenesis of thrombosis in EGPA calls for further studies.

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Otolaryngologic Lesions Are Not Rare and Closely Related with Pachymeningitis and Cranial Neuropathy in MPO-ANCA Associated Vasculitis. Takahiro Nunokawa, Naoto Yokogawa, Kota Shimada and Shoji Sugii. Tokyo Metropolitan Tama Medical Center, Tokyo, Japan.

Background/Purpose: Recently several case reports of serous otitis media (SOM), hypertrophic pachymeningitis (HP) and cranial neuropathy (CN) have been reported in connection with MPO-ANCA associated vasculitis (MPO-AAV). However, there are few clinical studies on the lesions. Herein, we address the frequency and the characteristics of these manifestations in patients with MPO-AAV.

Methods: This retrospective study focused on consecutive patients in whom MPO-AAV was diagnosed between 2003 and 2014 at Tokyo Metropolitan Tama Medical Center. We investigated their clinical and radiological profile by reviewing the medical records.

Results: A total of 111 patients with MPO-AAV were seen at the hospital in this period. There were 19 patients (17%) with at least one of the manifestations: SOM, HP, or CN. SOM was observed in 16 cases (14%), and constituted the first manifestation of the disease in 11 cases. HP and CN were seen in eight (7%) and seven (6%) patients, respectively. Of the patients presenting with SOM, seven patients had HP and/or CN (4 with HP and CN, 2 with CN, 1 with HP). Of three HP patients unassociated with SOM, CN was detected in one. There were no patients with isolated CN. Of the 11 patients examined by MRI, six patients demonstrated intense inflammation in the epipharynx. There was a significant difference in the rate of glomerulonephritis between the patients with the manifestations and those without them (32% vs. 73%; $P = 0.0006$). Furthermore, none of the patients with HP exhibited glomerulonephritis.

Conclusion: SOM is not a rare manifestation in MPO-AAV and often precedes other manifestations. There is a close relationship among SOM, HP and CN. Inflammation in the epipharynx might play a role as a pre-condition for the development of SOM and HP.

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Granulomatosis with Polyangiitis (Wegener's): Endoscopic Management of Tracheobronchial Stenosis - Results from a Multicenter Experience in 47 Patients. Benjamin Terrier[1], Agnes Dechartres[2], Charlotte Girard[3], Stéphane Jouneau[4], Jean-Emmanuel Kahn[5], Robin Dhote[6], Jean Cabane[7], Estibaliz Lazaro[8], Thomas Papo[9], Nicolas Schleinitz[10], Guillaume Le Guenno[11], Luc Mouthon[12] and Loïc Guillevin for the French Vasculitis Study Group[12]. [1]Cochin Hospital, Paris, France, [2]Hotel Dieu, Paris, France, [3]CHU, Lyon, France, [4]CHU, Rennes, France, [5]Internal Medicine, Foch Hospital, Suresnes, France, [6]Avicenne University Hospital, Bobigny, France, [7]Saint-Antoine, Paris, France, [8]CHU, Pessac, France, [9]Bichat Hospital, Paris, Paris, France, [10]APHM, marseille, France, [11]Internal Medicine department, Clermont-Ferrand, France, [12]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France.

Background/Purpose: Tracheobronchial stenosis (TBS) is noted in 12 to 23% in patients with granulomatosis with polyangiitis (GPA), and includes subglottic stenosis (SGS) and bronchial stenosis. The optimal systemic treatments and endoscopic interventions providing the best efficacy, and the best timing for such interventions, remain unclear, explaining why, in the 2010s, TBS remains a therapeutic challenge in the management of GPA patients.

Methods: To analyze the endoscopic management of TBS in GPA and to identify factors associated with the efficacy of endoscopic interventions, we conducted a French nationwide retrospective study that included 47 patients with GPA-related TBS. We also compared characteristics of GPA patients with TBS with GPA patients without TBS included in the French Vasculitis Study Group.

Results: Compared to patients without TBS, those with TBS were younger, more frequently female, and had less frequent kidney, ocular and gastrointestinal involvement and mononeuritis multiplex.

173 procedures were performed in 47 patients. Endoscopic procedures included 137 tracheal and 50 bronchial interventions, mainly endoscopic dilatation, local steroid injection and conservative laser surgery, and less frequently stenting. Per-endoscopic events were noted in only 5/173 cases (2.9%). After the first endoscopic procedure, cumulative incidence of endoscopic treatment failure was 49% at 1 year, 70% at 2 years and 80% at 5 years.

Factors significantly associated with a higher cumulative incidence of treatment failure were a shorter time from GPA diagnosis to endoscopic procedure [HR 1.08 (1.01–1.14); P=0.01] and a bronchial stenosis [HR 1.96 (1.28–3.00); P=0.002]. A prednisone dose ≥30 mg/day at the time of the procedure was associated with a lower cumulative incidence of treatment failure [HR 0.53 (0.31–0.89); P=0.02]. No difference was observed according to the immunosuppressive agents used.

Finally, 13 patients (28%) experienced recurrent bacterial bronchopulmonary infections as late complications of tracheobronchial involvement, fatal in 2 cases (4%).

Conclusion: TBS represent severe and refractory manifestations with high rate of restenosis. High-dose systemic corticosteroids at the time of the procedure and increased time from GPA diagnosis to bronchoscopic inter-

vention are associated with a better event-free survival. In contrast, bronchial stenoses are associated with a higher rate of restenosis than SGS.

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Predicting Relapse in Patients with Granulomatosis with Polyangiitis - the Potential Use of Monitoring *in Vitro* ANCA Production. Judith Land, Wayel H. Abdulahad, Coen A. Stegeman, Peter Heeringa and Abraham Rutgers. University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: Patients with granulomatosis with polyangiitis (GPA) suffer from frequent disease relapses, with up to 50% of patients relapsing within 5 years. Several risk factors for relapse have been described, such as persistent ANCA titers and *Staphylococcus aureus* nasal carriage. However, no method to predict a relapse in individual patients is currently known. Changes in measures that reflect the pathogenic process in the patient may be useful to improve relapse prediction in these patients.

Methods: Forty-nine patients with GPA were monitored for a period of 8–16 months, with 3–7 sampling moments for each patient. At each time point peripheral blood mononuclear cells were cultured in presence of CpG-oligodeoxynucleotides, B-cell activating factor and interleukin-21 for 12 days. Subsequently supernatants were analysed for PR3-ANCA by Phadia EliA, results being expressed in response units (RU), and production of total IgG was assessed by ELISA. Moreover, ANCA titers were determined by immunefluorescence. B cell phenotypes were analysed by using flow cytometry on whole blood stained for CD19, CD24, CD27 and CD38. With these markers percentages and total numbers of B cells were determined, and naive, transitional, memory and regulatory B cells were distinguished. Median values from the last measured time point before relapse were compared to non-relapsing patients. For non-relapsing patients the average value of all time points measured was used. All patients were also scored based on their inclusion sample and subsequently analyzed for differences in disease-free survival.

Results: During follow-up 12 patients relapsed. Patients that relapsed showed higher median values of *in vitro* PR3-ANCA (9.1 RU vs 2.2 RU) as well as higher ANCA titers compared to the non-relapsing patients. The higher levels of PR3-ANCA IgG were not a reflection of higher total IgG production, levels of IgG were in fact decreased in patients before relapse. Three patients relapsed directly after the inclusion sample, two of which showed >15 RU of *in vitro* PR3-ANCA. Of the remaining nine patients, six were positive for PR3-ANCA, and also showed an increase in this measure prior to relapse. Patients that had >2 RU of *in vitro* PR3-ANCA at inclusion showed lower disease-free survival, while no such difference was observed for ANCA titer or total IgG. The median percentages of memory and regulatory B cells, both CD24hiCD38hi and CD24hiCD27+, were lower in patients prior to relapse. However, no differences in disease-free survival were observed when patients were divided based on percentage at inclusion. When analyzing the absolute numbers of B cell subsets patients with low numbers of CD27+ memory B cells at inclusion were shown to be more prone to relapse.

Conclusion: This study shows a few promising factors to assist in the prediction of relapse in GPA patients, most notably *in vitro* ANCA production. Finding a better predictive factor for relapse in GPA would allow for timely intervention and possibly prevention of relapse in patients. Currently 80 PR3-ANCA positive GPA patients are being monitored with this method to strengthen these data.

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Factors Predictive of ANCA-Associated Vasculitis Relapse in Patients Given Rituximab-Maintenance Therapy. Benjamin Terrier[1], Christian Pagnoux[2], Guillaume Geri[1], Alexandre Karras[3], Chahéra Khouatra[4], Olivier Aumaitre[5], Pascal Cohen[6], Francois Maurier[7], Olivier Decaux[8], Hélène Desmurs-Clavel[9], Pierre Gobert[10], Thomas Quemeneur[11], Claire Blanchard-Delaunay[12], Pascal Godmer[13], Xavier Puéchal[6], Luc Mouthon[6] and Loïc Guillevin for the French Vasculitis Study Group[6]. [1]Cochin Hospital, Paris, France, [2]University of Toronto, Toronto, ON, [3]Hôpital Européen Georges Pompidou, APHP, Paris, France, [4]CHU Louis Pradel, Lyon, Lyon, France, [5]CHU, Clermont-Ferrand, France, [6]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [7]Department of Internal Medicine, Metz, France, [8]Rennes University Hospital, Rennes, France, [9]University of Lyon, LYON, France, [10]Centre Hospitalier d'Avignon, Avignon, France, [11]CH, Valenciennes, France, [12]Hôpital de Niort, Niort, France, [13]Department of Internal Medicine, Centre Hospitalier Bretagne Atlantique de Vannes, Vannes, France.

Background/Purpose: Rituximab (RTX) was shown to be as effective as cyclophosphamide to induce remission in patients with ANCA-associated vasculitis (AAV). The prospective MAINRITSAN trial compared RTX to azathioprine (AZA) to maintain AAV remission after a corticosteroid-and-cyclophosphamide induction regimen. Patients were randomly assigned to receive 500-mg RTX infusions on D1, D15 and 5.5 months later, then every 6 months until 18 months, or AZA for 22 months (initial dose: 2 mg/kg/d). Trial results demonstrated that RTX was superior to AZA at maintaining AAV remission during the planned 28 months of observation. Extended follow-up showed that late relapses could occur in RTX-treated patients. In this follow-up study, we analyzed these relapses occurring after RTX-maintenance therapy, aiming to identify factors predictive of them.

Methods: For the 57 patients randomized to the RTX arm, data on their relapses were recorded during the 28-month trial and extended follow-up, and factors predictive of relapse were identified with univariate and multivariate analyses.

Results: Fifty-six patients (men 64%; mean age 54±13 years) were analyzed, with median follow-up at 50 months. Fifteen (26%) patients experienced at least 1 major relapse after a median of 40 (range 8–52) months. Three relapses occurred during the 28-month trial, while 12 relapses occurred during extended follow-up. According to univariate analysis, relapse-associated factors were: granulomatosis and polyangiitis (Wegener's) diagnosis [HR 5.39 (0.70–41.5), P=0.11], proteinase-3 (PR3)-ANCA at AAV diagnosis [HR 6.29 (0.82–48.2), P=0.08], glomerular filtration rate <60 mL/min [HR 0.43 (0.14–1.36), P=0.15], and persistent ANCA-positivity 6 months [HR 2.21 (0.80–6.12), P=0.13] and 12 months [HR 4.45 (1.60–12.4), P<0.01] after starting maintenance therapy. Multivariate analysis retained the following factors as being significantly associated with relapse: PR3-ANCA–positivity [HR 12.5 (1.47–106), P=0.02] and persistent ANCA-positivity at 12 months [HR 7.79 (2.51–24.2), P<0.01]. The 50-month cumulative relapse rates were 82.5, 23.4 and 0%, respectively, for patients with PR3-ANCA and ANCA positivity at 12 months, patients with PR3-ANCA and negative ANCA at 12 months, and those with myeloperoxidase-ANCA.

Conclusion: A quarter of AAV patients who received RTX-maintenance therapy experienced late relapses during extended follow-up. Factors predictive of relapse for these patients were PR3-ANCA–positivity and persistent ANCA positivity 12 months after starting maintenance therapy. Our findings suggest that pursuing RTX-maintenance therapy in these patients could be beneficial to prevent relapses.

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***Staphylococcus Aureus* Nasal Carriage and Relapses, Bvas, ANCA-Positivity and Cotrimoxazole Use in ANCA-Associated Vasculitis.** Boun Kim Tan[1], Yoann Crabol[1], Jason Tasse[2], Frederic Laurent[2], Xavier Puechal[3], Christine Vinter[4] and Loïc Guillevin[1]. [1]Hôpital Cochin, University Paris V Descartes, Paris, France, [2]International Centre for Research in Infectious Diseases, Lyon, France, [3]French Vasculitis Study Group (FVSG), Paris, France, [4]Hôpital Cochin, Paris, France.

Background/Purpose: *Staphylococcus aureus* (SA) nasal carriage has been reported to be more frequent and associated with persistent ANCA-positivity and relapse in patients with granulomatosis with polyangiitis (GPA). Antibiotics, including cotrimoxazole (CTX), usually active against SA, have been shown to prevent relapses in some GPA patients. Nasal

carriage of SA and its small colony variants (SCV; intracellular SA with altered virulence phenotypes involved in chronic recurrent infection models) is unknown, respectively, during other ANCA-associated vasculitides (AAV), and those AAV and GPA.

Methods: All consecutive patients (09/2012–05/2013) with GPA, eosinophilic granulomatosis with polyangiitis (EGPA) or microscopic polyangiitis (MPA), followed at the French National Vasculitis Referral Center, and hospitalized patients, without vasculitis or specific risk factors for SA carriage (controls), were enrolled. All had bilateral anterior nasal swab cultures and SA-carriage frequencies were determined for each group. The French National Reference Center for Staphylococci identified the strains. Associations between SA nasal carriage and clinical manifestations, Birmingham Vasculitis Score (BVAS)-assessed disease activity, ANCA or C-reactive protein (CRP) level, and CTX impact on SA nasal carriage and BVAS were analyzed.

Results: A total of 119 AAV (GPA, n=80; EGPA, n=28; MPA, n=11) patients and 28 controls were enrolled. SA nasal carriage among the 3 AAV groups did not differ: 24 (30%) GPA, 8 (28.6%) EGPA and 3 (27.3%) MPA (P=0.971). Controls had non-significantly less frequent SA carriage (13.8%; P=0.39). SA-SCV phenotypes were identified in samples from 5/24 (20.8%) GPA, 1/8 (12.5%) EGPA and 2/3 (66.7%) MPA patients. SA nasal carriage was not significantly associated with number of prior relapse (P=0.866), BVAS (P=0.724), ANCA-positivity (P=0.657) or CRP level (P=0.340) for AAV, or GPA prior relapses (P=0.971) or BVAS (P=0.485). However, CTX use (usually as prophylaxis) was associated with a lower BVAS (P=0.029) and tended to be associated with a lower SA nasal carriage rate [9/43 (20.9%) patients on CTX vs 25/71 (35.2%) not on CTX; P=0.09].

Conclusion: Based on our results, SA nasal carriage did not differ among the AAV considered but seemed more frequent than in controls. Notably, CTX use, but not SA carriage, was associated with a lower BVAS and might reflect its intrinsic antiinflammatory rather than antimicrobial activity. Further bacterial analyses are needed to determine SA-strain susceptibility to CTX and identify known epidemic SA clones among those isolated from AAV carriers.

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Rituximab Versus Azathioprine for ANCA-Associated Vasculitis Maintenance Therapy: Impact in Health-Related Quality of Life. Grégory Pugnet[1], Christian Pagnoux[2], Alexandre Karras[3], Chahéra Khouatra[4], Olivier Aumaître[5], Pascal Cohen[1], Francois Maurier[6], Olivier Decaux[7], Jacques Ninet[8], Pierre Gobert[9], Thomas Quemeneur[10], Claire Blanchard-Delaunay[11], Pascal Godmer[12], Xavier Puéchal[1], Pierre-Louis Carron[13], Pierre-Yves Hatron[14], Nicolas Limal[15], Mohamed Hamidou[16], Eric Daugas[17], Thomas Papo[18], Bernard Bonnotte[19], Alfred Mahr[20], Benjamin Terrier[1], Philippe Ravaud[21], Luc Mouthon[1] and Loïc Guillevin[1]. [1]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [2]University of Toronto, Toronto, ON, [3]Hôpital Européen Georges Pompidou, APHP, Paris, France, [4]CHU Louis Pradel, Lyon, Lyon, France, [5]Division of internal Medicine, Centre Hospitalier Universitaire, Hôpital Gabriel Montpied, Clermont–Ferrand, Clermont–Ferrand, France, [6]Department of Internal Medicine, Metz, France, [7]Rennes University Hospital, Rennes, France, [8]Department of Nephrology and Internal Medicine, Hôpital Edouard Herriot, Lyon, France, Lyon, France, [9]Centre Hospitalier d'Avignon, Avignon, France, [10]CH, Valenciennes, France, [11]Hôpital de Niort, Niort, France, [12]Department of Internal Medicine, Centre Hospitalier Bretagne Atlantique de Vannes, Vannes, France, [13]Centre Hospitalier de Grenoble, Grenoble, France, [14]CHU Lille, Lille, France, [15]Hôpital Henri Mondor, APHP, Creteil, France, [16]CHU Hôtel Dieu, Nantes, Nantes, France, [17]AP-HP Hôpital Bîchat, Paris, France, [18]Bichat Hospital, Paris, Paris, France, [19]INSERM UMR 1098, Besançon; University of Burgundy, Faculty of Medicine, IFR100; Department of Internal Medicine and Clinical Immunology, Dijon, France, [20]Hospital Saint-Louis, University Paris 7, Paris, France, [21]AP-HP Cochin Hospital, Paris, France.

Background/Purpose: A key goal in the management of ANCA-Associated Vasculitis (AAV) is to improve and preserve health-related quality of life (HRQOL). Several studies have found that patients with AAV have reduced HRQOL. We conducted a non-blinded, randomized–controlled, remission-maintenance trial (MAINRITSAN) to investigate the effects of rituximab versus azathioprine for AAV maintenance therapy on health-related quality of life.

Methods: In the phase III MAINRITSAN study, once complete remission was obtained for eligible patients (18–75 years old) with a combined glucocorticoid and pulse cyclophosphamide, 115 patients with newly diagnosed (2/3 of the enrolments) or relapsing (1/3) AAV, who fulfilled the American College of Rheumatology classification criteria(5) and/or the Chapel Hill Consensus Conference definition classification for AAV (6), were enrolled and randomly assigned, at a 1:1 ratio, to receive a 500-mg rituximab (RTX) infusion on D1, D15, 5.5 months later, then every 6 months for a total of 5 infusions over 18 months, or azathioprine (AZA) maintenance therapy for 22 months at the initial dose of 2 mg/kg/d. Mean changes every 3 months in SF-36 and HAQ from baseline to month 24 were analyzed. ClinicalTrials.gov, http://clinicaltrials.gov/, NCT00748644.

Results: Mean improvements in HAQ, from baseline to month 24 were statistically significantly greater in the rituximab group (−0.16 points) than in the control group (P = 0.038). As demonstrated by SF-36, baseline HRQOL in study patients was significantly impaired compared with age- and gender-matched US norms. At month 24, mean changes from baseline in SF-36 PCS scores trended to be greater in rituximab group (−3.95 points, P = 0.067) but surprisingly mean changes from baseline in SF-36 MCS were statistically significantly greater in azathioprine group (−4.23 points, P = 0.041).

Conclusion: Rituximab treatment to maintain AAV remission in the MAINRITSAN trial resulted in statistically significant but maybe not clinically meaningful improvement in physical functions.

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Plasmapheresis Therapy in ANCA-Associated Vasculitides: A Single-Center Retrospective Analysis of Renal Outcome and Mortality. David Solar-Cafaggi, Yemil Atisha-Fregoso and Andrea Hinojosa-Azaola. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

Background/Purpose: ANCA-associated vasculitides (AAV) are rare, potentially fatal diseases with multiorgan involvement. Evidence for the use of plasmapheresis (PLEX) in patients with severe forms of AAV is limited and its long-term benefits on mortality and renal outcome are still unclear. The aim of our study was to evaluate renal outcome and mortality in clinical ground of AAV patients undergoing PLEX.

Methods: Retrospective study of patients with Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) and positivity for MPO or PR3-ANCA antibodies attended at our center from 2000 to 2012. In 25 patients, PLEX was added to conventional therapy (high-dose steroids plus one or more immunosuppressants); they were compared with 25 patients treated only with conventional therapy without PLEX, matched for age (± 7 years), activity of disease (BVAS/GW, range ± 6) and glomerular filtration rate (GFR) (MDRD range ± 16 ml/min) at the time of intervention. Demographic data, comorbidities, clinical and laboratory characteristics were recorded. Outcome variables were mortality, dialysis dependence and GFR at 12 months. Statistics: Descriptive statistics, Student T-test, Mann-Whitney U-test, Chi-square, Fisher exact test, McNemar's test and Kaplan-Meier survival analysis, log-rank test, $p<0.05$.

Results: Patients were mainly female (56%) and GPA (78%), mean age 47 years and BVAS/GW of 13. The only basal differences between patients with and without PLEX were more positivity for anti-PR3 (p=0.02), more frequency of methylprednisolone pulses ever (p=002) and lower accrued doses of CYP (p=0.01) in patients with PLEX. Main indication for PLEX was glomerulonephritis (96%).

At the time of intervention more patients in the PLEX group were on dialysis (p=0.02) and received concomitant methylprednisolone pulses (p=0.02) compared to patients without PLEX. At 12 months, both groups showed improvement in GFR before and after intervention (18.3±13.7 and 43.2±37.4 ml/min, p=0.001 in PLEX group; 23.5±14.5 and 39.6±25.1 ml/min, p=0.001 in conventional therapy group), but no difference was found between groups (p=0.85). No

differences were found in dialysis dependence between groups at 12 months (p=0.49), but more patients that completed one year of follow-up and were on dialysis at the time of intervention were free of dialysis at 12 months in the PLEX group (68% vs 32%, p=0.01) compared to patients without PLEX (20% vs 20%, p=1.0). Patients in the PLEX group presented more frequency of severe infections during the first 3 months (p=0.04). Survival at 12 months was 80% in the PLEX group and 96% in the conventional therapy group, with no differences in survival at outcome between groups (p=0.13, log-rank). Infection was the main cause of death in both groups.

Conclusion: In our population with AAV, both PLEX and conventional therapy improved renal function after the intervention, but no differences were found in dialysis dependence between groups at 12 months. Survival was similar in patients with and without PLEX, and infections were the main cause of death.

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1780

Outcomes of Triple Therapy (Plasma Exchange, Cyclophosphamide and Systemic Corticosteroid) for Anti-Neutrophil Cytoplasm Antibody (ANCA)-Associated Vasculitis. Joanna Ueng[1], Katerina Pavenski[2] and Laurence Rubin[3]. [1]University of Toronto, Toronto, ON, [2]St. Michael's Hospital, Toronto, ON, [3]St. Michael Hospital, Toronto, ON.

Background/Purpose: Microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and Churg-Strauss Syndrome (CSS) are syndromes known as ANCA-associated vasculitis (AAV). In addition to immunosuppressive therapy, plasma exchange (PLEX) may be indicated in patients with pulmonary hemorrhage and/or severe renal insufficiency. However, PLEX may be associated with serious adverse effects such as infection. The objective of this study was to characterize and examine outcomes in patients with AAV treated with PLEX, in addition to corticosteroid and cytotoxic agents, at a major referral centre for PLEX.

Methods: A retrospective chart review was performed on all patients with AAV treated with PLEX at a major referral centre for PLEX between January 1, 2002 to May 31, 2012. Patients with GPA, MPA, CSS, systemic p-ANCA vasculitis, and systemic c-ANCA vasculitis were included while those with incomplete 3 and 12 month follow-up were excluded. Demographic, clinical, laboratory, and radiographic data from electronic and paper medical records were collected. Acute kidney injury (AKI) was defined as an increase in serum creatinine by ≥26.5 umol/L within 48 hours, or a ≥1.5 times increase above baseline serum creatinine within 7 days. Disease activity was assessed by the Birmingham Vasculitis Activity Score (BVAS) (v.3). Primary outcomes were survival at 1 year, dialysis dependence at 1 year, and dialysis dependence at 3 months from initiation of PLEX. The study was approved by the institution's Research Ethics Board.

Results: Forty-nine patients with AAV were treated with PLEX during the study period. Outcomes are reported for 43 patients, which excludes 4 patients lost to follow up and 2 patients with 3 and 12 month follow up that occurred outside the study period. 58% were male, and the median age was 59 years (range 25–83). This was the first presentation of AAV for 60%. GPA, MPA, CSS, systemic p-ANCA vasculitis, and systemic c-ANCA vasculitis was the primary diagnosis in 39%, 28%, 0%, 5%, and 28% of patients. Both pulmonary hemorrhage and AKI were present in 66%. The mean BVAS (v.3) score at presentation was 17.9. Triple therapy with systemic corticosteroid, cyclophosphamide, and PLEX occurred in 90%. Survival at 1 year, dialysis dependence at 1 year, and dialysis dependence at 3 months was 88%, 28%, and 37%, respectively. Renal recovery amongst those who were dialysis-dependent at presentation was 37% and 47% at 3 months and 1 year, respectively. Infection, bleeding (non-pulmonary hemorrhage), symptomatic hypotension, and catheter-related thrombosis occurred in 44%, 20%, 5%, and 2% of patients.

Conclusion: With triple therapy, 88% of patients with AAV survived at least 1 year. Almost 50% of patients who were dialysis-dependent on presentation experienced renal recovery after 1 year. An international randomized controlled trial is currently underway to investigate the specific role of PLEX in the treatment of AAV.

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1781

Long-Term Outcomes Among Patients with Renal Disease Secondary to ANCA-Associated Vasculitis: Temporal Trends over 25 Years. Rennie L. Rhee[1], Susan L Hogan[2], Caroline J. Poulton[2], Julie Anne G. McGregor[2], J. Richard Landis[1], Ronald Falk[2] and Peter A. Merkel[3]. [1]University of Pennsylvania, Philadelphia, PA, [2]UNC Kidney Center, Chapel Hill, NC, [3]Vasculitis Center, University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Significant advances have been made in the diagnosis and treatment of patients with ANCA-associated vasculitis (AAV). However, little is known about how these advances have changed long-term outcomes especially among patients with renal involvement. The objective of this study was to examine temporal changes of long-term outcomes, including the impact of early diagnosis and duration of cyclophosphamide use in AAV.

Methods: An inception cohort of patients with AAV from the Glomerular Disease Collaborative Network diagnosed from 1985 and 2009 was evaluated. All patients had a positive test for ANCA and a renal biopsy consistent with AAV. Patients were categorized into 5-year time periods based on year of diagnosis. The primary outcome was occurrence of end-stage renal disease (ESRD) or death in 5 years; secondary outcome was occurrence of relapse in 5 years. Kaplan-Meier estimates, Cox proportional hazard models, and linear contrasts were used for analysis. Models were adjusted for age, sex, race, diagnosis (granulomatosis with polyangiitis, microscopic polyangiitis, or renal-limited vasculitis), ANCA type (C/PR3 or P/MPO), site (tertiary care or community practice), duration of disease before biopsy, extra-renal organ involvement, and serum creatinine (SCr) at time of diagnosis. In a subgroup of patients with no event by 12 months, duration on cyclophosphamide (CYCdur, months) up to 12 months was also included.

Results: Data was available on 568 patients who met the inclusion criteria. Across the 5 time periods, there were no significant differences in baseline characteristics or duration of follow-up; however, over time increasing proportions of patients were managed in a tertiary care center and baseline SCr decreased (**Table**). There was a decreasing 5-year risk of ESRD or death across the time periods and an increasing 5-year risk of relapse, p for trend $<$ 0.001 (**Figure**). After adjustment for baseline characteristics, the risk of relapse was similar between the time periods (p for trend = 0.698) but the risk of ESRD or death continued to decrease over time (p for trend = 0.008). SCr was the only significant predictor of decreasing risk of ESRD or death (HR 1.14, 95% CI 1.08–1.21, P<0.001) while CYCdur was not associated with risk of ESRD or death.

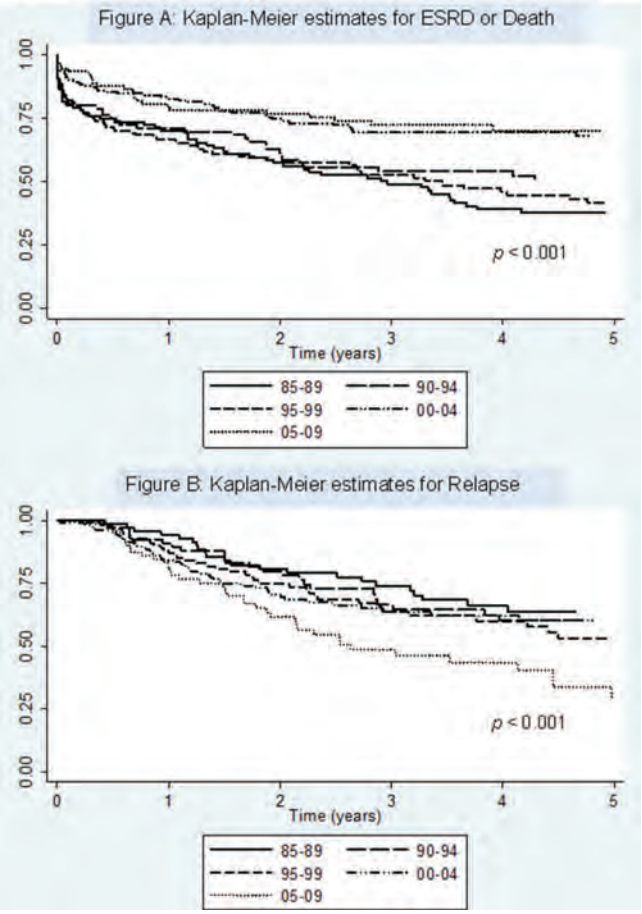
Conclusion: In patients with AAV, over 25 years, the risk of ESRD or death decreased and the risk of relapse has not changed. A lower SCr at diagnosis, a potential marker of earlier disease detection, is the strongest predictor of improvement in risk of ESRD or death.

Table: Patient characteristics at diagnosis

Characteristic	All	Time Period 85–89	90–94	95–99	00–04	05–09	*p*-value for trend
N	568	88	81	136	172	91	—
Median age, years (IQR)	60 (46–71)	61 (18–70)	61 (42–68)	64 (49–72)	58 (47–71)	58 (46–68)	0.32
Female, %	47%	47%	52%	46%	49%	42%	0.8
Race, %	85%	85%	84%	91%	84%	79%	0.17
White	9%	14%	10%	7%	8%	9%	0.61
Black	6%	1%	6%	1%	8%	12%	0.01
Other							
Diagnosis, %	20%	15%	21%	20%	20%	25%	0.62
GPA	55%	60%	49%	54%	56%	57%	0.68
MPA	24%	25%	30%	26%	24%	18%	0.48
RLV							
ANCA ELISA, %	41%	44%	35%	44%	41%	36%	
PR3/P	59%	56%	65%	56%	59%	64%	0.58
MPO/C							
Organ Involvement, %	50%	50%	41%	50%	52%	53%	0.49
Lung	41%	35%	35%	40%	44%	47%	0.39
Joint	35%	35%	28%	35%	33%	43%	0.43
Upper respiratory	22%	22%	26%	25%	19%	18%	0.52
Skin	11%	15%	16%	12%	8%	4%	0.08
GI	10%	14%	9%	15%	8%	7%	0.25
Neurologic	3%	6%	7%	2%	3%	0%	0.18
Muscle							
Mean serum creatinine, mg/dl (SD)	4.5 (3.5)	5.9 (4.1)	4.9 (3.7)	4.7 (3.4)	3.9 (3.2)	3.5 (2.6)	<0.001
Duration of follow-up, median months (IQR)	31 (11–66)	33 (5–68)	31 (7–72)	25 (7–48)	29 (14–91)	38 (11–55)	0.33
Tertiary care, % (vs community practice)	48%	31%	27%	41%	54%	82%	<0.001

**Test of significance for linear contrast of 5 time periods.
GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; RLV: renal-limited vasculitis.

Figure: Comparison of risk of ESRD or death (A) and relapse (B) in patients with ANCA-associated vasculitis across 5-year time periods



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1782

Long-Term Follow-up of Non-HBV Polyarteritis Nodosa and Microscopic Polyangiitis with Poor-Prognosis Factors. Maxime Samson[1], Xavier Puéchal[2], Hervé Devilliers[3], Pascal Cohen[2], Boris Bienvenu[4], Kim Heang Ly[5], Alain Bruet[6], Brigitte Gilson[7], Marc Ruivard[8], Edouard Pertuiset[9], Mohamed Hamidou[10], Benjamin Terrier[2], Christian Pagnoux[11], Luc Mouthon[2], Loic Guillevin[12] and The French Vasculitis Study Group (FVSG)[12]. [1]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France; Internal Medicine and Clinical Immunology, Dijon University Hospital, Dijon, France, [2]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [3]Department of internal medicine and systemic diseases, Dijon, France, [4]CHU Côte de Nacre, CAEN, France, [5]CHU Dupuytren, Limoges, Limoges, France, [6]Department of Nephrology and Internal Medicine, CH de Poissy Saint-Germain-en-Laye, Poissy, France, [7]Department of Nephrology and Internal Medicine, CH de Verdun, Verdun, France, [8]CHU Estaing, Clermont–Ferrand, Clermont–Ferrand, France, [9]René Dubos Hospital, Pontoise, France, [10]CHU Hôtel Dieu, Nantes, Nantes, France, [11]University of Toronto, Toronto, ON, [12]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France.

Background/Purpose: To study the long-term outcomes of 65 patients with non-HBV polyarteritis nodosa (PAN) or microscopic polyangiitis (MPA) enrolled in a prospective, randomized, open-label trial,[1] with Five-Factor Score (FFS)-defined poor-prognosis factors, focusing on survival, relapses, clinical and laboratory findings, therapeutic responses and sequelae.

Methods: Patients' data were updated in 2014. The new Chapel Hill criteria were applied to classify PAN and MPA. The following definitions were used: relapses: recurrence and/or new appearance of ≥1 vasculitis manifestation(s) after remission lasting ≥3 months; failure: no clinical remission with the assigned treatment. Times to relapse and/or death were calculated from treatment onset. For survival analyses, data were censored after 90 months of follow-up.

Results: Mean±SD overall follow-up was 65.6±47.5 months, comparable for PAN and MPA patients. For the 65 patients (41 MPA and 24 PAN), mean age at diagnosis was 55.3±17.0 years, mean Birmingham Vasculitis Activity Score 2003 23.7±8.8; FFS=1, 2 or ≥3 for 27, 30 or 8 patients, respectively; ANCA-positivity: 2 (8.3%) PAN (1 $cANCA^+$ and 1 $pANCA^+$, anti-myeloperoxidase [MPO]– and proteinase–3–negative) and 34 (82.9%) MPA ($pANCA^+$, 90.6% MPO-specific). Patients received 3 methylprednisolone pulses and corticosteroids (CS) and were randomized to receive 6 or 12 intravenous cyclophosphamide (CYC) pulses. After treatment, 53/65 (81.5%, 32 MPA and 21 PAN) entered remission. Treatment was intensified for the 12 nonresponders: 4 achieved remission and 8 died before remission. After remission, 25/57 (43.9%, 18 MPA, 7 PAN) patients relapsed 29.4±27.4 months after starting treatment. The respective 3-, 5- and 7-year overall survival rates were 79.5%, 72.3% and 64.4%, with no significant difference between PAN and MPA patients (p=0.241). Overall survival tended to be shorter for patients given 6 versus 12 CYC pulses (p=0.157). The respective 1-, 3- and 5-year relapse-free–survival rates were 84%, 68.4% and 52.4%, comparable for PAN and MPA patients. The relapse-free–survival difference between patients that received 6 versus 12 CYC pulses tended to decline during follow-up and was no longer significant at 90 months (p=0.07). At the last follow-up visit, 38/65 (58.5%) patients were still alive, 12/38 (31.6%) were still taking CS and 8/38 (21.1%) an immunosuppressant (IS). The mean vasculitis damage index score for the 57 patients with ≥1 remission(s) was 2.3±1.5, with the most frequent sequelae being hypertension (50%), chronic renal failure (creatininemia >150 μmol/L) (44.6%) and neuropathy (23.2%). Notably, 7 patients, all with MPA, progressed to end-stage renal failure and required chronic dialysis; 2 of them received kidney transplants.

Conclusion: For non-HBV PAN or MPA patients with FFS≥1 at diagnosis, overall survival at 7 years reached 64%. Relapses were frequent during long-term follow-up, even for patients who had received 12 CYC pulses at diagnosis, thereby confirming that PAN and MPA patients with FFS≥1 at diagnosis require post-remission maintenance therapy with an IS or biotherapy.

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1783

The Importance of Histopathological Classification of ANCA-Associated Glomerulonephritis in Renal Function and Renal Survival. Valeria Scaglioni[1], Marina Scolnik[1], Luis J. Catoggio[1], Carlos Federico Varela[2], Gustavo Greloni[2], Silvia Christiansen[3] and Enrique R. Soriano[1]. [1]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [2]Nephrology Service. Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Pathology Service. Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

Background/Purpose: Histological changes in renal biopsy are the gold standard for establishing the diagnosis of antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (GN). In 2010 a new histopatological classification for ANCA-associated GN (ANCA GN) was developed by an international working group of renal pathologist. The scheme divides ANCA GN into 4 categories: focal (≥50% normal glomeruli), crescentic (≥50% glomeruli with cellular crescents), mixed (<50% normal, <50% crescentic, <50% globally sclerotic glomeruli) and sclerotic (≥50% globally sclerotic glomeruli). It has been demonstrated that these categories at baseline correlate

strongly and independently with renal function at 1 and 5-years follow up.

Objective: The aim of this study was to determine whether the new histopathologic classification scheme is associated to changes in renal function and renal survival in a cohort of patients with ANCA associated vasculitis (AAV) who underwent kidney biopsy in a single center.

Methods: We included retrospectively all patients with diagnosis of ANCA GN between January 2002 and May 2013 and had at least 1 year of follow-up. Baseline date was defined as the date of the biopsy. Renal biopsies were reviewed and classified according to the new classification. Serum creatinine, estimated glomerular filtration rate (eGFR) at time of the biopsy, death, requirement of dialysis, use of immune suppression and plasmapheresis at follow up were recorded.

Results: Forty-four patients (77.2% females) were included (table 1). The mean age was 63.7 (SD:17.5). 25 (56.8%) patients were pANCA positive, 14 (31.8%) cANCA positive, and 5 (11.3%) were ANCA negative. Four patients died during first year of follow up (1 within each biopsy category). Among surviving patients, overall mean improvement in eGFR at 1 year was 13.2-ml/min/1.73 m^2. Age and sex were not significantly associated with the 1-year eGFR change. There was a significant difference in the mean change in eGFR at 1 year based on the histopathologic class (table 2). Focal biopsies were associated with the highest eGFR at presentation, whereas crescentic, mixed and sclerotic were associated with lower eGFRs. Crescentic class was associated with the greatest 1-year improvement in eGFR while sclerotic class did not show significant improvement.

Conclusion: Our study shows association between crescentic class and improvement in eGFR and association between sclerotic class and reduction in eGFR at 1-year. These results support the use of the histopathologic classification in determining renal prognosis of patients with ANCA GN.

TABLE 1

	Focal (n 11)	Crescentic n (14)	Mixed n (15)	Sclerotic n (4)	P
Age, mean (SD)	68.6 (15.4)	54.0 (16.9)	69.2 (15.3)	63.5 (24.5)	.25
Female, n (%)	10 (90.9)	9 (64.2)	12 (80.0)	3 (75)	
Baseline eGFR (mL/min/1.73 m^2), mean (IQR)	46.9 (12–78)	13.6 (9–17)	33.4 (20–53)	13.4 (6–17)	.0008
Baseline eGFR category (mL/min/1.73 m^2), n (%)					
≥ 90	2 (18)	0 (0)	0 (0)	0 (0)	
60–89	3 (27)	0 (0)	1 (7)	0 (0)	
30–59	2 (18)	0 (0)	5 (33)	0 (0)	
15–29	1 (9)	6 (43)	6 (40)	2 (50)	
< 15	3 (27)	8 (57)	3(20)	2 (50)	
ANCA immunofluorescence, n (%)					
cANCA	4 (36)	6 (43)	3 (20)	1 (25)	
pANCA	6 (55)	7 (50)	9 (60)	3 (75)	
Both negative	1 (9)	1 (7)	3 (20)	0 (0)	
BVAS at diagnosis, mean (SD)	14.8 (5.5)	16.7 (3.7)	13.4 (5.4)	12.7 (0.9)	.25
Treatments, n (%)					
Methilprednisolone	8 (66)	14 (100)	8 (53)	2 (50)	
Cyclophosphamide	9 (82)	13 (93)	12 (80)	2 (50)	
Rituximab	0 (0)	0 (0)	2 (13)	0 (0)	
Plasmapheresis	1 (9)	5 (36)	0 (0)	0 (0)	
Dialysis at diagnosis, n (%)	1 (9)	4 (29)	2 (13)	3 (75)	
Dialysis at 1 year, n (%)	0 (0)	1 (7.4)	0 (0)	2 (50)	

TABLE 2

Histologic class	n	Basal mean eGFR (mL/min/1.73 m^2), mean	1 year mean eGFR (mL/min/1.73 m^2), mean	Delta mean eGFR improvement (1year-basal)	Death within 1 year, n (%)
Focal	11	46.9	57.1	5.2*	1 (9.0)
Crescentic	14	13.6	49.7	35.8*#	1 (7.1)
Mixed	15	33.4	46.9	12.1#	1 (6.6)
Sclerotic	4	13.4	12	−1.5	1 (25)

* p=0.008; # p=0.026.

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1784

Prognostic Factors for Interstitial Lung Disease with Microscopic Polyangiitis. Takeshi Shoda, Tohru Takeuchi, Takaaki Ishida, Hideyuki Shiba, Youhei Fujiki, Daisuke Wakura, Shuzo Yoshida, Takuya Kotani, Shigeki Makino and Toshiaki Hanafusa. Osaka medical college, Osaka, Japan.

Background/Purpose: Many patients with interstitial lung disease (ILD) complicated by microscopic polyangiitis (MPA) show a UIP pattern on chest CT. The prognosis is poorer than that of ILD-free MPA(1). However, the details remain to be clarified.

To investigate the prognosis of pulmonary fibrosis with microscopic polyangiitis (MPA-ILD) and prognostic factors.

Methods: Of patients with MPA who were admitted to our hospital between 2001 and 2013 based on the EMEA classification in 2007, the subjects were MPO-ANCA-positive patients with ILD on HRCT. Using the clinical data and fibrosis score on HRCT(2), we examined prognostic factors.

Results: There were 42 patients with MPA-ILD, consisting of 20 males and 22 females, with a median age (interquartile range) of 73 years (range: 69–76 years). The MPO-ANCA, KL-6, Aa-DO2, %FVC, %DLco/VA, and RV/TLC values at the start of treatment were 189 (52–459) EU, 446 (261–615) U/mL, 25.7 (12–34), 81.3 (69–95)%, 61.4 (45–71)%, and 41.1 (33–50)%, respectively. Concerning HRCT images, 30 patients showed a UIP pattern, and 12 showed a non-UIP pattern. PSL was administered to 41 patients. In 37, it was combined with immunosuppressive drugs (CY was used in 16). In 8, apheresis was performed. In 37 patients, the MPO-ANCA level was maintained below the detection limit.

With respect to the prognosis, 8 patients died (exacerbation of interstitial pneumonia: 2, infection and alveolar hemorrhage: 2, pulmonary hypertension: 1, sudden death: 2, and renal failure: 1). The 5- and 10-year survival rates after the start of treatment were 81.6 and 68.0%, respectively.

Univariate analysis using Cox's proportional hazard model showed that prognostic factors for lung disease-associated death included the HRCT score ($p<0.001$), CPFE ($p=0.025$), and administration of CY ($p=0.041$). However, on multivariate analysis of these factors, the HRCT score was significantly correlated ($p=0.006$).

Conclusion: Treatment for MPA-ILD was continued, and the prognosis was more favorable than previously reported. Marked fibrosis and CPFE at the start of treatment were considered to be prognostic factors for lung disease-associated death. Immunosuppressive therapy early after onset may improve the prognosis of MPA-ILD.

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1785

Survival of Microscopic Polyangiitis (MPA) Patients with and without Pulmonary Fibrosis (PF). Lina María Saldarriaga Rivera, Natllely Ruiz and Luis F. Flores-Suarez. Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico.

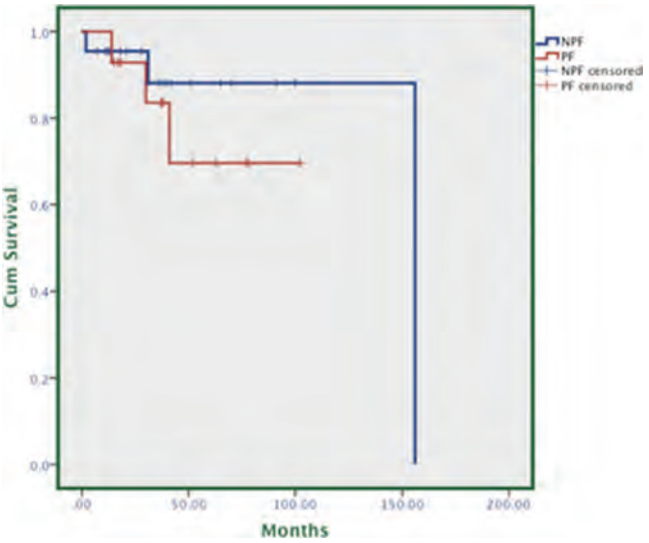
Background/Purpose: Pulmonary fibrosis (PF) occurs in up to 30% of patients with microscopic polyangiitis (MPA). Data suggest PF implies a higher mortality. We examined the survival of our MPA patients according to the presence or absence of PF.

Methods: Retrospective analysis of all MPA patients present in a single respiratory referral centre from 2003-present. All patients were defined according to the CHCC 2012 Nomenclature. Univariate analysis was used to establish proportions with means ± SD and medians calculated; bivariate analysis was used to compare groups, Student's t test for continuous variables and X^2 test with Yates correction for categorical variables. Kaplan-Meier analysis was done for survival. Significance was established when $p<0.05$.

Results: From 37 MPA patients (35 MPO-ANCA positive, 2 PR3-ANCA positive), the majority were females (67.5%); 15/37 (40.5%) had PF with equal gender distribution. Women were predominant in those without PF (77.2%, $p<0.05$). PF antedated other disease manifestations for more than a year in 14/15 PF patients. One developed it concurrently. The median survival of the group was 37 months (2–156). Myalgias were more frequent in those with PF (53.3% vs 18.2%), while hematuria (33.3 vs 56.5%), acute respira-

tory failure (6.7% vs. 36.7%) and lymphopenia (0 vs. 22.7%) were less frequent (all significant). Lung hemorrhage was more frequent in those without PF (68.2% vs 33.3%, p=0.08). No other significant differences in clinical or paraclinical variables were seen, being similar at disease onset in both groups. There were 6 deaths, 5 with and 1 without PF; 1 lost to follow-up patient without PF was censored as death for survival analysis. By 41 months, there is a trend for a better cumulative survival in patients without PF (88 vs 70%) (graph), irrespective of PF being present at onset or during disease evolution.

Conclusion: While we acknowledge the limitations of this study (sample size, need of longer follow-up), it suggests that patients with MPA and PF have a worst outcome than those without PF, even when patients without PF presented with more severe manifestations (respiratory failure, lung hemorrhage, renal symptoms). Interestingly the majority of these patients had PF antedating other MPA manifestations, probably due to referral bias. The influence of this mode of presentation and other factors in outcome is subject to further evaluation.



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1786

Vasculitis As Underlying Cause of Death in the United States: 1999 – 2010. Alicia Rodriguez-Pla[1], Paul A. Monach[2] and Jose Rossello-Urgell[3]. [1]Boston University, Boston, MA, [2]Vasculitis Center, Boston University School of Medicine, Boston, MA, [3]Baylor Institute for Immunology Research, Dallas, TX.

Background/Purpose: Current data on mortality rates of primary vasculitis, which were tradionally associated with a dreadful prognosis, are limited. Therefore, we aimed to estimate the mortality rates of the main primary vasculitis disorders using the most current publicly available mortality data in the USA.

Methods: To obtain mortality rates of vasculitis as the underlying cause of death, we used the CDC Wonder Underlying Cause of Death database and its query system, which contains data from 1999 to 2010. We used the following ICD-10 codes for the queries: D69.0 (Allergic purpura) for Henoch-Schonlein purpura, D89.1 (Cryoglobulinaemia), M30.0 (Polyarteritis nodosa), M30.1 (Polyarteritis with lung involvement [Churg-Strauss]) for eosinophilic granulomatosis with polyangiitis, M30.3 (Mucocutaneous lymph node syndrome [Kawasaki]), M31.0 (Hypersensitivity angiitis) for Goodpasture's syndrome, M31.3 (Wegener's granulomatosis) for granulomatosis with polyangiitis (GPA), M31.4 (Aortic arch syndrome [Takayasu]), M31.5 (Giant cell arteritis [GCA] with polymyalgia rheumatica [PMR]) and M31.6 (Other giant cell arteritis) for GCA, M31.7 (Microscopic polyangiitis), and M35.2 (Behcet's disease). Results were obtained by year, gender, and race. To obtain age-adjusted mortality rates we used year 2000 U.S. standard population. Mortality rates are given as number of deaths per million. Mantel-Haenszel chi-square was used to analyze trends.

Results: During the twelve-year period, vasculitis was the underlying cause of death of 7,888 patients. Age-adjusted mortality rate was 2.22 per million (95% CI: 2.17–2.27). There were more deaths in females (4,412) than in males (3,476), but the age-adjusted mortality rate was higher in males than in females (2.28 vs 2.16 per million). Age-adjusted mortality rate was clearly higher in Whites (2.34, 2.28–2.39) than in Black/African American population (1.19, 1.08–1.31). Regarding disease-specific mortality, GPA accounted for 51.2% of all vasculitis deaths. Interestingly, there were no deaths for GCA with PMR. Year 2000 showed the highest mortality (2.58, 2.40–2.77), whereas the lowest level was seen in 2008 (1.79, 1.64–1.94). Since 1999, there has been a significant trend to the decrease ($p<0.0001$).

Conclusion: The most current public data indicates that mortality by vasculitis remains very low, which is clearly related to the low incidence of these disorders. Age-adjusted mortality rate was higher in males and in White, which can be explained by the fact that GPA, which is more frequent in males and White, is responsible for half of the overall number of deaths. There is a clear trend to a progressive decrease of the mortality rates by primary vasculitis over the 12-year period of the study. Recent introduction of biological treatments, less toxic therapeutic regimens, such as shortening cyclophosphamide treatment, earlier diagnosis as a result of higher awareness and improved diagnostic tools may have presumably contributed to this decrease in mortality rates. Our findings should be taken with caution until quality studies to determine the reliability of the data about these rare diseases available in national databases are performed.

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***HLA-DRB1*01* Is Associated with Henoch- Schönlein Purpura in the Spanish Population.** Raquel López-Mejías[1], Fernanda Genre[1], Belén Sevilla Pérez[2], Santos Castañeda[3], Norberto Ortego-Centeno[2], Javier Llorca[4], Begoña Ubilla[1], Trinitario Pina Murcia[1], Vanesa Calvo-Rio[1], Ana Márquez[5], Luis Sala-Icardo[6], Jose A. Miranda-Filloy[7], Marta Conde-Jaldón[8], Lourdes Ortiz-Fernández[8], Juan María Blanco-Madrigal[9], Eva Galindez-Agirregoikoa[9], Francisca González Escribano[8], Javier Martin[10], Ricardo Blanco[11] and MA González-Gay[1]. [1]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, [2]Medicine Department, Hospital Universitario San Cecilio, Granada, Spain, [3]Hospital Universitario de La Princesa, IISP, Madrid, Spain, [4]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain, [5]Instituto de Parasitologia y Biomedicina López-Neyra (IPBLN-CSIC) and Systemic Autoimmune Diseases Unit, Hospital Clínico San Cecilio, Granada, Spain, [6]Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [7]Hospital Universitario Lucus Augusti, Rheumatology Division, Lugo, Spain, [8]Immunology department, Hospital Universitario Virgen del Rocío, Sevilla, Spain, [9]Rheumatology Department. Basurto University Hospital, Bilbao, Spain, [10]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain, [11]Hospital Marques de Valdecilla, Santander, Spain.

Background/Purpose: Henoch-Schönlein purpura (HSP) is essentially a childhood disease, being the most common type of vasculitis in children and an infrequent condition in adults. An increased familial occurrence supports a genetic predisposition for this vasculitis. In this context, the role of the HLA (human leukocyte antigen) region in the HSP pathogenesis has previously been studied. However, data reported so far on the potential association of HSP with HLA-DRB1 alleles are scarce and they were generally the result of small series of HSP patients with often contradictory results. To further investigate whether *HLA-DRB1* alleles are implicated in the susceptibility and severity of HSP, we performed a study that encompassed the largest series of HSP patients ever assessed for genetic studies in Caucasian individuals.

Methods: Our study population included 279 Spanish patients diagnosed with HSP and 335 sex and ethnically matched controls. HSP patients fulfilling the American College of Rheumatology (Arthritis Rheum 1990; 33: 1114–21) and the Michel et al (J Rheumatol 1992; 19: 721–8) classification criteria were recruited from Hospital Universitario Lucus Augusti (Lugo), Hospital Universitario Marqués de Valdecilla (Santander), Hospital Universitario La Princesa (Madrid), Hospital Universitario San Cecilio (Granada) and Hospital

Universitario de Basurto (Bilbao). HLA-DRB1 phenotypes were determined using PCR-SSOP Luminex.

Results: After adjusting the results for multiple testing corrections, we disclosed a statistically significant increased frequency of *HLA-DRB1*01* in HSP patients compared to controls ($p<0.001$, OR=3.98 [95% CI: 2.68–5.95]). In contrast, a significantly decreased frequency of *HLA-DRB1*03* was observed in HSP patients compared to controls ($p<0.001$, OR=0.18 [95% CI: 0.085–0.37]). When patients were stratified according to the presence of nephritis or gastrointestinal manifestations, we disclosed that although no specific HLA-DRB1 association with nephritis was observed, *HLA-DRB1*07* was significantly reduced in the group of HSP patients who experienced gastrointestinal manifestations ($p=0.0011$, OR=0.36 [95% CI: 0.19–0.71]) even after adjusting the results for multiple testing correction ($p=0.012$).

Conclusion: Our study supports an association of HSP with *HLA-DRB1*01*. In contrast, a protective effect against the development of HSP was observed in individuals carrying the *HLA-DRB1*03* allele. *HLA-DRB1*07* exerts a protective effect against the development of gastrointestinal manifestations in patients with HSP.

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Association of HLA-B*41 with Henoch-Schönlein Purpura in Spanish Individuals Irrespective of the HLA-DRB1 Status. Fernanda Genre[1], Raquel López-Mejías[1], Belén Sevilla Pérez[2], Santos Castañeda[3], Norberto Ortego-Centeno[2], Javier Llorca[4], Begoña Ubilla[1], Trinitario Pina Murcia[1], Vanesa Calvo-Río[1], Ana Márquez[5], Luis Sala-Icardo[6], Jose A. Miranda-Filloy[7], Marta Conde-Jaldón[8], Lourdes Ortiz-Fernández[8], Juan María Blanco-Madrigal[9], Eva Galindez-Agirregoikoa[9], Francisca González Escribano[8], Javier Martin[10], Ricardo Blanco[11] and MA González-Gay[1]. [1]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, [2]Medicine Department, Hospital Universitario San Cecilio, Granada, Spain, [3]Hospital Universitario de La Princesa, IISP, Madrid, Spain, [4]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain, [5]Instituto de Parasitologia y Biomedicina López-Neyra (IPBLN-CSIC) and Systemic Autoimmune Diseases Unit, Hospital Clínico San Cecilio, Granada, Spain, [6]Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [7]Hospital Universitario Lucus Augusti, Rheumatology Division, Lugo, Spain, [8]Immunology department, Hospital Universitario Virgen del Rocío, Sevilla, Spain, [9]Rheumatology Department. Basurto University Hospital, Bilbao, Spain, [10]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain, [11]Hospital Marques de Valdecilla, Santander, Spain.

Background/Purpose: Henoch-Schönlein purpura (HSP), the most common type of primary small-sized blood vessel leukocytoclastic vasculitis, is characterized by infiltration of the small blood vessels with polymorphonuclear leukocytes and presence of leukocytoclasia. Skin, joint, gastrointestinal tract and kidney involvement may be affected in patients with HSP. Although the etiology of HSP remains unknown, environmental factors and a susceptible genetic background have been associated with HSP. In this regard, the role of the HLA (human leukocyte antigen) region in the HSP pathogenesis has previously been studied in small series of HSP patients, but contradictory results were obtained. To further establish whether HLA-B alleles are implicated in the susceptibility and severity of HSP, we performed a study that encompassed the largest series of HSP patients ever assessed for genetic studies in Caucasian individuals.

Methods: Our study population included 279 Spanish patients diagnosed with HSP and 335 sex and ethnically matched controls. HSP patients fulfilling the American College of Rheumatology (Arthritis Rheum 1990; 33: 1114–21) and the Michel et al (J Rheumatol 1992; 19: 721–8) classification criteria were recruited from Hospital Universitario Lucus Augusti (Lugo), Hospital Universitario Marqués de Valdecilla (Santander), Hospital Universitario La Princesa (Madrid), Hospital Universitario San Cecilio (Granada) and Hospital Universitario de Basurto (Bilbao). HLA-B phenotypes were determined using PCR-SSOP Luminex.

Results: *HLA-B*41* was significantly increased in patients with HSP compared to controls ($p=0.0001$, OR=3.68 [95% CI: 1.75–8.27]) even after adjusting the results for multiple testing correction ($p=0.0018$). Since previous studies suggest a potential association between *HLA-DRB1*01* and HSP susceptibility, we also evaluated the implication of *HLA-B*41* independently of *HLA-DRB1*01* status in HSP patients and healthy controls. For this purpose we excluded from the analysis patients and controls carrying HLA-DRB1*01 alleles. Interestingly, the association remained statistically significant ($p=0.01$, OR=2.93 [95% CI: 1.20–7.14]).

Conclusion: Our study indicates that *HLA-B*41* is associated with the susceptibility to HSP in Spanish individuals, irrespective of *HLA-DRB1* status.

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Are EULAR/Printo/PRES Classification Criteria Appropriate for Classification of IgA Vasculitis in Adults? Alojzija Hočevar[1], Ziga Rotar[2], Vesna Jurcic[3], Joze Pizem[3], Sasa Cucnik[2], Alenka Vizjak[3] and Matija Tomsic[4]. [1]University Medical Centre Ljubljana, 1000 Ljubljana, Slovenia, [2]University Medical Centre Ljubljana, Ljubljana, Slovenia, [3]University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia, [4]BioRx.si, University Medical Centre Ljubjana, Ljubljana, Slovenia.

Background/Purpose: In 2010 EULAR/PRINTO/PRES proposed new classification criteria for pediatric IgA vasculitis (IgAV). In pediatric population these criteria have a higher diagnostic sensitivity than the 1990 American College of Rheumatology (ACR) criteria, while they have thus far not been evaluated in adults. Our main objective was to compare the diagnostic sensitivity of the EULAR/PRINTO/PRES and ACR classification criteria in adult IgAV.

Methods: Adult IgAV cases fulfilling the 2012 revised International Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides definition of IgAV at a secondary/tertiary rheumatology referral center were critically reviewed in partially retrospective (from January 1, 2010 to December 31, 2012) and partially prospective (from January 1, 2013 to April 30, 2014) manner and we assessed whether these patients also fulfilled either the ACR or EULAR/PRINTO/PRES criteria. Biopsy samples were retrieved from the archive and were reevaluated by two pathologists.

Results: Between January 1, 2010 and April 30, 2014 (52 months observation period) 100 consecutive new adult IgAV cases fulfilling the CHCC Nomenclature of Vasculitides definition of IgAV were identified. There were 60 males and 40 females. Median age was 63.2 years (range 18–92, interquartile range (IQR) 40.1–77.2). 4/100 patients were $\leq$ 20 years old at disease presentation. The mean symptom duration was 14 days (range 1–150). Purpura was present in all cases, necrotic in 46/100 and bullous in 11/100 cases. Joints (arthralgia or arthritis) were involved in 46/100, gastrointestinal tract in 38/100, and kidneys in 58/100 patients. General symptoms were present in 18/100 cases. In all patients IgA deposition in vessel walls was documented on direct immunofluorescence staining. Leucocytoclastic vasculitis was observed in 97/100 cases. Granulocytes in vessel wall were found in 85/100 cases. The diagnostic sensitivity of the EULAR/PRINTO/PRES classification criteria was 100 %, and 90 % for the ACR classification criteria (Figure 1).

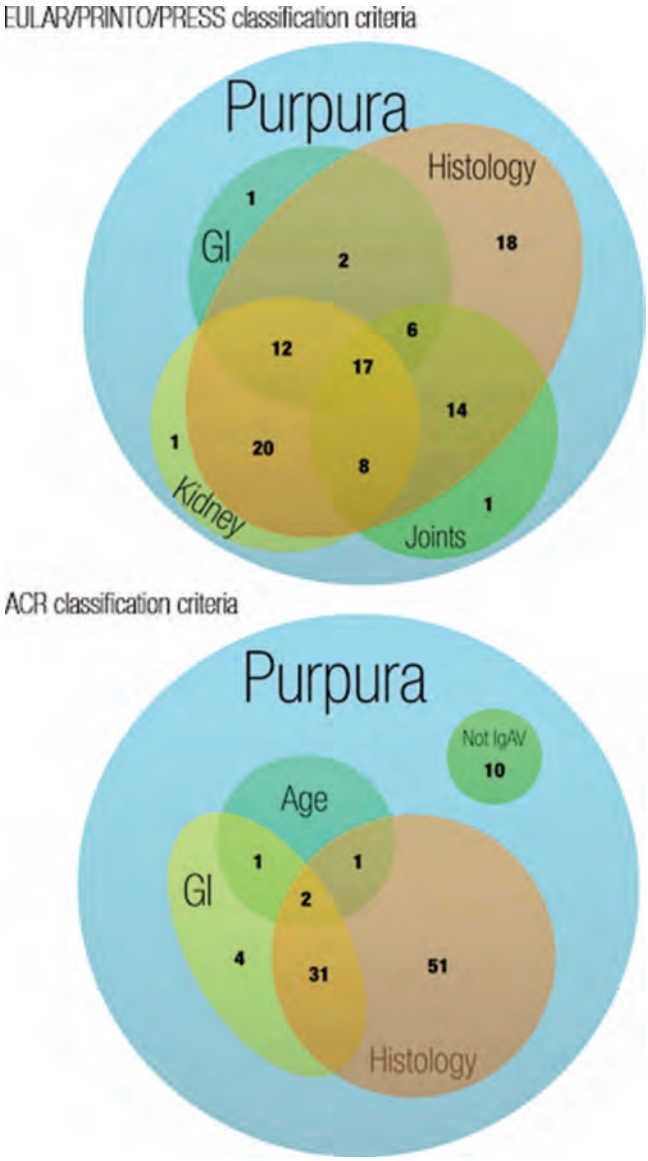

Figure 1. Venn diagram of fulfilled classification criteria items.

Conclusion: Our study supports the use of the 2010 EULAR/PRINTO/PRES criteria not only in children but also in the adult population and show that they are more sensitive than the 1990 American College of Rheumatology IgA vasculitis criteria.

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Follow up of an Unselected IgA Vasculitis (Henoch-Schönlein Purpura) Population at Single Rheumatology Center. Alojzija Hočevar[1], Ziga Rotar[2], Jaka Ostrovrsnik[2] and Matija Tomsic[3]. [1]University Medical Centre Ljubljana, 1000 Ljubljana, Slovenia, [2]University Medical Centre Ljubljana, Ljubljana, Slovenia, [3]BioRx.si, University Medical Centre Ljubljana, Ljubljana, Slovenia.

Background/Purpose: In our population IgA vasculitis (IgAV) has an annual incidence rate of 5.1 cases per 10^5 adults increasing with patients' age which makes it by no means uncommon contrary to common belief. Little data is available in the literature about the clinical picture and prognosis of adult IgAV. Available data is most often limited to adult IgAV cases with kidney disease. Our aim was to determine short-term outcomes in an unselected adult IgAV population diagnosed at a single secondary/tertiary rheumatology center.

Methods: We performed an electronic and paper chart review of all adult IgAV cases, diagnosed in our center between January 1, 2010 and December 31, 2013. Appropriate descriptive statistical methods and post hoc tests were used describe our cohort (e.g. Mann-Whitney test, Fisher exact test).

Results: During the observation period 96 new adult IgAV cases were identified. Clinical characteristics at presentation are shown in Table 1. Disease severity was higher in males (median BVAS3 13 vs. 9, p=0.027), and in patients with generalized purpura in contrast to purpura limited to lower limbs (median BVAS3 14 vs. 9, p=0.014). Treatment of IgAV consisted of systemic glucocorticoids (oral 67/96; additional i.v. metil prednisolone pulses 13/96), intravenous cyclophosphamide (9/96), hyperimmune gammglobulins (4/96), plasma exchange (2/96) and mycophenolate mofetil (1/96). During acute phase of the disease 3/96 patients died. Two deaths were attributed to vasculitis (intractable GI hemorrhage in the first; and alveolar hemorrhage in the second patient), while one succumbed following generalized CMV infection and heart failure attributable to immunosuppressive treatment. 18/93 (19.4%) survivors were lost to follow up. The remaining 75/93 (80.6%) patients were followed for a median of 8.4 (IQR 4.8–19.2) months. IgAV relapsed in 13/75 cases (one, two and three times in 8/75, 4/75 and 1/75 cases, respectively). 8/13 (76.9%) patients had a single organ, and 5/13 a multi-organ relapse. Skin was involved in 11, joints in 3, GI tract in 2, and kidney in 2 cases. At last visit urinary abnormalities were present in 13/68 patients. 13/68 had microhameturia (1+, 2+ and 3+ in 6, 3 and 4 cases, respectively); 4/68 had mild proteinuria and 1 patient had proteinuria >1 g per day. Renal function remained stable in 67/68, and worsened in 1/68 case. 7/75 (9.3%) patients died during follow up (cause of death: infection 2; cardiovascular disease 4; unknown 1). In 2/68 survivors malignancy was diagnosed (1 hematologic; 1 teratoma).

Table 1. Clinical characteristic of IgAV patients at presentation and at last follow up

Clinical characteristic of IgAV	at presentation N=96	at last follow-up visit N=68
% male	60	60
Age (median; IQR)	63.4 (40.8-77.3)	/
Purpura # (%)	96 (100)	6 (8.8)
necrotic # (%)	43 (44.8)	0
Joint involvement # (%)	44 (45.8%)	0
arthralgia # (%)	21 (42.7)	0
arthritis # (%)	41 (21.9)	0
GI tract involvement # (%)	35 (36.4)	2 (2.9)
Kidney involvement # (%)	56 (58.3)	13 (19.1)
nephritic or nephrotic syndrome # (%)	10 (10.4)	1 (1.5)
BVAS3 (median; IQR)	12 (6-17)	3 (1-3)*

**patients in remission not included
Legend: GI gastrointestinal tract

Conclusion: Our findings suggest that even in short-term IgAV might not be as benign as perceived thus far. From our data it is impossible to conclude whether this is due to the nature of the IgAV or due to the fact that IgAV seems to be more common in older adults, who also have more comorbidities.

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Applicability of the 2006 European League Against Rheumatism (EULAR) Criteria for the Classification of Henoch-Schönlein Purpura. an Analysis Based on 766 Patients with Cutaneous Vasculitis. Montserrat Santos-Gómez[1], Francisco Ortiz Sanjuan[1], Jose L. Hernández[1], Marcos A. González-López[1], Ricardo Blanco[1], Javier Loricera[1], Vanesa Calvo-Río[1], Trinitario Pina Murcia[2], Carmen Gonzalez-Vela[1], Marina Lacalle[1], Javier Rueda-Gotor[1], Lino Álvarez[1], Leyre Riancho-Zarrabeitia[1] and Miguel A. González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [2]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain.

Background/Purpose: The European League Against Rheumatism (EULAR) proposed in 2006 a new classification criteria for Henoch-Schönlein Purpura (HSP). We aimed to establish the applicability of these criteria in patients with primary cutaneous vasculitis (CV). We also compared these criteria with previously established classification criteria for HSP.

Methods: A series of 766 (346 women/420 men; mean age 34 years) consecutive unselected patients with CV was assessed. Of them, 124 with secondary CV or with CV associated to other well defined entities were excluded from the analysis. The 2006 EULAR criteria for HSP were tested in the remaining 642 patients with primary CV. Two sets of criteria for HSP were also used for comparisons: **a)** the 1990 American College of Rheumatology (Arthritis Rheum 1990; 33: 1114–21), and **b**) the ACR-modified criteria proposed by Michel et al. in 1992 (J Rheumatol 1992; 19: 721–8).

Results: 451 (70.2%) of 642 patients were classified as having HSP according to the EULAR-2006 criteria, 405 (63.1%) using the ACR-1990 criteria, and 392 (61.1%) by the Michel-1992 criteria. However, only 336 patients (52.3%) met at the same time the EULAR-2006 and the ACR-1990 criteria, and only 229 patients (35.7%) fulfilled both the EULAR-2006 and Michel et al criteria. Noteworthy, only 276 (43%) patients met the three set of criteria. Children fulfilled all the sets of criteria more commonly than adults (215 [66.6%] of 323 versus 61 [19%] of 319 respectively; $p<0.0001$).

Conclusion: According to our results, the EULAR-2006 criteria show a poor concordance with previous sets of classification criteria for HSP.

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Clinical-Biological and Pathological Spectrum and Outcome of IgA Vasculitis in Adults. Alexandra Audemard[1], Evangeline Pillebout[2], Patrice Cacoub[3], Noémie Jourde-Chiche[4], Zahir Amoura[5], Noemie Le Gouellec[6], Francois Maurier[7], Boris Bienvenu[8], Geoffrey Urbanski[9], Sébastien Sanges[10], Aurélie Hummel[11], Alban Deroux[12], Loic Raffray[13], Luc Mouthon[14], Loïc Guillevin for the French Vasculitis Study Group[14], Eric Thervet[15] and Benjamin Terrier[16]. [1]Centre Hospitalier Universitaire de Caen, Caen, France, [2]Saint Louis, Paris, France, [3]Groupe Hospitalier Pitié Salpétrière, Service de Médecine Interne, DHU i2B, Paris, France, [4]CHU, Marseille, France, [5]Pitié-Salpêtrière Hospital (AP-HP), Paris, France, [6]Internal Medicine, Lille, France, [7]Department of Internal Medicine, Metz, France, [8]CHU Côte de Nacre, CAEN, France, [9]CHRU, Lille, France, [10]Service de médecine interne, Centre National de Référence de la Sclérodermie Systémique, Hôpital Claude Huriez, CHRU Lille, Lille, France, [11]Necker Hospital, Paris, France, [12]CHU Grenoble, Grenoble, France, [13]INTERNAL MEDICINE, bordeaux, France, [14]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [15]Hopital Européen Georges Pompidou, APHP, PARIS, France, [16]Cochin Hospital, Paris, France.

Background/Purpose: IgA vasculitis is an immune-complex small-vessel vasculitis that mainly affects children and, more rarely, adults, in whom it seems to be more severe, because of gastrointestinal and renal involvements. Data on therapeutic management are lacking. The IGAVAS study was designed to describe IgA-vasculitis presentation and evaluate treatment efficacies. Here, we characterize its presentation and outcome.

Methods: French centers in university and general hospitals retrospectively included 235 patients with IgA vasculitis. We collected information on clinical-biological presentation and outcomes, particularly renal involvement, and analyzed the features associated with renal involvement from diagnosis through the last follow-up visit, and renal insufficiency, defined as estimated glomerular filtration rate (eGFR) using MDRD <60 ml/min/1.73 m^2.

Results: 235 patients (143 men and 92 women, mean age 50 ± 19 years) were enrolled. At disease onset, the most common manifestations were: purpura in all patients with skin necrosis (28%), glomerular nephropathy (64%), arthralgias/arthritis (63%) and gastrointestinal involvement (53%), mainly abdominal pain and intestinal bleeding; 34% had constitutional symptoms. Mean serum IgA level was 3.9 ± 1.8 g/L, with only 37% exceeding the upper the limit of normal (>3.5 g/L). Among the 150 patients with renal involvement, mean eGFR was 80 ± 34 ml/min/1.73 m^2, including 19% with eGFR <60 mL/min/1.73 m^2. Mean proteinuria was 2.56 g/24 h and 85% had microscopic hematuria. IgA vasculitis was always histologically confirmed, mainly in skin and kidney biopsies. The most frequent histological findings in the skin were leukocytoclastic vasculitis (92%), IgA deposits (81%) and fibrinoid necrosis (28%). In the kidney, IgA deposits were seen in 98%, and endocapillary and extracapillary glomerulonephritis in 51% and 42%, respectively. Among the 76% of the patients treated, 82% received corticosteroids alone, with immunosuppressants combined for 18%. After median follow-up of 31 months, 98% achieved initial renal remission but 23% relapsed. Six patients died, 3 of vasculitis flares. Among patients with renal involvement, mean eGFR at last follow-up was 81 ± 31 ml/min/1.73 m^2, including 27% with eGFR <60 mL/min/1.73 m^2. Three patients required dialysis and 1 had kidney transplantation. Older age, tubulointerstitial lesions on kidney biopsy and baseline eGFR were associated with a poor renal prognosis.

Conclusion: This large population enabled description of the clinical-biological presentation and outcome of IgA vasculitis in adults, and showed high frequencies of renal and gastrointestinal involvements and relapse rates. The analysis of the different therapeutic strategies is ongoing.

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1793

Efficacy and Safety of IFN-Alpha in Induction and Maintenance of Remission in Patients with Eosinophilic Granulomatosis with Polyangiitis (EGPA). Single Center Observational Study. Benjamin Seeliger[1], Martin Foerster[1], Anne Moeser[1], Janett Happe[1], Claus Kroegel[1] and Thomas Neumann[2]. [1]Jena University Hospital, Internal Medicine I, Jena, Germany, [2]Jena University Hospital, Internal Medicine III, Jena, Germany.

Background/Purpose: To evaluate the efficiency and safety of IFN-alpha in induction and maintenance of remission in patients with EGPA and to describe its effects on lung function tests and corticosteroid (CS) tapering.

Methods: Retrospective, single-center cohort study in patients with EGPA (according to ACR criteria), who were insufficiently controlled with CS and other immunosuppressant therapies (AZA, MTX, MMF). Patients were treated with Peg-IFN-alpha (135μg per week) or IFN-alpha2b (3×9 million units per week) for induction and maintenance of remission. Remission was defined as a Birmingham Vasculitis Activity Score (BVAS) of 0. After achieving remission, time to first relapse and total occurrence of relapses were recorded. Patients received lung-functioning tests before treatment and at time of remission. Adverse events were recorded.

Results: 25 patients, age of 50 (±9.5) years were evaluated for induction of remission and in 21 patients IFN was continued for maintenance of remission. Five-factor-score (FFS) at initiation of treatment was 0 in 18 (72%) and ≥1 in 7 (28%) in patients. Mean BVAS at initiation of treatment was 8.3 (2–21). Previous therapies were CYC (N=4), AZA (N=3), Omalizumab (N=3), MTX (N=1), MMF (N=1), Rituximab (N=1).

Treatment was discontinued in 18 of 25 (72%) patients and 7 (28%) were still on IFN after a mean time of treatment of 31 (2–131) months. Of 25 patients, 21 (84%) achieved remission and mean time to remission was 5 (3–12) months. CS were tapered from 18.75 (5–50) mg per day to 5 (0–30) mg per day at time of remission ($p<0.001$).

FEV1 increased from 74.8 (25–102) % to 89.1 (50–133) % at time of remission ($p=0.001$).

Four patients discontinued therapy before remission was achieved due to side effects (N=3) and treatment failure (N=1). Of 21 patients treated for maintenance of remission, 8 (38%) were still in remission after a median time of 21 (4–57) months without relapsing. 13 (62%) suffered a total of 15 relapses (4 major and 11 minor) after a median of 12 (4–42) months. Most relapses were associated with rapid CS-withdrawal.

Adverse events were frequent and forced discontinuation of treatment in 11 of 18 patients: depression (N=4), polyneuropathy (N=3), autoimmune hepatitis, toxic liver damage, anemia, alopecia and chronic nausea (each N=1). Other adverse events occurred as flu-like-symptoms (76%), leucopenia (44%) and thrombopenia (36%) but were transient and did not require a change in treatment regime. 4 of 18 patients IFN discontinued treatment due to lack of efficacy in remission induction (N=1) or prevention of relapse (N=3).

Conclusion: IFN is effective in both induction of remission and maintenance of remission while depression is the main side effect that limits therapy. As IFN showed good effect on CS-tapering and on asthma in particular, it can be considered as an alternate treatment in EGPA patients without life- or organ-threatening manifestations.

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The Sting Pathway Regulates Bone Remodeling in a Model of Autoimmune Disease. Rebecca Baum[1], Jason M. Organ[2], David B. Burr[3], Ann Marshak-Rothstein[1], Katherine A. Fitzgerald[1] and Ellen M. Gravallese[4]. [1]University of Massachusetts Medical School, Worcester, MA, [2]Indiana University School of Medicine, Indianapolis, IN, [3]Indiana University School of Medicine, Indianapolis, Indiana, [4]UMass Memorial Medical Center, Worcester, MA.

Background/Purpose: Cytosolic DNA sensors detect viral and bacterial DNA, inducing inflammatory cytokines and type I IFNs via the adaptor stimulator of interferon genes (STING) to clear infection. The STING pathway also responds to endogenous DNA from dying cells and contributes to autoimmune disease. We have identified a potentially important role for cytosolic DNA sensor pathways in bone by studying a mouse that develops inflammatory polyarthritis and articular erosions in the setting of DNA accrual. In this model, DNA accumulates in macrophages due to deletion of the lysosomal endonuclease DNaseII and is detected by cytosolic sensors that signal through STING. Type I IFNs in DNaseII−/− mice lead to anemia-related embryonic lethality; thus co-deletion of the type I IFN receptor is required (DNaseII/IFN-IR double deficient, (DKO) mouse). We investigated the impact of DNA and of the STING pathway in bone in this model of autoimmune disease.

Methods: STING−/− mice were intercrossed with DKO mice to generate STING/DNaseII/IFN-IR triple knock out (TKO) mice. uCT was performed on TKO, DKO, and control femurs from 6–16 month-old mice. Mesenchymal colony forming unit (CFU) assays were used to determine the number of osteoblast precursor cells in bone. uCT was performed on femurs from 6 month-old STING−/− and littermate controls. Finally, RNA from wild type (WT) osteoblasts was analyzed for the expression of cytosolic DNA sensors. To determine the potential for osteoblasts to respond directly to DNA, MC3T3 osteoblast-lineage cells were transfected with poly(dA:dT) and RNA was analyzed by qPCR.

Results: Inflammatory cytokines in the DKO model would be expected to induce bone loss in the axial skeleton, as well as articular erosions. Paradoxically, we found that bone accumulates in long bones, with significant replacement of the marrow cavity by 16 months. CFU assays demonstrate increased osteoblast precursor numbers, and osteoid is also significantly increased in DKO compared to controls (13,881 vs. 424 μm^2, p=0.02). Surprisingly, ectopic bone forms in DKO spleens, a site of DNA accrual in macrophages. We thus sought to define the contribution of cytosolic DNA sensor pathways to bone accrual. STING deficiency almost completely abrogates both arthritis and bone accrual in the spleen and long bones of DKO mice (BV/TV: Het = 0.44%, DKO = 11.47%, TKO = 1.99%, p<0.02 compared to DKO). STING also contributes to bone homeostasis, independent of DNaseII deficiency, as revealed by uCT performed on femurs from STING−/− and littermate controls (BV/TV: STING−/− = 1.39%, WT = 0.62%, p=0.011). Furthermore, cytosolic DNA sensors are expressed in osteoblasts and expression of several sensors is increased in osteoblasts upon transfection with a DNA ligand.

Conclusion: The STING pathway plays a role in bone remodeling in situations of DNA accrual as well as in bone homeostasis. Cytosolic DNA sensors are expressed in differentiating osteoblasts and expression is upregulated by DNA. These findings have relevance to SLE and other autoimmune diseases in which DNA plays a pathogenic role. Discovery of new pathways linking bone and the immune system may identify new targets for the treatment of bone loss in inflammatory autoimmune diseases.

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1795

Denosumab Restores Cortical Bone Loss at the Distal Radius Associated with Aging and Reduces Wrist Fracture Risk. Analyses from the Cross-over Group in the Extension of Denosumab Pivotal Fracture Trial. JP Bilezikian[1], CL Benhamou[2], CJF Lin[3], JP Brown[4], NS Daizadeh[3], PR Ebeling[5], A Fahrleitner-Pammer[6], E Franek[7], N Gilchrist[8], PD Miller[9], JA Simon[10], I Valter[11], CAF Zerbini[12] and C Libanati[3]. [1]College of Physicians and Surgeons, Columbia University, New York, NY, [2]CHR d'Orléans, Orléans, France, [3]Amgen Inc., Thousand Oaks, CA, [4]CHU de Québec Research Centre and Laval University, Quebec City, QC, [5]Monash University, Clayton, Australia, [6]Medical University, Graz, Austria, [7]Medical Research Center, Polish Academy of Sciences, Warsaw, Poland, [8]The Princess Margaret Hospital, Christchurch, New Zealand, [9]Colorado Center for Bone Research, Lakewood, CO, [10]George Washington University, Washington, DC, [11]Center for Clinical and Basic Research, Tallinn, Estonia, [12]Centro Paulista de Investigação Clinica, São Paulo, Brazil.

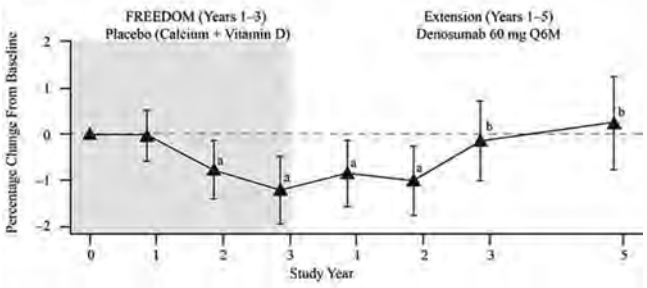
Background/Purpose: Cortical bone loss is a major determinant of increased fracture risk. Denosumab (DMAb) has been shown to increase BMD at sites of cortical bone, including the radius, a skeletal site not responsive to most osteoporosis treatments. Here, we evaluated changes over time in radius BMD and wrist fracture incidence during 3 years of placebo (Pbo) and up to 5 subsequent years of DMAb therapy in FREEDOM and its Extension (EXT).

Methods: We evaluated 2207 women who received Pbo during FREEDOM (3 years) and enrolled in the EXT to receive DMAb 60 mg Q6M (cross-over group); all women received daily calcium and vitamin D. A subset of these women (n=115) participated in a distal radius DXA substudy and were evaluated at baseline and during FREEDOM and EXT. Analysis of mean percentage changes in BMD over time from FREEDOM and EXT baselines consisted of a repeated measure model. Wrist fracture rates (per 100 subject-years), rate ratios, and 95% CI were computed.

Results: At FREEDOM baseline, the mean (SD) 1/3 radius T-score was –2.53 (1.18). During FREEDOM, daily calcium and vitamin D alone was associated with a progressive and significant loss of BMD at the 1/3 radius (–1.2%); however, during EXT, DMAb halted and reversed bone loss (Figure). With 5 years of DMAb treatment, a significant gain in BMD (1.5% at EXT Year 5) was observed, compared with EXT baseline. The wrist fracture rate during the Pbo period in FREEDOM was 1.02 (0.80–1.29) per 100 subject-years. During the first 3 years of EXT, BMD recovered to the original baseline levels in response to DMAb and the wrist fracture rate remained comparable to the FREEDOM Pbo rate (Table); with 2 additional years of DMAb treatment, BMD increased further and the wrist fracture rate declined to levels significantly lower than the FREEDOM Pbo rate (rate ratio=0.57, 95% CI=0.34–0.95; p=0.03).

Conclusion: In untreated women with postmenopausal osteoporosis, cortical bone density at the radius declined significantly. DMAb treatment for 3 years fully reversed this bone loss, and 2 additional years of treatment resulted in further BMD gains that translated to significantly lower wrist fracture rates, highlighting the clinical importance of reversing cortical bone loss.

Figure. Distal Radius BMD Percentage Change From FREEDOM Baseline Through Extension Year 5



BMD percentage change from FREEDOM baseline; data are least squares means (95% CI). [a]$p < 0.05$ compared with FREEDOM baseline; [b]$p < 0.05$ compared with Extension baseline. Q6M = every 6 months.

Table 1. Wrist Fracture Rates During FREEDOM and Through Extension Year 5 (N = 2207 Cross-over subjects)

	FREEDOM (Years 1–3) Placebo (Calcium + Vitamin D)	Extension (Years 1–5) Denosumab 60 mg Q6M			
Denosumab exposure	NA	Year 1	Year 2	Year 3	Year 4 Year 5
Wrist fractures, n	67	58			19
Fracture rate[a]	1.02 (0.80–1.29)	0.96 (0.74–1.25)			0.58 (0.37–0.90)

[a]Wrist fracture rate (95% CI) per 100 subject-years.

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Autotaxin Is Highly Expressed in Systemic Sclerosis (SSc) Skin, Mediates Dermal Fibrosis Via IL-6, and Is a Target for SSc Therapy. Flavia V. Castelino[1], Leaya M. George[1], Gretchen Bain[2], Lance Goulet[2], Robert Lafyatis[3] and Andrew M. Tager[1]. [1]Massachusetts General Hospital, Boston, MA, [2]PharmAkea Pharmaceuticals, San Diego, CA, [3]Boston University School of Medicine, Boston, MA.

Background/Purpose: Autotaxin (ATX) is an enzyme present in biological fluids that is responsible for the production of the lipid mediator, lysophosphatidic acid (LPA). We previously implicated LPA and its receptor, LPA_1 in SSc pathogenesis.[1] Here we studied the role of ATX in SSc dermal fibrosis using the bleomycin (BLM) mouse model and skin biopsy samples from SSc patients and healthy controls. We evaluated the role of IL-6, a cytokine implicated in SSc, in mediating ATX-induced fibrosis. Additionally, we investigated the therapeutic potential of targeting ATX, by using a novel ATX inhibitor, PAT-048 in this model.

Methods: BLM or saline (PBS) was administered subcutaneously to C57Bl/6 mice daily for 3, 7, 14 and 28 days. 6mm dermal punch biopsies were obtained and ATX levels were measured by qPCR and ELISA. ATX inhibition with PAT-048 (20mg/kg oral gavage daily) was assessed in the model. PAT-048 was administered concurrently with BLM or PBS for 28 days, or initiated at 7 or 14 days after BLM. Dermal thickness was measured using H&E-stained sections. Collagen was visualized by Masson's trichrome stain, and quantified by hydroxyproline measurement. Skin IL-6 expression was evaluated by immunohistochemistry (IHC). The effect of LPA-induced ATX expression was tested on human dermal fibroblasts transfected with IL-6 siRNA. Additionally, healthy and SSc dermal fibroblasts were stimulated with LPA and IL-6 *in vitro*, and IL-6 and ATX induction were evaluated by ELISA, respectively. Skin ATX expression was measured in SSc patients and healthy controls by qPCR, and IL-6 expression by IHC.

Results: ATX expression at both the mRNA and protein level was increased at Day 3 after BLM injection (3-fold increase, $p=0.05$) suggesting a role for ATX early in fibrosis. Treatment with PAT-048 attenuated BLM-induced dermal fibrosis in all treatment groups (50% reduction, Day 28, $p=0.01$), and reduced IL-6 expression in the dermis. *In vitro* studies of human dermal fibroblasts showed that LPA-induced ATX expression was attenuated with siRNA knockdown of IL-6 (65% reduction, $p<0.05$). SSc fibroblasts demonstrated increased LPA-induced IL-6 expression, and increased IL-6-induced ATX expression, compared to healthy fibroblasts. Furthermore, ATX expression was increased in SSc skin (n=7) compared to healthy controls (n=5; 3-fold increase, $p=0.006$) and IL-6 expression by IHC was increased in SSc skin compared to healthy controls (n=3 per group).

Conclusion: We demonstrate that ATX has an important role in SSc fibrosis. Pharmacologic inhibition of ATX with a novel inhibitor, PAT-048, attenuated dermal fibrosis and IL-6 expression. Knock-down of IL-6 in fibroblasts *in vitro* abrogated LPA-induced ATX expression, suggesting an autocrine loop for ATX/LPA/IL-6 signaling. Both ATX and IL-6 are increased in SSc skin compared to healthy controls, and LPA-induced IL-6 and IL-6-induced ATX expression are increased in SSc fibroblasts, further supporting an ATX/LPA/IL-6 autocrine loop in SSc. Targeting ATX may thus be an effective new therapeutic strategy for SSc fibrosis.

Reference

Castelino FV et al. Amelioration of dermal fibrosis by genetic deletion or pharmacologic antagonism of LPA_1 in a mouse model of scleroderma. *Arth Rheum*, 2011; 63(5):1405–15.

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One-Year Survival of Adults with Systemic Sclerosis Following Lung Transplantation: A Nationwide Cohort Study. Elana J. Bernstein, Eric R. Peterson, Joan M. Bathon and David J. Lederer. Columbia University College of Physicians & Surgeons, New York, NY.

Background/Purpose: Lung transplantation is a potentially life-saving treatment for patients with systemic sclerosis (SSc) who have developed end-stage lung disease due to interstitial lung disease and/or pulmonary hypertension. However, many transplant programs are hesitant to offer lung transplantation (LTx) to those with SSc due to concerns about extrapulmonary involvement that might affect short- and long-term survival. However, survival data for lung transplantation in SSc are sparse. The primary aim of this study was to determine whether adults with SSc have higher 1-year mortality rates after LTx compared to those with interstitial lung disease (ILD) or pulmonary arterial hypertension (PAH) not due to SSc. We hypothesized that adults with SSc would have higher 1-year mortality rates after LTx than those with ILD or PAH not due to SSc.

Methods: We performed a retrospective cohort study of adults who underwent double or single LTx in the United States between May 4, 2005 (the date of implementation of the lung allocation score) and September 14, 2012. Data were provided by the United Network for Organ Sharing, a non-profit organization that records data on all solid organ transplants performed in the US. Subjects were included if they were at least 18 years of age at the time of LTx; had a diagnosis of SSc, ILD, or PAH; and were transplanted at a center that has performed at least 1 LTx for SSc. Subjects were excluded if they had received a heart-lung transplant; if they received a LTx from a living donor; or if they had missing data on survival time. We modeled diagnosis (SSc) as the independent binary variable of interest in stratified Cox regression models where survival time was the dependent variable, adjusting for recipient, donor, and procedural factors (Table 1). We used multiple imputation to account for missing covariate data.

Results: A total of 3763 adults were transplanted during the study period and met inclusion criteria: 229 with SSc, 201 with PAH, and 3333 with ILD (Table 1). The 1-year unadjusted mortality rate following LTx per 100 person-years was 21.4 among adults with SSc, 19.0 among adults with PAH, and 17.8 among adults with ILD. A diagnosis of SSc was associated with a multivariable-adjusted 48% relative increase in the 1-year mortality rate compared to a diagnosis of ILD (HR 1.48, 95% CI 1.01–2.17). However, a diagnosis of SSc was not associated with a relative increase in the 1-year mortality rate compared to a diagnosis of PAH (HR 0.85, 95% CI 0.50–1.44).

Conclusion: Adults with SSc had a 48% increased risk of death at 1 year following LTx compared to adults with ILD, but no increase in risk of death at 1 year compared to adults with PAH. Rather than denying SSc patients LTx because of their SSc diagnosis, variables need to be identified that will enable risk stratification of these patients prior to LTx, with particular attention to modifiable risk factors.

Table 1: Recipient Characteristics and Covariates

Recipient Characteristics	SSc N = 229	PH N = 201	ILD N = 3333
Age, years	53 (44–59)	46 (34–57)	62 (56–66)
Female sex	135 (58.95%)	126 (62.69%)	941 (28.23%)
Race/Ethnicity			
White	162 (70.74%)	161 (80.10%)	2782 (83.47%)
Black	38 (16.59%)	17 (8.46%)	199 (5.97%)
Hispanic	25 (10.92%)	17 (8.46%)	261 (7.83%)
Asian	3 (1.313%)	5 (2.49%)	67 (2.01%)
Other	1 (0.44%)	1 (0.50%)	24 (0.72%)
LAS score	44.31 (38.03–52.48)	36.90 (33.93–46.00)	45.36 (39.42–58.10)
Height, cm	168.97 (10.29)	169.59 (9.62)	172.28 (9.56)
Body mass index (kg/m^2)	25.10 (4.21)	24.93 (4.36)	27.16 (3.99)
Steroid use	117 (52.00%)	45 (23.20%)	1741 (53.75%)
	N = 225	N = 194	N = 3239
Pulmonary artery systolic pressure, mmHg	48 (37–66)	83 (68–98)	39 (32–48)
	N = 223	N = 194	N = 3206

Forced vital capacity, %predicted	44 (34–60)	73 (60–87)	45 (36–57.5)
	N = 225	N = 197	N = 3300
Creatinine, mg/dL	0.8 (0.7–1.0)	1.0 (0.8–1.2)	0.9 (0.7–1.0)
			N = 3322
Extracorporeal membrane oxygenation	11 (4.80%)	5 (2.49%)	50 (1.50%)
Mechanical ventilation	23 (10.04%)	6 (2.99%)	232 (6.96%)
Oxygen requirement, L/min	5 (3–6)	4 (2–6)	4 (3–6)
	N = 228	N = 200	N = 3310

Covariates adjusted for in Cox regression models

Recipient factors	Age; Sex; Race/Ethnicity; LAS score; Height; BMI; Steroid use; Pulmonary artery systolic pressure; Forced vital capacity; Creatinine; Extracorporeal membrane oxygenation; Mechanical ventilation
Donor factors	Age; Sex; Height; Body mass index; PaO_2 on FiO_2 of 1.0; Pulmonary infection; ≥ 20 Pack-years smoking; Heavy alcohol use; Cause of death
Procedural factors	Ischemic time; Single vs. bilateral transplant; Transplant center; Distance from donor hospital to transplant center; Recipient-donor sex mismatch; CMV mismatch (D+/R-); ≤ 3 HLA mismatches

* Data presented as mean (SD), median (IQR), and frequency (percentage)
** LAS = lung allocation score; PaO_2 = arterial oxygen tension; FiO_2 = fraction of inspired oxygen; CMV = cytomegalovirus; D+ = donor positive; R- = recipient negative; HLA = human leukocyte antigen

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Interaction Between Innate Immunity and Anti-Ro52 Antibodies is Critical for the Induction of Sjogren's Syndrome-like Disease in Mice.
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Background/Purpose: Autoantibodies reactive with Ro52 are present in almost 70% of Sjögren's syndrome (SS) patients. This study was undertaken to investigate the role of Ro52 induced immune responses in the pathogenesis of SS in an experimental mouse model system.

Methods: New Zealand Mixed (NZM) 2758 mice were immunized with mouse Ro52, adsorbed on to alum adjuvant. Control mice were injected either with Maltose binding protein (MBP) or only with alum. Mice were monitored for anti-Ro52 antibody production, sialoadenitis, serum cytokine levels, and pilocarpine induced salivation. Antibody binding to salivary gland cells was analyzed *in vivo* and *in vitro* by immunofluorescence. Sera from immunized mice were passively transferred into untreated or alum injected NZM2758 mice. Internalization of antibodies by live cells was investigated by using the salivary gland cell line SCA9–15. Clinical data from the Oklahoma pSS patient cohort that met the AECG classification criteria for SS was analyzed for anti-Ro reactivity, minor labial salivary gland biopsy focus scores, and xerostomia.

Results: By day 30 post-immunization, Ro52 immunized mice generated immunoprecipitating anti-Ro52 antibodies and they had the maximum drop in saliva production. The glandular dysfunction in these mice was significantly associated with the level of anti-Ro52 antibody. Both Ro52 immunized and control mice showed evidence for very mild sialoadenitis. However, only Ro52 immunized mice had antibody deposition in their salivary glands. Passive transfer of Ro52 immune sera induced salivary gland dysfunction in the recipient mice, only if the recipients were pre primed with alum. The levels of IL-1α and CXCL1 were significantly upregulated in alum injected mice, indicative of the inflammasome pathway activation. *In vitro*, antibodies from Ro52 immune sera were internalized by SCA9–15 cells and the antibodies recognized cytoplasmic Ro52. The antibody internalization was inhibited by Cytochalasin D treatment, indicating it to be an active uptake process. Amongst the 298 pSS patients in Oklahoma cohort, 28 patients (9.3%) were anti-Ro positive and had a focus score of 0; and 37 anti-Ro positive patients (12%) had a focus score of >0 but <1. Several of these patients have dry mouth and dry eyes.

Conclusion: Our data show for the first time that antibodies induced by Ro52 are capable of inducing salivary gland dysfunction and this phenomenon is dependent on the activation of innate immunity. The mouse model presented in this study mimics a subset (22%) of pSS patients in our cohort, who are biopsy negative (or have low focus scores) and are anti-Ro antibody positive. In this group of patients, in the absence of sialoadenitis, it is possible that salivary gland dysfunction is caused by autoantibodies. Our data also suggests that antibody deposition within the salivary glands might be an important step for the induction of glandular dysfunction. Overall this study suggests that down modulation of autoantibody responses should constitute a major therapeutic strategy for the treatment of SS.

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Elevated Indoleamine-2,3-Dioxygenase (IDO) Activity and Kynurinene-3-Monooxygenase (KMO) Expression in Interferon Positive Primary Sjogrens Syndrome Patients Is Associated with Increased $CD25^{hi}FoxP3^{+}$ regulatory Tcells: A Skew Towards Neurotoxicity or an Attempt to Rescue?
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Background/Purpose: A role for indoleamine-2,3-dioxygenase (IDO) in suppression of effector T-cell function and promotion of regulatory T-cell (Treg) differentiation has been described. IDO - the rate-limiting enzyme in tryptophan (TRP) catabolism - is driven in part by type I and type II IFNs. Systemic overactivation of IFN-signaling is evident in Primary Sjögrens syndrome (pSS), and could shift the delicate regulatory balance towards a more auto-reactive state in these patients. Interestingly aberrant systemic TRP catabolism, resulting in a shift from neuroprotective towards neurotoxic downstream metabolites, has been associated with mood disturbances as well as neurophsychiatric consequences, and possibly contributes to symptoms of fatigue and depression in pSS. Here we investigate the role of IDO and downstream TRP catabolism in pSS and hypothesize an increase in Tregs, in concordance with increased IDO-activity in IFNpositive pSS patients.

Methods: In a Cohort of 20 Healthy controls (HC), 18 IFNnegative and 21 IFNpositive pSS patients, diagnosed according to the 2002 American-European criteria, $CD4^{+}CD45RO^{+}$ T helper (Th) memory cell populations defined by chemokine receptor expression: $CD25^{hi}FoxP3^{+}$ Tregs, $CCR6^{+}CCR4^{+}CXCR3^{-}CCR10^{-}$ Th17, $CCR6^{+}CCR4^{+}CXCR3$-$CCR10^{+}$ Th22, CCR6-CXCR3+CCR4- Th1 and $CCR6^{-}CXCR3^{-}CCR4^{+}$ Th2-cells were analyzed by flow cytometry in peripheral blood mononuclear cells (PBMCs). Analysis of TRP and Kynurenine (KYN) were performed simultaneously in serum using HPLC. $CD14^{+}$ monocyte mRNA-expression of $IDO_1$and downstream enzymes was assessed using real-time quantitative PCR, to investigate the direction of downstream TRP catabolism in pSS.

Results: Activity of IDO ($p=0.0054$) – as determined by measuring levels of the KYN/TRP-ratio in sera – and $CD25^{hi}FoxP3^{+}$ Tregs ($p=0.039$) were significantly increased in IFNpositive pSS patients. In addition, $CD25^{hi}FoxP3^{+}$ Tregs significantly correlated with the KYN/TRP-ratio ($p=0.002$;$r=0.509$) as well as the IFNscore ($p=0.011$;$r=0.375$). Peripheral monocytes showed an upregulation of IDO-expression ($p<0.0001$) in IFN-positive pSS, also highly correlating with the IFNscore ($p<0.0001$;$r=0.816$). Interestingly the neuroprotective downstream enzymes KAT1 ($p=0.0003$), KAT3 ($p=0.016$) and KAT4 ($p=0.04$) were downregulated, whereas the neurotoxic enzymes KMO ($p=0.0057$) and KYNU ($p=0.0001$) – which convert KYN into the neutoxic metabolite Quinolinic acid – were upregulated in these patients, suggesting a skew towards neurotoxicity.

Conclusion: Here we find enhanced IDO activity in coherence with increased $CD25^{hi}FoxP3^{+}$ Tregs, and evidence for a shift towards production of more neurotoxic metabolites – previously associated with "sickness behavior" – in IFNpositive pSS. This imbalance towards neurodegenerative effects might contribute to increased fatigue and depressive symptoms in these patients. However, whether this shift in Tregs reflects an immune rescue-mechanism or increases "tolerance to self" remains unknown. Intervening in these IFN and IDO-induced imbalances offers new possibilities for therapeutic interventions.

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1800

Objectively Measured Sedentary Behavior Is a Distinct Risk Factor from Low Moderate-to-Vigorous Activity in Predicting Subsequent Frailty: Evidence from Osteoarthritis Initiative. Jing Song[1], Lee A. Lindquist[1], Rowland W. Chang[1], Pamela A. Semanik[2], Linda S. Ehrlich-Jones[3], Jungwha Lee[1], Min-Woong Sohn[1] and Dorothy D. Dunlop[1]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Rush University Medical Center, Chicago, IL, [3]Rehabilitation Institute of Chicago, Chicago, IL.

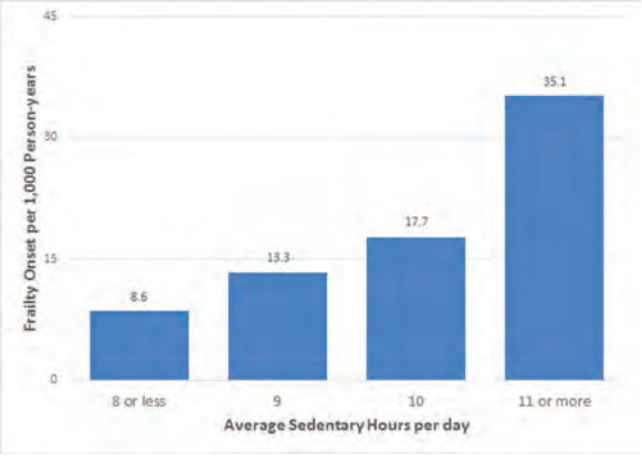
Background/Purpose: Physical frailty represents a state of high vulnerability for adverse health outcomes including disability and mortality. Physical activity interventions to improve health have largely focused on increasing moderate activities and paid limited attention to sedentary behavior. While being physically active is related to less frailty, it is not clear if time spent in sedentary behavior is a separate risk factor from low activity for frailty onset. If a distinct risk factor, the effectiveness of public health initiatives to reduce physical frailty and its sequelae may be improved by incorporating strategies to reduce sedentary behavior.

Methods: We prospectively examined the relationship between accelerometer measured sedentary time with incident physical frailty. We studied 1570 Osteoarthritis Initiative participants aged 49 years or older at elevated risk for developing physical frailty due to knee osteoarthritis (KOA) or KOA risk factors. Physical frailty ascertainment employed a validated definition based on objective assessments: low gait speed (<0.6 meters/second) or/and inability to perform one single chair stand without using arms. Hazard ratios for developing frailty during 2 years of follow-up were estimated from discrete survival methods controlled for time spent in moderate activities, socioeconomic (age, sex, race/ethnicity, marital status, income, education) and health factors (body mass index, chronic conditions, high depressive symptoms, radiographic knee OA, chronic knee symptoms, hip OA, chronic hip symptoms, general pain, smoking, alcohol), and waking hours.

Results: The incidence of frailty in this high risk group was 18.5 per 1,000 person-years. Greater sedentary time during waking hours was significantly related to subsequent frailty onset (unadjusted hazard ratio [HR] = 1.29 per sedentary hour, 95% confidence interval [CI]: 1.08, 1.54). Figure 1 demonstrates the strong relationship between sedentary time and incident frailty adjusting for age, gender, and BMI. Importantly, this relationship held (HR= 1.36 per sedentary hour, 95% CI: 1.04, 1.78) after controlling for moderate activity and other covariates.

Conclusion: These prospective data demonstrated a significant increased risk for the development of frailty per hour of sedentary time among adults with or at risk for knee OA. Importantly, sedentary time was significantly related to frailty onset, independent of time spent in moderate activities. These findings support sedentary behavior as a separate risk factor for frailty, distinct from insufficient moderate activity. Interventions which promote reducing sedentary behaviors in addition to increasing physical activity may help to diminish frailty onset.

Figure. Adjusted physical frailty incident rate.



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1801

The Association of Knee Shape with Sex: The Osteoarthritis Initiative. Barton L. Wise[1], Lisa Kritikos[1], Felix Liu[2], Neeta Parimi[2], John A. Lynch[2], Yuqing Zhang[3] and Nancy E. Lane[1]. [1]Center for Musculoskeletal Health, UC Davis School of Medicine, Sacramento, CA, [2]University of California at San Francisco, San Francisco, CA, [3]Boston University School of Medicine, Boston, MA.

Background/Purpose: Incidence of knee osteoarthritis (OA) is much higher in women than in men. Previous studies have shown that bone shape is a risk factor for knee OA. However, few studies have examined whether knee bone shape differs between men and women. The purpose of the present study was to determine whether there are differences between men and women in the shape of the bones that form the knee joint.

Methods: We used information from the NIH-funded Osteoarthritis Initiative (OAI), a cohort of persons aged 45–79 at baseline who either had symptomatic knee OA or were at high risk of it. Among participants aged between 45 and 60 years, we randomly sampled 339 knees without radiographic OA (i.e., Kellgren/Lawrence grade of 0 in central readings on baseline radiograph). We characterized distal femur and proximal tibia shape of these selected radiographs using Active Shape Modeling (ASM). ASM generates independent modes that together explain the variance in the shape of a bone across a population. We performed linear regression analysis to examine the association between sex and proximal tibia and distal femur shape, adjusting for age, race, body mass index (BMI) and clinic site. Beta coefficients and 95% confidence intervals were estimated to represent the difference in bone shape between women and men.

Results: The mean age was 52.7 years (±4.3 SD) for both men and women. There were 192 female and 147 male knees for the distal femur analysis. Thirteen modes were derived for femoral shape, accounting for 95.5% of the total variance. Distal femur Mode 1 had the greatest effect size for association with sex ($p<0.0001$); Modes 3, 5, 6, 8 and 12 were also significantly associated. For tibial shape, 191 female knees and 149 male knees were used for the analysis. Ten modes explained 95.5% of shape variance. Of the significantly associated modes in the femur, Mode 2 had the greatest effect size for the association with sex ($p=0.009$); Modes 3 and 4 were also significantly associated. See tables for effect sizes and descriptions of all modes significantly associated with sex.

Conclusion: The shapes of the distal femur and proximal tibia that form the knee joint differ by sex. Additional analyses are warranted to assess whether the difference in risk of OA between the sexes arises from bone shape differences.

Distal Femur Shape with Sex (Significant Modes)

Mode	Variance Explained (%)	Mode Description – primary alteration of shape with increasing value of mode	Standard deviation differences by mode between men and women (95%CI)	P-value for difference
1	43.1	Increased shaft width relative to epicondylar width, and deepening of intercondylar fossa.	1.044 (0.85 to 1.23)	<0.0001
3	11.5	Decreased inferior projection of medial and lateral condylar heads with respect to the patellar groove.	0.23 (0.03 to 0.43)	0.024
5	4.9	Increased excursion of the medial epicondyle, narrowing of the shaft, deepening of the groove between the lateral epicondyle and condyle.	−0.258 (−0.47 to −0.05)	0.017
6	3.1	Increased depth and acuity of the intercondylar fossa.	−0.306 (−0.52 to −0.09)	0.005
8	2.0	Decreased extension of the lateral epicondyle.	−0.487 (−0.7 to −0.27)	<0.0001
12	1.0	Decreased extension of lateral epicondyle with increased extension of medial epidondyle.	0.317 (0.1 to 0.54)	0.005

Proximal Tibial Shape with Sex (Significant Modes)

Mode	Variance Explained (%)	Mode Description – primary alteration of shape with increasing value of mode	Standard deviation differences by mode between men and women (95%CI)	P-value for difference
2	11.9	Tibial head shifted laterally in relation to the shaft, and head width increased. The lateral tibial plateau is more concave.	−0.30 (−0.51 to −0.08)	0.009
3	9.7	Slightly increased tibial width, depression of medial plateau and elevation of lateral plateau.	−0.22 (−0.43 to −0.01)	0.038
4	5.5	Lateral plateau extended laterally and elevated, with medial plateau depressed.	−0.25 (−0.46 to −0.04)	0.021

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1802

Are Outcomes after Total Knee Arthroplasty Worsening over Time? a Time-Trends Study of Activity Limitation and Pain Outcomes. Jasvinder A Singh[1] and David Lewallen[2]. [1]University of Alabama and VA Medical Center, Birmingham, AL, [2]Mayo Clinic college of medicine, Rochester, MN.

Background/Purpose: To examine whether function and pain outcomes of patients undergoing primary total knee arthroplasty (TKA) are changing over time.

Methods: The Mayo Clinic Total Joint Registry provided data for time-trends in preoperative and 2-year post-operative activity limitation and pain in primary TKA patients from 1993–2005. We used chi-square test and analysis for variance, as appropriate. Multivariable-adjusted analyses were done using logistic regression.

Results: In a cohort of 7,229 patients who underwent primary TKA during 1993–2005, mean age was 68.4 years (standard deviation (SD), 9.8), mean BMI was 31.1 (SD, 6.0) and 55% were women. Crude estimates showed that preoperative moderate-severe overall limitation were seen in 7.3% fewer patients and preoperative moderate-severe pain in 2.7% more patients in 2002–05, compared to 1992–95 ($p<0.001$ for both). At 2-years, crude estimates indicated that compared to 1992–95, moderate-severe post-TKA overall limitation was seen in 4.7% more patients and moderate-severe post-TKA pain in 3.6% more patients in 2002–05, both statistically significant **(**$p^2$0.018) and clinically meaningful. In multivariable-adjusted analyses that adjusted for age, sex, anxiety, depression, Deyo-Charlson index, body mass index and preoperative pain/limitation, patients had worse outcomes 2-year post-TKA in 2002–2005 compared to 1993–95 with an odds ratio (95% confidence interval (CI); p-value) of 1.34 (95% CI: 1.02, 1.76, $p=0.037$) for moderate-severe activity limitation and 1.79 (95% CI: 1.17, 2.75, $p=0.007$) for moderate-severe pain.

Conclusion: Patient-reported function and pain outcomes after primary TKA have worsened over the study period 1993–95 to 2002–05. This time-trend is independent of changes in preoperative pain/limitation and patient characteristics.

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1803

Knee Osteoarthritis and All-Cause Mortality: The Wuchuan Osteoarthritis Study. Qiang Liu[1], Xu Tang Sr.[2], Jingbo Niu[3], Xu Wu[2], Yan Ke[4], Jian Huang[5], Rujun Li[4], Hu Li[4], Xin Zhi[4], Kai Wang[4], Zhengming Cao[1] and Jianhao Lin[2]. [1]Arthritis Institute, People's Hospital, Peking University, Beijing, China, [2]Peking University Health Science Center, Beijing, China, [3]Boston University, Boston, MA, [4]Peking University People's Hospital, Beijing, China, [5]The Second Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China.

Background/Purpose: Several studies published recently found that knee osteoarthritis (OA) is associated with an increased mortality in Caucasians. While prevalence of knee OA is higher in Chinese than Caucasians, no study has examined whether knee OA increases mortality in Chinese population.

Methods: Between 8/2005-10/2005 1025 residents aged ≥ 50 years were recruited using door-to-door enumeration in randomly selected rural communities in Wuchuan, China. Subjects completed a home interview and had a hospital examination including weight-bearing posteroanterior semiflexed view of radiographs at TF joints and skyline view of radiographs at PF joints. We defined a knee as having whole ROA if either K/L score at TF joint ≥ 2 or presence of PFOA based on OARSI criteria. Symptomatic knee OA (SxOA) was recorded if both pain (i.e., knee pain occurred on most days in past month) and whole ROA were present at the same knee. Subjects were followed until November 31, 2013. Follow-up time for each subject was computed as the amount of time from the date of knee radiograph was obtained to the date of the first of the following events: death; the last date of contact; or the end of follow-up. All-cause mortality was calculated by dividing the number of deaths by the number of person-years of follow-up. We used a Cox-proportional hazard models to examine the relation of whole knee ROA and knee SxOA, respectively, to the all-cause mortality adjusting for age, sex, body mass index (BMI), education, income level, level of daily physical activity, and comorbidities.

Results: Among 1025 participants (men: 49.3%, mean age: 55.5 years, mean BMI: 22.4 kg/m^2) prevalence of whole knee ROA and SxOA at baseline was 17.7% and 6.2, respectively. For K/L grading, the weighted kappa for inter-rater reliability was 0.80 (95% confidence interval (CI): 0.72–0.88) and the intra-rater reliability was 0.92 (95% CI: 0.86–0.99). Over the follow-up period 99 subjects died. The mortality rate was higher among subjects with knee SxOA (32.6/1000 person-years) than those without SxOA (10.9/1000 person-years). After adjustment for age, sex and other potential confounders, subjects with knee SxOA had 90% higher mortality rate than those without SxOA (hazard ratio=1.9, 95% confidence interval(CI): 1.0–3.5). While mortality among subjects with whole knee ROA (20.1/1000 person years) was higher than those without it (10.5/1000 person-years), after adjusting for age, sex and other potential confounders the association was not statistically significantly (hazard ratio=1.2, 95% CI: 0.7–1.9) (Table).

Conclusion: Knee SxOA was associated with an increased risk of all-cause mortality among the residents in the rural areas of China. Future studies to understand the mechanisms underlying this association are needed.

Knee OA status	No. of subjects	Follow-up years	No. of death	Mortality rate (1/1000 P-YRs)	Adjusted hazard ratio (95% CI)*
Presence of knee SxOA					
No	962	7691.3	84	10.9	1.0 (reference)
Yes	63	460.8	15	32.6	1.9 (1.0,3.5)
Presence of ROA					
No	844	6759.4	71	10.5	1.0 (reference)
Yes	181	1392.6	28	20.1	1.2 (0.7,1.9)

* adjusted for age, sex, BMI, education, income level, level of daily physical activity, and comorbidities

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1804

Increased Mortality in Ankylosing Spondylitis - Results from a National Population Based Study. Sofia Exarchou[1], Elisabeth Lie[2], Johan Askling[3], Helena Forsblad-d'Elia[4], Carl Turesson[1], Lars Erik Kristensen[5] and Lennart T. Jacobsson[2]. [1]Section of Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, [2]Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, [3]Clinical Epidemiology Unit, Rheumatology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden, [4]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, [5]Lund University, Malmö, Sweden.

Background/Purpose: Ankylosing spondylitis (AS) is characterized both by inflammation of the axial skeleton and systemic inflammation, and may also involve joints, entheses and other organs. For other rheumatic chronic inflammatory diseases, such as rheumatoid arthritis, an increase in mortality compared to the background population has consistently been shown, whereas for AS, information on survival is scarce. The aims of the present study were to: 1) determine mortality in AS vs the general population, overall and by gender, and 2) to investigate factors associated with death in the AS cohort.

Methods: From the National Patient Register (NPR) we identified a nationwide cohort of patients who were diagnosed with AS at a rheumatology or internal medicine department at least once between Jan 2001 and Dec 2009. A general population comparator, matched on year of birth, gender at the first registered diagnosis year of the AS patient, was identified from the census register, with 5 matched controls per index-patient. Socioeconomic variables and comorbidities (prior to the start of follow up) were identified from Statistics Sweden, NPR and the national Drug Prescription Register. The period of risk began on Jan 1st 2006 or at the first date of registered diagnosis thereafter in those with previously undiagnosed AS and extended until death, emigration, or Dec 31st 2012 (end of observation). Incidence Rate Ratios (IRR) were calculated when comparing mortality in AS and control cohorts and Cox regression models were used to determine predictors for death in the AS cohort.

Results: Among the 8 600 AS patients and the 40 460 controls, there were 496 and 1533 deaths, respectively (34% vs 31% due to cardiovascular disease – CVD). Mortality was increased in AS with an overall IRR of 1.71 (95% CI: 1.55 – 1.90), as well as for men (IRR = 1.65, 95% CI: 1.47 – 1.86) and women (IRR = 1.89, 95% CI: 1.55 – 2.29) in separate analyses. Male gender and higher age predicted death in the AS cohort. In addition, lower level of education and several comorbidities, both general (CVD, diabetes, pulmonary

and malignant diseases) and AS-related (previous small or large joint surgery) were associated with increased risk of death in age/-sex adjusted analyses.

Conclusion: Mortality in this national, population-based AS cohort was increased both in men and women compared to matched controls from the general population. Both general and AS-related comorbidities predicted death suggesting that both traditional and AS-specific risk factors may affect survival.

Table: Predictors of Mortality in AS (age- and sex-adjusted analysis)

	Baseline frequencies (%)	Hazard Ratio	95% CI
Higher education *(12 yrs vs. ≤ 12 yrs)*	2648 (30.8)	0.67	0.52–0.85
Longer duration *(Diagnosis made before Jan 2006 vs after 2006)*	5846 (68.0)	1.49	1.19–1.86
General comorbidities registered before start of follow up:			
Cardiovascular disease or medication (CVD)	2954 (34.4)	2.04	1.62–2.55
Diabetes	418 (4.9)	1.94	1.52–2.47
Chronic lung disease	164 (1.9)	3.04	2.28–4.06
Malignancy	427 (5.0)	1.75	1.39–2.22
AS-related comorbidities registered before start of follow up:			
Joint surgery (small or large joints)	645 (7.5)	1.44	1.15–1.81
Aortic valve insufficiency	79 (0.9)	1.24	0.71–2.15
Inflammatory bowel disease	644 (7.5)	1.29	0.97–1.73
Anterior uveitis	1731 (20.1)	0.90	0.70–1.15
Psoriasis	512 (6.0)	1.18	0.85–1.64
Peripheral arthritis	1841 (21.4)	1.18	0.96–1.45

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1805

Prevalence and Associating Factors with Atypical Femoral Fractures: An Asian Single Center Based Case-Control Study. Dam Kim[1], Yoon-Kyoung Sung[1], Soo-Kyung Cho[1], Minkyung Han[1] and Yee-Suk Kim[2]. [1]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [2]Hanyang University Hospital, Seoul, South Korea.

Background/Purpose: Although the use of bisphosphonates has been shown to reduce vertebral and proximal femur fracture risk in patients with osteoporosis, current evidence suggests that there is an association between bisphosphonate use and atypical femoral fractures (AFFs). However, the extent of this risk remains unclear, especially in Asian population. In this study, we aimed to estimate the proportion of AFFs among total patients with femoral fractures and to compare the characteristics of patients with AFFs with that of patients with classic femoral fractures (CFFs).

Methods: Between 2003 and 2013, a total of 578 female patients with low-energy femoral fractures who had been hospitalized at an Asian single university hospital were retrospectively enrolled. Radiographs and medical records were reviewed by medical doctors. Patients were classified into two groups according to the site of fracture: AFF group for patients with subtrochanteric or diaphyseal femoral fractures and CFF group for patients with intertrochateric or neck fractures. After estimating the prevalence of AFF among patients with low-energy femoral fractures, we assessed the association of bisphosphonate use and AFFs with using multivariate logistic regression analysis.

Results: Twenty-seven patients (4.7%) with AFFs and 551 patients (95.3%) with CFFs were identified. Of the patients with AFFs, 11 (40.7%) had been treated with bisphosphonates compared with 40 (7.3%) in the CFF group. Patients with AFFs were younger than CFFs group (71.2 $\pm$ 9.5 vs. 76.9 $\pm$ 8.7, $p<0.01$). Without correction for age, patients with AFFs appeared to have a higher cortical thickness index (1.1 $\pm$ 0.4 vs. 0.98 $\pm$ 0.4, $p<0.05$) compared to patients with CFFs. With adjusting the age, body mass index, types of injury (slip or fall), and history of rheumatoid arthritis, bisphosphonate was the only predictor for atypical fractures (OR 9.8, CI 3.7–26.4). Among the patients with using bisphosphonate when they fractured (n=44), the proportion of AFFs was nearly 21% (n=9). The proportions of AFFs among femoral fractures were increased according to the duration of bisphosphonate; 15.4% (6 among 39 patients) in patients with less than 5 years and 60% (3 among 5 patients) in patients over 5 years, respectively.

Conclusion: The proportion of AFFs was around 5% among the patients with femoral fractures and AFF were associated with bisphosphonate use in Asian ethnicity. Longer duration of treatment resulted in augmented risk, though any period in bisphosphonate use could cause atypical femur fracture.

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1806 WITHDRAWN

1807

Problems with Fee for Service Payments for Academic Rheumatology Practices: A Need for Payment Reform:. Allen P. Anandarajah[1] and Christopher T. Ritchlin[2]. [1]Univ of Rochester Medical Ctr, Rochester, NY, [2]University of Rochester Medical Center, Rochester, NY.

Background/Purpose: The current fee-for-service model rewards providers for the volume of services. The model is designed to deliver higher compensation for care of more complex cases. Rheumatologists in tertiary care institutions, who provide care for a larger proportion of complex cases, however, are under increasing pressure to care for a higher volume of patients in shorter time intervals.

Purpose is to examine if care for more complex rheumatology cases provides higher financial compensation compared to less complex cases, in an outpatient, academic rheumatology practice.

Methods: We conducted a financial analysis of different faculty outpatient rheumatology clinics at the University of Rochester of Medical Center from July 2012 to June 2013. One clinic session was defined as a 4 hour block. We compared three clinics: one dedicated to care of patients with systemic lupus erythematosus (SLE) comprised of patients with complex medical problems, one comprised of rheumatoid arthritis (RA)patients, with conditions of moderate complexity and a general rheumatology (GR) clinic comprised of patients with less complex problems. The following independent variables were collected: total patient numbers, coding levels and procedures including joint injections and ultrasound. The outcome variable, average revenues for an average clinic, were analyzed.

Results: On average, a total of 7.5 patients, (0.6 new, 6.9 established patients) were seen in the SLE clinic. This compared with a total of 8.9 patients in the RA clinic (0.9 new, 8.0 established) and 6.5 patients in the GR clinic (1.2 new, 5.4 established). The SLE and RA clinics performed on average 0.7 and 1.9 joint injections respectively while the GR clinic had 4.3 joint injections and 1.2 ultrasounds per clinic. The coding patterns for the different clinics are shown in Table 1. The average revenues received for each level of visit, ultrasound and procedures was used to calculate the total revenue for each individual clinic. The average revenues and RVUs for the SLE clinic were calculated to be $1,034.58 and 13.3 respectively. The RA clinic generated 6.2% more in revenue ($1,098.66) and 19.3% more in RVUs (15.8) while the GR clinic collected 24.5% more in revenues ($1,287.81) and 65.9% more in RVUs (22.0) than the SLE clinic. The difference in payments for a year (based on 8 clinics a week for 46 weeks) was calculated to be $23,578.85 more for the RA and $93,186.36 for the GR clinics compared with the SLE clinic.

Conclusion: The current pay structure provides greater financial and RVU compensation for the care of less complex rheumatology cases than the care of complex multisystem diseases. Procedures may be a major contributor to the difference in revenues. Payment reforms are therefore needed to adeqaute compensation for the care of patients with complex rheumatologic problems.

Table 1: coding patterns in percentages for the different outpatient clinics

	FU 2	FU 3	FU 4	FU 5	NEW 3	NEW 4	NEW 5
SLE	0.2%	16%	39.5%	44.3%	3.5%	46.3%	50.2%
RA	0.2%	35.2%	65.2%	0.4%	0%	40.6%	59.4%
GR	0.6%	41.25	55.9%	2.3%	1.4%	27.2%	71.4%

FU= established patients; NEW= new patients

Disclosure: A. P. Anandarajah, None; **C. T. Ritchlin**, None.

1808

Role of HLA-B*5801 Genetic Testing and a Safety Programme When Initiating Allopurinol Therapy for Chronic Gout Management: A Cost-Effectiveness Analysis. Di Dong[1], Wei Chuen Tan-Koi[2], Gim Gee Teng[3], Eric Finkelstein[4] and Cynthia Sung[4]. [1]Duke-NUS Graduate Medical School, Singapore, Singapore, [2]Saw Swee Hock School of Public Health, National

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Background/Purpose: To conduct a cost-effectiveness analysis from a health system perspective of various strategies in managing chronic gout to mitigate risk of allopurinol-induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis, including three that utilize results of HLA-B*5801 genetic testing.

Methods: A decision tree model was developed to estimate costs and quality-adjusted life years (QALYs) over 20-year horizon for patients with chronic gout who fulfil the criteria for initiating ULT with either allopurinol or probenecid. Strategies modelled were: (a) Standard ULT with allopurinol as first-line drug (ULT); (b) Standard ULT with allopurinol as 1st line drug coupled to a safety programme (ULT+SP) that monitors for signs of SJS/TEN; (c) HLA-B*5801 genetic testing-guided ULT treatment (G->ULT) in which choice of 1st line ULT is based on test results (probenecid for test positive, allopurinol for test negative) and avoidance of allopurinol in HLA-B*5801 positive patients; (d) genetic testing to enrol test positive patients in a safety programme when initiating allopurinol (G->SP); test negative patients would receive allopurinol without SP; (e) HLA-B*5801 genetic guided ULT with the safety programme (G->ULT->SP) in which test positive patients are initially given probenecid, but non-responders are subsequently switched to allopurinol in the presence of the safety programme; (f) No ULT and treatment of acute flares only (no ULT). Although inputs are based on the Singapore context, the model is a general template that can be readily adapted to other populations and countries.

Results: No ULT and treating acute flares only has the lowest QALYs and highest costs. Compared with standard ULT, G->ULT increases cost by US$910 but reduces QALYs, despite the reduction in SJS/TEN risk. ULT+SP has an incremental cost-effectiveness ratio (ICER) of US$102,030/QALY compared to ULT alone. G->SP achieves the same QALYs as ULT+SP but at higher cost. G->ULT->SP results in an ICER of $93,030/QALY compared to standard ULT. (***Figure 1 and 2***)

Conclusion: Standard care with allopurinol as first line treatment for chronic gout without genetic testing remains the optimal strategy from a cost-effectiveness perspective based on a threshold of US$50,000/QALY. A safety programme for all patients is not cost-effective, but may become so if implementation costs decrease. If genetic testing costs decrease, testing may become cost-effective if results are used to guide the selection of 1st line ULT, with allopurinol as 2nd line ULT for HLA-B*5801 positive patients in the presence of a safety programme.

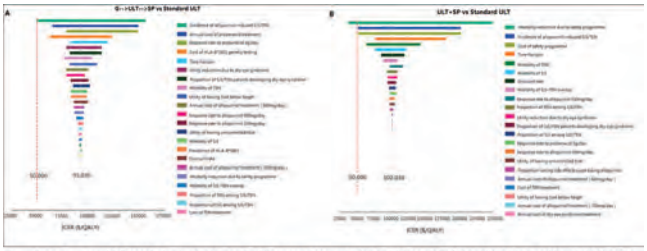

Figure 1. One-way sensitivity analysis. (Panel A) G->ULT->SP compared to standard ULT, yields an ICER of $93,030/QALY. Using $50,000/QALY as the threshold for cost-effectiveness, G->ULT->SP is not cost-effective unless when the incidence of allopurinol-induced SJS/TEN is higher than 0.4% in the population. Other inputs are not influential on the cost-effectiveness results when varies within the sensitivity range. (Panel B) ULT+SP compared to standard ULT, yields an ICER of $102,030/QALY. Using $50,000/QALY as the threshold for cost-effectiveness, ULT+SP is not cost-effective unless the safety programme can reduce SJS/TEN mortality by 60%, when the cost of safety programme is below $30, or when the incidence of allopurinol-induced SJS/TEN is higher than 0.4% in the population. Other inputs are not influential on the cost-effectiveness results when varies within the sensitivity range.

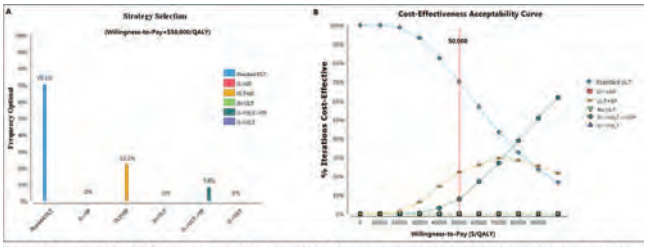

Figure 2. Probabilistic Sensitivity Analysis . (Panel A) In a simulation of 10,000 runs where all input variables are randomly drawn from the assigned distributions during each run, standard ULT was the optimal strategy in 70.1% of iterations. ULT+SP and G->ULT->SP are optimal in 22.1% and 7.8% of interations, respectively. G->SP, no ULT, and G->ULT are dominated strategies that are not preferred. (Panel B) Based on a willingness-to-pay of $50,000/QALY, Standard ULT is the optimal strategy. When the willingness-to-pay is higher than $80,000/QALY, G->ULT->SP becomes the optimal strategy.

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1809

Is Team Care Better? a Comparison of Rheumatoid Arthritis Disease Activity Among Patients Cared for in Practices with Nurse Practitioners and Physicians Assistants Versus Rheumatologist Only.

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Background/Purpose: The Affordable Care Act proposes more widespread use of mid-level providers (MLPs), such as nurse practitioners and physician assistants, but little is known about the process and outcomes of the care they provide. This is of particular interest in rheumatology, where there is a predicted workforce shortage by the year 2025. We set out to compare the outcomes of care provided by MLPs for rheumatoid arthritis (RA) in rheumatology practices with that provided by rheumatologists alone.

Methods: This study was conducted in 7 rheumatology practices in the US – 4 with MLPs and 3 without. The primary outcome was RA disease activity, categorized as remission, low, moderate, or high, using standardized measures (e.g., DAS28, RAPID3, CDAI). We abstracted the following information from medical records for patients with RA from the most recent 2 years: RA treatments, serologic status, disease duration, and disease activity measures. We compared patient characteristics and disease activity for visits across the MLP and rheumatologist only practices. We performed a repeated measures analysis to compare disease activity for visits with MLPs versus those with rheumatologists. These contrasts were made with ordinal logistic regression and expressed as proportional odds ratios. Sensitivity analyses also examined 1) the area under the curve (AUC) for disease activity over the 2-year study period (linear regression) and 2) the change in disease activity between visits (ordinal logistic regression).

Results: Records from 301 patients, including 1982 visits were reviewed: 1168 visits with MLPs and 814 with rheumatologists. Overall, patients had a mean age of 61 years and 77% were female. 69% of patients seen by MLPs and 70% of those seen by rheumatologists were seropositive. In the primary adjusted analysis, patients seen in MLP practices were more likely to have better disease activity (OR 0.32, p = 0.004, reduced probability for higher disease activity) than those seen in practices with only rheumatologists (see Table). Similar trends were observed in the AUC analysis. However, there were no differences in the change in disease activity comparing patients seen in practices with MLPs versus rheumatologist only.

Conclusion: While non-randomized trials are subject to confounding by indication, patients seen in practices with MLPs for RA had reduced disease activity over a 2-year observation period compared with those seen in rheumatology only practices; although no differences were observed in the change in disease activity between visits. Two competing possibilities emerge that further research can help clarify: patients seeing MLPs are less sick to begin with or their care is associated with better disease control when MLPs are part of the team.

Table: Categorical disease activity measures compared across patients seen in practices with mid-level providers versus those without, based on adjusted regression models*

Variable	Primary analysis (OR, 95% CI) †	Secondary analysis, change between visits (OR, 95% CI) †	Secondary analysis, area under the curve (b coefficient)**
Mid level provider (vs not)	0.32 (0.17-0.60)	0.98 (0.94-1.03)	−6.35 (p = 0.0055)
Disease activity category at baseline	. . .	. . .	9.85 (p < 0.001)
Age, per year	0.99 (0.98-1.02)	1.00 (0.99-1.00)	−0.005 (p = 0.95)
Female gender	2.24 (1.09-4.61)	0.98 (0.93-1.02)	0.34 (p = 0.89)
Duration of RA, per year	1.18 (0.87-1.61)	1.01 (0.99-1.03)	0.92 (p = 0.59)
Seropositive	1.26 (0.69-2.30)	1.02 (0.98-1.06)	1.08 (p = 0.59)
DMARD use, any	0.64 (0.43-0.95)	0.99 (0.94-1.03)	−2.85 (p = 0.20)

* The Disease activity category at baseline was not entered into all analyses since it was part of the outcome. Abbreviations: RA, rheumatoid arthritis; DMARD, disease-modifying anti-rheumatic drug. † Odds ratio denotes the probability of a one level increase in disease activity, with odds ratios less than one denoting a reduced probability. They were calculated using a proportional odds model that accounted for the hierarchical clustering. ** The b coefficients denote the area under the disease activity curve for the 24 months, with scores of 0-3 interpolated for each month. They were calculated in generalized linear models.

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1810

Improper Use of Antinuclear Antibody (ANA) Test Can Result in Misdiagnosis, Increased Patient Anxiety, and Wasted Health Care Resources. Sahar Eivaz Mohammadi[1], Imam H Shaik[1], Parag Chevli[1], Fernando Gonzalez-Ibarra[1], Sohini Sarkar[1], Saurav Acharya[1], Prerna Dogra[1], Hesam Hekmatjou[2], Maushmi Savjani[2], Waheed Abdul[2] and Valentin Marian[1]. [1]Jersey City Medical Center-Barnabas Health, Jersey City, NJ, [2]St. George's University SOM, St. George's, Grenada.

Background/Purpose: Results of serologic tests for autoantibodies, including tests for Antinuclear antibodies (ANAs) and antibodies to specific nuclear antigens such as double-stranded DNA (dsDNA), play an important role in the diagnosis of connective tissue disorders (CTDs) such as systemic lupus erythematosus (SLE). ANAs are often detected in many healthy individuals without CTDs (~13%). Although a negative ANA test makes SLE highly unlikely, the positive results without significant clinical and laboratory features will lead to inappropriate tests and misdiagnoses.

Methods: This is a retrospective chart review of patients on whom ANA test has been performed at a 330-bed community hospital in U.S. over a period of one year. All relevant details like demographics, locations, physician service, clinical features, history of CTDs, prior ANA results, additional tests and their results were noted. The justification for ordering the ANA test was compared against clinical and laboratory parameters included in the 2012 SLICC classification criteria for SLE.

Subsequently, true and false positive incidence was calculated. For all the negative or positive ANA tests, special attention was given to the indications of testing based on chart analysis. The 2012 SLICC clinical classification criteria were applied retrospectively to all cases regardless the ANA results; more than two positive parameters by SLICC criteria were proposed as a justification to order ANA test. The results are compared using 2×2 chi-square test.

Results: During one year period, ANA was ordered for a total of 465 patients (Male=151, Female=314). Among them, 12.47% (n=58) had prior history of CTDs and 0.98% (n=4) had prior ANA positivity. In the remaining 403 patients, ANA was found positive (titers ≥1:80) in 6.94% (n=28) and negative in 93.05% (n=375). By applying 2×2 chi-square test, was shown that ANA positivity or diagnosis of CTD is very unlikely if less than 2 SLICC parameters are present with a p value <0.05 (Table 1)

Out of all 465 cases, only one new case of Anti phospholipid antibody syndrome was identified. A total of $39,297 was spent on ANA, and $87,165 on additional tests ordered in conjunction or following a positive ANA. It was noted that a large number of cases where ANA sub-serologies are ordered without knowing the ANA. This ordering pattern is against recommendation by "Choosing Wisely" campaign endorsed by ABIM and ACR.

Conclusion: Testing for ANA and related serology had cost approximately $126,000/yr for a medium size hospital and lead to no new SLE cases. ANA sub-serologies had cost the hospital $87,165 and according to "Choosing Wisely" campaign, were not indicated in more than 93% of cases, as these were negative ANA by IIF. In our hospital the lab was instructed to cancel the additional sub-serologies unless the ANA turns positive.

Table 1.

	ANA negative	**ANA positive**	Marginal row totals
SLICC score 2 or above	**302** (297.77) [0.06]	**18** (22.23) [0.81]	320
SLICC score < 2	**73** (77.23) [0.23]	**10** (5.77) [3.11]	83
Marginal column totals	375	28	403 (Grand Total)

The Chi-Score statistic is 4.2058. The *P* value is 0.040287. The result is significant at p<0.05.

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1811

The Burden of Depression on Healthcare Utilization in a Population-Based Cohort of Patients with Systemic Lupus Erythematosus. Alfredo Aguirre[1], Gaobin Bao[1], S. Sam Lim[2] and Cristina Drenkard[1]. [1]Emory University, Atlanta, GA, [2]Emory University School of Medicine, Division of Rheumatology, Atlanta, GA.

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic disease that disproportionately strikes black women. Depression is a potentially debilitating co-morbidity that affects 15–75% of SLE patients and is more severe and unrecognized among blacks compared to whites. Data from a mostly white SLE cohort suggests an association between depression and high emergency department (ED) use. However, no study has assessed the impact of depression on healthcare utilization among patients representative of the SLE population in the Southeastern United States (US). We examined the relationship between depression and healthcare utilization in a predominantly black SLE cohort, expecting depression to be associated with increased ED and inpatient usage.

Methods: Georgians Organized Against Lupus (GOAL) is a longitudinal cohort of validated SLE patients largely drawn from a population-based lupus registry established in Atlanta, Georgia. Annual patient-reported surveys furnish data on demographics, disease outcomes and healthcare utilization from GOAL participants, of whom 78% are black, 35% live under the Federal Poverty Level and 11% are uninsured. All cases fulfilled at least 4 of the American College of Rheumatology (ACR) Classification Criteria for SLE, or 3 ACR criteria with a final diagnosis of SLE by the attending rheumatologist. We used data from the 2013–14 annual survey to examine the relationship between depression, as assessed by the 9-item Patient Health Questionnaire (PHQ-9), and utilization of inpatient and ED resources in the past year.

Results: 566 participants were included in this analysis. Nearly half (46%) of the GOAL participants had visited the ED, while 27% had been admitted to the hospital. Among those with depression (PHQ-9 score =/>10), 58% had visited the ED, as compared to 41% of those with a score <10 (p=0.0001). Patients with and without depression had a mean of 1.7 ED visits and 1.1 ED visits annually, respectively (p<0.0001).

Conclusion: A greater proportion of depressed SLE patients had accessed ED resources for care. In addition, increasing depression severity was associated with higher frequency of ED visits. We did not find an association between depression and hospitalization as was hypothesized, suggesting that depressed patients who visited the ED did not meet inpatient admission criteria. Our data gesture toward deficiencies in the routine care of depressed SLE patients that may contribute to avoidable ED utilization, and suggest the potential utility of depression screening modalities in the assessment of SLE patients who resort to the ED for care. Further research is needed to determine whether demographic factors have an effect on the association between depression and ED visits and whether increased ED utilization may be due to subpar quality, coordination or type of care for those with depressive symptoms.

Depression Severity and Healthcare Utilization in the Past 12 Months

	PHQ-9 Score					
Healthcare Utilization*	**Minimal (0-4) n=210**	**Mild (5-9) n=162**	**Moderate (10-14) n=102**	**Moderately Severe (15-19) n=62**	**Severe (20-27) n=30**	**P Value****
ED visits	1.0 ± 2.7	1.3 ± 2.0	1.7 ± 2.2	1.4 ± 1.9	2.3 ± 2.9	<0.0001
Hospital admissions	0.5 ± 1.4	0.7 ± 1.4	0.5 ± 1.3	0.5 ± 1.4	0.8 ± 1.2	0.057
Nights spent in hospital	2.9 ± 14.9	2.5 ± 6.0	5.9 ± 26.0	1.4 ± 3.1	2.6 ± 4.8	0.21
Visited ED, n (%)	73 (34.8)	76 (48.1)	57 (57.0)	32 (54.2)	19 (65.5)	0.0002
Admitted to hospital, n (%)	44 (21.0)	53 (33.5)	27 (27.3)	17 (29.3)	11 (36.7)	0.067

* Unless otherwise specified, values are depicted as mean ± SD; ** Kruskal-Wallis test.

Disclosure: A. Aguirre, None; **G. Bao**, GlaxoSmithKline, 2; **S. S. Lim**, NIH, 2, GlaxoSmithKline, 2, Emory University, 3; **C. Drenkard**, NIH, 2, Emory, 3, GlaxoSmithKline, 2.

ACR Concurrent Abstract Session
Innate Immunity and Rheumatic Disease
Monday, November 17, 2014, 2:30 PM–4:00 PM

1812

Investigation of the Sting/Interferon Pathway Activation in a Novel Vasculopathy and Pulmonary Syndrome. Yin Liu[1], Adriana Almeida de Jesus[2], Bernadette Marrero[1], Dan Yang[3], Gina A. Montealegre Sanchez[2], Steve Brooks[1], Zuoming Deng[2], Amy Paller[4], Manfred Boehm[3] and Raphaela Goldbach-Mansky[2]. [1]NIAMS/NIH, Bethesda, MD, [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, [3]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, [4]Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: We have recently studied a group of patients with a prominent interferon (IFN) signature in the blood, distinct from IL-1 mediated autoinflammatory diseases. Six patients with *de novo*

gain of function mutations in *TMEM173*, which encodes *ST*imulator of *I*nterferon *G*enes (STING), presented with early onset systemic inflammation, vasculopathy/vasculitis, and pulmonary inflammation. STING is an adaptor molecule for cytosolic DNA sensing pathway, which leads to IFNb production. The identification of an IFN activating mutation allows us to examine the cellular origin of the IFN and the IFN response signature in patients' cells.

Methods: Patients alive (n=4) were evaluated clinically and immunologically. STING ligand cGAMP was used to assess its function in stimulation assays in patients' and controls' Peripheral Blood Mononuclear Cells (PBMCs), fibroblasts and endothelial cells. Transfection studies of STING wildtype or mutant constructs in HEK293T cells were performed and IFNb transcription in patient peripheral blood cell subsets, fibroblasts, and healthy control endothelial cells were assessed.

Results: Whole blood transcriptional profiling by RNA_seq showed significant upregulation of IFN regulated genes compared with healthy controls. Constitutively increased transcription of IFNβ and other downstream targets of STING in patient PBMCs indicate constitutive STING/IFN pathway activation. qRTPCR analysis of RNA extracted from flow cytometer sorted cells indicates that monocytes produce by far the highest level IFNb. Transcriptional analysis by RNA_seq suggests that the STING/IFN pathway was also constitutively activated in patient fibroblasts. When stimulated with STING ligand cGAMP, patients' fibroblasts are more sensitive and have exaggerated transcription of IFNβ but not IL-1, IL-6 and TNF. STING is expressed in endothelial cells (EC) and *in vitro* STING pathway stimulation leads to EC activation and damage.

Conclusion: *S*TING-*A*ssociated *V*asculopathy with onset in *I*nfancy (SAVI) is a novel autoinflammatory disease caused by *de novo* gain of function mutations in *TMEM173*, which leads to constitutive STING activation and elevated IFNβ secretion. The identification of a mutation in the IFN pathway suggests the use of therapeutic agents blocking this pathway and allows us to study the cellular origin and the organ manifestations of the inflammation.

Disclosure: Y. Liu, None; **A. Almeida de Jesus**, None; **B. Marrero**, None; **D. Yang**, None; **G. A. Montealegre Sanchez**, None; **S. Brooks**, None; **Z. Deng**, None; **A. Paller**, None; **M. Boehm**, None; **R. Goldbach-Mansky**, None.

1813

DNA Sensors Regulate Inflammation in a Model of Autoimmune Arthritis. Rebecca Baum[1], Shruti Sharma[1], Sudesh Pawaria[1], Susan Carpenter[2], Katherine A. Fitzgerald[1], Ann Marshak-Rothstein[1] and Ellen M. Gravallese[3]. [1]University of Massachusetts Medical School, Worcester, MA, [2]University of California, San Francisco, San Francisco, CA, [3]UMass Memorial Medical Center, Worcester, MA.

Background/Purpose: Innate immune sensors such as cytosolic DNA sensors and toll-like receptors (TLRs) detect viral or bacterial DNA, resulting in production of proinflammatory cytokines and type I IFNs to clear infection. Pathways involved in detecting this foreign DNA include: 1) cytosolic DNA sensors that signal through stimulator of interferon genes (STING); 2) the cytosolic sensor absent in melanoma 2 (AIM2); and 3) endosomal TLRs that traffic via Unc93. DNA derived from endogenous retroelements or dying cells have also been shown to activate these pathways, contributing to autoimmune disease. We examined the role of DNA sensor pathways in a mouse model of inflammatory arthritis in which the lysosomal endonuclease DNaseII is deficient. In this model, DNA accrual results in production of proinflammatory cytokines and type I IFNs. Since type I IFNs lead to anemia-related embryonic lethality, co-deletion of the type I IFN receptor is required (DNaseII/IFN-IR double deficient (DKO) mouse).

Methods: To investigate the contribution of DNA sensor pathways to inflammatory polyarthritis, genes involved in DNA sensor signaling were deleted on the DKO background, yielding three triple knock out (TKO) strains: STING TKO, AIM2 TKO and Unc93 TKO mice. Inflammation was assessed by clinical scoring (scale of 1–12) and by scoring of histologic inflammation in ankle joints (scale of 1–4). Anti-nuclear antibody (ANA) staining was evaluated as another marker of disease. To determine whether STING contributes to inflammation in immune-complex mediated arthritis, serum transfer arthritis (STA) was induced in STING$-/-$ and littermate control mice.

Results: DKO mice develop significant distal polyarthritis. Clinical joint inflammation was completely absent in STING TKO mice, confirming a prior report (Ahn et al., PNAS 109:19386, 2013). However, STING deficiency did not diminish inflammation in the STA model, demonstrating that STING contributes to arthritis in the setting of DNA accrual. Clinical inflammation was significantly reduced in both AIM2 TKO and Unc93 TKO mice compared to DKO mice, demonstrating a role for the inflammasome and TLRs. Average clinical scores: DKO = 5, Het control mice = 0, STING TKO = 0, Unc93 TKO = 4, AIM2 TKO= 3.5 ($p<0.05$ for all strains compared to DKO). Histologic inflammation scores showed a similar pattern (DKO = 3.5, Het = 0, STING TKO = 0.5, AIM2 TKO = 2, Unc93 TKO = 3 ($p<0.05$ for all strains compared to DKO). The bright ANA staining pattern generated from sera of DKO mice was completely abrogated in the Unc93 TKO, but was unchanged in the STING TKO and AIM2 TKO strains.

Conclusion: These data indicate that stimulation of several innate immune sensor pathways by endogenous DNA can contribute to inflammatory polyarthritis. Although deletion of STING had the greatest impact in abrogating arthritis, the AIM2 and Unc93 pathways also contributed to joint inflammation. The TLR/Unc93 pathway, but not the STING or AIM2 pathways, mediated ANA production. These data are directly relevant to clarifying the mechanisms by which polyarthritis occurs in SLE and suggest new targets for treatment. In addition, these data demonstrate that distinct DNA sensing pathways play unique roles in disease mechanisms.

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1814

RNA-Containing Immune Complexes Shift Human Neutrophils from Phagocytosing Cells to Efficient Releasers of Oxidized DNA in a Process Requiring Crosstalk Between Toll-like Receptors and Fc Gamma Receptor IIa. Christian Lood[1], Xizhang Sun[1], Lena Tanaka[1], Andrew Oberst[2], Jeffrey Ledbetter[3] and Keith B. Elkon[1]. [1]University of Washington, Seattle, WA, [2]Department of Immunology, University of Washington, Seattle, WA, [3]Division of Rheumatology, University of Washington, Seattle, WA.

Background/Purpose: Neutrophil extracellular traps (NETs), the extrusion of chromatin to capture microbes, has recently emerged as a possible mechanism that may increase the autoantigenic burden as well as promote the prominent type I interferon (IFN) signature seen in most patients with systemic lupus erythematosus (SLE). Apparent spontaneous NETosis is observed *ex vivo* in low-density granulocytes, a cell population markedly increased in SLE. *In vitro* SLE RNA-containing immune complexes (RNA ICs) are reported to induce NETs from neutrophils obtained from SLE, but not healthy individuals. Since the precise requirements for RNA ICs and neutrophils in the induction of NETs have not been defined, we investigated the requirements for IC-induced NETosis in normal neutrophils, analyzed the crosstalk between FcgRs and TLRs, and characterized the released DNA material with regard to its source and oxidation.

Methods: Neutrophils, isolated from healthy individuals, were stimulated with RNA ICs, and DNA release and 8-OHdG content, analyzed by fluorescence microscopy and ELISA. The origin of the released DNA was assessed by analyzing 16S (mitochondria) and 18S (chromosomal) expression by qPCR. Phagocytosis was measured by flow cytometry.

Results: Immobilized IgG mimicking tissue-deposited ICs readily induced NETosis in neutrophils in a NADPH oxidase- and PAD4-dependent, but TLR-independent manner. In contrast, soluble endotoxin-free aggregated IgG (HAGG) did not induce NETosis whereas soluble RNA ICs were potent inducers of NETs. This process was dependent on TLR activation since addition of RNases efficiently degraded the RNA contained within the IC, and completely abrogated the ability of soluble RNA ICs to induce NETosis. Despite the fact that degradation of RNA inhibited NETosis, removal of the TLR ligand by RNase markedly increased the phagocytosis of RNA ICs by neutrophils suggesting that TLR activation suppressed phagocytosis. Consistent with this hypothesis, addition of a TLR agonist (R848) inhibited phagocytosis of ICs, but not beads, in neutrophils. Flow cytometric analysis revealed that the underlying mechanism involved rapid down-regulation of FcgRIIA on the neutrophil cell surface upon TLR activation, which reduced its phagocytic capacity and promoted progression into NETosis. The released DNA from RNA IC-activated neutrophils had high 8-OHdG content and was mainly of chromosomal origin, although some mitochondrial DNA was present as well. The chromosomal DNA was enriched for MPO, whereas the mitochondrial DNA was enriched for 8-OHdG oxidation.

Conclusion: i) Extensive aggregation of FcgR on neutrophils, as may occur in tissue deposits, appears sufficient to induce NETosis; ii) In the fluid phase, both FcgR aggregation and TLR ligation are necessary to stimulate

NETosis; iii) TLR-ligand activation in neutrophils downregulates FcgRIIA expression thereby inhibiting further phagocytosis of ICs but enabling NETosis; iv) ICs induce release of oxidized DNA of chromosomal and mitochondrial origin. Deciphering the underlying signaling pathways regulating the crosstalk between FcgRs and TLRs in induction of NETosis may provide novel therapeutic targets.

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1815

STAT3-Mediated Regulation of Mitochondrial Membrane Potential Is Critical for NLRP3 Inflammasome Activation. Jehad H. Edwan[1], Raphaela Goldbach-Mansky[2] and Robert A. Colbert[3]. [1]NIAMS NIH, Bethesda, MD, [2]NIH Building 10 Room 6D47B, Bethesda, MD, [3]NIAMS/NIH, Bethesda, MD.

Background/Purpose: Self-activating mutations in NLRP3 cause a spectrum of autoinflammatory diseases known as cryopyrin-associated periodic syndromes (CAPS). NLRP3 is a key component of a multiprotein complex known as the inflammasome that mediates the maturation of the proinflammatory cytokine IL-1beta, and can induce rapid cell death in a process known as pyronecrosis. Although several models for inflammasome activation have been proposed the precise molecular mechanism, as well as the role of NRLP3 mutations, remains to be elucidated. Emerging evidence suggests that mitochondria are involved in inflammasome activation. STAT3 associates with the mitochondrial inner membrane in a GRIM-19 dependent manner and has been implicated in regulating cellular respiration. Here we asked whether regulation of mitochondrial membrane potential plays a role in NLRP3 inflammasome activation.

Methods: We used whole blood cells from NOMID patients and healthy controls, THP-1 cells with STAT3, NLRP3, GRIM-19, or OSCP expression knocked down, and monocytes derived from NLRP3-deficient mice. Cells were stimulated with LPS in the presence of inhibitors of STAT3, followed by ATP. Cell supernatants were collected and incubated with IL-1beta-capturing beads. Cells were fixed and permeabilized. Then beads were added back to cells, and the mixture of cells with beads was stained with anti-IL-1beta, CD14, and CD16 antibodies and then evaluated by flow cytometry. LPS stimulated cells were also evaluated using immunofluorescence and western blot analysis.

Results: By flow analysis we provide evidence that inhibition of STAT3 function in NOMID and healthy control monocytes, as well as knockdown of STAT3 in THP-1 cells, results in a significant decrease in inflammasome activation. Using confocal microscopy to visualize pyronecrosis, we provide evidence that this process is NLRP3 dependent. Knockdown of GRIM-19 in THP-1 cells also inhibited NLRP3 activation, suggesting a requirement for mitochondrial STAT3. Enhancement of the mitochondrial membrane potential in STAT3 knockdown cells bypassed the effect of STAT3 knockdown, and reconstituted inflammasome activation, whereas knockdown of OSCP significantly reduced inflammasome activation.

Conclusion: These data suggest a previously unrecognized role for STAT3 in regulating mitochondrial membrane potential, which can regulate NLRP3 inflammasome activation. These results point toward mitochondrial STAT3 as a novel therapeutic target for NOMID and other NLRP3-mediated inflammatory diseases.

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1816

Toll-like Receptor 4-Induced Interleukin-1 Defines the Intestinal Microbiome and Mucosal Immune Response in Arthritis-Prone IL-1 Receptor Antagonist Deficient Mice. Tom Ederveen[1], Rebecca Rogier[1], Jos Boekhorst[1], Harm Wopereis[2], Johan Garssen[2], Sacha van Hijum[1], Fons A.J. van de Loo[1], Marije I. Koenders[1], Wim B. van den Berg[1] and Shahla Abdollahi-Roodsaz[1]. [1]Radboud university medical center, Nijmegen, Netherlands, [2]Danone Research, Wageningen, Netherlands.

Background/Purpose: Interleukin-1 (IL-1) plays a pivotal role in inflammation and autoimmunity. Mice deficient in the IL-1 receptor antagonist ($IL\text{-}1Ra^{-/-}$) spontaneously develop a T cell-driven autoimmune arthritis, which we previously showed to depend on the presence of commensal microbiota. Recent findings suggest alteration of intestinal microbiome in new-onset rheumatoid arthritis (RA). The aim of this study was to investigate the role of IL-1 receptor signaling and the involvement of Toll-like receptor (TLR) 2 and TLR4 in defining the intestinal microbiota and the associated mucosal and systemic immune response.

Methods: Multiplex 454 pyrosequencing of V5 and V6 hyper-variable regions of fecal bacterial 16S rRNA was used to define intestinal microbial communities in BALB/c wild type (WT), $IL\text{-}1Ra^{-/-}$ and IL-1Ra/TLR double knock-out (DKO) mice. For gene sequencing analysis, a customized workflow based on Quantitative Insights Into Microbial Ecology (QIIME version 1.2) was adopted. Intestinal T cell differentiation was studied in lamina propria lymphocytes using flow cytometry and gene expression was assessed by qPCR.

Results: Excessive IL-1R signaling strongly affected the composition of intestinal microbiota and resulted in a significant reduction in species diversity compared to WT mice. Both alpha diversity (number of unique taxonomic entities) and phylogenetic diversity (PD) whole tree (based on taxonomic distance) were significantly diminished in $IL\text{-}1Ra^{-/-}$mice compared to WT. Interestingly, the loss of species diversity was absent in IL-1Ra/TLR4 DKO, but not IL-1Ra/TLR2 DKO mice, suggesting that IL-1R-driven skewing of bacterial diversity depends on TLR4.

$IL\text{-}1Ra^{-/-}$ mice exhibited significantly increased abundance of the genus *Helicobacter* and reduced *Prevotella* ($p = 0.008$ and $p = 0.004$, respectively). Importantly, significant alterations in the genera *Xylanibacter*, *Prevotella*, *Streptococcus*, and *Ruminococcus* were markedly normalized in TLR4, but not TLR2, deficient mice, identifying a role for TLR4 in IL-1 mediated shifts in microbial community.

In line with the relevance of intestinal microbiota in mucosal helper T cell polarization, $IL\text{-}1Ra^{-/-}$ mice had greatly increased Th1 and Th17 in small intestine lamina propria, while Treg proportions were unaffected. Also, small intestine lamina propria lymphocytes produced increased levels of IL-17 when stimulated with PMA and ionomycin *ex vivo*. Although expression of IL-1 itself remained unaltered, intestinal IL-23p19 mRNA expression was increased in $IL\text{-}1Ra^{-/-}$ mice. Interestingly, mucosal expression of both IL-1β and IL-23 was significantly diminished in IL-1Ra/TLR4 DKO mice. Moreover, splenic expression of IL-6 and RORγt was increased in $IL\text{-}1Ra^{-/-}$, and suppressed in IL-1Ra/TLR4 DKO mice.

Conclusion: These data indicate a clear role for the IL-1 pathway in defining the intestinal microbiota and mucosal immune response in autoimmune prone mice, potentially driven by TLR4.Understanding the molecular and cellular mechanisms linking the intestinal T cell response with extra-intestinal disease may help identify novel therapeutic targets in autoimmune diseases including RA.

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1817

Connecting Two Pathways through Ca^{2+} Signaling: NLRP3 Inflammasome Activation Induced By a Hypermorphic *PLCG2* Mutation. Jae Jin Chae[1], Yong Hwan Park[1], Chung Park[2], Il-Young Hwang[2], Patrycja Hoffmann[1], John Kehrl[2], Ivona Aksentijevich[1] and Daniel L. Kastner[1]. [1]National Human Genome Research Institute, Bethesda, MD, [2]National Institute of Allergy and Infectious Diseases, Bethesda, MD.

Background/Purpose: Previously, we reported that a novel variant, p.Ser707Tyr, in phospholipase Cγ2 (PLCγ2) is the cause of a dominantly inherited autoinflammatory disease, APLAID (autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation). The APLAID patients suffered from early onset recurrent blistering skin lesions, pulmonary disease, arthralgia, inflammatory eye and bowel disease, and mild immunodeficiency. The hypermorphic mutation enhances the PLCγ2 activity and causes an increase in intracellular Ca^{2+} release from ER stores. As increased intracellular Ca^{2+}signaling has been associated with NLRP3 inflammasome activation, we studied the role of the NLRP3 inflammasome in the pathogenesis of this disease.

Methods: Human peripheral blood mononuclear cells (PBMCs) were isolated from healthy controls and two affected patients. Inflammasome activation was analyzed by Western blotting of secreted interleukin-1β (IL-1β). Intracellular Ca^{2+}levels were measured with the FLIPR Calcium 4 assay kit.

Results: First, we confirmed that PLC-inositol trisphosphate ($InsP_3$)-mediated Ca^{2+} release can trigger the activation of the NLRP3 inflammasome in human PBMCs in much the same way as was previously shown in the mouse. Since the S707Y APLAID mutation disrupts the autoinhibition of PLCg2, which leads enhanced PLCγ2 activity, patients' leukocytes had elevated basal levels of intracellular Ca^{2+}. Upon stimulation with extracel-

lular $CaCl_2$, an activator of the NLRP3 inflammasome, patients' cells release significantly higher amounts of Ca^{2+} into the cytosol than the cells of healthy controls. Consistent with that the increase of cytoplasmic Ca^{2+} mediates the activation of the NLRP3 inflammasome, in the absence of inflammasome activators, PBMCs from patients with APLAID secreted IL-1β whereas control PBMCs secreted IL-1β only following the stimulation with $CaCl_2$. The IL-1β secretion from LPS-primed patients' PBMCs was attenuated by use of a PLC inhibitor and intracellular Ca^{2+}blockers. Finally, we found that the constitutive IL-1β secretion from patients PBMCs was substantially reduced by the treatment with NKH477, the water-soluble analog of forskolin, which is a potent activator of adenylyl cyclase. These results suggest cAMP as a potential target for therapy of APLAID and other NLRP3 mediated diseases.

Conclusion: Our findings suggest that the inflammation in patients with APLAID is partially driven by the activation of the NLRP3 inflammasome. These data link two seemingly distinct molecular pathways and provide new insights in the pathogenesis of APLAID and autoinflammation.

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ACR Concurrent Abstract Session
Osteoarthritis - Clinical Aspects I: Imaging in Osteoarthritis
Monday, November 17, 2014, 2:30 PM–4:00 PM

1818

Subchondral Bone Mineral Density Improves Prediction of Knee Osteoarthritis Progression Compared with Clinical Factors Alone: Data from the Osteoarthritis Initiative. Michael P. Lavalley[1], Grace H. Lo[2], Lori Lyn Price[3], Jeffrey Driban[3], Charles Eaton[4] and Timothy E. McAlindon[3]. [1]Boston University, Boston, MA, [2]Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, [3]Tufts Medical Center, Boston, MA, [4]Center for Primary Care and Prevention, Memorial Hospital of Rhode Island, Providence, RI.

Background/Purpose: A prediction rule for knee osteoarthritis (OA) progression would have great clinical utility in identifying at-risk patients for intervention. Rules using clinically available measurements have so far demonstrated modest predictive ability. Dual energy X-ray absorptiometry is widely available and provides rapidly evaluable quantitative data on tibial subchondral bone mineral density (BMD) that is associated with OA severity.

Our goal was to create a prediction rule for medial joint space loss (a proxy for OA progression) based on clinical factors; and to quantify the benefit of adding the ratio of the periarticular medial to lateral bone mineral density (M:L paBMD) to the rule.

Methods: Subjects were from the Osteoarthritis Initiative (OAI) progression subcohort, with X-ray readings at both 24- and 48-month visits, medial joint space score < 3 at 24 months, and a valid 30- or 36-month BMD value. Weight-bearing PA fixed flexion knee X-rays were assessed for medial tibio-femoral joint space using the OARSI atlas. Knees were imaged with GE Lunar Prodigy Advance scanners, providing M:L paBMD values. Loss of medial joint space, including within OARSI grade worsening, between 24 and 48 months was used as the outcome in logistic regression for the prediction models. Clinical factors chosen for their predictive ability from 24 months were considered for the base model. M:L paBMD was added to the base model to determine if it materially improved prediction, with cross-validation used in this evaluation. Discriminative ability was based on the area under the ROC curve (AUC) and calibration by the Hosmer & Lemeshow test (H&L). The benefit of adding M:L paBMD was evaluated by 1) change in AUC, 2) net reclassification improvement (NRI) based on the percent of subjects with improved prediction, and 3) integrated discrimination improvement (IDI) based on the mean improvement in predicted probabilities.

Results: 496 subjects were included; 68 (14%) experienced medial joint space loss; 48% were female; 15%, 16%, 36%, 30%, and 3% respectively had Kellgren & Lawrence scores 0 – 4; 2% had recent knee injury; 35% had hand OA (> 3 nodes) on physical exam at OAI entry. The mean (SD) for age was 64.4 (9.2) years; BMI 29.5 (4.9) kg/m^2; VAS knee-specific pain 3.4 (2.9) on a 0–10 scale; femoral neck BMD. 96 (.15) g/cm^2; and M:L paBMD 1.1 (.14). The base model included age, BMI, gender, recent injury, knee pain, hand OA, and femoral neck BMD as predictors. The change in AUC, NRI and IDI were statistically significantly improved in the model with M:L paBMD (Table). The H&L test did not find poor calibration in either model.

Conclusion: The M:L BMD ratio provided a meaningful improvement in predictive ability for 2-year medial joint space loss compared to using only clinical predictors. An instrument combining clinical characteristics with M:L paBMD may be useful as a predictive tool for structural progression in patients with knee OA.

Table 1. Cross-Validated Measures of Model Prediction of Medial Joint Space Loss with addition of the Ratio of Periarticular Medial to Lateral Bone Mineral Density (M:L paBMD)

	Base Model*	Base Model* + M:L paBMD	Comparison (95% Confidence Interval), p-value
ROC Area Under the Curve (AUC)	0.645	0.745	0.102 (0.051, 0.154) 0.001
Hosmer & Lemeshow Calibration Test (H&L) p-value	0.330	0.102	
Net Reclassification Improvement (NRI)			0.681 (0.434, 0.923) 0.001
Subjects with medial joint space loss			
Net % Improved		32%	
Subjects with no medial joint space loss			
Net % Improved		36%	
Integrated Discrimination Improvement (IDI)			0.072 (0.043, 0.101) 0.001
Subjects with medial joint space loss			
Average Predicted Probability	0.176	0.239	
Subjects with no medial joint space loss			
Average Predicted Probability	0.140	0.125	

* Base model has the predictors: age, BMI, gender, recent injury, knee pain, hand OA (> 3 hand nodes), and femoral neck BMD; outcome in both models is medial joint space loss.

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1819 WITHDRAWN

1820

Discordance of Hip Pain with Radiographic Hip Osteoarthritis: The Osteoarthritis Initiative. Chan Kim[1], Michael C. Nevitt[2], Pia M. Jungmann[3], Irina Tolstykh[4], Nancy E. Lane[5], Thomas M. Link[4] and David T. Felson[6]. [1]Boston University, Boston, MA, [2]UCSF (University of California, San Francisco), San Francisco, CA, [3]Technische Universitaet Muenchen, Munich, Germany, [4]University of California, San Francisco, San Francisco, CA, [5]Center for Musculoskeletal Health, UC Davis School of Medicine, Sacramento, CA, [6]University of Manchester, Manchester, United Kingdom.

Background/Purpose: It is assumed that persons with hip pain from osteoarthritis (OA) are likely to have radiographic OA, making it possible to readily diagnose disease, but there is little data addressing the agreement of hip pain with x-ray OA. We previously reported poor agreement between hip pain and RHOA (radiographic hip osteoarthritis) in the Framingham population. However, the Framingham study used long limb x-rays that may have yielded imperfect RHOA estimates. We examined concordance of hip pain and RHOA in the Osteoarthritis Initiative (OAI) where subjects obtained pelvis x-rays and were asked a more comprehensive set of questions about hip pain.

Methods: OAI is a multicenter longitudinal cohort study of OA that included 4796 individuals aged 45–79. AP pelvis x-rays were obtained, and definite RHOA was defined using UCSF criteria: 1) definite osteophytes plus definite JSN (both score ≥ 2) OR 2) definite osteophytes or definite JSN plus sclerosis, cysts or femoral head flattening OR 3) definite femoral osteophytes regardless of other features OR 4) definite moderate-severe JSN (superolateral JSN $>=2$ or superomedial JSN $>=3$) regardless of other features. Using a card with visual homunculus, subjects were asked whether they had hip pain on most days in a month. Those who said 'yes' were defined as having frequent hip pain and were asked another question for location of pain: groin, front of the leg (anterior), outside the leg (lateral), lower back, buttocks, or 'don't know'. The pain evaluation was done for both hips. We examined sensitivity (Sn), specificity (Sp) and positive and negative predictive values (PPV, NPV) for location specific pain with RHOA. Sn was defined as % of hips with RHOA that had hip pain. PPV was % of hips with pain that have RHOA. To ensure that we included hips that may have OA and to increase our sensitivity, we did another analysis for possible RHOA.

Results: X-rays from 8732 hips were evaluated. The prevalence of definite RHOA was 6.3%, and possible RHOA was 12.3%. For definite RHOA, the Sn of frequent hip pain was only 23.8%, and the Sp was 84.1% and the PPV for hip pain was only 9.1% (table 1). However, for analysis restricted to hip pain localized to the groin, the PPV rose to 16.5%. Of those

with RHOA, only 7.1% had pain localized to the groin. Anterior hip pain resulted similarly to groin pain, but performance for other sites was diagnostically poorer. For possible RHOA (data not shown), the diagnostic test performance did not differ greatly from definite RHOA.

Conclusion: We found poor agreement between hip pain on most days and RHOA in the ipsilateral hip. Hip pain questions with the highest PPV were hip pain with groin or anterior pain, but most persons with this pain had negative radiographs for hip OA suggesting that x-rays are insensitive to the presence of disease. Many middle aged and older persons with chronic hip joint area pain may have OA even though x-rays are negative.

Table 1.

	Hip pain and definitive RHOA			
Pain definition* (prevalence) N = 8,732)	**Sensitivity: % of RHOA hips that have pain N = 550 (18.6%)**	**Specificity: % of No RHOA hips that have pain N = 8182 (81.4%)**	**PPV: % of painful hips that have RHOA**	**NPV: % of nonpainful hips that have RHOA**
Frequent hip pain in past year (16.4%)	23.8% (131/550)	84.1% (6880/8182)	9.1% (131/1433)	94.3% (6880/7299)
Persistent frequent (BL and 12m) (6.7%)	12.9% (71/550)	93.8% (7671/8182)	12.2% (71/582)	94.1% (7671/8150)
Groin** (2.7%)	7.1% (39/550)	97.6% (7984/8182)	16.5% (39/237)	94.0% (984/8495)
Anterior** (1.8%)	4.4% (24/550)	98.4% (8049/8182)	15.3% (24/157)	93.9% (8049/8575)
Lateral** (10.9%)	17.1% (94/550)	89.6% (327/8182)	9.9% (94/949)	94.1% (7327/7783)
Low back** (6.9%)	7.6% (42/550)	93.1% (619/8182)	6.9% (42/605)	93.7% (7619/8127)
Buttock** (5.6%)	7.1% (39/550)	94.5% (731/8182)	8.0% (39/490)	93.8% (7731/8242)
Groin or anterior (3.7%)	9.3% (51/550)	96.7% (7910/8182)	15.8% (51/323)	94.1% (910/8409)
Hip, not buttock or low back (12.3%)	20.4% (112/550)	88.3% (7223/8182)	10.5% (112/1071)	94.3% (7223/7661)
Hip, buttocks not low back (14.5%)	22.5% (124/550)	86.0% (7039/8182)	9.8% (124/1267)	94.3% (7039/7465)
Any hip pain past year (40.8%)	47.3% (260/550)	59.7% (882/8182)	7.3% (260/3560)	94.4% (882/5172)

Hip pain as an indicator of RHOA [Definite RHOA vs (Possible RHOA and None)]
*All definitions require pain on most days of a month in the past year.
** Hips with pain but not in the specific location are classified as no pain. Location specific pain includes hips with pain also in other locations.

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1821

The Co-Occurrence Patterns of MRI Lesions and Incident Knee Osteoarthritis: The MOST Study. Jingbo Niu[1], David T. Felson[2], Tuhina Neogi[2], Michael C. Nevitt[3], Cora E. Lewis[4], James Torner[5], Ali Guermazi[2], Frank Roemer[6] and Yuqing Zhang[2]. [1]Boston University, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]UCSF (University of California, San Francisco), San Francisco, CA, [4]University of Alabama, Birmingham, Birmingham, AL, [5]University of Iowa, Iowa City, IA, [6]Klinikum Augsburg, Augsburg, Germany.

Background/Purpose: MRI imaging provides insights of tissue-specific lesions of osteoarthritis (OA) and has the advantage of identifying earlier pathological changes that are not evident on radiographs. While MRI lesions often co-occur, the co-occurrence patterns and their relation to the risk of incident OA have not been well evaluated. We identified distinct subgroups of knees using a latent class model according to patterns of pathological changes on MRI and examined their relation to incident radiographic knee OA (incROA).

Methods: The MOST Study recruited 3,026 subjects with or at risk for knee OA. We obtained baseline knee MRI and knee radiographs at each visit. MRIs were scored using the Whole Organ Magnetic Resonance Score (WORMS). Tibiofemoral (TF) incROA was defined by a new occurrence of KL≥2 on PA view radiograph by Month 84, and patellofemoral (PF) incROA was defined by a new occurrence of PF OA on lateral view. For specific lesions on MRI in the *TF* joint, i.e., cartilage morphology, meniscal tear, meniscal extrusion, bone marrow lesion, synovitis, and effusion, we used the worst WORMS score among all sub-regions to represent the severity of that lesion in the knee. We performed latent class modeling (SAS: Proc LCA) to identify subgroups of knees by patterns of MRI lesions. Each knee was assigned to a specific subgroup according to its highest membership probability. We then examined the relation of subgroups of MRI lesions to the risk of *TF* incROA after adjusting for age, sex, race, clinic site, history of knee injury and surgery using logistic regression model. We took the same approach to identify subgroups of MRI lesions in the *PF* joint and assess their relation to *PF* incROA.

Results: Among 579 knees without *TF* OA (mean age: 60.1 years, BMI 29.2 kg/m^2, 59% women), we identified 4 subgroups based on baseline MRI lesions with average posterior probability 0.82: mostly normal (Group 1, 48.0%); predominantly cartilage lesion (Group 2, 24.9%); predominantly meniscal lesions (Group 3, 13.8%); and combined cartilage and meniscal lesions (Group 4, 13.3%) **(Table)**. In Group 3, meniscal tear was more prevalent than meniscal extrusion. Bone marrow lesion, synovitis, and effusion were common in Groups 2 and 4. The risk of *TF* incROA was 12.2%, 22.9%, 31.3% and 44.2%, for Group 1, 2, 3 and 4, respectively. The corresponding odds ratios (ORs) of TF incROA and 95% CI were 1.0, 2.5 (1.4, 4.4), 5.4 (2.8, 10.5), and 8.2 (4.3, 15.7). Similarly, 4 subgroups of MRI lesions were identified in *PF* joints among 660 knees without *PF* OA. The ORs of *PF* incROA for each subgroup were 1.0, 4.3, 8.9, and 17.0, respectively.

Conclusion: The latent class analysis allowed insights of the patterns of MRI lesions. Among the four subgroups of MRI lesions we identified, the co-occurrence of cartilage and meniscal lesion markedly increased the risk of incident ROA, and the meniscal lesion subgroup posed a higher risk than the cartilage lesion subgroup.

Table Baseline MRI lesions in the subgroups identified by latent class analysis

		Group1	**Group 2**	**Group 3**	**Group 4**
***TF* joint**		**Mostly normal**	**Predominantly cartilage lesion**	**Predominantly meniscal lesions**	**Combined cartilage and meniscal lesions**
N of knees		278	144	80	77
%*TF* cartilage morphology,	0 (no lesion)	62.2	0.0	37.5	0.0
2 (mild lesion)	13.7	24.3	30.0	7.8	
3-4 (moderate lesion)	14.4	47.2	32.5	46.8	
2.5/5-6 (lesion extending to bone)	9.7	28.5	0.0	45.5	
%Meniscal tear,	1+(any lesion)	0.0	20.8	100.0	58.4
%Meniscal extrusion,	1+(any lesion)	19.8	0.0	45.0	96.1
%*TF* bone marrow lesion	1+(any lesion)	18.0	65.3	31.3	68.8
%Synovitis,	1+(any lesion)	36.3	86.8	47.5	76.6
%Effusion,	1+(any lesion)	29.1	83.3	43.8	83.1
***PF* joint**		**Mostly normal**	**Combined mild/ moderate cartilage and meniscal lesions**	**Predominantly meniscal lesions**	**Combined moderate/ severe cartilage and meniscal lesions**
N of knees		203	121	94	242
%*PF* cartilage morphology,	0 (no lesion)	75.9	0.8	38.3	0.4
2 (mild lesion)	4.4	55.4	13.8	0.0	
3-4 (moderate lesion)	19.7	43.8	39.4	41.3	
2.5/5-6 (lesion extending to bone)	0.0	0.0	8.5	58.3	
%Meniscal tear,	1+(any lesion)	14.8	48.8	94.7	17.4
%Meniscal extrusion,	1+(any lesion)	19.7	22.3	89.4	30.2
%*PF* bone marrow lesion	1+(any lesion)	6.9	61.2	19.1	91.7
%Synovitis,	1+(any lesion)	36.9	62.8	66.0	68.2
%Effusion,	1+(any lesion)	24.1	55.4	77.7	69.4

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1822

Increasing Synovitis and Bone Marrow Lesions Are Associated with Incident Joint Tenderness in Hand Osteoarthritis. Ida K. Haugen[1], Barbara Slatkowsky-Christensen[1], Pernille Boyesen[1], Sølve Sesseng[1], Désirée van der Heijde[1] and Tore K. Kvien[2]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]PsAID taskforce, EULAR, Zurich, Switzerland.

Background/Purpose: As hand osteoarthritis (OA) studies with repeated MRI are lacking, longitudinal associations between synovitis and bone marrow lesions (BMLs) and pain are unknown. Our aim was to explore whether changes of synovitis and BMLs are related to changes in joint tenderness in a longitudinal hand OA study.

Methods: We included 70 patients (63 women, mean (SD) age 67.9 (5.5) years) from the Oslo hand OA cohort with 1.0T MRI and clinical joint examination at baseline and 5-year follow-up. All patients had longitudinal Short Tau Inversion Recovery (STIR) images of the interphalangeal joints of dominant hand, n=69 had longitudinal T1w fat-suppressed (fs) pre-Gadolinium (Gd) images, and n=48 had longitudinal T1w fs post-Gd images. The paired MRIs were scored according to the OMERACT hand OA MRI score for synovitis and BMLs on 0–3 scales. We allowed 0.5 increments for smaller changes. The same rheumatologist examined the finger joints for presence of joint tenderness at baseline and follow-up. Among joints without tenderness at baseline, we explored whether increase of synovitis and BMLs (no change/decreasing synovitis and BMLs as reference) were associated with incident tenderness in the same joint using Generalized Estimating Equations. Among joints with tenderness at baseline, we explored whether decrease or

loss of synovitis and BMLs (no change/increasing synovitis and BMLs as reference) were associated with loss of joint tenderness. Separate models were performed for synovitis and BMLs, respectively. The analyses were adjusted for age, sex, BMI and follow-up time.

Results: At baseline, synovitis was present in 204/379 (53.8%) joints (n=5 missing), of which the majority was grade 1 (n=139) and grade 2 (n=54). BMLs were present in 108/552 (19.6%) joints, of which the majority (n=80) was grade 1. Joint tenderness was found in 280/664 (40.2%) joints.

The mean (SD) follow-up time was 4.7 (0.4) years. Increase/incident synovitis and BMLs were seen in 96/373 (25.7%) and 88/551 (16.0%), respectively. Decrease of synovitis and BMLs occurred in 63/373 (16.9%) and 47/551 (8.5%) joints, and 39 (10.5%) and 30 (5.4%) joints had complete loss of synovitis and BMLs, respectively. Increasing/incident synovitis and BMLs were significantly associated with incident tenderness in the same joint (Table). The associations were independent of each other (data not shown). No associations were found between decreasing synovitis and BMLs and loss of joint tenderness during follow-up (Table). However, there was a non-significant trend that loss of synovitis was associated with loss of joint tenderness (OR 1.78, 95% CI 0.83, 3.77).

Conclusion: The Oslo hand OA cohort is the first hand OA study with longitudinal MR images of the hands. Increasing synovitis and BMLs were significantly associated with incident joint tenderness. Loss of synovitis was associated with loss of tenderness, but the association was statistically non-significant.

The association with incident joint tenderness (in joints without tenderness at baseline)

	N (%) joints with incident tenderness	Crude analysis OR (95% CI)	Adjusted analysis OR (95% CI)
Synovitis			
- No change/decrease	46/175 (26.3%)	1.0 (ref.)	1.0 (ref.)
- Increase	23/45 (51.1%)	2.53 (1.39, 4.61)	2.62 (1.35, 5.06)
Bone marrow lesions			
- No change/decrease	88/265 (33.2%)	1.0 (ref.)	1.0 (ref.)
- Increase	29/47 (61.7%)	2.73 (1.33, 5.59)	2.84 (1.22, 6.60)

The association with loss of joint tenderness (in joints with tenderness at baseline)

	N (%) joints with loss of tenderness	Crude analysis OR (95% CI)	Adjusted analysis OR (95% CI)
Synovitis			
- No change/increase	41/123 (33.3%)	1.0 (ref.)	1.0 (ref)
- Decrease	10/30 (33.3%)	0.99 (0.47, 2.10)	1.19 (0.54, 2.59)
Bone marrow lesions			
- No change/increase	57/203 (28.1%)	1.0 (ref.)	1.0 (ref.)
- Decrease	10/36 (27.8%)	0.80 (0.45, 1.42)	0.82 (0.42, 1.57)

OR=odds ratio, CI=confidence interval

Disclosure: I. K. Haugen, None; **B. Slatkowsky-Christensen**, None; **P. Boyesen**, None; **S. Sesseng**, None; **D. van der Heijde**, None; **T. K. Kvien**, None.

1823

Inflammation Is Associated with Erosive Progression in Patients with Hand Osteoarthritis: A Prospective Ultrasonography Study. Marion C. Kortekaas[1], Wing Yee Kwok[2], Monique Reijnierse[2], Theo Stijnen[2] and Margreet Kloppenburg[2]. [1]Flevoziekenhuis, Almere-Stad, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Erosive hand osteoarthritis (OA) is a subset that shows inflammatory features with ultrasound or MRI much more frequent than non-erosive hand OA, and can progress relatively fast. Whether inflammatory features are associated with erosive progression is unknown. Therefore, we investigated relationships between inflammatory ultrasound features and erosive progression over 2.3 years follow-up in hand OA patients.

Methods: In 56 consecutive hand OA patients (mean age 61 years, 86% female), recruited from the rheumatology outpatient clinic and all fulfilling ACR criteria, effusion, synovial thickening and Power Doppler signal (PDS) were assessed in all interphalangeal joints (IPJs) with ultrasound using standardized methods at baseline and after 2.3 years. Radiographs were scored at both time-points for osteophytes and joint space narrowing using the OARSI method and for erosive disease, defined as E(rosive)- and R(emodelled)-phase, using the Verbruggen-Veys method. Progression was defined as a non-erosive joint becoming erosive, or E-phase becoming R-phase. R-phases at baseline were excluded. Associations were analysed using GEE logistic regression, adjusting for age, gender, BMI and baseline structural abnormalities.

Results: At baseline 51 IPJs (18 patients) and at follow-up 100 IPJs (26 patients) were erosive, hence 49 IPJs showed erosive progression. Moderate/severe synovial thickening and PDS at baseline were associated with erosive progression: adjusted odds ratio (95% confidence interval) 6.3 (2.3–17.5) and 6.9 (2.0–23.3), respectively. Effusion showed a trend: 2.7 (0.94–7.7). Persistent inflammation, defined as inflammation present both at baseline and follow-up, showed stronger associations with erosive progression compared to inflammation present either at baseline or follow-up.

Conclusion: Inflammatory ultrasound features, especially when persistent, are associated with erosive progression in hand OA, implicating that inflammation plays a role in its pathogenesis and could be a therapeutic target.

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ACR Concurrent Abstract Session
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Pediatric Systemic Lupus Erythematosus
Monday, November 17, 2014, 2:30 PM–4:00 PM

1824

A Randomized Double-Blind Placebo-Controlled Trial of Vitamin D Supplementation in Juvenile-Onset Systemic Lupus Erythematosus: Improvement in Disease Activity and Fatigue Scores. Glauce Lima, Juliane Paupitz, Liliam Takayama, Eloisa Bonfa and Rosa M R Pereira. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: Vitamin D has an important immunomodulatory effect but there are no clinical trials that directly addressed the benefit from boosting the serum level of 25-hydroxyvitamin D in Juvenile-onset Systemic Lupus Erythematosus (JoSLE). The aim of this study is, therefore, to evaluate the vitamin D supplementation in disease activity scores and fatigue in JoSLE patients.

Methods: This study was a randomized double-blind placebo-controlled 24-week trial. Forty female JoSLE patients were randomized (1:1) to receive either oral cholecalciferol 50,000 IU/week (JoSLE-Vit D) or placebo (JoSLE-PL). Mean glucocorticoid dose and immunosuppressive medications remained stable throughout the study. Serum levels of 25 hydroxyvitamin D (25OHD) were measured using a radioimmunoassay technique (DiaSorin, Stillwater, Minnesota, USA). Disease activity was assessed by the SLE Disease Activity Index (SLEDAI) and by European Consensus Lupus Activity Measurement (ECLAM). Fatigue was assessed using Kids Fatigue Severity Scale (K-FSS), scores with an adapted range from 1 to 5 with low levels indicating higher fatigue. Longitudinal regression models were used to estimate the association between levels of 25OHD, disease activity and fatigue. T-test or Mann-Whitney test were performed to see differences between groups.

Results: Groups were similar regarding age (p=0.61), body mass index (p=0.28), frequency of organ involvements (p>0.05), mean glucocorticoid dose (11.90 ± 9.5 vs. 15.30 ± 14.82 mg/day, p=0.38) and frequency of immunosuppressive drugs (84 vs. 75%, p=0.490), SLEDAI (3.57 ± 2.87 vs. 4.35 ± 4.22, p=0.51), ECLAM (2.31 ± 1.74 vs. 2.35 ± 2.09, p=0.95), and fatigue scores at baseline (3.21 ± 0.90 vs. 2.90 ± 0.88, p=0.29). There was also no difference in the serum levels of 25OHD at the baseline between JoSLE-Vitamin D and JoSLE-PL (19.1 ± 6.6 vs. 19.5 ± 4.5 ng/mL, p=0.81). After 24 weeks of supplementation, the mean level of 25OHD was higher in JoSLE-Vit. D group compared to JoSLE-PL group (31.15 ± 8.89 vs. 16.56 ± 5.88 ng/mL, p<0.001). At the end of intervention, a decrease in SLEDAI score was observed in JoSLE-Vit. D compared to JoSLE-PL [Δ(final – baseline) SLEDAI: −0.58 ± 3.11 vs. 1.2 ± 3.67, p=0.01)] and a tendency of decrease in ECLAM score: (ΔECLAM: −0.63 ± 1.11 vs. 0.3 ± 0.20, p=0.083). Regarding fatigue evaluation, an improvement of fatigue related to social life score was found in JoSLE-VD compared to JoSLE-PL group (ΔFatigue: 0.47 ± 1.07 vs. −0.2 ± 0.95 vs. p=0.024). Cholecalciferol (50,000IU/week) intervention was well tolerated with no serious adverse events.

Conclusion: This study suggests that cholecalciferol supplementation 50,000IU/week for 6 months is effective to decrease disease activity and improve fatigue in JoSLE patients. (NCT01892748).

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1825

Cognitive Performance Scores for the Pediatric Automated Neuropsychological Assessment Metrics in Childhood-Onset Systemic Lupus Erythematosus. Patricia Vega-Fernandez[1], Shana Vanderburgh[2], Deborah M. Levy[3], Frank A. Zelko[4], Eyal Muscal[5], Natasha M. Ruth[6], Adam M. Huber[7], Marisa S. Klein-Gitelman[8], Kasha Wiley[9], Wenjie Zheng[9], Lori B. Tucker[10], Tresa Roebuck-Spencer[11], Jun Ying[2] and Hermine Brunner[12]. [1]Cincinnati Children's Hospital, Cincinnati, OH, [2]University of Cincinnati, Cincinnati, OH, [3]The Hospital for Sick Children and University of Toronto, Toronto, ON, [4]Northwestern University Feinberg School of Medicine, Chicago, IL, [5]Texas Children's Hospital, Houston, TX, [6]Medical University of South Carolina, Charleston, SC, [7]IWK Health Centre, Halifax, NS, [8]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [9]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [10]BC Children's Hospital and University of British Columbia, Vancouver, BC, [11]University of Oklahoma, Norman, OK, [12]PRCSG, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background/Purpose: Patients with childhood-onset SLE (cSLE) may experience neuropsychiatric SLE (NPSLE) manifested as neurocognitive dysfunction (NCD). Formal neurocognitive testing (FNCT) is the most accepted method for diagnosing NCD. However, access is limited and it is costly and time-consuming. The Pediatric Automated Neuropsychological Assessment Metrics (PedANAM) is a computerized test battery that assesses multiple domains of cognitive performance. However, it is unclear how PedANAM-generated variables can be interpreted in a clinical setting as measures of NCD.

Our purpose was to explore and initially test approaches to the calculation of a summary score (PedANAM Cognitive Performance Score (PedANAM-CPS)) to screen NCD in cSLE with high sensitivity.

Methods: Two cohorts were analyzed. The development cohort included cSLE patients (pts) and controls that completed the PedANAM and FNCT at two research study visits 18 months apart. The validation cohort consisted of cSLE pts and controls recruited in a clinical setting who completed the PedANAM and Pediatric Perceived Cognitive Function-43 questionnaire (PCF-43). Candidate PedANAM-CPSs were generated based upon the development cohort's first visit using 3 statistical methods: 1) *Simple-summary score:* Mean accuracy score of all PedANAM's subtests; 2) *Logit-based score* developed by logistic regression modeling; 3) *PCA-based score* derived from Principal Component Analysis (PCA). The latter 2 methods assigned in a different way a statistical weight to each subtest accuracy score. Receiver operating characteristic curve analysis was used to assess the accuracy of candidate scores as predictors of NCD in the study cohorts.

Results: A total of 166 pts were studied, including 108 cSLE pts (Table 1). As shown in Table 2 the candidate PedANAM-CPSs significantly differentiated between NCD and non-NCD groups. The Logit-based and PCA-based scores performed well and were able to detect NCD on the second visit of the development and validation cohorts. The usefulness of the 3 PedANAM-CPS scores and their cut-off scores to define NCD was confirmed when using visit 2 data of the development cohort and the validation cohort.

Conclusion: Candidate PedANAM-CPS showed good construct and criterion validity, with a Logit-based score performing somewhat better for discriminating cSLE pts based on the presence or absence of NCD. The PedANAM-CPS may be a useful tool to summarize cognitive performance in assessing for NCD in cSLE. Confirmation studies are required to confirm its overall accuracy and clinical usefulness in cSLE.

Table 1 Demographics of Development and Validation Dataset at Enrollment *

Variable	Category	Development Dataset			Validation Dataset		
		cSLE (n=40)	Controls (n=40)	p-value	cSLE (n=68)	Controls (n=18)	p-value
Age (years)		14.8 ± 2.3	13.9 ± 3.2	0.03	15.3 ± 3.3	14.0 ± 2.5	0.131
Age (years) in median (range)		14 (9, 17)	14 (9, 17)	0.767	15 (10, 20)	14 (11,18)	0.239
Female		85	85	1.0	91.2	72.2	0.032
Ethnicity							
White		30	32.5	0.98	30.9	94.4	<0.001
Black		45	47.5		30.9	5.6	
Hispanic		17.5	15		11.8	0	
Asian and other		7.5	5		26.5	0	
On Prednisone therapy		77.5			76.5		
Prednisone dose (mg/day)		19.8 ± 17.4			17.1 ± 16.1		
Disease activity(mean ± SD)‡		4.9 ± 4.4			4.3 ± 4.7		
PCF-43† T-score (mean ± SD)					60.5 ± 7.9	63.2 ± 5.8	0.167
Neurocognitive dysfunction¥		22.5	7.5		8.8	11.1	0.766

*Except where indicated otherwise, values are percentages; cSLE = childhood-onset systemic lupus erythematosus.
‡ Systemic Lupus Disease Activity Index 2k version, SLEDAI; range 0 – 104; 0 = inactive SLE.
† PCF-43 questionnaire: Perceived Cognition Functioning -43 questionnaire.
¥ Neurocognitive dysfunction categories are defined based on z-scores of the standardized tests completed for the formal neuropsychological testing (FNCT) on the research cohort, and on T-scores of the pediatric perceived cognitive function questionnaire-43 (PedsPCF-43) on the clinical cohort. FNCT measures following cognitive domains: working memory, psychomotor speed, attention and executive functioning, visuoconstructional ability.

Table 2 PedANAM-CPS performance to identify neurocognitive deficit^ in the development cohort, visit 1

Candidate PedANAM- CPS	Non-NCD (N=68)*	NCD (N=12)*	p-value†	AUC ¥	Sensitivity	Specificity
Simple Summary Score	0.08 ± 0.07	−0.39 ± 0.18	0.036	0.60	83.3%	37.3%
PCA-based Score	0.09 ± 0.08	−0.42 ± 0.19	0.027	0.60	83.3%	41.8%
Logit-based Score	−2.26 ± 0.16	−0.60 ± 0.37	0.001	0.77	91.7%	31.3%

PedANAM-CPS = Pediatric Automated Neuropsychological Assessment Metrics – Cognitive Performance Score. ^ Neurocognitive deficit as measured by formal neuropsychological assessment; NCD = neurocognitive deficit; AUC = area under the curve; PCA = Principal Component Analysis; Logit = logistic regression model
* Values are mean ± SD
† *P* values are adjusted for age
¥ Interpretation of AUC values: 1.0-0.91: outstanding, 0.81-0.90: excellent, 0.71-0.8: good, 0.61-0.7: fair, and <0.6: poor

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1826

A Renal Activity Index May Predict Histological Activity in Lupus Nephritis in Children. Khalid Abulaban[1], Michael Bennett[1], Marisa Klein-Gitelman[2], Stacy P. Ardoin[3], Kelly A. Rouster-Stevens[4], Lori B. Tucker[5], Kasha Wiley[6], Shannen Nelson[7], Karen Onel[8], Nora G. Singer[9], Kathleen M. O'Neil[10], Elizabeth Brooks[11], B Anne Eberhard[12], Lawrence K. Jung[13], Lisa F. Imundo[14], Tracey Wright[15], David Witte[16], Jun Ying[17], Prasad Devarajan[1] and Hermine I. Brunner[7]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Anne & Robert H Lurie Childrens Hospital of Chicago, Chicago, IL, [3]Ohio State University College of Medicine, Columbus, OH, [4]Emory University School of Medicine, Atlanta, GA, [5]BC Children's Hospital and University of British Columbia, Vancouver, BC, [6]Cincinnati Children's Hospital Medical Center, c, OH, [7]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [8]University of Chicago Hospitals, Chicago, IL, [9]Division of Rheumatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH, [10]Riley Hospital for Children, Indianapolis, IN, [11]Univ Hospitals of Cleveland, Cleveland, OH, [12]Cohen Children's Medical Center, Lake Success, NY, [13]Children's National Medical Center, Washington, DC, [14]Pediatric and Adult Rheumatology Columbia University Medical Center, New York, NY, [15]UT Southwestern Medical Center, Dallas, TX, [16]Cincinnati Children's Hospital, Cincinnati, OH, [17]University of Cincinnati, Cincinnati, OH.

Background/Purpose: Lupus Nephritis (LN) occurs in up to 80% of childhood-onset Systemic Lupus Erythematosus (cSLE) and it has a worse prognosis than adults. The current gold standard for diagnosing LN and assessing its activity is a kidney biopsy interpreted using the International Societies for Nephrology & Renal Pathology (ISN/RPS) classification. Kidney biopsies are invasive and too costly to assess the course of LN. The objective of this study is to develop and initially validate for Children a Renal Activity Index (C-RAI) to non-invasively monitor LN activity, considering both traditional measures of LN (LN-TM) and recently discovered renal biomarkers (RBM).

Methods: In this ongoing prospective study, 83 children with LN were studied at the time of the kidney biopsy; LN-TM [GFR, complements, anti-dsDNA antibodies, urinary protein/creatinine ratio], clinical indices [Systemic Lupus International Collaborating Clinics Renal Activity Score (SLICC-RAS), renal domain score of BILAG (BILAG-R) and SLEDAI (SLEDAI-R)] were all obtained, and the RBM (Table 1) were measured. Histological findings were rated by a single nephropathologist who provided ISN/RPS class, NIH Glomerular Activity Index (GLAI; range 0–24) and Tubulointerstitial Activity Index (TIAI; range = 0–21) scores (Criterion Standards). Prior to statistical analysis, RBM levels were normalized by urine creatinine and logarithmically transformed. LN-TM, RBM and clinical indices that showed significance in univariate analysis at a p-value<0.10 were considered in stepwise multivariate logistical regression models as C-RAI candidate predictors, using the GLAI and TIAI as dependent variable (outcome). The accuracy of the C-RAI of predicting and discriminating LN activity was assessed by receiver-operating characteristic curve (ROC) analysis.

Results: Means and percentages of the values of LN-TM, clinical indices and RBM levels are summarized inTable1. Based on multivariate logistical

regression modeling, histological activity measurement does not necessitate consideration of clinical indices but rather select LN-TM and RBM. Levels of C3, NGAL, CP, MCP1 and TF were found to be candidate C-RAI's for predicting high LN activity (GLAI>10) with outstanding accuracy [area under the ROC curve (AUC) = 0.9]. NGAL and HPX were excellent predictors of high interstitial inflammation with active LN (TIAI > 5; AUC = 0.88) (Figure1).

Conclusion: C3 level, NGAL, CP, MCP1, TF, and HPX are good potential components for C-RAI to measure histological LN activity in the glomeruli and interstitium. Confirmation in a larger data set is required.

Table 1: Comparisons of LN biomarkers between NIH GLAI and TIAI classes

	GLAI Score			TIAI Score		
LN biomarkers	**≤10**	**>10**	**p**	**≤5**	**>5**	**p**
SLEDAI-R*	7.45 (6.06, 8.84)	11.93 (10.15, 13.70)	0.000	8.20 (6.75, 9.64)	11.43 (8.96, 13.90)	0.031
BILAG-R*	10.37 (9.52, 11.23)	11.56 (10.48, 12.63)	0.096	10.93 (10.02, 11.83)	10.86 (9.33, 12.38)	0.940
SLICC-RAS*	4.38 (2.75, 6.02)	7.58 (5.57, 9.58)	0.019	5.20 (3.47, 6.92)	5.92 (2.86, 8.98)	0.686
Protein/ Cr ratio*	1.79 (1.20, 2.67)	2.85 (1.74, 4.67)	0.156	1.98 (1.31, 2.97)	2.67 (1.31, 5.42)	0.474
Urine Protein*	185.74 (101.62, 339.49)	423.73 (206.08, 871.27)	0.106	185.43 (107.15, 320.90)	541.85 (221.27, 1,326.88)	0.076
GFR*	115.07 (97.38, 135.97)	75.53 (61.04, 93.47)	0.003	108.48 (94.32, 124.78)	69.64 (54.81, 88.48)	0.003
Serum Cr*	0.63 (0.55, 0.74)	0.99 (0.82, 1.20)	0.001	0.66 (0.58, 0.76)	1.06 (0.85, 1.33)	0.001
C3 level*	64.28 (53.79, 76.82)	41.94 (33.44, 52.60)	0.005	53.31 (43.72, 65.01)	52.35 (37.43, 73.22)	0.928
C3 (Low)**	47.62%	15.38%	0.010	30.00%	28.57%	0.920
C4 level*	9.95 (7.92, 12.50)	6.35 (4.80, 8.41)	0.018	7.63 (6.04, 9.64)	7.67 (5.17, 11.39)	0.982
C4 (Low)**	30.95%	14.81%	0.137	25.00%	21.43%	0.788
DSDNA (Positive)**	16.67%	8.00%	0.334	11.43%	9.09%	0.828
NGAL	0.25 (0.15, 0.43)	0.65 (0.36, 1.17)	0.027	0.30 (0.17, 0.50)	0.93 (0.35, 2.42)	0.052
CP	118 (64, 215)	334 (173, 645)	0.028	199 (108, 367)	266 (87, 813)	0.661
MCP1	5.88 (3.85, 8.97)	24.04 (15.16, 38.10)	0.000	8.99 (5.42, 14.91)	30.25 (12.01, 76.23)	0.033
AGP	561 (232, 1,359)	1,101 (397, 3,057)	0.337	593 (232, 1,516)	3,752 (402, 35,064)	0.153
TGFB*	0.42 (0.26, 0.69)	1.27 (0.86, 1.86)	0.004	0.73 (0.46, 1.17)	1.56 (0.83, 2.91)	0.083
ADI	0.09 (0.03, 0.23)	0.51 (0.17, 1.49)	0.023	0.11 (0.04, 0.28)	1.35 (0.22, 8.33)	0.024
HEPCIDIN	0.55 (0.26, 1.15)	0.66 (0.29, 1.47)	0.753	0.56 (0.26, 1.21)	0.70 (0.15, 3.28)	0.802
LPGDS	2.71 (1.56, 4.70)	5.74 (3.15, 10.48)	0.080	3.24 (1.84, 5.69)	8.04 (2.87, 22.51)	0.141
TF	0.09 (0.05, 0.15)	0.17 (0.10, 0.31)	0.083	0.11 (0.07, 0.19)	0.18 (0.07, 0.45)	0.395
VDBP	5.43 (2.26, 13.07)	6.19 (2.38, 16.14)	0.844	3.95 (1.72, 9.08)	30.18 (6.62, 137.64)	0.030
HPX	17.15 (9.01, 32.65)	35.64 (17.97, 70.70)	0.138	17.52 (9.76, 31.45)	109.68 (35.05, 343.16)	0.010

*: Values in the cells are mean (95% CI);
**: Values in the cells are %.
NGAL: neutrophil gelatinase associated lipocalin, **MCP1**: monocyte chemoattractant protein-1, **CP**: ceruloplasmin, **AGP:** alpha1-acid glycoprotein, **TF:** transferrin, **LPDGS:** lipocalin-like prostaglandin-D Synthase, **ADI:** adiponectin, **HPX:** hemopexin, **TGFB:** TGF-beta, , **VDBP:** vitamin D binding protein.

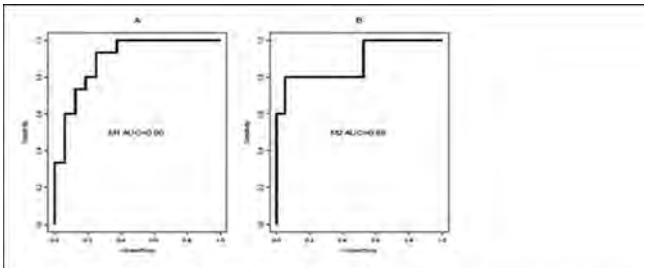

Figure 1 ROC curves of using panels of LN biomarkers to predict LN activity
A. LN activity is defined by GLAI>10. The panel of LN biomarkers is selected through a multivariate logistic model (M1) in the following
Logit(GLAI>10) = -1.57* Ln(C3)-0.79*Ln(NGAL/Cr)+0.83*Ln(CP/Cr)+1.94*Ln(MCP1/Cr)+0.79*Ln(TF/Cr)+1.88
B. LN activity is defined by TIAI>5. The panel of LN biomarkers is selected through a multivariate logistic model (M2) in the following
Logit(TIAI>5) = 1.09*Ln(NGAL/Cr)+0.89*Ln(HPX/Cr)-4.14

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1827

Anti-Ro and Anti-La Antibodies in the General Pregnant Population. Evelyn V. Rozenblyum[1], Sharon Sukhdeo[1], Edgar Jaeggi[2], Lisa Hornberger[3], Philip Wyatt[4], Carl A. Laskin[5] and Earl D. Silverman[6]. [1]University of Toronto, Toronto, ON, [2]The Hospital for Sick Children, University of Toronto, Toronto, ON, [3]Stollery Children's Hospital, Edmonton, ON, [4]North York General Hospital, Toronto, ON, [5]University of Toronto and LifeQuest Centre for Reproductive Medicine, Toronto, ON, [6]The Hospital for Sick Children, Toronto, ON.

Background/Purpose: Neonatal lupus erythematosus (NLE) is a passively transferred autoimmune disease that occurs in babies born to pregnant women with anti-Ro and anti-La antibodies. The most serious complication of NLE is congenital heart block (CHB). In pregnancies of women with a known autoimmune condition and positive anti-Ro antibodies, the incidence of CHB is approximately 1–2% of live births. We have previously shown that only pregnant women with moderate-high titre of antibodies were at risk to deliver a child with CHB. However, the rate of anti-Ro antibody positive pregnant women in an otherwise healthy population is unknown as is their risk for delivering a child with CHB.

Objectives: 1) Determine the rate of anti-Ro/La antibodies in the general pregnant population.

2) Determine if the incidence of CHB is increased in healthy pregnant women with positive Ro/La antibodies compared to pregnant women with known autoimmune disease and positive anti-Ro/La antibodies.

Methods: Antibody testing was performed on 15198 pregnant women who were having concurrent Maternal Serum Screening in the Metropolitan Toronto area. Maternal self-reported outcomes of prenatal, pregnancy, and post-natal medical conditions were reported, along with fetal outcomes of pre and post-natal illnesses. Autoantibody titres were stratified into negative, low, moderate, and high positive.

Results: 1152/151598 (7.6%) of the pregnant women had anti-Ro antibodies and 179/15198 (1.2%) had moderate-high titres (at risk to deliver a child with CHB). 779 (5.1%) had anti-La antibodies, with the majority being low titre. During the course of the study there were 13 cases of CHB that were unrelated to our maternal sample population- 10 to well women and 2 to women with an autoimmune disease. All of these women had moderate-high titre anti-Ro antibodies, while only 31% had moderate-high titre anti-La antibodies. During the course of the study 39 pregnant women with a known autoimmune disease and anti-Ro antibodies (at risk to deliver a child with CHB) were prospectively followed. 2/39 delivered a child with CHB. Both of these women had moderate-high titre anti-Ro antibodies while 15/37 pregnant women who delivered a child without CHB had moderate-high titre anti-Ro antibodies. Therefore 2/17 (11.8%) women with moderate-high titre anti-Ro antibodies and an autoimmune disease delivered a child with CHB.

Conclusion: The incidence of CHB is reported to be between 1:10–15,000 pregnancies. Therefore, based on our data showing 1.2% of otherwise well pregnant woman had moderate-high titre anti-Ro antibodies (at risk to deliver a child with CHB), for each child with CHB we predict that 120–180 children without CHB will be delivered to otherwise healthy women, and incidence of 0.5–0.8%. In contrast, in women with a known autoimmune disease and moderate-high anti-Ro antibody titre, we found a 11.8% incidence of CHB. Therefore the risk for a woman with a known autoimmune disease and moderate-high titre anti-Ro antibodies was approximately 10× that of otherwise healthy pregnant women. These data therefore suggest that the anti-Ro antibody repertoire differs between these 2 groups of pregnant women.

Disclosure: E. V. Rozenblyum, None; **S. Sukhdeo**, None; **E. Jaeggi**, None; **L. Hornberger**, None; **P. Wyatt**, None; **C. A. Laskin**, None; **E. D. Silverman**, None.

1828

Adverse Pregnancy Outcomes in Adolescents and Young Women with Systemic Lupus Erythematosus: A National Estimate. Nicole Ling, Isabel E. Allen, Erica F. Lawson and Emily von Scheven. University of California, San Francisco, San Francisco, CA.

Background/Purpose: Pregnant women with SLE have increased risk of adverse outcomes including lupus flare, spontaneous abortion, preeclampsia/eclampsia, premature birth and maternal death, but pregnancy outcomes among adolescents and young women with SLE have not been well-explored. Our goal was to compare pregnancy outcomes among adolescents and young women with and without SLE, and to identify associated risk factors.

Methods: We studied the 2000–2011 Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality. The NIS contains annual discharge data from all-payer hospital stays from about 1,000 nationwide hospitals, to approximate a 20% stratified sample of U.S. community hospitals. Hospitalizations of individuals age 21 or less with ICD-9 discharge diagnoses associated with pregnancy were included (delivery, liveborn, abortion, ectopic pregnancy, or intrauterine death). SLE hospitalizations were identified by a 710.0 ICD-9 code. After applying sampling weights, unadjusted odds ratios to estimate the risk of adverse pregnancy outcomes among individuals with and without SLE were calculated. Multi-variate logistic regression was performed to examine the independent effect of age, race, and socio-economic status on pre-eclampsia/eclampsia.

Results: 9,125,224 estimated hospitalizations were included in the analysis, of which 4,142 had SLE. Hospitalized women with SLE were slightly older (mean age 19.4 with range 14–21 vs.19 with range 8–21), more likely to be black (34% v. 21%), more likely to carry a discharge diagnosis of nephritis (11% v. 0.02%) or aPL (2.7% v. 0.1%), and more likely to undergo hemodialysis (0.35% v. 0.0%), all $p<0.0001$. Socioeconomic status repre-

sented by median household income quartiles for patient zip codes were not different across groups.

Table 1: Unadjusted weighted estimates of outcomes of unique pregnancies by hospital discharge data in those with and without SLE

Outcome	SLE N = 4,142	Non-SLE N = 9,121,082	P*	OR (95%CI) +
	N (%) unless noted			
Maternal Outcomes				
Pre-eclampsia and Eclampsia	657 (16)	417,676 (4.6)	<0.0001	3.9 (3.3 4.7)
Death during hospitalization	15 (0.37)	490 (0.005)	<0.0001	69.7 (22.6 214.6)
Fetal Outcomes				
Preterm	843 (20)	736,665 (8.1)	<0.0001	2.9 (2.5 3.4)
Low birth weight or fetal growth retardation	0 (0)	20 (0)	0.97	1 (0.0004 0.0005)
Spontaneous abortion or Intrauterine death	179 (4.3)	99,426 (1.1)	<0.0001	4.1 (2.9 5.8)
Induced abortion	90 (2.2)	11,749 (0.13)	<0.0001	17.2 (10.4 28.3)
Ectopic pregnancy	$^{2}10$ ($^{2}0.24$)^	30,293 (0.3)	0.61	0.7 (0.17 2.78)
Congenital Anomalies	58 (1.4)	29,185 (0.32)	<0.0001	4.4 (2.5 7.8)

* CHI^2 Analysis
\+ Unadjusted logistic regression
^**Unable to report cell sizes less than or equal to 10, per HCUP data use regulations.**

Conclusion: This large national dataset demonstrated increased risk of pre-eclampsia/eclampsia, maternal death, preterm labor, spontaneous and induced abortion, and congenital anomalies in pregnant adolescents and young women with SLE compared to those without SLE. This is similar to previous findings in the literature regarding adult women with SLE. Disease duration and activity, medication exposure and age of SLE onset for the study population are not known. Additional analyses are planned to further explore outcomes with multivariate modeling and to characterize risk factors associated with poor pregnancy outcomes among adolescents and young women with SLE.

Disclosure: N. Ling, None; **I. E. Allen**, None; **E. F. Lawson**, None; **E. von Scheven**, None.

1829

Role of Fluorinated Steroids in Preventing the Progression of Anti-SSA/Ro Associated Isolated Congenital Heart Block to Disease Beyond the Conduction System. Ummara Shah[1], Amit Saxena[1], Sara Sahl[1], Deborah Friedman[2], Jill P. Buyon[1] and Peter M. Izmirly[1]. [1]New York University School of Medicine, New York, NY, [2]New York Medical College, Valhalla, NY.

Background/Purpose: The cardiac manifestations of neonatal lupus (cardiac NL) characteristically present as conduction disease. A major concern is the extension of injury beyond the AV node, which can include endocardial fibroelastosis (EFE), dilated cardiomyopathy (DCM), and hydrops fetalis. Predictably, the overall case fatality for this more extensive disease is high, approaching 50%. Treatment of isolated block with fluorinated steroids (FS) to prevent disease progression has been considered but clear benefit has yet to be established. Moreover, this approach carries the potential for maternal and fetal toxicity. This study was initiated to determine whether FS given for the management of isolated advanced block prevents the development of disease beyond the AV node and whether in those cases FS has a survival benefit at 6 months.

Methods: Medical records from the Research Registry for Neonatal Lupus were reviewed. Inclusion was restricted to anti-Ro60 exposed cases presenting as isolated advanced block in utero and grouped according to whether FS were initiated within one week of detection or no treatment was given. Excluded were cases involving cardiac NL diagnosed after birth, inability to determine timing of FS initiation, FS initiation after one week of detection, and inability to determine timing of extranodal disease defined as EFE, DCM and/or hydrops fetalis.

Results: One hundred and seventy-four cases of cardiac NL met the study inclusion criteria. In the FS treated group (N=78), 12 (15.4%) fetuses developed extranodal disease compared to 12 (13.54%) in the untreated group (N=96), P=0.83. There were no significant differences in maternal age, race/ethnicity, diagnosis of Sjogren's syndrome and/or Systemic Lupus Erythematosus, or concomitant presence of anti-Ro52 or anti-SSB/La, between the FS and untreated groups. Although there was a significant difference between time of detection of advanced block between the groups (mean 22.4 weeks for FS vs. 24.5 weeks for untreated, P=0.004), the ventricular rate at detection was higher in the FS treated group (68.7 bpm) compared to the untreated group (63.1 bpm), P=0.052. There was no difference between the ventricular nadir between the two groups (53.5 bpm for FS vs. 52.9 bpm for untreated). The time from detection of advanced block to onset of extranodal disease tended to be longer in those receiving FS (5.78 weeks) compared to those untreated (1.9 weeks), P=0.28. For fetuses exposed to dexamethasone, there was no significant difference in cumulative dose between those that developed cardiomyopathy and those that did not (mean 318 mg vs. 251 mg, P=0.25). The case fatality rates at 6 months of post partum life were similar between the groups (7/78, 9% for FS vs. 8/96, 8.3% for untreated, P=1.0).

Conclusion: These data provide evidence for decision making regarding the use of dexamethasone in the management of isolated congenital heart block. The development of more advanced disease approaches 15% and institution of dexamethasone should not be routinely instituted solely for prevention of this complication.

Disclosure: U. Shah, None; **A. Saxena**, None; **S. Sahl**, None; **D. Friedman**, None; **J. P. Buyon**, None; **P. M. Izmirly**, None.

ACR Concurrent Abstract Session
Quality Measures and Quality of Care
Monday, November 17, 2014, 2:30 PM–4:00 PM

1830

A Novel Population Care Model in Rheumatoid Arthritis – Significant Improvement in Quality and Reduction in Cost of Care. Eric D. Newman[1], William T. Ayoub[2], David M. Pugliese[3], Chelsea Cedeno[1], Jason Brown[1], Thomas M. Harrington[1], Thomas P. Olenginski[1], Androniki Bili[1], Alfred E. Denio[1], Lisa L. Schroeder[1], Dennis Torretti[1], Tarun Sharma[1], Lyudmila Kirillova[1], Susan Mathew[1], Jonida Cote[1], Brian Oppermann[2], Cynthia Sullivan[2], Shantanu Bishwal[4], Brian DelVecchio[3] and Howard Aylward[2]. [1]Geisinger Health System, Danville, PA, [2]Geisinger Health System, State College, PA, [3]Geisinger Health System, Wilkes-Barre, PA, [4]Geisinger Health System, Wilkes Barre, PA.

Background/Purpose: Rheumatoid arthritis (RA) is a common chronic disease with significant morbidity, mortality, and cost. To optimize care for RA patients, we developed a novel value-based population care model - AIM FARTHER (**A**ttribution, **I**ntegration, **M**easurement, **F**inances, **A**nd **R**eporting of **THER**apies). AIM FARTHER was designed to improve quality and reduce cost of RA care.

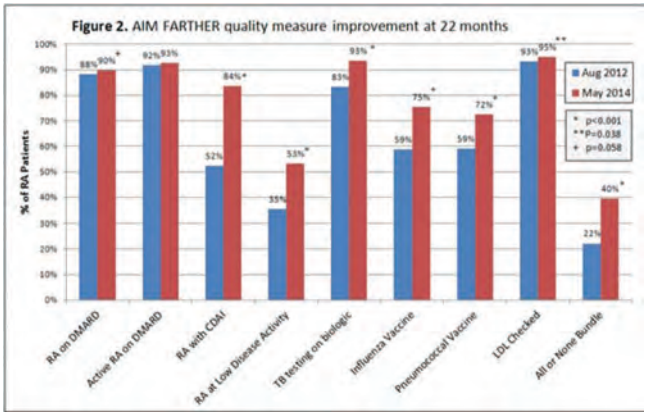
Methods: The AIM FARTHER model was designed and implemented for all RA patients cared for by the 17 rheumatologists within our health system (n=~2,300 patients). Components included 1) registry development; 2) defining roles and attribution; 3) integration of primary and specialty care; 4) strategic approach to RA care; 5) RA quality measure bundle development; 6) task management and performance reporting; and 7) a new financial/incentive model. The RA quality bundle included 8 measures – RA on DMARD (Disease Modifying Anti-Rheumatic Drug), Active RA on DMARD, RA with CDAI (Clinical Disease Activity Index), RA at low disease activity, TB testing if on biologic, Influenza vaccination, Pneumococcal vaccination, and LDL (low density lipoprotein) checked. These measures were collected electronically, providing the analytics for a patient scorecard (Figure 1). The scorecard was used to close care gaps, rolled up into provider and department performance reports, and shared transparently. Analysis of AIM FARTHER included quality (individual measures and "all or none" bundle score) and cost (biologic de-escalation savings).

Results: AIM FARTHER was implemented August 2012 (2,150 RA patients) with 22 month follow-up (2,378 RA patients). Significant improvement was noted in all quality measures except active RA on DMARD (92% to 93%)(Figure 2). Final values were RA on DMARD 90%, RA with CDAI 84%, RA at low disease activity 53%, TB testing on biologic 93%, Influenza vaccine 75%, Pneumococcal vaccine 72%, and LDL checked 95%. The all or none bundle improved from 22% to 40% (40% of the 2,378 RA patients had achieved 100% of their applicable quality measures). Cost savings from biologic de-escalation were $720,000 for 2013 with projected savings estimate of $1.2 million for 2014.

Conclusion: AIM FARTHER is a novel care model employing provider engagement, process redesign, measurement, and information technology to provide optimal care for patients with RA. AIM FARTHER showed significant improvement in quality measures and reduction in cost of care for a population of over 2,300 RA patients. Additionally, it supports the pivotal role that rheumatology can play in the systematic care of patients with RA.

Figure 1. Patient Quality Measure Scorecard

Disease Activity Measures		
RA on DMARD	ON DMARD	NON BIOLOGIC
Active RA on DMARD	ACTIVE RA ON DMARD	14.00
RA at Low Disease Activity	CDAI < 10	CDAI Date: 12/4/2013
CDAI Completed	CDAI COMPLETED	
Drug Safety Measures		
PPD if on Biologic	PPD N/A	
Flu Vaccine (Yearly)	FLUVAX NOT DONE	
Pneumococcal Vaccine	PNEUMOVAX DONE	
Comorbidity Measures		
LDL Checked	LDL COMPLETED	Most Recent LDL: 142



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1831

Monitoring Patients with Rheumatoid Arthritis in Routine Care – Experiences from a Treat-to-Target Strategy Using the Danbio Registry. Merete Lund Hetland[1], Dorte Vendelbo Jensen[2] and Niels Steen Krogh[3]. [1]DANBIO, Glostrup Hospital, Glostrup, Denmark, [2]DANBIO, Glostrup, Denmark, [3]ZiteLab ApS, Copenhagen, Denmark.

Background/Purpose: Monitoring patients with rheumatoid arthritis (RA) in clinical practice with regular assessment of disease activity (e.g. DAS28) is recommended as a part of a treat-to-target strategy, but little is known about its feasibility. In Denmark, prospective, nationwide collection of data on patients with RA in routine care has been conducted in the DANBIO database since year 2006 (1). We present the development over time in patient inclusion and disease control.

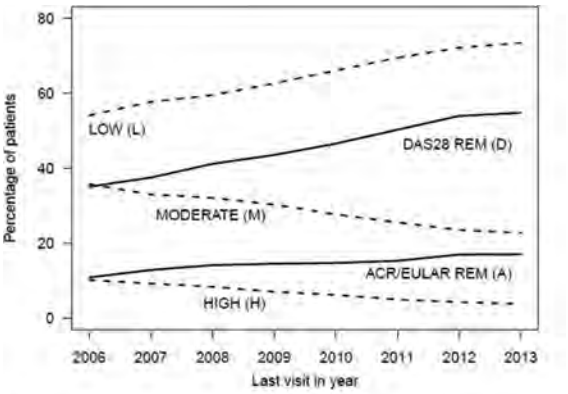
Methods: DANBIO serves as an electronic patient file in routine care. Disease activity score (DAS28) is presented in colour, encouraging a treat-to-target strategy. Patients are followed twice yearly.

Results: From Jan 1st 2006 to Dec 31st, 2013, the number of RA patients increased from 2,395 to 14,249 (age at time of inclusion: 60(50–59) (median(IQR)) years, 73% women, 87.2% IgM-RF positive, 54% erosive, disease duration 4 (0–11) years, HAQ 0.75(0.25–1.375), DAS28 3.9(2.7–5.1)).

By 2013, 9,054 patients were bDMARD naïve (MTX: 76%; other csDMARD: 21%), 4,254 pts received bDMARD (etanercept(28%) and adalimumab (21%) most prevalent; 66% in combination with MTX), and 941 pts had formerly received bDMARD.

In 2006, 54% of the 2,395 patients had low disease activity (DAS28<3.2) (figure). In 2013 it was 73% of 14,249 patients. For high disease activity it was 10% and 4%, respectively. The fraction of patients in DAS28 remission (DAS28<2.6) was 35% in 2006 and 55% in 2013. For ACR/EULAR remission it was 11% and 17%, respectively.

The prevalence of patients with RA in Denmark (which has ≈5.6 mill inhabitants) has in a medical technology review in 2002 been estimated to be ≈18,000 for patients who attend rheumatology clinics and departments, and ≈35,000 for patients with self-reported disease (2). By 2013, DANBIO's coverage may thus be estimated to be 40%–79%. For the subgroup receiving bDMARD, coverage is 94% (3).



Patients with data	2006	2007	2008	2009	2010	2011	2012	2013
L	1296	2632	3084	4511	6202	7662	9149	10471
M	856	1506	1664	2182	2595	2818	2984	3239
H	243	421	434	506	582	547	543	539
T	2395	4559	5182	7199	9379	11027	12676	14249
D	840	1711	2134	3135	4370	5545	6842	7808
A	260	586	733	1046	1381	1687	2151	2431

Figure. Number of RA patients in DANBIO by end of each year.
Patient distribution according to disease activity (L, M, H) and remission status (R, A)

Conclusion: By using an electronic platform, Danish rheumatologists included 40–79% of all RA patients into the DANBIO database during an 8 year period for prospective registration, thereby creating a data repository for quality improvement and research purposes with high external validity.

The demographic characteristics of the "real-life" cohort are typical for RA, and it covers all disease states regarding treatment, disability and disease activity. By 2013, 17% and 55% of patients were in ACR/EULAR remission and DAS28 remission, respectively, and 73% had low disease activity.

Thus, systematic monitoring of real-life RA patients with a treat-to-target strategy with real-time feedback to the physician is feasible, whereas the aim of treat-to-target is not achieved in a substantial proportion of patients in routine care.

(1) Hetland ML. Rheumatology 2011.
(2) Sundhedsstyrelsen CfEoMT. Med teknologivurdering 2002.
(3) DANBIO Annual Report 2013 (www.danbio-online.dk).

Disclosure: M. L. Hetland, None; **D. V. Jensen**, None; **N. S. Krogh**, None.

1832

National Quality Forum Measure Achievement and Costs in Rheumatoid Arthritis Patients in a Large Managed Care Population. Roxanne Meyer[1], Susan C. Bolge[2], Joseph Tkacz[3], Brenna Brady[3] and Charles Ruetsch[4]. [1]Janssen Scientific Affairs, Horsham, PA, [2]Janssen Scientific Affairs, LLC, Horsham, PA, [3]Health Analytics, LLC, Columbia, MD, [4]Health Analytics LLC, Columbia, MD.

Background/Purpose: The American College of Rheumatology and National Quality Forum (NQF) recommend monitoring quality measures among rheumatoid arthritis (RA) patients. Previously we described the proportion of RA patients within a large managed care population meeting the criteria of RA specific NQF quality measures[1–2]. This study examines the relationship between NQF measure attainment and healthcare expenditure.

Methods: Using the Optum™ Clinformatics™ database of insured individuals, 8 NQF RA quality measures (0054, 0589, 0590, 0592, 0597–0599, and 0601) were assessed among a sample of RA patients during calendar year 2011. NQF definitions may be found at http://www.qualityforum.org/QPS/. Mean specific healthcare costs, in addition to total healthcare costs, were calculated for all members eligible for analyses. The standard cost field, which is an estimate of the allowed payment for all provider services, was selected as the primary outcome of interest. **Results:** The majority of individuals were female and in their mid-fifties (mean age of 52.8). Measure achievement ranged from 55.9% (measure 0592) to 80.8% (measure 0054). The mean cost of care for individuals meeting the measure was $18,642, range 12,488-$21,300. Those patients who did not meet the measures had an average cost of care of $14,923, range $13,013 - $19,293. The primary drivers of cost were pharmacy and office expenses, accounting for 42.3% and 28.6% of total costs, respectively.

Table 1: Total HealthCare Costs (means) USD ($)

NQF Measure	Meeting the Measure	Not Meeting the Measure
NQF 0054 - DMARD Therapy	$21,314	$19,356
NQF 0589 - New DMARD Baseline Serum Creatinine	$15,182	$13,388
NQF 0590 - New DMARD Liver Function Test	$15,292	$13,314
NQF 0592 - Annual ESR or CRP	$17,945	$12,329
NQF 0601 - New RA patient ESR or CRP	$12,910	$13,624
NQF 0597 - Methotrexate Use Liver Function Test	$19,243	$17,787
NQF 0598 - Methotrexate User CBC Test	$19,173	$17,991
NQF 0599 - Methotrexate User Serum Creatinine	$19,526	$17,181

Conclusion: In general, meeting quality measures was associated with an increased cost of care. Pharmacy costs were similar between patients who did and did not meet the measures. Individuals who met the measures had higher office costs while those individuals who did not meet the measure trended towards higher inpatient costs and had significantly higher outpatient costs. These findings suggest that increased quality in healthcare may lead to lower inpatient and outpatient hospital costs, but that the overall cost of care for RA patients is likely to remain high due to intensive pharmacotherapy regimens.

1. Meyer, R., Ellis, L., Bolge, S., Tkacz, J., Kardel, P., and Ruetsch, C. (2013). National quality forum measures among rheumatoid arthritis patients in a large managed care population. Poster presented at the American College of Rheumatology 2013 Annual Meeting, San Diego, CA (abstract # 182).

2. Tkacz, J., Ellis, L., Meyer, R., Bolge, S., Brady, B., and Ruetsch, C. (2014). National Quality Forum measures for rheumatoid arthritis: Performance from members enrolled in a national health plan. *Manuscript under review: Journal of Managed Care & Specialty Pharmacy*.

Disclosure: R. Meyer, Janssen Scientific Affairs, LLC, 3; **S. C. Bolge**, Janssen Scientific Affairs, LLC, 3; **J. Tkacz**, Janssen Scientific Affairs, LLC, 5; **B. Brady**, Janssen Scientific Affairs, LLC., 5; **C. Ruetsch**, Janssen Scientific Affairs, LLC, 5.

1833

Quality of Primary Care Management of Patients with and without Rheumatoid Arthritis (RA). Jessica Widdifield[1], Claire Bombardier[2], Jacqueline Young[1], Noah Ivers[2], R. Liisa Jaakkimainen[3], Sasha Bernatsky[4], J. Michael Paterson[1], J. Carter Thorne[5], Pooneh S.Akhavan[6], Debra Butt[1], Vandana Ahluwalia[7] and Karen Tu[1]. [1]Institute for Clinical Evaluative Sciences, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]Sunnybrook Health Sciences Centre, Toronto, ON, [4]McGill University Health Centre, Montreal, QC, [5]Southlake Regional Health Centre, Newmarket, Newmarket, ON, [6]Mount Sinai Hospital, Toronto, ON, [7]William Osler Health Center, Brampton, ON.

Background/Purpose: Little is known about the quality of care received by patients with multiple chronic conditions in primary care and whether quality care is different for those with RA. Our aims were to evaluate the burden of specific types of co-morbidity and compare quality of care by primary care physicians for patients with and without RA.

Methods: We used the **E**lectronic **M**edical **R**ecord **A**dministrative data **L**inked **D**atabase (EMRALD), comprised of 163,039 adult patients from 271 primary care physicians in Ontario, Canada. We used a validated EMR-based algorithm with a 74.4% sensitivity, 99.9% specificity, 90.0% PPV, and 99.7% NPV for identifying patients with RA. All patients not identified by the algorithm were classified as non-RA patients. Validated disease-specific EMR-based algorithms were also used to identify patients with hypertension (HTN), diabetes mellitus (DM), and ischemic heart disease (IHD). Quality measures were adapted from published guidelines and expert opinion for each specific comorbidity. They include preventative (eg. vaccinations), screening (eg. cardiovascular risk control) and comorbidity management and treatment measures. Stratified analyses were performed among patients with vs without RA to identify the frequency of comorbidity and to assess performance of key process and outcome measures. Process measures indicating whether tests or assessments have been performed (eg. patients with DM whose HbA1c level were performed) were determined. Outcome measures reflect the results of the assessments (eg. patients with DM and HbA1c $< 7.0\%$). Logistic regression was used to adjust for age and sex for comparison between RA and non-RA patients.

Results: We identified 1,427 RA patients (prevalence 0.9%) and 74% were female. The average age of the RA and non-RA patient groups were 62 years and 51 years, respectively. Unadjusted for age and sex, RA patients had a higher documentation of influenza vaccinations and bone mineral density (BMD) tests than non-RA patients (table). RA patients also had significantly higher prevalence of HTN (39% vs 25%), DM (14% vs 10%), and IHD (10% vs 5%). Process measures in terms of the numbers of patients who were routinely monitored and treated for the management of these chronic conditions were similar in patients with and without RA. After adjusting for age and sex, no differences were observed between the groups on all measures except that RA patients were more likely to receive pneumococcal vaccinations and undergo BMD tests.

Conclusion: Ontario primary care physicians provide similar quality of care for patients with and without RA. Pneumococcal vaccination and BMD tests were more frequent among RA patients, likely due to corticosteroid/immunosuppressant use. Further research is required to evaluate how 'shared care' between primary care physicians and rheumatologists can optimize prevention and screening measures to help decrease the development of comorbidity in RA.

	Indicators	RA patients n=1,427	Non-RA patients n=161,612
Process	Influenza Vaccination in the past 18 months	718 (50.3%)	51,532 (31.9%)
Process	Pneumococcal vaccination ever	505 (35.4%)	27,832 (16.9%)
Process	> 65 years AND BMD test recorded ever	394 (62.7%)	18,061 (47.2%)
	Patients with HTN	**552 (38.7%)**	**39,424 (24.5%)**
Process	Patients with HTN AND BP tested in the past 15 mo.	509 (92.2%)	35,918 (91.1%)
Outcome	Patients with HTN and BP test < 160/100mmHg	398 (72.1%)	26,166 (66.4%)
	Patients with Diabetes	**204 (14.3%)**	**16,575 (10.3%)**
Process	Diabetics with HbA1c tested in the past 6 mo.	126 (61.8%)	11,372 (68.6%)
Outcome	Diabetics with HbA1c < 7.0% in the past 12 mo.	102 (50%)	7,388 (44.6%)
	Patients with IHD	**138 (9.7%)**	**8,223 (5.1%)**
Process	Patients with IHD AND on a statin in the past 15 mo.	110 (79.7%)	6,993 (85.0%)
Outcome	Patients with IHD AND LDL< 2.0mmol/L in the past 15 mo.	60 (43.5%)	3,675 (44.7%)

Disclosure: J. Widdifield, None; **C. Bombardier**, None; **J. Young**, None; **N. Ivers**, None; **R. L. Jaakkimainen**, None; **S. Bernatsky**, None; **J. M. Paterson**, None; **J. C. Thorne**, None; **P. S.Akhavan**, None; **D. Butt**, None; **V. Ahluwalia**, None; **K. Tu**, None.

1834

Uptake of the American College of Rheumatology's (ACR) Rheumatology Clinical Registry (RCR): Quality Measure Summary Data. Natalie Fisk[1], Melissa Francisco[1], Jinoos Yazdany[2] and Salahuddin Kazi[3]. [1]American College of Rheumatology, Atlanta, GA, [2]University of California, San Francisco, San Francisco, CA, [3]UT Southwestern Medical Center, Dallas, TX.

Background/Purpose: The RCR is designed to provide ACR members with an infrastructure for quality reporting related to rheumatoid arthritis, gout, osteoarthritis, osteoporosis, and drug safety. Currently in its fifth year of operation, the RCR contains data on over 38,000 patient encounters.

Here we report the uptake of the RCR by U.S. rheumatologists and performance on quality measures regarding functional status, disease modifying anti-rheumatic drug (DMARD) use, tuberculosis screening, prognosis, and disease activity assessment for RA patients in 2011, 2012, and 2013.

Methods: Data derive from retrospective medical records abstractions performed by providers and/or designated practice staff for a sample of patients seen by rheumatologists. Reporters submit data on quality measures via a secure, web-based registry system. Patients included in the denominator of all quality measures are >= 18 years of age with a diagnosis of RA who are receiving treatment by the reporting rheumatology provider. Additional details of each measure are listed in Table 1. We report the mean performance on each quality measure, defined as percentage of eligible patients receiving recommended care.

Results: Table 1 summarizes performance on RA measures reported through the RCR. The table includes data from the current reporting period (CY2013) as well as comparative data from CY2012 and CY2011. For the current reporting period, 215 rheumatology providers from 123 practices submitted data on 6,963 encounters with RA patients. During CY2012, 197 rheumatology providers in 115 practices submitted data on 9,154 encounters with RA patients. In CY2011, 224 rheumatology providers in 129 practices submitted data on 8,096 encounters with RA patients. Reporting providers practice in sites ranging from solo offices to large academic medical centers.

Table 1. Performance on RA Measures Assessed through the RCR

	CY2011		CY2012		CY2013	
	Patient Encounters (N)	QM Performance Rate	Patient Encounters (N)	QM Performance Rate	Patient Encounters (N)	QM Performance Rate
Disease activity assessed at least once within 12 months, using a standardized descriptive or numeric scale or composite index, and classified as low, moderate or high	8075	43.3%	6485	54.4%	5702	81.0%
Functional status assessment performed at least once within 12 months, and documented using a standardized descriptive or numeric scale, standardized questionnaire, or notation of assessment of the impact of RA on patient activities of daily living	8077	70.5%	6485	86.6%	6068	87.1%
Patient prescribed, dispensed, or administered at least one ambulatory prescription for a DMARD within 12 months	7808	97.9%	6485	86.6%	6748	96.8%

Documentation of TB screening performed and results interpreted within 6 months prior to receiving first course DMARD	1650	73.6%	1048	92.9%	909	90.5%
Assessment and classification of disease prognosis at least once within 12 months	7771	49.5%	6441	73.4%	5398	77.5%

Conclusion: Performance rates increased on four out of five measures from CY2011 to CY2012. Based on preliminary results, it appears that use of the RCR to track quality measures increases performance.

Disclosure: N. Fisk, None; **M. Francisco**, None; **J. Yazdany**, None; **S. Kazi**, None.

1835

Anti-Osteoporosis Medication Use after Hip or Vertebral Fracture. Robert A. Overman[1] and Chad L. Deal[2]. [1]University of North Carolina, Chapel Hill, NC, [2]Cleveland Clinic, Cleveland, OH.

Background/Purpose: Current National Osteoporosis Guidelines recommend treatment with an approved osteoporosis medication after hip and vertebral fracture. Only 20% of patients receive osteoporosis therapy after hip fracture. We examined the rates of treatment within 365 days of an osteoporosis medication after hip and vertebrae fracture in a large health care system.

Methods: We evaluated use of anti-osteoporosis medications after fracture by identifying all patients over age 40 who had a hip fracture that was surgically repaired and all vertebral fracture patients undergoing augmentation (kyphoplasty or vertebroplasty) based on administrative billing Common Procedure Terminology (CPT) codes between 2010 and September 2013. These patients were then linked to their electronic medical record (EMR) data. We define the index date as the date of the surgical procedure with patients followed until death, AOM use, or 365 days. AOMs in this analysis are bisphosphonates, denosumab, teriparatide, estrogen, or raloxifene. Dates of medication use are based on start and stop dates in the EMR. Basic demographic variables including age, race, gender, prior AOM use, and site of fracture, were collected from the patients EMR and are presented as mean (standard deviation [SD]) or n (%).We evaluated initiation or continuation of AOM at 90, 180, and 365 days post-index and factors associated with their initiation. Hazard ratios (HR) (95% confidence interval [CI]) were created with cox proportional hazards model and are adjusted for gender, race, age by decade, and site of fracture.

Results: There were 1,352 hip fractures and 296 vertebral fractures undergoing augmentation between January 2010 and December 2012. Mean age was 80.9 (SD 12.7) for hip and 75.0 (SD 12.5) for vertebral fractures. Women were the majority population for both hip (73.1%) and vertebral fractures (72.6%). Caucasians made up the majority of both populations (hip 89.6%; vertebral 92.2%). First event was AOM use for 16.1% (hip: 11.1%, vertebral: 39.2%) and death for 11.3% (hip: 12.5%, vertebral 5.7%) of the population. Prior to index date 24.2% of hip and 40.5% of vertebral fracture patients were prescribed an AOM. AOMs were used at fracture or within 90 days for 12.0%, 13.2%, and 14.6% for hip fracture and 34.5%, 37.8% and 45.3% for vertebral fractures at 90,180 and 365 days respectively. Vertebral fractures were associated with an increased likelihood of AOM treatment by 365 days (HR 3.1; 95% CI 2.4, 4.0), women (79.2% of population) were no more likely to be treated (HR 1.3 95% CI 0.9, 1.8) compared to men, and AOM use prior to fracture was associated with treatment by 365 days (HR 3.6; 95% CI 2.8, 4.7).

Conclusion: Treatment gaps continue to persist for hip fracture patients with 14.6% of patients receiving treatment by 365 days after fracture, and while only 45.3%% of vertebral fracture patients having augmentation receiving therapy by 365 days. Patients with a vertebral fracture and those who were treated before fracture were more often placed on AOM. Treatment after fracture helps has been demonstrated to reduce the likelihood of additional fractures and interventions are needed to increase treatment rates in these at risk populations.

Disclosure: R. A. Overman, None; **C. L. Deal**, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects III: Malignancies, Vaccinations, Pregnancy and Surgery
Monday, November 17, 2014, 2:30 PM–4:00 PM

1836

Safety of Zoster Vaccination Administration in Rheumatic Patients on Current Biologic Therapy. Stephen Lindsey[1], Brandi Oufnac[2] and Holly Walker[2]. [1]Ochsner Clinic Baton Rouge, Baton Rouge, LA, [2]Ochsner Health Systems, Baton Rouge, LA.

Background/Purpose: Herpes Zoster (HZ) occurs in 1 in 3 people in the U.S. during their lifetime. The greatest risk factor is age. Immune suppression from illness or medications is also a strong risk factor. RA increases zoster rates 1.5 – 2 times normal as does > 10mg prednisone per day. Studies are mixed on the role of Mtx and antiTNF's on HZ. Zoster vaccine has been shown to lower risk and is approved for all patients over 50 by the FDA and recommended for patients over 60 by the Advisory Committee on Immunization Practices (ACIP). Guidelines from the ACIP and ACR do not recommend HZ vaccine in patients on biologic therapies. However, recent large data-base studies have not found an increase in zoster complications in patients inadvertently given the vaccine while on biologics. These data encouraged our group to evaluate the safety of this vaccine in current biologic users.

Methods: Since July 2012, all 160 patients with RA, PSA & AS receiving IV biologics in our infusion center have been prospectively assessed for HZ vaccine as well as 142 patients on subq biologics for the same indications. RA accounts for 93% of infusion and 66% of subq patients. All biologics were represented. Remicade was the most common infusion followed by Orencia. Enbrel was the most common subq followed by Humira.

Inclusion/exclusion criteria for vaccination included: age > 50, no hx anaphylaxis to neomycin or gelatin, no episodes of HZ in last 4 years, pregnancy, patient consent, and disease activity stable - moderate or less on consecutive visits. No patients had an active infection or malignancy.

If patient meets criteria, vaccine given at next interval scheduled dose of biologic, which is **held**. Example - hold Enbrel 1 week, Humira 2 weeks, Orencia 4 weeks, Remicade 8 weeks. Mtx was held week of vaccine and restarted 1 week post vaccine. Biologic restarted 2 weeks after vaccine. In 17 Rituxan patients vaccine was given 2–4 weeks pre Rituxan or > than 6 months post Rituxan. No other vaccines were given the week of the HZ vaccine.

Results: Of 160 infusion patients 110 (68%) have been vaccinated; over 60% had been on biologic > 5 years, 5% < 1 year. No patient developed disseminated HZ. One patient had significant swelling and tenderness at the injection site. Most common reasons not to vaccinate: 11 with recent HZ, 14 < age 50, and 17 with disease activity issues. Of 142 subq patients, 42 (32%) have been vaccinated; over 50% had been on biologic > 5 years, 10% < 1 year. No patients developed disseminated HZ or had a significant local reaction. Most common reasons not to vaccinate: 74 patients < 50, 12 with disease activity issues, 5 with HZ vaccine concerns and 5 with recent HZ. No patients in either group developed HZ within the six weeks post vaccination. Two patients vaccinated since 2012 in our infusion cohort have developed HZ at 16 and 20 months and none in the subq patients. Prior to 2012, only 7 and 8 % of the cohorts had received HZ vaccine.

Conclusion: HZ vaccination in chronic RA, PSA or AS patients on current IV or subq biologic therapies appears safe using this protocol. No occurrence of disseminated HZ occurred. There was no increased incidence of HZ in the early post vaccination period.

Disclosure: S. Lindsey, None; **B. Oufnac**, None; **H. Walker**, None.

1837

First Results of a European Registries Collaborative Project to Compare the Spectrum of Lymphomas Between Different Exposure Groups in Rheumatoid Arthritis. Louise Mercer[1], Xavier Mariette[2], William Dixon[1], Eva Baecklund[3], Karin Hellgren[4], Lene Dreyer[5], Merete Lund Hetland[6], Lene Mellemkjær[7], Kimme Hyrich[8], Anja Strangfeld[9], Angela Zink[10], Helena Canhao[11], Fernando Martins[12], Victoria Hernández[13], Florence Tubach[14], Jacques-Eric Gottenberg[15], Jacques Morel[16], Jakub Zavada[17], Piet van Riel[18], Axel Finckh[19], Florenzo Iannone[20], Johan Askling[4] and Joachim Listing[9]. [1]The University of Manchester, Manchester, United Kingdom, [2]Université Paris-Sud, Le Kremlin Bicêtre, France, [3]Uppsala University, Uppsala, Sweden, [4]Karolinska Institutet, Stockholm, Sweden, [5]Copenhagen University Hospital at Gentofte, Gentofte, Denmark, [6]DANBIO, Glostrup Hospital, Glostrup, Denmark, [7]The Danish Cancer Society, Copenhagen, Denmark, [8]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [9]German Rheumatism Research Center, Berlin, Germany, [10]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, [11]Instituto de Medicina Molecular, Universidade de Lisboa, Lisbon, Portugal, [12]Instituto de Medicina, Universidade de Lisboa, Lisbon, Portugal, [13]BIOBADASER Registry, Madrid, Spain, [14]Universite Paris Diderot, Paris, France, [15]Department of rheumatology CHU, Strasbourg, France, [16]Universite′ Montpellier, Montpellier, France, [17]Charles University, Prague, Czech Republic, [18]Radboud University Medical Centre, Nijmegen, Netherlands, [19]University of Geneva, Geneva, Switzerland, [20]Reumatologia Universita e Policlinico di Bari, Bari, Italy.

Background/Purpose: Rheumatoid arthritis (RA) is associated with a 2–3 fold increased risk of both Hodgkin and non-Hodgkin lymphoma (HL; NHL). The risk of lymphoma, in particular diffuse large B-cell lymphoma (DLBCL) is greatest in patients with persistently active RA: those patients that are also most likely to receive biologics. There has been a concern that TNF inhibitors (TNFi) could increase the risk of lymphoma via reduced immunosurveillance. Conversely, TNFi may, by improved disease control, decrease lymphoma risk, especially risk of DLBCL. This abstract describes a EULAR initiative to describe the spectrum of lymphomas occurring in biologic-naïve patients with RA and those treated with biologics.

Methods: Patients with RA were included from 11 European biologics registers in 8 countries and followed prospectively for the occurrence of first ever lymphoma, confirmed with histology. Patients were considered to be exposed to a biologic agent after receiving the first dose and lymphomas were attributed to the most recently received biologic drug. For the TNFi cohort, prior exposure to biologic drugs was not permitted. Prior exposure to TNFi was allowed for other biologic drugs. Frequency of lymphoma subtypes was recorded for each drug class.

Results: Data for 130462 patients were available for the analysis (Sweden: n=61527, Denmark: n=21454, UK: n=17907, Germany: n=12581, Portugal: n=5031, Spain: n=4590, France: n=4512, Czech Republic: n=2860): mean age 59, 74% female. In total 520 lymphomas with subtype information were included in the table. Patient years were available for 493 lymphomas, corresponding to an overall crude incidence rate (IR) of 8.3 (95% CI 7.6, 9.1).

DLBCL was the most frequent subtype (37% of all lymphomas; Table). 9% of lymphomas were HL and 6% T-cell, with no cases of hepatosplenic T-cell lymphoma. Importantly, the distribution of subtypes was similar across treatment groups.

Conclusion: This large collaborative analysis of European registries has successfully collated subtype information on more than 500 lymphomas. There was no evidence of modification of the distribution of lymphoma subtypes reported in patients following exposure to biologics. This collaboration facilitates more detailed analyses, accounting for age, sex, country and specific TNFi, as well as RA-related factors.

Table. Subtypes of lymphoma reported in biologic-naïve and –exposed cohorts of patients with rheumatoid arthritis

	All N= 130462	sDMARD N=71866	TNFi N= 41078	RTX N=9880	TOC N= 4800	ABA N=2838
Total follow up time (person-years)	**592245**	**322422**	**226080**	**30606**	**7122**	**6015**
Female (%)	74.3	72.2	76.5	79.0	80.1	78.0
Age (mean)	58.7	60.7	55.4	57.9	55.9	56.8
Total number of lymphomas	**520***	**288**	**219***	**6**	**5**	**2**
Lymphoma subtypes: Number (% of total number)						
Hodgkin Lymphoma	**45 (9)**	**21 (7)**	**24 (11)**	**0**	**0**	**0**
B-cell lymphomas	**389 (75)**	**220 (76)**	**157 (72)**	**5 (83)**	**5 (100)**	**2 (100)**
Chronic lymphocytic /small cell lymphoma	55 (11)	28 (10)	24 (11)	1 (17)	2 (40)	0
B-HHL Lymphoplasmocytic lymphoma (Waldenstrom macroglobulinemia)	11 (2)	4 (1)	6 (3)	1 (17)	0	0
Marginal zone lymphoma	9 (2)	1 (0)	8 (4)	0	0	0
Follicular lymphoma	67 (13)	33 (11)	32 (15)	1 (17)	0	1 (50)
Mantle cell lymphoma	5 (1)	5 (2)	0	0	0	0
Diffuse Large B Cell lymphoma	194 (37)	113 (39)	75 (34)	2 (33)	3 (60)	1 (50)
Unspecified B-cell lymphomas	48 (9)	36 (13)	12 (5)	0	0	0
T-cell lymphomas	**32 (6)**	**17 (6)**	**14 (6)**	**1 (17)**	**0**	**0**
Peripheral T-cell lymphoma	12 (2)	6 (2)	5 (2)	1 (17)	0	0
Angioimmunoblastic lymphoma	5 (1)	3 (1)	2 (1)	0	0	0
Anaplastic large cell lymphoma	1 (0)	1 (0)	0	0	0	0
LGL T-cell leukaemia	0	0	0	0	0	0
Pleiomorphic T-cell lymphoma	2 (0)	0	2 (1)	0	0	0
Hepatosplenic T-cell lymphoma	0	0	0	0	0	0
Unspecified T-cell lymphomas	12 (2)	7 (2)	5 (2)	0	0	0
Unspecified non-Hodgkin lymphoma/ lymphoma	**53 (10)**	**30 (10)**	**23 (11)**	**0**	**0**	**0**

All percentages represent % of the total number of lymphomas in that cohort with % of Hodgkin lymphoma, B- and T-cell lymphomas and unspecified NHL/ lymphoma totaling 100%; *27 lymphomas, but no follow up time (person-years), are included from the RATIO registry, France. sDMARD synthetic disease modifying drugs; TNFi inhibitors of TNF; RTX rituximab; TOC tocilizumab; ABA abatacept.

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1838

No Increased Risk of Developing a First Invasive Melanoma in Rheumatoid Arthritis Patients Treated with Biologics: Results of a Collaborative Project of 11 European Biologics Registers. Louise Mercer[1], Johan Askling[2], Pauline Raaschou[2], William Dixon[1], Lene Dreyer[3], Merete Lund Hetland[4], Lene Mellemkjær[5], Anja Strangfeld[6], Angela Zink[7], Florenzo Iannone[8], Axel Finckh[9], Jakub Zavada[10], Helena Canhao[11], Fernando Martins[12], Xavier Mariette[13], Jacques Morel[14], Jacques-Eric Gottenberg[15], Adele Green[1], Victoria Hernández[16], Florence Tubach[17], Piet van Riel[18], Kimme Hyrich[19] and Joachim Listing[6]. [1]The University of Manchester, Manchester, United Kingdom, [2]Karolinska Institutet, Stockholm, Sweden, [3]Copenhagen University Hospital at Gentofte, Gentofte, Denmark, [4]DANBIO, Glostrup Hospital, Glostrup, Denmark, [5]The Danish Cancer Society, Copenhagen, Denmark, [6]German Rheumatism Research Center, Berlin, Germany, [7]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, [8]Reumatologia Universita e Policlinico di Bari, Bari, Italy, [9]University of Geneva, Geneva, Switzerland, [10]Charles University, Prague, Czech Republic, [11]Instituto de Medicina Molecular, Universidade de Lisboa, Lisbon, Portugal, [12]Instituto de Medicina, Universidade de Lisboa, Lisbon, Portugal, [13]Université Paris-Sud, Le Kremlin Bicêtre, France, [14]Universite′ Montpellier, Montpellier, France, [15]Department of rheumatology CHU, Strasbourg, France, [16]BIOBADASER Registry, Madrid, Spain, [17]Universite Paris Diderot, Paris, France, [18]Radboud University Medical Centre, Nijmegen, Netherlands, [19]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Swedish and Danish national biologics registers (*) have reported a possible increase in melanoma risk with TNF inhibitors. Since melanomas are uncommon, the association is difficult to evaluate in other individual registers. We therefore planned a EULAR collaborative project.

Methods: Patients with RA from 11 European biologics registers in 9 countries were included. Patients were followed prospectively from start of a new biologic treatment until the occurrence of first invasive histology-confirmed cutaneous melanoma, using an ever-exposed approach. For the TNFi cohort, prior exposure to biologic drugs was not permitted. Prior exposure to TNFi was allowed for other biologic drugs. For each register, incidence rates and standardized incidence ratios (SIR) of melanoma were calculated by using age- sex- and calendar year-specific rates from the general population of the corresponding country as reference. Poisson regression models were used to summarize the register-specific SIRs to overall SIR estimates. Rates of melanoma in biologic exposed patients were compared to those in biologic-naïve patients enrolled in participating registers by calculating incidence rate ratios (IRR). Overall SIRs and IRRs were calculated, taking the size of the registers into account.

Results: Overall, 114,291 patients were available for analysis: mean age 58 years; 74% female. 287 developed a first invasive melanoma. Background population rates varied due to differences in the incidence by country, calendar years and differences in the age and sex distribution of the corresponding RA cohorts (Table). The SIRs for biologic naïve patients were similar across the registers whereas there was variation in SIRs between TNFi cohorts (table). The overall IRRs did not show a significantly increased melanoma risk for any of the biologic therapies compared to biologic-naïve patients. Similar results were found with other drug exposure models (data not shown).

Conclusion: This large European collaborative project of 11 registers from 9 countries did not confirm an increased risk of melanoma following exposure to TNFi, although an association cannot be completely ruled out with these data.

Table. Number of melanomas, standardized incidence ratios and incidence rate ratios in different treatment groups of RA

		Person years	Pop. rate/ 100,000	N Obs.	N Exp.	SIR (95% CI) (Obs/Exp)	IRR (95% CI) (SIR bDMARD/ SIR Ref.)
Biologic-naïve	**total**	**300011**	**48**	**160**	**144.3**	**1.11 (0.9, 1.4)**	**Referent**
	Sweden	222496	52	133	115.5	1.15 (0.96, 1.4)	Ref. (Sweden)
	BSRBR, UK	22972	35	9	8.0	1.12 (0.5; 2.1)	Ref. (UK)
	DANBIO, Denmark	27469	57	14	15.7	0.89 (0.5; 1.5)	Ref. (Denmark)
	RABBIT, Germany	9916	33	4	3.3	1.22 (0.3, 3.1)	Ref. (Germany)
TNF ever-exposed	**Total**	**242814**	**35**	**106**	**85.5**	**1.24 (0.99, 1.6)**	**1.14 (0.8, 1.6)**
	ARTIS, Sweden	59166	44	39	26.0	1.50 (1.1; 2.1)	1.30 (0.9; 1.9)
	BSRBR, UK	90259	31	31	28.1	1.10 (0.8, 1.6)	0.98 (0.5, 2.3)
	DANBIO, Denmark	22972	49	18	11.3	1.59 (0.9, 2.5)	1.79 (0.8, 3.9)

	RABBIT, Germany	23103	31	7	7.1	0.99 (0.4; 2.0)	0.81 (0.2, 3.8)
	GISEA, Italy	16180	40	6	6.4	0.94 (0.3; 2.0)	n.a.
	SCQM, Switzerland	15605	26	3	4.1	0.74 (0.2; 2.2)	n.a.
	ATTRA, Czech Republic	8441	22	1	1.8	0.55 (0; 3.0)	n.a.
	Reuma.pt, Portugal	7088	9	1	0.7	1.49 (0; 8.3)	n.a.
RTX ever-exposed	**total**	**29619**	**35**	**13**	**10.3**	**1.26 (0.6, 2.5)**	**1.14 (0.5, 2.9)**
TOC ever-exposed	**total**	**5798**	**33**	**5**	**1.9**	**2.65 (0.8, 8.4)**	**2.39 (0.6,10.1)**
ABA ever-exposed	**total**	**4858**	**29**	**2**	**1.4**	**1.47 (0.1,30.9)**	**1.33 (0.2; 7.6)**

Table: Person-years, incidence rate in the general population(s) (Pop. rate), observed (obs.) and expected (exp.) melanoma cases, SIRs, and IRRs for biologic-naive, anti-TNF (TNF), rituximab (RTX), tocilizumab (TOC), and abatacept (ABA) exposed RA patients; n.a. not available (no biologic naïve cohort)

(*) Raaschou P et al., BMJ 2013;346:f1939; Dreyer L et al. Ann Rheum Dis 2013;72:79–82

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Risk of Recurrent Non-Melanoma Skin Cancer with Methotrexate and Anti-TNF Use in Rheumatoid Arthritis. Frank I Scott[1], Ronac Mamtani[1], Colleen Brensinger[1], Kevin Haynes[2], Zelma ChiesaFuxench[1], Huifeng Yun[3], Jie Zhang[4], Lang Chen[5], Fenglong Xie[5], David Margolis[1], James D. Lewis[2] and Jeffrey R. Curtis[6]. [1]University of Pennsylvania, Philadelphia, PA, [2]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [3]University of Alabama at Birmingham School of Public Health, Birmingham, AL, [4]Univ. of Alabama at Birmingham, Birmingham, AL, [5]University of Alabama at Birmingham, Birmingham, AL, [6]The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Methotrexate (MTX) and anti-TNF drugs have been hypothesized to increase the risk of a first non-melanoma skin cancer (NMSC). Among patients with prior NMSC, it is unknown what impact use of these medications has on a second NSMC.

Methods: We performed a cohort study using Medicare data from 2006–2011. We identified Caucasian patients with rheumatoid arthritis (RA) and a first recorded NMSC on the basis of a diagnostic code for NMSC and related surgical procedure within 60 days according to a validated algorithm. We assessed for MTX, anti-TNF, abatacept, and rituximab use before and after the initial NMSC diagnosis. Hydroxychloroquine and sulfasalazine (HCQ/SSA) were assessed as comparator therapies. We excluded individuals with HIV, organ transplant, xeroderma pigmentosa, albinism, and psoriasis. Follow-up began at the latest of either ≥1 year after the first NMSC surgery or a 6-month period without an NMSC diagnosis after surgery. The primary outcome was a second NMSC. Drug exposure was categorized as never, current, or recently discontinued after the start of follow-up. We adjusted for exposure to these drugs prior to incident NMSC. Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals, adjusted for age, sex, latitude, urban or nursing home residence, and covariates assessed at baseline including comorbidities, glucocorticoids, actinic keratosis, and number of dermatology visits.

Results: 5994 individuals with RA had a first NMSC; 847 developed a second NMSC. Baseline actinic keratoses were more common in those with a second NMSC (65.2% vs 53.2%). Other baseline characteristics were similar. Current exposure to MTX was associated with a significantly increased risk of a second NMSC (Table 1). When stratified by concomitant exposure to anti-TNFs, SSA, or HCQ as background therapies, MTX use was consistently associated with a numerically but not statistically significant increased risk of a second NMSC. Risk of a second NMSC increased with longer duration of MTX exposure relative to no MTX exposure. Use of an anti-TNF, abatacept, or rituximab were not associated with an increased risk of second NMSC compared to those not using each agent, with the exception of short-term anti-TNF use (HR 1.46, 95%CI 1.01–2.10).

Conclusion: Current MTX use increased the risk of a second NMSC among those with a prior NMSC. This association was not observed with anti-TNF drugs, rituximab, or abatacept.

Table 1: Impact of Current MTX on recurrent NMSC

Combination of interest	Adjusted HR (95% CI)*
Pooled analysis:	1.0 (ref)
SSA/HCQ or Anti-TNF monotherapy	
MTX with SSA/HCQ or anti-TNF	1.44 (1.09–1.90)
MTX with SSA/HCQ: SSA/HCQ monotherapy	1.0 (ref)
SSA/HCQ with MTX	1.59 (0.79–3.20)
MTX with Anti-TNF: Anti-TNF monotherapy	1.0 (ref)
Anti-TNF with MTX	1.61 (0.95–2.73)
MTX use stratified by cumulative duration (ref: unexposed)	
Short-Term (<1 year)	1.16 (0.88–1.53)
Long-Term (>1 year)	1.24 (1.03–1.49)
Recently discontinued	0.80 (0.57–1.11)

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1840

Pregnancy Outcomes Following Exposure to Abatacept during Pregnancy. M Kumar[1], L Ray[1], S Vemuri[2] and T Simon[1]. [1]Bristol-Myers Squibb, Hopewell, NJ, [2]Bristol-Myers Squibb, Plainsboro, NJ.

Background/Purpose: Limited data are currently available in the medical literature to guide counseling of patients regarding pregnancy outcomes when treated with abatacept, a selective T-cell co-stimulation modulator approved for the treatment of RA. We characterized pregnancy outcomes following maternal and paternal exposure to abatacept.

Methods: Pregnancy data were obtained on abatacept-exposed patients from clinical studies and the company post-marketing safety database. This dataset includes all medically confirmed cases of pregnancy with outcome data reported to the manufacturer, beginning with Phase I studies of abatacept (1995) until April 1, 2014. Pregnancies with maternal or paternal exposure to abatacept were captured. Congenital anomalies were identified using the Center for Disease Control's birth defects surveillance system, Metropolitan Atlanta Congenital Defects Program (MACDP; version 08/07).

Results: A total of 140 pregnancies with known outcomes were identified: 132 cases were maternal and 8 cases were of paternal exposure. Eighty cases (72 maternal; 8 paternal) were from clinical studies and 60 (all maternal) were from post-marketing reports. More than 50% of cases were from the United States, Canada, Argentina, and Mexico. The median maternal age was 32 years (15–44 years). Outcomes from pregnancies with maternal exposure to abatacept are reported in Table 1. Among the pregnancies with maternal exposure to abatacept, there were 7 MACDP-identified congenital anomalies out of 76 live births. Of the 8 pregnancies with paternal exposure to abatacept, there were 7 live births and 1 induced abortion, with no congenital anomalies identified. There did not appear to be any pattern of congenital anomalies for abatacept exposure. When data were available regarding concomitant medications, MTX was the most common relevant reported agent (see Table).

Table. Reported outcomes of pregnancies with maternal abatacept exposure

Outcomes	Count, n (%) n=132	Exposure to concomitant medications,** n (%) MTX	LFM	MMF/MMS	AZA
Births					
Total live births	76 (57.8)	28 (21.2)	6 (4.5)	4 (3.0)	3 (2.3)
Live births with congenital anomalies	7 (5.3)				
Cleft lip/cleft palate	1 (0.8)	–	–	–	–
Down syndrome*	1 (0.8)	–	–	–	–
Congenital aortic anomaly	1 (0.8)	–	–	–	–
Meningocele	1 (0.8)	–	–	1 (0.8)	–
Pyloric stenosis	1 (0.8)	–	–	–	–
Skull malformation	1 (0.8)	–	–	–	–
Ventricular septal defect; congenital arterial malformation	1 (0.8)	–	1 (0.8)	–	–
Abortion					
Spontaneous	33 (25.0)	15 (11.4)	1 (0.8)	2 (1.5)	1 (0.8)
Induced†	19 (14.4)	11 (8.3)	2 (1.5)	1 (0.8)	–
Late	1 (0.8)	–	–	–	–

Missed	1 (0.8)	–	–	–	–
Fetal death‡	2 (1.5)	2 (1.5)	–	–	–

*Resulted in fetal death.
†One case due to intrauterine fetal death.
‡Fetal death was defined as intrauterine death of a fetus >20 weeks.
**Only concomitant medications that are Pregnancy Category D or higher in the United States are listed.
AZA, azathioprine; LFM, leflunomide; MMF, mycophenolate mofetil; MMS, mycophenolate sodium.

Conclusion: As shown, the available data for abatacept do not indicate any pattern of congenital anomalies. Abatacept should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. The company continues to monitor and collect information on the outcomes of abatacept-exposed pregnancies, and an ongoing registry study with the Organization of Teratology Information Specialists (OTIS) continues to collect data that will be reported separately.

Disclosure: M. Kumar, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **L. Ray**, Bristol-Myers Squibb, 3; **S. Vemuri**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1; **T. Simon**, Bristol-Myers Squibb, 3.

1841

Eventual Joint Failure and Surgery Rates in Rheumatoid Arthritis Remain High in Patients with Moderate Disease Activity in the First 5 Years of Disease. Elena Nikiphorou[1], Lewis Carpenter[1], Sam Norton[2], Josh Dixey[3], Patrick Kiely[4], David Walsh[5] and Adam Young[6]. [1]University of Hertfordshire, Hatfield, United Kingdom, [2]King's College London, London, United Kingdom, [3]New Cross Hospital, Wolverhampton, United Kingdom, [4]St. Georges Healthcare NHS Trust, London, United Kingdom, [5]University of Nottingham, Nottingham, United Kingdom, [6]ERAS, St Albans City Hospital, St Albans, United Kingdom.

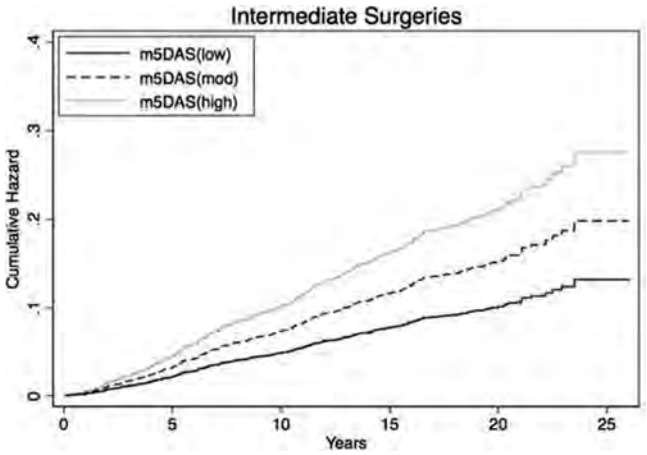
Background/Purpose: It is well-established that sustained high disease activity in RA results in worse outcomes. In reality many patients remain in low/moderate disease activity states, yet their outcomes, especially in the long term, are less well studied.

Methods: The study was based on the Early RA Study (ERAS, n=1465, 1986–1999) and the Early RA Network (ERAN, n=1236, 2002–2012). Standard clinical, radiological and laboratory measures were performed yearly for a maximum (median) 25(10) and 10(3) years respectively. Clinical databases were validated with national sources: the National Joint Registry (2003–2011), Hospital Episode Statistics (1997–2011) & National Death Register (1986–2011). Treatment regimens followed guidelines of the era, mainly conventional DMARDs +/− steroids, and latterly biologics. Joint interventions were categorized into major (large joint replacements), intermediate (mainly synovectomies and arthroplasties of wrist/hand, hind/forefoot) or minor (mainly soft tissue). Mean DAS was calculated for each patient from year 1 to 5 and categorized into either sustained low [m5DAS(low)] moderate disease [m5DAS(mod)] or high [mDAS(high)] disease activity if DAS28 was persistently lower than 3.2, between 3.2–5.1 or greater than 5.1 respectively.

Results: Of 2321 (86%) with complete 5year DAS data, 854 (37%) had m5DAS(low), 1066 (46%) m5DAS(mod) and 401 (17%) m5DAS(high). 770 (29%) patients had undergone a total of 1602 procedures over the 25 years of study; cumulative incidence rate of major interventions was 21.7% (19.4–24.0%) and of intermediate 21.5% (17.8–25.5%). In multivariate Cox regression models controlling for age at disease onset, gender, recruitment year, symptom duration, rheumatoid factor, BMI, HAQ, Haemoglobin, ESR and baseline erosions, patients with m5DAS(low) were 44% and 46% less likely to have intermediate and major joint surgery respectively compared to patients with moderate disease activity over the first 5 years ($P<0.05$). Patients with m5DAS(high) were 49% more likely to have intermediate surgery than those with m5DAS(mod) over the first 5 years ($P<0.05$) (Figure 1). A similar trend was observed for major surgery, but statistical significance was not reached.

Conclusion: Patients with sustained moderate disease activity in the first 5 years of disease, despite conventional DMARD therapy, still remain at high risk of joint failure and surgery. This poses important management challenges in health systems where restrictions exist in the use of biologic DMARDs, which are based on DAS28 levels and exclude moderate RA. The results demonstrate that any therapy that keeps patients in low disease activity or remission states is beneficial in terms of long-term outcomes.

Figure 1.



Disclosure: E. Nikiphorou, None; **L. Carpenter**, None; **S. Norton**, None; **J. Dixey**, None; **P. Kiely**, None; **D. Walsh**, Pfizer Inc, 2; **A. Young**, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy III: Innovative Therapeutic Strategies in Rheumatoid Arthritis
Monday, November 17, 2014, 2:30 PM–4:00 PM

1842

High Rates of Failure after Biological DMARD Discontinuation While in Remission in a Japanese Multi-Center Registry. Kazuki Yoshida[1], Mitsumasa Kishimoto[2], Helga Radner[1], Kazuo Matsui[3], Masato Okada[2], Yukihiko Saeki[4], Daniel H. Solomon[1] and Shigeto Tohma[5]. [1]Brigham and Women's Hospital, Boston, MA, [2]St. Luke's International Hospital, Tokyo, Japan, [3]Kameda Medical Center, Kamogawa, Japan, [4]Osaka-Minami Medical Center, Osaka, Japan, [5]Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan.

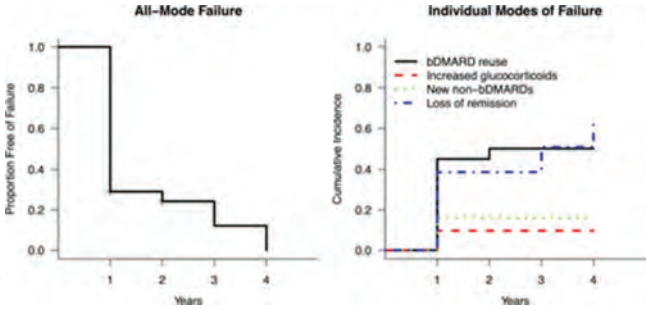
Background/Purpose: Since the introduction of biological disease-modifying antirheumatic drugs (bDMARDs) and tight control strategies, remission has become a more feasible treatment target for an increasing number of patients. As a result, there is an increased interest in appropriate treatment strategies after achieving disease control, such as bDMARD discontinuation while in remission. However, the outcome of such discontinuation in typical clinical practice has not been widely studied. We conducted a multi-center longitudinal observational study of bDMARD discontinuation while patients were in remission to describe the proportions of RA patients who remain in remission and how treatment or disease activity changes occur after discontinuation.

Methods: We utilized data from the National Database of Rheumatic Diseases by iR-Net in Japan (NinJa) multi-center registry. Patients who used bDMARDs on at least two consecutive visits and had visits in remission defined by the Clinical Disease Activity Index (CDAI) ≤ 2.8 followed by discontinuation of their bDMARDs while in remission were examined. The baseline variables were defined at the first visit off bDMARDs. The outcomes were defined as the rate of all-mode failure as well as the non-mutually exclusive individual modes of failure: reuse of bDMARDs, loss of CDAI remission, intensification of non-biological DMARDs or of oral glucocorticoids.

Results: Among 744 patients who initially achieved remission on bDMARDs, 31 patients discontinued their bDMARDs while remaining in remission and had additional follow up visits. In this 31-patient study cohort, 93.5% were female, the median disease duration was 6.0 [interquartile range 5.0, 9.0], 83.9% discontinued tumor necrosis factor inhibitors, 90.3% discontinued their first bDMARD, 72.4% had reported radiographical erosions. At the baseline, treatments were as follows: methotrexate use 54.8%, non-steroidal antiinflammatory drugs (NSAIDs) use 35.5%, oral glucocorticoid use 45.2% The probability of being free of all-mode failure was 29.0% at 1 year and 24.0% at 2 years. When dissected into individual modes of failure, loss of CDAI remission and reuse bDMARD were approximately 40% at 2 years, whereas non-biological treatment intensification was approximately 10–20%. Regarding changes in the non-biological treatment as non-failures,

35.5% remained in remission without bDMARDs at 1 year, and 29.6% at 2 years.

Conclusion: We found a high rate of failure by the all-mode failure, indicating difficulty of maintaining disease control after discontinuing bDMARDs even in patients who were in CDAI remission. Modification of non-biological treatment was observed in some of the patients who remained in remission. Considering the cost of bDMARDs, such coping strategy to maintain disease control after bDMARD discontinuation may need further investingation.



Disclosure: K. Yoshida, None; **M. Kishimoto**, Santen Pharmaceutical, Mitsubishi Tanabe Pharma, Pfizer, and Abbott Japan, 8; **H. Radner**, None; **K. Matsui**, None; **M. Okada**, Santen Pharmaceutical, Mitsubishi Tanabe Pharma, Pfizer, and Abbott Japan, 8; **Y. Saeki**, Tanabe-Mitsubishi Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd., Janssen Pharmaceutical Co., Ltd., Nippon-Kayaku Co., Ltd., and Nichi-Iko Co., Ltd, 2; **D. H. Solomon**, Eli Lilly, Amgen, and CORRONA, 2, UpToDate, 7, Pfizer, Novartis, and Eli Lilly, 6; **S. Tohma**, Pfizer Japan Inc., Eisai Co., Ltd, and Chugai Pharmaceutical Co., Ltd, 2.

1843

Randomised Controlled Non-Inferiority Study of Dose Reduction and Withdrawal of Adalimumab and Etanercept in Rheumatoid Arthritis.

Noortje van Herwaarden[1], Aatke van der Maas[1], Michiel Minten[1], Frank H.J. van den Hoogen[2], Ronald F. van Vollenhoven[3], Johannes W.J. Bijlsma[4], Bart van den Bemt[1] and Alfons A. den Broeder[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]Rheumatology Centre Sint Maartenskliniek and Radboud university medical center, Ubbergen (Nijmegen), Netherlands, [3]Unit for clinical therapy research (ClinTrid), Karolinska Institute, Stockholm, Sweden, [4]University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: TNF inhibitors (TNFi) have proven to be effective in the treatment of rheumatoid arthritis (RA). They are however associated with side effects and high costs, making dose reduction or discontinuation an attractive option. The primary aim of this study (DRESS) was to assess non-inferiority with regard to persistent disease worsening (flare) between a TNFi dose reduction strategy and usual care in daily clinical practice.

Methods: Patients with RA and low disease activity using adalimumab or etanercept were randomised (2:1) to a dose reduction strategy or usual care, both in tight control setting. The TNFi dose reduction strategy consisted of stepwise increasing the interval between injections every 3 months until flare or discontinuation.[1] In case of flare, the TNFi was restarted or escalated. A flare was defined as DAS28-CRP increase >1.2 or DAS28-CRP increase >0.6 and current DAS28-CRP ≥3.2, compared to baseline DAS28-CRP.[2] A persistent flare was defined as a flare duration ≥ 12 weeks. During 18 months follow up, data were collected on DAS28-CRP, HAQDI, EQ-5D, RA medication use, and costs. The primary outcome was the difference in proportions of patients with persistent flare between the two groups compared against a non-inferiority (NI) margin of 20%.

Results: 180 patients were included (table 1). Cumulative incidence of persistent DAS28-CRP flare was not significantly higher in the dose reduction group compared to the usual care group, 10% versus 12% of patients respectively (difference 2%, 95% CI −10 to 12), the upper limit of the 95% CI being clearly below the NI margin. Mean DAS28-CRP remained low, with only at 9 months follow up a significant, but small, difference between groups (figure 1A). HAQ scores remained stable in both groups (figure 1B) as did quality of life (figure 1C). In the dose reduction group, the TNFi could successfully be stopped at 18 months in 20% (95% CI 13 to 28) of patients, the interval successfully increased in 43% (95% CI 34 to 53) and in 37% (95% CI 28 to 46) of patients no dose reduction was possible. Incidence and nature of serious adverse events were similar between groups. Costs were significantly lower in the dose reduction group (mean difference per patient €9k).

Conclusion: A simple tight control TNFi dose reduction strategy has been shown to be non-inferior to usual care in maintaining disease control, function and quality of life, while reducing exposition to TNFi and costs.

References

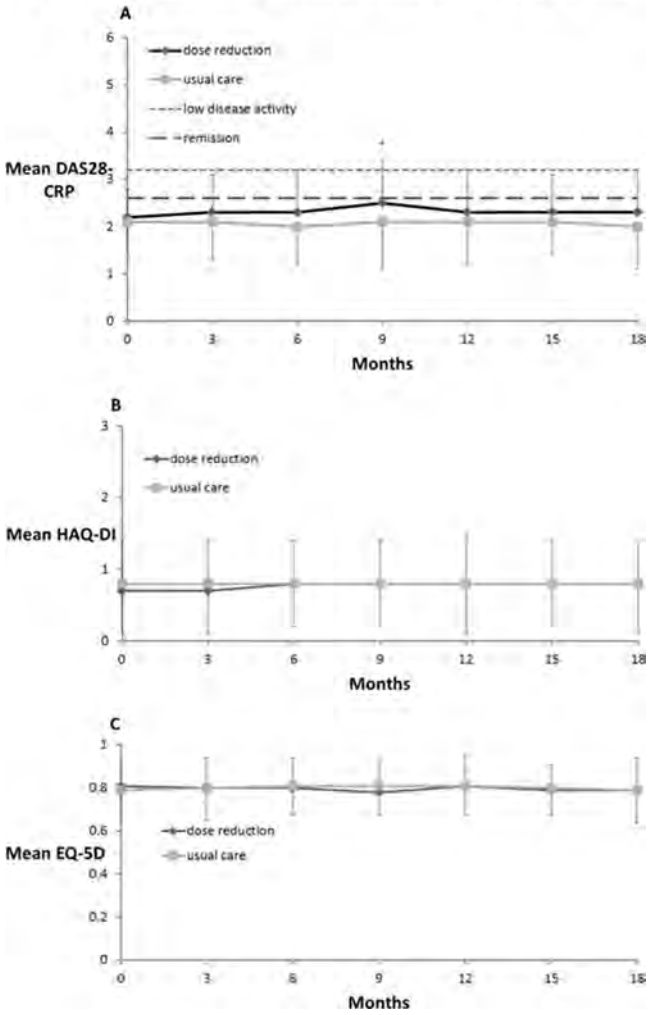
1: den Broeder et al. BMC Musculoskelet Disord. 2013 24;14:299.

2: van der Maas et al. Ann Rheum Dis. 2013;72(11):1800–5.

Table 1. Baseline Characteristics

	Dose reduction (n = 121)	Usual care (n = 59)
Age, years (SD)	59 (10.5)	58 (9.3)
Female, n (%)	75 (62)	41 (69)
Disease duration, years median [p25–p75]	10 [6–17]	10 [6–16]
Rheumatoid factor positive, n (%)	95 (78)	49 (83)
Anti-CCP positive, n (%)	86 (71)	45 (76)
DAS28 CRP at inclusion (SD)	2.2 (0.6)	2.1 (0.7)
DAS28 BSE at inclusion (SD)	2.5 (0.7)	2.5 (0.8)
2011 ACR/EULAR Boolean-based remission, n (%)	31 (26)	21 (36)
DAS28 CRP ≥ 3.2, n (%)	8 (7)	6 (10)
Etanercept/adalimumab (%)	79/42 (65/35)	39/20 (66/34)
Duration of current anti-TNF therapy, years (SD)	3.5 (2.5)	3.6 (2.3)
Previous DMARDs, median [p25–p75]	2 [1–3]	2 [1–3]
Previous anti-TNF, median [p25–p75]	0 [0–1]	0 [0–1]
Concomitant DMARD use, n (%)	73 (60)	47 (80)
Concomitant MTX use, n (%)	58 (48)	41 (69)
Concomitant corticosteroid use, n (%)	6 (5)	3 (5)
Concomitant NSAID use, n (%)	65 (54)	35 (59)
Employment, n (%)	44 (36)	21 (36)

Figure 1. Mean disease activity, functioning and quality of life during the study



Disclosure: N. van Herwaarden, None; **A. van der Maas**, Roche, MSD, 9; **M. Minten**, None; **F. H. J. van den Hoogen**, None; **R. F. van Vollenhoven**, Abbott, BMS, GSK, MSD, Pfizer, Roche, UCB, 2, Abbott, BMS, GSK, MSD, Pfizer, Roche, UCB, 5; **J. W. J. Bijlsma**, AbbVie, Roche, Pfizer, MSD, UCB, BMS, 2, AbbVie, Roche, Pfizer,

MSD, UCB, BMS, Jansen, 5; **B. van den Bemt**, Roche Pharmaceuticals, Pfizer, 2, Roche, Pfizer, MSD Abbvie, 5; **A. A. den Broeder**, None.

1844

Identification of a Patient Phenotype Which Impacts Response to Therapy in Rheumatoid Arthritis Clinical Trials: Certolizumab Pegol Phase 4 Trial Data. Jeffrey R. Curtis[1], Melvin Churchill[2], Alan Kivitz[3], Laura Gauer[4], Christopher Herrem[4], David Carter[5], Jeffrey Melin[4] and Yusuf Yazici[6]. [1]The University of Alabama at Birmingham, Birmingham, AL, [2]Arthritis Center of Nebraska, Lincoln, NE, [3]Altoona Arthritis & Osteoporosis Center, Duncansville, PA, [4]UCB Pharma, Smyrna, GA, [5]UCB Pharma, Brussels, Belgium, [6]New York University Hospital for Joint Diseases, New York, NY.

Background/Purpose: The PREDICT trial (NCT01255761) examined predictability of certolizumab pegol (CZP) treatment success at Week (Wk) 52 based on response at Wk12 assessed by RAPID3 and CDAI in RA patients (pts).[1] The objective of this post-hoc analysis was to evaluate whether a defined somatic comorbidity phenotype (SCP) influenced treatment response.

Methods: Pts were randomized to RAPID3 or CDAI for treatment response assessment and received CZP standard dosing regimen for 52 wks. Response at Wk12 was assessed (RAPID3 Responder, ≤6 or 20% improvement from Baseline [BL]; CDAI Responder, ≤10 or 20% improvement from BL), and pts with no improvement (<1 point CDAI improvement/no RAPID3 improvement) were to be withdrawn. The SCP, hypothesized to have suboptimal treatment response, was defined *a priori* as a diagnosis of depression, chronic pain, fibromyalgia or myalgias, and use of medications indicated for the treatment of depression, anxiety or neuropathic pain; insomnia diagnosis and narcotics were not included. The full analysis set (FAS; N=733), of which 313 pts had SCP at BL and ongoing during trial, is presented.

Results: At BL, 43% (313/733) of pts met the SCP classification: 23% due to medical diagnoses only (predominantly depression), 29% due to concomitant medications only (predominantly SSRIs, analgesics/antipyretics and other centrally acting agents), and the remaining 48% were due to both (predominantly depression and SSRI use). The proportion of pts with SCP was similar in the RAPID3 and CDAI arms; a similar proportion, with and without SCP, were withdrawn due to lack of efficacy by Wk12.

Among all pts randomized to CDAI (n=365), 79% without vs 73% with SCP were classified as Responders at Wk12 (Table); Wk12 Responders without SCP were approximately twice as likely to achieve LDA at Wk52 compared to those with the phenotype (41% vs 21%, respectively; Table). In addition, overall, pts without SCP were twice as likely to achieve LDA at Wk52 compared to those with the phenotype (32% vs 16%, respectively; Table).

In contrast, this phenotype was less differentiating among pts randomized to RAPID3 in the 3 outcomes examined (Table). Comparing CDAI to RAPID3, the likelihood of being classified as a Wk12 Responder was incrementally greater for those without (79% vs 63%) than those with the SCP (73% vs 68%) (Table).

Conclusion: In this large RA clinical trial population we have identified a potentially important phenotype that includes depression and chronic pain syndromes. Pts with this phenotype appear less likely to achieve LDA or be classified as a Responder when using CDAI as the outcome measure; however response rates were similar regardless of SCP when RAPID3 was used. Depending on the outcome measure used, enrolling large numbers of pts with this phenotype into an RA trial may affect the proportion able to achieve LDA/remission making it advisable to consider identifying such pts at screening.

Reference

1. Curtis J. Ann Rheum Dis 2014;73(S2):382.

Table 1. Patients with and without somatic comorbidity phenotype: A) LDA at Wk52, B) Response classification at Wk12, and C) LDA at Wk52 for Wk12 Responders (FAS; NRI)

Outcome	Somatic Comorbidity Phenotype	Management Tool Used CDAI	RAPID3
Achieve LDA [a] at Wk52, overall	No	32% (65/203)	21% (45/217)
	Yes	16% (26/162)	23% (34/151)
Classified as a Responder at Wk12 [b]	No	79% (160/203)	63% (136/217)
	Yes	73% (119/162)	68% (102/151)
Achieve LDA at Wk52 conditional on being classed as a Responder [b] at Wk12	No	41% (65/160)	32% (44/136)
	Yes	21% (25/119)	30% (31/102)

[a] DAS28 (ESR) ≤3.2; [b] RAPID3 Responder: ≤6 or 20% improvement from BL, CDAI Responder: ≤10 or 20% improvement from BL. LDA: low disease activity.

Disclosure: J. R. Curtis, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **M. Churchill**, Pharmaceutical companies, 9; **A. Kivitz**, Abbvie, Pfizer, Merck, Janssen, Novartis, Celgene, UCB. Consultant for: Celgene, Genentech, Pfizer, UCB, 2; **L. Gauer**, UCB Pharma, 3; **C. Herrem**, UCB Pharma, 3; **D. Carter**, UCB Pharma, 3; **J. Melin**, UCB Pharma, 3; **Y. Yazici**, BMS, Genentech, Celgene, 2, Abbvie, BMS, Celgene, Genentech, Pfizer, Samumed, UCB Pharma, 5.

1845

Tocilizumab Combination Therapy or Monotherapy or Methotrexate Monotherapy in Methotrexate-Naive Patients with Early Rheumatoid Arthritis: 2-Year Clinical and Radiographic Results from a Randomized, Placebo-Controlled Trial. Gerd Burmester[1], William Rigby[2], Ronald F. van Vollenhoven[3], Jonathan Kay[4], Andrea Rubbert-Roth[5], Ricardo Blanco[6], Ariella Kelman[7], Sophie Dimonaco[8] and Nina Mitchell[8]. [1]Charité-Universitätsmedizin Berlin, Free University and Humboldt University of Berlin, Berlin, Germany, [2]Geisel School of Medicine at Dartmouth, Lebanon, NH, [3]Karolinska Institute, Stockholm, Sweden, [4]UMass Memorial Medical Center, Worcester, MA, [5]University of Cologne, Cologne, Germany, [6]Hospital Marques de Valdecilla, Santander, Spain, [7]Genentech, South San Francisco, CA, [8]Roche Products Ltd., Welwyn Garden City, United Kingdom.

Background/Purpose: Treatment with tocilizumab (TCZ) in combination with MTX or as monotherapy (Mono) in MTX-naive patients (pts) with early RA resulted in improved signs and symptoms and inhibition of joint damage at wk 52 of the 104-wk, double-blind, placebo-controlled trial FUNCTION.[1] Results to wk 104 are presented.

Methods: Pts were randomized 1:1:1:1 to TCZ 8 mg/kg (TCZ8) + MTX, TCZ8 Mono, TCZ 4 mg/kg (TCZ4) + MTX, or MTX for 104 wks. Pts received IV TCZ q4w, with MTX escalated from 7.5 mg qw to 20 mg qw by wk 8. Inclusion criteria have been described.[1] At wk 52, TCZ4 + MTX and MTX pts who had not achieved low disease activity (DAS28 ≤3.2) switched to blinded escape therapy with TCZ8 + MTX. Efficacy end points (DAS28, ACR responses, and van der Heijde–modified Total Sharp Score) were assessed in the intent-to-treat (ITT) population, and a subgroup analysis was performed for postescape data. Adverse events (AEs) were evaluated under the treatment group in which the AE occurred. Wk 104 analyses were exploratory; no statistical testing was performed.

Results: At wk 52, 95/290 (33%) TCZ4 + MTX pts and 142/289 (49%) MTX pts switched to TCZ8 + MTX escape therapy. Baseline characteristics of escape pts were consistent with those of the full ITT population.[1] Clinical efficacy was maintained through wk 104 in the TCZ8 groups, with similar proportions at wks 52 and 104 achieving ACR20/50/70 responses and DAS28, ACR/EULAR Boolean/Index, and Clinical Disease Activity Index criteria remission. Inhibition/slowing of radiographic progression was also maintained. In TCZ4 + MTX and MTX pts who switched to escape with TCZ8 + MTX at wk 52, further improvement in efficacy from the point of escape was generally seen at wk 104. Despite the inhibition of structural joint damage after escape, joint damage was numerically greater than in pts who received TCZ8 Mono or TCZ8 + MTX throughout (Table). TCZ serum levels were similar with both Mono and combination TCZ treatment. AE rates were similar across groups, with serious AE and serious infection rates numerically higher in the TCZ groups (Table). There were 14 deaths (9 reported earlier[1]); 5 occurred in year 2. Underlying causes varied and included 4 due to infection (2 MTX; 2 TCZ4 + MTX), 3 due to malignancy (1 TCZ8 + MTX; 2 TCZ8 Mono), and 2 due to cardiovascular disease (1 TCZ4 + MTX; 1 TCZ8 Mono).

Conclusion: Pts with early RA who received TCZ8 + MTX or TCZ8 Mono for the duration of the study had sustained improvement in disease activity and maintained joint damage inhibition over 104 wks. Efficacy improved further in pts receiving MTX or TCZ4 + MTX who switched to escape with TCZ8 + MTX at wk 52; the overall degree of joint damage (though generally minor) was greater than that in pts who received TCZ8 for the entire study, highlighting the importance of early initiation of optimal therapy. Safety was consistent with the known safety profile of TCZ.

Reference:
1. *Arthritis Rheumatol*. 2013;65:S1182.

Table 1. Efficacy and Safety End Points

Originally Assigned Treatment (ITT population)	TCZ8 + MTX n = 290		TCZ8 Mono n = 292		TCZ4 + MTX n = 288		MTX n = 287	
Efficacy at wk 52 and wk 104								
Week	**52**	**104**	**52**	**104**	**52**	**104 Orig Tx (*escape Tx*[a])**	**52**	**104 Orig Tx (*escape Tx*[a])**
DAS28 remission (<2.6), %[b]	49.3	47.6	40.4	43.5	36.1	28.1 *(30.5)*	20.2	16.0 *(51.4)*
ACR20, %[b]	67.9	65.2	65.4	61.6	65.3	39.6 *(66.3)*	58.5	25.4 *(73.9)*
ACR50, %[b]	56.2	57.6	50.7	53.1	54.9	36.5 *(52.6)*	41.5	22.0 *(59.9)*
ACR70, %[b]	43.4	46.6	37.0	39.4	37.8	31.6 *(32.6)*	29.3	17.4 *(45.8)*
Mean ΔmTSS from BL[c]	0.13	0.19	0.30	0.62	0.75	1.43 *(0.56[d])*	0.97	1.88 *(1.57[d])*

Safety at wk 104				
Tx received (safety population)[e]	**TCZ8 + MTX n = 527**	**TCZ8 Mono n = 292**	**TCZ4 + MTX n = 289**	**MTX n = 282**
AEs, n (rate/100 PY)	2418 (336.6)	1701 (338.7)	1545 (391.5)	1249 (367.9)
Serious AEs, n (rate/100 PY)	83 (11.6)	67 (13.3)	58 (14.7)	31 (9.1)
Serious infections, n (rate/100 PY)	25 (3.5)	20 (4.0)	16 (4.1)	6 (1.8)
Deaths, n (rate/100 PY)	4 (0.56)	3 (0.60)	5 (1.27)	2 (0.59)

AE, adverse event; BL, baseline; mTSS, van der Heijde-modified Total Sharp Score; Orig Tx, originally assigned treatment; PY, patient-year; Tx, treatment.
[a]Data for 95 pts originally assigned TCZ4 + MTX and 142 pts originally assigned MTX after 52 wks of escape treatment with TCZ8 + MTX; these n values were used as the denominators for rates of response in escape pts.
[b]Pts who received escape therapy or withdrew prematurely or in whom a DAS28/ACR/EULAR response could not be calculated were set to "nonresponder."Data for pts who received escape therapy were also analyzed separately.
[c]Missing data imputed using linear extrapolation.
[d]Based on original baseline and using observed data (no imputation for missing data) with postwithdrawal data included.
[e]Pts assigned to treatment groups according to treatment they actually received.

Disclosure: G. Burmester, AbbVie, Pfizer, UCB, Roche, 2, AbbVie, BMS, Pfizer, Merck, MedImmune, UCB, Roche, 5, AbbVie, BMS, Pfizer, Merck, UCB, Roche, 8; **W. Rigby**, None; **R. F. van Vollenhoven**, AbbVie, BMS, GSK, Pfizer, Roche, UCB, 2, AbbVie, Biotest, BMS, GSK, Janssen, Lilly, Merck, Pfizer, Roche, UCB, Vertex, 5; **J. Kay**, AbbVie Inc., Ardea Biosciences, Inc., Eli Lilly and Company, and Roche Laboratories, Inc., 2, AbbVie Inc., Amgen, Inc., AstraZeneca, Bristol Myers Squibb Co., Crescendo BioScience Inc., Epirus Biopharmaceuticals, Inc., Genentech Inc., Hospira, Inc., Janssen Biotech, Inc., PanGenetics, B.V., Pfizer Inc., Roche Laboratories, Inc., and UCB, Inc., 5; **A. Rubbert-Roth**, Chugai, Roche, Pfizer, 2, Abbott, Chugai, BMS, Roche, UCB, Pfizer, MSD, 5; **R. Blanco**, Abbott, MSD, Roche, 2, Abbott, Pfizer, Roche, BMS, Janssen, MSD, 8; **A. Kelman**, Roche, 1, Roche Pharmaceuticals, 3; **S. Dimonaco**, Roche Pharmaceuticals, 3; **N. Mitchell**, Roche Pharmaceuticals, 1, Roche Pharmaceuticals, 3.

1846

The Association Between Hydroxychloroquine Treatment and Cardiovascular Morbidity Among Rheumatoid Arthritis Patients. Michael Shapiro[1] and Yair Levy[2]. [1]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [2]Meir Medical Center, Kfar Saba, Israel.

Background/Purpose: Accelerated atherosclerosis and cardiovascular disease are the main causes of mortality in Rheumatoid Arthritis (RA). The anti-malarial drug Hydroxychloroquine (HCQ) has long been used in the treatment of RA due to its anti-inflammatory properties. Recent studies have demonstrated that HCQ has additional beneficial effects on cardiovascular risk factors by lowering LDL levels, reducing the risk for diabetes and improving elasticity of atherosclerotic arteries. Our aim was to examine the independent effect of HCQ treatment on cardiovascular morbidity among RA patients.

Methods: We conducted a retrospective cohort study in the Meir Medical Center. Participants were diagnosed with RA, were 18 or older at the time of diagnosis and had been treated in the medical center between 2003 and 2013. Patients were divided into two groups, those who had been treated with HCQ during the course of their disease and those who had never received the drug. The two groups were compared in regard to possible confounding factors, including parameters of disease severity, common cardiovascular risk factors and additional medications. The endpoints of our study were arterial and venous events, including: Myocardial Infarction (MI), stroke, Transient Ischemic Attack (TIA), mesenteric event, Pulmonary Embolism (PE) and peripheral venous thrombosis. The two groups were compared using a multivariate logistic regression.

Results: We identified 514 RA patients that adhered to our inclusion criteria, 241 patients had been treated with HCQ for an average duration of 5 years and 273 patients had never been treated with the drug. We found that 13.3% of the treated patients suffered from cardiovascular events compared to 38.1% in the non-treated group. HCQ treatment had a significant protective effect for all cardiovascular events examined (OR=0.271, 95%CI 0.159 to 0.462). When comparing for specific endpoints we found a difference regarding the dosage of HCQ. A dose of 400mg per day of HCQ had a statistically significant protective effect for MI (OR= 0.405, 95%CI 0.181 to 0.908), for stroke and TIA (OR= 0.352, 95%CI 0.130 to 0.955) and for venous events (OR= 0.159, 95%CI 0.045 to 0.562). The lower dose of 200 mg per day demonstrated a protective effect for MI (OR=0.194, 95%CI 0.055 to 0.686), and no significant effect on other endpoints.

Conclusion: The use of HCQ is independently associated with decreased risk for cardiovascular morbidity among RA patients, particularly when using the higher dose of 400 mg per day. This newly demonstrated effect of HCQ should be considered in the overall management of RA.

Disclosure: M. Shapiro, None; **Y. Levy**, None.

1847

Effect of Disease Duration on Clinical Outcomes in Moderate Rheumatoid Arthritis Patients Treated with Etanercept Plus Methotrexate in the Preserve Study. Josef S. Smolen[1], David Collier[2], Annette Szumski[3], Heather Jones[3] and Lisa Marshall[3]. [1]PsAID taskforce, EULAR, Zurich, Switzerland, [2]Amgen, Inc., Thousand Oaks, CA, [3]Pfizer Inc., Collegeville, PA.

Background/Purpose: Previous studies evaluating various treatment strategies indicate that disease duration is a key determinant of outcomes in rheumatoid arthritis (RA). While data suggest that RA patients with longer established disease do not respond as well to treatment compared with patients with early disease, this evidence is limited. The objective of this sub-analysis was to determine the effect of disease duration on treatment response in patients with moderately active RA receiving induction therapy with etanercept (ETN) plus methotrexate (MTX) for 36 weeks in the PRESERVE study.

Methods: In the induction phase of the PRESERVE study, patients with moderately active RA (DAS28 >3.2 and ≤5.1) despite stable doses of oral MTX received open-label ETN 50 mg QW plus MTX (titrated to ≤25 mg/week as needed through week 28) for 36 weeks. Patients were stratified by disease duration at baseline: 0–≤6 mo, >6mo–≤2 yr, >2yr–≤5 yr, >5yr–≤10 yr and >10 yr. Baseline demographic and disease characteristics and treatment response (DAS28, CDAI, HAQ) were compared across disease duration categories. Analyses using observed cases (OC) were conducted in all patients who received ≥1 ETN/MTX dose (mITT population).

Results: A total of 833 patients receiving ETN50/MTX (baseline disease duration: 0–≤6 mo, n=41; >6mo–≤2 yr, n=198; >2yr–≤5 yr, n=204; >5yr–≤10 yr, n=172; >10 yr, n=218) were included. At baseline, more established disease was significantly associated with higher age and a higher swollen joint count (Table). In addition, a significantly greater proportion of patients with longer disease duration were rheumatoid factor and CCP3 antibody positive. HAQ score at baseline significantly correlated with greater duration of disease while baseline DAS28 and CDAI were similar across disease duration subgroups. Significant changes from baseline in DAS28, CDAI and HAQ were observed at Week 4 and at all time-points up to Week 36 in all disease duration categories (all P<0.0001). These observed improvements in clinical measures of disease activity and quality of life were similar among disease duration subgroups (Table).

	Disease Duration					
Characteristic	**0–≤6 mo (n=43)**	**>6mo–≤2 y (n=129)**	**>2yr–≤5 y (n=157)**	**>5yr–≤10 y (n=117)**	**>10 y (n=157)**	**P-value**
Baseline, Mean (SD) (unless stated)						
Age	47.7 (12.1)	46.3 (12.2)	46.3 (12.0)	48.7 (12.1)	52.0 (10.6)	<0.001*
RF Positive, n (%)	32 (78.0)	117 (59.7)	146 (71.9)	134 (77.9)	173 (80.1)	<0.001†
CCP3 Ab Positive, n (%)	34 (82.9)	126 (64.3)	157 (77.7)	143 (83.1)	181 (84.2)	<0.001†
Swollen Joint Count	3.2 (1.9)	3.5 (2.4)	3.6 (2.2)	3.9 (2.9)	4.4 (2.9)	0.001*
DAS28	4.4 (0.5)	4.3 (0.5)	4.4 (0.4)	4.4 (0.4)	4.4 (0.4)	0.401*
CDAI	17.2 (3.4)	17.8 (4.9)	17.4 (4.7)	17.7 (5.2)	18.5 (5.3)	0.180*
HAQ	1.1 (0.6)	1.1 (0.6)	1.1 (0.6)	1.2 (0.6)	1.3 (0.6)	0.003*
Week 36, Adjusted mean change (SE)						
DAS28	−2.0 (0.2)	−2.0 (0.1)	−2.1 (0.1)	−2.0 (0.1)	−1.9 (0.1)	NS‡
CDAI	−12.1 (1.0)	−12.2 (0.4)	−12.2 (0.4)	−12.0 (0.5)	−11.3 (0.4)	NS‡

HAQ	−0.52 (0.08)	−0.55 (0.04)	−0.59 (0.03)	−0.57 (0.04)	−0.58 (0.03)	NS‡

*1-way ANOVA; †Chi-square; ‡Not significant for all pair-wise comparisons

Conclusion: In the PRESERVE trial, improvements in clinical outcomes in response to open-label therapy with ETN plus MTX in patients with moderately active RA was largely unaffected by differences in disease duration before treatment initiation. The use of induction with ETN plus MTX in moderate RA may prevent the poorer outcomes often associated with longer disease duration.

Disclosure: J. S. Smolen, Abbvie, BMS, Janssen, MSD, Pfizer, UCB, 2, Abbvie, Amgen, Astra-Zeneca, Astro, BMS, Celgene, Glaxo, Janssen, Lilly, Medimmune, MSD, Novartis-Sandoz, Pfizer, Samsung, UCB, 5; **D. Collier**, Amgen, 3, Amgen, 1; **A. Szumski**, Pfizer Inc, 3; **H. Jones**, Pfizer Inc, 3; **L. Marshall**, Pfizer Inc, 1.

ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis III - Clinical Aspects Psoriatic Arthritis
Monday, November 17, 2014, 2:30 PM–4:00 PM

1848

Risk of Cancer in Patients with Severe Psoriatic Arthritis Requiring Tumour-Necrosis Factor Alpha Inhibition. Karen M. Fagerli[1], Louise K. Mercer[2], Kath D. Watson[2], Jonathon Packham[3], Deborah PM Symmons[4], Kimme L. Hyrich[5] and. On behalf of the BSRBR[6]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Arthritis Research UK Centre for Epidemiology, University of Manchester, Manchester, United Kingdom, [3]Institute of Science and Technology in Medicine, Keele, United Kingdom, [4]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [5]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, [6]British Society for Rheumatology, London, United Kingdom.

Background/Purpose: Few studies have explored risk of cancer in psoriatic arthritis (PsA). There are concerns that the risk may be raised, not only by the primary disease, but also by the treatments given including conventional disease modifying treatments (especially ciclosporin), tumour necrosis factor inhibitors (TNFi) and phototherapy. Skin psoriasis itself is associated with an increased risk of non-melanoma skin cancer (NMSC). Our objective was to compare the incidence of cancer among a cohort of patients with severe PsA patients receiving tumour TNFi to that in the general population.

Methods: All patients with PsA starting a TNFi in the British Society for Rheumatology Biologics Register (BSRBR, recruited 2002–2006) were included. Cancers were identified by flagging patients with the national cancer register which reported using the International Classification of Diseases version 10 (ICD 10). All patients were followed from registration (start of TNFi) until death or 2011/12/31, whichever came first. Standardised incidence ratios (SIR) with 95% confidence intervals (CI) were calculated using age and gender specific cancer rates for the general English population for (1) overall cancer risk (ICD 10: C1-C9) and (2) NMSC (C44) for the whole cohort and separately for men and women.

Results: 709 patients contributed 5286 patient years of follow-up; mean (SD) age was 45.7 (11.2), median disease duration (IQR) was 11 (6–17) years. Mean (SD) DAS28 was 6.0 (1.2). 11 (1.6%) patients had a cancer registered prior to baseline, none of which had a further cancer. Nearly all (98%) had previous or current exposure to methotrexate at baseline and 45.6% had previous or current exposure to ciclosporin. Information on baseline PUVA exposure was only available for 163 (23%) patients and 11 (6.7%) had been exposed. 27 cancers in 26 patients were observed, including 14 skin cancers (12 NMSC and 2 melanomas). Overall, there was no increased risk of malignancy observed in this cohort (SIR 0.87, 95% CI 0.58–1.27) compared to the general population. There was a significantly increased incidence for NMSC although the precision of the estimate was low (SIR 1.97, 95% CI 1.02–3.45) likely reflecting low number of events.

Table: Overall and non-melanoma skin cancer standardised incidence ratios

	Overall n=709		Male n=331		Female n=378	
Total follow-up (person-years)	5286		2437		2849	
	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)
All malignancies	27/30.9	0.87 (0.58–1.27)	13/12.8	1.02 (0.54–1.74)	14/18.1	0.77 (0.42–1.29)
NMSC	12/6.1	1.97 (1.02–3.45)	4/2.9	1.40 (0.38–3.58)	8/3.2	2.49 (1.07–4.91)

O = Observed, E = Expected

Conclusion: In this population of severely active PsA patients recruited early in the TNFi-era, the overall incidence of malignancy was reassuringly similar to that of the general population. Incidence of NMSC was increased, which may be related to PsA itself, skin psoriasis, phototherapy and/or immune-modulatory treatment.

Disclosure: K. M. Fagerli, None; **L. K. Mercer**, None; **K. D. Watson**, None; **J. Packham**, None; **D. P. Symmons**, None; **K. L. Hyrich**, Pfizer Inc, 9, Abbott Immunology Pharmaceuticals, 9; **On behalf of the BSRBR**, Pfizer Inc, Abbvie, UCB, Merck, Roche, 2.

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Risk of Malignancy Among Medicare Psoriasis/Psoriasis Arthritis Patients. Huifeng Yun[1], Kevin L. Winthrop[2], Lang Chen[3], Wilson Smith[3], Benjamin Chan[4], Fenglong Xie[3], Allison Taylor[3] and Jeffrey R. Curtis[3]. [1]University of Alabama at Birmingham School of Public Health, Birmingham, AL, [2]Oregon Health & Science University, Portland, OR, [3]University of Alabama at Birmingham, Birmingham, AL, [4]Oregon Health and Science University, Portland, OR.

Background/Purpose: The introduction of biologics has greatly changed the treatment of psoriatic arthritis (PsA) and psoriasis (PsO). However, there are concerns regarding the risk of malignancy associated biologic medications. This analysis evaluated the association between malignancy and biologics among US patients with PsA or PsO enrolled in the Medicare program

Methods: Using data from 2006–2011 for 100% of patients with patients with PsA and PsO, we defined separate PsA and PsO cohorts based upon >= 1 rheumatologist visit for PsA or >= 1 dermatologist visit for PsO, followed by a prescription or administration of etanercept (ETA), adalimumab (ADA), ustekinumab (UST), methotrexate (MTX), cyclosporine (CIC) or ultraviolet light therapy (UV). Patients could be in both cohorts if they meet criteria for each cohort. We identified new treatment episodes, defined specific to each drug as no use of that therapy in the prior 6 month 'baseline' period. Patients contributing treatment episodes with history of organ transplantation, infection with human immunodeficiency virus, advanced kidney (hemodialysis-dependent), severe liver disease, or cancer diagnoses were excluded. Eligible subjects were continuously enrolled in Medicare Parts A, B and D in baseline and throughout follow-up. We excluded treatment episodes of UV if patients were on biologics or DMARDS at baseline, and episodes of non-biologic therapy if patients were on biologics during the baseline. Follow up started from the drug initiation date and ended at the earliest date of: malignancy (exclude non-melanoma skin cancer), a 90 day gap in current exposure, death, loss of coverage or Dec 31, 2011. We identified malignancy using validated claims-based algorithm using physician diagnoses (ICD9 140–208, except 173.x), cancer-related procedures and chemotherapy. We calculated the incidence rate (IR) of malignancy for each exposure. Using pairwise propensity scores (PS) to balance multiple confounders, we compared malignancy risk using Cox regression, adjusting for PS quintile.

Results: We identified 10,261 PsA and 31,052 PsO new treatments episodes. For the PsA cohort, 50% of treatment-episode exposure time was in common with the PsO, and 20% of PsO exposure time was in common with PsA exposures. During follow up, patients in the PsA cohort experienced 13 (ADA), <11 (CIC), 10 (ETA), 50 (MTX), <11 (UV) malignancies, the PsO cohort experienced 29 (ADA), 26 (CIC), 28 (ETA), 123 (MTX), 64 (UV) malignancies. The overall IR in PsA was 8.1/1000, ranging from a low of 4.2 (UV) to a high of 11.3 (MTX). None of the hazard ratios for comparisons between biologic and non-biologic exposure groups reached statistical significance. The overall IR in the PsO cohort was 9.2/1000 ranging from 5.0(ETA) to 12.9 (CIC). After multivariable adjustment, there was a significantly lower risk for ETA compared to non-biologic therapies: ETA versus CIC (HR: 0.50 95% CI: 0.27–0.93), ETA versus MTX (HR: 0.56 95% CI: 0.35–0.87), ETA versus UV (HR: 0.49 95% CI: 0.29–0.83).

Conclusion: Among older patients with psoriasis and psoriatic arthritis, there was no evidence of an increased risk of malignancy for patients treated with biologics compared to non-biologic therapies, and some possibility of a reduced risk.

Disclosure: H. Yun, Amgen, 2; **K. L. Winthrop**, Pfizer Inc, 2, Pfizer, UCB, AbbVie, Genentech, 5; **L. Chen**, None; **W. Smith**, None; **B. Chan**, None; **F. Xie**, None; **A. Taylor**, None; **J. R. Curtis**, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

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The Incidence and Risk Factors for Psa in Patients with Psoriasis – a Prospective Cohort Study. Lihi Eder[1], Amir Haddad[1], Hua Shen[2], Cheryl Rosen[1], Vinod Chandran[1], Richard J. Cook[2] and Dafna D. Gladman[3]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Waterloo, Waterloo, ON, [3]Toronto Western Research Institute, Toronto Western Hospital, Toronto, ON.

Background/Purpose: There are limited data regarding the incidence of PsA in patients with psoriasis. We aimed to estimate the incidence of PsA in a prospective cohort of psoriasis patients and to identify risk factors for the development of PsA in these patients.

Methods: The setting is a prospective longitudinal cohort study of psoriasis patients without arthritis at baseline. Patient with a diagnosis of psoriasis confirmed by a dermatologist were enrolled. All patients were evaluated by a rheumatologist at baseline. Exclusion criteria included the presence of inflammatory arthritis or spondylitis in the past or at the time of assessment. All study participants were then reassessed annually by a rheumatologist for signs and symptoms of arthritis. Information was collected about their lifestyle habits, co-morbidities, skin activity and medications. Patients who developed inflammatory arthritis or spondylitis were classified as PsA if they fulfilled the CASPAR criteria. Patients who failed to come to the yearly assessment were requested to fill out the Toronto Psoriatic Arthritis Screen (ToPAS II) questionnaire, a screening questionnaire designed to detect PsA among patients with psoriasis. Subjects scoring ≥8 points on the ToPAS II were classified as suspected PsA. We summarize the results of 7 years of follow up and report the annual incidence of PsA from the onset of psoriasis that was estimated using an event per person-years analysis. Cox proportional hazard model, with time-dependent explanatory variables and date of enrollment as the time of origin, was used to compute the multivariate relative risk (RR) for incident PsA adjusting for sex and age.

Results: The results of the 579 patients who were recruited from January 2006 and followed until December 2013 are summarized. The mean duration of follow up was 3.5±1.9 years per person. A total of 46 patients developed PsA since enrollment and 9 additional patients were considered suspected cases of PsA according to their scoring in ToPAS II. The annual incidence rate of confirmed cases was 3.1 (95% confidence interval (CI) 2.2, 4.0) PsA cases per 100 psoriasis patients. When suspected cases were included in the analysis, the annual incidence rate increased to 3.7 (95% CI 2.7, 4.7) PsA cases per 100 psoriasis patients. The distribution of the time to development of PsA was fit with an exponential model, suggesting a constant hazard rate. The following variables predicted the development of PsA: flexural psoriasis (RR 4.9 p=0.03), nail pitting (RR 2.3 p=0.006), higher modified Nail Psoriasis Severity Index score (RR 2.8 p=0.008) and lower level of education (high school incomplete vs. University RR 3.33, p=0.04). Obesity vs. normal weight predicted the development of PsA when suspected cases of PsA were included in the analysis (RR 2.3 p=0.03)

Conclusion: The incidence of PsA in patients with psoriasis is higher than previously reported. Flexural psoriasis, psoriatic nail lesions, lower level of education and obesity predict the development of PsA in patients with psoriasis.

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1851

Serious Infection Events in the Psoriasis Longitudinal Assessment and Registry Study: Cumulative Experience. Robert Kalb[1], David Fiorentino[2], Mark Lebwohl[3], Craig Leonardi[4], John Toole[5], Kavitha Goyal[6], Steve Calabro[6], Wayne Langholff[7] and Steve Fakharzadeh[8]. [1]SUNY at Buffalo, School of Medicine and Biological Sciences, Buffalo, NY, [2]Stanford University, Redwood City, CA, [3]Mount Sinai Medical Center, New York, NY, [4]Central Dermatology, St. Louis, MO, [5]University of Manitoba, Dermadvances Research, Winnipeg, MB, [6]Janssen Services, LLC, Horsham, PA, [7]Janssen Research and Development, LLC, Spring House, PA, [8]Janssen Services, LLC, Spring House, PA.

Background/Purpose: To report the cumulative rates of serious infections in the Psoriasis Longitudinal Assessment and Registry (PSOLAR) study.

Methods: PSOLAR is a multicenter, longitudinal, observational study evaluating long-term safety and clinical outcomes for patients eligible to receive treatment with biologics and/or conventional systemic agents for psoriasis (includes patients with self-reported psoriatic arthritis. Serious infections are defined as serious events (e.g. requiring hospitalization) classified into the MedDRA system organ class of Infections and infestations. The rates of serious infections in PSOLAR overall and by treatment groups are reported through the most recent data cut-off date (Aug 23, 2013) using exposure within 91 days preceding the event. In cases of exposure to >1 therapy, the rule for attribution of serious infections to a treatment group is ustekinumab first, infliximab/golimumab second, other biologics third (nearly all adalimumab or etanercept), or non-biologic therapy fourth, which is consistent with the pre-specified analytic plan.

Results: PSOLAR is fully enrolled with 12 095 patients reflecting 31 818 cumulative patient-years of follow up. 36% of the 12 095 patients had a self-reported diagnosis of psoriatic arthritis. The median duration of follow-up is 2.5 years. Unadjusted rates of serious infection, based on exposure within 91 days preceding the event were: ustekinumab 0.95 events per 100 patient years of observation (PY)[95% CI: 0.71, 1.24; 52/5497 PY, infliximab 2.77 per 100PY[95% CI: 2.15, 3.51; 68/2457 PY], etanercept 1.67 events per 100 PY [95% CI: 1.32, 2.09; 78/4666 PY], adalimumab 1.88 per PY [95% CI: 1.54, 2.27; 106/5645 PY], non-biologics 1.26 per 100 PY[95% CI: 1.08, 1.46; 169/13421 PY], and overall 1.50[95% CI: 1.37, 1.64; 478/31817]. Limitations: Rates have not been adjusted for demographic and clinical differences among treatment groups and are subject to attribution rules.

Conclusion: With nearly 32 000 patient years of follow-up, the overall rate of unadjusted cumulative rate of serious infections in the PSOLAR registry population is 1.50 per 100 PY. The rates of serious infection for ustekinumab and the no biologic treatment groups are lower than rates for infliximab, adalimumab and etanercept. Future analyses may characterize infections further and adjust for differences among treatment groups.

Disclosure: R. Kalb, Janssen Scientific Affairs, LLC, 2; **D. Fiorentino**, None; **M. Lebwohl**, Janssen Scientific Affairs, LLC, 2; **C. Leonardi**, Janssen Scientific Affairs, LLC, 2; **J. Toole**, Janssen Scientific Affairs, LLC, 2; **K. Goyal**, Janssen Scientific Affairs, LLC, 3; **S. Calabro**, Janssen Scientific Affairs, LLC, 3; **W. Langholff**, Janssen Scientific Affairs, LLC, 3; **S. Fakharzadeh**, Janssen Scientific Affairs, LLC, 3.

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Increased Cardiovascular Risk in Patients Recently Diagnosed with Psoriatic Arthritis: A Population-Based, Cohort Study. Katelynn Wilton[1], Floranne C. Ernste[1], Cynthia S. Crowson[2], Eric L. Matteson[2], Hilal Maradit Kremers[2] and Marta Sánchez-Menéndez[3]. [1]Mayo Clinic Rochester, Rochester, MN, [2]Mayo Clinic, Rochester, MN, [3]Centro Medico de Asturias, Oviedo, Spain.

Background/Purpose: Patients diagnosed with rheumatoid arthritis and psoriatic arthritis (PsA) have an increased risk of multiple comorbidities that predispose them to cardiovascular disease (CVD). Although it has been documented that the Framingham Risk Score (FRS) underestimates the 10-year risk of CVD in patients with rheumatoid arthritis, the predictive accuracy of the FRS has not been evaluated in PsA.

Methods: The study population comprised a population-based inception cohort of patients with PsA who fulfilled the ClASsification of Psoriatic ARthritis (CASPAR) criteria between 1989 and 2008. Data on CVD risk factors and all CVD events (myocardial infarction, CV death, angina, revascularization procedures, heart failure, stroke and intermittent claudication) were collected via medical record review. For each patient, the 10 year FRS (Circulation 2008;117;743–753) was calculated at time of PsA diagnosis. Poisson regression models were used to obtain the standardized incidence ratio (SIR), which is the ratio of observed CVD in PsA to predicted CVD obtained from the FRS.

Results: Among 150 incident PsA patients without a history of CVD, 32 patients experienced a CVD event during a mean follow-up of 11.6 years corresponding to an absolute risk of 17.4 per 1000 person years. Of 126 patients who were ≥30 years of age and without a history of CVD at time of PsA diagnosis, the mean FRS was 9.7%. Accounting for length of follow-up, this translated to 10 predicted events. However, 18 patients experienced a CVD event in the first 10 years, corresponding to a 10 year cumulative incidence of 17% (95 % confidence interval [CI]: 10–24%). This was almost twice as high as predicted by the FRS (SIR: 1.80; 95% CI: 1.14–2.86; p=0.012). This two-fold increased CVD risk was consistent across age groups.

Conclusion: We observed a higher than expected incidence of CVD events within our inception cohort of patients with PsA, with an actual risk of about twice that predicted by the FRS. This increased risk underscores the need for close cardiovascular follow-up in this population.

Disclosure: K. Wilton, None; **F. C. Ernste**, None; **C. S. Crowson**, None; **E. L. Matteson**, None; **H. Maradit Kremers**, Amgen, 9; **M. Sánchez-Menéndez**, None.

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Persistence and Predictors of Biologic TNFi Therapy Among Biologic naïve Psoriatic Arthritis Patients in a US Registry. Philip Mease[1], David Collier[2], Chitra Karki[3], Guo Li[4], Bojena Bitman[5] and Jeffrey D. Greenberg[6]. [1]Swedish Medical Center, Seattle, WA, [2]Amgen, Inc., Thousand Oaks, CA, [3]Corrona, LLC., Southborough, MA, [4]Axio Research LLC, Seattle, WA, [5]Amgen, Inc., San Francisco, CA, [6]New York University School of Medicine, New York, NY.

Background/Purpose: Registry data regarding biologic DMARD therapy as a mono or combo (combined with a traditional oral DMARD) in subjects with Psoriatic Arthritis (PsA) are limited. Our aim was to characterize biologic naïve PsA patients who initiated TNFi as mono or combo therapy, estimate length of time on initial TNFi and identify characteristics associated with longevity of initial TNFi use.

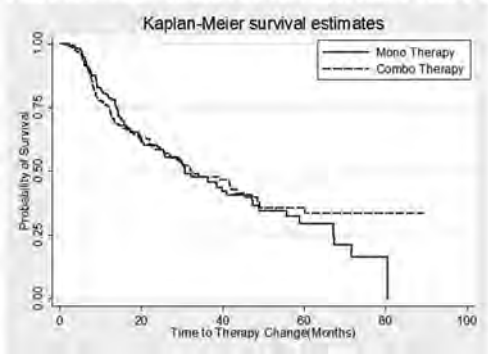
Methods: Data from the US Corrona registry was used. Patients (pts) with a diagnosis of PsA ≥ 18 yrs of age, bio-naïve and initiated TNFi on Jan 1st 2005 or later with at least 3m of follow-up were included. Survival analyses were performed using Kaplan-Meier curves estimating time on initial therapy since TNFi initiation, either as mono/combo therapy. Proportional hazard models were used to identify factors associated with risk of therapy change since initiation. A propensity score (PS) for mono vs combo was estimated and comparisons made using inverse probability weighting based on propensity probabilities. Median time to therapy change was calculated.

Results: 519 biologic naïve PsA pts met the inclusion criteria, with 61% vs. 39% initiating a TNFi as combo or mono therapy, respectively. 51% of pts initiating a TNFi were female, mean age was 51.6 yrs and mean disease duration of 6.3 yrs. The combination therapy group had significantly higher proportion of women (57.1% vs 42.3%), higher clinical disease activity index (CDAI) (mean (SD): 12.5 (11.1) vs 9.6 (9.9)), higher body mass index (mean(SD) 31.9 (7.4) vs 30.7 (6.5), higher proportion of history of diabetes (11.3% vs 6.5%) and higher history of methotrexate use (89.9% vs 68.2%) compared to monotherapy initiators.

Median time on combo and mono therapy since TNFi initiation in the PS matched pts was 32.8 months and 30.8 months respectively [Figure 1]. Significant factors associated with change in initial therapy were disability index measured by mHAQ (HR (95% CI): 2.6 (1.7–3.9)) and CDAI (HR (95% CI): 1.03 (1.01–1.04)). The models were adjusted for age, gender, body mass index, alcohol use, smoking history, mHAQ, and whether the patient was on mono/combo therapy. Persistency for mono vs combo therapy differed by individual TNFi. For example, pts on ETN mono therapy had higher persistency than combo therapy (47.3m on mono vs 19.1m in combo) with a HR of 1.93 (95% CI, 1.15–3.25). Among the pts on IFX, combo therapy was more persistent with a HR of 0.46 (95% CI, 0.24–0.88).

Conclusion: Over a third of PsA pts in the Corrona registry initiated TNFi as monotherapy. Even when adjusting for channeling bias with PS, overall survival on TNFi therapy was similar between mono and combo-treated pts. Greater degree of disability and disease activity use were associated with shorter duration of mono therapy. Some differences in survival on drug were noted between TNFi medicines, potentially related to background disease severity, immunogenicity, and/or other factors.

Figure 1: Kaplan-Meier Survival Curves of Time to Therapy Change, by Initial TNFi Therapy



Disclosure: P. Mease, Celgene, Merck, Novartis, Abbvie, Amgen, BiogenIdec, BMS, Genentech, Janssen, Lilly, Pfizer, UCB;, 2, Celgene, Merck, Novartis, Abbvie, Amgen, BiogenIdec, BMS, Crescendo, Genentech, Janssen, Lilly, Merck, Pfizer, UCB, Vertex;, 5, Abbvie, Amgen, BiogenIdec, BMS, Crescendo, Genentech, Janssen, Lilly, Pfizer, UCB, 8; **D. Collier**, Amgen, 3, Amgen, 1; **C. Karki**, Corrona, LLC., 3; **G. Li**, Axio Research, LLC., 3; **B. Bitman**, Amgen, 1, Amgen, 3; **J. D. Greenberg**, Corrona, LLC., 1, Corrona, LLC., 3, AstraZeneca, Celgene, Novartis and Pfizer, 5.

1854

Systemic Lupus Erythematosus Patients Have Increased Risk of Short Term Adverse Events after Total Hip Arthroplasty. Jordan Roberts[1], Lisa A. Mandl[2], Edwin Su[2], David J. Mayman[2], Mark P. Figgie[2], Arielle Fein[2], Yuo-Yu Lee[2], Ummara Shah[3] and Susan M. Goodman[2]. [1]Weill Cornell Medical College, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]New York University School of Medicine, NYC, NY.

Background/Purpose: Total Hip Arthroplasty (THA) is the most frequent orthopedic procedure performed in lupus (SLE) patients. Whether SLE patients have higher rates of complications after THA than osteoarthritis (OA) patients is unknown. This study compares 6 month adverse event (AE) rates in SLE to matched OA controls.

Methods: Patients enrolled in our institution's THA registry from 2007–2011 were eligible. SLE was identified by ICD-9 code 710.0, and the diagnosis confirmed by chart review. AEs were identified by chart review and self-report questionnaire. SLE patients were matched 2:1 with OA controls by age, gender, year of surgery and hip resurfacing vs. THA. Fractures and other autoimmune diseases were excluded. Baseline characteristics of SLE and OA patients were compared and regression analysis performed to identify independent predictors of AEs.

Results: 58 SLE THA were matched to 116 OA controls. Mean age was 52 years (SLE) vs. 50 years (OA) (p-value=0.57), 90.5% were female. Pre-operative corticosteroid use and perioperative "stress dose" steroids were more common in SLE than OA (44.8% vs. 0.9%; p-value<0.0001 and 53.7% vs. 1.7%, %; p-value<0.0001, respectively). 47.4% of SLE had Charlson-Deyo co-morbidity scores (excluding SLE) ≥1 vs. 13.1% of OA (p-value<0.0001). Spinal/epidural was more common in OA (98.3% OA vs. 82.5% SLE; p-value<0.0001); more SLE received spinal alone (14% SLE vs. 0.9% OA; p-value<0.0001). There was no difference in operative time (86.9 minutes SLE vs. 84.4 OA; p-value=0.65). Length of stay was longer in SLE (6.0 days vs. 4.7; p-value=0.0008). Within 6 months after surgery, SLE had more falls (10.3% vs. 1.7%; p-value=0.02), DVTs (5.2% vs. 0%; p-value=0.036), acute renal disease (8.6% vs. 0%; p-value=0.004), superficial wound infections (6.9% vs. 0.9%, p-value=0.043) and revision surgeries (5.2% vs. 0%; p-value=0.036). Overall, 50% of SLE had any AE vs. 19.8% OA (p-value<0.0001) and 34.5% of SLE had a major AE vs. 10.3% OA (p-value=0.0001). In a multiple logistic regression analysis controlling for comorbidities and anesthesia type, SLE had an increased risk of AEs compared to OA (OR 3.77; 95% CI 1.74–8.16). Interestingly, co-morbidity scores were not significantly associated with risk of AE (Table 1). Among SLE there were no significant differences in AE rates between those taking pre-operative corticosteroids vs. none or those receiving perioperative stress-dose steroids vs. none.

Conclusion: SLE is an independent risk factor for AE after THA. SLE patients had higher rates of fall, acute renal disease, DVT, infection, revision surgery, and longer lengths of stay than matched OA controls. AE rates within SLE were not significantly associated with steroid use. Further research is needed to better understand the causes of increased AE risk in SLE patients.

Table 1: Multivariate Logistic regression*

A) Any Adverse Event	Odds Ratio	95% Confidence Limits	P-value
SLE vs. OA	3.77	1.74–8.16	0.0008
Charlson-Deyo Comorbidity Index** >=1 vs. 0	1.69	0.76–3.76	0.20
Epidural Block vs. no	1.29	0.35–4.73	0.71

B) Any Major Adverse Event: (Major AE= DVT, PE, fall, fracture, additional surgery, acute renal disease, cardiac event– MI, cardiac event–dysrhythmia, deep surgical site infection, bleeding event requiring transfusion, pneumonia, neuropathy, death)

	Odds Ratio	95% Confidence Limits	P-value
SLE vs. OA	3.70	1.52–8.89	0.004
Charlson-Deyo Comorbidity Index** >=1 vs. 0	1.82	0.75–4.41	0.19
Epidural Block vs. no	0.87	0.22–3.35	0.84

C) Any Minor Adverse Event: (Minor Adverse Event= superficial infection, ecchymosis, erythema, incision site drainage, spinal headache, poor wound healing)

	Odds Ratio	95% Confidence Limits	P-value
SLE vs. OA	3.54	1.41–8.91	0.007
Charlson-Deyo Comorbidity Index** >=1 vs. 0	1.19	0.46–3.12	0.72
Epidural Block vs. no	1.91	0.37–9.86	0.44

* All models control for disease (SLE vs. OA), comorbidities and type of anesthesia
** Charlson-Deyo comorbidity index was calculated by excluding SLE

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Disclosure: J. Roberts, None; **L. A. Mandl**, None; **E. Su**, None; **D. J. Mayman**, None; **M. P. Figgie**, None; **A. Fein**, None; **Y. Y. Lee**, None; **U. Shah**, None; **S. M. Goodman**, None.

1855

Not Keeping up with the Times: High Mortality and Early Death Due to Disease in North American Natives with Systemic Lupus Erythematosus (SLE). Ripneet Puar[1], Carol A. Hitchon[1], David B. Robinson[1], Hani El-Gabalawy[1], Navjot Dhindsa[1] and Christine A. Peschken[2]. [1]University of Manitoba, Winnipeg, MB, [2]University of Manitoba, Canada, Winnipeg, MB.

Background/Purpose: Reports in recent decades show drastic improvements in survival of SLE patients, with 10–15 year survival rates of >90%. However, little is known about North American Natives (NAN) with SLE. We compared mortality in NAN SLE patients to Caucasian (CA) SLE patients.

Methods: Patients from a single academic center were followed from 1990–2013 using a custom database. Variables included date of birth, diagnosis, age at disease onset, ethnicity, clinic visits dates, and vital status if known. Records of all patients with a diagnosis of SLE (≥4 American College of Rheumatology criteria) were abstracted. For patients who had not been seen in the last 2 years, updated vital status was obtained from the hospital medical records department. Ethnicity was by self-report, and categorized into NAN, CA and other. Age at diagnosis, disease duration and age at last follow up or age at death was calculated and compared between ethnic groups. Survival time was compared between NAN and CA using Kaplan Meier and Cox proportional hazard models, and person years of life lost (PYLL) was calculated for the 2 groups.

Results: A total of 861 patients with SLE were identified: 217 (25%) NAN, 534 (62%) CA, and the remaining 110 (13%) were of other ethnic backgrounds and were excluded from subsequent analyses. NAN patients were younger at diagnosis (NAN = 32±15 years vs. CA = 37±15 years; p=0.001), and had a shorter disease duration at last follow-up compared to CA (NAN = 11±8 years vs. CA = 16±10 years; p=0.001), but more NAN compared to CA were deceased by the end of the follow-up period (25% vs. 17%, p = 0.013.) Proportion of females, damage scores (SDI) and mean number of ACR criteria met (ACRc) did not differ, but NAN had more frequent nephritis (48% vs. 29%, p < 0.001) and arthritis (90% vs. 67%, p < 0.001). Mean age at death was younger in NAN (NAN = 50±16 years vs. CA = 63±16 yrs p=0.001). Survival rates were significantly worse in NAN compared to CA: 5 year survival was 92% vs. 97%; 10 year survival 85% vs. 92%; 15 year survival 78% vs. 88% respectively (p<0.001) (Figure 1).

After adjustment for ACRc, SDI, gender, age at diagnosis, disease duration, and onset decade (to account for survival bias and changes in treatment over time) NAN were more than twice as likely to die (hazard ratio 2.4; 95%CI: 1.6–3.6) compared to CA. PYLL for NAN (123/1000) was strikingly high compared to CA (39/1000). CA were more likely to die of atherosclerosis or malignancy (54% vs 18%), while NAN were more likely to die of lupus or lupus complications (27% vs. 16%); p= 0.005.

Conclusion: While survival in our CA patients was comparable to recent standards, we have found a twofold higher risk of mortality and threefold increase in PYLL in NAN SLE compared to CA SLE patients. Reasons for this remain unclear and highlight an urgent need for improved care delivery for NAN with SLE to decrease the significant morbidity and mortality burden from this disease.

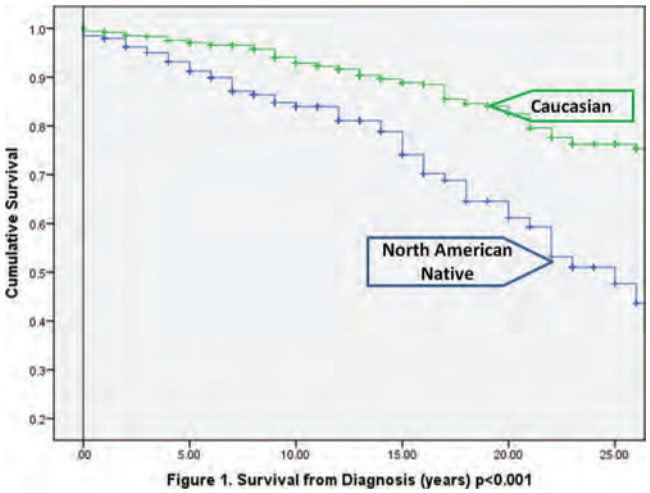


Figure 1. Survival from Diagnosis (years) p<0.001

Disclosure: R. Puar, None; **C. A. Hitchon**, None; **D. B. Robinson**, None; **H. El-Gabalawy**, None; **N. Dhindsa**, None; **C. A. Peschken**, None.

1856

National Hospitalization Trends in Lupus Reveal Rising Rates of Herpes Zoster and Declines in Pneumocystis Infections. Sara G. Murray, Gabriela Schmajuk, Laura Trupin, Lianne S. Gensler and Jinoos Yazdany. University of California, San Francisco, San Francisco, CA.

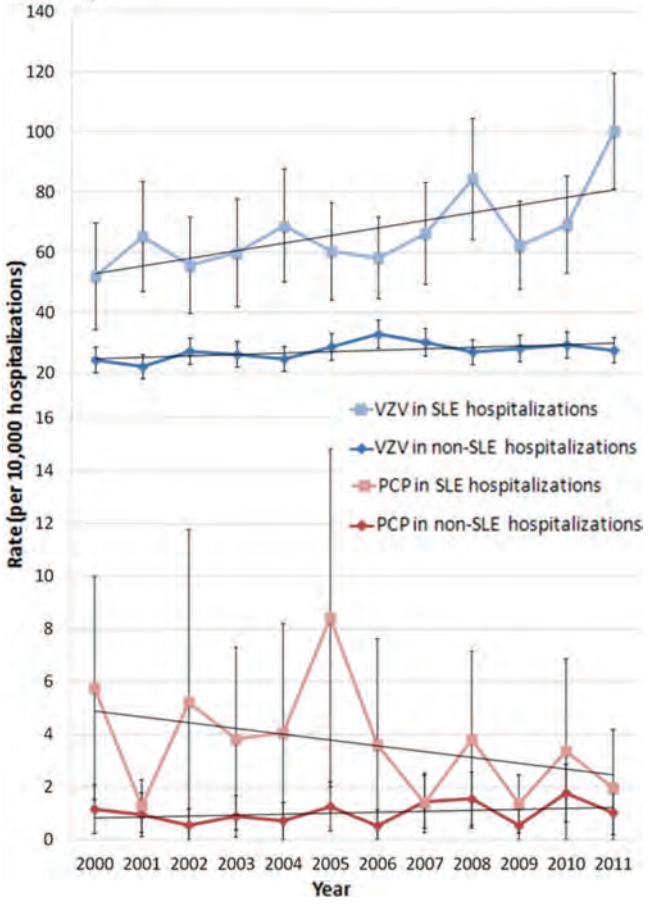
Background/Purpose: Infection is a major cause of morbidity and mortality in systemic lupus erythematosus (SLE). With changing therapeutic practices over the past 15 years, it is unknown whether infectious complications of SLE have also evolved. In this study, we used the Healthcare Cost and Utilization Project National Inpatient Sample (NIS) to evaluate trends in hospitalizations for severe infections in SLE patients.

Methods: Using data from the 2000 to 2011 NIS, a nationally representative 20% sample of all US hospitalizations, we compared hospitalizations among individuals ≥ age 18 who met a validated administrative definition of SLE to hospitalizations of non-SLE patients. Primary outcomes were a discharge diagnosis of a severe infection (bacteremia, pneumonia, opportunistic fungal infection, herpes zoster (VZV), cytomegalovirus, or pneumocystis jirovecii pneumonia (PCP)). Direct standardization was used to generate annual rates of infection in SLE hospitalizations adjusted for age, gender, and a modified Charlson Comorbidity Index in comparison to non-SLE hospitalizations. Adjusted logistic regression models with an effect modification term for SLE and year were used to investigate differences in rates of infections over time among SLE vs. non-SLE hospital discharges.

Results: We identified 361,484 hospitalizations for SLE between 2000 and 2011. Compared to non-SLE hospitalized patients, SLE patients were younger (51 vs. 62 years) and predominantly female (89% vs. 54%), but had a similar comorbidity index (1.2 for both groups). In adjusted logistic regression analyses, a diagnosis of SLE was significantly associated with discharge diagnoses for bacteremia (OR 1.5, 95% CI 1.5–1.6), pneumonia (OR 1.3, 95% CI 1.2–1.3), fungal infections (OR 3.0, 95% CI 2.8–3.2), VZV (OR 2.0, 95% CI 1.9–2.2), cytomegalovirus (OR 5.0, 95% CI 4.2–6.1), and PCP (OR 3.7, 95% CI 2.7–5.1). Between 2000 and 2011, hospitalizations for VZV in patients with SLE increased more rapidly than rates in the non-SLE population, from 52 to 100 cases per 10,000 SLE admissions compared to 24 to 27 cases per 10,000 non-SLE admissions, even after adjustment (p for effect modification 0.036, Figure 1). Conversely, hospitalizations for PCP in SLE decreased over time, from an adjusted rate of 5 to 2 per 10,000 admissions, but remained stable at 1 per 10,000 in the non-SLE population (p for effect modification 0.021).

Conclusion: Among patients with SLE, hospitalizations for VZV are rising at a rate disproportionate to the non-SLE population, while hospitalizations for PCP in SLE are declining. These trends likely reflect changing immunosuppressive treatments and practice patterns in SLE, although further research is needed to determine which therapies significantly affect risk.

Figure 1. Adjusted rates of SLE hospitalizations for Herpes Zoster (VZV) and Pneumocystis (PCP) in comparison to non-SLE hospitalizations between 2000 and 2011 (95% confidence intervals).



Disclosure: S. G. Murray, None; **G. Schmajuk**, None; **L. Trupin**, None; **L. S. Gensler**, UCB, 5, AbbVie, 5, Celgene Corporation, 9; **J. Yazdany**, None.

1857

Determinants of Annual Healthcare Utilization and Overall Cost of Care in Individuals with Systemic Lupus Erythematosus in a Large Insurance Claims Database: Glucocorticoid Use.

Shih-Yin Chen[1], Chan-Bum Choi[2], Qian Li[3], Wei-Shi Yeh[1], Yuan-Chi Lee[4], Amy H Kao[1] and Matthew H. Liang[5]. [1]Biogen Idec, Cambridge, MA, [2]VA Healthcare System, Boston, MA, [3]Evidera, Lexington, MA, [4]Formerly of Evidera, Lexington, MA, [5]Harvard Medical School, Boston, MA.

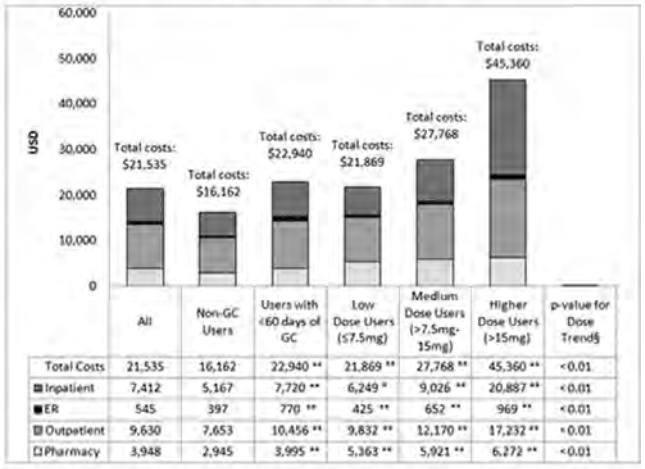
Background/Purpose: Newer therapeutic agents in systemic lupus erythematosus (SLE) may increase cost of care but their effect on limiting the duration and the dosage of glucocorticoids (GC) use ("steroid sparing") may reduce costs and improve other outcomes. This study investigated the determinants of healthcare utilization and costs with the use of GC among adult SLE patients (18–64 years old) in the US using a large administrative database.

Methods: This cross-sectional study analyzed insurance claims in 2007–2011 from established SLE patients identified by their ICD-9-CM diagnosis codes. Five patient groups defined by their oral GC use during the one-year study period were studied: non-GC users, <60 day of GC-use, ≥60 days of GC in low-dose (≤7.5mg), medium-dose (>7.5 to ≤15mg), or higher-dose (>15mg). Annual healthcare utilization and costs were compared across these groups and dose-response was examined among users with ≥60 days of GC. Incremental costs of GC groups, calculated as the difference in total healthcare costs compared with non-GC group, were estimated from multivariable regressions adjusting for demographic and clinical characteristics and stratified by immunosuppressant use. Immunosuppressant use as a surrogate for SLE disease severity was stratified to evaluate the potential cost-saving associated with GC-sparing therapies.

Results: A total of 50,230 patients with SLE were identified, including 52% non-GC users, 20% with <60 days of GC use, and 10% low-dose, 10% medium-dose, and 8% higher-dose with ≥60 days of GC use. GC users had higher healthcare utilization and costs (Figure 1). Incremental costs were significant (all $p<0.01$) for medium-dose ($5,319–$6,913) and higher-dose ($12,517–$15,019) GC groups, regardless of other immunosuppressant use (Figure 2). The incremental costs for low-dose GC group with concomitant immunosuppressants ($1,285; $p=0.04$) were smaller than the incremental costs for low-dose GC group without concomitant immunosuppressants ($2,514; $p<0.01$).

Conclusion: In this large national sample, any GC use especially at higher dose was associated with higher healthcare utilization and costs in patients with SLE. Therapies with GC-sparing effect that can allow patients to maintain on low GC dose may potentially reduce the healthcare economic burden in the treatment of SLE.

Figure 1. Average Healthcare Costs during One-year Follow-up by Study Cohorts

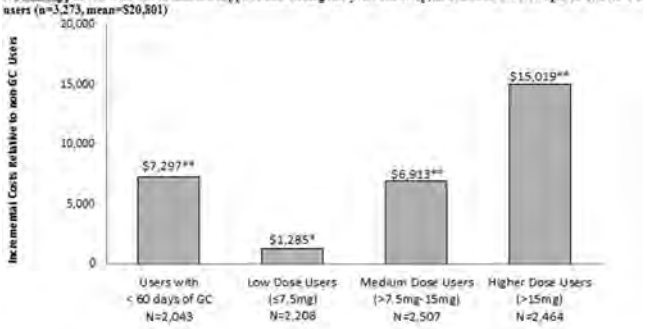


	All	Non-GC Users	Users with <60 days of GC	Low Dose Users (≤7.5mg)	Medium Dose Users (>7.5mg-15mg)	Higher Dose Users (>15mg)	p-value for Dose Trend§
Total Costs	21,535	16,162	22,940 **	21,869 **	27,768 **	45,360 **	<0.01
Inpatient	7,412	5,167	7,720 **	6,249 *	9,026 **	20,887 **	<0.01
ER	545	397	770 **	425 **	652 **	969 **	<0.01
Outpatient	9,630	7,653	10,456 **	9,832 **	12,170 **	17,232 **	<0.01
Pharmacy	3,948	2,945	3,995 **	5,363 **	5,921 **	6,272 **	<0.01

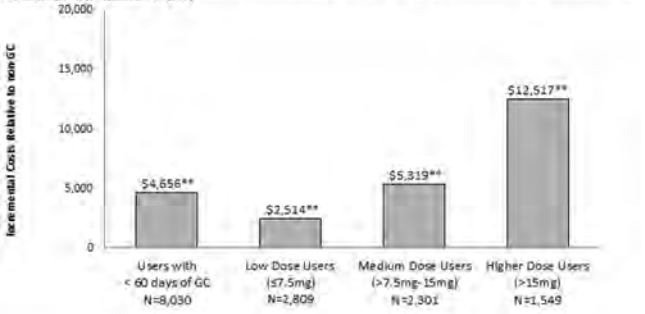
ER= emergency department; Non-GC= non-glucocorticoid
§ Trend test was done only among users with ≥ 60 days of GC
* p<0.05 compared to non-GC Users
** p<0.01 compared to non-GC Users

Figure 2. Estimated Incremental Total Costs during One-year Follow-up by Study Cohorts Compared with Non-glucocorticoid Users

2a) Among patients with use of immunosuppressants during one-year follow-up, incremental costs compared to non-GC users (n=3,273, mean=$20,501)



2b) Among patients without use of immunosuppressants during one-year follow-up, incremental costs compared to non-GC users (n=23,046, mean=$15,503)



* p<0.05 compared to non-GC Users
** p<0.01 compared to non-GC Users

Disclosure: S. Y. Chen, Biogen Idec, 1, Biogen Idec, 3; **C. B. Choi**, None; **Q. Li**, Evidera, 3; **W. S. Yeh**, Biogen Idec, 1, Biogen Idec, 3; **Y. C. Lee**, Qian Li, 3; **A. H. Kao**, Biogen Idec, 1, Biogen Idec, 3; **M. H. Liang**, None.

1858

Standardized Mortality Ratios for Cause-Specific Deaths in Lupus Patients Followed Prospectively at a Single Centre Lupus Clinic. Barry J. Sheane, Dominique Ibanez, Dafna D. Gladman and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Despite the significant improvement in survival rates of patients with systemic lupus erythematosus (SLE) over the last four decades, mortality rates have remained at least 3 times that of the general population. We have recently reported from our longitudinal cohort study that infection is responsible for almost half of all deaths in lupus within the first 5 years of disease, and for over a third of deaths overall.

The aim of this study was to examine the standardized mortality ratios (SMR) for all-cause and cause-specific deaths in SLE patients followed prospectively at a large lupus clinic between 1970 and 2012.

Methods: Primary causes of death were recorded and acquired from autopsy reports, discharge summaries, hospital notes, and death certificates and divided into 5 categories: active lupus, atherosclerosis-related, infection, malignancy and 'other', all as determined by the certifying clinician. For determination of the SMRs, cause-of-death data for the general population (by age, sex and year) were extracted from official records of the relevant provincial registry. SMRs were calculated as the ratio of observed deaths in the SLE cohort to the age, sex and year-match in the general population for all-cause and causes due to infection, atherosclerosis and malignancy.

SMRs were modelled using Poisson regression with the log of the expected number of events as an offset, and adjusted for age, sex, disease duration and decade of death.

Results: Of 259 patients known to have died, causes of death were established in 198 cases. Mean disease duration to time of death was 15.0 ± 11.3 years. Sixty-eight deaths were attributable to infection, 44 to atherosclerosis, 23 to malignancy and 39 due to active lupus.

For deaths due to all causes, the SMR falls significantly for the succeeding decade, from 12.02 (CI 7.67 – 18.82) for a female with < 5 years of SLE in the 1970s to 5.08 (CI 2.18 – 11.87) in the 2000s ($p < 0.0001$), with a similar decrease in those with SLE > 5 years.

For infection, there is a significant decade-on-decade reduction in the SMR, from 188 (CI 86 – 409) in the 1970s, to 117 (CI 42 – 324) in the 1980s, 73 (CI 21 – 256) in the 1990s and 46 (CI 10 – 203) in the 2000s ($p < 0.0001$), regardless of disease duration.

The SMRs for atherosclerosis and malignancy have also decreased over the 4 decades, from 14.09 (CI 9.99 – 16.86) and 1.79 (CI 1.12 – 2.87) in the 1970s, respectively, to 6.43 (CI 1.63 – 13.16) and 1.3 (CI 0.2 – 8.57) ($p > 0.05$).

Conclusion: Infection is the dominant cause of death in SLE, despite significant decreases in SMR over the last 40 years. Its prevalence as a cause-of-death is 40 times that of the general population. While primary prevention of cardiovascular disease should continue to be targeted in SLE, improvement in strategies to prevent and adequately treat infection in SLE require prioritisation.

Disclosure: B. J. Sheane, None; **D. Ibanez**, None; **D. D. Gladman**, None; **M. B. Urowitz**, None.

1859

Age-Specific Predictors of Mortality in SLE. Dominique Ibanez, Dafna D. Gladman and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Mortality is 3 to 5 times greater in SLE patients then it is in the general population – especially among younger patients where it can be over 10 times greater.

Aim: The aim of this study is to determine the age-specific predictors of mortality in Lupus patients.

Methods: All patients followed in a longitudinal cohort of lupus patients since 1970 were studied. Potential predictors for mortality were sex, coronary artery disease(CAD) ever (MI or Angina), Adjusted Mean SLEDAI-2K (AMS), SLICC/ACR Damage Index (SDI), current use of steroids, antimalarials, immunosuppressives, and infection. Each of the variables was evaluated at every clinic visit and used to predict mortality. Prediction models were evaluated using all of the deaths and for all visits with age < 40, for ages between 40 & 60 and for ages ≥ 60 separately. In the models with separate ages, AMS was evaluated only for the visits included in the period of analysis.

Statistical Analysis: Risk factors for death were evaluated using time-dependent covariate survival analysis.

Results: 1439 patients are included in the analysis. Depending on duration of followup, patients could be included in one or more age interval. 967 were seen at ages < 40, 730 were seen at ages between 40 & 60 and 262 were seen at ages ≥ 60. In total, there are 1264 (87.8%) female, 958 (67%) caucasian, 178 (12%) black, 140 (10%) Asian and 163 (11%) other. Age at SLE diagnosis was 30.3 ± 13.6.

A total of 211 patients died. 51 (24.2%) deaths occurred in patients aged < 40, 80 (37.9%) deaths in patients between the ages of 40 & 60 and 80 (37.9%) deaths occurred in patients over 60 years old.

Table 1 shows the hazard ratio for each of the potential predictors for mortality for age-specific intervals. The proportion of patients who died at each age interval increases from 5.3% for ages < 40, 11.0% for ages between 40 & 60, 30.5% for ages ≥ 60.

Disease duration is a predictor when all age groups are combined but not in age-specific analysis. Sex differences are only seen in older age with male at an increased hazard. AMS in the age specific intervals, SDI and steroids increases the hazard for death in all age intervals (with borderline significance in younger patients for steroids). Presence of infection increases the risk of death in patients aged < 60 while previous CAD ever increases the chance of mortality only in patients between the ages of 40 & 60. Antimalarials have a protective effect for patients under the age of 60. Immunosuppressives have a negligible effect in all age groups.

Conclusion: Predictors for mortality change with age intervals. Disease activity, damage and steroids are predictors of mortality in all age intervals. In older patients is male gender is a predictor and in younger patients infection and CAD ever are predictors for mortality. The use of antimalarials is protective for individuals younger than 60.

	Deaths Ages < 40			Deaths Ages 40 – 60			Deaths Ages ≥ 60		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
N death/N patients	51/967 (5.3%)			80/730 (11%)			80/262 (30.5%)		
Disease Duration	0.98	0.93, 1.04	0.56	0.97	0.94, 0.99	0.01	1.00	0.99, 1.02	0.66
Sex (male)	0.74	0.26, 2.11	0.57	1.55	0.87, 2.77	0.14	**1.87**	**1.06, 3.31**	**0.03**
AMS in period	**1.10**	**1.06, 1.15**	**<0.0001**	**1.09**	**1.05, 1.12**	**<0.0001**	**1.11**	**1.05, 1.18**	**0.0002**
SDI	**1.41**	**1.25, 1.59**	**<0.0001**	**1.23**	**1.11, 1.35**	**<0.0001**	**1.19**	**1.08, 1.31**	**0.0007**
Infection	**3.46**	**1.84, 6.50**	**0.0001**	**3.33**	**1.98, 5.60**	**<0.0001**	1.64	0.87, 3.08	0.12
CAD Ever	1.77	0.68, 4.60	0.24	**2.65**	**1.57, 4.48**	**0.0003**	1.07	0.64, 1.80	0.80
Steroids use	2.54	0.98, 6.59	0.06	**1.93**	**1.05, 3.53**	**0.03**	**1.99**	**1.15, 3.42**	**0.01**
Antimalarials use	**0.34**	**0.18, 0.65**	**0.001**	**0.37**	**0.22, 0.62**	**0.0001**	0.69	0.42, 1.14	0.14
Immunosuppressive use	0.94	0.51, 1.74	0.85	1.01	0.61, 1.65	0.98	0.55	0.29, 1.04	0.07

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ACR Concurrent Abstract Session
Vasculitis II
Monday, November 17, 2014, 2:30 PM–4:00 PM

1860

Serum Calprotectin and Disease Relapse in ANCA-Associated Vasculitis. Juliana B Draibe[1], Ruth J. Pepper[1], Peter A. Merkel[2], Alan D. Salama[1] and for The RAVE-ITN Investigators[3]. [1]University College London, London, United Kingdom, [2]Vasculitis Center, University of Pennsylvania, Philadelphia, PA, [3]Immune Tolerance Network, San Francisco, CA.

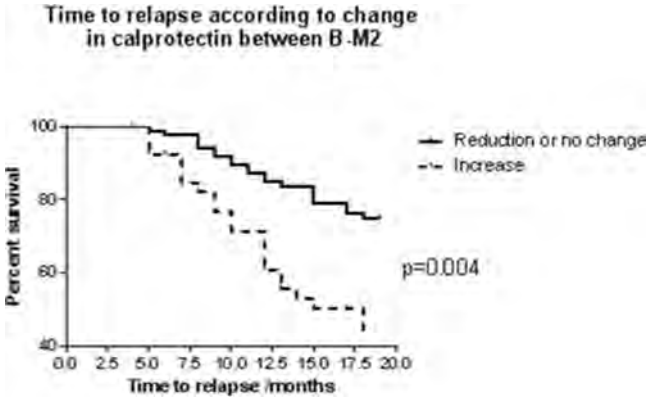
Background/Purpose: In ANCA-associated vasculitis (AAV) disease relapses remain common but there are no reliable means to predict them. We previously demonstrated that serum calprotectin levels were elevated during active AAV and that patients in the NORAM trial who relapsed had higher levels during initial presentation with active AAV than non relapsers. The objectives of this study were to validate calprotectin as a biomarker of relapse using samples from the Rituximab in ANCA-associated Vasculitis (RAVE) trial.

Methods: Serum samples were obtained from 182 subjects enrolled in the RAVE trial at baseline (B), 1 month (m1), and 2 months (m2) following enrollment and initiation of treatment. Serum levels of calprotectin were evaluated by ELISA. Absolute calprotectin levels and changes in levels from B to m1 or m2 and between m1 and m2 were calculated for subjects and stratified according to subsequent disease relapse by 18 months of follow-up.

Results: Serum levels of calprotectin were similar between relapsers and non-relapsers (NR) at B and m1, but at m2, levels were significantly higher in relapsers (relapsers median 4750 ng/ml, range 1364–26071 vs non-relapsers 3769 ng/ml, 1020–9964; $p=0.04$). There was no correlation between calprotectin and ANCA titer or CRP, and only weak correlation with white cell count ($r=0.27$, 0.3,

0.38, at B, m1, and m2 respectively, all p<0.0003). The percentage reduction in levels between m1 and m2 were significantly lower in relapsing patients compared to non-relapsing patients (relapsers +9.7% vs non-relapsers −9.8; p=0.035) confirming that relapsing patients failed to suppress calprotectin to the same extent as non-relapsers. Time to relapse was significantly faster in those patients with an increase in calprotectin between B and m2 or between m1 and m2, when compared to those in whom levels showed no change or reduction (p=0.0004 and p=0.04 respectively) [Figure].

Conclusion: Failure to suppress calprotectin following induction AAV treatment is associated with greater and faster rates of disease relapse. These findings have now been confirmed in two independent cohorts. Calprotectin may be a biomarker predictive of relapse in AAV and should be investigated for use in clinical trials and clinical practice.



Disclosure: J. B. Draibe, None; **R. J. Pepper**, None; **P. A. Merkel**, Genentech and Biogen IDEC Inc., 2, Bristol-Myers Squibb, 2, GlaxoSmithKline, 2, Actelion Pharmaceuticals US, 2, Actelion Pharmaceuticals US, 5, Sanofi-Aventis Pharmaceutical, 5, Chemocentryx, 5; **A. D. Salama**, None; **F. T. RAVE-ITN Investigators**, None.

1861

The Role of Macrophage Migration Inhibitory Factor (MIF) and *MIF* Gene Polymorphisms in the Pathogenesis of Granulomatosis with Polyangiitis. Antoine G. Sreih[1], Rana Ezzeddine[2], Juan Fan[3], Lin Leng[3], Simon Carette[4], David Cuthbertson[5], Gary S. Hoffman[6], Nader A. Khalidi[7], Carol A. Langford[8], Carol McAlear[9], Paul Monach[10], Philip Seo[11], Ulrich Specks[12], Steven R. Ytterberg[12], Peter A. Merkel[13] and Richard Bucala[14]. [1]The University of Pennsylvania, Philadelphia, PA, [2]Bristol-Myers Squibb, Wallingford, CT, [3]Yale University, New Haven, CT, [4]University of Toronto, Toronto, ON, [5]University of South Florida, Tampa, FL, [6]Center for Vasculitis Care and Research, Cleveland Clinic Foundation, Cleveland, OH, [7]St. Joseph's Hospital, McMaster University, Hamilton, ON, [8]Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, OH, [9]Vasculitis Center, University of Pennsylvania, Philadelphia, PA, [10]Boston University, Boston, MA, [11]Johns Hopkins Vasculitis Center, Johns Hopkins University, Baltimore, MD, [12]Mayo Clinic, Rochester, MN, [13]Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [14]Yale University School of Med, New Haven, CT.

Background/Purpose: Macrophage Migration Inhibitory Factor (MIF) is an immunoregulatory cytokine that may play a central role in the pathogenesis of granulomatous diseases. Two functional polymorphisms have been identified in the *MIF* gene promoter that correlate with MIF production *in vivo:* a -794 CATT repeat (*rs5844572*) and a −173 G/C SNP (*rs755622*). This project aimed to study the association of *MIF* polymorphisms and MIF cytokine in granulomatosis with polyangiitis (Wegener's, GPA) and to examine the role of MIF in a murine model of granulomatous vasculitis induced by *Candida albicans* water-soluble fraction (CAWS).

Methods: The human study involved 488 Caucasian patients with GPA and 551 healthy age- and sex-matched controls. Genotyping for the CATT site was performed by PCR plus capillary electrophoresis; SNP analysis was performed by real-time PCR. The frequencies of high expression *MIF* genotypes (>5 CATT repeats and -173 C SNP) were compared between patients and controls. MIF plasma levels were measured by ELISA in 78 patients and 45 controls. Wild type C57BL/6 mice and MIF lung-transgenic mice, some treated with anti-MIF, were injected with CAWS and analyzed for survival and for pulmonary pathology.

Results: The percentage of individuals carrying more than 5 CATT repeats (high *MIF* expression) was 60.9% in patients with GPA and 53.7% in controls (p=0.02). There was no difference in the −173 G/C SNP polymorphisms between these groups. Patients with GPA had higher mean plasma MIF levels than controls (15.9 +- 10.4 ng/dl vs. 6.7 +- 5 ng/dl, p<0.0001). A significantly higher percentage of MIF transgenic mice died when injected with CAWS as compared to wild type (Figure 1A). Injection of anti-MIF mAb protected transgenic mice from dying (Figure 1B). MIF lung-transgenic mice also exhibited more pulmonary granulomas than wild type mice (Mean number = 11.5 ± 0.8 /mm^2 in transgenic vs. 7.9 ± 1.4 /mm^2 in controls, p=0.1) (Figure 2A and 2B).

Conclusion: Compared to controls, patients with GPA have an increased frequency of high-expression *MIF* CATT, and higher plasma MIF levels. In a murine model of granulomatous vasculitis, higher MIF expression increased mortality and pulmonary granulomas while injection of anti-MIF mAb protected mice from dying. MIF seems to play a critical role in the pathogenesis of GPA. Pharmacologic MIF inhibition may offer a promising therapy for GPA.

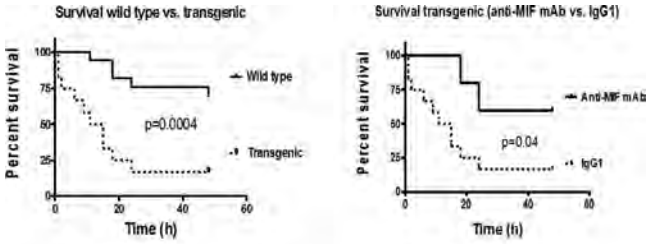


Figure 1A Figure 1B

Figure 1. A: Kaplan-Meyer survival analysis of MIF lung-transgenic compared to wild-type mice after CAWS injections (N=17 in each group). **B:** Survival of MIF lung-transgenic mice treated with anti-MIF mAb versus control immunoglobulin (IgG1) (N=5-10 per group).

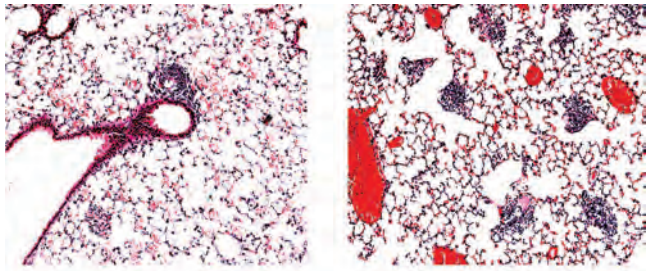


Figure 2A Figure 2B

Figure 2. A: Lung section (200x) of a C57BL/6 wild type mouse 48 hours after CAWS injection showing a few granulomas and pulmonary hemorrhage. **B:** Lung section (200x) of a MIF lung-transgenic mouse 24 hours after CAWS injection showing numerous early forming granulomas and microthromboses.

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1862

The Association of Low-Density Granulocytes with Disease Activity and Response to Treatment in ANCA-Associated Vasculitis. Peter C. Grayson[1], Carmelo Carmona-Rivera[1], Lijing Xu[2], Noha Lim[2], Adam Asare[2], Deborah J. Phippard[2], Mariana J. Kaplan[1], Peter A. Merkel[3] and Paul A. Monach[4]. [1]National Institutes of Health, Bethesda, MD, [2]Immune Tolerance Network, Bethesda, MD, [3]Vasculitis Center, University of Pennsylvania, Philadelphia, PA, [4]Vasculitis Center, Boston University School of Medicine, Boston, MA.

Background/Purpose: To discover new pathways involved in the pathophysiology of ANCA-associated vasculitis (AAV) and identify potential clinical biomarkers through use of whole-genome gene expression profiling. Given the recent discovery of a pathogenic link between AAV and neutrophil extracellular trap (NET) formation, the study also sought to determine if patients with AAV have low-density granulocytes (LDGs) in peripheral blood. LDGs are a distinct subset of neutrophils described in systemic lupus erythematosus (SLE) that separate with PBMC in density gradient preparations and are prone to form NETs.

Methods: The source of clinical data and link biospecimens was a randomized controlled treatment trial in AAV. RNA-sequencing of whole blood from 112 subjects with AAV was performed during active disease at the baseline study visit (BL) and during remission 6 months later (6M). Gene expression in subjects who met the primary trial outcome of clinical remission at 6M was compared to patients who did not enter remission at 6M (responders vs. nonresponders) using the generalized linear model likelihood ratio test. A multi-gene composite score was created by calculating z-scores on a per gene per sample basis. Enrichment of relevant gene set signatures was tested using Gene Set Enrichment Analysis (GSEA). Measurement of neutrophil-related gene expression in PBMC collected concomitantly to whole blood samples was performed by qPCR and compared by ANOVA. LDGs were directly isolated from PBMC fraction by negative selection in 5 additional patients with AAV not enrolled within the clinical trial.

Results: There were no baseline differences in disease activity, clinical features, treatment status, and neutrophil counts between responders (n=77) and nonresponders (n=35). After filtering transcripts expressed in <50% of subjects, there were 44,532 total aligned reads. Differential expression between responders and nonresponders was seen in 2,346 transcripts at BL visit ($p<0.05$). Unsupervised hierarchical clustering demonstrated a distinct cluster of granulocyte-related genes that included genes coding for myeloperoxidase (MPO) and proteinase 3 (PR3), the major autoantigens in AAV. A granulocyte gene signature composite score was 10-fold higher in nonresponders versus responders ($p<0.001$) and 4-fold higher in subjects during active disease (BL) than remission (6M) ($p<0.001$). The signature in AAV strongly overlapped an LDG signature seen in lupus ($FDR_{GSEA}<0.001$). Increased transcription of PR3, but not MPO, measured in PBMC collected in a subset of subjects was associated with active disease ($p<0.01$) and failure to meet the primary trial outcome of remission at 6M ($p<0.001$), validating the findings from whole-blood profiling and localizing the source of granulocyte gene expression to LDGs. In isolation studies, LDGs were found in every patient with AAV and, similar to SLE, were noted to readily form NETs in the absence of stimulation.

Conclusion: In patients with AAV increased expression of a granulocyte gene signature is associated with disease activity and response to treatment. The source of this signature is likely LDGs, which may be a key pathogenic cell in AAV.

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1863

CCX168, an Orally Administered C5aR Inhibitor for Treatment of Patients with Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Pirow Bekker[1], David Jayne[2], Annette Bruchfeld[3], Matthias Schaier[4], Kazimierz Ciechanowski[5], Lorraine Harper[6], Michel Jadoul[7], Mårten Segelmark[8], Daina Selga[9], Istvan Szombati[10], Michael Venning[11], Christian Hugo[12], Paul L. van Daele[13], Ondrej Viklicky[14], Antonia Potarca[15] and Thomas J. Schall[15]. [1]Chemocentryx, Inc., Mountain View, CA, [2]Addenbrookes Hospital University of Cambridge, Cambridge, United Kingdom, [3]Karolinska Institute, Stockholm, Sweden, [4]University of Heidelberg, Heidelberg, Germany, [5]Pomeranian Medical University, Szczecin, Poland, [6]University of Birmingham, Birmingham, United Kingdom, [7]Cliniques Saint-Luc, Brussels, Belgium, [8]Linkoping University, Linkoping, Sweden, [9]Lund University, Lund, Sweden, [10]Budaclinic, Budapest, Hungary, [11]Manchester University, Manchester, United Kingdom, [12]Dresden University, Dresden, Germany, [13]Erasmus Medical Center, Immunology, Rotterdam, Netherlands, [14]Instit of Clin and Exp Med, Prague, Czech Republic, [15]ChemoCentryx, Inc., Mountain View, CA.

Background/Purpose: CCX168 is a potent, specific C5aR inhibitor in clinical development for ANCA-associated vasculitis. The initial focus of this randomized, double-blind, placebo-controlled clinical trial was on renal disease activity, since CCX168 showed profound efficacy in a mouse model of MPO ANCA-induced glomerulonephritis. CCX168 indeed showed renal disease efficacy of oral 30 mg CCX168 given twice daily for 12 weeks based on eGFR (up to 6.8 mL/min/1.73 m^2 increase over 12 weeks), urinary ACR (mean decrease up to 63% over 12 weeks), and MCP-1:creatinine (up to 72% decrease over 12 weeks).

Methods: The purpose of this investigation was whether CCX168 treatment also has any effect on non-renal disease activity. The Birmingham Vasculitis Activity Index (BVAS) is a global disease activity index. Efficacy based on BVAS was evaluated to assess the potential non-renal disease activity of CCX168. 25 patients completed this clinical trial; 9 received placebo+cyclophosphamide (CYC)+full dose prednisone (60 mg/day), 8 received CCX168+CYC+low dose prednisone (20 mg/day), and 8 received CCX168+CYC+no prednisone.

Results: Baseline characteristics and Week 12 results on renal and non-renal disease activity are shown in the table.

		CCX168+CYC+Low-Dose Steroids (N=8)	CCX168+CYC+ No Steroids (N=8)	SOC: CYC+High-Dose Steroids (N=9)
Baseline Characteristics				
Age, years	mean (SD)	55.3 (16.3)	54.9 (15.0)	57.7 (14.0)
Gender, M/F	%	70/30	50/50	50/50
Duration of ANCA disease, months	median (range)	0.5 (0–162)	0 (0–53)	0 (0–32)
ANCA disease status, new/relapsed	%	70/30	75/25	88/12
Anti-MPO/Anti-PR3 positive	%	40/60	63/37	63/37
BVAS	median (range)	11 (5–30)	11 (5–28)	9 (3–15)
eGFR, ml/min/1.73 m^2	mean (SD)	56.8 (14.6)	52.4 (17.7)	56.9 (25.2)
U-Albumin:creatinine ratio, mg/g	mean (SD)	386 (346)	341 (287)	417 (416)
Efficacy Results				
Steroids rescue events	n (%)	0 (0%)	1 (13%)	1 (11%)
eGFR change at Wk 12, ml/min/ 1.73 m^2	mean (SEM)	6.8 (2.1)	0.6 (3.6)	2.2 (3.3)
U-ACR % change at Wk 12	mean	−63%	−59%	−9%
U-MCP-1:creatinine % change at Wk 12	mean	−72%	−52%	−37%
BVAS Total				
Response* at Wk 12	% of pts	86%	88%	44%
Remission** at Wk 12	% of pts	29%	25%	33%
BVAS Renal				
Response at Wk 12	% of pts	71%	50%	38%
Remission at Wk 12	% of pts	29%	25%	25%
BVAS Non-Renal				
Response at Wk 12	% of pts	83%	88%	57%
Remission at Wk 12	% of pts	67%	50%	43%
BVAS Total %Change at Wk12	mean ± SEM	−71 ± 9%	−65 ± 11%	−26 ± 25%
BVAS Renal %Change at Wk12	mean ± SEM	−64 ± 10%	−50 ± 15%	−16 ± 26%
BVAS Non-Renal %Change at Wk12	mean ± SEM	−81 ± 33%	−83 ± 29%	−15 ± 6%

* Response: BVAS decrease ≥50% plus no worsening in any body system; ** Remission: BVAS of 0 plus prednisone dose ≤10 mg/day.

Conclusion: In addition to an effect on renal disease activity, CCX168 treatment of patients with ANCA-associated vasculitis also resulted in a salutory effect on non-renal disease activity based on the non-renal component of the BVAS.

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1864

Granulomatosis with Polyangiitis or Microscopic Polyangiitis: Long-Term Outcomes of the Prospective Wegent Trial Comparing Azathioprine Vs Methotrexate for Remission-Maintenance in 126 Patients. Xavier Puéchal[1], Christian Pagnoux[2], Elodie Perrodeau[3], Mohamed Hamidou[4], Jean-Jacques Boffa[5], Xavier Kyndt[6], François Lifermann[7], Thomas Papo[8], Dominique Merrien[9], Amar Smail[10], Philippe Delaval[11], Catherine Hanrotel-Saliou[12], Bernard Imbert[13], Chahéra Khouatra[14], Marc Lambert[15], Charles Leské[16], Kim Heang Ly[17], Edouard Pertuiset[18], Pascal Roblot[19], Marc Ruivard[20], Jean-François Subra[21], Jean-Francois Viallard[22], Benjamin Terrier[1], Pascal Cohen[1], Luc Mouthon[1], Philippe Ravaud[3] and Loïc Guillevin for the French Vasculitis Study Group[1]. [1]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [2]University of Toronto, Toronto, ON, [3]Epidemiology, Université Paris-Descartes, Paris, Paris, France, [4]CHU Hôtel Dieu, Nantes, Nantes, France, [5]Hôpital Tenon, Paris, Paris, France, [6]CH, Valenciennes, Valenciennes, France, [7]CH Côte d'Argent, Dax, Dax, France, [8]Bichat Hospital, Paris, Paris, France, [9]CH Compiègne-Noyon, Compiègne, France, [10]CHU Amiens Nord, Amiens, France, [11]CHU Rennes Sud, Rennes, France, [12]CHU Cavale Blanche, Brest, Brest, France, [13]CHU, Grenoble, Grenoble, France, [14]CHU Louis Pradel, Lyon, Lyon, France, [15]Internal Medicine University Lille Hospital, Lille, Lille, France, [16]CH, Cholet, Cholet, France, [17]CHU Dupuytren, Limoges, Limoges, France, [18]René Dubos Hospital, Pontoise, France, [19]CHU, Poitiers, Poitiers, France, [20]CHU Estaing, Clermont–Ferrand, Clermont–Ferrand, France, [21]CHU, Angers, Angers, France, [22]Hôpital Haut-Lévêque, Bordeaux, CHU Bordeaux, France.

Background/Purpose: Results of the previously reported randomized–controlled WEGENT trial demonstrated that, at 28 months, methotrexate (MTX) is as effective as azathioprine (AZA) for maintaining remission of granulomatosis with polyangiitis (GPA, Wegener's) or severe microscopic polyangiitis (MPA) (NEJM 2008;359:2790–803). The long-term outcomes of patients included in the WEGENT trial were analyzed in this study.

Methods: Long-term outcomes were ascertained for 126 patients enrolled in the WEGENT trial between 1999 and 2004. Data on survival, relapse, immunosuppressant use, cancer, infection and cardiovascular morbidity were collected. All patients were analyzed according to their randomization group. Demographic, clinical and laboratory parameters at trial entry were evaluated as potential prognostic factors for death or relapse in multivariate models.

Results: Median follow-up was 11.8 years. The 10-year overall survival rate was 74.8% [95% CI 64.5–86.9] for the AZA arm and 79.9% [95% CI 70.3–90.7] for the MTX arm, with no between-arm survival difference (HR MTX vs AZA = 0.79 [95% CI 0.37–1.70]; P=0.55). No long-term between-arm differences were observed for adverse events, severe adverse events, infections, cancer, relapses and severe relapses. The 10-year survival rate without relapse was 26.3% [95% CI 17.3–40.1] in the AZA arm and 35.1% [95% CI 24.9–49.4] in the MTX arm, with no significant between-arm difference (HR MTX vs AZA = 0.78 [95% CI 0.51–1.20]; P=0.26). The 10-year survival rate without severe side effects was also comparable for the two groups (HR MTX vs AZA = 1.02 [95% CI 0.64–1.63]; P=0.93), as was survival without relapse and severe side effects (HR MTX vs AZA = 1.04 [95% CI 0.66–1.63]; P=0.87). Taking into account only the 97 GPA patients, no between-arm differences were observed for these survival parameters. Survival without relapse was shorter for GPA than MPA patients (HR 2.16 [95% CI 1.22–3.83]; P=0.009). Multivariate analyses retained the glucocorticoid dose at the end of the scheduled 12-month maintenance-drug regimen (HR 1.18 [95% CI 1.09–1.29]; P<0.001), glucocorticoid duration (HR 1.01 [95%CI 1.00–1.02]; P<0.04), and PR3-ANCA–positivity (HR 3.68 [95% CI 2.07–6.55]; P<0.001) as being significantly prognostic of long-term relapses. Each additional month or mg of glucocorticoid at the end of the maintenance regimen increased the probability of relapse or death by 1% or 15%, respectively.

Conclusion: This long-term analysis confirmed that AZA and MTX are comparable options for maintaining GPA or MPA remission. It showed that the overall survival is good, even though relapses and adverse events remain matters of concern. Further studies are needed to reduce the long-term relapse rate of ANCA-associated vasculitides.

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1865

Increased Risk of Myocardial Infarction and Cerebrovascular Accidents after Diagnosis of Granulomatosis with Polyangiitis: A General Population-Based Cohort Study. Neda Amiri[1], Natasha Dehghan[1], Eric C. Sayre[2], Kamran Shojania[1] and J. Antonio Avina-Zubieta[2]. [1]University of British Columbia, Vancouver, BC, [2]Arthritis Research Centre of Canada, Richmond, BC.

Background/Purpose: Limited literature is available on the incidence of myocardial infarction (MI) and cerebrovascular accidents (CVA) in patients with Granulomatosis with Polyangiitis (GPA). We assessed the risk of MI and CVA in cases with GPA compared to controls from the general population using hospitalization databases and physician billings that encompasses the entire province of British Columbia, Canada. We further determined the time trend risks of MI and CVA since diagnosis of GPA.

Methods: Our data included all visits to health professionals and all hospital admissions from 1990 to 2010 as well as all dispensed medication from 1996 to 2010 for all individuals.

We conducted a retrospective matched cohort study among new cases with GPA meeting a pre-defined criteria as follows: **a)** diagnosis of GPA (ICD-9-CM 446.4) in adults on at least two visits within a two-year period between 1996 and 2010 by a non-rheumatologist physician; **b)** diagnosis of GPA on at least one visit by a rheumatologist or from hospitalization; **c)** absence of a prior GPA diagnosis between January 1990 and December 1995 (to ensure incident GPA cases). Ten controls matched by birth year, sex and calendar year of follow-up were selected from the general population. **Incident MI and CVA** events based on hospitalization or death certificate were recorded as an outcome. We estimated relative risks (RRs) comparing GPA with age-, sex- and entry time-matched comparison cohorts, adjusting for potential cardiovascular risk factors. Sensitivity analyses were conducted to assess for unmeasured confounders (e.g. smoking).

Results: Among 640 incident cases of GPA (54.2% female, mean age 58.6), 28 developed a first time MI and 25 CVA events with an incident rate (IR) of 13.9 and 12.3 per 1000 person-years, respectively. Compared with the age, sex, and entry-matched controls, the incidence rate ratio (IRR) were 3.3 (95% CI 2.1–5.0) and 3.2 (95% CI 2.0–5.1) for MI and CVA respectively. The risk of developing MI and CVA was highest within the first year following diagnosis of GPA, decreasing over time and persisting after 5 years (**see table**). After adjusting for covariates, the results remained significant for both MI and CVA. The results also remained statistically significant after adjusting for the potential impact of unmeasured confounders (adjusted RRs ranging between 2.57 and 3.84 in all sensitivity analyses).

Conclusion: This large general population-based study found an increased an increased risk of MI and CVA in patients with GPA. Furthermore, the risk is highest in the first year of disease and decreases subsequently persisting at 5 years of follow up. Our results support increased monitoring for cardiovascular disease in patients with GPA, including management of traditional risk factors to reduce this risk.

Table: Risk of Incident MI and CVA according to GPA Status

	GPA N = 608	**Non-GPA N = 6,169**
Cases of MI, n	28	108
Incidence Rate/1000 PY	13.9	4.2
Age-, sex-, and entry time-matched RRs (95% CI)	3.3 (2.1–5.0)	1.0
1 year of disease duration	6.0 (2.7–12.7)	1.0
2 years	3.9 (1.9–7.4)	1.0
3 years	3.1 (1.6–5.6)	1.0
4 years	3.5 (2.0–5.9)	1.0
5 years	3.4 (2.0–5.6)	1.0
Multivariable RR (95% CI)	**3.9 (2.2–6.7)**	**1**
	GPA N = 623	**Non-GPAN = 6,307**
Cases of CVA, n	25	99
Incidence Rate/1000 PY	12.3	3.8
Age-, sex-, and entry time-matched RRs (95% CI)	3.2 (2.0–5.1)	1.0
1 year of disease duration	7.1 (3.3–14.5)	1.0
2 years	5.1 (2.7–9.2)	1.0
3 years	4.5 (2.5–7.8)	1.0
4 years	4.0 (2.3–6.8)	1.0
5 years	4.1 (2.4–6.7)	1.0
Multivariable RR (95% CI)	**3.1 (1.7–5.7)**	1.0

Disclosure: N. Amiri, None; **N. Dehghan**, None; **E. C. Sayre**, None; **K. Shojania**, None; **J. A. Avina-Zubieta**, None.

ACR/ARHP Combined Session
Pediatric Rheumatology
Monday, November 17, 2014, 2:30 PM–4:00 PM

1866

Birth Outcomes in Women with a History of Juvenile Idiopathic Arthritis. Debbie Ehrmann Feldman[1], Evelyne Vinet[2], Sasha Bernatsky[3], Ciaran Duffy[4], Elizabeth Hazel[5], Marie-Pierre Sylvestre[1], Garbis Meshefedjian[6] and Anick Bérard[1]. [1]Université de Montréal, Montréal, QC, [2]McGill University Health Center, Montreal, QC, [3]McGill University, Montreal, QC, [4]Children's Hospital of Eastern Ontario, Ottawa, ON, [5]McGill University Heatlh Center, Montreal, QC, [6]Public Health Department of Montreal, Montreal, QC.

Background/Purpose: Although there is a higher frequency of adverse birth outcomes in women with rheumatoid arthritis, little is known on the subject regarding women who had juvenile idiopathic arthritis (JIA) as children or adolescents. The objective of our study was to determine whether children born to women who had JIA in childhood and adolescence had more adverse birth outcomes than children born to mothers who never had JIA.

Methods: We designed a retrospective cohort study using administrative data that covered the entire population of the province of Québec, Canada. We identified 1756 females with a diagnosis of JIA who had given birth (first birth: stillbirth or live birth) between 01/01/1983 and 12/31/2010 from the

Quebec physician reimbursement and hospitalization databases. We also assembled a cohort of women from the population database who did not have a diagnosis of JIA, matched 4:1 for date of first birth (± 3 months), age (± 5 years) and region of residence (using the postal code) to serve as a control group (n=7024). We compared birth outcomes (stillbirth, prematurity, small for gestational age, and the presence of major congenital anomalies diagnosed within the first year post birth) in those who had JIA and those who did not. We used logistic regression, adjusting for maternal age, sex of the infant, maternal education, hypertension during pregnancy and gestational diabetes.

Results: For the entire cohort, the mean age at delivery was 24.9 years (standard deviation 4.4; range 16 to 46 years). There were more adverse birth outcomes in the JIA group, except for stillbirths. Women who had had JIA were at higher risk for having a premature baby (adjusted relative risk (95% confidence interval) 1.18 (1.00,1.4)), a small for gestational age baby (adjusted relative risk (95% confidence interval) 1.19 (1.04–1.36)), and a child with a major congenital anomaly (adjusted relative risk (95% confidence interval) 6.49 (4.88–8.10)). The prevalence of neural tube defects was especially high in the JIA group (1.7% vs 0.04% in the non JIA group) as were congenital heart and circulatory defects (1.2% in the JIA group vs 0.6% in the non JIA group).

Conclusion: Women who had JIA are at higher risk for adverse birth outcomes. The implications are that women with a history of JIA who are pregnant must be monitored closely. Further research is needed to understand possible pathophysiologic mechanisms in JIA and pregnancy as well as pharmaco-epidemiologic studies to explore the effects of medications during childhood and youth (including during the peri-pubescent period) on future birth outcomes.

Disclosure: D. Ehrmann Feldman, None; **E. Vinet**, None; **S. Bernatsky**, None; **C. Duffy**, None; **E. Hazel**, None; **M. P. Sylvestre**, None; **G. Meshefedjian**, None; **A. Bérard**, None.

1867

Mandibular Movement in Healthy Individuals from 4–17 Years of Age. Peter Stoustrup[1], Kasper Dahl Kristensen[2], Annelise Küseler[3], Thomas Klit Pedersen[4] and Troels Herlin[4]. [1]University of Aarhus, Aarhus C, Denmark, [2]Specialist Oral Health Center for Western Norway, Rogaland Stavanger, Norway, [3]Aarhus University, Aarhus, Denmark, [4]Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: Assessment of mandibular movement capacity is an important part of the clinical orofacial examination of patients with juvenile idiopathic arthritis (JIA). The aim of the present study was twofold: 1) To establish age-related normative values for maximal mouth opening capacity and mandibular laterotrusion in healthy individuals. 2) To establish a universal cut-off value for "normal" range of motion in children and adolescent patients to be used in future clinical orofacial examinations of patients with JIA.

Methods: A total of 1114 healthy Danish individuals between the ages of 4–17 years were included in this cross-sectional population-based study. During a routine dental examination the maximal mouth opening capacity and laterotrusion capacity (the sideway excursion of the mandible) were assessed in each individual according to a standardized measurement protocol with calibrated metallic rulers. The measurements were adjusted for overbite and midline deviations. Exclusion criteria: diagnosis with temporomandibular dysfunction, previous orofacial complaints, jaw fractures or hypermobility.

Results: The mean maximal mouth opening gradually increased from 38 mm (SD 6.1 mm) at age four to 54.5 mm (SD 6.8 mm) at age 17. A linear increase in the opening capacity was observed between the age of four to 11; Beyond the age of 11 only minor changes of 4 millimeters were observed. No inter-gender difference in maximal mouth opening capacity was observed ($p>0.15$).

The mean total laterotrusion capacity (right excursion + left excursion) gradually increased from 15.4 mm (SD 3.1 mm) at age four to 20.1 mm (SD 3.7 mm) at age 17. A statistical significant inter-gender difference of 0.8 mm (SD 0.4 mm) was observed in relation to the total laterotrusion capacity; however, the clinical relevance of this significant difference is questionable.

Conclusion: Normative values of maximal mouth opening capacity and laterotrusion capacity in individuals between four and 17 years of age were established. Our findings oppose the use of a single universal cut-off value for "normal" range of motion in children and adolescent patients. Instead we recommend including the age-related normative values of mandibular range of motion in the orofacial examination of patients with JIA.

Disclosure: P. Stoustrup, None; **K. D. Kristensen**, None; **A. Küseler**, None; **T. K. Pedersen**, None; **T. Herlin**, None.

1868

Can DAS 28 at 3 Months after the 1st Biologic Therapy Predict Subsequent Sustainable Clinical Remission in Polyarticular Juvenile Idiopathic Arthritis Patients? Tomohiro Kubota[1], Syuji Takei[2], Tsuyoshi Yamatou[3], Tomokazu Nagakura[4], Hiroyuki Imanaka[3], Yukiko Nonaka[3], Tomoko Takezaki[3], Harumi Akaike[3] and Mio Matsuura[5]. [1]Kagoshima University Hospital, Kagoshima City, Japan, [2]Kagoshima University, Kagoshima, Japan, [3]Kagoshima University Hospital, Kagoshima, Japan, [4]House of Meguminoseibo, Usuki, Japan, [5]Kagoshima University, Kagoshima-Shi, Japan.

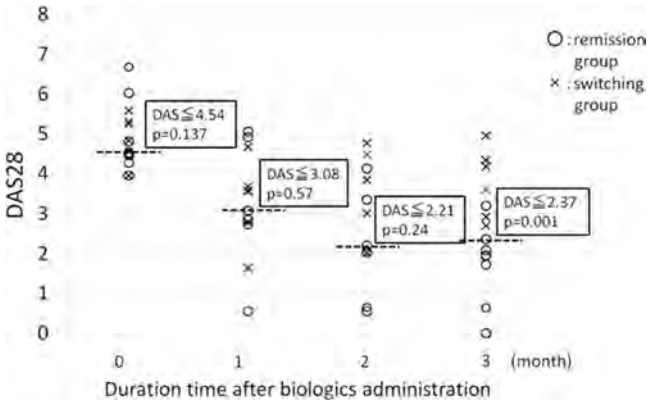
Background/Purpose: To avoid the progression of joint damage, early decision making is important in JIA patients who failed to achieve sustainable clinical remission by the 1st biologic agents. Therefore, we examined whether the scores of DAS 28 at 3 months after initiating the 1st biologic therapy can predict subsequent sustainable remission with the 1st biologic agents in the polyarticular JIA (pJIA) patients.

Methods: pJIA patients who had started the 1st biologic agents at the Kagoshima University Hospital were involved in this study. The patients were divided into two groups according to the subsequent efficacy of the 1st biologic agents; patients who successfully maintained clinical remission with the 1st biologic agents (remission group) and the patients who were eventually obliged to switch to the 2nd biologic agents due to the lack of efficacy (switching group).

Results: Scores of DAS28 of 14 pJIA patients involved in this study gradually improved after starting the 1st biologic agents. However, 6 of 14 patients (43%) failed to maintain their clinical remission and eventually switched to the 2nd biologic agents at 9 months (median, range 6–18 months) after initiating the 1st biologic agents (switching group). The rest of 8 patients (57%) achieved sustainable clinical remission with the 1st biologic agents (remission group).

There were no significant differences between the two patients' groups as to sex ratio, age at onset, disease duration at initiating biologics. However, Das28 score at 3 months of the 1st biologic therapy was significantly higher in switching group (1.75 ± 1.0) than that of remission group (3.8 ± 0.87)($p=0.001$) (Figure 1). The receiver operating characteristic (ROC) analysis revealed that the cut-off point of DAS28 to discriminate the two patients' group was 2.37 (sensitivity 100%, specificity 88.9%).

Conclusion: Evaluating DAS28 at 3 month after initiating biologic therapy was useful in predicting subsequent sustainable clinical remission. Patients with DAS28 >2.37 at 3 month after initiating the 1st biologic agents should be considered to switch to the 2nd biologic agents in the treatment of pJIA.



Disclosure: T. Kubota, None; **S. Takei**, None; **T. Yamatou**, None; **T. Nagakura**, None; **H. Imanaka**, None; **Y. Nonaka**, None; **T. Takezaki**, None; **H. Akaike**, None; **M. Matsuura**, None.

1869

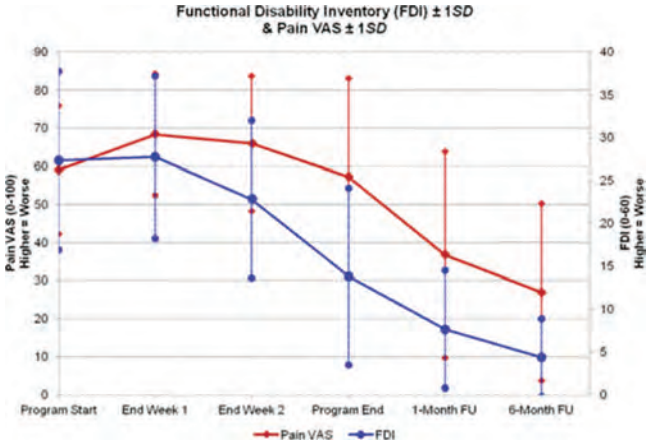
Child Pain, Function, and Psychological Outcomes in an Intensive Interdisciplinary Pediatric Pain Rehabilitation Program. Cara Hoffart, Rawni Anderson, Amy Chapman, Brandi Dorton, Danielle Feltrop, Misty Wilson and Dustin Wallace. Children's Mercy Hospital, Kansas City, MO.

Background/Purpose: We examined the functional, psychological, and pain-related outcomes among children with chronic pain completing an intensive interdisciplinary pediatric pain rehabilitation program. We hypothesized that baseline psychological measures (i.e. anxiety, depression) will predict longer treatment course while baseline pain severity would not correlate with program duration in an interdisciplinary pain rehabilitation program.

Methods: This outpatient program provides 5–6 hours of daily intensive physical and occupational therapy in addition to yoga, self-regulation training, and behavioral health intervention. All pain medications are discontinued, and no invasive therapeutic procedures are utilized. 31 patients (27 female) age 11–18 with chronic musculoskeletal pain completed Functional Disability Inventory, 100 mm Visual Analog Scale, PROMIS Anxiety, Depression, and Mobility, PRCQ-catastrophizing, and the Pain Acceptance Questionnaire for Adolescents at baseline, the end of each week, and 28 have completed a one-month follow-up and 14 have completed a six-month follow-up. Paired samples *t*-tests and correlations were conducted with SPSS (V.20) and supplemented with hierarchical linear modeling (HLM7) for time-series analyses of pain, functioning, and psychological factors.

Results: The mean program duration was 3.7 (± 0.9) weeks, determined by achievement of functional goals. Using paired samples t-tests, current pain (VAS 0–100) significantly decreased from 59.1 to 36.7 ($P<0.001$) and 26.9 ($P=.004$) at 1- and 6-month follow-up, respectively. FDI improved from 27.3 to 13.8 between baseline and program end ($P<0.001$), and continues to improve at 1- and 6-month follow-up to 7.7 ($P<0.001$) and 4.4 ($P=.006$) respectively, reflecting increased physical ability. Patient reported anxiety and depression decline significantly ($P<0.001$), while pain acceptance increases significantly during treatment ($P<.001$). Treatment program duration correlated with greater baseline disability (FDI $r=.462$; $P=.009$), and presence of conversion symptoms ($r=.548$; $P=.004$). Patients with greater pain acceptance (CPAQ-A; $r=-.433$; $P=.015$) at baseline required shorter treatment intervention.

Conclusion: Children with chronic musculoskeletal pain successfully restore function and improve pain without pharmacotherapy. Baseline functional disability and psychological factors correlate with treatment program duration. Prospective studies are warranted to determine long-term efficacy and effectiveness of this interdisciplinary program.



Disclosure: C. Hoffart, None; **R. Anderson**, None; **A. Chapman**, None; **B. Dorton**, None; **D. Feltrop**, None; **M. Wilson**, None; **D. Wallace**, None.

1870

Children and Parent Satisfaction in the Pediatric Rheumatology Clinic: Patient Orientated Quality Service Measures. Jenny Tekano[1], Lori B. Tucker[2] and Audrea Chen[3]. [1]BC Children's Hospital, Vancouver, BC, [2]BC Children's Hospital and University of British Columbia, Vancouver, BC, [3]research student, Vancouver, BC.

Background/Purpose: Patient satisfaction is a multidimensional concept, and is a component of quality care. Inclusion of patient experience with care is highly relevant in improving service delivery. There have been few attempts to measure satisfaction in the pediatric tertiary care setting, inclusive of child as well as parent assessment. We aimed to assess child and parent perspectives on their care in a multidisciplinary pediatric rheumatology outpatient service.

Methods: Parents and children (≥9 yrs) attending the Pediatric Rheumatology clinics over a 4 month period in 2013 at BC Children's Hospital, Vancouver, BC, were asked to complete a anonymous questionnaire to assess satisfaction with clinical care. The questionnaire items were addressing 3 general areas: 1) information 2) clinical care and services, 3) global impact of disease on children's quality of life. Separate parent and child questionnaires were given. Respondents were asked to rate agreement or disagreement with item statements on a 5 point Likert scale. There were 4 open ended questions asking most difficult issue in coping with disease, top likes and dislikes about the clinic services, and changes they would suggest in the clinic.

Results: 376 parents and 284 children completed the questionnaire, with patient diagnoses of juvenile idiopathic arthritis (146), systemic lupus, dermatomyositis or vasculitis (45), or other rheumatic disease (91). The majority of parents (92%) and children (85%) reported general satisfaction with care received, and most also felt their questions were answered in the clinic (parents 95%; children 87%). Although parents find written material provided in clinic helpful (80%), 40% of children do not find this information helpful. Only 22% of parents report they feel to be the best judge of whether their child requires treatment or a medication. Positive qualities of the staff (helpful, caring, friendly) were mentioned by a large number of parents (60%) and children (68%) in open ended questions about the clinic. Structural issues of clinic attendance (wait time, parking, travel) were issues reported by many parents and children. One quarter of parents and children report having a lot of pain due to their disease. 37% of children report being unable to fully participate in activities, and 29% report difficulty in school due to their illness. Physical restrictions, pain, and need for medications and procedures were the most frequent difficulties reported in open questions by children; parents reported feeling helpless and concern about unknown future as major difficulties for them in coping.

Conclusion: Children with rheumatic disease and their parents receiving care through a multidisciplinary pediatric rheumatology team expressed global satisfaction with care provided, particularly interpersonal aspects. Families and patients had difficulties with process quality measures. Results indicated gaps in understanding and engagement amongst children and teens, pointing towards a need to implement changes in this area. A critical analysis of patient and family experience is a valuable tool in ensuring that the services provided are tailored to the needs of patients and families.

Disclosure: J. Tekano, None; **L. B. Tucker**, None; **A. Chen**, None.

1871

Puberty and Disease Activity in JIA. Philomine A. van Pelt[1], Aike.a. Kruize[2], Anita C.S. Hokken-Koelega[3], Radboud JEM Dolhain[4], Johannes WJ Bijlsma[5] and Nico M. Wulffraat[5]. [1]Erasmus MC, Rotterdam, Netherlands, [2]University Medical Center Utrecht, Utrecht, Netherlands, [3]Erasmus Medical Center- Sophia Children's Hospital, Rotterdam, Netherlands, [4]Erasmus MC University Medical Center Rotterdam, Rotterdam, Netherlands, [5]University Medical Centre Utrecht, Utrecht, Netherlands.

Background/Purpose: Delayed puberty and decreased final length has been reported in chronic diseases like Crohn's disease and JIA with a disease onset at prepubertal age. This may be due to systemic effects of inflammation, undernutrition or medication, for example glucocorticoids or MTX. Treatment with anti TNF has shown to restore delayed growth in JIA.

Nowadays patients are treated intensively with disease modifying drugs including biologicals to reach remission. Our objectives are to describe growth, onset and progression of puberty in established JIA patients who are treated intensively.

Methods: All consecutive JIA patients aged 10 –24 years were asked to participate in this observational follow-up study. Demographic and disease related items were obtained yearly as well as Tanner puberty stages: Pubic Hair Girls (PHG), Breast stage (Bre), Menarche (Men), Pubic Hair Boys (PHB), Genital Stage (Gen). Reference Values were obtained from the Dutch National Growth Study. Median age at reaching each pubertal stage was estimated by Kaplan Meier survival estimates based on data from patients of Caucasian origin and younger than 21 years. The progression of puberty is defined as the difference in median age between the tanner stage 2 3&4 and 4&5. Parametric tests are used to determine differences between patients and healthy controls, non parametric tests are used to determine differences between patient groups.

Results: 138 patients were included; 91 girls (66%) and 47 boys (34%). Ten percent have systemic onset type of JIA, 24% oligo- persistent, 55% oligo-extended and polyarticular course, 11% other subtypes of JIA.

Median disease duration is 7,8 years (IQR 6,7). Median JADAS27 is 3,7 (IQR 6,7), median active joint count is 0,0 (2,0), median DAS 28 is 2,16 (1,30). MTX is used in 79% of the patients, anti TNF in 14% and systemic corticosteroids in 23%. Median SDS length is −0,29 (IQR 1,38), SDS weight −0,27 (1,46), SDS BMI −0,08 (1,71). PHG, Bre, PHB and Gen are delayed in all stages 2–5, more pronounced in stage 5. Median delay compared to healthy controls in PHG stage 5 is 3,4 years, in Bre stage 5 3,4 years, in Menarche 3,5 years, in PHB stage 5 1,6 years and in Gen stage 5 1,7 years. The progression of puberty was delayed between all stages in both girls and boys, most markedly delay was seen between stage 4&5 of PHG and Bre. No significant differences are seen between users and non-users of systemic corticosteroids, MTX or biologicals. Subtype of JIA, disease activity and age at onset did not significantly influence results.

Conclusion: Due to intensive treatment, disease activity in JIA patients is low and growth is comparable to healthy age related persons. However, puberty is still remarkably delayed. Further investigation into clinical relevance and cause of delayed puberty is needed.

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Disclosure: P. A. van Pelt, None; **A. A. Kruize**, None; **A. C. S. Hokken-Koelega**, None; **R. J. Dolhain**, None; **J. W. Bijlsma**, None; **N. M. Wulffraat**, None.

ACR Concurrent Abstract Session
Epidemiology and Public Health III: Gout and Systemic Lupus Erythematosus

Monday, November 17, 2014, 4:30 PM–6:00 PM

1872

Gout in Older Adult. Mara McAdams-DeMarco[1], Anna Kottgen[2], Bridget Burke[3], Andrew Law[4], Josef Coresh[1] and Alan N. Baer[5]. [1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [2]University Hospital Freiburg, Freiburg, Germany, [3]Johns Hopkins University, Baltimore, MD, [4]Johns Hopkins, Baltimore, MD, [5]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: To evaluate whether traditional and genetic risk factors in middle-aged members of a longitudinal population-based cohort predict the onset of gout in older age.

Methods: We studied the incidence and prevalence of gout in white older adults using the Atherosclerosis Risk in Communities Study, a prospective US population-based cohort study of middle-aged adults enrolled between 1987–1989 with ongoing follow-up. A genetic urate score (GUS) was formed from common urate-associated single nucleotide polymorphisms for eight genes. The adjusted hazard ratio (HR) and 95% confidence intervals (CI) of incident gout by traditional and genetic risk factors in middle age were estimated using a Cox Proportional Hazards model.

Results: Of the 9,526 participants, 46.2% were male and the mean (SD) age at cohort enrollment was 54.0 (5.7). The overall prevalence of gout was 8.9%; 31.9% of those with a history of gout reported a physician diagnosis of this inflammatory arthritis at age 65 or older. By age 65 the prevalence of gout was 9.0% for men and 3.3% for women, conditioned on survival to age 65. The cumulative incidence from middle age to age 65 was 8.6% in men and 2.5% in women as well as 8.0% for those in the 4th quartile of GUS, 5.0% for those in the 3rd quartile, 3.8% for those in the 2nd quartile and 3.3% for those in the 1st quartile, conditioned on survival to age 65 (Figure). In middle age, increased adiposity, beer intake, protein intake, smoking status, hypertension, diuretic use, and kidney function (but not sex) were associated with an increased risk of gout in older age. In addition, high genetic risk (100 μmol/L increase in GUS) was associated with a 3.29-fold (95% CI: 1.63, 6.63) increased risk of gout in older age.

Conclusion: In this US population-based cohort, traditional risk factors that were present in middle-age were associated with the development of gout in older age.

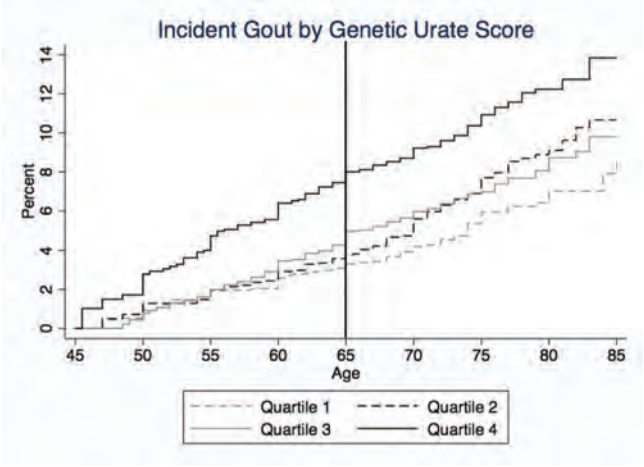


Figure: Cumulative incidence of gout by quartile of genetic urate score. The incidence of gout for participants of ARIC was estimated using a Kaplan-Meier approach. All cumulative incidences (%) should be interpreted as the percentage of participants with gout, conditioned on survival to that age. The genetic urate score is measured in μmol/L. Quartile 1 of the genetic urate score ranges from −59.1 to −13.1; quartile 2 from −13.2 to 0.3; quartile 3 from -.4 to 12.0 and quartile 4 from 12.1 to 60.8.

Disclosure: M. McAdams-DeMarco, None; **A. Kottgen**, None; **B. Burke**, None; **A. Law**, None; **J. Coresh**, None; **A. N. Baer**, None.

1873

Food Sources of Protein and Risk of Incident Gout in the Singapore Chinese Health Study. Gim Gee Teng[1], An Pan[2], Jian-Min Yuan[3] and Woon-Puay Koh[4]. [1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [2]Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore, [3]Division of Cancer Control and Population Sciences, University of Pittsburgh Cancer Institute, and Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, [4]Duke-NUS Graduate Medical School Singapore, Singapore, Singapore.

Background/Purpose: The Health Professional Follow up Study in Caucasian men showed that intakes of meat and seafood increased risk of gout, while dairy products, especially low-fat dairy products, reduced the risk (1). Purine rich vegetable intake had no association with incident gout (1). Studies evaluating diet on gout risk in Asian populations are lacking. Most of these studies focused on alcohol intake and evaluated on hyperuricemia rather than gout as the dependent variable. We examined the relation of dietary protein and protein sources with incident gout among Chinese men and women.

Methods: We used data from the Singapore Chinese Health Study, a prospective cohort study with 63,257 Chinese adults aged 45–74 years at recruitment from 1993 to 1998. Dietary information was collected via a validated food frequency question, and physician-diagnosed gout was self-reported during the two follow-up visits of 1999–2004 and 2006–2010. We conducted analysis among 51,114 participants without gout at baseline and who responded to the follow-up questionnaires. Cox proportional hazards models were used to calculate the relative risk (RR) and 95% confidence interval (CI) with adjustment for potential confounding factors, including age, sex, alcohol intake, body mass index and hypertension. All multivariate models were further adjusted for protein sources.

Results: Among 51,114 subjects interviewed at either or both interviews, after a mean follow-up of 11.1 (SD 3.7) years, there were 2,167 incident gout cases with mean age of onset at 61.3 (SD 8.1) years. Participants with gout were more likely to be men, more highly educated, ever smokers, weekly or daily alcohol drinkers and to have higher BMI then those without gout. 36.8% of gout subjects had hypertension compared with 21.4% among those without gout. Compared to the lowest quartile intake, the multivariate-adjusted RRs (95% CI) of incident gout in the highest quartile were 1.27 (1.12–1.44) for total protein (P_{trend}=0.001); 1.28 (1.12–1.47) for poultry (P_{trend}=0.001); and 1.16 (1.02–1.32) for fish and shellfish (P_{trend}=0.014). Conversely, intakes of soy and other legumes were associated with reduced risk, the RR (95% CI) in the highest quartile intake being 0.87 (0.77–1.00) for soy foods (P_{trend}=0.01) and 0.85 (0.74–0.97) for legumes (P_{trend}=0.02). There was no association between intake of red meat (including pork), eggs, dairy products, grain products, nuts and seeds, and risk of gout. There was no significant interaction between sex, BMI, history of hypertension, smoking and alcohol consumption status, and intake of foods on risk of gout.

Conclusion: Total protein intake, mainly contributed by poultry, fish and shellfish, was associated with increased risk of gout in this population. Conversely, soy and legume foods may be related to reduced risk of gout. The general advice of replacing red meat with "white meat" such as poultry may

not be advisable. Myths of deleterious effect of soy and legume intake on gout may be debunked. Other health benefits of soy plus a possible protective effect on gout makes it a plausible vegetable-based meat substitute.

Reference

1. Choi HK et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. NEJM. 2004;350(11):1093.

Disclosure: G. G. Teng, None; **A. Pan**, None; **J. M. Yuan**, None; **W. P. Koh**, None.

1874

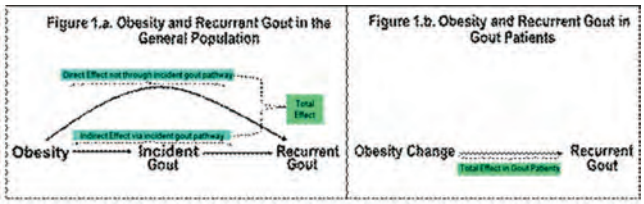
Obesity Paradox in Recurrent Gout – a Metrological Clarification and Remedy. Uyen Sa D.T. Nguyen[1], Qiong Louie-Gao[1], Yuqing Zhang[1], David T. Felson[1], Michael P. Lavalley[2] and Hyon Choi[3]. [1]Boston University School of Medicine, Boston, MA, [2]Boston University, Boston, MA, [3]Harvard Medical School, Boston, MA.

Background/Purpose: Obesity is a strong risk factor of incident gout, but previous research showed no such association with recurrent gout among gout patients. These paradoxical findings occur because the causal net effect (**i.e.,** *total effect*) of obesity on recurrent gout in gout patients cannot be validly estimated using conventional methods. We demonstrate that the paradox can be clarified using an appropriate mediation analysis, and illustrate a design to estimate the total effect of BMI on recurrent gout in incident gout patients.

Methods: We used data from the Multiple Risk Factor Intervention Trial (MRFIT), prospectively collected at baseline and annually over 7 years. BMI at baseline was categorized as: >30 kg/m^2(obese), 25–29.9 (overweight), and <25 (normal) and self-report of physician-diagnosis of gout was our outcome. We followed subjects without gout at baseline to determine the first occurrence of gout and their recurrent gouts by the 84-month visit. We assessed the effect of BMI on recurrent gout with the conventional method of restricting on incident gout patients and using logistic regression. We then clarified the paradox using marginal structural modeling (MSM) for mediation analysis. We estimated the total effect of BMI on recurrent gout by decomposing the *total effect* into its components **(Figure):** the *indirect effect* of BMI via its effect on incident gout, and the *direct effect* of BMI on recurrent gout not through its effect on incident gout. Finally, we determined the association of change in BMI categories **before and after** incident gout on risk of recurrent gout among incident gout patients. All analyses were adjusted for known confounders.

Results: Of 11,655 subjects without gout at baseline (mean age 46 years; 21% normal, 56% overweight, 23% obesity), 408 people developed incident gout, and 131 had recurrent gout. Conventional method showed that the adjusted odds ratio (OR) for recurrent gout was 1.10 (95%CI: 0.52,2.30) for obese compared with normal BMI (**Table**). Using MSM, the *indirect effect* of obesity compared with normal-weight on risk of recurrent gout (via its effect on incident gout) was 2.62 (95%CI:2.01,3.40); the *direct effect* not through incident gout was 1.13 (95%CI:0.82,1.56); and the *total effect* was 2.94 (95%CI:1.59,5.41) (**Table**). Among incident gout patients, the adjusted total effect of increasing BMI after incident gout on risk of recurrent gout was 1.84 (95%CI:1.02,3.32) (**Table**).

Conclusion: We showed that the effect of obesity at baseline on risk of recurrent gout is almost entirely through its effect on incident gout. Conditioning on incident gout and estimating the effect of baseline obesity on the risk of recurrent gout would provide only an estimate of its direct effect, as the indirect effect is blocked. In order to examine the total effect of obesity on recurrent gout in those with incident gout, BMI change must be assessed before and after incident gout.



Obesity and Recurrent Gout in the General Population*							Conventional Method*	Obesity and Recurrent Gout in Gout Patients*	
BMI	Baseline n=11665	Incident Gout n=408	Recurrent Gout n=131	Total Effect (OR) (95% CI)	Indirect Effect (OR) (95% CI)	Direct Effect (OR) (95% CI)	Restricted to Gout Patients (OR) (95%CI)	BMI Change After Incident Gout	Total Effect (OR) (95% CI)
Normal	2490	53	14	1.00	1.00	1.00	1.0	No Change	1.0
Over-Weight	6470	208	73	2.04 1.15,3.63	1.52 1.14,2.02	1.35 1.04,1.76	1.49 (0.75, 2.95)	Lose	0.98 0.55, 1.73
Obese	2705	147	44	2.94 1.59, 5.41	2.62 2.01,3.40	1.13 0.82,1.56	1.10 (0.52, 2.3)	Gain	1.84 1.02, 3.32

*Adjusted for baseline age, education, alcohol, hypertension

Disclosure: U. S. D. T. Nguyen, None; **Q. Louie-Gao**, None; **Y. Zhang**, None; **D. T. Felson**, None; **M. P. Lavalley**, None; **H. Choi**, Takeda, 5, AstraZeneca, 5.

1875

Can Allopurinol Survival Impact Reverse Depending on Patients' Characteristics? a Propensity-Score-Based Subgroup Analysis. Na Lu[1], Hyon Choi[2], Maureen Dubreuil[3], Qiong Louie-Gao[1] and Yuqing Zhang[1]. [1]Boston University School of Medicine, Boston, MA, [2]Harvard Medical School, Boston, MA, [3]Boston University Medical Center, Boston, MA.

Background/Purpose: Several studies have reported that allopurinol use is associated with a decreased risk of death or cardiovascular outcomes. While these studies reported the overall average effect of allopurinol, the impact may vary depending on the patients' characteristics. This line of research could help identify patients who will get the greatest benefit from allopurinol use, as well as those who may face a hazardous impact (thus conferring a patient-oriented, personalized medicine approach). To address these issues, we assessed whether the survival impact of allopurinol varies across the distribution of propensity scores (PS) in a general population-based cohort study.

Methods: We conducted an incident user cohort study with PS matching using a UK general population database. Eligible subjects were aged ≥40 years and had a record of hyperuricemia (serum urate >357 μmol/L for women and >416 μmol/L for men) between January 2000 and May 2010. For each 6-month period during the study follow-up, each allopurinol initiator was matched to a non-initiator by PS using the greedy-matching method. Subjects were followed until death, loss to follow-up, or the study period ended, whichever came first. We calculated the all-cause mortality rate and examined the association of allopurinol initiation with the risk of mortality using a Cox proportional hazard model. We then examined whether the effect of allopurinol varied across PS level categories (Table).

Results: Our study included 6,947 allopurinol initiators and 6,947 non-initiators. All measured potential confounders were evenly distributed between the two groups. The mortality rate was 39/1000 person-years in allopurinol initiators and 46/1000 person-years in non- initiators, resulting in an overall HR of 0.86 (95% CI: 0.78–0.96). Our subgroup analysis by PS showed a reversal of HR from hazardous in the lowest PS groups (HR of the lowest PS group, 1.67) to increasingly protective with higher PS groups (HR of the highest PS group, 0.65) (**Table**). The most obvious difference in patient characteristics between the top and bottom 20th percentile PS groups was the presence of gout (>98% vs. 38%), suggesting that treatment of gout patients is life-saving (compared to the hazardous impact of treating asymptomatic hyperuricemia).

Conclusion: Our findings suggest that the association of allopurinol with the risk of all-cause mortality may vary widely from conferring a protective versus hazardous impact, according to patients' characteristics (reflected in PS). However, a potential alternative explanation may be extreme levels of residual confounding. Nevertheless, if confirmed, these potentially opposite subgroup effects would help to identify individuals who will receive the maximum benefit from allopurinol, thus helping to achieve a germane patient-oriented, personalized medicine approach in this common practice context.

Table 1. Risk of Mortality Associated with Initiation of Allopurinol According to Propensity Score Categories

Propensity score percentile	Mean propensity score*	Allopurinol Initiator				Allopurinol Non-Initiator				
		No.	Death	Person-Year	IR	Death	Person-Year	IR	IRR	HR
<2%	0.006	278	17	435	0.039	11	468	0.024	1.66	1.67 (0.73–3.81)
2%–10%	0.016	1112	57	1524	0.037	44	1589	0.028	1.35	1.42 (0.96–2.22)
10%–20%	0.052	1388	79	1937	0.041	68	1987	0.034	1.19	1.34 (0.93–1.93)
20%–40%	0.093	2780	94	3780	0.025	109	3733	0.029	0.85	0.84 (0.62–1.15)
40%–60%	0.137	2780	92	4019	0.023	113	3863	0.029	0.79	0.81 (0.61–1.10)
60%–80%	0.198	2780	141	4173	0.033	155	4028	0.039	0.85	0.79 (0.61–1.01)
80%–90%	0.288	1388	115	2184	0.053	152	2039	0.075	0.71	0.76 (0.59–0.99)
90%–98%	0.423	1112	148	1602	0.092	175	1499	0.117	0.75	0.77 (0.60–1.00)
>98%	0.655	276	44	383	0.115	68	341	0.199	0.48	0.65 (0.42–1.00)

* Mean propensity score within the percentile; IR = incidence rate; IRR = incidence rate ratio; HR = hazard ratio

Disclosure: N. Lu, None; **H. Choi**, Takeda, 5, AstraZeneca, 5; **M. Dubreuil**, None; **Q. Louie-Gao**, None; **Y. Zhang**, None.

1876

Influence of Alcohol Consumption on the Risk of SLE Among Women in the Nurses' Health Studies. Medha Barbhaiya, Bing Lu, Shun-Chiao Chang, Jeffrey A. Sparks, Elizabeth W. Karlson and Karen H. Costenbader. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Prior case-control studies have reported an inverse association between moderate alcohol consumption and the development of SLE. However, case-control studies may be prone to recall bias and reverse causation. A prior prospective study did not demonstrate an association between alcohol intake and SLE development, although this study was limited by small sample size (34 confirmed cases, Formica MK et al, *J Rheum*, 2003). We assessed the association between alcohol consumption and risk of SLE among women followed in the Nurses' Health Study (NHS) and NHSII. We hypothesized that alcohol consumption, possibly through anti-inflammatory effects, would be associated with lower risk for SLE compared to no alcohol consumption.

Methods: The NHS enrolled 121,701 U.S. female registered nurses in 1976. NHS II began in 1989, enrolling 116,430 female nurses. Lifestyle and environmental exposures were collected through biennial questionnaires. Alcohol consumption was assessed with a semi-quantitative food frequency questionnaire completed every 4 years. Participants in NHS and NHSII who provided alcohol data at baseline (1980 in NHS and 1989 in NHSII) were included. Cumulative average alcohol consumption until 2–4 years prior to SLE diagnosis date (for cases) across repeated measures was used instead of one-time measure to best represent long-term alcohol consumption. The incident SLE cases were identified using the connective tissue disease screening questionnaire (CSQ), followed by medical record review. Cox proportional hazards models were used to assess associations, after controlling for time-varying covariates. HRs from the two cohorts were meta-analyzed using DerSimonian and Laird random effects models.

Results: 118 incident SLE cases developed in NHS from 1980–2008, and 92 incident SLE cases developed in NHSII, 1991–2009. Mean age at diagnosis was 53.6 (± 8.2) years in NHS and 43.4 (± 5.7) in NHSII. Most SLE cases (97% in NHS, 100% in NHSII) were ANA positive, while 33% of NHS SLE cases and 53% of those in NHSII had a positive anti-dsDNA antibody test at diagnosis. In both NHS and NHSII, there was a suggestion of a protective effect of alcohol intake on risk of SLE, although it was not statistically significant (**Table**). Meta-analysis of the multivariable-adjusted results from both cohorts demonstrated a suggested protective effect of alcohol consumption in women who consume >0 to 10 gms/day (HR 0.75, 95%CI 0.54, 1.04) and >10 gms/day (HR 0.61,95% CI 0.37, 1.01).

Conclusion: In these large prospective cohorts of women followed for many years before the diagnosis of SLE, we found a potential protective association between long-term alcohol consumption and reduced risk of developing SLE. Further studies are needed to confirm these findings.

Table. Cumulative Updated Alcohol Intake and Risk of SLE among women in the Nurses' Health Study (1980–2008) and the Nurses' Health Study II (1991–2009)

Alcohol intake(gms/day)†	NHS Cases, n=118	Person-Years	Age-adjusted HR (95% CI)	Multivariable HR (95% CI)*	NHSII Cases, n=92	Person-Years	Age-adjusted HR (95% CI)	Multivariable HR (95% CI)*	NHS & NHSII Meta-analysis Multivariable HR††
None	36	570176	1.0 (Ref.)	1.0 (Ref.)	40	621067	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
>0 to ≤10**	62	1255211	0.76 (0.50, 1.15)	0.80 (0.52, 1.22)	45	199079	0.78 (0.51, 1.20)	0.66 (0.42,1.04)	0.75 (0.54, 1.04)
>10	20	475801	0.64 (0.37, 1.10)	0.61 (0.34, 1.08)	7	84936	0.70 (0.32, 1.57)	0.66 (0.29,1.50)	0.61 (0.37, 1.01)
			p trend: 0.23	p trend: 0.09			p trend: 0.23	p trend: 0.10	

†Cumulative updated average of alcohol intake from all sources including beer, wine, and hard liquor.
*Multivariable model adjusted for: age in months, total daily energy intake (total kilocalories per day), oral contraceptive use (never, past, current), menopausal status and postmenopausal hormone use (premenopausal, postmenopausal-current, postmenopausal-past, postmenopausal-never), cigarette smoking (never, past, current), and husband's educational level (<high school, high school, college, > college), race (White, other).
††Meta-analyzed using DerSimonian and Laird random effects models.
**One standard alcoholic drink per day contains 10–15 grams of alcohol.

Disclosure: M. Barbhaiya, None; **B. Lu**, None; **S. C. Chang**, None; **J. A. Sparks**, None; **E. W. Karlson**, None; **K. H. Costenbader**, None.

1877

Pregnancy Outcomes in SLE: Before and after. Elizabeth V. Arkema[1], Kristin Palmsten[2], Christopher Sjöwall[3], Elisabet Svenungsson[4], Jane E. Salmon[5] and Julia F Simard[6]. [1]Karolinska Institutet, Stockholm, Sweden, [2]University of California, San Diego, La Jolla, CA, [3]Linköping University, Linköping, Sweden, [4]Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [5]Hospital for Special Surgery, New York, NY, [6]Stanford School of Medicine, Stanford, CA.

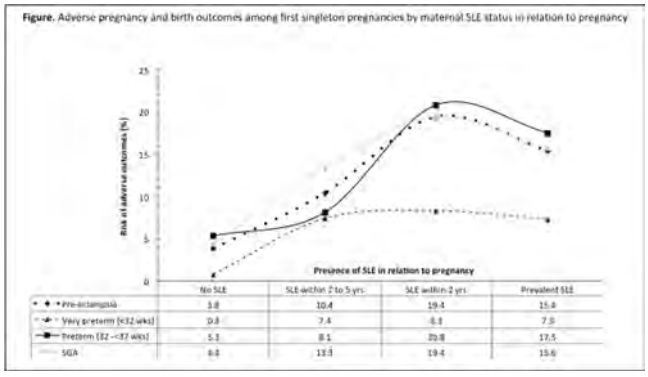
Background/Purpose: Numerous investigators have demonstrated that the risks of pre-eclampsia, preterm delivery, and fetal death are increased in lupus pregnancies. Adverse events during pregnancy, delivery, and the post-natal period occur for many reasons, and it is often unclear whether they are SLE-related. Furthermore, it is well established that before the clinical diagnosis of SLE, pathogenic autoantibodies are present in individuals who eventually develop lupus, and they may drive inflammation.

Given the challenges in identifying and accessing a proper comparator group, most published work has focused on clinical cohorts and case series. A few studies that used national or population-based data to answer such questions face different methodological limitations - particularly SLE misclassification due to use of a single ICD code to define cases. This work compares pregnancies and outcomes in women with SLE using a stricter classification and considers outcomes in women whose SLE is believed to onset after pregnancy.

Methods: Data from a matched cohort of individuals with SLE and the general population using national Swedish registers were linked to the Medical Birth Register (MBR) to identify all pregnancies between 1973 and 2011. SLE was defined as ≥2 SLE ICD codes in the Patient Register (PR) with ≥1 SLE code from a specialist. We restricted to first pregnancy and excluded multiple gestations. Using the first observed SLE interaction with the health care system as a proxy for diagnosis, we categorized SLE as prevalent at birth (n=604), incident within 0–2 (n=72) and 2–5 years (n=135) after birth, and none (n=18229). Maternal health and delivery characteristics were obtained from the MBR, PR, and Death Register. Outcomes included pregnancy morbidity such as pre-eclampsia, maternal death, size for gestational age, APGAR scores, and stillbirth. We compared frequency of outcomes by SLE exposure at pregnancy/birth (prevalent, in 0–2y, in 2–5y, and none). Modified Poisson regression with robust error variance estimated risk ratios and 95% CI with SLE as exposure for maternal and fetal outcomes adjusted for maternal age and other a priori determined confounders.

Results: Patients with SLE were more likely to have poorer pregnancy outcomes including small for gestational age (SGA), preterm deliveries, pre-eclampsia, stillbirths, and lower one minute APGAR compared to the general population. For many outcomes we saw a trend where the closer to pregnancy the diagnosis of SLE was made (with prevalent SLE being most proximal) the higher the risk of poor outcomes (**Figure**).

Conclusion: Maternal SLE is associated with adverse outcomes to mothers and their newborn. Mothers whose SLE presented shortly after pregnancy also had higher risk of these outcomes compared to pregnancies and births from the general population.



Disclosure: E. V. Arkema, None; **K. Palmsten**, None; **C. Sjöwall**, None; **E. Svenungsson**, None; **J. E. Salmon**, None; **J. F. Simard**, None.

ACR Concurrent Abstract Session
Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes II: Clinical Perspectives
Monday, November 17, 2014, 4:30 PM–6:00 PM

1878

A Combination of Celecoxib and Famciclovir Is Efficacious in the Treatment of Fibromyalgia: Results of a Phase IIa Randomized, Double-Blind, Placebo-Controlled Study. William Pridgen[1], Carol Duffy[2], Judith Gendreau[3] and R Michael Gendreau[3]. [1]Innovative Med Concepts, Tuscaloosa, AL, [2]University of Alabama, Tuscaloosa, AL, [3]Gendreau Consulting, LLC, Poway, CA.

Background/Purpose: Fibromyalgia (FM) is a common chronic pain syndrome with symptoms that include widespread pain, fatigue, sleep disruption and cognitive impairment. It is known that infections and other types of stressors are capable of triggering the development of FM. We hypothesize that these stressors could be responsible for triggering a reactivation of latent herpesviruses, and that this reactivation could in turn lead to the central nervous system dysregulation seen in this condition. The present study was designed to evaluate an anti-viral drug combination selected for activity against herpes class viruses.

Methods: A total of 143 patients selected using the ACR 2010 FM criteria were enrolled at 12 sites in a 16-week, double-blind, placebo-controlled trial. Patients were randomized (1:1) to receive a proprietary combination of celecoxib + famciclovir or placebo. Outcome measures included a 24-hour recall pain numeric rating scale (NRS), Fibromyalgia Impact Questionnaire (FIQ-R), Patient Global Impression of Change (PGIC), and the PROMIS fatigue short form at baseline, and after 6, 12 and 16 weeks of study participation.

Results: The primary efficacy endpoint was change in pain from baseline. Pain reduction was evaluated using the pain NRS and the 7-day recall pain item from the FIQ-R. Change from baseline was determined using an MMRM approach with LOCF/ BOCF imputation for missing data. A significant decrease in pain was observed for patients on treatment vs. placebo at 16 weeks by both measures. The absolute change on the NRS was −1.9 units vs −1.1, comparing active to placebo (p=0.031). On the FIQ-R item, the change was -2.2 vs −0.92 (p=0.001). Key secondary endpoints included analysis of the PGIC, where a value of "1" or "2" was considered a clinical responder. Significantly improved PGIC response rates were noted at endpoint: 33.3% for active vs 19.2% in placebo patients (p=0.031). Total FIQR score change at the endpoint visit was −17.54 vs −7.87 (p=0.002), while changes in the 3 domains were 14.29 vs −5.44 (p=0.004) for Function, −4.29 vs −1.89 (p=0.003) for Overall Impact, and −16.77 vs −7.90 (p=0.004) for Symptoms. In addition, improvements in fatigue were seen at endpoint on the PROMIS fatigue (−7.62 units vs −4.15; p=0.020).

The safety profile was especially encouraging. Despite the celecoxib component, gastrointestinal and nervous system treatment emergent adverse events were reported significantly more often in the placebo treatment group (GI: 29.0% vs 42.5%; nervous system: 17.4% vs 23.3%; active to placebo), and study completion rates favored active treatment over placebo (82.6% vs. 60.8%) (largely driven by higher placebo discontinuation rates due to adverse events and lack of efficacy).

Conclusion: A proprietary combination of famciclovir, which we postulate is inhibiting herpesvirus replication, and celecoxib, known to inhibit both herpesvirus replication and reactivation, was efficacious in treating multiple symptoms of FM. Given the simultaneous improvement in many domains and the surprising tolerability of this combination of drugs, we believe this combination warrants further study as a potential new therapy for fibromyalgia patients.

Disclosure: W. Pridgen, Innovative Med Concepts, 4, Innovative Med Concepts, 6; **C. Duffy**, Innovative Med Concepts, 2, Innovative Med Concepts, 6; **J. Gendreau**, Innovative Med Concepts, 5; **R. M. Gendreau**, Innovative Med Concepts, 5, Innovative Med Concepts, 6.

1879

The Efficacy of Pregabalin for Treating Fibromyalgia Patients with Moderate or Severe Baseline Widespread Pain. Andrew Clair and Birol Emir. Pfizer Inc, New York, NY.

Background/Purpose: Pregabalin has demonstrated efficacy for the treatment of fibromyalgia (FM), but insufficient evidence exists on how the efficacy of pregabalin may differ by baseline pain severity. The objective of these analyses was to assess the efficacy of 12 weeks of pregabalin treatment to provide symptomatic pain relief in FM patients with moderate or severe baseline pain scores.

Methods: These analyses used data from 5 Phase III clinical trials ranging between 8–15 weeks of pregabalin versus placebo (study numbers 1008105, A0081056, A0081077, A0081100, A0081208) to evaluate the efficacy of pregabalin at doses of 300 mg/day, 450 mg/day, or flexible dosing (300–450 mg/day BID) for the treatment of FM. FM was defined by ACR 1990 criteria at screening of widespread pain ≥3 months and pain in ≥11 of 18 specific tender point sites. Patients were adult (aged ≥18 years), with mean baseline pain scores that were classified as moderate (≥4–<7) or severe (≥7–10) and a score ≥40 mm on the Visual Analog Scale of Short-form McGill Pain Questionnaire. A mixed effects model repeated measures analysis was used to estimate change in pain at 12 weeks after treatment initiation by baseline severity (moderate or severe) and treatment.

Results: Overall, 679 (300 mg/d pregabalin), 670 (450 mg/d pregabalin), 250 (flexible dosing pregabalin), and 927 (placebo) patients were evaluated. The results of change in pain score at 12 weeks are displayed in the figure.

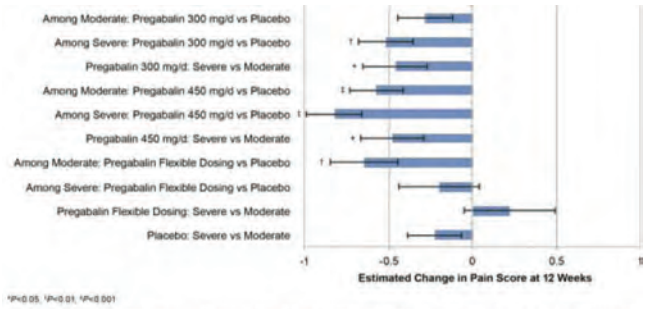


Figure. Estimated mean (SE) differences in change in pain score at 12 weeks in FM patients with moderate or severe baseline pain treated with pregabalin or placebo.

Among patients who had moderate baseline pain, significantly larger mean ± SE reductions in pain score were observed with pregabalin versus placebo at doses of 450 mg/d (−0.572 ± 0.161, $P<0.001$) and flexible dosing (−0.647 ± 0.203, $P=0.002$) with a non-significant reduction at the 300 mg/d dose (−0.282 ± 0.165). Patients with severe baseline pain showed significant improvements over placebo with pregabalin doses of 300 mg/d (−0.516 ± 0.164, $P=0.002$) and 450 mg/d (−0.822 ± 0.165, $P<0.001$), but not with flexible dosing (−0.200 ± 0.242). When patients were grouped by pregabalin dose assignment, patients with severe baseline pain exhibited greater improvements in pain score than patients with moderate baseline pain with 300 mg/day (−0.461 ± 0.191, $P=0.016$) and 450 mg/day doses (−0.476 ± 0.189, $P=0.012$), but not with flexible dosing (+0.220 ± 0.272).

Conclusion: Pregabalin is efficacious at 12 weeks of treatment in reducing pain in FM patients with baseline moderate pain and severe pain severity, with reductions that appear larger in patients with severe pain. The trend of larger changes following flexible dosing in patients with moderate versus severe baseline pain scores comes from a study of Japanese patients and additional research would be required to determine if this may be accounted for by differences in the average daily dose.

Disclosure: A. Clair, Pfizer Inc, 3, Pfizer Inc, 1; **B. Emir**, Pfizer Inc., 1, Pfizer Inc., 3.

1880

Moderate Alcohol Consumption Is Associated with Lower Risk (and severity) of Chronic Widespread Pain: Results from a Population-Based Study. Gary J. Macfarlane and Marcus Beasley. University of Aberdeen, Aberdeen, United Kingdom.

Background/Purpose: Amongst patients with fibromyalgia, alcohol consumption has been reported in a single clinical study to be associated with lower severity of symptoms. This study aimed to a) determine whether alcohol consumption is associated with the reporting of chronic widespread pain (CWP) in an unselected population sample, and whether a dose-risk relationship is evident; b) amongst persons with CWP confirm whether the level of reported alcohol consumption is associated with symptom severity.

Methods: The MUSICIAN study sampled patients, aged over 25 years, registered at general practices in two areas of Great Britain. Information, collected by postal questionnaire, included current pain and usual alcohol consumption. Respondents were classified according to whether they satisfied the definition of chronic widespread pain (CWP) in the ACR 1990 criteria for fibromyalgia. Pain intensity and disability was measured by the Chronic Pain Grade and disabling pain defined as grade III or IV. Respondents reported whether they had ever drunk alcohol regularly and if so how much they currently drank per week (in units). Potential confounders of the relationship collected were: age, body mass index, employment status and amount smoked. Analysis was by logistic regression with those who had never regularly consumed alcohol as the referent group compared with 0–5, 6–10, 11–12, 21–35, 35+ units/week.

Results: 13587 persons participated (mean age 55 yrs, 57% female) of which 2060 reported CWP and answered the questions on Chronic Pain Grade. There was a significant relationship between level of alcohol consumption and risk of reporting CWP. Risk decreased with increasing consumption with the lowest risk amongst those consuming 21–35 units/week (OR 0.61; 95% CI 0.50–0.75) while those consuming higher amounts did not have a reduced risk. This protective effect persisted after adjustment with only minor attenuation of effect (21–35 units/week 0.63; 0.51, 0.78). The effect was evident in both males and females. Amongst persons with CWP there was a strong and significant relationship between increasing alcohol consumption and lower likelihood of disability (table) which was not explained by measured confounders.

Number of units per week	CPG I/II	CPG III/IV	OR	Adjusted OR
Never drunk regularly	353 (52.9%)	314 (47.1%)	1.00	1.00
0 to 5	396 (67.1%)	194 (32.9%)	0.55 (0.44–0.69)	0.63 (0.49–0.82)
6 to 10	283 (75.5%)	92 (24.5%)	0.37 (0.28–0.48)	0.46 (0.34–0.63)
11 to 20	216 (82.1%)	47 (17.9%)	0.24 (0.17–0.35)	0.33 (0.22–0.49)
21 to 35	96 (81.4%)	22 (18.6%)	0.26 (0.16–0.42)	0.30 (0.17–0.52)
More than 35	23 (48.9%)	24 (51.1%)	1.17 (0.65–2.12)	0.67 (0.32–1.40)

Conclusion: Moderate alcohol consumption was associated with a lower prevalence of CWP and associated with markedly lower levels of disability in those with CWP. One possible mechanism is through alcohol's agonist effects on the neurotransmitter γ-aminobutyric acid (GABA) and disruptions to GABA pain inhibitory pathways have been suggested in persons with fibromyalgia. Another is through the psychological benefits of alcohol including stress relief and mood enhancement. However alcohol consumption as a marker for other lifestyle factors, or that people avoided alcohol because of their pain and disability, cannot be excluded.

Disclosure: G. J. Macfarlane, None; **M. Beasley**, None.

1881

Patients Who Fail Biologics Are More Likely to Have Concomitant Fibromyalgia. Robert S. Katz[1] and Jessica L. Polyak[2]. [1]Rush Medical College, Chicago, IL, [2]Rheumatology Associates, Chicago, IL.

Background/Purpose: One area not assessed by studies to evaluate the efficacy of new medications in patients with inflammatory arthritis is whether the patient may have concomitant fibromyalgia. This may well impact response to treatment. We evaluated whether patients who have inflammatory arthritis and failed various biologic therapies were more likely to also have fibromyalgia.

Methods: Patients taking biologics were evaluated in a rheumatology office practice. We determined patients whether they responded or failed various biologic therapies. Diagnoses included rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and lupus.

Results: 219 patients in a rheumatology office practice taking biologic response modifiers were divided into those with inflammatory arthritis (RA/PsA/AS/SLE) who were thought to have concomitant fibromyalgia (36pts, 16.4%) and those with only inflammatory arthritis but without fibromyalgia (183pts, 83.5%).

Of the patients with inflammatory arthritis or lupus with concomitant fibromyalgia, those who failed 2 or more biologics was 15, (41.7%). Patients with inflammatory arthritis or lupus but without concomitant fibromyalgia who failed 2 or more biologics was 41 pts (22.4%).

Conclusion: Patients who failed biological therapies often had concomitant fibromyalgia. This may be a significant factor in the lack of efficacy of these drugs. Whereas they may control the symptoms of inflammatory disease and patients get partial satisfaction, the fact that they want to try other biologic therapy may be due, in part, to the presence of concomitant fibromyalgia. This should be assessed in future studies to evaluate new medications for patients with inflammatory joint disease.

Disclosure: R. S. Katz, None; **J. L. Polyak**, None.

1882

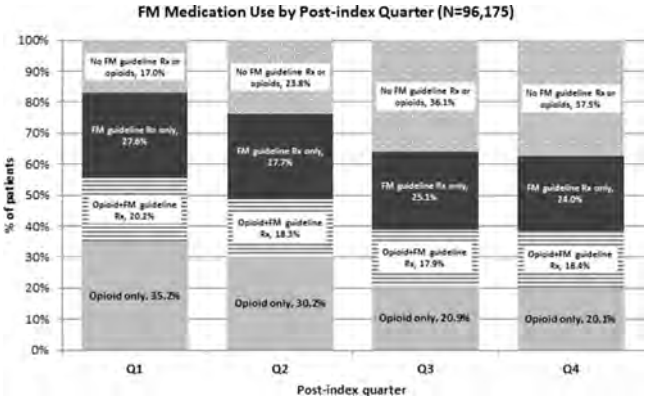
Examination of Patients Newly Diagnosed with Fibromyalgia: Use of Guideline-Recommended Therapies and Opioids in Clinical Practice. Sonali N. Shah[1], Rachel Halpern[2], Joseph C. Cappelleri[3], Elizabeth T. Masters[4], Andrew G. Clair[1], Cori Blauer-Peterson[2] and Damon Van Voorhis[5]. [1]Pfizer, Inc., New York, NY, [2]Optum, Eden Prairie, MN, [3]Pfizer, Inc., Groton, CT, [4]Pfizer Inc, New York, NY, [5]Optum Life Sciences, Eden Prairie, MN.

Background/Purpose: Fibromyalgia (FM) affects 2–5% of adults in the United States. Pregabalin (antiepileptic drug [AED]), and duloxetine and milnacipran (serotonin and norepinephrine reuptake inhibitors), are approved to treat FM. FM treatment guidelines also include gabapentin (AED), amitriptyline (tricyclic antidepressant), selective serotonin reuptake inhibitors (SSRIs), and tramadol; in general, opioids, particularly strong opioids, are not recommended. This study evaluated treatment patterns of recommended and non-recommended medications among patients newly diagnosed with FM.

Methods: This retrospective study used medical and pharmacy claims data and enrollment information for adult commercial health plan members of a large US health plan. Patients had ≥2 medical claims with a diagnosis (dx) of FM from January 2008-February 2009; the date of the first FM dx was the *index date*. Patients also had: 6 months of pre-index and 12 months of post-index continuous enrollment; no pre-index FM dx; and ≥1 pharmacy claim for an FM guideline medication (pregabalin, gabapentin, duloxetine, milnacipran, amitriptyline, or SSRI) or for an opioid on or within 6 months after the index date. The date of the first medication (Rx) was the *treatment date*. The principal outcomes were indicators identifying patients with ≥1 fill of an FM guideline Rx or opioid during each 3-month interval (quarter) of the 12-month post-index period. Descriptive analysis was conducted.

Results: The study sample was 96,175 patients with mean age 47.3 years and 72.5% female. Fifty-six percent of patients were prescribed opioids on their treatment dates and 44% received an FM guideline Rx; 17% of opioid recipients were prescribed tramadol. The figure shows that 55% of patients were prescribed opioids only or opioids as well as FM guideline Rx in the first quarter after FM dx. The percentage of patients with FM guideline Rx (with or without opioids) was consistent through the post-index period. The percentage of patients who received opioids only decreased over time. However, >20% of patients were treated only with opioids in each quarter and an additional 18% received opioids in addition to FM guideline Rx.

Conclusion: In the 12-month post-index, a substantial proportion of patients were prescribed opioids and more than half did not receive FM guideline Rx. These real-world utilization results indicate that an opportunity may exist for improved FM management using recommended therapies in clinical practice.



Disclosure: S. N. Shah, Pfizer, Inc., 1, Pfizer, Inc., 3; **R. Halpern**, Pfizer, Inc., 9; **J. C. Cappelleri**, Pfizer Inc., 1, Pfizer, Inc., 3; **E. T. Masters**, Pfizer, Inc., 1, Pfizer Inc, 3; **A. G. Clair**, Pfizer, Inc., 1, Pfizer Inc, 3; **C. Blauer-Peterson**, Pfizer Inc, 9; **D. Van Voorhis**, Pfizer Inc, 9.

1883 WITHDRAWN

ACR Concurrent Abstract Session

Genetics, Genomics and Proteomics I: Epigenetic Mechanisms in Autoimmunity

Monday, November 17, 2014, 4:30 PM–6:00 PM

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Differential DNA Methylation Associated with Rheumatoid Arthritis in Disease Discordant Monozygotic Twins. Amy Webster[1], Flore Zufferey[2], Darren Plant[3], Anne Barton[4], Frances Williams[2] and Jane Worthington[5]. [1]Arthritis Research UK Centre for Genetics and Genomics, The University of Manchester, Manchester, United Kingdom, [2]Dept Twin Research and Genetic Epidemiology, Kings College London, London, United Kingdom, [3]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academy of Health Sciences, Manchester, United Kingdom, [4]Arthritis Research UK Centre for Genetics and Genomics, University of Manchester, Manchester, United Kingdom, [5]The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Previous epigenetic studies of rheumatoid arthritis (RA) using prevalent cases and unrelated controls have indicated that DNA methylation is altered in patients with RA. However case control studies of unrelated individuals do not allow matching for important confounders such as the underlying genetic variability and environmental exposures, which may influence disease development and the epigenome. By investigating DNA methylation differences in disease discordant monozygotic (MZ) twins, such confounding effects may be mitigated, increasing the power to detect alterations to the methylome which might be associated with RA.

Objectives: To identify a DNA methylation signature in RA using disease discordant monozygotic twins.

Methods: Twin subjects were recruited from the Rheumatoid Arthritis Twin Study (Manchester) and TwinsUK (London). Each twin pair included one twin classified as having RA according to established classification criteria (n=63) while the other was classified as not having RA (n=63) at the time samples were collected. Whole blood DNA was bisulfite converted and an epigenome-wide association study was performed using the HumanMethylation450 BeadChip (Illumina). A detection threshold was applied and probes with a detection-p value >0.01 were removed. Differentially methylated positions (DMPs) were identified using linear regression following quantile normalisation.

Results: 30 CpG sites were differentially methylated at a false discovery rate of 10%. One of the most significant DMPs, cg07693617 ($p=1.05\times10^{-6}$) lies in the *PRKCZ* gene which contains 22 differentially methylated CpG sites in the gene body and 5' UTR. Interestingly this gene was found to be hypermethylated in RA fibroblast-like synoviocytes in a previous epigenome-wide association study.

Conclusion: This is the largest study to date of DNA methylation in RA discordant MZ twin pairs. We have identified 30 CpG sites with a potential role in RA development and added to the evidence for an association at PRKCZ. While further validation and replication studies are required, these preliminary data support the hypothesis that DNA methylation is altered in patients with RA and provides a plausible biological mechanism to account for the observed twin discordance in RA.

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1885

Integrative Omics Profiling Reveals Dysregulated Novel Pathways Mediated By microRNAs and DNA Methylation in Osteoarthritis. Kathleen M. Fisch[1], Ryuichiro Akagi[2], Oscar Alvarez-Garcia[1], Takeshi Teramura[1], Yuta Muramatsu[1], Masahiko Saito[3], Stuart Duffy[1], Shawn Grogan[1], Takahisa Sasho[4], Darryl D'Lima[1], Andrew I. Su[1] and Martin K. Lotz[1]. [1]The Scripps Research Institute, La Jolla, CA, [2]The Scripps Research Institute, San Diego, CA, [3]Toho University Sakura Medical Center, Sakura, Japan, [4]Chiba University School of Medicine, Chiba, Japan.

Background/Purpose: Osteoarthritis (OA) is a prevalent joint disease, with several identified clinical risk factors. However, the search for genetic risk factors by candidate gene and genome-wide association studies of human OA populations has identified only a small number of candidate genes and pathways potentially involved in the disease. Thus, we aim to build a genome-wide molecular profile of OA to elucidate regulatory mechanisms of OA pathogenesis and to identify possible therapeutic targets.

Methods: We extracted total RNA from full-thickness articular cartilage from 18 human donors (8 normal and 10 OA) and performed mRNA and microRNA sequencing on an Illumina HiSeq 2000 (single-end, 100bp reads). DNA was extracted from full-thickness articular cartilage from 23 different human donors (11 normal and 12 OA) and we performed a DNA methylation assay on the Illumina Infinium HumanMethylation450 BeadChip. The RNA sequencing data were analyzed using the Tuxedo package to align raw reads to the human genome, quantify gene expression and perform differential expression analysis. We used the Bioconductor package ChAMP to perform differential methylation analysis. We employed downstream functional enrichment analyses for transcription factors and microRNAs using Fisher's Exact Test, pathway analyses using the Bioconductor package SPIA, and network analyses using Cytoscape. Finally, we created an interaction network using the Human Integrated Protein-Protein Interaction Reference using enriched and additional OA related transcription factors. This network was annotated with differentially expressed mRNAs, microRNAs with validated targets in this network and their methylation status.

Results: Several genes, microRNAs and transcription factors are differentially expressed and reveal unique molecular signatures of OA (Figure 1). Many of these genes and microRNAs possess differentially methylated promoters. In addition, they are key regulators of a novel OA regulatory network (e.g., miR-21, miR-155, CEBPB, FOXO3) (Figure 2). We validated the microRNA targets in this network and the hypomethylation of the miR-21 promoter. We discovered that miR-21 targets the transcription factors HIF1A and CEBPB, providing a regulatory mechanism for the downregulation of these transcription factors and their targets.

Conclusion: Our findings reveal a complex regulatory interaction network of OA pathogenesis controlled by microRNAs, transcription factors and DNA methylation and suggest therapeutic targets to treat or delay disease progression.

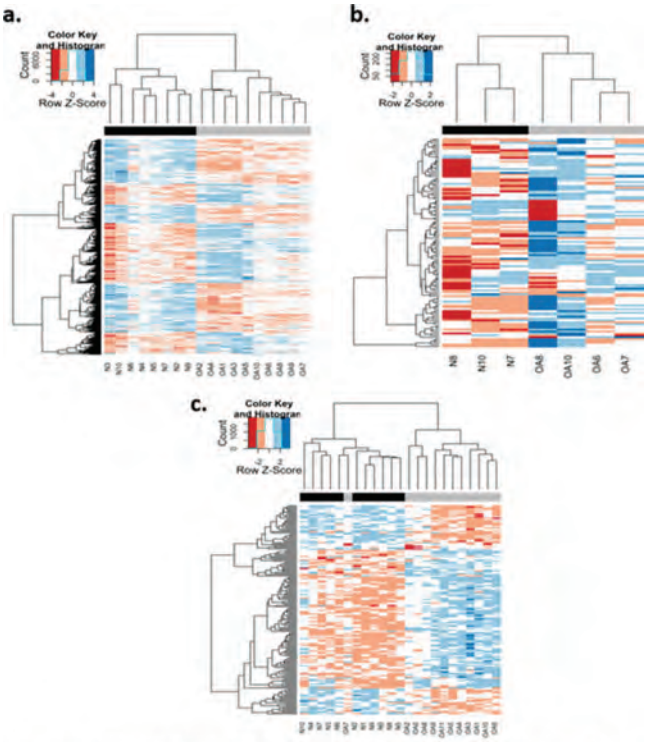

Figure 1. Hierarchical clustering of significantly dysregulated (a.) genes, (b.) microRNAs, (c.) CpG sites in articular cartilage from normal and OA donors reveals a distinct molecular signature of OA.

Figure 2. Novel OA pathway reveals that transcription factors enriched in the differentially expressed gene set are themselves differentially expressed. Several of these transcription factors are targets of differentially expressed miRNAs. In addition, several of these genes and microRNAs are differentially methylated. Pink: Upregulated; Green: Downregulated; Circle: Gene; Square: microRNA; Blue outline: Hypomethylated; Yellow outline: Hypermethylated; Red lines: validated microRNA targets.

Disclosure: K. M. Fisch, None; **R. Akagi**, None; **O. Alvarez-Garcia**, None; **T. Teramura**, None; **Y. Muramatsu**, None; **M. Saito**, None; **S. Duffy**, None; **S. Grogan**, None; **T. Sasho**, None; **D. D'Lima**, None; **A. I. Su**, None; **M. K. Lotz**, None.

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A Novel Monocyte-Specific Transcript Underlies the Chromosome 21q22 Intergenic Genetic Association in Ankylosing Spondylitis. Katelin Haynes, Tony Kenna, Evgeny Glazov, Matthew A. Brown and Gethin Thomas. University of Queensland Diamantina Institute, Brisbane, Australia.

Background/Purpose: A major finding of the GWAS era of common disease gene-mapping has been that observed associations more often involve intergenic locations than protein-coding regions. Whilst there has been substantial interest in the potential role of ncRNA in heritable diseases, as yet to our knowledge in no common disease has a polymorphism in a ncRNA been demonstrated to cause disease, and very few examples exist in monogenic diseases. Of the 43 independent genetic associations that have been reported for ankylosing spondylitis, most occur in intergenic, intronic or other untranslated regions of the genome. Two in particular, at chromosomes 2p15 and 21q22, occur in intergenic regions with no annotated transcription.

Methods: We have used a new technique known as CaptureSeq, which utilises RNAseq on samples enriched for transcripts from a genomic region of interest allowing the detection of transcripts expressed at too low levels for detection by conventional RNAseq. Using this technique, we undertook ultra-deep transcriptional profiling in peripheral blood mononuclear cells from 5 cases carrying the protective allele and 5 carrying the susceptibility allele at the 21q22 locus.

Results: We identified two completely novel divergently transcribed long non-coding RNAs (lncRNA) expressed from this region, which were upregulated in AS cases compared with healthy controls, as well as those subjects carrying the susceptibility allele. This overexpression in PBMCs was confirmed in two independent data sets, using both RNAseq and qPCR.

To further elucidate the potential function of this novel transcript we mined the FANTOM5 Atlas of human gene expression which showed expression of the 21q22 transcripts almost exclusively in CD14+ monocytes. We confirmed this in purified CD14+ cells from our PBMC samples with no expression seen in any other cell type. Expression was also significantly enhanced by stimulation of the monocytes with microbial components.

Conclusion: This is the first example of a role for a lncRNA in AS, and one of the first in any human disease where a polymorphism influences disease by effects on an ncRNA. Our findings strongly support a role for monocytes in AS aetiology possibly through responses to microbes. Monocyte antigen presentation has previously been implicated in AS and is strengthened by the identification of the *HLA-B27-ERAP1* genetic interaction. Aberrant microbial-induced CD14+ monocyte expression of the 21q22 transcript presents a novel potential mechanism by which AS might be influenced by microbes.

Disclosure: K. Haynes, None; **T. Kenna**, None; **E. Glazov**, None; **M. A. Brown**, None; **G. Thomas**, None.

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Genome-Wide DNA Methylation Analysis of Twin Pairs Discordant for Systemic Sclerosis Reveals Distinct Signatures in Blood and Dermal Fibroblasts. Paula S. Ramos[1], Rick Jordan[2], James Lyons-Weiler[2], Thomas A. Medsger Jr. [2] and Carol A. Feghali-Bostwick[1].[1]Medical University of South Carolina, Charleston, SC, [2]University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Systemic sclerosis (SSc) is a chronic, multisystem, autoimmune inflammatory disease with genetic and non-genetic contributions to risk. The etiology of SSc, including the reasons underlying the wide variation in disease heterogeneity and severity remain unknown. The low concordance rate (4.2%) between monozygotic twins suggests an important role for acquired genetic changes such as epigenetic factors in SSc susceptibility. In order to characterize the genome-wide DNA methylation profile of blood and dermal fibroblasts in SSc, we performed an epigenome-wide analysis of DNA methylation on twin pairs discordant for SSc.

Methods: DNA methylation profiling was performed using the Illumina Infinium HumanMethylation450 BeadChip, which allows the annotation of approximately 480,000 CpG sites. Genome-wide methylation was assessed in genomic DNA isolated from: (1) blood from 34 discordant twin pairs, and (2) skin fibroblasts cultured from dermal punch biopsies of 12 twin pairs discordant for SSc. An efficiency analysis was performed with caGEDA to determine best normalization and feature selection methods and identify differentially methylated probes between unaffected and affected twins. Ingenuity Pathway Analysis (IPA) was used for pathway analysis.

Results: We identified 68 CpGs in blood and 103 CpGs in dermal fibroblasts with significant changes in DNA methylation levels between the SSc-affected and healthy twins. These CpGs locate to 55 genes in the blood and 73 in the fibroblasts. While 45 (66%) CpGs were hypomethylated in the blood of the affected twin, 63 (58%) were hypomethylated in the dermal fibroblasts. Pathway analysis of the genes differentially methylated in the blood revealed an enrichment of genes in the antigen-presentation pathway (P=2.47E-06) and genes involved in dermatological, immunological and hematological diseases (P=1.98E-05). These enrichments were mostly driven by multiple probes in genes in the HLA region that consistently showed either hyper- or hypomethylation in the affected twins. In skin fibroblasts, pathway analysis revealed an enrichment of genes involved in gene expression (P=8.5E-06) and organismal development (P=1.90E-05). Prominent members of the differentially methylated genes included HOX and T-box transcription factor genes that showed multiple probes with consistent hyper- or hypomethylation in the affected twins.

Conclusion: These data support a role for DNA methylation differences in mediating susceptibility to SSc and identify gene sets with differential methylation that may be involved in the pathogenesis of the disease. The distinct methylation profiles observed between blood and dermal fibroblasts suggest that tissue-specific epigenetic signatures may be responsible for the clinical heterogeneity of the disease.

Disclosure: P. S. Ramos, None; **R. Jordan**, None; **J. Lyons-Weiler**, None; **T. A. Medsger Jr.**, None; **C. A. Feghali-Bostwick**, None.

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PU.1, Mitf, and Their Novel Co-Partner, Eomes, Set up a Transcription Factor Network That Is Critical for Osteoclast Differentiation. Heather Carey[1], Sankha Ghosh[1], Eason Hildreth III[1], Jennifer Cabrera[1], Dias Kurmashev[1], Wael N. Jarjour[2], Ramiro Toribio[1], Sudarshana Sharma[1] and Michael Ostrowski[1]. [1]The Ohio State University, Columbus, OH, [2]The Ohio State University Wexner Medical Center, Columbus, OH.

Background/Purpose: Osteoclasts are bone resorbing cells which differentiate from myeloid precursors. The crosstalk between osteoblasts and osteoclasts tightly regulates the dynamic and continuous process of bone remodeling. Deregulation of this delicate balance is implicated in osteoporosis pathology. A variety of transcription factors including PU.1, MITF, NFATc1, and cFOS are essential for osteoclast differentiation. However, the interplay between these factors is not fully defined. We have previously shown that the transcription factors MITF and PU.1 act as a complex to regulate multiple genes required for osteoclast function. This study was designed to understand the global transcriptional regulatory processes involved in osteoclast differentiation.

Methods: We examined transcriptional regulation of target genes by MITF and PU.1 in myeloid precursors and osteoclasts using ChIP-Seq to map the genome-wide binding of these factors. In parallel, microarray analysis was performed to monitor target gene expression changes over the course of differentiation. We also queried the sequences jointly bound by PU.1 and MITF to search for conserved binding sequences potentially indicating novel co-partners in osteoclasts. We used micro-computed tomography and histological analysis to examine the effects of myeloid lineage-specific and osteoclast-specific deletion of PU.1 and its copartners *in vivo* and *in vitro.*

Results: ChIP-Seq and microarray profiling revealed that MITF and PU.1 jointly regulate the transcription of over 1000 genes in developing osteoclasts. Most of the MITF/ PU.1 co-bound regions were found in distal enhancer-like elements at the same sites in both myeloid precursors and osteoclasts. Overlap of our ChIP-Seq and microarray data sets utilizing Gene Set Enrichment Analysis (GSEA) revealed that transcription factor genes were the only subset significantly enriched in genes with PU.1/ MITF co-bound regions. These transcription factors include NFATc1, c-FOS, and NFKB, which are already known to be essential for osteoclast differentiation. Additionally, 38% of genomic regions jointly bound by PU.1 and MITF in developing osteoclasts contained the binding motif of the T-box transcription factor EOMES. Conventional ChIP assays validated binding of EOMES to MITF/PU.1 bound regions. Micro-computed topography analysis of murine bone has demonstrated that the loss of PU.1 or EOMES in osteoclasts and

their myeloid precursors leads to a severe osteopetrotic phenotype in neonatal mice due to highly deficient osteoclast differentiation and function.

Conclusion: Our results demonstrate that MITF and PU.1 set up a transcription factor regulatory network in myeloid precursors which triggers osteoclast differentiation in response to cues from the bone microenvironment. Ablation of PU.1 or its novel copartner EOMES results in disruption of this transcription factor network and therefore halts the differentiation program.

Disclosure: H. Carey, None; **S. Ghosh**, None; **E. Hildreth III**, None; **J. Cabrera**, None; **D. Kurmashev**, None; **W. N. Jarjour**, None; **R. Toribio**, None; **S. Sharma**, None; **M. Ostrowski**, None.

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Rheumatoid Arthritis (RA)-Associated Risk Allele *LBH* Alters the Function of a Differentially Methylated *LBH* Enhancer. Deepa Hammaker[1], Gary S. Firestein[2], Wei Wang[3], John W. Whitaker[4] and Anna-Karin Ekwall[5]. [1]University of California San Diego, La Jolla, CA, [2]University of California at San Diego School of Medicine, La Jolla, CA, [3]UCSD, La Jolla, CA, [4]UCSD, San Diego, CA, [5]UC San Diego, La Jolla, CA.

Background/Purpose: Recent data suggest that epigenetics, including DNA methylation, contributes to imprinting RA fibroblast-like synoviocytes (FLS) and alters their behavior. To understand how RA-associated risk alleles and differential methylation affect cis-regulatory regions, we compared differentially methylated loci (DML) in RA FLS with fibroblast DNase I hypersensitive sites. The differentially methylated enhancers (DMEs) were then integrated with RA-associated SNPs to identify key regulatory sites. In this study, we found and characterized an RA-associated SNP that colocalized with a DME in a key cancer-related gene that regulates cell growth and differentiation, namely limb-bud and heart development (*LBH*).

Methods: 15,220 RA-associated DMLs identified using Illumina 450k chips from 11 RA and 11 OA FLS were integrated with DNase I hypersensitive sites in the ENCODE database for 125 cell-types/conditions, including lung fibroblasts. These DMEs were then compared with GWAS data. Genomic DNA was isolated and the 1.4kb region with the WT allele (G) or RA SNP (T) of *lbh* was cloned into minimal promoter pGL4.23-luciferase construct. For methylation studies, plasmids were methylated with the CpG-methyltransferase M.SssI and S-adenosyl methionine. Methylation of all CpGs was verified by bisulfite modification and pyrosequencing. The WT, RA SNP or control plasmids (1ug) were transfected into cultured RA FLS by nucleofection with Renilla construct. Firefly luciferase activity was normalized to renilla.

Results: A DNase I hypersensitive site that is hypomethylated in RA FLS was identified in a 1400 bp region upstream of the *LBH* gene transcription start site. An RA and SLE-associated SNP (rs906868, G/T) was identified in the same region. We first determined the transcription differences between the WT and RA SNP in transfected RA FLS. Surprisingly, luciferase activity was significantly decreased in the WT group compared with the RA SNP ($19\pm7\%$, $p=0.02$, $n=9$ lines), suggesting that the regulatory region decreases gene expression in WT cells. The RA SNP had no effect on luciferase expression compared with control. We then evaluated whether CpG methylation of the plasmids altered function of the enhancer region. Methylation of the RA SNP plasmid significantly decreased the luciferase activity by $46\pm4\%$ compared with the unmethylated ($p=0.0005$, $n=5$ lines). In contrast, methylation increased the luciferase activity in the WT group ($42\pm17\%$, $p=0.049$, $n=5$ lines) but not in the control group.

Conclusion: We identified a novel candidate regulatory region by integrating ENCODE with RA GWAS and RA DNA methylation databases. The RA-associated allele in *lbh* eliminated its regulatory function. This is the first demonstration that an RA risk allele in a regulatory region has functional effects. By altering enhancer function of a gene that is intimately involved with cell proliferation (*LBH*), the risk allele could contribute to the aggressive behavior of RA FLS. Furthermore, the functional effects of methylation are distinctly different between RA-associated alleles and WT. These data provide evidence that combinations of epigenetic and risk allele data can provide new clues to the pathogenesis of RA.

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1890

Consistent Inhibition of Bone Destruction By Denosumab in Important Subgroups of Japanese Patients with Rheumatoid Arthritis. Naoki Ishiguro[1], Yoshiya Tanaka[2], Hisashi Yamanaka[3], Toshiyuki Yoneda[4], Takeshi Ohira[5], Naoki Okubo[6], Harry K. Genant[7], Desiree van der Heijde[8] and Tsutomu Takeuchi[9]. [1]Nagoya University Graduate School of Medicine, Nagoya, Japan, [2]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [3]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [4]Indiana University School of Medicine, Indianapolis, IN, [5]Daiich Sankyo Co. Ltd, Tokyo, Japan, [6]Daiichi Sankyo Co. Ltd, Tokyo, Japan, [7]University of California, San Francisco, CCBR-Synarc, Newark, Tiburon, CA, [8]Leiden University Medical Center, Leiden, Netherlands, [9]Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Denosumab is a fully human monoclonal antibody (IgG_2 subclass) that binds specifically to RANKL, inhibits osteoclast-induced bone resorption by preventing the binding of RANKL to RANK, and has been examined in the DRIVE Study to determine its efficacy and safety in Japanese patients with rheumatoid arthritis (RA). The primary endpoint was the change in the bone erosion from baseline to 12 months. Subgroup analyses were undertaken to understand whether denosumab was broadly effective upon progression of the bone erosion in RA patients.

Methods: The DRIVE Study was a 12-month, phase II, randomized, double-blind trial in RA patients receiving methotrexate (MTX) treatment. Patients were randomized to one of four treatment groups which were denosumab (60 mg every 6 months (Q6M), 60 mg every 3 months (Q3M) or 60 mg every 2 months (Q2M)) or placebo. Randomization was stratified by glucocorticoid use and rheumatoid factor (RF) status at screening. All patients basically continued the MTX treatment and a supplement of calcium and vitamin D throughout the study. The bone erosion score was assessed by the modified Sharp-van der Heijde method. Subgroup analyses were conducted according to the risk factors for radiographic damage: RA disease duration, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), RF status, anti-cyclic citrullinated peptide (anti-CCP) antibody, swollen joints (SWJ), and glucocorticoid use.

Results: The analysis was performed in 340 patients (88 in placebo, 85 in Q6M, 82 in Q3M and 85 in Q2M). Denosumab significantly inhibited the progression of bone erosion from baseline to 12 months compared to placebo. Changes from baseline in modified Sharp erosion score at 12 months (Mean $\pm$ SD) were 0.99 ± 2.69 in placebo, 0.27 ± 0.98 in Q6M (compared to placebo, $p=0.0082$), 0.14 ± 0.53 in Q3M ($p=0.0036$), and 0.09 ± 1.52 in Q2M ($p<0.0001$). The subgroups with risk factors for radiographic damage tended to show consistent results for the primary endpoint in total group.

Change of modified Sharp bone erosion score from baseline to 12 months in subgroups

		Placebo N = 88	Denosumab 60 mg Q6M N = 85	Q3M N = 82	Q2M N = 85
RA disease duration (years)	< 3	0.68±1.51	0.37±1.09	0.18±0.53	−0.13±0.57
	≥ 3	1.65±4.20	0.03±0.64	0.04±0.55	0.59±2.63
CRP (mg/dL)	< 1.0	0.77±1.89	0.16±0.67	0.09±0.51	0.05±1.58
	≥ 1.0	1.69±4.35	0.89±1.89	0.42±0.61	0.32±1.03
ESR (mm/hr)	< 28	0.46±1.23	0.07±0.50	0.01±0.42	0.11±1.80
	≥ 28	1.88±3.97	0.81±1.60	0.42±0.64	0.03±0.77
RF status	Positive	1.18±3.08	0.25±0.73	0.21±0.55	0.15±1.83
	Negative	0.59±1.53	0.31±1.41	−0.02±0.46	−0.05±0.44
Anti-CCP antibody	Positive	1.30±3.04	0.26±0.75	0.16±0.57	0.09±1.73
	Negative	0.07±0.23	0.33±1.73	0.08±0.39	0.08±0.37
SWJ	< 10	0.59±1.55	0.07±0.63	0.03±0.37	0.14±2.04
	≥ 10	1.50±3.61	0.71±1.40	0.25±0.64	0.03±0.53
Glucocorticoid use	Presence	1.37±3.74	0.33±1.24	0.23±0.57	−0.07±0.73
	Absence	0.72±1.51	0.22±0.74	0.07±0.50	0.20±1.92

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 post-baseline measurement of the radiograph score.
Data are mean ± SD.
RA=rheumatoid arthritis, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, RF=rheumatoid factor, Anti-CCP=anti-cyclic citrullinated peptide, SWJ=swollen joints

Conclusion: Denosumab significantly inhibited the progression of the bone erosion at 12 months in Japanese patients with RA. While some subgroups were small, denosumab also consistently inhibited the progression of the bone erosion in important subgroups. These results indicate that

denosumab could inhibit the progression of bone destruction in RA patients with risk factors for radiographic damage.

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1891

Early MRI Endpoints Provide a Valid Measure of Structural Damage While Reducing Study Duration and Participant Numbers in Rheumatoid Arthritis Clinical Trials. Joshua Baker[1], Philip G. Conaghan[2], Paul Emery[3], Daniel Baker[4] and Mikkel Østergaard[5]. [1]Philadelphia VA Medical Center, Philadelphia, PA, [2]University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [3]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [4]Janseen R&D, Spring House, PA, [5]Copenhagen Center for Arthritis Research, Copenhagen University Hospital at Glostrup, Glostrup, Denmark.

Background/Purpose: We used data from a large randomized controlled clinical trial of an effective biologic (golimumab, GO-BEFORE study) to compare the associations of disease activity and disease severity with two imaging techniques to measure joint erosion: 1) early progression in rheumatoid arthritis magnetic resonance imaging scores (RAMRIS) and 2) radiographic progression. We subsequently assessed the potential impact of incorporating these MRI scores in clinical trial design.

Methods: MRI of the dominant hand was performed and RAMRIS scores were determined at baseline, week 12 and week 24. van der Heijde-Sharp (vdHS) scores were determined for x-rays at baseline and week 52. Progression in vdHS and RAMRIS erosion scores were defined as a change of >0.5. Associations between X-ray and MRI outcomes with clinical features associated with severe disease and structural damage were evaluated to assess convergent validity. Iterative Wilcoxon ranksum tests assessed the sample size requirements to detect a significant difference in the change in structural damage score between combination therapy (methotrexate+golimumab) and methotrexate monotherapy. Sample size calculations were also performed based on dichotomous progression outcomes.

Results: MRI progression at 12 and 24 weeks was associated with greater DAS28(CRP), CRP, and vdHS at baseline, and greater HAQ scores at 2-years (**Table 1**). These associations were similar in magnitude to those seen with X-ray progression at 1-year. Ranksum testing for differences in the change in structural damage between treatment and controls arms achieved significance ($p<0.05$) with fewer total study subjects when MRI erosion score was the outcome assessed (175 for MRI at 12/24 weeks v. 300 subjects for ΔvdHS at 52 weeks) (**Figure 1**). When the study sample was enriched with subjects with a synovitis score >5 (a level previously associated with MRI progression) at baseline, the study sample further decreased to 125. Sample size calculations demonstrated that a study enriched with 117 subjects with synovitis scores >5 would have 80% power to detect a difference in the proportion of subjects progressing on MRI at 12 weeks. A sample size calculation based on an unenriched population and using 1-year x-ray progression as the outcome estimated a study size of 470 subjects.

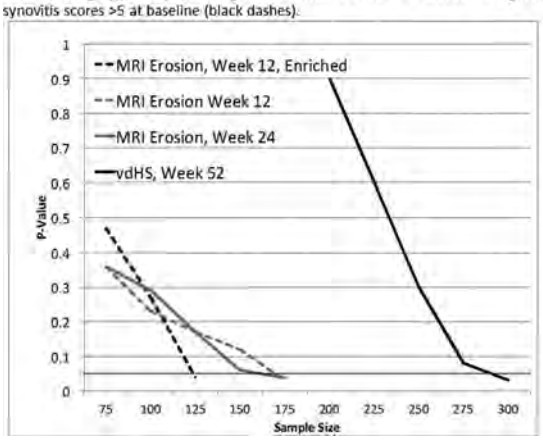
Conclusion: Early MRI erosion score outcomes have convergent validity comparable to that of 52-week x-ray progression. Use of MRI in clinical trials would decrease sample sizes and reduce length of follow-up for studies assessing differences in structural damage progression between groups.

Table 1: Clinical characteristics of MRI/x-ray progressors and non-progressors within the MRI sub-study (convergent validity).

	MRI 24 Weeks (N=238)			X-ray 52 Weeks (N=238)		
	Progression (N=52)	No Progression (N=186)	P Value	Progression (N=62)	No Progression (N=176)	P Value
Baseline DAS28(CRP)	5.81 (1.13)	5.53 (1.06)	0.1	5.79 (1.10)	5.52 (1.06)	0.09
Baseline CRP	1.8 (0.95, 3.4)	1 (0.4, 2.5)	0.002	2 (0.8, 4.2)	1 (0.4, 2.4)	0.001
Baseline vdHS	15 (3.25, 29.8)	4.5 (2, 13)	0.002	9 (2.9, 26)	4.5 (2, 15)	0.01
ΔHAQ Score (2-years)*	0.036 (0.78)	−0.14 (0.59)	0.08	−0.054 (0.74)	−0.12 (0.61)	0.5
24 Week ACR50, N (%)	14 (28%)	86 (47%)	0.01	21 (34%)	79 (45%)	0.1

* Adjusted for baseline HAQ

Figure 1: Iterative study of the sample size needed to demonstrate significant ($p<0.05$) differences between the golimumab + MTX combination and MTX monotherapy arms using the 1) change in x-ray at 52 weeks (solid black), 2) change in MRI erosion score at 12-weeks (gray dashes) or 3) 24-weeks (solid gray), and 4) the change in MRI erosion score at 12 weeks among those with synovitis scores >5 at baseline (black dashes).



Disclosure: J. Baker, None; **P. G. Conaghan**, Abbvie, 8, Merck Human Health, 8, Novartis Pharmaceutical Corporation, 8, Pfizer Inc, 8, Roche Pharmaceuticals, 8, UCB, 8; **P. Emery**, AbbVie, Bristol-Myers Squibb (BMS), MSD, Novartis, Pfizer Inc, Roche, and UCB Pharma, 2, AbbVie, Bristol-Myers Squibb (BMS), MSD, Novartis, Pfizer Inc, Roche, and UCB Pharma, 5; **D. Baker**, Janssen Research & Development, LLC., 3; **M. Østergaard**, None.

1892

In Vivo Visualization of Cortical Microchannels in Metacarpal Bones in Patients with Cutaneous Psoriasis By High Resolution Peripheral Computed tomography - Detecting Cortical Pathologies before the Clinical Onset of Psoriatic-Arthritis. David Simon, Francesca Faustini, Arnd Kleyer, Judith Haschka, David Werner, Axel J. Hueber, Michael Sticherling, Georg Schett and Juergen Rech. University of Erlangen-Nuremberg, Erlangen, Germany.

Background/Purpose: Normal bones present cortical micro-channels (CMC), which carry micro-vessels and ensure communication between the bone marrow and the synovial compartment. Only recently these structures have been visualized in vivo in rheumatoid arthritis patients through high resolution peripheral computed tomography (HR-pQCT). We hypothesized that it is possible to detect and characterize these channels in healthy subjects (HS) and subjects with cutaneous psoriasis (PSO), assuming that PSO patients could present changes in bone microstructure previous to the onset of joint involvement.

Methods: HR-pQCT (XtremeCT, Scanco Medical, Switzerland) scanning of the dominant hand was carried out on PSO patients without history of synovitis, dactylitis or enthesitis and HS. Image resolution was set at 82 μm voxel size. Images of the 2nd metacarpal head (MCH2) were downsized to the minimum of one slice with the 3D evaluation program provided by the manufacturer. Transversal, sagittal and coronal images were obtained using the subdim feature of the 3D evaluation program. Transversal slices (Fig.1) were projected at the level of the insertion of the joint capsule. Sagittal and coronal planes were set exactly into the middle of the MCH2. Demographic and clinical data were collected for the two groups of subjects. The study was

conducted upon approval by the local ethic committee and the National Radiation Safety Agency (BfS). Patients participated after signing informed consent.

Results: PSO patients (N=56,M/F: 36/20, mean age 47.0±13.8 y) were compared to HS (N=24, M/F: 10/14, mean age 43.8±11.9 y). The subjects were comparable per age and sex. PSO patients exhibited moderately severe disease (PASI 7.9±8.9) and disease duration of 12.7±14.3 y, the most frequent phenotype being psoriasis vulgaris (78.6%), 60.7% presented scalp lesions, 48.2% had nail lesions. Imaging analysis was blindly performed by two readers. Inter- and intra-reader reliability was high (r=0.96 and r=0.98). In PSO patients 607 CMC were found vs. 97 in HS in the MCH2. Expressed as mean number of CMC this accounts for 10.8±9.1 vs. 4.1±3.7 ($p<0.001$). No correlation was found for the CMC number in the PSO patients and the severity of the cutaneous disease and its duration nor for the age of the subjects.

Conclusion: Visualization of cortical pathologies as small as 81 microns can be obtained by this technique. These images resemble rather histopathologic slices in vitro (Fig. 1). In our study cutaneous psoriatic patients with no clinical history of arthritis showed a significant higher number of these cortical channels compared to healthy subjects, suggesting an increased communication between bone marrow and joint in this phase of disease previous to the onset of joint involvement.

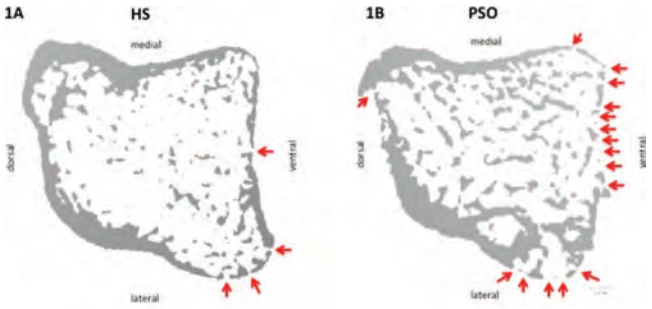


Figure 1 Transversal HR-pQCT slices of MCP joint 2
Panel A shows CMC in a healthy subject (arrows); panel B shows CMC in a PSO patient.
Arrows indicate cortical micro channels with a size smaller than 81 microns.

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Substantial Structural Lesions on MRI in the Sacroiliac Joints of Patients with Non-Radiographic Axial Spondyloarthritis Even in the Absence of MRI Inflammation. WP Maksymowych[1], S Wichuk[1], H Jones[2], A Szumski[2], L Marshall[2], J Bukowski[2] and RG Lambert[1]. [1]University of Alberta, Edmonton, AB, [2]Pfizer Inc., Collegeville, PA.

Background/Purpose: Treatment of axial SpA is increasingly aimed at intervention early in the disease course before radiographic sacroiliitis has appeared and when response to treatment is greatest. If radiographs do not indicate sacroiliitis, the Assessment of SpondyloArthritis (ASAS) classification criteria indicate that bone marrow edema (BME)/osteitis on MRI is a requirement, but this may also occur non-specifically, and some patients lack MRI inflammation. The purpose of this analysis was to assess the relative importance of structural lesions on MRI in the sacroiliac joints (SIJ) of patients with non-radiographic axial SpA (nr-axSpA).

Methods: Patients had axial SpA per the ASAS classification criteria, but did not meet modified NY radiographic criteria. Patients had symptoms for >3 months and <5 years, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and failed ≥2 NSAIDs. Patients were randomly assigned to etanercept 50 mg/week or placebo, then after 12 weeks, all patients received open-label etanercept 50 mg/week. Clinical and health outcomes were assessed throughout the study, and MRI of the SIJ and spine was performed by two central readers at baseline, weeks 12 and 48 to assess BME using the Spondyloarthritis Research Consortium of Canada (SPARCC) score. Additionally, a post-hoc analysis was conducted to score structural lesions using the SPARCC SIJ structural method, which assesses fat metaplasia, erosion, backfill, and ankylosis on T1-weighted spin echo (T1WSE) MRI. Two independent readers scored baseline and 48 week T1WSE MRI scans from 187 cases blinded to patients and short tau inversion recovery (STIR) MRI scans. Mean scores of the readers were used. SPARCC SIJ BME score ≥2 was used as the operational definition of positive MRI evidence of inflammation. For these analyses, all patients were combined, independent of randomization.

Results: Mean (SD) age was 32 (7.8) years, 60.5% were male, and mean (SD) duration of disease symptoms was 2.5 (1.8) years. A total of 73% of patients were human leukocyte antigen B27 (HLA-B27) positive and 81% met the ASAS MRI imaging criteria at baseline. Additionally, 61% had a structural lesion on MRI at baseline comprised of erosion (58%), backfill (23%), fat metaplasia (18%), and ankylosis (7%). Of the patients who were ASAS MRI positive, 65% had a structural lesion on MRI, compared to 43% who were ASAS MRI negative. Of the patients with SPARCC SIJ BME score ≥2 at baseline, 79% had a structural lesion on MRI compared to 35% with SPARCC SIJ BME score <2. Relative frequencies of MRI structural lesions in patients with SPARCC SIJ BME ≥2 vs <2 were: erosions (78% vs 30%), backfill (36% vs 5%), fat (22% vs 13%), and ankylosis (7% vs 7%).

Conclusion: Structural lesions on MRI occur frequently in nr-axSpA despite the absence of radiographic sacroiliitis and even in the absence of MRI inflammation. This finding strongly reinforces the concept of nr-axSpA as an early stage of axial SpA.

Disclosure: W. Maksymowych, Pfizer Inc, 2, Pfizer Inc, 5; **S. Wichuk**, None; **H. Jones**, Pfizer Inc, 3, Pfizer Inc, 1; **A. Szumski**, Pfizer Inc, 5; **L. Marshall**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Bukowski**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Lambert**, None.

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Is It Worth to Include MRI of the Spine in the ASAS Classification Criteria for Axial Spondyloarthritis? Manouk de Hooge[1], Jean-Baptiste Pialat[2], Antoine Feydy[3], Monique Reijnierse[1], Pascal Claudepierre[4], Alain Saraux[5], Maxime Dougados[3] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Hôpital Edouard Herriot, Lyon, France, [3]Descartes University, Cochin Hospital, Paris, France, [4]Henri Mondor Teaching Hospital, Creteil, France, [5]CHU de la Cavale Blanche, Brest Cedex, France.

Background/Purpose: Spinal MRI lesions suggestive of axial Spondyloarthritis (axSpA) are not included in the ASAS definition of a positive MRI, but do occur in the absence of affected sacroiliac joints (SIJ). It is unknown how often this happens and if it is useful to perform a MRI of the spine in patients (pts) with negative MRI-SIJ. The objective of this study was to investigate the prevalence of a positive MRI-spine in pts with short symptom duration and a negative MRI-SIJ.

Methods: Pts aged 18–50 with inflammatory back pain (IBP) (≥3 months, ≤3 years) from 25 participating centers in France were included in the DESIR-cohort (n=708). All available baseline MRIs of the spine were independently scored by 2 well-calibrated central readers who were blind to any other data. MRIs-SI were scored according to the ASAS definition[1] (lesions highly suggestive of sacroiliitis plus ≥1 lesion on ≥2 consecutive slices or >1 lesion on 1 slice). Inflammatory lesions on MRI-spine suggestive of spondylitis were scored when visible on ≥2 consecutive slices and according to the ASAS consensus definition[2] (≥3 lesions). In case of disagreement, an experienced radiologist served as adjudicator. MRI was considered positive if 2/3 readers agreed.

Results: All pts with MRI-spine and MRI-SIJ (n=650) were included in the analyses. There were 231 pts (35,5%) with a positive MRI-SIJ and 102 pts (15.7%) with a positive MRI-spine; 67 pts (10.3%) were positive for both MRI-SIJ and MRI-spine, 384 (59.1%) were negative for both; and 35 pts (5.4%) had a positive MRI-spine but a negative MRI-SI. Thirty of these were <45 years at symptom onset (entry criterion for ASAS axSpA criteria); 8 of these 30 pts fulfilled the modified New York criteria, 16 of these 30 pts fulfilled the clinical arm of the ASAS axSpA criteria and 6 pts did not fulfil the criteria. All these 6 pts were HLA-B27 negative. Therefore, if the MRI-spine would be considered to count for imaging for the ASAS criteria, 6 additional pts would have been classified and 16 pts would have fulfiled both the imaging and clinical arm; Two of the 5 pts with age >45 years at symptom onset fulfilled the mNY criteria.

Overall, only 25 pts (3.8%) had a pos MRI-spine without sacroiliitis on MRI or radiographs.

Conclusion: In 3.8% of IBP pts aged 18–50 ≥3 spinal inflammatory lesions suggestive of axSpA are found in absence of sacroiliitis on MRI or radiograph. Therefore the yield of including MRI-spine as additional imaging criterion in the ASAS axSpA classification criteria is considered unacceptably low.

References

1. Rudwaleit ARD 2009;68:1520–7.
2. Hermann ARD 2012;71:1278–88.

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1895

Sacroiliitis at Diagnosis in Children with Juvenile Spondyloarthritis. Pamela Weiss[1], Rui Xiao[2] and Nancy Chauvin[1]. [1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA.

Background/Purpose: The prevalence of sacroiliitis in children with juvenile spondyloarthritis (JSpA) at diagnosis is unknown. We aimed to evaluate: 1) the prevalence of sacroiliitis at diagnosis using radiographs and MRI; and 2) the association of physical examination and a history of back pain with acute sacroiliitis, using MRI as the reference standard.

Methods: We performed a single center prospective cross-sectional study of 39 children with newly diagnosed JSpA. Children were eligible for inclusion if they were diagnosed with enthesitis-related arthritis (ERA) or psoriatic arthritis (PsA) according to the International League of Associations for Rheumatology criteria in the prior 6 months. On the same day subjects had a musculoskeletal examination and imaging, which included a single AP pelvic radiograph and a non-contrast pelvic MRI with STIR. Radiographs were scored using the modified New York criteria. Acute sacroiliitis on MRI was defined as bone marrow edema within the sacrum or adjacent ilium with or without accompanying capsulitis, enthesitis, or effusion. Univariate logistic regression was used to test the association of clinical factors with acute sacroiliitis.

Results: Mean age of the JSpA subjects was 14.0 ± 2.7 years. 49% were male and 44% were HLA-B27$^+$. 35 and 4 children met criteria for ERA and psoriatic arthritis, respectively. Nine (23%) children had acute sacroiliitis; in 5 subjects it was bilateral. Of the 9 children with acute sacroiliitis on MRI, 7 (78%) had erosions or sclerosis on MRI and 5 (56%) had changes on conventional radiography. 2 subjects met radiologic criteria for ankylosing spondylitis. Of the subjects with acute sacroiliitis only 4 (44%) reported a history of back pain or tenderness on palpation of the sacroiliac joints. 3 (33%) and 14 (47%) of children with JSpA with and without sacroiliitis met the ASAS inflammatory back pain criteria. Male sex, hip arthritis, alternating buttock pain, higher c-reactive protein, HLA-B27 positivity, and decreased lateral flexion were associated with a higher odds of acute sacroiliitis, albeit statistically insignificant (Table).

Conclusion: This is the first study reporting the prevalence of acute sacroiliitis at diagnosis in children with JSpA. Sacroiliitis is common at diagnosis and may be asymptomatic. Nearly half the cases of sacroiliitis would have been missed if radiographs were the only imaging modality.

Table. Clinical features in MRI+ and MRI- subjects (N=39)

Clinical Feature	MRI+ N=9 N (%)	MRI− N=30 N (%)	p-value$^+$	OR of acute sacroiliitis (95% CI)
Psoriatic arthritis	1 (25)	3 (75)	0.92	–
Enthesitis-related arthritis	8 (23)	27 (77)	0.92	–
Age (years), mean±SD	14.0 ± 2.7	14.0 ± 2.7	0.97	1.00 (0.75, 1.32)
Male	6 (67)	13 (43)	0.20	2.62 (0.55,12.48)
AJC at diagnosis, mean±SD	1.1 ± 1.7	3.4 ± 5.4	0.22	0.79 (0.52, 1.22)
Tender enthesitis count at diagnosis, mean±SD	3.4 ± 3.7	4.2 ± 4.2	0.63	0.95 (0.78, 1.16)
Hip arthritis	1 (11)	3 (10)	0.92	1.13 (0.10, 12.36)
Patient-reported				
Back pain	4 (44)	18 (60)	0.68	0.53 (0.12, 2.40)
Back pain ≥ 3 months	2 (22)	10 (33)	0.84	0.57 (0.10, 3.27)
Insidious onset of back pain	2 (22)	11 (37)	0.42	0.49 (0.09, 2.81)
Back pain Improves with activity	2 (22)	7 (23)	0.95	0.94 (0.16, 5.59)
Alternating buttock pain	3 (33)	6 (20)	0.41	1.68 (0.38, 10.40)
AM back stiffness >30 min	2 (22)	13 (43)	0.59	0.65 (0.14, 3.12)
Nighttime back pain	2 (22)	10 (33)	0.41	0.49 (0.08, 2.81)
Inflammatory back pain$^\#$	3 (33)	14 (47)	0.48	0.57 (0.12, 2.72)
Laboratory features				
CRP at diagnosis (mg/dL)*, mean±SD	19.2 ± 39.9	2.2 ± 4.7	0.06	1.06 (0.96, 1.16)
HLA-B27+ ^	6 (75)	10 (36)	0.05	5.40 (0.91, 31.93)
Physical examination				
Decreased lateral flexion	5 (56)	14 (47)	0.64	1.43 (0.32, 6.39)
Loss of lumbar lordosis	4 (44)	15 (59)	0.77	0.80 (0.18, 3.57)
Positive FABER/Patrick's test	0 (0)	6 (20)	0.15	–
Decreased forward flexion	1 (11)	0 (0)	0.06	–
Sacroiliac tenderness	2 (22)	14 (47)	0.19	0.33 (0.06, 1.84)

Legend. $^+$P-value for chi-square or t-test comparisons of clinical features between subjects who had a positive or negative MRI. $^\#$ASAS inflammatory back pain (if ≥2 of the following positive: insidious onset, improvement with exercise, no improvement with rest, nocturnal pain). *CRP within 6 weeks of diagnosis available for 29 cases. ^ HLA-B27 available for 36 cases.

Disclosure: P. Weiss, None; **R. Xiao**, None; **N. Chauvin**, None.

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Validation of a Novel IFN-Regulated Gene Score As Biomarker in Chronic Atypical Neutrophilic Dermatosis with Lipdoystrophy and Elevated Temperature (CANDLE) Patients on Baricitinib, a Janus Kinase 1/2 Inhibitor, a Proof of Concept. Hanna Kim[1], Steve Brooks[2], Yin Liu[1], Adriana Almeida de Jesus[1], Gina A. Montealegre Sanchez[1], Dawn C. Chapelle[1], Nicole Plass[1], Yan Huang[1] and Raphaela Goldbach-Mansky[1]. [1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, [2]NIAMS/NIH, Bethesda, MD.

Background/Purpose: CANDLE syndrome is a novel autoinflammatory disease with strong IFN response signature. We hypothesize that IFN dysregulation may drive clinical manifestations in CANDLE and treatment with baricitinib, a JAK 1/2 inhibitor, will reduce the IFN-regulated genes (IRG) signature (Liu, 2012). Clinical improvement has been seen in CANDLE patients on baricitinib with significantly decreased steroid requirement and symptom scores (Montealetre, 2013). We assess IRG expression in CANDLE patients on increasing doses of bariticinib and validate an IRG score as a potential biomarker.

Methods: 12 CANDLE patients (1.8–24.7yo, 9 male) enrolled in a NIH compassionate use protocol for baricitinib were assessed at baseline and on increasing doses (2–11mg/day). Initial IRG list included all genes at least 2× upregulated in a chronic hepatitis patient and healthy peripheral blood mononuclear cells (PBMCs) exposed to IFN alpha was selected for IFN pathway genes in Ingenuity Pathway Analysis (IPA, Ingenuity® Systems). IFN alpha, beta, and gamma and IFN receptor genes were added. IRGs with lowest Z-scores and little variability from initial studies on 10 CANDLE patients were cut to reduce list to 31 IRGs. These and 4 housekeeping genes, were analyzed through RNA extracted from PAX gene tubes by the NanoString nCounter gene expression system (Seattle, WA). 3 healthy pediatric and 1 healthy adult were used as controls (HCs). IRG scores were calculated by a) summing Z-score IRGs (summary score) and b) summing normalized value for IRGs on 0–1 scale (normalized score) for the a) 31 genes selected above and b) 6 most highly expressed IRGs at baseline in 9 CANDLE patients from previous RNAseq data. The 6 and 31 gene IRG scores were assessed for correlation. Mean of 6 gene IRG scores from all baselines were compared to mean IRG scores on treatment via t-test. Paired t-test of 6 gene IRG scores in patients on the lowest and highest dose of treatment was also done excluding flaring patients.

Results: IRGs scores at 31 genes versus 6 genes highly correlate (linear model R^2: 0.95–0.99). Summary scores versus normalized scores strongly correlate (linear model R^2: 0.72–0.76). Normalized 6 gene IRG score significantly decreased (p=0.003) on treatment (mean 0.9, 5mg/day, 0.22mg/kg/day) from baseline (mean 1.9). With mean summary score (4828 vs. 2124), p value was 0.02. Paired analysis of 8 CANDLE patients showed significant decrease in normalized 6 gene IRG score (p=0.03, mean score 1.01 vs. 0.38) at higher dose versus lower dose (0.25 vs. 0.12 mg/kg/day) but summary score was not significant (mean score 1915 vs. 946).

Conclusion: 6 and 31 gene IRG score highly correlate. 6 gene normalized and summary IRG score significantly decrease in CANDLE patients on barcitinib treatment versus baseline with dose-dependent decrease with 6 gene normalized IRG. Preliminary analysis indicates normalized score may be a better biomarker than summary score. The IRG score may be useful as a biomarker in CANDLE syndrome and other autoinflammatory conditions with IFN-driven pathology, particularly for JAK inhibitor treatment. Further pharmacodynamics studies to correlate pharmacokinetics, IRG score, and clinical status are needed.

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Circulating T-Helper Cell-Associated Cytokines and Chemokines in Localized Scleroderma. Kathryn S. Torok[1], Katherine Kurzinski[2], Christina Kelsey[3], Kelsey Magee[4], Jonathan Yabes[4], Abbe N. Vallejo[4], Thomas A. Medsger Jr.[4] and Carol A. Feghali-Bostwick[5]. [1]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, [2]Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [3]University of Pittsburgh/UPMC, Pittsburgh, PA, [4]University of Pittsburgh, Pittsburgh, PA, [5]Medical University of South Carolina, Charleston, SC.

Background/Purpose: Localized scleroderma (LS) is an autoimmune disease of the skin and underlying tissues which results in disfigurement and orthopedic complications, especially when the onset is in childhood. LS has both inflammatory and fibrotic components, making it similar to systemic sclerosis (SSc), its 'companion' disease. Identifying potential biomarkers involved with disease propagation may lead to future therapeutic targets. T-helper (Th) cell subsets and their associated cytokines are thought to contribute to the pathogenesis of systemic sclerosis (SSc). Traditionally, a Th2 predominant response has been supported, but more recent data also implicate Th1, Th17 and various chemokine involvement. This concept in LS has only been partially investigated, with studies evaluating only a handful of cytokines associated with Th cell lineages, and not examined in reference to disease activity. This study was designed to extensively evaluate the Th-cell associated plasma cytokine and chemokine profiles of patients with pediatric LS.

Methods: Plasma samples were obtained from 69 pediatric LS patients and 71 healthy pediatric controls. Twenty-nine cytokines and chemokines were analyzed using a Th1, Th2, and Th17 Millipore luminex panel comparing LS to healthy controls, with additional analyses predetermined to be dedicated to disease activity parameter. The modified Localized Scleroderma Severity Index (mLoSSI) and the Physician Global Assessment of Disease Activity (PGA-A) were the main parameters compared to the cytokine/chemokine levels. Mann-Whitney U test was employed to compare cytokine levels between LS and healthy groups and Spearman rank correlation was used to determine relationships between individual analytes and clinical parameters ($p < 0.05$). Type I error due to multiple testing was controlled for using the Benjamini-Hochberg method.

Results: The levels of the following cytokines were significantly elevated in LS patients compared with healthy controls: IP-10, MCP-1, IL-17A, IL-12p70, GM-CSF, IFN-γ, IFN-α2 and PDGF-bb. When LS patients were further divided into active (n=30) and inactive states (n=39), IP-10 was significantly elevated in the active group compared to inactive (median: 2087.3 vs. 880.5 pg/ml, respectively). IP-10 levels were also significantly correlated with the Physician Global Assessment of Disease Activity (PGA-A) score ($r_s = 0.450$, $p = 0.005$) and with the modified Localized Scleroderma Severity index (mLoSSI) score ($r_s = 0.343$, $p = 0.004$).

Conclusion: SSc and LS share a similar histopathology with infiltration of lymphocytes and their associated effector cytokines in skin specimens. In the current study we demonstrated a serological presence of IP-10, MCP-1, IL-17A, IL-12p70, GM-CSF, IFN-γ and IFN-α2 in localized scleroderma, with IP-10 being highly correlated with active disease. Prior SSc studies have also found similar cytokine and chemokine profiles in the circulation, with recent literature supporting a potential role of IP-10 in SSc disease severity. These findings suggest a potential immunological link between these two clinically different diseases.

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1898

Identification of "autoinflammatory interferonopathies"? a New Class of Autoinflammatory Conditions? Adriana Almeida de Jesus[1], Zuoming Deng[1], Stephen Brooks[2], Yin Liu[1], Hanna Kim[1], Gina A. Montealegre Sanchez[1], Dawn C. Chapelle[1], Yan Huang[1], Philip Hashkes[3], Gulnara Nasrullayeva[4], Maria Teresa Terreri[5], Bita Arabshahi[6], Marilynn G. Punaro[7], Lakshmi N. Moorthy[8], Adam Reinhardt[9], Clovis A. Silva[10], Emilia I. Sato[11], Vibke Lilleby[12], Thomas Fleisher[13] and Raphaela Goldbach-Mansky[1]. [1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, [2]NIAMS/NIH, Bethesda, MD, [3]Shaare Zedek Medical Center, Jerusalem, Israel, [4]Azerbaijan Medical University, Baku, Azerbaijan, [5]University of Federal De Sao Paulo, Sao Paulo, Brazil, [6]Inova Fairfax Hospital for Children, Fairfax, VA, [7]University of Texas Southwestern Medical Center, Dallas, TX, [8]Robert Wood Johnson Medical School-Rutgers University, New Brunswick, NJ, [9]Children's Specialty Physicians, Omaha, NE, [10]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [11]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil, [12]Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway, [13]National Institutes of Health, Bethesda, MD.

Background/Purpose: The role of IL-1 in the pathogenesis of many of the monogenic autoinflammatory diseases is clinically validated by the response to IL-1 blocking therapies. However, patients who are unresponsive to IL-1 blocking therapy have more recently been identified. We have identified mutations in proteasome components as the cause of CANDLE syndrome and a mutation affecting IFN beta secretion as the cause for a severe vasculopathy and lung disease, SAVI. CANDLE and SAVI patients do not respond to IL-1 inhibition and consistently demonstrate marked up-regulation of IFN-inducible genes. These data suggest that autoinflammatory phenotypes can also be caused by IFN signaling dysregulation.

Methods: Total RNA was extracted from total blood collected in PaxGene tubes and RNA sequencing was performed using HiSeq 2000 Illumina® platform (Illumina). Blood DNA was extracted and whole exome sequencing was performed using human exome capture by Agilent V4 (51Mbp) exome enrichment kit, followed by next generation sequencing using Illumina HiSeq2000.

Results: Using RNA sequencing we have identified a group of 11 patients with markedly differentially expression of IFN inducible genes. WES was performed in 8 patients and parents (trios) and in 3 individual patients in order to identify genetic defects affecting the IFN signaling pathway. Seven probands were female and 4 were male; 4 probands were Hispanic, 2 were Asian and 1 proband was Caucasian, Israeli, Azerbaijani, Iranian and Norwegian, respectively. All patients presented with immunodysregulatory phenotypes with clinical similarities to the previously described interferonopathies, including skin vasculitis/vasculopathy, panniculitis, myositis and basal ganglion calcifications, but did not have a genetic diagnosis identified prior to evaluation at the NIH. The bioinformatics variant annotation, analysis and filtering workflow has allowed us to successfully identify *de novo* mutations in IFN-regulating genes in 2 of the 8 trios. In one patient, we found a disease causing *de novo* and somatic mutation in *TREX1*. This patient also presented with an in-frame deletion in *DHX9* inherited from her mother and a missense mutation in *MAVS* inherited from her father. In one patient, we identified a *de novo* mutation in *DHX9* and this patient was also a compound heterozygous for mutations in *IFIH1/MDA5*. In a third patient, we found a missense mutation in *TREX1* inherited from the mother and a heterozygous variant in *MB21D1* (gene encoding cGAS) was detected in one patient. For this last patient, parental samples are not available yet for evaluation of inheritance. All mutations described were confirmed by Sanger sequencing.

Conclusion: RNA sequencing and genetic analysis can be an important tool for the identification of patients with an IFN signature and guide the search for disease causing variants in IFN-regulating genes by WES. These preliminary findings need to be validated in larger groups of patients. The validation of the pathogenic role for interferon dysregulation in patients with autoinflammatory phenotypes may lead to the identification of a clinical subset with poor IL-1 responses that may respond to targeted therapies that block the IFN signaling pathways.

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Blockade of Interleukin-33 Signaling Prevents Death in a Mouse Model of Familial Hemophagocytic Lymphohistiocytosis. Julia Rood[1], Portia Kreiger[2], Erietta Stelekati[1], E. John Wherry[1] and Edward M. Behrens[3]. [1]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, [2]Alfred I. duPont Hospital for Children, Wilmington, DE, [3]The Children's Hospital of Philadelphia, Philadelphia, PA.

Background/Purpose: Cytokine storm syndromes, such as macrophage activation syndrome and familial hemophagocytic lymphohistiocytosis (FHL), represent important causes of mortality in pediatric rheumatology. Studies of a mouse model of FHL, in which lymphocytic choriomeningitis virus (LCMV) infection of perforin knockout (PKO) mice triggers the disease, have demonstrated that FHL is driven by an excess of LCMV-specific $CD8^+$T cells and their overproduction of interferon-γ (IFNγ). This over-exuberant T cell response is thought to arise from excess antigen stimulation through the T cell receptor (TCR). However, data from our lab and others suggest that other receptors may play an additional role, as mice deficient in both perforin and MyD88, a critical adaptor protein in non-TCR signaling, are protected from FHL.

Interleukin-33 receptor (IL-33R) is one of the receptors upstream of MyD88 and generates pro-inflammatory signals in response to the tissue damage-associated cytokine IL-33. Recent work has suggested that IL-33 signaling is necessary for mounting an effective anti-viral $CD8^+$ T cell response to LCMV in wildtype mice. However, the role of IL-33 signaling in

FHL has not been investigated. In this study, we sought to determine whether blockade of IL-33 signaling in the LCMV/PKO model of FHL would sufficiently limit the $CD8^+$T cell response to prevent the development of disease.

Methods: PKO mice were infected i.p. with 2×10^5 PFU LCMV-Armstrong and received 150 μg i.p. of either IL-33R-blocking antibody or isotype control every 2 days, beginning on day 3 post-infection. Mice were monitored for weight loss, survival, complete blood count, serum cytokines, spleen and liver histology, LCMV titers, frequency of antigen-specific $CD8^+$T cells, and T cell cytokine production.

Results: LCMV-infected PKO mice receiving IL-33R blocking antibody (IL-33RB) showed reduced weight loss (P=0.0170) and highly reduced mortality (HR =11.79, P=0.0021). IL-33R blockade reduced levels of serum IFNγ 16-fold (P=0.0005) and lowered frequencies of IFNγ-producing $CD8^+$ T cells (P=0.0003). Additionally, IL-33RB mice had reduced hepatic parenchymal damage, although leukopenia, anemia, and thrombocytopenia were not improved. Despite the reduced inflammation in IL-33RB mice, they maintained similar frequencies of LCMV-specific $CD8^+$T cells compared to isotype-treated controls and showed equivalent titers of LCMV in the spleen.

Conclusion: IL-33R blockade improves morbidity and mortality in a mouse model of FHL without exacerbating viral infection. Our results identify signaling via the tissue damage-associated cytokine IL-33 as an additional pathway contributing to disease and suggest blockade of this pathway as a viable treatment strategy for FHL.

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***HLA-DRB1*1101*, Regulatory Variants of the MHC, and a Regulatory Region Near an Intergenic Long Noncoding RNA on Chromosome 1 Are Risk Factors for Systemic Juvenile Idiopathic Arthritis.** Michael J. Ombrello[1], Elaine F. Remmers[2], Ioanna Tachmazidou[3], Alexei Grom[4], Dirk Föll[5], Alberto Martini[6], Marco Gattorno[7], Seza Ozen[8], Sampath Prahalad[9], Andrew S. Zeft[10], John F. Bohnsack[11], Norman T. Ilowite[12], Jane L. Park[13], Elizabeth D. Mellins[13], Ricardo A. G. Russo[14], Claudio A. Len[15], Sheila K. Feitosa de Oliveira[16], Rae SM Yeung[17], Lucy R. Wedderburn[18], Jordi Anton[19], Tobias Schwarz[20], Buhm Han[21], Richard H. Duerr[22], Jean-Paul Achkar[10], M. Ilyas Kamboh[22], Kenneth M. Kaufman[23], Leah C. Kottyan[4], Dalila Pinto[24], Stephen Scherer[17], Marta E. Alarcón-Riquelme[25], Elisa Docampo Martinez[26], Xavier Estivill[27], Ahmet Gul[28], Colleen Satorius[29], Paul I.W. de Bakker[30], Soumya Raychaudhuri[21], Carl D. Langefeld[31], Susan D. Thompson[4], Eleftheria Zeggini[3], Wendy Thomson[32], Daniel L. Kastner[29], Patricia Woo[33] and International Childhood Arthritis Genetics (INCHARGE) Consortium. [1]National Institute of Arthritis Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [2]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [3]The Wellcome Trust Sanger Institute, Cambridge, United Kingdom, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]University Children's Hospital Muenster, Muenster, Germany, [6]University of Genova, Genova, Italy, [7]Instituto Giannina Gaslini, Genoa, Italy, [8]Deptartment. of Pediatric Rheumatology, Hacettepe University, Ankara, Turkey, [9]Emory University School of Medicine, Atlanta, GA, [10]Cleveland Clinic, Cleveland, OH, [11]University of Utah, Salt Lake City, UT, [12]Albert Einstein College of Medicine, Bronx, NY, [13]Stanford University Medical Center, Stanford, CA, [14]Hospital de Pediatria Garrahan, Buenos Aires, Argentina, [15]Universidade Federal de São Paulo/Escola Paulista de Medicina, São Paulo, Brazil, [16]Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [17]The Hospital for Sick Children, Toronto, ON, [18]University College London (UCL) Institute of Child Health, London, United Kingdom, [19]Pediatric Rheumatology Unit. Hospital Sant Joan de Déu. Universitat de Barcelona, Barcelona, Spain, [20]University of Wuerzburg, Wuerzburg, Germany, [21]Broad Institute of MIT and Harvard, Cambridge, MA, [22]University of Pittsburgh, Pittsburgh, PA, [23]Cincinnati Children's Hospital Medical Center and the University of Cincinnati, Cincinnati, OH, [24]Icahn School of Medicine at Mount Sinai, New York, NY, [25]Arthritis and Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [26]GIGA-Université de Liège, LIege, Belgium, [27]Center for Genomic Regulation, Barcelona, Spain, [28]Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, [29]National Human Genome Research Institute, Bethesda, MD, [30]University Medical Center Utrecht, Utrecht, Netherlands, [31]Center for Public Health Genomics and Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, [32]Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [33]University College London, London, United Kingdom.

Background/Purpose: Systemic juvenile idiopathic arthritis (sJIA) is a severe inflammatory disease of unknown etiology. We utilized a genomic approach to interrogate the molecular pathogenesis of this disorder.

Methods: Single nucleotide polymorphism (SNP) genotypes from Illumina arrays were obtained in 988 children with sJIA and 431 healthy subjects and combined with *in silico* SNP data from 7579 healthy subjects. The collection was divided into 9 strata by country of origin, and after stringent quality control, we performed genome-wide SNP imputation and association testing in each stratum, followed by meta-analysis. A second round of imputation using a more densely genotyped reference panel was performed in regions with $p < 1E\text{-}7$. To investigate the role of specific major histocompatibility complex (MHC) proteins, we imputed classical HLA alleles and their subordinate amino acid positions. To assess whether sJIA-associated noncoding MHC variation conferred risk through regulatory mechanisms, we used RegulomeDB to analyze MHC SNPs with $p < 1E\text{-}5$. RegulomeDB integrates and queries regulatory information from over 100 tissues and cell lines, including DNAse hypersensitivity, transcription factor (TF) ChIP-seq and histone ChIP-seq data from ENCODE, plus expression quantitative trait loci (eQTL) data.

Results: Meta-analyses of >1.3M SNPs identified significant associations ($p < 1.5E\text{-}8$) between sJIA and 6 SNPs between *BTNL2* and *HLA-DQA1*, as well as a susceptibility locus in a noncoding region of chromosome 1 nearest to the long intergenic noncoding RNA, *LOC284661*. Conditional analysis of the phase 2 imputation data identified *HLA-DRB1* (p_{peak} = 1.6E-10) and *HLA-DQA2* ($p_{regression}$ = 4.6E-7) as independent susceptibility loci. It also revealed a 10kb sJIA-associated region on chromosome 1 that contained 8 sJIA-associated SNPs ($p < 1.5E\text{-}8$). Conditional analyses of imputed HLA alleles identified *HLA-DRB1*1101* (p_{peak} = 3.1E-9) and *HLA-DPB1*03* ($p_{regression}$ = 3.2E-4) as independent risk factors, while position 58 of HLA-DRB1, which defines the -DRB1*11 alleles, was also significantly associated with sJIA ($p = 1.4E\text{-}7$). Using RegulomeDB to examine 886 MHC SNPs with $p < 1E\text{-}5$, we found 13 sJIA-associated SNPs with strong evidence that they influenced transcription factor binding and were also linked to expression of a gene target (RegulomeDB scores 1a - 1f). These SNPs were located nearest to *HLA-DQA1*, *HLA-DRB1*, *HLA-DRA*, *TNXB*, *NOTCH4* and *C2*. 12 of 13 SNPs were *cis* eQTLs for 1 or more MHC class II (MHCII) genes in lymphoblastoid cell lines (LCLs) and/or monocytes, 8 of which were eQTLs for *HLA-DRB5*. 3 of 13 SNPs resided within TF ChIP-seq peaks in GM12878 LCLs. 7 of 13 SNPs resided in H3K27ac ChIP-seq peaks (marks of active enhancers) in GM12878 LCLs and/or monocytes, 6 of which were cell-type specific. In all, 9 of 13 SNPs were located within histone modification signatures that were specific to GM12878 LCLs.

Conclusion: This study implicates the MHCII locus and a region of chromosome 1 upstream of *LOC284661* in sJIA susceptibility. The data suggest that the MHCII locus influences sJIA susceptibility through both protein coding variation and noncoding variation that alters gene expression.

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1901

Interferon-γ (IFNγ) in Macrophage Activation Syndrome (MAS) Associated with Systemic Juvenile Idiopathic Arthritis (sJIA). High Levels in Patients and a Role in a Murine MAS Model. Claudia Bracaglia[1], Ivan Caiello[1], Kathy De Graaf[2], Giovanni D'Ario[2], Florence Guilhot[2], Walter Ferlin[2], Lidia Meli[1], Giusi Prencipe[1], Sergio Davi[3], Grant Schulert[4], Angelo Ravelli[5], Alexei Grom[4], Cristina De Min[2] and Fabrizio De Benedetti Sr.[1]. [1]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, [2]Novimmmune S.A., Plan-Les-Ouates, Geneva, Switzerland, [3]Istituto Giannina Gaslini, Genova, Italy, [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Istituto Giannina Gaslini and University of Genova, Genova, Italy.

Background/Purpose: IFNγ is the pivotal mediator in murine models of primary HLH. Given the similarities between primary and secondary (sHLH), including MAS, we analyzed IFNγ levels in patients with sJIA and MAS and evaluated the pathogenic role of IFNγ in a murine MAS model.

Methods: We measured levels of IFNγ, IFNγ-related chemokines (CXCL9, CXCL10, CXCL11), and IL-6 in patients with sHLH (n=14), and in patients with sJIA (n=54) of whom 20 had MAS at sampling using the Luminex multiplexing assay and evaluated their relation to disease activity. The effect of the anti-IFNγ antibody XMG1.2 was assessed in IL-6 transgenic (IL6TG) mice in which a MAS-like syndrome leading to death is triggered by TLR ligands (Strippoli, Arthritis Rheum 2012). An LPS LD50 (5 μg/gr body weight) was used, as a trigger for MAS, followed 10 hours later by administration of 100 μg/gr of XMG1.2.

Results: Levels of IFNγ and of IFNγ-related chemokines [median pg/ml(IQR)] were markedly elevated in active MAS and active sHLH, with no significant differences between active sHLH [IFNγ 34.7(23.9–170.1); CXCL9 33598(3083–127687); CXCL10 4420(799.7–8226); CXCL11 1327(189–2000)] and active MAS [IFNγ 15.4(5.1–52.6); CXCL9 13392(2163–35452); CXCL10 1612(424.8–4309); CXCL11 564.8(197.5–1007)]. Levels in active sJIA without MAS at sampling [IFNγ 4.88(3.2–8.7); CXCL9 836.5(470.9–2505); CXCL10 307.3(198.9–693.7); CXCL11 121.7(62–197.1)] were lower (all p-values <0.01) than in active sHLH or active MAS. IL-6 was not different between the three groups. In active MAS, platelet count was inversely related to IFNγ (r=−0.53; p=0.02), CXCL9 (r=−0.51; p=0.03) and CXCL10 (r=−0.58; p=0.009). In the murine MAS model, treatment with the anti-IFNγ antibody XMG1.2 resulted in increased survival (XMG1.2-treated 10 survivors/10 treated; control-treated 5/10; p=0.033).

Conclusion: IFNγ, and IFNγ-related chemokine levels were increased in patients with MAS compared to patients with active sJIA without MAS, and associated with low platelet count. Neutralization of IFNγ increased survival in murine MAS.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects IV: Promising Biomarkers
Monday, November 17, 2014, 4:30 PM–6:00 PM

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Utility of Glyca, a Novel Inflammatory Marker, for Assessment of Rheumatoid Arthritis Disease Activity. Michelle Ormseth[1], Cecilia P. Chung[1], Joseph F. Solus[1], Annette M. Oeser[1], Margery A. Connelly[2], Jim Otvos[2] and C Michael Stein[1]. [1]Vanderbilt University, Nashville, TN, [2]LipoScience, Inc., Raleigh, NC.

Background/Purpose: GlycA is a novel inflammatory biomarker measured from the nuclear magnetic resonance (NMR) spectra obtained for lipoprotein particle analysis. It represents a distinct peak composed primarily of glycosylated acute phase proteins. Glyc A is associated with inflammatory markers, and development of cardiovascular disease. We hypothesized that GlycA is a biomarker of disease activity and systemic inflammation in rheumatoid arthritis (RA).

Methods: We conducted a cross-sectional study including 166 patients with RA and 90 control subjects. GlycA was measured using a previously validated algorithm from the NMR lipoprotein particle profile which quantifies the NMR signal originating from N-acetylglucosamine and N-acetylgalactosamine residues on carbohydrate side chains of circulating glycoproteins. Disease activity of RA was quantified by DAS28 score and functional capacity by the modified health assessment questionnaire. Markers of inflammation including erythrocyte sedimentation rate (ESR), high sensitivity C-reactive protein (CRP), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) were measured. GlycA concentrations were compared between patients with RA and control subjects and correlated with disease activity and markers of inflammation in RA.

Results: Patients with RA had higher GlycA concentration (median [interquartile range]: 398 μmol/l [348, 473 μmol/L]) compared to control subjects (344 μmol/l [314, 403 μmol/l], P<0.001). Among patients with RA GlycA was strongly correlated with DAS28 and its components including tender and swollen joint count, global health visual analog scale score and acute phase reactants CRP and ESR (P < 0.001, Table). Similarly, GlycA was strongly associated with proinflammatory cytokines, IL-6 and TNF-α, and RA functional capacity (P ≤ 0.002, Table).

Table: Association between GlycA and RA disease activity and inflammation

	Spearman Rho	P value
DAS28	0.576	<0.001
Tender joints	0.283	<0.001
Swollen joints	0.288	<0.001
Global health	0.304	<0.001
CRP	0.614	<0.001
ESR	0.643	<0.001
IL-6	0.388	<0.001
TNF-α	0.245	0.002
mHAQ	0.235	0.002

Conclusion: GlycA is a novel inflammatory marker that is useful for assessment of disease activity and systemic inflammation in patients with RA.

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1903

Change in 14-3-3η Expression in Early RA Patients Treated with Dmards Corresponds with Change in DAS28 and Good EULAR *Responses*. Dirkjan van Schaardenburg[1], Mairead Murphy[2], Yuan Gui[2], Samina Turk[1], Walter P. Maksymowych[3] and Anthony Marotta[2]. [1]Reade, Amsterdam, Netherlands, [2]Augurex Life Sciences Corp., North Vancouver, BC, [3]University of Alberta, Edmonton, AB.

Background/Purpose: 14-3-3η is a mechanistic marker that up-regulates inflammatory and joint damage factors that are implicated in the RA pathophysiological process[1]. It is a potent inducer of TNF-α and IL-6 and we have previously described that low 14-3-3η levels prior to the initiation of anti-TNF and tocilizumab therapy marks good EULAR response and DAS remission. There is an unmet need for mechanistic biomarkers that enhance prediction of response to therapy. We also recently described that lower baseline plasma 14-3-3η levels mark good EULAR response in an RA cohort treated with DMARDs. In this study we tested plasma levels in the same cohort at year 1 to determine whether a change in 14-3-3η expression from baseline informs the change in DAS28 and response to therapy.

Methods: Three hundred and 80 (380) patients from the Reade early RA cohort were assessed for 14-3-3η titres at baseline and at year 1 follow up. All patients were DMARD naïve at baseline, mean age was 54 years, 73% were female and median duration of symptoms was 4 months (IQR 2–7). Fisher's Exact test was performed to assess the relationship between baseline to year 1 change in 14-3-3η and a Good EULAR response and DAS remssion (<2.6) at year 2 follow up. Spearman rank correlations were used to identify associations between change in 14-3-3η and change in DAS28. A nominal logistic regression, controlling for baseline DAS, was used to investigate if change in 14-3-3η is a predictor of Good EULAR response.

Results: Mean (SD) year 1 plasma 14-3-3η levels [3.3 ng/ml (6.0)] were significantly lower than baseline levels [4.4 ng/ml (6.9)], p=0.0004 reflecting the modifiability of 14-3-3η plasma concentrations over this period. The change in 14-3-3η titres significantly correlated with the change in DAS from baseline to year 2 (r=0.12, p=0.02) across the whole cohort. The Fisher Exact test revealed that a decrease in 14-3-3η from baseline to year 1 was significantly associated with a Good EULAR response [LR = 4.4, OR(95%CI)=1.6 (1.1–2.4), p=0.023] and remission [LR = 4.5, OR(95%CI)=1.3 (1.0–1.7), p=0.022] at year 2. In a bivariate model controlling for baseline DAS28, a decrease in 14-3-3η, was an independent predictor of a Good EULAR response yielding an LR of 4.2, p = 0.04. Both baseline DAS28 (LR=15.6, p<0.0001) and the change in 14-3-3η (LR=5.1 p=0.024) were independent predictors of remission at year 2.

Conclusion: 14-3-3η plasma levels decrease with DMARD therapy and their change correlates with the change in DAS28 and predict both a good EULAR response and DAS remission. These clinical findings align with the mechanistic understanding of 14-3-3η as a potent upregulator of inflammatory and joint damage factors and how a decrease in its expression corresponds with a reduced burden of disease.

Reference

1. Maksymowych, Walter P., et al. "14-3-3eta is a novel mediator associated with the pathogenesis of rheumatoid arthritis and joint damage." Arthritis research & therapy 16.2 (2014): R99.

Disclosure: D. van Schaardenburg, Augurex Life Sciences Corp, 5; **M. Murphy**, Augurex Life Sciences Corp, 3; **Y. Gui**, Augurex Life Sciences Corp, 3; **S. Turk**, None; **W. P. Maksymowych**, None; **A. Marotta**, Augurex Life Sciences Corp., 3.

1904

Rheumatoid Factor Isotype Testing to Identify Individuals in the Preclinical Period of Rheumatoid Arthritis. M. Kristen Demoruelle[1], Anthony Kahr[1], Mark C. Parish[1], Marie L. Feser[1], Ryan W. Gan[2], Jason R. Kolfenbach[1], William R. Gilliland[3], Jess D. Edison[3], Michael H. Weisman[4], James R. O'Dell[5], Ted R. Mikuls[6], Richard M. Keating[7], Peter K. Gregersen[8], Jane H. Buckner[9], Jill M. Norris[2], V. Michael Holers[1] and Kevin D. Deane[1]. [1]University of Colorado School of Medicine, Aurora, CO, [2]Colorado School of Public Health, Aurora, CO, [3]Walter Reed National Military Medical Center, Bethesda, MD, [4]Cedars-Sinai Medical Center, Los Angeles, CA, [5]Veteran Affairs Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, [6]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [7]Scripps Clinic, La Jolla, CA, [8]Feinstein Institute for Medical Research, Manhasset, NY, [9]Benaroya Research Institute at Virginia Mason, Seattle, WA.

Background/Purpose: Rheumatoid arthritis (RA)-related autoantibody (Ab) testing for Abs to cyclic citrullinated peptide (CCP) and rheumatoid factor (RF) are used in the clinical diagnosis of RA. In addition, RA-related Ab elevations in asymptomatic individuals indicate an increased risk of future RA and define a preclinical period of RA development. These at-risk subjects could be considered for prevention strategies in RA, but a challenge in effective identification of individuals at-risk for RA is the varied methods of Ab testing. For example, RF can be tested by nephelometry (RFneph) as is commonly used in clinical labs or by ELISA for RF isotypes (IgM/A/G). Studies demonstrate RFIgM and/or RFIgA is highly sensitive in classifiable RA, but the utility of RF isotype testing in addition to RFneph is not well known in preclinical RA.

Methods: We evaluated subjects with classifiable RA (1987 ACR criteria) from the Studies of the Etiology of RA (SERA) project (N=566) and the Department of Defense Serum Repository (DoDSR; N=83; all with pre-diagnosis and 47/83 with post-diagnosis samples). Controls were 200 random blood donors for SERA RA cases and 83 DoDSR matched controls for DoDSR RA cases. All subjects were tested for RFneph and RF isotypes (IgM/A/G by ELISA). Cut-off levels for all RF assays were determined as <5% positive in a separate set of 491 blood donors. CCP3.1 (IgG/IgA INOVA) testing was performed in all subjects using manufacturers cut-off levels.

Results: The diagnostic accuracy of Ab testing is listed in Table 1. All RFs and CCP3.1 had high specificity for classifiable RA including SERA RA and DoDSR post-diagnosis. In DoDSR pre-diagnosis testing, sensitivity for future RA was 41% for RFneph and 63% for CCP3.1. Sensitivity increased to 69% when positivity for the following Abs was considered: RFneph, CCP3.1, RFIgA or RFIgM. In DoDSR RA cases who were negative for RFneph and CCP3.1 in pre-diagnosis testing (N=29), adding RFIgA or RFIgM (but not IgG) testing identified an additional 10% of subjects who developed classifiable RA (Table 2).

Conclusion: Herein RFneph and CCP3.1 had fair diagnostic accuracy for future RA; however, RFIgA and IgM (but not IgG) testing allowed for identification of 10% more individuals who would develop future RA, while maintaining high specificity (93% for RFIgA or IgM pre-diagnosis). These findings suggest that RFneph misses some RF positivity that is detectable by isotype testing. As such, in addition to CCP3.1 and RFneph, RFIgM and RFIgA testing may be clinically meaningful in identifying subjects at-risk for future RA, especially if interventions become available to prevent progression from preclinical to classifiable RA.

Table. Sensitivity and Specificity of Rheumatoid Factor Isotypes in Classifiable and Preclinical RA

	RFIgA	RFIgM	RFIgG	≥1 RF isotype	RFIgA or RFIgM	RFneph	CCP3.1	RFneph or CCP3.1	RFIgA, RFIgM, RFneph or CCP3.1
SERA RA cases (N=566)†*									
Sensitivity	41.3	59.0	44.3	64.8	62.6	61.5	67.8	77.6	80.6
Specificity	98.0	94.5	94.5	91.0	94.0	95.0	94.0	89.0	85.5
DoDSR RA cases, post-diagnosis (N=47)‡									
Sensitivity	61.7	68.1	31.9	80.9	80.9	66.0	75.6	85.1	87.2
Specificity	91.7	93.6	100	87.2	87.2	95.7	89.4	85.1	78.7
DoDSR RA cases, pre-diagnosis (N=83)μ*									
Sensitivity	44.6	43.4	24.1	53.0	53.0	41.0	62.7	65.1	68.7
Specificity	94.0	98.8	98.8	92.8	92.8	97.6	92.8	90.3	87.5

†Sensitivity and specificity analyzed in comparison with 200 random blood donor controls
‡ 47 post-diagnosis samples were available for 83 DoDSR RA cases. Median time post-diagnosis = 2.2 years. Cases were compared to 47 matched controls
μ243 pre-diagnosis samples were available for 83 DoDSR RA cases. Calculated using 1 sample per case, and if ≥1 sample available, the sample closest to the time of diagnosis was used for analysis; median 1.4 years prior to RA diagnosis. Cases were compared to matched controls.
*SERA RA cases were older than DoDSR RA cases (median age 58 v. 40 years) and had a higher proportion of women subjects (77% v. 41%).

Table 2. RF Isotype Positivity in DoDSR RA Cases Negative for RF by Nephelometry and CCP3.1 in Pre-diagnosis Testing*

	Prevalence of positivity (%)		
	RFneph(−) (N=49)	CCP3.1(−) (N=31)	CCP3.1(−) and RFneph(−) (N=29)
RFIgM	14.3	12.9	6.9
RFIgA	14.3	6.5	3.4
RFIgG†	2.0†	3.2†	0†
≥1 RF isotypes	24.5	16.1	10.3
RFIgA or RFIgM‡	24.5	16.1	10.3

*From the 83 DoDSR RA cases, these results include testing of cases who were negative for RFneph and/or CCP3.1 in their pre-diagnosis sample that was closest to the time of their diagnosis; median 1.4 years prior to RA diagnosis.
†RFIgG testing did not identify any subjects pre-diagnosis of RA that were not identified as seropositive by CCP3.1 or RFneph testing.
‡RFIgA or RFIgM positivity was present in only 6 of 83 (7.2%) of DoDSR matched controls, and this high specificity (93.8%) adds further value to the identification of 4 of 29 (10.3%) preclinical RA subjects who will go on to develop classifiable RA.

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1905

Within-Day Variation and Influence of Physical Exercise on Circulating Galectin-3 in Patients with Rheumatoid Arthritis and Healthy Individuals. Saida Farah Issa[1], Anne Friesgaard Christensen[2], Tine Lottenburger[2], Kirsten Junker[3], Hanne M. Lindegaard[1], Kim Hoerslev-Petersen[4] and Peter Junker[1]. [1]Department of Rheumatology, Odense University Hospital, Odense, Denmark, [2]Department of Rheumatology, Vejle Hospital, Vejle, Denmark, [3]Institute of Molecular Medicine, Cardiovascular & Renal Research, University of Southern Denmark, Odense, Denmark, [4]Research Unit at King Christian X Hospital for Rheumatic Diseases, Graasten, Graasten, Denmark.

Background/Purpose: Galectin-3 has been suggested as a pro-inflammatory mediator in Rheumatoid Arthritis(1). Thus, Galectin-3 is over-expressed in RA-synovitis and bone erosions were significantly decreased in GAL-3 −/− mice compared with wild type animals (2,3). Furthermore, in long-standing RA, Galectin-3 was increased in synovial fluid and serum compared with osteoarthritis and controls (2). These findings indicate that Galectin-3 may serve as biomarker for synovitis pathology in RA.

The objectives of this study were to investigate whether serum Galectin-3 exhibits circadian variation and/or is influenced by physical exercise in patients with RA at different stages and controls.

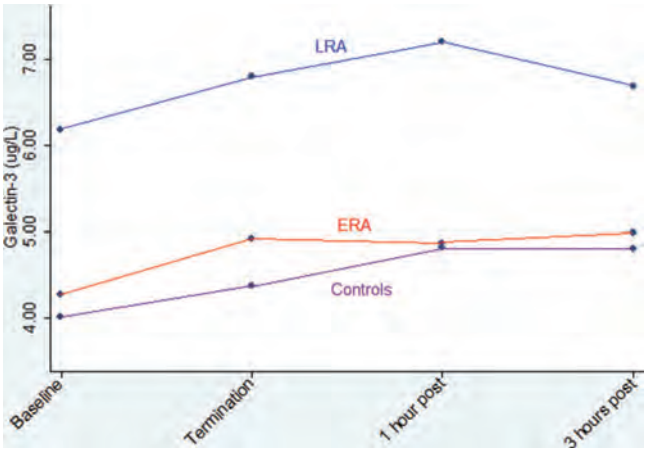
Methods: The study on circadian patterns comprised eleven patients with newly diagnosed RA, disease duration less than 6 months (ERA), 10 patients with long-standing RA (5–15 years (LRA)) and 16 self-reportedly healthy control subjects. During 24 hours 7 blood samples were drawn at 3-hour intervals starting at 10 a.m. through 10 p.m. and at 7 and 10 a.m. on the following day. The study on the effect of physical activity included 10 patients with ERA, 10 with LRA and 14 controls. The participants underwent a standardized exercise program and four blood samples were drawn before, during and after exercise. Serum Galectin-3 was quantified by ELISA (R&D systems). An age and sex adjusted mixed model analysis was applied in both substudies.

Results: Circadian variation substudy: Galectin-3 was borderline increased at baseline in ERA and LRA, 6.03 ug/l (*95% CI 4.44;7.61*) and 5.95 ug/l (*4.44;7.47*) vs. 4.51 ug/l (*3.48;5.53*) in control subjects (p = 0.08). There was no association between time of blood sampling and Galectin-3 in serum (p = 0.85).

Physical exercise substudy: Baseline mean Galectin-3 in both subsets was also elevated, however without reaching statistical significance in the ERA group; LRA 6.18 ug/l (*95% CI 4.46;7.89;* p = 0.01), ERA 4.27 ug/l (*3.23;5.30;* p = 0.68) vs controls 4.01 ug/l (*3.10;4.91*). A submaximal physical challenge elicited comparable Gal-3 increments at 10–15% above

baseline with peak values 1–3 hours post exercise in RA patients and controls (p-value < 0.001), fig. 1.

Figure 1. Galectin-3 increments in healthy controls, and in patients with early (ERA) and longstanding rheumatoid arthritis (LRA) before and after termination of exercise.



Conclusion: Circulating Galectin-3 was increased in early and longstanding RA. Galectin-3 did not exhibit circadian variation. Galectin-3 increased comparably in RA patients and healthy controls following submaximal exercise, which should be avoided before bloodsampling for Galectin-3 determination.

Acknowledgements: We would like to thank The Danish Rheumatism Association for financial support.

References:

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2) Ohshima S et al. Arthritis Rheum. 2003;48:2788–95.
3) Forsman H et al. Arthritis Rheum. 2011;63:445–54.

Disclosure: S. F. Issa, None; **A. F. Christensen**, None; **T. Lottenburger**, None; **K. Junker**, None; **H. M. Lindegaard**, None; **K. Hoerslev-Petersen**, None; **P. Junker**, None.

1906

IL-6 Blockade Reduces Circulating N-Terminal Pro-Brain Natriuretic Peptide Levels in Patients with Active Rheumatoid Arthritis. Atsuma Nishiwaki[1], Hitomi Kobayashi[1], Yasuyuki Kobayashi[2], Isamu Yokoe[1], Noboru Kitamura[1], Hidetake Shiraiwa[1], Takamasa Nozaki[1], Hirotake Inomata[1], Natsumi Ikumi[1], Kaita Sugiyama[1], Yousuke Nagasawa[1] and Masami Takei[3]. [1]Nihon University School of Medicine, Tokyo, Japan, [2]St.Marianna University School of Medicine, Kawasaki, Japan, [3]Nihon University School of Medicine, Itabashi Tokyo, Japan.

Background/Purpose: Patients with rheumatoid arthritis (RA) have a 1.5–2.0 fold higher risk of developing congestive heart failure (CHF) than the general population. Small increases in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels predict left ventricular (LV) dysfunction and cardiac stress. NT-pro BNP is also associated with pro-inflammatory cytokines such as interleukin 6 (IL-6). Data relating to the effects of IL-6 blocking agents (tocilizumab, TCZ) on circulating NT-proBNP levels in patients with active RA are lacking but may be informative. We therefore investigated the effects of TCZ therapy on the NT-proBNP levels in RA patients without cardiac symptoms before and after 24 weeks of treatment.

Methods: RA patients with active disease with an inadequate clinical response to non biologic DMARDs and non-RA healthy control were enrolled. Exclusion criteria were diabetes, previous cardiovascular events, cardiopathy, hypertension and renal disease. The RA patients received TCZ once a month for 24 weeks. Serum NT-pro BNP levels were measured at baseline and week 24. Clinical and biological monitoring was performed at baseline and 24 weeks after the start of TCZ treatment. We explored the associations between NT-pro BNP and the RA disease activity score for Simple Disease Activity Index (SDAI) scores. The anti-citrullinated protein antibody (ACPA) titre was divided into high and low levels using a cut-off of 30 units/mL. Fisher test and multivariable linear regression analyses were performed to identify the correlations.

Results: 90 patients (mean age, 56.4 ± 10.4 years; 85% female) and a matched 30-patient control group (mean age 55.6±3.4 years; 86% female) were enrolled. The SDAI at baseline was 22.5 ± 12.7. The 24-week SDAI scores were significantly lower than those at baseline ($p = 0.03$). The NT-proBNP levels at baseline were significantly higher than control group ($p=0.04$). The median (interquartile range) levels of the NT-proBNP significantly decreased from baseline (121.78 [52.81–230.24] pg/mL) to 24 weeks (57.13 [29.50–128.67] pg/mL, $p = 0.004$) following TCZ treatment. NT-proBNP levels in the high ACPA group tended to be higher than the low ACPA group ($p = 0.07$). The change in NT-proBNP levels was significantly correlated with the change in the SDAI score ($r = 0.455$, $p = 0.003$). After adjustment for age, gender, erythrocyte sedimentation rate (ESR), and RA duration, the association between the change in NT-proBNP levels and the change in SDAI remained significant ($p = 0.023$).

Conclusion: This is the first study to report the effect of IL-6 blocking agent on circulating NT-proBNP levels in patients with active RA. Our results suggest that blocking IL-6 in patients with RA without cardiac symptoms does not increase but rather decreases circulating NT-proBNP levels by around 52%, which was also related to a reduction in disease activity. Our data also suggest that RA-specific autoimmunity against citrullinated proteins might relate to subclinical cardiac stress. TCZ treatment may influence the presence of subclinical left ventricular dysfunction or cardiac stress which may progress to overt CHF.

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1907

Clinical Evaluation of Anti-Aminoacyl tRNA Synthase Antibodies in Rheumatoid Arthritis Patients. Masakazu Matsushita, Ken Yamaji, Naoto Tamura and Yoshinari Takasaki. Juntendo University School of Medicine, Tokyo, Japan.

Background/Purpose: Anti-Jo-1 is an autoantibody that is specifically detected in the blood sera of patients with polymyositis/dermatomyositis (PM/DM). The corresponding antigen is known to be histidyl-tRNA synthase, an aminoacyl-tRNA synthase (ARS) localized to the cytoplasm. Recently, autoantibodies to other ARSs have been identified and patients with these antibodies have distinguishing clinical symptoms such as lesions of the lung or skin, a condition known as anti-ARS antibody syndrome. We measured anti-ARS antibodies in rheumatoid arthritis (RA) patients and evaluated its clinical characteristics.

Methods: At our hospital, 228 ambulatory RA patients were selected for the study. We evaluated the positive rate of anti-ARS antibodies in the blood sera of these patients. Anti-ARS antibodies were measured using the EUROLINE Myositis Profile 3 test system (EUROIMMUN Inc., Lubeck, Germany). Five anti-ARS antibodies can be measured using this kit: anti-OJ, anti-EJ, anti-PL-12, anti-PL-7, and anti-Jo-1 antibodies. For blood serum testing positive for any one of these antibodies, we performed an indirect immunofluorescence assay by using HEp-2 cells to determine whether a reaction occurred in the cytoplasm. We grouped the participants into anti-ARS antibody-positive and -negative groups, and evaluated age, gender, male-to-female ratio, anti-CCP antibodies, rheumatoid factor levels, presence of interstitial pneumonia (IP), and frequency of usage of methotrexate or biologics.

Results: Anti-ARS antibodies were detected in 6.1% (14 patients) of all RA patients. Specifically, anti-PL-7 antibodies were detected in 6 patients (2.6%), anti-EJ antibodies in 4 patients (1.8%), anti-PL-12 antibodies in 2 patients (0.9%), anti-OJ antibodies in 1 patient (0.4%), and anti-Jo-1 antibodies in 1 patient (0.4%). When the blood sera of these patients were allowed to react with HEp-2 cells by using the indirect immunofluorescence method, we detected staining in the cytoplasm of all patients. When we compared the anti-ARS antibody-positive and -negative groups, differences in age or gender were not observed. However, the frequency of interstitial pneumonia in the anti-ARS antibody-positive group was significantly higher ($P < 0.05$). A detailed investigation of the antibodies revealed that anti-PL-7 and anti-PL-12 antibodies were detected at a significantly higher level in patients with IP. Biologics were administered in 3 patients in the anti-ARS antibody-positive group; however, concomitant myositis or exacerbation of IP was not observed. No significant difference was observed between the positive and negative groups in terms of anti-CCP antibody values or rheumatoid factor levels.

Conclusion: Anti-ARS is an autoantibody that is detected specifically in PM/DM patients; however, we demonstrated that it is also detected in RA

patients. In particular, anti-PL-7 and anti-PL-12 antibodies were detected efficiently in RA patients with IP, suggesting that these autoantibodies are associated with IP. Our investigation showed that biologics could be administered safely to RA patients with anti-ARS antibodies.

Disclosure: M. Matsushita, None; **K. Yamaji**, None; **N. Tamura**, None; **Y. Takasaki**, None.

ACR Concurrent Abstract Session

Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy IV: Safety of Biologics and Small Molecules in Rheumatoid Arthritis - Cardiovascular and Other Systems

Monday, November 17, 2014, 4:30 PM–6:00 PM

1908

Pregnancy Outcomes in the Tofacitinib RA Safety Database through April 2014. A. Marren[1], Y. Chen[1], D. Frazier[2] and J. Geier[3]. [1]Pfizer Inc, Collegeville, PA, [2]Pfizer Inc, Groton, CT, [3]Pfizer Inc, New York, NY.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Its effect in pregnant women is of interest, as tofacitinib has been shown to be fetocidal and teratogenic in rats and rabbits at exposures 146 times and 13 times (respectively) the maximum recommended human dose. There are no adequate, well-controlled tofacitinib studies in pregnant women; per the RA clinical development program protocols, all studies exclude pregnant subjects and require use of highly effective contraception by females with child-bearing potential, and study treatment discontinuation if a subject becomes pregnant. To understand potential effects of tofacitinib, pregnancies in the RA clinical development program were reviewed.

Methods: Cases were identified from Pfizer's internal safety database through April 30, 2014, from interventional (one clinical study is ongoing; database not locked) and non-interventional studies, plus cases from post-marketing reporting. Cases were limited to females administered tofacitinib/placebo/blinded therapy at time of conception and/or fetal subjects exposed to tofacitinib/placebo/blinded therapy through maternal exposure. Potential duplicate cases were eliminated; remaining cases were reviewed for any pregnancy-related outcome and abnormalities, which were categorized as healthy newborns, spontaneous abortion, medical termination, still-birth, pending, or lost to follow-up.

Results: A total of 35 cases were identified. In the tofacitinib RA clinical studies of ~6,000 subjects with nearly 17,000 patient-years of follow-up, there were 32 cases of maternal tofacitinib exposure. Subject age ranged from 22 to 40 years. Of the 32 cases, 31 received tofacitinib; 13 had 5 mg BID, 1 had 5 mg QD, 12 had 10 mg BID, 2 had 20 mg QD, 1 had 15 mg BID, and 2 whose therapy at conception is still blinded. One subject received placebo/methotrexate (MTX). Ten of the 32 cases were also taking MTX. The pregnancy outcomes with tofacitinib were: 14 healthy newborns (including 1 low birth weight and 1 pre-term birth), 6 spontaneous abortions, 4 medical terminations, 1 still-birth (at approximately 17 weeks gestation), 1 congenital malformation of pulmonary valvar stenosis reported in a 32-year-old subject with diabetes and hypertension, 2 pending outcome, and 3 lost to follow-up; the placebo-treated subject experienced a spontaneous abortion. The remaining 3 cases receiving tofacitinib were reported from other data sources including 2 cases from 2 non-interventional clinical studies and 1 from post-marketing reporting. Fetal subjects had maternal exposure to tofacitinib. Of the 3 cases, 1 had a spontaneous abortion; outcomes were still pending for the other 2 cases.

Conclusion: Most cases with reported outcomes had healthy newborns. Adverse outcomes including spontaneous abortions and congenital malformation were observed in RA subjects who became pregnant during tofacitinib therapy. Pregnancy outcomes in subjects receiving tofacitinib will continue to be monitored through routine pharmacovigilance and via a post-approval safety study within the Organization of Teratology Information Specialists (OTIS) registry.

Disclosure: A. Marren, Pfizer Inc, 1, Pfizer Inc, 3; **Y. Chen**, Pfizer Inc, 1, Pfizer Inc, 3; **D. Frazier**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Geier**, Pfizer Inc, 1, Pfizer Inc, 3.

1909

Incidence of Congestive Heart Failure in Subjects with Rheumatoid Arthritis Receiving Anti-Tumour Necrosis Factor Drugs: Results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Alper van Sijl[1], Mamas Mamas[2], Mark Lunt[3],. BSRBR Control Centre Consortium[4], Kath Watson[5], Deborah P. Symmons[4] and Kimme L. Hyrich[6]. [1]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom, [2]Manchester Heart Centre, Manchester Royal Infirmary, Oxford Road, Manchester, UK; Institute of Cardiovascular Sciences, University of Manchester, Manchester, United Kingdom, [3]University of Manchester, Manchester, United Kingdom, [4]Arthritis Research UK Centre for Epidemiology, University of Manchester, Manchester, United Kingdom, [5]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [6]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom.

Background/Purpose: Subjects with rheumatoid arthritis (RA) are at a higher risk of developing cardiovascular (CV) disease compared to the general population, with an increased incidence of congestive heart failure (CHF) possibly mediated by chronic inflammation. Anti-tumour necrosis factor (TNFi) drugs might reduce the incidence of new CHF by supressing inflammation. However, TNFi are associated with a worsening of existing CHF. The aim of this analysis was to compare the incidence of CHF in subjects with RA treated with TNFi to that in those receiving non-biologic drugs (nbDMARDs).

Methods: Patients with a physician diagnosis of RA enrolled in the British Society for Rheumatology Biologics Register, a national prospective cohort study established in 2001 to monitor the long-term safety of TNFi. Potential CHF events were verified according to Framingham criteria by a cardiologist from death certificates and from clinical follow-up forms of consultants. New CHF which occurred within 6 months after another cardiac event (eg. myocardial infarction) was excluded. Risk of CHF was compared between the two cohorts using a Cox regression model, propensity scores adjusted. Subjects were censored at first episode of CHF, death, first missed dose of TNFi + 180 days, last returned clinician follow-up or 31/01/2014, whichever came first.

Results: A total of 87 validated first CHFs were analysed: 48 in 3,662 nbDMARD subjects and 39 in 12,397 TNFi-exposed subjects. After adjustment for differences in baseline characteristics, the hazard ratio (95%-confidence interval) of CHF in patients on TNFi compared to nbDMARD was: 0.31 (0.18–0.52). Similar results were found for analysis limited to first TNFi only and in patients without prior history of ischaemic heart disease.

Conclusion: No increased risk of CHF was observed in those patients selected for TNFi therapy compared to those receiving nbDMARD therapy. A reduced risk of CHF was noted in patients treated with TNFi.

Table. Association between exposure to TNFi and development of first CHF

	nbDMARD (n=3662)	TNFi (n=12397)
Years of follow-up per subject, median (IQR)	5.0 (2.5–7.7)	5.1 (1.9–8.0)
Person-years of exposure, pyrs	18 698	62 244
Number of verified CHFs, n (%)	48 (1.31)	39 (0.31)
Crude incidence rate of verified CHFs per 10 000 person-years (95%-confidence interval)	25.67 (19.53–34.40)	6.27 (4.58–8.58)
Risk of CHF between nbDMARD and TNFi		
- Unadjusted HR (95%-CI)	Referent	0.24 (0.16–0.37)
- Age- and gender adjusted HR (95%-CI)	Referent	0.47 (0.30–0.72)
- PD-adjusted HR (95%-CI)	Referent	0.25 (0.14–0.44)

Fully adjusted model by propensity score (PD) consisting of age, gender, DAS28, disease duration, HAQ, steroid use, NSAIDs, COXIBs, hypertension, diabetes mellitus, angina pectoris, myocardial infarction, smoking history and use of statins, antiplatelets, ACE-inhibitors, warfarin and digoxin.

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1910

Risk of Hypersensitiviy Among Medicare Patients with Rheumatoid Arthritis Who Were Taking Biologics. Huifeng Yun[1], Fenglong Xie[2], Lang Chen[2], James Lewis[3] and Jeffrey R. Curtis[2]. [1]University of Alabama at Birmingham School of Public Health, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Healthcare providers have been alerted to the potential drug hypersensitivity reactions (HSRs, an adverse drug reaction that are uncommon but may be severe and can result in mortality) in patients (pts) with RA, especially those receiving intravenously (IV) administered biologics. One case of a fatal HSR has been reported and associated with tocilizumab (TCZ). The risks of HSRs in population-based RA cohorts are unclear, as is understanding whether risks differ by specific agent. We compared drug-specific risks for HSR among RA pts enrolled in the US Medicare.

Methods: Using Medicare data from 2006–2011 for 100% of pts with RA, we identified new users of infliximab (INF), abatacept (ABA), rituximab (RIT), TCZ and injected biologics (e.g. anti-TNF therapy).For each biologic administration (Adm), follow up started on the date of drug infusion/injection and ended at the earliest date of: HSR, subsequent biologic Adm, death, coverage loss, 30-day follow-up period, or Dec 31, 2011. We identified HSR using validated claims-based algorithms in three settings: A) Inpatient (IP) or emergency departments (ER) for anaphylactic shock, B) Outpatient (OTP) for anaphylactic shock plus a diagnosis of bronchospasm, stridor, hypotension, epinephrine, injection of diphenhydramine and CPR (Disease and symptom list); C) IP or ER for unspecified allergy plus a diagnosis from the above disease and symptom list. We calculated the incidence rate (IR) of HSR for each biologic within 0–1, 2–14 and 15–30 days of Adm. Robust Poisson regression was used to compare the HSR risks across biologics adjusting for age, gender, Charlson comorbidity score, concomitant steroid (GCs) and methotrexate (MTX) use. Sensitivity analysis was conducted using a nested case-crossover design to reduce within-person confounding.

Results: We identified 429,565 biologic Adms or prescription fills among 54,902 new biologic users. Of these, 29.9% were for ABA, 4.5% RIT, 2.2% TCZ, 23.2% INF, 43.8% injected biologics. Of 137 HSR cases we identified during follow-up, 77% occurred in an IP setting, 17.5% ED and 5.5% OTP. Among 64 cases occurring within 1 day of biologic Adm, 33%, 13.2%, 59.4% were identified by criterion A, B, and C respectively. The IRs for HSR ranged from 3.0 to 337.2 per 1,000,000 person years across different biologics and timing of exposure. After adjustment, and using abatacept 15–30 days as the referent, ABA, INF, RIT and TOC infusions were associated a significant higher risk of HSR (Table). Concomitant GCs had significant positive association with HSR whereas MTX had a significant inverse association with HSR. Sensitivity analysis yielded similar results. There were no additional deaths occurring within 30 days aside associated with HSRs.

Conclusion: Among RA pts taking biologics, rituximab and tocilizumab were most strongly associated with HSRs within one day of administration. The absolute IR of HSR events for all biologic exposures were low.

Table. Events, absolute incidence rate and adjusted risk ratio of hypersensitivity reaction, by biologic exposures and timing of exposure

Biologic and Timing of Exposure	Events	Incidence rate per 1,000,000 person days	Adjusted Risk Ratio* (95% CI)
0–1 days			
Abatacept	<11	31.1	5.30 (2.05–13.7)
Infliximab	36	180.3	35.7 (17.2–74.3)
Rituximab	13	337.2	44.1 (18.9–103.5)
Tocilizumab	<11	316.2	47.2 (16.8–132.6)
2–14 days			
Abatacept	<11	3.0	0.52 (0.17–1.55)
Infliximab	14	11.0	2.17 (0.94–5.02)
Rituximab	<11	12.6	1.66 (0.45–6.14)
Tocilizumab	<11	8.3	1.23 (0.16–9.73)
15–30 days			
Abatacept	<11	5.8	1.00 (Ref)
Infliximab	12	8.7	1.76 (0.74–4.17)
Rituximab	<11	0.5	0.74 (0.09–5.84)
Tocilizumab	<11	1.2	1.18 (0.15–9.36)
0–30 days, any injectable anti-TNF	27	0.5	0.84 (0.40–1.80)

* Adjusting for age, gender, Charlson comorbidity score, concomitant steroid and methotrexate use

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Disease Modifying Anti-Rheumatic Drug Use and the Risk of Incident Hyperlipidemia in Patients with Early Rheumatoid Arthritis: A Retrospective Cohort Study. Rishi Desai, Wesley Eddings, KP Liao, DH Solomon and Seoyoung C. Kim. Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Rheumatoid arthritis (RA) increases patients' risk of developing cardiovascular diseases (CVD). Hyperlipidemia is an important CVD risk factor in the general population. The objective of this study was to compare the risk of incident hyperlipidemia in early RA patients after initiation of disease modifying anti-rheumatic drugs (DMARDs).

Methods: We conducted a cohort study in patients receiving their first RA diagnosis after at least 12 months without evidence of RA or DMARD prescription, using insurance claims data (2001–2012). Four mutually exclusive groups were defined based on DMARD initiation, TNF-α inhibitors $\pm$ non-biologic (nb) DMARDs, methotrexate $\pm$ non-hydroxycholorquine nbDMARDs, hydroxychloroquine $\pm$ non-methotrexate nbDMARDs, and other nbDMARDs only. The primary outcome was incident hyperlipidemia as defined by a diagnosis and a prescription for a lipid-lowering agent. For the subgroup of patients with laboratory results available, we analyzed change in lipid levels as the secondary outcome. Multivariable Cox proportional hazard models estimated the relationship between DMARD use and incident hyperlipidemia. Propensity scores (PS) were calculated to improve confounding control. PS decile-stratified analyses were performed for each pairwise comparison after asymmetrically trimming at 2.5th and 97.5th percentile of the PS distribution to address confounding by indication.

Results: Of the 17,145 RA patients included in the study, 364 developed hyperlipidemia. The incidence rates (95% confidence interval (CI)) for hyperlipidemia per 1,000 person-years were 30.7 (21.9–41.8) for TNF-α inhibitors, 28.9 (24.9–33.4) for methotrexate, 20.1 (16.3–24.6) for hydroxychloroquine, and 36.4 (26.5–48.7) for other nbDMARDs. The adjusted hazard ratios(HR) (95% CI) for hyperlipidemia were 1.41 (0.99–2.00) for TNF-α inhibitors, 0.81 (0.63–1.04) for hydroxychloroquine, and 1.33 (0.95–1.84) for other nbDMARDs compared with methotrexate in the full cohort, while 1.18 (0.80–1.73), 0.75 (0.58–0.98) and 1.41 (1.01–1.98), respectively in the PS trimmed cohort. In the subgroup analysis, hydroxychloroquine use showed significant reduction in low density lipoprotein (−8.9 mg/dl, 95% CI −15.8, −2.0), total cholesterol (−12.3 mg/dl, 95% CI −19.8, −4.8) and triglyceride (−19.5 mg/dl, 95% CI −38.7, −0.3) from baseline compared with methotrexate.

Conclusion: Based on both a reduced adjusted HR for incident hyperlipidemia and a reduction in lipid levels, use of hydroxychloroquine may be associated with a lower risk of hyperlipidemia among early RA patients. A possible increase in the risk of hyperlipidemia in TNF-α inhibitor initiators was noted in our primary analysis, but not in the PS stratified analysis. These findings suggest a complex relationship between DMARDs, inflammation and lipids.

Table. Relative risk of hyperlipidemia in patients with early rheumatoid arthritis based on DMARD use

Exposure	Unadjusted HR (95% CI)	Multivariate adjusted* HR (95% CI)	Propensity score adjusted** HR (95% CI)
Methotrexate	Reference	Reference	Reference
TNF-α inhibitors	1.08 (0.76–1.52)	1.41 (0.99–2.00)	1.18 (0.80–1.73)
Hydroxychloroquine	0.70 (0.54–0.89)	0.81 (0.63–1.04)	0.75 (0.58–0.98)
Other nbDMARDs	1.25 (0.90–1.74)	1.33 (0.95–1.84)	1.41 (1.01–1.98)

*Adjusted for age, gender, cardiovascular risk factors and comorbidities, cardiovascular drug use, pain medications and healthcare use in the prior year in a cox proportional hazard regression model.
** Propensity score decile stratification was used to derive hazard ratios after asymmetrically trimming at 2.5th and 97.5th percentile of the PS distribution.

Disclosure: R. Desai, Biogen Idec, 1; **W. Eddings**, None; **K. Liao**, None; **D. Solomon**, None; **S. C. Kim**, Pfizer Inc, 2.

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Tocilizumab Therapy for Rheumatoid Arthritis Patients with Chronic Renal Insufficiency. Shunsuke Mori, NHO Kumamoto Saishunsou National Hospital, Kumamoto, Japan.

Background/Purpose: Renal involvement is relatively common in rheumatoid arthritis (RA) patients. Recent randomized controlled trials of anti-tumor necrosis factor-α (anti-TNFα) showed that the concomitant administration of methotrexate (MTX) is superior to monotherapy. However, the dose of MTX must be reduced in RA patients with chronic renal insufficiency (CRI) because MTX elimination is delayed in these patients. In contrast, the ACT-RAY trials indicated that the efficacy of tocilizumab (TCZ) monotherapy is comparable with combination therapy with MTX. The present study was intended to evaluate the efficacy and safety of TCZ therapy in RA patients with CRI.

Methods: The subjects were all patients with RA who had started TCZ therapy at our hospital from April 2008 to December 2013. Pretreatment characteristics were compared between patients with and without CRI. Clinical disease activity index (CDAI) levels and hemoglobin values as well as adverse events were recorded during the follow-up period of the first 24 weeks. CRI was defined as an estimated glomerular filtration rate (eGFR) $<$ 60 ml/min for 3 months.

Results: A total of 105 patients were included in this study and among these.37 patients (35.2%) were diagnoses with CRI. Mean eGFR levels in the CRI group and in non-CRI group were 43.7 ml/min and 80.9 ml/min, respectively. Sixty percent of CRI patients and 70% of non-CRI patients were refractory to anti-TNFα agents. CRI patients were significantly older (75.3 years versus 62.0 years, $p < 0.0005$) and had longer RA duration (9.8 years versus 5.4 years, $p = 0.005$). There was no significant difference in the other RA-related markers between both groups. Approximately 85% of patients in each group showed high or median disease activity. Biopsy-proven amyloidosis was observed in one patient in the CRI group. Hypertension was observed at a significantly higher rate in the CRI group (81% versus 36.8%, $p < 0.0005$). Of note, serum levels of hemoglobin were significantly lower in CRI patients compared with non-CRI patients (11.2 g/dl versus 12.5 g/dl, $p < 0.0005$). Eighty-one percent of CRI patients received TCZ monotherapy, while 49% of non-CRI patients used MTX concomitantly with TCZ. Mean changes of CDAI at week 24 from baseline were 17.1 (26.7 to 9.6) in the CRI group and 17.5 (25.8 to 8.3) in the group without CRI. Rates of patients with low disease activity or remission at week 24 were 62.2 % of CRI patients and 55.9% of non-CRI patients. Mean hemoglobin levels were significantly increased over time during TCZ therapy. At week 24, mean increases of 1.2 g/dl (11.2 to 12.4, $p < 0.0005$) and 0.8 g/dl (12.5 to 13.3, $p = 0.005$) were observed in the CRI group and in the non-CRI group, respectively. Adverse events occurred in two patients without CRI (diverticulitis and acute cholecystitis). Neither serious adverse event nor aggravation of renal function was reported in the CRI group.

Conclusion: TCZ therapy was effective in reduction of disease activity and improvement of hemoglobin levels in RA patients with CRI. In addition, TCZ showed stable safety and tolerability profiles even in CRI patients.

Disclosure: S. Mori, Chugai Pharmaceutical Co., 8;

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Rosuvastatin Induced Carotid Plaque Regression in Patients with Inflammatory Joint Diseases: The RORA-As Study. Silvia Rollefstad[1], Eirik Ikdahl[1], Jonny Hisdal[2], Inge C. Olsen[1], Ingar Holme[3], Hilde Berner Hammer[1], Knut T. Smerud[4], G Kitas[5], Terje R. Pedersen[6], Tore K. Kvien[7] and Anne Grete Semb[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Uslo University Hospital-Aker, Oslo, Norway, [3]Oslo University Hospital, Oslo, Norway, [4]Smerud Medical Research International AS, Oslo, Norway, [5]The Dudley Group of Hospitals NHS Foundation Trust, Dudley, United Kingdom, [6]University of Oslo, Oslo, Norway, [7]PsAID taskforce, EULAR, Zurich, Switzerland.

Background/Purpose: Patients with rheumatoid arthritis (RA) and carotid artery plaques (CP) have increased risk of acute coronary syndromes. Statin treatment with low density lipoprotein cholesterol (LDL-c) goal $\leq$ 1.8 mmol/L is recommended for patients with CP in the general population. In the **RO**suvastatin in **R**heumatoid **A**rthritis, **A**nkylosing **S**pondylitis and other inflammatory joint diseases (**RORA-AS)** study, the aim was to evaluate the effect of 18 months intensive rosuvastatin treatment on change in CP height.

Methods: Eighty-six patients (60.5% female) with CP and IJD [RA (n=55), ankylosing spondylitis (n=21) and psoriatic arthritis (n=10)] were treated with rosuvastatin to obtain LDL-c goal. CP height was evaluated by B–mode ultrasound.

Results: Age was 60.8±8.5 years (mean±SD). At baseline, median number and height of CP was 1.0 (range 1–6) and 1.80 mm (IQR 1.60, 2.10), respectively. Change in CP height after 18 months rosuvastatin treatment was −0.19±0.35 mm (p<0.001). Baseline and change in LDL-c was 4.0±0.9 mmol/L and −2.3±0.8 mmol/L (p<0.001). Mean LDL-c level during 18 months rosuvastatin treatment was 1.7±0.4 mmol/L (area under the curve). The degree of CP height reduction was independent of the LDL-c level exposure during the study period (p=0.36) (adjusted for age/gender/blood pressure)(Fig. 1a). Attainment of LDL-c ≤ 1.8 mmol/L or the change in LDL-c did not influence the degree of CP height reduction (p=0.44 and p=0.46, respectively) (Figure 1b). The higher the CP at baseline - the larger height reduction after 18 months with rosuvastatin treatment (p< 0.001) (Fig. 2). Disease activity during the study period measured by DAS28 (area under the curve) was inversely associated with change in CP height (p=0.02), so that patients with the highest disease activity had the smallest change in CP height and vice versa.

Conclusion: This is the first clinical study showing that intensive lipid lowering with statin induced regression of atherosclerosis in patients with IJD. Our results indicate that disease activity may influence the effect of anti-atherosclerotic treatment.

Figure 1

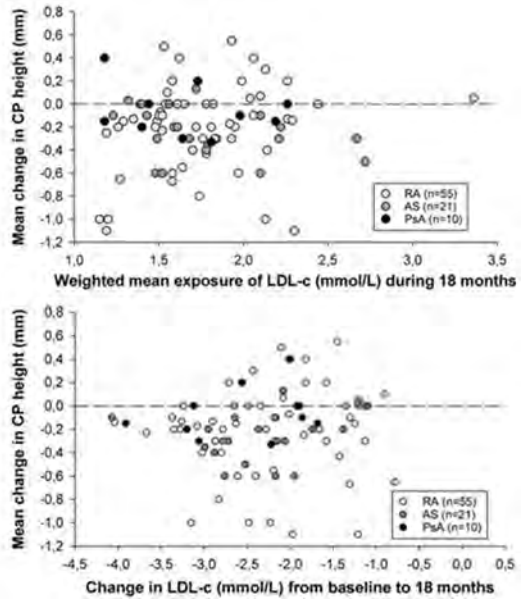
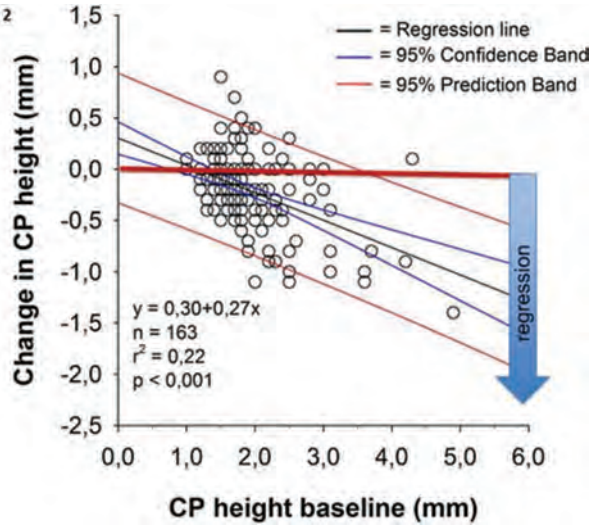


Figure 2



Disclosure: S. Rollefstad, None; **E. Ikdahl**, None; **J. Hisdal**, None; **I. C. Olsen**, None; **I. Holme**, None; **H. B. Hammer**, None; **K. T. Smerud**, None; **G. Kitas**, None; **T. R. Pedersen**, None; **T. K. Kvien**, None; **A. G. Semb**, None.

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IL-17A Deficiency Promotes Periosteal Bone Formation in a Model of Inflammatory Arthritis. Anita T. Shaw[1], Yukiko Maeda[1], Catherine Manning[1] and Ellen M. Gravallese[2]. [1]University of Massachusetts Medical School, Worcester, MA, [2]UMass Memorial Medical Center, Worcester, MA.

Background/Purpose: Enthesial and periosteal bone formation in spondyloarthropathies (SpAs) are important sequelae of disease that contribute to patient morbidity. Anti-TNF therapies do not significantly alter progression of this debilitating process; therefore, new agents that inhibit both inflammation and bone formation are being sought. IL-17A contributes to inflammation in many diseases, including SpAs, and is a potential therapeutic target. IL-17A promotes osteoclastogenesis through induction of RANKL in synovial fibroblasts and by inducing expression of the proinflammatory cytokines TNF, IL-1 and IL-6. However, the effects of IL-17A on bone-forming osteoblasts (OB) have not been fully elucidated and data are conflicting as to whether it promotes or protects from bone formation. We investigated the impact of IL-17A on OB differentiation *in vitro* and determined its role on bone formation in an *in vivo* murine model of arthritis.

Methods: The effect of IL-17A on the Wingless (Wnt) signaling pathway, a critical pathway for OB differentiation, was determined using calvarial OBs from TOPGAL mice containing a reporter construct for Wnt signaling. Cells were cultured in the presence of IL-17A throughout differentiation and Wnt activity was determined. Calvarial OBs were also treated with IL-17A at early, mid and late stages of differentiation and qPCR analysis of Wnt signaling antagonist expression was performed. Periosteal bone formation is a prominent feature in the K/BxN serum transfer arthritis (STA) model. To determine the effects of IL-17A on OB function *in vivo*, STA was induced in IL-17A null and wild type mice. Periosteal bone formation was quantitated and ankle joints were also analyzed for erosion severity.

Results: Long-term culture of TOPGAL calvarial OBs with IL-17A suppressed Wnt signaling, as reflected by a reduction in Wnt reporter activity. In addition, preliminary staining with von Kossa demonstrated inhibition of matrix mineralization in these cells cultured with IL-17A. Expression of the Wnt antagonists dickkopf (DKK)1, DKK2, DKK3, secreted frizzled related protein (sFRP)2 and sFRP4 mRNA expression in calvarial OBs was reduced to one-fifth of baseline levels by treatment with IL-17A at an early stage of differentiation (day 7). However, inhibition was reversed by day 21 of differentiation. IL-17A null and wild type mice displayed similar clinical and histologic inflammation scores, as well as similar articular bone erosion scores. Importantly however, IL-17A null mice formed significantly more periosteal bone than wild type mice ($p < 0.05$).

Conclusion: IL-17A may promote OB differentiation in early stages by suppressing expression of antagonists of Wnt signaling. However, the net effect of long-term treatment of OBs with IL-17A is inhibition of differentiation. These *in vitro* findings are borne out *in vivo*, as mice lacking IL-17A develop a significantly greater amount of periosteal bone than wild type mice. However, deficiency of IL-17A did not affect inflammation or the degree of bone erosion in this model. These findings have potential clinical significance, as blocking IL-17A in patients with SpAs may further exacerbate the extent of periosteal bone formation.

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IL-17 Gene Transfer induces Myeloid Precursor Cells That Initiate Epidermal Hyperplasia Independently of IL-23R$^+$/CD4$^+$ and $\gamma\delta$ T Cells. Erika Suzuki, Ritu Sarin, Emanual Maverakis and Iannis E. Adamopoulos. University of California at Davis, Sacramento, CA.

Background/Purpose: IL-17 is elevated in both the lesional skin and arthritic joints of psoriatic arthritis (PsA) patients. Although the IL-23/IL-17 axis has been linked with PsA pathology the direct effect of IL-17 on myeloid cells in PsA is elusive.

Methods: We performed gene transfer of IL-17 and GFP control by hydrodynamic delivery of minicircle (MC) DNA in control (C57BL/6) mice and mice treated with topical imiquimod. The psoriatic features were analyzed and scored for disease progression histologically. Further phenotypic analysis of cell populations was performed by flow cytometry, RT-qPCR, and *in vivo* imaging using nanoprobes. Characterization of molecular pathways was also performed in *Il23r*$^{-/-}$*Rag*$^{-/-}$ and *Tcrd*$^{-/-}$ transgenic mice.

Results: We have identified a unique IL-17R^{hi}CD11b$^+$Gr-1^{hi} cell subset induced by IL-17 that is associated with epidermal hyperplasia. Specifically 4 days post-IL-17 gene transfer we observed evidence of exacerbated epidermal hyperplasia, acanthosis, parakeratosis and Munro microabscess formation that were absent in GFP control mice. Gene expression of keratinocyte proliferation and inflammation biomarkers such as *Keratin 16 (K16), S100a7, S100a8, Cxcl1, Cxcr2* and *Ltb4r1* were consistently elevated post-IL-17 gene transfer and this correlated with an increase of Cxcl1 (a neutrophil chemoattractant) in the serum. Utilizing *Il23r*$^{-/-}$*Rag*$^{-/-}$ and *Tcrd*$^{-/-}$ mice, we demonstrated that genetic ablation of *IL-23r*, or the complete absence of T, B and $\gamma\delta$ T cells did not affect the pathologic features induced by IL-17. On the contrary, depletion of CD11b$^+$Gr-1^{hi} cells resulted in a complete rescue of skin pathology as evidenced by histology and gene expression.

Conclusion: Herein we demonstrate that IL-17 induces the expansion of an IL-17R^{hi}CD11b$^+$Gr-1^{hi} pathogenic cell subset, which is directly responsible for inducing a constellation of features that resemble human psoriatic disease. Collectively our data underscore the importance of innate immune cells in the pathogenesis of PsA and paves the way for the design of novel therapeutics to combat this disabling condition.

Disclosure: E. Suzuki, None; **R. Sarin**, None; **E. Maverakis**, None; **I. E. Adamopoulos**, None.

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Stromal Overexpression of Transmembrane TNF Induces Spa-like Arthritis and Spondylitis in Mice. Leonie M. van Duivenvoorde[1], Melissa N. van Tok[1] and Dominique L. Baeten[2]. [1]Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: The immunopathology of spondyloarthritis (SpA) is determined by inflammation and structural damage, in particular osteoproliferation, of axial and peripheral joints. The failure of TNF blockers to prevent ongoing osteoproliferation raised the concept that inflammation and osteoproliferation are uncoupled processes in SpA. However, inflammation and osteoproliferation are linked in HLA-B27 tg rats, high CRP is associated with radiographic progression in axial SpA, and NSAID treatment can retard osteoproliferation. Here, we propose that inflammatory mediators distinct from soluble TNF can drive pathologic osteoproliferation in SpA. Based on our observations on soluble versus transmembrane TNF (tmTNF) expression in SpA synovitis, we explored if and how tmTNF drives experimental spondyloarthritis.

Methods: tmTNF mice (TgA86)[1], provided by Dr Kollias (Athens), were studied clinically over time for arthritis and spondylitis development. At 3, 6 and 8 months joints were collected and analyzed for inflammation and osteoproliferation. To assess the contribution of stromal versus hematopoietic tmTNF expression, tmTNF tg mice and WT mice were lethally irradiated and rescued by bone marrow of either WT or tmTNF tg mice. Mice were evaluated for 16 weeks until sacrifice for histologic analysis.

Results: tmTNF mice (100%; n>50) spontaneously developed arthritis, visualized by deformed joints and loss of grip strength, and spondylitis as evidenced by crinkled tails and hunchback formation, starting at 4 weeks of age and progressing over time. Analysis of 3 months old mice revealed that arthritis was characterized by inflammation of synovium and enthesis. Hypertrophic chondrocytes, as marker for osteoproliferation, were observed outside the bone in the connective tissue next to the inflammation. In spondylitis, inflammation was found in connective tissue located at the junction of the annulus fibrosus with the vertebral bone. Hypertrophic chondrocytes were observed at the edge of the vertebral body, in conjunction with the ongoing inflammation. X-ray images from 8 months old mice also revealed bridging of the tail vertebra. These typical SpA-like features were not observed in any of the non-transgenic littermates.

In the functional experiments, irradiated tmTNF tg mice receiving tmTNF tg BM developed arthritis and spondylitis with 100% incidence 3 weeks after BMT, albeit the arthritis was less severe than in non-irradiated tmTNF tg mice. Interestingly, tmTNF tg mice receiving WT BM also developed both arthritis and spondylitis with the same incidence, onset and severity as the control group. In sharp contrast, WT mice that received tmTNF tg BM did not develop any arthritis, and spondylitis occurred less frequently (66%) and later (10 weeks after BMT) than in the control group.

Conclusion: tmTNF overexpression induces experimental arthritis and spondylitis with radiographic and histologic proven new bone formation,

indicating that inflammatory mediators can indeed drive osteoproliferation. The data indicate the relevance of the transmembrane form of TNF and the role of the stromal compartment in the pathophysiology of SpA.

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Disclosure: L. M. van Duivenvoorde, None; **M. N. van Tok**, None; **D. L. Baeten**, None.

1917

IL-23 Expression and Activation of Autophagy in Synovium and PBMCs of HLA-B27 Positive Patients with Ankylosing Spondylitis. Barbara Neerinckx, Shea Carter and Rik Lories. KU Leuven, Leuven, Belgium.

Background/Purpose: IL-23 may play a key role in the pathogenesis of ankylosing spondylitis (AS). Some studies describe indeed increased serum levels of IL-23 in AS patients compared to healthy controls [1–3]. Recent evidence also shows enhanced IL-23 production in the gut of AS patients. This upregulation of IL-23 expression in the gut seems to be the result of activation of autophagy rather than of an activated unfolded protein response [4]. We investigated IL-23 expression and the role of autophagy *ex vivo* in the synovium and peripheral blood mononuclear cells (PBMCs) of HLA-B27 positive AS patients.

Methods: Synovial tissues were obtained by needle arthroscopy from actively inflamed knees from patients with AS (HLA-B27 positive; n=11), other forms of spondyloarthritis (SpA) (HLA-B27 positive; n=9 or HLA-B27 negative; n=10), rheumatoid arthritis (RA) (HLA-B27 positive or negative; n=10) or other inflammatory joint diseases ('non SpA/RA inflammatory joint disease') (HLA-B27 positive or negative; n=10)) and from multiple organ donors as non-inflammatory controls (HLA-B27 negative; n=10). PBMCs were isolated from whole blood samples taken from patients with AS (HLA-B27 positive; n=17), RA (HLA-B27 negative; n=19) and healthy controls (HLA-B27 negative; n=12). None of the patients was treated with TNF inhibitors. Expression of IL-23 and autophagy genes in all samples was analyzed using quantitative RT-PCR (SYBR green) with primers for *IL23p19* and autophagy genes (*ATG16L1, IRGM, MAP1LC3A, ATG5, HSPA8* and *HSP90AA1).*

Results: In the synovial tissues, *IL-23p19* expression was consistently increased in the inflammatory samples compared to the non-inflammatory samples. There was no difference in *IL-23p19* expression in AS patients as compared to non-AS SpA and other inflammatory diseases. In PBMCs, surprisingly, the expression of *IL-23p19* was significantly lower in AS patients than in healthy controls with expression levels in RA patients extending over the whole range between AS patients and controls. No difference in expression of autophagy associated genes was found in the synovial tissues between the groups. In the PBMCs, there was a lower expression of *ATG16L1*, *IRGM* and *HSP90AA1* in AS patients compared to healthy controls. The expression of *MAP1LC3A*, *ATG5* and *HSPA8* was not statistically different between the three groups.

Conclusion: Notwithstanding the recent evidence in gut samples of AS patients, our data do not support evidence for higher IL-23 expression and activation of autophagy in synovium or PBMCs of HLA-B27 positive AS patients. The production of IL-23, possibly driven by autophagy, in AS patients seems to be a tissue specific phenomenon with an important role reserved for the gut.

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Disclosure: B. Neerinckx, None; **S. Carter**, None; **R. Lories**, Pfizer, 2.

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IL23 Overexpression Demonstrates Gut-Joint Inflammation Link and Increased Expression of Spondyloarthopathy Associated Genes *In Vivo*. Donald Souza II, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT.

Background/Purpose: It has been well established that a close relationship exists between gut inflammation and spondyloarthropathies. Polymorphisms in the receptor for IL23 are associated not only with ankylosing spondylitis (AS) but also with inflammatory bowel disease (IBD). AS and IBD are both associated with elevated concentrations of serum IL23. Moreover.IL23 is active at mucosal surfaces and is produced by the gut, suggesting that the intestinal mucosa could be a key site of IL23 production in spondyloarthropathy. Minicircles are small circular DNA vectors which can be used in vivo to provide for long-term transient expression of transgenes without the risk of immunogenic responses that can be caused by the bacterial backbone in standard plasmids. Recently, Sherlock et al. demonstrated that overexpression of IL23 using minicircle DNA technology in the hepatocytes of mice was sufficient to lead to severe entheseal inflammation with infiltration by macrophages and neutrophils, and expansion of periosteal osteoblasts. Disease features included sacroiliitis, axial enthesitis, psoriasis, and aortic root inflammation. However, no gut phenotype was reported.

Methods: IL23 minicircle DNA vector or empty vector was administered via hydrodynamic injection to adult B10RIII female mice obtained from Jackson Labs (Bar Harbor, ME). A volume equivalent of 10% body mass (~2mL) was injected IV to the lateral tail vein in 6–8 seconds to facilitate cellular uptake of material. Mice were monitored daily for signs of arthritis and skin lesions. Arthritis severity was graded using a 0–4 score per paw for a maximum score of 16. Upon sacrifice (14 and 28 days), serum was collected for cytokine analysis, paw and gut tissue for histologic assessment (Bolder Biopath, Boulder, CO), skin, entheses and gut tissues for mRNA analysis via RT-PCR.

Results: IL-23 overexpression using minicircle DNA transfection resulted in a similar rapid and pronounced rheumatic and skin phenotype as previously reported (e.g. development of synovitis, enthesitis, and psoriatic-like skin lesions). In addition, sustained and elevated serum concentration of IL23 is associated with intestinal inflammation. Significant and region specific gut expression of IL23 pathway associated genes IL17A, IL17F & IL22 induced by IL23 overexpression was demonstrated, with maximal expression seen in proximal ileum and lesser expression seen in colon. Furthermore, ileum expression of disease associated genes S100A8 and REG3g were increased with IL23 overexpression versus empty vector control. Histologic analysis also demonstrated region specific gut pathology, with colons displaying none to minimal inflammation and ileums displaying minimal to moderate inflammation with crypt abscesses, mild hyperplasia and inflammatory infiltrates in the lamina propria, characteristic of features seen in IBD.

Conclusion: These studies demonstrate that minicircle DNA transfection offers a powerful tool for interrogating molecular and tissue specific mechanisms in vivo and provides opportunities to dissect the influence of the IL-23 pathway on the inflammatory gut-joint link seen in spondyloarthropathies.

Disclosure: D. Souza II, Boehringer Ingelheim, 3;

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HLA-B27 Expression Shapes the Intestinal Microbiota. Mark Asquith[1], Phoebe Lin[1], Tejpal Gill[2], Justine Debelius[3], Patrick Stauffer[1], Sean Davin[1], Gail Ackermann[3], Robert A. Colbert[2], Rob Knight[3] and James Rosenbaum[4]. [1]Oregon Health and Science University, Portland, OR, [2]NIAMS/NIH, Bethesda, MD, [3]University of Colorado Boulder, Boulder, CO, [4]Legacy Hospital, Portland, OR.

Background/Purpose: The intestinal microbiota plays a central role in both health and disease. Beyond shaping local immune responses in the gut, it is increasingly clear that the microbiota also influences immune responses in the periphery. With respect to spondyloarthopathies (SpAs), the development of reactive arthritis following enteric infection and the resistance of germ-free animals to disease supports its contribution to pathogenesis. In this study we used the HLA-B27 transgenic rat model to test the hypothesis that expression of HLA-B27, a key SpA risk allele, shapes the intestinal microbiome and may contribute to B27-associated spondyloarthropathy.

Methods: We used both 16s sequencing and quantitative real-time PCR to analyze the microbiota community structure of WT and B27+ rats. Samples were collected from ileum, cecum and colon of rats during the post-weaning period (3–6 wks), at disease onset (8–12 wks) and after the establishment of disease (15+ weeks). Samples were collected from multiple rat lines expressing the HLA-B27 transgene, including those on the Fischer, Lewis and DA backgrounds.

Results: We identified a number of B27-dependent changes to the intestinal microbiome, including eight operational taxonomic units (OTUs) that were more abundant in the microbiota of B27 animals relative to controls on all three backgrounds examined. These included *Bacteroides, Clostridia* and *Lactobacilli spp.* Notably, segmented filamentous bacteria (SFB) were a dominant member of the ileal microbiota of disease-susceptible Lewis and Fischer rats but largely absent in disease-resistant DA rats. Mucus-degrading bacterium *Akkermansia muciniphila* was upregulated ~300 fold in B27 vs WT animals in disease-susceptible rats on the Fischer background. Many of these changes were not evident during the post-weaning period.

Conclusion: HLA-B27 expression strongly modulates the intestinal microbiota and B27-dependent changes were observed in all tissue sites examined. This provides compelling rationale to functionally examine the

contribution of defined bacteria to B27-mediated SpA and to identify their association with disease in humans. The strong age-dependent effects on the microbiota indicate this is a critical consideration for such studies.

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ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Biomarkers in Systemic Lupus Erythematosus
Monday, November 17, 2014, 4:30 PM–6:00 PM

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Predicting SLE Disease Activity in the Next Year Based on Measures of Four Gene Transcripts and Two Proteins. Laurence S Magder[1], Eric Zollars[2], Jadwiga Bienkowska[3], Chris Stebbins[4], Carrie Wager[4], Linda Burkly[4], Nicolas Wisniacki[5], Ann Ranger[4] and Michelle Petri[2]. [1]University of Maryland School of Medicine, Baltimore, MD, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Biogen Idec Inc., Cambridge, MA, [4]Biogen Idec, Cambridge, MA, [5]Formerly with Biogen Idec, Cambridge, MA.

Background/Purpose: Multiple gene transcripts and proteins in blood or urine have been observed to correlate with disease activity in SLE. However some observed associations might be spurious, due to confounding by correlation with other biomarkers or patient characteristics. In this study, we explored the relationship between six proposed biomarkers and SLE activity over a 1 year period while controlling for potential confounding variables.

Methods: At an initial visit, two proteins and four gene transcripts or signatures were measured in 280 SLE patients. Levels of the BAFF gene transcript, plasma cell (PC) gene signature, IFN gene signature, and an LDG-associated Neutrophil gene signature were assessed in PAXgene-preserved peripheral blood by global microarray and qPCR. For proteins, BAFF was measured in serum and TWEAK in urine (both by ELISA). Disease activity during the next year was quantified by SELENA-SLEDAI modified to exclude complement and dsDNA. Repeated measures linear regression models were fit to determine which markers were predictive of disease activity over a one year period, controlling for age, race, sex, and other markers. Non-linear relationships between biomarker levels and disease activity were also explored.

Results: In univariate analyses, all markers analyzed except BAFF protein were significantly associated with future disease activity. After controlling for race, the PC signature was no longer significantly associated. After controlling for BAFF mRNA levels, the IFN signature was no longer significantly associated. Controlling for sex, race, and other biomarkers we found that: 1) a 1 standard deviation (SD) increase in BAFF was associated with a mean SLEDAI increase of 0.26 in the follow-up ($p=0.0034$), 2) those patients within the top 15% of the Neutrophil gene signature expression had a 0.66 higher mean SLEDAI during follow-up ($p=0.0056$), and 3) the relationship between the SLEDAI score and urinary TWEAK protein was constant until the 85th percentile of TWEAK after which a 1 SD increase in TWEAK was associated with a 0.58 increase in mean SLEDAI ($p=0.0006$). In a similar analysis focusing on renal disease activity, a 1 SD increase in the IFN signature was associated with a mean renal SLEDAI increase of 0.11 ($p=0.04$). The Neutrophil signature remained significant at a similar level as for overall disease activity, and the relationship between renal SLEDAI score and urinary TWEAK was linear with a 1 SD increase in TWEAK being associated with a 0.25 increase in mean renal SLEDAI ($p<0.0001$).

Conclusion: BAFF gene transcript, LDG-associated neutrophil gene signature, and high levels of urinary TWEAK appear to be independently and additively associated with disease activity. Our results suggest that the association between IFN and overall disease activity is due to the association between IFN and BAFF. Our results also suggest that an observed association between PC and disease activity is due to confounding by race. Thus, given that biomarkers are correlated with each other and other risk factors for disease, it is important to adjust for confounding when assessing biomarker/disease relationships.

Disclosure: L. S. Magder, None; **E. Zollars**, Biogen Idec, 2; **J. Bienkowska**, Biogen Idec, 3, Biogen Idec, 1; **C. Stebbins**, Biogen Idec, 3; **C. Wager**, Biogen Idec, 3, Biogen Idec, 1; **L. Burkly**, Biogen Idec, 2; **N. Wisniacki**, Biogen Idec, 3; **A. Ranger**, Biogen Idec, 3; **M. Petri**, Biogen Idec, 2.

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The Deposition of Complement C4d Split Product on Platelets and Erythrocytes Correlate with Disease Activity and Improvement in Systemic Lupus Erythematosus. Joan T. Merrill[1], Aikaterini Thanou[1], Stan Kamp[1], John Conklin[2], Derren Barken[2] and Thierry Dervieux[2]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Exagen Diagnostics, Inc., Vista, CA.

Background/Purpose: We sought to evaluate the usefulness of cell bound complement activation products (C4d deposition on erythrocytes [EC4d] and platelets [PC4d]) in the monitoring of disease improvement in systemic lupus erythematosus (SLE).

Methods: 58 patients with SLE from the Oklahoma Lupus Cohort were evaluated at two visits (baseline and follow-up) with the stipulation that there must be at least mild/moderate disease activity, in the clinician's opinion, at the first visit. Standard of care treatments were given. Clinical assessments included the Systemic Lupus Erythematosus Disease Activity Index without the complement and anti-dsDNA descriptors (non serologic SLEDAI or ns-SLEDAI) and the British Isles Lupus Assessment Group (BILAG 2004) index. Serum C3 and C4 levels were measured with nephelometry. EC4d and PC4d were determined using flow cytometry (expressed as mean fluorescence intensity [MFI], and natural log transformed). Statistical analysis included linear regression, and multivariate linear mixed effect models using a random intercept and fixed slope.

Results: At baseline, mean ns-SLEDAI score was 6.4 ± 0.4 while the cumulative BILAG multiorgan score was 10.3 ± 0.9. At baseline, C3 and C4 levels were negatively associated with disease activity using the ns-SLEDAI score ($p<0.04$) but less consistently with the BILAG index score ($p>0.06$). Baseline natural log transformed EC4d and PC4d levels were both positively and significantly associated with the SLEDAI and BILAG scores ($p<0.05$). At the time of the follow-up visit (median 1.5 month, range 1–9 months from the baseline visit), there was a significant decrease in the SLEDAI (average decrease -2.4 ± 0.4) and BILAG (average decrease -3.1 ± 0.9) compared to baseline with linear mixed effects models indicating greater clinical improvement associated with the time to follow-up visit (Table). After adjusting for the time to follow-up, linear mixed effects model analysis revealed that the change in C3 or C4 levels correlated with the change in BILAG index scores ($p<0.05$) but less well with the ns-SLEDAI score ($p>0.10$). In contrast, the change in EC4d and BC4d correlated with the clinical change on both instruments ($p<0.03$). Finally, multivariate analysis of the change in the BILAG index score with PC4d, serum C3 and C4 as predictors (after adjusting for the time to follow-up) revealed that PC4d was associated with change in disease activity (slope estimate$=1.80\pm0.76$; $p=0.02$) while C3 and C4 were not ($p>0.7$).

Conclusion: These pilot findings suggest that cell bound complement measures could provide a sensitive marker for SLE disease improvement which might be useful for early optimization of treatment dosing.

Table. Linear Mixed Effects Model Estimates

	Non serologic SLEDAI score	BILAG Index score
Months since baseline	0.66 ± 0.18 $p<0.01$	1.12 ± 0.36 $p<0.01$
Complement C3 (mg/dL)	-0.02 ± 0.01 $p=0.12$	-0.05 ± 0.02 $p=0.02$
Complement C4 (mg/dL)	-0.06 ± 0.03 $p=0.11$	-0.13 ± 0.06 $p=0.04$
EC4d (Log_e net MFI)	$+0.88 \pm 0.41$ $p=0.04$	1.8 ± 0.8 $p=0.03$
PC4d (Log_e net MFI)	$+0.83 \pm 0.32$ $p=0.01$	2.1 ± 0.6 $p<0.01$

Disclosure: J. T. Merrill, Exagen, 2; **A. Thanou**, Exagen, 2; **S. Kamp**, Exagen, 2; **J. Conklin**, Exagen, 3; **D. Barken**, Exagen, 3; **T. Dervieux**, Exagen, 3.

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Hydroxylchloroquine Use Is Associated with Decreased Soluble TNF Receptor Levels in SLE Patient Samples. Rufei Lu[1], Adam Przebinda[1], Melissa E. Munroe[2], Joel M. Guthridge[2], Joan T. Merrill[2] and Judith A. James[2]. [1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disorder with a waxing and waning clinical course. Hydroxychloroquine (HCQ) is a well-tolerated and effective antimalarial medication which decreases disease flares and delays damage accrual in SLE. Additionally, a pre-disease study has shown that HCQ can potentially be a useful preventative therapy for delaying the onset of SLE. The exact mechanism by which HCQ might delay disease onset or flares is not well understood. One major obstacle of HCQ mechanistic studies is the confounding effects from other major immune modulating therapies used by SLE

patients. Our goal is to elucidate the effects of HCQ on cellular changes and circulating soluble mediator concentration without the confounding effects of other major immunosuppressants (IS) in human lupus patients *in vivo*.

Methods: As part of the Biomarkers of Lupus Disease (BOLD) study, 103 patients donated baseline blood samples of whom 41 had transient IM steroid therapy, then all IS and some hydroxychloroquine treatments stopped. Patients were followed until flare. Eligibility criteria included (> 4 ACR SLE classification criteria and SLEDAI > 6 or BILAG ≥ 2 B or 1 A scores. Cellular immunophenotyping and soluble mediators, including 52 cytokines, chemokines, and soluble receptors, were measured over time using xMAP multiplex technology and sandwich ELISA. Significant differences were determined using non-parametric tests. A longitudinal analysis was performed using mixed generalized linear models.

Results: At baseline, SLE patients taking HCQ (n=27) had significantly lower levels of soluble TNFR I [median, 112.67 pg/mL; interquartile range (IQR), 103.5 –144.6 pg/mL] and TNFR II (median, 318.6 pg/mL; IQR, 266.8 – 374.8 pg/mL) compared to SLE patients not taking HCQ (n=10) (TNFR I, median, 186.63; IQR, 120.09–301.44; TNFR II, median 519.6; IQR, 332.16–641.00; p-value <0.05). In addition to the soluble TNFRs, SLE patients taking HCQ had significantly lower frequency of CD194hi Naïve B cells population (median, 1.54%; IQR, 0.15% - 5.48%) compared to SLE patients not taking HCQ (median, 5.57%; IQR, 2.03% - 13.19%; p-value < 0.05). SLE patients that stayed on HCQ during the six month study (n=17) retained their low levels of TNFR II. Patients who had never taken HCQ or were taken off of HCQ (n=20) showed a significant reduction in their TNFR II levels at the time of the next flare (p-value <0.05). TNFR II levels did remain higher than those observed in individuals that remained on HCQ.

Conclusion: HCQ may contribute to disease suppression via an effective reduction in soluble TNF and other chemokine receptor levels. These findings suggest a likely focus for further pathophysiologic studies of SLE.

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Vitamin D Restores Lupus Myeloid Angiogenic Cell Function Via Down-Regulation of IP-10/CXCL-10. John A. Reynolds[1], David W. Ray[2], Yvonne Alexander[3] and Ian N. Bruce[4]. [1]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, United Kingdom, Manchester, United Kingdom, [2]Institute of Human Development, The University of Manchester, Manchester, United Kingdom, [3]Manchester Metropolitan University, Manchester, United Kingdom, [4]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Endothelial repair is important for the maintenance of vascular integrity and is impaired in patients with SLE. Myeloid angiogenic cells (MACs) contribute to endothelial repair via paracrine secretion of pro-angiogenic factors. These cells express vitamin D receptors (VDR) and so may be modulated by vitamin D status. Given the prevalence of vitamin D deficiency in SLE we aimed to determine whether vitamin D could restore MAC function in lupus.

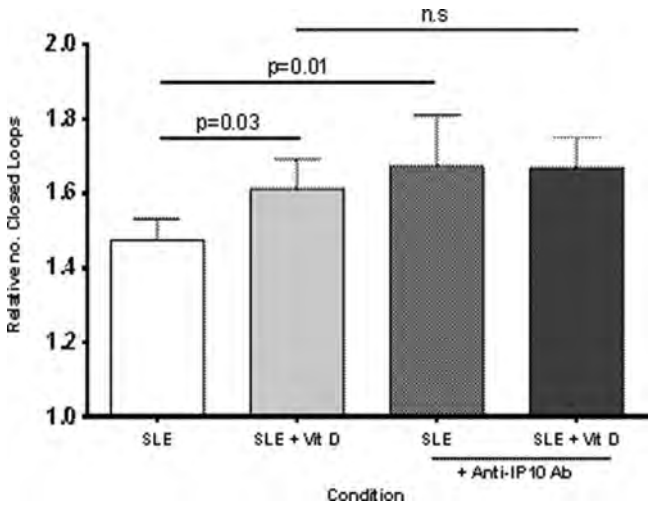
Methods: SLE patients were screened for vitamin D deficiency (25(OH)D<20ng/ml) using LC-MS and deficient patients were treated with high-dose cholecalciferol for 3 months. Myeloid angiogenic cells (MACs) were cultured from PBMCs of vitamin D deficient lupus patients (or healthy controls, HC) for 7 days. $1,25(OH)_2D_3$ (calcitriol) 10nM or vehicle was added at day 1 and replaced when the media was changed. Myeloid marker expression was measured using RT-qPCR. MAC migration towards SDF-1 was assessed using Transwell assays. Conditioned media from MACs was added to human aortic endothelial cells (HAoECs) on Matrigel for 14 hours and the resulting network analysed. Anti-IP-10 antibody was used to block the effects of IP-10 on network formation. Image analysis of network density (number of closed loops) was performed offline using ImageJ software. IP-10 was measured in the conditioned media by ELISA.

Results: Vitamin D deficient SLE patients had an increased number of MACs compared to controls (p=0.04). Despite this, these cells had impaired migratory capacity (p=0.006) and a trend toward reduced angiogenic capacity (p=0.13). Culture with vitamin D had no effect on lupus MAC migration.

Vitamin D significantly increased the number of MACs *in vitro*, and *in vivo* after the patients were treated (p=0.04 and p=0.03 respectively). MACs expressed surface markers consistent with M2 macrophages. The expression CD206 and CD68 was significantly increased in SLE and reversed by vitamin D.

HAoEC network formation was not affected by vitamin D directly but media from vitamin D-treated MACs significantly increased angiogenesis toward that seen in HCs (p=0.01). There was no correlation between MAC number and angiogenesis. IP-10 has previously been reported to be anti-angiogenic and vitamin D significantly reduced IP-10 expression by MACs (p<0.001). Blockade of IP-10 in the angiogenesis model restored the angiogenic capacity of MACs (figure).

Conclusion: MACs are important for endothelial repair and are dysfunctional in SLE. The addition of vitamin D *in vitro* restores the phenotype of the cells towards that of healthy subjects. Lupus MACs show reduced angiogenic capacity and vitamin D restores this via the down-regulation of the anti-angiogenic cytokine IP-10. Restoration of endothelial repair mechanisms is an important target to reduce vascular damage in SLE and vitamin D is a novel agent to improve MAC function.



Disclosure: J. A. Reynolds, None; **D. W. Ray**, None; **Y. Alexander**, None; **I. N. Bruce**, None.

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Cell Bound Complement Activation Products Have Higher Sensitivity Than Serum C3 and C4 Levels in Systemic Lupus Erythematosus. Rosalind Ramsey-Goldman[1], Richard Furie[2], Chaim Putterman[3], Anka Askanase[4], Jill P. Buyon[5], Kenneth Kalunian[6], W. Winn Chatham[7], E Massarotti[8], Kyriakos A. Kirou[9], A. Weinstein[10], Puja Chitkara[11], Susan Manzi[12], Joe Ahearn[13], Leilani Wolover[14], John Conklin[14], Tyler O'Malley[14], Claudia Ibarra[14], Derren Barken[14] and Thierry Dervieux[14]. [1]Northwestern University, Chicago, IL, [2]North Shore-LIJ Health System, Great Neck, NY, [3]Albert Einstein College of Medicine, Bronx, NY, [4]Colombia University, New York, NY, [5]New York University School of Medicine, New York, NY, [6]UCSD School of Medicine, La Jolla, CA, [7]University of Alabama at Birmingham, Birmingham, AL, [8]Brigham and Women's Hospital, Boston, MA, [9]Hospital for Special Surgery, New York, NY, [10]Washington Hospital Center, Washington, DC, [11]Sharp Memorial Hospital, San Diego, CA, [12]Division of Rheumatology, University of Pittsburgh School of Medicine, Pittsburgh, PA, [13]West Penn Allegheny Health System, Pittsburgh, PA, [14]Exagen Diagnostics, Inc., Vista, CA.

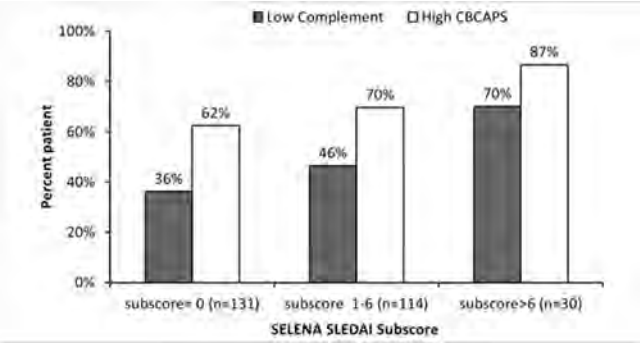
Background/Purpose: Elevated levels of cell bound complement activation products (CBCAPS) have been established as valuable biomarkers in the diagnosis of Systemic Lupus Erythematosus (SLE). In this study, we compared the sensitivity of CBCAPS to reduced complement C3 and C4 proteins levels in SLE. We also evaluated the relationship between elevated CBCAPS, reduced complement levels and SLE disease activity.

Methods: A total 288 SLE patients (mean age 41±1 years, 92% females) all meeting the 1982 American College of Rheumatology SLE classification criteria were enrolled. Serum complement C3 and C4 protein levels were determined using immunoturbidimetry while complement C4d fragment deposited on erythrocytes (EC4d) and B-lymphocytes (BC4d) were determined using flow cytometry (and expressed as net mean fluorescence intensity [MFI]). A group of 476 subjects comprising 274 patients with other rheumatic diseases and 202 healthy subjects was used to establish the cutoffs yielding 95% specificity for C3, C4, EC4d and BC4d. Among SLE subjects, disease activity was determined using the

Systemic Lupus Erythematosus Disease Activity Index SELENA Modification (SELENA-SLEDAI) subscore (without low complement and anti-dsDNA reactivity components). Difference in sensitivity (while controlling for similar specificity) was evaluated using $\chi 2$ test.

Results: Reduced C3 or C4 were both 32% sensitive for SLE (95% specific). In contrast, EC4d at a cutoff above 14 net MFI yielded 45% sensitivity (95% specific) while BC4d above 60 net MFI yielded 54% sensitivity (95% specific) ($p<0.002$). Elevated EC4d or BC4d (above their respective cutoffs as above) yielded a 22% higher sensitivity (66%) than reduced C3 or C4 (44%). Among 273 SLE patients with evaluable SELENA-SLEDAI subscores, the median subscore was 1 (range 0–23). Higher level of disease activity resulted in a higher proportion of patients testing positive for elevated CBCAPS ($p=0.027$) and reduced complement ($p=0.002$) (**Figure**). Among SLE with less active disease (SELENA-SLEDAI subscore=0) the difference in sensitivity was 26% greater for elevated CBCAPS (62%) than for reduced complement C3 or C4 (36%) ($p<0.001$). The difference in sensitivity remained higher (17%) for CBCAPS compared to low complement among SLE having a SELENA-SLEDAI subscore greater than 6 points but without reaching statistical significance ($p=0.21$).

Conclusion: Among all SLE patients, elevated CBCAPS have higher sensitivity than reduced C3 or C4. The higher sensitivity of CBCAPS is particularly significant among SLE with less active disease, and this supports the diagnostic utility of these markers for SLE



Disclosure: R. Ramsey-Goldman, None; **R. Furie**, Exagen, 2; **C. Putterman**, Exagen, 2, Exagen, 5; **A. Askanase**, Exagen, 2; **J. P. Buyon**, Exagen, 2; **K. Kalunian**, Exagen, 2, Exagen, 5; **W. W. Chatham**, None; **E. Massarotti**, None; **K. A. Kirou**, None; **A. Weinstein**, Exagen, 1, Exagen, 6, EXagen, 5; **P. Chitkara**, Exagen, 8; **S. Manzi**, EXagen, 5, Exagen, 7; **J. Ahearn**, Exagen, 5, Exagen, 7; **L. Wolover**, Exagen, 3; **J. Conklin**, Exagen, 3; **T. O'Malley**, Exagen, 3; **C. Ibarra**, Exagen, 3; **D. Barken**, Exagen, 3; **T. Dervieux**, Exagen, 3.

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Determinants of Blood Hydroxychloroquine Concentration Variations in Systemic Lupus Erythematosus Patients. Moez Jallouli[1], Lionel Galicier[2], Olivier Aumaître[3], Camille Francès[4], Véronique Le-Guern[5], F. Lioté[6], Amar Smail[7], Nicolas Limal[8], L. Perard[9], H. Desmurs-Clavel[10], Du Boutin[11], B. Asli[12], Jean Emmanuel Kahn[13], Jacques Pourrat[14], Laurent Sailler[15], F. Ackermann[13], T. Papo[16], Karim Sacre[17], O. Fain[18], J. Stirnemann[18], Patrice Cacoub[1], Gaëlle Leroux[1], Judith Cohen-Bittan[1], Js Hulot[19], Zahir Amoura[20], Jean-Charles Piette[1] and Nathalie Costedoat-Chalumeau[5]. [1]CHU Pitié-Salpêtrière, Paris, France, [2]Hopital St Louis, AP-HP, Paris, France, [3]Division of internal Medicine, Centre Hospitalier Universitaire, Hôpital Gabriel Montpied, Clermont–Ferrand, Clermont–Ferrand, France, [4]Hôpital Tenon, Paris Cedex 20, France, [5]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, [6]Hôpital Lariboisière, Université Paris-Diderot, Sorbonne Paris-Cité, Paris, France, [7]CHU Amiens Nord, Amiens, France, [8]Hôpital Henri Mondor, APHP, Creteil, France, [9]Hospices Civils de Lyon, groupement Hospitalier Edouard Herriot, Lyon, France, [10]Hospice civils de Lyon, Lyon, France, [11]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [12]Hopital Saint Louis, Université Paris Diderot, Sorbonne Paris Cité, Paris, France, [13]Hopital Foch, Suresnes, France, [14]CHU Toulouse, Hopital Rangueil, University of Paul Sabatier, Toulouse, France, [15]CHU Toulouse, Hopital Purpan, University of Paul Sabatier, Toulouse, France, [16]Hopital Bichat Claude Bernard, University of Paris Diderot, Sorbonne Paris cité, Paris, France, [17]University Paris-7, INSERM U699, APHP, Bichat Hospital, Paris, France, [18]Hopital Jean Verdier, University Paris Nord, Sorbonne Paris Cité, Paris, France, [19]CHU Pitié-Salpêtrière, UPMC, University Paris 6, Paris, France, [20]Pitié-Salpêtrière Hospital (AP-HP), Paris, France.

Background/Purpose: Hydroxychloroquine (HCQ) is now recognized as an important treatment of systemic lupus erythematosus (SLE). Blood HCQ levels ([HCQ]) can be quantified by high performance liquid chromatography (HPLC). [HCQ] varies widely between individual: a pharmacokinetic/pharmacodynamic (PK/PD) relation has been found in different situations, and very low [HCQ] is a simple marker of non-adherence to treatment (2). Accordingly, the interest in the [HCQ] measurement has recently grown, but little is known regarding the determinants of variation of [HCQ].

Methods: Retrospective analyses of our databases including the PLUS study (1) to determine the relationship between [HCQ] and different factors, including the daily dosage regimen, the weight and height, the renal function, the drug interactions, the smoking status and the ethnicity. Non-adherent patients ([HCQ] <200 ng/ml) were excluded.

Results: To have homogeneous pharmacological data, we restricted the analyses to the 509 patients treated with 400 mg/day. There was no correlation between [HCQ] and ethnicity or between [HCQ] and smoking. The median [HCQ] was 913 ng/ml [range: 213–2067], 951 [541–1701], and 916 [208–3316] in the patients who received enzyme inhibitors, enzyme inducers or none of these two groups of drugs respectively ($p=0.7$). Similarly, we did not find any significant differences in [HCQ] whereas the patient received or not antiacids.

In multivariate analysis, higher BMI ($p=0.008$), absence of treatment with corticosteroids ($p=0.04$), higher delay between the last tablet intake and the dosage of [HCQ] ($p=0.017$), lower platelet ($p<0.001$) and neutrophil ($p<0.001$) counts, and higher estimated creatinine clearance ($p<001$) were significantly associated with lower [HCQ].

Since patients with serum creatinine clearance lower than 60 ml/min were excluded from the PLUS study, we also studied 22 SLE patients with chronic renal insufficiency who were also treated with 400 mg/d of HCQ. Their median serum creatinine clearance was 52 ml/min [23–58]. Their median [HCQ] was significantly higher than those of the 509 patients from the PLUS study: 1338ng/ml [504–2229] versus 917 [208–3316] ($p<0.001$).

Finally, we studied 2 patients on long-term dialysis. Their [HCQ] did not change significantly after the dialysis and [HCQ] in the dialysis bath was undetectable for both patients (<50 ng/ml).

Conclusion: We report for the first time a comprehensive analyze of determinants of [HCQ]. Since this blood measurement is increasingly used, such data might be useful for clinicians.

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(2) Ann Rheum Dis. 2013;72:1786–92.

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ACR Concurrent Abstract Session

Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics II: Approaches to Cardiac and Vascular Manifestations in Systemic Sclerosis

Monday, November 17, 2014, 4:30 PM–6:00 PM

1926

Nailfold Videocapillaroscopy Patterns Associated with Calcinosis and Acro-Osteolysis in Systemic Sclerosis. Jerome Avouac[1], Laetitia Morardet[2], Maya Sammour[3], Andre Kahan[2], Antoine Feydy[3] and Yannick Allanore[1]. [1]Paris Descartes University, Rheumatology A Department and INSERM U1016, Cochin Hospital, Paris, France, [2]Paris Descartes University, Rheumatology A department, Cochin Hospital, Paris, France, [3]Paris Descartes University, Radiology B department, Cochin Hospital, Paris, France.

Background/Purpose: Calcinosis and acro-osteolysis are frequent in systemic sclerosis (SSc). They may be related to digital vasculopathy, which can be assessed by nailfold videocapillaroscopy (NVC). Our aim was to determine whether calcinosis and acro-osteolysis are associated with specific NVC features.

Methods: Consecutive SSc patients were consecutively included during a 24-month period. NVC was performed and analysed by one investigator (JA) blinded for the results of X-Rays and classified as early, active and late pattern (2). Two independent investigators carried out radiological assessment on standard anteroposterior views of the hands and wrists (LM, MS), followed

by a consensus reading (AF and YA). Calcinosis was defined by the presence of at least one calcification in soft tissue and acro-osteolysis by the presence of the resorption of at least one digit tip. Both were classified on X-rays as mild, moderate or severe according to their extent.

Results: 155 patients were included, with a mean age of 57±13 years and a mean disease duration of 9 ± 5 years; 65 (42%) had the diffuse cutaneous subset. 15 (10%) patients had a normal, 46 (30%) an early, 47 (30%) an active, and 47 (30%) a late NVC pattern. Regarding X-ray analysis, the kappa coefficient of inter-rater agreement was 0.75. 43 (28%) patients had calcinosis, of whom 26 (17%) had moderate or severe lesions; 25 (16%) patients had acro-osteolysis; of whom 13 (8%) had severe lesions. Patients with calcinosis were more likely to have acro-osteolysis ($p=0.02$), but Cramer's V coefficient of association was 0.19, supporting low association between these variables. Patients with calcinosis and acro-osteolysis were more likely to have the late NVC pattern ($p=0.04$ and $p<0.0001$ respectively). In line with this result, significant capillary loss was observed in patients with calcinosis (4±1.9 vs. 5.5±2.4 mean capillaries/finger, $p=0.001$) and acro-osteolysis (2.8±1.3 vs. 5.6±2.27 capillaries/finger, $p<0.001$). Of note, association with the late NVC pattern was stronger ($p=0.01$)and capillary loss was more pronounced in patients with moderate or severe calcinosis ($p<0.001$).No association was observed between calcinosis and irregular enlargement of capillaries (neoangiogenesis). Conversely, neoangiogenesis was more frequently observed inpatients with severe acro-osteolysis ($p=0.03$).Multivariate logistic regression analysis confirmed the independent association between calcinosis ($p=0.03$) and acro-osteolysis ($p=0.01$) with the late NVC pattern, together with a modified Rodnan skin score >14 ($p=0.008$) and positive antitopoisomerase-I antibodies ($p=0.01$).

Conclusion: We show for the first time an independent association between calcinosis/acro-osteolysis and the late NVC pattern, and in particular, with reduced number of capillaries. This result suggests that these lesions may be related to the severe capillary loss observed at this stage. Acro-osteolysis, but not calcinosis, was associated with neoangiogenesis, which may suggest an attempt to compensate bone resorption. Further studies are now needed to determine whether capillaroscopy may predict the further occurrence or worsening of these lesions.

Disclosure: J. Avouac, None; **L. Morardet**, None; **M. Sammour**, None; **A. Kahan**, None; **A. Feydy**, None; **Y. Allanore**, None.

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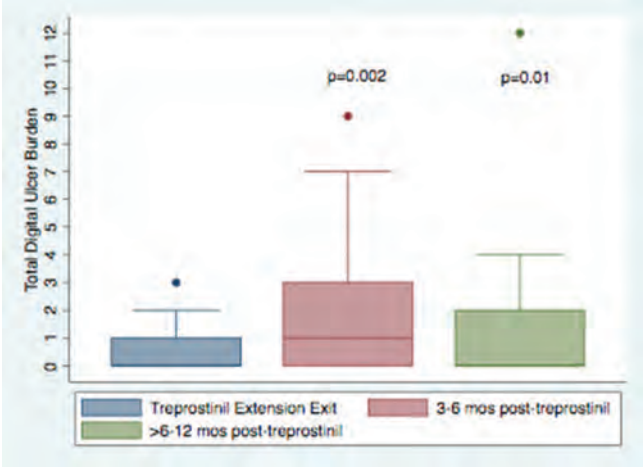
A Retrospective Look at the Recurrence of Digital Ulcers in Patients with Scleroderma after Discontinuation of Oral Treprostinil. Ami A. Shah[1], Elena Schiopu[2], Soumya Chatterjee[3], Mary Ellen Csuka[4], Tracy Frech[5], Avram Goldberg[6], Robert F. Spiera[7], Stanford L. Peng[8] and Virginia D. Steen[9]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of Michigan, Ann Arbor, MI, [3]Cleveland Clinic, Cleveland, OH, [4]Medical College of Wisconsin, Milwaukee, WI, [5]University of Utah, Salt Lake City, UT, [6]North Shore-LIJ Health System, Great Neck, NY, [7]Hospital for Special Surgery, New York, NY, [8]Benaroya Research Institute/Virginia Mason, Seattle, WA, [9]Georgetown University Medical Center, Washington, DC.

Background/Purpose: Ischemic digital ulcers (DU) occur in over 40% of systemic sclerosis (SSc) patients. Treprostinil diolamine, a newer prostacyclin analog that has been developed for oral delivery, improves cutaneous perfusion and temperature in SSc. A large randomized, double-blind, placebo-controlled clinical trial of treprostinil was conducted in SSc patients with DU. While this trial did not meet the desired endpoint (change in net ulcer burden at 20 wks), there was a significant improvement in several secondary endpoints that measured Raynaud's severity. Subjects enrolled into an open label extension study (DISTOL-EXT) after the clinical trial; after termination of DISTOL-EXT, all participants were withdrawn from oral treprostinil. We investigated whether active, indeterminate, and total DU burden increased in DISTOL-EXT participants after they discontinued treprostinil.

Methods: In this multi-center, retrospective study, medical records for the year after discontinuation of treprostinil were reviewed. Data from these routine clinical visits were abstracted into a template designed a priori to capture information on the number of active and indeterminate DU at the end of the extension study and at subsequent visits. Participants who did not have a subsequent visit with documentation of DU status were excluded. We examined the number of new DU that developed from the end of the extension study (baseline) through the first year after discontinuation of treprostinil. The number of active, indeterminate and total DU 3–6 months (time A) and >6–12 months (time B) after discontinuation of treprostinil were compared to baseline by the paired t-test.

Results: Fifty-one subjects from 9 SSc Centers were included for analysis. At the conclusion of the treprostinil extension study, the mean number of active, indeterminate and total DU was 0.25 (SD 0.63), 0.22 (SD 0.54) and 0.47 (SD 0.78), respectively. The number of active DU increased from baseline to time A (mean 1.62, $p=0.004$, $N=23$) and time B (mean 1.03, $p=0.076$, $N=30$). The number of indeterminate DU increased from baseline to time B (mean 0.42, $p=0.03$, $N=30$) but not time A. The total DU burden increased significantly from baseline to time A (mean 2.1, $p=0.002$, $N=23$) and time B (mean 1.45, $p=0.01$, $N=30$) as shown in the Figure. The majority of patients required intensive vasodilator therapy and pain medication: calcium channel blockers (60.8%), PDE 5 inhibitors (21.6%), any pain medication (58.8%), opioids (33.3%). Three patients were hospitalized for complications from digital ulcers, and 4 patients required surgical intervention. Five patients were subsequently diagnosed with pulmonary hypertension.

Conclusion: Total DU burden increased significantly after discontinuation of oral treprostinil diolamine. These data provide supportive evidence of a beneficial effect of oral treprostinil diolamine for the vascular complications of SSc.



Disclosure: A. A. Shah, United Therapeutics, 2; **E. Schiopu**, United Therapeutics, Actelion, MedImmune, Celgene, 2, United Therapeutics, 8; **S. Chatterjee**, United Therapeutics, 2; **M. E. Csuka**, United Therapeutics, 2; **T. Frech**, United Therapeutics, 2; **A. Goldberg**, United Therapeutics, 2; **R. F. Spiera**, United Therapeutics, 2; **S. L. Peng**, United Therapeutics, 2; **V. D. Steen**, Actelion Pharmaceuticals US, 8, United Therapeutics, 5, Gilead Science, 8, Roche Pharmaceuticals, 2, Sanofi-Aventis Pharmaceutical, 2, CSL Berhing, 2, Intermune, 2, Bayer, 5.

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A Multicenter, Prospective Cohort Study Using Nailfold Videocapillaroscopy and Other Clinical Characteristics to Determine the Risk of Developing New Digital Ulcers in Patients with Systemic Sclerosis. Vanessa Smith[1], Maurizio Cutolo[2], Ariane Herrick[3], Oliver Distler[4], Mike Becker[5], Emma Beltran[6], Patrick Carpentier[7], Clodoveo Ferri[8], Murat Inanc[9], Panayiotis Vlachoyiannopoulos[10], Harbajan Chadha-Boreham[11], Emmanuelle Cottreel[11], Thomas Pfister[11], Daniel Rosenberg[11] and Juan Torres.on behalf of the CAP study investigators[12], [1]Ghent University Hospital, Ghent, Belgium, [2]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, [3]Centre for Musculoskeletal Research, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [4]Zurich University Hospital, Zurich, Switzerland, [5]Charité University Hospital, Berlin, Germany, [6]Hospital La Fe, Valencia, Spain, [7]La Tronche Hospital, Grenoble, France, [8]University of Modena & Reggio E, Moderna, Italy, [9]Division of Rheumatology, Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey, [10]School of Medicine, National University of Athens, Athens, Greece, [11]Actelion Pharmaceuticals Ltd, Allschwil, Switzerland, [12]Syntax for Science SL, Basel, Switzerland.

Background/Purpose: Digital ulcers (DU) are painful and disabling and affect almost 50% of systemic sclerosis (SSc) patients. Nailfold videocapillaroscopy (NVC) non-invasively assesses SSc-related micro-angiopathy and may be useful in predicting clinical progression of digital vasculopathy, especially DU.[1–4] The objective of this study was to identify NVC variables and clinical characteristics which predict the occurrence of new DU in SSc patients.

Methods: International, prospective, multicenter cohort study in SSc. Eligibility was not restricted by medication use. SSc patients (American College of Rheumatology/LeRoy and Medsger) were enrolled in two strata:

'DU History' and 'No DU History'. The No DU History patients had early disease (≤2 years).

Variables were classified into bundles for statistical analysis: demographics, SSc clinical characteristics, DU characteristics, NVC characteristics and other clinical characteristics. NVC variables for fingers II–V were evaluated locally in a standardized way. Patients were followed up to 6 months for new DUs (confirmed by the investigator). Univariable Logistic Regression (ULR) was performed on all variables and Multivariable Logistic Regression (MLR) was performed within and across bundles to assess statistical significance (Wald chi-square $p<0.15$ for linear and $p<0.05$ for quadratic) and discriminatory ability (receiver operation characteristic area under the curve [ROC AUC]). Clinical relevance to predict new DU in 6 months was portrayed by model performance characteristics in a binary risk chart and two-by-two tables at different risk probability thresholds.

Results: Of the 623 patients enrolled in 59 centers, 591 had data on DU outcome (new DU or no new DU) during the study. 468 (79%) patients had a DU history, of whom 103 (22%) developed new DU. 123 (21%) patients had no DU history, of whom 5 (4%) developed new DU. Due to low event numbers in the no DU history group, the present analysis focuses on the DU history stratum. The mean age was 54.0 years, 79.5% were females, and 59.8% patients had limited cutaneous SSc. The final model consisted of the following 3 co-variables to predict the occurrence of DU within 6 months: number of DU at baseline visit categorized into 0, 1, 2 and ≥ 3, mean number of capillaries in the middle finger of the dominant hand (evaluated on two adjacent fields in the middle of the nailfold) and presence/absence of critical digital ischemia at enrolment. AUC of this model was 0.738 (C.I. 0.681–0.795). Internal validation through bootstrap generated AUC 0.633 [C.I. 0.510–0.756]). At a probability threshold of 37.3%, the binary risk table shows a specificity of 90.6%, a sensitivity of 39.4%, a negative predictive value (NPV) of 83.8% and a positive predictive value (PPV) of 54.9%.

Conclusion: The CAP study is the first and largest prospective study producing a simple prognostic model with acceptable performance which can be useful in the management of patients with presence or history of DU.

References

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Disclosure: V. Smith, Actelion Pharmaceuticals Ltd, 2; **M. Cutolo**, Actelion Pharmaceuticals Ltd, 2; **A. Herrick**, Actelion Pharmaceuticals US, 5, Pfizer Inc, 5; **O. Distler**, Actelion Pharmaceuticals US, 5, Pfizer Inc, 5, Ergonex, 5, Bristol-Myers Squibb, 5, Bayer, 5, United BioSource Corporation, 5, Roche/Genentech, 5, Medac, 5, Biovitrium, 5, Boehringer Ingelheim Pharma, 5, Novartis Pharmaceutical Corporation, 5, 4D Science, 5, Active Biotec, 5, Sinoxa, 5, Sanofi-Aventis Pharmaceutical, 5, Serodapharma, 5, GSK, 5, Epipharm, 5; **M. Becker**, None; **E. Beltran**, None; **P. Carpentier**, None; **C. Ferri**, None; **M. Inanc**, Actelion Pharmaceuticals US, 5; **P. Vlachoyiannopoulos**, None; **H. Chadha-Boreham**, Actelion Pharmaceuticals US, 3; **E. Cottreel**, Actelion Pharmaceuticals US, 3; **T. Pfister**, Actelion Pharmaceuticals US, 3; **D. Rosenberg**, Actelion Pharmaceuticals US, 3; **J. Torres, on behalf of the CAP study investigators**, Actelion Pharmaceuticals US, 3.

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Echocardiographic Phenomics for Novel Classification of Cardiac Involvement in Systemic Sclerosis. Monique Hinchcliff, Vistasp Daruwalla, Lauren Beussink-Nelson, Sofia Podlusky, Mary A. Carns, John Varga and Sanjiv J. Shah. Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Traditional studies of systemic sclerosis (SSc) cardiac involvement have examined one or a few echocardiographic (echo) variables; however, cardiac involvement in SSc can be multi-faceted and heterogeneous. We hypothesized that evaluation of dense quantitative echo phenotypic data using repurposed genetic analytic software would allow for novel classification of SSc cardiac involvement.

Methods: We studied 377 patients with SSc enrolled in the Northwestern Scleroderma Program. All patients underwent comprehensive echo with Doppler and tissue Doppler imaging using a standardized protocol for image acquisition and interpretation. A total of 57 unique, quantitative echo phenotypes were standardized to mean=0 and SD=±1. The quantitative phenotypic data was entered into gene expression analysis software (Cluster), and a phenotype heatmap ("pheno-map") was generated (TreeView). Cluster groups ("pheno-groups") were defined based on the resultant heriarchical dendogram. We used linear, logistic, and Cox regression analyses to determine differences in clinical, laboratory, pulmonary function testing, and survival characteristics among pheno-groups.

Results: The mean±SD age was 51±13 years, 82% were female, 51% had limited cutaneous SSc, 32% had diffuse cutaneous SSc, and 17% had other forms of SSc (e.g., overlap syndromes). Prevalence of SSc complications were as follows: PAH in 9%, ILD in 17.5%, and LV systolic dysfunction (EF<50%) in 4%. After the phenomapping analysis, 4 distinct, mutually exclusive pheno-groups were identified. The 4 groups differed significantly on clinical characteristics and outcomes. The pheno-groups did not differ by SSc subtype (limited vs. diffuse cutaneous SSc), but autoantibodies did differ by pheno-group (e.g., anti-centromere antibody was most prevalent in pheno-group #4 [38%]). PAH prevalence differed across groups (highest [18.5%] in pheno-group #1, P=0.002). Clinical ILD did not differ among groups (P=0.24), but FVC and DLCO were lowest in pheno-group #1 (P<0.001). LV, RV, and left atrial mechanics were also worse in pheno-group #1 (P<0.02 for all comparisons). Pheno-group #1 had the highest risk for death (HR 6.0, 95% CI 1.3–28.5; P=0.024 after adjustment for age, sex, SSc subtype, disease duration, ILD, and PAH).

Conclusion: Heirarchical cluster analysis of high-density, quantitative echo phenotypes results in novel, clinically relevant classification of cardiac structure/function in SSc. Further research into the identified echo pheno-groups of SSc may enhance pathophysiologic insight into SSc cardiac involvement.

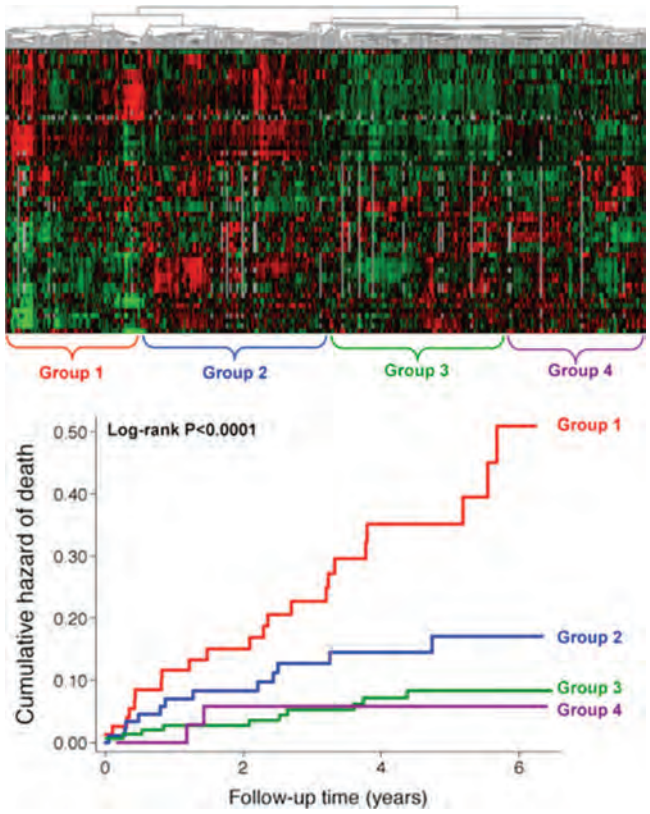

Figure. Echocardiographic Phenotype Heatmap "Pheno-Map" (top panel) and Cumulative Hazard for Death by Pheno-Group (bottom panel)

Disclosure: M. Hinchcliff, Gilead Science, 9; **V. Daruwalla**, None; **L. Beussink-Nelson**, None; **S. Podlusky**, None; **M. A. Carns**, None; **J. Varga**, None; **S. J. Shah**, None.

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The Value of Repeated Nailfold Capillaroscopy in Raynaud's Phenomenon in Daily Practice: A Follow-up Study in the Netherlands. B. de Boer[1], J. Meijs[1], J. van Aken[2], T.W.J. Huizinga[1], A.a. Schouffoer[3] and J.K. de Vries-Bouwstra[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Spaarne Ziekenhuis, Hoofddorp, Netherlands, [3]Haga Hospital, The Hague, Netherlands.

Background/Purpose: Nailfold capillaroscopy is an important tool to differentiate primary Raynaud's phenomenon (PRP) from secondary Raynaud's phenomenon (SRP). Based on possible transition from PRP to SRP (semi)annual capillaroscopy has been advocated to detect transition to SRP as early as possible.

Objective of this study is to evaluate the additive diagnostic value of repeated nailfold capillaroscopy after one year in patients with Raynaud's phenomenon (RP).

Methods: Patients with RP who underwent capillaroscopy at the outpatient clinic at least six months ago were invited for follow-up capillaroscopy. PRP was defined according to the definition of LeRoy (1); SRP was defined as RP associated with a connective tissue disease fulfilling applicable diagnostic criteria; the remaining patients were classified as suspected SRP (sSRP). The number of patients in which follow-up capillaroscopy resulted in change of diagnosis was determined.

Results: In total 107 patients with RP underwent capillaroscopy. Of these71 underwent follow-up capillaroscopy after a mean period of 12 months (range 6–25 months). At baseline, eight (11%) patients had PRP, 28 (40%) SRP and 35 (49%) sSRP. The rate of progression from PRP to SRP was 12.5% (one of eight patients). The rate of progression from sSRP to SRP was 3% (one of 35 patients). Capillaroscopy pattern changed in 21 (30%) patients: six (8%) worsened (Table 1) and 15 (21%) improved. In total five patients (7%) had a different diagnosis at follow-up, two of which based on clinical symptoms, three based on capillaroscopy pattern only: one changed from PRP to SRP, based on development of sclerodactyly, one changed from sSRP to SRP based on biopsy proven myositis, and three patients changed from sSRP to PRP due to normalization of capillaroscopy (Table 2). Thus, capillaroscopy contributed to change in diagnosis in three out of 43 patients (7%) with PRP or sSRP, all improving from sSRP to PRP.

Conclusion: Although progression from PRP to SRP was observed in 12.5% and progression from sSRP to SRP in 3%, changes in capillaroscopy did not contribute to change in clinical diagnosis in these patients.Based on the findings of this study, a follow-up capillaroscopy after one year in patients with PRP or sSRP without a change in clinical symptoms cannot be advocated. Extended follow-up in a larger population is needed to confirm this observation.

(1) LeRoy EC, Medsger TA, Jr. Raynaud's phenomenon: a proposal for classification. Clin Exp Rheumatol 1992 Sep;10(5):485–8.

Table 1. Capillaroscopy pattern at baseline and follow-up of patients with a worsened capillaroscopy over time

	Capillaroscopy		Diagnosis		
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Comments**
1	Normal/aspecific	Borderline	PRP	SSc	Diagnosis SSc before follow-up capillaroscopy because of sclerodactyly
2	Normal/aspecific	Borderline	Suspected SRP	Suspected SRP	–
3	Normal/aspecific	Borderline	UCTD	UCTD	–
4	Borderline	SSc	SSc	SSc	–
5	Borderline	SSc	SSc	SSc	–
6	Borderline	SSc	UCTD	UCTD	–

PRP primary Raynaud phenomenon, *SSc* systemic sclerosis, *SRP* secondary Raynaud phenomenon, *UCTD* undifferentiated connective tissue disease

Table 2. Capillaroscopy pattern and clinical diagnosis of patients with a changed diagnosis

	Diagnosis		Capillaroscopy		
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Comments**
1	PRP	SSc	Normal/aspecific	Borderline	Based on clinical findings before follow-up visit
2	Suspected SRP	DM	Borderline	Borderline	Diagnosis before follow-up visit
3	Suspected SRP	PRP	Borderline	Normal	No symptoms
4	Suspected SRP	PRP	Borderline	Normal	No symptoms
5	Suspected SRP	PRP	Borderline	Normal	No symptoms

PRP primary Raynaud phenomenon, *SSc* systemic sclerosis, *SRP* secondary Raynaud phenomenon, *DM* dermatomyositis

Disclosure: B. de Boer, None; **J. Meijs**, Actelion Pharmaceuticals Ltd, 2; **J. van Aken**, None; **T. W. J. Huizinga**, None; **A. A. Schouffoer**, None; **J. K. de Vries-Bouwstra**, None.

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Mycophenolate Mofetil (MMF) Use in Scleroderma Patients with Pulmonary Hypertension: Observations from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Cohort.

Lesley Ann Saketkoo[1], Matthew R. Lammi[2], Aryeh Fischer[3], Jerry A. Molitor[4] and Virginia D. Steen[5]. [1]Louisiana State University Health Sciences Center, New Orleans, LA, [2]Louisiana State University Health Sciences Center, Pulmonary and Critical Medicine, New Orleans, LA, [3]National Jewish Health, Denver, CO, [4]University of Minnesota, Minneapolis, MN, [5]Georgetown University Medical Center, Washington, DC.

Background/Purpose: Systemic sclerosis (SSc) related pulmonary hypertension (PH) carries a high mortality and patients with SSc-PH related to restrictive lung disease having an even worse prognosis. Speculation regarding the potential of MMF to exert anti-fibrotic and anti-remodeling effects on parenchymal lung and vascular intimal fibrosis, led us to query the possible differences in outcomes and survival between 4 groups based on forced vital capacity (FVC) and use of MMF in SSc PH.

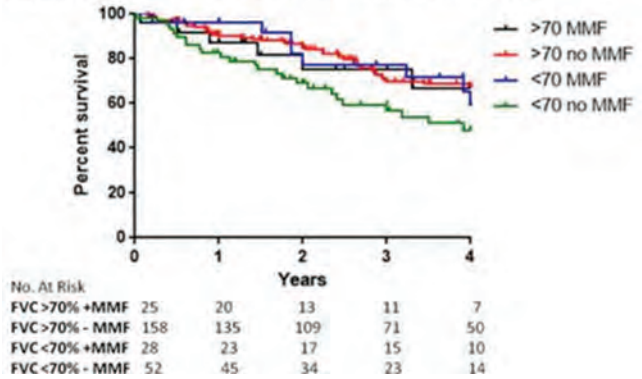
Methods: PHAROS is a prospective registry designed to provide substantive data to recognize aspects of PH unique to SSc. For this analysis patients were stratified by an FVC of >70% or ≤ 70% predicted on spirometry at the time of PH diagnosis by right heart catheterization (RHC) and then by MMF use greater than 6 months after the diagnosis of PH. Cyclophosphamide use was exclusionary to all groups. Calculations are derived from one-way ANOVA with Tukey's post test or Kruskal Wallis with Dunn's post-test. Categorical variables were compared with Chi square. These analyses were followed by Cox and stepwise backward regression analysis to assess baseline characteristics associated with risk of death and Kaplan-Meyer analysis.

Results: 256 cases from the PHAROS database matched criteria and had baseline spirometry results coincident with diagnostic RHC, of those 173 had a baseline FVC of >70% with 23 on MMF and 150 without; and 83 had a baseline FVC≤70% with 26 on MMF and 57 without. Across groups, no differences were found in age, disease duration, racial distribution nor surprisingly in skin score, 6 minute walk test for distance or NYHA Class. No detectable differences were found between groups in 6–18 month interval change from baseline FVC% in MMF- groups or from post-RHC initiation of MMF in the MMF+ groups. Of interest, baseline mPAP and PVR were lower in both MMF+ groups regardless of FVC. Though survival is numerically worst with FVC<70 without MMF at 4 years, it did not quite reach statistical significance in Kaplan-Meier analysis at 4 (p=0.06) or 3 years (p=0.08). Survival for both MMF groups was between 70% and 82% but only 56% for the patients with a low FVC not treated with MMF. Male sex was a significant independent predictor of death in all groups especially when FVC was <70%.

Table 1. Comparison between the baseline characteristics of the four groups at time of RHC, change of FVC between baseline RHC and from 6 to 18 months from RHC and regression analyses. Values reported in mean, unless otherwise stated. * = significant. NS = not significant

	FVC >70% + MMF	**FVC >70% − MMF**	**FVC <70% + MMF**	**FVC <70% − MMF**	
Number	23	150	26	57	
Age - yes, mean	56.70	60.33	53.31	56.25	NS
Time from diagnosis in years, mean	6.529	8.864	6.119	6.415	NS
Female sex %	69.6	91.3%	73	71	p = 0.0006
White race %	73.9	73	58	73	NS
Diffuse cutaneous %	52.2	27.2*	58.3	47.1	p = 0.0016
Skin score	11.38	8.3	10.00	10.87	NS
Moderate to Severe Fibrosis on HRCT % (n)	52.4 (11)	21 (21)*	65 (13)	44 (20)	p = 0.0001
NYHA Class III/IV % (n)	23.8 (5)	42.1 (61)	44 (11)	51.8 (29)	NS
PH Group I % % (n)	77.2 (17)	81.6 (115)*	34.8 (8)	47.2 (25)	< 0.0001
PH Group III % (n)	9 (2)	2.1 (3)	47.2 (11)*	40 (18)*	< 0.0001
FVC% predicted	87.43	82.79	52.08*	55.21*	< 0.0001
Change in FVC % (n)	11.38	8.350	10.00	10.87	NS
DLCO % predicted	44.34	44.82	36.06*	34.49*	p = 0.0011
FVC:DLCO Ratio	2.333	2.181	1.696*	1.816*	p = 0.0014
6MWT Distance	418.1	329.3	358.9	308.0	NS
mPAP (mmHg)	31.91*	36.82	31.77*	37.12	p = 0.0288
PVR	289.9*	478.8	290.9*	467.6	p = 0.0017
Survival at 1 year	95*	80	90	90	(p<0.05)
Survival at 3 years	82*	56	70	70	(p<0.05)
Univariate Predictors of Death in All Groups, ∧survived multivariate stepwise regression				Univariate Predictors of Death in FVC<70 group, ∧survived multivariate stepwise regression	
DLCO (p<0.0001)∧				DLCO (p = 0.005)∧	
FVC/DLCO (p<0.0001)					
6MWD (p<0.0001)				6MWD (p = 0.01)	
mPAP (p<0.0001)∧				mPAP (p = 0.003)∧	
PVR (p<0.0001)				PVR (p<0.0001)	
Male sex (p = 0.001)∧				Male sex (p = 0.007)∧	
NYHA (p<0.0001)∧				NYHA (p<0.0001)	
skin score (p = 0.04)				MMF Use (p = 0.07)	
MMF Use: (p = 0.06)					

Diagram 1. Survival across groups partitioned by FVC and MMF use.



No. At Risk					
FVC >70% +MMF	25	20	13	11	7
FVC >70% - MMF	158	135	109	71	50
FVC <70% +MMF	28	23	17	15	10
FVC <70% - MMF	52	45	34	23	14

Conclusion: The trend for improved survival in patients with PH with FVC <70 who were treated with MMF even in the absence of improvement of FVC is intriguing. Whether it has an effect on pulmonary artery remodeling should be considered. These findings warrant prospective controlled investigations of MMF in SSc PH particularly in those with restrictive lung disease.

Disclosure: L. A. Saketkoo, None; **M. R. Lammi**, None; **A. Fischer**, Actelion Pharmaceuticals US, 5, Gilead Sciences, 5, InterMune, 5, Gilead Sciences, 8; **J. A. Molitor**, UCB, 2, Actekion, 2; **V. D. Steen**, Actelion Pharmaceuticals US, 8, United Therapeutics, 5, Gilead Science, 8, Roche Pharmaceuticals, 2, Sanofi-Aventis Pharmaceutical, 2, CSL Berhing, 2, Intermune, 2, Bayer, 5.

ARHP Concurrent Abstract Session
Health Disparities/Social Determinants of Health
Monday, November 17, 2014, 4:30 PM–6:00 PM

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Increasing Access to Inflammatory Arthritis Education in Rural and Remote Communities Using Telemedicine. Carol Kennedy[1], Kelly Warmington[2], Carol Flewelling[1], Rachel Shupak[1], Angelo Papachristos[3], Caroline Jones[4], Dorcas Beaton[5], Sydney Brooks[6] and Denise Linton[1]. [1]St. Michael's Hospital, Toronto, ON, [2]The Hospital for Sick Children, Toronto, ON, [3]St Michael's Hospital, Toronto, ON, [4]St. Michael's Hospital, Aurora, ON, [5]Mobility Program Clinical Research Unit, Li Ka Shing Knowledge Institute, St. Michaels Hospital, Toronto, ON, [6]The Arthritis Society, Ontario Division, Toronto, ON.

Background/Purpose: Telemedicine-based approaches to healthcare service delivery improve access to care. It was recognised that people with inflammatory arthritis living in rural areas had limited access to patient education and could benefit from the "Prescription for Education (RxEd)" program, an evidence-based inflammatory arthritis education program. (format: one-day, audience: adults with inflammatory conditions, facilitators: specialized arthritis care providers). The one-day program includes a variety of short presentations and panel discussions by the team, and small group, facilitator-led discussions.

The program was adapted to be delivered via interactive videoconferencing through two workshops for local and rural facilitators: Telemedicine Best Practices/Adult Education Principles; Improved Public Speaking.

The objective of this study was to evaluate the effectiveness of telemedicine delivery of "Prescription for Education" in improving arthritis self-efficacy and other secondary outcomes (arthritis knowledge, coping efficacy, illness intrusiveness, and effective consumer).

Methods: Two group, pre-post design comparing two methods of delivery, local (I, in-person) versus videoconferencing (R, remote using telemedicine), of the RxEd program.

Data were collected at baseline (T1), immediately following RxEd (T2), and at 6 months (T3). Self-report questionnaires served as the data collection tool. Measures included demographics, disorder-related, Arthritis Self-Efficacy Scale (SE), arthritis knowledge [ACREU RA knowledge questionnaire (AK)], coping efficacy (CE), Illness Intrusiveness (II), and Effective Consumer Scale (ECS). Analyses included: Univariate statistics for primary and secondary outcomes; Repeated measures analyses of variance (MANOVA) to assess change in primary outcome (SE) across T_{1-3} (I vs R); and Repeated measures ANOVA to assess change from pre- to immediate-post (AK) and pre- to 6-month post (CE, II, ECS) (I vs R).

Results: 123 persons completed baseline questionnaires (I n=36; R n=87), with follow-up of 81% (n=100) immediate post (T2) and 61% (n=75) at 6 months (T3). No significant baseline differences were found for: demographics, disorder-related, SE, AK, CE, II, and ECS measures.

Both groups (I and R) showed immediate effect (improved SE) after the intervention that diminished slightly over 6 months. MANOVA significant across T_{1-3} $p<0.001$ for SE. No significant differences (SE $p=0.31$) between groups (I vs R).

Both groups showed significant increase in knowledge (AK) from pre- to immediate post RxEd ($p<0.0001$), and no significant difference I vs R (ANOVA $p=0.41$). Both groups showed significant improvement in CE ($p<0.0001$), II ($p=0.03$), and ECS ($p<0.0001$) from pre- to 6-month follow-up. No significant differences (ANOVA, p-values 0.20 – 0.78) between groups (I vs R) for all secondary outcomes.

Conclusion: Improvements in arthritis self-efficacy and other secondary outcomes were equally effective in local (in-person) and remote participant groups. Access to inflammatory arthritis education in rural and remote communities is greatly increased with using Telemedicine.

Disclosure: C. Kennedy, CIORA, 2, Abbvie, Roche, UCB, Janssen, 9; **K. Warmington**, None; **C. Flewelling**, None; **R. Shupak**, None; **A. Papachristos**, None; **C. Jones**, None; **D. Beaton**, None; **S. Brooks**, None; **D. Linton**, None.

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Getting a Grip on Arthritis Online: Web-Based Continuing Education Supports the Dissemination of Arthritis Clinical Practice Guidelines Among Rural/Remote Primary Care Providers. Sydney Lineker[1], Mary Bell[2], Lisa Fleet[3], Elizabeth M. Badley[4], Vernon Curran[3], Marlene Del Pino[5], Fran Kirby[3], Anne Lyddiatt[6], Lynn Moore[1], Karla Simmons[3], Raquel Sweezie[1], Peter Tugwell[7] and Ed Ziesmann[1]. [1]The Arthritis Society, Toronto, ON, [2]Sunnybrook Health Sciences Ctr, Toronto, ON, [3]Memorial University, St. John's, NF, [4]Division of Health Care and Outcomes Research, Toronto Western Research Institute; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, [5]Health Canada, Regina, SK, [6]Patient Partners in Arthritis, Toronto, ON, [7]Institute of Population Hlth, Ottawa, ON.

Background/Purpose: Primary care providers (physiotherapists, occupational therapists, nurses, family physicians) are often challenged with accessing relevant up-to-date arthritis information to enable delivery of optimal care. An online arthritis continuing health education program to disseminate arthritis clinical practice guidelines was developed, piloted, and evaluated to address this issue.

Methods: Online learning modules were developed for Osteoarthritis (OA) and Rheumatoid Arthritis (RA) based on published guidelines adapted for primary care (best practices), input from subject matter experts, and a needs assessment. The program was piloted in two rural/remote areas with high arthritis prevalence and health human resource shortages. Evaluation included 1) paired samples analyses of pre/post measurements of best practice recommendations and confidence and satisfaction with ability to manage arthritis, 2) evaluation of module content and design. Knowledge of best practice guidelines was measured by assigning one point for each best practice applied to a hypothetical case scenario and then summing the points into a total best practice score. Confidence and satisfaction were measured on 10 point numerical rating scales (0=not satisfied/not at all confident; 10=extremely satisfied/confident).

Results: Primary care providers that completed the modules (OA n=34; RA n=32) demonstrated significant improvements in best practice scores (OA pre=2.8/10, post=3.8/10, $p<0.01$; RA pre=3.9/12, post=4.6/12, $p<0.01$). More providers recommended occupational therapy/joint protection for the OA case scenario (pre=32.4%, post=58.8%, $p=0.01$) after taking the module and more providers recommended patient education for the RA case scenario (pre=46.9%, post=68.8%, $p=0.04$). Satisfaction with ability to manage arthritis also improved (OA pre=7.0, post=8.0, $p<0.01$; RA pre=6.0, post=7.0, $p<0.01$). Significant increases in confidence with different aspects of arthritis care were also observed ($p<0.05$). After taking the OA module, participants' confidence improved for the comprehensive musculoskeletal examination, prescribing/recommending corticosteroids, ordering/recommending serological tests, and managing common musculoskeletal conditions. After taking the RA module, participants' confidence improved for prescribing/recommending joint injections of the knee, DMARDs, and

corticosteroids, and managing common musculoskeletal conditions. Most respondents agreed that the modules were consistent with stated objectives (OA=97.5%; RA=97.1%), addressed learning needs (OA=87.2%; RA=94.3%) and were relevant to practice (OA=80.0%; RA=91.4%). The planned use of relevant resources in practice and with patients highlighted the participants' commitment to change.

Conclusion: With knowledge gained from the online modules, participants were able to apply a greater number of best practices and they reported an increase in both satisfaction and confidence with managing arthritis. The modules were also relevant to practice and the content addressed their learning needs. As a result of the success of the pilot evaluation, both modules were accredited and launched nationally at the end of February 2014.

Disclosure: S. Lineker, None; **M. Bell**, None; **L. Fleet**, None; **E. M. Badley**, None; **V. Curran**, None; **M. Del Pino**, None; **F. Kirby**, None; **A. Lyddiatt**, None; **L. Moore**, None; **K. Simmons**, None; **R. Sweezie**, None; **P. Tugwell**, Bristol-Myers Squibb, Chelsea, UCB, Canadian Reformulary Group Inc, Pfizer Canada, Hoffman La-Roche and Eli Lilly and Company, 5, OMERACT, 6, Elsevier, Little Brown, Wolters Kluwer Ltd. and John Wiley & Sons Ltd, 7, Astra Zeneca, 8, Elsevier Publishing Ltd, OMERACT, Ontario Rheumatology Association Ontario Biologics Registry Initiative Council, 9; **E. Ziesmann**, None.

1934

Examing Why Minority Women Are Risk Averse : A Qualitative Study.
Sonal Bhalla[1], Kristin Mattocks[2] and Liana Fraenkel[3]. [1]Yale-New Haven Hospital, New Haven, CT, [2]VA Central Western Massachusetts Healthcare System, University of Massachusetts Medical School, Leeds, MA, [3]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT.

Background/Purpose: Prior research has shown that when making choices about the risks and benefits of medications, women from minority ethnic groups tend to be more risk averse compared to their Caucasian counterparts. We conducted a qualitative study to better understand how young women of three racial groups: non-Hispanic Blacks, non-Hispanic Whites and Hispanics approach trade-offs between the risks and benefits of medications.

Methods: Participants were drawn from inpatient wards and infusions centers at a large academic hospital. Women age 20–45 years, able to speak English or Spanish, who self-identified as Hispanic Black, non-Hispanic White orHispanic were eligible to particpate. We performed individual in-depth interviews following a semi-structured interview guide. In the initial prompt, all participants were asked why they think minority ethnic groups tend to be more risk averse. Interviews were audiotaped and subsequently transcribed verbatim. Transcripts were analyzed using the constant comparative method of grounded theory. Coding ended with thematic saturation (36 interviews).

Results: We coded 36 transcripts (30.6% non-Hispanic Blacks, 33.3% non-Hispanic Whites and 36.1% Hispanics). The participants' mean age (SD) was 34.8 (6.8); 66.7% had a college education or higher, 58.3% had annual income $40k or more; 41.7% were employed full-time, and 55.6% were married. The four main themes that emerged from the transcripts were the impact of 1) constrained resources (limited means, responsibilities of work and family, lack of knowledge or information); 2) deep-rooted health beliefs (familial narratives, religious beliefs, mistrust); 3) perceived discrepancies in access to high quality healthcare (access to type of care, relationship with doctors, lack of communication and disclosure) and 4) erroneous illness perceptions (perceived susceptibility to side effects, inaccurate medication beliefs) on attitudes towards treatment. References were made towards constrained resources, family responsibilities and perceived susceptibility by both African American and Hispanic women. African American women made more references to mistrust and medical experimentation and lack of education whereas Hispanic women were most often influenced by beliefs in home remedies. White women endorsed the impact of constrained resources in the minority ethnicities. Examples of illustrative quotations are provided in the table below.

Conclusion: Decision making is influenced by factors far beyond the risks and benefits of proposed medications – and this is particularly true for minority women. An increased awareness of these factors is likely to improve shared decision making in clinical practice.

Emerging Themes	Illustrative Quotes
Impact of constrained resources	"They don't want to be sitting, lying around somewhere recovering. They want to be able to go to work and pay their bills, take care of their families!"
	"We are not that risky because in the end we really cannot afford what a lot of white people can afford."
Impact of deep-rooted health beliefs	"Maybe it is the way we are raised or something", "like your grandmother use to give you these old remedies to try instead of going to the doctor."
	"Homemade remedies don't give side effects."
Impact of perceived discrepancies in access to high quality healthcare	"...clinic doctors don't look you in the face ...They don't mention the side effects. They don't mention what could happen"
	"A lot of times doctors don't have time like they use to because of the current health care system of factory working, kind of pushing people out, getting them in and out."
Impact of erroneous illness perceptions	"There is a lot to lose. I rather hear that there is no fix, stay in pain, use my knee and avoid those side effects like not being able to use it or move it."
	"more minorities have health problems.... worse health problems than the white people seem to", "I am going to be that odd number because we are that odd number for everything else."

Disclosure: S. Bhalla, None; **K. Mattocks**, None; **L. Fraenkel**, None.

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Racial Disparities in Attitude Towards Treatment in Young Women.
Raluca Cozmuta[1], Sonal Bhalla[2] and Liana Fraenkel[3]. [1]Yale University School of Medicine, New Haven, CT, [2]Yale University, New Haven, CT, [3]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT.

Background/Purpose: Previous research has found that young minority women tend to be more risk averse compared to their Caucasian counterparts. The reasons underlying these differences, however, are not well understood. The objective of this study was to examine whether factors influencing perceived treatment importance vary by minority status.

Methods: Women between the ages of 20 and 45 receiving treatment at an academic hospital either as an inpatient or in an infusion center completed a survey. The survey ascertained sociodemographic data, affect, trust in healthcare systems, and medication beliefs using validated instruments. The survey included a hypothetical scenario in which subjects were asked to rate the importance of taking a medication for a patient with joint pain, migraines and fatigue that benefits 70% of people and is well tolerated except for the rare risk (1 per 100,000) of a neurologic disease that may cause weakness, trouble with vision and numbness. Associations between patient characteristics, affect, medication beliefs, and trust with perceived importance of taking the medication were evaluated using two sample t-test, Mann Whitney U test, and Spearman correlation as appropriate. Variables found to be statistically significant ($p < 0.05$) were subsequently evaluated using multiple linear regression. Minority women were defined as women who did not self-identify as White non-Hispanic.

Results: 174 women completed the survey. Patient characteristics by minority status are summarized in the table below. Perceived importance of taking the medication varied by minority status. Among minority women, perceived medication importance was correlated with trust in healthcare systems ($r= 0.2$, $p= 0.03$), hopefulness regarding the medication ($r= 0.3$, $p= 0.002$), and difficulty paying for medications ($z= -2.3$, $p= 0.03$). The relationship between trust and perceived importance was completely mediated by hopefulness. Among non-Hispanic White women, medication beliefs ($r= -0.5$, $p= 0.001$), hopefulness ($r= 0.5$, $p< 0.001$) and worry related to the medication ($r= -0.4$, $p= 0.002$) were correlated with perceived medication importance. Hopefulness and difficulty paying for medications remained significantly associated with perceived medication importance in the multivariate regression model among minority women, as did affect and medication beliefs in non-Hispanic White women.

Conclusion: In contrast to previous findings, minority women rated the importance of taking medication higher than non-Hispanic White women. Our findings confirm the important influence of affect on decision making, and suggest that financial constraints can influence the perceived value of treatment among minority women.

Table. Patient characteristics by minority status

Variable	Non-Hispanic White	Minority	P value
Age (mean, SD)	32.8 (7.2)	33.1 (7.9)	0.80
Medication beliefs (mean, SD)	20.9 (4.8)	21.8 (4.7)	0.22
Trust (mean, SD)	28.5 (5.3)	28.7 (6.0)	0.86
Hopefulness (mean, SD)	4.1 (1.6)	3.6 (1.6)	0.05
Worry (median, range)	5 (1–7)	5 (1–7)	0.07
Important (median, range)	5 (2–7)	6 (1–7)	0.01
Some college education (%)	79.1%	51.4%	(<0.001)
Difficulty paying for meds (%)	21.2%	25.7%	0.50

Disclosure: R. Cozmuta, None; **S. Bhalla**, None; **L. Fraenkel**, None.

1936

Ageism, Fear, and Competing Co-Morbidities - Why Older Patients May Not Seek Care for Restricting Back Pain: A Qualitative Study. Una Makris[1], Robin Higashi[2], Emily Marks[2], Liana Fraenkel[3], Joanna Sale[4] and CM Reid[5]. [1]Dallas VA Medical Ctr, Dallas, TX, [2]UT Southwestern Medical Center, Dallas, TX, [3]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT, [4]University of Toronto, St. Michael's Hospital, Toronto, ON, [5]Weill Cornell Medical College, New York City, NY.

Background/Purpose: Back pain is highly prevalent among older adults and often undertreated. The reasons for this gap in care are poorly understood, especially in older adults from diverse racial and ethnic backgrounds. Our objective was to understand why older adults, in a racially diverse population, with restricting back pain (RBP– back pain severe enough to restrict activity), may not seek care.

Methods: We conducted one-on-one interviews and focus groups with older adults (ages ≥65 years) who reported RBP within the past 3 months. We recruited participants from 3 different sources (interviews and focus groups in Connecticut and focus groups in New York) to ensure a racially diverse sample; recruitment efforts ended once saturation was achieved. A semi-structured discussion guide was used in both the interviews and focus groups to prompt participants to discuss their experiences with RBP, including beliefs and attitudes about management. Audio recordings were transcribed and subsequently analyzed (using NVivo) in an iterative process to develop thematic categories.

Results: We conducted 23 one-on-one interviews and 16 focus groups (n=70 participants), for a total of 93 participants. Participants were mostly female (68%), older (median age=83 years), over one-half lived alone, and 46% self-identified as belonging to a minority group. We identified 3 themes for why older adults may not seek care for RBP (Table 1): (1) participant and perceived provider beliefs about age-related inevitability of RBP, (2) participants' fear of medication and/or surgery, and (3) older adults' perceived relative importance of RBP versus other comorbidities. There did not appear to be any trends in our findings based on race/ethnicity.

Conclusion: Findings demonstrated that a range of illness perceptions influence older adults willingness to seek care for RBP. Many of the barriers discussed may be addressed by improved patient-physician communication. Understanding the older adult's perspective regarding reasons they may not choose to seek care is an important step toward identifying opportunities to improve the quality of care for older adults with RBP. Providers, in turn, might benefit from clinical guidance regarding the treatment of low back pain specifically in older adults (e.g. poly-pharmacy, frailty, multiple co-morbidities), that recognizes the impact of ageist myths and assumptions, and providers' focus on medical and surgical interventions.

Theme	Sample Quotes
1. Participant and provider beliefs about inevitability of back pain in older adults	I honestly think that at this point, my body is broken, it's worn out. I mean, [chuckle] that's why I say, someone in their 70s you could help a lot more, but I honestly don't know what could be done now outside of keeping comfortable.
	I'll tell you what the doctor thinks: "you're 93 years old!" I see that all the time when I go to the office. Like everything is taken very lightly.
2. Participant fear of medication and/or surgery	They [providers] always want to give me medicine. I don't want medicine [emphasis original]! Because I don't think it helps anyÉI don't want another medication.
	That's the thing. They don't tell you much. They'd rather give you medication.
	He told me [the surgery] was a success É he said "it worked out" from the X-ray, that it looks like it's going to be successful, but the painÉthat's what to me, what I would say is successful, if I didn't have any more pain. It was not successful!
3. Relative importance of back pain compared to comorbidities	I am having back pain right now for years. Not only for months, for years. My doctorÉ I have other problemsÉ So she even told me that they are only patching me up because I have other problems; prostate, liver, heart, and all different problems. That is what she told me about this pain.
	My concentration at this point is my diabetes. I've had that and I've had that for almost 30 years. And that has presented problems along the wayÉthey know more about that than what I'm going through with my back.

Disclosure: U. Makris, None; **R. Higashi**, None; **E. Marks**, None; **L. Fraenkel**, None; **J. Sale**, None; **C. Reid**, None.

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Model Examining Factors Related to Physicians' Ratings of Disease Activity in Patients with RA. Julia R. Ayeroff[1], Sarah R. Ormseth[2], David Hardy[3], Michael R. Irwin[2], Michael H. Weisman[4] and Perry M. Nicassio[2]. [1]University of Southern California, Los Angeles, CA, [2]University of California, Los Angeles, Los Angeles, CA, [3]Loyola Marymount University, Los Angeles, CA, [4]Cedars-Sinai Medical Center, Los Angeles, CA.

Background/Purpose: The purpose of this study was to examine a multidimensional, integrated model describing the interrelations among rheumatoid arthritis (RA) objective disease activity, patient-rated disease activity, tender joint count, and related psychosocial factors as determinants of physician-rated disease activity (see Figure 1). It was expected that objective disease activity would be positively associated with physician-rated disease activity, both directly and indirectly through the hypothesized mediators of patient-rated disease activity and tender joint count.

Methods: The data of 105 participants satisfying the ACR classification criteria for RA were drawn from baseline of a randomized comparative efficacy trial of psychosocial interventions for RA. In the hypothesized model, objective disease activity (DAS-28 Swollen Joint Count and ESR), patient-rated disease activity (Rapid Assessment of Disease Activity in Rheumatology total joint score and disease activity VAS), physician-rated joint tenderness score serve as determinants of physician-rated disease activity. EQS 6.1 was used to evaluate the structural model, and the significance of estimated indirect effects (calculated based on the Sobel method) was taken as evidence of mediation.

Results: The hypothesized model fit the data well, $\chi^2(28) = 21.97$, $p = .079$, CFI = 0.96, RMSEA = 0.07, and the specified predictors explained 84% of the variance in physician-rated disease activity (see Figure 1). Greater objective disease activity directly predicted physician-rated disease activity and contributed to higher levels of patient-rated disease activity, which, in turn, predicted a higher tender joint count which ultimately exerted a strong positive effect on physician-rated disease activity. While objective disease activity had a strong direct effect on physician-rated disease activity, partial mediation was established because the strength of this association diminished when the model included the hypothesized predictors (as evidenced by its significant indirect effect; $\beta_{indirect} = .24$, $p < .001$). With regard to patients' self-ratings of RA symptoms, depressive symptomatology and non-white ethnicity were shown as positively associated with higher self-perceived levels of disease activity. In contrast, non-white ethnicity was associated with significantly lower physician-rated tender joint scores.

Conclusion: Findings confirmed the importance of a multidimensional framework in evaluating RA disease activity and elucidated the mechanisms that perpetuate health disparities. These results identify a specific point in the clinical encounter where an increased awareness of patients' experiences of their disease can contribute to more accurate ratings and improved outcomes.

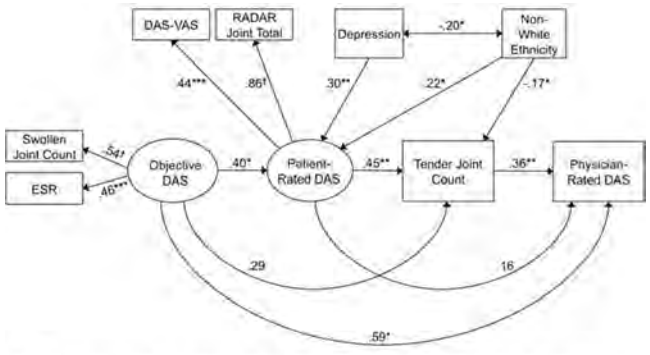

Figure 1. Final model with standardized path coefficients and factor loadings. ESR: Erythrocyte Sedimentation Rate; DAS-VAS: Disease Activity Score – Visual Analog Scale; RADAR Joint Total: Rapid Assessment of Disease Activity in Rheumatology Joint Total score; Objective DAS: Objective Disease Activity Score; Patient-Rated DAS: Patient-Rated Disease Activity Score; Physician-Rated DAS: Physician-Rated Disease Activity Score.
Note. $\chi^2(28) = 21.97$, $p = .079$, CFI = 0.96, RMSEA = 0.07.
†pathway set to 1.0.
*$p < .05$; **$p < .01$; ***$p < .001$.

Disclosure: J. R. Ayeroff, None; **S. R. Ormseth**, None; **D. Hardy**, None; **M. R. Irwin**, None; **M. H. Weisman**, None; **P. M. Nicassio**, None.

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Effects of Mesenchymal Stem Cells on Human B Cell Proliferation. Erin Collins, Maosong Qi and Gary S. Gilkeson. Medical University of South Carolina, Charleston, SC.

Background/Purpose: Human mesenchymal stem cells (MSC) are progenitor cells that have immunomodulatory properties. MSCs have been used to treat a variety of autoimmune diseases, including lupus. However, literatures have reported conflicting results of MSC function in regards to B cell biological behaviors. We tested the ability of MSCs from umbilical cords, and MSCs from healthy and lupus bone marrow in modulating the B cell functions of healthy and lupus patients.

Methods: Human MSCs were isolated from umbilical cords (UC), healthy bone marrow (HBM), and lupus patient bone marrow (LBM). Passages between 4 and 7 were used for these assays. B cells were isolated from peripheral blood of healthy and lupus donors using CD19 micro-beads, then labeled with CFSE for detection of proliferation. B cells were plated at $5x10^4$ per well in 96-well plates, with or without pre-plated MSCs, at the same number, within 24 hours. The cells were incubated at 37°C and 5% CO_2 for 96 hours ± stimulation (CpG, CD40L, IL2, and anti-human IgG/IgA/IgG). B cells were then collected and analyzed for proliferation by flow cytometry. Supernatants were collected for detection of antibodies and cytokines via ELISA.

Results: When co-cultured, UC-MSC and HBM-MSC inhibited healthy B cell proliferation better than LBM-MSC. However, only UC-MSC appeared to reduce the proliferation of lupus patient B cells. Regardless of proliferation, healthy B cells cultured in the presences of MSCs experienced increased IgM and IgG production. Supernatants of healthy B cells co-cultured with MSCs also presented increased the levels of IL-6 while having decreased amounts TNF-α when compared to the supernatants of wells with B cells alone.

Conclusion: In our experiments, MSCs obtained from umbilical cords exhibited strong activity in suppressing both healthy and lupus B cell proliferation while MSCs from healthy bone marrow suppressed healthy, but not lupus B cell proliferation. Lupus patient derived MSCs were unable to significantly suppress B cell proliferation from healthy or lupus patients. Furthermore, MSCs from all sources did not inhibit healthy B cell IgG or IgM secretion. These studies aim to improve our understanding of the *in vitro* effects of MSCs on B cell function in order to predict *in vivo* efficacy of MSCs to be used in the treatment of SLE.

Disclosure: E. Collins, None; **M. Qi**, None; **G. S. Gilkeson**, None.

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Development of Cell–Based Enzyme–Linked Immunosorbent Assay for the Quantification of Anti–M–type phospholipase–a–receptor Antibodies and Its Clinical Usefulness in Patients with Membranous Nephropathy. Yasuhiro Katsumata[1], Yuko Okamoto[1], Takahito Moriyama[1], Manabu Kawamoto[1], Hirotaka Kaneko[1], Yasushi Kawaguchi[1], Takahisa Gono[1], Masanori Hanaoka[1], Tomoaki Higuchi[1], Hidenaga Kawasumi[1], Keiko Uchida[1], Kosaku Nitta[1] and Hisashi Yamanaka[2]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Better risk prediction is needed to identify patients who will benefit from immunosuppressive therapy with idiopathic membranous nephropathy (MN) due to the variable natural course of the disease–spontaneous remission occurs in 40–50% of patients. It has recently been reported that many patients with idiopathic MN, but not patients with secondary MN, have circulating antibodies against the M-type phospholipase A2 receptor (PLA2R), a transmembrane protein located on podocytes. Although measuring anti–PLA2R levels has also been suggested to be a method to follow and predict response to treatment, widely available published measuring methods are only Western blot and a semi-quantitative immunofluorescence test. We aimed to develop cell–based enzyme–linked immunosorbent assay (ELISA) for the quantification of anti–PLA2R antibodies and investigate its clinical usefulness in patients with MN. We also aimed to validate the absence of anti–PLA2R antibodies in patients with systemic lupus erythematosus (SLE).

Methods: The synthesized human PLA2R gene was transfected into the HEK293T cells using the pcDNA3.1/Hygro (+) vector. Stable cell line expressing PLA2R was generated through limiting dilution and evaluated by flow cytometry and Western blot. Using this cell line, we developed a quantitative cell–based ELISA for anti–PLA2R antibodies as follows. HEK293T cells stably expressing PLA2R were seeded and cultured in wells of a flat–bottomed 96–well tissue culture plate coated with poly–D–Lysine. After the cells were fixed, serum samples were added. Subsequently, the peroxidase–conjugated anti–human IgG and TMB were added in order, and color development was measured. The usefulness of this test was studied in 26 patients with biopsy–proven primary MN, and 16 SLE patients with pure MN. Western blots using the lysates of HEK293T cells stably expressing PLA2R were also performed with these samples. Clinical data of these patients were retrospectively evaluated. Treatment was determined by physician preference in each individual based on clinically available information without prior knowledge of anti–PLA2R antibody positivity.

Results: Stable expression of PLA2R was detected in the HEK293T cells by flow cytometry and Western blot. Anti–PLA2R antibodies were positive in 7/26 (27%) by cell–based ELISA and 7/26 (27%) by Western blot. Cohen's κ coefficient of the 2 tests was 0.61 which means there is substantial agreement. Retrospective analyses revealed that all of the 7 patients who were anti–PLA2R positive by cell–based ELISA were treated with immunosuppressive therapy. In contrast, only 5 out of 26 patients with negative results received immunosuppressive therapy. Thus, the results of cell–based ELISA were associated with physicians' decision on immunosuppressive therapy ($p < 0.001$). Renal function did not decline in any of the anti–PLA2R negative patients. All of the 16 SLE patients with pure MN were negative for both cell–based ELISA and Western blot.

Conclusion: This study showed that our cell–based ELISA is reliable and clinically useful examination for MN. Anti–PLA2R antibodies may serve as predictive biomarker in MN. The absence of anti–PLA2R antibodies in patients with SLE was reconfirmed.

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A Novel Murine Model of B Cell-Mediated Glomerular Injury Is Mediated By Cytokines. Alfred Kim[1], Shreeram Akilesh[2], Ania Koziell[3], Sanjay Jain[2], Jeffrey Hodgin[4], Mark Miller[2], Jeffrey Miner[2] and Andrey Shaw[2]. [1]Washington Univ School of Med, St. Louis, MO, [2]Washington University School of Medicine, Saint Louis, MO, [3]King's College, London, United Kingdom, [4]University of Michigan, Ann Arbor, MI.

Background/Purpose: upus nephritis (LN) remains the leading cause of mortality for SLE patients, and is associated with proteinuria and foot process effacement. Podocyte foot process effacement is a feature of proteinuria, thought to be a stereotyped response of the podocyte to injury. The stimulus for podocyte injury and foot process effacement is unknown. B cell depletion therapies have demonstrated efficacy in some patients with proteinuria including those with minimal change disease. Since pathogenic antibodies are not causative, we hypothesized that a B cell derived cytokine might be capable of directly inducing podocyte injury and foot process effacement.

Methods: B cell model antigen model hen egg lysozyme (HEL) was biotinylated, complexed to avidin and injected into mice. Naive HEL-specific B cells were adoptively transferred and proteinuria assessed. Kidneys were processed for immunofluorescence and scanning electron microscopy (SEM). Cultured podocyte membrane ruffling was assessed with DIC videomicroscopy. IL-4 expression in mice was achieved by hydrodynamically injecting murine IL-4 in the piggyBac vector system. Human kidney biopsies were assessed for phospho-STAT6 by immunohistochemistry.

Results: We identified IL-4 as a B cell derived cytokine capable of altering actin cytoskeletal dynamics by stimulating podocyte membrane ruffling (lamellipodia). In addition, IL-4 generated foot process retractions on *ex vivo* fragments of renal cortex. Using a novel model of B cell induced proteinuria, B cells polarized to secrete IL-4 upon activation induced proteinuria and focal foot process effacement without antibody or complement deposition. Intravital two-photon microscopy demonstrated that HEL-specific B cells arrested trafficking within glomeruli only in the presence of glomerular-localized HEL. Inhibition of IL-4 signaling with a JAK1/3 inhibitor markedly reduced proteinuria in IL-4 overexpressing mice. A subset

of patients with steroid-sensitive nephrotic syndrome demonstrated glomerular STAT6 activation.

Conclusion: These findings suggest a potential explanation for the utility of immunosuppression and more targeted anti-B cell therapy with rituximab in the treatment of minimal change disease. These results supporting the role of IL-4 in human nephrotic syndromes and a novel therapeutic target.

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Neuropsychiatric Lupus Is Substantially Unaffected By B-Cell Deficiency. Jing Wen[1], Ariel Stock[1], Haowei Wang[2], Mark Shlomchik[2], Maria Gulinello[1] and Chaim Putterman[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]University of Pittsburgh School of Medicine, Pittsburgh, PA.

Background/Purpose: Neuropsychiatric lupus (NPSLE) is one of the earliest clinical manifestations in human lupus. However, its mechanisms are not fully understood. In lupus, a compromised blood brain barrier may allow for the passage of circulating autoantibodies into the brain, where they can induce neuropsychiatric abnormalities. Autoantibody titers can correlate with the severity of depressive-like behavior, and injection of anti-ribsomal P or anti-NMDA receptor antibodies into the brain induces neuronal damage and memory deficits. Since antibodies play an important role in lupus pathogenesis, B-cell depletion has been proposed as a targeted treatment approach. To determine if indeed B-cells and/or autoantibodies are instrumental in the pathogenesis of murine NPSLE, we evaluated neuropsychiatric disease in constitutively B cell deficient (JhD/MRL/lpr) and conditionally B-cell deficient mice (Cre-human CD20 MRL/lpr x Rosa26-Flox-STOP-DTA MRL/lpr, referred to as hCD20-DTA MRL/lpr, inducible by tamoxifen), as compared to MRL/lpr lupus mice.

Methods: hCD20-DTA MRL/lpr mice were B cell depleted at 13–14 weeks of age with tamoxifen treatment for 5 days. Blood and cerebrospinal fluid (CSF) were collected from JhD/MRL/lpr, hCD20-DTA MRL/lpr, MRL/lpr (positive controls) and MRL/MPJ (negative controls) at 18 weeks of age. Total IgG and IgG anti-dsDNA antibody concentrations in the serum and CSF were measured by ELISA. Comprehensive neurobehavioral testing including forced swim, anhedonia, open field, object recognition, object placement, and social preference were employed to evaluate the neuropsychiatric manifestations in the B cell sufficient and deficient MRL/lpr strains.

Results: Autoantibody levels were negligible (JhD/MRL/lpr) or significantly reduced (hCD20-DTA MRL/lpr) in the serum and CSF of B cell deficient mice. Nevertheless, we found that in the forced swim test, both JhD/MRL/lpr and hCD20-DTA MRL/lpr mice showed profound depressive-like behavior, which was no different from MRL/lpr mice. However, JhD/MRL/lpr mice displayed an increase in both total track length and number of rears (standing on the hind feet) in open field. Additionally, hCD20-DTA MRL/lpr mice exhibited an increased trend in preference score in object placement. No significant differences were observed in anhedonia, object recognition and social preference tests among all three strains. Interestingly, hCD20-DTA MRL/lpr mice demonstrated a significantly reduction in cellular infiltrates in the choroid plexus compared to MRL/lpr mice.

Conclusion: We found that B-cell depleted MRL/lpr mice surprisingly had no significant attenuation of key features of neuropsychiatric disease, including depressive-like behavior and cognitive dysfunction. However, increased motor activity was observed in JhD/MRL/lpr mice. Additionally, a trend toward improved visual memory was found in hCD20-DTA MRL/lpr mice. Finally, the decreased cellular infiltrates in the brain of hCD20-DTA MRL/lpr mice indicate that B cells play an important role in facilitating the immune cell entry into the choroid plexus.

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Regulation of the Responses of Human B Cell Subsets to Innate Immune Signals By Epratuzumab, a Humanized Monoclonal Antibody Targeting CD22. Natalia V. Giltiay[1], Geraldine L. Shu[1], Anthony Shock[2] and Edward A. Clark[1]. [1]University of Washington, Seattle, WA, [2]UCB Pharma, Slough, United Kingdom.

Background/Purpose: The B cell-associated receptor, CD22, functions to regulate adhesion and signaling through both the B cell receptor (BCR) and Toll-like receptors (TLRs) expressed in B cells. Epratuzumab is a humanized monoclonal antibody that targets CD22 on B cells and is currently being tested in phase 3 clinical trials in patients with systemic lupus erythematosus (SLE). This study was undertaken to determine how epratuzumab affects B cell activation through TLR and/or BCR pathways in tonsil-derived B cell subsets, which offers the opportunity to investigate the responses of B cells from human lymphoid tissue.

Methods: Purified $CD19^+CD20^+$ B cell subsets were isolated from human tonsils based on their relative expression of CD10, CD27 and other markers, and examined for CD22 expression and internalization after binding of epratuzumab using conventional flow cytometry and ImageStream® multispectral imaging cytometry. Isolated subsets were also treated with anti-IgM, R848 (a TLR7 agonist) and/or interferon (IFN)-α in the presence of epratuzumab or a human IgG_1 control. Changes in mRNA levels of a variety of genes 3 to 12 hours after activation were analyzed by qPCR. Cell proliferation was assessed by flow cytometry using CFSE staining. Cytokine production was measured by ELISA and intracellular flow cytometry after 3 days of *in vitro* culture.

Results: CD22 was expressed on all B cell subsets but $CD20^+CD10^{lo}CD27^{lo}$ mature naïve B cells expressed higher levels of CD22 (MFI 148) than $CD20^+CD27^{hi}CD10^{lo}$ memory B cells (MFI 120) or $CD10^{hi}CD27^+$ germinal center (GC)-associated B cells (MFI 130), and naïve B cells also internalized epratuzumab more uniformly compared to GC-associated B cells. Epratuzumab had no effect on IFN-α induced genes (eg. *TLR7, IRF7*) or BCR-induced genes (eg. *c-MYC*) in naïve B cells. However, epratuzumab did affect the expression of certain cytokine genes after TLR7 stimulation alone and/or in combination with anti-IgM (eg. IL-6). TLR7-driven IL-6 and IL-10 expression by naïve B cells were also differentially modulated by epratuzumab, with inhibition of IL-6 cytokine production but enhanced IL-10 expression. Finally, epratuzumab demonstrated a small but consistent enhancement of B cell proliferation induced with anti-IgM and anti-IgM+ R848.

Conclusion: These results suggest that one therapeutic effect of epratuzumab may be via down-regulation of the production of pro-inflammatory cytokines by B cells and an increase in the production of regulatory cytokines such as IL-10. These data have implications for understanding the functional consequences on B cell function of epratuzumab treatment in patients with autoimmune diseases such as SLE.

Disclosure: N. V. Giltiay, None; **G. L. Shu**, None; **A. Shock**, UCB Pharma, 3; **E. A. Clark**, UCB Pharma, 2.

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***In Vivo* Effects of Epratuzumab, a Monoclonal Antibody Targeting Human CD22, on B Cell Function in Human CD22 Knock-in (Huki) Mice.** Carolin Brandl*[1], Lamia Özgör*[1], Miriam Wöhner[2], Anthony Shock[3] and Lars Nitschke[1]. [1]University of Erlangen, Erlangen, Germany, [2]Research Institute of Molecular Pathology, Vienna, Austria, [3]UCB Pharma, Slough, United Kingdom.

Background/Purpose: Epratuzumab is a humanized monoclonal antibody that targets the B cell-specific protein CD22 currently in Phase 3 clinical trials in patients (pts) with systemic lupus erythematosus (SLE). Epratuzumab does not deplete B cells but does cause long-term changes in B cell numbers (~50–60% reduction after 9–12 months) in SLE pts. The mechanism of action of epratuzumab appears to involve immunomodulation of B cells e.g. by inhibiting activation through the B cell receptor (BCR).[1] It has also been shown to modulate B cell adhesion molecule expression and responsiveness to chemokines.[2] This study aimed to understand the effect of epratuzumab on B cells *in vivo* using human CD22 knock-in (Huki) mice in which B cells express the human, instead of murine, CD22 gene.[3]

Methods: Huki mice (n=4–8) received a single intravenous injection of epratuzumab (0.5mg) or phosphate-buffered saline (PBS) and at time points up to 12 weeks (wks) B cell sub-populations (immature, transitional, mature, germinal center, marginal zone) in peripheral blood, bone marrow, spleen and lymph nodes were measured along with B cell activation markers (CD69, MHCII) and the CD62L homing marker. *Ex vivo* functional assays were also performed: Ca^{2+} flux after anti-IgM BCR stimulation, apoptosis (based on numbers of sub-G1 phase cells) and CD22 internalization on B cells were measured (flow cytometry) and the proliferation of B cell subsets assessed after 7 days *in vivo* administration of BrdU.

Results: In Huki mice, a single dose of epratuzumab did not appear to affect absolute numbers or proportions of B cell subsets in

peripheral blood or lymphoid organs at Wks 3, 5 or 12 (comparable to PBS-treated Huki mice). Similarly, there were no consistent changes in activation markers or CD62L. However Huki mice receiving epratuzumab showed human CD22 internalization in B cells from blood and all other organs. Internalization was detected at 24 hours and maintained for 8 wks; long after antibody clearance. Splenic B cells purified 10 days after receiving epratuzumab demonstrated an increased rate of apoptosis when cultured *ex vivo* relative to PBS-treated mice and decreased BCR-activated Ca^{2+} flux was demonstrated in Huki mouse splenic B cells after epratuzumab treatment *in vitro*. BrdU incorporation in several B cell subsets was unchanged 7 days after administration of epratuzumab, suggesting there was no increase in proliferation.

Conclusion: Epratuzumab administration to Huki mice induced functional effects on B cells assessed *ex vivo* in keeping with *in vitro* data using human B cells. Specifically, epratuzumab decreased CD22 expression for a long time period, increased B cell apoptosis and reduced Ca^{2+} flux upon BCR activation. Single dose epratuzumab did not seem to strongly influence B cell development or B cell populations in blood and various organs. These data have implications for understanding the effects of epratuzumab treatment on B cell function in SLE pts particularly in relation to how BCR inhibition leads to long-term changes in the survival and physiology of B cells.

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Targeting CD22 with Epratuzumab Impacts Cytokine Production By B Cells. Vanessa Fleischer[1], Julia Sieber[1], Sarah J. Fleischer[2], Anthony Shock[3], Guido Heine[4], Capucine Daridon[1] and Thomas Dörner[1]. [1]German Rheumatism Research Centre Berlin, Berlin, Germany, [2]Charité University Medicine, Dept. Medicine/Rheumatology and Clinical Immunology/German Rheumatism Research Center (DRFZ), Berlin, Germany, [3]UCB Pharma, Slough, United Kingdom, [4]Charité University Medicine Berlin, Berlin, Germany.

Background/Purpose: CD22 is a negative co-receptor of the B-cell receptor (BCR) and, when targeted by epratuzumab, partially inhibits BCR signaling, for example by reducing Syk phosphorylation and Ca^{2+} flux. Cytokines produced by B cells have been described as playing important roles during certain stages of autoimmune diseases such as systemic lupus erythematosus (SLE) and their secretion is known to be driven by antigens and/or Toll-like receptor (TLR)-ligand stimulation. However, the impact of epratuzumab, a monoclonal antibody that targets CD22, on cytokine production has not yet been addressed. The current study therefore aimed to analyze the role of epratuzumab on the production of key cytokines by B cells, and compare the response of B cells from SLE patients to those from healthy donors (HD).

Methods: Peripheral blood mononuclear cells were isolated and B cells purified by Magnetic Activated Cell Sorting®. After 2 days of culture in the presence of TLR9 and/or BCR stimulation (CpG and anti-IgM/IgG, respectively), cytokine production (IL-6, TNF-α and IL-10) by B cells from SLE patients and HD was analyzed in the supernatants by bioplex. A special focus was made on IL-10-producing B cells using intracellular staining by flow cytometry. The balance between IL-10 and pro-inflammatory cytokines were assessed using the ratios of the concentrations of IL-10 to either IL-6 or TNF-α.

Results: The secretion of the pro-inflammatory cytokines TNF-α and IL-6 by anti-BCR activated HD and SLE B cells was significantly inhibited by epratuzumab co-treatment. The production of both cytokines was also inhibited by epratuzumab when B cells were stimulated concomitantly through the BCR and TLR9, although this failed to reach statistical significance for IL-6 production from HD. In contrast, the production of IL-10 in B cell supernatants was not affected by epratuzumab under any stimulation conditions; similarly, the development of IL10+ cells in culture, which was enhanced by TLR and BCR activation, was unaffected by epratuzumab. The cytokine balance between IL-10 and pro-inflammatory cytokines was influenced toward the regulatory cytokine IL-10.

Conclusion: Epratuzumab, through the targeting of CD22, inhibited the production of the pro-inflammatory cytokines IL-6 and TNF-α by B cells after stimulation through BCR and TLRs pathways, but had no effect on IL-10. This suggests that this antibody has the capacity to regulate the balance between the regulatory cytokine IL-10 and pro-inflammatory cytokines, and suggests a potential mechanism of action of epratuzumab on the effector function of B cells.

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Pharmacodynamic Effects of the CD22-Targeted Monoclonal Antibody Epratuzumab on B Cells in Patients with Systemic Lupus Erythematosus. Anthony Shock[1], Brian Kilgallen[2], Willem Koetse[2], Christian Stach[3], Sabine Bongardt[3] and Catrinel Galateanu[4]. [1]UCB Pharma, Slough, United Kingdom, [2]UCB Pharma, Raleigh, NC, [3]UCB Pharma, Monheim, Germany, [4]UCB Pharma, Brussels, Belgium.

Background/Purpose: Epratuzumab is a humanized monoclonal antibody (mAb) that targets the B cell-specific protein CD22 and is currently in Phase 3 clinical trials in patients (pts) with systemic lupus erythematosus (SLE). The mechanism of action of epratuzumab appears to involve immunomodulation of B cells, for example by inducing loss of B Cell Receptor (BCR)-related proteins from the cell surface, and inhibiting signaling through the BCR. The present analysis aimed to understand the effect of epratuzumab on B cells in SLE pts enrolled in the Phase 2b EMBLEM™ study (NCT00624351), and its open label extension (OLE), SL0008 (NCT00660881), in which epratuzumab produced clinically relevant, sustained improvements in disease activity in pts with moderate-to-severe SLE.[1–3]

Methods: In EMBLEM™, pts were treated with placebo or 1 of 5 cumulative doses (cd) of epratuzumab (200mg–3600mg cd over the 12-week [wk] study). In the OLE, all pts received 2400mg cd epratuzumab (1200mg at Wks 0 and 2 of repeating 12-wk cycles). Blood samples withdrawn at various time points were analyzed by flow cytometry using a panel of antibodies against cell surface markers (CD19, CD22, CD27, IgD, CD95) in order to identify B cell subsets; CD22 expression was monitored using S-HCL-1, a non-competing anti-CD22 mAb.

Results: In EMBLEM™ there was a small (10–15%) median decrease in the numbers of CD22+ naïve B cells and a quantitatively similar increase in CD22+ memory B cells in pts treated with epratuzumab but not placebo, which did not appear to be dose-dependent. During OLE, total B cell numbers continued to decline, reaching a median decrease of 50–60% after 9–12 months epratuzumab treatment before stabilizing with no further decrease. There was a rapid decrease (~80%) of CD22 expression on naïve, memory and transitional B cell subsets demonstrated at the first time point assessed (1 week) in the epratuzumab treatment groups (no changes were observed in the placebo group), which was maintained throughout the OLE. *In vitro* data demonstrated that this loss occurred primarily through epratuzumab-induced internalization of cell surface CD22. Moreover, the *in vitro* data demonstrated a bell-shaped concentration response, suggestive of bivalency. Finally, there was a gradual decline in the numbers of CD27-/IgD- B cells expressing CD95 throughout the OLE, from 41% at EMBLEM™ baseline to 27% at OLE Year 2.

Conclusion: Epratuzumab treatment of pts with SLE induced a protracted but defined reduction in the number of peripheral blood B cells over time, reaching a median reduction of 50–60% after 9–12 months treatment. CD22 expression was rapidly lost on all B cell subsets, and the loss maintained throughout the OLE. There was a gradual decline with epratuzumab treatment in the number of CD27-/IgD- B cells expressing CD95, a subset of activated memory B cells previously shown to be elevated in SLE and increased during lupus flare.[4]

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Disclosure: A. Shock, UCB Pharma, 3; **B. Kilgallen**, UCB Pharma, 3; **W. Koetse**, UCB Pharma, 1, UCB Pharma, 3; **C. Stach**, UCB Pharma, 1, UCB Pharma, 3; **S. Bongardt**, UCB Pharma, 3; **C. Galateanu**, UCB Pharma, 3.

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CD22 Is Required for Formation of Memory B Cell Precursors within Germinal Centers. Craig Chappell, Kevin Draves and Edward Clark. University of Washington, Seattle, WA.

Background/Purpose: CD22 is a sialic-acid binding co-receptor expressed primarily on B cells that has a number of functions including adhesion, regulation of B cell homeostasis and survival, and regulation of signaling through the B cell receptor (BCR) via ITIM and ITAM signaling motifs. Mice deficient in CD22 display hyper-responsive BCR signaling, decreased numbers of marginal zone B cells and dysregulated antibody (Ab) responses to T-independent antigens. CD22 deficiency or dysregulation also has been associated with the development of autoAbs and lupus-like disease. While primary T-dependent Ab responses are normal in CD22-deficient mice, the role of CD22 in the formation of B cell memory has not been thoroughly investigated. This study was undertaken to determine the impact of CD22 deficiency on the formation of germinal centers (GC), memory B cells and secondary recall responses.

Methods: B1–8^{hi} mice that harbor B cells specific for the hapten (4-hydroxy-3-nitrophenyl)acetyl (NP) were backcrossed to CD22-deficient mice to generate Ag-specific B cells lacking CD22 for adoptive transfer studies. Wild-type (WT) and CD22-deficient Ag-specific B cells were transferred to naïve hosts which were immunized with NP-CGG in alum. Following immunization B cell expansion, GC differentiation, Ag presentation and memory B cell formation were monitored among Ag-binding B cells by flow cytometry. Anti-NP serum Ab responses were monitored by ELISA. MHCII-mediated Ag presentation by GC B cell subsets was assessed by flow cytometry. WT and CD22-deficient mice were also assessed for many of the above parameters.

Results: CD22-deficient B cells mounted anti-NP Ab responses comparable to WT B cells during the early phase of the immune response (day 35). Detailed analysis of GC B cell subsets revealed that CD22-deficient B cells failed to form a small subset of GC B cells delineated by high CXCR4 and CD38 expression. Finally, CD22-deficient GC B cells presented similar amounts of Ag on MHCII as WT GC B cells.

Conclusion: These results demonstrate that CD22 plays a critical role in the formation of memory B cells under the conditions tested, and confirm earlier reports that CD22 is not required for early T-dependent Ab responses. CXCR4^{hi}CD38^{hi} GC B cells did not develop in absence of CD22, which correlated with loss of memory B cell formation and failure to mount secondary Ab responses. These results uncover a novel role for CD22 during T-dependent Ab responses and implicate BCR signaling regulation as a critical factor for proper formation of memory B cell precursors in the GC. They also suggest CD22-based immunotherapies could be useful for inhibiting formation of autoAg-specific memory B cells (supported by NIH grants AI44257 and AI52203).

Disclosure: C. Chappell, None; **K. Draves**, None; **E. Clark**, None.

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Prolactin Promotes Survival of Immature B Cells from MRL/Lpr Mice. Karina Chavez-Rueda[1], Rocio Flores-Fernández[1], Francisco Blanco-Favela[1], María Legorreta-Haquet[1], Luis Chávez-Sánchez[1], Rafael Hernández-González[2] and Emiliano Tesoro-Cruz[2]. [1]IMSS, Mexico DF, Mexico, [2]Instituto Nacional de Ciencias Médicas y Nutrición, Mexico DF, Mexico.

Background/Purpose: Prolactin (PRL) plays an important role in modulating the immune response. PRL is secreted by the pituitary gland as well as many other organs and cells, such as lymphocytes. In B cells, PRL enhances antibody production, including those with self-specificity; as such, PRL has been associated with B cell-triggered autoimmune diseases such as *systemic lupus* erythematosus (SLE). In this study, our aims were to determine the expression of PRL-receptor during bone marrow B cell development and whether the presence of high PRL serum concentration influences absolute numbers of developing populations and disease outcome in lupus-prone murine models.

Methods: All of the mice experiments were performed in accordance with approved guidelines established by Mexico (Norma Oficial Mexicana NOM-062-ZOO-1999). The NIH Guide for the Care and Use of Laboratory AnimalsC57BL/6 mice were purchased from Harlan, the MRL/MpJ (MRL) and MRL/MpJFAS^{lpr}(MRL/lpr) mice were purchased from the Jackson Laboratory. The pro-B, pre-B and immature B cells from the bone marrow of mice were purified by flow cytometry and were assayed for the expression of PRL receptor mRNA and protein. The nine weeks old mice were treated with metoclopramide for six weeks to induce high levels of PRL, accelerate SLE symptoms, and the absolute cell numbers of bone marrow B cell subsets were analysed.

Results: Using real time-PCR and flow cytometry, we observed that the PRL-receptor is expressed in bone marrow early B cells (pro-B, pre-B, immature); in lupus prone mice the highest level of expression was found in pro-Bs and immature cells. Immature cells from lupus-prone strains showed a decrease in the absolute numbers of cells with high PRL-receptor expression in response to PRL. Since immature B cells are permanently being subjected to anti-self-elimination mechanisms, we assessed the survival in immature B cell line and immature B cells from mice. Immature B cells incubated with an anti-IgM antibody have increased survival rates in hyperprolactinemic conditions, in the same way in immature B cells lines the mRNA expression of Bcl-xL was increased.

Conclusion: Taken together, these data indicate an important effect of PRL on B cell development, both favouring positive selection and counteracting mechanisms against self-specificity. In this scenario, increased PRL levels would result in the maturation of B cell clones with self-reactivity and an increased risk for developing auto-immune diseases.

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A Dual Role for IFN-γ in Development of Peripheral B Cells in Lupus-Prone MRL/*Lpr* Mice. Takeshi Machida[1], Natsumi Sakamoto[1], Gary S. Gilkeson[2] and Hideharu Sekine[1]. [1]Fukushima Medical University School of Medicine, Fukushima, Japan, [2]Medical University of South Carolina, Charleston, SC.

Background/Purpose: It had been reported previously that IFN-gamma and IFN-gamma-receptor-1 (IFNGR1) were required for auto-Ab production and development of renal disease in lupus-prone MRL/*lpr* mice. At ACR 2011, we reported that MRL/*lpr* mice deficient for the transcription factor IFN regulatory factor-4 (IRF-4), that is required for Th2/Th17 differentiation, developed granulomas in multiple organs with significantly increased numbers of IFN-gamma-producing CD4$^+$ T cells (Th1 cells) and high serum IFN-gamma levels after 12 weeks of age (Fig. 1A). Strikingly, unlike their WT littermates, they also exhibited total loss of splenic CD19$^+$IgM$^+$ B cells by 12 weeks of age. Similar B cell loss was observed in *Irf4*$^{-/-}$ MRL+/+ mice but not in *Irf4*$^{-/-}$ C57BL/6 mice, suggesting a role for IFN-gamma in survival of peripheral B cells in mice with an MRL background. This study aimed to further define roles for IFN-gamma in survival of peripheral B cells and in development of autoreactive B cells in MRL/*lpr* mice.

Methods: *Irf4/Ifng* or *Irf4/Ifngr1* double-gene knockout MRL/*lpr* mice were generated by backcrossing with C57BL/6 mice lacking corresponding genes for 8 generations. Expression levels of CD19, IgM, CD21, CD23, and IFNGR1 on splenic B cells were analyzed by flow. Splenic follicular (FO)- and marginal zone (MZ)-B cells were isolated by cell sorting and frequency of anti-dsDNA Ab-secreting cells was quantified by ELISPOT assay.

Results: The splenic B cell loss observed in *Irf4*$^{-/-}$ MRL/*lpr* mice was restored in *Irf4*$^{-/-}$*Ifng*$^{-/-}$ and *Irf4*$^{-/-}$*Ifngr1*$^{-/-}$ MRL/*lpr* mice even after 12 weeks of age (Fig. 1B).

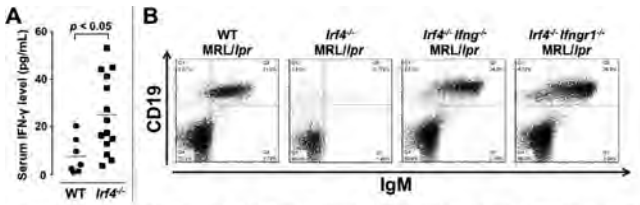

Fig. 1. Serum IFN-γ levels (A) and splenic CD19$^+$IgM$^+$ B-cell populations (B) of 12 weeks old MRL/*lpr* mice.

CD21^{hi}CD23^{lo} MZ-B cells of WT MRL/*lpr* and MRL+/+ mice showed high IFNGR1 expression levels compared to their CD21^{lo}CD23^{hi} FO-B cells. In contrast, MZ- and FO-B cells of C57BL/6 mice showed minimal IFNGR1 expression (Fig. 2A). MZ-B cells of MRL/*lpr* mice showed significantly increased frequency of anti-dsDNA IgM-secreting cells compared to their FO-B cells or MZ/FO-B cells of C57BL/6 mice (Fig. 2B).

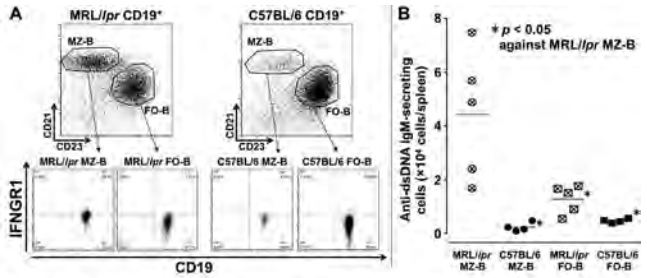

Fig. 2. A, Expression levels of IFNGR1 on splenic MZ- and FO-B cells. B, The numbers of anti-dsDNA IgM-secreting splenic MZ- and FO-B cells estimated by ELISPOT.

Conclusion: Our results suggest a dual role for IFN-gamma in peripheral B-cell development in murine lupus: expression of IFNGR1 on splenic B cells, especially on MZ-B cells, is required for development of autoreactive B cells whereas high levels of serum IFN-gamma impact on their survival.

Disclosure: T. Machida, None; **N. Sakamoto**, None; **G. S. Gilkeson**, None; **H. Sekine**, None.

1949

Defective PTEN Regulation and Function Contributes to B Cell Hyper-Responsiveness in Systemic Lupus Erythematosus. Xiangni Wu[1], Yanxia Ye[1], Jingwen Niu[1], Yang Li[1], Xin Li[1], Xin You[1], Hua Chen[1], Lidan Zhao[1], Xiaofeng Zeng[1], Fengchun Zhang[1], Fulin Tang[1], Wei He[1], Xuetao Cao[2], Xuan Zhang[1] and Peter E. Lipsky[3]. [1]Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [2]School of Basic Medicine, Peking Union Medical College, and Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Beijing, China, [3]NIH, Charlottesville, VA.

Background/Purpose: PTEN regulates normal signaling through the B cell receptor (BCR). In systemic lupus erythematosus(SLE), enhanced BCR signaling contributes to increased B cell activity. We, therefore, examined whether abnormalities in PTEN might contribute to increased B cell activity in SLE.

Methods: We mainly used B cells from peripheral blood of newly diagnosed untreated SLE patients (vs. HC) to determine whether PTEN plays a critical role in the immunodysregulation in patients with SLE. The expression of PTEN protein, and the phosphorylation of Akt and/or STAT3 were examined by flow cytometry and/or western blotting. Expression of candidate microRNAs that could regulate PTEN was identified by TargetScan prediction, and confirmed using a dual luciferase reporter gene assay with a reporter construct containing the *PTEN* 3' UTR. To determine whether the abnormal expression of PTEN and its regulation by these microRNA contribute to B cells function in SLE, we electroporated peripheral B cells with pre-microRNA or an microRNA antagomir in the presence or absence of siPTEN. The levels of PTEN mRNA and microRNAs were assessed by real-time PCR, and the intracellular calcium levels were assessed by Fluo4-AM and then measured by flow cytometry.

Results: By FACS analysis, we found all SLE B cell sub-sets, except for memory B cells, showed decreased expression of PTEN, and the level was inversely correlated with disease activity. Notably, IL-21 induced PTEN expression and also suppressed Akt phosphorylation induced by anti-IgM and CD40L stimulation in normal but not SLE B cells. However, IL-21-induced STAT3 phosphorylation was intact and IL-21 up-regulated PTEN mRNA in SLE B cells. Therefore, expression of candidate microRNAs that could regulate PTEN was examined and SLE B cells were found to express increased levels of miR-7, 21 and 22. These microRNAs down-regulated expression of PTEN, and IL-21 stimulation increased expression of miR-7 and 22 in both normal and SLE B cells. Decreased expression of PTEN in SLE B cells was associated with augmented calcium signaling induced by BCR engagement as well as increased IL-21-mediated B cell proliferation and plasma cells differentiation, and these abnormalities were corrected by a miR-7 antagomir. Moreover, knockdown of PTEN with siRNA significantly increased the baseline calcium signal, and this increase was not altered by either an miR-7 agomir or antagomir. In addition, IL-21-mediated inhibition of the BCR-induced calcium signal as well as Akt phosphorylation was altered when PTEN was knocked down in a very similar manner to that caused by miR-7.

Conclusion: Defective miR-7 regulation of PTEN contributes to B cell hyperresponsiveness in SLE and could be a new target of therapeutic intervention.

Disclosure: X. Wu, None; **Y. Ye**, None; **J. Niu**, None; **Y. Li**, None; **X. Li**, None; **X. You**, None; **H. Chen**, None; **L. Zhao**, None; **X. Zeng**, None; **F. Zhang**, None; **F. Tang**, None; **W. He**, None; **X. Cao**, None; **X. Zhang**, None; **P. E. Lipsky**, None.

1950

Circulating $CD19^+CD38^+CD43^+$ B Cell Subset in SLE Patients Have More Cell Cycle Related Genes Than Healthy Controls. Hiroshi Fujii, Tomoaki Machiyama, Kanae Akita, Yukiko Kamogawa, Ryu Watanabe, Yoko Fujita, Yuko Shirota, Shinichiro Saito, Tomonori Ishii and Hideo Harigae. Tohoku University, Sendai, Japan.

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease associated with deposition of autoantibodies such as anti DNA antibody. After activation of B cells in lymphoid tissues, B cells circulate in the blood as "plasmablast", migrate to bone marrow and reside as plasma cells which produce antibodies. Specific targeting of circulating plasmablast might be a novel strategy for SLE treatment. Recently, $CD19^+CD38^+CD43^+$ B cell subset from healthy control (HC) are reported to be "pre-plasmablast" phenotype based on gene expression profiling. The clarification of biological properties of $CD19^+CD38^+CD43^+$ B cell subset in SLE patients might provide us a clue to specific targeting to this population. In this study, we analyzed the gene profiling of the circulating $CD19^+CD38^+CD43^+$ B cells in HC and SLE using Agilent based microarray technologies.

Methods: Naïve B cell ($CD19^+CD27^-CD38^-CD43^-$), memory B cell($CD19^+CD27^+CD38^-CD43^-$) and $CD19^+CD38^+CD43^+$ B cell were sorted with FACS AriaII from HC and SLE (n=4, respectively). Total RNA were isolated and labelled, then mRNA was analyzed with Aglinet microarray. Gene profiling data was analyzed with GeneSpring and Ingenuity Pathway Analysis software. Statistic analysis was performed by Fisher's exact test in upregulator, canonical pathway and gene function analysis, and by modified t-test in comparative analysis between HC and SLE or each B cell subset.

Results: Comparison of gene profiling of $CD19^+CD38^+CD43^+$ B cell and naïve/memory B cell showed that genes differentially expressed in $CD19^+CD38^+$ $CD43^+$ B cell were significantly regulated by several transcriptional factors which play roles in cell cycle and proliferation, such as E2F1, MYC E2F3 ($p=4.47 \times 10^{-19}$, 1.69×10^{-16}, 3.73×10^{-9}, respectively) in addition to XBP-1, PRDM and PAX5 which are well known to function in differentiation from B cell to plasma cells. In comparison of each B cell subset between HC and SLE patients, 2467 genes were significantly changed in $CD19^+CD38^+CD43^+$ B cell. Among them, 1967 genes were changed only in $CD19^+CD38^+CD43^+$ B cell and 123 genes were changed commonly in $CD19^+CD38^+CD43^+$ B cell, naïve and memory B cell. Canonical pathway analysis showed that interferon signaling was significantly up-regulated in the commonly changed genes ($p=1.35 \times 10^{-6}$), in contrast, cell cycle related pathways, such as Role of BRCA1 in DNA Damage Response, Mismatch Repair in Eukaryotes and Cell Cycle Control of Chromosomal Replication were significantly increased ($p=7.41 \times 10^{-7}$, 3.09×10^{-6}, 2.82×10^{-5}, respectively) in only $CD19^+$ $CD38^+$ $CD43^+$ B cell increased genes. 266 genes were cell cycle related genes among 1516 genes up-regulated in $CD19^+$ $CD38^+$ $CD43^+$ B cell.

Conclusion: Gene profiling analysis suggested that $CD19^+CD38^+$ $CD43^+$ B cell have more proliferating properties than naïve, memory B cell subsets and this population of SLE patients express more cell cycle related genes than HC.

Disclosure: H. Fujii, None; **T. Machiyama**, None; **K. Akita**, None; **Y. Kamogawa**, None; **R. Watanabe**, None; **Y. Fujita**, None; **Y. Shirota**, None; **S. Saito**, None; **T. Ishii**, None; **H. Harigae**, None.

1951

A Novel $CD27^{(-)}$ Spleen Tyrosine Kinase (Syk) Bright Memory B-Cell Subset Is Expanded in SLE. Sarah Fleischer[1], Claudia Giesecke[1], Henrik Mei[1], Peter E. Lipsky[2], Capucine Daridon[3] and Thomas Dörner[3]. [1]Charité University Medicine Berlin, CC12, Dept. Medicine/Rheumatology and Clinical Immunology and German Rheumatism Research Center Berlin (DRFZ), Berlin, Germany, Berlin, Germany, [2]Peking Union Medical College Hospital, Beijing, China, [3]Charité University Medicine Berlin, Berlin, Germany.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease known to be associated with a breakdown of self-tolerance, B-cell hyperactivity and disturbed B-cell homeostasis of peripheral B-cell subsets. To analyze in more detail the extent to which the B- cell antigen receptor (BCR) proximal spleen tyrosine kinase (Syk) contributes to B-cell abnormalities in SLE, comprehensive functional and phenotypic analyses on SLE B-cells were performed.

Methods: B-cells from healthy donors (HD) and SLE patients were analyzed by flow cytometry to assess basal expression of Syk and phosphorylated (p-)Syk. B-cell subsets expressing distinct levels of Syk were identified and characterized phenotypically by flow cytometry, microscopy and molecularly to assess IgVH rearrangements. Their functions were analyzed by *in vitro*differentiation assays into plasma-cells and Syk induction by cytokines.

Results: A significantly increased frequency of $CD27^{(-)}$ B-cells with enhanced expression of Syk (Syk^{++}) was found specifically in SLE patients. $CD27^{(-)}Syk^{++}$ B-cells showed a substantially increased Syk and basal p-Syk expression as well as an increased cytoplasmic Syk accumulation and increased Syk phosphorylation upon BCR engagement compared to $CD27^{(-)}Syk^{+}$ B-cells. Furthermore, $CD27^{(-)}Syk^{++}$ B-cells were characterized as $CD38^{(-)}$ as well as $CD19^{++}$, $CD20^{++}$ and mainly $CD21^{(-)}$ with reduced ABC-B1 transporter activity and exhibited somatically mutated IgVH rearrangements. $CD27^{(-)}Syk^{++}$ B-cells showed an enhanced differentiation into IgG secreting plasma-cells in contrast to $CD27^{(-)}Syk^{+}$ cells. Finally, Syk^{++} B-cells were inducible *in vitro* by stimulation with IFN-γ, LPS or TNF-α.

Conclusion: SLE patients exhibit an increased frequency of a novel $CD27^{(-)}Syk^{++}$ subset of B-cells with memory B-cell characteristics which candidate as a source of increased plasma-cells characteristic of SLE patients. Moreover, the evidence indicates that the use of intracellular markers, such as Syk, permitted a distinction between naïve and memory B-cell subsets within the $CD27^{(-)}$ B-cells and and a more precise delineation of the $CD27^{(-)}$ memory B-cell subset.

Disclosure: S. Fleischer, None; **C. Giesecke**, None; **H. Mei**, None; **P. E. Lipsky**, None; **C. Daridon**, None; **T. Dörner**, None.

1952

Elucidation of Molecular Mechanisms of Breg Induction in Autoimmune Diseases. Shun-ichiro Ota, Hiroaki Niiro, Naoko Ueki, Yuri Hirosaki, Hirofumi Tsuzuki, Kumiko Noda, Siamak Jabbarzadeh-Tabrizi, Atsushi Tanaka, Hiroki Mitoma, Mitsuteru Akahoshi, Yojiro Arinobu, Hiroshi Tsukamoto and Koichi Akashi. Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan.

Background/Purpose: The advent of B-cell depletion therapy in autoimmune diseases identifies a novel B cell population, referred to as regulatory B cells (Bregs), that exerts regulatory functions via IL-10 production. We previously showed that human Bregs are strongly induced in IgM-memory B cell subsets following TLR9 stimulation and Breg induction is significantly impaired in systemic lupus erythematosus (SLE). The underlying mechanisms of these findings, however, remain largely elusive. In the present study we have sought to elucidate how Bregs are induced and their function is crippled in SLE patients.

Methods: Gene expression and protein production in B cells were assessed by quantitative PCR, ELISA and flow cytometry analysis. Bregs were co-cultured with T cells, and proliferation and IFNγ production of T cells were assessed. The knock-down vector of Blimp-1 was generated and transfected into B cells.

Results: We first tested the function of Bregs in healthy controls and SLE patients. TLR9-induced Bregs from healthy controls inhibited proliferation and IFN γ production of T cells, while such Bregs from SLE patients exerted less regulatory effects on the function of T cells. A previous study in the mouse system suggested that Breg induction is associated with plasma cell differentiation of B cells. In light of a critical role of Blimp-1 in plasma cell differentiation, we generated Blimp-1 knocked down B cells and found that Breg induction is impaired by Blimp-1 silencing. Intriguingly, fleshly-isolated B cells from SLE patients exhibited higher basal levels of Blimp-1 and IL-10 expression, while further induction of Blimp-1 by TLR9 stimulation was significantly abrogated along with less IL-10 production, highlighting the induction of Blimp-1, but not its levels, in Breg induction.

Conclusion: Together, these findings provide not only a better understanding of molecular mechanisms of Breg induction in humans, but also a novel clue to revitalizing Bregs for the treatment of SLE.

Disclosure: S. I. Ota, None; **H. Niiro**, None; **N. Ueki**, None; **Y. Hirosaki**, None; **H. Tsuzuki**, None; **K. Noda**, None; **S. Jabbarzadeh-Tabrizi**, None; **A. Tanaka**, None; **H. Mitoma**, None; **M. Akahoshi**, None; **Y. Arinobu**, None; **H. Tsukamoto**, None; **K. Akashi**, None.

1953

Circulating Plasmablasts from Patients with Systemic Lupus Erythematosus Produce Autoantibodies Reactive to Epstein-Barr Virus. Yangsheng Yu[1], Song Li[1], Run Fan[2], Yinshi Yue[1], Hongyan Liao[1], Zhixin Wang[1], Lin Huang[1], Qin Wang[3], Michelene Hearth-Holmes[1], Amy Cannella[1], W. Winn Chatham[2], Robert Kimberly[2], James O'Dell[1], Lynell Klassen[1], Robert Carter[2], Zhixin Zhang[1] and Kaihong Su[1]. [1]University of Nebraska Medical Center, Omaha, NE, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Shanghai Jiao Tong University, Shanghai, China.

Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by the over-production of high affinity autoantibodies. It is not clear how such autoantibodies are generated during the course of lupus. The purpose of this study was to analyze the antibody repertoire in circulating plasmablasts in adult SLE patients and explore the molecular basis for the generation of such antibodies in SLE.

Methods: Eight patients with active SLE and seven healthy controls were recruited for the study. Recombinant antibodies were cloned from circulating plasmablasts by single cell RT-PCR analyses. Auto and poly-reactivities of these antibodies were measured by indirect immunofluorescent anti-nuclear antibody assays (IFA-ANA) and ELISAs using a panel of antigens (dsDNA, ssDNA, insulin, and LPS) respectively. Anti-Epstein-Barr Virus (EBV) reactivity of antibodies was examined by ELISAs using EBV viral capsid antigen (VCA) as capturing antigens.

Results: In patients with active SLE, the relative frequencies of circulating plasmablasts were significantly increased compared to those of healthy controls (10.6% vs 1.0%, $p=0.0013$, n=8). Circulating plasmablasts from SLE patients, but not healthy controls, predominantly produced auto/polyreactive antibodies (autoreactive: 24.8% vs 4%, $p<0.0001$, n=8; polyreactive: 58.5% vs 11.3%, $p<0.0001$, n=8). Sequence analyses revealed excessive receptor editing and enrichment of V_H replacement products in immunoglobulin (Ig) genes derived from SLE patients (20.6% vs 7.9%, $p=0.0012$, n=8). Interestingly, 76.7% of the V_H replacement products derived from plasmablasts of SLE patients encoded auto/polyreactive antibodies. Furthermore, about 20% of circulating plasmablast-derived antibodies from SLE patients reacted with EBV VCA antigens. These SLE-derived anti-EBV antibodies cross-reacted with dsDNA and other nuclear antigens. V_H replacement products were also significantly enriched in Ig heavy chain genes encoding anti-EBV antibodies.

Conclusion: The elevated frequencies of auto/polyreactive antibodies, enrichment of V_H replacement products, and production of anti-EBV-VCA antibodies in plasmablasts from SLE patients indicate that autoreactive B cells in active SLE patients are positively selected by EBV antigens. This finding supports the hypothesis that preventing EBV infection is a beneficial intervention to limit active disease in SLE patients.

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1954

Successfull Long-Term Depletion of Memory Plasma Cells Requires a Combined Depletion of Plasma Cells and Their Precurors in NZB/W Mice. Adriano Taddeo[1], Laleh Khodadadi[1], Qingyu Cheng[2], Andreas H. Radbruch[1], Falk Hiepe[3] and Bimba F. Hoyer[2]. [1]Deutsches Rheumaforschungszentrum, Berlin, Germany, [2]Charité University Medicine, Department of Medicine/Rheumatology and Clinical Immunology and German Rheumatism Research Centre Berlin (DRFZ), Germany, Berlin, Germany, [3]Charité – University Hospital, Berlin, Germany.

Background/Purpose: Autoantibodies contribute significantly to the pathogenesis of systemic lupus erythematosus (SLE). **T**he long-lived plasma cells (LLPC) secreting such autoantibodies are unfortunately refractory to conventional immunosuppressive treatments. Although generated long before the disease becomes clinically apparent, the kinetic of their generation in established disease is unclear. Here, we analyze the generation of autoreactive LLPCs in lupus-prone NZB/W F1 mice over their lifetime, and LLPC regeneration after depletion.

Methods: BrdU-pulse chase experiments over two weeks in mice of different age were used to analyze the generation of LLPC. Treatments were performed using Bortezomib, cyclophosphamide and a combination of both for very short (36h), short (5 days) and "longterm" treatment (15 and 30 days). Plasma cell numbers were quantified using flowcytometry. Autoreactive plasma cells were analyzed using ELIspot.

Results: Autoreactive LLPCs are established in the spleen and bone marrow of lupus-prone mice very early in ontogeny, before week 8 and before the onset of symptoms. The generation of LLPCs then continues throughout life. LLPC counts in the spleen plateaued by week 10, but continued to increase in the bone marrow. After depletion of LLPCs by the proteasome inhibitor bortezomib, their numbers regenerate within two weeks. A persistent, therapeutic depletion of LLPCs was achieved only by combining a short treatment with bortezomib with a longterm depletion of plasma cell precursors.

Conclusion: In lupus-prone NZB/W F1 mice, autoreactive LLPCs are generated throughout life. Their sustained therapeutic elimination requires both, depletion of LLPCs and the inhibition of their regeneration by specific depletion of their precursors.

Disclosure: A. Taddeo, None; **L. Khodadadi**, None; **Q. Cheng**, None; **A. H. Radbruch**, None; **F. Hiepe**, None; **B. F. Hoyer**, None.

1955

Disparity in Internalisation of Monoclonal Antibodies Targeting B Cell Antigens and Regulation By Fc Gamma Receptor IIb: Implications for Targeted Therapy in SLE. Venkat Reddy[1], Geraldine Cambridge[2], David A. Isenberg[2], Mark Cragg[3] and Maria J. Leandro[2]. [1]Centre for Rheumatology Research, Division of Medicine, University College London, London, United Kingdom, [2]Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom, [3]Southampton University, Southampton, United Kingdom.

Background/Purpose: Monoclonal antibodies (mAbs) targeting B cell antigens CD20 and CD22 are used to treat patients with SLE either in the clinic or in clinical trials whilst anti-CD19mAbs have been studied *in vitro*. The main mechanisms of action of these mAbs are depletion and immunomodulation. Internalisation of antigens bound to mAbs is key to immunomodulatory action whereas retention of mAbs on cell surface evokes immune effector mechanisms triggering depletion.

Methods: We studied internalisation of anti-CD19 mAb (RFB9), type1 anti-CD20 mAb (Rituximab), type2 anti-CD20mAb (BHH2, glycosylated GA101), anti-CD22 mAb (4KB128) and anti-CD38mAb (AT13/5h) in 11 patients with SLE. Internalisation of mAbs was assessed using the surface fluorescence-quenching assay on isolated B cells. We used AT10, a mAb against the Fcgamma receptor II (CD32), to assess whether it regulated internalisation of mAbs. Isolated B cells were incubated with mAbs +/− AT10. Paired "t' test or Mann-Whitney U test was used to compare groups, as appropriate.

Results: We performed surface fluorescence-quenching assay in 11 patients with SLE, assessed internalisation of mAbs after 6 hours of incubation with mAbs (5 mcg/mL), with or without prior incubation with AT10 (50mcg/mL) in 6/11. The median % of surface accessible mAbs was 68, 48, 71, 23 and 76 for anti-CD19, type1 anti-CD20, type2 anti-CD20, anti-CD22 and anti-CD38, respectively. However, prior incubation with AT10 significantly reduced internalisation of *only*anti-CD20 antibodies, a mean reduction of 12% and 4% for type1 and type2, respectively (Figure 1.A). A remarkable variability between patients in both the extent of internalisation and reduction in internalisation with AT10 was noted for rituximab, but not BHH2 (type2 anti-CD20mAb).

Internalisation of type1 and 2 anti-CD20mAbs in B cell subpopulations Internalisation of type1, but not type2, anti-CD20mAbs was significantly lower for post-switched cells (IgD-CD27+) when compared with other B cell subpopulations (naïve, IgD+CD27+; unswitched, IgD+CD27+; and double negative, IgD-CD27-) ($p<0.05$ for all). AT10 reduced internalisation of type1, but not type2, mAb in all B cell subpopulations (Figure 1.B). Internalisation was also 9% greater for IgD+ vs IgD- Bcells ($p<0.005$) suggesting a role for IgD in internalisation of mAbs, probably in synergy with Fcgamma receptor IIb (as B cells predominantly express the inhibitory Fcgamma receptor IIb)(Figure 1.C).

Conclusion: Disparity in internalisation of mAbs occurs, with a high rate for anti-CD22mAb, probably related to its high physiological rate of endocytosis and less so for type1 anti-CD20 mAbs. Disparity between B cell subpopulations in internalisation of type 1 anti-CD20 mAbs may occur due to differential expression of IgD and Fcgamma receptor IIb. Therefore, internalisation of mAbs poses important therapeutic implications for targeted therapy in SLE.

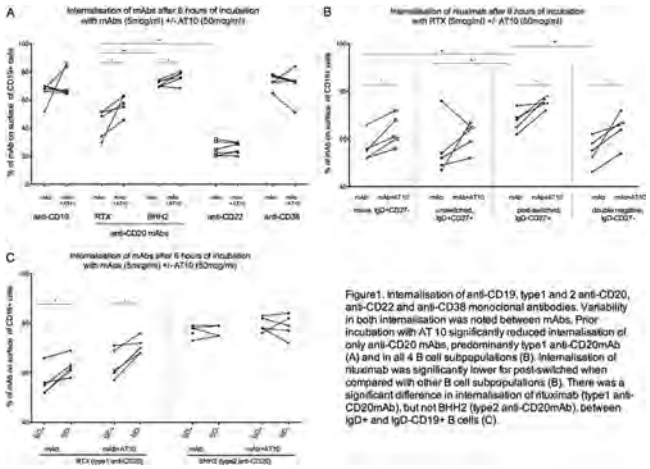

Figure1. Internalisation of anti-CD19, type1 and 2 anti-CD20, anti-CD22 and anti-CD38 monoclonal antibodies. Variability in both internalisation was noted between mAbs. Prior incubation with AT 10 significantly reduced internalisation of only anti-CD20 mAbs, predominantly type1 anti-CD20mAb (A) and in all 4 B cell subpopulations (B). Internalisation of rituximab was significantly lower for post-switched when compared with other B cell subpopulations (B). There was a significant difference in internalisation of rituximab (type1 anti-CD20mAb), but not BHH2 (type2 anti-CD20mAb), between IgD+ and IgD-CD19+ B cells (C).

Disclosure: V. Reddy, None; **G. Cambridge**, None; **D. A. Isenberg**, None; **M. Cragg**, None; **M. J. Leandro**, None.

1956

Increased IL-6 Production By Effector B Cells in Giant Cell Arteritis and Polymyalgia Rheumatica. Kornelis S.M. van der Geest[1], Wayel H. Abdulahad[1], Gerda Horst[1], Abraham Rutgers[1], Annemieke M.H. Boots[2] and Elisabeth Brouwer[3]. [1]University Medical Center Groningen, Groningen, Netherlands, [2]University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [3]UMCG, Groningen, Netherlands.

Background/Purpose: The role of B cells in auto-immunity may extend beyond the production of auto-antibodies. B cells can influence T cell responses via antigen presentation and secretion of cytokines. Pathogenic T cell responses are critical in giant cell arteritis (GCA) and polymyalgia rheumatica (PMR). Cytokine-producing B cells with distinct effects on T cells have been described. $B_{regulatory}$ cells suppress T cell responses via IL-10, whereas $B_{effector}$ cells promote inflammation via secretion of TNF-α and/or IL-6. IL-6 is currently considered important in the pathogenesis of GCA and PMR. Little is known on the contribution of $B_{effector}$ and $B_{regulatory}$ cells to the immunopathology of GCA and PMR. Here, we studied the distribution of $B_{effector}$ cells and $B_{regulatory}$ cells in GCA and PMR patients before and after corticosteroid treatment.

Methods: Circulating B cells were analyzed in 34 newly-diagnosed, non-treated patients with GCA and PMR, and in 44 follow-up samples of GCA and PMR patients receiving corticosteroids for 2 weeks and 3 months. For comparison, 40 age-matched, healthy controls (HCs) were included. Serum BAFF levels were determined by ELISA and temporal arteries were studied by immunohistochemistry. Intracellular staining for TNF-α, IL-6 and IL-10 was performed after stimulating B cells with PMA and Ca2+ ionophore in the presence of Brefelin A for 4 hours.

Results: Newly-diagnosed GCA and PMR patients had decreased numbers of circulating CD19+ B cells when compared to HCs. B cell numbers recovered rapidly in treated GCA and PMR patients in remission. This recovery was not achieved by compensatory hyperproliferation or enhanced bone marrow production. The low B cell counts in newly-diagnosed GCA and PMR patients were associated with an increase in serum levels of the B cell growth factor BAFF. Serum BAFF levels diminished upon the return of B cells during remission. Functional characterization of the B cells showed that circulating numbers of IL-10 producing $B_{regulatory}$ cells remain normal in GCA and PMR patients, irrespective of disease activity and treatment. In contrast, circulating numbers of TNF-α producing $B_{effector}$ cells were profoundly decreased in newly-diagnosed GCA and PMR patients, but recovered during remission. Moreover, the returning $B_{effector}$ cells in GCA and PMR patients demonstrated an enhanced capacity to produce IL-6. Few B cells were found in temporal artery biopsies of GCA patients.

Conclusion: Our combined data indicate that $B_{effector}$ cells, but not $B_{regulatory}$ cells, are redistributed during active disease and quickly return upon remission. These $B_{effector}$ cells are characterized by an enhanced capacity to produce IL-6. The role of these IL-6 producing $B_{effector}$ cells in GCA and PMR warrants further investigation, as B cells and IL-6/IL-6R are potential targets for treatment.

Disclosure: K. S. M. van der Geest, None; **W. H. Abdulahad**, None; **G. Horst**, None; **A. Rutgers**, None; **A. M. H. Boots**, MSD, 3; **E. Brouwer**, None.

1957

Dysregulation of CC Chemokines at Microvascular Endothelial Cells of Blood and Lymphatic Vessels Under Inflammatory Conditions. Lisa Rump-Goodrich[1], Ayman Askari[2], Derek Mattey[3] and Jim Middleton[4]. [1]Keele University, Gobowen, United Kingdom, [2]Robert Jones and Agnes Orthopaedic Hospital, Gobowen, United Kingdom, [3]Keele University, Stoke-on-Trent, United Kingdom, [4]Bristol university, Bristol, United Kingdom.

Background/Purpose: Inflammation in the rheumatoid arthritis (RA) synovium is directly associated with inflammatory cell migration across microvasculature endothelial cells (ECs), and their persistence within the synovium.

It has been shown that lymphatic vessel chemokine presentation increases in RA and so should increase the removal of the interstitial fluid containing the invading inflammatory cells which are at significant levels within the fluid. However, dysregulation of chemokine presentation between RA blood vessel and lymphatic vessel ECs may lead to reductions in removal of the ever increasing joint interstitial fluid and persistance of the inflammatory cells.

Methods: Immunohistochemistry was performed on human synovial tissue to using the pan-endothelial cell marker von-Willebrand factor, and the lymphatic EC marker LYVE-1 to assess the presence of CCL7, CCL14, CCL16 and CCL22.The number of vessels positive for each marker and the chemokine were counted to a maximum if 15 vessels over three fields of view (FOV) from 8 RA and 6 on-RA samples. Transmigration of mononuclear cells isolated from RA blood was performed over confluent human dermal lymphatic EC (HDLEC) monolayers in response to human CCL7 and analysed by FACS analysis. Inflammatory conditions were stimulated by activating overnight with 100ng/mL 100ng/mL TNF-α with 100ng/mL IFN-γ.

Results: Significant increases in CCL14 and CCL22 were obsereved in RA blood vessel ECs compared to non-RA ECs (P=0.0041 and 0.014 respectively). A significant decrease in CCL7 in RA lymphatic ECs compared to non-RA lymphatic ECs was observed ($p = 0.011$). Furthermore, significant increases in RA monocyte migration were observed in response to CCL7 ($p = 0.002$). The greatest increase to be at 250ng/ml CCL7 ($p = 0.013$) with a significant increase in monocyte migration also seen at 100ng/ml CCL7 ($p = 0.037$) compared to 0ng/ml.

Conclusion: The significant decrease of CCL7 in lymphatic ECs, combined with it having the greatest chemotactic ability for monocytes for the tested chemokines suggests CCL7 may be of importance in lymphatic removal of infiltrates in the inflamed RA synovium. Reduction in CCL7 may therefore be functional in leukocyte persistence and accumulation in the RA synovium.

Disclosure: L. Rump-Goodrich, None; **A. Askari**, None; **D. Mattey**, None; **J. Middleton**, None.

1958

Pyrrolopyrimidine Derivatives That Inhibit Binding of BAFF to Its Receptor, BR3, Are Drug Candidates for Primary Sjögren's Syndrome. Keiko Yoshimoto[1], Eriko Ishioka[1], Katsuya Suzuki[1], Takahiro Itou[2], Tomohiro Sugano[2], Hajime Yamada[2], Ayumu Okuda[2], Hiroyuki Ishiwata[2], Takeshi Doi[2], Takatsugu Hirokawa[3] and Tsutomu Takeuchi[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Kowa Co., Ltd., Higashimurayama-City, Japan, [3]National Institute of Advanced Industrial Science and Technology (AIST), Koto-ku, Japan.

Background/Purpose: We have been investigating the possible involvement of BAFF (B cell activating factor of TNF family) in the pathogenesis of primary Sjögren's syndrome (pSS). We found that soluble BAFF (sBAFF) robustly increased IL-6 production in vitro by peripheral monocytes of patients with pSS, and that the expression level of a BAFF receptor (BR3) was significantly elevated in pSS monocytes compared to that of normal monocytes. Additionally, the proportion of BR3-positive monocytes to total monocytes was positively and significantly correlated with the sBAFF-induced IL-6 production and the serum IgG level of pSS patients. These data collectively suggest that the elevated expression of BR3 on monocytes is involved in the pathogenesis of pSS. Consequently, our findings suggest that BR3 is a therapeutic target to treat pSS. However, no compounds except antibodies were reported to have inhibitory activities against BAFF signaling so far. In this study, we show some of our latest data about drug discovery for pSS aiming at BAFF signaling pathway.

Methods: High-throughput screening (HTS) of a chemical library was carried out to search for compounds that block binding of sBAFF to BR3. To this end, BR3 expressing CHO-K1 cells were established by transfection of a full-length cDNA of human BR3. Transfectants were cultured in the presence of FMAT Blue-labeled sBAFF and each compound in 384-well plates, and the binding of sBAFF to the cells was monitored by an Applied Biosystems 8200 Cellular Detection System.Hit compounds were further screened as follows: IFN-γ-stimulated THP-1, a human acute monocytic leukemia cell line, was cultured in vitro with sBAFF and each compound for 96 hr, and the cumulative amount of IL-6 produced by the cells was measured by ELISA. Cytotoxicities of the compounds were analyzed by measuring LDH in culture supernatants. The expression level of NF-κB in the cells was analyzed by quantitative PCR.

Results: A total of 18,562 compounds were examined for inhibitory activities of sBAFF binding to BR3. To eliminate false positives, inhibitory activities of the HTS-hits against IL-6 production by sBAFF-stimulated THP-1 were measured. Their cytotoxicities, which result in the reduction of IL-6 production, were also examined. As a result, two pyrrolopyrimidine derivatives, BIK12 and BIK13, showed substantial inhibition of sBAFF-binding. IC_{50} values for BIK12 and 13 were 11 and 6 μM, respectively. sBAFF-induced IL-6 production by THP-1 was significantly suppressed by these compounds in a dose dependent manner, while the compounds had no cytotoxicities. Additionally, the expression of NF-κB in the cells was also repressed by BIK12 and 13. These results collectively suggest that these compounds suppress IL-6 production by THP-1 through an inhibition of binding of sBAFF to its receptor, BR3, and possibly subsequent BAFF signaling pathway.

Conclusion: We have successfully discovered low molecular weight compounds which have inhibitory activities against BAFF signaling. Although IC_{50} values were not so low, these compounds may provide not only lead compounds for therapeutic drugs of pSS, but also novel tools to explore the pathological mechanism of pSS.

Disclosure: K. Yoshimoto, None; **E. Ishioka**, None; **K. Suzuki**, None; **T. Itou**, Kowa Co., Ltd., 3; **T. Sugano**, Kowa Co., Ltd., 3; **H. Yamada**, Kowa Co., Ltd., 3; **A. Okuda**, Kowa Co., Ltd., 3; **H. Ishiwata**, Kowa Co., Ltd., 3; **T. Doi**, Kowa Co., Ltd., 3; **T. Hirokawa**, None; **T. Takeuchi**, None.

1959

Interaction of PDE4 and β-Arrestin Reverses Anti-Inflammatory Effects of Catecholamine-Producing Cells in Chronic Arthritis Via Adrenoceptor Switching from Gαs to GαI Signalling. Zsuzsa Jenei-Lanzl[1], Janika Zwingenberg[2], Torsten Lowin[3] and Rainer Straub[2]. [1]1Laboratory of Experimental Rheumatology and Neuroendocrine Immunology, Regensburg, Germany, [2]University Hospital Regensburg, Regensburg, Germany, [3]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, University Hospital of Regensburg, Regensburg, Germany.

Background/Purpose: In recent studies, we confirmed the anti-inflammatory effects of tyrosine-hydroxylase (TH)-positive catecholamine producing synovial cells in chronic arthritis. Other studies described that inhibitors of the cAMP-degrading enzyme, phosphodiesterase 4 (PDE4), exhibit anti-inflammatory effects (see FDA-approved therapy with apremilast). Furthermore, Lefkowitz et al.[1] demonstrated that the interaction of PDE4 with β-arrestin at β-adrenoceptor can result in a catecholamine receptor switching from Gαs to Gαi signalling with subsequent ERK1/2 activation. Therefore, the aim of our study was to investigate whether and how PDE4 and catecholamine signaling interact and possibly influence inflammatory responses in chronic arthritis.

Methods: Immunostaining of PDE4 and β-arrestin and visualization of presumed PDE4/β-arrestin interaction (via proximity ligation assay) was performed in synovial tissue and in synovial cell culture of rheumatoid arthritis (RA) and osteoarthritis (OA) patients. Synovial cells were cultivated under normoxic or hypoxic conditions (the microenvironment of inflamed joints is hypoxic) with/without PDE4 inhibitor and/or different concentrations of catecholamine receptor agonists, adenosine receptor agonists, and/or blocker of Gαi-mediated pathways (pertussis toxin, ERK1/2 blocker). After 24 hours, supernatants were collected, cytokine concentrations were determined, and activation of ERK1/2 signaling was analyzed.

Results: Both, PDE4 and β-arrestin were detected in the synovial tissue and in synovial cell culture of OA and RA patients. Moreover, the interaction of PDE4/β-arrestin was demonstrated with proximity ligation assay. Under hypoxia, Gαs-coupled adrenoceptor agonists decreased TNF release in both OA and RA synovial cell culture. In contrast to normoxia, hypoxic incubation with PDE4 inhibitor alone and co-incubation with PDE4 inhibitor and catecholamine receptor agonists with Gαs-protein pathway increased TNF release, which was reversed by pertussis toxin or by ERK1/2 blocker. Western blot analyses demonstrated an increased ERK1/2 activation after treatment with Gαs-coupled adrenoceptor agonist alone or after co-incubation with PDE4 inhibitor and Gαs-coupled adrenoceptor agonist.

Conclusion: In summary, this study presents that PDE4 and b-arrestin interact at catecholamine receptors in human arthritic synovial tissue inducing catecholamine receptor switching from Gαs to Gαi signalling, which results in the reversal of catecholamine-induced anti-inflammatory effects at high neurotransmitter concentrations. This phenomenon might be responsible for possible reduced efficacy of PDE4 inhibitor treatment in some chronic arthritic diseases.

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Disclosure: Z. Jenei-Lanzl, None; **J. Zwingenberg**, None; **T. Lowin**, None; **R. Straub**, None.

1960

NF-κB-Inducing Kinase (NIK) Is Expressed in Synovial Endothelial Cells in Early Arthritis Patients and Correlates with Local Disease Activity and Systemic Markers of Inflammation. Karen I. Maijer[1], Ae-Ri Noort[2], Maria J. H. de Hair[1], Christiaan van der Leij[2], Katinka P.M. van Zoest[2], Danielle M. Gerlag[3], Mario Maas[2], Paul-Peter Tak[1] and Sander W. Tas[2]. [1]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [3]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands.

Background/Purpose: The NF-κB family of transcription factors is strongly involved in synovial inflammation. We have previously shown that NF-κB-inducing kinase (NIK) is a key regulator of inflammation-induced angiogenesis in rheumatoid arthritis (RA) synovial tissue (ST). In this study we investigated the expression of NIK in ST of early arthritis patients and in autoantibody-positive individuals at risk for developing RA, and correlated this with both systemic markers of disease activity (ESR and CRP) and with local disease activity in DMARD-naive early arthritis patients including magnetic resonance imaging (MRI) inflammation scores of the biopsied joint.

Methods: Arthroscopic ST biopsy samples were obtained from 154 early arthritis patients (arthritis duration less than 1 year, disease-modifying antirheumatic drug (DMARD) naïve; RA (n=64), unclassified arthritis (UA; n=61), crystal arthropathy (n=11), osteoarthritis (n=4) and spondyloarthritis (n=14)) and from 54 IgM-rheumatoid factor and/or anti-citrullinated peptide antibody positive individuals at risk for developing RA, who never had any evidence of arthritis upon physical examination. ST sections were stained for the expression of NIK and evaluated by digital image analysis. In addition, measures of disease activity such as ESR, CRP and swelling of the biopsied joint (score of 0 (no swelling) – 3 (severe swelling)) were collected. In a subset of these patients contrast enhanced MRI was performed in the same joint and scored for effusion, synovitis, edema, cartilage degeneration and erosions, each in 4–6 compartments. A score of 0–3 for each compartment was given and a total MRI score was calculated (0–81).

Results: In early arthritis patients, NIK was predominantly expressed in endothelial cells (EC) of small blood vessels. No significant difference in NIK expression was observed between baseline diagnosis groups. However, NIK^+ EC were significantly increased in UA patients that remained undifferentiated after 2 years. Furthermore, we observed that NIK^+ EC may correlate better with disease activity than vWF^+ EC, since NIK expression correlated with ESR ($r=0.184$; $p=0.024$), CRP ($r=0.194$; $p=0.017$), swelling of the biopsied joint ($r=0.297$; $p<0.001$), MRI effusion ($r=0.665$; $p<0.001$), MRI synovitis ($r=0.632$; $p<0.001$) and MRI total score ($r=0.569$; $p<0.001$). NIK expression did not significantly correlate with edema, cartilage damage and erosion scores. In 18.5% of autoantibody-positive individuals NIK^+ EC were present in the synovium before the clinical onset of arthritis, but this did was not predictive for the development of arthritis.

Conclusion: We demonstrate that NIK^+ EC are already present in the earliest phase of synovial inflammation and may be indicative of high angiogenic activity in the inflamed synovial tissue. Therefore, NIK^+ EC may play an important role in the persistence of synovial inflammation. Collectively, our data underscore the importance of angiogenesis in synovial inflammation and identify NIK as a potential therapeutic target in arthritis to prevent the switch from acute to chronic inflammation.

Disclosure: K. I. Maijer, None; **A. R. Noort**, None; **M. J. H. de Hair**, None; **C. van der Leij**, None; **K. P. M. van Zoest**, None; **D. M. Gerlag**, GlaxoSmithKline, 3; **M. Maas**, None; **P. P. Tak**, GlaxoSmithKline, 3; **S. W. Tas**, None.

1961

Chemokine-like Receptor 1 (CMKLR1) is Expressed on Synoviocytes and Proinflammatory Monocytes in Arthritis and is Predominantly Regulated By β arrestin 2 and G Protein Coupled Receptor Kinase (GRK) 6. D. Stephen Serafin[1], Maria F. Sassano[2], Daniel Mattox[1], Roman Timoshchenko[1], Matthew J. Billard[1], David P. Siderovski[3], Bryan Roth[2] and Teresa K. Tarrant[1]. [1]Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Dept. of Pharmacology, University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]West Virginia University School of Medicine, Morgantown, WV.

Background/Purpose: Chemokine-like receptor 1 (CMKLR1) is a G protein-coupled receptor (GPCR) expressed by inflammatory monocytes and up-regulated in fibroblast-like synoviocytes (FLSs), both of which are pathogenic in osteoarthritis (OA) and rheumatoid arthritis (RA). Its cognate ligand, chemerin, is a chemoattractant for invading inflammatory cells and is present in the synovial lining of arthritis patients. In OA and RA, chemerin/CMKLR1 signaling contributes to disease pathogenesis via recruitment of inflammatory leukocytes and stimulates breakdown of cartilage matrix by metalloproteases.

CMKLR1, like most GPCRs, is desensitized by recruitment of G protein receptor kinases (GRKs) and β-arrestins. Due to the significant role of chemerin/CMKLR1 interaction in human inflammatory arthritis, we examined the mechanism of CMKLR1 regulation by G protein receptor kinases (GRK) 2, 3, and 6 and β-arrestin-2.

Methods: De-identified, healthy, OA, and RA human FLSs were cultured for measurement of relative gene expression by qRT-PCR of CMKLR1, GRK2, GRK3 and GRK6 as compared to housekeeping gene IDUA (ΔCt).

A modified Tango assay was used to measure β-arrestin-2 recruitment to CMKLR1. HTLA cells were over-expressed with CMKLR1 and GRK2, GRK3, or GRK6 via calcium phosphate precipitation and stimulated with increasing concentrations of chemerin. After 24 hours, luminescence was measured on a Promega Glomax Multi+ Detection System.

Peritoneal activated monocytes/macrophages from C57Bl/6 wildtype (WT) and transgenic mice deficient in GRK2, GRK3, GRK6, or β-arrestin-2 (−/−) were studied *ex vivo* for CMKLR1 receptor internalization and migration. Calcein-labeled monocyte migration to media alone, SDF-1, or chemerin was examined using the FalconTM HTS FluoroBlok 96-Multiwell Insert System (3 μm pore-size) and a Fluoroskan Ascent Microplate Fluorometer. To measure CMKLR1 internalization, receptor surface expression was measured by flow cytometry at 30 sec, 1 min, 5 min and 10 min post-stimulation with chemerin and mean fluorescence intensity (MFI) normalized relative to 0 min on F4/80 positive cells.

Results: Relative gene expression of CMKLR1 is increased in both OA and RA FLS samples compared to normal controls. In addition, RA FLS show increased GRK2, -3, and -6 relative gene expression compared to controls. β-arrestin-2 recruitment to ligand-activated CMKLR1 is preferentially mediated by GRK6 as compared to GRK2 and -3. Additionally, GRK6−/− and β-arrestin-2 −/− murine peritoneal macrophages have enhanced chemotaxis to chemerin, as well as significantly decreased receptor internalization after ligand stimulation when compared to controls.

Conclusion: Chemerin/CMKLR1 signaling has an important role in the pathogenesis of OA and RA through the activation of cells within the joint, as well as recruiting proinflammatory monocytes to sites of inflammation. Chemerin-induced migration of proinflammatory monocytes and CMKLR1 receptor internalization is predominantly regulated by GRK6 phosphorylation and β-arrestin-2 recruitment.

Disclosure: D. S. Serafin, None; **M. F. Sassano**, None; **D. Mattox**, None; **R. Timoshchenko**, None; **M. J. Billard**, None; **D. P. Siderovski**, None; **B. Roth**, None; **T. K. Tarrant**, None.

1962

Inflammatory Properties of Inhibitor of DNA Binding 1 As a Unique Fibroblast Derived Nuclear Protein. Gautam Edhayan[1], Christine M. Ha[1], Ray A. Ohara[1], Takeo Isozaki[1], M. Asif Amin[1], Ali Arbab[2], Pei-Suen Tsou[3], Phillip L. Campbell[1], Elena Schiopu[3], Dinesh Khanna[3], Rachel Morgan[1], Sean C. Friday[1], David A. Fox[1] and Jeffrey Ruth[1]. [1]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [2]Georgia Regents University, Augusta, GA, [3]University of Michigan Scleroderma Program, Ann Arbor, MI.

Background/Purpose: Inhibitor of DNA binding 1 (Id1) is a nuclear protein containing a basic helix-loop-helix (bHLH) domain that regulates cell growth by selective binding and prevention of gene transcription. Id1 has shown pleiotropic effects: important in vasculogenesis in endothelial progenitor cells (EPCs), and important in angiogenesis in mature endothelial cells (ECs). Our group was the first to report that rheumatoid arthritis (RA) synovial fluid contains elevated amounts of Id1, and histologic analysis of RA synovial tissue (ST) revealed that Id1 is highly expressed in the vasculature of RA. We later found that the primary source of Id1 in STs were activated fibroblasts. Once released, Id1 acts as a potent inducer of angiogenesis, suggesting that Id1 may contribute to vasculogenesis as well as angiogenesis by independent mechanisms. This suggests that hyperproliferating fibroblasts produce Id1 that induces blood vessel growth. What is still unknown is the method of release of Id1 by synovial fibroblasts, as well as the potential importance of Id1 in other rheumatic diseases such as scleroderma (SSc).

Methods: Synovial fibroblasts from RA, osteoarthritis (OA), normal (NL), and dermal fibroblasts from NL and SSc patients were plated and cultured without cytokines or stimulated with tumor necrosis factor-α (TNF-α), CXCL16, Interleukin-17 (IL-17), transforming growth factor-β (TGF-β), or platelet-derived growth factor (PDGF). Supernatants were measured for Id1 expression by ELISA. Fibroblast supernatants were subjected to rate zonal centrifugation to isolate and purify exosomes. Whole and lysed (0.5% Triton X-100) exosome fractions were also measured for Id1 by ELISA. For signal transduction analysis, human dermal microvascular endothelial cells (HMVECs), EPCs, and synovial fibroblasts were plated and stimulated with human Id1. Western blot analysis was used to determine the kinetics of protein phosphorylation in cell lysates. Finally, we assessed the effects of Id1 signaling on angiogenesis using silencing RNA (siRNA) to inhibit HMVEC signaling pathways in the mouse Matrigel plug assay.

Results: NL and RA synovial fibroblasts increased Id1 production with stimulation by TGF- β. Similarly, dermal fibroblast supernatants from NL and SSc patients showed a marked increase in Id1 production after stimulation with PDGF and TGF-β. We assessed the role of exosomes to determine the mechanism of Id1 transport outside the cell. We found that Id1 is encapsulated by fibroblast exosomes and that 80% of the Id1 released by RA synovial fibroblasts is contained within exosomes. Cell signaling assays following stimulation by recombinant human Id1 showed the JNK pathway was upregulated in HMVECs, EPCs, and RA synovial fibroblasts, while P38 phosphorylation was increased in only EPCs. Furthermore, we show that inhibiting HMVEC associated JNK with siRNA reverses Id1 induced HMVEC vessel formation in Matrigel plugs.

Conclusion: Id1 is a pleotropic molecule that has significant effects on angiogenesis, vasculogenesis, and fibrosis. Our data shows that Id1 is not only an important nuclear protein, but also that it can be released from fibroblasts in exosomes, thus expanding its role in the orchestration of inflammatory lesions.

Disclosure: G. Edhayan, None; **C. M. Ha**, None; **R. A. Ohara**, None; **T. Isozaki**, None; **M. A. Amin**, None; **A. Arbab**, None; **P. S. Tsou**, None; **P. L. Campbell**, None; **E. Schiopu**, None; **D. Khanna**, None; **R. Morgan**, None; **S. C. Friday**, None; **D. A. Fox**, None; **J. Ruth**, None.

1963

Hierarchical Role of PI3K/Akt/mTOR Signaling Cascade on: Tissue Inflammation, Organization and Angiogenesis in Autoimmune Arthritis. Siba Raychaudhuri[1], Anupam Mitra[2], Ananya Datta Mitra[2], Christine Abria[2] and Smriti K. Raychaudhuri[2]. [1]Univ California Davis/VA Sac, Davis, CA, [2]VA Sacramento Medical Center, Mather, CA.

Background/Purpose: The PI3K/Akt/mTOR signaling proteins are pro-growth/pro-survival and thus likely to regulate inflammatory cascades in autoimmune diseases (1). The key pathologic outcome in psoriatic arthritis (PsA) and rheumatoid arthritis (RA) is 'uncontrolled proliferation' of synovial fibroblasts (FLS), endothelial cells (EC) and T cells. To identify the regulatory role of the PI3K/Akt/mTOR kinase cascade in FLS proliferation, immune response and neoangiogenesis in PsA and RA here we investigated the functional role of this kinase cascade in the target pathologic cells (FLS, EC, T cells) of these diseases.

Methods: Using the MTT assay we compared the antimitotic effect of Perifosine (Akt inhibitor), GDC-0941 (PI3K inhibitor), Rapamycin, NVP-BEZ235 (PI3K & mTOR inhibitor) and OSI-027 (mTORC1 & mTORC2 inhibitor) on FLS, T cells and human umbilical vein endothelial cells (HUVEC). FLS were derived from synovial tissues and T cells were obtained from the PBMC of PsA (n=5) and RA (n=5) patients. FLS were treated with PDGF and the T cells were activated with anti-CD3/CD28 cocktail. RTPCR was done to determine the effects of these mTOR inhibitors on regulation of genes associated with proliferation (MKI67), inflammation (IL-8, MMP3) and T cell activation (IFNG and IL2).

Results: All the inhibitors significantly inhibited PDGF induced FLS proliferation in RA and PsA (Figure 1). The dual mTOR inhibitor OSI-027 had a maximum inhibitory effect. In HUVEC and T cells the maximal inhibitory effect was noticed with PI3K inhibitor GDC-094. RTPCR results showed marked inhibition of the proliferation marker MKI67 mRNA in all the cell lines, inhibition of MMP3 gene expression in FLS and inhibition of IFNG and IL2 genes in T cells.

Conclusion: Dual inhibitor of mTORC1/mTORC2 and proximal kinase inhibitors (Akt or PI3K) have more potent antimitotic effect on FLS, HUVECs and T cells compared to Rapamycin. These observations open up a new paradigm in respect to the regulatory role of mTOR kinase cascade in inflammatory arthritis and provide novel targets for these diseases. Inhibition of mTORC1 by rapamycin results in an unopposed activation of mTORC2 and thus induces a positive feedback to the PI3K/Akt pathway and reduces its clinical efficacy. To overcome the therapeutic failure of rapamycin (mTORC1 inhibitors) here we have explored whether an alternative effective therapeutic approach could be a dual inhibition of mTORC1 and mTORC2 or more proximal inhibition of the mTOR cascade by targeting either Akt or PI3K.

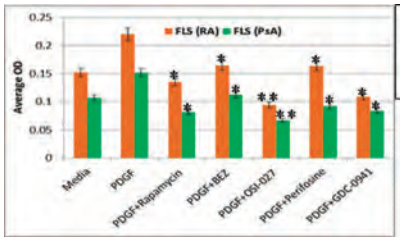

Figure 1: mTOR inhibitors significantly inhibited PDGF induced FLS proliferation in autoimmune arthritis. (*=p<0.01, **=p<0.001, ANOVA, as compared to PDGF)

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Disclosure: S. Raychaudhuri, None; **A. Mitra**, None; **A. Datta Mitra**, None; **C. Abria**, None; **S. K. Raychaudhuri**, None.

1964

Changes in Soluble CD18 Reflect Latency in the Immune System and Predict Radiographic Progression in Early Rheumatoid Arthritis. Tue Wenzel Kragstrup[1], Babak Jalilian[1], Kresten Krarup Keller[2], Kristian Stengaard-Pedersen[3], Merete Lund Hetland[4], Kim Hørslev-Petersen[5], Peter Junker[6], Mikkel Østergaard[4], Ellen Margrethe Hauge[3], Malene Hvid[1], Thomas Vorup-Jensen[1] and Bent Deleuran[2]. [1]Aarhus University, Aarhus, Denmark, [2]Aarhus University Hospital, Aarhus, Denmark, [3]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [4]Glostrup University Hospital, Glostrup, Denmark, [5]Research Unit at King Christian X Hospital for Rheumatic Diseases, Graasten, Denmark, [6]Odense University Hospital, Odense, Denmark.

Background/Purpose: In early rheumatoid arthritis (RA), clinical disease characterized by swollen and painful joints is caused by synovitis. However, presence of autoantibodies may precede the clinical onset of RA by several years, and joint damage can progress despite clinical remission. Therefore, early and aggressive synovitis suppression has become the principal goal in "treat-to-target" strategies. However, the temporal changes of immune system abnormalities during therapy and their significance remain poorly understood. Previously, we found a negative consequence of having low levels of the soluble form of CD18 (sCD18) in patients with chronic RA and spondyloarthritis[1,2]. Here, we study changes in plasma sCD18 levels in patients with early RA during a treat-to-target strategy (the OPERA regimen)[3], during

arthritogenesis in a murine model of chronic inflammatory polyarthritis (the SKG model) and in RA mononuclear cell cultures.

Methods: The level of sCD18 in plasma was analyzed with a time-resolved immunoflourometric assay in a study population of 152 patients with early treatment naïve RA at baseline and after 3, 6, and 12 months of treatment and during induced arthritogenesis in SKG mice. In vitro, synovial fluid mononuclear cells (SFMCs) and peripheral blood mononuclear cells (PBMCs) from 9 RA patients were cultured with either TNFα (40 ng/ml) or adalimumab (5μg/ml) for 48 hours. Data are expressed as median and IQR.

Results: Plasma levels of sCD18 were decreased in early RA patients at baseline (958.7 (766.2–1243) mU/ml) compared with healthy controls (HC) (1001 (872.0–1355) mU/ml) ($P<0.05$). The sCD18 plasma levels decreased further by 11% after 3 months ($P<0.05$), but after 12 months of treatment the levels returned to those of HC. The sCD18 increment between 3 and 12 months was most pronounced in patients who achieved an early ACR response compared with non-responders ($P<0.05$). Changes in plasma sCD18 between baseline and 12 months associated inversely with progression in total Sharpe score (rho=-0.18, $P<0.05$) and joint space narrowing (rho=-0.23, $P<0.01$) at the 24-month radiographic follow-up. Similarly, the serum level of sCD18 was decreased in SKG mice 6 weeks after arthritis induction (249 (151–282) mU/ml) compared with control SKG mice (334 (313–403) mU/ml) ($P<0.05$) and exhibited a biphasic course after arthritis induction with an initial increase above baseline ($P<0.05$) followed by a decline to levels below baseline ($P<0.05$). In vitro, shedding of CD18 from RA SFMC and RA PBMC cultures were increased 2–3 fold by TNFα (both $P<0.01$) and decreased by adalimumab ($P<0.05$ and $P<0.01$, respectively).

Conclusion: Concordant biphasic temporal patterns of sCD18 were observed in early RA and in a murine model of chronic inflammatory polyarthritis. The late increase in sCD18 was particularly pronounced in patients who achieved and early ACR response and may reflect latency in immune system restoration pertaining to the course of future radiographic progression.

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Disclosure: T. W. Kragstrup, None; **B. Jalilian**, None; **K. K. Keller**, None; **K. Stengaard-Pedersen**, None; **M. Lund Hetland**, None; **K. Hørslev-Petersen**, None; **P. Junker**, None; **M. Østergaard**, Abbott/Abbvie, Centocor, Merck, Schering-Plough, 2, Abbott/Abbvie, BMS, Boehringer-Ingelheim, Eli-Lilly, Centocor, GSK, Janssen, Merck, Mundipharma, Novo, Pfizer, Schering-Plough, Roche UCB, Wyeth, 5; **E. M. Hauge**, None; **M. Hvid**, None; **T. Vorup-Jensen**, None; **B. Deleuran**, None.

1965

Characterization of the Thyroid Hormone System in Rheumatoid Arthritis.

Anna-Sophia Pörings[1], Torsten Lowin[2], Luise Rauch[1], Tanja Späth[1], Angelika Graeber[2] and Rainer Straub[3], [1]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, Regensburg, Germany, [2]Laboratory of Exp. Rheumatology and Neuroendocrino-Immunology, University Hospital of Regensburg, Regensburg, Germany, [3]University Hospital Regensburg, Regensburg, Germany.

Background/Purpose: Chronic inflammation is characterized by an energy appeal reaction supporting high energy demand of the activated immune system. Thyroid hormones are strongly associated with catabolic effects and are therefore important mediators of energy allocation. Until now, the role of thyroid hormones in the locally inflamed joint is unknown. This study investigates metabolism of thyroid hormones in the joint and demonstrates expression and regulation of thyroid hormone regulating elements in rheumatoid arthritis (RA) and osteoarthritis (OA).

Methods: Typical thyroid gland –related autoantibodies were detected in order to exclude patients with autoimmune thyroid disease. TSH and thyroid hormones in serum were detected by ELISA. Thyroid hormone receptors TRα, TRβ, TA-1, deiodinases DIO1/DIO2/DIO3 and thyroid transporter MOT-8 were stained immunohistochemically in paraffin embedded synovial tissue samples. Influences of cytokines on above-mentioned thyroid hormone related proteins were detected by cell-based ELISA. Thyroid receptor-related signaling was analyzed by proteome profiling.

Results: In RA and OA, serum levels of reverse triiodothyronine (rT3), the degradation product of T3, is higher in synovial fluid than in plasma which is opposite for T3 and thyroxine (T4). Serum rT3 relative to free T3 was higher in RA than OA. rT3 levels in superfusate of synovial tissue were higher in RA compared to OA. Staining of synovial tissue revealed expression of thyroid converting enzymes DIO1–3, transporter MOT-8 and nuclear receptors TRa and TRb. The addition of TNF or IL-1β to RA or OA synovial fibroblast cultures increased protein levels of DIO1, DIO3 and TRα. Furthermore, high expression of TA-1, a receptor for the degradation product of T3, iodothyronamine, was detected. In addition, synovial fibroblast MAP kinase signaling and IL-6 production was altered by thyroid hormones.

Conclusion: Our data demonstrated that thyroid hormones are metabolized locally in the inflamed joint. This local inactivation is more pronounced in RA than OA (higher rT3 levels). Since cytokines alter the expression of DIO convertases and thyroid receptors, the thyroid hormone system might become dysregulated in the joint during chronic inflammation.

Disclosure: A. S. Pörings, None; **T. Lowin**, None; **L. Rauch**, None; **T. Späth**, None; **A. Graeber**, None; **R. Straub**, None.

1966

CTLA4-Ig (abatacept) Modulate *in Vitro* the ICAM1 and VEGFR-2 Expression in Human Endothelial Cells.

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Background/Purpose: CTLA4-Ig (abatacept) is employed as biological agent in rheumatoid arthtritis (RA) treatment and interacts with the costimulatory molecule CD86 expressed by different cells involved in synovitis [1,2]. The presence of CD86 has been shown on endothelial cell (EC) surface and their dysfunction is involved in the angiogenetic processes characterizing RA synovitis [3,4]. Since, ICAM1 (intercellular adhesion molecule 1) and VEGFR-2 (vascular endothelial growth factor receptor 2) are relevant molecules for the inflammatory and angiogenetic processes, their expression was evaluated *in vitro* on activated ECs at protein and gene expression level, following CTLA4-Ig treatment.

Methods: ECs (human microvascular endothelial cells, HMVECs, Lonza, Switzerland) were induced by gamma-IFN (500 U/ml for 48 hours) to activate and to express CD86. The cells were then treated for 24 hrs with CTLA4-Ig (10, 100, 500 micrograms/ml), and the protein expression levels for CD86, ICAM1 and VEGFR-2 were evaluated by flow cytometric analysis (FACS). After 3 and 24 hrs of CTLA4-Ig treatment, the protein expression levels of both ICAM1 and VEGFR-2 were also evaluated by Western blot analysis (WB) and their respective gene expression was evaluated by quantitative real time PCR (qRT-PCR). The statistical analysis was performed using the Mann-Whitney non-parametric t test.

Results: Activated ECs, after CTLA4-Ig treatment (10, 100, 500 μg/ml; 24 hrs), decreased their CD86-positivity at FACS by 66%, 59% and 51%, respectively, versus 68% of untreated cells (cnt), suggesting CTLA4-Ig/CD86 interaction and CD86 masking. All activated ECs, analysed by FACS, strongly expressed ICAM1 (99%) and VEGFR-2 (79%). Interestingly, after 24 hrs of CTLA4-Ig treatment, ECs showed a dose-dependent decrease in the mean fluorescence intensity for ICAM1, while VEGFR-2 positivity resulted unchanged. However, WB showed a significant decrease after CTLA4-Ig 500 μg/ml treatment for both ICAM1 and VEGFR-2 ($p<0.05$ at 3 and 24 hrs) while a significant decrease after CTLA4-Ig 100 μg/ml treatment was observed only for VEGFR-2 at 3 hrs ($p<0.05$). Similarly, qRT-PCR showed a significant decrease after CTLA4-Ig 500 μg/ml treatment for VEGFR-2 ($p<0.05$ at 3 and 24 hrs) and a significant decrease after CTLA4-Ig 100 μg/ml treatment for VEGFR-2 at 3 hrs ($p<0.05$). qRT-PCR at 3 hrs seemed to late to detect ICAM1 changes.

Conclusion: suggest a significant modulation by CTLA4-Ig of the gene expression and protein synthesis for ICAM1 and VEGFR-2 in cultured human ECs, which seems mainly due to the interaction between CTLA4-Ig and CD86 on activated ECs, possibly involving NFkB pathway downregulation, as previously reported [2]. Therefore, in the presence of chronic inflammatory reaction, such as in RA synovitis, ECs might be considered among other cells a further possible target for CTLA4-Ig modulation.

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1967

Transforming Growth Factor Beta Is a Major Regulator of Micro-RNA Synthesis in Rheumatoid Arthritis Synovial Fibroblasts. Anna Engler[1], Emmanuel Karouzakis[1], Christoph Kolling[2], Renate E. Gay[3], Steffen Gay[1] and Caroline Ospelt[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Schulthess Clinic, Zurich, Switzerland, [3]Zurich University Hospital, Zurich, Switzerland.

Background/Purpose: Transforming growth factor beta (TGFβ) modulates microRNA (miRNA) biogenesis in a variety of cell types. The expression of miRNAs is deregulated in the synovial fibroblasts from patients with rheumatoid arthritis (RASF). However, the role of TGFβ in the regulation of miRNAs in RASF was not investigated so far. The aim of the current study was to investigate the role of TGFβ in the regulation of miRNAs and in the inflammatory and matrix-destructive properties of RASF. Moreover, the effects of TGFβ on TNFα-induced signaling were analyzed.

Methods: Synovial tissues were obtained from RA patients undergoing joint replacement surgery. RASF (n=6) were stimulated with 10 ng/ml TGFβ, 10 ng/ml TNFα or with TGFβ and TNFα together in cultivation medium supplemented with 5% FCS for 24, 48 or 72 hours. Total RNA was isolated using Qiagen miRNeasy Kit. Global expression of miRNAs was analyzed by human miRNA Array analysis (Card A, Life Technologies) and verified by measurement of single miRNAs using real-time PCR with miRNA-specific TaqMan primers. The levels of interleukins (ILs) and matrix metalloproteinases (MMPs) were detected by Real-time TaqMan and SYBR green PCR.

Results: The global miRNA expression profile was altered by stimulation of RASF with TGFβ after 48h in all patients. The expression of 29 miRNAs was downregulated by 25–70% whereas the levels of 32 miRNAs were upregulated by 50–800%. TGFβ induced changes in several miRNAs that were previously reported to be deregulated in RASF. In particular, the levels of miR-155, miR-221, miR-222 and miR-335 were downregulated, while the expression of miR-18a, miR-22, miR-145 and miR-203 was significantly increased. We then investigated whether TGFβ can modify the effects of TNFα. Stimulation with TNFα alone increased the levels of miR-155 by 8.2-fold$\pm$1.2 (p=0.01), while the co-stimulation with TNFα and TGFβ resulted only in 4.3-fold$\pm$0.5 (p=0.03) increase in miR-155 levels. Treatment with TNFα decreased the expression of miR-145 by 0.7-fold$\pm$0.1 (p=0.03). However, co-stimulation with TNFα and TGFβ reversed this effect completely and increased the levels of miR-145 by 2.0-fold$\pm$0.3 (p=0.03). In contrast, TGFβ amplified TNFα-induced reduction in the expression of miR-222 and miR-335. Stimulation with TGFβ or TNFα alone already significantly reduced the expression of these miRNAs and co-stimulation with TGFβ and TNFα together led to a further decrease in the levels of miR-222 (by 0.35-fold$\pm$0.05, p=0.03) and miR-335 (by 0.4-fold$\pm$0.08, p=0.02). Moreover, TGFβ mitigated the matrix-destructive activities of RASF that were induced by TNFα by strongly decreasing TNFα-induced MMP1 expression (by 16-fold, p=0.04). In contrast TNFα-initiated IL6 production was increased by TGFβ(by 1.7-fold, p=0.03).

Conclusion: In the current study we found that TGFβ modulates the expression of miRNAs involved in the pathogenesis of RA. Moreover, TGFβ influences the inflammatory and matrix-destructive activities of RASF by reduction of TNFα-induced MMP1 expression and by enhancement of TNFα-initiated IL6 production. Thus, TGFβ has dual effects in the regulation of RASF and exhibits pro-inflammatory as well as anti-matrix-destructive properties.

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1968

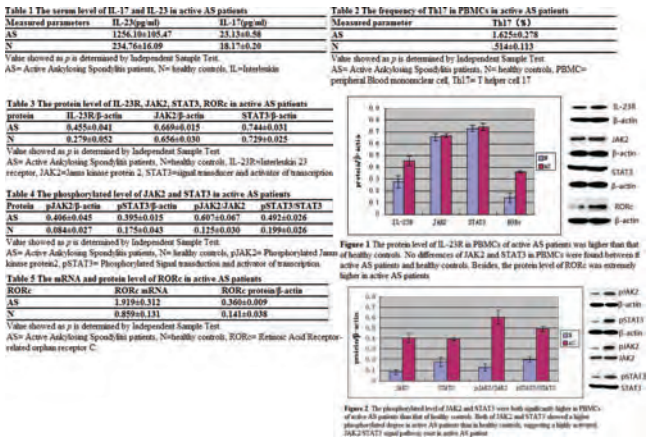
Highly activated IL-23/Th17 axis and JAK2/STAT3 signal pathway in PBMC of active AS patients involve in pathogenesis of AS. Hongxiao Liu[1], Peng Chen[2], Yingyan Zhou[2], Junyao Song[2], Benyong Liu[2], Xiaoyan Feng[2] and Xinghua Feng[2]. [1]Guang□'anmen Hospital, China Academy of Chinese Medical Sciences, Bei Jing, China, [2]Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Bei Jing, China.

Background/Purpose: T helper cell(Th17), the third lineage of CD4+T cells, has been determined its important role in pathogenesis of AS, and its main effector, IL-17, has a critical effect on mediating AS inflammation. Survival and function of Th17 is dependent on induction of IL-23. And JAK2/STAT3 signal pathway works on IL-23 signal transduction essentially. Here we investigate the role of JAK2/STAT3 signal pathway and IL-23/Th17 in pathogenesis of AS.

Methods: A total of 30 AS patients(average age, 27.6$\pm$ and 30 healthy controls(average age, 23.5$\pm$ without any tissue diseases participated in the experiments. All patients were diagnosed with AS by experienced rheumatologists and met with the modified New York criteria(Bath Disease Activity Score $\geq$4). The serum level of IL-17 and IL-23 in peripheral serum were detected by enzyme-linked immunosorbent assay(ELISA), the percentage of Th17 were detected by flow cytometry, the protein levels of JAK2/STAT3 signal pathway mainly involved in IL-23R, JAK2, pJAK2, STAT3, pSTAT3 and RORc(the lineage-specific transcription factor of Th17) were detected by Western blotting, and the mRNA level of RORc was detected by real-time quantitative PCR(qPCR).

Results: The serum IL-23 and IL-17 levels were significantly higher of active AS patients than that of the healthy controls(IL-23:p$\leq$¼0.001; IL-17: p$\leq$¼The frequency of Th17 in PBMCs were also elevated(p$\leq$¼as higher in PBMCs of AS patients than that of the healthy controls (p$\leq$¼s of JAK2 and STAT3 in PBMCs between AS patients and healthy controls(JAK2:p=0.538; STAT3:p=0.0.554), the phosphorylated levels of JAK2 and STAT3 were critically higher(pJAK2:p$\leq$¼; pSTAT3:p$\leq$¼Besides, the protein level and mRNA level of RORc were both significantly higher in PBMCs of AS patients than that of the healthy controls(protein level: p$\leq$¼0.001; mRNA level: p$\leq$¼0.001).

Conclusion: Our findings showed the exist of high serum IL-23 level, high activity degree of JAK2/STAT3 signal pathway and high protein and mRNA level of RORc in active AS patients. Important as IL-23 for Th17's differentiation and function, STAT3 phosphorylated by IL-23 signal can not only promote the expression of RORc, acting on differentiation of Th17, but bind to IL-17's promoter, being a direct regulator of IL-17. That's to say, high serum IL-23 level and its active JAK2/STAT3 signal pathway play a critical role in resulting in high serum IL-17 level and high frequency of Th17 existed in active AS patients. In this way, our results suggest the possible role of JAK2/STAT3 signal pathway and IL-23/Th17 axis in pathogenesis of AS.



Disclosure: H. Liu, None; **P. Chen**, None; **Y. Zhou**, None; **J. Song**, None; **B. Liu**, None; **X. Feng**, None; **X. Feng**, None.

1969

Neurotrophin Receptor p75 (CD271) Defines a Distinct Synovial Fibroblast Subset in Rheumatoid and Osteoarthritic Synovial Tissues with Enhanced Proinflammatory Potential. Manuel J. Del Rey[1], Regina Faré[1], Gabriel Criado[1], Alicia Usategui[1], Vanessa Miranda[1], Juan D. Cañete[2] and Jose L. Pablos[1]. [1]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain, [2]Hospital Clínic of Barcelona, Barcelona, Spain.

Background/Purpose: Synovial mesenchymal or stromal cells constitute a heterogeneous cell population difficult to characterize *ex vivo* due to a paucity of cell markers and are usually named synovial fibroblasts (SF). CD271, the low affinity receptor for neurotrophin nerve growth factor (NGF),

is considered a mesenchymal stem cell marker that is expressed by a small fraction of SF *ex vivo*. We have analyzed the location and relative proportion of CD271+ cells in synovial tissues from rheumatoid arthritis (RA), osteoarthritis (OA) and normal (N) individuals as well as their *ex vivo* functional properties in CD271+/− SF sorted cultures.

Methods: CD271 expression was analyzed by immunohistochemistry (IHC) in synovial tissues, and by flow cytometry (FC) in SF cultures from RA (n=10), OA (n=10), and normal synovial tissues (n=6). Isolation of CD271+ and CD271- OA SF (n=3) was carried out by magnetic beads sorting in passage 0 from OA explants. Supernatants of sorted CD271+/− SF were analyzed for IL-6, IL-8, MCP-1, MMP-1, MMP-3 and VEGF production by multiplex ELISA array (RayBiotech, Norcross, GA, USA). IL-6 data were confirmed by single specific ELISA. Quantitative data were analyzed by Mann-Whitney or ANOVA test where appropriate.

Results: CD271+ cells were observed by IHC in all types of synovial tissues with a perivascular distribution partially resembling pericytes. The number of CD271+ cells per area was significantly increased in both RA and OA tissues compared to normal synovial tissues (772±206, 802±221 and 206±100 per mm^2 respectively, $p<0.0001$ ANOVA). The frequency of CD271+ cells in SF cultures was highly variable but a trend towards a higher proportion of CD271+ cells in OA compared to RA and normal established SF cultures was observed (5.1±4.0%, 1.4±0.9% and 1.5±0.8% respectively). In individual OA SF cultures, cell passaging from passage 0 to 5 induced a progressive decrease in the percentage of CD271+ cells. OA CD271+ SF cultures sorted at passage 0 released significantly more IL-6 (3.1-fold increase) and metalloprotease MMP-1 (8.1-fold increase) than CD271- SF. A non-significant trend towards more IL-8, MMP-3 and VEGF production in CD271+ SF was also observed. MCP-1 production was similar in both SF subsets.

Conclusion: Our results demonstrate an expansion of CD271+ perivascular cells in inflammatory RA and OA synovial tissues. Cultured CD271+ SF showed increased production of proinflammatory factors *ex vivo* compared to CD271- SF. These data suggest that CD271+ stromal cells could play a proinflammatory role in OA and RA synovium.

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1970

T_H17 Inflammatory Responses Occur in a Subset of Patients with Erythema Migrans or Lyme Arthritis, but Are Not Predominant Responses in Joints. Klemen Strle, Elise E. Drouin and Allen C. Steere. Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Lyme disease usually begins with an expanding skin lesion, erythema migrans (EM), whereas arthritis is a late disease manifestation. The infection usually resolves with appropriate antibiotic therapy, but post-infectious symptoms following EM or persistent synovitis despite antibiotic therapy (antibiotic-refractory arthritis) may occur. Control of the infection in humans is attributed predominantly to innate and adaptive T_H1 immune responses, whereas the role of T_H17 responses is not yet well characterized. We recently showed that high levels of IL-23, a T_H17-associated cytokine, occur in a subset of European patients with EM, and are associated with more frequent post-infectious symptoms and autoantibody responses. Here, we characterized these responses in a large cohort of American patients with EM or Lyme arthritis to elucidate the role of T_H17-mediated immunity throughout the infection.

Methods: The levels of 20 cytokines and chemokines, representative of innate and adaptive T_H1 and T_H17 immune responses, were assessed by Luminex in matched acute and convalescent serum samples from 106 culture-positive patients with EM, in matched serum and synovial fluid (SF) samples from 159 patients with antibiotic-responsive or antibiotic-refractory arthritis, and in serum samples from 57 healthy control subjects.

Results: Compared with healthy subjects, acute-phase sera from EM patients contained significantly higher levels of the T_H17-associated mediators (IL-6, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25 and IL-27; P≤0.01). With the exception of IL-27, which down-regulates T_H17 responses, the levels of other T_H17-associated mediators remained elevated in convalescent sera obtained at the conclusion of antibiotic therapy. The levels of IL-23, the most highly induced T_H17 cytokine, correlated directly with antibody levels to the *B. burgdorferi* VlsE antigen (P=0.04) in both acute and convalescent samples, suggesting a role for T_H17-associated mediators in control of the infection. In patients with Lyme arthritis, the serum levels of IL-23 and other T_H17-associated mediators were generally lower than in patients with EM, and the levels of these mediators were only minimally concentrated, if at all, in SF. In contrast, innate (IL-8) and T_H1 mediators (CXCL9 and CXCL10) were 50-fold higher in SF than in serum. Compared with antibiotic-responsive patients, there was a trend toward higher levels of most of the T_H17-associated mediators, particularly IL-23, in SF in patients with antibiotic-refractory arthritis, and toward a greater frequency of autoantibody responses to human endothelial cell growth factor, the first known target of T and B cell responses in this disease.

Conclusion: A subset of patients with Lyme disease develops T_H17 immune responses. T_H17-associated mediators seem to be highest early in the infection and may play a role in control of the infection. In addition, T_H17 mediators may be one factor in shaping an immune response early in the illness in which autoantibody responses are more common, thereby contributing to subsequent antibiotic refractory Lyme arthritis.

Disclosure: K. Strle, NIH, Arthritis Foundation, 2; **E. E. Drouin**, None; **A. C. Steere**, ACR, NIH, Foundation, 2.

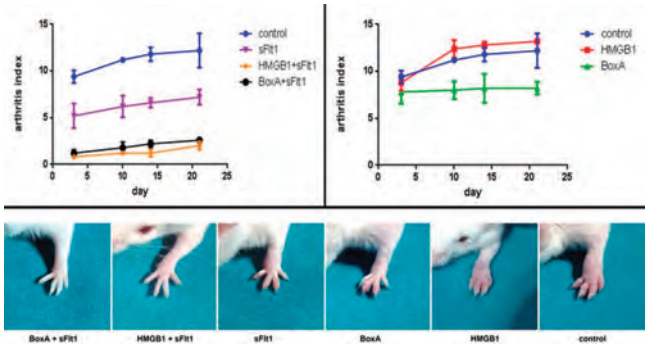
1971

The Role of the Proinflammatory Mediator High-Mobility Group Box Protein 1 (HMGB1) in Anti-Collagen-Antibody-Induced Arthritis Is Dependent on Vascular Endothelial Growth Factor (VEGF). Federico Biscetti[1], Andrea Flex[2], Giovanni Pecorini[2], Flavia Angelini[2], Vincenzo Arena[3], Egidio Stigliano[3], Barbara Tolusso[1], Elisa Gremese[1] and Gianfranco Ferraccioli[1]. [1]Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy, [2]Laboratory of Vascular Biology and Genetics, Catholic University School of Medicine, Rome, Italy, [3]Department of Pathology, Catholic University School of Medicine, Rome, Italy.

Background/Purpose: High-mobility group box 1 (HMGB1) is a non-histone nuclear protein that is released extracellulary and has been implicated in rheumatoid arthritis (RA) and angiogenesis. Although HMGB1 is abundantly expressed throughout the inflamed synovium, the mechanism by which this protein is involved in the development of RA is still not well known. The aim of this study was to better define the role of HMGB1 in the synovial angiogenesis and pathogenesis of RA.

Methods: Balb/c mice were injected with monoclonal anti-collagen antibody cocktail followed by lipopolysaccharide. Animals were evaluated every 3 days after the infusion of the antibody cocktail for arthritis incidence and each paw was evaluated and scored individually on a scale of 0–4, with 4 indicating the most severe inflammation. An arthritis index (AI) that expressed a cumulative score for all paws was calculated for each animal. To investigate the role of HMGB1 in pathological synovial angiogenesis in RA, three groups of mice were studied: mice treated with HMGB1, mice treated with HMGB1 inhibitor BoxA and untreated control mice. To further define and clarify the HMGB1 –VEGF interaction, additional groups of mice were treated with BoxA and with vascular endothelial growth factor (VEGF) inhibitor, the sFlt-1 plasmid.

Results: Immunohistochemical and ELISA analyses confirmed overexpression of HMGB1 and VEGF in the areas of the synovium where more inflammation and neoangiogenesis were present. Interestingly, the selective blockade of HMGB1 or of VEGF alternatively resulted in a lower severity of arthritis evaluated by AI ($p=0.003$ and $p=0.001$) (**Figure**).



Furthermore, exogenous HMGB1 administration caused a worsening of arthritis, associated with VEGF up-regulation and increased synovial angio-

genesis. Surprisingly, the selective inhibition of VEGF resulted in the lack of induction of arthritis also in mice receiving exogenous HMGB1 ($p<0.001$). ELISA analyses performed on peripheral blood and synovial fluid demonstrated a significant reduction of IL-1b ($p<0.001$), IL-6 ($p<0.001$) and TNF-a ($p<0.001$) in mice where HMGB1 and VEGF pathways were blocked. Interestingly, the selective blockade of HMGB1 and VEGF resulted in an increase of the peripheral IL-17A concentration ($p<0.001$).

Conclusion: The development of arthritis mediated by HMGB1 and the synovial angiogenesis can be blocked by inhibiting the VEGF activity. The pro-inflammatory and pro-angiogenic cytokine IL-17A is increased when HMGB1 is inhibited, but the synovial angiogenesis is nevertheless reduced in this model of arthritis. These data confirm that the blood vessels neoformation at the synovial level is dependent on VEGF. Taken together, these findings shed new light on the role of this nuclear protein in the pathogenesis of arthritis in an RA-like model.

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1972

Analysis of Anakinra in Primary Human Cell Systems Reveals an in Vitro Signature for Skin-Related Side Effects. Ellen L. Berg, Alison O'Mahony and Mark A Polokoff. BioSeek, South San Francisco, CA.

Background/Purpose: The therapeutic options for treatment of rheumatic diseases have grown and now include a variety of inflammatory pathway inhibitors, with diverse mechanisms, but having both shared and unique side effects. Understanding side effect mechanisms is important for guiding patient treatment choices and also for developing improved next generation therapies. We have successfully employed high throughput primary human cell-based models of tissue and disease, BioMAP Systems, to study failed and approved drugs and have previously identified in vitro activities that correlate with certain side effects. Here we compare the activity profiles of adalimumab (TNF inhibitor), MTX and anakinra (IL1RA) to test if activities can be correlated with differences in efficacy or safety.

Methods: BioMAP systems model disease biology in early-passage human primary cells and have been used extensively to characterize compounds based on phenotypic signatures. A panel of 12 BioMAP systems, including mono- and co-cultures of vascular, immune, and tissue cell types were used to generate profiles of anakinra, adalimumab, and MTX. Changes in protein-based and clinically relevant endpoints (biomarkers, including inflammatory, immune, tissue remodeling and hemostasis-related endpoints) as well as other cellular events (e.g., proliferation, cell cytotoxicity) were evaluated. For select activities, a comparison to a large reference database of approved and failed drugs, experimental chemicals, and other agents, was performed to elucidate potential mechanisms.

Results: The profiles for both anakinra and adalimumab show anti-inflammatory activities across the panel of BioMAP systems, including reduction in leukocyte recruitment molecules IL-8, E-selectin and MCP-1. Anakinra was more effective in blocking responses in a co-culture system of monocyte-driven (TLR4) vascular inflammation (LPS system) and differentially active in a model of T cell-dependent B cell activation (BT system), reducing IL-17A, IL-17F, and IL-6. In contrast, adalimumab was more effective in co-cultures driven by T cell or macrophage (TLR2) activation (SAg and/Mphg systems). The profile for MTX was distinct, reducing T cell proliferation (SAg system) and IgG production (BT system). Interestingly, in a fibroblast model of wound healing (HDF3CGF system), anakinra, but not adalimumab or methotrexate increased the levels of VCAM-1 and I-TAC (CXCL11). VCAM-1 and I-TAC (CXCL11) mediate recruitment of inflammatory lymphocytes into sites of inflammation. This combination of activities is an unusual feature, shared by MEK and p38 MAPK inhibitors, that we have previously associated with the potential for skin rash side effect.

Conclusion: Profiling of anakinra across a panel of primary human cell systems reveals an activity signature that has been correlated with skin side effects, and may be related to the cutaneous side effects observed with anakinra in patients. This signature is shared by inhibitors of MEK and p38 MAPK and suggests a common pathway mechanism. A better understanding of side effect mechanisms can help in the design and selection of novel therapies, or combinations.

Disclosure: E. L. Berg, BioSeek, 3; **A. O'Mahony**, DiscoveRx Corp (BioSeek division), 1, BioSeek, 3; **M. A. Polokoff**, BioSeek, a division of DiscoveRx, 3.

1973

Ectopic Lymphoid Neogenesis Is Strongly Associated with Activation of the IL-23/IL-17 Pathway in Rheumatoid Synovitis. Nataliya Yeremenko[1], Raquel Celis[2], Leonie M. van Duivenvoorde[1], Julio Ramirez[3], Iris C. Blijdorp[1], Sara Marsal[4], Jose L. Pablos[5], Raimon Sanmarti[3], Juan D. Cañete[3] and Dominique L. Baeten[1]. [1]Department of Clinical Immunology and Rheumatology and Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands, [2]Arthritis Unit, Rheumatology Dpt, Hospital Clinic of Barcelona and IDIBAPS, Barcelona, Spain, [3]Hospital Clínic of Barcelona, Barcelona, Spain, [4]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [5]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain.

Background/Purpose: The functional relevance of synovial ectopic lymphoid neogenesis (ELN) in rheumatoid arthritis (RA) remains unknown. As ELN correlates with the degree of tissue inflammation we investigated whether ELN was associated with specific cytokine profiles.

Patients and Methods: Paired synovial tissue (ST) (n=63) and fluid (SF) (n=44) was obtained from the inflamed knee joints of RA patients. Synovial inflammation and ELN was determined by immunohistology. CD21L was used as molecular marker of ELN. Cytokine expression was determined by ELISA and quantitative PCR in SF and ST, respectively.

Results: 48% of ST displayed ELN by histology. ELN+ samples had increased T and B lymphocyte infiltration ($p<0.001$) and CD21L expression ($p=0.014$). SF analysis showed higher expression of IL-23 ($p=0.018$) and IL-17F ($p=0.028$) in ELN+ versus ELN- samples, with a similar trend for IL-22 ($p=0.070$). Other cytokines, including IL-17A, IL-6, TNFa, Th1 cytokines and Th2 cytokines, were not different. In ST, IL-23 ($p=0.030$) mRNA levels were increased in ELN+ samples. Moreover, CD21L expression as molecular marker of ELN correlated significantly with mRNA expression of IL-23 ($r=0.70$), IL-17F ($r=0.42$), IL-21 ($r=0.30$) and IL-22 ($r=0.33$), but not IL-17A. The strong correlation between CD21L and IL-23, IL-17F, IL-21 en IL-22 was confirmed in an independent RA ST sample set (n=36). IFNγ and IL-2, but not IL-6 and TNFα, also showed some correlation with CD21L expression.

Conclusion: Synovial ELN in RA is strongly associated with increased expression of IL-23/IL-17-related cytokines. Whether patients depicting synovial ELN respond differently to therapeutic targeting of this pathway remains to be determined.

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1974

Sex Steroids, Interleukin-1, and Interleukin-10 Inhibit interferon–gamma (IFN-γ) Induced B Cell Activating Factor of the Tumor Necrosis Factor Family (BAFF) in Human Synovial Fibroblasts. Georg Pongratz, Marina Bäuml, Tanja Späth, Rainer Straub and Torsten Lowin. University Hospital Regensburg, Regensburg, Germany.

Background/Purpose: B cell activating factor of the tumor necrosis factor family (BAFF) is a cytokine important for the stimulation and survival of autoreactive B cells and therefore might play a role in several autoimmune disease, e.g. autoimmune arthritis. In psoriasis arthritis, BAFF correlates with disease activity and inversely with testosterone, but only in male patients, suggesting a role for sex hormones in the regulation of BAFF. It is also known that synovial fibroblasts (SFs) are capable of producing BAFF following INF-γ stimulation and that SFs possess sex hormone receptors. Therefore, we wanted to better characterize inflammatory stimuli that modulate BAFF in SFs and then test the hypothesis that sex steroids directly regulate BAFF production in SFs.

Methods: Fibroblasts isolated from synovial tissue of RA (n=10) and OA (n=10) patients were cultured in the presence or absence of different stimuli (IFN-γ, interleukin (IL)-1, lipopolysaccharide (LPS), tumor necrosis factor (TNF), cortisol, dihydrotestosterone, and estradiol). BAFF was determined by ELISA. Levels of phosphorylated and total STAT1 and STAT3 were determined by western blotting.

Results: IFN-γ in a concentration-dependent manner best induced BAFF in RA ($p<0.001$) and OA ($p<0.001$) fibroblasts. Since inflammation usually leads to hypoxic conditions, we also compared IFN-γ-induced BAFF production in RA (n=7) and OA (n=16) SFs under normoxic and hypoxic (oxygen content 2%) culture conditions. INF-induced BAFF is increased in hypoxic conditions in RA SFs ($p=0.015$) but not OA SFs ($p=0.362$) as

compared to the normoxic situation. In hypoxic ($p=0.005$) but not normoxic conditions ($p=0.471$), RA SFs produce more BAFF when exposed to the same IFN stimulation than OA SFs. IFN leads to a strong phosphorylation of STAT1 but to a reduction in phosphorylated STAT3. However, it has been suggested that concomitant phosphorylation of STAT3 further augments BAFF production. Therefore, we wanted to test if concomitant IL-1 or IL-10, which both lead to phosphorylation of STAT3, further increase IFN-induced BAFF in SFs. However, in the presence of IL-1 or IL-10, INF-induced BAFF was inhibited in a concentration dependent manner independent of oxygen content in both, OA ($p<0.001$) and RA ($p<0.001$) fibroblasts. Furthermore, inhibition of pSTAT3 resulted in further augmentation of IFN-induced BAFF. Finally, in the presence of dihydrotestosterone and estrogen, IFN-induced BAFF production in SFs was inhibited in a concentration dependent manner.

Conclusion: Taken together, BAFF production in synovial fibroblasts is induced by IFN-γ and pronounced under hypoxic conditions. STAT3 inducers like IL-1 and IL10 inhibit IFN-induced BAFF production. Also, the sex steroids dihydrotestosterone and estrogen inhibit BAFF production in OA and RA SFs. Therefore, the known correlation of endocrine factors with disease activity in arthritis might be in part mediated by regulating IFN-dependent BAFF production in SFs.

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1975

Profiling 14-3-3η in Human Primary Cell Based BioMAP® Disease Models Reveals a Unique Pro-Inflammatory Phenotypic Signature Consistent with RA-Inflammation Biology. Alison O'Mahony[1], Ellen L. Berg[1], WP Maksymowych[2], Yuan Gui[3] and Anthony Marotta[3]. [1]BioSeek, South San Francisco, CA, [2]University of Alberta, Edmonton, AB, [3]Augurex Life Sciences Corp., North Vancouver, BC.

Background/Purpose: 14-3-3 proteins represent a highly conserved seven-member family of ubiquitously expressed intracellular chaperonins that perform a broad range of signaling functions. The 14-3-3 eta (η) protein is an emerging diagnostic and prognostic biomarker for RA driving inflammation and joint erosion.[1] Elevated levels of the η isoform have been reported in synovial fluid and serum from patients with joint inflammation[2], but not with other diseases including psoriasis, osteoporosis, SLE, Crohn's and MS. Here we evaluate the impact of this RA-associated biomarker on the levels of clinically relevant biomarkers across a panel of human primary cell-based disease models in the BioMAP®platform.

Methods: BioMAP® systems model disease biology in primary human cells cultured alone or with different stimulus combinations and have been used extensively to characterize compounds based on phenotypic signatures.[2,3]Phenotypic activity profiles were generated for eight concentrations of 14-3-3η observed in RA patients (0.25–50 ng/ml) across a panel of 13 BioMAP systems modeling vascular, immune, inflammation and tissue remodeling biology relevant for various human diseases. Changes in protein-based, clinically relevant endpoints (biomarkers), cell proliferation and cytotoxicity were evaluated to identify activities of 14-3-3η relative to vehicle control. The resultant 14-3-3η BioMAP profile was analyzed and compared in a similarity search with more than 3000 compounds in the BioMAP database to identify common mechanistic signatures using Pearson's correlation.

Results: 14-3-3η messenger RNA (mRNA) is highly expressed in all BioMAP Diversity Plus Systems with stimulus coupled increases detected in B cell and Fibroblast based systems. The activity profile for 14-3-3η in BioMAP shows highly selective effects in two systems: 1. HPNo, a non-stimulated vascular endothelial cell-PBMC co-culture; 2. BT, a stimulated co-culture of $CD19^+$ B cells plus PBMC modeling T-cell dependent B cell activation. 14-3-3η caused an increase in levels of VCAM-1 and TNFα in HPNo and sIL-6 production in BT, activities consistent with an inflammatory phenotype. Comparison of the profile to the BioMAP database identified mechanistic matches with several pro-inflammatory TLR-like agonists including Pam3CSK4, a TLR-2/-1 agonist ($r = 0.735$), Flagellin, a TLR-5 agonist ($r = 0.723$) and HKLM, a TLR-2 agonist ($r = 0.721$). Of interest, the BioMAP profile of 14-3-3η was not similar to LPS, a potential bacterial endotoxin contaminant of biological preparations that also has TLR-agonist activities.

Conclusion: The BioMAP profile for 14-3-3η is consistent with activation of B cell responses that correlates with pro-inflammatory activity associated with disease-relevant biomarkers. This data supports the hypothesis that 14-3-3η may serve both as a diagnostic marker in early RA as well as an important target for therapeutic intervention.[5]

References:

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Disclosure: A. O'Mahony, Bioseek, 5; **E. L. Berg**, Bioseek, 5; **W. Maksymowych**, Augurex Life Sciences Corp, 5; **Y. Gui**, Augurex Life Sciences Corp, 3; **A. Marotta**, Augurex Life Sciences Corp., 3.

1976

Elevation and Functional Activity of Interferon Omega in Human Systemic Lupus Erythematosus. Jarrat Jordan[1], Jessica Schreiter[1], Hao Liu[2], Sreedevi Adhikarakunnathu[2], Chichi Huang[3] and Jacqueline Benson[1]. [1]Estrela Lupus Venture, Janssen Research and Development, LLC., Spring House, PA, [2]Immunology Research, Janssen Research and Development, LLC., Spring House, PA, [3]Biologics Research, Janssen Research and Development, LLC., Spring House, PA.

Background/Purpose: IFNα is emerging as a clinically validated target in SLE yet it is currently unclear if other type I IFNs are contributing to the IFN signature present in many SLE patients. In this study we analyzed SLE patient sera and plasma for the presence of IFNω protein and compared the biological effects imparted by recombinant IFNα and IFNω on human cells. We further examined the effects of blocking IFNα alone versus dual blockade of IFNα and ω using SLE patient-derived IFN stimuli in vitro.

Methods: SLE patient sera and plasma were analyzed for the presence of IFNα and IFNω using a multiplex ELISA. SLE sera or conditioned media from cells exposed to SLE patient immune complexes were utilized as stimuli in an ISRE reporter gene assay (RGA) with selectively neutralizing mAbs to IFNα or IFNω or isotype control. To examine the effects of IFNω treatment, PBMCs from 6 healthy human donors were treated with either recombinant IFNαA or ω and gene and protein expression were analyzed by microarray and, Luminex or ELISA, respectively. To assess the individual contribution of IFNα and IFNω on the IFN signature, unstimulated SLE whole blood from patients having an elevated IFN signature was treated with neutralizing mAbs to IFNα, IFNω or the combination of both and qPCR analysis was performed. A fully-human monoclonal antibody targeting IFNω and multiple subtypes of IFNα was developed and tested for its ability to neutralize IFNα and IFNω-induced IP-10 release in whole blood.

Results: IFNω and IFNα were found to be elevated in the plasma and serum of a subset of SLE patients. IFNω protein was also detected in conditioned media from SLE patient immune complex-stimulated PBMCs. Combined blockade of IFNα and IFNω resulted in further suppression of IFN activity in comparison to IFNα blockade alone using these endogenous preparations of type I IFN. Microarray data from IFN-treated PBMCs indicated that 99.25% of genes modulated by IFNαA treatment versus untreated control were modulated by IFNω at 24h. IFNω exhibited indistinguishable qualitative gene expression responses as compared to IFNαA-treated cells using a 21 gene IFN signature. IFNαA and IFNω treatment induced TLR7, IP-10 and BLyS gene expression. IFNω-mediated BLyS and IP-10 induction was confirmed at the protein level. To determine the impact of various IFN inhibitors on the IFN signature present in SLE donor whole blood, neutralizing antibodies targeting IFNα, IFNω, or the combination of both were added to unstimulated blood. Gene expression analysis by qPCR indicated that combined blockade of IFNα and IFNω resulted in greater reduction of multiple IFN-inducible genes than IFNα blockade alone. We further demonstrate a fully-human monoclonal antibody capable of dose-dependently inhibiting IP-10 release induced by both IFNω and IFNα.

Conclusion: IFNω antagonism enhanced the ability of IFNα antagonists to suppress IFN activity in SLE patient sera, SLE immune complex-induced preparations of IFN and the IFN signature in SLE patient whole blood in vitro. IFN signatures induced by recombinant IFNω and IFNα were found to be indistinguishable and our current data lends compelling support to the hypothesis that IFNω may contribute to the total type I IFN activity and signature present in some SLE patients.

Disclosure: J. Jordan, Janssen Research and Development, LLC., 3; **J. Schreiter**, Janssen Research and Development, LLC., 3; **H. Liu**, Janssen Research and Development, LLC., 3; **S. Adhikarakunnathu**, Janssen Research and Development, LLC., 3; **C. Huang**, Janssen Research and Development, LLC., 3; **J. Benson**, Janssen Research and Development, LLC., 3.

1977

The Proangiogenic Function of the Epigenetic Regulator EZH2 in Synovial Tissue Is Mediated By Fibroblasts in Rheumatoid Arthritis. Michelle Trenkmann[1], Steffen Gay[2], Douglas J. Veale[1] and Ursula Fearon[1]. [1]Translational Rheumatology Research Group, Dublin, Ireland, [2]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: The histone methyltransferase Enhancer of Zeste 2 (EZH2) is overexpressed in solid tumors and is associated with invasion, malignancy and tumor angiogenesis. EZH2 expression is upregulated in rheumatoid arthritis (RA) synovial fibroblasts (SF) whose activated phenotype drives them to invade and destroy articular cartilage. Another hallmark of the inflamed rheumatoid joint is angiogenesis and RASF are important regulators of this pathway secreting proangiogenic molecules and providing a molecular scaffold for blood vessel formation. Here, we studied the role of EZH2 in the interplay of RASF and endothelial cells in RA.

Methods: Fresh biopsies of synovial tissue (ST) from RA patients were stimulated with tumor necrosis factor alpha (TNFα, 10ng/ml) for 24h (explant culture) and RNA was isolated (n=3). Human microvascular endothelial cells (HMVEC) were stimulated with proinflammatory stimuli, Toll-like receptor (TLR) ligands or synovial fluid (2%, 5% and 10%) for different periods of time (n=3). RASF (n=4) were transfected with siRNA targeting EZH2. After 72h and 96h, cells were analyzed for EZH2, interleukin (IL)-6, IL8 and vascular endothelial growth factor (VEGF) expression at mRNA (by quantitative real-time PCR) and protein levels (by ELISA).

Results: *Ex vivo*, TNFα induced the expression of EZH2 in RA ST (1.8$\pm$0.3-fold) which was accompanied by an increase in the expression and copious secretion of proinflammatory and proangiogenic mediators, namely IL6 (from 77$\pm$88 ng/ml to 197$\pm$163 ng/ml) and IL8 (from 105$\pm$53 ng/ml to 220$\pm$30 ng/ml). Since RA ST explant cultures maintain the synovial architecture with cell-cell and cell-matrix contacts thus mimicking the *in vivo* situation, these data indicate that chronic inflammation within the RA synovium upregulates EZH2 expression *in vivo*. Our previous work demonstrated that TNFα upregulates EZH2 in RASF. Silencing of EZH2 in RASF changed the expression and secretion of IL6 and VEGF into cell culture supernatants whereas no significant changes were observed for IL8. Specifically, IL6 and VEGF were downregulated by EZH2 knockdown both under basal (by 39$\pm$17% and 29$\pm$8%) and TNFα-stimulated (by 30$\pm$18% and 38$\pm$6%) conditions which was confirmed at the protein level by ELISA. To elucidate whether other cell types show the same EZH2 expression pattern, HMVEC were studied for their response to pathogenetically relevant stimuli. No significant changes in EZH2 expression, however, were observed following proinflammatory stimuli (TNFα, IL-1β, IL-17), TLR stimulation (TLR2, 3 and 4) or treatment with synovial fluid, ruling out a direct effect of inflammation-induced EZH2 on endothelial cell behaviour.

Conclusion: Here we show that TNFα induces the expression of the epigenetic regulator EZH2 in RA ST explants *ex vivo*. *In vitro*, TNFα regulates EZH2 expression in RASF but not in endothelial cells. Silencing of EZH2 in RASF decreased the expression and secretion of IL6 and VEGF. These data imply that induction of EZH2 by TNFα in synovial tissue and RASF drives proinflammatory and proangiogenic mechanisms in RASF.

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1978

Role of Monocytes Subsets in the Pathology of Rheumatoid Arthritis: Involvement in Endothelial Dysfunction and Proinflammatory Profile. Chary Lopez-Pedrera, Patricia Ruiz-Limon, Carlos Perez-Sanchez, Rosario Carretero, Yolanda Jiménez Gómez, Ángeles Aguirre Zamorano, Jerusalem calvo-Gutierrez, Eduardo Collantes-Estevez, Alejandro Escudero-Contreras and Nuria Barbarroja. IMIBIC-Reina Sofia University Hospital, Cordoba, Spain.

Background/Purpose: Different frequency of monocytes subsets has been reported in rheumatoid arthritis (RA).Human monocytes are divided into three main subpopulations according to expression of the surface markers CD14 and CD16:'classic' CD14brightCD16- monocytes, 'non-classic' CD14dimCD16bright cells and 'intermediate' CD14brightCD16bright subpopulation.

Aim: to functionally characterize the different monocytes subsets in RA patients and analyze their role in the endothelial dysfunction, altered oxidative status and proinflammatory/prothrombotic profile associated to RA.

Methods: Thirty RA patients and 15 healthy donors were included in the study. Endothelial function was measured through post occlusive hyperaemia (PORH) using the Laser-Doppler linear Periflux 5010. Classic, intermediate and non-classic monocytes were characterized by flow cytometry. Different proinflammatory cytokines and peroxides levels were analyzed by flow cytometry in the three different subsets.CD14brightCD16- and CD16+ cells were isolated using immuno-magnetic selection.mRNA expression of inflammatory cytokines,endothelial adhesion markers and oxidative enzymes were analyzed in the two monocytes subsets.Correlation studies between clinical parameters, endothelial function and markers of inflammation and endothelial adhesion expressed by the different monocytes subsets were performed.

Results: CD16+(intermediate and non-classic)monocytes were extended in RA patients.These subsets had increased protein expression of TF, IKK and TNFa and lower peroxide levels compared to CD14brightCD16-.CD16+ monocytes displayed higher mRNA expression of TF, TNFa, TLR4, PPARg and MCP-1.In contrast, CD14brightCD16- cells had increased expression of IL8 and oxidative enzymes. All these parameters were significantly increased in RA patients. RA patients had impaired endothelial function, with a reduced perfusion value after ischemia.

Clinical parameters such as evolution time, CRP, anti-CCPs antibodies and rheumatoid factor levels strongly correlated with endothelial dysfunction, decreased percentage of classic monocytes and increased number of non-classic and intermediate subsets.Furthermore, higher expression of proinflammatory/prothrombotic molecules and endothelial adhesion markers in these CD16+ cells correlated with the alteration in endothelial function and the clinical parameters.

Conclusion: RA patients display an increased number of intermediate and non-classic monocytes directly associated to the autoimmune and inflammatory profile, the progression of the disease and the altered microvascular function. Therefore, CD16+ subpopulation might play a key role in the atherothrombotic pathogenesis of RA.

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1979

Pseudostarvation By AMPK Activator Therapy Is Associated with Reduced Disease Activity and Downregulation of Pro-Inflammatory Responses in Rheumatoid Arthritis (RA). Lorna Gallagher[1], Ursula Fearon[2], Douglas J. Veale[3], David Kane[1], Luke A. O'Neill[4] and Ronan Mullan[1]. [1]Department of Rheumatology, Tallaght Hospital, TCD, Dublin 24, Ireland, [2]Translational Rheumatology Research Group, Dublin, Ireland, [3]St. Vincent's University Hospital, Dublin 4, Ireland, [4]School of Biochemistry and Immunology, Dublin, Ireland.

Background/Purpose: AMP-activated protein kinase (AMPK) is a highly conserved, regulator of cellular energy status. In inflammation, AMPK inactivation is associated with increased glucose consumption through aerobic glycolysis, and up-regulation of pro-inflammatory effector responses. Pseudostarvation of cells through AMPK activation by hypoglycaemic therapy reverses these effects through downregulation of pro-inflammatory transcription factors, including NFκB/HIF-1α. Here we demonstrate AMPK upregulation in RA synovial tissues (RAST) after successful treatment, and inhibition of pro-inflammatory responses following pharmacological AMPK activation by metformin/phenformin *in vitro*.

Methods: RAST from RA patients during arthroscopy pre and 3/12 post treatment with anti-TNF therapy, were stained by immunohistochemistry for activated AMPK (pAMPK) and inactive AMPK (AMPK). Primary Human Microvascular Endothelial Cells (HMVEC) and K4 Synovial fibroblasts (K4 SF) were stimulated with LPS/TNFα (10ng/ml) in the presence of AMPK activators metformin/phenformin (0.5–2 mM). Culture supernatants were evaluated for IL-6 and IL-8 by ELISA. pAMPK and AMPK expression in K4 SF protein lysates were analysed by Immunoblotting normalized against β-actin.

Results: pAMPK was differentially expressed with low expression in highly inflamed RAST pre-treatment, and high expression post-treatment, in concert with a reduction in clinical disease activity.

In LPS and TNFα stimulated K4 SF, IL-6 and IL-8 production is decreased in the presence of metformin and phenformin in a dose dependent manner, with phenformin the more potent effect ($P < 0.0001$).

In LPS stimulated HMVEC, the production of IL-6 was also decreased in the presence of metformin or phenformin, dose dependent manner, with phenformin the more potent; 2428pg/ml (LPS) reduced to 2263pg/ml (Metformin 0.5mM), 149pg/ml (Metformin 1mM, $P=0.0005$), 1387 (Metformin 2mM, $P<0.0001$); 917pg/ml (Phenformin 0.5mM, $P<0.0001$), 629pg/ml (Phenformin 1mM, $P<0.0001$) and 306pg/ml (Phenformin 2mM, $P<0.0001$). Decreased production of IL-8 was seen with phenformin; 12572pg/ml (LPS) reduced to 8270pg/ml (0.5mM, $P<0.0001$), 5731pg/ml (1mM, $P<0.0001$) and 409pg/ml (2mM, $P<0.0001$). IL-8 production was not decreased in LPS stimulated cells in the presence of Metformin.

By immunoblot, pAMPK expression was strongly upregulated in the presence of metformin or phenformin (2mM) compared to unstimulated K4 SF cells indicating a role of both drugs in activating AMPK.

Conclusion: AMPK activation is associated with reduced RA disease activity and down-regulation of pro-inflammatory effector responses. AMPK activating drugs, such as Metformin, may be suitable as an additional therapeutic agent in the treatment of RA.

Disclosure: L. Gallagher, None; **U. Fearon**, None; **D. J. Veale**, Abbvie, 2, MSD, 2, Pfizer Inc, 2, Roche, 2, Pfizer, 5, Roche, 5, Abbott, 8, MSD, 8, Pfizer, 8, Roche, 8; **D. Kane**, None; **L. A. O'Neill**, None; **R. Mullan**, None.

1980

Thrombospondin-1 Is Elevetad in the Plasma of Patients with Antiphospholipid Syndrome and Is Correlated with Soluble Fas Ligand and Free Active TGF-B levels. Markos Patsouras, Marina Sikara, Athanasios G. Tzioufas and Panayiotis Vlachoyiannopoulos. School of Medicine, National University of Athens, Athens, Greece.

Background/Purpose: Antiphospholipid syndrome (APS) is an acquired thombophillia characterized by recurrent thromboembolism and pregnancy morbidity. Thrombospondin (TSP-1) is a matricellular glycoprotein with antiangiogenic and proapoptotic properties, which is secreted by platelets upon activation. It has been described to promote apoptosis through activation of caspases or induction of Fas ligand (sFasL) expression. Furthermore, TSP-1 is considered as the major activator of TGF-beta by releasing it from the Latency Acossiated Peptide. Herein, we sought to study the involvement of TSP-1 in antiphospholipid syndrome

Methods: Plasma, serum and platelets obtained from 90 patients fulfilling the diagnostic criteria of APS, 46 healthy individuals (healthy controls: HC) and 26 SLE patients, that served as disease controls were studied.

Human Umbilical Vein Endothelial Cells (HUVECs) were isolated from 2 APS patients and 3 HCs upon full term vaginal delivery by a standard protocol. HC-HUVECs were cultured in the presence of 10% plasma from HC ($n=10$) or APS patients ($n=20$) for 20 hours. Then, culture supernatants (SPN) were removed, cells were washed twice with HBS and fresh medium was added and left for two hours (hr). The 2 hr SPNs were collected and kept at $-20°C$ till use. Furthermore, HUVECs from APS patients were cultured in medium supplemented or not with their own plasma. TSP-1, soluble FasL (sFasL) and active cell-free TGF-b were determined by ELISA in plasma and cell culture SPNs.

Results: APS patients had significantly higher plasma levels of TSP-1, compared to HCs and SLE patients [Mean ng/ml [intarquartile range]: 390.0 [95.90–437.7] in APS patients vs 144.3 [46.3–236.6], $p<0.0001$, and: 153.0 [8.2–267.2], $p=0.029$ in HCs and SLE patients, respectively). TSP-1 was found to strongly correlate with sFasL and active TGFβ levels (Spearman $r=0.8785$, $p<0.0001$ and $r=0.827$, $p<0.0001$ respectively). Significantly higher levels of TSP-1 were detected in culture SPNs obtained from HUVECs treated with plasma from APS patients compared to those from HCs (mean concentration: 139.4 ng/ml in APS vs 22.8 ng/ml in HCs, $p=0.0009$). The analysis of correlations with clinical features, revealed that lower TSP-1 levels (mean value 130.1 ng/ml) were associated with pregnancy morbidity alone, whereas higher levels (403.2 ng/ml) with thromboembolic events with or without misacarriages ($p<0.05$).

Conclusion: Our findings implicate TSP-1 in APS pathogenesis, and associate it with the levels of sFasL and active TGF-b in the plasma of patients. Further studies are needed to clarify the exact role of TSP-1.

Disclosure: M. Patsouras, None; **M. Sikara**, None; **A. G. Tzioufas**, None; **P. Vlachoyiannopoulos**, None.

1981

A Qualitative Analysis of Methotrexate Injection Videos on Youtube. Rebekah Rittberg[1], Tharindri Dissanayake[2] and Steven J. Katz[2]. [1]University of Manitoba, Winnipeg, MB, [2]University of Alberta, Edmonton, AB.

Background/Purpose: Methotrexate (MTX) is one of the most commonly prescribed disease modifying antirheumatic drugs for rheumatoid arthritis. While data suggests subcutaneously administered methotrexate is more efficacious, there are many potential patient barriers to its use. Video assisted teaching has been shown to be an effective supplementary method for subcutaneous MTX education. This review evaluates the quality of video resources available for patients on YouTube for learning to self-administer subcutaneous MTX.

Methods: Using the search term "Methotrexate injection" on YouTube, 2 independent clinical reviewers in 2 different geographic locations analyzed the first 3 pages of search results (60 videos). Discrepancies were evaluated and resolved by a 3rd independent reviewer. Source and search rank of videos, audience views video duration and time since video was uploaded to YouTube were recorded. Videos were classified as useful, misleading or a personal patient view. Videos were rated for reliability using the DISCERN reliability tool (0–5, 5 being the most reliable), comprehensiveness (0–4; 1 point each as follows: needle preparation, MTX withdrawal, injection demonstration, needle disposal) & global quality scale (GQS; 1=poor video quality, 5= excellent video quality). Reasons for misleading videos were documented, and personal patient view videos were recorded as being either positive or negative towards MTX injection.

Results: A total of 51 English videos overlapped between the two geographic locations; 10 videos were classified as useful (19.6%), 14 as misleading (27.5%) & 27 as personal patient view (52.9%). Total views of videos were 161,028: 19.2% useful videos, 72.8% personal patient view videos, & 8.0% misleading videos. Mean GQS was 4.2 ($\pm$ 1.0) for useful videos, 1.6 ($\pm$ 1.1) for misleading videos & 2.0 ($\pm$ 0.9) for personal patient videos ($p<0.0001$). Mean reliability was 3.3 ($\pm$ 0.6) for useful videos, 0.9 ($\pm$ 1.2) for misleading videos, & 1.0 ($\pm$ 0.7) for personal patient videos ($p<0.0001$). Comprehensiveness was 2.2 ($\pm$ 1.9) for useful videos, 0.1 ($\pm$ 0.3) for misleading videos, & 1.5 ($\pm$ 1.5) for personal patient view videos ($p = 0.0027$). Of the personal patient view videos, 77.8% were positive, & 22.2% were negative. No significant correlation was found between the number of video views and quality of the video. The most common reason for a video being misleading was video content being unrelated to MTX injection. Of the 10 videos (19.6%) from university or professional organizations, 80% were useful and 20% misleading, while 72.7% of the 11 medical advertisements/for-profit organizations videos were misleading.

Conclusion: A qualitative review of MTX injection videos posted on YouTube shows a minority of useful videos for MTX injection, with the majority of viewers watching patient created videos. While many of these demonstrate MTX injection positively, this does not necessarily correlate with appropriate and safe technique. While web video may be an additional educational tool available for patients, clinicians need to be familiar with specific resources to help guide and educate their patients to ensure best outcomes.

Disclosure: R. Rittberg, None; **T. Dissanayake**, None; **S. J. Katz**, None.

1982

Final Year Medical Students Prefer E-Reading Content to Interactive Case-Based Quizzes in a Pediatric Rheumatology E-Learning Module. Taunton R. Southwood. Institute of Child Health, University of Birmingham and Birmingham Children's Hospital. Birmingham, United Kingdom.

Background/Purpose: Traditional medical student learning and teaching methods, such as lectures and bedside teaching, maybe inadequate for providing core knowledge and clinical skills in rheumatology, paediatrics and paediatric rheumatology, with reduction in undergraduate time allocated to paediatrics and increasing medical student numbers. To supplement paediatric knowledge and improve access to essential clinical skills, an e-learning module, "paediatric rheumatolog-e", was developed within a Canvas(c) learning management system. The design promoted revision of basic sciences (e.g. musculoskeletal anatomy,

inflammation and immunological processes), in the context of clinical sciences (e.g. pharmacology, rheumatology and child development). Learning content comprised videos of patient and family narratives, clinical skills and layered information on 4 key learning outcomes: joint swelling, limb pain, back pain and the limping child. Optional information on juvenile idiopathic arthritis was provided. Core knowledge was consolidated using interaction, reflection and formatively assessed case-based quizzes.

The aim of this study was to assess final year medical student use and acceptability of an e-learning module in paediatric rheumatology.

Methods: 341 final year medical students were notified of the e-learning module by email at the beginning of the academic year, and again 3 months later. Students beginning their paediatric rotation were reminded in the introductory lecture and written course materials. Use of the module was assessed 4 months into the academic year, after 3 blocks of medical students (193 students, 53% of the year) had undertaken a paediatric rotation. Canvas(c) embedded in-course analytics were used and acceptability was ascertained through online feedback and an email questionnaire.

Results: 187 students (55%) accessed the e-learning module (a mean of 14.8 pages per student, range 1–270, 28% 3); of these only 20 (11%) answered at least one clinical quiz. Higher median quiz scores were found in the joint swelling quiz and back pain quiz. Qualitative feedback indicated that the students found the quizzes took too much time and effort compared with reading through the other learning content and watching the clinical videos. There was a preference for accessing the module during a paediatric rotation (74/193 students to date, 62%). Time for completion of the module was 1–1.5 hours. Student acceptability of the entire module was high, with comments such as "thorough" and "engaging", and requests for more e-learning modules.

Conclusion: An e-learning module in a paediatric speciality was widely used and found to be acceptable by final year medical students. Students preferred written and video content to interactive clinical case quizzes due to the perceived time-inefficiency of clinical quizzes.

Disclosure: T. R. Southwood, None;

1983

Improving Resident Confidence with the Musculoskeletal Exam through a Rheumatology-Dedicated Musculoskeletal Workshop. Kimberly Fisher[1], Alexa Meara[2], Brian LaMoreaux[2], Hareth Madhoun[1], Irving Rosenberg[2], Xiaokui Mo[1], Lisa G. Criscione-Schreiber[3] and Nicole Bundy[4]. [1]The Ohio State University Wexner Medical Center, Columbus, OH, [2]The Ohio State University, Columbus, OH, [3]Duke University Health System, Durham, NC, [4]OSU Medical Center, Columbus, OH.

Background/Purpose: Musculoskeletal (MSK) complaints are among the most common complaints evaluated by primary care physicians. Thus, it is imperative that Internal Medicine (IM) residents learn how to perform and interpret a thorough MSK exam. Research suggests that IM residents lack confidence in performing a detailed MSK exam. If physicians find performing a procedure or exam difficult, they tend to avoid that behavior, which in the case of MSK complaints, could lead to over imaging and unnecessary referrals. Formalized clinical education has been shown to improve resident exam skills. To help improve IM residents' competence and confidence in the MSK exam, a dedicated MSK workshop was performed by the Rheumatology fellows at The Ohio State University with a Rheumatology faculty attending supervisor.

Methods: A single, 3 hour quality improvement workshop for IM residents was conducted by Rheumatology fellows supervised by an attending Rheumatologist. The residents were broken into small groups and rotated through twenty minute stations focusing on joint exams of the knee, hip, shoulder, wrist and hand. A validated pre-test survey created by Dr. Lisa Criscione-Schreiber assessing confidence and ability in the MSK exam was given to the residents in paper form prior to the workshop. The survey consisted of 10 questions, with 1–6 ranking system (1 being the lowest or no confidence in the listed skill). The same survey, in an on-line version was then administered to the residents 1 month after the workshop in to assess a change in proficiency. The data was analyzed by ANOVA with repeated measures since each subject answered 10 questions. The primary tests compare the scores between post and pre-workshop for question 1 and question 9. Multiplicities were adjusted by the Bonferroni method.

Results: 40 residents completed the pre-test and 20 residents completed the post-test. As shown in Table 1, there is a statistically significant improvement in confidence scores from the pre and post survey ($P < 0.05$) in most questions one through ten after completing this work shop.

Conclusion: Comfort and confidence in performing the MSK exam is an essential tool for Internists. There is a need for an efficient and cost effective way to teach IM residents clinical skills during their busy schedules. Using a validated survey created at Duke University, we found that a short, dedicated MSK exam workshop performed by Rheumatologists improved IM residents' confidence and ability to perform an MSK exam in statistically significant matter. Limitations were the small size of our study group and poor response rate to the post-survey evaluation. We were also unable to collect a sufficient number of responses from residents who did not participate in the workshop for a control comparison. We hope to perform this workshop on a larger scale with adequate control groups.

Table 1:

Survey Questions	Pre-test Average Ranking	Post-test Average Ranking	Adjusted p-value
Question 1: Identifying and naming common musculoskeletal deformities	3.4	4.3	0.014
Question 2: Taking a MSK pain history from a patient with pain in the following joints:			
Knee	3.6	4.7	0.0007
Spine	3.7	4.5	0.0162
Shoulder	3.4	4.3	0.0032
Hand/Wrist	3.4	4.4	0.0008
Hip	3.4	4.5	0.0004
Question 3: Describing the basic structure and function of the following joints:			
Knee	3.6	4.7	0.0007
Spine	3.6	4.5	0.0036
Shoulder	3.4	4.2	0.0089
Hand/Wrist	3.5	4.3	0.0091
Hip	3.6	4.5	0.0015
Question 4: Identifying the important surface markings when examining the following joints:			
Knee	3.1	4.7	<.0001
Spine	3.2	4.5	<.0001
Shoulder	3.0	4.4	<.0001
Hand/wrist	3.0	4.5	<.0001
Question 5: Assessing the following joint area for soft tissue swelling and/or effusion:			
Knee	3.5	4.9	<.0001
Spine	3.1	3.8	0.029
Shoulder	3.1	4.1	0.0005
Hand/wrist	3.2	4.8	<.0001
Question 6: Assessing the stability of the following joints:			
Knee	3.3	4.7	<.0001
Shoulder	3.0	4.4	<.0001
Question 7: Assessing the following joints for range of motion:			
Knee	3.8	5.0	<.0001
Spine	3.7	4.8	0.0001
Shoulder	3.6	4.7	0.0005
Hand/wrist	3.4	4.8	<.0001
Hip	3.6	4.7	0.0005
Question 8: Using information gained from physical exam of the following joint areas to make diagnoses:			
Knee	3.1	4.6	<.0001
Spine	3.1	4.0	0.0064
Shoulder	2.9	4.2	<.0001
Hand/Wrist	3.0	4.2	<.0001
Hip	3.0	4.0	0.0003
Question 9: Using information gained from physical exam of the following joint areas to guide medical decision making:			
Knee	3.1	4.7	<.0001
Spine	3.2	4.3	0.0021
Shoulder	2.9	4.5	<.0001
Hand/Wrist	3.0	4.4	<.0001
Hip	3.0	4.3	<.0001
Question 10: Performing and interpreting special diagnostic maneuvers on the following joints:			
Knee	3.0	4.5	<.0001
Spine	2.9	4.1	0.0001
Shoulder	2.8	4.3	<.0001
Hand/Wrist	2.9	4.0	<.0001
Hip	2.9	4.1	<.0001
Net Average All Questions	3.2	4.4	

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1984

Implementation and Performance of an Objective Structured Clinical Examination (OSCE) in a National Certification Process of Trainees in Rheumatology. Two Years of Experience. Virginia Pascual Ramos[1], Gabriel Medrano-Ramírez[1], Eunice Solis-Vallejo[1], Ana Bernard-Medina[2], Diana Flores[1], Margarita Portela Hernandez[1], Lilia Andrade-Ortega[1], Olga Lidia Vera-Lastra[1], Rolando Espinosa-Morales[1], Juan Miranda-Limón[1], M Maldonado-Velázquez[1], Luis Javier Jara[3], Luis M. Amezcua-Guerra[1], Judith Lopez-Zepeda[1], Miguel Angel Saavedra[1] and Cesar Alejandro Arce[1]. [1]Mexican Board of Rheumatology, Mexico City, Mexico, [2]Antiguo Hospital Civil de Guadalajara - Fray Antonio Alcalde, Mexico City, Mexico, [3]Hospital de Especialidades. Centro Médico La Raza, IMSS, Mexico City, Mexico.

Background/Purpose: We developed and conducted an OSCE to assess clinical skills of trainees in rheumatology (TRs) and determine its performance at two consecutive annual evaluations of the National Board of Rheumatology (NCR) certification.

Methods: Thirty-two (in 2013) and 38 (in 2014) TRs, underwent an OSCE and a 300-questions examination (MCQ). MCQ was annually developed by faculty and experienced test questions writers NCRS–certified members, who submitted questions based on pre-specified content areas. Each question was reviewed by a committee of 4 NCR members.

OSCE circuits were developed over a 10-month period by a trained NCR committee. At first, NCR members selected and designed stations using public core skills which included history-taking, physical examination, problem solving, studies interpretation, intra-articular injection (using a model) and capillaroscopy test; then, an expert consensus panel of rheumatologists validated each station (≥80% agreement); appropriated consented patients were selected and trained, as were examiners and each one was assigned to a particular station; finally, a pilot OSCE was performed by 3 certified rheumatologists who served as the "gold standard" control participants. Feedback was obtained. Final circuits consisted of 12 (in 2013) and 15 (in 2014) 8-minutes-stations, respectively, with 4 (2013) and 5 (2014) additional rest stations. Stations were scored by the same examiner in a previously validated check-list.

A composite OSCE score was obtained from each participant. Inter-station correlation was calculated using Pearson′s correlation coefficient. Concurrent validity was established by correlating MCQ scores and composite OSCE scores within each TR (Pearson′s correlation coefficient), by comparing OSCE scores between TRs and certified rheumatologists (Student t test) and by comparing distribution of TRs with MCQ pass scores among TRs with/without OSCE pass score (Wilcoxon rank sum).

Results: In 2013, mean (±SD) OSCE score in all the participants was 7.1(±0.6) and none received a failing score, meanwhile mean MCQ was 6.5(±0.6) and 7 TRs (21.9%) received a failing score (<6). In 2014, mean (±SD) OSCE score was 6.7(±0.6) and 3 TRs (7.9%) received a failing score (

In 2013, there was a significant correlation between MCQ score and composite OSCE score (r=0.44, p=0.006) meanwhile in 2014 correlation was not significant. At both consecutive years, certified rheumatologist had significantly higher OSCE scores than TRs. There were more TRs with a MCQ pass score among TRs with an OSCE pass score than among TRs with an OSCE failing score: 86% vs. 67%, p=0.02. TRs with an OSCE failing score were more frequently distributed in the bottom 2 quartiles on the MCQ (p=0.07).

Nine stations were applied at 2013 and 2014 OSCE circuits, and their (mean±SD) scores showed good correlation, r from 0.81 to 0.95, p≤0.01.

Conclusion: The OSCE was a valid and reliable tool to assess clinical skill competency in TRs.

Disclosure: V. Pascual Ramos, None; **G. Medrano-Ramírez**, None; **E. Solis-Vallejo**, None; **A. Bernard-Medina**, None; **D. Flores**, None; **M. Portela Hernandez**, None; **L. Andrade-Ortega**, None; **O. L. Vera-Lastra**, None; **R. Espinosa-Morales**, None; **J. Miranda-Limón**, None; **M. Maldonado-Velázquez**, None; **L. J. Jara**, None; **L. M. Amezcua-Guerra**, None; **J. Lopez-Zepeda**, None; **M. A. Saavedra**, None; **C. A. Arce**, None.

1985

Rheumatology Learning Management System. Rodney Tehrani, Rochella A. Ostrowski and Baltazar Espiritu. Loyola University Medical Center, Maywood, IL.

Background/Purpose: A learning management system (LMS) is software that facilitates the development, management, and tracking of training and education. To date, web based learning is a method of teaching that has been under-utilized in medical training. It has the advantage of being an efficient and easily accessible educational tool. We implemented a Rheumatology LMS for Internal Medicine residents. We hypothesized that the LMS would enhance the education and training of Internal Medicine residents in regard to Rheumatology through the use of dynamic and interactive software.

Methods: Five rheumatologic modules were created covering antiphospholipid syndrome, crystal arthritis, giant cell arteritis, myositis and rheumatoid arthritis in the LMS. All first year Internal Medicine residents completed the modules during dedicated educational time. Attendance and completion was mandatory. Modules were completed either in small groups or individually based on the preference of the learner. Residents completed the modules after their first Internal Medicine In-Training Examination (ITE) and prior to their second. We then analyzed the ITE performance of the first year Internal Medicine residents on the Rheumatology subsection to determine whether there was a statistical improvement in their scores compared from previous year residents who did not have access to the LMS.

Results: In the previous 2 years of residents who had not completed the modules, ITE mean examination scores in the rheumatology content changed from 58% to 53% and from 45% to 62%. National percentile ranking changes were 16% to 25% and 18% to 16% for the 2 groups respectively. Thirty four residents completed the modules. Mean examination scores improved from 48% correctly answered items on the year 1 ITE to 63% on the year 2 ITE (p value <0.0005). National percentile rank improved from 27% to 46% respectively. Twenty-eight residents had a rheumatologic experience defined as a clinic or rotation in rheumatology during their PGY1 year. Differences in examination scores before and after the module completion remained statistically significant even when stratifying residents according to whether or not they had a clinical rheumatologic experience.

Conclusion: The development and implementation of a LMS can enhance the education and training of Internal Medicine residents to the field of Rheumatology.

Disclosure: R. Tehrani, Rheumatology Research Foundation, 9; **R. A. Ostrowski**, None; **B. Espiritu**, None.

1986

Ambulatory Rheumatology Curriculum: Effect of Multimodal Curriculum Enhancement. Susan Kroop[1], Cecilia P. Chung[2], Mario Davidson[1], Laura Skaug[1], D. Alan Johnstone[1] and Charlene M. Dewey[1]. [1]Vanderbilt University School of Medicine, Nashville, TN, [2]Vanderbilt University, Nashville, TN.

Background/Purpose: Evidence suggests that Internal Medicine (IM) residents are not confident in basic rheumatologic skills (history taking, exams, and procedures). To improve IM residents' confidence in rheumatologic skills, we implemented and evaluated a multimodal simulation training session (MSTS) using standardized patients and mannequins to enhance Post Graduate Year (PGY) 1 IM residents' rheumatologic skills. To assess the utility and effectiveness of the MSTS enhancement, we conducted pre/post self-assessment of residents completing the curriculum.

Methods: We developed and implemented our MSTS for all PGY1 IM residents rotating on the 1 week ambulatory rheumatology block during the 2014 academic year. The two-part training consisted of a live standardized patient (SP) and deliberate practice with a mannequin for knee aspirations with feedback for both. PGY 1 residents performed a rheumatologic history and exam on a SP presenting with monoarticular inflammatory knee arthritis and practiced knee joint aspiration using a mannequin under the direct supervision of an attending rheumatology faculty member.

All PGY 1 residents completed an online, self-assessment survey on self-confidence (0=not confident, 100=extremely confident) in performing a rheumatologic history, physical examination and common rheumatologic procedures pre/post their rheumatology block as well as a separate MSTS evaluation form. Pre/post-rotation assessments were analyzed and 2014 results compared to the 2013 academic year, a historical control using the Wilcoxon Signed Rank test. IRB approval and consent was obtained prior to completing the survey.

Results: In 2013 and 2014, 22/27(81%) and 39/43 (91%) of PGY1 IM residents completed pre/post surveys respectively. Both cohorts significantly increased (p<0.05) their self-assessed confidence ratings from pre to post rotation in all variables other than trochanteric bursa injection in the 2013 cohort (Table 1). The 2014 cohort had significantly greater changes in self-assessed confidence ratings than the 2013 historical controls. The difference in the median in rheumatology history was 12, exam was 11, knee aspiration was 37 and knee injection was 34 (Table 1). 35/43 (81%) PGY1 IM residents strongly agreed and 8/43 (19%) agreed that the MSTS was a valuable training exercise.

Conclusion: Our results indicate that our MSTS enhanced curriculum improves residents' self-confidence in performing a rheumatologic history and exam and knee injection and aspiration techniques when compared to an unenhanced prior curriculum. Further study is required to assess if these results are sustained over time and whether this translates into IM residents performing more procedures competently during their training.

Table 1. Median Self-Assessed Confidence Levels for PGY 1 Residents with and without MSTS

	2013 Median (IQR)* Historical Control			2014 Median (IQR)* MSTS Curriculum			
Self-Assessed Confidence in Performing:	Pre-Rotation	Post-Rotation	P Value	Pre-Rotation	Post-Rotation	P Value	Difference in Median (95% CI)
Rheumatology History Taking	50 (27–62)	64 (53–79)	<0.001	34 (19–49)	70 (61–81)	<0.001	12 (2–22)
Rheumatologic Exam	36 (23–50)	63 (52–74)	<0.001	31 (12–39)	71 (59–83)	<0.001	11 (2–22)
Knee Injection	10 (2–33)	22 (6–36)	<0.05	9 (2–36)	60 (50–74)	<0.001	34 (20–46)
Knee Aspiration	13 (2–20)	28 (10–42)	<0.005	9 (0–30)	63 (56–75)	<0.001	37 (25–49)
Shoulder Injection	7 (1–13)	12 (5–27)	<0.05	7 (0–19)	27 (16–42)	<0.001	6 (−1–14)
Trochanteric bursa injection	7 (2–14)	13 (5–26)	<0.071	7 (0–19)	25 (8–52)	<0.001	9 (0–19)

Visual Analog scale (0, not confident-100, extremely confident).
*IQR: Interquartile Range.

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1987

Simulation in Continuing Education: Improving Evidence-Based Decisions for Rheumatoid Arthritis Management. Nimish Mehta[1], Martin Warters[2] and Douglas Blevins[2]. [1]Medscape, LLC, New York, NY, [2]Theraasim, Durham, NC.

Background/Purpose: In many patients with rheumatoid arthritis (RA), the disease is not adequately controlled, and only a minority of patients attain the goal of consistent remission or low disease activity. Underlying clinical practice gaps and educational needs were identified and a study was conducted to determine if online, simulation-based educational interventions could improve competence and performance of rheumatologists in managing patients with RA.

Methods: A cohort of US-practicing rheumatologists who participated in simulation-based educational interventions was evaluated. The interventions consisted of four cases presented in a platform that allowed physician learners to choose from numerous lab tests and assessment scales as well as thousands of diagnoses, treatments, and procedures. The clinical decisions made by the participants were analyzed using an artificial intelligence technology, and instantaneous or delayed clinical guidance was provided employing current evidence-based and expert faculty responses. Participant decisions were collected after clinical guidance and compared with each user's baseline data using a 2-tailed paired T-test to provide *P* values for assessing the impact of simulation-based education on the clinical decisions made by participants.

Results: The assessment sample consisted of185 rheumatologists who made at least one clinical decision within the simulation and proceeded to the end, debrief section. As a result of clinical guidance provided through simulation, significant improvements were observed in several areas of management of patients with RA, specifically:

- 32% improvement in the selection of a biologic agent in a patient with inadequate response to methotrexate (62% post intervention vs 30% baseline, $P<.001$)
- 11% improvement in recommendations for corticosteroids (77% post intervention vs 66% baseline, $P=.044$)
- 10% more participants correctly ordered clinical disease activity index and C-reactive protein to determine the level of disease activity (84% post intervention vs 74% baseline, $P<.03$)
- 16% improvement in selection of non-TNF biologic agent in a patient with RA not adequately controlled on methotrexate plus trials of etanercept and then adalimumab (60% post intervention vs 44% baseline; $P=.004$)
- 21% more participants selected an appropriate biologic in a patient failing an initial anti-TNF agent. (57% post-intervention vs 36% baseline, $P<.001$)

Conclusion: This study demonstrated the success of simulation-based educational interventions on improving the evidence-based practice patterns of rheumatologists in the management of patients with RA. Simulation-based instructions that lead to improvement in physician performance in a consequence-free environment can result in more evidence-based clinical decisions for RA and improvement in patient outcomes.

Disclosure: N. Mehta, None; **M. Warters**, None; **D. Blevins**, None.

1988

Process Outcomes and Community-Wide Efficacy of the Amigo Inter-Institutional Mentoring Initiative within Pediatric Rheumatology. Lakshmi N. Moorthy[1], Eyal Muscal[2], Meredith P. Riebschleger[3], Kelly A. Rouster-Stevens[4], Polly J. Ferguson[5], Rayfel Schneider[6], Marisa Klein-Gitelman[7], Hermine I. Brunner[8], Anna Huttenlocher[9] and Peter A. Nigrovic[10]. [1]Robert Wood Johnson Medical School-Rutgers University, New Brunswick, NJ, [2]Texas Children's Hospital, Houston, TX, [3]University of Michigan, Ann Arbor, MI, [4]Emory University School of Medicine, Atlanta, GA, [5]University of Iowa Carver College of Medicine, Iowa City, IA, [6]The Hospital for Sick Children, Toronto, ON, [7]Anne & Robert H Lurie Childrens Hospital of Chicago, Chicago, IL, [8]PRCSG, Cincinnati, OH, [9]Univ of Wisconsin Schl of Med, Madison, WI, [10]Brigham and Women's Hospital/Harvard University, Cambridge, MA.

Background/Purpose: Mentoring is considered a critical contributor to career success in academic medicine. Recognizing that pediatric rheumatologists may experience limited access to mentoring due to the small size of most clinical programs, the American College of Rheumatology (ACR) and Childhood Arthritis and Rheumatology Research Alliance (CARRA) cooperatively developed a subspecialty-wide inter-institutional mentoring program, entitled the ACR/CARRA Mentoring Interest Group (AMIGO). We report outcomes of this initiative three years after its inception as a small pilot program in 2011.

Methods: Two distinct sets of surveys were conducted: (1) AMIGO participants in the pilot phase were surveyed 17 months after matching to characterize mentor-mentee contact, and results compared with a subsequent survey of all participants following full program implementation. (2) All US/Canadian pediatric rheumatologists were surveyed before and after implementation of AMIGO to identify global changes in mentorship over this interval.

Results: (1) Participants in the pilot phase (19 dyads) and general implementation phase (112 dyads) reported comparable experiences with AMIGO, including success in establishing contact and suitability of mentor-mentee pairing. Pilot and general roll-out participants reported similar anticipated benefit from the program. (2) Respondents in the community wide surveys included 180 pediatric rheumatologists in 2011 and 177 in 2014, with comparable demographics. Among survey respondents, 31/36 fellows (86%), 17/58 junior faculty (29%), and 37/61 (61%) senior faculty reported participation in the AMIGO program. Over the interval from 2011 to 2014, overall satisfaction with mentoring increased for fellows ($p=0.01$) but not junior faculty. AMIGO mentees reported that participation in AMIGO provided benefit in the domains of research/scholarship (30/51, 61%), career development (35/51, 71%), work-life balance (21/51, 43%), and connectedness to the pediatric rheumatology community (33/61, 56%).

Conclusion: The AMIGO program has expanded successfully from its pilot phase and now serves the large majority of US and Canadian pediatric rheumatology fellows as well as many junior faculty members. AMIGO mentees reported benefit in the domains of research, career development, and work-life balance. Institution of AMIGO was associated with improved satisfaction with mentoring among fellows, where program penetration was greatest. These results confirm that a subspecialty-wide inter-institutional mentoring program is feasible and can translate into concrete gains measurable at the level of the whole community.

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1989

Application of an Experiential Learning Framework for Clinician Scholar Educator Training in a Rheumatology Fellowship. Reena Khianey[1], Jessica Berman[2], Stephen A. Paget[2], Anne R. Bass[1] and Juliet Aizer[1]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY.

Background/Purpose: Rheumatology training programs rely on capable clinician scholar educators to sustain the rheumatology workforce. No program for rheumatology fellow clinician scholar educator (CSE) training has been described in the literature. We describe application of iterative cycles of Kolb's experiential learning in a mentored rheumatology fellow CSE experience as a proof-of-concept model.

Methods: With mentorship from a faculty CSE, a second year rheumatology fellow at Hospital for Special Surgery contributed to implementation

of a learning module on fracture risk for New York Presbyterian Hospital (NYPH) internal medicine (IM) residents.

Applying an experiential framework (learning through experience), the fellow refined the fracture risk module through cycles of Reflective Observation (review of faculty-led sessions), Abstract Conceptualization (identification of effective techniques), Active Experimentation (enactment of proposed teaching vignettes), and Concrete Experience (teaching parts of sessions).

The fracture risk module itself was built on the same experiential framework; IM residents recalled patients with fractures, identified fracture risk factors, formed clinical approaches, and estimated fracture risk. From July 2013-June 2014, IM residents completing a rheumatology rotation participated.

Following sessions, the fellow and faculty CSE reflected on module content and format, and on the teaching experience. Verbal and written prompts elicited impact, challenges, and key elements.

Results: The fellow attended 24/36 (66.7%) sessions, and taught in 21/24 (87.5%) of attended sessions.

The fellow found the experience valuable and feasible. Confidence related to clinical mastery and self-efficacy regarding curricular design and teaching abilities increased. The fellow cited increasing comfort and ease preparing to teach sessions and answering questions from IM residents.

The fellow's suggestions were consistent with experiential learning techniques, demonstrating application of new knowledge. Greater knowledge of the clinical subject (fracture risk) was evident in increased ability to respond to residents' questions. The fellow's knowledge and scholarly approach resulted in publication of a review article.

Challenges included competing clinical and research demands. Key elements identified for the fellow's learning included longitudinal faculty mentorship, establishment of fellow's content expertise, shared curricular development, explicit application of an educational framework, iterative learning cycles around a recurring teaching module, and flexibility in involvement to allow for other research experiences.

Conclusion: This descriptive analysis demonstrates the utility and feasibility of rheumatology fellow CSE development. Application of an experiential framework to fellow teaching in a recurring teaching module promoted iterative cycles of learning. Fellow self-efficacy and knowledge related to both rheumatology and education increased. This model may be adapted to support rheumatology fellow CSE development more broadly and systematically as a programmatic element.

Disclosure: R. Khianey, None; **J. Berman**, None; **S. A. Paget**, None; **A. R. Bass**, None; **J. Aizer**, None.

1990

Pilot Musculoskeletal Workshop for Internal Medicine Residents. Sonali Khandelwal, Narender Annapureddy, Joel A Block, Andem Ekpenyong and Richard I Abrams. Rush University Medical Center, Chicago, IL.

Background/Purpose: Musculoskeletal (MSK) complaints in primary care are common but often underemphasized in residency training. There are few reports of methods residency programs have reported to address this need. Wilcox et. al reported an intervention for residents consisting of a monthly experience, and Houston et. al reported the experience of residents in a community clinic precepted by general internists. Both these interventions were scheduled as multi-week curricula. With limitation of work hours, residents spend less time on sub-specialty rotations such as Rheumatology, and so it becomes challenging to incorporate adequate exposure to the MSK examination. To address this need for more dedicated MSK teaching while remaining sensitive to the constraints of limited contact hours, a pilot MSK workshop consisting of a single 90 minute session was initiated.

Methods: As part of the ambulatory medicine curriculum for medicine residents at Rush University a MSK workshop was initiated. The workshop consisted of a lecture followed by assessment of preselected patients with MSK complaints. The residents assessed each patient through a focused history and dedicated musculoskeletal exam. Prior to the workshop a multiple choice pretest was administered. Subsequently, a post-test with different questions and an anonymous survey was completed. Informed consent was obtained from the patients. Paired t-test was used to compare pre-test and post-test scores. One-way ANOVA with Bonferroni correction was used to compare mean pre-test and post-test scores across PGYs.

Results: 45 medicine residents participated in the workshop. The mean±SD pretest score was 68.44 % ± 20.21. Post test scores are available for 26 residents. There was significant improvement in post test scores overall for PGY2 and PGY3, but none for PGY1s (table). One-way ANOVA with Bonferroni correction revealed no baseline differences at any PGY, but significant improvement among PGY2 and PGY3 compared to PGY1. Post workshop survey results are available for 19 residents. 92.9% of residents strongly agreed or agreed that the workshop was helpful and clinically useful. 89.3% strongly agreed or agreed that they were applying what they learned in their evaluation of patients in their continuity clinics and they felt more confident with their skills. Notwithstanding the PGY1 test results, there was no difference in their overall acceptance of the workshop compared to PGY2 or PGY3s.

	Pre-test Percentage (±SD)	Post-test Percentage (±SD)	P-Value
All PGY (n=26)	69.2 (21.3)	87.7 (12.7)	**0.001**
PGY1 (n=9)	64.4 (26.0)	77.8 (12.0)	0.111
PGY2 (n=8)	70.0 (18.5)	92.5 (10.3)	**0.0002**
PGY3 (n=9)	73.3 (20.0)	93.3 (10.0)	**0.003**
PGY1 vs. PGY2	66.7 vs. 66.7 (p-value =1.000)	77.8 vs.92.5 **(p-value=0.031)**	
PGY1 vs. PGY3	66.7 vs.72.0 (p-value=1.000)	77.8 vs.93.3 **(p-value=0.017)**	
PGY2 vs. PGY3	66.7 vs. 72 (p-value=1.000)	92.5 vs. 93.3 (p-value=1.000)	

Conclusion: These data suggest that an intervention requiring a single session may result in substantial and durable improvement in testable knowledge among PGY2 and PGY3 residents. The lack of improvement in post-test scores among PGY1 residents may indicate that this group needs more dedicated sessions. This is the first report to indicate that residents apply what is learned longitudinally in their long-term continuity experiences and a single session led them to feel more confident with their skills.

Disclosure: S. Khandelwal, None; **N. Annapureddy**, None; **J. A. Block**, None; **A. Ekpenyong**, None; **R. I. Abrams**, None.

1991

Integration of Nailfold Capillary Microscopy and Dermoscopy into the Rheumatology Fellows Curriculum. Daniele Lerner[1], Stephen A. Paget[2], Maurizio Cutolo[3], Vanessa Smith[4], Robert F. Spiera[1] and Jessica K. Gordon[1]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [3]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, [4]Ghent University Hospital, Ghent, Belgium.

Background/Purpose: Microvascular damage is an intrinsic and early pathological event in Systemic Sclerosis (SSc) and can be observed using nailfold capillaroscopy (NFC). NFC can be performed using different techniques, including dermoscopy, widefield microscopy, and videocapillaroscopy. Abnormal nailfold capillaries are part of the 2013 diagnostic criteria for systemic sclerosis and may be observed in other connective tissue diseases (CTD) as well. With the support of our Academy of Medical Educators, we developed and assessed an educational curriculum to teach adult and pediatric rheumatology fellows the techniques and skills required for NFC.

Methods: Our curriculum had three programmatic elements. First, the fellows were provided with dermatoscopes and were given the opportunity to learn both the normal exam and abnormal capillary patterns. They were then given a one-hour didactic session and workshop where they used dermoscopy and widefield microscopy to examine the normal and abnormal patterns on themselves and an SSc patient. The third part of the curriculum involved a full-day course given by two experts in NFC that incorporated videocapillaroscopy and patient cases. Tests of usage and interest were taken at three time points – prior to giving the dermatoscopes, following the one-hour didactic session, and following the full-day course. Tests of knowledge were given to attendees of the full-day course before and after and included fellows, rheumatology attendings, and others. Comparisons were made using Fischer Exact Tests.

Results: In our institution there are 12 pediatric and adult rheumatology fellows. Response rates were 100%, 83% and 75% at the 1st, 2nd and 3rd timepoints- respectively. At all time points 100% of fellows noted interest or strong interest in learning NFC techniques. After the course 67% felt confident in their ability to perform NFC while before the course only 17% felt confident, $p = 0.03$. Prior to the completion of the curriculum 25% of fellows responded that they used NFC frequently when they performed rheumatologic consultation compared to 67% after the course, $p = 0.09$.

Before and after the one-day course participants were asked to look at photographs of normal and abnormal NFC using a web-based application via

SurveyMonkey. Response rates were 36/70 (51%) prior and 19/70 (27%) after. In the pre-test 74% answered all questions correctly and 95.5% answered all questions correctly in the post-test. Improved identification of normal NFC was observed: 18/36 (50%) before the course and (18/18) 100% after the course on one question, $p<0.001$. Improved identification of neoangiogenesis was observed, 18% pre versus 77% post, $p<0.001$.

Conclusion: NFC is an area of interest for rheumatology trainees and attendings. This curriculum was feasible and led to improved ability of learners to distinguish normal from abnormal and to recognize and describe SSc-specific NFC changes that identify validated patterns of disease progression. This curriculum also led to improved confidence in examining nailfold capillaries and increased use of this skill in rheumatologic consultation.

Disclosure: D. Lerner, None; **S. A. Paget**, None; **M. Cutolo**, None; **V. Smith**, None; **R. F. Spiera**, None; **J. K. Gordon**, None.

1992

Resident's Guide to Rheumatology Mobile Application: An International Needs Assessment. Evelyn V. Rozenblyum[1], Niraj Mistry[1], Tania Cellucci[2], Tina Martimianakis[3] and Ronald M. Laxer[4]. [1]University of Toronto, Toronto, ON, [2]McMaster Children's Hospital, Hamilton, ON, [3]Hospital for Sick Children, Toronto, ON, [4]The Hospital for Sick Children, University of Toronto, Toronto, ON.

Background/Purpose: "A Resident's Guide To Pediatric Rheumatology" (the Guide) is a widely accepted resource for pediatric rheumatologists and trainees. In preliminary assessments, uptake of the Guide was broader than intended and it was used by trainees to help with clinical decision-making, learning and teaching. Users of the Guide suggested that it be developed into a mobile application (app).

The Technology Acceptance Model (TAM) provides a framework to assess the perceived usefulness and ease of use of a tool to predict future acceptance and use.

Objectives: (1) To determine the International demand amongst pediatric professionals and current trainees for a mobile app format of the Guide.

(2) To determine user preferred features, functions, and format to be included in a mobile app using the TAM.

Methods: An electronic survey was developed and distributed to pediatric residents at SickKids hospital and to both faculty and trainee members of the international Pediatric Rheumatology list server. The survey included respondent demographics, perceived usefulness, perceived ease of use, and behavioural intention to use the app based on the TAM. Data were analyzed using descriptive statistics.

Results: The survey was distributed to 75 pediatric residents and 1132 members of the Pediatric Rheumatology listserver and 135 (12% response rate) completed the survey. The majority of respondents were rheumatologists (53%), while the remainder consisted of Fellows (17%), Pediatric Residents (16%), and other allied health professionals (5%). 93% owned a smartphone and 58% owned a tablet. Most had medically related apps (75%) compared to e-books (38%), but had similar use for each- one to several times per week for 1–15 minutes each time on average.

The most useful features of an app would be clinical pictures (e.g. skin rashes), radiology images (e.g. joint x-rays), and definitions of key terms. Least useful features were games and multiple-choice questions. Additional features included a searchable index and links to journal articles.

Looking at the TAM, the vast majority of respondents thought that the mobile app would enhance trainees' learning and teaching effectiveness. Greater than 80% of respondents consistently supported its perceived ease of use. 55% stated that they were likely to use the app often.

86% felt it was important for the app to be developed. If the app was not available for free, a majority (43%) of respondents were willing to pay for the app with a most willing to pay up to $5.00, and 10% willing to pay up to $10 for access to the app.

Conclusion: Development of the Guide app was well supported with adding features such as clinical photographs, radiology images, definitions and searchable index. TAM showed the intention to use the app in the future will be most determined by the perceived ease of use which was consistently high in the survey. Interestingly, users were willing to pay for the app if it was not free.

Future steps include a qualitative study ultilizing focus groups to assess the perceived functionality, usability, facilitators and barriers in using the Guide app prototype to create the most targeted, user friendly app.

Disclosure: E. V. Rozenblyum, None; **N. Mistry**, None; **T. Cellucci**, None; **T. Martimianakis**, None; **R. M. Laxer**, None.

1993

Does Psychological Safety Impact Learning Environments Among Rheumatology Fellows: Findings from Veterans Affairs Learners' Perception Survey. Joe Gamboa[1], Karina Marianne D. Torralba[1], Chau Nguyen[1], Grant W. Cannon[2], Samuel Baz[3] and T. Michael Kashner[4]. [1]Loma Linda University, Loma Linda, CA, [2]Salt Lake City VA and University of Utah, Salt Lake City, UT, [3]Loma Linda University Medical Center, Loma Linda, CA, [4]Office of Academic Affiliation, VA Loma Linda Healthcare System, Loma Linda, CA.

Does Psychological Safety Impact Learning Environments among Rheumatology Fellows: Findings from Veterans Affairs Learners' Perception Survey

Gamboa JR, Torralba KD, Nguyen CN, Cannon GW, Baz S, Kashner TM

Background/Purpose: Each year, over 35% of all U.S. residents will rotate through a U.S. Department of Veterans Affairs (VA) medical center as part of their clinical training. The VA Learners' Perceptions Survey (LPS) was created to assess VA's performance in furthering its professional education training mission.

Objective: The purpose of our research is to assess how Rheumatology fellows rate psychological safety (PS) and their experiences with VA faculty/preceptor, along with clinical, learning, working, and personal environments.

Methods: The LPS is a validated instrument that measures health professions trainee satisfaction with clinical programs. We explored data from 70 Rheumatology fellows who responded to the LPS from July 2011 to January 2014 at 29 VA medical centers across the US. PS was assessed on a 5-point Likert scale ("strongly agree," "agree," "neither," "disagree," and "strongly disagree") with: "members of the clinical team of which I was a part are able to bring up problems and tough issues." This question accounted for 85% of the cumulative variance with other question formats: "I feel free to question decisions or actions of those with more authority," and "It is safe to take a risk on this clinical team."

Results: There were 44 (67%) of 66 respondents who were female, 36 (52%) of 69 were international medical school graduates, 37 (53%) of 70 were PGY 4. Among all 70 fellows, 66 (94%) reported satisfaction with their clinical learning environment, 65 (93%) with preceptors, and 64 (91%) with working, 65 (93%) personal, 66 (94%) clinical, and 61 (87%) medical systems environments. Of the 70 fellows, 67 (96%) agreed or strongly agreed that members of the fellow's clinical team could bring up problems and tough issues. Among those strongly agreeing their VA experience was psychologically safe, 35(79%) of 45 also rated being very satisfied with their clinical learning (versus 8 (32%) of 25 otherwise, $x^2(4)=16.272$ $p=.003$); 35 (80%) of 44 with the preceptors (versus 31% otherwise, $x^2(4)=20.089$ $p<.001$); 36 (84%) of 43 with working (versus 26%, $x^2(4)=24.364$ $p<.001$), 38 (81%) of 47 personal (versus 21%, $x^2(4)=22.993$ $p<.001$), 36 (82%) of 44 clinical environment (versus 27%, $x^2(3)=21.145$ $p<.001$), and 36 (84%) of 43 medical systems (versus 20%, $x^2(3)=27.044$ $p<.001$.

Conclusion: Our data suggests that Rheumatology fellows were satisfied with their VA clinical learning experience, and that psychological safety was strongly associated with the fellow's satisfaction of their VA learning, working, and clinical training environments.

Table 1. Overall ratings at VA facility by Rheumatology fellows 2001–2014 across major domains in LPS survey

	Very Satisfied		Somewhat satisfied		Not Satisfied		
Domain	Total N	N (%) strongly psychologically safe	Total N	N (%) strongly psychologically safe	Total N	N (%) strongly psychologically safe	x^2
Learning environment	45	35(78%)	21	8 (38%)	4	0 (0%)	$x^2(4)=16.3$, $p=0.003$
Preceptors	44	35 (80%)	21	7 (33%)	5	1 (20%)	$x^2(4)=20.1$, $p<.001$
Clinical environment	44	36 (82%)	22	6 (27%)	4	4 (33%)	$x^2(3)=21.145$, $p=0.000$
Physical environment	37	32 (87%)	28	11 (39%)	4	0 (0%)	$x^2(2)=22.144$, $p=0.000$
Working environment	43	36 (84%)	21	6 (29%)	6	1 (17%)	$x^2(4)=24.364$, $p=0.000$
Personal experience	47	28 (81%)	18	4 (22%)	5	1 (20%)	$x^2(3)=22.993$, $p=0.000$
Timeliness of staff and services	40	35 (88%)	24	7 (29%)	6	1 (17%)	$x^2(4)=27.443$, $p=0.000$
Quality of staff and services	41	31 (85%)	28	8 (29%)	1	0 (0.0%)	$x^2(2)=24.266$, $p=0.000$
System and process in dealing with medical errors	43	36 (84%)	18	4 (22%)	7	1 (14%)	$x^2(3)=27.044$, $p=0.000$

Disclosure: J. Gamboa, None; **K. M. D. Torralba**, None; **C. Nguyen**, None; **G. W. Cannon**, None; **S. Baz**, None; **T. M. Kashner**, None.

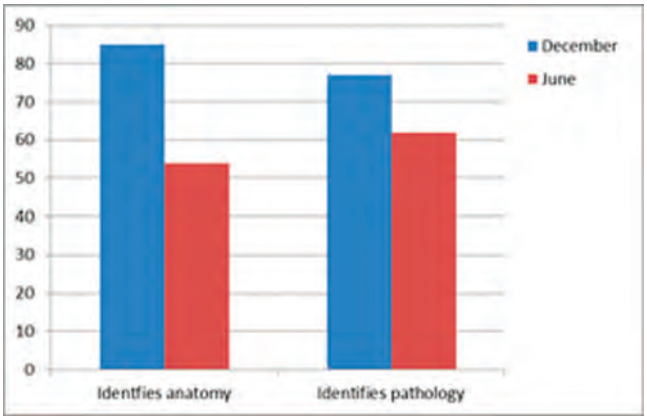
1994

Incorporation of Musculoskeletal Ultrasound Curriculum and 6-Month Assessment of Knowledge Retention into the 2nd Year of Medical Student Training. Kiley Toder[1], William Rennie[2], Ruth L. Marder[3] and Maria L. Barilla-LaBarca[4]. [1]Northshore LIJ, Great Neck, NY, [2]Hofstra North Shore LIJ School of Medicine, Hempstead, NY, [3]North Shore LIJ Health System, Great Neck, NY, [4]Hofstra North Shore LIJ Health System, Great Neck, NY.

Background/Purpose: Few medical schools offer a formal curriculum in musculoskeletal ultrasound (MSUS); the success of such a program in terms of skills and knowledge acquisition and durability of response has not been clearly documented. The purpose of this study was to assess second year students' ability to identify the presence of pre-loaded suprapatellar effusions using a cadaver model following a formal MSUS curriculum and assess their skill and knowledge retention rate at 6 months.

Methods: As part of a longitudinal US curriculum at Hofstra NSLIJ SOM, 3 sessions were reserved for MSUS during the 2nd year of study. There were pre-assigned readings prior to each session. The 1st session reviewed probe selection, patient positioning, and recognition of tissues (tendon, muscle, bone, cartilage, etc). The 2nd session demonstrated normal and pathologic knee anatomy on a cadaveric model. Multiple choice question style pre-assessment was given prior to this session. In the 3rd session, students performed a standard knee US exam with the guidance of MSUS-trained faculty. The summative assessment evaluated the students' ability to perform a standard knee exam, label knee anatomy on acquired images, and identify a suprapatellar "effusion" in a cadaver preinjected with a gelatin mixture. This exercise was repeated 6 months later in a smaller, voluntary group of students to assess retention of skills and knowledge.

Results: In the pre-assessment 22/57 (38.5%) students correctly identified the US image with a knee effusion although only 2 students could label it correctly compared to 37/57 (67%) in the summative assessment ($p = .003$ correct answer and $p < .0001$ labeling). Thirteen students volunteered to participate in the 6 month extension; they did not prepare in advance nor have significant opportunities for MSK US in the intervening months. Eleven of these students (84.6%) had identified the anatomy and 10 (76.9%) had identified the effusion during the summative assessment in December. In June, a decrease in both knowledge (table) and skills (84.6% of images were of poor quality or taken in non-standard locations) was found although the majority (61.5%) was still able to identify the pathology.



Conclusion: Following a formal MSUS curriculum, the majority of the 2nd year medical students were able to demonstrate their skill in the acquisition of images, distinguish pathologic from normal findings, and identify knee structures by US. However the retention rate for quality images and identifying anatomical structures decreased at 6 months. Yet, a majority of students identified fluid and bone in the knee that helped to obtain their respective images and assess the location and nature of the effusion. Thus, although anatomy would have to be further reinforced, student's identification of effusions was durable at 6 months.

Disclosure: K. Toder, None; **W. Rennie**, None; **R. L. Marder**, None; **M. L. Barilla-LaBarca**, None.

1995

Design and Implementation of a Clinical Teaching Tool for Approach to Children with Suspected New Rheumatologic Diagnosis. Kristen Hayward and Jennifer Hrachovec. Seattle Children's Hospital, Seattle, WA.

Background/Purpose: Approximately 1 in 1000 children suffer from a rheumatologic disorder. Despite the relative frequency of these conditions, there is a shortage of pediatric rheumatologists and many children with rheumatologic conditions will present to primary care providers for initial evaluation and management. Unfortunately, there is strong evidence that graduating pediatric residents are ill equipped to recognize and treat these children. In the University of Washington Pediatric Residency Program, exposure to rheumatology occurs through a month long, largely inpatient rotation. The inpatient focus presents an educational challenge to provide residents with fundamental concepts involved in the care of a primarily ambulatory patient population.

Methods: A literature search was conducted to identify previous relevant work. Although there are existing curricula for pediatric rheumatology electives, no curricula were identified to specifically address inpatient based pediatric rheumatology education. A clinical teaching tool was developed based on types of rheumatology admissions commonly available for pediatric resident involvement, as well as a desire to teach broad based concepts involved in evaluation of rheumatologic disorders. An evidence-based literature search identified supporting evidence for relevant clinical questions. The tool consists of a clinical pathway activated by an electronic medical record (EMR) based orderset which guides users through initial assessment and treatment considerations. The orderset is linked to a visual algorithm outlining the recommended approach. An accompanying web-based educational module has been developed along with an assessment tool designed to gauge changes in learner's knowledge and attitudes after completion of the module. Initial content validity for the assessment tool was developed through peer review by additional pediatric rheumatology providers at our institution.

Results: The Rheumatology New Diagnosis Pathway was implemented in Nov. 2011. The web-based educational module was added in March 2014. EMR derived utilization data reflects high acceptance from pediatric residents with an average of 10 patients on pathway per fiscal quarter (range 2–18). Informal feedback has been positive in terms of facilitation of order entry and appreciation of general concepts presented.

Conclusion: Given the scarcity of pediatric rheumatologists, it is imperative to provide pediatric residents with quality education about rheumatologic conditions. Given the constraints of current residency experiences, novel curricular developments are required to address this educational need. This teaching tool addresses the management of children admitted to the rheumatology service. By focusing on broad concepts involved in initial diagnosis and treatment of childhood rheumatologic disorders, this teaching tool offers a foundational model which can be translated to future patient encounters. Additional work is planned to assess the impact of the tool on trainee knowledge of and comfort with evaluation of children with rheumatologic conditions as well as potential for dissemination to additional institutions.

Disclosure: K. Hayward, None; **J. Hrachovec**, None.

1996

Improvement in Basic Bone Health Knowledge Among VA Primary Care Practitioners during a Focused Musculoskeletal Mini-Residency. Mathilde Pioro[1], Nancy Fisher[1], Marissa Grotzke[2], Grant W. Cannon[3] and Michael Battistone[4]. [1]Cleveland Veterans Affairs Medical Center, Cleveland, OH, [2]Salt Lake CIty Veterans Affairs Medical Center, Salt Lake CIty, UT, [3]Salt Lake City VA and University of Utah, Salt Lake City, UT, [4]University of Utah Health Sciences Center, Salt Lake City, UT.

Background/Purpose: Osteopenia and osteoporosis are common yet underrecognized in the veteran population.

Methods: We tested basic bone health related knowledge among Veterans Affairs (VA) primary care providers (PCPs) before and after a 3 day intensive musculoskeletal mini-residency. Principles and practice of bone health were reviewed during 6 hours of small group sessions led by a practicing VA endocrinologist with expertise in osteoporosis. Topics included dietary calcium, vitamin D supplementation, and screening for osteoporosis. Self-reported satisfaction with the program was evaluated at the conclusion. An 8-item medical

knowledge examination was administered at the beginning of the program (pre-test) and at the end (post-test). The post-test composite score was compared to the pre-test composite score for all participants.

Results: 17 full-time PCPs participated. 71% were female, with mean age 48.3 years (range 27–58), and mean number of years in practice 14.6 (range 1–23). 47% were physicians, 41% nurse practitioners, and 12% physician assistants. 79% practiced in community-based outpatient clinics and 29% at the associated tertiary care referral facility (Cleveland VA Medical Center).

Question	% correct PRE	% correct POST
Screening age for osteoporosis in men in the absence of risk factors (70 years)	25%	94%
Screening age for osteoporosis in women in the absence of risk factors (65 years)	47%	88%
Content of calcium in one cup of milk (300mg)	24%	31%
Recommended daily vitamin D intake for men over 70 years (1200mg)	65%	53%
Serum 25 (OH) D3 level minimally sufficient for bone health (30 ng/ml)	73%	94%
Identification of suitable candidates for FRAX screening algorithm	59%	71%
Significant level for 10 year probability of major hip fracture per FRAX algorithm (3%)	20%	47%
Significant level for 10 year probability of major osteoporotic fracture per FRAX algorithm (20%)	14%	35%

FRAX *www.shef.ac.uk/FRAX/tool.aspx*

The program evaluation showed 100% very satisfied with the training experience and over 95% reporting the program as applicable to their clinical practice. 77% of participants improved their overall composite bone health knowledge score at the end of the program. Non-MDs had better baseline knowledge than MDs for recommended screening age for osteoporosis in women and recommended daily vitamin D intake. Areas of persistent knowledge deficit at the end of the residency included dietary calcium content and interpretation of the FRAX osteoporosis screening algorithm.

Conclusion: Participants demonstrated an increase in overall bone health knowledge after a mini-residency program. Not all areas improved. Further educational efforts should be directed to VA PCPs to further address methods to improve basic identification and treatment of osteopenia and osteoporosis. Particular emphasis should be directed to the use and interpretation of the FRAX screening algorithm.

Disclosure: M. Pioro, None; **N. Fisher**, None; **M. Grotzke**, None; **G. W. Cannon**, None; **M. Battistone**, None.

1997

Structured Integrative Rheumatology Modules (SIRM). Sonia Manocha, Ingrid Cobb, Sobia Hassan, Stanley P Ballou and Marina N. Magrey. Case Western Reserve University, MetroHealth Medical Center, Cleveland, OH.

Background/Purpose: Medical students and internal medicine residents frequently rotate through the division of rheumatology, but there have been inconsistencies in specialty-based training. We hypothesized that the development of a structured curriculum is an effective and consistent method of improving students' and residents' core content knowledge of rheumatology during the elective. Our aim was to develop a comprehensive curriculum with structured, appropriate and timely information.

Methods: Utilizing rheumatology textbooks, relevant journal articles and educational websites, such as the American College of Rheumatology (ACR) website (Rheumatology Image Bank, Clinical Practice Guidelines and Rheum2Learn), we created a series of modules that address key learning objectives in rheumatology. The modules were organized into a series of interactive lectures for one hour three times a week. In addition to the lectures, rotators were required to attend clinic and give a presentation at the completion of their rotation.

To measure the effectiveness of this structured, module-based curriculum, we created a 25 question multiple-choice exam that was administered at the start of the rotation (pre-test) and again at completion of the rotation (post-test). Both pre-test and post-tests were scored together at the end of the rotation.

Pre and post-test results were analyzed using a two-tailed paired T-test.

Rotators were given a survey at the completion of their elective. It was comprised of questions relative to the teaching sessions as well as open-ended questions related to further improvement of the curriculum.

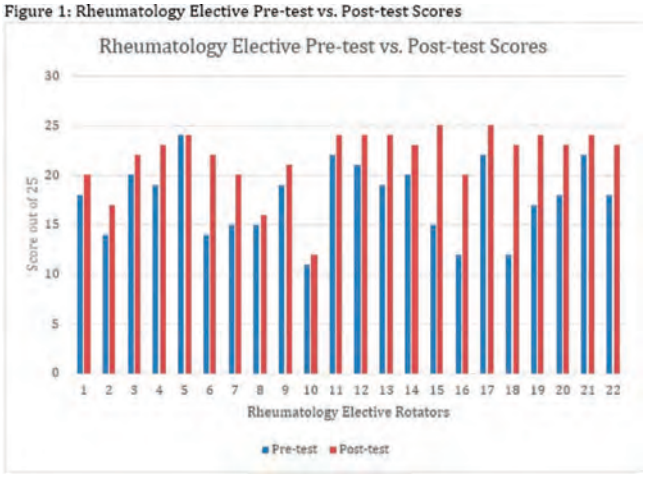
Results: Twenty-two rotators completed both pre-test and post-test examinations and were included in the data analysis. Rotators that did not complete both pre-test and post-test were excluded.

The mean post-test score (21.77, SD 3.23) showed significant improvement from the mean pre-test score (17.59, SD 3.66) at a p-value of 0.00024 as shown in figure 1.

In the final survey, rotators consistently expressed that the dedicated teaching sessions were a helpful addition to the rotation. They also suggested that we continue to expand and include more topics.

Conclusion: A comprehensive structured curriculum with consistent information for rheumatology helps to improve core content knowledge of rheumatic diseases and aids in consolidation of the clinical experience for medical students and residents during their rheumatology elective.

Figure 1: Rheumatology Elective Pre-test vs. Post-test Scores



Disclosure: S. Manocha, None; **I. Cobb**, None; **S. Hassan**, None; **S. P. Ballou**, None; **M. N. Magrey**, None.

1998

pGALS Training Increases Kenyan Pediatric Residents' Confidence in Performing a Musculoskeletal Exam. Tanya Glushko[1], Ines Colmegna[2], Helen Foster[3], Sasha Bernatsky[1], Carol Hitchon[4] and Rosie Scuccimarri[1]. [1]McGill University, Montreal, QC, [2]McGill University - Royal Victoria Hospital, Montreal, QC, [3]Newcastle University, Newcastle, United Kingdom, [4]University of Manitoba, Winnipeg, MB.

Background/Purpose: Musculoskeletal (MSK) manifestations are a common reason for outpatient consults accounting for 6–9% of pediatric clinic visits in developed countries. Patients are initially evaluated by primary care practitioners, general pediatricians and emergency physicians. It has been suggested that low confidence in pediatric MSK assessment is a key factor contributing to diagnostic delays and poor outcomes.

pGALS (pediatric Gait, Arms, Legs, Spine) is a simple tool for MSK assessment, which facilitates early recognition and prompt referral of patients with joint problems. When performed by non-pediatric specialists and compared with pediatric rheumatologists, pGALS has been shown to have excellent sensitivity (97–100%) and specificity (98–100%) for detecting abnormal joints.

We undertook this study to evaluate pediatric residents' confidence in conducting an MSK evaluation and the effect that a pGALS training session had on enhancing this perception.

Methods: Pediatric residents working at the two training centers in Nairobi, Kenya (Aga Khan University Hospital and Kenyatta National Hospital) participated in a 60 minute hands-on session on pGALS given by a pediatric rheumatologist. Written anonymized questionnaires performed prior and post training assessed the participants' level of confidence in examining the MSK system.

Results: Sixteen residents with an average of 2.9 ± 0.8 years of training completed the survey. Ten out of 16 (63%%) reported previous MSK exam training. None of the participants had been trained in pGALS before. A third of residents (31%) were not comfortable examining the MSK system, while the remaining felt comfortable in some aspects only. The level of confidence in examining the MSK system was significantly lower than that for all of the following systems: cardiovascular, respiratory, abdominal and neurological ($p<0.005$).

Ninety four percent of the residents reported increased level of confidence ($p<0.001$) following the pGALS training session. Most physicians considered the training session extremely beneficial (75%) or very beneficial (25%). Ten residents (63%) reported planning to use this tool for all patient visits, 4 (25%) in patients with minimal joint complaints and 2 (12%) in those with

obvious joint concerns. In their clinical setting, the residents thought that office posters (63%) and pocket cards (63%) would be more useful than web-based video demonstrations (25%) to facilitate the use of the pGALS in clinical practice. They felt that the best way to increase confidence in the MSK exam was with one-on-one bedside coaching (81%) rather than web-based video demonstrations (50%) and workshops (44%).

Conclusion: pGALS training together with routine reminders to facilitate pGALS incorporation into the regular exam translates into increased physician confidence, which may lead to earlier recognition of rheumatic diseases in children. pGALS teaching materials may need to be tailored to the clinical setting that they will be used in.

Disclosure: T. Glushko, None; **I. Colmegna**, None; **H. Foster**, None; **S. Bernatsky**, None; **C. Hitchon**, None; **R. Scuccimarri**, None.

1999

Internal Medicine Resident Confidence in Rheumatologic and Musculoskeletal Diseases: A Needs Assessment Survey. Cristina Savasta, Deborah Korenstein and Yousaf Ali. Icahn School of Medicine at Mount Sinai, New York, NY.

Background/Purpose: Small studies have demonstrated a lack of confidence and competency in the areas of rheumatology and musculoskeletal diseases among internal medicine physicians at various levels of training. This can lead to a delay in the diagnosis of rheumatologic disease and may result in suboptimal patient outcomes and increased morbidity. Increasing time devoted to teaching the subject has been shown to increase resident confidence, suggesting that an intervention could have a significant impact on residents' ability to diagnose and manage rheumatologic diseases. We aim to assess resident confidence in rheumatologic and musculoskeletal topics and skills in order to evaluate the need for an educational intervention.

Methods: We emailed a survey to the 137 residents in the Department of Medicine at a large, urban university hospital. The survey included 6 questions on a 5-point Likert scale measuring self-assessed knowledge of rheumatology topics and confidence in musculoskeletal exam skills. Questions regarding non-rheumatologic topics were included to control for increased confidence across post-graduate years related solely to increased experience.

Results: Seventy-one responses were collected for a response rate of 51.8%. Resident confidence in rheumatology was generally low. Fewer than 60% of respondents agreed or strongly agreed that they were confident diagnosing and managing musculoskeletal and joint diseases. Fewer than 50% of respondents reported confidence in skills such as interpreting rheumatologic serologies, performing a musculoskeletal exam or performing a joint aspiration or injection. This is in contrast to the more than 77% of respondents who reported confidence in diagnosing and managing hyperthyroidism or coronary artery disease. Similarly, more than 73% of respondents reported confidence in interpreting electrocardiograms or thyroid function tests. While confidence related to non-musculoskeletal diseases tended to improve from first to third year of training, confidence related to musculoskeletal diseases tended to remain poor despite increased experience. Respondents reported interest in receiving further training in musculoskeletal topics in which they lacked confidence.

Conclusion: Internal Medicine residents at our hospital have low self-assessed knowledge and skills in the areas of rheumatologic and musculoskeletal diseases. We believe our hospital is representative of residency training in the United States, and a dedicated educational curriculum to fill these gaps in training could improve resident confidence and knowledge. Ultimately, we hope this will impact patient care and improve rheumatologic outcomes.

Percentage of respondents who agreed or strongly agreed they were confident in the following topics or skills:

	Overall (n=71)	PGY*-1 (n=21)	PGY-2 (n=27)	PGY-3 (n=23)
Crystal-induced arthritis	59.2%	57.1%	63%	56.5%
Infectious arthritis	40.8%	47.6%	33.3%	43.5%
Autoimmune disorders	32.9%	28.6%	33.3%	36.4%
Spondyloarthropathies	7.0%	4.8%	7.4%	8.7%
Interpreting rheumatologic serologies	42.3%	38.1%	29.6%	60.9%
Musculoskeletal/joint physical exam	29.6%	23.8%	37%	26%
Joint injection/aspiration	9.9%	9.5%	3.7%	17.4%

*PGY: Post graduate year

Disclosure: C. Savasta, None; **D. Korenstein**, None; **Y. Ali**, None.

2000

The Effect of a Rheumatology Ambulatory Rotation for Medical Residents on Documentation of Musculoskeletal Complaints. Deana M. Lazaro[1], David Ozeri[2], Jenna Checchi Gibilaro[2] and Deena Hassuna[3]. [1]Brooklyn VA, Brooklyn, NY, [2]SUNY Downstate Medical Center, Brooklyn, NY, [3]SUNY Downstate Medical Center, Brooklyn, Algeria.

Background/Purpose: Musculoskeletal (MSK) complaints are commonly the reason for visits to Primary Care offices. Therefore, it is important to teach residents to recognize and manage them. Passive learning techniques such as reading may improve knowledge but do not necessarily teach residents to synthesize and apply that knowledge in a clinical encounter. The purpose of this study is to determine if an enriched rheumatology curriculum, using active learning techniques, leads to better assessment and management of MSK complaints in a primary care setting among medical residents.

Methods: This pilot study is a blinded, retrospective, case-controlled trial comparing residents who participated in a rheumatology elective in comparison to residents who had passive learning about rheumatology. Medical residents were assigned to rheumatology or another subspecialty elective. All residents were assigned rheumatology reading in preparation for a post-test and objective structured clinical examination (OSCE). Rheumatology elective residents were taught using active learning techniques such as arthrocentesis simulation and small group teaching for MSK examination. They attended rheumatology clinic for an average of 3 sessions weekly for 4 weeks. The other residents viewed videos on arthrocentesis and MSK physical examination.

Fifty medical records from Primary Care continuity clinic were analyzed for evaluation of MSK complaints. The selected outpatient records had MSK-related chief complaints and were completed within 18 months from the writers' rheumatology teaching in both groups. The performance of the residents was assessed using a predetermined grading system by two blinded evaluators. Evaluators reviewed specifics regarding history (10 points), physical examination (5 points), assessment (2 points) and management (2 points) for a possible total of 19 points. Evaluators also gave each record a summary score for documentation of history, physical examination, assessment or plan (possible total of 4 points) regarding the chief complaint.

Results: Results are displayed in Table 1. A 2-tailed T-test was performed comparing the total scores by evaluator 1 and evaluator 2; p values were 0.14 and 0.28 respectively.

Table 1 Mean scores with +/− standard deviation for chart review by evaluator 1 and evaluator 2

	Evaluator 1		Evaluator 2	
Resident assignment	**Rheumatology**	**Non-Rheum**	**Rheumatology**	**Non-Rheum**
History	4.2 (2.0)	4.7 (2.0)	4.3 (2.1)	4.4 (2.4)
Exam	1.2 (1.3)	1.8 (1.1)	1.2 (1.2)	1.9 (1.0)
Assessment	1.8 (0.9)	1.4 (0.9)	0.8 (0.6)	1.0 (0.7)
Management	1.8 (0.5)	1.6 (0.7)	1.7 (0.5)	1.6 (0.6)
Total	8.1 (3.2)	9.5 (3.3)	8.0 (3.1)	8.9 (3.3)
Summary score	3.2 (0.7)	3.6 (0.7)	3.2 (1.0)	3.5 (0.8)

Conclusion: We found no significant difference in documentation of medical care for MSK complaints between medical residents who had a rheumatology elective with active learning and medical residents who had passive learning for rheumatology. These results indicate that passive learning through reading and videos is as effective as small group teaching, at least for 4 week long elective experiences. Improvement in outcomes may require reinforcement over a longer period of time and in different clinical settings.

Disclosure: D. M. Lazaro, None; **D. Ozeri**, None; **J. Checchi Gibilaro**, None; **D. Hassuna**, None.

2001

The Musculoskeletal Mini-Residency Collaborative Network: A National Department of Veterans Affairs Interdisciplinary and Interprofessional Educational Innovation for Primary Care Providers. Michael J. Battistone[1], Andrea M. Barker[1], Marissa P. Grotzke[1], J. Peter Beck[1], Anna Quan[2], Michal Hose[2], Victoria Seligman[3], Roneka Ravenell[4], Pushpa Pavuluri[4], W. Neal Roberts[4], Mathilde Pioro[5], Nancy Fisher[5], Vanessa Osting[6], Betty Prihar[6], Joanne Hackman[7], Susan Kirsh[7] and Grant W. Cannon[1]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]San Diego VA, San Diego, CA, [3]Denver VA Medical Center, Denver, CO, [4]Louisville VA,

Louisville, KY, [5]Cleveland VA, Cleveland, OH, [6]Tampa VA, Tampa, FL, [7]Office of Specialty Care Transformation, Patient Care Services, VHA Central Office, Washington, DC.

Background/Purpose: To address the problem of insufficient training in Musculoskeletal (MSK) diseases by practicing primary care providers (PCPs), the Veterans Affairs (VA) Office of Specialty Care Transformation provided pilot funding through a competitive, peer-reviewed process, to develop and support a "MSK Mini-Residency" to train PCPs in evaluation and management of common MSK diseases.

Methods: The 3 day MSK mini-residency curriculum intersperses didactic lectures with small group workshops, as well as case based interactive small-group practice sessions and technology-enhanced simulation (see full schedule, Table 1). Participants' competency in performing and interpreting the physical examination of the shoulder and knee is evaluated by a 2-station Objective Structured Clinical Examination (OSCE), to ensure sufficient preparation for assessing patients in clinic. Course evaluation was conducted using the Kirkpatrick's model of assessing educational effectiveness, and Phillip's concept of Return on Investment. Table 1

-Day 1-		
7:30–8:00	Sign In/Lunch Sign In	
8:00–8:20	Course Introduction	
8:20–9:10	Introduction to Shoulder Exam	
	Group I	***Group II***
9:20–10:30	Small Group Shoulder Exam Practice	Bone Health
10:40–11:50	Bone Health	Small Group Shoulder Exam Practice
11:50-noon	Lunch Served	
noon–1:15	Shoulder Pathology/Lunch	
	Group I	***Group II***
1:30–3:00	Bone Health	Small Group Shoulder Cases
3:15–4:45	Small Group Shoulder Cases	Bone Health
4:45–5:00	Wrap Up	
-Day 2-		
7:30–8:00	Sign In/Lunch Sign In	
8:00–8:40	Introduction to Knee Exam	
	Group I	***Group II***
8:50–9:40	Bone Health Risk Factors	Small Group Knee Exam Practice
9:50–10:40	Small Group Knee Exam Practice	Bone Health Risk Factors
10:45–11:45	Practical Issues in Performing and Documenting Joint Injections	
11:45–12:00	Lunch Served	
12:00–1:00	Knee Pathology	
	Group I	***Group II***
1:00–2:55	Bone Health Cases/Shoulder OSCE	Small Group Knee Cases/ Injections
3:05–5:00	Small Group Knee Cases/ Injections	Bone Health Cases/Shoulder OSCE
-Day 3-		
7:30–8:00	cSign In/Lunch Sign In	
	Group I	***Group II***
8:00–10:30	Rheumatology Cases	Bone Health Cases/Knee OSCE
10:30–1:00	Bone Health Cases/Knee OSCE	Rheumatology Cases
1:00–1:30	Lunch Served	
1:30–2:30	Evaluation & Management of Back Pathology	
2:30–3:00	Practical Issues in Performing and Documenting Joint Injections	
3:00–4:00	Course **Conclusion**	

Results: From 2012–2014, the 3-day MSK Mini-Residency course has been presented at 12 VA medical centers, serving catchment areas centered in Los Angeles, San Francisco, Denver, Omaha, Louisville, Cleveland, Philadelphia, Tampa, Orlando, and Boston. Table 2 shows the distribution of participants by professional credential, as well as their pre- and post-course self-assessments of their ability and preparation to evaluate and manage shoulder and knee pain in their clinics.

Table 2

MSK Mini-Residency Participants	**Total**	**Physician**	**NP**	**PA**	**Unspecified**
Number, %	241 (100)	148 (61)	75 (32)	15 (6)	3 (1)
			Pre Course		**Post Course**
Able to evaluate and manage shoulder complaints			25%		99%
Able to evaluate and manage knee complaints			31%		98%
Prepared to aspirate/inject knee or subacromial space			29%		66%

Post course competency in examining the shoulder and knee, and in reporting, interpreting, and managing the cases using a framework of high-value care, was confirmed with 2-station OSCE. Course evaluations were extremely positive across all sites: over 95% of participants anticipate that the training will impact their job performance and would recommend the course to others.

Conclusions: The MSK Mini-Residency is an effective model for training and evaluating primary care providers in the diagnosis and management of common musculoskeletal diseases.

Disclosure: M. J. Battistone, None; **A. M. Barker**, None; **M. P. Grotzke**, None; **J. P. Beck**, None; **A. Quan**, None; **M. Hose**, None; **V. Seligman**, None; **R. Ravenell**, None; **P. Pavuluri**, None; **W. N. Roberts**, None; **M. Pioro**, None; **N. Fisher**, None; **V. Osting**, None; **B. Prihar**, None; **J. Hackman**, None; **S. Kirsh**, None; **G. W. Cannon**, None.

2002

Implementation of a Collaborative Rheumatology and Physiatry Musculoskeletal Ultrasound Training Program. Minna J. Kohler[1], Chloe Slocum[2], Imran Siddiqui[2], Kevin O'Connor[2] and Marcy B. Bolster[1]. [1]Massachusetts General Hospital/Harvard Medical School, Boston, MA, [2]Spaulding Rehabilitation Hospital/Harvard Medical School, Charlestown, MA.

Background/Purpose: Rheumatology musculoskeletal ultrasound (MUS) certification has been established and MUS teaching is rapidly being incorporated into U.S. rheumatology fellowship training programs. Similarly, MUS use by physiatrists is growing, and exposure to MUS and rheumatology teaching is now mandatory in physical medicine and rehabilitation (PM&R) residency programs. At this time, no standardized rheumatology MUS curriculum is required, but competency criteria are currently under discussion.

Methods: We describe the implementation of a novel, collaborative rheumatology/physiatry MUS training program at a single academic center. The program was developed by a rheumatology MUS expert in conjunction with the program directors of both rheumatology fellowship and PM&R residency to adequately expose fellows to MUS, and fulfill both rheumatology and MUS training requirements for residents. A self-assessment survey of the participating fellows and residents was obtained post-implementation, using a 3-point Likert formatted scale (1=no knowledge to 3= extensive knowledge).

Results: All 1st year rheumatology fellows (n=2) were required to participate in a twice monthly ½ day faculty-mentored, MUS clinic over one year. For 2nd year rheumatology fellows with a demonstrated interest in MUS (n=1), additional training included: longitudinal, weekly, faculty-mentored MUS clinics, participation in the USSONAR program, and MUS research. All PGY-3 PM&R residents (n=9) were required to participate in a 1-month rotation of faculty-mentored MUS clinics, 3 days per week. All rheumatology fellows and PM&R residents (n=12) participated in an introductory MUS lecture to review basic knobology, image acquisition, and reasonable use of MUS. Every other month, hands-on sessions reviewed anatomy and scanning protocols. Both groups had access to US equipment for self-directed learning. In the clinic, fellows/residents evaluated patients referred for musculoskeletal pain in a one-stop approach where MUS and guided injections may be performed, as indicated. All fellows and residents completed the survey (Table 1). Post-curriculum, 100% of participants felt they had adequate exposure to MUS and adequate MUS knowledge/ability. Ten of the 12 (84%) trainees participated in self-directed learning. The average range of MUS exams performed by all participants was 11–20; MUS-injections also ranged from 11–20. Six of the 12 trainees (50%) participated in MUS research activities.

Conclusion: Implementation of a collaborative MUS training program is beneficial to the education of both rheumatology fellows and PM&R residents. Improvement in MUS knowledge and ability was shown in both groups. A combined program can adequately fulfill the educational and research needs for both specialties, especially when the number of trained MUS instructors may be limited.

Table 1. Post-Implementation Survey (3-point Likert Scale)

Fellow/Resident Self-Assessment	**Pre-curriculum (mean)**	**Post-curriculum (mean)**
Basic MUS anatomy knowledge	1.36	2.55
Level of ability to optimally image structures	1.27	2.36
Level of ability to interpret MUS images	1.18	2.09
Ability to perform MUS-guided procedures	1.18	2.27
Understanding of indications for reasonable use of MUS	1.45	2.33

Disclosure: M. J. Kohler, None; **C. Slocum**, None; **I. Siddiqui**, None; **K. O'Connor**, None; **M. B. Bolster**, Johnson and Johnson, 1, Eli Lilly and Company, 2, ABIM

Rheumatology Speciality Board, Chair, 6, ABIM Rheumatology Test Writing Committee, Chair, 6, ACR COTW, Chair, 6, ACR Board of Directors, 6, RRF Board of Directors, 6.

2003

Pilot Study of a Web-Based Module on Gout. Bernadette Siaton[1], Elizabeth Clayton[2], Alexandra Kueider[3] and Matthew Rietschel[4]. [1]University of Maryland Medical System, Baltimore, MD, [2]University of Maryland, Baltimore, MD, [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [4]University of Maryland School of Nursing, Baltimore, MD.

Background/Purpose: The majority of internal medicine trainees complete residency with little exposure to rheumatology. We aimed to create a validated, self-directed, web-based, core curriculum in rheumatology for residents. The first module focused on gout. We also aimed to assess the efficacy of this educational product utilizing the script concordance testing (SCT) method. SCT assesses clinical data interpretation and decision making.

Methods: We obtained IRB exemption to perform this study that included internal medicine trainees at the University of Maryland Medical Center. Pre-test and post-test questions were examined for item validity. Pre- and post-test scores were compared to the scores of the expert panel, which was made up of 2 rheumatology fellows, 9 academic rheumatologists, and 1 community rheumatologist. Baseline knowledge was assessed via a pre-test on the Blackboard learning management system, followed by the educational intervention, an interactive didactic presentation on gout. The module included gout pathophysiology, clinical presentation, and therapeutic management. Immediate post-testing was performed. An ANOVA was used to compare trainee and expert groups as well as pre- and post-test scores. Cronbach's alpha was used to calculate test reliability. An effect size was calculated using Cohen's d.

Results: Ten trainees completed paired pre-and post-tests for analysis. The 20-case SCT achieved high reliability (Cronbach alpha for all 20 cases $>$ 0.75). At baseline, the trainees' average SCT score was 32 points ($M=32.45$, $SD=1.99$); whereas the experts' average SCT score was 40 points ($M=40.65$, $SD=1.72$). After the didactics, trainees' SCT scores increased by an average of 2.83 points $F(1, 18) = 9.33$; ($p<.01$). Cohen's d showed a strong effect size ($d=1.13$). Expert SCT scores were an average of 8.2 points ($SD = 0.81$) higher than trainee pre-test scores. Expert SCT scores were an average of 5.4 ($SD = 0.84$) points higher than trainee post-test scores. Both of these differences were statistically significant ($p<.0001$).

Conclusion: Trainee test scores significantly increased after the educational intervention in this pilot study. Expert SCT scores were higher at baseline and remained higher after the didactics, which lends support to the construct validity of the tool as the experts had higher clinical competence. The effect of the educational intervention will be tested on a larger group of internal medicine trainees. Future plans include subgroup analysis by post-graduate year, implementation of self-efficacy evaluations, and possible re-testing at 6 or 12 month intervals to assess durability of knowledge. Additional modules for the core curriculum will be developed.

Disclosure: B. Siaton, None; **E. Clayton**, None; **A. Kueider**, None; **M. Rietschel**, None.

2004

Osteoporosis Screening and Fracture Risk Assessment Tool Usage Among House Staff. Jordan Brodsky[1], Meghan Greenfield[2] and Erin Patton[2]. [1]Albert Einstein College of Medicine, Woodmere, NY, [2]Beth Israel Medical Center, New York, NY.

Background/Purpose: Despite increased awareness of the magnitude and consequences of osteoporosis and the availability of recommendations for screening and treatment by multiple organizations, osteoporosis is still under diagnosed and inadequately managed in the United States. Identifying patients at risk, making a timely diagnosis, implementing prevention measures and initiating pharmacologic therapy for appropriate patients can all help to minimize fracture risk. Academic hospitals with resident-led outpatient primary care providers are an area where there may be under-utilization of evidence-based fracture risk assessment tools, such as the Fracture Risk Assessment Tool (FRAX) score.

Methods: House staff of the Internal Medicine department at Beth Israel Medical Center where given an anonymous questionnaire. The goal was to assess the resident's knowledge of current practice guidelines and recommendations for osteoporosis and the utilization of the FRAX score.

Results: 48 residents of Internal Medicine, levels PGY 1, 2 and 3, filled out the questionnaire. 63% of residents estimated their female patient population was greater than 65 years old and 31% of their male patient population was greater than 70 years old. 77% of residents performed age appropriate DEXA scans on their patients. 58% of residents had knowledge of what the FRAX score was and 48% of resident knew the appropriate use in patient care. 62% used the FRAX score to identify patients who met criteria for the initiation of treatment for osteoporosis. 29% could identify the modifiable risk factors and 31% identified the non modifiable risk factors which calculate the FRAX score. 33% of residents said they would use the FRAX score on woman less than 65 years old. 79% of residents wanted to receive more information on the FRAX score and its appropriate applications.

Conclusion: Appropriate identification and prevention are imperative to reducing the risk of osteoporosis and osteoporosis-related fractures in individuals. Our study concluded that Internal Medicine residents at one academic medical center are following the current guidelines for screening for osteoporosis with DEXA scans, however, the use of the FRAX score for the identification of patients at high risk for fracture requiring the initiation of treatment for osteoporosis, is highly underutilized. There was also a discrepancy between the resident's knowledge of the FRAX score and its application in clinical practice. Further training and education regarding osteoporosis screening and the use of the FRAX score in a resident led outpatient primary care setting will be beneficial to resident providers and their patients.

Disclosure: J. Brodsky, None; **M. Greenfield**, None; **E. Patton**, None.

2005

Multimedia Patient Education Tool for Patients with Osteoporosis. Maria A. Lopez-Olivo[1], Aparna Ingleshwar[1], Robert Volk[1], Andrea Barbo[1], Maria Jibaja-Weiss[2], Heather Lin[1] and Maria E. Suarez-Almazor[1]. [1]The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]Baylor College of Medicine, Houston, TX.

Background/Purpose: Patient education materials incorporating video modelling can be effective in improving patients' outcomes. We conducted a randomized control trial to test the efficacy of a multimedia-patient education tool (MM-PtET) for patients with osteoporosis, including storylines and narratives.

Methods: 224 patients were recruited from three outpatient clinic systems and through advertisement. Inclusion criteria were: (i) diagnosis of osteoporosis/osteopenia, (ii) female gender, (iii) age $\geq$50 years (iv) at least 3 years post-menopausal, (v) adequate cognitive status, and (vi) ability to communicate in English or Spanish language. Participants were given materials to review based on randomization (Intervention=MM-PtET; Control=written booklet with same content as MM-PtET). All participants completed pre-post self-report questionnaires. Primary outcome measures included: a) Disease knowledge and, b) Decisional Conflict Scale- "Informed" and "Values clarity" scales. Secondary outcomes included: a) Ottawa Acceptability Instrument and b) Evaluation of the educational tool. Baseline demographic information and health literacy level were also obtained. Mean differences in knowledge scores (pre-post randomization) and between group differences in the Ottawa Acceptability and tool evaluation measures were calculated.

Results: 111 patients were randomly allocated to the MM-PtET intervention and 113 to the control booklet. Mean age of participants was 64 ± 9 years and 82% had adequate health literacy. Knowledge scores significantly increased in both groups, post randomization (MM-PtET: 9.5 ± 4.2 vs 12.8 ± 3.2 and Control: 9.1 ± 4.2 vs 12.5 ± 3.2; $p<0.05$ for both groups). Post randomization, participants in both groups had significantly lower "Informed" scores (pre vs post; Intervention: 55.3 ± 38.7 vs 15.8 ± 25.6 and Control: 54.0 ± 38.1 vs 17.7 ± 30.8; $p<0.05$ for both groups; lower scores=more informed) and "Values clarity" scores (pre vs post; Intervention: 49.8 ± 40.9 vs 16.9 ± 30.6 and Control: 55.1 ± 40.8 vs 18.6 ± 29.3; $p<0.05$ for both groups; lower scores=more values clarity). Compared to controls, participants in the MM-PtET group rated better explanation of the medical facts ($p=0.03$), and the understanding of the potential side effects ($p=0.03$). Similarly, when asked about the balance of the material (slanted towards self-care/lifestyle options, slanted toward medical therapies, balanced), greater number of intervention group participants found the material to be "balanced" ($p=0.004$).

Conclusion: The results of our study indicate that, when compared to standard written materials, the MM-PtET was better rated and was comparable in improving knowledge in women with osteopenia/osteoporosis.

Disclosure: M. A. Lopez-Olivo, None; **A. Ingleshwar**, None; **R. Volk**, None; **A. Barbo**, None; **M. Jibaja-Weiss**, None; **H. Lin**, None; **M. E. Suarez-Almazor**, None.

2006

Multiple Joint Osteoarthritis: Patient Preferences for a Generic Exercise and Self-Management Programme. Nicola E. Walsh[1], Geeta Patel[2] and Rachael Gooberman-Hill[3]. [1]University of the West of England Bristol, Bristol, United Kingdom, [2]University of the West of England, Bristol, Bristol, United Kingdom, [3]University of Bristol, Bristol, United Kingdom.

Background/Purpose: In the UK approximately 1.75 million people age 45 and over are diagnosed with multiple, peripheral joint osteoarthritis (OA), a figure that would increase significantly with the inclusion of degenerative spinal pain. Exercise and self-management are recommended core treatment strategies for OA, but evidence is generally based on single site presentations and interventions. In clinical practice patients frequently consult with either pain in more than one joint, or re-consult over time when symptoms manifest in other joints. We developed a 6-week group programme to Facilitate Activity and Self-management in Arthritis (FASA) for people with multisite OA of the hip, knee and/or lower back. The aim of FASA was to teach an exercise programme for these joints, and provide education regarding multiple joint pain management. This qualitative study, embedded within a randomised controlled trial (RCT), presents data from a focus group analysis to determine perceived benefits and acceptability of the intervention.

Methods: Nine semi-structured, focus group interviews facilitated by a researcher independent of the RCT were conducted with patients with OA who had participated in the FASA programme, and had completed their primary end point assessment at 6 months post-intervention. The interviews were audio-recorded, transcribed and analysed using thematic analysis. A second researcher independently coded a selection of transcripts to establish accuracy of interpretation.

Results: Forty-five participants (28 female), age 53–85 years (mean=68 years) with multisite OA joint pain participated in the focus groups. Thematic analysis demonstrated that individuals reported benefits from gaining confidence and knowledge of how to self-manage pain in other joints should it manifest. They also found it beneficial to undertake exercises that took into account their multisite presentations. Gaining insight of how others coped with their pain, irrespective of site, was also considered positive; participants also talked about valuing the shared pain experience. Whilst the majority of participants valued the more general joint pain approach, three people with lower back pain found it difficult to relate to those who did not experience back pain, and expressed a preference for a specific intervention tailored to their presentation.

Conclusion: An exercise and self-management intervention for multisite OA was perceived as beneficial and acceptable to the majority of participants, who reported increased confidence and knowledge for self-management. Further consideration regarding the suitability of integrating back pain patients into these generic sessions may be necessary. Embedding a qualitative analysis into an RCT enhances our understanding of interventions and provides valuable insight from a patient perspective.

Disclosure: N. E. Walsh, None; **G. Patel**, None; **R. Gooberman-Hill**, None.

2007

Using Photovoice Techniques to Empower Lupus Patients and Create Public Awareness: A Program Evaluation. Jessica Rowshandel and Diane Gross. S.L.E. Lupus Foundation, New York, NY.

Background/Purpose: *Lupus through the Lens* is a photography project for people with lupus to capture, in pictures, what it means to live with lupus. Created by the S.L.E. Lupus Foundation, it borrows from photovoice, a socially-engaged photography technique based on community-based participatory research and visual narrative inquiry. To our knowledge, photovoice has not been used within the lupus community. The Foundation's goals for the program were: 1. create public awareness about the shared lived experience of lupus since it is often misunderstood by both lay people and healthcare professionals, 2. aid participants in coping with their illness, and 3. aid viewers with lupus to feel less isolated and more validated in their experience through identification with photos and respective captions.

Methods: This was a 7-week workshop that met over 4 months with 6 participants, all with lupus. Participants were integral in developing project content: through group discussions, they chose the program title and photos to include on the project website; they developed captions, which further defined the meaning of their work. Participants were loaned cameras, and a participant with photography experience gave lessons on camera use and photography techniques. To create public awareness, photos were displayed on a dedicated website and via social media.

Results: Of 803 photos, 53 were selected for the project website. The Foundation's goals were met. Awareness is measured by website traffic; within its first 6-weeks, there were 26,000 views. Participants were aided in coping with their illness, as reported in their final evaluation indicated by a sense of pride, camaraderie, socialization, and self-expression; a new way to share lupus with others; and a deeper understanding of the personal impact of one's own lupus. Based on responses on the project website, Facebook, email and in-person communication, viewers shared that the project gave their experience a voice and they related to the photos on an emotional level.

Conclusion: The project resulted in powerful images and new ways to convey what it is like to live with lupus. The participants themselves defined it as a success. While the program is time-intensive, it is an inexpensive program that can be replicated by other lupus groups. The Foundation will continue in-person workshops, and the project will also grow through online submissions. Based on participants' feedback, the program has the potential to help reduce feelings of isolation and depression, and increase self-esteem and a sense of self-efficacy. More data are needed to confirm participants' reported outcomes. In the future, variables like self-efficacy, self-esteem, depression, and quality of life will be incorporated into the evaluation.

Disclosure: J. Rowshandel, None; **D. Gross**, None.

2008

Personalized Risk Education for Rheumatoid Arthritis Improves Self-Perceived Risk Accuracy and Risk Factor Knowledge in First-Degree Relatives. Jeffrey A. Sparks[1], Maura D. Iversen[2], Rachel Miller Kroouze[1], Nellie A. Triedman[1], Taysir G. Mahmoud[1], Sarah S. Kalia[1], Michael L. Atkinson[1], Robert C. Green[1] and Elizabeth W. Karlson[1]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Having a first-degree relative (FDR) with RA increases personal RA risk by four-fold. Other RA risk factors include demographics, genetics, auto-antibodies, and behaviors. We aimed to develop a personalized RA risk tool incorporating these risk factors, suitable for use in RA education trials. We explored changes in self-perceived RA risk and RA knowledge after personalized RA risk education among a group at increased RA risk due to having a relative affected with RA.

Methods: We conducted a pilot study on RA self-perceived risk, knowledge, and attitudes among FDRs recruited at a large academic hospital. Eligible participants had a FDR with RA. We developed a web-based interactive tool, the Personalized Risk Estimator for RA (*PRE-RA*), which provided RA education and calculated lifetime RA risk based on demographics, genetics (HLA shared epitope), auto-antibodies (RF and ACPA), and

behaviors (smoking, overweight/obesity, low fish intake, and dental health). RA knowledge and attitudes were assessed before and 6 weeks after the intervention: *PRE-RA* and health education. RA risk factor knowledge was evaluated by whether subjects agreed that an established risk factor, supported by literature, increased RA risk. An RA knowledge index was calculated by the total number of established factors agreed to increase RA risk. Self-perceived lifetime RA risk before and after the intervention was compared to the *PRE-RA*calculated lifetime RA risk using Wilcoxon rank-sum test. RA knowledge and attitudes before and after intervention were compared by Fisher's exact or Wilcoxon rank-sum tests.

Results: A total of 37 subjects enrolled in the study and 14 completed the *PRE-RA* tool with health education. Median age was 44 years (range 20–70) and 76% were female. Using demographics, behaviors, genetics, and auto-antibodies, the median personalized lifetime calculated RA risk was 5% (range 1–56, mean 12.4, SD 14.7; **Table**) and was significantly lower than self-perceived risk at baseline (median 50%, range 0–85, mean 38.6, SD 23.7; $p=0.0002$). After intervention, self-perceived risk approached the calculated *PRE-RA* risk but remained significantly higher (median 14%, range 1–80, mean 25.1, SD 26.5; $p=0.04$). RA knowledge index significantly improved after the *PRE-RA* tool (median 8, mean 8.6, SD 0.5) compared to baseline (median 6, mean 5.4, SD 1.6; $p<0.0001$). Only 20% agreed that smoking was a risk factor for RA at baseline, but 100% agreed after the intervention ($p<0.0001$).

Conclusion: We developed an interactive RA risk education tool, *PRE-RA*, personalized to demographics, behaviors, genetics, and auto-antibodies suitable for use in RA risk education trials. Subjects in our study had high self-perceived RA risk, compared to calculated risk, that became more accurate after personalized RA risk education. Knowledge of RA risk factors was low prior to intervention and significantly increased after the *PRE-RA* tool and health education.

Table. RA risk self-perception, knowledge, and attitudes at baseline and after the Personalized Risk Estimator for RA (*PRE-RA*) tool and health education among RA first-degree relatives.

Self-perceived vs. calculated lifetime RA risk

	Self-perceived lifetime RA risk (n = 37)	Calculated *PRE-RA* tool lifetime RA risk (n = 14)	*P* value
Baseline lifetime % RA risk, median (range)	50 (0–85)	5 (1–56)	**0.0002**
Post-intervention lifetime % RA risk, median (range)	14 (1–80)*	5 (1–56)	**0.04**

Baseline vs. 6-weeks after intervention

	Baseline (n = 37)	After *PRE-RA*tool and health education (n = 14)	*P* value
Lifetime % RA risk, median (range)	50 (0–85)	14 (1–80)	**0.043**
Smoking is a risk factor for RA, % agree	20%	100%	**<0.0001**
Diet is a risk factor for RA, % agree	53%	67%	0.68
Dental health is a risk factor for RA, % agree	7%	67%	**0.003**
Obesity is a risk factor for RA, % agree	40%	89%	**0.033**
RA knowledge index, median (range)	6 (3–8)	8 (7–9)	**<0.0001**
>45% lifetime RA risk for average person, % agree	16%	0%	0.17
18% lifetime risk of RA is low or very low, % agree	51%	36%	0.36

*A total of 14 subjects provided self-perceived risk after the *PRE-RA* tool and health education.

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2009

Development of Multimedia Patient Education Tools (MM-PtET) for Osteoarthritis (OA), Osteoporosis (OP) and Rheumatoid Arthritis Patients (RA). Maria A. Lopez-Olivo[1], Aparna Ingleshwar[2], Robert Volk[1], Andrea Barbo[1], Maria Jibaja-Weiss[3] and Maria E. Suarez-Almazor[1]. [1]The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]The University of Texas MD Anderson Cancer Center, Houston, TX, [3]Baylor College of Medicine, Houston, TX.

Background/Purpose: The purpose of our study was to develop and perform usability testing of Multimedia Patient Education Tools (MM-PtET) for patients with knee osteoarthritis, osteoporosis and rheumatoid Arthritis.

Methods: We developed three MM-PtETs following an Edutainment Model (one for each disease). The goals were designed to make the programs both didactic and entertaining and the navigation and graphical user interface as simple as possible. Entertainment education was provided via a storyline with several episodes linked to the consecutive learning modules which emphasized the content of the episodes. Learning objectives were drafted for each MM-PtET topic. After segments of the scenes were developed, we pre-tested them to ascertain that the stories had the appropriate cultural context and lifestyle. Refinements were made to the program after pre-testing to ensure accuracy. Ten cognitive interviews per disease were conducted to identify potential language and imagery issues in the MM-PtDA. Once the MM-PtET was finalized patients (20 per disease) were shown the tool and were interviewed. Their disease knowledge was tested with a self-report questionnaire (before and after viewing the MM-PtET).

Results: The general sequence of content was: (i) overview of the disease, (ii) description of treatments, (iii) testimonial I, (iii) description of the harms and benefits of each option (iv) testimonial II, (v) review of key facts and suggestions for questions to ask of the patient's doctor, and vi) testimonial III. Both the content and the instructions were narrated, and visual cues were provided to reach patients who are poor readers or who cannot read. We created both English and Spanish-language versions. After cognitive interviewing, 4 of the 10 patients suggested adding more content: for knee osteoarthritis, information on knee replacement and rehabilitation after surgery; for osteoporosis, providing more information on the difference between osteoporosis and osteoarthritis; and for rheumatoid arthritis: (i) including more information on nutrition to prevent anemia and bone decalcification and (ii) exercises to help with the stiffness. In the pilot testing, 60 participants were interviewed and in terms of acceptability, most patients in all disease groups found the length and amount of information presented in the MM-PtETs to be "just right", and the presentation as 'balanced". In terms of comprehension, all participants provided a favorable evaluation of the MM-PtET; all found the video easy to use, the vocabulary easy to understand and the material to be well organized. All participants felt they: 1) gained "clarity" on disease duration, symptoms, and time medication takes to start acting, 2) were "encouraged to see their doctor regularly", and 3) were more aware about taking their medications. Statistically significant differences were observed in pre-post knowledge questionnaire scores (OA, p=0.03; OP, p=0.001; RA, p<0.0001).

Conclusion: Multimedia tools that incorporate video modeling can help patients better understand and manage their disease. Patient involvement in the development process is essential to ensure relevant content and usability.

Disclosure: M. A. Lopez-Olivo, None; **A. Ingleshwar**, None; **R. Volk**, None; **A. Barbo**, None; **M. Jibaja-Weiss**, None; **M. E. Suarez-Almazor**, None.

2010

Reaching out to Physical Therapists: Results of a Survey on Physical Therapists Preferences for Learning about Evidence-Based Community Programs. Jennifer Hefelfinger[1], Teresa J. Brady[2], Jennifer Berktold[3], Marc Goldstein[4], Erika Bonilla[5], Mari Brick[6], Erica Odom[2], Angela Oliver[2] and Penney Cowan[7]. [1]National Association of Chronic Disease Directors, Atlanta, GA, [2]Centers for Disease Control and Prevention, Atlanta, GA, [3]Westat, Inc, Rockville, MD, [4]American Physical Therapy Association, Alexandria, VA, [5]Westat, Inc, Rickville, MD, [6]National Association of Chronic Disease Directors, Voorheesville, NY, [7]American Chronic Pain Association, Rocklin, CA.

Background/Purpose: Community resources such as evidence-based physical activity (PA) and self-management education (SME) programs, with their documented health benefits, can complement clinical care. These clinical-community linkages can be strengthened by Physical Therapists (PTs) awareness and recommendation of these resources to their patients. The purpose of this study was to explore PTs awareness of, and attitudes towards the use of arthritis-appropriate PA and SME programs, and factors that would influence their decision and facilitate a recommendation of these programs to their patients.

Methods: A stratified random sample of 10,000 members from the geriatrics, home health, orthopedics, and private practice sections of American Physical Therapy Association (APTA) received e-mail invitations to participate in an on-line survey exploring awareness of and preferences related to evidence-based community PA and SME programs. Inclusion criteria included PTs in clinical practice with > 50% adult patients. The survey questions and response options were based on earlier qualitative interviews and refined through pilot-testing.

Results: 1180 PTs responded to the invitation (response rate 11.6%), 84% of respondents met eligibility criteria; a total of 973 PTs participated in the survey. 67% of PTs surveyed were aware of some PA programs in the community; only 22% were aware of community SME programs. Willingness to refer to evidence-based programs was high (over 90% were somewhat or very likely to refer to PA and SME programs). PTs preferred to learn about these resources via means they can access at their convenience (e-mail-82%,

website-51%, direct mail-42%). The tool considered most helpful to facilitate a recommendation was patient handout materials (84%); the most desired patient materials were pamphlets (86%), flyers (57%), and website (57%). 81% would provide information about evidence-based community programs both during treatment and at discharge. Preferred sources of information were APTA (91%) and Arthritis Foundation (68%).

Types of information PTs needed to recommend a community program differed somewhat by program type. For both PA and SME programs, opportunity for post therapy PA (74%, 75% respectively), offered by credible organizations (76%, 69%), and evidence-base (71%, 69%) were important. For PA programs, coverage of techniques to exercise safely (81%), and certified instructors (77%) were most critical; for SME programs, helping patients take an active role in managing their chronic condition (75%) was essential.

Conclusion: Although awareness of PA and SME programs differed by program type, large number of PTs expressed willingness to recommend arthritis-appropriate evidence-based programs in the community, both during therapy and at discharge. PTs need patient materials to facilitate these recommendations, preferably brochures, flyers, or website. Preferred channel to receive program information was via website. These results can be used to shape methods, materials, and messages to encourage PTs to recommend evidence-based community programs and improve patient outcomes.

Disclosure: J. Hefelfinger, None; **T. J. Brady**, None; **J. Berktold**, None; **M. Goldstein**, None; **E. Bonilla**, None; **M. Brick**, None; **E. Odom**, None; **A. Oliver**, None; **P. Cowan**, None.

2011

What Do State Legislators Think about Arthritis? Results of Focus Groups with State Legislators. Mari Brick[1], Erica Odom[2], Teresa J. Brady[2], Carol McPhillips-Tangum[3], Angela Oliver[2], Dana Heyl[4] and Jennifer Hefelfinger[5]. [1]National Association of Chronic Disease Directors, Voorheesville, NY, [2]Centers for Disease Control and Prevention, Atlanta, GA, [3]Experion HealthCare Group LLC, Atlanta, GA, [4]Consultant, Atlanta, GA, [5]National Association of Chronic Disease Directors, Atlanta, GA.

Background/Purpose: Arthritis affects > 1 in 5 American adults, and is the most common cause of disability. Nearly ½ of people with diabetes or heart disease also have arthritis. Public health interventions such as community-based physical activity (PA) and self-management education (SME) programs have demonstrated health benefits among people with arthritis, yet availability is limited. State legislation addresses other chronic diseases, yet arthritis receives little attention. The purpose of this qualitative research was to explore state legislators' attitudes towards arthritis, factors influencing their attention to health issues, and potential legislative actions to increase availability of arthritis-appropriate community PA and SME programs.

Methods: The National Conference of State Legislatures (NCSL) invited a purposive sample of 20 state legislators and 2 legislative staff to participate in focus groups (FGs) that preceded the NCSL 2013 Legislative Summit. Selection criteria included: leadership of NCSL's Health Committee, appointment by presiding officers, or attendance at an arthritis education session at the 2012 Legislative Summit. 2 FGs were held; group assignment balanced Democrats and Republicans, men and women, geographic region, and previous education session attendance.

Each FG was conducted by an experienced moderator using a structured guide. The two moderators coded each FG transcript independently and met to identify key findings.

Results: 16 Legislators and 2 staff participated (82% response rate). The legislators were: 56% Democrat, 38% Republican, and <1% Independent. Legislators were both interested in and surprised by the national and state level arthritis statistics, but not compelled to take action (i.e. legislation, health benefit design). Participants identified perceived seriousness (particularly mortality) and belief that state action would save money as key factors influencing their health action decisions. Participants reported that advocacy groups could influence their thinking on health issues; yet few participants recalled any contact with arthritis advocates.

Arthritis was not perceived as a serious health issue warranting state legislator attention. Participants believed the most effective way to address arthritis was to include it with higher priority health conditions (e.g., heart disease, diabetes).

Participants were unaware of evidence-based PA or SME programs offered in the community, and had trouble distinguishing them from clinical interventions. There was no support for including these interventions in state-covered Medicaid benefits, but some support for including them in state employee benefit packages.

Conclusion: Arthritis is an invisible problem to state legislators; they are unaware of arthritis statistics and have not been contacted by arthritis advocates. Arthritis alone is not compelling enough to motivate legislator action. Attention to arthritis could be increased by educating state legislators on the role arthritis plays in complicating management of other chronic diseases, developing promising policy options, and addressing arthritis within the context of other chronic diseases.

Disclosure: M. Brick, None; **E. Odom**, None; **T. J. Brady**, None; **C. McPhillips-Tangum**, None; **A. Oliver**, None; **D. Heyl**, None; **J. Hefelfinger**, None.

2012

Moving Social Media Beyond Health Education and into Patient Engagement. Xiaohui Yan and R. Paola Daly. Lupus Foundation of America, Washington, DC.

Background/Purpose: During Lupus Awareness Month, Lupus Foundation of America conducted several social media-specific activities, including sharing facts with the end goal of increasing health knowledge in people with lupus, their friends and family. Topics ranged from lupus in different organ systems to coping strategies.

This abstract will evaluate social media as a means for engaging individuals in their health through Facebook conversation (thread) about mild cognitive dysfunction. We expect that individuals who responded at higher levels of engagement have the tools to better manage this aspect of lupus. More than 80% of patients with lupus present subjective complaints of cognitive difficulties (Wallace, 2013) and symptoms include feelings of confusion and memory loss. The causes are unknown.

Engagement is an indicator that links social media to action. Levels range from low (showing a preference) to medium (creating & sharing content) to high (engaging in offline events) (Neiger et al., 2012). Patients who are highly activated in their health are more likely to report higher quality of life & satisfaction with care (Mosen et al., 2007) and may show an increase in improved health behaviors (Hibbard et al., 2007).

Methods: Comments in the thread were collected and sorted into broad themes, assigning one or more theme to each comment. The thematic analysis yielded the following categories: validation, sharing experience/advice and increased knowledge.

Engagement actions, including number of likes, comments and shares, were obtained through Facebook Insights and categorized as low, medium or high levels.

Results: The thread resulted in 336 comments over the span of six days. 284(84%) comments were on-topic. Examples of statements of validation include "Thank you for addressing this. . .It's frustrating, embarrassing at times but now I know I am not alone." A characteristic response of increased knowledge was "I attributed it to my medications. I'll pay more attention now to see if it worsens."

Table 1: Thematic Analysis

Comment Theme	# of comments (%)
Validation	54 (20%)
Sharing experience/advice	239 (84%)
Increased knowledge	12 (4%)
Two or more categories	21 (8%)

Overall, the post reached 326,528 people. 263,808 (80%) people saw the post through others' engagement actions. Levels of engagement are listed in Table 2.

Table 2: Engagement Actions

Engagement Action	Number of Actions	Engagement Level
Comments	948	Medium
Shares	3620	Medium
Likes	5892	High

Conclusion: Results suggest that in addition to being an effective platform for health promotion and education, social media may also serve as an informal support system by providing validation of experiences and symptoms. Future studies will target specific health behaviors, measure outcomes of interest through pre and post testing, and potentially include an off-line component to promote high level of engagement.

Disclosure: X. Yan, Lupus Foundation of America, 3; **R. P. Daly**, Lupus Foundation of America, 3.

2013

Quality Appraisal of Educational Websites on Osteoporosis and Bone Health. Maria A. Lopez-Olivo[1], Noha Abdel-Wahab[1], Abhinav Dodeja[2], Gregory Pratt[1] and Maria E. Suarez-Almazor[1]. [1]The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]The University of Texas Health Science Center, School of Public Health, Houston, TX.

Background/Purpose: Osteoporosis, like many other chronic diseases, can have better outcomes when informed patients get involved in self-management, resulting in better ourtcomes. Bone health education publicly available through the Internet, if evidence-based and unbiased, could help patients to deal with issues such as decision making, maintaining healthy lifestyles, using medications correctly, and improving their communication with health professionals. The current study aimed to assess the quality of websites providing bone health-related information on the Internet.

Methods: We performed an environmental scan of the currently available osteoporosis and bone health patient education information on the World Wide Web. The sample websites were identified by using three separate search tools: Google Advanced, Bing, and Ask.com. We used the phrases "bone health" and "osteoporosis" in titles of Web pages and reviewed the first 100 results in each of the following domains: .gov, .org, & .com, plus links to 50 .edu websites. Only patient education websites were included. Websites that were part of clinical guidelines were excluded. Two independent investigators collected data regarding: information provided (accuracy and completeness), design, disclosures and references provided. Literacy was evaluated using the Flesch Grade Level readability formula.

Results: We identified 29 websites (92% non-profitable). Most websites were focused on risks factors of osteoporosis, preventive measures, screening recommendations, and topics to discuss with the physician. All websites provided adequate information describing treatment options; however, only 10.3% had information addressing duration of treatment, what happens when treatment stops, and the benefits and risks of various treatments. Only 50% of the websites had their content updated to 2014. Reading levels ranged from 7.8 to 14.8 (higher than the recommended 6-grade level). Ninety percent of the sites were static websites with no interactive features in their design; 94% were linear. Only 33% included an adequate disclosure statement and 25% cited their sources of information to support their content.

Conclusion: Websites with information about bone health and osteoporosis commonly fail to report adequate disclosure statements and sources of information. While they commonly present information about initial treatment choices, most fail to address risk-benefit issues, and common barriers than can occur throughout the course of the disease. In addition, most websites are written at a 9-grade level or above, rendering them unsuitable for low-literacy populations.

Disclosure: M. A. Lopez-Olivo, None; **N. Abdel-Wahab**, None; **A. Dodeja**, None; **G. Pratt**, None; **M. E. Suarez-Almazor**, None.

ACR/ARHP Poster Session C
Epidemiology and Public Health: Rheumatoid Arthritis Pathogenesis and Treatment
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

2014

Performance of Self-Reported Measures for Periodontitis in Rheumatoid Arthritis and Osteoarthritis. Brian Coburn[1], Harlan Sayles[2], Jeffrey Payne[3], Robert Redman[4], Jeffery Markt[1], Mark Beatty[3], Garth Griffiths[5], David McGowan[6] and Ted R. Mikuls[2]. [1]University of Nebraska Medical Center, Omaha, NE, [2]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [3]University of Nebraska Medical Center, Lincoln, NE, [4]Veterans Affairs Medical Center (VAMC), Washington, DC, [5]Dallas VA and University of Texas Southwestern, Dallas, TX, [6]George E. Wahlen VA Medical Center, Salt Lake City, UT.

Background/Purpose: Periodontitis (PD) is associated with many chronic health conditions including rheumatoid arthritis (RA). Affecting one-third to one-half of the US population, the high prevalence of PD underscores its potential impact. PD may play a role in initiating or worsening RA. Yet, studies are often hindered by resource intensive full-mouth exams required for PD diagnosis whereas new self-report methods can reduce cost. Many studies indicate that PD has a different presentation in RA patients. It is unknown whether this difference affects performance of self-report measures. The purpose of this study was to evaluate self-report against the reference standard of clinically-defined PD in RA and osteoarthritis (OA) patients after accounting for factors associated with PD.

Methods: Six self-report PD questions were evaluated in RA and OA patients. All RA patients met ACR criteria and OA patients were classified based on physician diagnosis or corresponding x-ray results. Self-report questions were validated against a reference standard of severe or moderate-to-severe PD based on full-mouth examination. Multivariable logistic regression was used to evaluate the performance of: 1) self-report alone; 2) age, sex, education, and smoking status; and 3) a combination of the above. Model performance was assessed using the c-statistic. Convergent validity of self-reported 'bone loss/deep pockets' and 'loose teeth' was assessed; associations of self-report with RA disease characteristics were explored.

Results: Self-report performed similarly in RA and OA, with individual specificity for PD $\geq$ 68% and sensitivity between 10% and 45%. Question-only models yielded c-statistics of 0.66–0.72 while risk factor-only models yielded c-statistics of 0.74–0.79. The best performing models incorporated both self-report questions and PD risk factors with c-statistics $\geq$0.79. Greater radiographic alveolar bone loss was observed among participants reporting 'bone loss or deep pockets' ($p<0.001$) and 'loose teeth' ($p<0.001$). Among RA patients, 'loose teeth', but not other self-report items, was associated with rheumatoid factor positivity ($p=0.047$) and higher disease activity ($p<0.001$).

Table 1. Logistic Regression for Final Models after Backward Stepwise Selection

Variables	Overall (n=592)		RA (n=275)		OA (n=317)	
	Severe PD	Mod-Sev PD	Severe PD	Mod-Sev PD	Severe PD	Mod-Sev PD
	Odds Ratio (95% Confidence Interval)					
Demographics						
Age, yrs	1.05 (1.03–1.08)	1.05 (1.03–1.08)	1.05 (1.02–1.08)	1.05 (1.01–1.08)	1.04 (1.03–4.94)	1.05 (1.02–1.09)
Male (Female *Ref.*)	2.43 (1.48–3.97)	2.77 (1.66–4.63)	2.71 (1.25–5.45)	2.51 (1.17–5.35)	2.75 (1.34–5.64)	3.12 (1.56–6.26)
Education	0.84 (0.76–0.94)	0.82 (0.72–0.94)	—	0.79 (0.65–0.95)	0.82 (0.70–0.95)	—
Smoke Status						
Never	*Ref.*	*Ref.*	*Ref.*	—	*Ref.*	*Ref.*
Former	1.99 (1.24–3.20)	1.46 (0.84–2.52)	1.69 (0.86–3.33)	—	2.52 (1.29–4.94)	2.43 (1.08–5.44)
Current	7.10 (3.79–13.3)	2.64 (1.10–6.36)	6.43 (2.81–14.7)	—	7.56 (2.78–20.5)	5.52 (1.18–25.7)
Questions						
Gums Bleed	2.85 (1.72–4.72)	2.32 (1.16–4.62)	3.58 (1.74–7.35)	—	2.77 (1.34–5.75)	3.13 (1.16–8.46)
Bone Loss/Deep Pockets	—	4.20 (1.72–10.2)	—	—	—	6.30 (1.41–28.1)
Periodontal Treatment	2.74 (1.73–4.32)	—	—	3.39 (1.12–10.3)	4.17 (2.14–8.13)	—
See Periodontist	—	—	—	—	—	—
Loose Teeth	2.98 (1.53–5.79)	—	4.44 (1.58–12.5)	—	3.01 (1.19–7.64)	—
Surgery	—	—	—	—	—	—
Final Model AUC	0.82	0.81	0.79	0.80	0.83	0.81

All odds ratios displayed have a p-value less than 0.05. Separate models are presented for each group: rheumatoid arthritis (RA), osteoarthritis (OA) and overall. Each group is analyzed by the severe and moderate-to-severe periodontitis (PD) definitions. Area under the curve (AUC). AUCs for question-only models: Overall & Severe PD – 0.70; Overall & Mod-Sev PD – 0.67; RA & Severe PD – 0.70; RA and Mod-Sev PD – 0.66; OA & Severe PD – 0.72; OA and Mod-Sev PD – 0.68. AUCs for risk factor-only models: Overall & Severe PD – 0.76; Overall & Mod-Sev PD – 0.76; RA & Severe PD – 0.74; RA and Mod-Sev PD – 0.72; OA & Severe PD – 0.76; OA and Mod-Sev PD – 0.77.

Conclusion: Patient self-report, when combined with other risk factors, performs well in identifying PD among patients with RA and OA. Self-report questions related to alveolar bone loss exhibit excellent convergent validity in these patient subsets.

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2015

Fine Particulate Air Pollution and Systemic Autoimmune Rheumatic Disease in Two Canadian Provinces. Sasha Bernatsky[1], Audrey Smargiassi[2], Cheryl Barnabe[3], Lawrence W. Svenson[3], Allan Brand[4], Marie Hudson[5], Steven M. Edworthy[6], Ann E. Clarke[3], Paul R. Fortin[7], Patrick Belisle[8] and Lawrence Joseph[9]. [1]McGill University Health Centre, Montreal, QC, [2]Université de Montréal, Montréal, QC, [3]University of Calgary, Calgary, AB, [4]Institut national de santé publique du Québec, Montreal, QC, [5]Lady David Institute for Medical Research and Jewish General Hospital, Montreal, QC, [6]The University of Calgary, Calgary, AB, [7]Laval University, Division of Rheumatology, Centre de Recherche du CHU de Québec and Department of Medicine, Quebec City, QC, [8]Research Institute of the McGill University Health Centre, Montreal, QC, [9]McGill University, Montreal, QC.

Background/Purpose: To estimate the degree to which fine particulate (PM2.5) air pollution is associated with systemic autoimmune rheumatic diseases (SARDs).

Methods: We used population-based administrative data from Alberta (1993–2007) and Quebec (1989–2010). The SARD case definition was based on at least 2 physician billing claim codes, or at least 1 rheumatology billing code, or at least 1 hospitalization diagnostic code (for systemic lupus, Sjogren's Syndrome, scleroderma, polymyositis, dermatomyositis, or undifferentiated connective tissue disease). Bayesian hierarchical latent class regression models estimated the probability that any given resident was a SARD case, given our three case definitions. Mean 2001–2006 residential exposures to ambient PM2.5 levels were assigned using satellite-derived data for Dissemination Area regions in Alberta, and *Local Community Services*-Centre (CLSC) regions in Quebec (both assigned from postal code of residence). The sum of individual level probabilities provided the total cases per region in each province, according to age, sex, urban-versus-rural residence, income, and PM2.5 levels. In Alberta, we also stratified by First-Nations(FN) status, which in Alberta represents about 3% of the population (Blackfoot, Cree, Chipewyan, Dene, Sarcee, Stoney/Nakoda Sioux, and others). The hierarchical model generated odds ratio (OR) estimates for being a SARD case, based on age, sex, urban-versus-rural residence, income, and PM2.5 levels. The model accounted concurrently for these characteristics, as well as an interaction term between age and sex. The model generated Bayesian 95% credible intervals (CrI, which are similar to the non-Bayesian confidence interval) for the OR estimates.

Results: The probability of being a SARD case was higher among females versus males and for residents aged > 45 versus younger, with the highest ORs for older females. Independently, the odds of being a SARDs case increased with PM2.5 levels. In Alberta, the effect was slightly greater for FN residents. Specifically, in Alberta, when we used a continuous variable for PM2.5, the adjusted OR (interpreted as increase in SARDs per unit increase in PM25) in FN residents was 1.38 (95% CrI 1.14, 1.68) whereas in non-FN Alberta residents the adjusted OR was 1.05 (95% CrI 1.01, 1.08). In Quebec, where information on FN status (1% of the Quebec population) was not available, the adjusted OR for PM2.5 as a continuous variable, was 1.05 (95% CI 1.05, 1.06).

Conclusion: Adjusting for demographics, exposure to PM2.5 is associated with an increased risk of SARDs. Our data suggest that FN populations may be particularly vulnerable to this effect. Improving air quality across the continent appears to be an important way to reduce chronic disease burden, not only for respiratory and cardiac disease, but also systemic autoimmune rheumatic diseases.

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2016

Occupation and Risk of Developing Rheumatoid Arthritis. Anna Ilar[1], Pernilla Wiebert[1], Lars Klareskog[2], Lars Alfredsson[3] and Camilla Bengtsson[1]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Karolinska Institute, Stockholm, Sweden, [3]The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: The role of environmental factors in the etiology of rheumatoid arthritis (RA) is still fairly unknown. Finding occupations associated with the risk of disease could generate knowledge about occupational hazards that might be involved in disease development. The objective was to study the association between different occupations and the risk of developing anti-citrullinated protein antibodypositive (ACPA+) RA or anti-citrullinated protein antibody-negative (ACPA−) RA in men and women.

Methods: The Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study is a population-based case-control study, which enrolls newly diagnosed cases of RA in defined geographical areas of Sweden. Participants were 18–70 years of age. In total, 3,295 cases and 4,912 controls participated in the study. A questionnaire was collected to obtain information on environmental/lifestyle factors, including occupational history. Blood samples were taken for serologic analyses. Occupations were coded according to the Nordic Classification of Occupations and divided into 69 occupational groups. We compared the last occupation before onset of disease symptoms with the rest of the workforce for occupations with at least 5 controls by calculating odds ratios (ORs) together with 95% confidence intervals (CIs) for ACPA+ RA or ACPA- RA, respectively, by means of logistic regression with adjustment for age and county. Potential confounding from smoking was also considered.

Results: Among women, *Nurses* had a reduced risk (OR: 0.7, 95 % CI 0.5–1.0) whereas *Assistant nurses & attendants in psychiatric care* (OR: 1.4, 95 % CI: 1.2–1.6) and *Rubber & plastic workers* (OR: 2.9, 95 % CI: 1.1–7.4) had an increased risk of ACPA+ RA.

Among men, *Technical, Physical & biological workers* (OR: 0.7, 95 % CI: 0.5–1.0) and *Clerical workers* (OR: 0.7, 95 % CI: 0.5–1.0) had a reduced risk whereas *Smelters & metal foundry workers* (OR: 2.8, 95 % CI: 1.0–7.4), *Bricklayers & concrete workers* (OR: 2.6, 95 % CI: 1.3–4.9), *Material handling & related equipment operators* (OR: 2.5, 95 % CI: 1.4–4.3) and *Electrical & electronics workers* (OR: 1.8, 95 % CI: 1.0–3.1) had an increased risk of ACPA+ RA.

For ACPA− RA, male *Administrators & managers* had a reduced risk (OR: 0.3, 95 % CI: 0.2–0.8), while *Shop managers & assistants* (OR: 1.9, 95 % CI: 1.2–3.1) and *Electrical & electronics workers* had an increased risk (OR: 2.1, 95 % CI: 1.1–4.0). Adjustment for smoking had a small effect on the estimates and mainly reduced the risk of ACPA+ RA.

Conclusion: The study found associations between several occupations and onset of RA. Among women, mainly occupations within the health care sector were associated with RA, whereas increased risks among men were detected in mechanical and technical occupations.

Disclosure: A. Ilar, None; **P. Wiebert**, None; **L. Klareskog**, None; **L. Alfredsson**, None; **C. Bengtsson**, None.

2017

Fish Consumption and Risk of Rheumatoid Arthritis Among Women in Large Prospective Cohorts. Jeffrey A. Sparks, Shun-Chiao Chang, Bing Lu, Susan Malspeis, Karen H. Costenbader and Elizabeth W. Karlson. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Prior studies have suggested a protective effect of fish intake on RA. However, these studies were limited by potential recall bias, short follow-up, and small sample sizes. We aimed to evaluate the effect of fish consumption on RA development in two large cohorts, the Nurses' Health Study (NHS) and NHSII.

Methods: We examined the effect of fish consumption on RA risk among women in two large, prospective cohorts. NHS is composed of 121,700 US nurses followed since 1976; NHSII is composed of 116,430 nurses followed since 1989. Lifestyle and environmental exposures were collected through biennial questionnaires. Diet and fish intake were assessed by a semi-quantitative food frequency questionnaire completed every 4 years. Participants who provided fish data at baseline in each cohort were analyzed. Incident RA cases were identified by screening questionnaire and validated by medical record review according to the 1987 ACR RA criteria. Cumulative average fish intake prior to RA development was used to represent long-term fish intake. Cox regression models estimated hazard ratios (HR) and 95% confidence intervals (CI) of fish intake and RA risk, adjusted for confounders, including age, total energy intake, smoking, body mass index, alcohol, and soda intake. HRs from the two cohorts were meta-analyzed using a random effects model.

Results: We validated 652 incident RA cases among 86,135 women in NHS and 322 incident RA cases among 92,984 women in NHSII with diet data. For women in NHSII, modest fish consumption (1–2 fish servings per week) was associated with a protective effect on RA (age-adjusted HR 0.63, 95% CI 0.42–0.96, **Table**) compared to never/rare fish consumption that was nearly significant in the multivariable model (HR 0.66, 95% CI 0.44–1.01). However, for women in NHS, modest fish consumption was not associated with RA (HR 0.86, 95% CI 0.57–1.32) compared to never/rare fish intake. In meta-analysis of the results, there was a suggestion of a protective effect for modest fish intake that was nearly statistically significant (HR 0.76, 95% CI 0.56–1.02). More frequent fish consumption was not statistically associated with RA (HR 0.94 for 2 to <3 servings/week; HR 0.88 for ≥3 servings per week compared to never/rare intake) and there was no statistically significant trend for fish consumption on RA risk.

Conclusion: In these large prospective studies of nearly 180,000 women, there was a suggestion of a protective effect of modest fish consumption (1–2 fish servings per week) on RA development compared to never/rare fish intake. This protective effect of fish intake on RA risk was more pronounced in NHSII than NHS, but was not statistically significant in meta-analysis of both cohorts. Cohort differences, such as age, secular diet trends, and age at RA onset, may explain these results or they may be due to chance. Further studies of nutritional components of fish, such as omega-3 fatty acids, may clarify the effect of fish intake on RA risk.

Table. Hazard ratios for RA development by categories of cumulative average updated fish intake serving frequency in NHS (n = 86,135), NHSII (n = 92,984), and meta-analysis of both cohorts

	Never to <1 time/month	1 to 3 times/month	1 to <2 times/week	2 to <3 times/week	≥3 times/week	*P* for trend
NHS						
No. of cases	25	57	210	180	180	
Person-years	76,884	217,399	744,346	589,110	558,495	
Age-adjusted HR (95% CI)*	1.0 (ref)	0.77 (0.48–1.25)	0.86 (0.57–1.31)	0.93 (0.61–1.43)	0.96 (0.63–1.47)	0.34
Multivariable HR (95% CI)**	1.0 (ref)	0.77 (0.47–1.24)	0.86 (0.57–1.32)	0.94 (0.62–1.44)	0.95 (0.62–1.47)	0.36
NHSII						
No. of cases	29	88	107	56	42	
Person-years	125,680	453,864	663,142	242,353	225,015	
Age-adjusted HR (95% CI)*	1.0 (ref)	0.78 (0.51–1.18)	**0.63 (0.42–0.96)**	0.81 (0.51–1.28)	0.68 (0.42–1.11)	0.66
Multivariable HR (95% CI)**	1.0 (ref)	0.76 (0.50–1.15)	0.66 (0.44–1.01)	0.86 (0.55–1.37)	0.73 (0.44–1.19)	0.91
Meta-analysis* **						
Age-adjusted HR (95% CI)*	1.0 (ref)	0.78 (0.57–1.07)	**0.74 (0.55–1.00)**	0.87 (0.64–1.19)	0.83 (0.59–1.15)	0.60
Multivariable HR (95% CI)**	1.0 (ref)	0.78 (0.57–1.07)	0.76 (0.56–1.02)	0.91 (0.66–1.24)	0.85 (0.61–1.17)	0.49

*Adjusted for age, questionnaire period, and total energy intake (continuous).
**Adjusted for age, questionnaire period, total energy intake (continuous), US region (New England, Mid-Atlantic, Southeast, Midwest, West), median household income (<$40k, $40k to <$50k, $50k to <$65k, $65k to <$80k, ≥$80k), cigarette smoking pack-years (never to 10, >10), body mass index (underweight/normal, overweight, obese), alcohol intake (never to <5, 5 to <10, ≥10 g/day), and sugar-sweetened soda intake (<1 serving per month, 1–4 per month, 2–6 per week, ≥1 per day).
***Meta-analysis performed using DerSimonian and Laird random effects model.

Disclosure: J. A. Sparks, None; **S. C. Chang**, None; **B. Lu**, None; **S. Malspeis**, None; **K. H. Costenbader**, None; **E. W. Karlson**, None.

2018

Do Mediterranean or Vegetarian Diets Influence Risk of Rheumatoid Arthritis? Kari Johansson[1], Maria Sandberg[2], Saedis Saevarsdottir[3], Martin Neovius[1], Lars Alfredsson[2], Johan Askling[1] and Camilla Bengtsson[2]. [1]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Lifestyle factors are of major importance for development of RA. Yet, regarding the role of diet surprisingly little is known. The Mediterranean diet, rich in fish, plant food, mono- and polyunsaturated fat, and including moderate wine consumption, has been suggested to protect against e.g. cardiovascular disease, but its effect on RA development has only been studied to a limited extent. The aim of this study was to investigate whether Mediterranean or vegetarian (vs. Western) diet influences the risk of developing RA.

Methods: In the Swedish case-control study Epidemiological Investigation of Rheumatoid Arthritis (EIRA), 1296 incident RA cases and 2661 randomly selected controls matched by age, sex and residential area were enrolled between 2005 and 2012. Type of diet the year before enrolment was ascertained by a single question in a food-frequency-questionnaire, including Western diet, Mediterranean diet, vegetarian diet, vegan diet, or other specified diet. Odds ratios (OR) were estimated for RA overall, and also stratified for anti-citrullinated peptide autoantibodies (ACPA) and rheumatoid factor (RF) status. Adjustments were made for the matching factors in the crude model and additionally for BMI, smoking, formal education and, physical activity in the adjusted model.

Results: 9% of the RA-cases (n=122/1269) reported to consume a Mediterranean diet the year before enrolment compared with 12% (309/2661) of the controls, and 4% (n=47/1269) of the RA-cases and 3% (80/2661) of the controls reported to consume a vegetarian diet. After adjustment for the matching factors, a Mediterranean diet was associated with a statistically significant decreased risk of RA compared with Western diet (OR 0.76; 95%CI 0.62–0.97; **Table**). However, after additional adjustment the association did not remain statistically significant (OR 0.86; 95%CI 0.68–1.08). The results did not change when stratifying by ACPA or RF-status, although there was a tendency towards lower risk with Mediterranean diet in ACPA+ and RF+ patients. Vegetarian diet was not associated with development of RA, neither overall nor in the stratified analysis (Table).

Conclusion: Self-reported Mediterranean diet was in itself associated with a lower RA risk, but this association disappeared after adjustment for the selected potential confounders. A tendency towards lower risk with Mediterranean diet in ACPA+ and RF+ patients was observed. No association was observed for a vegetarian diet.

Table. Mediterranean or vegetarian diet and risk of RA, stratified by ACPA and RF-status

	Case (n exposed/unexposed)	Controls (n exposed/unexposed)	OR (95%CI) Crude[a]	OR (95%CI) Adjusted[b]
		Mediterranean Diet		
Total	**122/1079**	**309/2151**	**0.76 (0.62–0.97)**	**0.86 (0.68–1.08)**
ACPA+	79/714	"	0.74 (0.57–0.97)	0.81 (0.61–1.07)
ACPA−	42/356	"	0.84 (0.59–1.19)	0.90 (0.63–1.29)
RF+	74/699	"	0.71 (0.54–0.94)	0.78 (0.58–1.03)
RF−	47/378	"	0.90 (0.65–1.25)	0.98 (0.70–1.39)
		Vegetarian Diet		
Total	**47/1079**	**80/2151**	**1.13 (0.77–1.61)**	**1.17 (0.79–1.71)**
ACPA+	35/714	"	1.28 (0.84–1.93)	1.36 (0.89–2.10)
ACPA−	12/356	"	0.82 (0.44–1.54)	0.87 (0.46–1.64)
RF+	34/699	"	1.20 (0.79–1.82)	1.23(0.80–1.92)
RF−	13/378	"	0.92 (0.50–1.69)	1.00 (0.54–1.85)

Unexposed=western diet. [a]Adjustment for the matching factors (age, sex and residential area). [b]Additional adjustment for BMI, smoking, education and physical activity.

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2019

Antibodies to Citrullinated Clusterin, Filaggrin, Vimentin, and Fibrinogen Are Associated with Blood Pressure in First-Degree Relatives of Rheumatoid Arthritis Patients: The Studies of the Etiology of Rheumatoid Arthritis. Jan M. Hughes-Austin[1], Ryan W. Gan[2], Kevin D. Deane[3], Peter K. Gregersen[4], Michael H. Weisman[5], Joachim H. Ix[1], Jeremy Sokolove[6], William H. Robinson[7], V. Michael Holers[3] and Jill M. Norris[2]. [1]University of California, San Diego, La Jolla, CA, [2]Colorado School of Public Health, Aurora, CO, [3]University of Colorado School of Medicine, Aurora, CO, [4]The Feinstein Institute for Medical Research, Manhasset, NY, [5]Cedars-Sinai Medical Center, Los Angeles, CA, [6]VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA, [7]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA.

Background/Purpose: Hypertension is common in rheumatoid arthritis (RA), but it is unclear whether this prevalence is due to RA-related medications or to the disease process itself. Prior work in first-degree relatives (FDR) of RA patients without clinically apparent RA, and thus without RA-related medications, has shown that markers of endothelial dysfunction were associated with antibodies to citrullinated protein antigens (ACPA), suggesting that ACPA may be involved in vascular injury. Thus, we sought to investigate associations between ACPA and systolic and diastolic blood pressure in FDRs.

Methods: In the Studies of the Etiology of RA (SERA) (a multicenter prospective study of preclinical RA), we evaluated associations between ACPA and systolic (SBP) and diastolic blood pressure (DBP) in 89 FDRs of RA patients. A panel of 15 ACPA were measured using a Bio-Plex bead-based assay; and were dichotomized as positive/negative based on pre-specified cut-offs in 200 RA patients and 98 blood bank controls. These cutoffs were developed using receiver operating characteristic (ROC) curves giving >90% specificity. Seventeen FDRs lacked ACPA measurements and were excluded, leaving 72 FDRs for analysis. SBP and DBP were measured 3 times and averaged. ANCOVA was used to evaluate associations between ACPA positivity and SBP and DBP, adjusting for age, sex, race, body mass index (BMI), pack-years of smoking, high sensitivity C-reactive protein (CRP), and current use of anti-hypertensive medications.

Results: Average age was 51 years, and 69% were female. Mean SBP was 119 ± 18 and DBP was 74 ± 9 mmHg. 46% of FDRs were positive for any ACPA; these individuals were younger and had lower BMI, more pack-years of smoking, and higher levels of hsCRP, and had marginally higher DBP. (Table) Positivity for antibodies to cit-fibrinogen A (211–230) was associated with 11.52 mmHg higher SBP; to cit-filaggrin was associated with 13.9 mmHg higher SBP; to cit-clusterin, cit-filaggrin, and cit-vimentin were associated with 7–8 mmHg higher DBP. Positivity for each additional ACPA was significantly associated with a 0.98 mmHg increase in SBP, and a 0.66 mmHg increase in DBP.

Conclusion: In FDRs without RA, ACPA positivity is associated with higher SBP and DBP, independent of risk factors and medications for hypertension. While cit-fib and cit-vimentin have been implicated in subclinical CVD in RA, these findings suggest ACPA play a role in the vascular changes leading to hypertension prior to RA.

Table. Proportion of SERA FDRs with ACPA, and associations of ACPA with blood pressure

		Systolic Blood Pressure		Diastolic Blood Pressure	
	n (%) positive	β (SD)	p	β (SD)	p
Any ACPA positivity	33 (45.8)	4.79 (3.40)	0.164	3.79 (2.17)	0.085
Apolipo E (277–296) cit2 cyclic	10 (13.9)	5.30 (4.89)	0.283	1.83 (3.16)	0.565
Biglycan (247–266) cit cyclic	9 (12.5)	8.28 (5.43)	0.133	6.47 (3.46)	0.066
Clusterin (221–240) cit	8 (11.1)	8.38 (5.33)	0.122	**7.67 (3.35)**	**0.026**
Enolase (5–21) cit	8 (11.1)	3.39 (5.44)	0.536	3.70 (3.47)	0.290
Fibrinogen A (211–230) cit cyclic	10 (13.9)	**11.52 (4.89)**	**0.022**	4.89 (3.22)	0.135
Fibrinogen A (41–60) cit3 cyclic	10 (13.9)	9.53 (5.05)	0.064	4.74 (3.28)	0.153
Fibrinogen A (556–575) cit cyclic	11 (15.3)	9.27 (4.78)	0.058	5.80 (3.08)	0.064
Fibrinogen A (616–635) cit3 cyclic	5 (6.9)	6.07 (6.65)	0.365	3.71 (4.27)	0.388
Fibrinogen A cit	11 (15.3)	0.40 (4.71)	0.932	0.75 (3.03)	0.805
Filaggrin (48–65) cit2 cyclic	7 (9.7)	**13.90 (5.67)**	**0.017**	**7.47 (3.69)**	**0.048**
Histone 2A (1–20) cit cyclic	13 (18.1)	6.85 (4.56)	0.138	3.42 (2.95)	0.251
Histone 2B (62–81) cit cyclic	13 (18.1)	5.49 (4.49)	0.226	5.31 (2.83)	0.066
Histone 2B-cit	5 (6.9)	5.54 (6.64)	0.408	5.54 (4.23)	0.195
Vimentin cit	8 (11.1)	6.22 (5.48)	0.261	**6.89 (3.44)**	**0.050**
Vimentin (58–77) cit3 cyclic	3 (4.2)	16.02 (8.54)	0.066	10.09 (5.49)	0.071
Number of ACPA, mean (SD)	1.88 (3.59)	**0.98 (0.48)**	**0.045**	**0.66 (0.30)**	**0.035**

*adjusted for age, sex, race, BMI, pack-years of smoking, high sensitivity C-reactive protein, and current use of anti-hypertensive medications

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2020

Circulating Carotenoids and Subsequent Risk of Rheumatoid Arthritis. Yang Hu[1], Karen H. Costenbader[2], Elizabeth W. Karlson[2] and Bing Lu[2]. [1]Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Antioxidant components in food may be biologically relevant to the prevention of rheumatoid arthritis (RA). Evidence from prospective cohort studies regarding the relationship between blood levels of food source antioxidants and risk of RA is limited. The aim of present study was to examine the association between circulating carotenoids and RA risk.

Methods: We conducted a nested case-control study consisting of 228 incident RA cases and 674 matched controls with prospectively measured plasma carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lycopene and lutein/zeaxanthin) levels in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II). Incident RA cases were diagnosed >3 months after blood draw, matched on birth year, race, menopausal status/hormone use, time of day and fasting status, with 3 controls. Smoking, alcohol intake, dietary data, body mass index (BMI) and physical activity were from the questionnaire prior to blood draw. Seropositive RA was defined as positive RF or ACPA by chart review or measurement. Logistic regressions models estimated odds ratios (OR) and 95% confidence intervals (CI) for RA risk associated with each circulating carotenoid.

Results: The median follow-up time from blood draw until RA diagnosis was 8.6 years (0.3 to 19 years). In the multivariable models, no significant associations were found between any plasma carotenoids and risk of all RA, or of seropositive RA. In contrast, we found circulating α-carotene, β-carotene, β-cryptoxanthin and total carotenoids were inversely associated with seronegative RA risk. Women in the highest quartile of α-carotene were associated with a 52% reduction in seronegative RA risk (OR=0.48; 95% CI, 0.25–0.92). The risk reduction of the highest quartile of β -carotene was 51% (OR=0.49; 95% CI: 0.24–1.00). Circulating β-cryptoxanthin was also associated with the reduced risk of seronegative RA (p trend 0.05). Being in the highest quartile of total plasma carotenoid concentration was associated with a 58% reduced seronegative RA risk (OR=0.42, 95% CI: 0.22–0.81, *p*trend 0.03). There was no significant inverse association of lycopene with seronegative RA.

Conclusion: Circulating carotenoid metabolites were associated with a reduced risk of seronegative RA, but not seropositive RA, suggesting different mechanisms for development of these two RA phenotypes. Further studies are needed to confirm our finding.

Table. The association between circulating carotenoids (quartiles) and risk of seropositive and seronegative RA (Odds ratio and 95% confidence interval)*

	Q1	Q2	Q3	Q4	P trend
Seropositive RA (n=135)					
Lutein/zeaxanthin	1.00	1.08 (0.62,1.89)	1.32 (0.76,2.28)	1.36 (0.79,2.37)	0.47
β-cryptoxanthin	1.00	0.87 (0.51,1.49)	1.00 (0.58,1.72)	1.17 (0.67,2.03)	0.93
Lycopene	1.00	1.40 (0.81,2.42)	1.53 (0.90,2.62)	1.20 (0.69,2.10)	0.74
α-carotene	1.00	0.96 (0.56,1.67)	1.09 (0.63,1.88)	1.28 (0.74,2.22)	0.82
β-carotene	1.00	1.50 (0.87,2.59)	1.10 (0.61,1.98)	1.72 (0.98,3.03)	0.44
Total carotenoids**	1.00	1.26 (0.72,2.22)	1.67 (0.97,2.90)	1.51 (0.85,2.69)	0.44
Seronegative RA (n=93)					
Lutein/zeaxanthin	1.00	1.43 (0.80,2.57)	0.81 (0.42,1.55)	0.64 (0.32,1.28)	0.07
β-cryptoxanthin	1.00	0.82 (0.46,1.45)	0.52 (0.27,0.99)	0.54 (0.28,1.05)	0.05
Lycopene	1.00	1.16 (0.63,2.12)	0.89 (0.47,1.70)	1.01 (0.55,1.88)	0.87
α-carotene	1.00	0.50 (0.27,0.91)	0.63 (0.34,1.14)	0.48 (0.25,0.92)	0.07
β-carotene	1.00	0.77 (0.42,1.39)	0.87 (0.48,1.58)	0.49 (0.24,1.00)	0.07
Total carotenoids**	1.00	0.37 (0.20,0.71)	0.62 (0.35,1.11)	0.42 (0.22,0.81)	0.03

* Total carotenoids were the sum of lutein/zeaxanthin, β-cryptoxanthin, total lycopene, α-carotene and β-carotene.
** Adjusting for matching factors (age, menopausal status, postmenopausal hormone use, and day, time, and fasting status at the time of collection), smoking status (never, past, current) and body mass index. Additional adjustment for alcohol consumption, healthy eating index, physical activity and total calories intake did not change the results.

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2021

The Association Between Rheumatoid Factor and Cardiovascular Disease in Healthy Adults. Chisun Min[1], Mitsumasa Kishimoto[1], Gautam A. Deshpande[2], Shunya Kaneshita[1], Masei Suda[1], Yuri Ohara[1], Yoichiro Haji[1], Ryo Rokutanda[1], Yasuhiro Suyama[1], Hisanori Shimizu[1], Tokutaro Tsuda[1], Ken-ichi Yamaguchi[1], Akira Takeda[3], Yukio Matsui[1] and Masato Okada[1]. [1]St. Luke's International Hospital, Tokyo, Japan, [2]St. Luke's Life Science Instutute, Tokyo, Japan, [3]International University of Health and Welfare Hospital, Nasu-shiobara, Japan.

Background/Purpose: Rheumatoid arthritis (RA) has been shown to be a risk factor for cardiovascular disease (CVD). Both elevated rheumatoid factor (RF) and anti-citrullinated protein antibodies have been reported to be associated with substantially higher risk of CVD and mortality among RA patients. However, the correlation between RF and CVD in the general population remains unclear. This study examines whether RF is associated with CVD in apparently healthy individuals.

Methods: All participants presenting to the Center for Preventive Medicine at St. Luke's International Hospital in Tokyo, Japan from April 2004 to March 2013 for an annual health screening were included in this retrospective, cross-sectional study. The goals of this employer-mandated screening program are early detection of chronic disease and identification of risk factors. In addition to various CVD risk factors, RF is also routinely measured for early detection of rheumatoid arthritis.

Participants were divided into two groups by the presence of self-reported CVD. Using this as the primary outcome, we compared several parameters including RF positivity (15 IU/ml), age, male gender, height, weight, body-mass index (BMI), waist circumference (WC), body fat percentage, systolic blood pressure (SBP), diastolic blood pressure (DBP), lipid profile, HbA1c, fasting blood glucose (FBG), uric acid (UA), C-reactive protein (CRP), percentage of ever-smokers and ever-drinkers, presence of self-reported CVD risk factors including dyslipidemia (DL), diabetes mellitus (DM) and hypertension (HTN), and family history of CVD. We evaluated whether whether RF positivity was independently associated with CVD using multivariate regression analysis.

Results: Of 111,021 individuals presenting for health checkup during the study period, 110,856 (99.9%) provided complete datasets regarding our parameters of interests. Of these, mean age was 46.0±12.0 (48.9% men) and 1,863 (1.7%) reported a history of CVD.

On univariate analysis, individuals with CVD were more likely to be male (70 vs. 48.5%), older (62.7 vs. 45.8 years), and have RF positivity (12.4 vs. 8.9%). Those with CVD also had poorer metabolic markers including BMI (23.7 vs. 22.3), WC (85.3 vs. 79.9cm), SBP (128 vs. 117mmHg), DBP (77.9

vs. 72.3mmHg), cholesterol ratio (3.7 vs. 3.4), HbA1c (5.9 vs. 5.5%), FBG (108 vs. 99mg/dl), CRP (0.19 vs. 0.12mg/dl). Health history was also suboptimal in the CVD group, including ever-smoking (57.8 vs. 40.0%); history of CVD risk factors such as DL, DM and HTN (22.3 vs. 4.4%, 2.4 vs. 0.3% and 35.9 vs. 7.1%, respectively); and family CVD history (37.1 vs. 22.2%). p-value < 0.001 for all.

On multivariate analysis, however, RF positivity was not correlated with CVD (1.06, 95%CI 0.91–1.22), in either men (1.03, 95%CI 0.85–1.23) or women (1.10, 95%CI 0.86–1.42) after adjustment for clinically established risk factors.

Conclusion: Despite its association with CVD in individuals with RA, RF does not appear to be correlated with CVD and appears to be inappropriate for use as a CVD screening test in apparently healthy individuals. Further investigations to clarify the reason for this discrepancy between RA patients and general population are warranted in the future.

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2022

First Nations Persons Have an Increased Risk of Developing Rheumatoid Arthritis with an Early Onset Age but Are Seen Less Frequently By Rheumatologists: A Population Based Study. Carol A. Hitchon, Sazzadul Khan, Brenda Elias, Hani S. El-Gabalawy, Alan Katz and Christine A. Peschken. University of Manitoba, Winnipeg, MB.

Background/Purpose: High global prevalence rates of rheumatoid arthritis (RA) have been reported in First Nations (FN). For our regional population of 1.2 million, health care is universally covered, and health services and diagnoses based on International Classification of Disease codes (ICD-9CM) are recorded in the Population Health Research Database (PHRD) from 1984. As a first step to addressing RA care in FN, we validated case definitions for RA for use with the PHRD and described the incidence, prevalence, and health care use for RA.

Methods: Records from April 1, 1995 to March 31, 2010 were accessed. FN people were identified using linkage with the Federal Indian Registry File (FIRF) which records all registered FN for the purposes of entitlement. Identification was expanded to include non-status Indians otherwise eligible (Metis, Inuit). Residents who resided in the province for $\geq$2 years were identified as having RA if they had $\geq$5 physician visits or hospitalizations with (ICD)-9-CM/ICD-10 codes 714/M05, M06 recorded. Persons resident for $<$2 years were identified as having RA if they had $\geq$3 such claims. This definition was validated for the years 2000–2010 by linkage with the Arthritis Centre database (includes self-identified nonFN, FN, Metis; RA n=2281; nonRA n=7044; definition sensitivity 77.12, specificity 90.30 Youden statistic 67.42). Crude and age standardized prevalence rates for FN and nonFN in 2000–2010 were determined. Onset age, (age at first RA code), was compared in prevalent cases. Using a 5 year run-in time to eliminate prevalent cases, incident RA cases were identified and compared between FN and non-FN using logistic regression and odds ratios with 95% CI reported. Physician visits and hospitalizations were compared between FN and nonFN from 2000–2010.

Results: While both crude and age standardized overall prevalence rates of RA increased from 2000–2010 (crude prevalence 0.34% to 0.65%), FN had higher rates than nonFN in each year. In 2009–2010, crude rates were 0.85% vs. 0.63% for FN vs. nonFN, while age adjusted rates were 1.0% vs. 0.4%; for a rate that was 2.48 times higher in FN than non-FN in 2009–2010 (95%CI 2.471–2.472; $p<0.0001$). The age standardized annual incidence of RA decreased from 0.07% in 2000 to 0.02% in 2010. The overall incidence of RA was higher in FN than nonFN at most years with FN having 2.23 times higher incidence of RA in 2009–2010 (CI 2.22–2.23; $p<0.0001$). RA onset age was earlier in FN than non-FN (41 vs. 55 years; $p<0.001$). Despite greater physician visits (110 vs 99; $p<0.0001$) (all rates are per person over 10 years) and more hospitalizations (3.4 vs 1.9 $p<0.0001$), FN had fewer rheumatologist visits (6.9 vs 8.2 $p<0.0001$), non-rheumatology specialist visits (15 vs 23 $p<0.0001$) and surgeries (3.7 vs 5.3 $p<0.0001$) than non FN.

Conclusion: While overall provincial RA incidence is decreasing, FN have more than twice the risk of developing RA, with a prevalence of 1% in 2009–2010, as well as an onset age 10 years earlier than the general population. When combined with generally more severe disease in FN and fewer rheumatology visits this demonstrates a significant care gap highlighting the need to optimize rheumatology care delivery to this population, particularly in view of the rapid growth of this population.

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2023

Prevalence of Inflammatory Arthritis Conditions in the First Nations Population of Alberta. Cheryl Barnabe[1], C. Allyson Jones[2], Don Voaklander[3], Deborah Marshall[1], Christine Peschken[4], Sasha Bernatsky[5], John Esdaile[6] and Brenda Hemmelgarn[1]. [1]University of Calgary, Calgary, AB, [2]Departments of Physical Therapy and School of Public Health, University of Alberta, Edmonton, AB, [3]University of Alberta, Edmonton, AB, [4]University of Manitoba, Winnipeg, MB, [5]McGill University Health Centre, Montreal, QC, [6]Arthritis Research Centre of Canada, Richmond, BC.

Background/Purpose: Canada's First Nations population reports higher rates of physician-diagnosed arthritis and rheumatism, and is known to have twice the rate of osteoarthritis. The prevalence of inflammatory arthritis conditions of Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), Reactive Arthritis (ReA), and Crystal Arthritis has not been widely studied, although variations between FN populations based on tribal ancestry are hypothesized. The Alberta First Nations population is rich in diversity with numerous Tribal Nations represented, including Blackfoot, Chipewyan, Cree, Dene, Sarcee, Saulteaux and Sioux Nations. Prevalence estimates from Alberta would therefore provide a good overall view of the arthritis landscape among First Nations populations in Canada. We report the prevalence of these inflammatory arthritis conditions in the population of Alberta, Canada, comparing rates in First Nations and non-First Nations.

Methods: Population-based healthcare administrative data (years 1993 to 2011), including physician billing claims and hospitalizations, was used to define cohorts of patients with RA, AS, Ps, ReA and crystal arthritis based on ICD-9-CA and ICD-10-CM codes (2 physician billing codes or 1 hospitalization). First Nations patients were identified based on premium payer status. Disease prevalence rates were calculated for fiscal year 2008/2009 as cases per 1000 persons, and the rate ratio calculated for First Nations relative to non-First Nations.

Results: RA, AS and ReA were estimated as being twice as frequent in the First Nations population (Table 1). In contrast, PsA was slightly less frequent in First Nations. Crystal arthritis surpassed RA as the most frequent type of inflammatory arthritis in the non-First Nations population, with a rate ratio three times that of the First Nations cohort.

Table 1. Prevalence Rate of Inflammatory Arthritis Conditions in Alberta (per 1000 persons), and Rate Ratio for First Nations compared to non-First Nations

Condition	Prevalence Rate in First Nations	Prevalence Rate in non-First Nations	Rate Ratio (95%CI), p value
Rheumatoid Arthritis	19.00	10.51	1.81 (1.74–1.88), $p<0.001$
Psoriatic Arthritis	0.65	0.85	0.77 (0.62–0.94), $p=0.0118$
Ankylosing Spondylitis	3.58	2.08	1.72 (1.57–1.88), $p<0.001$
Reactive Arthritis	0.09	0.04	2.23 (1.23–4.02), $p=0.0063$
Crystal Arthritis	4.44	12.82	0.35 (0.32–0.37), $p<0.001$

Conclusion: Our estimates demonstrate that RA is the most frequent inflammatory arthritis in the First Nations population of Alberta, whereas crystal arthritis is the most frequent inflammatory arthritis diagnosis in non-First Nations. RA, AS and ReA prevalence estimates in First Nations are twice that of the non-First Nations population, whereas PsA and crystal arthritis are less frequent. These results further explain the higher self-reported rates of arthritis conditions in the First Nations population beyond degenerative arthritis conditions, and validate the need for enhanced inflammatory arthritis health services to address disease burden.

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2024

Prevalence of Rheumatoid Arthritis in French West Indies, an African Ancestry Population. the Eppra Study. Michel De Bandt[1], Rishika Banydeen[2], Lauren Brunier[3], Katleen Polomat[4], Veronique Dehlinger[5], Serge Arfi[4], Christophe Deligny[4], Benedicte Garnery[6], Helene Cormier[1], Fabienne Dubreuil[7], Patrick Numeric[5], Danielle Dufrenot[8], Sabine Molcard[1], Loic Brithmer[1], Olivier Fuhrer[1], Lucien Louis-Joseph[7], Sylvie Merle[2] and Georges Jean-Baptiste[5]. [1]Unit of rheumatology, Fort de France, France, [2]Unit of epidemiology and biostatistics, Fort de FRance, France, [3]Unit of rheumatology, CHUM, 97200 Fort de France, France, [4]unit of internal medicine, Fort de France, France, [5]Unit of rheumatology, CHUM, Fort de France, France, [6]Unit of internal medicine, Fort de France, France, [7]Unit of rheumatology, Fort de FRance, France, [8]Unit of rheumatology, Fot de France, France.

Background/Purpose: Rheumatoid arthritis (RA) is a disabling chronic disease, regarded as the most frequent inflammatory rheumatism in adults, with a prevalence estimated between 0.3 and 1 %, and a feminine ascendancy. In metropolitan France this prevalence is estimated from 0.3 % to 0.5% of the general population. No precise data is available for French West Indies, and the prevalence of RA in this population of African ancestry is poorly evaluated.

Methods: The objective of the study is to estimate RA prevalence in the FWI by a census forward-looking epidemiological survey in the hospital and liberal sectors for one year duration. It is a unique tour with clinical examination, self-administered questionnaires and declaration. Secondary objectives are description of clinical and socio economical aspects of RA and cardiovascular comorbidities. We present the results for Martinique. Our survey was widely distributed (radio, press, patients' associations. . .) to ensure a good completeness. Data were analysed using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA). Throrough descriptive analysis of collected variables was conducted. Crude prevalence rates were adjusted to a standard population of Martinique (nationwide census in 2010). The 95% CIs were calculated using the Poisson distribution.

Results: Our completeness is good. 538 RA were collected, giving a prevalence in Martinique of 0.184% of the adult population (290 000), respectively 0.049 for men and 0.292 for women. 44% of these patients are treated in private practice and 56% in hospital. This cohort is composed of 88% women and 12% men; 92% were born in Caribbean and 7.7% elsewhere. Patients self declared of Afro Caribbean origin in 92.7%, Caribbean White in 1.7%, caucasian in 3% and other in 2.1%. Their mean disease duration was 9.7+10 years. RF and ACPA were positive in 82.2% (FR+ 392, ACPA+349, 35% low level, 65% high level) : CCP+FR+ in 306, FR+CCP- in 77, FR-CCP+ in 41, FR-CCP- in 96. 17% had extra articular manifestations. ACR1987 and ACR2010 criteria were pos in 94.4% and 78%. HAQ was <1 in 74%, >1and <2 in 20% and >2 in 3%. DAS28 were respectively <2.6 in 59%, <3.2 in 15.4%, <5.1 in 23% and >5.1 in 3%. Less than 5% are ever smoker. Parodontopathy is infrequent. Cardiovascular risk factors were noticed in 89,4% with a mean of 2 CVRF beside RA.

Conclusion: This work clarifies the prevalence of RA in this population of African origin. Some characteristics as: reduced prevalence, strong female representation, strong seropositivity, high levels of anti-CCP, no tobacco, differentiate our patients from other populations and evoke another etiology than tobacco.

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2025

Factors Associated with Time to Diagnosis from Symptom Onset in Early Rheumatoid Arthritis Patients. Yoon-Kyoung Sung[1], Soo-Kyung Cho[1], Dam Kim[1], Soyoung Won[1], Jiyoung Lee[1], Jung-Yoon Choe[2], Chan-Bum Choi[1], Seung-Jae Hong[3], Jae-Bum Jun[4], Tae-Hwan Kim[4], Eunmi Koh[5], Hye-Soon Lee[6], Jisoo Lee[7], Dae-Hyun Yoo[4], Bo Young Yoon[8] and Sang-Cheol Bae[1]. [1]Clinical Research Center for Rheumatoid Arthritis (CRCRA), Seoul, South Korea, [2]Catholic University of Daegu School of Medicine, Daegu, South Korea, [3]Kyung Hee University, Seoul, South Korea, [4]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [6]Hanyang University Guri Hospital, Guri, South Korea, [7]Ewha Womans University School of Medicine, Seoul, South Korea, [8]Inje University Ilsan Paik Hospital, Goyang, South Korea.

Background/Purpose: Early diagnosis and treatment is an optimal target for better outcomes in rheumatoid arthritis (RA) in clinical practice. To make an early diagnosis, it would be helpful to know the sociodemographic or clinical factors for recognition of disease. On this study, we aimed to identify the factors associated with time to diagnosis after symptom onset in early RA patients

Methods: Early RA patients with less than 1 year of disease duration in the KORean Observational study Network for Arthritis (KORONA) database were included in this analysis. The time to diagnosis was defined as the duration between symptom onset and the diagnosis of RA in each patient. Early RA patients were further divided into two groups according to the time to diagnosis: early diagnosis group (time to diagnosis <1year) and late diagnosis group (time to diagnosis°Ã1year). Using the multivariate regression model, we identified the factors associated with the early diagnosis. We also compared the disease status such as disease activity, hand radiographic change and functional disability on the point of RA diagnosis between early diagnosis group and late diagnosis group.

Results: Among the 714 early RA patients, 401 patients (56.2%) and the other 313 patients (43.8%) were classified as early diagnosis group and late diagnosis group, respectively. In multivariate analysis, older onset age (OR 1.03, 95%CI 1.02–1.05), higher education level (OR 1.72, 95%CI 1.15–2.57) and higher income (OR 1.47, 95%CI 1.03–2.10) were identified as associating factors for early diagnosis (See table). Disease activity scores (DAS) using 28 joints on diagnosis (3.81 ± 1.44 vs. 3.82 ± 1.42, p=0.92) and functional disability (0.65 ± 0.61 vs. 0.57 ± 0.62, p=0.07) were not different between two groups. However, hand joint erosions on X-ray (37.8% vs. 25.6% p<0.01) was common in late diagnosis group than early diagnosis group.

Conclusion: Old age at symptom onset, higher education level or income were the factors associated with short time to diagnosis in early RA patients. Hand joint erosion was more common in late diagnosis group when they diagnosed as RA.

Table. Factors associated with time to diagnosis in early RA patients

	Crude OR (95% CI)	Multi-adjusted OR (95% CI)
Onset age	1.01 (1.00–1.03)*	1.03 (1.02–1.05)*
Male	0.92 (0.64–1.32)	0.78 (0.52–1.15)
Family history of RA	0.82 (0.52–1.31)	0.85 (0.52–1.38)
Body Mass Index		
<18.5 kg/m^2	1	1
°Ã18.5 and <23.0 kg/m^2	1.36 (0.70–2.62)	1.13 (0.56–2.30)
°Ã23.0 kg/m^2	1.02 (0.53–1.97)	0.84 (0.41–1.73)
Education		
Middle school or less	1	1
High school or more	1.32 (0.97–1.78)	1.72 (1.15–2.57)*
Income		
<2 million won	1	1
°Ã2 million won	1.38 (1.02–1.86)*	1.47 (1.03–2.10)*
Exercise	1.32 (0.97–1.78)	1.19 (0.86–1.65)
First symptom in small joint	1.37 (0.99- 1.89)	1.31 (0.93–1.85)
Number of comorbidity		
=0	1	1
=1	1.12 (0.80–1.57)	0.99 (0.69–1.43)
°Ã2	1.11 (0.75–1.66)	0.94 (0.61–1.46)
Rheumatoid factor positivity	1.17 (0.73–1.89)	1.29 (0.77–2.15)

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2026

Treatment Delays and Worse Outcomes Associated with Lower Socioeconomic Status in Rheumatoid Arthritis. Emily Molina[1], Jose Felix Restrepo[2], Inmaculada del Rincon[1], Daniel Battafarano[3] and Agustin Escalante[2]. [1]University of Texas Health Science Center, San Antonio, TX, [2]University of Texas Health Science Center at San Antonio, San Antonio, TX, [3]San Antonio Military Medical Center, JBSA - Ft Sam Houston, TX.

Background/Purpose: Prompt and routine care in rheumatoid arthritis (RA) is critical for best outcomes. Low socioeconomic status (SES) RA patients use fewer health services and have higher disease activity. We sought to examine the role of SES, distance to the rheumatologist (DTR), and delays in DMARD treatment as determinants of outcome in RA.

Methods: RA outpatients were recruited from public, private, military and Veteran's Affairs rheumatology clinics. The recruitment period spanned nearly 15 years. We assessed SES based on education, occupation and income using the Nam & Powers scale. The time from RA symptom onset to DMARD initiation (DMARD lag) was determined by self-report of the two dates. The distance from a patient's address to the rheumatologist was obtained using Google Maps. We examined three specific clinical outcomes in RA: disease activity, determined by DAS28ESR; joint damage, determined from hand radiographs using the Sharp score; and physical disability, determined by the Modified Health Assessment Questionnaire (MHAQ). We used linear regression models to examine the association of the clinical outcomes with SES, DTR, and DMARD lag, adjusting for other confounders such as age, sex, ethnicity and duration of RA.

Results: We recruited 1,209 RA patients, 1159 of whom had received DMARD treatment. Average DMARD lag was 6.9 ± 8.9 years. Greater DMARD lag was associated with older age ($P \leq 0.001$), longer disease duration ($P \leq 0.001$) and worse status on all three clinical outcomes ($P \leq 0.001$). Lower SES was associated with a longer DMARD lag (beta coeff. -0.120, $P \leq 0.001$) and a shorter DTR (beta coeff. 0.261, $P \leq 0.001$). On average, patients with lower SES waited 8.5 ± 10.2 years after onset of RA symptoms to begin DMARD treatment, which was significantly longer than those in middle and upper SES tertiles who waited 6.1 ± 7.9 years ($P = 0.002$) and 6.1 ± 8.6 years ($P = 0.009$), respectively. Adjusting for confounders including DTR and DMARD lag, SES remained inversely associated with DAS28ESR (beta coeff. −0.282, $P \leq 0.001$), Sharp score (beta coeff. −0.135, $P \leq 0.001$) and MHAQ (beta coeff. −0.296, $P \leq 0.001$).

Conclusion: Low SES RA patients experience a significantly greater delay in DMARD treatment. Low SES and greater DMARD lag were independently associated with worse clinical outcomes, despite adjusting for potential barriers to care such as distance to the rheumatologist and other confounders. Strategies to reduce treatment delay in low SES RA patients are needed.

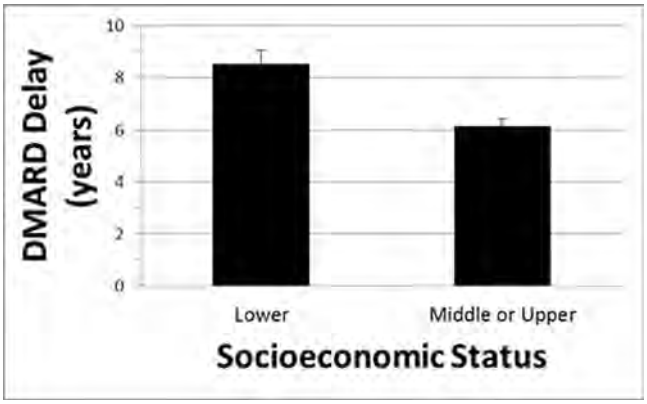

Figure 1. Average time from RA symptom onset to DMARD initiation according to socioeconomic status.

Disclosure: E. Molina, None; **J. F. Restrepo**, None; **I. del Rincon**, None; **D. Battafarano**, None; **A. Escalante**, None.

2027

Higher Educational Level Correlates with Retarded Onset and Less Severe Disease in Rheumatoid Arthritis Patients. Michael Zaenker[1], Udo Schwill[2], Petra Reutermann[3], Joachim Listing[4] and Christel Kordbarlag[5]. [1]Immanuel Klinikum Bernau, Rheumatology Center Northern Brandenburg, Bernau, Germany, [2]Immanuel Klinikum, Bernau, Germany, [3]KMG Elbtal Kliniken, Rheumatology Center Northern Brandenburg, Bad Wilsnack, Germany, [4]German Rheumatism Research Center, Berlin, Germany, [5]Ruppiner Kliniken, Rheumatology Center Northern Brandenburg, Neuruppin, Germany.

Background/Purpose: Compared to the general population, patients with RA are endangered by poverty due to treatment-related expenses, disability, unemployment, or early retirement. Additionally, there is impact of poverty on disease management and, still unexplained, increased prevalence of RA is associated with higher mortality in individuals with lower educational level. In this study we evaluate interrelationship between socioeconomic status of RA-patients and their disease severity in an unselected community-based cohort in Northern Brandenburg, Germany.

Methods: Prospective, cross-sectional study among 158 consecutively recruited RA-patients treated in our outpatient-clinic (Bernau) during 3 months. Inclusion criteria were written consent and diagnosis of RA, fulfilling ACR/EULAR-criteria. Using anonymized questionnaires, monthly disposable income, treatment-related expenses and effects of RA on social life were evaluated.

Results: Of all 155 returned questionnaires (return rate 98%), 143 were evaluable. Patient mean age±SD was 60.5±11.7 years, 64% females, mean age at RA-manifestation was 45.5±15.1 years. Monthly median equivalized disposable income (EDI) of RA-patients (1133€, IQR 835–1350) was 86% of the median EDI in the region (1323€), 80% of the median EDI in Germany (1413€). The at-risk-of-poverty-rate (RPR) using the 60% threshold (794 €) of mean EDI of the State Brandenburg was significantly higher compared to the population in the region (22% vs. 14% OR 1.83 $p<0.001$). Subgroups with different educational levels were equal with regard to mean age and gender. Further comparing subgroups with different educational level, we found in RA-patients with university degree and resulting higher median EDI (1333 IQR 967–1667 vs. 1000 IQR 735–1333 €) a mean age at disease onset that was 10 years higher (53.3 ±10.6 vs. 43.2±15.5 years, $p=0.001$), less functional limitations (mean FFbH 79.0±26.4 vs. 66.8±27.1%, $p=0.043$) and a lower rate of early retirement (9.7% vs. 30.4%, $p=0.021$) than in patients with lower educational level. Additionally, we found trends for lower rate of active smokers (19 vs. 28%, $p=0.48$) and higher proportion of early treatment within 6 months after disease onset (48 vs. 37%, $p=0.30$) in the group with university degree. Proportion of patients with biologics was higher in the group with lower educational level (53 vs. 35%, $p=0.11$), reflecting more severe disease.

Conclusion: Our data support the notion that poverty is not only result of disabling RA but educational level and income themselves may influence disease course. The factors contributing to less severe disease and later manifestation in individuals with higher educational levels are mostly unclear and need more elucidation.

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2028

Effect of Age at Rheumatoid Arthritis Onset on Clinical, Radiographic, and Functional Outcomes: The Espoir Cohort. Thomas Krams[1], Adeline Ruyssen-Witrand[1], Delphine Nigon[1], Bruno Fautrel[2], Francis Berenbaum[3], Alain G. Cantagrel[4] and Arnaud Constantin[5]. [1]Purpan University Hospital, Toulouse, France, [2]UPMC GRC08, Paris 06 University, Pitié Salpétrière Hospital, Paris, France, [3]INSERM - UMR S 938, Paris, France, [4]CHU Purpan - Hôpital Pierre-Paul Riquet, Toulouse, France, [5]Purpan University Hospital, Toulouse Cedex 9, France.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic disease with peak incidence in the fourth and fifth decades of age. To investigate whether age at disease onset determines clinical, radiographic or functional outcomes in a cohort of early RA, taking into consideration possible age-related differences in treatment modalities.

Methods: The ESPOIR cohort is a longitudinal, prospective, multicenter, observational study of adult patients with early arthritis. For this study, we selected data for patients fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism criteria for RA during the first 3 years of follow-up. Patients were pooled into 3 groups by age at RA onset: <45 years (young-onset RA [YORA]), 45 to 60 years (intermediate-onset RA [IORA]) and >60 years (late-onset RA [LORA]). The following outcomes were compared at baseline and during the first 3 years of follow-up by age at disease onset: Simple Disease Activity Index (SDAI) remission rate, one additional erosion, and Health Assessment Questionnaire Disability Index (HAQ-DI) score < 0.5. We also assessed first disease-modifying anti-rheumatic drug (DMARD) survival rate. A multivariate model (logistic regression) was built.

Results: We included 698 RA patients (median [interquartile range] age 50.3 [39.8–57.2] years; female 78.2%), 266 YORA, 314 IORA, and 118 LORA. The median SDAI was 28.5 (20.6–38.6) and median

HAQ-DI score 1 (0.5–1.5). At 1 year, SDAI remission was greater for patients with YORA than IORA and LORA (<0.0001). Having at least one additional erosion was greater for LORA and IORA than YORA patients after 1 year (41.1% [39/95] and 29.7% [81/272] vs 23.8% [51/214], p=0.009) and 3 years (48.2% [41/85] and 44.3% [105/237] vs 32.81% [63/192], p=0.017). The proportion of patients with HAQ score < 0.5 was greater for YORA than IORA and LORA at 1 year (p=0.007) and remained significant at 2 and 3 years. The first DMARD survival rate was lower for YORA than IORA and LORA patients during the 3 years (p=0.005). On multivariate analysis, young age at RA onset was independently associated with SDAI remission at 1 year, no additional erosion at 3 years and HAQ score < 0.5 at 1, 2 and 3 years.

Conclusion: In a cohort of early RA, young age at disease onset is associated with high rate of remission at 1 year, low radiographic progression at 3 years and low functional score during 3-year follow-up. Young age at disease onset is associated with low first DMARD survival rate over 3 years, which suggests that late-onset RA patients may receive less aggressive treatment strategies than younger patients.

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2029

Treatment Patterns of Multimorbid Rheumatoid Arthritis Patients: Results from an International Cross-Sectional Study. Helga Radner[1], Kazuki Yoshida[2], Ihsane Hmamouchi[3], Maxime Dougados[4], Josef Smolen[5] and Daniel H Solomon[6]. [1]Medical University Vienna, Vienna, Austria, [2]Kameda Medical Center, Kamogawa, Japan, Kamogawa, Japan, [3]Mohamed V Souissi University, Rabat, Morocco, [4]Descartes University, Cochin Hospital, Paris, France, [5]Medical University of Vienna, Vienna, Austria, [6]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: The presence of multimorbidity could lead to less intensive treatment of RA. This can increase RA disease activity and worsen outcomes such as function, quality of life and mortality.

The aim of the study is to describe the treatment profile of multimorbid RA patients in contrast to patients with RA only, and compare it across different international regions.

Methods: COMORA is a cross-sectional study assessing morbidities, RA related outcomes and treatment of RA patients, recruited in 17 countries worldwide. Patients were grouped according to their multimorbidity profile assessed by a counted multimorbidity index (cMMI), enumerating the particular number of morbidities for each patient. Treatment for RA was categorized according to the use of biologic DMARDs (bDMARD) and TNF-inhibitors (TNFi) in particular, use of synthetic DMARDs only (sDMARD), NSAID use and use of steroids for patients by their cMMI. Adjusted logistic regression models were examined to determine the odds ratio (OR) and 95% confidence interval (CI) of use of bDMARD, TNFi, sDMARD, NSAID or steroids, based on a patient's cMMI and global region, after adjusting for age, disease activity, disease duration, and previous DMARD therapy.

Results: The study cohort consisted of 3920 patients, and 2563 (65.4%) were multimorbid. Overall, 92.6% of the patients were on DMARD therapy, 32.7% received bDMARD; 59.2% sDMARD only; 51.1% NSAIDs and 54.8% corticosteroids. Regional differences could be observed with the most frequent use of bDMARDs in US (46.5%) and lowest frequency in North Africa (9.0%) (**Figure**). After adjusting for confounders in logistic regression analyses, the OR for use of bDMARDs was reduced for each additional morbidity (OR 0.90, 95%CI 0.83–0.97). Similarly, the probability for use of TNFi was also reduced (OR 0.92, 95%CI 0.84–0.99), whereas the OR for use of sDMARD was increased (OR 1.12, 95%CI 1.04–1.21). No change of OR was found for NSAID or steroid use (**Table**).

Conclusion: In our cohort, differences in bDMARD prescribing exist across global regions. After adjusting for covariates, the OR of bDMARD and TNFi use decreases 10% for each additional chronic morbid condition as assessed by cMMI, whereas the OR of sDMARD use increased, probably reflecting rheumatologists' greater comfort using these agents in patients with a greater multimorbidity burden.

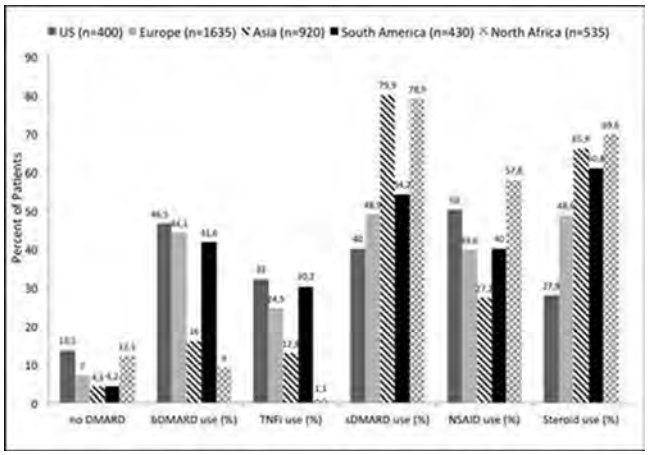

Figure: Regional differences of current treatment status

Table: Logistic regression models

Covariates	Odds Ratio (95% Confidence Interval) bDMARD	TNFi	sDMARD	NSAIDs	Steroids
Counted multimorbidity index	0.90 (0.83–0.97)*	0.92 (0.84–1.0)*	1.12 (1.04–1.21)*	1.06 (0.99–1.34)	1.01 (0.98–1.13)
Age (years)	0.99 (0.98–1.0)	0.99 (0.98–1.0)	1.0 (0.99–1.01)	0.98 (0.97–0.99)*	1.0 (0.99–1.0)
Disease duration (years)	1.02 (1.0–1.03)*	1.03 (1.01–1.04)*	0.99 (0.98–1.0)	1.01 (1.0–1.03)*	1.0 (0.99–1.01)
Number of previous DMARDs	1.27 (1.18–1.37)*	0.94 (0.87–1.02)	0.71 (0.65–0.77)*	1.05 (0.98–1.13)*	1.21 (1.12–1.30)*
Clinical disease activity index	0.98 (0.97–0.99)*	0.96 (0.95–0.97)*	1.0 (0.99–1.01)	1.03 (1.02–1.04)*	1.04 (1.03–1.06)*
Region US= reference	REF	REF	REF	REF	REF
Region Europe	0.57 (0.38–0.85)*	0.58 (0.39–0.85)*	2.11 (1.35–3.27)*	0.94 (0.65–1.37)	2.50 (1.67–3.73)*
Region Asia	0.15 (0.10–0.23)*	0.24 (0.15–0.39)*	8.49 (5.23–13.6)*	4.22 (2.74–6.50)*	6.43 (4.10–10.1)*
Region South America	0.56 (0.34–0.94)*	0.62 (0.37–1.06)*	2.51 (1.46–4.37)*	1.75 (1.06–2.90)*	2.56 (1.52–4.33)*
Region North Africa	0.06 (0.03–0.11)*	0.03 (0.01–0.08)*	9.07 (5.34–15.4)*	0.58 (0.37–0.92)*	5.10 (3.09–8.35)*

**p<0.05*

Disclosure: H. Radner, None; **K. Yoshida**, None; **I. Hmamouchi**, None; **M. Dougados**, None; **J. Smolen**, None; **D. H. Solomon**, None.

2030

Predicting Failure of Conventional Disease Modifying Antirheumatic Drugs in Treatment Naive Early Rheumatoid Arthritis Patients: A Single Centre Inception Prognostic Factor Cohort Study. Mette Axelsen[1], Trine Bay Laurberg[1], Robin Christensen[2], Ulrich Fredberg[3] and Torkell Ellingsen[4]. [1]Silkeborg Hospital, Silkeborg, Denmark, [2]MSU, The Parker Institute, Copenhagen University Hospital, Frederiksberg, Denmark, [3]Diagnostic Centre Region Hospital Silkeborg Denmark, Silkeborg, Denmark, [4]Diagnostic Centre Region, Hospital Silkeborg Denmark, Odense, Denmark.

Background/Purpose: Finding prognostic factors for treatment failure on synthetic disease modifying antirheumatic drugs (DMARD) in early treatment naive rheumatoid arthritis (RA) is a challenge. The purpose of this study is to investigate whether baseline characteristics and disease activity variables add value to predict failure of classical DMARD treatment in a multivariable model.

Methods: The study included DMARD naive patients consecutively diagnosed with RA according to the ACR/EULAR criteria 2010. The patients were enrolled between 1.10.2009 and 1.11.2012. They were followed for one year. Disease activity was registered in the DANBIO registry: number of swollen joints (NSJ)(38 joints), number of tender joints (NTJ)(40 joints), Health Assessment Questionnaire (HAQ), visual analog scales (VAS) 0–100 were used to assess pain, fatigue, patient and physician global assessment and DAS28-CRP, CRP, IgM-RF and anti-CCP. Treatment was oral methotrexate 15 mg per week initiated at time of diagnosis increased to 20 mg per week at week 6. If DAS28-CRP at this point was higher or equal to 3.2 and one or more swollen joints were present, treatment was intensified according to guidelines aiming at triple therapy (if tolerated). Intra-articular glucocorticoid injections were given in swollen joints. Treatment with biologics was applied according to guidelines. COX regression analysis was used to investigate if

baseline characteristics and disease activity variables could predict failure of DMARD treatment requiring substitution or addition of biologic treatment. Primary outcome was failure DMARD defined as mentioned above.

Results: 230 patients (41 % males), with a mean age of 59 yrs (range: 16–85 yrs) were enrolled at baseline. A total of 16 patients initiated biologic treatment during the first treatment year. Univariate COX regression analysis showed significant association between the need for biologic treatment and age (hazard ratio (HR) 0.95 (95% CI: 0.92 to 0.98), $p < 0.001$; i.e. inversely associated), CRP (HR 1.01 (95% CI: 1.00 to 1.02), $p=0.04$), VAS fatigue (HR 1.03 (95% CI: 1.01 to 1.05), $p=0.01$)) and VAS global (HR 1.04 (95% CI: 1.01 to 1.06), $p=0.007$). In the subsequent multivariable analysis (incl. the above mentioned variables simultaneously) age and CRP remained significantly associated (HR 0.95 (95% CI: 0.91 to 0.98), $p=0.002$; HR 1.03 (95% CI: 1.01 to 1.04), $p=0.002$, respectively). After one year of follow-up no significant differences in disease activity was found between the patients still on DMARD treatment (DAS28-CRP: 2.1) compared to the 16 patients that had initiated biologic therapy (DAS28CRP: 2.3).

Conclusion: In a pragmatic, single centre inception cohort, using the ACR/EULAR 2010 criteria for the diagnosis of early RA, regression analyses showed that young age and high CRP was significantly associated with failure on initial classical guideline applied DMARD strategy ($p=0.002$).

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2031

Early Adherence to Methotrexate in Rheumatoid Arthritis (RA) Is High: a Prospective Longitudinal Study of New Users. Holly Hope[1], Kimme Hyrich[2], James Anderson[1], Lis Cordingley[3] and Suzanne Verstappen[2]. [1]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, [2]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [3]Centre for Musculoskeletal Research, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Methotrexate (MTX) is the recommended first-line DMARD for rheumatoid arthritis (RA) in most countries, however response is not universal. Non-adherence may explain this to some degree. The aim of this analysis was to (1) describe patient self-reported adherence to MTX over the first 6 months of therapy and (2) identify factors associated with non-adherence.

Methods: Patients were enrolled in the Rheumatoid Arthritis Medication Study (RAMS) a 1 year prospective study of MTX new-users for RA in the UK. At baseline, data was collected on demographic factors, alcohol and smoking history, disease activity (DAS28) and disease duration. In addition patients completed the Health Assessment Questionnaire (HAQ), visual analogue scales (VAS) for pain and fatigue, The Beliefs about Medicines Questionnaire (BMQ), Brief Illness Perceptions Questionnaire (B-IPQ), Hospital Anxiety and Depression Scale (HADS), the EQ-5D quality of life questionnaire and the Compliance Questionnaire–Rheumatology (CQ-R), a self-report adherence measure. To measure adherence during the first 6 months after MTX commencement patients completed a weekly MTX diary detailing any missed doses including reasons. Proportional adherence was determined using number of non-adherent weeks compared to total number of eligible weeks. Nonadherence was defined as ≥1 dose missed against medical advice. The associations between patient characteristics, measures of illness and medicine cognitions, and adherence were assessed applying adjusted (age, sex, disease duration and disease activity) univariate logistic regression analysis.

Results: Analyses included the first 392 patients recruited to RAMS who completed the 6 month diary (median age 61 years, 70% female, mean DAS28 = 4.3 [sd 1.3]. In total, 20% (n=80) of patients reported 174 non-adherent weeks. Reasons for non-adherent weeks included (% weeks): no reason given (30%), adverse effects (28%), feeling unwell/ suspected infection (18%), forgetting (12%), taking a drug holiday (9%) or delayed prescription refill (3%). Overall mean proportional adherence was very high (98%). Of adherent patients, 19% missed at least one dose under medical advice. Factors associated in adjusted analyses with being ever non-adherent included higher baseline DAS28 score (OR 1.31 per unit DAS28 (95%CI:1.06, 1.61) and lower baseline CQ-R score (0.95 per unit CQ-R 95%CI:0.92, 0.99). BMQ concern and necessity scores, HADS depression score, illness perceptions and other patient characteristics were not associated with adherence.

Conclusion: Over 20% of individuals were nonadherent although as many patients missed doses under medical advice. The effects of relatively low levels of non-usage of MTX, either due to non-adherence or to advised withdrawal, on disease outcomes is yet to be evaluated, however, these data suggest that levels of overall adherence to MTX over the first 6 months of therapy were very high.

Table 1: Baseline characteristics of cohort and association with nonadherence

Baseline variable	n	Adherent	n	Nonadherent	Adjusted odds ratio (95%CI)‡	p
Age (years)	304	61.4 (51.5–70.1)	79	59.7 (48.6–69.0)	0.98 (0.96–1.00)	0.103
Gender-female	307	210 (68.4%)	79	60 (75.9%)	1.19 (0.65–2.18)	0.578
Currently drinks alcohol	292	213 (72.9%)	83	53 (63.9%)	0.63 (0.37–1.12)	0.116
Currently smokes	305	49 (16.1%)	80	19 (23.8%)	1.50 (0.791–2.85)	0.214
Disease duration (months)	304	9.6 (4.5–31.4)	80	12.9 (5.4–28.9)	1.00 (1.00–1.00)	0.712
1 current co morbidity	312	99(31.7%)	80	25 (31.3%)	1.01 (0.55–1.85)	0.981
≥1 current co morbidity	312	49 (15.7%)	80	17 (21.3%)	1.56 (0.75–3.22)	0.233
DAS-28	279	4.3 (3.3–5.3)	74	4.6 (3.9–5.7)	1.31 (1.06–1.61)	0.011*
VAS-pain	302	49 (28–70)	79	49 (25–73)	0.99 (0.98–1.00)	0.109
VAS-fatigue	304	50 (23–71)	78	59 (26–77)	1.00 (0.99–1.01)	0.780
Disability (HAQ)	303	1.0 (0.5–1.6)	80	1.1 (0.4–1.8)	0.89 (0.58–1.37)	0.595
HQOL (EQ-5D)	291	0.74 (0.62–0.80)	78	0.71 (0.62–0.80)	3.59 (0.20–64.0)	0.384
Depression (HAD)	300	8 (7–9)	78	8 (7–9)	1.12 (0.89–1.41)	0.339
Anxiety (HAD)	295	13 (12–15)	77	14 (12–15)	1.13 (0.95–1.34)	0.178
Necessary beliefs (BMQ)	288	19 (17–23)	76	20 (17.5–22)	0.99 (0.91–1.06)	0.740
Concerns (BMQ)	291	15 (12–17)	77	16 (14–18)	1.02 (0.95–1.10)	0.527
B-IPQ	280	46 (38–53)	71	47 (39–55)	1.00 (0.97–1.03)	0.907
CQ-R	142	75.4 (66.7–84.2)	36	69.3 (63.2–76.3)	0.95 (0.92–0.99)	0.009**

All values n(%) or median(IQR) unless stated.
*$p < 0.05$ ** $P < 0.01$ ‡adjusted for age, gender, DAS28, disease duration

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2032

Psychological Factors Predict Adherence to Methotrexate (MTX) in Rheumatoid Arthritis (RA); Findings from a Systematic Review of Rates, Predictors and Associations with Patient Outcomes. Holly Hope[1], James Bluett[1], Kimme Hyrich[2], Lis Cordingley[3] and Suzanne M. Verstappen[2]. [1]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, [2]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [3]Centre for Musculoskeletal Research, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Methotrexate (MTX) is a first line therapy for Rheumatoid Arthritis (RA). Treatment response to MTX is not universal, and nonadherence may partially explain poor treatment response to MTX, therefore it is imperative to investigate adherence to MTX specifically. Previous systematic reviews have evaluated adherence to all DMARDs. The aims of this systematic review were: 1) to summarise existing rates of adherence to MTX, 2) to identify predictors of adherence and 3) assess the association between non-adherence with patient outcomes.

Methods: A systematic search of papers published between January 1980 to 2014 was conducted in PubMed, PsycINFO, EMbase and CINAHL databases. Studies were eligible for inclusion if; 1) MTX was used as monotherapy or in combination with other therapies, 2) MTX was used in an RA or inflammatory polyarthritis population, 3) adherence was defined and measured as the extent to which patients followed their MTX regimen during the period of prescription, and 4) it was an original piece of research. Papers were reviewed by two researchers and consensus agreed with a third. A quality assessment (QA) tool formally assessed each included article.

Results: In total, ten studies met the inclusion criteria and eight were evaluated high quality using the QA tool. Rates of adherence ranged widely from 59% to 107%, and exposed differences in definitions of adherence, study methodologies and sample heterogeneity. The methods used to assess adherence included; Medication Event Monitoring Systems (n=2), Pharmacy Refill (n=5), validated self-report questionnaire (n=2) and 7 day diary (n=1) (Table 1). Twenty-one potential predictors of MTX adherence were identified; the strongest evidence occurred for beliefs in the necessity and efficacy of MTX, absence of low mood, mild disease and MTX as a monotherapy. Disease activity was the only patient outcome where the effect of nonadher-

ence was assessed. Three studies tested this association and each found nonadherence associated with poor treatment response.

Conclusion: Psychological factors were the strongest predictors of adherence rates in this first systematic review specific to MTX. It was the first to include synthesis of evidence on patient outcomes and show nonadherence to MTX affects treatment response in RA.

Table 1. Comparison of MTX rates of adherence across studies

Author	QA score	High/low quality	Adherence method used	Definition of MTX adherence	n	MTX adherence	95% CI/SD
MEMS							
Waimann et al. (2013) [19]	15	High	MEMS	% of correctly taken doses	76	63%	20%
de Klerk et al. (2003) [22]	12	Low	MEMS	% of correctly taken doses	23	107%	98–117
Pharmacy refill							
Cannon et al. (2010) [18]	15	High	MPR	=>80% prescriptions filled	85	80%	NP
	15	High	MPR	=>80% prescriptions filled	370	85%	NP
de Thurah et al. (2010) [20]	14	High	CMG	% of treatment gaps (reversed)	941	87.7%	86.8–88.5
Grijalva et al. (2010) [17]	9	High	MPR	% of prescription filled	NP	59%	31–82
Harley, Frytak & Tandon (2003) [16]	8	High	MPR	≥ 80% prescriptions filled	1668	63.70%	23.8–102
Grijalva et al. (2007) [15]	8	High	MPR	% of prescriptions filled excluding the last prescription	2933	80%	NP
Self report							
de Thurah et al (2010)a [21]	14	High	CQ-R	CQ-R score >25th percentile	85	BL 23.5%	NP
					65	9 mo. 23.1%	NP
Contreras-Yanezet et al. (2010) [23]	11	Low	7 day DRR	% of correct doses taken across 3 time points	10	78%	NP
Salt & Frazier (2011) [24]	9	Low	MARS	MARS score >39	77	92.10%	NP

(CQ-R = Compliance Questionnaire-Rheumatology, DRR = Drug Record Registry, MARS = Medication Adherence Revised Scale, MPR = Medication Possession Ratio, CMG = Continuous Medication Gap, NP= information not presented)

Table 2. Associations with patient outcomes

Author	Sample size	Predictor	Outcome	Statistical test	Unadjusted Strength of effect (95% CI)	P	Adjusted Strength of effect (95% CI)	P
Cannon et al. (2011) [17]:								
Full cohort	455 (71 non –adherent, 384 adherent)	MPR ≥ 80%	Mean difference in DAS28	Linear regression	−0.34 (−0.68, −0.06)	<0.05	−0.37 (−0.67, −0.07)	<0.05
First time user cohort	85 (17 non adherent 68 adherent)	MPR ≥ 80%	Mean difference in DAS28	Linear regression	−0.54 (−1.18, 0.11)	NS	−0.40 (−1.11, 0.30)	NS
Established cohort	370 (54 non adherent 316 adherent)	MPR ≥ 80%	Mean difference in DAS28	Linear regression	−0.38 (−0.67, −0.05)	<0.05	−0.37 (−0.72, −0.02)	<0.05
Waimann,C.A. et al. (2013) [19]	102	% of prescribed DMARD doses taken[a]	DAS28 at 2 years	Linear regression	−0.02 (−0.03, −0.001)	NP	−0.2	0.03
Contreras-Yanez,I. Et al. (2010) [23]	68 (54 maintained remission 14 disease flare)	MPR ≥ 80%[b]	Maintained remission (DAS28 < 2.4)	Logistic regression	NP	NP	NP	<0.001

[a] includes sDMARDS and bDMARDS. [b] includes other sDMARDS. NP = not presented. RF = rheumatoid factor. CCP = cyclic citrullinated peptide

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2033

Patient Factors Associated with Oral Glucocorticoid Prescribing Patterns in UK Primary Care for Patients with Rheumatoid Arthritis. Rachel J. Black[1], Rebecca Joseph[1], Benjamin Brown[2], Mohammad Movahedi[1], Mark Lunt[3] and William G Dixon[1]. [1]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [2]Centre for Health Informatics, Institute of Population Health, The University of Manchester, Manchester, United Kingdom, [3]University of Manchester, Manchester, United Kingdom.

Background/Purpose: Oral glucocorticoids (GCs) are commonly used in the treatment of rheumatoid arthritis (RA) and GC prescriptions are often issued in the primary care setting. The objective of this study was to describe the patterns of GC prescribing for patients with RA in UK primary care and to identify patient characteristics that are associated with GC use.

Methods: 16 536 patients with incident RA were identified from the Clinical Practice Research Datalink, a large UK general practice database. Descriptive statistics were used to identify patterns of GC prescribing for these patients. For patients who received more than one GC prescription over the observation period, the mean, minimum and maximum prednisolone equivalent doses were calculated. The median of these values across all treated patients was then calculated. Stepwise linear regression was used to identify baseline patient characteristics associated with GC prescriptions including: Demographics, Inflammatory comorbidities, GC-associated comorbidities and DMARDs.

Results: 7749 patients (47%) received at least one GC prescription during the follow up period. The median proportion of time spent on GCs was 24.3% (IQR 36.2%-64.2%). The median mean dose per treated patient was 7.5mg per day (IQR 5–15.7mg), the median minimum dose per treated patient was 5mg per day (IQR 2.5–7.5mg) and the median maximum dose per treated patient was 15mg per day (IQR 7.5–30mg).

Each 10-year increase in age was found to be associated with a 17% greater likelihood of being prescribed GCs (95%CI 1.14–1.20). There was no association with patient gender. Higher GC prescribing was seen in patients with inflammatory comorbidities of the lung: asthma (OR 1.59, 95%CI 1.43–1.76), chronic obstructive pulmonary disease (OR 1.65, 95%CI 1.35–2.01) and lower respiratory tract infections (OR 1.21, 95%CI 1.10–1.33). However, there was no association with inflammatory conditions of the skin or GI tract. The association with GC-associated comorbidities was less consistent. GC prescribing was higher in patients with cardiovascular disease (OR 1.27, 95%CI 1.05–1.53) and in current smokers (OR 1.22, 95%CI 1.13–1.32) but lower in patients with diabetes (OR 0.71, 95%CI 0.62–0.82) and high cholesterol (OR 0.86, 95%CI 0.76–0.97). There was no association with other GC-associated comorbidities including osteoporosis, avascular necrosis, myopathy, insomnia, depression, hypertension, peptic ulcer disease or pancreatitis. A previous GC prescription prior to RA diagnosis was the strongest predictor of ever use post-diagnosis (OR 9.38, 95%CI 8.41– 10.46). GC prescribing was lower with methotrexate (OR 0.81, 95%CI 0.66–0.98) and sulfasalazine use (OR 0.69, 95%CI 0.58–0.83), but higher with leflunomide (OR 1.76, 95%CI 1.19–2.61) and other DMARD use (OR 1.73, 95%CI 1.33–2.26).

Conclusion: The presence of certain comorbidities at diagnosis, in particular inflammatory lung conditions, influenced GC prescribing. GC therapy was prescribed more commonly in higher risk patients, including older patients and those with CVD. Other GC-associated comorbidities, such as diabetes and hyperlipidaemia, were associated with less GC prescribing.

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2034

A Treat-to-Target Strategy Preserves Work Capacity in Early Rheumatoid Arthritis (RA). Mihir D. Wechalekar[1], Steve Quinn[2], Susan Lester[3], Ella Shanahan[4], Robert Metcalf[5], E. Michael Shanahan[6] and Susanna Proudman[4]. [1]Flinders University School of Medicine, Adelaide, Australia, [2]Flinders University, Adelaide, Australia, [3]Queen Elizabeth Hospital, Woodville South, Australia, [4]Discipline of Medicine, Adelaide, Australia, [5]University of Adelaide, Adelaide, Australia, [6]Flinders University, Bedford Park, South Australia, Australia.

Background/Purpose: Historical data [(1)]indicate a third of patients with RA are unable to work within the first 5 years of diagnosis. Our aim was to quantify work disability in an inception cohort of patients with early (<12 months) RA (fulfilling ACR 1987 revised classification criteria) receiving treat-to-target combination DMARD therapy.

Methods: Patients received initial triple therapy (methotrexate, sulfasalazine and hydroxychloroquine) with escalation (using other DMARDs or biologic DMARDs) to achieve DAS28(ESR) remission. Patients completed an annual validated work and arthritis questionnaire. Random effect mixed modelling was used to assess associations between the primary outcome, average hours worked per week, and baseline prognostic factors, with subject entered as a random effect to account for correlated observations. Hours worked per week (HWPW) were compared with age, gender and period matched population averages.

Results: There were 541 observations on 139 patients. Patients were included in the analysis if they had complete data and were working at any time point, that is, those with at least one positive value for hours worked; this included 67 patients with 313 observations. The mean (SD) age at disease onset was 42.8 (11.0) years; 55/67 (82%) were women; median (IQR) duration of polyarthritis was 16 (12–28) weeks. The median (IQR) follow up time was 3 (2.0–5.2) years. At baseline, the proportion of patients in work at baseline was 67% and this did not significantly change with time (73% at the end of the follow-up period).

Males worked more hours; there was no significant loss of working hours over the mean follow-up period (Table 1). Anti-cyclic citrullinated peptide antibody positivity was associated with loss of working hours; there was no relationship between baseline or area-under-the-curve DAS28 and HAQ and working hours lost. When examined by profession 50% working as labourers

on enrolment gave up work on follow up as compared to only 7% of those in managerial roles. For the matched population averages HWPW increased by 3.7 over a comparable follow-up period (p=0.001).

Table 1.

	p-value
Males worked 14.5 (95% CI 6.4, 22.6) hours/ week more than females	<0.001
Patients with anti-cyclic citrullinated peptide (CCP) positivity were more likely [7.4 (95%CI 1.3, 13.7)] to reduce working hours	0.017
Loss of working hours over mean follow-up period was 0.85 (95%CI –1.65, 3.4)	0.52

Conclusion: In contrast to the era before the advent of more intensive treatment approaches, a treat-to-target strategy mainly using conventional DMARDs preserves work capacity in patients with RA over the first few years of disease. Patients with ACPA or in manual labouring roles were more likely to reduce working hours.

(1) Barrett EM et al. Rheumatology 2000;39:403-09.

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2035

Joint Distribution and Outcome in 350 Patients with Monoarthritis of Less Than 16 Weeks Duration: Data from a Multicenter Longitudinal Observational Study in Eastern Norway.

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Background/Purpose: Cohort studies are essential to provide better understanding of the prognosis of acute monoarthritis, but few studies have focused on this issue. Our objective was to study the joint distribution and 2-year outcome of patients with new-onset monoarthritis, with a particular focus on outcome according to the joint involved.

Methods: 1119 patients (age 18–75 years) with arthritis of less than 16 weeks duration were included in the NOR-VEAC study from 2004 to 2010. Patients with crystal arthritis, septic arthritis, osteoarthritis or arthritis due to trauma were excluded. 364 patients (33%) had monoarthritis (clinical synovitis of one joint only) at baseline. Follow-up data were available for 350 patients (96%), and 221 (63%) had 2-year follow-up data. Patients with incomplete follow-up were included to avoid bias, as more patients achieving versus not achieving remission tended to be lost to follow-up before 2 years.

Results: Median (25–75 percentiles) duration of joint swelling among the 350 patients with monoarthritis was 23 (7–48) days, mean (SD) age was 46 (14) years, 52.0% were females, 6.6% anti-CCP pos. (14% missing), 8.6% RF pos. (11% missing), 11% anti-CCP and/or RF pos. (14% missing). The most frequently affected joints were the knee (49.1%), ankle (16.9%) and wrist (14.0%) and relatively few patients had small joint involvement (table).

15 patients (4.3%) fulfilled the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA) at baseline; these had mostly wrist and small joint involvement. Two patients with clinical synovitis of the knee fulfilled the criteria as a result of additional tender joints. Nine additional patients fulfilled the criteria during follow-up, of whom 8 presented with large joint arthritis (table). No patient with ankle monoarthritis ever fulfilled the criteria, nor progressed to a clinical diagnosis of RA within 2 years of follow-up.

55 patients (16%) were diagnosed with reactive arthritis at baseline, 11 patients (3%) with psoriatic arthritis (PsA) and 3 patients (1%) with other spondyloarthritides (SpA). During follow-up only 5 more patients were classified as PsA and 2 more as other SpA. The patients finally diagnosed with PsA had monoarthritis of the knee (n=8), wrist (n=4), hand (n=2), elbow (n=1) and foot (n=1) at presentation. The corresponding numbers for other SpA were knee (n=2), ankle (n=2) and hip (n=1). In addition 5 (1.4%) patients were diagnosed as Lšfgren's sarcoidosis. In 261 patients (74.6%) the arthritis had resolved without DMARD treatment at last follow-up. 49 patients (14.0%) were prescribed with DMARDs, 188 (53.7%) received intra-articular corticosteroids, and 80 (22.9%) systemic corticosteroids.

Baseline and follow-up data according to joint distribution in 350 patients with monoarthritis

	Swollen joint at baseline	Fulfillment of RA criteria * at baseline	Fulfillment of RA criteria * later	DMARD use	Arthritis resolved **
	n=350	n=15 (4.3%)	n=9 (2.7%)	n= 49 (14.0%)	n=261 (74.6%)
Hand ***	23 (6.6%)	5 (21.7%)	0	5 (21.7%)	16 (69.6%)
Wrist	49 (14.0%)	5 (10.2%)	1 (2.3%)	14 (28.6%)	31 (63.3%)
Elbow	5 (1.4%)	0	0	1 (20.0%)	3 (60.0%)
Shoulder	7 (2.0%)	1 (14.3%)	2 (33.3%)	2 (28.6%)	4 (57.1%)
Hip	2 (0.6%)	0	0	0	2 (100%)
Knee	172 (49.1%)	2 (1.2%)	6 (3.5%)	23 (13.4%)	126 (73.3%)
Ankle	59 (16.9%)	0	0	1 (1.7%)	52 (88.1%)
Foot ****	30 (8.6%)	2 (6.7%)	0	3 (10.0%)	24 (80.0%)
Other*****	3 (0.9%)	0	0	0	3 (100%)

* 2010 ACR/EULAR classification criteria for rheumatoid arthritis.
** defined as no swollen joints at last contact and never used DMARDs.
*** metacarpophalangeal or interphalangeal joint.
**** tarsus, metatarsophalangeal or interphalangeal joint.
***** 1st carpometacarpal joint (2 patients), acromioclavicular joint (1 patient).

Conclusion: Few patients with acute or recent onset monoarthritis seem to develop chronic inflammatory joint disease over two years. The likelihood of developing RA or other chronic rheumatic diseases was lowest in patients with monoarthritis of the ankle.

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2036

Biologic Disease-Modifying Antirheumatic Drugs and Risk of High-Grade Cervical Dysplasia and Cervical Cancer in Women with RA.

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Background/Purpose: Human papillomaviruses (HPV) are causes of high-grade cervical dysplasia and cervical cancer. Persistent HPV infection, the major risk factor for cervical cancer, is associated with several factors including HPV genotypes, multiple sexual partners, history of sexually transmitted disease (STD), and immunosuppression. A recent large cohort study found a higher risk of high-grade cervical dysplasia and cervical cancer in patients with rheumatoid arthritis (RA) compared to non-RA patients. The objective of this study was to assess the risk of high-grade cervical dysplasia or cervical cancer related to use of biologic disease-modifying antirheumatic drug (DMARD) versus only non-biologic DMARDs for RA.

Methods: Using U.S. commercial insurance claims data (2001-12), we conducted a cohort study to examine the incidence rates (IR) of high-grade cervical dysplasia or cervical cancer in women who initiated biologic or non-biologic DMARDs for RA. The index date was defined as the date of the first biologic or non-biologic DMARD after ≥2 diagnoses of RA. Patients were required to have an enrollment period of ≥365 days prior to the index date for baseline covariate assessment. High-grade cervical dysplasia or cervical cancer was defined by a validated claims-based algorithm with a positive predictive value of ≥81%. The number of gynecologic (Gyn) visits or procedures during follow-up was also assessed. To control for potential confounders such as age, being sexually active, comorbidities including STD, medications, prior Papanicolaou test, and healthcare utilization, biologic DMARD initiators were matched to non-biologic DMARD initiators on the propensity score (PS) with a 1:1 ratio.

Results: 7,539 PS-matched pairs of biologic and non-biologic DMARD initiators were included with a mean age of 50 years. 39% had a Papanicolaou test at baseline. During a mean (SD) duration of active treatment of 1.4 (1.5) years, 20 developed high-grade cervical dysplasia or cervical cancer. The IR of high-grade cervical dysplasia or cervical cancer per 1,000 person-years was 1.12 in biologic DMARD initiators and 0.70 in non-biologic DMARD initiators. The hazard ratio was 1.63 (95%CI 0.62–4.27) for biologic DMARD compared to non-biologics (**Table**). The number of outpatient Gyn visits (Rate ratio [RR] 0.96, 95%CI 0.88–1.04) and Gyn procedures (RR 0.94, 95%CI 0.86–1.02) was not different between the groups.

Conclusion: Among women with RA, initiation of biologic DMARDs may be associated with a moderately increased, albeit not statistically significant, risk of high-grade cervical dysplasia or cervical cancer, although the absolute risk was low. Both biologic and non-biologic DMARD initiators had a similar number of Gyn visits and procedures during follow-up. Future

research should determine the need for more intensive cervical cancer screening strategy in RA patients.

Table. Risk of high-grade cervical dysplasia or cervical cancer associated with initiation of biologic versus non-biologic DMARDs: 1:1 propensity score matched as treated analysis

	Biologic DMARD (N=7,538)				Non-biologic DMARD (N=7,538)			
	Event	Person-years (PY)	IR * (95%CI)	HR (95%CI)	Event	Person-years (PY)	IR * (95%CI)	HR (95%CI)
High-grade cervical dysplasia or cervical cancer	14	12,452	1.12 (0.66–1.89)	1.63 (0.62–4.27)	6	8,536	0.70 (0.31–1.56)	Ref

* IR is per 1,000 person-years.
The propensity score model includes age, sex, calendar year, comorbidities, HPV vaccine, being sexually active, STD, other comorbidities, medication use including oral contraceptives and steroids, Pap test, HPV DNA test, and other health care utilization factors.

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2037

Incidence and Prevalence of Myasthenia Gravis in Rheumatoid Arthritis Patients with and without Treatment Compared with the General Population. Neil Accortt[1], Mary Anthony[1], Jennifer Schenfeld[2], Travis Wheeling[2], Anna Hassebroek[2], Cynthia O'Malley[1] and Michael Sprafka[1]. [1]Amgen, Inc., Thousand Oaks, CA, [2]Docs Global, Inc, North Wales, PA.

Background/Purpose: There is a dearth of information on the incidence rate of myasthenia gravis (MG) in the US and specifically among rheumatoid arthritis (RA) patients. RA patients have been shown to be at risk for other autoimmune diseases so we sought to describe the rate of MG among RA patients, with and without treatment.

Methods: We conducted a retrospective cohort study using an administrative claims database. There were 8 study cohorts: General population (GP); incident RA population regardless of treatment; and 6 RA sub-cohorts defined by treatment exposure. Inclusion criteria included a minimum of 2 years of continuous enrollment with pharmacy coverage between 01/01/2005 – 12/31/2011. To ensure incident RA, patients could not have any RA claims during the first 12 months of enrollment. RA patients were followed forward and assigned to exposure sub-cohorts: Untreated (RA-U), 3 cohorts of different disease modifying anti-rheumatic drugs (RA-DMARDS1, RA-DMARDS2, RA-DMARDS3); TNF-inhibitors (RA-TNF); and other biologic therapies (RA-OB). Patients could be in ≥ 1 sub-cohort. MG diagnosis was captured using diagnostic and procedure claims. Prevalent MG cases in the GP and RA cohorts were identified during the first 12 months of enrollment. Follow-up for GP began on day 366 following enrollment; for RA and RA-U it began on date they met the criterion for RA diagnosis, and for RA sub-cohorts it began on medication start date. Follow-up continued until MG diagnosis, disenrollment from the database, end of study, and for the sub-cohorts, 90 days after discontinuation or switch in treatment. Incidence rates and 95% confidence intervals per 100,000 person years were estimated for MG, excluding prevalent cases. Incidence and prevalence estimates were age- and sex- standardized to the GP.

Results: The mean age and sex distribution were 37.1 years and 52% female for GP and 56.3 years and 74% female for RA. Gender and age distributions in the RA sub-cohorts were similar to RA. Prevalence of MG was 24.3 per 100,000 in the GP cohort and 86.8 per 100,000 in the RA cohort while the incidence was 10.4 per 100,000 and 35.8 per 100,000 in the GP and RA cohorts, respectively. MG incidence was highest in the RA DMARD3 (azathioprine, cyclosporine, cyclophosphamide, gold salts or penicillamine) sub-cohort. Due to the small number of MG cases, there was no discernable incidence pattern in the other sub-cohorts. Sensitivity analyses allowing for different follow-up times or using different algorithms to define MG showed little difference in the results.

Conclusion: As with other autoimmune diseases, subjects with RA appear to be at a higher risk from MG than the general population. We found both the prevalence and incidence of MG to be 3–4 times higher among RA patients compared to GP, however, with the exception of the RA DMARD-3 cohort, treatment did not appear to influence the incidence of MG following RA diagnosis.

Table 1. Cases, exposure, incidence rates of Myasthenia Gravis

	GP	RA	RA Untreated	RA DMARD 1[a]	RA DMARD 2[b]	RA DMARD 3[c]	RA TNF[d]	RA OB[e]
N of Pts at Risk	**42,888,651**	**101,180**	**33,820**	**36,640**	**43,115**	**9,972**	**21,920**	**3,550**
PYE	122,274,542	298,174	73,592	51,781	68,168	8,215	36,193	3,697
No of Cases	6,532	72	22	20	20	17	11	3
Incidence rate[f]	10.4	35.8	52.7	91.9	38.8	219.1	37.3	52.2
(95% CI)	(10.1, 10.6)	(21.2, 50.3)	(3.8, 101.6)	(17.0, 166.8)	(16.1, 61.5)	(81.7, 356.5)	(12.4, 62.1)	(−8.6, 112.9)

Footnote:
a. RA pts had at least 1 prescription for chloroquine, hydroxychloroquine, or sulfasalazine
b. RA pts had at least 1 prescription for methotrexate, leflunomide or Tofacitinib
c. RA pts had at least 1 prescription for azathioprine, cyclosporine, cyclophosphamide, gold salts (auranofin, aurothioglucose), or penicillamine
d. RA pts had at least 1 prescription for certolizumab pergol, infliximab, adalimumab, golimumab, etanercept
e. RA pts had at least 1 prescription for abatacept, anakinra, rituximab or tocilizumab
f. Incidence Rate per 100,000 person-years, Age- and Sex- adjusted & Weighted to the Total MarketScan Population

Disclosure: N. Accortt, Amgen, Inc., 3, Amgen, Inc., 1; **M. Anthony**, Amgen, Inc., 1, Amgen, Inc., 3; **J. Schenfeld**, Amgen, Inc., 5; **T. Wheeling**, Amgen, Inc, 5; **A. Hassebroek**, Amgen, Inc., 5; **C. O'Malley**, Amgen, Inc., 1, Amgen, Inc., 3; **M. Sprafka**, Amgen, Inc., 1, Amgen, Inc., 3.

2038

Respiratory Cause Mortality Was Significantly Predicted By Incident Rheumatoid Arthritis (RA) and Higher Pre-RA Levels (0.50+ SD) of Soluble Interleukin-2 Receptor Alpha (sIL-2Rá): Results of a 21-Year Community-Based Cohort Survival Analysis. Alfonse T. Masi[1], Azeem Rehman[1], Huaping Wang[1] and Jean Aldag[2]. [1]University of Illinois College of Medicine at Peoria, Peoria, IL, [2]University of Illinois College of Medicince at Peoria, retired, Peoria, IL.

Background/Purpose: Interstitial lung disease (ILD) mortality is reported to be increased in RA (Bongartz T et al. A&R 2010; 62: 1583-91). However, non-malignant respiratory mortality has not been reported in population-based RA and CN subjects. This study aimed to analyze predictors of non-malignant respiratory cause mortality in a community-based cohort of incident RA vs non-RA control (CN) subjects as well as the relation of higher baseline levels of immunological biomarkers.

Methods: Total incident cases (n = 54) had onset of ACR-positive RA, 3 to 20 (mean 12) years, after cohort entry (n = 21,061 adults) in 1974. Cases were matched at entry with 203 CN by age, gender, and race (all Caucasian). All subjects (n=257) had baseline data on: demographic, cigarette smoking, and inflammatory or cytokine biomarkers (n = 7) tested on stored (−70°C) sera. A total of 113 deaths were identified from 1992 to 2013, and 100 of them had completed death certificates retrieved. Two investigators independently determined underlying causes of death from the completed certificate codes, without knowledge of RA vs CN status. The few differences in interpretation were also "blindly" resolved. Multiple imputation and aggregate methods were used to enter values for a minority of randomly missing test results on the analyzed biomarkers: acute serum amyloid A (ASAA); C-reactive protein (CRP); IL-1β; IL-1ra; TNFα; sTNF-R1, and sIL-2Rα. Biomarker values were normalized using z-scores within sexes to adjust for any dimorphic differences. Critical limits of biomarker levels were searched to identify associations with total mortality, e.g., 0.50+SE for sIL-2Rα. Non-malignant respiratory diseases included ICD-9 codes, 460–519, and ICD-10 codes, J00-J99. Cox regression models were used to estimate hazard ratios (HRs) for respiratory causes of death vs remaining subjects, adjusting for covariates.

Results: Non-malignant respiratory deaths occurred in 8 (14.8%) of 54 RA vs 5 (2.5%) of 203 CN, p = 0.001 by Fisher's exact test. The HR for respiratory deaths was 14.3 (95% CI 3.07–66.82), p = 0.001, in RA vs CN, after adjusting for cohort entry age, cigarette smoking, years of education, and the 7 immunological biomarkers. Respiratory death was independently predicted by: RA vs CN; entry age, and higher levels (0.50+SE) of sIL-2Rα, as shown in the below Cox survival model, adjusted for 9 additional covariates.

Conclusion: Respiratory deaths were significantly (p = 0.001) greater in incident RA (14.8%) than CN (2.5%), with an HR of 14.3 (3.07–66.82), and higher sIL-2Rα levels significantly (p = 0.001) predicted respiratory cause mortality, which deserve further investigation.

Variables in the Model	HR (95% CI)	P values
CN vs RA (CN=0, RA=1)	14.32(3.07-66.82)	0.001
Cohort Entry Age (yrs)	1.29(1.13-1.46)	0.000
sIL-2Rα (0.50+ SD), no = 0, yes = 1	37.65(4.68-302.90)	0.001
Degree of Smoking (7-scale)	1.01(0.65-1.59)	0.960
Sex (F= 0, M = 1)	2.71(0.57-12.90)	0.211
Completed Education (yrs)	0.95(0.72-1.24)	0.690
ASAA (0.0+ SD), no = 0, yes = 1	1.05(0.25-4.48)	0.948
CRP (0.0+ SD), no = 0, yes = 1	0.42(0.11-1.65)	0.214
IL-1β (continuous)	2.27(0.77-6.71)	0.139
IL-1ra (continuous)	1.61(0.51-5.12)	0.416
TNFα (continuous)	0.57(0.22-1.47)	0.243
sTNF- R1 (0.0+ SD), no = 0, yes = 1	1.21(0.32-4.63)	0.782

Disclosure: A. T. Masi, None; **A. Rehman**, None; **H. Wang**, None; **J. Aldag**, None.

2039

Among Persons Assayed with Lower Serum Interleukin-1 Beta (IL-1β) Levels, Serum Androstenedione (Δ4A) and Testosterone (T) Were Significantly Lower in a Community-Based Cohort of Rheumatoid Arthritis Multi-Years before Clinical Onset (Pre-RA) Than in Non-RA Matched Control (CN) Subjects. Alfonse T. Masi, Azeem A. Rehman and Jean C. Aldag. University of Illinois College of Medicine at Peoria, Peoria, IL.

Background/Purpose: Dysregulations in androgenic-anabolic (A-A) steroids and cytokines are recognized in RA and pre-RA subjects (Rheum Dis Clin N Am 2005; 31: 131-60). However, deviations in correlations of these interacting systems have not been reported. This study analyzed baseline serum levels of the IL-1 profile (IL-1β and IL-1ra), A-A steroids, and cigarette smoking in a cohort of pre-RA and CN subjects.

Methods: The community-based cohort enrolled 21,061 adults (12,381 F, 8,680 M) in 1974. Over 3–20 (median 12) yrs, 54 (36 F, 18 M) cases developed RA by 1988 ACR criteria. Four CN who did not develop RA were matched to each case on age (±2 yrs), sex, and race. Baseline stored (−70°C) sera were assayed in pre-RA-CN sets at national referral laboratories without knowledge of status. IL-1β and IL-1ra were assayed using ELISA immunoplates (R&D Systems Inc., Minneapolis, MN) and A-A steroids by RIA. Multiple imputation and aggregate methods were used to enter values for a minority of randomly missed test results. Biomarkers were normalized using z-scores within sexes to adjust for any dimorphism. Logistic regression searched for independent predictors of dependent lower vs higher IL-1β z-score subgroups. Predictors of A-A levels were identified by linear regression. Frequency distributions were determined for the dichotomous IL-1β subsets and the pre-RA vs CN subgroups with A-A steroids, IL-1ra, and baseline cigarette smoking (7-scale), and evaluated by Fisher's exact test.

Results: In 257 total subjects (54 pre-RA, 203 CN), lower (n=165) vs higher (n=92) IL-1β z-score subgroups strongly ($p < 0.0001$) associated with combined RA and CN lower vs higher IL-1ra frequencies (Table 1). Logistic regression confirmed that only IL-1ra levels predicted the IL-1β dichotomy, including 6 other variables in the model (Table 2). In 165 lower IL-1β subjects (36 pre-RA, 129 CN), pre-RA had significant deficits of higher Δ4A ($p < 0.0001$) and T ($p < 0.001$) vs CN (Table 1). Linear regression confirmed that the dependent A-A steroid levels were predicted by the pre-RA vs CN status at strengths equivalent to known negative correlations with age. In the 92 higher IL-1β subgroup, 9 (50%) of 18 pre-RA vs 8 (10.8%) of 74 CN had higher cigarette usage ($p < 0.001$), consistent with an inflammatory association of smoking and RA risk.

Conclusion: Androstenedione and testosterone levels were significantly lower in pre-RA than CN subjects who had lower IL-1β levels, whereas cigarette usage was respectively greater in the RA subjects who had higher IL-1β levels. The new findings support neuroendocrine immune interactions in the risk of developing RA.

Table 1. Frequency Distributions of Lower vs Higher and Total IL-1β z-Scores

Bivariates Subgrouped by Lower vs Higher Z-Scores	Lower IL-1β Z-Scores		Higher IL-1β Z-Scores		Total IL-1β Z-Scores	
	36 RA*	129 CN†	18 RA*	74 CN†	54 RA	203 CN
IL-1ra: Lower‡	21 (113)	92	9 (38)	29	30	121
: Higher	15 (52)	37	9 (54)	45	24	82
p-values (2×2 Frequencies)		0.158		0.434		0.642
Androstenedione: Lower	30	67	5	36	35	103
: Higher	6	62	13	38	19	100
p-values (2×2 Frequencies)		<0.0001		0.123		0.068
Testosterone: Lower	29	65	4	40	33	105
: Higher	7	64	14	34	21	98
p-values (2×2 Frequencies)		<0.0001		0.019		0.282
Clg7 Scale: Lower	32	119	9	66	41	185
: Higher	4	10	9	8	13	18
p-values (2×2 Frequencies)		0.508		0.0006		0.004

*In 54 RA alone, lower vs higher randrostenedione ($p < 0.0001$) and testosterone ($p < 0.0001$) correlated oppositely with lower vs higher IL-1β z-scores.
†In 203 CN alone, lower vs higher IL-1ra correlated positively with lower vs higher IL-1β z-scores, i.e. 92, 37, 29, 45 ($p < 0.0001$).
‡In 257 combined RA and CN, lower vs higher IL-1ra frequencies associated positively with lower vs higher IL-1β z-scores, i.e. 113, 52, 38, and 54 ($p < 0.0001$).

Table 2. Regression Analyses of Lower vs Higher IL-1β and Other Dependent Outcome Variables

Study Sample	N	Dependent Outcome Variable	Independent Predictors	p values	Exponent B	Non-significant Variables
Total subjects	257	Lower vs Higher IL-1β	IL-1ra	<0.001	2.269	Baseline age, sex, CN=0/RA=1, cigarettes (1–7), androstenedione, testosterone
Lower IL-1β	165	Androstenedione	CN=0/RA=1	0.001	−0.388	Sex, cigarettes
			Baseline age	<0.001	−0.411	Sex, cigarettes
Lower IL-1β	165	Testosterone	CN=0/RA=1	0.008	−0.207	Sex, cigarettes
			Baseline age	0.036	−0.163	Sex, cigarettes
Lower IL-1β	165	IL-1ra	Cigarettes	0.045	0.158	Baseline age, sex, CN=0/RA=1
Higher IL-1β	92	Androstenedione	None	NA	NA	Baseline age, sex, cigarettes, CN=0/RA=1
Higher IL-1β	92	Testosterone	Baseline age	0.012	−0.256	Sex, cigarettes CN=0/RA=1
Higher IL-1β	92	IL-1ra	Sex (F=0/M=1)	0.008	−0.285	Baseline age, cigarettes CN=0/RA=1

Disclosure: A. T. Masi, None; **A. A. Rehman**, None; **J. C. Aldag**, None.

2040

Opportunistic Infections in Patients Treated with Biologic Drug Therapy. Laura Encinas[1], Maria Haye Salinas[1], Veronica Saurit[1], Alejandro J. Alvarellos[2], Francisco Caeiro[1], Cristina Battagliotti[3], Ida Elena Exeni[4], Carla Gobbi[5], Bernardo Pons-Estel[6], Ingrid Strusberg[7], Sergio Paira[8], Eduardo Mussano[9], Maria Apaz[10], Ana Quinteros[11], Ana Capuccio[12], Mercedes De La Sota[13], Maria Larroude[14], Amelia Granel[15], Oscar Rillo[16], Enrique Soriano[17], Gustavo Citera[18], Diana Dubinsky[19], Mari Delgado[20], Analia Alvarez[21], Graciela Gómez[22], Gustavo Casado[23], Santiago Aguero[24], Monica Sacnum[20], Mercedes Garcia[20], Sidney Soares de Souza[25], Edson Javier Velozo[26], C Paruolo[20], Monica Patricia Diaz[27], Emilia Cavillion[28], Juan C. Barreira[29], Gimena Gómez[30] and E. Scheines[31]. [1]Hospital Privado de Córdoba, Córdoba, Argentina, [2]Hospital Privado Córdoba, Córdoba, Argentina, [3]Hospital de Niños Dr Orlando Alasia, Santa Fé, Argentina, [4]Sanatorio Parque, Cordoba, Argentina, [5]Hospital Còrdoba, Còrdoba, Argentina, [6]Sanatorio Parque, Rosario, Argentina, [7]Instituto Reumatológico Strusberg, Cordoba, Argentina, [8]Hospital Jose Maria Cullen, Santa Fe, Argentina, [9]Mariquita Sanchez 2304, Buenos Aires, Argentina, [10]Hospital de niños de cordoba, córdoba, Argentina, Argentina, [11]Centro Integral de Reumatología, Tucumán, Argentina, [12]Hospital cesar Milstein, Buenos Aires, Argentina, [13]Consultorio, Bahia Blanca, Argentina, [14]Consultorio, Buenos Aires, Argentina, [15]Hospital San Roque de Gonnet, La Plata, La Plata, Argentina, [16]Hospital Sirio Libanes, Buenos Aires, Argentina, [17]Hospital Italiano, Buenos Aires, Argentina, [18]Universidad de Buenos Aires, Buenos Aires, Argentina, [19]Hospital de Clinicas, Jose de San Martin, Capital Federal, Argentina, [20]consultorio, Buenos Aires, Argentina, [21]Cemic, Buenos Aires, Argentina, [22]Insituto de Investigaciones Medicas de la UBA, Capital Federal, Argentina, [23]Hospital Militar Central, Buenos Aires, Argentina, [24]Sanatorio Pasteur, Catamarca, Argentina, [25]REUMAR, Buenos Aires, Argentina, [26]Sanatorio Adventista Del Plata, Entre Rios, Argentina, [27]consultorio, Bariloche, Argentina, [28]Consultorio, Cordoba, Argentina, [29]British Hospital, Buenos Aires, Argentina, [30]Hospital Argerich, Buenos Aires, Argentina, [31]Hospital Manuel Rocca, Ciudad Autonoma de Buenos Aires, Argentina.

Background/Purpose: Biological drug therapy is frequently used to treat autoimmune diseases.

These drugs have an increased risk of infections, among them opportunistic infections.

To evaluate the frequency and type of opportunistic infections in patients with auto immune rheumatic diseases treated with biologic drugs compared to controls.

Establish whether disease and treatment features influence frequency and severity of opportunistic infections.

Methods: Biobadasar is database of rheumatic diseases patients treated with biologic drugs in Argentina. Created in 2010, it includes patients with a diagnosis according to accepted criteria treated with biologic drug therapy and controls not treated with biologic drugs.

Opportunistic infections (OI) are caused by pathogens (bacteria, viruses, fungi, parasites or protozoa), that usually do not cause disease in a healthy person (WHO).

The purpose of this work is to study the characteristics of opportunistic infections in patients with rheumatic diseases on biologic drug therapy compared with controls using the BIOBADAR database.

Statistical analysis was done using Chi-square test and t test with a significant $p \leq 0.05$.

Results: We included 2356 patients, 1275 54% on biologic drug therapy and 1081, 46% controls; 1862/2356, 79% were women, mean age 53.83 (SD6.02) years. Rheumatoid arthritis was the most common diagnosis 1829/2356, 77.6%.

Opportunistic infections were diagnosed in 40/1275 3.1% of patients treated with biologics, while 11/1081,1% of controls ($p = 0.0004$, OR 3.1, 95% CI 1.6–6.1).

Herpes Zoster was observed in 37 patients followed 6 Candidiasis, 2 Histoplasmosis, and one patient for each of the following, Cytomegalovirus, Pneumocystis jirovecii, hominis Blastocystis, Cryptosporidium, Echinococcus and Proteus.

Hospital admission was needed for 6/51, 11.7% of patients.

The median number of months from disease onset to the OI was 127 (IQR 46–223) months and from biological treatment onset to OI was 9 (IQR 4–18.5) months.

Table 1: Demographic Characteristics, Pathology and Treatment According to the Presence of Opportunistic Infections in Patients Treated with Biologics N: 1275

	With Opportunistic Infection (N:40)	Without Opportunistic Infection (N: 1235)	p	OR (IC95%)
Female n (%)	33 (82.5)	969 (72.5)	0.69	0.77 (0.33-1.76)
Years m±DS	**59.5 ± 14**	**53 ± 16**	**0.02**	
Month history M (RIQ)	60 (49-69)	56 (44-65)	0.07	
Neoplasia n (%)	**4 (10)**	**16 (1.3)**	**0.003**	**8.46 (2.69-26.59)**
Lymphoma n (%)	0	2 (0.2)	1	0.96 (0.95-0.97)
ischemic heart disease n (%)	1 (2.5)	18 (1.5)	0.45	1.73 (0.22-13.31)
Diabetes n (%)	3 (7.5)	78 (6.3)	0.73	1.2 (0.36-3.98)
kidney failure n (%)	**3 (7.5)**	**12 (1.0)**	**0.01**	**8.26 (2.23-30.5)**
Heart Failure n (%)	1 (2.5)	18 (1.5)	0.45	1.73 (0.22-13.31)
EPOC n (%)	0	26 (2.1)	1	0.96 (0.95-0.97)
Corticosteroids n (%)	**28 (70)**	**622 (51.0)**	**0.02**	**2.24 (1.12-4.44)**
Methotrexate n (%)	**17 (42.5)**	**892 (73.1)**	**0.00009**	**0.27 (0.14-0.51)**
Leflunomide n (%)	10 (25)	253 (20.7)	0.51	1.27 (0.61-2.64)
Sulfasalazine n (%)	1 (2.5)	96 (7.9)	0.36	0.30 (0.04-2.21)
Azathioprine n (%)	2 (5.0)	13 (1.1)	0.79	4.89 (1.06-22.43)

Conclusion: Opportunistic infections were more frequent in patients treated with biological drugs than in controls.

The most common opportunistic infection was Herpes zoster.

A history of cancer and renal failure, and concomitant treatment with corticosteroids were associated with of opportunistic infections.

Methotrexate therapy was not associated with OI.

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Performance of a Two-Step Latent Tuberculosis Screening Algorithm in Patients with Rheumatoid Arthritis, Psoriatic Arthritis or Ankylosing Spondylitis Prior to Treatment with Tumor Necrosis Alpha Inhibitors: Prospective Observational Data from the Biorx.Si Registry, 2014 Update.

Ziga Rotar[1] and Matija Tomsic[2]. [1]University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]BioRx.si, University Medical Centre Ljubljana, Ljubljana, Slovenia.

Background/Purpose: Reactivation of latent tuberculosis infection (LTBI) is a serious concern in patients treated with TNF-α inhibitors (TNFi). Conversely, TB chemoprophylaxis (CP) is time consuming, delays the initiation of required treatment, adds to the overall cost of treatment, and carries risk of adverse events itself. Since 2002 our national guidelines require following a two-step screening algorithm prior to the initiation of the first TNFi. The first step includes tuberculin skin test (TST), and a chest X-ray (CXR). If TST < 5 mm, and the radiologist finds no changes consistent with TB on CXR TNFi is prescribed. If any test is abnormal, the patient is evaluated by a pulmonologist who usually orders QuantiFERON TB Gold IT (QF) and decides whether TB CP (rifampicin/isoniazid 600/300 mg qd for 3 months) is required prior to TNFi treatment.

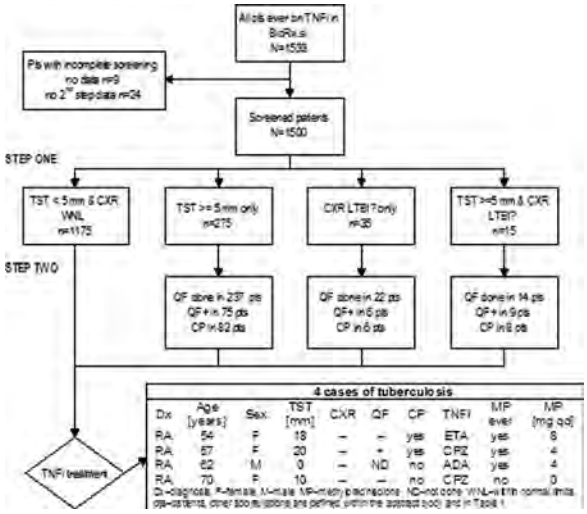
In February 2002 we showed that in a setting with low background annual TB incidence rate (IR) (i.e. 8.4 per 10^5) following of this algorithm resulted in TB IR of 0.11 (95% CI 0.01–0.38), and 0.16 (95% CI 0.02–0.58) per 100 person years (PY) overall, and in RA patients, respectively. The costly QF and CP were required in 13.9%, and 5.2% of patients, respectively. Our aim was to reevaluate the performance of this algorithm.

Methods: In March 2014 we cross-linked the data from the obligatory national registry of patients treated with biological DMARDs and the national TB registry to identify cases of TB in patients who were ever treated with TNFi.

Results: 1533 patients were treated with at least one TNFi for 3,846 PY (Table 1). Flow of patients through the screening algorithm and case patient characteristics are depicted in Figure 1. QF was performed in273/1500 (18.2%). 96/1533 (6.3%) patients received CP. Four cases of TB were identified, hence IR was 0.10 (95% CI 0.03–0.27), and 0.19 (95% CI 0.05–0.48) per 100 PY overall, and in RA patients, respectively. Only RA patients developed TB. The TB IR for certolizumab vs. other TNFi prescribed for RA was 1.3 (95% CI 0.16–0.47) vs. 0.1 (95% CI 0.01–0.37) per 100 PY ($p=0.027$ Fisher's exact test). The first two received appropriate CP (adherence was good, isolated M. tuberculosis strains were susceptible to CP) prior to TNFi, in the third patient the screening was stopped after 1st step and in the fourth one after the 2nd step. Interestingly, the 3rd case was screened for TB again before switching to rituximab. At repeated screening two months prior to TB diagnosis the TST was 10 mm, CXR neg. and QF–.

Table 1

	Rheumatoid arthritis	Ankylosing Spondylitis	Psoriatic arthritis
N (%)	**875 (57.1)**	**440 (28.7)**	**218 (14.2)**
% female	82	34	41
Age at screening (SD)	54.8 (12.1)	44.5 (13.4)	47.8(16.3)
% glucocorticoids at screening	46.9	/	/
% ever glucocorticoids	64.3	/	/
TNFi exposure years	2121	1205	520
% Adalimumab (ADA)	42.8	38.0	44.3
% Certolizumab (CZP)	7.1	0.0	0.3
% Etanercept (ETA)	36.7	29.1	26.3
% Golimumab (GOL)	3.2	9.0	12.1
% Infliximab (IFX)	10.2	23.9	17.0



Conclusion: At follow-up our two-step algorithm is still performing well. Further vigilance is warranted, especially in RA patients and those treated with CZP.

Disclosure: Z. Rotar, None; **M. Tomsic**, None.

2042

Tuberculin Conversion in Patients with Autoimmune Arthropathies Receiving Biologic Therapy.

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Aires, Argentina, [2]Instituto de Rehabilitación Psicofísica de Buenos Aires, Buenos Aires, Argentina, [3]Hospital San Roque de Gonnet, La Plata, La Plata, Argentina, [4]Hospital Gral. de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [5]Hospital General de Agudos Dr. E. Tornú, Buenos Aires, Argentina.

Background/Purpose: Patients receiving biologic DMARDs are at increase risk of developing tuberculosis (TB). Tuberculosis skin test (TST) is recommended to screen for TB infection prior starting biologic DMARDs. However, TST during treatment with biologic DMARDs is not routinely assessed. Objective: To investigate the frequency of TST conversion in patients receiving biologic DMARDs who initially had a negative result.

Methods: Patients with Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) and Spondyloarthritis (SPA) under treatment with anti-TNFα, Tocilizumab and/or Abatacept and who had a previous negative TST were included. A second TST was performed in all patients within a period of 2 months to 2 years after of the first TST. TST convertion was defined as a variation greater than 5 mm between the two tests. Sociodemographic and clinical data were recorded. Moreover, presence of comorbidities as alcoholism, diabetes (DM), malnutrition, poverty and overcrowding, previous infection, or contact with TB and concomitant treatment (steroids, DMARDs and biologic treatment) were also taken into account for the analysis. Chi^2 test, Mann Whitney U test and logistic regression analysis were performed.

Results: Eighty-five patients were included, 78.8% females, mean age 51.76±11.9. 74.1% had diagnosis of RA, 16.5% Psoriatic arthritis, 4.7% JIA, and 4.7% AS. 75.3% were receiving anti-TNF treatment, 15.3% tocilizumab, and 9.4% abatacept. 84.7% were receiving concomitant MTX, 21.2% leflunomide and 18.8% were on high doses of steroids. 12, 9% lived in overcrowded conditions, 10.6% had controlled DM, 5.9% had TB (complete treatment), and 2.4% reported having had contact with TB patients. Other risk factors were infrequent. TST conversion was observed in 9.4% (8 patients) being more common in males 62.5% vs. females 37.5% (p=0.009) and among those with longer mean disease duration 226±109 month in TST conversion patients vs. 130±105 month in TST negative patients (p=0.017). These results persisted even after adjusting for confounders. No association was observed with treatments and comorbid conditions. All patients with TST conversion received prophylactic isoniazid treatment, and one patient developed active TB and received appropiated treatment.

Conclusion: In patients receiving biologic DMARDs, TST conversion rate was 9.4% and was more frequent in males and in those with longer disease duration. No association was observed between TST conversion and underlying rheumatic disease, presence of comorbidities or treatments used.

Disclosure: O. L. Cerda, None; **M. D. L. A. Correa**, None; **A. Granel**, None; **A. I. Marcos**, None; **C. L. Giraldo**, None; **O. L. Rillo**, None; **G. Citera**, None.

2043

How Correct Are the Assumptions Made for Tuberculosis Screening Algorythms before TNF-Alpha Antagonists? Aysa Hacioglu[1], Yesim Ozguler[2], Sermin Borekci[3], Vedat Hamuryudan[1], Hanefi Deniz Kecebas[1], Ethem Koray Tascilar[2], Melike Melikoglu[4], Serdal Ugurlu[1], Emire Seyahi[1], Izzet Fresko[2], Huri Ozdogan[1], Sebahattin Yurdakul[1], Gul Ongen[3] and Gulen Hatemi[1]. [1]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [2]University of Istanbul, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, [3]University of Istanbul, Cerrahpasa Medical Faculty, Department of Pulmonary Diseases, Istanbul, Turkey, [4]Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey.

Background/Purpose: During the development of algorythms for screening latent tuberculosis before starting TNF-alpha antagonists, it is assumed that BCG vaccination causes false positive PPD and that concomitant medications such as corticosteroids cause false negative PPD results, favoring the use of Quantiferon or Elispot in these patients. Moreover it is assumed that INH is difficult to tolerate in this patient group. However we hypothesized that these assumptions may be wrong since there is a long time between BCG vaccination and TNF-alpha antagonist use in most of the rheumatology patients; there is no consistent data to show that disease modifying agents and corticosteroids in doses used for rheumatologic conditions are associated with negative PPD results; and INH is usually well tolerated by most of our patients.

Methods: We included patients who were prescribed a TNF-alpha antagonist for the first time between January 2011 and December 2012 in our clinic. Patients who had a previous tuberculosis infection were excluded since this could cause PPD positivity. We used logistic regression to analyse the determinants of a positive PPD (≥ 5mm). The variables were having a BCG scar, drugs (prednisolone, methotrexate, leflunomide, azathioprine, cyclosporine-A and cyclophosphamide), age, gender, diagnosis and disease duration. We also evaluated the frequency of being able to complete 9 months of INH treatment, the reasons for discontinuation and the frequency of developing tuberculosis among those who used and who did not use INH.

Results: A TNF-alpha antagonist was started in 961 patients (503 men, 458 women, mean age 41.28 ± 13.10 years, disease duration 6.54 ± 6.80 years). We excluded 75 patients who had previously used a TNF-alpha antagonist and 33 patients who had previous tuberculosis treatment. Among the remaining 853, an initial PPD test was available in 671 patients. At least one BCG scar was present in 592 patients. Logistic regression showed that BCG vaccination (OR=3.45, 95%CI 2.51–4.75, p<0.0001) and a diagnosis of ankylosing spondylitis (OR=1.79, 95%CI 1.21–2.65, p=0. 003) were associated with PPD positivity, while corticosteroid use was associated with a negative PPD (OR=1.96, 95%CI 1.09–3.51, p=0.023). INH was started in 525 patients and 391 had reliable data regarding INH use. 346 patients (87%) completed 9 months of treatment, 22 with interruptions. 45 had to stop INH after 3.85 ± 2.46 months. The reasons for discontinuation were hepatotoxicity in 26, allergic dermal reactions in 2, nausea in 2, dizziness in 2, pregnancy in 1, shortness of breath in 1, pancreatitis in 1 patient and non-willingness in 10 patients. Among the 26 who had to stop INH for transaminase elevation 13 were using concomitant methotrexate. None of the patients developed tuberculosis during our follow-up of up to 3 years.

Conclusion: BCG vaccination may still be a cause of false positive PPD in candidates for treatment with TNF-alpha antagonists. Corticosteroids seem to be associated with negative PPD while DMARDs are not. INH prophylaxis is generally well tolerated despite concomitant methotrexate. Longitudinal follow-up is necessary to determine the long term efficacy of INH treatment for preventing tuberculosis in these patients.

Disclosure: A. Hacioglu, None; **Y. Ozguler**, None; **S. Borekci**, None; **V. Hamuryudan**, None; **H. D. Kecebas**, None; **E. K. Tascilar**, None; **M. Melikoglu**, None; **S. Ugurlu**, None; **E. Seyahi**, None; **I. Fresko**, None; **H. Ozdogan**, None; **S. Yurdakul**, None; **G. Ongen**, None; **G. Hatemi**, None.

2044

Systematic Review of the Effect of Anti-Rheumatic Therapies upon Vaccine Immunogenicity. Megan Whittaker[1], James Galloway[1] and Sujith Subesinghe[2]. [1]King's College London, London, United Kingdom, [2]King's College Hospital NHS Foundation Trust, London, United Kingdom.

Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk of infection compared to the general population. The increased risk is attributable to factors relating to the underlying disease as well as the use of immunosuppression as the mainstay of management. Minimizing infection is an important challenge facing rheumatologists. Vaccination represents a unique opportunity to achieve this.

Current UK and European guidelines recommend annual influenza and one-off pneumococcal vaccination, however uptake of these vaccinations is poor. There is a paucity of data regarding vaccine immunogenicity in the context of rheumatic disease, and the evidence base for proving whether vaccinations reduce infections and associated mortality in RA is limited.

We conducted a systematic review of vaccination immunogenicity in the setting of anti-rheumatic therapy.

Methods: Studies evaluating the immunogenicity of either pneumococcal or influenza vaccinations in the setting of rheumatoid arthritis were identified using Pubmed, (Ovid, EMBASE). Search terms included (inflammatory arthritis OR rheumatoid arthritis) AND (immunization OR vaccination OR vaccine OR pneumovax OR prevenar).

This identified 3670 results, and1853 after limiting to humans. Abstracts were then manually reviewed by two authors (JG and MW) to identify articles reporting immunogenicity data for the vaccines of interest in adult patients with RA. The final selection identified 24 articles.

Results: The immunogenicity of vaccinations is influenced by factors including age, vaccine type, vaccine strain, disease and drugs. Concomitant drug therapy has the greatest effect on vaccine immunogenicity.

Two types of pneumococcal vaccines are currently licensed for use in the adult population, subunit polysaccharide (Pneumovax) and conjugate (Prevenar). Direct comparison between these vaccines demonstrated similar antibody responses.

Methotrexate, Rituximab and Abatacept are associated with decreased immunogenicity to both influenza and pneumococcal vaccination. Anti-TNF biologics, Tocilizumab and Sulphasalzine do not appear to have a negative effect on immunogenicity, although data is limited for the latter two.

Of the studies reporting the effect of vaccination on disease activity, none reported a significant change following vaccination.

Picture false

Table 1.

Drug	Control	Vaccine			
		Polysaccharide pneumococcal	Conjugate pneumococcal	Seasonal influenza	Pandemic influenza
Sulphasalazine	HV	(N) 1	No data	(N)1	No data
Methotrexate	HV	(Y) 2	(Y) 2	(N) 2[a] ⇓ 1	(Y) 4[b]
	RA	(N) (1) ⇓ (1)	No data	(Y) 2[c]	(Y)1
TNF	HV	(N) 2	(N) 1	(N) 3	(N) 3 (Y) 1[d]
	RA	(N) 3	No data	(N) 3 (Y) 1[e]	(N) 3
RTX	HV	No data	No data	(Y) 2[f]	(Y) 1
	RA	⇓ 2	No data	(Y) 3[g]	(Y) 1
Abatacept	HV	No data	No data	No data	(Y) 2
	RA	No data	No data	No data	(Y) 1
Tocilizumab	RA	No data	No data	(N) 1	No data

Key:
(N) no difference in response related to control
(Y) decreased response related to control
number= number of studies with findings with this result
[a]seroresponse decreased for one strain only, seroprotection not decreased vs RA controls
[b]seroprotection not decreased in 1 study
[c]seroresponse decreased for 2 strains, seroprotection not decreased
[d]third study found rates of seroconversion and seroprotection to be decreased for 1 of 7 serotypes only vs RA
[e]seroresponse decreased, but not seroprotection not decreased
[f]one study found seroresponse decreased to all strains. Seroprotection decreased to one strain only
[g]one study found decreased for 1 strain of 3 only.
Seasonal influenza vaccine: typically contains two strains of influenza A virus and one strain of influenza B virus (inactivated)
Pandemic influenza vaccine: contains one strain of influenza A H1N1, the agent responsible for the 2009 influenza pandemic

Conclusion: Although the humoral response to vaccination may be reduced by immunosuppressive agents, protective post vaccination titres are frequently achieved and accordingly vaccination is not precluded in this 'at-risk' population. Pneumococcal and influenza vaccination is safe in rheumatic disease and should be encouraged as part of the holistic management of RA patients. Challenges lie in determining the real world effectiveness of vaccination in RA, as well as how to maximise vaccine uptake through collaborative initiatives between primary and secondary care.

Disclosure: M. Whittaker, None; **J. Galloway**, None; **S. Subesinghe**, None.

ACR/ARHP Poster Session C
Epidemiology and Public Health (ARHP)
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

2045

Interaction Effects Between Genes and Blood Lead Level on a Composite Score of Multiple Joint Symptoms: The Johnston County Osteoarthritis Project. Youfang Liu[1], Amanda Nelson[2] and Joanne M. Jordan[3]. [1]University of North Carolina, Chapel Hill, NC, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]University of North Carolina Dept of Epidemiology, Chapel Hill, NC.

Background/Purpose: Previous studies suggested that blood lead level is associated with multiple joint symptoms. In this study, we conducted a Genome-Wide Gene-Environment Interactions analysis to search for genetic variations which may modify such associations.

Methods: Caucasians from the Johnston County Osteoarthritis Project (JoCo) with valid covariates and cleaned genotype data were included in this study. A composite score of multiple joint symptoms was calculated as the mean of summed 0–3 scores (none=0, 1=mild, 2=moderate, 3=severe) from seven joint sites including the hands, knees, hips and low back as previously reported. Whole blood lead level was measured by inductively coupled plasma-dynamic reaction cell-mass spectrometer analysis at the Centers for Disease Control and Prevention (Atlanta, GA). Genotyping was done using Illumina Infinium 1M-Duo bead arrays at Expression Analysis (Durham, NC). Original SNP data were imputed by software MACH using HapMap II Caucasian as the reference data. Linear models were applied across the genome-wide genetic data with adjustment for age, body mass index (BMI), sex, current alcohol use, smoking, and blood lead level. The residuals of the regression followed the normal distribution.

Results: Participants included 805 individuals, 63% of whom were women, with mean age 67 years (SD=10.5) and mean BMI of 30 (SD=6.4) kg/m^2. Log transformed blood lead level (median=0.53) was associated with multiple joint symptoms score with a p-value at 0.02. Two interactions between SNPs (rs2885880 and rs1598457) and lead significantly modified lead association with the multiple joint symptoms score (interaction P-value < 5x10E-08). Rs2885880 is located in gene RNF121 (ring finger protein 121). Based on Gene Ontology (GO) annotations, RNF121 might be related to zinc ion binding. Rs1598457 is located in gene GUCY1A2 (Guanylate Cyclase 1, Soluble, Alpha 2). Guanylyl Cyclases (GC) are a group of enzymes whose function requires the presence of metal ions such as Mg2+ or Mn2+. An additional promising interaction between fifteen SNPs (Table) and lead were identified (interaction p-values < 1E-06). For all the identified SNPs, the main effects of those SNPs were also significant with p-values < 0.05.

Conclusion: Two interactions between lead and SNPs were identified by the Genome-Wide Gene-Environment Interaction analysis. Those two SNPs are located in RNF121 and GUCY1A2, both related to handling of metals. These two genes may influence the impact of blood lead level upon symptoms in multiple joints. These results will require validation in independent datasets.

							Main		Interaction	
SNP	Gene	Chr	Position	A1	A2	Freq1	Beta	P-value	Beta	P-value
rs4850068	COLEC11	2	3633618	C	T	0.35	−1.20	1.41E-04	1.97	3.66E-07
rs7621594	CNTN6	3	1286742	A	G	0.87	1.94	1.49E-05	−2.74	4.76E-07
rs3772326	CNTN6	3	1288291	C	T	0.13	−1.94	1.49E-05	2.77	3.90E-07
rs3772317	CNTN6	3	1290911	A	T	0.87	1.95	1.14E-05	−2.80	2.98E-07
rs11708162	CNTN6	3	1292371	C	T	0.13	−1.96	9.60E-06	2.80	3.07E-07
rs11753124	AKAP7	6	1.32E+08	A	G	0.097	2.35	2.25E-05	−3.88	5.62E-07
rs12700548	OSBPL3	7	24824225	A	T	0.63	−0.74	1.97E-02	2.16	9.47E-07
rs2101116	CSMD1	8	3535362	A	G	0.38	1.26	2.62E-05	−2.03	8.34E-07
rs2086532	CSMD1	8	3535435	A	G	0.62	−1.26	2.79E-05	2.03	8.67E-07
rs2155141	RNF121	11	71320224	C	G	0.06	2.13	9.96E-04	−5.80	7.18E-07
rs7102192	RNF121	11	71325817	A	G	0.95	−2.13	9.63E-04	5.74	9.94E-07
rs7103210	RNF121	11	71326614	C	G	0.95	−2.13	9.63E-04	5.73	9.94E-07
rs10736781	RNF121	11	71328016	C	T	0.95	−2.13	9.66E-04	5.73	9.99E-07
rs2885880	RNF121	11	71333495	A	G	0.06	2.59	2.72E-05	−6.18	**1.09E-08**
rs1541306	RNF121	11	71385661	A	G	0.95	−2.13	9.62E-04	5.73	9.96E-07
rs12574588	GUCY1A2	11	1.06E+08	A	G	0.89	1.55	1.24E-03	−3.71	1.23E-07
rs1598457	GUCY1A2	11	1.06E+08	A	T	0.85	1.44	1.31E-03	−3.59	**3.64E-08**

Disclosure: Y. Liu, None; **Nelson**, None; **J. M. Jordan**, Algyomics, Samumed, Flexion, ClearView Healthcare Partners, Trinity Partners, 5.

2046

Perceived Discrimination in Individuals with Radiographic Knee and Hip Osteoarthritis. Rebecca J. Cleveland[1], Jordan B. Renner[2], Joanne M. Jordan[3] and Leigh F. Callahan[4]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]University of North Carolina Department of Radiology, Chapel Hill, NC, [3]University of North Carolina Dept of Epidemiology, Chapel Hill, NC, [4]University of North Carolina, Chapel Hill, NC.

Background/Purpose: To describe the characteristics of participants who reported feelings of discrimination among a cohort of participants with radiographic osteoarthritis (rOA) of the knee and/or hip in the Johnston County Osteoarthritis Project (JoCo).

Methods: A cross-sectional analysis was carried out on 766 individuals with rOA who were assessed in the second follow-up evaluation (2006–2010) of JoCo. rOA was defined as Kellgren-Lawrence grade ≥ 2 in at least one knee or one hip. Any perceived discrimination was assessed using a validated measure asking "how often have you been treated with less courtesy or less respect than other people?" Responses were assessed on a likert scale ranging from 1 to 4 (1=never, 2=occasionally, 3=frequently, 4=always). If indicating any discrimination, follow-up questions asked for the more specific reasons for discrimination such as gender, age, race, disability, education, religion and body size (yes or no). Descriptive characteristics were assessed and Chi-square statistics were performed to examine whether a participant perceived any type of discrimination, and if so, the specific reason for the discrimination. Additionally, we assessed discrimination according to whether an individual had knee or hip rOA, and according to demographic characteristics.

Results: Participants were on average 68 years old, mostly women (67.7%), African American (30.5%), and had a mean BMI of 31.5. There were 520 participants with knee rOA and 473 with hip rOA. Thirty-nine percent of participants reported feeling discrimination at least occasionally (36.7% occasionally, 2.5% frequently, 0.3% always). The most commonly

reported reason for perceived discrimination was disability (20.5%) followed by age (10.9%) and race (10.6%). Those with hip rOA reported any discrimination more often than those with knee rOA (40.6% vs. 36.5%) (Table 1.). Any perceived discrimination tended to be reported more often among those who were male and younger than age 67 and lived in areas with less poverty. Age discrimination was reported more often among those who lived in higher poverty areas ($p<0.01$) while those who reported discrimination for religion lived in lower poverty areas ($p=0.01$). African Americans reported discrimination for skin color more often than whites ($p<0.01$) and racial discrimination was reported more frequently among men ($p<0.01$).

Conclusion: Perceived discrimination is frequently reported in people with knee and/or hip rOA in this racially diverse population in North Carolina, with disability being the most commonly reported reason. Discrimination is also associated with several demographic characteristics that could have an important impact on rOA outcomes.

Disclosure: R. J. Cleveland, None; **J. B. Renner**, None; **J. M. Jordan**, Algynomics, 5, Samumed, 5, Flexion, 5, ClearView Healthcare Partners, 5, Trinity Partners, LLC, 5; **L. F. Callahan**, None.

2047

No Association of Serum Uric Acid with Hip Fracture Risk in Older Men and Women from the Framingham Original Cohort. Shivani Sahni[1], Kelsey Mangano[1], Katherine Tucker[2], Caroline Fox[3], Douglas P. Kiel[4], Xiaochun Zhang[5] and Marian T. Hannan[1]. [1]Institute for Aging Research, Hebrew SeniorLife, Dept. of Medicine Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [2]University of Massachusetts, Lowell, MA, [3]NHLBI's Framingham Heart Study and Center for Population Studies, Framingham, MA, [4]Institute for Aging Research, Hebrew SeniorLife, Dept. of Medicine Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [5]Institute for Aging Research, Hebrew SeniorLife, Roslindale, MA.

Background/Purpose: Serum uric acid (UA) has been linked with fractures in older men. Three different studies in older men showed conflicting results. The objective of this study was to examine the association of UA with hip fracture risk over 19.9y follow-up in men and women from the Framingham Original Cohort.

Methods: 2,969 men & women had measured UA concentration (mg/dl) at baseline (1973-76) and were followed for hip fracture until 2009. We used Cox-proportional hazards regression to estimate Hazard Ratios (HR) adjusting for age, sex and menopausal status (men, pre- and post-menopausal women), weight and height. An interaction between UA and sex was tested. Analysis was conducted on a combined sample of men and women, if the interaction term was not significant ($P>0.05$).

Results: The mean age was 66y (SD: 7.7, range: 53–85). 368 hip fractures occurred over the follow-up (mean of 19.9 years). The mean ± SD (mg/dl) uric acid at baseline was: 5.3 ± 1.4. Interaction between UA and sex was not statistically significant ($P=0.72$); therefore, men and women were analyzed together. An increase in one unit of UA was associated with a 7% decrease in hip fracture risk in the crude model [HR(95%CI): 0.93 (0.86–1.0); $P=0.048$]. Similar associations were observed when UA was analyzed as tertile categories (*P*-trend: 0.08). Participants in the highest tertile of UA [HR (95%CI):0.79 (0.61–1.03)] tended to have lower risk of hip fracture than those in the lowest tertile ($P=0.08$).These associations became non-significant after adjustment for covariates.

Conclusion: These results suggest that serum UA is not a risk factor for hip fracture risk in older adults.

Table. Association of serum uric acid (mg/dl) with risk of hip fracture in men and women

	N	HR(95% CI)	P-value
Crude	2,969	0.93 (0.86,1.0)	0.048*
Adjusted[1]	2,966	1.01 (0.93,1.1)	0.850

[1]Adjusted for: age, sex and menopausal status (men, pre-menopausal women, post-menopausal women), height and weight, *$P<0.05$.

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Disability in Discretionary Valued Life Activities and Self-Efficacy Explain a Significant Portion of RA Patients' Global Assessments. Patricia P. Katz, Jennifer Barton, Chris Tonner, Jinoos Yazdany, Mary Margaretten, Gabriela Schmajuk and Ed Yelin. University of California, San Francisco, San Francisco, CA.

Background/Purpose: Patient global assessments are components of RA disease activity calculations. Patient global assessments, however, do not consistently agree with physician assessments. This discrepancy leads to the question of how patients form global assessments, specifically the role of factors beyond generally recognized RA symptoms and health status. In this analysis, we evaluate the role of demographic factors, health status, functional limitations, psychological status, and disability in patient global assessments.

Methods: Data were from the Rheumatoid Arthritis Outcomes Study ($n = 438$), collected in structured telephone interviews conducted in English or Spanish. Patient global assessments were obtained with the item: "Considering all the ways that your arthritis affects you, how well are you doing?", with responses on a 0 – 100 (very poor – very well) scale. Demographic (age, sex, language, race/ethnicity, and education), health status (comorbid conditions, ratings of pain and fatigue, and current use of a DMARD, biologic therapy, or prednisone), functional limitations (measured with the Health Assessment Questionnaire, HAQ), depression, disability in valued life activities (VLAs), and self-efficacy were entered into sequential linear regression models to examine the contribution of each variable or group of variables to the overall disease assessment. The VLA scale was scored to provide mean difficulty in obligatory (i.e., necessary for independence and self-sufficiency), committed (associated with major life roles), and discretionary (e.g., socializing and engaging in activities that provide relaxation and pleasure) activities.

Results: Respondents were 88% female, mean age 60±13 years, 18% Spanish-speaking, and mean RA duration 23±12 years. Demographic factors alone yielded a model R^2 of 0.13 (Table 1). Addition of RA, health status and medications increased R^2 to 0.20; addition of functional limitations increased R^2 to 0.23. $R^2$was further increased by adding depression, VLA disability, and self-efficacy. Yet, the final model (Table 2) accounted for only 30% of the variation in patient global assessments, leaving the majority of such variation unexplained.

Conclusion: Difficulty in participating in discretionary valued life activities and self-efficacy – perhaps representing impact of disease on patients' daily lives and their evaluations of their ability to cope with RA – play significant roles in RA patients' global assessments of disease. The importance of these factors may provide insight into discrepancies between patient and physician assessments of disease.

Table 1. Summary of results of sequential linear regression models to estimate patient global assessments

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Model R^2	0.13	0.20	0.23	0.24	0.27	0.30
F (p-value) for difference in model from previous		4.24 (<0.001)	14.43 (<0.001)	9.26 (<.0001)	4.44 (<.0001)	17.58 (<.0001)

Model 1: age, sex, Spanish-speaking, African American, Asian, education
Model 2: Model 1 + comorbid conditions, pain, fatigue, use of DMARD, use of biologic, use of prednisone
Model 3: Model 2 + functional limitations (Health Assessment Questionnaire [HAQ])
Model 4: Model 3 + depression (Patient Health Questionnaire [PHQ] ≥ 5)
Model 5: Model 4 + VLA difficulty in obligatory, committed, and discretionary activities
Model 6: Model 5 + self-efficacy (Self-Efficacy for Managing Chronic Disease Scale)

Table 2. Variables in final regression model with $p<0.10$

	β	
Female	−6.9	
Spanish-speaking	−11.3	*
Asian	9.3	*
Less than high school education	−10.3	*
Fatigue moderate or greater	−12.5	***
Current use of biologic therapy	−5.1	*
Current use of prednisone	−4.8	*
Depression	−6.2	
VLA difficulty, committed activities	6.8	*
VLA difficulty, discretionary activities	−7.9	**
Self-efficacy	3.0	****

Model also included age, African American race, number of comorbid conditions, pain rating, use of DMARDs, and HAQ
* $p<0.05$; ** $p<0.01$; *** $p<0.001$; **** $p<0.0001$

Disclosure: P. P. Katz, None; **J. Barton**, None; **C. Tonner**, None; **J. Yazdany**, None; **M. Margaretten**, None; **G. Schmajuk**, None; **E. Yelin**, None.

2049

Fatigue Is a Risk Factor for Subsequent Functional Decline in SLE. Patricia P. Katz, Laura Trupin, Jennifer Barton, Gabriela Schmajuk, Mary Margaretten and Edward H. Yelin. University of California, San Francisco, San Francisco, CA.

Background/Purpose: In geriatrics, fatigue has been shown to be a harbinger of future functional decline. Fatigue is associated with poor function in systemic lupus erythematosus (SLE), but previous studies have not examined the longitudinal relationship between fatigue and poor function. In this analysis, we examine whether fatigue is a risk factor for subsequent functional decline among individuals with SLE.

Methods: Analyses use data from the Lupus Outcomes Study (2003–2011) obtained through annual structured telephone interviews. All participants have physician-confirmed SLE. Fatigue was measured with the SF-36 Vitality subscale. Scores range from 0–100, and higher scores reflect greater fatigue. Function was measured with the Valued Life Activities (VLA) disability scale, which has been validated in SLE. The VLA presents 28 life activities ranging from self-care to social, recreational, and work activities; respondents rate the difficulty they have in performing each on a 0 (no difficulty) to 3 (unable to perform) scale. Two VLA scores were calculated: mean difficulty and the percent of VLAs an individual was unable to perform. Analyses aimed to determine if fatigue at one time point (T1) was a risk factor for a decline in functioning between T1 and the subsequent year (T2). Declines were defined to approximate a clinically important difference: an increase of 0.5 SD in mean difficulty (0.3 points) or an increase ≥10% in the percent of VLAs unable to perform. Analyses include up to 8 pairs of years of interviews, using generalized estimating equations to account for multiple observations of individuals. Multivariate analyses controlled for age, sex, disease duration, disease activity (Systemic Lupus Activity Questionnaire, SLAQ), depressive symptoms (Center Epidemiologic Studies Depression scale, CESD), and presence of end-stage renal disease. A secondary analysis included only individuals under age 65.

Results: The primary analysis included 5105 observations of 1019 individuals, 92% female, with mean age 47±13 years, and mean disease duration 13±9 years. At initial interviews, mean fatigue score was 54.1±23.7. In 11.8% of paired observations, there was a functional decline by mean difficulty, and in 7.8%, a decline by percent of activities unable to perform. In bivariate analysis, T1 fatigue was a significant risk factor for subsequent functional decline between T1 and T2 (see table). After adjustment, T1 fatigue remained a significant risk factor for functional decline. Results of analyses including only age‹65 were similar.

Conclusion: Fatigue appears to be a risk factor for subsequent functional decline among individuals with SLE, even after accounting for other factors. Moreover, the risk is not confined to those age ≥65. High levels of fatigue may be a signal for impending functional decline, so can serve as an indicator for proactive intervention to prevent or minimize such declines.

Odds of functional decline associated with 10-point worsening of fatigue score

	OR (95% CI)	
	Bivariate	**Multivariate***
Total sample (5105 observations, 1019 individuals)		
Mean VLA difficulty (increase ≥0.5 SD, or 0.3 points)	1.11 (1.07, 1.15)	1.06 (1.01, 1.11)
% VLAs unable to perform (increase ≥10%)	1.28 (1.22, 1.35)	1.13 (1.06, 1.20)
Under 65 years only (4496 observations, 926 individuals)		
Mean VLA difficulty (increase ≥0.5 SD, or 0.3 points)	1.12 (1.07, 1.16)	1.05 (1.00, 1.11)
% VLAs unable to perform (increase ≥10%)	1.30 (1.23, 1.37)	1.13 (1.05, 1.22)

* adjusting for age, sex, disease duration, SLAQ, depressive symptoms, and ESRD.

Disclosure: P. P. Katz, None; **L. Trupin**, None; **J. Barton**, None; **G. Schmajuk**, None; **M. Margaretten**, None; **E. H. Yelin**, None.

2050

Knee Arthritis Is Positively Associated with Physical Impairment: Conclusion Based on Physical Examinations from a Cross-Sectional Study of 17708 Chinese Residents. Qiang Liu, Xu Tang Sr., Xu Wu, Zhengming Cao and Jianhao Lin. Peking University Health Science Center, Beijing, China.

Background/Purpose: The prevalence of knee arthritis is high in both urban and rural China. Although the association between knee arthritis and limitation of daily activity has been well documented in self-rated studies, no such conclusion has been made based on physical examinations from population-based study in China.

Methods: CHARLS (China Health and Retirement Longitudinal Study) is a population-based longitudinal survey among Chinese retired populations. During the baseline cross-sectional study period between 2011 and 2012, 17708 residents were recruited using door-to-door enumeration in 450 randomly selected communities in China. Subjects completed a home interview with a set of questions on self-rated health status and had a battery of performance-based physical examinations including test of balance, the 5 chair rise test and the gait speed. All the subjects were required to take the balance and the 5 chair rise test, while gait speed was examined only in those aged ≥60 years. Balance was evaluated by asking subjects to keep a stance with heel of one foot pressing the big toe of the other for at least 10 seconds. The 5 chair rise test was conducted using the regular method and gait speed was measured by recording the time each subject needed to pass 2.5 meters. Knee arthritis was only identified when both pain in knees and diagnosis of arthritis/rheumatism by a doctor were present. The association between knee arthritis and gait speed was examined using Linear regression, while the relation of knee arthritis to capacity of balance and the function of repeated sitting to standing was analyzed by Binary logistic regression, adjusting for age, sex, body mass index (BMI), smoking and drinking history, history of injury and hip fracture, and comorbidities.

Results: Among 17708 participants (men: 47.9%, mean age: 59.1 years, mean BMI: 23.4 kg/m^2), the prevalence of knee arthritis was 9.1%. 13521 (76.4%) and 13240 (74.8%) subjects, respectively, consented to take the test of balance and the 5 chair rise test. 5725 (72.7%) subjects participated the gait speed test. After adjustment for age, sex and other potential confounders, subjects with knee arthritis had increased failure rate of completing the test of balance (odds ratio=1.7, 95% confidence interval (CI): 1.3–2.3) and the 5 chair rise test (odds ratio=2.1, 95% confidence interval (CI): 1.5–2.9), as well as impaired gait speed (mean difference=0.204, 95% confidence interval (CI): 0.003–0.406) (Table).

Conclusion: Physical examination outcomes from the CHARLS study indicated that knee arthritis was positively associated with impaired physical function among the residents in China.

Knee arthritis	**Number of subjects**	**Number of subjects with failure**	**Prevalence (%)**	**OR (95% CI)***
Test of Balance				
Yes	1328	68	5.1%	1.7 (1.3-2.3)
No	12156	292	2.4%	1.0 (reference)
5 Chair Rise Test				
Yes	1280	59	4.6%	2.1 (1.5-2.9)
No	11921	243	2.0%	1.0 (reference)
Knee arthritis	**Number of subjects**	**Mean of Gait Speed (Second)**	**Mean Difference (95% CI)***	
Gait Speed				
Yes	666	5.019	0.204 (0.003–0.406)	
No	5061	4.700		

*adjusted for age, sex, BMI, smoking and drinking history, history of injury and hip fracture, and comorbidities

Disclosure: Q. Liu, None; **X. Tang Sr.**, None; **X. Wu**, None; **Z. Cao**, None; **J. Lin**, None.

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Modification of Effects of Household Income and Homeownership By Block Group Poverty on Health Outcomes in a Cohort of African Americans with Rheumatoid Arthritis. Rebecca Cleveland[1], Jennifer Smith[2], Antoine A. Baldassari[1], Beth L. Jonas[1], Doyt L. Conn[3], Larry W. Moreland[4], S. Louis Bridges Jr.[5] and Leigh F. Callahan[6]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]Ohio University, Athens, OH, [3]Emory Univ School of Medicine, Atlanta, GA, [4]University of Pittsburgh, Pittsburgh, PA, [5]University of Alabama at Birmingham, Birmingham, AL, [6]University of North Carolina, Chapel Hill, NC.

Background/Purpose: We previously found that household income less than $30k/yr and not owning a home influenced rheumatoid arthritis (RA) disease severity measures. We sought to further expand our findings to explore whether block group poverty (BGP) modified the associations between income and homeownership with RA health outcomes (RAHO).

Methods: We carried out a cross-sectional analysis in 898 African American participants with RA in the CLEAR Registry. We assessed the main effects of BGP (≥20% vs. <20%) on RAHO, and explored whether BGP modified the associations between income or homeownership and RAHO. Multivariate regression models for continuous, binary and count outcomes were used to estimate beta coefficients (β), odds ratios (OR) and prevalence rate ratios (PRR), respectively, and their 95% confidence intervals (CI). Associations between income and homeownership on RAHO were stratified by BGP and interaction p-values calculated. All analyses were

adjusted for gender, age, body mass index, disease duration, pack-years of smoking, number of comorbidities, current Methotrexate/Leflunomide use, current biologics use and study site.

Results: The cohort had a mean age of nearly 55 years, was largely female, and had disease duration of nearly 8 years. In regression models comparing the effects of BGP ≥20% with BGP <20% on RAHO, we observed strong positive associations with DAS, JSN and joint erosions as well as with HAQ score (Table 1). Stratification of the effect of income on RAHO by BGP poverty revealed no statistically significant interaction. However, when stratifying the analyses of homeownership, we observed effect modification that narrowly missed statistical significance (Table 2). Notably, among those who lived in an area with BGP ≥20%, non-homeowners had a 69% higher Joint Alignment and Motion (JAM) score than homeowners (PRR=1.69; 95% CI=1.09–2.62), whereas there was no association with JAM score for homeownership among those living in an area with BGP <20% (interaction p-value=0.11). Other associations which narrowly missed statistically significant interactions were observed for joint space narrowing, joint erosion, and DAS (interaction p-values=0.13, 0.05, and 0.14, respectively).

Conclusion: Our results suggest that block group poverty modifies the association between homeownership and joint damage measures. These findings suggest that further research is warranted to identify the underlying factors for these associations; for example monetary reasons precluding medication purchase or access to adequate medical care.

Table 1. Adjusted‡ estimates of cross-sectional associations of block group poverty≥20%≤ with disease severity of rheumatoid arthritis in the total cohort of CLEAR African Americans

Total Cohort (CLEAR I & II) (N=898)	Block group poverty ≥20%
Disease activity	
DAS (0-10)* (β)	**0.29 (0.08,0.50)¶**
CRP levels (log mg/L) (0-386) (β)	0.08 (−0.14,0.31)
No. of Joint swelling (0-42)*	1.07 (0.90,1.28)
No. of Joint tenderness (0-42)	1.14 (0.99,1.33)
Joint damage	
Erosion (0-180) (PRR)	**1.39 (1.01,1.90)¥**
JSN score (0-166) (PRR)	**1.28 (1.04,1.58)¥**
JAM score (0-126)* (PRR)	1.12 (0.89,1.42)
Autoantibody status	
ACPA, % Positive (OR)	1.20 (0.88,1.63)
IgA-RF, % Positive (OR)	1.05 (0.77,1.44)
IgM-RF, % Positive (OR)	0.97 (0.69,1.38)
Self-report health status	
Fatigue VAS (0-10) (β)	0.10 (−0.31,0.51)
Pain VAS (0-10) (β)	0.26 (−0.13,0.64)
HAQ Score (0-3) (β)	**0.15 (0.05,0.24)¶**
RAI Score (1-5) (β)	0.09 (−0.04,0.22)
HRQOL	
Limited activity days (0-30) (PRR)	1.03 (0.89,1.19)
Mentally Unhealthy days (0-30) (PRR)	0.95 (0.82,1.09)
Physically Unhealthy days (0-30) (PRR)	0.96 (0.85,1.07)

‡Adjusted for study site, gender, age, body mass index, disease duration, pack-years of smoking, number of comorbidities, current Methotrexate/Leflunomide use and current biologics
≤Referent=Block group poverty <20%
*90 outlying values omitted from analysis
€Odds ratios (95% confidence intervals)
¥P-value <0.05, ¶P-value <0.01
DAS: disease activity score; **CRP**: C-reactive protein; **JSN**: Joint-Space Narrowing; **JAM**: Joint Alignment and Motion
Score; **ACPA**: Anti-Citrullinated Peptide Antibodies; **IgA-RF**: Rheumatoid factor targeting Immunoglobulin A; **IgM-RF**: Rheumatoid factor targeting Immunoglobulin M; **VAS**: Visual Analog Scale; **HAQ**: Health Assessment Questionnaire (disability); **RAI**: Rheumatology Attitudes Index (helplessness); **HRQOL**: Health-Related Quality of Life.

Table 2. Adjusted‡ estimates for the association of household income <$30k≤ and not owning your home† with disease severity measures in the CLEAR cohort, stratified by block group poverty

	Household Income <$30k			Non-Homeowner		
RA outcome	**Poverty <20%**	**Poverty ≥20%**	**p€**	**Poverty <20%**	**Poverty ≥20%**	**p€**
Disease activity						
DAS (0-10)* (β)	0.31 (−0.02,0.64)	0.45 (0.04,0.85)¥	0.595	0.38 (0.07,0.70)¥	0.13 (−0.22,0.48)	0.141
CRP levels (log mg/L) (0-386) (β)	0.17 (−0.19,0.52)	0.03 (−0.40,0.46)	0.994	0.17 (−0.16,0.50)	0.13 (−0.24,0.50)	0.514
No. of Joint swelling (0-42)*	1.39 (1.06,1.82)¶	1.42 (1.03,1.98)¥	0.595	1.24 (0.96,1.61)	1.19 (0.87,1.61)	0.598
No. of Joint tenderness (0-42)	1.25 (0.99,1.57)	1.34 (1.02,1.76)¥	0.679	1.33 (1.07,1.66)¥	1.25 (0.98,1.59)	0.516
Joint damage						
Erosion (0-180) (PRR)	1.20 (0.74,1.94)	1.16 (0.54,2.51)	0.799	0.97 (0.62,1.52)	1.29 (0.68,2.44)	0.019
JSN score (0-166) (PRR)	1.29 (0.97,1.71)	1.30 (0.73,2.33)	0.962	1.08 (0.83,1.41)	1.37 (0.91,2.08)	0.143
JAM score (0-126)* (PRR)	1.26 (0.91,1.76)	1.22 (0.73,2.04)	0.852	1.23 (0.88,1.72)	1.69 (1.09,2.62)¥	0.109
Autoantibody status						
ACPA, % Positive (OR)	1.43 (0.90,2.28)	1.22 (0.68,2.21)	0.907	1.47 (0.95,2.28)	0.89 (0.54,1.49)	0.237
IgA-RF, % Positive (OR)	1.20 (0.74,1.95)	1.18 (0.66,2.10)	0.747	1.32 (0.83,2.08)	1.02 (0.61,1.69)	0.370
IgM-RF, % Positive (OR)	1.80 (1.06,3.06)¥	1.55 (0.83,2.90)	0.677	1.13 (0.68,1.87)	1.13 (0.65,1.95)	0.717
Self-report health status						
Fatigue VAS (0-10) (β)	0.33 (−0.29,0.95)	0.89 (0.09,1.69)¥	0.139	0.73 (0.16,1.31)¥	0.53 (−0.14,1.21)	0.802
Pain VAS (0-10) (β)	1.25 (0.66,1.83)μ	1.46 (0.73,2.19)μ	0.355	1.24 (0.69,1.78)μ	0.83 (0.21,1.45)¶	0.457
HAQ Score (0-3) (β)	0.40 (0.26,0.54)μ	0.30 (0.12,0.47)¶	0.538	0.26 (0.12,0.40)μ	0.18 (0.02,0.33)¥	0.549
RAI Score (1-5) (β)	0.46 (0.26,0.67)μ	0.52 (0.28,0.75)μ	0.677	0.37 (0.17,0.56)μ	0.43 (0.23,0.63)μ	0.878
HRQOL						
Limited activity days (0-30) (PRR)	1.27 (1.02,1.58)¥	1.23 (0.91,1.67)	0.935	1.16 (0.95,1.42)	1.20 (0.93,1.55)	0.508
Mentally Unhealthy days (0-30) (PRR)	1.20 (0.98,1.47)	1.44 (1.06,1.95)¥	0.285	1.25 (1.03,1.52)¥	1.08 (0.83,1.39)	0.329
Physically Unhealthy days (0-30) (PRR)	1.08 (0.91,1.29)	1.31 (1.04,1.65)¥	0.192	1.09 (0.92,1.28)	1.17 (0.96,1.42)	0.228

‡Adjusted for study site, gender, age, body mass index, disease duration, pack-years of smoking, number of comorbidities, current Methotrexate/Leflunomide use and current biologics
≤Referent=Annual household income ≥$30k; †Referent=Owning your home
€Interaction P-value
*90 outlying values omitted from analysis
¥P-value <0.05, ¶P-value <0.01, μP-value <0.001
DAS: disease activity score; **CRP**: C-reactive protein; **JSN**: Joint-Space Narrowing; **JAM**: Joint Alignment and Motion Score; **ACPA**: Anti-Citrullinated Peptide
Antibodies; **IgA-RF**: Rheumatoid factor targeting Immunoglobulin A; **IgM-RF**: Rheumatoid factor targeting Immunoglobulin M; **VAS**: Visual Analog Scale; **HAQ**:
Health Assessment Questionnaire (disability); **RAI**: Rheumatology Attitudes Index (helplessness); **HRQOL**: Health-Related Quality of Life.

Disclosure: R. Cleveland, None; **J. Smith**, None; **A. A. Baldassari**, None; **B. L. Jonas**, None; **D. L. Conn**, None; **L. W. Moreland**, None; **S. L. Bridges Jr.**, None; **L. F. Callahan**, None.

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Foot and Ankle Characteristics Associated with Falls in Adults with Rheumatoid Arthritis. Angela Brenton-Rule[1], Nicola Dalbeth[2], Priya Parmer[1], Sandra Bassett[1], Hylton B. Menz[3] and Keith Rome[1]. [1]AUT University, Auckland, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]La Trobe University, Bundoora, Victoria 3086, Australia.

Background/Purpose: People with rheumatoid arthritis (RA) have an increased risk of falls. The consequences of falls can be devastating including loss of confidence and independence, injury and death. The foot is a common site of pathology in RA and foot problems are reported in up to 90% of patients with established disease. Previous studies in non-RA populations have identified that foot and ankle problems are associated with falls and falls risk in older adults. The aim of this study was to determine whether foot and ankle characteristics are associated with falls in people with RA.

Methods: Adults with RA according to the 2010 ACR/EULAR classification criteria were recruited from rheumatology outpatient clinics in Auckland, New Zealand. All participants reported whether they had fallen in the preceding year, and the number of falls. The Prevention of Falls Network Europe (ProFanE) definition of, "an event that results in a person coming to rest unintentionally on the ground or other lower level", was used to identify falls. RA characteristics, common fall risk factors, and foot and ankle variables were measured. Foot and ankle testing included foot deformity, plantar sensation, muscle strength, ankle range of motion, gait speed, peak plantar pressures, postural stability, foot pain and self-reported foot impairment. Univariate parametric and non-parametric analysis compared fallers and non-fallers on all variables to determine significant differences. Logistic regression analysis identified variables independently associated with falls.

Results: Two hundred and one participants were prospectively recruited. At least one fall in the preceding 12 months was reported by 119 (59%) participants. Significant factors associated with falls in the univariate analysis are presented in Table 1. Fallers had significantly longer mean disease duration, more co-morbid conditions, slower gait speed, higher mid-foot peak plantar pressures and were more likely to have a history of stroke than non-fallers. Fallers also reported greater difficulty with the activities of daily living, increased fear of falling and greater self-reported foot impairment. In logistic regression analysis, including age, sex and all variables at a level of $p<0.15$ in the univariate analysis, increased mid-foot peak plantar pressures (odds ratio 1.12 [for each 20kPa increase], $p=0.037$) and self-reported foot impairment (odds ratio 1.16 [for each 3 point increase], $p=0.007$) were independently associated with a fall in the preceding 12 months.

Conclusion: Elevated mid-foot peak plantar pressures and self-reported foot impairment are associated with falls in people with RA. Assessment of foot deformity, foot function and self-reported foot impairment may be of benefit when considering falls prevention in people with RA.

Table 1. Significant factors associated with falls in univariate analysis. Data are presented as mean (SD) unless specified.

	Non-fallers n=82	Fallers n=119	*P* value
Clinical features			
Disease duration	13.6 (12.8)	17.4 (13.9)	0.03
HAQII	0.76 (0.60)	0.98 (0.62)	0.01
Number of co-morbid conditions	1.0 (0.9)	1.3 (1.1)	0.02
History CVA/TIA, no. (%)	0 (0)	9 (7.6)	0.03
Fear of falling (short FES-I)	11 (5)	13 (5)	0.002
Foot and ankle features			
6 metre walk time (s)	5.8 (2.1)	6.5 (2.9)	0.04
Peak Plantar Pressure mid-foot (Kpa)	100 (44)	122 (71)	0.048
Foot impairment ($LFIS_{AP}$)	12 (9)	16 (8)	0.002

HAQ, Health Assessment Questionnaire; FES-I, Falls Efficacy Scale-International; $LFIS_{AP}$, Leeds Foot Impact Scale Activities/Impairment subscale

Disclosure: A. Brenton-Rule, None; **N. Dalbeth**, None; **P. Parmer**, None; **S. Bassett**, None; **H. B. Menz**, None; **K. Rome**, None.

2053

Mortality Decreases in Patients with Rheumatoid Arthritis: a 15-Year Prospective Cohort Study. Joëlle van den Hoek[1], Hendriek C. Boshuizen[2], Leo D. Roorda[3], Gerard J. Tijhuis[4], Mike T. Nurmohamed[4], Trudi van den Bos[5] and Joost Dekker[6]. [1]Reade, Rehabilitation Rheumatology, Amsterdam, Netherlands, [2]National Institute of Public Health and the Environment, Bilthoven, Netherlands, [3]Amsterdam Rehabilitation Research Center Reade, Amsterdam, the Netherlands, Amsterdam, Netherlands, [4]Jan van Breemen Research Institute Reade, Amsterdam, Netherlands, [5]Academic Medical Center, Amsterdam, Netherlands, [6]VU University Medical Center, Amsterdam, Netherlands.

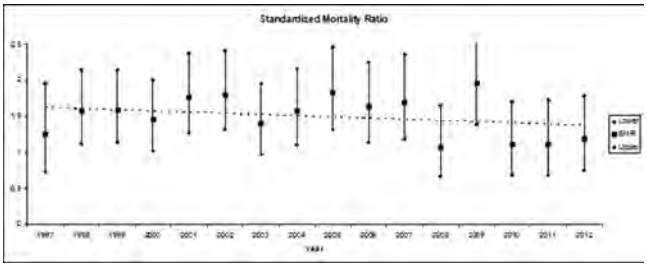
Background/Purpose: Patients with rheumatoid arthritis (RA) have a higher mortality risk than the general population, with similar patterns over the last decades. However, more recent studies show conflicting results. Given these conflicting results, there is an obvious need to evaluate the risk of mortality in patients with RA, over a long period, using more recent mortality data.

Objectives: To investigate a) the mortality in a clinical cohort of patients with established rheumatoid arthritis in comparison with the general Dutch population over 15 years, b) the trend in the mortality ratio during the study period, and c) the causes of death and compare these with the general population.

Methods: In 1997, a sample of 1222 patients was randomly selected from the register of a large rheumatology outpatient clinic in Amsterdam. Their mortality and causes of death between 1997 and 2012 were obtained from Statistics Netherlands. The Standardized Mortality Ratio (SMR) for all-cause mortality and the number of life-years lost in the study period were calculated. Linear poisson regression analysis was performed to evaluate change in all-cause SMR over time. Finally, the SMRs for cause-specific mortality were calculated.

Results: The mean age of the population at baseline was 60.4 (*SD* 15.4) years and 72.6% of the patients were women. The estimated SMR (95% CI) for all-cause mortality was 1.54 (1.41, 1.67) with about one life-year lost over the study period. The SMR decreased with 2% annually ($p = .05$). Mortality increased for diseases of the circulatory system, respiratory system, musculoskeletal system, and digestive system ($p < .05$).

Conclusion: The observed mortality among patients with RA was more than 50% higher than in the general population. More than one life-year was lost over 15 years and the mortality seemed to decrease over time. The most frequent causes of death were the same as those in the general population.



Annual Standardized Mortality Ratio and 95% Confidence Interval.

Disclosure: J. van den Hoek, None; **H. C. Boshuizen**, None; **L. D. Roorda**, None; **G. J. Tijhuis**, None; **M. T. Nurmohamed**, None; **T. van den Bos**, None; **J. Dekker**, None.

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Physical and Mental Functioning in Patients with Established Rheumatoid Arthritis over an 11-Year Follow-up Period: The Role of Specific Comorbidities. Joëlle van den Hoek[1], Leo D. Roorda[2], Hendriek C. Boshuizen[3], Gerard J. Tijhuis[4], Trudi van den Bos[5] and Joost Dekker[6]. [1]Reade, Rehabilitation Rheumatology, Amsterdam, Netherlands, [2]Amsterdam Rehabilitation Research Center Reade, Amsterdam, the Netherlands, Amsterdam, Netherlands, [3]National Institute of Public Health and the Environment, Bilthoven, Netherlands, [4]Jan van Breemen Research Institute Reade, Amsterdam, Netherlands, [5]Academic Medical Center, Amsterdam, Netherlands, [6]VU University Medical Center, Amsterdam, Netherlands.

Background/Purpose: Comorbidity in patients with Rheumatoid Arthritis (RA) is highly prevalent and plays an important role in determining RA related outcomes. Several studies have reported the negative association of comorbidity with functioning in general. The information about the association of specific comorbidities with functioning in patients with RA is limited. Evaluating specific comorbidities will provide valuable information for clinical practice and the management of patients with RA.

The aim of this study was to investigate the long term association of a wide range of specific comorbidities with physical and mental functioning in patients with RA.

Methods: Longitudinal data over a period of 11 years were collected from 882 patients with RA at study inclusion. Somatic comorbidity was measured at baseline, with a questionnaire including 20 chronic diseases, from which 9 categories of chronic somatic comorbidity were created. Comorbid depression was measured at baseline, with the Center for Epidemiologic Depression Scale. Physical functioning was measured with the Health Assessment Questionnaire (HAQ) and with the physical component summary of the Short Form 36 health survey (SF-36). Mental functioning was measured with the mental component summary of the SF-36. To determine the impact of specific comorbid conditions on functioning and on change in functioning we performed a longitudinal analysis.

Results: The mean age of the patients at was 59.3 (*SD* 14.8) years, 72% of the patients were women, their median disease duration was 5.0 (*IQR* 2.0–14.0) years, and 68% had ≥ 1 comorbid condition. The mean HAQ score for an average patient was 0.98 on average over the 11-years follow-up period. Circulatory conditions (mean HAQ score + 0.28) and depression (+0.38) were associated ($p<.05$) with low physical functioning according to the HAQ. An average patient with a circulatory condition had a mean HAQ score of 0.98 + 0.28 = 1.46. Circulatory (mean SF-36 score −3.23), respiratory (−2.74), musculoskeletal conditions (−2.85), cancer (−5.26) and depression (−3.36) were associated ($p<.05$) with low physical functioning according to the SF-36, while respiratory conditions (−2.28) and depression (−12.81) were associated ($p<.05$) with low mental functioning. The improvement in physical functioning according to the HAQ was 0.01 annually for an average patient. Genitourinary conditions were associated with a decline in physical functioning over time ($p<.05$). An average patient with a genitourinary condition declined in physical functioning with 0.01 – 0.04 = −0.03 annually. Digestive conditions were associated ($p<0.05$) with a decline in mental functioning.

Conclusion: Patients with specific comorbid conditions have an increased risk of low or declining functioning on the long term. Targeted attention for these specific comorbid conditions by clinicians and general practitioners is important. Diagnostics during the course of the disease, adequate referral to and working together with other specialists might improve physical and mental functioning in patients with RA.

Disclosure: J. van den Hoek, None; **L. D. Roorda**, None; **H. C. Boshuizen**, None; **G. J. Tijhuis**, None; **T. van den Bos**, None; **J. Dekker**, None.

ACR/ARHP Poster Session C
Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes: Research Focus
Tuesday, November 18, 2014, 8:30 AM– 4:00 PM

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Are There Immunological Abnormalities in Fibromyalgia Patients: Flow Cytometry Analysis. Robert S. Katz[1], Hannah Bond[2] and Daniel Pickrell[2]. [1]Rush Medical College, Chicago, IL, [2]Rheumatology Associates, Chicago, IL.

Background/Purpose: Fibromyalgia is not thought to have an immunological pathogenesis: However, few studies have been done to evaluate immunological abnormalities. We analyzed lymphocyte subsets in fibromy-

algia syndrome (FMS) patients and compared the results to established normal values in healthy controls.

Methods: 25 Patients (22 female and 3 male) with fibromyalgia meeting 2010 ACR criteria and followed in a rheumatology office practice had their blood analyzed by flow cytometry. Normal values for healthy controls were established by the University of Miami Immunology Laboratory where the analyses were performed.

Results: The following immunologic tests were abnormal in fibromyalgia patients

	Cd+4+CD38+	CD8+CD38+	CD8+CD95+	CD8+CD11a
Normal Cells/uL Range	0–138	125–595	160–473	139–472
FMS Patients Mean cells/uL	316.4	57.1	36.6	112.4

Conclusion: CD4+CD38+ helper Tcells were elevated in the FMS patients. CD8+CD38+, CD8+CD95+ and CD8+CD11a were reduced in FMS compared to normal healthy levels. This suggests possible increased T helper cell function and reduced CD8 cytotoxic/suppressor T cells in this group of fibromyalgia patients.)

The immune system could play a yet undetermined role in fibromyalgia.

Disclosure: R. S. Katz, None; **H. Bond**, None; **D. Pickrell**, None.

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Fibromyalgia Symptoms Beyond the Pain and Its Impact on the Patient. Abdelmoneim Helal[1], Dia MF Mohasseb[1], Noha AH El-Sawy[1] and Yousra H. Abdel-Fattah[2]. [1]Professor, Alexandria, Egypt, [2]Faculty of Medicine, University of Alexandria, Alexandria, Egypt.

Background/Purpose: Fibromyalgia (FM) has been promoted as the commonest cause of chronic, widespread non-articular musculoskeletal pain, stiffness and fatigue. Although pain is the central feature of FM there are other common clinical features associated with the disease including: sensations of muscle tension and morning stiffness, chronic headaches, non restorative sleep, fatigue and waking unrefreshed, post-exertional muscle pain, and cognitive dysfunction.

Methods: Twenty five female patients with a mean age of 30 years (18 to 57) diagnosed with primary FM according to 1990 American College of Rheumatology (ACR) diagnostic criteria as well as the 2010 ACR preliminary diagnostic criteria for FM were included in this study. Demographic characteristics and clinical data were collected from all patients. Pain severity, impact of the disease, sleep disturbance, severity of depression and anxiety where assessed by McGill Pain Questionnaire (MPQ), Fibromyalgia Impact Questionnaire (FIQ), visual analogue scale (VAS) for sleep evaluation, Hamilton Depression Rating Scale (HRSD) and Hamilton Anxiety Rating Scale (HAM-A) respectively.

Results: The median complaint duration was 24 months (3 to 180), and the median number of tender points was 14 (11 to 18). Fourteen patients (56%) complained of numbness with normal neurological examination. The median score of the MPQ presenting pain intensity - Visual Analogue Scale (PPI-VAS) was 80 (50 to100) and for the overall intensity was 3 (2 to 5). The FIQ showed a median score of 59.41 (41 to 76). Twenty two patients (88%) had irregular sleep patterns and poor sleep quality. Nineteen patients (76%) showed mild depression by HRSD with a median score of 14 (6 to 26). Fifteen patients (60%) showed mild anxiety by HAM-A with a median score of 15 (6 to 33).

There was a highly negative linear statistically significant correlation between the overall pain and sleep VAS ($p = 0.003$). There was as highly positive linear statistically significant correlation between the degree of anxiety and the degree of depression ($p<0.001$). Also the degree of anxiety & depression had a highly positive linear statistical significant correlation with the impact of the disease on the patients' life ($p<0.001$ & $p<0.001$).

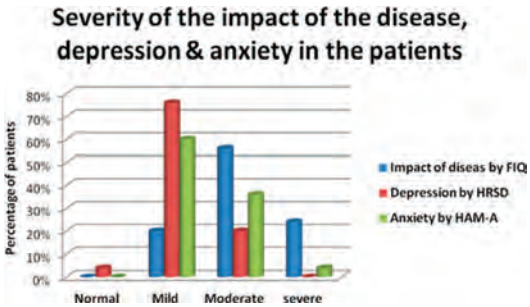

Figure (1): Distribution of FM patients according to severity of the impact of the disease, depression and anxiety.

Conclusion: Fibromyalgia highly influences the quality of life of the patients, and the severity of pain and associated symptoms significantly correlate with the impact of FM on the patients' life. There is a significant correlation between the severity of pain and the severity of associated symptoms of FM as depression and anxiety; in the same context depression as well as anxiety were found to be strongly associated with FM.

Disclosure: A. Helal, None; **D. M. Mohasseb**, None; **N. A. El-Sawy**, None; **Y. H. Abdel-Fattah**, None.

2057

Electrophysiological Evaluation of Autonomic Nervous System and Cutaneous Silent Period in Patients with Fibromyalgia Syndrome. Isil Ustun[1], Ilker Yagci[2], Gulseren Akyuz[3] and Feyza Unlu,Ozkan[4]. [1]Bagcilar Training Hospital, Istanbul, Turkey, [2]Marmara Universitesi T?p Fakultesi, Istanbul, Turkey, [3]Marmara University School of Medicine, Istanbul, Turkey, [4]Fatih Sultan Mehmet Training Hospital, Istanbul, Turkey.

Background/Purpose: This study was designed to investigate the autonomic nervous system (ANS) and spinal inhibitory circuits in FMS by electrophysiological studies and compare the results with healthy controls.

Methods: Thirty patients with FMS diagnosed according to ACR classification criteria and thirty 30 age matched healthy controls were recruited to the study. Patients were clinically examined and evaluated by Beck depression scale, SF-36 and fibromyalgia impact questionnare scales. Upper and lower extremity nerve conduction studies were performed to both groups to detect a large diameter peripheral neuropathy such as carpal tunnel syndrome or polyneuropathy. For evaluating the ANS, sympathetic skin response (SSR), R-R interval variation (Heart rate variability-RRIV) were studied. Spinal inhibitory circuits were assessed with cutaneous silent period (CSP).

Results: There were no statistically significant differences in distal latencies, amplitudes and nerve conduction velocities of motor and sensory nerves ($p>0.05$). Latencies and amplitudes of SSR recorded from median and tibial nerve, CSP latency and duration recorded from abductor pollicis brevis muscle and tibialis anterior muscle in FMS and healthy controls were also similar ($p>0.05$). Heart rate variability (RRIV) recorded from FS patients were significantly lower in comprasion to healthy controls ($p<0.05$).

Conclusion: Heart rate variability was the only significant abnormal electrophysiological parameter in patients with FMS which suggested that there was an ANS dysfunction in FMS. Despite SSR is one of the classical methods for the assesment of sympathetic fibers impairment to evaluate peripheral neuropathies, patients with FMS had no abnormality. We thought that this parameter is not sensitive enough to detect an abnormality in patients with FMS. We also evaluated cutaneous silent period (CSP) which refers to the brief interruption in voluntary contraction that follows strong electrical stimulation of a cutaneous nerve. The CSP is a protective reflex that is mediated by spinal inhibitory circuits and is reinforced in part by parallel modulation of the motor cortex. According to our study this reflex was not effected in patients with FMS.

Disclosure: I. Ustun, None; **I. Yagci**, None; **G. Akyuz**, None; **F. Unlu,Ozkan**, None.

2058

The Impact of Environmental Stress on Pain in Fibromyalgia Patients. Robert S. Katz[1], Ben J Small[2] and Susan Shott[3]. [1]Rush Medical College, Chicago, IL, [2]MacNeal Hospital, Berwyn, IL, [3]Rush University Medical Center, Chicago, IL.

Background/Purpose: Many fibromyalgia syndrome (FMS) report that their illness is significantly affected by environmental stress. We compared FMS and RA patients with respect to the impact of a variety of environmental conditions on their pain.

Methods: 211 office patients with either FMS (150; 130 women and 20 men; mean age 51±12) or RA (61; 45 women and 16 men; mean age 55±15) completed a questionnaire about the effect of various environmental conditions on their pain, rated as 1 = no effect, 2 = mildly worse, 3 = moderately worse, and 4 = severely worse. The two-sided Mann-Whitney test was done to compare FMS and RA patients with respect to these ratings, using 0.05 significance level.

Results: Compared to RA patients, FMS patients had significantly worse ratings for cold weather (2.7 ± 1.1 vs. 2.2 ± 1.0, $p = 0.003$), humidity (2.5 ± 1.1 vs. 2.0 ± 0.9, $p = 0.004$), rain (2.6 ± 1.1 vs. 2.2 ± 1.0, $p = 0.027$), weather change (2.8 ± 1.0 vs. 2.3 ± 0.9, $p = 0.004$), smells (1.4 ± 0.8 vs. 1.1 ± 0.4, $p = 0.002$), season change (2.2 ± 1.0 vs. 1.8 ± 0.9, $p = 0.018$),

loud noises (1.5 ± 0.8 vs. 1.1 ± 0.5, p = 0.001), emotional stress (2.6 ± 1.1 vs. 2.1 ± 1.0, p = 0.002), physical stress (2.7 ± 1.0 vs. 2.2 ± 1.0, p = 0.001), and air travel (1.8 ±1.0 vs. 1.4 ± 0.7, p = 0.007).

Conclusion: FMS patients, compared with RA patients, report significantly worse impact on their pain from many environmental conditions. Whether the etiology of fibromyalgia relates to central sensitization, hypervigilance, or an inherited somatoform trait, these patients are generally quite sensitive to environmantal stresses.

Disclosure: R. S. Katz, None; **B. J. Small**, None; **S. Shott**, None.

2059

Muscle Tension Is Increased in Fibromyalgia. Robert S. Katz[1] and Kerri Swiatnicki[2]. [1]Rush Medical College, Chicago, IL, [2]Rheumatology Associates, Chicago, IL.

Background/Purpose: Fibromyalgia patients have and widespread pain and tender muscles. Muscle tenderness was part of the older ACR criteria for the diagnosis of fibromyalgia. We studied muscle pressure in fibromyalgia patients.

Methods: A Stryker Pressure Monitor was inserted into the trapezius muscle to measure muscle pressure. Usually this monitor is used to detect anterior compartment syndrome in the swollen leg of a patient following trauma.

Results: 10 fibromyalgia patients meeting 2010 ACR criteria for the diagnosis and 5 controls were evaluated. The mean age of the fibromyalgia patients was 36.8; 9 females, 1 male. The mean age for the controls without fibromyalgia was 39.4; 3 females, 2 males. The fibromyalgia patients were, as expected, more tender than controls. Using dolorimetry, the pressure until an uncomfortable feeling occurred, was 8.9 in fibromyalgia, and 14.2 pounds of pressure in controls.

The mean muscle pressure, in millimeters of mercury using the Stryker Pressure Monitor was 36.8mmHg in fibromyalgia patients and 7.8mmHg in controls.

Conclusion: Muscle pressure is increased in fibromyalgia patients. This may be an important finding in explaining the widespread pain and muscle tenderness present in these patients. Methods to reduce muscle tension may be therapeutic.

Disclosure: R. S. Katz, None; **K. Swiatnicki**, None.

2060

Do Fibromyalgia Patients Have a Distinct Sleep Signature? Robert S. Katz[1] and Jessica L. Polyak[2]. [1]Rush Medical College, Chicago, IL, [2]Rheumatology Associates, Chicago, IL.

Background/Purpose: Fibromyalgia patients are known to have poor sleep, but no distinct sleep signature has been identified. We use a simple device called Jawbone to evaluate sleep in patients with fibromyalgia and controls.

Methods: Patients meeting the 2010 ACR criteria for the diagnosis of fibromyalgia were given the Jawbone device to wear on their wrist to monitor sleep. Controls also wore the same device. Patients' sleep was evaluated from the standpoint of number of awakenings, total duration of sleep, how deep was the sleep, and other factors.

Results: The total number of awakening of 12 of the fibromyalgia patients was 2.68, with the mean age being 46.5yrs, while the controls awakened an average of 1.2 times per night, with a mean age of 40.7.

The average period awake for the fibromyalgia group was 59 minutes, compared to 45.6 minutes for controls. Other totals were total sleep average 7.4 hours Fibromyalgia, 6.5 hours Controls. Sound sleep average, 4.0 hours Fibromyalgia, 3.2 hours Controls. Light Sleep average 3.4 hours fibromyalgia, 3.3 hours Controls. Total hours in bed, 8.4 hours fibromyalgia, 7.3 hours Controls. Time to fall asleep 17.7 minutes fibromyalgia, 27.7 minutes Controls. Out of the 12, most of the fibromyalgia patients were on a sleep aid, Elavil (7 patients), Doxepin (3 patients). The sleep study was preformed over one evening.

Conclusion: Fibromyalgia patients are known to sleep poorly. In this study we found that they awaken more often than controls and appear to be awake for longer periods of time. The reasons for this are unclear, but if there is a sleep pattern associated with fibromyalgia, it may simply be based on the number of awakenings in those without another clear factor, such as obstructive sleep apnea.

Using a sleep monitoring device, such as the Jawbone UP in this study, may be a simple method for patients and clinicians to monitor sleep, including the number of awakenings and the duration of non-sleeping time in FMS patients. One approach would be to evaluate patients' sleep before and after tricyclic treatment.

Disclosure: R. S. Katz, None; **J. L. Polyak**, None.

2061

Unexpectedly High Prevalence of Immunoglobulin Deficiency in Fibromyalgia. Xavier Caro and Earl Winter. Fibromyalgia Research and Treatment Center, Northridge, CA.

Background/Purpose: It has recently been shown that Fibromyalgia (FM) is commonly associated with clinical evidence of neuropathic pain language, laboratory evidence of small fiber and demyelinating neuropathy, and serologic evidence of a low-grade cytokinopathy. All of these findings suggest the presence of immune dysfunction leading to an immune mediated neural injury in FM. Any indication of a preexisting pro-inflammatory milieu in FM might help explain the presence of this immune dysfunctional state. Since primary immune deficiency (PID) states are well known to predispose to autoimmunity we surveyed a series of FM subjects for evidence of selected immunoglobulin (Ig) deficiency. We report our early findings here.

Methods: We retrospectively reviewed serum Ig concentration values on all FM subjects seen between July 2012 and December 2013 in an outpatient, rheumatology office setting. No other diagnosis precluded inclusion in the study unless it was likely that it might predispose to Ig deficiency. Charts on a total of 120 FM subjects were screened; 13 were excluded (e.g., family history of PID, SLE, Sjögren's syndrome, prior irradiation or cancer chemotherapy, or use of a DMARD). Data on 107 remaining FM subjects were reviewed; 38 (36%) had coincident RA (47 % of RA/FM subjects were positive for IgM RF). Ig deficiency was defined as an Ig value of at least 2 standard deviations (SD) below the mean reported by our reference laboratory; all deficient specimens were tested in duplicate. Ig abnormalities were confirmed by repeat analysis 6 – 9 weeks later.

Results: Our findings are listed below:

Serum Ig Deficiency in 107 FM Subjects Compared to Literature Based Controls

	Fibromyalgia Subjects				
Immunoglobulin	No. with Ig deficiency	No. without Ig deficiency	Prevalence of FM Ig Deficiency	Estimated Normal Prevalence†	P-value (2-tailed)††
IgG Subclass 1	48	59	45%	1/1200	<0.0001
IgG Subclass 2	13	94	12%	1/1200	<0.0001
IgG Subclass 3	47	60	44%	1/1200	<0.0001
IgG Subclass 4	6	101	6%	1/1200	<0.0001
IgA	12	95	11%	1/500	<0.0001
IgM	16	91	15%	3/100	0.003
IgE	4	103	4%	2.5/100	0.34
Any Ig	70	37	65%	1/1200	<0.0001

†Schroeder HW, et al: Immunoglobulin Structure and Function. *In* Fundamental Immunology. 7thEd. Ed: Paul, WE. Lippincott, New York 2013. †† Analysis was by X^2 test.

Our data showed that 71% of the FM subjects deficient in IgG Subclass 1 were also deficient in IgG Subclass 3. Thirty-one percent of those deficient in IgG subclass 2 were also deficient in IgG Subclass 4. A coincident diagnosis of RA did not significantly affect the prevalence of Ig deficiency. Of 56 FM subjects in whom Mannose Binding Lectin (MBL) was measured, 18 (32%) had levels <500 ng/ml, 9 (16%) had levels <100 ng/ml, and 8 (14%) had levels <50 ng/ml. The Odds Ratio (OR) for an FM subject having any Ig deficiency, compared to literature based norms, was 784 (95% CI 108 to 5703).

Conclusion: Our study shows that Ig deficiency, particularly IgG subclass deficiency, is a common accompaniment to FM. It also strengthens the argument that FM may be a disorder associated with immune dysregulation. The precise mechanism of this interaction remains unclear, but deserves further investigation.

Disclosure: X. Caro, None; **E. Winter**, None.

2062 WITHDRAWN

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Analysis of the Fibromyalgia Rapid Screening Tool Spanish Version to Detect Fibromyalgia in Primary Health Care Centers. B Casanueva[1], R Belenguer[2], Jv Moreno[3], J Urtiaga[4], B Urtiaga[5], F Genre[6], R López-Mejías[6], Jl Hernandez[7] and MA González-Gay[6]. [1]Rheumatologist. Rheumatology Service at the Specialist Clinic of Cantabria, Santander, Spain, [2]Rheumatologist. 12 de Octubre Hospital., Valencia, Spain, [3]Rheumatologist. Vall D'Hebron Hospital, Barcelona, Spain, [4]Professor of French., Madrid, Spain, [5]Professor of Spanish language and Literature, Madrid, Spain, [6]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, [7]Internist. Marqués de Valdecilla Hospital. IDIVAL, Santander, Spain.

Background/Purpose: The Fibromyalgia Rapid Screening Tool (FiRST) is a brief, simple and straightforward self-administered questionnaire with excellent discriminative value, of potential value for the detection of fibromyalgia in patients with diffuse chronic pain. To evaluate the usefulness of a Spanish version of the FiRST questionnaire for the detection of fibromyalgia (FM) in primary health care centers.

Methods: The Spanish translation of the original FiRST French questionnaire was carried out by Rheumatologists and Professors of French and Spanish Language. Translation was performed in second person, to enable self or hetero application (see annex). This study is prospective and multicenter, including 404 consecutive patients diagnosed with FM according to the 1990 ACR modified criteria and 2010 ACR criteria. FM was diagnosed by specialists in Rheumatology. We also included a control group of similar age and sex, consisting of 147 Rheumatoid Arthritis (RA) patients and 219 Osteoarthritis (OA) patients. The modified 2010 ACR criteria was applied, the number of tender points was evaluated, and the FiRST questionnaire and Fibromyalgia Impact Questionnaire (FIQ) were completed. Sensitivity, specificity and predictive value were analysed for each of the 6 items of the FiRST questionnaire and for the global score (5 or 6 positive items), as well as the correlation between the global score and other parameters. The results obtained were expressed as median and interquartile range and were analyzed with the Mann –Whitney U test using SPSS 15. P values less than 0.05 were considered significant.

Results: The mean age of patients with FM was 51.67 years. The mean FIQ score was 73.29. The median disease evolution was 12 years (IC: 6–21). Median tender points was 16 (IC: 14–18). 356 of 404 FM patients who met the 1990 ACR criteria and the 2010 modified criteria had a positive FiRST (scores 5 or 6). In the control group (AR + OA), 16 subjects had a positive FiRST and 343 a negative FiRST (scores or 4 or less). The sensitivity value for global score (5–6 positive ítems) with 95% interquartile range was 92 (88.9–95.1), the specificity 87.4 (80.8–94), positive predictive value 95.7 (93.3–98.1), and negative predictive value 78.2 (70.6–85.9). There was a significant correlation between total FiRST (scores 5 or 6) and Widespread Pain Index ($p < 0.0001$), Symptom Severity Scale ($p < 0.0001$), time to disease progression ($p < 0.0001$) and FIQ ($p < 0.0001$).

Conclusion: In patients with FM who met the 1990 ACR criteria and the 2010 modified ACR criteria, the overall sensitivity of the Spanish translation of the FiRST was slightly higher than in the original study. This questionnaire is easy to use and useful for the detection of FM patients in primary health care centers.

Disclosure: B. Casanueva, None; **R. Belenguer**, None; **J. Moreno**, None; **J. Urtiaga**, None; **B. Urtiaga**, None; **F. Genre**, None; **R. López-Mejías**, None; **J. Hernandez**, None; **M. González-Gay**, None.

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Assessment of the Spanish Version of the American College Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia. B Casanueva[1], F Garcia-Fructuoso[2], R Belenguer[3], C Alegre[4], R López-Mejías[5], F Genre[5], J.V. Moreno[6], J.L. Hernandez[7] and MA González-Gay[5]. [1]Rheumatologist. Rheumatology Service at the Specialist Clinic of Cantabria, Santander, Spain, [2]Rheumatologist. CIMA Hospital, Barcelona, Spain, [3]Rheumatologist. 12 de Octubre Hospital., Valencia, Spain, [4]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [5]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, [6]Rheumatologist. Vall D'Hebron Hospital, Barcelona, Spain, [7]Internist. Marqués de Valdecilla Hospital. IDIVAL., Santander, Spain.

Background/Purpose: Fibromyalgia (FM) requires an expert clinical examination that impedes an easy assessment of diagnostic criteria of American College Rheumatology (ACR) 1990 in some health settings. This problem delays its diagnostic, treatment, and referral to specialized services. To solve this drawback, a new screening criteria, the ACR Preliminary Diagnostic Criteria for FM was created. The aim of this study is to investigate the reliability and validity of the Spanish version of the 2010 ACR Preliminary Diagnostic Criteria for FM.

Methods: The traslation and cultural adaptation process of the ACR Preliminary Diagnostic Criteria for FM were adjusted to Spanish version to the perspective of the Rheumatology Spanish Society Study Group of Fibromyalgia. We recruited FM patients who met the previous criteria of the ACR 1990 diagnosed by a Rheumatologist, and other patients with diseases associated with chronic pain such as Rheumatoid Arthritis (RA) and Osteoarthritis (OA) who had not been diagnosed previously with FM, as control group, in a multicenter study. Informed consent was obtained and then baseline data were collected. Ethical Committee of the regional health authority approved the study protocol. FM were evaluated by tender points (TP), Fibromyalgia Impact Questionnaire (FIQ), Widespread Pain Index (WPI), and Symptom Severity Scale (SS). RA and OA patients were evaluated by WPI and SS. **Results** were expressed as median and interquartile range (IC) and data was analyzed with the Mann-Whitney U test. Sensitivity, specificity and predictive values were calculated. We used the SPSS 15 software for statistical analysis. P values < 0.05 were considered significant.

Results: This study included 1169 patients, divided into the FM group (777 females and 26 males) and non-fibromyalgia group (147 RA, and 219 OA). The mean of FIQ in the FM group were 73.29. The median of TP were 16 (Interquartile range 14–18). In the beginning of this study, the preliminary ACR 2010 criteria were satisfied by 665 FM patients. In the non-fibromyalgia group (RA + OA), 112 patients fulfill ACR 2010 criteria whereas 254 not achieve criteria. The comparison of FM patients who fulfill ACR 2010 criteria versus FM patients who no meet the criteria, exhibit significant differences in the number of TP ($p < 0.03$), FIQ ($p < 0.0001$), WPI ($p < 0.0001$) and SS ($p < 0.0001$). The sensitivity of the Spanish version of the modified 2010 ACR criteria was 87.7% (IC 95%: 85.3 to 90.1), the specificity was 69.4% (95% IC: 64.5 to 74,3), the positive predictive value was 85.6% (95% IC: 83.0 to 88.1) and the negative predictive value was 73.2% (95% IC: 68.4 to 78.0).

Conclusion: Our findings indicate that sensitivity of Spanish version of ACR preliminary diagnostic criteria (87.7%) were similar to the original study (88.1%). The specificity and predictive value of this version might be suitable for assessing FM among Spanish chronic pain populations.

Disclosure: B. Casanueva, None; **F. Garcia-Fructuoso**, None; **R. Belenguer**, None; **C. Alegre**, None; **R. López-Mejías**, None; **F. Genre**, None; **J. V. Moreno**, None; **J. L. Hernandez**, None; **M. González-Gay**, None.

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A Cross-Sectional Analysis of Psychological Symptoms, Sleep Quality, and Functional Balance in Fibromyalgia. Vicky Chen[1], William F. Harvey[2], Jeffrey B. Driban[2], Mei Chung[1], Lori Lyn Price[2] and Chenchen Wang[2]. [1]Tufts University School of Medicine, Boston, MA, [2]Tufts Medical Center, Boston, MA.

Background/Purpose: Previous studies suggest that FM may be associated with worse balance and falls. Balance requires the coordination of motor, sensory (ex. visual and vestibular), and cognitive abilities. These may be affected by the psychological symptoms present in FM. Depression, anxiety, and stress, have both cognitive (reduced attention) and somatic features (poor sleep quality and psychomotor slowing); and may therefore be related to the balance problems in FM. We intend to evaluate these relationships in this study.

Methods: We analyzed baseline data from a randomized trial comparing Tai Chi to aerobic exercise in individuals with FM. Balance was measured using a One-Leg Balance Test (OLBT): time standing on preferred leg with eyes closed; max time = 30 seconds. Psychological symptoms of depression, anxiety, and stress were measured using validated scales: Beck Depression Inventory (BDI-II); Participant-Reported Outcomes Measurement Information System (PROMIS) Emotional Distress rating of Anxiety; and Perceived Stress Scale (PSS). Higher scores reflect greater symptom severity. The mental component of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36 MCS) measured mental health related quality of life. Higher scores indicate better health status. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI). Higher scores reflect poor sleep quality. Chronic Pain Self-Efficacy Scale (CPSS) measured confidence in ability to perform a particular behavior or task. Higher scores reflect improved status. We used a logistic regression model to detect associations between balance times $\leq$3.02 seconds (defined by first quartile) and measures of psychological symptoms, self-efficacy, mental health-related quality of life, and sleep quality. Independent variables were analyzed in tertiles. Analyses were adjusted for age, gender, and BMI.

Results: 234 screened participants were included in our analysis. 90% were female. Mean age was 51.3 ± 11.8 years and mean BMI was 29.7 ± 6.8 kg/m^2. The median performance on OLBT was 4.7 seconds. **Table 1** shows the odds ratios for OLBT $\leq$3.02 seconds and BDI-II, PSS, SF-36 Mental Component, PROMIS anxiety, PSQI, and CPSS. Better sleep quality and fewer depressive symptoms were weakly associated with improved balance, but no significant associations were found between balance and measures of psychological symptoms and sleep quality.

Conclusion: We were unable to demonstrate any significant associations between balance and psychological symptoms or sleep quality. Small sample size may limit data interpretation and evaluation of the results. We recom-

mend that future studies assess factors more directly related to balance such as muscle strength, proprioception, and attention. Such research is critical to understanding the mechanisms underlying balance problems in FM and may identify novel therapeutic targets for future longitudinal studies.

Table 1. Descriptive Statistics and Odds Ratios: Adjusted for age, sex, and BMI.

Measure (range)	Tertile (Minimum, Maximum)	Odds Ratio (95% CI) One Leg Balance Test With Eyes Closed ≤3.02 seconds	P-Value
BDI-II (0-63)	Lowest (0.0,14.0)	REFERENCE	
	Middle (15.0, 26.0)	**1.23 (0.51, 2.99)**	0.65
	Highest (27.0, 61.0)	**1.47 (0.59, 3.69)**	0.41
PSS (0-40)	Lowest (0.0, 16.0)	REFERENCE	
	Middle (17.0, 23.0)	1.03 (0.45, 2.36)	0.93
	Highest (24.0, 40.0)	0.70 (0.27, 1.83)	0.47
SF-36 MCS* (0-100)	Lowest (18.0, 33.8)	REFERENCE	
	Middle (33.9, 43.4)	1.25 (0.52, 3.02)	0.60
	Highest (43.5, 66.8)	0.86 (0.35, 2.12)	0.75
PROMIS Anxiety 6a (36.3-82.7)	Lowest (36.3, 56.3)	REFERENCE	
	Middle (57.6, 61.3)	0.65 (0.27, 1.50)	0.35
	Highest (62.6, 82.7)	0.76 (0.32, 1.81)	0.54
PSQI (0-21)	Lowest (1.0, 9.0)	REFERENCE	
	Middle (10.0, 14.0)	**1.45 (0.59, 3.56)**	0.41
	Highest (15.0, 21.0)	**1.45 (0.56, 3.75)**	0.43
CPSS* (0-10)	Lowest (1.0, 4.0)	1.13 (0.47, 2.71)	0.78
	Middle (4.13, 6.0)	0.73 (0.73, 0.31)	0.48
	Highest (6.1, 10.0)	REFERENCE	

BDI-II=Beck Depression Inventory Second Edition; PSS=Perceived Stress Scale; SF-36 MCS=Medical Outcomes Short Form-36 Mental Component Summary; PROMIS=Participant-Reported Outcomes Measurement Information System; PSQI=Pittsburgh Sleep Quality Inventory; CPSS=Chronic Pain Self-Efficacy Scale
*Higher scores indicate better outcomes (for other measures, higher scores indicate greater symptom severity)

Disclosure: V. Chen, None; **W. F. Harvey**, None; **J. B. Driban**, None; **M. Chung**, None; **L. L. Price**, None; **C. Wang**, None.

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Ultra Orthodox Religious Orientation Associated with Reduced Rates of Pain, Anxiety and Fatigue in a Population Based Study. Valerie Aloush and Jacob N. Ablin. Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

Background/Purpose: Chronic pain, disturbed sleep and fatigue, as well as anxiety and depression, are symptoms characteristic of the fibromyalgia syndrome. These symptoms, as well as the syndrome itself, have often been associated with the effect of traumatic life events, as well as with external stress. Cognitive parameters, such as internal locus of control, are considered to have a positive effect on fibromyalgia symptoms, can be correlated with neuroimaging findings and are considered a target of cognitive behavioral therapy. On the other hand, spirituality and religiosity, characteristics which imply reliance on an external source of strength, are considered to be sources of resilience in the face of adversity.

The effect of religiosity on the spectrum of symptoms characteristic of fibromyalgia is not known.

Objective: To evaluate the effect of extreme religiosity on symptoms characteristic of the fibromyalgia syndrome in an Israeli population survey.

Methods: As part of a broader study, a telephone survey was conducted among 2030 Individuals residing in two Israeli towns, Sderot and Ofakim. As previously reported, these two similar populations were chosen to represent two basic conditions, i.e. a state of ongoing stress caused by continues cross – border missile attacks on Sderot, versus a state of relative normal conditions (Ofakim).

As part of the study protocol, individuals responding to the survey were questioned regarding their religious orientation. Individuals were thus ranked as belonging to either 'Haredi' (ultra – orthodox) Jewish level of religiosity, 'Orthodox', and 'religious' 'conservative – religious', 'conservative – not religious' or 'secular'. Haredi Jews belong to a highly traditional and relatively homogeneous religious group and adhere to strict traditions which encompass every aspect of life (e.g. clothing, diet etc).

Individuals were additionally questioned regarding the presence of symptoms including pain, fatigue, anxiety, depression, irritable bowel etc. Responses were ranked on a scale between 0 (no symptom present) and 10 (extreme symptom present).

Results were analyzed using one-way ANOVA with Tukey post- hoc test for multiple comparisons, using SPSS-17 software.

Results: Haredi individuals (174), reported significantly lower levels of sleep disturbances (mean 224) compared to all other individuals (total – 1780) ($P<0.01$).

Haredi individuals reported significantly lower levels of pain (mean – 2.9 vs. 3.7) lower levels of anxiety (mean 2.7 vs 4.5) and depression (mean – 1.2 vs 2.8) as compared with all other groups ($p<0.01$). No significant difference in the rate of IBS symptoms was observed.

Conclusion: Ultra-orthodox religiosity may be associated with reduced levels of symptoms, including pain, sleep disorders as well as anxiety and depression and may modulate the effect of stress and trauma on these symptoms. These results constitute a novel aspect in the analysis of the effects of locus-of-control and belief on these symptoms and on the association between religious faith and resilience. Further research may shed additional light on the role of spirituality/religious faith and on the mechanisms involved in these apparent protective effects.

Disclosure: V. Aloush, None; **J. N. Ablin**, None.

2067

Understanding the Factors Influencing Time to Diagnosis in Fibromyalgia. Howard Amital[1], Yaeli Bar-On[2], Varda Shalev[3], Dahlia Weitzman[3] and Gabriel Chodick[4]. [1]Department of Medicine B, Center for Autoimmune Diseases, Sheba Medical Center, Tel-hashomer, Israel, [2]Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel, [3]Maccabi Healthcare Services, Tel Aviv, Tel-Aviv, Israel, [4]Healthcare Services, Tel Aviv, Tel-Aviv, Israel.

Background/Purpose: Fibromyalgia (FM) is a chronic debilitating disorder considered to be part of a spectrum of central sensitization syndromes. The diagnosis of FM is a complex one, affected by many different factors including stigmatization of the disease, confounders such as comorbidities and different characteristics of patient and doctor.

Aim: Investigating the time passing from initial complaints till final diagnosis by an expert rheumatologist, and delineating the patient and physician characteristics affecting that time, using the comprehensive database of a large HMO in Israel.

Methods: Using a retrospective database search we identified patients diagnosed with FM by a rheumatologist or at release from hospitalization during ('confirmed FM patients'), and sex and age matched FM-free enrollees. Different complaint patterns were tested, to ascertain time of initial complaints. The pattern with the best combination of sensitivity and specificity was applied on an FM population of all patients diagnosed by a *primary physician*, rheumatologist, or at release from hospitalization, during the same period ('primary physician population'). Patient and primary physician factors associated with time between initial complaints and FM diagnosis were assessed. A multilevel generalized mixed linear model with a log-linked gamma distribution was used to account for clustering of patients associated with the same primary physician.

Results: Our study included 4,603 'confirmed FM patients', of whom 90.8% were women, with a mean age of 50.63 years (±11.37). The complaint pattern chosen, as time of initial complaints, comprised of >= 4 complaints within 6 months. This pattern was found in 73.2% (1,944/2,656) of the 'confirmed FM patients', 18.4% (1,685/9,173) of the FM-free patients. Applying this pattern on the primary physician population, revealed a mean time to diagnosis of 4.7±3.6 years. Within this time, the mean (SD) time that FMS patients were associated with the 'physician at diagnosis' was 2.9±2.8. The patient factors most significantly associated with a longer time to diagnosis, were older age, female gender and low socioeconomic status. The physician characteristics most significantly associated with a longer time to diagnosis were older age, internal or general specialty vs. family specialty, and physician's medical studies in West vs. East Europe.

Conclusion: The time to diagnosis of FM is significantly influenced by patients a and physician characteristics. This knowledge can contribute to future research and to better planning of physician education, concerning this disease.

Disclosure: H. Amital, None; **Y. Bar-On**, None; **V. Shalev**, None; **D. Weitzman**, None; **G. Chodick**, None.

2068

Joint Hypermobility Syndrome and Postural Orthostatic Tachycardia Syndrome (HyPOTS). Artan Kaso and Ali Askari. University Hospital Case Medical Center, Cleveland, OH.

Background/Purpose: Joint hypermobility syndrome (JHS) is a chronically disabling disorder manifested as a widespread musculoskeletal pain and/or fatigue, in the presence of generalized joint hypermobility. It is often masquerading as Fibromyalgia or Chronic fatigue syndrome. It is a condition that is often overlooked by clinicians.

Methods: Currently in our clinic, we have observed 25 patients between 22 and 58 yr who were diagnosed with JHS using the Brighton Criteria (1). All of them presented with one or more of these symptoms: chronic fatigue,

generalized musculoskeletal pain (arthralgias and myalgias), pre-syncope, palpitations, dizziness caring the diagnosis of fibromyalgia. They do not have any Marfanoid features or certain types of Ehlers-Danlos syndrome or skin involvement.

Out of 25 patients 16 (64%) had a positive diagnostic tilt table test consistent with the diagnosis of postural orthostatic tachycardia syndrome (POTS), 6 (24%) have not had a tilt table test done yet (financial, non compliance, etc) and 3 (12%) had a negative tilt table test.

Patient	Age	Gender	*Symptoms of Autonomic dysfunction	Tilt table test
1	22	F	+	+
2	39	F	+	+
3	38	F	+	+
4	28	F	+	+
5	32	F	+	Not done
6	40	F	+	-
7	37	F	+	+
8	28	F	+	+
9	32	F	+	+
10	48	F	+	-
11	36	F	+	+
12	32	F	+	+
13	38	F	+	+
14	39	F	+	+
15	36	F	+	+
16	35	F	+	-
17	35	F	+	Not done
18	26	F	+	+
19	33	F	+	Not done
20	22	F	+	+
21	36	F	+	Not done
22	33	F	+	+
23	55	F	+	+
24	58	F	+	Not done
25	28	F	+	Not done

*Patient presented with Symptoms of Autonomic dysfunction like, orthostatic hypotension, palpitation, dizziness, passing out, fatigue.

Results: We have noticed that most of these patients are young female with a mean age of 35 with a presentation consistent with fibromyalgia or chronic fatigue syndrome, however further work up showed presence of autonomic dysfunction clinically and confirmed by tilt table test in 64%. By applying standard of care treatment for POTS with fludrocrotison, increasing water and salt intake, using Ted Hose stocking, they showed improvement in their clinical presentation.

Conclusion: We conclude that there is a selective group of patients with JHS who have autonomic dysfunction which can contribute to the clinical presentations of these patients. These patients frequently are misdiagnosed as having Fibromyalgia or Chronic fatigue syndrome.

We have acronymed this entity "HyPOTS".

Potential manifestations of autonomic dysfunction include cardiac dysrhythmias, postural orthostatic tachycardia syndrome, orthostatic hypotension and orthostatic intolerance. Mechanisms leading to such phenomena in JHS patients may include weakened vascular tissue elasticity and impaired peripheral vasoregulation as a consequence of adrenoceptor or neuronal abnormalities (6, 7).

The pathophysiological basis for these symptoms needs to be further explored.

IRB approval for chart review was gained from University Hospital Case Medical Center.

Disclosure: A. Kaso, None; **A. Askari**, None.

2069

Investigation of the Effects of Physical Exercise on the Control Mechanisms of Cutaneous Circulation in Patients with Fibromyalgia Syndrome. Emre Esen and Alp Cetin.MD, Ankara, Turkey.

Background/Purpose: Sedentary lifestyle and disabling widespread pain in patients with fibromyalgia syndrome (FMS) may alter cardiovascular functions and can induce endothelial dysfunction. We evaluated cutaneous microvascular functions and their correlations with severity of disease assessed by revised fibromyalgia impact questionnaire (FIQ) and pain visual analog scale (VAS) in FMS patients, before and after participation in a moderate intensity 4-wk aerobic physical exercise program.

Methods: Forty female FMS patients without any known cardiovascular diseases and 20 healthy age-matched female controls were included in the study. Cutaneous blood flow was measured by a laser Doppler flowmeter (LDF) at the volar skin site of the forearm. Spectral analysis of LDF signals was used to assess the relative contribution of control mechanisms. The local thermal hyperemia was used to test the microvascular functions.

Results: Exercise improved pain VAS (from 8.5±1.5 to 4.7±1.4; $p<0.0001$) and FIQ scores (from 69.7±7.5 to 43.7±6.4; $p<0.0001$) and, improvement in myogenic and neurogenic mechanisms showed negative correlations with increase in FIQ scores. In contrast, cardiac signal was positively correlated with the FIQ scores, after exercise. Endothelial function was under the influence of pain, and basal nitric oxit (NO) activity was positively correlated with pain VAS.

Conclusion: These results suggest that the microvascular functions are impaired in FMS patients and, improvement in FIQ/pain score and the enhancement in vascular functions are possible by moderate exercise training.

Disclosure: E. Esen, None; **A. Cetin**, None.

2070

Elevated Serum Leptin Concentrations in a Subset of Fibromyalgia Patients with High Inflammatory Markers. Anne Quismorio[1], John Solyman[2], Lisa Asfahani[1] and Samy Metyas[3]. [1]Covina Arthritis, Covina, CA, [2]Research Associate, Covina, CA, [3]Assistant Clinical Professor Of Rheumatology, Covina, CA.

Background/Purpose: Previous studies suggest heterogeneity in the presentation of fibromyalgia (FM) with differences in biological variables including elevated sedimentation rate (ESR), cytokine profile, and hormone levels. Whether these variables identify subgroups within FM population remains to be established. We have previously reported primary FM patients with elevated inflammatory markers(Metyas SK, *et al*. Ann Rheum Dis, 2007;66(Suppl II):625.).

The diagnosis of FM is largely clinical, and specific biomarkers have yet to be identified. Vectra®DA is a multi-biomarker disease activity score, validated to measure disease activity in rheumatoid arthritis (RA). It is a commercially available test designed to measure serum concentrations of 12 biomarkers in RA.

The purpose of the study is to measure biomarkers using the Vectra®DA in FM patients with elevated inflammatory markers.

Methods: A cross-sectional, prospective study of 33 patients seen in an outpatient-based rheumatology practice in Los Angeles County was undertaken. Each met the 2010 ACR classification criteria for FM and had elevated ESR and/or CRP. None had clinical evidence of RA or other systemic rheumatic disease. Tests were negative for rheumatoid factor, anti-CCP antibodies, and HLA-B27. Serum specimens were tested using the Vectra®DA.

Results: Mean age was 43.5 years, 94% were female and 6% were male. The Vectra®DA was elevated for all patients with a mean score of 46.5 (range 30 to 84, or moderate to high activity). Among the twelve biomarkers (including IL-6 and CRP) serum concentrations were within the range reported in RA except leptin. 45% of subjects had leptin concentrations exceeding the range reported in RA (1–45 ng/mL). The mean leptin was 42.3 ng/mL (range 30–81 ng/mL).

There was a positive correlation between leptin concentration and BMI in the entire cohort; however, this correlation was not observed in the patient subgroup with leptin levels above the range in RA ($P= 0.6$). CRP but not ESR was positively correlated with the Vectra®DA score.

Conclusion: We have identified a subset of FM patients with elevated ESR and/or CRP. The elevated Vectra®DA scores support the concept of an associated inflammatory process in this subset of patients. The elevated levels of leptin in this subset, independent of BMI, suggest that factors other than obesity may account for this elevation. The emerging evidence that leptin plays a significant pro-inflammatory and immunomodulatory role warrants further investigation in the pathogenesis of this clinical subset of FM. Understanding this clinical subset may lead to different diagnostic and therapeutic strategies in FM.

Disclosure: A. Quismorio, None; **J. Solyman**, None; **L. Asfahani**, None; **S. Metyas**, Crescendo Bioscience, 8.

2071

Chronic Widespread Pain Versus Multi-Site Pain: Does the Distribution Matter? Marcus Beasley and Gary J. Macfarlane. University of Aberdeen, Aberdeen, United Kingdom.

Background/Purpose: The ACR 1990 diagnostic criteria for fibromyalgia includes a definition for chronic widespread pain (CWP) that depends on a particular distribution of pain sites. The new proposed ACR 2010 criteria instead has a Widespread Pain Index which takes into account the number of sites only. The purpose of this analysis was to see, amongst persons reporting multi-site pain, if the distribution of pain sites has any association with a number of potential risk markers after adjustment for the number of sites.

Methods: The MUSICIAN survey was a general population survey aimed at identifying people with CWP for an intervention study. A questionnaire was sent by post to adults registered at family doctors in two areas of the United Kingdom. Questions included age, gender, employment status, smoking behaviour, height, weight, and questions on pain included a manikin in 35 sections to indicate the location of the pain. Respondents were included in the analysis who indicated that they had between 3 and 16 areas of pain, and that the pain had lasted 3 months or more. (People with less than 3 sites could not meet the ACR 1990 definition of widespread pain, while most of those with more than 16 sites did). Participants were classed as having pain that was widespread or not according to the ACR 1990 criterion. A number of potential associations with having widespread pain were tested using logistic regression to provide odds ratios (OR) with 95% confidence intervals (CI). These models were then adjusted for number of pain sites to see if any associations with the distribution pattern remained after accounting for having pain in multiple areas.

Results: 14680 people responded to the questionnaire, of which 7536 reported some chronic pain (prevalence 51.3%). In those with chronic pain, the median number of pain sites was 5 (interquartile range 3 to 9), and the prevalence of pain that met the ACR 1990 criterion for being widespread was 32.1%. Included in the analysis were 5715 respondents with chronic pain in 3 to 16 areas, of which 2037 (35.6%) met the criterion for widespread pain. Gender age, smoking and employment status all had significant associations with ACR 1990 widespread pain (see table). After adjustment for number of pain sites most of these associations either became non-significant or were attenuated.

Conclusion: We have shown that when number of pain sites was taken into account, the particular distribution of sites did not continue to have significant relationships with many associated factors. This might indicate that is not so much that the pattern of pain locations that is important as the multiplicity of areas. This may have implications in conditions such as fibromyalgia where pain across multiple areas is involved. Based on this data, the use of a measure that looks at the number of pain sites rather than a particular distribution is acceptable as a diagnostic criterion.

	Not widespread		Widespread		Unadjusted		Adj for no. of sites	
	Number	Percentage	Number	Percentage	OR	95% CI	OR	95% CI
Gender								
Male	1600	68.00%	754	32.00%	1		1	
Female	2078	61.80%	1283	38.20%	1.31	1.17–1.46	1.13	0.98–1.30
Age								
Under 40	495	61.00%	317	39.00%	1		1	
40–49	647	63.60%	370	36.40%	0.89	0.74–1.08	0.9	0.71–1.14
50–59	821	65.80%	426	34.20%	0.81	0.67–0.97	0.81	0.65–1.02
60–69	822	63.30%	476	36.70%	0.9	0.75–1.08	0.85	0.68–1.07
Over 70	893	66.60%	448	33.40%	0.78	0.65–0.94	0.77	0.62–0.97
Smoking								
Never smoked	1951	65.70%	1019	34.30%	1		1	
Ex-smoker	1198	64.60%	657	35.40%	1.05	0.93–1.19	0.87	0.74–1.01
Current smoker	466	58.60%	329	41.40%	1.35	1.15–1.59	1.09	0.89–1.33
Employment								
Full-time	1369	66.30%	696	33.70%	1		1	
Part-time	533	66.80%	265	33.20%	0.98	0.82–1.16	0.84	0.67–1.04
Retired	1272	65.30%	677	34.70%	1.05	0.92–1.19	0.85	0.71–0.996
Unable to work	169	49.10%	175	50.90%	2.04	1.62–2.56	0.77	0.56–1.04
Student	26	54.20%	22	45.80%	1.66	0.94–2.96	1.32	0.64–2.73
Unemployed	34	53.10%	30	46.90%	1.74	1.05–2.86	1.42	0.74–2.71
Other	229	61.10%	146	38.90%	1.25	0.9996–1.57	0.93	0.70–1.24
BMI								
Under 20	163	59.90%	109	40.10%	1.2	0.94–1.57	1.1	0.80–1.52
20–25	1291	64.50%	711	35.50%	1		1	
25–30	1388	66.10%	713	33.90%	0.93	0.82–1.06	0.82	0.70–0.97
30–35	494	62.90%	291	37.10%	1.07	0.90–1.27	0.93	0.75–1.16
35 and over	342	61.60%	213	38.40%	1.13	0.93–1.37	0.83	0.65–1.07

Disclosure: M. Beasley, None; **G. J. Macfarlane**, None.

2072

Ultrasound Assessment of Both Hands in Fibromyalgia Patients: What Could We Detect? Maximiliano Bravo[1], Javier Rosa[2], Santiago Ruta[1], Ricardo Garcia-Monaco[3] and Enrique Soriano[1]. [1]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Radiology and Imagenology Department, Hospital italiano de Buenos Aires, Buenos Aires, Argentina.

Background/Purpose: Pain is the hallmark symptom of fibromyalgia (FM). The relationship with inflammation and/or structural changes in patients with fibromyalgia with pain localized in the hands is not clear. The aim of the present study was to describe the prevalence of different US abnormal findings at hand level in patients with FM.

Methods: Consecutive patients with FM according to 1990 ACR criteria in whom a scan of the small joints of both hands due to the presence of pain was performed, were included. Patients with other definite inflammatory autoimmune rheumatic condition and/or with a secondary FM were excluded. US examinations were performed by the same experienced rheumatologist blinded to all clinical data using a My Lab 70 machine (Esaote) provided with a linear transducer of 6–18 MHz. US assessments included both grayscale and power Doppler (PD) US and were performed according to reference standard methods. The following US abnormal findings were evaluated bilaterally at joint level (wrist, metacarpophalangeal (MCP), proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints): joint cavity widening (JCW) due to the presence of joint effusion and/or synovial hypertrophy, PD signal due to the presence of an increased abnormal vascularization and degenerative changes (osteophytes). Tenosynovitis due to the presence of tendon sheath distension (TSD) and/or PD signal (increased abnormal vascularization) was assessed at tendon level (flexor finger tendons and extensor tendons compartments of the wrist).

Results: A total of 94 patients with FM and with an US examination of both hands were included. Ninety-one (96.8%) patients were female, mean age was 57.4 years (SD: 12.1) and mean disease duration was 2.7 years (SD: 1.8). JCW was detected in 6 (6.4%) patients at PIP joints, in 6 (6.4%) patients at MCP joints and in 8 (8.1%) patients at wrist level. Tenosynovitis due to the presence of TSD was found in 12 (12.7%) patients at extensor tendon compartments of the wrist and in 7 (7.4%) patients at finger flexor tendons. None of the patients with JCW at joint level and/or TSD at tendon level showed increased abnormal vascularization by PD signal.Thirty (32%) patients showed osteophytes at small joints and 19 (20.2%) patients had also degenerative changes at trapeziometacarpal level (rizarthrosis).

There were no significant statistical differences regarding ESR, CRP, rheumatoid factor and CCP levels between patients with and without US abnormal findings ($p \geq 0.05$ for all comparisons).

Conclusion: A minority of patients with FM and hand pain showed US inflammatory abnormal findings on grayscale assessment and none of them showed abnormal vascularization by PD signal. The presence of degenerative changes (osteophytes) was the most frequent US abnormal finding.

Disclosure: M. Bravo, None; **J. Rosa**, None; **S. Ruta**, None; **R. Garcia-Monaco**, None; **E. Soriano**, None.

2073

Is Susceptibility to Fibromyalgia a Trait? Robert S. Katz[1], Ben J Small[2], Lauren Kwan[3], Hannah Bond[3], Jessica L. Polyak[3] and Susan Shott[4]. [1]Rush Medical College, Chicago, IL, [2]MacNeal Hospital, Berwyn, IL, [3]Rheumatology Associates, Chicago, IL, [4]Rush University Medical Center, Chicago, IL.

Background/Purpose: We asked patients, as part of an in-office survey, whether their immediate or extended family members had FMS.

Methods: 211 office patients with either FMS (150; 130 women and 20 men; mean age 51 +/− 12) and RA (61; 45 women and 16 men; mean age 55 +/−15) completed a questionnaire about FMS in family members. The chi-square test of association was used to compare the responses of FMS and RA patients, with a 0.05 significance level.

Results: FMS patients were significantly more likely than RA patients to report that members of their immediate families had FMS (24% vs. 7%, $p = 0.005$), and that members of their extended families had FMS (17% vs. 6%, $p = 0.041$). FMS patients were also significantly more likely than RA patients to report that some members of their families had widespread pain and chronic fatigue (52% vs. 18%, $p < 0.001$).

Conclusion: Patients with FMS appear to have more family members affected by this illness, compared to RA controls. One quarter to one half of family members of FMS patients may have fibromyalgia according to the patients. This suggests that widespread pain and the other symptoms of fibromyalgia may be inherited as a trait and may be present commonly in family members.

Disclosure: R. S. Katz, None; **B. J. Small**, None; **L. Kwan**, None; **H. Bond**, None; **J. L. Polyak**, None; **S. Shott**, None.

2074

Hypervigilance and FMS. Robert S. Katz, Rush Medical College, Chicago, IL.

Background/Purpose: In dangerous environments, hypervigilance conveys a survival value. A cave dweller who sleeps lightly and startles easily might escape a prowling bear while he is peacefully slumbering neighbor becomes a midnight snack. In safer environments.hypervigilance may cause dysfunctional stress. Some fibromyalgia syndrome (FMS) patients report symptoms of hypervigilance. We compared FMS and RA patients with respect to hypervigilance symptoms, and FMS patients with and without each hypervigilance symptom with respect to environmental stress.

Methods: 211 office patients with either FMS (150; 130 women and 20 men; mean age 51±12) or RA (61; 45 women and 16 men; mean age 55±15) completed a questionnaire about hypervigilance symptoms (present or absent) and the effect of various environmental conditions on their pain (rated as 1 = no effect, 2 = mildly worse, 3 = moderately worse, and 4 = severely worse). The chi-square test of association was done to compare FMS and RA patients with respect to percentages.

Results: Compared to RA patients, significantly higher percentages of FMS patients woke up more than once during the night (84% vs. 71%, $p = 0.033$), had trouble getting to sleep (63% vs. 38%, $p = 0.001$), and startled easily (53% vs. 30%, $p = 0.003$). FMS patients were uncomfortable in crowds (median 2.3 vs. 1.8, $p < 0.001$), FMS patients were made uncomfortable by people standing behind them (median 2.4 vs. 1.9, $p < 0.001$), FMS patients startled easily (median 2.1 vs. 1.9, $p = 0.004$), FMS patients did not feel at ease with strangers (median 2.2 vs. 1.9, $p = 0.029$), and FMS patients did not find it easy to trust strangers (median 2.3 vs. 1.9, $p = 0.009$).

Conclusion: FMS patients were significantly more likely to report hypervigilance symptoms compared to RA patients. The hypervigilance trait may be present in many fibromyalgia patients and could explain their hyper sensitivity traits to perceived environmental threats.

Disclosure: R. S. Katz, None.

2075

The Lumbar Spine in Fibromyalgia. Robert S. Katz[1], Alexandra Small[2] and Anthony Farkasch[3]. [1]Rush Medical College, Chicago, IL, [2]University of Illinois College of Medicine, Chicago, IL, [3]Rheumatology Associates, Chicago, IL.

Background/Purpose: Radiographs of the lumbar spine appear normal in fibromyalgia. However, a previous study (ArthRheum50:134, 2004) found a reduced lordotic curve in the cervical spine of patients with fibromyalgia. We measured the Cobb angle on radiographs of the lumbar spine in patients with fibromyalgia and other rheumatic disease patients.

Methods: Fibromyalgia patients meeting the 2010 ACR criteria with a complaint of back pain, and patients with other rheumatic disease disorders who had back pain (osteoarthritis, spinal stenosis, degenerative joint disease, herniated disc and other forms of lumbar radiculopathy, and ankylosing spondylitis) were evaluated for lumbar spine straightening using the Cobb angle of lateral lumbar spine radiographs.

The Cobb angle was measured by drawing a line parallel to the superior portion to L1 and another line parallel to the inferior portion to L5 and measuring the angle where the two lines intersect.

Results: The number of fibromyalgia patients studied was 148 and the number of non-fibromyalgia patients with back pain but not fibromyalgia was 59. The mean ages were 45.4 years for fibromyalgia patients and the mean age for the non-fibromyalgia patients 52.5 years. In the fibromyalgia group there were 136 females, and 12 males; and in the non-fibromyalgia group w back pain, who served as controls, there were 46 females, and 13 males.

The mean Cobb angle in the fibromyalgia patients was 14.0 degrees, and the mean Cobb angle in the rheumatic disease controls with back pain was 20.9 degrees.

Conclusion: FMS patients have a straight lumbar spine. We propose that increased muscle tension may be the cause of the reduced Cobb angle in these patients. Fibromyalgia patients have widespread pain over large muscle groups, muscle tenderness, and also have straight cervical spines and straight lumbar spines, by measuring the Cobb angle. It is quite possible that much of the pain experienced by fibromyalgia patients relates to increased muscle tension.

Disclosure: R. S. Katz, None; **A. Small**, None; **A. Farkasch**, None.

2076

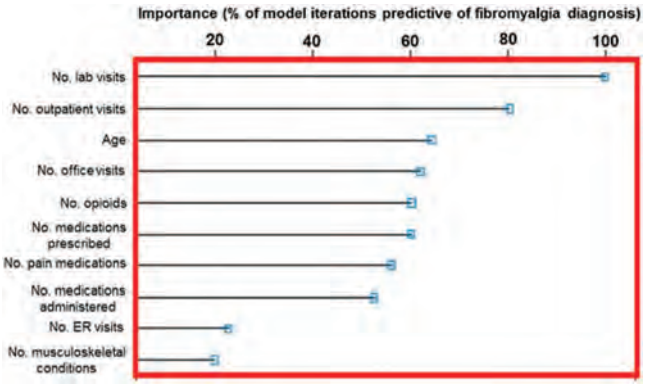
Predictive Modeling of a Fibromyalgia Diagnosis: Increasing the Accuracy Using Real World Data. Birol Emir[1], Jack Mardekian[1], Elizabeth T. Masters[1], Andrew Clair[1], Max Kuhn[2] and Stuart L. Silverman[3]. [1]Pfizer Inc, New York, NY, [2]Pfizer Inc., Groton, CT, [3]Cedars-Sinai Medical Center, UCLA Center of Excellence, Los Angeles, CA.

Background/Purpose: The number of symptoms and comorbidities associated with the chronic pain condition of fibromyalgia (FM) complicates its identification and diagnosis.

Methods: This retrospective analysis used structured de-identified electronic health records from the 2011–2012 Humedica database, including demographics, clinical characteristics, and healthcare resource use. An FM cohort was defined as subjects ≥18 years in 2011 with ≥2 ICD-9 codes for FM (729.1) ≥30 days apart during 2012; the no-FM cohort did not have the ICD-9 code. Univariate analyses characterized between-cohort differences and determined the demographic, clinical, and healthcare resource variables associated with an FM diagnosis. A Random Forest (RF) model was used to predict FM and non-FM subjects by entering all variables into the model (1500 bootstraps) with internal down-sampling (to account for imbalance between cohorts). Importance of the variables was computed using RF to determine the trade-off on accuracy when only the top 10 variables were fitted. For practical clinical application, a rule-based model was used to derive simple statements to help explain which patient sets have the largest effect on the likelihood of an FM diagnosis.

Results: Significant differences were observed between the FM (n=4,296) and no-FM (n=583,665) cohorts for demographics ($P<.0001$) except for age, for most evaluated comorbidities ($P<.0001$), and for healthcare resource use ($P<.0001$), with more comorbidities and resource use in FM subjects. Resources included proportions of subjects with utilization, and units used per subject for emergency room visits, outpatient visits, hospitalizations, and medications. The top 10 variables for predicting an FM diagnosis were identified from the RF models based on level of importance as reflected by the percent of model iterations in which the variable was predictive (Figure). A receiver operator characteristic curve confirmed the predictive accuracy of the model variables (area under the curve of 0.810). Rules were developed to identify patients with high predicted probability of an FM diagnosis; e.g., the average predicted probability of 0.54 for a subset of patients with outpatient visits excluding office visits >0 and prescriptions administered/ordered ≤3 and the number of musculoskeletal pain conditions >0 was more than double the 0.22 predicted probability for those not in the subset. Similarly, a rule to identify non-FM (opioid prescriptions administered/ordered/written =0; visits where diagnostic/laboratory tests were ordered =0; and number of musculoskeletal pain conditions =0) correctly classified 100% of the sample.

Conclusion: Random forest modeling can be applied to determine likelihood of an FM diagnosis. Rules can simplify this method with good accuracy. Further validation of RF may help facilitate earlier diagnosis and enhance management strategies.



Disclosure: B. Emir, Pfizer Inc., 1, Pfizer Inc., 3; **J. Mardekian**, Pfizer Inc., 1, Pfizer Inc., 3; **E. T. Masters**, Pfizer Inc., 1, Pfizer Inc., 3; **A. Clair**, Pfizer Inc., 1, Pfizer Inc., 3; **M. Kuhn**, Pfizer Inc., 3; **S. L. Silverman**, Amgen, Eli Lilly, Pfizer, 8, Amgen, Genentech, Eli Lilly, Novartis, Pfizer, 5, Amgen, Eli Lilly, Medtronics, Pfizer, 2.

2077

A New Tender Point on the Plantar Arch in Primary Juvenile Fibromyalgia: A Potential Point to be Considered. Walter J. Spindler, Cecilia Santarelli, Alberto J. Spindler, Alberto Berman, Horacio Berman and Mirta Santana. Centro Medico Privado de Reumatologia, Tucuman, Argentina.

Background/Purpose: Juvenile Primary Fibromyalgia Syndrome (JPFS) is a chronic and complex musculoskeletal disorder that may cause diffuse pain accompanied by defined tender points. Diagnostic dilemmas may frequently arise since 10 of these tender points are located on the cervical and shoulder area (ACR'90 Fibromyalgia Classification Criteria). For this reason, a tender point reproducible in a different area may be an advantage on the diagnosis of JPFS. The objective of this study was to assess sensitivity and specificity of a tender point located infero-medially in the distal third of the longitudinal plantar arch in JPFS patients and healthy controls.

Methods: The study included consecutive patients with JPFS (ACR'90) and healthy controls matched by age and gender. Informed consent was obtained for all study subjects. Pairs of the proposed point, those accepted by the ACR and control points (biceps, quadriceps and lateral foot area) were assessed with digital pressure of approximately 4 Kg/cm2 by previously trained rheumatologist and pediatrician in both subject groups. Sensitivity and specificity of all tender and control points examined were compared by unpaired t-test, ROC curve and the McNemar test.

Results: Out of a total of 22 JPFS patients, 19 were female (F) and 3 were male (M), ages between 13 and 17 (14±0.30). The healthy control group included 27 high school students of similar age (14±0.23) and gender (21 F and 6 M) than the patients. The new plantar point was positive in 20/22 JPFS patients (90.9%), bilaterally in 20 and unilaterally in 2 patients. None of the control group subjects had pain on the new plantar point. Sensitivity and specificity for the new tender point were 90.9% and 96.4% respectively (positive LR of 25.25, ROC Area = 0.937 with CI 95% =0.856 –1.00). Several ACR tender points presented lower sensitivity and/or specificity than the new plantar point: occiput was positive in 19/22 (86.4%) JPFS patients and in 6/27 (22%) of the control group, 86.4% sensitivity, 75% specificity (positive LR of 3.46 ROC Area = 0.807 with CI 95% =0.68 – 0.934), supraspinatus was positive in 20/22 (90.9%) JPFS patients and in 5/27 (18%) of the control group, 90.9% sensitivity, 78.6% specificity (positive LR of 4.25 (ROC Area = 0.847 with CI 95% =0.733 – 0.962), second rib was positive in 19/22 (86.4%) JPFS patients and in 1/27 (3.7%) of the control group, 86.4% sensitivity, 92.9% specificity (positive LR of 12.17 ROC Area = 0.896 with CI 95% =0.795 –0.997), lateral epicondyle was positive in 19/22 (86.4%) JPFS and in 1/27 (3,7%) of the control group, 86.4 sensitivity, 92.9 specificity (positive LR of 12.17 ROC Area = 0.896 with CI 95% =0.795 –0.997). In patients with JPFS, control points were negative in 17/19 patients (89%). The plantar site had good concordance in JPFM patients with tender sites such as occiput, trapezius, supraspinatus, lateral epicondyle (test McNemar, $p > 0.12$).

Conclusion: The plantar arch tender point has high sensitivity and specificity in patients with JPFS. Additionally, it presented higher specificity than other recognized tender points. Further investigations on this novel site appear warranted.

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2078

A Proposed Simple 3-Variable Index for Identification of Fibromyalgia, Analogous to Classification Criteria for RA and SLE. Sung-Hoon Park[1], Jung-Yoon Choe[2], Seong-Kyu Kim[3], Hwajeong Lee[4] and Theodore Pincus[5]. [1]Arthritis and Autoimmunity Research Center, Catholic University of Daegu School of Medicine, Daegu, South Korea, [2]Catholic University of Daegu School of Medicine, Daegu, South Korea, [3]Catholic University of Daegu,Daegu, South Korea, Daegu, South Korea, [4]Catholin university of Daegu School of medicine, Daegu, South Korea, [5]Rush univeristy medical center, Chiacago, IL.

Background/Purpose: A cumulative index that includes various quantitative data has been useful in developing classification criteria for various rheumatic diseases, including rheumatoid arthritis (RA)[1] and systemic lupus erythematosus (SLE).[2] Previous reports indicate that self-report patient scores on a multidimensional health assessment questionnaire (MDHAQ) provide clues to identify patients with fibromyalgia (FM).[3,4] Since the diagnosis of FM is made primarily on the basis of patient report of pain and other symptoms, a cumulative scale of quantitative patient self-report scores as well as a physician estimate of a level of FM might be useful to identify patients with FM. To analyze a simple 3-variable cumulative scale to identify patients with FM, and distinguish them from patients with RA, SLE, and ankylosing spondylitis (AS) seen in a usual care setting in Korea.

Methods: All patients seen at a Korean rheumatology setting complete an MDHAQ/RAPID3 (routine assessment of patient index data), which includes scores for physical function, visual analog scales (VAS) for pain, global status and fatigue, and a list of 60 symptoms as a checklist review of symptoms. Physicians also complete a RHEUMDOC form which includes a 0–10 VAS physician global estimate of patient status, and 0–10 VAS subscales for inflammation, damage, and level of symptoms not explained by inflammation and damage, such as FM. Preliminary cross tabulations were performed to compare scores for MDHAQ variables in patients with FM versus RA, SLE, and AS. Based on these preliminary analyses, a 3-variable cumulative scale was developed: ***1)*** VAS pain score of ≥5 out of 10, ***2)*** symptom checklist of ≥15 out of 60 symptoms, and ***3)*** physician estimate of FM level ≥3 out of 10. The numbers of patients with FM, RA, SLE and AS who scored 0, 1, 2, or 3 were computed; chi square tests and receiver operator curves (ROC) were used to analyze statistical significance.

Results: Data were available concerning 32 patients with FM, 18 with AS, 17 with SLE and 277 with RA. Overall, 53% of patients with FM had scores of 2 or 3 of these criteria, compared to 5.5% with AS, 20.2% with RA and 5.8% with SLE ($p \leq 0.001$). ROC area was 0.734, with standard error of 0.047 and 95% confidence interval of 0.642–0.826. A score of 2, which does not require any physician data, was associated with a positive likelihood ratio for FM of 2.9, sensitivity of 53.1 and specificity of 81, with 79% correctly classified. A score of 3 was associated with a positive likelihood ratio for FM of 7.1, with 90% correctly classified.

Dx	FM score, N (%) of patients				Total N
	0	1	2	3	
AS	10 (55.6%)	7 (38.9%)	1 (5.5%)	0	18
FM	5 (15.6%)	10 (31.3%)	9 (28.1%)	8 (25.0%)	32
RA	130 (46.9%)	91 (32.9%)	45 (16.2%)	11 (4.0%)	277
SLE	8 (47.1%)	8 (47.1%)	1 (5.8%)	0	17
Total	153 (44.5%)	116 (33.7%)	56 (16.3%)	19 (5.5%)	344

Chi square=38.32, p<0.001

Conclusion: A cumulative score analogous to classification criteria for RA or SLE may be useful in helping to identify FM. A limitation of this study is that it did not identify patients with a diagnosis of RA, SLE,or AS who might also have FM, who may account for patients with inflammatory rheumatic diseases and scores of 2 or 3 on the preliminary FM index.

Disclosure: S. H. Park, None; **J. Y. Choe**, None; **S. K. Kim**, None; **H. Lee**, None; **T. Pincus**, None.

2079

The Association Between Straight Neck and Fibromyalgia. Omar-Eloy Muñoz-Monroy[1], Laura-Aline Martinez-Martinez[2], Manuel Martínez-Lavín[2], Blanca-Adela Mota-Mondragón[1] and Evalorena Martínez-Hernández[1]. [1]Hospital Central Militar, Mexico City, Mexico, [2]Instituto Nacional de Cardiologia, Mexico City, Mexico.

Background/Purpose: It has been suggested that patients with fibromyalgia very often have radiographic straight neck. According to one study, 71% of patients with fibromyalgia lose the normal radiographic cervical lordosis. In this report, straight neck was defined as a Cobb angle < 14 degrees. (Katz & Farkasch. Abstract 1086, 2013 ACR Annual Meeting).

Objective: Our objective was to further investigate this potentially important clinical association. We set to define the prevalence of radiographic cervical spine straight neck in patients with fibromyalgia as compared with patients suffering from other musculoskeletal diseases.

Methods: Adult patients attending an outpatient rheumatology clinic of a military hospital were invited to participate in the study. A lateral cervical radiograph in neutral position was obtained in all instances. Cobb angle was used to label the radiographs as "normal" (Cobb angle > 18 degrees) "borderline" (Cobb angle between 14 and 18) and "straight neck" (Cobb angle < 14). A rheumatologist blinded to the radiograph results prospectively examined each patient from the "normal" and "straight neck" groups. The 1990 and 2010 ACR criteria were used to define the presence of fibromyalgia.

Results: Are summarized in the table. A total of 56 patients were studied. Only 14 of them had "normal" radiographic cervical lordosis. Of the total group, 35.7% fulfilled either the 1990 or the 2010 ACR fibromyalgia diagnostic criteria. Fibromyalgia was more frequent in the "normal" radiograph group (64%) than in the "straight neck" group (26%) ($p = 0.022$).

Conclusion: Fibromyalgia is very frequent in this military rheumatology clinic. Contrary to our working hypothesis, our results show that patients with

fibromyalgia have less radiographic straight neck when compared to patients with other rheumatic diseases.

Total n=56	"Primary" fibromyalgia n=14	Fibromyalgia + other rheumatic illness n=6	Other rheumatic disease without fibromyalgia n=17	Neither auto-immune disease nor fibromyalgia n=19	p
Age (years)	49.3 ± 8.9	42.8 ± 6.6	38.1 ± 10.8	35.8 ± 12.6	0.006
Women (%)	13 (92.9%)	6 (100%)	11 (64.7%)	14 (73.7%)	0.136
Cobb's angle (radial degrees)	14.9 ± 8.7	14.7 ± 7.1	11.1 ± 5.4	8.6 ± 6.4	0.054
Straight neck <14° (%)	7 (50%)	4 (66.7%)	14 (82.4%)	17 (89.5%)	0.058
Number of tender points	14.0 ± 2.5	14.3 ± 2.3	4.7 ± 4.9	2.5 ± 3.5	<0.0001
FM according 1990 ACR criteria (%)	11 (78.6%)	5 (83.3%)	3 (17.6%)	1 (5.3%)	<0.0001
Widespread pain index	12.7 ± 3.1	14.8 ± 4.4	4.1 ± 3.6	2.2 ± 2.1	<0.0001
Symptom severity score	7.5 ± 2.2	8.3 ± 1.6	3.4 ± 1.7	2.5 ± 1.5	<0.0001
FM according 2010 ACR criteria (%)	14 (100%)	6 (100%)	0 (0%)	0 (0%)	<0.0001

Disclosure: O. E. Muñoz-Monroy, None; **L. A. Martinez-Martinez**, None; **M. Martínez-Lavín**, None; **B. A. Mota-Mondragón**, None; **E. Martínez-Hernández**, None.

2080

Carryover Effects in Crossover Design Studies in Fibromyalgia and Other Pain Conditions. Lynne Pauer[1], Birol Emir[2], Ed Whalen[3], Joseph Scavone[1] and Andrew Clair[2]. [1]Pfizer Inc, Groton, CT, [2]Pfizer Inc, New York, NY, [3]Pfizer Inc., New York, NY.

Background/Purpose: Explore carryover effects and their influence on crossover and randomized withdrawal design (RWD) studies.

Methods: We examine pregabalin crossover and RWD studies in fibromyalgia (FM), painful diabetic peripheral neuropathy (pDPN), and post-herpetic neuralgia (PHN). Data visualization methods and meta-analytic summaries are used to explore the difference in carryover effects across studies and pain types. Weekly mean pain scores are compared for 4 crossover studies of similar design, 2 in FM (studies 1165 and 1275) and 2 in pDPN (1268, 1269), for patients randomized to the pregabalin to placebo treatment sequence (Pgb - Pla) or to the placebo to pregabalin (Pla - Pgb) treatment sequence (Figure 1).

Results: In fibromyalgia crossover studies, a greater return of pain occurred following pregabalin treatment than in the pDPN studies (Figure 1). There was a differential effect of period one treatment on period two outcomes. FM crossover studies returned to a common pain level regardless of period one treatment, whereas DPN crossover studies did not. Similar results hold for the pregabalin to placebo arm in the FM vs DPN RWD studies.

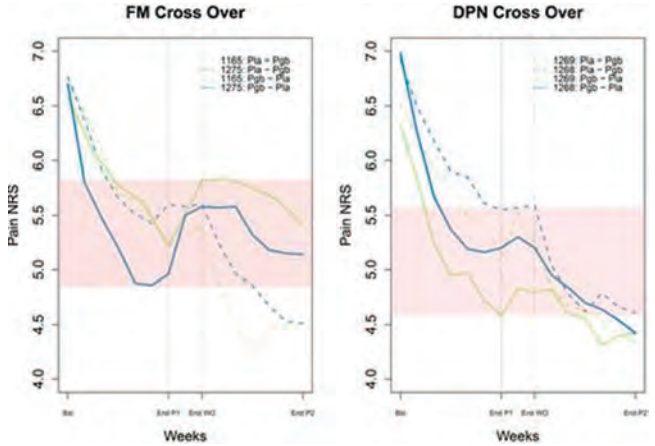

Figure 1. Crossover Studies in Fibromyalgia and Painful Diabetic Peripheral Neuropathy

FM: Fibromyalgia; DPN: Painful Diabetic Peripheral Neuropathy; Pain NRS: Pain Numeric Rating Scale; Pgb: Pregabalin; Pla: Placebo; Bsl: Baseline; P1: Period 1; P2: Period 2; W/O: placebo washout period.

Conclusion: The type of pain under study may affect the ability of crossover or RWD studies to determine the magnitude of treatment effect; pain type should be carefully considered when choosing among study designs for pain.

Disclosure: L. Pauer, Pfizer Inc., 1, Pfizer Inc., 3; **B. Emir**, Pfizer Inc., 1, Pfizer Inc., 3; **E. Whalen**, Pfizer Inc., 1, Pfizer Inc., 3; **J. Scavone**, Pfizer Inc., 1, Pfizer Inc., 3; **A. Clair**, Pfizer Inc., 1, Pfizer Inc., 3.

2081

Ehlers-Danlos Hypermobile (EDS-HT) Patients and Postural Instability: Another Clue to Explain Pain and Fatigue? Roland Jaussaud[1], Elodie Vlamynck[2], Rami Haidar[3], Dorothée Lambert[4], Violaine Laurant-Noel[5] and Amélie Servettaz[5]. [1]CHU de Reims, REIMS, France, [2]Cabinet d'Orthopédie, Versailles, France, [3]Cabinet d'Orthopédie, Lille, France, [4]CHU Reims, Reims, France, [5]Hôpital Robert Debré. CHU de Reims, Reims, France.

Background/Purpose: Postural instability was found in several functional disorders including dyslexia, chronic pain and fibromyalgia. Furthermore, the link between vertical heterophoria (VH) and postural control is now clearly established. EDS-HT patients shared symptoms usually encountered in patients presenting postural instability.

Methods:

Aim: To assess the presence of postural instability and the role of vertical heterophoria among patients suffering from EDS-HT.

Design of study: 30 patients meeting the Villefranche criteria for diagnosis of EDS-HT (generalized joint hypermobility, skin involvement, recurring joint dislocations, chronic joint/limb pain and positive family history) were prospectively examinated. Their postural performance was compared to that of 15 healthy subjects.

Methods: To measure postural instability, we used a force platform. The surface of the center of pressure (CoP) excursions, the standard deviations of lateral (SDx) and antero-posterior (SDy) body sways and the variance of speed were recorded. The surface area was measured with confidence ellipse including 90% of the CoP positions sampled, eliminating the extreme points. Vertical heterophoria (VH) was qualitatively detected with Maddox' rod. Pain was evaluated using a subjective visual analogical scale (VAS) of 10 cm validated for chronic pain. Fatigue severity scale (FSS) was used.

Results: Among the EDS-HT patients the mean VAS score was 67 mm. 84% had a FFS > 6. All these patients presented with symptoms of muscle hypertonia, disturbance of spatial location and other perception disorders. With respect to EDS-HT patients, they used more energy to stabilize postural sway during quiet upright stance than healthy subjects. The presence of vertical heterophoria was associated with a greater antero-posterior postural sway. Most of them had abnormal footprints (asymmetrical or hollow feet).

Conclusion: These data suggested that a dysfunction implicating somesthetic signals or central neurological integration could affect the balance control performance following the example of patients suffering from chronic low back pain. VH and hypermobility both or alone could be the sign or the trigger of this dysfunction. Postural instability could explained part of the symptoms of pain and fatigue in EDS-HT.

Disclosure: R. Jaussaud, None; **E. Vlamynck**, None; **R. Haidar**, None; **D. Lambert**, None; **V. Laurant-Noel**, None; **A. Servettaz**, None.

2082

Presence of Acrocyanosis in Patients with Joint Hypermobility. Ayhan Dinc[1] and Göksal Keskin[2]. [1]Patio Clinic, Ankara, Turkey, [2]Medical School of Ankara, Ankara, Turkey.

Background/Purpose: Joint hypermobility is a common but often poorly recognized connective tissue condition with joint laxity in the absence of any hereditary systemic disease. Acrocyanosis is symmetric, painless, blue discoloration in the distal parts of the body with aggravation by cold exposure, and frequent association with local hyperhidrosis of hands and feet. Primary acrocyanosis is mostly a disease of young adults, only few cases persist into middle age.

Methods: During 18 months, a group of 350 consecutive rheumatology patients (<45 yrs. old) investigated for joint laxity and acrocyanosis. For each patient a Beighton score measured and those with a score of >4 regarded as benign joint hypermobility due to Brighton criteria. Acrocyanosis was diagnosed clinically by proper history and physical examination. Other relevant clinical findings were also recorded.

Results: A total of 43 patients (F: M, 26:17) were diagnosed as hypermobility. Nearly all patients had a mild-moderate hypermobility. The mean Beighton score was 4.9±0.7. Of those patients, 19 had also acrocyanosis (44.1%). In the group lacking hypermobility (303), only 6 cases of acrocyanosis detected (0.02%). In the acrocyanosis patients, whether or not accompanied with hypermobility, average hand and foot sizes per stature are larger than those without.

Conclusion: It has been known that, patients with hypermobility may have some vascular problems, including Raynaud's phenomenon and vari-

cose veins. Our observation points out that, besides joint hypermobility, probable vessel wall laxity might cause to passive engorgement of vascular structures, namely acrocyanosis.

Disclosure: A. Dinc, None; **G. Keskin**, None.

2083

Evaporative Dry-Eye Disease and Aqueous Deficient Dry-Eye Disease Associated with Fibromyalgia. William Pachas[1], Jack Greiner[2] and Paula Oliver[3]. [1]Center for Rheumatology, Osteoporosis and Fibromyalgia, Boston, MA, [2]The Boston Ocular Surface Center, Boston, ME, [3]The Boston Ocular Surface Center, Boston, MA.

Background/Purpose: Fibromyalgia (FM) patients with ocular discomfort often describe symptoms characteristic of dry eye diseases, but frequently do not fulfill criteria diagnostic of Sjögrens syndrome. Thus, ophthalmologic subjective and objective testing were performed to (1) establish the association of FM with dry eye diseases and (2) attempt to identify the type(s) of dry eye diseases associated with FM.

Methods: Consecutive patients (n=30) meeting American College of Rheumatology criteria for FM were evaluated as part of a comprehensive rheumatological examination. Subjective evaluation employed dry eye questionnaires, Ocular Surface Disease Index (OSDI) and Standard Patient Evaluation of Eye Dryness (SPEED). Objective tests included determination of minimum tearfilm lipid layer thickness (LLT), tearfilm osmolarity (TOSM), tearfilm break-up time (TBUT), Schirmer tear test (STT), corneal fluorescein-staining, and meibomian gland assessment (MGA) scores.

Results: Measurements were compared with widely accepted "Normal Values" (NV). OSDI 32.38±SD 20.7 (range, 2.27–79.16) 60% higher than NV(<13); SPEED 11.38±7.1 (range, 0–23.5) 47% higher than NV (≤6); LLT 49.72±17.2 nm (range, 28–90) 38% lower than NV (≤80nm); TOSM 312.2±14.1 mOsm/l (range, 290–341) higher than NV (300 mOsm); TBUT 5.01±3.1 sec (range, 1–15.24) 50% lower than ≥(10 sec); STT 6.02±3.9 nm (range, 0–11.5) 40% lower than NV (≥10 mm); and MGA scores 11.70±5.1 (range, 4–27) lower than NV(>12).

Conclusion: Fibromyalgia patients demonstrate evidence for both evaporative and aqueous-deficient dry eye diseases. FM patients should be routinely questioned for signs or symptoms of dry eye disease(s) and referred for a comprehensive evaluation to determine the type(s) of their dry eye disease(s) in order to recommend appropriate treatment(s).

Disclosure: W. Pachas, None; **J. Greiner**, None; **P. Oliver**, None.

ACR/ARHP Poster Session C
Genetics, Genomics and Proteomics
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

2084

Are Genetic Markers Associated with Myocardial Infarction in Patients with Early Rheumatoid Arthritis? Lisbeth Ärlestig[1], Petros Zamout[2], Lena Innala[2], Eva Freyhult[3], Solveig Wållberg Jonsson[2] and Solbritt Rantapää-Dahlqvist[2]. [1]Institution of Public health and clinical medicine/Rheumatology, University of Umeå, Rheumatology, Sweden, Umea, Sweden, [2]Institution of Public health and clinical medicine/Rheumatology, University of Umeå, Rheumatology, Sweden, Umeå, Sweden, [3]Bioinformatics Infrastructure for Life Sciences, Uppsala, Sweden.

Background/Purpose: Cardiovascular disease (CVD) are increased in patients with rheumatoid arthritis (RA). Traditional as well as disease related risk factors seem to contribute to the development.

To evaluate the impact of genetic makers for development of myocardial infarction (MI) or angina pectoris (AP) leading to coronary intervention (PTCA or CGBP) in patients with early RA in relation to inflammation and traditional risk factors.

Methods: Patients with early RA (1987 American College of Rheumatology criteria) from northern Sweden and consecutively recruited since Dec 1995 into a national register were followed prospectively for disease progression, treatment and into a register for presence of CV risk factors. Of the patients 899 had donated DNA and were analysed for the genetic markers. The follow-up started at inclusion and ended at the first MI/AP, death or until Dec 31 2011 by co-analysing with the national registers of hospitalization and death in Sweden using classification of diseases (ICD-9 and 10). Genetic polymorphisms were analysed using Immunochip (SNP&SEQ Technology Platform Uppsala, Sweden). Univariate Cox regression and a likelihood ratio test was adopted to find SNPs most strongly associated with MI/AP. The potentially important (likelihood ratio p<0.05) clinical factors were also identified using univariate Cox regression. Selected clinical factors were combined with one SNP at the time in a multivariate Cox regression model and a likelihood ratio test was adopted to assess whether the SNP added significant information to a model based on only the selected clinical factors.

Results: Analysis using the Immunochip yielded 131,523 SNPs, whereof 44,367 independent SNPs were identified after linkage analyses. In total 795 patients are included in the statistical analyses (some are excluded due to many missing values in the genetic data). The total follow-up time was 5607 person years until first MI/AP after RA disease onset. 52 patients had experienced a MI or AP leading to intervention. The strongest SNPs related to MI/AP were rs241425 (p=3.02e-06), rs2239701 (p=8.12e-06), rs9262155 (p=8.62e-06), rs2269706 (p=1.41e-05), and rs222418 (p=3.08e-05). Besides sex and age, hypertension, previous CV event, HLA-shared epitope, and oral corticosteroids were indicated as important in univariate Cox models (p<0.05). Likelihood ratio p-values after adjusting for the clinical factors were slightly lower than in the univariate models; rs241425 (p=1.04e-04), rs2239701 (p=4.75e-04), rs9262155 (p=9.20e-05), rs2269706 (p=5.55e-05), and rs222418 (p=1.87e-04).

Conclusion: SNPs analysed by Immunochip could be associated with MI/AP in patients with RA unrelated to more traditional risk factors.

Disclosure: L. Ärlestig, None; **P. Zamout**, None; **L. Innala**, None; **E. Freyhult**, None; **S. Wållberg Jonsson**, None; **S. Rantapää-Dahlqvist**, None.

2085

Association of Circulating Mirnas with Spinal Involvement in Patients with Axial Spondyloarthritis. Klára Prajzlerová[1], Markéta Fojtíková[1], Šárka Forejtová[1], Astrid Jüngel[2], Steffen Gay[2], Karel Pavelka[1], Jiri Vencovsky[1], Ladislav Senolt[1] and Mária Filková[1]. [1]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [2]Zurich University Hospital, Zurich, Switzerland.

Background/Purpose: The altered expression of miRNAs and dysregulation of their target genes has been shown to contribute to the development and maintenance of autoimmune diseases. In addition, cell-free circulating miRNAs appear promising diagnostic and/or prognostic biomarkers. Our aim was to identify circulating miRNAs in patients with axial spondyloarthritis (AxSpA) and to investigate their relationship with spinal involvement.

Methods: The study included 20 patients with non-radiographic AxSpA (nr-AxSpA) according to the ASAS criteria with sacroiliitis confirmed by MRI, 48 patients with radiographic AxSpA (with and without spinal involvement, including 5 patients with a bamboo spine), and 29 healthy controls (HC). Total RNA from plasma was isolated using phenol-chloroform extraction and equal amount of RNA was used for reverse transcription. A comprehensive analysis of miRNAs was performed using TaqMan® Low Density Array (TLDA) in 5 samples from each group. dCt method was used for relative quantification as follows: dCt= Ct(array average)-Ct(miRNA) followed by x-fold change calculation. The expression of selected miRNAs was further validated by single assays in the remaining samples and the levels of miRNAs were normalized to an average of 3 spike-in controls of C. elegans origin: dCt= Ct(spike-in average)-Ct(miRNA). Data were analyzed using one-way ANOVA and unpaired t-test with Welch's correction.

Results: Out of total 760 miRNAs analysed by TLDA, 162 miRNAs were detected in a group of HC, 156 miRNAs in patients with nr-AxSpA and 110 in patients with radiographic AxSpA. All patients with AxSpA had at least 2-fold lower levels of 56 miRNAs when compared with HC. In patients with radiographic AxSpA, 72 miRNAs showed at least 2-fold decrease in comparison with nr-AxSpA.

Twenty-one miRNAs were selected according to the differential expression between groups of patients and possible relationship to the pathogenesis of AxSpA for further analysis. Out of 21 selected miRNAs, 14 miRNAs were significantly lower (p<0.05) in all patients with AxSpA compared to HC. MiR-625* (p=0.0055) and miR-222 (p=0.045) showed significantly lower levels in patients with nr-AxSpA compared with HC. In all patients with radiographic AxSpA, 20 miRNAs were significantly lower in comparison with the group of nr-AxSpA patients and HC, in particular miR-24, miR-27a, miR-106a, miR-222 or miR-223 (p<0.0001). Levels of these miRNAs were significantly lower (p<0.01 for miR-24, -27a, -106a, -223, p<0.05 for miR-222) in a subgroup of patients with bamboo spine compared with other patients with AxSpA.

Conclusion: Expression of circulating miRNAs is altered in patients with AxSpA. Reduced expression of several miRNAs was associated with the degree of spinal involvement, with the lowest expression observed in patients with the bamboo spine. Given the involvement of these dysregulated miRNAs in innate immunity and new bone formation, our data suggest their role in the pathogenesis of AxSpA and potential use of circulating miRNAs as biomarkers of disease progression.

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Disclosure: K. Prajzlerová, None; **M. Fojtíková**, None; **Forejtová**, None; **A. Jüngel**, None; **S. Gay**, None; **K. Pavelka**, None; **J. Vencovsky**, None; **L. Senolt**, None; **M. Filková**, MHCR project 023728, 2.

2086

Replication of PTPRC As Genetic Biomarker of Response to TNF Inhibitors in Patients with Rheumatoid Arthritis. Antonio Gonzalez[1], Aida Ferreiro-Iglesias[2], Juan Gomez-Reino[1] and on Behalf of Their Collaborators[3]. [1]Instituto Investigacion Sanitaria- Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [2]Insitituto Investigacion Sanitaria-Hospital Clinico Universitario de Santiago, Santiago de Compostela, Spain, [3]multiple, multiple, Spain.

Background/Purpose: The use of biomarkers to predict response to the different drugs available for treating rheumatoid arthritis (RA) is a very desirable goal. However, success of the many studies already performed has been limited. Genetic studies of response to the TNF inhibitors (TNFi) have reported multiple associations. At least 14 are from relative large candidate gene studies including hundreds of patients and other 16 are from GWAS also with hundreds of patients. A couple of them, in the *PTPRC* and *PDE3A-SLCO1C1* loci, have been replicated in a second study, but none has yet been confirmed with full confidence. We aimed to replicate here the 14 genetic associations proposed in large candidate gene studies.

Methods: We analyzed the response to TNFi treatment of 755 patients with RA naïve to biologic DMARDs and of European ancestry. They have been treated with the three most common TNFi (infliximab, N = 397; etanercept, N = 155; adalimumab, N = 203). Their response to these drugs was evaluated either as change in DAS28 (ΔDAS28) between baseline and 3, 6 and 12 months of treatment, or as classification according to the EULAR response criteria (good + moderate responders *vs.* non responders) at the same time points. The genotypes of the 14 previously associated SNPs plus the putative causal SNP at one of them were obtained with a single-base extension multiplex methodology. We considered the SNPs according to an additive genetic model in linear and logistic regression analyses, for ΔDAS28 and EULAR criteria, respectively. Baseline DAS28, gender and treatment were considered as covariates. Statistica 7.0 (Statsoft, Tulsa OK) software was used to perform these analyses.

Results: All the SNPs were successfully genotyped (call rate = 99.1 %; HWE $P > 0.05$). Only one of the 14 loci was associated with response to TNFi. This was the *PTPRC* SNP rs10919563 that is a confirmed RA susceptibility locus. The RA risk allele (G) of this SNP was associated with higher ΔDAS28 at 6 months (B = 0.33, [95% CI] 0.09 to 057, P = 0.006) and showed a trend to association with good response as defined with the EULAR criteria (odds ratio [OR] 1.49, [95% CI] 0.94 to 2.33, P=0.08). A second *PTPRC* SNP, rs6683595, very correlated with rs10919563, which is a putative causal polymorphism of this RA locus because it maps in an active regulatory region in $CD4^+$ T_{reg} cells showed an even stronger association: its G allele was associated with higher ΔDAS28 at 6 months (B = 0.39, [95% CI] 0.18 to 0.61, P=0.0003) and with good response (OR = 1.56, [95% CI] 1.04 to 2.37, P= 0.03).

Conclusion: We have obtained a new replication of the association of the PTPRC RA risk locus with response to TNFi. In this way, it has become the most replicated to date of the genetic biomarkers of response to these drugs with three studies including hundreds of patients each showing consistent results. In addition, we have found stronger association with a putative causal polymorphism in this locus that pave the way for functional studies exploring its involvement in RA and its treatment.

Disclosure: A. Gonzalez, None; **A. Ferreiro-Iglesias**, None; **J. Gomez-Reino**, None; **O. B. of Their Collaborators**, None.

2087

Defective Regulation of L1 Endogenous Retroelements in Primary Sjogren's Syndrome and Systemic Lupus Erythematosus: Role of Methylating Enzymes. Clio Mavragani[1], Adrianos Nezos[1], Irina Sagalovskiy[2], Surya V. Seshan[2], Kyriakos A. Kirou[2], Haralampos M. Moutsopoulos[1] and Mary K. Crow[2]. [1]School of Medicine, University of Athens, Athens, Greece, [2]Hospital for Special Surgery, New York, NY.

Background/Purpose: To investigate whether deranged methylating mechanisms are involved in the inappropriate expression of LINE-1 (L1) retroelements in primary Sjogren's syndrome (SS) and systemic lupus erythematosus (SLE).

Methods: Minor salivary glands (MSG) were obtained from 35 patients with primary SS [23 without adverse predictors for lymphoma development (SS-low risk) and 12 complicated by B-cell lymphoma (SS-lymphoma)] and 17 sicca controls (SC). Additionally, kidney biopsy specimens and PBMCs were obtained from 23 and 73 lupus patients respectively. Relative mRNA expression was quantified for full-length L1 transcripts, along with mediators of methylation. In an independent set of 22 MSG samples (8 SS-low risk, 11 SS-lymphoma and 3 SC), methylation levels of the L1 promoter were determined by bisulphite pyrosequencing.

Results: A strong positive correlation was demonstrated between L1 transcripts and gene products that mediate de novo and constitutive DNA methylation, DNA methyltransferase (DNMT)3B, DNMT1, and methyl CpG binding protein 2 (MeCP2), in both SS MSG and lupus renal tissues. A significantly negative correlation was observed between expression of L1 and lymphoid-specific helicase (LSH, encoded by HELLS) in both SS MSG and SLE kidney tissues, as well as between DNMT3A transcripts and L1 expression in SLE kidney tissues and PBMCs. Reduced levels of L1 promoter methylation along with increased DNMT3B, DNMT1, and MeCP2, but reduced LSH levels were detected in SS-low risk patients compared to both SS-lymphoma and SC. The SS-lymphoma group was also characterized by a profound decrease of MeCP2 and DNMT3B compared to SC.

Conclusion: Our data support a contributory role of altered methylation mechanisms in the pathogenesis of systemic autoimmune disorders and related lymphoproliferative processes and suggest that LSH and DNMT3A should be investigated as candidate upstream mediators of decreased L1 promoter methylation and increased L1 expression.

Disclosure: C. Mavragani, None; **A. Nezos**, None; **I. Sagalovskiy**, None; **S. V. Seshan**, None; **K. A. Kirou**, None; **H. M. Moutsopoulos**, None; **M. K. Crow**, None.

2088

Association of TNFAIP3 Gene Polymorphisms with the Risk for RA and Prediction of Therapy Outcome of TNFα-Blocker Treatment. Susanne Drynda, Marietta Gloetzner and Joern Kekow. Univ of Magdeburg, Clinic of Rheumatology, Vogelsang-Gommern, Germany.

Background/Purpose: The TNFα inducible protein 3 (TNFAIP3=A20) is an important regulatory protein for the inhibition of NFkB activation in TNFaR and TLR pathways. It belongs to a group of genes that have been described as regulated differentially in mononuclear blood cells from patients with rheumatoid arthritis treated with TNFα-blockers early in the course of treatment in association to the clinical outcome. Recently published studies demonstrated that sequence variations in the TNFAIP3 gene are associated with the risk for several autoimmune diseases including RA, SLE and psoriasis. It was the aim of our study to analyze the frequency of two independent SNPs (rs583522 T/C intron, and rs2230926 T/G, exon 3) in the TNFAIP3 gene in CCP-antibody positive and negative RA patients and to determine their potential role as a predictive biomarker for therapy outcome of anti-TNFα treatment.

Methods: 423 RA patients with high disease activity and 93 healthy controls were included in the study. Genotyping was performed with pre-designed TaqMan assays for rs583522 and rs2230926 in 5μl reaction mixtures containing 10 ng genomic DNA. HLA-Genotyping was performed using the HLA-DRB1 Shared epitope reverse Hybridization Kit (AID GmbH Germany). CCP-antibody levels were determined with the CCP-2 assay (Menarini, Italy). Disease activity and therapy response were assessed according to the EULAR criteria.

Results: For the intronic SNP rs583522 (T/C) a significant lower frequency of the minor allele was observed in RA patients compared to controls (p=0.014), no significant differences were seen in the allele frequency between CCP-antibody positive and negative RA patients nor in association to the shared epitope encoding alleles. A higher frequency of the

minor allele (G) was found in RA patients compared to controls for rs2230926 (T/G), without reaching statistical significance (p=0.160). CCP-antibody negative patients had a higher frequency of the T/G genotype compared to CCP-antibody positive patients. In contrast to the entire RA group, the subgroup of CCP-antibody negative RA patients had a significant higher allele frequency of the minor allele compared to healthy controls (p=0.042). Disease activity was comparable for the three genotypes of the intronic SNP. For rs2230926 a significant higher disease activity was observed in T/T genotype in contrast to T/G genotype (DAS28 5.78+0.08 vs 5.07+0.31, mean+SEM). No differences were found in the genotype distribution for both SNPs between TNF-blocker responders and non-responders.

Conclusion: Our data confirm earlier reports of an association of the non-synonymous polymorphism rs2230926 in exon 3 resulting in an amino acid substitution Phe/Cys with the risk for RA, particularly for CCP-negative disease. The association of the intronic SNP rs583522 with the risk for RA has not been described before. A predictive importance of the analyzed polymorphisms for therapy outcome of TNF-blocker therapies could not be observed. Due to the low frequency of the minor allele of rs2230926 data have to be considered preliminary and confirmed in larger cohorts.

Disclosure: S. Drynda, None; **M. Gloetzner**, None; **J. Kekow**, None.

2089

The APOL1 Gene Is Not Associated with Lupus Nephritis in Individuals with Enriched Amerindian Ancestry. Julio Molineros[1], Hannah Ainsworth[2], Robert Kimberly[3], Michelle A. Petri[4], Rosalind Ramsey-Goldman[5], Luis M. Vilá[6], John D. Reveille[7], Elizabeth E. Brown[8], Swapan Nath[1], Carl D. Langfeld[9], Bernardo Pons-Estel on behalf of GENLES[10], Graciela S. Alarcon[11] and Marta E. Alarcon Riquelme[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Wake Forest, Winston-Salem, NC, [3]University of Alabama, Birmingham, AL, [4]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [5]Northwestern University and Feinberg School of Medicine, Chicago, IL, [6]University of Puerto Rico Medical Sciences Campus, San Juan, PR, [7]University of Texas Health Science Center at Houston, Houston, TX, [8]University of Alabama at Birmingham, Birmingham, AL, [9]Wake Forest University Health Sciences, Winston-Salem, NC, [10]Sanatorio Parque, Rosario, Argentina, [11]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL.

The APOL1 Gene is not Associated with Lupus Nephritis in Individuals with Enriched Amerindian Ancestry Background/Purpose: The APOL1 gene coding variants G1 and G2 have been described to be associated with chronic renal disease and end-stage Renal Disease (ESRD) in patients of African descent with different nephropaties. The association of these genes with ESRD but not lupus nephritis (LN) per se has also been recently reported in SLE patients of African descent (1). Amerindian ancestry has been found to be associated with the occurrence of lupus (2) and LN (3) but whether risk variants in the APOL1 gene would be preferentially observed in those who develop LN and have a large Amerindian ancestral component has not been determined.

Methods: Patients with SLE (ACR criteria) from various sources across North and South America were genotyped for a complete GWAS using the OMNIv1 Illumina array. Data was QC filtered and analyzed using PLINK. Cases were those SLE patients who had LN as per the corresponding ACR criterion and compared to healthy controls. We used PCAdmix to determine local ancestry across the genome and selected the data within the APOL1 locus. We also investigated if we identified proxies for the G1 or G2 variants. The frequency distribution of Amerindian ancestry and APOL1 genes was then compared between cases and controls and a T-test was used to investigate differences between cases and controls within ancestries in the genomic segment.

Results: There were 400 cases and 1200 healthy controls. Table 1 shows the distribution of European (CEU), West African (YRI) and Amerindian (NAH) ancestry within the segments (windows) of APOL1 variants studied between cases and controls covering 322 SNPs. As the G1 and G2 variants were not genotyped, we attempted to identify proxies using GWAS data for Latin Americans. Two proxies for G1 were observed, but none for G2. The G1 proxies were nearly monomorphic in the Amerindian enriched individuals (maf = <1%). The proportion of African ancestry within the locus was <4%.

Table 1. Ancestry within the APOLI Genomic Segment is similar between cases with LN and health the segment was non-significant

Local ancestry windows	From SNP	start position	pos1M	Case_ CEU	Case_ YRI	Case_ NAH	Control_ CEU	Control_ YRI	Control_ NAM
APOLI Window1 [182 SNPs]	rs1573708	34757430	34,76	0.406648	0.030223	0.56313	0.4094346	0.0299441	0.54062129
APOL1 Window2 [141 SNPs]	rs2160907	35765846	35.77	0.40974	0.049058	0.541202	0.4157275	0.0455918	0.53868068

Conclusion: Variants within the nephropathy gene APOL1 were not associated with the occurrence of LN among these SLE patients from the Americas exhibiting a large Amerindian ancestral background. Our results can be ascribed to the low proportion of African ancestry within the locus.

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Disclosure: J. Molineros, None; **H. Ainsworth**, None; **R. Kimberly**, None; **M. A. Petri**, None; **R. Ramsey-Goldman**, None; **L. M. Vilá**, None; **J. D. Reveille**, None; **E. E. Brown**, None; **S. Nath**, None; **C. D. Langfeld**, None; **B. Pons-Estel on behalf of GENLES**, None; **G. S. Alarcon**, None; **M. E. Alarcon Riquelme**, None.

2090

Contribution of MTHFR Gene Polymorphisms in Sjogren's Syndrome Related Lymphomagenesis. Sofia Fragkioudaki[1], Adrianos Nezos[1], Aristea Papageorgiou[1], Michael Voulgarelis[1], Mary K. Crow[2], Haralampos M. Moutsopoulos[1] and Clio Mavragani[1]. [1]School of Medicine, University of Athens, Athens, Greece, [2]Hospital for Special Surgery, New York, NY.

Background/Purpose: Sjogren's syndrome (SS) exhibits the highest susceptibility, among systemic autoimmune diseases, to non-Hodgkin lymphoma (NHL) development. Genetic instability and DNA methylation have been previously implicated in the pathogenesis of lymphoproliferative disorders. Methylene tetrahydrofolate reductase (MTHFR) is an enzyme essential in DNA synthesis and methylation pathways. Two common polymorphisms of the MTHFR gene, C677T and A1298C, have been implicated in the development of NHL, as they reduce the MTHFR enzyme activity and may affect DNA methylation and stability. The aim of this study was to investigate the possible contribution of the MTHFR C677T and A1298C polymorphisms in SS-related lymphomagenesis.

Methods: 189 SS patients without NHL, 72 SS patients with NHL (57 with MALT and 15 with non-MALT lymphoma), 160 healthy controls (HC) and 124 rheumatoid arthritis (RA) patients were genotyped for the detection of the MTHFR gene polymorphisms (C677T and A1298C) using polymerase chain reaction followed by restriction fragment length polymorphism (PCR-RFLP). Methylation levels of CpG islands of the promoter of the long interspersed nuclear element 1 (LINE-1) -a marker of global methylation status- were also evaluated by pyrosequencing in genomic DNA derived from 23 salivary gland tissues from SS (10 with NHL and 13 without) patients.

Results: Non NHL SS patients had significantly reduced rates of the A1298C AC heterozygous genotype compared to both RA patients and HC (OR=0.57, 95%CI=0.36–0.91, p=0.02 and OR=0.57, 95%CI=0.37–0.88, p=0.01 respectively). In contrast, the prevalence of both MTHFR C677T and A1298C polymorphisms did not significantly differ between SS patients complicated by NHL compared to uncomplicated SS, RA and HC groups. Further analysis according to the lymphoma subtype revealed 677 T as a risk allele and the 1298 C as a protective allele for non-MALT NHL development in patients with SS (OR=2.1, 95%CI=0.99–4.45, p=0.05 and OR=0.19, 95%CI=0.04–0.80, p=0.01). The concomitant presence of 1298 AA and 677 TT genotype conferred an increased risk for non-MALT NHL development among SS patients (OR: 3.4, 95%CI: 1.1–10.9, p=0.04). Of interest, an association was observed between the presence of the MTHFR 677 T -but not MTHFR 1298 C allele- with lower methylation levels (TT vs CT vs CC: 67.9±2.2 vs 69.7±2.9 vs 72.3±2.1, p=0.027, by Kruskal Wallis-test), implying methylation defects as potential underlying mechanisms in the pathogenesis of SS related non-MALT lymphoma.

Conclusion: In the current study, we identified novel associations of MTHFR polymorphisms with non NHL SS as well as with SS complicated by non-MALT lymphoma. Preliminary data suggest that alterations of global methylation related to the presence of MTHFR 677 T variants may contribute to the pathogenesis of non-MALT lymphoma among SS patients.

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2091

Plasma Microparticle Protein Features Distinctively Classify Systemic Lupus Erythematosus and Systemic Sclerosis and Their Clinical Phenotype. Ole Østergaard[1], Christoffer T. Nielsen[2], Line V. Iversen[3], Anders A. Bengtsson[4], Søren Jacobsen[5] and Niels H. H. Heegaard[6]. [1]Statens Serum Institute, Copenhagen S, Denmark, [2]University Hospital Rigshospitalet, Copenhagen, Denmark, [3]Statens Serum Institut, Copenhagen, Denmark, [4]Lund University, Lund, Sweden, [5]Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [6]Odense University Hospital, Odense C, Denmark.

Background/Purpose: Plasma microparticles (MPs) comprise a heterogenous population of submicron membraneous vesicles shed from the cell-surface both constitutively and as a consequence of pathological processes. We isolate MPs from well-characterized patients with systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and from healthy controls (HCs) for thorough comparative analysis at the proteome levels.

Methods: MPs were isolated from 1 mL platelet poor citrate plasma by repeated ultracentrifugation using a standard protocol (1) before in-solution digestion with trypsin followed by analysis by tandem mass spectrometry for protein identification and quantification (2). In total, MPs from 45 SLE patients and 37 SSc patients (all fulfilled the relevant American College of Rheumatology Disease Criteria) were analyzed and compared to MPs from 35 age- and sex-matched healthy controls.

Results: More than 1000 proteins were identified from each group. Univariate statistics, hierarchical clustering, and principal component analysis were applied to analyze the protein intensities to search for disease classifiers. Samples from SLE patients showed increased levels of complement factors, immunoglobulin, galectin-3-binding protein, CD5-like protein and decreased levels of organellar and membrane associated proteins. In addition, proteins intensities from C1q, G3BP and 14-3-3 showed correlation with disease activity. SSc samples showed increased levels of complement factors and extracellular matrix proteins (fibulin, fibronectin) and decreased levels of tropomyosin-1 and various mitochondrial proteins. Principal component analysis on the centered dataset could differentiate the SLE samples from the NOR and SSc samples.

Conclusion: In-depth proteomic characterization of plasma MPs in SLE and SSc supports their putative role in disease pathology, immune regulation and as biomarkers.

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Disclosure: O. Østergaard, None; **C. T. Nielsen**, None; **L. V. Iversen**, None; **A. A. Bengtsson**, None; **S. Jacobsen**, None; **N. H. H. Heegaard**, None.

2092

Proteomic Phenotyping of Rheumatoid Arthritis Disease Activity. Yauheniya Cherkas, Sarah Lamberth, Carrie Brodmerkel and Mark Curran. Janssen Research & Development, LLC., Spring House, PA.

Background/Purpose: The use of objective biomarkers of clinical disease characteristics such as disease activity would be beneficial in informing patients, physicians and payers. Recently, a number of potential biomarkers for RA disease diagnosis, prognosis and activity have been described in the literature. However, the majority of these have not been validated in independent cohorts.

Methods: We assessed the performance of available biomarkers of RA disease as well as developed and validated novel tests using samples from multiple cohorts of moderate to severe RA patients. Serum samples from subjects enrolled in two Phase III studies (GO-FURTHER and GO-SAVE; clinicaltrials.gov – NCT00973479 and NCT01004432) and a Phase II study (NCT00718718) were obtained at multiple timepoints. Using samples from the GO-FURTHER (NCT00973479) cohort we evaluated commercially available correlates of disease activity as well as developed novel molecular readouts of disease activity.

Results: We were able to develop two serum-based alternatives to DAS28-CRP score with similar performance using both informed and inclusive approaches to protein selection. The two tests were developed using a set of proteins profiled via ELISA; and a highly multiplexed (SomaLogic) proteomic platform. The tests had consistently good performance in samples from cross-validation runs and samples from same subjects left out of the modeling step. We have also observed similar or better performance in patients enrolled in independent cohorts coming from other two clinical trials and additional replication is underway.

Conclusion: Validation of objective biomarkers of clinical disease state is important for advancing the evaluation and comparison of novel therapeutics in RA.

Disclosure: Y. Cherkas, Janssen Research & Development, LLC., 3; **S. Lamberth**, Janssen Research & Development, LLC., 3; **C. Brodmerkel**, Janssen Research & Development, LLC., 3; **M. Curran**, Janssen Research & Development, LLC., 3.

2093

Improvement of Rituximab Response Prediction in Rheumatoid Arthritis Via Correction for Prednisone-Related Suppression of Type I Interferon Response Gene Expression. Tamarah D. de Jong[1], Saskia Vosslamber[1], Marjolein Blits[1], Gertjan Wolbink[2], Michael T. Nurmohamed[2], Connie J. van der Laken[1], Gerrit Jansen[1], Alexandre E. Voskuyl[1] and Cornelis L. Verweij[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Jan van Breemen Research Institute Reade, Amsterdam, Netherlands.

Background/Purpose: Elevated type I IFN response gene (IRG) expression has been described to be clinically relevant in predicting the non-response to rituximab in rheumatoid arthritis (RA) patients. Interference between glucocorticoids (GCs) and type I IFN signaling has been demonstrated in vitro. Since the use and dose of oral GCs is highly variable among patients prior to the start of treatment with rituximab, we aimed to determine what the effect of GC usage is on the IRG expression in relation to the clinical response to rituximab.

Methods: The study was performed in two independent cohorts of established RA patients (n=32 and n=182) and a third cohort of 40 established RA patients that were candidates for rituximab therapy, recruited from the VU University medical center and the Jan van Breemen Institute Reade in Amsterdam. All patients fulfilled the revised American College of Rheumatology (ACR) 1987 criteria for the diagnosis of RA. In all patients, peripheral blood gene expression of 8 IRGs was determined by microarray or multiplex quantitative (q)PCR and an IFN-score was calculated. GC use consisted of oral prednisone in doses varying from 2.5–10mg/day in 19%, 29% and 70% of the patients in the three cohorts, respectively. The clinical response to rituximab was determined after 6 months of therapy based on the change in 28 joints Disease Activity Score (ΔDAS28); patients with ΔDAS28>1.2 were considered responders. The IFN score was tested for its predictive value using Receiver Operating Characteristics (ROC) curve analysis in the patients who started with rituximab (n=40).

Results: In all three cohorts, we consistently observed suppression of the IFN-score in patients using prednisone ($PREDN^+$) compared to patients that were not using prednisone ($PREDN^-$). No clinical differences were observed between $PREDN^-$ and $PREDN^+$ patients. The suppression of IFN-score appeared to be dose-dependent as it was most pronounced in the highest dose range (>10mg/day). In the rituximab cohort, separate ROC analysis on $PREDN^-$ patients alone revealed improved prediction of non-response to rituximab by baseline IFN-score with an AUC of 0.969 compared to 0.848 when analyzed in all patients, whereas prednisone use itself had no predictive value in this cohort. Using a subgroup-specific cutoff of the IFN-score in the $PREDN^-$ and $PREDN^+$ groups the sensitivity increased from 41% in all patients up to 88% in the $PREDN^-$ group, combined with a specificity of 100%.

Conclusion: Prednisone use in RA patients causes suppression of IRG expression. Rituximab response prediction based on the IFN-score at baseline could be considerably improved when prednisone use is taken into account.

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2094

Deep Sequencing Reveals Differential RNA Expression during Malignant Transformation in Major Salivary Glands in a Mouse Model of Sjogren's Syndrome. Kaiyu Jiang[1], Long Shen[2], Zihua Hu[3], Julian Ambrus[4] and James Jarvis[5]. [1]The University at Buffalo, Buffalo, NY, [2]SUNY at Buffalo, Buffalo, NY, [3]University at Buffalo, Buffalo, NY, [4]University Of Buffalo, Buffalo, NY, [5]SUNY Buffalo School of Medicine, Buffalo, NY.

Background/Purpose: – Sjšgren's syndrome (SS) is a chronic autoimmune disease of unknown etiology that targets salivary and lacrimal glands and may be accompanied bymultiorgan systemic manifestations. To further the understanding of immunopathology associated with SS and identify potential therapeutic targets, we examined the transcriptomeof salivary glands in a mouse models of Sjogren's syndrome through disease progression.

Methods: We isolated RNA from salivary glands of interleukin-14 alpha-transgenic mouse, a model of SS, at 3 different disease stages: pre-autoimmune, autoimmune and malignant. RNA samples were prepared for sequencing using the Illumina TruSeq RNA prep kit. Sequencing was performed using the Illumina HiSeq 2500. The pass filter reads were mapped to the genome (NCBI/build 37.2) using TopHat (version 2.0.4). Probable transcripts were assembled using Cufflinks (version 2.0.2), and differential expressed transcripts were determined using DESeq. Fold change (FC) calculations were obtained using the log2(FPKM) ratio, where FPKM is the fragments per kilobase of exon model per million mapped fragments.

Results: Salivary glands RNAs demonstrated disease-stage specificity. For example, when we compared autoimmune to pre-autoimmune stages, there were 26 DE genes (10 down-regulated, 16 up-regulated) that demonstrated a 2.46 fold change or greater. We found 22 DE genes (3 down-regulated, 19 up-regulated) that showed a 2.4 fold of greater difference when we compared malignant *vs* pre-autoimmune. Ingenuity pathway analysis demonstrated that the DE genes are associated with cancer, development disorders, hereditary disorder, ophthalmic disease, organismal injury and abnormalities, and reproductive system disease (e.g. *GSK3A, KRT12, KRT34, KRT36, KRTAP9-4, NEUROD6, OAS2, PRDM5, RHPN2, TPCN1*). Sixteen DE genes, including type I IFN response genes OAS2, were common to the autoimmune to pre-autoimmune and the malignant to pre-autoimmune comparisons. Further evidence that the 16 DE genes, which expression are up-regulated associated disease severity, i.e. gene expression level in malignant is higher than in autoimmune; and in autoimmune higher than in pre-autoimmune.

Conclusion: The sensitivity and dynamic range of RNAseq allow a detailed view of salivary glands transcriptome. Multiple RNA transcripts show disease-state specificity, suggesting that they may be directly involved in pathogenesis. These finding are expected to lead to new insights into SS pathogenesis and biologic processes leading to SS-associated malignancy.

Disclosure: K. Jiang, None; **L. Shen**, None; **Z. Hu**, None; **J. Ambrus**, None; **J. Jarvis**, None.

2095

Two Novel Serum Urate Levels Associated Genetic Loci Identified By GWAS in European Were Confirmed in Chinese Han Population. Minhui Hua[1], Wenfeng Tan[2] and Miaojia Zhang[3]. [1]the first affliated hospital with Nanjing medical university, nanjing, China, [2]THE FIRST AFFILIATED HOSPITAL OF NANJING MEDI, NANJING, China, [3]the first affliated hospital with nanjing medical univercity, nanjing, China.

Background/Purpose: Previous GWAS have identified four novel loci (SNP rs11264341, rs6770152, rs2941484 and rs7224610) were significant with serum urate levels in European. Here, we further assess the association of these 4 loci in the phenotypic expression of hyperuricemia in Chinese Han population.

Methods: A total of 1341 unrelated participants (701 hyeruricemia participants and 640 healthy individuals) were enrolled into our study. All individuals of this study participated from Jiangsu and Anhui Province. DNA samples were genotyped using TaqMan probes that specifically target the alternate alleles. We used χ^2-test to determine whether the genotypes of cases and controls of all SNPs deviated from Hardy-Weinberg equilibrium. Differences in allele frequencies between dichotomous traits were calculated employing the same method. Differences in continuous variables between groups were calculated using a two-tailed unpaired t-test. Power analysis was carried out using QUANTO1.2.4.

Results: SNP rs11264341 and rs7224610 were newly discoverred susceptible loci in mainland Chinese Han hyperuriccemia population. The distributions of SNP rs11264341 and rs7224610 were significantly different in hyperuricemia participants and healthy controls. The study also confirmed the association of SNP rs11264341 and rs7224610 with hyperuricemia ($p<0.05$) in Chinese Han population. C-allele in SNP rs11264341 seemed to be a risk factor in the influence of serum uric acid level. C-allele in SNP rs7224610 played a role of protection in the mean serum urate concentration ($p<0.05$).

Conclusion: This study confirmed 2 newly SNP rs11264341 and SNP rs7224610 were significant associated hyperuricemia susceptibly in Chinese Han and the genetic variation of these two SNPs could affect the serum urate concentration in Chinese Han population.

Disclosure: M. Hua, None; **W. Tan**, None; **M. Zhang**, None.

2096

Assessment of RA Heterogeneity in Two Independent Cohorts of Patients. Joshua Joung, Yauheniya Cherkas and Sarah Lamberth. Janssen Research & Development, LLC., Spring House, PA.

Background/Purpose: RA is known to be a heterogeneous disease, with heterogeneity existing in both clinical symptoms and responses to therapies. Molecular assessment of this heterogeneity would help to describe novel aspects of RA pathogenesis and potentially allow for more accurate predictions of which treatments will be most beneficial to a given patient. We examined the question of whether similar immune-relevant pathways are significantly enriched in different RA populations focusing on whole blood gene expression profiles of 2 large cohorts of clinical trial subjects.

Methods: Both cohorts included men and women aged ≥18 yrs with active RA for ≥ 3 months with inadequate response to methotrexate (MTX). Messenger RNA (mRNA) was collected from 487 baseline whole blood samples in Cohort 1 (Clinical study NCT00973479) and 89 baseline whole blood samples in Cohort 2 (Clinical study NCT01597739). Additionally, non-RA serum samples (healthy controls; Cohort 1 n=22, Cohort 2 n=24) were obtained from Bioreclamation (Hicksville,NY). All samples were profiled using the HT HG-U133+ PM Array (Affymetrix). Comparisons between the healthy control and diseased experimental groups were performed using iReport (Ingenuity; Redwood, CA) and pathway analyses were performed using IPA (www.ingenuity. com), NextBio (www.nextbio.com), and MetaCore (www.thomsonreuters.com/metacore). Statistical significance is based on p-value 0.05 and fold change 1.2.

Results; The disease profiles (DP) comparing baseline gene expression levels of RA and healthy controls contain 2203 and 1282 differentially expressed genes (DEGs) for Cohorts 1 & 2 respectively. There were 324 DEGs shared between the two cohorts, encompassing 14.7% and 25.5% of Cohort 1 and 2. On a pathway level, IPA identified 119 pathways that were present and significant (Fisher's Exact Test p-value) in at least one cohort. Of these, 21 (17.6%) were shared and significant in both cohorts and included inflammatory and immune response related pathways. 17 and 81 pathways were uniquely significant to Cohort 1 and Cohort 2 and included complementary pathways such as cell and cytokine signaling pathways. Analysis via MetaCore identified 406 total pathways; 134 were shared and significant to both cohorts, and 102 and 170 were uniquely significant to Cohorts 1 and 2 respectively. Shared and significant pathways primarily included those related to immune response; pathways unique to only one cohort were enriched for immune response signaling and inflammatory response.

Conclusion: Analysis of disease profiles from 2 independent cohorts via IPA and MetaCore analysis tools showed that the significant pathways common to both cohorts are enriched in inflammatory and immune response pathways. The uniquely significant pathways of Cohort 2 were notably enriched in inflammatory pathways and cell/cytokine signaling. A complimentary approach via MetaCore identified more enriched sets of overlapping and unique pathways relevant to Cohorts 1 and 2, as well as similar trends for unique and common pathways. These results reflect the complexity and diversity of RA across different cohorts and enhance understanding of the interplay of pathways in a given patient.

Disclosure: J. Joung, Janssen Research & Development, LLC., 3; **Y. Cherkas**, Janssen Research & Development, LLC., 3; **S. Lamberth**, Janssen Research & Development, LLC., 3.

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Identification of Diagnostic and Activity Metabolomic Urine Biomarkers in Six Immune-Mediated Inflammatory Diseases. Arnald Alonso[1], Jesús Tornero[2], Antonio Fernandez Nebro[3], Juan D. Cañete[4], Eugeni Domènech[5], Javier P. Gisbert[6], Carlos Ferrándiz[5], Eduardo Fonseca[7], Valle García[8],

Francisco Blanco[7], Jesus Rodriguez[9], Jordi Gratacós[10], Patricia Carreira[11], Toni Julia[1], Raül Tortosa[1], María América López-Lasanta[1], Xavier Correig[12] and Sara Marsal[1]. [1]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [2]Hospital Universitario Guadalajara, Guadalajara, Spain, [3]Hospital Regional Carlos Haya, Biomedical Research Institute of Malaga (IBIMA), Malaga, Spain, [4]Hospital Clinic, Barcelona, Spain, [5]Hospital Universitari Germans Trias I Pujol, Badalona, Spain, [6]Hospital Universitario de la Princesa, Madrid, Spain, [7]Complejo Hospitalario Juan Canalejo, A Coruña, Spain, [8]Hospital Universitario Reina Sofía, Córdoba, Spain, [9]Hospital Universitari de Bellvitge, Barcelona, Spain, [10]Hospital Parc Taulí, Sabadell, Spain, [11]Hospital Universitario 12 de Octubre, Department of Rheumatology, Madrid, Spain, [12]Metabolomics Platform, Reus, Spain.

Background/Purpose: Metabolomics is an emergent research field within the omics sciences aimed at characterizing the metabolome in complex biological samples. It provides a powerful approach to identify physiopathological processes and metabolites can be useful biomarkers in clinically relevant applications. The present study represents the first metabolomic analysis on a large cohort including multiple immune-mediated inflammatory diseases (IMIDs). Its objective is the identification of diagnostic and activity biomarkers through the analysis of the whole urine metabolome of 6 IMIDs.

Methods: Proton nuclear magnetic resonance (^{1}H-NMR) data of urine samples was acquired among 6 IMID cohorts (n=200 Spanish patients per cohort) including: rheumatoid arthritis (RA), psoriasis (PS), psoriatic arthritis (PA), Crohn's disease (CD), ulcerative colitis (UC) and systemic lupus erythematosus (SLE). Each IMID cohort was selected in order to include low and high activity patients according to the consensus activity indexes of each disease. Distributions of sex, age, extraction time and fasting time were matched between these cohorts to avoid false positive associations due to these confounding variables. ^{1}H-NMR data of 100 control individuals was also acquired in this study. Spectral processing was performed using Focus. Mann-Whitney U test was used to evaluate potential diagnostic and activity biomarkers. A multivariate analysis (i.e. logistic regression) was also performed to avoid false positive associations due to confounding epidemiological or clinical variables. A clustering analysis was also conducted to evaluate disease similarity according to the urine metabolome.

Results: After processing the spectral data n=473 peaks were identified. This set was reduced to n=145 peaks after applying several quality control filters. The statistical analysis identified 45 metabolic peaks significantly associated (*P*-Value<1E-4) in at least one of the performed disease diagnostic or activity tests (Figure 1). When analyzing each IMID cohort separately, RA, CD and UC obtained the largest number of diagnostic biomarker candidates: n=27, n=18 and n=21 respectively. Interestingly, CD and UC shared common metabolic disturbances although differential biomarkers between them were also identified. PS and PA showed a little impact on their metabolic profiles. On the other side, when comparing low to high disease activity patients a lower number of significant associations were observed, mainly related to CD and RA.

Conclusion: A significant number of diagnostic biomarker candidates have been identified on this first large cohort of IMIDs. Several candidates were found to be global IMID biomarkers and could target the common inflammatory process shared by these diseases. RA showed the largest burden on urine metabolic disturbances and interesting activity biomarkers were identified for RA and CD.

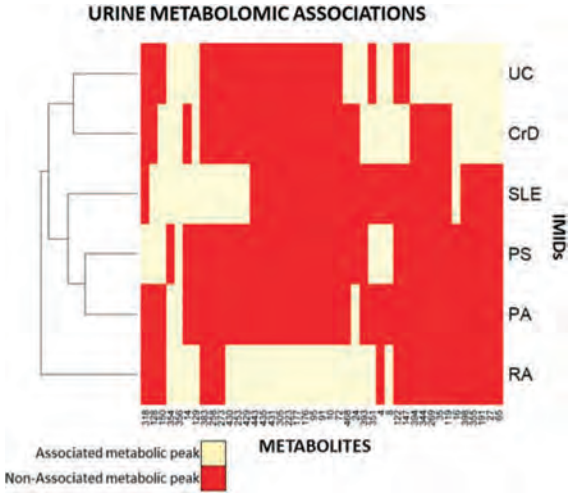

Figure 1. Urine metabolomic associations

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2098

Genetic Variants of the NLRP3 Inflammasome Are Associated with Stroke in Patients with Rheumatoid Arthritis. Alf Kastbom[1], Lisbeth Ärlestig[2] and Solbritt M. Rantapää-Dahlqvist[2]. [1]Linköping University, Linköping, Sweden, [2]Umeå University, Umeå, Sweden.

Background/Purpose: Inflammasomes are intra-cellular protein complexes important for the production of pro-inflammatory cytokines such as interleukin-(IL-)1β and IL-18. Cardiovascular disease is over-represented in patients with rheumatoid arthritis (RA), and chronic inflammation is believed, at least partly, to underlie this circumstance. Recent studies have suggested that the NLRP3 inflammasome influences both the severity of RA and development of atherosclerosis. NLRP3-Q705K and CARD8-C10X are functional polymorphisms which have been shown to influence inflammasome function, and to associate with plasma IL-1β levels in healthy individuals. Also, a number of reports have described synergistic effects between these polymorphism. Therefore, we sought to determine whether NLRP3-Q705K and CARD8-C10X influence the risk of cardiovascular disease (CVD) in patients with RA.

Methods: The incidence of CVD was assessed in 522 patients with established RA fulfilling the 1987 ACR criteria by a retrospective survey of medical records in combination with a 6 year prospective follow-up. CV events were defined as myocardial infarction (MI), severe verified angina pectoris treated with coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention, or stroke/transient ischaemic attack (TIA). NLRP3-Q705K and CARD8-C10X genotypes were analysed in relation to CVD by logistic regression analysis adjusting for traditional risk factors in addition to event preceding RA, treatment for RA, cumulative disease activity, and age at the onset of RA.

Results: From the onset of RA to the 6-year follow-up, 121 patients were recorded as undergoing a CV event(s): 74 had suffered an MI, 20 had angina pectoris with intervention and 50 experienced a stroke/TIA. Carriage of the minor allele of NLRP3-Q705K was associated with an increased risk of stroke/TIA (Odds ratio (OR) = 2.01, 95% Confidence interval (CI) 1.0–4.1, p=0.05), whilst CARD8-C10X did not associate with any type of CV event. Patients with ≥1 variant allele in both polymorphisms had an increased risk of a CV event (OR 2.2, 95% CI 1.1–4.5, p=0.026) when compared with those homozygous for the major alleles of each polymorphism. Stratification showed that this risk was exclusively confined to stroke/TIA (OR 3.4, 95% CI 1.5–7.7, p=0.003) and not to MI and/or angina pectoris (OR, 1.5, 95% CI 0.6–3.4). Adjusting for traditional risk factors and RA severity yielded higher ORs regarding any CV event (OR 2.6, 95% CI 1.1–5.9, p=0.023) and stroke/TIA (OR 5.9, 95% CI 2.1–17, p=0.001). Stratification for sex consistently showed higher risk estimates among female patients.

Conclusion: Genetic variants of the NLRP3 inflammasome influence the risk of stroke/TIA, but not of MI/angina pectoris in patients with established RA. Future work should include genetic variants in upstream signaling pathways. Also, the possible clinical value of NLRP3 and CARD8 genotyping of RA patients, in relation to the risk of CVD and its prevention, calls for further attention in larger patient cohorts.

Disclosure: A. Kastbom, None; **L. Ärlestig**, None; **S. M. Rantapää-Dahlqvist**, None.

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Serum C-X-C Motif Chemokine 10 (CXCL10) Is Elevated in Psoriasis Patients Prior to Psoriatic Arthritis Onset. Remy Pollock[1], Fatima Abji[1], Husain Shakil[1], Kun Liang[2], Vinod Chandran[1] and Dafna D. Gladman[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]University of Waterloo, Waterloo, ON.

Background/Purpose: Psoriatic arthritis (PsA) is a potentially destructive disease that develops in about 30% of patients with cutaneous psoriasis. Biomarkers that can predict which psoriasis patients are destined to develop PsA may help early diagnosis of PsA. This study aimed to determine if T cell and NK cell-associated cytokines IFNA2, IL-15, IL-17A, IL-23, and TRAIL, and chemokine CXCL10, are elevated in the serum of psoriasis patients who progress to develop PsA, compared to psoriasis patients who do not develop PsA.

Methods: Psoriasis patients were followed prospectively beginning in 2006, and were assessed yearly by a rheumatologist for the presence of PsA. Psoriasis patients who developed PsA were termed 'converters', and serum samples were taken at baseline from all and again at PsA diagnosis from a subset of converters. Age and sex-matched patients who did not develop PsA over the same duration of psoriasis were termed 'non-converters'. Serum CXCL10, IFNA2, IL-15, IL-17A, IL-23, and TRAIL were measured using a multiplexed microsphere-based assay on the Luminex 200 platform. Protein levels were compared between samples taken before and after PsA diagnosis by paired t-test, and between converters and non-converters by logistic regression.

Results: Forty-six psoriasis patients developed PsA. At baseline, these converters were 54.3% males, with a mean age of 46.1 ± 13.0 years, mean psoriasis duration of 25.5 ± 14.9 years, mean age at psoriasis onset of 20.9 ± 16.5 years, and mean PASI of 7.0 ± 7.2. Converters were compared to 46 non-converters who were 50% males, with a mean age of 45.5 ± 12.3 years, mean psoriasis duration of 27.5 ± 16.0 years, mean age at psoriasis onset of 18.9 ± 16.3 years, and mean PASI of 6.3 ± 6.1. Candidate biomarkers were first tested in half of the converter and non-converter samples (discovery cohort), then were validated in the remaining samples. In the discovery cohort, CXCL10 was significantly elevated in baseline samples from converters compared to non-converters (OR=1.6, 95% CI 1.2–2.2, p=0.005). TRAIL was also elevated in converters at baseline (OR=1.0, 95% CI 1.0–1.1, p=0.05) however it was not independent of CXCL10 in multivariate analyses. IFNA2, IL-15, IL-17A, and IL-23 were below the detectable range in several samples and were not significant. CXCL10 remained significantly elevated (OR=1.3, 95% CI 1.1–1.5, p=0.003) in a combined analysis of the discovery and validation cohorts. Twenty-three converters had samples taken at both baseline and at PsA diagnosis. Although mean CXCL10 level was high in baseline samples, it declined significantly following PsA onset from 932 ± 458 pg/ml to 543 ± 310 pg/ml (p<0.001), which is not significantly different from the mean CXCL10 levels observed in non-converters (421 ± 218 pg/ml, p=0.06).

Conclusion: We demonstrated that CXCL10 was elevated in the serum of psoriasis patients who later developed PsA, but following PsA onset returned to levels closer to those observed in psoriasis patients who did not develop PsA. Further studies are needed to elucidate of the dynamics of serum CXCL10 levels in the progression from psoriasis to PsA, and to determine how well CXCL10 levels indicate PsA risk in psoriasis patients.

Disclosure: R. Pollock, None; **F. Abji**, None; **H. Shakil**, None; **K. Liang**, None; **V. Chandran**, None; **D. D. Gladman**, None.

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Activation of NFkβ Pathways in Sjögren's Syndrome Related Lymphomagenesis-Role of the His159Tyr Mutation of the BAFF-R Receptor. Clio Mavragani[1], Adrianos Nezos[1], Aristea Papageorgiou[1], Haralampos M. Moutsopoulos[1], Athanasios G. Tzioufas[2] and Michael Voulgarelis[1]. [1]School of Medicine, University of Athens, Athens, Greece, [2]School of Medicine, National University of Athens, Athens, Greece.

Background/Purpose: Sjögren's Syndrome (SS) bears the highest risk for lymphoma development among all autoimmune diseases. A growing body of evidence suggests activation of NFκB pathways as a critical step in the pathogenesis of both SS and B-cell non Hodgkin's lymphomas (NHL), the major type of SS-related lymphomas. The mutation His159Tyr of the BAFF receptor has been found to confer increased risk in patients with NHL through activation of the NF-kB pathway. The aim of the current study was to evaluate the contribution of NFκB pathways activation in SS related lymphomagenesis and explore the potential role of the His159Tyr BAFF-R mutation.

Methods: Quantitative gene expression of both NFκβ1 and NFκβ2 transcripts was measured by real-time PCR in peripheral blood (PB) derived from 31 SS, 13 SS-lymphoma and 30 healthy controls (HC), in isolated B cells from 2 SS, 6 SS-lymphoma and 5 HC as well as in minor salivary gland tissues (MSG) tissues from 31 SS, 10 SS-lymphoma and 17 sicca controls (SC). The BAFF-R His159Tyr mutation was evaluated in 247 SS patients (177 non lymphoma and 70 SS-lymphoma patients), 145 systemic lupus erythematosus (SLE) patients, 101 rheumatoid arthritis (RA) patients and 180 healthy controls (HC), by PCR-RFLP and PCR-sequencing.

Results: NFκβ2 transcripts were significantly upregulated in the PB, MSG tissues and isolated B cells derived from SS patients complicated by lymphoma compared to HC in PB and B-cells, and to both SS-non lymphoma patients and SC in MSG tissues. At PB level, an opposite pattern was observed in regard to NFκβ1 transcripts; they were found to be significantly reduced in SS patients complicated by lymphoma compared to the HC group. As a result, NFκβ2/NFκβ1 ratio was significantly increased in the peripheral blood from SS patients complicated by lymphoma compared to both SS and SC with an area under the receiver operating characteristic (ROC) curve of the NFκβ2/NFκβ1 being 0.804, p=0.002, 95%CI (0.670–0.938). In regard to His159Tyr BAFF-R mutation, we observed an increased prevalence in SS patients compared to HC [17 out of 247 (6.9%) vs 3 out of 180 (1.7%), p=0.01)]. No such statistically significant difference was found among SS, SLE and RA groups, (6.9% vs 3.5% and 3% respectively, p-values>0.05 in all comparisons). Both SS subgroups exhibited significantly higher frequencies of the His159Tyr BAFF-R mutation compared to HC (SS-lymphoma: 8.6% and SS-non lymphoma: 6.2% vs 1.7% in HC). When we stratified the SS-lymphoma subgroup according to the lymphoma subtype and the age of SS onset, the His159Tyr BAFF-R mutation was detected in 71.4% of patients with mucosa associated lymphoid tissue (MALT) NHL and an age of SS onset between 31–40 years old, conferring an 147.5 fold increased risk compared to HC [(95% CI): (20.0–1087.5, p<0.0001)].

Conclusion: Taken together, our data suggest activation of alternative NFKB pathways as a central pathogenetic event in the malignant transformation in the setting of SS, with mutation of the BAFF-R receptor being a main contributor particularly in MALT patients with a SS onset at the fourth decade of life, though other concomitantly operating mechanisms cannot be excluded.

Disclosure: C. Mavragani, None; **A. Nezos**, None; **A. Papageorgiou**, None; **H. M. Moutsopoulos**, None; **A. G. Tzioufas**, None; **M. Voulgarelis**, None.

2101

Epigenetic Study of Advanced Ankylosis in Patients with Ankylosing Spondylitis. Darren O'Reilly[1], Yuhua Zhang[2], Nayef Al Ghanim[1], Rose Ardern[1], Alexandra Munn[1], Sean Hamilton[1], Guangju Zhai[2] and Proton Rahman[1]. [1]Memorial University of Newfoundland, St. John's, NF, [2]Discipline of Genetics, Faculty of Medicine, Memorial University of Newfoundland, St. John's, NF.

Background/Purpose: Ankylosing spondylitis (AS) is an inflammatory spinal disease characterized by ankylosis of the spine. A subset of patients develops significant ankylosis resulting in mobility issues. In this pilot study, we hypothesized that epigenetic modifications may account for differences in the degree of ankylosis of the axial spine.

Methods: AS patients satisfying the New York criteria with advanced ankylosing (characterized clinically with spinal flexion) and radiographically with at least 4 continuous ankylosed vertebrae were categorized as advanced ankylosis. Control AS patients had normal posture on clinical evaluation and had absence of syndesmophytes on plain radiographs. All patients were Caucasians of Northern European Ancestry. Genome-wide DNA methylation profiling was performed on the blood DNA samples from 23 AS patients with advanced ankylosis and 25 patients with no syndesmophytes. The profiling was performed using Illumina HumanMethylation450k Beadchip, which measures up ~480,000 different CpG sites per sample and covers 96% of RefSeq genes. The methylation level at each CpG site was measured by β values varying from 0 (no methylation) to 1 (100% methylation).

Results: Advanced ankylosis patients were predominantly males (22/23), with mean of disease onset at age 21.9 years and age at time of assessment (ankylosis) was 43.72. Meanwhile, AS patients with no syndesmophytes were also predominantly males (24/25), with mean of disease onset at age 24.6 years and age at time of assessment was 44.1 years. Methylation data were normalized using BMIQ method and no batch effects were detected by PCA analysis. Methylation analysis was performed on 382,232 autosomal CpG sites after quality controls. One outlier was identified and excluded in the subsequent analysis. Analysis revealed 100 locations where there was a difference between patients with and without spinal ankylosis. The three locations that differentiated the most included CPG sites in *KIAA0319* (hypomethylated) ($p=1.7x10^{-5}$); *JAKMIP3* ($p=6.4x10^{-5}$) and *LYG2* ($p=9.6x10^{-4}$). Based on functional relevance to AS pathogenesis, particularly antigen presentation, cytokine signalling, and bone remodeling, 5 candidate genes (4 hypomethylated; 1 hypermethylated) emerged: *GPC5* (beta diff=-0.222; p=0.006), SMAD3 (beta diff=-0.16664; p=0.047), *AKAP11*(beta diff=-0.177; p=0.007), *MATN4* (beta diff=0.119; p=0.008), and *NLRC5* (beta diff=-0.11542; p=0.052).

Conclusion: These preliminary results demonstrate that the global DNA methylation pattern in advanced AS differs from AS patients with no spinal damage. High priority candidate genes identified in this study warrants further validation.

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A Tissue-Specific Lincrna in the TRAF1-C5 Risk Locus As a Putative Cis-Regulator, Bridging Genetics and Disease. Tobias Messemaker, Rute Marques, Tom Huizinga, Alwin Adriaans, Aleida Bakker, Arend Berendsen, Nina Daha, R E M Toes, Harald Mikkers and Fina Kurreeman.Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: In the last decade genome wide association studies (GWAS) have identified genetic polymorphisms that associate with Rheumatoid arthritis (RA). However, the way these genetic regions contribute to disease remains ill defined. We previously identified the *TRAF1-C5* locus as a predisposing risk factor to the development of RA. In the present study we investigated functional consequences of this risk locus.

Methods: We finemapped likely causal variants by querying Eqtl datasets and identified a strong signal between TRAF1 and C5. We measured by RT-PCR the intergenic region in different tissue panels. We performed knockdown of the intergenic region using shRNA.

Results: Using expression quantitative trait loci (eQTL) datasets, we observed an association between the risk allele and expression of *TRAF1* and *C5* at the mRNA level in various blood-related cell types. As part of an underlying mechanism we identified a novel large non-coding RNA intergenic of *TRAF1* and *C5 (C5T1-lincRNA)*. The lincRNA is transcribed in the same orientation as *TRAF1* and *C5* by RNA polymerase II, is highly transcribed in liver, and its expression is rapidly induced in different immune cells by specific immune stimuli. Expression of *C5T1-lincRNA* correlated with either *C5* or *TRAF1* expression in a tissue specific manner. In addition, knockdown of the intergenic transcript in a hepatocyte cell line resulted in decreased C5 levels.

Conclusion: Together our data support the involvement of a novel lincRNA in regulating *C5* and *TRAF1* expression. We propose that this lincRNA, which is fully located within the associated region, is responsible for the RA associated altered RNA levels of TRAF1 and C5 and plays a role in RA susceptibility.

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Tuesday, November 18

ACR/ARHP Poster Session C
Health Services Research
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

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Benefits of Early Onset of DAS28 (CRP) E Alemao[1], S Joo[2], H Kawabata[1], S Banerjee[1], M Frits[3], C Iannaccone[3], N Shadick[3] and M Weinblatt[3]. [1]Bristol-Myers Squibb, Princeton, NJ, [2]Bristol-Myers Squibb, Hopewell, NJ, [3]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Guidelines in RA recommend that treatment should be aimed at reaching a target of remission or low disease activity (LDA) as soon as possible, and that treatment should be adjusted frequently (every 3–6 months) in patients (pts) not at target. However, there are limited data from clinical practice on the benefits of attaining rapid remission/LDA. The objective of the current analysis was to compare the clinical and resource use benefits of attaining LDA (DAS28 [CRP] <2.6) within 1 yr in pts with RA in a clinical practice setting.

Methods: Pts enrolled in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) Registry, established in 2003, were analyzed. The BRASS Registry mostly comprises pts with established RA who were evaluated semi-annually on multiple clinical patient-reported outcomes and resource utilization parameters. The current analysis is based on the first 5 yrs of pt follow-up in BRASS and includes pts who were not at DAS28 (CRP) <2.6 at baseline. Pts attaining DAS28 (CRP) <2.6 at 1-yr follow-up were considered as 'DAS <2.6 Soon' and those attaining DAS (CRP) <2.6 later than 1 yr were considered as 'DAS <2.6 Late'. Clinical (physical functioning measured by MHAQ), quality of life (QoL; measured by EQ-5D, SF-12 physical component summary [PCS], Patient Health Questionnaire-9 [PHQ-9]); and resource utilization (hospitalization, ER visits, durable medical equipment [DME] use) outcomes up to 5 yrs were compared in univariate analysis between pts attaining 'DAS <2.6 Soon' vs 'DAS28 <2.6 Late'. To control for differences in baseline covariates, generalized linear models were used for continuous outcomes of HAQ, SF-12, EQ-5D and PHQ-9; logit models were used for categorical outcomes of resource use. Covariates in the multivariate analysis included baseline demographics, duration of RA disease, smoking status, baseline disease status, and treatment.

Results: 417 pts with RA were included in the current analysis: 151 (36.2%) were 'DAS <2.6 Soon' and 266 (63.8%) were 'DAS <2.6 Late'. At baseline, pts in the two groups were similar, respectively, in sex (83 vs 84% females), mean age (SD) (54.2 [12.7] vs 58.3 [13.0] yrs) and never smoked status (53.0 vs 48.9%). Fewer pts in the 'DAS <2.6 Soon' group were on biologic DMARDs than in the 'DAS <2.6 Late' group (31.1 vs 38.7%, respectively). Pts in the 'DAS <2.6 Soon' group had significantly better MHAQ and QoL, as well as fewer hospitalizations, DME use and ER visits in univariate analysis than the 'DAS28 <2.6 Late' group. Similar findings for all outcomes, except hospitalization/ER visits, were observed in multivariate analysis (see table).

Table: Difference in Outcomes at 1 year and 2 years in Patients Attaining DAS28 <2.6 Soon vs Late

	1-year post evaluation		2-year post evaluation	
Outcomes	**Mean difference between DAS <2.6 Soon vs Late**	**p-value**	**Mean difference between DAS <2.6 Soon vs Late**	**p-value**
HAQ	−0.127	0.003	−0.097	0.0213
SF-12 PCS	Not available	–	3.84	0.0034
PHQ-9	Not available	–	−1.16	0.0035
EQ-5D	0.057	0.0001	0.036	0.0234
	Odds ratio for DAS <2.6 Soon vs Late	95 % CI	Odds ratio for DAS <2.6 Soon vs Late	95 % CI
Hospitalization	0.57	0.29-1.12	0.58	0.24-1.42
DME use	0.55	0.32-0.92	0.49	0.26-0.92
ER	1.17	0.34-4.03	1.52	0.40-5.68

Conclusion: Pts achieving LDA within 1 year benefit more (i.e. more improvement in HAQ and QoL outcomes and lower DME use during follow-up) vs those attaining LDA later. Programs geared towards earlier achievement of guideline targets can improve overall clinical and economic outcomes in RA.

Disclosure: E. Alemao, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **S. Joo**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **H. Kawabata**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **S. Banerjee**, Bristol-Myers Squibb, 1, Bristol-Myers Squibb, 3; **M. Frits**, None; **C. Iannaccone**, None; **N. Shadick**, AbbVie, Amgen, Genentech, 2, BMS, UCB, Crescendo Biosciences, 9; **M. Weinblatt**, BMS, Crescendo Bioscience, UCB, AbbVie, Roche, Janssen, 5, BMS, Crescendo Bioscience, UCB, 2.

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Effectiveness of a Workplace Integrated Care Intervention on Work Productivity in Workers with Rheumatoid Arthritis. Myrthe van Vilsteren[1], Cécile Boot[1], Dirkjan van Schaardenburg[2], Romy Steenbeek[3], A.E. Voskuyl[4] and Johannes Anema[5]. [1]Department of Public and Occupational Health, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, Netherlands, [2]Reade, Amsterdam, Netherlands, [3]Body@Work, Research Center Physical Activity, Work and Health, TNO-VU University Medical Center, Amsterdam, Netherlands, [4]VU University Medical Center, Amsterdam, Netherlands, [5]Research Center for Insurance Medicine AMC-UMCG-UWV-VU University Medical Center, Amsterdam, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease with a profound impact on a person's working life. Besides permanent work disability and sick leave, at-work productivity is often impacted by RA. It was shown that reduced at-work productivity has the greatest impact on costs for RA patients, followed by wage loss from stopping or changing jobs, decreased hours, and finally missed work days (absenteeism). At-work productivity decreases when a person is present at work, but is limited in meeting work demands. The Care for Work intervention program is a multidisciplinary intervention with the aim to improve at-work productivity. The intervention program consists of integrated care, coordinated by a clinical occupational physician, and a participatory workplace intervention, coordinated by an occupational therapist. The intervention was evaluated in a randomized controlled trial (RCT) which includes 113 participants.

Objectives: To determine the effects of the intervention program on work productivity, work instability, and supervisor support after 6 months of follow up in workers with rheumatoid arthritis compared to usual care.

Methods: This study is an RCT. Participants were RA patients who are involved in paid work for at least 8 hours per week, recruited from outpatient clinics of rheumatology. Outcome measures were at-work productivity

(measured with the Work Limitations Questionnaire, a higher score indicates more limitations at work), work instability (measured with the RAWIS, a higher score indicates more work instability), and supervisor support (measured with the subscale Supervisor Support of the Job Content Questionnaire, a higher score indicates more supervisor support). Data were analyzed using linear regression models according to the intention-to-treat principle.

Results: The intervention program did not show an effect on at-work productivity (B: 0.328, 95% CI -0.560 – 1.217), work instability (B: -0.697, 95% CI -2.05 – 0.66), and supervisor support (B: 0.10, 95% CI -0.12 – 0.32).

Conclusion: The intervention program did not show beneficial effects on at-work productivity, work instability and supervisor support after 6 months.

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2105

Nonsurgical Treatment Patterns in Patients with Chronic Spinal Cord Injury. Brian Le[1], Monique Bethel[1], Lauren Bailey[2], Frances Weaver[2], Stephen Burns[3], Jelena Svircev[3], Michael Heggeness[4] and Laura Carbone[5]. [1]Georgia Regents University, Augusta, GA, [2]Edward Hines Jr. VA Hospital, Chicago, IL, [3]VA Puget Sound Healthcare System, Seattle, WA, [4]University of Kansas School of Medicine, Kansas City, KS, [5]Charlie Norwood VA Medical Center, Augusta, GA.

Background/Purpose: Sublesional loss of bone mineral density is a common complication in patients with chronic spinal cord injury (SCI) putting them at high risk for low-impact fractures. Fracture management in patients with SCI is predominantly nonsurgical. However, to our knowledge, there are no large scale studies which report which nonsurgical procedures are most commonly used. The purpose of this study is to evaluate the distribution of nonsurgical treatments at different fracture sites in patients with SCI.

Methods: Males with chronic, traumatic SCI were identified from the Veterans Administration Spinal Cord Dysfunction data from fiscal years 2002–2007. From this population, patients with incident fractures were identified, excluding fractures due to external ("E-coded") and pathologic fractures. *Current Procedural Terminology* (CPT) codes for nonsurgical treatments of fractures were collected and subsequently categorized into four categories: splints, casts, closed reduction without internal fixation, or "other." The "other" category included knee immobilizers, walking boots, and other orthotic devices. These CPT codes were identified within six weeks following an incident upper extremity, lower extremity or unspecified fracture site. Differences in medical treatment modality were determined among fracture locations.

Results: 1,453 males with chronic traumatic SCI with non-traumatic and non-pathologic incident fractures were identified from 33,452 male SCI patients. 388 CPT codes for nonsurgical treatments of fracture were identified within 6 weeks post-fracture for 282 unique fractures. Fracture sites were grouped by number and location: single upper extremity, single lower extremity, single unspecified or multiple. Among fracture sites, there were significant differences among the types of nonsurgical treatments for single upper extremity fractures ($P=0.017$). Among single upper extremity fractures, forearm fractures were most frequently casted; carpal and metacarpal fractures, splinted; and phalangeal fractures, treated with closed reduction without internal fixation. In comparison, single lower extremity fractures were commonly treated with closed reduction for pelvic and femoral fractures; "other" for patellar, tibial/fibular, ankle, and tarsal/metatarsal fractures. Single unspecified fractures were frequently treated with closed reduction. In cases of multiple fractures, "other" outnumbered all other treatment modalities.

Conclusion: There are a number of different nonsurgical treatments done for single upper extremity, single lower extremity, single unspecified, and multiple fractures in men with chronic SCI.

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2106

Surgical Compared with Nonsurgical Management of Fractures in Men with Chronic Spinal Cord Injury. Monique Bethel[1], Lauren Bailey[2], Frances Weaver[2], Brian Le[1], Stephen Burns[3], Jelena Svircev[3], Michael Heggeness[4] and Laura Carbone[5]. [1]Georgia Regents University, Augusta, GA, [2]Edward Hines Jr. VA Hospital, Chicago, IL, [3]VA Puget Sound Healthcare System, Seattle, WA, [4]University of Kansas School of Medicine, Kansas City, KS, [5]Charlie Norwood VA Medical Center, Augusta, GA.

Background/Purpose: Patients with a chronic spinal cord injury (SCI) develop osteoporosis and are at high risk for fracture. However, there is limited information on how these fractures are currently treated. The purpose of this report was to examine treatment modalities (surgical compared with nonsurgical) of incident appendicular fractures in men with a chronic SCI of traumatic etiology.

Methods: Patients with a chronic spinal cord injury (SCI) develop osteoporosis and are at high risk for fracture. However, there is limited information on how these fractures are currently treated. The purpose of this report was to examine treatment modalities (surgical compared with nonsurgical) of incident appendicular fractures in men with a chronic SCI of traumatic etiology.

Results: 1453 male Veterans with 2464 incident fractures met inclusion criteria for the study. These fractures included 345 upper extremity fractures (ICD-9 codes 810.x-819.x), 1667 lower extremity fractures (ICD-9 codes 808.x, and 820.x-828.x) and 452 unspecified fractures (ICD-9 829.x). 875 patients (60%) sustained a single fracture, while the remainder had 2 or more fractures over the five year time period of the study. Only a minority of subjects (9.6%) were treated with surgical intervention, most commonly for hip fractures. Amputations accounted for 20.6% (32/155) of total surgical procedures, or 1.3% of all fractures. There were 20 above the knee amputations (AKAs), 6 below the knee amputations (BKAs), 4 occurring at other sites (foot, toe and finger) amputations, and 2 hip disarticulations one of which was associated with a femur fracture and the other a trochanteric hip fracture. Of the 32 amputations, 72% were done as delayed procedures.

Conclusion: Current patterns of appendicular fracture treatment in SCI indicate that the majority of fractures are managed nonsurgically within the VA healthcare system. A substantial number of surgical procedures were amputations. Many amputations were delayed, suggesting that they may represent failures of initial nonsurgical fracture treatment. There is a critical need to prospectively address optimal treatment (nonsurgical vs. surgical) by fracture site in patients with SCI. **Acknowledgements:** This material is based upon work supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development and the Rheumatology Research Foundation, Ephraim P. Engleman Resident's Preceptorship Award. **Disclaimer:** This work does not reflect the views of the Veterans Health Administration or the United States government.

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2107

Characterization of Social Stigma in Rheumatic Diseases and Correlation with Quality of Life and Medication Adherence. Gihyun Myung[1], Nancy D. Harada[2], Stephanie L. Fong[3], Cleopatra Aquino-Beaton[4] and Meika A Fang[3]. [1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]UCLA David Geffen School of Medicine, Long Beach, CA, [3]VA Greater Los Angeles Healthcare System, Los Angeles, CA, [4]UCLA School of Nursing, Los Angeles, CA.

Background/Purpose: Patients with rheumatoid arthritis and other rheumatic conditions may have physical deformities and functional limitations which make them vulnerable to health-related stigma. The objectives of this study were 1) to examine the prevalence of anticipated, enacted (discrimination), and internalized stigma (self-stigma) among people with rheumatologic conditions and 2) to assess the relationships between stigma, medication adherence, and quality of life.

Methods: We conducted a descriptive cross-sectional study by surveying patients from rheumatology clinics at a Veterans Affairs Healthcare System. Patients completed five sets of questionnaires including 1) sociodemographic questionnaire, 2) 12- item Chronic Illness Anticipated Stigma Scale (CIASS, score range from 1 [very unlikely] to 5 [very likely]) for anticipated sigma, 3) Neurology Quality-of-Life Stigma short form (Neuro-QoL, score range from 1 [never] to 5 [always]) for enacted and internalized stigma, 4) short form-36v2 (SF-36) for quality of life measurement, and 5) 8-item Morisky

Medication Adherence Scale (MMAS-8, score range 0–8.0 with higher scores reflecting better adherence). Pearson's correlation and analysis of variance were used to evaluate for any associations and significant differences respectively between stigma scores (anticipated, enacted, and internalized), quality of life, and medication adherence.

Results: 85 adults completed the questionnaires, including 74 males and 11 females. Mean age was 59 ± 13 years. The top five diagnoses were rheumatoid arthritis (38.8%), psoriatic arthritis (11.6%), gout (11.6%), osteoarthritis (10.9%), and ankylosing spondylitis (7.8%). 67% of the patients were working or retired. 62% of the participants had poor adherence to rheumatic disease medications. 29.4% of patients were somewhat to very likely to anticipate stigma from coworkers and employers versus 4.7% from family/friends and 9.4% from health care workers. 15.3% of patients were sometimes to always experience internalized stigma and 4.7% were sometimes to always experience enacted stigma. There was a significant negative correlation between the work-related CIASS stigma scores and the SF-36 physical ($p = 0.0003$) and mental composite scores ($p < 0.0001$). Higher work-related CIASS stigma score was significantly correlated with poor medication adherence ($p = 0.004$). Similarly, when participants were divided into poor versus good medication adherence groups, significantly more people in the poor adherence group were somewhat to very likely to anticipate work-related stigma.

Conclusion: These findings indicate that about 30% of patients with rheumatologic conditions anticipate stigma from co-workers and employers. Few patients reported anticipated stigma from family and friends, anticipated stigma from healthcare providers, enacted stigma, or internalized stigma. Anticipated work-related stigma was negatively correlated with mental and physical well-being and with medication adherence. Interventions to reduce anticipated work-related stigma have the potential to improve the health of patients with rheumatic diseases.

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Anxiety in Caregivers of Patients with Chronic Rheumatic Conditions. Anna Kristina Gutierrez-Rubio, Geraldine Racaza, Maria Lourdes Dianongco and Ester Penserga.Philippine General Hospital, Manila, Philippines.

Background/Purpose: People caring for patients with chronic illnesses, such as systemic lupus erythematosus, rheumatoid arthritis, or osteoarthritis, may experience depression and anxiety due to the burdens of managing debilitating and disabling diseases. Our primary objective was to determine the prevalence of anxiety and depression in caregivers of patients with SLE, RA, and OA.

Methods: Persons acting as the primary caregiver to patients with SLE, RA or OA were included in this study. Demographic data were collected. The hospital anxiety and depression scale (HADS), a 14-item rating scale with independent subscales for anxiety and depression, was administered to each patient. A score of 11 or higher indicated probable depression or anxiety.

Results: A total of 438 patients were included in this study. All patients included were acting as the caregiver of an individual with a rheumatic condition, with 182, 151, and 107 caring for patients with SLE, RA, and OA, respectively. The prevalence of probable depression among caregivers of patients with SLE, RA, and OA were 2.2 ± 10%, 0 ± 0%, and 1.9 ± 10%, respectively with a 95% CI. The prevalence of probable anxiety among caregivers of patients with SLE (17.58 ± 10%) was significantly higher than, RA and OA (9.93 ± 10% $p = 0.05$, and 8.57 ± 10% $p = 0.04$, respectively). Other variables, such as low income, presence of comorbid illnesses, or the number of hours per day spent caring for the patient were not found to be significant factors.

Conclusion: The prevalence of anxiety among caregivers of patients with SLE were found to be significantly higher than those of OA and RA, implying that the illness of the patient they are caring for impacts their risk for anxiety. More studies are needed to determine risk factors for anxiety among caregivers of patients with SLE, and the impact this may have on patient care.

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2109

Are Patient Ratings of Providers and Health Plans Associated with Technical Quality of Care in SLE? Edward H. Yelin, Laura Trupin, Jinoos Yazdany and Chris Tonner.University of California, San Francisco, San Francisco, CA.

Background/Purpose: Prior research has shown that the technical quality of SLE care is associated with the degree of subsequent accumulated damage. However, it is not known whether the patient experience with providers and health systems is associated with the technical quality of care.

Methods: We analyzed data from the UCSF Lupus Outcomes Study (LOS), a national sample of persons with SLE interviewed annually using a structured telephone survey. The survey includes batteries from AHRQ's Consumer Assessment of Health Plans (CAHPS) and the Interpersonal Processes of Care Scales (IPC) to rate care along six dimensions of patient care experiences with providers (patient-provider communication, shared decision-making, and trust) and health systems (promptness/timeliness of care, care coordination, and assessment of health plans) from 0–100. Because ratings were highly skewed, we dichotomized the measures at the lowest versus the highest three quartiles. The survey also includes the 13 technical quality indicators (QIs) for SLE that have been validated for patient report. The QIs were aggregated into a pass rate, defined as the number of QIs received as a proportion of those for which one is eligible. We used generalized estimating equations to model the relationship of the QI pass rate with being in the lowest quartile of ratings of each individual dimension and with being in the lowest quartile on 0, 1–3, and 4–6 of the dimensions. Models were adjusted for age, race/ethnicity, education, poverty status, presence and kind of health insurance, specialty of principal SLE physician, disease duration, disease activity (measured by SLAQ), and disease damage (measured by BILD).

Results: 640 LOS participants with ≥1 visit to their principal SLE provider in the year prior to interview were eligible for analysis. Mean age was 52.8±12.6 years and mean disease duration was 20.1±8.8 years. 38% were non-whites and 14% were in poverty. Overall pass rate was. 70 (95% CI. 68,. 71). Being in the lowest quartile of ratings on any one individual dimension was not associated with a statistically significant difference in QI pass rates. Being in the lowest quartile of ratings on 4–6 dimensions was associated with significantly lower pass rates (.63 vs.. 70 and. 71 for those in the lowest quartile on 1–3 or 0 dimensions, respectively [Table 1]).

Conclusion: Consistently low ratings on multiple dimensions of health care experiences may be a sentinel for poor technical quality of care. Because ratings of providers and health plans are in the public domain, individuals with SLE may find this information useful when choosing where to receive clinical care.

Table 1. Technical Quality of Care Pass Rates, by Number of Dimensions with Ratings of Health Care Experiences with Providers and Health Systems in the Lowest Quartila

Number of Dimensions	Q1 Pass Rate (95% CI)
None	.71 (.68, .74)
1–3	.70 (.67, .72)
4–6	.63 (.58, .68)

Disclosure: E. H. Yelin, None; **L. Trupin**, None; **J. Yazdany**, None; **C. Tonner**, None.

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Quality Measures and Adherence: Potential Hazards of Using Administrative Claims to Measure Biologic Specialty Pharmaceutical Immunology Product Adherence When days' Supply Is Unspecified. Chris Kozma[1], Andrew Paris[2] and Michael P. Ingham[3]. [1]CK Consulting, Saint Helena Island, SC, [2]Vigilytics, Victor, NY, [3]Janssen Scientific Affairs, LLC, Horsham, PA.

Background/Purpose: Published data on adherence of biologics shows a wide range of calculation methods. To compare methods of calculating adherence and persistence for immunology biologics.

Methods: Administrative medical and pharmacy claims from 11/1/2008 through 12/15/2011 were sourced from a leading national health care provider. The first biologic claim between 5/1/2009-6/30/2010 was the patient's index date (Index). Four methods of assigning days' supply were tested. Method I used the pre-Index period to establish induction period status and assign dosing intervals based on product labeling. Methods II & III were adaptive and infliximab (IFX)-specific, using either the first to second infusion interval criteria of ≤ 21 days (Method II), or alternatively, activity in the pre-Index period (Method III), to establish induction period status, followed by assignment of dosing intervals based on product labeling. Method IV used either days' supply from the pharmacy claim or estimated values for medical benefit transactions. These estimated values were based on

a qualitative a priori review of medical benefit transaction reporting frequencies. Adherence was measured using Proportion of Days Covered (PDC-"fixed period" 364 days post-index) and Medication Possession Ratio (MPR-"variable period" index to cessation of treatment or end of observation). Several new methods of reporting adherence were tested, including: Proportion of Patients with treatment gap ≥20% of expected (PPgap≥20), Sum of Gap Days ≥20% of expected (SoGD≥20), Sum of any Gap Days (SoGD), and Number of Gaps ≥10% of expected (NoG≥10). Persistence alternatives included Number of days from Index to a gap ≥90 days, and Number of days from Index to a gap ≥10% of expected interval. **Results** are reported descriptively using means, standard deviations (SD), and percentages.

Results: 636 patients had IFX claims; while in a separate sample, 523 chart review patients had only subcutaneous claims (SQ). Method III produced comparatively low adherence and persistence rates. PDC-type fixed period vs. MPR-type variable period consistently reported a 10–15% lower adherence rate, and a 30–50 day shorter time to event rate. For Method IV, variable period techniques – the IFX cohort had an MPR of 0.94 (SD 0.12) while the SQ cohort had MPR of 0.82 (SD 0.19). For alternative adherence measures, using Method IV, variable period techniques, comparing infusion (IFX cohort) vs. self-administered (SQ cohort) showed the PPgap≥20 was 39.8% vs. 74.2% respectively. The SoGD≥20 was more than twice as great for the SQ vs. IFX cohort (56.1 (SD 65.0) vs. 23.2 (SD 46.3) respectively). The SQ cohort reported more than 2.5 times the NoG≥10 vs. IFX cohort (2.59 (SD 2.14) vs. 0.97 (SD 1.22) respectively).

Conclusion: Substantial differences may result from assumptions made regarding missing days' supply and calculation methods for persistence and adherence when using medical claims. Quality reporting should include all details for days' supply assumptions and calculation methods. Alternative methods of reporting adherence may have greater clinical significance than MPR or PDC.

Disclosure: C. Kozma, Janssen Scientific Affairs, LLC, 5; **A. Paris**, Janssen Scientific Affairs, LLC, 5; **M. P. Ingham**, Janssen Scientific Affairs, LLC, 3, Johnson and Johnson, 1.

2111

Overcoming Barriers to Acute Patient Access: Is There a Need for Urgent Care Clinics in Rheumatology Practices? Ruchi Jain, Narender Annapureddy, Isabel Castrejón, Theodore Pincus, Daniel Garcia and Joel A. Block.Rush University Medical Center, Chicago, IL.

Background/Purpose: Urgent access for patients with rheumatic disease is limited in the United States, and it is often difficult to accommodate patients' requests to be seen for urgent issues such as flare. No reports of Rheumatologists with urgent care clinics (UCC) built into practices similar to primary care are available. Currently many Rheumatologists use reserved slots in a provider's schedule for urgent patients. This may be inadequate as these slots may be filled, particularly in academic practices which comprise providers who see patients only a few days per week, and may produce daily unpredictability in schedules. The primary objective of our study was to analyze a validated patient survey to determine a possible need to institute a dedicated UCC in our academic practice.

Methods: 390 patients were given validated surveys measuring access: Did you call for a concern that required urgent attention in the past 12 months? If so how often did you get an appointment as soon as you felt needed: Always Usually, Sometimes or Never. Patients in the Always group were compared with the group who marked Usually, Sometimes or Never. Confidence in the practice was measured using a visual analog scale (VAS): 0= not confident and 10= most confident. Patient demographic and primary diagnosis was collected. MDs were separated into those who provided clinical care 5 days per week and those who were available only 1–2 days weekly. Chi-square tests were used to compare categorical variables. Independent t-tests were used to compare continuous variables. A p-value of 0.05 was considered significant.

Results: 390 patients were surveyed, mean age 53.9, 83% female and 45% African Americans. 192 (49.2%) patients reported a need for urgent care in the past 12 months. 89 (46 %) felt they "always" were given a timely appointment (Adequate Access). 103 (53%) believed that they "usually", "sometimes", or "never" (Not Adequate Access) were given timely appointments to meet an urgent need. Mean available Confidence score for patients of 5 days providers (n=190) was 9.00 (1.76) compared with 8.26 (2.49) for non 5 day available providers (p=0.001). Mean Confidence scores for patients who did request an urgent appointment in past 12 months was 8.3 (2.50), compared with scores for patients who did not was 8.9 (1.82) (p=0.006) Table 1.

	5 Day Available Providers N=190	Non 5 Day Available Providers N=200	P-Value
Percentage of patient group who reported Not Adequate Access in obtaining urgent/timely appointment (N=103)	37.8% (39)	62.1% (64)	**0.002**
Mean confidence that future concerns will be addressed in a timely manner? (All patients)	9.0 (1.7)	8.2 (2.5)	**0.002**
Mean confidence that future concerns will be addressed in a timely manner among patients who had required urgent care in the last 12 months (N=191)	8.8 (2.0)	7.9 (2.8)	**0.012**
Not Adequate Access group (n=102)	7.4 (2.4)	6.9 (2.9)	0.349
Adequate Access group (n=89)	9.7 (0.9)	9.5 (1.3)	0.508
Mean confidence scores based on accessibility Adequate Access group vs. Not Adequate Access group	9.6 (1.1) vs. 7.1 (2.8)		**<0.001**

Patients reporting: Always= Adequate access group; Usually, Sometimes or Never= Not-Adequate Access group. All values are in means and standard deviations unless specified

Conclusion: We observed an unmet need to provide urgent care access for patients with rheumatic diseases in our academic practice. This need is heightened especially in patients of providers with limited clinics in a week. Furthermore, mean confidence scores appear to be driven more by access than by the frequency that the provider practices clinically. A dedicated UCC might improve patient access and confidence in Rheumatology practices.

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Patterns of Medication Use Before, During, and After Pregnancy Among Women with Systematic Lupus Erythematosus: A Population-Based Study. Mary De Vera[1], Eric C. Sayre[2], Corisande Baldwin[3], Jessica Galo[3] and J. Antonio Avina-Zubieta[2]. [1]University of British Columbia Faculty of Pharmaceutical Sciences, Vancouver, BC, [2]Arthritis Research Centre of Canada, Richmond, BC, [3]University of British Columbia, Vancouver, BC.

Background/Purpose: Systemic lupus erythematosus (SLE) disproportionately affects women during childbearing years. Given the limited data on perinatal medication use among patients, our objective was to characterize real-world therapy patterns among women with SLE before, during, and after pregnancy.

Methods: Our data include all visits to health professionals and all hospital admissions from Jan 1, 1990 to Dec 31, 2010 and all dispensed medications from Sept 1, 1995 to Dec 31, 2010. The case definition for SLE was: **a)** diagnosis of SLE on at least two visits within a two-year period between Jan 1996 and Dec 2010 by a non-rheumatologist physician; or **b)** diagnosis of SLE on at least one visit by a rheumatologist or from hospitalization. Cases with an ICD-9 code for SLE prior to 1996 were excluded. From this, we assembled a cohort of women, aged 18 or older, with pregnancies ending in a delivery as identified using ICD-9 codes in the hospitalization database. We calculated the estimated date of conception (EDC) as the date of delivery minus 270 days and created the following periods: **1)** pre-conception 1 (91–180 days before EDC); **2)** pre-conception 2 (90 days before EDC); **3)** 1st trimester; **4)** 2nd trimester; 5) 3rd trimester; **6)** post-delivery 1 (90 days after delivery); and **7)** post-delivery 2 (91 – 180 days after delivery). Using information on prescription date and days' supply, we determined the use of medications including disease modifying anti-rheumatic drugs (DMARDs), biologics, glucocorticosteroids, and non-steroidal anti-inflammatory drugs (NSAIDs) for each period.

Results: We identified 100 pregnancies with delivery date at age 18–45 and at least 450 days after SLE onset, from an incident cohort of 4,297 women with SLE. At delivery, mean age was 32.1 ± 4.4 years and SLE duration was 3.8 ± 1.9 years. We tabulated the proportion of exposed pregnancies according to each period and medication class (**Table**). The majority of DMARD pregnancy exposures were to hydroxychloroquine and/or chloroquine (41 to 45% of exposed pregnancy trimesters). In contrast to the decline in use during pregnancy compared to pre-conception periods for DMARDs and NSAIDs, we observed an increase in glucocorticosteroid exposures during pregnancy, as well as post-delivery.

Conclusion: This population-based study provide data on real-world patterns of perinatal medication use among women with SLE. Findings emphasize the importance of counseling women regarding childbearing decisions as well as the need for evaluation of the risk-benefit profiles of medications in pregnancy.

	Exposed SLE Pregnancies (%)						
	Pre-conception 1	Pre-conception 2	1st trimester	2nd trimester	3rd trimester	Post-delivery 1	Post-delivery 2
DMARDs	52	49	50	45	45	45	52
Biologics	0	0	0	0	0	0	0
Glucocorticosteroids	19	21	22	24	26	30	23
NSAIDs	9	14	10	9	8	12	11

Disclosure: M. De Vera, None; **E. C. Sayre**, None; **C. Baldwin**, None; **J. Galo**, None; **J. A. Avina-Zubieta**, None.

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The Number of Morbidities Drives the Health Care Expenditures and Presence of a Musculoskeletal Condition Is Additionally Accountable for Higher Costs. Antje van der Zee-Neuen[1], Polina Putrik[2], Sofia Ramiro[3], Andras Keszei[4], Astrid M. Chorus[5], Rob de Bie[1] and Annelies Boonen[2]. [1]Maastricht University, Maastricht, Netherlands, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Amsterdam Rheumatology Center, University of Amsterdam & Hospital Garcia de Orta, Almada, Portugal, Amsterdam, Netherlands, [4]RWTH Aachen University, Aachen, Germany, [5]Netherlands Organization for Applied Scientific Research, Leiden, Netherlands.

Background/Purpose: In Europe, 70– 80% of all healthcare expenses are attributable to chronic diseases and a large part of these are musculoskeletal conditions (MSKC).Having >1 disease (multimorbidity) is likely to increase the costs of care but little is known about the association of multimorbidity and health care costs (HCC) and the specific role of MSKC as co-morbid disease in this association. We aimed to explore1) whether the number of morbidities has an important association with costs of care and 2) whether MSKC have an additional impact when occurring as co-morbid disease.

Methods: In a Dutch cross-sectional study, 8904 subjects (>18 years) completed a questionnaire on sociodemographic and lifestyle factors, self-reported physician-diagnosed diseases (MSKC, diabetes, cardiovascular diseases, cancer, migraine, respiratory, skin, mental and bowel conditions) and health care use (general practitioner, rheumatologist, orthopedist, physiotherapist, other specialists, hospitalization in regular/academic hospital or nursing home, home care and domestic help).The total HCC were computed for a 3-months period using reference prices of the Dutch manual for pharmacoeconomic healthcare evaluations 2010, accounting for inflation by Consumer Price Index. Missing values were imputed by means of multiple imputation. To deal with skewness, zero-inflated negative binomial regression (ZINB) models were computed to assess 1) the association of number of diseases and HCC and 2) which disease or combination of diseases (in- or excluding MSKC) was associated with the largest increase of HCC using the healthy as reference. Models were adjusted for age, gender, education, origin (western vs. non-western), smoking status and BMI. For each of the different subgroups, based on number or combination of morbidities, raw and predicted 3-months HCC were presented for male/female patients. Predicted HCC were derived from the ZINB-models.

Results: SKC occurred in 1766 cases (20%).Multimorbidity was present in 1722 cases (19%). HCC increased steeply with increasing number of morbidities (e.g. HCC for 1 morbidity were approximately 2 times higher than for the healthy, exp(β)=1.8 [1.7–2.0]). Compared to any other condition, MSKC was associated with higher HCC when occurring alone or when occurring as co-morbid disease. For example, when 2 morbidities other than MSKC were co-occurring HCC were approximately 2 times higher than in the healthy (exp(β)=2.2 [2.0–2.7]) while when one of the two morbidities was MSKC the costs were 3 times higher than in the healthy(exp(β)=3.0 [2.7–3.7]) (Table 1).

Conclusion: The total HCC increase with increasing number of morbidities. MSKC are accountable for higher costs of care compared to other diseases independent of the number of morbidities. These important findings deserve the attention of policy makers, especially by prioritizing MSKC in healthcare budgets.

Table 1. Association of type (or combination) and number of morbidities with costs of health care utilization during a 3 month period

Morbidity or combination of morbidities†	exp(β) [95% CI]†	Raw costs (€), mean (SD) ♂/♀	Predicted costs (€)* ♂/♀
Musculoskeletal condition when occurring alone	2.2 [1.8–2.5]	575 (2169)/488 (1904)	328/483
Any other chronic morbidity when occurring alone	1.5 [1.4–1.7]	388 (1906)/401 (2801)	220/323
Any combination of 2 morbidities when MSK is one of them	3.0 [2.7–3.7]	664 (1863)/1094 (4895)	483/711
Any combination of 2 morbidities when MSK is not one of them	2.2 [2.0–2.7]	595 (1835)/626 (1928)	355/522
Any combination of ≥3 morbidities when MSK is one of them	6.1 [5.5–7.4]	2028 (6647)/2468 (7461)	955/1406
Any combination of ≥3 morbidities when MSK is not one of them	5.5 [5.0–6.7]	1314 (3503)/2786 (7599)	919/1353
Number of morbidities†			
1	1.8 [1.7–2.0]	437 (1979)/429 (2548)	256/380
2	3.0 [2.7–3.3]	622 (1844)/875 (3814)	423/627
3	5.5 [4.5–6.1]	1208 (3518)/2032 (7326)	746/1107
4	8.2 [6.7–11.0]	1864 (4244)/3465 (8680)	1208/1794
≥5	12.2 [8.2–16.5]	4429 (12384)/3328 (5918)	1692/2513

† Reference category: healthy/absence of disease
+ Estimates derived from zero-inflated negative binomial regression models adjusted for age, gender, BMI, education and smoking-status
*Predicted costs are presented for men and women with median age (54 yrs), normal BMI (18.5–25 kg/m2), non-smokers, middle or secondary professional education and western origin

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2114

Comorbidity Characteristics of Patients Starting First-Line Acute Gout Agents - Colchicine, NSAID, and Corticosteroids. Alfonso Perez[1], Robert Jackson[1], Jiao Yang[1], Aki Shiozawa[1], Shawn Yu[1], Yimin Qin[1], Huifang Liang[1] and Hyon K Choi[2]. [1]Takeda Pharmaceuticals International, Inc, Deerfield, IL, [2]Boston University School of Medicine, Boston, MA.

Comorbidity Characteristics of Patients Starting First-Line Acute Gout Agents - Colchicine, NSAID, and Corticosteroids

Background/Purpose: There is a remarkable, increasing disease burden of gout and its associated comorbidities in the US. The 2012 ACR gout management guidelines endorsed the use of colchicine, NSAIDs, and corticosteroids as appropriate first-line options for the treatment of acute gout. Cardiovascular-metabolic-renal comorbidities of gout should dictate the choice among these agents, but relevant data are scarce. To address this issue, we examined and compared the prevalence of major cardiovascular-metabolic-renal comorbidities in gout patients who were newly prescribed these three agents.

Methods: We used US insurance claims data (2009–2012) to conduct a population-based study. Subjects aged ≥18 years who had at least 1 visit coded with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 274.xx for gout were identified. Patients diagnosed with cancer (ICD-9-CM codes: 140.xx-208.xx, 230.xx-234.xx) any time before or after the index date were excluded. Acute gout attacks were identified by an outpatient visit coded for gout, followed by a new dispensing of colchicine, NSAIDs, or oral or injectable corticosteroids. We assessed the comorbidity status during the 180 days prior to initiation of these acute gout care agents.

Results: There were 2,181 colchicine, 10,773 NSAID, and 2,364 corticosteroid initiators for acute gout attacks. The mean ages were 52, 49, and 51 years and 85, 85, 80% were men, respectively. Compared with NSAID initiators, colchicine initiators had more comorbidities, including hypertension, hyperlipidemia, coronary heart disease, stroke, congestive heart failure, type 2 diabetes, and chronic kidney disease at the time of initiation (**Table 1**). Compared with corticosteroid initiators, colchicine initiators had higher prevalences of hypertension, coronary heart disease, stroke, and type 2 diabetes, although the difference was less (**Table 1**).

Conclusion: This large US insurance claims-based study indicates that patients who initiated colchicine for acute gout had more cardiovascular-metabolic comorbidities than those who initiated NSAIDs or corticosteroids. While some of these findings confirm expected prescription patterns, given the known adverse effects of these agents, the overall comorbidity profile of colchicine initiators was noteworthy. These prescription patterns and pre-existing comorbidities should be appropriately taken into account for comparative effectiveness studies of these agents.

Table 1. Comorbid Medical Conditions during the 180 Days Prior to Initiation of the First Line Acute Gout Agents

Comorbid Medical Conditions	Colchicine (N=2181) n (%)	NSAIDs (N=10773) n (%)	Corticosteroids† (N=2364) n (%)
Hypertension, n (%)	942 (43.19)	2994 (27.79)	873 (36.93)
Adjusted Prevalence Ratio (95% CI)*	Referent	0.74 (0.72,0.76)	0.88 (0.86,0.90)
Hyperlipidemia, n (%)	751 (34.43)	2679 (24.87)	747 (31.60)
Adjusted Prevalence Ratio (95% CI)*	Referent	0.82 (0.80,0.85)	0.95 (0.92,0.98)
Coronary heart disease, n (%)	203 (9.31)	423 (3.93)	181 (7.66)
Adjusted Prevalence Ratio (95% CI)*	Referent	0.55 (0.50,0.59)	0.86 (0.80,0.92)

Congestive Heart Failure, n (%)	48 (2.20)	90 (0.84)	65 (2.75)
Adjusted Prevalence Ratio (95% CI)*	Referent	0.47 (0.40,0.56)	1.08 (0.94,1.23)
Stroke, n (%)	64 (2.93)	121 (1.12)	57 (2.41)
Adjusted Prevalence Ratio (95% CI)*	Referent	0.50 (0.43,0.58)	0.78 (0.69,0.89)
Type 2 diabetes, n (%)	290 (13.30)	859 (7.97)	207 (8.76)
Adjusted Prevalence Ratio (95% CI)*	Referent	0.73 (0.69,0.78)	0.69 (0.65,0.74)
Chronic kidney disease ≥ stage 2, n (%)	66 (3.03)	75 (0.70)	94 (3.98)
Adjusted Prevalence Ratio (95% CI)*	Referent	0.28 (0.23,0.33)	1.28 (1.15,1.43)

NSAID: Non steroid anti-inflammatory drug.
*Prevalence ratios were adjusted for age and gender.
†Corticosteroids include prednisone and methylprednisolone.

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2115

Inflammatory Arthritis Treatment Outcomes at a First Nations Reserve Rheumatology Specialty Clinic. Erin Bell[1], Sharon Leclercq[1], Dianne P. Mosher[1], Hani El-Gabalawy[2], Tyler White[3], Marvin Fritzler[1] and Cheryl Barnabe[1]. [1]University of Calgary, Calgary, AB, [2]University of Manitoba, Winnipeg, MB, [3]Siksika Health Services, Siksika, AB.

Background/Purpose: Inflammatory arthritis (IA: rheumatoid arthritis, systemic lupus erythematosus, and spondyloarthritis) disproportionately affects Canada's First Nations population. Treatment outcomes may be ameliorated by health service models that mitigate logistical barriers to care and provide specialty services embedded in the primary care context. This study assessed the effectiveness of a specialized care model, delivered in a First Nations primary care setting, in achieving IA activity targets.

Methods: Consenting participants were recruited to an arthritis screening program held in a First Nations community between June 2011 and August 2012. Those determined to have IA (n=47) received ongoing follow-up with collection of disease activity measures and patient-reported outcomes, as well as treatment recommendations, at each visit. Repeated measures ANOVA was used to describe changes in disease activity measures over a 24 month period. The frequency with which a treatment change was recommended, based on moderate or high disease activity state determined from the DAS28, was calculated.

Results: A total of 131 visits by 47 participants (79% female, mean age 47 years, diagnosis of rheumatoid arthritis n=34) occurred over the 24 month study period. At the baseline visit, 70.6% of participants had moderate or high disease activity (DAS28>3.2). Significant decreases in joint counts (/28) were achieved (mean swollen joint count decrease of 7.0, 95% CI 3.5–10.4, p=0.0061; mean tender joint decrease of 7.2, 95% CI 4.1–10.3, p=0.0116). Patient-reported outcomes for pain, global assessment and physical function were not significantly improved during treatment. A recommendation for treatment change was made at 67% of visits where patients were classified in moderate or high disease activity.

Conclusion: Although the program adequately addressed physician-derived disease activity targets, patient-reported outcomes were not significantly improved during follow-up. This suggests that the program should be modified to include a multi-disciplinary team that can address holistic aspects of First Nations health and reduce loss to follow-up from specialty care. A quality improvement initiative will be introduced to document reasons for deviation from the treat-to-target protocol.

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2116

Hospitalization Rates and Utilization Among Rheumatoid Arthritis Patients: A Population-Based Study from 1987 to 2012. C. John Michet III[1], Katrina Strobova[2], Sara J. Achenbach[3], Cynthia S. Crowson[3] and Eric L. Matteson[3]. [1]Mayo Clinic College of Medicine, Rochester, MN, [2]Charles University, Prague, Czech Republic, [3]Mayo Clinic, Rochester, MN.

Background/Purpose: Patients with rheumatoid arthritis (RA) experience chronic management issues and are at risk for complex comorbidities. It is unknown, however, to what extent the complications of the disease may lead to hospitalization. The goal of this study is to discern whether patients with RA are at greater risk for all-cause hospitalizations when compared to the general population.

Methods: This retrospective, population-based cohort study utilized patients who were 18 years or older and diagnosed with RA (as defined by the 1987 ACR criteria) between 1/1/1980 and 12/31/2007, and a reference cohort of patients without RA matched on age, sex, and calendar year. Each patient's medical record was examined for hospitalizations from 1987 through 2012. For this analysis, follow-up began with the latter of index date or 1/1/1987 and ended at the earlier of death, last follow-up or 12/31/2012. Discharge diagnoses were grouped together using the Clinical Classifications Software for ICD-9-CM from Healthcare Cost and Utilization Project. Data were analyzed using person-year methods and rate ratios comparing RA to non-RA.

Results: The 799 RA and 797 non-RA cohorts each consist of patients with a mean age of 56 years (68% female) and a mean follow-up of 12 years and 13 years respectively. The patients with RA had 2968 hospitalizations and the non-RA patients had 2069 hospitalizations. RA patients proved to be at greater risk for all causes of hospitalization (Table 1). Increased risk for all-cause hospitalizations for patients with RA also held true for both sexes and all age groups.

Two discharge diagnoses are of interest. First, hospitalization for depression is a greater risk for male patients with RA (23 hospitalizations) than for the general male population (3 hospitalizations) (Rate Ratio [RR] 7.16, 95% Confidence Interval [CI] 2.78, 30.67). Second, patients with RA are at greater risk of hospitalization for diabetes (31 hospitalizations) than patients without RA (13 hospitalizations) (RR 2.45, CI 1.34, 4.89). Female patients with RA are at a significantly increased risk of hospitalization for diabetes (16 hospitalizations) when compared to the general female population (6 hospitalizations) (RR 2.65, CI 1.14, 7.45). An increased risk of hospitalization for diabetes is especially true for all RA patients age 45–64 (22 hospitalizations) when compared to the general population (0 hospitalizations) (RR 44.76, CI 8.32, 45072.3).

Conclusion: In this first ever analysis of all-cause hospitalizations in a population-based cohort, patients with RA appear to be at greater risk for hospitalization than patients without RA. This risk is true for both sexes and all age groups. RA patients are also markedly more likely to be hospitalized for depression if they are male. Furthermore, hospitalization for diabetes is prevalent among patients with RA, especially among females and patients in the 45–64 age group.

		RA Rate*	Non-RA Rate*	Rate Ratio	Confidence Interval
Overall		30.4	20.2	1.51	1.42,1.59
Sex	Female	29.0	19.2	1.51	1.41,1.62
	Male	33.6	22.4	1.50	1.36,1.65
Ages	18-44	12.4	8.6	1.44	1.14,1.84
	45-64	22.4	10.8	2.07	1.86,2.32
	65-84	41.1	28.1	1.46	1.36,1.58
	85+	70.3	55.6	1.26	1.09,1.46

*Rate of hospitalizations per 100 person-years

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Association Between Depression and High Utilization of Emergency Department in Patients with Systemic Lupus Erythematosus from the Southeastern United States: The Goal Cohort. Alfredo Aguirre[1], S. Sam Lim[2], Gaobin Bao[1], Charles T. Molta[3], Hong Kan[4] and Cristina Drenkard[1]. [1]Emory University, Atlanta, GA, [2]Emory University School of Medicine, Division of Rheumatology, Atlanta, GA, [3]GlaxoSmithKline, King of Prussia, PA, [4]GSK, Durham, NC.

Background/Purpose: Frequent visitors of the emergency department (ED) among the general population share several demographic, health system and disease characteristics, including older age, poverty, government-financed insurance and poorer health. The burden of depression is also high among frequent ED visitors. Depression strikes up to 75% of SLE patients and is more severe among blacks compared to whites. Previous reports among predominantly white SLE samples suggest that there is an association between depression and ED usage. We sought to examine whether the severity of depressive symptoms increases the risk of being a frequent user of the ED in a predominantly black SLE cohort in the Southeastern US.

Methods: Georgians Organized Against Lupus (GOAL) is a longitudinal cohort largely drawn from a population-based registry of people with SLE, which has been established in Atlanta, GA. Annual surveys furnish self-administered data on demographics, disease outcomes and healthcare utilization. Over 75% of participants are black, and 35% live under the poverty

level. We used the 9-item Patient Health Questionnaire (PHQ-9) to assess severity of depressive symptoms. PHQ-9 can be assessed as a continuous (score range 0–27) or categorical (5 categories from minimal to severe depressive symptoms) variable. Individuals who visited the ED ≥ 3 times in the past year were considered frequent ED users. We conducted logistic regression analyses to test the effect of depression severity on being a frequent ED user, after controlling for potential confounders.

Results: Of 566 SLE participants, 96 (17%) visited the ED at least 3 times in the past year. Frequent usage of the ED was found in 10%, 17%, 26%, 24%, and 28% of patients with minimal, mild, moderate, moderately severe, and severe symptoms of depression, respectively. Severity of depressive symptoms, demographic factors, type of insurance, disease activity, and organ damage were associated with frequent ED utilization (Table 1). The PHQ-9 score remained positively associated with the outcome after controlling for major confounders. PHQ-9 and self-reported disease activity (SLAQ) scores were highly correlated (rho=0.65). The association between the PHQ-9 score and frequent ED usage was not longer significant when SLAQ was included in the model (OR=0.98; p=0.85).

Conclusion: Our data suggest that the severity of depressive symptoms may modulate healthcare-seeking behavior in SLE. However, other factors often disproportionately prevalent among socioeconomically disadvantaged subgroups with SLE, such as severe organ damage, greater disease activity and being on Medicaid showed stronger association with the outcome. Longitudinal studies are needed to tease out the complex pathways implicated in the usage of avoidable healthcare resources among minorities with SLE, particularly among those stricken by depressive symptoms.

Table 1. Association of Depressive Symptoms with Frequent Usage of the Emergency Department

Characteristics	Univariable LR		Multivariable LR (stepwise)	
	Odds Ratio	P Value	Odds Ratio	P Value
Depressive symptoms (5-unit increase in PHQ-9 score)	1.43 (1.21–1.70)	<0.0001	1.30 (1.07–1.59)	0.009
Age at diagnosis (5 year increase)	0.91 (0.83–1.00)	0.051	0.85 (0.75–0.95)	0.006
Gender (female)	0.79 (0.35–1.79)	0.58		
Race (non-white)	2.68 (1.31–5.52)	0.0073	2.22 (0.95–5.19)	0.07
Disease duration (1 year increase)	0.99 (0.96–1.01)	0.29	0.96 (0.93–0.99)	0.009
Educational attainment (3 year increase)	0.80 (0.63–1.00)	0.051		
Household income below poverty level	2.90 (1.81–4.63)	<0.0001		
Insurance type (ref: Private)	2.83 (1.17–6.84)	0.021		
No Insurance			1.83 (0.71–4.75)	0.80
Medicare	3.29 (1.65–6.55)	0.0007	2.30 (1.08–4.90)	0.50
Medicaid	6.27 (3.22–12.23)	<0.0001	3.63 (1.76–7.47)	0.003
Married or living with partner	0.59 (0.37–0.94)	0.028		
Disease activity (5-unit increase in SLAQ score)	1.65 (1.44–1.88)	<0.0001	Not included*	
Organ damage (SA-BILD score)	2.07 (0.95–4.51)	0.067	1.89 (0.82–4.34)	0.76
Mild damage (1–2) vs. no damage (0)				
Severe damage (≥3) vs. no damage (0)	4.91 (2.34–10.33)	<0.0001	4.26 (1.84–9.86)	0.0001

Abbreviations: LR: logistic regression; PHQ-9: 9-item Patient Health Questionnaire; SA-BILD: Self-administered Brief Index Lupus Damage; SLAQ: Systemic Lupus Activity Questionnaire. * Because SLAQ was highly correlated with PHQ-9 (Pearson correlation coefficient =0.65; p<0.0001), it was not included in the multivariate model.

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Lower Socioeconomic Status at Disease Onset Is Associated with Higher Health Care Costs in Patients with Systemic Lupus Erythematosus: A General Population-Based Cohort Study. Natalie McCormick[1], Mohsen Sadatsafavi[2], Wenjia Chen[2], Carlo A. Marra[3] and J. Antonio Avina-Zubieta[4]. [1]University of British Columbia/Arthritis Research Centre of Canada, Vancouver, BC, [2]University of British Columbia, Vancouver, BC, [3]Univ of British Columbia, Vancouver, BC, [4]Arthritis Research Centre of Canada, Richmond, BC.

Background/Purpose: Low socioeconomic status (SES) negatively impacts health outcomes in the general population, as well as in systemic lupus erythematosus (SLE), but the impact on healthcare costs is unknown. In addition, there are little data on the long term costs of SLE cases beginning from diagnosis. To address these knowledge gaps, we examined the relationship between SES at diagnosis, and direct medical costs for 10 years following, in a general population-based context.

Methods: Data Source: Our administrative data captured *all* provincially-funded outpatient encounters and hospitalizations (1990–2010), and *all* dispensed medications (1996–2010) regardless of funding source, in British Columbia, Canada. Sample: We assembled a population-based cohort of all incident cases of SLE who received care from 1996–2010, based on the following validated algorithm: **a)** two ICD-9-CM codes for SLE at least 2 months apart but within a 2 year period by a non-rheumatologist physician; or **b)** one ICD code by a rheumatologist or hospitalization. Statistics Canada neighborhood income quintile data for the year of SLE diagnosis was used to define SES. Cost Calculation: Costs for outpatient services and prescriptions were summed directly from billing data. Case-mix methodology was used for hospitalizations. Statistical Analysis: While most cases (87%) had less than 10 years follow-up, estimating long-term costs exclusively from cases with complete follow-up can introduce survival bias, and underestimate costs. Thus, costs were predicted using data from *all* cases. To account for censoring, follow-up was divided into 90-day periods, and costs per-period were weighted by the person-specific inverse probability of being alive in each period. A generalized linear model was used to predict the cumulative 10-year costs (adjusted for censoring) for cases in each SES group. Parametric bootstrapping was used to obtain 95% confidence intervals (CI). Costs are reported in 2010 Canadian dollars.

Results: We identified 4,209 incident SLE cases (86% female, mean age 49 years) contributing 18,028 person-years. The 10-year costs from all cases totaled $132,762,777 with 30% from outpatient, 41% from hospitalizations and 30% from medications.

After adjusting for sex, age and baseline Charlson's comorbidity index, predicted costs were significantly greater (21%, p=0.01) for the lowest SES cases compared to the highest, and averaged $12,489 more per-patient over 10 years.

Hospitalization costs over 10 years were 64% greater for the lowest-SES cases versus the highest ($13,097 vs. $8,001, p=0.05), with most hospitalizations (85%) occurring within 12 months of SLE diagnosis. Medication costs were 18% greater for the lowest SES than the highest, but unlike hospitalization costs, these costs continued over time.

Conclusion: Lower SES at SLE diagnosis is associated with higher healthcare costs, with medication costs driving this disparity over the long term.

Socioeconomic Quintile at Diagnosis	N Cases	N Female (%)	Mean Age at Diagnosis (SD)	Median Baseline Charlson Comorbidity Score (IQR)	N Months of Follow-Up	N 90-Day Costing Periods	N Ever-Hospitalized (%)	Unadjusted Overall Costs	Covariate-Adjusted Mean Per-Person Predicted Costs (95% CI)			
									Overall	Outpatient	Hospital	Medication
All	4,209	3,630 (86%)	49.4 (15.8)	0 (1)	216,339	72,113	2,062 (49%)	$67,847	–	–	–	–
1=Lowest	928	790 (85%)	49.5 (16.5)	0 (1)	46,788	15,596	510 (55%)	$77,895	$72,688 ($67,250–$78,127)	$18,789 ($17,467–$20,111)	$13,097 ($9,910–$16,285)	$24,244 ($22,670–$25,817)
2	834	722 (87%)	49.0 (15.9)	0 (1)	41,976	13,992	422 (51%)	$70,331	$70,837 ($64,857–$76,817)	$20,937 ($19,244–$22,629)	$8,977 ($7,445–$10,509)	$21,662 ($20,143–$23,181)
3=Middle	859	746 (87%)	49.2 (15.4)	0 (1)	44,502	14,834	402 (47%)	$64,872	$67,545 ($54,500–$80,591)	$18,417 ($17,044–$19,790)	$9,501 ($6,900–$12,102)	$22,288 ($20,954–$23,623)
4	811	703 (87%)	49.1 (15.3)	0 (1)	42,135	14,045	382 (47%)	$63,692	$62,088 ($56,680–$67,495)	$18,530 ($17,679–$19,380)	$9,260 ($7,102–$11,418)	$21,985 ($20,517–$23,453)
5=Highest	777	669 (86%)	50.5 (15.8)	0 (1)	40,938	13,646	346 (45%)	$61,741	$60,200 ($56,074–$64,325)	$18,239 ($17,032–$19,447)	$8,001 ($6,531–$9,470)	$20,588 ($19,391–$21,785)

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Off Work Days Decreased RATE in Muskuloeskeletal Disease Patients: Usefulness of the EARLY Intervention Program. Francisco Miguel Ortiz Sanjuan, Isabel Martinez-Cordellat, Jose Ivorra, Jose Luis Valero, Inmaculada Chalmeta, Elena Grau, Carlos Feced, Rosa Negueroles, Luis Gonzalez-Puig, Cristobal Nuñez-Cornejo Piquer, Cristina Alcañiz, Eztizen Labrador and Jose Andres Roman Ivorra.Department of Rheumatology, Hospital Universitario y Politécnico La Fe., Valencia, Spain.

Background/Purpose: In March 2012, a new project was started at HUP La Fe following the pilot project carried out at San Carlos Clinical Hospital in Madrid, where patients who were off work for musculoskeletal causes were referred to us from Primary Care. The aim of the study is to analyze the variation in days off work in those individuals included in this program with respect to the normal average of days off.

Methods: Cohort, observational, cross-sectional study from April 2012 to December 2013, which included patients from the HUP La Fe area, referred for the first time to the Rheumatology Early Intervention consultation program because of temporary disability due to musculoskeletal problems. These patients are referred to a medical appointment with a maximum waiting time of one week and were provided medical treatment, ultrasound, joint injections and directed exercises if

needed. The patient is reviewed continuously until discharge. We excluded patients whose disabilities were due to trauma or surgery or if their situation could cause permanent disability.

Results: We included a total of 250 patients with a mean age of 48 years and 53% were women. The most frequently reported diseases were: back pain (33%), neck pain (16%), shoulder pain syndrome (13%) and other tendinopathies (10%). 100% of patients received medical treatment, 39% underwent articular ultrasound, 35% of them underwent injections and 82% were trained to perform physical therapy exercises at home. The pathology that had a higher average number of days from the first visit to the medical discharge was lumbar/sciatic pain (38 days), neck pain (30 days), and painful shoulder syndrome (34 days). Comparing our data with the control population in the San Carlos Hospital study, there was a decrease of the days off, being in the control group lumbociatalgia (57.6 days), neck (37.4 days) and neck pain (37.4 days).

Conclusion: Results obtained in our study show that early intervention by rheumatologists in patients with temporary disability of musculoskeletal origin decreases the number of days off work compared to patients who receive routine treatment and they can be incorporated in work early. Consequently, it saves all costs resulting from such temporary disability.

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Societal Preferences for Rheumatoid Arthritis Treatments. Evidence from a Discrete Choice Experiment. Mark Harrison[1], Carlo Marra[2], Kam Shojania[2] and Nick Bansback[2]. [1]University of Manchester, Manchester, United Kingdom, [2]University of British Columbia, Vancouver, BC.

Background/Purpose: The cost-effectiveness of new interventions is increasingly assessed using the cost per quality-adjusted life year (QALY). QALYs are calculated by multiplying the length of time spent in a health state by the value of that health state, usually representative of the general public and estimated using a generic preference-based measure such as the EQ-5D. A limitation of generic preference based instruments is that they may fail to describe benefits of a treatment that patients experience and that society might value such as the method or convenience of treatment. The aim of this study was to determine the value society places on aspects of rheumatoid arthritis treatment, including mode of administration

Methods: A discrete choice experiment (DCE) was administered using a web survey in a representative sample of the Canadian general population using an online panel. Focus groups led to the development of a DCE with 7 attributes (route and frequency of administration, chance of benefit, chance of serious and minor side-effects, confidence in benefit and side-effect estimates (based on GRADE definitions), and life expectancy. An experimental design led to the development of 120 choice sets. Each respondent was randomized to complete 10 of these. A conditional logit regression model was used to estimate the significance and relative importance of attributes in influencing preferences. The life years attribute enables the DCE to estimate values on the health utility scale for use in QALY calculations.

Results: Responses from 733 respondents who provided rational responses to the choices in the experiment were included in the analysis. They were recruited from all provinces and territories in Canada, and their mean age (44), gender (55% female) and education (45% had up to a high school education) were representative of the general population. Six attribute levels within four attributes significantly influenced preferences for treatments. Respondents were willing to give up to a year of life expectancy over a 10 year period to increase the probability of benefitting from treatment, or two thirds of a year to reduce minor or serious side-effects to the lowest level or improve the confidence in benefit/side-effect estimates. There was some evidence of a preference for oral drug delivery and sub-group analysis suggested this preference was restricted to injection naive respondents.

Conclusion: As expected, our study found society values the benefits and side-effects of treatments. However, our study also found that people also value the degree of confidence in the estimates of risks and benefits of treatments, and to a lesser extent, the route of administration. Since economic evaluations typically focus only on the health outcomes of treatments, they may miss process aspects of treatment that are valued by society. This study provides important evidence to policy makers determining the cost-effectiveness of treatments in arthritis.

Disclosure: M. Harrison, None; **C. Marra**, Pfizer Inc, 2; **K. Shojania**, Abbvie, Janssen, BMS, UCB, Roche, Amgen., 5; **N. Bansback**, None.

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Real-World Cost Comparison of Urate Lowering Therapies in Patients with Gout and Moderate to Severe Chronic Kidney Disease. Ghaith Mitri[1], Eric Wittbrodt[1], Robin Turpin[1], Beni Tidwell[2] and Kathy Schulman[2]. [1]Takeda Pharmaceuticals International, Deerfield, IL, [2]Outcomes Research Solutions, Inc., Waltham, MA.

Background/Purpose: Gout flare prevention relies heavily on urate-lowering therapies (ULT) such as allopurinol (ALP) and febuxostat (FBX) but clinical decision-making in patients with moderate to severe chronic kidney disease (CKD) is complicated by significant comorbidity. This study compared healthcare expenditure in ALP and FBX initiators after diagnosis with gout and CKD.

Methods: Gout patients (ICD-9-CM 274.xx), aged >18, with concurrent CKD (stage 3, 4), were selected from the MarketScan® databases (January 2009-June 2012) upon ALP or FBX initiation. Patients were followed until disenrollment, discontinuation of the qualifying ULT or use of the alternate study agent. Patients initiating on ALP were subsequently propensity score (PS) matched (1:1) to patients initiating on FBX. Mean monthly healthcare cost (2012 US$) was calculated in aggregate and for 4 disease specific conditions: gout, renal, diabetes (DM) and cardiovascular (CV). Five generalized linear models (GLM) were developed, each controlling for PS, to identify the incremental costs (vs ALP) associated with initiation on FBX after prior exposure to ALP and without prior exposure to ALP.

Results: PS matching yielded two cohorts, each with 1,486 patients (65% male, mean (SD) age 67.4 (12.8)). Post-match, 75% of patients had stage 3 CKD, 83% CV disease and 42% DM. The post-match sample was well-balanced on numerous comorbidities and medication exposures with the following exception. Fifty percent of FBX initiators had baseline exposure to ALP while only 3% of ALP initiators had baseline exposure to FBX. There were no differences ($p=0.27$) in follow-up gout flare frequency. There were no significant differences in mean monthly per patient expenditure, unadjusted, ($1,490 ALP, $1,525 FBX, $p=0.8$). CV, renal, DM and gout specific costs represented, respectively, 31%, 14.3%, 13% and 10.9% of total cost.

GLM model results suggest that FBX users with recent ALP exposure incurred significantly ($p<0.01$) more cost than ALP users while FBX users without recent exposure to ALP incurred significantly ($p<0.01$) less cost than ALP users. Multivariate models also found that both FBX cohorts, with and without recent exposure to ALP, had significantly ($p<0.0001$) higher gout-specific cost, due almost entirely to higher FBX acquisition cost. However, increased gout-specific expenditure in the FBX cohort without recent ALP exposure was offset by significantly lower CV ($p<0.0001$) and renal- ($p<0.0001$) related cost. There were no significant differences, adjusted, in either renal or CV costs between the ALP cohort and FBX patients with baseline exposure to ALP. Similarly, there was no significant difference in DM-related expenses between any of the cohorts.

Conclusion: The use of FBX in first- and second-line settings may confound outcome evaluation since FBX use after ALP failure may suggest more aggressive disease. Gout patients with concurrent CKD, initiating on FBX in a first-line setting incurred significantly less total cost than patients initiating on ALP. Higher acquisition cost for treatment with FBX should not be a barrier to appropriate treatment, especially in patients with co-morbid CV and renal conditions.

Disclosure: G. Mitri, Takeda Pharmaceuticals International, 3; **E. Wittbrodt**, Takeda Pharmaceuticals International, 3; **R. Turpin**, Takeda Pharmaceuticals International, 3; **B. Tidwell**, Takeda Pharmaceuticals International, 5; **K. Schulman**, Takeda Pharmaceuticals International, 5.

2122

Variation in the Prescribing Practices of Biologic Dmards. Heather O. Tory[1], Josephine A. Awosogba[2], Amish J. Dave[2], Jonathan S. Coblyn[2], Daniel H. Solomon[2] and Sonali P. Desai[2]. [1]Boston Children's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: Biologic DMARDs (bDMARDs) are effective yet expensive treatments for RA. Variability in the prescribing practices of rheumatologists using these agents may be attributable to patient-specific clinical factors. We performed a quality improvement project to better

understand this variability, comparing practice to an adapted standardized treatment pathway.

Methods: A standardized treatment pathway was developed based on the 2012 ACR guidelines for treatment of patients with early moderate to severe RA (Singh JA et al., 2012) and was endorsed by the rheumatologists in our practice (**Figure 1**). This pathway differed from the ACR guidelines primarily by liberalizing the duration required for each treatment step.

We reviewed charts of 224 patients with ≥ 3 ICD 9 codes for RA (714.0) seen at our single center academic practice who initiated a new bDMARD (first time use or a change from prior bDMARD) from January through December 2013. Data were abstracted using a standardized form, including demographics, RA characteristics, complete available medication history and reasons for medication choices. Each patient was included only once. We categorized patients as having treatment courses that did or did not follow the treatment pathway. Inter-rater reliability (kappa), assessed by re-review of charts of patients with treatment courses that varied from the pathway, was 0.82, $p < 0.001$. When reviewers disagreed, final adjudication occurred through a consensus process.

Results: 224 patients initiated a new bDMARD during the study period. Mean age was 53 (range 20–84) and 183 (82%) were female. 197 (88%) had disease duration of over 2 years. Erosive disease was seen in 99 (44%) and 116 (52%) were seropositive. Only 13 patients (6%) had treatment courses that did not follow the treatment pathway (**Table 1**). The reasons for these variations included co-morbidities (n = 8), disease severity (n = 1) and initial care at other institutions (n = 4). None of the included patients had failed oral triple therapy prior to initiation of a biologic.

Conclusion: We examined practice patterns for the prescription of bDMARDs at our institution and found little variability based on an adapted standardized treatment pathway. Variations from the pathway were justified by patient co-morbidities and disease characteristics, suggesting that existing variability may be appropriate.

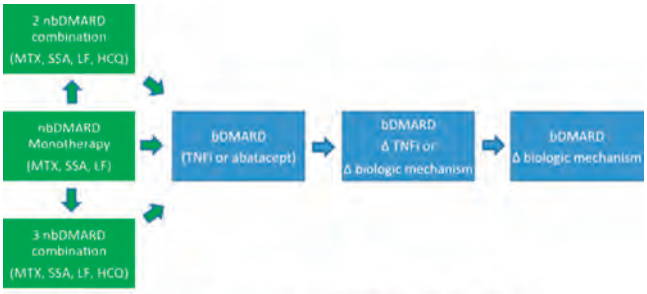


Figure 1: Adapted standardized treatment pathway for patients with RA.
nbDMARD: Non-biologic DMARD; MTX: Methotrexate; SSA: Sulfasalazine; LF: Leflunomide; HCQ: Hydroxychloroquine; bDMARD: Biologic DMARD; TNFi: Tumor necrosis factor inhibitor

Table 1: Reasons for patient treatment not following suggested pathway (N=13 out of 224)

Deviation	Number	Reason
Etanercept as initial DMARD	8	Therapy started at another institution (4) Co-morbidity considerations (4) -Liver disease (1) -Lung/liver disease, sulfa allergy (1) -Pregnancy/post-partum breastfeeding (2)
Infliximab + methotrexate as initial DMARDs	1	Severe symptoms with high disease activity (1)
Rituximab as initial biologic DMARD	4	Co-morbidity considerations (4) -Multiple sclerosis (1) -Active leiomyosarcoma (1) -Interstitial lung disease (1) -Latent tuberculosis (1)

Disclosure: H. O. Tory, None; **J. A. Awosogba**, None; **A. J. Dave**, None; **J. S. Coblyn**, CVS caremark, 5; **D. H. Solomon**, None; **S. P. Desai**, None.

2123

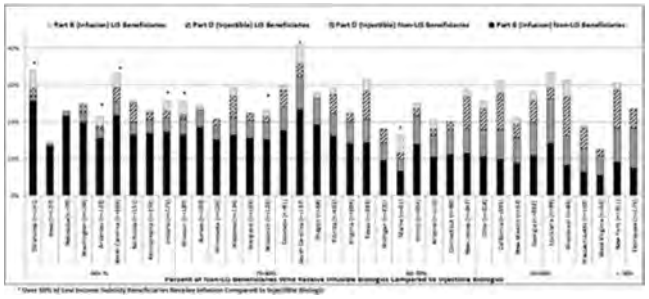
Significant State-Level Variation in Source of Biologic Drug Coverage Among Beneficiaries with Rheumatoid Arthritis. Chris Tonner, Gabriela Schmajuk and Jinoos Yazdany.University of California, San Francisco, San Francisco, CA.

Background/Purpose: Biologic drugs can be obtained both through Medicare's Part B medical benefit (physician administered drugs) or Part D pharmacy benefit (self-administered drugs). Coverage for biologics is additionally complicated by the low-income subsidy (LIS), whereby Medicare beneficiaries with low socioeconomic status face minimal costs for Part D biologics (while non-LIS beneficiaries pay less out of pocket for Part B drugs). Despite the complexity of biologic benefit design, variation in biologic use and coverage in the Medicare program has not been adequately studied. We performed a nationwide study of Medicare beneficiaries with rheumatoid arthritis (RA) to investigate geographic variations in payment source for biologic drugs. We hypothesized that there would be consistent use of Part D biologics among LIS patients.

Methods: We used data from nationwide Medicare fee-for-service claims files for 2009 for a 5% random sample of beneficiaries, including all medical and pharmacy claims. Included beneficiaries had RA (2 face-to-face visits coded as 714.xx within the calendar year), were continuously enrolled in a pharmacy plan, and had at least one prescription for a disease-modifying drug. Source of biologic coverage (Part B or Part D) was tabulated for all biologic users according to LIS status and stratified by state. We calculated the proportion of LIS vs. non-LIS beneficiaries receiving Part B biologics in each state and examined the correlation between these variables within states. Individuals residing in states with fewer than 50 eligible beneficiaries were censored from this analysis to increase the precision of our estimates.

Results: 7190 beneficiaries received a DMARD for RA; 1901 (26%) received biologic drugs. 25% of biologic users received a low-income subsidy (LIS). Among LIS recipients, 8% received their biologic through Part B and 20% through Part D. Conversely, among non-LIS patients, 18% received their biologic through Part B and 8% through Part D. Across states, Part B biologic use ranged from 5–26% for non-LIS patients (median 9, IQR 14–22) and 0–5% (median 2, IQR 1–3) for LIS patients (Figure). Proportions of non-LIS and LIS patients using Part B biologics within a state were modestly correlated (r^2=0.15).

Conclusion: We found substantial variations between states in the proportion of patients with RA receiving biologics, and whether patients received biologics through Medicare Part B or Part D. Variations were even observed for those receiving LIS, suggesting that factors other than cost-sharing influence biologic drug selection. Further studies should examine how both insurance coverage policies and physician practice variation impact the choices available to patients.



Disclosure: C. Tonner, None; **G. Schmajuk**, None; **J. Yazdany**, None.

2124

Characteristics of Medicare Beneficiaries Travelling Long Distances to Visit a Rheumatologist. Gabriela Schmajuk[1], Chris Tonner[2] and Jinoos Yazdany[2]. [1]UCSF/San Francisco VA, San Francisco, CA, [2]University of California, San Francisco, San Francisco, CA.

Background/Purpose: Studies of the distribution of rheumatologists across the United States suggest that a significant number of patients travel long distances to visit a rheumatologist. The geographic, health care market, and patient factors associated with travel distances have not been described. We examined individual and area-level predictors of travelling long distances to see a rheumatologist.

Methods: Data derive from nationwide Medicare fee-for-service medical claims for 2009 for a 5% random sample of beneficiaries. All patients ≥ age 18 with 12 months of continuous enrollment in Medicare Parts A and B who had at least 1 visit to a rheumatologist were included. We calculated distance

between the center of the patient's 5-digit ZIP code and the center of the rheumatologist's office 5-digit ZIP code for the first rheumatologist seen during the calendar year. We compared the characteristics of patients travelling ≥ 50 miles to see a rheumatologist to all others based on sociodemographic (age, sex, race, dual Medicare/Medicaid eligibility, and state buy-in, a measure of personal income) and area-level variables (ZIP-code level socioeconomic status, state-level supply of rheumatologists per 100,000 residents, state-level price-adjusted total Medicare spending per person). Two percent of observations were censored due to missing data. Included variables were tested for noncolinearity. We used general estimating equations to adjust for individual and area level characteristics in a single multivariate model.

Results: We studied 42,571 Medicare patients who had at least one visit to a rheumatologist during 2009. Median distance traveled was 9.3 miles (IQR 4–22); 9% of patients travelled ≥50 miles to see a rheumatologist. Patients who travelled ≥50 miles were more likely to be younger (age 70.7 vs. 73.3) male (25% vs 20%), White (92% vs. 88%), and live in a low-SES ZIP code (40% vs. 21%). They were also more likely to reside in regions with the lowest supply of rheumatologists (34% vs. 23%). In the adjusted model, the effects of age, sex, race, area-level SES, and rheumatologist supply remained significant although area-level SES had the strongest effect (Table).

Conclusion: Patients travelling very long distances to visit a rheumatologist are more likely to be male, White, and live in lower-SES areas compared to patients travelling less far. Sociodemographic effects are at least as strong as the effect of low rheumatologist supply. These findings suggest that interventions beyond increasing the number of rheumatologists in low supply areas will be necessary to reduce travel distances and improve access to rheumatology care in the U.S.

Table Individual and Area-level Predictors of Traveling ≥ 50 Miles to See a Rheumatologist.

Variable	Adjusted odds ratio (95% Confidence Interval)*
Individual Characteristics	
Age	
Age ≤ 67	1.62 (1.48, 1.78)
Age 68–74	1.42 (1.29 (1.57)
Age 75–80	1.32 (1.19, 1.45)
Age ≥ 81	Referent
Male (vs. female)	1.20 (1.11, 1.29)
Race	
African-American	0.42 (0.37, 0.49)
Asian	0.50 (0.32, 0.80)
Other	1.16 (0.91, 1.47)
White	Referent
State buy-in (vs. none)	0.73 (0.66, 0.81)
No Part D coverage (vs. yes)	0.87 (0.81, 0.94)
Area-level Characteristics	
ZIP-level SES index	
Quintile 1 (low)	5.15 (4.52, 5.82)
Quintile 2	2.92 (2.58, 3.31)
Quintile 3	1.95 (1.71, 2.23)
Quintile 4	1.27 (1.10, 1.47)
Quintile 5 (high)	Referent
Regional rheumatologist supply†	
Quartile 1 (low)	1.90 (1.72, 2.11)
Quartile 2	1.84 (1.66, 2.03)
Quartile 3	1.05 (0.94, 1.17)
Quartile 4 (high)	Referent
Regional Medicare spending (price-adjusted)‡	
Quartile 1 (low)	1.65 (1.51, 1.80)
Quartile 2	0.87 (0.79, 0.96)
Quartile 3	1.00 (0.91, 1.10)
Quartile 4 (high)	Referent

*Adjusted for all variables shown
†Rheumatologist supply data from the Dartmouth Atlas (2006).
‡Regional Medicare spending estimates from Dartmouth Atlas Data (2009); estimates adjust for age, sex and race of the underlying Medicare population and regional differences in prices.

Disclosure: G. Schmajuk, None; **C. Tonner**, None; **J. Yazdany**, None.

2125

Burden of Illness in Refractory Gouty Arthritis: A One-Year Prospective Multinational, Observational Study. Louis Bessette[1], Frédéric Lioté[2], Carmen Moragues[3], Rüdiger Moericke[4], Zhang Zhiyi[5], Alberto Ferreira[6], Pascal Lecomte[6], Sophia Kessabi[6], Haijun Tian[7] and Jasvinder Singh[8]. [1]CHUL, Quebec, QC, [2]Hôpital Lariboisière & University Paris Diderot, Paris, France, [3]Hospital Platón, Barcelona, Italy, [4]Institut für Präventive Medizin & Klinische Forschung GbR, Magdeburg, Germany, [5]The First Affiliated Hospital of Haerbin Medical University, Haerbin, China, [6]Novartis Pharma AG, Basel, Switzerland, [7]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [8]Mayo Clinic, Rochester, MN.

Background/Purpose: Refractory gouty arthritis (RGA) is a condition characterized by appearance of recurrent flares and contraindication, intolerance, or lack of efficacy to first-line anti-inflammatory therapy (NSAIDs/colchicine/steroids) and conventional uric acid lowering therapies (ULT). The objective of the study was to assess the humanistic and economic burden of RGA over 1 year during presence or absence of a flare.

Methods: This 12-month, multinational (6 countries), prospective, observational study investigated the disease impact in patients suffering from RGA who had experienced 3 or more flares in past 12 months. Patients who were enrolled were also refractory to first-line anti-inflammatory therapy (NSAIDs, colchicine, or steroids) or to ULTs. Patients were divided in two groups as per the presence or absence of gout flares. Summary statistics pooled for all visits are presented as mean and SD for continuous variables, and proportions for categorical variables. The utility score derived from the combinations of responses to the five questions of the EuroQol Health Status Questionnaire 5D (EQ-5D) was used as the primary outcome measure. Secondary outcomes included Gout Assessment Questionnaire–Gout Impact Scale (GAQ-GIS) and Healthcare resource utilization (ER visit, hospitalization, physician visit and home care).

Results: A total of 454 eligible patients were enrolled in the study (mean age: 56, males: 86.1%). Patients who were having a flare experienced greater difficulty on all 5 dimensions of the EQ-5D descriptive system and mean EQ-5D utility scores pooled across all the visits were worse for patients having a flare [0.614; 95%CI 0.600, 0.628] as compared to patients without a flare [0.867; 95%CI 0.861, 0.872]. The results for mean EQ-5D VAS scores were lower in patients having a flare [60.7; 95%CI 59.3, 62.1] than patients without a flare [79.5; 95%CI 78.9, 80.1]. The mean GAQ-GIS scores for patients with a gout flare vs. those without a gout flare were higher for various parameters such as overall gout concern [81.27 vs 70.06], medication side effects [59.12 vs 51.26], unmet treatment needs [48.26 vs 37.19], wellbeing during attack [57.32 vs 45.23], and gout concern during attack [63.58 vs 54.09]. Furthermore, higher healthcare utilization was observed in patients experiencing a flare (table 1).

Conclusion: RGA imposes a considerable humanistic and economic and burden. Gout flares were associated with increased healthcare resource utilization and diminished quality of life. These findings suggest unmet medical needs in refractory gout patient population.

Table 1. Healthcare resource utilization survey over 12 months' observation period (All locations)

	Patients having a gout flare N = 334	Patients not having a gout flare N = 119
Percent of patients visited emergency unit for gout in the last year	21.3%	6.7%
Percent of patients admitted to the hospital for gout in the last year	15.0%	5.9%
Percent of patients who visited their doctor or another physician for gout in the last year	62.0%	49.6%
Percent of patients who needed help at home due to gout in the last year	43.7%	21.8%

Disclosure: L. Bessette, Novartis, 2; **F. Lioté**, Novartis, Ipsen, Sanofi, 1, Novartis, SOBI, Astra-Zeneca, Savient, Ipsen, Menarini, Mayoly-Spindler, 2, Novartis, Ipsen, Menarini, Savient, Astra-Zeneca, Mayoly-Spindler, 5; **C. Moragues**, Novartis, 2; **R. Moericke**, Novartis, 2; **Z. Zhiyi**, Novartis, 2; **A. Ferreira**, Novartis Pharma AG, Basel, 3; **P. Lecomte**, Novartis Pharma AG, Basel, 3; **S. Kessabi**, Novartis Pharma AG, Basel, 3; **H. Tian**, Novartis Pharmaceuticals Corporation, East Hanover NJ, 3; **J. Singh**, Takeda, Savient, Novartis, 2, Savient, Takeda, Regeneron and Allergan, 5.

2126

The Utility of Digital Activity Fluorescence Optical Imaging in Quantifying Hand and Wrist Inflammation in Rheumatic Diseases. Yogan Kisten[1], Noémi Györi[1], Hamed Rezaei[2], Adrian Levitsky[1], Anna Karlsson[1], Erik af Klint[2] and Ronald van Vollenhoven[2]. [1]The Karolinska Institute,Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), Stockholm, Sweden, [2]The rheumatology clinic of the Karolinska University Hospital, Stockholm, Sweden.

Background/Purpose: The objective detection and quantification of disease activity in its earliest pathophysiological stage is critical for achieving optimal therapy results. Fluorescence optical imaging (FOI) is a novel imaging modality for the hands & wrists, and automated quantification of the ensuing images using DACT (Disease ACTivity)-FOI as a novel algorithm representing activity. This study was designed to determine the utility of FOI as a diagnostic tool, and whether it could be used in lieu of color/power Doppler ultrasound (US) to quantify and ascertain apparent & non-apparent active synovitis.

Methods: A total of 872 hand/wrist joints in 26 patients (18 female, 8 male, average age 51.5 years) with various rheumatic diseases (RA: 12, JIA, SLE, DM, FM, PsA & polyarthritis 1–2 each) were examined by standard clinical assessment, US and DACT-FOI. Joints swollen & tender or swollen only were considered clinically inflamed. Active synovitis was defined as having synovial thickening & Doppler activity on US. Joints positive by FOI displayed abnormal focal optical intensities by visual inspection. Silent synovitis was defined as showing synovitis by US but not clinically. The DACT value was digitally quantified per patient by an automated computer-based algorithm of the composite image (240 frames). After clinical, US and FOI positive joints for each hand were calculated, the sensitivity, specificity & kappa statistics computed & compared with the mean DACT values for all patients.

Results: Out of 872 joints, 242 (16%) were inflamed clinically, 241 (28%) by US, and 229 (26%) by FOI. There was moderate agreement for synovitis detection between clinical examination & US (kappa 0.524 ± 0.033; 95% CI: 0.459 – 0.589) and between clinical examination & FOI (kappa 0.450 ± 0.035; 95% CI: 0.381 – 0.519). Of the 241 inflamed joints by US, 196 (81%) were also inflamed by FOI, while only 119 (49%) were inflamed clinically. Agreement between US and FOI in synovitis detection was good (kappa 0.773 ± 0.024; 95% CI: 0.725 – 0.821). Depending on the gold standard used to define inflammation, FOI was 73–83% sensitive and 86–95% specific for detecting synovitis.

Out of 730 non-inflamed joints by clinical examination, 608 (83%) were non-inflamed by US and 605 (83%) were non-inflamed by FOI. Of these clinically non-inflamed joints, 122 (17%) were inflamed by US. For detecting silent synovitis, FOI was 80% (98/122) sensitive and 96% (581/608) specific.

The number (mean ±SD) of active joints detected by clinical, US and FOI was 5.4 ±7.6; 9.4 ±9.8; and 9.3 ±9.7 respectively, and the overall automated disease activity DACT-FOI was 4.3 ±2.1. There was a strong positive correlation (r = 0.556; p=0.003) between the clinical detection of synovitis & DACT-FOI. The mean DACT values also correlated significantly with US (r = 0.479; p=0.013) and semi-quantitative FOI (r = 0.515; p=0.007).

Conclusion: FOI and the automated analysis DACT-FOI were technically feasible with high reproducibility and agreement with clinical scoring & US. For detecting synovitis semi-quantitatively, FOI had a lower sensitivity but similar specificity compared to US. FOI may be particularly useful in identifying patients with clinically non-apparent hand/wrist inflammation (silent synovitis).

Disclosure: Y. Kisten, None; **N. Györi**, None; **H. Rezaei**, None; **A. Levitsky**, None; **A. Karlsson**, None; **E. af Klint**, None; **R. van Vollenhoven**, None.

2127

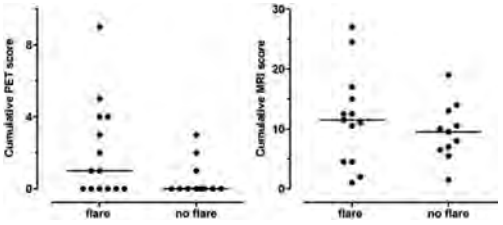
Subclinical Arthritis Is Detected By Macrophage Targeting and Positron Emission Tomography (PET) in Early RA Patients in Clinical Remission. Y.Y.J. Gent[1], M.M. ter Wee[1], D den Uyl[1], N. Ahmadi[1], W.F. Lems[2], O.S. Hoekstra[2], A.E. Voskuyl[1] and C.J. Van der Laken[2]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]VU Medical Center, Amsterdam, Netherlands.

Background/Purpose: Recurrent flares in RA patients in complete remission (CR) are not an uncommon phenomenon. Studies with advanced imaging techniques have suggested that residual subclinical synovitis can still be present despite clinical remission and has been linked to ongoing radiological damage. Our group has shown that positron emission tomography with macrophage targeting (^{11}C-*(R)*-PK11195 PET) is a highly sensitive and specific technique to visualize (subclinical) arthritis activity. In the current study we investigated if ^{11}C-*(R)*-PK11195 PET can depict residual disease activity in early RA patients who reached CR and whether the inflammatory activity on the scans was associated with the development of a flare (as compared to MRI).

Methods: ^{11}C-*(R)*-PK11195 PET (HRRT, CTI/Siemens) of hands/wrists was performed in 25 RA patients that had no tender or swollen joints after treatment with combined DMARD therapy (DAS44<1.6). *(R)*-^{11}C-PK11195 uptake (visual score: 0 (low)-3 (high)) in metacarpophalangeal, proximal interphalangeal and wrist joints (n=22 joints/patient) was scored and corrected for background uptake. Individual joint scores were summed to obtain a cumulative PET score (range 0–66). Follow-up duration was 1 year after PET. Flare of clinical disease activity was defined as ≥ 1 swollen joint.

Results: Of the included patients, 14 out of 25 (56%) developed a clinical flare of arthritis anywhere within 1 year of follow-up. *(R)*-^{11}C-PK11195 PET showed enhanced tracer uptake in at least one scanned joint in 11/25 (44%) patients. Cumulative PET scores of patients developing a flare tended to be higher than that of patients without a flare (median (IQR) 1 (0–4) vs 0 (0–1), p=ns) (Fig left). Within the flare subgroup, patients with a flare in hands/wrists (n=6), had significantly higher cumulative PET scores than patients without a flare (n=11)(p=0.04). Patients with a cumulative PET score of 4 and higher, all developed arthritis in hands/wrists within 6 months. As comparison, MRI scans of all included patients were positive regardless of flaring, not distinguishing between subgroups of flare and no flare (Fig right).

Conclusion: Macrophage targeting by *(R)*-^{11}C-PK11195 PET can visualize subclinical synovitis in hand/wrist joints of drug-induced remission in early RA. Uptake of *(R)*-^{11}C-PK11195 was higher in patients with with a flare compared to those without a flare. High cumulative PET scores seem to be associated with short-term development of flare. In comparison to MRI, PET may have superior diagnostic value with respect to specificity. Larger cohort studies are needed to confirm these data.



Disclosure: Y. Y. J. Gent, None; **M. M. ter Wee**, None; **D. den Uyl**, None; **N. Ahmadi**, None; **W. F. Lems**, None; **O. S. Hoekstra**, None; **A. E. Voskuyl**, None; **C. J. Van der Laken**, None.

2128

Effectiveness of ^{18}f-Fluoro-Dexoxyglucose Positron Emission Tomography for the Diagnosis of Polymyalgia-like Illness. Hideyuki Horikoshi, Takashi Nakanishi, Reiko Takahashi, Fumihiko Kimura and Kenji Itoh.National Defense Medical College, Tokorozawa, Japan.

Background/Purpose: Polymyalgia rheumatica (PMR) is an inflammatory condition that affects the elderly. It is characterized by pain and stiffness in the shoulder and pelvic girdles. Various inflammatory conditions such as infection, vasculitis, and neoplasms can mimic PMR. Owing to the low specificity of the diagnostic criteria of PMR, it is often difficult to distinguish PMR from the so-called 'polymyalgia-like illness.' In previous reports of PMR imaging studies, rheumatic diseases such as rheumatoid arthritis were used as controls. Therefore, the differentiation of PMR from polymyalgia-like illness including paraneoplastic syndrome has not been discussed yet. Herein we performed ^{18}f-Fluoro-Dexoxyglucose Positron Emission Tomography (FDG-PET/CT) in polymyalgia-like illness, and report on the findings.

Methods: Twenty-five cases of polymyalgia-like illness (PMR, 17 cases; paraneoplastic syndrome, 3; infection, 2; vasculitis, 1; others, 2) were analyzed using FDG-PET/CT.

Results: All patients met the diagnostic criteria of Bird et al. and the 2012 ACR/EULAR criteria. The average scores of PMR and non-PMR cases using

these criteria were 4.35 and 4.13, respectively, and no differences were observed between these two groups in clinical presentations. FDG-PET/CT revealed that all PMR cases showed a high FDG uptake in PMR-specific accumulation sites, including the shoulder joints, sternoclavicular joints, hip joints, spinous processes, ischial tuberosities, and greater trochanters. However, non-PMR cases showed various patterns of accumulation. Furthermore, no non-PMR case showed a high FDG uptake in the PMR-specific accumulation sites.

Conclusion: These results indicate the usefulness of FDG-PET/CT for the differential diagnosis of polymyalgia-like illness including paraneoplastic syndrome. Together with the current diagnostic criteria, accumulation of FDG in PMR-specific sites is useful to more accurately diagnose PMR. Various patterns of FDG uptake on FDG-PET/CT in patients with polymyalgia-like illness reveal the diversity of pathogenesis in similar clinical presentations.

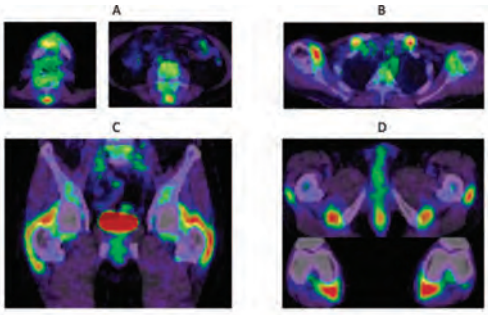


Figure 1. Typical FDG-PET/CT findings in a patient with PMR. PMR case showed a high FDG uptake in PMR-specific accumulation sites, including cervical and lumbar spinous processes (A), shoulder joints and sternoclavicular joints (B), hip joints and greater trochanters (C) ischial tuberosities, and knee joints (D).

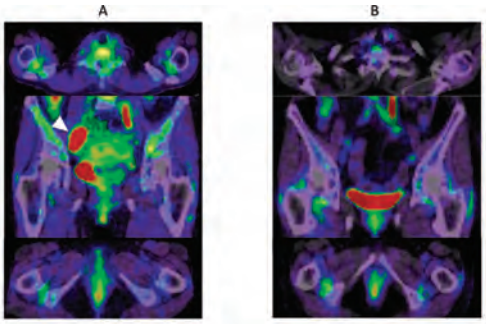


Figure 2. FDG-PET/CT findings in non-PMR cases.
A, A 50-year-old woman with Polymyalgia-like Illness (ovarian cancer). Strong FDG uptake was seen in the ovary (arrowhead). Weak FDG uptake was seen in the shoulder joints, however, an accumulation was not observed in other joints.
B, A 59-year-old woman with Polymyalgia-like Illness (coxsackie virus). FDG uptake was not observed in PMR-specific accumulation sites.

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2129

Sensitivity and Specificity of the "Green Nail" Sign in Fluorescence Optical Imaging in Psoriatic Arthritis. Oliver Wiemann[1], Stephanie G. Werner[1], Hannah Röver[1], Gudrun Lind-Albrecht[1], Sabine Mettler[1], Marina Backhaus[2] and Hans-Eckhard Langer[1]. [1]RHIO (Rheumatology, Immunology, Osteology), Duesseldorf, Germany, [2]Charite University Hospital, Berlin, Germany.

Background/Purpose: ICG-enhanced fluorescence optical imaging (FOI) is a novel technology for the assessment of inflammation in arthritis [1,2]. Recent work suggested that a "green nail" sign in a FOI sequence could possibly be diagnostic for psoriatic arthritis (PsA) [3]. The objective of this study was to determine the sensitivity and specificity of this finding.

Methods: 215 consecutive FOI sequences (n=54 PsA, n=29 RF+ RA, n=67 RF- RA, n=19 uA, n=16 SpA, n=30 other) were read for PVM, P1, P2 and P3 [1] separately. "Green nail" was defined as a caldera-like configuration with a larger rounded green area in the center of the nail and a smaller surrounding of circular or semicircular red or white FOI signals (fig).

Results: The green nail sign was observed in 18/54 subjects with PsA (33%), 2/29 RF+ RA (7%), 10/67 RF- RA (15%), 4/19 uA (21%) and 5/46 other diagnoses (11%) (sensitivity of 0.33, specificity of 0.87). In 9 subjects with green nails and diagnoses different from PsA clinical findings (e.g. nail changes, enthesitis, dactylitis) were suspicious to PsA. After exclusion of those cases specificity increased to 0.93. In PsA green nails were observed predominantly in FOI phase 1 or in early phase 2. The finding was observed more frequently in advanced (> 24 months, 13/36, 36%) than in early arthritis (5/18, 28%). The green nail sign has to be distinguished from a green dot phenomenon that was observed in some cases with RA (small green dot at the borderline between nail and nail fold) and from signs of impaired perfusion in connective tissue diseases and vasculitis that are typically located in the distal, acral regions of the fingers.

Conclusion: While the prevalence of the green nail sign in FOI sequences is relatively low the high specificity for psoriatic arthritis suggests that this finding could provide important additional information for differential diagnosis.

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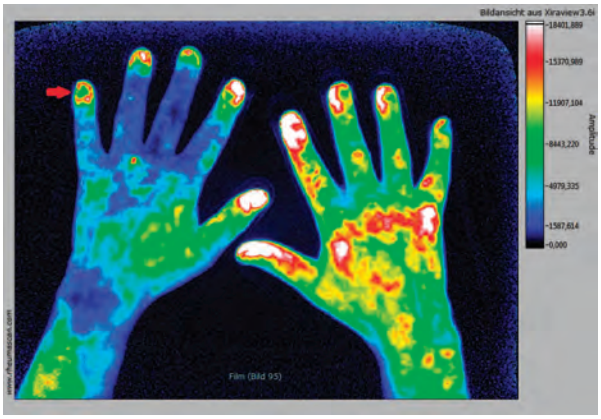

Fig.: Green nail sign (red arrow) in a FOI sequence of a 63-year old male patient with PsA. FOI sequences usually show intense red or white signal intensities in the nail area. In contrast the "green nail" displays a caldera-like green area with a relatively sharp demarcation from the surrounding red FOI signals.

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2130

Bone Microstructure in Patients with Cutaneous Psoriasis and No History of Psoriatic Arthritis Shows Bone Anabolic Changes at a Greater Extent Than in Healthy Controls. David Simon[1], Francesca Faustini[1], Matthias Englbrecht[1], Arnd Kleyer[1], Roland Kocijan[2], Judith Haschka[1], Stephanie Finzel[1], Sebastian Kraus[1], Axel J. Hueber[1], Michael Sticherling[1], Georg Schett[1] and Jürgen Rech[1]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]St. Vincent Hospital, Vienna, Austria.

Background/Purpose: Psoriasis (PSO) is a frequent disease which affects about 1–2% of the population and can be associated to arthritis (PsA). Skin disease often predates the onset of PsA and the transition from skin to joint pathology has been not yet fully elucidated. PsA bone changes include erosions and new bone formation. Aim of the present study was to investigate whether patients with PSO, without clinical history of synovitis, dactylitis or enthesitis at any time and no fulfillment of CASPAR criteria show early changes of the periarticular bone that are typical of PsA.

Methods: PSO patients and healthy subjects (HS) underwent HR-pQCT (XtremeCT, Scanco Medical, Switzerland) scans of the dominant hand which focused on the metacarpal head and phalangeal base of the MCP joints 2 and 3. Erosions, defined as cortical breaks within the joint and visible in two planes, were assessed by frequency and volume (mm^3). Bony spurs, defined as bony projections emerging from the cortical shell and located in the periarticular region were assessed by frequency and maximal height (mm) i.e.

the distance between the highest surface of the lesion and the original cortical surface). Patients participated after signing informed consent. The study was conducted upon approval by the local ethic committee and the National Radiation Safety Agency (BfS).

Results: Images were acquired from 55 PSO patients (mean age 49.5±11.5 y, 36.4% females) and 47 HS (mean age 45.8±13.0 y, 48.9% females). Mean age and sex distribution were comparable. PSO patients had mean disease duration of 15.2±15.4 y, a mean PASI score of 6.2±8.0, while the most prevalent subtype was psoriasis vulgaris (73%). Nail psoriasis was present in 51 % and scalp involvement in 29%. Erosions were identified in PSO and HS (27 vs 18). The most frequent location of the erosions was the radial aspect of the metacarpal head 2 in both groups. The volume of the erosion was not significantly different between the groups. An average number of 6 bony spurs was found in the PSO patients while this accounted for 3 in the HS (total number 306 vs 138). A similar trend of distribution of bony spurs was found in both groups with the majority of them locating in the metacarpal head 2 (palmar and dorsal aspect). PSO patients showed larger bony spurs compared to the HS in each region of interest. For the metacarpal head 2 the mean size accounted for 1.7±0.8 vs. 1.2±0.5 mm respectively, *p=0.001;* metacarpal head 3: 1.2±0.6 and 0.8±0.3 mm, *p=0.001*. In the phalangeal base 2 the PSO patients showed a mean size of 1.3±0.7 mm, and the HS of 0.7±0.3 mm, *p<0.001*. In the phalangeal base 3 mean values accounted for 1.2±0.7 mm and 0.8±0.2 respectively, *p=0.003*.

Conclusion: Analysis of the bone microstructure indicates that patients with PSO without PsA show more pronounced anabolic changes than healthy subjects. Periarticular new bone formation could be an early expression of altered bone remodeling previous to the onset of PsA.

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2131

The Impact of Patient-Reported Flares on Radiographic Progression in Rheumatoid Arthritis Patients with Low-Disease Activity: Secondary Analyses from a Randomized Trial. Dorota Kuettel[1], Jette Primdahl[2], Lykke Midtbøll Ørnbjerg[3], Hans Christian Horn[4], Robin Christensen[5] and Kim Hørslev-Petersen[6]. [1]King Christian X's Hospital for Rheumatic Diseases, Graasten, Denmark, [2]Danbio Registry, Glostrup, Denmark, [3]Copenhagen Center for Arthritis Reasearch, Center for Rheumatology and Spine diseases, Glostrup Hospital, Copenhagen, Denmark, [4]Odense University Hospital, Odense, Denmark, [5]MSU, The Parker Institute, Copenhagen University Hospital, Frederiksberg, Denmark, [6]Research Unit at King Christian X Hospital for Rheumatic Diseases, Graasten, Denmark.

Background/Purpose: Flares, potentially disabling and disease worsening even when a patient is in low disease activity, are common features in patients with rheumatoid arthritis (RA) that may escape the routine clinical control. Consequently the current treat-to-target goal to achieve remission or low disease activity fails to take into account the potential of flares to represent the persistence of disease activity and it remains unknown whether these flares can worsen radiographic joint damage. The aim of this study was to see whether transient flares increase the risk for radiographic progression.

Methods: From 287 patients included in the AMBRA trial, 276 RA patients with low disease activity (DAS28-CRP < 3.2, and no swollen joints at baseline) with radiographs available at baseline and data about flares, were followed for two years. An annual clinical evaluation was performed by a senior rheumatologist and at the same occasion the patients were asked to recall the occurrence of flares during the past year, according to: No flares, transient flares or persistent joint complaints with tender and swollen joints. X-rays of hands and feet were performed at baseline and after two years and scored according to the Sharp/van der Heijde method. The change in Total Sharp Score (TSS) and its components (Joint Space Narrowing (JSN) and Erosions (E)) were calculated. The proportion of patients who progressed (ΔTSS/ ΔJSN/ ΔE > 0 units) across the three groups were compared using Chi-square test and interpreted based on Relative Risks (RR).

Results: 70% of patients were women, median age [IQR] was 63 years [55;70], 73% were rheumatoid factor positive, 71% anti-CCP positive and all had established RA (median [IQR] 7 years [4;13]). In total 268 out of the 276 patients had two year radiographic scores: Radiographic progression depicted by either ΔTSS, Δ JSN, or ΔE, respectively, was seen in 33%, 7%, and 28% of no-flares group (n=82); 36%, 17%, and 31% of patients with transient flares (n=144) and in 46%, 24%, and 34% of patients with persistent joint complaints (n=50). Only differences in worsening of JSN (Figure 1) were statistically significant (P=0.026): RR was 2.37 for the transient flares group and 3.28 for the group with persistent joint complaints compared to the no flares group. Worsening of TSS and E showed some tendencies according to the flare phenotype, but they were not statistically significant.

Conclusion: RA patients with established low active disease, who report transient flares or persistent joint complaints with tender and swollen joints, have more radiographic damage on JSN (which has recently been reported as the main driver of physical disability) in comparison to no-flares patients.

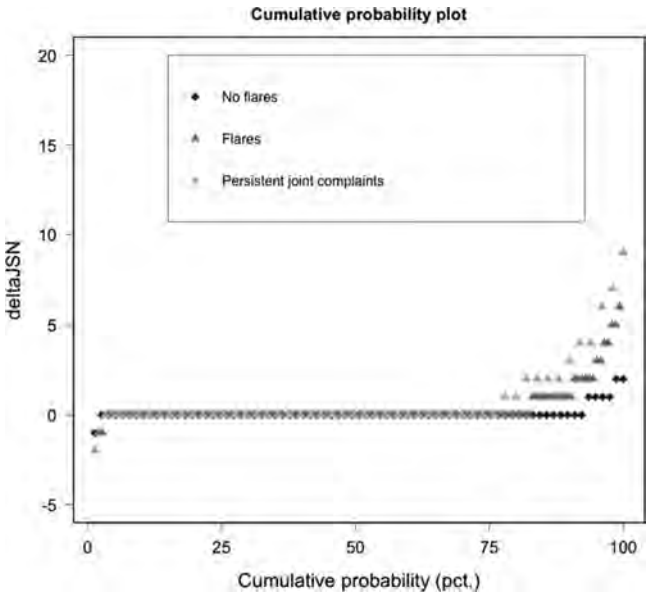


Figure 1: Cumulative probability plot of the three flare phenotypes (no flares; flares; persistent joint complaints) for delta JSN

Disclosure: D. Kuettel, None; **J. Primdahl**, None; **L. M. Ørnbjerg**, None; **H. C. Horn**, None; **R. Christensen**, None; **K. Hørslev-Petersen**, None.

2132

What Is Associated with X- Ray Progression at 5 Years in Rheumatoid Arthritis (RA) Patients in Low Disease Activity? Violaine Foltz[1], Lisa Biale[2], Frederique Gandjbakhch[1], Laure Gossec[1], Pierre Bourgeois[1], Benjamin Granger[1] and Bruno Fautrel[1]. [1]UPMC Paris 06 University, GRC 08, Paris France and Pitié Salpétrière Hospital Paris France, Paris, France, [2]Instruction des Armées Begin hospital, Saint-mande, France.

Background/Purpose: Persistent inflammation on Power Doppler (PD) by ultrasound (US) was associated with relapse and structural progression after one year of follow up in a cohort of RA patients in low disease activity (LDA).

Methods: Patients with RA (1987 ACR criteria) were included in 2007–2008 in one centre if their diagnosis of RA was recent (≤ 2.4). All patients underwent clinical and biological assessments every year. Hands and forefeet X-ray were performed at baseline and at 5 years and evaluated blindly by two investigators (van der Heijde Sharp score: mTSS). Progression was defined as a variation of the mTSS superior to the smallest detectable difference (SDD) of 6.6 points. The metacarpophalangeal (MCPs) joints 2–5 and wrist of the dominant hand were examined with a 0.2T dedicated MRI (ESAOTE C-scan); and bilateral wrists, MCPs 2, 3, 5 and metatarsophalangeal 2, 3, 5 were studied with high resolution US (ESAOTE Technos) at baseline and evaluated blindly using validated acquisition and OMERACT scoring systems (Skuldarek for US and RAMRIS for MRI). The association between the structural progression at 5 years and MRI/US covariates was measured by Wilcoxon Mann-Whitney tests or Fisher's exact test, then by a multivariate logistic regression (forward and backward procedure) to explain a progression $>$ SDD.

Results: 85 patients were included: mean age 50.7 (±13.5) yrs; mean disease duration 35 (±20.7) months, 63.5% patients were anti-CCP positive and mean DAS44 was 1.5 (± 0.54). At baseline the median score [interquartiles] of the grade of synovitis for US and MRI was respectively 3 [1;5] and

3 [4;7]. The median of the number and the grade of synovitis PD positive were 0 [0;1]. The median of the number and the grade of bone marrow edema (BME) were 0 [0;0]. 17 patients (20%) and 8 patients (9%) had respectively score of PD or BME above the median. At 5 years, 13 patients of 70 followed up, were considered in progression. In bivariate analysis X-ray progression at 5 years was associated with baseline number of synovitis PD >0 (p= 0.0001), grade of synovitis DP>0 (p= 0.0001), and total RAMRIS>14 (p=0.03). In multivariate analysis the number of synovitis PD>0 (adjusted OR 9.8 [95% CI 1.7–4.1] was associated with X-ray progression.

Conclusion: Persistence of Doppler signal on US was the best predictor of structural progression on X-ray at short and long term, in a cohort of patients in LDA. Further studies should assess whether patient management guided by US may decrease relapses and X-ray progression.

Disclosure: V. Foltz, None; **L. Biale**, None; **F. Gandjbakhch**, None; **L. Gossec**, None; **P. Bourgeois**, None; **B. Granger**, None; **B. Fautrel**, None.

2133

Efficacy of Tocilizumab Therapy in Patients with Rheumatoid Arthritis Based on FDG-PET/CT. Koichi Okamura[1], Yukio Yonemoto[1], Chisa Okura[2] and Kenji Takagishi[1]. [1]Gunma University, Maebashi, Japan, [2]Gunma University Graduate School of Medicine, Maebashi, Japan.

Background/Purpose: A humanized anti-interleukin-6 receptor (anti-IL-6R) antibody, tocilizumab (TCZ), is one of the biologics and the C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) immediately decrease after the initiation of TCZ therapy. Therefore, it has been proposed that the Disease Activity Score in 28 Joints (DAS28) is an inappropriate marker for assessing the effectiveness of TCZ therapy for RA patients. In fact, clinical physicians are sometimes confused as to how to judge the efficacy of TCZ therapy. Positron emission tomography (PET) with 2-[18F]-fluoro-2-deoxy-D-glucose (18F-FDG) can be used to precisely recognize an increase in synovitis in affected joints, imaging studies with ^{18}F-FDG PET have been performed to assess the metabolic activity of synovitis in RA patients and evaluate the disease activity of RA. Hence, in the present study, we evaluated whether TCZ suppresses synovitis in RA patients after three or six months of treatment and whether conventional assessments of the DAS 28, DAS28-CRP, simplified disease activity index (SDAI) and clinical disease activity index (CDAI) for patients treated with TCZ reflect the improvements in inflammation observed on ^{18}F-FDG PET.

Methods: Seventeen patients (5 males, 12 females; average age: 59.9 ± 11.7 (30–82) years) were enrolled in this study. All patients were diagnosed according to the American College of Rheumatology (ACR) criteria revised in 1987 and had a history of a clinically inadequate response to previous treatment with non-biologic disease modifying antirheumatic drugs (DMARDs), including methotrexate (MTX) and biologic agents, including TNF inhibitors only. ^{18}F-FDG PET was performed at baseline and three and six months after the therapy. The maximum SUV (SUVmax) of the bilateral shoulder, elbow, wrist, hip, knee and ankle joints were totaled (total SUV) and used to assess the degree of FDG uptake as a representative parameter. Wilcoxon's signed-rank sum test was used to assess differences in the effects of treatment. Spearman's rank correlation test was applied to test for correlations between the different parameters recorded in this study.

Results: The disease activity scores of the DAS 28, DAS28-CRP, SDAI and CDAI, and total SUV were significantly decreased at three months after the initiation of TCZ. The disease activity and total SUV scores were also found to be further decreased at six months compared to baseline. The ΔSUV, the differences in the total SUV at baseline and three/ six months after treatment, positively correlated with the ΔDAS28 (r = 0.615 p = 0.009/ r = 0.775 p < 0.001), ΔDAS28-CRP (r = 0.696, p = 0.002/ r = 0.828, p < 0.001), ΔSDAI (r = 0.652, p = 0.005/ r = 0.686, p = 0.002) and ΔCDAI (r = 0.662, p = 0.004/ r = 0.711, p = 0.001) for each period.

Conclusion: A reduction in the FDG uptake was observed at three months after the initiation of TCZ therapy. Our results indicate that conventional parameters of TCZ efficacy in RA patients match the disease activity estimated on ^{18}F-FDG PET. ^{18}F-FDG PET can be used to evaluate the response of RA patients to TCZ therapy.

Disclosure: K. Okamura, None; **Y. Yonemoto**, None; **C. Okura**, None; **K. Takagishi**, None.

2134

Baseline Scintigraphic Detection of TNFá As a Predictor of Therapy Response after Treatment with Certolizumab Pegol in Rheumatoid Arthritis and Spondyloarthritis Patients. Philippe Carron[1], Bieke Lambert[2], Filip De Vos[3], Gust Verbruggen[1], Dirk Elewaut[1] and Filip van Den Bosch[1]. [1]Department of Rheumatology Ghent University Hospital, Ghent, Belgium, [2]Department of Nuclear Medicine Ghent University Hospital, Ghent, Belgium, [3]Department of Radiopharmacy Ghent University, Ghent, Belgium.

Background/Purpose: A major challenge in the biologic era is to predict clinical response. A large variability in the level of TNFα expression has been recognized which may influence the outcome of TNF antagonism. Thus far, treatment decisions are solely based on clinical disease activity. In this way, only 40% of rheumatoid arthritis (RA) and spondyloarthritis (SpA) patients achieve a clinically important response (ACR50 or ASAS40). We hypothesized that *in vivo* assessment of TNFα by scintigraphy with 99mTc-radiolabeled anti-TNFα antibodies may be helpful to optimize and monitor the effect of TNFα blockade. This technique may facilitate 'evidence-based biological therapy' by *in vivo* measurement in inflamed joints of a target cytokine, prior to therapeutic administration of a biologic.

Objective: Predict response to therapy by baseline immunoscintigraphy before starting anti-TNF treatment in active RA and SpA patients.

Methods: Certolizumab pegol (CZP)was radiolabeled with Tc99m. Whole body images and static images of hands and feet were acquired immediately following administration, 4–6 hours and 24 hours post injection. Immunoscintigraphic findings were scored as either negative (no or faint uptake) or positive (clear uptake). All patients were treated with CZP for 6 months and standard clinical assessments were performed. Statistical analysis for the joint based response (tender and swollen) was based on a logistic regression model including patient as random effect to accommodate for clustering of the joints in the patient and using the odds ratio (OR) as summary statistic.

Results: 20 patients were included (RA n=5, SpA n=15), scanned and treated according to the protocol. Images 4–6 hours post-injection yielded the best discriminatory results of radiolabeled uptake. Immunoscintigraphy was a good predictor for a joint being swollen at baseline as only 2.2% of the scintigraphic negative joints were swollen compared to 63.5% of the scintigraphic positive joints.The mid scintigraphic evaluation had a significant predictive value on the tender (OR=18.7, P<0.0001) and swollen joint count (OR=44.4, P<0.0001) at baseline, implying that clear uptake increases the odds of having a problematic joint. After 24 weeks, the odds of joints remaining painful was significantly smaller in joints with a positive scintigraphic result as compared to joints with a negative scintigraphic result (OR=0.41, P=0.04):32 out of 114 (28.1%) painful negative scintigraphic joints at baseline remained painful at week 24, whereas only 18 out of 58 (13.8%) painful positive scintigraphic joints at baseline remained painful at week 24. No significant results were found for the swollen joints.

Conclusion: Baseline scintigraphic detection of TNFα with radiolabeled anti-TNFα has a significant predictive value at baseline and after 24 weeks treatment with CZP on the tender joint count. Tender joints not identified by immunoscintigraphy respond to a lesser degree to anti-TNF treatment, potentially indicating another biological reason for a painful joint. Therefore TNF-immunoscintigraphy could offer a new tool to identify good clinical responders to biological treatment.

Disclosure: P. Carron, None; **B. Lambert**, None; **F. De Vos**, None; **G. Verbruggen**, None; **D. Elewaut**, None; **F. van Den Bosch**, None.

2135

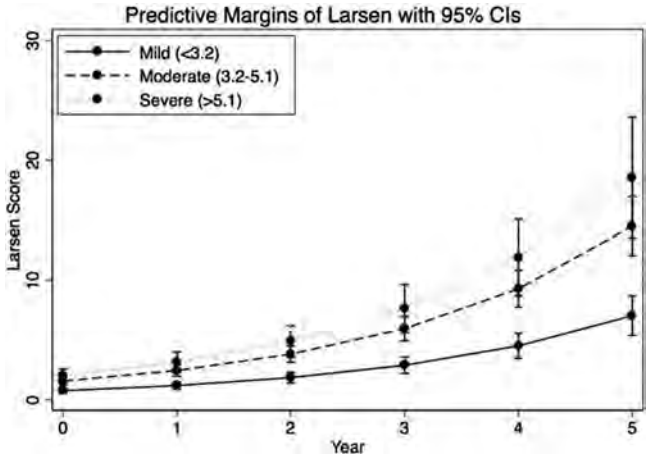
Patients with Moderate Disease Activity in the First 5 Years of Rheumatoid Arthritis Still Progress Radiographically Despite Conventional Disease Modifying Therapy. Lewis Carpenter[1], Elena Nikiphorou[1], Sam Norton[2], Keeranur Jayakumar[3], Josh Dixey[4] and Adam Young[5]. [1]University of Hertfordshire, Hatfield, United Kingdom, [2]King's College London, London, United Kingdom, [3]Heart of England NHS Foundation Trust, Birmingham, United Kingdom, [4]New Cross Hospital, Wolverhampton, United Kingdom, [5]ERAS, St Albans City Hospital, St Albans, United Kingdom.

Background/Purpose: Patients with moderate disease are an important, and often poorly studied, patient subgroup. The extent to which traditional DMARD therapies adequately control the disease is an important research question. Radiographic damage is a crucial indicator of the success or failure of treatment to adequately control the disease.

Methods: The Early Rheumatoid Arthritis Study (ERAS) is an inception cohort that recruited 1,465 recent onset, DMARD naïve, RA patients from 9 hospitals in England between 1986 and 1998, with follow up for up to 25 years. Data collected included demographics, disease activity (DAS), functional disability (HAQ) and radiographs of hands and feet (Larsen). A total of 1,409 (96%) patients had at least one DAS score over the first 5 years of follow-up. Patients mean DAS score over the first 5 years was calculated, and patients were split into three categories based on this score. Patients with a mean score of 5.2 as severe (n=304), in accordance with the EULAR definitions. A mixed effects negative binomial regression was conducted to analyse the rate of Larsen progression over the first 5 years of disease. Follow-up year, age at onset, sex, treatment at 5 years, baseline HAQ and baseline HB were controlled for in the model.

Results: Patients in the severe group were older, more likely to be female, Rheumatoid Factor positive, higher baseline HAQ, lower baseline HB and shorter mean follow-up. Patients in the moderate group had the highest mean time from symptom onset to first secondary care visit. Patients in the mild and moderate groups were more likely to be on mono-therapy DMARD and steroids, while those patients in the severe group were more likely to be on DMARD step up or add-on treatment. Larsen significantly increased over the first 5 years of disease ($P<0.001$). Those patients in the moderate group had a significantly higher progression of Larsen over the 5 years compared to those patients in the mild group ($P<0.001$). There was no significant difference in 5 year Larsen progression between the moderate and severe groups.

Conclusion: Patients with moderate disease had similar radiographic progression to severe disease, whilst controlling for treatment. Similarly, patients with moderate disease had significantly higher Larsen progression compared to those with mild disease. Results highlight that targeting this group and aiming for remission, or at least better disease control, is as important as for those with high disease.



Disclosure: L. Carpenter, None; **E. Nikiphorou**, None; **S. Norton**, None; **K. Jayakumar**, None; **J. Dixey**, None; **A. Young**, None.

2136

Rheumatoid Arthritis Erosion Detection and Measurement in Longitudinal Datasets Using High-Resolution Peripheral Quantitative Computed Tomography.

Stephanie Finzel[1], Cheryl Barnabe[2], Kathryn Stok[3], A. Scharmga[4], Andrew J. Burghardt[5], Ellen-Margrethe Hauge[6], Hubert Marotte[7], Stephanie Boutroy[8], Klaus Engelke[9], Dominique Toepfer[1], Sebastian Kraus[1], Roland Kocijan[10], Xiaojuan Li[5] and J. de Jong[4]. [1]University of Erlangen-Nuremberg, Erlangen, Germany, [2]University of Calgary, Calgary, AB, [3]ETH Zurich Institute for Biomechanics, Zurich, Switzerland, [4]Maastricht University Medical Center, Maastricht, Netherlands, [5]Musculoskeletal Quantitative Imaging Research, UCSF, San Francisco, CA, [6]Aarhus Universitetshospital, Aarhus C, Denmark, [7]University Hospital of Saint Etienne, Saint Etienne, France, [8]INSERM U1033 and University of Lyon, Hôpital Edouard Herriot, Lyon, France, [9]Institute of Medcial Physics Synarc, Hamburg, Germany, [10]St. Vincent Hospital, Vienna, Austria.

Background/Purpose: An operational case definition for identification of erosions imaged by HR-pQCT was achieved and tested in a first reliability exercise (RELEX-1) using cross-sectional data. Aim of the study: oo test the case definition and define landmarks for measurement of erosion size in 2D in a longitudinal dataset.

Methods: Patients meeting the new ACR/EULAR classification criteria for RA at various stages of disease duration and severity received a HR-pQCT scan of the 2nd and 3rd MCP joints at 0 and 12 months. Standard image acquisition and segmentation was performed for a 2.7 cm scan area. Images were evaluated for erosions at 8 surfaces per joint (ulnar, radial, dorsal, palmar surfaces of the proximal phalanx and metacarpal head). The erosion case definition requires the presence of a definite interruption in the cortical bone extending over at least 2 consecutive slices, visualized in 2 orthogonal planes, with loss of underlying trabecular bone and being non-linear in shape. The maximal width of the cortical break is identified and measured in the axial multiplanar resolution (MPR), with the maximal depth recorded perpendicular to this line. This same method is repeated in the corresponding MPR. Five readers blinded to patient identity and time sequence of the scan scored 36 baseline and follow-up images (18 joints from 9 patients). Percent agreement and a kappa score for erosion detection (minimum of 2 readers in agreement) was calculated. The variation in width and depth measurements of erosions in axial and perpendicular planes between readers was calculated using the root-mean-square coefficient of variance (RMSCV). McNemar's test was used to test for a significant change in the number of erosions identified from 0 to 12 months. Paired t-tests were used to calculate the average width and depth changes from 0 to 12 months.

Results: Agreement for the presence or absence of an erosion was 92.9% (k=0.711, 95%CI 0.539–0.839). Mean (SD) dimensions of the erosions were: axial width 1.66 (SD 0.99) mm, perpendicular width 1.60 (SD 0.78) mm, axial depth 1.16 (SD 0.66) mm, and perpendicular depth 1.17 (SD 0.57) mm. The respective RMSCV were 36.4%, 30.3%, 15.7% and 27.3%. Seven erosions were detected at both 0 and 12 month timepoints (k=0.755, 95%CI 0.616–0.895) and all readers agreed on a single new erosion developing between 0 and 12 months for 1 subject (McNemar's test p=1.00). Erosion dimensions did not significantly change over 1 year but a trend to reduction in mean size was observed, with an axial width decrease of 0.171 mm (95%CI -0.168, 0.509, p=0.310), perpendicular width decrease of 0.014 mm (95%CI -0.202, 0.230, p=0.898), axial depth increase of 0.007 mm (95%CI -0.147, 0.133, p=0.917), perpendicular depth decrease of 0.133 mm (95%CI -0.075, 0.340, p=0.201).

Conclusion: The case definition for erosions imaged by HR-pQCT is valid in longitudinal datasets. Despite variability in measurements, a trend towards changes in erosion size is demonstrated.

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Linear Extrapolation of Missing Radiographic Progression Scores Does Not Spuriously overestimate overall Radiographic Progression in Rheumatoid Arthritis.

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Background/Purpose: Linear Extrapolation (LE) is a frequently applied method to impute missing radiographic data in trials. However, there is frequent critique that LE overestimates overall progression. Therefore, 'Last Observation Carried Forward' (LOCF) has been suggested by regulatory bodies as a more conservative method. In the OSKIRA-1 trial (NCT01197521), radiographs were taken at the 12 week (wk) time point, where early escape was possible, in all patients thus providing an excellent opportunity to compare extrapolations based upon LOCF and LE to the truly observed radiographic progression.

Methods: The phase 3 OSKIRA-1 trial enrolled rheumatoid arthritis patients (pts) with an inadequate response to methotrexate. Films of hands and feet were obtained at baseline, wk 12 and 24 in those pts still on study, and were assessed by two readers in random time order using the van der Heijde modified total Sharp score (mTSS). Ten datasets with an artificially, randomly selected sample of 20% missing wk 24 data were created, based upon pts with complete sets of films. First, these missing data were imputed using LE as (mTSS at wk 12 + progression wk 0 – 12, corrected for the actual days between films). Second, the missing data were imputed using LOCF. This approach was iterated for 10 random samples with 50% missing data and 10 random samples with 80% missing data. The datasets obtained with LE and LOCF were compared to the dataset with truly observed data at week 24.

Results: Complete sets of films were available for 579 pts. All our analyses were essentially similar in the 3 treatment arms, so here we present the analysis on pooled data. Mean (SD) observed progression from baseline to wk 24 was 0.33 (2.42). Table 1 shows the average (SD) and range of the mean radiographic progression in the 10 random samples. Using LE, the mean progression estimates were close to the observed data, and not affected by the proportion of missing data. The SD however increased by increasing proportions of missing data. Using LOCF, the mean progression estimates were consistently lower than the observed progression. LOCF increasingly underestimated observed progression by increasing proportions of missing data. As expected, the SD of the LOCF estimates remained stable by increasing proportions of missing data.

Conclusion: In contrast to LOCF, linear extrapolation gives a more accurate impression of true mean radiographic progression at a group level and is less influenced by the proportion of missing data. Since LE inflates the standard deviation of progression scores, the statistical power to detect a significant difference between active treatment and placebo may decrease by increasing proportions of missingness. LE does therefore not overestimate mean treatment effects and is a more robust method than LOCF in this respect.

Table 1: Change in the van der Heijde modified total Sharp score (mTSS) from baseline to week 24.

		Observed change in mTSS in patients completing 24 weeks, mean (SD): 0.33 (2.42)					
	Method	*Mean of the mean**	*Mean of the SD**	*Minimum mean**	*Maximum mean**	*Minimum SD**	*Maximum SD**
20% missing data	LOCF	0.29	2.43	0.28	0.32	2.38	2.48
	LE	0.32	3.02	0.27	0.39	2.60	4.44
50% missing data	LOCF	0.25	2.41	0.21	0.29	2.32	2.49
	LE	0.34	3.83	0.22	0.42	2.73	4.61
80% missing data	LOCF	0.19	2.41	0.18	0.21	2.37	2.44
	LE	0.30	4.19	0.21	0.36	3.05	4.74

*of 10 random samples
LE, linear extrapolation; LOCF, last observation carried forward; mTSS, van der Heijde modified total Sharp score; SD, standard deviation.

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Radiological Outcomes after Two Years of Remission Steered Treatment in Early Arthritis Patients. G. Akdemir[1], L. Heimans[1], K.V.C. Wevers-de Boer[1], M.K. Verheul[1], A.a. Schouffoer[2], M. van Oosterhout[3], J.B. Harbers[4], C. Bijkerk[5], G.M. Steup-Beekman[6], L.R. Lard[7], T. W. J. Huizinga[1], L.a. Trouw[1] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Haga Hospital, The Hague, Netherlands, [3]GHZ Hospital, Gouda, Netherlands, [4]Franciscus Hospital, Roosendaal, Netherlands, [5]Reinier de Graaf Gasthuis, Delft, Netherlands, [6]Bronovo Hospital, The Hague, Netherlands, [7]MCH Antoniushove Hospital, Leidschendam, Netherlands.

Background/Purpose: We investigated whether early, remission steered treatment can prevent damage progression in patients with early rheumatoid arthritis (RA) or undifferentiated arthritis (UA), and aimed to identify potential predictive factors for damage progression.

Methods: 610 patients with early RA (2010 criteria) or UA suspected to be early RA started treatment with methotrexate (MTX) and a tapered high dose prednisone in the IMPROVED study. After four months patients achieving a Disease Activity Score (DAS) <1.6 (early remission) tapered prednisone to zero. If remission was maintained at eight months MTX was tapered to zero. Patients not in early remission were randomized to MTX plus hydroxychloroquine, sulphasalazine and prednisone (arm 1) or to MTX plus adalimumab (arm 2). Every four months medication was tapered and next stopped in case of remission but increased or switched in case of no remission. Radiological joint damage was assessed on radiographs of hands and feet at baseline and yearly in random order by two independent readers using the Sharp/van der Heijde score (SHS). Progression scores were compared between treatment arms and between RA and UA patients. Potential predictors of radiological progression were assessed using logistic regression analysis.

Results: Progression scores were available for 488 patients with a median (IQR) SHS progression of 0 (0-0) point. There was no difference in median SHS progression score between RA and UA patients nor between treatment arms. In only 10% (50/488 patients) radiological progression (≥0.5 SHS) was seen: 33/50 (66%) were in the early remission group, 9 (18%) in arm 1, 5 (10%) in arm 2 and 3 (6%) were treated outside the protocol. In 98 patients (7 in the early remission group and 1 in arm 2) the progression score was ≥5 points (minimal clinically important difference) after two years. Age (OR (95% CI) 1.03 (1.00–1.06)) and the combination of anti-CarP (anti-carbamylated protein antibodies) positivity and ACPA (anti-citrullinated protein antibodies) positivity (2.54 (1.16–5.58)) were independent significant predictors for radiological progression.

Conclusion: After 2 years of remission steered treatment in early arthritis patients radiological progression in the majority of patients was practically zero, regardless of diagnosis RA or UA and regardless of treatment arm following initial combination therapy with methotrexate and a tapered high dose of prednisone. Predictors for radiological progression were age and the combination of anti-CarP positivity and ACPA positivity.

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Predictors of Radiologic Disease Progression during the Rheumatoid Arthritis Comparison of Active Therapies Trial. Alan Erickson[1], Denis Rybin[2], Mary Brophy[2], Robert Lew[2], Ted R. Mikuls[1], Timothy Moore[3], Keri Hannagan[2], Edward Keystone[4] and James O' Dell[1]. [1]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [2]VA Boston Heathcare System, Boston, MA, [3]University of Nebraska Medical Center, Omaha, NE, [4]University of Toronto and Mount Sinai Hospital, Toronto, ON.

Background/Purpose: Halting joint damage is a central goal in the treatment of rheumatoid arthritis. Much research has been conducted to identify factors associated with progressive radiographic damage typically measured by the Sharp/van der Heijde score (SHS). Trials have also suggested that treatment choices impact disease course including the development of rapid radiographic progression, defined as a threshold change in SHS ≥ 5U/year. In the 48-week, double-blind, noninferiority RACAT trial, 353 patients with suboptimal methotrexate response were randomized to two treatment strategies, either first adding sulfasalazine and hydroxychloroquine (triple therapy or T) or first adding etanercept (E). After 24 weeks of treatment patients not achieving a DAS28 improvement of 1.2 were switched in a blinded fashion to the other therapy. We explored the associations of strategy and baseline factors with SHS progression.

Methods: Two expert readers provided SHS for patients at baseline and 48 weeks. Using the mean value of the two readers, SHS change was categorized as a an increase ≤ 0.5 U or > 0.5U. Possible baseline predictors of change evaluated included swollen and tender joint count, ESR, Global Health Assessment, DAS28, gender, smoking, RF status, disease duration and baseline SHS. From logistic regression models we obtained odds ratios (OR) for each predictor alone and in multivariable models with all factors. We analyzed all participants, the two strategy subgroups (T and E) and the four treatment subgroups (T-only, E-only, T switch to E, and E switch to T).

Results: Of 304 participants with week-48 Sharp scores, only 4.3% (13 of 304) had increases in SHS ≥5U evenly spread over the four treatment groups, while 23% demonstrated increases >0.5 units again evenly spread over treatments. Approximately 60% demonstrated changes of −0.5, 0, or 0.5U, and 17% showed improvement (<−0.5 change).

Baseline SHS values were significantly different for increases ≤ 0.5U compared to increases >0.5U (15.3 vs. 26.4, p=0.006). In multivariable analyses, only baseline SHS consistently predicted disease progression (see Table). Other measures, including treatment strategy, were not predictive of radiographic progression. No evidence suggested that any of the four treatments was associated with change defined either as >0.5U or as ≥5U. Only 4% had changes ≥5U.

Table: Univariate and multivariable associations of patient factors with SHS progression (increase >0.5U) over 48 weeks (same results obtained using stepwise up or down selection to detect intercorrelation); *model includes all variables shown

	Univariate		Multivariable*	
Baseline Characteristic	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Sharp Score at Baseline	1.02 (1.01,1.03)	0.002	1.02 (1.01,1.03)	0.007
Male Gender	1.04 (0.61,1.78)	0.881	1.18 (0.66,2.11)	0.584
Ever Smoked	0.58 (0.34,1.01)	0.052	0.60 (0.33,1.08)	0.090
DAS28	1.22 (0.91,1.65)	0.185	1.23 (0.49,3.10)	0.660
Swollen Joint Count	1.02 (0.97,1.07)	0.487	1.00 (0.93,1.07)	0.950
Tender Joint Count	1.00 (0.96,1.04)	0.986	0.99 (0.91,1.08)	0.861
Erythrocyte Sedimentation Rate	1.01 (1.00,1.02)	0.042	1.00 (0.98,1.03)	0.862
Patient Global Health Assessment	1.00 (0.99,1.01)	0.779	1.00 (0.98,1.02)	0.771

Disease Duration	1.01 (0.98,1.04)	0.524	0.98 (0.94,1.02)	0.304
RF Status	1.59 (0.87,2.89)	0.131	1.46 (0.78,2.74)	0.240

Conclusion: Similar to other trials, we found that radiologic progression is most strongly associated with baseline SHS. A weak and non-significant association with positive RF status was observed. We found no significant radiographic advantage with either of the two treatment strategies or among the 4 treatment groups. Rapid radiographic progression, an increase in SHS≥5U, was uncommon (less than 4.3%) regardless of strategy.

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Agreement Among FDG-PET/CT, Ultrasound and Physical Examination in Patients with Inflammatory Arthritis. Alexis Ogdie[1], Shiv Sehra[1], Viviane Khoury[1], Yihui Jiang[1], Shawn Rose[2], Nehal N. Mehta[1], Sally W. Pullman-Mooar[3], Abass Alavi[1], Joel Gelfand[4] and Joshua Baker[5]. [1]University of Pennsylvania, Philadelphia, PA, [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, [3]University of Pennsylvania and Philadelphia Veterans Hospital, Philadelphia, PA, [4]University of Pennsylvania., Philadelphia, PA, [5]University of Pennsylvania and Philadelphia VAMC, Philadelphia, PA.

Background/Purpose: The lack of tools to accurately measure and quantify joint inflammation is a challenging problem in the study of inflammatory arthritis. No gold standard method for identifying and quantifying the presence of inflammation exists. The joint examination has relatively poor inter-rater reliability and ultrasound (US) can identify inflammation but is operator-dependent. Joint inflammation can also be seen on 18F-Flurorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET/CT) but little is known about how this compares to other modalities. The objective of this study was to examine the agreement among three methods of assessing joint inflammation: physical examination (swelling/tenderness), US (grayscale/Doppler), and FDG-PET/CT visual assessment. We hypothesized that there would be good agreement among the measures.

Methods: Ten patients with active inflammatory arthritis underwent physical examination, US and FDG-PET/CT. Exclusion criteria included pregnancy, elevated fasting glucose (>150) or diabetes. The examination was performed by an attending rheumatologist. US was performed by an US-trained rheumatology fellow or a trained ultrasonography technician. US images were read by a US-trained rheumatologist or musculoskeletal radiologist blinded to the clinical examination. PET/CTs were read by a rheumatology fellow blinded to the examination and US results. Previously reported grading scales for US synovitis, doppler and PET/CT were used but for analysis these variables were converted to binary measures (yes/no inflammation) for analysis. Agreement among the modalities was examined using Cohen's kappa. Confidence intervals were generated using a bootstrapping method to account for clustering by individual.

Results: Four patients with rheumatoid arthritis and 6 with psoriatic arthritis were enrolled with mean age 52.7 years and 80% male. All patients were on therapy at the time of the assessments and had relatively mild disease activity. Among the 10 patients, 300 joints were included in the analysis (340 examined, 300 PET/CT, 180 US). Of these, 46 were swollen, 50 were tender, 56 had FDG uptake on PET/CT, 26 had signs of inflammation on US grayscale and 14 were Doppler positive. Agreement among the imaging modalities and examination was low (**Table**), with κ ranging from 0.01–0.22. Restricting the analysis to only large peripheral joints did not substantially change agreement.

Conclusion: This is the first study to examine agreement among PET/CT, US and physical examination in the assessment of joint inflammation. In this small pilot study, we found low agreement among PET/CT with US and both PET/CT and US with physical examination findings among patients on therapy with mild disease activity. It may be that each modality measures a distinct property of inflammation, all equally valuable in measuring the construct of inflammation.

	All joints				Large Peripheral Joints*			
	PET	Grayscale	Doppler	Tenderness	PET	Grayscale	Doppler	Tenderness
US-Grayscale†	0.18 (−0.03–0.39)				0.15 (−0.10–0.40)			
US-Doppler†	0.11 (−0.08–0.31)	0.49 (0.22–0.75)			0.10 (−0.13–0.32)	0.47 (0.08–0.86)		
Tenderness	0.01 (−0.16–0.18)	0.10 (−0.16–0.35)	0.18 (−0.07–0.42)		0.09 (−0.14–0.31)	0.10 (−0.28–0.48)	0.25 (−0.15–0.64)	
Swelling	0.22 (−0.06–0.51)	0.07 (−0.13–0.27)	−0.02 (−0.20–0.16)	0.44 (0.10–0.79)	0.18 (−0.14–0.50)	0.13 (−0.17–0.44)	−0.01 (−0.25–0.23)	0.58 (0.22–0.94)

Cohen's kappa values and confidence intervals are presented in this table. Kappa ranges from -1 to 1 where positive values suggest systematic agreement and negative values suggest systematic disagreement. Confidence intervals were generated based on a cluster bootstrap method. †Ultrasound was performed on ankles, knees, elbows, wrists, shoulders second and third MCPs, and second and third PIPs bilaterally. FDG uptake was assessed for ankles, knees, elbows, wrists, shoulders, MCPs, and PIPs. In patients with psoriatic arthritis, DIPs, hips, and SI joints were also assessed. *Large peripheral joints included ankles, knees, wrists, elbows and shoulders.

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Sensitivity to Change of Joint Space Width Measurements in Hand Osteoarthritis in a Two Year Follow-up Study. W. Damman, S.E. de Bruin, B.C. Stoel, R. van 't Klooster and M. Kloppenburg. Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Cartilage loss, represented by joint space width (JSW) on radiographs, is an important outcome measure in hand OA disease course. JSW can be assessed quantitatively in a valid, reliable and feasible way. However, it is not known whether this method is sensitive over time and was therefore subject of this 2-year follow-up study.

Methods: We used data of 276 participants (mean age 61 yrs, 88% women, mean BMI 27 kg/m^2, 93% fulfilled ACR criteria, median number of joints with pain 2 (range 0–24)) in the ongoing HOSTAS (Hand OSTeoArthritis in Secondary care) study, including consecutive primary hand OA patients diagnosed by their treating rheumatologist.

During physical examination (PE) in the 2nd to 5th DIP and PIP joints the number of joints painful upon palpation, with bony swellings, soft-tissue swelling, limited Range Of Motion (ROM) and deformity was assessed (all 0–16). Digital hand radiographs (dorsal-volar views) were taken at baseline and after two years.

JSW was measured in 2nd to 5th DIP, PIP and MCP joints (n=24) with a semi-automatic quantification method (van 't Klooster Osteoarthritis Cartilage 2008; 16: 18–25. Openly available through www.lkeb.nl (software downloads)). ICC were calculated based on repeat measurement in 40 radiographs to determine reliability. Smallest Detectable Differences (SDDs) of all joints and per joint group were calculated by measuring two radiographs from 21 patients acquired within a 6-months (max 196 days) time-interval, assuming no progression over such short time.

Progression was defined as a change more than the SDD. Progression on patient level was defined when at least 1 joint had progressed.

Generalized Estimating Equations (GEE) were used to test on joint level in 2nd to 5th DIP and PIP joints which factors associate with progression. Adjustments were made for patient (age, sex, BMI) and joint characteristics (all five PE assessments and baseline JSW).

Results: After two years, of 192 patients both baseline and follow-up radiographs were available to assess progression. Of the 4570 joints measured, 8.8% progressed, which was seen most often in the DIP joints. On patient-level, 76.6% progressed. The results are depicted in table 1. The reliability was high with ICC 0.97.

Variables at joint level associated with progression are JSW at baseline OR 9.9 (95%CI 5.1;19.0), pain upon palpation dichotomized to present/absent 1.4 (1.02;1.9) and limited ROM 1.9 (1.4;2.5). All the other variables had no significant association.

Conclusion: Semi-automated JSW measurement is sensitive to change over 2 years. Risk factors for progression on joint level are: a relatively large JSW on baseline, pain upon palpation and limited ROM.

Table 1: JSW, SDD and progression in 195 patients with hand osteoarthritis

	JSW at baseline, mean (SD)	JSW at two years, mean (SD)	SDD, mm	Progression, %
Total (n=4570)	0.92 (0.17)	0.91 (0.17)		
DIP joints (n=1524)	0.63 (0.18)	0.63 (0.18)	0.116	10.8
PIP joints (n=1522)	0.78 (0.19)	0.77 (0.18)	0.135	6.9
MCP joints (n=1524)	1.34 (0.25)	1.32 (0.25)	0.202	8.7

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Sensitivity and Precision of Automated Osteophyte Volumetric Measurement in Knee Osteoarthritis over Four Years. Michael Hakky[1], Charles Ratzlaff[2], Mohamed Jarraya[3], Ali Guermazi[3] and Jeffrey Duryea[4]. [1]Lahey Clinic, Burlington, MA, [2]Harvard Medical School / Brigham and Women's Hospital, Boston, MA, [3]Boston University School of Medicine, Boston, MA, [4]Brigham & Women, Boston, MA.

Background/Purpose: Osteophyte formation and evolution is a hallmark of knee OA, and their radiographic identification and progression is fundamental in clinical practice, observational research and randomized clinical trials. The most commonly used grading scales are ordinal, requiring subjective judgment and expert reading time potentially hampering precision and responsiveness. We have developed a semi-automated method for osteophyte volumetric analysis on MRI. Our objective was to evaluate the sensitivity and precision of this method to osteophyte volume change over four years in subjects with established knee OA according to Kellgren and Lawrence (KL) grade.

Methods: Ninety subjects (51 KL 2 and 39 KL 3) were selected from the Osteoarthritis Initiative (OAI) Progression Cohort. Double echo steady state 3D sagittal images were obtained on a 3T Siemens Trio MR system. Measurements were performed on coronal reformatted series. A reader (MH) used software to segment marginal femoral and tibial osteophytes of all 90 knees at baseline and 48 months, blinded to order of visit. The first and last slice of the central weight bearing region were identified and an edge detection algorithm demarcated the bone margins. The reader then 'closed off' each osteophyte by marking the expected normal bone contour. The software calculated the total volume (V) for each compartment, bone and knee. Reliability was assessed using an experienced MSK radiologist (MJ) on a random sub-sample of 20 subjects.

The primary outcome was change in osteophyte volume (ΔV). Statistics used were the average change (ΔV), the standard deviation of ΔV (SD), the standardized response mean of (SRM, defined as ΔV/SD), and the percentage of subjects with net increase in V. Intraclass correlation coefficient (ICC) and root mean square of the standard deviation (RMSSD) were used to assess reliability.

Results: The average change in osteophyte volume (ΔV) was 196 mm^3(272), and the SRM was 0.72. A net increase in osteophyte volume from baseline to 48 months was observed for 84% (76/90, 40 KL 2 and 36 KL 3) of the subjects. The average reading time was approximately 10 minutes per knee.

Table 1 – Responsiveness to change over 48 months

Baseline KL grade (n)	Net Increase	Mean ΔV	SD ΔV	SRM
KL 2 + KL 3 (90)	76 (84%)	196 mm^3	272 mm^3	0.72
KL 2 (51)	40 (78%)	155 mm^3	233 mm^3	0.67
KL 3 (39)	36 (92%)	250 mm^3	309 mm^3	0.81

Table 2 — Responsiveness to change by compartment

	Mean ΔV	SD ΔV	SRM
Medial Compartment	53mm^3	88 mm^3	0.60
Lateral Compartment	45 mm^3	95 mm^3	0.48
Medial Femur	72 mm^3	99 mm^3	0.72
Lateral Femur	60 mm^3	115 mm^3	0.52
Medial Tibia	34 mm^3	72 mm^3	0.47
Lateral Tibia	30 mm^3	66 mm^3	0.45

The intra- reader ICC was 0.98, and RMSSD 82 mm^3, while inter- reader ICC was 0.97 and RMSSD 91 mm^3.

Conclusion: A new computer-assisted method of osteophyte volume measurement is reliable and sensitive. It may provide a more responsive and rapid method for osteophyte change than traditional ordinal methods, making it feasible to assess a large number of knees in a short period of time.

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Cortical Breaks and Bone Erosions in the Hand Joints: A Cadaver Study Comparing Conventional Radiography with High-Resolution and Micro-Computed Tomography. A. Scharmga[1], A. van Tubergen[1], J. van den Bergh[1], J. de Jong[1], M. Peters[1], B. van Rietbergen[2] and P. Geusens[1]. [1]Maastricht University Medical Center, Maastricht, Netherlands, [2]Eindhoven University of Technology, Eindhoven, Netherlands.

Background/Purpose: Conventional radiography (CR) is considered the gold standard for diagnosing bone erosions in rheumatic diseases. However, High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT) and microCT (μCT) allow analysis of bone erosions in finger joints at micro level. This study aimed to quantify cortical breaks and erosions in hand joints assessed from CR, HR-pQCT and μCT images.

Methods: Eight metacarpal phalangeal and four proximal interphalangeal joints from eight female human cadaveric index fingers with unknown medical history were scanned by HR-pQCT (82 μm, Scanco XtremeCT) and μCT (18μm, Scanco μCT 80). Also radiographs were taken. A modified SPECTRA (Study grouP for xtrEme Computed Tomography in Rheumatoid Arthritis) algorithm was used by one reader to assess all cortical breaks and erosions. A cortical break was defined as an interruption of cortical bone on two consecutive slices on two orthogonal planes for HR-pQCT, and similarly, but on eight consecutive slices, on μCT. An erosion was defined as a definite cortical break, with irregular shape, and loss of underlying trabecular bone on two consecutive slices on two orthogonal planes on HR-pQCT, and eight consecutive slices on two orthogonal planes on μCT. CRs were independently scored for erosions by two rheumatologists. Descriptives, paired samples t-test, Wilcoxon signed-rank test, kappa and intraclass correlation coefficients (ICC) were calculated ($p<.05$ was considered significant).

Results: Figure 1 shows a picture obtained from the three imaging modalities used in this study. In total, twelve joints (mean± SD age 82.6±9.1 years) were imaged by HR-pQCT and μCT. In total, 79 cortical breaks were detected on HR-pQCT (6.5±2.5 per joint) and 163 on μCT (13.5±4.9 per joint). A total of 11 erosions were detected on HR-pQCT (0.9±0.9 per joint) and 47 on μCT (3.9±3.0 per joint). The ICC for number of cortical breaks was. 122 ($p=.150$), and for number of erosions -.090 ($p=.699$). On CR, the total number of erosions scored was four by Reader 1, and two by Reader 2. Kappa was fair ($\kappa=.250$).

Conclusion: Three times more erosions were detected on HR-pQCT than CR and four times more erosions were detected on μCT than HR-pQCT. Furthermore, twice the number of cortical breaks was scored on μCT compared to HR-pQCT. These results indicate that further research, such as histological and longitudinal studies, will be necessary to reveal the prevalence, incidence and significance of cortical breaks and erosions as found by HR-pQCT and μCT of hand joints.

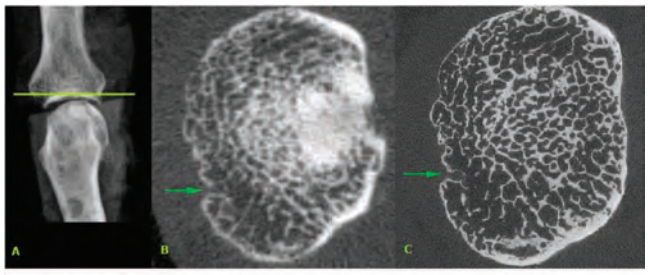

Figure 1. CR of MCP joint in posterior-anterior position (A), arrows indicating a cortical break on dorsal side on transversal slice of HR-pQCT (B) and corresponding µCT (C) image.

Disclosure: A. Scharmga, None; **A. van Tubergen**, None; **J. van den Bergh**, None; **J. de Jong**, None; **M. Peters**, None; **B. van Rietbergen**, Scanco Medical AG, 9; **P. Geusens**, None.

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Cuantification of Hand Bone Mineral Density By Radiogrammetry and Dual X-Ray Absorptiometry in Early Arthritis Patients. Irene Llorente Cubas*[1], Leticia Merino-Meléndez*[1], Saturnino González Ortega[2], Ana M. Ortiz-García[1], Eugenio Escolano[2], Esther Vicente-Rabaneda[1], Rosario Garcia-Vicuña[3], Isidoro González-Alvaro[3] and Santos Castañeda-Sanz[4].

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Background/Purpose: The evaluation of cortical bone mineral density (BMD) on metacarpal bones by digital radiogrammetry (DXR) has been proven to be a simple, reliable and predictive method to evaluate the severity of the disease in patients with early arthritis (EA). However, DXR is a tool that is not usually available in our environment. By contrast, dual X-ray absorptiometry (DXA) is a more familiar and accessible technique in our clinical practice.

Purpose: The aim of this study was to compare the association between BMD measurements of the hand by DXR and DXA with parameters of activity and severity at two years of follow-up in a cohort of patients with EA.

Methods: A prospective longitudinal study of patients with EA was done. DXR was performed in a total of 111 patients (87.4% women) and DXA was implemented in a total of 378 (82% women). Mean age at disease onset was 57 years [46 – 65 (p25 - p50)] in the DXR group and 54 years [44 – 66 (p25 - p50)] in the DXA group. Anthropometric and clinical data were collected per protocol during 2 years of follow-up. Forty-two percent of patients in the DXR group presented citrullinated peptide antibodies and 41.3% in the DXA group. In both, the 57% fulfilled RA 2010 criteria at the start of follow up (43% undifferentiated arthropathy). Each patient underwent a digital radiograph of both hands (GE © DX Definium 8000) at 0, 3, 12 and 24 months, determining BMD of each hand and the mean of both measures by DXR (Sectra, Linköping, Sweden). Also, DXA of global hand and metacarpophalangeal joints (MCPs) of the nondominant hand were performed and analyzed using a Hologic QDR -4500 Elite© densitometer at 0, 6, 12 and 24 months. In addition, a variable that measures the intensity of cumulative treatment received during the 2 year follow-up was specifically generated as a marker of severity. Statistical analysis was performed using the statistical package STATA 12.

Results: Our data show a good correlation between values of BMD obtained by DXR and DXA in the different locations studied (global hand and MCPs: $r=0.830$ and 0.718, respectively, $p=0.0001$), both at the baseline visit and along the two years of monitoring. In the bivariate analysis, a negative association is observed between baseline BMD values measured by DXA and disease activity by DAS28 at 2 yrs, which disappears when adjusting for other variables (age and sex). However, we found an inverse relationship between the intensity of cumulative treatment at two years and baseline BMD measured by DXA, both at global hand ($r = -2.51$, $p=0.041$, $n=220$) and MCPs ($r = -3.45$, $p=0.007$, $n=221$). The DXR association was not significant, probably due to the small sample size of the population ($n=32$).

Conclusion: BMD of the global hand and MCPs of the nondominant hand assessed by DXA predicts disease severity and the intensity of cumulative treatment at two years of follow-up in a population of patients with EA. By contrast, the predictive value of the hand DXR was not significant. Further studies with a larger population are needed to obtain more consistent conclusions.

*Irene Llorente and Leticia Merino have contributed equally to this work.

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2145

Diagnostic Performance and Disease Activity Assessment By FDG-PET in Large-Vessel Vasculitis: A Systematic Literature Review and Meta-Analysis. Michael Soussan[1], Patrick Nicolas[2], Catherine Schramm[3], Sandrine Katsahian[3], Veronique Eder[4], Olivier Fain[5] and Arsene Mekinian[6]. [1]Nuclear Medicine, Avicennes Hospital, Bobigny, France, [2]Avicenne Hospital, 93000, France, [3]Centre de Recherche des Cordeliers, Equipe 22, Paris 5, Paris 6, Paris, France, paris, France, [4]Avicenne Hospital, Bobigny, France, [5]Hôpital Saint Antoine, DHU i2B, Service de Médecine Interne, paris, France, [6]Internal Medicine, DHUi2B Saint Antoine Hospital, paris, France.

Background/Purpose: FDG-PET is increasingly used in the work up of large-vessel vasculitis (LVV)**.** The purpose of this study is to perform a systematic review and meta-analysis of the value of FDG-PET for the diagnosis of LVV.

Methods: MEDLINE and Cochrane Library were searched for articles that evaluated the value of FDG-PET in LVV, from 01/2000 to 12/2013. Inclusion criteria were: American College of Rheumatology (ACR) criteria for the diagnosis of Giant Cell Arteritis (GCA) or Takayasu Arteritis (TA), definition of PET positivity threshold, and > 4 cases included. Data were pooled to compare clinical/biological data and PET results. Sensitivity and specificity of FDG-PET for the diagnosis of LVV were calculated from each included individual study, then pooled for meta-analyses with a random effects model.

Results: Were included 21 studies with a total of 413 patients and 299 controls. Pooled sensitivity and specificity of FDG-PET for the diagnosis of LVV were 0.77 (95% CI,0.69– 0.83) and 0.95 (95% CI,0.92–0.95), respectively. When GCA subgroup was considered, sensitivity increased to 0.9 (95% CI,0.79–0.96) and specificity to 0.98 (95% CI,0.94–0.99), with a decrease in inconsistency (I-square). Pooled sensitivity and specificity of FDG-PET to assess TA disease activity were 0.87 (95% CI,0.78– 0.93) and 0.73 (95% CI,0.63– 0.81), respectively. Sub-analysis of studies using NIH criteria for disease activity assessment, showed that the specificity increased to 0.84 [0.73; 0.92], with a decrease in inconsistency. High vascular uptake ($>$ liver uptake) was the most reliable PET threshold for the diagnosis of aortitis. As a limitation, PET technology and threshold used to define the presence of vascular inflammation varied among the studies. Furthermore, no systematic comparison with conventional cross imaging was available.

Conclusion: FDG-PET has an overall valuable performance for the diagnosis of LVV, especially for GCA, and for the assessment of the activity in TA. Further studies are needed to better determine the utility of PET for management of LVV.

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Optimal Hand Position for Reliable Volumetric Joint Space Width Measurements Using High-Resolution Peripheral Quantitative Computed Tomography. Cheryl Barnabe, Sarah Manske, Britta Jorgenson and Steven K. Boyd. University of Calgary, Calgary, AB.

Background/Purpose: Joint space narrowing is an important outcome measure in rheumatoid arthritis, linked tightly to function and disability. High-resolution peripheral quantitative computed tomography (HR-pQCT) allows detection of bone margins with high precision. Based on this capability, we have devised a software script to quantify volumetric joint space width based on the method of 'fitting maximal spheres'. The reproducibility of this method may be affected by the angular positioning of the joint. Our study assesses variability of 3D volumetric joint space measurements with variations in joint flexion between 0 and 30 degrees.

Methods: The 2nd and 3rd MCP joints of six cadaver hands were imaged with HR-pQCT ($n=12$ joints). Using a positioning device, the MCPs were placed at 7 different angles of flexion (0, 5, 10, 15, 20, 25 and 30 degrees). Actual angles of acquisition were verified in the sagittal plane post-hoc. Descriptive statistics were used to calculate the mean, median, minimum, and maximum joint space widths and total volume measurements, by degree of angulation. The coefficient of variation (root-mean-square deviation), CV(RMSD), was calculated to determine the variability caused by angulation.

Results: There was little variation in positioned angle and post-hoc angle measurement up to 15 degrees of flexion (measured angle mean 2.1, 5.7, 10.7, 15.3 vs positioned angle 0, 5, 10 and 15 respectively). At greater degrees of flexion, positioning error was significant, with the post-hoc angle measurement ranging from 20.8 to 32.5 at 30 degrees. Mean, median, maximum and minimum joint space increased linearly between 5 and 30 degrees (Figure 1). The CV(RMSD) was optimized between 5 and 15 degrees of flexion (Table 1). Minimum joint space measurements were highly variable at all degrees of flexion.

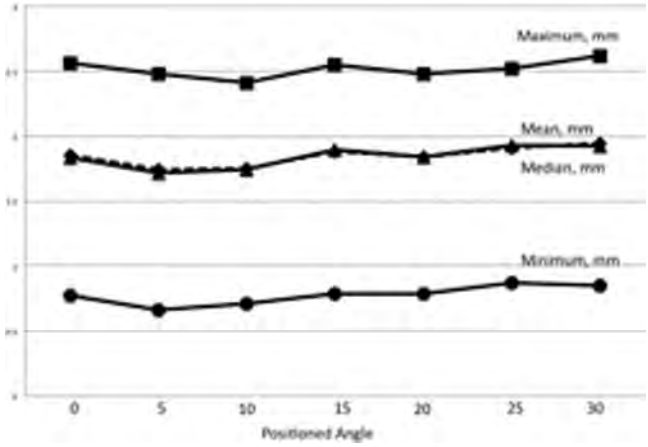

Figure 1. Plot of Obtained Measurements by Degree of Angulation.

Table 1. Coefficient of Variation (Root-Mean Square Deviation) for Joint Space Measurements by Angle of Flexion of the MCP Joints

Angles	Mean	Median	Minimum	Maximum	Volume
0-10	4.8%	5.2%	14.6%	4.0%	3.2%
0-15	5.0%	5.9%	20.2%	4.5%	3.8%
5-15	4.4%	5.5%	18.0%	4.3%	3.4%
0-20	5.4%	6.7%	22.4%	5.0%	4.2%
0-25	6.1%	7.3%	35.8%	5.3%	5.2%
0-30	6.7%	7.5%	35.9%	5.7%	5.2%

Conclusion: Our 3D volumetric measurement method of joint space width for images acquired with HR-pQCT technology is reliable for MCP flexion angles of 0 to 20 degrees. Reproducibility metrics are optimized between 5 and 15 degrees. Care should be given to remaining in this parameter for longitudinal or repeated measures studies using this technology for joint space width assessment.

Disclosure: C. Barnabe, None; **S. Manske**, None; **B. Jorgenson**, None; **S. K. Boyd**, None.

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Automatically Extracted Quantitative Biomarkers for Assessing Connective Tissue Disease Using Nailfold Capillaroscopy. Michael Berks[1], Graham Dinsdale[2], Andrea Murray[2], Tonia Moore[3], Chris Taylor[1] and Ariane Herrick[2]. [1]Centre for Imaging Sciences, University of Manchester, Institute of Population Health, Manchester, United Kingdom, [2]Centre for Musculoskeletal Research, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom, [3]Salford Royal Hospital NHS Foundation Trust, Salford, United Kingdom.

Background/Purpose: Videomicroscopy can capture high-magnification images of nailfold capillaries, allowing non-invasive assessment of microvasculature change indicative of connective tissue disease. Whilst images may be qualitatively graded visually, quantitative biomarkers are required for detailed analysis and tracking disease progression. To overcome the problems of manual measurements (time consuming, subjective), we have developed fully automated software to measure the spatial density, width and tortuosity of capillaries[1]. Our objective was to assess how well these automated biomarkers differentiate between healthy controls (HC), subjects with primary Raynaud's phenomenon (PRP), patients with systemic sclerosis (SSc), and patients with an undifferentiated connective tissue disease (UCTD).

Methods: Our software was used to analyze 577 nailfold images (85 HC; 46 PRP; 402 SSc, 44 UCTD). Analysis is performed in four stages: the software 1) detects all vessels, measuring the orientation and width for each 2) locates the apex of each capillary and determines which belong to the distal row 3) extracts measures that characterize the size and shape of each distal capillary 4) combines these measurements to compute a single value of density, width and tortuosity for each image. For each biomarker one-way ANOVA, followed by Tukey's range test, was used to check for differences between the means of each subject group.

Results: ANOVA tests showed significant group-wise differences for all biomarkers (all $p < 0.001$). The group mean and 95% confidence interval of each biomarker are shown in Table 1, along with the pairs of groups that showed significantly different means under Tukey's test.

Table 1: Group-wise means and confidence intervals for each automatically measured capillaroscopy biomarker. Pairs of groups with significantly different means are listed in the rightmost column.

	Subject group means (95% confidence intervals)				Groups with significantly different means under Tukey's test
Biomarker type	HC (n=85)	PRP (n=46)	SSc (n=402)	UD (n=44)	
Capillary density (per mm)	12.6 (12, 13.3)	13.4 (12.5, 14.2)	9.02 (8.74, 9.3)	11.5 (10.6, 12.3)	HC v SSc (p< 0.001); PR v SSc (p< 0.001); UD v SSc (<0.001 PR v UD (p=0.011);
Mean apical width (mm)	10.5 (11, 10.1)	11.2 (11.9, 10.5)	14.3 (14.7, 14)	12.5 (13.4, 11.7)	HC v SSc (p<0.001); PR v SSc (p<0.001); UD v SSc (p =0.0017); HC v UD (p<0.001);
Mean capillary tortuosity (no units)	4.42 (4.38, 4.46)	4.33 (4.27, 4.39)	4.55 (4.53, 4.57)	4.41 (4.35, 4.47)	HC v SSc (p<0.001); PR vSSc (p<0.001); UD v SSc (p<0.001);

Conclusion: Images from patients with SSc had significantly lower capillary density and higher width and tortuosity than all other subject groups (including UCTD), matching findings from earlier studies using manual or semi-automated analysis[2]. No significant differences were observed between healthy controls and PRP, again, matching clinical expectations. Images from patients with UCTD generated biomarkers that lay in between healthy controls/PRP and SSc. These highly promising results suggest our software produces clinically useful biomarkers of connective tissue disease. Automatic analysis is potentially a major step forward, enabling large datasets of images to be assessed quickly and efficiently, and obviating the inherent subjectivity of manual assessment.

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2. Murray, Non-invasive Imaging Techniques in the Assessment of Schleroderma Spectrum Disorders, Arthritis Care and Research, 61(8), 2009.

Disclosure: M. Berks, None; **G. Dinsdale**, None; **A. Murray**, None; **T. Moore**, None; **C. Taylor**, None; **A. Herrick**, Actelion Pharmaceuticals US, 5, Pfizer Inc, 5.

2148

Dual Energy CT Scanning: Variable Sensitivity for Gout in Non-Tophaceous and Tophaceous Disease and in Individual Erosions. Tracie Kurano[1], Uma Thakur[1], Gaurav Thawait[1], Elliot Fishman[1], Mara McAdams-DeMarco[1], Janet W. Maynard[1], Matthew Fuld[2], John A. Carrino[3] and Alan N. Baer[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Siemens Medical Solutions USA, Inc., Baltimore, MD, [3]Hospital for Special Surgery, New York, NY.

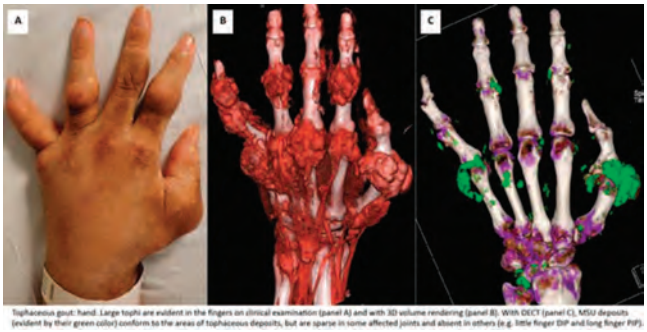
Background/Purpose: Dual energy computed tomography (DECT) is emerging as a diagnostic tool for gout, but its sensitivity has not been established. We assessed the sensitivity of DECT for the detection of monosodium urate (MSU) deposits in both non-tophaceous and tophaceous gout.

Methods: Twenty-one patients with gout (per Wallace criteria) agreed to participate in this study funded by Siemens Medical Solutions and underwent DECT of their hands, wrists, elbows, knees, ankles, and feet. Eleven had non-tophaceous gout confirmed by the demonstration of MSU crystals in a joint aspirate. Ten patients had tophaceous gout (crystal-proven in 7), defined by the presence of palpable tophi (n=5), the presence of erosions of the first metatarsal head on radiograph (n=3), or gross MSU deposits in a surgical specimen (n=2). Scans were performed using a SOMATOM Definition Flash Dual Source CT scanner (Siemens Healthcare) with simultaneous acquisition of images at 80 and 140 kV. Post-processing was performed using Siemens software with predefined standard parameters; the threshold ratio parameter was set at 1.36. Sensitivity was defined as the percentage of gout patients who were correctly identified by DECT.

Results: The 21 patients included 17 men, with a mean age of 61 years (range, 43 – 83). Among the 11 patients with non-tophaceous gout, MSU deposits were only detected by DECT in the joint proven to be affected by aspiration in 2 (sensitivity=18%). However, the MSU deposits were evident in ≥1 joint area evaluated by DECT in 7 patients (overall sensitivity=64%), ≥1 clinically affected joint in 4 (57%) patients and ≥1 clinically unaffected joint in 6 (86%) patients. The number of MSU deposits correlated with the

maximum recorded serum urate (r^2=0.502, p=.022) but not with gout duration. Among the 10 patients with tophaceous gout, 9 had MSU deposits evident by DECT (sensitivity=90%). In an index case of tophaceous gout (Figure), we were surprised to see tophi evident by clinical examination (panel A), 3D volume rendering (Panel B), and bony erosion (panel C-little finger DIP), that were negative by DECT (panel C-lack of green deposits). This prompted us to evaluate the sensitivity of DECT for individual gouty erosions (defined by the presence of an overhanging edge in a joint not affected by severe joint space loss). In 3 patients with extensive foot involvement, MSU deposits were detected by DECT within or immediately adjacent to 13/26 (50%) erosions.

Conclusion: DECT detected MSU deposits in non-tophaceous gout, with 65% sensitivity on scanning of both upper and lower extremity joints and only 18% on scanning of the crystal-proven joint. The sensitivity was 90% in tophaceous gout, but remained inadequate when evaluated on the basis of individual erosive lesions. The detection of MSU deposits by DECT may relate to their density and this could potentially be improved with an adjustment of algorithm input parameters.



Tophaceous gout: hand. Large tophi are evident in the fingers on clinical examination (panel A) and with 3D volume rendering (panel B). With DECT (panel C), MSU deposits (evident by their green color) conform to the areas of tophaceous deposits, but are sparse in some affected joints and absent in others (e.g. little finger DIP and long finger PIP).

Disclosure: T. Kurano, None; **U. Thakur**, None; **G. Thawait**, None; **E. Fishman**, None; **M. McAdams-DeMarco**, None; **J. W. Maynard**, None; **M. Fuld**, Siemens Health, 3; **J. A. Carrino**, Siemens, 2; **A. N. Baer**, None.

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Relationship Between the Magnitude of Bone Formation in the Anterior Vertebral Corners, As Assessed through 18F-Fluoride Uptake, and Lumbar Spine Bone Mineral Density in Patients with Ankylosing Spondylitis.

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Background/Purpose: 18F-fluoride uptake represents active osteoblastic bone synthesis. We investigated the relationship between the magnitude of bone formation in anterior vertebral corners, as assessed through 18F-fluoride uptake on positron emission tomography (PET) and lumbar spine bone mineral density (BMD) in patients with ankylosing spondylitis (AS).

Methods: Twelve male patients with AS who was biologics-naïve underwent whole body 18F-fluodride PET and dual energy X-ray absorptiometry (DXA). The maximum standardized uptake value (SUVmax) of 18F-fluoride uptake at the anterior vertebral corner (L1 upper to L4 lower) was analyzed to determine the degree of active bone formation; the BMD of the lumbar spine in the AP (L1 to L4) and lateral (L2 to L4) projections was measured using DXA (Figure 1). At each lumbar vertebra level, the relationship between the sum of the SUVmax in the upper and lower anterior vertebral corners and the BMD of the corresponding lumbar vertebral body was assessed using a generalized estimating equation (GEE) to adjust within-patient correlation.

Results: A total of 48 lumbar vertebrae were analyzed. In correlation analyses, the sum of SUVmax in upper and lower anterior vertebral corners positively correlated with in both the lumbar AP (Spearman correlation coefficient=0.273, p=0.039) and lateral spine BMD (Spearman correlation coefficient=0.206, p=0.04). In the GEE model, the sum of SUVmax in upper and lower anterior vertebral corners was significantly associated with the both lumbar AP (β=0.012, p=0.002) and lateral spine BMD (β=0.013, p<0.001). This association remained significant after adjusting for disease duration and the presence of syndesmophytes.

Conclusion: Active bone formation in the anterior vertebral corners, as assessed through 18F-fluoride uptake on PET was associated with increased BMD of corresponding vertebral bodies in patients with AS. This finding suggests that the precise measurement of lumbar spine BMD using DXA can be hampered by active bone formation in AS.

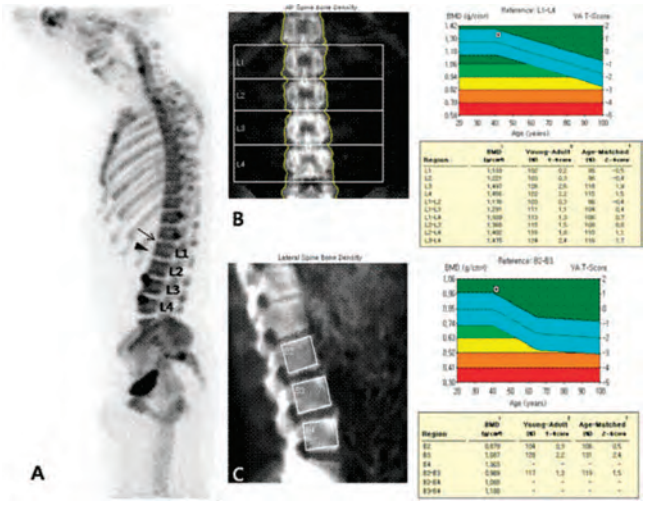

Figure 1. 18F-fluoride positron emission tomography (PET) scan (A) and dual energy X-ray absorptiometry evaluating bone mineral density in the AP (B) and lateral (C) projection of a 42-year-old man with ankylosing spondylitis. On PET scan, the maximum standardized uptake value of 18F-fluoride uptake in the upper (arrow in A) and lower (arrowhead in A) parts of the anterior vertebral corner was measured from L1 to L4.

Disclosure: S. G. Lee, None; **E. K. Park**, None; **G. T. Kim**, None; **S. Y. Lee**, None; **J. W. Lee**, None.

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The Craniocervical Junction in Ankylosing Spondylitis: A Computed Tomography Based Study.

Gleb Slobodin[1], Arsen Shpigelman[1], Hanna Dawood[1], Doron Rimar[2], Simona Croitoru[1], Nina Boulman[2], Michael Rozenbaum[2], Lisa Kaly[1], Itzhak Rosner[1] and Majed Odeh[1]. [1]Bnai Zion Medical Center, Haifa, Israel, [2]Bnai Zion Medical Center / Technion Faculty of Medicine, Haifa, Israel.

Background/Purpose: Available studies of craniocervical junction (CCJ) involvement in ankylosing spondylitis (AS) are based on conventional radiography, which has limited ability in the definition of many elements of the CCJ. The goal of the present study was to describe the spectrum of computed tomography (CT) findings in the CCJ in a cohort of patients with AS.

Methods: CT scans of the cervical spine of 11 patients with AS were reviewed and imaging findings related to the CCJ assessed. The standard anatomic intervals describing the CCJ were measured and compared to accepted normal standards. Findings, representing pathology were described, categorized by localization and relation to joints or ligaments of the CCJ.

Results: All patients were males with median age of 48 years and median disease duration of 20 years. The calculated median modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) for the cervical spine was 8.5, ranging from 0 to 27. Disease-related changes in one or more elements of the CCJ were detected in all patients. Patients with AS had a strong tendency to the narrowing of the atlanto-occipital joints and atlanto-dental interval, with some patients demonstrating complete fusion of these articulations. Atlanto-occipital joints were involved in 8 patients, while 3 patients had disease of the atlanto-dental articulation. Enthesopathy of the CCJ was observed in 7 patients. Significant changes of CCJ were observed also in patients with very low mSASS.

Conclusion: The CCJ is frequently involved in AS patients with advanced disease and may be independent on the mSASSS. Both articulations and ligaments of CCJ may be affected in AS patients.

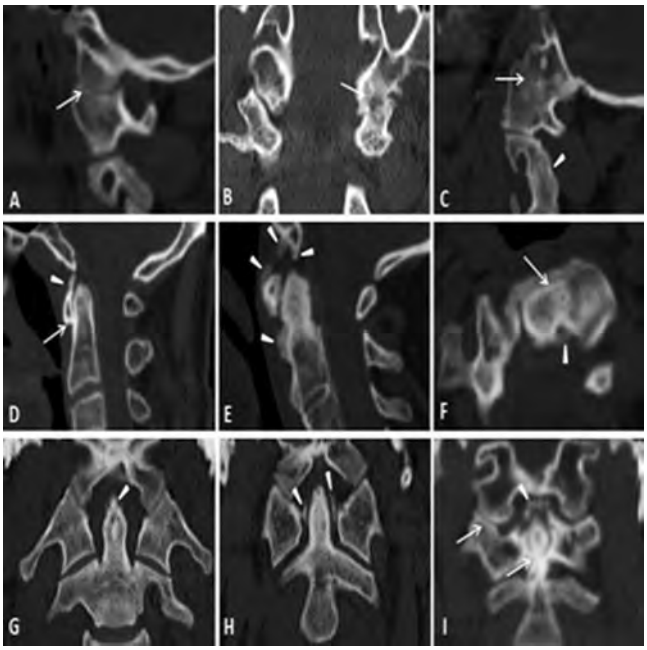

Fig 1. Ankylosing spondylitis of craniocervical junction.

1. Mild atlanto-occipital joint space narrowing (arrow), saggital view
2. Significant narrowing of the left atlanto-occipital joint with erosion (arrow) and osseous sclerosis; right atlanto-occipital joint looks normal
3. Total ankylosis of the atlanto-occipital joint (arrow) with secondary osteopenia. Fusion of C2 and C3 parts is also seen (arrowhead)
4. Anterior atlanto-dental interval shortening (arrow) and ossification of the anterior atlanto-occipital ligament (arrowhead)
5. Severe osseous sclerosis of the dens and C1 arch. Rude proliferative enthesopathy of the anterior longitudinal ligament and ossification of the occipital attachment of the apical ligament (arrowheads)
6. Ankylosis of the atlanto-axial joint (arrow), axial view; ossification of the left part of the transverse ligament (arrowhead)
7. Apical ligament enthesopathy (arrowhead), coronal view
8. Transverse ligament ossification (arrowheads), coronal view
9. Alar ligament ossification (arrowhead), coronal view. Narrowing of the right atlanto-occipital and atlanto-axial joints are seen (arrows)

Disclosure: G. Slobodin, None; **A. Shpigelman**, None; **H. Dawood**, None; **D. Rimar**, None; **S. Croitoru**, None; **N. Boulman**, None; **M. Rozenbaum**, None; **L. Kaly**, None; **I. Rosner**, None; **M. Odeh**, None.

ACR/ARHP Poster Session C
Infections, Infection-related Biomarkers and Impact of Biologic Therapies
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

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Abatacept Related Infections: No Association with Gammaglobulin Reduction. Valquiria Dinis, Vilma S. T. Viana, Elaine P. Leon, Clovis A Silva, Carla G.S. Saad, Julio C. B. Moraes, Eloisa Bonfá and Ana C.M. Ribeiro. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: A recent study reported that abatacept (ABA) reduces rheumatoid arthritis (RA) related autoantibodies and gammaglobulins levels. However, the possible association of these findings with infections was not assessed. The aim of this study was, therefore, to evaluate immunoglobulins levels and infections in RA patients treated with ABA compared to anti-TNF agents, biological agents without any effect in immunoglobulin production.

Methods: Eighteen RA (ACR criteria) patients undergoing abatacept (ABA-RA) were selected and compared to 18 patients treated with anti-TNF (aTNF-RA) agents. Total and specific (IgG, IgM and IgA) gammaglobulin levels were assessed before and 6 months after biological treatment. Before entry, all patients were vaccinated for influenza/ pneumococcus and they were evaluated for tuberculosis. A systematic clinical screening protocol for infection was performed before each dose and at least monthly and when indicated virus, bacteria and fungus etiologies were investigated. Central nervous system, upper/lower respiratory tracts, cutaneous, gastrointestinal and genitourinary infections were classified in mild/moderate or severe (hospitalization). Demographic, clinical and laboratory data were also collected. Exclusion criteria were: low gammaglobulin level at baseline (<0.7) and previous abatacept or rituximab treatments.

Results: At baseline, median current age (55 vs. vs. 53 years, $p=0.96$), frequencies of female gender (78 vs. 78%, $p=1.0$), DAS28 (5.73 vs. 5.67, $p=0.34$), ESR (21.5 vs. 22mm/1sth, $p=0.84$.), CRP (15.5 vs. 12mg/dL, $p=0.37$) and lymphocyte counts (2,200 vs. 1,800/mm^3, $p=0.42$) were comparable in ABA-RA and aTNF-RA groups. Medians of gammaglobulin (1.4 vs. 1.35 g/dL, $p=0.71$), IgG (1167.5 vs. 1078.5 mg/dL, $p=0.84$), IgM (107.2 vs. 112.6 mg/dL, $p=0.38$) and IgA (333 vs. 322 mg/dL, $p=0.74$) were also alike in both groups. At 6 months, median percentage variations of gammaglobulin levels from baseline were distinct with a significant reduction for ABA-RA compared to aTNF-RA: total (−20 vs. +4%, $p<0.001$), IgG (−11 vs. +8 %, $p<0.001$), IgM (−15 vs+26%, $p<0.001$), IgA (−13 vs. +2%, $p=0.002$). Frequency of infections was similar in both groups (61 vs. 67%, $p=0.73$) with only one severe infection in ABA–RA and no death. Respiratory tract was the most frequent site in both groups (33 vs. 50%, $p=0.34$) followed by skin (29%) in aTNF-RA and urinary tract (28%) in ABA-RA. Of note, antibiotics or antifungal therapy were indicated less often for ABA than aTNF (44 vs. 85%, $p= 0.028$). ABA patients with and without infections had comparable levels at baseline and 6 months of IgG ($p=0.28$ and $p=0.08$) and IgM ($p=0.78$ and $p=0.83$).

Conclusion: The present work provides novel data demonstrating that infection in ABA-RA patients is not associated with the observed reduction in gammaglobulins induced by this co-stimulatory agent. Infections seems, however, to be less severe with this agent than with aTNF agents.

Disclosure: V. Dinis, None; **V. S. T. Viana**, None; **E. P. Leon**, None; **C. A. Silva**, FAPESP 2009/51897-5, CNPq 302724/2011-7 and Federico Foundation, 2; **C. G. S. Saad**, None; **J. C. B. Moraes**, None; **E. Bonfá**, None; **A. C. M. Ribeiro**, None.

2152

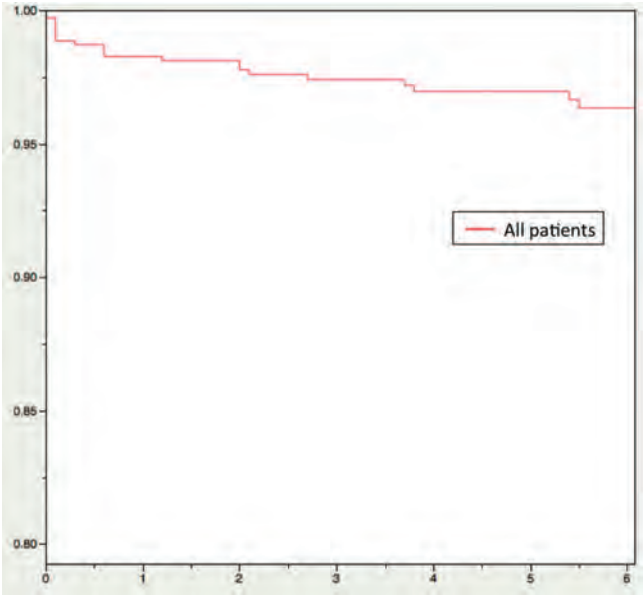
Frequency of Postoperative Deep Infection in Patients with Rheumatoid Arthritis. Masayuki Azukizawa and Hiromu Ito. Kyoto University, Kyoto, Japan.

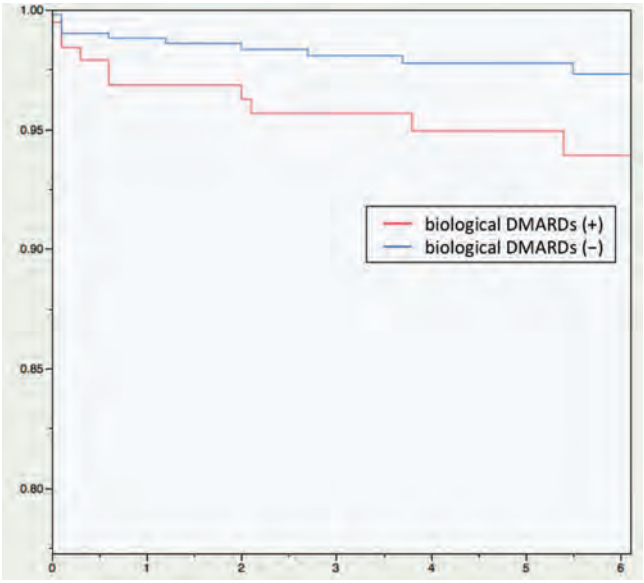
Background/Purpose: Rheumatoid arthritis (RA) is known to be associated with an increased risk of serious infection. It has been discussed about the risk of the surgical site infection in the RA patients. However there are few reports about the postoperative deep infection in those patients. The aims of the study were to investigate the postoperative deep infection in RA patients treated in our institution and to clarify the frequency of the postoperative deep infection.

Methods: We reviewed a total of 696 orthopaedic surgeries for RA patients underwent between January 2004 and December 2013. We investigated the cases of deep infection after surgery, the sites of infection, and surgical techniques. We researched the postoperative deep infection free rate for the RA patients.

Results: The mean follow-up period was 4.7 years. 27.3% of all RA patients used Biological DMARDs. Twenty-five cases (3.6%) were suffered from the postoperative deep infection. Infection sites (surgical procedures) are 5 hips (bipolar hemiarthroplasty and total hip arthroplasty), 6 knees (total knee arthroplasty), 6 elbows (total elbow arthroplasty), one shoulder (total shoulder arthroplasty), 2 hands (metacarpophalangeal joint arthroplasty and proximal interpharangeal joint arthroplasty), one ankle (ankle arthrodesis) and 4 spines (Magerl technique, cervical posterior fixation, transforaminal lumbar interbody fusion). According to the Kaplan-Meier survival analysis, the cumulative deep infection free rate of all patients in 3 months, in 2 years and in 5 years was 98.7%, 97.8%, and 97.0%, respectively. That of the patient treated with biologic DMARDs was significantly lower than that of without biologic DMARDs. (Log-rank Test: $p = 0.0068$)

Conclusion: These results suggest that the postoperative deep infection is likely to occur within the first 3 months after surgery in the RA patients, and that the use of biological DMARDs is a risk factor for postoperative deep infection. We should pay more attention to the postoperative deep infection within 3 months of a procedure.





Disclosure: M. Azukizawa, None; **H. Ito**, None.

2153

Clinical Characteristics and Outcomes in Synovial Fluid Culture-Negative Septic Arthritis. Sarah B. Lieber, Ziv Paz and Robert H. Shmerling. Beth Israel Deaconess Medical Center, Boston, MA.

Background/Purpose: Delays in diagnosis and treatment of septic arthritis may be associated with significant morbidity. While many patients with suspected or proven septic arthritis are treated surgically, aggressive surgical intervention may be unnecessary when the diagnosis is not secure. This includes patients with negative synovial fluid cultures, representing up to 40% of patients with clinically suspected septic arthritis. We aim to characterize patients with presumed septic arthritis who were treated surgically, but who had negative synovial fluid cultures. This may help predict which patients could be treated safely without surgical intervention.

Methods: We conducted a restrospective cohort study of patients 18 years and older admitted to a single tertiary care center from January 2010 to May 2014 with a presumptive diagnosis of septic arthritis leading to operative management. Patients were stratified into culture-positive and culture-negative groups based on synovial fluid testing. Length of hospital stay (LOHS) was designated as the primary outcome. Secondary outcomes included 60-day readmission rate and establishment of an alternative diagnosis to explain the index admission within a year of discharge.

Results: Of 208 patients with clinically suspected septic arthritis who underwent surgical intervention, 90 (43.3%) were synovial fluid culture-positive. The culture-positive and culture-negative groups were similar with respect to gender (approximately half were female), age (mean of 63 years), frequency of prosthetic joint involvement (about 60%), and frequency of knee involvement (about 60%). For the culture-positive group, mean LOHS and 60-day readmission rate were 11.4 days and 26.7%, respectively; in the culture-negative group, mean LOHS and 60-day readmission rate were 9.9 days and 36.4%, respectively ($p = 0.09$ for LOHS; $p = 0.18$ for 60-day readmission rate). An alternative diagnosis to explain the index admission was made in 3 (3.3%) cases in the culture-positive group and in 10 (9.3%) cases in the culture-negative group ($p = 0.16$). Among patients with native joints, mean LOHS, 60-day readmission rate, and frequency of alternative diagnosis did not differ significantly between the culture-negative groups.

Conclusion: In our medical center, the majority of patients with clinically suspected septic arthritis managed operatively had negative synovial fluid cultures at the time of diagnosis. While those with positive and negative synovial fluid cultures had similar baseline features, we observed a trend toward shorter length of hospital stay and more alternative diagnoses in the culture-negative group. The inclusion of additional presenting features (currently underway), including the presence of comorbidities, prior use of antibiotics, systemic signs of infection, and synovial fluid characteristics, may identify a subset of patients with suspected septic arthritis who may be managed safely without surgery.

Disclosure: S. B. Lieber, None; **Z. Paz**, None; **R. H. Shmerling**, None.

2154

Risk for Developing Adult T-Cell Leukemia in Patients with Human T Lymphotropic Virus Type-I Carrier Receiving Immunosuppressive Therapy. Kensuke Nakanishi[1], Rita Mcgill[2] and Mitsuyo Kinjo[1]. [1]Okinawa Chubu Hospital, Uruma City Okinawa, Japan, [2]AGH Nephrology Associates, Pittsburgh, PA.

Background/Purpose: Human T-lymphotropic virus type-I (HTLV-1) is a retrovirus associated with Adult T-cell leukemia (ATL) that is commonly seen in endemic areas. Several case reports suggest that immunosuppressants, including biologic agents, may be related to development of ATL in HTLV-I carriers. The purpose of this study was to evaluate the risk for developing ATL in HTLV-1 carriers who received immunosuppressive therapy for rheumatic or inflammatory bowel diseases, or cancer.

Methods: Medical records were reviewed at Okinawa Chubu Hospital to locate all HTLV-1+ patients from 2010 to 2013. After excluding 8 renal transplant patients, there were 727 HTLV-1+ patients. Incidence and progression of ATL were compared between subjects with and without immunosuppressive therapy. Data were collected on clinical features, medications and peripheral smears.

Results: We identified 83 HTLV-1+ subjects who received immunosuppressive therapy, including prednisolone, disease-modifying anti-rheumatic drugs (DMARDs) or biologic agents: 52/83 (64%) had rheumatic diseases. 90 subjects (12%) had non-ATL malignancy including solid cancer and hematological malignancy with or without chemotherapy (Table). Median observation period was 26 months (2–50) in patients receiving immunosuppressive therapy, and 26 months (2–50) in controls. Incidence of ATL did not differ between subjects on and off immunosuppressive therapy (P=0.6). In 7 patients on biological agents (5 etanercept, 1 infliximab and 1 abatacept), no ATL occurred during the observation period (median 22 months, range 9–50).

Conclusion: No cases of ATL developed among HTLV-1+ patients on immunosuppressants over an observation period of 26 months. Immunosuppressive therapy may not promote development of ATL in HTLV-1+ patients with rheumatic diseases.

	Immunosuppressive therapy (n=83)	P	Non-ATL malignancy (n=90)	P	Control (N=542)
Age + SD years	64 + 14	0.002	73 + 12	0.12	70 + 17
Female sex	51/83 (61%)	1	39/90 (43%)	0.0005	336/542 (62%)
Hemodialysis	5/83 (6.0%)	0.32	2/90 (2.2%)	0.072	56/539 (10%)
Diabetes mellitus	18/83 (22%)	0.35	13/90 (14%)	0.55	92/539 (17%)
Liver cirrhosis	0/83 (0%)	0.24	5/90 (5.6%)	0.18	14/540 (2.6%)
Strongyloides infection	1/50 (2.0%)	0.22	6/43 (14%)	0.25	21/257 (8.2%)
Prevalent ATL	2/83 (2.4%)	0.070	4/90 (4.4%)	0.29	44/542 (8.1%)
Incident ATL	0/83 (0%)	0.60	0/86 (0%)	0.60	7/498 (1.4%)
Progress ATL	0/2 (0%)	1	1/4 (25%)	0.16	1/44 (2.3%)

Disclosure: K. Nakanishi, None; **R. Mcgill**, None; **M. Kinjo**, None.

2155

Chikungunya Fever in Patients Under Biologics. Lauren Brunier[1], Katleen Polomat[2], Christophe Deligny[2], Veronique Dehlinger[3], Patrick Numeric[3], Georges Jean-Baptiste[3], Serge Arfi[2] and Michel De Bandt[4]. [1]Unit of rheumatology, CHUM, 97200 Fort de France, France, [2]unit of internal medicine, Fort de France, France, [3]Unit of rheumatology, CHUM, Fort de France, France, [4]Hopital Zobda-Quitman. CHU La Meynard., Fort de FRance, France.

Background/Purpose: Chick is an epidemic disease due to an arthropod-borne virus (*Alphavirus*) transmitted by *Aedes* mosquitoes. CHIKV causes an acute illness with a febrile phase, followed by a period of severe polyarthritis that can persist for long time. There is no specific treatment, the best prevention is mosquito control and avoidance of bites. Martinique (French West Indies) is currently experiencing an outbreak of CHIK with 40 000 reported cases (June 1st). No data is available regarding the prognosis of Chikungunya in patients under biologics. We have observed 22 patients with Chik infection while on biotherapy and DMARDS for rheumatic diseases, between January and May 2014.

Methods: Physicians prescribing biologics were asked to declare patients under biologics experiencing Chik. For each patient we collected diseases characteristics and course, current treatment (steroids, immunosuppressant, biologics. . .), changes in the treatment during infection, and outcome. 22 patients were included, all with a diagnosis confirmed by PCR (20/22) or serology.

Results: Among these patients were 19 women and 3 men, 3 Caucasians and 19 Afro-Caribbean's. There were 5 spondyloarthritis (3 associated with Crohn), 1 psoriatic rheumatism, 2 systemic lupus, 1 antisynthetase syndrome and 13 RA. 17 had methotrexate (mean dose 21.6 mg), 3 Plaquenil, 2 Imuran, 1 cellcept, 2 cyclophosphamide. 11/22 were under steroids (mean dose of 8.6 mg / d). All experienced fever (mean duration 1.7 day), skin rash (15/22, mean duration 1.3 d), and acute disabling polyarthritis (mean pain VAS 8.4, mean SJC 9.6, mean TJC 6.8) for a mean 11.5 days duration. Nine had back pain and 4 tenosynovitis. None of them showed any organ failure, one single episode of transient thrombopenia was noted. None of them was hospitalized for Chik. Analgesic treatment (alone 4/22), associated with NSAIDs (17/22) or prednisone (1/22) and rest were sufficient to overcome the crisis. All but one patient maintained their previous treatment (DMARDS, Biologic, steroids. . .) without specific complication. All patients were able to differentiate between Chik related complains and those related to their preexisting condition. Mean clinical disease scores before and after Chik (DAS, BASDAI, SLEDAI) remained unchanged.

Conclusion: This is the first report of the occurrence of Chik in patients under biologics. Patients under biologics are at increased risk for serious infections either viral or bacterial, but no data has been published regarding Chik. This study was not conducted to discover all cases of Chik among patients under biologic. Chik does not seem to be deleterious in patients under biologics who do not exhibit more severe or prolonged disease than common forms. Chik does not seem to aggravate pre-existing disease. It does not seem necessary to modify the basic treatment of rheumatism in the announcement of a Chik as the clinical pictures observed in these patients are quite benign. NSAIDs and best rest are mostly effective. Chik does not seem harmful in patients receiving biological and this issue should be given to travellers.

Disclosure: L. Brunier, None; **K. Polomat**, None; **C. Deligny**, None; **V. Dehlinger**, None; **P. Numeric**, None; **G. Jean-Baptiste**, None; **S. Arfi**, None; **M. De Bandt**, None.

2156

Persistent Arthralgia Following Chikungunya Fever. Anna Kristina Gutierrez-Rubio and Ester Penserga. Philippine General Hospital, Manila, Philippines.

Background/Purpose: Chikungunya fever is a reemerging viral infection in the Philippines and neighboring countries. Persistent arthralgia following Chikungunya infection has been observed during previous epidemics, but few studies have discussed this aspect of the disease.

Methods: Adult patients who were diagnosed to have Chikungunya fever were included in this study. Patients were assessed at the time of acute infection and were followed-up at least 12 months after the acute disease occurred. Patients were asked questions regarding musculoskeletal symptoms and were examined on follow-up.

Results: Fourteen patients were included in this study. Ten (71%) were female, and the mean age was 31.67± 14.23 years. Mean duration of follow-up was 13.9 months. None of these patients reported a history of preexisting arthralgia. Eight (57%) had arthritis lasting at least 6 weeks following the acute infection, with a mean duration of 13.6 ± 5.72 weeks. Seven of the 14 patients (50%) had persistent arthralgia, with five (71%) having intermittent arthralgia, and 2 (29%) having continuous arthralgia. Two patients had recurrent chronic arthritis. One patient had a traumatic fracture of the third right metatarsal on the third month of illness. Arthralgia was symmetric and polyarticular in all cases, with the ankles being the most commonly affecred joint area (71%).

Conclusion: Chikungunya can result in severe, debilitating arthralgia that affects daily activities, and may persist for as long as a year. Further studies are needed to determine the prevalence of persistent arthralgia, identify risk factors, and establish the real burden of disease.

Disclosure: A. K. Gutierrez-Rubio, None; **E. Penserga**, None.

2157

Tuberculosis Reactivation Risk in Patients Treated with Tumor Necrosis Factor Alpha Inhibitors: A Turkish Experience with Higher Mortality and Different Background Diseases. Bunyamin Kisacik[1], Omer Pamuk[2], Ahmet Mesut Onat[3], B. Erer[4], Gulen Hatemi[5], Yesim Ozguler[6], Yavuz Pehlivan[7], Levent Kilic[8], Ihsan Ertenli[8], Meryem Can[9], Haner Direskeneli[9], Gökhan Keser[10], Fahrettin Oksel[10], Ediz Dalkilic[11], Sedat Yilmaz[12], Salih Pay[13], Ayse Balkarli[14], Veli Cobankara[15], Gozde Yildirim Cetin[16], Mehmet Sayarlioglu[17], Ayse Cefle[18], Ayten Yazici[18], Ali Berkant Avci[19], Ender Terzioglu[20], Suleyman Ozbek[21], Servet Akar[22] and Ahmet Gül[4]. [1]Gaziantep University, School of Medicine, Gaziantep, Turkey, [2]Trakya Üniversitesi, edirne, Turkey, [3]Gaziantep University School of Medicine, Gaziantep, Turkey, [4]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [5]Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, [6]University of Istanbul, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, [7]Uludag University, School of Medicine, Bursa, Turkey, [8]Hacettepe Üniversity, Ankara, Turkey, [9]Marmara Üniversitesi, Ystanbul, Turkey, [10]Ege Üniversitesi, Ýzmir, Turkey, [11]Uludað Üniversitesi, Bursa, Turkey, [12]GATA, ANKARA, Turkey, [13]GATA, Ankara, Turkey, [14]Pamukkale Üniversitesi, Denizli, Turkey, [15]Denizli Üniversitesi, Denizli, Turkey, [16]Sutcu Imam University, School of Medicine, Department of Internal Medicine, Division of Rheumatology, Kahramanmaras, Turkey, [17]Ondokuz Mayis University School of Medicine, Samsun, Turkey, [18]Kocaeli University, Kocaeli, Turkey, [19]Antalya University, School of Medicine, Department of Internal Medicine, Division of Rheumatology, Antalya, Turkey, [20]Akdeniz University, Antalya, Turkey, [21]Cukurova Üniversitesi, Adana, Turkey, [22]Katip Çelebi Üniversitesi, Ýzmir, Turkey.

Background/Purpose: Tumor necrosis factor alpha inhibitors (anti-TNF) are a breakthrough for the treatment of inflammatory rheumatic diseases and tuberculosis (TB) is the prevailing and vitally important infectious complication. This retrospective data analyzes the risk of tuberculosis reactivation and demographic features of patients treated with anti-TNF drugs in Turkey, where TB is still a widespread endemic disease.

Methods: The study is held by **Tu**rkish Mul**t**i-centered **I**nvestigators **P**latform in Rheumatology (TULIP).10.434 patients treated with anti-TNF drugs, 73 (0.69%) patients were diagnosed with TB (M/F: 39/34), 7.695 patients with accurate and complete data of laboratory and clinical history were enrolled as control group.

Results: Among 73 patients diagnosed with TB, 38 patients were diagnosed with ankylosing spondylitis, 25 with rheumatoid arthritis, 4 with psoriatic arthritis, 5 with Behcet's syndrome, and a patient with vasculitis. TB frequency in patients using infliximab (1.27%) was significantly higher than patients using etanercept (0.3%) and adalimumab (0.57%) ($p < 0.001$ and 0.008, respectively). Six patients out of 73 TB cases (8.2%) died under follow-up. Thirty-four cases (46.6%) out of 73 TB patients had pulmonary tuberculosis. In the logistic regression model, type of anti-TNF (infliximab) (OR: 3.4, 95%CI: 1.88–6.1, $p=0.001$) and insufficient prophylaxis (<9 months) (OR: 3.15, 95%CI: 1.43– 6.9, $p=0.004$) were independent predictors of TB development among anti-TNF treated patients.

Conclusion: Our results suggest that TB is an important complication of anti-TNF therapies in Turkey, where the disease is still endemic. TB chemoprophylaxis less than nine months and the use infliximab therapy were independent risk factors for TB development.

Disclosure: B. Kisacik, None; **O. Pamuk**, None; **A. M. Onat**, None; **B. Erer**, None; **G. Hatemi**, None; **Y. Ozguler**, None; **Y. Pehlivan**, None; **L. Kilic**, None; **I. Ertenli**, None; **M. Can**, None; **H. Direskeneli**, None; **G. Keser**, None; **F. Oksel**, None; **E. Dalkilic**, None; **S. Yilmaz**, None; **S. Pay**, None; **A. Balkarli**, None; **V. Cobankara**, None; **G. Yildirim Cetin**, None; **M. Sayarlioglu**, None; **A. Cefle**, None; **A. Yazici**, None; **A. B. Avci**, None; **E. Terzioglu**, None; **S. Ozbek**, None; **S. Akar**, None; **A. Gül**, None.

2158

Severe Neutropenia in Patients with Rheumatic Diseases at a Tertiary Care Hospital in South Korea. Chang-Nam Son[1], Ji-Min Kim[1], Sang-Hyon Kim[1], Soo-Kyung Cho[2], Yoon-Kyoung Sung[2], Tae-Hwan Kim[2], Jae-Bum Jun[2], Sang-Cheol Bae[3] and Dae-Hyun Yoo[2]. [1]Keimyung University School of Medicine, Daegu, South Korea, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea.

Background/Purpose: Neutropenia is relatively common in patients with rheumatic diseases. Neutropenia is characterized by an absolute neutrophil count (ANC) of less than 1,500/μL. It is associated with diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) or it may be caused by the side effects of medications or accompanying infection. The risk of neutropenia-related infection increases with an ANC near 1,000/μL (moderate neutropenia) and rises dramatically as ANC falls below 500/μL (severe). Some patients with neutropenia require hospitalization in an isolation ward and are administered recombinant human granulocyte colony stimulating factor (rhG-CSF) or antibiotics to treat neutropenic fever. Our aim was to investigate the possible causes and clinical characteristics of severe neutropenia in Korean patients with rheumatic diseases.

Methods: The study participants (n=64) were enrolled from September 2003 to August 2013 from a population of patients with rheumatic diseases who were admitted to a tertiary care center. These subjects had severe neutropenia and received rhG-CSF at least once during hospitalization. We retrospectively examined data of the subjects including age, gender, initial diagnosis, concomitant medications, serial complete blood count, and bone marrow biopsy.

Results: The most frequent initial diagnoses were SLE (n = 35; 55%), RA (n = 13; 20%), and inflammatory myositis (n = 6; 9%). The possible causes of severe neutropenia were therapeutic drugs (n = 31; 48%), association with lupus (n = 17; 27%), infection (n= 12; 19%), and hemophagocytic syndrome (n = 4; 6%). During hospitalization, nine deaths occurred (14%, 9/64). Mortality was higher in patients with sepsis than in patients with neutropenia associated with other causes (Table). Pneumonia was the most common cause of sepsis in patients with neutropenia (58.3%, 7/12). The frequency of sepsis and death was higher in the long-term recovery group (≥ 28 days) than in the other groups (< 7 days and 7–27 days).

Possible cause	Drug Toxicity (n = 31)	Disease activity of SLE (n = 17)	Sepsis (n = 12)	*P*-value
Age (yrs, Mean±SD)	41.7 ± 17.4	28.6 ± 8.8	50.1±15.3	0.001
Women, no. (%)	24 (77.4)	15 (88.2)	10 (83.3)	0.647
Disease duration (yrs, Mean±SD)	7.7 ± 8.8	4.2 ± 3.7	9.7 ± 12.9	0.552
Any immunosuppressive drug	23 (74.2)	9 (52.9)	9 (75.0)	0.238
Leucocytes (Mean±SD, /μL)	1258.1 ± 653.6	1117.6 ± 304.6	1058.3 ± 550.1	0.581
Hemoglobin (Mean±SD, g/dL)	9.1 ± 2.2	9.6 ± 1.5	8.6 ± 1.5	0.401
Platelets (Mean±SD, X 10^3/μL)	118.9 ± 82.5	132.9 ± 77.4	115.9 ± 70.7	0.688
Neutrophils (Mean±SD, /μL)	262.9 ± 462.7	376.2 ± 313.0	366.3 ± 471.1	0.301
Pancytopenia, no. (%)	22 (71.0)	11 (64.7)	9 (75.0)	0.828
Recovery time of neutropenia	5.3 ± 5.3	8.1 ± 13.9	19.3 ± 37.1	0.515
Death, no. (%)	4 (10.5)	1 (5.6)	4 (50)	0.033

Conclusion: In patients with rheumatic diseases, drug toxicity was the most common cause of severe neutropenia. Among the causes of neutropenia, sepsis is of greatest concern; therefore, physicians need to pay attention to the early detection of infection.

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2159

Human T-Lymphotropic Virus Type 1 Biomarkers in Patients with Rheumatoid Arthritis. Akihiko Okayama[1], Masako Iwanaga[2], Yasuko Sagara[3], Toshihiko Hidaka[4], Kunihiko Umekita[1], Kazumi Nakano[5], Toshiki Watanabe[5], Yoshihisa Yamano[6], Yoshiro Horai[7], Hideki Nakamura[8] and Atsushi Kawakami[8]. [1]University of Miyazaki, Miyazaki, Japan, [2]The Jikei University of School of Medicine, Tokyo, Japan, [3]Japanese Red Cross Kyushu Block Blood Center, Fukuoka, Japan, [4]Zenjinkai Shimin-No-Mori Hospital, Miyazaki, Japan, [5]Graduate School of Frontier Sciences, The University of Tokyo, Tokyo, Japan, [6]St. Marianna University School of Medicine, Kanagawa, Japan, [7]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [8]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Background/Purpose: Human T-lymphotropic virus type 1 (HTLV-1) is the causative agent of adult T-cell leukemia (ATL). It has been debated recently whether or not immunosuppressive agents for HTLV-1 carriers with a variety of inflammatory/immunological conditions can increase the risk of developing ATL, which is of important in terms of the pros and cons of anti-rheumatic treatment for HTLV-1 positive patients with RA. Through HTLV-1 biomarkers, whether the immunosuppressive medicines or biologics for HTLV-1 positive rheumatoid arthritis (RA) patients may affect adversely to the risk of ATL was speculated.

Methods: HTLV-1 antibody was screened for 808 patients with RA diagnosed in two regions in Japan, Nagasaki and Miyazaki prefectures, endemic areas of HTLV-1 infection. Among those, HTLV-1 positive RA patients treated with anti-rheumatic medicines including biologics (anti-TNFs, tocilizumab, and abatacept) were selected to be subjects for this study and evaluated about the levels in blood samples of HTLV-1 proviral load (PVL) by real-time PCR, antibody titer by particle agglutination assay, and soluble IL-2 receptor (sIL-2R) by enzyme immunoassay. The levels of the biomarkers were compared with those of age and sex matched asymptomatic HTLV-1 carriers (ACs) using Wilcoxon rank sum test.

Results: The HTLV-1 seroprevalence in patients with RA was 8.2% (66/808). Blood samples were available in 33 among the 66 HTLV-1 positive RA patients. The median HTLV-1 PVL of the 33 patients was 0.52 copies per 100 peripheral blood mononuclear cells (PBMCs), which was lower than that of age and sex matched 99 ACs (1.0 copy per 100 PBMCs) (p=0.08). The median antibody titer of the 33 patients was $2^{8.9}$, which was lower than that of age and sex matched 99 ACs ($2^{9.7}$) (p=0.03). The level of sIL-2R was not different between 2 groups (p=0.10).

Conclusion: The HTLV-1 seroprevalence in patients with RA in the endemic area in Japan was higher than we expected. Both HTLV-1 PVL and antibody titer in HTLV-1 positive RA patients treated with anti-rheumatic medicines showed lower values comparing with those in ACs. These findings, when viewed in light of a previous report that high HTLV-1 PVL is considered as the risk factor for developing ATL, suggest that treatment by anti-rheumatic medicines including biologics may not necessarily increase the risk for ATL development in HTLV-1 positive patients with RA. Further long-term follow-up study can determine the safety of anti-rheumatic treatment in HTLV-1 positive patients with RA.

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2160 WITHDRAWN

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Interest of Systematic Lyme Serology in Context of Recent Onset Arthritis. Dewi Guellec[1], Valérie Narbonne[1], Divi Cornec[2], Thierry Marhadour[3], Maxime Dougados[4], Jean-Pierre Daures[5], Sandrine Jousse-Joulin[1], Valerie Devauchelle[6] and Alain Saraux[7]. [1]CHU Brest, Brest, France, [2]Brest Occidentale University, Brest, France, [3]CHU de la Cavale Blanche, Brest, France, [4]INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France., Paris, France, [5]INSERM, Montpellier, France, [6]Brest university medical school, EA 2216, Lab Ex, INSERM, IGO,UBO and CHU de la Cavale Blanche,, Brest, France, [7]CHU Brest and EA 2216, UBO, Brest, France.

Background/Purpose: Lyme arthritis is a late manifestation of a tick-transmitted spirotechal infection, mainly caused by *Borrelia burdorgferi*. Lyme arthritis typically presents as a mono- or oligoarticular arthritis primarily affecting the large joints. However, various presentations including polyarthritis and polyarthralgias are possible (*Puius et al.*). It results that spirotechal infection is sometimes evoked by the rheumatologist in context of recent-onset arthritis, even in non-endemic regions.

The aim of this study was to determine the utility of systematic Lyme serology in a French cohort of patients with recent-onset arthritis, by determining the seroprevalence of Lyme antibodies according to the region of inclusion, the prevalence of Lyme arthritis and the diagnostic accuracy of serological testing.

Methods: The present study is an ancillary project from a French prospective and multicentric cohort study monitoring clinical, biologic, and radiographic data for patients with inflammatory arthritis lasting 6 weeks to 6 months (*Combe et al.*). Patients were included during the period of December 2002 to March 2005 in 14 regional centers. Antibodies against *Borrelia* at baseline were detected in 2006, using an IgG and IgM Immune Assay, from blood samples collected at baseline, without Western blot confirmation. This procedure was conducted independantly of the physician's strategy to detect

a possible spirotechal infection. The final diagnosis was recorded after two years of follow-up. Global and regional seroprevalence of Lyme antibodies were determined. The proportion of patients with a final diagnosis of Lyme arthritis and the diagnostic accuracy of Lyme serology in context of recent-onset arthritis were recorded. The clinical and biological characteristics of patients according to the results of Lyme serology were analyzed in detail.

Results: Among the 814 patients included in the ESPOIR cohort, 810 were tested for the presence of *Borrelia* antibodies (99.5%). Of these patients, 7,6% had positive serology (62/810) and 2,6% had equivocal results (21/810). Average positivity of Lyme serology varied significantly by region of inclusion (2.4% - 14.9%), the highest value being found in an endemic area. After two-years of follow-up, no cases of definite Lyme arthritis were identified, although it was the main diagnostic hypothesis at baseline for 2 patients. Thus, diagnostic accuracy of lyme serology in context of recent-onset arthritis seems very low despite a relatively high proportion of patients having an IgG positive serology. Additional analyzes revealed an association between the positivity of the immune assay and renal failure (p: 0.0005).

Conclusion: In France, where there is an heterogeneous risk of borrelia infection by region, the diagnosis of polyarthritis linked to borrelia was never considered by the clinician. In contrast, serology, even IgM with positivity, is not rare. This study does not support the routine use of Lyme serology and highlight the risk of difficulty to interpret the results in a context of recent-onset arthritis and confirm the results previously obtained by other authors, in France and in the Netherlands (*van Burgel et al*, *Muller et al*.).

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2162

Immunological Abnormalities in Adult Patients with Parvovirus B19 Infection: A study of 23 Cases. Edouard Pertuiset, Farid Kemiche, Mehdi Yahia and Isabelle Cerf-Payrastre. Centre Hospitalier René Dubos, Pontoise, France.

Background/Purpose: In adults, parvovirus B19 infection can induce joint symptoms and cutaneous manifestations which are known to be transient most of the time. It has been associated with the production of various antibodies directed against various autoantigens. In this study we report the immunological results in 23 adult patients with parvovirus B19 infection.

Methods: Between 1996 and 2014, 23 adult patients (mean age 35.4 ± 8.9 years; 19 women and 4 men) have been diagnosed with parvovirus B19 infection in our rheumatology department. All patients have been examined by a rheumatologist with a mean delay of 2 weeks after the onset of symptoms and had biological tests including autoimmunity in most cases. In all cases anti-parvovirus B19 IgM were present at a level greater than anti-parvovirus B19 IgG. All patients had arthralgias, 52% of them had mild arthritis and/or tenosynovitis. Cutaneous manifestations were observed in 65% of patients. In all patients, acute joint symptoms resolved in two months, except in one who developed a HLA-B27 negative spondyloarthropathy. Autoimmune tests included search for antinuclear antibodies (ANA) in all patients, rheumatoid factor (RF) in 19 patients, anti-keratine or anti-CCP antibodies in 11 patients, anticardiolipin antibodies (ACL) in 11 patients. Furthermore, C3 and C4 were evaluated in 19 patients and cryoglobulinemia was search in 13 cases.

Results: ESR was 29 ± 17 mm/1sth. Two patients had thrombocytopenia. Five patients (22%) had ANA at moderate levels (160 in 4 cases, 320 in one case) without any specificity (no case of anti-ENA or anti-DNA antibodies). RF was positive in 2 patients (10%) and no patient had anti-CCP antibodies. ACL antibodies were detected in seven cases (63%). In three cases diagnosed before 2009, they were IgG anti-ACL at low levels (20–28 U). Since 2009, our laboratory tests both IgG and IgM ACL antibodies: 4 patients had IgM ACL at levels ranged from 22 to 51 U (normal 0–19), without IgG ACL antibody. A decrease of C3 was observed in one patient (5%) and a decrease of C4 was present in 5 patients (26%). Search for cryoglobulinemia was positive in 6 cases (46%). In five cases it was a type III cryoglobulinemia at low level and in one case these level was too small for identification.

Conclusion: Some immunological abnormalities including ANA, RF, ACL antibodies, low C4 level and cryoglobulinamia are quite often encountered in parvovirus B19 infection in adults with rheumatologic symptoms. The presence of IgM ACL antibodies and mixed type III cryoglobulinemia appears frequent in our most recent experience. These abnormalities are asymptomatic and transient, but can lead to misdiagnosis and highlight some relationships between innate immunity activation and autoimmune response.

Disclosure: E. Pertuiset, None; **F. Kemiche**, None; **M. Yahia**, None; **I. Cerf-Payrastre**, None.

2163

Genetic Variants of *TNFAIP3* in Patients with HCV Related Lymphoma Are Associated with the Presence of Rheumatoid Factor (RF). Gaetane Nocturne[1], Saida Boudaoud[2], Caroline Besson[3], Frederic Davi[4], Danielle Canioni[5], Patrice Cacoub[6], Olivier Hermine[7] and Xavier Mariette[8]. [1]Paris sud university, Le Kremlin Bicetre, France, [2]INSERM U1012, Le Kremlin Bicêtre, France, [3]Paris Sud University, Le Kremlin Bicêtre, France, [4]Department of Pathology, Hôpital de la Pitié Salepetrière, Paris, France, [5]Service d'anatomo-pathologie, Hôpital Necker,, Paris, France, [6]Groupe Hospitalier Pitié Salpétrière, Service de Médecine Interne, DHU i2B, Paris, France, [7]Service d'hématologie, Centre de référence des mastocytoses, Hôpital Necker Enfants malades, Université Paris V, IFR Necker,, Paris, France, [8]Université Paris-Sud, Le Kremlin Bicêtre, France.

Background/Purpose: HCV chronic infection is associated with an increased risk of non-Hodgkin lymphoma (NHL) occurrence. HCV-associated NHL share homologies with primary Sjögren Syndrome (pSS)-associated NHL, and especially an association with chronic antigenic stimulation. *TNFAIP3* encodes the A20 protein that plays a key role in controlling NF-kB activation. We have previously demonstrated that genetic impairment of A20 plays a key role in lymphomagenesis in the context of pSS. The aim of this study was to assess the role of variants of *TNFAIP3* in patients with HCV related NHL.

Methods: Sixty-one cases with available germline DNA were drawn from the 116 patients included in the LymphoC study. Total exon sequencing of *TNFAIP3* was performed in a discovery set of 31 cases. Then 30 additional cases and 53 controls (HCV patients without NHL) were used for extension (ie genotyping of the rs2230926 and the TT>A dinucleotide). All our cases and controls were European. Case-only associations were tested with Fischer's exact test. Differences in lymphoma histologic type and immunological status were assessed using Fisher's exact test.

Results: Among the 61 cases, histology subsets were 23 diffuse large B cells lymphomas (DLBCL), 17 marginal zone lymphomas (MZL), 6 splenic marginal zone lymphoma (SMZL), 5 mantle cells lymphomas, 8 follicular lymphomas, 1 chronic lymphoid leukemia and 1 chronic EBV-related lymphoproliferation. RF and mixed cryoglobulinémie (MC) were present in 30/61 (49.2%) and 25/43 (58.1%) of the patients respectively. Among the 53 controls, RF and MC were present in 31/53 (58.5%) and 28/53 (52.8%) of the patients respectively. We found the rs2230926G variant in 6/61 (9.8%) patients with NHL and in 7/53 (13.2%) patients without NHL meaning that there was no association between this SNP and HCV-associated NHL (OR=0.72 [95%CI 0.22– 2.28] p=0.77). We did not find any association between the variant and the marginal zone subtype of the lymphoma. However, we found that, among NHL patients, the rs2230926G allele was associated with the positivity of RF (6/30 (20%) in RF+ patients compared to 0/31 (0%) in RF- patients, OR=16.7 [95%CI 0.9 – 311.5], p=0.01). We did not find any association between the rs2230926 variant and the presence of MC patients probably due to the amount missing data and the variability of the technic of detection.

Conclusion: Again in situation of chronic stimulation of RF+ B cells, a coding mutation of *TNFAIP3* leading to a small functional defect of A20 function and of control of activation of NK-kB, is enough for favoring the lymphomatous escape of these autoimmune B cells.

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ACR/ARHP Poster Session C
Innate Immunity and Rheumatic Disease: Mediators, Cells and Receptors
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

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Self-Phospholipids Regulate Inflammation Via Activation of CD1d-Restricted T-cells and Induction of 'anti-inflammatory' Myeloid-Derived Suppressor Cells (MDSC). Ram Raj Singh[1], Cynthia Tran[1], Priti Prasad[1], Jing Wang[2], Dirk Zajonc[2] and Ramesh Halder[1]. [1]UCLA, Los Angeles, CA, [2]La Jolla Institute of Allergy and Immunology, La Jolla, CA.

Background/Purpose: Self-lipids play an increasingly appreciated role in immunity and inflammation. Lipid antigens are presented by CD1d and CD1a-d molecules in mouse and human, respectively, to T cells. Glycolipids (GL) such as βGluCer, and phospholipids (PL) such as phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanoloamine (PE), phosphatidylinositol (PI), and phosphatidylserine (PS), have been eluted and identified by mass spectrometry as natural human CD1d ligands, and PC and PE have been eluted from murine CD1d. Crystallography shows that complexes of CD1d bound to PL can exist. Diverse subsets of T cells that recognize self lipids have been reported, including invariant natural killer T cells (iNKT). Extensive work shows protective or pathogenic roles of GL αGalCer-reactive iNKT cells in a wide range of diseases. However, the functions of T cells that recognize abundant self PL are not known. Here, we identified and characterized self PL-reactive T cells (PLT), investigated their in vivo functions, and elucidated the cellular and molecular participants in PL mediated immune homeostasis.

Methods: CD1d tetramers were loaded with 8 PL or GL antigens, and cells analyzed by flow cytometry. Chemical binding of PL to CD1d was assessed by isoelectric focusing/gel shift analysis. CD1d-PA complex was crystallized by sitting drop vapour diffusion. Autoimmune hepatitis that is mediated by iNKT cells was induced by injecting concanavalin A (ConA), and assessed by serum ALT, morphology, and histology.

Results: CD1d tetramers loaded with PL, namely PA, PC, PE, PI, PS and BMP (bismonoacylglycerophosphate), identify 0.4–4% T cells in the lymphoid organs of wild-type and iNKT–deficient $J\alpha18^{-/-}$ mice but not in $CD1d^{-/-}$ mice. PLT cells don't recognize GL-loaded tetramers and don't respond to αGalCer, suggesting that PLT cells are distinct from iNKT cells. PLT cells expand, express CD69, and produce cytokines upon in vivo priming. Chemical binding and crystal structure show that PA binds CD1d in the absence of lipid transfer proteins, and is centrally located in the CD1d-binding groove opening for TCR recognition. Although PA bound slightly weaker to CD1d than a self GL, it competed with αGalCer to load onto CD1d. All PL tested profoundly inhibited the proliferation and cytokine production by iNKT cells. Such PL-induced inhibition of iNKT cells was abrogated upon depletion of granulocytes by gemcitabine that preferentially depleted the MDSC subset called monocyte-MDSC (mMDSC). Furthermore, PL induced IL-10 producing mMDSC that inhibited iNKT cell proliferation in an IL-10-dependent manner. Finally, treatment with a PL ameliorated ConA–hepatitis, reduced pro-inflammatory cytokines, granulocyte accumulation and $IFN\gamma^+$ mMDSC, but promoted $IL\text{-}10^+$ mMDSC that upon adoptive transfer reduced the incidence/severity of ConA–hepatitis.

Conclusion: We identified a new role for self PL that activate a distinct subset of CD1d-restricted T cells that inhibit iNKT cells by competitive inhibition and via induction of $IFN\gamma^-IL10^+$ mMDSC that ameliorate autoimmune hepatitis. These results have important implications for conditions with altered lipid metabolism and inflammation such as atherosclerosis and autoimmune disease.

Disclosure: R. R. Singh, None; **C. Tran**, None; **P. Prasad**, None; **J. Wang**, None; **D. Zajonc**, None; **R. Halder**, None.

2165

Myeloid-Derived Suppressor Cells in Rheumatoid Arthritis: Friend or Foe? Fanlei Hu[1], Chunqing Guo[2], Xiang-Yang Wang[2] and Zhanguo Li[1]. [1]Peking University People's Hospital, Beijing, China, [2]Virginia Commonwealth University School of Medicine, Richmond, VA.

Background/Purpose: Although myeloid-derived suppressor cells (MDSCs) have been linked to T-cell tolerance, their role in rheumatoid arthritis (RA) remains exclusive. Here, we investigated the potential association of MDSCs with the disease pathogenesis using specimen collected from RA patients and the experimental model of collagen-induced arthritis (CIA).

Methods: The frequency of MDSCs in the peripheral blood and the synovial fluids of RA patients (n = 59), osteoarthritis patients (OA, n = 15), and healthy individuals (n = 20) was detected by flow cytometry. And their association with the disease severity and the levels of IL-17A was analyzed. Similarly, MDSCs in the peripheral blood, lymphoid tissues, inflamed paws, or synovial fluid and their association with disease severity, tissue inflammation, and the levels of pathogenic T-helper (Th) 17 cells was examined in CIA mice. The MDSCs in arthritic mice were also characterized for their phenotype, inflammation status, T-cell suppressive activity, and their capacity of pro-Th17 cell differentiation. The contribution of MDSCs to Th17 response was examined by co-culturing MDSCs with naïve $CD4^+$ T cells under Th17-polarizing conditions both in RA patients and mice. Moreover, their pathogenic role in RA was further revealed by antibody depletion of MDSCs in CIA mice.

Results: MDSCs expanded significantly in RA patients and in CIA mice, which were correlated positively with disease severity and an inflammatory Th17 response. While displaying T-cell suppressive activity, MDSCs from arthritic mice produced high levels of inflammatory cytokines (e.g., IL-1β, and TNF-a). Both human MDSCs ($CD11b^+CD33^+$) and mouse MDSCs ($CD11b^+Gr\text{-}1^+$) efficiently promoted Th17 cell polarization *ex vivo*. Elimination of MDSCs in CIA mice markedly ameliorated disease symptoms concomitant with reduced levels of Th17 cells.

Conclusion: Our studies revealed the unrecognized pathogenic role of MDSCs in RA with the capacity of driving Th17 cell differentiation. This cell population might be served as novel therapeutic target for RA.

Disclosure: F. Hu, None; **C. Guo**, None; **X. Y. Wang**, None; **Z. Li**, None.

2166

Bim Suppresses the Development of Glomerulonephritis By Inhibiting M2 Polarization. Fu-Nien Tsai Northwestern University, Chicago, IL.

Background/Purpose: Only recently have monocytes and macrophages been accepted as critical players in the pathogenesis of SLE. However.very little is known regarding the molecular rheostats that control the actions of monocytes and macrophages and their state of polarization. Previous studies have shown that loss of Bim, a pro-apoptotic protein, in all cells leads to SLE-like disease and early mortality. We have shown that reduction of Bim alters macrophage function independent of its role in apoptosis. Thus, we hypothesize that Bim is essential in monocytes and macrophages to limit the development of SLE-like disease.

Methods: We generated mice lacking Bim specifically in myeloid cells ($Cre^{LysM}Bim^{flox/flox}$) and assessed mice at 8, 16, 24, 36 and 48 weeks of age for characterization of SLE-like disease. Macrophage turnover, activation, and polarization were examined *in vivo* and *in vitro*using flow cytometric analyses and luminex based assays.

Results: $Cre^{LysM}Bim^{flox/flox}$ mice displayed splenomegaly, lymphadenopathy, heightened amounts of serum pro-inflammatory cytokines, hypergammaglobulinemia, IC deposition in the kidney, proteinuria, GN, and early mortality as compared to $Bim^{flox/flox}$ and mice lacking Bim in either lymphocyte compartments. Bim functions independently of its role in apoptosis in macrophages and monocytes, since macrophages from $Cre^{LysM}Bim^{flox/flox}$ and from $Bim^{flox/flox}$ mice had equal BrdU uptake. Moreover, MyD88 is not necessary as $Cre^{LysM}Bim^{flox/flox}MyD88^{flox/flox}$ mice also developed SLE-like disease. The protein kinase Akt was increased in macrophages from $Cre^{LysM}Bim^{flox/flox}$ mice and was co-immunoprecipatated with Bim in wild type cells. Additionally, the BH3 domain, which is essential for its apoptotic function is necessary for suppressing inflammatory response in macrophages. Mixed bone marrow chimeras were sufficient to reduce development of SLE-like disease in $Cre^{LysM}Bim^{flox/flox}$ mice, which suggests that Bim may affect macrophage development or polarization. To this end, we show that Bim is necessary to prevent the skewing of macrophages towards M2, pro-fibrotic phenotype.

Conclusion: The expression of Bim in monocytes and macrophages is sufficient to inhibit SLE-like pathogenesis. These data suggest that Bim acts through its BH3 domain to reduce the intensity of inflammation and polarization status in macrophages through suppression the activity of Akt. These studies are crucial for understanding the development and the persistence of SLE, as well as for translational studies leading to the development of new targets for SLE.

Disclosure: F. N. Tsai, None;

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Snapin Is Critical for Cathepsin D Activation and the Normal Lysosomal Function. Bo Shi, Qi Quan Huang, Robert Birkett, Renee E. Koessler, Andrea Dorfleutner, Christian Stehlik and Richard M. Pope. Northwestern University Feinberg school of Medicine, Chicago, IL.

Background/Purpose: Our recent data indicates that Snapin, a SNAP associated protein, is critical for maintaining healthy autophagy and monocytes to macrophage (MFs) differentiation which requires functional autophagy. Snapin and autophagosomes are increased in MFs from the joints of patients with rheumatoid arthritis. Reduction of Snapin hindered the maturation of autophagosomes, resulting in autolysosome accumulation and delayed bacterial clearance in macrophages. Failure to digest the sequestered cargos in

these vacuoles might have resulted from deficient capacity of lysosomal hydrolysis. Here, we examined cathepsin D activity, a major hydrolase in lysosomes, in macrophages following the forced reduction of Snapin.

Methods: The reduction of Snapin in primary human MFs was performed using siRNA, while in the J774A murine MF cell line it was reduced by infection with a lentiviral vector expressing Snapin shRNA. Cell fractions enriched with lysosomes were isolated using a density gradient separation method. The protein levels of non-active pro-form and active cathepsin D were detected by Western blot analysis. The active cathepsin D in cells was also detected by staining with bodipy-pepstatin A which binds to catalytic portion of cathepsin D. Autophagosomes were identified by the accumulation of LC3 punctae. Acidification of autophagosomes was assessed by transfection of tandem fluorescent LC3 plasmid expressing a tandem red (not pH dependent) and green (quenched at low pH) fluorescence-tagged LC3. **Results:** Following the reduction of Snapin, bodipy-pepstatin A staining was greatly reduced in lysosomes in primary human MFs, suggesting a reduction of active cathepsin D. The forced reduction of Snapin in MFs resulted in 30% reduction in the active form of cathepsin D, identified by immunoblot analysis, in whole cell lysates, compared to control MFs, while the pro-form of cathepsin D was slightly increased. Cathepsin D extracted from lysosome enriched fractions from Snapin reduced J774A MF cells showed a 40% reduction in the active form, but no reduction of the pro-form, indicating the cathepsin D activation was disturbed, rather than the delivery of hydrolases to lysosomes. Interestingly, cathepsin B activation was unchanged in both whole cell lysates and in lysosome enriched fractions. Cathepsin D is activated in a low pH environment. Disrupting the acidification process in lysosomes or in autophagosomes will reduce cathepsin D activation. The forced reduction of Snapin in HEK293 cells increased green LC3 punctae, indicative of an increased pH in the autophagosomes/autolysosomes.

Conclusion: Snapin in macrophages is necessary for cathepsin D activation in lysosomes and autophagosomes, preventing the maturation of autolysosomes, by limiting the degradation of cargo within the autophagosomes. Snapin may contribute to the pathogenesis of rheumatoid arthritis by maintaining healthy autophagy and monocyte to MF differentiation.

Disclosure: B. Shi, None; **Q. Q. Huang**, None; **R. Birkett**, None; **R. E. Koessler**, None; **A. Dorfleutner**, None; **C. Stehlik**, None; **R. M. Pope**, None.

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Extramedullary Myelopoiesis Drives Persistent Toll-like Receptor-Mediated Inflammation. Lehn K. Weaver[1] and Edward M. Behrens[2]. [1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]Childrens Hospital of Philadelphia, Philadelphia, PA.

Background/Purpose: Many rheumatic diseases are driven by chronic, repeated activation of Toll-like receptors (TLR) causing the initiation and perpetuation of disease. However, TLR-activated innate immune cells undergo the well-known immunoregulatory phenomenon of TLR tolerance, whereby the initial activation of TLRs results in impaired proinflammatory responses to subsequent TLR stimuli. Therefore, it is unclear how TLR-driven inflammation persists *in vivo*. Our well-characterized model of repeated TLR9-driven inflammation demonstrates that repeated activation of TLR9 results in a feed-forward, interleukin (IL)-12-mediated inflammatory response culminating in systemic immunopathology rather than tolerance. Using this model, we dissect the cellular mechanisms utilized to bypass TLR9 tolerance *in vivo*.

Methods: *In vitro* mixed TLR9 sufficient and deficient cell cultures were stimulated with CpG1826, a TLR9 agonist, to demonstrate that IL-12 is a readout of cell-intrinsic TLR9 activation. Yet40 IL-12-reporter mice were treated with 4 doses of CpG1826 before tissue leukocytes were isolated and analyzed by flow cytometry to identify the IL-12-producing cells. Bone marrow, peripheral blood, and tissue leukocytes from CpG-treated mice were stained for myeloid progentor cell markers to determine if myelopoiesis is altered during TLR9-mediated systemic inflammation.

Results: We demonstrate that inflammatory monocyte-derived dendritic cells increase in frequency and total numbers during TLR9-mediated systemic inflammation, and are the key IL-12-producing cell in this model. To determine the origin of these inflammatory tissue-invading cells, we tested peripheral blood and bone marrow of CpG-treated mice to enumerate the number of inflammatory monocytes and myeloid progenitor cells. To our surprise, the total number of peripheral blood inflammatory monocytes and bone marrow myeloid precursors was unchanged during TLR9-induced systemic inflammation. In contrast, extramedullary myeloid precursors were markedly increased in peripherally inflamed tissues of CpG-treated mice.

Conclusion: Our data highlight an important mechanism whereby persistent TLR9 activation bypasses TLR tolerance *in vivo* by increasing extramedullary myelopoiesis. Increased extramedullary myelopoiesis provides a continuous source of new TLR9-responsive cells that perpetuates TLR-driven inflammation. These new insights into the mechanisms driving persistent TLR-mediated inflammation may lead to novel therapeutic targets to ameliorate TLR9-mediated rheumatic diseases by intervening to suppress TLR-driven extramedullary myelopoiesis.

Disclosure: L. K. Weaver, None; **E. M. Behrens**, None.

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Targeting ITGAM+ Cells Successfully Treats a Model of Anti-RNP-Associated Pulmonary Hypertension. Vineet Gupta[1], Yunjuan Zang[2], Karen Young[2], Jian Huang[2], Irina Fernandez[2] and Eric L. Greidinger[2]. [1]Rush University Medical Center, Chicago, IL, [2]University of Miami, Miami, FL.

Background/Purpose: Aggressive immunotherapy has shown modest effectiveness for pulmonary hypertension in anti-RNP Autoimmunity, but with high morbidity. We studied the ability of an ITGAM-targeted therapy that has been previously reported to have immunomodulatory properties to treat a model of this condition.

Methods: Following IACUC-approved protocols, study mice were adoptively transferred with splenic dendritic cells from anti-RNP-immunized syngeneic donor mice, and screened for elevations in serum Brain Naturietic Peptide (BNP) levels. Mice developing increased BNP levels received a single IV dose of the ITGAM-specific small molecule agonist Leukadherin-1 (LA-1), a chemically similar compound without ITGAM specificity (LA-C), or sterile PBS. Mice were then followed for BNP levels and/or underwent right heart catheterization to directly assess pulmonary circulation hemodynamics.

Results: The majority of splenic CD11c+ dendritic cells from anti-RNP+ donor mice express ITGAM by FACS. Treatment of these cells in vitro induces massive dendritic cell death, and prevents the development of adoptive transfer-induced lung disease. Mice receiving intact CD11c+ dendritic cells from anti-RNP donor mice develop substantial elevations in serum BNP levels, that correlate with increases in pulmonary pressures on right heart catheterization. Treatment of mice with established high serum BNP levels with LA-1 (but not controls) leads to rapid normalization of serum BNP levels and hemodynamic indices in 80% of study mice. No LA-1-induced toxicity was observed.

Conclusion: Adoptive transfer of ITGAM+ dendritic cells can induce pulmonary hypertension and ITGAM-targeted therapy can treat established pulmonary hypertension in a model of anti-RNP autoimmunity. These findings emphasize the potential importance of dendritic cells as mediators of tissue damage in anti-RNP autoimmunity, and raise the question whether the genetic associations of ITGAM with autoimmune disease risk could be mediated through effects on dendritic cells. LA-1 is a promising compound to develop for potential human trials.

Disclosure: V. Gupta, Adhaere Pharmaceuticals, 4; **Y. Zang**, None; **K. Young**, None; **J. Huang**, None; **I. Fernandez**, None; **E. L. Greidinger**, Adhaere Pharmaceuticals, 9.

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Human Tolerogenic Dendritic Cells Generated with Protein Kinase C Inhibitor Are Optimal for Regulatory T Cell Induction-a Comparative Study. Endy Adnan, Hitoshi Hasegawa, Takuya Matsumoto, Jun Ishizaki, Sachiko Onishi, Koichiro Suemori and Masaki Yasukawa. Ehime University Graduate School of Medicine, Toon, Japan.

Background/Purpose: Tolerogenic dendritic cells (tDCs) are a promising tool for autoimmune diseases, transplantation and allergy. Actually, tDCs have been tried for the therapy of rheumatoid arthritis and type 1 diabetes. To date, immunomodulatory DCs are prepared from monocytes for in vitro experiments by using various agents. Previously, we generated stable tDCs with protein kinase C inhibitor (PKCI) in human and mouse and PKCI-tDCs prevented graft-versus-host disease in a murine model (J Immunol 191: 2247, 2013). The following functional characteristics are required for clinically applicable tDCs: efficient induction of functional regulatory T cells (Treg); CCR7-dependent migration; and stability under proinflammatory conditions. In this study, to select the optimal agent for clinically applicable tDCs, we compared the clinical-grade tDCs generated with various agents.

Methods: We compared tDCs generated with the following agents; vitamin D3 (Vit D3), dexamethasone (Dexa), bisindolylmaleimide I (PKCI), PPAR gamma plus retinoic acid (PPAR+RA), rapamicin (Rapa), IL-10, and TGF-beta. tDCs were prepared by adding these agents prior to the induction of maturation using TNF-alpha, IL-1beta and PGE2. We evaluated the effects of each agent on phenotype, CCR7-dependent migration, cytokine produc-

tion, phagocytosis, stability, T-cell suppression, and induction of IL-10-producing T cells and functional Foxp3^{+} Treg cells.

Results: All tDCs except Rapa-tDCs showed an immature or semi-mature phenotype, whereas the phenotype of Rapa-tDCs resembled that of mature DCs. PKCI-tDCs, TGF-tDCs and Rapa-tDCs had moderate and high CCR7 expression, whereas tDCs generated with PPAR+RA, Vit D3, Dexa or IL-10 had very low CCR7 expression. IL-10 production by IL-10-tDCs and PKCI-tDCs was high. Immature DCs (iDCs) and PKCI-tDCs showed high production of TGF-beta. Functionally, iDCs, PKCI-tDCs, PPAR+RA-tDCs, Vit D3-tDCs and IL-10-tDCs strongly suppressed T-cell activation, whereas Dexa-tDCs, TGF-tDCs and Rapa-tDCs weakly suppressed. All tDCs showed phagocytic ability and stable tolerogenic properties under proinflammatory conditions. From these findings, PKCI-tDCs showed moderate expression of CCR7, leading to migrate toward CCR7 ligands, maintained stability, and strongly suppressed T-cell activation by generating IL-10-producing T cells and functional Foxp3^{+} Treg cells.

Conclusion: PKCI-tDCs appear to be optimal for clinically applicable tDCs. We expect that PKCI-tDCs are useful for tolerance-inducing therapies.

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Polymorphisms in the *FCN1* Gene Coding for M-Ficolin Are Associated with Disease Activity, Radiographic Damage and Are the Strongest Predictors of DAS28 Remission in 180 DMARD naïve Early Rheumatoid Arthritis Patients.

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Background/Purpose: M-ficolin is a pattern recognition molecule that collaborates with associated serine proteases as an activator of the complement system. High M-ficolin levels are strongly associated with high disease activity in early RA and low levels at baseline are strong predictors of both remission and low disease activity after one year(1). Single nucleotide polymorphisms (SNPs) in the M-ficolin gene *FCN1* have been shown to influence the concentration and function of M-ficolin(2) and are associated with outcome in patients with systemic inflammation. We have now investigated associations of 7 *FCN1* SNPs with DAS28, modified Total Sharp Score (mTSS), low disease activity (LDA, DAS28<3.2), and remission (DAS28≤2.6) in a cohort of 180 early RA patients.

Methods: 180 DMARD naïve RA patients with disease duration <6 months were included in a randomized double blind placebo-controlled trial (OPERA-study,NCT00660647) of methotrexate, intra-articular glucucorticoids plus either adalimumab or placebo. SNPs were analyzed with TaqMan OpenArray system (2). The associations between SNPs and endpoints were evaluated using linear or logistic regression analysis adjusted for age, sex, anti-CCP and treatment with the common allele homozygous genotype selected as reference.

Results: Baseline characteristics were similar in the two groups, Table 1. Table 2 states the four SNPs of which the minor allele was previously shown to be associated with higher plasma M-ficolin levels in healthy adults(2). Homozygosity of the minor allele in any of these 4 SNPs was associated with higher DAS28 at both baseline ($p<0.005$) and after one year of aggressive treatment ($p<0.009$), while no effect was observed in the heterozygote state. Homozygosity of the minor allele in the 4 SNPs was further associated with increased mTSS at both baseline ($p<0.02$) and at year one ($p<0.04$), except for rs7657015 ($p=0.06$). The four SNPs were, in multivariate logistic regression analyses, the only variables able to predict LDA at year one (OR between 0.16 to 0.18) and the strongest predictors of remission (OR between 0.24 to 0.26) followed by treatment with adalimumab (OR between 2.49 to 2.66).

Conclusion: Homozygosity of the minor allele of 4 *FCN1* SNPs is associated with higher DAS28 levels and modified Total Sharp Score in early RA. The four SNPs were the only variables capable of predicting LDA and the strongest predictors of DAS28 remission. These data consolidate our previous findings that M-ficolin, a molecule of the innate immune system, is a strong prognostic marker at both the protein and gene level.

(1) Arthritis Rheum.2013 Dec;65(12):3045–50.
(2) PLoS One.2012;7(11):e50585.

Table 1. Patient characteristics

	OPERA Placebo treated group (n=91)	OPERA Adalimumab treated group (p=89)	P value
Baseline characteristics			
Female sex	69%	63%	0.46
Age, years	54 (28-77)	56 (26–78)	0.71
Disease duration, days	83 (42–150)	88 (42–162)	0.74
Anti-CCP positive	70%	60%	0.17
IgM-RF positive	74%	70%	0.67
DAS28	5.6 (3.8–7.3)	5.5 (3.8–7.8)	0.53
C-reactive protein, mg/l	15 (7–109)	15 (7–133)	0.54
Tender joint count(28)	11 (3–24)	10 (3–27)	0.78
Swollen joint count(28)	8 (2–22)	8 (2–26)	0.66
VAS-patient global, mm	65 (17–96)	70 (12–100)	0.27
X-ray erosions (ES≥1)	52%	54%	0.94
Disease activity, 1 year			
DAS28	2.6 (1.7–4.7)	2.0 (1.7–5.2)	0.009
DAS28 < 3.2	76%	80%	0.65
DAS28 ≤ 2.6	49%	74%	
C-reactive protein, mg/l	7 (7–44)	7 (7–21)	0.21

Values are medians with 5-95% percentile values in parentheses, unless otherwise stated. Anti-CCP = anti-cyclic citrullinated peptide, RF = rheumatoid factor, DAS28 = disease activity score 28 joints, VAS = visual analogue scale, ES = Sharp/van der Heijde Erosion Score.

Table 2. Linear regression analyses of the *FCN1* genotype effect on the DAS28 and modified Total Sharp Score and logistic regression analyses with DAS28<3.2 and DAS28≤2.6 as endpoints.

			DAS28 - baseline		DAS28 – year one		mTSS - baseline		mTSS – year one		DAS28<3.2 at year one		DAS28≤2.6 at year one	
rs-number	Geno-type	%	β	P value	β	P value	β	P value	β	P value	OR (CI)	P value	OR (CI)	P value
rs2989727	T T	36	ref.		ref.		ref.		ref.		ref.		ref.	
	T C	47	−0.32	0.08	−0.20	0.16	**−2.05**	0.04	−2.27	0.03	2.01 (0.82–4.93)	0.13	1.91 (0.88–4.19)	0.10
	C C	17	−0.09	0.70	0.07	0.71	**−3.05**	0.02	−3.74	**0.008**	1.39 (0.43–4.47)	0.58	1.11 (0.41–3.01)	0.83
rs7857015 *	A A	49	ref.		ref.		ref.		ref.		ref.		ref.	
	A G	39	0.06	0.73	0.10	0.44	0.67	0.49	0.40	0.70	0.85 (0.33–2.18)	0.73	0.47 (0.22–1.01)	0.06
	G G	12	**0.79**	**0.002**	**0.54**	0.009	**3.34**	0.02	2.91	0.06	**0.18 (0.06–0.55)**	0.003	**0.26 (0.09–0.78)**	0.02
rs28909068	T T	81	ref.		ref.		ref.		ref.		ref.		ref.	
	T C	19	−0.07	0.73	−0.02	0.89	−0.59	0.60	−0.44	0.72	1.50 (0.47–4.73)	0.49	1.47 (0.57–3.80)	0.43
rs10120023 *	C C	49	ref.		ref.		ref.		ref.		ref.		ref.	
	C T	39	0.10	0.57	0.11	0.40	0.72	0.45	0.48	0.64	0.83 (0.32–2.15)	0.71	**0.46 (0.21–0.99)**	0.05
	T T	12	**0.77**	**0.004**	**0.57**	0.007	**3.64**	**0.01**	3.21	0.04	0.16 (0.05–0.52)	0.002	**0.24 (0.08–0.75)**	0.01
rs28909976	del del	35	ref.		ref.		ref.		ref.		ref.		ref.	
	del T	47	−0.31	0.09	−0.20	0.17	**−1.99**	**0.05**	−2.22	0.04	2.09 (0.84–5.16)	0.11	1.95 (0.89–4.29)	0.10
	T T	18	−0.11	0.64	0.03	0.87	**−3.01**	0.02	−3.72	**0.007**	1.57 (0.49–5.02)	0.45	1.27 (0.48–3.41)	0.48
rs10117466 *	G G	49	ref.		ref.		ref.		ref.		ref.		ref.	
	G T	39	0.08	0.66	0.03	0.81	0.48	0.62	0.35	0.74	1.07 (0.41–2.76)	0.89	0.55 (0.25–1.17)	0.12
	T T	12	**0.75**	**0.005**	**0.57**	0.006	**3.73**	**0.01**	3.23	0.04	0.18 (0.06–0.57)	0.003	**0.26 (0.08–0.79)**	0.02
rs10858293 *	C C	49	ref.		ref.		ref.		ref.		ref.		ref.	
	C A	39	0.12	0.48	0.07	0.59	0.82	0.39	0.56	0.58	1.06 (0.41–2.74)	0.90	0.55 (0.26–1.17)	0.12
	A A	12	**0.79**	**0.003**	**0.56**	0.008	**3.71**	**0.01**	3.30	0.04	0.18 (0.06–0.56)	0.003	**0.26 (0.08–0.79)**	0.02

Both linear and logistic regression analyses are corrected for treatment (placebo/adalimumab), age, gender and anti-CCP status. mTSS=modified Total Sharp Score, ref.=reference, β=correlation coefficient, OR = Odds Ratio, * indicate that SNPs is associated with plasma M-ficolin concentration in 346 healthy adults (2)
Statistic significant results are highlighted in bold

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***PTPN22* Promotes TLR-Induced Amelioration of Arthritis.**

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Background/Purpose: Rheumatoid arthritis (RA) synovial fluid exhibits high levels of type 1 interferons (IFN). Type 1 IFN may exert potent anti-inflammatory effects, since a TLR3 agonist suppresses inflammatory arthritis in a type 1 IFN-dependent manner. *PTPN22*, encoding Lymphoid Tyrosine Phosphatase (Lyp), is a "risk" gene for RA. A *PTPN22* disease-associated variant encodes an R620W substitution-bearing protein "LypW". We showed previously that *PTPN22* promotes Toll-like receptor (TLR) signaling and type 1 IFN production. Further, we found that LypW exhibits reduced function in poly(I:C)-mediated suppression of inflammatory arthritis in the K/BxN "serum-transfer" arthritis model. TLR9 agonists can also suppress arthritis through an unknown mechanism. We tested the hypothesis that *PTPN22* is required for TLR9 agonist-driven amelioration of arthritis.

Methods: Serum-transfer arthritis was induced in control or *Ptpn22*$^{-/-}$ mice by intraperitoneal injection of K/BxN mouse serum. Mice were then injected with ODN 1668 (10 nmol), a CpG oligonucleotide agonist of TLR9.

Arthritis scores were monitored. Synovial RNA was assayed for type 1 interferon and interferon-dependent gene expression via RT-qPCR.

Results: Confirming previous reports, ODN 1668 treatment ameliorated serum-transfer arthritis in control mice. However, *Ptpn22*$^{-/-}$ mice exhibited diminished suppressive response to ODN 1668. Reduced arthritis amelioration in *Ptpn22*$^{-/-}$ mice correlated with impaired TLR9 induction of *Ifna4* and *Cxcl10* (type 1 IFN-dependent chemokines) in synovium (Figure 1).

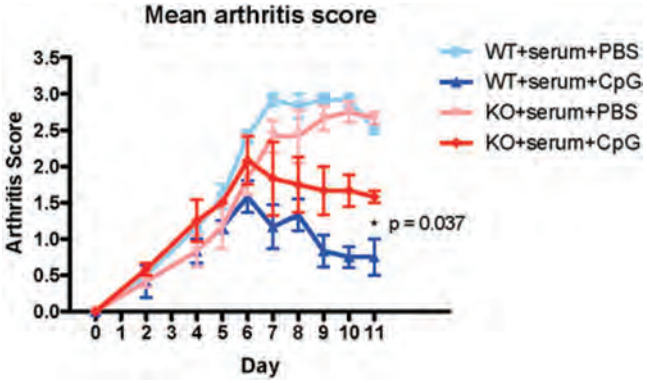

Figure 1: Mice (n = 3 per group) were injected with K/BxN serum together with ODN 1668 or vehicle alone. Arthritis severity scores (mean± SEM) are shown. WT, wild-type; KO, *Ptpn22*$^{-/-}$.

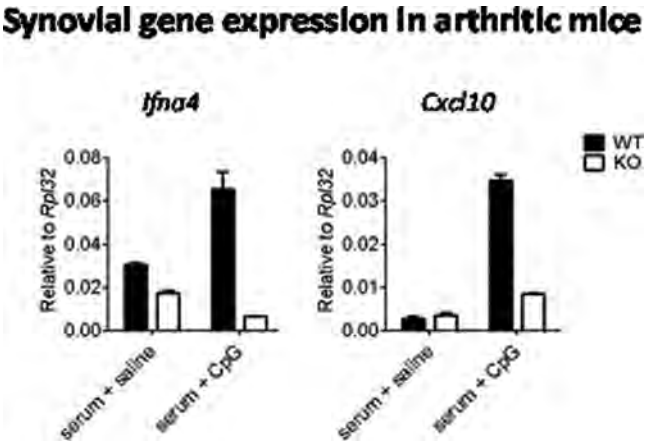

Figure 2: Expression of *Ifna4* and the IFN-inducible gene *Cxcl10* in synovium at day 11 post injection of serum was determined by qPCR.

Conclusion: *Ptpn22* is required for CpG-induced amelioration of inflammatory arthritis, and for upregulation of type 1 IFN-dependent genes in synovium. These data support a model wherein Ptpn22 exerts anti-inflammatory effects by promoting TLR signals that induce type 1 IFN and type I IFN-dependent genes.

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Role of Natural Killer Cells and Gamma Delta T Cells in Enthesitis Related Arthritis Category of Juvenile Idiopathic Arthritis. Priyanka Gaur, Ramnath Misra and Amita Aggarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: Enthesitis Related Arthritis (ERA) is the most common form of Juvenile Idiopathic Arthritis (JIA) in India. ERA is associated with increased frequency of Th17 cells and synovial fluid (SF) IL-17 levels. Recently innate immune cells like Natural Killer (NK) cells, γδ T cells have been reported to produce IL-17 and contribute to disease pathogenesis in Ankylosing spondylitis. Thus we have studied the frequency and effector functions of innate cells in ERA.

Methods: Fifty JIA-ERA, 21 other JIA patients (disease controls) and 25 healthy controls were enrolled in the study and peripheral blood (PB) was collected.19 paired synovial fluids were also studied. Frequency of NK cells, NKT cells, γδ T cells, expression of perforin in NK cells and KIR3DL1/2 on NK cell and T cells were measured by flow cytometry. Frequency of IL-17 producing T cells, NK cells and γδ T cells were quantified by Flow cytometry.

Results: Patients with ERA as compared with healthy controls had normal frequency of NK cells (9.52% ± 4.67 v/s 9.62% ± 2.65) and NKT cells (2.93% ± 1.96 v/s 2.42% ± 1.78) but had increased frequency of γδ T cells (9.31% ± 4.61 v/s 5.12% ± 2.61; p<0.001). Further NK cells in ERA patients had low expression of perforin (56.19% ± 15.67) and high KIR3DL1/2 expression (31.33% ± 12.13) as compared to controls (82.79% ± 9.43; p < 0.001, 21.32% ± 11.05, p=0.001 respectively). Frequency of IL-17 producing NK cells were increased in PB of JIA-ERA patients (n=10, 3.69% ± 2.72) as compared to healthy controls (n= 6, 0.83% ± 0.80; p = 0.01). Also the IL-17 producing γδ T cells were high in JIA-ERA (2.22% ± 2.20) than healthy controls (0.35% ± 0.56, p=0.02). In paired samples the frequencies of these cells were similar but as compared to PB,SF NK cells had reduced expression of perforin (56.64% ± 17.08 v/s 1.55% ± 2.5, p=0.001)and KIR3DL (31.39 ± 9.66 v/s 10.89% ± 10.84, p < 0.001).

Conclusion: NK cells in ERA patients have CD56 bright phenotype with low perforin expression suggestive of cytokine producing cells. Further increase in KIR3DL1/2 expression on NK cells suggests that they may interact with HLA B27 and have enhanced survival. Increased frequency of IL-17 producing NK cells and γδ T cells in ERA suggests that in addition to Th17 cells they may also contribute to IL-17 in ERA.

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MicroRNA-146a in Salivary Gland Epithelial Cells Inhibits Co-Stimulatory Molecule CD80 Expression and Increases Autoreactive T Cell Activation in Sjögren's Syndrome. Adrienne Gauna[1], Jun-O Jin[2], Qing Yu[3], Carol Stewart[1] and Seunghee Cha[1]. [1]University of Florida, Gainesville, FL, [2]Fudan University Shanghai Medical College, Shanghai, China, [3]The Forsyth Institute, Cambridge, MA.

Background/Purpose: Sjögren's syndrome (SS) causes severe dry mouth and eyes. The presence of immune cell infiltration in the salivary (SG) and lacrimal glands suggests a response to local antigens, presumably from resident antigen presenting cells (APCs) and exocrine epithelium stimulation of autoreactive CD4+ T cells. Recent studies in our lab identified co-stimulatory molecule CD80 as a target of microRNA (miR)-146a and showed reduced CD80 in the SG cells of SS-prone mice (C57BL/6.NOD-*Aec1Aec2*, B6DC). Co-stimulatory molecule CD80 is presumed to promote T cell regulatory phenotypes by binding to CTLA-4 or PD-L1. Therefore, we sought to identify which cell subsets were contributing to the reduced CD80 in SGs and whether there were alterations in regulatory (Treg) and conventional (Tconv) T cell functional markers in B6DC mice.

Methods: Single cell suspension of submandibular SGs and draining lymph nodes (dLNs) of 20–24-week-old B6DC and C57BL/6 (B6) mice (n = 5–9 per group) were evaluated by flow cytometry. To identify potential APC subsets, cells were assessed for CD19, CD11c, CD11b, and F4/80. SG epithelial cells (SGECs) were negatively selected using anti-CD45 microbeads and identified using CD326. APCs and SGECs were evaluated for co-stimulatory molecules CD80 and CD86. In addition, Treg (CD4+Foxp3+) and Tconv (CD4+Foxp3-) cells were assessed for cell surface proteins CD25, CTLA-4, PD-L1, and intracellular IL-10 and TGF-β1. Quantitative real-time-PCR was used to evaluate the expression of miR-146a in SGECs relative to RNU6b. Data were analyzed by two-tailed-unpaired t-test or linear regression where $P < 0.05$ was considered significant.

Results: SG APCs contributed to less than 5% of total SG cells. The CD19+CD11c- B cells, CD11c+CD11b+F4/80+CD19+ macrophages, CD11c+CD11b+F4/80-CD19- dendritic cells and CD11c+CD11b+F4/80+CD19- macrophages showed reduced percentages of CD86+CD80+ cells. Analyses of B6DC SGECs revealed a 29% reduction in CD80 mean fluorescence intensity (MFI), but no alteration in CD86 MFI in comparison to B6 mice. The ratio of CD86:CD80 MFI was increased and the relative expression level of miR-146a was elevated by 2.09-fold in B6DC SGECs. Furthermore, CD80 MFI showed a negative relationship to the relative expression level of miR-146a (slope = −0.376, r^2 = 0.511). Also, B6DC SG Tregs were increased (+56%) and had increased CTLA-4 (+81%) and PD-L1 (+37%) positive cells; while Tconv had increased PD-L1 (+43%) and decreased IL-10 (−60%) positive cells. The dLN Tregs had increased CTLA-4 (45+%) or PD-L1 (+8.7%) positive cells along with 28% decrease in IL-10 positive cells; whereas Tconv cells showed 8.8% increase in PD-L1 positive cells.

Conclusion: SGECs are major contributors to reduced total CD80 expression in the SG since contributions of resident APCs were minimal. Therefore, it is presumed that the imbalance of CD86:CD80 in SGECs, due

to aberrantly expressed miR-146a, could contribute to the abnormal activation of T cells in the affected tissues of SS. This is supported by the observed reduction in regulatory cytokine IL-10 in SG T cells despite elevated expression of regulatory CTLA-4, PD-L1, and the number of Foxp3+ Tregs.

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Macrophages from the Synovium of Active Rheumatoid Arthritis Exhibit an Activin a- Dependent Pro-Inflammatory Profile. Elena Izquierdo[1], Blanca Soler Palacios[2], Lizbeth Estrada-Capetillo[2], Gabriel Criado[3], Concha Nieto[1], Cristina Municio[2], Isidoro González-Álvaro[4], Paloma Sánchez-Mateos[2], Jose L. Pablos[5], Ángel L. Corbí[1] and Amaya Puig-Kröger[2]. [1]Centro de Investigaciones Biologicas (CSIC), Madrid, Spain, [2]Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain, [3]Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain, [4]Hospital Universitario La Princesa, Instituto de Investigación Sanitaria Hospital Universitario La Princesa, Madrid, Spain, [5]Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain.

Background/Purpose: Synovial macrophages are key effector cells in rheumatoid arthritis (RA), where they are a major source of pro-inflammatory cytokines and contribute to the cartilage and bone destruction. Macrophages are phagocytic cells present in all tissues and show a remarkable plasticity in response to environmental signals. However, the polarization state of macrophages in RA has not been fully uncovered. To dissect the molecular basis for the tissue-damaging effects of macrophages in RA joints, we have characterized the phenotype and transcriptome of RA synovial macrophages. Moreover, we have studied the macrophage polarizing ability of the synovial fluid of RA (RA-SF) patients.

Methods: Human monocytes (obtained from buffy coats from normal donors) and macrophages from RA-SF (RA-SF MØ) were isolated by Ficoll gradient and subsequent magnetic cell sorting using anti-CD14 microbeads. Monocytes were cultured for 7 days in RPMI containing GM-CSF or M-CSF to generate GM-CSF-polarized macrophages (GM-MØ) or M-CSF-polarized macrophages (M-MØ). The phenotypic and transcriptomic characterization of ex-vivo isolated CD14+ RA-SF macrophages was accomplished by flow cytometry and quantitative real time PCR. In normal and synovial tissues, the expression of macrophage-polarization markers was analyzed by immunofluorescence labeling. To assess the RA-SF polarizing ability, RA-SF was added onto monocytes or M-MØ (ratio 1:1 in culture medium) in the presence or absence of a blocking anti-activin A antibody for 72 hours and the expression of macrophage-polarization markers was analyzed by qRT-PCR and Western Blot.

Results: Flow cytometry and gene profiling indicated that RA-SF macrophages express pro-inflammatory polarization markers (MMP12, EGLN3, CCR2), lack expression of markers associated to homeostatic and anti-inflammatory polarization (IGF1, HTR2B), and exhibit a transcriptomic profile that resembles the activin A-dependent gene signature of pro-inflammatory *in vitro* generated macrophages. *In vitro* experiments on monocytes and macrophages indicated that RA-SF promote the acquisition of pro-inflammatory markers (INHBA, MMP12, EGLN3, CCR2), but led to a significant reduction in the expression genes associated to homeostasis and inflammation resolution (FOLR2, SERPINB2, IGF1, CD36), thus confirming pro-inflammatory polarization ability of RA-SF. Importantly, the macrophage polarizing ability of RA-SF was inhibited by an anti-activin A neutralizing antibody, thus demonstrating that activin A mediates the pro-inflammatory macrophage polarizing ability of RA-SF. Moreover, and in line with these findings, multicolor immunofluorescence evidenced that macrophages within RA synovial membranes (RA-SM) express pro-inflammatory polarization markers whose expression is activin A-dependent.

Conclusion: Altogether, our results demonstrate that macrophages from RA synovial fluid and membrane exhibit an MMP12+ EGLN3+ CCR2+ pro-inflammatory polarization state whose acquisition is partly dependent on activin A from the synovial fluid.

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Macrophages-Mediated Response to Uric Acid Crystals Is Modulated By Their Functional Polarization. Emma Garcia-Melchor[1], Monica Guma[2], Jordi Yagüe[1], Manel Juan[1] and Jacquie Harper[3]. [1]Hospital Clinic Barcelona, Barcelona, Spain, [2]University of California, San Diego, La Jolla, CA, [3]Malaghan Institute of Medical Research, Wellington, New Zealand.

Background/Purpose: Macrophages have been involved in both initiation and resolution of gout flares. Accordingly, these cells are characterized by their plasticity as the environment modulates their phenotype exerting inflammatory or anti-inflammatory functions depending on their activation or polarization state. Macrophages in the presence of interferon-γ and lipopolysaccharide (LPS), what is known as classical activation, acquire an inflammatory phenotype and are also termed M1 macrophages. On the other hand, M2 or alternatively activated macrophages with IL-4 have anti-inflammatory and homeostatic functions. Equivalently, in the presence of granulocyte macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) macrophages become M1 or M2 respectively. As M-CSF is present in the blood stream at steady state some authors propose that M2 macrophages polarized with M-CSF could represent the population of resident macrophages. In this work we investigated M2 macrophages response to monosodium urate (MSU) crystals *in vitro*.

Methods: Macrophages were derived from peripheral blood monocytes of healthy donors after informed consent. Peripheral blood mononuclear cells were separated from whole blood by centrifugation with a density gradient. Monocytes were then isolated by negative selection with magnetic beads and cultured for 1 week with GM-CSF (1000 I.U./ml) or M-CSF (20 ng/ml) to obtain M1 or M2 macrophages respectively. Macrophages were then stimulated with MSU (200 μg/ml), LPS (100 ng/ml) or both for 18 hours and quantification of IL-1β and IL-10 in supernatants was performed by ELISA. Activation of caspase-1 in M1 and M2 macrophages was analyzed by flow cytometry with the Caspase-1 FLICA™ Detection Kit (Immunochemistry Technologies). Cytoplasmic pro-caspase-1 and pro-IL-1β were analyzed by western blot. Flow cytometry and statistics analysis were performed with the FACSDiva and GraphPad Prism 5 respectively.

Results: As expected, M1 macrophages produced inflammatory cytokines in response to LPS, whereas M2 macrophages were unable. Both M1 and M2 failed to produce IL-1β after MSU stimulation. However, when challenged with MSU and LPS, M2 macrophages produced IL-1β (mean+/−SEM, LPS 2.59+/−1.37 pg/ml, MSU+LPS 111.4+/−30.44 pg/ml, p= 0.0078) and reduced IL-10 production (mean+/−SEM, LPS 3738+/−230 pg/ml, MSU+LPS 1587+/−386.4 pg/ml, p= 0.0039). Resting M2 macrophages exhibited lower levels of active caspase-1 and pro-caspase-1. MSU stimulation increased active caspase-1 levels in both M1 and M2 macrophages and the presence of MSU and LPS had a synergic effect in pro-IL-1β.

Conclusion: M1 and M2 macrophages failed to produce inflammatory cytokines after MSU challenging, according with the fact that MSU crystals can be found in asymptomatic joints. However, after MSU phagocytosis, M2 macrophages were able to produce IL-1β after LPS stimulation, explaining the requirement of a trigger, such as a copious meal or alcohol intake, for the initiation of an acute flare in gout. M2 macrophages also had lower levels of caspase-1 and pro-caspase-1, than M1 macrophages.

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Class a Scavenger Receptor (SR-a) Exacerbated Synovial Fibroblasts-Mediated Inflammation in Rheumatoid Arthritis. Yingni Li[1], Fanlei Hu[1], Li Zheng[1], Linchong Su[2], Lianjie Shi[1], Pei Song[1] and Zhanguo Li[1]. [1]Peking University People's Hospital, Beijing, China, [2]Hubei Minzu University, Enshi, China.

Background/Purpose: Class A scavenger receptor (SR-A/CD204), mainly expressed on macrophages, plays an important role in the pathogenesis of atherosclerosis and in the pattern recognition of pathogen infection. However, its role in rheumatoid arthritis (RA) has not been defined. The aim of this study was to reveal the expression of SR-A in synovial fibroblasts (RASF) and its impact on synovial inflammation.

Methods: Immunohistochemistry (IHC) was performed to detect the expression of SR-A in the synovial tissues from RA and osteoarthritis (OA) patients. The expression of SR-A in RASF was demonstrated by both qPCR and western blot. To reveal the effects of SR-A on synovial inflammation, RASF were treated with either recombinant SR-A protein or SR-A specific

siRNA. Then, the expression of pro-inflammatory cytokines (TNF-α, IL-6, and IL-8) and MMPs (MMP-1, MMP-3, and MMP-9) were determined by real-time PCR and ELISA. Accordingly, the activation of the MAPKs and NF-κB signaling pathways was evaluated by western blot when SR-A was silenced.

Results: The level of SR-A was higher in the synovial tissues from RA patients than those from OA patients. Moreover, we for the first time demonstrated that SR-A was expressed in RASF. SR-A protein stimulated pro-inflammatory cytokine and MMP expression in RASF. On the contrary, knocking down SR-A by specific siRNA suppressed the expression of these factors, with dampened activation of the ERK, JNK, p38 and NF-κB signaling pathways.

Conclusion: SR-A exacerbated synovial inflammation and cartilage erosion in RA. Targeting SR-A might provide novel therapeutic strategies for overcoming this stubborn disease.

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2178

Extensive Natural Killer Cell Receptor Phenotyping on NK and T Cells Discloses Differences in RA and Psa, Potentially Mirroring Diverse Immunoregulatory Functions. Marta Cossu[1], Sandra TA van Bijnen[2], Mieke Roeven[2], Tim Jansen[2], Frank Preijers[2], Harry Dolstra[2] and Timothy Radstake[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Radboud University Medical Center, Nijmegen, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are immune-mediated diseases, which share clinical features, but differ in the mechanisms, leading to aberrant immune responses. Natural killer (NK) cells tune the innate immune response depending on the integration of signals coming from a complex network of activating and inhibitory surface receptors. Here, we aim to elucidate the potential role of NK and T cells in inflammation and autoimmunity in RA and PsA and we focused on extensive characterization of the NK cell receptor (NKR) (co-) expression patterns on their surface.

Methods: The frequency of T and NK cells expressing Killer like immunoglobulin Receptors (KIR), NKG2 and Natural Cytotoxicity receptors was assessed by 10-color flow cytometry (FCM) in peripheral blood of 23 RA patients (ACR 1987 revised criteria), 12 PsA patients (Taylor et Al, 2006 Classification of Psoriatic Arthritis Study Group criteria for PsA) and 18 healthy controls (HC). Cytotoxicity of NK cells against K562 cells before and after stimulation with IL-12 and IL-18 as broad activating signals was assessed in a FCM-based cytotoxicity assay in 8 additional RA patients and 8 additional HC; during co-culture, NK degranulation was measured by cell surface expression of CD107a and IFNγ intracellular expression was also assessed in parallel.

Results: RA patients, but not PsA patients, had an increased frequency of NK cells expressing the inhibitory receptor NKG2A compared to HC, particularly in patients with rheumatoid factor positivity. The NKG2A+ NK population was predominantly $CD56^{dim}$and lacked expression of KIRs and activating NKG2C. No differences were observed in the expression of the other NKRs between HC and RA nor PsA patients.

RA patients showed decreased cytotoxicity against K562 cells in the 10:1 Effector:Target ratio, when compared to HC, but the capability of killing in RA NK cells was restored after IL-12/IL-18 stimulation. Degranulation and IFNγ expression were similar in HC and RA patients.

T cells expressing the Fcγ receptor CD16 were more frequent in RA than in HC. Compared to HC, we found higher frequencies of T cells expressing the KIRs CD158ah in both RA and PsA, and CD158e1e2 in RA. $CD4^{+}$T cells expressing the KIRs CD158ah, CD158b1b2j and CD158e1e2, although present at low frequency, were also significantly elevated compared to HC.

Conclusion: The differences in NKR expression on NK and T cells in RA and PsA could mirror the diverse pathogenic mechanisms implicated in these diseases; in particular, the immature phenotype (NKG2A+/KIR-) of circulating NK cells in RA and the reversible impairment in their cytotoxic ability could reflect the activation status of the NK population described in RA synovial fluid and provide growing evidence for the potential of the exploitation of NKG2A blockade in this disease.

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2179

The Monocyte-Phagocyte System in Gout: Enhanced Inflammasome Activity and Expansion of CD14++CD16+ Monocytes in Patients with Gout. Emma Garcia-Melchor[1], Cesar Diaz-Torne[2], Monica Guma[3], Europa Azucena Gonzalez-Navarro[1], Francesc Xavier Alemany[1], Jordi Yagüe[1] and Manel Juan[1]. [1]Hospital Clinic Barcelona, Barcelona, Spain, [2]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [3]University of California, San Diego, La Jolla, CA.

Background/Purpose: The central role of the monocyte-macrophage system in gout has been highlighted during the last years. Macrophages initiate the inflammatory response to monosodium urate (MSU) crystals and produce inflammatory cytokines and chemokines that induce migration of blood monocytes to further amplify the inflammatory response. Different subpopulations of blood monocytes have been recognised: classical (CD14++CD16-), intermediate (CD14++CD16+) and non-classical (CD14+CD16++); characteristically intermediate monocytes are expanded in infectious and inflammatory diseases. One of the questions that remain unanswered is why some patients with hyperuricemia, and even with MSU deposits, remain clinically asymptomatic. We investigated the possibility that it could be due to a greater inflammasome reactivity to MSU crystals in patients who develop gout. Moreover, we analyzed the distribution of monocyte subpopulations in patients with gout.

Methods: Seventeen patients with gout were selected, 13 asymptomatic and in 4 patients samples were obtained during an acute flare. Nineteen healthy donors were selected for comparison. Inflammasome activity was assessed by the increase of active caspase-1 after stimulation with MSU in peripheral blood mononuclear cells (PBMCs) by flow cytometry using Caspase-1 FLICA™ Detection Kit (Immunochemistry Technologies). Phagocytosis of MSU crystals was quantified by flow cytometry, as cells that phagocyte crystals increase their side scatter (SSC) values. PBMCs were cultured for 24 hours in the presence of MSU (200 μg/ml), LPS (100 ng/ml) or both and IL-1β was quantified by ELISA. Samples of peripheral blood were stained with CD45, HLA-DR, CD16, and CD14 antibodies and analyzed by flow cytometry. Uric acid, creatinine and C-reactive protein (CRP) were quantified in sera. Flow cytometry and statistics analysis were performed with the FACSDiva and GraphPad Prism 5 respectively.

Results: No differences were observed in active caspase-1 at baseline between patients and controls. However, when stimulated with MSU, monocytes from gout patients exhibited a higher increase of active caspase-1 (mean+/−SEM, gout 2.20+/−0.15, controls 1.66+/−0.18, p= 0.0419). Differences in phagocytosis of MSU crystals were excluded, as in both groups monocytes exhibited equivalent phagocytic capability. PBMCs of patients with gout exhibited diminished IL-1β production when challenged with LPS and MSU (p=0.0473). Regarding monocyte subpopulations, the intermediate phenotype was expanded in patients with gout during an acute flare and a weak correlation between intermediate monocytes and CRP was observed.

Conclusion: Monocytes of patients with gout exhibited an enhanced inflammasome activation with MSU crystals, suggesting that the reduced threshold in the inflammatory response could be involved in the development of clinical gout. The expansion of intermediate monocytes was observed during gout flares and, although it cannot be excluded that intermediate monocytes could be "innocent bystanders" in the context of inflammation, it could suggest that these monocytes participate in the inflammatory response to MSU crystals.

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Macrophage Depletion Ameliorates Nephritis Induced By Pathogenic Antibodies. Samantha Chalmers[1], Leal Herlitz[2], Violeta Chitu[1], Richard Stanley[3] and Chaim Putterman[1]. [1]Albert Einstein College of Medicine, Bronx, NY, [2]Columbia-Presbyterian Medical Center, New York, NY, [3]Albert Einstein College of Medicine, Bronx, NJ.

Background/Purpose: Kidney involvement affects up to 60% of lupus patients, and is responsible for significant morbidity and mortality. Previous studies using a variety of methods to reduce the number of macrophages have reached conflicting conclusions regarding the role of macrophages in lupus nephritis (LN). Moreover, "off target" effects occur in mice congenitally deficient in macrophages. In this study we investigated the role of macrophages in an inducible model of LN, using a novel depletion method that minimized the confounding factors seen in previous studies.

Methods: To determine the role of macrophages in the antibody mediated nephritis associated with lupus, we utilized the nephrotoxic serum nephritis model. This is an inducible model of nephritis which closely mimics LN, and which is often used to model immune complex mediated renal disease. Mice received nephrotoxic serum (NTS) containing rabbit anti-mouse glomerular antibodies which deposited within the kidney to initiate nephritis. GW2580, an oral kinase inhibitor monospecific for the CSF-1 receptor, was used as a novel and highly selective method for macrophage depletion. GW2580 was delivered via oral gavage over a 10 day period (n=18). A second group of mice received a control gavage of PBS in addition to the NTS transfer (n=18). A third group was neither gavaged nor given NTS, and served as a healthy control population (n=9).

Results: We found that NTS challenged mice, when treated with GW2580 from day 0, did not develop the significant increases in proteinuria, serum creatinine or BUN seen in control treated mice. Furthermore, GW2580 treated mice were protected from the robust kidney expression of inflammatory cytokines associated with LN seen in control treated mice, including RANTES, IP-10, VCAM-1, MCP-1 and IL-6. Flow cytometry analysis of kidney single cell suspensions revealed a significant decrease in inflammatory macrophages ($CD11b^{+}F480^{lo}$) in GW2580 treated mice. Furthermore, IBA-1 staining confirmed profound depletion of macrophages within glomeruli of treated mice. There was no significant change in circulating monocyte numbers with GW2580 treatment; however, there was a significant decrease in the number of macrophages in the spleen. Importantly, GW2580 did not interfere with the induction of the disease model. Finally, treatment with GW2580 at a later time point in the disease model (beginning day 5) was also effective at attenuating nephritis.

Conclusion: Our results support an important role of macrophages in LN pathogenesis, and suggest targeting this cell type as a promising approach to the treatment of LN.

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Investigating Myeloid and Plasmacytoid Dendritic Cell Activation within the Synovium and Peripheral Blood of Rheumatoid Arthritis Patients. Mary Canavan, Michael Anthony O'Rourke, Douglas J. Veale and Ursula Fearon. Translational Rheumatology Research Group, Dublin, Ireland.

Background/Purpose: Dendritic cells (DC) are a heterogeneous population of professional antigen presenting cells which link both the innate and adaptive arms of the immune system. Myeloid and plasmacytoid DC represent the two major DC subsets and can be distinguished based on their morphology, expression of surface markers and gene expression profiles. In this study we compared the percentage and activation status of myeloid versus plasmacytoid DC at the site of inflammation in RA compared to systemic circulation.

Methods: DC whole blood phenotyping was assessed using multicolour flow cytometry on the Beckman Coulter Cyan system using FlowJo software for subsequent analysis. DC were defined as $HLADR^{+}$, $Lineage^{-}$, and further subdivided as either myeloid ($CD11c^{+}$, $CD1^{+}$ or $CD141^{+}$) or plasmacytoid DC ($CD123^{+}$). Cell surface expression of CD80, CD83 and CD40 was used to assess the activation and maturation status of each subtype. For characterisation of synovial tissue DC, biopsies were digested using the GentleMACs mechanical and enzymatic digestion system. Viable CD45 cells were gated and subsequently assessed for DC pan markers in addition to maturation and activation markers. In parallel, synovial fluid and peripheral blood were comparatively assessed to profile DC from blood, fluid and tissue. To assess the effect of the synovial environment on DC maturation, immature DC were derived from CD14+ monocytes in the presence of GM-CSF (70ng/ml) and IL-4 (50ng/ml). Synovial tissue explants were cultured for 24hr allowing the spontaneous release of cytokines and soluble mediators into the culture medium. Monocyte derived dendritic cells (MoDC) were cultured in the presence of this explant conditioned media for 24hr after which the expression of maturation markers was analysed on $CD11c^{+}$ $CD14^{-}$DC.

Results: RA patients have a decreased percentage of CD11c mDC circulating in peripheral blood compared to that of healthy controls. The percentage of CD123 pDC between RA and healthy controls is not significantly different however the expression of CD40 on pDC in RA patients is significantly increased compared to healthy control ($p<0.001$). A comparative analysis of mDC and pDC in peripheral blood, synovial fluid and synovial tissue highlighted an increase in DC maturation as DC migrate from blood, to fluid and finally tissue. CD40 and CD83 expression on mDC is increased in tissue compared to that of fluid or blood. Similarly an increase in CD40 and CD83 on pDC was found in synovial tissue compared to that of fluid or peripheral blood. Finally immature monocyte derived DC cultured in the presence of explant conditioned media have increased expression of CD80 and CD83 compared to basal DC medium.

Conclusion: DC have a more mature and activated phenotype in the synovial tissue compared to that in synovial fluid or peripheral blood. Given that there are also lower circulating levels of DC in RA patients compared to controls our data suggest that peripheral blood DC are recruited to the joint where they undergo a programme of maturation. Ongoing studies aim to elucidate the mechanisms in which these subsets are activated and matured.

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Investigating the Roles of Factor H-Related Proteins in Systemic Lupus Erythematosus (SLE) and Other Autoimmune Diseases. Alexandra Antonioli, Brandon Renner, Joshua Thurman, V. Michael Holers and Jonathan Hannan. University of Colorado School of Medicine, Aurora, CO.

Background/Purpose: Complement plays a central role in the pathogenesis of systemic lupus erythematosus (SLE) wherein inappropriate activation of complement leads to substantial tissue damage, especially in the kidney. Factor H is a complement regulatory protein that controls activation of the alternative pathway in the fluid phase and on cell surfaces. Recent human linkage data implicate a role for a group of genes, encoding a family designated Factor H-Related (FHR) proteins, in the pathogenesis of SLE. Specifically, a FHR3-1Δ deletion is associated with a higher risk for the development of SLE, while also demonstrating a protective association in age-related macular degeneration. To date, few functional studies have been carried out on the mouse FHR proteins, and these molecules have not been studied in any *in vivo* models of inflammatory or autoimmune disease. Our central hypothesis is that FHR proteins act as antagonists of FH function and increase complement deposition which exacerbates inflammation and injury.

Methods: To test our hypothesis that FHR proteins compete with FH-mediated complement regulation we: **1)** Generated recombinant forms of the murine FHR proteins (mFHR-A and mFHR-B) using transiently transfected 293-F cells grown in serum free media. **2)** Evaluated the capacity of each of these molecules to inhibit FH function using a hemolysis protection assay. **3)** Performed ELISA assays to detect cross-species reactivity between murine FHRs and human complement components. **4)** Used flow cytometry to evaluate C3b deposition on the surface of nucleated cells (Retinal Pigment Epithelial (ARPE-19) and/or murine tubular epithelial cells (TEC)) upon addition of mFHRs under both oxidatively stressed and non-stressed conditions. We are also producing antibodies directed to the murine FHRs in order to better understand how the FHRs may be involved in SLE and other autoimmune diseases and whether FHR levels are altered during different disease activity states (i.e. during SLE disease flares).

Results: Addition of 1uM of mFHR-A or mFHR-B results in 100% and 50% hemolysis, respectively, of sheep red blood cells which are normally resistant to complement mediated lysis due to their lack of membrane associated complement regulators. We also observe a significant increase in C3b deposition under both stressed and non-stressed conditions on the surface of at least one type of nucleated cell (ARPE-19) upon addition of mFHR-A (mean fluorescence intensity is two-fold greater than serum only control). These results suggest that the murine FHRs are excellent surrogates by which to interrogate the underlying mechanisms linking variations within the human *CFH* gene family to complement deregulation in tissues such as the kidney or eye.

Conclusion: Our preliminary work supports recent studies which have shown that the FHR proteins modulate complement by competing with FH for binding to its major ligand, complement component C3b, likely disrupting FH-driven complement regulation on specific biological surfaces. The long-term objective of this work is to determine whether the FHR proteins are suitable therapeutic targets for the treatment of complement-driven inflammatory diseases such as SLE.

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Release of Enzymatically Active Peptidyl Arginine Deiminases (PADs) By Neutrophils Allows Generation of Citrullinated Extracellular Autoantigens in the Synovial Fluid of Patients with Rheumatoid Arthritis. Julia Spengler[1], Bozo Lugonja[1], Andrew Creese[1], Jimmy Ytterberg[2], Karin Lundberg[3], Michael Milward[1], Mark Pearson[4], Christopher Buckley[1], Andrew Filer[1], Karim Raza[1], Paul Cooper[1], Iain Chapple[1] and Dagmar Scheel-Toellner[1]. [1]University of Birmingham, Birmingham, United Kingdom, [2]Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [4]University of Birmihgham, Birmingham, United Kingdom.

Background/Purpose: Citrullinated proteins are important autoantigens in the inflamed joints of patients with rheumatoid arthritis (RA). Several of these proteins are derived from proteins generally found in the extracellular space, such as fibrinogen and type II collagen. It is therefore important to understand the source of extracellular peptidyl deiminases, (PAD) the enzymes responsible for citrullination. After entering the joints of RA patients, neutrophils are activated and release DNA in an active process termed NETosis. As this process involves histone citrullination by PAD4 we hypothesized that neutrophils undergoing NETosis in the rheumatoid joint release enzymatically active peptidyl arginine deiminases.

Methods: Extracellular DNA was quantified in the synovial fluid (SF) of patients with RA (n=27) and osteoarthritis (OA) (n=15). Presence of decondensed DNA in association with neutrophil elastase was studied on smear preparations of RA SF and synovial tissue. Release of PAD2 and PAD4 was examined during in vitro induced NETosis using Western Blotting and verified by mass spectrometry and immunofluorescence. NETS isolated from in vivo and in vitro activated neutrophils were isolated and probed on western blots. PAD activity in the supernatant of in vitro stimulated neutrophils and in the SF of patients with RA (n=7) and OA (n=9) was determined by a conversion assay involving citrullination of target peptides.

Results: Extracellular DNA was detected in the SF from RA patients at significantly higher levels than in OA SF ($p<0.001$) and correlated with SF neutrophil cell counts (n=15, $R^2=0.68$, $p=0.002$) and with PAD activity (n=14, $R^2=0.32$, $p=0.03$) in the SF. Immunofluorescence revealed the co-localization of neutrophil elastase with decondensed DNA in RA SF and within neutrophil precipitates on the surface of the synovial lining layer. Furthermore, PAD activity was detected at significantly higher levels in the SF of RA patients when compared to SF from OA patients ($p<0.001$) and the isoenzymes PAD2 and PAD4 were both found to be present in the SF of RA patients. Significantly higher PAD activity could also be detected in the supernatant of in vitro stimulated neutrophils when compared to unstimulated cells ($p<0.05$). Western blotting revealed the release of free PAD2 and PAD4 into the supernatant and also the association of both isoenzymes with isolated NETs. The loss of nuclear PAD4 signal during NETosis was confirmed by immunofluorescence staining.

Conclusion: These results demonstrate the enzymatic activity of PADs in the synovial fluid of RA patients. Combined with our findings from in vitro stimulated neutrophils the data suggest that neutrophils undergoing NETosis are a source of this extracellular activity. The correlation of the measured PAD activity with DNA levels and neutrophil cell counts in the synovial fluid of RA patients are in line with this hypothesis. This study highlights the possibility that activated neutrophils recruited into the joints could continuously release enzymatically active PADs which contribute to the continuous generation of citrullinated autoantigens and thus drive an inflammatory response in the joint.

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Selective Consumption of C2 Component in HCV Patients. Atila Granados Afonso de Faria[1], Luis Eduardo C. Andrade[2] and Maria Lucia Gomes Ferraz[3]. [1]Universidade Federal de Sao Paulo, Sao Paulo, Brazil, [2]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil, [3]Universidade Federal de São Paulo, São Paulo, Brazil.

Background/Purpose: Hepatitis C virus (HCV) causes immunologic disorders (vasculitis, myositis, arthritis) and high frequency of autoantibodies and mixed cryoglobulinemia (CRYO). Recently, we observed that some HCV patients present absent serum C2 hemolytic activity without consumption of other components of the Complement System (CS). Liver enzyme (AST/ALT) serum levels were registered as the times the upper limit of normal (ULN). This study characterizes this phenomenon in a large series of consecutive HCV patients.

Methods: 1021 samples from 716 consecutive HCV patients were analyzed for CS parameters: functional assessment of C2 (radial immune-hemolysis); C2, C3 and C4 protein concentration (immune-precipitation). Clinical and laboratory data were obtained from a structured medical form.

Results: Samples were classified into three groups according to C2 hemolytic activity: 1) Absent activity (n=154; 15.1%); 2) Decreased activity (n=154; 15.1%); 3) Normal activity (n=713; 69.8%). Most samples with decreased/absent C2 activity had decreased serum C2 protein concentration. Serum C3 and C4 was normal in 89 (82%) and 82 (72%), respectively, of samples with absent C2 activity. Analysis of multiple sequential samples from 192 patients showed that the selective decrease in C2 activity is a transient phenomenon with variable duration in time. Patients with absent C2 activity had higher serum liver enzymes (AST/ALT) (2,46±1,25 ULN and 2,29±2,15 ULN) and lower serum albumin (4,0±0,6mg/dL) than those with normal C2 activity (AST 1.46±1,25 ULN $p<0.001$; ALT 1.62±1.47 ULN; $p=0.03$; albumin 4,3±0,5; $p=0.01$). Samples with absent C2 activity had higher frequency of CRYO (13%) than those with normal C2 activity (0.8%) ($p<0.001$). In vitro exposure of normal to CRYO induced selective decrease in C2 activity in a dose-dependent manner. C2 activity status was not associated with other clinical and laboratory parameters.

Conclusion: Selective decreased C2 activity is transiently observed in 30% of HCV patients. This phenomenon was associated with liver biochemical abnormalities and CRYO. Further studies are warranted to define the role of these and other yet unknown factors on selective C2 deficiency in HCV patients.

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Alterations in B Cell Complement Processing Related to a Lupus-Associated Variant in Complement Receptor 2. Brendan M. Giles and Susan A. Boackle. University of Colorado School of Medicine, Aurora, CO.

Background/Purpose: We have recently identified a variant in intron 1 of complement receptor 2 (CR2/CD21) that is associated with decreased risk of lupus (rs1876453; $P_{meta}=4.2\times10^{-4}$, OR=0.85). Its effect was strongest in subjects with anti-dsDNA antibodies ($P_{meta}=7.6\times10^{-7}$, OR=0.71), suggesting a preferential association with this B cell-driven endophenotype. Peripheral blood B cells from healthy subjects with the rs1876453 minor allele had increased levels of complement receptor 1 (CR1/CD35) resulting in an altered CR1:CR2 ratio on the cell surface. CR1 binds the C3b and iC3b fragments of C3 and is a required cofactor for the degradation of C3b to the CR2-specific ligand C3dg. While crosslinking of CR2 and the B cell antigen receptor is known to lower the activation threshold, the role of CR1 during complement-dependent B cell activation remains unclear. We hypothesize that increased CR1 levels associated with the protective allele facilitate complement processing and modify B cell activation.

Methods: A novel CR1 ligand (biot-C3b) was developed by biotinylating C3b in the thioester domain, the site of antigen attachment. The biotin orientation enables multimers of biot-C3b to be formed that mimic the natural C3b-coated immune complexes that are targets for CR1-mediated processing. Multimeric and monomeric CR1 ligands were generated by incubating biot-C3b with and without streptavidin, respectively. For analysis of CR1-mediated processing, ligand binding was evaluated by flow cytometry using primary B cells and cofactor activity was determined by incubating CR1 (soluble or cell bound) with biot-C3b and factor I followed by SDS-PAGE.

Results: Multimers of biot-C3b were processed by CR1 more efficiently than monomers as demonstrated by increased B cell binding and more complete degradation to C3dg. In solution, higher CR1 concentrations resulted in more rapid conversion of biot-C3b to its degradation products. On primary B cells, elevated levels of CR1 associated with the protective allele enhanced biot-C3b processing with increased binding capacity ($p<0.05$) and hastened degradation kinetics.

Conclusion: Here, we show that increases in CR1 levels, both in solution and on primary cells, enhance the processing of biot-C3b multimers. These data suggest that the elevated B cell CR1 levels associated with the protective minor allele at rs1876453 will result in increased generation of C3dg-coated complexes that bind CR2. Further characterization of the downstream effects of these augmented signals through CR1 and CR2 are likely to provide mechanistic insights into the protective effect of rs1876453 as well as enhance the understanding of how the complement system modulates B cell activation.

Disclosure: B. M. Giles, None; **S. A. Boackle**, None.

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Clinical and Immunologic Correlates in Cocaine Users with Serum Anti-Neutrophil Cytoplasmic Antibodies. Christian Lood and Grant C. Hughes. University of Washington, Seattle, WA.

Background/Purpose: Illicit cocaine use is associated with the development of serum anti-neutrophil cytoplasmic autoantibodies (ANCA) and a variety of clinical manifestations. However, the mechanisms linking cocaine use and autoimmunity remain obscure. A causal link between cocaine use and ANCA is suggested by known immunostimulatory properties of cocaine, and its frequent contamination with levamisole, an immunomodulatory chemical. Here, we describe the immunologic and clinical characteristics of a series of cocaine users found to have extremely high-titer serum ANCA. The purpose of this report is to generate testable hypotheses regarding possible links between cocaine use and autoimmunity.

Methods: Chart review of 12 consecutive patients referred for rheumatologic evaluation at 2 tertiary referral centers from 2008 and 2013 for active cocaine use and high-titer serum ANCA. Clinical and immunologic parameters with complete or near-complete data sets were chosen.

Results: Results are summarized in the table below. The majority of subjects were female users of crack cocaine. Half presented with hematologic abnormalities, but only a minority (2) presented with purpura, a frequently reported manifestation. Interestingly, 2 patients presented with diffuse alveolar hemorrhage (DAH) not readily explained by vasculitis or cryoglobulinemia. 3 patients presented glomerular disease. One presented with supraglottic inflammation, and another with ischemic bowel. Arthralgia/arthritis was common.

All patients had high-titer P-ANCA reactivity with variable MPO and PR reactivity, suggesting reactivity against unmeasured neutrophil antigens (Ags). High-titer ANA was not observed in any patient, although some displayed reactivity against select ANA-associated Ags. Most patients showed serum IgM (but not IgG) cardiolipin and/or b2-glycoprotein reactivity, along with frequent lupus inhibitor positivity, again consistent with previous reports. Hypocomplementemia was frequent among those patients with active HCV infection. Finally, there were no clear correlations between route/nature of cocaine exposure and either clinical or immunologic features.

Conclusion: We observed a wide variety of clinical manifestations in cocaine users with high-titer serum ANCA reactivity. Immunologically, patients were more homogeneous, showing near-exclusive P-ANCA reactivity, frequent IgM (but not IgG) cardiolipin/b2-glycoprotein reactivity and a complete absence of significant titer ANA – suggesting loss of immune tolerance to a limited set of self-Ags. That MPO reactivity was variably present further suggests P-ANCA reactivity was directed against other perinuclear neutrophil cytoplasmic Ags. The nature of these Ags in cocaine-users, as well as the effects of cocaine and levamisole on neutrophils, are the subjects of ongoing investigation.

Age at presentation	42	49	52	49	28	46	54	35	53	39	43	46
Sex	F	F	F	F	F	F	F	F	M	F	F	F
Clinical manifestations												
Skin	P	–	–	–	–	P	–	–	–	U	U	U
Hematologic	Pan	Pan	Pan	N	N	–	–	–	–	–	–	N
Kidney	–	–	–	GN+	Amyloid	–	GN-	–	–	–	–	–
Lung	–	DAH	–	DAH	–	–	–	–	–	–	–	–
Other	–	–	–	–	Arth	GI isch.	–	Glottitis	Arth	Arth	Arth	Arth
Immunologic parameters												
ANCA IF (titer)	1:4,096	1:4,096	>1:65,536	>1:65,536	1:4,096	1:4,096	1:16,384	1:16,384	1:4,096	1:8,192	1:16,384	1:1,024
ANCA IF (pattern)	P,C	P	P	P	P	P	P,C,N	P	P	P	P	P
anti-PR3	+	+	+	–	–	+	+	–	–	–	–	–
anti-MPO	–	–	+	+	–	+	+	–	+	+	+	+
ANA IF (titer)	–	–	–	–	1:80	1:80	–	–	–	–	–	–
ANA-assoc. autoAbs	NT	–	–	SSA, RibP	Ch	dsDNA, Ch	SSA, Ch	dsDNA, Ch	dsDNA, Ch	–	–	NT
Anti-cardiolipin	IgM	IgM	–	IgM	IgM	NT	IgM	IgM	NT	IgM	IgM	NT
Anti-b2 glycoprotein	NT	IgM	IgM	IgM	–	NT	–	IgM	NT	IgM	–	NT
Lupus inhibitor	–	+++	+/–	–	+++	NT	NT	+/–	NT	+	–	++
Rheumatoid factor	–	–	–	–	–	NT	–	–	–	–	–	–
Hypocomplementemia	–	–	+	+	+	+	+	+	–	–	–	–
Cryoglobulinemia	–	+/–	+	–	–	–	+	–	NT	+	–	–
Active viral infection	–	–	HCV	HCV	HCV	HCV	HCV	–	HCV	–	–	–
Nature of cocaine exposure	C	C	P	P	IV	IV, C	IV, C	C	C	P	C	C

Abbreviations. NT, not tested, -, negative/normal, **Skin** (P, purpura; U, ulcers), **Hematologic** (Pan, pancytopenia; N, neutropenia), **Kidney** (GN+, glomerulonephritis – immune complex; GN-, glomerulonephritis – pauci-immmune), **Lung** (DAH, diffuse alveolar hemorrhage), **Other** (Arth, arthralgia/arthritis), **ANCA IF pattern** (P, perinuclear; C, cytoplasmic; N, nuclear), **ANA-associated Abs** (RibP, ribosomal P; Ch, chromatin), **Nature of cocaine exposure** (C, crack/smoked/inhaled; P, powder/inhaled; IV, intravenous)

Disclosure: C. Lood, None; **G. C. Hughes**, None.

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Revisiting RS3PE after Twenty Five Years: A Systematic Review of 250 Cases. Paras Karmacharya[1], Anthony Donato[2], Madan Aryal[1], Sushil Ghimire[1], Ranjan Pathak[1], Kalpana Shah[3], Pragya Shrestha[4], Ananta Subedi[5], Smith Giri[6], Leena Jalota[1], Dilli Poudel[1] and David George[2]. [1]Reading Health System, West Reading, PA, [2]Reading Health System, Reading, PA, [3]Mymensingh Medical College, Mymensingh, Bangladesh, [4]Nanjing Medical University, Nanjing, China, [5]Good Samaritan Hospital, Baltimore, MD, [6]University of Tennessee Health Science Center, Memphis, TN.

Background/Purpose: Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome is a rare inflammatory arthritis, first described by McCarty *et al* in 1985 characterised by abrupt onset of symmetrical distal synovitis, marked pitting edema of the dorsum of the hands and/or feet, absence of rheumatoid factor (RF), and favorable response to corticosteroids. The aim of our study is to further delineate the clinical and laboratory features, their correlation with various rheumatologic diseases and malignancies; and response to treatment.

Methods: A systematic electronic search of Medline, PubMed, and EMBASE for case reports, case series, and related articles of RS3PE published from 1985 till Feb 2014 was carried out. Statistical analysis was done using EXCEL and SPSS version 20.0, comparing categorical variables with Chi-square tests and frequencies of means via t-tests.

Results: Two hundred fifty cases of RS3PE were identified from 91 articles. RS3PE was found predominantly in males (70%) and the age at onset was 69±11 years. It was symmetrical in most cases (98%) and majority involved dorsum of the hands. Patients had a mean white cell count of 8,800/mm3 and elevated erythrocyte sedimentation rate (63±35mm/hr) and C-reactive protein (569±2687mg/dl). RF was negative in most cases (97%). Vascular endothelial growth factor (VEGF) was found to be significantly elevated (2–3 times above normal) in the 5 cases reporting it. Radiographic joint erosions were found in 2%. Most patients responded to low dose prednisone (16.39±10 mg/day). Prednisone dose was not associated with reported presence of malignancy (16 vs 18 mg, p=not significant). NSAIDs were useful in the acute setting in addition to the steroids. Other therapies such as hydroxychloroquine and methotrexate were used with variable efficacy. Concurrent malignancy was present in 13.6% (3.6% hematological, 10% solid organ malignancies). These patients were found to have more severe disease requiring higher dose of prednisone (16 vs. 22 mg). Other rheumatological diseases were present in 2.8%. CRP was significantly higher in those with underlying malignancy (3293 vs. 374, $p<0.001$), but ESR was not (65 vs 62 mm, $p=0.4$).

Conclusion: RS3PE seems to be a distinct entity rather than a subset of other rheumatologic diseases or a paraneoplastic syndrome. Although we cannot establish an association between malignancy and RS3PE from this study, clinicians should be aware that patients with concurrent cancer tend to have more severe presentation and resistance to low-dose steroids. The cost effectiveness of aggressive cancer screening for patients with RS3PE compared to age-appropriate screening will need further research. Serum VEGF levels may be associated with its pathogenesis and it might be useful for the diagnosis and monitoring of disease activity. Uncomplicated cases of RS3PE usually have an excellent prognosis.

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2188

Incidence and Mortality of Relapsing Polychondritis in the United Kingdom: A Population-Based Cohort Study. Nisha Hazra[1], Alex Dregan[1], Judith Charlton[1], Martin C Gulliford[1] and David P. D'Cruz[2]. [1]King's College London, London, United Kingdom, [2]Louise Coote Lupus Unit, Guy's and St Thomas' Hospital, London, United Kingdom.

Background/Purpose: To estimate the incidence, prevalence and mortality of Relapsing Polychondritis (RP), and to describe the clinical features of RP, in a large population.

Methods: All participants diagnosed with RP were sampled from the Clinical Practice Research Datalink (CPRD). Prevalence and incidence rates for 1990–2012 were estimated. Relative mortality of RP cases was estimated in a time-to-event framework using UK life tables for reference. A questionnaire validation study was performed.

Results: There were 117 participants with RP ever recorded. In the validation study, 47/58 (81%) of cases were confirmed by a physician and unconfirmed cases were excluded. The analysis included 106 participants (42 men, 64 women) diagnosed with RP. The mean age (range) at diagnosis in men was 55 (17 to 81) years and in women 51 (11 to 79) years. There was a median interval of 1.9 years from first symptom consultation to diagnosis. The incidence of RP between 1990 and 2012 was 0.71 (0.55 to 0.91) per million population per year. There were 19 deaths from any cause. There were 16 observed deaths eligible for survival analysis and 7.4 deaths expected for the UK population of the same age, sex and period. The standardised mortality ratio was 2.16 (1.24 to 3.51), $p<0.01$. Respiratory disease, cardiac conditions and cancer were the most frequent causes of death.

Conclusion: The incidence of RP may be lower than previously estimated and diagnostic misclassification and delay may be frequent. Mortality in RP is more than twice that of the general population.

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Multicentric Reticulohistiocytosis- Case Series from a Tertiary Care Center. Namrata Singh[1], Karolyn A Wanat[1], Mary Stone[1], Zuhair K. Ballas[2] and Jacob W. Ijdo[1]. [1]University of Iowa, Iowa City, IA, [2]Iowa City VA and the University of Iowa, Iowa City, IA.

Background/Purpose: Multicentric Reticulohistiocytosis (MRH) is a rare systemic inflammatory disease with skin nodules and arthritis. On skin or joint biopsy the hallmark is the presence of multinucleated giant cells and histiocytes with a ground glass appearance of the cytoplasm secondary to lipid inclusions. In the past solitary or multiple cutaneous reticulohistiocytoma without joint involvement were thought to be a separate entity because it only affects the skin, albeit the histopathology is identical. Due to the rarity of the disease little is known about pathophysiology or treatment. Anecdotal reports suggest that the use of TNF inhibitors and bisphosphonates may be beneficial. We wished to review the combined experience of this rare condition at a tertiary care institution.

Methods: After obtaining IRB approval, we searched the electronic medical records at the University of Iowa Hospital and Clinics (UIHC) to identify all patients with MRH or cutaneous reticulohistiocytoma seen between January 2000 and December 2013. The aims of this retrospective study are to describe the different treatments and outcomes and concomitant diagnoses in patients with MRH/cutaneous reticulohistiocytoma with or without joint involvement.

Results: We have identified 16 patients of which 4 had both skin and joint involvement and 12 cases with cutaneous involvement only that were diagnosed and treated at UIHC. All cases had a skin biopsy consistent with non-Langerhans reticulohistiocytosis. The age of patients with MRH ranged from 48–66 years old. Hands, wrists and knees were the most commonly affected joints. Treatments varied from intravenous infusions of zoledronic acid to TNF-inhibitors (adalimumab and etanercept) with varying responses. Two patients were treated with cyclophosphamide with improvement of disease. None of the patients were diagnosed with a malignancy.

Conclusion: Multicentric reticulohistiocytosis and cutaneous reticulohistiocytoma share identical histopathology but have different distribution and organ involvement. The pathogenesis and mechanism for different organ distribution of this systemic inflammatory disease is unknown. We report here the largest case series to date (16 cases) from a single academic institution in the last 13 years. It seems that MRH includes a wide spectrum ranging from no joint involvement to severe destructive arthritis. Follow up of patients with solitary and multiple cutaneous reticulohistiocytoma is warranted as joint involvement may develop with time.

Disclosure: N. Singh, None; **K. A. Wanat**, None; **M. Stone**, None; **Z. K. Ballas**, None; **J. W. Ijdo**, None.

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Features of Interstitial Lung Disease Associated with Connective Tissue Disease in a Spanish Southwest Cohort. Adela Gallego Flores[1], Carmen Carrasco Cubero[2], Raul Veroz Gonzalez[1], Luz Maria Mellado Narciso[1], Tamara Libertad Rodriguez Araya[1], Juan Jose Aznar Sánchez[1] and Eugenio Chamizo Carmona[1]. [1]Hospital de Mérida, Mérida, Spain, [2]Hospital de Merida, Mérida, Spain.

Background/Purpose: Diffuse interstitial lung disease (ILD) can be associated with connective tissue diseases (CTD), and can increase morbidity and mortality significantly. The predominant patterns of ILD associated with CTD are often nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP). UIP is more common in rheumatoid arthritis (RA). Pulmonary involvement in rheumatic diseases can be the first manifestation of these pathologies, preceding the onset of extrapulmonary symptoms. The presentation, clinical features and evolution of ILD associated with CTD can be variable, and therefore, it's important to improve the prognosis by early diagnosis and treatment. The aim of this study is to describe the clinical features, treatments and outcome of patients with ILD associated with CTD found in the General Hospital of Mérida.

Methods: We systematically collected all cases of ILD associated with CTD reported in the Rheumatology Department from January 2008 to January 2014. We included patients over 18 years old, who had a CTD and radiological diagnosis of ILD.

Results: We found 36 patients with ILD associated with CTD: 17 rheumatoid arthritis (RA), 10 scleroderma (ES), 6 antisynthetase syndromes (SAS) and 3 Sjögren's syndrome (SS). The mean age was 66.08 years, with a female predominance (2-1). History of smoking was present in 33.3% of the sample, and previous lung pathology in 18.7%. The diagnosis of CTD preceded the diagnosis of ILD in 58,3 % (21). The ILD patterns were: 17 NSIP (47,2 %), more frequent in ES (6 pac) and SAS (5 pac); and 19 UIP (52,8%), predominantly in RA. Thirty patients were treated with IV cyclophosphamide (CF) and 14 with rituximab (RTX). We observed a sustained response in 13 patients (10 NSIP and 3 UIP): 2 patients had received CF, 6 RTX, 4 CF+RTX, and 1 antiTNF. All RA patients were rheumatoid factor (RF) positive, 33,3 % with a title over 100. The predominant pattern was UIP (73,2 %). Methotrexate was used in 64.2% of patients and it was suspended at the diagnosis of ILD, although no cases of pneumonitis were found by this drug. Patients with ES, SAS and SS were younger at diagnosis (63.7, 62 and 64.3 years respectively) than RA patients (69,23 years) and a predominance of NSIP pattern (66.7, 80 and 66.6 % respectively). All these patients had negative RF. ANAs were positive in 100 % of SAS, with a predominance of anti Ro 52 and anti JO1 (3 and 4 patients) and 77.8% of ES and 66.6 % of SS. Two patients presented with poor responses to CF, one with UIP (ES) and 1 with NSIP (SAS), who died from infectious complications.

Conclusion: Usually the first manifestation of an ETC is due to the ILD, so it is advisable to maintain close cooperation with pneumologist. According to the literature, all patients with RA and ILD in our sample had RF+, as it usually occurs in rheumatoid extraarticular involvement. Otherwise, the UIP was the predominant pulmonary pattern. Rest of ETC associated ILD had a predominance of NSIP pattern and positive ANAs, especially anti Ro, and anti Jo1 in SAS. The RF was negative in all cases. Nine patients treated with RTX or sequentially with CF + RTX achieved better response. However, more studies need to be undertaken to reach better conclusions on the ways forward in treatment.

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2191

Intravenous Sodium Thiosulfate for Treatment of Refractory Calcinosis in Rheumatic Disease. Ross Thibodaux, Bahnsen Miller and Stephen Lindsey. Louisiana State University Health Science Center, Baton Rouge, LA.

Background/Purpose: Calcinosis, or dystrophic calcification, is a poorly understood, debilitating condition commonly manifested in connective tissue diseases such as scleroderma and polymyositis. Despite treatment of the rheumatologic disease, patients typically endure pain, infections, and decreased joint mobility. Therapeutic options for calcinosis, including coumadin, corticosteroids, diltiazem, probenecid, and colchicine, have shown little success, and treatment failure is common. Intravenous sodium thiosulfate (IV STS) is commonly used to treat calciphylaxis, and several mechanisms are proposed for its effects. Intriguingly, the chelating properties of IV STS form water soluble calcium-thiosulfate, which aids in dissolving deposited calcium

salts. Additionally, STS increases production of glutathione and nitric oxide, which improve endothelial function, vasodilate blood vessels, and decrease tissue ischemia. Physiologically, it is feasible to hypothesize that IV STS may treat refractory calcinosis, but data is not available regarding its use. The following patient chart reviews illustrate this hypothesis:

Methods: Patients #1, a 63 yo Caucasian female with limited scleroderma, and #2, a 46 yo Black female with polymyositis, suffer with recurrent calcinosis deposits of the skin and soft tissue causing pain and functional loss. Patient #1 reported severe pain and decreased mobility of her hands, and patient #2 reported deposits in her posterior thigh causing severe pain on sitting down and standing up. Aggressive therapy, including corticosteroids, colchicine, calcium channel blockers, and surgical interventions, yielded little improvement in pain and function. Each patient regularly reported pain scores of 8–9/10. After discussing IV STS therapy and obtaining consents, infusions were started at 12.5 grams over one hour weekly and advanced as tolerated. The maximum doses achieved in patients #1 and #2 were 15 gm/week and 25 gm/week, respectively. Infusions were continued weekly for approximately seven months. The infusions were tolerated well, and the most common patient reported side effects were nausea and blurry vision. The most common laboratory abnormality was a non-gap metabolic acidosis.

Results: As early as two weeks after starting the infusions, improvements in pain scores and softening of calcinosis deposits were observed. Both patients reported improved pain scores of 3–4/10 at two weeks and 0–1/10 at four weeks, and this persisted throughout therapy. At four weeks, functional status improved; specifically, patient #1 was able to grip a drinking glass without difficulty, and patient #2 was able to sit and stand with ease.

Conclusion: The clinical improvements observed may be attributed to the inherent properties of IV STS. Intravenous STS therapy is approved for calciphylaxis as well as cyanide and chemo-related toxicities. Although calcinosis is pathologically different from calciphylaxis, the physiologic properties of IV STS may contribute to the clinical improvements outlined above. These findings illustrate the potential of IV STS to treat painful calcinosis and the need for further studies of its use in rheumatic disease.

Disclosure: R. Thibodaux, None; **B. Miller**, None; **S. Lindsey**, None.

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Successful Therapy with Intravenous Sodium Thiosulfate for Adult Dermatomyositis Associated Calcinosis. Maria Constanza Florestano[1] and Mauricio Álamo[2]. [1]University of Valparaiso, Chile, Santiago de Chile, Chile, [2]Clinica Dávila, Santiago of Chile, Santiago of Chile, Chile.

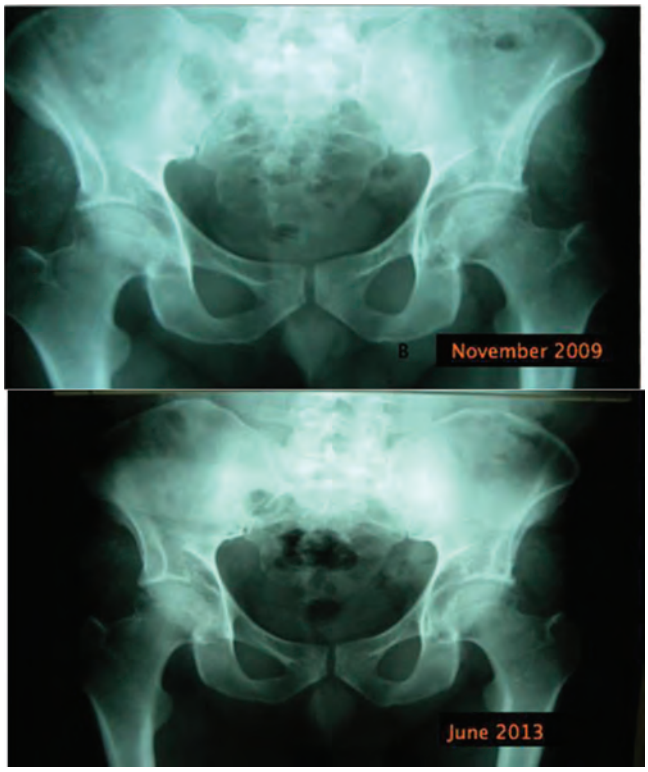
Background/Purpose: Calcinosis cutis is the deposition of insoluble calcium salts in skin or subcutaneous tissue. In cases related to CTD, presents with normal calcium/phosphorus metabolism, and is frequently associated with SSc and DM. Despite therapies available, treatment response is often poor.

Methods: The subject is a 38-year-old male that presented with classic DM in 2007. Secondary causes were ruled out. He was treated with corticosteroids and methrotrexate, with recovery of muscle strength and normalization of creatinkinase. In May 2008 without DM activity, he presented progressive painful subcutaneous calcifications in the axillary, gluteal and popliteal region, hands and back, confirmed by x-ray. Metabolic studies were normal.

Infliximab was initiated (200mg tid every 8 weeks totaling 5 doses), with poor response and progression of calcinosis.

Results: In August 2009 therapy with sodium thiosulfate was initiated: 50ml at 25% (12,5gr) in prolonged infusion over 60 minutes qid, with 10 doses per session. He received 17 monthly sessions, with a slow but significant regression of pain and calcinosis. Adverse effects were nausea, headache and infusion site pain, all mild. The patient has remained asymptomatic, without new calcinosis.

Conclusion: Sodium thiosulfate is a calcium chelating agent, with unknown mechanisms of action, such as the formation of soluble complexes, antioxidant, protector of the endothelium, vasodilator, antithrombotic, antimetaloproteases and increases endogenous calcification inhibiting proteins. Recent studies show benefit in dialysis-associated calcification. Its systemic use in the treatment of CTD associated calcinosis has been only communicated through case reports. Our patient presented with favorable outcome, with clinically significant reduction of calcifications and reduction of pain without major adverse effects, which might lead to a more effective therapy than available options.



Disclosure: M. C. Florestano, None; **M. Álamo**, None.

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Prevalence of Raynaud's Phenomenon and Nailfold Capillaroscopic Abnormalities in Fabry's Disease: A Cross-Sectional Study. Samuel Deshayes[1], Roland Jaussaud[2], Bernard Imbert[3], Olivier Lidove[4], Jean-Jacques Parienti[1], Nathalie Triclin[5], Laurent Auboire[6] and Boris Bienvenu[1]. [1]CHU Côte de Nacre, CAEN, France, [2]CHU de Reims, REIMS, France, [3]CHU, Grenoble, Grenoble, France, [4]Hôpital Croix-Saint-Simon, PARIS, France, [5]Association des Patients de la Maladie de Fabry, VENDRESSE, France, [6]UMR Imagerie et Cerveau, TOURS, France.

Background/Purpose: Fabry's disease (FD) is a lysosomal disorder leading to progressive systemic involvement, including neurologic and vascular. We hypothesize that the microangiopathy observed in FD could be documented, including at an early stage, by using nailfold capillaroscopy and assessing the presence of Raynaud's phenomenon (RP). The objective of this study was to measure the prevalence of RP and nailfold capillaroscopic abnormalities in FD.

Methods: This cross-sectional study included a standardized questionnaire and a nailfold capillaroscopy assessing previous reported patterns in FD (dystrophic and giant capillaries, avascular fields, irregular architecture, dilatation and density of capillaries, hemorrhage), and was conducted on 32 Fabry patients and 39 controls. Two independent blinded reviewers carried out the analysis of capillaroscopic photographs.

Results:

Table 1: Demographic and clinical characteristics of Fabry patients and controls

	Fabry patients	Control group	p value
n	32	39	
Age, mean ± SD	45,5 ± 13,8	48,2 ± 11,5	0.38
Sex-ratio (males/females)	0,46 (10/22)	1,6 (24/15)	**0.02**
Smoking, n (%)	1 (3)	4 (10)	0.37
Cannabis, n (%)	0 (0)	0 (0)	1
Hypertension, n (%)	8 (25)	4 (10)	0.1
Hyperlipidemia, n (%)	4 (13)	4 (10)	1
Diabetes, n (%)	1 (3)	3 (8)	0.63
Pain in the extremities, n (%)	28 (88)	0 (0)	**<0.001**
Enzyme replacement therapy, n (%)	25 (78)	0 (0)	**<0.001**

Table 2: Characteristics of patients suffering from Raynaud's phenomenon (RP)

	Fabry patients	Control group	p value
Males with RP, n (%)	5/10 (50)	0/24 (0)	**<0.001**
Females with RP, n (%)	7/22 (32)	2/15 (13)	0.27
Total with RP, n (%)	12/32 (38)	2/39 (5)	**<0.001**

Patients with FD and RP all suffered from pain in the extremities, whereas none in the control group did ($p = 0.011$). RP was concomitant or prior to the occurrence of pain in the extremities in 42% of Fabry patients. Significantly more ramified capillaries were observed in Fabry patients (12/32, 38%) than in controls (5/39, 15%, $p = 0.016$). No other statistically significant difference was observed by nailfold capillaroscopy.

Conclusion: This study is, to the best of our knowledge, the largest one assessing nailfold capillaroscopy and the presence of RP in FD. RP was highly prevalent in our series of Fabry patients (38%) and involved 50% of males. FD should thus be considered as a cause of secondary RP. RP was concomitant or prior to the occurrence of pain in the extremities in almost 50% of Fabry patients. It could be, at least in part, a causal factor of these pains. Secondary RP should lead to a screening for FD, especially in men. By extension, in high-risk populations (i.e. hypertrophic cardiomyopathy, dialysis patients, stroke in young people), the presence of ramified capillaries and RP should also be assessed.

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Blue Digit Syndrome: The Rheumatologist's Perspective. Helena Borrell[1], Javier Narváez[2], Eulalia Armengol[1], Milagros Ricse[1], Gloria Albert[1], Sergi Heredia[1], Andrea Zacarias[1], Carmen Gomez Vaquero[1] and Joan Miquel Nolla[1]. [1]Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain.

Background/Purpose: Blue or purple digit syndrome (or sign) is a cutaneous manifestation of multiple diseases that produce acute or subacute ischemic compromise in one or more fingers or toes. The most frequent cause of this syndrome is a reduction in arterial blood flow due to compromise or occlusion of small peripheral vessels, with preservation of the distal pulses.

The finger or toe affected by ischemia turns blue or violet and may develop necrosis. Whatever the cause, blue digit syndrome is a medical emergency requiring rapid diagnosis and specific treatment, given the risk of progression to irreversible necrosis. Only a very small percentage of cases need surgical intervention; the great majority of patients can be safely managed by medical therapy. Given their nature, medical cases should be managed by rheumatology services. Our aim was to evaluate the frequency, etiology and outcome in a series of patients admitted with blue digit syndrome in the Department of Rheumatology of the University Hospital of Bellvitge, a tertiary care teaching institution in Barcelona, Spain.

Methods: Ambispective cohort study of all patients admitted to our department with blue digit syndrome between 1990 and the first quarter of 2014.

Results: 41 patients (12 women and 19 men) were identified, with a mean age at diagnosis of 55 ± 18.8 years (range: 23–86 years). In 75% (31/41) of patients showed ischemic compromise of one or more fingers (being the second and third fingers most commonly affected), in 15% (6/41) were affected one or several fingers feet, and in 10% (4/41) remaining fingers and toes are affected simultaneously. The main etiologies are summarized in Table 1.

	Number of cases
Autoimmune diseases	11
Buerger's disease	3
Crioglobulinemia related to Sjogren's syndrome or HCV infection	7
Other primary systemic vasculitis or Vasculitis Associated with Systemic Disease (RA, SLE)	10
Systemic sclerosis (scleroderma)	1
Mixed connective tissue disease (MCTD)	
Pseudovasculitis	2
Cholesterol crystal embolism	2
Antiphospholipid syndrome	2
Paraneoplastic acral vascular síndrome	1
Hypothenar hammer syndrome	
Myeloproliferative síndromes (essential thrombocythemia)	1
Arteriosclerosis	1

Sixty per cent of patients (24/41) also had cardiovascular risk factors, the most common being active smoking and high blood pressure. Three of the patients with Buerger's disease were cannabis smokers.

Ninety per cent of patients (37/41) progressed well with conservative medical treatment and only 10% (4/41) required amputation (one case with arteriosclerosis and three patients with scleroderma).

Conclusion: In our experience, the most common causes of blue digit syndrome are systemic sclerosis and vasculitis. Differential diagnosis should also include pseudovasculitis, observed in a considerable percentage (17%) of these patients. Despite its severity, the ischemia usually responds to conservative medical treatment and amputation is unnecessary in most cases.

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Eculizumab Treatment of Malignant Atrophic Papulosis (Köhlmeier-Degos Disease): World Experience to Date. Aixa Toledo-Garcia, Lee S. Shapiro and Jessica F. Farrell. The Center for Rheumatology, Albany, NY.

Background/Purpose: Malignant atrophic papulosis (MAP) is an obliterative vasculopathy which presents with distinctive cutaneous lesions but can progress over months to years to systemic disease with a rapidly fatal course. Pathologic findings of involved tissues reveal dense deposition of membrane attack complex (MAC). Eculizumab is a monoclonal antibody which prevents activation of C5 to C5b and C5a. Within the past five years, based on immunopathology of the disease, eculizumab has been used in MAP. The relative importance of inhibition of formation of C5a and of inhibition of formation of MAC has not been determined.

Methods: A literature review and personal communication with physicians treating MAP patients throughout the World identified survivors and treatment failures (deaths). We attempted to identify those characteristics which distinguished the survivors from those who died.

Results: We identified eight patients who were treated with eculizumab at different stages of disease and in different circumstances. Among those eight patients, only three are alive, two for nearly five years since initiation of eculizumab. Two out of the three survivors presented with GI perforations and cardiovascular decompensation and were placed on eculizumab with an immediate and dramatic response. They did not receive systemic steroids. The third live patient presented with CNS involvement affecting the right eye requiring enucleation. Treprostinil was started after that event, temporarily suppressing cutaneous lesions, but because of gastrointestinal disease progression, eculizumab was later added. All other patients had received high doses of systemic steroids and may have had bacteremia at the time of treatment with eculizumab. In addition, one patient had very aggressive dermatomyositis overlap.

Conclusion: Our results suggest that eculizumab is a vital treatment option for patients with rapidly progressive systemic MAP. These individuals have a life expectancy of less than one year if left untreated. Treatment benefits likely arise both from the inhibition of C5a formation and from inhibition of formation of membrane attack complex. Treatment experience to date has been associated with high mortality, which we feel most likely is the consequence of increased risk of bowel perforation and septicemia in those who had already received systemic steroids. The avoidance of systemic steroid therapy is essential for a good outcome. Also, earlier identification of those at high risk for bowel perforation should improve outcome by reducing risk of bacteremia developing during treatment. We report long term survival of several individuals, but in none was eculizumab effective long-term as monotherapy.

Disclosure: A. Toledo-Garcia, None; **L. S. Shapiro**, None; **J. F. Farrell**, None.

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Treprostinil Use in Malignant Atrophic Papulosis (Köhlmeier-Degos Disease): Review of Worldwide Experience to Date. Lee S. Shapiro[1], Aixa Toledo-Garcia[2] and Jessica F. Farrell[2]. [1]Steffens Scleroderma Center, Saratoga Springs, NY, [2]The Center for Rheumatology, Albany, NY.

Background/Purpose: Malignant atrophic papulosis (MAP) is a rare thrombo-occlusive vasculopathy that presents with cutaneous only lesions but can progress after months or years to rapidly fatal systemic involvement. Until the very recent past, there were no reports of effective treatment of the systemic disease. A recent publication described successful use of treprostinil, a prostacyclin analog, in treatment of systemic MAP and in MAP-scleroderma-SLE overlap.

Methods: We performed a retrospective analysis of six patients using data collected from treating physicians worldwide through personal communications and our own experience. We also employed PUBMED for a literature search, which yielded 200 articles, using the keywords malignant atrophic papulosis and Degos disease. We evaluated outcomes of six MAP patients who were treated with treprostinil to identify discriminating factors between survivors and non-survivors.

Results: Among the six treprostinil MAP treated patients we know four are alive. Our first treprostinil treated patient was a female with scleroderma/SLE overlap who developed MAP lesions without systemic MAP involvement. As a result of pulmonary hypertension she was started on treprostinil. Cutaneous lesions subsequently resolved. We then treated a primary MAP male who had progressive CNS disease despite ongoing therapy with eculizumab. Within months after treprostinil was started MRI showed resolution of the lesions. Another male on eculizumab with disease progression was started on treprostinil with resolution of symptoms. The fourth patient was a female with biopsy proven MAP who already had CNS involvement with loss of vision in the right eye that led to enucleation. Treprostinil was started with temporary stabilization of symptoms. In the fifth patient, treprostinil was started after severe systemic involvement had taken place. She had GI perforations and CNS involvement which led to death. Eculizumab was not the first line therapy in patients four and five. Lastly, through a literature search we found a sixth patient who was a female on treprostinil for pulmonary hypertension related to systemic sclerosis. She then developed a restricted form of MAP while on treprostinil and is possibly alive, making a total of five patients alive today.

Conclusion: MAP is a rapidly fatal systemic disorder with a life expectancy of less than one year after development of visceral involvement. After comprehensive review of treprostinil use for MAP, we found the majority of patients treated (4/5) are still alive up to 42 months after initiation of therapy. All survivors with systemic disease are on dual therapy with eculizumab. The first patient with cutaneous MAP and scleroderma/SLE overlap had resolution of skin lesions on treprostinil alone. Patient six developed a restricted form of MAP while on treprostinil leading the authors to believe treprostinil limited the MAP vasculopathic process. The efficacy of treprostinil in MAP may be related not only to antithrombotic and vasodilatory effects but also to its reported ability to increase the number of endothelial progenitor cells.

Disclosure: L. S. Shapiro, None; **A. Toledo-Garcia**, None; **J. F. Farrell**, None.

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Malignant Atrophic Papulosis (MAP) Complicating Connective Tissue Diseases (CTDs). Aixa Toledo-Garcia, Lee S. Shapiro and Jessica F. Farrell. The Center for Rheumatology, Albany, NY.

Background/Purpose: Malignant Atrophic Papulosis (MAP) is a rare vasculopathy of unknown etiology commonly presenting with cutaneous lesions, but can progress to multisystem disease with a fatal outcome. MAP has been reported in the setting of other CTDs. Currently, there is a limited understanding of the association between CTDs and overlapping MAP. We theorize that MAP can present independent or complicating a vasculopathic CTD.

Methods: We performed a retrospective review on approximately 200 MAP cases obtained through a PubMed literature search, personal experience and communications with treating physicians worldwide. Cases were then analyzed for overlapping CTDs and further stratified for factors associated with disease outcomes.

Results: Of the 200 MAP cases, we identified 33 with an overlapping CTD diagnosis. These included: 11 SLE, 1 chronic cutaneous lupus erythematosus (CCLE), 3 SSc, 8 DM, 1 amyopathic DM, 6 APL syndrome (including patients positive for antibodies) 1 undifferentiated CTD, 1 granulomatous polyangiitis, and 1 RA. Patients with systemic MAP had fatal outcomes. Patients positive for APL antibodies with cutaneous MAP have survived but patients with APL syndrome and MAP have died. DM patients given steroids have died. In the setting of SSc there are two females who are alive and one male who died of fulminant SSc. Both females were on treprostinil for pulmonary hypertension.

Conclusion: MAP complicating CTD represents a challenging picture diagnostically and therapeutically. The presence of MAP may be a marker of more severe microvascular disease in those with SSc and DM and may be associated with worse prognosis because of concurrent steroid use. Steroids have been associated with increase risk of GI perforations and death. We believe MAP can present in the setting of a CTD in both cutaneous only and systemic forms. Histologically lupus and MAP can have similar findings but are not the same disease. MAP is not a systemic vasculitis but in its initial stages can present with an inflammatory infiltrate that later changes to the characteristic dermal necrosis and atrophic dermis with non-inflammatory endarterial thrombotic occlusion, leading to wedge-shaped skin necrosis, sclerosis and mucinosis. When MAP affects the CNS, the CNS pathology could have a perivascular lymphocytic infiltrate like a vasculitis, but MAP is not a vasculitis and seems to respond very poorly to steroids. Early intervention of systemic MAP can be lifesaving.

Disclosure: A. Toledo-Garcia, None; **L. S. Shapiro**, None; **J. F. Farrell**, None.

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The Aromatase Inhibitor Induced Musculoskeletal Syndrome: Is There a Potential Role of Osteoporosis Therapy and Menopause Timing? Zsolt Kulcsar[1], Clinton Morgan[2], Peter Kaufman[1], Jonathan Jones[3] and William Rigby[4]. [1]Dartmouth Hitchcock Medical Center, lebanon, NH, [2]Dartmouth Hitchcock Medical Center, Lebanon, NH, [3]Dartmouth-Hitchcock Medical Center, Lebanon, NH, [4]Dartmouth-Hitchcock Medical Center and Dartmouth Medical School, Lebanon, NH.

Background/Purpose: Aromatase Inhibitor (AI) therapy is the most effective hormonal treatment in post-menopausal estrogen receptor (ER) positive breast cancer. These patients may be seen by rheumatologists due to the side effects of arthralgias, termed aromatase inhibitor induced musculoskeletal syndrome (AIMSS), which limit their use in some patients. We evaluated factors associated with AIMSS and explored possible therapeutic options in a large cohort of patients.

Methods: We performed an IRB-approved retrospective review of breast cancer patients seen in the Norris Cotton Cancer Center clinics from April 2011 to January 2013. 378 patients were included in our chart review on the basis of taking an AI for breast cancer with follow up documented in the electronic health record. Statistical analysis was performed by chi squared test for dichotomous variables and students t-test for continuous variables.

Results: In our cohort 91% of patients were taking an AI as adjuvant therapy (9% for metastatic disease) with 41% (n=153) reporting new or worsening arthralgias after initiation of an AI. AIMSS was 42.5%(95%CI: 0.375 to 0.478) in the adjuvant and 22.7%(95%CI: 0.101 to 0.434) in the metastatic groups. The median time to symptom onset was 120 days. 2.1% (n=8) discontinued AI therapy due to AIMSS. There was no association with prior chemotherapy, baseline arthralgia, BMI, or statin use. We found an apparent increased risk of developing AIMSS with more recent menopause ($p=0.055$), and therapy in the adjuvant setting ($p=0.067$). We also note a potential association with baseline osteoporosis and osteoporosis therapies with lower rates of AIMSS ($p<0.05$; Table 2). Management options included temporary discontinuation of AI, switching between AI, and non-steroidal anti-inflammatory therapy (NSAIDs). Nearly all had improvement with temporary discontinuation, 24.5% improved after AI switch, and 84% had symptomatic benefit on NSAIDs.

Conclusion: The incidence of AIMSS in our review was 41%. Patients treated for metastatic disease may have a lower rate of AIMSS. Our cohort revealed that more recent menopause did seem to be a risk factor. Baseline osteoporosis and osteoporosis treatments have a potential association to be explored. Management options included switching between AIs, temporary discontinuation, and NSAID treatment. Updated analysis will be presented.

Table 1. Baseline patient characteristics

Characteristic	*N* (%)
Patients on AI therapy	375
Type of Aromatase Inhibitor Used	
Anastrazole	206 (54.9)
Letrazole	132 (35.2)
Exemestane	37 (9.9)
Baseline T-score by Dexa Scan	316
Normal (T-score 0 to −1.499)	101 (26.9)
Osteopenia (T-score−1.499 to −2.5)	173 (46.1)
Osteoporosis (T-score < −2.5)	41 (10.9)
Total patients experiencing AIMSS	153 (40.8)

Median time from start of AI to AIMSS in days	120
Average age at AI initiation [SD]	61.8[±10]
Attempted an AI switch	38 (24.8)
Reported improved symptoms after switch	27 (24.5)
Needed to stop drug temporarily due to AIMSS	52 (17.0)
Needed to stop drug permanently due to AIMSS	8 (2.1)

AIMSS = Aromatase Inhibitor Induced Musculoskeletal Syndrome, DEXA = Dual-energy x-ray absorptiometry

Table 2. Potential risk factors for the development of AIMSS.

Characteristic	N	(−)*Arthralgia* N (%)	(+)*Arthralgia* N(%)	p-value
Type of AI Used				
Anastrazole	204	112 (55.9)	92 (45.1)	0.19
Letrazole	131	83 (63.4)	48 (36.6)	
Exemestane	36	23 (64.9)	13 (36.1)	
Menopause timing				
LMP <5 years prior to AI start	151	79 (52.3)	72 (47.7)	0.055
LMP 5–10 years prior to AI start	40	23 (57.5)	17 (42.5)	
LMP >10 years prior to AI start	155	102 (65.8)	53 (34.2)	
Type of therapy				
Adjuvant	348	200 (57.5)	148 (42.5)	0.067
Metastatic	22	17 (77.3)	5 (22.7)	
Baseline T-score by DEXA Scan				
Normal (T-score 0 to −1.499)	112	55 (49.1)	57 (50.9)	0.049
Osteopenia (T-score −1.499 to −2.5)	171	96 (56.1)	75 (43.9)	
Osteoporosis (T-score < −2.5)	40	29 (72.5)	11 (27.5)	
On active osteoporosis therapy†				
(−) Therapy	218	118 (54.1)	100 (45.9)	0.03
(+) Therapy	127	81 (63.8)	41 (32.3)	

†Bisphosphonate/denosumab, LMP = Last menstrual period, AI = Aromatase Inhibitor, DEXA = Dual-energy x-ray absorptiometry

Disclosure: Z. Kulcsar, None; **C. Morgan**, None; **P. Kaufman**, Pfizer Inc, 5; **J. Jones**, None; **W. Rigby**, None.

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Intravenous Immunoglobulin Therapy for Secondary Hemophagocytic Lymphohistiocytosis: A Retrospective Study of 46 Patients. Bertrand Dunogué[1], Magdalena Gerin[2], Claire Larroche[3], Catherine Montagnier-Petrissans[4], Loïc Guillevin[1] and Luc Mouthon[1]. [1]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [2]Hôpital Jean Verdier, Bondy, France, [3]Hôpital Avicenne, Bobigny, France, [4]Groupe d'Expert AP-HP, Paris, France.

Background/Purpose: Intravenous Immunoglobulins (IVIg) have been reported as giving good results in infectious, but also auto-immune related forms of hemophagocytic lymphohistiocytosis (HLH), but only in case reports and small retrospective studies.

The objective of this study was to evaluate the use of IVIg as a treatment of secondary HLH in a wide hospital-based population.

Methods: A multicenter retrospective study of all cases of secondary HLH treated with IVIg in Parisian hospitals between January 2000 and December 2006.

Results: Of the 162 IVIg-treated patients for declared secondary HLH, 46 met the HLH-2004 criteria (29 male (63%), median age 47.5 yr (min 15; max 87)). Thirty-three (72%) had a history of immunodepression (AIDS (15/46), hemopathy (12/46), systemic disease (5/46)). Causes of HLH were: infection (18/46, 39.1%), malignant hemopathy (20/46, 43.5%), systemic disease (3/46, 6.5%), or undetermined (5/46, 10.8%). IVIg were administered mostly at 2 g/kg (25/46, 52%), with a median delay of 2 days (−12; 253) after diagnosis. One adverse event to IVIg administration occurred (shock). Other therapies included: corticosteroids (32/46, 70%), etoposide (10/46, 21.7%), chemotherapy (9/20 of the hemopathy group), anti-infectious agents (41/46, 89%), red blood cell (38/46, 82.6%) and platelet (30/46, 65%) transfusions. Twenty-nine patients (63%) required intensive care (respectively 10 (55.5%), 14 (70%), and 4 (80%) in the infection, hemopathy, and undetermined groups). Twenty-five patients (54.3%) died of HLH (respectively 6 (33.3%), 13 (65%), 2 (66.6%), and 4 (80%) in the infection, hemopathy, systemic disease, and undetermined groups), with a median time to death of 12 days (1; 142). While long-term survival was better in the infection group, short-term survival (at 20 and 60 days) and evolution of cytopenias did not vary significantly among the different etiological groups.

Conclusion: Short-term evolution of IVIg-treated HLH patients seems to be equally severe in all etiological groups, despite IVIg treatment. The impact of IVIg treatment on lower long-term mortality in the infectious-related group is hard to establish, owing to a higher long-term mortality related to the underlying cause in the hemopathy group.

Disclosure: B. Dunogué, None; **M. Gerin**, None; **C. Larroche**, None; **C. Montagnier-Petrissans**, None; **L. Guillevin**, None; **L. Mouthon**, None.

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Elevated Serum Ferritin Levels in Adult Inpatients As a Predictor of in-Hospital Mortality and Association with Macrophage Activation Syndrome. Matthew Mullen, Marcin Trojanowski, W. Winn Chatham and Bita Shakoory. University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Macrophage Activation Syndrome (MAS) is a syndrome similar to Familial Hemophagocytic Lymphohistiocytosis (HLH) characterized by increased proliferation and activity of T-cells and macrophages leading to massive systemic inflammation, multi-organ system failure, and often significant morbidity/mortality. Elevated serum ferritin is part of the diagnostic criteria for MAS/HLH and studies have shown that extremely elevated levels of serum ferritin have a high specificity for MAS. We sought to determine the correlation between significantly elevated ferritin levels (>2000) and in-hospital mortality as well as associated presence of MAS among adult inpatients.

Methods: Using Cerner EHR, patients were selected for study inclusion based on serum ferritin levels >2000 obtained during hospital admissions. Patients with hemoglobinopathy associated ferritin elevation were excluded. Patient charts during hospitalizations corresponding to the elevated serum ferritin were reviewed for mortality, diagnostic criteria for MAS, and treatment interventions. Patients were determined to have likely MAS based on either 1) whether current case definition criteria for HLH were met with at least 5 of the following: fever >100.4 degrees F, splenomegaly, two or more cytopenias (Hgb ^{9}/L, ANC $<1.0\times10^{9}$/L), hypertriglyceridemia (fasting >265 mg/dl), hypofibrinogenemia (meters checked, if they met 4 out of the 5 clinical/laboratory criteria: fever, splenomegaly, two or more cytopenias, hypertriglyceridemia, and hypofibrinogenemia or new coagulopathy defined as INR >1.5 if no fibrinogen level available.

Results: Patients were stratified into groups by peak serum ferritin levels: 2–5,000, 5–10,000, 10–20,000, and >20,000. Mortality rates were 70/370 (19%) in the 2–5000 group, 28/78 (36%) in the 5–10,000 group 11/40 (28%) in the 10–20,000 group, 15/39 (39%) in the >20,000 group. A total of 48 patients met the designated criteria for MAS, comprising 2% of patients in the 2–5,000 group; 6% of the 5–10,000 group; 30% of the 10–20,000 group and 61% of the >20,000 group. In addition to treatment with corticosteroids, 29 of these 48 patients received treatment with the IL-1 inhibitor anakinra, 10 of whom died during the hospitalization (in-hospital mortality of 34.5%); among the 19 patients with identified MAS who did not receive anakinra as part of their treatment there were 15 in-hospital deaths (in-hospital mortality of 79%).

Conclusion: Our results demonstrate a correlation between elevations in serum ferritin levels and increased in-hospital mortality in adult patients. Furthermore, our results suggest that at least part of the increased mortality observed in patients with extremely elevated serum ferritin is attributable to unrecognized or undertreated MAS.

Disclosure: M. Mullen, None; **M. Trojanowski**, None; **W. W. Chatham**, None; **B. Shakoory**, None.

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Haematological Complications in Rheumatic Diseases: Not Only Lymphomas. Elena Elefante[1], Chiara Baldini[1], Alice Parma[1], Elisa Cioffi[1], Francesco Ferro[1], Roberta Vagelli[1], Martina Rousseau[2], Rosaria Talarico[1], Sara Galimberti[2] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Hematology Unit, Pisa, Italy.

Background/Purpose: Several immunological abnormalities have been reported among patients affected by myelodisplastic syndrome (MDS). On

the other hand, a relatively limited number of studies have explored the occurrence of MDS during the course of systemic autoimmune diseases (AD) Aim of the study: to estimate characteristics and frequency of MDS among patients with systemic autoimmune diseases (AD).

Methods: A retrospective systematic search through the electronic health records of the patients admitted at our Rheumatology University Medical center from 2009 and 2014 was performed to select those patients with systemic AD and MDS. To refine the search the ICD-9-CM diagnosis code for MDS was utilized. Medical charts of eligible patients were retrieved and data were collected with regard to demographics, type of AD, AD duration, prior treatments, serum haematologic indices, bone marrow aspiration and biopsy data. Categorical variables were compared using chi square test and Fisher's test; continuous variables were compared using Student's t-test. A 2-tailed value of $p < 0.05$ was taken to indicate statistical significance.

Results: Out of the medical records of 3800 patients, we identified 23 patients with AD and MDS. Patients' mean (SD) age at the diagnosis of MDS was 65.3±12.6 years with a 1.09:1 female to male ratio. Rheumatoid arthritis and seronegative arthritis were the most frequent underlying AD condition (7/23, 30%) followed by large and small vessel vasculitis (7/23, 30%), Systemic Lupus Erythematosus (3/23, 13%), Sjogren's syndrome and myositis (2/23, 8%). Moreover, one patient was affected by Systemic Sclerosis and one by Behçet's syndrome. Anaemia (21/23, 91%) was the most common haematologic presenting abnormality followed by thrombocytopenia (9/23, 39%) and neutropenia (8/23, 35%). Three patients out of 23 presented with a trilineage cytopenia (13%). In the majority of the patients the diagnosis of MDS was subsequent to that of AD with a mean period between the two diagnosis of 4±6.3 yrs. Prior to MDS diagnosis, about one third of the patients received cytotoxic drugs, among which MTX was the most commonly prescribed (5/23, 22%) followed by azathioprine and cyclophosphamide (2/23, 8%). Regarding MDS, the most common diagnosis was refractory anemia with excess of blasts (RAEB I and II) (4/16, 25%) followed by sideroblastic anemia (2/16, 12%) and refractory anemia (2/16, 12%). A progression to leukemia was documented in 2 patients.

Conclusion: Our study is limited by its retrospective design. However, our results documented that the frequency of MDS in AD is not negligible and might be suspected especially in older patients presenting with "unexplained" cytopenias.

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Pilot Study of Tocilizumab in Patients with Erdheim-Chester Disease. Giulio Cavalli[1], Alvise Berti[1], Barbara Gulgielmi[1], Marco Gelpi[1], Riccardo Biavasco[1], Corrado Campochiaro[1], Alessandro Tomelleri[1], Marina Ferrarini[2], Maria Grazia Sabbadini[1] and Lorenzo Dagna[1]. [1]Vita-Salute San Raffaele University, Milan, Italy, [2]Department of Oncology, San Raffaele Scientific Institute, MIlan, Italy.

Background/Purpose: Erdheim-Chester disease (ECD) is a rare, systemic disorder of unknown etiology, characterized by tissue infiltration with CD68+, CD1a- foamy histiocytes. ECD is a chronic, debilitating disease without a gold-standard treatment. Growing evidence suggests that inflammatory cytokines and chemokines are responsible for histiocytes recruitment and activation. In particular, IL-6 is strongly expressed in ECD lesions and increased serum levels of IL-6 have been implicated in the systemic manifestations observed in ECD. We intended to assess the efficacy and safety of IL-6 blockade in the management of ECD.

Methods: We are conducting an open-label, single-arm, phase II, prospective, pilot study of tocilizumab (TCZ) in ECD (ClinicalTrials.gov NCT01727206; Eudra-CT 2012–003151–11). We planned to treat 6 patients (with contraindications or unresponsive to IFN-α) with the IL-6 receptor inhibitor TCZ 8 mg/kg monthly. We are collecting clinical, laboratory and radiological data, by means of total-body computed tomography (CT) scan, Technetium-99m methylene diphosphonate (99mTc-MDP) bone-scan, fluorine-18-2-fluoro-d-glucose positron emission tomography (FDG-PET), brain and cardiac Magnetic Resonance Imaging (MRI).We are also evaluating the levels of pro-inflammatory cytokines and chemokines before, during and after therapy, in order to evaluate whether TCZ treatment modulates the network of soluble factors involved in ECD pathogenesis. The Mann-Whitney U test for unpaired was chosen to compare data obtained from ECD patients and controls. The significance level was set at 0.05 (two-tailed p distribution).

Results: We present data from per protocol interim analysis on the first three patients who completed the protocol so far. All patients achieved significant improvement of all the clinical manifestations and laboratory findings (follow up at 12 months). Repeated whole-body CT scans, FDG-PET imaging and 99mTc-MDP bone scans confirmed the clinical and biochemical improvement in all patients. Cardiac MRI of the patient who had cardiovascular involvement showed an improvement of the diastolic function. However, the single patient who had CNS involvement had neurological progression, albeit showing improvement of other disease sites. During follow-up, we demonstrated a progressive reduction of circulating pro-inflammatory cytochemokines levels found to be increased before treatment. Plasma levels of IL-6 increased in all patients after the first infusion, as already shown in patients with other diseases treated with TCZ.

Conclusion: Although data must be completed with the final analysis and possibly by larger studies, the interim analysis of the trial support the efficacy and safety of IL-6 targeting with TCZ in ECD patients, in particular when CNS is not involved. Of interest, TCZ showed beneficial effects on ECD cardiovascular involvement, which has been shown to be poorly responsive to most currently available treatments.

References: Stoppacciaro A et al. Arthritis Rheum. 2006; Dagna L et al. Rheumatology (Oxford). 2010; Arnaud L et al. Blood. 2011.

Disclosure: G. Cavalli, None; **A. Berti**, None; **B. Gulgielmi**, None; **M. Gelpi**, None; **R. Biavasco**, None; **C. Campochiaro**, None; **A. Tomelleri**, None; **M. Ferrarini**, None; **M. G. Sabbadini**, None; **L. Dagna**, None.

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Adalimumab Therapy Improves Insulin Sensitivity in Non-Diabetic Psoriatic Patients: A 6-Month Prospective Study. Trinitario Pina Murcia[1], Raquel López-Mejías[1], Fernanda Genre[1], Begoña Ubilla[1], Susana Armesto[2], Marcos A. González-López[2], María del Carmen Gonzalez-Vela[3], Javier Llorca[4], Ricardo Blanco[5] and MA González-Gay[1]. [1]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, [2]Dermatology Division, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain, [3]Dept. of Pathology, Hospital Universitario Marqués de Valdecilla, Universidad de Cantabria, Santander, Spain, [4]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain, [5]Hospital Marques de Valdecilla, Santander, Spain.

Background/Purpose: psoriasis is a systemic inflammatory condition that shares similarities with other inflammatory immune disorders. In this context, patients with psoriasis are at an increased risk of cardiovascular death, as it has also been reported in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Accelerated atherosclerosis plays an important role in this regard. Several studies have reported a beneficial effect of anti-TNF-α therapy on the mechanisms associated with accelerated atherogenesis in inflammatory arthritis, including a beneficial effect on insulin resistance. In the present study, we aimed to prospectively evaluate for the first time whether the anti-TNF-α monoclonal antibody adalimumab may improve insulin sensitivity in patients with moderate-to-severe psoriasis.

Methods: A 6-month prospective study of adult patients (>18 years old) diagnosed with moderate-to-severe psoriasis who were put on treatment with adalimumab 40 mg every other week as a subcutaneous injection based on clinical indication (Spanish guidelines). Patients with history of cardiovascular or cerebrovascular disease, hypertension, diabetes, high body mass index (>35) or treatment during the previous 6 months before recruitment with corticosteroids or biologic therapies were excluded. At the time of enrollment and after six months of treatment, all patients were assessed for insulin sensitivity using the Quantitative Insulin Sensitivity Check Index (QUICKI). Laboratory tests including glucose, insulin, serum creatinine, ultra sensitive C-reactive protein [usCRP] and erythrocyte sedimentation rate [ESR], and data regarding disease activity (percent of body surface area affected [BSA], Psoriasis Area and Severity Index [PASI], Psoriatic Arthritis Screening and Evaluation questionnaire [PASE], Nail Psoriasis Severity Index [NAPSI] and physician′s global assessment of disease severity [PGA]) were also collected at the onset of the treatment (time 0) and at month 6.

Results: thirty-three consecutive patients (52% women), with moderate-to-severe psoriasis (mean BSA 37.2±16.4%, mean PASI 18±7.9) were recruited from the Dermatology outpatient clinics of the Hospital Universitario Marques de Valdecilla (Santander, Northern Spain). The mean age was 38.6±10.7 years. A statistically significant improvement (p-value 0.008) of insulin sensitivity (QUICKI) was observed after six months of treatment with adalimumab (QUICKI at time 0: 0.35±0.04 versus 0.37±0.04 at month 6).

Also a significant improvement ($p<0.05$) of ESR, usCRP, BSA, PASI, NAPSI, PGA and PASE was found at month 6.

Conclusion: in keeping with previous results on patients with chronic inflammatory rheumatic diseases, our findings show an improvement of insulin sensitivity following treatment with adalimumab. Therefore, adalimumab could have a beneficial effect on the mechanisms associated with accelerated atherogenesis in patients with psoriasis.

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2204

New Onset Vitiligo Under Biological Agents: A Case Series. Laure Mery-Bossard[1], Emmanuelle Mahé[2], Guillaume Charby[3], François Maccari[4], Nathalie Quilès[5], Ziad Reguiai[6], Abdallah Khemis[7], Anne Grasland[8], Morgane Guerin[9], Denis Jullien[10], Kelly Bagny[11], Jean Sibilia[12], Eric Toussirot[13] and Resopso Le CRI[14]. [1]Centre hospitalier, Mantes la Jolie, France, [2]Centre hospitalier, Argenteuil, France, [3]University hospital, Amiens, France, [4]Centre hospitalier, Saint Mandé, France, [5]University hospital, Marseille, France, [6]Uniersity hospital, Reims, France, [7]University hospital, Nice, France, [8]University hospital, Colombe, France, [9]University hospital, Lyon, France, [10]Hopital Edouard Herriot, Lyon, France, [11]University hospital, La Réunion, France, [12]University Hospital of Strasbourg, Strasbourg, France, [13]Rheumatology Department, Univesity Hospital, besancon, France, [14]University Hospital, Paris, France.

Background/Purpose: biological agents are now widely used in clinical practice for the treatment of chronic cutaneous, rheumatic and gastrointestinal inflammatory diseases. Various cutaneous lesions have been described in the patients receiving biologics (including infections, paradoxical psoriasis or tumoral lesion). The development of depigmenting disorders is an unusual event under these treatments.

Objectives: to describe the characteristics of patients developing a depigmenting skin disorder while receiving a biological agent for the treatment of psoriasis, inflammatory bowel disease (Crohn's disease or ulcerative disease-UC-) or inflammatory rheumatic disease (rheumatoid arthritis-RA-, ankylosing spondylitis-AS- or psoriatic arthritis).

Methods: a call for observations of new cases of vitiligo following biological (anti-TNFa, rituximab, tocilizumab, abatacept, anakinra, ustekinumab) treatment was sent to the members of the French specialist networks "Resopso" (dermatologist), "Club Rhumatismes & Inflammation" (CRI) (rheumatologist and internal medicine). The skin lesion has to be confirmed by a dermatologist. The current and previous biological agents were recorded.

Results: 12 cases were reported over a one year period: 9 M, 3 F, mean age 42 $\pm$13.5 years. The underlying condition requiring a biological agent was plaque psoriasis in 5 cases, AS in 3 cases, RA in 3 cases and an UC in 1 case. They all had new onset non segmental vitiligo (achromic patches involving the face, hands, chest or back), excepting leucotrichia (lashes and brows) in one case. 7 patients received adalimumab, 1 infliximab, 2 ustekinumab, 1 abatacept and 1 secukinumab. The mean delay between biologic agent initiation and development of hypopigmentated lesions was 15.9 $\pm$ 15.8 months (range 1–72). This was the first line of biologics in 10 cases. Laboratory testing ruled out thyroid disease. The biological agent was maintained in 7 cases, without worsening of hypopigmentated lesions while it was stopped or switched for the other cases. Excepting dermocorticosteroids, no specific treatment was given for the hypopigmentation.

Conclusion: experimental evidences have shown that TNF-α may play a role in the pathogenesis of non segmental vitiligo, and successful cases of vitiligo treated with TNFα inhibitors have been reported. However, a vitiligo may occur during a biological treatment. In this series, anti TNFα was the main (but not exclusive) biologic class associated with this event. Only non segmental vitiligo was observed allowing the maintenance of the treatment. Concomitant occurrence of vitiligo and inflammatory disease such as RA, AS or UC, although rare, has been described. On the other hand, the depigmentation may be related to the biological agent and could represent a new paradoxical side effect.

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2205

Management of Asymptomatic Coccidioidomycosis in Patients with Rheumatic Disease. Dominick Sudano[1], Varun Bhalla[1], Neil M. Ampel[2] and Jeffrey R. Lisse[1]. [1]University of Arizona, Tucson, AZ, [2]Southern Arizona Veteran's Affairs Medical Center, Tucson, AZ.

Background/Purpose: In the Southwestern United States, coccidioidomycosis (valley fever) is an endemic fungal infection which typically causes a self-limited pulmonary illness. Immunosuppressed patients, including those with rheumatic disease on disease-modifying antirheumatic drugs (DMARD) or biologic response modifiers (BRM), are at higher risk of more severe infection. The routine practice at our institution is to screen patients for coccidioidomycosis before initiating BRM therapy, and then annually thereafter. Through this process, patients have been identified with asymptomatic positive serologies. This is concerning as it indicates recent active infection in these patients. There are currently no guidelines regarding the management of these patients; however, a recent retrospective study proposed continuing antirheumatic therapy rather than stopping it.

Methods: A prospective chart review at two centers in Tucson, Arizona identified patients who developed coccidioidomycosis while on DMARD or BRM therapy. Several of those patient had asymptomatic illness as defined as a positive serology found on surveillance labs, not ordered in response to symptoms, and no concurrent signs or symptoms of active disease. Patients were seen at least once between 2007 and 2014. Review emphasized management of BRM/DMARD therapy, as well as antifungal therapy and duration.

Results: Seventy one patients with rheumatic disease were diagnosed with coccidioidomycosis, and 18 of them had positive serologies and no symptoms. Most (16/18) had rheumatoid arthritis, 1 had psoriatic arthritis, and 1 had dermatomyositis. Fifteen patients were identified during routine annual surveillance, and three were identified during pre-BRM therapy screening. Six patients were on BRM alone, 10 on BRM with a DMARD, and 2 on a DMARD alone. Three patients were also on prednisone. All but 6 patients continued their antirheumatic therapy. BRM therapy was restarted in 5 of these patients, most resuming therapy within 1 month of infection (range 0.5 – 12 mos). One did not resume therapy due to osteonecrosis of the jaw. Six patients received fluconazole, duration ranging from 6 to 73 months (median 30.5 mos). One of these patients remains on fluconazole for persistently positive serologies (42 mos.). Eight patients neither reduced antirheumatic therapy, nor started antifungal treatment. The median follow up is 31.5 months, and no patients have developed symptomatic illness. Three patients have been lost to follow up.

Conclusion: Positive coccidioidomycosis serologies are concerning in asymptomatic patient as they indicate a recent active infection. At present, the optimal screening interval and management in patients with rheumatic disease remains unclear. This series supports the management strategy of continuing BRM therapy in patients with asymptomatic disease. It also suggests that antifungal therapy may be reserved for those with persistently positive serologies. Future studies are needed to determine the significance of positive serologies in immunosuppressed patients with rheumatic disease, and the safest management strategy.

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2206

The Incidence of Zoster in Patients with Cutaneous Lupus Erythematosus and Dermatomyositis Is Increased Compared to the Average U.S. Population. Elizabeth S. Robinson[1], Joyce Okawa[2], Rui Feng[2], Aimee S. Payne[2] and Victoria P. Werth[1]. [1]Veteran Affairs Medical Center, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Herpes zoster is a common condition that causes significant pain and, often, post-herpetic neuralgia. In the United States the incidence of zoster per 1,000 person-years is 6 for people 60 years old and increases with age to nearly 11 for people above 80 years old. The incidence of zoster may be increased in autoimmune diseases, but few studies have looked specifically at cutaneous autoimmune diseases. Prior studies have found that the incidence of zoster in systemic lupus erythematosus is up to 32.5 per 1,000 person-years (n=303).

Methods: This retrospective chart review examined the incidence of zoster in patients with cutaneous lupus erythematosus (CLE) (n=105), dermatomyositis (DM) (n=66) and pemphigus vulgaris (PV) (n=55) seen in the practices of two dermatologists between April 1, 2013 and September 31, 2013. An incidence of zoster was determined according to a matched text search for "zoster" or "shingles" in all available electronic medical records.

The date of the zoster episode, if known, and the medications that the patient was taking at the time of the episode were recorded. The date of each patient's earliest visit with his dermatologist recorded in the electronic medical record until the most recent visit through September 31, 2013 or an episode of zoster, whichever was earlier, was used to estimate the time that the person had been at risk. The total number of incidences of zoster divided by the total number of person-years at risk was used to determine the incidence rate. Patients with a known history of zoster prior to the start of their electronic medical records and patients whose date of zoster was unknown were excluded from the incidence rate calculations.

Results: The incidence rate of zoster per 1,000 person-years was 23 for CLE, 54 for DM, and 7 for PV. The incidence rates were based on 6 episodes of zoster per 257.9 person-years for CLE, 8 episodes of zoster per 149.5 person-years for DM and 1 episode of zoster per 145.4 person-years for PV. Six CLE, 7 DM and 3 PV subjects had an unknown date of zoster. One CLE, 5 DM and 2 PV patients had zoster prior to the start of their electronic medical records. The mean (SD) duration of follow-up was 2.7 (1.7) years for CLE, 2.8 (1.7) years for DM and 3.0 (1.8) years for PV. The mean age (standard deviation) of each group was: 46.2 (14.1) for CLE, 55.9 (14.2) for DM and 56.1 (13.8) for PV. Fourteen of the 16 patients who had zoster were on immunosuppressive medications at the time of the zoster episode. Some patients were on more than one immunosuppressive therapy at the time of their zoster episode. The immunosuppressive medications were: mycophenolate mofetil (n=7), prednisone (n=6), methotrexate (n=1) and azathioprine (n=1). The majority of patients in each disease group were Caucasian women.

Conclusion: The incidence rate of zoster in CLE and DM is higher than in the average U.S. population at or above 80 years old. The incidence of zoster in PV is close to that of the average U.S. population of a similar age. The use of immunosuppressive therapies may play a role in the increased incidence of zoster in CLE and DM.

Disclosure: E. S. Robinson, None; **J. Okawa**, None; **R. Feng**, None; **A. S. Payne**, None; **V. P. Werth**, None.

2207

Decreased Bone Mineral Density in Patients with Ehler-Danlos Syndrome. Narender Annapureddy, Joel A. Block and Sonali Khandelwal. Rush University Medical Center, Chicago, IL.

Background/Purpose: Ehler-Danlos Syndrome (EDS) constitutes a heterogeneous group of inherited connective tissue disorders characterized by abnormalities of collagen I, III, V, or fibronectin, and primarily affects the joints, skin and blood vessel walls. Other "true connective tissue diseases", such as osteogenesis imperfecta, a disease of collagen I, are characterized by severe osteoporosis and fractures; however these are not commonly described in EDS. Two case-series have examined bone mineral density in EDS: seven EDS patients with early onset osteoporosis were described by Deodhar et al., and Coelho et al. described 4 young Portuguese EDS patients who had osteopenia/osteoporosis primarily of the lumbar spine. Here, we have examined bone mineral density in a cohort of EDS patients followed at the Rush Connective Tissue diseases clinic.

Methods: Patients with a diagnosis of EDS where identified from the Rush Inherited connective tissue disease repository from 2010- June 2014. The study was approved by the Institution's IRB and informed consent was obtained from each participant prior to inclusion in the study. Demographics were recorded and areal bone mineral density (BMD) was assessed by dual photon X-ray absorptiometry (DEXA).

Results: 14 subjects with a diagnosis of EDS underwent bone mineral densitometry. Baseline demographics are described in the table. Of the 14 patients, two were male. None had prior exposure to glucocorticoids, though two did receive such treatment after having undergone DEXA (one for mast cell degranulation syndrome and one for possible undifferentiated inflammatory arthritis). Of the 14 participants, 6 had osteopenia and 1 had osteoporosis. Those with low bone mineral density were older than those with normal density (43.0± 10.9 vs. 28.7± 10.8, p=0.03, mean ±S.D.). Mean T-score at the femoral neck in the patients with decreased BMD was -1.44 (−2.8 to -1.1) and the mean T-score at the Lumbar spine was – 0.97 (−2.7 to +1.2). 5 out of the 7 patients had both their femoral neck and Lumbar spine T-scores < -1.0 and the remaining 2 patients had femoral neck T-score < -1.0.

Table

Patient Characteristics (N=14)

Age, years (mean, S.D.)	35.9 (12.8) Range: 20–58
Female	12 (85 %)
Current Smokers	3 (21 %)
Patients with decreased bone mineral density	7 (50 %)
Osteopenia	6
Osteoporosis	1
Subtypes of EDS	2
Type 1	8
Type 3	1
Type 4	3
Non-characterized	
Mean T-score at the femoral neck in patients with decreased BMD	−1.44 (Range: −2.8 to −1.1)
Mean T-score at the Lumbar spine in patients with decreased BMD	−0.97 (Range: −2.7 to +1.2)

Conclusion: Our data suggest that EDS may be associated with decreased BMD. Patients with EDS with decreased BMD were more likely to be older than EDS patients with normal BMD. Nevertheless, the mean age of those patients is still lower than when traditional screening for osteoporosis is considered. If these findings are replicated in other cohorts, then it would suggest that EDS should be considered an indication for early BMD screening. Nonetheless, the clinical significance of these findings remains unclear, as does the role of potential therapy to prevent or treat such low BMD.

Disclosure: N. Annapureddy, None; **J. A. Block**, None; **S. Khandelwal**, None.

2208

Ovarian Reserve Alterations in Premenopausal Women with Rheumatoid Arthritis, Behcet's Disease and Spondyloarthritis – Impact on Anti-Muellerian Hormone Levels. Joerg C. Henes[1], Julia Froeschlin[2], Andre Taran[3], Theodoros Xenitidis[1] and Melanie Henes[4]. [1]University Hospital Tuebingen, Tuebingen, Germany, [2]University Tuebingen, Tuebingen, Germany, [3]University Hospital for Women Tuebingen, Tuebingen, Germany, [4]University Hospital for Women, Tuebingen, Germany.

Background/Purpose: Recent publications showed a negative influence of systemic lupus erythematosus and antiphospholipid antibody syndrome on female ovarian reserve (OR). Other authors did not find a significant impact of Crohn's disease or early rheumatoid arthritis (RA) on anti-Muellerian hormone (AMH) levels. This study aimed to investigate the potential effect of Behcet's disease (BD), RA and spondyloarthritis (SpA) on OR, as reflected by serum AMH levels.

Methods: Serum samples of 33 RA, 32 SpA and 30 BD patients without previous cytotoxic – especially cyclophosphamide – treatment were analyzed and compared to age matched, healthy controls. AMH was quantified using a standard ELISA with standard value 1–8μg/l; values $< 1\mu$g/l defined as reduced, $< 0.4\mu$g/l as severely reduced fertility. All patients gave written informed consent and filled out a questionnaire on menstrual irregularities, lifestyle, pregnancy outcomes and contraception. For statistical analysis SPSS 19.0 was used and $p<0.05$ considered statistically significant.

Results: The median age was 26, 28.5 and 33 years and the disease duration was 6, 5.9 and 7 years for RA, SpA and BD patients, respectively. Compared to healthy controls the patients had significant reduced AMH levels with a median value for RA of 1.83 (control. 2.44; p=0.009), SpA 1.46 (control: 2.3; p=0.013) and for BD of 1.08 (control; 1.93; p=0.007). The mean number of children was 0.4 for RA, 0.5 for SpA and 1.0 for BD patients. The HLAB51 status and origin in BD patients were not associated with significant reduced AMH levels.

Conclusion: This is the first study to show the reduced OR in patients with RA, SpA and BD. Together with the findings in SLE we conclude a negative influence of chronic rheumatic diseases on OR.

Disclosure: J. C. Henes, None; **J. Froeschlin**, None; **A. Taran**, None; **T. Xenitidis**, None; **M. Henes**, None.

2209

Novel Biomarkers of Extracellular Matrix Remodeling in Inflammatory Bowel Disease: Different Patterns of Gut Injury in UC and CD. Joachim Høg Mortensen[1], Line Elberg Godskesen[2], Michael Dam Jensen[2], Lone Gabriels Klinge[2], Jens Kjeldsen[2], Aleksander Krag[2], Morten Karsdal[3] and Anne C. Bay-Jensen[4]. [1]Cartilage Biomarkers and Research, Nordic Bioscience, Købehavn, Denmark, [2]Odense University Hospital, Odense, Denmark, [3]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [4]Cartilage Biomarkers and Research, Nordic Bioscience, Herlev, Denmark.

Background/Purpose: About 10 % of patients with IBD have symptoms that match both Crohn's disease (CD) and ulcerative colitis (UC), termed

inflammatory bowel disease unclassified (IBDU). The hallmark of both diseases is inflammation, which leads to excessive extracellular matrix (ECM) remodeling and release of specific protein fragments, called neoepitopes. However, the pathophysiology, clinical manifestations and treatment is still different among the two diseases. Consequently, to ensure the best possible patient care, accurate diagnosis is essential. Therefore, we speculate that the biomarker profile panel of UC and CD represents a heterogeneous expression pattern, and thus these biomarkers will be a valuable non-invasive diagnostic tool to aid the diagnosis of UC and CD.

Methods: 37 patients with active CD (>150 CDAI) of which 24 had inflammation in colon or colon/ileum, and 56 patients with active UC (St. Marks score >2) were included in this study. All patients had standardized work-up at inclusion, including medical history, physical examination, endoscopy, C-reactive protein. Biomarkers of degraded collagens I, III-IV (C1M, C3M, and C4M), collagen type 1 formation (PINP) and citrullinated and MMP-degraded vimentin (VICM) secreted by activated macrophages were evaluated by a competitive ELISA assay system. Receiver operator characteristics (ROC) curve analysis was carried out to evaluate the discriminative power of the biomarkers. The combination of biomarkers was investigated by a backward logistic regression model.

Results: The serum level of the biomarkers, C3M and VICM, was significantly different between patients with either active UC or CD. C3M was significantly elevated in patients with UC compared to CD ($P=0.039$). In contrast, VICM was highly elevated in patients with CD compared to UC ($P<0.0001$). The biomarkers C3M and VICM showed the highest discriminative value were seen (ROC analysis). The biomarkers were adjusted for demographic variations (age, gender, BMI, and smoking). VICM showed an AUC of 0.76 ($P<0.0001$) (CD vs. UC), while C3M showed a more modest AUC of 0.62 ($P=0.039$) (CD vs. UC) (table 1). Furthermore a logistic regression model was developed to find the best combination of the biomarkers. The best combination of biomarkers was VCIM, C3M, and C4M with an AUC of 0.85 ($P<0.0001$) (table 1). When including only the patients with colon and ileocolonic inflammation the AUC was improved to 0.92 ($P<0.0001$) (table 1).

Conclusion: These data provide new insights into differences in mechanisms of gut injury in CD and UC. We observed a clinical relevant potential of VICM and C3M as novel biomarkers to differentiate between UC and CD. This suggest that activated macrophages (VICM) and MMP mediated destruction of type III collagen (C3M) are essential disease drivers in IBD, and may discriminate these pathologies.

Table 1: The AUC, sensitivity, specificity, and percentage of cases correctly classified of each ROC-analysis

	AUC (CI)	Sensitivity	Specificity	Percent of cases correctly classified
Biomarkers: CD vs. UC				
C3M	0.63 (0.52–0.73)	23.6%	80.0 %	66.3%
C3M*Adjusted*	0.69 (0.57–0.78)	48.9%	80.0 %	63.0%
VICM	0.76 (0.66–0.85)	64.9%	83.6 %	69.6%
VICM*Adjusted*	0.77 (0.66-0.86)	64.9%	86.67%	76.8%
[C3M, VICM, C4M]	0.85 (0.75–0.91)	78.4	87.3	83.7%
[C3M, VICM, C4M] *Adjusted*	0.85 (0.75–0.92)	73.0	91.1	80.5%
[C3M, VICM, C4M-) *Adjusted* (colon and ileocolonic inflammation)	0.92 (0.83–0.97)	79.2	93.3	88.4%

CI: Confidence interval
*: The logistic regression model was adjusted for age, BMI, tobacco smoking, and gender

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ACR/ARHP Poster Session C
Muscle Biology, Myositis and Myopathies: Immunological Aspects of Inflammatory Myopathy
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

2210

Redefining Dermatomyositis: Description of New Diagnostic Criteria That Differentiate Pure Dermatomyositis from Overlap Myositis with Dermatomyositis Features. Marie-Pier Payette[1], Yves Troyanov[1], Ira N. Targoff[2], Jean-Pierre Raynauld[1], Suzanne Chartier[3], Jean-Richard Goulet[1], Josiane Bourré-Tessier[1], Eric Rich[1], Tamara Grodzicky[1], Marvin J. Fritzler[4], France Joyal[5], Martial Koenig[5] and Jean-Luc Senécal[1]. [1]Division of Rheumatology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, [2]Veterans Affairs Medical Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]Division of Dermatology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, [4]Mitogen Advanced Diagnostics Laboratory, Faculty of Medicine, University of Calgary, Calgary, AB, [5]Division of Internal Medicine, Centre Hospitalier de l'Université de Montréal, Montreal, QC.

Background/Purpose: Dermatomyositis (DM) is a major form of autoimmune myositis (AIM). The characteristic DM rash (Gottron's papules, heliotrope rash) and perifascicular atrophy (PFA) at muscle biopsy are regarded as diagnostic. However, new concepts are challenging the definition of DM. A modified Bohan and Peter clinical classification (mcBP) of AIM was proposed. In the mcBP, overlap features in presence of myositis allow a diagnosis of overlap myositis (OM), irrespective of the presence or absence of the DM rash or PFA. Therefore, our objective was to further differentiate DM from OM.

Methods: Using the mcBP, we performed a longitudinal study of 100 AIM patients, including 44 patients with a DM phenotype, defined as DM rash, and/or DM-type calcinosis and/or PFA at biopsy. Overlap features, DM rash course, adermatopathic DM (aDM), cancer and survival were evaluated, as well as DM-specific and overlap autoantibodies by protein A immunoprecipitation.

Results: Two subsets were identified in patients with a DM phenotype: *pure DM* (n=24) and OM with DM features, or *OMDM* (n=20). In pure DM, the rash of DM was the first disease manifestation, was always present at the time of myositis diagnosis, and was chronic and associated with a high cutaneous score. Concurrent heliotrope rash and Gottron papules (PPV 91%), as well as the V-sign and/or shawl sign (PPV 100%), were diagnostic of pure DM. Anti-Mi-2, anti-MJ and anti-p155 autoantibodies were restricted to pure DM (PPV 100%) and present in 50% of patients. 21% of patients had cancer. Fifteen-year survival was high (92%).

In contrast, in OMDM the first manifestation was proximal muscle weakness or other skeletal muscle-related complaints. The DM rash appeared at diagnosis or followup and was associated with a low cutaneous score. aDM, absent in pure DM, predicted OMDM (PPV 100%). Autoantibodies, found in 70% of patients, included anti-Jo-1, anti-PL-7, anti-PM-Scl, anti-U1RNP and anti-U5-RNP. OMDM was not associated with cancer but 15-year survival was only 65%.

PFA occurred as commonly in OMDM (n=6/20 patients, 30%) as in pure DM (n=4/24, 17%). These 6 OMDM patients had aDM at the time of myositis diagnosis. Only one of them developed a DM rash at follow-up, emphasizing the lack of specificity of PFA for pure DM.

Conclusion: Using the mcBP allowed identification of OMDM, a new clinical subset of OM. Furthermore, identification of OMDM allowed in turn recognition of pure DM as a new entity, distinct from OMDM or from OM without DM features. However, the absolute specificity of a DM rash and PFA for the diagnosis of pure DM was lost.

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2211

Epidemiologic and Clinical Features of Patients with Adult and Juvenile Dermatomyositis, Polymyositis and Inclusion Body Myositis from Myovision, a National Myositis Patient Registry. Abdullah Faiq[1], Payam Noroozi Farhadi[1], Nastaran Bayat[1], Mikaela Chase[1], Anna Jansen[1], Karen Malley[2], Jesse Wilkerson[3], Kathryn Rose[4], Caroll Co[4], Lukasz Itert[5], Anne Johnson[5], Richard Morris[4], Christine Parks[6], Edward H. Giannini[5], Hermine I. Brunner[5], Frederick W. Miller[1], Bob Goldberg[7] and Lisa G. Rider[1]. [1]Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD, [2]Malley Research Programming, Inc, Bethesda, MD, [3]Social and Scientific Systems, Inc., Research Triangle Park, NC, [4]Social and Scientific Systems, Inc., Durham, NC, [5]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [6]NIEHS, NIH, Research Triangle Park, NC, [7]The Myositis Association, Alexandria, VA.

Background/Purpose: The myositis syndromes are rare systemic autoimmune diseases, little is known about their epidemiology. We describe the demographics and comorbidities of patients in a large myositis patient registry.

Methods: Between December 2010 and July 2012, nine thousand two hundred eleven questionnaires were mailed to patients with adult and juvenile dermatomyositis (DM, JDM), polymyositis (PM, JPM), inclusion body myositis (IBM), and other forms of myositis in the US and Canada that had registered with The Myositis Association or learned of the survey from other sources. The questionnaire queried demographics, clinical features, environmental exposures, and quality of life. The response rate was 24.2% (N=2209). One thousand two hundred sixty six participants were re-contacted to resolve missing and discrepant responses.

Results: One thousand eight hundred six patients (708 DM, 483 PM, 466 IBM, 139 JDM, 10 JPM) met probable or definite Bohan and Peter criteria or possible Griggs criteria and were included in the analyses. The median date of diagnosis was March 2002 with a median disease duration of 9.2 yrs. IBM patients were older at diagnosis (median 62.3 years) than PM and DM (47.8 and 46.4 years, p=0.009). Most patients were female (84% DM, 75% PM, 78% JDM), except for IBM (41%, p<0.0001). Most patients were non-Hispanic Caucasian (86% DM, 82% PM, 94% IBM, and 88% JDM); blacks were more frequent among PM patients (12%) than DM (5%), IBM (3%), or JDM (0.7%, P<0.003 for all). Twenty-two percent of patients reported having a graduate degree and 28% had a college degree. The majority of DM and PM patients were diagnosed by an adult rheumatologist (59% and 52%), whereas IBM patients were more often diagnosed by a neurologist (76%, p<0.005) and JDM patients by a pediatric rheumatologist (48%, p<0.016). DM and JDM frequently had skin rashes as a major clinical manifestation (85% vs. 14% PM, 6% IBM, p<0.0001 for all); DM most often had arthritis (49% vs. 34% PM, 21% IBM, p< 0.0001); DM and PM were more likely to have lung disease (31% vs. 15% IBM, p < 0.0001); and DM most often had fever (23% vs. 17% PM, 5% IBM, p<0.008 for all). The overall age-, gender-and race-adjusted prevalence rate of self-reported diagnosis with another autoimmune disease was 23%, with an increased odds of RA (OR 2.1) and autoimmune thyroid disease (OR 2.5) in DM and PM vs. IBM. The odds of SLE were higher in DM vs. IBM (OR 4.4). Multivariable modeling showed female gender (OR 2.5), arthritis (OR 1.7) and rashes (OR 1.5) to be risk factors for an associated autoimmune disease in DM. The age-, gender- and race-adjusted self-reported prevalence of malignancy, excluding skin cancers, within 2 years of myositis diagnosis was 3.8% of DM, 2.1% of PM and 2.5% of IBM patients. Age was a risk factor for malignancy in DM (OR 1.1) and dysphagia was protective in IBM (OR 0.39).

Conclusion: A nationwide registry of myositis patients has been established with similar demographic and clinical features to other myositis cohorts. Our results suggest that there is considerable variation in the demographic and comorbidity profiles of patients by myositis subtype. MYOVISION registry data will be useful in further clinical and epidemiological studies.

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Serum Adipokines in Dermatomyositis: Correlation with Risk Factors Associated to Cardiovascular Diseases and Metabolic Syndrome. Marilda Guimarães Silva, Suzana Beatriz Veríssimo de Mello and Samuel Katsuyuki Shinjo. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: Adipokines are a group of cytokines produced by adipose tissue, which include adiponectin, resistin and leptin. The adiponectin has anti-diabetic, anti-inflammatory and anti-atherogenic effects, whereas leptin and resistin are considered atherogenic and pro-inflammatory associated with peripheral insulin resistance. Adipokines have been evaluated in many systemic autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis. However, there is no description of these cytokines in patients with dermatomyositis (DM), who have a high prevalence of risk factors to cardiovascular diseases and metabolic syndrome.

Methods: This one-center and cross-sectional study included 78 adult patients with DM (Bohan and Peter criteria, 1975), in the period of 2011 to 2013. As a control group, 120 healthy individuals were included in the same period. Metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program - Adult Treatment Panel III (NCEP/ATP III). Blood samples were collected in fasting and processed immediately for further adipokines analysis, basing on the multiplex assay according to the manufacturer's protocol Millipore.

Results: Age, gender and ethnicity were comparable between patients with DM and control (*P*0.05). The mean duration of DM was 4.9±5.6 years. DM patients compared to the control group, showed a high prevalence of risk factors for cardiovascular disease: hypertension, diabetes mellitus, family history of cardiovascular disease, increased body mass index, waist circumference, serum triglycerides, insulin and glucose levels, lower serum levels of HDL cholesterol, and higher frequency of metabolic syndrome ($P<0.05$). Moreover, we noted higher serum adiponectin concentration [73.5 (56.1 to 101.9) pg/mL *vs.* 60.4 (43.2 to 81.2) pg/mL, $P=0.009$] and lower leptin [3.7 (0.2 to 25.5) pg/mL *vs.* 15.4 (6.9 to 29.0) pg/mL, $P<0.001$] in patients with DM compared to control group. Serum resistin was similar in both groups. Further analysis showed that adiponectin was significantly correlated with serum levels of HDL cholesterol (rho=0.307, $P=0.006$) and negatively correlated with serum creatine kinase (rho=-0.223, $P=0.050$), aldolase (rho=-0.271, $P=0.016$), triglycerides (rho=−0.313, $P=0.005$) and metabolic syndrome (rho=−0.238, $P=0.036$) in patients with DM. Leptin correlated positively with serum insulin level (rho=0.305, $P=0.010$), interleukin-6 (rho=0.24, $P=0.040$) and C-reactive protein (rho=0.282, $P=0.010$).

Conclusion: The results of this study showed high serum adiponectin and low serum leptin in patients with DM which may mitigate the inflammatory response. Further studies are necessary to assess the possible role of these adipokines in patients with DM.

Disclosure: M. G. Silva, None; **S. B. V. D. Mello**, None; **S. K. Shinjo**, None.

2213

Gene Expression Profiling of T Helper Subsets in Blood and Affected Muscle Tissues Reveals Differential Activation Pathways in Patients with Juvenile and Adult Dermatomyositis. Consuelo Lopez de Padilla[1], Molly S. Hein[1], Cynthia S. Crowson[1], Richard S. Pendegraft[2], Erik J. Peterson[3], Emily Baechler[3] and Ann M. Reed[1]. [1]Mayo Clinic, Rochester, MN, [2]Biomedical Statistics and informatics, Rochester, MN, [3]University of Minnesota, Minneapolis, MN.

Background/Purpose: The molecular and cellular basis for juvenile and adult dermatomyositis (JDM and ADM) presumably is similar. However, important differences in the clinical features, outcome and associated disorders suggest that different mechanisms, at least partially, may be involved. The aim of this study was to identify shared and differential molecular pathways in peripheral blood and affected muscle between JDM and ADM, and examine their association with disease activity.

Methods: Cytokine mRNA expression profiles were analyzed in paired PBMCs and muscle specimens in 7 JDM and 5 ADM. In addition, cytokine mRNA expression in blood in 21 ADM and 26 JDM subjects over 2 study visits (baseline and 6 months visit). Disease activity was also measured by IMACS core set measures and other validated tools. Expressions of type 1 helper (Th1)-related genes (*IL-2, IL-12β, IFN-γ, TBX21, STAT4, TNFα, TNFSF1*), Th2 (*IL-4, IL-5, IL-9, IL-10, IL-13, IL-12p70, STAT6, GATA3, IRF4*), Th17 (*IL-1β, IL-6, IL-21, IL-23A, IL-17A, IL-17D, IL-17F, IL-27, TGF-β1, STAT3, RORC*), Tregs (*FoxP3+, STAT5β*), Th22 (*AHR, IL-22*) and Tfh (*BCL6*), and of innate-related genes (MIP-1α/CCL3, CCL8/MCP2, IFNα2, IFN-β and IL-8) were examined using a custom RT2 Profiler PCR Array. Wilcoxon tests, Spearman correlations and paired t-tests were used for analysis. All reported p-values were adjusted for multiple comparisons using the Bonferroni method.

Results: Expressions of cytokine mRNAs for *IL-23A* (p<0.001), *IL-6* (p<0.001), *IL-17F* (p=0.022), *IRF4* (p<0.001), and *BCL6* (p=0.014) were significantly up-regulated in blood of JDM compared to ADM. In the muscle, however, there were no significant differences between JDM and ADM, probably due to the small sample sizes. We also compared the gene expression profiles in paired blood samples and muscle biopsies among 12 patients (7 JDM and 5 ADM). Expressions of *AHR* (p=0.007), *IFN-γ* (p=0.054), *IL-23A* (p=0.050), *STAT5β* (p=0.022), *TBX21* (p=0.047), *TGF-β1* (p=0.036), *TNFSF1* (p=0.011), CCL3 (p=0.022) were found at higher levels in muscle compared to blood of JDM/ADM patients, the majority of these genes were Th1 and Th17 pathway-associated genes. Finally, among 16 patients with samples tested at baseline and 6 months visits, there were no significant correlations between changes in gene expression profiles in blood and disease activity measures over time.

Conclusion: We observed differences in gene expression profiling in blood between new onset JDM and ADM, many of the overexpressed genes in JDM were Th17-cytokine genes. The upregulation of Th1 and Th17-related genes was apparent in muscle compared to blood in JDM/ADM patients and may reflect activation of different Th pathways between muscle and blood.

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2214

Power Doppler Ultrasonography for Detection of Abnormal Fascial Vascularity: A Potential Early Diagnostic Tool in Fasciitis of Dermatomyositis. Ken Yoshida[1], Makiko Nishioka[1], Satoshi Matsushima[1], Kensuke Joh[2], Yosuke Oto[1], Yoshiga Masayuki[1], Kazuhiro Otani[1], Haruyash Ito[1], Kenichiro Hirai[1], Kazuhiro Furuya[1], Taro Ukichi[1], Kentaro Noda[1], Isamu Kingetsu[1] and Daitaro Kurosaka[1]. [1]Jikei University School of Medicine, Tokyo, Japan, [2]Tohoku University Graduate School of Medicine, Sendai, Japan.

Background/Purpose: We have previously demonstrated that fasciitis is a common lesion of dermatomyositis (DM) detectable early after disease onset by *en bloc* biopsy combined with magnetic resonance imaging (MRI). Furthermore, we have shown by *en bloc* biopsy that the fascial microvasculature, rather than intramascular microvasculature, is one of the primary sites for inflammatory cell infiltration. Serial MRI findings showed that inflammation progresses from the fascia into the muscle. These facts indicate that fasciitis may cause muscle symptoms such as myalgia even when the muscle biopsy reveals a lack of evidence of myositis. Therefore, the detection of fasciitis plays an important role in the diagnosis of DM especially in its early stage. Power Doppler ultrasonography (PDUS) is useful method for detection of inflammation and vascularity in rheumatic diseases. We examined whether fasciitis is also detectable by PDUS in patients with DM.

Methods: Five patients newly diagnosed with DM and 5 patients newly diagnosed with polymiositis (PM), who fulfilled the Bohan and Peter criteria, were recruited from the Division of Rheumatology of Jikei University Hospital in Tokyo, Japan. In this study, all patients underwent MRI, PDUS, and *en bloc* biopsy before treatment with prednisolone and immunosuppressive agents. The muscles were resected *en bloc* with the skin, subcutaneous tissue, and fascia on the site at which patients were conscious of muscle pain, weakness, or stretched a feeling and/or in which STIR and gadolinium-enhanced fat-suppressed T1-weighted MR images showed an abnormal hyperintense area as described previously (Arthritis Rheum. 2010;62:3751–9). Hematoxylin and eosin staining and immunohistochemical staining for CD31 were performed on paraffin-embedded sections.

Results: MRI showed significant fasciitis findings in 3 patients with DM, while in no patients with PM. PDUS showed abnormal stippled blood flow signals along the fascia in all patients with DM, but in no patients with PM. Fasciitis was histologically detected in 4 patients with DM, while in no patients with PM. Although fasciitis was not detected histologically in only the fifth patient with DM, there were mild perivascular inflammatory infiltrates and neovascularization along the fascia. Immunohistochemical staining for CD31 showed abnormal growth of capillaries and venules along the fascia in all patients with DM, not in any patients with PM. This suggests that PDUS did show the blood flow of neovascularity along the fascia in patients with DM.

Conclusion: Fasciitis, demonstrated histologically by *en bloc* biopsy, was detected by PDUS in patients with DM. Mild fasciitis undetectable by MRI can also be detected by PDUS. Our data suggests that PDUS allows early diagnosis of fasciitis associated with DM.

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2215

Clinical Characteristics and Prognosis of Malignancies Associated with Active Myositis. Sang Jin Lee[1], Eun Ha Kang[2], Yun Jong Lee[2], Eun Young Lee[3] and Yeong Wook Song[4]. [1]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine,Seoul National University Bundang Hospital, Seongnam, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, [4]Department of Molecular Medicine and Biopharmaceutical Sciences, BK 21 plus Graduate School of Convergence Science and Technology, and College of Medicine, Seoul National University, Seoul, South Korea.

Background/Purpose: To examine the clinical features and prognosis of cancers associated with active myositis and to compare them with cancers found in patients with myositis but unrelated to myositis activity.

Methods: Medical records of 289 patients who had been diagnosed as having polymyositis or dermatomyositis according to Bohan and Peter criteria were reviewed to identify fifty two cancer cases. Patients were screened for malignancies at the diagnosis of myositis but active cancer screening was not done during follow-up unless suspicious symptoms developed or their myositis worsened. Cancers were defined to be associated with active myositis if they were present during active phase of myositis (group A). If cancers were not detectable during active phase of myositis, they were defined to be unrelated to myositis activity (group B).

Results: Thirty patients were included in group A consisting of those who developed myositis and cancer together (n =25), whose myositis recurred with cancer development (n=2), or who developed myositis when their cancers progressed/recurred (n=3). Twenty two patients in group B were comprised of those who developed myositis during remission state of cancers with no further relapse of cancer (n=6) or whose cancers were detected during remission state of myositis with no further relapse of myositis (n=16). Group A tended to be male (14/30 vs 5/22, p=0.077) and had an older age at myositis diagnosis compared with group B (60.5±11.1 vs 49.3±16.6 years, p=0.022). Group A patients had shorter intervals between the diagnoses of myopathy and cancer (5.4±9.0 vs 71.6±46.6 months, p<0.001); 90% of cancers in group A developed within 1 year of myositis diagnosis whereas 90% in group B beyond 1 year. Muscle power grades and enzyme levels were not significantly different between the two groups at baseline. Dysphagia was more frequent (p=0.002) and interstitial lung disease less frequent (p=0.001) in group A. Notably, stages at cancer diagnosis were far advanced in group A (stage 3 and 4, 24/29 vs 7/22, p<0.001). Fewer patients in group A achieved normal muscle power during their course of myositis than in group B (p=0.036). The recovery to normal muscle power was associated with induction of cancer remission (p=0.036). Group A patients showed poor survival compared to group B patients (hazard ratio for mortality [95% confidence interval], 7.4 [2.6–21.2], p<0.001), which was still significant when adjusted for age and gender (4.3 [1.5–12.7], p=0.008 by Cox regression model).

Conclusion: In patients with myositis, clinical features of cancers associated with active myositis were distinctive from those of cancers unrelated to myositis activity. The former were found to develop within 1 year of myositis in contrast to the latter, and to be more advanced at diagnosis. The outcome of associated myositis in the former cases was worse in terms of muscle power recovery. Successful cancer treatment was associated with better outcome of myositis. Patients who had cancers associated with active myositis showed poor survival compared to those who had cancers unrelated to myositis activity.

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2216

Muscle Type I Interferon Gene Expression May Predict Therapeutic Responses to Rituximab in Myositis Patients. Kanneboyina Nagaraju[1], Svetlana Ghimbovschi[2], Sree Rayavarapu[3], Aditi Phadke[3], Lisa G Rider[4], Eric Hoffman[3] and Frederick W. Miller[5]. [1]Children's National Medical Center, Washington DC, DC, [2]Children's National Medical Center, Washington DC, WA, [3]Children's National Medical Center, Washington, DC, [4]Environmental Autoimmunity Group, Program of Clinical Research, National Institute of Environmental Health Sciences, National Institutes of Health, US Department of Health and Human Services, Bethesda, MD, [5]Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD.

Background/Purpose: To identify muscle gene expression patterns that predict rituximab responses and assess the effects of rituximab on muscle gene expression in polymyositis (PM) and dermatomyositis (DM).

Methods: In an attempt to understand the molecular mechanism of response and non-response to rituximab therapy, we performed Affymetrix gene expression array analyses on muscle biopsies taken before and after rituximab therapy from eight PM and two DM patients in the Rituximab in Myositis study. We also analyzed selected muscle-infiltrating cell phenotypes in these biopsies by immunohistochemical staining. Partek and Ingenuity pathway analyses were used to identify gene pathways and networks.

Results: Microarray analysis of gene expression changes in the skeletal muscle of myositis patients before and after rituximab treatment showed differential expression of innate immune and inflammatory genes. Supervised hierarchical clustering analysis of these genes resulted in myeloid clusters (clusters 1 and 2) and non-myeloid clusters (cluster 3–5). Myeloid clusters include cluster 1(STAT4, SDC1, ITGB8, MAVS, RFX3, IFNAR2, IRF4, UBA7, and IFRD1) cluster 2 (ICAM1, IRF1, CASP2, SIGLEC1, CD68, and

IFI44). Non-myeloid clusters include predominantly type 1IFN genes (cluster 3 (CD19, IFI35, IFNA1, MX2, UBE2L6, LY6E, XAF1, SP110), cluster 4 (OAS1, USP18, ISG15, IFIT5, MEG3, RTP4, MX1, OAS3, and IFNA2), and cluster 5 (OAS2, OASL, IFIT3, IFIT2 and IFNB1). Type 1 Interferon (IFN) signature genes were expressed at higher levels at baseline in the skeletal muscle of rituximab responders than in non-responders. These genes are known to have immunomodulatory effects on the infiltrating immune cells as well as skeletal muscle. Also, IFN signature genes were significantly down-regulated post-treatment in patients who had a clinical response when compared to non-responder patients. The decrease in the type I IFN signature following administration of rituximab may be associated with the decreases in muscle-infiltrating CD19+ B cells and CD68+ macrophages in responders. Further, analysis of muscle-infiltrating CD138-positive plasma cells showed an increase in non-responder patients.

Conclusion: Our study confirms that myeloid and type 1 IFN signatures are important in myositis pathogenesis and rituximab treatment alters these signatures. Our findings also suggest that high levels of muscle type I IFN gene expression predict responses to rituximab in PM/DM and that rituximab responders also have a greater decrease in the expression of these genes. These data add further evidence to recent studies defining the type I IFN signature as both a predictor of therapeutic responses and a biomarker of myositis disease activity.

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2217

Ultrasonography Analysis of Carotid Parameters in Patients with Idiopathic Inflammatory Myopaties: Correlation with Demographic Profile and Disease Activity. Simone Barsotti[1], Maria Aurora Morales[2], Rosaria Talarico[3], Claudia Ferrari[1], Nicole Di Lascio[2], Anna d'Ascanio[1], Elisabetta Bianchini[2], Stefano Bombardieri[3] and Rossella Neri[1]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Institute of Clinical Physiology, CNR, Pisa, Italy, [3]Rheumatology Unit, Pisa, Italy.

Background/Purpose: Subclinical cardiovascular (CV) involvement is frequent in patients with idiopathic inflammatory myositis (IIM). Growing interest exists on the role of markers of subclinical CV involvement including vascular parameters assessed at carotid artery. The primary aim of our study was to explore Intima-Media-Thickness (IMT), mean arterial diameter (mAD) and distensibility coefficent (DC) in consecutive IIM patients; the secondary aim was to correlate these parameters with demographic and clinical profile.

Methods: Twenty-one IIM patients (F/M 15/6; mean age 55.9±8.7; mean disease duration 8.7±7.5 years) fulfilling the Bohan and Peter criteria were prospective enrolled. We collected demographic data and disease activity parameters according to IMACS criteria. CV risk factors were collected: smoking habits, diabetes mellitus, hypertension, family history of CV disease, body mass index (BMI).

Each patient underwent a B-mode ultrasonography sampling of right common carotid artery, 1 cm beneath the bifurcation; the images were automatically analyzed (Carotid Studio, Quipu) for the measurement of IMT and mAD. Cross-sectional DC was computed as $DC=\Delta A/(PP*A)$ where A is the diastolic lumen area, ΔA the stroke change in lumen area and PP the local pulse pressure estimated by tonometry (Pulsepen, Diatecne). The results were compared with 17 healthy subjects, comparable for sex, age and CV risk factors.

Results: The patients presented mean CK and aldolase levels respectively of 175±159 UI/ML (NV <175) and 8.6±3.2 UI/L (NV <7). MMT8 mean values were 72.5±7.8, HAQ 0.6±0.58, patient and physician VAS respectively 4±2.7 cm and 2±2.1 cm. Three patient were smokers, 4 ex-smoker, 9 hypertensive, 4 affected by diabetes mellitus, 15 had familiar history of CV disease. BMI mean values were 25.5±3.39.

Mean IMT, mAD and DC data in patients and healthy subject were reported in table 1; mAD was significantly higher in IIM patients. In IIM group the association between mAD and hypertension (p=0.02) and BMI (p=0.022) was found. Elevation of IMT positively correlate with age (p=0.02). No correlation was found between the other parameters studied.

Conclusion: Our data have shown that IIM patients presented higher mAD than healthy subjects; ultrasonographic data seem to be influenced by hypertension, BMI and age but not with activity and duration of the disease. Further data are necessary to confirm our observation.

Table 1: Carotid parameters in IIM patients and healthy subjects

	IIM patients	Healthy subjects	p
Intima media thickness – IMT (mean±SD)	0.62 ± 0.1	0.65 ± 0.16	ns
Mean arterial diameters – mAD (mean±SD)	7.5 ± 1	6.9 ± 0.7	**0.04**
Distensibility coefficient – DC (mean±SD)	25 ± 8.2	30 ± 12	ns

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2218

Endoplasmic Reticulum (ER) Stress-Induced Mitochondrial Dysfunction and Atrophy Can be Prevented By Pharmacological Upregulation of Heat Shock Protein 70 (HSP) in Cultured Murine Myotubes. Adam P. Lightfoot, Malcolm J. Jackson, Anne McArdle and Robert G. Cooper. University of Liverpool, Liverpool, United Kingdom.

Background/Purpose: The symmetrical proximal muscle weakness typical of myositis often fails to improve completely with any treatment, due to irreversible muscle fibre degeneration. Although inflammatory cell infiltration is a primary feature of myositis, increasing evidence suggests that muscle weakness correlates poorly with the degree of infiltration (Englund et al. 2001; Li et al. 2004), and in fact may precede inflammatory cell infiltrates (Nagaraju et al. 2001). Research suggests that non-immune cell-mediated mechanisms contribute to muscle weakness, including activation of the ER stress response which is associated with muscle fibre dysfunction and damage (Nagaraju et al. 2005; Yoshida 2007). The mechanisms which mediate ER stress-induced muscle dysfunction in myositis remain unelucidated. However, studies suggest that interplay between the ER stress response, mitochondrial dysfunction and oxidative damage may be involved(Yuzefovych et al. 2013; Cao et al. 2014). Targeted transgenic up-regulation of molecular chaperones, termed Heat Shock Proteins (HSPs), specifically HSP70, attenuates muscle dysfunction and oxidative damage in muscle of old rodents (McArdle et al. 2004; Broome et al. 2006). Similarly, pharmacological increases in HSP70 content of muscle using 17-N-allylamino-17-demethoxygeldanamycin (17AAG), provided an enhanced functional recovery of muscle following exercise-induced damage (Kayani et al. 2008). We hypothesised that, in myositis, ER stress induces mitochondrial dysfunction and oxidative damage, which is a major non-immune cell mediated factor contributing to muscle weakness. We further hypothesised that targeted pharmacological up-regulation of HSP70 could provide a therapeutic strategy to protect muscle fibres in myositis.

Methods: C2C12 myoblasts were grown in standard cell culture conditions (5% CO_2, 37°C) and differentiated to myotubes in growth media (DMEM) supplemented with 2% horse serum. Myotubes were treated with 1mg/ml Tunicamycin to induce ER stress, in the prescence and abscence of 17AAG (0.1mg/ml) for a period of 24 hours. Cells were harvested and oxygen consumption assessed using a clark electrode (Hansatech Instruments), in the presence of electron transport chain (ETC) substrates and inhibitors: Succintate/Rotenone and Glutamate/Malate to determine the respiratory control ratio (RCR) and Phosphate/Oxygen (P:O) ratio. ATP generation was quantified using bioluminescence assay (Roche). Specific ER stress markers were measured using SDS-PAGE/western blotting and qPCR. Myotube morphology changes were assessed using light microscopy.

Results: Activation of the ER stress response in C2C12 myotubes resulted in mitochondrial dysfunction, evidenced by declines in RCR, P:O ratio and in ATP generation. Cells treated with Tunicamycin in the presence of 17AAG showed full preservation of mitochondrial function and ATP generation. ER stress-induced atrophy of C2C12 myotubes was prevented by the presence of 17AAG.

Conclusion: Data demonstrate that pharmacological up-regulation of HSP70 provides protection against ER stress-induced mitochondrial dysfunction and atrophy in C2C12 myotubes.

Disclosure: A. P. Lightfoot, None; **M. J. Jackson**, None; **A. McArdle**, None; **R. G. Cooper**, None.

2219

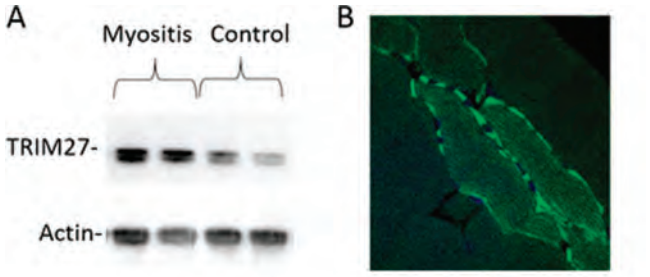
Contribution of Tripartite Motif Proteins Modulating Membrane Repair to the Pathogenesis of Autoimmune-Mediated Myositis. Jenna Alloush[1], Nicholas A. Young[2], Kevin McElhanon[1], Wael N. Jarjour[2] and Noah Weisleder[1]. [1]The Ohio State University College of Medicine, Columbus, OH, [2]The Ohio State University Wexner Medical Center, Columbus, OH.

Background/Purpose: The idiopathic inflammatory myopathies are a heterogeneous group of diseases that result in autoimmunity toward muscles and lead to tissue destruction, but the pathogenesis remains largely unknown. Synaptotagmin VII-knockout (Syt $VII^{-/-}$) mice display mild myositis and we have previously demonstrated that combining this genetic defect with

regulatory T-cell deficiency (FoxP3$^{-/Y}$) results in a robust inflammatory myositis when adoptively transferred into immunodeficient (RAG1$^{-/-}$) recipients. Interestingly, Syt VII$^{-/-}$ mice have impaired sarcolemmal membrane resealing capacity, which allows exposure of intracellular antigens. Tripartite motif (TRIM) proteins have also been linked to membrane repair capacity and are associated with myopathy in human patients. Here, we examined protein expression levels and subcellular localization of several novel TRIM proteins linked to membrane repair capacity in muscle tissue from mice using the Syt VII$^{-/-}$/FoxP3$^{-/Y}$ model of myositis.

Methods: Membrane repair was monitored *in vitro* in cells using an established assay where the membrane of cultured cells is physically disrupted by glass microbeads. Mouse skeletal muscle was collected from wild type mice exercised on a treadmill or RAG1$^{-/-}$ mice adoptively transferred with lymph node preparations from Syt VII$^{-/-}$/FoxP3$^{-/Y}$ mice. Tissue was analyzed by standard Western immunoblotting and by immunohistochemistry.

Results: We identified multiple TRIM family proteins that can modulate membrane repair capacity in cultured cells. Our results show that TRIM27 translocates to the membrane of injured muscle cells *in vivo*, as shown by immunohistochemistry. Similarly, when mice were exposed to membrane disruption due to eccentric contractions during treadmill running, there was translocation of TRIM27 from a diffuse pattern to the damaged membrane. In skeletal muscle of RAG1$^{-/-}$ mice, expression of several TRIM proteins, including TRIM27, was altered and displayed differential subcellular localization.



Increased TRIM27 expression and membrane localization in muscle tissue of mice with myositis. Skeletal muscle from RAG1 deficient mice adoptively transferred with lymph node preparations from synaptotagmin VII / FOXP3 double knockout mice was collected and processed for (A) immunoblotting of whole muscle extract or (B) immunofluroesence microscopy.

Conclusion: We have identified altered expression and localization of TRIM proteins in muscle in this mouse model of myositis. These results highlight an association of decreased sarcolemmal membrane integrity in the development of myositis and suggest a mechanism that could be targeted for diagnostics and therapeutics in these diseases.

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2220

Overexpression of Ankyrin Repeat Domain Containing Protein 1 Gene (*ANKRD1*) in Polymyositis Muscle Biopsies Is Correlated to Hypoxia. Samuel Katsuyuki Shinjo, Sueli Mieko Oba-Shinjo, Miyuki Uno and Suely Kazue Nagahashi Marie. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: *ANKRD1* codes for ankyrin repeat domain containing protein 1, which belongs to the muscle ankyrin repeat protein family involved in a mechano-signaling pathway that links myofibrillar stress response to muscle gene expression. In addition, *ANKRD1* has an important role in transcriptional regulation, myofibrillar assembly, cardiogenesis and myogenesis. Recently, at first time, our group had demonstrated that *ANKRD1* was overexpressed in dermatomyositis muscle specimens. Herein, we analyzed *ANKRD1* expression in muscle biopsies of patients with polymyositis (PM).

Methods: RNA was extracted from frozen muscle biopsies samples of 33 untreated adult with PM (Bohan and Peter's criteria, 1975). As a control group, we analyzed 20 muscle biopsies with no histological change from untreated adult patients with non-inflammatory myopathy diseases. Additional to *ANKRD1*, the gene coding for hypoxia-inducible factor 1, alpha subunit (*HIF1A*) was also analyzed to estimate hypoxia degree. The *ANKRD1* and *HIF1A* transcript expression levels were determined by quantitative real time PCR using Sybr Green method. Muscle biopsies were analyzed histologically by semi-quantitative method of HE stained biopsies. Expression and localization of ANKRD1 and HIF1a in muscle biopsies was accessed by immunohistochemistry.

Results: Higher *ANKRD1* and *HIF1A* expressions levels were observed in PM samples relative to control group ($p<0.001$ and $p<0.001$). In addition, the expression levels of both genes were correlated ($r=0.380$, $P=0.029$). We also observed a positive correlation of both genes to degree of muscle impairment and inflammatory infiltration. However, *ANKRD1* and *HIF1A* expression levels did not correlate to demographic, clinical and laboratory features ($p0.05$). Immunohistochemistry showed that *ANKRD1* and *HIF1*a were expressed mainly by affected muscle fibers.

Conclusion: Our results demonstrated *ANKRD1* is overexpressed and correlated to *HIF1A* and to infiltrate inflammation found in PM muscle specimens. *ANKRD1* involvement in myogenesis and angiogenesis mechanism will be further investigated.

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Reduction of Ovarian Reserve in Adult Patients with Dermatomyositis. Fernando Henrique Carlos de Souza[1], Samuel Katsuyuki Shinjo[1], Lucas Yugo Shiguehara Yamakami[2], Vilma dos Santos Trindade Viana[1], Edmund Chada Baracat[1], Eloisa Bonfa[2] and Clovis Artur Almeida Silva[1]. [1]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil.

Background/Purpose: Dermatomyositis (DM) affects female gender during reproductive age, in which ovarian reserve and future fertility are major topics of interest. However, there is no systematic study assessing these abnormalities in patients with DM. Therefore, the aim of the present study was to evaluate ovarian reserve markers and anti-corpus luteum (anti-CoL) antibodies in patients with DM.

Methods: All 40 female patients with DM (Bohan e Peter criteria, 1975), aged between 18 and 42 years, followed at our tertiary center, from March 2011 to December 2012, were invited to participate. Exclusion criteria were hormonal contraceptive use in the last six months (n=13), neoplasia (n=3), overlap systemic autoimmune diseases (n=3), pregnancy (n=2), gynecological surgery (n=1) and did not agree to participate (n=2). The remaining sixteen DM patients and 23 healthy controls were evaluated at early follicular phase of menstrual cycle. IgG anti-CoL (immunoblotting), follicle stimulating hormone (FSH), estradiol, inhibin B, anti-Müllerian hormone (AMH) serum levels (ELISA) and sonographic antral follicle count (AFC) were determined.

Results: DM patients and controls had comparable mean age (33.4±6.8 *vs.* 31.4±6.8 years, $P=0.337$), ethnicity and socioeconomic class ($P0.05$). DM mean age of onset was 29.1±4.7 years and disease duration of 5.6±3.2 years. Comorbidities and life style were similar in both groups ($P0.05$). Menstrual cycles were alike in both groups with a similar frequency of age at menarche, gynecological age, duration and length of menstrual cycle ($P0.05$). Of note, AMH ≤ 1 ng/mL (50% *vs.* 13%, $P=0.027$) and number of the AFC (10.5±5.6 *vs.* 17.3±0.7, $P=0.017$) were significantly reduced in DM patients compared to controls. Serum FSH (6.2±2.0 *vs.* 6.6±3.8 IU/L, $P=0.617$) and inhibin B levels (49.8±31.5 *vs.* 45.2±29.0 ng/mL, $P=0.616$) were comparable to controls whereas serum estradiol level [45.0 (29–126) *vs.* 34 (24–128) pg/mL, $P<0.001$] was higher in DM patients. Ovarian volumes [6.2 (4.7–8.2) *vs.* 5.5 (1.4–15.8) mm^3, $P=0.214$], and the frequency of anti-CoL antibody (6.5% *vs.* 0%, $P=0.398$) were also alike in both groups ($P0.05$).

Conclusion: The present study was the first to identify that patients with DM may have a shortened reproductive lifespan. Further studies are necessary to assess the possible role of disease and treatment related factors underlying ovarian impairment in these patients.

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Predictors of Myositis Treatments Received and Associated Treatment Responses in Myovision, a National Myositis Patient Registry. Abdullah Faiq[1], Payam Noroozi Farhadi[1], Jesse Wilkerson[2], Nastaran Bayat[1], Anna Jansen[3], Kathryn Rose[4], Lukasz Itert[5], Anne Johnson[5], Christine Parks[6], Edward H. Giannini[5], Hermine I. Brunner[7], Bob Goldberg[8], Richard Morris[4], Frederick W. Miller[1] and Lisa G. Rider[1]. [1]Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD, [2]Social and Scientific Systems, Inc., Research Triangle Park, NC, [3]NIEHS / EAG, Bethesda, MD, [4]Social and Scientific Systems, Inc., Durham, NC, [5]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [6]NIEHS, NIH, Research Triangle Park, NC, [7]PRCSG, Cincinnati, OH, [8]The Myositis Association, Alexandria, VA.

Background/Purpose: Little is known about medications received for myositis and patients' responses to therapies. We present information on self-reported myositis therapy use and responses from a national patient registry.

Methods: MYOVISION consists of 1796 patients who met probable or definite Bohan and Peter criteria for DM/PM (708 DM, 483 PM, 139 JDM) or possible Griggs criteria for IBM (466 IBM) with a median diagnosis date of March 2002. Enrolled patients were queried about myositis treatments received and treatment effectiveness. Logistic regression modeling, using a backwards elimination approach, was used to determine demographic and clinical covariates; a significance level of <0.1 was required to retain variables in the model.

Results: Most DM, PM and JDM patients reported receiving prednisone (96–98%) and methotrexate (MTX) (70–84%); these treatments were reported less commonly in IBM patients (54% and 28%, $p<0.0001$ respectively). Use of azathioprine (41%, 47%) and rituximab (ritux) (14%, 16%) were reported more frequently in DM and PM, in contrast to IBM and JDM (11%, 15%, $p<0.012$ and 9%, 10% $p<0.007$, respectively). JDM patients reported receiving hydroxychloroquine (60%), IV methylprednisolone (54%), IVIG (48%), and cyclosporine (19%) more frequently than other subgroups (2–10% $p<0.021$ for all). Overall, ritux was the most common biologic therapy (13%), and anti-TNFs were received by 10% of patients. Factors associated with MTX treatment among DM, PM and IBM patients included younger age, geographic region, absence of lung disease, and type of treating physician (rheumatologist) ($p=0.022$ - < 0.0001). Younger age, SES, and being treated by a neurologist were factors associated with receipt of IVIG in DM and PM, and presence of dysphagia, fever, and lung disease were additional factors for DM.

Overall, prednisone was reported to be the most helpful medication (39% $p<0.007$), followed by IVIG (35%, $p<0.005$), mycophenolate mofetil (31%) and ritux (24%, $p<0.029$). Some patients (17%) did not find any treatments helpful, and 46% of these had IBM. Absence of dysphagia in DM (OR 0.66), presence of fever in IBM (OR 5.66), and fewer myositis therapies (OR 0.68 – 0.76) were factors associated with a response to prednisone in DM, PM and JDM. Absence of an overlapping autoimmune disease in PM (OR 0.35) and fewer myositis therapies in DM (OR 0.67) were associated with response to IVIG. IBM patients reported physical therapy as the most effective treatment (38%). Older age (OR 1.03), overlapping autoimmune diseases (OR 2.6), absence of fever (OR 0.13), lung disease (OR 2.1) and receipt of fewer myositis therapies (OR 0.48) predicted a positive response to physical therapy in IBM.

Conclusion: Prednisone and MTX are the most frequently prescribed medications in DM, PM, IBM and JDM. Patients vary substantially in their assessment of the effectiveness of these and other treatment approaches. Demographics, clinical features and the specialty of the treating physician appear to influence which therapies are received by myositis patients and the perception of their effectiveness. In the absence of controlled clinical trials, prospective registries of inception cohorts may aid in identifying effective therapies in rare disorders.

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High Prevalence of Hepatitis C Virus Infection in a Japanese Inclusion Body Myositis Cohort.

Akinori Uruha[1], Satoru Noguchi[1], Yukiko K. Hayashi[2], Ikuya Nonaka[1] and Ichizo Nishino[1]. [1]National Center of Neurology and Psychiatry, Tokyo, Japan, [2]Tokyo Medical University, Tokyo, Japan.

Background/Purpose: There have been several case reports of inclusion body myositis (IBM) that appeared after chronic hepatitis C virus (HCV) infection. However, the relationship between HCV infection and IBM remains unclear. In this study, we assessed the prevalence of HCV infection in IBM patients and re-evaluated the clinicopathological aspects of HCV-positive IBM by using our cohort.

Methods: We analyzed the presence/ absence of anti-HCV antibodies of 118 patients (mean age 69.0 ± 8.1y) who were pathologically diagnosed as IBM in 2002 to 2012. As a control, we analyzed likewise 44 age-matched patients (69.0 ± 7.5y) who were pathologically diagnosed as polymyositis in the same period. Then we compared HCV-positive IBM group with HCV-negative group in terms of clinicopathological features including intervals in years from first symptom onset to each onset of symptoms characteristic for IBM and frequencies of fibers with rimmed vacuoles and ragged-red fibers.

Results: In IBM group, anti-HCV antibodies were detected in 34 patients (28.8%). This rate was higher than that of the polymyositis group and of the Japanese general population in the sixties (4.5% and 3.4%, respectively) ($p < 0.001$). No significant difference was seen between HCV-positive and -negative IBM groups, in terms of age at onset (66.6 ± 8.0 vs. 64.1 ± 8.6 years of age), sex ratio (1.4: 1 vs. 1.4: 1), periods after onset showing inability to squat (3.8 ± 3.6 vs. 3.9 ± 2.5 years), inability to open a bottle (4.2 ± 3.2 vs. 4.1 ± 2.3 years), dysphagia (4.9 ± 4.8 vs. 4.5 ± 2.3 years), non-ambulatory (6.1 ± 4.0 vs. 7.1 ± 3.2 years), and pathological findings including the frequency of fibers with rimmed vacuoles [1.7 (0.17–8.1) vs. 2.2 (0.2–23.6)%] and that of ragged-red fibers [0.5 (0.1–5.7) vs. 0.4 (0–4.8)%].

Conclusion: Our results confirm the association between HCV infection and IBM, and suggest a possible causal role of HCV infection in the pathogenesis of IBM.

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Increased Immune Complex Levels in Children with Juvenile Dermatomyositis Are Not Associated with Levels of Von Willebrand Factor Antigen, C4, Duration of Illness, Disease Activity Score, or the Absolute NK Count.

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Background/Purpose: A potential mechanism for the vasculopathy of Juvenile Dermatomyositis (JDM), the most common pediatric inflammatory myopathy, has been attributed to complement mediated immune complex damage to endothelial cells with subsequent release of von Willebrand Factor Antigen (vWF:Ag). Although we previously reported that JDM C4 levels were decreased in 30% patients, associated with decreased gene copy number [Arthritis Rheum, 2012; 64(S10):S826], the role of C4 in this process has not been documented. The purpose of this cross-sectional study was to determine the concentration of immune complexes in JDM sera compared with healthy controls and their association with levels of C4, duration of illness, disease activity scores, vWF:Ag, and absolute number of natural killer cells (NKs)– previously found to be decreased in active disease in 55.7% of JDM.

Methods: 62 children with definite JDM and 20 healthy controls were enrolled and their sera were obtained for immune complex measurement. Among the JDM patients, 29 had normal levels of C4 (21 girls and 8 boys; mean age 14.7 ± 6.8 years) and 32 had low C4 (22 girls and 10 boys, mean age 15.0 ± 3.8 years). The healthy control group was composed of 11 girls and 9 boys, mean age 12.5 ± 3.5 years. Immune complex level, measured as an aggregated human γ-globulin equivalent, was determined by ELISA. The association of immune complex levels with clinical variables was determined: disease activity scores (DAS, skin, muscle, total score), duration of untreated disease (DUD), and vWF:Ag**.** ANOVA was used to test the difference of immune complex levels among low, normal C4, and control groups. The Tukey post-hoc was used to test the pair-wise mean difference.

Results: The immune complex level in pediatric healthy controls was 317 ± 332.4 μg/mL (n=20) (AHG equivalent), 506 ± 347 μg/mL in JDM with low C4 (n=32) and 534 ± 350 μg/mL in JDM with normal C4 (n=29). The immune complex levels in JDM with low or normal C4 was significantly higher than that in healthy controls ($p=0.01$). However, there was no difference in the immune complex levels between children with JDM with low C4 and JDM with normal C4 levels ($p=0.99$). Furthermore, no significant correlation was observed between immune complex levels and a range of clinical features, including duration between disease onset and first treatment ($p=0.99$), DAS skin ($p=0.14$), DAS muscle ($p=0.15$), DAS total ($p=0.25$), level of vWF:Ag ($p=0.86$), or between immune complex level and the absolute NK count ($p=0.29$) among the patients with JDM.

Conclusion: We conclude that that immune complex levels are increased in children with JDM irrespective of C4 levels and are not associated with disease duration, activity or evidence of vascular damage. It is not known if these immune complexes are antigenic, or if they play a role in the initiation or perpetuation of disease.

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Does Previous Corticosteroid Treatment Affect the Inflammatory Infiltrate Found in Polymyositis Muscle Biopsies? Mayara Mendes Pinhata, Juliana Jesus do Nascimento, Suely Kazue Nagahashi Marie and Samuel Katsuyuki Shinjo. Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: We conducted this study because there have been no studies evaluating the effect of the use of corticosteroids (CE) on the presence of inflammatory infiltrates in muscle biopsies of patients with polymyositis (PM).

Methods: This single-center retrospective study, conducted from 2002 to 2013, evaluated 60 patients with defined-PM (Bohan & Peter criteria, 1975) with clinical and laboratory disease activity. Two researchers systematically and independently evaluated muscle biopsy samples that had been obtained at the time of the investigation and diagnosis of PM. The patients were divided into three groups according to the degree of the inflammatory infiltrate (semi-quantitative) present in the muscle biopsies: (a) minimal inflammatory infiltrate present only in an interstitial area of the muscle biopsy (endomysium, perimysium) or in a perivascular area; (B) moderate inflammatory infiltrate in one or two areas of the interstitium of the muscle biopsy or of the perivascular area; and (C) moderate inflammatory infiltrate throughout the interstitium or intense inflammation in at least one area of the interstitium of the muscle biopsy or of the perivascular area.

Results: The three groups (A=10, B=23 and C=27 patients) were comparable regarding the age at the time of the muscle biopsy, gender, ethnicity distributions, interval time between the muscle biopsy and the symptom onset, clinical manifestations, degree of muscle weakness and serum muscle enzyme measurements (P0.05). Approximately half of the patients in each group were using CE at the time of the muscle biopsy. The median (interquartile) duration of CE use [4 (0–38), 4 (0–60) and 5 (0–60) days: groups A, B and C, respectively] and the median cumulative CE dose used [70 (0–1200), 300 (0–1470) and 300 (0–1800) mg] were similar between the groups (P0.05).

Conclusion: Previous CE use did not influence the presence or the degree of inflammatory infiltrates found in muscle biopsies in PM with clinical and laboratory disease activity. Our study showed that muscle biopsies should be performed this population, even in individuals who have already been taking CEs.

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Systemic Treatment for Clinically Amyopathic Dermatomyositis. Janice Lin[1], Alisa Femia[2], Mital Patel[1], Joseph Merola[1] and Ruth Ann Vleugels[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]NYU Langone Medical Center, New York, NY.

Background/Purpose: Clinically amyopathic dermatomyositis (CADM) is an important subset and accounts for approximately 20% of patients with dermatomyositis (DM). CADM is characterized by the presence of pathognomonic cutaneous findings without symptoms of muscle weakness. Cutaneous DM can be difficult to treat and is often refractory to photoprotection and topical therapy, frequently requiring additional systemic treatment even in the absence of muscle involvement. In our series, we investigate the use of systemic medications for treating CADM in our tertiary care center.

Methods: Retrospective chart review was conducted using the Partners Healthcare Research Patient Data Registry, which includes over 1.8 million outpatient visits in a university setting. Patients with CADM (including amyopathic and hypomyopathic DM) diagnosed and treated by any dermatology provider between January 2010 and January 2014 were identified. Data collected included demographics, referral type, diagnosis, medications used for DM, medication side effects, and laboratory tests including anti-nuclear antibody (ANA) and anti-Jo-1 (Jo-1).

Results: We identified 36 patients with CADM (6 hypomyopathic and 30 amyopathic). 47% of patients were referred from dermatology providers, 38.8% from rheumatology, 8.3% from primary care, and 5.5% were self-referred. Only one male patient was identified. One patient was Asian, the remainder Caucasian. Mean age of diagnosis was 50 years (±17.1, range 21–86). 41% of patients were diagnosed within 6 months from the onset of their rash. 36.1% were treated with hydroxychloroquine and topical corticosteroids alone, while 63.9% required at least one additional immunosuppressive therapy. Medications used for control of cutaneous disease included, methotrexate (47.2%), IVIG (30.6%), prednisone (30.5%), mycophenolate mofetil (16.7%), azathioprine (5.6%), rituximab (8.3%), and others including but not limited to dapsone and thalidomide (13.9%). Notably, 25% of patients developed a cutaneous hypersensitivity reaction to hydroxychloroquine. Of the 31 patients with laboratory data available, most (64.5%) had a positive ANA, while no patient had a detectable Jo-1 antibody.

Conclusion: Our series demonstrates that photoprotection, topical therapy, and hydroxychloroquine control disease in only a third of patients with CADM, thus underscoring the frequently refractory nature of skin disease and the need to treat with additional systemic therapy. Methotrexate and IVIG were the most commonly used additional therapies to treat CADM. Furthermore, the risk of cutaneous hypersensitivity reaction to hydroxychloroquine in this series of patients with CADM was similar to that reported in the literature for patients with DM.

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Physical Impairment in Patients with Idiopathic Inflammatory Myopathies Is Predicted By the American College of Rheumatology Functional Status Measure. Laura Cleary[1], Leslie J. Crofford[2], Archana Srinivas[1], Heather Bush[1], Catherine Starnes[1], Qian Fan[1], Jidan Duan[1], Kirk Jenkins[1], Natasha Fraser[1], Matthew Rutledge[1] and Beatriz Hanaoka[1]. [1]University of Kentucky, Lexington, KY, [2]Vanderbilt University, Nashville, TN.

Background/Purpose: The American College of Rheumatology classification criteria of functional status (ACR-FS) in Rheumatoid Arthritis is used as a measure of the consequences of impairment in patients with IIMs. However, studies on the utility of applying the ACR-FS on data derived from chart review of patients with IIMs, as well as the relationships among ACR-FS, patient-reported outcome measures of health and physical activity, and objective measures of muscle strength, endurance and fatigability in IIMs are unknown. The goals of this study were to evaluate the predictive value of ACR-FS with known and suspected risk factors of disability, and to relate it with measures of muscle function in IIMs.

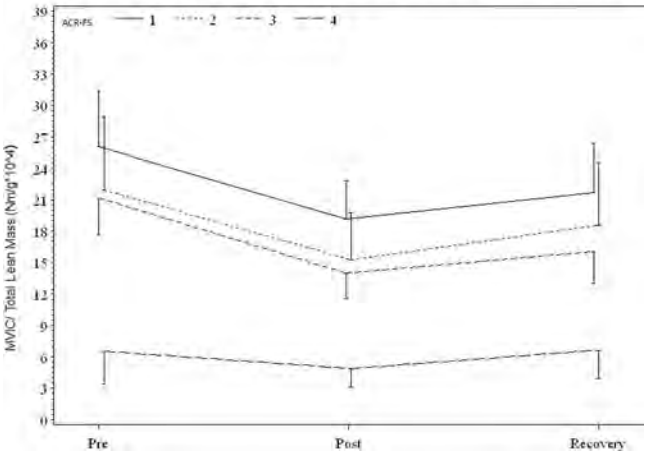
Methods: Demographic and clinical data on 118 patients with IIMs were obtained through retrospective chart review. Current ACR-FS was obtained by chart abstraction and direct patient report. Clinical and functional status evaluation, IPAQ, SF-36v2, muscle strength [manual muscle testing (MMT-8) and knee extensor maximal voluntary isometric contraction (MVIC)], muscle fatigability (percent loss of MVIC immediately following a fatigue protocol and after 12 minutes of recovery), muscle endurance (functional index-2) and body composition (Dual x-ray absorptiometry) measures were performed on a subset of 21 patients. Spearman's correlations were used to examine the relationships between ACR-FS derived from chart abstraction and direct patient report; as well as between physical function, body composition measurements and ACR-FS assessments.

Results: Older age at diagnosis was associated with lower functional status (p=0.045). There was strong correlation between ACR-FS derived from chart abstraction and direct patient report (r=0.782, p=0.0001). There were strong to moderate correlations between ACR-FS assessments and measures of general health, physical function, physical activity, muscle strength and endurance ($p<$ 0.05). ACR-FS correlated best with lower extremity portions of the FI-2. Previous research has shown that performance tests of lower extremity function alone can accurately predict disability across diverse populations. **Figure 1** shows pre, post and recovery MVIC normalized to total lean mass by ACR-FS by patient report. Pre, post and recovery MVICs clearly distinguished patients with no disability, mild to moderate disability, and severe disability. Pre, post and recovery MVICs were largely reduced in patients with severe functional status impairment, although this was not statistically significant.

Conclusion: Age related frailty is likely an important contributor of functional impairment in older IIM patients. The ACR-FS is a simple measure of disability that can be used in chart abstraction studies involving IIM patients. We have demonstrated that ACR-FS correlates well with muscle performance tests of strength, endurance

and fatigue, in general.

Figure 1. Fatiguing protocol: pre, post and recovery MVICs by current direct patient reported ACR-FS



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Has MRI an Added Value over Serum Creatine Kinase Measurement in Myositis? Nicolo Pipitone[1], Antonella Notarnicola[2], Giulio Zuccoli[3], Lucia Spaggiari[1], Gabriele Levrini[1], Arnaldo Scardapane[4], Florenzo Iannone[2], Giovanni Lapadula[2] and Carlo Salvarani[1]. [1]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [2]D.I.M.I.M.P, Rheumatology Unit - University of Bari, Bari, Italy, [3]Children's Hospital of Pittsburgh, Pittsburgh, PA, [4]University of Bari, Bari, Italy.

Background/Purpose: MRI is widely used to assess inflammation in myositis. Muscle edema on short tau inversion recovery (STIR) sequences is thought to reflect active inflammation. However, it is unclear whether MRI has an added value over the cheaper, easier-to-obtain measurement of serum creatine kinase (sCK) levels. Our aim was to assess the concordance between sCK and MRI edema in a cohort of patients with myositis at their first presentation to our centers.

Methods: We enrolled in 2 Rheumatology centers 73 patients, 34 with dermatomyositis (DM) and 39 with polymyositis (PM) diagnosed according to Bohan and Peter criteria. In all patients, sCK were measured and MRI sequences were acquired at the same time. MRI edema (1= present, 0= absent) was assessed bilaterally in 17 thigh and pelvic floor muscles. An MRI composite edema score (0–17) was calculated by adding the separate scores bilaterally and dividing them by two as described elsewhere (1). sCK was considered positive if values were above the upper limit of normal (190 U/l), while MRI was considered positive if the edema score was at least 1. The (single measures) intraclass correlation coefficient (ICC) between the Radiologists involved was 0.78. Muscle strength was measured by MMT (manual muscle testing) and graded according to the Medical Research Council extended scale (0–5). The ICC between the 2 physicians performing the MMT was 0.8.

Results: sCK and MRI were discordant in 47% of patients with myositis, more frequently in DM (59%) than in PM (39%). 56% of patients with DM, but only 15% of those with PM had a positive MRI with normal sCK.

	All patients (=73)	DM (=34)	PM (=39)
sCK+ MRI+	32	11	21
sCK- MRI-	7	3	4
sCK + MRI-	9	1	8
sCK- MRI+	25	19	6

There was a significant correlation between MRI score and muscle strength of the hip flexors (Spearman's rho 0.26, p 0.028) but not between MRI score and overall muscle strength.

Conclusion: MRI is a useful tool to assess disease activity in myositis, especially in DM, where it can be identify a sizeable number of patients who have normal sCK. Further studies of larger cohorts are warranted to confirm our findings.

References:
(1) Clin Exp Rheumatol 2012; 30:570–3

Disclosure: N. Pipitone, None; **A. Notarnicola**, None; **G. Zuccoli**, None; **L. Spaggiari**, None; **G. Levrini**, None; **A. Scardapane**, None; **F. Iannone**, None; **G. Lapadula**, None; **C. Salvarani**, Novartis Pharma AG, 2.

2229

How Often Are Clinically Amyopathic Dermatomyositis Patients Truly Amyopathic? Edward J. Oberle[1], Michelle Bayer[2], Dominic O. Co[1] and Yvonne Chiu[2]. [1]Medical College of Wisconsin, Milwaukee, WI, [2]Children's Hospital of Wisconsin, Milwaukee, WI.

Background/Purpose: Juvenile dermatomyositis (JDM) is a chronic inflammatory disorder primarily involving the skin and striated muscle. Classic JDM presents with rash, proximal muscle weakness, and objective evidence of muscle inflammation. A subset of patients presenting with cutaneous manifestations in the absence of muscle weakness have been variably termed dermatomyositis sine myositis or amyopathic dermatomyositis. The prevalence in adult populations has been reported up to 20% while the prevalence in children is unclear. The extent of the evaluation for myositis in pediatric patients varies between individual practitioners. Given the variability in evaluation, we hypothesized that truly amyopathic JDM is rare when a comprehensive evaluation for myopathy is performed.

Methods: A chart review of the initial evaluation was performed on all patients with the diagnosis code for dermatomyositis (ICD-9 code 710.3) seen at the Children's Hospital of Wisconsin between January 2000 and April 2013. Patients with disease onset after age 18 years or those previously treated with systemic anti-inflammatory therapy were excluded. Data collected included patient demographics, presenting symptoms and exam findings, muscle enzyme panel (AST, ALT, LDH, CK, and aldolase), muscle biopsy, electromyography (EMG), and magnetic resonance imaging (MRI).

Results: Forty-six patients were evaluated for JDM and met study criteria. All presented with typical cutaneous features of JDM. Twenty-six patients (57%) reported weakness as a symptom, while thirty-six (78%) demonstrated weakness on exam. Therefore, ten patients (22%) were classified as clinically amyopathic. The sensitivity of detecting myositis in the entire study population was 95% when all five enzymes were checked. All ten clinically amyopathic patients had a full muscle enzyme panel, nine had an MRI of the thigh to assess for myositis, one had an EMG, and one had a muscle biopsy. Six amyopathic patients had at least one abnormal muscle enzyme. Of the four amyopathic patients with normal enzymes, two had an abnormal MRI consistent with myositis while the other two were normal. The two with normal MRIs and enzymes did not have any additional testing and were labeled as amyopathic based on these studies alone. The one muscle biopsy was done in a patient with abnormal MRI and elevated enzymes; however it did not demonstrate pathologic features consistent with JDM. The EMG was performed on a patient with elevated enzymes and normal MRI; the EMG was normal.

Conclusion: In children, true clinically amyopathic dermatomyositis is rare when a full panel of muscle enzymes and other ancillary studies are performed. In our series, EMG and muscle biopsy were not consistently done, and it is not clear how much these studies contribute to the diagnosis. In patients with negative evaluation (enzymes and MRI), a muscle biopsy should be considered to confirm that the disease is truly amyopathic. Further research is necessary to define the natural history of true clinical amyopathic patients to determine if such a comprehensive evaluation is necessary and to help identify the appropriate therapy to initiate at time of diagnosis.

Disclosure: E. J. Oberle, None; **M. Bayer**, None; **D. O. Co**, None; **Y. Chiu**, None.

ACR/ARHP Poster Session C
Osteoarthritis - Clinical Aspects: Therapeutics
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

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Treatment of Symptomatic Knee Osteoarthritis with Oral Salmon Calcitonin: Results from Two Phase 3 Randomized Clinical Trials. Morten Asser Karsdal[1], Anne C. Bay-Jensen[2], Asger Bihlet[3], Peter Alexandersen[4], Inger Byrjalsen[3], Jeppe Andersen[3], Bente J. Riis[3] and Claus Christiansen[3]. [1]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [2]Cartilage Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, [3]Nordic Bioscience, Herlev, Denmark, [4]Center for Clinical and Basic Research, Vejle, Denmark.

Background/Purpose: To evaluate the structure-modifying and symptom efficacy, as well as safety and tolerability of oral salmon calcitonin (sCT) formulated with a 5-CNAC carrier (a molecule based on Eligen® technology), in osteoarthritis (OA) patients with moderate to severe knee pain and joint structural damage classified as Kellgren-Lawrence 2–3.

Methods: This is the combined reporting of two randomized, double-blind, multi-center, placebo-controlled trials (CSMC021C2301 and CSMC021C2302), evaluating the efficacy and safety of oral salmon calcitonin in patients with painful knee OA, enrolling 1,176 and 1,030 patients, respectively. The subjects had painful knee OA with structural manifestations. Study subjects were randomized (1:1) to oral sCT 0.8 mg twice daily or placebo (PBO) for 24 months. The primary efficacy objectives were to examine the treatment effect compared to placebo on change over 24 months in joint space width (JSW) in the signal knee measured by X-ray, and to examine the change in pain and function using the WOMAC questionnaire. Other study parameters included patient and physician global assessment, cartilage volume measured by MRI technology, and biochemical markers of bone resorption (CTX-I) and cartilage degradation (CTX-II). The primary safety objective was to characterize the safety and tolerability profile based on adverse events incidence and changes in laboratory profiles.

Results: At the 24 month endpoint there was no statistically significant treatment effect on JSN in any of the two studies. In CSMC021C2301 there was a statistically significant ($p<0.0001$) treatment effect on WOMAC (sum of pain, function, stiffness, and total scores) as well as on the biomarkers of bone and joint metabolism ($p=0.0003$). None of the WOMAC scores or the biomarkers achieved a statistically significant treatment effect in the CSMC021C2302 study.

Conclusion: The present formulation of oral calcitonin did not provide reproducible clinical benefits in patients with symptomatic knee OA. (NCT00486434, NCT00704847).

Disclosure: M. A. Karsdal, Nordic Bioscience Diagnostic, 3; **A. C. Bay-Jensen**, Nordic Bioscience Diagnostic, 1; **A. Bihlet**, Nordic Bioscience Diagnostic, 1; **P. Alexandersen**, CCBR, 3; **I. Byrjalsen**, Nordic Bioscience Diagnostic, 3; **J. Andersen**, Nordic Bioscience Diagnostic, 1; **B. J. Riis**, Nordic Bioscience Diagnostic, 1; **C. Christiansen**, Nordic Bioscience Diagnostic, 1.

2231

Combined Chondroitin Sulfate and Glucosamine Is Comparable to Celecoxib for Painful Knee Osteoarthritis. Results from a Multicenter, Randomized, Double-Blind, PHASE IV NON-Inferiority TRIAL. Marc Hochberg[1], Johanne Martel-Pelletier[2], Jordi Monfort[3], Ingrid Moller[4], Juan Ramon Castillo[5], Nigel K. Arden[6], Francis Berenbaum[7], Jean-Pierre Pelletier[8], Francisco J. Blanco[9], Philip G. Conaghan[10], Yves Henrotin[11], Thomas Pap[12], Pascal Richette[13], Allen Sawitzke[14], Patrick du Souich[15] and Moves Investigation Group[16]. [1]University of Maryland School of Medicine, Baltimore, MD, [2]Osteoarthritis Research Unit CR-CHUM, Notre-Dame Hospital 1560 Sherbrooke St East, Montreal, QC, [3]Department of Rheumatology, Grup de recerca cel●lular en inflamació i cartílag. IMIM (Institut de Recerca Hospital del Mar), Barcelona, Spain, [4]Instituto Poal, Barcelona, Spain, [5]Head of Clinical Pharmacology Unit Hospital Universitario Virgen del Rocío, Sevilla, Spain;, Sevilla, Spain, [6]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom, [7]Sorbonne University, INSERM UMR S938, UPMC, University of Paris 06, DHU i2B, Paris, France, [8]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, [9]INIBIC-Hospital Universitario A Coruña, A Coruña, Spain, [10]Leeds Institute of Molecular Medicine, University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [11]Physical Therapy and Rehabilitation Department, Princess Paola Hospital, Marche-en-Famenne, Belgium, [12]Institute of Experimental Muskuloskeletal Medicine University Hospital Münster, Münster, Germany, [13]INSERM 1132, Université Paris-Diderot, Hôpital Lariboisière, Paris, France, [14]University of Utah Medical Center, Salt Lake City, UT, [15]University of Montreal, Montreal, QC, [16]Spain, Germany, France and Poland, Barcelona, Spain.

Background/Purpose: The Multicentre Osteoarthritis interVEntion trial with Sysadoa (MOVES) compared efficacy and safety of Chondroitin sulfate (CS) and Glucosamine Hydrochloride (GH) with that of Celecoxib (CE) in patients with knee osteoarthritis (OA) and severe knee pain.

Methods: 606 patients with knee OA (Kellgren-Lawrence grade 2 or 3) and moderate to severe pain (WOMAC pain >300) were randomized to 400 mg CS + 500 mg GH tid or 200 mg CE qd for 6 months.

Methods: Primary outcome was decrease in WOMAC pain (0–500 scale) from baseline to 6 months; non-inferiority margin was set at 40 (corresponding to 8 mm on a 0–100 mm scale). Secondary outcomes included WOMAC function/stiffness, VAS pain, joint swelling/effusion, use of rescue medication, OMERACT-OARSI Responder Index and EuroQoL-5D.

Patients were excluded if they had a history of known cardiovascular or gastrointestinal disease.

The main study analyses were performed using PP population. Primary efficacy analysis was also performed according to ITT to test the robustness of results.

Results: Mean age at baseline was 62.7 years, 83.9% were women, WOMAC pain was 371.3 (41.6) and 62.6% had KL grade 2. There were no differences between treatment groups.

Adjusted mean change (95% CI) from baseline to 6 months in WOMAC pain was –185.7 (–200.3; –171.1) (50.1% decrease) in CS+GH group and –186.8 (–201.7; –171.9) (50.2% decrease) in CE group (Figure 1). The mean difference at 6 months met non-inferiority margin: –1.11 (–22.0; 19.8). All sensitivity analyses confirmed the non-inferiority conclusion.

There were no differences at 6 months between treatment groups in the secondary outcomes, including WOMAC stiffness, with a decrease of 46.9% and 49.2% ($P=0.434$); WOMAC function, 45.5% and 46.0% ($P=0.530$); and VAS, 48.0% and 48.8% ($P=0.924$); in GH+CS and CE groups respectively. Similarly, there were no significant differences in patient and physician global assessments of disease activity or response to therapy. Over 70% of patients in both groups fulfilled OMERACT-OARSI responder criteria at 120 days with ~ 80% response rate at 6 months. Both groups had a reduction (>50%) in joint swelling from baseline, from 12.5% to 5.9% for CS+GH, and from 14.0% to 4.5% for CE. Use of rescue medication was low and similar between treatments. There was no difference in proportion of patients with treatment-emergent or SAEs between groups; no deaths occurred in this study.

Finally, there were no significant subgroup by treatment interactions for either efficacy or safety confirming consistence of non-inferiority of CS+GH across clinically relevant subgroups.

Conclusion: The MOVES trial confirms that CS+GH is comparable to CE in reducing pain in patients with knee OA and extends results from GAIT. This fixed-dose CS+GH combination should offer a safe and effective alternative for those patients with cardiovascular or gastrointestinal conditions who have contraindications to celecoxib.

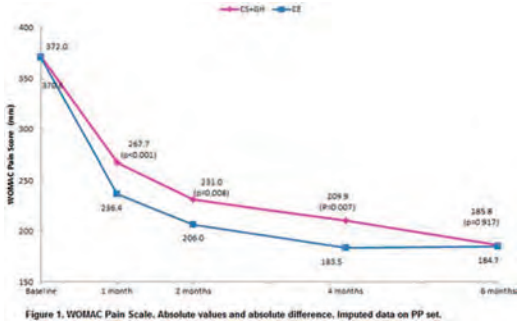

Figure 1. WOMAC Pain Scale. Absolute values and absolute difference. Imputed data on PP set.

Disclosure: M. Hochberg, Consultant, 6; **J. Martel-Pelletier**, None; **J. Monfort**, None; **I. Moller**, None; **J. R. Castillo**, None; **N. K. Arden**, None; **F. Berenbaum**, None; **J. P. Pelletier**, None; **F. J. Blanco**, None; **P. G. Conaghan**, None; **Y. Henrotin**, None; **T. Pap**, None; **P. Richette**, None; **A. Sawitzke**, None; **P. du Souich**, None; **M. Investigation Group**, None.

2232

Cost-Effectiveness of Glucosamine, Chondroitin Sulfate, Their Combination, Celecoxib,Non-Selective Non-Steroidal Anti-Inflammatory Drugs, and Placebo in Treating Knee Osteoarthritis. Vishvas Garg[1], Dennis Raisch[2], Ning Yan Gu[2], Matthew E Borrego[2] and Daniel O. Clegg[3]. [1]University of New Mexico (at the time of research), Grayslake, IL, [2]University of New Mexico, Albuquerque, NM, [3]George Wahlen VA Medical Center/University of Utah, Salt Lake City, UT.

Background/Purpose: Knee osteoarthritis (KOA) affects 13.8% of the US population aged ≥26, causing significant burden-of-illness. We compared the cost-effectiveness of conventional medicines such as non-steroidal anti-inflammatory drugs (NSAIDs) and celecoxib (CXB) with complementary and alternative medicines (CAM) therapies to treat KOA from the US health care payers' and patients' perspectives, with 24-week, 2-year, and 10-year time-horizons.

Methods: We constructed a Markov cohort model (10-year analysis) and a decision-tree model (24-week and 2-year analyses). All costs were obtained from

the published literature (converted to 2012 USD) and included both direct and indirect health care costs of medications, drug-associated adverse events, and total knee replacement surgery. Clinical efficacies for treatment strategies were obtained from the Glucosamine/CS Arthritis Intervention Trial (GAIT). Effectiveness was measured using quality-adjusted life-years (QALYs) gained, estimated from the SF-6D data collected during GAIT. Patients were stratified into mild pain only and moderate-to-severe pain groups based on their severity of knee pain. Published literature was used to obtain the rest of the modeling parameters. Base-case results were varied in both one-way and probabilistic sensitivity analyses.

Results: We found that, among the mild, moderate, and severe patients together (from time-horizon of 24 weeks and years 2 and 10), CAM therapies were cost-effective versus conventional medicines to treat KOA in the US, with CS being the most cost-effective treatment ($1,332 per QALY gained) and glucosamine the next most cost-effective ($ 120,367 per additional QALY gained). However, in a 24 week time-horizon among KOA patients with mild pain CXB was also incrementally cost-effective versus CS ($49,988 per QALY gained). Among moderate-to-severe pain patients from 24-week time-horizon, the combination of glucosamine and CS was the most cost-effective ($3,279 per QALY gained). A major driver of cost-effectiveness of CAM therapies over conventional medicines in the 10 year time horizon was the lack of evidence of adverse events (AEs), compared to NSAIDS and CXB which have extensively-documented AEs.

Conclusion: Our analysis indicates CAM therapies to be more cost-effective than conventional medicines in treating KOA, due to lack of known adverse events rates and lower drug utilization costs from CAM. Prescribers may want to consider the findings of our study; however, future research is needed regarding the long-term effectiveness and safety of CAM therapies in treating KOA.

Disclosure: V. Garg, AbbVie, 3; **D. Raisch**, None; **N. Y. Gu**, None; **M. E. Borrego**, None; **D. O. Clegg**, GAIT trial was supported by the National Center for Complementary and Alternative Medicine and the National Institute of Arthritis and Musculoskeletal and Skin Diseases., 2.

2233

A PHASE 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy Study of Apremilast (CC-10004) in Subjects with Erosive Hand Osteoarthritis.

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Background/Purpose: We report on a phase II, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study in subjects with erosive hand osteoarthritis. Subjects must have had a minimum of 6 months' history of EHOA immediately prior to enrolment to this study.

Methods: Subjects must have had a diagnosis of erosive hand osteoarthritis (EHOA), fulfilling the classification criteria of the American College of Rheumatology (ACR) with a disease duration for at least 6 months. The study included four phases: a pre-randomization phase for up to 35 days, a 91-days double-blind treatment phase, a 77-days open-label treatment phase, and a 28-days observational follow-up phase (to monitor worsening of EHOA). Subjects meeting eligibility criteria at the baseline visit (Visit 2/Day 1) were randomized in parallel 2:1 to either 20 mg PO BID of apremilast or placebo. The primary objective of the study was to evaluate the 84-day efficacy of apremilast 20 mg twice per day [BID], subsequent to a 7-day dose titration, compared with placebo, on the symptoms of erosive hand osteoarthritis.

Results: Until day 85 no patient achieved a 70% improve in AUSCAN and only 2 (7%) achieved a 50% improvement (1 in the apremilast and 1 in the placebo group). 44% of the patients achieved a 20% improve in AUSCAN at day 85 (42% in the apremilast and 50% in the placebo group) and 81% of the patient ended at day 85 with an AUSCAN below the baseline value (89% in the apremilast and 63% in the placebo group). None of the response rates showed a significant difference between apremilast treatment and placebo in the double blind treatment phase. There were small to modest correlations between AUSCAN and HOAMRIS scores (Table 78 and Figure 45) with a correlation coefficient of 0.30 for the linear correlation of the sum of HOAMRIS scores and the total AUSCAN score.

Conclusion: Given the lack of treatment options for patients with EHOA there is unmet need for effective treatment for this disease. Considering the pathophysiology of PDE4 inhibitors we initially considered apremilast as an interesting treatment option for patients with EHOA. However, regarding our pre-limary results we have to conclude that due to the high placebo response rate apremilast failed to meet the primary and secondary objectives in our study. Detailed MRI sub-analyses of responders and non-responders with respect to HOAMRIS scores may allow to define responder profiles in patientes with EHOA.

Disclosure: J. Rech, None; **F. Faustini**, None; **A. J. Hueber**, None; **W. Ochs**, None; **W. Spieler**, None; **H. Kellner**, None; **U. Muller-Ladner**, None; **M. Grünke**, None; **M. Schneider**, None; **G. Schett**, None.

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Safety and Efficacy of Liposome Intra-Articular Injection in Moderate Knee Osteoarthritis. a Prospective Randomized Double-Blinded Study.

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Background/Purpose: Bio-lubrication is a prerequisite for proper joint mobility and is crucial for prevention of degradative changes of the joint. Phospholipids are components of the synovial fluid and are known to serve as natural lubricants of cartilage surfaces. MM-II is a novel intra-articular bio-lubricant made of liposomes suspended in aqueous solution.

Purpose: to test the safety and effectiveness of intra-articular injection of MM-II in osteoarthritic patients compared with intra-articular hyaluronic acid (HA) up to 3 months of follow-up in a double-blind, randomized clinical study.

Methods: Patients with symptomatic unilateral knee OA with baseline pain on VAS of more than 40 mm and a stage 2–3 Kellgren Lawrence score on X-ray, were recruited. 40 patients were randomized into two groups of 20, to receive a single intra-articular injection of either MM-II or HA (Durolane®). Effectiveness measures included maximal global pain in the target knee, recorded by a 100mm VAS; WOMAC subscales; OMERACT OARSI responder criteria; PGA, PASS, PAE questions and consumption of paracetamol/acetaminophen, which was the only authorized rescue medication. Tolerability was assessed by local manifestation defined by an increase of at least 3 cm in knee circumference, measured at 2 cm above the upper border of the patella or local pain increase of more than 30 mm on a 100 mm VAS. Adverse events were recorded through 90-days of follow-up.

The study was FIM Exploratory non-powered, with descriptive statistics.

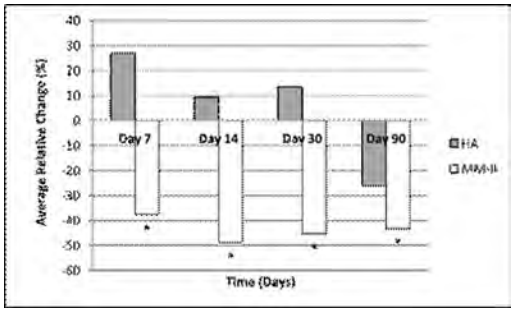
Results: All patients completed the study. **Results:** relating to WOMAC A pain, summarized in Figure 1, show a faster response with MM-II, with maximal effect observed on day 14, which was maintained over time and was associated with a statistically significant difference from baseline pain from day 7. In the HA group, the onset of pain relief was slower, with an improvement statistically significant change from baseline observed only on day 90.

Daily acetaminophen intake was lower in the MM-II group, with a reduction of more than 50% in the number of days and total dose of rescue medication consumption seen following MM-II administration, compared with HA injection.

The percent of responders to treatment according to the OMERAC-OARSI response criteria was 52.6, 66.7, 70 & 60 at the day 7, 14, 30 & 90 respectively compared to 30, 36.8, 25, 45 at the HA group (data not shown).

Local adverse events (inflammatory flare) were observed in one patient at day 3 in the MM-II group and in 4 pts at day 1, 1 pt at day 3, and 1 pt at day 7 in the HA group.

Patient's Relative Change in WOMAC A in Target Knee over Time



*statistically significant difference from baseline

Conclusion: Intra-articular injections of MM-II were found to be safe and effective. The pain-reduction action was more rapid and sustained up to 3 months compared with HA. Larger randomized controlled trials are needed to confirm these encouraging results.

Disclosure: L. Kandel, MM-II, 2; **Y. Dolev**, Stock options, 1; **R. Shimonov**, None; **G. Rivkin**, None; **M. Liebergall**, None; **Y. Mattan**, None; **X. Chevalier**, MM-II, 6.

2235

Cost-Effectiveness of Long-Term Opioid Use in the Treatment of Knee Osteoarthritis in Older Patients with Multiple Comorbidities. Jeffrey N. Katz[1], Savannah Smith[1], Jamie E. Collins[1], Joanne M. Jordan[2], David J. Hunter[3], Edward H. Yelin[4], Lisa Suter[5], A. David Paltiel[6] and Elena Losina[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]University of North Carolina Dept of Epidemiology, Chapel Hill, NC, [3]Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, Australia, [4]University of California, San Francisco, San Francisco, CA, [5]Yale University, New Haven, CT, [6]Yale School of Public Health, New Haven, CT.

Background/Purpose: Because older patients with osteoarthritis (OA) and multiple comorbidities face high risk of toxicity from nonselective non-steroidal antiinflammatory drugs (NSAIDs) and Cox-2 inhibitors, opiates (including tramadol) have been proposed as an analgesic strategy. We evaluated clinical and economic outcomes of using prototypic medications (tramadol, naproxen, and celecoxib) in such patients.

Methods: We used the Osteoarthritis Policy Model, a validated computer simulation of knee OA, to project long-term clinical outcomes, costs and incremental cost-effectiveness ratios (ICERs) of OA treatment strategies in patients with mean age 70, knee OA, diabetes and coronary heart disease whose pain persists after initial therapy with acetaminophen, steroid injections and physical therapy (PT). We examined four treatment strategies: 1) continuing PRN acetaminophen; 2) tramadol; 3) naproxen and 4) celecoxib. Pain was the primary determinant of quality of life and its relief was assessed with the Western Ontario McMaster (WOMAC) Pain Scale. Treatment efficacies and toxicities were estimated from published literature and influenced time on regimen. Mean WOMAC change was 22 points for tramadol; 15 for naproxen and celecoxib. Annual medication costs and major toxicities for the first and subsequent years are shown in the Table. Toxicities included CVD and – for tramadol – fractures. We adopted a societal perspective, discounting outcomes at 3%, and assumed a willingness to pay (WTP) of $100,000 per quality adjusted life year (QALY) gained. ICERs below this threshold defined cost-effective strategies.

Results: Patients remained on tramadol for 1.98 years and the other regimens for 2.36 years. Twice as many experienced major toxicity with tramadol as with the other agents. The Table lists the cost-effectiveness results. The ICER for tramadol exceeded that for naproxen; thus, we compared naproxen directly to PRN acetaminophen and observed that naproxen had an ICER of $78,848/QALY. However, tramadol cost effectiveness was highly sensitive to its toxicity. When tramadol toxicity was reduced by just 10% it became cost-effective (ICER $53,968/QALY), and ICERs for the naproxen-based strategy then exceeded the WTP threshold (ICER=$102,000/QALY) compared to the tramadol-based strategy.

Conclusion: In patients with OA and multiple comorbidities who have pain despite acetaminophen, steroid injection and PT, naproxen was cost-effective at a WTP=$100,000. Tramadol became cost effective following a 10% reduction in its overall toxicity. The cost of celecoxib precluded its offering acceptable value. The impact of tramadol toxicity on these estimates underscores the need for further research on toxicity of opiates in frail patients; the limited number of years on regimen highlights the need for therapies with better efficacy and toxicity profiles.

Table: Cost-effectiveness, toxicity and years on regimen among individuals treated with acetaminophen, tramadol, naproxen and celecoxib

	Inputs			Results			
Regimen	Toxicity (first yr, subseq yrs)	Costs	QALE	COST	ICERs	Average Years on Regimen	Proportion Experiencing Major Toxicity attributable to treatment
Acetaminophen PRN		$71	6.328	$131,558			
Tramadol	21%, 6.0%	$755	6.363	$133,817	Dominated	1.98	33.7%
Naproxen	9.3%, 4.8%	$2,642	6.410	$137,983	$78,848	2.36	15.3%
Celecoxib	9.5%, 4.9%	$4,750	6.406	$142,610	Dominated	2.36	15.5%

PRN = as needed; Toxicity=coronary heart disease, gastrointestinal, fracture
QALE=quality adjusted life expectancy; ICER = incremental cost effectiveness ratio.
Dominated = Agent costs more and provides less benefit than some other agent or combination of agents

Disclosure: J. N. Katz, None; **S. Smith**, None; **J. E. Collins**, None; **J. M. Jordan**, Algynomics, 5, Samumed, 5, Flexion, 5, ClearView Healthcare Partners, 5, Trinity Partners, LLC, 5; **D. J. Hunter**, None; **E. H. Yelin**, None; **L. Suter**, None; **A. D. Paltiel**, None; **E. Losina**, None.

2236

Plant–Derived Products Are Effective for Treatment of OA Pain and Safer Than Other Active Therapies. Laura Laslett, Xingzhong Jin and Graeme Jones. University of Tasmania, HOBART, Australia.

Background/Purpose: Osteoarthritis (OA) is a leading cause of chronic disability. There are no approved treatments for modifying the disease course, therefore disease management consists of symptom control, with patients often eventually requiring joint replacement. The controversy surrounding use of the COX–2 inhibitor class of NSAIDs and heightened cardiovascular risk highlights the importance of finding safer treatment options to minimise adverse side effects, such as natural therapies. Plant–derived therapies are traditionally used as medicines. However, such therapies have not typically been studied with the same rigour as pharmaceutical agents. This review summarises use of plant–derived products compared to placebo and active comparator for the treatment of OA pain and function.

Methods: 62 RCT's of plant–based therapy for OA were identified from literature databases (PubMed, EMBASE), and summarized for pain (assessed using visual analog scores (VAS), numeric rating scales (NRS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or Knee Injury and Osteoarthritis Outcome Score (KOOS) pain scales, function and safety outcomes using standardised mean differences (SMDs) and relative risks (RR), with trials grouped by class where possible.

Results: Overall, plant–derived therapies are effective for treating pain compared to placebo, assessed using VAS and NRS scores (SMD 1.08; 95% CI 0.72 – 1.44), or WOMAC/KOOS pain scales (SMD 0.98; 95% CI 0.62 – 1.35). Classes demonstrating overall efficacy in more than one trial for either VAS or WOMAC pain included *Boswellia serrata*, capsaicin, and ginger; there was single trial evidence of efficacy for another 9 agents (pine bark, willow bark, NR–INF–02, UP446, E–OA–07, passion fruit peel, phytalgic, Aquamin–F, SKI306X). Plant–derived therapies have similar efficacy to active comparator (most commonly NSAIDs), assessed using VAS and NRS scores (SMD 0.32, p=0.08) or WOMAC/KOOS pain scales (−0.08, p=0.14). Therapies are also effective for functional outcomes compared to placebo (SMD 0.92, p<0.001). However, significant heterogeneity remains for all pain and function outcomes, indicating results need to be interpreted with caution. Risk of adverse events was similar to placebo (RR 1.13, p=0.1), but reduced compared to active comparator (RR 0.75, p<0.001).

Conclusion: Plant–derived therapies may be efficacious in treating osteoarthritic pain and functional limitation and appear safer than other active therapies. However, quality trials and long term data are lacking, and the number of trials for each therapy is limited. Comparison of efficacy would be assisted by trial standardisation.

Disclosure: L. Laslett, Arthritis Relief Plus Pty Ltd, 2; **X. Jin**, Arthritis Relief Plus Pty Ltd, 2; **G. Jones**, Arthritis Relief Plus Pty Ltd, 2.

2237

Interleukin-1 Dual-Variable Domain Immunoglobulin Reduces Multiple Inflammatory Markers in Knee Osteoarthritis Patients. Susanne X. Wang[1], Jeroen Medema[1], Matthew Kosloski[1], Wei Liu[1], Mary Saltarelli[1] and Morten Asser Karsdal[2]. [1]AbbVie Inc., North Chicago, IL, [2]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark.

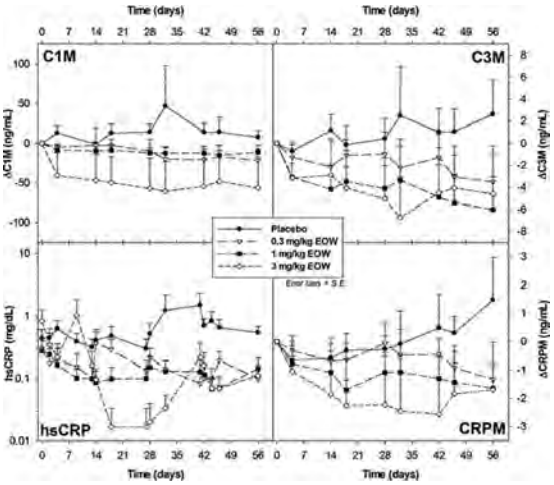
Background/Purpose: Osteoarthritis (OA) may comprise multiple phenotypes, one of which is inflammation-driven OA. Consequently, a selected subpopulation of OA patients may benefit from optimally targeted anti-inflammatory treatment. Interleukin-1 (IL-1) is a potent catabolic cytokine thought to play a major role in the development and progression of OA both in terms of disease (structural progression) and symptoms (pain and functional deterioration). The anti-inflammatory effects of a novel human DVD-Ig targeting IL-1α and IL-1β (ABT-981) were evaluated in knee OA patients using a panel of biomarkers that are elevated in the presence of tissue degradation secondary to joint inflammation.

Methods: This was a randomized, double-blind, placebo-controlled trial of the safety, pharmacokinetics, and pharmacodynamics of multiple subcutaneous injections of ABT-981 in knee OA patients (N=36). Three groups of patients (n=27) received 4 doses of ABT-981 or matching placebo (7:2) every other week (EOW) at 0.3, 1, and 3 mg/kg. Serum samples were collected on days 1, 5, 15, 19, 29, 33, 43, 47, and 57. The panel of inflammation and joint-degradation biomarkers included high-sensitivity C-reactive protein (hsCRP); matrix metallopeptidase (MMP)-9; vascular endothelial growth factor (VEGF); MMP degradation products of type I, II, and III collagen (C1M, C2M, and C3M) and CRP (CRPM); and circulating levels of citrullinated and MMP-degraded vimentin (VICM). Biomarker response for patients on active drug in each group was compared with the pooled placebo response across groups. Statistical analysis was performed on least-square means using SAS 9.2.

Results: Mean serum hsCRP levels in all ABT-981 groups were significantly decreased vs placebo (p value range, 0.003–0.031). Mean serum C1M levels decreased in a dose-dependent manner (p=0.062, 0.027, and 0.015 for 0.3, 1, and

3 mg/kg groups, respectively). Mean serum C3M levels exhibited a nonsignificant decreasing trend in the 1 and 3 mg/kg groups (p=0.062 and 0.090, respectively). Mean serum CRPM levels were decreased with ABT-981; however, a statistical difference was only established from day 33 on (p value range, 0.097–0.025; Figure). No other markers showed significant changes or trends.

Conclusion: Through inhibition of IL-1α and IL-1β, ABT-981 significantly reduced serum hsCRP and markers of joint metabolism that are elevated in inflammation-driven joint destruction diseases, suggesting a reduction in systemic inflammation. ABT-981 significantly decreased C1M, suggesting a dampening of inflammation-mediated joint destruction by reducing connective tissue turnover. The observed serum C3M and CRPM decreases suggest the potential of ABT-981 to ameliorate inflammation-mediated tissue destruction and chronic tissue inflammation. Thus, ABT-981 may provide clinical benefit to a selected subpopulation of patients with inflammation-driven OA.



Disclosure: S. X. Wang, AbbVie Inc., 1, AbbVie Inc., 3; **J. Medema**, AbbVie Inc., 1, AbbVie Inc., 3; **M. Kosloski**, AbbVie Inc., 1, AbbVie Inc., 3; **W. Liu**, AbbVie Inc., 1, AbbVie Inc., 3; **M. Saltarelli**, AbbVie Inc., 1, AbbVie Inc., 3; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 3, AbbVie Inc., 5.

2238

Exploratory Six Month Phase IIa Study of a Potential Disease Modifying Drug in Patients with OA of the Knee. Ketan Desai Voltarra Pharma, Easton, PA.

Background/Purpose: No disease modifying drugs exists to treat osteoarthritis. Recently, a phase II study from Tasmania showed that Zoledronic Acid, a bisphosphonate, has an effect on decreasing bone marrow lesions in patients with osteoarthritis of the knee. However, this was associated with post-dose syndrome with the once-a-year infusion. A new combination of Zoledronic Acid and an established drug. Volt01, was devised to decrease the post-dose syndrome.

Methods: In a single blind study (patients were blinded), 36 subjects with knee OA were given a single intravenous infusion of either Zoledronic Acid or Volt01 in a 1:1 ratio. Patients who had bilateral knee OA had the worse joint selected as the index joint. No patient with knee OA was rejected based on severity of OA. Patients with concomitant diseases were excluded. Patients were evaluated at baseline with the visual analogue pain score (VAS) and bone mineral density with a DEXA scan. VAS was evaluated at 1 month, 3 months, and six months. DEXA scan was repeated at six months to confirm no decrease in BMD.

Results: At six months, after a single infusion, there was no difference in bone mineral density in either cohort. The number of patients complaining of post-dose syndrome in the cohort treated with Zoledronic Acid was significantly worse that in those treated with Volt01 (9/16 versus 2/16). The improvement in pain as measured by VAS at six months was also significantly better in the Volt01 cohort than the Zoledronic Acid cohort (−35mm versus -10mm)

Cohort	PDS (# reporting/total)	ΔBMD	Δ Mean VAS
ZA=16	9/16	0	−10mm
VOLT01 =16	2/16	0	−35mm

Conclusion: Zoledronic Acid has been recently shown to have disease modifying properties in a large phase II study in patients with OA of the knee. In the study presented in this abstract, Volt01, a new combination with Zoledronic Acid, was both safer and more effective than Zoledronic acid after a single infusion in patients with knee OA for at least six months. Volt01 thus has the potential to be a disease modifying drug for knee OA. Larger studies using MRI will need to be undertaken to confirm this observation.

Disclosure: K. Desai, Voltarra Pharma, 4;

2239

Efficacy of Ketoprofen Lysine Salt in Reducing Inflammation and Pain in Primary Osteoarthritis of the Hand: Preliminary Results of a Retrospective and Prospective Clinical Trial. Maurizio Muratore[1], Laura Quarta[1], Antonella Grimaldi[1], Daniela Costanza[1], Luigi Lanata[2], Michela Bagnasco[2], Alessandra Monguzzi[2] and Eugenio Quarta[1]. [1]Department of Rheumatology, Hospital Galateo, San Cesario di Lecce, Italy, [2]Dompé SpA, Milan, Italy.

Background/Purpose: Osteoarthritis (OA) is a common progressive joint disease and a leading cause of musculoskeletal pain and functional disability worldwide. Despite various interventional treatment approaches such as non-steroidal antinflammatory drugs (NSAIDs), pain management of OA remains suboptimal. Among NSAIDs, ketoprofen lysine salt (KSL) has a marked analgesic effect, through both its anti-inflammatory action and a central action. The primary aim of our study was to evaluate the efficacy of KSL in reducing the severity of osteoarticular pain. Secondary aims were grip strength assessment, duration and severity of swelling, acute exacerbations frequency and inflammation grade.

Methods: This was a retrospective and prospective clinical trial, including 58 post-menopausal women (>50 years) affected by primary osteoarthritis of the hand. All patients (pz) reported pain and swelling at least in 3 interphalangeal joints (IF) of the hands. Pz were randomized into 2 groups: Group A (30 pz, 105 IF) took KSL (160 mg/die) for 10 days plus glucosamine (500 mg) and chondroitin sulphate (400 mg) for 20 days. Group B (28 pz, 95 IF) received only glucosamine (500 mg) and chondroitin sulphate (400 mg) for 20 days. Pulsed wave (PW) *Doppler (Esaote Mylab 25 Gold equipped with a 12–18 MHz multi-frequency transducer)* was performed on the dorsal and palmar side of IF, with longitudinal and transverse scans, assessing synovitis/effusion and PW-Doppler signal (OMERACT scale: 0–3). *Clinical assessments of pz were performed at day 1 (T0)* and after 5,10,15,20 days (T1,T2,T3,T4). At each visit *Visual Analog Scale* for *Pain* (*VAS Pain)* and grip strength were recorded.

Results: Pain improved in 24 Group A pz (mean VAS score decreased from 70 to 16) and 70/105 IF showed an improvement in PW Doppler. None of these pz reported exacerbations. Also grip strength improved by an average of 50%. On the contrary, only 10/28 Group B pz obtained an improvement of pain (mean VAS score decreased from 70 to 55). PW Doppler improved in 20/95 IF, ≥1 exacerbations were reported by 12 pz and grip strength remained unchanged.

Conclusion: These results demonstrate that the addition of KSL is highly effective in reducing joint inflammation and pain in women with primary osteoarthritis of the hand. The reduction in the number of exacerbations in the group of patients treated with KSL also suggests that the use of this NSAID may reduce relapses lessening the bone and cartilage damage and joint deformities.

Disclosure: M. Muratore, None; **L. Quarta**, None; **A. Grimaldi**, None; **D. Costanza**, None; **L. Lanata**, Dompè SpA, 3; **M. Bagnasco**, Dompè SpA, 3; **A. Monguzzi**, Dompè SpA, 3; **E. Quarta**, None.

2240

An Exploratory 4-Week Study of a P2X3 Antagonist AF-219 in the Treatment of Patients with Osteoarthritis (OA) of the Knee. Vibeke Strand[1], Michael Kitt[2], Alan Kivitz[3], Anthony Ford[2], Peter Butera[2] and Bruce McCarthy[2]. [1]Stanford University, Portola Valley, CA, [2]Afferent Pharmaceuticals, Inc., San Mateo, CA, [3]Altoona Center for Clinical Research, Duncansville, PA.

Background/Purpose: Targeting P2X3 receptors that mediate the sensitizing effects of ATP released from inflamed and damaged tissues on the primary afferent neurons (PAN) of musculoskeletal structures may interrupt processes that drive hyperalgesia and allodynia. P2X3 blockade in a range of rodent hyperalgesia models has demonstrated efficacy. Recently, AF-219, a selective P2X3 antagonist, has shown efficacy in patients with refractory chronic cough. This was a multicenter phase 2 study to assess safety and efficacy of AF-219 versus placebo in patients with moderate to severe pain due to OA of the knee over 4

weeks. Secondary objectives assessed changes in physical function, stiffness, global assessment of OA, and health related quality of life.

Methods: Eligible patients, 40–80 years with Kellgren-Lawrence grade ≥2 and OA of ≥6 months duration required baseline average daily pain between 5 and 9 on the Numeric Pain Rating Scale (NPRS) following pain medication washout. Primary endpoint analysis of change from Baseline (Week 4) of weekly average daily NPRS used a mixed effects model with repeated measures yielding an overall 1-sided α=0.0225.

Results: The Full Analysis Population included 164 patients (AF-219 n=78, placebo n=86) who received ≥ one dose of study medication and completed ≥50% of week 1 daily NPRS scores. 134 patients completed 4 weeks treatment (AF-219 n=56, placebo n=78) due to early discontinuations for taste-related adverse events (AEs) with active treatment and lack of efficacy in placebo. Reduction in weekly average daily NPRS in AF-219 treated patients was numerically greater than placebo at each week. This difference was greatest in week 2 (p=0.0436).

Normalized pain, stiffness, physical function, and total WOMAC scores revealed larger numeric mean reductions at all end of treatment analyses; the Week 1 normalized total WOMAC score was significantly better in AF-219 treated patients (p=0.0176). Patient (PGIC) and Clinician Global Impression of Change (CGIC) and Short Form-36 physical component summary and role physical and bodily pain domains at end of treatment were significantly improved compared with placebo. Placebo patients took significantly more rescue medication over all 4 weeks.

There were no deaths or SAEs during the treatment phase. AEs were generally mild. 88% AF-219 treated patients reported dysgeusia/hypogeusia and 19% discontinued treatment due to dysgeusia.

Conclusion: In patients with OA of the knee, treatment with the P2X3 antagonist AF-219 resulted in improvement in pain and symptoms compared with placebo.

References: Ford A., Purinergic Signalling, 2012, Abdulqawi R., Eur Respir J 2013, Jarvis M., Proc Natl Acad Sci USA, 2002

Disclosure: V. Strand, Afferent Pharmaceuticals, Inc., 5; **M. Kitt**, Afferent Pharmaceuticals, Inc., 3; **A. Kivitz**, None; **A. Ford**, Afferent Pharmaceuticals, Inc., 3; **P. Butera**, Afferent Pharmaceuticals, Inc., 3; **B. McCarthy**, Afferent Pharmaceuticals, Inc., 3.

2241

Intermittent Analgesic Use and Risk of Pain Exacerbation in Knee Osteoarthritis: A Web Based Case-Crossover Study. Tahereh Erfani[1], Yuqing Zhang[2], Joanna Makovey[1], Ben Metcalf[3], Lyn March[1], Kim Bennell[3] and David J. Hunter[1]. [1]Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, Australia, [2]Boston University School of Medicine, Boston, MA, [3]University of Melbourne, Melbourne, Australia.

Background/Purpose: The pain experienced by osteoarthritis (OA) patients is neither constant nor stable and most patients experience episodes of pain exacerbations or flares. A number of factors have been hypothesized that could increase the risk of pain exacerbations in people with knee OA. Using a web based case-crossover study design, we evaluated whether intermittent use of analgesics is a risk factor for pain exacerbations in people with knee OA.

Methods: Participants with a diagnosis of symptomatic knee OA were recruited and followed for 3 months at 10-day intervals (control periods). Participants were also instructed to log on to the study website if they experienced a knee pain exacerbation during the follow-up period (case periods). Via the internet, we collected data on triggers occurring during "control periods" as well as "case periods". Pain exacerbation was defined as an increase of 20 mm in a participant's VAS knee pain score (VAS 0–100) over the follow-up period from his/her mildest pain score reported at the baseline visit. We collected data on analgesic use type and pattern during 7 days prior to the exacerbation dates. We asked participants whether they have taken analgesic over a specific time span (1 day, 2 days, 3–7 days prior). We assessed the effect of intermittent analgesic use on the risk of pain exacerbation compared with regular use using the conditional logistic regression model. Intermittent use was defined as taking analgesic in one of the three time spans only. Regular use was defined as taking analgesic daily over the prior 7 days.

Results: Of 268 participants (women: 61%, mean age: 62 years, mean BMI: 29.4 kg/m^2) recruited in the study, 153 participants experienced at least one episode of knee pain exacerbation. Intermittent use of any analgesic during the prior 7 days was associated with an increased risk of flares with OR of 1.57 (95% CI 0.92, 2.67) (Table). This odds ratio differed greatly amongst different categories of analgesics; intermittent use of Meloxicam (COX 2-Selective) had the highest effect on pain exacerbation with OR of 7.02 (95% CI 1.70, 29.1).

Conclusion: This study suggests that intermittent use of analgesics (compared with regular use) is associated with an increased risk of pain exacerbation in persons with symptomatic knee OA. The relationship was strongest for Meloxicam. Further work to better elucidate this connection will be important, as this may represent an important target for efforts designed to prevent and treat OA pain exacerbations.

Table Association of Intermittent Analgesic Use and Risk of Pain Exacerbation

			95 % CI	
	P	**OR**	**Lower**	**Upper**
Any Analgesic				
Regular Use (n*=411)		1.00	Ref	
No Analgesic Use (n=574)	0.18	0.68	0.39	1.19
Intermittent Use (n=313)	0.10	1.57	0.92	2.67
Aspirin				
Intermittent Use (n=48)	0.06	5.82	0.95	35.5
Ibuprofen				
Intermittent Use (n=59)	0.06	0.10	0.01	1.09
Meloxicam				
Intermittent Use (n=40)	**0.007**	**7.02**	**1.70**	**29.1**
Paracetamol				
Intermittent Use (n=172)	0.55	0.82	0.43	1.56
Tramadol				
Intermittent Use (n=13)	0.69	0.58	0.04	8.39
Celecoxib				
Intermittent Use (n=33)	0.09	0.19	0.03	1.26
Diclofenac				
Intermittent Use (n=35)	0.30	2.48	0.44	13.8

* Note: n=number of assessments

Disclosure: T. Erfani, None; **Y. Zhang**, None; **J. Makovey**, None; **B. Metcalf**, None; **L. March**, None; **K. Bennell**, None; **D. J. Hunter**, None.

2242

Effects of Intraarticular (IA) Corticosteroid Injections on Bone Markers and Endogenous Cortisol in Patients with Knee Osteoarthritis (OA): A Randomized, Double-Blind, Placebo Controlled Trial. Muhammad Imran[1], Aruna Baratham[2], Jo Wick[3], Barbara Lukert[4] and Herbert Lindsley[3]. [1]University of Kansas Medical Center, Kansas City, KS, [2]Private Community Practice, Kansas city, KS, [3]Kansas University Med Ctr, Kansas City, KS, [4]Kansas University Medical Center, kansas city, KS.

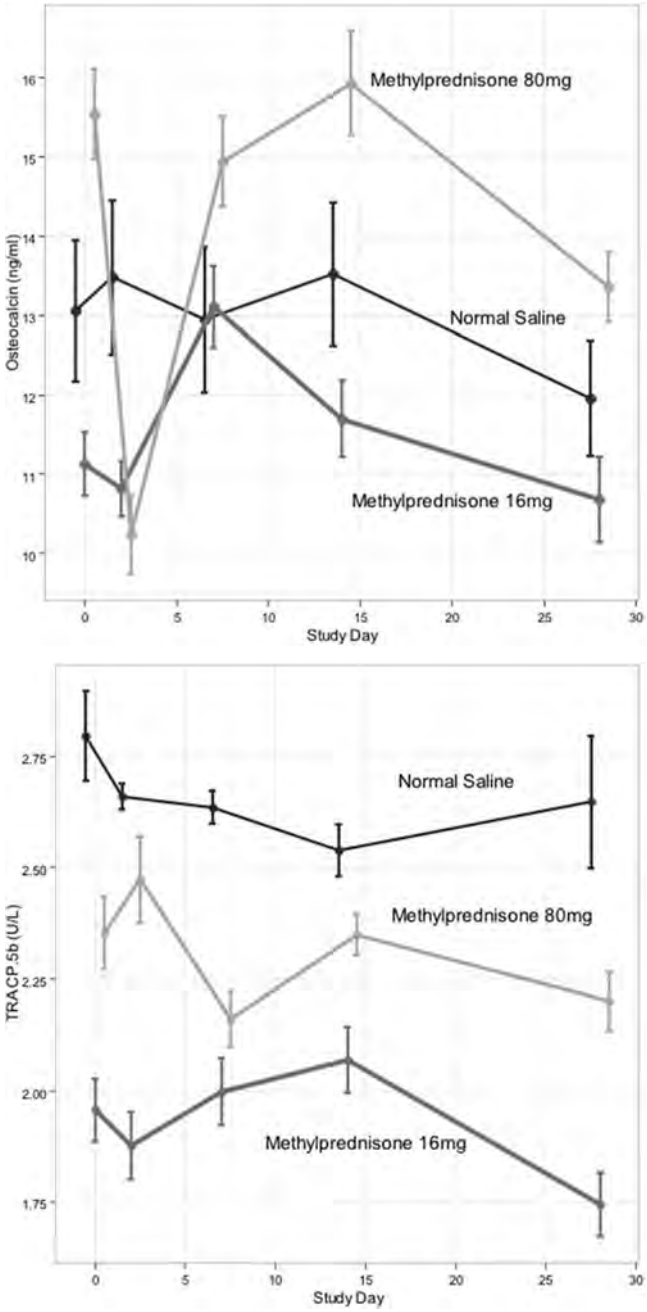
Background/Purpose: IA steroids are used to treat knee OA. Little is known about the systemic effect of intraarticular steroid injections on bone or the hypothalamic-pituitary- adrenal axis (HPA).

Methods: We describe a 2:2:1 randomized, double blind, placebo controlled study. 25 subjects (20 females, 5 males) with knee OA, age range 45–83 years were identified from our clinical practice. Ten subjects (Group 1) were injected with Depo-methylprednisolone 80 mg plus lidocaine 20 mg, 10 additional subjects (Group 2) were injected with Depo-methylprednisolone 16 mg plus lidocaine 20 mg and 5 subjects (Group 3) were given normal saline with lidocaine 20 mg. Blood draws were performed 5 times (Days 0, 2–3, 7, 14 and 28). Means and 95% CI were reported by time and group. All plots show mean (+/− SEM). Between and within-group comparison *p*-values were generated by *t*-tests. All parametric assumptions were verified.

Results: Mean levels of serum osteocalcin, a bone formation marker, reached a nadir (10.2 ng/ml (95% CI 9.3–11.2) from baseline of 15.5 ng/ml (95% CI 14.4–16.7) by Days 2–3 with recovery by Day 7 (14.9 ng/ml (95% CI 13.8–16.1)) after IA corticosteroids only for Group 1, with mean change of 5.3 ng/ml (95% CI 2.4–8.2) (p = 0.01). No change was seen in Groups 2, 3 (Fig 1, p> 0.05). In contrast, the bone catabolic marker Tartrate-resistant Acid Phosphatase Form 5b (TRACP-5b) showed no consistent change for any of the three groups over 28 days (range 1.7–2.7 U/L) (Fig 2). Mean baseline endogenous cortisol level reached a nadir by Days 2–3 for Group 1 (8.9 mcg/mL (95% CI 8.0–9.8)) and by Day 7 for Group 2 (8.9 mcg/ml (95% CI 8.0–9.7). Both returned at least to baseline by day 14. Baseline vitamin D levels did not differ significantly between groups (p > 0.05), though Group 1 levels were not as low (range 22–47 ng/mL) as Group 2 (range 8.3–51.5 ng/mL) or Group 3 (range 8.6–38.5 ng/mL). In control subjects, lower baseline levels of vitamin D were associated with greater decreases in

osteocalcin at Day 2 – 3 ($r = 0.9$, $p < 0.05$). Low levels of vitamin D were associated with greater levels of suppression of osteocalcin at Day 7 in Group 2 ($r = -0.7$, $p = 0.03$).

Conclusion: IA corticosteroids have a transient adverse effect on bone formation with significant recovery of osteocalcin levels by one week and no change in bone catabolism. Cortisol levels decrease slightly at one week of IA administration and rebound above baseline by two weeks. In contrast to daily oral corticosteroids, single doses of IA steroids have no persistent adverse effect on bone or the HPA axis.



Disclosure: M. Imran, None; **A. Baratham**, None; **J. Wick**, None; **B. Lukert**, None; **H. Lindsley**, None.

2243

Comparison Between Two Diclofenac Diethylamine Gel Formulations, 1.16% Vs 2.32%: Is It Only Increasing the Strength of the Active Ingredient Enough? Giuseppa Quartarone[1] and Nathalie Hasler-Nguyen[2]. [1]Novartis CH R&D OU Italy Greece, Milan, Italy, [2]Novartis CH Global R&D, Nyon, Switzerland.

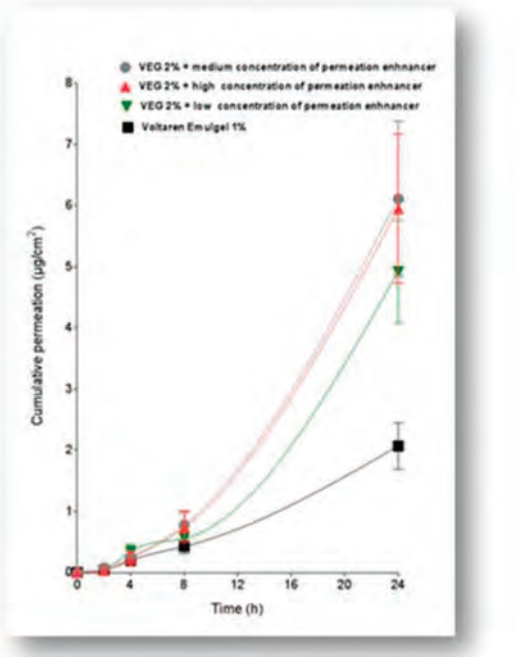
Background/Purpose: Topically applied non-steroidal anti-inflammatory drugs (NSAIDs) can produce clinically effective drug concentrations at a peripheral site, but with low systemic concentrations and thus a lower risk of AEs. Various factors influence penetration and absorption of topical NSAIDs such as chemical properties of adjuvants included in the formulation and inter-individual variability in skin absorption. Modulating skin permeation is a pivotal factor in the development of new formulations as well as their posology and duration of therapeutic effect. Diclofenac diethylamine (DDEA) 1.16% gel (Voltaren® Emulgel™ [VEG 1%], Novartis Consumer Health, Nyon Switzerland) is used topically to relief pain and inflammation; it is applied to the affected site 3 or 4 times daily. We compared the *in vitro* skin permeation of VEG 1% with a new double-strength formulation of DDEA 2.32% [VEG 2%] including different doses of a permeation enhancer (PE) to assess the hypothesis of increased skin permeation that may result in delivering higher drug amounts to target tissues when applied every 12h.

Methods: *In vitro* skin penetration studies were performed at 35°C in glass Franz static diffusion cells (Bernard Gallas, Antibes, F; 1.54 cm^2) using human skin. Samples of donor abdomens were obtained from the NDRI Institute (USA) and the WHRTB Institute (HU) and kept frozen at –80°C until use. The comparison of *in vitro* skin permeation of VEG 1% vs VEG 2% was performed. Then VEG 1% was tested against VEG 2% containing low (0.5%), medium (0.75%) and high (1.0%) amounts of a permeation enhancer. All samples were applied at 20 mg/cm^2 in a single dose, equivalent to the maximum daily dose of 4 applications of 5 mg/cm^2 under *in use* conditions.

Results: Addition of the PE at the VEG 2% gel resulted at a dose-dependent (up to 3-fold) increase in diclofenac's skin permeation (Fig. 1). Medium and high PE concentration resulted in similar cumulative permeation.

Conclusion: Addition of PE to VEG 2% resulted in an up to 3-fold increased diclofenac skin permeation which correlated with the PE dose concentrations. The new gel is expected to have a lasting effect, e.g. up to 12h, potentially attributed to the release of a higher amount of drug at the application site as confirmed in a RCT (Predel 2012), where 2 daily doses significantly reduced pain and improved joint function vs placebo. This could be useful when treating flares of peripheral joint conditions such as OA.

Fig. 1 In vitro Skin permeation of diclofenac from VEG 2% with various amounts of PE vs VEG 1%



Disclosure: G. Quartarone, None; **N. Hasler-Nguyen**, None.

2244

Multimedia Patient Education Tool for Patients with Osteoarthritis. Aparna Ingleshwar[1], Maria A. Lopez-Olivo[1], Robert Volk[1], Andrea Barbo[1], Maria Jibaja-Weiss[2], Heather Lin[1] and Maria E. Suarez-Almazor[1]. [1]The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]Baylor College of Medicine, Houston, TX.

Background/Purpose: The use of video modelling in patient education can result in positive patient outcomes including informed decision-making and improved self-management. The purpose of our study was to test the efficacy of a multimedia patient education tool (MM-PtET) for patients with knee osteoarthritis (OA).

Methods: We randomized 219 participants to receive a MM-PtET including storylines and testimonials n=109), and 110 to receive a written booklet with the same content (n=210). Inclusion criteria were: (i) age ≥50, (ii) prior diagnosis of knee OA (unilateral or bilateral) by a physician, (iii) adequate cognitive status, and (iv) ability to communicate in English or Spanish language. Upon completion of the baseline questionnaire, participants reviewed the materials (MM-PtET or written booklet) to which they were allocated, and then completed a post-questionnaire. Primary outcome measures included: a) Disease knowledge and, b) Decisional Conflict Scale (DCS). Secondary outcomes included: a) Ottawa Acceptability Instrument, and b) Evaluation of the educational materials. Demographics and health literacy (Adequate vs Inadequate) were also collected at baseline. We compared difference in knowledge scores (pre-post randomization) between the intervention and control groups, and within the groups themselves. Linear regression was employed to assess the influence of the intervention and patient characteristics on the knowledge score adjusting by age, sex and pre-randomization knowledge score.

Results: Mean age was 65±8 years, 76% were female, 82% had adequate health literacy, and 17(%) spoke Spanish. Mean difference in knowledge scores was higher in the MM-PtET group compared to controls (p=0.03). No statistically significant difference was observed in DCS scores between groups (p0.05, for both scales). However, significant improvement in DCS scores was observed in both groups after the intervention; patients perceived being more informed (p<0.001) with higher values clarity (p<0.001). Regression analysis indicated that intervention group, female gender, and higher level of educational attainment were predictive of higher knowledge improvement scores (p<0.05 for all, Adjusted R^2=0.11). Compared to control group, MM-PtET group participants were more likely to answer "Yes" to the following questions: (1) Did the video/booklet meet your needs for information about knee osteoarthritis? (94% vs 81%, p<0.01), and (2) Did you like the explanation of the medical facts in the video/booklet? (100% vs 95%, p=0.04). Compared to the control group, intervention group participants were more likely to rate the presentation of information about impact of OA and, self-care options as "Excellent" (47% vs 27% and 47% vs 32%, respectively; p<0.05 for both questions).

Conclusion: The results of our study support the efficacy of the MM-PtET over written booklets in improving disease knowledge in patients with knee OA.

Disclosure: A. Ingleshwar, None; **M. A. Lopez-Olivo**, None; **R. Volk**, None; **A. Barbo**, None; **M. Jibaja-Weiss**, None; **H. Lin**, None; **M. E. Suarez-Almazor**, None.

2245

Characteristics of Conventional Footwear and Their Association with Reductions in Knee Loading with a Flexible Footwear Intervention. Najia Shakoor[1], Roy H. Lidtke[1], Chris Ferrigno[2], Anjali Nair[1], Markus A. Wimmer[1], Laura E. Thorp[1], K. Douglas Gross[3] and Joel A. Block[1]. [1]Rush University Medical Center, Chicago, IL, [2]Rush University, Chicago, IL, [3]Boston Univ School Medicine, Boston, MA.

Background/Purpose: The peak external knee adduction moment (KAM) as measured through gait analyses has been associated with severity, progression and pain in medial knee osteoarthritis (OA); thus, biomechanical approaches to knee OA aim to reduce the KAM. We previously reported that flat flexible footwear may reduce the KAM compared to wearing conventional footwear. However, the characteristics of conventional footwear that influence the magnitude of this reduction remain unclear. Here we evaluate the footwear of participants with knee OA to identify the properties associated with response to a flexible footwear intervention.

Methods: Participants with medial compartment knee OA were provided with a flexible study shoe (previously described "mobility shoe") and were asked to bring their own conventional shoes that they used most often for walking activities. Their own shoes were evaluated for stability/flexibility with the following 3 tests: 1) Sagittal stability: the shoe was held perpendicular to a flat surface with the tip of the toe on the ground and approximately 5 pounds of load was applied vertically on the heel; 2) Torsional stability: the shoe was held parallel to the ground with a hand at the heel and the toe and about 5 pounds of torque was applied; 3) Heel counter stability: about 5 pounds of force was applied to the medial and lateral heel counter using the thumb and index finger. With all three tests, the resistance to deformation was classified on a 3-point grading scale (0: rigid, 1:supportive, 2: flexible). The heel height of the shoes was also measured. Gait analyses were performed while walking in subjects' own shoes and the flexible study shoes. Paired t-tests were used to evaluate overall percent reduction in the KAM with the flexible footwear compared to participants' own shoes, and the association between reduction in the KAM and measures of their own shoe flexibility/stability was evaluated using Spearman's coefficient.

Results: 22 participants (15 women, mean age (SD) of 62±11 yrs) were evaluated. Overall, the use of the flexible study shoes was associated with a significant 6% reduction in the KAM (2.55±1.00 vs 2.40±1.00 %BW*ht, p=0.007). The percent reduction demonstrated in the KAM was significantly associated with the sagittal (rho=−0.470, p=0.027), torsional (rho=−0.470, p=0.027), and heel counter stability (rho=−0.551, p=0.008) of the participant's own shoe, with more rigid footwear being associated with greater KAM reduction. The assessments for sagittal and torsional stability did not appear to provide unique information since they were strongly correlated (rho = 1.0) with one another. Interestingly, heel height was not associated the extent of KAM reduction (rho=0.181, p=0.488).

Conclusion: Footwear has been associated with knee joint loading and choice of footwear may be an important consideration in knee OA. This study suggests that those wearing more rigid footwear may expect the greatest benefit in medial knee load reduction with transition to flexible footwear and supports the concept that flexibility is an important load-reducing feature of footwear. Simple protocols to evaluate footwear such as those used in this study may be beneficial in helping patients make choices regarding footwear.

Disclosure: N. Shakoor, DJO and Dr. Comfort, 7; **R. H. Lidtke**, DJO and Dr. Comfort, 7; **C. Ferrigno**, None; **A. Nair**, None; **M. A. Wimmer**, None; **L. E. Thorp**, None; **K. D. Gross**, None; **J. A. Block**, None.

2246

Reduction of Knee Osteoarthritis Symptoms in a Cohort of Bariatric Surgery Patients. Andrea Leyton-Mange, Janice Lin, Ryan Flanagan, Evan Wilder, Jay Bhatia, Farah Taufiq, Lauren Browne, Mukundan Attur, Renata La Rocca Vieira, Manish Parikh, Christine Ren-Fielding, Steven B. Abramson and Jonathan Samuels. NYU Langone Medical Center, New York, NY.

Background/Purpose: Obesity is a modifiable risk factor of knee osteoarthritis (KOA). While medical treatments can have limited beneficial effects, an alternative strategy would target weight loss to delay or avoid joint replacement. Limited retrospective data have shown improvement in KOA pain after bariatric surgery. We initiated a prospective study to evaluate painful KOA in the obese population, and track whether weight loss after bariatric surgery affects KOA-related pain and physical function.

Methods: We screened consecutive patients (N=537) prior to laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy, or gastric bypass (RYGB). Patients age ≥21 with knee pain for ≥1 month and a visual analog scale pain score ≥30mm were enrolled, excluding lupus, inflammatory arthritis, or psoriasis. Baseline pre-op assessments included x-rays for OA severity by Kellgren-Lawrence (KL) grade, the Knee Injury and Osteoarthritis Outcome Score (KOOS), and the Western Ontario McMasters Universities Osteoarthritis Index (WOMAC) with a Likert scale calculated from the KOOS. Patients are completing the questionnaires and being measured for BMI and % excess weight loss (%EWL) at intervals through 12 months post-op.

Results: In total, 307 patients reported knee pain, and of those, 175 met criteria and consented (89.7% female, mean BMI 43 kg/m^2±7, range: 32–60, mean age 42 ±11, range: 18–73). X-rays were completed on 160 patients: KL0=38, KL1=31, KL2=33, KL3=33, KL4=25. The mean pre-op KOOS scores were 46 (0=worst, 100=best) for both pain and ADLs, the mean WOMAC pain score was 11 (0=best, 20=worst), and the mean overall WOMAC index was 52 (0=best, 96=worst). Higher KL correlated with symptoms; mean KOOS pain was 54, 49 and 37 for KL0, KL1–2, and KL3–4 (p=0.0006 for KL1–2 vs 3–4), with similar trends across other KOOS and WOMAC scores. Higher BMI also correlated with worse pre-op knee symptoms, as the quartiles with the lowest and highest BMIs (32–38 and 49–61) had mean KOOS pain scores of 48 and 43. Thus far, 117 patients have had surgery (31 RYGB, 64 sleeve, 22 LAGB). Improvement in average KOOS and WOMAC scores over baseline has been observed at all intervals (46, 36, 31 and 7 responses at 1,3,6,12 month visits), with more improvement farther after surgery. At 6

months post-op, mean KOOS scores improved 29 points for pain, with mean WOMAC pain and index improving by 6 and 22 points. The %EWL correlated with knee symptoms at each interval and for all followups combined, as the smallest and largest %EWL quartiles (4–29%, 54–92%) showed mean improvements of 18 and 31 points ($p=0.03$) in KOOS pain - mirrored across KOOS and WOMAC scores. RYGB and sleeve yielded higher %EWL than LAGB (44%, 43% vs. 37%) across all intervals, and greater improvement in mean KOOS and WOMAC scores (e.g. mean KOOS pain increased by 28, 29 and 8). Neither presence nor severity of KOA severity affected knee pain improvement from weight loss.

Conclusion: These data suggest that bariatric surgery improves patients' KOA pain proportional to weight loss, with durability over time. RYGB and sleeve gastrectomy have more impact on knee symptoms than LAGB. While patients with worse KL grades report more baseline pain and disability, x-ray severity did not impact the response to weight loss.

Disclosure: A. Leyton-Mange, None; **J. Lin**, None; **R. Flanagan**, None; **E. Wilder**, None; **J. Bhatia**, None; **F. Taufiq**, None; **L. Browne**, None; **M. Attur**, None; **R. La Rocca Vieira**, None; **M. Parikh**, None; **C. Ren-Fielding**, Apollo Endosurgery, 5; **S. B. Abramson**, None; **J. Samuels**, None.

2247

Bariatric Surgery Improves Quality of Life in Patients with Osteoarthritis and Obesity Compared to Non-Surgical Weight Loss. Christopher Chong[1], Sangeeta Kashyap[1], Philip Schauer[1], Colin O'Rourke[1] and M. Elaine Husni[2]. [1]Cleveland Clinic, Cleveland, OH, [2]Cleveland Clinic Foundation, Cleveland, OH.

Background/Purpose: Numerous studies support obesity as a strong risk factor for development and progression of knee osteoarthritis (OA). The potential benefits of massive weight loss, as seen after bariatric surgery, have not been well studied. The study objective is to examine if massive weight loss after bariatric surgery is associated with improved OA symptoms and quality of life (QoL) compared with medical management alone in obese patients.

Methods: A total of 150 patients were screened for clinical and radiographic evidence of OA within the STAMPEDE trial (March 2007 – Jan 2011). The STAMPEDE trial examined the effects of bariatric surgery vs. medical management alone in obese patients with diabetes. 100 patients received bariatric surgery (50 sleeve gastrectomy and 50 Roux-en-Y gastric bypass) and 50 patients were medically managed. Clinical data, medication usage, and QoL scores were collected before and 12 months after intervention. OA was defined by physician diagnosis at an office visit and/or radiographic evidence of OA (joint space narrowing and osteophytes) of the hip, knee, ankle, or foot. The change in 12 month post-intervention SF-36 scores between the surgical group and medically managed group were compared. Scores were compared using linear regression models, adjusting for baseline score. Baseline scores were centered at their median value.

Results: 67 patients with OA had baseline and follow up data available for review. Demographics between the bariatric surgery and medical group were similar (mean age 51, female gender 44/67, mean BMI 36.6). 49 patients were in the surgery group and 18 in the medical group. There was a statistically significant difference in BMI change, over 12 months, between the surgical group and medical group (BMI −9.12 and −2.24 respectively). The surgical group improved in each of the SF-36 physical health scales (Figure 1). There was a significant improvement in the surgical group compared to the medical group in the physical functioning (P 0.03), general health ($P<0.001$), and overall physical health scores (P 0.004) (Table 1). There was no significant difference between the groups in pain or role-physical scores.

Conclusion: Patients with OA who underwent massive weight loss after bariatric surgery had significant improvement in SF 36 physical functioning and general health scores when compared to patients treated with medical management of weight loss alone. There was also a trend suggesting improvement in bodily pain and role-physical.

Table 1: Adjusted SF-36 improvement in surgical compared to medical group at 12 months

SF-36 Scale	SF-36 difference	95% CI	p-value
Physical Functioning	11.47	1.15–21.79	0.03
Role Physical	8.55	−7.12–24.21	0.28
Bodily Pain	9.44	−2.77–21.65	0.13
General Health	19.24	12.25–26.23	<0.001
Physical Health Summary	11.87	3.94–19.81	0.004

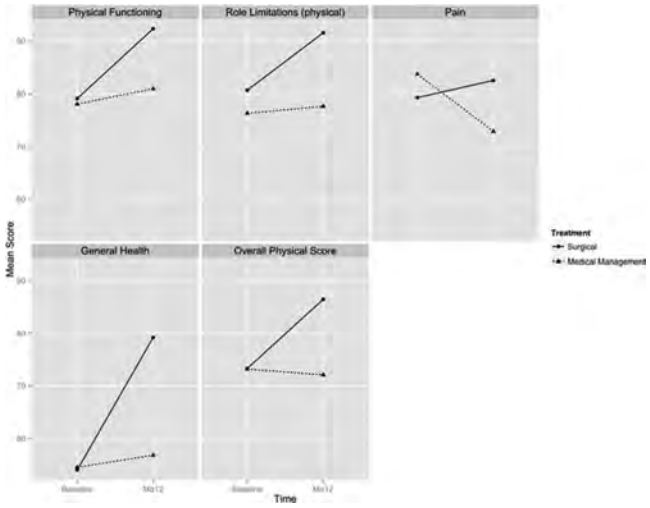


Figure 1: Average SF-36 scores at baseline and 12 months

Disclosure: C. Chong, None; **S. Kashyap**, None; **P. Schauer**, None; **C. O'Rourke**, None; **M. E. Husni**, None.

2248

Clinical Outcomes, Neuropathic Pain and Patient Satisfaction over a 15 Year Period Following Primary Tka: A Repeat-Cross-Sectional Analysis. Anne Lübbeke, Matthieu Zingg, Daniel Fritschy, Pierre Hoffmeyer and Hermes Miozzari. Geneva University Hospitals, Geneva, Switzerland.

Background/Purpose: Studies evaluating patient-reported long term outcomes (>10 years) after primary TKA are lacking. Moreover, variability in patient satisfaction after TKA has been reported for the short and mid term, but has not been investigated over the long term and in relation to presence or absence of neuropathic pain.

Our objective was to assess pain, function, general health, and patient satisfaction at short, mid and long term following primary TKA.

Methods: Patients eligible for this study were part of a prospective hospital-based cohort of all primary TKAs operated upon since March 1998. All patients operated in 2012, 2010, 2007, and 2004–1998, who were alive and still living in the area, received a postoperative questionnaire by mail between 2012 and 2013. We performed repeat cross-sectional analyses of pain, function, general health and patient satisfaction at the following time-points: prior to surgery, and 1, 2, 5, 9–11 and 12–15 years postoperative. Pain was evaluated with use of WOMAC and VAS score, neuropathic pain with DN4 (=neuropathic pain diagnostic questionnaire), function with WOMAC, general health with the SF-12, and satisfaction was evaluated with use of a five-item satisfaction rating.

Results: 1451 TKAs were eligible (68.4% women, mean age 71 (±9) years, mean BMI 29.6 kg/m^2). Of those, 1021 returned the questionnaire (response rate 70.4%). Their mean age was 71 years, mean BMI was 29.5 kg/m^2 and 67.8% were women. Mean values of pain, function and general health were clinically significantly higher (effect sizes 0.22–1.71) one year postoperative as compared to prior to surgery (see Table). For pain and satisfaction there was an ongoing clinically significant "improvement" between 1 and 2 years postoperative. Results remained similar between 2 and 10 years with minimally lower (effect size <0.2) outcomes between 10 and 15 years. Neuropathic pain was reported in 12.4% preoperative, 14% at 1 year, 10% at 2 years and 5–7% 5–15 years after surgery. Its presence was significantly ($p<0.001$) associated with dissatisfaction.

Conclusion: Clinical outcomes and patient satisfaction were similar between 2 and 15 years after primary TKA. Neuropathic pain when present was strongly associated with dissatisfaction.

	Prior to surgery	n	1 yr. post surgery	n	2 yrs. post surgery	n	5 yrs. post surgery	n	10 yrs. post surgery	n	12-15 yrs. post surgery	n
WOMAC, mean, SD												
Pain	39.8 (±17.9)	785	72.2 (±22.1)	529	77.9 (±22.0)	111	82.3 (22.6)	100	78.8 (±23.6)	145	75.5 (±26.4)	136
Function	43.7 (±19.3)	769	70.1 (±21.8)	526	68.1 (±22.7)	107	69.1 (±25.0)	102	69.8 (±26.4)	144	67.2 (±28.8)	136
VAS pain, mean, SD	5.9 (±1.8)	389	2.4 (±2.2)	522	2.0 (±2.3)	106	1.6 (2.4)	103	2.0 (±2.5)	138	2.0 (±2.5)	140
SF-12, mean, SD												
pcs	34.3 (±7.6)	777	40.4 (±8.8)	521	40.2 (±9.8)	106	39.8 (±10.5)	98	38.9 (±10.0)	136	37.5 (±9.9)	126

mcs	44.9 (±11.2)	777	47.3 (±11.0)	521	47.9 (±10.3)	106	46.9 (±9.9)	98	47.5 (±11.2)	136	45.9 (±10.0)	126
DN4 score ≥ 4 (%)*	14 (12.4)	113	27 (14.4)	187	11 (10.3)	107	7 (6.9)	102	8 (5.8)	138	7 (5.1)	136
Satisfaction (%)				520		109		103		151		142
Very satisfied			252 (48.5)		54 (49.5)		48 (46.6)		90 (59.6)		81 (57.0)	
Satisfied			157 (30.2)		39 (35.8)		39 (37.9)		42 (27.8)		37 (26.1)	
Somewhat satisfied			73 (14.0)		10 (9.2)		8 (7.8)		10 (6.6)		10 (7.0)	
Somewhat dissatisfied			15 (2.9)		2 (1.8)		4 (3.9)		2 (1.3)		5 (3.5)	
Dissatisfied			23 (4.4)		4 (3.7)		4 (3.9)		7 (4.6)		9 (6.3)	
DN4 score ≥ 4 in Dissatisfied (%)**			46.2 %		66.7%				17.9%***			

*DN4 score = neuropathic pain diagnostic questionnaire; **among dissatisfied and somewhat dissatisfied patients taken together; ***5–15 years after surgery combined

Disclosure: A. Lübbeke, None; **M. Zingg**, None; **D. Fritschy**, None; **P. Hoffmeyer**, None, 9; **H. Miozzari**, None.

2249

Criteria for Clinically Important Worsening in Knee and Hip Osteoarthritis. Elien A.M. Mahler[1], Alfons A. den Broeder[1], Vincent J.J.F. Busch[1], Johannes W.J. Bijlsma[2] and Els van den Ende[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Clinically important worsening in OA has not been well defined. Validated worsening criteria are important for research but also clinical practice to make informed treatment choices. The goals of this study are 1) to select candidate clinical worsening criteria and 2) to validate criteria for clinically important worsening.

Methods: Data were used from a cohort of knee and hip OA outpatients visiting our department who received standardised evidence-based tailored conservative treatment in a stepped-care format for 3 months. The development cohort comprised 218 patients with three-months follow up and the validation cohort consisted of 296 patients with two-years follow up. For this study baseline and three month data were used.

In the first round, an expert group (methodologists, orthopaedic surgeon, physical therapists, psychologist, rheumatologists) reviewed previously proposed criteria for clinical worsening and selected on the basis of consensus and face-validity the criteria that should be tested. Furthermore, the expert group decided that newly defined criteria of worsening should contain both pain and function and optional PGA and embed both an absolute and a relative change. Then, 15 new criteria of worsening criteria were constructed. In the second round, first we examined the sensitivity and specificity of the newly developed criteria of worsening in development cohort using an anchor-based 7-point Likert transition scale (much worse-much better). Second, we evaluated all the selected criteria from the literature and newly developed criteria of worsening criteria in the validation cohort using the transition scale.

Results: The expert group's review of existing criteria yielded five criteria that were included in the validation round and the sensitivity of these previously proposed criteria for clinical worsening was low while specificity was high. Of the expert group's proposed criteria, the sensitivity and specificity of the newly developed worsening criteria ranged from 1 to 65% and 60 to 97% respectively. The three newly defined sets of criteria that performed best incorporated smaller relative and absolute changes compared with improvement criteria. Set 1 and 3 performed best, with sensitivity and specificity ranging between 50 and 75% in both the development and the validation cohort (Table 1).

Conclusion: Previously proposed criteria for clinical worsening in knee or hip OA are specific but lack sensitivity. Our results suggest that, compared with improvement criteria, criteria for worsening should incorporate relatively small absolute and relative changes. Our newly developed criteria pairs acceptable sensitivity with acceptable specificity and can be used to measure clinically important worsening in knee/hip OA studies and clinical care.

Table 1. Sensitivity and specificity of newly developed worsening criteria, in the development and validation cohort

	Newly developed criteria	Development cohort Sensitivity %	Development cohort Specificity %	Validation cohort Sensitivity %	Validation cohort Specificity %
Set 1	Set 1: worsening in ● pain ≥20% and absolute change ≥20 or ● function ≥10% and absolute change ≥10 or ● PGA ≥10% and absolute change ≥10				
	with NRSpain	53	70	58	75
	With WOMACpain	50	71	55	69
Set 2	Set 2: worsening in ● pain ≥20% and absolute change ≥ 20 or ● function ≥10% and absolute change ≥5 or ● PGA ≥10% and absolute change ≥5 or				
	with NRSpain	55	65	65	70
	With WOMACpain	58	62	63	65
Set 3	Set 3: worsening in ● pain ≥10 % and absolute change ≥ 10 or ● function ≥10 % and absolute change ≥ 10 or ● PGA ≥10 % and absolute change ≥ 10				
	with NRSpain	65	60	64	69
	With WOMACpain	55	68	54	68

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2250

The Effects of Treatment on Disease Symptoms and Progression of Structural Changes in Knee Osteoarthritis Participants from the Osteoarthritis Initiative Progression Cohort. Jean-Pierre Pelletier[1], Camille Roubille[1], François Abram[2], Marc Dorais[3], Philippe Delorme[1], Jean-Pierre Raynauld[1] and Johanne Martel-Pelletier[1]. [1]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC, [2]Medical Imaging Research & Development, ArthroLab Inc., Montreal, QC, [3]StatSciences Inc., Notre-Dame de l'Île-Perrot, QC.

Background/Purpose: In the perspective of personalized management of osteoarthritis (OA), a clinically relevant concern is the impact of meniscal extrusion on response to treatment. This study evaluated the role of meniscal extrusion on the effects of conventional OA pharmacological treatments and of the combination of glucosamine and chondroitin sulfate (Glu/CS) on knee structural changes.

Methods: Participants (n=600) from the OAI progression cohort were stratified based on whether or not they received conventional OA pharmacological treatment (analgesics/NSAIDs), the presence/absence of medial meniscal extrusion at baseline, and whether or not they received Glu/CS for 24 consecutive months (T24). The main outcomes were knee structural changes including cartilage volume measured by quantitative MRI and loss of joint space width (JSW).

Results: In both - and + analgesics/NSAIDs groups (n=300 each), participants with meniscal extrusion had more severe disease at baseline, more JSW loss ($p \leq 0.0001$) and cartilage volume loss in the medial compartment ($p=0.003$) compared to those without meniscal extrusion. In both analgesics/NSAIDs groups, no significant effect on JSW loss was found at T24 between groups regardless of the presence or absence of meniscal extrusion and of the consumption or not of Glu/CS, whereas significant differences emerged for cartilage volume loss. In the –analgesics/NSAIDs group, at T24, while no difference was found within the participants without meniscal extrusion (mild disease), in participants with meniscal extrusion (more progressive disease), Glu/CS had a protective effect on cartilage volume loss in the medial plateau ($p=0.01$, univariate analysis; $p=0.009$, multivariate analysis). In the +analgesics/NSAIDs group, in participants without meniscal extrusion (moderate disease), Glu/CS protected the cartilage volume in the lateral plateau($p=0.007$, univariate analysis; $p=0.013$, multivariate analysis). No effect was found in participants from the +analgesics/NSAIDs group with meniscal extrusion (severe disease).

Conclusion: This study is the first to demonstrate, using qMRI, the response to conventional and Glu/CS treatments in subjects with meniscal extrusion. Data first revealed that Glu/CS prevented cartilage volume loss in patients with mild to moderate disease, i.e., subjects with meniscal extrusion not taking analgesics/NSAIDs and those without meniscal extrusion but taking analgesics/NSAIDs. The non-effect on patients without meniscal extrusion not taking analgesics/NSAIDs, representing very mild disease, probably reflects that the cartilage volume loss was small and unlikely to provide an accurate estimate. Moreover, in subjects with meniscal extrusion who took analgesics/NSAIDs (severe disease), the non-effect observed likely reflects irreversible cartilage damage. The present data argue for MRI based diagnosis of meniscal extrusion in clinical practice to help physicians identify knee OA patients more susceptible to benefit from DMOAD treatment. These data also support the added benefit of using

qMRI as an alternative to X-ray for the evaluation of DMOAD agents, especially in patients with less advanced disease.

Disclosure: J. P. Pelletier, ArthroLab, 9; **C. Roubille**, None; **F. Abram**, ArthroLab, 3; **M. Dorais**, ArthroLab, 5; **P. Delorme**, ArthroLab, 3; **J. P. Raynauld**, ArthroLab, 5; **J. Martel-Pelletier**, ArthroLab, 9.

2251

Kneeling Disability Associated with the Treatment of Osteoarthritis: Analysis of a Copcord Study in Mexico. Alexia Hernández-Cáceres[1], Jacqueline Rodríguez-Amado[1], Ingris Peláez-Ballestas[2], David Vega-Morales[3], Mario Garza-Elizondo[1], Roberto Negrete-López[1], Lorena Pérez-Barbosa[1] and Janett Riega-Torres[1]. [1]Servicio de Reumatología, Departamento de Medicina Interna del Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León, Monterrey, Mexico, [2]Departamento de Reumatología Hospital General de México "Dr. Eduardo Liceaga", Distrito Federal, Mexico, [3]Hospital Universitario UANL, Monterrey, Mexico.

Background/Purpose: Osteoarthritis (OA) is the most prevalent rheumatic disease in Mexico. The core treatment, a combination of pharmacological and non-pharmacological modalities, is mainly performed in primary care.

Objective: To describe which are the most employed therapeutic resources for osteoarthritis and their associated factors in the urban and rural population of Nuevo León.

Methods: Analysis of a cross-sectional study of patients with OA from a COPCORD study database that included the adult population ≥ 18 years of a representative sample of the State of Nuevo León who met the diagnosis of clinical OA and had information about the anatomical location of the disease. All variables in the COPCORD questionnaire were included and performed a descriptive analysis. For the univariate analysis, the population was divided between those who did and those who didn't receive treatment. For the multivariate analysis, a regression logistic analysis of all the variables with statistical significance was performed.

Results: There were 696 patients with OA with an average age of 58yr (SD 14.1), 484 (69.5%) women and 579 (83.2%) patients were living in urban areas. Five hundred and two patients (85.1%) had pain in the last 7 days, with a mean VAS pain of 6 (IQR 3); 507 (72.8%) patients had a VAS pain ≥4. Functional disability was present in 133 (19%) patients and a mean HAQ of 0.37 (IQR 0.75) was found. The most common places of OA where knee (356, 51.5%), hand (224, 37%) and generalized OA (93, 13%); 259 (37%) patients already knew their diagnosis by the time of the examination. Four hundred and ninety four (71%) patients reported having treatment for OA, being the most frequently prescribed NSAIDS (289, 58.5%), mostly diclofenac (198, 68.5%). Analgesics were used by 100 (20.2%) patients, mostly acetaminophen (73, 77%). There was more utilization of NSAIDS by physicians (231/289, 79.9%) and of analgesics by self-prescribers (35/100, 35%). In the univariate analysis, the variables associated with treatment where age >58yr (OR 1.3, 95% CI 1.0–1.5), female gender (OR 1.17, 95% CI 1.0–1.3), VAS pain ≥ 4 (OR 1.3, 95% CI 1.1–1.4), functional disability (OR 2.6, 95% CI 1.6–4.1), HAQ > 0.375 (OR 1.9, 95% CI 1.5–2.4), and past diagnosis of OA (OR 5.1, 95% CI 3.3–8.0). In a multivariate analysis, VAS pain ≥ 4 (OR 1.9, 95% CI 1.2–2.8), kneeling disability (OR 3.15, 95% CI 1.3–7.4) and previous diagnosis of OA (OR 7.6, 95% CI 4.5–12.9) had statistical significance.

Conclusion: Associated factors with treatment of OA are VAS pain ≥ 4, kneeling disability and previous diagnosis of OA.

Disclosure: A. Hernández-Cáceres, None; **J. Rodríguez-Amado**, None; **I. Peláez-Ballestas**, None; **D. Vega-Morales**, None; **M. Garza-Elizondo**, None; **R. Negrete-López**, None; **L. Pérez-Barbosa**, None; **J. Riega-Torres**, None.

2252

Autoimmune Thyroid Disease Is Associated with a Higher Frequency of Spinal Degenerative Disc Disease. Asha Shrestha, Hillel Cohen and Clement Tagoe. Albert Einstein College of Medicine, Bronx, NY, Bronx, NY.

Background/Purpose: Autoimmune thyroid disease (AITD) has been linked to a number of rheumatic syndromes including arthritis and generalized pain. Although AITD has been associated with back pain, the relationship with spinal degenerative disc disease (DDD) in particular is unknown. We therefore investigated the association between AITD and spinal DDD.

Methods: We identified adult patients with anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibodies tested from January 1997 through January 2014 in the Clinical Looking Glass database at the Montefiore Medical Center. We performed a cross-sectional analysis of patients with and without AITD. Main variable of interest was AITD, defined as abnormal levels of anti-TPO and/or anti-TG antibodies. Main outcome measure was spinal DDD confirmed by radiological evidence of disc disease. Adjusted odds ratios were estimated with multivariate logistic regression model. The model was adjusted for covariates including age, gender, race, ethnicity, smoking, diabetes (DM), and body mass index (BMI). We did sub-analysis by stratifying patients according to BMI, thyroid stimulating hormone (TSH) levels, and by excluding patients with known connective tissue diseases.

Results: Out of 7094 patients with anti-TG and anti-TPO levels, we included 4383 patients with complete data on thyroid autoantibodies, spinal DDD, and the covariates. Of those, 1557 (35.5%) patients had AITD. Compared to patients without AITD, patients with AITD were more likely to be women (86% vs 81%, $p < 0.001$); more likely to be hypothyroid (24% vs 8%, $p<0.001$); more likely to be on levothyroxine (31% vs 9%, $p<0.001$); less likely to be euthyroid (50% vs 73%, $p<0.001$); less likely to have DM (21% vs 27%, $p=0.02$); and less likely to be black (25% vs 37%, $p<0.001$). BMI in the 2 groups were comparable. There were no significant differences for age, smoking, and known connective tissue diseases between the 2 groups.

The unadjusted odds ratio (OR) with 95% confidence interval (CI) for AITD of having spinal DDD was 1.5 (1.3,1.7), $p<0.001$. After adjustment for the covariates, the association of AITD with spinal DDD was stronger with an OR of 1.8 (1.5 2.1), $p<0.001$, table 1. When stratifying by BMI and TSH levels, the results were similar within the strata. Further sub-analysis by excluding patients with known connective tissue diseases showed a similar positive association.

Conclusion: AITD is significantly associated with a higher frequency of spinal DDD, both in patients with and without known connective tissue diseases, independent of BMI and TSH levels. This finding is novel and suggests a possible important link between thyroid autoimmunity and spinal DDD. Further studies are needed to determine if AITD has a causal link with spinal DDD.

Table 1: Adjusted odds ratio for AITD and spinal DDD

	Outcome = Spinal degenerative disc disease	
Variables	**Adjusted OR (95%CI)**	**P-value**
AITD	**1.75 (1.49, 2.05)**	**<0.001**
Age	1.11 (1.12, 1.19)	<0.001
Age squared	0.99 (0.99, 1.00)	<0.001
Black	0.93 (0.75, 1.15)	0.51
Hispanic	1.32 (1.07, 1.63)	0.01
Other race	0.73 (0.55, 0.97)	0.03
BMI	1.02 (1.00, 1.03)	0.01
Female	1.13 (0.93, 1.38)	0.19
Smoker	1.16 (0.99, 1.35)	0.06
Diabetes	1.71 (1.45, 2.01)	<0.001

Disclosure: A. Shrestha, None; **H. Cohen**, None; **C. Tagoe**, None.

ACR/ARHP Poster Session C
Osteoporosis and Metabolic Bone Disease - Clinical Aspects and Pathogenesis: Osteoporosis: Treatment, Safety, and Long Term Outcomes
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

2253

Effect of Teriparatide in Patients with Osteoporosis with Prior Vertebral Fracture. Guillermo Valenzuela[1], Douglas Yim[2], Douglas Beall[3], Michael Gordon[4], John H. Krege[5] and Kelly D. Krohn[5]. [1]Integral Rheumatology and Immunology Specialists, Plantation, FL, [2]Division of Vascular & Interventional Radiology, University of California, Irvine Medical Center, Orange, California, Orange, CA, [3]Clinical Radiology of Oklahoma, Edmond, Oklahoma, Edmonda, OK, [4]Newport Orthopedic Institute, Newport Beach, California, Newport Beach, CA, [5]Eli Lilly and Company, LLC, Indianapolis, Indiana, Indianapolis, IN.

Background/Purpose: The Direct Assessment of Nonvertebral Fracture in Community Experience (DANCE) study was an open-label, prospective, observational study that examined occurrence of nonvertebral fragility fractures in osteoporotic men and women

treated with teriparatide for ≤2 yr. and followed for up to 2 more yr. in a community based setting. In DANCE, teriparatide decreased the incidence of nonvertebral fragility fractures in patients treated for >6 mo. (6–24 mo.) vs. ≤6 mo. of therapy (2.12% vs. 3.70%, p=0.002). This retrospective analysis assessed the effects of teriparatide in patients who entered DANCE with prior vertebral fractures, including those with previous vertebral augmentation, vs. those without.

Methods: We compared baseline demographics, safety, and teriparatide effectiveness in patients with or without prior vertebral fractures. Patients with previous vertebral fractures included those that did or did not have vertebral augmentation before study enrollment. Incident rates of nonvertebral fracture following 6–24 vs. 0–6 mo. of teriparatide therapy were compared using a Poisson regression model.

Results: Of 4085 patients who received ≥1 dose of teriparatide 20 μg/day, 715 had documented prior vertebral fractures of which 202 had previous vertebral augmentation. Patients with prior vertebral fractures vs. those without were older (mean [SD] age, 71.85 [10.66] vs. 67.07 [11.92] yr., respectively), more likely to have had prior fragility fractures (95.2% vs. 47.8%), had higher L1-L4 T-scores (−2.35 [1.47] vs. −2.50 [1.35]), had more baseline clinical conditions (2.21 [1.58] vs. 1.72 [1.37]), and a higher proportion had comorbid conditions (88.4% vs. 81.6%) (all p-values <0.04). Mean teriparatide exposure was similar for both groups (541.8 [283.1] vs. 542.3 [292.2] days). Bone density in the spine, total hip, and femoral neck increased similarly in patients with or without prior vertebral fracture (all p-values ≥0.06), with similar results in patients who did or did not have vertebral augmentation (all p-values ≥0.08). Compared with the first 6 mo., the incidence of nonvertebral fractures during months 6–24 was 52% lower (absolute difference 3.76%) in patients with and 37% lower (absolute difference 1.08%) in those without prior vertebral fractures. The reduced incidence of nonvertebral fracture over time was statistically consistent in both groups (effect of time by subgroup interaction p=0.38). Reduction in nonvertebral fracture during months 6–24 vs. the first 6 mo. of treatment was 62% lower (absolute difference 4.33%) for patients with prior vertebral augmentation and 41% (absolute difference 1.44%) for those without. Teriparatide was well tolerated.

Conclusion: Patients with prior vertebral fractures were older and had more fragility fractures and comorbid conditions at baseline than patients without previous vertebral fracture. In this post-hoc analysis, teriparatide improved bone density and reduced the incidence of nonvertebral fractures with >6 mo. vs. ≤6 mo. of therapy in osteoporosis patients with and without prior vertebral fracture, including those with prior vertebral augmentation.

Disclosure: G. Valenzuela, Eli Lilly and Company, 8, Amgen, 8, Janssen Pharmaceutica Product, L.P., 8, Questcor, 8; **D. Yim**, Eli Lilly and Company, 5; **D. Beall**, Eli Lilly and Company, 5, Medtronic, 5, Benvenue, 5, Vertiflex, 5, Medical Metrics, 5; **M. Gordon**, Eli Lilly and Company, 5, Newport Orthopedic Instutend HOAG orthopedic inse, 4, Globus corporation, 5; **J. H. Krege**, Eli Lilly and Company, 3; **K. D. Krohn**, Eli Lilly and Company, 3.

2254

Changes in Subject Characteristics in the Denosumab Pivotal Fracture Trial and Its Extension for up to 8 Years. JD Adachi[1], CJF Lin[2], PR Ho[2], MA Bolognese[3], HG Bone[4], P Hadji[5], S Papapoulos[6], C Recknor[7], NS Daizadeh[2], P Dakin[2], RB Wagman[2] and S Ferrari[8]. [1]McMaster University, Hamilton, ON, [2]Amgen Inc., Thousand Oaks, CA, [3]Bethesda Health Research Center, Bethesda, MD, [4]Michigan Bone and Mineral Clinic, Detroit, MI, [5]Philipps-University of Marburg, Marburg, Germany, [6]Leiden University Medical Center, Leiden, Netherlands, [7]United Osteoporosis Centers, Gainesville, GA, [8]Geneva University Hospital, Geneva, Switzerland.

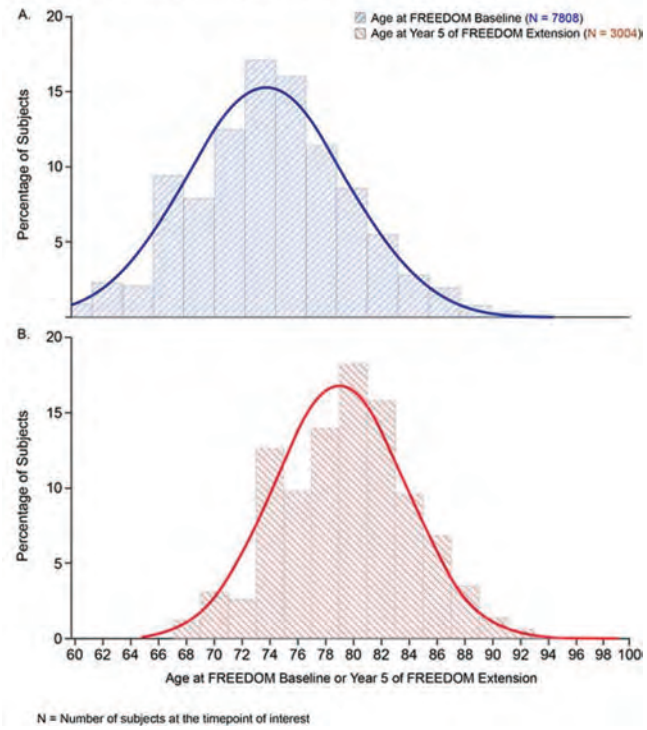
Background/Purpose: Changes in demographics of study population enrolled in long-term osteoporosis clinical trials may affect interpretation of efficacy/safety outcomes. Denosumab is being evaluated for up to 10 years in the 3-year FREEDOM trial and 7-year Extension. Denosumab for up to 8 years is associated with low fracture incidence, continued BMD increases, and adverse event profile similar to what has previously been reported (Papapoulos et al., *JBMR.* 2013;28:S1). We compared the FREEDOM and Extension populations at baseline and in the Extension to assess potential selection bias that might influence long-term treatment outcomes.

Methods: In FREEDOM, women were randomized to placebo or denosumab 60 mg every 6 months. All FREEDOM subjects who had not missed >1 dose of investigational product, completed the 3-year visit, and consented to enroll were eligible to receive open-label denosumab in the Extension. We assessed whether older age and incident fractures contributed to attrition at Year 5 of the Extension, representing 8 years of follow-up.

Results: In FREEDOM, 6478/7808 (83%) subjects completed the trial. Of 5928 subjects eligible for the Extension, 4550 (77%) enrolled. Through Year 5 of the Extension, 3004 (66%) remained on study. While baseline characteristics were similar in FREEDOM and Extension, all subjects were 3 years older at Extension baseline, prevalent vertebral fracture rate in placebo-treated subjects was higher at Extension baseline compared with FREEDOM baseline (25% vs 22%), and denosumab-treated subjects had higher mean BMD at Extension baseline. Age distribution after 5 years of Extension remained consistent with the antecedent 3 years in FREEDOM, with no preponderance of younger subjects (Figure). As expected, older subjects were more likely to discontinue, however, 62% of subjects who were ≥75 years at Extension baseline remained on study through Year 5. While subjects who fractured were more likely to discontinue in FREEDOM and in the Extension, 88% and 83% of placebo and denosumab fractured subjects, respectively, completed the 3-year FREEDOM trial, and 72% of fractured subjects in the Extension remained enrolled through Year 5.

Conclusion: In this large-scale, long-term study of denosumab, Extension population maintained similar characteristics to the original FREEDOM cohort. During Extension, a high percentage of subjects at increased risk for fractures due to older age and incident fracture remain on study. This suggests that the low fracture incidence and consistent safety profile reflect the long-term denosumab treatment effect.

Figure. Age Distribution at FREEDOM Baseline (A) and Year 5 of FREEDOM Extension (B)



Disclosure: J. Adachi, Amgen Inc., Eli Lilly, Merck, 2, Amgen Inc., Eli Lilly, Merck, Warner Chilcott, 5, Amgen Inc., Eli Lilly, Warner Chilcott, 8; **C. Lin**, Amgen Inc., 1, Amgen Inc., 3; **P. Ho**, Amgen Inc., 1, Amgen Inc., 3; **M. Bolognese**, Amgen Inc., Regeneron, Lilly, 2, Amgen Inc., 8; **H. Bone**, Amgen Inc., Merck, Novartis, NPS, 2, Amgen Inc., Merck, Novartis, Tarsa, Noven, 5; **P. Hadji**, Amgen Inc., Elli Lilly, 5, Amgen Inc., Elli Lilly, 8; **S. Papapoulos**, Amgen Inc., Merck & Co, Novartis, Axsome, Gador, 5, International Osteoporosis Foundation, 6, Amgen Inc., GSK, Novartis, Roche, 8; **C. Recknor**, None; **N. Daizadeh**, Amgen Inc., 1, Amgen Inc., 3; **P. Dakin**, Amgen Inc., 1, Amgen Inc., 3; **R. Wagman**, Amgen Inc., 1, Amgen Inc., 3; **S. Ferrari**, Amgen Inc., MSD, 2, Amgen Inc., MSD, Lilly, GSK, Bioiberica, 5.

2255

Vertebral Cortical Bone Mass and Structure Significantly Improved with Romosozumab Compared with Teriparatide: HR-QCT Analyses of Postmenopausal Women with Low BMD from a Phase 2 Study. T Damm[1], C Libanati[2], J Peña[1], G Campbell[1], R Barkmann[1], DA Hanley[3], S Goemaere[4], MA Bolognese[5], C Recknor[6], C Mautalen[7], YC Yang[2] and CC Glüer[1]. [1]Christian-Albrechts-Universität zu Kiel, Kiel, Germany, [2]Amgen Inc., Thousand Oaks, CA, [3]University of Calgary, Calgary, AB, [4]Ghent University Hospital, Ghent, Belgium, [5]Bethesda Health Research Center, Bethesda, MD, [6]United Osteoporosis Centers, Gainesville, GA, [7]Centro de Osteopatias Medicas, Buenos Aires, Argentina.

Background/Purpose: Understanding the effect of therapies in the vertebral compartments is relevant to bone biology and clinical practice. We developed an improved technique using cortical shell segmentation-based layering of high resolution quantitative computed tomography (HR-QCT) scans of T12 vertebral bodies to evaluate compartment-specific changes in BMD and microstructure.

Methods: In an international, randomized, phase 2 study (McClung et al., *N Engl J Med.* 2014), postmenopausal women with low BMD supplemented with calcium and vitamin D received subcutaneous (SC) romosozumab (210 mg monthly), teriparatide (20 mcg SC daily), or placebo (PBO). A subset of these women underwent HR-QCT scanning of T12 (N=11 romosozumab, 12 teriparatide, 8 PBO) at baseline and month 12. For cortical HR-QCT analysis (blinded to treatment assignment), adjacent 200 micron thin films of the cortical shell were evaluated to determine changes from the outer soft tissue bordering the vertebrae to the medullary spongiosa (Figure). In addition to the standard cancellous compartment variables previously described (Graeff et al., *J Bone Miner Res.* 2007), this improved method allows accurate determination of cortical variables in the subregions, including apparent and corrected (deconvolved) cortical thickness, bone mineral content (BMC), and BMD. Changes in cortical thickness are modeled assuming an average 50% mineralization of newly added matrix.

Results: At baseline, mean (SD) apparent cortical thickness of 1.37 (0.13) mm was corrected to a cortical thickness of 0.29 (0.05) mm. At month 12, romosozumab significantly improved cortical BMC and BMD from baseline and in comparison to teriparatide or PBO (all $P \leq 0.0003$; Table). These gains were attained by both endosteal and periosteal bone matrix apposition. Improvements in cancellous BMD were similar between romosozumab and teriparatide.

Conclusion: Using HR-QCT scans of the spine, it is possible to evaluate changes across the cortical shell of the vertebral bodies and determine alterations in the endosteal and periosteal regions. The anatomical location and magnitude of these changes could impact changes in bone strength and thus affect fracture risk. Romosozumab administration was associated with significant increases in cortical thickness and improvement in all measured cortical parameters at 12 months compared with teriparatide or PBO. The clinical effect of romosozumab to reduce fractures is being evaluated in an ongoing phase 3 clinical program.

Figure. 3D Visualization of Vertebral Cortex (left) and Schematic Drawing of Bone Apposition (right)

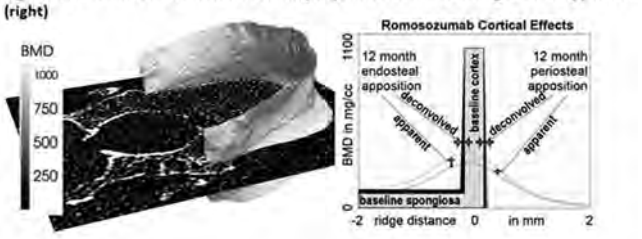


Table. Changes From Baseline in Cortical Thickness, BMC, and BMD at Month 12

Region	Romosozumab N = 11	Teriparatide N = 12	Placebo N = 8
Deconvolved cortical thickness (microns)	157 (12)*†	61 (12)‡	10 (14)
Cortical BMC (% of baseline)	22 (2)*†	11 (2)‡	−1 (2)
Apparent cortical BMD (mg/cm³)			
Periosteal apposition at 0.2 to 0. 6 mm from ridge	37 (4)*†	16 (4)‡	0 (5)
Endosteal apposition at −0.2 to −0.6 mm from ridge	59 (6)*†	19 (6)	0 (7)
Subcortical apparent BMD (mg/cm³)	28 (3)†	22 (3)‡	1 (4)
Spongiosa apparent BMD (mg/cm³)	20 (3)†	19 (3)†	−4 (3)

Values are mean (SD).
*P value ≤ 0.0003 compared with teriparatide.
†P value < 0.0001 compared with placebo.
‡P value < 0.05 compared with placebo.

Disclosure: T. Damm, Amgen Inc., 2; **C. Libanati**, Amgen Inc., 1, Amgen Inc., 3; **J. Peña**, None; **G. Campbell**, None; **R. Barkmann**, None; **D. Hanley**, Amgen Inc., Eli Lilly, Merck, 9, Amgen Inc., Eli Lilly, Merck, Novartis, 5, Amgen Inc., Eli Lilly, Merck, Novartis, 2; **S. Goemaere**, Amgen Inc., MSD, Novartis, 2, Amgen Inc., UCB, Eli Lilly, MSD, Novartis, 5, Amgen Inc., Eli Lilly, MSD, Novartis, Servier, Rottapharma, Willpharma, Takeda, 8; **M. Bolognese**, Amgen Inc., Regeneron, Lilly, 2, Amgen Inc., 8; **C. Recknor**, None; **C. Mautalen**, Merck, Servier, 5; **Y. Yang**, Amgen Inc., 1, Amgen Inc., 3; **C. Glüer**, Amgen Inc., Lilly, 2, Amgen Inc., Lilly, 5, Amgen Inc., Lilly, 8.

2256

Effects of Pre-Dosage Alendronate Treatment on Bone Metabolic Indices and Bone Mineral Density in Patients Treated with Glucocorticoids: A Prospective Study. Yasuo Kuroki[1], Hiroshi Kaji[2], Mika Yamauchi[3] and Toshitsugu Sugimoto[4]. [1]Kobe Century Memorial Hospital, Kobe, Japan, [2]Kinki University Faculty of Medicine, Osakasayama, Japan, [3]Shimane University Faculty of Medicine, Izmo, Japan, [4]Shimane University Faculty of Medicine, Izumo, Japan.

Background/Purpose: Glucocorticoids (GCs) treatment induces secondary osteoporosis characterized by rapid bone loss and an increase in fracture risk, although GCs are used to treat a wide variety of rheumatic and autoimmune diseases. We have ever investigated the effects of GC therapy on bone metabolic indices and bone mineral density (BMD) in a prospective study. Our previous study indicated that the biochemical markers of bone metabolisim are affected from the early term of GC therapy (day3), and that the simultaneous treatment of alendronate (ALN) with GC therapy (co-dosage group) suppresses the changes of bone turnover markers at the early stage of GC therapy. Moreover, ALN was effective to suppress a reduction in BMD induced by GC. However, the simultaneous treatment of ALN was not effective to suppress an increase in bone resorption markers on day 7 of GC therapy and a reduction in BMD on 1 month. In the present study, we investigated the effects of pre-dosage ALN treatment before GC therapy on rapid bone loss in GC-treated patients prospectively.

Methods: Twenty-one patients (62.0±9.9 y.o.) treated with prednisolone (PSL) at the dose of over 20 mg received weekly 35mg ALN one day or several days before the initiation of GC therapy (pre-dosage group), and serum Ca, intact parathyroid hormone (PTH), osteocalcin (OC), bone-type alkaline phosphatase (BAP) and urinary levels of type I collagen cross-linked N-telopeptide (NTx) were measured on 7 days, 1, 3 and 6 months after the initiation of GC therapy. BMD values were measured by dual-energy X-ray absorptiometory at the lumbar spine (L2–4) and femoral neck on 1,3,6 and12 months. The subjects were divided into the following two groups; 10 patients receiving PSL at doses[3]a40mg/day (H) and 11 patients receiving PSL at doses [3]a20mg/day (M).

Results: The pre-dosage ALN treatment caused decreases in serum Ca levels and urinary Ca excretion as well as a significant increase in serum PTH levels ($p<0.05$) on day 7 of GC treatment, which were not observed in the co-dosage group of our previous study. As for bone-formation indices, serum BAP levels were significantly decreased after 1 month only in the pre-dosage group, although serum OC levels were decreased on day 7 of GC administration in both co-dosage and pre-dosage groups. Although ALN was not effective to suppress an increase in bone resorption markers on day 7 of GC therapy in the co-dosage group, ALN decreased urinary NTx levels in the pre-dosage group. Moreover, BMD at lumbar spine were not decreased at 1 month and significantly increased 6 months after the initiation of GC therapy in the pre-dosage group, although ALN was not effective to suppress a reduction in BMD at 1 month in the co-dosage group. No significant reduction of BMD at femoral neck was observed in the pre-dose group. These results were similar in the subgroup analysis dividing into H and M groups.

Conclusion: The present study suggests that pre-dosage ALN treatment before GC therapy is more effective for the preservation of GC-induced osteoporosis, which might be attributed by early suppression of GC-stimulated bone resorption.

Disclosure: Y. Kuroki, None; **H. Kaji**, None; **M. Yamauchi**, None; **T. Sugimoto**, None.

2257

How Does Non-Compliance to Prolia® (DENOSUMAB) Impact the Change in Bone Mineral Density (BMD) in Osteoporotic Patients? Aashish Kalani[1], Matt Wong-Pack[1], Jacob Hordyk[2], Arthur N. Lau[3], George Ioannidis[4], Robert Bensen[5], William G. Bensen[1] and Jonathan D. Adachi[1]. [1]McMaster University, Hamilton, ON, [2]University of Ottawa, Hamilton, ON, [3]Division of Rheumatology, McMaster University, Hamilton, ON, [4]St Joseph's Healthcare Hamilton, Hamilton, ON, [5]Rheumatology Health Team, Dr. Bensen's Rheumatology Clinic, Hamilton, ON.

Background/Purpose: Denosumab (Prolia®) has shown to be a safe and efficacious therapy for osteoporotic patients in many clinical trials. Unfortunately, few studies have explored its effectiveness in clinical practice. Currently, best practice guidelines suggest that denosumab should be administered subcutaneously every six months. However, in clinical practice, patients do not always receive subsequent denosumab as prescribed. This non-compliance may have a significant impact on the effectiveness of the drug. The objective of this study is to assess the impact that noncompliance with the regular dosing regimen has on bone mineral density (measured at the lumbar spine [LS] and femoral neck [FN]) compared to patients who receive their scheduled dosing regimen.

Methods: A retrospective cohort study was conducted from August 2012 to August 2013. We included all osteoporotic patients from a single academic center who received a minimum of two injections of denosumab with a follow-up BMD measurement since May 2010 for analysis. Patients who have only received their first subcutaneous injection and patients without a corresponding BMD score were excluded from the study. Patients were classified into 3 categories and analyzed in these groups: 1) subsequent injection less than five months, 2) between five to seven months, 3) more than seven months after their initial subcutaneous injection. Interval changes in BMD (at the LS and FN) over a 1-year follow-up period was analyzed between these three groups.

Results: Of the 924 charts examined, 436 patients met eligibility criteria. Multi-variable regression analysis was conducted comparing the change in BMD after one year of denosumab therapy at both the LS and FN for the three pre-specified groups. The group receiving an injection 7 months after their initial injection was used as a reference. The change in BMD (95% confidence interval) after one year was −0.00008 (−0.01335 to 0.01168) and 0.02073 (−0.00697 to 0.04843) for patients receiving a subsequent injection between 5–7 months later, at LS and FN respectively. The change in BMD (95% confidence interval) after one year was 0.00515 (−0.00619 to 0.01649) and 0.01474 (−0.01042 to 0.03990) for patients receiving a subsequent injection less than 5 months later, at LS and FN respectively. The relationship between the timing of drug administration and change in BMD over 1 year was not statistically significant ($p>0.05$).

Conclusion: This observational study proposes that the efficacy of denosumab (as measured by BMD measurements at the lumbar spine and femoral neck) has great efficacy in the treatment of osteoporosis especially when patient compliance was maintained. This emphasizes the importance of patient compliance and the need for programs available to patients to help ensure this compliance. However, in the small subset of patients who were unable to receive their subsequent denosumab injection within the 5 to 7 month window, there was no difference in BMD measurements. This suggests that although compliance is essential, a delay in a subsequent injection may be acceptable in extenuating circumstances. A follow-up study with a larger sample size and longer follow-up duration is required to further characterize this relationship.

Disclosure: A. Kalani, None; **M. Wong-Pack**, None; **J. Hordyk**, None; **A. N. Lau**, Amgen, Roche, 8, Amgen, Roche, 2; **G. Ioannidis**, None; **R. Bensen**, None; **W. G. Bensen**, None; **J. D. Adachi**, Amgen Inc., Astra Zeneca, Eli Lilly, GSK, Merck, Novartis, Nycomed, Pfizer, Procter & Gamble, Roche, Sanofi-Aventis, Servier, Wyeth, and Bristol-Myers Squibb, 5, Amgen Inc., Eli Lilly, GSK, Merck, Novartis, Pfizer, Procter & Gamble, Roche, Sanofi-Aventis, Wyeth, and Bristol-Myers Squibb., 2.

2258 WITHDRAWN

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Changes in serum Soluble RANKL and Osteoprotegerin Levels after Teriparatide Administration in Rheumatic Disease Patients with Glucocorticoid-Induced Osteoporosis. Makoto Kaburaki, Kaichi Kaneko, Kotaro Shikano, Mai Kawazoe, Emiko Shindo, Hiroshi Sato, Natsuki Fujio, Sei Muraoka, Nahoko Tanaka, Tatsuhiro Yamamoto, Natsuko Kusunoki, Tomoko Hasunuma, Shinichi Kawai and Shotaro Masuoka. School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan.

Background/Purpose: Osteoporosis is one of the serious complications of systemic glucocorticoid therapy. Reduced bone formation is the key process in patients with glucocorticoid-induced osteoporosis (GIOP), however, the significance of increased bone resorption in these patients is still under consideration. We reported that serum soluble receptor activator for nuclear factor-κB ligand (sRANKL) level might be a predictive factor in patients under glucocorticoid therapy (J Clin Endocrinol Metab. 97: E1909-917, 2012). Teriparatide, a recombinant form of parathyroid hormone, is an option of treatment for GIOP, especially to the severe cases. Its daily injection stimulates bone formation, resulting increase of bone volume and reduction of bone fracture. Thus, we observed the effect of teriparatide on serum sRANKL and osteoprotegerin (OPG) levels as bone resorption markers in patients with rheumatic disease under glucocorticoid therapy. The aim of this study is to evaluate the effect of teriparatide on serum sRANKL and OPG levels in patients under glucocorticoid therapy.

Methods: Patients were recruited at Toho University Omori Medical Center. This study was approved by the Ethics Committees at Toho University Omori Medical Center (approval number; 24–97). Twenty postmenopausal women (71±6 yr [mean ± SD]) with rheumatic diseases (rheumatoid arthritis 9, vasculitis syndrome 6, polymyalgia rheumatica 3, polymyositis 1, and systemic lupus erythematosus 1) were included in this study. All the patients were changed from oral bisphosphonates to daily s.c. injections of teriparatide (20 μg) for treatment of GIOP. Patients who received mean prednisolone at doses of 6.7±5.4 (SD) mg daily were eligible for this study. We measured serum sRANKL, OPG, bone formation markers (OC, ucOC, BAP, and P1NP), and bone resorption markers (TRACP-5b and NTX) during teriparatide treatment. The bone mineral density (BMD) was measured before and 6 months after start of teriparatide treatment. Data were expressed as the median with the interquartile range.

Results: Serum sRANKL levels were significantly decreased after teriparatide treatment (0.066 [0.0–0.188] to 0.0 [0.0–0.008] pmol/L, $p < 0.05$). In contrast, serum OPG levels were not changed after the treatment (6.71 [5.79–8.13] to 7.17 [5.69–8.92] pmol/L, $p = 0.584$). All of serum bone formation markers (OC; 3.6 [2.9–5.8] to 10.0 [8.2–18.0] ng/mL, ucOC; 1.4 [0.9–4.6] to 5.2 [3.4–9.1] ng/mL, BAP; 10.9[8.8–16.0] to 15.5 [11.6–22.3] U/L, and P1NP; 26.8 [12.5–43.2] to 88.8 [48.1–196.0] ng/L) and resorption markers (TRACP-5b; 227 [171–506] to 353 [269–506] mU/L and NTX; 12.7 [10.7–22.4] to 21.9 [16.9–26.6] nmolBCE/L) were significantly ($p < 0.05$) increased after teriparatide treatment. Mean BMD was significantly increased when compared to that of pretreatment value (0.65 [0.59–0.71] to 0.72 [0.65–0.84], $p < 0.05$).

Conclusion: It is suggested that the improvement of bone density by teriparatide might be explained not only by activation of bone formation but also by decreased bone resorption due to reduction of sRANKL in patients under glucocorticoid therapy.

Disclosure: M. Kaburaki, None; **K. Kaneko**, None; **K. Shikano**, None; **M. Kawazoe**, None; **E. Shindo**, None; **H. Sato**, None; **N. Fujio**, None; **S. Muraoka**, None; **N. Tanaka**, None; **T. Yamamoto**, None; **N. Kusunoki**, None; **T. Hasunuma**, None; **S. Kawai**, None; **S. Masuoka**, None.

2260

Effects of Daily Teriparatide on the Spine and Femoral Strength Assessed By Finite Element Analysis of Clinical Computed Tomography in Rheumatoid Arthritis Patients. Kumiko Ono[1], Satoru Ohashi[2], Hiroyuki Oka[3], Yuho Kadono[1], Tetsuro Yasui[1], Yasunori Omata[1], Naoko Shoda[1] and Sakae Tanaka[1]. [1]The University of Tokyo Hospital, Tokyo, Japan, [2]Sagamihara Hospital,National Hospital Organization, Kanagawa, Japan, [3]22nd Century Medical & Research Center, faculty of medicine, the university of Tokyo, Tokyo, Japan.

Background/Purpose: Rheumatoid arthritis (RA) decreases bone mineral density and bone quality, and exposes patients to an increased risk of fracture. In RA treatment, improvement of systemic osteoporosis using anti-osteoporotic agents is important, as is suppression of fracture risk by controlling inflammation with a combination of disease-modifying anti-rheumatic drugs or biological agents. However, few studies have examined the effects of anti-osteoporosis drugs on patients with RA. Therefore, this study quantitatively evaluated the effects of daily teriparatide (TPTD) in RA patients at high risk of fracture after 6 months using several methods.

Methods: A total of 30 RA patients were enrolled in this prospective study. All patients receiving TPTD were evaluated according to changes in two bone turnover markers from baseline to 1, 3, and 6 months. The markers used were serum procollagen type 1 N-terminal propeptide (P1NP) and

tartrate-resistant acid phosphatase-5b (TRACP-5b). Assessments were also made according to bone mineral density (BMD) by dual x-ray absorptiometry (DXA) and bone strength by quantitative computed tomography (CT) at baseline. Reevaluation was performed after 6 months. Nonlinear finite element analysis (FEA) was performed on CT to estimate spinal and femoral predicted bone strength (PBS). We adopted two loading conditions, stance and fall configurations, on femoral PBS.

Results: Patients were 67.7±8.2 years old and the duration of symptoms was 12.2±10.7 years. The majority of subjects showed moderate disease activity (mean baseline 28-joint Disease Activity Score, 3.0±1.3). Mean values at baseline and at 1, 3, and 6 months were 42 μg/L, 141 μg/L, 144 μg/L and 153 μg/L for PINP, and 423 mU/dL, 527 mU/dL, 583 mU/dL and 601 mU/dL for TRACP-5b. Patients had significantly greater levels of serum PINP and TRACP-5b ($p<0.05$ compared with baseline) at all points measured. Mean values at baseline and at 6 months were 0.89 g/cm^2 and 0.94 g/cm^2 ($p<0.01$) for BMD-spine (median change 6.1%), 0.62 g/cm^2 and 0.63 g/cm^2 ($p=0.31$) for BMD-femoral neck (median change, 1.1%), 3584 N and 3971 N ($p<0.01$) for PBS-spine (mean change 12.1%), 4146 N and 4194 N ($p=0.3$) for femoral PBS-stance (mean change 1.9%) and 1485 N and 1504 N ($p=0.2$) for femoral PBS-fall (mean change, 1.9%) (Fig. 1).

Conclusion: Our results show that TPTD can increase BMD and FEA on RA patients, and bone loss in patients with RA can be prevented by TPTD. FEA appears to detect the effects of TPTD more sensitively than DXA. We will have to follow these effects in the longer term.

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2261

A Meta-Anlaysis of Bisphosphonate and Parathyroid Hormone (PTH) Use in Osteoporosis. Zsolt Kulcsar[1], Lena Saleh[2], Shravani Gangidi[3] and Poonam Khadka[1]. [1]Dartmouth Hitchcock Medical Center, lebanon, NH, [2]The Dartmouth Institute For Healthcare Policy and Clinical Practice, Lebanon, NH, [3]The Dartmouth Institute For Healthcare Policy and Clinical Practice, lebanon, NH.

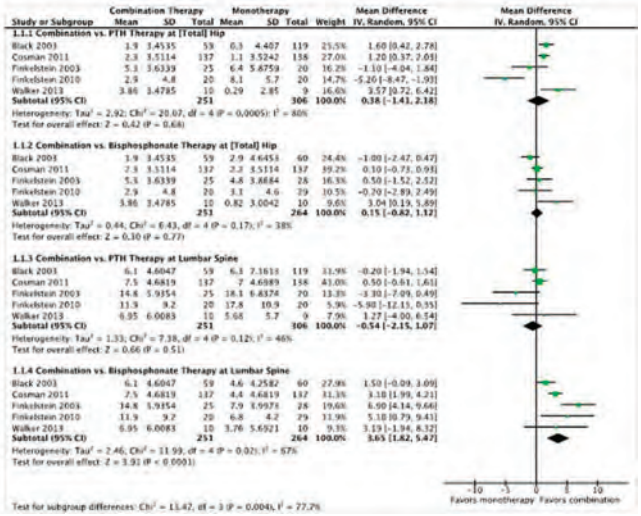
Background/Purpose: Bisphosphonates are currently the drug of choice for treatment of osteoporosis. While anabolic agents like parathyroid hormone (PTH) have shown greater improvements in bone mineral density (BMD) in severe osteoporosis, their use is limited to a maximum of 2 years due to risk of osteosarcoma with rapid loss of gained BMD after cessation of treatment. Given the limits of both agents, we want to assess the effects of PTH and bisphosphonate combination therapy versus monotherapy with either agent on BMD in patients with osteoporosis.

Methods: We searched MEDLINE, the Cochrane Library, and Clinical-Trials.gov from inception to October 2013. We also reviewed reference lists of included studies and searched the abstracts of the last four years of relevant scientific meetings. We included randomized trials comparing combination therapy with bisphosphonate and PTH versus monotherapy with either agent in men and post-menopausal women with osteoporosis followed for at least 3 months. Studies had to report mean change in BMD as measured by dual-energy X-ray absorptiometry (DEXA) at either the total hip or lumbar spine. Data collection and analysis was done by at least two reviewers independently collected data from each study using a standardized form. We used random effects models to calculate pooled weighted mean differences (WMD) and relative risks (RR).

Results: Of 332 studies identified, six met all inclusion criteria. Combination therapy led to small increases in % change in BMD at the total hip compared to PTH alone (WMD 0.38, 95% CI -1.41 to 2.18, $I^2=80\%$, 5 studies) and bisphosphonate alone (WMD 0.15, 95% CI −0.82 to 1.12, $I^2=38\%$, 5 studies). Similarly, combination therapy resulted in larger increases in % change in BMD at the spine compared to bisphosphonate alone (WMD 3.65, 95% CI 1.82 to 5.47, $I^2=67\%$, 5 studies), however PTH alone was superior to combination therapy at the lumbar spine (WMD −0.54, 95% CI −2.15 to 1.07, $I^2=46\%$, 5 studies). Based on 6 studies, there was a significant risk in developing hypercalcemia with combination therapy compared to monotherapy (11.83% vs. 7.04%, RR 1.68, 95% CI 1.18 to 2.41).

Conclusion: Combination therapy with PTH and bisphosphonates leads to greater improvements in BMD only at the lumbar spine compared to bisphosphonate therapy alone, however at the cost of increased risk of hypercalcemia.

Figure 1. Mean percent change in BMD by DXA at [total] hip and lumbar spine.



Disclosure: Z. Kulcsar, None; **L. Saleh**, None; **S. Gangidi**, None; **P. Khadka**, None.

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Raloxifene for Osteoporosis in Postmenopausal Women with Rheumatic Diseases. Won Seok Lee[1], Yun Jung Choi[2], Yun-Hong Cheon[1], Myong-Joo Hong[3], Chang-Hoon Lee[4], Myeung Su Lee[4], Sang-Il Lee[5] and Wan-Hee Yoo[1]. [1]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [2]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, JeonJu, South Korea, [3]Department of internal Medicine, Presbyterian Medical center, Jeonju, South Korea, [4]Department of Internal Medicine, School of Medicine, Wonkwang University, Iksan, Chonbuk, South Korea, [5]Gyeongsang National University School of Medicine, Jinju, South Korea.

Background/Purpose: Raloxifen is a selective estrogen receptor modulator that has been extensively studied. We studied the efficacy of raloxifene on disease activity and bone mineral density (BMD) in postmenopausal women with rheumatic diseases receiving long-term glucocorticoids (GC).

Methods: Postmenopausal women with rheumatic diseases and osteoporosis were included. Patients with a history of thromboembolism or antiphospholipid antibody positivity were excluded. They were managed with raloxifene (60 mg/day) plus elemental calcium (1,200 mg/day). BMD of the hip and spine (primary outcome) was measured initially and at month 12, and disease activity (secondary outcome) was serially assessed using DAS28 and SELENA-SLEDAI.

Results: Between January 2010 and December 2013, 130 patients (86 assigned to receive GC and 44 patients not receiving GC, mean ± SD age 60.1 ± 9.0 vs. 59.3 ± 7.0 years) were recruited. 81 rheumatoid arthritis, 15 Sjogren's syndrome, 11 scleroderma, 11 Behcet's disease, 7 lupus and 5 other rheumatic diseases were included. Demographic data, osteoporotic risk factors and BMD at various sites were similar between the two groups of patients. The duration and dose of prednisolone received was 72.5 ± 24 months and 3.3 ± 1.6 mg/day. At month 12, a significant gain in the lumbar spine (+0.9 ± 0.7%; p = 0.04 vs. +0.4 ± 0.1%; p=0.05) and total hip BMD (+1.1 ± 0.5%; p = 0.03vs. 1.5 ± 0.7%; p = 0.04) was observed in patients receiving GC or not. However, femoral neck BMD was decreased in both groups. No patient had a major flare of lupus and rheumatoid arthritis. No fracture and thromboembolic events were reported.

Conclusion: Raloxifene was well tolerated in postmenopausal female patients with rheumatic diseases who had inactive disease and in whom hypercoagulability was not identified. Raloxifene increased total hip and lumbar spinal BMD in patients receiving corticosteroids or not.

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Continued Zoledronic Acid Use in a Large Healthcare System. Robert A. Overman[1], Julie C. Lauffenburger[1], Margaret L. Gourlay[1] and Chad L. Deal[2]. [1]University of North Carolina, Chapel Hill, NC, [2]Cleveland Clinic, Cleveland, OH.

Background/Purpose: Oral bisphosphonates adherence has been reported as less than 50% at one year. With patients frequently having refill gaps greater than 30 days. Zoledronic acid (ZA) is a once yearly injectable bisphosphonate anti-osteoporosis medication (AOM) with 100% adherence for 12 months. We evaluated what proportion of patients who continued ZA after the first infusion and for those receiving a second dose how close to 365 days that dose was administered.

Methods: We identified new ZA users using billing data between January 1, 2010 and December 2012 from a large healthcare system based on healthcare procedure codes J3488 and Q2051 and linked to electronic medical record data. Included patients had at least two rheumatology office visits and first receipt of ZA was in or after 2010. We excluded patients who had received ZA before the study period but not other AOM. **Results:** are presented as mean (standard deviation [SD]) or %.

Results: There were 771 patients who met inclusion criteria. A second ZA infusion was given to 489 patients (63.4%) and 6.5% not continuing ZA were prescribed another AOM. Women (89.5%) and Caucasian (89.0%) race were the majority of the cohort with a mean age of 68.1 (10.9). The mean number of AOMs used prior to ZA was 1.7 (1.3) with 18.7% not having an AOM prescribed within the health system. Previous fractures were present in 20.4%, mean Charlson Comorbidity score of 1.9 (2.5), and 29.7% had GERD or gastric ulcers at first ZA administration. Persistence of ZA is presented in Table 1. Of the 489 patients who received a second ZA infusion 307 (63%) were within 365 ±30 days (a care gap of >30 days is defined as lack of persistence with oral agents). By 180 days 445/489 (91%) and 365 days 486 (99%) had received a second ZA infusion.

Conclusion: Although ZA adherence is by definition superior to oral BPs at one year, 36.6% of patients in our cohort did not receive a second infusion. Of those receiving a second infusion only 63% do so within the first 30 days although 99% had a second infusion at 365 days. Considering recent data suggesting that a single dose of ZA may reduce fracture for longer than one year, a gap of >30 days may be too strict a criterion for lack of persistence. ZA is approved for use at 24 month intervals for prevention. Since 36% of patient did not receive a second ZA dose, reasons for discontinuation and delay in a second infusion should be further investigated. Additionally, physician offices should have a method for scheduling yearly ZA infusions as a quality metric.

Table 1 Zoledronic Acid Treatment Gaps

Treatment Gap	% Treated
±30 days	62.8%
+60 days	77.7%
+90 days	85.7%
+120 days	87.5%
+150 days	90.0%
+180 days	91.0%
+365 days	99.4%

ZA: Zoledronic Acid; 2nd ZA administration was assessed at 365 days after first administration

Disclosure: R. A. Overman, None; **J. C. Lauffenburger**, None; **M. L. Gourlay**, None; **C. L. Deal**, None.

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Denosumab for Long-Term Glucocorticoid Users Who Have Inadequate Response to the Bisphosphonates: A 12-Month Randomized Control Trial. Chi Chiu Mok, Ling Yin Ho and Kwok Man Ma. Tuen Mun Hospital, Hong Kong, Hong Kong.

Background/Purpose: To evaluate the efficacy of denosumab on bone mineral density (BMD) in long-term glucocorticoid users who have inadequate response to oral bisphosphonate treatment.

Methods: Patients who were receiving long-term prednisolone treatment for their underlying medical illnesses were recruited. The inclusion criteria were: (1) adult patients >=18 years of age; (2) Daily dose of prednisolone >2.5mg within 3 months of study entry; (3) Inadequate BMD response (<2% increase in BMD or remaining osteoporotic) or the development of new fracture despite oral bisphosphonates for >=2 years. Participants were randomized to receive either: (1) Denosumab (60mg subcutaneously every 6 months) + discontinuation of bisphosphonates; or (2) Continuation of oral bisphosphonates (control group). Calcium (3g/day of caltrate), vitamin D (rocaltrol 0.25ug/day) and other medications were continued. Baseline and follow-up BMD (femoral neck, femoral trochanter, total hip, lumbar spine and whole body) at 6 and 12 months were performed. Markers of bone turnover (serum osteocalcin, P1NP and CTX) were also assayed at the same time points. The primary outcome was the difference of lumbar spine BMD at month 12 between the two groups.

Results: 42 women were recruited (age 54.7±12.9 years)- 21 shifted to denosumab and 21 continued on bisphosphonates. Underlying medical diseases were: SLE (76%) and RA (24%). The duration of prednisolone therapy was 101±66.3 months and the daily dose was 4.4±2.1mg. 30 (71%) patients were postmenopausal and the mean duration of menopause was 12.3±7.2 years. The mean body mass index (BMI) was 22.3±4.1kg/m^2 (21% patients had BMI^2). The bisphosphonates being used by the patients were alendronate (79%), risedronate (12%) and ibandronate (10%). Pre-existing vertebral fracture was present in 7 (17%) patients and 3 patients (7%) had a family history of fragility fractures. Baseline demographic data, osteoporotic risk factors, and BMD at various sites were not significantly different between the two groups. At month 12, a significant gain in BMD at the lumbar spine (+3.4±0.9%; p=0.002) and the hip (+1.4±0.6%; p=0.03) was observed in denosumab-treated patients, whereas the corresponding change was +1.5±0.4% (p=0.001) and +0.80±0.5% (p=0.12) in the bisphosphonate group. The spinal BMD at month 12 was significantly higher in the denosumab than bisphosphonate group after adjustment for baseline BMD values, age and other parameters (p=0.03). No new fractures occurred in any participants at month 12. Minor upper respiratory tract infection was more commonly reported with denosumab treatment (33% vs 5%; p=0.045) while other adverse events occurred at similar frequency between the two groups. One patient of each group was withdrawn from the study because of non-compliance. None of the patients withdrew from study because of adverse events.

Conclusion: In patients receiving long-term glucocorticoids but not having adequate response to bisphosphonates, shifting to denosumab was more effective in raising the BMD at the spine after 12 months' therapy. Denosumab was well tolerated.

Disclosure: C. C. Mok, None; **L. Y. Ho**, None; **K. M. Ma**, None.

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Comparative Effects of Raloxifene and Bisphosphonate on Bone Mineral Density and Osteoporotic Fracture Outcomes in Rheumatoid Arthritis Patients. Kowoon Joo, Won Park, Seong-Ryul Kwon, Mie-Jin Lim and Kyong-Hee Jung. Inha University Hospital, Incheon, South Korea.

Background/Purpose: Rheumatoid arthritis (RA) accelerates bone loss, increasing the risk of osteoporosis and osteoporotic fractures. We evaluated the effect of raloxifene and bisphosphonate on bone mineral density (BMD) and osteoporotic fractures in RA patients.

Methods: We retrospectively examined data of 112 seropositive RA patients who were diagnosed with osteoporosis and started on either raloxifene or bisphosphonate from January 2006 to December 2010 with no prior history of either medication. Patients with baseline BMD and at least one follow up BMD were included. The patients were examined for maximum of 3 years with mean follow up period of 2.1 years. Bisphosphonates consisted of risendronate, alendronate or oral ibandronate. Vertebral fractures were defined using Genant's semiquantitative classification.

Results: Forty-four patients were in the raloxifene group and 68 patients were in the bisphosphonate group. The patients in the raloxifene group were older and lighter in weight compared to the bisphosphonate group (Table 1). The patients in the bisphosphonate group consumed higher doses of calcium and vitamin D through medication compared to the raloxifene group. There was no significant difference in duration of RA, the daily dosage of prednisolone and medication possession ratio between the 2 groups. Thirty-six patients in the raloxifene group and 67 patients in the bisphosphonate group had follow up BMD at 1 year of treatment (Table 2). Nineteen patients in the raloxifene group and 40 patients in the bisphosphonate group had follow up BMD at 2 years of treatment. There was no significant difference in the yearly change of lumbar, total hip and femoral neck BMD from baseline and the number of vertebral fractures between the 2 groups at 1 year and at 2 years of treatment. Eighteen patients in the raloxifene group and 29 patients in the bisphosphonate group had follow up BMD at 3 years of

treatment. There was no significant difference in the mean change of lumbar and femoral neck BMD from baseline and the number of vertebral and non-vertebral fractures between the 2 groups at 3 years of treatment. However the mean change of total hip BMD was higher in the bisphosphonate group compared to the raloxifene group.

Conclusion: There was no significant difference in BMD changes and osteoporotic fractures in RA patients treated with raloxifene and bisphosphonate.

Table 1. Baseline characteristics

		Raloxifene (n = 44)	Bisphosphonate (n = 68)	*P* value
Female (%)		45 (100)	46 (68)	< 0.001
Age (yr)		62 ± 9	58 ± 9	0.023
Weight (kg)		52.3 ± 10.3	55.8 ± 9.0	0.04
Height (cm)		152.5 ± 6.2	157.9 ± 7.6	< 0.001
Alcohol		0	0	
Smoking (%)		1 (2)	11 (16)	0.026
Diabetes mellitus (%)		1 (2)	7 (10)	0.107
Menopause (%)		43 (98)	38 (56)	<0.001
Rheumatoid arthritis duration (mo)		70 ± 80	65 ± 57	0.666
Follow up duration (yr)		2 ± 1	2 ± 1	0.629
Methotrexate (%)		17 (39)	34 (50)	0.238
Cyclosporine (%)		1 (2)	5 (7)	0.244
Selective serotonin reuptake inhibitors		0	0	
Proton pump inhibitors		2 (4)	3 (4)	0.973
Calcium (mg/day)		253.2 ± 120.8	284.2 ± 89.2	0.012
Vitamind D (IU/day)		341 ± 310	535 ± 348	0.003
Prednisolone (mg/day)	None	12 (27)	13 (19)	
	<2.5	3 (7)	5 (7)	0.454
	2.5 ≤ P<7.5	27 (59)	38 (57)	
	≥7.5	3 (7)	11 (16)	
ESR		36 ± 29	36 ± 28	0.945
CRP		1.49 ± 2.42	1.98 ± 3.18	0.714
Lumbar BMD (g/cm^2)		0.706 ± 0.108	0.732 ± 0.099	0.213
Total hip BMD (g/cm^2)		0.635 ± 0.114	0.668 ± 0.090	0.095
Neck BMD (g/cm^2)		0.548 ± 0.102	0.565 ± 0.081	0.331
Medication possession ratio (%)	1 year	90 ± 12	87 ± 21	0.865
	2 year	92 ± 9	89 ± 18	0.576
	3 year	89 ± 15	92 ± 12	0.331

Table 2. Mean change of BMD from baseline and fracture outcomes.

		Raloxifene (n = 44)	Bisphosphonate (n = 68)	p value
At 1 year of treatment				
BMD	No. (%)	36 (82)	67 (99)	
Mean change from baseline (%) ± SD	Lumbar spine	5.5 ± 12.6	7.1 ± 11.1	0.203
	Total Hip	5.6 ± 8.1	3.7 ± 8.7	0.198
	Femoral Neck	6.0 ± 15.0	5.8 ± 14.4	0.836
Vertebral Fracture	No. (%)	3 (8)	3 (4)	0.419
	Fracture/1000 patient-years	80	40	
Nonvertebral Fracture	No. (%)	0	0	
At 2 years of treatment				
BMD	No. (%)	19 (43)	40 (59)	
Mean change from baseline (%) ± SD	Lumbar spine	7.8 ± 12.7	13.6 ± 14.1	0.253
	Total Hip	7.4 ± 12.2	8.29 ± 9.35	0.604
	Femoral Neck	14.4 ± 20.8	13.3 ± 17.7	0.922
Vertebral Fracture	No. (%)	2 (11)	0	0.1
	Fracture/1000 patient-years	53	0	
Nonvertebral Fracture	No. (%)	0	0	
At 3 years of treatment				
BMD	No. (%)	18 (41)	29 (43)	
Mean change from baseline (%) ± SD	Lumbar spine	10.6 ± 16.2	19.5 ± 14.9	0.078
	Total Hip	5.5 ± 10.3	12.5 ± 10.7	0.038
	Femoral Neck	13.1 ± 19.6	21.1 ± 15.2	0.12
Vertebral Fracture	No. (%)	3 (17)	3 (10)	0.662
	Fracture/1000 patient-years	59	35	
Nonvertebral Fracture	No. (%)	2 (11)	1 (3)	0.549
	Fracture/1000 patient-years	37	11.5	

Disclosure: K. Joo, None; **W. Park**, None; **S. R. Kwon**, None; **M. J. Lim**, None; **K. H. Jung**, None.

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Risk Factors for Treatment Failure in Osteoporotic Patients with Rheumatoid Arthritis.

Kyung-Eun Lee, Lihui Wen, Dong-Jin Park and Shin-Seok Lee. Chonnam National University Medical School, Gwangju, South Korea.

Background/Purpose: No available anti-osteoporotic medication has been shown to completely prevent declines in bone mineral density (BMD) and the resulting increased risk of fracture. The objective of this study was to investigate the risk factors associated with treatment failure in osteoporotic patients with rheumatoid arthritis (RA).

Methods: A retrospective cohort study of 103 patients with RA and osteoporosis was conducted. Subjects were selected from patients who visited the Rheumatology Department of Chonnam National University Hospital between January 2002 and December 2012. All participants fulfilled the 1987 American College of Rheumatology revised criteria for RA and the World Health Organization criteria for osteoporosis. Baseline demographics, clinical characteristics, bone mineral density (BMD), laboratory results and treatment-related data were collected from the patients' chart review. Patients were divided into two groups for comparison: those whose osteoporosis treatment was effective and those whose treatment failed. Risk factors for treatment failure were identified by univariate and multivariate logistic regression using variables that differed significantly between the groups.

Results: Osteoporosis treatment failed in 66 of 103 patients (64.1%). During 14.01 months of (SD: 1.89 months) follow-up, non-adherence to bisphosphonate use (OR = 12.997; $p = 0.006$) was the most powerful risk factor for treatment failure. Daily glucocorticoid dosage ≥ 7.5 mg/day before the first BMD measurement (OR = 6.230; $p = 0.015$), immobilization > 3 months (OR = 4.773; $p = 0.006$), and DAS28 ≥ 3.2 (OR = 4.428; $p = 0.009$) were also significantly related to treatment failure.

Conclusion: Our findings indicate that osteoporosis treatment fails frequently in RA patients and adherence to bisphosphonate use, daily glucocorticoid dosage, immobilization, and DAS28 score should be taken into consideration when treating osteoporotic patients with RA.

Disclosure: K. E. Lee, None; **L. Wen**, None; **D. J. Park**, None; **S. S. Lee**, None.

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Percentage of Women Achieving Non-Osteoporotic BMD T-Scores at the Spine and Hip over 8 Years of Denosumab Treatment.

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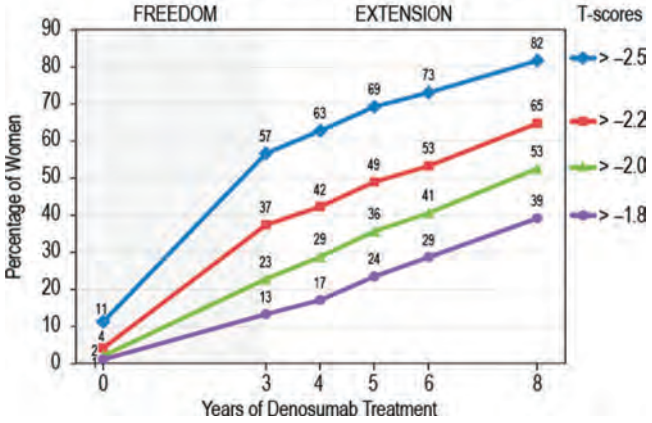
Background/Purpose: Guidelines for the treatment of chronic conditions such as hypertension and diabetes include specific biomarker targets. This differs from osteoporosis treatment guidelines, which currently do not define treatment targets or goals. In general, absence of BMD loss and absence of fracture are considered treatment successes. This is far from ideal because success defined by the lack of a negative outcome does not set a real goal for therapy. Potential goals for osteoporosis treatment might include reaching a BMD T-score value somewhere above –2.5 which represents an acceptable level of fracture risk. To provide insight into T-score values achieved over time with denosumab (DMAb), we report on the percentage of women who achieved a range of possible target BMD T-scores at both the lumbar spine and total hip over 8 years of treatment.

Methods: For these analyses, women received 3 years of DMAb (60 mg subcutaneously every 6 months) during FREEDOM and 5 years of DMAb during the Extension for a total of 8 years of continued treatment. The percentage of women with T-scores > −2.5, > −2.2, > −2.0, and > −1.8 at both the lumbar spine and total hip, and T-scores > −2.5 at either the lumbar spine or total hip at baseline and over 8 years of DMAb treatment were determined. The influence of baseline T-score on subsequent T-score improvement was also explored.

Results: At FREEDOM baseline, mean (standard deviation) lumbar spine and total hip T-scores were −2.83 (0.67) and −1.85 (0.79), respectively, for the DMAb Extension participants (N = 2,343). The percentage of women with T-scores > −2.5, > −2.2, > −2.0, and > −1.8 at both the lumbar spine and total hip progressively increased from baseline over 8 years of DMAb treatment as follows: 11% to 82% (> −2.5), 4% to 65% (> −2.2), 2% to 53% (> −2.0), and 1% to 39% (> −1.8) (Fig. 1). At individual sites, the percentage of women with a T-score > –2.5 increased from baseline over 8 years of DMAb treatment from 19% to 86% (lumbar spine) and from 75% to 94% (total hip). Baseline T-scores by quartile remained largely consistent throughout the 8 years of DMAb treatment, which showed similar trajectory in BMD across subjects regardless of initial BMD (not shown).

Conclusion: DMAb enables a substantial proportion of women with osteoporosis to achieve non-osteoporotic T-scores. The data reported here contribute insightful information to discussions on the topic of treatment goals for osteoporosis.

Fig. 1. Percentage of Women Achieving a Particular T-score at Both the Lumbar Spine and Total Hip



Disclosure: S. Ferrari, Amgen Inc., MSD, 2, Amgen Inc., MSD, Lilly, GSK, Bioiberica, 5; **C. Libanati**, Amgen Inc., 1, Amgen Inc., 3; **C. J. F. Lin**, Amgen Inc., 1, Amgen Inc., 3; **S. Adami**, Merck, Amgen Inc., Eli Lilly, Abiogen, AbbVie, 5; **J. P. Brown**, Actavis, Amgen Inc., Eli Lilly, Merck, Novartis, 2, Amgen Inc., Eli Lilly, 5, Amgen Inc., Eli Lilly, 8; **F. Cosman**, Amgen Inc., Lilly, Merck, 2, Lilly, Amgen Inc., Merck, Pfizer, 5, Lilly, Amgen Inc., 8; **E. Czerwinski**, Amgen Inc., Pfizer, 2, Servier, Roche, Amgen Inc., 9; **L. H. de Gregório**, Amgen Inc., Merck, Jansen, 2, GSK, 8; **J. Malouf**, Amgen Inc., and Eli Lilly, 5, Amgen Inc., Eli Lilly, 8; **J. Y. Reginster**, Servier, Novartis, Negma, Lilly, Wyeth, Amgen Inc., GlaxoSmithKiine, Roche, Merckle, Nycomed-Takeda, NPS, IBSA-Genevrier, Theramex, UCB, Asahi Kasei, 5, Bristol Myers Squibb, Merck Sharp & Dohme, Rottapharm, Teva, Roche, Amgen Inc., Lilly, Novartis, GlaxoSmithKiine, Servier, Pfizer, Theramex, Danone, Organon, Therabel, Boehringer, Chiltern, Galapagos, 2, Merck Sharp and Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKiine, Merckle, Teijin, Teva, Analis, Theramex, Nycomed, NovoNordisk, Ebewee Pharma, Zodiac, Danone, Will Pharma, 9; **N. S. Daizadeh**, Amgen Inc., 1, Amgen Inc., 3; **A. Wang**, Amgen Inc., 1, Amgen Inc., 3; **R. B. Wagman**, Amgen Inc., 1, Amgen Inc., 3; **E. M. Lewiecki**, Amgen Inc., Merck, Lilly, 2, Amgen Inc., Merck, Lilly, Radius Helath, AgNovos, 5; **S. Cummings**, Amgen Inc., Merck, Lilly, 5.

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Odanacatib Anti-Fracture Efficacy and Safety in Postmenopausal Women with Osteoporosis: Results from the Phase III Long-Term Odanacatib Fracture Trial. Michael R. McClung[1], Bente Langdahl[2], Socrates Papapoulos[3], Kenneth G. Saag[4], Silvano Adami[5], Henry G. Bone[6], Tobias de Villiers[7], Douglas P. Kiel[8], Annie Kung[9], Prasanna Kumar[10], Sung-Kil Lim[11], Xu Ling[12], Kurt Lippuner[13], Carlos Mautalen[14], Toshitaka Nakamura[15], Jean-Yves Reginster[16], Ian R. Reid[17], José Adolfo Rodríguez-Portales[18], Christian Roux[19], Jesus Walliser[20], Nelson B. Watts[21], José R. Zanchetta[22], Cristiano A.F. Zerbini[23], Andrea Rybak-Feiglin[24], Dosinda Cohn[24], Carolyn A. DaSilva[24], Rachid Massaad[25], Arthur Santora[24], Boyd B. Scott[24], Nadia Verbruggen[25], Albert Leung[24] and Antonio Lombardi[24]. [1]Oregon Osteoporosis Center, Portland, OR, [2]Aarhus University Hospital, Aarhus, Denmark, [3]Leiden University Medical Center, Leiden, Netherlands, [4]The University of Alabama at Birmingham, Birmingham, AL, [5]Rheumatology Department, University of Verona, Verona, Italy, [6]Michigan Bone and Mineral Clinic, Detroit, MI, [7]Stellenbosch University, Stellenbosch, South Africa, [8]Institute for Aging Research, Hebrew Senior Life, Harvard Medical School, Boston, MA, [9]University of Hong Kong, Pokfulam, Hong Kong, China, [10]Bangalore Diabetes Centre, Bangalore, India, [11]Yonsei University, Seoul, South Korea, [12]Peking Union Medical College Hospital, Beijing, China, [13]Bern University Hospital, Bern, Switzerland, [14]Centro de Osteopatías Médicas, Buenos Aires, Argentina, [15]University of Occupational & Environmental Health, Fukuoaka, Japan, [16]CHU-Centre Ville, Policliniques BRULL, Liege, Belgium, [17]University of Auckland, Auckland, New Zealand, [18]Pontificia Universidad Católica de Chile, Santiago, Chile, [19]Paris Descartes University, Cochin Hospital, Paris, France, [20]Bone Metabolism Clinic, Hospital Angeles del Pedregal, Mexico City, Mexico, [21]Mercy Health Osteoporosis and Bone Health Services, Cincinnati, OH, [22]IDIM Instituto de Investigaciones Metabolicas, Buenos Aires, Argentina, [23]Centro Paulista de Investigações Clinicas, São Paulo, Brazil, [24]Merck Sharp and Dohme Corp., Rahway, NJ, [25]MSD Europe Inc., Brussels, Belgium.

Background/Purpose: Odanacatib (ODN), a selective oral inhibitor of cathepsin K, is in development for the treatment of osteoporosis. The Phase III Long-Term Odanacatib Fracture Trial (LOFT; NCT00529373) and its pre-planned blinded extension in which patients continue on their originally assigned treatment, evaluated the efficacy and safety of ODN in reducing the risk of fractures in postmenopausal women with osteoporosis.

Methods: This randomized, double-blind, placebo-controlled, event-driven study enrolled women ≥65 years of age with a BMD T-score ≤−2.5 at the total hip (TH) or femoral neck (FN) or with a radiographic vertebral fracture (VFx) and a T-score ≤−1.5 at the TH or FN. Participants were randomized to either ODN 50 mg once-weekly or placebo (1:1) and received weekly vitamin D_3(5600IU) and daily calcium supplements to ensure a total daily calcium intake of ~1200 mg. Primary efficacy endpoints of the trial were new morphometric vertebral, clinical hip, and clinical non-vertebral fractures. Secondary endpoints included safety and tolerability, clinical VFx, spine and hip BMD, and bone turnover markers.

Results: A total of 16,713 participants were randomized at 387 centers in 40 countries, with 16,071 included in the analyses, and 642 excluded from all analyses due to study site closure (n=483), duplicate randomization (n=3), or failure to take any study drug (n=156). At baseline, mean (SD) age was 72.8 (5.3) years, 57% were Caucasian, 46.5% had a VFx prior to study entry, and mean BMD T-scores were: lumbar spine −2.7, TH −2.4, and FN −2.7. A total of 237 patients with hip fracture were estimated to provide statistical power. A prespecified interim analysis was performed when ~70% of targeted events had accrued. An external Data Monitoring Committee (DMC) reviewed these data and recommended that the base study be closed early due to robust efficacy and a favorable benefit/risk profile. The DMC noted that safety issues remained in certain selected areas. Both safety and efficacy continue to be monitored in the ongoing blinded extension trial. Data from an average follow-up of 40.8 months have been accrued from the base and extension studies, with 7,081 patients completing at least 4 years of follow-up. At the time this abstract was written, final data analyses were not complete.

Conclusion: The blinded, placebo-controlled base and extension study periods of LOFT will provide data on the efficacy of ODN on fractures and BMD and general safety. A separate presentation will discuss in depth the safety profile for ODN from this trial.

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Efficacy and Safety of High Dose Infliximab in the Treatment of Uveitis in Pediatric Patients. Liza Mariel Bermudez[1], Patricia Irigoyen[1], Anca Askanase[1], Michael Weiss[2], Joyce Hui-Yuen[1], Amy J. Starr[1], Lisa F. Imundo[3], Andrew H. Eichenfield[1] and Josephine Isgro[1]. [1]Columbia University Medical Center, New York, NY, [2]Division of Ophthalmology Uveitis Service College of Physician And Surgeons of Columbia University, New York, NY, [3]Pediatric and Adult Rheumatology Columbia University Medical Center, New York, NY.

Background/Purpose: Chronic uveitis, an inflammatory eye disease, is a leading causes of childhood blindness and often has a chronic recurrent course. This study reviews the efficacy and safety of high dose (≥10–20 mg/kg) infliximab (IFX) in children with uveitis.

Methods: Retrospective chart review of 125 children and young adults with uveitis requiring systemic treatment. Data were collected on demographics, disease characteristics, infliximab dose, concomitant medications, treatment outcomes and side effects. Remission was defined as inactive eye disease ≥ 3 months after discontinuing all treatment; with 'inactive disease' was defined as grade 0 inflammatory cells. Descriptive statistics and Fisher's exact were employed.

Results: Of 125 patients with uveitis, 33 (26.4%) were treated with high-dose IFX (≥10–20 mg/kg). An additional 19 patients received alternate TNF inhibitors (adalimumab 17(13.6%), etanercept 2 (1.6%)). The median age at diagnosis was 10 years (IQR 2,22), 76 (61%) were female. The ethnic distribution was 78 (62%) Caucasian, 26 (21%) Hispanic, 4 (4%) African American, 3 (1%) Asian, and 14 (11%) not specified. Uveitis was associated with JIA (JIA-U) in 62 (50%); 56 (45%) oligoarticular-JIA, 4 (4%) poly-JIA and 2 (2%) systemic-JIA. Forty-nine (40%) patients had idiopathic uveitis; other causes included sarcoidosis 6 (5%), tuberculosis 1 (1%), Behcet's 1 (1%), Vogt-Koyanagi-Harada 1 (1%).

For the 33 patients on high-dose IFX, the median length of follow-up after initiation of treatment was 6 years, with a mean cumulative dose of 23 grams ± 16.7 (mean 7.2 mg/kg/dose ± 20.4). Fourteen were first started on methotrexate (MTX) and topical steroids (TS) with a median time to initiation of IFX of 17 months (IQR 7, 26), 12 were started on MTX and IFX simultaneously, and 7 received IFX monotherapy. Twenty-one (64%) achieved inactive eye disease, while 12 (36%) had persistently active disease. Of 73 patients treated with MTX/TS alone, 23 (32%) had inactive disease while 50 (68%) were active at last visit, showing increased inflammatory ophthalmic disease in patients not on IFX ($p<0.0013$). This difference was maintained when comparing all 52 patients on TNF inhibitors to those on MTX alone, 33 (63%) of patients on TNF inhibitiors had inactive disease compared to 23 (32%) on MTX ($p<0.0005$).

Ophthalmologic complications of uveitis included band keratopathy in 13 (10%), cataracts in 9 (7%), posterior synechiae in 8 (6%), and glaucoma in 4 (3%). The majority of complications were seen prior to starting IFX. No significant differences were seen between patients on IFX and those on MTX.

No malignancies or serious infections requiring hospitalization were seen in these patients. One patient on adalimumab developed dilated cardiomyopathy and 1 herpes zoster. At the end of study, 28 (85%) patients remain on IFX and 3 on adalimumab, 1 on etanercept and 1 on leflunomide/rituximab.

Conclusion: This is the largest study assessing the efficacy and safety of high-dose infliximab in the treatment of pediatric uveitis. Our data demonstrate favorable outcomes in patients on IFX, with 64% achieving inactive disease vs 32% on MTX. Extended use of high-dose infliximab did not appear to be associated with increased risk of serious infection or malignancy.

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Changes in Cerebral Blood Flow Velocity in Patients with Familial Mediterranean Fever. Gozde Yildirim Cetin[1], Uygar Utku[2], Nurhan Atilla[3], Kadir Gisi[3] and Mehmet Sayarlioglu[4]. [1]Sutcu Imam University, School of Medicine, Department of Internal Medicine, Division of Rheumatology, Kahramanmaras, Turkey, [2]Kahramanmaras Sutcu Imam University, Medical Faculty, Kahramanmaras, Turkey, [3]Sutcu Imam University, School of Medicine, Kahramanmaras, Turkey, [4]Ondokuz Mayis University School of Medicine, Samsun, Turkey.

Background/Purpose: Familial Mediterranean fever (FMF) is a hereditary and an auto-inflammatory disease predominantly characterized by repeated attacks of fever, abdominal pain, pleuritic chest pain, arthritis and erysipelas-like erythema. The MEditerranean FeVer (MEFV) gene mutations altering the structure and function of pyrin protein play a significant role in the pathophysiology of the disease. Mutated pyrin is associated with the loss of delicate control of the inflammatory pathways, which results in a prolonged or augmented inflammation that predisposes these patients to a pro-inflammatory state. This increased inflammation might lead to susceptibility to vascular comorbidities in FMF patients. The aim of this study was to assess the effects of this increased inflammation on cerebral blood flow velocity with transcranial Doppler (TCD) ultrasonography.

Methods: In this study, 30 subjects were enrolled for FMF and healthy control groups. All patients with FMF were under colchicine treatment and they were in an attack free period. Bilateral middle cerebral artery (MCA) peak-systolic, end-diastolic, and mean blood flow velocities; Gosling's pulsatility index values; and Pourcelot's resistance index values were recorded and compared with each other.

Results: There were 30 subjects in each group. Men/women ratio and mean age in FMF and control groups were 4/3, 26/27 and 34,7±5,9 *vs.*32,3±4,7 respectively. Peak-systolic, end-diastolic, and mean blood flow velocities of bilateral MCA were significantly higher in FMF group when compared with the control group (Table 1).

Table 1 Transcranial Doppler data of FMF group compared with control group.

	FMF group (mean±SD)	Control group (mean±SD)	p-value
L-peak-systolic BFV	143,3 ± 19,5	104,5 ± 13	**<0,001**
L-end-diastolic BFV	56,4 ± 13,5	38,4 ± 6,2	**<0,001**
L-mean BFV	90,9 ± 13,8	61,8 ± 8,2	**<0,001**
L-PI	0,85 ± 0,07	0,9±0, 09	0,02
L-RI	0,59 ± 0, 03	0,6±0,05	0,57
R-peak-systolic BFV	145,2 ± 22,3	103,5 ± 17,05	**<0,001**
R-end-diastolic BFV	59,5 ± 13	36,7 ± 12,36	**<0,001**
R-mean BFV	90,7 ± 15,47	63,2 ± 10,5	**<0,001**
R-PI	0,8 ± 0,08	0,85 ± 0, 09	0,89
R-RI	0,56 ± 0,04	0,63 ± 0, 06	**0,002**

L, left; R, right; PI, pulsatility index; RI, resistance index; BFV; blood flow velocity.

Conclusion: There has been recently considerable attention concerning the possible causal role of systemic inflammation in the development of atherosclerosis in patients with rheumatic diseases. The attacks of FMF with clinical inflammation is only the tip of the iceberg, inflammation maintains in attack-free remission periods in 30% of patients with FMF. This maintaining subclinical inflammation induces endothelial dysfunction, and increases the risk of developing significant complications such as atherothrombosis, anemia, splenomegaly, decreased bone mineral density, heart disease, and life-threatening secondary systemic amyloidosis. In this study, we investigated the effects of clinical and subclinical inflammation regarding FMF disease on cerebral blood flow parameters. In our study, the mechanisms that underlie significantly increased blood flow velocities of the FMF group is most likely to be due to mild diffuse subclinical atherosclerosis. Consequently, our results suggest that persistent clinical and subclinical inflammation in FMF patients causes increased cerebral blood flow velocities.

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Symptom and Treatment Characteristics of Juvenile Primary Fibromyalgia Syndrome: Are Males and Females Created Equal? Jennifer E. Weiss[1], Kenneth N. Schikler[2], Alexis Boneparth[3], Cara Hoffart[4], Mark Connelly[4] and The CARRA Registry Investigators[5]. [1]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [2]Univ of Louisville Schl of Med, Louisville, KY, [3]Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ, [4]Children's Mercy Hospital, Kansas City, MO, [5]Childhood Arthritis and Rheumatology Research Alliance, Durham, NC.

Background/Purpose: Children and adolescents with persistent widespread musculoskeletal pain frequently present to pediatric rheumatologists for evaluation. Limited data are available on the characteristics and treatments used for these patients, particularly for males. Using the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry, we sought to evaluate the overall demographic, symptom, and treatment characteristics of patients diagnosed with juvenile primary fibromyalgia syndrome (JPFS) and to compare these characteristics as a function of gender.

Methods: Deidentified data on demographics, symptoms, functional measures and treatment characteristics were extracted from the baseline visits of JPFS patients in the CARRA registry between May 2010 and May 2014.

Results: There were 181 patients (28 males), ages 8–21 years (M = 15.4 +/− 2.3) included. Patients were symptomatic for a mean of 1.7 +/− 2.2 years prior to their first visit to a pediatric rheumatologist, with no significant difference between males and females (M = 2.1 versus 1.6 respectively, $t(173)=1.06$, $p=.29$). The most commonly reported symptoms at baseline included widespread pain (91%), fatigue (84%), disordered sleep (82%), headaches (68%), and extremity numbness/tingling (32%). Females were more likely to report numbness/tingling (36% versus 13% respectively, $\chi^2 = 5.09$, $p = 0.02$). Table 1 lists treatments tried and recommended. Males were significantly more likely to have used gabapentin (25% versus 8%, $\chi^2 = 7.41$, $p < 0.01$). Of the 64 patients using non-pharmacologic treatment, the most commonly used treatment was physical therapy (59%), with females significantly more likely to have used massage and yoga (Table 1). Less then 10% of patients tried opioids, serotonin norepinephrine reuptake inhibitors, craniosacral therapy, hypnosis, and biofeedback.

Mean pain scores at baseline were moderate to severe (6.3+/− 2.5/10) and were significantly positively related to CHAQ functional impairment scores ($r = .35$, $p < .01$), patient ratings of impairments in health-related quality of life (HRQOL) ($r = .42$, $p < .01$), and patient ratings of impairments in overall well-being ($r = .64$, $p < .01$). Males were found to be reliably more disabled based on *subjective* (patient/parent report) functioning measures (HRQOL and CHAQ), although no differences were observed on physician report measures (physician global assessment and ACR functional class).

Table 1. Treatments tried and recommended for JPFS patients (N=181)

Treatment	Percent of Patients: Females (N=154)	Males (N=27)	Total
Medical treatments tried (N=117)			
Daily non-steroidal anti-inflammatory drugs	42%	48%	43%
Selective serotonin reuptake inhibitors	29%	14%	26%
Tri-cyclic antidepressants	27%	24%	26%
Gabapentin	12%	33%*	16%
Non-pharmacological treatments tried (N=64)			
Physical therapy	59%	62%	59%
Dietary supplements	22%	46%	27%
Therapeutic massage	29%*	8%	25%
Mindfulness/meditation	18%	23%	19%
Chiropractic	18%	8%	16%
Acupuncture/acupressure	16%	8%	14%
Yoga	14%*	0%	11%
Treatments recommended/started at baseline visit (N=181)			
Pain education	92%	89%	91%
Graded aerobic activity	78%	67%	76%
Sleep hygiene	72%	57%	70%
General counseling	52%	54%	52%
Physical therapy	56%	57%	56%
Medications	50%	57%	51%
Referral to pain clinic	46%	43%	46%
Cognitive-behavioral therapy	41%	50%	42%
Biofeedback	7%	14%	8%

*Significant gender difference, $p<.05$.

Conclusion: Based on data from the largest known cohort of JPFS patients, there appear to be few significant gender differences in disease characteristics and treatment. However, higher levels of disability are reported by male patients despite no comparable differences observed on physician severity measures, suggesting the need to consider gender on evaluation and treatment of JPFS.

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Assessment of Transition Readiness in Adolescents and Young Adults with Rheumatic and Other Chronic Health Conditions. Gabrielle Paul[1], Stephanie LaCount[1], Charles H. Spencer[2], Gloria C. Higgins[3], Karla Jones[4], Brendan Boyle[5], Manmohan K. Kamboj[5], Christopher Smallwood[6] and Stacy P. Ardoin[7]. [1]Ohio State University, Columbus, OH, [2]Nationwide Childrens Hospital, Columbus, OH, [3]Nationwide Childrens Hosp, Columbus, OH, [4]Nationwide Children's Hospital, Ohio, OH, [5]Nationwide Children's Hospital, Columbus, OH, [6]Ohio State Univeristy, Columbus, OH, [7]Ohio State University College of Medicine, Columbus, OH.

Background/Purpose: The transition from pediatric to adult care is a vulnerable period. The lack of objective measures of transition readiness is a barrier to improving care. The Transition Readiness Assessment Questionnaire (TRAQ) is a disease-neutral, patient-reported tool with 33 questions across 2 domains (self-management and self-advocacy). Items are scored on a 1 to 5 ordinal scale representing stages of change model (precontemplation, contemplation, preparation, action and maintenance). The TRAQ has not previously been assessed in adolescents and children with rheumatic or gastroenterologic (GI) conditions.

Methods: 89 adolescents and young adults (16 – 25 years) with chronic rheumatic, endocrine or GI conditions at a single pediatric center were enrolled. Participants completed surveys including demographics, transition experience, TRAQ. Clinical information was obtained via chart review. Data were analyzed with descriptive statistics. Mean TRAQ scores were compared across specialty and age groups using one way ANOVA.

Results: The 89 participants were 65% female, 18.3 years, 72% Caucasian, 86% non-Hispanic and had rheumatic (54%), GI (21%) or endocrine (23%) conditions (Table 1). The 50 participants with rheumatic diseases had JIA/RA (25), SLE or MCTD (13), vasculitis (6), overlap or other disease (6). Only 40% of participants reported discussing with current provider seeing an adult subspecialty provider in the future. Participants reported seeing subspecialist independently for part of visit never (31%), rarely (15%), sometimes (20%), often (24%) or always (8%). TRAQ self-management and advocacy scores did not differ significantly by specialty but the TRAQ self-advocacy score increased with age (Tables 2 and 3).

Conclusion: Despite guidelines that transition processes begin at age 14, fewer than half of these 16–25 year old respondents reported ever discussing future transition to adult providers and almost 1/3 had never seen provider independently for portion of clinic visit. Mean TRAQ scores for this group represented the preparation stage of change. The TRAQ is a promising tool for measuring transition readiness and can be used clinically and to assess intervention efficacy. These results underscore the need for improved transition processes for adolescents and young adults with chronic disease.

Table 1: Transition Readiness Assessment: Participant Characteristics

Age, mean ± SD years	18.2 ± 1.6
Sex, no. (%) female	58 (65)
Race, no. (%) white	72 (81)
Ethnicity, no. (%) Hispanic/Latino	3 (3)
Current education status	
Currently in school, no. (%)	72 (82)
9th to 12th grade, no. (%)	46 (52)
College/Technical School, no. (%)	42 (47)
Highest Parental Education, no. (%)	
Some high school	3 (3)

Graduated high school	20 (22)
Some college/technical school	27 (30)
Graduated college/technical school	28 (31)
Graduate degree	9 (10)
Unknown or not reported	2 (2)
Annual household income, no. (%)	
<$25,000	11 (12)
$25,000 to 49,999	16 (18)
$50,000 to 74,999	13 (15)
$75,000 to 99,999	6 (7)
$100,000 to 150,000	8 (9)
$150,000	7 (8)
Not reported/unknown	28 (31)
Employment	
Not employed, no. (%)	47 (53)
Part time, no. (%)	36 (40)
Full time, no. (%)	6 (7)
Single, no. (%)	86 (97)
Insurance status	
Parental private insurance, no. (%)	58 (65)
Personal private insurance, no. (%)	0
Public insurance, no. (%)	28 (31)
Other/unknown, no. (%)	3 (3)
Health condition, no. (%)	
Rheumatic	49 (56)
Endocrine	20 (22)
Gastroenterologic	19 (21)
Duration of disease, mean ± SD years	5.0 ± 4.1
Time seeing current provider, mean ± SD years	4.2 ± 3.3
Self-Management TRAQ Domain 1, mean ± SD	3.16 ± 1.70
Self-Advocacy TRAQ Domain 2, mean ± SD	3.79 ± 1.55

Abbreviations: GI = Gastroenterologic; TRAQ = Transition Readiness Assessment Questionnaire

Table 2: Transition Readiness Assessment Questionnaire Scores by Specialty

	Rheumatic (n=50)	GI (n=19)	Endocrinologic (n=20)	F	P value
Self-Management TRAQ Domain 1, mean ± SD	3.18 ± 1.70	3.14 ± 1.67	3.17 ± 1.72	0.09	0.91
Self-Advocacy TRAQ Domain 2, mean ± SD	3.78 ± 1.56	3.97 ± 1.46	3.63 ± 1.61	1.32	0.27

Abbreviations: GI = Gastroenterologic; TRAQ = Transition Readiness Assessment Questionnaire

Table 3: Transition Readiness Assessment Questionnaire Scores By Age

	16 to 18 years (n=51)	19 to 20 years (n= 28)	≥21 years (n=8)	F	P value
Self-Management TRAQ Domain 1, mean ± SD	3.01 ± 1.68	3.38 ± 1.71	3.38 ± 1.65	1.54	0.22
Self-Advocacy TRAQ Domain 2, mean ± SD	3.65 ± 1.57	3.90 ± 1.52	4.3 ± 1.39	4.24	0.02

Abbreviations: TRAQ = Transition Readiness Assessment Questionnaire

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Does a Standardized Multidisciplinary Approach Improve Outcomes for Children with NMDA Receptor Antibody Encephalitis?: A Preliminary Assessment of a Single Center Experience.

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Background/Purpose: NMDA receptor antibody encephalitis (NMDAR) is a potentially devastating isolated autoimmune condition affecting children and young adults that was mostly unrecognized prior to 2007. The clinical phenotype includes encephalopathy, neurocognitive deficits, seizures, and abnormal movements. The largest published observational study to include children suggests that earlier diagnosis, and utilization of immunotherapy (rituximab or cyclophosphamide) in refractory cases may decrease relapse rates and neurologic morbidity (Titulaer MJ et al. Lancet neurology 2013: 12;157–165). Yet, best care practices regarding multi-disciplinary care, the role of pediatric rheumatologists, and timing of immunotherapy modalities have not been validated for children.

Methods: A standardized multidisciplinary approach to NMDAR care was designed at our institution after struggling with initial cases during 2009–2011. A task force composed of physicians from neurology, rheumatology, intensive care, and transfusion medicine services reviewed the literature and approaches of other pediatric hospitals. Institutional criteria were developed regarding the use of therapeutic plasma exchange (TPE) and early B-cell depletion with rituximab. In our algorithm, patients remaining at a moderate disability level one week after first-line therapy (corticosteroids + IVIG or TPE) received rituximab. We assessed initial presentations, interventions, and neurologic outcomes for all children diagnosed with NMDAR during the period of 2009–2013 after obtaining IRB approval. Only descriptive statistics were analyzed due to the small sample size of our cohort.

Results: We identified 13 patients with the appropriate clinical phenotype and NMDA receptor antibodies in serum and/or CSF. There were 9 females (70%), median age at presentation was 10 (range 3–17), and median time from symptom onset to diagnosis and initial treatment was 16 days (range 2–90 days). Of the first six children treated at our institution (median follow-up time 20.5 months) without a standardized approach (2009-July 2012) only 1 received rituximab, and 4 had relapses (66.6%; 3 children within the first year and one child at 19 months). Since July 2012, 7 children have been treated according to a standardized approach. Six of these children (86%) received rituximab and there have been no relapses during the first year of follow-up (median 10 months). Median time to diagnosis was similar in both cohorts (15 vs. 24 days). A greater percentage of children in the standardized cohort (71% vs. 33%) achieved a modified Rankin score of 0 (no deficits) OR 1 (mild deficits, no impairment).

Conclusion: Preliminary analyses of children presenting with NMDAR since 2009 reveal lower relapse rates and disability scores in the recent cohort receiving standardized care and early utilization of rituximab. It is not apparent whether low relapse rates status post rituximab will be sustained with longer follow up. The institutional task force aims to address best care practices for psychiatric, neuropsychological, and rehabilitation services.

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TNF Inhibitors Provide Long-Term Clinical Benefits in 6 Patients with Early-Onset Sarcoidosis.

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Background/Purpose: Early-onset sarcoidosis (EOS) is a NOD2 gene-associated chronic autoinflammatory disease, characterized by the triad of arthritis, rash, and uveitis, which usually occurs in children younger than 4 years of age. The aim of this study was to evaluate the clinical benefits of TNF inhibitors (TNFi) in EOS.

Patients and Methods: Six EOS patients treated with biologic agents at our hospital were reviewed. To evaluate the benefits of biologic agents, patients were retrospectively assessed at baseline, 3, 6, 12 and 36 months and the last visit after initiating the therapy. Severity of each clinical symptom such as arthritis, camptodactyly, uveitis, and skin rash was assigned by scoring from 0 (none) to 3 (severe). Laboratory findings such as CRP, ESR, or matrix metalloproteinase-3 (MMP-3) were also evaluated. In addition, the accumulated continuation rate of each biologic agent was analyzed by Kaplan-Meier method.

Results: The biologic agents were initiated after 10.9 years from onset (0.8–18.1y). The 1st biologic agents (1st Bio) used were infliximab (IFX) in 2, etanercept (ETA) in 2, adalimumab in 1, and IL-6 inhibitor (IL-6i) tocilizumab (TCZ) in 1. Four patients maintained clinical remission with the 1st biologic agents. The rest of 2 had switched to the 2nd biologic agents due to the lack of efficacy, and one of the 2 had switched to the 3rd one. One of the 2 cases treated with ETA showed refractory arthritis; subsequently required to switch to the 2nd Bio (TCZ) followed by the 3rd Bio (IFX) to achieve a clinical remission. A case treated with TCZ showed no clinical improvements; she finally attained clinical remission after switching to the 2nd Bio, IFX. During the TNFi therapy, clinical improvement was observed in joint pain/swelling (6/7), cystic swelling (2/7), uveitis (3/4), and skin rash (4/7), except in camptodactyly (0/7) (Fig.1). On the other hand, patients treated with IL-6i showed poor clinical response. The accumulated continuation rate after 3 years of each biologic therapy was 85.7% in TNFi and 0% in IL-6i ($p=0.022$, the log-rank test) (Fig.2). Of 4 patients with uveitis at initiating biologic agents, 3 patients treated with IFX attained substantial improvement of uveitis, while one treated with TCZ did not. The other 2

patients who had started biologic therapy without uveitis kept uveits free by the age of 14.6 or 15.3 years old at their last visit.

Conclusion: TNF inhibitors appear to be more effective than IL-6 inhibitor in the treatment of EOS, and may have a potential to prevent the onset of uveitis.

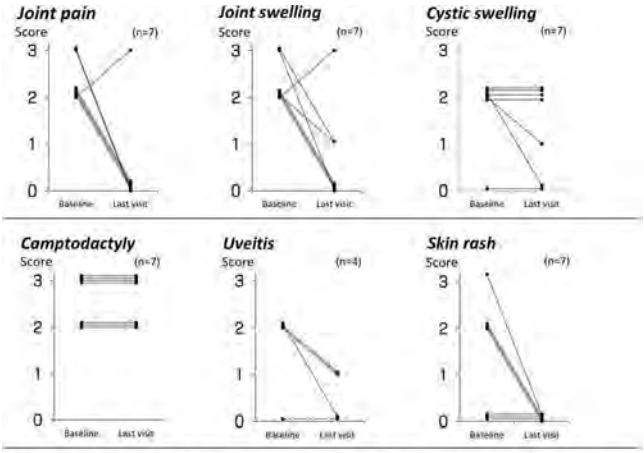

Figure.1 Changes in clinical score during TNF inhibitor therapy.

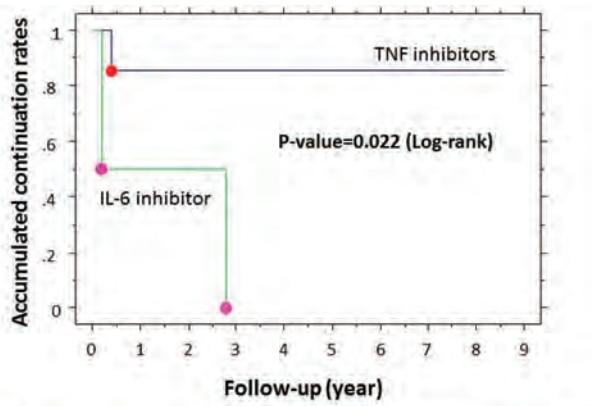

Figure.2 The accumulated continuation rates of TNF/IL-6 inhibitors in the treatment of EOS.

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Immunization Status and Barriers in Childhood Rheumatic Diseases. Shine Vazhappilly[1], Otto Vanderkooi[2], Susanne Benseler[3], Tommy Gerschman[4], Nicole Johnson[3], Nadia Luca[3], Paivi Miettunen[3], Dwaraka Veeramreddy[1] and Heinrike Schmeling[3]. [1]University of Calgary, Calgary, AB, [2]Department of Pathology and Laboratory Medicine & Microbiology Immunology & Infectious Diseases/University of Calgary, Calgary, AB, [3]Department of Pediatrics/University of Calgary, Calgary, AB, [4]Alberta Children's Hospital, Calgary, AB.

Background/Purpose: To determine the vaccination status of children with rheumatic diseases, and identify immunization knowledge of families and potential barriers to vaccination.

Methods: A cross-sectional study of children with rheumatic diseases followed at a tertiary care center outpatient clinic was performed between October 2013 and March 2014. Demographics, diagnosis and current treatments were obtained from health records. Children were considered immunosuppressed, if they were currently received corticosteroids, non-biologic or biologic disease-modifying agents. A unique provincial electronic database that records accurate vaccine history was used to obtain actual patient vaccination history. Perceived immunization barriers, concerns and knowledge regarding contraindications to vaccination, and sources of immunization information were captured from a patient/parent questionnaire. Descriptive statistical methods were used to analyze the data.

Results: A total of 82 children were recruited into the study. The median age was 11.7 years. The most common diagnoses were juvenile idiopathic arthritis (65%), systemic lupus erythematosus (9%), and juvenile dermatomyositis (5%). Fifty eight (71%) children were considered immunosuppressed.

Vaccination database: Patients received most recommended vaccines, with the exception of the Influenza (2013/2014) and Hepatitis B vaccines (recommended for age of 10 [grade 5] in Canada). Influenza was missed 40% of the time in the 1 – 3 years old group, 18% of the time in the 4 – 9 years old group, and 27% of the time in the 10 – 17 years old group. Hepatitis B was missed at a rate of 4% in the 10 – 17 years old group.

Patient/parent questionnaire: Nine patients reported previous adverse reactions to vaccination (Influenza [5], Measles, Mumps, and Rubella (MMR) [2], Hepatitis B [2] and Varicella [2]). In 38% at least one vaccination was withheld, most commonly for active disease (26%), recommendation against receiving vaccinations by health care provider (23%), uncertainty about whether or not a vaccine should be given (19%), concerns about disease flare (13%) and/or side effects post vaccination (5%). Several sources of information were utilized by patients and families for vaccination information, and satisfaction with this information was fairly high. Patients and parents identified the following information gaps: 1) risks and contraindications of vaccinations in childhood rheumatic diseases, 2) age-appropriate vaccination schedules and modalities, 3) best practice of vaccination documentation. Vaccination reminders were identified as useful, with several comments indicating that e-mail alerts, reminders, and a method to track this information would be useful.

Conclusion: The majority of children with rheumatic illnesses received the recommended vaccines. Immunization gaps were identified for Influenza and Hepatitis B. Knowledge regarding contraindications to vaccination is good. Concerns about perceived safety limit vaccination completeness.

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Consensus Statement on the Transition Process from Pediatric Care to Adult Care in Patients with Chronic Inflammatory Rheumatic Diseases with Childhood-Onset. Maria Inmaculada Calvo-Penedes[1], Jordi Anton Lopez[2], Sagrario Bustabad-Reyes[3], Marisol Camacho[4], Jaime De Inocencio[5], Maria Luz Gamir Gamir[6], Genaro Graña[7], Lucía La Cruz[8], Juan Carlos Lopez-Robledillo[9], Marta Medrano[10], Rosa Merino[11], Consuelo Modesto[12], Esmeralda Nuñez[13], Maria Jesus Rua Elorduy[14],Vicente Torrente[15], Carmen Vargas-Lebrón[16] and Estibaliz Loza[17]. [1]H. de la Fe, Valencia, Spain, [2]University Childrenxs Hospital, Barcelona, Spain, [3]Hospital Universitario de Canarias, La Laguna, Spain, [4]Hospital Universitario Virgen del Rocío, Sevilla, Spain, [5]Hospital 12 de Octubre, Madrid, Spain, [6]Hospital Universitario Ramón y Cajal, Madrid, Spain, [7]Complejo Hospitalario Universitario A Coruña, La Coruña, Spain, [8]Hospital Universitari Son Dureta, Mallorca, Spain, [9]Hospital Niño Jesus, Madrid, Spain, [10]Hospital Universitario Miguel Servet, Zaragoza, Spain, [11]Hospital Universitario La Paz, Madrid, Spain, [12]Hospital Valle de Hebron, Barcelona, Spain, [13]Hospital Regional Universitario Carlos Haya, Málaga, Spain, [14]Hospital de Cruces, Barakaldo, Spain, [15]Hospital Sant Joan de Déu, Esplugues de Llobregat, Spain, [16]Hospital Virgen Macarena, Seville, Spain, [17]Institu, Madrid, Spain.

Background/Purpose: many young people with childhood-onset diseases, including rheumatic diseases, continue to require medical care into adult life. There are many differences between pediatric and adult health care. Although there is an extensive evidence base for the need of transitional care, there is a paucity of robust outcome data and a great variability on the models of transitional care. The aim of this study was to develop recommendations on the transition from pediatric care to adult care in patients with chronic inflammatory rheumatic diseases with childhood-onset based on the best evidence and experience.

Methods: recommendations were generated following nominal group methodology and Delphi technique. A panel of experts was established (8 pediatricians, 8 rheumatologists). A systematic literature review (on transitional care) and a narrative review (websites, clinical guidelines and other relevant documentation) were performed and presented to the panel in the 1st panel meeting to be

discussed and to help define recommendations. A first draft of recommendations was generated and circulated for comments and wording refinements. Focal groups with adolescents, young adults and parents were separately. In a 2nd panel meeting the focus group results along with the input from invited psychologist was used to established definitive recommendations. Then, a Delphi process (2 rounds) was carried out. A large group of 70 pediatricians and rheumatologists took part. Recommendations were voted from 1 (total disagreement) to 10 (total agreement). We defined agreement if at least 70% voted ≥7. The level of evidence and grade or recommendation was assessed using the Oxford Centre for Evidence-based Medicine Levels of Evidence.

Results: transition care was defined as a purposeful, planned process that addresses the medical, psychosocial and educational/vocational needs of adolescents and young adults with chronic inflammatory rheumatic diseases with childhood-onset as they move from child-centred to adult-oriented health care systems. The consensus covers: transition needs, barriers and facilitators, transitional issues (objectives, participants, content, phases, timing, plans, documentation, and responsibilities), physicians and other health professionals knowledge and skills requirements, models/programs, strategies and guideline for implementation. Preliminary recommendations and agreement grade are shown in the table (1st Delphi round).

Conclusion: these recommendations are intended to provide pediatricians, rheumatologists, patients, families and other stakeholders with a consensus on the transition process from pediatric care to adult care in patients with chronic inflammatory rheumatic diseases with childhood-onset.

#	RECOMMENDATIONS	% ≥7
1	Transition in pediatric rheumatology should be considered as a continuous, natural and flexible process	92%
2	To standardize, plan ahead, and to define specific protocols related to transitional care	94%
3	To promote outpatient care during transition	47%
4	To endorse specialized nursing care during transition	88%
5	During transitional care, health professionals should convey to patients and parents normality, optimism, sincerity, and should listen to and dialog with them efficiently	97%
6	To support and reinforce patients autonomy and participation adapted to the age/maturity of them during transition	99%
7	To facilitate (evidence based) useful written information (electronic, paper) about disease most relevant issues, management and other aspects for patients and parents	91%
8	To actively involve patients and parents in all of the processes of the transitional care	94%
9	To inform patients and parents about the disease and transitional processes including adult care	99%
10	To monitor adherence (to treatments, visits, etc)	90%
11	To endurance effective communication, collaboration and coordination, among all health professionals involved in the transitional care	78%
12	To endurance effective communication, collaboration and coordination, between health professionals involved in the transitional care and patients educators	64%
13	To develop clinical sessions between pediatric rheumatologists and adult rheumatologists and with other specialists involved in transitional care	90%
14	Adaptations to patients academic needs should be considered	34%
15	An specific training on transitional care as a part of the pediatric training	58%
16	To promote multidisciplinary care by implementing a transitional care model based on each center characteristics, resources and needs	97%
17	The implementation of a transition care model should be planned carefully as well as the strategies to assure the implementation	94%
18	When transferring a patient to the adult care, a full report on the disease course, impact, treatments, and other relevant aspects should be delivered	100%
19	To set up reference units of transitional care	37%

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Inpatient Pediatric Rheumatic Diseases: Characteristics, Cost and Trends. Monica Mahajan, Mohammad Shah, Mary Toth, Neil McNinch and Moussa El-Hallak. Akron Children's Hospital, Akron, OH.

Background/Purpose: Childhood rheumatic diseases (cRD) have wide spectrum of complexity and disease course from mild disease to acute fulminate disease and even sudden death. Physicians and policy makers are increasingly interested in admission rates and resource utilization of chronic illnesses. We aimed to describe temporal trends in inpatient hospitalizations and service costs for patients with cRD.

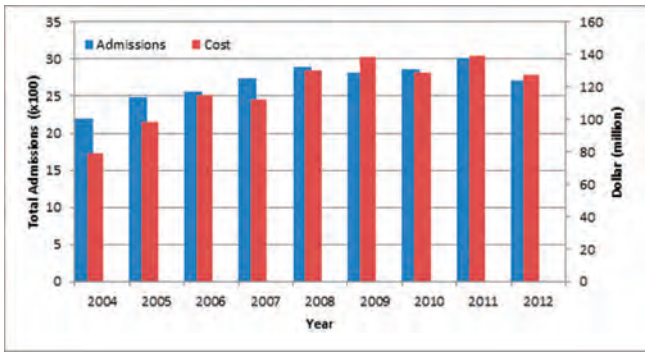
Methods: Pediatric Health Information System database was used to query children with rheumatic conditions between 2004 and 2012. Clinical variables, including age, gender, ethnicity, diagnoses, length of stay (LOS), payer type, admission costs (adjusted for hospital location then rescaled to 2012 dollar), chronic condition indicator and co-morbidity were determined. We excluded patients with LOS ≤1 day as these patients may not represent unplanned admissions.

Results: This study comprised 24,291 discharges from pediatric hospital inpatient units. There were more female (53%) than male (47%) patients. Mean age (±SD) was 7 years (±5.76 years). There was an increase in the total number of admissions and inpatient adjusted service cost during the 9 year study period (Figure 1). Linear trend for admissions and adjusted costs were significant at $p=0.01$ and <0.001 respectively. Lupus, vasculitis and scleroderma admissions were associated with more chronic co-morbidities and chronic diagnoses than the rest of cRD groups.

Kawasaki disease accounted for nearly half of the admissions, lupus for 21.7%, Henoch-Schonlein Purpura for 10.2%, juvenile idiopathic arthritis (JIA) for 7%, vasculitis for 5%, inflammatory myositis for 5% and scleroderma for $p<0.001$) and increased with number of chronic co-morbidities ($p<0.001$).

During the 9-year study period, the total number of inpatient admissions increased by 24% from 2,194 in 2004 to 2,715 in 2012. After rescaling to 2012 dollar, the median adjusted inpatient services cost of cRD increased by 53% and the total costs increased by 61.5% from 78 million in 2004 to 127 million in 2012. Patients with government supported insurance had higher median adjusted admission cost $25,344 compared to patients with commercial insurance $24,284.

Conclusion: Both, rate of hospitalization and cost of admission for cRD increased over the study period of 2004 to 2012. The observed trends highlight the burden of cRD on patients, families and payers. Further research and development of management strategies to support high-value pediatric care and resource targeting is warranted to ensure patients with cRD are cared for in the most efficient manner without compromising quality. This study also reinforces the need for pediatric rheumatologists in the United States.



Disclosure: M. Mahajan, None; **M. Shah**, None; **M. Toth**, None; **N. McNinch**, None; **M. El-Hallak**, None.

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Orbital Pseudotumor As the Presenting Symptom of Pediatric ANCA-Associated Vasculitis. Amanda Schlefman[1], Maureen Leffler[2], AnneMarie C. Brescia[3] and Carlos D. Rose[4]. [1]A.I. DuPont Hospital for Children, Wilmington, DE, [2]AI duPont Hospital for Children, Wilmington, DE, [3]Thomas Jefferson University/ AI duPont Hospital for Children, Wilmington, DE, [4]Division of Rheumatology, Nemours A.I. duPont Hospital for Children, Thomas Jefferson University, Wilmington, DE.

Background/Purpose: Ocular involvement, particularly orbital pseudotumor, has been reported as the initial manifestation of ANCA-

associated vasculitis (AAV) in the adult population, predominantly in granulomatosis with polyangiitis (GPA) with less frequency in Churg-Strauss syndrome (CSS) and microscopic polyangiitis (MPA). There are several cases in the literature of pediatric patients with GPA presenting with orbital pseudotumor, however to our knowledge there are no published cases of this type of presentation in childhood CSS or MPA.

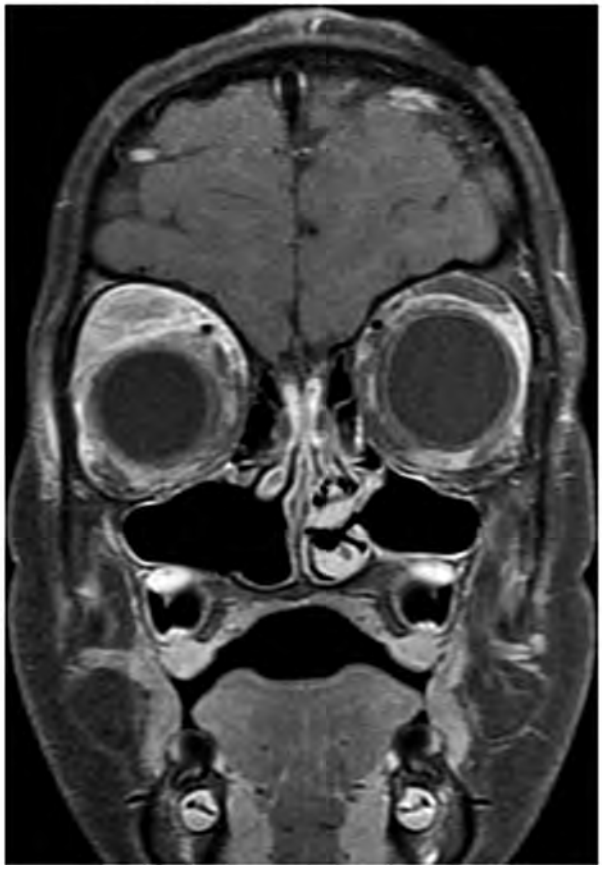
Methods: During the period between 2009 and 2014 three cases of orbital pseudotumor were diagnosed in our Pediatric Rheumatology Division. A thorough chart review was conducted on these patients regarding clinical presentation, laboratory data, imaging studies and pathology. A literature review was then completed in PubMed looking for individual reports of pediatric ANCA-associated vasculitis, as well as previously reported cases of orbital pseudotumor in both adults and children.

Results: Four reports in PubMed were published regarding orbital pseudotumor and ANCA-associated vasculitis in pediatrics. Within these studies there were 15 cases of pediatric AAV presenting as orbital pseudotumor, all of which were limited to GPA. There was no published evidence of this initial presentation in either CSS or MPA in the pediatric population. The characteristics of our patients are listed below:

Table 1.

Case	Age (years), Gender	Serology	Diagnosis	Diagnostic Modality	Disease Course	Treatment	Outcome
1	11, Female	+p-ANCA	Churg-Strauss Syndrome	Biopsy of flank lesions	- Erythema Induratum-like flank lesions	Steroids Cyclophosphamide	Remission
		+MPO Antibody			- Glomerulonephritis		
					-Hashimoto's thyroiditis		
2	6, Female	+p-ANCA	Microscopic Polyangiitis	Renal biopsy	- Glomerulonephritis	Steroids Cyclophosphamide Rituximab	Remission
		+MPO Antibody			-Dialysis complicated by peritonitis		
					- Kidney transplant		
3	3, Female	+p-ANCA	ANCA-vasculitis, Not otherwise specified	Biopsy of orbital mass	No systemic involvement at this time	Steroids	Remission
		+MPO Antibody					

MRI Brain/Orbit of one patient revealing an enhancing mass within the superolateral post-septal soft tissues of the right orbit, as well as signal abnormality along the pre-septal soft tissues involving the superior eyelid.



Conclusion: When pediatric patients present with orbital pseudotumor the differential should be widened regarding types of ANCA-associated vasculitides to include CSS and MPA. Recognizing these possibilities would allow for early screening and monitoring for potential multi-organ involvement.

Disclosure: A. Schlefman, None; **M. Leffler**, None; **A. C. Brescia**, None; **C. D. Rose**, None.

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Evidence Based Recommendations for Diagnosis and Management of Tumor Necrosis Factor Receptor-1 Associated Periodic Syndrome (TRAPS).

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Background/Purpose: Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS) is a rare hereditary autoinflammatory syndrome that can lead to significant morbidity. Evidence-based guidelines are lacking and management is mostly based on physician's experience. Consequently, treatment regimens differ throughout Europe. In 2012, a European initiative called SHARE *(Single Hub and Access point for pediatric Rheumatology in Europe)* was launched to optimize and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases. One of the aims of SHARE was to provide evidence based recommendations for diagnosis and treatment of TRAPS.

Methods: Evidence based recommendations were developed using the European League Against Rheumatism (EULAR) standard operating procedure. An expert committee was instituted, consisting of pediatric and adult rheumatologists. The expert committee defined search terms for the systematic literature review. Two independent experts scored articles for validity and level of evidence. Recommendations derived from the literature were evaluated by an online survey. Those with less than 80% agreement on the online survey or with relevant comments of the experts were reformulated. Subsequently, all recommendations were discussed at a consensus meeting using the nominal group technique. Recommendations were accepted if more than 80% agreement was reached.

Results: The literature search yielded 523 articles, of which 22 were considered relevant and therefore scored for validity and level of evidence. Eighteen were scored valid and used in the formulation of the recommendations. Seventeen recommendations were suggested in the online survey and discussed during the consensus meeting. Five general recommendations on management, two recommendations for diagnosis, seven for monitoring and eight for treatment were accepted with more than 80% agreement. Topics covered are the following:

- *general recommendations:* use of the multidisciplinary team, treatment goals and vaccinations
- *diagnosis:* TNFRSF1A screening, interpretation of R92Q and P46L variants
- *monitoring:* monitoring frequency and minimal assessments in TRAPS patients, the use of AIDAI score in clinical studies and risk assessment of amyloidosis

● *treatment:* NSAIDS and/or glucocorticoids during attacks, IL-1 blockade, etanercept, anti-TNF monoclonal antibodies, switching between biologicals

Conclusion: The SHARE initiative provides recommendations for diagnosis and treatment for TRAPS and thereby facilitates improvement and uniformity of care throughout Europe.

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Evidence Based Recommendations for the Management of Cryopyrin Associated Periodic Syndromes (CAPS). Nienke ter Haar[1], Marlen Oswald[2], Luca Cantarini[3], Marco Gattorno[4], Michael Hofer[5], Isabelle Kone-Paut[6], Jordi Anton Lopez[7], Karyl Barron[8], Paul Brogan[9], Joost Frenkel[1], Caroline Galeotti[6], Gilles Grateau[10], Veronique Hentgen[11], Tilmann Kallinich[12], Helen Lachmann[13], Huri Ozdogan[14], Seza Özen[15], Ricardo Russo[16], Anna Simon[17], Yosef Uziel[18], Carine Wouters[19], Brian Feldman[20], Bas Vastert[1], Nico Wulffraat[1], Susanne Benseler[20] and Jasmin Kuemmerle-Deschner[2]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]University Hospital Tuebingen, Tuebingen, Germany, [3]University of Siena, Siena, Italy, [4]Instituto Giannina Gaslini, Genoa, Italy, [5]Centre Multisite Romand de Rhumatologie Pediatrique, Lausanne, Switzerland, [6]Bicêtre Hospital, University of Paris SUD, Paris, France, [7]University Childrenxs Hospital, Barcelona, Spain, [8]NIH, Bethesda, MD, [9]Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [10]Hopital Tenon, Paris, France, [11]Versailles Hospital, Le Chesnay Cedex, France, [12]Charite, University Medicine Berlin, Berlin, Germany, [13]University College London Medical School, London, United Kingdom, [14]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [15]Hacettepe University, Ankara, Turkey, [16]Hospital De Pediatria, Buenos Aires, Argentina, [17]Radboudumc, Nijmegen, Netherlands, [18]Tel-Aviv University, Sackler School of Medicine, Tel-Aviv, Israel, [19]University of Leuven, Laboratory of Pediatric Immunology, University Hospital Leuven, Leuven, Belgium, [20]The Hospital for Sick Children, Toronto, ON.

Background/Purpose: Cryopyrin-associated periodic syndromes (CAPS) is a group of rare monogenetic autoinflammatory disorders. Evidence-based guidelines are lacking and management is mostly based on physician's experience. Consequently, treatment regimens differ throughout Europe. In 2012, a European initiative called SHARE *(Single Hub and Access point for pediatric Rheumatology in Europe)*was launched to optimize and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases. One of the aims of SHARE was to provide evidence based recommendations for management (treatment and monitoring) of CAPS.

Methods: Evidence based recommendations were developed using the European League Against Rheumatism (EULAR) standard operating procedure. An expert committee was instituted, consisting of pediatric and adult rheumatologists. The expert committee defined search terms for the systematic literature review. Two independent experts scored articles for validity and level of evidence. Recommendations derived from the literature were evaluated by an online survey. Those with less than 80% agreement on the online survey or with relevant comments of the experts were reformulated. Subsequently, all recommendations were discussed at a consensus meeting using Nominal Group Technique. Recommendations were accepted if more than 80% agreement was reached.

Results: The literature search yielded 1698 articles, of which 25 papers on treatment were considered relevant and therefore scored for validity and level of evidence. Seventeen were scored valid and used in the formulation of the recommendations. Fifteen recommendations were suggested in the online survey and discussed during the consensus meeting. Six general recommendations on management, five for monitoring and four for treatment were accepted with more than 80% agreement. Topics covered are the following:

● *General recommendations*: use of the multidisciplinary team, treatment goals, adjunctive therapies, psychosocial support and vaccinations

● *Monitoring*: monitoring frequency, minimal assessments in all CAPS patients and monitoring of severe phenotypes

● *Treatment*: IL-1 blockade, NSAIDs and/or glucocorticoids during attacks and DMARDS/biologicals other than IL-1 blockade

Conclusion: The SHARE initiative provides recommendations for the management of CAPS and thereby facilitates improvement and uniformity of care throughout Europe.

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Dissecting the Heterogeneity of Macrophage Activation Syndrome. Francesca Minoia[1], Sergio Davì[1], AnnaCarin Horne[2], Francesca Bovis[3], Erkan Demirkaya[4], Alessandro Consolaro[1], Jonathan Akikusa[5], Nuray Aktay Ayaz[6], Patrizia Barone[7], Bianca Bica[8], Isabel Bolt[9], Luciana Breda[10],Zane Davidsone[11], Carmen De Cunto[12], Jaime De Inocencio[13], Sandra Enciso[14], Romina Gallizzi[15], Thomas Griffin[16], Teresa Hennon[17], Gerd Horneff[18], Maka Ioseliani[19], Michael Jeng[20], Agneza Marija Kapovic[21], Bianca Lattanzi[1], Jeffrey M Lipton[22], Silvia Magni-Manzoni[23], Clarissa Nassif[24], Ingrida Rumba-Rozenfelde[25], Claudia Saad-Magalhães[26], Sulaiman Almayouf[27], Wafaa Al-Suwairi[28], Kimo C Stine[29], Olga Vougiouka[30], Lehn K. Weaver[31], Nicolino Ruperto[32], Alberto Martini[1], Randy Q. Cron[33] and Angelo Ravelli[34]. [1]Istituto Giannina Gaslini, Genova, Italy, [2]Karolinska Institutet, Karolinska University Hospital Solna, Stockholm, Sweden, [3]PRINTO - Istituto Giannina Gaslini, Genoa, Italy, [4]Gulhane Military Medical Faculty, Ankara, Turkey, [5]Royal Children's Hospital, Melbourne, Australia, [6]Bakırkoy Maternity and Childrens Education and Research Hospital, Istanbul, Turkey, [7]Azienda Policlinico Università di Catania, Catania, Italy, [8]Hospital Universitário Clementino Fraga Filho, Rio de Janeiro, Brazil, [9]Kinderspital Zuerich, Universitaetskinderklinik, Zurich, Switzerland, [10]University of Chieti G. D'Annunzio, Chieti, Italy, [11]Children's University Hospital, Riga, Latvia, [12]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [13]Hospital 12 de Octubre, Madrid, Spain, [14]Hospital Infantil de Mexico Federico Gomez in Mexico City, Mexico City, Mexico, [15]University of Messina, Messina, Italy, [16]Levine Children's Hospital, Carolinas Medical Ctr, Charlotte, NC, [17]Women & Children's Hospital of Buffalo, Buffalo, NY, [18]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany, [19]M. Iashvili Children's Central Clinic, Tbilisi, Georgia, [20]Stanford University, Stanford, CA, [21]Children's Hospital Zagreb, Zagreb, Croatia, [22]Steven and Alexandra Cohen Children's Hospital of New York, New York, NY, [23]Ospedale Pediatrico Bambino Gesù, Roma, Italy, [24]Hospital das Clínicas da Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, [25]University of Latvia, Riga, Latvia, [26]Botucatu Medical School, Botucatu, Brazil, [27]King Faisal Specialist H.,Riyadh, Riyadh, Saudi Arabia, [28]King AbdulAziz Medical City, Riyadh, Saudi Arabia, [29]Arkansas Children's Hospital, Little Rock, AR, [30]P. A. Kyriakou Childrens Hospital of Athens University, Athens, Greece, [31]Children's Hospital of Philadelphia, Philadelphia, PA, [32]Istituto Giannina Gaslini, Genoa, Italy, [33]University of Alabama at Birmingham, Birmingham, AL, [34]University of Genova, Genova, Italy.

Background/Purpose: Macrophage activations syndrome (MAS) occurring in the context of systemic juvenile idiopathic arthritis (sJIA) can pursue a rapidly fatal course. However, the diagnosis of the syndrome is often challenging as its features may be mimicked by those of confusable conditions, such as flares of the underlying disease or systemic infections. In addition, the clinical spectrum of MAS is known to be heterogeneous. The aim of this study is to seek insights into the heterogeneity of MAS by comparing the characteristics of patients enrolled in a large multinational survey in relation to geographic origin of patients, specialty of attending physician, demonstration of hemophagocytosis (HP), and outcome.

Methods: Patient data were collected retrospectively by pediatric rheumatologists (PR) or pediatric hemato-oncologists (PHO) and entered in a web-based database. Clinical and laboratory features, therapeutic interventions and outcome were compared between subgroups by means of Mann-Whitney U test or chi-square/Fisher exact test, as appropriate. "Severe course" was defined as the occurrence of ICU admission or death.

Results: A total of 362 patients with sJIA-associated MAS were collected by 95 investigators from 33 countries. 179 patients (49.4%) were enrolled in Europe (EU), 72 (19.9%) in North America (NA) and 111 (30.7%) in other continents (OC). 283 (88.2%) patients were included by PR and 79 (21.8%) patients by PHO. Bone marrow HP was detected in 160 (44.2%) patients and was not detected or looked for in 202 (55.8%) patients. Severe course was reported in 92 (25.4%) patients. Comparison by geographic origin showed a lower frequency of CNS disease and higher levels of liver transaminases in EU patients. NA physicians used more frequently iv Ig and biologics than did physicians from EU and OC. Patients entered by PHO had a greater frequency of multiorgan failure and were given more commonly biologics and etoposide, whereas patients seen by PR received more frequently cyclosporine. Patients with demonstration of HP had shorter duration of sJIA at MAS onset, higher prevalence of hepatosplenomegaly, lower levels of platelets and fibrinogen and higher levels of triglycerides, and were given more frequently cyclosporine, iv Ig and etoposide. Patients with severe course were older, had a longer duration of sJIA at MAS onset and had a greater frequency of haemorrhages and CNS dysfunction, lower levels of ESR, albumin and fibrinogen, higher levels of LDH, triglycerides and D-dimer, and were treated more commonly with cyclosporine, iv Ig and etoposide.

Conclusion: Clinical, laboratory and histopathologic features of sJIA-associated MAS were overall comparable among patients from different continents, whereas there was a disparity in the therapeutic choices made by specialists practicing in different geographic areas or fields. Patients with demonstration of HP or severe course presented with a more acute clinical and laboratory picture and were treated more aggressively.

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Evidence Based Recommendatinos for Diagnosis and Management of Mevalonate Kinase Deficiency (MKD). Nienke ter Haar[1], Jerold Jeyaratnam[1], Jordi Anton[2], Caroline Galeotti[3], Karyl Barron[4], Paul Brogan[5], Luca Cantarini[6], Marco Gattorno[7], Gilles Grateau[8], Veronique Hentgen[9], Michael Hofer[10], Tilmann Kallinich[11], Isabelle Kone-Paut[3], Jasmin Kuemmerle-Deschner[12], Helen Lachmann[13], Huri Ozdogan[14], Seza Ozen[15], Ricardo Russo[16], Yosef Uziel[17], Carine Wouters[18], Brian Feldman[19], Bas Vastert[1], Nico Wulffraat[20], Anna Simon[21] and Joost Frenkel[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]Pediatric Rheumatology Unit. Hospital Sant Joan de Déu. Universitat de Barcelona, Barcelona, Spain, [3]Bicêtre Hospital, University of Paris SUD, Paris, France, [4]NIH, Bethesda, MD, [5]Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [6]University of Siena, Siena, Italy, [7]Istituto Giannina Gaslini, Genova, Italy, [8]Hopital Tenon, Paris, France, [9]Versailles Hospital, Le Chesnay Cedex, France, [10]Centre Multisite Romand de Rhumatologie Pediatrique, Lausanne, Switzerland, [11]Charite, University Medicine Berlin, Berlin, Germany, [12]University Hospital Tuebingen, Tuebingen, Germany, [13]University College London Medical School, London, United Kingdom, [14]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [15]Deptartment. of Pediatric Rheumatology, Hacettepe University, Ankara, Turkey, [16]Hospital De Pediatria, Buenos Aires, Argentina, [17]Tel-Aviv University, Sackler School of Medicine, Tel-Aviv, Israel, [18]University of Leuven, Laboratory of Pediatric Immunology, University Hospital Leuven, Leuven, Belgium, [19]The Hospital for Sick Children, Toronto, ON, [20]Wilhelmina Children's Hospital/ UMC Utrecht, Utrecht, Netherlands, [21]Radboudumc, Nijmegen, Netherlands.

Background/Purpose: Mevalonate kinase deficiency (MKD) is a rare hereditary autoinflammatory syndrome that can lead to significant morbidity. Evidence-based guidelines are lacking and management is mostly based on physician's experience. Consequently, treatment regimens differ throughout Europe. In 2012, a European initiative called SHARE (*Single Hub and Access point for pediatric Rheumatology in Europe*) was launched to optimize and disseminate diagnostic and management regimens in Europe for children and young adults with rheumatic diseases. One of the aims of SHARE was to provide evidence based recommendations for diagnosis and treatment of MKD.

Methods: Evidence based recommendations were developed using the *European League Against Rheumatism* (EULAR) standard operating procedure. An expert committee was instituted, consisting of pediatric and adult rheumatologists. The expert committee defined search terms for the systematic literature review. Two independent experts scored articles for validity and level of evidence. Recommendations derived from the literature were evaluated by an online survey. Those with less than 80% agreement on the online survey or with relevant comments of the experts were reformulated. Subsequently, all recommendations were discussed at a consensus meeting using the nominal group technique. Recommendations were accepted if more than 80% agreement was reached.

Results: The literature search yielded 618 articles, of which 28 were considered relevant and therefore scored for validity and level of evidence. Fourteen were scored valid and used in the formulation of the recommendations. Sixteen recommendations were suggested in the online survey and discussed during the consensus meeting. Six general recommendations on management, three recommendations for diagnosis, six for monitoring and seven for treatment were accepted with more than 80% agreement. Topics covered are following:

- *general recommendations:* the use of the multidisciplinary team, treatment goals, and vaccinations
- *diagnosis:* diagnostic value of Gaslini diagnostic score, IgD and urinary mevalonic acid excretion
- *monitoring:* the use of AIDAI in clinical studies, monitor frequency, minimal assessments in all MKD and additional assessments in severe MKD patients, risk of infection and macrophage activation syndrome
- *treatment:* NSAIDs, glucocorticoids, IL-1 blockade, etanercept, switching biologicals, colchicine, statins and hematopoietic stem cell transplantation

Conclusion: The SHARE initiative provides recommendations for diagnosis and treatment for MKD and thereby facilitates improvement and uniformity of care throughout Europe.

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Steroid-Sparing Effect of Anakinra (Kineret®) in the Treatment of Patients with Severe Cryopyrin-Associated Periodic Syndrome. Bengt Hallén, Mika Leinonen, Torbjörn Kullenberg and Hans Olivecrona. Swedish Orphan Biovitrum, Stockholm, Sweden.

Background/Purpose: Cryopyrin-Associated Periodic Syndromes (CAPS) include a group of rare inherited autoinflammatory diseases consisting of FCAS, Muckle-Wells Syndrome and the most severe form, NOMID. Reduction in the use of steroids as concomitant medication is a treatment goal for anakinra-treated CAPS patients, since inappropriate use of steroids could lead to increased toxicity. Adverse events (AEs) related to the cardiovascular system are along with infections most frequently reported in steroid-treated patients with rheumatic diseases (Hoes et al Ann Rheum Dis. 2007;66,1560–67). Among 16 patients with severe CAPS treated with anakinra and taking steroids at baseline, the mean daily prednisone-equivalent dosage has been reported to decrease from 0.80 mg/kg/day at baseline to 0.033 mg/kg/day after 60 months (Sibley et al. Arthritis Rheum. 2012;64:2375–86). The objective of the present analysis is to further evaluate the steroid-sparing potential and its consequences in an expanded cohort of patients with severe CAPS treated with anakinra.

Methods: A prospective, open-label withdrawal design study of anakinra treatment with long-term extension including 43 patients was conducted at the National Institutes of Health (Goldbach-Mansky et al. NEJM. 2006;355:581–92). The primary efficacy endpoint, Diary Symptom Sum Score (DSSS), collected daily up to 60 months, included 5 symptoms (fever, rash, joint pain, vomiting, headache); each scored from 0 (no symptoms) to 4 (severe symptoms). Use of steroid medication was obtained from the patient diary.

The prednisone dose was to be decreased by 20% at each study visit in which the subject's disease activity was "moderately" or "significantly" improved. Different types of steroids were converted into prednisone-equivalent doses to enable comparisons. The AEs were analyzed with the infection rate (number of infections per patient years of treatment).

Results: During the study, the proportion of patients in the ITT population on steroids decreased from 47.1% at baseline to 33.3% at Month 60. Among the patients using steroids at baseline the mean (SEM) prednisone-equivalent dose was 0.76 (0.31) mg/kg at baseline, but a prompt tapering of their doses during the first 6 months to 0.15 (0.03) mg/kg was seen. At Month 36 and Month 60 there was a further decline in the prednisone-equivalent dose to 0.08 (0.02) and 0.05 (0.02) mg/kg, respectively. There was a rapid significant decrease of DSSS both in patients not using steroids at all and in patients reducing the steroids dose. The decrease was maintained up to Month 60 ($p<0.001$ in both subgroups at each follow-up visit). Among the patients reducing the steroid dose, the rate of infections was reduced from 3.4 events/patient year (Year 1) to 1.4 (Year 5).

Conclusion: The use of steroids expressed as mean prednisone equivalent dose decreased from 0.76 mg/kg to 0.05 mg/kg after 5 years of treatment with anakinra. The treatment effect evaluated by DSSS was maintained at the same low level throughout the study.

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Joint Involvement in Pediatric Crohn's Disease Is Related to Higher Disease Activity and Worse Quality of Life. Beata Derfalvi, Gabor Bozsaki, Doloresz Szabo, Aron Cseh, Katalin Eszter Muller, Andras Arato and Gabor Veres. Semmelweis University, Budapest, Hungary.

Background/Purpose: The incidence of arthritis and arthralgia in pediatric patients with Crohn's disease (CD) is reported to be 2–15% and 22%, respectively. The aim of our study was to assess joint involvement with Pediatric CD Activity Index (PCDAI) and to assess quality of life (IMPACT-III). While arthritis in pediatric Crohn's disease is associated with the enthesitis-related JIA subgroup, subclinical sacroiliitis and HLA-B27-association may also be found.

Methods: A cross-sectional study was conducted in 82 pediatric patients with CD (age: 13.7±3.2 years, male:female ratio = 1.2:1, disease duration: 21.6±21, median: 15 months) to assess the prevalence of arthritis, lower extremity enthesitis and arthralgia. Detailed joint physical examination and a modified JAMAR (Juvenile Arthritis Multidimensional Assessment Report) were performed by a pediatric rheumatologist. Regarding disease activity, a PCDAI, IMPACT-III questionnaire and basic laboratory parameters including CRP and platelet count were determined, as well as sacroiliac MRI (n=62) and molecular genetic testing for HLA-B27 (n=72) were assessed.

Results: Altogether 35% (29/82) of the patients had arthritis. At the time of the examination, only 1 child had active enthesitis, 8/29 children had active arthritis indicated by swollen joint(s) - including 4 patients with also restricted range of motion in one or more other joints, suggestive of previous arthritis. Another 15/29 children had evidence of previous arthritis on joint examination. Another 5 patients had a remote history of documented active arthritis. Hip (12/29) and knee (11/29) joints were most commonly affected. Cumulative incidence of arthralgia during the entire course of the disease was 48% (39/82), of whom 22% (18/39) had arthralgia, without arthritis, usually affecting the knee. There was a significant association between arthritis and lower quality of life (IMPACT-III score, $p < 0.01$). In addition, incidence of arthritis and arthralgia correlated with higher CRP and PCDAI independent of age and sex. Arthritis was significantly more common in patients requiring infliximab treatment. None of the patients had sacroiliitis based on MRI, and HLA-B27 positivity was not related to arthritis.

Conclusion: The prevalence of joint involvement such as arthritis and arthralgia in pediatric CD was higher than previously reported when assessment is done by a pediatric rheumatologist. Arthritis was associated with more severe disease, as reflected by higher CRP, PCDAI score, as well as lower quality of life. Enthesitis was uncommon and sacroiliitis and HLA-B27 positivity were not significant associations in our pediatric CD cohort.

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Safety and Efficacy of Rilonacept in Patients with Deficiency of Interleukin-1 Receptor Antagonist (DIRA). Dawn C. Chapelle Neal[1], Adriana Almeida de Jesus[1], Yan Huang[2], Yin Liu[2], Raphaela Goldbach-Mansky[2] and Gina Montealegre[1]. [1]NIAMS/NIH, Bethesda, MD, [2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD.

Background/Purpose: Deficiency of interleukin-1 receptor antagonist (DIRA) is a neonatal-onset autoinflammatory syndrome caused by recessive mutations in *IL1RN* gene, the gene encoding the interleukin-1-receptor antagonist. It is clinically characterized by a perinatal-onset of pustular dermatosis, aseptic multifocal osteomyelitis, and marked elevation of acute phase reactants. In our treated patients, IL-1 blockade with daily anakinra leads to rapid and complete resolution of symptoms and normalization of the acute phase reactants. There is a need, however, for longer acting IL-1 blocking agents that are more convenient to administer and are less likely to cause injection site reactions.

Objectives: The primary objective of this study is to assess the ability of rilonacept to achieve/maintain remission in patients with DIRA who have shown response to anakinra. The secondary objective is to assess the safety of rilonacept in DIRA patients, and to assess its ability to prevent new organ damage.

Methods: Patients with a genetically confirmed diagnosis of DIRA and an adequate response to anakinra are eligible for the study. Per protocol, anakinra was discontinued 24 hours prior to first dose of study medication. A loading dose of rilonacept of 4.4 mg/kg/ week was given and then decreased to a maintenance dose of 2.2 mg/kg/week. Patients who met flare criteria were subsequently escalated to 4.4 mg/kg/week with the option to increase to 6.6 mg/kg/week if needed. Diary and Dermatology scores in addition to ESR and CRP were collected at each visit. Paired t-test analyses were used to compare baseline and the most recent clinic visit data.

Results: Six Caucasian patients have been enrolled**,** 50% male, with a mean age of 4.8 years SD (±1.3). All patients were in remission on anakinra (diary score 0) with a mean dosage of 3.21 mg/kg/day SD (±0.48). The mean follow-up time has been 4.5 months. The diary scores have increased to 0.09 at the last visit, reflecting the onset of nail changes in one patient. All patients (except one) required an escalation in dosage from 2.2 mg/kg/week to 4.4 mg/kg/week due to a transient increase in micropustular lesions mostly in hyperkeratotic areas of the skin (elbow and knee). The micropustular lesions lead to the increase in dermatology scores from 1.3 to 3.2. Despite the mild skin lesions, no new bone lesions were detected and the acute phase reactants have decreased from baseline. No SAE's have occurred and four adverse events have been reported.

Conclusion: Preliminary data in six DIRA patients suggest that doses of rilonacept at 4.4 mg/kg/week are required to achieve remission. Rilonacept treatment provides increased quality of life due to weekly injections. Long acting IL-1 inhibition with rilonacept seems to be a viable option in the treatment of DIRA.

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Food Allergy and Celiac Disease in Children with Juvenile Idiopathic Arthritis. Trevor E. Davis[1], Mei-Sing Ong[2], Diana Milojevic[3], Jyoti Ramakrishna[3] and Marc D. Natter[4]. [1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [2]University of New South Wales, Sydney, Australia, [3]Floating Hospital for Children at Tufts Medical Center, Boston, MA, [4]Children's Hospital Boston, Boston, MA.

Background/Purpose: There are multiple strong associations between gut pathology and rheumatologic diseases. This connection, between primary GI disease and rheumatologic diseases, is manifest in both autoimmune and infectious GI diseases. For example, arthritis is a component of several GI infections (Reactive arthritis following *Salmonella, Shigella, Yersinia, or Campylobacter* species, Whipples disease, and multiple parasitic infections) as well as inflammatory bowel disease and behcet's. Arthritis is also a known extra-intestinal manifestation of celiac disease. There is controversy regarding the prevalence of celiac in adult arthritis and to date only a few small studies exist in children. Additionally, both in children and adults, little is known regarding possible association of food allergies and arthritis. With this study, we endeavored to assess the risk of food allergy and celiac disease in a large population of children with juvenile idiopathic arthritis (JIA).

Methods: We analyzed electronic medical records from Boston Children's Hospital, between the years 1993 and 2014. Children with JIA, food allergy and celiac disease were identified, using tools of the National Center for Biomedical Computing "Informatics for Integrating Biology to the Bedside" (i2b2). We assessed the risk of food allergy and celiac disease in JIA patients, in comparison with the children without JIA.

Results: A total of 1,933,719 children were included in our study. Of this total population 0.21% (n=4,128) had documented JIA, 1.14% had food allergy, and 0.18% had celiac disease (Table 1). Of the subjects with JIA 1.99% had documented food allergy and 1.02% had celiac disease. Children with JIA had an elevated risk of developing food allergy (OR 1.75; 95% CI 1.41 – 2.18; $p<0.0001$), and celiac disease (OR 5.58; 95% CI 4.11 – 7.58; $p<0.0001$).

Table 1.

Disease	Number of patients (%)
Study population (n=1,933,719)	
JIA	4,128 (0.21)
Food allergy	21,953 (1.14)
Celiac disease	3,559 (0.18)
JIA population (n=4,128)	
Food allergy	82 (1.99)
Celiac disease	42 (1.02)

Conclusion: We again find evidence of an association between the gut and rheumatologic disease. We clearly demonstrate an increased risk of celiac in JIA, consistent with the limited data on the subject. We also find a statistically significant increased risk of food allergies in JIA. In celiac evidence supports improvement or resolution of the associated arthritis with the removal of the trigger food, gluten. We do not yet know if the same holds true for food allergies. It is possible food allergies can exacerbate JIA but further work must be done to answer this question.

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Cartilage Thickness and Bone Health in Children with Juvenile Idiopathic Arthritis. Marinka Twilt, Dan Pradsgaard, Anne Helene Spannow, Arne Horlyck, Carsten Heuck and Troels Herlin. Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: Although treatment options have increased and morbidity has decreased in the last decade Juvenile Idiopathic Arthritis (JIA) may still result in disability. Increasingly ultrasonography (US) has been used to measure cartilage thickness in children with JIA and normal values have been established. Although treatment of JIA has moved away from the use of long term steroids bone health remains a consistent worry in patients with JIA. The relation between cartilage thickness and bone health in patients with JIA has not been studied before. The aim of this study is to determine if there is a correlation between cartilage thickness and bone health index in children with JIA.

Methods: We clinically examine joint activity in 68 children with JIA. Joint cartilage thickness was assessed by greyscale USin knee, ankle, wrist, metacarpophalangeal, and proximal interphalangeal (PIP) joints. Measurements were compared to reference values of a healthy cohort of a previous study. Medical records were reviewed for JIA subtype, treatment and disease duration. Automated determination of bone health index and bone age was made by using BoneXpert (Visiana) software implying digital programmetry (DXR) and conventional hand radiographs.

Results: In total 68 patients (17 males, 51 females) with a median age at investigation of 11 years (range 5–15 years) and median disease duration of 42 months were included. Subtypes represented were; 26 oligoarticular persistent; 13 oligoarticular extended; 17 polyarticular rheumatoid factor (RF) negative; 4 polyarticular RF positive; 8 systemic onset. In total 680 joints were examined for cartilage thickness. Decreased cartilage thickness was present in 27% of the examined joints (181 joints). Most common joint with decreased cartilage thickness was the PIP, followed by the wrist, the least common was the ankle joint. 34 patients had a decreased bone health index and 23 patients a decreased bone age; only 14 patients examined showed a combined decreased bone health index and decreased bone age. Decreased cartilage thickness of the left wrist is found in 29 patients; 48% of these patients also have a decreased bone health index but only 17% have a decreased bone age.

Conclusion: Decreased cartilage thickness is a prominent and frequent feature in JIA. Decreased bone health and bone age is found in approximately half of the patients. Cartilage thickness seems to be correlated with decreased bone health, but less with decreased bone age. Further studies are necessary to study these correlations as decreased cartilage thickness might be an indicator for future bone health and steer treatment decisions.

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The Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh Out) Cohort: Independent Risk Factors and Medication Use in New Onset Uveitis in Juvenile Idiopathic Arthritis. Jennifer JY Lee[1], Ciarán M. Duffy[1], Jaime Guzman[2], Nick Barrowman[3], Deepti Reddy[3], Kimberly Morishita[2], Lynn R. Spiegel[4], Elizabeth Stringer[5], Michele Gibbon[1], Rae S.M. Yeung[4], Lori B. Tucker[2], Kiem Oen[6], Karen N Watanabe Duffy[1] and ReACChOut Investigators[1]. [1]Children's Hospital of Eastern Ontario and University of Ottawa, Ottawa, ON, [2]BC Children's Hospital and University of British Columbia, Vancouver, BC, [3]Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON, [4]The Hospital for Sick Children and University of Toronto, Toronto, ON, [5]IWK Health Centre, Halifax, NS, [6]University of Manitoba, Winnipeg, MB.

Background/Purpose: The Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh Out) cohort is a multi-centre prospective inception cohort of newly diagnosed Juvenile Idiopathic Arthritis (JIA) patients. From our analysis of JIA associated new onset uveitis, we reported the first true incidence of uveitis of 2.9% per year and prevalence of 6.9%, the latter considerably lower than previously reported. We identified a positive ANA and young age at diagnosis of JIA (< 7 years) as independent risk factors for uveitis. In this study, we examined the association between medications, uveitis and these independent risk factors.

Objectives: 1) to assess medications administered prior to uveitis and after diagnosis 2) to determine the association between the independent risk factors for uveitis and specific medication use and 3) their association with asymptomatic versus symptomatic presentation.

Methods: The ReACCh Out cohort recruited newly diagnosed JIA patients from 16 Canadian centres between January 2005 and December 2010. Prospective data was collected every 6 months for 2 years, then yearly. Clinical and laboratory data, medications, the presence of uveitis and complications determined by an ophthalmologist, was documented at each visit. Descriptive statistics characterize the uveitis cohort and frequencies were obtained for the medications used. We calculated the relative risk for certain medications, controlled for by the presence or absence of independent risk factors.

Results: 1104 newly diagnosed (≤ 6 months) JIA patients with ≥1 follow-up visit were included. Patients were predominantly female (63%), median age at diagnosis of 9.3 (3.9, 13.0) years. Time from diagnosis to enrollment was 0.3 (0, 1.6) months. Follow-up to last visit was 34.2 (21.5, 48) months. 23 patients, uveitis status not available, were excluded. 77 patients with new onset uveitis were identified. Patients were on the following systemic medications prior to uveitis diagnosis: NSAIDs (71; 92.2%), Methotrexate (34; 44.2%), other DMARDs (7; 9.1%), systemic glucocorticoids (20; 26%), biologics (12; 15.6%). Following diagnosis: NSAIDs (45; 58.4%), Methotrexate (56; 72.7%), other DMARDs (10; 13%), systemic glucocorticoids (23; 30%), biologics (11; 14.3%).

58 (75.3%) patients had asymptomatic uveitis: 43 (74.1%) ANA positive compared to 13 (22.4%) ANA negative. ANA positive uveitis patients were 2.48 and 1.10 times more likely to be placed on methotrexate and biologics respectively, compared to those who were ANA negative. 52 (90%) of the asymptomatic uveitis patients were < 7 years old, compared to 6 (10%) of patients ≥ 7 years old and were 1.29 and 1.32 times more likely to be on methotrexate and biologics respectively, compared to the older group.

Conclusion: In a large inception cohort of newly diagnosed JIA patients followed prospectively, we evaluated medications administered prior to and after the diagnosis, uveitis presentation and independent risk factors for uveitis. The majority of ANA positive patients and of a younger age (< 7 years) at diagnosis of JIA, presented with asymptomatic uveitis, highlighting the important role of these independent risk factors for uveitis screening.

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Accuracy of the Use of Administrative Diagnostic Codes to Identify Pediatric in-Patient Musculoskeletal Conditions in an African Tertiary Hospital.

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Background/Purpose: The spectrum and frequency of pediatric rheumatic conditions in East Africa are unknown. Administrative data that is systematically collected using International Classification of Disease (ICD) codes can provide insight into this issue. The aim of this study was to assess the accuracy of using ICD-10 diagnostic codes in identifying either inflammatory or infectious musculoskeletal conditions requiring hospitalization at the largest pediatric center in East-Africa.

Methods: We reviewed the hospital records of all patients identified as having diseases of the musculoskeletal (MSK) system and connective tissues (CT) by ICD-10 diagnostic codes (M-codes) at discharge from Gertrude's Children's Hospital in Kenya, during a one year period from January to December 2011. ICD coding at this center is performed by medical records personnel based on the diagnosis provided by the treating physician. We evaluated the concordance rate between the physician's diagnosis at discharge and the ICD-10 code assigned.

Results: The total number of admissions during 2011 was 8,011. Among these, 42 patients had an "M-code" diagnosis at discharge (0.5%) and 39 of these had charts available for review. Among those with M-code diagnoses, concordance rates between the ICD-10 code assigned by an administrator and the treating physician's discharge diagnosis was 66.7% (26/39). Specifically, when only the infectious and inflammatory categories of M-codes were included (26 cases), concordance improved to 76.9% (20/26). The specific diagnosis in those with musculoskeletal infections (n=10) included septic arthritis (7/10), pyomyositis (2/10) and infective bursitis (1/10). Seven of these cases were coded correctly (70%). The diagnoses for those with inflammatory conditions (n=16) included 4 with Kawasaki disease; 2 with inflammatory arthropathies; and 10 with non-specific inflammatory M-codes such as unspecified arthritis, arthralgia or joint effusion. The concordance among the inflammatory M-codes was 81.3% (13/16 were coded correctly including all KD cases).

Conclusion: Overall, the concordance of ICD-10 codes assigned in comparison to the physician's discharge diagnosis for categories of inflammatory and infectious musculoskeletal conditions is acceptable. Inflammatory conditions are coded less specifically due to the physicians' use of descriptive terms instead of definitive diagnoses at discharge. Therefore, administrative diagnostic codes could be used to estimate overall frequencies of rheumatic diseases in in-patients in East Africa however, their utility in estimating the frequency of specific inflammatory conditions is limited.

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Race and Other Risk Markers of Uveitis in a Prospective Cohort of Children with Juvenile Idiopathic Arthritis.

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Background/Purpose: Juvenile idiopathic arthritis-associated uveitis (JIA-U) can lead to poor visual outcomes. American Academy of Pediatric guidelines recommend screening every 3 months in children with oligoarticular (oligo) or polyarticular (poly) rheumatoid factor (RF) (−) subtype, ANA positivity, <4 years of arthritis, and onset <7 years old. Identification of other risk markers could help modify current screening and improve outcomes.

Methods: In our prospective cohort of 250 JIA patients, rheumatology and ophthalmology medical record reviews and parent/patient based questionnaires were completed every 3–6 months (2011–2014). We collected data on demographics, arthritis and uveitis, and quality of life/function. We compared children with JIA and JIA-U, and African American (AA) and Caucasians (W) with uveitis.

Results: Our cohort was primarily W females with oligo persistent and poly RF (−) JIA. There were 45/250 (18%) with uveitis of whom 15.6% were AA (Table 1). Compared to JIA alone, JIA-U were more frequently of the oligo persistent JIA subtype (p = <0.001), younger at arthritis diagnosis (p = <0.001), ANA positive (p = 0.029), anti-CCP negative (p = 0.018) and had reduced vision related quality of life and function (p = < 0.001). No children with JIA-U had psoriatic (p = 0.030), systemic (p=0.029) or poly RF (+) (p=0.133) JIA.

On regression analysis, young age at diagnosis (OR = 0.88, (95% CI 0.81–0.98), p <0.001) and oligo persistent JIA (OR 3.15, (95% CI 1.42–6.98), p = 0.011) were predictors for uveitis. AA race approached significance (OR = 2.56, (95% CI = 0.93–7.02), p = 0.068). ANA was not significant after adjustment.

Comparing JIA-U by race, there were fewer AA children then W overall (7/40 (17.5%) vs. 33/40 (82%)) (Table 2). However, there was no significant difference in the frequency of uveitis between AA and W (7/33 (21%) vs. 33/190 (17%), p=0.624). They were similar in age at arthritis diagnosis, JIA subtype, ANA positivity, arthritis characteristics, and treatment. AA were older at uveitis diagnosis (p = 0.018) with more ocular complications –synechiae (p<0.027) and band keratopathy (p<0.011).

Conclusion: In our cohort, uveitis was less frequent in AA children overall. However, we found a similar likelihood of uveitis in AA compared to W (21% vs 17%). AA were older when diagnosed and suffered more ocular complications. We also confirmed known uveitis risk factors (young age at JIA diagnosis and JIA subtype). Further investigation into the role of race should be conducted as uveitis may be more common in AA but diagnosed later leading to increased visual complications, or may be more severe in AA.

Table 1 Characteristics of children with JIA and JIA-associated uveitis

Characteristics N (%)[1]	Group JIA N=205	Group JIA-U N=45	p-value
Demographics			
Age (yrs), *Mean ± SD*	11.1 ± 4.6	9.6 ± 4.9	0.053
Gender, female	144 (70.2%)	35 (77.8%)	0.310
Hispanic	16 (7.8%)	7 (15.6%)	0.104
Race			
Caucasian	157 (76.6%)	33 (73.3%)	0.582
African American	26 (12.7%)	7 (15.6%)	0.219
Other	22 (10.7%)	5 (11.1%)	0.465
Disease Characteristics			
Age at arthritis diagnosis (yrs), *Mean ± SD*	8.1 ± 4.7	5.0 ± 4.9	<0.001*
Duration of JIA (yrs), *Mean ± SD*	2.9 ± 3.1	4.6 ± 4.0	0.012*
JIA subtype			
Oligoarticular persistent	65 (31.7%)	31 (68.9%)	<0.001*
Oligoarticular extended	12 (5.9%)	2 (4.4%)	0.754
Polyarticular RF (−)	55 (26.8%)	6 (13.3%)	0.056
Polyarticular RF (+)	13 (6.2%)	0 (0.0%)	0.133
Systemic	20 (9.8%)	0 (0.0%)	0.029*
Psoriatic	10 (4.9%)	0 (0.0%	0.030*
Enthesitis related arthritis	27 (13.2%)	4 (8.9%)	0.4300
Undifferentiated	2 (1.0%)	0 (0.0%)	1.00
Labs			
ANA (+)	74 (37.8%)	24 (55.8%)	0.029*
RF (+)	26 (12.7%)	1 (2.2%)	0.059
Anti-CCP (+)	23 (11.3%)	0 (0.0%)	0.018*
HLA-B27 (+)	20 (14.3%)	5 (17.9%)	0.771
Quality of Life/Function scores (child)[2]			
PedsQL[3] (Total), *Mean ± SD*	76.4 ± 19.1	76.5 ± 20.5	0.982
PedsQL[3] (Psychosocial), *Mean ± SD*	77.8 ± 16.11	75.0 ± 16.4	0.325
CHAQ[4], *Mean ± SD*	0.44 ± 0.46	0.43 ± 0.53	0.907
EYE-Q[5], *Mean ± SD*	3.60 ± 0.37	3.32 ± 0.41	<0.001*
Quality of Life/Function scores (parent)[2]			
PedsQL[3] (Total), *Mean ± SD*	73.9 ± 20.7	78.8 ± 18.6	0.154
PedsQL[3] (Psychosocial), *Mean ± SD*	79.4 ± 16.3	80.3 ± 16.7	0.746
CHAQ[4], *Mean ± SD*	0.43 ± 0.45	0.35 ± 0.48	0.266
EYE-Q[5], *Mean ± SD*	3.70 ± 0.28	3.41 ± 0.41	<0.001*

[1]N(%) unless otherwise specified; [2]Indicates missing data; [3]Pediatric Quality of Life Inventory; [4]Childhood Health Assessment Questionnaire; [5]Effects of Youngsters' Eyesight on Quality of Life
*p value <0.05

Table 2 Comparison of Caucasian and African American children with JIA-associated uveitis

Characteristics *N (%)*[1]	Group Caucasian (n =33)	(African American n = 7)	p-value
Demographics			
Age, *Mean ± SD*	8.7 ± 4.1	13.5 ± 5.4	0.011*
Gender, female	26 (78.8%)	4 (57.1%)	0.338
Hispanic	6 (18.2%)	0 (0.0%)	0.103
Arthritis Disease Characteristics			
Age at arthritis diagnosis (yrs), *Mean ± SD*	4.4 ± 4.1	9.6 ± 7.6	0.169
Duration of JIA (yrs), *Mean ± SD*	4.5 ± 3.5	4.2 ± 5.7	0.916
JIA subtype			
Oligo persistent	24 (72.7%)	3 (42.9%)	0.187
Oligo extended	1 (3.1%)	0 (0.0%)	1.000
Poly RF (−)	4 (12.1)%)	2 (28.6%)	0.567
ERA	3 (9.1%)	1 (14.3%)	1.000
Uveitis Disease Characteristics			
Age at uveitis diagnosis (yrs), *Mean ± SD*	5.6 ± 3.9	9.9 ± 4.9	0.018*
Anterior Location	27 (81.2%)	5 (83.3%)	0.611
Bilateral involvement	24 (72.7%)	4 (66.7%)	0.410
Complications			
Cataracts	8 (24.2%)	3 (42.9%)	0.369
Glaucoma	2 (6.1%)	0 (0%)	1.000
Synechiae	8 (24.2%)	5 (71.4%)	0.027*
Band keratopathy	4 (57.1%)	3 (9.1%)	0.011*
Cystoid macular edema	2 (6.1%)	2 (28.6%)	0.134
Labs			
ANA (+)	18 (58.1%)	4 (50.0%)	1.000
HLA-B27 (+)	5 (23.8%)	0 (0.0%)	0.545
Medication use			
Methotrexate all routes	28 (84.5%	5 (71.4%)	0.584
Oral	21 (63.6%)	5 (71.4%)	1.00
Subcutaneous injection	24 (72.7%)	5 (71.4%)	1.00
Anti-TNF Use	15 (45.5%)	4 (57.1%)	0.689
Infliximab	10 (30.3%)	3 (42.9%)	0.662
Adalimumab	2 (6.1%)	1 (14.3%)	0.448
Quality of Life/Function scores (child)[2]			
PEDSQL[3] (Total), *Mean ± SD*	74.0 ± 16.5	78.7 ± 15.1	0.490
PEDSQL[3] (Psychosocial), *Mean ± SD*	73.1 ± 16.7	78.7 ± 15.1	0.405
CHAQ[4], *Mean ± SD*	0.45 ± 0.52	0.38 ± 0.62	0.790
EYE-Q[5], *Mean ± SD*	3.33 ± 0.34	3.44 ± 0.63	0.741
Quality of Life/Function scores (parent)[2]			
PEDSQL[3] (Total), *Mean ± SD*	79.2 ± 17.3	77.4 ± 16.9	0.804
PEDSQL[3] (Psychosocial), *Mean ± SD*	79.9 ± 18.1	77.6 ± 14.9	0.753
CHAQ[4], *Mean ± SD*	0.36 ± 0.46	0.43 ± 0.71	0.817
EYE-Q[5], *Mean ± SD*	3.42 ± 0.34	3.23 ± 0.71	0.512

[1]N(%) unless otherwise specified; [2]Indicates missing data; [3]Pediatric Quality of Life Inventory; [4]Childhood Health Assessment Questionnaire; [5]Effects of Youngsters' Eyesight on Quality of Life
*p value <0.05

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Canakinumab in Biologic-naïve Versus Previously Biologic-Exposed Systemic Juvenile Idiopathic Arthritis Patients: Efficacy Results from a 12 Week Pooled Post Hoc Analysis. A Grom[1], P Quartier[2], N Ruperto[3], H.I Brunner[1], K Schikler[1], M Erguven[3], L Goffin[3], M Hofer[3], T Kallinich[3], K Marzan[1], C Gaillez[4], K Lheritier[4], K Abrams[5], A Martini[3] and D.J Lovell[1]. [1]PRCSG, Cincinnati, OH, [2]Hôpital Necker-Enfants Malades, Paris, France, [3]PRINTO-Istituto Gaslini, Genova, Italy, [4]Novartis Pharma AG, Basel, Switzerland, [5]Novartis Pharmaceutical Corporation, East Hanover, NJ.

Background/Purpose: Efficacy and safety of canakinumab (CAN), a selective, human, anti-IL-1β monoclonal antibody, was previously demonstrated in 2 phase III trials.[1] Out of these trials ≥60% of the patients (pts) received a previous biologic and were switched to CAN due to lack of efficacy or for safety reasons, and may be more refractory to another biologic therapy. Efficacy of CAN in biologic-naïve (BN) pts and those previously exposed to biologics (BE) during the first 12-weeks are evaluated.

Methods: Pooled data from CAN naïve pts, enrolled in two phase III trials[1] and an extension phase (up to interim data lock 10 August 2012) were considered. Pts (2–19 yrs) with active SJIA were enrolled and received CAN 4 mg/kg for 12 weeks. CAN naïve pts who entered the trials and received at least one dose of CAN were included in this analysis (N=178 CAN naïve pts). Descriptive efficacy analyses of adapted ACR-JIA responses at Week 12 are provided for the BN and BE pts groups.

Results: At baseline, there were 66 (37%) BN pts whereas anakinra (ANA), tocilizumab (TCZ), etanercept (ETN) and adalimumab (ADA), were the biologics received by 78 (44%), 10 (6%), 58 (33 %) and 9 (5%) pts, respectively. The main reasons for discontinuation of biologics in BE group (n=112) was lack of efficacy (ANA, n=32; TCZ, n=7; ETN, n=56; ADA, n=9) or safety/tolerability (ANA, n=20; TCZ, n=4, ETN, n=0). At Week 12, the BN and BE groups were similar in aACR-JIA 30 and 50 response rates. Numerically higher aACR-JIA 70 and 90 response rates were achieved in BN vs BE pts (Table). aACR-JIA 70 and 90 response rates were similar in pts previously exposed to ANA vs those not exposed to ANA at 12 weeks (aACR-JIA70: 58% vs 63% and aACR-JIA 90:47% vs 50%). Compared to pts who discontinued ANA due to lack of efficacy, there was a trend towards numerically higher aACR-JIA 70 and 90 response rates at Week 12 in pts who stopped ANA for other reasons (aACR-JIA70: 34% vs74%; aACR-JIA90: 25% vs 63%). A numerically higher aACR-JIA 30, 50, 70 and 90 response rates were observed in TCZ naïve pts vs. those pts exposed to TCZ (n=10) at week 12 [aACR-JIA30: 71% vs 50%; aACR-JIA50: 70% vs 50%; aACR-JIA70: 61% vs 50%; aACR-JIA90: 49% vs 40%]. Numerically higher aACR-JIA 70 and 90 responses were observed for ETN naïve pts vs those exposed to ETN at week 12 [aACR-JIA70: 67% vs 48%; aACR-JIA90: 58% vs 31%]; while ADA- naïve pts had similar responses to CAN as ADA-exposed pt (aACR-JIA 70: 61% vs 56%) and they had higher aACR-JIA 90 response (aACR-JIA90: 50% vs 22%) at week 12.

Table. Percentage of patients with adapted JIA ACR (aACR) response* at Week 2, 4 & 12

	Previous exposure to biologics					
	Week 2		Week 4		Week 12	
Total patients N=178	No (n=66)	Yes (n=112)	No (n=66)	Yes (n=112)	No (n=66)	Yes (n=112)
aACR50	75.8%	67.0%	77.3%	69.6%	74.2%	65.2%
aACR70	66.7%	51.8%	72.7%	53.6%	69.7%	55.4%
aACR90	36.4%	36.6%	54.5%	34.8%	60.6%	42.0%

*aACR response= ACR response level plus absence of fever

Conclusion: In general, BE pts achieved aACR-JIA 50,70 and 90 responses to CAN quickly in the first 2 weeks, and maintained their response up to Week 12; albeit at a numerically lower level than BN pts. These data support the consistent efficacy of CAN across different subgroups of pts.

Reference:

Ruperto N, et al. N Engl J Med 2012;367(25).

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Demographic, Clinical and Treatment Characteristics of the Childhood Arthritis and Rheumatology Research Alliance Registry Systemic JIA Cohort. Ginger L. Janow[1], Laura Schanberg[2], Soko Setoguchi[3], Elizabeth D. Mellins[4], Rayfel Schneider[5], Yukiko Kimura[6] and The CARRA Registry Investigators[7]. [1]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [2]Duke University, Durham, NC, [3]Duke Clinical Research Institute, Durham, NC, [4]Stanford University Medical Center, Stanford, CA, [5]The Hospital for Sick Children, Toronto, ON, [6]Hackensack Univ Medical Ctr, Hackensack, NJ, [7]Childhood Arthritis and Rheumatology Research Alliance, Durham, NC.

Background/Purpose: Systemic JIA (sJIA) is a rare disease whose treatment has changed in the past 10 yrs. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry contains a large cohort of sJIA pts. We aimed to: (1) describe the characteristics of the CARRA Registry sJIA cohort; (2) identify medication usage trends; and (3) identify subgroups at increased risk for poor outcomes.

Methods: 54 US/Canadian sites enrolled 528 sJIA pts as a cross-sectional convenience sample from 2010–2013. Only pts with complete datasets were included in this analysis. We tested binary and continuous variables for subgroup differences among or across groups, using a chi-square or ANOVA, respectively.

Results: 435 pts were included (Table 1). Disease activity was low: 15% had rash, 7% fever, median joint count 0, and median physician global assessment 1. Significant changes in medication usage occurred over the study period: DMARD and TNF inhibitor use decreased while IL-6 inhibitor (IL-6i) use increased (Fig 1). 29% were on corticosteroids at enrollment. African Americans (AA) had higher CHAQ, worse quality of life and poorer ACR functional class (p 0.0004). Pts diagnosed at a younger age (< 2 yrs) had more frequent biologic use and lower overall well being. Joint damage on imaging increased with younger age at diagnosis (p 0.0003). 259 pts had follow-up visits at least 3 mos from enrollment, and disease activity measures improved in these pts. Of 234 pts without active systemic features, 91 had active arthritis (median active joints=4). There were no other disease or demographic differences in the subset with persistent arthritis, but there was increased current IL-6i, steroid and NSAID use and past biologic use compared to those without persistent arthritis.

Conclusion: This study describes the largest sJIA cohort reported to date. Significant changes occurred in medication usage over the study period, but corticosteroids are still frequently used. AA pts had more severe disease, as did pts diagnosed at a younger age. A significant proportion has persistent arthritis despite new treatments. Predictors of persistent arthritis are needed to improve treatment and outcomes in this subgroup.

Table 1. Demographic Features (n=435)

Subject age at baseline visit, median (years)	11.0 (6.8–14.6)
Subject age at onset of symptoms, median (years)	4.6 (2.3–9.3)
Ethnicity, No.(%)	
• Non Hispanic or Latino	381 (87.6%)
• Hispanic or Latino	54 (12.4%)
Race, No. (%)	
• White	342 (78.6%)
• Black or African American	45 (10.3%)
• Other	48 (11.0%)
Gender, Male, No. (%)	197 (45.3%)

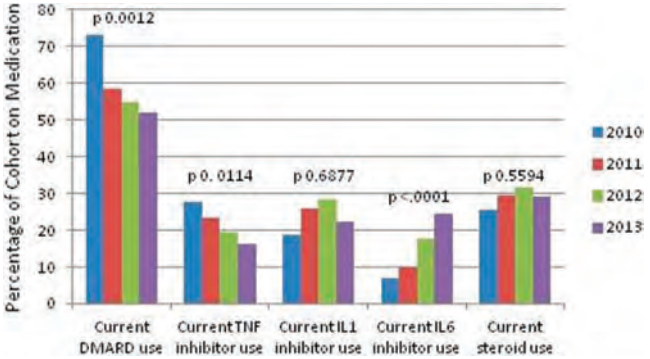

Figure 1: Current Medication Usage by Year of Visit (baseline and follow-up visits)

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Preliminary Results from the Childhood Arthritis and Rheumatology Research Alliance Systemic JIA Consensus Treatment Plans Pilot Study. Yukiko Kimura[1], Esi Morgan-DeWitt[2], Kelly L. Mieszkalski[3], Thomas Brent Graham[4], Timothy Beukelman[5], Maria F. Ibarra[6], Norman T. Ilowite[7], Marisa S. Klein-Gitelman[8], Karen Onel[9], Sampath Prahalad[10], Marilynn G. Punaro[11], Sarah Ringold[12], Dana Toib[13], Heather Van Mater[14], Pamela F. Weiss[15] and Laura Schanberg[16]. [1]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Duke University Medical Center, Durham, NC, [4]Vanderbilt Children's Hospital, Nashville, TN, [5]University of Alabama at Birmingham, Birmingham, AL, [6]Children's Mercy Hospital, Kansas City, MO, [7]Albert Einstein College of Medicine, Bronx, NY, [8]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [9]University of Chicago, Chicago, IL, [10]Emory University School of Medicine, Atlanta, GA, [11]University of Texas Southwestern Medical Center, Dallas, TX, [12]Seattle Children's Hospital, Seattle, WA, [13]St. Christopher's Hospital for Children, Philadelphia, PA, [14]Duke University Medical Center, Hillsborough, NC, [15]The Children's Hospital of Philadelphia, Philadelphia, PA, [16]Duke University, Durham, NC.

Background/Purpose: Treatment options for systemic JIA (sJIA) have recently expanded to include IL1 and IL6 inhibitors in addition to traditional treatments such as glucocorticoids (GC) and methotrexate (MTX). The Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed standardized consensus treatment plans (CTPs) for new onset sJIA to study comparative effectiveness of these treatments using an observational registry. A pilot study was conducted to assess the feasibility of using the CTPs for this purpose.

Methods: New onset untreated sJIA patients (pts) enrolled in the CARRA Registry are treated according to the CTP selected by the treating physician (GC alone; MTX ± GC; IL1 inhibitor (IL1i) ± GC; IL6 inhibitor (IL6i) ± GC). Data is collected at standard intervals for 9 mos from baseline. Physicians could deviate from the chosen CTP for inadequate response at any time. If GC is started, the CTPs suggest an aggressive taper (<50% of the starting dose by 3 mos). Biospecimens are being collected from consenting pts for future use.

Results: 13 of 15 CARRA study sites enrolled at least 1 pt (total 30, range 1–6 pts/site) (Table 1). As of 6/2014, 8 (27%) of 30 pts had reported completing the study. The GC-only CTP was used in only 2 pts (7%) and a biologic was used as initial therapy in 22 (73%). The chosen CTP varied by site, especially with regard to use of biologics vs non-biologics (Table 2). Most common reasons cited for choosing non-biologic CTPs were: usual treatment at site (63%), perceived safer treatment (63%), and pt preference (38%); most common reasons for choosing biologic CTPs: will likely work best (77%), better tolerated (59%), and perceived safer (45%). As of 6/2014, 13 pts (43%) had changed or deviated from the starting CTP. 67% of patients did not consent for specimen collection.

Conclusion: The CARRA sJIA CTP pilot study successfully reached its target enrollment. The study is ongoing for most patients. Despite the absence of randomization, CTP choice is reasonably balanced aside from the GC CTP and appears to be based on physician/center preference. Most providers found the CTPs acceptable to use, and enrollment of additional patients at more CARRA sites to study comparative effectiveness of the CTPs appears feasible. Exploring barriers and improving processes for biospecimen collection consent may increase participation in future studies.

Table 1: sJIA Patients Enrolled in CTP Pilot Study

	Number	SD or percent
Study participants	30	
Mean age (range) years	7.0 (1–16.8)	4.5
Gender		
Female	25	83.3%
Race		
White	17	56.7%
Black or African-American	7	23.3%

Other	6	20.0%
Ethnicity		
Hispanic	9	30.0%
CTP chosen		
GC only	2	6.7%
MTX ± GC	6	20.0%
IL1i ± GC	12	40.0%
IL6i ± GC	10	33.3%
Consented for biospecimen collection	10	33.3%

Table 2: Selection of CTP by Site

SITE	CTP chosen (number of patients)
1	GC (1)
2	IL6i (5)
3	IL1i (1)
4	MTX (2)
5	IL1i (3)
	IL6i (3)
6	IL1i (1)
7	GC (1)
	MTX (2)
8	MTX (1)
	IL1i (1)
	IL6i (1)
9	IL1i (1)
10	MTX (1)
11	IL1i (1)
12	IL1i (1)
	IL6i (1)
13	IL1i (3)

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The Presentation and Initial Treatment of Systemic Juvenile Idiopathic Arthritis According to Observational Data from the United States and the United Kingdom. Timothy Beukelman[1], Roberto Carrasco[2], Yukiko Kimura[3], Laura Schanberg[4], Wendy Thomson[5], Kimme L. Hyrich[6], For the CARRA Registry Investigators[7] and For the CAPS Investigators Group[8]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]The University of Manchester, Manchester, United Kingdom, [3]Hackensack Univ Medical Ctr, Hackensack, NJ, [4]Duke University, Durham, NC, [5]Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom, [6]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, [7]CARRA, Durham, NC, [8]CAPS, Manchester, United Kingdom.

Background/Purpose: Systemic JIA (sJIA) treatment has changed dramatically with the introduction of biologic agents, although treatment approaches may differ between countries. We characterized and compared presenting features and initial treatment of sJIA at pediatric rheumatology (PR) centers in the United States (US) and United Kingdom (UK).

Methods: The US data source was the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, an observational registry established in 2010 that collects clinical data on children with incident or prevalent rheumatic disease from >55 clinical sites throughout the US. Children with sJIA who were enrolled in the Registry within 9 weeks of their first encounter with PR were included in the analysis of presenting features and children with clinical data available from 9 to 15 months following their first encounter with PR were included in the analysis of initial treatment. The UK data source was the Childhood Arthritis Prospective Study (CAPS), an observational study established in 2001 that collects clinical data at regular intervals from a cohort of children with newly diagnosed JIA from 7 UK PR centers. All children with sJIA were included in the analysis of presenting features and children with clinical data available from the 12 month visit were included in the analysis of initial treatment. We also evaluated a subset of CAPS children enrolled since 2009 to match the CARRA enrollment period. Presenting features and initial treatments were compared using chi-square, Fisher's exact, and Wilcoxon ranksum tests.

Results: Presenting features are shown in Table 1 and medication use in the first 12 months is shown in Table 2. Disease manifestations were similar between the US and UK except hepatosplenomegaly was more frequent in the US ($p=0.01$). Elapsed time from first symptom to evaluation by PR was similar but slightly shorter in the US ($p=0.01$), and overall most children were evaluated within 2 months. Differences in enrollment procedures precluded valid comparisons of disease activity measures. US patients were more likely to receive biologic agents (specifically anakinra) and systemic glucocorticoids in the first 12 months of disease compared to UK patients.

Conclusion: Presenting features of children with sJIA were generally similar in the two countries. Compared to the UK, initial treatment of sJIA in the US more frequently included anakinra and, to a lesser extent, systemic glucocorticoids, which may represent differences in medication coverage.

Table 1. Presenting Features.

Characteristic	CARRA Registry (US) (N = 64)	CAPS (UK) (N = 90)	CAPS (UK) enrolled since 2009 (N = 21)
Age at first encounter with pediatric rheumatologist (years) (median, IQR)	5.8 (3.2-10.7)	6.7 (3.5-10.6)	7.8 (3.6-10.6)
Female (n, %)	43 (67%)	58 (64%)	12 (57%)
Caucasian race (n, %)	53 (83%)	76 (88%)	17 (90%)
Elapsed time from symptom onset to first encounter with pediatric rheumatologist (months) (median, IQR)	1.0 (0.5-2.4)	1.5 (0.75-3.5)	1.8 (1.2-3.5)
Active joint count (median, IQR)	3 (1-7)	3 (1-6)	5 (2-8)
Physician global assessment (median, IQR)	4 (2-6)	5.6 (3.6-7.2)	6.1 (5.2-6.9)
Parent global assessment (median, IQR)	5 (2-7)	3.4 (0.7-6.2)	5.5 (3.4-8.5)
Pain score	5 (2-7)	4.8 (1.1-7.1)	7.2 (3.8-8.0)
CHAQ score	0.6875 (0.25-1.75)	1.25 (0.375-2.06)	1.43 (0.625-2.125)
Evanescent rash (n, %)	52 (81%)	75 (83%)	16 (76%)
Lymphadenopathy (n, %)	20 (31%)	26 (29%)	7 (33%)
Hepatosplenomegaly (n, %)	15 (23%)	8 (9%)	3 (14%)
Serositis (n, %)	6 (9%)	3 (3%)	0 (0%)

Table 2. Initial Medication Use in the First 12 Months of Disease

Medication	CARRA Registry (US) (N=75)	CAPS (UK) (N=74)	CAPS (UK) enrolled since 2009 (N=21)	P value for comparison between CAPS enrolled since 2009 and CARRA
Systemic Glucocorticoid	60 (80%)	62 (84%)	12 (57%)	0.03
Methotrexate	46 (61%)	65 (88%)	16 (76%)	ns
Cyclosporine	6 (8%)	7 (10%)	1 (5%)	ns
Any Biologic	46 (61%)	16 (22%)	6 (29%)	0.008
Any IL-1 Inhibitor	33 (44%)	3 (4%)	1 (5%)	0.0006
Anakinra	28 (37%)	3 (4%)	1 (5%)	0.003
Canakinumab	1 (1%)	0 (0%)	0 (0%)	ns
Rilonacept	4 (5%)	0 (0%)	0 (0%)	ns
Tocilizumab	9 (12%)	6 (8%)	5 (24%)	ns
Any TNF Inhibitor	12 (16%)	11 (15%)	1 (5%)	ns

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A Pharmacometric Based Analysis of the Occurrence of Selected Safety Events of Special Interest and Canakinumab Exposure in Systemic Juvenile Idiopathic Arthritis Patients. Micha Levi[1], Thomas Dumortier[2], Nicolino Ruperto[3], Hermine H. Brunner[4] and Olivier Luttringer[2]. [1]Novartis Pharmaceutical Corporation, East Hanover, NJ, [2]Novartis Pharma AG, Basel, Switzerland, [3]Istituto Giannina Gaslini, Genoa, Italy, [4]PRCSG-Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

Background/Purpose: Canakinumab (CAN), a human, selective anti-interleukin-1β monoclonal antibody, has demonstrated rapid and sustained efficacy in systemic juvenile idiopathic arthritis (SJIA) patients,[1]and is approved in >30 countries including USA, EU, Canada, UK and Russia. Given the nature of the disease (pediatric

population, rare condition), the phase III program only included limited placebo data. In such a context, the safety profile of CAN has been characterized via a model-based analysis of the dose-exposure-safety event relationship. The purpose of the study is to explore the relationship between CAN concentration and the occurrence of adverse events of special interest (ESI) and related laboratory abnormalities.

Methods: The analysis considered the open-label, part I of phase III trial wherein SJIA patients received CAN 4mg/kg (300 mg max.) every 4 weeks for a maximum of 8 consecutive doses (n=188). Individual CAN concentration time-profiles have been predicted for those patients, by combining the patients' CAN and IL-1β concentration-time data and an established population PK model. This model is a PK-binding model parameterized in terms of clearance of drug and ligand (IL-1β), central and peripheral volume for the drug, interstitial flow rate, ligand production rate and binding affinity which has been developed using all the data available from the entire CAN program. The average serum CAN concentration (Cavg) was calculated from the concentration time profiles for each patient and dosing interval. In each dosing interval, Cavg were compared between patients with and without the following safety events of special interest: AEs of abdominal pain, cough, headache, infection, serious AE infection, pyrexia, and vomiting, as well as lab abnormalities of thrombocytopenia (>3XULN [upper limit normal]), leucopenia (≤0.8 XLLN [lower limit normal]), >20g/L decrease from baseline hemoglobin, neutropenia (<0.9 X LLN), transaminases elevation (>3XLLN), elevated total cholesterol (≥1.5XULN), triglycerides (≥5.7 mmol/L), and >25% decrease from baseline estimated glomerular filtration rate for 2 consecutive visits.

Results: For all adverse ESIs and related laboratory abnormalities, except neutropenia, Cavg was not different for patients who experienced an event compared with those who did not. The mean Cavg for patients with neutropenia was comparable to the 74thpercentile of those patients without neutropenia, however this higher Cavg was not found to be associated with more infection.

Conclusion: A pharmacometric based analysis in SJIA patients treated with a therapeutic dose of CAN, did not find, in the range of CAN exposure observed, any relationship between average CAN exposure and the occurrence of any safety ESI, except for neutropenia. This increased Cavg in patients with neutropenia was not associated with increased infections. These data support the effective and safe use of CAN4mg/kg every 4 week for the treatment of SJIA in patients >2 years old.

[1]Ruperto N. et al. N Engl J Med 2012; 367 (25):2396–406

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Tocilizumab Therapy in Children with Systemic Juvenile Idiopathic Arthritis. DATA from Russian Register of Sjia. Ekaterina Alexeeva[1], Saniya Valieva[1], Rina Denisova[1], Tatyana Bzarova[1], Kseniya Isayeva[1], Tatyana Sleptsova[1], Elena Mitenko[1], Evgeniya Chistyakova[2], Anna Fetisova[1] and Olga Lomakina[1]. [1]Scientific Center of Children's Health of RAMS, Moscow, Russia, [2]I.M.Sechenov First Moscow State Medical University, Moscow, Russia.

Background/Purpose: Systemic Juvenile Idiopathic Arthritis (sJIA) is classified as an acquired autoinflammatory disease. The interleukin-1 and interleukin-6 play a pivotal role in pathogenesis of this disease. The systemic manifestations as well as arthritis in sJIA are related to interleukin-6 action. Tocilizumab is effective drug for the treatment of systemic arthritis refractory to immunosuppressive drugs.

Objectives: To evaluate safety and efficacy of tocilizumab treatment in children with systemic juvenile idiopathic arthritis.

Methods: 829 patients with sJIA were included in the register. 212 received tocilizumab. Analysis of efficacy and safety tocilizumab therapy was performed in 75 patients, whom follow up period was 2 years. Median age was 7,5 years (range; 0,9 to 15 years) and median disease duration was 2,5 years (range; 0.3 to 12 years). Tocilizumab was administrated intravenously at a dose of 8–12 mg/kg every 2 weeks during 2 months then every 4 weeks. All patients received DMARDs, 38 patients received prednisolone at dose 9.5 (6.5; 12) mg/day. Efficacy end points included the American College of Rheumatology (ACR) Pediatric criteria for improvement 30 (ACR30), ACR50, ACR70, ACR90 and criteria of inactive disease and remission. During the follow-up period, significant side-effects were sought and the reduction in oral prednisolone was recorded too.

Results: The ACR Pedi 30, 50, 70 and 90 improvement were achieved by 100%, 75%, 58% and 30% of patients at Week 12 (n=73), by 100%, 90%, 80% and 55% of patients at Week 24 (n=72) and by 100%, 100%, 95% and 70% of patients at Week 52 (n=60), by 100%, 98%, 98% and 85% of patients at Week 104 (n=52), respectively. Inactive disease was achieved by 18/75 of patients at week 12, by 36/75 of patients at week 24, by 42/75 of patients at week 52, by 44/75 of patients at week 104. Remission was achieved by 44/75 of patients at Week 104. The mean dose of oral glucocorticoid was decreased from 0,5 (0,4; 0,7) to 0,1 (0,04; 0,2) mg/kg/day at week 52 ($p<0.001$), was dicontinued in 5 patients by Week 104. The frequently observed non-severe adverse events were nasopharyngitis, upper respiratory tract infections and gastroenteritis. No cases of opportunistic infections, malignancies or death were reported. There were three cases of pneumonia and cellulitis. 30 patients had incidences of neutropenia, 2 – trombocytopenia, 15 – high level of ALT and AST. Tocilizumab treatment was discontinued in 23 patients during the follow-up 52 weeks period. The causes for cancellation were relapse of disease (n=9), lack of efficacy (n=8), self-cancellation by parents because of remission (n=2), parent's refusal (n=1), infusion reaction (n=2) and Crohn's disease (n=1). 7 patients were switched to canakinumab, 3- to rituximab and 4 – to antiTNF blockers. Survival of tocilizumab treatment was 96% at Week 24, 81% - at Week 52, 69% - at Week 104.

Conclusion: Tocilizumab induced remission of extra-articular manifestations, arthritis and normalized laboratory parameters of the disease activity without initiation of treatment with oral prednisolone and increase its dose, thus avoiding severe irreversible complications of glucocorticoid therapy.

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Efficacy of Canakinumab in Patients with Systemic Juvenile Idiopathic Arthritis (SJIA) using JADAS Criteria - an Analysis of 12-Week Pooled Data. A. Ravelli[1], H. I. Brunner[2], N. Ruperto[1], P. Quartier[3], A. Consolaro[1], N.M. Wulffraat[4], K. Lheritier[5], C. Gaillez[5], A. Martini[1] and D.J. Lovell[2]. [1]PRINTO-Istituto Gaslini, Genova, Italy, [2]PRCSG, Cincinnati, OH, [3]Necker-Enfants Malades Hospital, Paris, France, [4]UMC Utrecht, Utrecht, Netherlands, [5]Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: Chronic active disease and persistent synovial inflammation can lead to structural damage, joint destruction and impairment of physical function in patients with systemic juvenile idiopathic arthritis (SJIA). The JADAS score[1, 2] 27-CRP (J27), 10-CRP (J10), and cut-off values for inactive (ID), low (LDA), moderate (MDA) and high disease activity (HDA) were designed to monitor the level of disease activity in all JIA subtypes[1]. The efficacy of canakinumab (CAN), a selective, human, anti-IL-1β monoclonal antibody, was previously demonstrated in SJIA in phase III trials using aACR-JIA response criteria. The level of disease activity in CAN-treated SJIA patients, using J10 and J27 in a 12-week pooled (phase III studies) data set is presented.

Methods: Patients (2–19 years of age) with active SJIA were enrolled and received sc CAN 4 mg/kg. This post-hoc analysis focused on a 12-week pooled dataset (from three phase III studies) in a total of 178 CAN-naïve patients, assessing the J10 and J27 scores at Days (D) 15, 29, 57, 85, and applies the appropriate cut-off values for ID, LDA, MDA, and HDA.

Results: The median [Q1, Q3] J10 for completer patients (i.e. patients who complete 12 weeks treatment) was 29.1 [23.1, 33.2] at baseline. The median change [Q1, Q3] from baseline at D15 and D85 was −19.4 [−25.7, −13.4] and −21.2 [−27.7, −16.7], respectively. Results for J27 were very similar. The disease status at all-time points for J10 and J27 is reported in Table 1. Median change from baseline at each time point was consistent between the completers and the full analysis dataset for J10 and J27 (data not shown).

Table 1. J10 and J27-related disease criteria applied to the full analysis dataset (%)

%	Disease state*	Baseline N=178	D15 N=172	D29 N=157	D57 N=131	D85 N=125
J10	ID	0.0	18.0	26.8	34.4	33.6
	LDA	0.0	14.0	11.5	16.8	24.8
	MDA	0.6	19.2	19.7	20.6	16.8
	HDA	99.4	48.8	42.0	28.2	24.8

J27	ID	0.0	18.0	26.8	34.4	33.6
	LDA	0.0	14.0	11.5	16.8	25.6
	MDA	0.6	15.1	16.6	17.6	12.8
	HDA	99.4	52.9	45.2	31.3	28.0

*Cut-off values for ID, LDA, MDA, and HDA, respectively for J10: ≤1, >1–≤3.8, >3.8–≤10.5, >10.5; and for J27: ≤1, >1–≤3.8, >3.8–≤8.5, >8.5

Conclusion: There was a dramatic reduction in disease activity from baseline to D85, with much of the reduction taking place by D15 onwards in both completers and in the full analysis dataset. An increasing proportion of CAN patients achieved ID or LDA - according to J10 and J27 — in the first 12 weeks of treatment, despite corticosteroid tapering, consistent with the previous ID definition from the phase III trials. These data confirm the early onset of effect as well as the short-term and sustained efficacy over 12 weeks of CAN, and suggest that JADAS may represent a useful tool to monitor treatment response.

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Canakinumab Treatment Shows Maintained Efficacy in Systemic Juvenile Idiopathic Arthritis (SJIA) Patients at Individual Patient Level: An Analysis of 12 Week Pooled Data. A. Ravelli[1], H.I. Brunner[2], N. Ruperto[1], P. Quartier[3], A. Consolaro[1], N.M. Wulffraat[4], K. Lheritier[5], C. Gaillez[5], A. Martini[1] and D.J. Lovell[2]. [1]Istituto Gaslini-PRINTO, Genova, Italy, [2]PRCSG, Cincinnati, OH, [3]Necker-Enfant Malades Hospital, Paris, France, [4]UMC Utrecht, Utrecht, Netherlands, [5]Novartis Pharma AG, Basel, Switzerland.

Background/Purpose: Key objectives of biologic therapies in systemic juvenile idiopathic arthritis (SJIA) are to induce and maintain inactive disease, according to the ACR 2011 definition. Recent advances in the management of SJIA consider the induction or maintenance of inactive disease according to the JADAS 10-CRP (J10) or 27-CRP (J27) scoring system[1, 2]. The efficacy of canakinumab (CAN), a selective, human, anti-IL-1β monoclonal antibody, was demonstrated in the withdrawal phase of 2 phase III trials[3], but was not evaluated at the individual level. Here, we assessed the maintenance of efficacy at individual level from Week 2 to 12, using the adapted ACRJIA response criteria (aACR) as well as J10 and J27 on the 12-week pooled data set (3 phase III studies).

Methods: For this post-hoc analysis of the CAN Phase III program in SJIA, the change in disease states between Day (D) 15 and D85 for a total of 178 CAN-naïve patients was assessed. Subjects were 2–19 years of age and had active SJIA at enrollment. This shift analysis considered the aACR response and disease activity states related to J10 and J27: Inactive Disease (ID), Low Disease Activity (LDA), Moderate Disease Activity (MDA); High Disease Activity (HDA).

Results: J10 changes during the study period are provided in Table 1. Results for the J27 were very similar to the J10 observations. The D15-D85 aACR shift analyses, including only patients who had a D15 and a D85 value, likewise indicated that the majority of patients maintained or improved their response: NR (n=32): 12.5% of patients improved; aACR30 (n=14): 0.0% were maintained/78.6% improved; aACR50 (n=21): 33.3% were maintained/42.9% improved; aACR70 (n=36): 25.0% were maintained/58.3% improved; aACR90 (n=26): 30.8% were maintained/57.7% improved; aACR100 (n=34): 82.4% were maintained.

Table 1 J10 shift analysis table from D15 to D85*

N (%)	Disease state at Day 15*	Disease state at Day 85* ID	LDA	MDA	HDA
ID	28 (100)	24 (85.7)	1 (3.6)	3 (10.7)	0 (0.0)
LDA	20 (100)	10 (50.0)	10 (50.0)	0 (0.0)	0 (0.0)
MDA	30 (100)	5 (16.7)	12 (40.0)	10 (33.3)	3 (10.0)
HDA	44 (100)	2 (4.5)	6 (13.6)	8 (18.2)	28 (63.6)

*Only patients with both a Day 15 and a Day 85 value are included.

Conclusion: A majority of SJIA patients treated with CAN either maintained or improved their JADAS status or aACR response level from Week 2 to 12. These data confirm the consistent maintenance of efficacy of CAN at the individual level in the first 3 months, irrespective of the measure of treatment response, that is aACR criteria or JADAS-derived criteria, and extend previous findings at group level.

References:
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2. Nordal et al. Ann Rheum Dis. 2012;71(7).

Disclosure: A. Ravelli, Pfizer Inc, 2, Abbvie, Bristol Myers Squibb, Novartis, Pfizer, Roche and Johnson & Johnson, 8, Abbvie, Bristol Myers Squibb, Novartis, Pfizer, Roche and Johnson & Johnson, 5; **H. I. Brunner**, Roche, Novartis, 8, Novartis, Roche, BMS, Pfizer, Biogen, Boehringer-Ingelheim, Jannsen, Astrazeneca, 5; **N. Ruperto**, Abbott, AstraZeneca, BMS, Centocor Research & Development, Eli Lilly and Company, "Francesco Angelini", Glaxo Smith & Kline, Italfarmaco, Novartis, Pfizer Inc., Roche, Sanofi Aventis, Schwarz Biosciences GmbH, Xoma, Wyeth Pharmaceuticals Inc., 2, AstraZeneca, Bristol Myers and Squibb, Janssen Biologics B.V.,Roche, Wyeth/Pfizer, 8; **P. Quartier**, Abbvie, BMS, Novartis, 2, Abbvie, BMS, Chugai-Roche, Novartis, Pfizer, MEDIMMUNE and SOBI, 5, Novartis, Chugai-Roche, 8; **A. Consolaro**, Novartis., 5; **N. M. Wulffraat**, Novartis, Pfizer, 5, Abb Vie, 2; **K. Lheritier**, Novartis., 3, Novartis., 1; **C. Gaillez**, Novartis., 1, Novartis., 3; **A. Martini**, Abbott, Bristol Myers and Squibb, Francesco Angelini S.P.A., Glaxo Smith Kline, Janssen Biotech Inc, Novartis, Pfizer Inc, Roche, Sanofi Aventis, Schwarz, 2, Abbott, Amgen, Biogenidecm Bristol MyersSquibb, Astellas, Behringer, Italfarmaco, Janssen, MedImmune, Novartis, NovoNordisk, Pfizer, Sanofi, Roche, Servier, 5, Abbott, Amgen, Biogenidecm Bristol MyersSquibb, Astellas, Behringer, Italfarmaco, Janssen, MedImmune, Novartis, NovoNordisk, Pfizer, Sanofi, Roche, Servier, 8; **D. J. Lovell**, National Institutes of Health- NIAMS, 2, Astra-Zeneca, Centocor, Amgen, Bristol Meyers Squibb, Abbott, Pfizer, Regeneron, Roche, Novartis, UBC, Forest Research Institute, Horizon, Johnson & Johnson, 5, Novartis, Roche, 8.

2299

M-Ficolin and Masp-2 As Inflammatory Markers in Oligoarticular and Systemic Juvenile Idiopathic Arthritis. Christine Petri[1], Steffen Thiel[2], Jens Christian Jensenius[2] and Troels Herlin[1]. [1]Aarhus University Hospital, Aarhus, Denmark, [2]Aarhus University, Aarhus, Denmark.

Background/Purpose: The lectin pathway of the complement plays a crucial role in the pathogenesis of various inflammatory processes. The lectin pathway proteins are activated through the recognition of pathogens by the pattern recognition molecules (PRMs), which include the mannan-binding lectin (MBL), and H- and M-ficolin in collaboration with MBL-associated serine proteases (MASPs). PRMs reportedly play a role in rheumatoid arthritis (RA) indicating a correlation between the concentration of these proteins and RA disease activity. The aim was to evaluate the possible pathogenic role of the PRMs in Juvenile Idiopathic Arthritis (JIA).

Methods: We measured MBL, M-ficolin, H-ficolin, MASP-1, -2, -3, and the two alternative splice products, MAp44 and MAp19, in plasma and synovial fluid (SF) of 109 children with persistent oligoarticular JIA and 19 children with systemic JIA. The concentrations of the eight proteins were measured by in-house time-resolved immunoflurometric assays (TRIFMA) using monoclonal antibodies.

Results: We observed significantly higher levels of M-ficolin and MBL-associated serine proteases in plasma from patients with systemic JIA compared to persistent oligoarticular JIA ($p<0.001$). Notably higher levels of M-ficolin and MASP-2 were also found in synovial fluid from patients with systemic JIA (n=11) compared to SF from patients with oligoarticular JIA (n=36). Plasma/SF ratio of the lectin pathway proteins were calculated in paired samples for oligoarticular JIA (n=36) and systemic onset JIA (n=11). We observed significantly high plasma/SF for both subtypes for M- and H-ficolin, MASP-1 and

-2, MAp44 and MAp19, but the MASP-3 levels was significantly higher in SF than in plasma for both subtypes. M-ficolin and MASP-2 was significantly related to erythrocyte sedimentation rate (ESR), C-reactive protein, white blood cell count, platelet count ($p<0.001$). In addition M-ficolin was significantly related to the number of active joints ($p=0.008$) and conversely related to hemoglobin levels ($p=0.017$).

Conclusion: Our results suggest plasma M-ficolin and MASP-2 as inflammatory markers in juvenile idiopathic arthritis. The level of the proteins is higher in plasma than in SF, except for MASP-3, indicating that MASP-3 may be secreted into or produced locally in the joint.

Disclosure: C. Petri, None; **S. Thiel**, None; **J. C. Jensenius**, None; **T. Herlin**, None.

2300

Biologic Treatment in Systemic Juvenile Idiopathic Arthritis: Single Center Experience. Buthaina Al adba[1], Rayfel Schneider[2] and Earl Silverman[3]. [1]sickkids hospital, Toronto, ON, [2]The Hospital for Sick Children, Toronto, ON, [3]Hosp for Sick Children, Toronto, ON.

Background/Purpose: The prevalence of juvenile idiopathic arthritis (JIA) is approximately 3.3/1000 children and 10– 15% have the systemic form (SJIA). Biologics, specifically anti-IL -1 and anti-IL-6 agents have been introduced to decrease the need for corticosteroids and therefore ameliorate the associated morbidity including growth failure, cataracts, fractures and body image problems.

Methods:

Study design:

Retrospective chart review of 306 patients diagnosed with SJIA at Hospital of sick children from January 1980 to December 2012. Exclusion criteria: Diagnosis not confirmed, <1 year follow-up, <1 visit per year and unable to obtain complete medical record.

Data analysis:

1) Number of patients treated with biologics.

2) Response of: i) Systemic features (fever or rash) and ii) Arthritis.

3) Definition of response for systemic features i) Complete response: no symptoms off steroids. ii) Partial response: no symptoms but on steroids.

4) Definition of response for arthritis: i) Complete response: no active arthritis ii) Partial response: >50% improvement in active joint count.

Results: The cohort consisted of 306 SJIA patients which 58 of them (18%) have received biologic. 28/58 (48%) Since 2009. The main biologic used are anti-IL-1, anti-IL-6 and anti TNF. 41/58 needs one biologic, 10/58 two biologic and 7/58 three or more. Some patients used same biologic more than once. Anti IL-1 was used 47 times in the 58 patients (81%), anti IL-6 used 14 times (24%) and anti TNF used 38 times (65%). The complete response of systemic features was about 70% in both anti IL-1 and anti IL-6 group, however it was 20% in anti TNF group. The complete response of arthritis was 64%, 48% and 31% in anti IL-6, anti IL-1 and anti TNF respectively.

SUMMARY: 1) 58/306 received biologic during the study- 28/58 (48%) since 2009. 2)The main biologics used were: anti-IL-1, anti-IL-6 and anti-TNF agents.3) A complete response of systemic features was found in about 70% for both anti-IL-1 and anti- IL-6 groups but only 20% in the anti-TNF group. 4)A complete response of arthritis was seen in 64%, 48% and 31% in the anti-IL-6, anti-IL-1 and anti-TNF groups respectively.

Conclusion: 1) Since 2009 there was a significant increase in the use of biologic therapies in SJIA. 2) Systemic features responded well to anti- IL-1 and anti- IL-6 but not anti-TNF treatment.3) Arthritis improved by >66% with anti-IL-1 and anti-IL-6 in all patients but not with anti-TNF treatment.4) Further studies with large number of patients are needed to evaluate anti-IL-1 and anti-IL-6. 5) With anti-IL-1 and anti-IL-6 agents, a substantial proportion of patients were able to discontinue steroid.

Disclosure: B. Al adba, None; **R. Schneider**, None; **E. Silverman**, None.

2301

The New Proposal Classification Criteria for Juvenile Spondyloarthropaties. Ozgur Kasapcopur[1], Metin Sezen[1], Kenan Barut[1] and Cengizhan Acikel[2]. [1]Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey, [2]Gulhane Military Medical Academy, Ankara, Turkey.

Background/Purpose: Juvenile spondyloarthropathies (JSpA) are a group of rheumatologic diseases with a disease onset before 16 years of age and are characterized with enthesitis, lower extremity oligoarthritis, involvement of the axial skeleton and HLA B27 positivity. The main problem in the classification of this group of diseases is the difficulty of diagnosis at disease onset and the difficulty to differentiate them from juvenile idiopathic arthritis. The aim of our study was to evaluate the pre-determined classification criteria for children with JSpA and to develop new classification criteria.

Methods: The study group consisted of 113 patients with the diagnosis of JSpA and 150 patients with juvenile idiopathic arthritis (JIA). Enthesitis related arthritis (ERA) and juvenile psoriatic arthritis (JPsA) were included into the JSpA group. Eligible criterion of atypical spondyloarthropathy criteria which can also be used for children, SEA syndrome, ERA, Garmisch- Partenkirchen, ESSG, Amor, ASAS peripheral SpA, ASAS axial SpA criteria were applied to all of the enrolled patients. Odds ratios were determined for the variables of these criteria and for clinical findings in the classification of JSpA and JIA cases. Variables of the major findings of JSpA disease were determined by using probability analysis and clinical characteristics, Specificity, sensitivity and kappa values were determined for the new set diagnostic criteria proposed by us and for the pre-determined criteria in order to evaluate which diagnostic criteria were superior for the diagnosis of JSpA.

Results: Major clinical variables of JSpA group of diseases by using pre-existing criteria are; oligoarthritis, enthesopathies, onset of disease after 6 or 10 years of age, inflammatory lumbar pain, hip arthritis, tarsometatarsal joint arthritis, male sex, rapid response to nonsteroidal antiinflammatory drugs, sacroiliitis (MRI or radiography confirmed), HLA B27 positivity, limitation in lumber mobility test (below 4 cm), family history of SpA group of disease, dactylitis, psoriasis or presence of inflammatory bowel disease. All the variables had a kappa value over 0,8. The usefullness of all of the pre-determined criteria in children was low. The variables of the new set criteria that were determined in our study were summarized below:

Major criterion: Oligoarthritis, enhesopathy, disease onset after 6 years of age, inflammatory lumbar pain.

Minor criterion: Hip arthritis, tarsometatarsal arthrtitis, male sex**,** NSAID response**,** sacroiliitis (in MR or radiography), HLA B27 positivity, limitation in schober test **(,** psoriasis or presence of IBD.

Diagnosis: 2 major+3 minor or 3 major variables. The sensitivity, specificity and kappa value of this criteria were found as 90.3%, 90.7% and 0.807, respectively.

Conclusion: We found that the pre-determined criteria were inadequate for the classification and diagnosis of juvenile spondyloarthropathies. We suggest that new set criteria proposed by us could be used in the diagnosis and classification of JSpA. However, neither the pre-determined criteria nor the new set criteria are adequate and efficacious for the classification and diagnosis of this disease.

Disclosure: O. Kasapcopur, Novartis Pharmaceutical Corporation, 5; **M. Sezen**, None; **K. Barut**, None; **C. Acikel**, None.

2302

Classification of Juvenile Spondyloarthropathies According to ASAS Criteria. Marìa M. Katsicas[1] and Ricardo A. G. Russo[2]. [1]Hospital de Pediatrìa Garrahan, Buenos Aires, Argentina, [2]Hospital de Pediatria Garrahan, Buenos Aires, Argentina.

Background/Purpose: The juvenile spondyloarthropathies (JSpA) are a group of related seronegative rheumatic diseases characterized by involvement of the axial, peripheral large joints and entheses. Sets of classification have been developed in adult patients with SpA. The ASAS classification criteria for axial and peripheral SpA have not been validated in pediatric populations.

Objectives: To assess the sensibility[sen] and specificity[sp] of the ASAS criteria for patients with JSpA. To compare the performance of the ASAS criteria with that of ESSG classification criteria. To identify associations between criteria fulfillment and disease features.

Methods: Consecutive patients with JSpA (defined as ERA, JPsA or UA according to ILAR) followed in our center with complete records were included. Clinical charts and databases were retrospectively reviewed. Randomly selected patients with oligoarthritis, systemic arthritis and polyarthritis RF negative served as controls. Demographic and clinical characteristics, disease duration at first visit and follow up time were recorded. Items corresponding to the ASAS, ESSG, AMOR, seronegative enthesopathy and arthropathy (SEA) syndrome and Modified New York (NY) criteria for SpA and Ankylosing Spondylitis were obtained from first visit and during disease course. Descriptive, summary statistics ([sen], [sp], positive predictive value [PPV],

negative predictive value [NPV]) and Wilcoxon Rank Sum test were used.

Results: 109 patients with JSpA (104 ERA, 2 JPsA, 3UA) were included (M:93), age at onset: 10 (1–15) years, disease duration at first visit 10 (1–15) months, follow-up time 4(1–12)years. Controls: 69 patients with JIA (25 oligoarthritis, 24 polyarthritis RF negative, 20 systemic)**.** At first visit cases showed: 106 (97%) arthritis, 89 (82%) asymetrical oligoarthritis, 69 (63%) elevated CRP, 53 (49%) limitation of lumbar spine motion, 53 (49%) HLA-B27, 46 (42%) enthesitis, 44 (40%) tarsitis, 40 (37%) low back pain (LBP), 32 (29%) good response to NSAIDS, 27 (25%) positive family history, 21 (19%) radiographic bilateral sacroiliitis grade 2–4, 14 (13%) dactylitis, 8 (7%) uveitis, 7 (6%) unilateral sacroiliitis grade 3–4, 7 (6%) diarrhea, 5 (4%) infectious previous disease, 2 (2%) urethritis, 2 (2%) inflammatory bowel disease, 2 (2%) buttock pain, 1 (1%) psoriasis. At first visit (109 patients): 81(74%) patients fulfilled ASAS criteria, 81 (74%) peripheral (p)ASAS, 80 (73%) ESSG criteria, 71 (65%) Amor, 33 (30%) SEA, 26 (24%) NY(23 definite, 3 probable), 26 (24%) axial ASAS. Disease course (102 patients): 100 (98%) fulfilled ESSG criteria, 97 (95%) ASAS, 97 (95%) pASAS, 94 (92%) Amor,75 (74%) NY (63, 12), 42 (41%) SEA, 41 (40%) axial ASAS. ASAS sen 74%, sp 97%, PPV 97%, NPV 71%. ESSG sen 73% sp 94% PPV 95%, NPV 69 %. When tarsisis was added to the ASAS and ESSG criteria, sen increased to 82 and 84% respectively. Fulfillment of pASAS was associated with HLA-B27 (p=0,0022). Axial ASAS with LBP (p=0,00001), sacroiliitis (p=0,0007),HLA-B27 (p=0,0012).

Conclusion: In our cohort ASAS criteria performed as well as ESSG for classification of JSpA. The addition of tarsitis as a clinical criterion would improve the performance of these criteria sets.

Disclosure: M. M. Katsicas, None; **R. A. G. Russo**, None.

2303

Clinical Observation on Ankylosing Spondylitis Patients with Different Phenotypes. Zhiming Lin[1], Jun Qi[2], Jieruo Gu[1] and Pingping Zhang[3]. [1]The Affiliated Third Hospital of Sun Yat-san University, Rheumatology, Guangzhou, China, [2]The Third Affiliated Hospital of Sun Yat-sen University, guangzhou, China, [3]Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

Background/Purpose: Juvenile and adult forms of ankylosing spondylitis (AS) have been shown different in initial symptoms, clinical presentation, imaging manifestations and prognosis. So, according to the diagnostic criteria of adult ankylosing spondylitis (AAS),it is difficult to diagnose early and treat timely for the Juvenile ankylosing spondylitis(JAS).Meanwhile, the JAS mostly will progress to adulthood, the delayed diagnosis and treatment may seriously affect the prognosis and the quality of life in adulthood, We did this retrospective analysis to compare the similarities and differences between the two phenotypes of AS in southern Chinese Han patients, so as to provide foundation for the early diagnosis and treatment for JAS.

Methods: Case records of 576 patients diagnosed as AS according to modified New York criteria(1984) were reviewed. All the patients satisfied the ACR classification criteria for AS.They were grouped according to age: those with onset of symptoms before the age of 16 years were classified as JAS, and patients older than 16 at onset were classified as AAS. Data on age at disease onset, initial symptoms, clinical features, uveitis and imaging manifestations were recorded.

Results: There were 165 patients with JAS and 411 with AAS. The former had higher male preponderance(10.8:1 VS 4.3:1, P<0.01) and more frequent onset with peripheral arthritis(P<0.001), while most AAS with initial symptoms of lumbosacral pain. Peripheral joints involved in JAS include lower extremity joints such as the hip, knee, ankle and heel, followed by the upper limb joints, such as the shoulder, elbow and wrist. Positive family history was present in 28 JAS patients (16.97%) and 84 (28.44%) in JAS(p0.05).JAS patients also had greater involvement of hip joints than AAS(P<0.001).The incidence of spinal involvement was significantly lower in JAS than that in AAS(P<0.001).Through the x - ray examination, the spinal lesions in JAS were characterized by osteoporosis and blurred articular surface, but in AAS were sclerosis of spine bone, formation of syndesmophyte and bony bridge, bone loss and osteoporosis. The incidence of anterior uveitis was also comparable: 4.91% (8 patients) in JAS and 11.44%(47 patients) in AAS(P<0.05).BMD T-score at the femoral neck was significantly lower in JAS than that in AAS(p<0.05). In addition, the mean time from onset to final diagnosis was much longer in JAS than in AAS (P < 0.01);for those patients with the onset symptoms of Peripheral joints, the mean time from onset to symptoms of axial joints much longer in JAS than in AAS (P < 0.001).

Conclusion: Gender advantage in JAS was more obvious, and JAS had onset more often with peripheral arthritis than with Spinal symptoms. Hip joint involvement was more common in JAS than AAS. The femoral neck BMD was reduced much seriously in JAS compared with that in AAS, while there was lower incidence of ophthalmia in JAS than AAS, clinicians should focus on the different manifestations in JAS and AAS,so as to make early diagnosis, provide aggressive treatment and prevent complications.

Disclosure: Z. Lin, None; **J. Qi**, None; **J. Gu**, None; **P. Zhang**, None.

2304

Positive HLA-B27 in Juvenile Spondyloarthritis Is Associated to Early Sacroiliitis and Progression to Ankylosing Spondylitis. Mariana O Perez[1], Nadia E Aikawa[1], Solange Carrasco[1], Percival D Sampaio-Barros[2], Celio R. Gonçalves[2], Carla G.S. Saad[2], Julio C. B. Moraes[2] and Cláudia Goldeinstein-Schainberg[2]. [1]University of São Paulo, São Paulo, Brazil, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: Juvenile spondyloarthritis (JSpA) manifests with axial and peripheral involvement, enthesitis and HLAB27+ in 60–90% children. Radiological sacroiliitis may occur within 10 years, representing an important prognostic factor. To determine initial and long term clinical profiles of JSpA patients from a single tertiary university center; HLAB27 prevalence and relationship with disease progression to ankylosing spondylitis (AS), according to ASAS criteria.

Methods: Descriptive cross-sectional study of a cohort of JSpA subjects. Demographic, clinical and radiological data were obtained by chart review and HLA-B27 tested by flow cytometry (Becton Dickinson). Fisher and McNemar′s tests were used for statistical analyses and p<0.05 considered significant.

Results: Fifty patients with JSpA were evaluated, mean age=31.5±11.1yrs (15–60), mean age at onset=12.2±2.73yrs (7–16), mean age at diagnosis=19.8±9.0yrs (7–44), mean disease duration=18.9±11.4yrs (3–44). Most were males (44M:6F,88%) and whites (n=42,84%). Eleven (22%) children had a 1st-degree relative with SpA and 87% (34/39) were HLAB27+. At diagnosis (Table), peripheral manifestations prevailed, particularly asymmetric oligoarthritis while axial involvement was mainly inflammatory back and buttocks pain; 21 (42%) had enthesitis, all at the Achilles insertion; major extra-articular manifestation was anterior uveitis. After a mean follow up period of 12.8±9.13yrs (1–45), 5 patients were lost, axial involvement was predominant, none had uveitis and enthesitis remained in 13/21 (Table). Radiological sacroiliitis developed in 96% (n=48) patients: 41.7% (n=20) ≤5yrs, 16.7% (n=8) within 6–10yrs and 41.7% (n=20) >10yrs of initial symptoms. Remarkably, HLA-B27+ children had earlier sacroiliitis ≤5yrs of diagnosis (p=0.02), high ESR at diagnosis (p=0.04) and developed AS (p=0.02). Sacroiliitis progression was not prevented (p0.05) despite daily NSAIDs therapy intake by all patients. Sulfasalazine was used by 86% and MTX by 72%. Currently 49% are receiving anti-TNF drugs.

Table: Clinical manifestations of patients with JSpA

Manifestations	At Diagnosis (n=50), n (%)	Currently (n=45), n (%)	p values
Peripheral	35 (70)	13 (28.8)	0.0001
Asymmetry oligoarhritis	24 (68.5)	8 (61.5)	0.19
Symmetry oligoarthritis	1 (2.8)	1 (7.6)	0.002
Polyarthritis	10 (28.5)	5 (38.4)	0.008
Axial	29 (58)	43 (95.5)	0.001
Pain in buttocks	22 (75.8)	0	0.0001
Inflammatory back pain	25 (86.2)	18 (41.8)	0.001
Extra-articular	14 (28)	1 (2.2)	0.03
Anterior uveitis	12 (85.7)	0	0.01
Gastrointestinal	2 (14.3)	1 (100)	0.009
Oral ulcers	1 (7)	0	0.009
Enthesitis	21 (42)	13 (28.8)	0.26
Calcaneus	21 (100)	11 (84.6)	0.02
Hips	0	1 (7.7)	0.12
Spinous process L5	0	2 (15.3)	0.05

Conclusion: Brazilian JSpA patients are typically white males with initial peripheral joint and enthesitic involvement that progress to axial disease. The high prevalence of HLAB27+ in JSpA associated to early sacroiliitis, elevated ESR at diagnosis and development of AS strengthen its role as a genetic marker of disease severity in children.

Disclosure: M. O. Perez, None; **N. E. Aikawa**, None; **S. Carrasco**, None; **P. D. Sampaio-Barros**, None; **C. R. Gonçalves**, None; **C. G. S. Saad**, None; **J. C. B. Moraes**, None; **C. Goldeinstein-Schainberg**, None.

ACR/ARHP Poster Session C
Quality Measures and Quality of Care
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

2305

Improving Screening for Hyperlipidemia in Patients with Rheumatoid Arthritis at an Academic Rheumatology Practice. Ashwini Komarla and Alexis Ogdie. University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Cardiovascular disease is the leading cause of mortality in the rheumatoid arthritis (RA) population. However, cardiovascular risk factors such as hyperlipidemia are undertreated in patients with RA compared to other high risk groups like diabetics. We examined the effectiveness of two interventions to increase screening for hyperlipidemia among patients with RA within the rheumatology practice of an academic medical center.

Methods: Interventions included a web-based survey regarding attitudes towards lipid screening in patients with RA sent to physicians in the division of rheumatology at the University of Pennsylvania on 1/6/14 and posters and flyers about cardiovascular risk in inflammatory arthritis posted in each clinic's check-in area and exam rooms between 2/1–2/28/14. A query of our electronic health record was used to generate a list of patient visits with an ICD-9 code for RA seen in the practice between 7/1/13 - 4/15/14. Charts were reviewed for a random sample of 100 patient visits for the periods before and after the interventions (7/1 - 1/5/14 and 2/1 – 4/15/14 respectively). Patients were excluded if the rheumatologist had not documented a diagnosis of RA in the encounter note. If multiple visits for the same patient were found in the sample, the last visit in that period was used. The outcome was achieved if lipid screening was documented as performed in the encounter note or if results were recorded in the encounter note or in the laboratory section within 3 years of the visit date. The prevalence of up to date lipid screening in each period was assessed, and the groups were compared using the chi-squared test.

Results: Seventy-eight patients in the pre-intervention group and 82 in the post-intervention group satisfied inclusion criteria. Demographics are listed in the Table. Lipid screening was considered up to date in 39 of the 78 patients (50.0%) in the pre-intervention group and 57 out of the 82 patients (69.5 %) in the post-intervention group ($p=0.01$).

Conclusion: Among patients with RA, the management of traditional cardiovascular risk factors, including lipid screening, is suboptimal. Flyers and posters increased the prevalence of documented lipid screening in the short term. The survey of physician attitudes towards lipid screening likely also increased awareness of practice patterns among rheumatologists. Further quality improvement initiatives are needed to identify long term solutions to improve the recognition and management of traditional cardiovascular risk factors among patients with RA.

Table. Demographics of the Pre and Post Intervention Groups

		Before N= 78	After N=82
Practice	Presbyterian Medical Center	15	24
	Perelman Center	61	51
	Fellows' Clinic	2	7
Age- Median (Range)		60 (27-89)	60 (32-87)
Gender	Female	63 (81%)	74 (90%)
Primary Care Physician Location	Outside of the University of Pennsylvania System	53 (68%)	44 (53%)
Diabetes		12 (15%)	16 (20%)
Disease Activity	Not Recorded	4	7
	Remission	23	23
	Low	18	27
	Moderate	24	20
	High	9	5
Lipid Lowering Drugs Used	Statin	22	23
	Fish oil/Omega-3-acid ethyl esters	12	9
	Flaxseed oil	2	1
	Ezetimibe	1	1
	Fenofibrate	1	1
Service Ordering Lipid Screening	Primary Care	19	35
	Rheumatology	11	17
	Cardiology	6	2
	Endocrine	0	2
	Inpatient Medicine	0	1
	Oncology	1	0
	Renal	1	0
	Not Clear	1	0

Disclosure: A. Komarla, None; **A. Ogdie**, None.

2306

Quality of Care for Cardiovascular Prevention in RA: Compliance with Diabetes Screening Guidelines. Timothy J Schmidt[1], J Antonio Avina-Zubieta[1], Eric C. Sayre[2], Michal Abrahamowicz[3], John M. Esdaile[4] and Diane Lacaille[5]. [1]University of British Columbia, Department of Experimental Medicine, Vancouver, BC, [2]Arthritis Research Centre of Canada, Richmond, BC, [3]McGill University, Montreal, QC, [4]University of British Columbia, Department of Medicine, Division of Rheumatology, Vancouver, BC, [5]Arthritis Research Centre of Canada, Vancouver, BC.

Background/Purpose: Comorbidities are increasingly recognized as significant contributors of decreased quality of life, and increased mortality in RA. RA is associated with an increased risk of diabetes and cardiovascular mortality. Previous research suggests that RA populations receive sub-optimal care for their non-RA health related issues.

Our aim was to evaluate the quality of care for cardiovascular disease prevention in RA by measuring compliance with general population diabetes screening guidelines in RA compared to the general population.

Methods: We conducted a retrospective matched cohort study among patients with RA who received care between Jan 1996 and Mar 2006 and followed-up until Dec 2010. RA cases were selected if they had ≥2 MD visits more than 2 mos apart with an RA code. Cases were excluded if they had ≥2 subsequent MD visits for other inflammatory arthritis; if they saw a rheumatologist and RA diagnosis was never confirmed; or if there were no subsequent RA diagnoses over a follow-up > 5 yrs (N=36,458). Controls were selected from the general population and matched 1:1 to RA cases on gender, age, and calendar year. Administrative data was obtained on all physician visits, hospital admissions, tests ordered and medications.

Outcome: Compliance with current screening guidelines for diabetes defined as testing for plasma glucose (PG) at least once every 3 years for individuals ≥ 45years, excluding individuals with previous diabetes. Individuals' follow-up was divided into 3-year eligibility windows, when they were eligible for the screening guideline. Each individual could contribute up to four three-year eligibility windows. Compliance was measured as the proportion of eligibility windows with at least one PG test performed within the time period. Compliance rates between RA and controls, using eligibility windows as the unit of analysis, were compared via a GEE model to account for the lack of independence of observations obtained from the same patient, adjusting for age and gender. Compliance rate per patient was also calculated, as the proportion of eligible windows per patient during follow-up when screening was performed. Mean compliance rates in the RA sample were compared to controls using a Mann-Whitney U test.

Results: We identified 27,650 individuals with RA (68.8% female, mean [SD] age 62.5 [12.9] yrs), contributing 49,515 three-year eligibility windows; and 30,486 controls (68.6% female, age 62.3 [12.9] yrs), contributing 62,942 three-year eligibility windows. Overall, PG was measured in 71.2% of the eligible time windows in the RA sample and in 74.4% for controls (OR=0.89 [95% CI; 0.86, 0.92], $p<.0001$). RA individuals met the recommended screening guidelines in 72.1% (SD=37.1%) of their eligible time windows, compared to 74.1% (SD=35.3%) for controls ($p<.001$).

Conclusion: Compliance with screening guidelines for diabetes was slightly lower in our RA cohort than the general population. Although the difference was statistically significant, it may not be a clinically relevant difference. Regardless, given the increased prevalence and burden of cardiovascular diseases in RA, diabetes screening is sub-optimal for RA individuals.

Disclosure: T. J. Schmidt, None; **J. A. Avina-Zubieta**, None; **E. C. Sayre**, None; **M. Abrahamowicz**, None; **J. M. Esdaile**, None; **D. Lacaille**, None.

2307

Cardiovascular Disease Prevention in Rheumatologic Disease: Assessing Screening in a Primary Care Setting. Micaela Bayard[1] and Magdalena Cadet[2]. [1]New York Hospital of Queens/ Weill Cornell Medical Center, New York, NY, [2]Duke University School of Medicine, Durham, NC.

Background/Purpose: To determine the proportion of patients diagnosed with rheumatologic disease receiving preventive health care according to US Preventive Services Task Force recommendations with emphasis on hypertension, dyslipidemia, and glucose tolerance screening. Cardiovascular disease is the most prevalent co-morbidity for patients with Rheumatoid Arthritis, specifically ischemic cardiac disease. Studies have shown that more than half of premature deaths in people living with Rheumatoid Arthritis are attributable to cardiovascular disease. Studies also demonstrate a significantly increased risk of coronary artery disease in other inflammatory diseases including Systemic Lupus Erythematous, Gout, and Psoriatic Arthritis. Enhanced atherosclerosis in rheumatic disease is a result of higher rates of systemic inflammation. Despite the recognized risk of cardiovascular disease in rheumatologic disease, little is known about cardiovascular risk management in these patients.

Methods: Clinical data from June 2013 to November 2013 was abstracted from outpatient electronic medical records of patients seen in rheumatology clinic with primary care follow-up with one of the following International Classification of Diseases, Ninth Revision (ICD-9) codes: Rheumatoid Arthritis (714.0), Systemic Lupus Erythematous (710.0), Psoriatic Arthritis (696.0), and Gout (274.0). 69% had Rheumatoid Arthritis, 13% had Systemic Lupus Erythematous, 18% had Psoriatic Arthritis, and 13% had Gout, this included patients with more than one of the 4 ICD-9 codes. Charts were reviewed for blood pressure testing at the most recent primary care visit, a lipid profile within the last year, and glucose or Hemoglobin A1C testing within the last year. These probabilities were summarized and compared between disease categories using Pearson's chi-square test.

Results: A total of 46 men and 121 women, with a mean age of 55.2 years, were identified. 79 were identified by having at least one of the four target ICD-9 codes. In this cohort, 100% were screened for hypertension, 24% for hyperlipidemia, and 27% for diabetes. Of the women, 100% were screened for hypertension, 24% for hyperlipidemia, and 29% for diabetes. There was no significant difference in screening between men and women. Rheumatoid Arthritis patients were more likely to be screened for diabetes, when compared to patients with Systemic Lupus Erythematous, Gout, or Psoriatic Arthritis (43% vs 12%, $p < .05$).

Conclusion: This data suggests that patients with rheumatologic diseases known to accelerate risk for cardiovascular disease are not being consistently screened in primary care settings. The data also suggests that physicians may be more aware of recommendations for cardiovascular screening in rheumatoid arthritis and less in other rheumatologic diseases. Although traditional cardiovascular risk factors may be suboptimal screening tools for patients with rheumatologic disease, studies must first identify gaps in existing screening and intervention. Further research is needed to develop cardiovascular screening guidelines and risk stratification models, as seen in diabetes, which are specific to rheumatologic disease.

Disclosure: M. Bayard, None; **M. Cadet**, None.

2308

Quality of Care for Cardiovascular Disease Prevention in RA: Compliance Lipid Screening Guidelines. Timothy J Schmidt[1], J Antonio Avina-Zubieta[2], Eric C. Sayre[3], Michal Abrahamowicz[4], John M. Esdaile[5] and Diane Lacaille[6]. [1]University of British Columbia, Department of Experimental Medicine, Richmond, BC, [2]University of British Columbia, Department of Experimental Medicine, Vancouver, BC, [3]Arthritis Research Centre of Canada, Richmond, BC, [4]McGill University, Montreal, QC, [5]University of British Columbia, Department of Medicine, Division of Rheumatology, Vancouver, BC, [6]Arthritis Research Centre of Canada, Vancouver, BC.

Background/Purpose: Comorbidities are increasingly recognized as significant contributors of reduced quality of life and increased mortality in RA. Cardiovascular diseases are the leading cause of premature death in RA. Previous research suggests that RA populations may receive sub-optimal care for their non-RA health related issues.

Our aim was to evaluate the quality of care for cardiovascular disease prevention in RA by measuring compliance with general population hyperlipidemia screening guidelines in RA compared to the general population.

Methods: We conducted a retrospective matched cohort study among patients with RA who received care between Jan 1996 and Mar 2006 and followed-up until Dec 2010. RA cases were selected if they had ≥2 MD visits more than 2 mos apart with an RA code. Cases were excluded if they had ≥2 subsequent MD visits for other inflammatory arthritis; if they saw a rheumatologist and RA diagnosis was never confirmed; or if there were no subsequent RA diagnoses over a follow-up > 5 yrs (N=36,458). Controls were selected from the general population and matched 1:1 to RA cases on gender, age, and calendar year. Administrative data was obtained on all physician visits, hospital admissions, tests ordered and medications.

Outcome: Compliance with current screening guidelines for hyperlipidemia defined as testing for lipids at least once every 5 years for women ≥ 50 and men ≥ 40, excluding individuals with previous diabetes, coronary artery disease, or hyperlipidemia. Individuals' follow-up was divided into 5-year eligibility windows, when they were eligible for the screening guideline. Each individual could contribute up to two five-year eligibility windows. Compliance was measured as the proportion of eligibility windows with at least one lipid test performed within the time period. Compliance rate between RA and controls, using eligibility windows as the unit of analysis, were compared via a GEE models to account for the lack of independence of observations obtained from the same patient, adjusting for age and gender. Compliance rate per patient was also calculated, by measuring the proportion of eligible windows per patient during follow-up when screening was performed. Mean compliance rates in the RA sample were compared to controls using a Mann-Whitney U test.

Results: We identified 13,117 individuals with RA (64.5% female, mean [SD] age 59.0 [11.3] years), contributing 5,273 five-year eligibility windows; and 14,694 controls (65.0% female, age 59.0 [11.4] years), contributing 7,228 five-year windows. Overall, lipids were measured in 75.4% of the eligible time windows in the RA sample and in 76.7% for the control sample (OR[95% CI]=0.94 [0.86, 1.02], p=0.12). RA individuals met the recommended screening guidelines in 77.6% (SD= 37.5%) of their eligible time windows, compared to 78.5% (37.0%) for controls (p=0.22).

Conclusion: In our population-based RA cohort, compliance with general population guidelines for diabetes and hyperlipidemia screening was similar in people with RA and the general population. However, given the increased prevalence and burden of cardiovascular disease, plasma glucose and lipid screening was sub-optimal for RA individuals.

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2309

A Novel Approach to Assess Wait-Times to Rheumatologists. Jessica Widdifield[1], Claire Bombardier[2], J. Carter Thorne[3], R. Liisa Jaakkimainen[4], J. Michael Paterson[1], Sasha Bernatsky[5], Jacqueline Young[1], Laura Wing[1], Noah Ivers[2], Debra Butt[1], Vivian Poon[1], Vandana Ahluwalia[6] and Karen Tu[1]. [1]Institute for Clinical Evaluative Sciences, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]Southlake Regional Health Centre, Newmarket, Newmarket, ON, [4]Sunnybrook Health Sciences Centre, Toronto, ON, [5]McGill University Health Centre, Montreal, QC, [6]William Osler Health Center, Brampton, ON.

Background/Purpose: Previous studies quantifying delays in assessment of patients by rheumatologists have studied patients from rheumatology clinics and thus include all patients who ultimately had access to rheumatologists. Our study estimates overall wait times for initial rheumatology consultations for patients referred by their primary care physician.

Methods: We employed a novel approach to identify first-time rheumatology referrals from the primary care Electronic Medical Record Administrative data Linked Database (EMRALD), representing comprehensive EMR data from 168 primary care physicians across Ontario, Canada (32 rural, 39 suburban and 97 urban physicians). We randomly sampled patients with rheumatology referral letters and performed linkage with administrative data to retrospectively confirm that patients had no prior rheumatologist assessments. Using a standardized data abstraction tool, the entire patient medical record was reviewed to categorize each patient according to their diagnosis: systemic inflammatory conditions, mechanical/degenerative/arthritic conditions, chronic pain, regional musculoskeletal (MSK) syndromes, osteoporosis/osteopathies, and other (e.g., abnormal diagnostic tests). Administrative data were then used to identify the date of the first rheumatologist visit subsequent to the date recorded on the referral identified in the EMR. The time in days from the date the first referral letter was sent to the date of the first rheumatologist visit was determined overall and for each diagnostic category.

Results: Among 1086 patients with first-time referrals, 99% of referrals analyzed occurred between 2006 and 2013. The majority of referrals were for mechanical/degenerative conditions (34%) and systemic inflammatory conditions (30%). Overall, 36% of patients were seen by a rheumatologist within 6 weeks from referral and 67% within 3 months. 68 (6%) patients were waiting longer than 12 months to be seen (Table). The average wait time to

see a rheumatologist for any condition was 142 days (median 61) post-referral. For patients with systemic inflammatory conditions, the median time to be seen was 47 days (interquartile range 18–97). The median wait times for individuals with conditions deemed non-urgent (osteoarthritis, chronic pain) were roughly 2 weeks longer.

Conclusion: Using EMRs from a representative sample of Ontario primary care practices revealed longer wait times to see a rheumatologist than previous Canadian reports that sampled patients from urban rheumatology clinics. 33% of patients were still waiting >3 months to be seen, exceeding current Canadian recommendations. Individuals with systemic inflammatory conditions were seen earlier compared to other types of referrals. An analysis of wait times along each component of the care pathway is currently underway.

	Overall N = 1086	Systemic Inflammatory Conditions n = 321 (30%)	Mechanical/ Degenerative/ Arthritic Conditions n = 370 (34%)	Regional MSK Syndromes n = 181 (17%)	Chronic Pain Conditions n = 134 (12%)	Osteoporosis/ Osteopathies n = 16 (2%)	Other n = 64 (6%)
Age at Time of referral, mean (SD) years	54 (16)	55 (16)	57 (15)	53 (15)	48 (14)	50 (19)	46 (16)
Female, n (%)	734 (68%)	173 (54%)	256 (69%)	127 (70%)	116 (87%)	15 (94%)	47 (73%)
Seen by a rheumatologist within <6 weeks, n (%)	391 (36%)	153 (48%)	102 (28%)	71 (39%)	40 (30%)	<5	21 (33%)
Seen by a rheumatologist between 6 weeks to 3 months, n (%)	331 (31%)	83 (26%)	127 (34%)	56 (31%)	42 (31%)	<5	20 (31%)
Seen by a rheumatologist between 3 to 6 months, n (%)	214 (20%)	45 (14%)	87 (24%)	31 (17%)	28 (21%)	7 (44%)	16 (25%)
Seen by a rheumatologist between 6 to 9 months, n (%)	56 (5%)	16 (5%)	20 (5%)	5 (3%)	11 (8%)	<5	<5
Seen by a rheumatologist between 9 to 12 months, n (%)	26 (2%)	7 (2%)	9 (2%)	6 (3%)	<5	0 (0%)	<5
Seen by a rheumatologist after 12 months, n (%)	68 (6%)	17 (5%)	25 (7%)	12 (7%)	10 (8%)	0 (0%)	<5
Time from referral to first rheumatologist visit, Mean (SD), days	142 (332)	133 (345)	161 (377)	126 (257)	149 (284)	101 (60)	130 (308)
Time from referral to first rheumatologist visit, Median (IQR), days	61 (29-114)	47 (18-97)	70 (39-124)	56 (28-100)	69 (35-135)	112 (58-153)	58 (39-117)

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2310

Improving Access to Health Care in Rheumatology Practices through Initiation of an Outpatient Urgent Care Clinic, a Paradigm Shift. Ruchi Jain, Meenakshi Jolly, Theodore Pincus, Isabel Castrejón, Annie Huang and Joel A. Block. Rush University Medical Center, Chicago, IL.

Background/Purpose: Urgent care clinics are built into some primary care practices, but no reports are available of urgent care clinics in rheumatology settings. Many rheumatologists currently reserve slots in their schedules to accommodate patients with urgent needs. However, this practice may be inadequate as the slots may become filled by waitlisted, follow-up, or new patients, particularly in academic practices where providers may see patients only a few days per week. A survey of patients with rheumatic diseases indicated that 50% reported inadequate provider access for urgent concerns, which was greater among patients of providers whose clinical activities involved fewer rather than 5 days per week. We studied patients seen at an academic rheumatology urgent care clinic to analyze possible reduction in emergency room (ER) visits, and possible improved patient confidence that timely care by their rheumatologist is available.

Methods: A weekly urgent care clinic was initiated for established patients under care at an academic rheumatology setting who had issues that could not wait until their next appointment, as well as for recently discharged inpatients with need of early outpatient follow up. A control group of 100 patients seen sequentially in routine care was identified, and compared to the urgent care group using t tests and chi square tests. Each patient in the control and urgent care group completed a multidimensional health assessment questionnaire (MD-HAQ) at each visit as part of routine care, with scores for physical function, pain, patient global assessment, RAPID3 (routine assessment of patient index data), and demographic data. Each physician scored a contemporaneous physician global assessment. An additional survey for urgent care clinic patients queried if patients would have gone to the ER if not seen today (Yes or No) and the level of the patients' confidence that future urgent concerns would be met (0=no confidence - 10=great confidence).

Results: Demographics of the 42 patients and 100 controls are in Table 1. Those seen in the urgent care clinic were older, less likely to work full time, and more likely to have osteoarthritis than the controls. MDHAQ scores were significantly higher in the urgent care clinic vs controls (Table 1**).** 61% of urgent care patients reported that they would have gone to the ER if the urgent care clinic were not available, and mean confidence score of patients in the urgent care clinic group was 9.75 on a 0–10 scale.

	Control Group N=100	Urgent Care Group N=42	P
Female, n (%)	81 (81.0%)	34 (80.9%)	0.99
Age, mean (SD)	51.8 (16.8)	59.9 (15.8)	0.01
Ethnicity, n (%)	–	–	–
Caucasian	48 (48%)	13 (31.7%)	0.11
Afro-American	36 (36%)	22 (53%)	
Hispanic	8 (8%)	5 (12.2%)	
Others	8 (8%)	2 (3.1%)	
Education, mean (SD)	14.6 (2.9)	14.1 (2.7)	0.45
Work Full time, n (%)	34 (40%)	5 (19%)	0.05
Diagnosis, n (%):	–	–	–
RA	29 (29%)	9 (21.9%)	0.037
OA	9 (9%)	10 (24.4%)	
SLE	16 (16%)	2 (4.8%)	
Crystal Diseases	3 (3%)	5 (5.7%)	
Other Diseases	43 (43%)	16 (43.2%)	
Physician Global (0-10), mean (SD)	3.6 (2.2)	5.4 (1.0)	<0.001
Patient Global (0-10), mean (SD)	4.3 (2.9)	7.2 (1.6)	<0.001
PAIN (0-10), mean (SD)	4.6 (3.3)	7.3 (2.2)	<0.001
FUNCTION (0-10), mean (SD)	2.3 (2.2)	4.5 (2.9)	<0.001
RAPID3 (0-30), mean (SD)	10.9 (7.4)	17.7 (4.3)	<0.001
Anxiety (0-3.3)	0.57 (0.77)	0.91 (0.16)	0.03
Depression (0-3.3)	0.44 (0.73)	0.82 (0.97)	0.018

All scores are mean (standard deviation=SD)

Conclusion: Patients seen in the urgent care clinic had poorer clinical status than control patients, with higher patient and physician scores. 61% would have gone to the ER had they not been seen in the urgent care clinic. These patients also expressed high confidence that timely access would be available in the future. Improved patient access for urgent needs may be met by a dedicated urgent care clinic.

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2311

Tele-Rheumatology: Despite Improved Access Could There be a Potential Delay in Care without a Skilled "Presenter"? Zsolt Kulcsar[1], Daniel A. Albert[2], Krista Merrihew[3] and John Mecchella[4]. [1]Dartmouth Hitchcock Medical Center, lebanon, NH, [2]The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH, [3]Dartmouth-Hitchcock Medical Center, Lebanon, NH, [4]Giesel school of medicine and Dartmouth Hitchcock Medical Center, Lebanon, NH.

Background/Purpose: Arthritis treatment in New Hampshire (NH) is complicated by the fact that a large proportion of the population lives in rural areas (60%) with limited resources and access to care. Tele-rheumatology services developed at Dartmouth-Hitchcock Medical Center (DHMC) in partnership with Weeks Memorial Hospital (Critical Access Hospital in Northern NH) bring arthritis care to these rural regions, thus improving access. In addition to the providers and patients tele-medicine utilizes a "presenter," an individual who sits with patients at the remote site (medical assistant, nurse, etc.) to facilitate the visit. We sought to learn what challenges and accomplishments our early tele-medicine program has encountered since inception.

Methods: As part of a quality improvement initiative we performed an IRB-exempt retrospective review of the charts for patients seen in the tele-rheumatology clinic at DHMC from October 2011 to January 2013. We also interviewed the participants: including providers, presenters and patients regarding their experience of care. We used descriptive statistics to summarize our findings.

Results: In our cohort of 22 patients there were 63 encounters (18 initial consults and 45 follow-up visits) with either of the two participating rheumatologists. 27% (n=6) of the patients seen initially by tele-rheumatology needed to be seen in-person for clarification of the joint exam. 83% (n=5) of the patients seen in-person had findings of synovitis not seen via telemedicine. The average time from initial consult to in-person evaluation was 81 days. These patients went without aggressive anti-inflammatory therapy for longer than the recommended 42 days (6 weeks) according to current guidelines. Providers expressed concern about not being able to lay hands on patients, and the inability of the "presenter" to perform and convey the findings of the joint exam which may have contributed to the delay in care. The top two diagnosis that patients presented with during the tele-rheumatology visits were inflammatory arthritis (n=10) and fibromyalgia (n=9). 40% of the patients seen by tele-rheumatology were ultimately started

on high risk medications such as high dose steroids (prednisone>20mg/daily), biologics, and DMARDs (Table 1).

Conclusion: The use of tele-rheumatology has successfully increased access to arthritis care in rural regions of NH allowing for shorter travel and intense anti-inflammatory therapy. The lack of musculoskeletal training for the presenter and inability of providers to lay hands on patients could lead to increased delay in initiation of this therapy for inflammatory arthritis. Initial strategies are being developed to improve the training of the presenters and to shorten this interval to meet current guidelines.

Table 1. Dartmouth-Hitchcock Medical Center Tele-rheumatology Services Patient Characteristics

Characteristic	N (%)
Providers	
Patients seen by Provider #1	5 (22.7)
Patients seen by Provider #2	17 (77.3)
Total # of Patients seen since inception	22
Total # of visits	63
Patients	
Age (avg. in years)	56.8
Sex (% female)	12 (54.5)
Avg. Distance from home to DHMC one way (miles)[1]	99.6
Avg. Distance from home to Weeks Memorial (miles)[1]	10.7
Visit Type (# of encounters)	
Consult	18 (28.6)
Follow-up	45 (71.4)
Required in-person follow up for joint exam	6 (27.3)
Avg. time from initial visit to in-person follow-up (days)	80.8
Discrepancy in joint exam after in person visit[2]	5 (83.3)
Started on high risk medication[3]	9 (40.9)
Diagnosis Seen in Clinic[4]	
Fibromyalgia	9 (40.9)
Inflammatory Arthritis (RA, PsA, Ank Spon)	10 (45.5)
Osteoarthritis (DJD)	2 (9.0)
Crystal Arthropathy (Gout, CPPD)	1 (4.5)
Osteoporosis	1 (4.5)
Other	1 (4.5)

RA = Rheumatoid Arthritis, PsA = Psoriatic Arthritis, Ank Spon = Anylosing Spondylitis, CPPD = Calcium Pyrophosphate Dihydrate Crystal Deposition Disease, DHMC = Dartmouth- Hitchcock Medical Center
1. Miles calculated using zipcodes.com calculator
2. Synovitis appreciated on exam which was not seen initially via tele-medicine
3. DMARDs (i.e.: methotrexate), colchicine, high dose steroids (equivalent of prednisone >20 mg daily), denosumab.
4. Diagnosis is greater than 100% as some patients had overlapping diagnosis (ie: both rheumatoid arthritis and fibromyalgia).

Disclosure: Z. Kulcsar, None; **D. A. Albert**, None; **K. Merrihew**, None; **J. Mecchella**, None.

2312

Use of Physician Extenders to Improve Quality and Efficiency of Clinical Visits. Carl Orr[1], Francis Young[1], Lorraine O' Neill[1], Mairead Murray[1], Phil Gallagher[2] and Douglas J. Veale[3]. [1]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [2]St. Vincent's University Hospital, Dublin, Ireland, [3]St. Vincent's University Hospital, Dublin 4, Ireland.

Background/Purpose: Logistical difficulties associated with managing a large, publically funded secondary service, means that service delivery is costly in terms of physician time. Patients frequently do not have medication lists with them when they attend clinic. Recent results are not available to the physician at the time of clinic visit. Disease activity scores to assist in informing clinical decisions with a treat-to-target approach, are not calculated. Patient reported outcome measures (PROM) are rarely formally assessed and recorded, because these too are often time consuming.

Physician Extenders (PE) have been used to improve efficiency in out-patient clinics.(1) In this action-research endeavour(2), we introduced changes both to the structure and process of how return patients are assessed, making use of a PE to prepare for patient visits.

The specific aims were:

1. To decrease the time physicians spend with inflammatory arthropathy (IA) return patients.
2. To perform a standardised and validated measurement of disease activity for all patients.
3. To increase the proportion of patients acquiring staging hands and feet plain film radiographs every two years in compliance with the consensus of rheumatologists at the hospital.

Methods: The PE recorded the results of the last inflammatory markers and plain film radiographs of hands and feet in a pro-forma. Where these results were not recent (2 weeks for blood results and 2 years for radiographs), the PE liaised with a physician, on a scheduled basis, to arrange for the latter to complete the required ordering forms.

The PE assembled and mailed the pro-forma and ordering forms to returning IA patients 2 weeks in advance of their clinic visit. The pro-forma included a patient global assessment; other PROMs, e.g. HAQ-DI, SF-36; as well as an accurate current medication list. Patients were asked to complete the pro-forma, and to have the bloods and radiographs taken a few days before their appointment.

Patients presented to clinic with a self-completed pro-forma as well up to date results.

Results: 125 patients (85 female) with IA were sent pro-formas before their clinic visit.

Mean time a physician spent at clinic per patient was decreased from 23 minutes to 15 minutes.

120 (96.0%), patients had DAS28-CRP scores calculated, 5 (4%) did not have scores calculated because of a piece of missing data.

68/125 (54.4%) had no radiographs in the three 3 years before their clinic visit. Of the 68 who had no radiographs taken during this time, 49 (72.1%) had radiographs directly as a result of this action-research.

Conclusion: The use of a PE in preparation for clinic visits decreases the time physicians need to spend reviewing patients, and increases the quality of the visit as measured by the collection of DAS scores, and PROMs, and relevant radiological investigations. A cost analysis needs to be done to demonstrate that this approach is cost effective.

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2313

Best Practices for Best Practice Alerts: Evaluation of a Best Practice Alert to Detect Chronic Glucocorticoid Use. Mingyuan Zhang[1], Catherine Staes[1], Lara Kapp[2] and Karla L. Miller[3]. [1]University of Utah, Salt Lake City, UT, [2]University of Utah School of Medicine, Salt Lake City, UT, [3]University of Utah School of Medicine, SLC, UT.

Background/Purpose: Chronic glucocorticoid (GC) use is a known risk factor for osteoporosis and fracture. Patients with chronic GC use often receive suboptimal osteoporosis prevention, diagnosis, and treatment. We sought to create a best practice alert (BPA) to identify chronic GC users in our electronic health records (EHR) to recommend bone density testing. Daily dosage and duration of prescription data were not uniformly available for building the BPA. To improve identification of these patients, our objectives were to 1) describe the quality of medication data available for triggering a BPA to prompt bone density screening for patients on chronic GCs, and 2) assess alternative criteria using existing data.

Methods: Our target population was patients ≥50 years of age on chronic GCs defined as taking ≥7.5mg of prednisone daily or equivalent, for 30 days or more. We extracted medication orders from the University of Utah Healthcare clinical data warehouse for all GCs ordered between July 1 and December 31, 2013 for patients ≥ 50 years. The extract included refill number, quantity dispensed, difference between order start and end date, frequency, signature, and dosage per episode. We manually reviewed and classified each order as 'yes', 'no', or 'unable to determine' for chronic GC use. We assessed the frequency of data available for each data field, and stratified by records created using the structured versus free-text order template. We assumed that records without the paired dosage and frequency information were entered using the free text template. Finally, we assessed sensitivity and positive predict value (PPV) of selected medication data elements to identify the target population.

Results: Among the 1,699 GC prescriptions identified, 17% (292) were determined to be chronic GC use; 52% (881) were entered using a structured

template. The structured and free-text templates resulted in similar rates of data populating Refills (97% vs 98%), Quantity dispensed (97% vs 98%), Order start date (99.7% vs 99.9%), and 'Sig' (99.9% vs 99.8%), respectively. In contrast, rate of data availability differed between structured verses free-text templates: Order end date (90.5% vs 71%), Frequency (99.9% vs 0%) and Dosage (100% vs 0%), respectively.

Data Field	Structure of Data	% of Records with Computable Data	Criteria	Sensitivity	PPV
Refill	Structured	97.3%	1 or more refill	72%	41%
	Free text	97.7%		72%	42%
Quantity Dispensed	Structured	97.5%	dispensed >=30 tablets	97%	44%
	Free text	98.5%		93%	44%
	Structured	97.5%	dispensed >=45 tablets	79%	48%
	Free text	98.5%		84%	64%
	Structured	97.5%	dispensed >=60 tablets	75%	50%
	Free text	98.5%		79%	68%
Difference Between Order Start and End Date	Structured	90.2%	Date difference between order start and end date	67%	43%
	Free text	71.1%		50%	19%
Refill and Quantity Data	Structured	97.0%	Refill >0 and quantity data >=30	71%	46%
	Free text	97.6%		72%	64%

In the absence of daily dosage and duration information, quantity dispensed ≥ 30 tablets performed best with the highest sensitivity, and mid-range PPV (Table 1).

Conclusion: Medication data in the EHR are subject to variability and detecting chronic medication use requires adequate evaluation of medication data quality, available data fields, and clinician practice patterns. This is particularly challenging with GCs given their widespread use both chronically and in short-term tapers. Successful alert designers must evaluate both the accuracy of data used to generate an alert, and triggering criteria, to improve identification of the desired population.

Disclosure: M. Zhang, None; **C. Staes**, None; **L. Kapp**, None; **K. L. Miller**, None.

2314

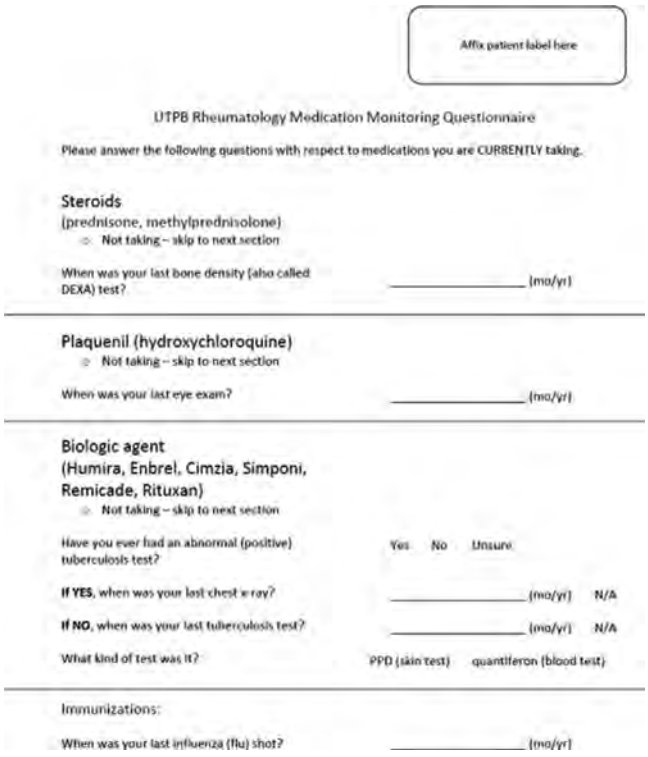
Dexa Testing in Long-Term Steroid Use. Beth Scholz University of Texas Health Science Center at Houston, Houston, TX.

Background/Purpose: Risk stratification in the ACR glucocorticoid-induced osteoporosis guidelines includes DEXA testing, which is not universally implemented at our rheumatology clinic. DEXA utilization should be increased to screen for this effect of long-term glucocorticoid use.

Methods: As a quality improvement project, institutional policy exempted this study from IRB review. As a baseline, charts were reviewed from 50 patients on steroids (equivalent to prednisone ≥5 mg/day, ≥ 3 months) seen in rheumatology clinic in August 2013. DEXA status was categorized as never, current, or out-of-date (>2 years ago). Patient gender, menopausal status, steroid dose, and duration of steroid use were also recorded. Then a medication monitoring questionnaire (see Figure 1) was administered to all patients at the time of visit during the intervention pilot period in January 2014 with the intention of triggering more DEXA orders by providers. Other drugs and monitoring tests were included on the form for clinical utility but were not measured for this project. Charts from the 44 patients on qualifying steroid therapy seen during the pilot period were reviewed.

Results: During the baseline period.32% of patients had a current DEXA. Status distribution was similar regardless of menopausal status or prednisone dose (>5 versus ≤5 mg/day). Of 9 male patients, 7 (78%) had current DEXA as opposed to 10 of 41 female patients (24%). During the intervention period, current DEXAs (including DEXAs ordered at the visit) increased to 48% (see Figure 2). The number of patients with "never" status was similar; most of the gain to "current" status resulted from updating DEXA testing.

Conclusion: A medication monitoring questionnaire at routine clinic visits can serve as a reminder to trigger appropriate DEXA orders in patients on long-term steroids. This intervention could be modified for other chronic medication monitoring parameters as well. Future interventions will target increasing FRAX calculation and documentation.


Affix patient label here

UTPB Rheumatology Medication Monitoring Questionnaire

Please answer the following questions with respect to medications you are CURRENTLY taking.

Steroids
(prednisone, methylprednisolone)
Not taking – skip to next section

When was your last bone density (also called DEXA) test? _____ (mo/yr)

Plaquenil (hydroxychloroquine)
Not taking – skip to next section

When was your last eye exam? _____ (mo/yr)

Biologic agent
(Humira, Enbrel, Cimzia, Simponi, Remicade, Rituxan)
Not taking – skip to next section

Have you ever had an abnormal (positive) tuberculosis test? Yes No Unsure

If YES, when was your last chest x-ray? _____ (mo/yr) N/A

If NO, when was your last tuberculosis test? _____ (mo/yr) N/A

What kind of test was it? PPD (skin test) quantiferon (blood test)

Immunizations:

When was your last influenza (flu) shot? _____ (mo/yr)

Figure 1. Medication monitoring questionnaire

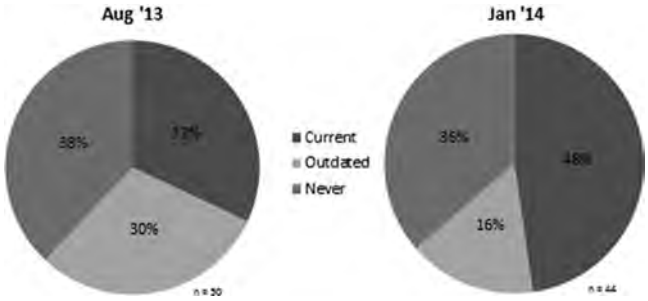


Figure 2. DEXA status during baseline and pilot periods

Disclosure: B. Scholz, None;

2315

Glucocorticoid Induced Osteoporosis Screening and Treatment in a Cohort of Male Patients with Underlying Rheumatologic Diagnosis in a Tertiary Care Setting. Hajra Shah, Narender Annapureddy, Joel A. Block and Ruchi Jain. Rush University Medical Center, Chicago, IL.

Background/Purpose: One-fourth of hip fractures occur in men. Three groups of men are at high risk for fracture: those who have already suffered a fragility fracture, those treated with androgen deprivation therapy for prostate cancer, and men treated with oral glucocorticoids for at least 3 months. Rapid bone loss occurs in the first 3 months of steroid use, peaks at 6 months and slows with continued use. In addition hypogonadism in chronic disease also may contribute to fracture risk. Men with rheumatic diseases taking glucocorticoids may not receive adequate screening or treatment compared to females. The American College of Rheumatology recommends that males over age 50 who take chronic glucocorticoids be screened for treatment and prevention of osteoporosis (OP). We assessed adherence to these guidelines in a busy academic practice.

Methods: A retrospective chart review identified male patients 50 years or older with a rheumatic diagnosis seen from 2010 to 2013. Inclusion criteria were 1. Patients who received any dose of prednisone

for at least 3 months; and 2. Seen for at least 3 clinic visits. Exclusion criteria were 1. Recognized osteoporosis; and 2.Prior bisphosphonate use. Most patients had incident prednisone use. We collected demographic data, dose and length of steroid use, timing of DXA from initiation of prednisone use, T-score and calcium and vitamin D supplementation use. We defined appropriate care as screening with a baseline DXA within 6 months of initiation of prednisone, calcium and vitamin D supplementation and bisphosphonates use when indicated. Patients not meeting these criteria were defined as receiving sub-optimal care. Fisher's exact test was used to compare categorical variables.

Results: 100 patients met inclusion criteria; 50% were Caucasians with a mean age of 63.4 (SD 8.4 (51 – 85)) and had rheumatoid arthritis. 76% were taking 7.5 mg of prednisone or higher for at least 3 months and 62% for greater than 12 months. T-scores were available for 57 patients. 61% of T-Scores were found to be abnormal. 53% were treated with calcium and vitamin D and only 31% with bisphosphonates when indicated. 78% of the patients received sub-optimal care for glucocorticoid induced osteoporosis (GIOP) management. 35% of junior faculty (< 5 years out of fellowship) compared with 13% of senior faculty (> 5 years from fellowship) managed patients appropriately (P= 0.014). OP screening for Vasculitis and PMR was more likely compared to other diseases (Figure 1).

Conclusion: The majority of patients who took significant amounts of prednisone for > 3 months received sub-optimal osteoporosis care. To our knowledge, this study is the first to analyze this problem, and identifies a potential gender gap in management of OP in a vulnerable population with inflammatory diseases taking steroids. More vigilance appears needed to managing GIOP, a potentially modifiable risk factor in male patients with rheumatic diseases.

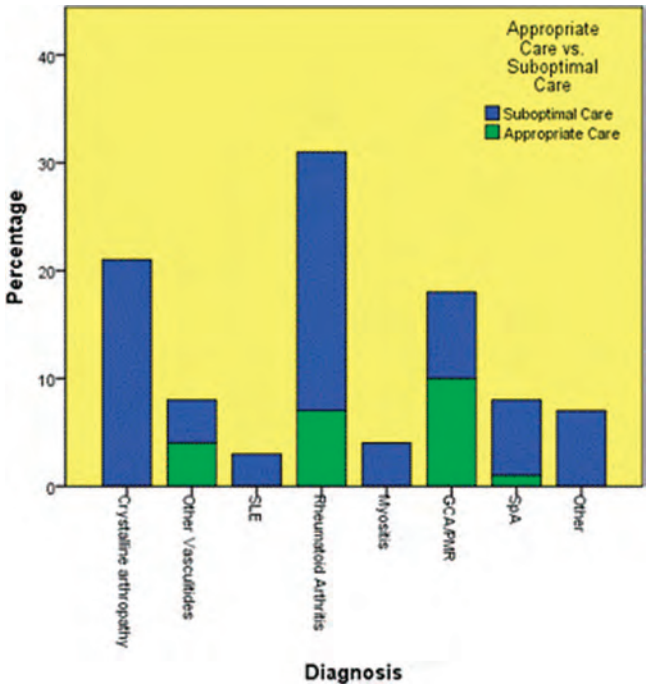


Figure 1.

Disclosure: H. Shah, None; **N. Annapureddy**, None; **J. A. Block**, None; **R. Jain**, None.

2316

Adherence to Denosumab in a Large Healthcare System. Robert A. Overman[1], Julie C. Lauffenburger[1], Margaret L. Gourlay[1] and Chad L. Deal[2]. [1]University of North Carolina, Chapel Hill, NC, [2]Cleveland Clinic, Cleveland, OH.

Background/Purpose: Oral bisphosphonates adherence has been reported as less than 50% at one year. Adherence to denosumab has been reported to be higher than alendronate in several clinical trials. We evaluated adherence rates for denosumab, an anti-osteoporosis medication (AOM) administered in office as an injection every six months, by rheumatologists in a large healthcare system.

Methods: We identified new denosumab users using billing data between June 2010 and October 2013 based on HCPCS code J0897 or J3590 with denosumab as the listed biologic. Patients had at least 183 days (6 months) follow-up and were administratively censored at two years post-denosumab initiation, for death, or on 6/1/2014 (end of study period). These data were linked to electronic medical record data and only included patients who had at least two office visits in a rheumatology clinic. Patient characteristics were assessed prior to first administration. Adherence to denosumab was assessed with proportion of days covered (PDC) based on a 183 day coverage period (dosing interval for denosumab). After initiation, PDC was calculated at a maximum of one and two years or censored at study end. We defined a patient as adherent if they had ≥80% of days covered. **Results** are presented as mean (standard deviation [SD]) or %.

Results: Five hundred patients met inclusion criteria. Included patients had a mean age of 71.9 (SD 11.0), 92.6% were women, and 88.8% Caucasian. Denosumab was the first AOM in 9.8% of patients. In those with a history of previous therapy, a mean of 2.3 (SD 1.5) AOMs were prescribed. Prevalent fractures were present in 32.8%, mean Charlson Comorbidity score of 2.0 (SD 2.7), and 25% had diagnoses for either gastric ulcers or GERD at first denosumab administration. Eighty-three percent of patients had 12 months follow-up and 26% had 24 months of follow-up. Two denosumab injections were given in 82.3% of patients, 3 in 53% and 4 in 30% of patients. Of those who didn't receive a second administration 2.6% were prescribed another AOM. Mean 1 year PDC, 85.5% (SD 19.0), and 80.7% (SD 21.6) at 2 years. PDC ≥80% was achieved in 72.8% and 62.0% of patients at 1 and 2 years, respectively.

Conclusion: In patients treated with denosumab 72.8% of patients were adherent at 12 months and 62.0% were adherent at 24 months. Only 9.8% of patients started on denosumab were treatment naïve. Adherence rates were higher than those reported for oral bisphosphonates. Other studies have suggested that higher adherence rates for denosumab may be related to in office administration, patient preference and convenience, and a favorable side effect profile. Since studies have suggested that adherence rates <50% are associated with little anti-fracture effect, the greater adherence with denosumab may have important implications for fracture prevention.

Disclosure: R. A. Overman, None; **J. C. Lauffenburger**, None; **M. L. Gourlay**, None; **C. L. Deal**, None.

2317

Towards Reliable Implementation and Optimal Use of Medication Decision Aid Cards for Shared Decision Making in Juvenile Idiopathic Arthritis. Esi Morgan DeWitt[1], Janalee Taylor[1], Karla B. Jones[2], Murray H. Passo[3], Catherine C. Mims[3], Jesse Pratt[1], Ellen A. Lipstein[1], Nancy Griffin[1], Sheetal S. Vora[4], Beth S. Gottlieb[5], Elizabeth Roth-Wojcicki[6] and William B. Brinkman[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Nationwide Children's Hospital, Columbus, OH, [3]Medical University of South Carolina, Charleston, SC, [4]University of North Carolina Chapel Hill, Chapel Hill, NC, [5]Cohen Children's Medical Center of New York, New Hyde Park, NY, [6]Medical College of Wisconsin, Milwaukee, WI.

Background/Purpose: The purpose of the study was to improve communication and shared decision-making (SDM) between clinicians and parents of patients with juvenile idiopathic arthritis (JIA), and patients with JIA, regarding the choice of medication. SDM aims to ensure medication choices match families' goals and preferences. A treatment plan that is a good fit may be more reliably implemented at home, leading to better health outcomes. This project aimed to develop reliable care processes within a subset of centers in the Pediatric Rheumatology Care & Outcomes Improvement Network (PR-COIN) to 1) identify patients with JIA facing a decision to start or switch medicine, 2) provide SDM support during visits with our JIA 'medication discussion cards' that we developed and 3) measure the outcomes that accrue. Tests of implementation strategies across sites followed the Model for Improvement.

Methods: Volunteer PR-COIN sites employed iterative Plan-Do- Study-Act cycles to reliably implement the materials. To track the quality of interaction and the fidelity of use with the SDM cards, sites collected a short, voluntary, anonymous survey from parents after the visit. The post-visit survey contained information from two validated scales: 1) CollaboRATE is a 3-item measure of SDM (scale range 0 –100). 2) SURE is a 4-item measure of unmet decision support needs (scale range 0–4). The survey also contained 3 parent-report items that we developed with yes/no response options to assess the extent to which the decision aid cards were used as intended during the visit, or "fidelity of use." The first fidelity item asks parents "Did you discuss starting or switching medicine to treat your child's arthritis?" The

second item shows a picture of the cards and asks "Did your clinician show you the tool (pictured) during your visit?" The third item asks, "If "yes", did your clinician ask you to pick the first topic to discuss?" Outcomes were tracked on run charts including: proportion of eligible patient visits where 'JIA medication discussion cards' were used, percent of card use visits with cards used as intended. Separate run charts depict the weekly mean score for each proximal decisional outcome measure.

Results: 78 surveys were collected from 3 sites from March – June 2014. Decision aid cards were used in 33% of visits where a parent reported a medication start/switch. Cards were used as intended during 71% of visits. There was a ceiling effect with both outcome measures. CollaboRATE scores were 100 for all but 3 parents, one who reported card use and two who did not. 75 of 78 parents had maximal SURE scores; the two parents with the greatest number of unmet decisional needs did not report use of the cards.

Conclusion: Uptake of decision aid cards was achieved in approximately 1/3 of visits where a parent reported a medication start or switch. When cards were used, there was moderate fidelity (71%) to intended use. Due to ceiling effects it was difficult to estimate if the use of cards was associated with improved proximal decisional outcomes. Next steps are to collect a different measure of decisional quality and expand the number of sites assessing outcomes, including a control site. We will develop and test new approaches with PDSAs to increase reliability and fidelity of use.

Disclosure: E. Morgan DeWitt, None; **J. Taylor**, None; **K. B. Jones**, None; **M. H. Passo**, None; **C. C. Mims**, None; **J. Pratt**, None; **E. A. Lipstein**, None; **N. Griffin**, None; **S. S. Vora**, None; **B. S. Gottlieb**, None; **E. Roth-Wojcicki**, None; **W. B. Brinkman**, None.

2318

Increasing Rates of Remission in Juvenile Idiopathic Arthritis through a Quality Improvement Learning Network – the Pediatric Rheumatology Care and Outcomes Improvement Network.

Esi Morgan DeWitt[1], Stacy P. Ardoin[2], C. April Bingham[3], Beth S. Gottlieb[4], Ronald M. Laxer[5], Nancy Griffin[1], Jesse Pratt[1], Anne Paul[1], Daniel Lovell[6], Judyann C. Olson[7], Murray H. Passo[8], Jennifer E. Weiss[9], Tzielan C. Lee[10], Sheetal S. Vora[11], Melissa M. Hazen[12] and Peter Margolis[13]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Ohio State University College of Medicine, Columbus, OH, [3]Penn State Hershey Children's Hospital, Hershey, PA, [4]Cohen Children's Medical Center of New York, New Hyde Park, NY, [5]The Hospital for Sick Children, University of Toronto, Toronto, ON, [6]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati, Cincinnati, OH, [7]Medical College of Wisconsin, Milwaukee, WI, [8]Medical University of South Carolina, Charleston, SC, [9]Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [10]Stanford University School of Medicine, Stanford, CA, [11]University of North Carolina Chapel Hill, Chapel Hill, NC, [12]Boston Children's Hospital, Boston, MA, [13]Cincinnati Children's Hospital, Cincinnati, OH.

Background/Purpose: The Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) since 2011 has used quality improvement (QI) methods, chronic illness care model interventions, and a modified, sustainable, Breakthrough Series Collaborative approach to operations. As the network matures in use of population management and pre-visit planning interventions measureable improvements in remission outcomes for children with juvenile idiopathic arthritis (JIA) are being realized.

Methods: Teams conduct Plan-Do-Study-Act cycles using the Model for Improvement. Sites contribute data to a shared registry. Informed consent is obtained from patients for research uses. Data is displayed in run charts, funnel charts, and Pareto charts. Strategies for use of the Population Management Tool include peer review of patients with more than mild disease activity assessed by Physician Global Assessment >3 with decision support treatment algorithms. Pre-visit planning increases reliability of completion of process measures of care (medication safety lab tests, uveitis eye screening) and flags patients for needed services such as PT, OT, or if there is inadequate disease control. Patients are being engaged at network and local levels to inform priorities and contribute to improvement work. Teams share resources, materials and best practices on monthly webinars, "Learning Labs", and semi-annual face-to-face "learning sessions".

Results: 8 of 11 participant sites submit data to the registry (ACR Rheumatology Clinical Registry). 1,457 patients contribute 7,040 encounters. Rates of clinical remission on medication for 6 months were statistically increased from baseline of 37.2% to 48.4% in the aggregate. There is variability in current site performance by >20%, with remission rates for May 2014 ranging from 39.4% – 62.7% at individual sites.

Conclusion: PR-COIN has marked a turning point from early improvement in process measures of care to demonstrable improvement in outcomes as teams are more experienced in QI methods and more reliably implementing pre-visit planning and using population management approaches. Variability in site performance provides opportunity for shared best practices. Challenges to growth have included delays in regulatory approval, and currently a single IRB model is being implemented. Double data entry is a barrier to efficient participation and teams are jointly developing "SmartForms" for electronic health records to facilitate standardized data collection and electronic data transfer. Patient engagement is a new direction expected to support enrollment and influence self-management initiatives.

Disclosure: E. Morgan DeWitt, None; **S. P. Ardoin**, None; **C. A. Bingham**, None; **B. S. Gottlieb**, None; **R. M. Laxer**, None; **N. Griffin**, None; **J. Pratt**, None; **A. Paul**, None; **D. Lovell**, None; **J. C. Olson**, None; **M. H. Passo**, None; **J. E. Weiss**, None; **T. C. Lee**, None; **S. S. Vora**, None; **M. M. Hazen**, None; **P. Margolis**, None.

2319

Standardizing and Documenting Patient Education and Disease Indices in Childhood-Onset Systemic Lupus Erythematosus.

Julia G. Harris[1], Elizabeth Roth-Wojcicki[1], Marsha Malloy[1], Kristyn I. Maletta[2], Dominic O. Co[1] and Judyann C. Olson[1]. [1]Medical College of Wisconsin, Milwaukee, WI, [2]National Outcomes Center, Children's Hospital of Wisconsin, Milwaukee, WI.

Background/Purpose: Systemic lupus erythematosus (SLE) can affect many organ systems and lead to significant morbidities. **Methods** to standardize and improve care in this patient population have recently been established with development of quality indicators. Education is a common theme throughout many of the quality domains addressed. Our project sought to create a standard process for providers to educate SLE patients and their families and document its occurrence, in addition to collecting data pertaining to disease activity and damage. This pilot study will also establish baseline performance of these parameters that can lead to future quality improvement work.

Methods: Patient education materials were compiled pertaining to certain quality indicators: sun precautions, eye exams, vitamin D and calcium recommendations, smoking avoidance and cessation, risk of hypertension, risk of diabetes, weight management, exercise, and vaccination against influenza, pneumococcus, meningococcus, and *Haemophilus influenzae*. Previsit planning identified SLE patients and what educational topics they were in need of. Teaching materials pertaining to the identified educational topics were given to the patient at each routine visit and education was provided. A SLE-specific flow sheet was created and incorporated into our electronic medical record where education was documented and tracked. Additional information including provider global assessment, parent/patient global assessment, disease activity score, and disease damage score were recorded in the flow sheet as well.

Results: Preliminary results have been recorded on 45 SLE patients during 99 clinic visits in a 15-week period from February to May 2014. A total of 162 separate educational variables (range 0–10 per person) were discussed in 88.9% of patients. The most common educational topics discussed (Table 1) and documented include: sun precautions (53.3% of patients), annual eye exams (51.1%), vitamin D recommendation (48.9%), calcium recommendation (46.7%), and pneumococcal vaccination (31.1%). Provider global assessment was recorded at least once in 93.3% of patients and patient/parent global assessment in 66.7%. Disease activity and disease damage scores were calculated in 64.4% of patients.

Conclusion: Our pilot study has been successful in developing an educational curriculum for our SLE patients, establishing a process for documenting and tracking educational topics, and creating a method for recording disease activity and disease damage parameters. Baseline performance on these measures is helpful to target areas for future quality improvement efforts.

Table 1 Educational variables from select SLE quality indicators (n = 45)

Educational topics	Number of times discussed (range per person)	Number of patients (%)
Sun precautions	36 (0–4)	24 (53.3%)
Annual eye exams	30 (0–4)	23 (51.1%)
Vitamin D recommendation	26 (0–3)	22 (48.9%)
Calcium recommendation	24 (0–3)	21 (46.7%)
Pneumococcal vaccination	17 (0–3)	14 (31.3%)
Weight management	15 (0–2)	13 (28.9%)
Exercise	26 (0–4)	17 (28.9%)
Smoking avoidance and cessation	15 (0–2)	12 (26.7%)
Hypertension risk	7 (0–2)	5 (11.1%)

Diabetes risk	5 (0–1)	5 (11.1%)
Influenza vaccination	9 (0–4)	5 (11.1%)
Meningococcal vaccination	2 (0–2)	1 (2.2%)
Haemophilus influenzae vaccination	0	0 (0%)

Disclosure: J. G. Harris, None; **E. Roth-Wojcicki**, None; **M. Malloy**, None; **K. I. Maletta**, None; **D. O. Co**, None; **J. C. Olson**, None.

2320

Initial Benchmarking of the Quality of Medical Care of Childhood-Onset Systemic Lupus Erythematosus. Ahmad I. Zaal[1], Rina Mina[1], Simone Appenzeller[2], Julia Harris[3], Marco F. Silva[4], Jiha Lee[5], Prachi Khandekar[6], Maraisa Centeville[2], HaiMei Liu[1], Joshua D. Pendl[1], Anne Johnson[1], Jennifer L. Huggins[1], Raju Khubchandani[6], Stacy P. Ardoin[7], Marisa S. Klein-Gitelman[8], Clovis A. Silva[4] and Hermine I. Brunner[1]. [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil, [3]Children's Hospital of Wisconsin, Milwaukee, WI, [4]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [5]University of Cincinnati Medical Center, Cincinnati, OH, [6]Jaslok Hospital and Research Center, Mumbai, India, [7]Ohio State University College of Medicine, Columbus, OH, [8]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL.

Background/Purpose: Quality indicators (QI) are minimum standards of medical care in support of optimal disease outcomes. In childhood-onset systemic lupus erythematous (cSLE), 26 QI's, which are categorized into nine domains, have recently been developed based on international consensus and scientific evidence. The current level at which these QI's are followed has not been well documented. Hence, the objective of this study is to assess the current quality of medical care received by patients with cSLE at tertiary pediatric rheumatology centers.

Methods: Cross-sectional data pertaining to the QI's were acquired via chart review and analyzed collectively in 483 cSLE patients followed at seven international tertiary pediatric rheumatology centers – four in the United States, two in Brazil, and one in India. All cSLE patients followed in the participating centers were enrolled. The QI's were adjudicated to be satisfactorily met if they were performed and documented for[3] 80% cSLE patients they were applicable for.

Results: Adherence to the QI's varied widely, ranging from 61 to 100%. The QI with the highest adherence (100%) fell under the *Pregnancy* domain. Most of the QI's were satisfactorily met while six QI's were not (Table 1). These six QI's were classified under the following domains: *Medication Management, General Prevention, Lupus Nephritis and Hypertension Management, Bone Health, and Education on Cardiovascular Risk Factors*. Adherence to the QI's was similar across centers, supporting the suitability and appropriateness of the current cSLE QI's for international use.

Conclusion: Based on this benchmarking effort, the medical care of patients with cSLE at the participating international tertiary pediatric rheumatology centers is very good. Further efforts are warranted to improve the performance of several QI's especially those pertaining to *Education on Cardiovascular Risk Factors*.

Table 1 Adherence to the Quality Indicators

Quality Indicators by Domain	Results (%)
Laboratory Testing at Diagnosis and Screening	
Obtained diagnostic/confirmatory labs within first two visits	96
Obtained lab surveillance of complete blood count, renal, liver function test every 12 months	99
General Prevention	
Prescribed influenza and/or encapsulated organisms vaccination, unless contraindicated	85
Discussed and documented education on sun avoidance at least once in the medical record (e.g., wearing protective clothing, applying sunscreens whenever outdoors, and avoiding sunbathing)	82
Discussed transition plan to appropriate adult healthcare providers with patient age $\geq$ 14 years	62
Lupus Nephritis (LN) and Hypertension Management	
Kidney biopsy discussed/ordered/performed if developed proteinuria $>$ 500 mg/day, or worsening glomerular filtration rate (GFR), or urinary sediment	86
Evaluated by a nephrologist in the last year for LN and of hypertension	67
Evaluated by rheumatologist every 3 months in last year if a patient has known LN regardless of disease activity	97
Received kidney biopsy when diagnosed with LN	80
If LN Class III/IV, treated with immunosuppressive and glucocorticoids within 1 month	96
Angiotensin receptor blocker or Angiotensin-converting enzyme inhibitor were prescribed if ongoing proteinuria $>$ 500 mg/day or worsening GFR in last year of care.	94
Check assessments (kidney function, urine sediment, and proteinuria) every three months	89
Medication Management	
If started new medications, discussed risk vs. benefit of therapy	96
Currently prescribed any antimalarial therapy	91
Attempted to taper a dose of steroids not acceptable for chronic use	90
Attempted to taper and unable to decrease steroid; added/ increased steroid sparing agent	61
Surveillance for medication safety done at regular intervals	99
Bone Health	
Received at least one bone mineral density testing DEXA scan	68
Repeat bone mineral density testing if baseline testing outside normal limits (Z score ≤ -2)	80
Prescribed calcium/vitamin D if a patient is on any steroid therapy	88
Ophthalmological Surveillance	
Receives eye exams annually while on anti-malarial therapy	81
Receives eye exams annually while on glucocorticoids	82
Education on Cardiovascular Risk Factors	
Education on cardiovascular risk factors (smoking, hypertension, high body mass index) every 1 year with patient and parent if patient is 13 years or older	68
Discussed lifestyle modifications (smoking cessation, weight control, exercise) every 2 years with parent and patient 13 years or older	70
Pregnancy	
Anti-SSA, anti-SSB and anti-phospholipid antibodies have been assessed during pregnancy	100
Neuropsychiatric Manifestations	
Prescribed Immunosuppressive therapy if patient has major neuropsychiatric manifestations in the last year of care (optic neuritis, coma, psychosis, etc.)	94

Disclosure: A. I. Zaal, None; **R. Mina**, None; **S. Appenzeller**, None; **J. Harris**, None; **M. F. Silva**, None; **J. Lee**, None; **P. Khandekar**, None; **M. Centeville**, None; **H. Liu**, None; **J. D. Pendl**, None; **A. Johnson**, None; **J. L. Huggins**, None; **R. Khubchandani**, None; **S. P. Ardoin**, None; **M. S. Klein-Gitelman**, None; **C. A. Silva**, Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP 11/12471–2), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 302724/2011–7), Federico Foundation and by Núcleo de Apoio à Pesquisa "Saúde da Criança e do Adolescente, 2; **H. I. Brunner**, None, 2.

2321

Quality Improvement in the Identification of Crystals from Synovial Fluid: Hospital Laboratory Versus Rheumatology Department Evaluation. Joanne Szczygiel Cunha[1], Anthony Reginato[2] and Stuart Schwartz[2]. [1]The Warren Alpert School of Medicine at Brown Univeristy, Providence, RI, [2]The Warren Alpert School of Medicine at Brown University, Providence, RI.

Background/Purpose: It has been well studied and accepted that the best method for evaluating joint disease is examination of synovial fluid. Synovial fluid analysis is critical to establish a definite diagnosis, whether the patient has a septic joint or a crystal arthropathy. Our study aims at studying the consistency of crystal identification between the Rheumatology department and the hospital laboratories as well as identifying the factors contributing to the misidentification of crystals.

Methods: A retrospective study of synovial fluid analysis performed by the Rheumatology Department and the Rhode Island Hospital (RIH) laboratories was done over a year. Synovial fluid was gathered by arthrocentesis performed by the Rheumatology faculty for anyone with suspected crystal induced arthritis. Synovial fluid samples were analyzed by an attending physician with a compensated polarized microscope in the office and reviewed by another attending and/or fellow. Synovial fluid sent to the RIH lab was analyzed within the hour. A standard protocol was used for each sample which included cell count and differential. For this analysis the fluid was diluted with normal saline. Afterwards, part of the sample was dry centrifuged to examine for crystals. Both the wet prep of the sample as well as the dry centrifuged slides were examined by laboratory technicians for crystals. Within 24 hours, all dry centrifuged samples were reviewed by a pathologist. **Results** from the Rheumatology department were compared to the laboratory results on the same sample fluids.

Results: A total of 64 synovial fluid samples were examined. 18 discrepancies were found between the Rheumatology Department and the

hospital laboratories. 14 of the samples reviewed by the faculty were found to have crystals, while the laboratory reported these to be negative. A McNemar's test was used to evaluate the data set. For each type of crystal, the p-value was not statistically significant (p-value MSU = 0.45, CPP = 0.07) but the p-value for both crystals was statistically significant at 0.02. Sensitivity for each was calculated, with specificity being 100%, and compared between the faculty and the laboratory. The sensitivity for the detection of any crystals by the faculty was found to be 0.92, while for the laboratory it was 0.66. The sensitivity of MSU crystal detection by the faculty was 0.89 and by the laboratory, 0.74. Similar results were seen for the detection of CPP crystals by the Rheumatologists with the sensitivity being 0.90, while the laboratory's sensitivity was much less, only at 0.57.

Conclusion: The results of our study are consistent with previous studies showing that there are still discrepancies in synovial fluid analysis. Many factors may be contributing to these variations including observer error, differences in time spent examining the fluid, technician training and crystal concentration. When analyzed separately, not all of our findings reached statistical significance, but when examined together, statistical significance was met. We believe that this study has profound clinical significance. Errors in crystal detection can have serious impacts on disease management and patient care.

Disclosure: J. Szczygiel Cunha, None; **A. Reginato**, None; **S. Schwartz**, None.

2322

Aim for Better Gout Control: A Retrospective Analysis of Preventable Hospital Admissions for Gout. Tarun S. Sharma[1], Thomas M. Harrington[2] and Thomas P. Olenginski[2]. [1]Geisinger Medical Center, Danville, PA, [2]Geisinger Health System, Danville, PA.

Background/Purpose: ACR/EULAR guidelines have been published on the management of gout. Despite these guidelines, many patients with gout suffer recurrent flares and hospitalizations resulting in poor disease control and increased health care utilization. We aim to analyze the hospitalizations related to gout, determine whether these admissions were preventable and calculate imputed hospitalization costs.

Methods: A retrospective cohort of adult patients hospitalized at our institution with a primary discharge diagnosis of gout (defined as ICD-9 274, 275 or 712) from 01/01/2009 to 12/31/2013 was constructed (n=79). The primary diagnoses were validated and preventable admissions ascertained on chart review. A preventable admission was defined as an admission where the primary admitting diagnosis was a mono or polyarthritis subsequently diagnosed as gout on hospitalization and without any concomitant illness on presentation warranting admission. We reported demographic characteristics, including clinical diagnosis on admission, prior history of gout, possible risk factors for gout (Diabetes, Cardiovascular disease, chronic kidney disease, diuretic or low dose aspirin use), gout medications, serum uric acid levels within 1 year prior to admission, timing of arthrocentesis, if done, surgical procedures performed and hospitalization costs.

Results: Fifty six (56) of 79 patients were found to have adjudicated primary diagnosis of gout. Of these 56 gout admissions, 50 (89%) met the definition of preventable admission. On admission, the clinical diagnosis was septic arthritis (76%), inflammatory polyarthritis (14%) or cellulitis (8%). Of the 50 preventable admissions, 33 patients underwent arthrocentesis, 24 of which were performed in the Emergency Room. Thirty-five (35) patients (70%) had a previous history of gout and 21 (42%) had ≥3 risk factors for gout. Of the 35 patients with a prior history of gout, 74% were managed by primary care, whereas 26% were being managed by rheumatology. Of the 26 patients managed by family physicians, 8 (31%) were on urate lowering therapy (ULT) and 5 (19%) were on colchicine prophylaxis. Twenty three serum uric acid levels within 1 year of the date of hospitalization were recorded of which 18 (78%) were not at goal of <6 mg/dL. Of 15 patients on long term gout treatment, 33% were non-compliant. Three (3) patients underwent orthopedic procedures: toe amputation (1), arthroscopic debridement (2) and were subsequently diagnosed as gout.

Total additive length of stay for the preventable admissions was 171 days (mean 3.42 days). Total hospitalization-related-costs were $208,000 with average cost per admission of $4160.

Conclusion: We conclude that 89% of the hospitalizations with primary diagnosis of gout were preventable. Defined gaps in clinical care include: ACR/EULAR guidelines not followed, lack of crystal-confirmed diagnoses, patients presenting to emergency room for care, and medication non-compliance. Consequently, this population incurred unnecessary health care costs in the emergency room and costly and preventable admission care expenditures. Steps to reassess the care of gout at our institution have begun as a direct result of these study findings.

Disclosure: T. S. Sharma, None; **T. M. Harrington**, None; **T. P. Olenginski**, None.

2323 WITHDRAWN

2324

Only 30% Rheumatologists Collect Basdai in Patients with Axial Spa in Daily Practice: The Potential Role of a Consensual Meeting to Improve It. Hélène Che[1], Adrien Etcheto[1], Emmanuelle Dernis Labous[2], Henri Nataf[2], Patrick Boumier[2], Philippe Breuillard[2], Marianne Durandin-Truffinet[2], Jacques Fechtenbaum[1], Veronique Gaud-Listrat[1], Bernard Giraud[2], Christophe Hudry[2], Sylvain La Batide Alanore[2], Patricia Le Devic[2], Patrick Le Goux[2], Agnes Lebrun[1], Emmanuel Maheu[2], Bertrand Moura[2], Minh Nguyen[2], Antoinette Sacchi[2], Xavier Ayral[2], Anne Blanchais[1], Severine Neveu[1], Maxime Dougados[3] and Anna Molto[3]. [1]Université Paris René Descartes and Hôpital Cochin, Paris, France, [2]Réseau Hôpital et Ville en Rhumatologie (RHEVER) Network, Paris, France, [3]INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France., Paris, France.

Background/Purpose: The current recommendations for optimal monitoring of axial spondyloarthritis (SpA) are to assess regularly disease activity. The two proposed tools comprise clinical aspects as well as laboratory abnormalities, e.g. BASDAI and C-Reactive Protein, or ASDAS [1].

To evaluate the tools used by rheumatologists in axial SpA patients in their daily practice and the potential interest of a meeting during which rheumatologists achieved a consensus on the tools to be used for such monitoring after a presentation of a systematic literature review (consensual meeting).

Methods: The medical chart of out-patients seen by rheumatologists (office-based or hospital-based) have been checked by an independent investigator. The patients had to have visited twice the same rheumatologist within one year (within six months before and after the consensual meeting) to be retained for this analysis For each visit, the existence of the following informations in the medical chart (BASDAI score, CRP, ASDAS score) were collected.

Results: In total, 456 medical charts issued from 228 patients (mean age: 44.6 (±12.6) years old, 147 (64.5%) males, mean disease duration: 11.7 (±10.7) years) who visited 23 rheumatologists (9 (39.1%) hospital-based and 14 (60.9%) office-based, mean age 51.6 (±10.3) years old and with 22.2 (±10.1) median years of practice of rheumatology), visiting a mean of 62 (±37.1) patients per week of whom 17.8% were diagnosed with axial spondyloarthritis) were reviewed.

Before the consensual meeting, the frequency of reported tools in the medical chart was 65 (28.5%), 117 (51.3%), 38 (16.7%) and 2 (0.9%) for BASDAI, CRP, BASDAI and CRP and ASDAS respectively. After the consensual meeting, these frequencies changed to 118 (51.7%), 119 (52.2%), 72 (31.6%) and 14 (6.1%) respectively.

An increase in the frequency of the reported tools, was more frequently observed in office-base rheumatologists (e.g. BASDAI score from 32 (23.2%) to 70 (50.8%) medical charts, before and after the consensual meeting, respectively).

Conclusion: This study suggests that 1) despite existing recommendations, tools permitting the evaluation of disease activity are not frequently collected in daily-practice and 2) a reminder through regular meetings could be considered in order to improve this situation.

Reference

[1] Smolen et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. Ann Rheum Dis. Jan 2014; 73(1): 6–16

Disclosure: H. Che, None; **A. Etcheto**, None; **E. Dernis Labous**, None; **H. Nataf**, None; **P. Boumier**, None; **P. Breuillard**, None; **M. Durandin-Truffinet**, None; **J. Fechtenbaum**, None; **V. Gaud-Listrat**, None; **B. Giraud**, None; **C. Hudry**, None; **S. La Batide Alanore**, None; **P. Le Devic**, None; **P. Le Goux**, None; **A. Lebrun**, None; **E. Maheu**, None; **B. Moura**, None; **M. Nguyen**, None; **A. Sacchi**, None; **X. Ayral**, None; **A. Blanchais**, None; **S. Neveu**, None; **M. Dougados**, None; **A. Molto**, None.

ACR/ARHP Poster Session C
Rehabilitation Sciences (ARHP)
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

2325

A Systematic Review of the Educational Approach of Occupational Therapy for Rheumatoid Arthritis. Kristine Carandang and Elizabeth Pyatak. University of Southern California, Los Angeles, CA.

Background/Purpose: In order to enhance daily functioning for patients with chronic conditions, occupational therapists employ a range of techniques and strategies. Among these strategies, interventions within the educational approach have been reported as having limited to no evidence despite being used regularly in clinical practice (Steultjens, et al. 2002). Over a decade later, this study seeks to provide an update of current literature through the following aims: (1) to identify occupational therapy interventions that target patients with rheumatoid arthritis (RA) and (2) to systematically review the effectiveness of the identified interventions that utilize an educational approach.

Methods: To fulfill the first aim, a list of the most commonly used occupational therapy textbooks was obtained, and textbooks were searched for interventions targeting patients with RA. Data were grouped and categorized into specific intervention domains. To fulfill the second aim, MedLine, CINAHL, and select occupational therapy journals, were searched utilizing designated medical subject headings. Inclusion criteria were randomized control trials of educational interventions determined within the first aim, published between 2002 and 2013, and included adult participants (over 18 years old) diagnosed with RA. Study characteristics were extracted, and individual studies were reviewed for 6 criteria to determine methodological risk of bias. Studies lacked sufficient construct and assessment agreement to conduct a meta-analysis; therefore, a between-studies qualitative synthesis was conducted to determine levels of evidence for primary outcomes designated within individual trials.

Results: Twelve intervention categories emerged within the occupational therapy scope of practice, including four within the educational approach. 375 articles were screened and 21 studies (2478 participants) were included for data extraction (see Table for overview of characteristics). The identified studies evaluated a wide range of outcomes using diverse measures (over 30 assessments of pain, fatigue, disease activity, functional status, and psychosocial constructs). Interventions that utilized a combination of educational techniques demonstrated strong evidence to improve disease knowledge and disease activity, as well as psychosocial interventions to improve pain and disease activity. Moderate evidence was found for the effectiveness of joint protection/energy conservation on joint protection behaviors. Limited or no evidence existed for the remaining outcomes.

Conclusion: Although the number and quality of studies evaluating educational interventions have increased, there continues to be limited evidence that these approaches impact meaningful outcomes for patients with RA.

Reference:
Steultjens EMJ et al. Arthritis Care Res 2012; 47:672–85.

Intervention Category (Number of Trials)	Examples of Interventions	Individual Trial Quality Analysis Risk of Bias*			Between Trials Analysis *Levels of Evidence***; Trial Outcome Measures (Primary constructs only)
		Low	High	Unknown	
Disease Education (3)	• Drug information leaflet • Weekly educational program			3	• *Level 3:* Quality of life • *Level 4:* Disease specific knowledge
Pain Management (1)	• Pain Coping Skills Training	1			• *Level 3:* Joint pain; Problem-focused coping; Emotion-focused coping; Coping efficacy • *Level 4:* Pain days; Mood
Psychosocial Intervention (4)	• Autogenic training • Written disclosure • Spoken disclosure	2	2		• *Level 1:* Pain rating; Disease activity • *Level 3:* Mood; Anger; Tension • *Level 4:* Quality of life
Joint Protection & Energy Conservation (3)	• Individual joint protection sessions w/theoretical base	1	2		• *Level 2:* Joint protection behaviors • *Level 3:* Pain rating; Patient health status; Physical function; Self-reported symptoms; Social interaction • *Level 4:* Disease activity; psychological functioning; Work
Combination (10)	• Cognitive behavioral therapy • Multidisciplinary education • Therapeutic education & functional readaptation	8	1	1	• *Level 1:* Disease knowledge; Disease activity • *Level 3:* Physical functioning; Psychological functioning; Social functioning; Fatigue impact • *Level 4:* Pain rating; Patient health status; Functional status; Overall symptoms

*Risk of bias criteria obtained from Cochrane's quality checklist for randomized studies:
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

** Criteria for levels of best evidence obtained from previous exemplar study:
van Tulder, M. W., Cherkin, D. C., Berman, B., Lao, L., & Koes, B. W. (1999). The effectiveness of acupuncture in the management of acute and chronic low back pain: a systematic review within the framework of the Cochrane Collaboration Back Review Group. *Spine*, *24*(11), 1113-1123.

Disclosure: K. Carandang, None; **E. Pyatak**, None.

2326

Investigation of Parameters Used to Test Quadriceps Muscle Power Using Isokinetic Dynamometer in Arthritis. Maria Beatriz Catelani, Samannaaz S. Khoja, Gustavo J. Almeida and Sara R. Piva. University of Pittsburgh, Pittsburgh, PA.

Background/Purpose: Muscle power (MP) plays an important role in daily activities that require force generated at fast speeds such as climbing stairs. MP is decreased in individuals with arthritis and its contribution to disability has been suggested to be above that of muscle weakness. Yet, there is no consensus on testing parameters such as angular speed and muscle contraction curve to assess MP using isokinetic dynamometers. The purpose of this study was to investigate testing parameters used to assess quadriceps MP in subjects with arthritis. Aim 1 tested the associations of angular speed (or slope of angular speeds) and muscle contraction curve with a well-accepted performance-based measure of MP – the stair climbing test (SCT). Aim 2 investigated whether MP explains variability in SCT beyond that of demographic variables related to muscle performance and muscle strength.

Methods: Adults diagnosed with rheumatoid arthritis were invited to participate. This cross-sectional study used an isokinetic dynamometer to measure quadriceps maximal voluntary isometric contraction (MVIC) and MP. MP was measured using four angular speeds of contraction (240, 180, 120, and 60 degrees per second). Then, values of MP were retrieved from the dynamometer using 3 methods: 1) MP of the whole muscle contraction curve (maximum knee flexion to knee extension); 2) MP of partial curve up to peak torque (maximum knee flexion to peak torque), and 3) MP of partial curve deleting 10° of acceleration and deceleration from whole curve. We also calculated power slopes using MP of the 4 speeds for each curve method. SCT was measured in seconds as the time to go up 11 steps. Bivariate correlations were calculated to determine the associations between SCT and MP at the 4 angular speeds and power slope for each curve method. Separate hierarchical regression models were built to determine the contribution of each method to measure MP on SCT after controlling for age, gender, BMI, and MVIC.

Results: Sixty one subjects participated (age 59 $\pm$ 1 years, 82% female, BMI 31 $\pm$ 0.9 kg/m^2). All bivariate correlations coefficients between MP and SCT were significant and ranged from -.35 to -.54 ($p < 0.001$). Hierarchical regression analyses demonstrated that age, gender, and BMI explained 46% of variability in SCT. After adjusting for these variables, MP explained significant variability in SCT regardless of the angular speed or curve method used (7% to 17%). In separate regression models, after adjusting for demographics, MVIC was added and explained additional 15% of variability. Then, MP measures were added to the models. The only variable that contributed significantly to SCT in this model was the MP slope measured by the curve method that excluded acceleration/deceleration (Beta -.326; $p=0.027$).

Conclusion: The contribution of MP to SCT was beyond demographics and muscle strength only when measured as MP slope (combining all angular speeds) and used the curve method that discarded acceleration/deceleration. When measuring MP, utilization of MP slope rather than a single speed of contraction and carefully selection of the curve method are encouraged.

Disclosure: M. B. Catelani, None; **S. S. Khoja**, None; **G. J. Almeida**, None; **S. R. Piva**, None.

2327

Delivering *ESCAPE-Pain (Enabling Self-Management and Coping of Arthritic Pain through Exercise)* - an Online Guide for Healthcare Professionals. Michael V. Hurley[1], Andrea Carter[1], Des Carter[1], Lonan Hughes[2], Aoife Ni Mhuiri[2] and Nicola E. Walsh[3]. [1]Health Innovation Network South London, London, United Kingdom, [2]Salaso Health Solutions, Tralee, Ireland, [3]University of the West of England Bristol, Bristol, United Kingdom.

Background/Purpose: Worldwide, chronic joint pain is a major cause of suffering, impaired mobility, physical and psychosocial function, quality of life, dependency and healthcare expenditure. *Enabling Self-management and Coping of Arthritic Pain through Exercise (ESCAPE-pain)* is a programme that integrates the core interventions recommended by clinical management guidelines - patient education, self-management, coping strategies and exercise. Robust evaluation shows ESCAPE-*pain* is more effective and cost-effective than usual care, has sustained benefits, is popular with patients and therapists and reduces healthcare costs. Wide implementation would enable many more people to benefit from the *ESCAPE-pain*programme.

Objective: To facilitate implementation of *ESCAPE-pain*by developing a "free to access" website that encapsulates the programme's ethos, description, content and format for healthcare professionals (HCP) who want to deliver the programme.

Methods: Focus groups and interviews were held with approximately 30 HCPs to determine what information they required in order to deliver *ESCAPE-pain*. Using this information a clinical web and multimedia content development team constructed a prototype website describing the content, format and practicalities of delivering *ESCAPE-pain*. "Think aloud" interviews were conducted with 10 HCPs experienced in delivering *ESCAPE-pain*

and 10 HCPs with no experience of delivering the programme. Field notes of user's likes, dislikes, preferences, difficulties and opinions of the website were recorded, analysed, summarised and feedback to the web-developers who revised the to incorporate this feedback. The users re-evaluated the revised website and from their comments an updated website produced.

Results: The opinions of HCPs guided the content and aesthetic format of a website describing delivery of the *ESCAPE-pain* programme. HCPs experienced in delivering *ESCAPE-pain* determined the information they considered needed to encapsulate the ethos of ESCAPE-pain, detail the essential content and format. The final website contains videos of the programme in action (exercise and education sessions), contains the resources required to deliver the programme (downloadable therapist and patient handbooks), PDFs of research evidence-base. Users can feedback the experiences of patients and therapists to improve the programme and website. The opinions of clinicians who had never delivered *ESCAPE-pain* tested the website to ensure it contained and conveyed the information necessary to enable "naïve" clinicians to set up and deliver *ESCAPE-pain*.

Conclusion: Through an iterative process, clinicians and a clinical web and multimedia development team collaborated to produce a website describing the content, format and resources required to implement *ESCAPE-pain*. Making access to the website, the downloadable resources and permission to deliver the *ESCAPE-pain*programme completely free available will facilitate implementation of the programme enabling many more people to benefit.

The website is available at www.escape-pain.org.

Disclosure: M. V. Hurley, None; **A. Carter**, None; **D. Carter**, None; **L. Hughes**, None; **A. Ni Mhuiri**, None; **N. E. Walsh**, None.

2328

The Physical and Psychosocial Effects of Exercise on Chronic Hip and Knee Pain: A Cochrane Review with Meta-Analysis. Professor Mike Hurley[1], Dr Nicola E. Walsh[2], Sandy Oliver[3], Hanan Hauari[3], Kelly Dickson[4], Robert Grant[1] and Jo Cumming[5]. [1]St George's University of London and Kingston University, London, United Kingdom, [2]University of the West of England, Bristol, United Kingdom, [3]Institute of Education University of London, London, United Kingdom, [4]Institute of education University of London, London, United Kingdom, [5]Arthritis Care, London, United Kingdom.

Background/Purpose: Chronic peripheral joint pain is extremely prevalent and a major cause of physical and psychosocial problems. Exercise improves pain and physical function, but the effect of exercise on psychosocial function (health beliefs, depression, anxiety and quality of life) is unknown. To improve our understanding of the inter-relationship between pain, physical and psychosocial function and exercise we conducted a Cochrane Review with meta-analysis of clinical trials that reported the effect of exercise interventions on psychosocial variables.

Methods: Twenty three clinical, public health, psychology, social care databases and 25 other relevant resources were searched. References of included studies were checked for relevant studies. Key experts were asked about unpublished studies. Quantitative synthesis of randomised controlled clinical trials of exercise-based rehabilitation programmes for chronic peripheral joint pain was conducted. Four of the authors independently assessed studies against inclusion/exclusion criteria and methodological quality, and entered extracted data into a database.

Results: Twenty four trials (with 2640 participants) met criteria for inclusion in the quantitative synthesis. There were large variations in the exercise programme's content, mode of delivery, frequency and duration, participant's symptoms, duration of symptoms, outcomes measured, methodological quality and reporting. Design and reporting of the trials was moderate/good, though some were ambiguous, complex and difficult to understand. Many of the trials small (less than 50 participants per group) with low power to detect medium effect size. Outcome measures were heterogeneous, often self-reported, subject to recall and socially desirable biases. Most of the trials reported changes immediately after completing an exercise programme, or had short (less than 6 months) follow-up.

Exercise reduced pain (SMD, 95% CI: −0.22, −0.36 to −0.08), improved physical function (−0.20, −0.31 to −0.09), self-efficacy (0.41, 0.24 to 0.57) and depression (−0.16, −0.28 to −0.03) but not anxiety (−0.38, −1.13 to 0.36). The effect of exercise on health-related quality of life measured in few studies using the SF-36 with significant benefit on social function (6.58, 2.78 to 10.38), borderline significance in mental health (2.90, 0.15 to 5.65), non-significant effect on role emotional (1.20, −4.12 to 6.53) and vitality (3.90, 0.55 to 7.25).

Conclusion: Exercise not only improves pain and physical function, but also has moderate benefits on psychosocial functioning and quality of life. Heterogeneity in the programmes and lack of well-designed trials with psychosocial variables as the primary outcome impedes our understanding. In addition, whether and how to enhance moderate treatment effects, and sustain improvements needs to be determined.

Disclosure: P. M. Hurley, None; **D. N. E. Walsh**, None; **S. Oliver**, None; **H. Hauari**, None; **K. Dickson**, None; **R. Grant**, None; **J. Cumming**, None.

2329

Course and Outcome of Rehabilitation Care in Different Rheumatological Diagnosis Groups. a Descriptive Study Using the STAR-Etic Registry. Elisabet Lindqvist[1], Margreth Grotle[2], Kim Hoerslev-Petersen[3], Theodora P.M. Vliet Vlieland[4] and Ann B. I. Bremander[5]. [1]Lund University and Skåne University Hospital, Lund, Sweden, [2]National Resource Centre for Rehabilitation in Rheumatology, Diakonhjemmet Hospital, N-0319 Oslo, Norway, [3]Research Unit at King Christian X Hospital for Rheumatic Diseases, Graasten, Denmark, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Spenshult Research and Development Center, Halmstad, Sweden.

Background/Purpose: The frequency of admission to rehabilitation varies among countries but also among diagnosis groups. So far research describing and comparing the rehabilitation in various diagnosis groups using a similar set of endpoint measures is missing.

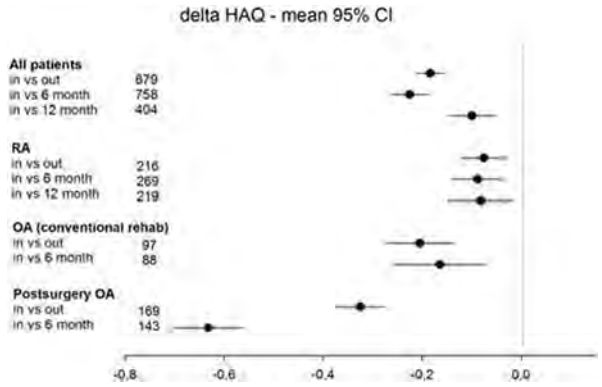
Aim: To describe the course and outcome of rehabilitation care in different rheumatological diagnosis groups.

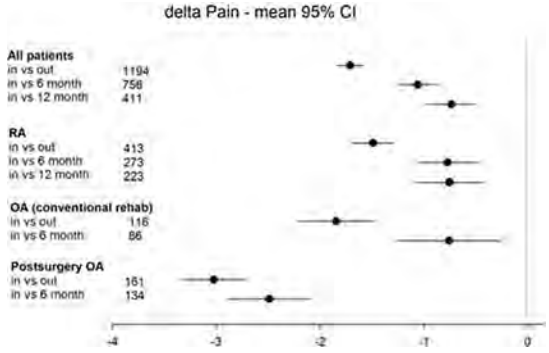
Methods: Multicenter prospective observational study in 4 North-European countries (18 study sites) including patients with various rheumatic diseases admitted for rehabilitation. Assessments were done at admission, discharge and after 6 and 12 months. Assessments included pain, fatigue (numeric rating scales, NRS, 0–10), physical functioning (Health Assessment Questionnaire, HAQ, 0–3), Quality of Life (EQ-5D and SF-36). In addition, at baseline sociodemographic and health characteristics were recorded. Moreover, the setting and duration of the rehabilitation were registered. Comparisons of baseline characteristics among diagnosis groups were made using multivariate or logistic regression analysis. Changes over time were analysed within diagnosis groups using analysis of variance, including all available data.

Results: 1215 patients were evaluated. The different diagnosis groups were Rheumatoid arthritis, 418 patients, Spondylarthropathies, 300 patients, systemic rheumatic diseases, 104 patients, unspecified arthritis, 22 patients, fibromyalgia/chronic pain 45 patients, non-inflammatory back pain, 26 patients and osteoarthritis 119 patients. 181 patients participated in rehabilitation post large joint surgery of which 171 patients were diagnosed with osteoarthritis and the 10 remaining patients had an inflammatory arthritis.

In all diagnosis groups, patients improved significantly between baseline and the discharge assessments in pain, fatigue, HAQ. The mean change in pain was -1.7 (confidence interval (CI) −1.8 - −1.6), in fatigue −1.6 (CI −1.7 - −1.5) and in HAQ −0,18 (CI −0.21 - −0.16). After 6 months the mean change from baseline in pain was −1.1 (CI −1.2 - −0.9), in fatigue −0.7 (CI −0.9 - −0.5) and in HAQ −0.22 (CI −0.26 - −0.19). The improvements were similar in all diagnosis groups except for the post-surgery osteoarthritis patients where the improvements were remarkably higher.

Conclusion: Using a standardized framework across diagnosis groups we were able to demonstrate improvement after rehabilitation within 10 rheumatological diagnosis groups. The use of similar endpoint measures in national registries is advocated. It is of importance to register all treatments apart from drugs.





Disclosure: E. Lindqvist, None; **M. Grotle**, None; **K. Hoerslev-Petersen**, None; **T. P. M. Vliet Vlieland**, None; **A. B. I. Bremander**, None.

2330

Construct Validity of the Adult Myopathy Assessment Tool in Individuals with Inclusion Body Myositis. Michael Harris-Love[1], Galen Joe[2], Todd Davenport[3], Joseph Shrader[2], Beverly McElroy[2], Goran Rakocevic[4], Olavo Vasconcelos[5] and Marinos Dalakas[4]. [1]VA Medical Ctr, Washington, DC, [2]National Institutes of Health, Bethesda, MD, [3]University of the Pacific, Stockton, CA, [4]Thomas Jefferson University, Philadelphia, PA, [5]Richmond Veterans Affairs Medical Center, Richmond, VA.

Background/Purpose: The Adult Myopathy Assessment Tool (AMAT) is a 13-item performance-based battery developed to assess function and anaerobic endurance in adults with muscle disease. The AMAT has been shown to be a valid assessment of physical status in people with neuromuscular disease, and has demonstrated intrarater and interrater reliability among clinicians rating patients with idiopathic inflammatory myopathy. The purpose of this study was to determine the construct validity of the AMAT in patients with sporadic inclusion body myositis (sIBM).

Methods: The AMAT was administered to 43 participants with sIBM (31 men, 12 women; age: 66.0 ±7.5 years; disease duration: 9.9 ±4.3 years) by a single practitioner at a Federal hospital. Peak isometric force measurements were obtained using quantitative muscle testing, and temporal characteristics of gait during habitual and fast walking conditions were measured using a portable gait analysis system. The participants also completed assessments for depression (Beck Depression Inventory), psychosocial fatigue (Fatigue Severity Scale), physical activity levels (Human Activity Profile), and self-reported physical status (36-item Short Form Health Survey, Ver. 2, Physical Component Summary).

Results: The participants attained a mean AMAT score of 30.1 (±5.7; range, 18–44). AMAT scores were significantly associated with strength ($r = 0.40$–0.43, $p < 0.01$), gait speed ($r = 0.69$–0.73, $p < 0.001$), physical activity levels ($r = 0.67$, $p < 0.001$) and self-reported physical status ($r = 0.50$, $p < 0.005$), but not depression or psychosocial fatigue (p 0.05). These relationships were independent of age, disease duration, and age of onset. No floor or ceiling effects were observed as no participant attained the minimum or maximum score (0–45).

Conclusion: The construct validity of the AMAT is supported by its significant associations with muscle strength, functional performance, physical activity, and self-reported physical status. However, anaerobic endurance as measured by the AMAT differs from estimates of psychosocial fatigue in our sample. The AMAT is a standardized, performance-based tool that may be used to assess functional limitations and anaerobic endurance in patients with sIBM.

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2331

People's Views, Beliefs and Experiences of Exercise for Chronic Hip and Knee Pain: Cochrane Review with Qualitative Synthesis. Professor Mike Hurley[1], Kelly Dickson[2], Hanan Hauari[3], Dr Nicola E. Walsh[4], Robert Grant[1], Jo Cumming[5] and Sandy Oliver[3]. [1]St George's University of London and Kingston University, London, United Kingdom, [2]Institute of education University of London, London, United Kingdom, [3]Institute of Education University of London, London, United Kingdom, [4]University of the West of England, Bristol, United Kingdom, [5]Arthritis Care, London, United Kingdom.

Background/Purpose: Chronic peripheral joint pain is extremely prevalent and a major cause of physical and psychosocial dysfunction. Exercise improves pain and physical function, but the effect of exercise on psychosocial function (health beliefs, depression, anxiety and quality of life) is unknown. To improve our understanding of the inter-relationship between pain, physical and psychosocial function and exercise we conducted a Cochrane Review of qualitative studies that reported people's views, beliefs, feelings and experiences of exercise.

Methods: Twenty three clinical, public health, psychology, social care databases and 25 other relevant resources were searched for relevant studies. Two reviewers independently read and extracted data and used a thematic analysis to match the data against a conceptual framework and identify broad themes and sub-themes. Reviewers compared their individual coding, considered the extent to which each sub-theme was mutually exclusive and how they understood the data in relation to their individual coding. They reached a consensus on which *a priori* themes were supported by the data, and whether new themes identified by the reviewers did actually map to the pre-existing broad theme. This approach has provided a clear path from the original research data, to individual study author's descriptions and analyses to the findings of the qualitative review synthesis.

Results: Nine studies met the inclusion criteria. Their design, methodological rigor and reporting was good. Most of the studies gave clear descriptions of their methodology, clearly reported their findings, and took steps to ensure transparency and minimise the bias arising from researcher's values and opinions in their reporting, interpretation and conclusions.

Chronic hip and knee pain affects all domains of people's lives. Beliefs about chronic pain shaped people's attitudes and behaviors about how to manage their pain. With little information or advice from healthcare professionals people attributed joint pain to "wear and tear", ageing processes and/or familial disposition. Physical activity was often associated with onset or increase in pain and interpreted as causing additional joint damage, so people avoided activity for fear of causing additional harm.

People's views about their symptoms, health beliefs and psychosocial experiences revealed implications for practice which included: providing people with more and better information and advice about the safety and benefits of exercise; tailoring exercise to ensure they are enjoyable and seen by people as being relevant; challenging unhelpful health beliefs; providing practical support.

Conclusion: The uptake and effectiveness of exercise might be improved by challenging inappropriate health beliefs, providing better information and advice about the safety and value of exercise, tailoring exercise programmes to individual's preferences, abilities and needs and provide better support.

Disclosure: P. M. Hurley, None; **K. Dickson**, None; **H. Hauari**, None; **D. N. E. Walsh**, None; **R. Grant**, None; **J. Cumming**, None; **S. Oliver**, None.

2332

Use of Wrist Hand Orthoses during Hand Function Skills and Functional Tasks By Adults with and without Rheumatoid Arthritis. Janet L. Poole[1], Kelly Nunez[2] and Patricia Burtner[3]. [1]University of New Mexico, Albuquerque, NM, [2]Veteran's Administration Medical Center, Albuquerque, NM, [3]University of New Mexico, Greenbank, WA.

Background/Purpose: To determine changes in muscle activation in the upper extremity using electromyography (EMG) when static and dynamic orthoses are worn by adults with and without rheumatoid arthritis (RA) during hand function skills and functional tasks.

Methods: Ten adults with Rheumatoid Arthritis and five controls were tested in four orthosis conditions (no, static, hinged, spiral) during hand function measures of grip, pinch and dexterity as well as functional tasks of drinking from a 12 ounce soda can, pouring from a 1 liter pitcher, turning a knob on a simulated door, and inserting a coin in a slot. Each participant completed three trials for the strength, dexterity and functional tasks. The order in which the orthoses were worn and was counterbalanced to control for effects of practice and fatigue. Muscle activity of eight muscles involved with reach and grasp were recorded in the dominant upper extremity using surface electromyography (EMG) during execution of the hand function measures and functional tasks. Computer software calculated average integrated EMG of muscles for each participant in each orthosis condition for each measure and functional task which were converted to percentage of maximum voluntary contraction (%MVC). EMGs by shoulder, elbow and wrist muscle groupings were expressed as combined %MVC during grip, pinch, dexterity and functional tasks and were compared across orthotic conditions using multivariate analyses of variance (MANOVAs).

Results: Orthosis use on individuals with RA and controls did not increase or hinder grip or pinch strength or increase speed in dexterity tasks.

Compared to the controls, adults with RA demonstrated lower strength on grip and pinch measures and took longer to complete the dexterity task in all orthosis conditions ($p < .05$). Other group differences were noted in muscle activation (% MVC in shoulder, elbow and wrist muscles) with individuals with RA having less muscle recruitment than controls in all strength, dexterity and functional tasks and in all orthosis conditions ($p < .05$). EMG differences varied when individuals wore orthoses. During grip, wrist and elbow muscle recruitment was greater than shoulder muscles in both groups in all orthosis conditions. Increased muscle activation in all muscles was noted during two point pinch in both groups when orthoses were worn ($p < .05$). When all subjects wore orthoses, muscle activation decreased at the wrist during drinking ($p < .01$). Similarly, individuals used more muscle activation in all muscles during pouring when no orthosis was worn ($p < .05$). There were no differences in EMG activity between the groups or orthosis conditions for turning the door knob or inserting a coin.

Conclusion: Adults with RA showed less muscle activation than controls during all strength, dexterity, and functional tasks. Both groups had greater EMG activity in the elbow and wrist as compared to the shoulder muscles in all orthosis conditions. Our findings suggest therapists might want to consider the type of tasks their patients need to perform when recommending orthoses as muscle activation may vary depending on the tasks.

Disclosure: J. L. Poole, None; **K. Nunez**, None; **P. Burtner**, None.

2333

The Natural Use of Activity Pacing in Daily Life Does Not Result in Lower Symptoms in Osteoarthritis. Susan L. Murphy[1], Anna Kratz[1] and Mark P. Jensen[2]. [1]University of Michigan, Ann Arbor, MI, [2]University of Washington, Seattle, WA.

Background/Purpose: To examine the how individuals naturally use the behavioral strategy of activity pacing in daily life and how its usage relates to pain and fatigue within days among older adults with knee or hip osteoarthritis. Specifically, we hypothesized that pain and fatigue increases would precede increased natural use of pacing (i.e., pacing behavior would be symptom-contingent) and that individuals would experience a "pay-off" from pacing in that pain and fatigue would decrease after using pacing.

Methods: Participants ($N=147$) were community-living adults 65 years and older who reported mild to moderate pain severity with evidence of osteoarthritis in a corresponding hip or knee joint. Participants wore a wrist-worn accelerometer for five days and were asked to report frequency of activity pacing behaviors (modified from the activity pacing scale of the Chronic Pain Coping Inventory), pain severity, and fatigue severity five times per day. Physical performance and survey data were also collected.

Results: Multi-linear mixed models ($N = 147$), including key demographic and clinical variables, showed that both pain and fatigue increases were associated with subsequent increased use of natural pacing. The increased use of pacing was associated with subsequent increases in both pain and fatigue.

Conclusion: The natural use of pacing appears to be symptom-contingent which is different from how pacing is taught as part of behavioral treatment. Natural use of pacing was not shown to be adaptive in terms of short-term symptom reduction; rather self-reported pacing behaviors were related to increased symptoms. Future studies are warranted to further examine these relationships by capturing more complex contextual issues such as medication effects, social context, and momentary mood.

Disclosure: S. L. Murphy, None; **A. Kratz**, None; **M. P. Jensen**, None.

2334

Understanding the Experiences of Rural Community-Dwelling Older Adults in Using a New DVD-Delivered Otago Exercise Programme. Arun Agha, Teresa Liu-Ambrose, Catherine Backman and Linda C. Li. University of British Columbia, Vancouver, BC.

Background/Purpose: Arthritis is known to increase the risk of injurious falls. The home-based Otago Exercise Programme (OEP) has been shown to reduce the occurrence of falls in community-dwelling seniors. We recently developed a new OEP DVD that was designed to be delivered with minimal coaching by a physiotherapist (PT), for people living in rural communities. The current study aimed to: 1) understand older adults' experiences in using the DVD-delivered OEP, and 2) explore barriers and facilitators to implementing the DVD-delivered OEP from the participants' perspectives.

Methods: Thirty-two rural community-dwelling older adults (≥75 years old) who participated in a 6-month DVD-delivered OEP study were invited to participate in this qualitative study. Two small group interviews were initially conducted to explore the breadth of participants' experiences with the program. These were followed by semi-structured individual interviews to gain an in-depth understanding of these experiences. An inductive constant comparison analysis involving coding of transcripts was performed. Methodological rigour was ensured through field note taking, journaling and maintaining an audit trail. Further, peer-review was performed to detect issues in the analysis such as overemphasized or underemphasized points, vague descriptions, and assumptions made by the researcher.

Results: Five participants partook in group interviews and 16 in individual interviews. Fifteen participants were female; eight participants received at least some university education. Participants' ages ranged from 74 to 97 years. Three themes emerged. Theme 1, 'The OEP DVD: Useful training tool but in need of more pep', reflected participants' experiences that the DVD provided important guidance at program onset, but was too slow and low-energy for longer-term use. Theme 2, 'Providing greater control over one's exercise regimen, but sometimes life gets in the way of staying active', described participants' appreciation of the program's flexibility, but personal health concerns and everyday lives imposed challenges for adhering to the program. Theme 3, 'Social creatures: Wanting greater human connection during exercise', described how some participants desired further social interactions for enhancing motivation and sense of guidance.

Conclusion: In general, participants were positive about the OEP DVD, but it might not be needed once they are familiar with the program. Our findings also suggest that the program should be prescribed with strategies to address barriers to exercising and tips to increase adherence, such as encouraging older adults to exercise with family members or peers.

Disclosure: A. Agha, None; **T. Liu-Ambrose**, None; **C. Backman**, None; **L. C. Li**, None.

ACR/ARHP Poster Session C
Research Methodology (ARHP)
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

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Reliability and Validity of the Arthritis Helplessness Index in Systemic Sclerosis. Shadi Gholizadeh[1], Sarah D. Mills[1], Rina S. Fox[1], Philip J. Clements[2], Suzanne Kafaja[2], Vanessa L. Malcarne[3], Daniel E. Furst[2] and Dinesh Khanna[4]. [1]SDSU/UCSD Joint Doctoral Program in Clinical Psychology, San Diego, CA, [2]University of California, Los Angeles, Department of Medicine, Los Angeles, CA, [3]SDSU/UCSD Joint Doctoral Program in Clinical Psychology; Department of Psychology, San Diego State University, San Diego, CA, [4]University of Michigan Health System, Ann Arbor, MI.

Background/Purpose: The unpredictable and uncontrollable course of rheumatic diseases has made them an interesting area of study in the learned helplessness and health outcomes literature. The Arthritis Helplessness Index (AHI), a 15-item self-report measure of helplessness, was developed to address a gap in the understanding of psychological correlates of rheumatoid arthritis (RA). The AHI was initially conceptualized as a unidimensional measure, however subsequent factor analytic studies identified two subscales: Helplessness and Internality. Though developed and validated in RA patients, the AHI and its adaptation, the Rheumatology Attitudes Index (RAI), have been used across rheumatic conditions, including among patients with systemic sclerosis (SSc). The present study examines the reliability and validity of the AHI among SSc patients.

Methods: A sample of patients ($N= 208$) with physician-confirmed SSc completed the AHI as part of participation in the University of California Los Angeles (UCLA) Scleroderma Quality of Life Study. Baseline data from the study were used to explore the structural validity of the measure via confirmatory and exploratory factor analytic methods. Internal consistency reliability was evaluated with Cronbach's alpha, and convergent validity was explored via Pearson product-moment correlations with measures of depression (CES-D), mental and physical functioning (SF-36v2 Physical and Mental Component Scores, HAQ-DI) and pain (SF-36v2 Bodily Pain).

Results: Because confirmatory factor analysis failed to demonstrate a tenable one or two factor solution, exploratory factor analysis using a geomin-rotated matrix was undertaken to examine the structure of the AHI among SSc patients. A revised two-factor model fit well both statistically (c^2 [19, $N = 208$] = 22.32, $p = .269$), and descriptively (CFI = .985, RMSEA = .029, SRMR = .032). Nine items were retained in the final solution, with the original five Helplessness items comprising Factor 1,

Helplessness, and four of the original seven Internality items comprising Factor 2, Internality. Internal consistency reliability was marginal for both subscales (five-item Helplessness factor: a =. 634; four-item Internality Subscale a =. 634), and convergent validity was supported by significant correlations of AHI scores in the expected directions with the CES-D, SF-36v2 relevant subscale scores, and the HAQ-DI.

Conclusion: The present study derived a revised version of the AHI for use among patients with SSc. Several items that were appropriate for RA patients (e.g., regarding flares) dropped out of the revised version of the measure, suggesting that helplessness is not identical between the two conditions. Although the updated two-factor structure of the shortened nine-item measure fit the data well, it is unlikely that the present measure fully captures the construct of helplessness in SSc. Until future revisions of the measure incorporating patient involvement and input are completed, it is recommended that research examining helplessness in SSc use the updated 9-item, two-factor structure identified in the Arthritis Helplessness Index-Scleroderma version (AHI-SSc).

Disclosure: S. Gholizadeh, None; **S. D. Mills**, None; **R. S. Fox**, None; **P. J. Clements**, None; **S. Kafaja**, None; **V. L. Malcarne**, None; **D. E. Furst**, Abbott, Actelion, Amgen, BMS, Janssen, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB, 5; **D. Khanna**, Actelion, Bayer, Biogen-Idec, BMS, DIGNA, Genentech/Roche, Gilead, InterMune, Merck, Sanofi-Aventis, United Therapeutics, 5, Patient Health Organization, 6, Scleroderma Foundation, 6, K23/K24, 2.

2336

Evaluating the Use of Video-Stimulated Recall to Research the Osteoarthritis Consultation in Primary Care: Reaching Parts Other Methods don't Reach. Zoe Paskins, Tom Sanders, Peter Croft and Andrew Hassell. Keele University, Keele, United Kingdom.

Background/Purpose: Video-stimulated recall (VSR) is a method of enhancing participants' accounts of a consultation using a video recording of the event to encourage and prompt participant recall in a post-consultation interview. VSR is used in education and education research, and to a lesser extent in medical and nursing research, although little is known about the validity, utility and acceptability of the method. This abstract describes an evaluation of the use of VSR in a study of the Osteoarthritis (OA) consultation in primary care in the UK.

Methods: With ethical approval and informed consent, 195 doctor-patient consultations were video-recorded with patients aged ≥ 45. Seventeen consultations in which OA was discussed were the subject of post-consultation interviews using VSR. VSR interviews were conducted with 17 patients and 13 General Practitioners (GPs). Evaluation of the method was achieved by thematic analysis of comments made during video playback, in addition to analysis of observations, field notes, consultation and interview transcripts. Empirical quotes will be presented to illustrate the findings.

Results:

Validity

There was evidence of the video altering both GPs' and patients' behaviour in the consultation with GPs particularly keen to demonstrate 'desirable' behaviours. However, GPs frequently expressed surprise that their actions did not reflect what they felt was best practice, and so we conclude that any altered behaviour would not bias study findings and would likely help interpretation of clinical behaviour during VSR.

Utility

The method was useful to explore meanings behind specific sections of talk in the consultation and both patients and clinicians often adopted a more critical stance to the consultation following playback. VSR resulted in subtly different 'added value' to interviews with patients and doctors. Patients were more empowered to reveal emotional narratives following video playback. VSR gently challenged GPs' descriptions of their "normal" consultations.

Acceptability

Both GPs and patients reported finding the method broadly acceptable with some reporting enjoyment and educational value. However, occasional distress and anxiety occurred in interviews, to which the video playback may have contributed.

Conclusion: This study adds to the existing literature on VSR by describing specifically how this method enables a more critical, specific and in-depth response from participants to events of interest during clinical encounters, and in doing so, generates multiple perspectives on such encounters. The benefits of VSR for clinical and educational research need to be considered in conjunction with the important ethical considerations and the potential for this method to be intrusive.

Disclosure: Z. Paskins, None; **T. Sanders**, None; **P. Croft**, None; **A. Hassell**, None.

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The Cost and Effectiveness of Various Recruitment Strategies in a Mind Body Clinical Trial Among Older Adults with Knee Osteoarthritis. Jade V. Goldsmith, Lori Lyn Price, Jeffrey B. Driban, William F. Harvey and Chenchen Wang. Tufts Medical Center, Boston, MA.

Background/Purpose: Recruitment and adherence are important and challenging factors that can determine the success of a clinical trial. Mind body therapies are an emerging and controversial field; therefore, recruiting people to these types of trials can be difficult. The primary objective of this study was to compare the costs and effectiveness of recruitment strategies employed in a clinical trial of older adults with knee osteoarthritis (KOA). We also sought to determine which recruitment strategies provided the most adherent participants. The aim of these analyses was to identify successful strategies to improve recruitment for future studies.

Methods: We assessed recruitment strategies, cost, and adherence from a clinical trial of Tai Chi and physical therapy among older adults with KOA in the Boston area. All participants met ACR criteria for symptomatic KOA and were recruited between Dec. 2010 and May 2013. Recruitment strategies included: 1) clinical referrals, 2) other referrals (studies, staff, and class members), 3) electronic ads (Patientslikeme, Facebook, Clinicalconnections, clinicaltrials.gov, Craigslist, employee newsletter) and 4) paper ads (local newspapers, flyers). Costs were calculated by adding printing, posting, and personnel expenses. We calculated the percent of participants screened (# screened/prescreen), randomized (# randomized/screen), and able to complete their 12-week evaluation (# 12 week/randomized). We also calculated the yield (# randomized/ total prescreened), cost per randomized participant as well as median adherence to class schedule (# classes attended/total classes).

Results: 1195 people were phone prescreened, 282 were screened in person (mean age 59.7 years) and of these 72% were randomized; the cost per randomized participant was $178.43 (See Table). Sixteen participants were randomized who did not report recruitment source. Paper ads resulted in the highest number of prescreens and randomized participants. Clinical referrals and the senior expo generated the lowest number randomized. The yields for paper, electronic, and other referrals were highest. Clinical referrals resulted in the lowest yield. With the exception of clinical referrals, adherence was high for all recruitment methods as measured by attendance (>79%) and completion of a 12-week evaluation (>76%). Cost per participant was $253.51 for paper and $7.62 for electronic ads. There were no costs associated with referral methods.

Conclusion: Electronic ads are an effective tool in this older population and had minimal cost. Their effectiveness is likely to further increase with time. Paper ads still play a prominent role in effective recruitment. There were no costs associated with clinical referrals but this strategy was not the most effective given the low yield. Additional educational material for clinicians may encourage more referrals.

Table 1. Yield and Cost of Recruitment Strategies in a TaiChi and Physical Therapy Study for Older Adults with Knee Osteoarthritis

	Paper[a]	Electronic[b]	Clinical Referrals	Other Referrals[c]	Senior Expo	Unknown[g]	Total
Telephone Prescreens Completed	695	90	38	87	4	281	1195
In Person Screens Completed	189	29	4	30	2	28	282
Randomized (# randomized/screens completed)	140 (74%)	21 (72%)	3 (75%)	23 (77%)	1 (50%)	16 (57%)	204 (72%)
Attendance (Median)	83.3	87.5	25.0	83.3	79.2	83.3	83.3
12-week evaluation Completed (# 12 week/randomized)	114 (81%)	16 (76%)	2 (66%)	21 (91%)	1 (100%)	13 (81%)	167 (81%)
Cost per Randomized participant	$253.51[d]	$7.62[e]	$0.00	$0.00	$749.00[f]	NA	$178.43
Total Cost	$35,491.50[d]	$160.00[e]	$0.00	$0.00	$749.00[f]	NA	$36,400.50
Yield (# randomized/ # prescreened)	20%	23%	8%	26%	25%	6%	17%

[a]Flyers displayed within the hospital, Metro advertisements, newspapers, magazines
[b]Clinical connections, clinicaltrials.gov, Craigslist, social media, Employee newsletter
[c]Research groups, hospitals, Word of mouth, participant referrals
[d]Advertising fees, staff time, printing, supplies
[e]Advertising fees
[f]Booth fee, staff time, printing, supplies
[g]Participants did not report recruitment method

Disclosure: J. V. Goldsmith, None; **L. L. Price**, None; **J. B. Driban**, None; **W. F. Harvey**, None; **C. Wang**, None.

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Cost-Effectiveness and Yield of Different Recruitment Strategies Utilized in an Exercise Trial of Fibromyalgia Patients. Anna Schmid, William F. Harvey, Lori Lyn Price and Chenchen Wang. Tufts Medical Center, Boston, MA.

Background/Purpose: In a large-scale clinical trial with a long-term outcome, it is essential to use recruitment strategies that are both cost-

effective and likely to yield eligible participants. The objective of this study is to evaluate the different recruitment methods utilized to date in the Tai Chi and Aerobic Exercise for Fibromyalgia study in terms of a.) yield (% prescreened, % screened, and % randomized) and b.) cost-effectiveness.

Methods: All participants were recruited within a 20-month time period between January 2012 and September 2013. Recruitment strategies included 1.) clinical referrals; 2.) word of mouth; 3.) ads posted in electronic sources (Craigslist, Google, NIH website, clinicalconnection.com, clinicaltrials.gov, and Tufts website); 4.) ads placed in a local newspaper, the Boston Metro; 5.) flyers posted in the hospital and in the surrounding neighborhood; and 6.) direct mailings to patients. Recruitment costs were calculated by summing advertising, printing, and personnel costs. Percentages were calculated for prescreened, screened, randomized into an intervention arm, and yield (#randomized/#participants contacted). We compared the strategies in terms of yield and cost-effectiveness.

Results: 492 participants were prescreened, 195 were screened at baseline (40% of prescreened) and 165 (85% of screened) were randomized. Ads placed in the Boston Metro yielded the most randomized participants (76) and second highest percentage of randomized participants per prescreen (38.38%) but also had highest associated costs ($273.65/participant). Mailings to patients produced the second highest number of randomized participants (27) and the highest percentage of randomized participants/prescreen (38.57%) and had much lower associated costs ($23.44/participant). Flyers posted within the hospital and in the surrounding neighborhood generated 32.69% of randomized participants/prescreen, 17 participants, and had associated costs of $17.50/participant. Clinical referrals produced 18 randomized participants (29.03% randomized/prescreen) and had no associated costs. Other referrals generated 2 randomized participants and 12.50% of those prescreened. Electronic ads produced 15 randomized participants, 32.61% of those prescreened by this method, and had no associated costs.

Table 1 Yield and cost of clinical referrals, word of mouth, electronic advertising, advertising in local newspaper, flyers posted in hospital, and direct mailings to patients.

	Clinical referral	Word of Mouth	Electronic ad	Newspaper/ magazine	Flyer	Direct mailing
Participants prescreened	62	16	46	198	52	70
Screened	24	2	18	90	21	30
Randomized	18	2	15	76	17	27
Yield	29.03%	12.50%	32.61%	38.38%	32.69%	38.57%
Cost per enrolled	$0	$0	$0	$273.65	$17.50	$23.44
Total Costs	$0	$0	$0	$20800[a]	$297.45[b]	$632.90[c]

[a]Advertising
[b]Printing, personnel
[c]Printing, personnel, postage

Conclusion: Ads placed in the Metro were significantly more costly than any of the other strategies, but yielded 46.06% of participants randomized in the study. Clinical referrals, word of mouth, and electronic ads were the most cost-effective strategies; however, they yielded the fewest randomized participants. In future studies conducted with this population in this location, a strong recruitment strategy would include placing Metro ads and expanding the patient mailing list and number of referring physicians through the mechanism of educating more physicians about the study.

Disclosure: A. Schmid, None; **W. F. Harvey**, None; **L. L. Price**, None; **C. Wang**, None.

ACR/ARHP Poster Session C
Rheumatoid Arthritis - Animal Models
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

2339

Detecting Inflammation *in Vivo* Using Activatable Fluorescence Contrast Agents in Inflammatory Arthritis. Monica Guma[1], Beatrix Bartok[1], Viet Anh Nguyen Huu[1], Mathieu L. Viger[1], Jacques Lux[1], Shivanjali Joshi-Barr[1], Adah Almutairi[1] and Gary S. Firestein[2]. [1]University of California, San Diego, La Jolla, CA, [2]University of California at San Diego School of Medicine, La Jolla, CA.

Background/Purpose: Current medical imaging technology detects structural rather than functional manifestations of disease. Imaging agents designed to enhance signal based on molecular mechanisms might permit earlier diagnosis and personalized treatment. We examined whether optical contrast agents whose fluorescence properties may be switched from OFF to ON in response to specific biological stimuli can identify inflammation *in vivo* in the murine serum transfer-induced arthritis model.

Methods: Mice were injected with 150 ml of K/BxN sera on day 0. At day 5, mice were injected intravenously with an imaging agent and visualized by IVIS® in vivo imaging system. Clinical arthritis scores were assessed. The imaging agent consists of H_2O_2- and acid-responsive polymeric particles (size: 250 nm) packed with a high concentration of near infrared (NIR) dyes. The close proximity of the dye molecules quenches their fluorescence, thus creating an "off-state". The signal of this agent is "turned on" through the cleavage of protecting moieties on the polymer backbones upon exposure to either H_2O_2 or acidic pH, which reveals hydroxyl groups and thus increases the material's hydrophilicity. After the hydrophobicity switch, dye molecules diffuse out of the polymer matrix, relieving the particle from fluorescence quenching ("on-state") (Figure 1).

Results: After injecting particles (dose: 100 mL of 0.7 mg/mL Hy-Dex-IR780 in DPBS) intravenously on day 5 after arthritis induction, mice were imaged by IVIS®. Regions of inflammation exhibited significantly higher fluorescence intensity measured as an average of radiant efficiency of paws between non-arthritic and arthritic joints (1.91E+07±1.5E+06 vs 4.44E+07±1.85E+07; $p<0.05$). This activation results from inflammation-triggered release of dye molecules, as fluorescence was insignificant in healthy animals, and a non-responsive control version poly(lactic-co-glycolic acid)-IR780 was not activated by inflammation. Radiant efficiency in each paw significantly correlated with their clinical score. For example, a paw with a clinical score of 4 had radiant efficiency of 6.95E+07 while a paw with clinical score of 1 had 2.58E+07.

Conclusion: These results suggest that a novel activatable bioimaging agent can detect inflammation *in vivo* for clinical diagnosis of inflammatory conditions or to assess inflammation in animal models.

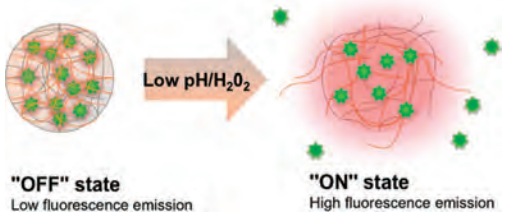

Figure 1. Particles composed of H_2O_2- and acid-responsive polymers partially disassemble upon exposure to either stimulus, activating fluorescence by relieving the particle from self-quenching. Since the NIR dye is not fluorescent in aqueous environments, only the particles light up.

Disclosure: M. Guma, None; **B. Bartok**, None; **V. A. Nguyen Huu**, None; **M. L. Viger**, None; **J. Lux**, None; **S. Joshi-Barr**, None; **A. Almutairi**, None; **G. S. Firestein**, None.

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Human Osteoclasts Are Mobilized in Erosive Arthritis of Epstein-Barr Virus-Infected Humanized NOD/Shi-*Scid*/IL-2Rγ^{null} Mice. Yosuke Nagasawa[1], Natsumi Ikumi[1], Takamasa Nozaki[1], Hirotake Inomata[1], Kenichi Imadome[2], Noboru Kitamura[1], Mitsuhiro Iwata[1], Shigeyoshi Fujiwara[2] and Masami Takei[1]. [1]Nihon University School of Medicine, Tokyo, Japan, [2]National Research Institute for Child Health and Development, Tokyo, Japan.

Background/Purpose: Various studies of the relationship between Epstein-Barr virus (EBV) and rheumatoid arthritis (RA) have not produced convincing evidence. Many human viruses do not infect mice; thus, it is difficult to conduct biomedical research. At this congress, we previously reported that EBV infection induces erosive arthritis that resembles RA in humanized NOD/Shi-*scid*/IL-2Rγ^{null} (NOG) mice. However, the mechanisms underlying arthritis in this mouse model are unknown.

In this mouse model, osteoclast-like cells are observed during bone erosion. To determine whether the human or mouse immune system activates bone erosion, we analyzed the origin of osteoclasts in this mouse model.

Methods: The NOG mouse is a highly immunodeficient mouse strain. Seven-week-old female NOG mice were intravenously injected with human CD34$^+$ stem cells from cord blood (1.0×10^5 cells/mouse). Characterization of human hematoimmune system reconstitution (we termed it humanization) was then performed. Human CD4$^+$, CD8$^+$, and CD45$^+$ cells in peripheral blood of these humanized mice were quantified every week using flow cytometery. The engraftment rate of human cells and characteristics of lymphocytes were determined. After 3 months of humanization, these mice were intravenously infected with EBV (1.0×10^1 TD50/mouse). EBV was purified from EBV-producing cells (AKATA or B95-8). After 8–10 weeks of EBV infection, these mice were sacrificed. The joint tissue samples were stained with hematoxylin-eosin, stained for tartrate-resistant acid phosphatase (TRAP) with an immunoenzyme method,

and immunostained for human cathepsin K (specific to humans and dogs). To let osteoclasts differentiate with progenitor cells, bone marrow cells from EBV-infected humanized NOG mice were cultured with human receptor activator of nuclear factor κB ligand (RANKL) and human macrophage colony-stimulating factor (M-CSF) in slide chambers. These stimulated multinucleated cells were subjected to TRAP staining and immunostaining for human cathepsin K and human mitochondria.

Results: After humanization, >40% of peripheral-blood lymphocytes in these mice were human $CD45^+$ cells. When the number of human $CD8^+$ T-cells increased and surpassed the number of human $CD4^+$ T-cells in peripheral blood, erosive arthritis was observed histologically at a high rate (approximately 90%). Multinucleated cells present in the bone erosion zone were positive for human cathepsin K and TRAP staining. Multinucleated giant cells resembling osteoclasts were observed among cultured bone marrow cells stimulated with human RANKL and M-CSF. Human cathepsin K, mitochondrial, and TRAP staining were all positive in these multinucleated cells.

Conclusion: In this mouse model, we achieved a high engraftment rate. The relationship between the degree of arthritis and the ratio of $CD4^+$ to $CD8^+$ T-cell numbers in peripheral blood was evident. Osteoclasts present in the bone erosion zone originated from human cells. In addition, observed that multinucleated giant cells among bone marrow cells cultured with human RANKL and M-CSF were osteoclasts and originated from human cells.

Disclosure: Y. Nagasawa, None; **N. Ikumi**, None; **T. Nozaki**, None; **H. Inomata**, None; **K. Imadome**, None; **N. Kitamura**, None; **M. Iwata**, None; **S. Fujiwara**, None; **M. Takei**, None.

2341

The Combination Therapy of Cell Cycle Regulation Therapy Combined and TNF Blockade Ameliorated the Established Arthritis. Tadashi Hosoya[1], Kimito Kawahata[2], Hideyuki Iwai[2] and Hitoshi Kohsaka[1]. [1]Japan Science and Technology Agency–CREST Program, Tokyo, Japan, [2]Tokyo Medical and Dental University (TMDU), Tokyo, Japan.

Background/Purpose: The pathogenesis of rheumatoid arthritis (RA) is characterized by infiltration of inflammatory cells to the synovial tissues and their hyperplasia. Activated synovial fibroblasts become another source of inflammatory cytokines and a platform inducing further recruitment of inflammatory cells.

Cyclin-dependent kinases (CDK) are known to be key regulators of the cell cycle progression and targets in cancer treatment. We have revealed that a highly selective small-molecule CDK4/6 inhibitor (CDKI) ameliorated an animal model of RA, even with a dose one-fifth lower than the dose used in a cancer treatment model. Furthermore, CDKI combined with a cytokine blocker ameliorated early stage of arthritis additively without inhibiting antigen-specific immune responses.

In the clinical setting, we often treat RA patients with high disease activity. However, few agents were proven effective in treating established arthritis models. The drug effectiveness is usually estimated with early stage of arthritis in the pre-clinical study and is sometimes discrepant between animal models of arthritis and human RA. Therefore, it is difficult to predict which drug is promising in the patients with RA based on the results of arthritis models. However, the drug would be promising if it could ameliorate the established arthritis model. The present studies were carried out to discern if combination of CDKI and TNF blocker is effective in treating established arthritis.

Methods: DBA/1J mice immunized with bovine type II collagen emulsified in complete Freund's adjuvant twice and evaluated for arthritis score and the joint deformity. Mice with collagen-induced arthritis (CIA) were divided into 4 groups equated the mean arthritis score of individual groups 30 days after the initial immunization and were treated with 20 mg/kg of CDKI, 3 mg/kg of (ETN), a combination of both, or a vehicle solution from 30 days until 42 days after the initial immunization.

Results: The arthritis became established with 9.1 of the mean arthritis score 30 days after the initial immunization. Mice with CIA were treated with a vehicle solution or CDKI or ETN - separately or together. The mean arthritis score changed from 9.1 to 10.4, 8.4, 8.1, and 6.4 respectively 42 days after the initial immunization. The percentage of deformed limbs was observed at 25%, 18%, 7%, and 4% respectively. Both monotherapies inhibited further development of arthritis and decreased the arthritis score, but their efficacies were not statistically significant. Combination therapy decreased the arthritis score significantly and inhibited the joint deformity.

Conclusion: The combination therapy of CDKI and TNF blocker is effective on established arthritis and could prevent joint deformity. Because TNF blockade disturbs the proliferative signaling and CDKI directly prohibits cell cycle progression, the combination of the two might act synergistically based on their mechanisms. We expect that the combination therapy of CDKI with cytokine blockers should help to increase the remission induction rate in RA patients even with high disease activity.

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Redox Regulation of a New Autoimmune Mouse Model, Glucose-6-Phosphate Isomerase Peptide Induced Arthritis in Mice. Min Yang[1] and Rikard Holmdahl[2]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Karolinska Institute, Stockholm, Sweden.

Background/Purpose: Rheumatoid arthritis (RA) is a perpetuating disease, which affects approximately 1% of the population. Until now, the pathogenic mechanisms of RA remain elusive and currently no cure for the disease. Animal models of arthritis have provided valuable platforms to investigate the potential mechanisms of RA and test new therapeutic principles before initiating clinical trials in humans. Based on the well-known K/BxN model, a spontaneous arthritis mouse model, we have established glucose-6-phosphate isomerase (G6PI) peptide induced arthritis in mice. Since the G6PI peptide used in this model has two cysteines inside, therefore, we focus on how redox balance could affect antigen recognition and thereby affect the pathogenesis of autoimmunity.

Methods: G6PI peptide-induced arthritis is established by immunizing C57Bl/6N.Q (B6N.Q) mice or Ncf1*/* mice with single injection of G6PI peptide emulsified in complete freund's adjuvant. Cysteine(s) in the peptide is substituted with serine to test whether redox can influence peptide itself. APCs from both wild type and Ncf1*/* mice are isolated, loaded with G6PI peptide or substituted peptide and cocultured with peptide-specific T cell hybridoma for 24hr. Supernatants are collected then to compare the IL-2 secretion level.

Results: Immunized B6N.Q mice start to develop arthritis on day 10–12, reach to the peak value of severity on day 14–20 and then recover during following 7–10 days. Moreover, both female and male B6N.Q mice could be induced arthritic diseases by G6PI peptide and the incidence is over 80%. Obviously, this peptide-induced arthritis mouse model represents an acute arthritic disease progression. To establish a chronic mouse model with this peptide, we inject pertussis toxin together with G6PI emulsion. It turns out that pertussis toxin not only increases the severity of the disease but also prolong the disease progression over two months. To investigate whether cysteine inside of the peptide is regulated by redox, Ncf1 mutant mice were used. N*cf1* encodes $p47^{phox}$ subunit, which is an essential cytosolic subunit of NADPH oxidase 2 (Nox2). The mutation of Ncf1 results in the deficiency of ROS production. The in vitro assay suggest that APCs from Ncf1*/* mice show higher capability to present G6PI peptide. However, when either one or both of the cysteine substituted with serine, there is no difference at all in antigen presenting between wild type and Ncf1*/* mice. Furthermore, peptide immunized Ncf1*/* mice exhibit more severe and chronic disease comparing with immunized wild type mice.

Conclusion: Taken together, we have established a peptide-induced arthritis mouse model. The model is induced with a defined peptide, leading to a high reproducibility and allowing a more precise investigation of the pathogenicity. Since the peptide per se is sensitive to ROS level, therefore, this model provides unique possibility to investigate redox regulation in autoimmune disease including RA.

Disclosure: M. Yang, None; **R. Holmdahl**, None.

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Therapeutic Effects of Mesenchymal Stem Cells, Anti-Tumor Necrosis Factor and Anti-CD20 Treatment on Collagen Induced Arthritis. Yue Sun, Xuebing Feng and Lingyun Sun. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

Background/Purpose: Tremendous progress has been made in the development of non-conventional therapies for rheumatoid arthritis (RA). In this study, the effects of mesenchymal stem cells (MSCs) transplantation on established

collagen-induced arthritis (CIA) were evaluated and compared with two kinds of biologic agents, anti-tumor necrosis factor (TNF) and anti-CD20 antibody.

Methods: CIA was induced with the immunization of type II collagen (CII) and CFA in DBA/1J mice. Human umbilical cord derived MSCs (5×10^6), anti-TNF antibody (100ug) and anti-CD20 antibody (200ug) were intraperitoneally injected into 3 groups of mice on day 28 after the immunization. The control group was treated with human fibroblasts (5×10^6). All mice were sacrificed 3 weeks later and arthritis severity was assessed by clinical and histology scoring. The frequency of CD4+ T cell subsets, B cells and plasma cells in spleen was analyzed by flow cytometry. Serum levels of autoantibody to mouse CII were determined by ELISA. The ability of MSCs to modulate Treg/Th17 cell percentages in CD3/CD28 stimulated DBA/1J T cells was assessed in vitro.

Results: MSCs treatment significantly decreased the severity of arthritis and pathology scores, which was comparable to anti-TNF or anti-CD20 treatment. Anti-CD20 treatment depleted nearly half of B220+ cells, and markedly reduced the frequency of plasma cells and serum levels of autoantibody compared to the control group (738±187 *vs.* 1817±447 U/ml, $p<0.001$). The decrease of autoantibody level was also detectable in those with anti-TNF treatment (663±336 U/ml) and MSCs treatment (1057±362 U/ml), but neither of these two treatments had an impact on the percentage of B cells or plasma cells. All of the three treatments resulted in a decrease in Th1 subset, but none of them altered the percentage of Th2 subset. Except anti-CD20 treatment, both MSCs and anti-TNF treatment significantly decreased the percentages of Th17 cells. Notably, only MSCs treatment increased the percentages of regulatory T cells (11.39±0.85 % *vs* 7.37±1.82 % in the control group, $p<0.01$). In vitro study confirmed that MSCs could induce the generation of Foxp3+ T cells but reduce the percentages of pathogenic IL-17+Foxp3+ T cells.

Conclusion: MSCs exerted comparable therapeutic effects as biological agents on CIA through different mechanisms. MSCs may provide a promising approach for the treatment of RA.

Disclosure: Y. Sun, None; **X. Feng**, None; **L. Sun**, None.

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Amelioration of Collagen-Induced Arthritis By Water-Soluble Fullerene $C60(OH)_{36}$ Nanoparticles through the Inhibition of Angiogenesis. Chia-Tse Weng[1], Shih-Yao Chen[2], Yu-Hung Chen[2], Chao-Liang Wu[2], Ming-Fei Liu[2], Ai-Li Shiau[2] and Chrong-Reen Wang[2]. [1]National Cheng Kung University Hospital, Tainan, Taiwan, [2]National Cheng Kung University Medical College, Tainan, Taiwan.

Background/Purpose: Our previous study has shown that injection of 13-nm gold nanoparticles ameliorates collagen-induced arthritis (CIA) through the inhibition of angiogenesis by binding to VEGF. Fullerene derivatives, strong scavengers of superoxide radicals, have been recently identified as potential therapeutic agents for arthritis, with the ability to inhibit proinflammatory mediators. In this study, we demonstrate amelioration of CIA by treatment with $C60(OH)_{36}$nanoparticles through the suppression of proinflammatory cytokine production, bone/cartilage erosion and synovial angiogenesis.

Methods: Physical properties of newly synthesized $C60(OH)_{36}$ nanoparticles were characterized by X-ray photoelectron spectrometer, infra-red spectroscopy, fast-atom bombardment and matrix-assisted laser desorption/ionization mass spectroscopy, transmission electron microscope and dynamic light scattering analysis. Their ability to remove superoxide radicals was confirmed by the electron paramagnetic resonance spectrometer and the inhibition of intracellular reactive oxygen species formation in RAW 264.7 cells. Eight-week-old male Sprague-Dawley rats were immunized with bovine type II collagen emulsified in complete Freund's adjuvant on day 0 and 7. Articular index was used to evaluate the therapeutic effect of the nanoparticles on arthritic joints receiving intra-articular injection of 10 mg nanoparticles or PBS as control (16 joints per group) on day 7. Histological and radiographic scores of arthritic joints were calculated upon sacrifice on day 21. Proinflammatory cytokines (IL-1b and TNF-a) and VEGF concentrations in homogenized synovium extracts were measured by enzyme-linked immunosorbent assay. Synovial angiogenesis was examined by counting microvessel numbers after immunohistochemical staining. The ability of nanoparticles to suppress endothelial cell proliferation was tested by using VEGF-treated human dermal microvascular endothelial cells-1 (HMVEC-1).

Results: Articular indexes of nanoparticles-injected joints were reduced as compared with PBS-treated counterparts. There were lower histological and radiographic scores with less pannus formation and erosion of cartilage/bone in nanoparticles-treated synovium. Reduced IL-1b concentrations were identified in the treatment group. Notably, nanoparticles-treated synovium had decreased microvessel density without reduction of VEGF levels, and nanoparticle treatment inhibited VEGF-induced HMVEC-1 proliferation in a dose-dependent manner, suggesting that the mechanism of angiogenesis inhibition was through the interference in the signal transduction pathway rather than physical adsorption of the growth factor.

Conclusion: This study demonstrates first that intra-articular injection of $C60(OH)_{36}$ nanoparticles ameliorates CIA through anti-angiogenesis effect, further implicating a novel mechanism in application of certain fullerene derivatives as potential therapeutic agents in rheumatoid joints.

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Anti-IL-6 Receptor Antibody Prevents Deterioration in Bone Structure in a Mouse Model of Collagen-Induced Arthritis. Hiroto Yoshida, Mika Yagoto, Miho Suzuki, Keisuke Tanaka, Misato Hashizume and Yoshihiro Matsumoto. Chugai Pharmaceutical Co., Ltd., Gotemba, Japan.

Background/Purpose: Rheumatoid arthritis (RA) is a disease that typically induces secondary osteoporosis, which increases the risk of bone fractures and, consequently, mortality. Bone fracture is induced not only by lower BMD but also by deterioration in bone structure. It is not clear whether anti–human IL-6 receptor antibody (tocilizumab) affects bone structure in RA patients, and the purpose of this study is to examine the changes in bone structure that occur when arthritis develops and the effects of anti-IL-6 receptor antibody on those changes, using a mouse model of collagen-induced arthritis (CIA).

Methods: CIA was triggered in DBA/1J mice by an intradermal injection of bovine type II collagen on Days 0 and 21. Mice were injected intraperitoneally either with anti-mouse IL-6 receptor antibody (MR16-1) on Days 0 and 21 or with TNF receptor-Fc (TNFR-Fc) 3 times per week from Day 0 to Day 56. Urine and serum were sampled on Day 35, the peak of swelling. Urinary CTX, a bone resorption marker, and serum P1NP, a bone formation marker, were measured by ELISA. Femurs and lumbar spine were excised on Day 56, after swelling subsided. In the distal femur and L5 lumbar spine, the bone structure of trabecular bone and cortical bone was analysed by micro-computed tomography (μCT).

Results: In CIA mice, urinary CTX and serum P1NP were significantly higher and lower, respectively, than in non-immunized mice. Trabecular bone volume (BV/TV), trabecular number (Tb. N), trabecular thickness (Tb. Th), and cortical bone thickness (Ct) of the distal femur, and BV/TV and Tb. N of the L5 lumbar spine in CIA mice were significantly lower than in non-immunized mice. Both MR16-1 and TNFR-Fc suppressed the development of arthritis. An increase in urinary CTX during development of CIA was prevented by MR16-1 and TNFR-Fc. On the other hand, a decrease in serum P1NP was prevented by only MR16-1. MR16-1 treatment significantly suppressed the deterioration in bone structure (BV/TV, Tb. N, Tb. Th, and Ct in the distal femur, and BV/TV and Ct in the L5 lumbar spine). TNFR-Fc treatment significantly suppressed the decrease of BV/TV and Tb. N in the distal femur.

Conclusion: We demonstrated that CIA induced severe deterioration in bone structure through an imbalance of bone turnover that was a result of not only increased bone resorption but also decreased bone formation. Moreover, our results indicated that proinflammatory cytokines such as IL-6 and TNF play an important role in bone structure deterioration. Our findings indicate that anti-IL-6 receptor antibody improves the imbalance in bone turnover by suppressing both the increase in bone resorption and the decrease in bone formation and thus prevents the deterioration in bone structure.

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Specific Overexpression of FPR2 (FPRL-1) on Th1 Cells in GPI-Induced Arthritis and Patients with Rheumatoid Arthritis. Yuki Tanaka[1], Isao Matsumoto[2], Asuka Inoue[1], Naoto Umeda[3], Chinatsu Takai[4], Yuko Kurashima[5], Hoshimi Kawaguchi[5] and Takayuki Sumida[2]. [1]University of Tsukuba, Tsukuba city, Ibaraki, Japan, [2]Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [3]University of Tsukuba, Tsukuba City, Japan, [4]University of Tsukuba, Ibaraki, Japan, [5]University of Tsukuba, Tsukuba, Japan.

Background/Purpose: $CD4^+$T cell are critical to the pathogenesis of rheumatoid arthritis (RA). In glucose-6-phosphate isomerase (GPI) induced-arthritis (GIA), Th1 and Th17 cells are indispensable for both the induction and the effector phase. We recently identified the highly expression of formyl

peptide receptor 2 (FPR2) in splenic $CD4^+$T cells from GIA mice by DNA microarray. The FPR2 (human homologue: FPRL-1) is a G-protein coupled receptor showing pro- and anti-inflammatory effect. To clarify the function of FPR2 in CD4+ T cells in the generation of arthritis, we investigated the expression of FPR2 in GIA and FPRL-1 in patients with RA.

Methods:

(1) To confirm the results of DNA microarray, we analyzed the fluctuated expression of FPR2 mRNA on $CD4^+$T cells in GIA (day0, day 7: induction phase, day 14: effector phase, day 28: contraction phase) by real-time PCR.

(2) To determine the Th subsets expressing FPR2, we sorted $FPR2^+$ or $FPR2^-$ $CD4^+$T cells from lymph nodes of GIA (on day7), and the mRNA expression of various markers on $CD4^+$T cell subsets (Th1, 2, 17, Tfh and Treg) was examined.

(3) We analyzed the expression of FPR2 on Th1 or Th17 cells in the polarized condition in vitro.

(4) In human, we analyzed the expression of FPRL-1 mRNA on peripheral blood mononuclear cells (PBMC) and $CD4^+$T cells from healthy subjects (HS), patients with Sjogren's syndrome (SS), and RA patients.

(5) We assessed the expression of FPRL-1 on human Th1 cells in the polarized condition in vitro.

Results:

(1) The FPR2 mRNA was significantly highly expressed on $CD4^+$T cells in GIA on day7 ($p<0.05$).

(2) The T-bet and IFNγ were higher expressed on $FPR2^+CD4^+$T cells than those on $FPR2^-CD4^+$T cells, whereas each marker for Th2, Th17, Tfh and Treg cells were not.

(3) The expression of FPR2 was frequently detected on Th1 polarized cells, but not on Th17 polarized cells.

(4) The expression of FPRL-1 on PBMC and $CD4^+$ cells was significantly higher in RA compared with HS and SS ($p<0.05$).

(5) FPRL-1 expression was significantly increased on human Th1 polarized cells.

Conclusion: We identified that $FPR2^+$T cells showed Th1 phenotype in mice and FPRL-1 was highly detected on $CD4^+$T cells in patients with RA. Th1 polarized cells in mice and humans also expressed FPR2 and FPRL-1, respectively, suggesting $FPR2^+$ ($FPRL\text{-}1^+$) T cells might play a crucial role in the pathogenesis of RA.

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Therapeutic Effect of a Novel Histone Deacetylase 6 Inhibitor, CKD-L, on Collagen Induced Arthritis and Peripheral Blood Mononuclear Cells from Patients with Rheumatoid Arthritis. Bo Ram Oh[1], Hyojin Lim[2], Daekwon Bae[2], Nina Ha[2], Young il Choi[2], Hyun Jung Yoo[1], Jin Kyun Park[3], Eun Young Lee[4], Eun Bong Lee[3] and Yeong Wook Song[1]. [1]Department of Molecular Medicine and Biophamaceutical Sciences, BK 21 plus Graduate School of Convergence Science Technology, Colleage of Medicine, Seoul National University, Seoul, South Korea, [2]Department of Pharmacology and Toxicology, CKD Research Institute, CKD Pharmaceutical Company, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [4]Seoul National University College of Medicine, Seoul, South Korea.

Background/Purpose: Epigenetic regulation plays an important role in inflammatory arthritis, including rheumatoid arthritis (RA). Histone deacetylase inhibitor (HDACi) has been recently reported to have therapeutic effect in collagen induced arthritis (CIA). CKD-L is a new HDAC6i developed by Chong Kun Dang Pharmaceutical Corporation. We investigated the therapeutic effect of selective HDAC6 inhibitors (CKD-L and Tubastatin A) on CIA, peripheral blood mononuclear cells (PBMCs) and regulatory T (Treg) cells.

Methods: CIA was induced by bovine type II collagen (CII) in DBA/1 mouse. Mice were treated with vehicle (n=10), CKD-L (15, 30 mg/kg, n=10, respectively) or Tubastatin A (30 mg/kg, n=10) by subcutaneous injection every day for 18 days. Arthritis score was assessed twice weekly after the onset of arthritis. Histological analysis was performed by H&E stain. $CD4^+CD25^-$ cells were isolated from C57BL/6 mice spleen and activated with anti-CD3/CD28 beads, TGF-β and HDAC6i (1~10 μM) for 6 days. Cytotoxic T lymphocyte associated protein 4 (CTLA-4) expression in induced Treg (iTreg) cells was analysed by flow cytometry. Natural Treg (nTreg) cells and $CD4^+CD25^-$ (Teff) cells were isolated from C57BL/6 mice spleen. nTreg cells were incubated with anti-CD3/CD28 bead, HDAC6i (200~2000 nM) and carboxyfluorescein succinimidyl ester (CFSE)-labeled Teff cells for 3 days (Treg:Teff ratio=1:2). Proliferation of Teff cells was analysed by flow cytometry. RA PBMCs were stimulated with lipopolysaccharide 100 ng/ml and HDAC6i (10–5000 nM) for 24 hours. Multiplex cytokine assay was performed with supernatant. RA $CD4^+CD25^-$ cells were cultured with anti-CD3 Ab, anti-CD28 Ab, IL-2, TGF-β and $1,25(OH)_2VD_3$ for 5 days. iTreg cells were incubated for 3 days with CFSE-stained Teff cells in the presence of anti-CD3/CD28 beads and HDAC6i (10–5000 nM). Proliferation of Teff cells was analysed by flow cytometry.

Results: In CIA, CKD-L and Tubastatin A significantly reduced arthritis score and histological score. CTLA-4 expression in mouse iTreg cells was increased after treatment of CKD-L ($P<0.001$) and Tubastatin A ($P<0.05$). And mouse nTreg cells inhibited the proliferation of Teff cells after treatment with CKD-L (67.8 %) and Tubastatin A (68.3 %) compared to no treatment (80.1 %). In RA PBMC, TNF-α was decreased after treatment with CKD-L ($P<0.001$) and Tubastatin A ($P<0.001$). IL-10 was increased after treatment CKD-L ($P=0.051$) and Tubastatin A ($P=0.083$). In co-culture with iTreg cells and Teff cells, CKD-L efficiently inhibited the proliferation of Teff cells (13.9 %) compared to no treatment (32.6 %). Tubastatin A had no effect on proliferation of Teff cells (30.1%).

Conclusion: CKD-L was effective on the suppression of arthritis in CIA. CKD-L increased CTLA-4 expression and function of Treg cells. These results suggest that CKD have beneficial effect in the treatment of RA.

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Activatory Fc Gamma Receptor IV Plays a Crucial Role in Pathogenesis of Experimental Immune Complex Mediated Chronic Arthritis. Irene Di Ceglie[1], Arjen Blom[1], Sjef Verbeek[2], Peter van der Kraan[1], Wim van den Berg[1] and Peter L. van Lent[1]. [1]Experimental Rheumatology, Radboud University, Nijmegen, Netherlands, [2]Human Genetic, Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Rheumatoid arthritis is characterized by Immune complex dependent chronic joint inflammation and severe cartilage and bone destruction. Earlier we found that in the absence of activatory FcγRI and III, joint destruction during the early murine phase of antigen-induced arthritis (AIA) was protected (1) but the role of FcγRIV has not yet been elucidated.

Methods: AIA was induced by injection of mBSA into the knee joint of $Fc\gamma RI,II,III^{-/-}$, $Fc\gamma I,II,III,IV^{-/-}$and wild type (WT) control mice previously immunized with mBSA/CFA. Histology of total knee joints was taken at day 7 and 21 after arthritis induction. Joint inflammation was scored using an arbitrary scale. Cartilage damage was measured as proteoglycan (PG) depletion. Bone destruction was determined using an arbitrary score. mBSA antibody titers were determined using ELISA.

Results: Both KO strains showed antibody titers against mBSA comparable to immunized control mice. In the early phase of AIA (day 7), joint inflammation was significantly higher in $Fc\gamma RI,II,III^{-/-}$ (infiltrate 47% and exudate 107% higher) when compared to WT controls. In $Fc\gamma RI,II,III,IV^{-/-}$however, although comparable antibody titers, inflammation was significantly lower (infiltrate 30% and exudate 46% lower) than in WT controls. Early cartilage destruction was protected in both strains reflected by significantly lower PG depletion (34% and 20% lower respectively) when compared to their WT controls.

During the chronic phase at day 21, joint inflammation in $Fc\gamma I/II/III^{-/-}$ was still significantly higher (infiltrate 450% and exudate 170% higher) when compared to WT controls. Protection of cartilage damage seen in early AIA was lost and PG depletion significantly increased in $Fc\gamma RI,II,III^{-/-}$by 260 %. Bone erosion also increased by 150%. These results suggest that FcγRI and III regulate destruction in the early phase whereas FcγRIV may be more important in chronic stages of arthritis.

In line with this we found that joint inflammation in $Fc\gamma RI,II,III,IV^{-/-}$ was much lower when compared with $Fc\gamma I/II/III^{-/-}$ and remained at the same level as their WT controls, implying an active role of FcγRIV in inflammation during the chronic phase. The amount of PG depletion in $Fc\gamma RI,II,III,IV^{-/-}$was comparable to that observed in WT. In contrast erosion of cartilage matrix but also bone were found to be significantly lower when compared to WT controls (76% and 34% lower respectively).

Conclusion: Activatory FcγRIV is crucial in regulating joint inflammation during acute and chronic phase of AIA and became crucial in mediating cartilage and bone destruction during the chronic phase of the disease.

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Early Sympathectomy Inhibits Egress of Lymphocytes in Control and Arthritic Animals and Ameliorates Arthritic Disease. Susanne Klatt and Rainer Straub. University Hospital Regensburg, Regensburg, Germany.

Background/Purpose: The sympathetic nervous system (SNS) plays an important role in course and development of autoimmune diseases like arthritis. In type II collagen- induced arthritis (CIA), early activation of the SNS is proinflammatory, but the SNS is anti-inflammatory in later stages of disease. Early sympathectomy (SYX) prior to immunization ameliorates disease severity, but beneficial mechanisms of early SYX are not completely understood. The aim of this study was to determine how the SNS influences energy expenditure in lymph nodes / spleen and, in parallel, egress of lymphocytes from draining lymph nodes / spleen of control and arthritic animals.

Methods: A new technique termed "spatial energy expenditure configuration (SEEC)" was developed to demonstrate bodily areas of high energy demand. SEEC is based on removal of tissue during the course of arthritis in DBA/1 mice, and subsequent determination of oxygen consumption *in vitro* as a measure of local energy expenditure (immune cell activation). SEEC was applied to healthy control animals, arthritic animals, and animals that underwent early SYX. We evaluated homing behaviour of labelled donor splenocytes, expression of CCR7 on lymphocytes by flow cytometry, concentration of CCL21 in lymphocyte cell culture supernatants, and levels of sphingosine-1-phosphate (S1P) in serum of arthritic, sympathectomized arthritic, and control animals.

Results: In draining lymph nodes and spleens of arthritic mice, we observed a marked increase in oxygen consumption and organ weight during the course of arthritis. Although early SYX ameliorated later CIA, early SYX increased energy consumption and cell numbers in arthritic but also in control lymph nodes. This was interpreted as a probable sign of lymphocyte retention in lymphoid organs in healthy and arthritic animals. Splenocyte migration to the spleen was enhanced in early SYX compared to control mice. After early SYX, we observed an elevated expression of CCR7 on lymph node cells and a higher level of CCL21 in lymphocyte cell culture supernatants. This probably contributes to retention of T cells and dendritic cells within lymph nodes. Egress of lymphocytes requires an S1P gradient, low in the lymph node parenchyma and high at the exit site in the vascular lumen. The measurement of S1P in mouse serum revealed a significant higher concentration in CIA animals when compared to controls. Importantly, early SYX decreased S1P concentration in arthritic animals to control levels.

Conclusion: By using the SEEC technique, we identified draining lymph nodes as target organs of the sympathetic nervous system. SYX-induced disease amelioration is probably exerted by sequestration of lymphocytes in secondary lymphoid organs. This might prevent recirculation of immune cells to peripheral sites of inflammation.

Disclosure: S. Klatt, None; **R. Straub**, None.

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A Humanized Monoclonal Antibody Raised Against a Heat Shock Protein Epitope Suppresses Autoimmune Inflammatory Diseases By Skewing the Immune System Selectively Towards an Anti-Inflammatory Response. Yaakov Naparstek[1], Rina Ulmansky[1], Galia Katzavian[2], Ronit Meyuhas[2], Eli Moallem[1], Shira Yair[2], Dorit Landstein[2] and Virginie Loeb[2]. [1]Hadassah - Hebrew University Medical Center, Jerusalem, Israel, [2]ProtAb Ltd., Jerusalem, Israel.

Background/Purpose: We have previously shown that resistance to Adjuvant Arthritis (AA) is due to the presence of anti-heat shock protein (HSP) antibodies, directed at peptide-6, a 16 amino acid epitope of Mycobacterium Tuberculosis (MT) HSP65. Furthermore, we have shown that polyclonal rat anti-peptide-6 antibodies suppress AA and bind to the whole MT HSP65 molecule as well as its mammalian homolog, HSP60. In this work, we have studied the effect of a humanized anti-peptide-6 monoclonal antibody, termed Prozumab, on various models of autoimmune arthritis and colitis and the mechanism of its anti-inflammatory effect.

Methods: We have recently developed a humanized anti-peptide-6 antibody, termed Prozumab, and evaluated its potential as a therapeutic immunomodulatory drug. We tested its binding to MT HSP65 and mammalian HSP60, its effect on cytokine modulation from human PBMCs, and its therapeutic effects in acute and chronic animal models of arthritis and colitis.

Results: Prozumab bound similarly to recombinant MT HSP65 and mammalian HSP60. Its ability to modulate cytokine balance was established as it induced IL-10 secretion from human PBMC. Moreover, in the presence of Prozumab, a reduction in secretion of IFNg and IL-6 from anti-CD3 activated human PBMC was observed. Administration of this antibody to mice and rats with collagen induced arthritis, adjuvant arthritis and TNBS colitis, induced a change in the cytokine balance and suppression of disease. Treatment with this antibody suppressed disease severity in spontaneous IL-10 knock-out colitis in mice as well. The level of natural anti-peptide-6 antibodies in the serum of patients with rheumatoid arthritis was significantly lower than in healthy controls.

Conclusion: We conclude that HSP65 contains protective B-cell epitopes exposed on its surface, and that natural and acquired resistance to autoimmune arthritis is associated with the ability to develop an antibody response to these epitopes. These antibodies cross react with the human HSP60, modulate cytokine production from human PBMCs and ameliorate disease in experimental autoimmune inflammatory disease models. The high homology between the peptide-6 region in MT HSP65 and the mammalian HSP60 and the similarity of the in vitro binding suggest that HSP60 is its target on mammalian cells. Presence of HSP60 on various mammalian cells has been shown previously. Lower levels of anti-peptide-6 antibodies in patients with RA suggest that they play a role in protection against human autoimmune diseases as well. The monoclonal humanized anti-peptide-6 antibody may serve as a new therapeutic tool for suppression of human arthritis and inflammatory bowel diseases by skewing the immune system selectively towards an anti-inflammatory response.

Disclosure: Y. Naparstek, ProtAb Ltd., 6, ProtAb Ltd., 1, ProtAb Ltd., 5; **R. Ulmansky**, ProtAb Ltd., 1; **G. Katzavian**, ProtAb Ltd., 1; **R. Meyuhas**, ProtAb Ltd., 1; **E. Moallem**, ProtAb Ltd., 1; **S. Yair**, ProtAb Ltd., 1, ProtAb Ltd., 3, ProtAb Ltd., 6; **D. Landstein**, ProtAb Ltd., 1, ProtAb Ltd., 3; **V. Loeb**, ProtAb Ltd., 3.

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Ligand of Glucocorticoid-Induced Tumor Necrosis Factor Receptor Enhances Th17 Cells Response in Collagen-Induced Arthritis Via P38 MAPK and STAT3 Pathway. Xinyi Tang[1] and Shengjun Wang[2]. [1]Jiangsu University Affiliated People's Hospital, Zhenjiang, China, [2]Jiangsu University Affiliated People's Hospital, Zhenjiang, China.

Background/Purpose: Helper T lymphocyte-17 (Th17) has recognized to be an important factor in rheumatoid arthritis (RA) pathogenesis. The natural ligand of glucocorticoid-induced tumor necrosis factor receptor (GITRL) could exacerbate autoimmune arthritis via the enhancement of Th17 cells expansion. It has reported that GITRL/GITR could trigger phosphorylation of p38 mitogen-activated protein kinase in T cell. The purpose of this study is to investigate the role of p38 signaling during the enhancement of Th17 expansion and exacerbation of autoimmune arthritis by GITRL stimulation.

Methods: We used mouse GITRL (mGITRL) protein as a co-stimulatory factor for Th17 differentiation in presence or absence of p38 inhibitor and detected ability of Th17 differentiation. Activated naïve $CD4^+$T cells were pretreated with or without p38 inhibitor before stimulated with mGITRL and phosphorylation of p38 and STAT3 were examined by western blot. And we injected mGITRL protein into collagen induced arthritis (CIA) mice alone or combine with the p38 inhibitor, and observed development of arthritis.

Results: In previous study, we have certificated a function of GITRL in exacerbating autoimmune arthritis via the enhancement of Th17 cells expansion. In this study, naïve $CD4^+$T cells could differentiate into higher frequency of Th17 cells under the mGITRL co-stimulated and be attenuated in a concentration dependent manner by p38 inhibitor treatment. Also, the relative expression of RORγt and IL-17 mRNA was impaired with p38 inhibitor in a concentration dependent manner. Phosphorylation of p38 was reinforced in activated naïve $CD4^+$T cells after stimulated with GITRL protein. STAT3 has two important phosphorylation sites, tyrosine705 (Tyr705) and serine727 (Ser727). An enhancement of STAT3Ser727 phosphorylation by mGITRL stimulate was observed and been attenuated in activated naïve $CD4^+$T cells with p38 inhibitor pretreated. CIA models were established for investigate the function of p38 in the process of arthritis. Compared with the group treated by mGITRL protein (mGITRL-CIA group), the group injected with mGITRL and p38 inhibitor (mGITRL-SB203580-CIA group) had a later onset of symptoms and reached the peak score gently. There were more serious inflammatory changes in the mGITRL-CIA group. Th17 cells and the level of IL-17 in serum of the mGITRL-group increased significantly compared with the mGITRL-SB203580-CIA group.

Conclusion: Our results suggested that the enhancement of Th17 cells differentiation with mGITRL stimulation was influenced by p38-STAT3 singnaling pathway activation; the exacerbation of CIA development in mice by mGITRL can be released with p38 inhibitor treatment and correlate with

the attenuation of Th17 cells. This phenomenon may provide a new insight in the study of RA pathopoiesis and clinical treatment.

Disclosure: X. Tang, None; **S. Wang**, None.

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RORγt Expressing Foxp3$^+$ Regulatory T Cells Regulates the Development of Autoimmune Arthritis in Mice. Yuya Kondo[1], Masahiro Tahara[1], Mana Iizuka[1], Masahiro Yokosawa[1], Shunta Kaneko[1], Hiroto Tsuboi[1], Satoru Takahashi[2], Isao Matsumoto[1] and Takayuki Sumida[1]. [1]Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [2]Laboratory Animal Resource Center, University of Tsukuba, Tsukuba, Japan.

Background/Purpose: To determine the effect of RORγt overexpression in T cells on the development of collagen induced arthritis (CIA).

Methods: Arthritis was induced with chicken type II collagen (CII) in both C57BL/6 (B6) and CD2 T cell-specific RORγt Transgenic (RORγt Tg) mice. Anti-CII antibody in sera was measured by ELISA. At 10 days after the first immunization of CII, lymph node (LN) cells were cultured with or without CII, and then the expression level of cytokine, transcription factor and chemokine receptor on CD4$^+$ T cells were analyzed by flow cytometer and RT-PCR. Cytokine levels in culture supernatants were measured by ELISA. Joint infiltrating cells were also examined by flow cytometer. Cytokine production and suppressive function of Foxp3$^+$ regulatory T cells was analyzed in vitro. Total draining lymph nodes cells or CD4$^+$cells were harvested from B6 mice or RORγt Tg mice at 10 days after the first immunization of CII, and cells were injected into B6 mice intravenously at 10 days after the immunization of CII. Mice were also immunized with CII in CFA intradermally on 11 days after the cell transfer.

Results: CIA was significantly suppressed in RORγt Tg mice compared with B6 mice. Anti-CII antibody in sera was also reduced in RORγt Tg mice. RORγt expression and IL-17 production in CII reactive CD4$^+$ T cells was significantly increased in RORγt Tg mice. Although there was no difference in IFNγ production and T-bet and Foxp3 expression between B6 mice and RORγt Tg mice, RORγt expression in Foxp3$^+$ regulatory T cells were significantly higher in RORγt Tg mice than B6 mice. Most of Foxp3$^+$ regulatory T cells expressed chemokine receptor 6, and which highly infiltrated in joints after the induction of CIA in RORγt Tg mice. Moreover, Foxp3$^+$ regulatory T cells in RORγt Tg mice retain the expression of CD25, the suppressive function of effector CD4$^+$ T cells in vitro, and IL-10 production as well as Foxp3$^+$ regulatory T cells in B6 mice. In adoptive transfer of draining LN cells or CD4$^+$cells from immunized mice, arthritis was significantly attenuated in recipient B6 mice transferred with cells from RORγt Tg mice.

Conclusion: CIA was significantly suppressed in RORγt Tg mice, although IL-17 production and RORγt expression in CII reactive T cells was markedly higher than that of B6 mice. In vitro analyses and cell transfer experiments proposed the possibility that RORγt induced expression of CCR6 in Foxp3$^+$ regulatory T cells, and these cells might regulate the development of CIA.

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The Nitric Oxide Receptor Soluble Guanylyl Cyclase Is Found in Lymphatic Vessels of Arthritic Mice and Inhibition Alters Lymphatic Pulse. Homaira Rahimi[1], Yawen Ju[2], Echoe M. Bouta[3], Ronald Wood[4], Christopher T. Ritchlin[4] and Edward M. Schwarz[2]. [1]University of Rochester/Golisano Children's Hospit, Rochester, NY, [2]University of Rochester, Rochester, NY, [3]University of Rochester School of Medicine and Dentistry, Rochester, NY, [4]University of Rochester Medical Center, Rochester, NY.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic erosive inflammatory condition that is characterized by episodes of "flare" due to synovitis of an affected joint. It has been shown in the tumor necrosis factor transgenic (TNF-Tg) mouse model of RA that the popliteal lymph node (PLN) can serve as a biomarker of arthritic flare. Prior to onset of knee flare, the PLN is expanded and an intrinsic lymphatic pulse is maintained. However, at some point following chronic ankle arthritis, the PLN suddenly collapses, the lymphatic pulse is lost, and knee arthritis occurs. Here, we show that the nitric oxide (NO) signaling pathway, known to be involved in blood vasculature contractility, is involved in lymphatic vessel contractility, and that the NO receptor soluble guanylyl cyclase (sGC) may be a key regulator.

Methods: Immunofluorescent microscopy was performed on fresh frozen histology sections of PLN from wild type (WT) and TNF-Tg mice stained for alpha (a1, a2) and beta (b1) subunits of sGC and co-localized with smooth muscle actin. In WT mice, near infrared indocyanine green (NIR-ICG) imaging was performed to determine and quantify lymphatic pulse. The sGC inhibitor NS2028 or control vehicle was injected into the footpads of mice, and lymphatic pulse was measured with NIR-ICG imaging 30 minutes later.

Results: Immunohistochemistry confirmed the presence of all sGC subunits in PLN from both WT and TNF-Tg mice. Of the six footpads injected with sGC inhibitor NS2028, a clear alteration in the lymphatic pulse with more frequent doublet and triplet spikes compared to control was observed (Figure 1). Quantification of the pulse showed an increased lymphatic pulse in the drug treated limb compared to control (2.66 vs 1.39 pulse per minute, respectively, $p<0.05$).

Conclusion: The presence of sGC receptor subunits in the lymphatic tissue of WT and TNF-Tg mice strongly supports a role for nitric oxide signaling in lymphatic contractility. Furthermore, local injection of sGC inhibitor in WT mice results in a dysregulated lymphatic pulse with an increased rate. This novel finding of increased lymphatic pulse rate with sGC inhibition suggests resumption of the lymphatic pulse in arthritic flare in mice via specific targeting of the sGC receptor may ameliorate flare in inflammatory arthritis.

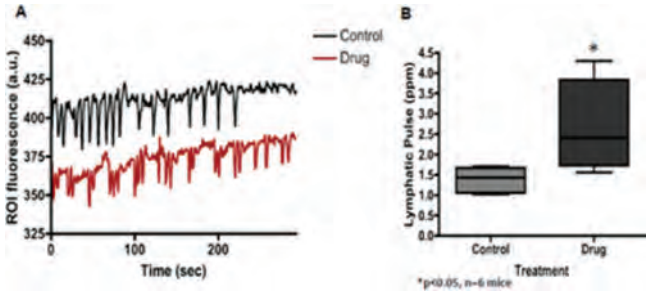

Figure 1.

Disclosure: H. Rahimi, None; **Y. Ju**, None; **E. M. Bouta**, None; **R. Wood**, None; **C. T. Ritchlin**, None; **E. M. Schwarz**, None.

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Efficacy of a Novel Orally Bioavailable JAK1 Selective Compound in a Preclinical Rat Collagen-Induced Arthritis Model. Lily Y. Moy, Chi-Sung Chiu, Robert Faltus, Mark Zielstorff, Kalyan Chakravarthy, Sujal Deshmukh, Ilona Kariv, Joel Klappenbach, Jason Brubaker, Duan Liu, Tony Siu, Jonathan Young, Hongshi Yu, Fiona Elwood and Milenko Cicmil. Merck Research Laboratories, Boston, MA.

Background/Purpose: Janus kinase (JAK) is a family of four tyrosine kinases that play a critical role in cytokine signaling and downstream lymphocyte activation and function. Inhibition of JAK enzymes as therapeutic targets in rheumatoid arthritis (RA) has been validated by multi-JAK inhibitors that modify disease in clinical studies. However, there is also evidence from these trials that JAK inhibition with Tofacitinib increases the risk of infections as well as highlighting other potential toxicity concerns. These side effects are thought to be attributable to JAK2 inhibition, suggesting that better therapeutic ratios might be achieved with selective JAK inhibitors that spare JAK2 activity. Here we report the *in vitro* and *in vivo* preclinical characterization of a highly selective JAK1 inhibitor (Compound B) as compared to the effects of a multi-JAK inhibitor (Compound A).

Methods: Biochemical assays were used to determine JAK family kinase potencies. Cellular assays included: 1) IL-6 induced pSTAT3 driven gene expression in ME-180 cells and 2) erythropoietin induced pSTAT5 driven gene expression in TF1 cells. Collagen-induced arthritis (CIA) in female Lewis rats was performed with a subcutaneous injection of bovine collagen on Days 1 and 8. Inflammation was monitored by measuring paw thickness; μCT imaging and histopathological evaluation were also performed in the ankle joint at the end of the study. Inhibition of baseline hematological parameters was assessed separately in naïve female Lewis rats following compound administration.

Results: Compounds A and B are reversible ATP competitive inhibitors of JAK1 and JAK2. Compound A has comparable activity in both enzymatic and cellular assays, whereas Compound B displays ~10X selectivity for JAK1 to JAK2 in the same assays. Therapeutic administration of both compounds dose-dependently inhibited the inflammation resulting from CIA in rats *in vivo*. Compound exposure levels corresponding to 50% inhibition were approximately 70μM*hr and 12μM*hr for Compounds A and B,

respectively. Inhibition of hematological parameters (reticulocytes, hemoglobin and hematocrit levels) in naïve rats was observed with compound administration at exposures comparable to that required for efficacy in the rat CIA model for the non-selective JAK inhibitor, Compound A. In contrast, for the JAK1 selective Compound B, changes in these parameters were not observed until >10X exposures of that required for efficacy in the rat CIA model were achieved. Furthermore, Compound B inhibited bone mineral density loss by μCT and attenuated inflammation, pannus formation, and cartilage damage by histopathology.

Conclusion: We identified a JAK1 selective compound using enzymatic and cellular assays where selectivity translated to *in vivo* selectivity in rats. These data demonstrate that a similar degree of preclinical efficacy is achievable with a JAK1 selective inhibitor as compared to a multi-JAK inhibitor. Importantly, the JAK1 selective inhibitor provided ~10X therapeutic window to adverse events. The optimal JAK selectivity profile to achieve maximal clinical efficacy with minimal side effects in patients remains to be determined.

Disclosure: L. Y. Moy, Merck Pharmaceuticals, 3; **C. S. Chiu**, Merck Pharmaceuticals, 3; **R. Faltus**, Merck Pharmaceuticals, 3; **M. Zielstorff**, Merck Pharmaceuticals, 3; **K. Chakravarthy**, Merck Pharmaceuticals, 3; **S. Deshmukh**, Merck Pharmaceuticals, 3; **I. Kariv**, Merck Pharmaceuticals, 3; **J. Klappenbach**, Merck Pharmaceuticals, 3; **J. Brubaker**, Merck Pharmaceuticals, 3; **D. Liu**, Merck Pharmaceuticals, 3; **T. Siu**, Merck Pharmaceuticals, 3; **J. Young**, Merck Pharmaceuticals, 3; **H. Yu**, Merck Pharmaceuticals, 3; **F. Elwood**, Merck Pharmaceuticals, 3; **M. Cicmil**, Merck Pharmaceuticals, 3.

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Apremilast, a Novel Phosphodiesterase 4 Inhibitor, and Methotrexate Independently Prevent Inflammation *in Vivo* and *in Vitro*. Miguel Perez-Aso[1], M. Carmen Montesinos[2], Aranzazu Mediero[3], Peter H. Schafer[4] and Bruce N. Cronstein[5]. [1]New York University, New York City, NY, [2]Universitat de València, Valencia, Spain, [3]NYU School of Medicine, New York, NY, [4]Celgene Corporation, Summit, NJ, [5]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Phosphodiesterase 4 (PDE4) inhibitors have clear immunoregulatory effects in laboratory studies, and the clinical application of this class of drug in the field of rheumatology is now beginning with the introduction of the novel PDE4 inhibitor apremilast, which was recently approved by the FDA for the treatment of psoriatic arthritis. Although apremilast is known to increase intracellular cAMP levels, less is known about its downstream signaling mediators. We therefore undertook this work to delineate intracellular signaling pathways for apremilast and to examine interactions between apremilast, methotrexate (MTX), and adenosine A2A receptors ($A_{2A}R$).

Methods: After apremilast and lipopolysaccharide incubation, intracellular cAMP, TNF-α, IL-10, IL-6, and IL-1α were measured in the Raw264.7 mouse monocytic cell line. PKA, Epac1/2 (signaling intermediates for cAMP), and A_2R knockdowns were performed by shRNA transfection and interactions with $A_{2A}R$ and $A_{2B}R$. Apremilast and MTX were tested *in vivo* in the murine air pouch model.

Results: *In vitro*, apremilast increased intracellular cAMP (apremilast 1 μM: 240.0±57.7% of control, n=3, $P<0.001$) and reduced TNF-α release ($pIC_{50}=6.98\pm0.20$, n=8), and MTX reduced TNF-α release (maximum inhibition 50.9±10.2% of vehicle, n=3). The specific $A_{2A}R$-agonist CGS21680 (1 μM) increased apremilast potency ($pIC_{50}=7.59\pm0.20$, n=8), suggesting that apremilast-mediated TNF-α inhibition can be enhanced by signaling through $A_{2A}R$. In this mouse-derived cell line, apremilast increased IL-10 (apremilast 100 nM: 576.3±32.8% of control, n=3, $P<0.001$) and IL-6 (apremilast 100 nM: 257±53.1% of control, n=3, $P<0.05$). PKA, Epac1, and Epac2 knockdowns reduced TNF-α inhibition and IL-10 stimulation by apremilast. In the murine air pouch model, both apremilast and MTX significantly inhibited leukocyte infiltration, while apremilast, but not MTX, significantly inhibited TNF-α release (apremilast 5 mg/kg: leukocyte accumulation 72.5±11.6% of vehicle, n=6, $P<0.05$; TNF-α release 65.5±7.7% of vehicle, n=6, $P<0.001$; MTX 1 mg/kg: leukocyte accumulation 54.6±3.9% of vehicle, n=20, $P<0.001$; TNF-α release 83.7±8.9% of vehicle, n=5, $P>0.05$). The addition of MTX (1 mg/kg) to apremilast (5 mg/kg) yielded no more inhibition of leukocyte infiltration or TNF-α release than that of apremilast alone.

Conclusion: The immunoregulatory effects of apremilast appear to be mediated by cAMP through the downstream effectors PKA, Epac1, and Epac2. $A_{2A}R$ agonism potentiated TNF-α inhibition by apremilast, consistent with the cAMP-elevating effects of that receptor. Because $A_{2A}R$ is also involved in the anti-inflammatory effects of MTX, the mechanism of action of both drugs involves cAMP-dependent pathways and is therefore partially overlapping in nature.

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Toluenesulfonylamido-Chalcone, 4-(p-toluenesulfonylamido)-4-Hydroxychalcone (TSAHC) Suppresses Inflammatory Response and Joint Destruction in an Experimental Arthritic Mice and Fibroblast-like Synoviocytes. Yun-Hong Cheon[1], Wan-Hee Yoo[2], Young Sun Suh[3], Min-Gyu Jeon[3], Hyun-Ok Kim[3] and Sang-Il Lee[3]. [1]Department of Internal Medicine, Chonbuk National University Medical School and Research Institute of Clinical Medicine, Jeonju, South Korea, [2]Chonbuk National University School of Medicine, Jeonju, South Korea, [3]Gyeongsang National University School of Medicine, Jinju, South Korea.

Background/Purpose: TSAHC, a toluenesulfonylamido-chalcone, 4-(p-toluenesulfonylamido)-4-hydroxychalcone is a compound to block proliferation and metastatic potential of cancer cells. Fibroblast-like synoviocytes of rheumatoid arthritis (RA-FLS) have inflammatory phenotypes and tumor-like characteristics such as abnormal proliferation, apoptotic resistance, migration, and invasion. Thus, this study was performed to determine whether TSAHC suppress inflammation and joint destruction in K/BxN serum transfer arthritic mice and RA-FLS.

Methods: TSAHC was synthesized with a purity > 99.0%. Treatment included intravenous injections of PBS, vehicle, or TSAHC (5mg/kg once every other day, n=9–10 for each group) for 10 days in K/BxN serum transfer model. Arthritis severity and ankle histology was evaluated using a semi-quantitative scoring system. The levels of inflammatory cytokines in the joints and serum were measured by ELISA and quantitative PCR. The NF-kB activation and cytokine expression were assessed by Western blotting and quantitative PCR using RA-FLS.

Results: The mice injected with TSAHC showed less severe arthritis than vehicle group in clinical score (5.4 ± 0.39 vs. 3.9 ± 0.79, mean ± SE, $p < 0.05$) and the change of ankle thickness (0.49 ± 0.04 vs. 0.29 ± 0.04 mm, $p < 0.01$). The pathologic analysis also showed decreased inflammation and bone erosion in TSAHC group. The levels of TNF-α, IL1-β, and sRANKL were decreased in serum and ankle tissue of TSAHC group than vehicle. In addition, IL-10 was increased nearly by 51% in TSAHC group than vehicle ($p<o.o5$). 20uM of TSAHC, which observed as the highest non-toxic concentration on the cell viability, decreased IL-6 production with reduction of nearly 40% than vehicle ($p<0.05$) and inhibit nuclear translocation of NF-κB in TNF-α-stimulated RA-FLS.

Conclusion: This study indicates that TSAHC inhibit inflammation and bone destruction in arthritic mice and decrease IL- 6 production in RA-FLS via inhibition of NF-κB activation. Therefore, TSAHC may have therapeutic potential for the treatment of RA.

Disclosure: Y. H. Cheon, None; **W. H. Yoo**, None; **Y. S. Suh**, None; **M. G. Jeon**, None; **H. O. Kim**, None; **S. I. Lee**, None.

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Vascular Adhesion Molecule-1 Overexpression in Collagen-Induced Arthritis: Modeling Vascular Dysfunction in Rheumatoid Arthritis. Luca Semerano[1], Gaelle Clavel[2], Delphine Lemeiter[3], Marie-Christophe Boissier[4] and Anne Denys[5]. [1]Avicenne Teaching Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP),, Bobigny, France, [2]Fondation Ophtalmologique A. De Rothschild, Paris cedex 19, France, [3]INSERM UMR 1125, Li2P, University Paris 13, Sorbonne Paris Cité, Bobigny, France, [4]AvicenneTeaching Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Bobigny, France, [5]INSERM UMR U1125, University Paris 13, Sorbonne Paris Cité, Bobigny, France.

Background/Purpose: Rheumatoid Arthritis (RA) patients are at risk of developing primary coronary heart disease earlier than general population. Increased cardiovascular risk in RA is attributed to both traditional Framingham risk factors and systemic inflammation over a long period.

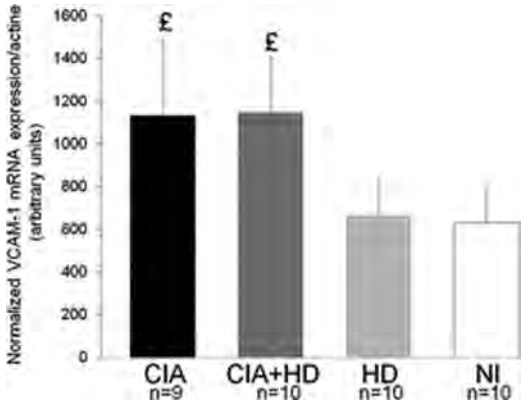
Limited experimental data exist on vascular involvement in arthritis models.

The aim of our study was to model vascular dysfunctions and inflammation in RA using CIA. We focused on VCAM-1, IL-17 and iNOS expression in aorta removed 15 weeks after arthritis induction.

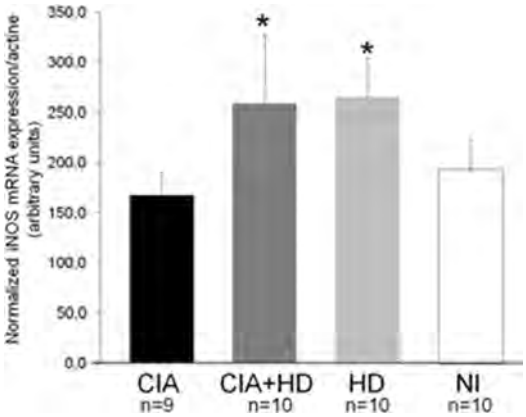
Methods: Arthritis was induced in C57BL mice (11 week old) by 2 injections within 21 days of chicken CII (cCII) emulsioned in Adjuvant (CFA). Half of these mice (n=12) were fed with a hyperlipidic diet (HD and the other half (n=12) with a standard diet. The control mice were not immunized (NI) but were fed either the standard diet (n=12) or HD (n=12). Aorta and synovial membranes were removed 15 weeks after the first immunization. We analysed VCAM-1, iNOS and IL-17 mRNA level in aorta by real time quantitative PCR (qRT-PCR). VCAM-1 localisation in the aortic sinus layers (intima, media and adventitia) was determined by immunohistochemistry (IHC).

Results: VCAM-1 expression was increased in aorta from CIA mice compared to NI mice, regardless of the fed diet (fig.1). Conversely, iNOS expression was increased in aorta from HD fed mice, whether immunized or not (fig.2). The expression of IL-17 in the aorta was not affected by collagen immunization or diet

Conclusion: CIA in C57BL6 mice is accompanied by large vessel inflammation. Collagen immunization induced vascular dysfunctions marked by VCAM-1 overexpression independently of the diet. Conversely, HD diet induced a distinct profile of vessel inflammation characterized by high iNOS expression. CIA may be a pertinent model to study cardiovascular disease in RA.



≤: p<0.05 vs.HD and NI



*: p<0.05 vs. CIA and NI

Disclosure: L. Semerano, None; **G. Clavel**, None; **D. Lemeiter**, None; **M. C. Boissier**, None; **A. Denys**, None.

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The Role of Dendritic Cells during Inflammatory Arthritis. Antonia Puchner[1], Victoria Saferding[1], Eliana Goncalves-Alves[1], Josef S. Smolen[2], Kurt Redlich[1] and Stephan Blüml[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria.

Background/Purpose: Dendritic cells (DCs) play an important role in bridging the innate and the adaptive immune response by serving as antigen presenting cells and are therefore implicated in the initiation of chronic autoimmune diseases, including rheumatoid arthritis. Using two different models of inflammatory arthritis, K/BxN serum transfer arthritis as well as hTNFtg arthritis, both depending only on the innate immune system, we investigated the innate role of dendritic cells in inflammatory arthritis.

Methods: We analyzed histological sections of K/BxN serum transfer arthritis as well as hTNFtg arthritis for the presence of $CD11c^+$ cells by immunohistochemistry. We also performed synovial biopsies and analyzed the cellular composition of the inflammatory infiltrate with respect to DCs. We used CD11c-diphteria toxin receptor (DTR) transgenic mice, which express the human diphtheria-toxin receptor under the CD11c promoter, allowing for specific depletion of $CD11c^+$ cells by administration of diphtheria toxin (DT). K/BxN serum transfer arthritis was induced, and mice were given either DT or PBS. In addition CD11c DTR mice were crossed into hTNFtg animals and also received either DT or PBS. The severity of arthritis was determined clinically and histologically.

Results: We show that $Cd11c^+$ cells are present in significant numbers in the synovia of K/BxN and TNF driven arthritis. Both myeloid dendritic subsets, $CD8^+$ $CD11c^+$ and $CD11b^+$ $CD11c^+$, can be found in synovial tissue. In K/BxN serum transfer arthritis, clinical scores showed that CD11c-DTR transgenic mice that received DT had significantly reduced paw swelling and loss of grip strength compared to PBS treated animals. Histological analysis found reduced inflammation after the depletion of $CD11c^+$ cells in K/BxN arthritis. In addition local bone destruction and the number of osteoclasts was significantly reduced. Also in TNF-driven arthritis in CD11c-DTR/hTNFtg mice, depletion of $CD11c^+$ cells led to a significant reduction of synovial inflammation, as well as local bone erosions. To exclude unspecific effects of DT in mice, wild type animals received DT showed identical clinical and histological signs of arthritis as PBS treated animals.

Conclusion: These data show that $CD11c^+$ cells are involved in innate reactions leading to inflammatory arthritis and suggest that dendritic cells could be an important therapeutic target for patients suffering from rheumatoid arthritis.

Disclosure: A. Puchner, None; **V. Saferding**, None; **E. Goncalves-Alves**, None; **J. S. Smolen**, None; **K. Redlich**, None; **S. Blüml**, None.

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CGEN-15001, a Novel Immunomodulatory Fusion Protein of the B7 Family Induces Immune Tolerance and Shows Efficacy in Mouse Models of Rheumatoid Arthritis and Psoriasis. Iris Hecht[1], Kay McNamee[2], Aviad Keren[3], Joseph R. Podojil[4], Ilan Vaknin[1], Anat Oren[1], Galit Rotman[1], Eyal Neria[1], Stephen D. Miller[4], Amos Gilhar[3] and Richard O. Williams[2]. [1]Compugen Ltd., Tel Aviv, Israel, [2]Oxford University, Oxford, United Kingdom, [3]Technion Institute of Technology, Haifa, Israel, [4]Northwestern University, Chicago, IL.

Background/Purpose: CGEN-15001 is an Fc-fusion protein consisting of the extracellular domain of a novel B7-like protein, discovered based on shared family characteristics. CGEN-15001 inhibits T cell activation and demonstrates immunomodulatory activity by inhibiting Th1 and Th17 responses while promoting Th2 responses and IL-10 secretion. Potential re-establishment of immune tolerance by CGEN-15001 is suggested by durable long term efficacy observed following short course therapeutic treatment in the EAE model of multiple sclerosis and in the NOD mouse model of type 1 diabetes. Tolerance induction is further supported by prevention of graft rejection in the H-Y minor Ag mismatch bone marrow transplantation model and by enhancement of Tregs. CGEN-15001 is also efficacious in a CIA model of rheumatoid arthritis (RA) and we sought to further study its mode of action in this model. Furthermore, the efficacy of CGEN-15001 was tested in a humanized psoriasis mouse model to elucidate its therapeutic potential for this disease.

Methods: CIA was induced by immunizing DBA/1 mice with type II collagen (CII) in CFA. Efficacy was evaluated following therapeutic treatment starting at onset of arthritis symptoms. On day 10 of arthritis paws and sera were collected for analysis. For mode of action studies, treatment was given from the day of disease induction, and *ex-vivo* recall responses were tested on draining lymph nodes (dLN) cells harvested on day 10 and re-stimulated with CII or anti-CD3. Proliferation and cytokine secretion were evaluated.

Psoriasis was induced in normal human skin grafted onto SCID mice by intradermal injection of activated PBMCs from psoriatic patients. Treatment began at time of disease induction.

Results: CGEN-15001 demonstrated a potent therapeutic effect in the CIA model with significant reduction of clinical score and joint swelling. Reduced inflammation and joint erosion were observed by histological analysis of the arthritic joints. In addition, CGEN-15001 treatment resulted in increase of the CII-specific IgG1/IgG2a ratio in the serum, which is in line with a Th1/Th17 to Th2 shift observed previously in vitro and in vivo.

Recall responses of dLN cells from CGEN-15001 treated mice results in inhibition of proliferation and secretion of IL-17 and GM-CSF in cultures reactivated with the inducing antigen, CII.

In the psoriasis model, CGEN-15001 treatment resulted in prevention of psoriasiform features in 55% of grafts, and in significant reduction in epidermal thickness. In addition, decrease in hallmark pathologic and inflammatory features of psoriatic skin were shown by IHC.

Conclusion: The therapeutic effect of CGEN-15001 in the CIA model of RA and in the humanized mouse model of psoriasis support its therapeutic potential for these diseases. These findings might also indicate a potential clinical value for psoriatic arthritis, a disease which combines both skin and joint pathologies and is underserved by current therapies. Its effect on key pathologic mechanisms of these and other autoimmune diseases, including downregulation of Th1 and Th17 inflammatory responses, induction of regulatory T cells and restoration of immune tolerance suggest a broad therapeutic potential with durable long-term effect.

Disclosure: I. Hecht, Compugen Ltd., 3; **K. McNamee**, Compugen Ltd., 2; **A. Keren**, Compugen Ltd., 2; **J. R. Podojil**, Compugen Ltd., 2; **I. Vaknin**, Compugen Ltd., 3; **A. Oren**, Compugen Ltd., 3; **G. Rotman**, Compugen Ltd., 3; **E. Neria**, Compugen Ltd., 3; **S. D. Miller**, Compugen Ltd., 2; **A. Gilhar**, Compugen Ltd., 2; **R. O. Williams**, Compugen Ltd., 2.

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Glucocorticoids and Vascular Function in Arthritis: Benefic or Deleterious Effects? Study in Rat. Frank Verhoeven[1], Katy Maguin-Gaté[2], Perle Totoson[3], Daniel Wendling[4] and Céline Demougeot[5]. [1]CHU jean Minjoz, Besançon, France, [2]EA 4267 « Fonctions et Dysfonctions Epithéliales », Faculté de Médecine-Pharmacie, Besançon, France, [3]EA 4267 "Fonctions et Dysfonctions Epithéliales", besançon, France, [4]CHU J Minjoz, Besancon, France, [5]EA 4267 "Fonctions et Dysfonctions Epithéliales", Besançon, France.

Background/Purpose: Rheumatoid Arthritis (RA) is associated to an increase of cardiovascular (CV) risk explained in part by an accelerated atherosclerosis as a consequence of endothelial dysfunction. Glucocorticoids (GCs) are widely prescribed in RA patients. Surprisingly, despite the commonly held belief that glucocorticoids worsen the CV risk, data concerning their impact on endothelial function in RA are lacking. The present study investigate the effect of prednisolone on vascular function in arthritic rats and identified the underlying mechanisms.

Methods: Adjuvant-induced arthritis (AIA) was induced in 6 weeks old male Lewis rats by injection of *Mycobacterium butyricum* in adjuvant at the basis of the tail. At the onset of arthritis, rats were daily treated (i.p) with prednisolone at 10 (high dose) or 0.1 mg / kg (Low dose) or saline (Vehicle) for 21 days. Arthritis score and tarsus diameter were daily monitored. At the end of treatment, thoracic aortas were harvested to measure the relaxation to acetylcholine on pre-constricted aortic rings in the presence or not of inhibitor of nitric oxide (NO) synthase (L-NAME), arginase (nor-NOHA), COX-2 (NS-398), EDHF (Apamin/Charybdotoxin), or a superoxide dismutase analog (Tempol). The relaxing effect of a NO donor (sodium nitroprussiate, SNP) was studied on endothelium-denuded aortic rings. Blood pressure and heart rate, glycaemia, triglyceride and total cholesterol levels and radiological score of hind paws were also assessed.

Results: Compared to "Vehicle", AIA "High dose" exhibited reduced ($p<0.05$) arthritic score, paw diameters and radiological damage. This dose of GC significantly ($p<0.05$) improved Ach-induced relaxation through increased NO synthase activity and EDHF production, decreased arginase and COX-2 activities and decreased superoxide anions production. Blood pressure and triglyceride level were significantly ($p<0.05$) higher in AIA "high dose". By contrast, the low dose of prednisolone modified nor arthritis severity neither blood pressure, glycaemia and triglycerides levels. On the vascular side, this dose decreased the production of superoxide anions and increased EDHF, but failed to improve endothelial function in AIA rats. The response of rings to the NO donor was unchanged after GC treatment whatever the dose.

Conclusion: Our study demonstrates for the first time that a high dose of prednisolone during a short time is beneficial for endothelial function in case of arthritis, even though it induced deleterious cardio-metabolic effects. From a clinical perspective, these results raise the question of the use of high doses of GC during a short period to reverse endothelial dysfunction along with a rapid disease control. Whether this beneficial vascular effect of GC depends on the reduction of disease activity or not deserves further investigations.

Disclosure: F. Verhoeven, None; **K. Maguin-Gaté**, None; **P. Totoson**, None; **D. Wendling**, None; **C. Demougeot**, None.

2361

the Role of CD146 in the Therapeutic Potential of Mesenchymal Stem Cells in Favor of CD146$^+$ Cells for Experimental Arthritis. Deh-Ming Chang[1] and Cheng-Chi Wu[2]. [1]Taipei Veteran's General Hospital, Taipei, Taiwan, [2]National Defense Medical Center, Taipei, Taiwan.

Background/Purpose: To illustrate whether the subtypes of mesenchymal stem cells (MSCs) have different cellular characteristics and therapeutic potentials, we separated CD146+/− mesenchymal stem cells and investigated their effects on chondrogenesis, osteogenesis, the Treg/TH17 cells expression and arthritis model.

Methods: We isolated CD146+ cells from human umbilical cords mesenchymal stem cells by beads sorting and then investigated the chondrogenesis and osteogenesis in a conditioned medium. The cytokine levels of IL-6 and TGFβ1 in CD146$^{+/-}$ cells and the effects of CD146$^{+/-}$ cells on Treg/Th17 cell population were analyzed by flow cytometry. CD146+/− cells were injected intraarticularly (IA) in experimental mice model, and then analyzed the clinical scores and the histological findings.

Results: CD146$^+$ cells showed significant higher chondrogenesis than CD146$^-$ cells. CD146$^+$ cells also expressed lower levels of IL-6 than CD146$^-$ cells. Furthermore, TH17 cells were significantly induced post addition of CD146$^-$ cells *in vitro* and *in vivo*. Our data also showed that the intraarticular injection of CD146$^+$ cells attenuated the disease progress *in vivo*. The immunohistological stains showed that only HLA-A$^+$ CD146$^+$ cells could be detected in the cartilage of CIA mice, and may preserve proteoglycans expression.

Conclusion: We firstly demonstrated that CD146$^+$ cells have higher multilineage potency and can suppress the activation of TH17 cells *in vitro* and suppress disease activities *in vivo*. These data suggest that CD146$^+$ cells have more therapeutic potentials than CD146$^-$ cells for inflammatory arthritis.

Disclosure: D. M. Chang, None; **C. C. Wu**, None.

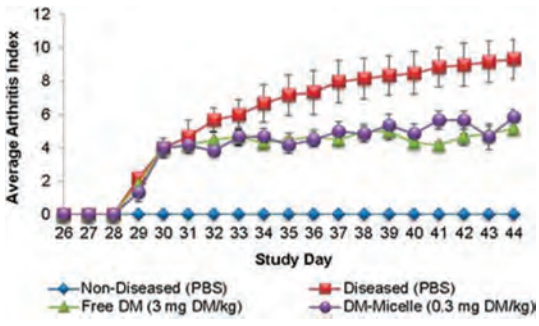
2362

Enhanced Efficacy of Dexamethose with Synovial Fibroblast Targeted Micelles in a Collagen-Induced Arthritis Mouse Model. Rebecca A. Bader, David R. Wilson, Arundhati Ramani and Patricia R. Wardwell. Syracuse University, Syracuse, NY.

Background/Purpose: A number of conventional, disease modifying anti-rheumatic drugs (DMARDs) are associated with severe side effects due to non-specific targeting and impaired immune function. To improve therapeutic efficacy and reduce negative consequences, our research group has developed a platform for site-specific delivery to the synovial tissue based upon the self-assembly of polycaprolactone modified polysialic acid (PSA-PCL) into micelles. Hydrophobic DMARDs, such as dexamethasone (DM), can be entrapped within the micelles at a loading capacity of 0.1 mg DMARD/mg of PSA-PCL. To further enhance specificity, targeting of the overexpressed CD44 receptor on RA synovial fibroblasts was achieved by modifying the PSA-PCL with hyaluronic acid (HA) oligomers to yield PSA-PCL-HA micelles. The goal of this study was to establish the *in vivo* therapeutic efficacy of DM-loaded, PSA-PCL-HA micelles using a collagen-induced arthritis (CIA) mouse model.

Methods: 24 male, DBA/1J mice were divided into four treatment groups: non-diseased, diseased (with no drug therapy), free DM (3.0 mg DM/kg), and DM-loaded micelle (3.0 mg PSA-PCL-HA/kg ~ 0.3 mg DM/kg). At day 28 following induction of collagen-induced arthritis (CIA) in 18 of the 24 mice, each mouse was scored for arthritis index (AI). Treatments were administered via tail-vein injection starting on day 32. Subsequently, the mice received IV doses every 3 days until completion of the study on day 44. Treatment groups designated as diseased and non-diseased received tail vein injections of PBS alone (10 mL/kg).

Results: Based upon the average AI, DM, alone and when entrapped within the PSA-PCL-HA micelles, reduced the symptoms of RA. Mice that were administered treatments of DM-loaded micelles were provided with 1/10th the DM dose received by mice within the free DM treatment group. Despite the significantly reduced dose, the DM-loaded micelles yielded a decrease in average AI that was comparable to that obtained with free DM.



Conclusion: This study demonstrated that our targeted, drug delivery platform can be used to enhance the therapeutic efficacy of hydrophobic DMARDS. DM loaded into the PSA-PCL-HA micelles was as effective as free DM when administered at 1/10th the dose to mice with CIA.

Disclosure: R. A. Bader, None; **D. R. Wilson**, None; **A. Ramani**, None; **P. R. Wardwell**, None.

2363

Leucine-Rich Alpha-2 Glycoprotein Is a Potential Disease Activity Marker Under IL-6 Suppression in Autoimmune Arthritis. Yusuke Takahashi[1], Minoru Fujimoto[2], Satoshi Serada[3] and Tetsuji Naka[2]. [1]Osaka university, Suita city, Japan, [2]National Institute of Biomedical Innovation, Ibaraki, Japan, [3]National Institute of Biomedical Innovation, Laboratory for immune signal, Japan, Ibaraki, Japan.

Background/Purpose: C-reactive protein (CRP) is frequently used to evaluate inflammation in patients with rheumatoid arthritis (RA). However, CRP is normalized when IL-6 function is potently suppressed by anti-cytokine biologics such as tocilizumab. Therefore, novel biomarkers are required for accurate and sensitive assessment of the inflammation during anti-cytokine therapy. By proteomic screening of sera from patients with rheumatoid arthritis (RA), we previously identified serum leucine-rich alpha-2 glycoprotein (LRG)as a potential biomarker that reflects disease activity in RA better than CRP.

This study is aimed to investigate the clinical significance of LRG as a biomarker of RA disease activity during anti-IL6 therapy.

Methods: As a preclinical testing, cynpmolgus monkeys with collagen induced arthritis (CIA) were treated with anti-IL-6 receptor antibody (anti-IL-6-R mAb) and joint sewelling and rigidity were scored for clinical assessment of arthritis throughout the experiment. At the time of sacrifice, blood samples were collected to be subjected to the measurement LRG and CRP were evaluated.

Results: In CIA monkeys with anti-IL-6R mAb treatment, plasma LRG levels correlated better with disease activity than plasma CRP levels, presumably due to the fact that LRG levels were elevated in some animals with negative CRP in spite of high arthritis scores. Furthermore, among tocilizumab-treated patients for 6months with normalized CRP levels ($<$0.2mg/dL), serum LRG levels were significantly higher in patients with active RA (defined by CDAI$>$10) than those with RA with low disease activity (CDAI$\leq$10).

Conclusion: Our study indicates that LRG is a promising biomarker for monitoring disease activity in RA, even when CRP levels are reduced or normalized by anti-cytokine therapy.

Disclosure: Y. Takahashi, None; **M. Fujimoto**, None; **S. Serada**, None; **T. Naka**, None.

2364

PET-CT Imaging of Joints: A Quantitative Tool for Developing Novel Anti-Inflammatory Drugs. Siba Raychaudhuri[1], Anupam Mitra[2], Smriti K. Raychaudhuri[2] and Abhijit Chaudhari[3]. [1]Univ California Davis/VA Sac, Davis, CA, [2]VA Sacramento Medical Center, Mather, CA, [3]UC Davis School of Medicine, Sacramento, CA.

Background/Purpose: Mouse collagen induced arthritis (CIA) is the most commonly used preclinical model to screen new drug candidates for inflammatory arthritis. The conventional read out of this model are clinical score and histopathology. These read outs have several limitations including (i) longitudinal studies using the same mouse cannot be performed; (ii) clinical and histopathological scores are subjected to observer bias; (iii) *in vivo* cellular events cannot be captured in its native environment. Thus, an *in vivo* drug screening tool is the unmet need of the day. Herein, we validated ^{18}F-FDG PET as an *in vivo* drug screening tool for new anti-inflammatory drugs using the mouse CIA model.

Methods: Animal handling was performed in accordance with the approved UC Davis IACUC protocol. Arthritis was induced using bovine type II collagen in 8–12 week old male DBA/1J mice (n=20), out of which 15 mice showed clinical signs of arthritis on day 28. After the disease progressed, on the day 42 to identify the pre-treatment histopathology 5 mice were sacrificed. In the remaining 10 mice, 5 mice received I.P 300 μg of anti-mouse TNF-α antibody (CNTO5048, Janssen Biotech, PA, USA) every alternate day for next 10 days, and 5 mice remained untreated (negative control). Mice were scored clinically and had ^{18}F-FDG PET scan on day 42 and 52. Histological score (HS) of the joint tissues were performed in all the mice.

Results: The pre-treatment mean clinical score (CS), histopathological score (HS), and ^{18}F-FDG uptake were 3.8$\pm$1.1, 9$\pm$1 and 340$\pm$22 kBq/cc (Mean$\pm$SD), respectively. In the untreated group, the CS, HS and ^{18}F-FDG uptake progressed on day 52 to 5.4$\pm$1.2 ($p<0.05$), 13.4$\pm$1.3 ($p<0.05$) and 480$\pm$32 KB1/cc ($p<0.05$), respectively. Anti-TNF therapy successfully arrested the disease progression as evident by CS and HS at day 52, 0.75$\pm$0.06 ($p<0.01$) and 2.5$\pm$1.1 ($p<0.01$), respectively compared to untreated group. ^{18}F-FDG PET uptake in this group was also significantly decreased at day 52 to 200$\pm$12 KBq/cc ($p<0.01$) (Figure 1). The PET uptake significantly correlated with changes in CS ($r^2=0.74$, $p<0.01$) and HS ($r^2=0.9$, $p<0.01$). Among CS and HS, the correlation of ^{18}F-FDG PET with HS was higher than that observed with CS.

Conclusion: Our observation strongly suggest that ^{18}F-FDG PET scan can be considered as an *in vivo* preclinical drug screening tool for anti-inflammatory drugs of autoimmune arthritis. PET-CT imaging will reduce the number of animals required for a study and also the same animal can be studied at different stages of the disease, which will eventually reduce the effect of intra-species biological variations. The use of this *in vivo* imaging tool will allow longitudinal quantitative evaluation of the degree of joint inflammation in the same mouse.

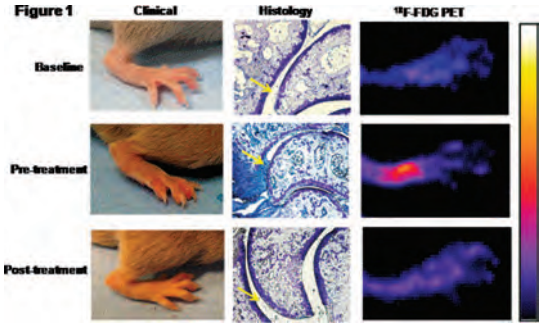


Figure 1: ^{18}F-FDG PET is an useful i*n vivo* tool to assess therapeutic potential of antiinflammatory drugs (representative image).

Disclosure: S. Raychaudhuri, None; **A. Mitra**, None; **S. K. Raychaudhuri**, None; **A. Chaudhari**, None.

ACR/ARHP Poster Session C
Rheumatoid Arthritis - Clinical Aspects: Impact of Various Interventions and Therapeutic Approaches
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

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Comparison of the Effects of a Pharmaceutical Industry Decision Guide and Decision Aids on Patient Choice to Intensify Rheumatoid Arthritis Therapy with Etanercept. Richard Martin[1], Ryan Enck[2], Andrew J. Head[3], James Birmingham[1] and Aaron T. Eggebeen[2]. [1]Michigan State University, College of Human Medicine, Grand Rapids, MI, [2]Michigan State University College of Human Medicine, Grand Rapids, MI, [3]College of Human Medicine, Michigan State University, Grand Rapids, MI.

Background/Purpose: To evaluate the comparative effects of a pharmaceutical industry decision guide (Pharm Booklet) and International Patient Decision Aids Standard (IPDAS) compliant patient decision aids (PtDA) on patient choice to intensify rheumatoid arthritis (RA) therapy.

Methods: We conducted a mail survey of 797 biologic naïve RA patients in a community rheumatology practice. Patients were presented with a hypothetical decision scenario where they were asked to consider adding Enbrel™ (etanercept) to their current regimen. Each was randomized to review 1 of 3 forms of etanercept specific decision support: a long 24 page PtDA (LONG DA), a short 2 page PtDA (SHORT DA), or the manufacture's Enbrel™ decision guide (Pharm Booklet). Each subject was evaluated for: their decision to intensify therapy, beliefs about etanercept viewed through the Integrated Model of Behavioral Prediction, pre and post intervention etanercept related knowledge and decisional conflict.

Results: 402 anti-TNF naïve RA patients participated (response rate 52%). 30.6% of patients randomized to Pharm Booklet elected to initiate etanercept. Only 14.6% and 14.0% of patients who reviewed the LONG DA or SHORT DA choose to take etanercept ($\chi^2=15.7$; $P<.001$). A binary logistic regression model explained 44.2% ($R^2=$.

442) of patient choice to intensify therapy by initiating etanercept. The strongest predictor of choice to intensify therapy were beliefs about etanercept: Improve Symptoms (OR = 2.55), Social Normative Beliefs about intensifying therapy with etanercept (OR = 2.24), and likelihood of Adverse Event (AE) (OR= 0.59). LONG and SHORT DA produced greater increase of relevant knowledge, but greater knowledge and feeling of being informed did not impact patient beliefs about etanercept, decisional conflict or their choice to intensify therapy. After controlling for other co-variates, gender, low income, minority status, HAQ and CDAI did not add to the predictive power of the model. The brief 2 page PtDA was acceptable to patients, and lead to similar knowledge gains and decisional conflict as a 24 page IPDAS compliant PtDA.

Conclusion: PHARM Booklet may nudge patients towards adopting a proposed commercial product without critical consideration of the drug attributes. Patient decision aids offer a balanced alternative that clinicians could use to structure complex medication discussions and support more informed patient choice. We believe patients would benefit if they used them more.

Disclosure: R. Martin, None; **R. Enck**, None; **A. J. Head**, None; **J. Birmingham**, None; **A. T. Eggebeen**, None.

2366

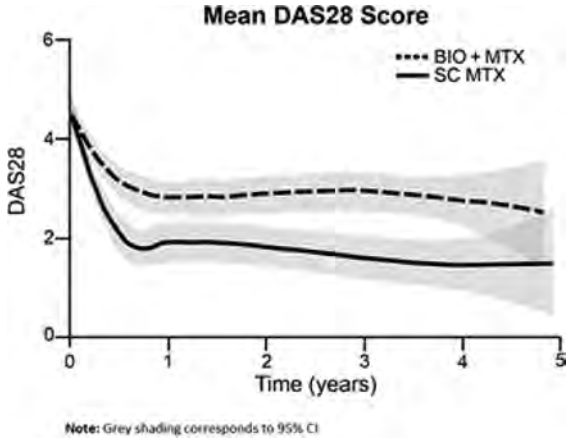
Effectiveness, Tolerability, and Safety of Subcutaneous Methotrexate in Early Rheumatoid Arthritis: Clinical Data from the St. Gallen Cohort. Ruediger Mueller[1], Johannes von Kempis[1], Michael H Schiff[2] and Sarah Haile[3]. [1]St. Gallen Hospital, CH- 9007 St.Gallen, Switzerland, [2]University of Colorado, Denver, CO, [3]University of Zurich, Switzerland, Zurich, Switzerland.

Background/Purpose: MTX is the cornerstone of RA treatment, although limitations of systemic exposure of oral MTX may affect its efficacy. Subcutaneous (SC) MTX has greater bioavailability than oral MTX, which may result in better efficacy and tolerability. Few clinical studies have assessed the efficacy and tolerability of SC MTX. We assess the clinical effectiveness and tolerability of SC MTX among pts with RA naïve at baseline to both conventional and biologic DMARDs at our center.

Methods: DMARD-naïve RA pts fulfilling the ACR/EULAR-2010 criteria and had ≥ 1 follow-up visit were selected through sequential chart review until 70 were identified using a prospectively designed retrospective analysis. Pts received SC MTX at varying doses (10–25 mg/week, mean 18.2 mg) w/ 5 mg folic acid/wk. The primary endpoint was a change in DAS28 (ESR); secondary endpoints included time to employment of the first biologic agent and cumulative MTX doses. Pts were followed until SC MTX administration was terminated or their last clinical visit. Decision for adding biologic agents was at the discretion of the treating physician.

Results: 70 pts remained in follow-up for a mean ± SD of 1.8 ± 1.6 years (range, 0.13–7.1) after initiating SC MTX treatment. During this time 33 (47%) required the addition of a biologic therapy (BIO+MTX), and 37 (53%) remained on SC MTX without any biologics (SC MTX). Mean weekly MTX doses were 19.1 mg for BIO+MTX pts and 17.4 mg for SC MTX pts. Compared to SC MTX pts, BIO+MTX pts were more frequently female (63.6% vs 51.4%), and less frequently ACPA-positive at baseline (33.3% vs 51.4%). Mean baseline DAS28 scores were 4.9 (range 2.42–7.4) for BIO+MTX pts and 4.7 (range 1.6–7.7) for SC MTX pts. During follow-up, BIO+MTX pts had a higher DAS28 score (mean ± 95% CI) than SC MTX pts (see figure). Both LDAS and remission were achieved by slightly fewer BIO+MTX than SC MTX pts (LDAS, 78.8% vs 81.1%; remission, 69.7% vs 75.7%). Among BIO+MTX pts, biologic therapy was required after a mean ± SD of 387 ± 404 days (range 54–2164). Over the the study period, SC MTX was discontinued in 32 pts (46%). Most common discontinuation reasons were gastrointestinal discomfort (n=7), inefficacy (n=7), disease remission (n=3), patient's decision (n=3), interstitial lung disease (n=1), and cough (n=1). Severe infections occurred in 3/33 (9%) of BIO+MTX pts and in 3/37 (8%) of SC MTX pts.

Conclusion: SC MTX is an effective, well-tolerated option for pts with RA in real life. Remission was achieved by a majority of pts following the initiation of SC MTX, and the addition of biologics was not needed throughout the study period for about half of pts. SC MTX delayed need for biologic therapy for about 1 year for almost half of the pts.



Disclosure: R. Mueller, AbbVie, Antares Pharma, Pfizer, Roche, and UCB, 5, Scientific grants: Bristol-Myers Squibb, Roche, and UCB, 2; **J. von Kempis**, AbbVie, Antares Pharma, Bristol-Myers Squibb, MSD, Pfizer, Roche, and UCB, 5, ristol-Myers Squibb, Roche, and UCB, 2; **M. H. Schiff**, AbbVie, Amgen, Antares Pharma, Bristol-Myers Squibb, Horizon, Lilly, Novartis, and UCB, 5; **S. Haile**, None.

2367

Physician Awareness of Suboptimal Patient Adherence to MTX: Results from a Large U.S. Rheumatoid Arthritis Registry. Jeffrey R. Curtis[1], Aseem Bharat[1], Lang Chen[1], Jeffrey D. Greenberg[2], Joel M. Kremer[3] and Dimitrios A. Pappas[2]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Corrona, LLC., Southborough, MA, [3]Albany Medical College and the Center for Rheumatology, Albany, NY.

Background/Purpose: Most rheumatoid arthritis (RA) registries capture information about medication use using data captured at office visits. The extent to which this information may be misclassified or over-estimated for RA medications, including methotrexate (MTX), is unknown.

Methods: In 1Q and 2Q 2014, we conducted an Internet-based survey of RA patients participating in the comparative effectiveness CERTAIN substudy (n= 2485 unique biologic initiations as of April 2014) nested within the Corrona RA registry. Patients were eligible if they had valid email addresses (n=991 unique patients).. Patients were asked whether they were taking methotrexate and if so, how many MTX doses in the last 4 weeks they had taken. Patient report from the survey was used as the gold standard and compared to the use of MTX routinely recorded in the registry at the previous and next office visits. A subgroup analysis was conducted for the additional patients who had not yet had a follow-up visit in the registry. A sensitivity analysis restricted the interval of time between the survey and the previous registry visit to <=6 months to assess whether misclassification of MTX use was related to the interval of time between registry visits.

Results: A total of 433 patients answered the survey, a 44% response rate. Overall, survey respondents had mean (SD) age 53.5 (12.5) age, were 80.8% women, and 78.9% RF+ or CCP+. Mean (SD) disease activity measured at the previous visit using CDAI was 17.4 (14.7). Of the subgroup of patients who were recorded at the prior and next registry visit as consistently being on MTX (n=88), only 1 (1%) of patients indicated that they were not actually taking MTX. However, 10% of the remaining patients indicated that they had missed one or more doses in the last 4 weeks. Results were similar for the 111 additional patients who had not yet had a follow-up registry visit; 15% indicated that they had missed one or more doses in the last 4 weeks. Of the patients who missed one or more doses in the last 4 weeks, approximately one-third to one-half missed more than 1 dose. Results were robust in sensitivity analysis.

Conclusion: In this large U.S. registry, MTX use was generally ascertained accurately at office visits. However, up to 15% of patients recorded by their rheumatologist to be on MTX had missed doses in the last month. Clinicians need to be aware of potentially suboptimal adherence when assessing response to MTX. Further efforts to detect low adherence to MTX and identify reversible barriers to adherence are needed.

Disclosure: J. R. Curtis, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo AbbVie, 2, Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo AbbVie, 5; **A. Bharat**, None; **L. Chen**, None; **J. D. Greenberg**, Corrona, LLC., 1, Corrona, LLC., 3, AstraZeneca, Celgene, Novartis and Pfizer, 5; **J. M. Kremer**, Corrona, LLC., 3, Corrona, LLC., 1; **D. A. Pappas**, Corrona, LLC, 3, Novartis Pharmaceutical Corporation, 9.

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Impact of Physicians' Adherence to Treat-to-Target Strategy on Outcomes in Early Rheumatoid Arthritis. Laura Kuusalo[1], Kari Puolakka[2], Hannu Kautiainen[3], Marjatta Leirisalo-Repo[4] and Vappu Rantalaiho[5]. [1]Turku University Hospital, Turku, Finland, [2]South Karelia Central Hospital, Lappeenranta, Finland, [3]Medcare Oy, Äänekoski, Finland, [4]Helsinki University Central Hospital, Helsinki, Finland, [5]Tampere University Hospital, Tampere, Finland.

Background/Purpose: We have previously shown that in early rheumatoid arthritis (RA) remission targeted, intensive combination treatment, regardless of initial infliximab, results in remission in most patients. Still, patients' adherence to medication in RA is often poor and difficult to improve. Little attention, however, has been focused on the effect of physicians' adherence.

Methods: In the Neo-RACo study 99 patients with early, active RA were treated with methotrexate, sulfasalazine, hydroxychloroquine and low-dose prednisolone for 2 years. Patients were randomized to receive either infliximab or placebo for 6 months from week 4. All swollen joints had to be injected with intra-articular glucocorticoids. After 2 years, medication could be tapered down in the case of remission. In non-remission, treatments were unrestricted, including the use of biologics. At all times, treatment aimed at strict Neo-RACo remission defined as no swollen or tender joints and presence of 5 out of the 6 following criteria: morning stiffness <15 minutes; no fatigue; no joint pain; no tender joints; no swelling in joints or tendons; and ESR <30 mm/h in women and <20 mm/h in men. During a 5-year follow-up, strict remission rates, disease activity score 28 (DAS28) levels, radiological changes, anti-rheumatic medication after 2 years, and cumulative days off work were assessed. Physicians' ($n=30$) adherence during 15 study visits between 0 and 24 months was evaluated with a scoring system. On every visit, lack of glucocorticoid injections (0.2–0.4 points), lack of medication adjustments (0.4 points), and poor filling of the study forms (0.2 points) were assessed. Also, 0.5–1.0 points were given if a study visit was cancelled. The patients were divided into tertiles by the sum of the points for inactivity between 0 and 24 months. Factors contributing to remission rates at 3 and 24 months were evaluated.

Results: Follow-up data were available on 93 patients. Mean of the sum of the points for inactivity was higher in the placebo group (2.67 ± 2.25) than in the infliximab group (2.09 ± 1.71, $p=0.032$). Physicians' adherence ($p<0.001$), duration of symptoms ($p=0.037$) and the use of infliximab ($p=0.016$) predicted strict remissions in a multivariable model at 3 months, whereas at 24 months physicians' adherence ($p<0.001$) was the sole independent predictor. We found a relationship favoring active treatment on strict Neo-RACo remission rates, which were 77.4%, 62.7% and 46.7% ($p=0.018$) in the actively treated, the intermediately treated, and the inactively treated at 2 years. The respective figures at 3 years were 80.0%, 56.3% and 53.3% ($p=0.048$), at 4 years 73.3%, 75.0% and 41.4% ($p=0.025$), and at 5 years 63.6%, 65.6% and 51.7% ($p=0.40$). In addition, the DAS28 levels were lower in the actively treated than in the intermediately and the inactively treated at all time points. There were no significant differences in radiological progression and cumulative days off work between tertiles of treatment activity. After the first 24 months, biologics were used more often among the inactively treated compared with the intermediately and the actively treated ($p=0.024$).

Conclusion: Physicians' active stance is crucial for the targeted treatment of RA to work.

Disclosure: L. Kuusalo, None; **K. Puolakka**, Abbvie inc, BMS, Pfizer inc, MSD, Roche, UCB, 5; **H. Kautiainen**, Abbvie inc, Pfizer inc, 5; **M. Leirisalo-Repo**, MSD Finland, 5; **V. Rantalaiho**, None.

2369

Management of Perioperative Tumor Necrosis -á Inhibitors in Rheumatoid Arthritis Undergoing Arthroplasty: A Systematic Review and Meta-Analysis. Susan M. Goodman[1], Indu Menon[2], Rie Smethurst[2], Paul Christos[3] and Vivian P. Bykerk[1]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, NY, NY, [3]Weill Cornell Medical College, NY, NY.

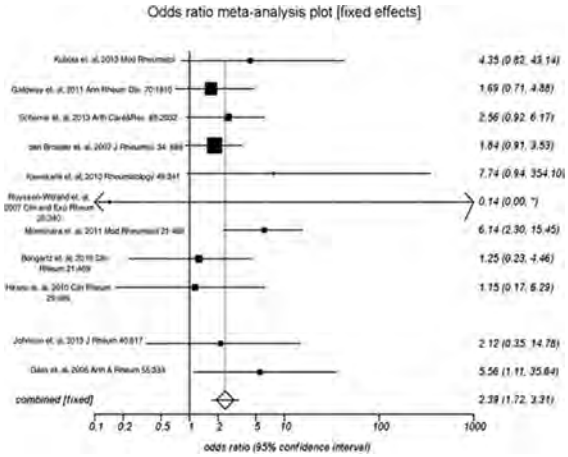
Background/Purpose: Tumor Necrosis Factor α inhibitors (TNFi) are widely used in patients with RA (Rheumatoid Arthritis) undergoing orthopedic surgery, yet its optimal perioperative management is unknown. The objective of this study is to systematically review the available literature regarding perioperative TNFi management and post-operative infections and to formulate clinical practice recommendations for the optimum perioperative use of TNFi.

Methods: A librarian assisted search was conducted in PUBMED, EMBASE, and the Cochrane Central Register of Controlled Trials, with defaulted date range of each database using the following key terms: Rheumatoid Arthritis, TNF- α, antirheumatic agent, surgical site infections (SSI), surgery/infection, arthroplasty, anti-TNF- α, infliximab, etanercept, adalimumab, risk factor, perioperative, postoperative. Studies were included if most patients had RA, age ≥ 18, and were undergoing orthopedic surgery. The intervention was use of TNFi. The comparison group was patients not treated with TNFi. The outcome of interest was surgical site infection. Study quality was assessed using Oxford Center for Evidence Based Medicine Levels of Evidence. No randomized controlled trials were available; high quality cohort studies (2b) and case control studies (3b) were included.

Results: A total of 2,004 studies were found. After abstract review, 30 studies met inclusion criteria. After detailed quality assessment, 11 studies met criteria with low risk of bias, representing 3730 RA patients with recent exposure to TNFi's (TNF+) and 4,307 with no recent exposure to TNFi's at the time of surgery (TNFi-). These studies were included in the final analysis. There was no consistent reporting of corticosteroid use. If the non-combinability p-value was greater than 0.20, a fixed-effects model was used to estimate the pooled odds ratio (OR); if $p\leq0.20$, a random effects model was used to estimate the pooled odds ratio (a forest plot is presented).

Patients in the TNF+ group for all orthopedic surgeries had a 2.39-times greater likelihood of developing SSI compared to patients in the TNF- group (pooled fixed-effects OR=2.39; 95% CI=1.72, 3.31; $p<0.0001$). A smaller group of cases with only total hip and total knee replacement were also meta-analyzed; here patients in the TNF+ group had a 3.08-times greater likelihood of developing SSI compared to patients in the TNF- group (pooled random-effects OR=3.08; 95% CI=0.87, 10.95; $p=0.08$). The Begg-Mazumdar test and Egger test did not reveal any evidence of publication bias ($p = 0.88$ and $p=0.91$, respectively).

Conclusion: Perioperative exposure to TNFi is associated with a higher risk of infection in all orthopedic surgery, although the risk in total hip and knee replacement is less clear. These data support withholding TNFi prior to orthopedic surgery.



Disclosure: S. M. Goodman, None; **I. Menon**, None; **R. Smethurst**, None; **P. Christos**, None; **V. P. Bykerk**, None.

2370

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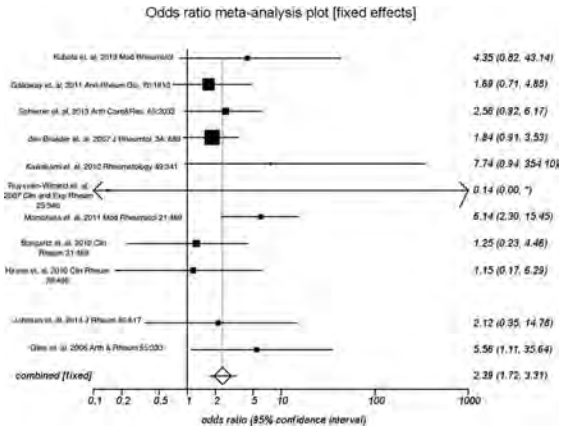


Disclosure: S. M. Goodman, None; **I. Menon**, None; **R. Smethurst**, None; **P. Christos**, None; **V. P. Bykerk**, Amgen, 5, Bristol-Myers Squibb, 5, Pfizer Inc, 5, UCB, 5.

2371

Efficacy of First Line Biological Monotherapy in RA: Data from the Czech Registry Attra. Herman F. Mann[1], Sarka Forejtova[2], Katerina Jarosova[2], Ladislav Senolt[3], Jakub Zavada[4], Michal Uher[5], Karel Hejduk[5] and Karel Pavelka[6]. [1]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Prague, Czech Republic, [2]Institute of Rheumatology, Prague, Czech Republic, [3]Revmatologicky ustav, Prague, Czech Republic, [4]Charles University, Prague, Czech Republic, [5]Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic, [6]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic.

Background/Purpose: The biological disease-modifying anti-rheumatic drugs (bDMARDs) should be used for the treatment of rheumatoid arthritis (RA) in combination with conventional synthetic DMARDs (csDMARDs). However a significant proportion of patients receive bDMARDs in monotherapy.

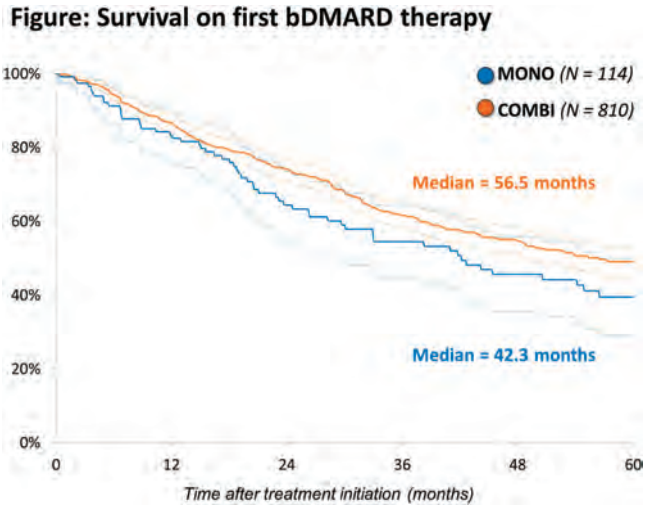
Methods: Baseline demographic data and efficacy parameters of the first bDMARD treatment of RA patients initiating bDMARD monotherapy (MONO) or combination (COMBI) therapy between 2007 and 2012 were retrieved from the national registry ATTRA. ATTRA is a centralized prospective computerized registry of patients receiving bDMARD therapy collecting data on efficacy, safety and quality of life of all patients treated with bDMARDs. bDMARD therapy was indicated after failure of at least 1 csDMARD (DAS28 $\geq$5.1).

Results: 1378 patients initiated bDMARD treatment after 2007, prospective data regarding disease activity were available for 924 of them and this subgroup was further analyzed. The 114 patients (12%) who were started on bDMARD monotherapy were older (58 versus 52 years; P<0.001) with longer disease duration (10.1 versus 6.8 years; P=0.001) and more failed csDMARDs in the past (4 versus 3; P=0.002). The baseline DAS28 scores were similar in both groups (5.9 versus 5.8; P=0.083). The most commonly used first line bDMARDs in both groups were antiTNFα drugs (93.9% vs 94.4%; p=0.8). 61.4% MONO patients remained on the same therapy after 12 months, further 21.1% had a csDMARD added to their initial bDMARD. 75.3% COMBI patients remained on the original therapy, 9.7% more were on monotherapy with the first bDMARD. Remission (DAS28<2.6) was reached by 37.8% MONO patients and 41.6% COMBI patients after 12 months. Longitudinal binary logistic regression model was used to calculate the likelihood of reaching remission for both groups at various time points.

Month		Crude estimate		Adjusted estimate*	
		OR (95% IS)	P value	OR (95% IS)	P value
3	COMBI	*reference*		*reference*	
	MONO	**0.59** (0.35; 0.98)	**0,041**	**0.60** (0.36; 1.02)	0.059
6	COMBI	*reference*		*reference*	
	MONO	**0.60** (0.37; 0.98)	**0,040**	**0.61** (0.37; 1.01)	0.055
12	COMBI	*reference*		*reference*	
	MONO	**0.68** (0.44; 1.07)	0,093	**0.67** (0.42; 1.07)	0.093

*Adjusted for gender, age, disease duration, number of previous csDMARDs, glucocorticoid use and baseline DAS28.

The median survival on the first bDMARD was 42.3 months in the MONO and 56.5 months in the COMBI group (HR 1.29; P=0.073) (Figure).



Conclusion: The results of this observational study suggest that bDMARD efficacy and retention is lower when used as monotherapy, however most observed differences did not reach statistical significance.

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Disclosure: H. F. Mann, None; **S. Forejtova**, None; **K. Jarosova**, None; **L. Senolt**, None; **J. Zavada**, None; **M. Uher**, None; **K. Hejduk**, None; **K. Pavelka**, None.

2372

Fatigue and Related Factors in Patients with Rheumatoid Arthritis Treated with Tocilizumab in Daily Clinical. H Corominas[1], C Alegre de Miguel[2], M Rodríguez-Gómez[3], C Marras Fernández-Cid[4], F Maceiras Pan[5] and ACT-AXIS Study Group. [1]Hospital de Sant Joan Despí Moisès Broggi, Barcelona, Spain, [2]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [3]Complejo Hospitalario Cristal Piñor, Ourense, Spain, [4]Hospital Universitario Virgen de la Arrixaca, Murcia, Spain, [5]Complejo Hospitalario Arquitecto Marcide-Profesor Novoa Santos, A Coruña, Spain.

Background/Purpose: Fatigue in RA possibly resulting from alterations in the HPA axis like occurs with others RA symptoms as morning stiffness, and mood and sleep alterations. In addition, improvement of IL-6-induced anemia noted in RA patients appears to be associated with disease activity, even with fatigue. This, together with the effect of tocilizumab (TCZ) in reducing morning stiffness, pain and fatigue, and improving Hb levels, has led us to investigate the correlation between the change in fatigue and related factors as serum Hb levels, SJC, morning stiffness, pain, sleepiness and depression.

Methods: A prospective, observational and multicenter study in patients with moderate to severe RA, non-responders or intolerants to DMARDs or TNF-inhibitors who initiated treatment with TCZ. Data were collected at the time of TCZ-beginning (baseline visit) and at 2 routine follow-up visits closest to the weeks 12 and 24. The variance of fatigue outcomes relative to associated factors was calculated by multiple regression analysis.

Results: Of 122 patients included, 120 were evaluable (87% female; mean age: 52.2±12.6 years; mean disease duration: 9.1±7.8 years). At baseline: Hb (g/dL), 12.4±1.4; CRP (mg/L), 12.5±16.9; DAS28 score, 5.6±1.0; TJC, 8.6±6.3; SJC, 5.9±4.2; pain (visual analogue scale, cm), 6.7±2.3; morning stiffness duration (hours), 1.3±2.4; FACIT_F fatigue outcome, 23.7±11.1; Beck depression score, 18.5±13.0; Epworth sleepiness score, 6.1±4.5. At 12 and 24 weeks, DAS28 had significantly decreased 2.5±1.1 and 2.7±1.4 points, respectively, fatigue scores had significantly fallen to 19.2±10.6 and 18.8±10.7, and 51% and 61% of patients were good EULAR responders. Significant improvements were also observed in the other RA-related factors evaluated (Table). Sleepiness and depression were significant correlates in the multivariate model explained 35% of the variance in fatigue scores.

Mean changes (SEM) in fatigue outcomes and related factors from baseline

Variable	Week 12	*p*-value*	Week 24	*p*-value*
FACIT_F fatigue	−4.7 (0.9)	*<0.001*	−5.2 (1.0)	*<0.001*
Serum Hb levels (g/dL)	0.6 (0.1)	*<0.001*	0.6 (0.1)	*<0.001*
CRP levels (mg/L)	−10.7 (0.9)	*<0.001*	−11.2 (2.1)	*<0.001*
SJC	−3.7 (0.5)	*<0.001*	−4.1 (0.4)	*<0.001*
Morning stiffness (hours)	−0.9 (0.3)	*<0.001*	−1.0 (0.2)	*<0.001*
Pain VAS (cm)	−2.6 (0.2)	*<0.001*	−2.7 (0.3)	*<0.001*
Epworth sleepiness score	−0.6 (0.4)	*0.162*	−1.0 (0.3)	*<0.001*
Beck depression score	−3.6 (0.9)	*<0.001*	−3.9 (1.1)	*<0.005*

*Based on paired samples t-test. No multiple comparison adjustment was made.
Abbreviations: SEM, standard error mean.

Conclusion: Tocilizumab improves fatigue outcomes in patients with RA, a benefit that may be mediated by its effect on disease activity as shown by the reduction of DAS28. Tocilizumab reduces the concentration of acute-phase reactants and improves Hb levels, which can also contribute to decreasing fatigue experienced by RA patients. However, if the improvements observed in morning stiffness duration, pain, and sleepiness and depression scores are the result of the improvement in patient's fatigue cannot be concluded. Fatigue highly correlates with sleepiness and depression, having these RA-symptoms a significant role in explaining fatigue in RA.

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2373

Compliance in the Rheumatoid Arthritis Comparison of Active Therapies Trial: Triple Vs Etanercept. Sarah Leatherman[1], Hongsheng Wu[2], Edward Keystone[3], Mary Brophy[1] and James O'Dell[4]. [1]VA Boston Healthcare System, Boston, MA, [2]Wentworth Institute of Technology, Boston, MA, [3]Mount Sinai Hospital, Toronto, ON, [4]University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: In the 48-week, double-blinded, noninferiority RACAT trial, 353 methotrexate suboptimal responders were randomized to two treatment strategies, either the addition of sulfasalazine and hydroxychloroquine (triple therapy) or the addition of etanercept. If subjects showed no clinical improvement in DAS28 at 24 weeks, their treatment strategy was switched. Compliance to the study medications as well as placebo is an important aspect for any clinical outcome and an important consideration for the application of results to treatment of patients. This is particularly relevant since many have questioned the tolerability of triple therapy.

Methods: Compliance with placebo and study medications was calculated using returned pill counts. Participants were defined as medication compliant if they took 80% or more of dispensed study medication. Baseline characteristics were compared between active drug compliant and non-compliant subjects for both the 24-week and 48-week follow-up periods. Administration method (pills versus injection) compliance, treatment strategy (active drug versus placebo) compliance, and the association between compliance and treatment response were also explored.

Results: Within active drug group, there were no significant differences at 24 or 48 weeks between compliant and non-compliant subjects for any of the baseline variables except that the Physician Global Assessment score for compliant was significantly better than that of non-compliant ($p=0.01$ and $p=0.01$, respectively). Injection compliance was significantly higher than pill compliance at both 24 weeks (94.6% versus 86.4%, $p = 0.0003$) and 48 weeks (96.4% versus 90.6%, $p = 0.0034$). There were no differences in compliance of active and placebo medications at 24 weeks (90.0% versus 90.9%) and 48 weeks (93.9% versus 93.8%). Unlike some other studies, we found no relationship between compliance and treatment response. Other factors previously found to be associated with good compliance, such as demographic variables, treatment assignment, and treatment response, were not significantly related.

Conclusion: Subjects taking pills were less likely to be compliant than those having injections. Patients were equally likely to take active therapy and placebo therapy. Despite differences in compliance, treatment strategies were comparable and both strategies were well tolerated.

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2374

Use of Hydroxychloroquine Associated with Improved Lipid Profile in Rheumatoid Arthritis Patients. Jose Felix Restrepo[1], Inmaculada del Rincon[2], Emily Molina[3], Daniel Battafarano[4] and Agustin Escalante[1]. [1]University of Texas Health Science Center at San Antonio, San Antonio, TX, [2]UTHSCSA, San Antonio, TX, [3]University of Texas Health Science Center, San Antonio, TX, [4]San Antonio Military Medical Center, JBSA - Ft Sam Houston, TX.

Background/Purpose: Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in rheumatoid arthritis (RA). CVD risk factor reduction, such as reducing cholesterol and plasma glucose may be beneficial for preventing CVD. Hydroxychloroquine (HCQ), a DMARD with a good safety profile and low cost, has been reported to improve lipid profiles and glucose level in RA. We aimed to examine the association between HCQ with plasma lipid and glucose levels in a large RA cohort.

Patients and Methods: We recruited RA patients from public, private, military and Veterans Administration rheumatology clinics, and invited them for yearly follow up evaluations in which we assessed demographic and laboratory features, as well as hydroxychloroquine use.

We performed cross sectional analyses at baseline comparing fasting lipid profiles and plasma glucose between patients that were currently taking HCQ and those that were not. We subsequently used cross-sectional time- series regression models including all follow up visits, dividing patients into three groups based on hydroxychloroquine exposure: Those who had never taken HCQ during the time of our study, those who took it intermittently, and those who took it continuously.

Results: We studied 1261 patients (938 female, 323 male) with a mean ± SD age of 59.6±11.5 years. At baseline 254 patients were on HCQ. After adjusting for age, sex, ethnicity and lipid lowering medications, patients taking HCQ had significantly lower total cholesterol (TC) (P-value= 0.001), LDL (P-value≤0.001), triglycerides (TG) (P-value=0.013), and lipid profile ratios TC/HDL (P-value ≤0.001) and LDL/HDL (P-value ≤0.001). Furthermore, HDL was significantly higher in patients taking HCQ (P-value≤0.001). Plasma glucose level was not significantly associated with HCQ.

Patients were followed for a total of 4,646 visits between 1996 and 2014, and each patient was classified by HCQ exposure. After adjusting for confounders, patients that were continuously exposed to HCQ showed significantly lower lipid levels in TC, LDL, TG, TC/HDL, LDL/HDL, and higher HDL compared to the other two groups (P-value ≤ 0.01). Plasma glucose levels were only significantly different only when comparing patients never exposed to HCQ with those that were taking it at all visits (P-value = 0.003) (Table 1).

Table 1. Pooled follow-up visits of 1,261 RA patients divided by HCQ exposure

	None	Intermittent	Continuous	P_{adj}*
No of patients/No of visits	836/2935	316/1411	109/301	------
Female, n(%)	2,134 (73)	1,055 (75)	239 (79)	------
Non-Hispanic White, n(%)	1,059 (36)	372 (26)	123 (40)	------
Duration of RA, mean ± SD	15.3 ± 10.9	13.3 ± 9.3	11.9 ± 9.5	≤0.001, ’0.001
Laboratory				
TC mg/dl, mean (SD)	185.6 ± 40.4	182.0 ± 38.0	181.2 ± 35.6	0.005, 0.006
LDL mg/dl, mean (SD)	106.5 ± 33.6	102.9 ± 30.7	97.5 ± 29.7	≤0.001, ≤0.001
HDL mg/dl, mean (SD)	52.7 ± 16.3	54.6 ± 17.2	60.4 ± 18.4	≤0.001, ≤0.001
TG mg/dl, mean (SD)	132.2 ± 81.2	122.9 ± 62.7	115.1 ± 56.9	≤0.001, ≤0.001
TC/HDL, mean (SD)	3.8 ± 1.5	3.6 ± 1.3	3.2 ± 1.1	≤0.001, ’0.001
LDL/HDL, mean (SD)	2.21 ± 1.1	2.08 ± 1.1	1.8 ± 0.8	≤0.001, ’0.001
Glucose mg/dl, mean (SD)	103.0 ± 39.5	101.9 ± 37.6	95.1 ± 30.4	0.4, 0.003

**P-values were adjusted (P_{adj}) for age, sex, ethnicity and if the patients were currently on lipid lowering medications.*

Conclusion: HCQ use was associated with significantly lower TC, LDL, TG, and TC/HDL and LDL/HDL ratios, and with higher HDL. The association of HCQ with plasma glucose was not as strong as that with lipids. These findings support the need for a randomized trial to establish the role of HCQ in CVD prevention in RA patients.

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2375

Should Physician Reduce patients’ Glucocorticoids to Offset the Risk of Serious Infection Event Among RA Patients Who Switched from Non-Biologic Dmards and Glucocorticoid to Biologics? Huifeng Yun[1], Lang Chen[2], George W. Reed[3], Joel M. Kremer[4], Jeffrey D. Greenberg[5] and Jeffrey R. Curtis[2]. [1]University of Alabama at Birmingham School of Public Health, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Corrona, LLC., Southborough, MA, [4]Albany Medical College and the Center for Rheumatology, Albany, NY, [5]New York University School of Medicine, New York, NY.

Background/Purpose: Glucocorticoids (GCs) and biologic disease-modifying antirheumatic drugs (DMARDs) have previously been associated with serious infection events (SIEs) among rheumatoid arthritis (RA) patients. For patients on non-biologic DMARDs (nbDMARD) and GCs,, it is unclear whether any increased risk for SIEs associated with adding a biologic might be offset if patients are able to reduce their GC exposure.

Methods: Using 2002–2013 Corrona RA registry data contributed by U.S rheumatologists and their RA patients, we identified eligible index visits where patients were on a nbDMARD and GCs, but not on biologics. Biologic DMARDs include etanercept, adalimumab, certolizumab, golimumab, infliximab, abatacept, rituximab and tocilizumab. Patients with psoriasis arthritis and malignancy were excluded. Follow up started at this time (i.e. index date), and ended at the earliest date of: a hospitalized infection, a visit when patient was on nbDMARDs only without GC, GCs without nbDMARD or no RA treatment, death, an 18-month gap between CORRONA visits, or 6/30/13. As a time-varying exposure, we categorized each person day into the following five exposure categories: nbDMARDs + GC (prednisone <5mg/day), nbDMARDs + GC (≥5mg/day), biologic DMARD + GC (<5mg/day), biologic DMARDs + GC (≥5mg/day), and biologic DMARD without GCs. Biologic exposure could have included concomitant nbDMARD use. At each visit, physicians reported the occurrence of SIEs. Events were confirmed in two stages, both by reporting physicians and with medical records. We calculated the incidence rate of SIEs for each exposure and compared risks using Cox regression adjusting for age, gender and clinical disease activity index (CDAI) at the index date.

Results: Of 12,851 eligible index visits where patients initiated nbDMARDs and GCs, 23% were with GC <5mg/day and 77% with GC ≥5mg. For patients were treated with nbDMARDs and GCs <5mg/day at the start of follow-up, 14.4% subsequently initiated biologics. For these individuals, 45.9% were able to discontinue GCs, 32.6% were on GC <5mg/day and 12.5 were on GC ≥5mg at the end of follow-up. Of 1,779 (20%) patients starting on nbDMARDs and GCs ≥5mg and then initiated biologics, 41.7% were able to discontinue glucocorticoids, and 9.8% were able to reduce GC dose to < 5mg by end of follow-up. After excluding 7% of SIEs that could not be confirmed, we identified 293SIEs yielding an incidence rate for SIEs of 1.8 per 100 person years across all exposures. After adjustment and compared to exposure of nbDMARDs + GCs (≥5mg/day), patients on biologic DMARDs without steroid use were less likely to have a SIE (Table). Both age and CDAI at the index date were positively associated with SIEs (not shown).

Conclusion: Many RA patients treated with nbDMARDs and glucocorticoids who initiate biologics are subsequently able to discontinue glucocorticoids. These individuals are at reduced risk for serious infections.

Table: Events, absolute incidence rate and adjusted hazard ratio of serious infections by DMARD, biologic, and glucocorticoid exposure

Biologic Exposures	Events	Incidence rate per 100 person years	Adjusted Hazard Ratio (95% CI)
nbDMARDs + GCs (≥5mg/day)	162	2.10	1.0 (referent)
Biologic DMARDs + GCs (≥5mg/day)	47	2.71	1.34 (0.94–1.91)
nbDMARDs + GCs(<5mg/day)	55	1.63	0.79 (0.58–1.08)
Biologic DMARDs + GCs (<5mg/day)	12	1.56	0.76 (0.41–1.40)
Biologic DMARDs without GC	17	0.75	0.41 (0.24–0.70)

* Adjusted for age, gender and CDAI at the index date
DMARD = disease-modifying antirheumatic drugs
NbDMARDs = non biologic disease-modifying antirheumatic drugs
GC = glucocorticoid; CI = confidence interval;

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Safety of Rapid Rituximab Infusion in Rheumatoid Arthritis in a Single Community Practice. Rafat Faraawi[1], Kelly Roth[2] and Sameeka Malik[3]. [1]K-W Musculoskeletal Research Inc, Kitchener, ON, [2]K-W Musculoskeletal Research Inc., Kitchener, ON, [3]KW Musculoskeletal Research Inc., Kitchener, ON.

Background/Purpose: Rituximab, a chimeric monoclonal anti-CD20 antibody, is approved to be infused over 4 hours and 15 minutes (first infusion), and 3 hours and 15 minutes (second infusion) due to the potential for infusion reactions. The risk of infusion reactions has been shown to be the greatest with the first infusion. Previously we reported our experience with rapid rituximab infusion in 10 rheumatoid arthritis patients, receiving a total of 26 rapid infusions. We now report a current safety analysis of 28 patients receiving a total of 132 rapid infusions in a single rheumatology practice. The objective is to evaluate the safety, tolerability, and practicality of a rapid infusion protocol for rituximab in RA patients (n=28) in a single community setting.

Methods: Patients, who were prescribed rituximab for the treatment of moderate to severe RA, were recruited from October 2006 to November 2013 and given the opportunity to participate in the rapid infusion protocol. All patients provided written informed consent. Each treatment course consisted of 2 rituximab 1000 mg infusions given 2 weeks apart. The first infusion followed the conventional infusion schedule. Rapid infusion protocol was administered on the second and/or all subsequent infusions over 2 hours. All patients received premedication. Vital signs were recorded at baseline and at 15, 30, 60, 90, and 120 minutes.

Results: A total of 57 patients received rituximab infusions (280 infusions) from October 2006 to November 2013. Out of these, 50 patients with a diagnosis of rheumatoid arthritis met the criteria to be followed on the short infusion protocol. A total of 28 patients agreed to be followed on rapid rituximab protocol. 132 infusions were included in this analysis with the mean treatment interval of 9.4 months. 93% of the patient population had failed or were intolerant to prior TNF-alpha inhibitors and 7% were biologic naïve. A total of 7 infusion reactions were reported over 132 rapid rituximab infusions (28 patients), as compared to 8 infusion reactions over 148 conventional infusions (22 patients). There was no significant difference in the incidence of infusion reactions between rapid and conventional infusions (p=0.97). In both rapid and conventional infusions, no patients discontinued rituximab due to infusion related symptoms or reactions. Overall, all symptoms reported were mild and resolved within 24 hours after the infusion. No serious infections or serious adverse events were reported in either rapid or conventional infusion groups.

Conclusion: The current analysis provides reassurance that rapid rituximab infusion is safe and well tolerated. Our experience of administering this protocol over 7 years proves that rapid infusion is as safe as the conventional infusion. In addition to safety, patients reported greater satisfaction with the short infusion duration. This data and previously reported data on rapid infusion in rheumatoid arthritis patients assures physicians that this strategy can be safely implemented in a single community practice setting.

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A Pilot Randomized Controlled Trial of a Tailored Smoking Cessation Intervention for Rheumatoid Arthritis Patients. Pip Aimer[1], Gareth Treharne[2], Simon Stebbings[2], Christopher Frampton[1], Vicky Cameron[1], Sandra Kirby[3] and Lisa K. Stamp[1]. [1]University of Otago, Christchurch, Christchurch, New Zealand, [2]University of Otago, Dunedin, New Zealand, [3]Arthritis New Zealand, Wellington, New Zealand.

Background/Purpose: Smoking adversely influences comorbidities in rheumatoid arthritis (RA) and may affect progression of RA. The combination of negative health effects makes a compelling case for smoking cessation in RA. The aim of this pilot was to determine whether a targeted 3-month smoking cessation intervention for RA patients increases smoking cessation.

Methods: Thirty-eight RA patients who were currently smoking were recruited and randomized on a 1:1 ratio. All participants were given the current local standard of care for smoking cessation (brief advice and subsidised nicotine replacement therapy: ABC). Participants randomized to the intervention arm (ABC+) received additional advice from trained Arthritis New Zealand educators for 3 months. Advice was tailored to participants' specific needs from a range of intervention tools developed from previous qualitative consultation and focused on education about the relationship between smoking and RA, pain control, exercise, coping, and support. The primary outcome measure was smoking cessation at 6 months. The secondary outcome was sustained reduction in smoking at 6 months. The assessor was blind to intervention allocation. Disease and psychosocial characteristics of quitters and non-quitters were examined statistically.

Results: Thirty-five participants completed the 6 month trial; the 3 who withdrew were in the intervention arm. The overall smoking cessation rate was 24%. There was no significant difference in smoking cessation rate between the ABC+ and ABC groups (26% vs 21%; P=0.70). The mean number of cigarettes smoked per day reduced by 56% (P<0.001) but did not differ between ABC+ and ABC groups (mean reduction 59% vs 53%; P=0.72). There was no difference in smoking cessation rates between participants with disease duration 2 years (27% vs 22%; P=0.74). Successful quitters had a greater number of years in education beyond high school and had smoked less across their lifetime, but these differences were not statistically significant. The successful quitters did appear to have less severe disability and pain, and better psychosocial factors including less depression, perceived stress, and an enhanced quality of life but these did not reach statistical significance (*Table 1*). No other demographic, disease, or psychosocial variables predicted quitting.

Conclusion: This pilot randomized controlled trial evaluated the effects of an individually tailored smoking cessation programme in patients with RA. The smoking cessation rate and reduction in number of cigarettes smoked were high compared to previous smoking cessation studies. The lack of added benefit of the tailored intervention suggests brief advice is the best practice supporting RA patients who wish to quit smoking. RA patients with fewer years of education or longer history of smoking may require particular cessation support.

Table 1: Baseline disease and psychosocial factors associated with smoking cessation. All data are presented as mean (SD)

Baseline disease and psychosocial factors*	Successful Quitters (n=9)	Non-quitters (n=29)	Total (n=38)	P
Education (years)	12.56 (1.88)	11.48 (1.33)	11.74 (1.52)	0.06
Cumulative pack-years of smoking (years)	25.58 (10.44)	41.68 (24.47)	37.76 (22.86)	0.07
Current age (years)	55.22 (12.34)	56.90 (11.83)	56.50 (11.80)	0.72
Socio-economic deprivation	5.00 (3.32)	5.31 (2.61)	5.24 (2.75)	0.77
ASES pain	6.87 (2.17)	6.15 (1.97)	6.32 (2.01)	0.36
ASES mood	7.54 (2.02)	7.15 (2.10)	7.24 (2.06)	0.62
HADS anxiety	6.67 (3.39)	6.72 (3.95)	6.71 (3.78)	0.97
HADS depression	3.67 (1.94)	4.79 (3.46)	4.53 (3.18)	0.36
PSS stress	19.00 (7.53)	22.48 (8.75)	21.66 (8.51)	0.29
HAQ	0.56 (0.42)	0.87 (0.77)	0.80 (0.71)	0.26
PI HAQ	1.95 (1.36)	2.45 (2.18)	2.33 (2.01)	0.52
EQ VAS	76.33 (15.64)	70.76 (19.23)	72.08 (18.40)	0.44
EQ-5D	0.73 (0.24)	0.65 (0.19)	0.67 (0.21)	0.31
Smoking self-efficacy internal	12.67 (5.94)	13.14 (6.35)	13.03 (6.18)	0.85
Smoking self-efficacy external	14.33 (3.46)	13.69 (6.15)	13.84 (5.60)	0.77
Fagerstrom Nicotine Dependence	3.78 (1.64)	4.03 (1.94)	3.97 (1.85)	0.72

*Abbreviations: ASES, Arthritis Self-Efficacy Scale; HADS, Hospital Anxiety and Depression Scale; PSS, Perceived Stress Scale; HAQ, Health Assessment Questionnaire; PI-HAQ, Personal Impact Health Assessment Questionnaire; EQ-VAS, Euroqol visual analogue scale; EQ-5D, Euroqol health utility

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Ethnic Minorities with Rheumatoid Arthritis Achieve a Meaningful Clinical Response at 12 Months Despite Infrequent Use of Biologic Therapies. Gail S. Kerr[1], Yusuf Yazici[2], Christopher Swearingen[3], Sharon Dowell[4], Luis R. Espinoza[5], Edward Treadwell[6], Theresa Lawrence-Ford[7], Yvonne Sherrer[8], Angelia Mosley-WIlliams[9], Rodolfo Perez Alamino[10], Ignacio Garcia-Valladares[11], Akgun Ince[12], Mercedes Quinones[13], Chunqiao Luo[3], Adrian Godoy[4] and John Amatruda[4]. [1]Washington DC VAMC, Georgetown and Howard University, Washington, DC, [2]New York University School of Medicine, New York, NY, [3]University of Arkansas, Little Rock, AR, [4]Howard University, Washington, DC, [5]LSU Medical Center, New Orleans, LA, [6]E Carolina Univ Sch of Med, Greenville, NC, [7]North Georgia Rheumatology Group, PC, Lawrenceville, GA, [8]Centre Rheum Immunol Arthritis, Fort Lauderdale, FL, [9]Detroit VAMC, Detroit, MI, [10]LSUHSC, New Orleans, LA, [11]Hospital General de Occidente, Zapopan, Jal., Mexico, [12]St. Louis University, St. Louis, MO, [13]Howard University Hospital, Washington, DC.

Background/Purpose: Ethnic minorities with rheumatoid arthritis (RA) often, for varied reasons, receive less biologic therapies despite more severe disease. Yet, data in this patient subset regarding time to meaningful clinical response and the clinical determinants are lacking. We examined the prevalence of meaningful clinical response (MCR) and its clinical associations in RA ethnic minority patients.

Methods: Ethnic Minority RA Consortium (EMRAC) patients with at least one follow up visit were evaluated. Comparisons of demographic (age, gender, race, education, smoking), RA disease status (RF, ACPA, nodules/erosions), RA treatment (prednisone, DMARD, biologics) variables amongst ethnic subsets were made as well as frequencies of MCR (DRAPID3 [-3.6]) at 3, 6, and 12 months from enrollment. Baseline differences between ethnic subsets were compared using Chi-square for categorical and Kruskal-Wallis for continuous variables. Logistic regression associating outcome at 3, 6 and 12 months with ethnic subset were estimated adjusting for age, gender, education, disease duration, baseline RAPID3, DMARD and biologic use.

Results: EMRAC analysis is shown in (Table). African Americans (AA) and Hispanics had fewer years of education, but had longer follow up periods and more frequent clinic visits. Despite higher ACPA and RF titers, frequencies of erosions and baseline RAPID3 scores, both ethnic minority subsets received less biologic but more frequent DMARD therapies. A MCR was more prevalent in AA and Hispanics. While the frequency of a MCR in Hispanics was significant at 3 months (p<0.001) compared to other ethnic subsets, it was similar in AA and Caucasians. However at 6 and 12 months – achievement of a MCR was more frequent in both AA and Hispanic patients.

Conclusion: Despite more severe RA disease and infrequent biologic use, frequent follow up visits in ethnic minority patients result in the achievement of a meaningful clinical response within 6 months of disease management. The long term outcome of these variations in RA therapies among ethnic subsets, particularly with regards to cardiovascular disease, requires further study.

Table: Clinical Characteristics of EMRAC cohort and Frequencies of Meaningful Clinical (RAPID3) Response

	Total	Caucasian	African-American	Hispanic	P
N	671	299	225	147	
# of Followup visits	3.0 (2.7)	2.7 (2.7)	2.9 (2.4)	3.6 (3.0)	**<0.001**
Followup Length (months)	9.4 (8.2)	7.4 (5.0)	12.2 (11.5)	9.0 (5.6)	**<0.001**
Age (years)	55.8 (15.4)	54.7 (16.5)	58.0 (14.6)	54.9 (13.9)	0.079
Female (N %)	541 (80.6%)	231 (77.3%)	193 (85.8%)	117 (79.6%)	**0.047**
Duration (years)	9.6 (9.6)	9.2 (9.7)	10.1 (9.8)	9.1 (9.2)	0.338
Education (years)	14.3 (3.6)	15.6 (3.1)	13.4 (3.3)	12.8 (4.1)	**<0.001**
RAPID3 [0-30]	11.7 (7.4)	10.5 (7.4)	12.5 (7.0)	12.8 (7.7)	**0.004**
Hx Smoking (N %)	160 (32.7%)	77 (36.0%)	57 (31.8%)	26 (27.1%)	0.289
RF+ (N %)	277 (50.9%)	72 (31.2%)	147 (73.1%)	58 (51.8%)	**<0.001**
ACPA+ (N %)	167 (31.6%)	27 (11.7%)	106 (55.8%)	34 (31.2%)	**<0.001**
ACPA	143.6 (103.8)	83.4 (96.0)	175.3 (92.2)	115.1 (109.8)	**<0.001**
RF	279.8 (337.3)	247.5 (375.0)	259.8 (294.5)	366.7 (380.2)	**0.043**
Hx Nodules (N %)	33 (8.0%)	11 (6.1%)	15 (8.9%)	7 (11.3%)	0.374
Hx Erosions (N %)	110 (25.1%)	21 (11.2%)	69 (38.5%)	20 (28.2%)	**<0.001**
Prednisone (N %)	228 (34.0%)	83 (27.8%)	94 (41.8%)	51 (34.7%)	**0.004**
DMARD (N %)	474 (70.6%)	195 (65.2%)	181 (80.4%)	98 (66.7%)	**<0.001**
Biologic (N %)	234 (34.9%)	127 (42.5%)	50 (22.2%)	57 (38.8%)	**<0.001**

RAPID3 Response D-3.6 Points					
3 Months	73 (10.9%)	27 (9.0%)	19 (8.4%)	27 (18.4%)	**0.001***
6 Months	127 (18.9%)	46 (15.4%)	48 (21.3%)	33 (22.4%)	**0.004***
12 Months	164 (24.4%)	60 (20.1%)	59 (26.2%)	45 (30.6%)	**0.007***

* Logistic Regression adjusting for Age, Gender, Duration, Education, Baseline RAPID3, DMARD and Biologic Use.

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Minimal Radiographic Progression in RA Patients Receiving Routine Care in the Espoir Early Arthritis Cohort: Similar Prognosis According to 6 Different Remission Criteria. Isabel Castrejón[1], Maxime Dougados[2], Bernard Combe[3], Francis Guillemin[4], Bruno Fautrel[5] and Theodore Pincus[1]. [1]Rush University Medical Center, Chicago, IL, [2]Université Paris René Descartes and Hôpital Cochin, Paris, France, [3]Hôpital Lapeyronie, Montpellier, France, [4]Nancy University Hospital, Nancy, France, [5]UPMC GRC08, Paris 06 University, Pitié Salpétrière Hospital, Paris, France.

Background/Purpose: Remission has become a more achievable goal in rheumatoid arthritis (RA). Several criteria for remission are available in RA, including one based on RAPID3 (routine assessment of patient index data 3) with <1 swollen joint (RAPID3≤3+SJ≤1), which identifies remission similarly to Boolean and SDAI criteria [1]. It would be of value to know if any remission criteria predict radiographic progression more effectively than others. We analyzed radiographic progression according to remission status in the ESPOIR French early arthritis cohort, in which only 18.3% of patients received a biological DMARD over a 5 year follow-up as part of their routine care [2].

Methods: Radiographic progression over 1 year was analyzed in the ESPOIR cohort, which includes early arthritis patients who received routine care. Remission was assessed 12 months after baseline, according to 6 different criteria: ACR Boolean criteria; simplified disease activity index (SDAI) ≤3.3; clinical disease activity index (CDAI) ≤2.8; disease activity score (DAS28) <2.6; RAPID3 ≤3; and RAPID3≤3+SJ≤1.The numbers of patients whose radiographic progression according to the Sharp van der Heijde score was ≥5 -the smallest detectable difference (SDD) [3], ≥10 or ≥20 units at 24 months (12 months after the remission assessment) were analyzed, according to whether patients had been in remission 12 months earlier for each of the 6 criteria, using chi-square tests for statistical significance.

Results: Radiographic progression ≥5 units (SDD) was seen in 10.1%-11.8% of patients in remission compared to 13.0%-13.8% of patients not in remission; differences were not statistically significant (p>0.3) (Table). Progression ≥10 units was seen in 1.4–4.3% of patients in remission versus 6.5–7.6% of those not in remission, a 2-fold difference; only differences by DAS28 and RAPID3≤3+SJ≤1 were statistically significant (p<0.05). Progression ≥20 units was seen in 0.1–1.1% of those in remission versus 2.6–3.1% of those not in remission, a 3-fold difference, statistically significant for SDAI, CDAI, DAS28 and RAPID3≤3+SJ≤1. A sub analysis including 179 patients with radiographic damage at baseline and rheumatoid factor positivity was performed, with similar results.

		Radiographic progression (%) over 1 year according to remission status					
		≥ 5 units		≥ 10 units		≥ 20 units	
Remission Criteria	Remission vs Non remission	Remission	No Remission	Remission	No Remission	Remission	No Remission
Boolean	140 vs 492	10.9%	13.0%	3.6%	6.5%	0%	2.6%
SDAI ≤ 3.3	135 vs 467	10.4%	13.3%	3.0%	6.9%	0%	2.8%*
CDAI ≤ 2.8	135 vs 467	10.4%	13.3%	3.0%	6.9%	0%	2.8%*
DAS28 ≤ 2.6	247 vs 355	10.9%	13.8%	3.6%	7.6%*	0.8%	3.1%*
RAPID3 ≤ 3	187 vs 415	11.8%	13.0%	4.3%	6.8%	1.1%	2.7%
RAPID3≤3+SJ≤1	139 vs 463	10.1%	13.4%	1.4%	7.3%*	0%	2.8%*

$p \leq 0.05$

Conclusion: Very little radiographic progression was seen in patients receiving routine care in recent years although only 18.3% of patients received a biological agent. Differences between patients in remission or non become apparent when applying higher cut-off points to define radiographic progression.

References:
1. J Rheumatol 2013;40:386-93.
2. J Rheumatol 2013;40:1650-7
3. Arthritis Rheum 2002;46:913–20

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Durability of First Biologic Is Not Influenced By Initial/Early DAS28. Gina Rohekar[1], Binu Jacob[2], Janet E. Pope[3] and Claire Bombardier[4]. [1]St. Joseph's Hospital, London, ON, [2]University Health Network, Toronto General Research Institute, Toronto, ON, [3]Western University, London, ON, [4]University of Toronto, Toronto, ON.

Background/Purpose: The Ontario Best Practices Research Initiative (OBRI) collects data on RA treatment in a real-world setting. Patients are enrolled and prospectively followed to assess response to biologic and DMARD therapy as well as to collect data on other factors. The objective of this study is to look at a real-world population and determine if initial disease activity influences the durability of the first used biologic in RA treatment.

Methods: Biologic-naïve RA patients were included if they started a biologic at baseline or at any time after entry into OBRI. For initial DAS, we used the DAS28 value when it was measured between 6 months before and 3 months after the start of the first biologic, whichever was closer to the date of biologic use. This was done so as the initial DAS28 would best reflect the patient's DAS at start of biologic. Patients were censored at treatment stop date or discontinuation date, date of death, or up to 18 months after initiation of biologic, whichever occurred first. Persistence was defined as the length of time the patients continued to receive the drug, irrespective of change in dose, route, or addition of any other DMARD, steroids, etc. If the drug was stopped for <60 days after which the patient restarted the same medication, it was considered a continuation and the duration was calculated accordingly. Survival was first compared using KM curves and then again using Cox-regression analysis. Analysis was performed for all years and also censored at 1.5 years.

Results: 471 patients were included. At 1 year, the survival probability was 0.76 (95% CI 0.68–0.81). Median survival was 5.005 years (95% CI 3.466–8.337). Patients who were on biologic monotherapy, with no concomitant DMARD use, has worse persistence of their initial biologic.

Patients were divided into three groups for analysis based on initial DAS28 score: remission (≤ 2.60), medium to high DAS28 (2.61–5.10) and severe (>5.10). Figure 1 shows the KM Plot of survival on biologic stratified by DAS28.

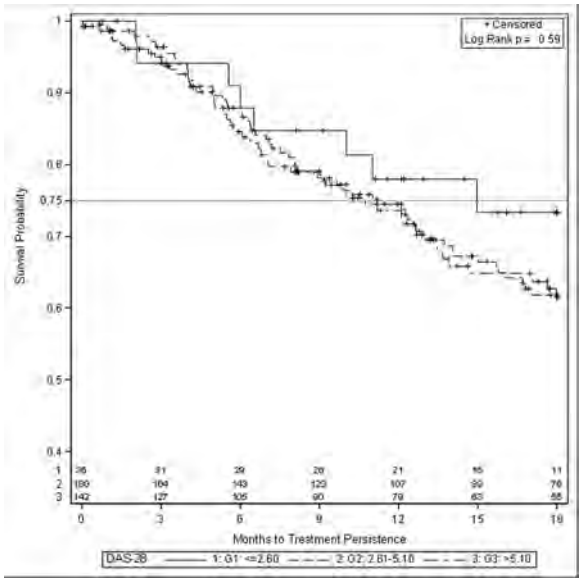

Figure 1: Despite the initial trend towards better survival associated with lower initial DAS, this was not statistically significant. Similarly, type of insurance (public/private) did not impact survival. As seen in other studies, the only significant factor to impact survival on initial biologic was use of DMARD with the biologic.

Conclusion: Early/initial DAS28 score did not impact persistence on their initial biologic, nor did insurance type. This suggests that initial DAS28 score does not influence the durability of the initial biologic Combination of DMARD and biologic was more durable than biologic monotherapy.

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Adherence to a Treat-to-Target (T2T) Strategy in Early Rheumatoid Arthritis. Is It Feasible in Daily Clinical Practice? Christian A. Waimann[1], Gustavo Citera[2], Fernando Dal Pra[3], Maria Celeste Orozco[2], Federico Ceccatto[4], Sergio Paira[5], M Gauna[6], Anastasia Secco[6], M Mamani[6], Lucila Marino[6], Francisco Caeiro[7], AC Alvarez[8], Maria Haye Salinas[7], L Encinas[9], Javier Rosa[10], Valeria Scaglioni[11], Enrique R. Soriano[12], Josefina Marcos[13], Mercedes García[13], A Salas[13], Alejandro Martinez[14], Rafael Chaparro del Moral[14], Oscar Luis Rillo[14], Horacio Berman[15], Alberto Berman[15], Francisco Colombres[15], Edson Veloso[16], Ricardo V. Juárez[17], Maria Elena Crespo[18], Ana Quinteros[19], M Leal[19], Gabriela Salvatierra[20], C Ledesma[20], Mónica P. Sacnun[21], R Quintana[22] and Marcelo Abdala[23]. [1]Hospital Olavarria, Olavarria, Argentina, [2]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [3]Instituto de Rehabilitacion Psicofisica, Buenos Aires, Argentina, [4]Hospital Jose María Cullen, Santa Fé, Argentina, [5]Hospital Jose Maria Cullen, Santa Fe, Argentina, [6]Hospital Bernardino Rivadavia, Buenos Aires, Argentina, [7]Hospital Privado de Córdoba, Córdoba, Argentina, [8]Hospital Privado Centro Médico de, Córdoba, Argentina, [9]Hospital Privado Centro Medico De Córdoba, Cordoba, Argentina, [10]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [11]Rheumatology Unit, Internal Medical Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [12]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [13]HIGA San Martín, La Plata, Argentina, [14]Hospital General de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [15]Centro Medico Privado de Reumatologia, Tucumán, Argentina, [16]Sanatorio y Universidad Adventista Del Plata, Entre Rios, Argentina, [17]Hospital Señor del Milagro, Salta, Argentina, [18]Hospital Señor Del Milagro, Salta, Argentina, [19]Centro Integral de Reumatología, Tucumán, Argentina, [20]Instituto Provincial De Rehabilitación Integral, Stgo. del Estero, Argentina, [21]Hospital Provincial, Rosario, Argentina, [22]Hospital provincial, Rosario, Argentina, [23]Hospital Provincial del Centenario, Santa Fe, Argentina.

Background/Purpose: The treat-to-target (T2T) strategy has become the new paradigm for the treatment of Rheumatoid Arthritis (RA); however the question is whether this strategy is feasible in daily clinical practice. The purpose of the study was to evaluate the adherence to a T2T strategy aiming at remission in a cohort of DMARD naïve patients with early RA.

Methods: We included DMARDs naïve patients with diagnosis of early RA belonging to a prospective cohort of patients with diagnosis of early arthritis (<2 years of disease duration). Data was collected every 3 months, including sociodemographic characteristics, functional status (HAQ), disease activity (DAS28) and medication. Clinical remission was defined as DAS28 < 2.6. The primary outcome measure was the proportion of cohort visits in which therapy was adapted according to disease activity, stratified by remission state. Compliance with the T2T recommendations was defined as a change in drug treatment in patients failing to achieve clinical remission. Treatment strategies were stratified in seven groups: i) addition or dose escalation of NSAIDs, ii) addition/change of DMARDs, iii) dose escalation of DMARDs, iv) addition/change of biologic agents, v) addition or dose escalation of oral prednisone, vi) administration of parenteral corticosteroids, vii) administration of intra-articular corticosteroids. Compliance with T2T and treatment strategy was evaluated on each visit. The statistical analysis was carried out using STATA 12.

Results: We included 535 DMARDs naïve patients with early RA. Mean age was 51 ± 14 years, 82% were female and disease duration was 7 ± 6 months. The patients contributed to a total of 3022 visits (mean follow-up = 24 ± 16 months). Mean HAQ and DAS28 score during follow-up were 0.9 ± 0.6 and 3.9 ± 1.2, respectively. Patients did not achieved remission in 2063 (68%) of the visits. A change in drug treatment was registered in 42% of these visits. The most frequent strategy was addition/change of DMARDs (31%), followed by addition/dose escalation of oral prednisone, addition/dose escalation of NSAIDs, dose escalation of DMARDs, intra-articular corticosteroids, parenteral corticosteroids and addition/change of biologic agents (9%, 9%, 8%, 3%, 3% and <1%; respectively).

Conclusion: In our cohort, including patients with early rheumatoid arthritis in "real world", the compliance with the T2T treatment recommendations were low. A change in drug treatment was registered in less than half of the visits where patients were not in remission.

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2382

Adherence to Dmards in the First Six Months of Treatment in Early Arthritis Patients; Comparing Three Adherence Measures. Annelieke Pasma[1], Ethan den Boer[1], Adriaan van 't Spijker[1], Reinier Timman[1], Jan van Busschbach[1] and J.M.W. Hazes[2]. [1]Erasmus MC University Medical Center, Rotterdam, Netherlands, [2]Erasmus University Medical Center, Rotterdam, Netherlands.

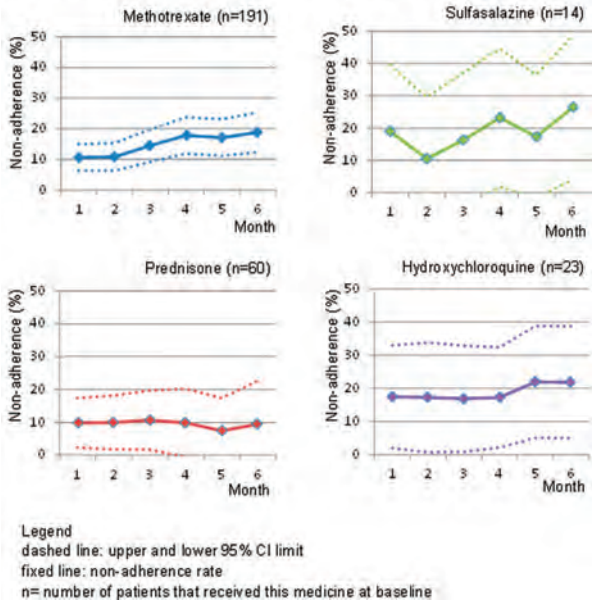
Background/Purpose: Non-adherence to DMARDs is an important indicator for the effectiveness of treatment in early arthritis patients. Reported non-adherence rates differ widely, because studies use different adherence measures. Electronic measurement is considered as a 'gold standard', but other measures have other attractive features. This study compared three methods to ascertain how non-adherence should be measured: the Compliance Questionnaire Rheumatology (CQR), the intracellular uptake of methotrexate (MTX) in the form of methotrexate-polyglutamates (MTX-PGs) and Medication Event Monitoring Systems (MEMS).

Methods: Adult patients diagnosed with arthritis who started DMARDs were included in a cohort study. MTX-PGs were collected and the CQR was filled out after three and six months of treatment. Non-adherence was continuously measured with MEMS. When there was a discordance between the observed opening and the expected opening of the MEMS cap, this was assigned as a non-adherence event. The CQR and MEMS were compared with Pearson correlations. Sensitivity and specificity of adherence measured with MEMS against a CQR discriminant cut-off score was calculated at three and six months. To assess the influence of adherence measured with MEMS on MTX-PGs, a multivariate linear regression (backward selection) with MTX-PGs as dependent variable and with non-adherence measured with MEMS the 12 weeks before MTX-PG measurement (continuous score), age, gender, time of treatment and dosage as independent variables was performed.

Results: Two hundred and one patients entered the study. As measured with MEMS, non-adherence rates varied over time and between different DMARDs (figure 1). For sulfasalazine and hydroxychloroquine, the non-adherence rates were highest. For all medicines, except for prednisone, the non-adherence rate rose over time. The CQR did not correlate with MEMS at any of the time points of therapy. At both time points, the ROC curves showed no discrimination between non-adherence measured with MEMS against the CQR cut-off score. Non-adherence (B 0.548, p=0.035), time of treatment (B 0.947, p=0.006) and age (B 2.052, p<0.000) significantly contributed to MTX-PGs, but only accounted for 18.8% of explained variance.

Conclusion: Non-adherence rates for prednisone are lowest and stable. This might be explained by the fact that patients immediately experience the effect of prednisone, and that most patients tapered prednisone. The non-adherence rate for MTX was low, probably because rheumatologists emphasize the necessity of MTX. The CQR is not associated with MEMS, but MTX-PGs are weakly associated with MEMS. This can be due to several reasons, such as individual differences in the uptake of MTX. We have to learn more about the uptake of MTX over time per patient, before we can use MTX-PGs in daily practice as a non-adherence measure.

Figure 1. Non-adherence rates measured with MEMS per medicine per month



Disclosure: A. Pasma, None; **E. den Boer**, None; **A. van 't Spijker**, None; **R. Timman**, None; **J. van Busschbach**, None; **J. M. W. Hazes**, None.

2383

The 12-Years Retention Rate of the First-Line TNF-Inhibitor in the Treatment of Rheumatoid Arthritis: Real-Life Data from a Local Registry. Ennio Giulio Favalli[1], Martina Biggioggero[2], Francesca Pregnolato[3], Andrea Becciolini[2], Alessandra Emiliana Penatti[2], Antonio Marchesoni[1] and Pier Luigi Meroni[2]. [1]Department of Rheumatology, Gaetano Pini Institute, Milan, Italy, [2]Chair and Division of Rheumatology, Gaetano Pini Institute, University of Milan, Milan, Italy, [3]Experimental Laboratory of Immunological and Rheumatologic Researches, IRCCS, Istituto Auxologico Italiano, Milan, Italy.

Background/Purpose: Data on over-10-years drug survival of TNF inhibitors (TNFi) are still lacking. The aim of the study is to analysed the long-term retention rate of the first TNFi and to compare the drug survival of infliximab (IFX), etanercept (ETN) and adalimumab (ADA) for the treatment of rheumatoid arthritis (RA) in a setting of real-life.

Methods: We extracted data from a local registry that includes all RA patients (all fulfilling ACR/EULAR 2010 classification criteria) treated with biologic therapies between October 1999 and May 2014 in our Rheumatology Unit, limiting the analysis to patients treated with IFX, ETN, or ADA as first-line biologic drug. Data were collected through 31 May 2014. Drug survival up to 12-year follow-up was evaluated overall by the Kaplan-Meier method and compared according to anti-TNF agent after matching for propensity scores (based on age, sex, health assessment questionnaire [HAQ], disease duration, concomitant DMARDs therapy, concomitant corticosteroids, Disease Activity Score 28 [DAS28], ESR and CRP) by a stratified logrank test.

Results: The analysis included 583 patients (mean age [±SD]=54 [±12.4] years, mean disease duration 8.6 [±18.9] years), treated with IFX (n=222), ADA (n=182), or ETN (n=179). The median time of receiving TNFi was 44.3 months and the overall 5-years and 12-years TNFi retention rates were 44.1% and 19.39%, respectively. Drug inefficacy (51.1%) and toxicity (41.2%) represented the main causes of treatment discontinuation. Combination with MTX was significantly associated with a higher TNFi retention rate ($p<0.01$). ETN showed a significant lower probability of discontinuation compared with both IFX ($z=6.52$, $p<0.0001$) and ADA ($z=5.66$, $p<0.0001$). No significant differences emerged between IFX and ADA ($z=0.19$, $p=0.85$).

Conclusion: In a real-life setting, the 12-years retention rate of the first TNFi was lower than 20% and the most frequent reason for discontinuation was inefficacy (51.1%). The drug survival of ETN was significantly higher compared with anti-TNF monoclonal antibodies.

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2384

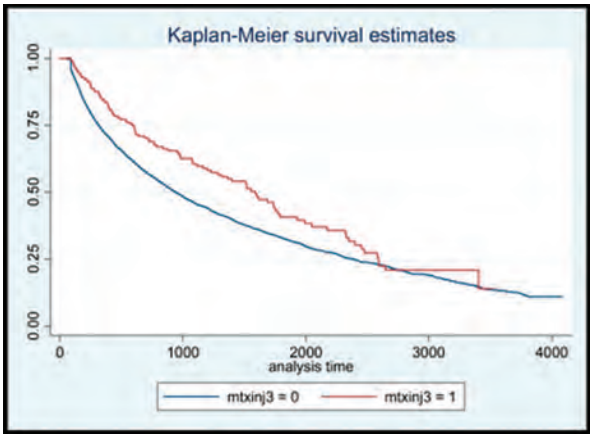
Factors Associated with Methotrexate Treatment Duration, Including Subcutaneous Use, in Patients with Rheumatoid Arthritis: Observations from the VA Database. Bernard Ng. U.S. Department of Veterans' Affairs- Puget Sound Healthsystem, Seattle, WA.

Background/Purpose: A previous analysis of RA patients in national administrative databases of the Department of Veterans Affairs (VA) suggested that injectable MTX was associated with a higher likelihood to remain on MTX monotherapy. We seek to determine whether RA patients in the VA database treated with injectable MTX after being unable to tolerate or having inadequate response to oral MTX remain on MTX monotherapy longer than those treated only with oral MTX. We also compare the rates of liver enzyme abnormalities between patients using injectable MTX monotherapy and those using oral MTX monotherapy.

Methods: The duration of MTX monotherapy before a therapeutic change was required (defined as switching to or adding another DMARD or biologic agent) was compared between patients treated with injectable MTX for at least 30 days and those who were treated only with oral MTX using a Wilcoxon-Matt-Whitney test. Factors that could potentially influence the duration of MTX monotherapy in subjects with therapeutic change included the use of injectable MTX.gender, age, race, starting MTX dose, maximum MTX dose, and modified Charlson comorbidity score. These factors were assessed using a log-rank test and Kaplan-Meier curves; in order to correct for patient variables, linear regression models were also run. Liver enzyme abnormalities were compared between patients on injectable and oral MTX who received MTX monotherapy for >90 days; abnormal alanine aminotransferase (ALT) levels and aspartate aminotransferase (AST) levels were defined as exceeding twice the upper limit of normal.

Results: Of the 7107 patients who were treated with MTX monotherapy for >90 days, 3910 required a therapeutic change (3808 were treated with oral MTX, 102 with injectable MTX). Patients treated with oral MTX remained on MTX monotherapy for a mean (SD) of 627 (636.5) days compared with 962 (786.6) days for patients treated with injectable MTX monotherapy ($P<0.001$). Based on log-rank tests (see figure) and linear regression models, the use of injectable MTX was significantly associated with longer duration of MTX monotherapy ($P=0.0018$ and $P<0.001$, respectively). When adjusted for patient variables, the duration of MTX monotherapy was also significantly associated with age, race, starting MTX dose, and maximum MTX dose. Of the patients treated with MTX who also had ALT and/or AST levels assessed, the rates of abnormal ALT and AST levels were not significantly different between those receiving oral and injectable MTX ($P=0.870$ and $P=0.056$, respectively).

Conclusion: Among patients identified in the VA database, the use of injectable MTX was associated with a significantly longer duration of MTX monotherapy compared with oral MTX. No significant differences in liver enzyme abnormalities were found between patients treated with injectable MTX and oral MTX.



Disclosure: B. Ng, Antares Pharma, 2.

2385

Reasons for Non-Vaccination in Rheumatoid Arthritis and Spondyloarthritis Patients. Charlotte Hua[1], Jacques Morel[1], Bernard Combe[1] and Cédric Lukas[2]. [1]Hôpital Lapeyronie, Montpellier, France, [2]Hopital Lapeyronie, Montpellier, France.

Background/Purpose: Patients with inflammatory rheumatic diseases are at increased risk of infections when compared to healthy controls. Despite the fact that part of these infections could easily be prevented by available vaccines, vaccination coverage remains very low in France. The aim of this study was to evaluate the reasons why rheumatoid arthritis (RA) and spondyloarthritis (Sp) patients had not been vaccinated against influenza and streptococcus infections.

Methods: In this French observational multicenter study, questionnaires were completed by RA and Sp patients referred to rheumatology departments from December 2012 to November 2013. The questionnaires consisted of questions about pneumococcal or influenza vaccinations, about the prescribing physician and, if applicable, about the reasons of non-vaccination. Clinical and demographic data were also collected.

Results: 268 RA patients and 189 Sp patients from 4 centers were included. Vaccination coverage was respectively 53% and 54.5% for pneumococcal vaccine and 59.7% and 47.1% for influenza vaccine. Lack of proposal was the main reason for non vaccination for pneumococcal (78.2% for RA and 78.9% for Sp patients- Figure 1) and influenza vaccine (48.1% and 61.1%- Figure 2). For pneumococcal vaccine, predictive factors for proposal were: history of RTX treatment (p= 0,0001) for RA patients and treatment with anti-TNFα (p=0.006) for Sp patients. For influenza vaccine, predictive factors for proposal were: increased age (p= 0.01) and current biologic treatment (p=0.002) in RA patients and presence of co-morbidities (p=0.004) in Sp patients.

Conclusion: Despite the recognized usefulness of vaccination among patients with inflammatory rheumatic diseases and the current international recommendations, we found that the vaccination coverage of patients from 4 French centers is low, mainly due to the lack of vaccine proposal by the practitioners. These findings are consistent with data from other countries and highlight the need of pursuing information of the patients and their doctors.

Figure 1: Pneumococcal vaccine

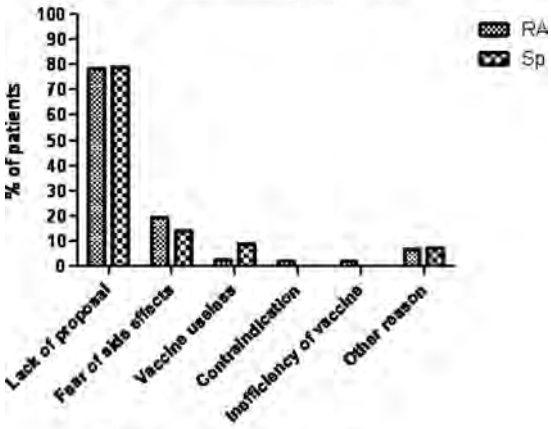
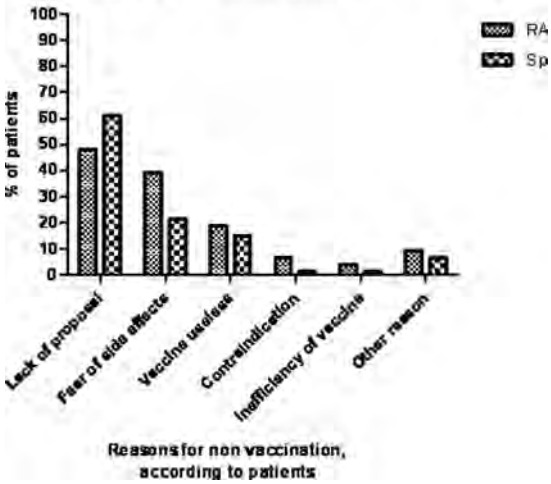


Figure 2: Influenza vaccine



Disclosure: C. Hua, None; **J. Morel**, None; **B. Combe**, None; **C. Lukas**, None.

2386

Patients' Interpretations of Rheumatoid Arthritis Model Disease States in a Safety-Net Rheumatology Clinic. Carol Bledsoe[1], Lisa A. Davis[2], Vivian Tran[3], Angela Keniston[3], Liron Caplan[4], Itziar Quinzanos[5] and Joel M. Hirsh[3]. [1]The Brody School of Medicine - East Carolina University, Greenville, NC, [2]Denver VAMC and Univ of Colorado School of Medicine, Aurora, CO, [3]Denver Health and Hospital Authority, Denver, CO, [4]Denver VA and Univ of Colorado School of Medicine, Aurora, CO, [5]University of Colorado School of Medicine, Aurora, CO.

Background/Purpose: Patient assessment of disease activity (PtGA) measured by visual analog scale (VAS) is often a barrier to patients achieving remission in rheumatoid arthritis (RA). The Boolean and Simplified Disease Activity Index (SDAI) criteria for remission mandate a PtGA of ≤10mm and ≤33mm, respectively. For this reason, it is critical to understand the patient perspective on model disease states, including remission. The objective of our study was to determine how a diverse cohort of RA patients interprets case scenarios of disease states, and to identify variables that were associated with rating the remission model disease state at ≤10mm and ≤33mm.

Methods: We enrolled English- and Spanish-speaking patients at our clinic who met American College of Rheumatology 2010 criteria for RA. We asked subjects to rate their health on a VAS if their arthritis were like that described in each of four case scenarios ranging from remission to severe RA disease activity. These scenarios included the domains: engagement in activities of daily living; personal care; anxiety related to the course of disease; leisure activity; pain; and side effects of treatment. Responses were classified according to **Figure 1**. We performed multivariate logistic regression to identify predictors of: 1) scorable responses with the remission disease state rated lower than the severe disease state (category 4 [Cat 4]); 2) rating the remission model disease state ≤10mm; or ≤33mm.

Results: We enrolled 300 subjects. Only 128 subjects were grouped into Cat 4, indicating understanding of the scenarios. By multivariate regression, higher health literacy (HL) (OR 1.20) and increasing education (OR 2.02) were associated with being grouped in Cat 4. The mean score for the remission scenario for Cat 4 was 17 mm. Of the Cat 4 subjects, 70% and 79% assigned the remission model scenario a score that would satisfy the Boolean and SDAI remission criteria, respectively. No socio-demographic variable predicted responses ≤10mm. Increasing income (OR 5.37) and decreasing pain scores (OR 0.79) predicted classification of the remission model scenario at a level of ≤33mm (**Table 1**).

Conclusion: Limited HL and education are associated with responses to the remission scenario that are inconsistent with understanding the VAS line or question content. Approximately 30% of the patients in Cat 4 rated the remission model disease state at a level that would preclude them from being judged in remission by the Boolean criteria. These results expand what is known about patient perspectives of remission and the challenges of meeting remission criteria in clinics caring for diverse and disadvantaged populations.

Figure 1: Responses to rheumatoid arthritis case scenarios of remission and severe rheumatoid arthritis disease activity, grouped into categories according to completion, scorability, and appropriateness of responses

Cat 1 No response n=31	Cat 2 Unscorable responses such as writing along VAS line, circling anchor, etc. n=45
Cat 3 Scorable responses, but remission scenario not rated lower than severe scenario n=95	Cat 4 Scorable responses and remission scenario rated lower than severe scenario n=128

Cat: category; RA: Rheumatoid arthritis

Table 1: Predictors of patient rating the clinical scenario describing remission rheumatoid arthritis with a patient global score ≤ 33mm (remission according to the Simplified Disease Activity Index, SDAI)

		Univariate				Multivariate		
Variable	**OR**	**95% CI**		**p-value**	**OR**	**95% CI**		**p-value**
Age, years	1.02	0.99	1.05	0.204				
Sex (male)	0.50	0.18	1.38	0.181	0.31	0.08	1.18	0.085
Education Level								
Some High School	REF							
High School Degree or GED	2.21	0.68	7.24	0.190	2.06	0.45	9.38	0.349
Trade School	0.95	0.19	4.68	0.947	1.61	0.20	13.16	0.657
Some College	3.32	0.89	12.34	0.074	2.73	0.53	14.05	0.230
College Degree or above	1.80	0.51	6.38	0.362	0.66	0.12	3.48	0.620
Income = $15,000/ year*	**3.83**	**1.23**	**11.92**	**0.020**	**5.37**	**1.33**	**21.63**	**0.018**
S-TOFHLA total score, (0-10)	1.12	0.91	1.37	0.284				
Spanish language**	0.45	0.17	1.20	0.109	0.31	0.08	1.18	0.085
Confidence in Filling out medical forms								
Not at all	REF							

A little bit	4.00	0.12	136.96	0.442				
Somewhat	1.90	0.11	33.70	0.662				
Quite a bit	3.75	0.19	74.06	0.385				
Extremely	5.64	0.33	96.96	0.234				
MDHAQ score (0–3)	0.37	0.18	0.75	0.006	0.52	0.19	1.43	0.206
Fatigue Score (0–10)	0.93	0.80	1.07	0.301				
Pain Score (0–10)	**0.78**	**0.66**	**0.93**	**0.005**	**0.79**	**0.62**	**1.00**	**0.047**

OR: odds ratio; S-TOFHLA: short test of functional health literacy in adults; MDHAQ: multi-dimensional health assessment questionnaire; GED = General Educational Development; * comparator is

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2387

Relation Between Disease Activity Indices and Their Individual Components and Radiographic Progression in Rheumatoid Arthritis: A Systematic Literature Review. Victoria Navarro-Compán[1], Ana Maria Gherghe[2], Josef S. Smolen[3], Daniel Aletaha[4], Robert B. M. Landewé[5] and Désirée van der Heijde[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Carol Davila University of Medicine and Pharmacy & Cantacuzino Hospital, Bucharest, Romania, [3]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [4]Medical University of Vienna, Vienna, Austria, [5]Amsterdam Rheumatology Center, Amsterdam, Netherlands.

Background/Purpose: Composite indices and single items are available to monitor disease activity in rheumatoid arthritis (RA). Their relation to radiographic progression is an important aspect to select the most appropriate as target. The objective of this study was to investigate the relationship between different disease activity indices (DAIs) and their individual components and radiographic progression in patients with RA.

Methods: A systematic literature review until July 2013 was performed by two independent reviewers using Medline and EMBASE databases. The research question was formulated according to the PICO method: Population (RA patients); Intervention (DAI including DAS, DAS28, SDAI, CDAI, RADAI and RAPID and individual items or scales including patientxs global health (GH), patientxs global disease activity, pain, evaluatorxs global disease activity (EGA), all on a VAS, CRP, ESR, SJC and TJC); Outcome (radiographic progression). Longitudinal studies with ≥ 12 months of follow up assessing the relation between DAIs and single items and radiographic progression were included. Risk of bias of the studies was evaluated according to Hayden tool (range 1–6). The results were grouped based on the means of measuring (baseline versus time-integrated) and analysis (univariable or multivariable).

Results: Fifty five studies from 1232 citations were included. Most of the studies were prospective cohorts and had an overall quality score ≥ 4 points. Radiographic progression was mainly assessed using the modified Sharp van der Heijde or Larsen scoring methods and the period to evaluate progression ranged between 12 and 240 months. The table shows a summary of the studies included in the SLR. All published studies that assessed the relationship between any time-integrated DAI and radiographic progression reached a statistically significant association. Among the single items, only SJC and ESR were associated with radiographic progression, while no significant association was found for TJC. Data with respect to CRP is conflicting. Data on patientxs GH, pain assessment and EGA is limited and does not support a positive association with progression of joint damage.

Conclusion: Published data indicates that composite disease activity scores including swollen joints are more related to radiographic progression than their individual components. Therefore, these are the optimal tools to monitor disease activity in patients with RA. The best performing single items are SJC and ESR.

Table: Summary of studies evaluating the relationship between disease activity indices and their individual components and radiographic progression; Data show total number of studies and the percentage of studies that reached statistically significance (% sig) based on the type of measure and analysis employed.

		Baseline measure		Time-integrated measure	
	Number of studies	Univariable studies n, (% sig)	Multivariable studies n, (% sig)	Univariable studies n, (% sig)	Multivariable studies n, (% sig)
Disease activity index					
DAS	11	7 (29)	1 (100)	-	3 (100)
DAS28	18	6 (17)	2 (50)	6 (100)	4 (≥75)
SDAI	7	1 (100)	-	5 (100)	1 (100)
CDAI	5	1 (0)	-	3 (100)	1(100)
RADAI	2	2 (50)	-	-	-
RAPID	0	-	-	-	-
Item or scale					
TJC	24	16 (31)	3 (33)	3 (100)	3 (0)
SJC	34	20 (44)	5 (60)	3 (100)	6 (67)
GH	2	1 (0)	1 (100)	-	-
PGA	4	2 (0)	-	2 (100)	-
VAS pain	8	4 (25)	2 (50)	1 (100)	1 (0)
EGA	7	5 (20)	-	1 (100)	1 (100)
ESR	37	14 (43)	12 (83)	6 (100)	5 (60)
CRP	36	18 (50)	8 (63)	6 (67)	4 (50)

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DMARD Use after an Initial Acute MI Is Associated with Reduced Risk of a Recurrent Event and Mortality. Jie Zhang[1], Fenglong Xie[2], Lang Chen[2], Huifeng Yun[3], Paul M. Muntner[2], Emily Levitan[2], Monica Safford[2], Kenneth G. Saag[4], Jasvinder Singh[2] and Jeffrey R. Curtis[2]. [1]Univ. of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]University of Alabama at Birmingham School of Public Health, Birmingham, AL, [4]The University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: Previous studies have suggested that disease modifying anti-rheumatic drugs (DMARDs) may reduce cardiovascular risk among patients with rheumatoid arthritis (RA). This analysis examined whether DMARD use after an initial acute myocardial infarction (MI) was associated with reduced risk of having a recurrent MI and mortality among older RA patients.

Methods: We identified RA patients who were enrolled in Medicare (which covers more than 90% of all individuals 65 or older in the U.S.) and had an acute MI from 2006 to 2011. Eligibility criteria included the following: 1) had ≥2 rheumatologist visits with a diagnosis code for RA during a baseline period of at least 365 days prior to follow-up start; 2) had an acute MI defined as having an inpatient hospital claim with a discharge ICD-9 diagnosis code 410.X (excluding 410.x2) in any position and at least one overnight inpatient stay, unless the patient died. Follow-up started at time of discharge from the hospital after the initial MI. We used multivariable proportional hazard regression to examine the association between DMARD use after the initial MI and risk of having a recurrent MI and mortality, adjusting for factors ascertained during baseline (socio-demographics and CHD risk factors [diabetes, hypertension, chronic kidney disease, abdominal aortic aneurism, peripheral arterial disease, atrial fibrillation, hyperlipidemia, tobacco use, overweight/obese, heart failure, chronic obstructive pulmonary disease]), and after MI (medications for hypertension, hyperlipidemia, and RA). Exposure to DMARDs after MI was categorized into the following exclusive hierarchical groups: 1) any anti-TNF biologic DMARD use; 2) any non-anti-TNF biologic DMARD use; 3) any methotrexate (MTX) use; 4) any non-MTX non-biologic DMARDs use (reference group, mostly hydroxychloroquine, sulfasalazine, and leflunomide use); and 5) no DMARD use.

Results: We identified 13,985 eligible RA patients with mean age 74 (SD 11) years, 74% of whom were women. Compared to the reference group of any non-biologic and non-MTX DMARD use, non-TNF biologic DMARD use was associated with reduced mortality (hazard ratio [HR] 0.30 and ; 95% confidence interval [CI] 0.14–0.68]) and recurrent MI (HR: 0.22, 95% CI: 0.07–0.69). Compared to the same reference group, any MTX use was associated with reduced mortality (HR: 0.71, 95% CI: 0.62–0.81) but not with recurrent MI. Oral glucocorticoid use (compared to no use) was significantly associated with increased mortality at low (≤ 7.5mg/d [HR: 1.26, 95% CI: 1.18–1.34]) and high doses (> 7.5mg/d [HR: 1.73, 95% CI: 1.60–1.87]) and with recurrent MI at doses > 7.5 mg/d (HR: 1.29, 95% CI: 1.12–1.48).

Conclusion: Our findings suggest that among older RA patients, non-TNF biologic use and MTX use after an acute MI were associated with reduced risk of having a recurrent MI and mortality compared to non-biologic and non-MTX DMARD use, where glucocorticoid use was associated with increased risk of both outcomes. These results should be interpreted with caution given the possibility of residual confounding in observational studies.

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MRI Osteitis at Baseline Predicts the Development of Rapid Radiographic Progression at 1 Year Toward Patients with Early-Stage Rheumatoid Arthritis. Yoshikazu Nakashima[1], Mami Tamai[2], Junko Kita[3], Sousuke Tsuji[1], Shoichi

Fukui[1], Masataka Umeda[1], Ayako Nishino[1], Takahisa Suzuki[1], Yoshiro Horai[1], Akitomo Okada[4], Tomohiro Koga[1], Shinya Kawashiri[5], Naoki Iwamoto[1], Kunihiro Ichinose[1], Yasuko Hirai[1], Kazuhiko Arima[5], Hideki Nakamura[1], Tomoki Origuchi[6], Masataka Uetani[7], Kiyoshi Aoyagi[5], Katsumi Eguchi[8] and Atsushi Kawakami[1]. [1]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Departments of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [4]Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan, [5]Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [6]Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [7]Department of Radiological Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [8]Sasebo City General Hospital, Sasebo, Japan.

Background/Purpose: EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis (RA) states that magnetic resonance imaging (MRI) bone oedema (osteitis) is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic indicator. The development of rapid radiographic progression (RRP) is considered as a representative poor outcome in patients with RA.We have tried to examine whether MRI osteitis predict the further development of RRP in patients with early-stage RA from Nagasaki University Early Arthritis Cohort.

Methods: This is a 1-year observational study from seventy-six early-stage RA patients recruited consecutively from Nagasaki University Early Arthritis Cohort in which the subjects received Gd-enhanced MRI of both wrists and finger joints. All of the patients had been received DMARDs during 1 year after entry. Synovitis, osteitis and bone erosion determined by Gd-enhanced MRI was scored by Rheumatoid Arthritis Magnetic Resonance Imaging score (RAMRIS). Plain radiographic outcome of both wrists and finger joints was scored by Genant-modified Sharp score and the development of rapid radiographic progression (RRP) at 1 year in this study was identified as a score $>$ 3/year. The clinical response toward introduction of DMARDs at each point (every 3 months) was defined according to DAS28-EULAR response criteria. Variables with a *p* value less than 0.20 were selected for the following multivariate logistic regression analyses. Starting with a full model, the most appropriate model was selected on the basis of Akaike's information criteria in the SAS system®, version 9.2.

Results: Median age and disease duration at entry were 54.5 y.o and 3 months, respectively. Median RAMRIS synovitis score, RAMRIS osteitis score, RAMRIS bone erosion score and Genant-modified Sharp score at entry were 9, 1, 0, 0, respectively. RRP was developed in 12 patients at 1 year. Fifteen variables including gender, age, disease duration, DAS28-CRP, CRP (mg/dl), matrix metalloproteinase-3 (ng/dl), presence of RF, presence of ACPA, initial therapy with MTX, use of biologic DMARDs within the first 6 months, HAQ, RAMRIS synovitis score, RAMRIS osteitis score, RAMRIS bone erosion score and mTSS were evaluated to explore the development of RRP at 1 year. Multivariate logistic regression analyses have identified that RAMRIS osteitis score at baseline (1 increase, Odds ratio: 1.12, 95% C.I.: 1.06–1.19, p = 0.0002) is the only independent predictor toward the development of RRP at 1 year.

Conclusion: Present data suggest that MRI osteitis is closely associated with poor radiographic outcome in patients with early-stage RA. Physicians should especially consider the tight control of disease activity if MRI osteitis is obvious in early RA patients.

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Determinants and Impact of Early Initiation of Disease-Modifying Anti-Rheumatic Drug Therapy in Rheumatoid Arthritis. Chandana Keshavamurthy[1], Kevin Kuriakose[1], Deepak Chandra[1], Aneet Kaur[1], Horace Spencer[1] and Nasim A. Khan[2]. [1]University of Arkansas for Medical Sciences, Little Rock, AR, [2]University of Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR.

Background/Purpose: Early initiation of disease-modifying anti-rheumatic drug (DMARD) therapy is recommended to improve rheumatoid arthritis (RA) outcomes. The aim of this study was to determine a) characteristics associated with early DMARD initiation ($<$ 6 month of RA symptom) and b) impact of early DMARD therapy on outcomes at one year.

Methods: This is a retrospective study of newly diagnosed RA patients at a single academic center. Eligibility criteria were RA diagnosis made by a board-certified rheumatologist, follow-up of at least 12 months and no prior history of DMARD use (except corticosteroids). Data on socio-demographics; dates of symptom onset, visit to referring healthcare provider (PCP), receipt of referral, Rheumatologist appointment and DMARD therapy initiation; functional status by Multi-Dimensional Health Assessment Questionnaires (MDHAQ) & disease activity by Routine Assessment of Patient Index Data 3 (RAPID3); and initial and one year DMARD(s) therapy were extracted in standardized manner from medical records.

Results:103 patients [71 (68.9%) females, 73 (70.9%) white; median (interquartile range, IQR) age of 50 (43–58) years, 74% anti-cyclic citrullinated peptide antibody positive] were found eligible. 50 (48.5%) were uninsured, 37 (35.9%) had Medicaid or Medicare and 16 (15.5%) had private insurance. Median (IQR) time from RA symptom onset to DMARD initiation was 51 (26–83) weeks. 25 (24.3%) patients had early DMARD therapy initiation. The delay from symptom onset to PCP visit contributed most to non-early DMARD therapy initiation followed by duration for receipt of PCP referral to Rheumatology appointment (Table). Uninsured patients were significantly less likely to receive early DMARD therapy, and were more likely to present with longer symptom duration to the PCP (p =. 029), and have longer wait before getting Rheumatology appointment (p =. 015). No other socio-demographic factor was associated with early DMARD initiation. There were no differences in MDHAQ, RAPID3, or initial DMARD agent among the early and late DMARD therapy groups. However, early DMARD therapy group had better functional status and lesser requirement of traditional and biological DMARDs after 12 month.

Conclusion: Only about one-fourth of RA patients received early DMARD therapy. Lack of insurance was associated with late DMARD therapy. Improved outcome and lesser need for intensive therapies were associated with early DMARD therapy. Our results supports need for improved insurance coverage as well improving awareness of early RA symptoms in general population and improving access to Rheumatology services.

Table: Comparison of patients who received early and late DMARD therapy.

Characteristics[1]	Early DMARD therapy (< 6 m)	Late DMARD therapy (≥ 6 m)	p[2]
Sex, female	68	69.2	.908
Age, years	51 (39–65)	49 (44–55)	.360
Race, white	84	66.7	.097
Education, > 12y	38.1	28	.401
Marital status, married	65.2	59.3	.623
Insurance Private			
Uninsured	32	53.8	.017
Medicaid or Medicare	60	28.2	
Private	8	17.9	
Patient's home to Rheumatology clinic distance, miles*	67 (14.2–131)	50 (17–102)	.646
Symptom onset to PCP visit*, wks	4.5 (2.2–8)	44 (22–92.5)	
PCP visit to referral placement*, wks	2 (0–4)	1 (0–3)	.130
Referral receipt to rheumatology appointment*, wks	5 (2–6)	7.5 (4–13)	.001
Rheumatology 1st appointment to DMARD therapy*, wks	0 (0–1.5)	0 (0–3.2)	.133
MDHAQ, 1st visit* (0-3)	1.3 (6.5–19.5)	1.3 (7.2–18.7)	.897
RAPID3, 1st visit* (0-30)	19.7 (14.8–23.3)	18.8 (14.3–23)	.898
RA treatment, 1st visit			
Methotrexate	60	62.8	.800
Hydroxychloroquine	60	71.8	.267
Corticosteroid	68	56.4	.305
Other DMARD	4	4.5	.819
RA treatment, 12 month			
Methotrexate	84	72.4	.242
Hydroxychloroquine	80	90.8	.148
Corticosteroid	12	31.6	.069
Other DMARD	0	14.5	.010
Biologics			
MDHAQ, 12 month* (0–3)	10.2 (5.0–13.1)	14.2 (7.5–19.8)	.027
RAPID3, 12 month* (0–30)	0.6 (0–0.8)	1 (0.3–1.3)	.090

[1]All values in percentage (%), except variables with * represent median (IQR).
[2]P values from Chi-square, Fisher's exact test or Mann-Whitney U test.

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Sustained Rheumatoid Arthritis Remission and Low Disease Activity: Analysis of 13 Years of Follow up in Clinical Practice. G. Avila[1], Arnald Alonso[1], María América López-Lasanta[1], Andrea Pluma-Sanjurjo[2], C. Diaz[2] and Sara Marsal[1]. [1]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [2]University Hospital Vall d'Hebron, Barcelona, Spain.

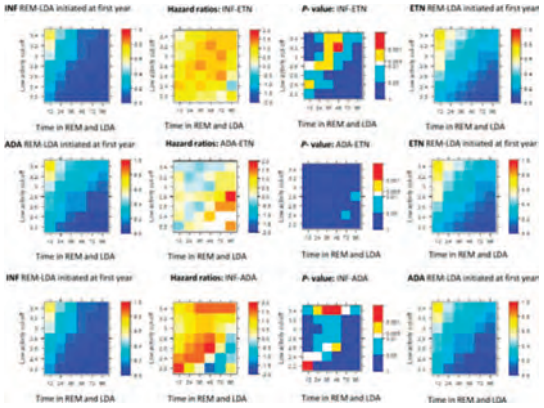
Background/Purpose: Biological therapies (BTs) have greatly improved the outcomes in RA patients and nowadays clinical remission (REM) and low disease activity (LDA) have become realistic goals. Only few studies have examined sustained REM and LDA in clinical practice during large periods of time. Our objective was to analyze the duration of clinical REM and LDA in RA patients in clinical practice in a university hospital.

Methods: RA patients treated with ≥ 1 anti-TNF (infliximab, etanercept, adalimumab) during the period December'99-March'13 were included. Only those treatments with ≥ 12 weeks of follow-up were analyzed. A large number of data were collected (gender, erosions, nodules, RF, ACPA, disease duration, previous BTs and concomitant corticosteroids/DMARDs...etc). DAS28 score was recorded every 3 months in all patients.

DAS28 records for each patient were interpolated to increase time resolution on the disease activity variations. We performed a parametric survival analysis in order to analyze the time until each patient reaches the first sustained period of low activity (LDA and REM). Survival curves were analyzed according to (i) DAS28 threshold that determines a low activity, (ii) minimum period of time in which one patient must be below DAS28 threshold to be considered as sustained low activity. DAS28 thresholds were 2.6 for REM and 3.2 for LDA. The periods to consider sustained low activity were 12, 24, 48 and 96 wks. The Cox regression model was used to evaluate differences in survival times. To analyze the differences between anti-TNFs, the model included DAS28 at baseline, gender and disease duration.

Results: 222 RA patients were included (87% female, 78% erosive, 75% RF (+), 77% ACPA (+)). 452 BTs met the inclusion criteria and were analyzed. In the global survival analysis we found that 44%, 20% and 10% of patients started a sustained REM period of at least 12, 24 and 96 wks during the first year of treatment. The analysis stratified by clinical variables showed that the absence of erosions was associated with sustained REM for periods longer than 48 weeks (*P*-value=7.94e-03; HR=0.49[0.32–0.76]). The differential analysis between anti-TNFs showed higher clinical remission rates in patients treated with Etanercept (ETN) compared to infliximab when longer periods were analyzed. Large periods of sustained LDA were also associated to ETN (*P*-value=8.1e-04; HR=2.42 [1.57–3.73]). Figure 1 shows heat maps representing (1) DAS28 for each treatment and time in low activity (external columns), (2) comparative analysis between treatments (central columns).

Conclusion: In our series of RA patients treated with anti-TNF therapies it was observed that 20% of patients initiate sustained clinical remission for at least 24 weeks during the first year of treatment. Patients treated with ETN are more likely to reach large periods of clinical remission and low disease activity measured by DAS28 score.



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Anti-Carbamylated Antibodies (anti-CarPA) Are Associated with Long Term Disability and Increased Disease Activity in Patients with Early Inflammatory Arthritis: Results from the Norfolk Arthritis Register (NOAR). Jenny H. Humphreys[1], Marije K Verheul[2], Anne Barton[3], Tarnya Marshall[4], Bo Fu[5], René E.M. Toes[2], Deborah PM Symmons[1], Leendert A. Trouw[2] and Suzanne MM Verstappen[1]. [1]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Arthritis Research UK Centre for Genetics and Genomics, University of Manchester, Manchester, United Kingdom, [4]Norfolk and Norwich University Hospitals Trust, Norwich, United Kingdom, [5]The University of Manchester, Manchester, United Kingdom.

Background/Purpose: Anti-CarPA have been shown to predict development of rheumatoid arthritis (RA) in patients with arthralgia. However, little is known about their association with disease activity and long term outcomes such as disability; or whether they provide additional prognostic information to anti-citrullinated protein antibodies (ACPA). The aims of this study were (i)to investigate the association between anti-CarPA status, disability and disease activity over 20 years follow up in patients with early inflammatory arthritis (EIA), and (ii)to examine these associations in the subgroups of patients with and without ACPA.

Methods: Adults presenting to primary care with recent onset swelling of ≥2 joints for ≥4 weeks were recruited to NOAR since 1990. Baseline assessment included joint examination, smoking status and patient recording of the HAQ. CRP, rheumatoid factor (RF), ACPA and anti-CarPA were measured on stored sera obtained at baseline or in the first year of follow up. DAS28-CRP was calculated and 2010 ACR/EULAR classification criteria for RA were applied. Further HAQ scores were obtained at 1, 2, 3, 5, 7, 10, 12, 15 and 20 years follow up, and DAS28-CRP every 5 years. Generalized estimating equations (GEE) were used to test the association between anti-CarPA status and longitudinal HAQ and DAS28 scores including a time interaction term; then additionally adjusting for age, gender, smoking status, year of inclusion and ACPA status. The analyses were repeated in the ACPA negative and positive subgroups and in patients who fulfilled RA classification criteria without adjustment for ACPA.

Results: 1995 patients were included; 1310 (66%) were female, median age at onset (IQR) was 55 years (43–66) and median symptom duration (IQR) was 33 weeks (17–68). Anti-CarPA were positive in 460 (23%) patients and 1221 (61%) satisfied the 2010 ACR/EULAR classification criteria for RA. 539 (26%) were current smokers. ACPA were tested in 1465 patients, 373 (25%) were positive. Median follow up time (IQR) was 7 years (5–11). Baseline median HAQ and DAS28 were higher in anti-CarPA positive vs negative patients (1.125 vs 0.875 and 4.23 vs 3.73 respectively). In the GEE analysis, patients who were anti-CarPA positive had significantly more disability over time and higher levels of disease activity than those who were negative; multivariate model for the HAQ including adjustment for ACPA gave a β coefficient (95% confidence interval) 0.13 (0.03–0.23) (Table 1). Statistically significant associations were also seen in the ACPA negative subgroups. In the ACPA positive and RA subgroups there were significant associations with DAS28 and trends approaching statistical significance with HAQ scores.

Conclusion: The presence of anti-CarPA is associated with increased burden of disability and higher disease activity over time in patients with EIA. Our results suggest anti-CarPA may be useful in identifying ACPA negative patients with poor prognosis.

Table 1 Association between anti-CarpA positivity and HAQ and DAS28 throughout follow up

	Total cohort n=1995 *β coefficient (95% CI)*	**ACPA –ve** n=1092 *β coefficient (95% CI)*	**ACPA +ve** n=373 *β coefficient (95% CI)*	**RA patients** n=1221 *β coefficient (95% CI)*
HAQ				
Univariate*	0.20 (0.13–0.28)	0.16 (0.02–0.31)	0.13 (−0.01–0.28)	0.06 (−0.03–0.15)
Multivariate$	0.13 (0.03–0.23)	0.15 (0.02–0.29)	0.12 (−0.03–0.28)	0.08 (−0.01–0.17)
DAS28				
Univariate*	0.47 (0.33–0.61)	0.29 (0.03–0.55)	0.30 (0.03–0.56)	0.16 (0.01–0.32)
Multivariate$	0.31 (0.12–0.49)	0.37 (0.11–0.63)	0.30 (0.02–0.57)	0.21 (0.04–0.37)

*includes interaction term with time variable.
$adjusted for interaction term with time variable, age at symptom onset, gender, baseline smoking status and year of inclusion in the cohort. ACPA status was also included as a covariate in the total cohort multivariate model.

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Similar Improvements in Physical Function, Quality of Life and Work Productivity Among Rheumatoid Arthritis Patients Treated with 2 Different Doses of Methotrexate in Combination with Adalimumab. Gurjit S. Kaeley[1], Midori Jane Nishio[2], Daryl MacCarter[3], Jenny Griffith[4],

Hartmut Kupper[5], Vishvas Garg[6] and Jasmina Kalabic[5]. [1]University of Florida, Jacksonville, FL, [2]Diablo Clinical Research, Walnut Creek, CA, [3]Coeur d'Alene Arthritis Clinic, Coeur d'Alene, ID, [4]AbbVie, Inc., North Chicago, IL, [5]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany, [6]AbbVie Inc., North Chicago, IL.

Background/Purpose: Methotrexate (MTX) is used in monotherapy or in combination with other DMARDs in the treatment of patients (pts) with rheumatoid arthritis (RA). We evaluated the effects of low and high MTX doses in combination with initiation of ADA on patient-reported outcomes (PROs), in MTX-inadequate responders (MTX-IR) with moderate-to-severe RA.

Methods: MUSICA (NCT01185288) was a double-blind, randomized, controlled trial evaluating the efficacy of 2 different dosages of MTX, 7.5 or 20 mg/week (wk) in combination with ADA (40 mg every other wk) for 24 wks in MTX-IR RA pts. Pts entering the study had been receiving ≥15 mg/wk MTX for at least 12 wks. At each study visit, from baseline (BL) to wk 24, the following PROs were recorded: physical functioning, work productivity and activity impairment, and health-related quality-of-life (HRQoL), using the health assessment questionnaire-disability index (HAQ-DI), work productivity and impairment (WPAI), and the short-form 36 (SF-36) questionnaires, respectively. Last observation carried forward (LOCF) was used to account for missing values.

Results: 154 pts were enrolled in the 7.5 mg/wk MTX+ADA arm, and 155 pts in the 20 mg/wk MTX+ADA arm. Both arms were similar for BL demographics (mean age 54.8, mean disease duration 5.3 years) and disease characteristics (mean DAS28(CRP) of 5.8). In the low and high MTX dosage groups respectively, mean BL HAQ-DI scores were 1.5, mean percentages (%) of time in absenteeism at BL were 9.2 and 10.1; mean % of time in presenteeism at BL were 45.0 and 47.6; mean % of activity impairment at BL were 57.0 and 61.9. BL SF-36 (physical component) scores were 31.5 for both groups, and BL SF-36 (mental component) scores were 44.7 and 41.9 for the low and high-dosage groups respectively. After 24 wks, significant improvements from BL were observed for both MTX dosage groups, in the WPAI (except for absenteeism), HAQ-DI and the physical and mental components of the SF-36 (table). Differences in physical function, QoL and work productivity observed between the low and high dosage MTX groups were not statistically significant.

Table 1 Effect of treatment with ADA + low or high dose MTX on patient outcomes at week 24

Outcome measure	n	Change from BL to wk 24, mean (95% CI)	*P*-value (BL and wk 24 mean scores)	wk 24, mean score (95% CI)	*P*-value (between wk 24 mean scores of dosage groups)
HAQ					
7.5mg/wk MTX+ADA	151	−0.5 (−0.6, −0.4)	<.001	1.0 (0.9, 1.1)	0.476
20mg/wk MTX+ADA	154	−0.5 (−0.6, −0.4)	<.001	1.0 (0.8, 1.1)	
WPAI-absenteeism					
7.5mg/wk MTX+ADA	63	−2.9% (−8.4, 2.5)	0.288	6.3% (1.9, 10.6)	0.261
20mg/wk MTX+ADA	61	0.6% (−7.1, 8.2)	0.882	10.6% (4.7,16.6)	
WPAI-presenteeism					
7.5mg/wk MTX+ADA	66	−17.9% (−24.5, −11.3)	<.001	27.1% (20.9, 33.3)	0.700
20mg/wk MTX+ADA	63	−21.0% (−28.4, −13.6)	<.001	26.7% (20.0, 33.3)	
WPAI- Overall Work impairment					
7.5mg/wk MTX+ADA	63	−19.0% (−26.6, −11.4)	<.001	29.2% (22.9, 36.4)	0.580
20mg/wk MTX+ADA	61	−17.5% (−26.5, −8.4)	<.001	32.7% (24.7, 40.7)	
WPAI-Activity impairment					
7.5mg/wk MTX+ADA	137	−14.9% (−19.6, −10.2)	<.001	42.1% (37.0, 47.3)	0.278
20mg/wk MTX+ADA	143	−20.4% (−25.3, −15.4)	<.001	41.5% (36.5, 46.6)	
SF-36-physical component					
7.5mg/wk MTX+ADA	150	7.2 (5.7, 8.7)	<.001	38.8 (37.0, 40.5)	0.835
20mg/wk MTX+ADA	152	7.4 (6.1, 8.8)	<.001	38.9 (37.3, 40.6)	
SF-36-mental component					
7.5mg/wk MTX+ADA	150	3.7 (1.9, 5.6)	<.001	48.8 (47.0, 50.5)	0.759
20mg/wk MTX+ADA	152	4.8 (2.9, 6.7)	<.001	46.5 (44.7, 48.3)	

P-values between dosage groups at wk 24 determined by ANCOVA

Conclusion: Similar to observations in pts with early RA,[1]the addition of ADA to MTX in pts with moderate to severe disease and insufficient MTX response, led to improvements in physical function, work productivity and quality of life after 24 wks. The improvements were observed regardless of the MTX dosage. Similar improvements in the two MTX dosage groups support the idea that MTX dose could be reduced in some MTX-IR pts while initiating ADA therapy.

Reference:

1. Burmester GR et al. *Ann Rheum Dis* 2014;0:1–8

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Sustained Remission Improves Physical Function in RA Patients Treated with Tumor Necrosis Factor Inhibitor. Jon T. Einarsson[1], Meliha C. Kapetanovic[1] and Pierre Geborek[2]. [1]Lund University, Lund, Sweden, [2]Section of Rheumatology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden.

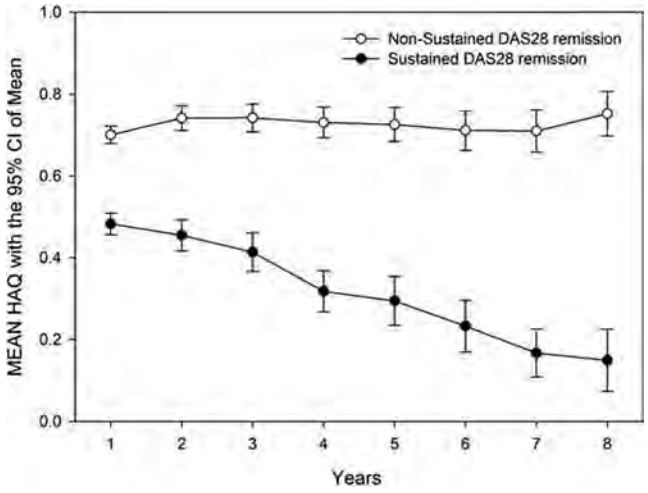
Background/Purpose: Remission is increasingly becoming a treatment goal in rheumatoid arthritis (RA) patients. Despite their limitations DAS28 remission criteria are widely used. It is not clear whether achieving remission is sufficient or weather the goal should be sustained remission. Physical function measured by health assessment questionnaire (HAQ) is a major outcome in RA. HAQ is shown to be one of the strongest predictors of long-term outcomes including quality of life, work disability and mortality.

The purpose of this study was to investigate the physical function over a long time period in RA patients treated with Tumor Necrosis Factor inhibitors (aTNF) who achieved sustained remission (SR) compared to that of patients occasionally achieving remission (non-sustained remission, nonSR).

Methods: Anti-TNF treated RA patients included in the observational South Swedish Arthritis Group register were eligible for this study. We identified patients with DAS28<2.6 at some point and those that achieved sustained remission in consecutive visits for at least 6 months. The course of functional status was assessed using HAQ at each visit.

Results: Of 2416 patients included, 1194 (49.4%) reached DAS28 remission at some point. Of those fulfilled 382 (15.8 %) the criteria for SR with median duration of 5.25 years while 812 (33.6%) had non-sustained remission. The nonSR group had mean disease duration of 11.5 years at treatment start compared to 10.1 years in the SR group, and mean HAQ of 1.3 compared to 1.0 in the SR group. Figure1 show the mean HAQ in each year after remission start with the 95% confidence interval of mean. In the first year the mean HAQ in the SR group was 0.48(95%CI of mean 0.026) and then continued to improve in every year for 7 years. The HAQ is significantly lower in year 4 (0.32; 95%CI 0.050) and again in year 7 compared to year 4 (0.167; 95%CI 0.058). In the nonSR group the mean HAQ in the first year was 0.701 and did not change significantly over 8 years.

Conclusion: Physical function measured by HAQ improves in patients with established RA reaching sustained remission and continues to improve while in remission. This suggests that treatment should be aimed at maintaining sustained remission.



Disclosure: J. T. Einarsson, None; **M. C. Kapetanovic**, None; **P. Geborek**, None.

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Understanding Patient Preferences Associated with the Use of Therapies for Rheumatoid Arthritis: Results of a Conjoint Analysis. K. Saverno[1], A. Louder[1], A. Singh[2], J. Cappelleri[3], A. Aten[4], A. Koenig[5] and M. Pasquale[1]. [1]Comprehensive Health Insights Inc, Louisville, KY, [2]Pfizer Inc, Groton, CT, [3]Pfizer Inc, New York, NY, [4]Humana Inc, Louisville, KY, [5]Pfizer Inc, Collegeville, PA.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Tofacitinib provides patients with a new oral alternative to biologic therapies; however, little is known about the

patient preference of modern treatments for RA. Here, we determined patient preferences for attributes associated with therapies used in the treatment of RA.

Methods: A choice-based conjoint survey was mailed to 1400 randomly selected Humana adult (21–80 years old) members diagnosed with RA (continuously enrolled and had ≥2 medical claims with an ICD-9-CM diagnosis code of RA [714.0] between 5/1/2012 and 4/30/2013) and no prior use of a biologic indicated for RA. Attributes included route of administration (ROA); monthly out-of-pocket cost; frequency of administration (FOA); ability to reduce daily joint pain and swelling; likelihood of serious side effects (SAE); improvement in the ability to perform daily tasks and activities; and medication burden (methotrexate co-administration). Mean attribute importance scores (AIS) were calculated after adjusting for various member demographics (e.g. age, gender, region, years since RA diagnosis). Mean AIS scores were used to rank order patient preferences for the attributes. An aggregate logit analysis was implemented to estimate average utilities & preference shares for two treatments – a twice daily oral and every other week self- injection.

Results: A total of 380 commercially enrolled members (response rate of 27.1%) in Humana returned the survey (mean ± standard deviation [SD] age 54.9 ± 9.3 years, 9.7% had a history of joint surgery due to RA, 81.6% female). After an adjustment for demographic and clinical characteristics, commercial members' ranking of attribute importance was as follows in decreasing order (mean AIS ± SD): ROA 34.08 ± 15.53; FOA 16.43 ± 6.82; SAE 12.01 ± 9.32; cost 10.12 ± 6.21; medication burden 9.75 ± 8.15; joint pain reduction 8.86 ± 3.82; and improvement in daily tasks 8.76 ± 4.70. Within the route of administration attribute, the oral formulation was the level with the highest part-worth utility (preference score) compared with subcutaneous and intravenous routes of administration. Based on the part-worth utility, it was estimated that 62% of RA patients included in the sample would prefer oral therapy.

Conclusion: Route of administration is an important consideration for those diagnosed with RA and naïve to biologic therapy. Given the variety of RA therapies available, gaining a better understanding of the attributes considered important to patients in their treatment may help inform payer and prescriber decisions in selecting therapies that will lead to higher patient satisfaction and improved medication adherence.

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2396

Treat to Target in Routine Clinical Practice. Mohammad Solaiman[1], Olga Semenova[1], Helen Thompson[1], Joanne Cunnington[1], Elaine Baguley[1], Sathish Kallankara[2], Olanbambo Ogunbambi[1] and Yusuf Patel[3]. [1]Hull Royal Infirmary, Hull, United Kingdom, [2]Hull Yoyal Infirmary, Hull, United Kingdom, [3]Hull and East Yorkshire NHS Trust, Hull East Yorkshire, United Kingdom.

Background/Purpose: In order to overcome obstacles with overbooked outpatient clinics and lack of capacity to see rheumatoid patients frequently for treatment escalation, we established a protocol-driven clinic run by a speciality doctor and nurse in 2010. All newly diagnosed patients with Rheumatoid Arthritis were seen on a 4–6 weekly basis by the team to escalate DMARD treatment according to disease activity as measured by DAS28-CRP. To assess DAS28-CRP remission rate in this cohort of patients (after 1, 2 and 3 years of therapy). We also looked at rates of low disease activity (LDA) - DAS 28 CRP≥2.6 but≤3.2 and categorisation by DMARD monotherapy, combination therapy, or Biologic therapy.

Methods: Treatment escalation was done by agreed departmental protocol which included oral Methotrexate (up to 25mg/week, followed by S/C injections if necessary). This was followed by addition of Hydroxychloroquine and then either Leflunomide or sulphasalazine if DAS28-CRP indicated activity. UK NICE guidelines allow use of Biologics if the DAS > 5.1 at 6 months, hence this was the next step followed on the protocol. We collected additional outcome data for HAQ score, work stability data, and radiological erosion data. We have 331 patients through the clinic to date and present outcome data for those completing 1year (127), 2years (75) and 3years (36).

Results: 127 patients have completed 1year, of which 20% achieved DAS28 scores <3.2 (LDA) and 60% <2.6 (remission). 64% needed combination DMARD therapy and 7 patients (5.5%) needed biologics, 30% remaining on DMARD monotherapy at 1 year. Mean HAQ scores reduced from 1.1 (+−0.01) to 0.32 (+−0.07) and radiological erosions progressed in only 10%. Job retention at one year was 90%.

75 patients completed 2 years of follow-up, 68% in DAS-remission and 16% LDA. 8% are on Biologics at end of year 2, 32% on DMARD monotherapy.

36 patients completed 3 years follow-up, with LDA in 25% and remission 61%. At year 3, Biologics use is 5.5%, with DMARD monotherapy in 20%.

DAS28 remission is maintained at 60% over the course of the 3years, with LDA increasing from 20% to 25% at year3. The active group (>3.2 DAS <5.1) who do not satisfy NICE criteria for Biologics reduced from 20% (year1) to 14% (year 3) on combination DMARD therapy.

Conclusion: Targeted protocol-driven treatment of early RA with rapid escalation of therapy using conventional DMARDs/biologics resulted in remission of 60% at 1 year and maintained remission of 68% and 61% at 2 and 3 years. The DAS28 remission rates and other outcomes achieved in this relatively 'routine' clinic are comparable to results achieved in controlled clinical trials. The innovative use of limited human resources and clinic appointments has provided good outcomes for patients with potential savings in expenditure on Biologic therapy.

Table: Comparison between Disease activity and therapy on consecutive 3 years

			YEAR 1 (2011)	YEAR 2 (2012)	YEAR 3 (2013)
Total number of patient= n			**N=127**	**N=75**	**N=36**
Disease activity	**Active DAS-28 CRP > 3.2**		26 (20%)	12 (16%)	5 (14%)
	Therapy	Monotherapy	6 (23%) one patient not on DMARD	4 (33%)	0 (0%)
		Combination	15 (58%)	5 (42%)	4 (80%)
		Biologics	4 (15%)	3 (25%)	1 (20%)
	Low DAS-28 CRP ≥2.6 but ≤ 3.2		25 (20%)	12 (16%)	9 (25%)
	Therapy	Monotherapy	9 (36%)	4 (33%)	1 (11%)
		Combination	15 (60%)	7 (59%)	8 (89%)
		Biologics	1 (4%)	1 (8%)	0 (0%)
	Remission DAS-28 CRP is < 2.6		76 (60%)	51 (68%)	22 (61%)
	Therapy	Monotherapy	23 (30%)	16 (31%)	6 (27%)
		Combination	51 (67%)	33 (65%)	15 (68%)
		Biologics	2 (3%)	2 (4%)	1 (5%)

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2397

Improvement of Fatigue in Patients with Rheumatoid Arthritis Treated with Biologics: Relationship with Sleep Disorders, Depression and Clinical Efficacy. A Prospective, Multicenter Study. Marlène Genty[1], Marie Kostine[2], Elodie Ardouin[3], Bernard Combe[4] and Cédric Lukas[5]. [1]CHU Lapeyronie, Montpellier, France, [2]Rheumatology, CHU Pellegrin, Bordeaux, France, [3]Rheumatology, Limoges University Hospital, Limoges, France, [4]Hôpital Lapeyronie, Montpellier, France, [5]Hopital Lapeyronie, Montpellier, France.

Background/Purpose: The functional burden of disease in Rheumatoid arthritis (RA) patients, mainly caused by inflamed joints, is often worsened by extra-articular manifestations, among which asthenia remains the most frequently reported. Most biologics have shown overall efficacy on fatigue, but whether this is due to overall improvement of disease or to more specific aspects of the disease like sleep disorders due to overnight pain and awakenings remains unknown. The aim of this study was to evaluate potential predictive factors of improvement in related fatigue in RA patients newly receiving biologic therapy, and more specifically the potential influence of the improvement in sleep disorders.

Methods: We conducted a multicenter prospective study in RA patients (100% fulfilling ACR/EULAR classification criteria) requiring initiation or change of biologic therapy. The improvement in fatigue was assessed by the FACIT fatigue scale at inclusion (M0) and after 3 months (M3). Sleep disorders and evaluation of depression were respectively measured by Spiegel scale and Beck Depression Inventory. Potential confounders like presence of anemia, thyroid dysfunctions, iron deficiency, psychotropic or corticosteroids medications were adjusted for. The association between evolution of fatigue (improvement/no improvement according to predefined validated cutoffs) and

other characteristics were evaluated by univariate (Chi2) then multivariate (logistic regression) analyses.

Results: We included and followed-up 99 patients (72,7% women, aged 58,2±12,1 with initially active disease (DAS28 5,1±1,4). FACIT scores at inclusion revealed frequently reported fatigue: 89% with scores more severe than expected in general population, high prevalence of sleep disorders (95%: abnormal 68%, pathologic 27%) and depression (67%: mild 33%, moderate 24%, severe 11%). Anti-TNF drugs were started in 50 patients, other biologics in 49 patients (tocilizumab N=19, abatacept N=16, rituximab N=14). Clinical response was beneficial in most patients: 36% good EULAR response, 40% moderate, 24% no response. Improvement of fatigue, sleep quality and depression according to predefined cutoffs was observed in respectively 58.6%, 26.3% and 34.3% of cases. Factors associated with an improvement in fatigue at M3 were an elevated sedimentation rate at M0 (OR=5.7[2.0–16.0], p=0.001) and a favorable EULAR response at M3 (OR=4.8[1.6–14.8], p=0.006). Furthermore, a number of swollen joints >5 at baseline (OR=0.3 [0.1–0.8]) and the use of psychotropic drugs (OR=0.2[0.04–0.9]) were predictive of an absence of improvement in fatigue. No significant association with the improvement in sleep disorders could be demonstrated: of 29 patients with improvement in sleep quality, 17 (58.6%) considered their level of fatigue had decreased, while 41/70 (58.6%) did so among those without correction of sleep disorders (p=0.9).

Conclusion:. Our study confirmed that fatigue in RA is frequent, as well as depression and sleep disorders, and is usually improved by effective treatment (i.e. via decrease in disease activity). Our results indicate that improvement of sleep disorders is more likely a surrogate of therapeutic efficiency rather than an independent outcome.

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2398

Continued Participation in a 10-Year Tight Control Treat-to-Target Study in Rheumatoid Arthritis: Why Keep Patients Doing Their BeSt?
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Background/Purpose: To identify risk factors for premature study termination and patients' motives for adherence to a long term follow-up clinical trial in rheumatoid arthritis (RA).

Methods: In 508 patients with early RA enrolled in the BeSt study, risk factors for premature study discontinuation were identified through univariable and then multivariable logistic regression analysis. In this analysis, for every patient ten endpoints were generated (still under follow-up at the end of a year, yes/no), and baseline characteristics and clinical characteristics as present in the preceding year of follow-up were entered as determinants. Patients who completed 10-year follow-up were asked to fill in a questionnaire on study experiences and possible motives for study adherence.

Results: In total, 313/508 patients (62%) attended the final visit, and 288 (92%) filled in the questionnaire. Mean age of completers was 61 years and 67% were female. Based on 508 included patients, risk factors for early termination were a higher age (odds ratio, OR 1.04, 95% confidence interval, CI 1.03 – 1.06), worse functional ability during the preceding year (measured with the health assessment questionnaire, OR 1.63, 95% CI 1.27 – 2.08), having achieved drug-free remission during the preceding year (OR 1.85, 95% CI 1.38 – 2.47) and suffering a severe adverse event during the preceding year (OR 1.71, 95% CI 1.18 – 2.49). In the first part of the questionnaire, the majority of patients mentioned contributing to scientific research (97% of patients agreed), helping other patients (91%), 'I have nothing to lose' (80%), gaining understanding of new treatment strategies (84%) and of their disease (85%) as reasons to continue participation. Next, patients were asked to mark one or more possible reasons to continue participation. In total, 278 patients marked 912 reasons: tight disease control (202/278 patients), good treatment strategy (128/278), good medication prescribed by the protocol (117/278) and good half-time results (102/278) were most often mentioned. Over 95% of patients experienced participation 'as expected' or 'better than expected'. In particular care by the study nurses was appreciated: 55 – 75% answered 'better than expected' to 4 questions regarding this issue. Additional examinations during the yearly visits (additional questionnaires, imaging techniques) were mentioned 'worse than expected' (10% of patients) as was filling in the 3-monthly questionnaires (7%). Most patients (74%) would participate in another trial and 94% would recommend participation to friends and family.

Conclusion: Continued participation during 10 year follow-up in the BeSt study was relatively high (62%), although impaired functional ability, higher age, experiencing severe adverse events and achieving drug-free remission in the previous year were predictors for early termination. Motivators to continue participation were a wish to contribute to scientific research, to learn more about their disease and its treatment, personal benefit of available therapies, and a good rapport with the study nurse. By cultivating these motivators, early termination in future long-term follow-up studies might be reduced.

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Non-Adherence to Disease-Modifying Anti-Rheumatic Drugs in Patients with Rheumatoid Arthritis: An Italian Survey.
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Background/Purpose: Approximately 50% of patients (pts) with chronic diseases are non-adherent to the therapeutic regimen assigned. In pts with rheumatoid arthritis (RA), the non-adherence to therapy may impair the efficacy of treatment and is often associated with the disease flare and increased disability; moreover, non-adherence is a dynamic feature, unpredictable, because pts initially compliant to treatment may become non-adherent. The objectives of this survey were to evaluate the presence, to quantify the extent and to identify reasons for non-adherence to treatment with conventional disease-modifying anti-rheumatic drugs alone (cDMARDs) or with biological DMARDs (bDMARDs) in RA pts in Italy.

Methods: This was a self-reported survey performed in RA pts treated with cDMARDs in Italy. In the hospital waiting room, pts were asked to fill out an anonymous paper based questionnaire, without either nurses or physicians support. Fieldwork: December 3rd 2013 - February 24th 2014.

Results: A total of 1,000 RA pts treated with cDMARDs were recruited from 25 Italian centers (females: 76.3%; mean age: 57 years; mean time since RA diagnosis: 9 years): 360 pts were treated with cDMARDs alone and 640 pts were treated in combination with a biologic drug.

Overall, the proportion of pts reporting non-adherence to cDMARDs was 37.2% (n=372): 28.9% (n=104) treated with cDMARDs alone and 41.9% (n=268) treated in combination cDMARDs + biologic drug. cDMARDs non-adherent pts were asked to report how often they do not take the cDMARDs treatment: the frequency of non-adherence was reported as "sometimes" by 55.38% of pts, "seldom" by 34.14%, "often" by 9.68% and "always" by 0.8%.

The main reason given for cDMARDs pts non-adherence was forgetfulness (54.8%); other reasons reported were: side effects fear (15.1%), the feeling they were taking too many drugs (14.2%), the thought of feeling better (9.4%) and the difficulty to remember drug dose and frequency of administration (6.5%). Interestingly, pts who did not mention cDMARDs non-adherence to their physician were 37.6% of the total 372 cDMARDs non-adherent pts, particularly younger pts (aged ≤ 40 years). More details are shown in Figures 1 and 2.

Conclusion: This extensive research about non-adherence to cDMARDs treatment, carried out in a large sample of RA pts, allowed to obtain an extensive local real life data set, representing Italian clinical practice. Results show that non-adherence to cDMARDs is fairly widespread (37.2%) among RA pts; furthermore, a considerable proportion of non-adherent pts (37.6%) find difficult to talk to their physician about this issue.

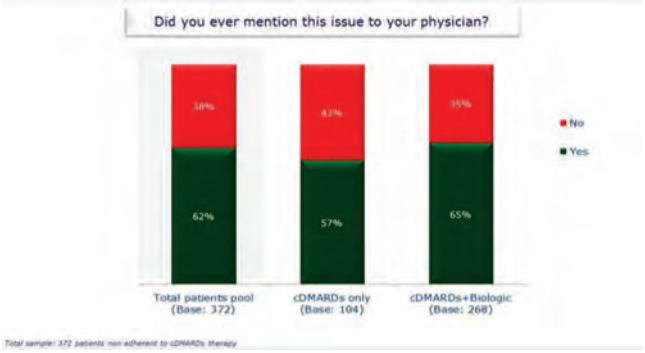

Fig 1

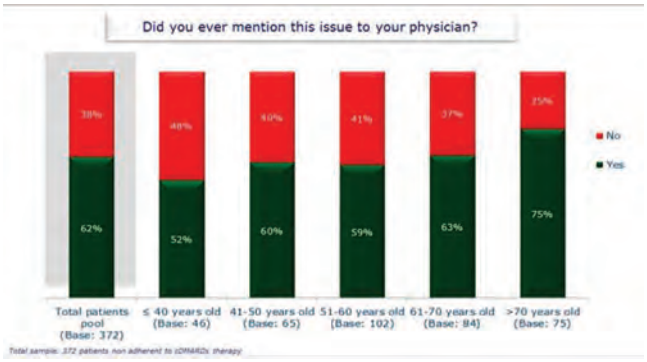

Fig 2

Disclosure: G. Bianchi, None; **A. Carletto**, None; **O. M. Epis**, Abbott Laboratories; Pfizer, Roche; BMS; AbbVie; Fidia Farmaceutici, 2, Fidia farmaceutici, Roche, Sanofi-Aventis; Laborest; BMS;AbbVie, Abbott, Pfizer, 5, Abbvie, BMS, Pfizer, Roche, Laborest, Sanofi-Aventis, MSD, Fidia Farmaceutici, 8; **C. Scioscia**, None; **A. Semeraro**, None; **L. Bianchino**, Roche Spa, 9; **L. Bazzichi**, None; **G. Lapadula**, None; **L. Sinigaglia**, Amgen, 8, Abbvie, 8, Eli Lilly and Company, 8, MSD, 8; **A. Lo Monaco**, Roche Pharmaceuticals, 5.

2400

Comparing a Tapering Strategy to the Standard Dosing Regimen of TNF Inhibitors in Patients with Rheumatoid Arthritis in Remission or with Low Disease Activity.

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Background/Purpose: There is a growing interest about optimization of biological therapies but for now no strong evidence is available to support a tapering strategy in clinical practice.

Our aim was to compare the clinical outcomes of a tapering strategy to the standard dosing regimen of TNF inhibitors (TNFi) in patients with rheumatoid arthritis (RA) and low disease activity during long-term follow-up.

Methods: In this retrospective observational study, two groups of RA patients on TNFi with DAS28<3.2 were compared: the tapering group (TG: 67 pts from Spain) and the control group with the standard therapy regimen (CG: 77 pts from the Netherlands). DAS28 was measured at different time points: visit 0 (prior starting TNFi), visit 1 (prior to starting tapering in TG and at least 6 months with DAS28<3.2 after starting TNFi in the TG and CG), visit 2 (6 months after visit 1), visit 3 (1 year after visit 1) and visit 4 (the last visit available after visit 1).

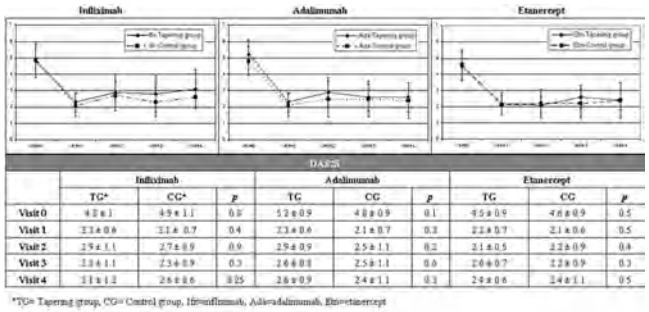
Results: The demographic characteristics are summarized in Table 1. Despite an overall reduction of administered drug at visit 4 in the TG (an interval elongation of 32.8% in infliximab, 52.9% in adalimumab and 52.6% in etanercept), no significant differences were found in the clinical activity between the groups at the end of the study (DAS28: 2.7±0.9 in TG vs. 2.5±1 in CG, p=0.1) (Figure 2). The number of patients with flares was similar in both groups [28/67 (42%) in TG vs. 36/75 (48%) in CG, p=0.5]. No significant differences were seen in the proportions of patients who dropped out [10/67 (15%) in TG vs. 6/77 (8%) in CG, p=0.17].

Conclusion: The tapering strategy of TNFi in RA patients with low disease activity results in an important reduction in the amount of drug administered, while the disease control remains similar to that of patients on the standard dosing regimen.

Table 1. Demographic Characteristics of 144 RA patients

RA patients n = 144 patients	Infliximab			Adalimumab			Etanercept		
	TG* n = 23	CG* n = 22	p	TG n = 23	CG* n = 27	p	TG n = 21	CG n = 28	
Female, no (%)	20 (87%)	15 (68%)	0.1	20 (87%)	22 (82%)	0.6	15 (71%)	21 (75%)	0.8
Age (years), mean ± SD	63 ± 15	62 ± 9	0.6	57 ± 11	55 ± 9	0.6	57 ± 15	59 ± 11	0.9
Disease duration (years), mean ± SD	15 ± 6	15 ± 6	0.77	19 ± 7	19 ± 6	0.9	16 ± 8	18 ± 10	0.2
RF*, n/N(%)	18/23 (78%)	18/20 (90%)	0.3	20/23 (87%)	20/27 (74%)	0.3	14/21 (67%)	20/28 (71%)	0.7
ACPA*, n/N(%)	17/23 (74%)	14/14 (100%)	0.037	17/23 (74%)	16/27 (59%)	0.3	14/21 (67%)	19/21 (91%)	0.4
Smoking habit, n/N (%)	1/23 (4%)	2/15 (13%)	0.3	3/23 (13%)	7/25 (28%)	0.2	4/21 (19%)	10/28 (36%)	0.2
Prior biological use, no (%)	1 (4%)	5 (23%)	0.070	2 (9%)	3 (11%)	0.8	5 (24%)	8 (29%)	0.7
Duration of inactive disease prior visit 1, mean ± SD (years)	1.4 ± 1.1	1.3 ± 0.8	0.75	1 ± 0.9	0.7 ± 0.2	0.3	0.8 ± 0.6	0.8 ± 0.2	0.2
Duration of follow-up between visit 1-visit 4, m ± SD (years)	2.5 ± 1.3	2.6 ± 0.6	0.4	2.5 ± 1.3	2.4 ± 1.2	0.6	2.1 ± 0.7	2.3 ± 0.7	0.1
Baseline co-therapy									
Methotrexate (MTX)	15 (65.2%)	22 (100%)	0.002	18 (78%)	23 (85.2%)	0.5	13 (62%)	25 (89%)	0.023
Other DMARDs (OD)	15 (65.2%)	6 (27.3%)	0.011	11 (48%)	2 (7.4%)	0.001	8 (38%)	6 (21%)	0.2
MTX + OD	9 (39.1%)	6 (27.3%)	0.4	7 (30%)	2 (7.4%)	0.035	5 (24%)	5 (18%)	0.6
TNFi monotherapy	2 (8.7%)	0 (0%)	0.2	1 (4%)	4 (15%)	0.2	5 (24%)	2 (7%)	0.1

*TG = Tapering group, CG = Control group, RF = rheumatoidfactor, ACPA = anti-cyclic citrullinated peptide antibodies



*TG= Tapering group, CG= Control group, Ifx=infliximab, Adl=adalimumab, Etn=etanercept

Figure 2. Comparison of clinical activity (DAS28) between in tapering and control groups in each TNFi. The clinical activity was measured by DAS28 (mean ±SD; represented as X-axis) in each TNFi at different time points during the study: visit 0 (prior starting TNFi), visit 1(pre-tapering), visit 2 (6 months after visit 1), visit 3 (1 year after visit 1) and visit 4 (last visit available after visit 1).

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2401

Interrupted and Delayed Care in First Nation Patients with Rheumatoid Arthritis: The Best Target for Therapy?

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Background/Purpose: Severe disease and poor outcomes have been described in First Nation (FN) patients with Rheumatoid Arthritis (RA). We examined the contributions of interrupted and delayed care to the outcomes of FN RA patients compared with Caucasian (CA) patients with RA.

Methods: Our academic Arthritis Centre maintains a prospective database on all patients seen since 1990, with records of more than 10,000 patients. The database includes patients' diagnoses, demographics, year of disease onset, and date of first and subsequent clinic visits, and self-reported ethnicity. At each visit, patients complete a modified health assessment score (mHAQ), disease activity visual analogue scales (VAS), while physicians complete joint counts, physician global VAS, and current treatment information. A Lansbury Index (LBI), a weighted joint count, is calculated each visit. After excluding patients if disease duration was >15 or <1 year, or if there were <2 clinic visits, records of the most recently assessed 150 FN and 150 CA RA patients were abstracted. The database was supplemented with search of the provincial electronic imaging and laboratory databases for each patient, to determine serology, acute phase reactants, and radiologic damage or documented joint deformities.

Results: Records of 154 CA and 150 FN patients were abstracted**.** Disease duration and gender distribution were similar in CA compared to FN (9 ±4 vs 8 ±5 years; and 79% vs. 85% female respectively). Mean distance from care was 73 km for CA and 408 km for FN, with 35% of FN living >500 km away compared to 1% of CA, (p <0.001). FN patients were younger at disease onset than CA, (40 ±13 vs 49 ±17 years; p < 0.001). At clinical presentation, FN were more likely to be seropositive for both RF and ACPA compared to CA, (59% vs 46%; p = 0.02) and had higher RF titers (405 ±551 vs 236 ±485; p = 0.005), and ACPA titres (114 ±88 vs 68 ±82; p < 0.001) The two groups did not differ in mHAQ, ESR, CRP, VAS, tender, or swollen joint counts at first visit, but FN had higher LBI scores (40 ±36 vs 28 ±33; p = 0.012). FN had greater delays from symptom onset to first DMARD (19 months ±26 vs 15 ±35; p = 0.2), and first biologic (57 months ±34 vs 46 45; p = 0.06), but had more total DMARD trials over their disease course (5.1 ±3.2 vs 3.7 ±2.5; p = <0.001), and were off DMARD therapy for longer periods in total (36 months ±30 vs 25 ±40; p = 0.009), had fewer clinic visits/year (5 ±12 vs 3 ±7; p = 0.072, and received more frequent intramuscular steroid injections (IMS) for flares: 21% of FN had received 3–5 IMS vs. 12% of CA, and 11% had received ≥ 6 IMS vs 3% of CA; p<0.001. At the last visit, FN had higher mHAQ scores (.71 ±.47 vs. 42 ±.52; p <0.001), higher LBI (34 ±37 vs 20 ±30; p = 0.003), and more frequent joint damage/deformity, (85% vs 74%; p = 0.02).

Conclusion: The younger onset age, more frequent seropositivity, and higher LBI suggest biologically more severe disease, but our data suggests differential care delivery with modifiable factors over the disease course that likely impact outcomes, including treatment delays, missed appointments, and interrupted treatment. Improved care delivery models, particularly incorporating outreach care, have the potential to improve outcomes substantially for this population.

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2402

Evaluation of Perceived Self-Efficacy, Learned Helplessness and Functional Capacity in Patients with Rheumatoid Arthritis. Facundo Vergara[1], Emmanuel Bertiller[2], Celeste Orozco[3], Javier Rosa[1], Erika Catay[1], Maria de los Angeles Gallardo[4], Emilce Schneeberger[5], Maria Victoria Garcia[1], Gustavo Citera[6], Marcos G. Rosemffet[6], Mirtha Sabelli[1] and Enrique R. Soriano[7]. [1]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [3]Instituto Rehabilitacion Psicofisica, Buenos Aires, Argentina, [4]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, BUENOS AIRES, Argentina, [5]Instituto de Rehabilitacion Psicofisica, Buenos Aires, Argentina, [6]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [7]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina.

Background/Purpose: Rheumatoid Arthritis (RA) is an inflammatory chronic disease that involves cognitive and emotional aspects of patients, from the beginning of diagnosis. One relevant cognitive factor is perceived self-efficacy, which is defined as the individual's abilities to cope with the disease. Another important cognitive factor in the perception of RA control is the learned helplessness. We could define it as an inadequate perception of the disease generating feeling of defenselessness, behaviors of passivity, loss of self-esteem and belief that nothing you do can improve your situation.

It has been reported that petients with high levels of self-efficacy have less pain, learned helplessness and functional disability. On the other hand patients with higher learned helplessness, have more pain and functional disability.

Our objective was to assess the association between perceived SE and LH with disease activity, functional disability, and educational level.

Methods: Consecutive patients, older than 18 years, with definite diagnosis of RA according to 2010 ACR/EULAR criteria, seen at the outpatient rheumatology unit between March and April 2014, were included. During the inclusion visit the following data were collected: Demographics; socioeconomic status (Graffar scale); educational level; disease duration; swollen and tender joint counts (28 joints); CDAI (Clinical Disease Activity Index); HAQ-A (Health Auto Questionnaire-simplified Argentinean validation); pain by visual analogue scale (VAS); fatigue (VAS); patient and physician global assessment of disease activity (VAS); morning stiffness (VAS), depression screening measured by CES D-7; perceived SE measured by Arthritis Self-auto-efficacy Scale; LH measured from Rheumatology Attitudes Index (RAI) (spanish validation).

Descriptive statistics were calculated. Correlations were calculated using Pearson test. SE and LH were compared between patients in remission and with active disease.

Results: One hundred and two patients were included. Patient's characteristics are shown in table 1.There was a significant positive correlation between LH and pain (r=0.67; p<0.001); HAQ (r=0.64; p<0.001), and CDAI (0.41; p<0.001); and a negative correlation between SE and pain (r= − 0.43; p<0.001); HAQ (r= − 0.41; p<0.001); and CDAI (r= -0.34; p<0.001). Patients on remission (n=30) according to CDAI, had significantly higher SE (70.3 vs. 56.8; p<0.001) and lower LH (7.2 vs. 11.6; p<0.001) than patients not in remission. There was a poor correlation between LH and SE with educational level (years of education) (r = 0.39 and −0.19, respectively).

Features	
Female, n (%)	85 (83, 3)
Age, media (DS)	59 (12,7)
Years from diagnosis, media (DS)	12,7 (10, 7)
Nacionality (n=100)	
Argentine, n (%)	94 (94)
Foreign, n (%)	6 (6)
Education level (n=102)	
Incompleted elementary school, n (%)	6 (5, 9)
Completed elementary school, n (%)	20 (19, 6)
Incompleted high school, n (%)	11 (10, 8)
Completed high school, n (%)	30 (29, 4)
Tertiary, n (%)	16 (15, 7)
University, n (%)	19 (18, 6)
Marital status (n= 100)	
Unmarried	20 (20)
Married	55 (55)
Divorced	13 (13)
Widowed	12 (12)
Positive RF, n (%)	66 (70, 2)
Positive Anti-CCP, n (%)	57/70 (81, 4)
Methotrexate, n (%)	80 (78, 4)
Biologic agents, n (%)	37 (36, 3)
Corticosteroids, n (%)	21 (20, 6)
Socio-economic level (Graffar)(n = 99)	
I**, n (%)**	5 (5)
II**, n (%)**	31 (31)
III**, n (%)**	42 (42)
IV**, n (%)**	21 (21)
CDAI, Median (IQR)	5,2 (2,1–12,5)
HAQ, Median (IQR)	0,5 (0–1,25)
PGA (VAS), Median (IQR)	20 (10–30)
PaGA (VAS), Median (IQR)	19,5 (5–47)
Pain (VAS), Median (IQR)	22 (5–50)
Stiffness (VAS), Median (IQR)	7 (0–30,5)
Fatigue (VAS), Median (IQR)	12,5 (1–45)
LH, Median (IQR)	9 (6–14)
SE, Median (IQR)	62 (53–73)
CES-D7, Median (IQR)	3 (1–7)

Conclusion: LH and SE are potentially modifiable cognitive factors that correlate with functional disability and disease activity. This might have potential clinical implications.

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2403

From Early Arthritis Clinic to Remission Clinic: Short-Term Outcome and Ultrasonographic-Synovitis Dynamics in Rheumatoid Arthritis Patients in DMARD-Induced SDAI-Remission during Drug-Free Follow-up. Antonio Manzo, Francesca Benaglio, Garifallia Sakellariou, Martina Scarabelli, Elisa Binda, Barbara Vitolo, Serena Bugatti, Roberto Caporali and Carlomaurizio Montecucco. Rheumatology and Translational Immunology Research Laboratories (LaRIT), Division of Rheumatology, IRCCS Policlinico S.Matteo Foundation/University of Pavia, Pavia, Italy.

Background/Purpose: The introduction of DAS-driven intensive treatment strategies in early rheumatoid arthritis (RA) has considerably improved outcome and patients' quality of life. Previous studies have also suggested the possibility, in selected cases, of maintenance of an acceptable clinical status for prolonged periods following treatment suspension. Despite these observations, three critical issues remain partly unsolved: 1) whether systemic

suppression of inflammation can coincide with reversal of the pathogenic process, 2) the possibility to define exploitable parameters able to predict in which patients treatment can be suspended, 3) the primary dynamics as well as the anatomic-biologic substrate of relapse. The aim of the current study was to investigate the clinical-radiographic-functional outcome and ultrasonographic-synovitis dynamics of RA patients in DMARDs-induced SDAI remission, during 12 months drug-free follow-up.

Methods: From December 2011, all RA patients followed at our Early Arthritis Clinic achieving stable clinical remission and candidate to treatment suspension are referred to a dedicated Remission Clinic. Referral criteria: 1) introduction of DMARDs treatment within 12 months from symptoms' onset, 2) ≥24 months DMARDs treatment with a DAS28-driven intensive protocol, 3) stable DAS28 remission (DAS28steroids. All patients allowed to drug-free follow-up are monitored at three months' intervals through complete clinical, ultrasonographic (hands-feet-axillary lymph nodes' PD-US) and immunologic screenings. Hands-feet radiographs are performed at baseline and every 12 months. Treatment is re-introduced in case of moderate disease activity (DAS283.2) or radiographic progression.

Results: 40 consecutive RA patients in DAS28 and SDAI remission (SDAI≤3.3) at the baseline visit have been followed-up for 12 months in drug-free regimen and monitored every 3 months. Maintenance of stable DAS28 remission (T0-T12) was observed in 18/40 patients (45%), while treatment re-introduction due to disease relapse was required in 13/40 patients (32.5%). No significant radiographic progression (SHS) and functional impairment (HAQ) was detected at a group level during drug-free follow-up. Ultrasonographic stratification at baseline showed the absence of power Doppler signal (hands-wrists) in 29/40 (72.5%) (SDAI≤3.3-PD=0). Despite stringent remission and absence of sub-clinical signs of synovitis at recruitment, 8/29 (27.5%) patients relapsed, while in 12/21 (57.1%) a transient or persistent reappearance of defined PD signal (PD>1) was detected during follow-up despite the lack of requirement of DMARDs re-introduction according to study criteria.

Conclusion: Suspension of DMARDs with short term maintenance of good clinical status is an achievable goal after treat-to-target and tight control strategies in early RA. However, despite stringent clinical and ultrasonographic remission, relapse or signs of disease reactivation can occur early after drug withdrawal, supporting the requirement of additional patho-biologic insights for a more specific stratification of RA remission phase.

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2404

RA Patients with Inadequate Response to Oral MTX Maintain Satisfactory Disease Control and Durable Long-Term Response When Switched to SC MTX Monotherapy. Anthony Hammond[1] and Michael Batley[2]. [1]Maidstone and Tunbridge Wells NHS Trust, Kent TN13 2JD, United Kingdom, [2]Maidstone and Tunbridge Wells Hospital, Kent, United Kingdom.

Background/Purpose: Methotrexate (MTX) is the cornerstone of rheumatoid arthritis (RA) therapy, but many patients do not achieve adequate response to oral therapy for reasons of tolerability or efficacy.[1,2] Subcutaneous (SC) MTX should be considered for RA patients who have an unsatisfactory response to oral MTX.[3] In this analysis, RA patients switched from oral MTX to SC MTX monotherapy were evaluated to understand durability of response and disease control.

Methods: A prospective analysis of retrospective RA patient data collected from 2003–2011 at single site in the U.K.[4] was performed. Per institutional practice, incremental oral MTX dose increase was followed by a switch to SC MTX. Folic acid (5–15 mg) was given 1 day after SC MTX treatment as a matter of routine practice. Mean duration on SC MTX monotherapy following switch from oral MTX was documented via patient record review.

Results: 112 RA patients were eligible for analysis. Mean age was 60.9 yrs (range 26–83 yrs) and mean disease duration was 8.3 years (range 0.5–46 yrs). 49 (44%) patients with an inadequate response to oral MTX for reasons of tolerability or efficacy were switched to SC MTX monotherapy and included in this analysis. (Table 1) 20 patients (41%) switched from oral MTX to SC MTX for reasons of tolerability. Amongst these: Mean DAS28 improved by 18% (−1.05), patients remained on SC MTX monotherapy for a mean of 28.6 months before additional treatment was added and 40% (8) achieved low disease activity (LDA) of DAS28 ≤3.2; 29 patients (59%) switched for reasons of efficacy. Amongst these: Mean DAS28 scores improved 25% (−1.26), patients remained on SC MTX monotherapy for a mean of 34.58 months before addition of other therapies and 24% (7) achieved LDA.

Conclusion: In this single-center analysis, RA patients with an inadequate response to oral MTX for reasons of efficacy and/or tolerability maintained satisfactory disease control and durable, long-term response when switched to SC MTX monotherapy.

Table 1.

Evaluable (n=49)	n	Pre-Switch DAS 28	Post-Switch DAS 28	DAS28 Change (Value, %)	Mean Duration on SC MTX monotherapy (months)	LDA (≤3.2) (n,%)	Remission (≤2.6) (n,%)
Inadequate Response to Oral MTX (Tolerability)	20	4.46	3.65	−1.05 (18%)	28.6	8 (40%)	6 (30%)
Inadequate Response to Oral MTX (Efficacy)	29	5.34	4.08	−1.26 (25%)	34.58	7 (24%)	2 (7%)

Disclosure: A. Hammond, None; **M. Batley**, None.

2405

Quality of Patient- Clinician Communication in a Diverse Cohort of Adults with Rheumatoid Arthritis. Jennifer Barton[1], Chris Tonner[1], Laura Trupin[1], Patricia P. Katz[2] and Edward H. Yelin[1]. [1]University of California, San Francisco, San Francisco, CA, [2]University of California, San Francisco, CA.

Background/Purpose: To assess correlates of the quality of patient-clinician communication in a diverse cohort of adults with rheumatoid arthritis (RA).

Methods: Data were obtained through structured 30-minute telephone interviews conducted in English or Spanish. Subjects were enrollees of the Rheumatoid Arthritis Outcomes Study (RA OS), a longitudinal cohort of adults with RA. Two questions from the Consumer Assessment of Healthcare Providers and System (CAHPS) were used to assess RA patients' experience of communication with their rheumatologist: "How often did this doctor check to make sure you understood everything?" and "How often did this doctor spend enough time with you?" Responses options consisted of 5 choices ranging from "never" to "always." We report the proportion of subjects who responded "always" which is considered by CAHPS as the "Top-box" score. Logistic regression was used to model the quality of communication as a function of demographics (age, gender, race/ethnicity), education, health literacy (single-item literacy screener), English language proficiency, disease characteristics (duration, fatigue, disease activity), depression (score ≥10 on the Patient Health Questionnaire 9), and insurance.

Results: 395 adults with RA were surveyed with a mean age of 61 years, 89% were female, 46% white, 31% Latino. Nearly one-third (31%) had limited health literacy (LHL) and 17% had limited English language proficiency (LEP). Mean disease duration was 23 ± 12 years, 39% reported moderate fatigue and 18% severe, and 17% had a PHQ-9 score ≥10. In multivariate models controlling for disease activity, fatigue, and depression (see table), RA patients with LHL and LEP were more likely to report that their rheumatologist always checked for understanding. However, patients with LEP were less likely to report that their doctor always spent enough time with them, as were Latinos (compared to all other race/ethnic groups)..

Conclusion: Despite the finding that over 90% of RA patients with limited English language proficiency perceive that rheumatologists always check for understanding, only 38% of these same patients and 40% of Latinos report that doctors spend enough time with them. These results were independent of disease activity and depression. Providing high quality, patient-centered care in RA is important for all patients, especially those with barriers to communication. Awareness and interventions to enhance quality of communication and that address cultural expectations for care are needed for vulnerable populations.

Table Proportion of subjects who responded "always" to communication questions about rheumatologists among 395 adults with rheumatoid arthritis, from multivariate models^

	Overall percent (95% CI)	
	Check to be sure you understood	Spend enough time with you
Sociodemographics	74 (69, 78)	59 (54, 63)
Race/ethnicity		
Latino	74 (64, 84)	**40 (29, 50)**
Asian/Pacific Islander	71 (52, 89)	**69 (51, 87)**
African American	75 (61, 89)	**76 (64, 90)**

Mixed/Other/ Unknown	85 (71, 94)	**72 (60, 85)**
White	71 (65, 78)	**61 (54, 69)**
Limited English language proficiency	*	*
No	**70 (65, 76)**	**61 (56, 67)**
Yes	**93 (83, 99)**	**38 (18, 57)**
Limited health literacy		*
No	**70 (65, 76)**	58 (52, 64)
Yes	**84 (74, 90)**	60 (52, 69)

Ĉontrolled for age, gender, education, insurance, disease activity, disease duration, fatigue, depression (PHQ-9≥10), and all variables listed in table.
* P<0.05

Disclosure: J. Barton, None; **C. Tonner**, None; **L. Trupin**, None; **P. P. Katz**, None; **E. H. Yelin**, None.

2406

Primary Non-Adherence, Associated Clinical Outcomes and Healthcare Resource Utilization Among Rheumatoid Arthritis Patients Prescribed Injectable Biologics. J. Harnett[1], D. Wiederkehr[1], R. Gerber[2], D. Gruben[2], J. Bourret[3] and A. Koenig[3]. [1]Pfizer Inc, New York, NY, [2]Pfizer Inc, Groton, CT, [3]Pfizer Inc, Collegeville, PA.

Background/Purpose: Injectable biologics are commonly used to treat patients (pts) with moderate to severe rheumatoid arthritis (RA); the frequency with which they are prescribed but not filled is unknown. This exploratory analysis aimed to evaluate filling of newly prescribed injectable biologics for RA and characterize pt outcomes.

Methods: In a retrospective cohort design, pts (age ≥18 years during study period) with an RA diagnosis (ICD9: 714.XX) in 2007–2013 were selected from a de-identified database of clinical information from electronic health records (EHR; Humedica) linked to healthcare claims (Optum) from commercial and Medicare Advantage health plans. First injectable biologic prescription date in EHR was the index date. Pts without continuous pharmacy coverage for ≥6 months pre- and post- index, with evidence of pre-index injectable biologic administration in EHR or claims, or with hospitalization within 30 days post-index were excluded. Pts were categorized as filling the biologic prescription within 30 days (early fillers), 31–180 days (late fillers), or not at all within 180 days (non-fillers) of index. Pt baseline characteristics, including claims-based index of RA severity, RA prescribing patterns, and pt-reported pain scores (0–10; provider-determined scales) from EHR were assessed across all pts; 6-month post-index healthcare resource utilization (including biologic fills) and costs as identified within claims were assessed in pts with continuous medical and pharmacy coverage.

Results: Of 381 pts meeting inclusion criteria, 171 (45%) and 60 (16%) filled an injectable biologic prescription within 30 days and 31–180 days of index, respectively; 90% of prescriptions were written for TNF inhibitors (TNFi). Early fillers were younger, more likely to be female, had higher baseline RA severity, and filled more prescriptions for any reason pre-index. Of non-fillers, 65% were Medicare pts vs 18 and 37% of early and late fillers, respectively. Filling of nonbiologic DMARD prescriptions within 30 days of index was highest in early biologic fillers (45.6%) and lowest among non-fillers (23.3%); however, during days 31–180, the rate was 5.9% in early biologic fillers vs 34.0% in non-fillers. Of early fillers, 14% did not have another biologic prescription filled after 30 days. In the small subgroup of pts with both pre- and post-index pain scores, mean pain scores decreased in early fillers (−1.6; n=11), but increased in late fillers (0.5; n=6) and non-fillers (1.1; n=7). In pts with pharmacy and medical coverage for 180 days post-index (n=375), early fillers had greater RA-related pharmacy (84% of cost difference) and medical resource use and costs than late and non-fillers combined.

Conclusion: Over half (55%) of pts prescribed injectable biologics (90% TNFi) did not fill the prescription within 30 days; 40% had not filled by 180 days. For evaluation of clinical outcomes, documentation of pain scores in the EHR was limited for structured analysis. As expected, healthcare resource use/costs were higher in early fillers over short-term observation. Future research will need to focus on long-term consequences of under-treatment on clinical and economic outcomes.

Disclosure: J. Harnett, Pfizer Inc, 1, Pfizer Inc, 3; **D. Wiederkehr**, Pfizer Inc, 1, Pfizer Inc, 3; **R. Gerber**, Pfizer Inc, 1, Pfizer Inc, 3; **D. Gruben**, Pfizer Inc, 1, Pfizer Inc, 3; **J. Bourret**, Pfizer Inc, 1, Pfizer Inc, 3; **A. Koenig**, Pfizer Inc, 1, Pfizer Inc, 3.

2407

Early Treatment in Rheumatoid Arthritis and Its Effect on Patient Outcomes. Laurent Chanroux and Joan Casellas. The Research Partnership, London, United Kingdom.

Background/Purpose: It is generally thought that the early treatment of patients with rheumatoid arthritis (RA) leads to improved patient outcomes over time. Our study aims to better understand if early treatment alone is sufficient to achieve these goals and assess whether measures such as DAS, joint count and perceived severity are sufficiently sensitive for this purpose.

Methods: We used data collected as part of an online treatment survey conducted among a panel of 500 European rheumatologists between April 2008 and May 2014 across EU5 (Fr, Ge, It, Sp, UK). In order to assess whether earlier treatment has an effect on patients current disease status we ran a linear regression using patients' current DAS, current disease severity (as perceived by their physicians) and the number of joints affected by their disease as dependent variables (DV) and included the following as independent variables (IV):

- Time from cDMARDs initiation until first bDMARDs initiation (β_1)
- Time from diagnosis until cDMARDs initiation(β_2)
- Time from diagnosis until bDMARDs initiation(β_3)
- Severity at diagnosis(β_4)
- Number of cDMARDs before bDMARDs initiation(β_5)
- Current bDMARDs (Brand) (β_6)

We focused our analyses on patients diagnosed post 1998 to ensure patients had access to bDMARDs and only considered those currently prescribed their first line of bDMARD therapy to avoid any confounding effects caused by patients' treatment history. We also accounted for possible differences in patients' disease severity, both at diagnosis and at the time of their first bDMARD treatment, as well as the length of time they had been on their current bDMARD treatment.

Results: We considered data from a sample of 43,769 patient record forms and on average, our patients had a DAS of 2.9 with 85.8% classified as having moderate to severe RA. In addition, the mean time from diagnosis to cDMARD initiation and bDMARD initiation was 12.1 and 45.5 months, respectively.

Preliminary results from the regression analysis show that we can explain very little of the variability in our DV with an adjusted R square of just 5% for DAS, 2% for current severity and 5% for the number of affected joints. Therefore, we considered the coefficients of each model to measure the effect of our IV.

β_1 and β_2 have a low positive effect on DAS and current disease severity however, the choice of Enbrel, Humira and RoActemra as a first bDMARD has a strong negative effect on these two DV. In addition, β_2 and β_5 both have a strong positive effect on patients' number of affected joints, while $\beta_1$has a low positive effect.

Finally, we see that patients who have been on their first bDMARD for a shorter period of time (up to 2 years) better explained the variation seen in our DV.

Conclusion: Our analyses demonstrate that simply initiating treatment with cDMARDs and bDMARDs early on in patients' disease is not enough to optimise patient outcomes. Instead, early treatment must be combined with close monitoring and aggressive step-up treatment strategies such a treat-to-target to maximise patients' response to treatment and control their disease. In addition, our data also suggest that the impact that early treatment may have could be limited in time with disease statuses becoming more similar as the duration of bDMARD therapy increases.

Disclosure: L. Chanroux, None; **J. Casellas**, None.

2408

Frequency of Rheumatoid Arthritis Flares in Clinical Practice: Analysis of a Monocentric Cohort of Patients in Stable Remission or Low Disease Activity. Francesca Ometto[1], Costantino Botsios[2], Livio Bernardi[1], Bernd Raffeiner[2], Leonardo Punzi[2] and Andrea Doria[2]. [1]University of Padova, PADOVA, Italy, [2]University of Padova, Padova, Italy.

Background/Purpose: Rheumatoid arthritis (RA) flares are predictive of structural damage even in case of stable disease course. No definition for flare has been validated to date. The objective of our study was to determine the rate of flares in RA patients on stable LDA or remission. We considered flares assessed at each visit (FV), self-reported flares (SRF), and major flares (MF) defined as flares requiring a change in the DMARD or in the biologic dose or

lasting more than 30 days. We investigated the relationships between flare rate and baseline characteristics of patients or treatments. We further investigated whether flare rate could be related to survival of remission or LDA.

Methods: We conducted an observational study on RA patients, treated with subcutaneous anti-TNF-alpha, on stable (> 6 months) LDA or remission, with a minimum follow up of one year. We investigated associations of flare rates with age, sex, disease duration, baseline activity indices, positive ACPA and RF, concurrent fibromyalgia, smoking, previous biologic failures, treatment with methotrexate (MTX), prednisone (PDN) dose, and dose of biologics. Survival of remission or LDA according to flare rate was calculated with Kaplan-Meier curves.

Results: Out of 86 patients, 11 patients were excluded because of pregnancy or little reliability in recalling events, and 55 patients achieved a stable LDA or remission. We observed 237 flares in 55 patients with a mean follow up of 70.72 ± 30.41 months: 91 FV, 146 SRF, and 18 MF. Overall flare rate was 0.80 ± 0.79 flares/year, rate of FV was 0.26 ± 0.28, rate of SRF was 0.54 ± 0.70 and rate of MF was 0.05 ± 0.10. Flare rates on remission or LDA were not significantly different (0.67 ± 0.75 and 1.08 ± 1.29 flares/year, respectively). Mean time to flare was 23.62 ± 21.21 months and was inversely correlated with flare rate on LDA periods (Spearman's correlation, $R^2 = -0.405$, p 0.024). Overall flare rate and SRF rate were higher in patients with concurrent fibromyalgia and active smokers (Table). No significant differences were seen between full dose and low dose biologic, between different PDN doses or between combination with and without MTX, although fewer flares were observed on MTX (Table). Patients naive to biologics had many fewer flares than those who had a failure of one biologic or specifically of one anti-TNF-alpha (Table). PDN was the most used medication in case of flare (138/237, 58.2% of flares). Mean increase of PDN compared with previous dose was 3.66 ± 5.81 mg daily. Flare rate < 1 flare/year or a SRF rate < 0.5 flares/year were associated with a longer survival of LDA/remission (p 0.029 and p 0.037 respectively).

Conclusion: Flares are frequent on LDA or remission. Patients that have already failed a biologic treatment, active smokers and with concurrent fibromyalgia patients seem to be more prone to experience flares. SRF account for most of the flares and have the greatest impact on survival of remission.

Table. Flare rate

	N	Flare rate*	p value**
Concurrent fibromyalgia	11 (20.0%)	1.12 ± 0.72	p 0.037
No fibromyalgia	44 (80.0%)	0.72 ± 0.80	
Active smokers	9 (16.4%)	1.38 ± 1.31	p 0.049
Non smokers	46 (83.6%)	0.64 ± 0.55	
Naive patients	32 (58.2%)	0.49 ± 0.48	p 0.000
Patients that failed one previous anti-TNFα failure	23 (41.8%)	1.23 ± 0.93	
Combination therapy with methotrexate		0.38 ± 0.75 74 flares over 119.8 years	p 0.073
Combination therapy without methotrexate		0.79 ± 1.19 163 flares over 204.7 years	

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2409

Omega-3 Fatty Acids and Mediterranean Diet As Complimentary Therapies for Rheumatoid Arthritis. Ana Carolina Araújo[1], Maria Francisca Moraes-Fontes[1], Lèlita Santos[2] and Nuno Riso[1]. [1]Hospital de Curry Cabral, Centro Hospitalar Lisboa Central, Lisbon, Portugal, [2]Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting the synovial joints, often with a progressive and destructive course, leading to disability. Nowadays, there are several drugs available to treat this condition. However, in some patients the disease can be quite difficult to manage, due to refractoriness and expense of therapy. Complimentary therapies to manage RA may contribute to this unmet need. The anti-inflammatory effect of the Mediterranean diet (MedDiet) has been increasingly recognized in the last forty years together with the anti-inflammatory properties of omega-3 fatty acids (n-3 FA) [1,2].

This study aimed to evaluate the effects of n-3 FA supplements and MedDiet upon disease activity and laboratory measures of a cohort of RA patients.

Methods: This is a prospective randomized controlled trial including 37 RA patients (fulfilling ACR 1987 classification criteria). Patients were assigned to n-3 FA supplements (n=11) or MedDiet (n=8) and compared to a control group (n=15), during a 6 month follow-up period. Demographic characteristics, number of tender and swollen joints, global health status, ESR, CRP, and DAS-28 were obtained before and after the intervention. The analysis of dietary intake was performed with a semi-quantitative food frequency questionnaire. Patients were further stratified according to biological therapy. The statistical analysis was performed by Wilcoxon and Kruskal-Wallis tests with a significance level of 0,05.

Results: A significant reduction in ESR was noted after 6 months of n-3 FA but there was no significant variation in the remaining measures after 6 months, independently of the study group and the ongoing therapy for RA. However, a trend towards a reduction in DAS-28 and VAS was noted (table 1).

Table 1 Evaluated parameters at the beginning and after 6 months of intervention

	n-3 FA				MedDiet				Control Group				
Parameter	Beginning	6 months	n	p	Beginning	6 months	n	p	Beginning	6 months	n	p	p
ESR	32,18 ± 19,42	19,64 ± 13,27	11	0,01	21,75 ± 17,32	24,75 ± 13,72	8	0,58	28,00 ± 21,03	22,13 ± 12,02	15	0,12	>0,05
DAS-28	3,65 ± 1,26	3,41 ± 1,10	11	0,76	3,30 ± 1,02	3,53 ± 1,65	8	0,55	3,58 ± 0,91	3,94 ± 1,13	15	0,36	>0,05
EVA GH	39,09 ± 26,16	38,18 ± 29,17	11	0,84	46,25 ± 17,68	43,75 ± 22,80	8	0,94	46,67 ± 26,10	51,00 ± 28,55	15	0,36	>0,05
Tender Joints	3,54 ± 6,29	3,82 ± 5,51	11	0,73	3,00 ± 5,24	4,12 ± 5,03	8	0,13	2,33 ± 3,27	4,40 ± 5,18	15	0,10	>0,05
Swollen Joints	1,45 ± 2,50	1,00 ± 1,79	11	0,44	0,25 ± 0,46	1,12 ± 1,88	8	0,25	0,53 ± 0,83	1,13 ± 2,06	15	0,25	>0,05
CRP	0,14 ± 0,10	0,31 ± 0,40	6	1,00	0,45 ± 0,45	1,50 ± 2,35	5	0,13	0,82 ± 1,21	0,70 ± 0,41	9	0,16	>0,05

Mean ± standard deviation; n,number of patients.

Conclusion: Omega-3 fatty acids supplements were associated with a reduction in the ESR after 6 months in accordance to other studies. The trend towards a reduction in DAS-28 observed in this study encourages the need for further studies in larger samples.

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Working Status and Improvements in Work Productivity over Time in an Early Rheumatoid Arthritis (ERA) Cohort. Bindee Kuriya[1], Daming Lin[2], Cheryl Barnabe[3], Gilles Boire[4], Boulos Haraoui[5], Carol Hitchon[6], Shahin Jamal[7], J. Carter Thorne[8], Diane Tin[9], Janet E. Pope[10], Edward Keystone[11] and Vivian P. Bykerk[12]. [1]University of Toronto, Toronto, ON, [2]Mount Sinai Hospital, Toronto, ON, [3]University of Calgary, Calgary, AB, [4]CHUS - Sherbrooke University, Sherbrooke, QC, [5]Centre Hospitalier de l'Université de Montréal, Montréal, QC, [6]University of Manitoba, Winnipeg, MB, [7]Vancouver Coastal Health, Vancouver, BC, [8]Southlake Regional Health Centre, Newmarket, Newmarket, ON, [9]Southlake Regional Health Centre, Newmarket, ON, [10]Western University, London, ON, [11]University of Toronto and Mount Sinai Hospital, Toronto, ON, [12]Hospital for Special Surgery, New York, NY.

Background/Purpose: To describe working status in an ERA population in the first year of disease, and factors associated with improved work productivity.

Methods: Patients in the Canadian Early Arthritis Cohort who completed the Work Productivity and Activity Impairment (WPAI) questionnaire at baseline and month 12 (commencing in 2010) were included. Differences in working status at baseline were compared using chi-square or student's t-tests. A change in employment status and overall activity impairment was calculated as change from baseline to month 12. A change in absenteeism (work hours missed) and presenteeism (impact of RA on work productivity) was only calculated for those working at baseline. Multivariate logistic regression analyses tested whether age, sex, symptom duration, DAS28 score, HAQ-DI or treatment at month 6 were associated with improvements in WPAI domains.

Results: Of 2524 patients in the cohort, 729 had completed at least one WPAI questionnaire. Of these, 190 were eligible (423 did not have serial WPAI and 306 were missing month 6 variables for analysis). At baseline, the 190 patients had mean age 56 years, symptom duration 5.6 months, baseline DAS28 score 4.85; 110 were in paid employment at baseline. Individuals not in paid employment at baseline less frequently had high school or college education, had lower income, were older, had moderate-to-high DAS28

scores, and demonstrated higher HAQ-DI scores. Improvements in WPAI domains are shown (Table). Among working individuals, by 12 months, 78% had an improvement in working hours missed, 67% reported improved productivity and 72% had reduced activity impairments. The largest change occurred for absenteeism (9.57 fewer hours/week missed). Younger age (OR 0.93, CI 0.89–0.98), DAS28 remission (OR 10.52, CI 1.4–79) and higher HAQ-DI at month 6 (OR 4.01, CI 1.2–13.1) were associated with gaining employment by month 12. DMARD or biologic use at month 6 was not associated with change in WPAI domains but corticosteroid use was negatively associated with presenteeism (OR 0.23, CI 0.06–0.89).

Conclusion: Differences in demographic and disease-related variables exist between ERA patients who are working versus those who are not. The majority of working individuals show improvements in WPAI domains over time but establishing the minimum clinically important difference for these domains is needed to help guide clinical interpretability. The impact of disease activity and functional ability on work productivity warrants further exploration in larger samples.

Table. Mean (SD) in WPAI domain scores at baseline, month 12 and change from baseline to month 12

		Working hours missed due to RA in past 7 days? (0-100 hours)		In past 7 days, how much did RA affect productivity while working? (0-10 scale)		In past 7 days, how much did RA affect daily activities? (0-10 scale)	
		Improved	Not Improved	Improved	Not Improved	Improved	Not Improved
Working at baseline (N=110)	N (%)	76 (78)	21 (22)	55 (67)	27 (33)	80 (72)	30 (28)
	Baseline score	9.95 (8.51)	0.58 (4.61)	4.69 (2.43)	0.81 (1.49)	4.95 (2.38)	2.47 (2.91)
	Month 12 score	0.38 (1.75)	1.71 (7.17)	1.51 (1.83)	1.74 (2.40)	1.19 (1.42)	3.70 (3.10)
	Change in score	−9.57 (8.45)	1.13 (5.58)	−3.18 (1.87)	0.93 (1.44)	−3.76 (2.08)	1.23 (1.61)
Not working at baseline (N=80)		-	-	-	-	53 (66)	27 (34)
						5.66 (2.53)	2.44 (2.69)
						1.70 (1.96)	3.59 (3.33)
						−3.96 (2.43)	1.15 (1.94)

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Assessing Treatment Durability of Infliximab in the Management of Psoriatic Arthritis and Rheumatoid Arthritis Patients in a Canadian Setting. John Kelsall[1], Algis Jovaisas[2], Proton Rahman[3], Dalton Sholter[4], Michael Starr[5], William Bensen[6], Maqbool Sheriff[7], Wojciech Olszynski[8], Michel Zummer[9], Rafat Faraawi[10], Andrew Chow[11], Suneil Kapur[2], Emmanouil Rampakakis[12], John S. Sampalis[12], Francois Nantel[13], Susan Otawa[13], May Shawi[13] and Allen J Lehman[13]. [1]The Mary Pack Arthritis Centre, Vancouver, BC, [2]University of Ottawa, Ottawa, ON, [3]Memorial University of Newfoundland, St. John's, NF, [4]University of Alberta, Edmonton, AB, [5]McGill University Health Centre, Montreal, QC, [6]St Josephs Hospital and McMaster University, Hamilton, ON, [7]Nanaimo Regional General Hospital, Nanaimo, BC, [8]University of Saskatchewan, Saskatoon, SK, [9]Université de Montréal, Montreal, QC, [10]McMaster University, Hamilton, ON, [11]McMaster University, Hamilton and Credit Valley Hospital, Mississauga, ON, [12]JSS Medical Research, Montreal, QC, [13]Janssen Inc., Toronto, ON.

Background/Purpose: The efficacy of anti-TNF in the management of psoriatic arthritis (PsA) and rheumatoid arthritis (RA) has been demonstrated in numerous controlled clinical trials. The objective of this analysis was to assess in Canadian routine clinical practice the durability of treatment with infliximab (IFX) in PsA and RA and the determinants associated with sustainability of IFX.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with infliximab or golimumab as first biologics or after having been treated with a biologic for less than six months. Patients with PsA or RA treated with IFX who were enrolled between 2002 (2005 for PsA patients) and 2012 were included in this analysis. Dose optimization was defined as an increase in the frequency and/or dosing of IFX. Kaplan Meier (KM) estimates and Cox proportional models were used in the analysis.

Results: A total of 92 PsA and 830 RA patients were included in the analysis. Mean (SD) age of the PsA and RA patient cohorts was 48.7 (9.9) and 55.8 (13.4) years, respectively, and mean (SD) duration since diagnosis was 6.8 (9.1) and 10.2 (10.1) years, respectively. Twenty seven (29.3%) PsA patients and 407 (49.0%) RA patients had discontinued treatment. Overall KM-based mean (SE) duration of treatment was 41.4 (3.6) months and 61.3 (2.2) months for PsA and RA patients, respectively. Longer treatment duration was associated with significantly greater improvements in pain (parameter estimate PsA: -0.21, P=0.020; RA: -0.27, P<0.001), patient global (PsA: -0.35, P<0.001; RA: -0.28, P<0.001) and HAQ-DI (PsA: -0.01, P<0.001; RA: -0.01, P<0.001). Significant associations with duration of treatment in PsA patients were observed for disease duration (HR=1.04), previous biologic (HR=2.10), baseline TJC28 (HR=1.10), baseline PASI (HR=0.86) and concomitant use of traditional DMARD(s) (HR=0.16) or NSAID(s) (HR=0.38). For RA patients, IFX dose optimization (HR=0.72) and concomitant use of steroids (HR=1.78) were identified as significant predictors of treatment durability.

Conclusion: The results of this observational study have shown a high durability of treatment with IFX for patients with PsA or RA in a real-world setting. Concomitant medication use significantly impacts treatment durability. Furthermore, longer disease duration, higher TJC, less severe skin disease at initiation and previous biologic use in PsA, and absence of IFX dose optimization in RA, may be associated with reduced treatment durability.

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Regime of Use of Rituximab in Patients with Rheumatoid Arthritis in Daily Clinical Practice. Leticia Merino-Meléndez[1], Irene Llorente[1], Santos Castañeda[2], Teresa Velasco[1], Luis Sala-Icardo[3], Rosario Garcia-Vicuña[3], Alberto Garcia-Vadillo[1], Juan P. López-Bote[3], Jorge López-López[1], Federico Herrera[1], Cecilia Muñoz-Calleja[1], JM Álvaro-Gracia[1] and Isidoro González-Alvaro[3]. [1]Hospital Universitario de La Princesa, Madrid, Spain, [2]Hospital Universitario de La Princesa, IISP, Madrid, Spain, [3]Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain.

Background/Purpose: The recommended therapeutic regime for Rituximab (RTX) in Rheumatoid Arthritis (RA), according to prescribing information, includes two 1000-milligram infusions given two weeks apart, every 6 months. However, this is often not the case in clinical practice, since both consensus documents and information from clinical trials consider other alternatives. Our objective in this study was to analyze the pattern of use of RTX in RA in daily clinical practice.

Methods: This is a retrospective study that includes patients treated with RTX between 1998 and 2013 in a single university hospital. We reviewed medical records and collected demographic data, number of cycles, doses and intervals of RTX administered to the patients, response duration, as well as frequency and reasons of treatment discontinuation. Descriptive analysis was performed using the statistical package Stata v. 12.

Results: Ninety-three patients were studied, of which 83% were women. Median age at disease onset was 51 years with an interquartile range (IQR) of 39 to 60 years. Median age at the start of treatment with RTX was 60 [IQR: 51–70] years. Out of the 93 patients, 11 had negative rheumatoid factor. The number of cycles of RTX administered to each patient ranged from one to nine. Treatment was discontinued in 33% of the patients. The reasons for discontinuation were inefficacy (16%), adverse effects (7%) and others (10%). RTX was most commonly withdrawn during the first two cycles. The main data related to use of RTX in our study are summarized in the following table.

CYCLE OF RTX	1	2	3	4	5	6	7	8	9	TOTAL
Patients (N)	93	78	53	45	35	25	12	10	5	356
Fixed regime [1](%)	16	10	13	11	6	0	0	0	0	11.2
Dose (mg)/cycle[2]	1956	1736	1711	1704	1735	1708	1727	1444	1250	1663
Response duration (months)	10	10	10	11	11	10	12.5	9.5	8	10.2
Administration interval (months)	10	11.6	10.3	11.4	13	14.8	13.6	9.9	–	11.8
ADMINISTRATION YEAR	1998-2005	2006	2007	2008	2009	2010	2011	2012	2013	
Patients (N)	7	12	25	36	50	56	44	44	35	
Fixed regime[1](%)	36	33	13	16	17	6	4	0	0	
Dose (mg)/cycle[2]	2000	1944	1946	1953	1733	1716	1652	1818	1485	
Response duration (months)	15	10	11	10	9	10	10	12	7	
Administration interval (months)	16	11.2	12	10.4	9.4	10.3	11.5	13.1	–	
Cost Savings compared to fixed regime[3] (%)	60	42	47	41	42	48.5	50	54.5	–	

[1] Fixed regime: administration of two 1000-milligram infusions given 2 weeks apart, every 6 months.
[2] Mean value.
[3] Calculated percent saving in direct yearly drug cost compared to the fixed regime.
* All unspecified data are given in median value.

Response duration in males tended to be longer [12 months; IQR: 8–13] than in females [10 months; IQR: 7–12], but this didn't reach statistical significance (p = 0'11, Mann-Whitney's test). Longer response duration was observed in patients with a longer RA history (r = 0.24, P = 0.001, Pearson's test). RTX dose per cycle did not modify the response duration (1 vs 2 grams, 9.5 and 10 months respectively).

Conclusion: Our data show that, in daily clinical practice, RTX is more frequently used on demand, tending to abandon the fixed regime of 2 grams every six months. In addition we observe a tendency to an increased use of 1 gram cycles with time. This results in cost savings without apparent decrease in healthcare quality.

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Similar Response Rates to Anti-Tumor Necrosis Factor and Non-Anti-Tumor Necrosis Factor Biologic Therapies in Ethnic Minority Patients at 6 Months.

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Background/Purpose: Biologic therapies have expanded the treatment options and strategies for rheumatoid arthritis (RA). While anti-tumor necrosis factor (anti-TNF) biologic response rates are well established, in multi-ethnic populations, the response to anti-TNF and non- anti-TNF agents is unknown. Hence, we evaluated the response rates to RA biologic therapies in a diverse ethnic cohort.

Methods: Ethnic Minority RA Consortium (EMRAC) patients with follow up data were evaluated. Comparisons of patient socio-demographic (age, gender, race, education, smoking), RA disease status (disease duration, RF, ACPA, nodules/erosions), DMARD use, and disease activity (RAPID3) were made between anti-TNF and non-anti-TNF therapies using chi-square test of categorical variables and Wilcoxon-Mann-Whitney test for continuous variables. A logistic regression analysis associating RAPID3 outcome (low/moderate disease vs severe disease) at last follow-up encounter with anti-TNF and non-anti-TNF therapies adjusting for age, disease duration, gender, smoking, race and baseline RAPID3 was performed.

Results: EMRAC analysis of biologic responses in 350 subjects with an average followup of 8 months was performed (Table) More Caucasians received biologic therapies and anti-TNF use was most common. Anti-TNF patients were similar to non-anti-TNF patients in all demographic and clinical characteristics, including use of DMARD therapy. While, baseline RAPID3 was significantly higher in non-anti-TNF than anti-TNF patients, there was no significant difference in proportions of patients achieving RAPID3 outcome between biologic groups (P=0.969), adjusting for age, duration, gender, smoking, and baseline RAPID3. Moreover, no differences between races were observed in achieving RAPID3 outcome (P=0.688, regression).

Conclusion: There is a similar prevalence of use and response to anti-TNF and non-anti-TNF biologic agents in ethnic minority RA patients in routine clinical care. Follow up analyses are needed to assess sustained clinical response and outcomes to the varied biologic armamentaria, inclusive of ethnic subsets.

Patient Characteristics of Biologic Use in EMRAC Cohort

	Biologics		
	Anti-TNF	**Other**	**P**
N	276	74	
Age (years)	52.0 (14.6)	53.9 (14.7)	0.366
Education (years)	14.7 (3.5)	14.8 (3.5)	0.862
Duration (years)	9.7 (7.8)	10.6 (8.5)	0.475
Drug Treatment (months)	7.9 (6.0)	7.5 (5.5)	0.654
ACPA	161.9 (93.9)	174.9 (104.2)	0.564
RF	337.2 (373.7)	436.7 (555.5)	0.903
Baseline RAPID3	11.8 (7.4)	15.4 (6.5)	**<0.001**
Female (N %)	230 (83.6%)	63 (85.1%)	0.755
Hx Smoking (N %)	66 (31.7%)	15 (36.6)	0.544
Hx Erosion (N %)	41 (21.7%)	12 (35.5%)	0.086
Hx Nodules (N %)	15 (8.5%)	5 (17.9%)	0.123
DMARD Use (N %)	212 (76.8%)	56 (75.7%)	0.838
Race			0.119
Caucasian	111 (46.4%)	37 (53.6%)	
African-American	48 (20.1%)	12 (17.4%)	
Hispanic	51 (21.3%)	18 (26.1%)	
Other	29 (12.1%)	2 (2.9%)	
Final RAPID3			0.432*
Low/Moderate	58 (28.3%)	8 (13.6%)	
Severe	147 (71.7%)	51 (86.4%)	

* Logistic Regression adjusting for Age, Duration, Race, Smoking and Baseline RAPID3.

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Etanercept in Mono Therapy or in Combination with MTX: Results from a Sub Analysis of a German Non-Interventional Study.

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Background/Purpose: Although a combination with MTX is recommended for all biologics, data from different registries around the world show that in real life around 30% of all RA patients are treated in mono therapy. However, data on safety and efficacy of Etanercept (ETN) as mono therapy in dally practice are rare.

Methods: Adults with RA newly initiating ETN have been included into this non-interventional study.

Due to the non-interventional nature of the study, no specific requirements were specified with regard to the management of treatment. The physician could decide on dosing and the duration of treatment according to the treatment needs of each individual patient. At seven data collection points the course of the disease was documented for up to 52 weeks. Safety, efficacy as well as health outcome parameters have been assessed.

Results: 4871 patients have been included into this study. 1090 of these have continuously been treated with ETN and 1441 with ETN + MTX. There have been no statistically differences regarding all baseline characteristics. The mean disease duration was 10.6±10.3 years in the ETN and 9.7±8.9 years in the ETN + MTX group. They have been pretreated with 2.9±1.6 and 2.7±1.2 DMARDs respectively. From a mean baseline value of 5.5±1.3

and 5.3±1.3 score points, the DAS28 continually decreased to 3.4±1.4 and 3.2±1.3 at visit 7. At week 52 slightly less patients with ETN reached DAS28 remission (DAS28<2,6) as with ETN+MTX (32.5% [29.0–36.1%] vs. 35.4% [32.5–38.3%]). Concurrently with the DAS28 also the mean disease activity (patient global assessment, visual analogue scale VAS), pain (VAS) and fatigue (VAS) improved in both treatment groups. Duration of morning stiffness decreased in the ETN group from 78.7±88.1 to 26.2±50.6 min and in the ETN + MTX group from 72.6±81.1 to 21.8±50.6 min. 38.4 % [35.1 – 41.7%] of patients with ETN reached a functional remission (FFbH) at week 52 (vs. 44.3 % [41.5 – 47.2%] under ETN+MTX therapy). In both groups the treatment was well tolerated and no new safety signals have been observed.

Conclusion: Etanercept rapidly reduces diseases activity in combination with MTX as well as in mono therapy. Abaout half of the patients stay on their initial treatment regime (mono or combination with MTX) in daily practice over 52 weeks. Within this study no new safety signals occurred and Etanercept was well tolerated in mono and combination therapy.

Disclosure: K. H. Goettl, Pfizer Inc, Roche, Janssen -Cilag, MSD, 5, Pfizer Inc, Abbvie, 8; **M. Gaubitz**, Pfizer Inc; Abbvie, Chugai, MSD, Roche, BMS, 5, Pfizer Inc; Abbvie, Chugai, MSD, Roche, BMS, 8; **A. Krause**, Abbvie, Roche, 2, Pfizer Inc, Abbvie, Roche, BMS, MSD, 5, Pfizer Inc, Abbvie, Roche, BMS, MSD, UCB, 8; **U. Lendl**, Pfizer Inc, 3; **R. Lippe**, Pfizer Inc, 1, Pfizer Inc, 3; **T. Meng**, Pfizer Inc, 1, Pfizer Inc, 3; **P. A. Loeschmann**, Pfizer Inc, 1, Pfizer Inc, 3.

2415

Characteristics of Rheumatoid Arthritis Patients Not Receiving Early Initiation of Disease Modifying Therapy. Dimitrios A. Pappas[1], Jeffery D. Kent[2], Jeffrey D. Greenberg[3], Marc Mason[4], Joel M. Kremer[5], Amy Y. Grahn[2] and Robert J. Holt[6]. [1]Columbia University, New York, NY, [2]Horizon Pharma, Inc., Deerfield, IL, [3]New York University School of Medicine, New York, NY, [4]Corrona, LLC., Southborough, MA, [5]Albany Medical College and the Center for Rheumatology, Albany, NY, [6]University of Illinois - Chicago, Chicago, IL.

Background/Purpose: Early and aggressive therapy of Rheumatoid Arthritis (RA) with Disease Modifying Anti-Rheumatic Agents (DMARDs), glucocorticoids, and biologic agents is recommended by current treatment guidelines and supported by interventional studies with treat to target principles.(1) However, delays in initiation of therapy might be observed in real life. The objective of this analysis was to evaluate how frequently RA therapy is instituted promptly and to describe the characteristics of patients who are not treated early upon diagnosis.

Methods: The percentage of patients who at the time of enrollment in the Corrona Registry were not receiving any RA directed therapy was evaluated and their characteristics were summarized. The time to subsequent initiation of any RA directed therapy was also estimated.

Results: Out of the 35,485 patients enrolled in CORRONA, 20,317 (57.3%) had no prior use of prednisone, 18,299 (51.6%) had no prior biologic use, 16,930 (47.7%) had no prior DMARD use (excluding MTX), 15,335 (43.2%) had no prior MTX use. 2,166 (6.1%) had no prior nbDMARD use, and 750 (1.2%) had no history of receiving any RA directed therapy at the time of enrollment. For the patients without any history of RA directed therapy: age at the time of enrollment (mean ± SD) was 57.5±14.7 and age at RA onset was 52.3 ± 15.4 years. 69.4% were seropositive for RF and 60.6% for CCP antibodies. Patients had an overall established disease duration of 5.5 ± 9.0 years with only half (50.7%) having early disease (duration ≤1 year). CDAI was 18.3 ± 15.0; 34% of the patients had high and 27.6% moderate disease activity by CDAI. Subjects graded their fatigue as 35.6 ± 31.4 on a visual analog scale (0–100). Patients with no history of directed RA therapy did not have lower disease activity at enrollment compared with those receiving directed therapy. These patients were followed for a median (95% CI) time of 29.5 months (24.6–33.8). During the follow-up period, only 372 out of 750 (49.6%) patients initiated any RA directed therapy. The median time to initiation of any DMARD was 15.9 months (12.2–18.4) and to initiation of any RA directed therapy was 12.1 months (9.3–14.8). The Kaplan Meier survival estimates of RA therapies are shown in Figure 1.

Conclusion: In this registry analysis, a high percentage of patients with RA did not have a history of receiving directed therapy within a mean of approximately 5 years of RA onset. In those patients that had not received any RA directed therapy previously, approximately 50% did not initiate any therapy in 12 months of registry follow-up.

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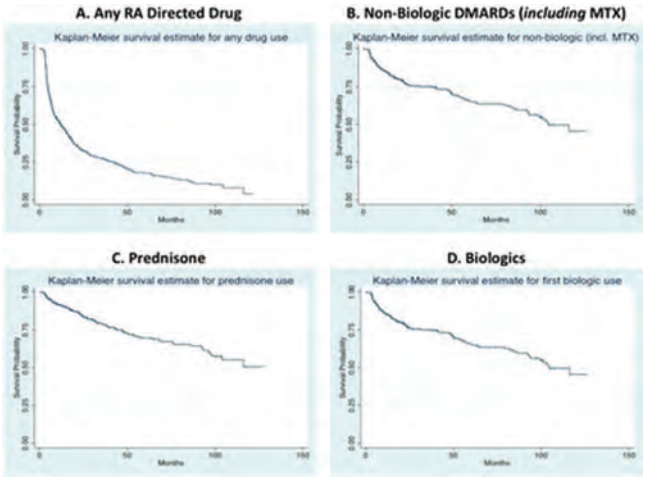

Figure 1. Kaplan Meier survival estimate to initiation of any RA Directed Drug (N=750)(Panel A), Non-Biologic DMARDs (including MTX) (Panel B), Prednisone (Panel C), and first Biologic (Panel D)

Disclosure: D. A. Pappas, Corrona, LLC, 3, Novartis Pharmaceutical Corporation, 9; **J. D. Kent**, Horizon Pharma, Inc., 1, Horizon Pharma, Inc., 3; **J. D. Greenberg**, Corrona, LLC., 1, Corrona, LLC., 3, AstraZeneca, Celgene, Novartis and Pfizer, 5; **M. Mason**, Corrona, LLC., 3, NIH, 6; **J. M. Kremer**, Corrona, LLC., 1, Corrona, LLC., 3, Abbvie, Amgen, BMS, Lilly, Pfizer, UCB, Antares, Medac; research support from same companies except BMS and Medac, 5; **A. Y. Grahn**, Horizon Pharma, Inc, 1, Horizon Pharma, Inc., 3; **R. J. Holt**, Horizon Pharma, Inc., 5.

2416

Do Patterns of Joint Swelling or Tenderness in Rheumatoid Arthritis Patients Impact Disease Activity Outcomes and Pain? Implications for Clinical Practice. Regan Arendse[1], John Kelsall[2], J. Antonio Avina-Zubieta[3], Philip Baer[4], Erica Weinberg[4], Jude Rodrigues[5], Algis Jovaisas[6], Isabelle Fortin[7], Maqbool Sheriff[8], Majed M. Khraishi[9], Emmanouil Rampakakis[10], John S. Sampalis[10], Francois Nantel[11], Susan Otawa[11] and Allen J Lehman[11]. [1]University of Saskatchewan, Saskatoon, SK, [2]The Mary Pack Arthritis Centre, Vancouver, BC, [3]Arthritis Research Centre of Canada, Richmond, BC, [4]Private Practice, Scarborough, ON, [5]Clinical Research and Arthritis Centre, Windsor, ON, [6]University of Ottawa, Ottawa, ON, [7]Centre de Rhumatologie de l'Est du Québec, Rimouski, QC, [8]Nanaimo Regional General Hospital, Nanaimo, BC, [9]Memorial University of Newfoundland, St Johns, NF, [10]JSS Medical Research, Montreal, QC, [11]Janssen Inc., Toronto, ON.

Background/Purpose: This analysis aimed to describe the pattern of specific joint involvement (tender and/or swollen) pre- and post-TNFi treatment and the impact of specific joint pattern involvement on composite score outcomes and pain.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with infliximab (IFX) or golimumab (GLM). In this analysis, RA patients included those treated with IFX between 2002–2014 or with GLM between 2010–2014. Based on joint involvement 7 groups were created: shoulder(s), elbow(s), metacarpophalangeal (MCP(s)), wrist(s), proximal interphalangeal (PIP(s)), knee(s), and thumb(s). The impact of specific joints on disease activity indices and pain was assessed with the independent-samples t-test; linear regression produced adjusted estimates.

Results: A total of 1030 RA patients were included with 5177 assessments. At baseline, MCP(s) (84.8%) and wrist(s) (66.1%) were the most commonly swollen joints. Tenderness was most frequent at baseline in these two joint types (81.1% and 70.9% of patients, respectively). Swelling/tenderness rates in all joint groups were significantly lower (Table 1) among patients enrolled in 2010–2013 vs. those enrolled in 2002–2005; no significant differences, however, were observed in joint involvement pattern.

Swelling and tenderness in all joint groups were associated with significantly (P<0.001) higher pain. Upon adjusting for age, gender and the total number of swollen (SJC28) or tender (TJC28) joints, swollen shoulder(s) and knee(s), and tender shoulder(s) and elbow(s) had the biggest impact on pain. Swollen MCP(s), knee(s) and thumb(s) had the greatest impact on DAS28, while for CDAI and SDAI swollen thumb(s) and swollen thumb(s) and

knee(s), respectively, showed the highest association. Tender wrist(s), shoulder(s), and knee(s) showed the highest association with DAS28, while tender MCP(s) had the greatest impact on CDAI and SDAI. However, all indices were significantly higher among cases with swollen thumb(s) (unstandardized coefficient (B): B_{DAS28}=0.25, P=0.006; B_{CDAI}=2.09, P=0.001; B_{SDAI}=2.66, P=0.001).

Conclusion: Although joint swelling/tenderness documented at anti-TNF initiation has decreased over time, the profile of affected joints has remained stable. Swelling/tenderness in specific joint groups was differentially associated with pain, with larger joints having the greatest impact. Furthermore, differences were observed in levels of disease activity based on the type of affected joint which could be attributed to their impact on patient global assessment. These results suggest that location of joint involvement, in addition to the number of affected joints, has an independent impact on pain.

Table 1: Pattern of Swelling or Tenderness by Enrolment Period

Swelling/Tenderness by Joint Type	Enrolment Period 2002-2005 (N=412)	2010-2014 (N=278)	P-value
Swollen Joint Count, mean (SD)	13.1 (7.1)	7.4 (6.1)	P<0.001
Swollen Shoulder(s)	22.1%	12.2%	*<0.001*
Swollen Elbow(s)	35.7%	18.0%	*<0.001*
Swollen MCP(s)	90.5%	78.8%	*<0.001*
Swollen Wrist(s)	76.7%	51.1%	*<0.001*
Swollen PIP(s)	75.0%	48.9%	*<0.001*
Swollen Knee(s)	48.5%	25.9%	*<0.001*
Swollen Thumb(s)	42.0%	12.6%	*<0.001*
Tender joint Count, mean (SD)	15.2 (8.0)	8.4 (7.3)	*<0.001*
Tender Shoulder(s)	65.0%	40.6%	*<0.001*
Tender Elbow(s)	49.0%	24.1%	*<0.001*
Tender MCP(s)	87.6%	69.1%	*<0.001*
Tender Wrist(s)	80.8%	55.4%	*<0.001*
Tender PIP(s)	76.7%	48.6%	*<0.001*
Tender Knee(s)	61.2%	38.5%	*<0.001*
Tender Thumb(s)	46.8%	17.6%	*<0.001*

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Is Remission Really Achievable in EARLY Rheumatoid Arthritis? Olga Addimanda[1], Pierluigi Macchioni[2], Andrea Caruso[1], Niccolò Possemato[1], Mariagrazia Catanoso[1] and Carlo Salvarani[2]. [1]Arcispedale Santa Maria Nuova, I.R.C.C.S., Reggio Emilia, Italy, [2]Arcispedale S Maria Nuova, Reggio Emilia, Italy.

Background/Purpose: To stress the need of routine use of US imaging in treat to target strategies aiming to achieve remission in early rheumatoid arthritis.

Methods: 54 patients with early rheumatoid arthritis (ERA) or undifferentiated arthritis (UA) diagnosed according to 2010 ACR/EULAR criteria were enrolled. Demographic (age, gender, disease duration,BMI), clinical (total SJC and TJC, DAS28, CDAI, SDAI, HAQ, EULAR response), serological (ESR, CRP, RF, anti-CCP) data has been collected. Ultrasonographic hand (MCP, PIP and DIP joints), wrists (intercarpic and radiocarpic joints) and feet (MTP, PIP, DIP as well as ankle joints) evaluation was performed according to OMERACT recommendations. The patients were evaluated at baseline, after three and six months:all 54 patients have complete 3rd month follow-up data, only 38 have already completed 6th month follow-up.

Results: 11 UA (20,4%) and 43 RA (79,6%) were enrolled from November 2012 to January 2014.Mean disease duration was 15,5 ± 7,8 weeks (min – max 4 – 24). 26 (48,1%) were RF positive (Mean ± sd values 121.7 ± 90.5) and 25 (46,3%) were CCP positive (Mean ± sd values 361,0 ± 448,2). Only 8 (14,8%) showed radiographic erosions at baseline. We observed a progressive reduction in all clinical and clinimetric features not associated with statistically significant improvement in US findings (Table). When analyzing for predictive factors of good response only increased values of ESR and CRP at baseline were found to be associated with better clinical response altough not always reaching statistically significant value (ESR t0-t3 p = 0,024; ESR t0-t6 p = 0,766; CRP t0-t3 p = 0,822; CRP t0-t6 p = 0,071). Baseline number of joints with US synovitis or power-Doppler (PD) signal were not different between responder and not responder at 3 and 6 months. The number of joints with US synovitis or US presence of PD were not statistical different between moderate or good responder at 6 months.

Conclusion: Clinical remission could not be considered enough to avoid erosive progression in rheumatoid arthritis and US remission is needed in order to avoid structural damage.

Table. Clinical and US features

	Baseline (A)	T-3 (B)	T-6 (C)	P value (A vs B)	P value (B vs C)
CLINICAL FEATURES					
DAS28	5,2 ± 1,3	2,3 ± 0,8	1,3 ± 1,0	**<0,0005**	**<0,0005**
REMISSION n° of pts (%)	3/54 (5,6)	22/54 (40,7)	11/38 (28.9)	**<0,0005**	**<0,0005**
LDA n° of pts (%)	1 (1,9)	6 (11,1)	9/38 (23.7)	**<0,0005**	**<0,0005**
MDA n° of pts (%)	26 (48,1)	18 (33,3)	14/38 (36.8)	**<0,0005**	**<0,0005**
HDA n° of pts (%)	24 (44,4)	5 (9,3)	4/38 (10.5)	**<0,0005**	**<0,0005**
EULAR RESPONSE					
GOOD n° (%)	/	24/54 (44.4)	20/38 (52.6)		
MODERATE n° (%)	/	24/54 (44.4)	17/38 (44.7)		
NO RESPONSE n° (%)	/	3/54 (5.6)	1/38 (2.6)		
US FEATURES					
SYNOVITIS n° of pts (%)	46/54 (85.2)	38/54 (70.4)	33/35 (94.3)	n.s. (0.743)	n.s. (0.803)
POWER-DOPPLER n° of pts (%)	40/54 (74.1)	30/54 (55.6)	27/35 (77.1)	n.s. (0.097)	n.s. (0.324)
EROSIONS n° of pts (%)	**15/54 (27.8)**	**17/54 (31.5)**	**14/35 (40.0)**	**<0.0005**	**<0.0005**

Disclosure: O. Addimanda, None; **P. Macchioni**, None; **A. Caruso**, None; **N. Possemato**, None; **M. Catanoso**, None; **C. Salvarani**, None.

2418

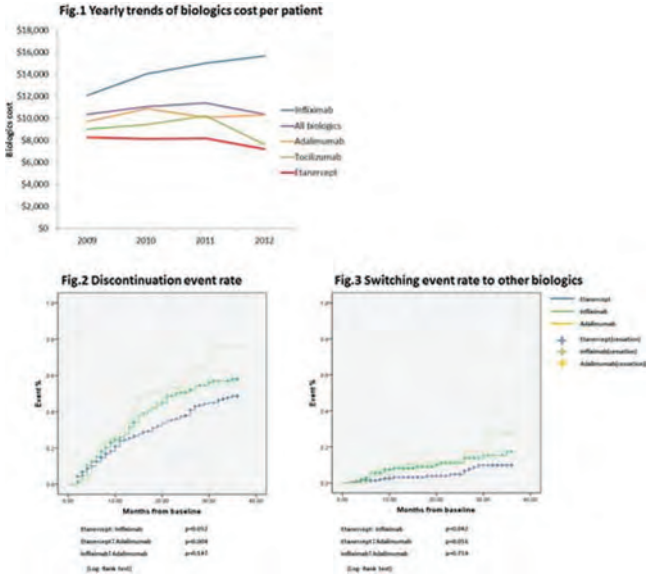
Treatment Pattern and Direct Cost of Biologics for Rheumatoid Arthritis Patients: A Real-World Analysis of Nationwide Japanese Claims Data. Naonobu Sugiyama M.D., Ph.D.[1], Tatsunori Murata, M.S.[2], Yosuke Morishima[1], Yuri Fukuma[1], Yoshiyuki Shibasaki[1] and Lisa Marshall[3]. [1]Pfizer Japan Inc. RA & Inflammation Area Medical Affairs Department, Tokyo, Japan, [2]Health Economics Research Group, CRECON Research and Consulting Inc., Tokyo, Japan, [3]Pfizer Inc. Inflammation Immunology Disease Group, Collegeville, PA.

Background/Purpose: Biologics such as etanercept (ETN), adalimumab (ADA), infliximab (IFX) and tocilizumab (TCZ) have led dramatic improvement in the treatment of rheumatoid arthritis (RA), but the impact of their high drug costs on medical expenditure remains a concern. The aim of this study is to characterize the treatment patterns of patients with RA treated with biologics and evaluate the direct biologics cost and medical cost using Japanese claims data provided by Japan Medical Data Center Co., Ltd.

Methods: Patients with RA (defined by ICD10 code) treated with ETN, IFX, ADA, and TCZ between Jan, 2005 and Mar, 2013 were included. Annual costs of the biologics per patient, based on average daily dose and NHI drug price, were calculated from 2009 to 2012 for ETN, IFX, ADA, and TCZ. Patients were grouped based upon their initial prescription for either ETN, IFX, ADA, or TCZ. One year biologics cost including all biologics (including second or more, e.g. golimumab) and total medical cost following initial prescription were compared between ETN and the other treatment groups. Discontinuation and switching event rates to other biologics in each group were estimated using Kaplan-Meier survival analysis. Dose changes, based on +/−50% change in average dose per administration, at 3 month intervals were also evaluated up to 4 years following initial prescription.

Results: A total of 524 patients were identified for longitudinal analysis, with 45% (n=238) initiating ETN, 41% (n=217) initiating TFX, and 13% (n=69) initiating. The cross-sectional annual biologics cost was $8,000 in 2009 and $7,200 in 2012 in patients with ETN, $10,000 both in 2009 and in 2012 in patients with ADA, $12,000 in 2009 and $16,000 in 2012 in patients with IFX, $9,000 in 2009 and $8,000 in 2012 in patients with TCZ (Fig.1). The one year total medical costs from the initial prescription in ETN, IFX and ADA groups were approximately $19,000, $26,000 and $23,000, respectively (ETN: IFX p<0.001, ETN: ADA p<0.001). A similar trend was also observed in the biologics cost. The discontinuation event rates at 36 months was 48.6%, 58.0% and 75.8% in ETN, IFX and ADA group, respectively (ETN: IFX p=0.052, ETN: ADA p=0.004) (Fig.2). The switching event rate to other biologics at 36 months was 9.9%, 17.4% and 27.7% in ETN, IFX and ADA group, respectively (ETN: IFX p=0.042, ETN: ADA p=0.052) (Fig.3). The longitudinal dose changing trend in IFX was different from ETN and ADA group.

Conclusion: The biologic and total medical costs, along with discontinuation and switching event rates were lowest in ETN group. Although there are limitations such as channeling bias, these findings might imply the clinical cost reductive benefits in ETN first line treated group.



Disclosure: N. Sugiyama M.D., Ph.D, Pfizer Inc, 3; **T. Murata, M.S.**, Pfizer Inc, 5; **Y. Morishima**, Pfizer Inc, 3; **Y. Fukuma**, Pfizer Inc, 3; **Y. Shibasaki**, Pfizer Inc, 3; **L. Marshall**, Pfizer Inc, 3.

2419

Efficacy of Biologic Medications in Active Rheumatoid Arthritis: A Systematic Review. Lynden Roberts[1], Kathleen Tymms[2], Julien de Jager[3], Geoffrey Littlejohn[4], Hedley Griffiths[5], David Nicholls[6], Paul Bird[7], Jennifer Young[8] and Jane Zochling[9]. [1]JCU Clinical School, Townsville, QLD, Australia, [2]Canberra Rheumatology, Canberra, ACT, Australia, [3]Olser House, Southport, QLD, Australia, [4]Monash Medical Centre and Monash University, Clayton, VIC, Australia, [5]Barwon Rheumatology Service, Geelong, VIC, Australia, [6]Coast Joint Care, Maroochydore, QLD, Australia, [7]Combined Rheumatology Practice, Sydney, NSW, Australia, [8]Roche Products Pty Limited, Sydney, NSW, Australia, [9]Menzies Research Institute Tasmania, Hobart, TAS, Australia.

Background/Purpose: In the last decade, biologic medications have transformed the management of RA. The effectiveness of these medications has been reported in numerous randomized controlled trials and cohort studies. A summary of the effect size for biologic medications would be useful to inform expectations of rheumatologists and patients when considering and commencing these medications. Further, with an increased interest in real-life effectiveness data from clinical registries, comparisons between controlled trial and registry effectiveness outcomes would be of interest.

Methods: Using PRISMA methodology, a pre-specified search and review strategy was devised to answer the question "what are the EULAR response rates for biologic medications in adults with active RA?" MEDLINE and EMBASE were searched for Rheumatoid Arthritis (Both Mesh term and free text) in Title/Abstract AND Name of biologic drug (free text) in Title/Abstract OR Biologic Therapy (Mesh term) OR 'Biologic' (free text) in Title/Abstract AND EULAR response (free text) in Entire Document AND Adult (free text) Entire Document. All articles were reviewed independently by 2 experts; duplicates and non-primary research articles were removed along with those using medication doses outside of the approved Australian indications, and only patients with ≥ moderate DAS or tender/swollen joint count ≥ 4 were included. Whether the patients were naïve to biologic DMARD and whether the response assessment was at 3 (2.0 – 4.5) months or 6 (4.5 – 7.0) months was recorded. The percentage of patients achieving a moderate, good, or either EULAR response was calculated overall and for subgroups.

Results: Overall, 27,280 patients were included representing 62 studies. Mean baseline DAS28 was 6.0 (SD=0.6). Good (G) and moderate (M) EULAR responses were achieved in 25.8% and 47.3% respectively, with 28.1% failing to achieve a Good or Moderate EULAR response when all patients were pooled. Response rates were similar for patients who were naïve to biologics (G-24.0% & M-47.5%), those who had failed to respond to at least 1 biologic (G-28.1% & M-47.1%) and at both 3 months (G-27.1% & M-50.4%) and 6 months (G-25.2% & M- 46.3). Sufficient data was present for separate analyses of adalimumab (ADA), etanercept (ETN) and tocilizumab (TCZ) and EULAR response rates were similar, however tocilizumab had a higher rate of good EULAR response [37.4% (TCZ), 28.2% (ADA), 27.6% (ETN)].

Conclusion: A systematic review of studies reporting EULAR response rates for biologic medications in active RA showed that only 28.1% of patients fail to achieve at least a moderate EULAR response. Response rates were similar for patients who were naïve or had previous exposure to biologics, for 3 and 6 months assessment time points, and for different biologic medications. Comparison of these controlled trial data with real life response rates reported in clinical registries will be of interest.

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2420

Quality Assessment of Controlled Trials Evaluating Chinese Herbal Medicine in Patients with Rheumatoid Arthritis: a Systematic Review. Xin Pan, Maria A. Lopez-Olivo, Pratibha Nayak and Maria E. Suarez-Almazor. The University of Texas, MD Anderson Cancer Center, Houston, TX.

Background/Purpose: Chinese herbal medicine (CHM) is a mainstay in the treatment of rheumatoid arthritis (RA) in China. We conducted a systematic review to appraise the methodological quality of controlled clinical trials evaluating the efficacy and safety of CHM in patients with RA.

Methods: We searched electronic databases (Medline, EMBASE, The Cochrane Library, and Web of Science) from inception until May 2014 for controlled trials (randomized or not) evaluating the use of CHM including herbals and decoctions (i.e., "tang"), in patients with RA. The search was not limited by language, year of publication or type of publication. Study selection was performed by 2 independent reviewers. Data extraction and the methodological quality of the trials was assessed using the Cochrane risk of bias tool for randomized trials and Newcastle Ottawa Scale for controlled non-randomized studies. Descriptive statistics were used to report on risk of selection, performance, detection, attrition, reporting biases and others (i.e., conflict of interests) for randomized trials and selection, comparability and outcome biases for cohort studies.

Results: Out of 2,125 unique citations only 54 studies were included (51 randomized trials and 3 non-randomized studies) including 7,792 patients. Only one study was conducted in the US, the remaining in China. There were 3,446 patients receiving CHM. In the control groups 2,283 patients received a disease modifying anti-rheumatic drug (DMARD) (i.e., methotrexate, leflunomide, sulfasalazine, and etanercept), 182 non-steroidal anti-inflammatory drugs (NSAIDs), and 164 inert placebo. Additionally, 1,717 received combined CHM + either DMARD or NSAIDs. In 23 studies patients were described as having active disease, 13 included patients with more than 1 year disease duration, 1 included patients with RA and anemia, and 17 included patients with one or two traditional Chinese medicine (TCM) 'pathological factors' (i.e., *feng*, *shi*, and/or *han*). Discontinuations were not reported in 31 studies, but ranged from 0 to 55% in the remaining studies. For the randomized studies, when evaluating selection bias 54% of the studies were judged to have an adequate random sequence generation, but 77% had inadequate allocation concealment. 79% had a high risk of performance bias (not blinding participants and/or personnel) and detection bias was unclear in 56% of the studies; 62% of the studies reported how missing data was handled, therefore attrition bias was judged to be low. In 87% no disclosure of interest or source of founding was reported. For non-randomized studies, all the studies were representative of RA patients, had an adequate ascertainment of intervention with comparable groups, but only one demonstrated that the outcome of interest was not present at start of study or provided the rate of lost to follow-up.

Conclusion: Studies evaluating CHM often fail to meet expected methodological criteria, and high quality evidence is lacking. Future studies of CHM should be methodologically robust and adhere to reporting guidelines such as the CONSORT statement for TCM.

Disclosure: X. Pan, None; **M. A. Lopez-Olivo**, None; **P. Nayak**, None; **M. E. Suarez-Almazor**, None.

2421

Patient Treatment Goals in Rheumatoid Arthritis: Results of Focus Groups Among Rheumatologists, English and Spanish-Speaking Patients. Jennifer Barton[1], Christopher J. Koenig[2], Diana Martinez[3], Gina Evans-Young[2], Patricia P. Katz[1] and Edward H. Yelin[1]. [1]University of

California, San Francisco, San Francisco, CA, [2]UCSF, San Francisco, CA, [3]UCSF/San Francisco General Hospital, San Francisco, CA.

Background/Purpose: Treatment guidelines in rheumatoid arthritis (RA) frame provider's therapeutic goal as disease remission. Although goal concordance between providers and patients has been shown to positively impact outcomes in other chronic diseases, like diabetes, patient-provider goal sharing has not been well-studied in RA. We performed a literature review and conducted focus groups to identify goals important to RA patients.

Methods: A systematic review using PubMed from 1966 to 2013 included terms for RA and patient goals. The results were used to inform domains discussed in focus groups. We conducted 2 patient focus groups (1 in English, 1 in Spanish), and one with rheumatologists. A professional qualitative researcher conducted the English-language patient and physician groups and trained a bilingual moderator who conducted the Spanish group. We used a two-phase structured process where participants first reflected on personal functional and treatment goals as a way to discuss a wide range of goals. The physician group used a similar process, and included a presentation of goals from patient focus groups. We used Grounded Theory to organize goals thematically and combined patient results with goals identified in the literature review.

Results: 865 papers were identified and after review, 28 articles remained; from these, 110 goals were abstracted. Patient goals from focus groups and literature review fell into one of six categories: symptoms, function/quality of life, treatment, research/policy, social support, and system-level goals. Goals identified by both Spanish and English-speaking patients (Table 1) included symptom goals (less pain), function (ability to open jars), and social support (help family understand severity of disease and what to expect), and treatment (more affordable medications). Areas of difference included goals of improved mood (Spanish), more time with providers (Spanish), more coordination among multiple providers (English), sex and intimacy without shame (English). Providers' goals included remission, cheap and simple medications, and holistic treatments. Physicians expressed surprise with many of the patient-generated goals, including desire for complementary and alternative medication, and felt overwhelmed and ill-supported to manage mood-related issues.

Conclusion: The elicitation of patient goals and goal setting in RA is an important, understudied area especially among vulnerable populations. More research to study the role of eliciting goals, goal concordance, and its impact on outcomes in diverse populations is needed. Interventions to improve goal concordance may improve self-efficacy, adherence, and outcomes in RA.

Table. Patient-reported goals organized by themes from focus groups in English (n=7, all female) and Spanish (n=4, 3 females, 1 male)

Themes and individual goals	Both groups	English only	Spanish only
Symptom goals			
Less pain	X		
Less mobility limitations	X		
Improved mood			X
Function/quality of life goals			
Ability to open cans and jars (easily)	X		
Ability to work consistently/meet expectations	X		
Have flare interfere less with activities	X		
Being able to exercise safely	X		
Transportation/take public transit vs. paratransit/be able to drive		X	
Sex and intimacy without shame and/or fear		X	
Be able to do housework without "paying the price"			X
Social support goals			
Help family understand the severity of the disease and what to expect	X		
Social support: Access to support groups/ counseling/social workers		X	
Would like doctor to ask about emotional well-being, not just physical			X
System-level goals			
To find a cure	X		
Want more doctor communication around drug treatments and condition	X		
More coordination of care between provider types		X	
Be understood by their doctor(s)			X
Would like to be able to drink safely (and have more doctor input on subject)			X
Research/policy goals			
More access to drugs/more affordable drugs	X		
Develop a more sensitive/functional Visual Analog Scale for pain		X	
Longer visits to allow for full discussion of RA			X
Treatment goals			
More information around nutrition	X		
Less surgeries		X	

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2422

A Tailored Approach to Reduce Dose of TNF Inhibitors Is Equally Effective, but Substantially Less Costly Than Standard Dosing in Patients with Rheumatoid Arthritis over One and Two Years: A Prospective Cohort Study. Jakub Zavada[1], Michal Uher[2], Katarina Sisol[3], Sarka Forejtova[3], Katerina Jarosova[3], Liliana Sedova[3], Zuzana Urbanova[3], Olga Sleglova[3], Jiri Vencovsky[4] and Karel Pavelka[5]. [1]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Prague, Czech Republic, [2]Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic, [3]Institute of Rheumatology, Prague, Czech Republic, [4]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [5]Charles University, Prague, Czech Republic, Prague, Czech Republic.

Background/Purpose: To compare effectiveness and costs of standard versus individually tailored reduced doses of TNF inhibitors (TNFi) in patients with Rheumatoid Arthritis (RA) after achieving low disease activity.

Methods: This was a single center prospective observational study performed within the national biologics registry. The TNFi dose tapering strategy was chosen by treating physicians, without pre-specified protocol. Patients with RA treated for at least 6 months by TNFi who reached low disease activity (LDA) were eligible for this analysis. LDA was defined as DAS28≤3.2. Firstly, we selected one "baseline" visit for each patient in the standard dosing group, which would be most comparable to baseline visits in the reduced dosing group (=start of dose reduction) using 3 parameters (duration of TNFi treatment, DAS28 and HAQ) to find the best match. Secondly, a propensity score (PS) was used to control for all other confounders associated with starting TNFi dose reduction. The co-primary outcomes were change (D) in HAQ and loss of LDA (defined as DAS28 $>$ 3.2 & DDAS28 $\geq$ 0.6). Secondary outcomes were DAS28 area under the curve (AUC), HAQ AUC, and annual cost of anti-TNF therapy. The outcomes after one and two years of treatment (since baseline visit) by standard vs reduced doses of TNFi were assessed by generalized linear regression after adjustment on PS.

Results: In the reduced dosing group the mean dose of TNFi corresponded to 0.64, 0.66 and 0.69 of the standard dose initially, at 12 and 24 months resp. After PS adjustment, baseline demographic and clinical characteristics between the groups were well balanced (table 1). 48 (32) and 136 (76) patients in the reduced vs standard dosing group after 1 year (2 years) resp. were available for analysis. Both co-primary outcomes were similar between both groups after one and two years since baseline (table 2 and 3). Annual cost of TNFis per patient was lower by ~4,000 € in the reduced dosing group.

Conclusion: In RA patients after reaching LDA, a tailored approach to reduce doses of TNFi produced similar clinical outcomes at 1 and 2 years resp., but was substantially less costly.

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Table 1 Baseline characteristics

		Standard dosing group n=136	Reduced dosing group n=48	Crude p-value	Adjusted p-value[1)]
Female	*n (%)*	115 (84.6 %)	34 (70.8 %)	**0.040**	0.156
Age (years)	*Mean (SD)*	52.9 (11.1)	51.4 (11.8)	0.416	0.924
Weight (kg)	*Mean (SD)*	71.7 (13.5)	73.5 (15.7)	0.446	0.922
Smoking	*n (%)*	47 (41.2 %)	17 (38.6 %)	0.766	0.966
Working or employable	*n (%)*	70 (51.5 %)	24 (50.0 %)	0.861	0.898
Disease duration prior to start of anti-TNF therapy (years)	*Mean (SD)*	13.4 (8.5)	11.7 (6.2)	0.537	0.899
Duration of anti-TNF therapy (months)	*Mean (SD)*	33.1 (22.0)	46.4 (30.6)	**0.006**	0.594

Number of previous sDMARD	*Mean (SD)*	3.1 (1.3)	2.9 (1.4)	0.337	0.800
RF +	*n (%)*	112 (84.8 %)	40 (85.1 %)	0.966	0.895
Anti-CCP+	*n (%)*	82 (76.6 %)	28 (84.8 %)	0.319	0.548
Steinbrocker stage I	*n (%)*	18 (13.3 %)	8 (17.0 %)	0.535	0.775
DAS28	*Mean (SD)*	2.19 (0.59)	1.93 (0.58)	**0.009**	0.533
DAS28 <2.6	*n (%)*	97 (71.3 %)	41 (85.4 %)	0.057	0.592
Number of swollen joints/28	*Mean (SD)*	0.9 (1.28)	0.3 (0.57)	**0.001**	0.436
Number of tender joints/28	*Mean (SD)*	0.9 (1.2)	0.9 (1.4)	0.568	0.189
CRP (mg/l)	*Mean (SD)*	4.1 (7.0)	2.4 (2.8)	0.050	0.068
ESR (mm/h)	*Mean (SD)*	18.0 (13.2)	13.2 (9.1)	0.096	0.187
Patients global assessment	*Mean (SD)*	17.2 (13.4)	15.8 (13.0)	0.259	0.298
HAQ	*Mean (SD)*	0.77 (0.62)	0.64 (0.65)	0.214	0.799
HAQ ≤ 0.5	*n (%)*	61 (44.9 %)	26 (54.2 %)	0.268	0.775
EuroQol	*Mean (SD)*	0.73 (0.15)	0.74 (0.21)	0.876	0.793
Concomitant glucocorticoids	*n (%)*	81 (59.6 %)	13 (27.1 %)	**<0.001**	0.056
Anti-TNF monotherapy	*n (%)*	33 (24.3 %)	13 (27.1 %)	0.698	0.974
Concomitant methotrexate	*n (%)*	84 (61.8 %)	32 (66.7 %)	0.546	0.642
Concomitant leflunomide	*n (%)*	15 (11.0 %)	1 (2.1 %)	0.092	0,147
Concomitant sulfasalazine	*n (%)*	9 (6.6 %)	2 (4.2 %)	0.542	0.267
Etanercept	*n (%)*	60 (44.1 %)	22 (45.8 %)	0.837	0.142
Adalimumab	*n (%)*	43 (31.6 %)	20 (41.7 %)	0.209	0.440
Infliximab	*n (%)*	33 (24.3 %)	6 (12.5 %)	0.092	0.097
First anti-TNF	*n (%)*	114 (83.8 %)	45 (93.8 %)	0.097	0.592

1) p-values are adjusted to propensity score (PS) using multivariate generalized linear regression.

Table 2 Primary and secondary outcomes after 1 year of standard vs reduced dosing of TNFis

		Standard dosing group n=136	Reduced dosing group n=48	Adjusted p-value[1)]
HAQ at baseline	*Mean (SD)*	0.77 (0.62)	0.64 (0.65)	0.799
HAQ at 12 months	*Mean (SD)*	0.88 (0.65)	0.72 (0.70)	0.388
Change in HAQ after 12 months	*Mean (SD)*	0.11 (0.38)	0.08 (0.30)	
Adjusted difference of changein HAQ after 12 months	*Difference (95% CI)*	*reference*	−0.082 (−0.220; 0.057)	0.248
Loss of LDA during 12 months *(DAS28 > 3.2 & DDAS28 ≥ 0.6)*	*n (%)*	61 (44.9 %)	22 (45.8 %)	
Adjusted OR of LDA loss during 12 months	*OR (95% CI)*	*reference*	1.164 (0.374; 3.621)	0.793
DAS28 AUC during 12 months	*Mean (SD)*	2.72 (0.83)	2.27 (0.71)	
Adjusted difference of DAS28 AUC	*Difference (95% CI)*	*reference*	−0.341 (−0.648; −0.034)	**0.030**
HAQ AUC during 12 M	*Mean (SD)*	0.84 (0.61)	0.66 (0.65)	
Adjusted difference of HAQ AUC	*Difference (95% CI)*	*reference*	−0.106 (−0.345; 0.133)	0.383
EuroQol AUC during 12 M	*Mean (SD)*	0.70 (0.17)	0.72 (0.19)	
Adjusted difference of EuroQol AUC	*Difference (95% CI)*	*reference*	0.031 (−0.037; 0.098)	0.369
Annual cost of anti-TNF therapy (€)	*Mean (SD)*	12 000 (−)	8 080 (1 785)	
Adjusted difference of annual cost (€)	*Difference (95% CI)*	*reference*	−3 963 (−4 311; −3 615)	**<0.001**

1) p-values are adjusted to propensity score (PS) using multivariate generalized linear regression.

Table 3 Primary and secondary outcomes after 2 years of standard vs reduced dosing of TNFis

		Standard dosing group n=76	Reduced dosing group n=32	Adjusted p-value[1)]
HAQ at baseline	*Mean (SD)*	0.83 (0.62)	0.63 (0.68)	0.888
HAQ at 24 months	*Mean (SD)*	1.01 (0.72)	0.72 (0.75)	0.583
Change in HAQ after 24 months	*Mean (SD)*	0.18 (0.45)	0.09 (0.29)	
Adjusted difference of change in HAQ after 24 months	*Difference (95% CI)*	*reference*	−0.130 (−0.346; 0.086)	0.237
Loss of LDA during 24 months *(DAS28 > 3.2 & DDAS28 ≥ 0.6)*	*n (%)*	52 (68.4 %)	16 (50.0 %)	
Adjusted OR of LDA loss during 24 months	*OR (95% CI)*	*reference*	0.615 (0.169; 2.236)	0.461
DAS28 AUC during 24 months	*Mean (SD)*	3.06 (0.81)	2.19 (0.70)	
Adjusted difference of DAS28 AUC	*Difference (95% CI)*	*reference*	−0.566 (−0.969; −0.163)	**0.006**
HAQ AUC during 24 months	*Mean (SD)*	0.95 (0.62)	0.68 (0.71)	
Adjusted difference of HAQ AUC	*Difference (95% CI)*	*reference*	−0.070 (−0.409; 0.269)	0.684
EuroQol AUC during 24 months	*Mean (SD)*	0.65 (0.20)	0.71 (0.21)	
Adjusted difference of EuroQol AUC	*Difference (95% CI)*	*reference*	0.039 (−0.069; 0.147)	0.481
Annual cost of anti-TNF therapy (€)	*Mean (SD)*	12 000 (−)	8 221 (1 958)	
Adjusted difference of annual cost (€)	*Difference (95% CI)*	*reference*	−3 550 (−4 106; −2 995)	**<0.001**

1) p-values are adjusted to propensity score (PS) using multivariate generalized linear regression.

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2423

Prevalence of Subclinical Synovitis Detected By Ultrasound in Rheumatoid Arthritis and Psoriatic Arthritis Patients Receiving Anti-TNF-α Therapy with Extended Interval of Administration. José M. Senabre-Gallego[1], José Rosas-Gómez de Salazar[1], Esteban Salas-Heredia[1], Gregorio Santos-Soler[1], Francisca Llinares-Tello[1], Carlos Santos-Ramirez[2], Mabel Sánchez-Barrioluengo[3], Xavier Barber-Vallés[4], Rafaela Ortega[2], Ana Pons[1], Catalina Cano[1] and Maria Luisa Lorente-Betoret[1]. [1]Hospital Marina Baixa, Villajoyosa, Spain, [2]Hospital Marina Salud, Denia, Spain, [3]Universitat Politècnica de València, Valencia, Spain, [4]University Miguel Hernández, Elche, Spain.

Background/Purpose: To estimate the prevalence of subclinical synovitis detected by ultrasound in rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients in clinical remission receiving anti-TNFα therapy with extended interval of administration (EIA).

Methods: Prospective observational study. Population: Patients diagnosed with RA and PsA, being in clinical remission and receiving anti-TNFα therapy with EIA. 12-joint ultrasound assessment (elbows, wrists, 2nd and 3rd metacarpo-phalangeal, knees and ankles) (Naredo E. Arthritis Rheum 2008,59:515-22) was performed (MyLab 25 Esaote s.p.a, Firenze, Italy), evaluating synovitis through B-mode (BM) and Color Doppler signal (CD), both by semiquantitative scale from 0 to 3 points. Subsequently, a BM and CD score was calculated, summing the highest score obtained from any one of the synovial sites evaluated at each joint to a maximum of 36 points. The sonographer was blinded to the clinical and laboratory data.

Results: 26 patients were included in the study, 76.9% were women, mean age was 59 years [31–79] and mean duration of disease was 14 years [3–46]. The diagnosis was RA in 24 patients (92%) and APs in 2 (7%). In 83% of RA patients rheumatoid factor was positive, and in 79% the citrullinated protein antibody was positive. Ultrasound assessment prior to EIA was available in 17 patients. Clinical activity and ultrasound scores are summarized in Table 1. Ultrasound detects some synovitis by CD in 50% of EIA patients, and by BM in 96% of EIA patients. Nevertheless most of them had a low CD score (average 1.42 out of 36 points). No statistically significant differences were found when comparing prior and after EIA clinical and ultrasound scores (data not shown). The mean time from the beginning of EIA was 15 months (range 1 to 48 months). The EIA treatments were etanercept (ETN) in 14 patients and adalimumab (ADA) in 12 patients, with the following patterns: ETN/10 days (11 pat.), ETN/14 days (3 pat.), ADA/18 days (1 pat.), ADA/21 days (10 pat.), ADA/30 days (1 pat.). 10 patients (not included in the study) never began EIA due to clinical decision, and 7 (27%) had to return to the standard administration pattern due to worsening of disease activity.

Table 1 Clinical and ultrasound scores

	Prior to EIA ultrasound	After EIA ultrasound
n	17	26
DAS28-VSG, mean [range]	1.55 [0.63–2.64]	1.74 [0.51–4.06]
DAS28-PCR, mean [range]	1.69 [1.13–2.89]	1.75 [1.13–3.38]
SDAI, mean [range]	3.58 [2.10–10.10]	4.05 [2.10–16.1]
CDAI, mean [range]	3.35 [2–10]	3.92 [2–16]
Color Doppler score >0, n (%)	12 (70.6%)	13 (50.0%)
Color Doppler score, mean [range]	1.06 [0–3]	1.42 [0–5]
B-mode SH score >0, n (%)	14 (82.4%)	25 (96.2%)
B-mode SH score, mean [range]	4.18 [0–19]	4.46 [0–17]

EIA: Extended interval of administration of anti-TNFα; DAS28: Disease Activity Score in 28 joints; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; SH: synovial hypertrophy.

Conclusion: Some synovitis was detected by Color Doppler ultrasound in 50% of patients in clinical remission receiving anti-TNFα therapy with extended interval of administration. Most of them had a low Color Doppler ultrasound score. Synovial hypertrophy was detected by B-mode ultrasound in 96% of them. No statistically significant differences were found when comparing prior and after EIA clinical and ultrasound scores.

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2424

Comparison of Medication Use in Rheumatoid Arthritis Patients Between University and Private Settings – Results from Ontario Best Practice Research Initiative. Thomas McKeown[1], Binu Jacob[1], Xiuying Li[1], Sandra Couto[1], William Bensen[2], Vandana Ahluwalia[3], Arthur Karasik[4] and Claire Bombardier[5]. [1]University Health Network, Toronto General Research Institute, Toronto, ON, [2]St Josephs Hospital and McMaster University, Hamilton, ON, [3]William Osler Health Center, Brampton, ON, [4]Courtesy Staff Appointment St. Joseph's Health Centre, Toronto, ON, [5]University of Toronto, Toronto, ON.

Background/Purpose: The objective of this study was to compare the characteristics and patterns of medication use among rheumatoid arthritis (RA) patients in university and community settings.

Methods: Descriptive analyses were performed using data collected from the Ontario Best Practice Research Initiative (OBRI), a clinical registry of RA patients followed in routine care. Patients were categorized as university if their rheumatologist worked in a teaching hospital, mentored medical students and/or had their Research Ethics Board (REB) located at a hospital. The patients of a community rheumatologist worked at a community center and/or had their REB at a location other than a hospital. A group of mixed Physicians (n=12), who were affiliated with an academic site, but practiced at a community site were excluded from the analysis. Patient baseline demographics, clinical characteristics, socioeconomic features and treatment regimens were compared between university and community patients using chi-square and t-tests.

Results: Among 1583 RA patients, 512 (32%) were from university and 1071 (67%) from community sites. Compared to community patients, university patients were younger (55.5 ± 12.9 vs. 57.9 ± 13.3 yrs, p=0.004), had longer RA disease duration (11.3 ± 10.9 vs. 6.9 ± 8.5yrs, p<0.0001), and were highly educated with higher household incomes. Prevalence of depression was higher among community patients (26%) compared to university (21%), p=0.04. The disease activity measures and functional status at baseline were similar between the two groups. The use of Biologics was more in university patients (31% vs. 17%, P<.0001) with fewer use of DMARDS (61% vs. 73%, P<.0001).

Conclusion: RA patients in community settings appeared to be older with longer disease duration, had lower socio-economic status and a lower utilization of biologics. The results does not represent the clinician practice patterns as the referral criteria might have biased the patients enrolled in the study. Further analysis is required to evaluate whether the care gap due to differential utilization of biologics have an impact on disease severity in subsequent years.

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2425

Rheumatoid Arthritis Stable Follow up Visits – 3 Month Versus 6 Month Intervals. Mark C. Fisher and Deborah S. Collier. Massachusetts General Hospital, Boston, MA.

Background/Purpose: Specialist visits are a contributing factor to the rising cost of healthcare and payment models increasingly encourage decreased outpatient specialty visits.

Due to monitoring of methotrexate, sulfasalazine, or leflunamide, many rheumatologists see patients with stable Rheumatoid Arthritis (RA) every 3 months for routine follow up. We hypothesized that decrease in utilization and cost of outpatient specialty services can be achieved without compromising patient care or safety by seeing these patients every 6 months, with a lab check every 3 months.

Methods: Patients with RA on either methotrexate or sulfasalazine in stable remission or low disease activity were offered visits every 6 months instead of every 3 months, with labwork done at 3 months. This was part of a Quality Improvement initiative to decrease healthcare costs.

Outcomes included number of eligible patients for two full time providers over a 6 month period, percent of total established RA patients for these providers deemed appropriate for inclusion, percent of patients who had their labs done, percent of patients with new cytopenia or liver function test (LFT) abnormality, percent of patients who had problems requiring a follow up visit during the 6 month interval, and estimated cost savings.

Results: Over 6 months, 21 eligible patients were identified. Clinical features are noted in Table 1. Overall, 14/21 patients were seropositive, either for RF or CCP antibodies, and 12 were positive for both. 10 patients were on combination therapy with a biologic. The 21 RA patients were out of 184 established RA patients seen for followup visits by two full time providers (11.4%) during the study period (Table 2). 14 of 21 patients (66.7%) had their labs drawn at 3 months. There were no new cytopenias or LFT abnormalities. No patients required additional follow up for RA. One patient required a follow up visit during the 6 month interval for new diagnosis of Giant Cell Arteritis. Each saved visit equaled an estimated cost savings of between $92 and $356, depending on the insuror, with an average of $161 saved per visit and $362 per patient annually.

Conclusion: Patients with RA in stable remission or low disease activity can safely and cost effectively be seen at 6 month intervals with labs drawn at 3 months. There were no new RA issues between visits, and no new laboratory abnormalities. Patient compliance was good, but could be improved. This intervention saved an average of $362 per patient annually.

Table 1: Clinical Characteristics

Age	56.8
Gender (female)	82.3%
Ethnicity	
White	15
Hispanic	6
RF+	13
CCP +	10
Erosive disease	10
Disease duration (years)	8.8
On MTX	24
On SSZ	5
On Leflunamide	1
On Plaquenil	2
On prednisone	1
On biologic (in combination)	10
Etanercept	5
Adalimumab	3
Golimumab	1
Abatacept	1

Table 2: Outcomes

Total Established RA Patient Visits	184
Eligible RA patients	21 (11.4%)
Labs done	14/21 (66.7%)
New Cytopenias	0
New LFT abnormalities	0
Interval Visits	1

Disclosure: M. C. Fisher, None; **D. S. Collier**, None.

2426

Comparison of Patient Self-Reported and Physician Reported Rheumatoid Arthritis Medication Use - Results from the Ontario Best Practices Research Initiative. Binu Jacob[1], Xiuying Li[1], Angela Cesta[2], Bindee Kuriya[3], Edward Keystone[4] and Claire Bombardier[3]. [1]University Health Network, Toronto General Research Institute, Toronto, ON, [2]University Health Network, Toronto, ON, [3]University of Toronto, Toronto, ON, [4]Mount Sinai Hospital, University of Toronto, Toronto, ON.

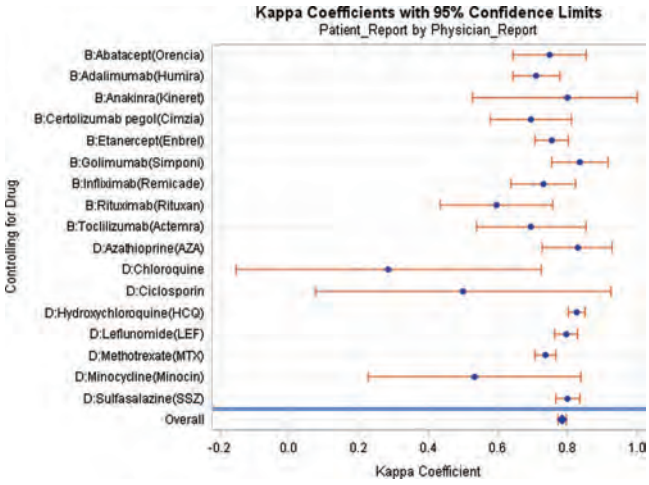
Background/Purpose: Patient self-reported medication histories may be prone to misclassification and recall bias. We aimed to assess the agreement between patient (Pt) and physician (MD) reported medication use in a cohort of RA patients.

Methods: Patients enrolled in the Ontario Best Practices Research Initiative (OBRI), a clinical registry of RA patients followed in routine care, were included. Following patient consent, data were extracted from physician charts using a structured questionnaire on patient demographics, comorbidities, disease activity and use of RA medications. Patients are assessed every 3 months through telephone interviews according to a standardized protocol to collect additional socio-economic characteristics, disease activities measures, and medication use. We examined the concordance of reporting

medication names and the level of agreement between Pt and MD reported RA medications. RA medications (only DMARDs and BIOLOGICS) were categorized as (yes/no) for both self-reported and physician reported data and kappa statistics with 95% confidence intervals were computed at baseline and 12 month period to assess chance-corrected agreement between the two sources of data. Percent agreement was also calculated as a measure of agreement. In addition, dose reported for various drugs were compared at baseline and one year. Wilcoxon signed rank test was used to compare the mean difference of doses reported.

Results: Of the 2347 patients included in the study, 77% of patients were female with a mean (SD) age of 57.4 (12.9) years, and the majority (85%) were Caucasian. Patients had moderate disease activity according to both mean (SD) DAS28 scores 4.5 (1.5) and CDAI scores 21(14). At baseline, substantial agreement was found between Pt and MD reported medication use (kappa =0.78, 95% confidence interval (CI), 0.77–0.79); agreement=97.4%), and use of specific BIOLOGIC and DMARDS with agreement ranged from 88 to 100% (Figure, kappa range 0.50–0.85). The degree of agreement was lowest for methotrexate (kappa=88%). The MD reported mean dose was significantly higher than Pt except for MTX. At one year, the overall agreement of reported medication name increased with kappa=0.84 (95% CI 0.83–0.85) and there was no significant difference in reported dose between Pt and MD.

Conclusion: Similar level of agreement between patients and physicians suggest that differential misclassification is unlikely in the reporting of RA medication use. Furthermore, the accurate reporting of doses at one year suggests that patient's ability to report their medications improves over time.



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2427

Attainment of Low Disease Activity Is Predictive of Maintenance of Disease Control upon Adalimumab Discontinuation for Two Years Following Combination Therapy in Japanese Patients with Early Rheumatoid Arthritis. Yoshiya Tanaka[1], Hisashi Yamanaka[2], Naoki Ishiguro[3], Nobuyuki Miyasaka[4], Katsuyoshi Kawana[5], Katsutoshi Hiramatsu[5], Aki Kuroki[5] and Tsutomu Takeuchi[6]. [1]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [3]Nagoya University Graduate School of Medicine, Nagoya, Japan, [4]Tokyo Medical and Dental University, Tokyo, Japan, [5]Abbvie, Tokyo, Japan, [6]Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Although available data has suggested successful withdrawal of a monoclonal antibody TNF blocker after achieving low disease activity (LDA) or remission over the short-term for a large proportion of patients with early rheumatoid arthritis (RA), longer term follow-up data are needed to predict maintenance of biologic-free disease control. The purpose of this study was to identify the factors associated with maintenance of disease control for 2 years of adalimumab (ADA) discontinuation after treatment with ADA plus methotrexate (MTX) in patients with early RA.

Methods: In the HOPEFUL-1 study, patients with early RA were randomized to receive ADA 40 mg every other week (EOW) plus weekly MTX 6–8 mg, or only MTX 6–8 mg every week for 26 weeks. Thereafter, all patients received open-label ADA 40 mg EOW plus weekly MTX for 26 weeks. At week 52, patients could enroll in HOPEFUL-2, an observational follow-up study, where they received ADA plus MTX (ADA-continued group) or MTX alone (ADA-withdrawn group) for 52 weeks based on investigator and/or patient decision. At week 104, patients could enroll in HOPEFUL-3, a 104-week follow-up extension. Data at week 156 were used in this interim analysis. Using multivariate analysis, factors associated with remaining in ADA-withdrawn group as well as sustaining LDA in the ADA-withdrawn group at week 156, were analyzed. The 28-joint disease activity score based on erythrocyte sedimentation rate (DAS28-ESR), Health Assessment Questionnaire Disability Index (HAQ-DI), and modified total Sharp score (mTSS) were also examined.

Results: Among the 220 HOPEFUL-2 patients, 172 were enrolled in the HOPEFUL-3 study, 79 from ADA-continued and 93 from ADA-withdrawn. Patient characteristics at the baseline of HOPEFUL-2 were similar in the ADA-continued and -withdrawn groups, except for SJC, which was significantly higher in the former group. At week 156, 73 patients out of 93 (78%) remained in the ADA-withdrawn group, with the remainder of patients either discontinuing from the study or continuing/restarting treatment with ADA. At week 156, there were no differences in clinical, functional, and structural outcomes between the patients in ADA-withdrawn group and the remainder of patients. (table). The predictive factors for remaining in the ADA-withdrawn group at week 156 were level of CRP at week 0, as well as SJC, CRP, and titer of rheumatoid factor at week 52 (cut-offs =week 0 CRP, 2.04; week 52 CRP, 0.21; week 52 SJC, 0). Moreover, DAS28-ESR 2.6 at week 52 distinguished 44 patients, those who were able to sustain LDA without using ADA at week 156.

Conclusion: The attainment of low disease activity based on serological markers at the onset and at the time of ADA withdrawal was the key determinant for maintenance of biologic-free disease control for up to 2 years in early RA patients.

Table 1.

	ADA-withdrawn (n = 73)	Others (n = 99)	P
DAS28-ESR[a]	2.83 ± 0.97	2.91 ± 1.43	p=0.473[b]
HAQ-DI[a]	0.26 ± 0.45	0.25 ± 0.41	p=0.605[b]
Percentage of patients with ΔmTSS ≤ 0.5	67.1%	71.2%	p=0.717[c]
Percentage of patient in LDA	62.0%	71.3%	p=0.245[c]
Percentage of patient in remission	42.3%	52.6%	p=0.212[c]
HAQ-remission	83.8%	84.6%	p=1.000[c]

[a]Data are indicated in mean ± SD.
[b]Wilcoxon two-sample test.
[c]Fisher's exact test.

Disclosure: Y. Tanaka, BMS, MSD, Chugai, Mitsubishi-Tanabe, Astellas, Abbvie and Daiichi-Sankyo, 2, UCB, Mitsubishi-Tanabe, Abbott, Abbvie, Eisai, Chugai, Janssen, Pfizer, Takeda, Astellas, Daiichi-Sankyo, GSK, AstraZeneca, Eli Lilly, Quintiles, MSD and Asahi Kasei, 5, UCB, Mitsubishi-Tanabe, Abbott, Abbvie, Eisai, Chugai, Janssen, Pfizer, Takeda, Astellas, Daiichi-Sankyo, GSK, AstraZeneca, Eli Lilly, Quintiles, MSD and Asahi Kasei, 8; **H. Yamanaka**, Abbott, AbbVie, Asahikasei, Astellas, AstraZeneca, Bristol-Myers Squib, Chugai, Daiichi Sankyo, Eisai, GlaxoSmithKline, Janssen, Mitsubishi Tanabe, MSD, Nippon Kayaku, Pfizer, Santen, Taishotoyama, Takeda, Teijin, 2, Abbott, AbbVie, Astellas, AstraZeneca, Bristol-Myers Squib, Chugai, Daiichi Sankyo, Eisai, Mitsubishi Tanabe, Nippon Kayaku, Pfizer, Takeda, Teijin Speakers bureau: Abbott, AbbVie, Astellas, Bristol-Myers Squib, Chugai, Eisai, Mitsubishi Tanabe, Pfizer, T, 5; **N. Ishiguro**, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 5, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 8; **N. Miyasaka**, Abbvie GK, Astellas Pharma, Banyu Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Daiichi Sankyo, Eisai Co., Ltd., Janssen Pharmaceuticals, Inc., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Company, and Teijin Pharma Limited, 2; **K. Kawana**, Abbvie, 3; **K. Hiramatsu**, Abbvie, 3; **A. Kuroki**, Abbvie, 3; **T. Takeuchi**, Abbott Japan Co., Ltd., Astellas Pharma, Bristol–Myers K.K., Chugai Pharmaceutical Co, Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Sanofi–Aventis K.K., Santen Pharmaceutica, 2, Abbott Japan Co., Ltd., Bristol–Myers K.K., Chugai Pharmaceutical Co,. Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., Astellas Pharma, Diaichi Sankyo Co.,Ltd., 8, Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., Asahi Kasei Medical K.K., Abbivie GK, Daiichi Sankyo Co.,Ltd., 5.

2428

Comparative Study of Rheumatoid Arthritis Disease Activity Indices in Two Populations of Meteor Database. Helena Canhão[1], Fernando Magalhaes Martins[2], Jose Antonio Melo Gomes[3], Maria Jose Santos[4], Augusto Faustino[5], José Antonio Costa[6], Cornelia Allaart[7], E. Gvozdenovic[8], Pedro

Machado[9], Jaime C. Branco[10], João E. Fonseca[11] and José Pereira Da-Silva[12]. [1]Hospital Santa Maria, Lisboa, Portugal, [2]Portuguese Society of Rheumatology, Lisbon, Portugal, [3]Instituto Português de Reumatologia, Lisbon, Portugal, [4]Hospital Garcia de Orta, Almada, Portugal, [5]Clínica de Reumatologia de Lisboa, Lisbon, Portugal, [6]Centro Hospitalar do Alto Minho, Hospital de Ponte de Lima, Ponte de Lima, Portugal, [7]Leiden Univ Med Ctr, Leiden, Netherlands, [8]Leiden University Medical Center, Leiden, Netherlands, [9]University College London, London, United Kingdom, [10]Centro Hospitalar de Lisboa Ocidental, Hospital Egas Moniz, Lisboa, Portugal, [11]Lisbon Academic Medical Center, Lisbon, Portugal, [12]Hospitais da Universidade de Coimbra, Coimbra, Portugal.

Background/Purpose: Our aims were to assess disease activity states using DAS28ESR, CDAI and SDAI and to compare their outcomes in two rheumatoid arthritis (RA) populations of METEOR database.

Methods: A total of 24605 visits from 5870 Dutch patients and 20120 visits from 3185 Portuguese patients were analyzed. We also selected and replicated the same analyses in a subset of one random visit per patient. K-statistics and z-tests were applied to assess agreement and differences between groups. The relative contribution of each RA core set measure was determined for the three indices.

Results: We found significant differences in the distribution of RA disease activity states between Dutch and Portuguese populations when DAS28ESR was used. SDAI and CDAI attenuated those differences. The percentage of Dutch and Portuguese visits classified as "in remission" was very similar with CDAI, SDAI and ACR/EULAR remission criteria. Contrary, using DAS28ESR, a significant higher proportion of Dutch visits was classified in remission. ESR was lower in Dutch visits and this component was determinant for lowering DAS28 scores in this group of patients.

Conclusion: CDAI and SDAI assigned distinct RA activity states when compared to DAS28 in our two populations from METEOR database.

Table – Comparing means of the components of the disease activity indices within each disease activity state between Dutch and Portuguese populations

	Remission		Low		Moderate		High	
	z	p-value	Z	p-value	z	p-value	z	p-value
A. DAS28 original								
PGA	6.73	<0.0001	4.49	<0.0001	8.39	<0.0001	5.82	<0.0001
TJC28	6.24	<0.0001	6.84	<0.0001	−2.61	0.0090	−13.61	<0.0001
SJC28	3.65	0.0003	**1.94**	**0.0520**	**−0.88**	**0.3791**	−5.32	<0.0001
ESR	−14.33	<0.0001	−9.59	<0.0001	−13.41	<0.0001	−3.57	0.0004
DAS28	−7.34	<0.0001	**−0.49**	**0.6245**	−7.94	<0.0001	−10.44	<0.0001
B. CDAI								
PGA	1.99	0.0465	−3.71	0.0002	4.64	<0.0001	4.40	<0.0001
MDGA	10.63	<0.0001	11.84	<0.0001	10.4	<0.0001	7.75	<0.0001
TJC28	**1.37**	**0.1713**	−3.38	0.0007	−7.95	<0.0001	−11.06	<0.0001
SJC28	−4.59	<0.0001	−4.26	<0.0001	−6.11	<0.0001	−5.99	<0.0001
CDAI	5.87	<0.0001	**−0.85**	**0.3949**	−2.85	0.0044	−8.76	<0.0001
C. SDAI								
PGA	−3.56	0.0004	**−1.77**	**0.0763**	4.52	<0.0001	**1.67**	**0.0955**
MDGA	3.66	0.0003	9.13	<0.0001	13.58	<0.0001	6.79	<0.0001
TJC28	**1.90**	**0.0575**	**0.06**	**0.9515**	**−0.31**	**0.7548**	−2.37	0.0179
SJC28	**−1.91**	**0.0555**	−3.39	0.0007	−5.78	<0.0001	−3.52	0.0004
CRP	**−1.54**	**0.1232**	−2.4	0.0162	−7.27	<0.0001	**−1.62**	**0.1050**
SDAI	**−0.86**	**0.3912**	**1.31**	**0.19**	**1.22**	**0.2233**	−2.94	0.0033

Visits = Number of visits (%); PGA = Patient assessment of disease activity (100mm) TJC28 = 28 tender joint count.
SJC28 = 28 swollen joint count; MDGA = Physician assessment of disease activity (100mm) CRP = C-reactive protein (mg/l).
ESR = Erythrocyte sedimentation rate (mm/h); DAS28 = Disease activity score evaluating 28 joints.
CDAI = Clinical disease activity index; SDAI = Simplified disease activity index.
z = z-test for equality of two independent means (z>0 if the mean for Dutch group is higher than for Portuguese group).

Disclosure: H. Canhão, None; **F. Magalhaes Martins**, None; **J. A. Melo Gomes**, None; **M. J. Santos**, None; **A. Faustino**, None; **J. A. Costa**, None; **C. Allaart**, None; **E. Gvozdenovic**, None; **P. Machado**, None; **J. C. Branco**, None; **J. E. Fonseca**, None; **J. Pereira Da-Silva**, None.

2429

Seasonal Changes May Influence Activity of Rheumatoid Arthritis. Ryuji Nagamine. Sugioka Memorial Hospital, Fukuoka, Japan.

Background/Purpose: RA activity during the year was assessed to investigate whether seasonal changes influenced parameters of RA activity.

Methods: This study was performed in Fukuoka, a Japanese city with four distinct seasons. From September 1, 2009 to August 31, 2011, parameters of RA activity were assessed in a total of 3811 visits by 348 patients (mean age, 62.1 years; mean duration of RA, 10.8 years), including 2174 visits by 140 patients treated with biologics (mean age, 63.0 years; mean duration of RA, 11.9 years). The following parameters were assessed: C-reactive protein (CRP); erythrocyte sedimentation ratio (ESR); matrix metalloproteinase (MMP)-3; rheumatoid factor; DAS28-CRP and DAS28-ESR. All parameters in each month in the first and second years were assessed and results were compared among months. Monthly mean temperature and mean atmospheric pressure in Fukuoka in the 2 years of the study are shown in Figure 1.

Results: For all cases, mean CRP level was 0.65 mg/dl from October to December, and 0.53 mg/dl from July to September. In cases treated using biologics, mean CRP level was 0.67 mg/dl from October to December and 0.50 mg/dl from January to March. These differences were significant ($p<0.05$). CRP level from April to June (mean, 0.70 mg/dl) was also significantly higher than that from January to March ($p<0.01$). CRP was significantly higher in autumn and spring than in summer and winter, even in patients treated with biologics. Seasonal changes thus clearly influenced CRP levels. No significant differences in other parameters were found, although MMP-3 levels were also higher from October to December and from April to May compared to other months (Fig. 2).

Conclusion: The results clearly show that seasonal changes significantly influence CRP levels. In the city, the temperature rapidly fell and atmospheric pressure rose in autumn to early winter, and the reverse occurred in spring. RA activity may correlate with changes in temperature and atmospheric pressure.

Fig. 1 Monthly average temperature and atmospheric pressure

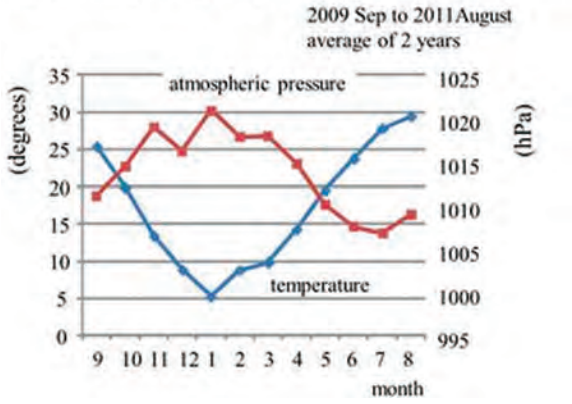
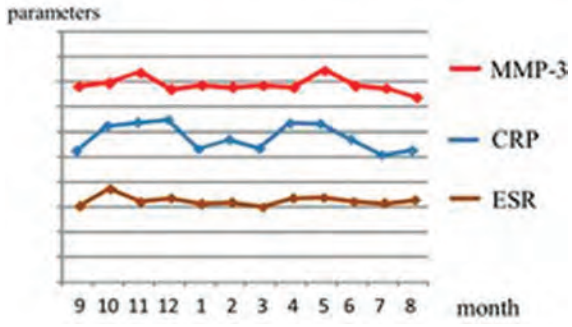


Fig. 2 Monthly average three parameters



Disclosure: R. Nagamine, None.

ACR/ARHP Poster Session C
Clinical Practice/Patent Care (ARHP)
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

2430

Serological and Clinical Characteristics of a Large Collection of Incomplete Lupus Erythematosus Patients. Teresa Aberle[1], Virginia C. Roberts[1], Julie M. Robertson[1], Joel M. Guthridge[1], Kathy L. Sivils[1], Astrid Rasmussen[1], David R. Karp[2] and Judith James[1], [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]UT Southwestern Medical Center, Dallas, TX.

Background/Purpose: Incomplete lupus (ILE) is defined as a condition in which patients present with signs of systemic autoimmunity and clinical manifestations compatible with systemic lupus erythematosus (SLE) but do not fulfill the American College of Rheumatology (ACR) classification

criteria. Some of these individuals may transition to classified SLE or another systemic autoimmune rheumatic disease; however, many will remain ILE patients without major organ involvement. Differentiating between these groups is clinically challenging and better clinical, demographic and molecular biomarkers which define ILE patients would be clinically helpful and would also allow better identification of high-risk individuals for prevention trials or for closer monitoring.

Methods: For this analysis, we examined participants enrolled to the Lupus Family Registry and Repository (LFRR). Medical records were reviewed to assess for ACR SLE classification criteria and medications; individuals who met only 3 ACR classification criteria were designated as ILE for this study (n=443). Additionally, each participant completed connective tissue screening questionnaires (CSQ), detailed clinical questionnaires, demographic and therapeutic information. Autoantibody testing for ANA with titer/pattern, anti-dsDNA by IIF, anti-cardiolipin (aCL), and autoantibodies against Ro, La, Sm, nRNP and ribosomal P by precipitin, ELISA or by multiplexed assay were also measured.

Results: In this cohort, individuals with ILE (n=443) were most commonly European-American or African-American females on average 46.0 ± 13.9 years of age with an average CSQ score of 6.03 ± 2.39. Among the 443 individuals meeting 3 ACR classification criteria, 311 (70%) never took an immunomodulating drug (methotrexate, azathioprine, hydroxychloroquine/chloroquine, corticosteroids) and 375 (85%) never took a major immunosuppressant (cyclophosphamide, mycophenolate mofetil, cyclosporine, biologic). The most prevalent ACR classification criteria that ILE individuals presented with were ANA (97.2%), immunologic criteria (62.3%), arthritis (44.2%), photosensitivity (24.6%), and hematologic criteria (25.3%). aCL (46.5%), anti-dsDNA antibodies (27.3%), leukopenia (14.6%), and lymphopenia (12.4%) were the most prevalent ACR sub-criteria present. When 13 autoantibodies were examined using a high-throughput multiplex assay, anti-chromatin (34.5%), anti-Ro (27.7%), anti-RNP (24.3%), anti-Sm/RNP (20.9%), anti-dsDNA (14.9%), and anti-Sm antibodies (11.5%) were the most prevalent autoantibodies.

Conclusion: Large numbers of individuals with ILE can be identified and their clinical presentation is characterized by immunologic and hematologic findings, as well as arthritis and cutaneous disease. Multiple lupus-associated autoantibodies are enriched in these patients. Longitudinal studies are warranted to better understand the individuals at the highest risk of transition to systemic autoimmune rheumatic disease, as well as to understand the biologic processes which help prevent individuals from progressing to major organ involvement.

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2431

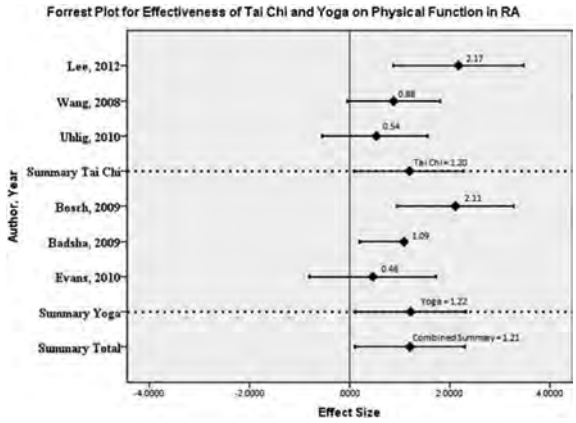
Tai Chi and Yoga Are Effective for Improving Physical Function in Adults with Rheumatoid Arthritis- a Meta-Analysis. Heather Greysen and Kathy Lee. School of Nursing, University of California San Francisco, San Francisco, CA.

Background/Purpose: Recent research suggests that mind-body physical activity such as yoga and tai chi can significantly improve physical function in rheumatoid arthritis (RA). Yoga and Tai Chi are gentle physical activities that promote strength, flexibility, balance and positive mental health. However, it is difficult to assess the effectiveness of these activities given that prior studies have small sample sizes. Therefore we conducted a systematic meta-analysis to assess the effectiveness of these exercises on improvement of physical function in adults with RA.

Methods: Medline was searched using the keywords: Yoga, Tai Chi, Physical Function, and Rheumatoid Arthritis. Included articles were those which measured the pre-intervention and post-intervention physical function scores using a validated physical function measurement tool for adults with a clinical diagnosis of RA who participated in a yoga or Tai Chi intervention lasting at least 6 weeks. Articles were excluded if the population was younger than 18, if the physical function measure was not a validated tool and if the reported results combined disease conditions such as RA and lupus. Effect sizes with confidence intervals were calculated using a fixed effects model for each intervention study by comparing the mean pre-intervention physical function score to the mean post-intervention score.

Results: The Medline search retrieved 219 English articles. The final analysis included 6 articles. There were 3 tai chi studies, 1 RCT and 2 pre/post intervention assessments, with a total of 22 participants. There were 3 yoga studies, 2 controlled clinical trials and 1 pre/post intervention assessment, with a total of 30 participants. There is strong evidence for the effectiveness of Tai Chi (standardized mean difference (SMD) = 1.20, 95% confidence interval (CI) = 0.13, 2.31) and for yoga (SMD = 1.22, 95% CI = 0.10, 2.27) on improving physical function in adults with RA who have participated in a physical activity program for at least 6 weeks. See Forrest plot.

Conclusion: Our data suggest that Tai Chi and Yoga are largely effective in improving physical function in adults with RA. Providers may be able to assist in improving the physical function of this population by discussing health promotion strategies such as yoga or tai chi physical activity programs.



Disclosure: H. Greysen, None; **K. Lee**, None.

2432

Nutritional Assessment in Patients with Systemic Lupus Erythematosus and Systemic Sclerosis. Sabrina Vagnani[1], Chiara Tani[1], Linda Carli[1], Francesca Querci[1], Alessandra Della Rossa[1], Anna d'Ascanio[1], Ilaria Ermini[2], Marco Ceroti[2], Saverio Caini[2], Domenico Palli[2], Stefano Bombardieri[3] and Marta Mosca[1]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute, ISPO, Florence, Itay., Florence, Italy, [3]Rheumatology Unit, Pisa, Italy.

Background/Purpose: Systemic Lupus Erythematosus (SLE) and Systemic Sclerosis (SSc) can be both associated with various degrees and types of malnutrition, with different pathogenetic mechanisms. It's well known that a balance between nutritional needs, energy intake and nutrients can contribute to the control of the inflammatory processes and can have a beneficial effect on osteoporosis, metabolic syndrome, hypertension, cardiovascular disease and neoplasia. Nutritional therapy is a promising way to approach SLE and SSc, indeed, a diet rich in vitamins, minerals and mono/polyunsaturated fatty acids could promote a beneficial protective effect against inflammatory activity and tissue damage as well as comorbidities. The aim of this study was to assess the nutritional status and food intake of a cohort of SLE and SSc patients in comparison to healthy subjects.

Methods: Twenty patients with SLE and 20 patients with SSc were included in the nutritional assessment. Twenty healthy age and sex matched subjects (H) were used as controls. Food intake was assessed using a Food Frequency Questionnaire, validated in the European Prospective Investigation into Cancer (EPIC) Cohort Study. All individual questionnaires were checked and coded by trained dieticians, computerized and then transformed into estimates of intake for a series of over 30 nutrients. At enrollment, weight, height, waist and hip circumferences were measured for each participant.

Results: The average age of SLE, SSc patients and controls was 36 ± 10, 40 ± 9 e 35 ± 10 years respectively (p=n.s.). The majority of SLE patients (90%) resulted normal weight: the body index mass (BMI) ranged between 18,5 and 24,99 kg/m^2. The rest of the group was overweight (25 ≤ BMI ≤ 29,99 kg/m^2). No obesity or underweight was observed. No differences in BMI were observed between SLE patients and H.

More than half of the SSc patients (66%) was normal weight; the rest of the group was underweight (89% slightly underweight with 17 ≤ BMI ≤ 18,49 kg/m^2 and 13% moderately underweight with 16 ≤ BMI ≤ 16,99 kg/m^2). SSc patients showed a lower mean value of BMI if compared with both SLE patients and H.

The annual frequency consumption of fruit, leafy vegetables, legumes, vegetables, milk, pasta, meat, and fish was similar in all the groups. On the contrary, the annual energy intake (kcal) was significantly lower in SSc patients if compared to SLE patients and H (p<0.02).

Conclusion: In this study we investigated the nutritional status of patients affected by two systemic autoimmune diseases. Our preliminary data showed an inadequate consumption of nutrients in SSc patients if compared to SLE patients and controls, probably due to a more severe gastro-enteric involvement. These results highlight the importance of an individualized nutrition approach in these patients according to disease-related specificities and pharmacological therapies.

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2433

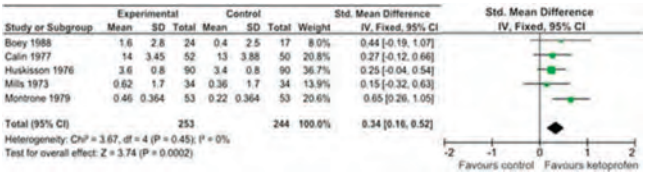
Efficacy of Ketoprofen Vs Ibuprofen and Diclofenac for Treating Pain in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Fabiola Atzeni[1], Alessandra Monguzzi[2], Elisabetta Grillo[2], Luigi Lanata[2] and Piercarlo Sarzi-Puttini[1]. [1]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy, [2]Dompé SpA, Milan, Italy.

Background/Purpose: Patients with rheumatic diseases, including rheumatoid arthritis (RA), describe symptoms such as pain and stiffness as important factors affecting their quality of life. The most widely used drugs to decrease inflammation and manage mild-to-moderate pain in RA patients are NSAIDs. In our previous meta-analysis, we demonstrated that ketoprofen was superior to ibuprofen and/or diclofenac in relieving different kinds of moderate-to-severe pain conditions, and so the aim of this systematic review of the literature and meta-analysis of randomised controlled trials (RCTs) was to compare the clinical efficacy of these drugs in patients with the specific pain associated with RA.

Methods: We made a systematic search of the Medline and Embase databases from their inception to March 2014 in accordance with the Cochrane Collaboration guideline in order to identify RCTs directly comparing the recommended therapeutic doses of oral ketoprofen (50–200 mg/day), ibuprofen (600–1800 mg/day) and diclofenac (75–150 mg/day) for RA pain relief. The meta-analysis was made using the standardized mean difference (SMD) of each included RCT and a fixed effects model.

Results: Five RCTs, involving a total of 456 patients met the inclusion criteria. The meta-analysis showed a statistically significant difference in clinical efficacy in favour of ketoprofen (SMD= 0.34; CI 95% 0.16–0.52; p=0.0002). The heterogeneity test for the efficacy outcome was not statistically significant and equal to zero (χ^2=3.67 - df=4 - P=0.45 - I^2=0%), thus demonstrating the homogeneity of the trials and the validity of the meta-analysis findings. The meta-analysis did not reveal any significant differences between drugs in terms of tolerability (the percentage of patients developing adverse events) or safety (withdrawn patients).

Conclusion: The result of this meta-analysis shows that therapeutic doses of ketoprofen are more efficacious than ibuprofen and diclofenac in managing RA-related pain, thus supporting its use in clinical practice.



Disclosure: F. Atzeni, None; **A. Monguzzi**, Dompè SpA, 3; **E. Grillo**, Dompè SpA, 3; **L. Lanata**, Dompè SpA, 3; **P. Sarzi-Puttini**, None.

2434

Gait Instability in the Elderly: A New Dedicated out-Patients Consultation. Vincent Goeb[1], Bernard Auvinet[2] and Claude Touzard[3]. [1]University Hospital, AMIENS, France, [2]Polyclinic, LAVAL, France, [3]Hospital of Laval, LAVAL, France.

Background/Purpose: Gait instability which represents a common but non-specific complaint, mainly in the elderly, is of major interest in PubMed (6038 references). Gait Instability can be the first step towards risk of falling, exposure to dementia, and disability [1]. Despite the frequency of this symptom and its major devastating consequences, few dedicated out-patients consultations have been initiated, in order to provide a practical management approach. A two year study will highlight the interest and perspectives of such an out-patients consultation.

Methods: Patients were recommended either by their general practitioner for gait abnormalities, or following an out-patients memory consultation. The assessment included six steps: self-questionnaires (*Dizziness Handicap Inventory*, *Hospital Anxiety and Depression Scale*), nurse evaluation, balance tests (one leg balance, Timed Up and Go score, Timed chair rise test), Mini Mental Score, clinical examination, and ambulatory Gait Analysis under simple and dual task conditions (counting backwards). We measured, using a validated ambulatory gait analysis system (Locometrix®), 3 main gait variables: walking speed, cadence, and stride regularity index. According to the results, additional specialized out-patients consultation and tests can be carried out (geriatrician, neurologist, otolaryngologist, brain magnetic resonance imaging. . .).

Results: - 80 patients were included (M=41, F=39, age: 68±14 y, BMI: 25±5 kg/m^2).

- 3 main subgroups of patients with gait complaints were identified (gait instability and cautious gait (n=38), recurrent falls (n=24) and memory impairment (n=18),

- Gait analysis was found with no abnormality in thirteen patients under simple task, in these cases gait abnormalities occurred only during the dual task test

- A broad diversity of diagnosis and syndromes were identified as the main pathology (Mild Cognitive Impairment (n=23), dementia (n=9), leukoaraiosis (n=9),vestibular disease (n=7), frail people (n=9), musculoskeletal disorders including spinal stenosis (n=7), brain stroke attack sequel (n=6), hydrocephaly (n=2), peripheral neuropathy (n=1), Charcot Marie Tooth disease (n=1), myopathy (Facio-scapulo-humeral dystrophy) (n=1), brain haemosiderosis (n=1), and patients without any diagnosis (n=4).

Conclusion: The complaint of gait instability has to be taken into account by the clinician, and necessitates a multi-disciplinary network. Clinical examination remains a key point, but gait analysis provides a measurement of gait instability, which can sometimes occur only under dual task conditions. A decrease in gait variability under the dual task test may explain the mechanism of an unexplained fall. Moreover a large decrease in one or more of the gait variables highlights for the clinician about a decrease in the cognitive reserve of the patient. Thus this condition provides key information to the clinician who has to look for brain pathology in addition to musculoskeletal deterioration.

1 Montero-Odasso M et al. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. JAGS 2012; 60: 2127-36.

Disclosure: V. Goeb, None; **B. Auvinet**, CentaureMetrix, 1; **C. Touzard**, None.

2435

'It's like the Worst Toothache You've Ever Had' – How Persons with Rheumatoid Arthritis Describe and Manage Pain in Daily Life. Maria Bergström[1], Inger Ahlstrand[2], Ingrid Thyberg[3], Torbjörn Falkmer[4], Björn Börsbo[5] and Mathilda Björk[6]. [1]School of Health Sciences, Jönköping University, Jönköping, Sweden, [2]School of Health Sciences Jönköping University, Jönköping, Sweden, [3]Linköping University Hospital, Linkoping, Sweden, [4]School of Occupational Therapy and Social Work, CHIRI, Curtin University, Perth, WA, Australia, Perth, Australia, [5]Linköping University, Linköping, Sweden, [6]Rehabilitation Center and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden.

Background/Purpose: Although it is reported that biological treatment has a positive effect on Rheumatoid arthritis (RA), pain intensity is still moderate to high in the majority of those affected, causing activity limitations and thus participation restrictions. Indeed, persons with RA have identified pain as the predominant health status impairment most important to reduce. However, pain in RA is commonly assessed using a visual analogue scale (VAS), which does not capture the complexity of pain and certainly does not address the management of it in daily activities. The purpose was to describe how persons with RA experience and manage pain in their daily life.

Methods: A focus group study was conducted. The participants were recruited with a purposive sample from three Rheumatology Units in Sweden. The inclusion criteria were seropositive RA, ≥4 years duration and pain intensity >40 mm as reported by VAS over the last two clinical visits. Of 77 eligible patients, 33 agreed to participate (34 to 73 years old). Seven semi-structured focus groups discussions were conducted and analyzed using content analysis. A RA-patient research partner was involved in the study confirming the interview guide and the results from a patient perspective. The study protocol was approved by the Regional Ethical Committee.

Results: The analysis revealed four categories: (1) *Pain expresses itself in different ways;* referring to descriptions of RA pain as overwhelming, painful

and as a feeling of stiffness in joints. While pain was described as closely related to fatigue and stress, sometimes it was invisible to others in the participants' social environment. (2) *Managing by easing the pain;* referring to the use of heat and/or cold treatments, medications and activities as distractions. (3) *Managing by adapting to pain;* referring to the strategies of learning to live with the pain, to plan activities in daily life to reduce pain, to use assistive devices or to sometimes simply stop doing some activities. (4) *Managing pain in a social context;* referring to the social environment as being both supportive and uncomprehending, the latter causing the participants to sometimes hide their pain.

Conclusion: Pain in RA was described as complex and multifaceted. To manage pain the participants used a wide range of strategies, ranging from personal strategies to those applied in their social context. This wide range of strategies could possibly complement the traditional methods used in clinical settings to manage pain. These findings further suggest that assessment of pain needs to be extended beyond the linear VAS measurement to cover its complexity.

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Analytical and Clinical Evaluation of an Immunoassay for Estimating Immunogenicity of Infliximab and Etanercept in Indian Population. Canna Ghia[1], Shashank Akerkar[2], Shailaja Sabnis[3], Rao RK Uppuluri[4] and Gautam Rambhad[5]. [1]Medical Advisor, Pfizer Limited, India, Mumbai, India, [2]Mumbai Arthritis Clinic and Research Centre, Mumbai, India, [3]Sneh Nursing Home,, mumbai, India, [4]Sri Deepti Rheumatology Centre, Hyderabad, India, [5]Associate Director Medical Services, Pfizer Limited, India, Mumbai, India.

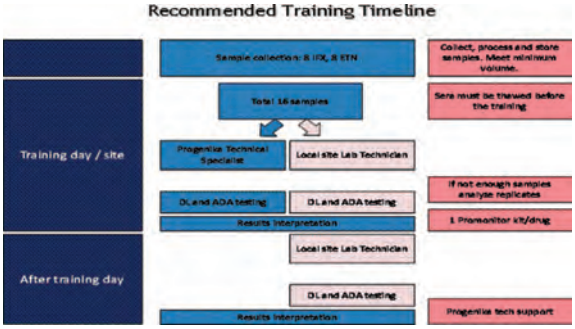
Background/Purpose: Biologic anti-TNFs in India have improved the patient management. Significant proportions of patients lose response over time or do not respond. Possible explanations are suboptimal trough anti-TNF*a* concentrations or antibodies to anti-TNFs[1].

Anti-infliximab antibodies are found in 12%-44% of patients[2] vis-à-vis anti-etanercept antibodies (0%-18%). Anti-etanercept antibodies are without apparent effect on effectiveness or adverse events[2]. Clinicians should have access to immunogenicity testing facility in India.

The aim of this project was to set up and standardize an independent laboratory to test immunogenicity of anti-TNF biologics (infliximab and etanercept) with the help of pharmaceutical partnership.

Methods: Three rheumatologists piloted this project approved by independent ethics committee and carried out in compliance with ICH/GCP guidelines. Pfizer supplied the immunogenicity kits to the independent laboratory (SRL labs). After informed consent, blood (5 mL) was collected before infusion of infliximab (n=8) or injection of etanercept (n=8). Following all precautions, the blood samples were transported to the laboratory. Promonitor® was the ELISA test used for testing of biological levels and anti-TNF*a* antibodies in patients samples. Laboratory staff was trained by Progenika specialist from Spain (Table I).

Table I



DL – Drug level; ADA – Anti-drug antibody

Results: Mean age of 16 patients was 42.06 ± 12.89 years. Table II represents the assay cut points and Table III lists the drug and antibody concentrations for patients.

Table II

	Cut-point	Interpretation
Infliximab	0.035 ug/mL	1) ≤ 0.035 ug/mL – Negative 2) 0.035-1.5 ug/mL – Low positive 3) ≥ 1.5 ug/mL – Positive
Anti-Infliximab antibodies	2 AU/mL	1) > 2 AU/mL – Positive 2) ≤ 2 AU/mL – Negative
Etanercept	0.035 ug/mL	1) ≤ 0.035 ug/mL – Negative 2) ≥ 0.035 ug/mL – Positive
Anti-Etanercept antibodies	142 AU/mL	1) ≤ 142 AU/mL – Negative 2) ≥ 142 AU/mL – Positive

Table III

	Drug level	Interpretation
Infliximab	<0.035 ug/mL (n=4)	Negative
	0.8217 ug/mL (n=1)	Low positive
	Range 2.706 to 8.079 ug/mL (n=3)	Positive
Anti-Infliximab antibodies	>2 AU/mL (n=1; 12.5%)	Positive
Etanercept	4.20 ± 3.23 ug/mL (n=8) (Range 2.000–9.712 ug/mL)	All patients positive
Anti-Etanercept antibodies	<142 AU/mL (n=8)	Negative for all patients

While 4 patients tested negative for infliximab, one patient tested low positive and 3 patients were positive. Anti-infliximab antibody was detected in 1/8 patient (12.5%) and the blood level of infliximab was negligible. When anti-TNF*a* are used, thereapeutic drug monitoring is of help for optimal clinical outcomes. It might be more cost effective to adjust anti-TNFα dosages according to serum drug concentrations[1,3,4]

Conclusion: This study met its objective of setting up and standardizing an independent laboratory for immunogenicity testing of anti-TNF biologics in India.

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Why Doesn't Participation in Activity Increase Following Hip or Knee Replacement? Aileen Davis[1], Viji Venkataramanan[1], Jessica Bytautas[2], Rose Wong[1], Lisa Carlesso[1], Anthony Perruccio[3] and Fiona Webster[2]. [1]Division of Health Care & Outcomes Research, Toronto Western Research Institute, University Health Network, Toronto, ON, [2]Department of Family and Community Medicine, University of Toronto, Toronto, ON, [3]Toronto Western Hospital, University Health Network, Toronto, ON.

Background/Purpose: Activity is critical for healthy aging. Our prior work demonstrated that despite improved pain and function, people did not increase their participation in activity post total hip or knee replacement (TJR). Our subsequent qualitative work identified that not only had people given up many activities prior to TJR, they experienced new comorbidity or symptomatic joints that limited their engagement. They also described significant life changes that impacted participation. This study evaluated if these health and social contextual factors were associated with change in participation.

Methods: We conducted a retrospective analysis of our TJR cohort. The primary outcome was change in participation frequency (Late Life Disability Index (LLDI) frequency subscale) pre- to 1 year post-surgery. Predictors were: surgical complication, new comorbidity, another primary TJR, and positive and negative life events (Life Experience Survey) in the year following TJR. Analyses included multivariable regression for the TKR and THR cohorts, adjusting for age, sex, education, pre-surgery BMI, comorbidity, and frequency, and change pre- to 1 year post-TJR in depression, WOMAC pain and function and LLDI limitations.

Results: The 418 TKR patients (mean age=65, 36% male, 69% >high school education) had a mean BMI of 30 and 49%, 6%, 13%, 12% had hypertension, CVD, diabetes, lung disease respectively. 74 episodes of new comorbidity (29 hypertension, 27 CVD, 8 diabetes, 10 lung disease) occurred. 38 (12%) had a complication, 39 another TJR, 151 (36%) reported a positive life event and 273 (65%) a negative life event. In adjusted analyses, pre-operative frequency, having a complication and negative life events were associated with less change in frequency.

The 376 THR patients (mean age=64, 46% male, 77% >high school education) had a mean BMI of 28 pre-surgery. 157 (42%) had hypertension, 28 (7%) had CVD, 31 (8%) had diabetes and 19 (5%) had lung disease. 34 (9%) had a complication and 33 (9%) another TJR. 54 episodes of a new comorbidity were reported (19 hypertension, 19 CVD, 4 diabetes, 12 lung disease). In adjusted analysis, lower pre-surgery frequency was associated with less change and positive life events were associated with greater change in frequency.

Conclusion: Low activity pre-TJR coupled with social context influenced changes in engagement in activity post TJR. Although additional health issues occurred, other than complications of TKR, none were associated with change in frequency. To promote healthy aging in people having TJR, appropriate timing of surgery, pre-surgical interventions to maintain activity and targeted programs post-surgery considering social context are required to enhance activity.

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A Multi-Centre Survey of Tolerability Problems for Patients on Regular Methotrexate. David Walker[1], Emmanuel George[2], Sarah Gibson[3], Una Martin[4], Hilary Wrightson[5], Peta S. Heslop[6], Peter Prowse[7], Matthew Kalinowski[7], Adewale O. Adebajo[8], David Marshall[9], Michael Reed[9] and Sandra M. Robinson[6]. [1]Freeman Hospital, Newcastle Upon Tyne, United Kingdom, [2]Wirral University Teaching Hospital NHS Foundation Trust, The Wirral, United Kingdom, [3]Wirral University Teaching Hospital NHS Foundation Trust, The Wirral, United Kingdom, [4]Waterford Regional Hospital, Waterford, United Kingdom, [5]Northumbria Healthcare NHS Foundation Trust, North Shields, United Kingdom, [6]North Tyneside General Hospital, North Shields, United Kingdom, [7]Hampshire Hospitals NHS Foundation Trust, Basingstoke, United Kingdom, [8]University of Sheffield, Sheffield, United Kingdom, [9]Inverclyde Royal Hospital, Greenock, United Kingdom.

Background/Purpose: Methotrexate has become the core DMARD for the treatment of Rheumatoid Arthritis. It has also found utility in treating other forms of inflammatory arthritis including Psoriatic, and can be used to reduce corticosteroid therapy. We were struck by the number of patients who complain of side effects that interfere with their lives but are not sufficiently serious to need withdrawal. We surveyed our own patients and found that 57% had at least 1 side effect. We were interested to see if this pattern was repeated in other places in the UK and to determine whether patients reported side effects and adherence differently to Doctors and Nurses.

Methods: A steering group of participants was organised to reflect a wide geographical spread throughout England Scotland and Ireland and included nurses and consultants. The questionnaire was slightly modified to include questions about adherence. 50 consecutive patients on Methotrexate for any reason, who were on a stable dose and planning to continue, were surveyed from each site, 100 patients were surveyed from Glasgow in Scotland.

Results: The patient report rate of any side effect was higher in all of the new centres compared to our first survey ranging between 67% to 86%. The biggest report rate difference was fatigue where there was an increase of up to 3.5 fold of patients reporting this side effect. Up to twice as many patients were reporting other side effects than were reported in the original survey.

Adherence was explored with questions about choosing not to take and forgetting to take. Choosing not to take ranged from 2% to 8%, with high VAS scores for severity of side effects which suggests that the decision to choose not to take Methotrexate was related to severity of side effects. Patient response to forgetting to take Methotrexate showed more variation, ranging from 0 to 18% and they rated lower VAS scores for severity of side effects. It is interesting to note that the survey completed by the nurse produced the highest disclosure of non-adherence by the patients; this may reflect on the way nurses communicate with patients. Numbers of missed weeks ranged between 2 and 4.

Conclusion: These surveys have shown a very high rate of side effects that patients are prepared to put up with for the benefits they get from Methotrexate. The main variation is in the complaint of Fatigue which is very subjective. The variation in admission of non adherence is interesting and merits further study as it may be an underestimate.

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Knee Joint Pathology in Patients with Rheumatoid Arthritis and Osteoarthritis Using a Validated Ultrasound Scoring System: A Cross Sectional Study. Karen Ellegaard[1], Marius Henriksen[2], Birgit Falk Riecke[3], Søren Just[4], Jakob Espesen[5], Mohammed Yusuf Naderi[6] and Henning Bliddal[3]. [1]The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark, Frederiksberg, Denmark, [2]The Parker Institute, Copenhagen University Hospital at Frederiksberg, Copenhagen F, Denmark, [3]The Parker Institute, Copenhagen, Denmark, [4]Svenborg Sygehus, Svendbotg, Denmark, [5]Odense Universitetshospital, Odense, Denmark, [6]Esbjerg Sygehus, Esbjerg, Denmark.

Background/Purpose: Ultrasound (US) signs of inflammation in joints are synovial hypertrophy, effusion, and Doppler activity (increased perfusion), which have been demonstrated in both osteoarthritis (OA) and rheumatoid arthritis (RA). It might be expected that inflammatory signs are more pronounced in patients with RA however, a comparison of RA and OA with respect to US changes remains to be performed.

Methods: A standardized US examination and scoring technique in patients with OA has been developed and validated in a group of patients with knee OA. This validated technique was applied on a group of RA patients and a group of OA patients – both with knee involvement. The diagnoses of OA and RA were according to the ACR criteria. RA and OA patients were examined by US according to the standardized procedure at baseline before onset of biologics. In the present study the validated US scoring were performed in all patients (RA and OA). All US images were scored by the same person (KE). The amount of synovial hypertrophy (mm) and Doppler (+/− scored as 1/0) were measured in five positions (supra patellar; medial and lateral joint space and recess). Synovial hypertrophy measures for all 5 positions were summed and Doppler presence was summed for the medial and lateral joint space and recess (4 positions). Presence and size of Baker's cyst were registered and any Doppler activity in or around the cyst was registered. Statistics: The difference between US findings in the two diseases was evaluated with both non-parametric and parametric statistics. The level of significance was $2\alpha=0.05$.

Results: Eighteen RA patients were included, the percentage of women was 66% and mean age was 66 years (range26.3–73). The mean DAS28 was 4.9 (range 3.5–7.0). The OA group consisted of 99 patients the percentage of women was 59 and the mean age was 64 (range42.3–84.4). See table.

Conclusion: On US examination statistically significantly more synovial hypertrophy and more Baker's cysts were seen in the OA knees as compared to the RA knees. Little Doppler activity (increased blood flow) was found with no difference between the two patient groups. These results support that inflammation is an important pathological feature in OA.

Acknowledgement: the study was supported by an unrestricted grant from Pfizer, Cambridge Weight Plan and the Oak Foundation.

	OA (n=99) Median [IQ] mean (SD)	RA (n=18) Median [IQ] mean (SD)	p-value (t-test)	p-value (Wilcoxon)
Synovial	21.8 [17.1; 27]	14.35 (14.12; 6.0)	<0.0001	<0.0001
hypertrophy (mm)	24.54 (11.91)	[11.6; 20.2]		
Baker's cyst (0–12)	0 [0; 5]	0 [0; 0]	<0.0001	0.0044
	2.19 (2.52)	0.24 (0.66)		
Doppler (0–7)	0 [0; 1]	0 [0; 1]	0.94	
	0,69 (1, 18)	0.67 (0.97)	0.80	

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Factors Influencing Health Related Quality of Life (HR-QOL) for Korean Patients with Rheumatoid Arthritis. SeungIn Paek[1], Kyeong Yae Sohng[2] and Sung-Hwan Park[3]. [1]ST Mary's Hospital, Seoul, South Korea, [2]The Catholic Univ of Korea, Seoul, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea.

Background/Purpose: The purpose of this study was to identify factors influencing the Health-related quality of life (HR-QOL) for Korean patients with rheumatoid arthritis and factors associated with each domain of the Health-related quality of life(SF-36).

Methods: A total of 299 patients with rheumatoid arthritis were recruited from one University Hospital in Seoul, Korea. Their clinical and socio-demographic data were widely collected by means of interviews, self-administered questionnaires and clinical examinations. Disease activity score in 28 joints (DAS28), patient visual analogue pain scale (100mm), functional disability measured with Korean Health assessment questionnaire (KHAQ), The Functional Assessment of Chronic Illness Therapy-Fatigue, (FACIT-Fatigue), Centers for Epidemiologic Studies Depression (CES-D), sleep scale were assessed. The HR-QOL was assessed by Short Form Health Survey-36 (SF-36). Pearson's correlation coefficient, stepwise multiple regression analyses were performed to determine the factors influencing HR-QOL and associated with each domain of the SF-36.

Results: Of the 299 subjects with RA, 272 (91%) were women and mean age was 49.5±10.5 years. The mean disease duration was 117 ± 91.2 months. The mean scores of SF-36 physical component summary (PCS) and mental component summary (MCS) were 42.5 ± 7.9, 45.8 ± 10.9.The mean scores of DAS 28, functional disability (KHAQ), visual analog pain scale were 3.83±1.41, 0.57±0.63, 34.95±24.43 and FACIT-Fatigue was 36.25±10.43, depression (CES-D) was 15.28±10.07 and sleep quality scale was 44.58±8.46.

On the socio-demographic features, educational level, occupation state, exercise were associated with HR-QOL (SF-36).History of hospitalization within 2 years, ESR(mm/hr), CRP(mg/dl), DAS28 score, visual analog pain, KHAQ, disability index, FACIT-Fatigue, depression (CES-D) and sleep quality scale were associated with all domains of HR-QOL (SF-36). Visual analog pain was strong association with HR-QOL(SF-36) domain of bodily pain (BP) (r=−0.74,p=<.0001) and depression(CES-D) was also strong association with mental component summary (MCS)(r=−0.73,p=<.0001).

In multiple stepwise regression model, KHAQ disability index (p=<.0001) was significant predicting variable of the physical component summary (PCS) and depression (CES-D) (p=<.0001) was significant predicting variable of the mental component summary (MCS) of HR-QOL (SF-36).KHAQ disability index (p=<.0001) was significant predicting variable on the domain of PF(Physical Functioning), RP(Role-Physical), SF(Social Functioning) and the FACIT-Fatigue (p=<.0001) was significant predicting variable on the domain of GH(General Health), RE(Role-Emotional), VT(Vitality) of HR-QOL (SF-36).

Conclusion: The factors influencing HR-QOL were functional disability, fatigue, depression and pain. However various factors are influencing the quality of life for patient with rheumatoid arthritis. It suggests that all healthcare professionals should pay more attention to improve fatigue, depression, pain and prevent progressing disability of patient with rheumatoid arthritis.

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Prevalence and Determinants of Treatment Adherence Among Patients with Rheumatoid Arthritis. Maria Celeste Orozco[1], Maria Florencia Marengo[1], Christian A. Waimann[1], Ana Inés Marcos[2], Amelia Granel[2], Sofia Velez[3], Federico Zazzetti[3], Juan C. Barreira[4], Paula Kohan[5], Oscar L. Rillo[6], María Victoria Collado[7], Graciela Gómez[8], Ricardo V. Juárez[9], Veronica Lencina[9], Andrea D'Orazio[10], Gustavo Rodriguez Gil[10], Mariana Salcedo[11] and Gustavo Citera[1]. [1]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Hospital San Roque de Gonnet, La Plata, La Plata, Argentina, [3]Hospital Britanico, Buenos Aires, Argentina, [4]British Hospital, Buenos Aires, Argentina, [5]Hospital Gral. de agudos Dr. E. Tornú, Buenos Aires, Argentina, [6]Hospital General de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [7]Instituto de Investigaciones Medicas Alfredo Lanari, Buenos Aires, Argentina, [8]Insituto de Investigaciones Medicas de la UBA, Capital Federal, Argentina, [9]Hospital Señor del Milagro, Salta, Argentina, [10]Hospital Municipal de agudos Dr. Leonidas Lucero, Bahía Blanca, Argentina, [11]Consultorio Privado, San Nicolás, Argentina.

Background/Purpose: Treatment adherence is a crucial part of successfully managing rheumatic diseases such as Rheumatoid Arthritis (RA). Low adherence to treatment has been related to poor radiographic and clinical outcomes in these patients. The aim of our study was to determine the prevalence and factors associated with non-adherence in patients with RA.

Methods: We designed a multicenter cross sectional study. Consecutive patients with RA (ACR'87 and or ACR/EULAR 2010) were recruited from 7 rheumatology clinics. Data collected included comorbidities, demographic and clinical variables. Patient-reported clinical outcomes included the Clinical Disease Activity Index (CDAI) and the Health Assessment Questionnaire (HAQ). Adherence to treatment was assessed using the Compliance Questionnaire Rheumatology (CQR; 0 – 100, 0 low adherence). Patients were categorized as having low or acceptable adherence using the traditional cutoff (≤80). Frequencies and distribution of adherence were calculated. The association between adherence and clinical/demographic variables were assessed using univariate and multivariate models.

Results: Three hundred and thirty-eight patients were included, 84 % were female, mean age was 53 ± 12 years, disease duration 13 ± 10 years, CDAI 13 ± 11 and HAQ 1.00 ± 0.75. Mean adherence to the treatment regimen as determined by CQR score was 86 ± 10. Two hundred and sixty-two patients (81%) had acceptable level of adherence. These patients had significantly higher age (p=0.03), higher level of education (p=<0.01), were more frequently unemployment (p=0.03), and had longer disease duration (p=<0.01). After adjusting for multiple confounders, only longer disease duration (OR= 1.1, CI95%=1.01–1.08, p =0.04) and live alone (OR= 0.3, CI95%=0.1–0.6, p = <0.01) remained significantly associated with acceptable adherence (Table 1).

Conclusion: In our population, only one fifth of patients with RA showed low self-reported adherence to treatment. These patients had shorter disease duration and more frequently live alone. Physicians must be aware of patients at high risk of low treatment adherence in order to avoid long-term consequences.

Table 1 Logistic regression using level of adherence as dependent variable (CQR ≥80 =1; CQR <80 =0)

	OR	95% Confidence interval	p-value
Age (years)	1.02	0.99–1.05	0.10
Female	0.90	0.39–2.09	0.81
Disease duration (years)	**1.04**	**1.00–1.08**	**0.04**
Years of education	1.02	0.95–1.11	0.54
Number of comorbidities	1.2	0.81–1.89	0.33
Live alone	**0.26**	**0.11–0.61**	**0.002**
CDAI	1.00	0.97–1.04	0.79
HAQ	1.27	0.74–2.21	0.38

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Aligning Ethics with Digital Health Technologies and Shared Decision-Making: Interview Accounts of Patients and Clinicians. Anne F. Townsend[1], Paul Adam[2], Jenny Leese[1], Linda C. Li[1], Michael McDonald[3], Sheila Kerr[4], Gordon Whitehead[4] and Catherine Backman[3]. [1]Arthritis Research Centre of Canada, Richmond, BC, [2]Mary Pack Arthritis Centre, Vancouver, BC, [3]University of British Columbia, Vancouver, BC, [4]Arthritis Patient Advisory Board, Richmond, BC.

Background/Purpose: Medical ethics evolves as health care develops. Digital health technologies are transforming health care delivery and patient and clinician relationships. Ethical approaches are shifting from a clinician focus on beneficence and improving patient health as emphasized in the Hippocratic oath, to patient-centered models of care, which emphasize patient autonomy in medical decision-making and patients as partners in their care. We have little understanding however, of how digital technologies promote a more patient-centered model of decision-making. Specifically we know little about how clinicians are altering their practices to support patients in making informed choices, and how patients are making treatment decisions. The study aimed to examine the role of various digital technologies in supporting patient choice and informed shared decision-making.

Methods: We present preliminary findings of a qualitative interview study, informed by narrative and phenomenology to understand patient and clinicians' experiences of new technologies and shared decision-making. Eligible participants were: adults with multi-morbidity including arthritis; clinicians with relevant caseloads. Recruitment was via online ads, notices, and word of mouth. The interview guides were consistent for both groups and explored broadly: 1) Use of a range of digital technologies e.g. apps, devices, Internet information, social media; 2) How use influenced illness management and patient-clinician interactions and relationships. An iterative, con-

stant comparative analysis with independent open coding of transcribed data by 2 researchers is ongoing.

Results: We purposively sampled 18 participants for maximum variation (11 patients, 7 clinicians) to take part in 2 in-depth interviews. Three emerging themes have been identified. First, participants described how digital health technologies were changing their roles and responsibilities, involving new types of 'work' for both patients and clinicians. Second, patients and clinicians emphasized the benefits of the Internet in preparing patients for discussions in consultations, while identifying the potential burdens of accessing extensive and unreliable sources. Third, mutual trust and respect was integral to effective patient-clinician discussions, sharing online information and informed, shared decision-making.

Conclusion: Preliminary findings imply that new technologies support autonomy in terms of informed patient choice and shared decision-making, but only when mutual trust and respect underpin patient-clinician interactions. Understanding how patient-clinician relationships are changing in the era of digital health is critical for ethical, clinical practice.

Disclosure: A. F. Townsend, None; **P. Adam**, None; **J. Leese**, None; **L. C. Li**, None; **M. McDonald**, None; **S. Kerr**, None; **G. Whitehead**, None; **C. Backman**, None.

2443

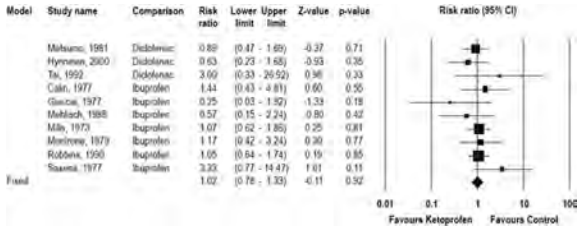
A New Meta-Analysis on Safety of Ketoprofen Vs Ibuprofen and Diclofenac: Risk and Benefit of Nsaids Beyond Efficacy Meta-Analysis. P. Sarzi-Puttini[1], F. Atzeni[1], Luigi Lanata[2], Alessandra Monguzzi[2] and Michela Bagnasco[2]. [1]Rheumatology Unit, L. Sacco University Hospital of Milan, Milan, Italy, [2]Dompé SpA, Milan, Italy.

Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for management of mild-to-moderate pain, chronic inflammatory and degenerative joint diseases. Among NSAIDs, ketoprofen, ibuprofen and diclofenac have been widely used for the last 30 years and particular attention should be taken into account when choosing a NSAIDs in order to achieve the best risk/benefit ratio for patients. Recent publication of our comparative meta-analysis demonstrating that efficacy of oral ketoprofen is greater than ibuprofen and/or diclofenac, raised many questions about safety profile of these molecules. For this reason we performed this meta-analysis of randomised controlled trials (RCTs) in order to compare the safety of orally administered ketoprofen vs ibuprofen and diclofenac and to obtain a complete comparative assessment of risk/benefit profile of these NSAIDs.

Methods: A systematic literature search was performed on main databases (Medline, Cochrane Central and Embase) until July 2013 to identify RCTs comparing directly therapeutic doses of oral ketoprofen (50–200 mg/day) vs ibuprofen (600–1800 mg/day) or diclofenac (75–150 mg/day). In accordance with the Cochrane Collaboration guideline, two rheumatologists carried out independently study selection.

Results: A total of 10 RCTs involving 826 patients met the inclusion criteria. Five of the 10 RCTs included patients with systemic rheumatic diseases. Findings from this meta-analysis did not reveal any difference in safety for ketoprofen compared to ibuprofen and/or diclofenac. The difference between ketoprofen and the pooled ibuprofen/diclofenac data was not statistically significant (risk ratio; RR=1.02, 95% CI 0.78–1.33; P=0.92) at all point-estimates of the mean weighted size effect. Further sub-analysis also confirmed that ketoprofen was not significantly different to either diclofenac (RR=0.86; 95% CI 0.51–1.45; P=0.58) or ibuprofen (RR=1.08; 95% CI 0.79–1.48; P=0.65) at all point-estimates. Heterogeneity for the safety measures analysed were not statistically significant for all meta-analyses.

Conclusion: Findings of this meta-analysis show that ketoprofen is well tolerated, with a safety profile at least comparable to ibuprofen and diclofenac, and no serious AEs. In light of superior efficacy demonstrated in our previous meta-analysis, these further safety results support recommendation that oral ketoprofen has the best risk/benefit profile vs ibuprofen and diclofenac.



Disclosure: P. Sarzi-Puttini, None; **F. Atzeni**, None; **L. Lanata**, Dompè SpA, 3; **A. Monguzzi**, Dompè SpA, 3; **M. Bagnasco**, Dompè SpA, 3.

2444

Pharmacist-Developed Letters May Enhance Success in Obtaining Insurer Approval for Off-Label Use of Biologics. Jessica F. Farrell[1], Lee S. Shapiro[1], Joel M. Kremer[2] and Aixa Toledo-Garcia[1]. [1]The Center for Rheumatology, Albany, NY, [2]Albany Medical College and the Center for Rheumatology, Albany, NY.

Background/Purpose: A growing number of publications suggest that biological DMARDs, predominantly approved for RA, can be efficacious treatment options for several rare rheumatic diseases. These potentially efficacious treatments are often "out of reach" because of inability to obtain insurance coverage. Insurers routinely deny coverage of "off-label use" because of the absence of double-blind placebo controlled studies demonstrating efficacy. This type of evidence is only infrequently available for these rare rheumatic diseases. The medical director for the insurer often has no familiarity with the disease, the potential consequences of non-treatment or the inadequacy of more accessible therapies. The addition of a pharmacist as part of a multidisciplinary team can provide an effective resource in successfully navigating the medication prior authorization process.

Methods: Our approach involves the use of a clinical pharmacist in development of comprehensive, evidence-based appeal letters. These letters are drafted by a clinical pharmacist (PharmD.) and pharmacy interns who perform extensive literature searches including all relevant case reports and clinical data related to disease state and drug therapy. The PharmD's then summarize that data as justification for use of therapy. Appeal letters are then drafted to include an explanation of the patient's circumstances, disease manifestations, progression, prognosis, as well as the treatment history, and the comprehensive review of current literature on the rationale for and experience with the proposed therapy.

Results: Since January 2009, our pharmacist has drafted and submitted approximately 141 letters. We have decreased the rate of initial "denials" for off-label use to near zero. We estimate that we have saved the physicians and support staff approximately 100 hours while achieving the desired outcome for both patients and physicians. We estimate that the average rheumatologist will have a need for between 5– 15 of these letters per quarter. If we calculate the value of physician time based upon billable dollars, we would estimate a net saving for individual physicians of between $1000 and $4000 hours per quarter. Additionally, we have decreased the time associated with the approval process from an average of 4–6 weeks to less than 4 weeks.

Conclusion: The issuance of an evidence based approach to the off-label appeal process has decreased the time associated with approvals and prevented the need for mention of litigation or liability. Due to time constraints, the ability to provide this level of patient care would not be possible without the assistance of the clinical pharmacist. The practice of pharmacy has expanded its scope to include extensive clinical training beyond the preparation and dispensing of medication. Pharmacists have the capacity to provide a wide range of patient-oriented services. As part of their education, PharmD's have extensive training in scientific literature evaluation and drug information. Based on our experience and success, it is clear that PharmD's are an underutilized resource in the ambulatory care setting and can greatly improve patient-care outcomes.

Disclosure: J. F. Farrell, None; **L. S. Shapiro**, None; **J. M. Kremer**, Corrona, 1, Corrona, 4; **A. Toledo-Garcia**, None.

ACR/ARHP Poster Session C
Rheumatoid Arthritis - Human Etiology and Pathogenesis
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

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A Distinct Profile of Circulating Microparticles Is Associated with Disease Features in Rheumatoid Arthritis Patients and Impairs Endothelial Functionality in Vitro. Javier Rodríguez-Carrio[1], Mercedes Alperi-López[2], Patricia López[1], Sara Alonso-Castro[2], Santiago Rubén Carro-Esteban[1], Javier Ballina-García[2] and Ana Suárez[1]. [1]University of Oviedo, Oviedo, Spain, [2]Rheumatology Department, Hospital Universitario Central de Asturias, Oviedo, Spain.

Background/Purpose: Cell-derived microparticles (MPs) could be considered biomarkers of cell damage and activation and they are thought to have a role in cardiovascular (CV) and inflammatory diseases. Since Rheumatoid Arthritis (RA) is characterized by immune and endothelial activation, the main aim of this study was to evaluate MP counts in RA patients.

Methods: MPs were analyzed by flow cytometry following a total-labelling procedure in platelet-poor plasma from 33 healthy controls (HC), 72 individuals with marked CV risk (CVR: diabetes, n=24; dyslipidemia, n=27; and hypertension, n=41) and 114 RA patients (61.4% RF, 61.4% αCCP, DAS28: 3.61(1.97), 42.1% erosive disease). Different subsets were identified by their surface markers: platelet- ($CD41^+$, PMPs), endothelial- ($CD146^+$, EMPs), granulocyte- ($CD66^+$, GMPs), monocyte- ($CD14^+$, MoMPs) and Tang-derived ($CD3^+CD31^+$, Tang-MPs). TNFα serum levels were quantified by ELISA. In vitro assays on Matrigel with HMEC-I cells were performed to assess the effect of MPs on endothelial functionality. Clinical and immunological parameters as well as traditional CV risk factors (diabetes, hypertension, dyslipidemia, obesity and smoking) were registered from clinical records and all data were analyzed by Principal Component Analysis (PCA).

Results: Total MPs count was increased in RA compared to both HC ($p<0.0001$) and CVR ($p=0.0009$) and was positively correlated with traditional CV risk factors (BMI, TC/HDL ratio, triglycerides and number of risk factors). Additionally, specific MPs subsets were increased in RA (EMPs $p<0.0001$, GMPs $p<0.0001$, Tang-MPs $p=0.006$ and MoMPs $p=0.028$). Clinical data were integrated with PCA and 4 components were identified. Notably, different MP subsets correlated with different components (table 1), thereby involving specific disease features in MPs profile. Interestingly, TNFα correlated with Tang-MPs in RA after adjusting by traditional risk factors ($r=0.218$, $p=0.036$). Finally, MPs from RA patients were able to impair endothelial cell functionality (measure as tube formation and number of branching points) in vitro in a dose-dependent manner, linked to an upregulation of endothelial activation markers (CD62E, CD144 and VEGFR2). This effect appeared even within the physiological range and it was not present with HC or CVR MPs.

Conclusion: MPs analysis in RA patients revealed an increased damage in several cell types. Circulating MPs from RA patients displayed a unique quantitative and qualitative profile as the result of both disease-specific and traditional CV risk factors. These differences are independent of comorbidities. Accordingly, this MP profile could underlie the detrimental effects on endothelial cells in vitro, thus supporting their role as biomarkers of endothelial damage and vascular repair failure.

Table 1: PCA components

	Rheumatic-related	Traditional CV-related	Duration-related	Inflammation-related
Total MPs	0.110	**0.381**	0.065	0.022
	0.345	**0.0007** ***	0.576	0.848
PMPs	0.018	0.078	0.096	0.050
	0.881	0.506	0.410	0.668
EMPs	−0.016	0.017	**0.302**	−0.091
	0.894	0.884	0.005 **	0.446
GMPs	**0.277**	−0.004	0.042	0.050
	0.022 *	0.975	0.721	0.667
Tang-MPs	**0.299**	−0.035	−0.028	0.134
	0.003 **	0.768	0.816	0.262
MoMPs	−0.098	−0.111	−0.153	0.114
	0.414	0.356	0.202	0.343

Disclosure: J. Rodríguez-Carrio, None; **M. Alperi-López**, None; **P. López**, None; **S. Alonso-Castro**, None; **S. R. Carro-Esteban**, None; **J. Ballina-García**, None; **A. Suárez**, None.

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DNA Methylation Profiles That Distinguish Rheumatoid Arthritis from Osteoarthritis in Fibroblast-like Synoviocytes Can be Detected in Immune Cells from Peripheral Blood. Brooke Rhead[1], Calliope Holingue[1], Michael Cole[1], Xiaorong Shao[1], Hong L. Quach[1], Diana Quach[1], Lisa F. Barcellos[1] and Lindsey A. Criswell[2]. [1]University of California, Berkeley, Berkeley, CA, [2]University of California, San Francisco, Rosalind Russell/Ephraim P. Engleman Rheumatology Research Center, San Francisco, CA.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease with potential to cause substantial disability, primarily due to the erosive and deforming process in joints. RA etiology is complex, with contributions from genetic and non-genetic factors. Epigenetic changes, such as altered patterns of DNA methylation, are also present in RA. Recent work by Firestein and colleagues (Nakano, 2013) compared genome-wide DNA methylation profiles in synovium-derived fibroblast-like synoviocytes (FLS) from RA patients and osteoarthritis controls and identified a set of differentially methylated genes that appear to distinguish these two forms of arthritis. Given the greater accessibility of peripheral blood compared to synovium-derived FLS, we set out to determine whether similar methylome signatures were present in immune cell subsets in peripheral blood.

Methods: We generated over 400 genome-wide DNA methylation profiles for 101 women (70 cases and 31 controls) using Illumina HumanMethylation450 BeadChips. Four FACS-sorted immune cell types were assayed for each individual: CD14+ monocytes, CD19+ B cells, CD4+ memory T cells, and CD4+ naive T cells. All samples were background subtracted using the lumi Bioconductor package and normalized using all sample mean normalization (ASMN) followed by beta-mixture quantile normalization (BMIQ). All study individuals were fully characterized for whole genome SNP profiles using the Illumina OmniExpress BeadChip. We excluded CpG sites near SNPs known to be common (>1%) from analysis, as well as sites with a low detection p-value, leaving 367,704 sites for analysis.

Results: We examined the top differentially hypo- and hypermethylated (n = 17 and 18, respectively) loci from the Firestein study in each immune cell type and found strong evidence for overlapping RA methylome signatures between FLS and immune cells. The most significantly differentially methylated genes in cases vs. controls include STK24, ADAMTS2, CABLES1, CD55, COL4A1, COL4A2, CYFIP1, FOXO1, ITGB8, ITGBL1, MAP3K1, PHLPP1, PTPN14, RXRA, TGFBR2, and TIMP2. The strongest evidence for replication of differential methylation in candidate gene regions was observed for naive CD4+ T cells; more than 20% of CpG sites tested were hypermethylated in cases compared to controls.

Conclusion: Methylation patterns that distinguish RA cases from controls in FLS are also present in immune cells from peripheral blood. Our investigation of DNA methylation underscores the importance of epigenetic mechanisms in RA pathogenesis and represents the largest study, to date, of methylome profiles derived from immune cells.

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2447

The Role of TET3-Mediated DNA Demethylation By Pro-Inflammatory Cytokines in Rheumatoid Arthritis. Kazuhisa Nakano, Kunihiro Yamaoka, Akira Kurozumi, Akio Kawabe, Kaoru Yamagata and Yoshiya Tanaka. University of Occupational and Environmental Health, Japan, Kitakyushu, Japan.

Background/Purpose: In the pathogenesis of Rheumatoid arthritis (RA) RA fibroblast-like synoviocytes (RA FLS) exhibit a unique aggressive phenotype that contributes to the cytokine milieu and joint destruction. We previously revealed that persistent exposure of pro-inflammatory cytokines contribute to passive DNA demethylation through decreased expression of DNMT in FLS. We here assessed the involvement of a novel active DNA demethylation enzyme, Ten-eleven-translocation (TET), in cytokine-mediated activation of RA-FLS.

Methods: FLS were obtained from patients with RA and osteoarthritis (OA) synovium at total joint replacement and studied in the 4th through 6th passage. The study was approved by the ethical committee of the university and informed consents were obtained by each patient. cDNA, Nuclear extracts and genomic DNA were purified from control or stimulated FLS. Gene expression was determined by qPCR and protein expression by Western blot and immunostaining. 5-hmC was determined by dot blot. Secretion of cytokines and MMPs was measured by Cytometric Bead Array and latex agglutination method. Cell migration was assessed using a wound healing scratch assay.

Results: TET3 and its product, 5-hydroxymethylcytosine (5-hmC), are detected in the intimal lining layer of synovium in patients with active RA, while TET1 and TET2 were observed marginally there. TET3 was characteristically expressed in both cytoplasm and nuclear of FLS, whereas TET1 and TET2 were not detected in nucleus. Although unstimulated RA and OA FLS expressed similar amounts of TET3 mRNA (n=6 each; n.s.), stimulation with TNFα (10 ng/ml) and IL-1β (1 ng/ml) for 2 hrs significantly increased TET3 mRNA expression in FLS (>3-fold and >4-fold respectively). Western blot analysis showed expression levels of TET3 protein in nucleus in RA FLS were significantly increased by stimulation with TNFα within 48 hrs and were maintained for 96 hrs. Dot blot analysis showed that 5-hmC was also increased by TNFα when FLS were cultured continuously for 96 hrs with TNFα. TET3-knockdown of FLS with siRNA not only inhibited TNF-induced expression of key migratory genes, including CCL2 and ICAM-1, but also reduced TNF-induced FLS-migration completely.

Conclusion: We initially report that a novel DNA methylation enzyme TET3 is characteristically induced in RA FLS through TNF/IL-1 stimulation.

Taken together with our previous report, persistent exposure to pro-inflammatory cytokines in the synovium not only decreases DNMT expression but also increases TET3 expression, resulting in promotion of DNA demethylation. In addition to demonstrating a critical role for TET3 in FLS in cytokine milieu, our study suggests that targeting the TET3–5-hmC pathway may be a therapeutic strategy for preventing FLS from TNF-mediated imprinting in RA.

Disclosure: K. Nakano, None; **K. Yamaoka**, None; **A. Kurozumi**, None; **A. Kawabe**, None; **K. Yamagata**, None; **Y. Tanaka**, None.

2448

DNA Methylation Analysis of Lymph Node Stromal Cells of Rheumatoid Arthritis Patients. Emmanuel Karouzakis[1], Caroline Ospelt[1], Janine Hähnlein[2], Renate E. Gay[3], Paul Peter Tak[4], Danielle Marie Gerlag[5], Michel Neidhart[1], Steffen Gay[1] and Lisa G.M. van Baarsen[2]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [3]Zurich University Hospital, Zurich, Switzerland, [4]University of Cambridge,Cambridge and GlaxoSmithKline, Stevenage, United Kingdom, [5]GSK,Clinical Unit Cambridge,R&D Projects Clinical Platforms & Sciences, Cambridge, United Kingdom.

Background/Purpose: Lymph node stromal cells (LNSC) build the scaffold that enables migration and interaction of lymphocytes in the lymph node. More recently, it has been shown that during inflammation LNSC play a crucial role in shaping the immune response and maintaining tolerance. Since DNA methylation changes have been reported in autoimmune diseases, we analysed the DNA methylation profile of LNSC from healthy individuals and rheumatoid arthritis (RA) patients.

Methods: Needle biopsies of inguinal lymph nodes were strained through a 70μm nylon mesh and the resulting stromal part was cultured in DMEM with 10% FCS. Adherent cells were passaged 4 times before total genomic DNA was isolated. DNA samples (healthy n=4 and ACPA+ RA n=5) were subjected to the Illumina HumanMethylation 450 array, which allows the analysis of 485.000 methylation sites per sample. It covers the promoters, 5-UTR, 3-UTR, gene body, first exon of 99% RefSeq genes and 96% of CpG islands. After strict quality control analyses we calculated the differential methylated regions using the COHCAP bioinformatics package in R (version 3.0.1). The results obtained by array analyses were validated for a selected number of probe sequences by pyrosequencing.

Results: The bioinformatics analysis between healthy and RA LNSC revealed 557 significantly differential methylated CpG sites (delta β-value >0.25, $p<0.05$. We found 57% of the differentially methylated CpG sites to be hypomethylated and 43% hypermethylated. 374 genes were found to be associated with the differential methylated sites. Functional annotation clustering was performed using the hypermethylated (167 genes) and hypomethylated (207) genes. For the hypermethylated genes, the highest enrichment was associated with homophylic cell adhesion and positive regulation of cell death pathways. For the hypomethylated genes, pathways associated with cell adhesion, cell projection, regulation of cell growth and cell motion were significantly differentially methylated. Next, we analysed for specific genes with differentially methylated CpG islands. Interestingly, we identified the hypermethylated genes CXCL4 (RA β-value=0.46 - healthy β-value=0.20, p=0.008) and Lactotransferin (RA β-value=0.52 – healthy β-value=0.25 p=0.016) that have previously associated with RA. In addition, other gene targets were found to be strongly hypomethylated such as NTGN1 (RA β-value =0.13 - healthy β-value=0.40, p=0.016) and KCNE1 (RA β-value=0.09-healthy β-value=0.35, p=0.010).

Conclusion: This the first study reporting epigenetic modifications in LNSC of RA patients. Specifically, DNA methylation analysis identified interesting known and novel gene targets altered in the LNSC of RA patients.

Disclosure: E. Karouzakis, None; **C. Ospelt**, None; **J. Hähnlein**, None; **R. E. Gay**, None; **P. P. Tak**, GSK, 3; **D. M. Gerlag**, GSK, 3; **M. Neidhart**, None; **S. Gay**, None; **L. G. M. van Baarsen**, None.

2449

Microrna-346 Regulation of Follicular Helper T Cells Is Involved in the Pathogenesis of rheumatoid Arthritis Disease. Xinyi Tang[1], Jie Ma[2] and Shengjun Wang[3]. [1]Jiangsu University Affiliated People's Hospital, Zhenjiang, China, [2]Jiangsu University Affiliated People's Hospital, Zhenjiang, China, [3]Jiangsu University Affiliated People's Hospital, Zhenjiang, China.

Background/Purpose: Follicular helper T (Tfh) cells have been identified as a new subset of effector helper T cells that are essential in regulating the development of antigen-specific B-cell immunity. Tfh differentiation is regulated by specific transcription factor Bcl-6. Several studies have certified the vital role of Tfh cells in the pathogenesis of autoimmune diseases. MicroRNAs (miRNAs) could negatively regulate gene expression post-transcriptionally and participate in the development of autoimmunity. The purpose of this study is to investigate the function of miR-346 in enhancement of Tfh cells during the pathogenesis of RA.

Methods: We detected the proportion of Tfh cells, concentration of IL-21, relative expression of Bcl-6 and IL-21 mRNA as well as miR-346 in RA patients and healthy donors. A Luciferase reporter assay was undertaken for directly proves that Bcl-6 is the functional target of miR-346.The level of Bcl-6 protein in Jurkat cells which were transfected with the miR-346 mimics was detected. Percentage of $CD4^+CXCR5^+$ T cells in circulating $CD4^+$ Tcells from healthy donor transfected with miR-346 mimics was examined.

Results: A significantly increased frequency of $CD4^+CXCR5^+$ and $CD4^+CXCR5^+ICOS^{high}$ circulating Tfh cells was detected in RA patients, compared with that in healthy controls. Frequency of the circulating Tfh cells showed a positive correlation with anti-CCP antibody in plasma from RA Patients. It has reported that Tfh differentiation is regulated by specific transcription factor Bcl-6. IL-21 is derived from activated Tfh cells and could enhance B cells to produce antibodies. In this study, Bcl-6 and IL-21 mRNA expression in $CD4^+$T cells of RA patients was higher than that in control. Also, a higher IL-21 concentration was found in RA Patients.

A sequence motif of the 3'UTR of Bcl-6 matches with miR-346. And level of miR-346 expression in circulating $CD4^+$T cells from RA patients was significantly downregulated. We found that miR-346 inhibited the luciferase activity of reporters containing the wild-type UTR1 or UTR2 but not that of the reporter with a mutated 3'UTR unable to bind miR-346.

As Bcl-6 is also expressed in Jurkat cells, miR-346 suppressed the expression of Bcl-6 mRNA in a dose-dependent manner. Manipulation of miR-346 in Jurkat cells also regulated the amount of endogenous Bcl-6 protein.

The percentage of $CD4^+CXCR5^+$ T cells in miR-346-transfected group was decreased than that in control group. It could certify the negative function of miR-346 in the differentiation of Tfh cells.

Conclusion: In summary, we found that miR-346 could regulate Tfh cells differentiation by targeting Bcl-6, and in RA patients, miR-346 expression was downregulated, which correlated with increased proportion of Tfh cells and disease severity. Collectively, our results may facilitate the validation of miR-346 as a new therapeutic target for the treatment of patients with rheumatoid arthritis.

Disclosure: X. Tang, None; **J. Ma**, None; **S. Wang**, None.

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Downregulation of Mirna-196a and Its Downstream HOXC8 Target Gene in Rheumatoid Arthritis Synovial Fibroblasts. Maria Filkova[1], Michelle Trenkmann[1], Borbala Aradi-Vegh[1], Lenka Pleštilová[1], Joanna Stanczyk[1], Beat A. Michel[2], Ladislav Senolt[3], Renate Gay[1], Steffen Gay[4] and Astrid Juengel[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich Schlieren, Switzerland, [2]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [3]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [4]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: Comprehensive analysis of 260 miRNAs suggested a downregulation of miR-196a in rheumatoid arthritis (RA) synovial fibroblasts (SF) compared with osteoarthritis (OA) SF. Mature miR-196a originates from 2 regions in human genome: MIR-196-A1 (chromosome 17) and MIR-196-A2 (chromosome 12) both located in HOX- gene clusters. The altered expression of miR-196a has been reported in multiple conditions, such as cancer. Our aim is to analyze the expression and regulation of miR-196a in cells from patients with RA.

Methods: Expression of pri-miRNA precursor and mature miR-196a was analyzed in RA/OA synovial tissue, SF under proinflammatory and hypoxic conditions, peripheral blood mononuclear cells (PBMC), synovial fluids and sera using TaqMan RealTime-PCR. Chromatin immunoprecipitation (ChIP) was used to analyze histone methylation and acetylation within both promoters MIR-196A1 and MIR-196A2 in SF. Ilumina sequencing with subsequent single assay verification was performed following Lipofectamine transfection with pre-miR-196a or anti-miR-196a to identify miR-196a targets genes.

Results: Expression of miR-196a is significantly lower in RA synovial tissues (n=6) compared with OA (n=4, p=0.01) as well as RASF (n=19) compared with OASF (n=15, p<0.0001). No difference was observed in PBMC or synovial fluids while a lack of cell-free miR-196a was detected in RA and OA sera. The precursor pri-miR-196A1 was expressed neither in RA nor OA SF while pri-miR-196A2 was significantly downregulated in RASF vs. OASF (n=4 each, p<0.05). Expression of miR-196a in SF was not affected by proinflammatory cytokines (TNFα, IL-1β), TLR ligands (LPS), 1% hypoxia or 5'AZA mediated DNA demethylation. ChIP of MIR-196A2 promoter revealed significantly higher methylation of repressive H3K27me3 (p=0.005), lower methylation of activating H3K4me3 (p=0.001) and hypoacetylation of H3 (p=0.008) in RASF (n=13) compared to OASF (n=10) explaining the downregulation of the mature miR-196a in RASF. Using Ilumina sequencing after pre-miR transfection of RASF (n=2) HOXC8 and HOXA7 were identified as most likely direct miR-196a targets. Downregulation HOXC8 (p=0.01) as well as HOXA7 (p<0.0001) pre-miR-196a transfection (n=5), and upregulation of HOXC8 (p=0.11) and HOXA7 (p=0.56) and upon anti-miR-196a transfection (n=5) suggest these HOX genes as direct targets. However, unexpectedly, significant downregulation of HOXC8 was observed in RASF (n=17) vs. OASF (n=18, p=0.004) while the expression HOXA7 was not significantly different between RASF and OASF (p=0.91).

Conclusion: MiR-196a is one of the few miRNA showing a significant dowregulation in resident cells of synovial tissue in RA patients regulated by histone modifications. Although HOXC8 and HOXA7 are suggestive of being direct targets of miR-196a, their distinctive role in unique RASF behavior remains to be investigated. Given low expression of miR-196a in RASF and location within HOXC cluster, we hypothesize that expression of HOXC8, except regulation by miR-196a, may be influenced by additional epigenetic features similar to those regulating miR-196a.

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Mir-155 Expression Correlates with Clinical Disease Activity and Has Effector Function in Rheumatoid Arthritis. Aziza Elmesmari[1], Derek G. Gilchrist[2], Mariola Kurowska-Stolarska[2] and Iain B. McInnes[2]. [1]Institute of Infection,Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom, [2]University of Glasgow, Glasgow, United Kingdom.

Background/Purpose: MicroRNAs are fine tuners of biological pathways that function via post-transcriptional regulation of target mRNA life span. MicroRNA 155 (miR155) is particularly implicated in Rheumatoid Arthritis (RA) pathology through regulation of synovial macrophage cytokine and chemokine production. Thus far miR155 expression across disease activity status has not been examined – to this end we have developed a novel assay of absolute copy number to facilitate such investigation.

Methods: Peripheral blood (PB) was obtained from healthy controls and RA patients who met the 2010 ACR/EULAR diagnostic criteria. CD14+ cells (monocytes) were isolated using micro-beads. The absolute copy numbers of miR-155 transcripts and housekeeping short RNA (U1) in peripheral blood (PB) and synovial fluid (SF) macrophages of RA and healthy controls were assessed using a novel qPCR methodology**.**

Results: RA PB (n=24) and SF $CD14^+$ monocytes (n=11) expressed higher copy numbers of miR-155 compared with healthy controls (n=22). As expected, RA SF macrophages exhibited the highest expression levels of miR-155 ($75318.2/10^6$ copies of RNU1A). In PB monocytes, miR-155 levels were higher when derived from patients with high or moderate disease activity (according to DAS28; p<0.05) than those in remission or healthy controls. The copy number of miR-155 expression was significantly increased in anti-citrullinated protein antibody (ACPA) positive RA (n=17) compared with ACPA negative RA (n=7). The RA PB monocyte miR-155 copy number correlated positively and significantly with DAS28 as a continual variable. There was no correlation between observed increase in miR-155 copy number and patients' age, disease duration or medication.

Conclusion: Our data demonstrate that miR-155 levels may reflect RA disease activity and could be a potential clinical disease activity biomarker for RA. Moreover our data suggest that circulating monocytes in RA patients exhibit an early activation signature, which is primed for subsequent cytokine release.

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Protective Effect of the *IL33* rs3939286 Gene Polymorphism in the Development of Subclinical Atherosclerosis in Patients with Rheumatoid Arthritis. Raquel López-Mejías[1], Fernanda Genre[1], Mercedes García-Bermúdez[2], Alfonso Corrales[1], Carlos González-Juanatey[3], Begoña Ubilla[1], J. Llorca[4], Encarnación Amigo[5], Jose A. Miranda-Filloy[6], Trinitario Pina Murcia[1], Ricardo Blanco[7], Santos Castañeda[8], Javier Martin[9] and Miguel A González-Gay[1]. [1]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, [2]Instituto de Parasitologia y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain, [3]Hospital Universitario Lucus Augusti. Cardiology Division, Lugo, Spain, [4]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain, [5]Hospital Universitario Lucus Augusti, Rheumatology Division, Lugo, Spain, [6]Division of Rheumatology, Hospital Lucus Augusti, Lugo, Spain, [7]Hospital Marques de Valdecilla, Santander, Spain, [8]Hospital Universitario de La Princesa, IISP, Madrid, Spain, [9]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain.

Background/Purpose: Rheumatoid arthritis (RA) is a complex inflammatory disease characterized by chronic inflammation, accelerated atherosclerosis and increased cardiovascular (CV) mortality. Interleukin 33 (IL-33) is a cytokine with a pathogenic role in some autoimmune diseases and a potential protective effect on atherosclerosis. Recently, an association between the *IL33* rs3939826 polymorphism and inflammatory bowel disease (a well-established chronic inflammatory disorder) has been described in Caucasian individuals. In the present study, we aimed to establish for first time whether this gene polymorphism influences the development of subclinical atherosclerosis in patients for RA.

Methods: 567 patients with RA from Northern Spain without a previous history of CV events were assessed by carotid ultrasonography (US) to determine the carotid intima-media wall thickness (cIMT). Also, the *IL33* rs3939286 polymorphism was genotyped in these patients by TaqMan single-nucleotide polymorphism genotyping assays in a 7900 HT real-time polymerase chain reaction system.

Results: Patients with RA carrying the TT genotype had lower cIMT values than those homozygous for the CC genotype (mean ± standard deviation [SD]: 0.71 ± 0.14 mm in TT versus 0.76 ± 0.14 mm in CC carriers). Moreover, patients carrying the CT genotype had intermediate cIMT values (mean ± SD: 0.73 ± 0.17 mm). In keeping with these observations, patients with RA carrying the mutant allele T exhibited significantly lower cIMT values than those carrying the wild allele C (mean ± SD: 0.72 ± 0.16 mm versus 0.75 ± 0.18 mm, respectively; p=0.04). The association of allele T with lower values of cIMT in patients with RA remained statistically significant after adjusting the results for sex, age at the time of the carotid US study, follow-up time and traditional CV risk factors (p=0.02).

Conclusion: Our results indicate a protective effect of the *IL33* rs3939286 gene polymorphism in the susceptibility to subclinical atherosclerosis in patients with RA.

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High-Density Genotyping of Risk Loci in African Americans with RA. Maria I. Danila[1], Richard Reynolds[1], Qi Yan[1], Nianjun Liu[1], Peter K. Gregersen[2], CLEAR Investigators[1], Donna K. Arnett[1] and S. Louis Bridges Jr.[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Feinstein Institute for Medical Research, Manhasset, NY.

Background/Purpose: Genetic studies have identified 101 risk loci for RA in individuals of Caucasian and Asian descent. However, to date the genetic determinants of RA in African Americans, an admixed population, are poorly understood. We sought to determine whether genetic markers of autoimmunity validated in European and Asian population influence the occurrence of RA in African Americans.

Methods: Using the ImmunoChip custom array, which contains 196,525 single nucleotide polymorphisms (SNPs) from 186 autoimmune disease associated loci, a total of 814 African Americans with RA and 933 African American healthy controls were genotyped. After quality control procedures (related samples, sex inconsistency, marker call rate >98.5% and sample call rate >90%,), 100,268 SNPs with minor allele frequency (MAF) greater than 5% were available for analysis in 601 cases and 830 controls. Set-based association analysis using the sequence kernel association test (SKAT) was also performed in the autoantibody-positive and the autoantibody-negative subsets. Fine mapping of loci identified from the Caucasian RA ImmunoChip study was performed by association testing all markers +/− 500 kB conditionally on the top Caucasian SNP for each RA locus.

Results: Among the 601 cases, 479 (80%) individuals were autoantibody-positive. In the single marker association analysis adjusted for global European admixture, the strongest statistical associations with seropositive RA were found in the MHC region in chromosome 6. However, when the analysis was restricted to the 122 cases with autoantibody-negative RA, no statistical significant association for the MHC region was found. Since many of the markers were weakly associated with RA, we also performed set-based analysis using SKAT. SNPs were assigned to 17,529 genes if they were located within 100 kb 5' or 3' of the coding region. We found that *AP1*, transporter 1 ATP-binding cassette, subfamily B, a gene on chromosome 6 in the MHC region, previously associated with primary immunodeficiency, was associated with seropositive RA ($p = 3.5 \times 10^{-7}$). Conditional analyses indicated no ethnic specific SNPs refined the top association observed from the Caucasian RA Immunochip study.

Conclusion: The present study provides further evidence to support the importance of MHC region in African-Americans with RA.

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Genetic Influences on Rheumatoid Arthritis in African-Americans. Vincent A. Laufer[1], Richard J. Reynolds[1], Maria I. Danila[1], Gordon Wu[1], Amit Patki[1], Devin Absher[2], Carl D. Langefeld[3], R. Curtis Hendrickson[1], Elliot J. Lefkowitz[1], Ted R. Mikuls[4], Peter K. Gregersen[5], Elizabeth E. Brown[1], Robert P. Kimberly[1], John B. Harley[6], Donna K. Arnett[1], Hemant K. Tiwari[1] and S. Louis Bridges Jr.[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Hudson Alpha Institute for Biotechnology, Huntsville, AL, [3]Wake Forest School of Medicine, Winston-Salem, NC, [4]Veteran Affairs Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, [5]Feinstein Institute Medical Research and North Shore-Long Island Jewish Health System, Manhasset, NY, [6]Cincinnati Children's Hospital Medical Center; US Department of Veterans Affairs Medical Center, Cincinnati, OH.

Background/Purpose: Rheumatoid arthritis (RA) affects 0.5–1% of the population worldwide. The genetics of RA has been analyzed in large European and Asian studies, but much less is known about RA in African-Americans. Trans-ethnic analysis has found similarities and differences in RA genetics, making both validation and novel gene association important goals in African-Americans (AA). We present genome-wide association (GWA) data on African-Americans with RA alongside analysis of whole genome sequencing (WGS) data on a subset of the population. These data were analyzed in the context of publically available datasets on RA.

Methods: 535 AA cases (from the CLEAR Registry and the VARA Registry) and 1,506 AA controls (from CLEAR and SLEGEN) were genotyped using Illumina Omni 1M and 1S platforms. Inclusion thresholds were: sample call rate > 98.5%, SNP call rate > 98%, HWE p-value > 1×10^{-7}, MAF >0.05. The top principal component was included as a covariate. Imputation was carried out using IMPUTE2 with 1000 Genomes. The number of SNPs after merging was 1,790,756, and the total number of pruned SNPs after imputation was 8,380,261. After this, genomic inflation was 1.031. Associated and suggestive loci were defined as 500kB on either side of lead SNPs with a p-value of $<10^{-8}$, or $< 10^{-5}$, respectively. We gathered available GWAS, transcriptomic, methylomic data, and other data in RA for these loci. Next, we integrated this with analysis of copy number, structural, and rare variation (CNV, SV and RV) from WGS of 62 AA RA patients who were also genotyped on the Illumina platform and, 80 Yoruban (YRI), and 96 Northern European (CEU) genomes sequenced by CGI. We annotated rare variants with Combined Annotated Dependent Depletion (CADD) scores as well as according to 27 other ontologies to aid interpretation.

Results: One associated and 44 suggestive loci were identified among African-Americans with RA through GWA analysis. Two of these loci were previously associated with RA and another ten have been identified in other GWAS on autoimmune diseases or immunologic conditions. Multiple CNV were identified in the regions circumscribed by GWAS, some of which were several times more common in genomes of cases than controls. We found neither large deletions nor insertions unique to the RA population in the loci. Gene Burden Testing (GBT) reaffirms prior associations (e.g. *SYNGR1* displays 2.71 times more RV per genome than a weighted average of the CEU and YRI genomes). GBT appears particularly effective at enabling identification of associated antisenseRNAs and microRNAs. Most importantly, integrated analysis of our data displays internal consistency; for instance *SEMA6D* is in a locus defined by GWAS, is differentially methylated in RA, and is identified by GBT using WGS.

Conclusion: This co-analysis of GWAS, WGS, and publically available data allows refinement of gene and variant-level associations. This study re-confirms the importance of CNV in RA, but in loci not yet reported to have such. Finally, our results show that GBT enables confirmation and refinement of associations as well as the identification of RV likely to be deleterious in the context of RA.

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IL-6 Proximal Promoter SNP rs18000795 Genotype Strongly Correlates with Synovial Fibroblast IL-6 Expression. Erika Noss, Sook Kyung Chang, Gerald Watts and Michael Brenner. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Interleukin (IL)-6 is an important driver of rheumatoid arthritis (RA) pathology, and synovial fibroblasts are a major source of IL-6 in the RA synovium. We noted large differences in IL-6 expression across several human synovial fibroblast lines. Our objective was to better define the variation in IL-6 expression between synovial fibroblasts and identify mechanisms mediating these differences.

Methods: Human synovial fibroblast lines were derived from discarded surgical specimens by serial passage from ten RA or osteoarthritis (OA) donors. Human CD14+ monocytes were isolated from healthy donor peripheral blood mononuclear cells by magnetic bead positive selection. IL-6 was measured in cell culture media by ELISA. IL-6 mRNA expression was measured by quantitative reverse transcription polymerase chain reaction (qRT-PCR). IL-6 transcript stability was determined by measuring IL-6 mRNA decay after actinomycin D inhibition of transcription. Cell genotype at the IL-6 proximal promoter single nucleotide polymorphism (SNP) rs18000795 (otherwise known as IL-6 –174 G/C) was determined by restriction fragment length polymorphism analysis.

Results: Human synovial fibroblast lines reproducibly segregated into low, medium, and high IL-6 producers after tumor necrosis factor-alpha (TNF-α) stimulation, independent of cell passage and disease state. The IL-6 expression pattern after TNF-α stimulation correlated significantly with the expression pattern observed in unstimulated cells or cells stimulated with IL-1 or lipopolysaccharide (LPS), indicating that this pattern was not secondary to differences in TNF-α signaling pathways. The IL-6 expression pattern also correlated strongly with total mRNA expression, but not with differences in IL-6 mRNA stability, suggesting it was driven by transcriptional rather than post-transcriptional mechanisms. Given that the proximal promoter SNP rs18000795 has been associated with diverse effects on IL-6 levels and disease expression in many systems, we analyzed synovial fibroblast IL-6 production as a function of rs18000795 genotype. We found that high IL-6 expression was significantly associated with the homozygous minor allele (CC) genotype. We then tested if a similar genotype effect was seen in stimulated CD14+ monocytes, since macrophage lineage cells are another major IL-6 producer in the RA synovium. We found, in contrast to synovial fibroblasts, that the rs18000795 genotype had a modest and opposite effect on CD14+ monocyte IL-6 expression, with a trend toward higher production in the major allele (GG) homozygotes.

Conclusion: This study reports that synovial fibroblast IL-6 expression is significantly influenced by genetic differences in linkage with the IL-6 proximal promoter SNP, rs18000795. In contrast, little association between

rs18000795 and monocyte IL-6 expression was found in this study, showing that SNP associations may have divergent effect when analyzed in different cell types. These results highlight that analysis of the role of disease-associated SNPs on gene expression and pathologic processes must consider the effect of that genetic variation in different cell types.

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Associations of Toll-like Receptor (TLR)-4 Single Nucleotide Polymorphisms and Rheumatoid Arthritis Disease Progression. Marshall Davis[1], Tricia LeVan[2], Fang Yu[1], Harlan Sayles[3], Jeremy Sokolove[4], William H. Robinson[5], Kaleb Michaud[6], Geoffrey M Thiele[7] and Ted R. Mikuls[3]. [1]University of Nebraska Medical Center, Omaha, NE, [2]Univ of Nebraska Med Ctr, Omaha, NE, [3]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [4]VA Palo Alto Healthcare System and Stanford University, Palo Alto, CA, [5]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [6]National Data Bank for Rheumatic Diseases, Wichita, KS, [7]Omaha VA and the University of Nebraska Medical Center, Omaha, NE.

Background/Purpose: Toll-like receptor (TLR)-4 signaling pathways have been implicated in both the innate and adaptive immune responses that characterize rheumatoid arthritis (RA). In this study, we examined the associations between TLR-4 single nucleotide polymorphisms (SNPs) and RA using a large well-characterized RA cohort.

Methods: A total of 1,559 patients were genotyped for three TLR4 SNPs (rs1927911, rs11536878, and rs4986790), which were selected using a haplotype tagging strategy. Measures of disease severity included the Disease Activity Score-28 (DAS28), Multidimensional Health Assessment Questionnaire (MD-HAQ), Clinical Disease Activity Index (CDAI), and Simplified Diseases Activity Index (SDAI). Associations of TLR4 SNPs with these measures were examined longitudinally (mean of 10 visits, range: 0–60) using generalized estimating equations in both univariate and multivariate analyses, adjusting for age, sex, race, comorbidity, body mass index, smoking, erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and anti-CCP positivity, methotrexate and anti-tumor necrosis factor use. Based on existing data showing that anti-citrullinated protein antibody (ACPA)-containing immune complexes may drive TLR4 signaling in RA, analyses were also stratified by ACPA positivity including antibody positivity to anti-CCP and anti-citrullinated fibrinogen (cFb) antibody.

Results: RA patients homozygous for the minor allele of TLR4 rs1927911 demonstrated lower disease activity over follow-up including lower DAS28 ($p<0.001$), CDAI ($p=0.002$), and SDAI ($p=0.010$) in univariate analysis and lower DAS28 ($p<0.001$) and CDAI ($p=0.007$) in multivariate analysis (Table). Disease activity among those homozygous for the minor allele tended to be numerically lower in groups with elevated anti-CCP and anti-cFb antibody though no significant differences by ACPA status were identified. There were no associations of TLR4 rs11536878 and rs4986790 SNPs with any of the RA disease activity measures.

Conclusion: We found TLR4 rs1927911 genotypes are associated with the rate of disease progression over time independent of other factors. Although further studies are needed to identify mechanisms by which variation in rs1927911 impacts inflammatory burden, these data are consistent with reports in other disease states suggesting that this SNP is associated with a meaningful anti-inflammatory effect and support the concept of TLR4 as a potential therapeutic target in RA.

Table: Associations of TLR-4 rs1927911 genotype with RA disease progression (DAS28, HAQ, CDAI, and SDAI differences per year of follow up); p-values < 0.0167 (Bonferroni correction) considered to be statistically significant

	Univariate Analysis			Multivariate Analysis		
		DAS28			DAS28	
Genotype	Beta-Coef	95% CI	P-Value	Beta-Coef	95% CI	P-Value
CC	*Ref.*	—	—	*Ref.*	—	—
CT	−0.010	−0.022, 0.003	0.130	−0.016	−0.030, −0.003	0.019
TT	−0.038	−0.056, −0.020	**<0.001**	−0.029	−0.047, −0.012	**<0.001**
		MD-HAQ			MD-HAQ	
	Beta-Coef	95% CI	P-Value	Beta-Coef	95% CI	P-Value
CC	*Ref.*	—	—	*Ref.*	—	—
CT	0.002	−0.004, 0.009	0.472	0.001	−0.005, 0.007	0.755
TT	−0.007	−0.015, 0.001	0.102	−0.006	−0.015, 0.002	0.154
		CDAI			CDAI	
	Beta-Coef	95% CI	P-Value	Beta-Coef	95% CI	P-Value
CC	*Ref.*	—	—	*Ref.*	—	—
CT	−0.065	−0.185, 0.056	0.292	−0.125	−0.293, 0.043	0.145
TT	−0.250	−0.408, −0.091	**0.002**	-0.274	−0.472, −0.076	**0.007**
		SDAI			SDAI	
	Beta-Coef	95% CI	P-Value	Beta-Coef	95% CI	P-Value
CC	*Ref.*	—	—	*Ref.*	—	—
CT	−0.075	−0.203, 0.052	0.248	−0.116	−0.284, 0.053	0.178
TT	−0.232	−0.410, −0.054	**0.010**	-0.247	−0.453, −0.041	0.019

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Anti-Major Histocompatibility Complex Class I-Related Chain a (MICA) Antibodies in Rheumatoid Arthritis Patients with Interstitial Lung Disease. Hiroshi Furukawa[1], Shomi Oka[1], Kota Shimada[2], Akiko Komiya[1], Naoshi Fukui[1], Naoyuki Tsuchiya[3] and Shigeto Tohma[1]. [1]Sagamihara Hospital, National Hospital Organization, Sagamihara, Japan, [2]Tokyo Metropolitan Tama Medical Center, Tokyo, Japan, [3]Faculty of Medicine, University of Tsukuba, Tsukuba, Japan.

Background/Purpose: Interstitial lung disease (ILD) is frequently associated with rheumatoid arthritis (RA), and is designated RA-associated ILD (RA-ILD) that influences the prognosis of the disease. Transfusion related acute lung injury is defined as an acute lung injury associated with blood transfusion; one of its causes is thought to be anti-HLA antibody. Here, we investigated the anti-HLA antibody profiles to determine whether they may be useful for diagnosing RA-ILD.

Methods: Anti-HLA antibody levels were analyzed using the Lambda Array Beads Multi-Analyte System (LABScreen Mixed Assay, One Lambda, Canoga Park, CA), using a LabScan 100 system (Luminex, Austin, TX), in 34 RA patients with or without RA-ILD. This study was reviewed and approved by the ethics committees of each participating institute. Informed consent was provided by all subjects.

Results: Average anti-major histocompatibility complex class I-related chain A (MICA) antibody levels were higher in RA patients with ILD than in those without ($P=0.0013$, Mann-Whitney's U test). Average anti-HLA class I or class II antibody levels were not significantly different between RA patients with or without ILD ($P=0.6419$ and 0.2486, respectively). The ratio of (average anti-MICA antibody levels) / (average anti-HLA class I antibody levels) was increased in RA patients with ILD than in those without ($P=4.47\times10^{-5}$). The area under the curve value of receiver operating characteristic curves of the ratio was 0.912. The optimized cut-off level of the ratio was determined for RA-ILD, and the specificity and the sensitivity were 88.2% and 82.4%, respectively.

Conclusion: To the best of our knowledge, this is the first report of anti-HLA antibody profiles in RA-ILD. The ratio of (average anti-MICA antibody levels) / (average anti-HLA class I antibody levels) could be a better marker for diagnosing RA-ILD. Further large-scale studies would provide a possibility of generating better markers for RA-ILD.

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Targeting IL-6, JAK or SYK? : An Analysis of Transcriptome Alteration in Peripheral Blood By RA Treatments. Yoshinobu Koyama[1], Motohiko Tanino[2], Shuji Nagano[3], Toshiyuki Ota[3] and Toshie Higuchi[1]. [1]Japan Red Cross Okayama Hospital, Okayama, Japan, [2]DNA Chip Research Inc., Yokohama, Japan, [3]Iizuka Hospital, Iizuka, Japan.

Background/Purpose: The advances in understanding of the molecular nature of immune cell receptors enabled to offer new oral, targeted therapies. Tofacitinib (TOF) is the first selective kinase inhibitor to be approved to treat rheumatoid arthritis (RA). TOF inhibits Janus kinase (JAK) 1, JAK3 and, to a lesser extent, JAK2, which is known to lead inhibition of cytokine signaling including interleukin (IL)-6. Tocilizumab (TCZ), an anti-IL6 receptor monoclonal antibody, also block IL-6 signaling by preventing IL-6 from binding to both membrane-bound and soluble receptors. IL-6 is known to have a wide range of biological activities including B cell and T cell differentiation. As Spleen tyrosine kinase (SYK) participates in the activation of B cells and T cells, a Syk kinase inhibitor, fostamatinib (FOS) have been a candidate for RA

treatment. Although the targets of these three treatments are specific, the downstream biological activities seem to be wide. In order to investigate whether the effect of these treatments share common biological process or are disparate, we conducted transcriptome analysis with using next-generation sequencing.

Methods: The study includes a total of 30 RA patients treated by these three medications (TOF 6–20mg/d:15, FOS 100–200mg/d:4, TCZ 8mg/kg/4w:11). Peripheral blood was drawn at just before (pre) and 3 months after (post) these treatments. Total RNAs were then extracted with using PAXgene miRNA kit. After constructing single-stranded, strand-specific libraries (length 50bp), multiplex sequencing was done. After quantifying the expressions of transcripts, hierarchical clustering analysis was performed. And then, differentialy expressed genes (DEGs) were selected by paired comparison (post vs. pre), setting thresholds at 2-fold change up/down and less than P=0.05 in corrected paired T-test.

Results: In total, 57571 genes/transcripts including 976 newly predicted genes were quantified. By a hierarchical clustering analysis, the pre and the post of FOS or TOF treatment were segregated each other while those of TCZ treatment were nearest neighbors, indicating that TCZ has the least influence over the transcriptome. The 118, 344 and 121 genes were selected as DEGs from the comparison of post vs. pre treatment of TOF, FOS or TCZ, respectively. Disparate gene ontology (GO) terms were enriched in each DEGs group. Terms relevant to immunity including 'JAK-STAT cascade' were enriched in the down-regulated genes in the TOF group. Of 344 DEGs from the FOS group, 30 were related to "ribosomal proteins" and 29 of them were up-regulated. In the TCZ group, terms related to "extra cellular matrix", such as "extracellular matrix binding" and "wound healing" were detected.

Conclusion: Although some of downstream biological cascade for JAK, SYK or IL-6 appear to share, the influence of these treatments over the transcriptome in the peripheral blood seems to be disparate. The hierarchical clustering shows TCZ treatment has the least influence on transcriptome. On the other hand, it is noteworthy that FOS treatment seems to have much greater influence upon transcriptome as compare with others. Enrichment analysis using GO terms indicated that different biological processes were involved in the effect of each treatment.

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Osteoprotegerin CGA Haplotype Protection Against Cerebrovascular Complications in Anti-CCP Negative Patients with Rheumatoid Arthritis. Fernanda Genre[1], Raquel López-Mejías[1], Mercedes García-Bermúdez[2], Santos Castañeda[3], Carlos González-Juanatey[4], Javier Llorca[5], Alfonso Corrales[1], Begoña Ubilla[1], Jose A. Miranda-Filloy[6], Encarnación Amigo[6], Trinitario Pina Murcia[1], Carmen Gómez-Vaquero[7], Luis Rodriguez-Rodriguez[8], Benjamin Fernández Gutierrez[8], Alejandro Balsa[9], Dora Pascual-Salcedo[9], Francisco Javier López-Longo[10], Patricia Carreira[11], Ricardo Blanco[12], Isidoro González-Alvaro[13], Javier Martin[14] and Miguel A González-Gay[1]. [1]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, [2]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Granada, Spain, [3]Hospital Universitario de La Princesa, IISP, Madrid, Spain, [4]Hospital Universitario Lucus Augusti. Cardiology Division, Lugo, Spain, [5]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain, [6]Hospital Universitario Lucus Augusti, Rheumatology Division, Lugo, Spain, [7]Hospital Universitari de Bellvitge - IDIBELL, Barcelona, Spain, [8]Hospital Clínico San Carlos, Department of Rheumatology, Madrid, Spain, [9]Hospital Universitario La Paz, Department of Rheumatology, Madrid, Spain, [10]Hospital General Universitario Gregorio Marañón, Department of Rheumatology, Madrid, Spain, [11]Hospital Universitario 12 de Octubre, Department of Rheumatology, Madrid, Spain, [12]Hospital Marques de Valdecilla, Santander, Spain, [13]Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [14]Instituto de Parasitología y Biomedicina López-Neyra, IPBLN-CSIC, Armilla (Granada), Spain.

Background/Purpose: Rheumatoid arthritis is an inflammatory disease with a high incidence of cardiovascular disease due to accelerated atherosclerosis. Osteoprotegerin (OPG) has been associated with an increased risk of atherosclerotic disease in the general population. Several polymorphisms in the *OPG* gene with functional effects on cardiovascular disease in non-rheumatic individuals have been described. Therefore, we aimed to analyze the effect of three of these functional *OPG* polymorphisms on the risk of cardiovascular disease in a large and well-characterized cohort of Spanish patients with rheumatoid arthritis.

Methods: Three *OPG* gene variants (rs3134063, rs2073618 and rs3134069) were genotyped by TaqMan assays in 2,027 Spanish patients with rheumatoid arthritis. All the patients fulfilled the 1987 American College of Rheumatology (ACR) and also the 2010 classification criteria for RA. Anti-cyclic citrullinated peptide (anti-CCP) antibody testing was positive in 997 out of the 1,714 tested. Also, 18.3% of the whole series had experienced cardiovascular events, including 5.4% with cerebrovascular accidents. The relationship between *OPG* variants and cardiovascular events was assessed using Cox regression.

Results: No association between *OPG* gene variants and cardiovascular disease was observed in the whole group of rheumatoid arthritis patients or in anti-CCP positive patients. Nevertheless, a protective effect of CGA haplotype on the risk of cardiovascular disease in general, and specifically in the risk of cerebrovascular complications after adjusting for sex, age at disease diagnosis and traditional cardiovascular risk factors was disclosed in anti-CCP negative patients (HR=0.54; 95%CI: 0.31–0.95; p=0.032 and HR=0.17; 95%CI: 0.04–0.78; p=0.022, respectively). These results were in accordance with a reduced risk of developing cerebrovascular complications observed in those anti-CCP negative patients who carried the *OPG* rs2073618 GG genotype after adjusting for potential confounder factors (HR=0.17; 95% CI: 0.03–0.89; p=0.035).

Conclusion: Our results indicate a protective effect of the *OPG* CGA haplotype on cardiovascular risk, mainly due to a protective effect against cerebrovascular events in anti-CCP negative rheumatoid arthritis patients.

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Phospho-STAT1/3 and Gene Expression Measurement in Circulating CD4$^+$ T Cells As Diagnostic Tools in Early Autoantibody-Negative Rheumatoid Arthritis. Amy E. Anderson[1], Arthur G Pratt[1], Mamdouh Sedhom[2], Nisha Nair[3], Jonathan Massey[3], Christine Routledge[1], Ben Hargreaves[1], Philip Brown[1], Anne Barton[4], John D Isaacs[1] and Ranjeny Thomas[2]. [1]NIHR Newcastle Biomedical Research Centre, Newcastle Hospitals Foundation Trust and Newcastle University, Newcastle upon Tyne, United Kingdom, [2]The University of Queensland Diamantina Institute, Queensland, Australia, [3]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academy of Health Sciences, Manchester, United Kingdom, [4]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, Manchester, United Kingdom.

Background/Purpose: Early diagnosis of rheumatoid arthritis (RA) improves outcomes but is challenging, particularly amongst anti-citrullinated peptide auto-antibody (ACPA) negative individuals. Previously we identified an IL-6 mediated CD4$^+$T cell transcriptional signature, enriched for signal transduction and activation of transcription-3 (STAT3) target genes, which had discriminatory value for this purpose. In the present work we sought a more readily applicable diagnostic assay, and insight into mechanisms of disease induction.

Methods: Amongst early arthritis patients and controls naïve to immunomodulatory treatment, constitutive and IL-6-induced expression of phosphorylated STAT1 and 3 (pSTAT1/3) were determined in circulating lymphocytes using flow cytometry. Contemporaneous serum cytokine levels were measured using a validated, highly sensitive immuno-assay, and normalised CD4$^+$T cell gene expression of the previously described STAT3 target gene-enriched signature was determined using microarray.

Results: In 187 early arthritis patients, constitutive pSTAT3 correlated with serum IL-6 levels maximally in $CD4^+$ T cells, compared with other circulating leukocyte subsets. Increased constitutive pSTAT3, but not pSTAT1, was observed in circulating $CD4^+$ T cells of early ACPA negative RA patients compared with disease controls. Amongst patients presenting with undifferentiated arthritis (UA) the ratio of constitutive pSTAT3:pSTAT1 in $CD4^+$ T cells could be incorporated into an algorithm for predicting progression to classifiable RA with high accuracy (area under ROC curve = 0.91; $p<0.001$). The comparable utility of the previously described $CD4^+$T cell gene signature as a discriminatory tool, and the accuracy of pSTAT3: pSTAT1 as a surrogate for target gene expression, are the subject of on-going analyses.

Conclusion: Our findings support a particular role for IL-6-driven $CD4^+$ T cell activation via STAT3 during the induction of RA, which may be of particular importance in the pathogenesis of ACPA-negative disease. $CD4^+$ pSTAT measurements show promise as biomarkers of progression to RA in sero-negative UA.

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Osteprotegerin Concentrations Are Independently Related to Established Cardiovascular Disease in Rheumatoid Arthritis. Raquel López-Mejías[1], Begoña Ubilla[1], Fernanda Genre[1], Alfonso Corrales[1], José L Hernandez[2], Ivan Ferraz-Amaro[3], Linda Tsang[4], Javier Llorca[5], Ricardo Blanco[6], Carlos González-Juanatey[7], MA González-Gay[1] and Patrick H Dessein[4]. [1]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain, [2]Department of Internal Medicine, Hospital Universitario Marques de Valdecilla, University of Cantabria, RETICEF, IDIVAL, Santander, Spain, [3]Servicio de Reumatologia. Hospital Universitario de Canarias, Tenerife, Spain, [4]Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, [5]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain, [6]Hospital Marques de Valdecilla, Santander, Spain, [7]Hospital Universitario Lucus Augusti. Cardiology Division, Lugo, Spain.

Background/Purpose: We determined whether osteoprotegerin (OPG) concentrations are associated with established cardiovascular disease (CVD) amongst patients with rheumatoid arthritis (RA).

Methods: OPG concentrations were measured by an enzyme-linked immunosorbant assay in 151 (54 with CVD) RA patients and 62 age and sex matched control subjects without CVD. Concentrations of the endothelial activation marker angiopoietin 2 were also evaluated in a subgroup of 85 RA participants.

Results: In RA patients, age, body mass index (BMI), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody positivity, and joint erosion status were associated with OPG concentrations (partial R (p)=0.175 (0.03), -0.277 (0.0009), 0.323 (<0.0001), 0.217 (0.008) and 0.159 (0.05)), respectively. Median (interquartile range) OPG concentrations increased from 6.38 (3.46–9.31) to 7.07 (5.04–10.65) and 8.64 (6.00–11.52) pmol/l in controls and RA patients without and with CVD, respectively (p=0.0002). Upon adjustment for age, sex, traditional risk factors and BMI in mixed regression models, OPG concentrations remained lower in controls compared to RA patients without CVD (p=0.05) and in the latter compared to those with CVD (p=0.03); the association of OPG concentrations with CVD amongst RA patients also persisted after additional adjustment for RF and anti-CCP antibody positivity, and erosion status (p=0.04). OPG concentrations related independently to those of angiopoietin 2 in RA patients with but not without CVD (partial R (p)=0.545 (0.003) and 0.076 (0.6)).

Conclusion: OPG concentrations are associated with disease severity and CVD prevalence in RA patients. Whether consideration of OPG concentrations can improve CVD risk stratification in RA merits future longitudinal investigation.

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Centrosomal Protein 70kDa Is Down-Regulated By Decoy Receptor 3 in Specifically Rheumatoid Synovial Fibroblasts. Koji Fukuda[1], Yasushi Miura[2], Toshihisa Maeda[2], Shinya Hayashi[2] and Masahiro Kurosaka[2]. [1]Kakogawa City Hospital, Kakogawa, Japan, [2]Kobe University Graduate School of Medicine, Kobe, Japan.

Background/Purpose: Decoy receptor 3 (DcR3) is a secreted decoy tumor necrosis factor receptor and competitively binds and inhibits the TNF family including Fas-ligand, LIGHT, and TL1A. DcR3 is overexpressed in tumor cells and might benefit tumors by helping them to avoid cytotoxic and regulatory effects of the ligands. We previously reported that DcR3 overexpressed in rheumatoid synovial fibroblasts (RA-FLS) stimulated by TNFα protects the cells from Fas-induced apoptosis [1]. We recently reported that DcR3 binds to TL1A expressed on RA-FLS resulting in the negative regulation of cell proliferation induced by inflammatory cytokines [2]. Further, we newly revealed the gene expression profiles in RA-FLS regulated by DcR3 by using microarray data analysis. The profiles indicated centrosomal protein 70kDa (Cep70) was down-regulated by DcR3 (fold change 1.87) [3]. Centrosome forms the backbone of cell cycle progression mechanism. Further, CEP family protein is the active component of centrosome and plays a vital role in centriole biogenesis and cell cycle progression control [4]. In this study, we studied Cep70 as one of the key molecules in DcR3-TL1A signaling in RA-FLS based on the genes expression profiles regulated by DcR3.

Methods: *Real-time polymerase chain reaction (real-time PCR).* RA and osteroarthritis (OA) -FLS were stimulated with 1ng/ml of recombinant human TNFα or IgG1 for 24 hours, or with various concentration of DcR3-Fc or control IgG1 for 12 hours. Further, RA-FLS were incubated with DcR3-Fc for 12 hours after overnight pre-incubation with anti-TL1A antibody. The relative expression levels of Cep70 mRNA were quantified by real-time PCR.

Immunohistochemistry. Anti-Cep70 antibody was applied to frozen sections of synovial tissues from patients with RA or OA for over night. Sections were stained with HistoFine simple stain Kit and DAB chromogen, followed by counterstaining with hematoxylin.

Results: Real-time PCR revealed that the expression of Cep70 mRNA in RA-FLS was higher than that in OA-FLS and that TNFα significantly decreased the expression of Cep70 mRNA in RA and OA-FLS (RA, 51%; OA, 59%). DcR3-Fc also significantly decreased the expression of Cep70 mRNA in RA-FLS in a dose dependent manner (81% with 10ng/ml, 73% with 100ng/ml, and 57% with 1000ng/ml). In contrast, DcR3-Fc did not decrease Cep70 mRNA in OA-FLS. Anti-TL1A antibody inhibited the down-regulation of Cep70 expression in RA-FLS induced by DcR3-Fc. Immunohistochemistry revealed that Cep70 protein was expressed more in superficial lining layer of rheumatoid synovium than that of OA synovium.

Conclusion: In this study, we revealed that Cep70 was increased in RA-FLS and that the expression of Cep70 in RA-FLS was decreased by DcR3 by binding to membrane-bound TL1A in a disease-specific fashion. DcR3 may affect the pathogenesis of RA through Cep70.

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Stromal Cell Markers Are Differentially Expressed in the Synovial Tissue of Patients with Early Arthritis. Ivy Y.K. Choi[1], Olga N. Karpus[2], Jason D. Turner[3], Debbie L. Hardie[3], Maria J. H. de Hair[1], Karen I. Maijer[1], Paul-Peter Tak[1], Karim Raza[3], Jörg Hamann[2], Christopher Buckley[3], Danielle Marie Gerlag[1] and Andrew Filer[3]. [1]Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Department of Experimental Immunology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [3]Rheumatology Research Group, MRC Centre for Immune Regulation, School of Immunity and Infection, University of Birmingham, Birmingham, United Kingdom.

Background/Purpose: Previous studies have shown increased expression of stromal markers in synovial tissue (ST) of patients with established rheumatoid arthritis (RA). Here, the expression of tissue expressed stromal markers in early arthritis in relationship to diagnosis and outcome was studied.

Methods: ST from 67 patients included in two different early arthritis cohorts (Birmingham and Amsterdam) and seven non-inflammatory controls was analysed using immunofluorescence to detect the stromal markers CD55, CD248, fibroblast activation protein (FAP) and podoplanin. Diagnostic classification (gout, psoriatic arthritis, unclassified arthritis (UA), parvovirus associated arthritis, reactive arthritis and RA) and outcome (resolving or persistent) was determined at baseline and after follow-up. The relationship between the expression of the stromal markers and diagnosis and outcome was determined.

Results: We observed expression of all stromal markers in ST of early arthritis patients, independent of diagnosis or prognostic outcome. Expression of FAP and podoplanin was significantly higher in patients with early RA compared to non-inflammatory controls ($p=0.003$ and $p=0.021$, respectively). Significantly greater expression of FAP was found in anti-citrullinated peptide antibody (ACPA)-negative RA patients and in patients with UA fulfilling classification criteria for RA after follow-up compared to patients with resolving disease and patients with persistent disease who did not fulfil classification criteria for RA after follow-up ($p=0.030$ and $p=0.020$, respectively for ACPA-negative RA patients and $p=0.045$ and $p=0.024$, respectively for UA patients fulfilling classification criteria for RA after follow-up).

Conclusion: The stromal cell markers CD55, CD248, FAP and podoplanin, are expressed in the synovium in the earliest stage of arthritis. Expression of FAP is higher in early unclassified arthritis patients who fulfil classification criteria for RA over time and in ACPA-negative RA compared to resolving or non-RA arthritides. These results suggest that significant fibroblast activation occurs in RA in the early window of disease.

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Anti-Arthritic Effect of Tubastatin A, a Novel Histone Deacetylases-6 Inhibitor, Is Mediated By Stabilization of IkB Via Suppression of Ubiquitin-Proteasome Pathway. Eun Chung Hong[1], Hemin Jeong[2], Jiwon Hwang[2], Eun-Kyung Bae[1], Hyungjin Kim[2], Joong Kyong Ahn[3], Hoon-Suk Cha[2], Eun-mi Koh[2] and Jaejoon Lee[2]. [1]Samsung Biomedical Research Institute, Seoul, South Korea, [2]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Sungkyunkwan univ. school of medicine, Seoul, South Korea.

Background/Purpose: Histone deacetylase-6 (HDAC-6) functions as a non-epigenetic deacetylase for non-histone substrates and regulates microtubule-mediates processes such as cell migration, cell cycle arrest, and angiogenesis. We have previously demonstrated that Tubastatin A suppresses synovial inflammation and joint destruction in a collagen antibody-induced arthritis mouse model. However, the exact mechanism through which Tubastatin A exerts its anti-arthritic effect is not fully understood. The aim of the study is to investigate whether ubiquitin-proteasome pathway is involved in the anti-arthritic mechanism of Tubastatin A.

Methods: Fibroblast-like synoviocytes (FLS) were treated with TNF-α in a time-dependent manner (control, 5, 15, 30 minutes) and the phosphorylation activity of NF-κB and IκB was measured using Western blot analysis. FLS were stimulated with TNF-α after treatment with different doses of proteasome inhibitor (MG-132) or Tubastatin A, and the expression of IL-6 were measured using ELISA. FLS were stimulated with TNF-α after treatment with different doses of Tubastatin A and phosphorylation of nuclear NF-κB and of cytosolic IκB were measured using Western blot analysis. FLS were stimulated with TNF-α in a time dependent manner (15, 30, 45, 60 min) after pretreatment with Tubastatin A or control and expression of phosphorylated IκB was measured using Western blot analysis. FLS were treated with TNF-α after treatment with different doses of Tubastatin A, and cytosolic proteasome activity was measured using 20S Proteasome Activity Assay Kit.

Results: The phosphorylation of NF-κB and IκB were increased after stimulation of TNF-α at 5 minutes. After stimulation with TNF-α, the expression of IL-6 was attenuated in FLS treated with Tubastatin A or MG-132 compared with controls. At 3μM of Tubastatin A, the phosphorylation of NF-κB induced by TNF-α was suppressed, and phosphorylated IκB in cytosol was increased. Furthermore, the total cytosolic IκB remained the same. Phosphorylated IκB appeared in the cytosol 30 min after incubation with TNF-α after treatment with Tubastatin A, but no effect was seen when treated with TNF-α alone. After stimulation with TNF-α, the cytosolic proteasome activity was significantly decreased after treatment of Tubastatin A or MG-132 compared with controls.

Conclusion: Our study demonstrates that Tubastatin A exerts its anti-arthritic effect, at least in part, through preventing degradation of IκB by attenuating ubiquitin-proteasome pathway, and thus inactivating nuclear translocation of NF-κB.

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Cyclic Phosphatidic Acid (cPA) Suppresses MMP-3, a Disintegrin and Metalloproteinase with Thrombospondin Motifs(ADAMTS)-4, -5 and Stimulates HAS2 Expression in Inflammatory Rheumatoid Synovial Fibroblasts Induced with IL-1β and/or TNF-α. Ikuko Masuda[1], Kodo Okada[2], Hisashi Yamanaka[3] and Shigeki Momohara[3]. [1]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan, [2]SANSHO, Co. Ltd., Tokyo, Japan, [3]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Cyclic phosphatidic acid (cPA) is one of bioactive lipid, has been implicated as an mediator of various biological effects including i) antiproliferative effect on eukaryotic cell cycle, ii) regulation of Ca^{2+} release, iii) regulation of actin rearrangement, iv) inhibition of tumor cell invasion. Furthermore, on human skin fibroblasts, cPA stimulates high molecular hyaluronic acid (HA) production through up-regulating HA synthase (HAS). cPA also has shown to have antinociceptive effect on animal models of acute and chronic pain. We have previously confirmed that cPA also stimulated HAS2 production on human osteoarthritic chondrocytes and synovial fibroblasts in vitro. Furthermore, we have shown that intra-articular administration of cPA suppressed pain, swelling, and articular cartilage degeneration in rabbit experimental osteoarthritis. These compelling results lead to a hypothesis that cPA may have direct role on anti-inflammation and protection of cartilage in arthritic condition. The aim of this study was to evaluate the effects of cPA on rheumatoid synovial fibroblasts which are under more severe inflammatory condition than osteoarthritis.

Methods: In vitro studies were performed using synovial fibroblasts obtained from rheumatoid arthritis patients at joint replacement surgery. cPA 0–25 μM was added to synovial fibroblasts cultures and effects of cPA on synovial fibroblasts on HAS, HYAL, ADAMTS-4, ADAMTS-5, MMP-3, TIMP-3 expression were assessed at 24 and 48hrs by real time PCR using specific primers to corresponding genes. Synovial fibroblasts were also cultured with IL-1β and/or TNF-α, to study attenuated effect of cPA. Beta-actin was used as endogenous expression control.

Results: cPA stimulated endogenous HA synthesis from synovial fibroblasts as time and dose-dependent manner in vitro. HAS2 gene was up-regulated as dose–dependent manner. IL-1β and/or TNF-α addition didn't effect much on HAS2 expression, however addition of cPA stimulated HAS2 on synovial fibroblast with cytokines. On the other hand, cPA repressed HYAL-1 and HYAL-2 expression, and IL-1β (and/or TNF-α) stimulated HYAL-1 and -2, and cPA further repressed HYAL expression stimulated by cytokines. Not only with HYAL, cartilage degenerating enzymes, ADAMTS-4, ADAMTS-5, MMP-3 in synovial fibroblasts were all repressed by cPA, even after stimulated by cytokines.

Conclusion: The in vitro results confirmed that cPA had stimulatory effects on HA synthesis by rheumatoid synovial fibroblasts. The suppressing effect of HYAL, ADAMTS-4, ADAMTS-5, and MMP-3 on rheumatoid synovial fibroblasts by cPA shown here, might have played direct role to suppressing inflammation and also protecting articular cartilage of arthritic condition. Molecular mechanism of cPA to prevent cartilage degeneration remains to be elucidated, however, further study should be warranted for cPA as a novel candidate for therapeutic agent of arthritis.

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Increased Risk of Rheumatoid Arthritis (RA) Among Shared Epitope-Negative (SE-) Mothers with Shared Epitope-Positive (SE+) Children.

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Background/Purpose: RA (RA [MIM 180300]) disproportionately affects women of reproductive age, implicating pregnancy-related factors. Fetal microchimerism (FMC), or the persistence of a small population of cells in the mother, is a natural consequence of pregnancy. FMC is present more often in RA cases than in controls. Mother-child histocompatibility could determine long-term FMC, possibly increasing risk of RA through exposure to fetal HLA-antigens. We hypothesized that RA cases are more likely to have histocompatible (HC) children compared to controls.

Methods: The MCIS included 5,000+ individuals; mothers with RA or SLE and controls (n=750), their children and fathers. RA cases with 1+ birth before diagnosis were recruited at UC San Francisco. Controls were primarily recruited from blood donors. Mothers provided information on their reproductive history, history of transfusion, transplant and infections. Comprehensive MHC region SNP genotyping was conducted using the Illumina MHC panel (n=1,783), ImmunoChip (n=8,842), and 660K (n=1,991) arrays. Four-digit genotype data for *HLA-A, B, C, DPA1, DPB1, DQA1, DQB1* and *DRB1* were imputed using the T1DGC reference panel and BEAGLE. We estimated ancestry proportions from 384 markers using STRUCTURE. A child was HC from the mother's perspective if the paternal allele did not differ from the non-inherited maternal allele. Carrier status (+ or −) of any *DRB1* allele associated with RA risk (Raychaudhuri, 2012) and corresponding to SE amino acid sequences QKRAA and QRRAA (*01:01, 04:01, 04:04, 04:05, 04:08)* and DERAA *(01:03, 04:02, 11:02, 13:01, 13:02)* was determined for mothers and children. We used logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between RA and a) HC at each HLA locus and b) exposure to any SE+ and DERAA+ children, stratifying on maternal carrier status.

Results: Increased HC among cases was only evident at *DQB1* (25.3% vs. 17.4%, $p=0.03$). Having any SE+ children significantly increased risk of RA for SE- mothers (n=218) (OR 2.56; 95% CI, 1.43–4.58) but not SE+ mothers (n=248) (OR 1.48; 95% CI, 0.83–2.62). No association was found with DERAA+ children, regardless of maternal carrier status. Ancestry, parity, and history of transfusion did not impact results.

Conclusion: Exposure to SE+ children and *DQB1* HC may contribute to RA etiology and could contribute to RA's female-predominance. This is the largest study confirming the association between RA and SE+ children in SE− mothers.

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Effectiveness and Safety of Tocilizumab in Biologics Naïve RA Patients - Interim Analysis of PMS for Investigating Success in Achieving Clinical and Functional Remission and Sustaining Efficacy with Tocilizumab in Biologics-Naïve RA Patients Study.

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Background/Purpose: The all-patient PMS study of tocilizumab (TCZ) followed 7901 RA patients for 28 wks. That study (hereafter, PMS7901) showed patients with a high probability of remission and a low probability of developing serious infection to be those most likely to have early and less advanced RA and to have not received biologics previously. The FIRST Bio study is designed to investigate effectiveness and safety of TCZ in RA patients who had not received any biologics (i.e. bio-naïve) in a real clinical setting.

Methods: FIRST Bio is a 52-wk observational postmarketing surveillance study which enrolled bio-naïve RA patients who met the ACR/EULAR 2010 classification criteria for RA, experienced inadequate response or were intolerant to one or more DMARDs, and had DAS28-ESR > 3.2. Patients received 8 mg/kg TCZ every 4 wks intravenously with or without DMARDs at the investigators' discretion. Patient characteristics and safety and effectiveness data were collected. This interim analysis reports the results of 24 wks' observation. A paired t-test was used to detect statistically significant differences in disease activity (CDAI, DAS28-ESR) and Health Assessment Questionnaire (HAQ) score compared to baseline.

Results: This report analyzes 551 of 855 patients enrolled. Mean disease duration and percentage of patients who had less advanced Steinbrocker's stage and class and had comorbidities were lower in the FIRST Bio study than in PMS7901 (Table 1). At Wk 24, 87.2% of patients were continuing TCZ treatment. Mean CDAI improved from 23.4 at baseline to 7.5 at Wk 24 ($p < 0.0001$). DAS28-ESR also improved from 5.2 at baseline to 2.2 at Wk 24 ($p < 0.0001$). At Wk 24, rate of CDAI remission (CDAI ≤ 2.8) was 30.9%, DAS28-ESR remission (DAS28-ESR < 2.6) was 66.5%, and Boolean remission was 27.8%. The Boolean remission rate in the FIRST Bio study was almost twice that in PMS7901 (15.1%) (Table 2). The mean HAQ score improved from 1.0 at baseline to 0.5 at Wk 24 ($p < 0.0001$), and in 59.8% of patients the HAQ score decreased to <0.5 (i.e. HAQ remission). The incidence rates of total and serious AEs were 25.2% and 6.4%, respectively. Infections were the most frequent AEs (6.4%) and the most frequent serious AEs (2.0%). Malignancies were reported in 2 patients (0.4%). Gastrointestinal disorders were reported in 19 patients (3.4%), including 1 (0.2%) gastrointestinal tract perforation. One patient died (0.2%). The incidence rates of serious AEs and serious infections were lower in the FIRST Bio study than in PMS7901 (Table 2). Mean dose of concomitant MTX decreased from 9.1 mg/wk at baseline to 7.3 mg/wk at Wk 24. Mean dose of concomitant corticosteroid also decreased from 5.7 mg/day at baseline to 3.6 mg/day at Wk 24.

Conclusion: The FIRST Bio study revealed that in the real clinical setting TCZ showed high effectiveness and safety in those patients who have less advanced RA and who have not previously received biologics.

Table 1 Patient background

	FIRST Bio study	PMS7901
Mean age (SD), years	59.4 (13.7)	58.7 (12.9)
Mean disease duration (SD), years	7.2 (8.7)	10.4 (9.2)
% of patients (pts) whose Steinbrocker's stage was I or II	63.5	35.2
% of pts whose Steinbrocker's class was 1 or 2	81.5	73.8

% of pts who had any comorbidities (% of pts who had respiratory disease as comorbidity)	56.8 (11.3)	70.6 (14.5)
% of pts with prior use of biologics	0	62.8
% of pts with concomitant use of MTX (mean dose in pts using MTX)	60.8 (9.1mg/wk)	55.8 (7.0mg/wk)
% of pts with concomitant use of corticosteroids (mean dose in pts using corticosteroids)	55.4 (5.7mg/day)	74.0 (5.3mg/day)

Table 2. Comparing safety and effectiveness

	FIRST Bio study At Wk 24	PMS7901 At Wk 28
Boolean remission rate, %	27.8	15.1
Incidence rate of AEs (serious AEs), %	25.2 (6.4)	43.9 (9.6)
Incidence rate of infections (serious infections), %	6.4 (2.0)	11.0 (3.7)

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Stringent Criteria for Low Disease Activity and Remission after 12 Months of Treatment, and after Treatment Withdrawal, with Abatacept Monotherapy, Abatacept with Methotrexate or Methotrexate Alone in Early Rheumatoid Arthritis. Gerd Burmester[1], D E Furst[2], B G Combe[3], T W J Huizinga[4], Vivian P. Bykerk[5], D Wong[6], C S Karyekar[6] and P Emery[7]. [1]Charité – University Medicine Berlin, Berlin, Germany, [2]University of California at Los Angeles, Los Angeles, CA, [3]Montpellier University Hospital, Montpellier, France, [4]Leiden University Medical Center, Leiden, Netherlands, [5]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [6]Bristol-Myers Squibb, Princeton, NJ, [7]University of Leeds, Leeds, United Kingdom.

Background/Purpose: Clinical remission is associated with better long-term outcomes[1,2] and should be the goal of therapy in RA. In the Assessing Very Early Rheumatoid arthritis Treatment (AVERT) trial, greater percentages of patients (pts) achieved DAS28 (CRP) <2.6 following 12 mths of treatment with SC abatacept + MTX and 6 mths after withdrawal of all RA therapy, compared with MTX alone. At most time points, abatacept monotherapy was more effective than MTX alone.[1] Here, we report clinical efficacy and remission rates from AVERT, using stringent criteria at Mth 12 and after treatment withdrawal (Mth 18).

Methods: AVERT enrolled pts who were MTX-naïve, anti-cyclic citrullinated peptide 2 seropositive (CCP2+), aged ≥18 yrs, with active synovitis ≥2 joints for ≥8 wks, DAS28 (CRP) ≥3.2, and disease onset of ≤2 yrs. Pts were randomized to 12 mths of weekly SC abatacept (125 mg) + MTX, SC abatacept (125 mg) or MTX. All RA treatment was withdrawn after 12 mths (abatacept immediately, MTX and steroids over 1 mth) in pts with DAS28 (CRP) <3.2. Percentages (%) of pts achieving DAS28 (CRP) <2.6 or <2.4, Major Clinical Response (MCR: ACR70 response for ≥6 consecutive mths), or remission (CDAI ≤2.8, SDAI ≤3.3, Boolean criteria) at Mth 12, and the % who maintained these reduced disease activity states at Mth 18 were analyzed.

Results: 351 pts with early RA were enrolled (n=119, abatacept + MTX; n=116, abatacept monotherapy; n=116, MTX alone). Mean characteristics at baseline were: disease duration 0.6 yrs, DAS28 (CRP) 5.4, HAQ-DI 1.4, 95.2% RF+ and anti-CCP2+). At Mth 12, higher % of pts in the abatacept + MTX group achieved DAS28 (CRP) <2.6 (primary analysis) as well as the more stringent clinical endpoint DAS28 (CRP) <2.4 or remission (CDAI, SDAI, Boolean), compared with MTX alone (Table). Rates of low disease activity and remission with abatacept monotherapy were intermediate between abatacept + MTX and MTX alone (Table). Higher % (95% CI) of abatacept-treated pts achieved MCR at Mth 12, compared with MTX alone (abatacept + MTX and abatacept monotherapy vs MTX alone: 31.9% [23.6, 40.3] and 17.2% [10.4, 24.1] vs 8.6% [3.5, 13.7]). Following treatment withdrawal, a small but higher % of abatacept-treated pts (with MTX or monotherapy) sustained low disease activity or remission than in the MTX group (Table).

Criteria	Reduced disease activity at Mth 12: Abatacept + MTX (n=119)	Reduced disease activity at Mth 12: Abatacept monotherapy (n=116)	Reduced disease activity at Mth 12: MTX (n=116)	Sustained levels of reduced disease activity (at both Mth 12 and 18): Abatacept + MTX (n=84)	Sustained levels of reduced disease activity (at both Mth 12 and 18): Abatacept monotherapy (n=66)	Sustained levels of reduced disease activity (at both Mth 12 and 18): MTX (n=73)
Primary analysis						
DAS28 (CRP) <2.6*	60.9% (52.0, 70.0)	42.5% (33.4, 51.6)	45.2% (36.1, 54.3)	14.8% (8.3, 21.3)	12.4% (6.3, 18.5)	7.8% (2.9, 12.7)
	Abatacept plus MTX vs MTX alone: OR (95% CI): 2.0 (1.2, 3.4); p=0.01			Abatacept plus MTX vs MTX alone: OR (95% CI): 2.5 (1.0, 6.2); p=0.045		
	Abatacept monotherapy vs MTX alone: OR (95% CI): 0.9 (0.6, 1.6)			Abatacept monotherapy vs MTX alone: OR (95% CI): 2.0 (0.8, 5.1)		
Stringent clinical endpoint						
DAS28 (CRP) <2.4*†	53.0% (43.9, 62.2)	38.1% (29.1, 47.0)	36.5% (27.7, 45.3)	13.0% (7.5, 20.6)	9.7% (5.0, 16.8)	3.5% (1.0, 8.7)
	Abatacept plus MTX vs MTX alone: OR (95% CI): 2.1 (1.3, 3.7); p=0.006			Abatacept plus MTX vs MTX alone: OR (95% CI): 7.3 (2.1, 25.3); p=0.002		
	Abatacept monotherapy vs MTX alone: OR (95% CI): 1.1 (0.7, 1.9)			Abatacept monotherapy vs MTX alone: OR (95% CI): 5.1 (1.4, 18.2)		
Stringent remission criteria						
CDAI ≤2.8	42.0%‡ (33.2, 50.9)	31.0% (22.6, 39.5)	27.6% (19.5, 35.7)	9.2% (4.0, 14.5)	9.5% (4.2, 14.8)	5.2% (1.1, 9.2)
SDAI ≤3.3	42.0%‡ (33.2, 50.9)	29.3% (21.0, 37.6)	25.0% (17.1, 32.9)	9.2% (4.0, 14.5)	7.8% (2.9, 12.6)	6.0% (1.7, 10.4)
Boolean remission	37.0%‡ (28.3, 45.7)	26.7% (18.7, 34.8)	22.4% (14.8, 30.0)	6.7% (2.0, 12.8)	6.0% (2.5, 12.0)	1.7% (0.2, 6.1)

OR, odds ratio
Percentages calculated using all randomized patients (N=351), unless otherwise stated. Data given as % (95% CIs).
*Percentages from adjusted logistic regression analysis.
†Percentages calculated using 115 (abatacept plus MTX) or 116 (abatacept monotherapy and MTX-alone treatment arms) patients.
‡p<0.05 for treatment difference vs MTX (95% CI for the estimate of treatment difference did not cross 0)

Conclusion: In early RA, abatacept + MTX for 12 mths resulted in higher rates of low disease activity and remission according to stringent criteria, than MTX alone. Few pts who achieved these stringent clinical measures at 12 mths could maintain them 6 mths after all RA treatment had been withdrawn. These findings indicate that treatment with abatacept + MTX early in the course of RA can achieve high remission rates at 12 mths, which may be sustained on withdrawal of all RA therapy in a small but higher proportion of pts than using MTX alone.

References:
1. Westhovens R, et al. *Ann Rheum Dis* 2009;**68**:1870–7.
2. Emery P, et al. *Ann Rheum Dis* 2010;**69**:510–6.

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The Efficacy and Safety of Tocilizumab Subcutaneous Q2W and Following Escalation from Q2W to QW Therapy in Combination with Traditional Dmards in Patients with Moderate to Severe Rheumatoid Arthritis at 96 Weeks. Alan Kivitz[1], Ewa Olech[2], Michael A. Borofsky[3], Beatriz M. Zazueta[4], Federico Navarro-Sarabia[5], S. C. Radominski[6], Joan T. Merrill[7], Jinglan Pei[8], Lucy Rowell[9], Clare Nasmyth-Miller[9], Sunethra Wimalasundera[9] and Janet E. Pope[10]. [1]Altoona Arthritis & Osteoporosis Center, Duncansville, PA, [2]University of Nevada School of Medicine, Las Vegas, NV, [3]Clinical Research Center of Reading, Reading, PA, [4]Centro de Investigacion en Enfermedades Reumaticas, Mexicali, Mexico, [5]University Hospital Virgen Macarena, Sevilla, Spain, [6]Universidade Federal do Paraná, Curitiba, Brazil, [7]Oklahoma Medical Research Foundation, Oklahoma City, OK, [8]Genentech, South San Francisco, CA, [9]Roche, Welwyn Garden City, United Kingdom, [10]St Joseph Health Care, London, ON.

Background/Purpose: The BREVACTA study assessed the efficacy and safety of subcutaneous tocilizumab (TCZ SC) in patients (pts) with RA who had an inadequate response to ≥ 1 DMARD (21% previously failed aTNF therapy). The primary objective assessed efficacy and safety to Week 24. Superiority over placebo (PBO) was observed, with a safety profile comparable to intravenous (IV) TCZ. We now report the efficacy and safety data for TCZ SC every 2 weeks (q2w) and TCZ weekly (qw) following escalation from either TCZ q2w or PBO q2w to Week 96.

Methods: This phase 3, randomized, multicenter, parallel arm study included a 24 week double blind, PBO controlled period followed by a 72 week open label phase and a further 8 weeks of safety follow up. Pts were initially randomized 2:1 to receive TCZ SC 162 mg q2w (n=437) or PBO SC q2w (n=219) via prefilled syringe (PFS) with prestudy DMARD(s). At Week 24, pts in both arms were rerandomized 1:1 to receive open label TCZ SC q2w via PFS or autoinjector pen. These data focus on pts who were rerandomised at Week 24 and received TCZ SC regardless of injection device. Escape therapy with TCZ SC qw was available for pts with an inadequate efficacy response from Week 12. At the first dose on escape therapy pts were rebaselined; efficacy is from time of escape up to Week 84 and safety is from time of escape to the end of the study.

Results: In the open label phase, 338 pts (77%) were maintained on TCZ SC q2w and 119 (54%) switched from the PBO to TCZ SC q2w. For the escape pts, in the double blind phase, 72 (16.5%) escaped from the TCZ arm and 90 (41.3%) from the PBO arm, while in the open label phase 27 (5.9%) escaped from the TCZ SC q2w arm. In the TCZ q2w arm, the proportion of pts who achieved ACR20/50/70 responses increased up to Week 96. In the TCZ q2w arm, the rates of AEs and SAEs, including serious infections, remained stable or decreased up to Week 96. No anaphylaxis or serious hypersensitivity occurred. By Week 96, 31 pts (7.1%) withdrew due to AEs and 7 pts (1.6%) died. Nine pts (2.1%) developed antiTCZ antibodies postbaseline without loss of efficacy or clinically significant hypersensitivity. For escape pts, the proportion of pts who achieved an ACR20 response increased after escape in both the TCZ or PBO arms; although there was a higher ACR20 response in escape pts from the PBO arm than the TCZ q2w arm (86.4% and 63%, respectively) at Week 84. The rate of AEs per 100 pt years, following escape therapy was similar between pts who previously received TCZ or PBO (331.9 and 360.5, respectively) and comparable to the TCZ q2w arm (332.8).

Conclusion: TCZ SC q2w demonstrated long term efficacy, including sustained ACR responses over 96 weeks. The AE profile for TCZ SC at 96 weeks was comparable to 24 weeks. For escape pts, there were improvements in ACR20 response rates in pts who previously received PBO and escalated from q2w to qw. TCZ SC will offer an alternative route of administration and the possibility of self administration for pts with RA.

	TCZ SC q2w + DMARD Week 24 (N = 437)		TCZ SC q2w + DMARD Week 96 (N = 437)
Randomized, n	437		437
Rerandomized at Week 24, n (%)	338 (77)		338 (77)
Intention to treat (ITT)[a]	437		338
Withdrew from TCZ SC q2w regimen (ITT)[a], n (%)	26 (6)		67 (15)
Withdrew from escape therapy,[c] n (%)	2 (<1)		2 (<1)
Efficacy (completer population)[b]		**N = 279**	
ACR20, %	61		82
ACR50, %	40		66
ACR70, %	20		48
Safety (safety population),[d] rate/ 100 PY (95% CI) [no. events]			
Patient years of exposure	182.68		615.95
N	437		437
Rate of AEs per 100 PY	439.56 (409.68, 471.04) [803]		332.82 (318.57,347.55) [2050]
Rate of SAEs per 100 PY	13.68 (8.86, 20.20) [25]		11.20 (8.72,14.18) [69]
Rate of serious infections per 100 PY	6.57 (3.39, 11.40) [12]		3.24 (1.98, 5.01) [20]
Rate of injection site reactions per 100 PY	31.20 (23.63, 40.43) [57]		19.81 (16.45, 23.65) [122]
Anti-TCZ antibodies, n (%)	7 (1.6)		9 (2.1)
Rate of withdrawals due to AEs	4.93 (2.25,9.35) [9]		5.52 (3.82, 7.71) [34]
Rate of deaths	1.64 (0.34, 4.80) [3]		1.14 (0.46,2.34) [7]

AE, adverse events; DMARD, disease-modifying antirheumatic drug; PY, patient years; q2w, every other week; SAE, serious adverse events; SC, subcutaneous; TCZ, tocilizumab.
[a] ITT population at Week 96 comprised all pts who completed Week 24, were re-randomized at Week 24, and received at least one dose of re-randomized study treatment (338 pts).
[b] Completer population included all patients who met the ITT criteria and additionaly completed up to Week 96 (279 pts).
[c] Escape therapy with TCZ SC qw (PFS) was available for pts who had <20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) between Weeks 12 −48 or who had <70% improvement from baseline in both SJC and TJC after Week 48, could receive open-label TCZ SC 162 mg every week (qw). Escape pts were not rerandomized to PFS or AI at Week 24 and remained on TCZ SC qw using the PFS for the remainder of the study. Escape pts were rebaselined, such that their first dose on qw = baseline.
[d] The safety population included all pts (n = 437) who received at least one dose of study drug and had at least 1 post-dose safety assessment.

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Treatment Strategy for Maximizating the Effect of Adalimumab in Japanese Patients with Rheumatoid Arthritis : Retrospective Analyses of Data Collected from the Patient Treated with Adalimumab in Routine Clinical Practice in Hamamatsu Area. Toshiaki Miyamoto. Seirei Hamamatsu General Hospital, Hamamatsu, Japan.

Background/Purpose: Adalimumab (ADA) showed highly efficacious in rheumatoid arthritis (RA) in the clinical trials, although there is little evidence in daily clinical practice. The clinical usefulness and treatment continuation rate of 52 weeks of a ADA treatment in rheumatoid arthritis (RA) patients were investigated over time.

Methods: The subjects were 124 analyzable patients that had been introduced to ADA treatment at this institution from May 2009 to October 2012. In patients' background, mean age was 53 years, mean duration of illness 7.2 years, rate of concomitant MTX treatment 96% (116 patients), mean MTX dose 11.4 mg/week, and rate of concomitant PSL treatment 16.1%. Of these patients, 35 had a duration of illness below 2 years (<2 group), 89 a duration of at least 2 years (≥ 2 group), 85 were Bio Naive (N group), 39 were Switch (S group), 95 received MTX ≥10 mg/week (≥10 group), and 24 received MTX<10 mg/week (<10 group). There was no significant difference in baseline disease activity between the groups. Treatment efficacy up to 52 weeks after ADA treatment in each group was investigated comparatively.

Results: The DAS28 (CRP) remission rate for all the patients at 4, 24, and 52 weeks was 36%,62%,and 70%, respectively, showing that from 4 weeks, about 40% of the patients achieved clinical remission. Changes in DAS 28 (CRP) remission rates for the <2 and ≥2 groups at 4, 24, and 52 weeks were 29% vs. 39%, 69% vs. 60%, and 83% vs. 65%, respectively. Similarly, changes in DAS 28 (CRP) in the N and S groups were 34% *vs* 41%, 67% *vs* 51%, and 74% *vs* 62%, respectively; in the ≥10 and < 10 mg groups, they were 43% *vs* 13%, 72% *vs* 25%, and 77% *vs* 46%, respectively, showing that the values were significantly high in the ≥ 10 group at all the time points. Moreover, HAQ remission rate for the overall patients at 52 weeks was 82%, and treatment continuation rate was 72%. Excluding the patients that discontinued treatment for reasons such as hospital transfer, of the 82% on concomitant MTX treatment, response was good in 90%.

Conclusion: With ADA, remission could be induced from very early on in the treatment at 4 weeks in about 40% of the patients. The best way to apply ADA treatment is to use it concomitantly with an adequate dose of MTX in early-stage RA and Bio Naïve patients. By so doing, the potential of ADA can be exploited maximally.

Disclosure: T. Miyamoto, None.

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Effect of Teriparatide in Patients with Osteoporosis and Rheumatoid Arthritis. Robin Dore[1], Kenneth G. Saag[2], Guillermo Valenzuela[3], Kathleen Taylor[4], Qiu He[4], Jahangir Alam[4] and Kelly D. Krohn[5]. [1]University of California, Los Angeles, CA, [2]The University of Alabama at Birmingham, Birmingham, AL, [3]Integral Rheumatology and Immunology Specialists, Plantation, FL, [4]Eli Lilly and Company, Indianapolis, IN, [5]Eli Lilly and Company, LLC, Indianapolis, Indiana, Indianapolis, IN.

Background/Purpose: A common complication in rheumatoid arthritis (RA) is osteoporosis (OP) with increased incidence of fragility fractures. RA is the only disease specifically included in the World Health Organization fracture prediction algorithm, FRAX®. The effect of teriparatide (TPTD) on the incidence of clinical vertebral (VERT) and nonvertebral (NV) fragility fractures, bone mineral density

(BMD), and safety was examined in the subgroup of OP patients with RA enrolled in the DANCE trial.

Methods: This was a post hoc analysis of patients with RA enrolled in the DANCE open-label, prospective, observational study, treated with TPTD 20 mg/day for ≤2 years (treatment phase), and followed for up to 2 more years (cessation phase). Mixed model repeated measures analysis was used to evaluate BMD changes over 18 months (mo). Incident rates of new clinical VERT or NV fragility fractures (traumatic fractures excluded) after 6–24 mo vs 0–6 mo of TPTD therapy were compared using a Poisson regression model. Time to new NV fragility fracture was compared using Kaplan-Meier analysis. Rates of incident NV fractures were assessed at intervals over treatment and cessation phases vs the first 6-mo treatment (reference) period.

Results: Of 4085 patients who received ≥1 dose of TPTD, 544 had documented RA. Patients with vs without RA at baseline had similar age (mean [SD] age, 68.6 [11.5] vs 67.8 [11.9] years), but significantly more history of prior NV fractures (60.8% vs 55.4%, p=0.017), higher L1-L4 T-scores (−2.21 [1.44] vs -2.51 [1.36], p<0.001), more baseline clinical conditions (3.1 [1.4] vs 1.6 [1.3], p<0.001), and more glucocorticoid use (32.5% vs 7.1%, p<0.001). Mean TPTD exposure was similar (523.0 [303.9] vs 545.4 [288.4] days). Over 18 mo, bone density in the spine, femoral neck, and total hip increased similarly in patients with vs without RA (all p-values>0.1). Incident rates of new VERT with or without back pain or NV fragility fractures decreased in mo 6–24 vs the first 6 mo. There was no significant difference in the decrease in fracture incidence in mo 6–24 vs the first 6 mo in the patients with RA compared with those without, regardless of the type of fracture (all interaction p>0.15). There was no difference in the time to a new NV fragility fracture (log-rank p>0.2) by RA status. NV fracture incidence rates/100 patient years decreased vs reference baseline during treatment and stayed down during cessation phase vs reference baseline (Figure 1). In the overall DANCE study, TPTD was well tolerated and no new significant safety findings were observed.

Conclusion: Patients with rheumatoid arthritis receiving teriparatide showed similar increases in BMD at the spine, femoral neck, and total hip and similar reduction over time in the incidence of NV fractures compared with osteoporosis patients without RA. Compared to baseline, the incidence of NV fractures remained down after drug cessation.

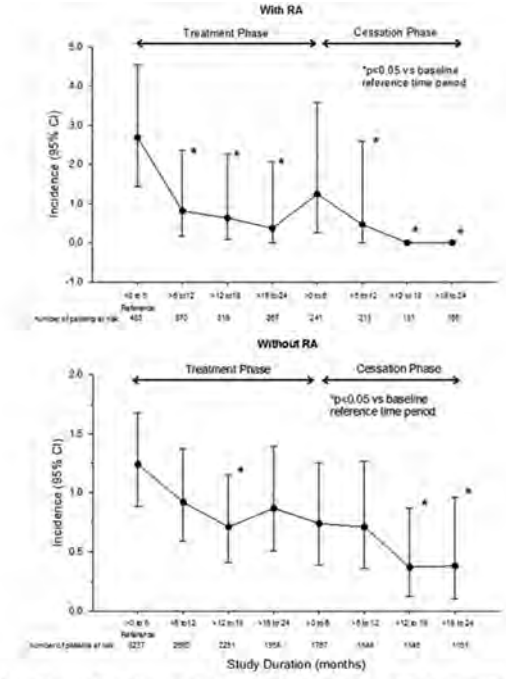

Figure 1. Incidence of New Nonvertebral Fracture During Treatment With Teriparatide and After Treatment Cessation in Patients with Rheumatoid Arthritis and without Rheumatoid Arthritis. Incidence = Number of patients with new nonvertebral fractures/Number of patients at risk × 100. CIs were derived from Clopper Pearson method; *p* value was derived from a one-sample binomial proportion test vs. the first period incidence rate

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The First, Multicenter, Double-Blind, Randomized, Parallel-Group Study of Certolizumab Pegol in Early Rheumatoid Arthritis Demonstrates Inhibition of Joint Damage Progression.

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Background/Purpose: The efficacy and safety of certolizumab pegol (CZP)+methotrexate (MTX) therapy compared to MTX alone, in Japanese MTX-naïve early rheumatoid arthritis (RA) patients (pts) with poor prognostic factors from the C-OPERA trial, have not been previously reported.

Methods: Pts with ≤12 months persistent arthritis fulfilling 2010 ACR/EULAR classification criteria[1] were enrolled in this multicenter, double-blind, randomized study (NCT01451203). Eligible pts were MTX-naïve, with at least moderate disease activity (DAS28[ESR]≥3.2), high-positive anti-CCP (>3xULN), and were either rheumatoid factor positive or had bone erosion on radiographs of hands/feet. Pts were randomized 1:1 to CZP+MTX or placebo (PBO)+MTX. Unless precluded by tolerability, MTX dose was rapidly escalated to 16mg by Week (Wk) 8. The primary endpoint was change from baseline (CFB) in van der Heijde modified total Sharp score (mTSS) at Wk52. Secondary endpoints were CFB in mTSS at Wk24, and clinical remission rates by DAS28[ESR], ACR/EULAR (SDAI), and ACR/EULAR (Boolean) at Wk24 and 52. Post-hoc analyses assessed whether higher radiographic progression amongst PBO+MTX treated pts occurred within certain categories of baseline (BL) factors (eg. CRP, HAQ-DI, MMP-3).

Results: A total of 316 pts (CZP+MTX: n=159, PBO+MTX: n=157) were randomized and received ≥1 dose of study drug. Groups were well-balanced at BL, with mean (±SD) age: 49.2±10.5 yrs, symptom duration: 4.1±2.9 months, DAS28[ESR]: 5.45±1.15 and mTSS: 5.55±12.43. Average MTX dose was 11.6±2.8 mg/wk. CFB in mTSS at Wk52 and 24 for CZP+MTX were, on average, 0.36 and 0.26, and for PBO+MTX were 1.58 and 0.86, respectively (Figure). Statistical comparison of CFB in mTSS by nonparametric approach (ANCOVA on ranks) was significantly greater for CZP+MTX than PBO+MTX at Wk52 (p<0.001) and Wk24 (p=0.003) (Figure). CZP+MTX remission rates were significantly greater than for PBO+MTX at Wk52 (SDAI: 57.9% vs 33.8% [p<0.001]; Boolean: 45.3% vs 28.0% [p=0.002]; DAS28[ESR]: 57.2% vs 36.9% [p<0.001]) and at Wk24 (SDAI: 48.4% vs 29.3% [p<0.001]; Boolean: 36.5% vs 22.3% [p=0.007]; DAS28[ESR]: 52.8% vs 30.6% [p<0.001] Fisher's Exact test). Higher BL DAS28[ESR], CRP, mTSS, HAQ-DI and serum MMP-3 seemed associated with more radiographic progression in the PBO+MTX group, whereas CZP+MTX still inhibited progression of structural damage in these pts despite this higher risk of progression (Table). CZP+MTX was well tolerated, with no unexpected safety signals observed.

Conclusion: CZP+MTX was significantly more effective than PBO+MTX in inhibiting disease progression, as well as in achieving clinical remission, in MTX-naïve Japanese early RA pts with poor prognostic factors.

Reference

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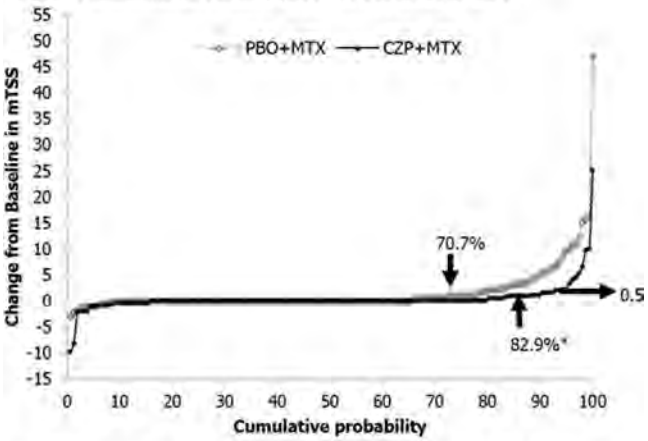
Figure: Cumulative probability plot of CFB in mTSS at Wk52



The percentage of patients with non-progression at Wk52 was significantly higher in CZP+MTX as compared to PBO+MTX (70.7% vs 82.9%; Fisher's exact test; *p=0.011).

Table: Sub-group analysis of CFB in mTSS at Wk52 by baseline characteristics

Baseline characteristics	PBO+MTX		CZP+MTX		P-value[a]
	n	Mean±SD	n	Mean±SD	
DAS28(ESR)					
≤3.2	3	0.00±0.00	5	0.10±0.22	NA[b]
>3.2-≤5.1	54	0.71±3.14	60	0.20±0.83	0.804
>5.1	100	2.10±5.59	93	0.49±3.46	<0.001
CRP (mg/dL)					
≤0.5	69	0.39±2.12	75	0.13±0.74	0.652
>0.5-≤1.0	27	1.85±3.23	22	0.00±0.52	0.003
>1.0	61	2.82±6.97	61	0.78±4.25	0.007
mTSS					
≤0.5	56	0.42±0.99	55	0.20±0.64	0.120
>0.5	101	2.23±5.93	103	0.45±3.32	0.002
HAQ-DI					
≤0.5	43	0.52±2.71	43	0.27±1.61	0.827
>0.5-≤1.0	41	1.60±4.09	44	0.10±0.98	0.010
>1.0	73	2.21±6.04	71	0.58±3.76	0.004
MMP-3 (ng/mL)					
≤50	33	0.01±0.42	36	0.09±0.50	0.910
>50-<100	50	1.44±3.17	59	0.31±0.97	0.176
≥100	74	2.38±6.47	63	0.57±4.17	<0.001

[a] P-value for difference between CZP+MTX vs PBO+MTX (ANCOVA on the ranks with treatment as factor and baseline rank as covariate); [b] The calculation is not applicable due to the low number of pts in this subgroup category.

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Post-Marketing Surveillance of Efficacy and Safety of Tacrolimus Add-on Therapy in Japanese Rheumatoid Arthritis Patients Who Failed to Show an Adequate Response to Biological Dmards : Interim Analysis.

Tsutomu Takeuchi[1] and Kota Ishida[2]. [1]School of Medicine, Keio University, Tokyo, Japan, [2]Astellas Pharma Inc., Tokyo, Japan.

Background/Purpose: Tacrolimus (TAC) is an immunosuppressive macrolide that blocks T cell activation by specifically inhibiting calcineurin, and it is widely administered following organ transplantation. TAC was approved in Japan for the treatment of rheumatoid arthritis (RA) in 2005. We report here the interim results of Post-marketing surveillance we have been conducting to evaluate the safety and efficacy of TAC adding on to biological disease-modifying anti-rheumatic drugs (DMARDs) in Japanese RA patients who failed to show an adequate response to biological DMARDs in a real clinical setting.

Methods: The observation period of this study was 24 weeks. One hundred and seventy-two patients were included in the safety population and 165 patients were included in the efficacy population. An inadequate response to biological DMARDs was defined as that all of the following conditions were met: Simplified Disease Activity Index (SDAI) >3.3 when TAC was started; Both tender joint count and swollen joint count were the same or increased compared to those at four to eight weeks prior to TAC; Biological DMARDs were used for at least eight weeks prior to TAC. Efficacy was evaluated using the SDAI, DAS28-CRP (Disease Activity Score 28-C-reactive protein), EULAR (European League Against Rheumatism) response criteria. SDAI improvement was defined as SDAI≤11. DAS28-CRP improvement was defined as DAS28-CRP <2.7.

Results: Mean age was 61.9 years and the mean disease duration was 11.0 years. The mean TAC dose was 1.3 mg during the observation period. Adverse drug reactions (ADRs) occurred in 18 patients and serious ADRs was observed in two patients (Herpes zoster, Myocardial infarction). One patient (age 76) who developed herpes zoster was resolved during the observation period. One patient (age 89) who developed myocardial infarction died on the day when it occurred. SDAI remission rate was 13.3% at week 24, SDAI improvement rate was 58.5% at week 24 and the mean SDAI was decreased from 20.1 at baseline to 11.7 at week 24. DAS28-CRP remission rate was 33.3% at week 24, DAS28-CRP improvement rate was 48.9% at week 24 and the mean DAS28-CRP was decreased from 4.0 at baseline to 2.9 at week 24. Based on EULAR response criteria, moderate or good response rate was 69.8% at week 24.

Conclusion: TAC is well tolerated and effective when added on to the biological DMARDs in Japanese RA patients who failed to achieve an adequate response to biological DMARDs in a real clinical setting.

Disclosure: T. Takeuchi, AbbVie GK, Asahi Kasei Medical K.K, Astellas, Astra Zeneca, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly Japan K.K, Mitsubishi Tanabe Pharma Co, Novartis Pharma K.K, 5, AbbVie GK, Astellas, Bristol-Myers Squibb K.K, Chugai Pharmaceutical Co,,Ltd., Daiichi-Sankyo Co,,Ltd.,, Eisai Co,, Janssen Pharmaceutical K.K, Mitsubishi Tanabe Pharma Co,, Pfizer Japan Inc, Takeda Pharmaceutical Co., 8, AbbVie GK, Astellas, Bristol-Myers Squibb K.K, Chugai Pharmaceutical Co,,Ltd., Daiichi-Sankyo Co,,Ltd.,, Eisai Co,,Mitsubishi Tanabe Pharma Co,, Pfizer Japan Inc, Takeda Pharmaceutical Co. Santen Pharmaceutical Co., Ltd., Teijin Pharma Ltd., Asahikasei P, 2; **K. Ishida**, Astellas Pharma Inc., 3.

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Efficacy and Tolerability of Subcutaneous Methotrexate for Inflammatory Arthritis: A Retrospective Observational Cohort Study.

Jessica Gunn, Aikaterina Panopolou and Alan Steuer. Wexham Park Hospital, Slough, United Kingdom.

Background/Purpose: Methotrexate (MTX) monotherapy or MTX in combination with other conventional and biologic disease-modifying anti-rheumatic drugs (DMARDs) is standard treatment for patients with inflammatory arthritis. A significant number of patients discontinue therapy with oral (PO) MTX because of intolerance or a lack of efficacy. Standard practice at our institution involves switching such patients to subcutaneous (SC) MTX prior to the addition of other agents. This study was designed to assess the therapeutic outcomes of this approach in the outpatient setting.

Methods: We retrospectively reviewed electronic medical records within our patient cohort from 2001 to the present, and included patients who switched from PO to SC MTX. Records were analyzed for baseline demographics, reasons for switching to SC MTX, doses of PO and SC MTX at the time of the switch, duration of SC MTX use, reasons for discontinuation of SC MTX (if applicable), and whether the addition of biologic agents was required.

Results: The records of 240 patients who switched to SC MTX were examined. Fifty-eight patients were excluded because of incomplete data. Of the 182 patients included, 125 (68%) were female, and the average age at starting SC MTX was 52.5 years (range 17–82). Underlying diagnoses included rheumatoid arthritis (n=144), psoriatic arthritis (n=20), juvenile idiopathic arthritis (n=7), ankylosing spondylitis (n=2), undifferentiated inflammatory arthritis (n=6), systemic lupus erythematosus (n=1), and vasculitis (n=2). Reasons for switching from PO to SC MTX included intolerance (n=55), inefficacy (n=118) and unknown (n=9). One hundred ten patients (60%) were receiving no other DMARDs at the time of the switch. In the majority of the remaining patients (n=60), MTX was used in combination with sulfasalazine (n=21), hydroxychloroquine (n=21), prednisolone (n=11), leflunomide (n=4), or anti-tumor necrosis factor-α therapies (n=3). At the time of switching patients were taking an average dose of 20mg/week PO MTX and were switched to an average dose of 15mg/week SC MTX (range for both 5–25mg/week). One hundred thirty-three (73%) patients remain on SC MTX to date; 49 patients discontinued SC MTX because of intolerance (n=26), adverse drug reaction (n=10), inefficacy (n=6), disease remission (n=2), or undocumented reasons (n=5). Thirty-nine percent of those who discontinued SC MTX required the addition of a biologic, compared with 28% of those who continued with SC MTX. Sixty-five percent of those who switched to SC MTX because of intolerance were able to continue with this drug, for an average duration of 46 months (range 2–144 months) to date; 40 to 45% of those who switched to SC MTX because of intolerance or inefficacy, respectively, did not require the addition of another DMARD or biologic agent.

Conclusion: This evidence strongly supports the use of SC MTX as a tolerable and efficacious alternative after failure of PO MTX. After the switch to SC MTX, 65% of patients who were intolerant of PO MTX continued with MTX, either as monotherapy or in combination with other DMARDs or biologic agents. Furthermore, patients who continued with SC MTX were less likely to require biologic agents. Further evaluation of this approach may be warranted.

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Multiple Approaches for Implementation of Long-Term Efficacy: Interpretation of Certolizumab Pegol Data in Rheumatoid Arthritis Case Study. Edward C. Keystone[1], Josef S. Smolen[2], Vibeke Strand[3], Thomas Kumke[4], Irina Mountian[5], Susan Walker[6] and Robert B. M. Landewé[7]. [1]Mount Sinai Hospital, Toronto, ON, [2]Medical University of Vienna and Hietzing Hospital, Vienna, Austria, [3]Biopharmaceutical Consultant, Portola Valley, CA, [4]UCB Pharma, Monheim, Germany, [5]UCB Pharma, Brussels, Belgium, [6]UCB Pharma, Raleigh, NC, [7]Amsterdam Rheumatology Center, Amsterdam, Netherlands.

Background/Purpose: Use of imputed or observed data, as well as the patient (pt) population evaluated (eg. intention-to-treat [ITT], completer), affects the interpretation of long-term efficacy data. Statistical analysis of data from long-term studies must consider the impact of missing values, which result from pt drop-out due to various reasons. Imputation methods should link such reasons with assumptions made for missingness. Missing completely at random (MCAR) approaches (eg. last observation carried forward [LOCF], non-responder imputation [NRI]), assume that missingness is independent of observed and unobserved outcomes. In contrast, missing at random (MAR) methods (eg. mixed models with repeated measures [MMRM]) assume that missingness is dependent on observed outcome.

Methods: Data from pooled analysis of Rheumatoid Arthritis Prevention of Structural Damage (RAPID) 1 and 2 RCTs and open-label extensions (OLE) (NCT00152386[1], NCT00175877[2], NCT00160602[3] and NCT00160641[4]) were used. RAPID1[1] and 2[3] evaluated safety and efficacy of certolizumab pegol (CZP) with methotrexate. Efficacy data were collected up to 256 weeks (wks) of CZP exposure for clinical measures, including DAS28(ESR) (LOCF), HAQ-DI (LOCF) and ACR20/50/70 (modified NRI [mNRI]). Observed and imputed (MCAR, MAR) data are presented for CZP ITT (all pts randomized to CZP in RCT) and CZP Completer (CZP ITT pts who completed RCT and reconsented into OLE) populations.

Results: Improvements from baseline in DAS28(ESR) and HAQ-DI were evident in CZP Completer and ITT populations at 256 wks. The use of LOCF and MMRM imputation gave results consistent with observed data (Table). Long-term CZP exposure resulted in sustained ACR response. mNRI determined rates were, per definition, lower than observed data (Table), but were in line with data observed in blinded periods.[1,3] MMRM imputation followed long-term mean treatment response more closely and was more homogeneous between patient populations compared to LOCF/mNRI. Different reasons for discontinuation lead to distinct differences in imputed results. Imputed mean response was more homogeneous in the completer population.

Conclusion: Considering multiple populations and imputation approaches enables more reliable long-term efficacy data interpretation. Pooled RAPID1 and 2 results revealed similar patterns between observed and imputed data, although differences were observed between different imputation methods and reasons for withdrawal. Analysis of the ITT population gives a less biased estimate of efficacy compared with CZP Completers. Nonetheless, results were consistent with maintained improvements in RA signs and symptoms following 256 wks of exposure to CZP.

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3. Smolen J.S. Ann Rheum Dis 2009;68:797–804
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Table 1. Comparison of observed and imputed efficacy data following 256 wks of CZP treatment

Efficacy Outcome	CZP Completers Observed, n		MCAR (n=850)	MMRM (n=850)	CZP ITT population Observed, n		MCAR (n=1275)	MMRM (n=1275)
mean change from BL DAS28(ESR)[a,b]	−3.59	n=314	−3.35	−3.54	−3.51	n=417	−3.01	−3.39
mean change from BL HAQ-DI[a,b]	−0.81	n=343	−0.73	−0.77	−0.74	n=456	−0.63	−0.69
% ACR20[c,d]	87.9	n=348	70.7	90.4	83.6	n=464	57.7	88.5
% ACR50[c,d]	69.3	n=348	53.2	67.0	63.1	n=464	41.8	58.7
% ACR70[c,d]	42.0	n=348	34.0	37.9	36.9	n=464	25.9	30.4

[a] Data is presented as mean change from RCT BL; [b] LOCF MCAR imputation was used for continuous outcomes; [c] Data is presented as % response compared to RCT BL; [d] mNRI (MCAR) was used for binary outcomes; BL: baseline

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2476 WITHDRAWN

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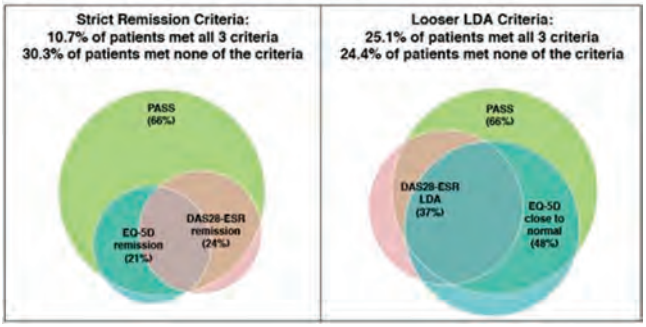
Integrating Treatment Goals of Physicians, Patients, and Payers during Treatment with Golimumab in Patients with Rheumatoid Arthritis. B Combe[1], DJ Veale[2], R Burgos-Vargas[3], G Sz″ucs[4], M Leirisalo-Repo[5], R Yao[6], S Huyck[6], R Lyu[6], M Govoni[7], N Vastesaeger[8] and HH Weng[6]. [1]Monpellier University Hospital, Montpellier, France, [2]St. Vincent's University Hospital, Dublin, Ireland, [3]Cliditer S.A. de C.V. and Hospital General de Mexico, Mexico City, Mexico, [4]University of Debrecen Faculty of Medicine, Debrecen, Hungary, [5]Helsinki University Central Hospital, Helsinki, Finland, [6]Merck & Co., Inc., Whitehouse Station, NJ, [7]MSD Italy, Rome, Italy, [8]MSD Belgium, Brussels, Belgium.

Background/Purpose: Physicians, patients, and payers may have different ideas about what constitutes successful treatment and how treatment goals should be defined for rheumatoid arthritis (RA). This analysis was designed to evaluate overlap between attained treatment goals that are important to physicians, patients, and payers after 6 months of add-on golimumab (GLM) in patients with active RA, and to determine baseline predictors of patients who achieve all 3 goals.

Methods: GO-MORE was an open-label, multinational, prospective study in biologic-naïve patients with active RA (28-joint disease activity score using erythrocyte sedimentation rate [DAS28-ESR] ≥3.2) despite disease-modifying antirheumatic drug (DMARD) treatment. Patients received 50-mg subcutaneous (SC) GLM once monthly for 6 months. Efficacy outcomes including DAS28-ESR, patient-acceptable symptom state (PASS; 1 yes/no question of patient satisfaction with their current disease state), and EuroQol 5-dimension (EQ-5D) were evaluated at month 6. The overlap in achievement of strict remission treatment goals was evaluated (DAS28-ESR remission, normal EQ-5D [≥.8], and met PASS); looser low disease activity (LDA) goals were also evaluated (DAS28-ESR LDA, EQ-5D near normal [≥.7], and met PASS). A multivariate regression analysis identified baseline predictors of patients who achieved the intersection of the 3 criteria.

Results: In 3280 efficacy-evaluable patients, mean disease duration was 7.6 years; mean DAS28–ESR was 5.97 (SD=1.095). As previously reported, 23.9% of 3280 efficacy-evaluable patients achieved remission, and 37.4% achieved LDA (based on DAS28-ESR) at month 6.[1] 21% of patients achieved normal QoL, and 48% achieved close-to-normal QoL (EQ-5D ≥.7). 66.0% of patients achieved PASS. Overlap in patients who achieved each goal is shown (figure). 10.7% of patients (350/3280) met all 3 strict criteria, and 25.1% (823/3280) met all 3 looser criteria. Significant baseline predictors of achieving all 3 strict remission criteria were absence of comorbidities; lower DAS28, Health Assessment Questionnaire (HAQ), and swollen joint count scores; and greater anti-cyclic citrullinated peptide levels and EQ-5D Index scores. When PASS was replaced with HAQ ≤.5 (minimal or no functional impairment, achieved by 37.4% of patients) in either the set of strict or looser criteria, the percentage of patients who met all 3 criteria was similar to when PASS was used.

Figure. Overlap in Achieving Strict and Looser Treatment Goals



Conclusion: In patients with active RA who failed ≥1 DMARD and received add-on GLM for 6 months, overlap in achievement of LDA goals of physicians, patients, and payers was attained in 25.1% of patients. Overlap was smaller when strict remission goals were evaluated. Several measures of lower disease activity at baseline predicted achievement of all 3 strict remission criteria.

Reference:

1. Combe B et al. *Ann Rheum Dis.* doi:10.1136/annrheumdis-2013–203229.

Disclosure: B. Combe, BMS, Lilly, Merck, Pfizer, Roche-Chugai, and UCB, 5; **D. Veale**, Abbott, Janssen, MSD, Pfizer, and Roche, 2, MSD, Pfizer, Roche, and UCB, 5; **R. Burgos-Vargas**, Abbvie, BMS, Janssen, MSD, Pfizer, Roche, and UCB, 9; **G. Szücs**, None; **M. Leirisalo-Repo**, MSD, 5; **R. Yao**, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, 3; **S. Huyck**, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, 3; **R. Lyu**, Employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, 3; **M. Govoni**, MSD Italy, 3; **N. Vastesaeger**, MSD Belgium, 3; **H. Weng**, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, 3.

2478

Analysis of the Clinical Sustained Response after Retreatment with a Lower Dose of Rituximab in Patients with Chronic Inflammatory Arthropathies. M. Victoria Hernández[1], Andrea Cuervo[1], Sonia Cabrera[1], Jose Inciarte-Mundo[1], Julio Ramirez[1], Virginia Ruiz-Esquide[1], Juan D. Cañete[2] and Raimon Sanmarti[1]. [1]Hospital Clínic of Barcelona, Barcelona, Spain, [2]Hospital Clinic, Barcelona, Spain.

Background/Purpose: The dosage of rituximab (RTX) approved for the treatment of active rheumatoid arthritis (RA) is two intravenous (iv.) 1 g infusions, separated by two weeks. However, it has recently been reported that, after initial treatment with the standard dosage, RTX retreatment at a lower dose may have comparable efficacy and be more cost-effective[1]. Our objective was to analyse whether retreatment with RTX at a lower dose (1 g total dose) is equally effective in maintaining the clinical response as the standard dosage of cycles of 2g.

Methods: Observational, descriptive, retrospective study. We analysed the long-term efficacy of RTX retreatment with 1 g (total dose) cycles (2 iv. 500 mg infusions separated by 2 weeks; or 1 g iv single infusion) in routine clinical practise. All patients had initially been treated with at least one 2g (total dose) cycle, with a good response according to clinical judgment. The main efficacy variables were: mean DAS-28 score at the last follow-up visit and at the follow-up visit previous to RTX dose reduction; need to increase the RTX dose to the standard 2g dose; treatment withdrawal due to inefficacy. Secondary variables were: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values after retreatment in order to analyse variations between the last follow-up visit (dosage of 1g total dose) and the follow-up visit previous to RTX dose reduction (2g total dose).

Results: From 2006 to 2013, 53 patients (86.8% RA) attended by our Department received at least, one cycle of 2g RTX (standard dosage); 41 out of 53 (77.3%) had a good response. Since September 2011, RTX retreatment was administered at a reduced 1g (total dose)/ cycle in 29 patients (mean age: 59.5±10.4 years; 86.2% female; disease duration 11.7±7.9 years; 79.3% positive for rheumatoid factor/anti-cyclic citrullinated peptides). 79.3% of patients received concomitant disease-modifying antirheumatic drugs (DMARD) and 86.2% glucocorticoids. The mean number of RTX cycles received per patient before RTX dose reduction was 2.03±1.35. No increase in the DAS-28 score was found at the last follow-up visit (2.85±0.98) compared to the follow-up visit previous to RTX dose reduction (3.66±1.17) ($p<0.0001$). After a follow-up of 20.7±9.3 months, none of the 29 patients required a RTX dose increase or treatment withdrawal due to loss of efficacy. No significant differences were observed in ESR and CRP values between the last follow-up visit and the follow-up visit previous to the RTX dose reduction (mean ESR: 18.1±12.3 vs 18.4±13.1 mm/h, respectively; $p=0.50$; mean CRP: 0.6±0.8 vs 0.9±1.2 mg/dl, respectively; $p=0.07$). We observed no increase in the frequency of RTX cycles required after dose reduction (8.5±3.2 (1g total dose) vs 8.2±2.8 (2g total dose) months).

Conclusion: After an initial favourable response to the standard dose of RTX, posterior retreatment with a total dose of 1g/cycle maintained the clinical response over time and was more cost-effective.

Reference:

[1]Mariette X et al. Ann Rheum Dis. 2013 May 30

Disclosure: M. V. Hernández, None; **A. Cuervo**, None; **S. Cabrera**, None; **J. Inciarte-Mundo**, None; **J. Ramirez**, None; **V. Ruiz-Esquide**, None; **J. D. Cañete**, None; **R. Sanmarti**, None.

2479

Utility of Adjustment of Administration Interval in Tocilizumab in Rheumatoid Arthritis. Shuntaro Saito, Keisuke Izumi, Yuko Kaneko, Katsuya Suzuki and Tsutomu Takeuchi. Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: Interleukin-6 (IL-6) is considered a key cytokine in the pathogenesis of rheumatoid arthritis (RA). Tocilizumab (TCZ) is a monoclonal antibody which binds to membrane-bound and soluble forms of human IL-6 receptor, and has proved to be effective in the treatment of RA. In the standard protocol for RA, TCZ is administered intravenously every four weeks. However, given that the impact of IL-6 presumably differs among patients, treatment might be optimized by shortening or prolonging the administration interval of TCZ. Here, we evaluated the usefulness of modifying the protocol based on the treat-to-target concept in daily practice.

Methods: We retrospectively surveyed all 453 patients treated with TCZ (8mg/kg) at our institution between 2008 and 2014. Patients administered TCZ at an interval of ≤ 3 weeks or ≥ 5 weeks were analyzed as the shortened or prolonged interval group, respectively. Clinical information, including disease activity, was collected and statistically analyzed.

Results: A) Patients administered TCZ at a shortened interval (administration interval ≤ 3 weeks).

Among 453 patients, 25 (5.5%) were administered TCZ at a shorter interval due to insufficient effectiveness after administration at a 4-week interval for a median of 33.8 weeks. Disease activity was significantly improved after two administrations at this shortened interval, with disease activity score (DAS) 28 changing from 5.10 to 3.40 ($p<0.05$). Among these

25 cases, interval could be returned to 4 weeks in 15. In contrast, the remaining 10 required continuous administration at a shortened interval for more than 1 year due to exacerbation of RA activity on return to a 4-week interval.

B) Patients administered TCZ at a prolonged interval (administration interval ≥ 5 weeks).

Sixty-three patients (13.9%) were administered TCZ at a prolonged interval, after having achieved remission after a median of 70.0 weeks at a 4-week interval. The prolonged interval ranged from 5 to 8 weeks. Of these 63 patients, 48 (76.2%) were able to continue TCZ administration at a prolonged interval for more than 1 year, while 15 (24.8%) required returning to a 4-week interval due to exacerbation of RA activity after a median of 51.1 weeks at a prolonged interval. All 15 cases achieved low disease activity equivalent to the original level before interval prolongation.

Conclusion: Our study highlighted the importance of administration interval in the effectiveness of TCZ in RA. Adjustment of interval according to disease activity in individual patients is a promising way to optimize treatment.

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2480

Is there a Difference in the Effectiveness in the Treatment of Rheumatoid Arthritis with Rituximab when Using a Dose of 1 or 2 Grams per Cycle? a Systematic Review. Ana M. Ortiz[1], María Piedad Rosario[2], Carmen Martínez[2] and Isidoro González-Alvaro[1]. [1]Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [2]Spanish Society of Rheumatology, Madrid, Spain.

Background/Purpose: Since the description of the efficacy of rituximab (RTX) in treating patients with rheumatoid arthritis (RA), the use of this drug has been extended. The recommendation in fact sheet is the administration of two infusions of 1 g in each cycle but some studies have used two infusions of 500 mg. Currently the most suitable pattern for its use is not established. The purpose of this work was to systematically review the published evidence to date regarding on the difference in efficacy in the treatment of RA with RTX when used at a dose of 2 × 500 mg (1 g) or 2 × 1000 mg (2 g) per cycle.

Methods: A sensitive search of all published studies on the difference in the efficacy of RTX in RA patients used at a dose of 1 and 2 g per cycle was performed in Medline, Embase and Cochrane Central databases since its inception until July 2013. We selected all studies involving adult patients with RA treated with RTX in which intervention was described as treatment with RTX at a dose of 1 g per cycle and comparator as the administration of RTX at a dose of 2 g per cycle. Any standardized measure of efficacy in RA was considered as outcome measure at two years of follow-up. Although meta analysis, systematic reviews, clinical trials and cohorts well designed were preferably selected, finally we also included open studies and all studies that showed a methodologically correct subanalysis related to the question even if it had not been his main objective. After removing duplicates, an initial selection by reading titles, a second selection after reading abstracts and, finally, full reading of selected studies, assessing the methodological quality by levels of the Oxford Centre for Evidence Based Medicine Evidence (2001 update) where applicable, was carried out. A manual search of the references of included studies was also performed.

Results: A total of 451 citations about the treatment of RA patients with RTX used at a dose of 1 and 2 g per cycle were identified, which were reduced to 46 after removing duplicates and selection by reading titles and abstracts. Of the 46 articles selected, finally 14 were included in the review, 3 reviews, 2 of them systematic and one not systematic, 5 corresponding to 4 clinical trials, 3 open studies and 3 abstracts, two of them about the same retrospective cohort and, the third one, an open study previously included as a publication. Although published outside the period included in this review, an article about a systematic review and meta-analysis was included because it provides valuable information for the same.

Conclusion: RTX shows an equivalent overall clinical efficacy administered at doses of 1 and 2 g per cycle in the treatment of RA patients (level of evidence 1a, grade of recommendation A). However, there may be differences in extreme efficacy parameters with trend, not statistically significant, to a more ACR70 response or EULAR good response at the dose of 2 g per cycle.

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Disclosure: A. M. Ortiz, Spanish Society of Rheumatology, 2; **M. P. Rosario**, None; **C. Martínez**, None; **I. González-Alvaro**, Spanish Society of Rheumatology, 2.

2481

Which Factors Influence the Prescription of Tocilizumab Alone or in Combination with DMARDs in Rheumatoid Arthritis Patients in a Real Life Setting? An Interim Analysis of Safety and Efficacy at 6 Months. Jacques Tebib[1], Isabelle Idier[2], Mathieu Coudert[3], David Pau[4], Rene-Marc Flipo[5] and Jean-Francis Maillefert[6]. [1]University Hospital Lyon, Lyon, France, [2]Chugai Pharma, La Defense, France, [3]Experis IT, Nanterre, France, [4]Roche, Boulogne-Billancourt, France, [5]University Hospital Lille, Lille, France, [6]University Hospital Dijon, Dijon, France.

Background/Purpose: Baseline factors influencing the use of tocilizumab (TCZ) in monotherapy (Mono) instead of combination with DMARDs (Combo) in real-life practice in RA patients (pts) as described previously in the Act Solo study were: no MTX treatment over the past 2 years, past-history of severe infection, age ≥ 65 years and an increased DAS28-ESR[1].

Objective: To describe drug retention rate, efficacy and tolerance of TCZ in real life in RA patients at 6 months.

Methods: *Study design*: prospective, multicenter, longitudinal, non interventional 12-month study. *Patients*: RA requiring TCZ treatment according to their physician. *Treatment:* TCZ as prescribed in real life. *Primary endpoint*[1]: Baseline factors influencing the use of TCZ in Mono or in Combo. *Secondary endpoints*: drug retention rate, premature withdrawals, safety and efficacy. *Data collected*: pts' characteristics at baseline and after TCZ initiation, monthly disease activity components, RA treatments. *Statistical analysis*: pts fulfilling inclusion and non-inclusion criteria and with ≥1 TCZ infusion were analyzed.

We herein present only the results at 6 months.

Results: 608 patients were recruited of whom 603 were analysed for safety and 577 (Total) for other endpoints. Baseline characteristics: mean age 57±13 years, 454 (79%) females, at least 1 co-morbidity: 409 (71%), mean RA duration 11±9 years, RF or ACPA positive: 479 (86%), erosive disease: 435 (77 %), mean DAS28-ESR 5.2±1.3. Past RA treatments included DMARDs in 98% and biologics in 75%. MTX was previously prescribed in 94% of pts and in 69% within the last 2 years. TCZ Mono was initiated in 229 (40%) pts and TCZ Combo in 348 (60%) pts of whom 74% received MTX (mean dose 16±5mg). Steroids were used in 385 (67%) pts (mean dose 10±7mg). 386 pts completed M6. 86 pts had no M6 visit. 105 pts withdrew for: AE 38 pts, inefficacy 28, patient's wish 6, lost to follow-up 15, remission 1, wish of pregnancy 1, unknown 14. 2 pts died: stroke 1, inhalation pneumopathy 1. At M6, drug retention rate was 78% in Total, 75% in Mono, 79% in Combo. Among the 577 pts, 211 (37%) pts remained without DMARD, 366 (63%) received TCZ+DMARD. DMARD was added in 18 TCZ Mono pts (twice on a temporary way) and definitely stopped in 23 TCZ Combo pts. 199 (34%) pts experienced at least 1 dose modification (temporary or definitive stop, dose changing) in TCZ infusions, 90 (39%) pts in TCZ Mono and 109 (31%) in TCZ Combo group. During the period 362 (63%) pts received steroids; at M6, 235 (41%) pts remained on steroids. Mean DAS28-ESR in Total, Mono and Combo were 2.80±1.49, 2.89±1.50 and 2.74±1.49 respectively. DAS28-ESR remission was 31% in Total, 28% in Mono, 33% in Combo. DAS 28-ESR LDA was 40% in Total, 38% in Mono, 42% in Combo. No new safety signal was reported. 264 (44%) patients had at least one AE, 46 (8%) had at least one serious AE.

Conclusion: In this 6-month interim analysis, drug retention rate was 78% in pts receiving TCZ in real life. In Total mean DAS 28-ESR decreased from 5.2±1.3 to 2.80±1.5 No new safety signal occurred. Both TCZ Mono and TCZ Combo groups were comparable for drug retention, efficacy and safety.

This study was conducted thanks to an unrestricted grant from Roche Chugai France.

Ref.:

1. Maillefert et al. ACT SOLO EULAR 2014 SCIE-1154

Disclosure: J. Tebib, Roche Chugai, 5; **I. Idier**, Chugai Pharma, 3; **M. Coudert**, Roche Pharmaceuticals, 3; **D. Pau**, Roche Pharmaceuticals, 3; **R. M. Flipo**, Roche Pharmaceuticals, 5; **J. F. Maillefert**, Roche Pharmaceuticals, 5.

2482

Use of Biologic Therapy As Monotherapy in Patients with Rheumatoid Arthritis. Antonio Gómez-Centeno[1], Olga Martínez[2], Francisco Javier Ballina[3], José Manuel Rodríguez[4], Jenaro Graña[5], Manuel Brito[6], Juana Sampedro[7], Gerardo Iglesias[8], Concepción Delgado[9] and Indalecio Monteagudo[10]. [1]Hospital Parc Taulí, Sabadell, Spain, [2]Hospital Virgen de la Concha, Zamora, Spain, [3]Hospital Central de Asturias, Oviedo, Spain, [4]Hospital Getafe, Getafe, Spain, [5]Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, [6]Hospital Nuestra Señora Candelaria, Santa Cruz de Tenerife, Spain, [7]Hospital Virgen de la Salud, Toledo, Spain, [8]Complejo Hospitalario Palencia, Palencia, Spain, [9]Hospital Clínico Lozano Blesa, Zaragoza, Spain, [10]Hospital Gregorio Marañón, Madrid, Spain.

Background/Purpose: The treatment for Rheumatoid Arthritis (RA) is based on synthetic or biological disease-modifying drugs (DMARDs). Current guidelines recommend biologics in combination with methotrexate as this shows better control of disease progression. However several studies show that up to 30% of patients are treated with biologic monotherapy for different reasons. The aim of the study was to know the characteristics of patients receiving biologic monotherapy, including previous treatments and reasons for treatment change.

Methods: Observational, cross-sectional, retrospective and multicentric study with the participation of 38 rheumatology units in Spain. Patients were consecutively included if they were >18, with moderate to severe RA with an inadequate response or intolerance to synthetic or biologic DMARD (as recommended by the Spanish Rheumatology Society, SER), treated with biologic DMARD in monotherapy for >6 months and gave informed consent.

Collected variables included sociodemographic (age, gender), clinical (RA diagnosis date, extra-articular manifestations, DAS28, CDAI and SDAI, presence of joint damage), and treatment (prior treatments with DMARD and reasons for change).

Results: Two hundred and nine patients were included, 82.8% were women, mean (SD) age was 57.6 (13.6). Mean (SD) time since RA diagnosis was 13.5 (8.8) years. Most had RF (59.8%), 38.3% anti-CCP antibodies, 73.7% joint damage; 28.5% had extra-articular manifestations.

At study visit, 58.4% of patients were receiving tocilizumab, 18.7% etanercept, 12.4% adalimumab, and 10.5% other biologics. Mean (SD) number of tender joints was 1.9 (3.0), of swollen joints was 0.84 (2.1); mean (SD) CRP level was 4.0 (7.7), and ESR was 14.6 (13.4). Mean (SD) DAS28 score was 2.7 (1.1), CDAI index was 8.4 (6.9), and SDAI index was 8.8 (7.1), with 49.8%, 15.8%, and 20.1% of patients on in remission, respectively.

28 of the 122 patients (23.0%) receiving monotherapy with tocilizumab were on first-line treatment, while 70.4% of patients with anti-TNF on monotherapy were on first-line.

The first synthetic DMARD prescribed was methotrexate (62.3%), followed by gold salts (17.9%). Mean time (months) since first DMARD prescription was 19.5 (52.8) [mean (SD)] and 89.8 (86.4) since the first biologic use.

Patients had received a mean (SD) of 2.6 (1.4) synthetic DMARDs and 1.7 (0.9) biologics.

Just before initiating monotherapy, 45.5% of patients had received synthetic+biologic DMARD, 30.6% synthetic DMARD as monotherapy, and 23.9% another biologic as monotherapy (30.0% adalimumab and 28.0% etanercept).

The most frequent reason for treatment withdrawal before monotherapy was lack of effectiveness (61.2%), intolerance (10.5%), adverse events (10.0%), and lack of adherence (1.5%).

Conclusion: The clinical control with biologics as monotherapy was good, with a mean DAS28 of 2.7. Patients with RA treated with biologic DMARD as monotherapy had previously received more than 2 synthetic DMARD. The withdrawal of the DMARD was mainly due to lack of effectiveness, intolerance, or adverse event. Treatment with biologics as monotherapy is a therapeutic alternative for patients who do not tolerate or cannot receive synthetic DMARD.

Disclosure: A. Gómez-Centeno, Pfizer, Abbvie, Menarini, Roche, Amgen, MSD., 2, UCB, Boehringer Ingelheim, Roche, Abbvie, Pfizer., 5, Pfizer, Roche, Abbvie, MSD, UCB, Menarini., 8; **O. Martínez**, None; **F. J. Ballina**, None; **J. M. Rodríguez**, None; **J. Graña**, None; **M. Brito**, None; **J. Sampedro**, None; **G. Iglesias**, None; **C. Delgado**, None; **I. Monteagudo**, None.

2483

Treatment Adjustment Strategy after Achieving Remission or Low Disease Activity in Rheumatoid Arthritis : A Systematic Review and Meta-Analysis. Sophie Henaux[1], Thomas Barnetche[2], Adeline Ruyssen Witrand[3], Bruno Fautrel[4], Alain G. Cantagrel[5] and Arnaud Constantin[3]. [1]Hopital Purpan, Toulouse, France, [2]Bordeaux University Hospital, Bordeaux, France, [3]CHU Purpan - Hôpital Pierre-Paul Riquet, Toulouse, France, [4]GRC-UPMC 08; AP-HP, Rheumatology dépt, Pitié Salpêtrière Hospital, Paris, France, [5]Centre Hospitalier Universitaire de Toulouse, Toulouse, France.

Conflict of interest:[r] NONE.

Background/Purpose: Attaining remission or at least low-disease activity (LDA) is a goal achieved in a significant proportion of rheumatoid arthritis (RA) patients thanks to the development of TNF blockers. In these patients, reduction or withdrawal of anti-TNF represent the main adjustment strategies in view to decrease the use of TNF blockers for safety and economic concerns.

Our aim was to 1) compare the maintenance of remission or LDA after anti-TNF withdrawal in comparison to anti-TNF continuation 2) compare the maintenance of remission or LDA after anti-TNF dose reduction in comparison to anti-TNF continuation.

Methods: A systematic literature review searching for controlled trials comparing anti-TNF withdrawal or anti-TNF dose reduction and anti-TNF continuation in RA patients achieving LDA or remission was conducted using the Embase, PubMed, Cochrane library, and ACR/EULAR meeting databases, updated until June 2014. The two primary endpoints were 1) maintenance of remission or LDA after anti-TNF withdrawal 2) maintenance of remission or LDA after anti-TNF dose reduction. Meta-analysis was performed using the inverse variance approach and statistical heterogeneity was assessed with the Cochran Q-test and I^2 values.

Results: After systematic literature review, 6 controlled trials comparing anti-TNF withdrawal (725 RA patients in 4 trials) or anti-TNF dose reduction (694 RA patients in 4 trials) and anti-TNF continuation in RA patients achieving LDA or remission were selected for meta-analysis. For the comparison of anti-TNF withdrawal versus anti-TNF continuation, meta-analysis indicates ORs (95% CI) of 4.29 (3.04–6.07) for maintenance of remission ($p<0.00001$) and 5.33 (3.65–7.79) for maintenance of LDA ($p<0.00001$) (Figure 1), in favour of anti-TNF continuation. For the comparison of anti-TNF dose reduction versus anti-TNF continuation, meta-analysis indicates ORs (95% CI) of 1.60 (1.15–2.24) for maintenance of remission ($p=0.006$) and 1.31 (0.88–1.95) for maintenance of LDA (not significant) (Figure 2), in favour of anti-TNF continuation.

Conclusion: Anti-TNF dose reduction appears as a possible strategy for maintenance of LDA or even remission, while anti-TNF withdrawal appears as a risky strategy in RA patients who achieved LDA or remission.

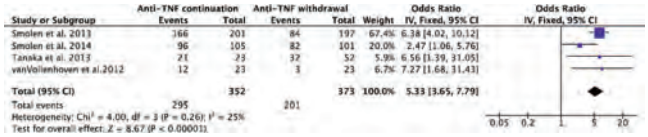

Fig 1 – Meta-analysis of controlled trials assessing the maintenance of LDA after anti-TNF withdrawal in comparison to anti-TNF continuation in RA.

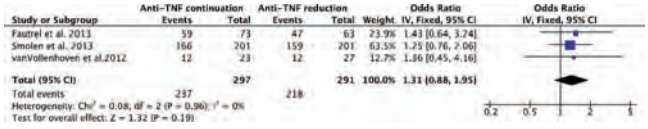

Fig 2 – Meta-analysis of controlled trials assessing the maintenance of LDA after anti-TNF dose reduction in comparison to anti-TNF continuation in RA.

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2484

Adding an Initial Six-Month Course of Infliximab to an Active Combination Treatment Is Cost Saving in Working-Aged Early Rheumatoid Arthritis Patients. Vappu Rantalaiho[1], Kari Puolakka[2], Janne Martikainen[3], Hannu Kautiainen[4] and Marjatta Leirisalo-Repo[5]. [1]Tampere University Hospital, Tampere, Finland, [2]South Karelia Central Hospital, Lappeenranta, Finland, [3]University of Eastern Finland, Kuopio, Finland, [4]Turku University Hospital, Turku, Finland, [5]University of Helsinki, Helsinki, Finland.

Background/Purpose: To study the cost-effectiveness of adding initial infliximab to a remission-targeted combination treatment with disease modifying antirheumatic drugs (DMARDs) in early rheumatoid arthritis (RA).

Methods: Economic evaluation was conducted alongside the NEO-RACo trial with a 2-year follow-up. A total of 99 patients with early, DMARD-naïve RA, receiving a triple combination of DMARDs and prednisolone, were randomized to double-blindly receive either added-on infliximab (FIN-RACo+INFL) or placebo (FIN-RACo+PLA) infusions during the first 6 months. All the patients fulfilled the ACR 1987 classification criteria for RA, were 18 to 60 years of age, and available for the workforce.

Direct costs during the 2-year follow-up were estimated on a micro-costing level. The consumed resources were collected from the study forms including all RA-related visits, medications, intraarticular injections, physiotherapy, splints and aids, as well as another person's help. The unit costs were obtained from the national list of health care costs and other public sources. In addition, data about the lost workdays due to RA were gathered, and the monetary value of lost productivity was estimated by the human capital method. The quality-adjusted life-years (QALYs) gained were calculated on the basis of SF-6D utilities. Both the costs and the QALYs were discounted by 3%.

Results: Over the 2-year follow-up, the average direct costs were 13,574 Euro for the patients in FIN-RACo+INFL group and 6,160 Euro for those in FIN-RACo+PLA group. In FIN-RACo+INFL the patients lost 51 workdays and in FIN-RACo+PLA 101 workdays. The respective lost productivity was 8,841 Euro and 17,387 Euro, while the total costs amounted 22,415 Euro and 23,548 Euro. In FIN-RACo+INFL group the patients gained on average 1.5533 QALYs and in FIN-RACo+PLA group 1.5267 QALYs with difference of 0.0266 (95% CI: – 0.065 to 0.1139, by bias-corrected and accelerated bootstrapping). Based on the direct costs only, the 2-year incremental cost-effectiveness ratio of adding an initial 6-month course of INFL on the FIN-RACo combination was 278,918 Euro. However, when taking also the indirect costs into account, the FIN-RACo-INFL treatment was a dominant option (i.e., less costly and more effective).

Conclusion: From the societal point of view, the induction treatment of early RA by adding a six-month course of infliximab on a targeted treatment with combination DMARDs and prednisolone is cost saving in working-aged patients.

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Predictors of Drug-Free Remission Following Treatment with Abatacept (in Combination with Methotrexate or as Monotherapy) in Early Rheumatoid Arthritis. P Emery[1], Gerd Burmester[2], Vivian P. Bykerk[3], B Combe[4], D E Furst[5], E Barre[6], C S Karyekar[7], D Wong[7] and T W J Huizinga[8]. [1]University of Leeds, Leeds, United Kingdom, [2]Charité – University Medicine Berlin, Berlin, Germany, [3]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [4]Monpellier University Hospital, Montpellier, France, [5]University of California at Los Angeles, Los Angeles, CA, [6]Bristol-Myers Squibb, Braine-L'Alleud, Belgium, [7]Bristol-Myers Squibb, Princeton, NJ, [8]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: In the Phase IIIb, randomized, double-blind, active-controlled AVERT study, abatacept (ABA) + MTX and ABA monotherapy induced protocol-defined DAS remission (DAS28 [CRP] <2.6) in 60.9% and 42.5% of pts with early RA after 12 months (mths) on treatment (vs 45.2% with MTX alone); DAS-defined remission was also maintained in 14.8% and 12.4% of pts 6 mths after rapid withdrawal of all RA treatment (vs 7.8% with MTX alone).[1] We further investigated predictors of drug-free DAS-defined remission at 6 mths after ABA withdrawal.

Methods: Pts with early RA (active synovitis in ≥2 joints, onset of symptoms ≤2 years) and DAS28 (CRP) ≥3.2, who were anti-CCP2 positive and MTX-naïve, were randomized to weekly SC ABA 125 mg + MTX, ABA monotherapy or MTX alone for 12 mths. At 12 mths, pts with DAS28 (CRP) <3.2 stopped all RA treatment (ABA immediately and MTX and steroids tapered over 1 mth). Co-primary endpoints were the proportion of pts with DAS-defined remission at (i) Mth 12 and at (ii) both Mths 12 and 18, for ABA + MTX versus MTX alone. To assess predictive characteristics of drug-free DAS-defined remission, *post hoc* analyses were performed in all treatment groups: (i) descriptive analysis of the proportion of pts with DAS-defined remission at both Mths 12 and 18 by baseline characteristic subgroups and (ii) clinical variables were tested individually by logistic regression in a univariate analysis and variables with p<0.20 were entered into a multivariate model.

Results: Descriptive analysis showed that in both ABA treatment arms, the proportion of pts with DAS28 (CRP) <2.6 at both Mths 12 and 18 was numerically higher in pts with lower baseline DAS28 (CRP), lower baseline HAQ-DI and shorter symptom duration; these factors were not associated with remission at Mths 12 and 18 in the MTX-alone group). Predictive factors for DAS28 (CRP) <2.6 at both Mths 12 and 18 identified in the univariate analysis are shown in the figure. In the multivariate model, adjusted for corticosteroid use and restricted to pts with DAS28 (CRP) <2.6 at Mth 12, baseline DAS28 (CRP) (OR [95% CI] = 1.676 [1.176, 2.387], p=0.0043) and duration of remission in the first 12 mths while on treatment (0.913 [0.807, 1.033], p=0.1484) were identified as predictors of DA28 (CRP) <2.6 at both Mths 12 and 18.

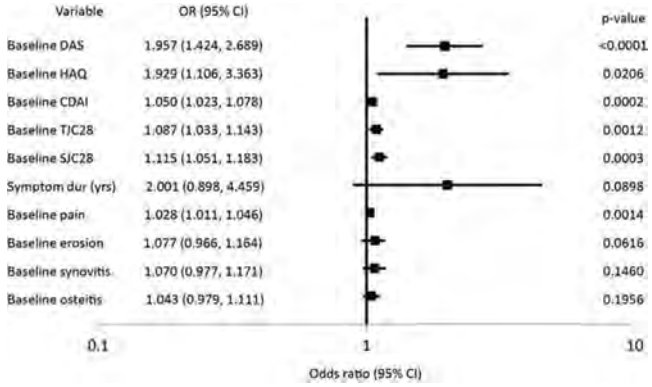

Figure. Predictors of DAS28 (CRP) <2.6 at both Mths 12 and 18 identified by univariate analysis

Conclusion: A small but significant number of patients treated with abatacept plus MTX achieved drug-free remission 6 months after drug withdrawal. According to descriptive and multivariate analyses, less severe disease activity at baseline and longer duration in DAS-defined remission on treatment were predictors for drug-free remission following abatacept withdrawal.

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Patient-Reported Outcomes Following 12 Months of Therapy with Abatacept (Plus Methotrexate or as Monotherapy) or Methotrexate and up to 6 Months after Treatment Withdrawal in Patients with Early Rheumatoid Arthritis. D E Furst[1], Vivian P. Bykerk[2], Gerd Burmester[3], B Combe[4], T W J Huizinga[5], E Alemao[6], D Wong[6], C S Karyekar[6] and P Emery[7]. [1]University of California at Los Angeles, Los Angeles, CA, [2]Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, [3]Charité – University Medicine Berlin, Berlin, Germany, [4]Monpellier University Hospital, Montpellier, France, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Bristol-Myers Squibb, Princeton, NJ, [7]University of Leeds, Leeds, United Kingdom.

Background/Purpose: Early biologic use can improve long-term control of RA,[1,2] potentially leading to improved physical function and reduced pain. Recent EULAR recommendations support shared decisions between the patient (pt) and rheumatologist,[3] emphasizing the need for more pt-focused outcomes to assess treatment targets. In the Assessing Very Early Rheumatoid arthritis Treatment (AVERT) trial, greater % of pts achieved DAS28 (CRP) <2.6 after 12 mths of treatment with SC abatacept (ABA) + MTX and 6 mths after withdrawal of all RA therapy, compared with MTX alone. At most time points, ABA monotherapy was more effective than MTX alone in controlling signs and symptoms of RA.[4] Here, pt-reported outcomes (PROs)

are presented over 18 mths (12 mths of treatment and 6 mths after withdrawal of all RA therapy) in the AVERT trial.

Methods: AVERT enrolled pts who were MTX naïve, anti-cyclic citrullinated peptide 2 seropositive (CCP2+), aged ≥18 yrs, with active synovitis ≥2 joints for ≥8 wks, DAS28 (CRP) ≥3.2, and a disease onset of ≤2 yrs. Pts were randomized to 12 mths of weekly SC ABA (125 mg) + MTX, SC ABA (125 mg) + placebo or MTX + placebo. All RA treatment was removed after 12 mths (ABA immediately and MTX and steroids tapered over 1 mth) in pts with DAS28 (CRP) <3.2. Fatigue was measured by 100-mm visual analog scale, physical function by HAQ-DI, and health-related quality of life by Short Form-36 (SF-36; Bodily Pain, Physical and Mental Component Summary subscores [PCS and MCS] presented). Improvement in activity limitation and work productivity/activity were estimated using the Activity Limitation Questionnaire (APaQ) and Work Productivity Activity Impairment Questionnaire (WPAI:RA). Adjusted mean change from baseline in PROs was calculated using a longitudinal repeated measures model.

Results: 351 pts with early RA were enrolled (n=119, ABA + MTX; n=116, ABA monotherapy; n=116, MTX monotherapy; at baseline: mean disease duration 0.6 yrs, mean DAS28 (CRP) 5.4, mean HAQ-DI 1.4, 95.2% RF+ and anti-CCP2+). Adjusted mean changes in PROs during treatment (baseline to Mth 12) and treatment withdrawal (Mth 12 to Mth 18) are presented (Table).

Adjusted mean change in PROs (95% CI)

	Baseline to Mth 12 (Treatment period)			Mth 12 to Mth 18* (Treatment withdrawal)		
Outcome	**Abatacept + MTX**	**Abatacept monotherapy**	**MTX**	**Abatacept + MTX**	**Abatacept monotherapy**	**MTX**
Fatigue, 100 mm VAS	n=81; −34.9† (−39.8, −29.9)	n=82; −26.1 (−31.2, −20.9)	n=80; −26.7 (−32.1, −21.4)	n=43; 17.2 (9.2, 25.3)	n=36; 10.8 (1.5, 20.2)	n=33; 13.3 (4.6, 21.9)
HAQ-DI	n=90; −0.87 (−0.99, −0.76)	n=82; −0.73 (−0.85, −0.61)	n=77; −0.72 (−0.85, −0.60)	n=35; 0.36 (0.16, 0.55)	n=29; 0.25 (0.04, 0.46)	n=25; 0.39 (0.17, 0.61)
SF-36	n=94	n=88	n=91	n=48	n=40	n=37
Bodily pain	36.5 (31.9, 41.2)	29.4 (24.6, 34.2)	30.8 (26.1, 35.6)	−22.6 (−30.4, −14.8)	−14.8 (−23.6, −5.9)	−17.4 (−26.2, −8.7)
PCS	13.9† (12.1, 15.8)	10.2 (8.3, 12.1)	10.9 (9.1, 12.8)	−7.8 (−10.5, −5.0)	−5.7 (−8.8, −2.5)	−4.7 (−7.8, −1.5)
MCS	7.7 (5.6, 9.7)	5.5 (3.4, 7.6)	7.2 (5.2, 9.3)	−4.9 (−8.1, −1.8)	−1.1 (−4.7, 2.4)	−5.0 (−8.5, −1.5)
Activity limitation, days	n=82; −8.7 (−10.0, −7.4)	n=74; −6.2 (−7.5, −4.9)	n=71; −7.9 (−9.3, −6.6)	n=44; 3.5 (0.7, 6.2)	n=36; 2.9 (−0.4, 6.1)	n=33; 3.7 (0.8, 6.7)
WPAI, %						
Work time missed	n=39; −7.7% (−14.26, −1.18)	n=35; −4.8% (−11.56, 1.89)	n=29; −1.0% (−8.44, 6.45)	n=25; 3.1% (−7.4, 13.6)	n=18; 4.9% (−7.8, 17.6)	n=12; 3.8% (−10.8, 18.4)
Impairment while working	n=36; −28.8% (−36.0, −21.6)	n=34; −24.1% (−31.3, −16.9)	n=26; −22.3% (−30.7, −14.0)	n=25; 16.8% (5.2, 28.4)	n=18; 11.1% (−2.2, 24.4)	n=12; 10.5% (−4.8, 25.8)
Overall work impairment	n=36; −23.3% (−29.7, −17.0)	n=34; −19.2% (−25.5, −12.8)	n=26; −17.4% (−24.7, −10.0)	n=25; 12.7% (2.3, 23.2)	n=18; 8.0%† (−3.9, 20.0)	n=12; 4.2% (−9.6, 17.9)
Activity impairment	n=82; −31.0% (−35.8, −26.1)	n=74; −27.7% (−32.8, −22.7)	n=71; −27.8% (−33.0, −22.6)	n=44; 15.4% (6.5, 24.2)	n=36; 11.1% (0.7, 21.4)	n=33; 13.5% (4.0, 23.1)

MCS, Mental Component Summary subscore; PCS, Physical Component Summary subscore; SF-36, Short Form-36;
VAS, visual analog scale; WPAI, Work Productivity Activity Impairment Questionnaire.
*Pts with assessments available at both Mth 12 and Mth 18.
†$p<0.05$ for treatment difference vs MTX (95% CI for the estimate of treatment difference did not cross 0).

Conclusion: In pts with early RA, abatacept + MTX, abatacept monotherapy and MTX alone showed improvements in PROs, with greater improvements seen for abatacept + MTX at 12 mths, compared with MTX alone. PROs worsened in all groups after treatment withdrawal but remained below baseline values. These results indicate that treatment with abatacept + MTX early in the course of RA leads to notable improvements in outcomes that are important to pts, such as fatigue, physical function, pain and participation in daily activities, and that some improvement may be maintained up to 6 mths following treatment withdrawal.

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Effects of Tofacitinib on Health Care Resource Utilization and Work Productivity in US Patients with Rheumatoid Arthritis.

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Here we describe health care resource utilization (HCRU) and work productivity in RA patients from the US treated with tofacitinib.

Methods: Data for US patients enrolled in two global, Phase 3, randomized, controlled trials of 6 months' (ORAL Step, NCT00960440) and 24 months' (ORAL Scan, NCT00847613) duration were reviewed: these two Phase 3 trials were chosen as, for both trials, the patient populations reflected how tofacitinib is mainly prescribed in the US. Tofacitinib was dosed at 5 or 10 mg twice daily (BID) in combination with non-biologic disease-modifying antirheumatic drugs (DMARDs) (mainly methotrexate) in patients with inadequate responses to ≥1 non-biologic or biologic DMARDs. Patients receiving placebo (in combination with DMARDs) were advanced to tofacitinib at Month 3 (ORAL Step) or by Month 6 (ORAL Scan). Analysis of endpoints for both studies occurred at Month 3, before patients receiving placebo were advanced to tofacitinib. The 17-item RA HCRU Questionnaire (v1.1) assessed the impact of RA across three domains: health care resource use, work-related activities, and daily activities. The composite Work Loss Index assessed work productivity in US patients; work productivity for the entire study population was assessed with the 25-item Work Limitations Questionnaire.

Results: Representative questions from each domain of the HCRU questionnaire are shown (Table). With the exception of doctor office visits, there was generally infrequent use of health care resources by patients receiving tofacitinib (both doses) at Month 3 in both studies, and was comparable to placebo. In ORAL Step and ORAL Scan, patients treated with both tofacitinib doses reported numerically lower impact on daily and work-related activities vs placebo at Month 3. The work productivity results reflect those of the entire study population, where US patients in ORAL Step receiving either tofacitinib 5 or 10 mg BID reported significant improvements in least squares mean (LSM) changes in work loss index from baseline vs placebo at Month 3: -1.73 ($p<0.05$) and -2.10 ($p<0.01$), respectively, vs placebo (1.36). In ORAL Scan, only US patients treated with tofacitinib 10 mg BID had significant improvements in LSM changes from baseline: -2.38 ($p<0.05$) vs -0.33 for placebo. Overall, the tofacitinib responses reported at Month 3 were maintained up to Month 6 (ORAL Step) and Month 24 (ORAL Scan).

Conclusion: At Month 3, US patients receiving tofacitinib in these two Phase 3 studies reported similar use of health care resources as placebo. At Month 3, patients receiving tofacitinib reported numerically less impact of RA on daily and work-related activities compared with patients receiving placebo.

Table Health care resource utilization in US patients with RA treated with tofacitinib during participation in two Phase 3 studies

		ORAL Step†			ORAL Scan‡		
		Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID**	**Placebo**	**Tofacitinib 5 mg BID**	**Tofacitinib 10 mg BID**	**Placebo**
Health care resource use, % YES (total number of RA-related visits)		**N=52***	**N=61***	**N=53***	**N=56***	**N=54***	**N=23***
Doctor Office visit	Month 3	72 (35)	81 (82)	83 (44)	52 (22)	56 (17)	70 (11)
	Month 6	71 (45)	84 (74)	NA	71 (22)	75 (24)	NA
	Month 24	NA	NA	NA	84 (26)	73 (29)	NA
Hospitalizations	Month 3	2 (0)	0 (0)	0 (0)	2 (0)	2 (0)	0 (0)
	Month 6	6 (0)	5 (1)	NA	0 (0)	2 (0)	NA
	Month 24	NA	NA	NA	8 (0)	6 (1)	NA
Outpatient surgeries or procedures	Month 3	13 (2)	4 (1)	7 (1)	4 (0)	4 (1)	0 (0)
	Month 6	2 (0)	2 (0)	NA	9 (0)	2 (0)	NA
	Month 24	NA	NA	NA	10 (3)	12 (0)	NA
Use of assistive devices or aids for daily functioning	Month 3	20	11	26	17	26	15
	Month 6	22	10	NA	22	21	NA
	Month 24	NA	NA	NA	18	18	NA
Work-related, % YES (duration reported as mean number of days)		**N=39***	**N=51***	**N=41***	**N=46***	**N=51***	**N=21***
Absent or on sick leave	Month 3	8 (31.7)	11 (2.8)	16 (2.6)	11 (23.8)	6 (2.3)	11 (2.0)
	Month 6	8 (36.3)	7 (3.0)	NA	6 (4.0)	4 (3.5)	NA
	Month 24	NA	NA	NA	13 (5.8)	9 (17.0)	NA
Part-time instead of full-time work	Month 3	5 (12.0)	6 (6.0)	7 (2.7)	5 (25.0)	6 (2.3)	16 (31.7)
	Month 6	5 (2.5)	4 (12.0)	NA	3 (3.0)	7 (8.7)	NA

	Month 24	NA	NA	NA	8 (21.0)	7 (32.0)	NA
Daily activities, % YES (duration reported as mean number of days)	**N=52***	**N=59***	**N=53***	**N=55***	**N=53***	**N=23***	
Unable to complete household duties	Month 3	44 (32.2)	39 (16.6)	62 (24.2)	48 (20.3)	33 (10.5)	50 (9.9)
	Month 6	41 (22.4)	33 (18.2)	NA	39 (18.8)	31 (30.5)	NA
	Month 24	NA	NA	NA	39 (30.4)	39 (19.8)	NA

*Reflects the number of all responses at baseline: this changed with time.
†After Month 3, patients on placebo in ORAL Step advanced to either tofacitinib 5 mg BID or tofacitinib 10 mg BID. ‡After Month 3, some patients on placebo in ORAL Scan advanced to either tofacitinib 5 mg BID or tofacitinib 10 mg BID; all patients advanced after Month 6.
BID, twice daily; N, number of all responses; NA, not applicable; RA, rheumatoid arthritis

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Relationship Between Different Clinical Measurements and Patient-Reported Outcomes. Roy Fleischmann[1], V Strand[2], B Wilkinson[3], K Kwok[4] and E Bananis[3]. [1]Metroplex Clinical Research Center, University of Texas Southwestern Medical Center, Department of Medicine, Dallas, TX, [2]Biopharmaceutical Consultant, Portola Valley, CA, [3]Pfizer Inc, Groton, CT, [4]Pfizer Inc, New York, NY.

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Here we compare the relationship between clinical measures and patient-reported outcomes (PROs) in patients (pts) with RA treated with tofacitinib or methotrexate (MTX).

Methods: MTX-naïve pts with RA from a double-blind, parallel group, Phase 3 trial (ORAL Start; NCT01039688) were randomized (2:2:1) and treated with tofacitinib 5 mg twice daily (BID) monotherapy (N=373), tofacitinib 10 mg BID monotherapy (N=397), or MTX titrated from 10 to 20 mg/week (N=186). Clinical measures included: the proportion of pts achieving ACR50 and ACR70 responses, the proportion achieving low disease activity (LDA) measured by Clinical Disease Activity Index (CDAI LDA, CDAI≤10), and Simplified Disease Activity Index (SDAI LDA, SDAI≤11), and the proportion achieving remission (REM) measured by CDAI REM (CDAI≤2.8) and SDAI REM (SDAI≤3.3). PROs included: proportion of pts achieving improvements in physical function measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI, to normative values <0.5).

Results: At Month 6, a greater proportion of pts achieved ACR responses, LDA, and REM with tofacitinib 5 mg or 10 mg BID than with MTX (Tables). Most pts who achieved LDA and REM by one measure also achieved LDA and REM by other measures (Tables); however, discordance was observed between different measures of LDA and REM, and appeared greater with MTX vs either tofacitinib dose (Tables). As expected there was a high degree of concordance between CDAI LDA and SDAI LDA (Table 1) and CDAI REM and SDAI REM (Table 2). Overall, pts achieving LDA or ACR50 showed less improvement from baseline in patient-reported pain, and patient global assessment of disease compared with tender joints, swollen joints, physician global assessment of disease, and HAQ-DI: pts receiving MTX showed an overall lower improvement in these PROs compared with tofacitinib 5 mg or 10 mg BID. In general, better improvements and consistency in PROs were observed in ACR50 responders compared with measures of LDA. Pts achieving ACR70, CDAI REM, and SDAI REM showed similar improvements across PROs and similarly between MTX and tofacitinib.

Conclusion: A higher proportion of MTX-naïve pts receiving tofacitinib 5 or 10 mg BID achieved a clinical response compared with pts receiving MTX. While most pts achieve similar responses across different clinical measures, many may achieve a response in one measure but not the other. Variability of responses with clinical.

Table 1 ACR50 and LDA clinical disease activity outcomes at Month 6

	Treatment	ACR50	CDAI LDA	SDAI LDA	HAQ-DI (<0.5)
Overall Responders, n/N (%)	Tofacitinib 5 mg BID	171/340 (50)	160/339 (47)	170/338 (50)	151/340 (44)
	Tofacitinib 10 mg BID	226/367 (62)	223/366 (61)	226/366 (62)	197/366 (54)
	Methotrexate	50/158 (32)	54/158 (34)	53/158 (34)	42/158 (27)

n, number of responders; N, number of patients assessed at Month 6

		1st Outcome			
2nd Outcome (% achieving a response that were also responders for the 1st outcome)	**Treatment**	**ACR50 responder**	**CDAI LDA responder (≤10)**	**SDAI LDA responder (≤11)**	**HAQ-DI responder (<0.5)**
ACR50 responder, %	Tofacitinib 5 mg BID	NA	79	78	80
	Tofacitinib 10 mg BID	NA	86	85	81
	Methotrexate	NA	69	70	60
CDAI LDA responder (≤10), %	Tofacitinib 5 mg BID	74	NA	94	70
	Tofacitinib 10 mg BID	85	NA	98	81
	Methotrexate	74	NA	96	67
SDAI LDA responder (≤11), %	Tofacitinib 5 mg BID	77	100	NA	72
	Tofacitinib 10 mg BID	85	99	NA	82
	Methotrexate	74	94	NA	62
HAQ-DI (<0.5), %	Tofacitinib 5 mg BID	71	66	64	NA
	Tofacitinib 10 mg BID	70	72	71	NA
	Methotrexate	50	52	49	NA

Numbers of patients available for assessment varied between parameters ACR, American College of Rheumatology; ACR50, ≥50% improvement from baseline in both tender and swollen joint counts and ≥50% improvement in ≥3 of the 5 remaining ACR core set measures (pain, disability, C-reactive protein or erythrocyte sedimentation rate, patient and physician global assessments); BID, twice daily; CDAI, Clinical Disease Activity Index; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDA low disease activity; NA, not applicable; SDAI, Simplified Disease Activity Index

Table 2 ACR70 and REM clinical disease activity outcomes at Month 6

	Treatment	ACR70	CDAI REM	SDAI REM	HAQ-DI (<0.5)
Overall Responders, n/N (%)	Tofacitinib 5 mg BID	94/340 (28)	44/339 (13)	46/338 (14)	151/340 (44)
	Tofacitinib 10 mg BID	149/367 (41)	79/366 (22)	84/366 (23)	197/366 (54)
	Methotrexate	23/158 (15)	14/158 (9)	15/158 (9)	42/158 (27)

n, number of responders; N, number of patients assessed at Month 6

		1st Outcome			
2nd Outcome (% achieving a response that were also responders for the 1st outcome)	**Treatment**	**ACR70 responder**	**CDAI REM responder (≤2.8)**	**SDAI REM responder (≤3.3)**	**HAQ-DI responder (<0.5)**
ACR70 responder, %	Tofacitinib 5 mg BID	NA	82	83	52
	Tofacitinib 10 mg BID	NA	94	92	59
	Methotrexate	NA	71	73	38
CDAI REM responder (≤2.8), %	Tofacitinib 5 mg BID	38	NA	96	26
	Tofacitinib 10 mg BID	50	NA	90	34
	Methotrexate	43	NA	93	24
SDAI REM responder (≤3.3), %	Tofacitinib 5 mg BID	40	100	NA	26
	Tofacitinib 10 mg BID	52	96	NA	36
	Methotrexate	48	100	NA	26
HAQ-DI (<0.5), %	Tofacitinib 5 mg BID	84	89	87	NA
	Tofacitinib 10 mg BID	79	84	85	NA
	Methotrexate	70	71	73	NA

Numbers of patients available for assessment varied between parameters ACR, American College of Rheumatology; ACR70, ≥70% improvement from baseline in both tender and swollen joint counts and ≥70% improvement in ≥3 of the 5 remaining ACR core set measures (pain, disability, C-reactive protein or erythrocyte sedimentation rate, patient and physician global assessments); BID, twice daily; CDAI, Clinical Disease Activity Index; HAQ-DI, Health Assessment Questionnaire-Disability Index; NA, not applicable; REM, remission; SDAI, Simplified Disease Activity Index

Disclosure: R. Fleischmann, Pfizer Inc, 2, Pfizer Inc, 5; **V. Strand**, AbbVie, Afferent, Amgen, Biogen Idec, Bioventus, BMS, Carbylan, Celgene, Celltrion, CORRONA, Crescendo, Genentech/Roche, GSK, Hospira, Iroko, Janssen, Lilly, Merck, Novartis, Pfizer Inc, Regeneron, Sanofi, SKK, Takeda, UCB, Vertex, 5; **B. Wilkinson**, Pfizer Inc, 1, Pfizer Inc, 3; **K. Kwok**, Pfizer Inc, 1, Pfizer Inc, 3; **E. Bananis**, Pfizer Inc, 1, Pfizer Inc, 3.

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Analysis of Early Neutropenia, Clinical Response, and Serious Infection Events in Patients Receiving Tofacitinib for Rheumatoid Arthritis. V. Strand[1], A. Dikranian[2], J. Beal[3], K. Kwok[3], S. Krishnaswami[4], S. Wood[4] and C. Nduaka[4]. [1]Biopharmaceutical Consultant, Portola Valley, CA, [2]San Diego Arthritis Medical Clinic, San Diego, CA, [3]Pfizer Inc, New York, NY, [4]Pfizer Inc, Groton, CT.

Background/Purpose: Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Post-baseline (BL) decreases in mean peripheral neutrophil count were observed in Phase (P) 3 trials, although no association between neutropenia and serious infection events (SIEs) was observed.[1] Given the role of neutrophils in initiation and progression of RA,[2] we further evaluated early post-treatment neutrophil changes to identify any trends with early clinical responses (ER) or SIEs in patients (pts) receiving tofacitinib 5 or 10 mg twice daily (BID).

Methods: Data were pooled from 6 P3 studies. Pts recruited to 4 of these received stable doses of background DMARDs, mainly methotrexate (MTX). Decreases from BL in neutrophil counts were evaluated at Week (W) 4.

Quartile categories (Q): 0 to <650 (Q1); 650 to <1410 (Q2); 1410 to <2500 (Q3); ≥2500 (Q4) were defined by quartiles obtained from pts with a mean decrease from BL in neutrophil counts (cells/μL) at W4. ER: decrease from BL in DAS28-4 ESR ≥1.2 at W4. Incidence rates (IRs) for SIEs were compared between categories. Pts receiving tofacitinib (all 6 trials) were included in the analysis presented for tofacitinib 5 and 10 mg BID.

Results: At BL and W4, 1488, 1506, 622 and 179 pts were evaluable for neutrophil counts for tofacitinib 5, 10 mg BID, placebo (PBO), and MTX, respectively. The proportions of pts with any decrease from BL in neutrophil counts were 69%, 73%, 52% and 56% with tofacitinib 5, 10 mg BID, PBO, and MTX, respectively. At W4, pts with neutrophil decreases in the tofacitinib 5 mg BID group were evenly distributed between categories. With tofacitinib 10 mg BID, a higher proportion of pts had neutrophil decreases within Q3 and Q4 than within Q1 and Q2 (Table). Neutrophil decreases with PBO and MTX were mostly within Q1 and Q2 (Table). In general the proportion of pts per category with an ER was slightly higher with tofacitinib 10 vs 5 mg BID. With tofacitinib, a higher proportion of pts with an ER was observed in categories with greater reductions in neutrophil counts (Table). SIEs occurred in 30 and 27 pts in the tofacitinib 5 and 10 mg BID groups, respectively. The distribution of pts with SIEs across categories was variable and there were no consistent trends to indicate an association between SIEs and decreases in neutrophil counts (Table), reflecting studies that did not find associations between SIEs and neutropenia.[3,4]

Conclusion: A trend was observed between decreases in neutrophils and ER with tofacitinib. ERs were most commonly seen in pts with the largest category decreases in neutrophil count at W4. No differences were noted between categories with respect to decreases in neutrophil counts and SIEs.

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Table Patients with quartile category decreases in neutrophil counts from baseline, and rate of DAS28-4 ESR early response and serious infection events after 4 weeks of treatment (by quartile categories)

	Quartile category decreases from baseline in neutrophil count at Week 4 (cells/μL)			
	1 (0 to <650)	2 (650 to <1410)	3 (1410 to <2500)	4 (≥2500)
Patients with decreases from baseline in neutrophil count, n (%) [95%CI]				
Tofacitinib 5 mg BID (N=1488)	266 (17.88) [15.96, 19.92]	257 (17.27) [15.38, 19.29]	257 (17.27) [15.38, 19.29]	247 (16.60) [14.74, 18.59]
Tofacitinib 10 mg BID (N=1506)	204 (13.55) [11.86, 15.38]	261 (17.33) [15.45, 19.34]	297 (19.72) [17.74, 21.82]	339 (22.51) [20.42, 24.71]
Placebo (N=622)	125 (20.10) [17.02, 23.46]	91 (14.63) [11.95, 17.66]	67 (10.77) [8.45, 13.48]	39 (6.27) [4.50, 8.47]
Methotrexate (N=179)	44 (24.58) [18.46, 31.56]	23 (12.85) [8.32, 18.65]	17 (9.50) [5.63, 14.77]	17 (9.50) [5.63, 14.77]
Patients with DAS28-4 early responses at Week 4, n (%) [95%CI]				
Tofacitinib 5 mg BID (N=297)	63 (21.21) [16.70, 26.31]	64 (21.55) [17.01, 26.67]	82 (27.61) [22.60, 33.07]	88 (29.63) [22.49, 35.18]
Tofacitinib 10 mg BID (N=372)	50 (13.44) [10.14, 17.33]	89 (23.92) [19.68, 28.59]	109 (29.30) [24.72, 34.21]	124 (33.33) [28.56, 38.38]
Placebo (N=20)	7 (35.00) [15.39, 59.22]	7 (35.00) [15.39, 59.22]	5 (25.00) [8.66, 49.10]	1 (5.00) [0.13, 24.87]
Methotrexate (N=28)	10 (35.71) [18.64, 55.93]	9 (32.14) [15.88, 52.35]	5 (17.86) [6.06, 36.89]	4 (14.29) [4.03, 32.67]
Patients with SIEs, overall study duration, n/N (IR per 100 pt-yr [95% CI])				
Tofacitinib 5 mg BID*	6/266 (2.099 [0.943, 4.671])	10/257 (3.370 [1.813, 6.264])	7/257 (2.326 [1.109, 4.879])	4/247 (1.346 [0.505, 3.587])
Tofacitinib 10 mg BID†	3/204 (1.364 [0.440, 4.228])	10/261 (3.229 [1.737, 6.001])	8/297 (2.190 [1.095, 4.379])	9/339 (2.236 [1.163, 4.297])

*Total pt-yrs of exposure for tofacitinib 5 mg BID per category (1–4) were 286.05, 300.02, 303.30, and 297.11
†Total pt-yrs of exposure for tofacitinib 10 mg BID per category (1–4) were 220.00, 310.15, 365.69, and 402.90
Studies included: ORAL Step (NCT00960440), ORAL Scan (NCT00847613), ORAL Solo (NCT00814307), ORAL Sync (NCT00856544), ORAL Standard (NCT00853385), ORAL Start (NCT01039688)
Categories are defined by quartiles obtained from a mean decrease from baseline of all treated patients in the included protocols at Week 4
BID, twice daily; DAS28-4, disease activity score in 28 joints; IR, incidence rate; pt-yr, patient years; SIE, serious infection event

Disclosure: V. Strand, AbbVie, Afferent, Amgen, Biogen Idec, Bioventus, BMS, Carbylan, Celgene, Celltrion, CORRONA, Crescendo, Genentech/Roche, GSK, Hospira, Iroko, Janssen, Lilly, Merck, Novartis, Pfizer Inc, Regeneron, Sanofi, SKK, Takeda, UCB, Vertex, 5; **A. Dikranian**, Pfizer Inc, Abbvie, 8, Pfizer Inc, Abbvie, 9; **J. Beal**, Pfizer Inc, 1, Pfizer Inc, 3; **K. Kwok**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Krishnaswami**, Pfizer Inc, 1, Pfizer Inc, 3; **S. Wood**, Pfizer Inc, 1, Pfizer Inc, 3; **C. Nduaka**, Pfizer Inc, 1, Pfizer Inc, 3.

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Assessment of Structural Benefits of SC Abatacept Using MRI in Patients with RA Who Have Failed 1 or 2 TNFs and Correlated with Clinical Outcomes As Measured By DAS28(ESR). Norman B. Gaylis[1], Steven Needell[2] and Joanne Sagliani[1]. [1]Arthritis & Rheumatic Disease Specialties, Aventura, FL, [2]Boca Radiology, Boca Raton, FL.

Background/Purpose: Previous studies[1–2] suggest the structural benefit of IV abatacept in patients with RA who have previously failed MTX, TNF therapy or both.

Objectives: This study evaluates the structural benefit of SC abatacept in a cohort of patients with RA, comparing the structural findings with clinical outcomes and measuring any difference between 1 or 2 TNF failure cohorts on stable MTX. average 17 mg/wk.

Methods: 34 patients were enrolled over 18-months into an open-label 1-year trial. Patients received SC abatacept 125 mg/week on background MTX. Patients on prednisone remained on a stable dose <10 mg. daily. MRIs of the hands/wrists were performed on a 0.3T Esaote S-Scan and scored blinded using a modified OMERACT/RAMRIS scoring system at Baseline, Wks. 12, 24 and 48. A global response of progression, regression, or no change was calculated for each time point. Clinical outcomes were measured by a DAS28(ESR) at similar time points.

Results: 27 patients completed; 7 patients discontinued including 3 treatment failures. Of the 27 patients who completed the trial, 15 patients had prior exposure to 1 TNF and 12 patients had prior exposure to 2 TNFs. The clinical and structural findings of each group were analyzed independently since individual clinical responses did not directly correlate with the structural response due to disease duration, disease activity at the time of trial entry, and prior drug exposure. Structurally, there were patients in both groups who showed improvement in synovitis and osteitis by MRI, however, the patients who had only 1 prior TNF exposure had a more robust response overall for both synovitis and osteitis. Of the 27 completed patients, 25 were positive DAS28 responders. 2 patients were non-responders. Clinical remission was achieved in 4 patients, low disease activity in 6 patients, moderate disease activity in 8 patients, and high disease activity remained in 7 patients. Clinically, there was no clear trend to distinguish any difference between the two groups. Both clinical and structural responses occurred within 6-months. 2 patients who had a clinical response at 6 months failed to sustain a response at 12 months. No adverse events were noted.

Conclusion: Overall, this small cohort of patients suggests that SC abatacept has clinical and structural benefit in patients who have had treatment with either 1 or 2 TNFs and is a viable choice of therapy. The structural findings were comparable to the benefits of IV abatacept which have been previously published.[1] The group that had 1 TNF exposure showed a greater improvement with respect to synovitis and osteitis than the population with 2 TNF exposure. It is possible that the structural benefit may be more robust when a switch from TNF therapy to an alternative mechanism of action such as abatacept is made after only 1 TNF failure. Further analysis is needed to determine if 6 months can be used as a cut-off point that prognosticates the value of continuing further therapy in the face of a lack of clinical and/or structural response. In addition, a better understanding of the clinical/structural disconnect demonstrated is necessary to provide optimal management of RA patients.

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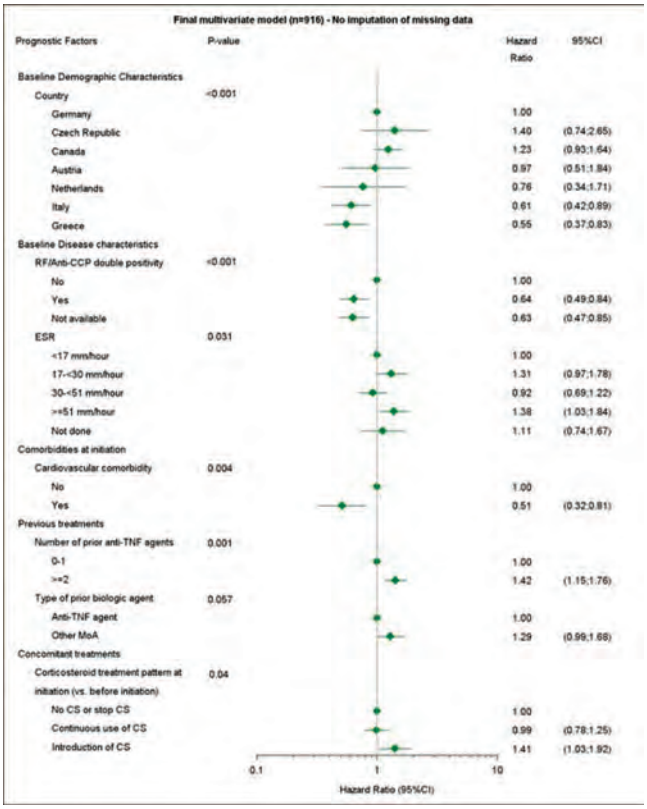
Prognostic Factors for IV Abatacept Retention in Patients Who Have Received at Least One Prior Biologic Agent: 2-Year Results from a Prospective, International, Real-World Study. H Nüβlein[1], R Alten[2], M Galeazzi[3], HM Lorenz[4], MT Nurmohamed[5], WG Bensen[6], Gerd Burmester[7], H-H Peter[8], P Peichl[9], K Pavelka[10], M Chartier[11], C Poncet[12], C Rauch[13] and M Le Bars[14]. [1]Internistische Schwerpunktpraxis, Nürnberg, Germany, [2]Schlosspark-Klinik University Medicine, Berlin, Germany, [3]University of Siena, Siena, Italy, [4]University Hospital, Heidelberg, Germany, [5]VU Univ Medical Center/Jan van Breeman Research Institute, Amsterdam, Netherlands, [6]St Josephs Hospital and McMaster University, Hamilton, ON, [7]Charité-Universitätsmedizin, Berlin, Germany, [8]University of Freiburg, Freiburg, Germany, [9]Evangelisches Krankenhaus, Vienna, Austria, [10]Institute of Rheumatology, Prague, Czech Republic, [11]Chiltern International, Neuilly, France, [12]Docs International, Nanterre, France, [13]Bristol-Myers Squibb, Munich, Germany, [14]Bristol-Myers Squibb, Rueil-Malmaison, France.

Background/Purpose: To identify prognostic factors of retention for abatacept (ABA) treatment in patients (pts) with moderate-to-severe RA, using final results from the real-world ACTION study.

Methods: ACTION was a 2-year follow-up, non-interventional, international, multicenter, cohort study that evaluated retention and effectiveness of

IV ABA in adults with moderate-to-severe RA in Europe and Canada (May 2008–Jan 2011). Socio-demographics, disease characteristics, previous/concomitant therapies, and comorbidities at ABA initiation were considered potential prognostic variables of retention. Pts who had received ≥1 prior biologic agent in countries with sufficient pt numbers to explore between-country effects were included. Clinically relevant variables, known risk factors and prognostic factors with a p≤0.10 (univariate analysis) were entered into a multivariate Cox proportional hazards regression model, with clustered data adjusted for one investigator. Factors with p≤0.10 after backward selection were retained in the final model. Co-linearity and interactions were assessed. Additional analysis to account for missing data in covariates was performed using multiple imputation by chained equations.

Results: 1009/1131 (89.2%) evaluable pts had failed ≥1 prior biologic agent. The crude retention rate (95% CI) at 24 months (Kaplan–Meier method) for pts exposed to ≥1 prior biologic agent was 53.4% (50.1, 56.6%).[1] 995 of 1009 pts were included in the analysis of prognostic factors. Final multivariate model results (n=916) are shown in the Figure. Pts had significantly higher likelihood of ABA retention if they were both RF and ACPA positive or had cardiovascular comorbidity at initiation. Prior anti-TNF agents, high baseline ESR and corticosteroid (CS) use were also prognostic factors for discontinuation. Despite showing borderline significance in the first model (Figure), use of a non-anti-TNF biologic agent before ABA (n=143, 15.6%) was an additional prognostic factor of lower retention (1.29 [1.00, 1.66]; p=0.049) in the model with imputation of missing data (not shown). Disease duration, ABA monotherapy and BMI were not identified as prognostic factors.



Conclusion: ACTION is one of the first studies to identify and report prognostic factors of long-term abatacept retention in a real-world setting. Double ACPA and RF positivity and cardiovascular comorbidity at initiation were prognostic of higher retention. Consistent with other reports,[2,3] higher number of prior anti-TNFs, country and more severe disease (suggested by higher baseline ESR and introduction of CS) were identified as prognostic factors of lower retention. These results will support individualized biologic treatment strategies in pts with moderate-to-severe RA.

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Disclosure: H. Nüβlein, Bristol-Myers Squibb, Abbott, Chugai, UCB, Essex, Wyeth, Pfizer, MSD, Novartis and Roche, 5; **R. Alten**, Bristol-Myers Squibb, 2, Bristol-Myers Squibb, 5; **M. Galeazzi**, None; **H. Lorenz**, Bristol-Myers Squibb, 5; **M. Nurmohamed**, BMS, Janssen, 5, Roche, Abbvie, Pfizer, UCB, 8, Roche, Abbvie, Pfizer, MSD, UCB, BMS, 2; **W. Bensen**, Abbott, Amgen, BMS, Janssen, Merck, Lilly, Novartis, Pfizer, Proctor and Gamble, Roche, Sanofi -Aventis, Schering, Takeda, UCB, Warner Chilcott, Wyeth, 2, Abbott, Amgen, BMS, Janssen, Merck, Lilly, Novartis, Pfizer, Proctor and Gamble, Roche, Sanofi -Aventis, Schering, Takeda, UCB, Warner Chilcott, Wyeth, 5, Abbott, Amgen, BMS, Janssen, Merck, Lilly, Novartis, Pfizer, Proctor and Gamble, Roche, Sanofi -Aventis, Schering, Takeda, UCB, Warner Chilcott, Wyeth, 8; **G. Burmester**, AbbVie, Pfizer, Roche, UCB, 2, AbbVie, BMS, MSD, Medimmune, Novartis, Pfizer, Roche, Sandoz, UCB, 5, AbbVie, BMS, MSD, Pfizer, Roche, Sandoz, UCB, 8; **H. H. Peter**, None; **P. Peichl**, None; **K. Pavelka**, MSD, AbbVie, Pfizer, UCB, Roche, Amgen, Menarini, BMS, 5; **M. Chartier**, None; **C. Poncet**, Bristol-Myers Squibb, 9; **C. Rauch**, Bristol-Myers Squibb, 3; **M. Le Bars**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1.

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Does Body Mass Index Impact Long-Term Retention with Abatacept in Patients with RA Who Have Received at Least One Prior Biologic Agent? 2-Year Results from a Real-World, International, Prospective Study.

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Background/Purpose: In RA, reduced efficacy with anti-TNF therapy[1] and dose escalation[2] have been reported for obese patients (pts) compared with non-obese pts. Clinical trials have shown that BMI does not affect abatacept (ABA) efficacy or pharmacodynamics[3] and real-world data show that short-term ABA retention, dosing and treatment outcomes are unaffected by BMI.[4–6] We assessed the impact of BMI on the long-term retention of pts using IV ABA who had previously failed ≥1 biologic in clinical practice across Europe and Canada.

Methods: ACTION was a 2-year, non-interventional, international, multicenter, cohort study that evaluated the retention and effectiveness of IV ABA in adults with moderate-to-severe RA. Pts who received ≥1 prior biologic and enrolled in countries with sufficient pt numbers to explore between-country effects were included in this analysis. Pts were stratified by their baseline BMI.[7] Crude 2-year retention rate was estimated using the Kaplan–Meier method. The effect of BMI was analyzed through a multivariate Cox proportional hazard model clustered for site effects with conditional imputation of missing data for covariates. Hazard ratios and corresponding 95% CI were adjusted for socio-demographic variables, disease characteristics, comorbidities at initiation and treatment characteristics. Pts were considered adherent to ABA if the ratio of the number of infusions received to the number expected was between 80 and 120%.

Results: 1009/1131 (89.2%) evaluable pts had received ≥1 prior biologic; 995 were included in the analysis. Pts with higher BMI had shorter disease duration, more severe disease (assessed by TJC, DAS28, HAQ-DI), were more likely to have comorbidities, but were less likely to be RF or anti-cyclic citrullinated peptide positive. Crude retention rates and adjusted HR are shown in Table 1. Similar proportions of pts were considered adherent to ABA therapy in all BMI groups as follows: BMI <25 kg/m^2 = 82.8%, BMI 25–<30 kg/m^2 = 79.5%, BMI 30–<35 kg/m^2 = 85.0%, BMI ≥35 kg/m^2 = 84.1%.

Table 1

BMI class[7]	n (%)	Crude retention rate, % (95% CI)	Adjusted hazard ratio	95% CI	p-value
Underweight/normal <25 kg/m^2	359 (36.1)	53.8 (48.3, 59.0)	1		
Overweight 25–<30 kg/m^2	324 (32.5)	57.4 (51.5, 62.8)	0.90	0.72, 1.13	0.365
Obese class I 30–<35 kg/m^2	168 (16.9)	50.5 (42.4, 58.1)	0.96	0.71, 1.31	0.815
Obese class II/III ≥35 kg/m^2	85 (8.5)	53.2 (41.3, 63.7)	0.86	0.58, 1.26	0.437

Conclusion: In this analysis of the real-world ACTION study, BMI did not impact long-term retention of IV abatacept in pts who had previously received ≥1 biologic, when adjusted on differences in disease severity and comorbidities between BMI classes. Increased BMI was not associated with an increased number of infusions, indicating that IV abatacept can be an effective treatment option irrespective of BMI, without need for dose adjustment.

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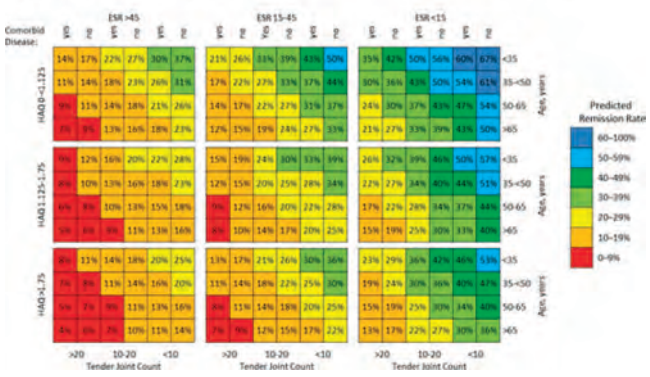
Prediction of Remission and Low Disease Activity in DMARD-Refractory Patients with RA Treated with Golimumab. N Vastesaeger[1], P Durez[2], B Dasgupta[3], B Combe[4], H Schulze-Koops[5], I Louw[6], J Wollenhaupt[7], CAF Zerbini[8], A Beaulieu[9], K Pavelka[10], M Lazaro[11], A Garcia Kutzbach[12], RJ Moots[13], H Amital[14], S Huyck[15], B Fu[15], M Govoni[16] and HH Weng[15]. [1]MSD Belgium, Brussels, Belgium, [2]Université Catholique de Louvain, Bruxelles, Belgium, [3]Southend University Hospital, Essex, United Kingdom, [4]Monpellier University Hospital, Montpellier, France, [5]University of Munich, Munich, Germany, [6]Panorama Medical Centre, Cape Town, South Africa, [7]Schön Klinik Hamburg-Eilbek, Hamburg, Germany, [8]Centro Paulista de Investigação Clinica, Sao Paulo, Brazil, [9]Centre de Rhumatologie, St-Louis, QC, [10]Revmatologicky Ustav, Praha, Czech Republic, [11]IARI Instituto de Asistencia Reumatologica Integral, Buenos Aires, Argentina, [12]AGAR Francisco Marroquin University, Guatemala City, Guatemala, [13]University Hospital Aintree, Liverpool, United Kingdom, [14]Sheba Medical Center, Tel-Hashomer, Israel, [15]Merck & Co., Inc., Whitehouse Station, NJ, [16]MSD Italy, Rome, Italy.

Background/Purpose: EULAR recommendations for RA therapy suggest addition of a biologic only if poor prognostic factors such as high disease activity are present. However, low baseline disease activity is associated with better biologic treatment outcomes. Better tools to predict remission/low disease activity (LDA) and aid in selection of patients for anti-TNF treatment are important.

Methods: GO-MORE was an open-label, multinational, prospective study in biologic-naïve patients (pts) with active RA despite DMARD therapy. Pts received 50-mg subcutaneous golimumab (GLM) once monthly for 6 months in addition to their background DMARDs. The following baseline characteristics were first evaluated in univariable models predicting 28-joint disease activity score based on ESR (DAS28-ESR) LDA and remission at 1 and 6 months: age, sex, smoking history, comorbidities, number of failed DMARDs, methotrexate dose, disease duration, tender joint count-28 (TJC28), swollen joint count-28 (SJC28), ESR, patient global assessment of disease activity (PGA), and HAQ. Factors were evaluated in a stepwise fashion. Those with significant associations ($P<.10$) were included in a final multivariable model. Factors that predicted both LDA and remission at 1 and 6 months were used in the final model. The ability of the models to predict LDA and remission at month 6 was investigated using receiver operating characteristic (ROC) analyses.

Results: 3280 pts were included in the analysis: 82.8% female, mean age 52.3 years, mean disease duration 7.6 years, mean baseline DAS28–ESR 5.97 (standard deviation=1.095). DAS28-ESR remission and LDA were achieved by 7.7% and 16.6% of pts, respectively, after 1 month of GLM treatment (1 injection), and by 23.9% and 37.4%, respectively, after 6 months of treatment. In multiple regression models, LDA at 1 month was associated with male sex; absence of comorbidities; and lower age, TJC28, SJC28, PGA, HAQ, and ESR. Remission at 6 months was associated with male sex; absence of comorbidities; and lower age, HAQ, ESR, and TJC28. The final model included sex, comorbidities, age, HAQ, ESR, and TJC28 as continuous variables and had an area under the ROC curve (AUC) of 0.81, 0.74, and 0.71 to predict remission at 1, 3, and 6 months, respectively, and an AUC of 0.80, 0.73, and 0.71 to predict LDA at 1, 3, and 6 months, respectively. When CRP replaced ESR or SJC replaced TJC, predictive ability was slightly reduced. The model for remission at 6 months had an AUC of 0.71 and showed remission rates from 4% to 67% in females (figure) and from 7% to 76% in males.

Figure. Prediction model estimates of 6-month DAS28-ESR remission in female patients using categorical variables as predictors.



Conclusion: Sex, age, ESR, HAQ, absence of comorbidities, and TJC28 at baseline allow accurate prediction of remission and LDA in the first 6 months of GLM therapy in patients failing DMARDs. This prediction model allows better selection of anti-TNF candidates.

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Persistence on Single Disease Modifying Anti-Rheumatic Drug Therapy in US Veterans with Rheumatoid Arthritis Is Extremely Rare. Jonathan Kruger[1], Michael Morgan[1], Andreas Reimold[2], Ted R. Mikuls[3], Gail Kerr[4] and Grant W. Cannon[1]. [1]Salt Lake City VA and University of Utah, Salt Lake City, UT, [2]Dallas VA and Univ of TX Southwestern Med Ct, Dallas, TX, [3]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [4]Washington DC VA and Georgetown and Howard University, Washington, DC.

Background/Purpose: Few rheumatoid arthritis (RA) patients are managed successfully with a single disease modifying anti-rheumatic drug (DMARD). This investigation determined the prevalence and clinical characteristics of US veterans with RA treated with a single DMARD in comparison to patients receiving multiple DMARDs.

Methods: Patients in the Veterans Affairs RA (VARA) registry, a long-term observational cohort, enrolled at or before four years of disease onset (to allow at least one year of VA-based observation) had DMARD exposures recorded during their first five years of RA. DMARD exposure was determined by chart annotation for DMARD use occurring prior to VA enrollment and VA pharmacy databases for DMARD exposure after VA enrollment. Patients who had died within five years of RA diagnosis were excluded. Patients who received only a single DMARD during the first five years were classified as monotherapy persistent (MONO) and patients receiving more than one DMARD either alone or in combination during the first five years were classified as polytherapy (POLY). Demographic information, serologic status, smoking history, disease characteristics at the time of

VARA enrollment, HLA-DR1 genotyping for shared epitope status, mean multidimensional health assessment questionnaire (MDHAQ), and mean disease activity score (DAS28) during observation were compared in the two groups. Chart review was conducted on all MONO patients to determine status of RA disease control and if specific reasons were present for not using additional DMARD therapy.

Results: Of 2,079 enrolled VARA patients, 486 met enrollment criteria with 50 (10.3%) MONO patients and 436 (89.7%) POLY patients. MONO DMARDs were methotrexate 36 (72%), hydroxychloroquine 11 (22%), and one (2%) each for leflunomide, sulfasalazine, and etanercept. Reasons documented for MONO persistence included adequate disease control (n=46; 92%), poor medication adherence (n=3; 6%), and contraindications to other DMARDs because of frequent infections (n=1; 2%). MONO were older at diagnosis ($p<0.02$), and were less likely to be seropositive for anti-CCP ($p<0.01$), less likely to have rheumatoid nodules ($p<0.03$), and less likely to have DRB1 shared epitope ($p<0.05$). MONO patients had lower average DAS28 scores ($p<0.05$) (Table).

Table: RA patient characteristics among those using persistent MONO compared to POLY during the first five years of disease; *chi-square test for categorical variables, t-test for continuous variables

	Monotherapy N=50	Polytherapy N=436	p-value*
Age at Diagnosis	64.7±13.5	58.8±11.8	<0.02
Gender (Male)	45 (90%)	382 (88%)	NS
Smoking Status			
Never	7 (14%)	93 (21.3%)	NS
Former	31 (62%)	190 (43.6%)	
Current	12 (24%)	153 (35.1%)	
Rheumatoid Factor Positive	32 (65.3%)	326 (77.8%)	NS
Anti-CCP Positive	27 (56.3%)	310 (74.2%)	<0.01
Rheumatoid Nodules	6 (12.5%)	116 (28.5%)	<0.03
X-ray Changes at Enrollment	11 (22%)	139 (32.7%)	NS
HLA-DRB1 Shared Epitope Status			
SE positive – 2 copies	4 (8%)	66 (15%)	<0.05
SE positive – 1 copy	16 (32%)	205 (47%)	
No Copies	26 (42%)	118 (27%)	
Average MDHAQ	0.8±0.5	0.9±0.5	NS
Average DAS28 Score	3.0±1.0	3.8±1.2	<0.05

Conclusion: While sustained treatment with a single DMARD during the first five years of RA treatment in US veterans is rare, most of these patients have adequate disease control. Patients on persistent monotherapy were older at disease onset, less likely to be seropositive, less likely to have rheumatoid nodules, and less likely to carry the DRB1 shared epitope in comparison to patients receiving multiple DMARDs.

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Impact of Golimumab on Physical Function and Employability of Patients with Rheumatoid Arthritis: 5-Year Data from 3 Phase III Clinical Trials.

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Background/Purpose: To assess the impact of golimumab (GLM) on physical function and employability in patients with rheumatoid arthritis (RA) with various prior treatment histories, after 5 years of therapy.

Methods: The efficacy and safety of GLM were assessed in methotrexate (MTX)-naïve RA patients (GO-BEFORE, N=637), patients with inadequate response to MTX (GO-FORWARD, N=444), and patients previously treated with TNF-inhibitors (TNFi, GO-AFTER, N=445). Patients with active RA were randomized to placebo (PBO), GLM 100mg+PBO (GO-BEFORE and GO-FORWARD), or GLM (50 or 100mg), q4w. Patients in GO-BEFORE and GO-FORWARD could receive concomitant MTX or no MTX and crossed-over to GLM after wk24 (GO-FORWARD) OR wk52 (GO-BEFORE), while patients in GO-AFTER were on background (with or without) MTX and crossed-over to GLM after wk24. Clinical remission was defined as DAS28 (ESR) <2.6. Physical function was measured using Health Assessment Questionnaire (HAQ) and employability was defined as being employed or being able to work if job was available (Yes/No). 5 year data were presented by 3 patient populations.

Results: At baseline, the percent of patients with disability (HAQ-DI score >0.5) in each of 3 RA populations were 90.9% in patients who were MTX-naïve, 87.6% in patients who were MTX-inadequate responders and 92.3% in patients who were TNFi-experienced. Among the analyzed patient population for employability (not retired and age<65 years), the percent of patients unemployable due to their RA at baseline were 9% in MTX-naïve patients, 8.1% in MTX-inadequate responders and 13.1% in TNF-experienced patients. After treatment with GLM, among those who had disability at baseline, 46.8% of MTX-naive patients, 37.5% of MTX-inadequate responders and 27.5% of TNFi-experienced patients had no disability (HAQ-DI score≤0.5) at wk256; among patients unemployable at baseline, 29.5% of MTX-naive patients, 28.6% of MTX-inadequate responders and 5.4% of TNFi-experienced patients regained employability at wk256. Similar trends of better outcomes on disability and employability of MTX-naïve patients were observed among those who achieved remission at wk256: 65.1% in MTX- naive patients, 54.4% in MTX-inadequate responders and 53.1% in TNFi-experienced patients achieved no disability; and 73.3% in MTX-naive patients, 50% in MTX-inadequate responders and 50.0% in TNFi-experienced patients regained employability.

Conclusion: This analysis indicates that effective treatment at an early stage may result in reduction in disability and improvement in employability over the long-term.

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Predictors of ACR/EULAR Boolean and SDAI Remission in Patients with Established Rheumatoid Arthritis Treated with Anti-TNF: An Analysis from the Prospective, Observational, Biological Treatment Registry Across Canada.

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Background/Purpose: Early achievement of remission is associated with improved clinical, functional and radiographic outcomes1. Recent recommendations of the Canadian Rheumatology Association dictate that treatment target should be remission or, when not possible, low disease activity. The aim of this analysis was to define the predictive factors of time to disease remission in established rheumatoid arthritis (RA) patients treated with infliximab.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with infliximab or golimumab as first biologics or after having been treated with a biologic for <6 months. RA patients treated with infliximab

who were enrolled between 2002–2012 and had ≥1 follow-up assessment were included. Remission was defined according to the ACR/EULAR Boolean criteria (TJC28≤1, SJC28≤1, CRP≤1 mg/dL, and PtGA≤1) or CDAI≤2.8. Independent predictors of remission were identified by multivariate Cox regression considering as potential confounders parameters showing a statistical trend (P<0.150) in univariate analyses.

Results: A total of 671 patients were included of whom 494 (73.6%) were female. At baseline, mean (SD) age was 56.0 (13.5) years and mean (SD) disease duration was 10.3 (10.1) years. Median time to CDAI and Boolean remission was 47.3 and 54.1 months, respectively. In univariate analysis, the following factors showed a statistical trend in their association with longer time to CDAI remission: earlier enrolment period (P=0.117), increased age (P=0.070), longer disease duration (P=0.008), female gender (P=0.143), and increased baseline disease activity as indicated by TJC28 (P<0.001), SJC28 (P<0.001), morning stiffness (P=0.003), pain (P<0.001), PtGA (P<0.001), MDGA (P<0.001), HAQ-DI (P<0.001), and CDAI (P<0.001). Rheumatoid factor (RF) status, number of previous DMARDs, and initial (first 6 months) treatment with DMARD(s), NSAID(s) or steroid(s) did not predict achievement of remission. In multivariate analysis, baseline CDAI [HR (95%CI): 0.97 (0.96,0.98); P<0.001] and disease duration [0.98 (0.97,1.00); P=0.018] were identified as independent predictors of time to CDAI remission. Similarly, multivariate survival analysis showed that increased disease duration [0.98 (0.96,1.00); P=0.047] and increased pain [0.98 (0.98,0.99); P<0.001] at baseline were associated with a lower chance of achieving ACR/EULAR Boolean remission.

Conclusion: Upon adjusting for potential confounders, increased disease duration before anti-TNF initiation is an independent predictor of longer time to remission. The results of these real-world Canadian data support findings that earlier initiation of anti-TNF agents may be associated with increased remission rates when stringent definitions of remission are considered.

References:

1. Smolen JS et al. Ann Rheum Dis. 2009;68:823-7.

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Correlation Between Time to Switch and Clinical Response Amplitude to Rituximab in Second Line Treatment in Rheumatoid Arthritis Patients with Treatment Failure to Tumor Necrosis Factor Inhibitors: 3-Year Data from Repeat Observational Study.

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Background/Purpose: In recent years we assist to an increasing interest to get more clinical data to improve the control of disease course in rheumatoid arthritis (RA) patients. According to treat to target principle, best practice still needs to be better defined in patients that encounter inadequate response after a variable period of time to anti-TNF treatment.

To investigate the clinical impact of switching to rituximab (RTX) according to the length of previous anti-TNF treatment in routine practice setting in patients suffering from RA and failure to TNF inhibitors.

Methods: REPEAT is an open-label, multicenter, prospective observational local study, 1087 patients with active RA and inadequate response to at least one TNF inhibitor received initial RTX (2×1000 mg IV, at 2 weeks apart) and subsequent RTX courses have been enrolled from 2010 to 2013. The patients were stratified according to the length of anti-TNF treatment before switch: <12 months (group A=260), 12–24 months (group B=278) and >24 months (group C=526). Clinical assessments including 28-joint disease activity score (DAS-28) were performed at baseline (switch moment) and after each retreatment course at 6, 12, 18, 24, 30 and 36 months. For the purpose of this analysis, median DAS-28 values were calculated for each group (A,B and C)and followed by median Delta Δ DAS-28 values calculation, as differences between values found at two successive evaluations and also from baseline to each evaluation. Statistical analyses were performed with STATA SE 11.0 software. Comparison between all previous treatments and evaluations for disease activity were performed using Nptrend and ANOVA tests.

Results: Median values for Δ DAS-28 obtained for group A, group B and group C from baseline to 6 months were -1,65;-1,35;-1,33 (P=0.01), from baseline to 12 months: -2,43;-2,05;-2,17 (P=0.02), from baseline to 18 months: -2,96;-2,59;-2,49 (P=0.009), from baseline to 24 months: -3,26;-2,83;-2,57 (P=0.01), from baseline to 30 months: -2,58;-2,7;-2,66 (P=0.15) and from baseline to 36 months: -2,56;-2,54;-2,83 (P=0.9). The median Δ DAS-28 achieved in group A at 1 year (−2.43) is comparable with Δ DAS-28 obtained at 18 month in group B (−2.59) and group C (−2.49). Across evaluations Nptrend test was P<0.0001 and ANOVA was P<0.0001.

Conclusion: 1. The median values of Δ DAS-28 as a measure of the amplitude of response to RTX show robust data that support the sustained clinical response to RTX across all 3 groups of patients over the 36 months treatment observation.

2. It is a significant difference between median values of Δ DAS-28 for group A and group B and C, showing a deeper and faster clinical response achieved in patients who were switched earlier to RTX in second line after anti-TNF treatment failure, with a pick at 24 months.

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Characteristics of Responding Versus Non-Responding Moderate Rheumatoid Arthritis Patients Treated with Etanercept Plus Methotrexate.

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Background/Purpose: While synthetic or biologic disease-modifying antirheumatic drugs (DMARDs) are often effective, treatment with such agents does not adequately control disease activity in all patients. Early identification of those unlikely to achieve long-term therapeutic goals is a clinically relevant strategy that may allow for appropriate modification in patient management to achieve optimal outcomes. The objective of this subanalysis was to determine disease characteristics of patients with moderately active RA responsive (defined by achievement of DAS28<2.6) and non-responsive to treatment with etanercept (ETN) plus methotrexate (MTX) after 36 weeks in the PRESERVE study.

Methods: In the induction phase of PRESERVE, subjects with moderately active RA (DAS28 >3.2 and ≤5.1) despite stable doses of oral MTX received open-label ETN 50 mg QW plus MTX (titrated to ≤25 mg/week as needed through week 28) for 36 weeks. Baseline demographic and disease characteristics and treatment response (DAS28, CDAI, HAQ) were compared in responders (defined as patients with DAS28<2.6) and non-responders (DAS28 ≥2.6) at week 36. Analyses using observed cases (OC) were conducted in all patients who received ≥1 ETN/MTX dose (mITT population).

Results: Of 764 patients receiving ETN50/MTX, 515 (67.4%) were classified as responders and 249 (32.6%) as non-responders at week 36. At baseline, responders were significantly younger (46.9 vs 50.9 years, P<0.001) with a lower BMI (25.4 vs 26.4, P=0.008) compared with non-responders. Responders also had significantly lower ESR (21.2 vs 24.7, P<0.001), CRP (11.4 vs 14.4, P=0.02), DAS28 (4.3 vs 4.5, P<0.001), CDAI (17.5 vs 18.3, P<0.001) and HAQ (1.1 vs 1.3, P<0.001) values than non-responders at baseline. Among responders and non-responders, significant changes from baseline in DAS28, CDAI and HAQ were observed at Week 4 and at all time-points up to Week 36 (all P<0.0001). Reductions in DAS28, CDAI, and HAQ were significantly greater among responders than non-responders after 4 weeks and this difference between groups was maintained for all clinical outcomes for the duration of the study period (Table).

Table: Differences in disease characteristics at baseline (BL) and week 36 in responders and non-responders to ETN50/MTX at week 36 (OC)

Characteristic	Mean (SD)/Adjusted Mean Change (SE) Responders	Non-Responder	Mean Difference (95% CI)	P Value
DAS28 at BL	4.3 (0.4)	4.5 (0.4)		<0.001
Week 36	1.9 (0.5)/−2.5 (0.03)	3.4 (0.9)/−1.0 (0.04)	−1.5 (−1.6, −1.4)	<0.0001
CDAI at BL	17.5 (4.8)	18.3 (5.2)		
Week 36	3.5 (2.6)/−14.2 (0.2)	10.7 (7.5)/−7.2 (0.3)	−7.0 (−7.7, −6.3)	<0.0001
HAQ at BL	1.1 (0.6)	1.3 (0.6)		
Week 36	0.4 (0.5)/−0.7 (0.02)	0.9 (0.6)/−0.3 (0.03)	−0.4 (−0.5, −0.4)	<0.0001

Conclusion: In the PRESERVE trial, patients with moderately active RA who achieved DAS28<2.6 after treatment with ETN plus MTX showed lower disease activity and functional improvement at baseline than those patients who did not achieve treatment target. Understanding the difference between responders and non-responders may help guide treatment practices and provide the best therapeutic options to these different patient sub-types.

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2499

Early Response Indicator early Predicts Clinical Response to Certolizumab in Rheumatoid Arthritis Patients. Massimiliano Cazzato[1], Laura Bazzichi II[2], Stefano Bombardieri[1] and Camillo Giacomelli[2]. [1]Rheumatology Unit, Pisa, Italy, [2]Rheumatology, pisa, Italy.

Background/Purpose: In the last few years the introduction of biological agents has radically changed the clinical outcome of patients with Rheumatoid Arthritis (RA). However, no single drug is able to control all patients with RA and it is known that each drug may be poorly effective in a sizable proportion of the treated patients (1). For these reasons, the early identification of clinical responder patients would be a crucial advantage for both a clinical and socioeconomic point of view.

Certolizumab pegol (CZP), a PEGylated, Fc-free anti-TNF, demonstrated a fast response in rheumatoid arthritis (RA). The peculiarity of the clinical response to CPZ at 12 weeks is already predictive of efficacy over time (2,3). Recently, mathematic algorithms, based on classical clinical parameters, have been proposed to predict the clinical response to anti TNF (4).

In the present study we have applied a mathematic algorithm recently proposed (ERI)(4) to predict early response to anti TNF on our cohort of patients treated with CZP.

Objectives: To evaluate the ability of ERI to predict the early response to CZP in RA patients already after the first 4 weeks of treatment.

Methods: We retrospectively collected the data of 52 RA patients followed in our unit and treated with CZP. We enrolled for this study 35 patients (72% female; mean age ± SD 56.63±15.58; DAS28 at the onset: 5.77 ±0.90; DAS28 at 12 weeks: 1.99 ± 0.43). The mathematic algorithm ERI utilizing the following parameters: tender Joint, swollen Joint, Illness activity VAS by Physician and patient, pain VAS, ESR and CRP, was applied to calculate the putative responders after one month of treatment (ERI≤0.67)and this value was compared with the DAS28 responders at 3 months. The patients were classified as good responders if they had a delta DAS28≥1.2 (EULAR criteria).

Results: 35 out of a total of 52 patients treated with CZP were assessed. 17 patients were excluded because: 3 interrupted CZP due to side effects, 5 had a follow-up inferior to 12 weeks, 9 patients had insufficient data (lost or poor compliance to follow-up) to calculate ERI and/or DAS28. No one had received other biologics prior to the assessment; all had associated a synthetic DMARD to CZP, mainly MTX. Using EULAR criteria we identified 21 responders at week 12, while ERI recognized 23 responders at week 4, with a concordance of 94%. Using EULAR criteria as the gold standard with ERI analysis we observed 1 false negative and 3 false positive subjects.

Conclusion: It is very important to identify subject who are responders to anti TNF agents such as CZP. CZP-treated patients with improvement at week 12 (ΔDAS28≥1.2) have a much higher probability of low disease activity at week 52 (3,5). In our cohort, ERI is a simple formula which can early recognize the CZP-RA responders, already after the first 4 weeks of treatment. In a socio-economic context, early identification of responders could be an opportunity to reduce spending. Moreover, to take advantage of any proposals for reimbursement, even on the part of pharmaceutical companies.

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2. Keystone E,. Arthritis Rheum 2008
3. Schiff M Ann Rheum Dis 2009
4. Bazzichi L Rheumatol Int 2010,
5. Curtis JR Arthritis Car Res 2012

Disclosure: M. Cazzato, None; **L. Bazzichi II**, None; **S. Bombardieri**, None; **C. Giacomelli**, None.

2500

Genetic Variation in the *TLR5* Locus Is Associated with Anti-TNF Response Among Rheumatoid Arthritis Patients Jacob Sode[1], Ulla Vogel[2], Steffen Bank[3], Paal Skytt Andersen[4], Merete Lund Hetland[5], Henning Locht[6], Niels H. H. Heegaard[7] and Vibeke Andersen[8]. [1]University of Southern Denmark, Odense, Denmark, [2]National Research Centre for the Working Environment, Copenhagen, Denmark, [3]University of Aarhus, Aarhus, Denmark, [4]Statens Serum Institut, Copenhagen S, Denmark, [5]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup Hospital, Glostrup, Denmark, [6]Frederiksberg Hospital, Frederiksberg, Denmark, [7]Odense University Hospital, Odense C, Denmark, [8]OPEN (Odense Patient data Explorative Network), Odense, Denmark.

Genetic Variation in the *TLR5* Locus is Associated with Anti-TNF Response among Rheumatoid Arthritis Patients

Background/Purpose: In a recent study (paper in press) of Danish rheumatoid arthritis (RA) patients we found single nucleotide polymorphisms (SNPs) in the *NLRP3* and interferon-γ genes to be associated with response to tumor necrosis factor a inhibitors (anti-TNF). The aim of this study was to extend and corroborate these associations by analyzing a new set of functional polymorphisms in the NLRP3-inflammasome and interferon-γ pathways in RA patients treated with anti-TNF.

Methods: Twenty-three functional single nucleotide polymorphisms (SNPs) in 14 genes involved in the inflammasome and interferon-gamma pathways were assessed in 538 anti-TNF naive Danish RA patients. Prospectively collected clinical data including functional status (HAQ), patient global score, smoking status, tender and swollen joint counts, treatments, rheumatoid factor (RF) status and C-reative protein (CRP) were obtained from the DANBIO registry. Multivariable logistic regression analyses adjusting for sex, age, HAQ, CRP, baseline disease-modifying anti-rheumatic drugs and RF status were performed to test associations between genotypes and EULAR response—good vs. moderate/none and good/moderate vs. none—at 3–6 months follow-up. ACR50 response was also analyzed to enable comparison with other studies. Subgroup analysis was performed for patients positive for RF (N=407).

Results: Polymorphisms in *IL12B* (rs6887695), *TLR1* (rs4833095) and *TLR5* (rs5744174) were significantly ($p<0.05$) associated with EULAR response (Table 1). *TLR1* rs4833095 was also associated with ACR50 response. None of the associations reached significance when corrected for multiple testing by false discovery rate adjustment.

TLR5 rs5744174 variant C allele is associated with an improved anti-TNF response and maps 71 bp from another polymorphism (no linkage data exists) previously found to be associated with RA anti-TNF response in a Dutch cohort (1) and it has been associated with higher PBMC IFN-γ secretion and altered CCL20 production. *TLR1* rs4833095 has been associated with high PBMC *TLR1* expression.

Subgroup associations were found for seropositive RA in *CARD8* (rs2043211), *IL18* (rs187238) and *TLR1* (rs4833095) (data not shown) but due to low power these results are preliminary.

Conclusion: Our results confirm association between a *TLR5* locus and EULAR response to anti-TNF treatment. Previous studies suggest that this polymorphism is functional and associated with a phenotype with altered cytokine expression. The associations found for other polymorphisms need validation in a new cohort.

Table 1 Associations between gene variants and anti-TNF treatment response

Gene (SNP)	Genotype	N	ACR50 response yes vs. no Adj. OR (95% CI), P-value	EULAR response G vs. M/N Adj. OR (95% CI), P-value	EULAR response G/M vs. N Adj. OR (95% CI), P-value
TLR1	TT	312			
rs4833095	TC	178	1.38 (0.92–2.05), 0.118	1.02 (0.70–1.50), 0.903	1.11 (0.73–1.68), 0.631
	CC	21	3.43 (1.38–8.52), 0.008**	3.11 (1.18–8.19), 0.022*	1.34 (0.47–3.81), 0.584
	TC/CC	199	1.52 (1.04–2.24), 0.031*	1.15 (0.79–1.66), 0.462	1.13 (0.76–1.69), 0.555
TLR5	TT	170			

rs5744174	TC	234	1.27 (0.82–1.96), 0.281	1.53 (1.01–2.33), 0.044*	1.17 (0.76–1.81), 0.470
	CC	107	1.40 (0.83–2.36), 0.206	1.89 (1.14–3.13), 0.014*	1.38 (0.80–2.38), 0.247
	TC/CC	341	1.31 (0.87–1.97), 0.192	1.64 (1.11–2.42), 0.013*	1.23 (0.82–1.85), 0.310
IL12B	GG	241			
rs6887695	GC	224	1.14 (0.76–1.69), 0.529	0.82 (0.56–1.19), 0.291	0.63 (0.42–0.95), 0.027*
	CC	51	1.44 (0.76–2.73), 0.267	0.87 (0.46–1.64), 0.664	1.68 (0.77–3.67), 0.197
	GC/CC	275	1.19 (0.82–1.73), 0.369	0.83 (0.58–1.18), 0.294	0.74 (0.50–1.09), 0.129

G/M/N: good/moderate/none response

(1) Coenen MJ et al. PLoS One 2010; 5(12):e14326.

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2501

Indirect Comparison of Tocilizumab and Tofacitinib in Patients with Rheumatoid Arthritis. Stacey Chang[1], Laura Sawyer[1] and Fred Dejonckheere[2]. [1]Symmetron Limited, London, United Kingdom, [2]F. Hoffmann-La Roche, Basel, Switzerland.

Background/Purpose: Tocilizumab (TCZ) is a recombinant, humanized, monoclonal antibody directed against the cytokine interleukin-6 receptor, and tofacitinib (Tofa) is an oral, synthetic, disease-modifying antirheumatic drug (DMARD) inhibiting Janus kinases (JAKs). Both are licensed for use in combination with other conventional DMARDs or as monotherapy in patients with moderately to severely active rheumatoid arthritis (RA) who have had inadequate responses to ≥1 DMARDs. The purpose of this study was to evaluate the effectiveness of TCZ compared with Tofa in their licensed populations (ie, RA patients with inadequate responses to conventional nonbiologic or biologic DMARDs [cDMARD-IR or bDMARD-IR]) based on publicly available evidence to date.

Methods: Efficacy was assessed for each treatment compared with placebo using available randomized controlled trial (RCT) evidence, after which treatments were indirectly compared with each other using the Bucher method.[1] Four comparisons were performed, each developed based on similarities between TCZ and Tofa studies in terms of population characteristics and treatment type (monotherapy and combination therapy). Comparative efficacy was assessed on the proportion of patients achieving American College of Rheumatology (ACR) scores of 20, 50, and 70 and Disease Activity Score using 28 joints (DAS28)–defined remission (DAS28 <2.6). Results are presented as risk ratios. Sensitivity analyses were undertaken to test the inclusion/exclusion of studies contributing to statistical heterogeneity.

Results: Across the 4 comparisons, 6 RCTs of TCZ and 6 RCTs of Tofa were included. In both monotherapy and combination therapy in cDMARD-IR and combination therapy in methotrexate (MTX)-IR patients, TCZ was more likely to generate ACR response and DAS remission than Tofa. In bDMARD-IR patients, TCZ in combination with MTX generated more ACR20 and ACR50 responders and DAS remitters than Tofa + MTX. Treatment effects between TCZ and Tofa failed to reach statistical significance in all but 3 instances (Table 1, Figure 1). The trends observed were robust to the sensitivity analyses performed.

Conclusion: Results of the indirect comparisons suggest TCZ and Tofa have broadly similar efficacy across different RA populations. There is a consistent trend (significant in 3 instances) favoring TCZ across all licensed RA populations on the outcome of DAS remission and ACR response.

Reference:

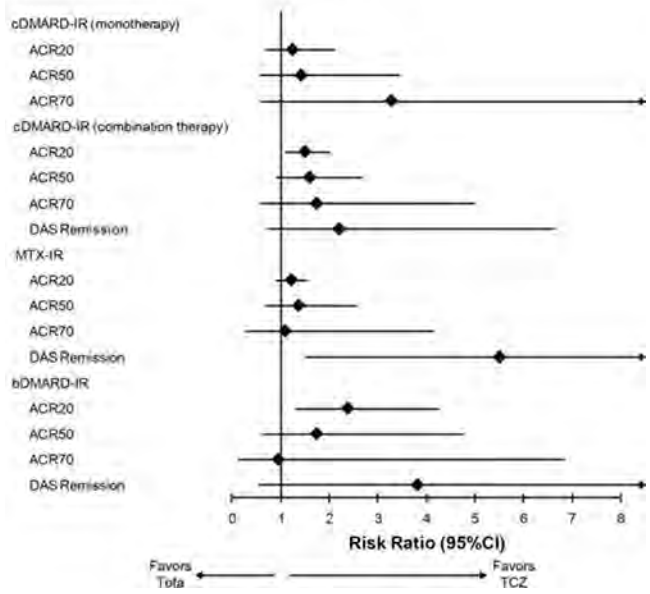
1. Bucher HC et al. *J Clin Epidemiol*. 1997;50:683–691.

Table 1. TCZ vs Tofa Across Different RA Populations

Population	Treatment Type	Risk Ratio (95% Confidence Interval) - TCZ vs Tofa ACR20	ACR50	ACR70	DAS Remission	RCTs
cDMARD-IR	Monotherapy	1.21 (0.69, 2.13)	1.39 (0.55, 3.47)	3.25 (0.60, 17.60)	NA	ADACTA, van de Putte 2004[b], ORAL-Solo
cDMARD-IR	Combination therapy	1.47 (1.08, 2.00)[a]	1.57 (0.91, 2.70)	1.71 (0.59, 4.99)	2.18 (0.71, 6.65)	TOWARD, ORAL-Sync
MTX-IR	Combination therapy	1.19 (0.91, 1.55)	1.34 (0.69, 2.58)	1.06 (0.27, 4.15)	5.48 (1.51, 19.92)[a]	CHARISMA, LITHE, OPTION, ORAL-Scan, ORAL-Standard, Kremer 2012[c]
bDMARD-IR	Combination therapy	2.35 (1.29, 4.27)[a]	1.71 (0.62, 4.76)	0.92 (0.12, 6.85)	3.79 (0.54, 26.59)	RADIATE, ORAL-Step

[a]Statistically significant treatment effects between TCZ and Tofa.
[b]van de Putte LBA, et al. Ann Rheum Dis. 2004;63:508–16.
[c]Kremer JM, et al. Arthritis Rheum. 2012;64:970–81.

Figure 1. TCZ vs Tofa across different RA populations



Disclosure: S. Chang, F. Hoffmann-La Roche, 5; **L. Sawyer**, F. Hoffmann-La Roche, 5; **F. Dejonckheere**, F. Hoffmann-La Roche, 5.

2502

Ten Year Follow-up Results of Four Dynamic Treat to Target Strategies in Patients with ACPA Negative Rheumatoid Arthritis. I.M. Markusse[1], G. Akdemir[1], L. Dirven[1], M. van den Broek[1], K.H. Han[2], H.K Ronday[3], P.J.S.M. Kerstens[4], W.F. Lems[5], T.W.J. Huizinga[1] and C.F. Allaart[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]MCRZ hospital, Rotterdam, Netherlands, [3]Haga Hospital, The Hague, Netherlands, [4]Jan van Breemen Research Institute Reade, Amsterdam, Netherlands, [5]VU Medical Center, Amsterdam, Netherlands.

Background/Purpose: To determine the optimal treatment strategy in patients with anti-citrullinated protein antibodies (ACPA) negative (−) rheumatoid arthritis (RA), as it has been suggested that these patients require a different treatment approach than ACPA positive (+)patients.

Methods: 184 ACPA− patients were randomized to 1. sequential monotherapy, 2. step-up therapy, 3. initial combination with prednisone, 4. initial combination with infliximab, as were 300 ACPA+ patients. Treatment adjustments were based on 3-monthly disease activity score (DAS) measurements, aiming at DAS ≤2.4. Functional ability (health assessment questionnaire, HAQ), radiographic progression (Sharp van der Heijde score, SHS) and (drug-free) remission (DAS <1.6) percentages over 10 years were compared between the 4 arms in ACPA− patients and between ACPA− and ACPA+ patients per randomisation arm.

Results: At 3 months, ACPA− patients achieved more often DAS ≤2.4 (52% versus 18%, p<0.001), remission (17% vs 5%, p<0.001) and improvement in functioning (mean HAQ 0.6 vs 1.0, p<0.001) on initial combination therapy than on initial monotherapy. These differences remained until year 1. After 10 years of targeted therapy, over time no differences were retrieved (p=0.551 for HAQ, p=0.851 for remission). Table 1 shows the main outcomes at year 10.

Drug survival (achieve and maintain DAS ≤2.4) on methotrexate monotherapy (1st step in arm 1 and 2) was similar in ACPA− and ACPA+ patients (median survival 10 vs 7 months, p=0.750), as also drug survival on sulphasalazine (2nd step in arm 1 and 2, median survival 3 vs 3 months, p=0.659). At year 1, in arm 3 18/55 ACPA− (33%) and 31/68 ACPA+ patients (46%) tapered to monotherapy (p=0.310). In arm 4, 17/43 ACPA− (40%) and 38/82 ACPA+ patients (46%) discontinued infliximab (p=0.466).

Drug-free remission (DFR) was more often achieved and longer sustained in ACPA− than in ACPA+ patients, in all treatment arms (26% vs 8% in arm 1, p=0.077; 24% vs 9% in arm 2, p=0.048; 30% vs 2% in arm 3, p=0.002; 28% vs 6% in arm 4, p<0.001, median DFR duration averaged in 4 arms 69 vs 32 months, p=0.073). Over time, radiographic progression (Δ≥0.5 in SHS) in ACPA− patients was not different between the 4 arms (p=0.082). SHS progression was more often observed in ACPA+ patients than in

ACPA− patients in arm 1, 2 (both p<0.001) and arm 3 (p=0.016), but not in arm 4 (p=0.849).

Conclusion: On the short term, patients with ACPA− RA benefit more from initial combination therapy with prednisone or infliximab than from monotherapy, as also ACPA+ patients. During subsequent DAS steered therapy, ACPA− patients respond similarly to treatment steps in all 4 treatment arms to ACPA+ patients, suggesting that both groups require a similar treatment approach. After 10 years of targeted therapy, ACPA− patients achieve more often sustained drug-free remission than ACPA positive patients and show less radiographic progression, except in arm 4.

Table 1: Main outcomes at year 10 for ACPA negative patients in the four treatment arms

	Sequential monotherapy	Step-up therapy	Initial combination with prednisone	Initial combination with infliximab	
	N = 40	N = 45	N = 56	N = 43	p value
Drop out, n (%)	14 (35)	20 (44)	21 (38)	16 (37)	0.738
DAS, mean ± SD	1.7 ± 0.9	1.8 ± 0.8	1.6 ± 0.8	1.4 ± 0.8	0.431
HAQ, mean ± SD	0.5 ± 0.5	0.7 ± 0.7	0.5 ± 0.5	0.5 ± 0.5	0.580
DAS-remission, n (%)	11 (46)	9 (41)	17 (49)	17 (63)	0.434
Drug-free remission, n (%)	7 (26)	7 (24)	11 (30)	9 (28)	0.742
On initial treatment step, n (%)	10 (39)	7 (28)	18 (51)	15 (56)	0.161
Use of infliximab, n (%)	3 (12)	3 (12)	4 (11)	4 (15)	0.978
Use of prednisone, n (%)	0 (0)	0 (0)	3 (9)	2 (7)	0.226
SHS progression, year 0–10, median (IQR)	0.3 (0–1.4)	0 (0–6.3)	1.0 (0–5.3)	0 (0–1.3)	0.639
SHS progression ≥5, n (%)	1 (4)	5 (24)	8 (28)	3 (14)	0.132
SHS progression ≥10, n (%)	1 (4)	3 (14)	5 (17)	1 (5)	0.324
Total AE, n*	293	292	368	312	0.872
Patients with AE, n (%)	36	39	55	41	0.113
Total SAE, n*	50	33	60	43	0.183
Patients with SAE, n (%)	25 (63)	19 (42)	27 (48)	22 (51)	0.300
Patients with serious infection, n (%)	9 (23)	5 (11)	5 (9)	3 (7)	0.124
Patients with malignancy, n (%)	3 (8)	2 (4)	8 (14)	6 (14)	0.310
Deceased, n	1	4	1	4	0.220

ACPA, anti-citrullinated protein antibodies; AE, adverse event; DAS: disease activity score; HAQ: health assessment questionnaire (scale 0–3);IQR, interquartile range; SAE, severe adverse event; SHS, Sharp van der Heijde score; SD, standard deviation.
*More events per patient possible

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2503

Early Response to Full-Dose Etanercept-Plus-Methotrexate Induction Therapy Predicts Sustained Remission with Reduced-Dose Combination Therapy in Early Rheumatoid Arthritis Patients. Paul Emery[1], Ronald Pedersen[2], Jack Bukowski[2] and Lisa Marshall[3]. [1]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds., United Kingdom, Leeds, United Kingdom, [2]Pfizer Inc, Collegeville, PA, [3]Pfizer Inc., Collegeville, PA.

Background/Purpose: In early rheumatoid arthritis (RA), achievement of clinical remission and low disease activity (LDA) limits joint damage and disability.[1] Anti-TNF agents are effective in rapidly inducing remission in early RA, which may improve the likelihood of long-term treatment success.[2] According to current EULAR guidelines, biologic withdrawal should be considered after a good clinical state is achieved,[1] but little is yet known about which patients are the best candidates for treatment reduction or withdrawal. In the PRIZE study, the impact of demographic and disease characteristics and early treatment response on the achievement of sustained remission was assessed in patients with early RA.

Methods: Methotrexate (MTX)-/biologic-naïve patients with early moderate-severe RA who achieved DAS28 ≤3.2 at week 39 and <2.6 at week 52 after open-label treatment with etanercept (ETN) 50 mg+MTX 10–25 mg (Phase 1 [P1]) were randomized to ETN 25 mg+MTX, MTX alone, or placebo (PBO) for 39 weeks in the double-blind phase (Phase 2 [P2]). With Mantel-Haenszel chi-square tests, the association between baseline (BL) characteristics and P1 treatment responses and achievement of P2 sustained remission (ie, DAS28 <2.6 at week 76 and 91, without corticosteroids for week 52–64) was analyzed. BL demographic and disease characteristics will also be analyzed in patients who achieved early P1 remission (ie, first DAS28 remission on day 0–178) vs late P1 remission (ie, first DAS28 remission after day 178).

Results: Predictors of P2 sustained remission in the ETN 25 mg+MTX group included: achievement of DAS28 sustained remission over weeks 13–52 (vs patients without this P1 response: 79% vs 54%; *P*=0.044); DAS28 LDA over weeks 13–52 (76% vs 41%; *P*=0.007); and ACR/EULAR Boolean remission at week 52 (71% vs 44%; *P*=0.049). Rapid and robust responses in P1 (ie, first DAS28 remission in days 0–179, mean DAS28 ≤1.91 at week 52) were associated with P2 sustained remission in this reduced-dose combination group (table). Predictors of P2 sustained remission in the MTX group included: achievement of DAS28 LDA over weeks 13–52 (49% vs 23%; *P*=0.044), younger age at BL, and lower levels of CRP at week 52. Predictors in the PBO group were: seronegative status at BL for anticyclic citrullinated peptide (seronegative vs seropositive: 48% vs 11%; *P*=0.001) and for rheumatoid factor (41% vs 11%; *P*=0.005) antibodies.

Table Baseline and response predictors of sustained remission for active treatment groups.

Predictor	Quartiles of Response, n/N (%)				*P* value*
	ETN 25 mg+MTX				
First DAS28 remission	**Days 0-57**	**58-179**	**180-273**	**≥274**	0.003
	12/15 (80)	16/20 (80)	8/16 (50)	4/12 (33)	
First DAS28 LDA	**Days 0-29**	**30-57**	**58-183**	**≥184**	0.041
	12/14 (86)	12/20 (60)	10/15 (67)	6/14 (43)	
Mean DAS 28, week 52	**DAS28 ≤1.55**	**>1.55–1.91**	**>1.91–2.16**	**>2.16**	0.014
	14/16 (88)	11/16 (69)	7/15 (47)	8/16 (50)	
		MTX			
Age, BL	**19-39 years**	**40-48**	**49-60**	**≥61**	0.024
	11/15 (73)	8/22 (37)	2/15 (13)	5/13 (39)	
CRP level, week 52	**0-0.5 mg/L**	**>0.5-1.09**	**>1.09-2.91**	**>2.91**	0.005
	9/16 (56)	8/14 (57)	6/18 (33)	2/16 (13)	

*Mantel-Haenszel chi-square correlation (trend) test.

Conclusion: Early onset of response to induction therapy with etanercept plus MTX predicted sustained remission with the reduced-dose combination maintenance regimen. These results are clinically important as prompt identification of patients unlikely to reach target responses may promote more timely adjustments in therapy and ultimately improved long-term outcomes.

References:
1. Smolen JS, et al. *Ann Rheum Dis* 2010;69: 964–75. 2. Emery P, et al. *Ann Rheum Dis* 2012;71:989–92.

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2504

Impact of Concomitant Methotrexate on the Enhanced Clinical Efficacy of Abatacept after 24 Weeks in Rheumatoid Arthritis Patients. Nobunori Takahashi[1], Toshihisa Kojima[1], Yuji Hirano[2], Yasuhide Kanayama[3], Koji Funahashi[1] and Naoki Ishiguro[1]. [1]Nagoya University Graduate School of Medicine, Nagoya, Japan, [2]Toyohashi Municipal Hospital, Toyohashi, Japan, [3]Toyota Kosei Hospital, Toyota, Japan.

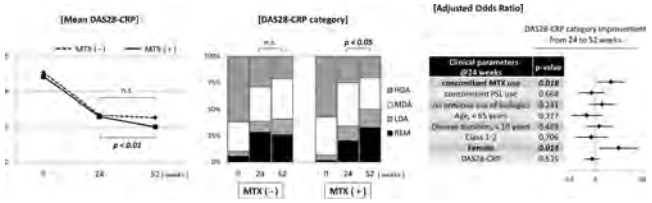
Background/Purpose: Abatacept (ABT), a selective co-stimulation modulator, is the first in a new class of biologic agents for the treatment of rheumatoid arthritis (RA) that inhibits T cell activation by binding to CD80/86, and modulating its interaction with CD28. Although some reports demonstrated that concomitant methotrexate (MTX) had little enhancing effect on short-term clinical efficacy of ABT, there have been only few long-term studies. We studied whether background MTX treatment enhanced the ABT efficacy after 24 weeks, by using data from Japanese multicenter registry system for RA patients using biological DMARDs.

Methods: All RA patients who underwent ABT treatment for at least 52 weeks (n = 254) in Nagoya University Hospital and 12 other institutes (Tsurumai Biologics Communication Registry Study Group) were enrolled in this study. Demographic data and the following parameters of disease activity were collected; tender joint count (TJC) and swollen joint count (SJC) on 28 joints, patient global assessment (VAS), ESR, and serum CRP and MMP-3 levels at baseline, 24 weeks, and 52 weeks. We compared these clinical data between the patients treated without concomitant MTX (ABT-mono, n = 130) and those treated with concomitant MTX (ABT-MTX, n = 124, mean MTX dose of 7.4 mg/week). The last observation carried forward (LOCF) method was used in each analysis.

Results: In the baseline characteristic data, the ABT-mono group had higher pulmonary comorbidity rate (21.5 vs 6.5%, p = 0.001) compared to the ABT-MTX group while no other clinical parameters showed significant difference including the proportion of patients with previous biological DMARDs history (47.7 vs 47.6, p = 0.986) or the all disease activity indices such as DAS28 (4.48 and 4.54). As shown in Figure Left and Middle panel,

the ABT-MTX group demonstrated statistically significant decreasing of DAS28 from 24 to 52 weeks while no difference in the ABT-mono group. We next studied the patients that still adhered on ABT therapy in spite of their poor clinical efficacy (moderate or high disease activity, DAS28-CRP > 2.7) at 24 weeks. Logistic regression analysis identified the concomitant MTX therapy and female as independent predictors of DAS28 category improvement (e.g. high to moderate disease activity) from 24 to 52 weeks (Figure Right panel).

Conclusion: Concomitant MTX therapy significantly decreased the disease activity after 24 weeks, while it seemed not to have enhancing effect on short-term clinical efficacy of ABT. It is true that the ABT efficacy is still significant even in the patients without MTX usage. However, it would be beneficial to use concomitant MTX in most of RA patients without serious comorbidity for MTX usage.



Disclosure: N. Takahashi, Abbott Japan Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Co. Ltd, Chugai Pharmaceutical Co. Ltd., and Bristol-Myers Squibb Co. Ltd., 8; **T. Kojima**, Takeda Pharma Corporation, Janssen Pharmaceutical, and Astellas Pharma Corporation., 2, Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Eisai Pharma Corporation, Abbvie, Bristol-Myers Squibb, Pfizer and Chugai Pharma Corporation, 8; **Y. Hirano**, Abbott Immunology Pharmaceuticals, 8, Mitsubishi-Tanabe Pharma, 8, Pfizer Inc, 8, Eisai, 8, Chugai, 8, Bristol-Myers Squibb, 8, Astellas Pharma, 8; **Y. Kanayama**, Astellas Pharma, 8, Eisai, 8, Mitsubishi Tanabe Pharma Corporation, 8, AbbVie Inc, 8, Chugai, 8; **K. Funahashi**, Abbott Japan Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Co. Ltd, Chugai Pharmaceutical Co. Ltd., and Bristol-Myers Squibb Co. Ltd., 8; **N. Ishiguro**, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 5, AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe, Pfizer and Takeda., 8.

2505

Long-Term Treatment with Tocilizumab (TCZ) Strongly Suppresses Joint Destruction in Biologic-naïve Patients with Rheumatoid Arthritis (RA) Regardless of Inflammation Status. Akira Sagawa. Sagawa Akira Rheumatology Clinic, Sapporo, 060-0001, Japan.

Background/Purpose: It is still difficult to completely prevent the progression of joint destruction with any of the currently available biologics. It has been reported that baseline CRP may predict early improvement of synovitis and bone erosion by TCZ therapy[1]. However, only a few reports have described whether TCZ may prevent joint destruction for a long period of time in clinical settings.

TCZ was administered for 3 years to identify risk factors for the progression of joint destruction in clinical settings and utilize the data to build treatment plans in RA patients.

Methods: TCZ was administered at a dose of 8 mg/kg every 4 weeks in combination with DMARDs including methotrexate. The effect on joint destruction was assessed on the basis of X-ray findings at baseline and year 3 of treatment using the modified total Sharp score (mTSS). Statistical analysis was performed using chi-square tests and Wilcoxon tests.

Results: and **Conclusion:** Among 57 patients registered, 51 patients evaluable with X-ray were assessed. At baseline, patients were 53.5 years in average, had suffered from RA for 10.9 years, and had a DAS28-ESR of 5.31 and an mTSS of 100.6. Biologic-experienced patients at baseline accounted for 66%, and PSL users 68.6%. One patient received TCZ as monotherapy. The mean DmTCC at year 3 was 1.0, and the structural remission rate (i.e., percentage of patients with DmTCC <1.5/3y) was 75%. A comparison of patients with and without progressive joint destruction revealed significant differences in CRP and ERS at baseline. Baseline CRP was 3.6 and 1.2 in patients with and without progressive joint destruction, respectively ($p = 0.024$). Logistic regression analysis revealed that the cut-off point of baseline CRP was 2.8 (specificity 92.1%; sensitivity 46.5%; $p=0.003$). The mean DmTSS values at year 3 in patients above and below the cut-off value were compared in groups of biologic-naïve patients and biologic-experienced patients. The mean DmTSS was -0.3 for biologic-naïve patients with CRP <2.8, and 0.3 for those with CRP ³2.8, indicating that TCZ prevented joint destruction regardless of inflammation status ($P=0.739$). In biologic-experienced patients, the mean DmTSS was 0.2 for those with CRP <2.8, and 8.0 for those with CRP ³2.8, with a significant difference between the two subgroups ($p=0.011$). This significantly higher score in the latter subgroup may be explained by the presence of severe inflammation not controlled with previous treatment as well as the higher DAS28-ESR, swollen joint count and ESR at baseline ($p<0.05$).

Long-term treatment with TCZ prevented joint destruction of RA patients, and a high structural remission rate was obtained. Our findings suggest that TCZ, if given to biologic-naïve patients, may strongly prevent the progression of joint destruction regardless of inflammation status.

Reference

1) ARTHRITIS AND RHEUMATISM Vol.62 No.10 Sup. P.S49–S50 (2010.10)

Disclosure: A. Sagawa, None.

2506

Decrease in the Number of Peripheral Leukocytes and Neutrophils and Increase of the Percentage of Eosinophils at 4 Week Predict the DAS28-ESR Remission at 24 Weeks after Administration of Tocilizumab. Tamao Nakashita[1], Shinji Motojima[2] and Akira Jibatake[3]. [1]Kameda Medical Center, Kamogawa-city, Japan, [2]Kameda Medical Center, Kamogawa City, Japan, [3]Kameda Medical Center, Kamogawa city, Japan.

Background/Purpose: Tocilizumab (TCZ) is a monoclonal anti-IL-6 receptor antibody, and is very effective in controlling RA activity. However we had noticed that the change in leukocyte number after the administration of TCZ is different from that of TNF-inhibitor, and the change in leukocyte number by TCZ is rapid occurring within few days of administration. We analyzed retrospectively the relationship between the change in leukocyte number at 4 week and disease activity evaluated by DAS28-ESR at 24 weeks.

Methods: Subjects were 50 patients with RA (male/ female = 10/40, mean age 56.7 +/− 12.7 years-old). The mean doses +/− SD of PSL (n = 35), MTX (n = 45), SSZ (n = 7), and bucillamine (n = 4) were 4.5 +/− 1.9 mg/day, 7.4 +/− 2.4 mg/week, 1000 +/− 0 mg/day, and 163 +/− 48 mg/day, respectively, at the introduction of TCZ. Patients were administrated with 8 mg/kg of TCZ every 4 weeks, and blood test and physical examination were done at the time of TCZ administration. Of the 50 patients, 19 were biologics naïve.

Results: The mean DAS28-ESR at week 0 and 24 were 4.72 and 2.22, respectively, and the difference was statistically significant. Thirty-one out of 50 patients reached DAS28-ESR remission at 24 weeks. The changes of leukocyte number after administration of TCZ are summarized as follows; total leukocyte number: decrease, neutrophil number: decrease, % of neutrophil: decrease, eosinophil number: no changes, % of eosinophil: increase as a result of the decrease in total leukocyte number. The changes of leukocyte number occurred at 4 weeks and did not change thereafter until 24 weeks. The change of DAS28-ESR, on the other hand,occurred gradually and reached plateau at 16 weeks. The decrease of the number of total leukocyte and neutrophil at 4 weeks significantly correlated with the decrease of DAS28-ESR at 24 weeks. The increase of % of eosinophil at the sum of 4 and 8 weeks significantly correlated with the decrease of DAS28-ESR at 24 weeks. Positive predictive values (PPV) for DAS28-ESR remission at 24 weeks were 76 %, 77 %, and 75 %, respectively, when total leukocyte and neutrophil count decreased by more than 1000 at 4 weeks, and when % of eosinophil increased by 0.5 % at 4 weeks, respectively.

Conclusion: The administration of TCZ induced significant changes of leukocyte count at 4 weeks, which is a good predictor of reaching DAS28-ESR remission at 24 weeks.

Authors have no COI.

Disclosure: T. Nakashita, None; **S. Motojima**, None; **A. Jibatake**, None.

2507

Is There an Autoinflammatory Component in Rheumatoid Arthritis Associated with Better Response to Anakinra (Kineret®)? Barbara Missler-Karger[1], Hans-Eckhard Langer[2], Mika Leinonen[3] and Björn Pilström[4]. [1]Rheumatology consultant, Cologne, Germany, [2]RHIO Research Institute, Düsseldorf, Germany, [3]4Pharma AB, Stockholm, Sweden, [4]Swedish Orphan Biovitrum AB, Stockholm, Sweden.

Background/Purpose: 458 patients with rheumatoid arthritis (RA) and inadequate response to traditional DMARDs alone and/or TNFα blocking agents were treated with the IL-1 receptor antagonist anakinra. The initial analysis showed no difference between TNFα blocker non-responders and

TNFα blocker naïve RA patients (1). In order to identify factors that could predict response to anakinra treatment we performed a *post hoc* analysis of the original study data.

Methods: Original study data including demographic parameters, concomitant diseases and other anti-rheumatic treatment were subject to multivariate statistical analysis to identify independent factors that impact on the DAS score difference and EULAR response after one year of anakinra treatment. Cohort analyses of patients leaving the study were performed to identify characteristics predictive for study dropout. Data from patients leaving the study prematurely were imputed based on the LOCF (last observation carried forward) methodology.

Results: Patients leaving the study prematurely (non-completers) were characterised by less DAS improvement and higher age than completers. Adverse events did not increase the risk of dropout. 79% of patients had high disease activity at baseline which was reduced to 48% after one month's treatment. Over the 12-month study most patients obtained moderate disease activity or better and 15–19% reached low disease activity or remission. A multivariate analysis of DAS score reduction over time concluded that the most predictive factors were disease severity (DAS28) at baseline ($p<0.001$), previous use of biologics ($p<0.05$), no or low-dose steroids ($\leq$7.5 mg prednisolone/day, $p=0.06$) and the prevalence of diabetes ($p=0.14$).

Conclusion: In a study with 458 RA patients treated with anakinra, further post hoc analysis of the raw data suggests that higher disease severity, no or low-dose steroid use or concomitant diabetes are predictive of a better response to anakinra treatment. We speculate that there may be two distinct cohorts of RA patients, one with a more autoimmune, steroid responsive disease, the other with a more autoinflammatory, steroid non-responsive disease.

References:

(1) Langer H E, Missler-Karger B (2003). *Int J Clin Pharm Res* **23**: 119–128.

Disclosure: B. Missler-Karger, Swedish Orphan Biovitrum AB, 5; **H. E. Langer**, Swedish Ophan Biovitrum AB, 5; **M. Leinonen**, Swedish Orphan Biovitrum AB, 5; **B. Pilström**, Swedish Orphan Biovitrum AB, 1, Swedish Orphan BIovitrum AB, 3.

2508

Tocilizumab Serum Trough Levels and Its Relationship with Disease Activity and Drug Dosage in Rheumatoid Arthritis Patients. Virginia Ruiz-Esquide[1], Azucena Gonzalez-Navarro[2], Jordi Yagüe[3], Jose Inciarte-Mundo[1], M. Victoria Hernández[1], Julio Ramirez[1], Sonia Cabrera-Villalba[1], Juan D. Cañete[1] and Raimon Sanmarti[1]. [1]Hospital Clínic of Barcelona, Barcelona, Spain, [2]Hospital Clinic of Barcelona, Barcelona, Spain, [3]Hospital Clinic Barcelona, Barcelona, Spain.

Background/Purpose: Tocilizumab (TCZ) is a humanized monoclonal antibody against interleukin-6 receptor used for the treatment of active rheumatoid arthritis (RA). The response to this treatment may depend on the serum levels achieved, which depends on the interval and the total dose administered.

Purpose To analyze TCZ serum trough levels and antidrug antibodies (ADA) in a cohort of RA patients in chronic treatment with TCZ; and to evaluate its relationship with disease activity, serum levels of IL6 and CRP and drug levels.

Methods: Cross-section study including all RA patients attended in our Arthritis Unit undergoing chronic treatment with TCZ. Analysis of demographic data, disease activity IL6 and CRP serum levels together with TCZ serum levels and ADA (LISA TRACKER Tocilizumab LTT005 DuoDrug + ADAb) was done. All drug levels were measured before treatment infusion. Drug levels were correlated with different clinical and serological parameters.

Results: 33 RA patients were included (91% women, age 53 $\pm$12 years, disease duration 15.3 $\pm$ 9.7 years, anti-CCP+ 66.7%, monotherapy 22.2%, DAS28 2.9 $\pm$ 1.1). No patient showed presence of ADA. In 14 patients (42%) serum levels of TCZ were non-detectable (<1 ug/ml). Patients with detectable levels of TCZ showed higher levels of IL6 and lower levels of CRP than those with non-detectable levels (Table). 15 patients received reduced dose of TCZ (4–6 mg/Kg) due to persistent remission or low disease activity. In these patients serum levels of TCZ were lower than in those with standard dose, without differences on disease activity or CRP between groups. A significant positive correlation was found between IL6 levels and TCZ serum levels ($R2=0.268$, $p=0.005$), but not with DAS28 or CRP. In 3 patients, all of them with low disease activity, a curve of TCZ serum levels was done by TCZ dosage at baseline (before drug infusion) and 10, 20 and 28 days thereafter. In two patients, TCZ serum levels were not detectable by day 20. The third patient showed adequate levels through the entire period.

Conclusion: In a clinical setting of RA patients in treatment with TCZ no ADA were found. An important proportion of RA patients treated with TCZ had undetectable serum trough levels (42%), showing higher CRP levels, and lower IL-6, but no differences were found in disease activity measured by DAS28-ESR.

Distribution of patients according to TCZ serum trough levels

	Non detectable drug levels (< 1 ug/ml) n=14	Detectable drug levels (> 1 ug/ml) n=19	p
Dose interval (days – mean)	31.9 $\pm$ 3	29.9 $\pm$ 3	0.323
Serum IL6 levels (ug/ml)	2.8 $\pm$ 2.3	7.8 $\pm$ 2	0.012
CRP (mg/dl)	1.1 $\pm$ 1.4	0.1 $\pm$ 0.3	0.001
Hemoglobin (g/dl)	13.5 $\pm$ 15	12.8 $\pm$ 12	0.214
Reduced dose of TCZ (%)	79%	42%	0.053
DAS28-ESR	3.1 $\pm$ 1	2.8 $\pm$ 1	0.499
Remission (DAS28-ESR<2.6) (%)	29%	37%	0.956

Disclosure: V. Ruiz-Esquide, None; **A. Gonzalez-Navarro**, None; **J. Yagüe**, None; **J. Inciarte-Mundo**, None; **M. V. Hernández**, None; **J. Ramirez**, None; **S. Cabrera-Villalba**, None; **J. D. Cañete**, None; **R. Sanmarti**, None.

2509

ADAM-10 As a Tocilizumab Treatment Predictive Factor in Rheumatoid Arthritis. Takeo Isozaki, Sakiko Isojima, Takahiro Tokunaga, Masayu Umemura, Hidekazu Furuya, Ryo Yanai, Ryo Takahashi, Kuninobu Wakabayashi, Nobuyuki Yajima, Yusuke Miwa and Tsuyoshi Kasama. Showa University School of Med, Shinagawa-ku Tokyo, Japan.

Background/Purpose: A disintegrin and metalloproteinases (ADAMs) are a family of transmembrane and secreted proteins. ADAM-10 has been reported to be the enzyme responsible for the release of a number of chemokines and cytokine receptors. We have shown that ADAM-10 is overexpressed on rheumatoid arthritis (RA) synovial tissue endothelial cells (ECs) and lining cells compared with osteoarthritis and normal tissues. We also demonstrated that ADAM-10 mediates EC migration and tube formed. In this study, we examined ADAM-10 as a predictive treatment factor in RA.

Methods: The serum was collected from patients before the initial treatment with biological therapies. Fifteen patients were treated with adalimumab (ADA), and 20 patents were treated with tocilizumab (TCZ). ADAM-10 and fractalkine/CX3CL1 were measured by enzyme-linked immunosorbent assay at 0, 12, 24 and 54 weeks. Clinical disease activity was evaluated by disease activity score 28 (DAS28). Following biological therapies, we defined biologic-responders as patients whose DAS28 scores decreased by more than 1.2 at 24 weeks. ADAM-10 baseline was compared between responders and nonresponders.

Results: There were no significant differences were observed in the mean age, gender ratio, dosages of predonisolone and methotraxate between ADA and TCZ groups. In ADA group, baseline DAS28 for the 15 patients was 4.8 $\pm$ 0.3 (2.5–7.2). On the other hands, baseline DAS28 for the 20 patients was 4.8 $\pm$ 0.3 (2.5–6.8) in TCZ group. There were no differences between ADA and TCZ groups. RA patients with an insufficient response to ADA or TCZ showed highly significant improvement of DAS28 after 12 weeks (2.9$\pm$0.3 and 2.2$\pm$0.4, respectively), and 24 weeks (2.5$\pm$0.4 to 2.2$\pm$0.2, respectively). ADAM-10 highly correlates with fractalkine/CX3CL1. Serum ADAM-10 levels were no remarkable change after treatment with ADA despite decrease of disease activity of RA. On the other hand, serum ADAM-10 levels in patients who were treated with TCZ were significantly diminished following successful treatment and clinical improvement (baseline 408$\pm$88 pg/ml and 54 weeks 138$\pm$51 pg/ml, $p<0.05$). ADAM-10 baseline in TCZ responder was significantly higher than TCZ nonresponders at 24 weeks (620$\pm$134 pg/ml and 109$\pm$25 pg/ml, respectively, $p<0.05$).

Conclusion: This study indicates that ADAM-10 is correlated with RA disease activity, and is higher in TCZ responders. These results suggest that ADAM-10 may be a predictor of treatment effectiveness for RA with TCZ.

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2510

Good Response to Methotrexate (MTX) and/or MTX Plus Adallimumab (ADA): 3 Yrs Study Results in Patients with Rheumatoid Arthritis (RA).

Kazuko Shiozawa[1], Takashi Yamane[1], Miki Murata[1], Chihiro Tanaka[1], Noriaki Yo[1], Ryosuke Yoshihara[1], Yasushi Tanaka[1], Ken Tsumiyama[2] and Shunichi Shiozawa[2]. [1]Kohnan Kakogawa Hospital, Kakogawa, Japan, [2]Kyushu University Beppu Hospital, Beppu, Japan.

Background/Purpose: To achieve comprehensive disease control (CDC; defined as simultaneous achievement of DAS28 < 3.2, HAQ-DI < 0.5 and ΔmTSS ≤ 0.5) or comprehensive disease remission (CDR; defined as simultaneous achievement of DAS28 < 2.6, HAQ-DI < 0.5 and ΔmTSS ≤ 0.5) is our therapeutic goal of treating RA. Owing to 2010 ACR/EULAR recommendation for early treatment of RA (Aletaha D et al, Ann Rheum Dis 69:1580, 2010), we found, in line with the finding of O'Dell et al. (Arthritis Rheum 65:1985, 2013), that 69/137 (50.4%) of RA patients given low-dose methotrexate (MTX) monotherapy showed no radiographic progression over 3 years when the patients were treated continuously with MTX monotherapy until significant adverse events or radiographic progressions were suspected. However, it remains unclear if the CDC and/or CDR are comparable between the patients treated with MTX monotherapy and those with MTX plus biologics. We here compared the clinical efficacy of MTX monotherapy and adalimumab (ADA) + MTX: 161 patients who showed adequate responses to methotrexate (MTX) (MTX group) were compared with 96 patients treated with ADA + MTX for inadequate response to MTX (MTX-IR) (ADA group) as to the effects on functional and structural outcomes for 3 years.

Methods: Grip strength, CDR and CDC rates and patients' proportions with structural remission (ΔmTSS ≤ 0.5), clinical relevant radiographic progression (CRRP; ΔmTSS >3) and rapid radiographic progression (RRP; ΔmTSS>5) were measured in MTX group (n=161, mean disease duration: 4.4 years) or ADA group (n=96, mean disease duration: 8.5 years) every year for 3 years.

Results: There was no significant difference in clinical remission rates (DAS28-ESR<2.6) between MTX and ADA groups at 3 years (LOCF). While, CDR rates for 3 years were much higher in ADA group (43.2%) than MTX group (18.3%) as well as those of CDC (45.9% vs. 24.0%, respectively). Moreover, about the structural change, ratios of patients with RRP were decreased in both MTX and ADA group at 3 years compared to the status at first year, however the ratio of patients with RRP in MTX group was 10% whereas that of patients with RRP in ADA group was 3%. Reflecting this result about the structural change, grip strength in ADA group was improved every year, but that was gradually decreased in MTX group after 1 year, even the baseline grip strength in MTX group was much stronger than that in ADA group143 vs. 177 mmHg, p=0.0001.

Conclusion: It was demonstrated that grip strength gradually decreased from 1 year after the initiation of MTX treatment in the patients with MTX monotherapy, while ADA treatment to MTX-IR patients improved grip strength in a time dependent manner, which was supported by significantly better CDC and CDR rates over 3 years in the ADA group than those in the MTX group. Thus, the treatment in combination with biologics seems preferable for the patients with increased disease activity in face of MTX monotherapy.

Disclosure: K. Shiozawa, None; **T. Yamane**, None; **M. Murata**, None; **C. Tanaka**, None; **N. Yo**, None; **R. Yoshihara**, None; **Y. Tanaka**, None; **K. Tsumiyama**, None; **S. Shiozawa**, None.

2511

Predictors of Discontinuation of Biologic DMARD Therapy Due to Remission in Patients with Rheumatoid Arthritis in a National Registry.

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Background/Purpose: Remission is considered an achievable goal for many patients under biologic therapies. However, currently there is limited information about predictors of discontinuation of biologic therapy in patients with RA. Our aim was to conduct a cohort study of patients enrolled in a National Registry of Biologic therapies to clarify how often biologic DMARD are discontinued due to remission and to identify predictors of discontinuation according to baseline characteristics at the time of initiation of biologic treatment.

Methods: We conducted a retrospective, observational cohort study of previously collected data from one national registry. We included RA patients who had at least 3 consecutive months on the same first biologic DMARD. Patients receiving rituximab were excluded. The index date was defined as visit when biologic therapy was started. The study period included patients recorded in the registry from April 1998 until December 2013. The endpoint of interest was defined as discontinuation of biologic DMARD due to remission defined by treating physician. Censoring occurred administratively (end of registry data), when patients stopped the treatment for other causes (side effects, lack of efficacy or pregnancy among others) or by loss to follow up. We used multivariable proportional sub-distribution hazards (SHR) models to examine the association between several predictors with discontinuation due to remission with loss to follow-up, discontinuation due to lack of efficacy, side effects or other causes as competing events.

Results: The study included 3,516 patients with diagnosis of RA and of these 3,161 patients having received at least 3 months of biologic DMARD. 753 patients stopped treatment due to side effects, 867 patients discontinued treatment due to lack of efficacy, 101 were loss of follow-up, 143 for other reasons, 48 patients for pregnancy. In 15 cases the cause of discontinuation was not established. 1175 patients still receiving biological DMARD until the end of the study. Only 59 (1.8%) patients were able to discontinue biologic therapy due to remission. Baseline characteristics of patients at the moment of starting biologic DMARDs are in **Table.** After multivariate SHR analysis, sex (female) (SHR 2.81 95% CI 1.01–7.83), age at onset (SHR 1.04 (95% CI 1.01–1.07) and disease duration (HR 0.94, CI 95% 0.90–0.98) were significant predictors of discontinuation due to remission adjusting by methotrexate and steroids use.

Conclusion: A small proportion (<2%) of patients with RA were able to discontinue biologic DMARD therapy due to disease remission. Sex, age at onset and disease duration were predictors of such discontinuation. The prognosis of biologic-free patients after remission is still unknown and further studies are needed to elucidate their clinical course.

Table. Baseline characteristics at the moment of starting biologic DMARDs.

	No remission N=3,102	Discontinuation for remission N=59	p value
Mean age (Years, SD)	53.9 (13.2)	58.5 (12.4)	**0.007**
Sex (Female %)	79.9	88.1	0.11
Mean disease duration (years, SD)	9.3 (8.7)	7.0 (6.0)	**0.04**
Seropositive RA (%)	89.3	89.8	0.89
Current smoking	12.2	6.8	0.20
Extra-articular disease (%)	20.1	15.3	0.35
Nodular disease (%)	7.4	5.1	0.25
Mean DAS-28 (SD)	3.75 (2.85)	4.22 (2.47)	0.21
Methotrexate (ever, %)	56.7	62.7	0.35
Steroids use (at index date, %)	53.4	59.3	0.37
DMARDs use (at index date, %)	71.2	71.2	0.99
Anti-TNF therapy (as first treatment, %)	93.9	98.3	0.15

Disclosure: J. A. Gomez-Puerta, None; **M. V. Hernández**, None; **F. Sanchez-Alonso**, None; **K. Yoshida**, None; **R. Sanmarti**, None; **D. H. Solomon**, None; **J. J. Gomez-Reino**, None; **O. B. O. BIOBADASER 2.0 study group**, None.

2512

Golimumab Therapy Retention Rates in Patients with Rheumatoid Arthritis and Seronegative Spondyloarthritis: Data from the Italian Lorhen Registry.

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Golimumab therapy retention rates in patients with rheumatoid arthritis and seronegative spondyloarthritis: data from the Italian LORHEN registry.

Background/Purpose: The efficacy of Golimumab (GLM) treatment in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) has been widely documented. In everyday clinical practice, however, many patients discontinue therapy due to adverse events (AE), lack of efficacy or other reasons. [1] We compared first year retention rates of GLM treatment among RA, PsA and AS, using the first one as reference standard, in a multicentric observational cohort (the LORHEN Registry).

Methods: All patients in the LORHEN database who started GLM were included. All patients were treated according to current EULAR recommendations for the management of RA and spondyloarthritis. Drug survival during the first year of treatment was measured, along with specific reasons for discontinuation (inefficacy or adverse events). We compared drug retention rates using the Kaplan-Meier method. Cox regression analyses, using RA as reference category, were used to adjust for age, sex, disease duration, number of previous csDMARDs and treatment with low dose prednisone.

Results: 134 RA patients, 84 PsA patients and 108 AS patients were included. 49 (37%) RA patients, 29 (35%) PsA patients and 22 (20%) AS patients discontinued treatment during the first year. Thirty-six (27%) and 12 (9%) RA patients, 17 (20%) and 11 (13%) PsA patients, 14 (13%) and 7 (6%) AS patients discontinued GLM due to lack of efficacy or AE, respectively.

Patients with a diagnosis of AS showed a lower, but not significant, risk of discontinuation, with an adjHR (95%CI) of 0.35 (0.10 – 1.17).

Patients treated with low dose prednisone showed a reduced risk of discontinuation with an adjHR (95%CI) of 0.35 (0.14 – 0.86). Age, sex, disease duration and number of previous csDMARDs did not significantly influence the risk of discontinuation.

Conclusion: AS patients seem to have better GLM retentions rates with respect to RA and PsA patients; however this difference is significantly reduced after adjusting for confounders.

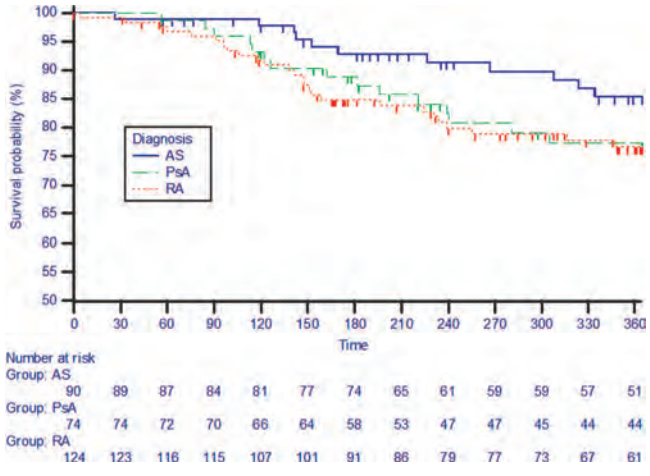
The significantly lower adjHR observed for low dose prednisone therapy might reflect a beneficial effect even in patients treated with bDMARDs.

References

[1] Scirè CA et al. Clin Exp Rheumatol. 2013;31:857–63.

Table 1. Patients at baseline. IQR: interquartile range

	RA	PsA	AS	Total
Number of patients	134	84	108	326
Male (%)	24 (18%)	41 (49%)	60 (56%)	125 (38%)
Age (years), mean (±sd)	53,42 (±17,58)	48,10 (±13,29)	48,48 (±11,92)	49,42 (±15,19)
Disease duration (yrs), mean (±sd)	8,47 (±13,79)	10,68 (±17,17)	22,56 (±33,31)	13,71 (23,62)
Active smokers, num (%)	20 (15%)	13 (15%)	21 (19%)	54 (17%)
Previous csDMARDs, num (IQR)	2 (1 – 3)	2 (1 – 2)	1 (0 – 1)	2 (1 – 2)
Treatment with prednisone, num (%)	117 (87%)	71 (85%)	68 (63%)	256 (79%)



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2513

The Monitoring of Infliximab Levels at Early Stages Can Predict the Development of Anti-Infliximab Antibodies in a Cohort of Rheumatoid Arthritis Patients Treated with Infliximab.

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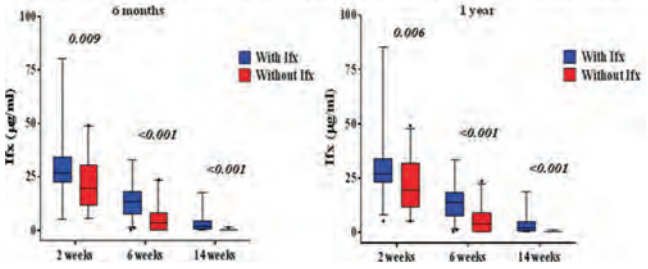
Background/Purpose: There is a close association between serum Infliximab (Ifx) levels and the Antibodies To Infliximab (ATI) with the clinical activity in rheumatoid arthritis (RA) patients. Several markers have been described to predict the response to biological therapy but for now no evidence of serological markers during the TNFi therapy is available. Our aim was to analize whether Ifx drug levels at 2, 6 and 14 weeks after starting Ifx can predict the disappereance of serum Ifx levels and ATI detection at 6 months and 1 year in a cohort of RA patients treated with Ifx.

Methods: 85 RA patients were included in this is ambispective observational study. The clinical activity was measured by DAS28 at baseline, 6 months and 1 year. The serum samples were obtained before each infusion at baseline, 2, 6 and 14 weeks after starting Ifx, 6 months and 1 year. Ifx and ATI levels were measured by ELISA. Receiver-operator characteristics (ROC) analysis were used to establish a cutt-off value for Ifx levels (2, 6 and 14 w) between patients with or without detectable Ifx levels at 6 months and 1 year. Area under the curve (AUC), sensitivity (S), specificity (SP) and positive likelihood ratio (LR+) were calculated at any studied point. The Last observation was carried forward (LOCF) for patients who dropped out before 1 year.

Results: Ifx levels at early stages (2, 6 and 14 weeks) of Ifx therapy were significantly lower in RA patients without detectable Ifx levels at 6 months and 1 year (Figure 1). Ifx levels lower than 21.2μg/ml at 2 weeks, 4.4μg/ml at 6 weeks and 0.4μg/ml at 14 weeks were predictive to Ifx disappearance at 6 months (2 weeks: AUC 0.708, S 67%, SP 87%, LR+5.1; 6 weeks: AUC 0.810, S 70%, SP 88%, LR+ 6.03; 14 weeks: AUC 0.923, S 83%, SP 92%, LR+10.4) and 1 year (2 weeks: AUC 0.708, S 64%, SP 89%, LR+5.8; 6 weeks: AUC 0.800, S 63%, SP 90%, LR+ 6.3; 14 weeks: AUC 0.923, S 75%, SP 94%, LR+13.1).

Conclusion: The monitoring of Ifx levels at early stages of therapy has a high value to discriminate which RA patients will have a faster Ifx clearance with the subsequent ATI detection and poor clinical outcomes. Patients with Ifx trough levels lower than 21.2, 4.4 and 0.4 μg/ml at 2, 6 and 14 weeks, respectively, have a high probability to develop ATI in the 1st year under the therapy.

Figure 1. Association between Ifx levels at early stages (2, 6 and 14 weeks) and Ifx status at 6 months and 1 year



Disclosure: C. Plasencia-Rodriguez, Pfizer Inc, 2; **D. Pascual-Salcedo**, Pfizer Inc, 2; **M. G. Bonilla**, None; **A. Villalba**, None; **D. Peiteado**, None; **L. Nuño**, None; **P. Aguado**, None; **T. Jurado**, None; **E. Martín-Mola**, None; **A. Balsa**, Pfizer Inc, 9.

2514

Biological Treatment for Rheumatoid Arthritis (RA): A Fifteen Years Multicentric Overview.

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Background/Purpose: During the last fifteen years, the role of biologics in the management of RA, the number of available biologics, and the recommendations of use, have changed. Moreover, several observational experiences pointed out a suboptimal adherence to the principles of treat-to-target.

The aim of this study is to assess differences in baseline characteristics of patient who started a first line biologic agent over time in a multicentric observational cohort (the LORHEN Registry) from 1999 until today.

Methods: In the LORHEN Registry, we identified all adult RA patients starting a first line biologic agent between 1 January 1999 and 31 May 2014. For the purpose of our analysis, we divided the patients in three time groups, according to the date of assessment of baseline disease variables: from 1999 to 2004 [99-04], from 2005 to 2010 [05–10] and from 2011 to May 2014 [11–14]. The comparison of baseline demographics, disease characteristics and previous treatments with csDMARDs in the 3 subgroups was performed.

Results: A total of 2373 RA patients from eight different rheumatologic centers were included. Patients treated in the [11–14] time group had a statistically significant lower baseline DAS28 and HAQ compared with previous time group. DAS28 at first switch was significantly lower in [11–14] patients, shrinking to mean values of moderate disease activity from those of high disease activity observed for patients in the [05–11] group. Disease duration and time before first switch did not differed significantly between groups.

Conclusion: The disease activity status at which RA patient starts biological treatment has progressively reduced: clinicians are now aiming at tighter control of RA activity.

The vast majority of patients starts biologic treatment only after years of csDMARDs, with an established disease, in conflict with the principles of treat-to-target. The incomplete availability of biological drugs over territory and economical concerns, in addition to incomplete adherence to international recommendations, might at least in part explain this occurrence.

The observation that real life population treated with biological drugs significantly differs for duration of disease from those selected in the majority of clinical trials should be taken into account when applying inferences from randomized controlled trials to everyday clinical practice.

Table 1. Patients at baseline. IQR: interquartile range. *Student' T test. ● Wilcoxon-Mann-Whitney' test

	Total	1999–2004	2005–2010	p with 1999–2004	2011–2014	p with 1999–2004	p with 2005–2011
Patients, num	2373	837	997		539		
Female, num (%)	1942 (80,61%)	697 (79,84%)	813 (80,15%)		432 (80,15%)		
Age in years, mean (±sd)	54,32 (±13,54)	54,81 (±13,48)	53,181 (±13,70)	ns *	55,68 (13,19)	ns *	ns *
Disease duration in year, median (IQR)	5,06 (1,74 – 11,85)	5,83 (1,26 – 12,61)	5,03 (1,83 – 11,14)	ns ●	4,74 (1,96 – 10,95)	ns ●	ns ●
Previous csDMARDs, median (IQR)	2 (2 – 3)	3 (2 – 4)	2 (1 – 3)	<0,05 ●	2 (1 – 3)	<0,05 ●	ns ●
DAS28, mean (±sd)	5,59 (±1,25)	5,93 (±1,04)	5,26 (±1,27)	<0,05 ●	5,07 (±1,28)	<0,05 ●	<0,05 ●
HAQ, median (IQR)	1,25 (0,875 – 1,875)	1,375 (1,000 – 2,000)	1,25 (0,875 – 1,625)	<0,05 ●	1,125 (0,625 – 1,625)	<0,05 ●	<0,05 ●

Table 2. Disease variables at first switch. IQR: interquartile range. *Student' T test. ● Wilcoxon-Mann-Whitney' test

	Total	2005–2010	2011–2014	p
Patients, num	626	394	232	
Months before first bDMARD discontinuation, mean (±sd)	28,77 (±28,69)	26,90 (±24,70)	31,94 (±34,25)	ns ●
DAS28, mean (±sd)	4,97 (±0,70)	5,15 (±1,30)	4,68 (±1,34)	<0,05 ●
HAQ, median (IQR)	1,125 (0,625 – 1,625)	1,250 (0,750 – 1,750)	1,125 (0,625 – 1,500)	ns ●

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2515

Serum Survivin in Early Rheumatoid Arthritis. Adrian Levitsky[1], Malin Erlandsson[2], Maria Bokarewa[2] and Ronald F. van Vollenhoven[3]. [1]The Karolinska Institute,Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), Stockholm, Sweden, [2]University of Gothenburg, Gothenburg, Sweden, [3]Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), the Karolinska Institute, Stockholm, Sweden.

Background/Purpose: The proto-oncogene survivin regulates cell division and inhibits apoptosis. Elevated levels may be found in patients with rheumatoid arthritis (RA) and their presence has been associated with joint destruction. Here, we investigated if survivin may be a marker or predictor of clinical disease activity and/or response to treatment in patients with early RA.

Methods: Serum levels of survivin were measured using ELISA at baseline in 302 patients enrolled in the Swedish pharmacotherapy (SWEFOT) trial, with follow-up at 3, 12 and 24 months. After methotrexate (MTX) monotherapy for 3 months, disease non-active patients (DAS28≤3.2, NAPs) remained on MTX, while active patients (APs) were randomized to triple therapy (MTX+sulfasalazine+hydroxychloroquine) or anti-TNF (MTX+infliximab). Analyses were based on intention-to-treat and performed with respect to baseline (BL) survivin status; conversion status from BL to 3 months; or from 3 to 12 (or 24) months, (+/+) vs. (+/−) or (−/−) vs. (−/+), respectively. Values >0.45 ng/mL were considered (+). Outcome measures included the reductions from BL to 3 months or from 3 to 12 months in the DAS28 and core-set outcomes; actual values at 3, 12, or 24 months; as well as EULAR responses.

Results: Out of 302 patients, 114 (38%) were survivin (+) at BL. The survivin (+) patients were significantly more often RF (+) (81% vs. 58%, p<0.001), but no differences were found over time vs. (−) at BL in the majority of outcome measures.

Among 294 patients with 3-month status, survivin-negative patients (−/−) (n=167) had a significantly better DAS28 and swollen joint count at 12 months vs. 3-month converters (-/+) (n=14) (median 2.89 vs. 3.76, 1.0 vs. 4.5, respectively; p<0.050). Converters to negative (+/−) by 3 months (n=11) vs. non-converters (+/+) (n=28) among NAPs had significantly greater reductions at 3 months in DAS28 and patient's global visual analog scale (PG-VAS) (3.5 vs. 2.5, 40.0 vs. 23.5, respectively; p<0.010). Among APs, converters (+/−) by 3 months had improvements by 12 months.

Conversion (+/−) from 3 to 12 (or 24) months led to significant reductions among triple therapy from 3 to 12 months (n=12) vs. (+/+) (n=15) (PG-VAS, 19.5 vs. 0.0, p=0.024), which was not observed in the same interval among anti-TNF. The positive DAS28 reduction among triple therapy (+/−) vs. anti-TNF (+/−) (1.52 vs. 0.55, p=0.082) led to significantly more EULAR Good responders from 3 to 12 months (58% (7/12) vs. 0% (0/6), p=0.038).

Conclusion: Survivin status at BL did not predict the 3-month response to MTX. Non-elevated survivin (−/−) leads to better outcomes than (−/+) after 3 months' MTX treatment, whereas conversion (+/−) by 3 months is associated with greater clinical improvements than (+/+) primarily among MTX responders at 3 months, but also by 12 months among 3-month MTX non-responders. Among patients randomized to triple therapy, those whose survivin converted (+/−) from 3 to 12 months had better 12-month outcomes than non-converters (+/+). This association was not seen for patients randomized to anti-TNF, suggesting that survivin may be associated with TNF-independent inflammatory pathways.

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2516

Reasons and Risk Factor for Discontinuation of Biologic Agents in Rheumatoid Arthritis Patients. Kenya Terabe[1], Toshihisa Kojima[1], Nobunori Takahashi[1], Koji Funahashi[1], Atsushi Kaneko[2], Yuji Hirano[3], Yasuhide Kanayama[4], Yuichiro Yabe[5] and Naoki Ishiguro[1]. [1]Nagoya University Graduate School of Medicine, Nagoya, Japan, [2]Nagoya Medical Center, Nagoya, Japan, [3]Toyohashi Municipal Hospital, Toyohashi, Japan, [4]Toyota Kosei Hospital, Toyota, Japan, [5]JCHO Tokyo Shinjuku Medical Center, Tokyo, Japan.

Background/Purpose: Rheumatoid arthritis (RA) patients who failed a first biologic agent due to any reasons have the option of switching to a second one along with the strategy of biologic agent treatment. Patients go

over switching to the next one at failing their biologic agent. On the other hand, there are some patients who discontinue any biologic agent treatment due to various reasons such as tolerability concern, complications, economic issue, remission and so on. The impact of this concern has been less studied.

The objective of this study was to investigate the reasons and the risk factors for discontinuation any biologic agent in RA patients.

Methods: In total patients (n=2179) who underwent biologic agent treatment between 2003 and 2011 at Nagoya University Hospital and 12 other institutes (Tsurumai Biologics Communication Study Group), 1966 patients who were confirmed continuation or discontinuation of biologic agent treatment were enrolled. We analyzed the retention rate of biologic agent treatment and the reasons for discontinuation. To identify the risks for discontinuation, baseline demographics were compared between the continuing group and the disccontinuing group using cox hazard regression analysis.

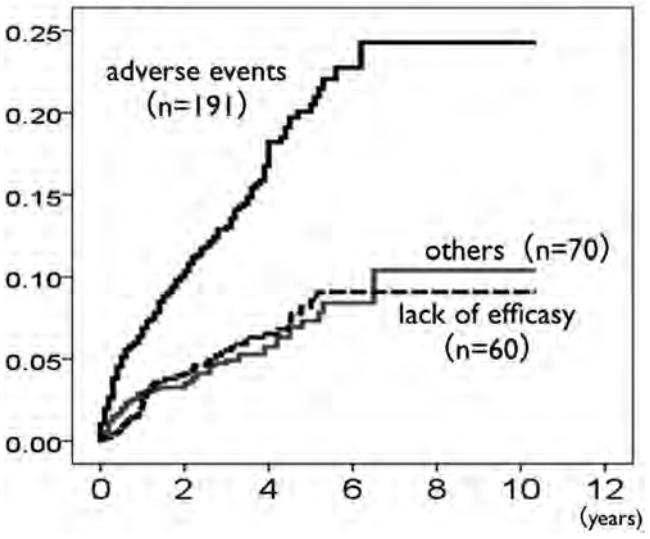
Results: In total 1966 patients, 1479 patients were administered biologics continuously, 487 patients were withdrew. Table 1 showed the demographic date in total patients. The retention rate was 72% (n=1563) at least 1 year from starting biologics treatment, 68.7% (n=866) at 3 years, 65.6% (n=360) at 5 years. In 327 patients who were confirmed the reasons of discontinuation, the reasons were adverse events in 191 patients, lack of effectiveness in 66 patients, others in 70 patients. Comparison of incidence for discontinuation using cumulative hazard function, the reason of adverse events was significantly higher than others reasons (Figure 1). To identify o the risks of discontinuation, we used cox hazard model regression in patients who discontinued treatment due to adverse events and lack of effectiveness, the risk factors were over 70 years of age (OR 1.80 [1.31–2.46]), male (OR 1.79 [1.27–2.52]), over 3 of steinblocker class (OR 1.51 [1.12–2.04]). Non concomitant with methotrexate (OR 1.47 [1.06–2.04]).

Conclusion: The most common reason for discontinuation was adverse events. In a numerically greater proportion of patients who discontinued any biologic agent treatment, timing of discontinuation was within a first year from starting treatment. In addition, the risk factors for discontinuation were similar with those of adverse events.

Table 1.

Age (years)		60 ± 18
Gender	n (% male)	326 (17%)
	n (% female)	1547 (83%)
Disease duration (years)		14.6 ± 10.3
stage	I, II	29%
	III, IV	71%
class	1, 2	62%
	3,34	38%
Methotrexate use, no (%)		1018 (75%)
Corticosteroid use, no (%)		782 (58%)
DAS-ESR at starting		5.26 ± 1.27

Figure 1



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2517

Long-Term Clinical, Structural, and Functional Consequences of Not Adopting Treatment in MTX Suboptimal Responders.

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Background/Purpose: Methotrexate (MTX) is used as first line therapy for treatment of rheumatoid arthritis (RA). Current recommendations state that therapy should be adjusted if patients (pts) fail to attain remission or low disease activity (LDA) after 6 mo of MTX, and TNF inhibitors could be considered for pts with high risk of aggressive disease. The objective of this post hoc analysis was to identify the benefits of treatment adjustment vs no treatment adjustment in pts who did not achieve a stable LDA after 6 mo of MTX.

Methods: A post hoc analysis from OPTIMA and PREMIER was conducted in MTX-naïve, early RA pts. In OPTIMA, non-achievers (NAs) were defined as pts failing to achieve a stable LDA target of DAS28(CRP) <3.2 at weeks (wks) 22 and 26 following placebo (PBO)+MTX for 26 wks. Pts who were NAs to MTX switched to open-label (OL) ADA+MTX for an additional 52 wks. In PREMIER, following MTX monotherapy, NAs were defined as pts failing to achieve a stable LDA target at wks 20 and 24; however, these pts continued MTX monotherapy up to 104 wks. Clinical and functional outcomes were evaluated at wk 78 and 76 for OPTIMA and PREMIER, respectively, while radiographic outcomes were evaluated at wk 78 for OPTIMA and both wks 52 and 104 for PREMIER. Additionally, ANOVA and logistic regression analysis was conducted on continuous and dichotomized endpoints, respectively, with the following baseline characteristics as variables: age, sex, RA duration, RF status, previous DMARD use, tender joint count, swollen joint count, C-reactive protein, DAS28 score, HAQ-DI, mTSS, erosion score, and estimated annual TSS progression.

Results: 348 out of 517 total pts in OPTIMA and 172 out of 257 total pts in PREMIER did not achieve a stable LDA target of DAS28(CRP) <3.2 after 26 and 24 wks of MTX monotherapy. In those NAs, mean disease duration at baseline was 0.3 and 0.8 for OPTIMA and PREMIER, respectively. In OPTIMA, the mean DAS28(CRP), HAQ-DI, and mTSS at baseline for NAs were 6.1, 1.7, and 11.7, respectively. In comparison, the mean DAS28(CRP) at baseline from the NAs in the PREMIER trial was 6.4, while the HAQ-DI and mTSS were 1.6 and 23.4, respectively. There was a significant decrease compared to baseline in the clinical and functional outcomes for both pts who were given OL ADA+MTX as well as pts who remained on MTX monotherapy; however, compared with pts who continued MTX, there was a significant increase in the percentage of pts achieving LDA and remission, according to all scores used, for those who switched to combination therapy with ADA+MTX (Table). Additionally, a larger proportion of pts showed no radiographic progression in the OPTIMA trial, where pts were switched to OL ADA+MTX after 26 wks.

Table. Clinical, Functional, and Radiographic Outcomes at Week 78 and 76 for Patients who were Non-Achievers to MTX Monotherapy in OPTIMA and PREMIER

n (%)	OPTIMA[a] N=348[c]	PREMIER[b] N=172[c]	P-Value
DAS28(CRP), mean (SD)	2.9 (1.2)	3.7 (1.2)	<0.001[d]
DAS28(CRP) <2.6	138 (39.7)	23 (13.4)	<0.001[e]
DAS28(CRP) <3.2	185 (53.2)	51 (29.7)	<0.001[e]
SDAI ≤3.3	92 (26.4)	11 (6.4)	0.006[e]
CDAI ≤2.8	94 (27.0)	11 (6.4)	0.005[e]
HAQ-DI, mean (SD)	0.7 (0.6)	0.8 (0.7)	0.062[d]

HAQ-DI <0.5	125 (35.9)	49 (28.5)	0.091[e]
DHAQ-DI ≤0.22 from week 26	161 (46.3)	36 (20.9)	0.016[e]
mTSS, mean (SD)	12.6 (18.2)	29.6 (25.6)	<0.001[d]
DmTSS ≤0.5 from week 26	237 (68.1)	63 (36.6)	<0.001[e]
CDC[f] from week 26	77 (22.1)	7 (4.1)	<0.001[e]

CDAI, clinical disease activity index; CDC, comprehensive disease control; CRP, C-reactive protein; DAS28, 28-joint disease activity score; HAQ-DI, disability index of the health assessment questionnaire; mTSS, modified total Sharp score; SDAI, simplified disease activity index.
[a]Clinical, functional, and radiographic outcomes at week 78. [b]Clinical and functional outcomes at week 76 and radiographic and CDC outcomes shown for week 52. [c]N consists of patients treated with PBO+MTX who do not achieve a DAS28(CRP) <3.2 at week 24/26 or week 20/24 for OPTIMA and PREMIER, respectively. [d]p-values derived from ANCOVA model adjusted for baseline values. [e]p-values based upon the difference between the OPTIMA and PREMIER study using a logistic regression model adjusted for baseline characteristics. [f]CDC is defined as DmTSS ≤0.5, DAS28(CRP) <2.6, and HAQ-DI <0.5.

Conclusion: Not adjusting treatment in pts who did not receive a stable LDA after 6 mo of initial MTX appears to result in worse long-term clinical, functional, and structural outcomes compared to pts whose treatment was adjusted by adding ADA.

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2518

What Is the Level of Agreement Between Disease Activity Indices and Response Criteria Among Rheumatoid Arthritis Patients Treated with TNF Inhibitors? Edward C. Keystone[1], Philip Baer[2], J. Antonio Avina-Zubieta[3], Anna Jaroszynska[4], Jude Rodrigues[5], Regan Arendse[6], Dalton Sholter[7], Michael Starr[8], Ariel Masetto[9], John S. Sampalis[10], Emmanouil Rampakakis[10], Francois Nantel[11], May Shawi[11], Allen J Lehman[11] and Susan Otawa[11]. [1]University of Toronto, Toronto, ON, [2]Private Practice, Scarborough, ON, [3]Arthritis Research Centre of Canada, Richmond, BC, [4]Private Practice, Burlington, ON, [5]Clinical Research and Arthritis Centre, Windsor, ON, [6]University of Saskatchewan, Saskatoon, SK, [7]University of Alberta, Edmonton, AB, [8]McGill University Health Centre, Montreal, QC, [9]CHUS, Fleurimont, QC, [10]JSS Medical Research, Montreal, QC, [11]Janssen Inc., Toronto, ON.

Background/Purpose: Several standardized response criteria and disease activity indices are used to assess treatment efficacy in rheumatoid arthritis (RA). These measures comprise different types and number of variables resulting in different weighting of individual variables within each of them (1). The aim of this analysis was to compare the performance of ACR, SDAI major and minor, and HAQ response criteria and to determine their level of agreement with the DAS28, SDAI, and CDAI definitions of low disease activity (LDA) and remission in RA patients treated with infliximab (IFX) or golimumab (GLM) in a real-world, Canadian, clinical practice setting.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, AS, or PsA with IFX or GLM. The analysis was based on RA patients treated with IFX between 2002–2014 or GLM between 2010–2014. **Response** was assessed with ACR20, ACR50, ACR70, HAQ improvement of 0.22 and 0.5, SDAI major (≥22) and minor improvement (≥10). **Disease state** was assessed with DAS28, SDAI, and CDAI definitions of LDA (<3.2, ≤11, ≤10, respectively) and remission (<2.6, ≤3.3, ≤2.8, respectively). The level of agreement was assessed with the proportion of concordant pairs over the total number of cases in each cross-tabulation and the Kappa statistic.

Results: A total of 830 RA patients with 4,100 available observations were included. The criteria for each definition of response/disease state were met for the following proportion of cases: ACR20 (66.4%), ACR50 (44.5%), ACR70 (26.4%), ΔHAQ≥0.22 (65.5%), ΔHAQ≥0.5 (53.4%), SDAI major improvement (55.8%), SDAI minor improvement (80.8%), DAS28 remission (29.4%), CDAI remission (20.4%), SDAI remission (21.8%), CDAI LDA (57.5%), SDAI LDA (58.1%), and DAS28-ESR LDA (46.0%).

Table 1 summarizes the level of agreement between different efficacy measures. Statistically significant (Kappa P<0.001) associations were observed for all combinations of variables examined. Overall, the ACR response criteria performed better than the HAQ and SDAI response criteria in their agreement with LDA and remission. In general, higher levels of response in all three measures (ACR20 vs. ACR50 vs. ACR70; ΔHAQ≥0.22 vs. ΔHAQ≥0.5; SDAI minor vs. major) showed better agreement with LDA and remission. The highest level of agreement between response criteria and disease state was observed between the strictest definitions, namely between ACR70 and CDAI / SDAI remission; whereas, SDAI minor improvement showed the lowest level of agreement with remission, irrespective of definition.

Conclusion: This analysis showed that significant variation exists in the agreement between the various efficacy outcome measures. Thus, the choice of outcome measure used to make treatment decisions could have a significant impact on patient management.

Reference:
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Table 1: Percent agreement of response criteria

Disease Parameter	DAS28 LDA	SDAI LDA	CDAI LDA	DAS 28 Remission	SDAI Remission	CDAI Remission
ACR 20	61.7	72.1	71.4	52.0	72.4	48.4
ACR 50	70.0	76.3	75.1	67.1	68.6	68.9
ACR 70	71.1	69.2	68.8	74.5	82.1	82.6
HAQ 0.22	56.1	63.1	62.0	47.2	44.1	44.3
HAQ 0.5	59.6	64.2	63.0	55.8	55.6	56.2
SDAI Major	54.8	62.3	61.4	49.3	52.5	52.3
SDAI Minor	52.9	64.9	63.9	39.7	37.2	36.6

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2519

Are Patients with Rheumatoid Arthritis Initiating a TNF Biologic Comparable to Patients Initiating a Non TNF? Kaleb Michaud[1], Kunal Gandhi[2], Teresa Simon[3] and Sofia Pedro[1]. [1]National Data Bank for Rheumatic Diseases, Wichita, KS, [2]Bristol-Myers Squibb, Princeton, NJ, [3]Bristol-Myers Squibb, Hopewell, NJ.

Background/Purpose: Comparative research has gained attention in the field of Rheumatology. Evaluations of baseline characteristics in patients receiving similar treatments are critical in the conduct of comparative observational research to assess medication safety and effectiveness in rheumatoid arthritis (RA). Appropriate methods used in comparative research are critical. Making certain assumptions regarding the underlying distribution of baseline characteristics and the targeted population is important. Most patients receive TNF inhibitors (TNFi) as a first biologic for the treatment of RA; however, increasing numbers are starting with a non TNFi (NTNFi) biologic as an initial biologic treatment. The purpose of this analysis is to compare baseline characteristics of RA patients receiving abatacept (ABA) and other NTNFi with those taking TNFi as their first biologic.

Methods: RA patients in the National Data Bank for Rheumatic Diseases (NDB) provide treatment and other characteristics (demographics, comorbidities, and clinical status) through self-reported biannual questionnaires. Data during the period of 2005 through 2013 were used as this timeframe includes data when the first NTNFi biologics were marketed. We also limited analyses to patients who completed a questionnaire within 6-months prior to initiating their first biologic. P-values were based on ANOVA test for continuous and Chi^2 tests for categorical measures.

Results: A total of 2,125 RA patients *(1,916 TNFi; 129 NTNFi; 80 ABA)* initiated their first biologic therapy after 2005. ABA patients were significantly older and have a higher proportion of diabetes and cancer when compared to TNFi (see Table). ABA patients reported significantly higher pain, fatigue, and activity scores than TNFi initiators. When compared to the NTNFi patients, ABA patients are older and reported slightly higher baseline pain. The NTNFi patients are more likely to have diabetes and hypertension.

	ABA (N=80)	TNFi (N=1,916)	NTNFi (N=129)
Age (yrs)*	64.6 (12.5)	58.5 (12.7)	60.8 (13.4)
BMI (kg/m2)	29.2 (6.2)	28.9 (7.1)	29.1 (6.7)
Disease Duration (yrs)	13.3 (13.5)	14.2 (10.9)	14.3 (11.1)
Ever Smoked (%)	51.3	52.3	56.6
Comorbidity Index (0–9)*	2.2 (1.8)	1.6 (1.5)	2.1 (1.7)
Cancer (%)*	32.5	19.2	31.8
Hypertension (%)*	33.8	35.2	47.3
Diabetes (%)*	13.8	10.5	17.1
Hospitalized Infection (%)	0.0	1.5	2.3
Congestive Heart Disease (%)	0.0	0.6	0.0
Prednisone (%)	38.8	32.7	37.2
MTX (%)*	65.0	67.5	45.7
Other DMARD (%)	22.5	15.2	24.8
HAQ (0–3)*	1.2 (0.7)	1.0 (0.7)	1.2 (0.7)
Pain VAS (0–10)*	5.1 (3.0)	4.2 (2.8)	4.4 (2.9)
Fatigue VAS (0–10)*	5.4 (3.3)	4.6 (3.1)	5.3 (3.1)
Patient Activity Scale (0–10)*	4.2 (2.2)	3.1 (0.7)	3.4 (0.7)

*P value < 0.05

Conclusion: RA patients who receive a NTNFi as their first biologic differ from those initiating TNFi. Proper application of statistical methods and careful examination of baseline characteristics including co-morbid chronic conditions, prior/concomitant medications and biologic use is critical when performing comparative effectiveness analyses. Line of therapy should also be considered in future comparative research analyses.

Disclosure: K. Michaud, None; **K. Gandhi**, Bristol-Myers Squibb, 3; **T. Simon**, Bristol-Myers Squibb, 3; **S. Pedro**, None.

2520

Patient, Genetic and Disease Factors Influence the Response to the Disease Modifying Anti-Rheumatic Drug Leflunomide. Michael D. Wiese[1], Ashley Hopkins[1], Llew Spargo[2], Leah McWilliams[2], Catherine O'Doherty[1], Leslie G. Cleland[2] and Susanna Proudman[3]. [1]University of South Australia, Adelaide, Australia, [2]Royal Adelaide Hospital, Adelaide, Australia, [3]Royal Adelaide Hospital, SA, Australia.

Background/Purpose: Leflunomide is a disease modifying anti-rheumatic drug that is used in the treatment of rheumatoid arthritis (RA). Leflunomide is converted to teriflunomide by the Cytochrome P450 enzymes 1A2, 2C19 and 3A4, which is cleared via secretion into the gastro-intestinal tract by the transporter ABCG2. The primary mechanism of action is inhibition of di-hydroorotate dehydrogenase (DHODH) by teriflunomide. It is very effective in some patients, but treatment can be limited by intolerance and/or lack of efficacy. This study aimed to determine steady state teriflunomide concentration in a group of patients with RA and correlate steady state concentrations with response to leflunomide.

Methods: Patients with RA taking a stable dose of leflunomide according to a treat-to-target strategy were recruited from the Royal Adelaide Hospital Early Arthritis Clinic. Blood samples were taken for determination of free teriflunomide concentration and genetic differences in CYP1A2, CYP2C19, ABCG2 and DHODH. Disease activity was assessed by the 28-joint disease activity scores (DAS28). Factors associated with teriflunomide concentration and DAS28 were assessed by multivariate linear regression.

Results: 55 patients were included. The average leflunomide dose was 16.1mg/day, and the free teriflunomide concentration was 0.062mg/L - there was a 150-fold difference between maximum and minimum concentration. Leflunomide dose accounted for 10% of the variability in free teriflunomide concentration, and this increased to 38% when *CYP1A2* and *ABCG2* genotype were considered. 25 patients took leflunomide for at least 9 months (no other agents were added for treatment failure) and 76% of the variability in DAS28 was accounted for by considering baseline DAS28, shared epitope carriage, *DHODH* haplotype and free teriflunomide concentration.

Conclusion: Pharmacokinetic and pharmacogenomic variables appear to be associated with response to leflunomide in a group of RA patients treated according to a treat-to-target strategy, but this should be assessed in a prospectively recruited cohort.

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2521

Analysis on Predictors for Long-Term Clinical Efficacies of Golimumab in Patients with Rheumatoid Arthritis. Tsutomu Takeuchi[1], Yutaka Ishii[2], Kimie Tanaka[3], Yoshifumi Ukyo[4] and Hiroshi Sekine[3]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Janssen Pharmaceutical K.K, Tokyo, Japan, [3]Janssen Pharmaceutical K.K., Tokyo, Japan, [4]Janssen Pharmaceutical K.K., Japan, Tokyo, Japan.

Background/Purpose: The GO-FORTH, phase 2/3 clinical trial was conducted to examine the efficacy and safety of Golimumab (GLM) plus MTX in Japanese patients (pts) with active RA despite MTX therapy (NCT00727987). In treatment for RA, it has been recommended to assess the clinical disease activity at least every 3 months according to the treat to target (T2T) recommendation. Therefore, predictors of long-term efficacy with GLM treatment using clinical data at baseline and 3 months would seem to be extremely important.

Objective

To assess the predictability of using clinical data at baseline and week 12 (W12) after GLM treatment in GO-FORTH study, for achievement of each remission criteria after 1-year.

Methods: GO-FORTH was a multicenter, randomized, double-blind, placebo-controlled study in pts with active RA despite MTX therapy. Pts were randomized to Placebo (PBO), GLM50 mg or GLM 100 mg q4 wks combined with MTX (6–8 mg/ week). Data of all pts who were randomized to GLM 50 mg or GLM 100mg as active treatment were used for analysis. Several definitions of remission at week 52 (W52) were used and defined as: DAS remission (DAS28ESR <2.6), HAQ remission (HAQ <0.5) and radiographic remission (‡TMTSS $<=0$). Akaike Information Criteria (AIC) were calculated to assess predictability with all possible predictors using univariate logistic regression model. Area under the curves (AUC) were calculated to assess the performance of possible predictors using receiver operating characteristics (ROC) curves. Cutoff values were also calculated using Euclidean method. The correlations between possible predictors were carefully considered to determine predictor.

Results: DAS28ESR score at W12 was chosen based on the values of AIC as a possible predictor of DAS remission at W52. HAQ score at W12 was also chosen as a possible predictor of HAQ remission at W52. Similar trends were observed in the both scores at baseline. The cutoff point (AUC) of DAS28ESR for DAS remission with GLM 50 mg and GLM 100 mg at W12 were 3.0 (0.876) and 3.5 (0.863), then cutoff point of HAQ score for HAQ remission with them were 0.625 (0.880) and 0.500 (0.958), respectively (see table). The results of baseline and PPVs/ NPVs for each determined predictors were also calculated as table shown. Both potential predictors showed larger AUC and smaller cutoff values at W12 than those at the baseline. There were no noticeable differences between GLM 50mg and GLM 100mg in the potential predictors. Predictors for radiographic remission were not specified by this analysis.

Conclusion: These analyses suggest that DAS28ESR and HAQ score at baseline and W12 can be predictors for DAS remission and HAQ remission at W52 in Japanese pts treated with GLM combined with MTX individually. In particular in terms of DAS remission, it seems to be important to achieve LDA within 3 months to maintain long term clinical remission.

Table. AUC and PPV/NPV for each possible predictor calculated with GLM pts data

			Baseline		12 weeks	
Prediction (1-year)	**Group**	**Possible Predictor**	**AUC [PPV, NPV]**	**Cutoff Value**	**AUC [PPV, NPV]**	**Cutoff Value**
DAS remission	GLM 50mg	DAS (ESR)	0.736 [70.0%, 73.8%]	5.1	0.876 [85.7%, 81.8%]	3.0
	GLM 100mg	DAS (ESR)	0.748 [55.2%, 82.2%]	5.3	0.863 [63.3%, 88.6%]	3.5
HAQ remission	GLM 50mg	HAQ	0.749 [75.0%, 70.6%]	0.875	0.880 [82.9%, 83.9%]	0.625
	GLM 100mg	HAQ	0.800 [84.2%, 55.6%]	0.875	0.958 [95.2%, 75.0%]	0.500

Disclosure: T. Takeuchi, Abbott Japan Co., Ltd., Astellas Pharma, Bristol–Myers K.K., Chugai Pharmaceutical Co, Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Sanofi–Aventis K.K., Santen Pharmaceutica, 2, Abbott Japan Co., Ltd., Bristol–Myers K.K., Chugai Pharmaceutical Co,. Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., Astellas Pharma, Diaichi Sankyo Co.,Ltd., 8, Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., Asahi Kasei Medical K.K., Abbivie GK, Daiichi Sankyo Co.,Ltd., 5; **Y. Ishii**, Janssen Pharmaceutical K.K., 3; **K. Tanaka**, Janssen Pharmaceutical K.K., 3; **Y. Ukyo**, Janssen Pharmaceutical K.K., 3; **H. Sekine**, Janssen Pharmacetutical K.K., 3.

2522

Effect of Infliximab Dose Increase in Rheumatoid Arthritis at Different Trough Concentrations. Alejandro Balsa[1], Chamaida Plasencia-Rodriguez[2], Maria Gema Bonilla[3], Alejandro Villalba[2], Diana Peiteado[2], Sara Garcia-Carazo[4], Laura Nuño[1], Teresa Jurado[5], Emilio Martín-Mola[6] and Dora Pascual-Salcedo[3]. [1]Hospital La Paz-IdiPaz, Madrid, Spain, [2]Hospital La Paz - IdiPaz, Madrid, Spain, [3]La Paz University Hospital, Madrid, Spain, [4]Hospital La Paz-Idipaz, Madrid, Spain, [5]La Paz University Hospital-Idipaz, Madrid, Spain, [6]Hospital Universitario La Paz, Madrid, Spain.

Background/Purpose: To evaluate the effects of infliximab (Ifx) dose increase in active rheumatoid arthritis (RA) patients, presenting different serum infliximab concentrations.

Methods: Retrospective study including 42 RA patients treated with increased Ifx following insufficient response (DAS28 > 3.2). Serum concentrations of Ifx and antibodies to Ifx (ATI) were recorded together with DAS28 and EULAR clinical response parameters throughout a year prior (T1) and after increasing dose (T2: immediately post-increase, T3: 6 months after T1 and T4:1 year after T1). Analyses were carried out with three patient groups defined by Ifx serum concentration prior to treatment enhancement: no detectable levels, (NL), low levels (LL< 1.1 μg/ml) or high levels (HL≥1.1 μg/ml). This cut-off was chosen empirically, based on most patients with Ifx levels >1.1 μg/ml experienced clinical improvement in our cohort.

Results: The demographic characteristics are shown in the Table 1. Twenty patients (47.6%) were classified in NL, while 13 (30.9%) and 9 (31.4%) showed LL and HL respectively. Due to drug interference with ELISA, ATI were only detected in NL patients. DAS28 improved immediately after increasing Ifx dosage, from baseline (4.55±1.01 *vs* 3.95±1.22; p<0.05 after Bonferroni correction), but the improvement did not persist at 1 year (3.98±1.22; p=0.075 after Bonferroni correction). The change in DAS28 from baseline (deltaDAS28) followed a similar pattern (−0.63±1.18 at T2 to 1.17±1.45 at T4 (p<0.001))(Figure 1). Overall, 5 (13.2%) patients achieved a good response by EULAR response after the first dose increase, whereas 18 (47.4%) patients had no response. At T4, 3 (10.7%) patients showed a good response and 18 (64.3%) remained non-responders.

Conclusion: These results suggest that the effectiveness of Ifx dose increase after therapeutic failure is limited, independently of pre increase serum trough infliximab concentrations.

Figure 1. (A) Changes in DAS28 over time in all patients. T1 (baseline), T2 (post-infliximab dose increase), T3 (at 6 months), T4 (at 12 months). *p<0.05 *vs* DAS28 in T1 after Bonferroni correction. **(B) DAS28 and delta DAS28 from T1 in patients with No, Sub-therapeutic (ST) and High Infliximab serum concentrations.** T1 (baseline), T2 (post-infliximab dose increase), T3 (at 6 months), T4 (at 12 months)

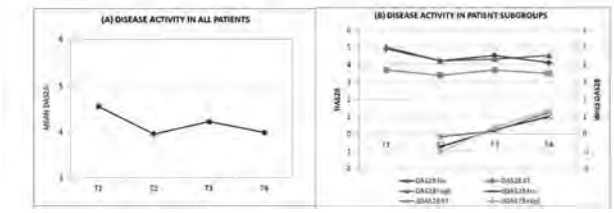

Table 1. Demographic and clinical characteristics of patients

	Overall study population (n=42)	No detectable infliximab levels (n=20)	Sub-therapeutic infliximab levels (n=13)	High infliximab levels (n=9)
Age at onset (years), mean ± SD	57.1 ± 14.0	49.6 ± 14.5	61.6 ± 10.8	67.4 ± 6.1
Female, n (%)	37 (88.1%)	19 (95%)	9 (69.2%)	9 (100%)
Disease duration (years), mean ± SD	19.4 ± 10.4	16.3 ± 6.3	17.9 ± 10.1	28.3 ± 13.8
Duration of Ifx treatment (years), median (IQR)	62 (1–13)	4.25 (1.23–8.63)	6.25 (4.38–10.75)	8.25 (8.25–10.25)
ACPA-positive, n (%)	36 (85.7%)	19 (95%)	12 (92.3%)	5 (55.6%)
RF-positive, n (%)	35 (83.3%)	18 (90%)	10 (76.9%)	7 (77.8%)
Concomitant methotrexate before Ifx dose increase, n (%)	30 (71.4%)	X	X	X
Methotrexate dose mg/week, median (IQR)	12.5 (0–25)	15.0 (0–15)	7.5 (0–20)	0.0 (0–15)
Other DMARDs*, n (%)	X	X	X	X
Concomitant use of glucocoticoids, n (%)	X	X	X	X
DAS28 at the start infliximab treatment, mean±SD	5.50 ± 1.20	5.68 ± 1.29	5.03 ± 1.04	5.77 ± 1.12
Baseline DAS28 before infliximab increase, mean±SD	4.55 ± 1.01	4.91 ± 0.73	3.72 ± 0.90*	4.97 ± 1.06
Trough infliximab levels before dose increase (μg/mL), median (IQR)	94.5 (0–10.5)	ND	574 (16–1024)	2112 (1152–10464)
ATI levels before infliximab increase, (AU/mL) median (IQR)	0 (0–60000)	1068 (3775–12,328)	0 (0–0)	ND
Treatment withdrawal, n (%)	X	X	X	X

Abbreviations: ATI: Anti-infliximab antibodies; SD: standard deviation; RA: rheumatoid arthritis; RF: rheumatoid factor; ACPA: anti-critrullinated peptide antibodies; DAS28: disease activity score in 28 joints; IQR: interquartile range; AU/mL: arbitrary units per ml; ND: not detectable.

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2523

Are Biologic Agents Effective on the Treatment of Secondary Amyloidosis: A Multicenter Report on Turkish Rheumatoid Arthritis and Ankylosing Spondylitis Patients. Omer Nuri Pamuk[1], Umut Kalyoncu[2], Kenan Aksu[3], Salim Donmez[4], Yavuz Pehlivan[5], Yonca Cagatay[6], Ahmet Omma[7], Orhan Küçükşahin[8], Gozde Yildirim Cetin[9], Özün Bayındır[10], Fatih Yildiz[11], Ayse Balkarli[12], Levent Kilic[13], Necati Cakir[14], Bunyamin Kisacik[15], Ahmet Mesut Onat[15], Mustafa Ferhat Özgür[16], Veli Cobankara[12] and Mehmet Sayarlioglu[17]. [1]Trakya University Medical Faculty, Edirne, Turkey, [2]Hacettepe University School of Medicine, Ankara, Turkey, [3]Ege University School of Medicine, Izmir, Turkey, [4]Trakya University School of Medicine, Edirne, Turkey, [5]Uludag University, School of Medicine, Bursa, Turkey, [6]Bilim University Faculty of Medicine, Istanbul, Turkey, [7]IST. UNV. TIP FAK. HASTANESI, ISTANBUL, Turkey, [8]Trakya University Medical Faculty, İstanbul, Turkey, [9]None, Kahramanmaras, Turkey, [10]Ege University Medical Faculty, Izmir, Turkey, [11]Cukurova University, School of Medicine, Adana, Turkey, [12]Pamukkale University School of Medicine, Denizli, Turkey, [13]Hacettepe University Faculty of Medicine, Ankara, Turkey, [14]Fatih Sultan Mehmet State Hospital, İstanbul, Turkey, [15]Gaziantep University School of Medicine, Gaziantep, Turkey, [16]Uludag University Medical Faculty, Bursa, Turkey, [17]KahramanmarasSutçü ImamUniversity School of Medicine, Kahramanmaras, Turkey.

Background/Purpose: Biologic drugs including anti-TNF agents have been used in the treatment of secondary amyloidosis, however, there is no controlled study concerning the efficacy of therapy. In this study, we retrospectively analyzed the clinical features and outcome of RA and AS patients with clinically symptomatic secondary amyloidosis who were treated with any of the biologic agents in various rheumatology centers in Turkey.

Methods: The hospital files in 10 university hospitals were examined to determine the presence of clinically apparent amyloidosis in RA and AS. Data concerning the clinical features, extraarticular involvement and biologic and other treatment response were obtained from hospital records.

Results: 27 RA (17F, 10M, mean age: 52.2), 42 AS (11F, 31M, mean age: 45.6) patients were included. Rheumatoid factor (RF) was positive in 24 (88.9%) RA patients. In 25 RA patients, the initial presentation of amyloidosis was with proteinuria; one had hematuria; and one patient prsented with renal dysfunction. Eight patients with proteinüria had also renal dysfunction.

The disease duration of RA patients before amyloidosis was 127.9 months; the duration of biologic therapy was 47.9 months. The first-line therapy was TNF-blockers in 21 RA patients; rituximab and abatacept in 2; and tociluzumab in one. Second-line biologicals were used because of side effects in 1 patient; and because of nonefficacy in 8 (2 TNF blocker, 4 rituximab, 2 tocilizumab, 1 abatacept). Third-line therapy was given to 4 patients. Renal function and/or proteinuria improved in 7 patients; however, they got worse in 7; and remained stable in 13. When patients who improved were compared to others, it was seen that there were more females (100% vs. 50%, p=0.026); and significantly longer duration of biologic therapy in this group. 2 patients using biologics developed tuberculosis; 3 patients died during follow-up because of nondrug-related causes. Renal replacement therapy was needed in 5 RA patients. 28 AS patients presented with proteinuria, 2 with hematuria, and 4 with isolated renal dysfunction. At the time of diagnosis for amyloidosis, 13 patients had also renal dysfunction. The disease duration of RA patients before amyloidosis was 101.2 months. All had been given anti-TNF agents as first-line therapy (infliximab in 13; etanercept in 19; adalimumab in 7; golimumab in 3 patients). 10 patients were switched to a second anti-TNF (because of serious side effects in 2 and nonefficacy in 8). Proteinuria and/or renal functions improved in 11 cases, got worse in 14, and remained stable in 9 after anti-TNF therapy. The results could not be evaluated in 8 patients. Initial CRP levels of patients who had any kind of improvement with anti-TNF therapy were significantly higher than others (p=0.007). There was requirement for renal replacement therapy in 11 AS patients.

Conclusion: Amyloidosis develops in RA and AS nearly 10 years after diagnosis; and it generally presents with proteiuria and/or renal dysfunction. In RA, the response to biologics was associated with a longer response to biologics and female sex. In AS patients, having a high CRP at the time of diagnosis of amyloidosis was associated with response to anti-TNF agents.

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2524

Smoking and Response to Rituximab in Anti-CCP Positive and Negative Rheumatoid Arthritis – Results from an International European Collaboration.

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Background/Purpose: Smoking has been identified as an important negative predictor of response to antirheumatic therapy. The aim of this study was to assess whether smoking status influenced the clinical response to rituximab (RTX) in an observational patient cohort with rheumatoid arthritis (RA).

Methods: Pooled data from the Collaborating European Registries for RTX in RA (CERERRA) project were used. Patients with RA who received at least 1 cycle with RTX and had at least 2 follow-up visits were included in the analyses. Smoking status was defined as smokers (current smokers) and non-smokers (never and ex-smokers). Baseline characteristics were compared by means of descriptive statistics. Analysis of co-variance (ANCOVA) was performed with DeltaDAS28 at 6 months as the dependent variable and smoking status as well as other baseline variables (age, sex, disease duration, number of prior biologic DMARDs) as covariates. Separate analyses were made for anti-CCP positive and negative patients.

Results: A total of 2431 patients with available smoking information were included - 1916 (79%) were non-smokers and 515 (21%) were smokers. 81% were female and 80% (out of 1199 patients with available anti-CCP status) were anti-CCP positive. Smokers had shorter disease duration than non-smokers (mean±SD = 9.9±7.9 vs. 11.9±8.7, $p<0.0001$), higher number of prior biologic DMARDs (1.3±1.1 vs. 1.0±1.0, $p<0.0001$) and lower DAS28 at baseline (5.1±1.7 vs. 5.7±1.5, $p<0.0001$). 16% of females and 42% of males were smokers ($p<0.0001$). 84% of smokers and 78% of non-smokers were anti-CCP positive ($p=0.04$).

Smokers had less improvement in disease activity than non-smokers at 6 months follow-up (mean±SD DeltaDAS28 -1.5±1.7 vs. -1.8±1.7, respectively, $p=0.01$). However, the difference was no longer significant after adjustment for baseline differences (age, sex, disease duration, number of prior biologic DMARDs, concomitant corticosteroids and DMARDs; $p=0.40$). When the analysis was stratified by anti-CCP status, smoking did not influence the response to therapy in the anti-CCP negative subset ($p=0.39$) but there was a trend in the anti-CCP positive subset ($p=0.06$, see figure 1). Similar trends were observed for EULAR good/moderate response rates. For the anti-CCP negative RA patients, 63% of non-smokers and 60% of smokers achieved EULAR response ($p=0.51$), while in the anti-CCP positive subgroup the respective response rates were 73% among non-smokers and 67% among smokers ($p=0.07$).

Conclusion: Smoking was negatively associated with the clinical response to rituximab therapy in RA patients who were anti-CCP positive.

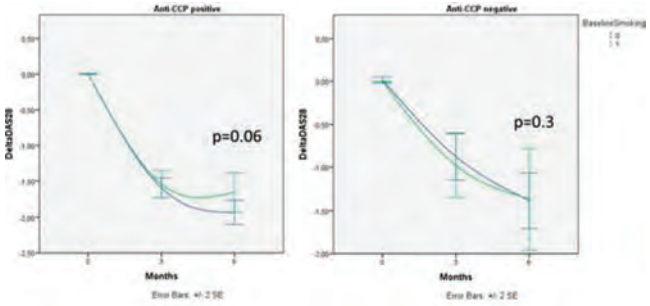

Figure 1. DeltaDAS28 during the first 6 months from baseline in anti-CCP positive and anti-CPP negative RA patients treated with rituximab according to smoking status (0=never or past smokers, 1= current smokers).

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Infliximab Versus Conventional Combination Treatment and Work Loss in Early RA over 7 Years: A Randomized Trial.

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Background/Purpose: The introduction of TNF inhibitors has improved the treatment of RA, but at a substantial cost. The randomized Swefot trial compared the addition of infliximab vs conventional disease-modifying anti-rheumatic drugs in patients with early RA who had failed initial MTX monotherapy. From the Swefot trial we previously reported superior 2-year radiographic outcomes in the infliximab group, while disease-activity, quality of life and work loss improved similarly. Here we report work loss over 7 years after randomization.

Methods: In this multicenter, two-arm, parallel, randomized, active-controlled, open label trial RA patients with <1y symptom duration were recruited from 15 rheumatology clinics in Sweden between October 2002 and December 2005. After 3–4 months of MTX monotherapy, patients not achieving low disease-activity were randomized to addition of biologic treatment with infliximab or further conventional treatment with sulfasalazine+hydroxychloroquine. Register-based follow-up continued despite protocol breach, and treatment was thereafter decided by the responsible rheumatologist.

The main outcome measure in this study was yearly sick leave and disability pension days at 7 years after randomization, retrieved from the nationwide Swedish Social Insurance Office register. The analysis were by intention to treat, including all working age patients (<65y), and adjusted for work loss 1 year before randomization. Patients were followed for a maximum of 7 years and were excluded from the yearly average calculations if they (in the current year) had emigrated, died, or turned 65y.

Results: Of 210 patients in working age, 109 were randomized to infliximab (mean age=48.4y, [median=50.6y]; n women=80 [73%]) and 101 to conventional treatment (48.7y, [52.9y]; 78 [77%]). Seven patients in the infliximab and 4 in the conventional treatment group never received the study drug. The year before randomization the mean number of work days lost per year was 127 (median 112) in the infliximab arm and 118 (median 105) in the conventional treatment group (mean difference, 9; 95%CI, −22 to

39; **Figure**). Compared to the year before randomization, the mean changes at 7 years were −25 days in the infliximab and −26 days in the conventional treatment group (adjusted mean difference, 11; 95% CI, −24 to 46).

The cumulative work loss days over 7 years was 846 in the infliximab group and 701 in the conventional treatment group (adjusted mean difference, 105; 95% CI, −61 to 273).

Conclusion: The radiological superiority at 2 years of infliximab+MTX compared to conventional combination therapy did not translate into better long-term work loss outcomes in patients with early RA who had had an insufficient response to MTX.

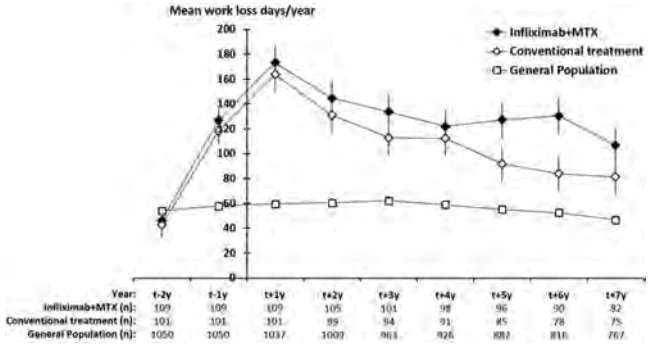

Figure Mean work loss days per year in the infliximab+MTX and the conventional treatment group in relation to randomization, as well as in general population comparators.

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2526

Efficacy of Biological Therapies in Rheumatoid Arthritis: Graphical Modeling of DAS28 Components' Evolution over Time. G. Avila[1], Arnald Alonso[1], María América López-Lasanta[1], Andrea Pluma-Sanjurjo[2], C. Diaz[2] and Sara Marsal[1]. [1]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [2]University Hospital Vall d'Hebron, Barcelona, Spain.

Background/Purpose: The wide use of biological therapies (BTs) has clearly modified the therapeutic approach in rheumatoid arthritis (RA). One of the most commonly used tools to measure the efficacy of BTs in RA is the DAS28 score. Little is known about how each of the DAS28 components varies over time. Our aim was to graphically evaluate the evolution of the DAS28 components over time for the most common anti-TNF treatments and to compare them with anti-IL6 therapy.

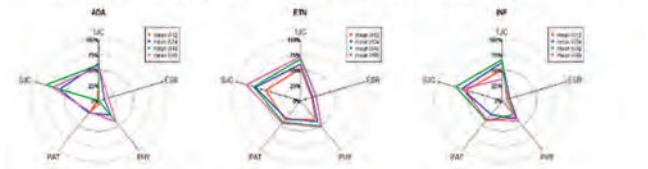
Methods: 222 RA patients treated with BTs during the period between Dec'99 and March'13 were included. The data on the components of DAS28 score were collected from baseline and at every 3 months of therapy. First, we visually analyzed the relative improvement of each variable for each anti-TNF (infliximab (INF), etanercept (ETN), adalimumab (ADA)). Second, we grouped the anti-TNFs and compared their combined evolution to tocilizumab (TCZ). In order to obtain a precise visualization of the changes in time of each of the DAS28 components, we used the radar charts. In this type of multivariate data visualization technique, each one of the components is represented as different circle axes and, at each time point, the mean relative improvement (i.e. percentage of reduction from baseline) for each component is connected by a line.

Results: A total of 347 BTs were analyzed (INF=100, ETN=126, ADA=79, TCZ=42). No statistically significant differences were found in the DAS28 changes between the 3 anti-TNFs. However, when comparing the graphical patterns of these therapies we found different patterns of evolution of the DAS28 components over time (Figure 1). Compared to ADA or INF, ETN had a clearly regular expanding pattern of the improvement. In ADA and INF the relative weight of each DAS28 component at each time period was variable, suggesting a different mode of action for monoclonal therapies.

When we compared the radar charts of the combined anti-TNFs against the anti-IL6 treatment (Figure 2), we found a markedly different pattern of action. While the treatment with anti-TNFs showed rapid and greater improvement in the articular component (i.e. SJC and TJC), the treatment with anti-IL6 showed a higher improvement of the ESR (Figure 2). In both treatments, the physician and patient global assessment showed a similar evolution over time.

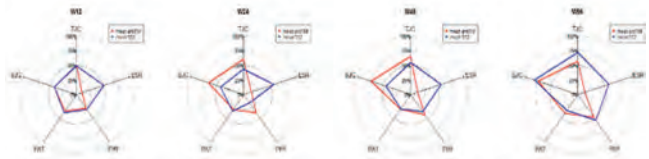
Conclusion: Using a graphical analysis approach we have identified, for the first time, the differential time patterns of the DAS28 score components for the most commonly used anti-TNF therapies. Combining all anti-TNF therapies into a single entity and comparing to a BT targeting IL6, we have also found key differences in the temporal evolution of each of the DAS28 components. The results of this study are useful to understand the differential mechanisms of action of each treatment and could help to explain the differences observed in clinical trials, meta-analyses or observational studies.

Figure 1 Visual approach of changes in DAS28 components during anti-TNF treatment



TJC: tender joint count, SJC: Swollen joint count, ESR: eritrosedimentation rate, PAT: patient global assessment, PHY: physician global assessment.

Figure 2 Visual approach of changes in DAS28 components during anti-TNF and anti-IL6 treatments



Red line: anti-TNF, Blue line: Tocilizumab, TJC: tender joint count, SJC: Swollen joint count, ESR: eritrosedimentation rate, PAT: patient global assessment, PHY: physician global assessment.

Disclosure: G. Avila, None; **A. Alonso**, None; **M. A. López-Lasanta**, None; **A. Pluma-Sanjurjo**, None; **C. Diaz**, None; **S. Marsal**, None.

2527

The Effect of Biological Agents on Work in Patients with Chronic Inflammatory Arthritides: A Meta-Analysis of Randomized Controlled Trials and Controlled Cohorts. Amandine Tubery[1], Cristel Castelli[1], Florence Erny[1], Françoise Barchechath-Flaisler[1], Sabrina Dadoun[2], Bruno Fautrel[3] and Cecile Gaujoux Viala[1]. [1]Nîmes University Hospital, Rheumatology Department, Nimes, France, [2]Sorbonne Universités, UPMC Univ Paris 06, GRC-08, Institut Pierre Louis d'Epidémiologie et de Santé Publique, paris, France, [3]UPMC Paris 06 University, GRC 08, Paris France and Pitié Salpétrière Hospital Paris France, Paris, France.

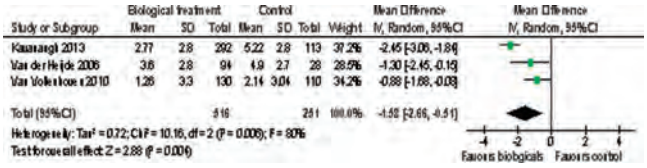
Background/Purpose: The addition of biological agents in treatment strategies in chronic inflammatory arthritides have improved the possibility of controlling disease activity and slowing the progression of joint damage. However their impact on work participation is unclear.

Objectives: To assess the effect of biological agents on work among patients with chronic inflammatory arthritides (CIAs).

Methods: A systematic review of the literature using PUBMED and the Cochrane library was performed until January 2014. All randomized controlled trials (RCTs) and controlled cohorts (CCs) reporting the effect of biological agents on work among patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) or psoriatic arthritis (PsA) were selected. Data extraction: Data were collected using a predetermined form. The outcomes were accumulated missed workdays, number of patients losing worktime du to CIAs, impact on productivity (on a visual analogue scale) and employment loss. Statistical analysis determined in each study effect size (ES) or odds-ratios (OR) as appropriate to assess the magnitude of treatment effect. Pooled ES and OR were computed by meta-analysis. A random effect model was used in case of heterogeneity.

Results: 14 RCTs and 7 CCs were analyzed i.e. 15881 patients treated by biological agents (adalimumab, etanercept, infliximab, certolizumab, golimumab and abatacept) and 9713 controls. Among those 25594 patients, 24670 suffered from RA, 319 from AS, and 605 from PsA. Pooled analyses indicated that biological agents significantly reduced accumulated missed workdays at week 24 (2 trials): ES= −0.34 [95%CI −0.60 to −0.08], the number of patients losing hours (3 trials): OR=0.54 [95%CI 0.36 to 0.79] and improved work productivity (3 trials): ES=−1.58 [95%CI −2.66 to −0.51]

(figure). The positive effect on employment loss was nearly significant (8 trials): OR=0.60 [95% CI 0.33 to 1.09].



Conclusion: Despite the heterogeneity of the data, this meta-analysis showed the beneficial effect of biologics agents on both absenteeism and presenteeism in chronic inflammatory rheumatism. Thus the high cost of biologic agents could be partly balanced with savings in indirect costs.

Disclosure: A. Tubery, None; **C. Castelli**, None; **F. Erny**, Abbvie, 9, Amgen, 9; **F. Barchechath-Flaisler**, Abbvie, 9, Amgen, 9; **S. Dadoun**, None; **B. Fautrel**, None; **C. Gaujoux Viala**, Abbvie, 9, BMS, 9, Janssen Pharmaceutica Product, L.P., 9, MSD, 9, Pfizer Inc, 2, UCB, 9, Roche Pharmaceuticals, 9.

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Efficacy Meta-Analysis of Randomized Controlled Trials (RCTs) of Biologics in Methotrexate-Naive Patients with Early Rheumatoid Arthritis. Yusuf Yazici[1], Chunqiao Luo[2] and Christopher Swearingen[3]. [1]New York University Hospital for Joint Diseases, New York, NY, [2]Biostatistics, Little Rock, AR, [3]University of Arkansas, Little Rock, AR.

Background/Purpose: NNT analysis is a useful tool for putting RCT efficacy results into perspective in patient care. For clinical decision making, the NNT is a useful measure to convey statistical and clinical significance to the doctor (i.e. number of patients needed to treat to achieve 1 additional response compared to control). The most reliable data regarding how a biologic would work comes from MTX naïve RCTs as all patients are receiving active drug for the first time and selection biases may play a lesser role in determining outcomes. We performed a NNT analysis of biologics in MTX-naive pts with early RA.

Methods: PubMed was searched for randomized double-blind, MTX-controlled studies of biologics in MTX-naive pts with early RA from Jan 1990 through Dec 2013. Response rates specified by each RCT were used to assess NNT of biologic (active) versus MTX (control) where $NNT=[1/(RR_{active}-RR_{control})]*100$. Outcomes assessed included ACR20, ACR50, and ACR70 responses as well as DAS28 remission (DAS28 <2.6).

Results: Nine published RCTs were identified.[2–5]Baseline age were similar across the studies (average age 50.2 yrs, range [47.2, 57.5]), but some variability in disease duration (average duration 3.3, range [0.7, 9.3]). All biologics achieved >50% response in ACR 20, although one adalimumab trial was outperformed by MTX only, leading to a negative estimated NNT. All biologics outperformed MTX only with ACR50, ACR90 and DAS28 outcomes.

Conclusion: In MTX-naïve pts with early RA, abatacept and anti-TNF agents have similar efficacy when RCT endpoints, such as ACR responses, are analyzed by NNT. Difference in efficacy appeared when more aggressive treatment goals, such as MCR and DAS28 remission, were evaluated and suggested that the likelihood of achieving these endpoints in patients was less with infliximab than other anti-TNFs or abatacept. In the absence of head-to-head clinical trial data, NNT analysis can be a useful tool for determining the relative efficacy of biologics in routine clinical practice.

Paper	Medication	N	Age (Years)	Duration (Years)	ACR20 N (%)	ACR20 NNT	ACR50 N (%)	ACR50 NNT	ACR70 N (%)	ACR70 NNT
OPTIMA	MTX Only	517	50.4 (13.6)	4.5 (7.2)	295 (57%)		176 (34%)		88 (17%)	
	Adalimumab 40mg+MTX	515	50.7 (14.5)	4.0 (3.6)	361 (70%)	8	268 (52%)	6	180 (35%)	6
HIT HARD	MTX Only	85	52.5 (14.3)	1.6 (1.7)	64 (74%)		44 (51%)		30 (34%)	
	Adalimumab 40mg+MTX	87	47.2 (12.1)	1.8 (2.1)	57 (66%)	-10	46 (53%)	90	35 (40%)	20
TEAR	MTX Only	255	48.6 (13.0)	2.9 (5.6)	125 (51%)		84 (34%)		46 (19%)	
	Etanercept 50mg+MTX	244	50.7 (13.4)	3.5 (6.4)	124 (51%)	56	93 (38%)	19	55 (23%)	22
IMAGE	MTX Only	252	48.1 (12.7)	0.91 (1.1)	161 (64%)		106 (42%)		63 (25%)	
	Rituximab 2×500 mg+MTX	252	47.9 (13.4)	0.99 (1.1)	194 (77%)	8	149 (59%)	6	106 (42%)	6
	Rituximab 2×1000 mg+MTX	251	47.9 (13.3)	0.92 (1.3)	201 (80%)	6	163 (65%)	4	118 (47%)	5
COMET	MTX Only	268	52.3 (0.8)	9.3 (0.4)	163 (59%)		119 (43%)		69 (25%)	
	Etanercept 50mg+MTX	274	50.5 (0.9)	8.8 (0.4)	220 (80%)	5	181 (66%)	5	124 (45%)	5
AGREE	MTX Only	253	49.7 (13.0)	6.7 (7.1)	157 (61%)		107 (42%)		69 (27%)	
	Abatacept 10mg/kg+MTX	256	50.1 (12.4)	6.2 (7.5)	195 (76%)	7	147 (57%)	7	109 (43%)	7
ASPIRE	MTX Only	282	50 (13)	0.9 (0.7)	151 (42%)		91 (25%)		60 (17%)	
	Infliximab 3mg/kg+MTX	359	51 (12)	0.8 (0.7)	223 (62%)	12	165 (46%)	7	115 (32%)	9
	Infliximab 6mg/kg+MTX	363	50 (13)	0.9 (0.8)	240 (66%)	8	183 (50%)	6	135 (37%)	6
GOBEFORE	MTX Only	160	48.6 (12.9)	2.9 (4.8)	79 (50%)		47 (30%)		25 (16%)	
	Golimumab 50mg+MTX	159	50.9 (11.3)	3.5 (5.7)	98 (62%)	8	64 (40%)	9	38 (24%)	12
	Golimumab 100mg+MTX	159	50.2 (11.9)	3.6 (6.1)	98 (62%)	8	58 (36%)	14	29 (18%)	38
PREMIER	MTX Only	257	52.0 (13.1)	0.8 (0.9)	144 (53%)		111 (41%)		72 (26%)	
	Adalimumab 40mg+MTX	268	51.9 (14.0)	0.7 (0.8)	185 (69%)	8	158 (59%)	6	126 (47%)	5

Paper	Medication	DAS28 N (%)	DAS28 NNT
ASPIRE	MTX Only	60 (17%)	
	Infliximab 3mg/kg+MTX	115 (32%)	9
	Infliximab 6mg/kg+MTX	135 (37%)	6
GOBEFORE	MTX Only	25 (16%)	
	Golimumab 50mg+MTX	38 (24%)	12
	Golimumab 100mg+MTX	58 (36%)	14
PREMIER	MTX Only	72 (26%)	
	Adalimumab 40mg+MTX	126 (47%)	5

Paper	Medication	DAS28 N (%)	DAS28 NNT
OPTIMA	MTX Only	88 (17%)	
	Adalimumab 40mg+MTX	180 (35%)	6
HIT HARD	MTX Only	30 (34%)	
	Adalimumab 40mg+MTX	35 (40%)	20
TEAR	MTX Only	46 (19%)	
	Etanercept 50mg+MTX	55 (23%)	22
IMAGE	MTX Only	63 (25%)	
	Rituximab 2×500 mg+MTX	106 (42%)	6
	Rituximab 2×1000 mg+MTX	118 (47%)	5
COMET	MTX Only	69 (25%)	
	Etanercept 50mg+MTX	124 (45%)	5
AGREE	MTX Only	69 (27%)	
	Abatacept 10mg/kg+MTX	109 (43%)	7

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2529

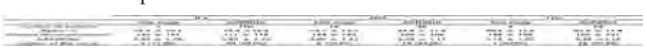
Efficacy of Infliximab, Adalimumab, and Tocilizumab Can be Improved Under the Baseline ADAMTS5 Selection. Kensei Tsuzaka[1], Yoko Akiyama[2] and Masayoshi Nagata[1]. [1]Iruma Heart Hospital, Iruma, Saitama, Japan, [2]Kaytee Bio, Co&Ltd, Funabashi, Chiba, Japan.

Background/Purpose: We have previously (2010ACR, 2013ACR) reported that the efficacy of biologics, infliximab, adalimumab, and tocilizumab can be predictable using baseline blood a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5) mRNA level. In this study presented here, we investigated whether the efficacy of these biologics could be improved if they were administered to RA patients who were diagnosed as effective of those biologics using the baseline ADAMTS5 mRNA levels.

Methods: Whole blood was collected from 41 RA patients at baseline and total RNA was isolated. ADAMTS5 mRNA was quantified using real-time PCR (BiologicMate®) followed by the reverse transcription. ADAMTS5 mRNA was calculated as the ratio against b-actin mRNA (Index). Out of 41 patients, 12 (29.3%) have been refractory to infliximab (IFX). IFX, adalimumab (ADA), and tocilizumab (TCZ) was administered if the baseline ADAMTS5 was lower than 1.2, higher than 1.7, and higher than 1.6 Index, respectively. Efficacy of IFX at 14 weeks, ADA at 20 weeks, and TCZ at 12 weeks was estimated using EULAR response. Clinical data (Clinical remission rate, etc) of the RA patients treated with these biologics according to the baseline ADAMTS5 mRNA was compared with those of our data presented at ACR2010 (IFX and ADA) and ACR2013 (TCZ).

Results: All of 12 patients refractory to IFX revealed high level (> 1.2 Index) of the baseline ADAMTS5 mRNA. Out of 41 RA patients, 7 (5 bio-naïve and 2 bio-switch), 18 (6 bio-naïve and 12 bio-switch), and 5 patients (1 bio-naïve and 4 bio-switch), were received IFX, ADA, and TCZ according to the baseline ADAMTS5 mRNA levels (ADAMTS5 selection). As a result, the clinical remission (DAS28-ESR<2.6) rate (4/7; 57.1%) with IFX under ADAMTS5 selection was higher than that with IFX of ACR 2010 data (32/100; 32.0%). On the other hand, the clinical remission rate (12/18; 66.7%) with ADA under ADAMTS5 selection was significantly (p=0.0002) higher than that with ADA of ACR 2010 data (9/48; 18.8%). Furthermore, the clinical remission rate (4/5; 80.0%) with TCZ under ADAMTS5 selection was significantly (p=0.0083) higher than that with TCZ of ACR 2013 data (13/54; 24.0%).

Conclusion: Thus the efficacy of infliximab, adalimumab, and tocilizumab can be improved with the baseline ADAMTS5 selection.



Disclosure: K. Tsuzaka, Kaytee Bio, CoLtd, 1; **Y. Akiyama**, None; **M. Nagata**, None.

2530

PRE.MARK-TNF Test Based on Iga-Specific Autoantigens Predicts Therapy Response in Rheumatoid Arthritis Patients Treated with TNFα Inhibitors. Karl Skriner[1], Jörg Hollidt[2], Gerd Burmester[1] and Zoltan Konthur[3]. [1]Charité - Universitätsmedizin Berlin, Berlin, Germany, [2]Drug Response DX GmbH, Berlin, Germany, [3]Drug Response DX GmbH, Hennigsdorf, Germany.

Background/Purpose: One third of rheumatoid arthritis patients treated with biologicals targeting TNFα are therapy non-responders. We have earlier investigated the difference in seroreactivity of patients being responder and non-responder to anti-TNFα therapies prior and after therapy and identified a set IgA-specific autoantigens. So far no mechanism for non-response has been described. Here we present a fist study on the diagnostic applicability of the found autoantigenic biomarkers.

Methods: Screening with >200 well defined patient sera on 5 different autoantigenic biomarker candidates, which were expressed recombinantly in *E. coli* by ELISA.

Results: Pretreatment sera from patients with diagnosis of RA based on the ACR classification criteria who were initiated on therapy with TNFα inhibitors were analyzed for the presence of autoantibodies against a set of 5 biomarker proteins (RAB11B, PPP2R1A, KPNB1, COG4, FTFT1) using ELISA assays. In total, analyses of 203 patients were carried out, of which 162 were clearly defined as Responder and 41 were clearly defined as Non-Responder after 6 month treatment. 81% of Non-responder could be clearly identified with the pre.markTNF Test. The assay has currently a specificity 94%.

Moreover, of the 203 samples, 57 samples were baseline sera from an early intervention study with Humira. In this subset, all 3 non-responder were identified and the specificity of the assay was 98 %. Only one – an intermediate responder after 6 months of treatment with Humira – gave any signal in the assay on IgA-level.

Conclusion: These data suggests that IgA-autoantibodies against a set of protein biomarkers (pre.markTNF test) might be diagnostically applied for the identification of anti-TNFα therapy non-responders prior treatment.

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ACR/ARHP Poster Session C
Sjögren's Syndrome: Clinical Science
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

2531

Risk of Venous Thromboembolism in Patients with Sjögren's Syndrome: A Systematic Review and Meta-Analysis. Patompong Ungprasert[1], Charat Thongprayoon[2], Karn Wijarnpreecha[3], Wisit Cheungpasitporn[2], Praveen Ratanasrimetha[4] and Promporn Suksaranjit[5]. [1]Bassett medical center, Cooperstown, NY, [2]Mayo clinic, Rochester, MN, [3]Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, [4]Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [5]University of Utah School of Medicine, Salt Lake City, UT.

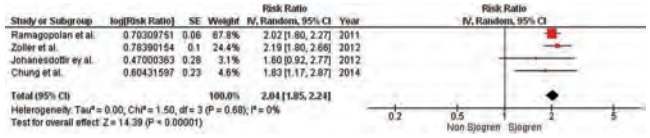
Background/Purpose: Venous thromboembolism (VTE) is a common medical problem with a significant morbidity and mortality. Chronic inflammatory state, though not generally regards as a conventional risk factor for VTE, is increasingly recognized as its potential predisposing factor. In fact, several chronic inflammatory disorders, such as systemic lupus erythematosus and rheumatoid arthritis, have been shown to increase VTE in large epidemiologic studies. However, the data on Sjogren's syndrome (SS), another common chronic inflammatory disorder, remain unclear due to conflicting studies. Thus, to further investigate this possible association, we conducted a systematic review and meta-analysis of observational studies that compared the risk of VTE in patients with SS versus participants without it.

Methods: Two investigators (P.U. and C.T.) independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception to March 2014 using the terms for Sjogren's syndrome in conjunction with the terms "venous thromboembolism", "pulmonary embolism" and "deep venous thrombosis". A manual search of references of retrieved articles was also performed. The inclusion criteria were as follows: (1) observational studies published as original studies to evaluate the association between SS and VTE and (2) odds ratios (OR's), relative risk (RR's) or hazard ratio (HR's) or standardized incidence ratio (SIR's) with 95% confidence intervals (CI's) were provided. Study eligibility was independently determined by the two investigators noted above. Newcastle-Ottawa scale was used to assess the quality of included studies.

RevMan 5.2 software was used for the data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird. Given the high likelihood of between study variance, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran's Q test.

Results: Out of 382 potentially relevant articles, four studies (three retrospective cohort studies and one case-control study) were identified and included in our data analysis. The pooled risk ratio of VTE in patients with SS was 2.04 (95% CI, 1.85 to 2.24). The statistical heterogeneity of this meta-analysis was not significant with an I^2 of 0%.

Conclusion: Our study demonstrated a statistically significant increased VTE risk among patients with SS.



Disclosure: P. Ungprasert, None; **C. Thongprayoon**, None; **K. Wijarnpreecha**, None; **W. Cheungpasitporn**, None; **P. Ratanasrimetha**, None; **P. Suksaranjit**, None.

2532

Characteristics of Primary Sjögren Syndrome in the Black Population of Martinique. Katlyne Polomat[1], Serge Arfi[2], Lauren Brunier-Agot[1], Véronique Dehlinger[3], Michel DeBandt[1], Georges Jean Baptiste[4] and Christophe Deligny[5]. [1]Centre Hospitalier universitaire de Fort de France, Fort de France, Martinique, [2]Centre hospitalier Universitaire de Fort de France, Fort de France, Martinique, [3]Centre Hospitalier universitaire de Fort de France, Fort De France - Martinique, Martinique, [4]Centre Hospitalier Universitaire de Fort de France, Fort de France, Guadeloupe, [5]CHU Fort de France, Fort de France, France.

Background/Purpose: There is very limited data on the clinical, biological characteristics and evolution of primary Sjögren syndrome (pSS) in black patients of African origin. And yet, other connective tissue diseases such as lupus have particularities in this population.

Methods: Retrospective study of all pSS patients fullfiling American-European consensus criteria followed as out and in patients in the rheumatology and internal medicine units from the academic hospital of Fort de France, Martinique.

Results: 70 patients were recruited since 1991 : 68 women, 2 men (female:male ratio, 34:1). Mean age at diagnosis was 49.5 yo (range: 17– 74). Mean follow up time was 3.5 years (range 1–17). Main characteristics were: xerostomia 82.8 % (n = 58), xerophtalmia 91.4 % (n=64). Objective ocular tests were found positive in 70.3 % (n= 45/64). The minor salivary gland biopsy was positive in 92.5 % (n = 62/67). Other characteristics were: Raynaud's phenomenon 29.8 % (n = 20/67), arthralgia 55.7 % (n=39), arthritis 21.4 % (n= 15), interstitial lung diseases 8.5 % (n= 6), peripheral neuropathy 8.5 % (n=6), central nervous system involvement 5.7 % (n = 4), pericarditis 1.4% (n=1), pleurisy 2.8 %(n =2), vasculitis 1.4 % (n =1), no pancreatitis. Some other auto-immune diseases were associated to pSS: anti-phospholipid syndrome 7.1 % (n =5), thyroiditis 7.1% (n =5), Evans syndrome 1.4 % (n =1). Antinuclear antibodies were positive for 86.9 %, anti-SSA for 62.8 % (n=44). ESR or c reactive protein were elevated in 33 patients (47.1 %). HTLV-1 positivity was present in 2 patients. In 245 patients. years of follow up, 1 patient experienced lymphoma (0.4 lymphoma for 100 patients.years of follow up). No death was to deplore.

Conclusion: This is the first series of pSS available concerning patients of African origin. Compared to the largest Caucasian pSS cohort published by Ramos Casals et al, there seems to be no major particularities, but men are less frequently suffering from pSS and vasculitis seems less frequent than in the Caucasians.

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2533

Utility of the American-European Consensus Group and American College of Rheumatology Classification Criteria for Sjögren's Syndrome in Patients with Systemic Autoimmune Diseases in the Clinical Setting. Gabriela Hernandez-Molina[1], Carmen Ávila-Casado[2], Carlos Núñez-Álvarez[1], Carlos Hernández-Hernández[1], Maria Luisa Calderillo[1], Martha Marroquín[1], Claudia Recillas-Gispert[1], Juanita Romero-Díaz[1] and Jorge Sánchez-Guerrero[3]. [1]Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico, [2]University Health Network, Toronto Canada., Toronto, ON, [3]Mount Sinai Hospital and University Health Network, Toronto Canada, Toronto, ON.

Background/Purpose: To evaluate the feasibility and performance of the AECG and ACR Classification Criteria for Sjögren's syndrome (SS) in patients with systemic autoimmune diseases.

Methods: 350 patients with primary SS (n=50), systemic lupus erythematosus (n=100), rheumatoid arthritis (n=100), or scleroderma (n=100) were randomly selected from our patients' registry. Each patient was clinically diagnosed as probable/definitive SS or non-SS by two rheumatologists following a standardized evaluation including clinical symptoms and manifestations, confirmatory tests (fluorescein staining test, non-stimulated whole salivary flow, Schirmer-I test) autoantibodies (antinuclear antibodies, anti-Ro/SSA, anti-La/SSB, rheumatoid factor), lip biopsy, and medical chart review. Using the clinical diagnosis as gold standard, the degree of agreement with each criteria set, and between both criteria sets was estimated. We estimated the sensitivity, specificity, positive predictive value, and negative predictive value with 95% CI. We used the kappa statistic.

Results: 154 (44%) patients were diagnosed with SS. The AECG criteria were incomplete in 36 (10.3%) and the ACR criteria in 96 (27.4%), P<0.001. Nevertheless, their ability in classifying patients was almost identical, sensitivity 61.6 vs. 62.3, specificity 94.3 vs. 91.3, respectively. Either criteria were met by 123 (80%); 95 (61.7%) met AECG and 96 (62.3%) ACR criteria, but only 68 (44.2%) patients met both sets. The concordance rate between clinical diagnosis and AECG or ACR criteria was moderate, k statistic 0.58 and 0.55, respectively. Among 99 patients with definitive SS the sensitivity was 83.3 vs. 77.7, and specificity 90.8 vs. 85.6, respectively. A discrepancy between clinical diagnosis and criteria was seen in 59 (17%) patients. Patients classified by the AECG criteria were older, had more sicca symptoms, parotid enlargement, positive Schirmer-I test, and lower NSWSF rate; whereas those classified through the ACR criteria had more often keratoconjunctivitis sicca, focal sialadenitis, rheumatoid factor, and the combination of rheumatoid factor plus antinuclear antibodies >1:320.

Conclusion: The feasibility applying the AECG is superior to the ACR criteria; however the performance of both sets was similar among patients with systemic autoimmune diseases. Nevertheless, a subset of patients still is missed by both criteria sets.

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2534

Ocular Surface Temperature in Early Sjogren's Syndrome and Established Disease. Andreea Coca[1], Ranjini Kottaiyan[1], Mircea Coca[2], Debbie Campbell[3], Holly Hindman[1] and James Aquavella[1]. [1]University of Rochester, Rochester, NY, [2]University of Texas Medical Branch, Galveston, TX, [3]Univerity of Rochester, Rochester, NY.

Background/Purpose: Due to a variety of factors it is challenging to make a definite diagnosis in the early stages of Sjögren's syndrome (SS). The ocular examination, including fluorescein and tear break-up time (TBUT), have been a critical part of the diagnosis algorithm. Limitations of these techniques are their relative invasiveness and lack of specificity. They can also have intrinsic toxicity, including cellular morphologic changes, including loss of cellular motility, cell detachment and death. We propose ocular surface temperature (OST) measurements as a novel, non-invasive technique that can potentially overcome these limitations.

Methods: We evaluated 5 subjects with SS that fulfilled American European Consensus Group criteria (AECG SS), 5 subjects with early disease (early SS), and 5 healthy controls (HCs). The early SS was defined as presence of autoantibodies suggestive of SS, ocular dryness less than 5 years, not fulfilling the AECG criteria. OST measurements were taken on both eyes over a 5 second interval, 30 measurements per second. In addition, tear film break-up time (TBUT), Schirmer, and fluorescein staining scores were obtained for each patient and each eye. For the early SS and AECG SS subjects we also obtained SF36, visual analog scale (VAS) for dryness, ESSDAI (EULAR SS Disease Activity Index) and standard of care laboratory analysis.

For each patient, the OST measurements from both eyes were averaged to create a single observation for each individual. Receiver operating characteristic (ROC) curves were fit using the different potential metrics under two different classification scenarios: HC vs early SS and SS, and SS vs HC and early SS.

Results: Clinically, subjects with early SS had a lower SF36, VAS, ESSDAI, ESR, CRP, ANA and anti-Ro titers, and lower IgG compared with AECG SS. They also had a higher WBCs and complement levels. Although none of these differences reached statistical significance, they are suggesting that subjects with early SS had less active immunological disease and less subjective dryness than subjects with AECG SS.

An exponential transformation on OST and a log transformation on TIME produced an approximately linear relationship. The interaction was found to be statistically significant ($p < 0.0001$). This interaction indicates that early SS had a significantly less negative slope than the other two groups. The slope of the transformed linear relationship appeared to be the best metric for classifying AECG SS vs HC and early SS.

Conclusion: Using OST we showed that subjects with early SS had a slower fall in their ocular temperature (indicative of less dryness) than patients with AECG SS and clearly separated from HCs. The ocular temperature measured at each second correlated best with the tear break up time (TBUT), suggesting that it could be used in conjunction with standard of care ocular dryness measurement, potentially improving the sensitivity of ocular measurements. Although the clinical characteristics of the AECG SS vs. early SS did not reach statistical significance, the trends suggested that early SS had less dryness, and less actively immunological disease (lower level of autoantibodies, lower inflammatory markers and IgG level), consistent with early disease.

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2535

Performance of the Ocular Staining Score (OSS) *Vs.* the Van Bijsterveld Score in the Assessment of Sjögren's Syndrome-Related Keratoconjunctivitis Sicca. Astrid Rasmussen[1], Michael Brown[1], Donald U Stone[2], Keith Earley[3], Kimberly S. Hefner[4], Lida Radfar[5], David M. Lewis[5], Stephen Young[5], Nelson L. Rhodus[6], Barbara M. Segal[7], Christopher J. Lessard[1], Courtney G. Montgomery[1], R. Hal Scofield[8] and Kathy L. Sivils[5]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Dean McGee Eye Institute, Oklahoma City, OK, [3]US Air Force, Oklahoma City, OK, [4]Hefner Eye Care and Optical Center, Oklahoma City, OK, [5]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [6]University of Minnesota, Minneapolis, MN, [7]Hennepin County Medical Center, Minneapolis, MN, [8]US Department of Veterans Affairs Medical Center, Oklahoma City, OK.

Background/Purpose: Sjögren's syndrome (SS) is a complex autoimmune disorder characterized by xerostomia and xerophthalmia due to exocrine gland dysfunction. There is no single diagnostic test for SS and multiple research classification criteria have been proposed. Currently, a combined EULAR-ACR working group is dedicated to resolve discrepancies and weaknesses between two systems presently in use: the American-European Consensus Group (AECG) criteria and the SICCA (ACR) criteria, with the ultimate goal of establishing a new consensus classification. A point of contention has been the assessment of keratoconjunctivitis sicca either by the van Bijsterveld score (vBS) for AECG classification or the Ocular Staining Score (OSS) for ACR classification. We present a direct comparison of the two scoring systems to help clarify the matter.

Methods: We performed all tests for AECG and ACR classification in a multidisciplinary sicca clinic. Complete vBS and OSS evaluations were available for 716 participants; a subset of 587 were classified by AECG criteria either as pSS (n=257) or sicca (n=330). The remaining 129 had other diseases or overlap/secondary SS. Initial analysis of concordance (vBS=OSS) or discordance (vBS≠OSS) of the ocular scores was done for n=716 subjects but the correlations with classification criteria and clinical features was restricted to the pSS/sicca subset.

Results: Of the 716 subjects, 538 (75.1%) were concordant while 178 (24.9%) were discordant for vBS *vs.* OSS. The discordant subjects had significantly higher vBS (Wilcox rank sum $p<2.2\times10E\text{-}16$); the same held

true if only pSS vs. sicca were compared. ROC curves comparing the sensitivity and specificity of the vBS and OSS both in the two study groups showed that the accepted vBS cutoff of 4 has a sensitivity of 0.59–0.68 and specificity of 0.74–0.79; similar sensitivities for the OSS are observed at scores of 4 (sensitivity 0.63–0.74; specificity 0.72–0.78) and 5 (sensitivity 0.54–0.62; specificity 0.79–0.83). Discordant participants were significantly more Ro (+), La (+), and biopsy (+) than the concordant cases ($p=1.7xE10-10$; $4.3\times10-6$; $1.8\times10E-10$ respectively). The patches of confluent staining were the most common cause of discordance in the scores. When analyzing the three additional corneal staining points of the OSS, their presence was highly associated with participants meeting criteria for pSS ($p=8.4\times10E-7$ to $1.73\times10E-13$); with (+) Schirmer's ($p=3.1\times10E-6 - 6.5\times10E-10$), Ro ($p=2.7\times10E-5 - 2.9\times10E-10$), La ($p=0.01 - 8.8\times10E-6$), biopsy ($p=1.8\times10E-5 - 3.4\times10E-10$), and WUSF ($p=0.0007 - 1\times10E-6$). In all cases, the patches of confluent staining were the most highly associated with markers of disease severity while the corneal filaments were the least significant.

Conclusion: The OSS was introduced as an objective measure of KSS in the ACR classification and was considered abnormal if ≥3. However, more recent studies indicate it has poor specificity. Our results in a large sicca cohort suggest that a cutoff between 4 and 5 would maintain a good sensitivity while increasing the specificity significantly; a matter of great importance when applying the criteria for patient selection for clinical trials.

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The Sjögren's Syndrome Responder Index, a Data-Driven Combined Endpoint, Could Detect Biologics Efficacy. Divi Cornec[1], Valerie Devauchelle-Pensec[2], Xavier Mariette[3], Sandrine Jousse-Joulin[4], Jean-Marie Berthelot[5], Aleth Perdriger[6], Xavier Puéchal[7], Véronique le Guern[8], Jean Sibilia[9], Jacques Gottenberg[10], Laurent Chiche[11], Eric Hachulla[12], Pierre-Yves Hatron[13], Vincent Goëb[14], Gilles Hayem[15], Jacques Morel[16], Charles Zarnitsky[17], Jean Jacques Dubost[18], Raphaèle Seror[19], Jacques-Olivier Pers[4], Emmanuel Nowak[4] and Alain Saraux[20]. [1]Brest Occidentale University, Brest, France, [2]Brest Occidentale university, Brest, France, [3]Université Paris-Sud, Le Kremlin Bicêtre, France, [4]CHU Brest, Brest, France, [5]CHU Nantes (Nantes University Hospital), Nantes, France, [6]Rhumatologie, Rennes, France, [7]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [8]Hôpital Cochin, Paris, France, [9]University Hospital of Strasbourg, Strasbourg, France, [10]Strasbourg University Hospital, Strasbourg, France, [11]CHU Marseille, Marseille, France, [12]National Scleroderma Centre, Lille CEDEX, France, [13]CHU Lille, Lille, France, [14]Amiens University Hospital, Amiens, France, [15]CHU Bichat, Paris, France, [16]Hôpital Lapeyronie, Montpellier, France, [17]Le Havre General Hospital, Le Havre, France, [18]CHU G.-Montpied, Clermont-Ferrand, France, [19]Université Paris Sud, Le Kremlin Bicêtre, France, [20]CHU de la Cavale Blanche and Université Bretagne occidentale, Brest Cedex, France.

Background/Purpose: Efficacy of rituximab remains debated in primary Sjögren's syndrome (pSS), but that could be partly due to the absence of validated endpoint. To determine which outcome measures could detect rituximab efficacy and to create an alternative combined endpoint which could be tested in future trials in pSS.

Methods: We have conducted a post-hoc analysis of the randomized, placebo-controlled, TEARS study (Rituximab versus placebo) conducted in 14 university hospitals in France and included 120 pSS patients. Several outcome measures were prospectively collected at week (W)0, W6, W16 and W24 in the TEARS study. The outcome measures which were able to detect rituximab effect were associated to create a new composite endpoint that we called the Sjögren's Syndrome Responder Index (SSRI). The SSRI was then tested in the TRIPSS study (Infliximab versus placebo).

Results: The 5 selected outcome measures were fatigue, oral dryness, ocular dryness (patient's assessment on visual analog scales), unstimulated whole salivary flow and erythrocyte sedimentation rate. In the TEARS study, the proportion of patients fulfilling at least 30% improvement of at least 2/5 outcome measures (SSRI-30 response) was, in the rituximab and placebo groups, respectively 47% vs 21% at W6; 50% vs 7% at W16; and 55% vs 20% at W24 ($p<0.01$ for all comparisons). The same analysis in the TRIPSS study (Infliximab versus placebo) confirmed that infliximab is not effective in pSS.

Conclusion: We determined a core set of outcome measures which would be able to detect rituximab efficacy in pSS, and we propose response criteria which could be tested as primary outcome measures in future trials in pSS.

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Diagnostic Accuracies of Sialography and Salivary Ultrasonography in Sjogren's Syndrome Patients: A Meta-Analysis. Young Ho Lee[1] and Gwan Gyu Song[2]. [1]Korea University Medical Center, Seoul, South Korea, [2]Korea Univ College of Medicine, Seoul, South Korea.

Background/Purpose: Ultrasonography (US) may come to replace conventional invasive examinations in clinical practice. However, the diagnostic accuracy of salivary US has not been clearly compared with sialography, and there is as of yet no consensus on the use of US as an alternative method for the assessment of salivary gland involvement in Sjogren's syndrome (SS) patients. Salivary US been studied in the context of SS in comparison with sialography with respect to diagnostic accuracy. However, published results on the diagnostic accuracies of sialography and US are controversial and inconclusive. This may be due to small sample sizes, low statistical power, and/or clinical heterogeneity. The purpose of this study was to compare the diagnostic performance of sialography and salivary ultrasonography (US) for Sjogren's syndrome (SS) patients.

Methods: We searched Medline, Embase, and the Cochran library, and performed two meta-analyses on the diagnostic accuracy of sialography and salivary US in SS patients.

Results: A total of six studies including 488 patients and 447 controls from two European and four Asian studies were available for the meta-analysis. The pooled sensitivity and specificity of sialography were 80.0% (95% confidence interval [CI] 76.4–83.2) and 89.0% (85.8–91.8), respectively, and 77.4 (73.7–80.9) and 81.5 (77.6–85.0) for US, respectively. For sialography, the PLR, NLR, and DOR were 9.296 (4.200–20.57), 0.228 (0.170–0.305), and 46.51 (16.14–134.0), respectively, and for US were 4.631 (2.707–7.864), 0.302 (0.226–0.403), and 17.48 (10.03–30.45), respectively. The area under the curve (AUC) of sialography was 0.824, and the Q* index was 0.757, while the AUC of US was 0.864, and its Q* index was 0.794, indicating that the diagnostic accuracy of US is comparable with sialography in SS patients. A subgroup meta-analysis according to the diagnostic criteria did not change the overall diagnostic accuracy.

Conclusion: Our meta-analysis of published studies demonstrates that the diagnostic accuracy of salivary US is comparable with sialography in SS patients.

Disclosure: Y. H. Lee, None; **G. G. Song**, None.

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Ultrasound-Guided Core Needle Biopsy of the Major Salivary Glands Is a Safe and Useful Diagnostic Tool in the Evaluation of Suspected or Established Sjögren's Syndrome. Anand Narayan, Thomas Grader-Beck, Julius Birnbaum, Jean Kim, Qing Kay Li, Deborah Belchis, Joel Fradin and Alan N. Baer. Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Ultrasound-guided core needle biopsy (CNB) has greater inherent risks than fine-needle aspiration for the diagnosis of major salivary gland neoplasms, but provides tissue for histologic analysis. We sought to evaluate the safety and utility of CNB in the evaluation of salivary gland abnormalities in patients with suspected or established Sjögren's syndrome (SS).

Methods: We identified 19 patients who underwent ultrasound-guided CNB of either the parotid or submandibular gland as part of a diagnostic evaluation in our SS Center between 7/2009-5/2014. CNBs of the parotids were obtained using a posterior-inferior approach from the tail of the superficial lobe to avoid injury to the facial nerve. Patients were contacted one day after the procedure to assess for complications. The patient charts were reviewed retrospectively, using a protocol approved by the institutional review board.

Results: The 5 men and 14 women had a median age of 55 years (range, 19–74). Seven patients had an established SS diagnosis and underwent the procedure to exclude lymphoma as the cause for symmetric or asymmetric salivary gland enlargement. The remaining 12 with suspected SS underwent the procedure because of bilateral salivary gland enlargement and/or induration (n=11) or an elevated serum IgG4 level (n=1), but only one was diagnosed with SS. The 19 procedures involved sampling of parotid (n=14) or submandibular (n=5) gland parenchyma and constituted CNB alone (n=9) and CNB with FNA (n=10); flow cytometry was performed on 7/10 FNA samples. None of the patients reported complications one day post-procedure or during longitudinal follow-up [median (range) duration=172 days (1–924)]. Among the established SS patients, 3/6 had a clonal B-cell population on FNA flow cytometry, but lymphoma was only diagnosed in 1 based on CNB histology. The remaining 2 patients with abnormal FNA flow cytometry had CNB histology of benign lymphoepithelial sialadenitis and did not develop signs of lymphoma during follow-up of 2.3–2.5 years. One patient with established SS underwent CNB alone and the histology showed no lymphoid aggregates. Among the 12 patients with suspected SS, final pathologic diagnoses from CNB included: eosinophilic sialadenitis (n=2), normal parotid gland tissue with/without fatty infiltration (n=8), chronic sialadenitis not related to SS (n=1), and extensive fibrosis (n=1). The utility of CNB as a diagnostic tool for salivary gland disease was supported by its identification of: 1) pathologic abnormalities (lymphoid infiltrates or >50% fibrosis) in 10/10 patients with abnormal salivary gland ultrasound echotexture and 2) lymphoid infiltrates in 5/8 patients with established SS. Three patients with enlarged parotid glands but normal ultrasound echotexture had a CNB showing fatty infiltration with normal acinar tissue.

Conclusion: Ultrasound-guided CNB of the major salivary glands can be done safely and provides useful diagnostic information about salivary gland abnormalities in the evaluation and management of SS. The evaluation of possible lymphoma should include both CNB and FNA with flow cytometric analysis of the sample since the finding of a clonal B-cell population is not sufficient to make a diagnosis of lymphoma.

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Antibodies to Human Interferon-Inducible Protein-16 Are Present in Primary Sjögren's Syndrome and Systemic Lupus, but Are Rare in Dermatomyositis. Alan N. Baer[1], Michelle Petri[1], David Fiorentino[2], Tao Wang[1], Jungsan Sohn[1], Antony Rosen[1] and Livia Casciola-Rosen[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Stanford University School of Medicine, Redwood City, CA.

Background/Purpose: Interferon inducible protein-16 (IFI16) is an intracellular DNA receptor involved in innate immunity. We evaluated the frequency and clinical significance of anti-IFI16 antibodies in cohorts of primary Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), and dermatomyositis (DM). Expression levels of IFI16 in relevant target tissues were quantified.

Methods: Anti-IFI16 antibodies were assayed by ELISA using sera from patients with primary SS (n=133; Sjögren's International Collaborative Clinical Alliance Biorepository), SLE (n=132: Hopkins Lupus Cohort), DM (n=114; Stanford Dermatology Clinic) and healthy controls (n=47). Immunoprecipitation was used to determine whether antibodies recognized the N-or C-terminus. Expression of IFI16 in lysates made from salivary gland and skin was quantified by immunoblotting.

Results: Anti-IFI16 antibodies were present in 38/133 (29%) SS, 31/132 (23.5%) SLE, and 3/114 (2.6%) DM patients, and 1/47 (2.1%) controls (SS vs controls, $p<0.0002$; SLE vs controls, $p=0.0006$; DM vs controls, $p=1.0$). The levels of anti-IFI16 antibodies were higher in SS [median (25^{th}–75^{th} percentile): 0.334 (0.244–0.591)] as compared to SLE [0.242 (0.164–0.477); $p=0.0002$]. In SS, anti-IFI16 antibodies were associated with an abnormal Schirmer's test ($p=0.0032$), IgG> 1445 mg/dl ($p=0.0189$), ANA ≥1:320 ($p=0.0152$), germinal centers ($p=0.0130$), and higher rheumatoid factor levels [median (25^{th}–75^{th} percentile): 56.5 IU/ml (10.75–97) vs 25 (8–54), $p=0.0132$] and focus scores [3.4 (2.63–6.38) vs 2.4 (1.6–3.7), $p=0.0053$]. With the exception of germinal centers, these associations remained significant in the subgroup of 98 SS patients with positive SSA/B serology. In SLE, this specificity was associated with anti-DNA antibodies ($p=0.0017$). Among patients with high antibody levels, anti-IFI16 antibodies were directed against the C-terminus in 9/13 (69%) SS and 4/15 (26.7%) SLE patients ($p=0.056$). DNA antibodies were present in 10/11 (91%) of the SLE patients with antibodies to the N-terminus and in 1/4 (25%) of the patients with antibodies to the C-terminus ($p=0.033$). IFI16 was expressed in 4/5 (80%) of SS and 1/6 (16.7%) of control labial glands, and 4/8 (50%) of SLE skin and 0/3 (0%) of control skin biopsies.

Conclusion: Anti-IFI16 antibodies are found in primary SS and SLE with similar frequencies (24–29%), but not in DM, despite a role for interferon in the pathogenesis of all 3 diseases. These antibodies correlate with a more severe phenotype in SS and with the presence of DNA antibodies in SLE. Anti-IFI16 antibodies target different portions of the molecule in SS and SLE. Expression of IFI16 in relevant target tissues correlates with the presence of antibody to this molecule.

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Sjö™, an Advanced Diagnostic Panel for Detection of Sjögren's Syndrome Autoantibodies. Mark Jasek[1], Kishore Malyavantham[2], Lakshmanan Suresh[3], Julian Ambrus Jr.[4] and Dennis Pardo[1]. [1]Nicox Inc, Fort Worth, TX, [2]IMMCO Diagnostics Inc., Amherst, NY, [3]State University of New York/Buffalo, Buffalo, NY, [4]State University of New York at Buffalo, Buffalo, NY.

Background/Purpose: Sjögren's syndrome (SS) is a complex autoimmune disease involving the salivary and lacrimal glands along with various systemic manifestations. It is a difficult disease to identify especially in its early stages. Average time from disease onset to diagnosis is 4.7 years. The serological markers suggested by the American College of Rheumatology for diagnosis of SS are antinuclear antibodies (ANA), rheumatoid factor (RF), anti-Ro, and anti-La. Novel SS autoantibodies, anti-salivary gland protein 1 (SP1), anti-carbonic anhydrase 6 (CA6) and anti-parotid secretory protein (PSP), often expressed earlier compared to traditional SS biomarkers, have been identified in animal studies and clinical trials. An approved diagnostic blood panel (Sjö™) incorporating classic and novel biomarkers was integrated as standard procedure in ophthalmic/optometric practices across 12 geographic markets.

Methods: Serum samples from patients with idiopathic dry eyes were analyzed with the Sjö™ panel through the end of May 2014. These patients had not previously been diagnosed with SS. Antibodies to RF, anti-Ro, anti-La, anti-SP1, anti-CA6 and anti-PSP were tested using enzyme linked immunosorbent assay. ANA was analyzed by indirect immunofluorescence using Hep-2 substrate.

Results: By the end of May 2014, 2306 samples had been analyzed. Of the dry eye patients analyzed, 608 (27%) turned out to be positive for SS markers. Of the positive patients, 62.6% were identified solely by the novel markers SP-1, CA6, and PSP. Only 13.2% of the patients were identified with solely the classic markers. Majority of samples were from women (88%), of whom 24% were positive for SS markers. In the subset of male dry eye patients tested (n=273), 64 were identified as positive for SS (23%).

Conclusion: The current data illustrates many patients with "idiopathic" dry eyes have autoantibodies consistent with early SS, at a frequency higher than currently reported in the literature. The majority of patients express the novel autoantibodies associated with an early stage of SS, anti-SP1, anti-CA6 and anti-PSP, without anti-Ro or anti-La. Earlier diagnosis of SS in these patients may lead to better management of their dry eye and other systemic manifestations via referral/co-management with rheumatologists and other health care providers.

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Autoantibodies in Pediatric Sjogren's Patients. Lakshmanan Suresh[1], Minako Tomiita[2], Akira Hoshioka[3], Long Shen[4], Kishore Malyavantham[5] and Julian Ambrus[6]. [1]State University of New York/Buffalo, Buffalo, NY, [2]Chiba Children's Hospital, Chiba, Japan, [3]Chiba Children's Hospital,, Chiba,

Japan, [4]SUNY at Buffalo, Buffalo, NY, [5]IMMCO Diagnostics Inc., Amherst, NY, [6]University Of Buffalo, Buffalo, NY.

Background/Purpose: Sjogren's syndrome (SS) is a common autoimmune disease involving the salivary and lacrimal glands along with various other organs. It is generally seen in adult females and it is considered 'rare' in children. However, there are not a few pediatric SS patients, and their clinical features are different from those of adults. It is because pediatric patients are in early stages of the disease. The current studies were designed to characterize SS in a population of pediatric patients and whether anti-SP1, anti-CA6 and anti-PSP antibodies could be a new disease marker of early stages of SS.

Methods: Sera were obtained from 15 patients, 4 fulfilled the revised Japanese diagnostic criteria for SS and 11 who probably have SS from the Department of Allergy and Rheumatology, Chiba Children's Hospital, Chiba City, Japan. Their age range was 3–18 years with a mean age of 10.98 years. Fifty pediatric normal controls who were age and sex matched were obtained from Promedx Corporation, USA. ANA was evaluated by HEp2-IFA (Immunofluorescence), RF (Rheumatoid Factor), anti-Ro, anti-La, anti-SP1, anti-CA6 and anti-PSP by ELISA as previously described.

Results: Of the 15 pediatric patients, 11 were females (73%), 2 had SS secondary to SLE and 1 had MCTD. The majority of the patients (80%) expressed ANA and 40% RF. Anti-Ro was expressed by 7 patients of whom 2 also expressed anti-La and 1 also expressed anti-SP1 whose sialography was negative. One 6 year-old patient expressed anti-CA6 and anti-PSP without anti-Ro or anti-La. Of the 50 pediatric normal controls, ANA, anti-Ro, anti-La, anti-CA6 were all negative. Four normal controls expressed RF, 1 had a low titer for anti-PSP and one a low titer for anti-SP1.

Conclusion: Pediatric patients with SS are frequently ANA and anti-Ro positive. One patient lacking these autoantibodies expressed anti-CA6 and anti-PSP and one patient whose sialography was negative expressed anti-SP1. These antibodies may be new disease markers of SS in early stages. In general, a larger percentage of pediatric Sjogren's patients compared to adult patients were male.

The pattern of autoantibody expression in pediatric Sjogren's patients was different from what has been historically seen in adult Sjogren's patents. Further studies will be necessary to look at a larger population of pediatric Sjogren's patients over time to evaluate the progression of their disease and the pattern of their autoantibody expression.

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La Positive, Ro60 Negative Subset of Primary Sjögren's Syndrome Is a Reality. Debashish Danda[1], Dat Truong[2], Marshall Shaw[3], Celia Quang[3], Kristi A. Koelsch[4], Biji T. Kurien[5], Harini Bagavant[2], Umesh Deshmukh[2] and R. Hal Scofield[6]. [1]Christian Medical College, Vellore, India, Vellore, India, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [4]Oklahoma Medical Research Foundation, Okalahoma City, OK, [5]U.S. Department of Veterans Affairs Medical Center, Oklahoma City, OK, [6]US Department of Veterans Affairs Medical Center, Oklahoma City, OK.

Background/Purpose: Twenty-nine sera from 348 primary Sjögren's syndrome patients were identified as anti-Ro60 (anti-SSA) negative and anti-La (anti-SSB) positive by immunodiffusion, line immunoassays and multiplex bead assays. We hypothesize that a significant portion of these are falsely negative for anti-Ro60.

Methods: Twenty-nine sera from primary Sjögren's syndrome patients, fulfilling four AECG criteria, were tested for the presence of antibodies directed against La and Ro60 autoantigen. Anti-La was detected on bovine La treated with or without DNAase and RNAase (to check for false positivity, since anti-La can bind DNA and RNA). Anti-Ro60 antibodies in the sera were detected using HEp-2000 substrate (in which cells are transfected with human Ro60) and HEp-2 substrate. Anti-Ro60 and Ro-52 were also tested by *in vitro*transcription/translation/immunoprecipitation assay.

Results: Out of the 29 sera, 25 were unequivocally negative on HEp-2000 (1:40 dilution). Four samples were clearly found to be Ro60 positive with a speckled pattern and three of the four continued to be positive up to 1:320 dilution, as against only two positive samples on HEp-2 at 1:40 dilution. This finding suggests false negativity for Ro60 exists in a small fraction (14 percent) of primary Sjogren's syndrome patients. However, all the samples were negative for Ro60 and Ro52 by *in vitro*transcription/translation/immunoprecipitation assay.

Conclusion: Contrary to our hypothesis, we found only a small fraction of Ro negative, La positive sera to show positive HEp-2000 pattern. This suggests that a subset of primary Sjogren's syndrome is probably a true entity with Ro60 negativity and La positivity. The clinical significance of the subset will be revealed during the follow up of our patients.

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Anti-Ro/SSA Positive Incomplete Sjögren's Syndrome. R. Hal Scofield[1], Anne Igoe[2], Donald U Stone[3], Lida Radfar[4], Kimberly S. Hefner[5], David M. Lewis[4], Stephen Young[4], Judy Harris[6], Kiely Grundahl[6], Biji T. Kurien[7], Jacen Maier-Moore[8], Kristi A. Koelsch[9], James Chodosh[10], Nelson L. Rhodus[11], Raj Gopalakrishnan[11], Barbara M. Segal[12], A. Darise Farris[6], Courtney G. Montgomery[6], Christopher J. Lessard[6], Kathy L. Sivils[4] and Astrid Rasmussen[6]. [1]US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [2]Metro Health, Cleveland, OH, [3]Dean McGee Eye Institute, Oklahoma City, OK, [4]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [5]Hefner Eye Care and Optical Center, Oklahoma City, OK, [6]Oklahoma Medical Research Foundation, Oklahoma City, OK, [7]U.S. Department of Veterans Affairs Medical Center, Oklahoma City, OK, [8]University of Texas at El Paso, El Paso, TX, [9]Oklahoma Medical Research Foundation, Okalahoma City, OK, [10]Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, [11]University of Minnesota, Minneapolis, MN, [12]Hennepin County Medical Center, Minneapolis, MN.

Background/Purpose: Sjögren's syndrome (SS) is a systemic disease characterized by dry eyes and mouth resulting from immune mediated damage and dysfunction of the lacrimal and salivary glands. Clinical diagnosis often takes 6–10 years, leading to a lag in potential preventive and therapeutic strategies. Research classification is most often based on the American European Consensus Group (AECG) criteria. For classification as primary SS (pSS), the AECG criteria require ≥4/6 components with at least 1 being autoantibodies or abnormal histopathology. A significant number of subjects with sicca manifestations have "incomplete" syndrome (iSS) and exhibit less than 4 AECG criteria. We describe the clinical and serologic features of a subgroup of iSS patients.

Methods: In a multidisciplinary sicca clinic, we assessed features of salivary and lacrimal gland dysfunction and autoimmunity as defined by AECG criteria, identifying 573 iSS participants. We compared the features of iSS based on the presence or absence of anti-Ro/SSA autoantibodies (Ro(+) iSS and Ro(−) iSS, respectively.

Results: Of 573 iSS participants, 467 had complete clinical and laboratory data; 19 of them were Ro(+) (4.1%), and 448 were Ro(−) (95.9%). When compared to Ro(−) iSS, Ro(+) iSS patients were younger (43 ± 5.72 vs. 53 ± 13.27 $p=0.001$) and less often Caucasian (52.6% vs. 95.7%, $p=1.95 \times 10^{-7}$); had more anti-La/SSB (+) (46.2% vs. 2.1%, $p=8.8 \times 10E\text{-}6$), hypergammaglobulinemia and lymphopenia ($p=0.02$ and $p=0.009$, respectively). Furthermore, Schirmer's I test scores, ocular surface staining, and whole unstimulated salivary flow were less abnormal than the Ro(−) iSS participants (19.05 ± 9.85 vs. 14.19 ±10.55, $p=0.05$; 1.5±1 vs. 2.84 ± 2.25, $p<0.0001$; and 5.77 ± 3.66 vs. 2.32 ± 2.3, $p<0.001$ respectively). These differences in age, race, anti-La, hypergammaglobulinemia, and lymphopenia were also statistically significant when comparing the Ro(+) iSS subjects to Biopsy(+) iSS or Ro(−)/Biopsy(−) iSS. Finally, Ro(+) iSS patients presented a variety of extraglandular manifestations: 6 had hypothyroidism and/or autoimmune thyroid disease, 5 arthritis/arthralgias, 5 leuko and/or lymphopenia, 5 low CH50, 4 hypergammaglobulinemia, 3 interstitial lung disease, 2 Raynaud's phenomenon, 2 photosensitivity, and 1 neuromyelitis optica.

Conclusion: A small percentage of patients with iSS have anti-Ro autoantibodies but do not meet the classification criteria for SS. It is possible that these patients will remain as a *forme frustre* of SS or anti-Ro positive undifferentiated connective tissue disease, but given their younger age and multiple manifestations, it is plausible that they may progress to pSS. Of any possible line of autoimmune disease prevention research, understanding the early events of the disease have the strongest potential to lead to improve-

ments in prevention, early diagnosis, and therapeutics. Thus, this group of patients warrants careful follow up to characterize the transition from iSS to full-blown pSS and pinpoint indicators of early autoimmunity that may help identify those at risk for further disease progression.

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How Does a Younger Age at the Onset of Sjögren's Syndrome (pSS) Influence the Clinical Presentation and the Clinical Course of the Disease? Chiara Baldini[1], Luca Quartuccio[2], Elena Bartoloni-Bocci[3], Roberta Priori[4], Francesco Carubbi[5], Alessia Alunno[3], Roberto Gerli[3], Guido Valesini[4], Salvatore De Vita[2] and Stefano Bombardieri[6]. [1]Rheumatology Unit, Pisa, Italy, [2]DSMB, University Hospital Santa Maria della Misericordia, Udine, Italy, [3]University of Perugia, Perugia, Italy, [4]Department of Internal Medicine and Medical Specialties, Sapienza University, Rome, Italy, [5]Rheumatology Clinic, University of L'Aquila, L'Aquila, Italy, [6]Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: (1) To analyze the clinical presentation and the clinical course of Sjögren's Syndrome (pSS) in Caucasian patients with an "early-onset" pSS and (2) to compare the characteristics of the disease between this group of patients and a control group of patients with pSS and a "typical onset" of the disease.

Methods: A retrospective systematic search through an Italian computerized pSS database, including 1445 patients, was performed in order to select the patients with an "early-onset" of the disease who were defined as those patients aged below the 10th percentile at the time of pSS diagnosis. All the patients enrolled in the database have been recruited at 5 Rheumatology University Italian medical centers and the data have been systematically entered in a standardized form and updated at regular intervals during follow-up since 2009. For all patients, the following parameters were retrieved: age at diagnosis, sex, disease duration, glandular and extra-glandular disease-related manifestations, laboratory features, serological profiles, medical treatments and lymphoproliferative complications. Categorical variables were compared using chi square test; continuous variables were compared using Student's t-test. A 2-tailed value of $p < 0.05$ was taken to indicate statistical significance.

Results: The systematic search selected 1192 pSS patients out of the entire cohort (AECG 2002). Median (IQR) age at pSS diagnosis was 52 (42–62) years and the tenth percentile was 33 years. By using the tenth percentile as a cut-off, we identified 125/1192 (10.5%) as the "early-onset" group whereas the remaining 1067/1192 (89.5%) represented the control group. Median (IQR) disease duration was significantly longer in the "early-onset" group (7 (3–14) versus 3 (1–8) years, $p \leq 0.0001$). Patients with an early disease onset presented a lower frequency of subjective dry mouth ($p=0.003$) and a higher prevalence of parotid enlargement ($p \leq 0.0001$), Raynaud's phenomenon ($p=0.04$) and tubular renal disease ($p=0.04$). Moreover, patients with an "early-onset" pSS presented more frequently a positivity for rheumatoid factor (RF) ($p \leq 0.0001$), anti-Ro/SS-A ($p \leq 0.0001$), and anti-La/SS-B antibodies ($p \leq 0.0001$), low C3 levels ($p=0.006$), hypergammaglobulinemia ($p \leq 0.0001$), and leukocytopenia ($p=0.006$). No differences were detected between the two groups regarding low C4 levels, cryoglobulins, purpura, peripheral nervous system involvement and lymphoproliferative complications.

Conclusion: The age at the onset of pSS may influence the diagnostic algorithm of the disease due to the lower prevalence of subjective sicca symptoms. Parotid enlargement, kidney involvement, laboratory and serological abnormalities seemed to be distinctive features of the "early-onset" pSS. However, despite the higher frequency of parotid gland enlargement, patients with "early-onset" pSS apparently did not present a phenotype at higher risk of lymphoma.

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Risk of Cervical Root and Incisal Caries in Patients with Sjogren's Syndrome. Nicola Berman[1], Jonathan S. Dunham[2], Joshua Baker[3] and Frederick B. Vivino[4]. [1]Pennsylvania Hospital, Philadelphia, PA, [2]Univ of Pennsylvania, Philadelphia, PA, [3]Philadelphia VA Medical Center, Philadelphia, PA, [4]Penn Presbyt Med Ctr, Philadelphia, PA.

Background/Purpose: Pathologic (cervical root and incisal caries) cause significant morbidity in patients with Sjogren's syndrome (SS). Identifying risk factors for pathologic caries may facilitate prevention strategies for dental complications in this population. We assessed whether primary (pSS) and secondary Sjogren's syndrome (sSS) were associated with an increased risk of pathologic caries compared with subjects with non-Sjogren's related xerostomia. We also evaluated risk factors for pathologic caries amongst SS patients with and without dental complications.

Methods: We retrospectively reviewed medical records of 225 consecutive patients with sicca symptoms who were evaluated at the Penn Sjogren's center. Subjects underwent complete physical examination, minor salivary gland biopsies, objective tests for dry eyes/dry mouth, serologic testing, and Technetium^{99} pertechnetate salivary scintigraphy. Prevalence of pathologic caries was determined by retrospective review of dental records. SS patients were diagnosed based on 2002 AECG Criteria. Subjects with Sjogren's syndrome (pSS and sSS) were compared to non-Sjogrens subjects (nSS). Patients who did not meet criteria included those with chronic sialadenitis, sclerosing chronic sialadenitis, non-specific chronic inflammation, undifferentiated connective tissue disease, or medication-induced xerostomia. We used t-tests, Wilcoxon rank sum tests and chi-squared tests to evaluate group differences. We further evaluated independent associations with pathologic caries using parsimonious multivariable logistic regression models.

Results: Compared with nSS, patients with SS were more likely to have pathological caries (57.7% vs 42.1%, $p=0.02$), abnormal scintigraphy (63.8% vs 38.6, $p=0.02$), and lower median unstimulated flow rates [0.46 (0.24, 1.06) vs 0.85 (0.30, 1.49) $p=0.005$]. There was no difference in stimulated salivary flow rates between the groups (**Table 1**). In multivariable logistic regression models adjusting for age and differences in unstimulated salivary flow, SS was associated with increased odds of pathologic caries [OR 1.81 (1.06, 3.12) $p=0.03$]. Among SS patients, only greater age was significantly associated with a greater risk pathologic caries ($p=0.03$).

Conclusion: SS is associated with an increased risk of pathologic caries compared to other causes of dry mouth. SS patients had significantly reduced unstimulated salivary flow rates and abnormal salivary scintigraphy compared with nSS patients. However, differences in caries prevalence in SS patients were not explained by differences in flow rates. Qualitative differences in saliva may be a more important cause of pathologic caries in SS than quantitative differences in flow. Further study is needed to optimize prevention strategies for caries in this group.

Table 1: Characteristics of subjects with and without Sjogren's syndrome.

	Sjogen's Syndrome	Non-Sjogrens	P Value
Number of Subjects	104	121	
Age	53.8 (13.7)	51.9 (13.2)	0.3
Female	86.4%	90.7%	0.3
Current Smoking	5.8%	5.0%	0.8
Median Duration of Dry Mouth	36 (12, 93)	36 (14, 91)	0.8
Median Duration of Dry Eye	48 (19.5, 117.5)	48 (22, 111)	0.8
SJOGREN'S TESTS			
ANA/RF+ Positive	11.5%	2.5%	0.01
SSB/SSB+ Positive	65.4%	15.7%	<0.001
Schirmer <5mm/5min	41.4%	38.8%	0.7
Focus Score	0.9 (0, 2.0)	0 (0, 0)	<0.001
DRUG USE			
Anticholinergic drugs	51.9%	57.0	0.4
Cholinomimetic drugs	22.1%	19.0%	0.6
DENTAL OUTCOMES			
Median number of pathologic caries	0 (0, 2)	0 (0, 0)	0.002
Any pathologic caries (%)	57.7%	42.1%	0.02
Presence of Dentures (%)	10.6%	9.1%	0.7
Patients with Missing Teeth (%)	59.6%	47.1%	0.06
SALIVARY FLOW			
Median Unstimulated SFR (mL/min)	0.46 (0.24, 1.06)	0.85 (0.30, 1.49)	0.005
Abnormal USFR*	12.5%	9.1%	0.4

Median Stimulated SFR	0 (0, 0)	0 (0,0)	0.1
Abnormal Stimulated SFR**	74.0%	70%	0.5
Abnormal scintigraphy*** (N=90)	63.8%	38.6%	0.02

Data presented as mean (standard deviation) or median (inter-quartile range) for skewed data.
* Abnormal flow rate <0.1 mL/min defined as abnormal.
** Abnormal stimulated flow rate defined as <0.150 ml/min.
*** Defective uptake or resting/stimulated discharge.

Disclosure: N. Berman, None; **J. S. Dunham**, None; **J. Baker**, None; **F. B. Vivino**, Andrea Cavitolo Foundation, 2, NiCox Inc., 5, Immco, Inc., 5, Norartis, Inc., 5, Biogen Idec, 5, Takeda, Inc, 5.

2546

Metabolic Disorders Causing Fatigue in Sjogren's Syndrome. Lakshmanan Suresh[1], Julian Ambrus[2], Long Shen[3] and Sahana Vishwanath[4]. [1]State University of New York/Buffalo, Buffalo, NY, [2]University Of Buffalo, Buffalo, NY, [3]SUNY at Buffalo, Buffalo, NY, [4]SUNY- Buffalo, buffalo, NY.

Background/Purpose: Sjogren's syndrome (SS) is a complex disorder involving both the innate and immune system. Fatigue is a common feature of the disease. Mitochondrial dysfunction has been associated with chronic inflammatory diseases, including SLE, and can result in fatigue and exercise intolerance.

Methods: We evaluated 32 patients meeting the ACR criteria for SS who presented with profound fatigue for disorders of aerobic and anaerobic metabolism. Serum lactate, carnitine and ischemic forearm tests were performed. In selected patients, muscle biopsies were done for genetic and biochemical studies.

Results: Of these SS patients, 30 had elevated lactic acid at rest and 3 had abnormal ischemic forearm tests. Nine of the patients underwent muscle biopsies. Four had mitochondrial respiratory chain abnormalities, 2 had carnitine palmitoyl transferase deficiency, 1 had very long chain acyl CoA dehydrogenase deficiency and 2 had glycogen storage diseases (myophosphorylase deficiency, lactate dehydrogenase deficiency). Appropriate treatment led to symptomatic improvement in all cases.

Conclusion: Metabolic disorders are common in patients with SS and contribute to symptoms such as fatigue and exercise intolerance. Treatment of these disorders leads to symptomatic improvement. Further studies are needed to determine the incidence of metabolic disorders in SS, the incidence of SS in patients with metabolic disorders and the mechanisms by which SS and metabolic disorders are interrelated.

Disclosure: L. Suresh, None; **J. Ambrus**, None; **L. Shen**, None; **S. Vishwanath**, None.

2547

The Impact of Primary Sjögren's Syndrome on Female Sexual Function. Jolien F. van Nimwegen, Suzanne Arends, Greetje S. van Zuiden, Arjan Vissink, Frans G.M. Kroese and Hendrika Bootsma. University Medical Center Groningen, University of Groningen, Groningen, Netherlands.

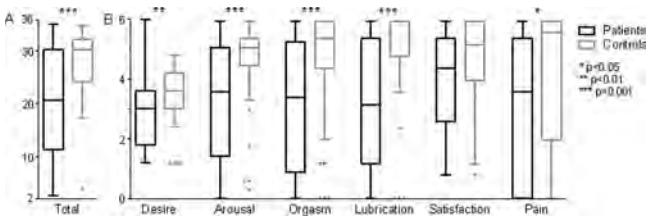
Background/Purpose: Primary Sjögren's syndrome (pSS) is a chronic and disabling disease, characterized by sicca symptoms of the eyes and mouth as well as fatigue. Besides these well-known symptoms, multiple studies have shown that women with pSS often experience complaints of vaginal dryness and dyspareunia. Our aim was to evaluate sexual dysfunctioning and sexual distress in women with pSS compared to healthy controls, as well as to assess parameters that are associated with sexual dysfunctioning and distress in pSS.

Methods: 46 women with pSS according to the AECG criteria (mean age 46.3 ± 10.5) and 43 age-matched healthy controls (mean age 44.4 ± 11.3) were included. Median disease duration of the patients was 7 years (IQR 4–14). Participants completed self-administered questionnaires, viz. Female Sexual Function Index (FSFI), Female Sexual Distress Scale (FSDS), Multidimensional Fatigue Inventory (MFI), Hospital Anxiety and Depression Scale (HADS), Maudsley Marital Questionnaire (MMQ) and RAND 36-item health survey (RAND-36). In addition, EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and Patient Reported Index (ESSPRI) were completed in pSS patients.

Results: Women with pSS had impaired sexual functioning compared to healthy controls (median FSFI 20.6 vs. 30.3, $p<0.001$), as reflected by significantly lower scores in the domains of desire, arousal, orgasm, lubrication and pain (figure 1). Furthermore, pSS patients experienced more sexual distress (median FSDS 7 vs. 4, $p<0.05$) and were sexually active less frequently than controls (76% vs. 93%, $p<0.05$). In total, 67% of the patients never talked about sexual problems with their rheumatologist. Sexual dysfunctioning correlated significantly with depressive symptoms (HADS), higher ESSPRI score, more symptoms of fatigue (MFI), lower mental quality of life (RAND-36) and relationship dissatisfaction (MMQ), but not with systemic disease activity (ESSDAI).

Conclusion: Women with pSS have impaired sexual function and more sexual distress compared to healthy controls. Sexual dysfunctioning and distress are associated with more patient-reported symptoms of pSS, fatigue and depression. More research is needed to obtain knowledge on the pathogenesis of vaginal sicca symptoms in pSS and the best treatment for this complaint.

Figure 1: FSFI total (A) and subscale (B) scores in patients with pSS and healthy controls. Box-and-whiskers plots (Tukey); boxes indicate medians with IQRs; whiskers indicate 1.5 times the interquartile distances; ● indicate outliers.



Disclosure: J. F. van Nimwegen, None; **S. Arends**, None; **G. S. van Zuiden**, None; **A. Vissink**, None; **F. G. M. Kroese**, None; **H. Bootsma**, None.

2548

Primary Sjögren's Syndrome Is Associated with Significant Cognitive Dysfunction. Mehmet Engin Tezcan[1], Seminur Haznedaroglu[2], Emine Belgin Kocer[2], Cemile Sonmez[3], Ridvan Mercan[4], Aysegul Atak Yucel[2], Hale Zeynep Batur[2], Berivan Bitik[4] and Berna Goker[4]. [1]Lutfi Kirdar Kartal EA Hospital, Istanbul, Turkey, [2]Gazi University School of Medicine,, Ankara, Turkey, [3]Public Health Institution of Turkey, Ankara, Turkey, [4]Gazi University School of Medicine, Ankara, Turkey.

Background/Purpose: Primary Sjögren's syndrome (PSS) is an autoimmune exocrinopathy with multiple clinical manifestations.

We aimed to evaluate the frequency and type of cognitive dysfunction and its association with anti-ganglioside antibodies in patients with PSS.

Methods: Twenty-eight female cases with PSS fulfilling the American-European consensus criteria and 20 female control subjects matched in terms of age and education level, examined between June, 2011 and August, 2013 were enrolled into the study. The mean age was 45,7±10,6 in PSS, and 42,1±10,3 ($p=0,27$) in the control group.

Neuropsychological tests including attention, information processing speed, short term memory, long term memory, visual memory and visual-spatial perception were examined in both group. Verbal frequency functions were examined and measured by COWAT, naming concentration by BNT, verbal learning by SDLT, immediate, short term and long term verbal memory by AVLT, visual spatial perception with BJLOT, and immediate, short term and long term visual memory with RCFT. Cognitive dysfuntion was defined as "mild" if there was a deterioration in 1 or 2 test performances, and as "severe" if an impairment in 3 or 4 test performances was observed.

A standard western blot test (Euroimmun, Germany) was used to investigate IgM and IgG anti-ganglioside antibodies (GM1, GM2, GM3, GD1a, GD1b, GT1b, GQ1b) in the patients and healthy controls.

Results: Primary Sjögren's syndrome patients had lower performance in tests evaluating verbal learning, verbal memory and visual-spatial perception in SDLT and BJLOT compared to healthy controls ($p<0,01$) in PSS group (Table 1). Lower performance was also observed in the patient group in clock drawing, COWAT, PASAT, and AVLT tests, however the difference did not reach a significant level ($p>0,05$).

	Patient (n=28)	Healthy control (n=20)	P
Clock Drawing	6,71 ± 0,71	7,00 ± 0,00	0,07
COWAT	25,71 ± 10,69	28,15 ± 8,43	0,38
PASAT	46,85 ± 8,65	51,00 ± 7,07	0,10
SDLT	8,0 ± 7,34	16,50 ± 4,34	**<0,01**
AVLT			
Immediate verbal memory	6,32 ± 1,92	7,40 ± 1,84	0,78

Long term verbal memory	10,32 ± 2,34	10,75 ± 2,02	0,63
BNT	33,50 ± 1,87	32,60 ± 2,58	0,21
BJLOT	21,07 ± 3,75	24,45 ± 2,46	**<0,01**

IgM anti-ganglioside antibodies were positive in 9 patients with PSS, and 2 in healthy controls. Three PSS patient had two IgM anti-ganglioside antibody positivity (GM1-GM2, GM3-GD1b, GT1b-GQ1b). IgG anti-ganglioside antibodies were positive in 3 patients with PSS, and 1 in healthy controls.

Conclusion: We found impairment in attention, information processing speed, long term memory and short term memory in PSS patients. Anti-ganglioside IgM antibodies may play a role in cognitive dysfunction in PSS by autoimmune neuroinflammation.

Implementing detailed neuropsychological tests is helpful in assessing subclinical cognitive dysfunction in PSS and early treatment.

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Renal Involvement in Primary Sjögren's Syndrome: A Multicenter French Study of 95 Biopsy Proven Cases. Benjamin Terrier[1], Magali Jasiek[2], Hélène Francois[3], Rafik Mesbah[4], Laurent Chiche[5], Anne-Laure Fauchais[6], Guillaume Moulis[7], Guillaume Le Guenno[8], Estibaliz Lazaro[9], Nathalie Costedoat-Chalumeau[1], Raphaèle Seror[10], Luc Mouthon[1], Loïc Guillevin[1], Xavier Mariette[11], Eric Thervet[12], Alexandre Karras[13] and Véronique Le Guern[1]. [1]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [2]Nephrology, Bicêtre Hospital, University Paris Sud, France, Paris, France, [3]1Nephrology, Bicêtre Hospital, University Paris Sud, France, PARIS, France, [4]Nephrology, Hôpital Boulogne sur Mer, France, Boulogne Sur Mer, France, [5]CHU Marseille, Marseille, France, [6]Department of Internal Medicine A, Dupuytren Hospital, Limoges University Hospital, Limoges, France, [7]Internal Medicine department, Toulouse, Toulouse, France, [8]Internal Medicine department, Clermont-Ferrand, France, [9]Hôpital Haut-Lévêque, Pessac, France, [10]Université Paris Sud, Le Kremlin Bicêtre, France, [11]Université Paris-Sud, Le Kremlin Bicêtre, France, [12]Hopital Européen Georges Pompidou, APHP, PARIS, France, [13]Hôpital Européen Georges Pompidou, APHP, Paris, France.

Background/Purpose: Renal involvement is reported in 5 to 25% of patients with primary Sjögren's syndrome (pSS). However, data on pSS-related nephropathy with renal biopsy (RB) remain scarce. This observational study was undertaken to describe the clinical and histopathological characteristics of pSS-related nephropathies and their outcomes.

Methods: We conducted a French multicenter and transdisciplinary retrospective study on pSS patients with RB-proven nephropathies. Inclusion criteria were patients diagnosed with pSS based on American-European Consensus Group (AECG) criteria or study-specific enlarged AECG criteria (presence of ≥3 of 4 AECG items), and who underwent a RB.

Results: Ninety-five patients were included (sex ratio F/M 9/1, mean age 49 years), 84% and 16% fulfilling AECG criteria and enlarged AECG criteria respectively. pSS was isolated in 88% or associated with other organ-specific autoimmune disorders (12%), including primary biliary cirrhosis, autoimmune hepatitis and thyroiditis. Renal disease was diagnosed prior to pSS for 20%, with a median interval of 17 months. For 41%, the 2 conditions were diagnosed simultaneously and, for 39%, after pSS, with a median interval of 36 months. Renal manifestations consisted of renal failure (86%), glomerular-range proteinuria (26%), electrolyte disturbances alone (18%), lithiasis (10%) and/or nephrocalcinosis (5%). RB exhibited acute or chronic tubulointerstitial nephritis (77%) with numerous plasma-cell infiltrates (69%). Glomerular lesions were found in 23%, associated with interstitial infiltrates in most patients. Glomerular disease was mainly cryoglobulinemic glomerulonephritis, focal and segmental glomerulosclerosis or membranous nephropathy. Eighty patients (84%) received corticosteroids (CS). In 21 patients (22%), standard immunosuppressive drugs (n=8) and/or rituximab (n=18) was added on top of CS in a first or a second line of treatment. Baseline mean estimated glomerular filtration rate (eGFR) was 40 mL/min/1,73m2. After a median follow-up of 53 months, eGFR improved significantly (47 mL/min/1,73m2, P=0.001), and only 3 patients progressed to end-stage renal disease. Multivariate analyses found age and tubulointerstitial lesions as significantly associated factors with poor renal prognosis, even though overall outcome was good.

Conclusion: In pSS, the main renal lesion is tubulointerstitial nephropathy associated with significant and frequent renal dysfunction. Systemic treatments can significantly improve renal function. Analysis of renal prognosis associated with the different therapeutic strategies is ongoing.

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2550

Impaired Speckle Tracking As a Marker of Subclinical Left Ventricular Dysfunction in Patients Affected By Primary Sjögren's Syndrome. Fabiola Atzeni[1], Stefano Galaverna[2], Chiara Colombo[2], Luigi Gianturco[2], Laura Boccassini[1], Piercarlo Sarzi-Puttini[1] and Maurizio Turiel[2]. [1]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy, [2]Cardiology Unit, IRCCS-Galeazzi Orthopedic Institute,, Milan, Italy.

Background/Purpose: Primary Sjögren's syndrome (pSS) is a common chronic autoimmune disease that particularly affects the salivary and lachrymal glands, and leads to dry eyes and dry mouth. We have previously shown that plasma asymmetric dimethylarginine (ADMA) levels and coronary flow reserve (CFR) are impaired in patients with pSS. The aim of this study was to investigate the use of impaired speckle tracking as a marker of subclinical left ventricular dysfunction predicting congestive heart failure in patients with pSS and a normal ejection fraction.

Methods: The study involved 49 outpatients who fulfilled the American-European Consensus Criteria (AECG) criteria for pSS (14 males and 35 females; mean age 57 ±6.9 years), and 22 healthy controls matched in terms of age, gender and other anthropometric characteristics. Cardiovascular (CV) risk profiles were assessed by means of standard electrocardiography (ECG), conventional and stress trans-thoracic echocardography with the measurement of CFR, carotid ultrasonography and pulse wave velocity (PWV). Two-dimensional echocardiographic images were obtained using the apical 4-chamber view at a high frame rate of 70–80 frames/s, and three cardiac cycles were stored in cine-loop format for off-line analysis using commercially available QLAB 9 software (Philips Medical System, USA) in order to assess end-systolic LV longitudinal strain (ε).

Results: All of the patients had extra-extraglandular systemic involvement pSS: 30 were being treated with hydroxychloroquine (HCQ) 400 mg/day, 11 with azathioprine (AZA) at a mean dose of 150 mg/day (range 50–200 mg), and eight with methotrexate (MTX) at a mean dose of 7.5 mg/weekly. None of the patients showed any signs or symptoms of CV disease, pulmonary involvement, or any other complication. The patients' mean EF and E/A ratios were respectively 59.11±6.35% and 0.94±0.0.24, which were not significantly different from those of the controls; however, although within the normal range, their CFR was lower (median 2.7, IQR 2.40–2.90 *vs* 3.20, IQR 3.06–3.33; $p<0.0001$). Right and left pulse wave velocity (PWV) (PWV m/sec median 8.8, IQR 7.26–10.32 *vs* 6.86, IQR 6.66–7.10; $p<0.0001$) and right and left coronary intima media thickness (cIMT) (cIMT mm: median 0.6, IQR 0.5–0.7 *vs* 0.53, IQR 0.50–0.60; $p=0.08$) values were all higher in the pSS patients, but the differences were not statistically significant The results of the speckle tracking analysis were significantly different between the two groups, with global longitudinal strain deformation in the apical 4-chamber view (Long. ε 4c) being significantly lower in the pSS patients than in controls (Long ε 4c %: median 15.28, IQR 12.3–16.2 *vs* 19.8, IQR 19.3–20.40; $p<0.0001$).

Conclusion: LV myocardial longitudinal ε measured by means of speckle tracking echocardiography was impaired in our pSS patients in the absence of any clinical evidence of CV disease and when traditional echocardiographic evaluations were still negative, thus suggesting a myocardial alteration. However, further studies are required to define more precise methods of assessing CV disease in patients with pSS.

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2551

Presence of Germinal Centers at Baseline Is Associated with Clinical Response of Glandular Essdai Domain after Abatacept Treatment in Primary Sjogren's Syndrome. Erlin A. Haacke, Frans G.M. Kroese, Petra M. Meiners, Bert van der Vegt, Arjan Vissink, Fred K.L. Spijkervet and Hendrika Bootsma. University Medical Center Groningen, University of Groningen, Groningen, Netherlands.

Background/Purpose: Abatacept inhibits the costimulatory interaction of T-lymphocytes and antigen-presenting cells. Treatment of early and active primary Sjögren's Syndrome (pSS) with abatacept decreases disease activity. The aim of this study was to assess the histopathological changes in the parotid gland tissue after treatment with abatacept in pSS patients.

Methods: 15 patients (12 female, 3 male) were included in the open-label Active Sjögren Abatacept Pilot (ASAP) study and received 8 intravenous abatacept infusions on days 1,15, 29 and every 4 weeks thereafter. Before treatment and at 25 weeks of follow up a parotid gland biopsy was taken. Hematoxilin-eosin stains were evaluated for focus score (foci of 50 lymphocytes/4mm^2), lymphoepithelial lesions (LELs) and presence of germinal centers. A CD45 stain was used to calculate the area of lymphocytic infiltrate (Aperio ImageScope v12.0). The infiltrate was further analysed for numbers of CD20+ B-cells, CD3+ T-cells and IgA, IgG and IgM positive plasma cells using HistoQuest.

Results: At baseline 5 out of 15 patients (33%) showed presence of germinal centers in parotid gland tissue. In all these 5 patients germinal centers were absent after abatacept treatment. One patient showed only limited germinal center activity after treatment. The mean number of germinal centers decreased from 0,06 GC/mm^2 to 0,01 GC/mm^2. Importantly, the number of germinal centers/mm^2 at baseline is associated with a clinical improvement in the glandular domain of the ESSDAI. Abatacept treatment did not affect focusscore, LELs, amount of infiltrated B-cells and T-cells. Analysis of the plasma cell population is currently in progress.

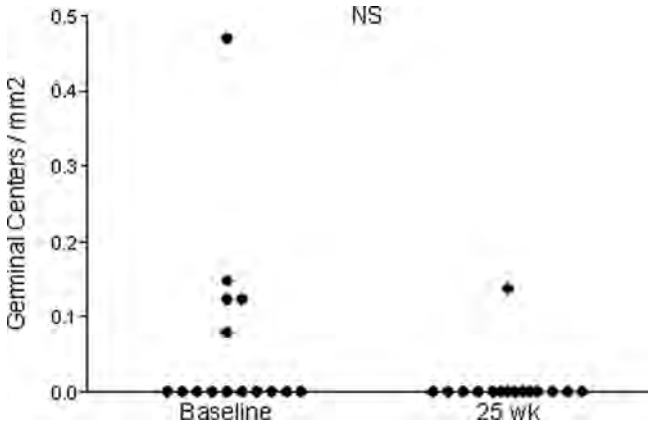


Figure 1: Number of germinal centers in parotid gland tissue decline after treatment with abatacept.

Conclusion: Presence of germinal centers at baseline in parotid gland tissue is associated with clinical respons in the glandular domain of the ESSDAI after treatment with abatacept in primary Sjogren's syndrome. Histopathological analysis of parotid gland tissue may therefore be helpfull in assessing treatment efficacy. As expected, abatacept does not affect the lymphocytic infiltrate in terms of overall numbers of T- and B-cells.

Disclosure: E. A. Haacke, None; **F. G. M. Kroese**, None; **P. M. Meiners**, None; **B. van der Vegt**, None; **A. Vissink**, None; **F. K. L. Spijkervet**, None; **H. Bootsma**, BMS, 2.

2552

Effectiveness and Safety of Low-Dose Cyclosporine a in Patients with Primary Sjögren's Syndrome (pSS) with Articular Involvement – Results of a Pilot Study. Claudia Kedor, Jan Zernicke, Anja Hagemann, Kathrin Mattat, Gerd Burmester and Eugen Feist. Charité University Medicine, Berlin, Germany.

Background/Purpose: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease, where musculoskeletal manifestations are usually treated by symptomatic measures and different conventional DMARDs by off-label use. Cyclosporine A (CyA), as an approved DMARD for treatment of arthritic joint involvement in different rheumatic disorders, is mainly used for local treatment of keratoconjunctivitis sicca in pSS, whereas reports on systemic effects are limited to small cohorts so far. Since low-dose CyA has shown promising effects and improved tolerability in different autoimmune disorders, the aim of this pilot study was to investigate the effects of a reduced dosage on articular involvement in patients with pSS.

Methods: For this single-center, open-label, non-controlled phase II trial n=30 patients with pSS (29 females, average age 54.9 years, mean disease duration of 6 years) fulfilling the European-American Classification Criteria were included. All patients had active articular involvement with a minimum of 3 tender and/or 3 swollen joints. Oral NSAIDs and systemic steroids (£10mg/d prednisone equivalent) were permitted at stable doses for at least 4 weeks prior to inclusion. In 18 patients, at least one DMARD (not CyA) had failed prior to study entry. Primary endpoint was to evaluate the therapeutic effects of low-dose CyA (2mg/kg divided in two intakes a day) on articular involvement (reduction of tender and swollen joint counts) after 16 weeks of treatment.

Results: Introduction of low-dose CyA improved significantly joint involvement in patients with pSS. At week 16, the DAS28 decreased from 5.1 to 4.2 ($p=0.003$), the Tender Joint Count (out of 68) decreased from 17 ± 13 to 10 ± 11 ($p=0.003$), the Swollen Joint Count (out of 66) decreased from 3 ± 3 to 1 ± 3 ($p<0.001$) Furthermore, a clear treatment effect was observed on overall disease activity by the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) reduction from 5.3 ± 3.3 to 3.0 ± 3.1 ($p=0.001$). Ultrasonography of the three predominanty affected joints confirmed improvement of joint effusion and synovitis ($p<0.05$) at week 16. There was no significant effect on HAQ or sicca-symptoms measured by Schirmer- and Saxon-tests. Overall, the treatment was well tolerated and adverse events were consistent with the known safety profile of CyA (e. g. hypertension, headache, grade I creatinine increase).

Conclusion: In this pilot-study, promising effects of low-dose CyA treatment on articular involvement and disease activity were observed in patients with pSS. The safety profile was comparable to known side effects of CyA.

Disclosure: C. Kedor, None; **J. Zernicke**, None; **A. Hagemann**, None; **K. Mattat**, None; **G. Burmester**, AbbVie, Pfizer, UCB, Roche, 2, AbbVie, BMS, Pfizer, Merck, MedImmune, UCB, Roche, 5, AbbVie, BMS, Pfizer, Merck, UCB, Roche, 8; **E. Feist**, Roche/Chugaipharma, 6, Roche/Chugaipharma, 2.

ACR/ARHP Poster Session C
Spondyloarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment
Tuesday, November 18, 2014, 8:30 AM–4:00PM

2553

Compromised Volumetric Bone Density, Bone Microarchitecture and Bone Strength in Patients with Ankylosing Spondylitis: High-Resolution Peripheral Quantitative Computerized Tomography (HRpQCT) Based Study. Nisha Nigil Haroon[1], Eva Szabo[2], Janet Raboud[3], Ammepa Anton[4], Robert Josse[1], Robert D. Inman[1] and Angela Cheung[1]. [1]Department of Medicine, University of Toronto, Toronto, ON, [2]Osteoporosis Program, UHN, TOronto, ON, [3]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, [4]University Health Network, Toronto, ON.

Background/Purpose: Patients with ankylosing spondylitis (AS) have high fracture risk. BMD, bone microarchitecture and strength determine fracture risk. However, in AS, DXA-based BMD measurements of the lumbar spine may be falsely normal due to the presence of syndesmophytes. Also, DXA cannot differentiate between trabecular and cortical bone. The effect of AS on bone microarchitecture and strength is also unknown. We assessed bone microarchitecture and strength in patients with AS and compared that with non-AS controls.

Methods: AS was defined by the modified New York criteria. Disease activity of AS was measured by BASDAI, mSASSS, serum ESR and CRP levels. Volumetric BMD (vBMD) and microarchitecture were measured using HRpQCT, and bone strength was estimated using finite element analysis (FEA). Multivariable linear regression was used to analyze the effect of AS on HRpQCT parameters.

Results: There were 44 cases (82% Caucasian). The mean (+SD) age and BASDAI were 44+2 and 6.3+ 1.8 respectively. Median (IQ) disease duration was 20 (7.3–27.8 years). Twenty-three subjects had mSASSS >0. Four cases (9%) reported a history of fragility fracture. Use of TNF inhibitors (none), bisphosphonates (n=2) and corticosteroids (n=2) was negligible. Mean serum ESR, CRP and SAP levels were 22.0+23.6, 12.6 +15.6 and 96.2 +43.2 IU respectively. In multivariable linear regression models adjusted for age and gender, cases (n=44) had lower vBMD (trabecular, cortical and total), cortical thickness, BV/TV, bone stiffness and stress, and higher cortical porosity and trabecular separation at the radius (Table 1) when compared to non-AS controls (n=85). Tibial vBMD, BV/TV and cortical porosity were also abnormal in cases. But trabecular architecture at tibia was not different between cases and controls.

Conclusion: This study documents abnormalities of bone structure and strength in patients with AS. Patients with AS had lower volumetric BMD and worse microarchitecture at the trabecular and cortical regions compared to controls. Bone stiffness and stress at the radius and tibia, as estimated by FEA, also tended to be lower in cases than controls. These abnormalities might partly explain the high fracture risk in patients with AS.

Table 1: Multivariable linear regression showing abnormal bone microarchitecture and strength in patients with AS (44 cases and 85 controls).

		Exposure variable Cases vs. controls		Covariate 1 Age		Covariate 2 Gender	
Site	Outcome variables	Beta	p	Beta	p	Beta	p
Radius	Trabecular vBMD	−.232	.032	−.211	.048	.444	.000
	Cortical vBMD	−.294	.008	−.530	.000	−.143	.092
	Total vBMD	−.351	.003	−.394	.001	.128	.148
	Trabecular number	−.208	.071	−.057	.613	.328	.000
	Trabecular thickness	−.195	.068	−.310	.003	.421	.000
	Trabecular separation	.242	.035	.090	.422	−.318	.000
	BV/TV	−.231	.033	−.210	.049	.443	.000
	Cortical thickness	−.327	.003	−.604	.000	−.019	.822
	Cortical porosity	.215	.029	.661	.000	.298	.000
	Stiffness, *K* (kN/mm)	−.337	.004	−.254	.028	.136	.129
	Stress	−.337	.004	−.254	.028	.137	.129
Tibia	Trabecular vBMD	−.232	.044	−.103	.359	.328	.000
	Total vBMD	−.271	.019	−.403	.000	.136	.122
	Cortical vBMD	−.246	.019	−.636	.000	−.008	.918
	Trabecular number	−.153	.182	−.040	.722	.333	.000
	Trabecular thickness	−.122	.313	−.076	.521	.101	.276
	Trabecular separation	.213	.067	.050	.660	−.299	.001
	BV/TV	−.233	.043	−.104	.353	.329	.000
	Cortical thickness	−.176	.065	−.719	.000	−.191	.010
	Cortical porosity	.227	.025	.685	.000	.092	.233
	Stiffness, *K* (kN/mm)	−.209	.073	−.361	.002	.109	.222
	Stress	−.212	.068	−.363	.002	.108	.228

Disclosure: N. Nigil Haroon, None; **E. Szabo**, None; **J. Raboud**, None; **A. Anton**, None; **R. Josse**, None; **R. D. Inman**, Advisory board and grant, 5; **A. Cheung**, Grant and honoraria, 5.

2554

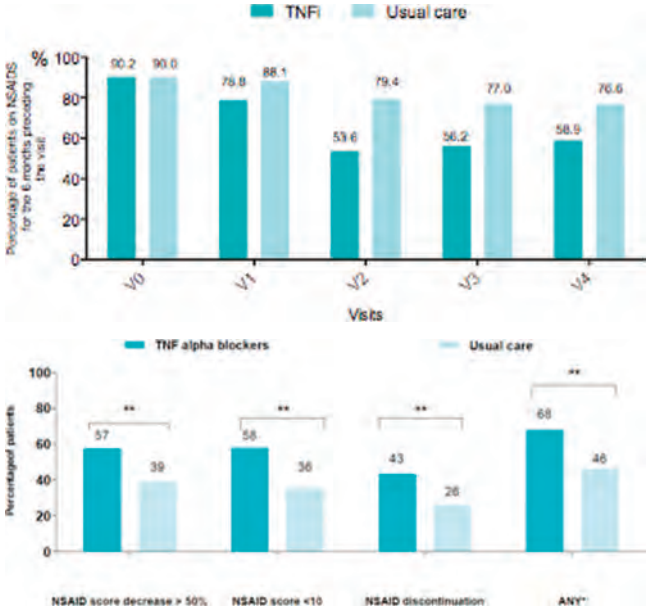
Do TNF Alpha Inhibitors Have an NSAID Sparing Effect in Real Life in Early Axial Spa? Results from the DESIR Cohort. Anna Moltó[1], Benjamin Granger[2], Daniel Wendling[3], Maxime A. Breban[4], Maxime Dougados[5] and Laure Gossec[6]. [1]GRC-UPMC 08 (EEMOIS); UPMC Univ Paris 06.AP-HP, Pitié Salpêtrière Hospital, Department of Rheumatology, Paris, France., Paris, France, [2]Université Pierre et Marie Curie - Paris 6 ; AP-HP, Paris, France, [3]CHU J Minjoz, Besancon, France, [4]Ambroise Paré Hospital, and Versailles Saint Quentin en Yvelines University, Boulogne-Billancourt, France, [5]INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France., Paris, France, [6]UPMC GRC08, Paris 06 University, Pitié Salpétrière Hospital, Paris, France.

Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are the keystone in the treatment of axial Spondyloarthritis (axSpA), but have potential side effects (cardiovascular and gastrointestinal). Effectiveness of TNF alpha inhibitors (TNFi) in early axial SpA has already been established-but the NSAID-sparing-effect of TNFi in real life has not been evaluated. The aim of this study was to evaluate the effect of TNFi on NSAID intake in an early axSpA cohort over the first 2 years of follow-up.

Methods: *Study design:* prospective, multi-centre, observational study (DESIR cohort) of patients with early inflammatory back pain; management and treatment of these patients was decided by their treating rheumatologists. *Data of interest at each visit over 2 years:* NSAID intake (yes/no) and ASAS-NSAID intake score. *Statistical analysis:* matching of patients receiving a TNFi or not by a propensity score; ANCOVA of the ASAS-NSAID intake score between groups over follow-up.

Results: Of the 627 patients followed-up, 181(28.9%) received a TNFi and were matched to 181 patients receiving usual care. Baseline characteristics were comparable (mean age 34 years and 40%males)NSAID-Sparing effect:Initially, 90.2% and 90.0% of patients received an NSAID (TNFi/usual care, respectively), with a greater decrease over time in the TNFi group (Figure1. The decrease in the median NSAID intake score was significantly greater in the TNFi group (from 54.9 to 1.9 vs. 41.9 to 22.3, p=0006), and the percentage of patients that could either decrease by 50% their NSAID intake or decrease their score under 10 or discontinuate NSAID treatment was greater in the TNFi group (67.6% vs 46.2%, p=0.002) (Figure2).

Conclusion: TNFi treatment is associated with a decrease in the proportion of patients taking NSAIDS, and even with a greater decrease in the overall intake of NSAIDs, confirming the NSAID-sparing effect of TNF alpha blockers in early axSpA in real life.



Disclosure: A. Moltó, None; **B. Granger**, None; **D. Wendling**, None; **M. A. Breban**, None; **M. Dougados**, None; **L. Gossec**, None.

2555

The Effect of Co-Medication with Conventional Synthetic (cs)Dmards on Achieving Low Disease Activity While Persisting on Adalimumab Therapy in Patients with Ankylosing Spondylitis/Axial Spondylarthritis (AS)–Analysis from the Czech Biologics Registry Attra. Karel Pavelka[1], Jakub Zavada[2], Marketa Fojtikova[3], Sarka Forejtova[1] and Karel Hejduk[4]. [1]Institute of Rheumatology, Prague, Czech Republic, [2]Charles University, Prague, Czech Republic, [3]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [4]Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic.

Background/Purpose: The role of combined treatment with csDMARDs and anti-TNF therapy in AS is not well established.

Methods: Main goal of this study was to compare the probability of achieving low disease activity (LDA) while persisting on adalimumab (ADA) therapy in AS patients treated by either ADA alone, or by combination of ADA + csDMARDs. This analysis was conducted within the national biologics registry with mandatory registration for all patients with AS who start treatment with biologics. All patients with AS treated with ADA as a first line anti-TNF drug with available baseline BASDAI and CRP were included in the analysis. To get reimbursement for anti-TNF therapy, all AS patients had to have high baseline disease activity (defined as BASDAI >4, and CRP > 10 mg/l). LDA was defined as BASDAI < 4 and CRP <5 mg/l. Pre-specifed sensitivity analyses were conducted in patients with pure axial, and combined axial+peripheral forms of AS.

Results: Data for 481 patients were available for the analysis (table). There was no difference in the primary outcome either in the total cohort (figure 1), or in the subset of patients with combined axial and peripheral involvement. In patients with pure axial form of AS, higher probability of achieving LDA while persisting on ADA therapy was observed in some, but not all time-points of follow-up (figure 2). Patients on co-therapy with methotrexate (n=55) fared similarly as those on sulfasalazine (n=141).

Conclusion: Co-therapy with csDMARDs did not increase the overall probability of reaching LDA and drug survival on ADA in AS patients.

Acknowledgements: This work was supported by project of MHCR for conceptual development of research organization 023728.

Table 1 – baseline characteristics

	ADA monotherapy (N=259)	ADA+ csDMARD (N=222)	p-value
Female (%)	24.3		0.029
Age (years)	39 (10)	39 (11)	0.513
Disease duration (years)	9,6 (9,4)	7,7 (7,6)	0.088
Pure axial form n(%)	118 (45.6%)	75 (33.8)	0.009
Axial and peripheral form n(%)	141 (54.4%)	147 (66.2)	
CRP (mg/l)	23,2 (20,2)	28,2 (26,7)	0.111
BASDAI	6,1 (1,7)	6,3 (1,8)	0.160
HAQ	1,1 (0,5)	1,1 (0,5)	0.692

Data are mean (SD) if not stated otherwise

Figure 1

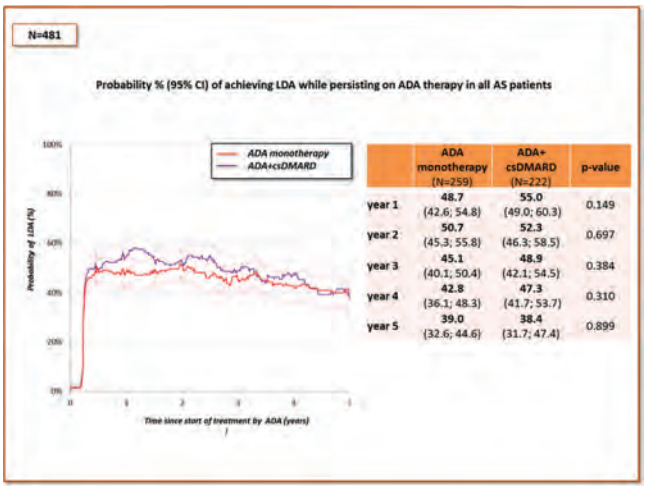
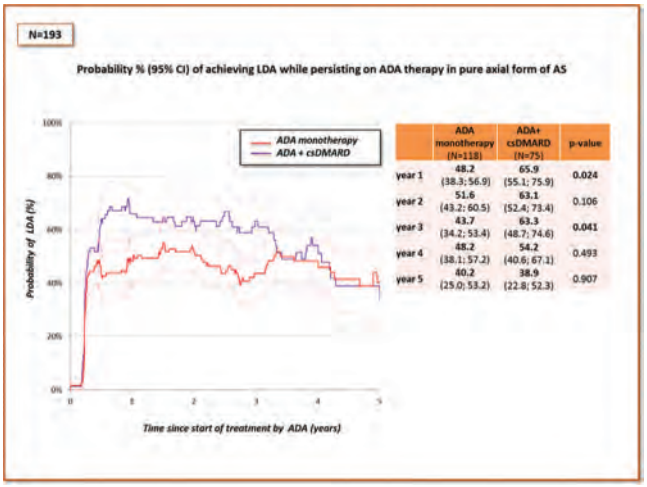


Figure 2



Disclosure: K. Pavelka, None; **J. Zavada**, None; **M. Fojtikova**, None; **S. Forejtova**, None; **K. Hejduk**, None.

2556

Is the Degree of NSAID Treatment in Early Axial Spondyloarthritis a Reflection of the physician's Diagnosic Confidence? Results from the DESIR Cohort. Anna Moltó[1], Benjamin Granger[2], Daniel Wendling[3], Maxime Dougados[4] and Laure Gossec[5]. [1]GRC-UPMC 08 (EEMOIS); UPMC Univ Paris 06.AP-HP, Pitié Salpêtrière Hospital, Department of Rheumatology, Paris, France., Paris, France, [2]Université Pierre et Marie Curie - Paris 6; AP-HP, Paris, France, [3]CHU J Minjoz, Besancon, France, [4]INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France., Paris, France, [5]UPMC GRC08, Paris 06 University, Pitié Salpétrière Hospital, Paris, France.

Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are the keystone in the treatment of axial Spondyloarthritis (axSpA). Diagnosis is often not easy in early forms due to the paucity of structural/inflammatory lesions and the clinical gestalt of the physician is an important part of the treatment decision in clinical. Our hypothesis was that NSAID prescription might be a reflection of the degree of the physician's diagnostic confidence in inflammatory back pain (IBP) suggestive of axSpA. Our objective was a) to describe the population of IBP patients suggestive of axSpA that were almost never exposed to NSAID over 3 years and to compare such population to the exposed patients; b) to compare both groups with regard to the fulfillment of the ASAS criteria and physicians' diagnostic confidence and c) to explore the correlation between NSAID intake and physicians' diagnostic confidence.

Methods: *Study design and patients:* Observational prospective, multicentre study (DESIR cohort) of patients with early IBP (>3 months and < 3 years symptom duration) suggestive of axSpA, and available data over 3 years.*Diagnosis:* ASAS axSpA criteria and physician's diagnostic confidence in axSpA (from 0 to 10, where 10= highest confidence).*NSAID intake:* the almost never exposed (ANE) group was defined as the patients who had an ASAS-NSAID score < 5 at each visit over follow-up (e.g. patients who had received <6 days/6 months of diclofenac). The rest of the cohort was the exposed (E) group.*Statistical analysis:* by Chi-square and T tests and spearman correlation.

Results: Of the 606 patients, 26 (4.3%) patients were classified in the ANE group. Patient and disease characteristics were comparable in both groups, except for history of inflammatory bowel disease (IBD): 6 (23%) vs. 17 (2.9%), in the ANE and E groups, respectively (p<0.001). Diagnosticconfidence: a) baseline: the percentage of patients fulfilling the ASAS criteria at baseline (and each arm) was similar in both groups (ASAS criteria :69.2% and 72.8%, for the ANE and E groups, respectively), as was the mean physician's axSpA diagnostic confidence (7.1±2.6 and 7.1±2.5). A quite moderate correlation between physician's axSpA diagnostic confidence and NSAID intake score was found (rho= 0.15, p=0.0002); b) at 3 years: no differences were observed in the fulfillment of the ASAS criteria (69.2% and 74.9%);no differences were observed either with regard to the mean physician's axSpA diagnostic confidence at the end of follow-up, (8.11±2.5 and 7.8 ±2.8) and no correlation was found between the physician's axSpA diagnostic confidence and the NSAID intake score (rho= 0.06, p=0.183).

Conclusion: Less than 5% of patients with IBP suggestive of SpA were almost never exposed to NSAID during follow-up; these patients did not differ from the rest of the cohort, except with regard to the presence of IBD. This suggests that lack of NSAIDs exposure is more driven by the presence of IBD than the lack of diagnosis confidence.

Disclosure: A. Moltó, None; **B. Granger**, None; **D. Wendling**, None; **M. Dougados**, None; **L. Gossec**, None.

2557

Are We over-Treating with Nsaids Our Early Axial Spa Patients? Results from the DESIR Cohort. Anna Moltó[1], Benjamin Granger[2], Daniel Wendling[3], Maxime Dougados[4] and Laure Gossec[5]. [1]GRC-UPMC 08 (EEMOIS); UPMC Univ Paris 06.AP-HP, Pitié Salpêtrière Hospital, Department of Rheumatology, Paris, France., Paris, France, [2]Université Pierre et Marie Curie - Paris 6 ; AP-HP, Paris, France, [3]CHU J Minjoz, Besancon, France, [4]INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France., Paris, France, [5]UPMC GRC08, Paris 06 University, Pitié Salpétrière Hospital, Paris, France.

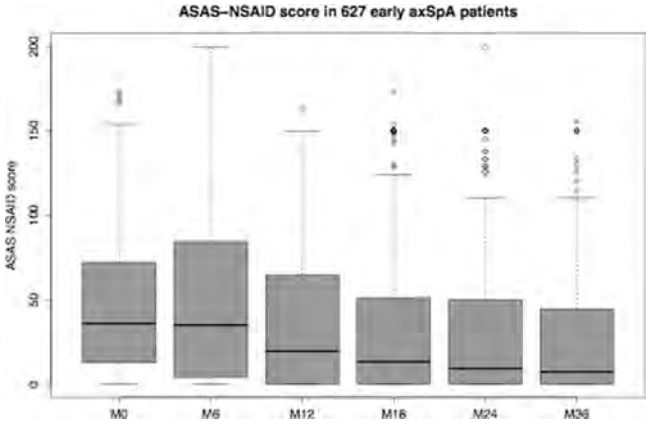
Background/Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are the keystone in the treatment of axial Spondyloarthritis (axSpA), and even in early forms, patients symptoms may lead to an over-treatment by NSAIDs. However, the current recommendation is to use NSAIDs at the lowest efficacious dose for the shortest period of time, due to safety issues (cardiovascular and gastro-intestinal side effects). The aim of our study was to describe the real-life NSAID use in an observational cohort of inflammatory back pain suggestive of axial SpA over a 3 years period of follow-up.

Methods: *Study design:* Observational prospective, multi-centre study (DESIR cohort) of patients with early inflammatory back pain (IBP) suggestive of ax-SpA. *Patients:* Patients who attended all 6 visits (every 6 months during the fist 2 years and yearly at 3 years) and for whom NSAID information was available were included in this analysis. *Data collected at every visit over 3 years:* NSAID intake and ASAS-NSAID intake score for the 6 months preceding the visit. The ASAS-NSAID intake score reflects the overall intake of NSAID during a period and ranges from 0 to 200 or more (where a 100 =150 mg of Diclofenac/day every day of the period of interest); "highly doses" were defined as score > 75. *Statistical analysis:* descriptive

analysis of the NSAID intake (as a binary variable "NSAID intake during the last 6 months" yes/no, and as a continuous variable by the ASAS-NSAID intake score for the last 6 months). Variation of the ASAS-NSAID score over time was tested by analysis of variance (ANOVA).

Results: 627 patients (46.1% males, mean age 33.7(8.7)) were assessed. 181 (28.9%) patients received a least one TNF alpha blocker during follow-up. At inclusion, 582 patients (92.8%) patients were taking NSAIDs; this proportion decreased over time, with the lowest proportion being 70.2% at 18 months. At all visits, more than 70% patients were treated with NSAIDs. Median ASAS-NSAID intake score was 36 (13–72) at inclusion, and substantially decreased to reach 7 (0–44) after 3 years ($p<0.0001$) (Figure) "Highly treated" patients represented 10% of the population at inclusion, and 4% after 3 years, with only 3 patients with a sustained score > 100 over time.

Conclusion: more than 70% of this early axSpA population received an NSAID treatment over the 3-years of follow-up, but intake significantly decreased over time, with only very few "highly treated" patients. This suggests that rheumatologists do not over-treat early axSpA patients with NSAIDS. Further studies should focus on those patients with sustained high doses of NAIDS over time.



Disclosure: A. Moltó, None; **B. Granger**, None; **D. Wendling**, None; **M. Dougados**, None; **L. Gossec**, None.

2558

Etanercept Increases Bone Mineral Density in Ankylosing Spondylitis, but Does Not Prevent Vertebral Fractures. M.a.C. van der Weijden[1], J.C. van Denderen[1], W.F. Lems[2], M.T. Nurmohamed[2], B.a.C Dijkmans[2] and I.E. van der Horst-Bruinsma[2]. [1]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands, [2]VU University Medical Center, Amsterdam, Netherlands.

Background/Purpose: Ankylosing spondylitis (AS) is characterized by chronic inflammation often leading to ankylosis of the spine, but also by a decrease of bone mineral density (BMD) and high prevalence of vertebral fractures (VF). Treatment with TNF blocking agents decreases inflammation and has shown to be effective in increasing BMD. We studied the effects of etanercept on BMD and VF in AS patients after two years of treatment. Furthermore we studies changes in bonemarkers (CTXI, CTXII, RANKL, OPG, Osteocalcin) and radiological damage.

Methods: Patients with active AS, treated with etanercept for two years, were included. BMD lumbar spine and hips was measured at baseline and after two years, as well as the radiological damage (mSASSS, including thoracic spine), VF (Genant method) and change in bone-markers.

Results: Forty-nine AS patients were included (Table**).** After two years of etanercept, hip BMD raised with 2.2% ($p=0.014$) and lumbar spine BMD with 7.0% ($p<0.001$). The BASDAI decreased significantly ($p<0.001$) as well as CRP and ESR ($p<0.001$). Despite etanercept therapy, the number of patients with vertebral fractures more than doubled (from 6 to 15 patients, $p=0.004$) as well as the severity. Also the radiological damage mSASSS+ThSpine increased significantly over time (from 12.1 to 18.5, $p<0.001$). No significant change in bone-markers was found.

Clinical characteristics N=49	Baseline	After 2 years etanercept
Men[a]	40 (81.6)	
Age[b], years	41.8 (9.2)	
Disease duration[b], years	12.2 (9.1)	
ESR[c], (mm/hr) [<20]	20.0 (6.0–39.0)	6.5 (3.0–16.0)*
CRP[c], (mg/l) [<10]	14.0 (3.0–39.0)	2.5 (1.0–9.8)*
BASDAI[b], (0–10)	5.7 (1.6)	2.9 (2.1)*
BASFI[b], (0–10)	5.7 (2.1)	3.5 (2.9)*
BASMI[b], (0–10)	4.4 (2.3)	4.0 (2.4)
Total mSASSS[c], (0–72)	10.0 (3.8–35.5)	15.5 (5.5–42.5)*
Total mSASSS+ThSpine[c], (0–90)	12.1 (6.8–42.7)	18.5 (8.7–52.0)*
sBMD hip[b]	0.903 (0.152)	0.921 (0.146)*
sBMD L2-L4[b]	1.141 (0.203)	0.213 (0.200)*
Number vertebral fractures[a]	8 (16.3)	21 (42.9)*
Patients with vertebral fractures[a]	6 (12.2)	15 (30.6)*

[a]number (%), [b]mean (SD), [c]median (IQR), *significant change $p<0.05$

Conclusion: This prospective longitudinal observational cohort study in AS patients showed that after two years etanercept treatment, BMD of the hip and spine increased significantly. However, the number and severity of vertebral fractures increased, as well as the radiological progression, including the thoracic spine. Thus, the favourable effect of etanercept on BMD in AS is accompanied by unfavourable outcomes on vertebral fractures and radiological damage.

Disclosure: M. A. C. van der Weijden, None; **J. C. van Denderen**, None; **W. F. Lems**, None; **M. T. Nurmohamed**, None; **B. A. C. Dijkmans**, None; **I. E. van der Horst-Bruinsma**, None.

2559

Vitamin D insufficiency and Deficiency in Two European Cohorts of Patients with Inflammatory Rheumatic Disorders. Alessandra Vacca[1], Giovanni Porru[1], Grazia Dessole[1], Alessandro Mathieu[1], Catherine Cormier[2], Yvonne Fulla[2], Andre Kahan[2] and Yannick Allanore[3]. [1]Unit and Chair of Rheumatology, University Hospital of Cagliari, Cagliari, Italy, [2]Rheumatology A Department, Cochin Hospital, APHP, Paris Descartes University, Paris, France, [3]Paris Descartes University, Rheumatology A Department and INSERM U1016, Cochin Hospital, Paris, France.

Background/Purpose: Vitamin D plays an important role in the modulation of immune system and epidemiologic data indicate low vitamin D levels in autoimmune diseases such as rheumatoid arthritis (RA), connective tissue disorders, inflammatory bowel diseases and multiple sclerosis. Several studies reported contradictory results regarding correlation between disease activity and vitamin D levels in these diseases. Our objective was to assess 25-OH vitamin D concentrations in 2 independent cohorts of patients affected by inflammatory rheumatic disorders (IRD) and correlations with disease activity and disability.

Methods: We retrospectively analyzed 420 patients (246 RA, 100 ankylosing spondylitis (SA), 74 psoriatic arthritis (PsA) followed at Rheumatology tertiary centers in Northern France (Paris) and Southern Italy (Cagliari). All patients underwent clinical and laboratory evaluation including serum calcium and phosphorus levels, 25-OH vitamin D and parathyroid hormone (PTH). Vitamin D concentrations < 30 ng/ml were considered insufficiency, while values < 10 ng/ml were classified as deficiency. Disease activity was assessed by DAS 28 in RA and PsA patients, and by BASDAI and BASFI in AS patients.

Results: Vitamin D insufficiency and deficiency was very high : respectively 66% and 19% in RA, 76% and 10% in AS, 83% and11% in PsA. Their incidence was comparable between the two populations in RA (68% and 20% versus 62% and 18%, P = ns, respectively in the French and Italian patients), while it was significantly higher among French compared to Italian patients in AS and PsA (86% and 23% versus 61% and 0, P = 0.005 and P = 0.002; 89% and 20% versus 55% and 3%, P = 0.002 and P = 0.02, respectively in AS and PsA). Vitamin D supplementation was statistically different only in RA patients (53% versus 34%, P = 0.003, respectively in French and Italian patients). In the combined populations, in RA patients, no correlation was observed between vit D and DAS score but treated patients with anti-TNF alpha agents had higher vitamin D levels (P = 0.01). In SA patients low vitamin D concentrations correlated with higher BASFI (R = -0,02; P < 0.05). We did not find any correlation between vitamin D levels and the other evaluated parameters.

Conclusion: A high incidence of vitamin D deficiency was found in IRD in the two populations, independently of geographic origin for RA, while a higher incidence was seen in French AS and PsA patients, suggesting a potential different influence of vitamin D on these diseases. By contrast, no correlations with disease activity were found except for disability index BASFI in AS patients. In our study, TNF alpha agents seem to improve vitamin D levels as well as disease activity, but it remains controversial if this is an effect linked to disease activity modulation or it directly depends from immunomodulatory properties of vitamin D.

This finding encourage to perform randomized controlled studies for confirming that vitamin D supplementation could reduce the risk of autoimmunity or that it eases disease activity, although there is still not a clear consensus about the optimal circulating 25-OH vitamin D levels and the supplementation dosage for maintaining immune homeostasis.

Disclosure: A. Vacca, None; **G. Porru**, None; **G. Dessole**, None; **A. Mathieu**, None; **C. Cormier**, None; **Y. Fulla**, None; **A. Kahan**, None; **Y. Allanore**, None.

2560

Sustained Improvements in Workplace and Household Productivity and Social Participation with Certolizumab Pegol over 96 Weeks in Patients with Axial Spondyloarthritis, Including Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis. Desiree van der Heijde[1], Juergen Braun[2], Martin Rudwaleit[3], Oana Purcaru[4] and Arthur Kavanaugh[5]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Endokrinologikum, Berlin, Germany, [4]UCB Pharma, Anderlecht, Belgium, [5]University of California San Diego, La Jolla, CA.

Background/Purpose: Axial spondyloarthritis (axSpA) includes both ankylosing spondylitis (AS, meeting modified New York criteria) and axSpA with no sacroiliitis on X-ray (non-radiographic axSpA, nr-axSpA). Previous results show significant improvements in workplace and household productivity and social participation with certolizumab pegol (CZP) vs placebo (PBO) up to Week (Wk) 24 in the RAPID-axSpA study, which were continued to Wk48.[1] This report investigates the long-term effect of CZP on workplace and household productivity up to 96 wks in patients (pts) with axSpA, including AS and nr-axSpA.

Methods: The ongoing RAPID-axSpA trial (NCT01087762),[2] a 204-wk Phase 3 study in axSpA pts, is double-blind and PBO-controlled to Wk24, dose-blind to Wk48 and open-label to Wk204. Pts had active axSpA, according to ASAS criteria,[3] including both AS and nr-axSpA pts. Pts originally randomized to CZP (200mg Q2W or 400mg Q4W, following 400mg loading dose [LD] at Wks 0, 2, 4) continued on their assigned dose in the OLE; PBO pts entering dose-blind phase were re-randomized to CZP LD followed by CZP 200mg Q2W or CZP 400mg Q4W after Wk24 or, for non-responders, after Wk16. The validated arthritis-specific Work Productivity Survey (WPS; administered Q4W)[4] assessed the impact of axSpA on workplace and household productivity. WPS responses (LOCF imputation) in pts originally randomized to CZP are summarized descriptively over 96 wks.

Results: A total of 325 pts were randomized, of whom 218 received CZP (200mg Q2W or 400mg Q4W) from Wk0. Of the pts randomized to CZP at baseline (BL), 93% completed Wk24, 88% Wk48 and 80% Wk96. At BL, 72% of CZP pts were employed outside of the home. Pts randomized to CZP reported ~1 wk of paid work, ~2 wks of household duties, and mean 4.0 days of social activities affected over previous month. Employed pts in both CZP groups reported reductions in workplace absenteeism and presenteeism to Wk24, with continued improvements to Wk96 (Table). CZP pts reported continued improvements in household productivity and social participation up to Wk96 (Table). Similar improvements were observed in AS and nr-axSpA pts (Table).

Conclusion: The initial improvements with CZP in workplace and household productivity and increased participation in social/leisure activities were continued to Wk96 in axSpA, AS and nr-axSpA pts.

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Table 1. Workplace and household productivity over 96 wks in the RAPID-axSpA trial (FAS population [a]; LOCF)

		axSpA CZP 200 mg Q2W + CZP 400 mg Q4W n=218		AS CZP 200mg Q2W + CZP 400mg Q4W n=121		nr-axSpA CZP 200mg Q2W + CZP 400mg Q4W n=97	
WPS responses		**Mean**	**Median**	**Mean**	**Median**	**Mean**	**Median**
Productivity at workplace (employed patients)							
Work days missed due to arthritis per month[b]	BL	1.8	0.0	1.7	0.0	2.0	0.0
	Wk24	0.8	0.0	0.7	0.0	1.0	0.0
	Wk96	0.6	0.0	0.7	0.0	0.4	0.0
Days with work productivity reduced by ≥50% due to arthritis per month[b,c]	BL	5.2	0.0	4.6	0.0	6.0	3.5
	Wk24	2.6	0.0	2.5	0.0	2.7	0.0
	Wk96	1.4	0.0	1.4	0.0	1.3	0.0
Level of arthritis interference with work productivity (0–10 scale) [b,d]	BL	4.5	5.0	4.5	5.0	4.5	5.0
	Wk24	2.1	1.0	2.1	1.0	2.1	1.0
	Wk96	1.3	0.0	1.2	0.0	1.4	0.0
Household productivity and social participation (all patients)							
Household work days missed due to arthritis per month	BL	5.8	1.0	4.8	1.0	5.8	3.0
	Wk24	2.3	0.0	2.0	0.0	2.5	0.0
	Wk96	1.5	0.0	1.3	0.0	1.7	0.0
Household work days with productivity reduced by ≥50% due to arthritis per month [c]	BL	7.5	5.0	7.0	4.0	8.1	5.0
	Wk24	3.3	0.0	3.0	0.0	3.6	0.0
	Wk96	1.9	0.0	1.6	0.0	2.2	0.0
Level of arthritis interference with household productivity (0–10 scale) [d]	BL	4.8	5.0	4.9	5.0	4.7	5.0
	Wk24	2.3	1.0	2.4	2.0	2.2	0.0
	Wk96	1.7	0.0	1.5	0.0	1.8	0.0
Days missed family/social/leisure activities due to arthritis per month	BL	4.0	1.0	3.4	0.0	4.8	1.0
	Wk24	1.5	0.0	1.4	0.0	1.6	0.0
	Wk96	0.8	0.0	0.7	0.0	1.0	0.0

[a] FAS; all patients who received ≥1 dose of study medication and had a valid baseline and post-baseline measurement for ASAS20; [b] Based only on employed pts at the specific visit; pts employed at BL (CZP 200 mg Q2W+CZP 400mg Q4W): axSpA (157), AS(89), nr-axSpA(68); [c] Does not include work days missed counted in the previous question; [d] 0–10 scale, 0 = no interference 10 = complete interference.

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Low Cardio-Respiratory Fitness Is Associated with Increased Arterial Stiffness in Patients with Ankylosing Spondylitis. Inger Jorid Berg, Anne Grete Semb, Silje H. Sveaas, Camilla Fongen, Désirée van der Heijde, Tore K. Kvien, Hanne Dagfinrud and Sella A. Provan. Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: We have previously shown that patients with ankylosing spondylitis (AS) have lower cardio-respiratory fitness (CRF) than population controls. CRF is inversely associated to risk of cardiovascular disease (CVD) in the general population. Arterial stiffness is a marker of CVD risk, and AS patients have increased arterial stiffness compared to controls. The objective was to assess associations between CRF and arterial stiffness in AS patients.

Methods: This is a cross-sectional study on AS patients (mNY criteria) where information on demographics and medication was assessed from questionnaires. Arterial stiffness (Pulse Wave Velocity (PWV) and Augmentation Index (AIx)) was recorded using the Sphygmocor apparatus (AtCor). CRF was assessed as peak oxygen uptake (VO_2peak) by a maximal walking treadmill test (modified Balke protocol). Statistics were performed using SPSS version 21. Univariate associations between lnPWV/AIx (dependent variable) and VO_2peak as well as possible confounders and factors with effect on the outcome were analyzed in separate linear regression models adjusted for age and gender. Variables with p-value<0.25 were included in backwards multivariate linear regression models.

Results: The 113 AS patients had the following characteristics: Mean (SD) age 48.4 (11.3) years, 72 (64 %) males, 18 (16%) smokers, mean (SD) BMI (kg/m^2) 25.6 (3.5), median (IQR) CRP (mg/l) 3 (2–10), 73 (65%) used NSAIDs, 24 (21%) used TNF-inhibitors, 14 (12%) used statins and 28 (25%) used antihypertensive medication. In regression models VO_2peak was significantly inversely associated with lnPWV independent of other factors (table). Similar results were found for AIx (table).

	Outcome: lnPWV		**Outcome: AIx**	
	Univariate Beta (95%CI)	**Multivariate Beta (95%CI)**	**Univariate Beta (95%CI)**	**Multivariate Beta (95%CI)**
Age	0.012 (0.009, 0.014)*	0.009 (0.006, 0.012)*	0.74 (0.60, 0.88)*	0.48 (0.32, 0.64)*
Gender (male)	0.03 (−0.04, 0.11)	0.11 (0.04, 0.17)*	−11.48 (−15.82, −7.13)*	−9.44 (−12.61, −6.24)*
VO_2peak (mg/kg/min)	**−0.003 (−0.007, 0.002)**	**−0.005 (−0.010, −0.001)***	**−0.38 (−0.62, −0.15)***	**−0.33 (−0.55, −0.10)***
Current smoking	−0.07 (−0.15, 0.01)		2.29 (−1.82, 6.41)	
BMI	0.01 (−0.012, 0.014)		0.20 (−0.24, 0.64)	
NSAIDs	−0.03 (−0.09, 0.03)		0.20 (−3.03, 3.42)	
TNFα-inhibitors	0.01 (−0.06, 0.08)		0.97 (−2.84, 4.78)	
Statins	−0.01 (−0.09, 0.08)		3.27 (−1.12, 7.66)	
Antihypertensives	0.00 (−0.07, 0.07)		−0.10 (−3.95, 3.75)	
CRP (mg/l)	0.003 (0.000, 0.005)*		0.09 (−0.05, 0.24)	
Loss of height (cm)	−0.008 (−0.016, −0.001)*	−0.011 (−0.020, −0.002)*		
Height (cm)			−0.16 (−0.43, 0.03)	
Central mean arterial pressure (mmHg)	0.006 (0.004, 0.008)*	0.005 (0.002, 0.007)*	0.24 (0.11, 0.37)*	0.27 (0.14, 0.40)*

*p-value<0.05

Conclusion: CRF measured by VO_2peak was inversely associated with arterial stiffness indicating that reduced CRF can be related to increased risk

for CVD in AS patients. Studies on the effect of increasing CRF on risk of CVD in AS patients are warranted.

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The Comparative One-Year Drug Survival Rate of Tumor Necrosis Factor Inhibitors in Patients with Rheumatoid arthritis and ankylosing spondylitis; results from Turkbio Registry. Ismail Sari[1], Umut Kalyoncu[2], Ahmet Mesut Onat[3], Omer Nuri Pamuk[4], Omer Karadag[2], Bunyamin Kisacik[3], Niels Steen Krogh[5], Soner Şenel[6], Fatih Saritaş[4], Ihsan Ertenli[2], Sedat Kiraz[2], Pinar Cetin[1], Fatos Onen[1] and Nurullah Akkoc[1]. [1]Dokuz Eylul University School of Medicine, Izmir, Turkey, [2]Hacettepe University School of Medicine, Ankara, Turkey, [3]Gaziantep University School of Medicine, Gaziantep, Turkey, [4]Trakya University School of Medicine, Edirne, Turkey, [5]ZiteLab Aps, Copenhagen, Denmark, [6]Erciyes University School of Medicine, Kayseri, Turkey.

Background/Purpose: Three different anti–tumor necrosis factor α (anti-TNFα) drugs (infliximab, etanercept, and adalimumab) are approved for patients with rheumatoid arthritis (RA) and particular ankylosing spondylitis (AS) in Turkey. Their efficacy has been well shown not only in randomized controlled clinical trials, but also in clinical practice setting. Comparative drug survival analyses across different diagnoses have been published in few studies. No data is yet available for the Turkish population.

The primary goal of this study was to compare the 1-year drug retention rates of TNF inhibitors in patients with AS and RA who were enrolled in the Turkish biologic registry, TURKBIO.

Methods: TURKBIO biological registry, which was established in October 2011, is a nationwide biological registry contributed by 10 different centers across Turkey. As of December 2013, 3380 patients who are receiving biologic treatment for RA (n=1355, 40.1%) or AS (n=2025, 59.9%) were enrolled in the database. However this analysis includes only 789 patients, who initiated biologic treatment after the participation of the individual centers in TURKBIO. Demographic and clinical data including age, sex, disease type, disease duration, and previous or current treatment with DMARDs and biological drug durations are stored in the database.

Results: Of the 789 patients included in this analysis, 386 patients (48.9%) were being treated for RA and 403 patients (51.1%) for AS. There were significant differences between the two groups in regard with age, gender distribution, DMARD use at baseline and DMARD use at last visit (Table). Preference for individual anti-TNF agents were also different between the RA and AS patients; infliximab, etanercept and adalimumab were used by 11.7%, 28.2% and 25.1% of the RA patients, respectively and 26.3%, 32.8% and 32.8 of the AS patients, respectively. AS patients had a shorter diagnosis duration than the RA patients. One year drug survival for the first anti-TNF agent was 60.8% for RA, and 78.3% for AS (P=0.0007).

Conclusion: The proportion of AS patients treated with biologic agents in the TURKBIO registry was slightly higher than that of RA. These results also suggest that the drug survival rate of anti-TNF agents in AS patients seems to be higher than in RA. This finding may explain the higher percentage of AS patients in the whole registry population, which included patients who had started biologics before the establishment of the TURKBIO registry.

Table 1: Demographical and clinical features of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) patients at baseline and one year drug survival data

	RA (n=386)	AS (n=403)	P value
Age (years)	49 (38–58)	39 (30–46)	<0.00001
Female (%)	73.1	41.7	>0.05
Disease duration (years)	7 (3–13)	7 (3–13)	0.09
Diagnosis Duration	4 (2–10)	2 (0.75–6)	<0.00001
Biological duration (months)	9 (5–13)	10 (5–13)	>0.05
Number of biologic drugs used	1	1	>0.05
Prior DMARD use (%)	82.4	73.9	0.005
Number of DMARD use	4 (2–6)	2 (1–3)	<0.00001
DMARD use at last visit (%)	67.4	21.6	<0.00001
1-year drug retention rate of TNFi (%)	60.7	78.3	0.0007

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The Distribution of Inflammatory Lesions in the Anterior and Posterior Structures of the Spine in Patients with Active Ankylosing Spondylitis and the Effect of TNF-α-Blockade. Xenofon Baraliakos[1], Kay-Geert A. Hermann[2], Stephen Xu[3], Benjamin Hsu[3] and Jürgen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Charité Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany, [3]Janssen Research & Development, LLC., Spring House, PA.

Background/Purpose: Magnetic resonance imaging (MRI) is a key tool for the assessment of inflammatory lesions used for diagnosis and the monitoring of treatment effects in patients (pts) with ankylosing spondylitis (AS). Using data from the anti-tumor necrosis factor (TNF) agent golimumab (GLM) in AS study (GO-RAISE), we analyzed the distribution and course of inflammatory spinal lesions in different parts of the axial skeleton in detail before and after treatment with GLM in pts with active AS.

Methods: Complete MR images at baseline (BL), 3 months (week 14 of the placebo [PBO]-controlled phase) and 2 years (end of open-label extension) of the study were available from 98 AS patients. Among all pts with inflammatory MRI activity at BL, the number (nr.) of spinal lesions at different time points was assessed. Both, general (total nr. of inflammatory lesions in the entire spine) and detailed (nr. of inflammatory lesions in the cervical [CS], thoracic [TS] and lumbar [LS] spine, in single vertebral units [VUs], in the upper and lower edges for anterior and posterior site of each vertebra, and in the zygoapophyseal joints [ZAJ] were assessed. Improvement in inflammation was defined as any decrease in the MRI score from baseline to year 2 of the study.

Results: Overall, evaluable inflamed VU and ZAJ lesions were seen in 81.6% and 31.6% of pts, respectively, while 22.4% of VUs/ZAJs had inf at BL. In patients showing inflammatory activity, the mean number of lesions/patient was 6.7 for VUs and 3.6 for ZAJs, with no difference between pts randomized to GLM or PBO. ZAJ inflammation without concomitant VU inflammation was present in 43 (0.97%) of all VUs and in 19 (20.9%) of patients. In detail, 7.2% of VU+ZAJ lesions were found in the CS, 27.9% in the TS and 27.9% in the LS. VU inflammation was detected more frequently in the anterior (23.5%) than in the posterior (8.5%) part of the LS. This difference was not observed in the CS and TS. The most frequently inflamed region in the CS was C7/T1, in the TS it was T8/9-T11/12 and in the LS, there was a fairly evenly distribution across VUs. After 3 months of GLM treatment, the percentage of VUs/ZAJs with inflammation decreased by 2.7%/0.7% in the CS, 17.3%/3.6% in the TS, and 17.6%/2.7% in the LS, while almost no change was observed in the PBO pts. The decreased VU/ZAJ involvement afforded by GLM treatment was sustained through 2 years. Similarly, after up to 2 years of GLM treatment, the mean number of lesions/pt showing inflammatory activity decreased to 2.7 for VUs and 2.0 for ZAJs.

Conclusion: This analysis confirms the predominance of inflammatory spinal lesions at the lower TS and the LS. While ZAJ inflammation was evident in a substantial nr. of patients it was uncommon for it to occur in isolation in a non-inflamed VU. Inflammatory lesions of VUs and ZAJs are supplementary information to MRI scoring systems and may contribute to a better understanding of clinical trial data. The already reported significance of the lower TS in the inflammatory process in AS clearly needs further study.

Disclosure: X. Baraliakos, Janssen R and D, LLC, 2; **K. G. A. Hermann**, Janssen R and D, LLC, 2; **S. Xu**, Janssen R and D, LLC, 3; **B. Hsu**, Janssen Research & Development, LLC., 3; **J. Braun**, Abbott, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 5, Abbott, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 2.

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Ileocolonoscopic Findings in the Korean Patients with Ankylosing Spondylitis. Soo Min Ahn, Bin Yoo, Chang-Keun Lee, Yong-Gil Kim, Seokchan Hong, Seung-Hyeon Bae and Doo-Ho Lim. University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea.

Background/Purpose: The prevalence of concurrent Ankylosing spondylitis (AS) and inflammatory bowel disease, either Crohn's disease (CD) or Ulcerative colitis (UC), is estimated at 5–10%. Up to 50% of patients with AS have subclinical gut inflammation seen on ileocolonoscopy. This study was purposed to evaluate the association between reasons for ileocolonoscopy and the ileocolonoscopic findings in the patients with AS.

Methods: The retrospective study has included 108 AS patients who had ileocolonoscopy at a single tertiary hospital from January 2000 to April 2014.

Patients with a history of CD, UC, intestinal tuberculosis, or colon cancer were excluded. Patients were divided into two groups based on ileocolonoscopic results: 1) negative inflammatory lesions (including colon polyps, hemorrhoids and diverticulums) and 2) positive inflammatory lesions (including ulcers, erosion and inflammation). The clinical features including HLA-B27 profiles, inflammatory indices, and reasons for ileocolonoscopy including regular health checkup without symptoms (for screening), abdominal pain, rectal bleeding, diarrhea, constipation, anemia and positive stool occult blood were evaluated.

Results: As shown in Table, inflammatory lesions in ileocolonoscopic findings were found in 40 (37.0%) patients out of the 108 patients. Mean age was significantly lower in the group with inflammatory lesions than the group without inflammatory lesions (36.9 vs. 41.9 years, p=0.017). Mean ESR and mean CRP were significantly higher in the group with inflammatory lesions than the group without inflammatory lesions. Presence of symptoms or signs (n=34) was associated with risk of inflammatory ileocolonoscopic findings compared to for screening (n=6) (OR=3.96, 95% CI 1.46, 10.71, p=0.005). Among the patient's symptoms or signs, abdominal pain (n=13) was associated with inflammatory ileocolonoscopic findings most importantly (vs. negative abdominal pain (n=20); OR=2.47, 95% CI 0.88, 6.99, p=0.087). Among 40 patients with inflammatory lesions, 12 as CD, 1 as UC, and 4 as intestinal tuberculosis were diagnosed finally. However, most of them, 23 patients were considered as subclinical gut inflammation.

Conclusion: Considerable proportion of AS patients showed inflammatory gut lesions, even in the patients without gastrointestinal symptoms. Moreover, abdominal pain increased a possibility of inflammatory gut lesions in AS patients. Therefore, regular checkup with ileocolonoscopy could be recommended in AS patients.

Table. Patient's characteristics

	(−) inflammatory lesion (n=68)	(+) inflammatory lesion (n=40)	*p*-value
Age, mean years (SD)	41.9 (13.5)	36.9 (11.9)	0.017
Gender, male (%)	53 (77.9)	33 (82.5)	0.570
HLA-B27(+), n (%)	55 (84.6)	30 (78.9)	0.407
ESR (mm/hr) mean (SD)	24.1 (21.79)	39.3 (33.34)	0.014
CRP (mg/dL) mean (SD)	0.72 (1.265)	3.14 (4.539)	0.002
Reasons for ileocolonoscopy, n (%)			
For screening	28 (41.2)	6 (15.0)	
Abdominal pain	10 (14.7)	5 (12.5)	
Diarrhea	8 (11.8)	13 (32.5)	
Rectal bleeding	12 (17.6)	10 (25.0)	
Anemia	2 (2.9)	1 (2.5)	
Constipation	4 (5.9)	4 (10.0)	
Stool occult blood (+)	4 (5.9)	1 (2.5)	

ESR; erythrocyte segmentation rate, CRP; c-reactive protein

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The Effect of DMARD Co-Therapy on the Clinical Efficacy of Anti-TNF Medications in Patients with Axial Spondyloarthritis. Michael J. Nissen[1], Adrian Ciurea[2], Juerg Bernhard[3], Rudiger Muller[4], Giorgio Tamborrini[5], Martin Toniolo[6], Cem Gabay[7] and Axel Finckh[1]. [1]Geneva University Hospital, Geneva, Switzerland, [2]Rheumaklinik, Universitatsspital Zurich, Zurich, Switzerland, [3]Solothurn Hospital, Solothurn, Switzerland, [4]Kantonsspital St. Gallen, St. Gallen, Switzerland, [5]Bethesda Hospital Basel, Basel, Switzerland, [6]University Hospital of Zurich, Zurich, Switzerland, [7]University Hospitals of Geneva/SCQM Registry, Geneva, Switzerland, Geneva, Switzerland.

Background/Purpose: Randomized clinical trials and current recommendations suggest little role for disease-modifying anti-rheumatic drugs (DMARDs) as co-therapy with anti-TNF (aTNF) agents in patients with axial-spondyloarthritis (axSpA), although many physicians continue to prescribe this combination. Our aim was to investigate whether aTNF agents with concomitant DMARDs demonstrate superior clinical efficacy compared with aTNF monotherapy.

Methods: This is an observational cohort study of all patients in the Swiss Clinical Quality Management (SCQM) registry diagnosed with axSpA by a board-certified rheumatologist. The exposure of interest was use of aTNF monotherapy (mono) versus aTNF in combination with conventional synthetic DMARDs (combo). Exclusion criteria included aTNF initiation > 1 month prior to inclusion in the registry or missing follow-up assessments. The primary outcome was the change in BASDAI at 12 months. Secondary outcome measures were: BASDAI-50, ΔASDAS, ASDAS-CII and ASDAS-ID. When clinical outcome measures were unavailable at 12 months (+/− 3 months), we used longitudinal interpolation with mixed-effects linear regression to impute missing values. Adjustments were made for potential confounders including age, sex, disease duration, education level, number of prior aTNF agents and calendar year initiation of aTNF.

Results: We included 1310 axSpA patients with a total of 2236 aTNF treatment courses. The baseline characteristics of the mono and combo groups for all treatment courses are presented in the table. 80.1% were treated with aTNF monotherapy and 19.9% with co-therapy. The predominant DMARDs utilized were methotrexate in 69.7%, sulfasalazine in 19.3% and leflunomide in 9.6%. Disease characteristics were balanced between the 2 groups, with the exception that the co-therapy group was less frequently HLA-B27 positive, was less often ASAS criteria positive and had longer follow-up. DMARD co-therapy was prescribed significantly more often with infliximab and significantly less often with adalimumab and golimumab.

At 12 months follow-up, the mean (SD) reduction in BASDAI was 1.0 (0.8) and the mean reduction in ASDAS-CRP was 0.8 (0.7) for all treatment courses. The mean reductions in BASDAI and ASDAS-CRP for the first aTNF treatment course were 1.4 (1.6) and 1.1 (0.8) respectively. In adjusted analyses, there was no difference in the reduction in BASDAI score between the mono and the combo groups (p=0.65, CI -0.11:0.18). Similarly, there was no statistically significant benefit for DMARD co-therapy with regards to reduction in ASDAS-CRP, BASDAI-50, ASDAS-CII or ASDAS-ID.

Conclusion: This study of "real-life" patients supports the current recommendation that co-therapy with DMARDs is of no additional benefit compared with aTNF monotherapy in axSpA.

Table: Baseline characteristics. Unless otherwise stated, the values represent the mean.

	Monotherapy (n=1790) (80.1%) (n=1615)	Co-therapy (n=446) (19.9%)	p value
Age (years) [SD]	**40.8 [12.1]**	**41.6 [11.9]**	**0.24**
Sex (%, male)	**54.9**	**54.0**	**0.75**
Higher education (% university)	**20.9**	**22.6**	**0.42**
Disease duration (median, years) [p25, p75]	**8.6 [3.4–16.6]**	**8.3 [3.0–14.8]**	**0.15**
Follow-up (years) [SD]	**5.3 [2.6]**	**6.5 [2.6]**	**<0.001**
HLA-B27 (% positive)	**67.2**	**58.5**	**0.002**
CRP [SD]	**10.6 [15.9]**	**11.9 [20.7]**	**0.27**
MNYC positive (%)	**52.3**	**49.8**	**0.33**
ASAS positive (%)	**64.2**	**49.8**	**<0.001**
BASDAI [SD]	**5.1 [1.8]**	**5.0 [1.8]**	**0.31**
BASFI [SD]	**3.9 [2.3]**	**4.0 [2.3]**	**0.52**
Infliximab (%)	**23.2**	**37.4**	**<0.001**
Adalimumab (%)	**36.6**	**32.2**	**0.001**
Etanercept (%)	**31.0**	**28.4**	**0.08**
Golimumab (%)	**9.0**	**1.7**	**0.001**
Certolizumab (%)	**0.2**	**0.3**	**0.62**

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Spinal Mobility in the Cervical and the Lumbar Spine Correlates with Magnetic Resonance Imaging Findings in Patients with Ankylosing Spondylitis. Xenofon Baraliakos[1], Kay-Geert A. Hermann[2], Stephen Xu[3], Benjamin Hsu[3] and Jürgen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Charité Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany, [3]Janssen Research & Development, LLC., Spring House, PA.

Background/Purpose: Spinal mobility, as assessed by the Bath Ankylosing Spondylitis Metrology Index, BASMI, and imaging findings have been reported to correlate on the group level. Treatment with anti-TNF leads to improvement of both spinal inflammation as assessed by magnetic resonance imaging (MRI) and total BASMI scores. Using data from the golimumab

(GLM) in ankylosing spondylitis (AS) study (GO-RAISE), we analyzed the relationship between single components of BASMI and MRI scores of the corresponding spinal segments in anti-TNF-treated AS patients.

Methods: Complete MR imaging sets and spinal mobility data were available for 91 pts who participated in GO-RAISE. The MRI scores for active (ASspiMRI-a) and chronic changes (ASspiMRI-c) of the cervical and lumbar spine were compared to BASMI values for the cervical (cervical rotation [CR] and tragus-to-wall [TTW]) and the lumbar (lumbar flexion [LF] and lateral lumbar flexion [LLF]) spine using the linear definition. Spearman correlation coefficients were calculated for baseline scores and for changes in both BASMI and ASspiMRI-a and -c measurements of patients treated with GLM or placebo (PBO) after 14 weeks and after 2 years of GLM therapy. Subanalyses were performed with regard to age.

Results: At baseline, ASspiMRI-a scores of the cervical spine correlated with TTW ($r=0.31$, $p=0.003$) and CR ($r=0.32$, $p=0.002$) measurements, while ASspiMRI-a scores of the lumbar spine correlated with LF and LLF scores (both $r=0.41$, $p<0.0001$). In addition, ASspiMRI-c scores of the cervical spine correlated with TTW ($r=0.46$) and CR ($r=0.45$), both $p<0.0001$, while ASspiMRI-c scores of the lumbar spine correlated with LF ($r=0.34$, $p=0.001$) and LLF scores ($r=0.41$, $p<0.0001$). ASspiMRI-a scores correlated better in patients <40 years (TTW: $r=0.31$, $p=0.04$, LLF: $r=0.42$, $p=0.005$), while ASspiMRI-c scores correlated better in patients > 40 years (TTW: $r=0.35$, $p=0.015$, LLF: $r=0.48$, $p<0.001$). In contrast, no significant correlations were found in change scores (data not shown). There was a negative correlation between MRI chronicity scores and lateral lumbar flexion at 2y: $r=-0.26$, $p=0.037$.

Conclusion: Our data confirm earlier reports on patients with active AS which showed that both inflammation and structural changes contribute to impairments of spinal mobility. In addition, we demonstrate significant correlations of MRI findings with detailed spinal mobility measures before anti-TNF treatment was started. Inflammatory changes had greater impact on spinal mobility in younger patients, while structural changes had more influence on spinal mobility in older patients. The correlation of the observed changes in MRI scores and spinal mobility was significant but not high. This may be due to the different mixture of active and chronic changes in individual patients.

Disclosure: X. Baraliakos, Janssen R and D, LLC, 2; **K. G. A. Hermann**, Janssen R and D, LLC, 2; **S. Xu**, Janssen R and D, LLC, 3; **B. Hsu**, Janssen Research & Development, LLC., 3; **J. Braun**, Abbott, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 5, Abbott, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 2.

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Vascular Endothelial Growth Factor and C-Reactive Protein Serum Levels Lack Predictive Value for Radiographic and Magnetic Resonance Imaging Outcomes in Patients with Active Ankylosing Spondylitis Treated with the Tumor Necrosis Factor-Inhibitor Golimumab.

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Background/Purpose: Using data from GO-RAISE, we analyzed correlations between serum vascular endothelial growth factor (VEGF) and C-reactive protein (CRP) levels, radiographic progression and inflammation as detected by MRI.

Methods: 98 patients with active AS received golimumab or placebo up to wk16/24 and then golimumab up to 2y. All had sera, lateral spinal radiographs at baseline, wk104, and wk208 scored by the mSASSS and spinal MRIs at baseline, wk14, and wk104 scored with the ASspiMRI-a by two blinded readers. The relationship between VEGF or CRP levels and both mSASSS and MRI-a score was assessed by Spearman correlation analyses and logistic regression analyses were conducted to assess if VEGF levels conferred an increased risk of syndesmophyte formation from baseline to wk104 or wk208.

Results: CRP serum levels correlated with mSASSS scores at baseline, but not with radiographic progression or changes in MRI-a scores. No significant correlations were observed between VEGF serum levels and mSASSS at any time point. Logistic regression analyses failed to show an increased risk of changes towards syndesmophyte formation at wk104 and wk208 associated with VEGF (odds ratio, range: 0.990–1.006, all p=n.s). While a good correlation was observed between changes in ASspiMRI-a and VEGF level at wk14 ($p=0.0008$), the analysis showed that baseline and wk14 VEGF levels were not predictive of MRI-a scores including change scores at wk104

Conclusion: CRP serum levels correlated with baseline mSASSS scores but did not predict radiographic progression or remaining spinal inflammation after anti-TNF treatment. Similarly, both VEGF and CRP serum levels at baseline were not predictive of either radiographic progression or spinal inflammation in these anti-TNF treated patients. Overall, our data suggest that suppression of VEGF and CRP is not sufficient to halt new bone formation in AS.

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Routine Assessment of Patient Index Data (RAPID3) Provides Similar Information Compared to Ankylosing Spondylitis Specific Indices: Analyses of the DESIR French Cohort.

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Background/Purpose: The Bath Ankylosing Spondylitis (AS) Disease Activity Index (BASDAI) –an index of only patient-self-report measures - has been the most widely used measure in axial spondyloarthritis (SpA). More recently the AS Disease Activity Score (ASDAS) has been developed as an algorithm that combines BASDAI elements and patient global assessment with laboratory measures. Both indices are specifically designed for AS patients. In busy clinical settings, it is more feasible to ask all patients to complete the same questionnaire, such as a multidimensional health assessment questionnaire (MDHAQ), with a Routine Assessment of Patient Index Data (RAPID3) score, which has proved useful in most of rheumatic diseases. RAPID3 may facilitate implementation of quantitative measures in routine care. This study compared RAPID3, BASDAI and ASDAS-CRP with one another and versus patient and physician global estimates.

Methods: The Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) is a prospective longitudinal cohort in France, which includes 708 patients with inflammatory back pain suggestive of SpA. 461 patients who fulfilled the Assessment of SpondyloArthritis International Society classification (ASAS) criteria for axial SpA were included in this analysis. As there is no universal gold standard to assess disease activity in AS, predefined external criteria were used based on patient and physician global estimates with 1, 3 and 6 as the specific cut points to define disease activity state: 'inactive', 'low', 'moderate', and 'high'. Additionally, patients were classified using the disease activity cut points for BASDAI (3, 3.5 and 4), ASDAS-CRP (1.3, 2.1, 3.5) and RAPID3 (3, 6 and 12). Spearman correlations were performed and the level of agreement evaluated using weighted kappas.

Results: RAPID3 showed a high correlation with BASDAI ($rho=0.84$, $p<0.001$), ASDAS-CRP ($rho=0.74$, $p<0.001$), physician global estimate ($rho=0.62$, $p<0.001$), and patient global estimate ($rho=0.90$, $p<0.001$). The percentage of patients with inactive disease ranged from 9 to 31% and with high disease ranged from 18% to 56%, according to various disease activity measures (Table). Using PATGL as reference the strength of agreement was good for RAPID3 and moderate for BASDAI and ASDAS-CRP. Using DOCGL as reference, the strength of agreement was moderate for ASDAS-CRP and fair for BASDAI and RAPID3. The strength of agreement of RAPID3 with BASDAI and ASDAS-CRP was similar.

	Disease Activity States				Level of Agreement		
	Inactive Disease	Low Disease	Moderate Disease	High Disease	PATGL % (Kappa)	DOCGL % (Kappa)	RAPID3 % (Kappa)
PATGL (1/3/6)	11%	24%	31%	34%	–	79% (0.41)	89% (0.70)
DOCGL (1/3/6)	12%	29%	42%	18%	79% (0.41)	–	77% (0.38)
BASDAI (3/3.5/4)	31%	7%	6%	56%	78% (0.51)	71% (0.37)	81% (0.55)
RAPID3 (3/6/12)	9%	17%	29%	45%	89% (0.70)	77% (0.38)	–
ASDAS-CRP (1.3/2.1/3.5)	14%	23%	45%	18%	81% (0.46)	81% (0.41)	79% (0.44)

Conclusion: RAPID3 provide a similar disease activity score as BASDAI and ASDAS-CRP, which are specific measures for AS patients. Further studies are required to evaluate different psychometric properties such as the discriminant capacity and predictive validity of these tools. A generic

measure for all rheumatic diseases such as RAPID3 may provide a feasible approach to quantitative assessment of AS patients in busy clinical settings.

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Profiles of Switches in Patient with Ankylosing Spondylitis: Comparing Adalimumab, Etanercept, Infliximab, Golimumab and Certolizumab. Jean-Pierre Raynauld[1], Louis Bessette[2], Denis Choquette[1], Isabelle Fortin[3], Boulos Haraoui[1], Jean-Pierre Pelletier[4], Marie-Anaïs Rémillard[1], Diane Sauvageau[1], Edith Villeneuve[1] and Louis Coupal[1]. [1]Institut de rhumatologie de Montréal (IRM), Montréal, QC, [2]Centre d'ostéoporose et de rhumatologie de Québec (CORQ), Québec, QC, [3]Centre de rhumatologie de l'est du Québec (CREQ), Rimouski, QC, [4]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Montreal, QC.

Background/Purpose: As much a 40% of patients with ankylosing spondylitis will fail (BASDAI≥ 4) different non-steroidal anti-inflammatory agents and will eventually be treated with an anti-TNF agents. Response is usually satisfactory but retention on drug may vary from one agent to the other and from one patient to the other. Reasons for stopping ad/or switching are either inefficacy, intolerance or spontaneous improvement of the disease activity in a given individual. The goal of this analysis is to explore the first 6, 12 and 18 month period after first exposure to an initial agent and assess the cycling incidence from different anti-TNF agents namely adalimumab (ADA), etanercept (ETA), infliximab (INF), golimumab(GOL) or certolizumab (CERTO).

Methods: Patients with ankylosing spondylitis as diagnosed by their treating rheumatologists and exposed to either adalimumab, etanercept, infliximab, golimumab or certolizumab in first intention after failing two different non-steroidal anti-inflammatory agents for a minimum of 3 months each were extracted from the Quebec inflammatory database Rhumadata®. Demographics and baseline characteristics includes age, gender, disease duration, Hla-B27, BASDAI, BASFI, patient global (vas) and ASDAS (crp). Cycling from one agent to another was then explore at 6, 12 and 18 month time point. Proportion of patients switching vs not switching at each time point are assessed. Reason for switching at each time point (Inefficacy, AEs infections, surgery or death) are expressed in percentages.

Results: The data from 296 patients with ankylosing spondylitis and prescribed either adalimumab (114=39%), etanercept (61=21%), golimumab (31=10%) or infliximab (90=30%) as first biologic agent were extracted. These patients were treated for a period ranging from 0.4 to 173.2 months with a mean treatment duration of 44.0 (StD=36.3) months. At 6, 12 and 18 months, 11.8%, 25.7% and 35.8% of patients had either stopped or switched their medication. The reported reasons for stopping or switching medication were inefficacy (76.4%), adverse events (5.7%), surgery (14.2%) and lost to follow-up (3.6%).

Conclusion: Switches at the 6 month time point vary from 4.4% (ADA) to 9.8% (ETA). The percentage of switches increase with time for all agents except golimumab (9.7% at 12 and 18 months). A significantly higher proportion of patient stops golimumab and do not switches to another agent (51.6%). Main reason for stopping or cycling to another agent is inefficacy.

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Validation of Modified Disease Activity and Functional Status Questionnaires in Spondyloarthritis. Itziar Quinzanos[1], Phat Luong[1], Sushmitha Bobba[2], J. Steuart Richards[3], Vikas Majithia[4], Lisa A. Davis[5] and Liron Caplan[6]. [1]Denver VA Medical Center, Denver, CO, [2]Department of Veterans Affairs, Denver, CO, [3]Washington DC VA and Georgetown University, Washington, DC, [4]University of Mississippi Medical Center, Jackson, MS, [5]Denver VAMC and Univ of Colorado School of Medicine, Aurora, CO, [6]Denver VA and Univ of Colorado School of Medicine, Aurora, CO.

Background/Purpose: Patients with new onset ankylosing spondylitis (AS) and those naïve to the Ankylosing Spondylitis Disease Activity Score (ASDAS) have voiced confusion over the use of the term "AS" in these instruments. Our previous abstract (EULAR 2013) compared the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) against a modified BASDAI and determined the relationship between working status and disability with Bath Ankylosing Spondylitis Functional Index (BASFI), BASDAI and modified BASDAI. It is unknown whether these tools may be applied to other forms of spondyloarthritis (SpA). In this abstract we: 1) validate slightly modified versions of the ASDAS questionnaires for use in non-AS SpA by assessing its ability to predict working status and disability; and 2) compare the disease-specific patient global assessment used in the ASDAS (PG) with the MD-HAQ version, and the disease activity scores based on these instruments.

Methods: Adult patients with SpA-associated conditions from three locations of the Program to Understand the Longterm outcomes of SpondyloARthritis (PULSAR) completed both traditional ASDAS questionnaire and modified version of the ASDAS instrument (PULSAR-modified ASDAS, [PuASDAS]) during visits with health care providers. The PuASDAS replaces references to "AS" with the term "inflammatory arthritis" and uses a non-disease specific patient global assessment that is similar to the multidimensional **health assessment questionnaire** global assessment (MD-HAQ); Scores from traditional and modified questionnaires were compared using Spearman correlations. The association of ASDAS and PuASDAS scores with disability status (according to federal program criteria) and self-reported working status were determined using logistic regression.

Results: Sixty-two patients participated in the study. Correlation between ASDAS and PuASDAS scores was high, recapitulating the previously demonstrated correlation between BASDAI and PuBaDAI (Spearman's rho=0.84, p<0.001, and Spearman's rho=0.92, p<0.001, respectively). Similarly, the PG had good correlation with the MD-HAQ (rho=0.766, p<0.001). The ASDAS (OR 1.34, 95% C.I. 1.02–1.76) and PuASDAS (OR 1.62, 95% C.I. 1.07–2.49) predicted federally-determined disability.

Conclusion: Preliminary data suggest that the PuASDAS may be used in non-AS SpA and that scores from these instruments correlate well with traditional form of the questionnaire. Correlation between the two versions of the patient's global assessments was good. PuASDAS scores predicted disability status at least as well as the ASDAS.

Table 1: Spearman correlation coefficients. *Italics indicate information previously presented at EULAR meeting 2013.*

Compared instruments	Question or total score that is compared	Corr. Coef.	p	95% CI Lower	95% CI Upper
BASDAI vs. PuBaDAI	*Nocturnal pain question*	*0.774*	*<0.001*	*0.649*	*0.859*
BASDAI vs. PuBaDAI	*Neck, back, or hip pain question*	*0.855*	*<0.001*	*0.735*	*0.896*
ASDAS vs. PuASDAS	Overall assessment question, (PG vs.MD-HAQ)	0.766	<0.001	0.608	0.838
ASDAS vs. PuASDAS	Total instrument score, entire cohort	0.845	<0.001	0.760	0.934
ASDAS vs. PuASDAS	Total instrument score, AS patients only	0.763	0.015	0.532	0.944
ASDAS vs. PuASDAS	Total instrument score, non-AS patients only	0.839	<0.001	0.785	0.963
BASDAI vs. PuBaDAI	*Total instrument score, entire cohort*	*0.920*	*<0.001*	*0.891*	*0.960*
BASDAI vs. PuBaDAI	*Total instrument score, AS patients only*	*0.922*	*<0.001*	*0.869*	*0.973*
BASDAI vs. PuBaDAI	*Total instrument score, non-AS patients only*	*0.912*	*<0.001*	*0.864*	*0.965*
BASDAI vs. ASDAS	Total instrument score, entire cohort	0.780	<0.001	0.621	0.889
BASFI test-retest	*Total instrument score, entire cohort*	*0.917*	*<0.001*	*0.895*	*0.961*

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; PuBaDAI = PULSAR-modified Bath Disease Activity Index; PG= Patient Global assessment from the ASDAS; MD-HAQ=Multi-Dimensional Health Assessment Questionnaire; BASFI = Bath Ankylosing Spondylitis Functional Index; ASDAS= Ankylosing Spondylitis Disease Activity Score; PuASDAS= PULSAR-modified Ankylosing Spondylitis Disease Activity Score; AS = Ankylosing Spondylitis.

Table 2: Relationship of BASFI, BASDAI, PuBaDAI, ASDAS and PuASDAS with current working status and disability rating.

	Odds Ratio	p	95% Conf. Intervals	
	Association with current work status			
BASFI	*0.75*	*0.103*	*0.52*	*1.06*
BASDAI	*0.92*	*0.600*	*0.66*	*1.27*
PuBaDAI	*0.92*	*0.597*	*0.66*	*1.27*
ASDAS	0.96	0.757	0.75	1.21
PuASDAS	0.87	0.285	0.66	1.12
	Association with current disability status*			
BASFI	*1.67*	***0.012***	*1.12*	*2.48*

BASDAI	*1.40*	*0.055*	*0.99*	*1.98*
PuBaDAI	*1.41*	*0.057*	*0.99*	*2.01*
ASDAS	1.34	**0.034**	1.02	1.76
PuASDAS	1.62	**0.024**	1.07	2.49

* Disability status determined by federal institution.
Italics indicate information previously presented at EULAR meeting 2013.

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Disease Activity and Risk of Cardiovascular Disease in Patients with Ankylosing Spondylitis with High and Low Body Mass Index. Inger Jorid Berg[1], Anne Grete Semb[1], Désirée van der Heijde[2], Tore K. Kvien[1], Hanne Dagfinrud[1], Jonny Hisdal[3] and Sella A. Provan[1]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Leiden University Medical Center, Leiden, Netherlands, [3]University of Oslo, Oslo, Norway.

Background/Purpose: Patients with ankylosing spondylitis (AS) have increased risk of cardiovascular disease (CVD), but the mediators of this increased risk are not known. Obesity is related to increased risk of CVD in the general population. Adipose tissue is an endocrine organ secreting pro-inflammatory cytokines which may be relevant both to the pathology of inflammatory diseases and CVD. The aim of this study was to explore the impact of body mass index (BMI) on disease activity and CVD risk in AS.

Methods: Cross-sectional study of 159 AS patients diagnosed according to the mNY criteria. Data-collection included questionnaires, blood samples and clinical examination. Carotid intima-media thickness (c-IMT) was measured by ultrasound. Height and weight were measured and BMI was calculated (kg/m^2). The patients were categorized according to the BMI, with cut-off value between normal weight and over weight: BMI<25 kg/m^2 (BMI-low) and BMI≥25kg/m^2 (BMI-high). We compared markers of disease activity and CVD risk factors between the BMI-low group and BMI-high group in linear regression models with adjustments for age, gender and smoking habits. Additional adjustments for use of non-steroidal anti-inflammatory drugs (NSAIDs) were also performed.

Results: AS patients had comparable age(years) in both groups (BMI-low vs. BMI-high), mean (SD) 50.5 (13.2) vs. 50.5 (11.3), but the BMI-low differed from the BMI-high regarding other variables: Male gender 53% vs.71%, p=0.02; CRP (mg/l), median (IQR) 2 (1–5) vs. 5 (2–13) p=0.003; use of NSAIDS, 56% vs. 74%, p= 0.01. In regression analyses the BMI-high group had higher ASDAS and BASDAI than the BMI-low group. High BMI was associated with lower high-density lipoprotein (HDL), higher triglycerides, total cholesterol/HDL ratio, systolic and diastolic pressure as well as IMT (table). Additional adjustment for use of NSAIDs did not alter results.

	BMI-low (n=81)	BMI-high (n=78)	p-value
Disease activity			
ASDAS	2.1 (1.8, 2.4)	2.6 (2.4, 2.9)	0.004
BASDAI	3.6 (3.2, 4.1)	4.3 (3.9, 4.8)	0.02
BASFI	1.9 (1.5, 2.3)	2.3 (1.9, 2.8)	0.09
$BASMI_{linear}$	3.1 (2.7, 3.5)	3.3 (2.9, 3.7)	0.54
CVD risk			
Total cholesterol (mmol/l)	5.2 (4.9, 5.5)	5.4 (5.2, 5.7)	0.15
LDL (mmol/l)	3.0 (2.7, 3.2)	3.3 (3.0, 3.5)	0.10
HDL (mmol/l)	1.7 (1.6, 1.8)	1.4 (1.3, 1.5)	<0.001
Triglycerides (mmol/l)	1.0 (0.9, 1.2)	1.5 (1.3, 1.7)	<0.001
Total cholesterol/HDL	3.2 (2.8, 3.5)	4.1 (3.8, 4.4)	<0.001
Systolic blood pressure (mmHg)	119 (116, 123)	129 (126, 133)	<0.001
Diastolic blood pressure (mmHg)	75 (72, 78)	81 (78, 83)	<0.001
c-IMT (mm)	0.62 (0.60, 0.65)	0.66 (0.64, 0.68)	0.01

Presented with estimated marginal means and 95% confidence intervals.

Conclusion: AS patients with high vs. low BMI had both worse disease activity and increased traditional CVD risk factors. Thus, obesity can be a common factor related to both disease activity and increased CVD risk and should be addressed in future observational studies in AS and considered as a potential confounding variable in future randomized controlled clinical trials.

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Recognition of Spondyloarthritis By General Practitioners in Daily Practice and the Effect of Education on This; A Study with Standardized Patients. Marloes van Onna[1], Simone Gorter[2], Bas Maiburg[3], Gerrie Waagenaar[3] and Astrid van Tubergen[2]. [1]Maastricht University Medical Center, division of Rheumatology, Maastricht, Netherlands, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Maastricht Univerisity, department of General Practice, Maastricht, Netherlands.

Background/Purpose: Timely recognition and referral of patients with spondyloarthritis (SpA) is challenging due to the insidious disease onset and frequently unawareness of the clinical picture by primary care physicians. The aims of this study were to assess the current practice performance of general practitioners (GPs) and GP-residents in recognizing SpA, and to investigate the influence of education on this performance.

Methods: All GP-residents and their supervising GPs were visited in two rounds by standardized patients (SPs) during their regular outpatient clinic, simulating axial SpA (axSpA), peripheral SpA (perSpA) (i.e. dactylitis) or carpal tunnel syndrome (CTS), respectively. Participants were unaware of the nature of the medical problem and purpose of the study. CTS was included as a diversionary tactic. Each case was simulated by a male and a female, in random order, according to a predefined schedule. After the 1st round, half of the GP-residents were educated about SpA, as part of the GP specialty training without referring to the actual study. The other half of the GP-residents and all GPs served as controls. Next, all participants were visited by SPs again in the 2nd round. Participants ranked their differential diagnosis based on their probabilities (rank order: 1=most likely to 3=less likely) and indicated whether referral to a hospital physician would be appropriate. Descriptive statistics and chi-square tests were used to analyse the data.

Results: Sixty-eight (38 GP-residents (mean age 27.9 yrs, 32% male) and 30 GPs (mean age 52.5 yrs, 80% male) participated. Both rounds of SP-encounters were completed by 61 (90%) and 59 (87%) participants for the axSpA and perSpA case, respectively. Table 1 shows that axSpA was ranked as the no. 1 diagnosis by 12/61 (20%) participants, whereas perSpA was correctly diagnosed by none of participants in the 1st round. Participants who received the educational intervention, were more likely to rank axSpA and perSpA as the no. 1 diagnosis in the 2nd round when compared to the control group (axSpA 72% vs. 14% (p<0.001); perSpA 21% vs 3% (p=0.017)). All 18 participants, who received the educational intervention, listed axSpA in their differential diagnosis in the 2nd round and were more likely to refer the patient or considered referral to the rheumatologist optional (axSpA 77% vs. 25% (p<0.001); perSpA 53% vs. 5% (p<0.001)).

Conclusion: Patients with SpA are not adequately recognized by general practitioners. Providing an educational programme to GP-residents markedly improved the recognition of SpA and referral of patients with SpA to the rheumatologist.

Table 1. Pre- and post-intervention results of the educational and control group regarding diagnosis and referral of patients suspected for axial and peripheral spondyloarthritis

	Educational intervention (yes vs no)	Diagnosis and referral of SPs	Round 1 (%)	Round 2 (%)
Axial SpA (n = 61)	Educational intervention (n = 18)	Ranked axial SpA as no. 1 diagnosis	4 (22)	13 (72)
		Ranked axial SpA in differential diagnosis (no. 1, 2 or 3)	12 (66)	18 (100)
		Referral rheumatologist	1 (6)	6 (33)
		Referral rheumatologist optional	0 (0)	8 (44)
	No educational intervention (n = 43)	Ranked axial SpA as no. 1 diagnosis	8 (19)	6 (14)
		Ranked axial SpA in differential diagnosis (no 1, 2 or 3)	22 (51)	33 (77)
		Referral rheumatologist	2 (5)	4 (9)
		Referral rheumatologist optional	2 (5)	7 (16)
	Educational intervention (yes vs no)	**Diagnosis and referral SPs**	**Round 1 (%)**	**Round 2 (%)**
Peripheral SpA (n = 59)	Educational intervention (n = 19)	Ranked peripheral SpA as no. 1 diagnosis	0 (0)	4 (21)
		Ranked peripheral SpA in differential diagnosis (no. 1, 2 or 3)	0 (0)	5 (26)
		Referral rheumatologist	1 (0)	8 (42)
		Referral rheumatologist optional	0 (0)	2 (11)

No educational intervention (n = 40)	Ranked peripheral SpA as no. 1 diagnosis	0 (0)	1 (3)
	Ranked peripheral SpA in differential diagnosis (no. 1, 2 or 3)	2 (5)	1 (3)
	Referral rheumatologist	2 (5)	1 (2)
	Referral rheumatologist optional	0 (0)	1 (2)

SPs = standardized patients, SpA = spondyloarthritis. Values are expressed as number (percentage) of participants.

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Preferences of Patients with Spondyloarthritis for the Items of the ASAS Health Index : A Best Worst Scaling. Uta Kiltz[1], Mickaël Hiligsmann[2], D van der Heijde[3], Juergen Braun[1], Alarcos Cieza[4], Walter P Maksymowych[5], William Taylor[6] and Annelies Boonen[7]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]University of Liege, Liege, Belgium, [3]Leiden University Medical Center, Leiden, Netherlands, [4]University Southampton, Southampton, United Kingdom, [5]University of Alberta, Edmonton, AB, [6]University of Otago Wellington, Wellington, New Zealand, [7]Maastricht University Medical Center, Maastricht, Netherlands.

Background/Purpose: The ASAS Health Index (ASAS HI) is a disease-specific questionnaire aiming at measurement of health in patients with spondyloarthritis (SpA) which has been developed by Assessment of SpondyloArthritis international Society (ASAS). The 17 items of the ASAS HI address aspects of pain, emotional functions, sleep, sexual functions, mobility, self-care and community life based on the International Classification of Functioning, Disability and Health (ICF). These items can serve as the starting point to develop a disease-specific utility instrument that will enable to calculate disease specific quality adjusted life-years. To construct such utility instrument, the development steps require that the number of items should be reduced to a more manageable number of items. This selection should be based on items, which are most essential to patient's health and on items which are most preferred by patients. It is not know which aspects of health matter most to patients with SpA and also the knowledge about patient's preferences is limited. The objective is to understand the relative importance of the different items of the ASAS HI for functioning and health of patients with SpA.

Methods: A best-worse experiment was conducted using a questionnaire in patients with SpA from 20 countries worldwide. Patients answered 17 choice tasks that were constructed using the Sawtooth software. In each task, patients were asked to choose the most important item and the least important from a set of four items about their functioning and health.. The estimated hierarchical Bayes method was used to generate the mean relative importance score for each item.

Results: 206 patients (59.7% male, mean (SD) age 42.4 (13.9) years, mean (SD) BASDAI 3.8 (2.3)) with SpA completed the experiment. The five most important items are pain, sleep, standing, exhausting, and motivation to do anything that requires physical effort (figure 1). Eight items addresses concepts which are less important for the patients: toileting, sexual relations, driving, contact with people, walking outdoors, concentration, washing hair, and be able to overcome difficulties. Four items addresses concepts, which showed intermediate results addressing concepts of running, frustration, traveling, and financial changes. Subgroup analysis regarding subgroups of SpA and European versus Non-European countries showed robust results among subgroups.

Conclusion: This study provides information on the relative importance for patients with spondyloarthritis of the items of the ASAS Health Index that will be used for the development of a utility-based instrument.

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2574

Do Patients with Axial Spondyloarthritis (AxSpA) Perform Enough Physical Activity? a Cross-Sectional Study of 207 Patients. Stephanie Fabre[1], Anna Molto[2], Sabrina Dadoun[2], Christopher Rein[2], Christophe Hudry[2], Sarah Kreis[2], Bruno Fautrel[2], Edouard Pertuiset[1] and Laure Gossec[2]. [1]René Dubos Hospital, Pontoise, France, [2]UPMC GRC08, Paris 06 University, Pitié Salpétrière Hospital, Paris, France.

Background/Purpose: Regular exercise is considered a cornerstone of AxSpA treatment, together with medication. Little data are available regarding the level and type of physical activity in AxSpA. The objective of this study was to assess the levels of physical activity and to explore its explanatory factors.

Methods: A cross-sectional study was performed in two tertiary care hospitals and one private practice in France. Patients had definite AxSpA according to the rheumatologist. Questionnaires evaluating the level of physical activity (International Physical Activity Questionnaire-Long form, IPAQ-L[1]) and perceived benefits of and barriers to exercising (Exercise Benefits/Barriers Score, EBBS[2]) were collected. The frequency of aerobic exercise (lasting more than 30 minutes) and the type of exercise were also investigated. Analyses included descriptive statistics and multiple logistic regression analyses to explain physical activity above 150 minutes per week (cut-off for appropriate exercise according to the World Health Organisation, WHO guidelines).

Results: In all, 207 patients had full data available: mean age, 45.9±11.5 years, 53.1% were males, mean BMI was 25.8±13.5 kg/m2. Mean disease duration was 14.6±10.2 years, mean BASDAI (0–100) 38.1±20, and mean BASFI (0–100) 29.1±26. Seventy percent were taking anti-TNF treatment, reflecting the tertiary care recruitment. The mean total level of physical activity (IPAQ) was 5409±6953 (median, 2913 [IQR 1259 to 6949]) MET-min/week: 99 (47.8%) were in the high activity category, 85 (41.1%) in the moderate and 23 (11.1%) in the low activity category. In all, 112 (54.1%) were above the recommendations of the WHO. Aerobic exercise (lasting more than 30 minutes) was performed at least once a week by 62/201 (30.8%) patients. The most frequently practiced sports included walking for at least 30 minutes (N=69, 31%), swimming and stretching ((N=43, 21% for both). The 2 main benefits of exercising were: increased acceptance from others and help to carry out normal activities without becoming tired; and the 2 main barriers: lack of encouragement of family members and people looking funny in exercise clothes. Physical activity above the WHO recommendation was not predicted by demographic variables, nor SpA activity/severity (Basdai, Basfi).

Conclusion: AxSpA patients in this study had moderate levels of physical activity. Only one half performed enough physical activity according ot the WHO recommendations. Levels of physical activity did not appear to be explained by disease-related variables but rather by other non-disease related variables. Physical activity is an important part of AxSpA management and patients should be encouraged to exercise more.

[1]The International Physical Activity Questionnaire. 2005. http://www.ipaq.ki.se
[2]Sechrist et al. Res Nurs Health. 1987;10(6):357–65

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Validation of the RAPID-3 Questionnaire in a Cohort of Patients with Axial Spondyloarthritis. Maria Celeste Orozco[1], Luis Alejandro Cayetti[1], Emilce Schneeberger[2], Natalia Zamora[3], Fernando Andres Sommerfleck[1] and Gustavo Citera[1]. [1]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Instituto de Rehabilitacion Psicofisica, Buenos Aires, Argentina, [3]Echeverría 955, Buenos Aires, Argentina.

Background/Purpose: RAPID3(Routine Assessment of Patient Index Data 3) is a simple index which was developed initially for RA but has been reported informative and many rheumatic diseases. A major advantage of RAPID3 over disease specific questionnaires and indices is that a single questionnaire can be completed by all patients with any diagnosis while waiting to see a rheumatologist, with minimal interference with work flow in busy clinical settings. We analyzed RAPID3 in patients with axial spondyloarthritis (axSpA).

Materials and Methods: Consecutive patients ≥ 18 years of age with diagnosis of axSpA (modified New York criteria 1987 and / or ASAS 2009) were included. Socio-demographic data (age, gender, marital status, occupation, years of education) and disease-related data (disease duration, extra-spinal manifestations, comorbidities, treatments) were recorded. All patients completed RAPID-3, ASQoL (Ankylosing Spondylitis Quality of Life), BASDAI and BASFI. Disease global assessment by both patients and physicians was determined by visual analog scale (VAS). Physical examination included 44 joint counts and evaluation of enthesitis was performed using MASES score (Maastricht Ankylosing Spondylitis Enthesitis Score). HLA -B27, and erythrocyte sedimentation rate (ESR) were collected. Ankylosing Spondylitis Disease Activity Score, was calculated (SASDAS-ESR, Clin Rheumatol 2012,31:1599–603). *Statistical analysis*: Categorical variables were compared using Fisher exact test and continuous variables by means of Mann- Whitney and Kruskal Wallis. Correlation of RAPID3 and other disease variables were assessed by Spearman Rho, and reproducibility using intraclass correlation coefficient (ICC) in a group of patients who completed the questionnaire twice. Finally, we determined the association of the preestablished cut-off values of RAPID-3 used in RA patients and preestablished cut-off values of SASDAS-ESR.

Results: 51 patients were studied, 39 males (76.5 %), with a median age of 42 years old (IQR 33–51) and a median disease duration of 20 years (IQR 10.3–27.6). 90.5 % were HLA -B27 positive. Median RAPID-3 was 9 (IQR 3–12.8), BASDAI 3.35 (IQR 1.6–6), BASFI 3.4 (IQR 1.1–5.6), ASQoL 5 (IQR 1–9), SASDAS-ESR 15.9 (IQR 8–22.6), MASES 1 (IQR 0–3). RAPID-3 proved to have an excellent reproducibility (ICC=0.97). The median time to complete it was two minutes (IQR 0.91 to 3), and the median time to calculate it ten seconds (IQR 6–15). RAPID-3 was correlated significantly with SASDAS-ESR (Rho: 0.87), BASDAI (Rho: 0.89), BASFI (Rho: 0.8) and ASQoL (Rho: 0.83) and at lower levels with MASES (Rho: 0.44). A significant association was seen between the preestablished cut points of RAPID-3 and SASDAS-ESR (Kappa: 0.5, p= 0.001).

Conclusion: RAPID-3 is a valid, reliable and reproducible questionnaire to evaluate disease activity and functional capacity in patients with axSpA, and more easily applied in busy clinical settings that axSpA specific-indices.

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2576

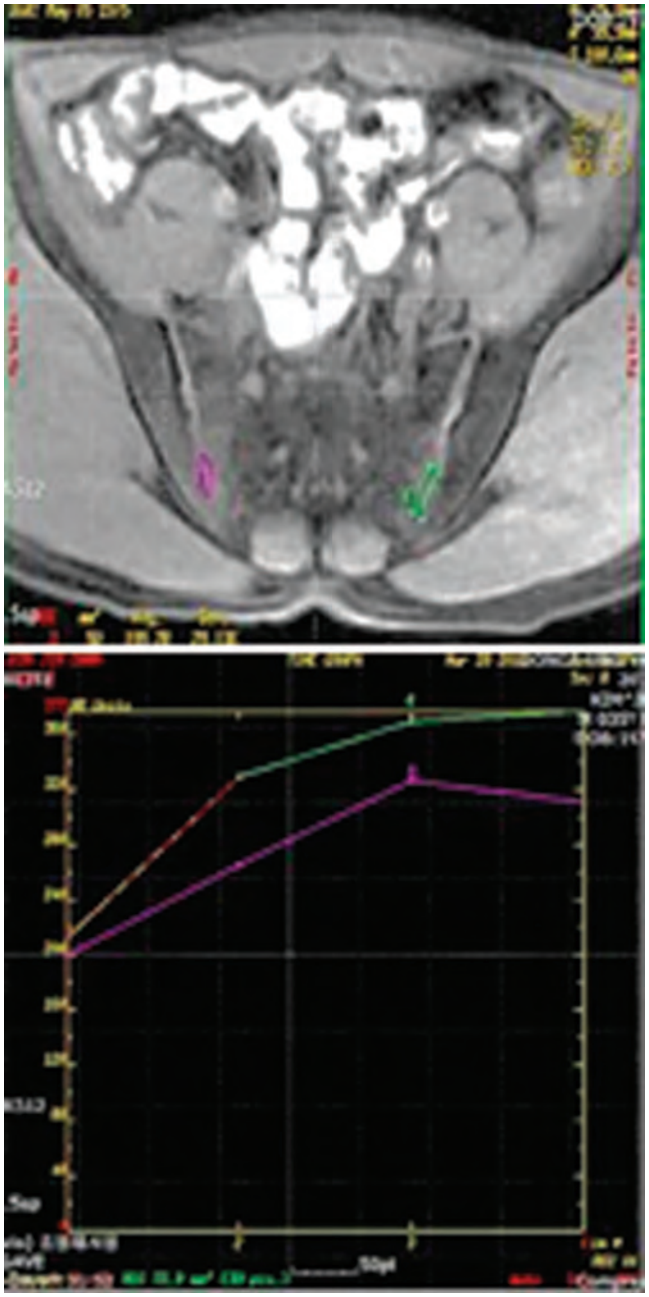
Diffusing Weight Magnetic Resonance Imaging May Suggest the Treatment Strategy in Ankylosing Spondylitis. Sang-Yeob Lee Division of Rheumatology, Department of Internal Medicine, Dong-A University College of Medicine, Busan, South Korea.

Background/Purpose: With the advanced MRI techniques, pathologic features can be detected at an early stage and quantitatively evaluated. resulting in the advantages of early diagnosis and prompt treatment. This study aimed to determine the value of diffusion-weighted MR imaging (DWI) in determined of ankylosing spondylitis (AS) treatment strategy and assess the role of quantitative MRI in the evaluation of AS treatment outcome.

Methods: 18 patients with the diagnosis of early AS were included in this study. Disease activity was measured according to clinical instruments and laboratory tests. For each patient, both inflamed sacroiliac (S-I) joint lesion was checked quantitatively at first diagnosis by diffusion-weighted imaging (DWI) measuring the apparent diffusion coefficient (ADC) and by dynamic contrast-enhanced imaging (DCEI) with evaluation of the enhancement factor (f_{enh}) and enhancement gradient (g_{enh}). All patients were revaluated by pelvis computer tomography (CT) for bone change in S-I joint, after two year.

Results: Clinical and quantitative MRI parameters diminished significantly with regression of the inflammatory activity. Median ADC values in AS patients were (1.118 ¡¾ 0.122) ¡¿ 10^{-3} mm^2/s in S-I joint. The high ADC (>1.118 ¡¾ 0.122) ¡¿ 10^{-3} mm^2/s, f_{enh} (>1.65) and g_{enh} (2.09 %/S) were associated severe disease activity and early administration of biologics ($p<0.05$). In each individual, the high ADC, f_{enh} and g_{enh} of S-I joint lesion was associated more severe localized pain than the other S-I joint, despite treatment ($p<0.05$). Paradoxically, early administration of biologics group who was high disease activity at the diagnosis had minimal bone change of S-I joint, compared to only NSAIDs used group who was low disease activity in pelvis CT finding two year later.

Conclusion: Diffusion-weighted imaging and DCEI were shown to be effective in quantifying changes in inflammation in S-I joint at the diagnosis of AS, and could be convenient for assessing treatment strategy. To the best of our knowledge this is the first time DWI was used to evaluate the treatment strategy and treatment outcome of AS.



Disclosure: S. Y. Lee, None;

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The Ankylosing Spondylitis Disease Activity Score More Closely Reflects MRI Parameters of Sacroiliitis Than the Bath Ankylosing Spondylitis Disease Activity Index in Patients with Non-Radiographic Axial Spondyloarthritis. WP Maksymowych[1], S Wichuk[1], H Jones[2], A Szumski[2], L Marshall[2], J Bukowski[2] and RG Lambert[1]. [1]University of Alberta, Edmonton, AB, [2]Pfizer Inc., Collegeville, PA.

Background/Purpose: Validation of clinical measures of disease in non-radiographic axial SpA (nr-axSpA) has been limited, especially using inflammatory and structural lesions on MRI as gold standard. Ankylosing Spondylitis Disease Activity Score (ASDAS) has been proposed as an optimal outcome measure, but is less feasible than Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) due to the need to assess CRP. We assessed which clinical measures best reflect the spectrum of MRI lesions in the sacroiliac joints (SIJ) of patients with nr-axSpA, and the effect of treating with an anti-TNF agent.

Methods: Patients had axial SpA per the Assessment of SpondyloArthritis (ASAS) classification criteria, but did not meet modified NY radiographic criteria. Patients had symptoms >3 months and <5 years, BASDAI ≥4, and failed ≥2 NSAIDs. Patients were randomized to etanercept (ETN) 50 mg/wk or placebo; after 12 wks, all patients received open-label ETN 50 mg/wk. Clinical endpoints were evaluated throughout the study; MRI of SIJ and spine was performed by 2 central readers at baseline (BL), wks 12 and 48, to assess bone marrow edema using the Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ score. In a post-hoc analysis, structural lesions were scored using the SPARCC SIJ structural (SSS) method, assessing fat metaplasia, erosion, backfill, and ankylosis on T1-weighted spin echo (T1WSE) MRI. Two independent readers scored BL and 48 wk T1WSE MRI scans from 187 cases blinded to outcomes and short tau inversion recovery (STIR) MRI; readers' mean scores were used. SPARCC score ≥2 for SIJ defined positive MRI evidence of inflammation. For the analysis, patients were pooled, and wk 48 change was analyzed using Spearman correlations, adjusted for treatment.

Results: Mean (SD) age was 32 (7.8) years, 60.5% were male, mean (SD) duration of symptoms was 2.5 (1.8) years. A total of 73% of patients were human leukocyte antigen B27 (HLA-B27) positive; 81% met the ASAS MRI imaging criteria at BL. A significant decrease in clinical (ASDAS, BASDAI, CRP) and MRI (SPARCC SIJ inflammation, SSS erosion) measures of active disease was noted by wk 48. There were no significant correlations at BL between BASDAI and any MRI lesion scores. There was significant BL correlation between SPARCC SIJ inflammation score and ASDAS (r=0.19, p=0.005) and CRP (r=0.22, p=0.002). Over 48 wks, there was significant correlation between change in ASDAS and changes in SPARCC SIJ inflammation (r=0.40, p<0.0001), SSS erosion (r=0.25, p=0.0007), and SSS backfill (r=-0.23, p=0.002). Change in CRP correlated significantly with changes in SPARCC SIJ inflammation (r=0.35, p<0.0001) and SSS erosion (r=0.18, p=0.02). Change in BASDAI correlated significantly with changes in SPARCC SIJ inflammation (r=0.25, p=0.0008), SSS backfill (r=-0.18, p=0.02), and SSS erosion (r=0.16, p=0.03). Correlations between ASDAS and MRI measures of sacroiliitis were strongest in the ETN group through 48 wks.

Conclusion: ASDAS is the preferred clinical measure of disease activity in nr-axSpA. Of all MRI assessments, change in SPARCC SIJ inflammation seems most closely aligned with changes in ASDAS, CRP and BASDAI, though the correlations are modest.

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Disease Activity Is the Major Determinant of Quality of Life and Physical Function in Patients with Early Axial Spondyloarthritis. Results from the Esperanza Cohort.

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Background/Purpose: Main objective: to describe health related quality of life (HRQoL), physical function (PF) and spinal mobility (SM) in patients with early axial Spondyloarthritis (axSpA). Second, to analyze the associations between HRQoL, PF and SM with disease activity and radiographic damage.

Methods: Baseline data from 259 patients fulfilling ASAS axSpA criteria from the Esperanza cohort were included. Validated versions of Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) and Bath Ankylosing Spondylitis Functional Index (BASFI) were used to evaluate HRQoL and PF. SM was assessed using Bath Ankylosing Spondylitis Metrology Index (BASMI). Disease activity was measured by means of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), patient's global and night back pain VAS and physician' VAS, Maastricht AS Enthesitis Score (MASES) and CRP (mg/L). Radiographic damage was assessed through Bath Ankylosing Spondylitis Radiographic Index for the spine (BASRI-s) and sacroiliac joints scoring as in mNY criteria. Linear regression analyses were employed to evaluate the associations between disease activity and radiographic damage with HRQoL, PF and SM.

Results: 259 axSpA patients, 67% men, 39% AS. Mean ± SD disease duration 13.3±6.8 months; age 32.2±6.9 years; BASDAI 3.8±2.3; ASDAS 2.3±1.0; patient's global and night back pain and physician VAS 4.2±2.7, 3.8±2.9 and 2.9±2.2; MASES 0.6±1.4; CRP 9.7±13.2 mg/L and BASRI-s 1.7±1.6.

Outcome values (Mean ± SD): ASQoL 5.9±4.8; BASFI 2.4±2.3 and BASMI1.4±1.3. *HRQoL and PF* associations with all disease activity parameters (table 1) were observed in the univariable analysis, whereas HRQoL and PF associations with radiographic damage were weaker or not significant. Multivariable analysis only showed associations with disease activity for both outcomes (table 2).

Table 1: Linear regression **univariable** analysis **adjusted** for age and gender.

	ASQoL		BASFI		BASMI	
	Std Beta	**p value**	**Std Beta**	**p value**	**Std Beta**	**p value**
CRP (mg/L)	0.272	p<0.01	0.300	p<0.01	0.187	p<0.01
ESR (mmHg)	0.113	p<0.1	0.186	p<0.01	0.074	NS
VAS (0–10) physician	0.558	p<0.01	0.616	p<0.01	0.285	p<0.01
VAS (0–10) patient	0.640	p<0.01	0.650	p<0.01	0.117	p<0.1
VAS (0–10) night back pain	0.597	p<0.01	0.593	p<0.01	0.106	p<0.1
BASDAI	0.645	p<0.01	0.691	p<0.01	0.167	p<0.01
ASDAS	0.564	p<0.01	0.608	p<0.01	0.193	p<0.01
MASES	0.239	p<0.01	0.239	p<0.01	0.052	NS
BASRI spine	0.149	p<0.05	0.154	p<0.05	0.322	p<0.01
Sacroiliitis xRay	0.078	NS	0.146	p<0.05	0.282	p<0.01

Table 2: Linear regression **multivariable** analysis **adjusted** for age and gender.

	ASQoL	BASFI	BASMI			
	Std Beta	**p value**	**Std Beta**	**p value**	**Std Beta**	**p value**
CRP (mg/L)	0.107	0.07	0.126	0.02	0.032	0.7
VAS (0–10) physician	0.207	0.01	0.266	<0.001	0.246	0.02
VAS (0–10) night back pain	0.203	0.02	0.058	0.4	−0.085	0.4
BASDAI	0.336	<0.001	0.473	<0.001	0.043	0.7
MASES	0.096	0.1	0.078	0.2	–	–
BASRI spine	−0.011	0.9	−0.058	0.4	0.198	0.06
Sacroiliitis xRay	–	–	0.093	0.2	0.022	0.8

SM was mainly associated with radiographic damage (univariable), but only a trend was observed for this association in the multivariable analysis.

Conclusion: In patients with early axSpA, HRQoL and physical function are already impaired and primarily associated with disease activity.

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How Should We Calculate the ASDAS If the Conventional C-Reactive Protein Is below the Limit of Detection? – an Analysis in the DESIR Cohort.

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Background/Purpose: The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite measure of disease activity in axial spondyloarthritis. It was suggested that when the conventional CRP (cCRP) is below the limit of detection, and high sensitivity CRP (hsCRP) is not available, 50% of the threshold value should be used to calculate ASDAS-CRP. However, this recommendation was not data driven and requires further testing. Our aims were to investigate the most appropriate ASDAS-C-reactive protein (ASDAS-CRP) calculation method when the cCRP is below the limit of detection, to study the arithmetic influence of low CRP values in ASDAS-CRP results and to test agreement between different ASDAS formulae.

Methods: Baseline data from the Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort was used. Patients with axial spondyloarthritis and cCRP below the limit of detection (5mg/L, n=257) were selected. ASDAS-cCRP was calculated using eleven imputation strategies for the cCRP (range 0–5, at 0.5 intervals). ASDAS-high sensitivity CRP (hsCRP) and ASDAS-ESR were also calculated. Agreement between ASDAS formulae was tested. The effect of low CRP values in ASDAS-CRP results was studied.

Results: ASDAS-CRP(1.5), ASDAS-CRP(2) and ASDAS-erythrocyte sedimentation rate (ESR) had better agreement with ASDAS-hsCRP than

other imputed formulae (table). Disagreement was mainly in lower disease activity states (inactive/moderate disease activity). When the CRP value is <2mg/L, the CRP component of the ASDAS-CRP formula can take very low values that may result in inappropriately low ASDAS-CRP values.

Table: Agreement between ASDAS-hsCRP and other ASDAS formulae (ASDAS-cCRP with multiple imputation strategies and ASDAS-ESR)

	ASDAS-hsCRP			
	ASDAS values		ASDAS disease activity states	
ASDAS formulae	ICC (95% CI)	Mean difference (95%CI)	Weighted kappa (95%CI)	Disagreement (%)
ASDAS-CRP(0)	0.78 (−0.06 to 0.94)	−0.52 (−1.02 to −0.03)	0.51 (0.44 to 0.57)	46.7%
ASDAS-CRP(0.5)	0.89 (0.33 to 0.96)	−0.29 (−0.79 to 0.21)	0.73 (0.67 to 0.79)	25.0%
ASDAS-CRP(1)	0.94 (0.89 to 0.96)	−0.12 (−0.62 to 0.38)	0.73 (0.67 to 0.79)	24.4%
ASDAS-CRP(1.5)	0.95 (0.93 to 0.96)	0.01 (−0.49 to 0.51)	0.75 (0.69 to 0.81)	21.9%
ASDAS-CRP(2)	0.94 (0.90 to 0.96)	0.11 (−0.38 to 0.61)	0.76 (0.70 to 0.81)	21.8%
ASDAS-CRP(2.5)	0.92 (0.70 to 0.96)	0.20 (−0.29 to 0.70)	0.71 (0.65 to 0.77)	25.3%
ASDAS-CRP(3)	0.89 (0.37 to 0.96)	0.28 (−0.22 to 0.78)	0.66 (0.60 to 0.73)	29.1%
ASDAS-CRP(3.5)	0.86 (0.11 to 0.96)	0.35 (−0.15 to 0.85)	0.64 (0.58 to 0.70)	31.6%
ASDAS-CRP(4)	0.83 (0.00 to 0.95)	0.41 (−0.09 to 0.91)	0.61 (0.54 to 0.67)	4.3%
ASDAS-CRP(4.5)	0.81 (−0.04 to 0.94)	0.47 (−0.03 to 0.96)	0.59 (0.53 to 0.65)	35.8%
ASDAS-CRP(5)	0.78 (−0.06 to 0.94)	0.52 (0.02 to 1.01)	0.50 (0.44 to 0.57)	43.6%
ASDAS-ESR	0.91 (0.85 to 0.94)	0.13 (−0.52 to 0.79)	0.69 (0.63 to 0.76)	8.1%

Conclusion: When the cCRP is below the limit of detection or when the hsCRP is <2mg/L, the constant value of 2mg/L should be used to calculate ASDAS-CRP. There is good agreement between ASDAS-hsCRP and ASDAS-ESR; however, formulae are not interchangeable. ASDAS is increasingly being used as a measure of disease activity in clinical practice, clinical trials and observational studies. This study contributes to further standardisation of the ASDAS and to a more homogeneous and reproducible application of this new index.

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A Comparison of Baseline Characteristics and Real-Life Effectiveness of Anti-TNF Therapy in Non-Radiographic Axial Spondyloarthritis Versus Ankylosing Spondylitis – a Single Center Cohort Study. Sarka Forejtova[1], Jakub Zavada[2], Michal Uher[3], Karel Hejduk[3] and Karel Pavelka[4]. [1]Institute of Rheumatology, Prague, Czech Republic, [2]Charles University, Prague, Czech Republic, [3]Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic, [4]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic.

Background/Purpose: The recent Assessment of SpondyloArthritis international Society (ASAS) classification criteria proposed the concept of axial spondylarthritis (axSpA) to enable earlier treatment not only for patients fulfilling the modified New York (mNY) criteria for ankylosing spondylitis (AS), but also for patients with non-radiographic axSpA (nr-axSpA). There is uncertainty whether the benefit of anti-TNF therapy in patients with nr-axSpA is as impressive as in patients with established AS, especially when the ASAS criteria and therapeutic recommendations are applied in real clinical practice.

Methods: Our aim was to compare the baseline characteristics and one year clinical outcome of anti-TNF therapy in axSpa patients prospectively followed in a large academic rheumatology center. This was a single center study conducted within the national biologics registry. To get reimbursement for anti-TNF therapy, all AS patients had to have high baseline disease activity (defined as BASDAI >4, and CRP > 10 mg/l). ASAS classification criteria were applied retrospectively using the data recorded in the source clinical documentation. All patients with inflammatory back pain fulfilling either ASAS criteria for nr-axSpA, or mNY criteria for AS starting treatment with anti-TNF therapy were included in the analysis.

Results: At baseline, patients with nr-axSpa had shorter disease duration, higher number of swollen peripheral joints, and were more often treated with glucocorticoids and synthetic DMARDs. There were no statistical significant differences in the effect of biologics on the improvement in BASDAI, BASFI, EUROQOL and spinal pain during first 12 months of treatment. Also, the QALY area under the curve was no different between both groups. There was significantly larger improvement in CRP in the group of AS patients, while in the nr-axSpA group there was greater change in the improvement of SJ, but these differences in range of change appeared to be caused by the ceiling effect of uneven baseline values of these measures.

Conclusion: Although there were some important baseline differences between both cohorts, the amount of improvement in axial symptoms, physical function and quality of life during the first 12 months of the anti-TNF treatment was similar in nr-axSpA and AS patients.

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Table: Baseline characteristics and outcome of 12 months of anti-TNF therapy in AS and nr-axSpA patients

		AS (N=275)	nr-axSpA(N=39)	p-value
Female	n (%)	68 (24.7%)	15 (38.5%)	0.069
Age (years) at baseline	mean (SD)	38.0 (10.4)	37.9 (12.2)	0.713
HLA B27 positivity	n (%)	252 (92.0%)	32 (84.2%)	0.117
Disease duration prior to start of anti-TNF therapy of anti-TNF therapy (years)	mean (SD)	9.0 (8.6)	4.9 (6.3)	**<0.001**
Peripheral joint involvement ever	n (%)	94 (34.3%)	24 (64.9%)	**<0.001**
Concomitant glucocorticoids at baseline	n (%)	23 (8.4%)	11 (28.2%)	**<0.001**
Concomitant DMARD at baseline	n (%)	57 (20.7%)	21 (53.8%)	**<0.001**
CRP (mg/l) at baseline	mean (SD)	25.5 (21.2)	21.9 (30.1)	**0.013**
CRP (mg/l) at 12 months	mean (SD)	5.3 (8.2)	4.8 (8.9)	0.232
CRP (mg/l) change per year	mean (SD)	−19.9 (22.2)	−17.3 (30.3)	**0.013**
BASDAI at baseline	mean (SD)	6.1 (1.9)	5.8 (2.5)	0.841
BASDAI at 12 months	mean (SD)	2.1 (1.7)	1.8 (1.5)	0.256
BASDAI change per year	mean (SD)	−4.1 (2.3)	−4.2 (2.8)	0.909
BASFI at baseline	mean (SD)	4.9 (2.2)	4.1 (2.7)	0.115
BASFI at 12 months	mean (SD)	2.6 (2.1)	1.4 (1.2)	**0.002**
BASFI change per year	mean (SD)	−2.3 (2.1)	−2.7 (2.7)	0.607
HAQ at baseline	mean (SD)	0.9 (0.5)	0.8 (0.6)	0.449
HAQ at 12 months	mean (SD)	0.5 (0.5)	0.4 (0.3)	0.636
HAQ change per year	mean (SD)	−0.4 (0.5)	−0.5 (0.5)	0.719
Spinal pain (BASDAI Q2 0-100) at baseline	mean (SD)	70.5 (22.1)	63.5 (27.4)	0.256
Spinal pain (BASDAI Q2 0-100) at 12 months	mean (SD)	27.9 (22.4)	24.0 (20.5)	0.392
Spinal pain (BASDAI Q2 0-100) change per year	mean (SD)	−44.9 (28.0)	−40.0 (33.8)	0.414
Number of swollen joints/44 at baseline	mean (SD)	1.8 (3,4)	3.4 (4.8)	**0.002**
Number of swollen joints/44 at 12 months	mean (SD)	0.3 (1.2)	1.1 (2.5)	**0.002**
Number of swollen joints/44 change per year	mean (SD)	−1.3 (3.0)	−2.6 (4.8)	0.055
EUROQOL	mean (SD)	0.4 (0.3)	0.4 (0.3)	0.699
EUROQOL	mean (SD)	0.8 (0.2)	0.7 (0.2)	0.462
QALY EQ-5D (area under the curve)	mean (SD)	0.7 (0.2)	0.7 (0.1)	0.525

Mann-Whitney U test, Pearson Chi-Square test (or Fisher exact test when frequencies are low) and Gamma test were used when comparing continuous, nominal and ordinal variables, respectively.

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Clinically Active Non-Radiographic Axial Spondyloarthritis Patients Who Initially Have a Negative MRI and Normal CRP May Develop a Positive MRI or Elevated CRP at a Later Timepoint. Xenofon Baraliakos[1], Joachim Sieper[2], Su Chen[3], Aileen L. Pangan[3] and Jaclyn K. Anderson[3]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Charité Universitätsmedizin Berlin, Berlin, Germany, [3]AbbVie Inc., North Chicago, IL.

Background/Purpose: Patients (pts) with non-radiographic axial spondyloarthritis (nr-axSpA) and active disease may have objective evidence of inflammation, either as bone marrow edema (BME) on magnetic resonance imaging (MRI) of the sacroiliac joints (SIJ) or spine, and/or an elevated CRP level. These pts may benefit from adalimumab (ADA) therapy. The objective was to determine whether untreated pts with clinically active disease but initially negative MRI or normal CRP, can develop objective evidence of inflammation and respond to ADA treatment.

Methods: ABILITY-1 was a phase 3, double blind (DB), randomized, controlled trial in pts with nr-axSpA who had an inadequate response, intolerance, or contraindication to NSAIDs. A 12-week (wk) DB period of ADA 40 mg every other wk (eow) or placebo (PBO), was followed by an open-label (OL) period, in which pts could receive ADA 40 mg eow for up to an additional 144 wks. MRI of the spine and SIJ were performed at baseline (BL) and wk 12. A positive MRI (MRI+) was defined as SPARCC MRI score ≥2 in either the SIJ or spine. C-reactive protein (CRP) levels were measured every 4 wks. This post hoc analysis evaluated 1) PBO-treated pts with negative MRI and normal CRP levels at BL, to determine if subsequent evidence of inflammation by MRI or CRP level occurs in untreated pts; and 2) if pts with a positive MRI or elevated CRP subsequent to the BL visit can

achieve an ASAS40 response at wk 24, similar to that observed in ADA-treated patients at wk 12.

Results: In the DB period, 9/29 (31.0%) of the PBO-treated pts with both a negative MRI of the SIJ and spine at BL, were MRI+ in either the SIJ or spine at wk 12 (table). Of the 57 PBO-treated pts with normal CRP at BL, 14 (24.6%) had elevated CRP at a timepoint between BL and wk 12. 20 PBO-treated pts had a negative MRI of the SIJ and spine and a normal CRP at BL; of these pts 10 (50.0%) had a positive MRI of either the SIJ or spine and/or an elevated CRP at ≥1 post-BL timepoint through wk 12. 5/10 (50.0%) of these pts achieved ASAS40 response at wk 24 (after 12 wks of OL ADA).

Table. Proportion of PBO patients who had a +MRI and/ or elevated CRP through wk 12, among those who had a –MRI and/or normal CRP at Baseline*

Status at Baseline N	Status at Wk 12 n (%)
Spine MRI - : 43	Spine MRI + : 11 (25.6)
SIJ MRI - : 54	SIJ MRI+ : 5 (9.3)
Spine and SIJ MRI- : 29	Spine or SIJ MRI+: 9 (31.0)
Normal CRP : 57	Elevated CRP : 14 (24.6)
Spine and SIJ MRI- and normal CRP: 20	Spine or SIJ MRI+ and/or elevated CRP: 10 (50.0)

*MRI was repeated at wk 12, CRP was repeated every 4 wks through week 12.

Conclusion: Among PBO-treated pts who did not have objective signs of inflammation at BL, but who demonstrated either a positive MRI or elevated CRP at a later timepoint, 50.0% achieved ASAS40 response after 12 wks of OL ADA treatment (wk 24). Although the sample size is small and higher response rates are expected with OL therapy, this is similar to that observed in the MRI+/elevated CRP ADA-treated population at wk 12 (41.0%). Thus, patients with clinically active disease but without objective inflammation at one point, may benefit from subsequent re-testing for inflammation, and if present, from initiation of ADA therapy.

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Serum Levels of Bone Morphogenetic Protein-7 and Sclerostin Are Elevated in Ankylosing Spondylitis, but Not Linked with Structural Damage. Weiping Kong[1], Xiaotong WANG[1], Tongliang Zhou[1], Yue Jin[2], Qingwen TAO[1], Yuan Xu[1], Yingze Zhang[1], Jianming WANG[1] and Xiaoping Yan[1]. [1]China-Japan Friendship Hospital, BEIJING, China, [2]Beijing University of Chinese Medicine, BEIJING, China.

Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by new bone formation that progressively leads to ankylosis and functional disability. The mechanisms of new bone formation in AS are yet to be characterized. Several biomarkers are involved in bone remodeling in AS, such as Dickkopf-1 (Dkk-1) and sclerostin, which down-regulate bone formation by inhibition of Wingless proteins (Wnt) and bone morphogenic proteins (BMPs). Wnt and BMPs are key inducers of osteoblastogenesis and new bone formation. The aim of this study was to determine serum concentrations of BMP7, Dkk-1 and sclerostin in patients with AS and to investigate their relationship to clinical manifestations and structural damage.

Methods: Serum levels of BMP-7, DKK-1, Sclerostin were detected by enzyme-linked immunosorbent assay in 40 AS patients with syndesmophyte (male: 36, female: 4, age: 32.43±7.63), 40 AS patients without syndesmophyte (male: 35, female: 5, age: 29.8±7.18) and 23 healthy controls (male: 32, female: 8, age: 31.95±9.42). Clinical manifestations such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score and Bath Ankylosing Spondylitis Functional Index (BASFI) score were evaluated in AS patients. Cervical and lumbar spine x-rays were performed in 80 patients to measure modified Stoke's Ankylosing Spondylitis Spine Score (mSASSS). SPSS17.0 was performed to analyze statistical difference. P-values less than 0.05 were considered statistically significant.

Results: Serum level of BMP-7 in AS patients with and without syndesmophyte (74.39±49.53 pg/ml, 89.17±83.31 pg/ml) was significantly higher than healthy control group (40.30±16.19 pg/ml, P=0.001, P=0.002). Sclerostin level in AS patients with and without syndesmophyte (184.46±316.08 pg/ml,187.79±223.53 pg/ml) was significantly higher than healthy control group (87.40±34.28 pg/ml, P=0.044, P=0.002). There was no significant differences of BMP-7 and sclerostin level in AS patients with or without syndesmophyte. No significant differences of DKK-1 level had been found in AS patients with (1174.29±863.90 pg/ml) or without syndesmophyte (971.44±677.9 pg/ml) and control group (1090.05±809.75 pg/ml). Serum DKK-1 level in AS patients was positively correlated with ESR (P=0.029). However, no biomarkers showed significant correlation with age, sex, course of disease, sacroiliitis grade, BASDAI, BASFI and structural damage (mSASSS). Furthermore, there was no correlation between three biomarkers.

Conclusion: Both osteoinductive factor BMP-7 and its inhibitor sclerostin increased in AS patients. This may reflect a counter-balancing mechanism in AS new bone formation leading to bone remodeling.

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Unexpected High Prevalence of Cardiac Disease in Patients with Ankylosing Spondylitis. S.C. Heslinga[1], Thelma C. Konings[1], Irene E. Van der Horst - Bruinsma[1], M.L. John[1] and Mike T. Nurmohamed[2]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Jan van Breemen Research Institute | Reade, Amsterdam, Netherlands.

Background/Purpose: Ankylosing spondylitis (AS) is associated with an increased cardiovascular (CV) risk that is caused by accelerated atherosclerosis as well as specific cardiac manifestations: valvular disease, conduction disturbances and congestive heart failure due to decreased ventricular function. In this study we investigated the prevalence of cardiac disease in AS patients with high disease activity.

Methods: We performed a cross sectional study in patients with AS eligible for treatment with TNF blocking therapy. Patients were screened for cardiac disease using standard transthoracic echocardiography that included two-dimensional, three-dimensional and M-mode echocardiography, spectral Doppler, color Doppler and tissue Doppler imaging. The ejection fraction (EF) was used to assess systolic left ventricular (LV) function, with systolic LV dysfunction defined as EF<50%. For diastolic LV function a combination of echocardiographic measurements, i.e. peak early diastolic filling velocity (E), late diastolic filling velocity (A), E/A ratio, early diastolic mitral annular velocity (E'), deceleration time (DT) and isovolumetric relaxation time (IVRT) were used. Based on these parameters diastolic LV dysfunction is graded into three categories: mild (grade I), pseudonormal (grade II) and restrictive (grade III). Valvular and aortic abnormalities were evaluated according to the current echocardiographic guidelines. Data was compared with data from literature using one-sample t-test.

Results: Forty-three consecutive AS patients were included with a mean age of 43±12 years and a mean disease duration of 10±12 years. In total, 10 out of 43 (23%) patients had diastolic LV dysfunction grade I, of which one was female. This was significantly higher compared to literature, in which the prevalence of diastolic LV dysfunction grade I is approximately 5% in an age matched control group ($p<0.01$)[1]. Two patients had a prior myocardial infarction of which one had systolic LV dysfunction, with an EF of 49%. Three patients had mild aortic regurgitation and seven other patients had mild mitral regurgitation. Five patients had mild aortic dilatation. Overall, 19 out of 43 AS patients (44%) had some form of cardiac dysfunction or disease which is substantially higher compared to the general population, as the prevalence of cardiac disease in the general population is approximately 8%[2].

Conclusion: Patients with AS have an increased prevalence of cardiac disease compared with the general population, with increased prevalence's of left ventricular dysfunction and valvular disease. This increased prevalence may increase CV risk in AS patients. As cardiac disease could be attributable to the general inflammation process affecting the heart, further studies are warranted that investigate whether or not anti-inflammatory treatment, such as TNF blockers, improves cardiac function or prevents early cardiac complications. Also, the impact of (mandatory) screening AS patients with echocardiography on CV disease should be investigated.

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2584

Smoking Is Not Associated with Response to TNF Blockers in Patients with Axial Spondyloarthritis. Anna Dellyes, Pierre Lafforgue, Vincent Pradel and Thao Pham. APHM, Aix Marseille University, Marseille, France.

Background/Purpose: Smoking has been reported as associated with increase disease activity, more functional impairment, poorer quality of life and more radiographic damages in patients (pts) with axial spondyloarthritis (SpA). However, there is little information available about a potential effect of smoking on the effectiveness of anti-rheumatic treatment such as TNF blockers. The study objective was to examine the association of smoking with clinical outcome after treatment with TNF blockers in patients with axial SpA.

Methods: A monocenter ambispective observational study in 96 patients with active axial SpA starting a treatment with a first TNF blocker. BASDAI, pain VAS, analgesics and NSAIDs consumption, and variables known as treatment response predictive factors were collected at baseline, 3, 6 and 12 months. The main outcome was the percentage of BASDAI 50 responders at M6. Secondary outcomes were BASDAI variation, pain VAS variation and NSAIDs consumption at M3, M6 and m12. We analyzed disease activity and response to treatment in current smokers vs. non-smokers using a chi-square test or one-way analysis of variance (depending on categorical/continuous variables). SPSS 17.0 version was used for the management and statistical analysis.

Results: Patients' demographic and clinical characteristics at baseline are shown in table 1. Thirty-five pts (36%) were current smokers (14.6±6.4 cigarettes/day). No significant differences were observed between current smokers and non-smokers at baseline. Patients were mainly treated with infliximab (84%). The percentage of BASDAI 50 responders at M6 was 34%(12/35) and 39%(24/61), in the smokers and the non-smokers group, respectively ($p>0.6$). No statically significant differences were observed between current smoker and nonsmokers in BASDAI variation, pain VAS variation or treatment consumption at each evaluation time.

Conclusion: Smoking status seems not to be a predictive factor of response to TNF-blockers in patients with axial SpA.

Baseline	Smokers N = 35	Non-smokers N=61	p
Gender, male (n, %)	17 (48.6%)	35 (57.4%)	0.52
Age, years, (mean, SD)	44 (14)	44 (9)	0.99
Disease duration, years, (mean, SD)	11.6 (11.1)	12.0 (9.1)	0.84
DMARDs, yes (n, %)	6 (17.1%)	11 (18.0%)	0.91
NSAIDs, yes (n, %)	26 (74.3%)	42 (68.9%)	0.57
BASDAI (0–100), (mean, SD)	6.0 (1.6)	5.4 (1.7)	0.07
Pain EVA (0–10), (mean, SD)	6.3 (2.3)	5.8 (1.9)	0.26
CRP mg/l, (mean, SD)	16.0 (22.0)	10.0 (16.0)	0.09

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Association of Smoking with Acute Phase Reactants and Molecules Involved in Bone Formation in Patients with Ankylosing Spondylitis. Grigorios Sakellariou[1], Spyros Gerou[2], Dimitrios Oikonomou[1] and Fares Sayegh[3]. [1]424 General Military Hospital, Thessaloniki, Greece, [2]Laboratories "Analysis", Thessaloniki, Greece, [3]"Papageorgiou" General Hospital, Thessaloniki, Greece.

Background/Purpose: In patients with ankylosing spondylitis (AS), smoking is associated with increased disease activity and more radiographic damage. However, the mechanisms underlying the effects of smoking are still unknown. The aim of the study was to investigate the relationship between smoking and acute phase reactants, and serum levels of molecules involved in bone formation in patients with AS.

Methods: This was an observational, cross-sectional study. Serum samples for total Dickkopf-1 (Dkk-1), sclerostin and vascular endothelial growth factor (VEGF) were obtained from TNF inhibitor naïve patients with AS according to the modified New York criteria. Patients with at least the last 3 months use of glucocorticoids, DMARDs or high dose NSAIDs (a mean NSAIDs intake index ≥50) were excluded. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), BASDAI, BASFI and radiographic severity (assessed by mSASSS and BASRI-s) were assessed for each patient. Demographic variables and smoking history were obtained, and smoking pack-years were calculated.

Results: Sixty-five patients were included in the study [mean age 41.3±1.5 years; duration of symptoms 13.4±1.2 years; male gender 61 patients (93.8%)]. Using Mann-Whitney U test, CRP (18.9±12.5 mg/l vs 12.4±9.3 mg/l, $p=0.019$) and VEGF levels (381.6±121.4 pg/ml vs 310.9±131.5 pg/ml, $p=0.02$) were higher in patients with current smoking compared with those without, while there was no difference for ESR and the levels of Dkk-1 and sclerostin. Ever smokers had higher VEGF levels (369.9±128.7 pg/ml vs 252.7±94.4 pg/ml, $p=0.006$) compared with never smokers, while there was no difference for ESR, CRP and the levels of Dkk-1 and sclerostin between the two groups. Among acute phase reactants and molecules involved in bone formation, only VEGF levels were correlated with smoking pack-years ($r=0.389$, $p=0.001$). In multiple linear regression analysis, which involved all demographic, clinical and radiographic variables that presented significant association with smoking pack-years in the bivariate correlations, VEGF levels were an independent variable of smoking pack-years ($\beta=0.497$, $p<0.001$).

Conclusion: It seems that VEGF levels are positively associated with smoking in patients with AS. The effect of smoking on disease activity and/or radiographic spinal progression to be mediated by increased VEGF levels could be supposed.

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2586

Which Characteristics of Inflammatory Back Pain (CBP) Forecast the Presence of Sacroiliitis on Magnetic Resonance Imaging (MRI)? Results from the Esperanza Cohort. Victoria Navarro-Compán[1], Raquel Almodóvar González[2], Azucena Hernández[3], Emma Beltrán[4], Eugenio de Miguel[5], Robert B. M. Landewé[6], Désirée van der Heijde[7] and Pedro Zarco[8]. [1]University Hospital La Paz and Leiden University Medical Center, Madrid, Spain, [2]Hospital Universitario Fundación Alcorcón, Madrid, Spain, [3]Hospital Virgen de la Salud, Toledo, Spain, [4]University General Hospital of Valencia, Valencia, Spain, [5]University Hospital La Paz - IdiPaz, Madrid, Spain, [6]Amsterdam Rheumatology Center, Amsterdam, Netherlands, [7]Leiden University Medical Center, Leiden, Netherlands, [8]Fundación Hospital Alcorcon, Alcorcon, Madrid, Spain.

Background/Purpose: CBP is often the starting point for a suspicion of axSpA. In the ASAS-criteria for axial SpA either MRI of the SI-joints or HLA-B27-testing are dominant. But, CBP is an extremely common presenting symptom and not all patients can be followed up by MRI and/or HLAB27 testing. This analysis was undertaken to investigate which characteristics of back-pain forecast a positive MRI of the SI-joints.

Objectives: To evaluate which inflammatory characteristics of CBP are associated with the presence of sacroiliitis on MRI in patients with a suspicion of axSpA.

Methods: Baseline dataset from the EsPeranza cohort (<45 years old, symptoms duration 3–24 months and with inflammatory back pain -IBP- or asymmetrical arthritis or spinal/joint pain plus ≥1 SpA features) was used. For this study, only data from all patients with axial symptoms who underwent sacroiliac joint (SIJ) MRI were analysed. Univariable and multivariable logistic regression analyses were employed to estimate odds ratio for the association between IBP characteristics (morning stiffness, improve with exercise and not with rest, alternating buttock pain, insidious onset, awakening at 2nd half of night and good response to NSAID) and their different combinations with a positive SIJ MRI (ASAS definition). Furthermore, diagnostic utility measures were also calculated.

Results: Data from 326 patients (53.7% male, 45% HLA-B27 positive, mean (SD) age 32.8 (7) years and mean (SD) symptoms duration 12.6 (6.4) months) were included in this analysis. A total of 130 (40%) patients had sacroiliitis on MRI. Table shows the association between each separate characteristic (1A) and each possible IBP definition (1B) with a positive MRI. Alternating buttock pain ($OR=3.43$;$p<0.001$), insidious onset ($OR=2.15$; $p<0.05$) and awakening at 2nd half of the night ($OR=1.71$;$p<0.05$) were significantly and positively associated with a positive MRI. The combination of these three characteristics (92%) and the addition to the ASAS-definition of IBP of alternating buttock pain (94%) or NSAID response (86%) had highest specificity, but insufficient sensitivity.

Conclusion: Alternating buttock pain is a distinguishing IBP characteristic strongly associated with a positive SIJ MRI in patients with suspected axSpA. The addition of this criterion in the decision to perform MRI of the SIJ may improve diagnostic efficiency in patients with suspected axSpA.

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Disclosure of Interest: None declared.

Table: Association between each of the CBP characteristics and each of the possible IBP definitions with a positive MRI.

	Sacroiliitis positive (N=130)	Sacroiliitis negative (N=196)	Univariable analysis	Multivariable analysis	Diagnostic utility measures					
	N (%)	N (%)	OR	OR	Sen	Spe	PPV	NPV	LR+	LR−
Table 1A: Individual Characteristic of IBP										
Morn. Stiff > 30 min	89 (68.5)	106 (54.1)	1.84*	1.30	68.5	45.9	45.6	68.7	1.27	0.69
Imp. exercise, not rest	41 (31.5)	56 (28.6)	1.15		31.5	71.4	42.3	61.1	1.10	0.04
Alter. buttock pain	62 (47.7)	36 (18.4)	4.05**	3.43**	47.7	81.6	63.3	70.2	**2.59**	0.64
Insidious onset	114 (87.7)	142 (72.4)	2.71**	2.15*	87.7	27.6	44.5	77.1	**1.21**	0.44
Awake 2nd half night	84 (64.6)	85 (43.4)	2.39**	1.71*	64.6	56.6	49.7	70.7	**1.49**	0.63
Response to NSAIDs	90 (69.2)	110 (56.1)	1.76*	1.32	69.2	43.9	45.0	68.3	1.23	0.70
Table 1B: IBP Definition										
Calin criteria	67 (51.5)	57 (29.1)	2.59**	–	51.5	70.9	54.0	68.8	1.77	0.68
Berlin criteria	94 (72.3)	97 (49.5)	2.67**	–	72.3	50.5	49.2	73.3	1.46	0.55
ASAS criteria	62 (47.7)	45 (23.0)	3.06**	–	47.7	77.0	57.9	68.9	1.45	0.67
Night + Insidious + Buttock (2/3)	93 (71.5)	80 (40.8)	3.65**		71.5	59.2	53.8	75.8	1.75	0.48
Night + Insidious + Buttock (3/3)	89 (33.8)	15 (7.7)	6.17**	–	33.8	92.3	74.6	67.8	**4.39**	0.72
Calin + Night (5/6)	52 (40.0)	41 (20.9)	2.52**	–	40.0	79.1	55.9	66.5	1.91	0.76
Berlin + Insidious (3/5)	89 (68.5)	81 (41.3)	3.08**	–	68.5	58.7	52.4	73.7	1.66	0.54
ASAS + Buttock (5/6)	40 (30.8)	11 (5.6)	7.48**	–	30.8	94.4	78.4	67.3	**5.50**	0.73
ASAS + NSAIDs (5/6)	48 (36.9)	27 (13.8)	3.66**	–	36.9	86.2	64.0	67.3	2.67	0.73
ASAS + Buttock + NSAIDs (6/7)	28 (21.5)	7 (3.6)	7.41**	–	21.5	96.4	80.0	64.9	**5.97**	0.81

$p<0.05$; $^{**}p<0.001$

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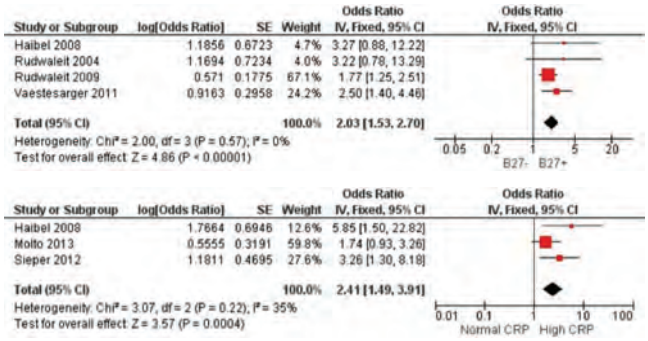
Predictors of Treatment Response to Tumor Necrosis Factor-Alpha Blockers in Spondyloarthritis: Systematic Review and Meta-Analysis. Pauline Manicki[1], Jacques Morel[1], Bernard Combe[1] and Cédric Lukas[2]. [1]Hôpital Lapeyronie, Montpellier, France, [2]Hopital Lapeyronie, Montpellier, France.

Background/Purpose: TNF blockers have demonstrated substantial clinical efficacy in spondyloarthritis patients, and are usually indicated in patients showing active disease after failure to conventional treatment with NSAIDS or conventional DMARDs in peripheral presentations of the disease. However the relevant but inconstant and "only" symptomatic efficacy of the drugs in axial disease, together with the cost and possible side effects may argue to a better selection of suitable patients before starting TNF blockers. Our objective was to identify the baseline factors potentially predictive of a good response to TNF blockers in patients with spondyloarthritis.

Methods: A systematic search of literature up to January 2014 was performed, in MEDLINE, EMBASE, the Cochrane library and abstracts from the ACR, EULAR and French national congresses from 2010 to 2013. Studies were included if they reported the response to TNF blockers based on the baseline parameters. After systematic collection of available data, a meta-analysis was conducted for every suitable outcome reported with potentially relevant baseline variables in at least 3 independent studies.

Results: The literature search identified 2340 articles and 1 congress abstract. Finally, 33 articles and one abstract could be included according the predefined requirements. The meta-analysis of data of 4 studies showed a significantly increased treatment response BASDAI 50 in patients HLA B27 positive (OR 2.03 [95%CI 1.53–2.70]). Lower BASFI was predictor of response BASDAI 50 to treatment (OR 0.88 [95%CI 0.84–0.93] per BASFI unit/10), likewise younger age (OR 0.97 [95%CI 0.96–0.98] per additional age in years) in meta-analysis of data of 4 studies, and shorter disease duration (OR 0.95 [95%CI 0.90–1.00] per additional age in years). Elevated C-reactive protein concentration was predictor of achieving ASAS 40 response (OR 2.66 [95%CI 1.39–5.08]) in meta-analysis of data from 3 studies.



Conclusion: This meta-analysis has identified increased acute phase reactants, younger age, shorter disease duration and HLA-B27 positivity as baseline predictors for achieving good clinical response to TNF-a blocking therapy. This may help clinicians in making treatment decisions in daily practice.

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2588

Which Characteristics of Inflammatory Back Pain (CBP) Forecast the Presence of HLA-B27? Results from the Esperanza Cohort. Victoria Navarro-Compán[1], Juan Jose Aznar[2], Luis F Linares[3], Eduardo Collantes-Estévez[4], Robert B. M. Landewé[5], Désirée van der Heijde[6] and Pedro Zarco[7]. [1]University Hospital La Paz and Leiden University Medical Center, Madrid, Spain, [2]Hospital de Mérida, Mérida (Badajoz), Spain, [3]University Hospital Virgen de la Arrixaca, Murcia, Spain, [4]IMIBIC/University Hospital Reina Sofía, Córdoba, Spain, Córdoba, Spain, [5]Amsterdam Rheumatology Center, Amsterdam, Netherlands, [6]Leiden University Medical Center, Leiden, Netherlands, [7]Fundación Hospital Alcorcon, Alcorcon, Madrid, Spain.

Background/Purpose: CBP is often the starting point for a suspicion of axSpA. In the ASAS-criteria for axial SpA either MRI of the SI-joints or HLA-B27-testing are dominant. But, CBP is an extremely common presenting symptom and not all patients can be followed up by MRI and/or HLAB27 testing. This analysis was undertaken to investigate which characteristics of back-pain forecast a positive HLA-B27.

Objectives: To evaluate which inflammatory characteristics of CBP are associated with the presence of HLA-B27 in patients with a suspicion of axSpA.

Methods: Baseline dataset from the EsPeranza cohort (<45 years old, symptoms duration 3–24 months and with inflammatory back pain -IBP- or asymmetrical arthritis or spinal/joint pain plus ≥1 SpA features) was used. For this study, only data from all patients with axial symptoms and HLA-B27 assessed were analysed. Univariable and multivariable logistic regression analyses were employed to estimate odds ratio for the association between IBP characteristics (morning stiffness, improve with exercise and not with rest, alternating buttock pain, insidious onset, awakening at 2nd half of night and good response to NSAID) and their different combinations with a positive HLA-B27 (local lab testing). Furthermore, diagnostic utility measures were also calculated.

Results: Data from 653 patients (54.2% male, mean (SD) age 33.0 (7.1) years and mean (SD) symptoms duration 11.0 (6.6) months. A total of 270 (41%) patients were HLA-B27 positive) were included in this analysis. Table shows the association between each separate characteristic (1A) and each possible IBP definition (1B) with a positive HLA-B27. Awakening at second half of night (OR=1.53;$p<0.05$) and good response to NSAID (OR=1.46; $p<0.05$) were significantly and positively associated with a positive HLA-B27. Among the existing criteria to define IBP, the ASAS criteria had the highest specificity (81%), but insufficient sensitivity. The addition of these two characteristics to the Calin-definition of IBP (88%) as well as the addition of NSAID response to the ASAS-definition of IBP (86%) just increased the specificity slightly.

Conclusion: Awakening at second half of night and good response to NSAIDs are distinguishing IBP characteristics associated with the presence of HLA-B27 in patients with suspected axSpA. However, the addition of these characteristics to the existing IBP definitions in the decision to test HLA-B27 does not significantly improve diagnostic efficiency in patients with suspected axSpA. Further, the most specific IBP definition for a positive HLA-B27 is the ASAS-definition.

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Disclosure of Interest: None declared.

Table: Association between each of the CBP characteristics and each of the possible IBP definitions with a positive HLA-B27.

	HLA-B27 + N=270	HLA-B27 - N=383	Univariable analysis	Multivariable analysis	Diagnostic utility measures					
	N (%)	N (%)	OR	OR	Sen	Spe	PPV	NPV	LR+	LR−
Table 1A: Individual Characteristic of IBP										
Morn. Stiff > 30 min	171 (63.3)	216 (56.4)	1.34*	1.10	63.3	43.6	44.2	62.8	1.12	0.84
Imp. exercise, not rest	91 (33.7)	114 (29.8)	1.20		33.7	70.2	44.4	60.0	1.13	0.94
Alter. buttock pain	86 (31.9)	110 (28.7)	1.16		31.9	71.3	43.9	59.7	1.11	0.96
Insidious onset	184 (68.1)	241 (62.9)	1.26		68.1	37.1	43.3	62.3	1.08	0.86
Awake 2nd half night	149 (55.2)	163 (42.6)	1.66***	1.53**	55.2	57.4	47.8	64.5	**1.30**	0.78
Response to NSAIDs	182 (67.4)	217 (56.7)	1.58***	1.46**	67.4	43.3	45.6	65.4	**1.19**	0.75
Table 1B: IBP Definition										
Calin criteria	98 (36.3)	99 (25.8)	1.63**	–	36.3	74.2	49.7	62.3	1.41	0.86
Berlin criteria	173 (64.1)	194 (50.7)	1.74**	–	64.1	49.3	47.1	66.1	1.26	0.73
ASAS criteria	85 (31.5)	74 (19.3)	1.92***	–	31.5	80.7	53.5	62.3	**1.63**	0.85
Night + NSAID response (2/2)	108 (40.0)	109 (28.5)	1.68**	–	40.0	71.5	49.8	62.8	1.40	0.84
Calin + Night + NSAID response (6/7)	58 (21.5)	45 (11.7)	2.06**	–	21.5	88.3	56.3	61.5	1.84	0.89
Berlin + NSAID response (3/5)	154 (57.0)	153 (39.9)	2.00***	–	57.0	60.1	50.2	66.5	1.43	0.72
ASAS + NSAID response (5/6)	66 (24.4)	51 (13.3)	2.11***	–	24.4	86.7	56.4	61.9	**1.83**	0.87
ASAS + Buttock + NSAIDs (6/7)	29 (10.7)	22 (5.7)	1.98**		10.7	94.3	56.9	60.0	**1.88**	0.95

*p<0.1; **p<0.05; ***p<0.01.

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EULAR Recommendations for the Use of Imaging in Spondyloarthritis in Clinical Practice. Peter Mandl[1], Victoria Navarro-Compán[2], Pauline Bakker[2], Lene Terslev[3], Philippe Aegerter[4], Désirée van der Heijde[2], Maria-Antonietta d'Agostino[5], Xenofon Baraliakos[6], Susanne Juhl Pedersen[7], Anne G. Jurik[8], Esperanza Naredo[9], Claudia Schueller-Weidekamm[1], Ulrich Weber[10], Marius Wick[11], Emilio Filippucci[12], Philip G. Conaghan[13], Martin Rudwaleit[14], Georg A. Schett[15], Joachim Sieper[14], Simon Tarp[16], Helena Marzo-Ortega[13] and Mikkel Ostergaard[3]. [1]Medical University of Vienna, Vienna, Austria, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Copenhagen University Hospital at Glostrup, Copenhagen, Denmark, [4]Versailles-Saint Quentin en Yvelines University- APHP, Ambroise-Paré Hospital,, Boulogne-Billancourt,, France, [5]Versailles-Saint Quentin en Yvelines University, Boulogne-Billancourt, France, [6]Rheumazentrum Ruhrgebiet, Herne, Germany, [7]Copenhagen Center for Arthritis Research, Copenhagen, Denmark, [8]Aarhus University Hospital, Aarhus, Denmark, [9]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [10]University of Alberta, Edmonton, AB, [11]Karolinska University Hospital, Stockholm, Sweden, [12]University of Ancona, Jesi, Italy, [13]University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [14]Charité Universitätsmedizin Berlin, Berlin, Germany, [15]University of Erlangen-Nuremberg, Erlangen, Germany, [16]Copenhagen University Hospital at Fredriksberg, Copenhagen, Denmark.

Background/Purpose: Reflecting the perceived need for developing evidence-based recommendations on the use of imaging of the joints in the clinical management of spondyloarthritis (SpA) a European League Against Rheumatism (EULAR) task force was convened to develop evidence-based recommendations on the use of imaging of the joints in the clinical management of both axial and peripheral SpA.

Methods: The task force comprised an expert group of 21 rheumatologists, radiologists and methodologists from 11 countries. Twelve key questions on the role of imaging in SpA were generated using a process of discussion and consensus. Imaging modalities included conventional radiography (CR), ultrasound (US), magnetic resonance imaging (MRI), computed-, positron emission- and single photon emission computed tomography, dual-emission x-ray absorptiometry (DXA) and scintigraphy. Experts used research evidence obtained from a systematic literature review using MEDLINE and EMBASE to develop a set of 10 recommendations. The strength of recommendation (SOR) was assessed by the group members using a visual analogue scale. Quality assessment of the included studies was performed using the QUADAS-2 tool.

Results: A total of 7550 references were identified in the search process, from which 158 studies were included in the systematic literature review. Ten recommendations were produced encompassing the role of imaging in making a diagnosis of axial- or peripheral SpA, monitoring inflammation and damage, predicting outcome, response to treatment, and detecting spinal fractures and osteoporosis (OP) (Table 1). The SOR for each proposition varied, but was generally very high (mean 8.9–9.5).

Conclusion: Ten recommendations for the role of imaging in the clinical management of SpA were developed using research-based evidence and expert opinion.

LOE, level of evidence; categories of evidence: Ia, evidence for meta-analysis of randomized controlled trials; Ib, evidence from at least one randomized controlled trial; IIa, evidence from at least one controlled study without randomization; IIb, evidence from at least one other type of quasi-experimental study; III, evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case–control studies; IV, evidence from expert committee reports or opinions or clinical experience of respected authorities, or both. CRP, C-reactive protein; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axial spondyloarthritis; SI, sacroiliac; SpA, spondyloarthritis; SOR, strength of recommendation, mean (range) of visual analogue scale; STIR, short tau inversion recovery; TNF, tumor necrosis factor alpha; US, ultrasonography.

Table 1. EULAR imaging recommendations for spondylarthritis in clinical practice

		SOR	LOE
1	**Axial SpA: diagnosis** In general, X-ray of the SI joints is recommended as the first imaging method to diagnose sacroiliitis as part of axial SpA. In certain cases, such as young patients and those with short symptom duration, MRI of the SI joints is an alternative first imaging method. If the diagnosis of axial SpA cannot be established based on clinical features and X-ray, and axial SpA is still suspected, MRI of the SI joints is recommended. On MRI, both active inflammatory lesions (primarily bone marrow edema) and structural lesions (such as bone erosion, new bone formation, sclerosis and fat infiltration) should be considered. MRI of the spine is not generally recommended to diagnose axial SpA, as it provides little added diagnostic value over and above MRI of the SI joints. Other imaging modalities are not generally recommended as the first imaging choice. CT may provide additional information on structural damage if X-rays are negative and MRI cannot be performed. Scintigraphy and US are not recommended for diagnosis of sacroiliitis as part of axial SpA.	9.5 (9.2–9.8)	III
2	**Peripheral SpA: diagnosis** When SpA is suspected, US or MRI may be used to detect peripheral enthesitis, which may support the diagnosis of SpA. Furthermore, US or MRI may be used to detect peripheral arthritis, tenosynovitis and bursitis.	9.4 (9.0–9.8)	III
3	**Axial SpA: monitoring activity** MRI of the SI-joints and/or the spine may be used to assess and monitor disease activity in axial SpA, providing additional information on top of clinical and biochemical assessments. The decision on when to repeat MRI depends on the clinical circumstances. In general, STIR sequences are sufficient to detect inflammation and the use of contrast medium is not needed.	9.2 (8.8–9.6)	Ib
4	**Axial SpA: monitoring structural changes** X-ray of the SI joints and/or spine may be used for long-term monitoring of structural damage, particularly new bone formation, in axial SpA. If performed, it should not be repeated more frequently than every 2nd year. MRI may provideadditional information.	9.3 (8.8–9.8)	Ib
5	**Peripheral SpA: monitoring activity** US and MRI may be used to monitor disease activity (particularly synovitis and enthesitis) in peripheral SpA, providing additional information on top of clinical and biochemical assessments. The decision on when to repeat US/MRI depends on the clinical circumstances. US with high-frequency color or power Doppler is sufficient to detect inflammation and the use of US contrast medium is not needed.	9.3 (8.9–9.7)	Ib

6	**Peripheral SpA: monitoring structural changes** In peripheral SpA, if the clinical scenario requires monitoring of structural damage, then X-ray is recommended. MRI and/or US may provide additional information.	8.9 (8.4–9.4)	III
7	**Axial SpA: predicting outcome/severity** In patients with AS (not nr-axSpA), initial X-rays of the lumbar and cervical spine are recommended to detect syndesmophytes, which are predictive of development of new syndesmophytes. MRI (vertebral corner inflammatory or fatty lesions) may also be used to predict development of new radiographic syndesmophytes.	9.0 (8.5–9.5)	Ib
8	**Axial SpA: predicting treatment effect** Extensive MRI inflammatory activity (bone marrow edema), particularly in the spine in AS patients, may be used as a predictor of good clinical response to anti-TNF treatment in axial SpA. Thus, MRI may aid in the decision of initiating anti-TNF therapy, in addition to clinical examination and CRP.	8.9 (8.3–9.5)	Ib
9	**Spinal fracture** When spinal fracture in axial SpA is suspected, X-ray is the recommended initial imaging method. If X-rays are negative, CT should be performed, MRI is an additional imaging method to CT, which can also provide information on soft tissue lesions.	9.3 (8.9–9.7)	IV
10	**Osteoporosis** In axial SpA patients without syndesmophytes in the lumbar spine on X-ray, osteoporosis should be assessed by hip DXA and AP-spine DXA. In patients with syndesmophytes in the lumbar spine on X-ray, osteoporosis should be assessed by hip DXA, supplemented by either spine DXA in lateral projection or possibly QCT of the spine.	9.4 (9.0–9.8)	III

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Comparison of Radiographic Damage Score in Ankylosing Spondylitis According to Tumor Necrosis Factor Inhibitor: Observation Study of Korean Spondyloarthropathy Registry (OSKAR) Data. Tae-Jong Kim[1], JI Hui SHIN[2], Il-Hoon Sung[2], Seunghun Lee[3], Kyung-Bin Joo[4] and Tae-Hwan Kim[2]. [1]Chonnam Nat'l University Medical School&Hospital, Gwangju, South Korea, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Department of Radiology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [4]Department of Radiology, Hanynag University Hospital for Rheumatic Diseases, Seoul, South Korea.

Background/Purpose: To evaluate the influence of tumor necrosis factor (TNF) blocker on the radiographic damage in ankylosing spondylitis (AS).

Methods: A total of 610 AS patients from the Observation Study of Korean spondyloArthropathy Registry (OSKAR) data were recruited for this study. The subjects were stratified in relation to the using state of TNF blocker. We evaluated collected clinical and radiographic parameters at two different time points. Then we compared radiographic progression between groups. To use the mSASSS, cervical and lumbar spinal radiographs were examined. Univariable and multivariable regression analyses were done after adjusting for potential confounding factors, such as age, gender, disease duration, history of eye involvement, history of peripheral arthritis, juvenile onset AS, baseline CRP level, baseline mSASSS, and NSAID intakes.

Results: The mean age (SD) of the AS patients was 37.9(18.3) years, and the mean disease duration (SD) was 17.3 (18.3) years at baseline. In this data, 88.7% of the patients were male, and 96.9% were HLA–B27 positive. 40.7% of the patients had history of peripheral arthritis. Of these patients, 44.1% (269 patients) had received TNF blockers. The mean mSASSS unit (SEM) at baseline was significantly different between groups (TNF blocker naïve 17.6 ± 0.9 vs TNF blocker user 21.0 ± 1.2, $P = 0.02$). Radiographic follow-up duration from the first mSASSS assessment were comparable (4.9 ± 0.1 vs 5.1 ± 0.1, $P = 0.28$). However, Patients treated with TNF blockers had a higher CRP level (2.5 ± 0.2 vs 1.6 ± 0.1, $p < 0.01$) at baseline. On simple analysis, the TNF blocker naïve patients had comparable radiographic progression to those with TNF blocker (3.7 ± 0.5 vs 3.7 ± 0.8, $p = 0.99$). After adjustment for multiple comparisons by the Bonferroni correction, gender, history of peripheral arthritis, disease duration, baseline mSASSS, and NSAID intake had statistically significance in our registry. However, the radiographic progression between groups was no significant difference (OR 0.60, [95% CI 0.22–4.72], $P = 0.44$).

Conclusion: Treatment with TNF inhibitors has no influence on radiographic progression in AS.

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Effects of Self-Management Model on the Disease-Related Knowledge, Joint Function and Quality of Life in Patients with Ankylosing Spondylitis. Pingping Zhang[1], Jun Qi[2], Zhiming Lin[3], Minjing Zhao[2] and Jieruo Gu[3]. [1]Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, [2]The Third Affiliated Hospital of Sun Yat-sen University, guangzhou, China, [3]The Affiliated Third Hospital of Sun Yat-san University, Rheumatology, Guangzhou, China.

Background/Purpose: Ankylosing spondylitis is a kind of chronic inflammatory diseases, inflammation of the sacroiliac joint and spine attachment points are the main symptoms, as a kind of chronic disease, the patients' self-management is very importantTo investigate and evaluate the effect a new kind of health management model on disease-related knowledge, joint function and quality of life in patients with ankylosing spondylitis(AS).

Methods: 84 patients with AS Who have signed the informed consent in China were included in this study. All the patients satisfied the ACR classification criteria for AS.Doctors and AS patients co-builded a club which was a new kind of self-management model in the follow-up 6 months. In the club, the medical staff could give AS patients psychological guidance, pain guidance, dietary guidance and life guidance, patients could also give others positive impact. before and after six months of this management model of club, we evaluate the disease-related knowledge, compliance, joint function, psychological quality, and life quality by questionnaire of AS health management and Bath AS Function Index (BASFI).

Results: The questionnaire score of disease-related knowledge in AS patients increased significantly from (58.14 ± 11.62) to (74.77 ± 10.16) ($p = 0.000$); In the long process of treatment, many AS Patients despair and feel hopeless because they thought it impossible to Work like a healthy person, but after this management model, the ration has been significantly reduced from14.1% (11/84) to 3.57% (3/84)($P = 0.017$). Meanwhile, patients willing to cooperate with doctors and face life actively increased significantly from 72.62% (61/84) to 90.48% (76/84), ($P = 0.003$).Patients unwilling to insist long-term drug therapy for fear of side effects dropped significantly from 35.71% (30/84) to 4.76% (4/84) ($P = 0.000$);Patients who quit smoking and drinking, and could diet reasonably rose significantly from 45.24% (38/84) to 79.76% (67/84), ($P = 0.000$); BASFI score improved from 5.25 ± 1.93 to 3.90 ± 1.87 ($P = 0.000$); Patients with satisfaction of health education increased significantly from 72.62% (61/84) to 100% (84/84), $P = 0.000$.

Conclusion: AS club could mobilize patients' initiative, make them cooperate actively with doctors. By this new kind of management model, AS patients could gain more knowledge about health and improve their joint function; And what's more, this kind of management model also increased the patients' ability of self-management, improved their life quality.

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Assessment of Spondyloarthritis International Society Endorsed Recommendations for Early Referral of Patients Suspected for Axial Spondyloarthritis. Denis Poddubnyy[1], Astrid van Tubergen[2], Robert Landewé[3], Joachim Sieper[1] and Désirée van der Heijde[4]. [1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [4]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: There is a substantial gap of 5 to 8 years between the onset of symptoms (usually back pain) and the diagnosis of axial spondyloarthritis (SpA). One of the reasons for such a delay is a late referral of patients to a rheumatologist by general practitioners and other physicians encountering patients with back pain. Several referral approaches have been proposed and tested over the last 10 years, however, no universal and widely accepted referral strategy exists until now. The aim was, therefore, to develop consensual recommendations under the umbrella of the Assessment of Spondyloarthritis international Society (ASAS) for early referral of patients suspected for axial SpA by primary care physicians or non-rheumatology specialists.

Methods: Development of the ASAS endorsed referral recommendations for patients suspected for axial SpA by primary care physicians or non-rheumatology specialists consisted of the following phases: 1) systematic literature review, 2) the first Delphi round aimed at identification of unmet needs and development of the referral parameter candidate list, 3) the second Delphi round aimed at identification of the most useful combination of the referral parameters, 4) final discussion on the proposal for the recommendations and voting on it at ASAS annual meeting in 2014.

Results: The following consensus on the referral recommendation was achieved within ASAS as a result of the Delphi process and final voting.

"Patients with **chronic back pain (duration ≥3 months)** and **back pain onset before 45 years of age** should be referred to a rheumatologist if at least one of the following parameters is present:

- Inflammatory back pain;
- HLA-B27 positivity;
- Sacroiliitis on imaging if available (X-rays or magnetic resonance imaging);
- Peripheral manifestations (arthritis, enthesitis, dactylitis);
- Extra-articular manifestations (psoriasis, inflammatory bowel disease, uveitis);
- Positive family history for SpA;
- Good response to non-steroidal anti-inflammatory drugs;
- Elevated acute phase reactants."

Conclusion: A consensual ASAS endorsed referral recommendation for patients suspected for axial SpA by primary care physicians or non-rheumatology specialists was developed as a flexible and universal tool to be used in clinical practice. The diagnostic value of this tool applied in different settings should be determined in future studies.

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Patients with Non-Radiographic Axial Spondyloarthritis and Ankylosing Spondylitis Demonstrate the Same Clinical Disease Course over Two Years: Results from the Gespic Cohort. Denis Poddubnyy[1], Hildrun Haibel[1], Jürgen Braun[2], Martin Rudwaleit[1] and Joachim Sieper[1]. [1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]Rheumazentrum Ruhrgebiet, Herne, Germany.

Background/Purpose: In cross-sectional studies it has been demonstrated that non-radiographic axial spondyloarthritis (nr-axSpA) does not differ from ankylosing spondylitis (AS) with respect to clinical signs of disease activity. Prospective studies comparing clinical course of the disease over time are, however, lacking. The purpose of this analysis was to investigate the clinical course of the disease over two years in patients with nr-axSpA in comparison to AS.

Methods: In total, 210 patients with early axSpA (115 with AS according to the modified New York criteria and symptom duration ≤10 years, and 95 with nr-axSpA and symptom duration ≤5 years) with complete radiographic data over 2 years from the German Spondyloarthritis Inception Cohort (GESPIC) were included. Clinical assessment, which included standard disease activity (BASDAI, C-reactive protein – CRP), function (BASFI) and spinal mobility (BASMI) assessments, as well as therapy recording, was performed at baseline and every 6 months thereafter. Starting from the visit at month 6, the ASDAS-CRP and the ASAS NSAID intake score were calculated.

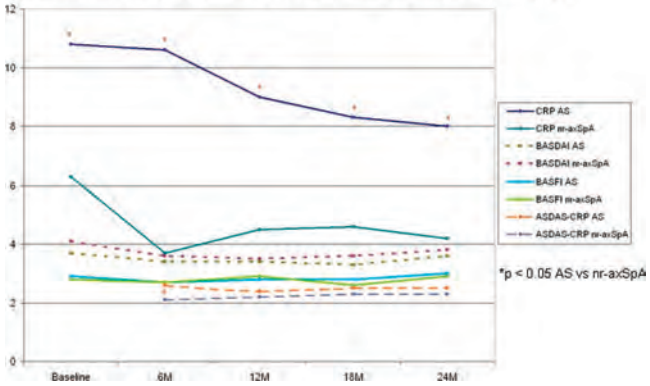
Results: The majority of patients were included in GESPIC and followed-up prior to marketing authorisation of TNF blockers for AS and nr-axSpA. However, 17 AS patients (14.8%) and 5 nr-axSpA patients (5.3%) received at least one prescription of a TNF blocker during 2 years of follow-up and were excluded from the further analysis. Remaining patients with nr-axSpA (n=90) did not differ from AS patients (n=98) with respect to the BASDAI and the BASFI at any time point during 2 years of follow-up (figure). AS patients had however significantly higher level of CRP at all time points but ASDAS-CRP was significantly higher in AS at 6M only (figure).

There were also no substantial differences in the treatment between two groups. Spinal mobility (as measured by BASMI) was generally better in nr-axSpA as compared to AS, but this difference was statistically significant only at two time points (6 and 12 months).

Among all patients who did not receive a TNF-Blocker during 2 years of follow-up, 10 patients with nr-axSpA and 22 patients with AS had at baseline BASDAI≥4 and elevated CRP. Low disease activity state at at least 2 time points during 2 years of the follow-up as defined by BASDAI<4 was achieved by 57% of nr-axSpA and by 40% of AS patients, BASDAI<4 and normal CRP by 25% and 13%, BASDAI≤2 by 13% and 13%, and ASDAS inactive disease by 25% and 0% of nr-axSpA and AS patients, respectively. All differences were statistically non-significant.

Conclusion: Patients with nr-axSpA and AS demonstrated the same course of the disease over 2 years as evaluated by the level of symptoms, functional status and NSAIDs treatment (except anti-TNF). Only a small proportion of patients with nr-axSpA and AS reached a stricter definition of low disease activity over two years of follow-up without TNF-blocker treatment.

Figure. Diasease activity parameters and functional status over time in patients with nr-axSpA (n=90) and AS (n=98) in the GESPIC cohort



Disclosure: D. Poddubnyy, None; **H. Haibel**, None; **J. Braun**, None; **M. Rudwaleit**, None; **J. Sieper**, None.

2594

Differences in Localization and Activity of the Entheseal Involvement Between Non-Radiographic and Radiographic Axial Spondyloarthritis By the Ultrasound Assessment. Marketa Fojtikova[1], Karel Pavelka[1], Sarka Forejtova[2] and Jindra Gatterova[3]. [1]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [2]Institute of Rheumatology, Prague, Czech Republic, [3]Institute of rheumatology, Prague 2, Czech Republic.

Background/Purpose: Inflammatory involvement of peripheral enthesis belongs to an important sign of spondyloarthritis (SpA). It may occur in patients with long-term as well as newly diagnosed disease and in those with definite ankylosing spondylitis (AS) and without radiological sacroiliitis, non-radiographic axial SpA (nr-ax-SpA).

In our work we look for active and non-active entheseal changes by an ultrasound detection in four localization: Achilles tendon, patellar ligament, plantar aponeurosis and quadriceps insertion in patients suffering from newly diagnosed nr-ax-SpA and AS.

Methods: The total of 34 patients with newly diagnosed SpA (with established diagnosis maximally within 2 years) underwent the clinical and ultrasound examination. Disease activity was determined by ASDAS CRP and BASDAI. Conventional two-dimensional power Doppler ultrasonography was performed by one radiologist/musculoskeletal ultrasound specialist. Six ultrasound changes like tendon structural changes and thickening of tendon insertion, calcifications, bone erosions, bursitis, and Doppler signal was determined in four locations and Naredo et al. classification for active/non active lesions was used. The $\chi 2$ test for comparison each group, Fisher exact test and correlation for activity a tendon changes was used.

Results: Altogether, 26 nr-ax-SpA patients and 8 AS patients BASDAI 3.27±0.56 and 1.95±0.2 respectively, ASDAS CRP 1.88±0.63 and 2.07±0.29 respectively, underwent the ultrasound detection for entheseal changes.

When we look for any changes in all tested tendons there were non-active changes in only 37.90 % nr-ax-SpA compared to 71.88 % AS ($p < 0.0001$). However the active changes were distributed evenly in nr-ax-SpA and AS, 4.80 % and 7.81%, respectively.

The Doppler positive changes in any locations were found in 19.20% nr-ax-SpA and 37.5% AS (p=ns), whereas the non-active changes in 280.77% nr-ax-SpA a 100% AS (p=ns).

The Achilles tendon and the patellar ligament were the most common involved sites in both patients groups, nr-ax-SpA (32.70 and 26.92%, respectively) and AS (50.0 and 25.0% respectively), all p=ns.

There is no correlation between ASDAS CRP and/or BASDAI and active and non-active lesions in both group.

Conclusion: Our study demonstrates the usefulness of soft tissue ultrasound for active and non-active tendon changes in SpA. Interestingly, both patients with nr-ax-SpA and those with definite AS develop the same number of active entheseal changes, but non-active entheseal changes are more common AS. The presence of active and non-active entheseal changes do not correlate with disease activity.

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2595

Using Iphone Compass Application for the Assessment of Cervical Rotation in Patients with Ankylosing Spondylitis. Gokce Kenar, Berrin Zengin, Handan Yarkan, Pinar Cetin, Ismail Sari, Fatos Onen, Merih Birlik and Nurullah Akkoc. Dokuz Eylul University School of Medicine, Izmir, Turkey.

Background/Purpose: Cervical rotation reflects restriction of mobility in axial disease in ankylosing spondylitis (AS) and it can be assessed in several approaches based on the use of either an inclinometer, a goniometer or a tape measure. New generations of smartphones are equipped with a gyroscope and an accelerometer which in combination with a smartphone's operating system or specific software applications can be used for various inclinometric functions. The aim of the study was to assess the reliability and validity of using iphone built in compass application, as compared to using goniometer in the assessment of cervical rotation patients with AS.

Methods: The study sample included 20 AS patients (6 females, 14 males) with a mean age of 47.8 (± 10.2). BASMI scores were obtained from patient charts. Two examiners measured cervical rotation of each patient using iPhone4 compass application and also goniometer, twice with each method. A cap with a velcro patch on top and an iphone case with a Velcro patch on the bottom were used to stabilize the iphone's position during measurements. Intra-rater and inter-rater reliability were examined with intra-class correlation coefficients (ICC). The agreement between the two methods was assessed by by Bland-Altman method.

Results: The mean BASMI score of AS patients was 43 (± 22.7). The mean scores for BASDAI, ASDAS and BASFI were 3.7 (± 19.9), 2.9 (± 0.96) and the 3.5 (± 2.4), respectively. We observed an excellent intra and inter-rater reliability in the whole study sample for both methods (Table 1 and Table 2). Bland-Altman analysis also showed a good agreement between the two methods (iphone-goniometer) with a mean difference (bias) of −1.7 for examiner 1 (95% CI −5.9 to −2.7) and -4.6 for examiner 2 (95% CI -8.9 to -0.4). Upper and lower limits of agreement were 16.6 (95% CI 9 to 24.2) and −19.9 (95% CI −27.4 to −12.3), for examiner 1 and 13.1(95% CI 5.7 to 20.4) and -22.3 (95% CI -29.6 to -15) for examiner 2.

Conclusion: Using iPhone compass application is a simple and accessible way of measuring cervical rotation in patients with AS. Measurements obtained with iphone show excellent intra and inter-rater reliability and a very good agreement with measurements obtained with goniometer.

Table. 1 Mean cervical rotation measurements (degrees) with iPhone and goniometer and Intra-rater reliability for both methods

Method	Examiner 1				Examiner 2			
	Trial 1 (Mean ± SD)*	Trial 2 (Mean ± SD)*	ICC	95% CI for ICC	Trial 1 (Mean ± SD)*	Trial 2 (Mean ± SD)*	ICC	95% CI for ICC
Goniometer	46.8 ± 16.5	46.3 ± 16.5	0.98	0.97–0.99	46.5 ± 16.9	46.4 ± 16.6	0.98	0.97–0.99
iPhone	48.3 ± 22.1	48.1 ± 21.3	0.98	0.96–0.99	51.8 ± 21.3	50.3 ± 20.1	0.96	0.90–0.98

*Mean of the right and left cervical rotation

Table 2 Mean cervical rotation measurements (degrees) with iPhone and goniometer and inter-rater reliability for both methods

	Examiner 1 (Mean ± SD)*	Examiner 2 (Mean ± SD)*	ICC	95% CI
Goniometer	46.6 ± 16.44	46.5 ± 16.91	0.99	0.97–0.99
iPhone4	48.2 ± 21.6	51.05 ± 20.49	0.93	0.84–0.97

*Mean of the two measurements by the same examiner

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2596

Similarities and Differences Between Axial and Peripheral Predominant Forms in patients with Early Spondyloarthritis (SpA): Results from the Esperanza Cohort. . Pilar del Río-Martínez[1], Victoria Navarro-Compán[2], Concepción Castillo-Gallego[2], M. Carmen Castro[3], Eduardo Collantes-Estévez[3] and Eugenio de Miguel[2]. [1]Rheumatologist, Zaragoza, Spain, [2]Rheumatologist, Madrid, Spain, [3]Rheumatologist, Córdoba, Spain.

Background/Purpose: Based on the predominant manifestation of the disease, the ASAS classification criteria for spondyloarthritis (SpA) distinguish two clinical forms:

- Axial SpA, including non-radiographic SpA and Ankylosing Spondylitis (AS).
- Peripheral SpA.

Although both forms are considered as part of the same disease, published data are limited, especially in early disease. The purpose of this study is to describe and compare the characteristics of patients fulfilling the ASAS criteria for axial SpA versus peripheral SpA in patients with recent symptoms onset.

Methods: -Population.- Baseline dataset from the early SpA ESPERANZA cohort was used, with the following referral criteria: Age <45 years, symptoms duration 3–24 months and with inflammatory back pain (IBP) or asymmetrical arthritis or spinal/joint pain plus ≥1 SpA features.

-Inclusion criteria.- Patients fulfilling the ASAS classification criteria for SpA.

-Outcome.- To compare socio-demographic and disease characteristics between patients with axial SpA and patients with peripheral SpA.

-Statistical analyses: Variables were compared using Student t test (continuous) or Chi-square test (categorical).

Results: Data from 377 patients were analysed. Two hundred ninety (77.2%) patients were classified as axial SpA (109 AS and 182 non-radiolographic SpA) and 86 (22.8%) patients as peripheral SpA. Table 1 shows the results (mean ± SD or relative frequency) for the comparison of demographic and disease characteristics between groups. Age, sex and disease activity scores were similar in both groups. However, axial SpA was more related to a delay in referral time, uveitis and positive HLA-B27 while peripheral SpA was associated with enthesitis, psoriasis, dactylitis and inflammatory bowel disease (IBD).

Conclusion: Early SpA patients with predominant axial symptoms have a higher delay in the referral to rheumathologist than patients with peripheral symptoms. However, the degree of disease activity is similar in both groups. Uveitis and HLA-B27 are more frequent in patients with predominant axial symptoms while psoriasis, enthesitis, dactylitis and IBD are more frequent in patients with peripheral involvement.

Table 1 shows mean ± SD and p value

Characteristic	Axial SpA N (%)= 291 (77.2)	Peripheral SpA N (%) = 86 (22.8)	P value
Age (years)	32.0 ± 7.0	32.8 ± 7.8	0.4
Male	191 (65.6)	50 (58.1)	0.2
Symptoms duration (months)	13.0 ± 6.7	9.3 ± 6.2	**<0.001**
Enthesitis	57 (19.6)	43 (50)	**<0.001**
Psoriasis	33 (11.3)	28 (32.6)	**<0.001**
Dactylitis	16 (5.5)	28 (32.6)	**<0.001**
IBD	9 (3.1)	10 (11.6)	**0.001**
Uveitis	23 (7.9)	1 (1.2)	**0.02**
Diarrhea, cervicitis, urethritis	11 (3.78)	5 (5.8)	0.4
Family history	101 (34.7)	31 (36)	0.8
HLA-B27	219 (75.3)	28 (32.6)	**<0.001**

CRP (mg/L)	10.8 ± 15.2	13.7 ± 31.2	0.3
ESR (mmHg)	13.6 ± 13.5	14.1 ± 13.4	0.8
SJC	0.3 ± 1.3	1.4 ± 2.4	**<0.001**
VAS (0–10) physician	2.9 ± 2.2	2.4 ± 2.1	0.1
VAS (0–10) patient	4.2 ± 2.7	3.1 ± 2.5	**<0.01**
BASDAI	3.8 ± 2.3	3.5 ± 2.3	0.2

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2597

Impact of Repeating Imaging of the Sacro-Iliac Joints over One Year on the Classification According the ASAS Axial Spa Criteria of Patients. Pauline Bakker[1], Manouk de Hooge[1], Rosaline van den Berg[1], Floris van Gaalen[1], Monique Reijnierse[1], T.W.J. Huizinga[1] and Désirée van der Heijde[2]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: It is known that in axial spondyloarthritis (axSpA) inflammatory lesions on MRI of the SI joints (MRI-SI) can change over time. The usefulness of repeating imaging in the diagnostic process is unclear. The aim is to investigate how patients with short-term chronic back pain are classified by the ASAS axSpA- criteria at baseline and after 1 year follow-up, with a focus on the role of imaging.

Methods: Patients in the SPACE cohort (back pain: ≥ 3 months, ≤ 2 years, onset < 45 years) with (suspicion of) axSpA underwent MRI and X-rays of the sacroiliac joints at baseline and 1 year follow-up. Only patients with complete MRI- and X-SI data at both baseline and year 1 were included in the analysis (n=80). MRI-SI and X-SI were scored independently by 3 well-calibrated readers according to the ASAS definition for a positive MRI and the mNY-criteria. Readers were blinded for patient characteristics and time sequence. Fulfillment of ASAS or mNY criteria was considered positive if 2/3 readers agreed. For each timepoint, patients were classified according the ASAS axSpA criteria and grouped in different arms (imaging arm: mNY+/− or MRI+/−; clinical arm, fulfillment of both arms and possible axSpA). In contrary to the normal application of the criteria, where a positive feature remains positive, we grouped patients according to the finding at one year, ignoring previous imaging findings.

Results: At baseline, 41/80 patients (32.8%) fulfilled the ASAS criteria (clinical arm: 22; imaging arm: 12, both arms: 7) (table). After 1 year, 3 additional patients fulfilled the criteria (2 clinical arm; 1 imaging arm). After 1 year, in 5 patients MRI-SI became positive and 1 patient fulfilled the mNY criteria. On the other hand, MRI-SI became negative after 1 year in 4 other patients. Of these patients, 3 still fulfilled the ASAS criteria (imaging arm (mNY+, n=1) or clinical arm (n=2)). Only 1 patient (classified axSpA at baseline) would be missed if imaging would have been performed at 1 year only (due to a negative MRI).

Conclusion: With one year longer symptom duration, 3/39 (8%) of the possible SpA patients could be classified additionally as axSpA because of additional SpA features (5%) or positive MRI (3%), while 1/41 (2%) of the axSpA patients would not be classified due to a normal MRI. Therefore, our data show the robustness of the axSpA criteria and does not support repeating imaging after one year.

			1 year							
			Both arms			Imagingarm				
			mNY+ MRI+	mNY+ MRI−	mNY− MRI+	mNY+ MRI+	mNY+ MRI−	mNY− MRI+	Clinical arm	Possible SpA
Baseline	Both arms	mNY+MRI+	2	1						
		mNY+MRI−								
		mNY−MRI+			2				2	
	Imaging arm	mNY+MRI+	1			2				
		mNY+MRI−		1			4			
		mNY−MRI+			2	1				1
	Clinical arm				3				19	
	Possible SpA							1	2	36

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2598

Disease Characteristics Associated with the Presence of Dactylitis in Patients with EARLY Spondyloarthritis: Results from Esperenza Cohort. Maria Isabel Tévar Sánchez[1], Victoria Navarro-Compán[2], Raquel Almodóvar González[3], Maria Pilar Fernández Dapica[4], Pedro Zarco[5] and Eugenio De Miguel[6]. [1]Hospital Vega Baja, Orihuela, Alicante, Spain, [2]University Hospital La Paz, Madrid, Spain, [3]Hospital Universitario Fundación Alcorcón, Madrid, Spain, [4]University Hospital 12 de Octubre, Madrid, Spain, [5]Fundación Hospital Alcorcon, Alcorcon, Madrid, Spain, [6]Department of Rheumatology, Hospital Universitario La Paz, Madrid, Spain.

Background/Purpose: Dactylitis is a typical manifestation in patients with SpA. Despite dactylitis has traditionally been related to the coexistence of psoriasis and peripheral arthritis, it was included as SpA feature for both (axial and peripheral) ASAS classification criteria. However, data supporting this is scarce, especially in patients with recent onset. The objective of this study was to determine the prevalence of dactylitis and which disease characteristics are associated with its presence in patients with early SpA.

Methods: Baseline dataset from the EsPeranza cohort (<45 years, symptoms duration 3–24 months and with inflammatory back pain -IBP- or asymmetrical arthritis or spinal/joint pain plus ≥1 SpA features) was analysed. For this study, 609 patients diagnosed of SpA by their physician were included. Logistic regression analysis was used to investigate the association between disease characteristics and the presence of dactylitis. These characteristics included family history of SpA, clinical manifestations (chronic back pain –CBP-, inflammatory back pain–IBP-, peripheral arthritis, enthesitis, uveitis, psoriasis, nail lesions, inflammatory bowel disease –IBD- and urethritis or cervicitis), activity parameters (SJC, physicianxs VAS, patientxs VAS and BASDAI), metrology (BASMI), function (BASFI), lab tests (HLA B27, ESR and CRP), and imaging (sacroiliitis on x-Ray or MRI by ASAS definition).

Results: Fifty eight (10.5%) patients had current or previous dactylitis. The presence of dactylitis was associated with peripheral arthritis, enthesitis, psoriasis, nail lesions, SJC, physicianxs VAS and CRP in the univariable analysis. Moreover, CBP, IBP and sacroiliitis were associated with absence of dactylitis. No significant differences were found for the rest of variables. In the multivariable analysis the presence of dactylitis was associated with peripheral arthritis, enthesitis, psoriasis and physicianxs VAS (Table). However, 14 (24%) patients did not have peripheral arthritis but had axial symptoms/signs.

Further, patients with dactylitis were classified as patients with dactylitis and psoriasis (n=19; 32.8%) and patients with dactylitis and no psoriasis (n=39; 67.2%). Disease characteristics were compared between both groups. Male were more frequent in the psoriasis group (84% vs 51%;$p<0.05$). The group without psoriasis had higher frequency of CBP, IBP, enthesitis, HLA-27 and sacroiliitis but these differences did not reach statistical significance.

Conclusion: Dactylitis is a frequent manifestation in patients with SpA even at early stages of the disease. Its presence is mainly associated with peripheral manifestations and psoriasis. However, the majority of patients with dactylitis do not have psoriasis and 24% of them have axial manifestations in absence of peripheral arthritis.

Table: Association between SpA characteristics and the presence of dactylitis

Characteristic	OR	95% CI
Chronic back pain	0.44	0.12 to 1.07
Inflammatory back pain	0.44	0.18 to 1.06
Peripheral arthritis	*4.83*	*2.00 to 11.7*
Enthesitis	*2.49*	*1.24 to 5.03*
Psoriasis	*3.62*	*1.63 to 8.04*
Nail lesions	0.61	0.12 to 3.18
Diarrhea, cervicitis, urethritis	2.17	0.54 to 8.77
CRP	0.99	0.97 to 1.01
ESR	1.01	0.99 to 1.03
Sacroiliitis	1.26	0.52 to 3.07
Physicianxs VAS	*0.82*	*0.70 to 0.96*

Disclosure: M. I. Tévar Sánchez, None; **V. Navarro-Compán**, None; **R. Almodóvar González**, None; **M. P. Fernández Dapica**, None; **P. Zarco**, None; **E. De Miguel**, None.

2599

Do Patients Diagnosed As Axial Spondyloarthritis (AxSpA) Who Have Primary Inefficacy to Anti-TNF Really Have AxSpA? a Five-Year Follow-up Study of 27 Patients with Primary Inefficacy to Anti-TNF. Sandra Kossi[1], Sabrina Dadoun[2], Bruno Fautrel[2], Maxime Dougados[3] and Laure Gossec[4]. [1]Hopital La Pitie Salpetrière, Paris, France, [2]UPMC GRC08, Paris 06 University, Pitié Salpétrière Hospital, Paris, France, [3]INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France., Paris, France, [4]Sorbonne Universités, UPMC Univ Paris 06, GRC-08, Institut Pierre Louis d'Epidémiologie et de Santé Publique, paris, France.

Background/Purpose: The diagnosis of AxSpA is not easy and there are cases of overlap with fibromyalgia for example. Anti-TNF have been shown to have great efficacy in AxSpA, and primary inefficacy is rare. Do patients who have primary inefficacy to anti-TNF, really have a diagnosis of AxSpA?

Objective: To assess the evolution and final diagnosis of all patients with primary inefficacy to anti-TNF in AxSpA over a period of two years in one tertiary referral center, with a follow up of five years.

Methods: Systematic retrospective study of all patients receiving an anti-TNF for AxSpA in one tertiary referral centre (ref). Patients had AxSpA according to the rheumatologist and were started on a first course of anti-TNF according to usual practice. Primary inefficacy was defined by the rheumatologist's opinion after three months of treatment by anti-TNF, when the treatment was then discontinued. Five years later, these patients were recontacted and were seen in outpatient clinic if possible, filled in questionnaires including FIRST for fibromyalgia, and a final diagnosis was defined.

Results: Of 222 patients receiving a first anti-TNF for AxSpA, 27 (12.2%) were considered as having primary inefficacy to their first anti-TNF. The characteristics of these patients were slightly different from the others, with more females (48 vs 27%, p=0.04), older age (46 vs 40 yrs; p=0.04), higher BASFI (68 vs 42, p=0.001) and less increased CRP (50% vs 78%, p=0.008). Among the 27 patients, a second anti TNF was prescribed for 16 (59.2%) patients, 7 (7/16=43.7%) had primary inefficacy to the second anti-TNF and retention rate of the second anti-TNF at one year was 50%.

At the 5 year follow-up, 14 patients were seen in outpatient clinic and 9 follow-up medical files were available; 4 patients could not be evaluated (2 were lost to follow-up and 2 refused).

The diagnosis of AxSpA was confirmed for 20/23 (86.9%) patients according to the ASAS criteria and 23/23 (100%) patients according to the rheumatologist; but 16/23 (69.6%) had at least one other cause of pain/symptoms: 10 (43.5%) had osteoarthritis, 7 (30.4%) patients had depression and 3 (13.0%) had fibromyalgia.

Conclusion: Primary inefficacy to anti-TNF in AxSpA is rare, and patients with primary inefficacy have slightly different characteristics from the other AxSpA patients. Long-term follow-up indicates most of these patients have a definite diagnosis of AxSpA but often have other causes of pain/symptoms. We suggest patients with primary inefficacy to anti-TNF should be screened for comorbidities like fibromyalgia, osteoarthritis or depression that may interfere with AxSpA impact and assessment.

Reference

Dadoun and al. Switching between tumor necrosis factor blockers in spondyloarthritis : a retrospective monocenter study of 222 patients. Clin Exp Rheumatol;29:1010–3

Disclosure: S. Kossi, None; **S. Dadoun**, None; **B. Fautrel**, None; **M. Dougados**, None; **L. Gossec**, None.

2600

Gender-Attributable Differences in Outcome of Ankylosing Spondylitis: Long-Term Results from the Outcome in Ankylosing Spondylitis International Study. Casper Webers[1], Ivette Essers[1], Sofia Ramiro[2], Carmen Stolwijk[3], Robert Landewé[4], Désirée van der Heijde[5], Filip van Den Bosch[6], Maxime Dougados[7] and Astrid van Tubergen[3]. [1]Maastricht University Medical Center, Maastricht, Netherlands, [2]Amsterdam Rheumatology Center/University of Amsterdam, Amsterdam, Netherlands, [3]Maastricht University, Maastricht, Netherlands, [4]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Department of Rheumatology Ghent University Hospital, Ghent, Belgium, [7]Paris-Descartes University, Paris, France.

Background/Purpose: In ankylosing spondylitis (AS), gender-attributable differences have been reported with respect to clinical and radiographic outcome. However, longitudinal studies exploring gender-attributable differences in the outcome of AS are scarce, and have limited follow-up. The aim of the present study was to investigate gender-attributable differences with respect to clinical outcomes (disease activity, function and quality of life (QoL)) and radiographic damage in patients with AS over time.

Methods: Clinical and radiological data from patients included in the Outcome in AS International Study (OASIS) were used. Disease activity was assessed by the Bath AS Disease Activity Index (BASDAI), the AS Disease Activity Score (ASDAS), and C-reactive protein (CRP); physical function by Bath AS Functional Index (BASFI); QoL by the Short Form-36 (SF-36), ASQoL and EuroQoL; radiographic damage by the modified Stoke AS Spine Score (mSASSS). First, cross-sectional comparative analyses were done at baseline. Second, separate models were created to assess gender-attributable differences on each outcome measure over time using time-adjusted generalized estimation equations (GEE). All analyses were performed in the total population and in those patients who completed the total 12 years of follow-up.

Results: 216 patients (154 (72.3%) men, mean age 43.6 years (SD 12.7), symptom duration 20.5 years (SD 11.8), mean follow up duration 8.3 years (SD 4.1)) were included. At baseline, male compared with female patients had lower self-reported disease activity (BASDAI 3.2 vs. 3.9, p=0.03) but more radiographic damage (mSASSS 13.8 vs. 6.5, p=0.02). No significant differences in other clinical parameters between gender were found at baseline. In univariable analysis, a significant association between male gender and better QoL (lower ASQoL and higher EuroQoL), and between male gender and more radiographic damage (higher mSASSS) over time was found.

Also in multivariable analysis, male gender was, compared with female gender, significantly associated with a better ASQoL (B= -1.10, 95%CI -2.11 to -0.09, p=0.03), and in a separate multivariable analysis also with higher mSASSS over time (B=8.52, 95%CI 4.55 to 12.50, p<0.01). Similar results were found for the 12-year completers.

Conclusion: In this longstanding observational cohort study in patients with AS, no gender-attributable differences in disease activity and function over time were found. However, male gender, compared with female gender, was found to be associated with more radiographic damage, but also better QoL. It is likely that gender differences in AS are determined by both biological and psychological factors, and that male and female patients differ in the way they cope with pain and disability.

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2601

Serum Biomarkers Associated with Changes in ASDAS and MRI Following Treatment of Ankylosing Spondylitis with Golimumab. Robert D. Inman[1], Xenofon Baraliakos[2], Kay-Geert A. Hermann[3], Jürgen Braun[2], Atul A. Deodhar[4], Désirée van der Heijde[5], Stephen Xu[6] and Benjamin Hsu[6]. [1]University of Toronto and Toronto Western Hospital, Toronto, ON, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Charité Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany, [4]Oregon Health and Sciences University, Portland, OR, [5]Leiden University Medical Center, Leiden, Netherlands, [6]Janssen Research & Development, LLC., Spring House, PA.

Background/Purpose: Serum biomarkers that can predict subsequent clinical or imaging outcomes would aid decision-making in the management of ankylosing spondylitis (AS). Using data from the golimumab (GLM) study, GO-RAISE, in patients with active AS, we analysed correlations between multiple serum biomarkers and inflammation as detected by magnetic resonance imaging (MRI) and AS Disease Activity Score (ASDAS).

Methods: In GO-RAISE, patients with moderately to severely active AS were randomized to SC GLM 50mg, 100mg, or PBO q4wks. PBO-treated patients crossed over to receive GLM at wk16 or 24. Spinal MRIs in the sagittal plane were acquired using 1.5T scanners with T1 and short tau inversion recovery (STIR) sequences at BL and wk14. 98 patients were scored for activity (ASspiMRI-a) and structural (ASspiMRI-c) scores. Radiographs and MRIs were assessed by 2 readers who were blinded to treatment and image time order. Mean scores were used for analyses. Sera were collected from 140 patients at baseline and wk14 for analysis of markers by ELISA and/or using a multiplex platform (Rules Based Medicine). Spearman correlation analyses with Bonferoni p-value adjustment and logistic regression were conducted to assess the relationship between 76 serum biomarker levels and, ASDAS using C-reactive protein (ASDAS), ASspiMRI-a, or MRI-c score at various time points.

Results: Baseline ASDAS showed significant correlations with serum biomarkers for inflammation (IL-6, ICAM-1, haptoglobin, amyloid P) and lipid metabolism (Complement C3). BL IL-6 or TIMP-1 correlated with the reduction of ASspiMRI-a at wk14 in GLM-treated patients (Table). Wk4 change in IL-6 and C3 also showed correlation with change in ASspiMRI-a at wk14. Development of new fatty degeneration in the spine at wk14 correlated with BL biomarkers involved in lipid metabolism (leptin, C3) and tissue remodeling (TIMP-1). Previously described predictors such as insulin, MMP-3, VEGF, or bone resorption markers did not have significant correlations with clinical or imaging outcomes.

Conclusion: This analysis suggests that serum biomarkers IL-6, TIMP-1, and C3 may be linked to a reduction in spinal inflammation in AS patients following GLM treatment. In addition, ICAM-1, haptoglobin and amyloid P correlate with baseline disease activity and may implicate novel roles for these factors in AS-related inflammation.

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Prevalence of Subclinical Atherosclerosis in Patients with Spondyloarthritis without Clinically Evident Cardiovascular Disease Using Carotid Intima-Media Thickness. Elena Alonso Blanco-Morales[1], Carmen Bejerano[2], Carlos Fernandez-Lopez[3], Natividad Oreiro[4], Javier De Toro[4], Francisco J. Blanco Garcia[3] and Jose A Pinto-Tasende[3]. [1]INIBIC. Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, [2]INIBIC, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, [3]Rheumatology Department, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain, [4]Rheumatology Department, A Coruña, Spain.

Background/Purpose: AS and PsA patients without clinically evident cardiovascular disease have a high prevalence of subclinical cardiovascular disease in form of increased carotid intima-media thickness (IMT) and carotid plaques compared to matched controls.

To evaluate subclinical atherosclerosis by determining carotid IMT and the presence of atheromatous plaques in a sample of patients with PsA and AS, and analyze its relationship with genetic, demographic, clinical and analytical characteristics.

Methods: Observational and cross-sectional study of 86 spondyloarthritis patients (48 PsA according CASPAR classification criteria and 38 AS according to the New York modified criteria) were randomly selected from our cohort in 2013. We recorded age and sex of patients, disease duration, joint count, VAS for pain and for global disease activity, BASDAI and BASFI score, ESR, CRP, HLA-B27 and Cw0602, CV risk factors as systolic and diastolic blood pressure, smoking status, glycemia, lipid profile and BMI. IMT (mm) and carotid plaques were measured in the right common carotid artery and the study was performed using high-resolution B-mode ultrasound. Continuous variables were compared using Student's *t*-test or Mann-Whitney U test. Proportions were compared by chi-square test or Fisher's exact test. Correlation between carotid IMT and continuous variables was tested via estimation of Pearson's partial correlation coefficient adjusted by age at the time of the study. Two-sided *P* values less than 0.05 were considered to indicate statistical significance. Statistical analysis was performed with the SPSS 17.0 program. It was considered $p < 0.05$ as significant.

Results: Carotid IMT was 0.66 (0.16) and correlated with age (rho = 0.444, p< 0.0001), abdominal circumference (r = 0.409, p= 0.001) and CRP level (r = 0.496, p= 0.001). Uveitis and dactylitis were associated with higher IMT (0.74 vs 0.62, p= 0.046; 0.84 vs 0.62, p 0.023). Also high blood pressure was associated with higher IMT (0.73 vs 0.59, p= 0.02). Patients with history for hypertension had higher carotid IMT (p 0.013). All the other variables were not significantly associated with IMT. Patients with PsA had slightly greater carotid artery IMT than AS (0.67 vs 0.60, p = 0.076).

Conclusion: In our patients with SAp the carotid intima-media thickness is associated with older age, hypertension, obesity, higher C-reactive protein serum levels, dactylitis and uveitis.

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2603

Short-Term Non-Steroidal Anti-Inflammatory Drug (NSAID) Use Induces Subclinical-Kidney-Injury in Spondyloarthritis Patients: Urinary Biomarker Study. Anuj Shukla, Mohit kumar Rai, Narayan Prasad and Vikas Agarwal. Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background/Purpose: NSAIDs are the first-line therapy for spondyloarthritis (SpA) patients and are associated with the risk of kidney injury. Long-term NSAID use is known to cause poor urine concentrating abilities. Short-term NSAID induced subclinical-kidney-injury is not well studied. Herein, we studied the effect of short-term NSAID use on kidney injury by measuring serum and urine biomarkers.

Methods: In cross-sectional study, 40 healthy controls with minimal-NSAID-exposure (cohort-A) and 40 SpA patients on regular-NSAIDs for >3 months (cohort-B) were included. In another cohort, 17 SpA-patients with minimal baseline NSAID-exposure (cohort-C) were treated with regular-NSAIDs for 6 weeks. Urine and serum samples were collected at 0, 1 and 6 weeks. In addition, 6 healthy volunteers (cohort-D) were treated with 7 days of daily NSAID. Daily urine and weekly blood samples were collected for 14 days; including 7 days after the drug was stopped. Biomarkers like NGAL, KIM1, cystatin-C and micro-albumin (ELISA) were measured. Creatinine (Jaffe's method) was measured in all samples.

Minimal-NSAID-exposure was defined as nil in last week, <15 tablets in last month, <2 tablets/week in last year or <1000 tablets lifetime exposure. Normal-renal-function was ensured in all subjects as eGFR ≥90ml/min, <1+dipstick proteinuria and inactive urine sediments.

Results: Median age of cohort-A and B was 27 (IQR 26–35) and 30 (IQR 24–38) years respectively with male to female ratio of 3:1. Duration of NSAID use in cohort-B was 7 (IQR 5–12.5) months. There was no significant difference in serum creatinine and eGFR in both cohorts while biomarker levels were raised in cohort-B compared to cohort A (Mann-Whitney test, table).

Median age of cohort-C was 35 (IQR 28–40) years and male to female ratio of 9:8. Urine biomarker levels showed a significant rise on treatment with NSAIDs at 1 week, (Wilcoxon test) cystatin C p=0.01, NGAL p=0.02, KIM1 p=0.08 and micro-albumin p=0.1. There was a further significant rise in urine and serum levels at 6 weeks (Friedman test, table). Cohort-D showed a rise in urine and serum levels of biomarkers at 7 days followed by a fall to baseline in urine levels at 10th day while serum levels showed partial fall at 14th day.

Conclusion: Short-term NSAID use may induce subclinical-kidney-injury represented by rise of urine and serum biomarkers, even in absence of changes in serum creatinine or eGFR. These levels start rising as early as 7 days of NSAID use.

Table

Changes in urine and serum levels of Kidney-Injury Biomarkers

U=urine, S=serum, Cr=creatinine, results represented as median with interquartile range, Estimated GFR (eGFR) calculated by Cockcroft-Gault Equation

Biomarkers	Cohort-A N=40	Cohort-B N=40	p value	Cohort-C Baseline N=17	Cohort-C 1-week N=17	Cohort-C 6-week N=17	p value
S Creatinine mg/dl	0.79 (0.7–0.9)	0.78 (0.7–0.85)	0.56	0.85 (0.7–1.0)	–	0.85 (0.77–0.95)	0.74
eGFR ml/min	117 (100–137)	108 (95–139)	0.37	107 (101–121)	–	123 (105–134)	0.59
U KIM1/Cr ng/mg	0.07 (0.05 to 0.1)	0.2 (0.01–0.28)	<0.0001	0.03 (0.02–0.12)	0.08 (0.04–0.14)	0.18 (0.10–0.54)	<0.0001
U NGAL/Cr ng/mg	7.1 (4.2 to 15.6)	22.22 (10.35–48.31)	<0.0001	4 (3.2–7.4)	6.8 (5.2–11.6)	37 (20.6–72.6)	<0.0001
U Cystatin-C/Cr ng/mg	71.6 (63.2–102.7)	136.6 (64–216)	0.03	50 (40.7–86)	74 (51–94.3)	123 (93.3–208)	0.0007
Micro-albumin/Cr µg/mg	7.7 (4.3–12)	8.4 (3.6–19.5)	0.55	5.4 (3.4–8.2)	5.5 (5–9.5)	9 (7.6–36.3)	0.003
S KIM1 pg/ml	230 (123–412)	391 (296–494)	0.001	221 (166–248)	–	397 (321–449)	<0.0001
S NGAL ng/ml	137 (90–170)	187 (132–214)	0.001	101 (45.5–130)	–	140 (86–171)	<0.0001
S Cystatin-C mg/ml	0.15 (0.13–0.16)	0.18 (0.12–0.28)	0.07	0.07 (0.06–0.08)	–	0.09 (0.08–0.1)	<0.0001

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2604

Ankylosing Spondylitis and Non- Radiographic Axial Spondyloarthritis: the Same Syndrome or Different Diseases? Analysis from Esperanza Cohort. Azucena Hernández-Sanz[1], Victoria Navarro-Compán[2], Cristina Fernández-Carballido[3], Carlos Montilla-Morales[4], Juan Mulero[5] and Eugenio De Miguel[6]. [1]H. Virgen de la Salud, Toledo, Spain, [2]University Hospital La

Paz, Madrid, Spain, [3]University General Hospital Elda, Elda (Alicante), Spain, [4]H. de Salamanca, Salamanca, Spain, [5]University Hospital Puerta de Hierro, Majadahonda (Madrid), Spain, [6]Department of Rheumatology, Hospital Universitario La Paz, Madrid, Spain.

Background/Purpose: New ASAS criteria for axial spondyloarthritis (axSpA) have two entrances: the imaging and clinical arm (presence of HLA B27). The imaging arm allows classifying patients as non radiolographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS).

The importance of the concept of nr-axSpA or the clinic arm in the classification of SpA is questioned currently, so it is interesting to investigate how homogeneous or different populations are compared to the classical AS.

Prymary objetive was to compare the characteristics of AS and nr-axSpA of recent onset. Secondary one was to compare the characteristics between groups axial SpA diagnosed by clinical and imaging arm.

Methods: Population: Baseline dataset from the ESPeranza cohort (<45 yrs, symptoms duration 3–24 months and with inflammatory back pain -IBP- or asymmetrical arthritis or spinal/joint pain plus ≥1 SpA features).

Inclusión criteria: Patiens who met ASAS criteria for axSpA.

Variables: Demographic, clinical, activity indices (BASDAI and CRP), mobility (BASMI) and physical function (BASFI) were compared.

Statistical analysis: **Results** are presented in mean ± standard deviation for continuous variables and n,(%) for categorical variables.

Results: A total of 775 patients were included in the "ESperanza" program- From these, 291 met ASAS criteria for axSpA: 194 imaging arm (43.8% nr-axSpA and 56.2 % EA), and 97 clinical arm.

Sixty five percent were male with a mean age of 32 ± 7 years and mean disease duration of 13 ± 6.7 months. Males were more frequently observed in patients with AS compared to nr-axSpA group. Only diarrhea and genito-urinary disease were more frequent in the group of nr-axSpA (Table). Mobility was more impaired in the AS group. No significant differences in the activity or other baseline characteristics were observed. Peripheral and genito-urinary disease, arthritis, enthesitis, uveitis, diarrhea, and family history were significantly more frequent in patients in the clinical arm, while physical function was more impaired in patients on image arm.

Conclusion: Patients with nr-axSpA have very similar clinical features to AS patients in the early stages of the disease, except higher frequency of males and mobility limitation in the AS group.

Patients with axial axSpA in the clinical arm presented more often peripheral involvement that the imaging arm, while no significant differences in the presence of psoriasis and inflammatory bowel disease and activity rates.

	Clinical arm n 97 (33%)	Imaging arm n 194(67%)				
		Global	nr-axSpA (n = 85)	AS (n = 109)	p* value	p** value
Age (years)	31.9 ± 7.5	32.1 ± 6.8	31.3 ± 6.7	32.7 ± 6.8	0.2	0.8
Male	64 (66.0)	127 (65.5)	46 (54.1)	81 (74.3)	<0.01	0.9
Symptoms duration (m)	12.0 ± 6.9	13.5 ± 6.6	13.0 ± 6.8	13.9 ± 6.4	0.3	0.08
Morning stiffness	60 (61.9)	138 (71.1)	57 (67.1)	81 (74.3)	0.3	0.1
IBP (ASAS definition)	35 (36.1)	77 (39.7)	35 (41.2)	42 (38.5)	0.7	0.6
Peripheral arthritis	25 (25.8)	28 (14.4)	9 (10.6)	19 (17.4)	0.2	0.02
Enthesitis	36 (37.1)	21 (10.8)	11 (12.9)	10 (9.2)	0.4	<0.001
Psoriasis	14 (14.4)	19 (9.8)	11 (12.9)	8 (7.3)	0.2	0.2
Dactyitis	10 (10.3)	6 (3.1)	2 (2.4)	4 (3.7)	0.6	0.01
IBD	1 (1.0)	8 (4.1)	2 (2.4)	6 (5.5)	0.3	0.2
Uveitis	12 (12.4)	11 (5.7)	4 (4.7)	7 (6.4)	0.6	0.046
Diarrhea, cervicitis, urethritis	8 (8.2)	3 (1.5)	3 (3.5)	0	0.048	<0.01
Family history	45 (46.4)	56 (28.9)	25 (29.4)	31 (28.4)	0.8	<0.01
HLA-B27	97 (100)	122 (62.9)	49 (58.3)	73 (67.6)	0.2	<0.001
CRP (mg/L)	10.9 ± 16.4	10.8 ± 14.6	9.8 ± 13.8	11.5 ± 15.3	0.4	0.9
VAS (0–10) night pain	3.4 ± 2.9	4.0 ± 2.9	3.9 ± 2.9	4.1 ± 3.0	0.7	0.9
VAS (0–10) physician	2.5 ± 2.1	3.1 ± 2.2	2.7 ± 2.1	3.4 ± 2.2	0.047	0.5
VAS (0–10) patient	4.1 ± 2.6	4.2 ± 2.7	4.3 ± 2.9	4.1 ± 2.6	0.7	0.5
BASDAI	3.8 ± 2.2	3.8 ± 2.3	3.7 ± 2.1	4.0 ± 2.4	0.4	0.8
BASFI	2.0 ± 2.0	2.5 ± 2.4	2.3 ± 2.4	2.7 ± 2.5	0.3	0.02
BASMI	1.2 ± 1.0	1.6 ± 1.3	1.2 ± 1.2	1.8 ± 1.4	<0.01	0.1

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Profiling Ankylosing Spondylitis Patients Likely to Respond to NSAID Treatment. Mohamed Bedaiwi[1], Arane Thavaneswaran[2], Nigil Haroon[3], Ammepa Anton[4] and Robert D. Inman[5]. [1]clinical and research fellow, Toronto, ON, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, [3]Toronto Western Research Institute, Toronto, ON, [4]University Health Network, Toronto, ON, [5]Department of Medicine, University of Toronto, Toronto, ON.

Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease with unpredictable course of progression. Treatment of AS thus should be tailored according to disease manifestation. There is group of patient with ankylosing spondylitis controlled with non-steroidal anti-inflammatory drugs alone, while the other subset may show high disease activity despite conventional treatments with NSAIDS and may require further therapeutic agents. The aim of study is to compare AS patients well controlled with NSAIDS alone with the other group requiring biologic therapy because of NSAID-nonresponsiveness.

Methods: This retrospective study involved data collection from the last clinic visit for 417 patients with a diagnosis of AS based on the modified New York criteria for AS. NSAID-treated patients (n=124) were defined as having a BASDAI<=4 at the last clinic visit while being treated with only NSAIDs, Biological-treated patient (n= 187) had failed to respond to a trial of ≥ NSAIDS. The comparison of NSAID treated (NS-TR) and biologic treated (B-TR) was done in relation to multiple social, clinical and laboratory variables.

Results: NS-TR patients were found to have a lower incidence of smoking (P<0.0009), lower CRP (p=0.01), lower incidence of kidney stones (P= 0.02), increase in hyperlipidemia (P= 0.02) and better spinal mobility (P<0.0001). There were no significant differences in the following variables: gender, age of onset, eye disease, hypertension, diabetes, cardiac disease, uveitis, psoriasis, inflammatory bowel disease.

Conclusion: This study showed that the NSAID-responsive AS patients tend to be non-smokers, with lower baseline CRP, and less impairment in spinal mobility at baseline. Conversely, age, gender, and B27 status which have previously been implicated as markers of severity, did not correlate with NSAID-responsiveness. This analysis begins to provide a profile of AS patients who at baseline are likely to require biologic therapy for their disease.

Table 1. Comparison of NSAID and biological treated patient with AS

Variable	Mean (sd) or Frequency (%) NS-TR N = 124	B-TR N = 187	P-value
Sex (Males)	96 (77.4%)	137 (73.3%)	0.41
Age	36.1 (14.9)	37.6 (12.0)	0.34
Age at start of back pain	22.8 (10.7)	23.0 (8.4)	0.89
Age at diagnosis of AS	27.7 (12.2)	29.7 (10.6)	0.12
Duration of AS	13.3 (12.5)	14.6 (11.1)	0.33
Current smoking status			0.009
None:	86 (70.5%)	104 (55.6%)	
Current:	19 (15.6%)	57 (30.5%)	
Past:	17 (13.9%)	26 (13.9%)	
ESR	14.9 (18.3)	19.1 (17.7)	0.06
CRP	11.0 (14.6)	17.6 (27.5)	0.01
Trauma	5 (5.6%)	20 (13.7%)	0.05
Conjunctivitis	4 (3.5%)	1 (0.6%)	0.07
Iritis	28 (22.6%)	47 (25.1%)	0.61
Mucous membrane	3 (2.6%)	7 (3.9%)	0.75
Hypertension	14 (11.3%)	19 (10.2%)	0.75
Angina	1 (0.8%)	2 (1.1%)	1.00
Congestive heart failure	1 (0.9%)	0 (0%)	0.41
MI ever	0 (0%)	3 (1.6%)	0.28
IBD	13 (17.1%)	25 (23.2%)	0.32
Urethritis	2 (2.1%)	1 (0.7%)	0.56
Kidney stones ever	1 (1.1%)	13 (8.4%)	0.02
CVA	1 (1.1%)	0 (0%)	0.38
Psoriasis	6 (6.3%)	13 (8.3%)	0.63

Nail lesions	3 (3.2%)	3 (1.9%)	0.68
Hyperlipidemia	7 (6.2%)	2 (1.1%)	0.02
Liver disease	2 (1.8%)	6 (3.4%)	0.49
Diabetes	4 (3.3%)	3 (1.6%)	0.44
BASMI	1.8 (2.2)	3.3 (2.6)	<0.0001

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2606

How to Classify Spondyloarthritis after a Two Year Follow up? Results from the French Recent onset spondyloarthritis Cohort. Pierre Gazeau[1], Divi Cornec[2], Marie Agnès Timsit[1], Valerie Devauchelle[3], Sandrine Jousse-Joulin[1], Thierry Marhadour[4], Emmanuel Nowak[1], Maxime Dougados[5] and Alain Saraux[6]. [1]CHU Brest, Brest, France, [2]Brest Occidentale University, Brest, France, [3]Brest university medical school, EA 2216, Lab Ex, INSERM, IGO, UBO and CHU de la Cavale Blanche,, Brest, France, [4]CHU de la Cavale Blanche, Brest, France, [5]INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France., Paris, France, [6]CHU Brest and EA 2216, UBO, Brest, France.

Background/Purpose: In early arthritis, after a two years follow up, rheumatologist diagnosis of rheumatoid arthritis agrees well with 2010 ACR/EULAR criteria (Saraux A et al. Arthritis care Arthritis Res (Hoboken). 2013;65:1227–34). Today, we do not have straightforward rules to diagnose spondyloarthritis (SpA) after a two year follow up, and we do not know the gap between rheumatologist diagnosis and SpA defined using all potential methods to classify patients having inflammatory low back pain (IBP).

Methods: We used the nationwide, longitudinal, prospective cohort (DESIR) of patients with IBP suggestive of SpA at baseline. After 2 years, patients were classified based on: imaging (MRI, X-rays), the certainty with which the rheumatologist diagnosed SpA (evaluated on 0–100 visual analogue scales), treatment used (non-steroidal anti-inflammatory drugs [NSAID] and/or TNF-alpha blockers) and classification criteria (any among axial Assessment of SpA international Society [ASAS] criteria, European SpA Study Group [ESSG] and Amor). First, we described clinical, biological and imaging characteristics, the items of all classification criteria and the diagnosis established by the rheumatologists after 2 years. Second, we evaluated the certainty in the diagnosis of SpA at inclusion and after a 2 year follow-up. Third, using ROC curves, we determined the best end point of the diagnosis certainty using the validated classification criteria (AMOR, ESSG, and ASAS) as gold standards. Then, we evaluated agreement between all potential methods to classify patients having IBP based on Cohen's kappa coefficient in the whole group and in the group having a MRI.

Results: On the 708 patients initially included, 548 had information on rheumatologist's certainty after 2 years. Using ROC curves, we found that a certainty of diagnosis ≥ 75% gave the best balance of sensitivity and specificity. This certainty of diagnosis increased with the follow up [357 of 548 (65.1%) patients had a certainty≥75% after a two year follow up versus 265 (48.3%) at inclusion]. Certainty of diagnosis≥75% after a two year follow up was statistically associated with all classification criteria (AMOR p: 0.005; ESSG p: 0.003; ASAS p<0.0001) and the ASAS criteria had the best agreement, although it was low (kappa 0.09, 0.11 and 0.25 for AMOR, ESSG and ASAS, respectively). None of the various other potential classifications items had a better agreement.

Conclusion: Rheumatologist diagnosis of SpA certainty after 2 years does not agree well with the various previously published criteria for SpA.

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Fatigue in Ankylosing Spondylitis: A Multivariable Analysis Implicates Inflammation As the Key Determinant of Disability. Mohamed Bedaiwi[1], Arane Thavaneswaran[2], Nigil Haroon[3], Ammepa Anton[4] and Robert D. Inman[5]. [1]clinical and research fellow, Toronto, ON, [2]University of Toronto, Toronto Western Hospital, Toronto, ON, [3]Toronto Western Research Institute, Toronto, ON, [4]University Health Network, Toronto, ON, [5]Toronto Western Hospital, University of Toronto, Toronto, ON.

Background/Purpose: Fatigue is one of the cardinal features of ankylosing spondylitis (AS). The clinical and laboratory correlates of fatigue in AS however are not well defined. In the current study we undertake a systematic analysis of fatigue in a longitudinal observation cohort of AS patients.

Methods: A systematic review of 950 AS patients (671 male and 279 female) followed in a longitudinal clinic which entails regular clinic visits using a standardized protocol. Fatigue was recorded using the Fatigue Severity Scales (FSS). T tests were used to compare continuous variables and Chi-Squared tests for categorical variables. Multivariate analysis was conducted using logistic regression to assess associations between FSS and various clinical features. P-value <0.05 was used to define statistical significance.

Results: In the univariate analysis there were a number of clinical variables showing association with FSS. This was followed by logistic regression analysis. Figure 1 outlines selected covariates based on a p-value<0.05 in univariate models and included in the full model. Stepwise selection was used to determine the variables most associated with (FSS). In the reduced model the clinical domains with the strongest correlation with FSS were morning stiffness, Bath AS Functional Index (BASFI), and Short Form (36) Health Survey (SF36-MCS). For patients with morning stiffness, there is an expected 2.13 increase in the FSS. For every unit increase in the BASFI, there is a 0.37 increase expected in the FSS. For every unit increase in the SF36-MCS, there is a 0.11 decrease in FSS.

Conclusion: Fatigue continues a frequent and sometimes disabling aspect of AS. The strong correlation with stiffness suggests that these two variables may reflect a common underlying process. Since morning stiffness is considered a surrogate indicator of inflammation, fatigue may fall into this conceptual framework as well. The level of disability as measured by BASFI shows stronger correlation with fatigue than with mSASSS suggesting this fatigue may impose greater functional restrictions on patients than structural progression of the disease does. The reversed SF36-MCS correlation with FSS indicates more vitality, bodily pain, emotional, social and mental health functionality impairment in fatigued AS patient.

TABLE: Linear Regression Models to Assess Variables associated with Fatigue (FSS)

	Full Model		Reduced Model	
Covariate	Estimate (SE)	p-value	Estimate (SE)	p-value
Age	0.05 (0.05)	0.29	—	—
Age at diagnosis of AS	−0.04 (0.06)	0.53	—	—
Sex	1.28 (2.28)	0.58	—	—
ESR	0.005 (0.05)	0.92	—	—
CRP	0.02 (0.05)	0.71	—	—
Enthesitis	3.84 (2.32)	0.12	—	—
Morning stiffness	2.47 (1.61)	0.15	2.13 (0.79)	0.01
Peripheral arthritis	−0.89 (1.44)	0.55	—	—
Nocturnal back pain	0.49 (1.09)	0.66	—	—
MSASS	−0.02 (0.04)	0.64	—	—
BASDAI	0.03 (0.29)	0.92	—	—
BASFI	0.51 (0.30)	0.11	0.37 (0.13)	0.009
ASQoL	0.14 (0.20)	0.50	—	—
EQ5D	−1.58 (3.30)	0.64	—	—
SF36-PCS	0.05 (0.08)	0.57	—	—
SF36-MCS	−0.05 (0.05)	0.39	−0.11 (0.03)	0.0005
HAQ	−1.80 (1.38)	0.21	—	—
NSAIDs	1.79 (1.14)	0.14	—	—
Biologics	1.14 (0.87)	0.21	—	—

Disclosure: M. Bedaiwi, None; **A. Thavaneswaran**, None; **N. Haroon**, None; **A. Anton**, None; **R. D. Inman**, None.

2608

Do You Assess Gastro-Intestinal Auto-Antibodies and Symptoms in Patients with Spondyloarthritis?. Consuelo Romero Sanchez[1], Wilson Bautista-Molano[1], Viviana Parra-Izquierdo[2], Carlos Martínez[3], Ferney Garcia[3], Juliette De Avila[4], Haroldo Juliao[5], Juan Manuel Bello[1], John Londoño[6] and Rafael Valle-Oñate[1]. [1]Faculty of Medicine, Universidad Militar Nueva Granada, Bogotá, Colombia, [2]Spondyloarthritis Group. Rheumatology Department. Hospital Militar Central/Universidad de La Sabana. Bogotá. Colombia, Bogota, Colombia, [3]Coloproctology Deparment, Hospital Militar Central, Bogotá, Colombia, [4]UIBO Institute (Oral Basic Research Unit) School of Dentistry Universidad El Bosque, Bogotá, Colombia, [5]Gastroenterology Deparment, Hospital Militar Central, Bogotá, Colombia, [6]Spondyloarthritis Group. Rheumatology Department. Hospital Militar Central/Universidad de La Sabana. Bogotá. Colombia, Bogotá, Colombia.

Background/Purpose: Spondyloarthritis (SpA) are a group of chronic inflammatory rheumatic diseases. Extra-articular manifestations affect approximately 30% of patients with SpA, and gastrointestinal manifestations

(GI) represents about 5 to 10%. The relationship between gut and joint inflammation suggest that there is an increase in intestinal permeability and abnormal levels of intestinal bacteria that stimulate pathologic immune responses. The persistence of joint disease activity is primarily associated with intestinal inflammation. Therefore, the aim of this study is to investigate the association between gastrointestinal symptoms, disease activity of SpA and the presence of auto-antibodies including patients with inflammatory bowel disease (IBD).

Methods: A cross sectional study was designed, including 103 patients with SpA fulfilling ESSG classification criteria and 117 healthy subjects (HS). Twenty nine patients had a diagnosis and clinical activity compatible with IBD as confirmed by histologic examination.

Anti-*Saccharomyces cerevisiae* IgG/IgA (ASCA), 6 antigen associated with anti polymorphonuclear neutrophil (ANCA), anti-transglutaminase (tTG) IgG/IgA, anti-deaminated gliadin peptide (DGP) IgG/IgA auto-antibodies, ANAS and IgA were measured in all patients by ELISA technique. A specific questionary was applied asking for GI symptoms in the SpA and IBD group. Descriptive epidemiology was analized and association between clinical manifestations and auto-antibodies were evaluated using Chi square test and Mann Whitney U-Test as appropriate.

Results: Mean age in SpA patients was 42.2 years (SD 15.5) with a predominance of uSpA subtype (59.8 %). BASFI >4 was reported in 60.6% and BASDAI>4 in 67.7%. Respect to treatment, 49 % of patients were receiving anti-TNF therapy. HLA-B27 was positive in 39%.

ASCA IgG/IgA were positive in 28.2% of SpA patients and 75.8% of them were IgG isotype. ANCA was present in 8.8 % (six antigens evaluated), celiac auto-antibodies (1%) and ANAS (49.5%). In HS, 2.6% were ASCAS positive (50% of these were IgA subtype) and 6.8% were ANCAS positive. There was a significant difference in the frequency of autoantibodies IgG/IgA ASCAS, p-ANCAS and ANAS between SpA and HS (p=<0.001), and SpA and IBD (p=<0.001). Significant association was found between BASDAI>4 and the presence of abdominal pain (p=0,003), diarrhea (p=0.017), abdominal inflammation (p=<0.001), discomfort (p=0.004) and total IgA levels (p=0.005); as well as between abdominal inflammation and BASFI > 4 (p=0.028).

Additionally, significant difference was found in the presence of abdominal pain between SpA (54.4%) and IBD (27.5%) patients (p=0.012). Both groups (SpA and IBD) had similar frequency of mucus (30% vs 31%).

Conclusion: The presence of ASCAS IgG/IgA, p-ANCAS, ANAS, IgA and the reporting of GI symptoms, are associated with higher disease activity in SpA. There are differences in the presence of GI manifestations according to SpA subtypes, but not differences between IBD and SpA regarding the presence of mucus. It may suggest that subclinical IBD should be actively screened in Colombian SpA patients probably due to environmental conditions.

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2609

Treating Axial-Spa to Target: Prevalence of *Ankylosing Spondylitis Disease Activity Score* (ASDAS) Inactive Disease in a Cohort of Patients Treated with Anti-TNFα Agents.

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Background/Purpose: Treating disease to target is emerging as the recommended strategy also in the management of axial-SpA (axSpA) (1). Reaching remission, defined as inactive disease (ID), constitutes the ideal target in clinical practice. Using the new composite disease activity index-"*Ankylosing Spondylitis Disease Activity Score*" (ASDAS) (2) we assessed the prevalence of ID in a cohort of patients with axSpA treated with anti-TNFα agents. Potential patient- and disease-related factors influencing the status of ID were analyzed.

Methods: The study population was selected from outpatients with axSpA treated with anti-TNFα attending our Rheumatology Department. Disease activity was evaluated in terms of BASDI and ASDAS-CRP during the latest follow up visit. ID was defined as ASDAS-CRP< 1.3 (2).Statistical analysis was performed with STATA.

Results: General characteristics of the 53 enrolled patients are presented in Table 1. A BASDAI < 4 was recorded for 70% of the study population, while only 31% showed ID according to ASDAS-CRP (Figure 1). As expected, a strict correlation between the two disease activity indices was confirmed (Spearman's r = 0.76; p < 0.0001). Multivariate logistic regression demonstrated an inverse correlation of ID status with NSAIDs intake (OR 0.15; CI95% 0.45–0.54). ID achievement resulted independent from sex, disease duration, BASMI, DMARDs, type of anti-TNFα agent.

Conclusion: In our cohort of axSpA treated with biological agents, only one third achieved ID according to ASDAS-CRP. Even with the limitations of the small sample size, ID does not correlate with the principle patient- and disease-related features but is inversely associated with NSAIDs intake. Further studies are needed to optimize the targeted treatment of axSpA and to identify potential predictive factors of ID.

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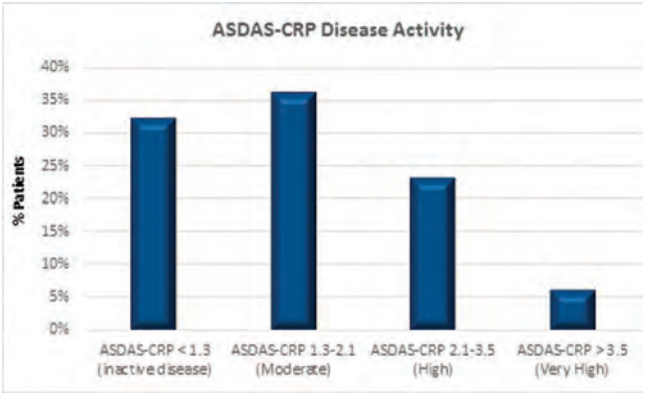
Table 1. General characteristics of the study population

Variable	Number/ Mean ± SD	Percentage (%)
Total number of patients	53	
Male	30	57%
Female	23	43%
Diagnosis: axSpA:		
AS	41	76%
non-radiographic axSpA	12	23%
Peripheralinvolvement	34	64%
Age atsymptomsonset	35 (±12)	
Age atdiagnosis	39 (±13)	
Diseaseduration (years)	10 (±9)	
Patients on second line anti-TNFα	10	19%
ConcomitantNSAIDsintake	34 (15/19)	64% (28/36)
DMARD combinationtherapy	21	40%
Type of anti-TNFα agent		
Infliximab	14	26%
Adalimumab	15	28%
Golimumab	14	26%
Etanercept	10	19%
Time from anti-TNFα treatment initiation (months)	33 (±31)	

Figure 1. Proportion of patients according to ASDAS-CRP disease activity cutoffs



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2610

The Role of IL-20 in the Pathogenesis of Ankylosing Spondylitis with Peripheral Joint Involvement.

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Background/Purpose: The interleukin-20 (IL-20) is a pro-inflammatory cytokine of the IL-10 family and sequence amino acid is very similar. It has been reported to be involved in the pathogenesis of several autoimmune diseases, but pathophysiological importance is poorly understood. TNF alpha plays an important role in AS patients with axial and peripheral joint involvement. It has been reported that TNF alpha induce IL-20 in macrophage and synovial cells. For this reason, we investigated serum IL-20 levels in AS patients with axial and peripheral joint involvement who had not received anti- TNF treatment.

Methods: 63 patients with AS (11 female, 52 male) and 17 healthy controls (2 female, 15 male; mean age 26.5 ± 6.9 years) were enrolled in this study. Thirty-eight of the AS patients were axial involvement (mean age; 25,9 ± 7.2 years, median disease duration 7 years) and the other 24 patients were peripheral joint involvement (mean age; 27.3 ± 6.9 years, median disease duration; 9 years). Serum IL-20 levels were determined by ELISA.

Results: The median serum IL-20 levels were 55,2 pg/ml in healthy controls, 308.5 pg/ml in the patients with peripheral joint involvement and 109.3 pg/ml in the patients with axial involvement. Serum IL-20 levels in patients with AS were significantly higher than in healthy controls ($p<0.001$). Serum IL-20 levels were significantly high in the patients with peripheral joint involvement compared with in the patients with axial involvement ($p<0.001$). in the patients with peripheral joint involvement, there are statistically significant correlation between serum IL-20 and serum CRP and ESR ($r=0.645$, $p<0.001$, and $r=0.588$, $p<0.001$ respectively). In the patients with axial involvement, it was not correlated with CRP and ESR ($r=0.262$, $p=0.298$ and $r=0.292$, $p=0.355$ respectively).

Conclusion: Serum IL-20 levels are high in the AS patients with peripheral joint involvement and, correlated with CRP and ESR. So, it may be involved in pathogenesis of the disease.

Disclosure: G. Keskin, None; **B. Mavi**, None; **L. Ozisik**, None; **R. Ilikci**, None; **M. Yildiz**, None.

2611

Short Term Efficacy of Tumor Necrosis Factor Inhibitors in Patients with non–radiographic Axial Spondylarthritis and ankylosing Spondylitis; Results from Turkbio Registry.

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Background/Purpose: Axial spondylarthritis (AxSpA) has been proposed as an umbrella term for ankylosing spondylitis (AS) and non-radiographic (nr) AxSpA). This new concept makes diagnosis of AS possible at an early stage in the absence of radiographic sacroiliitis. Disease burden in AxSpA patients with or without radiographic sacroiliitis have been shown to be similar in different cohorts, which suggest that both diseases should be treated with the same approach. Recent randomized clinical trials showed that TNF inhibitors (TNFi) are effective also in treating signs and symptoms of nr-AxSpA. However, the efficacy of anti-TNF agents in patients with nr-AxSpA remains to be shown in daily rheumatology practice. The objective of this study is to compare the efficacy of TNF inhibitors in patients with AS and nr-AXSpA in daily clinical setting.

Methods: A total of 326 patients with AxSpA (195 M; 39.8 ±10.6) from four centers, who contribute to TURKBIO, a biological database in Turkey, and who could provide detailed data on imaging for patients with AxSpA, were included in this study. Of these patients 208 had AS according to the *modified New York criteria* and 118 *patients had nr-ax SPA. (20% fulfilling the clinical arm, 80% fulfilling the imaging arm)*

Results: Baseline demographics and clinical characteristics are summarized in the table-1. Patients with nr-AxSpA were significantly younger, had a shorter disease duration and had a higher female predominance than patients with AS. After three months of treatment with TNF inhibitors, mean BASDAI and ASDAS decreased significantly (Table 1). The response rates for minimal clinical improvement (ΔASDAS ≥1.1) and major clinical improvement (ΔASDAS ≥2) were similar in patients with nr-AxSpA (66% vs 72%) and those with AS (43.8% vs 39.1%). Similarly good response rates were observed for BASDAI 50 in the two groups; 56.8 % and 58.5%, respectively.

Conclusion: The results of our study suggest that TNFi, which have been clearly shown to be effective in treating signs and symptoms of AS, seem to be equally effective in the treatment of nr-AxSPA.

Table 1. Demographics and clinical characteristics of the AxSpA and AS patients.

	Non-radiographic axial spondylarthritis (n=118)	Ankylosing spondylitis (n:208)	p value
Age	36.8 (±9.6)	41.5 (±10.7)	p<0.001
Disease Duration (years)	7.22 (±6.4)	12.56 (±8.4)	p<0.001
Diagnosis Duration (years)	3.6 (±3.3)	7.51 (±6.4)	p<0.001
Female (%)	53.4	32.7	p<0.001
Mean CRP mg/l (baseline)	20.1 (±32)	24.9 (±32.9)	p:0.213
Mean ESR (baseline)	28.2 (±24.5)	35.5 (±24.9)	p:0.050
HLA B27 positivity (%)*	53%	74%	p:0.02
Mean BASFI (baseline)	5.33 (±2.88)	5.06 (±2.58)	p:0.414
Mean BASDAI (baseline)	6.43 (±1.9)	5.93 (±1.8)	p:0.02
Mean ASDAS-CRP (baseline)	3. (±0.98)	3.65 (±1.08)	p:0.689
Mean ΔBASDAI (at month 3)	3.4 (±2.37)	3.1 (±2.24)	p:0.261
Mean ΔASDAS (at month 3)	1.74 (±1.2)	1.75 (±1.1)	p:0.951
Biologic drugs used			
Infliximab (%)	26.3	25.5	
Etanercept (%)	33.1	31.3	
Adalimumab (%)	27.9	27.4	
Golimumab (%)	12.7	15.9	

*In the patients with available data

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2612

Different Performance of the Major Disease Activity Measures ASDAS and Basdai in Patients with Axial Spondyloarthritis Treated with Non-Steroidal Anti-Inflammatory Agents – Results from a Prospective Study.

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Background/Purpose: The ASAS/EULAR recommendations for the management of patients (pts) with axial spondyloarthritis (axSpA) have established non-steroidal anti-inflammatory agents (NSAIDs) as first choice of medical treatment in this condition. However, the outcome of this strategy has not been prospectively tested to date. Standardized measures (BASDAI, ASDAS) are routinely used to assess disease activity in pts with axSpA. Both measures are composite scores but only the ASDAS also includes CRP values as an objective measure. However, a direct comparison between ASDAS and BASDAI in axSpA pts treated with NSAIDs in a prospective study has not been performed to date. We prospectively compared the performance of BASDAI and ASDAS to identify candidates for anti-TNF therapy among patients with axSpA with high disease activity who were treated with full-dose NSAIDs over 4 weeks, as suggested in the ASAS treatment recommendations.

Methods: Consecutive patients (pts) with axSpA (both n=50 for nr-axSpA and AS, respectively) were included in a prospective study if their BASDAI level was ≥4, and if they had not received the maximally approved dose of NSAIDs nor anti-TNF agents to date. After inclusion into the study the maximal dose of NSAIDs was administered over 1wk and the dose was then adapted in case of BASDAI<4. In case of BASDAI ≥4 of in case of NSAID intolerance, the NSAID was changed and the pt was treated for another 3 wk at the maximal dose. Clinical and laboratory parameters and dosage of drugs were assessed by using the ASAS NSAID-index. Data were collected before (BL) and after 1 and 4 wk of treatment.

Results: The baseline (BL) characteristics of AS and nr-axSpA patients were similar, with exception in the mean CRP levels (nr-axSpA: 0.6±0.9 vs. AS: 1.2±1.1, $p<0.001$). Despite all patients having BASDAI ≥4 prior to treatment, an ASDAS >2.1 was found in only 74% and 76% of pts with AS and nr-axSpA, respectively. There was a significant overall decrease at both timepoints in both ASDAS-CRP (BL: 2.5±0.6, 1wk: 1.9±0.8, 4wk: 1.6±0.8) and BASDAI (BL: 5.8±1.3 1wk: 4.1±2.1 4wk: 2.1±3.1). After 4

weeks of standardized treatment with NSAIDs, there were 44% of all axSpA pts with a BASDAI ≥4 (AS 42% und % nr-axSpA 46%), while 33% of all axSpA pts (AS 32% and nr-axSpA 34%) had an ASDAS > 2.1. Overall, the two scores were in agreement in 81%. In 15% of pts, the BASDAI score would have possibly led to treatment with TNF blockers – despite an ASDAS <2.1, and, on the other hand, in 4% of cases the ASDAS would have initiated anti-TNF treatment but the not the BASDAI. In the univariate logistic regression analysis both, ASDAS (OR: 3.6, p=0.002) and BASDAI (OR: 1.8, p=0.001) predicted the eligibility for anti-TNF therapy after 4wk of NSAIDs at BL.

Conclusion: These data challenge the concept of only using the BASDAI cut-off ≥4 for the treatment decisions of initiation of TNF-blocker therapy. The question on whether BASDAI or ASDAS should be used as the appropriate cut-off for such treatment needs to also include the comparison of the subjective information on disease activity with CRP and MRI data and by assessing the predictive value of the response to NSAIDs for the response to TNF blockers in future studies.

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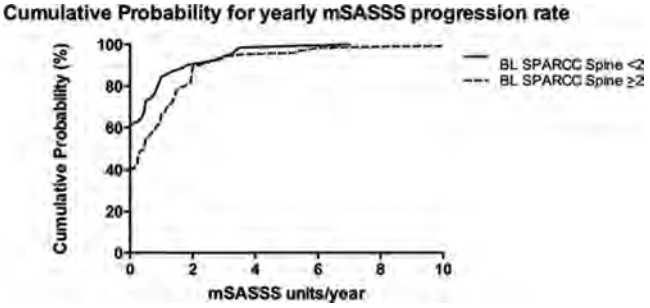
2613

Positive Spine MRI for Inflammation Predicts Radiographic Progression in Patients with Ankylosing Spondylitis. WP Maksymowych[1], S Wichuk[1], Z Zhao[2], P Chiowchanwisawakit[3], RG Lambert[1] and Sj Pedersen[4]. [1]University of Alberta, Edmonton, AB, [2]PLA General Hospital, Beijing, China, [3]Mahidol University, Bangkok, Thailand, [4]Copenhagen Center for Arthritis Research, Copenhagen, Denmark.

Background/Purpose: Inflammation at vertebral corners on MRI has been shown to predict development of syndesmophytes in patients with AS. However, it is unclear at a patient level whether a positive spine MRI for inflammation identifies patients at higher risk for radiographic progression and whether this is also associated with the degree of spinal inflammation. We used the SPARCC MRI spine score to assess whether the proposed cut-off of ≥2 for positive spine MRI and the absolute score are predictive of radiographic progression.

Methods: Spinal inflammation was scored blinded to time point (baseline, 2 years) using the SPARCC spine score by two readers and an adjudicator using pre-specified rules for adjudication. MRI scans were assessed from a prospective cohort of 195 AS patients (mean age 40.3 years, mean symptom duration 16.6 years, 59% on anti-TNF) followed for mean 2.3 years. Two readers and an adjudicator independently scored pairs of radiographs (baseline, 2 years) from the same patients using the mSASSS. Radiographic progression was compared in patients with and without positive spine MRI (SPARCC ≥2 or <2) and the degree of spinal inflammation at baseline (absolute SPARCC score) was compared in patients with and without radiographic progression (mSASSS >0 or =0) using Mann-Whitney and cumulative probability. Multivariate regression analyses included variables significant in univariate analyses (age, sex, symptom duration, CRP, baseline mSASSS) and treatment.

Results: Radiographic progression was significantly greater in those with positive spine MRI (p=0.004) (figure), and especially in patients who only received non-biologic therapy (p=0.006). Baseline SPARCC spine inflammation scores were significantly higher in those who developed radiographic progression compared to those without (14.5 vs 8.7, p=0.002). Positive spine MRI and the degree of spinal inflammation score were both significantly associated with radiographic progression in multivariate analysis (β=0.26 (p=0.019) and β=0.006 (p=0.036), respectively).



Conclusion: Both a positive spine MRI for inflammation and the degree of spinal inflammation are significantly associated with radiographic progression in patients with AS.

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2614

Reliability of Electronic Patient Self-Assessment of Swollen and Tender Joints in Psoriatic Arthritis: A Comparison Study with B-Mode Ultrasonography, Physician and Nurse Assessments. Agnes Szentpetery[1], Muhammad Haroon[2], Eileen O'Flynn[1], Phil Gallagher[1], Shafeeq Alraqi[1] and Oliver FitzGerald[1]. [1]St. Vincent's University Hospital, Dublin, Ireland, [2]Cork University Hospital, Cork, Ireland.

Background/Purpose: 68 tender (TJC) and 66 swollen joint counts (SJC) are recommended for disease activity assessment in psoriatic arthritis (PsA). However there are time constraints and these counts may not be performed. It has been shown in rheumatoid arthritis that patient's self-reported joint counts correlate well with functional disability, pain and global disease severity. Information concerning patients' self-assessed joint counts however is limited in PsA.

The aim of this study was to evaluate the reliability of patient self-assessed joint counts versus joint counts obtained by a physician, a nurse and B-mode ultrasonography (US) in PsA.

Methods: PsA patients fulfilling the CASPAR criteria were recruited. Following a training session on the detection of tender and swollen joints by a nurse, each patient assessed their 68 joints using an electronic digital mannequin on touchscreen. A joint examination by a different nurse and a rheumatologist, both blinded to the patients' clinical data was completed. US evaluation was performed by a further consultant rheumatologist on 34 joints assessing wrists, MCPs and PIPs, ankles and MTPs, and all extensor/flexor tendons of the fingers and toes. Presence of joint effusion, synovial proliferation and tenosynovitis on grayscale (GS); and synovitis/tenosynovitis on power Doppler (PD) signal were evaluated.

Results: 50 patients (33 female and 17 male) were enrolled to the study with a mean age of 50 (±13.7) years. Patients mean GVAS was 47 (±24) mm. Focusing on the 34 joints also assessed by US, mean TJC assessed by the patients, physician and nurse was 9 (±8), 7(±7) and 7(±7), mean SJC was 4 (±6), 1 (±2) and 3 (±3) respectively. Mean number of affected (swollen or tender) joints as per patient, physician, nurse and US evaluation was 10 (±8), 7 (±7), 8 (±7) and 6 (±4.5), respectively.

Patient and nurse-assessed SJC was significantly higher than physician-counts (p=0.0005; p=0.01, respectively). Similarly, patient and nurse-assessed SJC was significantly higher compared to physician-counts when using 28, 44 or 68 joint counts.

Patients scored their number of affected joints significantly higher than physicians irrespective of using 28, 34, 44 or 68 joint counts. The number of affected joints was higher as evaluated by patients compared to US (p=0.01).

Joint effusion was detected by US in 74%, synovitis in 78% on GS and 68% on PD and 30% of the patients had tenosynovitis.

TJC did not correlate significantly with any of the US measurements irrespective of the assessors. Patients SJC significantly correlated with US-assessed joint effusion, and with synovitis (GS and PD). Physician and nurse-reported SJC correlated with US-derived synovitis scores. The number of affected joints as assessed by patients and physician correlated with the US measurements (r=0.28, p=0.04; r=0.29, p=0.04; respectively).

Conclusion: Patients scored their SJC and number of affected joints higher than physicians and US measurements. Patient-reported SJC correlated with both effusion and synovitis as detected by US suggesting that patients' self-evaluated SJC may be valid in routine clinical practice for monitoring disease activity in PsA.

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2615

Preliminary Assessment of a Multi-Biomarker Disease Activity Test for Axial Spondyloarthritis. WP Maksymowych[1], Stephanie Wichuk[1], P. Scott Eastman[2] and Eric H. Sasso[3]. [1]University of Alberta, Edmonton, AB, [2]Crescendo Bioscience, Inc., South San Francisco, CA, [3]Crescendo Bioscience Inc., South San Francisco, CA.

Background/Purpose: There has been limited validation of soluble biomarker measures of disease activity in patients with axial spondyloarthritis (SpA). C-reactive protein (CRP) is most commonly used in clinical practice but sensitivity in ankylosing spondylitis AS is only 40–50%. The Ankylosing Spondylitis Disease Activity score (ASDAS) has been proposed as a treat-to-target outcome measure for effective suppression of disease activity in patients with SpA. BASDAI has also been used but does not incorporate objective measures of disease activity. We have performed an exploratory study of the association between a multi-biomarker disease activity (MBDA) score, which measures 12 serum biomarkers and has been validated in RA, and clinically-based measures of disease activity in patients with axial SpA.

Methods: Disease activity measures based on erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ASDAS, and BASDAI were analyzed for 40 patients with axial SpA who met modified New York criteria from a systematic, prospective follow-up cohort. The MBDA score was measured in serum samples and is based on the following 12 biomarkers: vascular cell adhesion molecule 1, epidermal growth factor, vascular endothelial growth factor A, interleukin 6, TNF receptor I, matrix metalloproteinases 1 and 3, bone glycoprotein 39 (YKL-40), leptin, resistin, serum amyloid A and CRP. These biomarkers were measured by electrochemiluminescence-based multiplexed immunoassays on the Meso Scale Discovery Multi-Array platform. The measured levels for each of the 12 biomarkers were weighted and combined using a formula validated in RA to derive the MBDA score (Vectra®DA score), which ranges from 1 to 100. Correlations between disease activity measures used Pearson correlation coefficient. Group differences were assessed using unpaired t-tests. We also determined to what degree biomarker scores reflected low and high disease activity cut-offs for the ASDAS (<1.3, >3.5) and the BASDAI (<4, ≥ 4).

Results: Patients were of mean (SD) age, 43 (11) years; number (%) males (%), 26 (65); mean (SD) disease duration, 19 (10) years; number (%) B27+, 30 (75); mean (SD) ESR, 24 (22) mm/h; mean (SD) CRP, 19 (19) mg/L; mean (SD) BASDAI, 4.2 (2.5); mean (SD) ASDAS-CRP, 2.9 (1.4); mean (SD) ASDAS-ESR, 2.7 (1.2). The MBDA score correlated significantly with the ASDAS-ESR ($r=0.63$), ASDAS-CRP ($r=0.68$) and BASDAI ($r=0.30$). The modified MBDA score calculated without CRP correlated significantly with the 12-biomarker MBDA score, which includes CRP ($r=0.98$), ASDAS-ESR ($r=0.58$), ASDAS-CRP ($r=0.63$) and BASDAI ($r=0.26$). Significant differences were observed in MBDA scores between patients with ASDAS-CRP >3.5 versus those with ASDAS <1.3 (57 vs. 25, $p=0.002$) and patients with BASDAI ≥ 4 versus BASDAI < 4 (51 vs. 37, $p=0.01$). Several of the MBDA biomarkers, including CRP, correlated strongly with the clinical composite measures. For ASDAS-CRP, serum concentrations of CRP, SAA, IL-6, TNF-R1, and YKL-40 correlated at $r > 0.5$ (range $0.51-0.71$).

Conclusion: The MBDA score was associated with available measures of clinical disease activity in patients with axial SpA and correlated most strongly with the ASDAS.

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2616

Comparison of Characteristics of Ankylosing Spondylitis in Association with Familial Mediterranean Fever with Those of Typical Ankylosing Spondylitis. Dilek Solmaz[1], Servet Akar[2], Bunyamin Kisacik[3], Sule Apras[4], Soner Senel[5], Ahmet Mesut Onat[3], Timucin Kasifoglu[6], Kenan Aksu[7], Ismail Sari[8], Mehmet Akif Ozturk[9], Mehmet Sayarlioglu[10], Ali Akdogan[4], Pinar Cetin[8] and Nurullah Akkoc[8]. [1]Namik Kemal University School of Medicine, Tekirdag, Turkey, [2]Izmir Katip Celebi University School of Medicine, Izmir, Turkey, [3]Gaziantep University School of Medicine, Gaziantep, Turkey, [4]HacettepeUniversity School of Medicine, Ankara, Turkey, [5]Kayseri Erciyes University School of Medicine, Kayseri, Turkey, [6]Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey, [7]Ege University School of Medicine, Izmir, Turkey, [8]Dokuz Eylul University School of Medicine, Izmir, Turkey, [9]GaziUniversity School of Medicine, Ankara, Turkey, [10]KahramanmarasSutçü ImamUniversity School of Medicine, Kahramanmaras, Turkey.

Background/Purpose: Several case reports and a few published studies suggest a link between Familial Mediterranean Fever (FMF) and ankylosing spondylitis (AS). There is very limited data on the clinical features of AS that develops in patients with FMF. The aim of this study is to compare the demographic and clinical features of patients with AS in association with FMF to patients with AS alone.

Methods: 73 patients with AS in coexistence with FMF (AS-FMF) who have been followed at 8 different hospitals were compared to 81 consecutive patients with AS alone from the same centers, in regard with demographic and clinical features. All of the patients fulfilled the modified New York criteria for AS and the patients with FMF additionally met the Livneh criteria for FMF. Patients' demographic and clinical data including latest disease activity (BASDAI) and functional status (BASFI) were extracted from patients' charts; MEFV genotypes, HLA B27 status and C reactive protein levels and radiographic results were also recorded if available. The independent t test was used to compare differences in continuous data. Comparisons of categorical data between groups were tested using the chi-square test.

Results: Patients in the AS-FMF group were younger and had a shorter disease duration. Gender distribution and age of onset of AS were similar in both groups; but diagnostic delay was longer and family history (for SpA) was reported more frequently in the AS group. Peripheral arthritis and heel enthesitis were more prevalent among AS-FMF patients, whereas a higher proportion of patients in the AS group had HLA-B27 and had radiographic evidence of spinal involvement. BASDAI and BASFI and the other spondyloarthritis related features were not different between the two groups. Demographic and clinical features of the patient groups are summarized in the Table below. M694V allelic variation was detected in 78.7% of the patients who had both AS and FMF.

Conclusion: Clinical characteristics of AS in association with FMF may show some differences from typical AS, such as less spinal involvement. However, this finding may also be, at least partially, explained by shorter disease duration in this group of patients. Relatively higher prevalence of M694V variant among patients who have both FMF and AS, than those reported in the historic FMF cohorts; as well as the lower prevalence of HLA-B27 in this group than those previously reported in Turkish AS patients suggest that such genetic differences may be accounted for some of the differences between the patients with AS alone and those with AS in association with FMF.

Table. Demographics, and clinical features of the patient groups

Features	AS (n:81)	FMF-AS (n:73)	P
Age, mean ± SD	45 ± 12.4	37 ± 11.9	**<0.001**
Male gender n; %	54; 66.7	49; 67.1	Not significant
Disease duration, mean± SD	10 ± 8.2	6 ± 5.8	**0.007**
Age of onset of back pain, mean ± SD	24 ± 8.4	23 ± 9.9	Not significant
Age of diagnosis of AS, mean ± SD	36 ± 12.2	30 ± 11.2	**0.013**
Diagnostic delay, mean ± SD	11 ± 13.0	6 ± 6.0	**0.002**
Smoking status, n (%)	52/78 (66.7)	46/72; 63.9 63.0%	Not significant
Peripheral artrhritis, n; %	20/79; 24.7%	49/71; 69.0 67.1%	**<0.001**
Heel enthesitis, n; %	32/79; 40.5 39.5%	43/72; 58.9	**0.018**
Dactylitis, n; %	1; 1.2	3; 4.2	Not significant
Acute anterior uveitis, n; %	10; 12.3%	11; 15.06%	Not significant
Psoriasis, n; %	1; 1.3	2; 2.7	Not significant
Inflammatory Bowel Disease, n; %	1; 1.3	0	Not significant
Family History (excluded FMF), n; %	32; 39.5%	18; 24.7%	**0.02**
BASFI, mean ± SD	3.1 ± 2.3	3.5 ± 2.5	Not significant
BASDAI, mean ± SD	3.7 ± 2.5	4.2 ± 2.7	Not significant
CRP mg/L, mean ± SD	11 ± 13.0	15± 29.0	Not significant
HLA B27 positivity, n; %	45/63; 71.4	17/67; 25.4	**<0.001**
Syndesmophytes any, n; %	31/55 (56.4)	18/54 (33.3)	**0.016**

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No Evidence of Accelerated Atheromatosis, Increased Arterial Stiffness or Hypertrophy in Ankylosing Spondylitis: A Systematic Case-Control Study. Aikaterini I. Arida[1], Maria Konsta[1], Alexios Iliopoulos[2], Maria Tektonidou[3], George Konstantonis[1], George D. Kitas[4], Athanasios D. Protogerou[1] and Petros P. Sfikakis[1]. [1]First Department of Propedeutic Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece, [2]Department of Rheumatology, Veterans Administration Hospital, Athens, Greece, [3]First Department of Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece, [4]The Dudley Group of Hospitals NHS Foundation Trust, Dudley, and Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom.

Background/Purpose: Chronic inflammatory arthritis is associated with increased cardiovascular disease (CVD) risk. The mechanisms behind this link include chronic inflammation, comorbidities and disease-related drugs. CV risk management according to local guidelines with aggressive suppression of inflammation for patients with RA, AS and PsA has been recommended. However, in contrast to RA where the bulk of supporting evidence exists, fewer studies have addressed CVD risk in AS. Moreover, the beneficial impact of anti-TNF agents, which are increasingly used in AS, has been extensively reported biasing somehow the link between AS *per se* and CVD risk. We aimed to compare subclinical atherosclerosis burden between AS patients to healthy controls and patients with RA.

Methods: We examined 81 consecutive non-diabetic AS patients free of clinical CVD (age 46.8±13.3, 85% men, disease duration 10 years (2–24), BASDAI 1.4 (0.4–3.2), BASFI 2.0 (0.95–2.85)). Current smokers were 62% of patients, 16% had dyslipidemia and 31% had hypertension, whereas 62% were receiving anti-TNF treatment. A subgroup of 68 AS patients could be exactly matched 1:1 with healthy controls for age, gender, smoking, dyslipidemia and hypertension. We also matched 14 AS patients with more than 10 years of disease duration 1:1 to non-diabetic RA patients, for age, gender and disease duration. Finally, we identified 24 of the 31 anti-TNF treatment-naïve patients whom we were able to match 1:1 for age and gender, smoking dyslipidemia and hypertension with 24 healthy controls. We evaluated subclinical atheromatosis in aortic and femoral arterial beds (presence of plaques), arterial hypertrophy (intimal-medial thickness adjacent to plaques when present; cross sectional area), and arterial carotid/aortic stiffness (by ultrasound and pulse wave velocity).

Results: Fewer patients with AS than controls had plaques (n=24 vs n=32, respectively, p=0.163). This observation was extended to the subgroup of 35 AS patients with more than 10 years of disease duration (n=14 vs n=22, respectively, p=0.056). Even when taking into consideration anti-TNF-naïve patients, there were no differences compared to controls. Neither BASDAI nor BASFI scores were found to be associated with the presence of plaques. Finally, and despite the small number of matched patients, presence and multiple localization of plaques were more prevalent in RA than in AS patients with more than 10 years disease duration (p=0.053 and 0.045, respectively). Notably, all indices of arterial hypertrophy and arterial carotid/aortic stiffness were comparable between AS patients and their matched controls.

Conclusion: In this group of relatively young Greek patients, AS (even long-standing disease) – in contrast to RA - does not associate with accelerated atheromatosis compared with very closely matched healthy controls. The differential CVD risk between AS and RA requires further investigation as it may have significant clinical implications in terms of prevention strategies.

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2618

Impact of Ustekinumab on Active Inflammation and Post-Inflammatory Structural Changes As Detected By Magnetic Resonance Imaging in Patients with Active Ankylosing Spondylitis: Results of a 28-Week, Prospective, Open-Label, Proof-of-Concept Study. Denis Poddubnyy[1], Kay-Geert Hermann[1], Johanna Callhoff[2], Joachim Listing[2] and Joachim Sieper[1]. [1]Charité Universitätsmedizin Berlin, Berlin, Germany, [2]German Rheumatism Research Center, Berlin, Germany.

Background/Purpose: Ustekinumab – a fully human monoclonal antibody against interleukins 12 and 23 – has been shown to be effective in reduction of symptoms of active ankylosing spondylitis (AS) in a proof-of-concept study (TOPAS) [1]. The purpose of the current work was to investigate the impact of ustekinumab on active inflammation and post-inflammatory structural changes in the sacroiliac joints (SIJ) and in the spine as detected by magnetic resonance imaging (MRI) in the TOPAS study.

Methods: In the TOPAS study, ustekinumab in a dose of 90 mg was administered subcutaneously at baseline, week 4 and week 16 in 20 patients with active AS (BASDAI score of ≥ 4 at screening) despite treatment with non-steroidal anti-inflammatory drugs. MRI of the SIJ and of the spine was performed at baseline and at week 24. Images were scored according to the Berlin scoring system for active inflammation and for chronic changes, including a detailed fatty degeneration score for SIJ, independently by two trained readers in a concealed and randomly selected order, blinded for all clinical data.

Results: Complete MRI sets (baseline and follow-up) were available in 17 patients (13 ASAS40 responders and 4 non-responders; in 3 ASAS40 non-responders no follow-up MRIs were available). There was a significant reduction of active inflammation on MRI at week 24 as compared to baseline both in the SIJ (osteitis change score -2.2±3.8 corresponding to 41% reduction) and in the spine (osteitis change score -1.2±2.3 corresponding to 31% reduction) – table. Reduction of active inflammation after 24 weeks was more prominent and statistically significant in patients with clinical response (ASAS40): osteitis change score in the SIJ was -3.1±3.8 in responders as compared to +0.6±1.3 in non-responders, p=0.015; similarly, osteitis change score in the spine was -1.9±1.9 in responders as compared to +1.0±2.4 in non-responders, p=0.023. Notably, clinical response (ASAS40) to ustekinumab was associated with higher level of inflammation at baseline in the SIJ (osteitis score 6.7±4.9 in responders vs. 2.0±1.7 in non-responders, p=0.030), and in the spine (4.9±3.6 in responders vs. 3.6±4.1 in non-responders, p=0.2).

There were no substantial changes in the scores for post-inflammatory lesions including fatty lesions in the entire group – table. However, the SIJ fatty lesion score increased significantly in patients with improvement of SIJ osteitis score by at least one point at week 24 (n=11): +0.8±1.1 vs.-0.4±0.8 in patients without osteitis improvements, p=0.022.

Conclusion: Ustekinumab effectively reduced active inflammation in the axial skeleton as detected by MRI in patients with AS after 24 weeks of treatment with a clear correlation between clinical and MRI responses. Higher level of active inflammation at baseline was associated with good clinical response.

Reference:

1. Poddubnyy D, et al. Ann Rheum Dis 2014;73:817–23.

Table 1. Changes in MRI scores over 24 weeks in patients with active AS (n = 17) treated with ustekinumab.

Parameter	Baseline	Week 24	p-value
SIJ osteitis score (0–24)	5.4 ± 4.9	3.2 ± 3.4	0.026
SIJ fatty lesion score (0–24)	11.9 ± 7.1	12.2 ± 7.2	0.2
SIJ erosion score (0–6)	4.0 ± 2.4	4.1 ± 2.3	0.3
SIJ sclerosis score (0–2)	1.2 ± 0.6	1.2 ± 0.6	1.0
SIJ ankylosis score (0–2)	0.4 ± 0.8	0.4 ± 0.8	0.3
Spine osteitis score (0–69)	4.1 ± 3.6	2.8 ± 3.0	0.041
Spine fatty lesion score (0–69)	5.9 ± 4.8	6.2 ± 4.3	0.2
Spine erosion score (0–46)	0.5 ± 1.1	0.5 ± 1.1	1.0
Spine bone proliferation score (0–69)	2.6 ± 5.9	2.7 ± 5.8	0.3

Disclosure: D. Poddubnyy, Abbvie, 5, MSD, 5, Pfizer Inc, 5, UCB, 5, Novartis Pharmaceutical Corporation, 5, Janssen Pharmaceutica Product, L.P., 5; **K. G. Hermann**, Abbvie, 5, Janssen Pharmaceutica Product, L.P., 5, MSD, 5; **J. Callhoff**, None; **J. Listing**, None; **J. Sieper**, Abbott, Merck, Pfizer, UCB Pharma, Novartis, Lilly, Janssen, 5, Abbott, Merck, Pfizer, UCB Pharma, Novartis, Lilly, Janssen, 8.

ACR/ARHP Poster Session C

Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Epidemiology, Women's Health, Cardiovascular and Central Nervous System

Tuesday, November 18, 2014, 8:30 AM–4:00PM

2619

Low Socioeconomic Status (SES) As Measured By Education Is (not) Associated with Worse Outcome in SLE: Data from the 1000 Canadian Faces of Lupus. Angela George[1], Christine Peschken[2], Earl Silverman[3], Christian A. Pineau[4], C Douglas Smith[5], Hector Arbillaga[6], Michel Zummer[7], Ann Clarke[8], Sasha Bernatsky[9], Marie Hudson[10], Carol A. Hitchon[2], Paul R. Fortin[11] and Janet E. Pope[12]. [1]University of Western Ontario, London, ON, [2]University of Manitoba, Winnipeg, MB, [3]Toronto Hospital for Sick Children, U of Toronto, Toronto, ON, [4]McGill University Health Center, Montreal, QC, [5]TOH Riverside Campus, Ottawa, ON, [6]Lethbridge Rheumatology practice, Lethbridge, AB, [7]U of Montreal, Montreal, QC, [8]U of Calgary, Calgary, AB, [9]McGill UHC/RVH, Montreal, QC, [10]McGill University, Montreal, QC, [11]Laval University, Division of Rheumatology, Centre de Recherche du CHU de Québec and Department of Medicine, Quebec City, QC, [12]St Joseph Health Care, London, ON.

Background/Purpose: To determine whether socioeconomic status, as measured by education, impacts disease activity (measured by SLAM-2,

SLEDAI-2K) or disease damage (measured by SLICC SDI) in patients with systemic lupus erythematosus (SLE).

Methods: Data from the 1000 Canadian Faces of Lupus, a multi-center, prospective cohort database included adult SLE patients from June 2005 onward. Socioeconomic status, as measured by education was defined as being either low (did not complete high school) or high (completed high school or further). The relationships between education and SLE outcomes were evaluated using one-way ANOVA and logistic regression analyses.

Results: 484 patients met inclusion criteria (mean age 47 years, 91.5% female, mean disease duration of 10 years); 80.4% had completed high school education or higher and 19.6% had not. One-way ANOVA analyses demonstrated: SLEDAI-2K ($p=0.01$), SLAM-2 ($p<0.3$) and SLICC ($p=1.0$). Proportionately more Aboriginal people were in the low education group (6.4% in high education vs. 17.9% in low education) and work disability was twice as common in low education group (13.6% vs. 28.4%). Income was higher in high education stratum. Logistic regression did not demonstrate significance between education and SLEDAI-2K when adjusting for age, sex, ethnicity, and disease duration. See table for results.

*P<0.05	High SES	Low SES
Total (% of group)	389 (80.4)	95 (19.6)
Female	360 (92.5)	83 (87.4)
Age, mean (SD), years	44.9 (12.8)	54.9 (13.2)
Ethnicity†		
Caucasian	287 (73.8)	72 (75.8)
Black	38 (9.8)	4 (4.2)
Asian	39 (10)	2 (2.1)
Aboriginal	25 (6.4)	17 (17.9)*
Work Disabled ¤	53 (13.6)	27 (28.4)*
Disease Duration	10.4 (8.9)	10.8 (9.6)
Income Level††	30 (7.7)	19 (20)
Per annum household income	47 (12.1)	8 (8.4)
<$15,000	68 (17.5)	16 (16.8)
$15,000 - $29,999	136 (35)	8 (8.4)*
$30,000-$49,999		
≥$50,000		
Disease Activity		
SLAM-	6.01 (3.8)	5. (4.1)
SLEDAI-2K	4.40 (4.1)	5.67 (5.2)
Disease Damage		
SLICC	1.34 (1.8)	1.33 (1.8)

Conclusion: This was mostly a prevalent, cohort so low income and work disability could be a result of SLE disease activity and damage. This cohort was literate and had access to lupus specialists so data may not be generalizable. Socioeconomic status, as measured by education, did not impact damage or disease activity in this cohort.

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Mortality and Survival in Systemic Lupus Erythematosus Patients: Trends in a Spanish Cohort from 1985 to 2013. Sergi Heredia[1], Javier Narváez[2], Andrea Zacarias[1], Milagros Ricse[1], Gloria Albert[1], Eulalia Armengol[1], Helena Borrell[1], Olga Capdevila[1], Francesca Mitjavila[1], Toni Rozadilla[1], Xavier Juanola[3] and Joan Miquel Nolla[1]. [1]Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, [3]University Hospital Bellvitge, Barcelona, Spain.

Background/Purpose: To study the mortality, survival and causes of death in a Spanish cohort of patients with systemic lupus erythematosus (SLE) over a 28-year period (1985–2013).

Methods: The sample comprised 219 patients with SLE treated between 1985 and 2013 at a tertiary university hospital that does not attend pediatric populations. Patients were registered in a specific database. Survival over time was studied by the Kaplan-Meier method. For patients who died or were lost to follow-up, data were censored at the last clinical visit.

Results: Mean age at diagnosis of SLE of the 219 patients recruited (189 women) was 46 ± 14 years, and mean follow-up was 8.47 ± 4.12 yrs (58% of patients were followed ≥ 10 yrs and 43% < 10 yrs).

During follow-up, 14 patients (6%) died: five due to cardiovascular disease, four of cancer, four due to infection (one invasive pulmonary aspergillosis, one *Pneumocystis jirovecii* pneumonia, one necrotizing fasciitis, and one *Pseudomonas aeruginosa*-induced sepsis), and one due to SLE activity.

The median time from diagnosis of disease to death was 106 months in patients who died of cardiovascular disease, 185 months in cases of infection, and 206.5 months in patients with cancer. Cumulative survival from onset was 99% at 5 years (95% CI 0.977–1.000), 97.6% at 10 years (0.954–1.000), 93% at 15 years (0.885–0.977), 87.8% at 20 years (0.808–0.953) and 82.1% (0.726–0.930) at 25 years. Overall mortality rate increased from 2005 to 2013. The mean age at death increased with time.

Conclusion: Long-term survival in a series of Spanish patients with SLE was high, with a cumulative survival from diagnosis of 97.6% at 10 years and 87.8% at 20 years. Cardiovascular disease (35%), infections (29%) and cancer (29%) represented the main causes of death.

Disclosure: S. Heredia, None; **J. Narváez**, None; **A. Zacarias**, None; **M. Ricse**, None; **G. Albert**, None; **E. Armengol**, None; **H. Borrell**, None; **O. Capdevila**, None; **F. Mitjavila**, None; **T. Rozadilla**, None; **X. Juanola**, None; **J. M. Nolla**, None.

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Health-Related Quality of Life in Patients with Systemic Lupus Erythematosus. Jin-Shei Lai[1], Karen Kaiser[1], Jennifer Beaumont[1], Sally Jensen[1], Amy H Kao[2], David Van Brunt[3] and Shih-Yin Chen[2]. [1]Northwestern University, Chicago, IL, [2]Biogen Idec, Cambridge, MA, [3]Formerly of Biogen Idec, Cambridge, MA.

Background/Purpose: Systemic lupus erythematosus (SLE) is a multi-organ chronic autoimmune disease that can negatively affect patients' health-related quality of life (HRQOL). This cross-sectional study collected HRQOL data from a sample of SLE patients using questionnaires from the Patient-Reported Outcomes Measurement Information System (PROMIS) and Quality of Life in Neurological Disorders (Neuro-QoL) to assess its association with patient-reported SLE disease severity.

Methods: Individuals with SLE were recruited via patient advocacy organizations to complete an online survey consisting of the PROMIS-29 health profile, PROMIS Psychosocial Illness Impact-Negative, and Neuro-QoL Applied Cognition. Patients self-rated their SLE disease severity to be negligible, mild, moderate, or severe. PROMIS and Neuro-QoL scores have mean=50, standard deviation (SD)=10 in the US general population. Analysis of variance was used to compare HRQOL scores between SLE disease severity groups.

Results: Of the 333 survey participants (mean age: 45 years; 92% female; 26% Black; mean disease duration=12 years), 55.6% reported their SLE disease severity as moderate or severe. Mean HRQOL scores were worse than those of the general population by half a SD or more with the greatest deficits observed in Fatigue, Applied Cognition, Psychosocial Illness Impact-Negative, Pain Interference, and Physical Function [Figure 1] [Figure 2]. Greater patient-reported SLE disease severity was associated with worse mean HRQOL scores (all $p<0.05$). Reliability exceeded 0.70 for all PROMIS and Neuro-QoL scores.

Conclusion: Relative to the general population, patients with SLE reported substantial deficits in HRQOL that correlated with their severity disease, especially in fatigue, pain, cognition, physical function and psychosocial illness impact. These deficits should be monitored in clinical practice in care for SLE patients and considered when investigating new therapies.

Figure 1. Negative HRQOL attributes by SLE severity (general population mean=50)

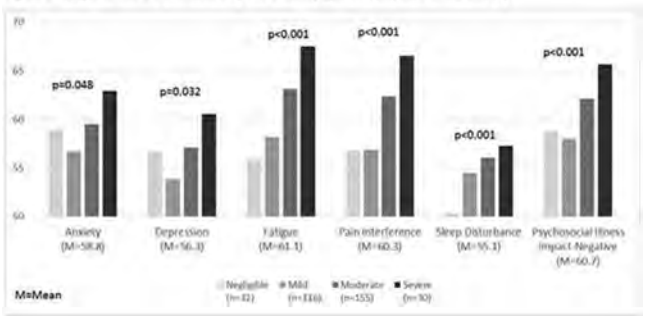
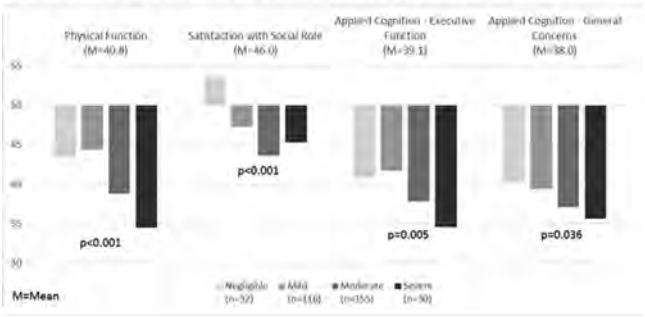


Figure 2. Positive HRQOL attributes by SLE severity (general population mean=50)



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"Systemic LUPUS Erythematosus in Spanish Males". Anne Riveros-Frutos[1], Irma Casas[2], Iñigo Rúa-Figueroa[3], José Maria Pego-Reigosa[4], M. Jesús García de Yebenes[5], Alejandro Olivé[2], Jose Rosas[6], Paloma Vela[7], Monica Ibanez Barcelo[8], Vicente Torrente[9], Ivan Castellvi[10], Javier Narváez[11], Mireia Moreno[12], R. Blanco Alonso[13], Víctor Martínez Taboada[14], Jaime Calvo-Alen[15], Mª Angeles Aguirre[16], Mercedes Freire[17], Enrique Raya[18], Celia Erausquin[19], Esther Uriarte[20], Elvira Díez Álvarez[21], Tomás Vázquez Rodríguez[22], Antonio Fernández Nebro[23], Eva Tomero[24], Paloma García de la Peña[25], Ana Sánchez Atrio[26], Monica Fernández de Castro[27], Antonio Zea[28], Patricia Richi[29], Francisco Lopez Longo[30], María Galindo-Izquierdo[31], Patricia Carreira[32], Gema Bonilla[33], Carlos Marras Fernández Cid[34], Maria Loreto Horcada[35], Carlos Montilla[36], Blanca Hernández-Cruz[37], José Marenco de la Fuente[38], Marian Gantes[39], Olaia Fernández Berrizbeitia[40], Juan J. Alegre[41], Ángela Pecondón Español[42], Manuel Rodríguez-Gómez[43], Victor Quevedo[44], José Hernández Beirain[45] and Lucía Silva Fernández[46]. [1]Hospital Universitario Germans Trias i Pujol, Badalona, Spain, [2]Hospital Universitari Germans Trias i Pujol, Barcelona, Spain, [3]Hospital Doctor Negrin, Las Palmas de Gran Canaria, Spain, [4]Hospital Meixoeiro, Vigo, Spain, [5]Research Unit of the SER, Madrid, Spain, [6]Hospital Marina Baixa. Villajoyosa, Villajoyosa, Spain, [7]Hospital General de Alicante. Spain, Alicante, Spain, [8]H. Son Llatzer, Palma de Mallorca, Spain, [9]Hospital Moisès Broggi, Barcelona, Spain, [10]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [11]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain, [12]Hospital Parc Taulí, Sabadell, Spain, [13]Hospital Universitario Marques de Valdecilla, Santander, Spain, [14]Marqués de Valdecilla, Santander, Spain, [15]Hospital de Sierrallana. Torrelavega. Spain, Torrelavega, Spain, [16]IMIBIC-Reina Sofia Hospital, Cordoba, Spain, [17]Hospital Universitario Juan Canalejo, La Coruña, Spain, [18]University Hospital San Cecilio, Granada, Spain, [19]Hospital Dr, Negrín, Las Palmas Gran Canarias, Spain, [20]Hospital de Donosti, San Sebastian, Spain, [21]Hospital de León. Spain, León, Spain, [22]Hospital Lucus Augusti, Lugo, Spain, [23]Hospital Carlos Haya. Malaga, Malaga, Spain, [24]Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain, [25]Hospital Norte Sanchinarro, Madrid, Spain, [26]Hospital Príncipe de Asturias, Immune System Diseases/Rheumatology department, Alcalá de Henares, Madrid, Spain, [27]Hospital Puerta del Hierro, Madrid, Spain, [28]Hospital Universitario Ramon y Cajal, Madrid, Spain, [29]Hospital Infanta Sofía, Madrid, Spain, [30]Hospital Gregorio Marañón, Madrid, Spain, [31]Hospital 12 de octubre, Madrid, Spain, [32]Hospital Universitario 12 de Octubre, Madrid, Spain, [33]Hospital La Paz, Madrid, Spain, [34]Hospital Virgen de la Arrixaca, Murcia, Spain, [35]Complejo Hospitalario de Navarra, Pamplona, Spain, [36]Hospital Clínico Universitario de Salamanca, Salamanca, Spain, [37]University Hospital Virgen Macarena, Sevilla, Spain, [38]Hospital de Valme, Sevilla, Spain, [39]Hospital Universitario de Canarias, Tenerife, Spain, [40]Hospital de Basurto, Bilbao, Spain, [41]Hospital Universitario Dr Peset, Valencia, Spain, [42]Hospital Miguel Servet, Zaragoza, Spain, [43]Complejo Hospitalario Universitario de Ourense, Ourense, Spain, [44]Hospital de Monforte, Lugo, Spain, [45]Hospital Insular de Gran Canaria, Las palmas Gran Canarias, Spain, [46]Hospital Universitario de Guadalajara, Guadalajara, Spain.

Background/Purpose: To describe the demographic, clinical and immunological manifestations in male patients with Systemic Lupus Erythematosus (SLE).

Methods: Patients diagnosed of SLE that were in the RELESSER data base (National Registry of Patients with Systemic Lupus Erythematosus of the Spanish Society of Rheumatology) were included. This is a multicenter retrospective cross-sectional study. We analyzed 3658 patients with SLE. All met the ACR criteria. Socio- demographic variables, comorbidities, classification, clinical and immunological manifestations were evaluated. Pearson's chi–square test, t-Student, ANOVA and multivariate logistic regression analysis were performed

Results: A total of 3658 patients were included: 353 men (9.7%) and 3298 women (90.2%), with an average onset of symptoms of 37 ± 17 and 32 ± 14 years of age respectively. In 7(0.1%) the gender was unknown. The male/female ratio was 9/1.The age of onset of symptoms and age at diagnosis was higher in men than in women (P<0.0001). Diagnosis in males was sooner than in females (P=0.04).The most common age range at diagnosis in both genders was 21–49 years(P<0.0001).

Table 1 Clinical manifestations

		MISSING N	MALE (N:353) N(%)	WOMEN (N:3298) N(%)	VALUE OF P
Systemic Manifestations	Weight loss	68	48 (13,7%)	309 (9,5%)	0,01
	Lymphadenopathy	74	49 (14%)	320 (9,9%)	0,02
	Splenomegaly	108	19 (5,5%)	99 (3,1%)	0,02
Cutaneous manifestations	Exanthema	62	190 (54,3%)	2180 (67,1%)	<0,0001
	Alopecia	86	54 (15,8%)	1229 (38%)	
Osteoarticular manifestations	Erosive arthritis	60	20 (5,8%)	342 (10,5%)	0,01
	Avascular bone necrosis	67	30 (8,5%)	121 (3,7%)	<0,0001
	Fibromyalgia	94	1 (0,3%)	223 (6,9%)	<0,0001
Pulmonary Manifestations	Pleural fibrosis	43	8 (2,3%)	25 (0,8%)	<0,0001
	Pulmonary thromboembolism	33	18 (5,1%)	86 (2,6%)	0,01
Cardiovascular manifestations	Libman Sachs endocarditis	103	7 (2%)	28 (0,9%)	0,04
	Angina or coronary bypass	52	19 (5,4%)	50 (1,5%)	<0,0001
	Acute myocardial infarction	61	24 (6,9%)	47 (1,4)	<0,0001
	Cardiomyopathy	79	20 (5,8%)	84 (2,6%)	<0,0001
	Pericarditis	52	15 (4,3%)	59 (1,8%)	<0,0001
Peripheral vascular manifestations	Claudication for more than 6 months	45	8 (2,3%)	23 (0,7%)	<0,0001
	Deep vein thrombosis	50	24 (6,9%)	119 (3,7%)	<0,0001
	Raynaud	142	80 (23,7%)	1114 (35%)	<0,0001
Renal manifestations	Lupus nephritis	89	156 (44,8%)	933 (29%)	<0,0001
	HTA in the first outbreak	182	68 (20,1%)	330 (10,5%)	<0,0001
	Hematuria	247	130 (38,70%)	908 (29,5%)	<0,0001
	Creatinine clearance = 50 irreversible	112	31 (9%)	161 (5%)	<0,0001
	Proteinuria = 3,5g/24hs	126	21 (6,1%)	114 (3,6%)	0,02
	Terminal renal insufficiency	146	16 (4,7%)	82 (2,6%)	0,03
Neuro psychiatric manifestations	Lupus headache	89	10 (2,9%)	204 (6,3%)	<0,0001
	Seizures	76	32 (9,2%)	156 (4,8%)	<0,0001
	Depression	89	36 (10,3%)	574 (17,8%)	<0,0001
Immunology	Ac anti DNA positive	99	271 (78,6%)	2342 (72,9%)	0,02
	AC anti RO positive	96	94 (27,5%)	1300 (40,8%)	<0,0001
	Positive lupus anticoagulant	1007	86 (34,11%)	547 (22,8%)	<0,0001

Women had more frequently a history of autoimmune thyroid disease (P<0.001). Males have more cardiovascular comorbidities (P<0.001). Comparing comorbidities in men with SLE by age range, it was found that SLE patients over 50 years of age had more comorbidity with p<0.05. A total of 68%(236) of males with SLE required hospitalization in comparison with 53%(1713) female (P< 0.001). During follow-up 208 patients died, 30(9.3%) were male and 178 (5.9%) women (P=0.02). On multivariate analysis, the only statistically significant variable was age. It was seen that patients over 50 year-old had a higher mortality than those under 50 year-old, regardless of gender, delay in diagnosis, risk factors and clinical features OR: 5.32 (CI: 3.61 to 7.84) P<0.001.

Conclusion: Patients with SLE older than 50 years old are at increased risk of mortality. In male patients with SLE: the age at diagnosis and the onset of symptoms is higher than in women. The diagnostic delay is lower in men than in women. Men have more cardiovascular comorbidities, especially those over 50 years-old and also more serositis, renal and cardiovascular involvement than women.

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Treatment Patterns and Resource Utilization of Systemic Lupus Erythematosus Patients Newly Initiating Standard of Care: United States Commercial and Medicare Supplemental Claims Analysis. Shonda A Foster[1], Emily Durden[2], Brett Maiese[2], Sarah Al Sawah[1] and Kathleen Solotkin[1]. [1]Eli Lilly and Company, Indianapolis, IN, [2]Truven Health Analytics, Bethesda, MD.

Background/Purpose: Currently, there is not a standard treatment algorithm for the management of Systemic Lupus Erythematosus (SLE); however, there are medications that may be considered standard of care (SOC) for the treatment of SLE. Treatment may vary among patients depending on disease activity, presenting signs and symptoms, extent of organ involvement and access to care. Thus, there is a need to understand the range of treatment patterns in SLE patients.

Methods: The MarketScan®Commercial Claims and Encounters and Medicare Supplemental Databases from Truven Health Analytics were used to retrospectively analyze SLE patients newly initiating SOC treatment (i.e., antimalarials, glucocorticoids, immunosuppressants, and monoclonal antibodies). Demographic and clinical characteristics, treatment patterns (e.g., augmentation, switching, and discontinuation), all-cause healthcare resource utilization and costs (i.e., sum of patient-paid out-of-pocket costs and plan-paid amounts) were examined in the 12 months following initiation of SLE SOC treatment (index date). Included were adult SLE patients who had ≥1 prescription claim for an SLE SOC treatment between January 2008 and December 2011 (without prior SOC treatment) and continuous medical and prescription coverage ≥12 months prior to and ≥12 months following the index date.

Results: There were 8,098 patients included in the study. Mean age of the cohort was 49 (± 13.8) years, 88.3% were female, and 12.1% were insured by Medicare. Most patients (98.7%) had ≥1 comorbidity; the most frequent comorbidities in the pre-index period were hypertension (32.6%) and anemia (13.9%). At index, 26.6%, 64.0%, 2.9%, and 0.2% of patients initiated treatment with antimalarials, glucocorticoids, immunosuppressants, or monoclonal antibodies, respectively, compared to 56.6%, 63.8%, 20.3%, and 1.1% during the 12-month post-index period. At index, 6.3% of patients initiated on some combination of the classes. During the 12-month post-index period, the index medication class was discontinued by 0.5%, 29.2%, 6.8%, and 84.2% of those who received antimalarials, glucocorticoids, immunosuppressants, and monoclonal antibodies, respectively, and 24%, 31%, 26%, and 5% added another SLE SOC class, respectively. The percentages of patients who switched from the index SOC class to a different SOC class were low, ranging from 0.0% to 5.3% among index therapies. During the 12-month follow-up period, almost all patients incurred outpatient visits (99%) and laboratory and radiology services (98%). Also, 21% of patients had an inpatient admission and 40% had an emergency room visit. The mean total healthcare cost was $24,575 during the 12-month follow-up period, including $8,329 inpatient, $13,069 outpatient, and $679 in SLE-related medication costs.

Conclusion: This analysis reveals the wide range of treatment patterns and substantial healthcare resource utilization and costs in SLE patients newly initiating SOC treatment. Understanding these treatment patterns in the context of associated disease activity, symptoms, and organ involvement may assist clinicians and payers in evaluating current and future therapies in the treatment of SLE.

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Impact of Provider Specialty on the Diagnosis and Management of Systemic Lupus Erythematosus in the American Indian/Alaska Native Population. John McDougall Jr.[1], Charles G. Helmick[2], S. Sam Lim[3], Caroline Gordon[4] and Elizabeth Ferucci[5]. [1]Dartmouth Hitchcock Medical Center, Lebanon, NH, [2]Centers for Disease Control and Prevention, Atlanta, GA, [3]Emory University School of Medicine, Division of Rheumatology, Atlanta, GA, [4]Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, [5]Alaska Native Medical Center, Anchorage, AK.

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex disease that is traditionally diagnosed and managed by specialists, typically rheumatologists. Higher SLE prevalence in racial/ethnic minorities such as American Indian/Alaska Native (AI/AN) people, often residing in areas with less access to rheumatologists, may necessitate diagnosis and management of SLE by primary care providers (PCP) in some cases. The purpose of this analysis was to identify areas of potential difference between PCP and specialist diagnosis and management of SLE in a population-based lupus registry of AI/AN people.

Methods: All individuals with SLE meeting our inclusion criteria were selected from the 2009 Indian Health Service lupus registry population. Inclusion in this analysis was limited to individuals with a final diagnosis of SLE made by a PCP or specialist (dermatologist, nephrologist or rheumatologist) and documented in the medical record. Based on medical record abstraction, SLE classification criteria were validated for each individual. Testing for biologic markers of SLE and medication use at any time during the course of the disease were also abstracted.

Results: Of the 320 patients identified with a documented physician diagnosis of SLE, 71 had been diagnosed by a PCP. SLE diagnosis by a specialist was associated with a higher median number of American College of Rheumatology (ACR) classification criteria (5 vs. 2), a higher percentage of patients meeting the definition of SLE by ACR criteria (79% vs. 22%), the Boston Weighted criteria (82% vs. 32%), and an abridged version of the Systemic Lupus International Collaborating Clinics (SLICC) criteria (83% vs. 35%) ($p<0.001$ for all comparisons). Additionally, specialist diagnosis was associated with an increased proportion with any testing for anti-double-stranded DNA antibody (93% vs 73%) and complement C3 and C4 (84% vs 52%) documented in the medical record ($p<0.001$ for all). Lastly, specialist diagnosis was associated with ever treatment with hydroxychloroquine (86% vs. 64%, $p<0.001$) as documented in the medical record at any time during their disease course.

Conclusion: Within the population studied, specialist diagnosis of SLE was associated with a higher number of SLE classification criteria met, a higher percentage of patients tested for biomarkers of disease, and a higher percentage of patients ever treated with hydroxychloroquine.

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Work Productivity in Systemic Lupus Erythematosus: Relationship with Clinical Features. Micaela Ana Cosatti[1], Sebastian Muñoz[2], Paula Alba[3], Claudia Andrea Helling[4], Susana Roverano[5], Judith Sarano[6], Samanta Malm-Green[7], Anastasia Secco[8], Maria Danielsen[9], Danith Medina Bornachera[10], Analia Alvarez[11], Alicia Eimon[1], Dora Pereira[12] and Cecilia N. Pisoni[1]. [1]CEMIC, CABA, Argentina, [2]Hospital Fernandez, CABA, Argentina, [3]Hospital Córdoba, Cordoba, Argentina, [4]Omi, CABA, Argentina, [5]Hospital J. M. Cullen, Santa Fe, Argentina, [6]Instituto de Investigaciones Médicas Alfredo Lanari, CABA, Argentina, [7]Hospital Bernardino Rivadavia, CABA, Argentina, [8]Hospital Bernardino Rivadavia, Buenos Aires, Argentina, [9]Hospital Regional, Santiago del Estero, Argentina, [10]Hospital Penna, CABA, Argentina, [11]Hospital Penna, CABA, Argentina, [12]Hospital Ricardo Gutierrez, La Plata, La Plata, Argentina.

Background/Purpose: To measure work productivity and the related risk factors in patients with systemic lupus erythematosus (SLE) from Argentina.

Methods: Employment status of 171 consecutive SLE patients was assessed using a standardized data collection form. Patients fulfilled 1987 ACR criteria for SLE. Sociodemographic data, employment status, type of employment, work physical demand, disease characteristics (ACR criteria, SLE duration, SLEDAI, SLICC/ACR-DI, treatment, LupusQol) and comorbidities were collected. Work productivity and activity impairment question-

naire (WPAI) was performed. The association between clinical characteristics with work productivity was examined by standard statistical tests.

Results: 171 patients were included, 91 % women, age was 40 (SD 12.13), 39 % white, 51% mestizo and 10% afro Latin-American. Hundred and thirty six patients (80 %) had more than 12 years of education and 59 (35.5 %) had no health insurance.

SLE disease duration was: 10.3 years (SD 9.2). SLEDAI score was 2 (SD 3.2), SLICC-SDI score was 0 (range 0–7), fatigue visual analogue scale (VAS) was 4 (SD 3), pain VAS was 3.5 (SD 4.8), patients global VAS was 1.7(SD 2) and physician global VAS was 2.8 (SD 2.8). Charlson comorbidity index was 1 (1–2.5).

LupusQol in the different domains was: physical health 72.2 (SD 23.5), emotional health 64.6 (SD 23.4), burden to others 56.1 (SD33.5), intimate relationships 67 (SD32.6), body image 69.5 (SD28.3).

Eighty seven patients (51%) were working, 84 (49%) were not working (unemployed, retired, housewives and students). Seventy one patients (83 %) perform mild or sedentary jobs by Soler Pujol scale.

Absenteeism and presenteeism were measured in employed SLE patients with WPAI questionnaire. Fifty four (62%) patients did not miss hours of work in the past week, 21 (24%) of patients miss >= 8 hours of work last week. Mean of missed hours of work last week due to SLE was 2.8 (SD 7.8), the average hours worked last week was 29 (SD 20.6).

Presenteeism: 41 % of patients (n = 36) presented some degree of work impairment. The degree of work impairment performance on 0–10 likert scale was 2.4 (SD 2.8).

Employed patients with SLEDAI >=6 did not experienced significantly reduced work productivity than employed patients with SLEDAI < 6 (p=0.99), patients with SLICC-SDI >=1 did not experienced significantly reduced work productivity than employed patients with SLICC-SDI <1 (p= 0.96). Work productivity was reduced among employed SLE patients with more severe pain (p<0.001), fatigue (p<0.001) and worse scores in Lupus-Quol physical (p<0.001) and emotional domains (p<0.001).

In the multiple regression analysis considering work impairment as dependent variable (adjusting by age, disease duration, VAS pain, VAS fatigue, LupusQuol physical and emotional domains), we found the physical domain of LupusQuol (OR 0.84 CI 0.71–0.98) as unique associated variable.

Conclusion: SLE patients with worse physical domain of LupusQuol showed higher work productivity compromise. Reduction of work productivity was not associated with more active SLE neither with more damage.

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Relationship of Socio-Demographic and Disease Factors with Loss-to-Follow-up and Appointment Noncompliance in Indigent Patients with Systemic Lupus Erythematosus.

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Background/Purpose: The relationship of medical noncompliance with poor health outcomes has been described in chronic diseases, including systemic lupus erythematosus (SLE). These outcomes are amplified in SLE due to its multi-organ involvement and high-risk immunosuppressant therapy. The association of noncompliance with socio-demographic and disease factors has been poorly studied and inconsistently identified. In past studies, noncompliance in SLE has been defined as rate of loss to follow-up (LTF) of scheduled outpatient appointments. Reported LTC rates have ranged from 24% to 48%. We investigate the relationship of socio-demographic and disease factors with noncompliance and focus on self-reported damage, health status, and depression in a predominantly indigent Black cohort.

Methods: We selected a sample of indigent SLE patients from the Grady Lupus Clinic who consented into the Georgians Organized Against Lupus (GOAL). GOAL is a longitudinal population-based cohort of patients with validated SLE from Atlanta, Georgia, who are surveyed annually on disease outcomes and access to care. Grady Lupus Clinic (GLC) is the only lupus clinic in GA that serves a large indigent population with SLE. Data on appointment compliance was abstracted from GLC electronic medical records. The first outcome, LTF, was defined as no GLC visits for the past 12 months within the past 24-month period. The second outcome, rate of appointment noncompliance, was calculated as 1 minus the rate of accomplished GLC visits in the past 12-month period. Logistic regression and multi-way ANOVA analyses examined the association of socio-demographic and disease factors with outcomes.

Result: The sample consisted of 127 patients, predominantly non-white (94%), females (91%) and living below 100% the poverty threshold (73%). Depression increased the risk of LTF, while longer disease duration and poverty protected against LTF (Table 1).

The adjusted appointment noncompliance rate was higher in patients who self-reported severe disease activity (34%; 95% CI 19–48%), compared to those with mild disease activity (18%; 95% CI 1–35%), p-value 0.058. In contrast, patients with organ damage tended to have lower appointment noncompliance (22%; 95% CI 8–26%) than those without organ damage (33%; 95% CI 16–50%), although the difference was not statistically significant (p 0.083).

Conclusion: Barriers to optimizing SLE outcomes include medical noncompliance defined as loss to follow-up and appointment noncompliance. The first step in overcoming this barrier is recognizing the associated socio-demographic and disease factors. Our data show that lower compliance is seen in patients with depression, shorter disease duration, higher income, and higher self-reported disease activity. With these factors in mind, targeted intervention for improved outcomes can be tailored for those within this vulnerable population.

Table 1 Risk factors of lost to follow-up in indigent SLE patients. Multivariable analysis

Factor	Odds Ratio	P Value
Depression (PHQ-9 score >=10)	**5.26 (1.11–24.80)**	**0.036**
Age at diagnosis (5-year increase)	1.06 (0.80–1.41)	0.67
Disease duration (1-year increase)	**0.90 (0.82–0.98)**	**0.019**
Education (3-year increase)	0.97 (0.48–1.97)	0.94
Gender (Female)	0.79 (0.12–5.29)	0.81
Below 100% the poverty threshold	**0.20 (0.05–0.73)**	**0.015**
Married/living with partner	0.96 (0.25–3.66)	0.95
No insurance or under-insured	2.50 (0.66–9.52)	0.18
Disease Activity Moderate (SLAQ = 11-16)	1.52 (0.24–9.47)	0.89
Severe (SLAQ >= 17)	1.88 (0.33–10.74)	0.53
Organ damage (SA-BILD ≥ 1)	0.58 (0.15–2.16)	0.41
Poor or fair health	0.28 (0.06–1.32)	0.11

PHQ-9 = 9-question Patient Health Questionnaire; SLAQ = Systemic Lupus Activity Questionnaire; SA-BILD = Self-Administered Brief Index of Lupus Damage.

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Comparison of Disease Characteristics and Organ Damage in Patients with Juvenile and Adult-Onset Systemic Lupus Erythematosus in Large Cohort from Turkey.

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Background/Purpose: Systemic lupus erythematosus (SLE) is a multi-systemic disease that may cause a broad spectrum of clinical and immunological manifestations. Age at onset has been shown to effect the clinical course and outcome of the disease. Herein, we aimed to define the differences in clinical characteristics and organ damage between patients with juvenile-onset (jo-SLE) and adult-onset (ao-SLE) SLE followed up in two tertiary referral centres.

Methods: This analysis included 935 patients 846 of whom attended the lupus outpatient clinic at Istanbul faculty of medicine between 1975 and May 2012 and 89 of whom were followed in the paediatric rheumatology outpatient clinic at Cerrahpaşa faculty of medicine between 2004 and 2013. At the time of recruitment, all patients fulfilled the ACR classification criteria for SLE. The data presented was the cumulative clinical and serological manifestations throughout the follow-up period. jo-SLE was defined as diagnosis at the age of 18 or younger according to the Paediatric Rheumatology International Trials Organization (PRINTO). Seven hundred nineteen (76.9 %) patients with ao-SLE and 216 (23.1 %) patients with jo-SLE were examined. Demographic characteristics, clinical features, autoantibody pro-

files and damage data (SLICC damage index) were compared between the groups. Statistical analyses were performed using SPSS, version 17.

Results: Comparison of demographics revealed significant differences in age at onset (13.5 ± 3.5 vs 34 ± 11.3 years) and duration of disease (86.5 ± 96.2 vs 111.6 ± 83.9 months) between juvenile and adult groups respectively ($p<0.05$). Of clinical symptoms, photosensitivity (71.6 vs 56.5 %), malar rash (73.6 vs 45.6 % and oral ulcers (23.1 % vs 15.4 %) were significantly more frequent in jo-SLE ($p<0.05$). As was previously reported, renal involvement was significantly more prevalent in the jo-SLE affecting 53.2 % of the patients compared to patients with ao-SLE (28.9 %) ($p<0.05$). Autoimmune haemolytic anaemia (AIHA) did also occur more often in the jo-SLE (33.3 vs 9.5 %, $p<0.05$) whereas reverse was true for pleuritis (11.6 vs 18.4 %, $p<0.05$). Of the autoantibodies, a higher frequency of anti-dsDNA (78,7 vs 69 %), anticardiolipin IgG (31.9 vs 21 %) and IgM (36.6 vs 19.3 %) were observed in the jo-SLE group. However, there were significantly more patients with anti-Sm positivity in ao-SLE (19.6 vs 10.2 %, $p<0.05$). According to the SLICC damage index, renal damage was significantly more frequent in the jo-SLE (22.8 %) than the ao-SLE (8.4 %) ($p<0.05$). However, damage in musculoskeletal system, namely avascular necrosis was more prominent in the ao-SLE (14.1 vs 8.4 %, $p<0.05$).

Conclusion: Our study confirms that clinical and serological differences exist between jo-SLE and ao-SLE. jo-SLE was associated with a higher frequency of renal involvement and damage. We also report a higher frequency of cutaneous symptoms, oral ulcers, AIHA and anti-dsDNA positivity in the jo-SLE. As renal involvement is a major predictor of prognosis and outcome, this study highlights the importance of awareness of the age of onset of SLE and supports the necessity of vigilant follow-up of this subgroup.

Disclosure: B. Artim-Esen, None; **O. Kasapcopur**, None; **S. Sahin**, None; **K. Barut**, None; **A. Omma**, None; **Y. Sahinkaya**, None; **S. Kamali**, None; **L. Ocal**, None; **M. Inanc**, None.

2628

Risk of Cancer Is Not Increased in Patients with Cutaneous Lupus Erythematosus: A Population-Based Study. Abha G. Singh, Cynthia S. Crowson, Mark Davis, Hilal Maradit Kremers, Eric L. Matteson and Vaidehi Chowdhary. Mayo Clinic, Rochester, MN.

Background/Purpose: Systemic immune dysregulation associated with chronic autoimmune diseases such as systemic lupus erythematosus (SLE) as well as immunomodulatory medications used for their treatment have been associated with an increased risk of malignancy. The pathogenesis of cutaneous lupus erythematosus (CLE) is similar to SLE. It is unclear whether CLE is associated with an increased risk of malignancy. Hence, we estimated the cumulative incidence of malignancy in a population-based cohort of patients with CLE, and compared the risk with an age- and sex-matched cohort without CLE.

Methods: Patients with subtypes of CLE (discoid, subacute cutaneous lupus, lupus panniculitis and bullous lupus) were identified from a population-based cohort in 1965–2005. Age- and sex-matched subjects without CLE were selected from the same population. Non-CLE subjects were assigned an index date corresponding to the CLE diagnosis date of the matched CLE patient. For a random sample of 66 of the 156 patients with CLE and the non-CLE subjects matched to them, data were collected on all cancers via medical record review. The cumulative incidence of cancer after CLE diagnosis was estimated using Kaplan–Meier methods. Cox models were used to estimate the relative risk of malignancy in patients with CLE as compared to non-CLE adjusted for age, sex and calendar year of index date.

Results: We identified 66 patients with CLE (mean age at time of CLE diagnosis, 55±14y; 64% females; 68% Caucasian; mean BMI, 27.3±7.2 kg/m^2; 34.8% smokers), who were followed over a median follow-up of 12.0 years (interquartile range [IQR], 8.1–17.3y). Positive antinuclear antibody, anti-SSA and anti-SSB were seen in 48%, 47% and 18% of patients with CLE, respectively. Median ESR was 11 mm/hour (IQR, 4.0–25.0) and CRP 2.9 mg/dL (IQR 1.5–3.9). Overall, we observed 14 cases of incident cancer (including 5 cases of non-melanoma skin cancer). The cumulative 1-, 5- and 10-year incidence of any malignancy after diagnosis of CLE was 3.4%, 10.9% and 14.6%, respectively. As compared to age- and sex-matched non-CLE controls, the overall risk of malignancies was not increased in patients with CLE (hazard ratio [HR], 1.09; 95% CI, 0.51–2.37; p=0.81) (Figure 1). The cumulative 1-, 5- and 10-year incidence of all malignancies except non-melanoma skin cancers in patients with CLE was 1.7%, 7.1% and 11.1%, respectively. As compared to matched controls, the risk of all malignancies except non-melanoma skin cancer in patients with CLE was not increased (HR, 0.88; 95% CI, 0.36–2.14; p=0.78).

Conclusion: The 10-year risk of any malignancy in a population-based cohort of patients with CLE is 14.6%. This risk is not increased as compared to age- and sex-matched subjects without CLE.

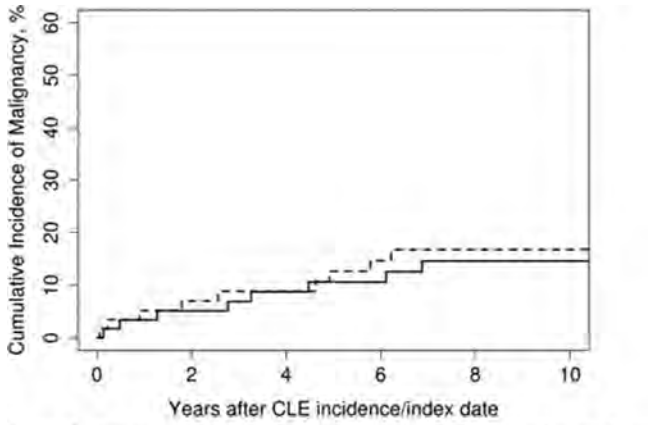


Figure 1. Cumulative incidence of malignancy in patients with cutaneous lupus erythematosus (CLE – solid line) and age- and sex-matched subjects without CLE controls (dashed line).

Disclosure: A. G. Singh, None; **C. S. Crowson**, None; **M. Davis**, None; **H. Maradit Kremers**, None; **E. L. Matteson**, None; **V. Chowdhary**, None.

2629

Childhood-Onset and Adult-Onset Systemic Lupus Erythematosus: Distinctions in an Underserved Ethnic Minority Cohort. Rebekah Neal[1], Kimberly DeQuattro[2], Elizabeth C. Ortiz[1] and Francisco P. Quismorio Jr. [3]. [1]University of Southern California, Los Angeles, CA, [2]LAC+USC Medical Center, Los Angeles, CA, [3]Keck School of Medicine, University of Southern California, Los Angeles, CA.

Background/Purpose: Previous studies suggest differences between childhood-onset SLE (cSLE) and adult onset SLE (aSLE). Whereas the prevalence of nephritis, neuropsychiatric, dermatologic, and hematologic manifestations are higher in cSLE, Raynaud's phenomenon, pleuritis, and sicca symptoms are more common in aSLE. cSLE tends to have more severe organ involvement at presentation and higher scores on damage indices. The purpose of our study is to determine whether such differences exist among an urban, poor, uninsured, ethnic minority SLE patient population in Southern California.

Methods: This is a single center, cross sectional, retrospective study of 250 consecutive SLE patients. All patients met ACR criteria for the classification of SLE and were diagnosed at < 40 years of age. cSLE and aSLE patients were defined as age at diagnosis < 18 years and ≥18 years, respectively. Gender, ethnicity, age at diagnosis, and duration of follow up were noted. Outcome measures included prevalence of nephritis, other disease manifestations, cyclophosphamide use and SLICC scores. Group characteristics were summarized by descriptive statistics and differences between groups were analyzed by the chi square test and the student's t test.

Results: There were 76 patients in the cSLE group and 174 patients in the aSLE group. Overall 76% of patients were Hispanic, 8% Black, 14% Asian, 1% Caucasian, and 1% other. Ethnic breakdown was similar between cSLE and aSLE groups as was gender (84% women, 16% men). The average age at entry into study in the cSLE group was 25.5 years (range 17–37 years) and 31.0 years (range 19–39 years) in the aSLE group. The average duration of follow up was 12.4 years and 6.8 years for cSLE and aSLE, respectively. The frequency of nephritis (54% vs 53%), neuropsychiatric lupus (9.5% vs 8.6%), cytopenias (46% vs 47%) and anti-phospholipid syndrome (6.6% vs 8.6%) were not significantly different between cSLE and aSLE, respectively, within the first two years of diagnosis. Use of cyclophosphamide was significantly higher in the cSLE group than the aSLE group (46% vs 24%, $p < 0.01$). At the time of entry into the study, cSLE patients showed a trend towards higher SLICC scores than aSLE. However, when the duration of follow up was accounted for, there were no significant differences between the two groups at 5, 10, 15, and 20 years of follow up.

Conclusion: In an underserved Hispanic and other ethnic minority SLE population, there is no difference in the frequency of nephritis, neuropsychiatric lupus, and other clinical manifestations between childhood-onset and

adult-onset SLE at presentation. This study differs from previous studies in the large proportion of Hispanic patients included and that the studied population was all adults at the time of inclusion. As these findings differ from previous, more studies are necessary within this population.

Disclosure: R. Neal, None; **K. DeQuattro**, None; **E. C. Ortiz**, None; **F. P. Quismorio Jr.**, None.

2630

An Evaluation of Quality of Life of Patients with Systemic Lupus Erythematosus Attending Rheumatology Clinic in Kenyatta National Hospital, Nairobi, Kenya. Jackline Odhiambo University of nairobi, nairobi, Kenya.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that affects all organs of the body. Due to its chronicity SLE has been known to affect the quality of life (QoL) of those affected by it. There is minimal data on SLE in East Africa and especially in Kenya. The quality of life of SLE patients in this country has never been assessed.

Methods: Patients diagnosed with SLE as by the ACR criteria and confirmed by a rheumatologist. were recruited into the study. Informed consent (assent for minors), was obtained from all participants. The patient's demographic data and last prescription was acquired from the file. Patients clinical history was taken and a physical exam was then done looking for the presence of malar rash, discoid rash, arthritis/athralgia, serositis and photosensitivity. These were defined as per the ACR criteria. After this the patient was given the LUPUS QOL questionnaire to fill. All the patients who attended the clinic at the study period were included in the study. Demographic variables (age) were summarized into means/medians while gender, was presented using percentages. Correlation of HRQOL and age, duration of illness and medication used was done using regression analysis.

Results: Sixty two patients were recruited into the study, 96% were female. Mean age of the population was 37.3yrs (12.2), ranging from 14–17 years. All the patients had some form of education with 61% having some form of tertiary education. Mean age at diagnosis was 34.5 yrs (12.2).

Majority of the patients (88.7%) had arthritis or athralgia. This was followed by oral ulcers at 32.3%, malar rash 59.7%, photosensitivity 58.1%, serositis 32.2%, CNS involvement 27.4% The least common clinical feature was discoid rash 17.7%.

On assessment of the HRQoL, The population scored globally poor in all the domains. The domain with the highest scores was planning (63.7), followed by burden to others, (58.9), fatigue (57.5), pain (56.6), physical health (54.0), body image (47.1) and the lowest intimate relationships (41.1).

Most common drug in use was prednisone at 46(74.2%), hydroxychloroquine (HCQ) 43(69.4%), NSAIDS 34 patients (54.8), Azathioprine (37.1%), Methotrexate 14 (22.6%), Mycofenolate Mofetil (MMF) 5(8.1%), CCB 7 (11.3%), cyclosporine 2(3.2).

Quality of life scores of the population were correlated with age for each domain. Positive correlation was found between Physical health (r 0.306 p= 0.016), burden to others (r=0.272 p= 0.032) and emotional health (r=0.315, p= 0.013) and advance in age.

There was found to be no significant association between HRQOL and the duration of illness or drugs used in all the domains.

Conclusion: This study demonstrates that patients with Lupus in Kenya have a poor quality of life. Lupus affects all aspects of their lives both physically and emotionally. In this study, older patients were found to have better quality of life when it came to physical health and emotional health. They were also found to be less affected by fatigue and thought of themselves as being less of a burden to others. The drugs used by the patients and the duration since diagnosis did not affect their quality of life.

Disclosure: J. Odhiambo, None.

2631

Overall Cause and Cause-Specific Mortality in a Multinational Inception Cohort of SLE. Murray B. Urowitz[1], Dafna D. Gladman[1], Nicole Anderson[2], Dominique Ibanez[1] and Systemic Lupus International Collaborating Clinics (SLICC)[3]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]Toronto Western Hospital Research Institute, Toronto, ON, [3]University of Toronto, Toronto Western Hospital (Coordinating Center), Toronto, ON.

Background/Purpose: A large multicenter multinational inception cohort was established initially to study risk factors for atherosclerosis (AS) in SLE. The aim of this study was to determine all cause and cause-specific mortality and their risk factors during the first 10 years of observation.

Methods: Patients enter the cohort within 15 months of SLE diagnosis (≥4 ACR criteria). Clinical and laboratory features of SLE and comorbidities are gathered in a standardized protocol at yearly intervals. Deaths are recorded as they occur and the cause of death was coded according to ICD9. Overall and Cause-Specific Survival curves were obtained using a Cumulative Incidence Competing Risk Analysis. Prediction models for overall survival and cause-specific for the three major causes were done using time-dependent covariate analysis for competing risks using date of birth as time zero. Variables included were geography of origin, ethnicity, sex, disease duration, disease activity, damage and medication use. The selection of variable retained was done using the stepwise approach.

Results: 1677 patients had follow-up beyond enrolment. At the time of data cut 78 patients had died. Cause of death included: atherosclerosis 11, active SLE 17, infection 27 and all other causes 23 (cancer in 5, other in 8, and unknown in 10). At enrolment 89.0% were female with a mean age at diagnosis of 34.9 ± 13.4 yrs and a disease duration of 0.5 ± 0.4 yrs. Mean SLEDAI-2K was 5.4 ± 5.4, SDI 0.12 ± 0.50 (SDI > 0: 131 (7.9%)). Patients on steroids 1167 (69.8%), on antimalarials 1124 (67.3%) and on immunosuppressives 671 (40.2%). 825 (49.2%) were Caucasian, 275 (16.4%) Black, 260 (15.5%) Hispanic, 255 (15.2%) Asian and 61 (3.6%) other. Geography of origin included USA 460 (27.4%), Canada 398 (23.7%), Europe 450 (26.8%), Mexico 160 (9.5%), and Asia 209 (12.5%). The Competing –Risk survival Analysis is presented in the Table.

	Hazard Ratio	95% Confidence Interval	P value
ALL CAUSES			
Mexico	4.02	2.30, 7.02	<0.0001
Disease Duration	0.90	0.82, 0.98	0.02
SDI	1.47	1.29, 1.66	<0.0001
On Steroids at Visit	3.97	2.01, 7.82	<0.0001
On Antimalarials at Visit	0.56	0.35, 0.89	0.01
ATHEROSCLEROSIS			
SDI excluding cardiac damage	1.56	1.17, 2.06	0.002
ACTIVE LUPUS			
Mexico	9.73	3.31, 28.59	<0.0001
Sex Male	4.40	1.51, 12.82	0.007
Disease Duration	0.70	0.55, 0.91	0.006
SDI	1.58	1.17, 2.13	0.003
INFECTION			
Hispanic	4.50	1.70, 11.92	0.002
SDI	1.59	1.32, 1.93	<0.0001
On Steroids at Visit	25.27	3.35, 190.66	0.002
On Antimalarials at Visit	0.39	0.17, 0.92	0.03
On Immunosuppressives at Visit	0.27	0.12, 0.61	0.002

Damage was an important risk factor for all cause and cause-specific mortality. Demographic factors, disease activity and treatment contribute differently to mortality both all cause and cause specific. Anti-malarials are protective for all-cause mortality and mortality due to infection.

Conclusion: Risk factors differ for all cause mortality and mortality related to active lupus, atherosclerosis and infection and all must be considered in pursuing preventive strategies.

Disclosure: M. B. Urowitz, None; **D. D. Gladman**, None; **N. Anderson**, None; **D. Ibanez**, None; **S. L. I. C. C. (SLICC)**, None.

2632

The Cornerstone to Reasonable Allocation of Health Resource: Valuation of Health Utility in Systemic Lupus Erythematosus. Suli Wang and Liangjing Lu. Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China.

Background/Purpose: In a time of increasing economic constraints, it is crucial that health systems optimize their resource use to ensure that they generate the maximum possible health gain. Therefore, it is necessary for health interventions to be evaluated and compared across therapeutic boundaries. Undertaking such an evaluation requires a generic utility-based mea-

sure. But it remains uncertain whether the utility values obtained by direct or indirect methods are comparable and which approach is the most appropriate in Systemic Lupus Erythematosus (SLE) population. The objective of this study was to compare the utility values obtained using an indirect method based on the EuroQol scale (EQ-5D) and direct utility instruments, the standard gamble (SG) and visual analog scale (VAS), in patients with SLE.

Methods: 240 consecutive patients with stable SLE underwent assessment of disease activity SLE Disease Activity Index (SLEDAI)] and damage [Systemic Lupus Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI)] and completed a disease-specific health-related quality of life (HRQoL) measure, LupusQoL, and 3 utility measures: VAS, SG, and EQ-5D. Pearson's correlations were calculated between the LupusQol domains and the utility measures to assess validity. To assess reliability, intraclass correlations or kappa coefficients were calculated between first and second assessments, performed from 2 weeks apart, in patients without important clinical change in disease activity. Multiple regression models were performed for VAS and SG to determine predictor of utility.

Results: Disease activity from SLEDAI varied from 0 to 25 (median = 2). All domains of the LupusQoL correlated well with the VAS [r: 0.329–0.632, 95% confidence interval (CI) (0.30, 0.56)] and EQ-5D value [r: 0.299–0.757, 95%CI (0.35, 0.69)] except body image (r=0.162 and 0.165, p=0.018 and 0.016, respectively), and poorly with the SG [maximum r = 0.360, CI (0.0, 0.375); minimum r = 0.044, CI (0.0, 0.375)]. Test-retest reliability intraclass correlations for the VAS [ICC = 0.793, 95% CI (0.707, 0.856)], SG [ICC=0.770, 95% CI (0.676, 0.839)] were good. The kappa coefficient was poor (0.284) for the EQ-5D domain of Anxiety/Depression, but excellent (Mobility: 0.786; Self-care: 0.849; Usual activities: 0.972; Pain/Discomfort: 0.796) for the remaining domains. A model incorporating the SLEDAI score and LupusQoL domains of emotional health and pain were good predictors of VAS (R^2=0.56) and SG (R^2=0.221) utility measures.

Conclusion: The VAS, EQ-5D, and to some extent, SG, when compared with the disease-specific HRQoL survey LupusQoL, are valid and reliable measures to assess HRQoL in a group of patients with SLE and have emerged as promising outcome measures for future research in this population. It may also be used as a basis for further studies to obtain utility data with larger samples across SLE patients and provide helpful information to seek for theoretical basis for reasonable allocation of health resources.

Disclosure: S. Wang, None; **L. Lu**, None.

2633

Factors Associated with Damage Accrual and Survival in Chinese Patients with Systemic Lupus Erythematosus (SLE): A Prospective Cohort Analysis of 747 Patients. Chi Chiu Mok[1], Sau Mei Tse[1], Ling Yin Ho[1] and Chi Hung To[2]. [1]Tuen Mun Hospital, Hong Kong, Hong Kong, [2]Chelsea Heights, Hong Kong, Hong Kong.

Background/Purpose: To evaluate the factors associated with accrual of organ damage in a longitudinal cohort of Chinese patients with SLE

Methods: A longitudinal cohort of 747 southern Chinese patients who fulfill >=4 of the 1997 ACR criteria for SLE from 1995 to 2014 was studied. Organ damage in 12 systems was assessed by the ACR SLICC damage scores (SDI). The cumulative rate of survival was studied by Kaplan-Meier's plot. In those who died or were lost for follow-up, data were censored at the time of death and the last clinic visits, respectively. Early damage accrual was defined as occurrence of organ damage ($SDI^3$1) within the first year of SLE onset. Factors associated with damage accrual and mortality over time were studied by multivariate regression models.

Results: 747 SLE patients were studied. There were 691 women (93%) and 56 men (7%). The mean age at SLE onset was 33.0±13.5 years and the mean duration of follow-up was 111±89.1 months. Seventy-six patients (10%) died and 28(4%) patients were lost to follow-up. Early damage occurred in 191 (26%) patients. The frequency of organ damage in these patients, in decreasing order, was neuropsychiatric (29%), musculoskeletal (19%), renal (17%), dermatological (16%), pulmonary (9.4%), ocular (8.9%), cardiovascular (8.4%) and peripheral vascular (5.8%). Compared with those patients without early damage, patients with early organ damage were older at onset of SLE (37.4±15.2 vs 31.4±12.5 years; p<0.001) and were more likely to be men (13% vs 6%; p=0.009). Patients with early damage had accrued a significantly higher cumulative SDI score than those without (1.59±1.6 vs 0.84±1.5; p<0.001). Logistic regression revealed that the male sex (RR 2.20 [1.22–3.95]; p=0.008) and the age of SLE onset (RR 1.04[1.02–1.05]; p<0.001) were independently associated with early damage after adjustment for the use of corticosteroids, antimalarials and immunosuppressive agents that included cyclophosphamide, azathioprine and mycophenolate mofetil. In the entire cohort, 344 patients (46%) eventually developed organ damage ($SDI^3$1) and the median time to damage was 28 months. The cumulative survival of the patients studied was 98% at 12 months, 96% at 36 months, 94% at 60 months and 89% at 120 months. The SDI score was associated with mortality (age and sex adjusted HR for each point of increase in SDI 1.31[1.18–1.44]; p<0.001). Cox regression analysis showed that early damage (HR 6.49[3.84–11.0]; p<0.001) was independently associated with mortality after adjustment for age of SLE onset, sex and the use of medications that included prednisolone, cyclophosphamide, azathioprine, mycophenolate mofetil and hydroxychloroquine.

Conclusion: In this large longitudinal cohort of Chinese patients with SLE, the male sex and older age of onset were associated with early organ damage, which occurred most frequently in the neuropsychiatric, musculoskeletal and renal systems. The presence of early organ damage increased SLE mortality by more than 6-fold.

Disclosure: C. C. Mok, None; **S. M. Tse**, None; **L. Y. Ho**, None; **C. H. To**, None.

2634

A Signal of Improvement in Lupus Disease Activity at 3 Months Predicts Further Valid Improvement at 6 Months. Zahi Touma, Dafna D. Gladman, Dominique Ibanez and Murray B. Urowitz. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: In patients with active disease, physicians look for an early signal in response to treatment to guide their therapeutic decisions.

Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) measures disease activity in 24 descriptors, generates a total score describing disease activity overall. SLEDAI-2K records descriptors of disease activity as present or absent. In the SLEDAI-2K Responder Index 50 (S2K RI-50), each of the 24 descriptors has a definition for a ≥ 50% improvement resulting in an appropriate 50% score for the corresponding descriptor and a total score describing disease activity overall.

We aimed to determine if a signal of improvement in disease activity at 3 months predicts further improvement at 6 months.

Methods: Consecutive active lupus patients who attended the clinic between 2012 and 2014 were screened for inclusion. Patients were included if they: 1) had at least 1 of the following 5 SLEDAI-2K clinical organ systems active (vascular, renal, musculoskeletal, serosal or skin); central nervous system was excluded and 2) started or increased prednisone therapy and/or immunosuppressants. All patients had to have a follow-up visits at 3 and 6 months.

Outcome measures: Disease activity was measured by SLEDAI-2K at all visits and by S2K RI-50 at 3 months.

Study definitions: Signal of improvement by SLEDAI-2K is defined as a decrease by ≥1 in SLEDAI-2K score at 3 months. Signal of improvement by S2K RI-50 is defined as a decrease by ≥1 in S2K RI-50 score at 3 months.

Study endpoints: Based on the change in the total SLEDAI-2K score (baseline – last visit), each of the patients at last visit were grouped as: 1) improved (SLEDAI-2K decreased by ≥4) and not improved (SLEDAI-2K decreased <4).

First, we identified the patients with SLEDAI-2K signal at 3 months and those who did not have a SLEDAI-2K signal were further evaluated for possible S2K RI-50 signal. Patients with signals were reevaluated at 6 months to determine if they had further improvement.

Results: 87 patients with mean SLEDAI-2K at baseline visit was 8.9±5.1 were studied. 90% were female, age at baseline visit was 40.0±12.4 and disease duration was 13.2±9.6 years.

Signals of improvement: Of the 87 patients, 54 (62%) had a SLEDAI-2K signal at 3 months. Of the 33 patients who did not have a SLEDAI-2K signal, a S2K RI-50 signal was identified in 11 (33%) patients.

Study endpoints: Of the 54 patients with SLEDAI-2K signal at 3 months, 28 (52%) patients improved at 6 months. Of the 11 patients with S2K RI-50 signal at 3 months, 5 (46%) improved at 6 months.

Conclusion: A signal of improvement at 3 months predicts further improvement in disease activity at 6 months. S2K RI-50 signal at 3 months, which is not discern by SLEDAI-2K, predicts improvement in half of the patients at 6 months. S2KRI-50 can identify non responders at 3 months who will respond at 6 months.

Disclosure: Z. Touma, None; **D. D. Gladman**, None; **D. Ibanez**, None; **M. B. Urowitz**, None.

2635

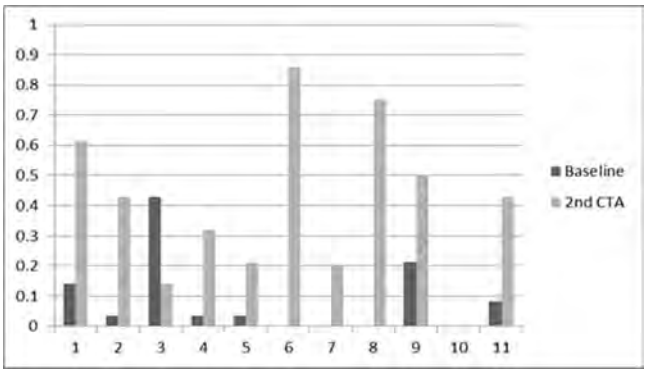
Noncalcified Plaque Progression in Systemic Lupus Erythematosus. Adnan Kiani[1], Armin Zadeh[1], Joao Lima[1], Laurence S. Magder[2] and Michelle Petri[3]. [1]Johns Hopkins University, Baltimore, MD, [2]University of Maryland, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Coronary atherosclerosis is a major cause of morbidity and mortality in SLE. New technology, computed tomoangiography (CTA) can measure non-calcified coronary plaque (NCP), which is more inflammatory, unstable and more prone to rupture. The aim of our current study was to determine the progression of noncalcified coronary plaque in SLE.

Methods: Repeat computed tomoangiography (CTA) was done in 11 (73% female, 91% Caucasian, 9% African-American, mean age 53 years) SLE patients after a baseline CTA. The CTA scans were evaluated quantitatively by a radiologist, using dedicated software. The correlation coefficient between the overall NCP score between 2 observers was 0.93. The kappa statistic for the assessment of noncalcified plaque (present or absent) in the 71 vessel segments was 0.42. The Noncalcified plaque score was the sum of plaque severity multiplied by the plaque composition, divided by the number of vessels examined.

Results: Figure 1 shows the baseline and second CTA results in these 11 patients. Nearly all (9/11) had progression of noncalcified plaque. One patient had no NCP and one patient had regression of noncalcified plaque. Four of five patients who progressed on calcified plaque, also had progression of noncalcified plaque. Out of 11 patients, 6 were on statins, 2 mycophenolate mofetil and 1 azathioprine. All 3 on immunosuppressants progressed.

Figure 1: Noncalcified Coronary Plaque Change Over Time in SLE Patients



Statins	+	+	+			+	+				
IS*	+				+						+

***Immunosuppressive drug**

Conclusion: Noncalcified plaque – the most risky coronary plaque– progressed in the majority of SLE patients. All those with progression were under the care of a dedicated cardiologist; 5 were on statin therapy. Even the 3 on immunosuppression showed progression. This, in particular, is disappointing, as in lupus mice, mycophenolate has been proven to reduce progression of atherosclerosis. Our study proves that NCP can be the outcome in intervention trials in SLE.

Disclosure: A. Kiani, None; **A. Zadeh**, None; **J. Lima**, None; **L. S. Magder**, None; **M. Petri**, None.

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Vitamin D Improves Endothelial Function in Patients with Clinically Stable Systemic Lupus Erythematosus (SLE). John A. Reynolds[1], David W. Ray[2], Terence O'Neill[3], Yvonne Alexander[4] and Ian N. Bruce[5]. [1]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, United Kingdom, Manchester, United Kingdom, [2]Institute of Human Development, The University of Manchester, Manchester, United Kingdom, [3]University of Manchester, Manchester, United Kingdom, [4]Manchester Metropolitan University, Manchester, United Kingdom, [5]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and repair, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom.

Background/Purpose: SLE patients have an increased risk of cardiovascular disease (CVD). Vitamin D deficiency has been associated with both CVD risk factors and subclinical CVD in lupus patients. There is currently no evidence that vitamin D therapy can reduce cardiovascular risk in SLE. Patients with SLE have endothelial dysfunction and restoration of vascular function may reduce CVD risk. We conducted an experimental study to determine the effect of vitamin D on endothelial function.

Methods: Clinically stable female SLE patients were recruited from a single site (Central Manchester). Serum 25(OH)D was measured by LC-MS and patients were classed as deficient (<20ng/ml) or replete (>30ng/ml). Patients were treated by their general practitioner according to local protocols (typically 400,000IU cholecalciferol over 10 days then 20,000IU weekly). Replete patients were not treated and acted as controls. Patients were assessed at baseline and after 3 months. Endothelial function was measured using flow-mediated dilatation (FMD) and expressed as endothelium dependent/endothelium independent (ED/EI) dilatation. Arterial stiffness (pulse-wave velocity, aPWV) was measured using Arteriograph. Cytokines were measured by ELISA. Disease activity was measured using the SLEDAI-2K and BILAG-2004 indices.

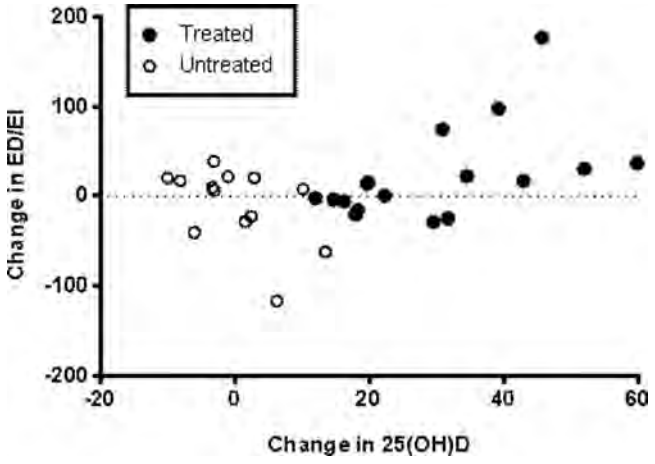
Results: We recruited n=22 vitamin D deficient patients and n=18 replete patients (median 25(OH)D 13.1 and 34.5ng/ml respectively). All patients were female and 36/40 (90%) had ≥4 ACR criteria. Deficient patients were younger (47.0 vs 57.9 years, p=0.007) and more likely to have a history of lupus nephritis (31.8% vs 5.6%, p=0.039) or require steroid (45.4% vs 5.6%, p=0.005) or immunosuppressant therapy (54.5% vs 11.1%, p=0.004).

FMD was strongly influenced by age and the baseline brachial arterial diameter. ED/EI in contrast was not related to either age or arterial diameter.

Serum 25(OH)D significantly increased in the deficient/treated group compared to the replete/untreated (median change 28.6 vs -0.62ng/ml, p<0.0001) and PTH significantly decreased (-8.6 vs 2.5pg/ml, p=0.039). There was no change in aPWV, disease activity, serum complement or cytokines (IL-6, TNFα, IP-10 or BAFF).

Change in 25(OH)D was strongly correlated with the change in ED/EI (r=0.650, p=0.006) in the treated group but not the replete group (r=-0.462, p=0.115) (figure). No association was seen between change in ED/EI and calcium, PTH or blood pressure. In an ordered logistic regression model the change in ED/EI remained associated with change in 25(OH)D after adjustment for age (OR 1.12 [1.02,1.24], p=0.017).

Conclusion: Increase in serum 25(OH)D significantly improved endothelial function over a short time period. This improvement was not due to changes in blood pressure or lupus disease activity. Vitamin D may be a novelvasculoprotective agent for SLE patients even in the absence of active disease.



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Assessment of Plaque Thickness and Area in Patients with SLE As Measures of Atherosclerosis - Associations with Disease Activity. Sara Croca[1], Maura Griffin[2], David Isenberg[3], Andrew Nicolaides[4] and Anisur Rahman[1]. [1]University College London, London, United Kingdom, [2]Vascular Screening and Diagnostic Centre, London, United Kingdom, [3]Arthritis Research UK Centre for Adolescent Rheumatology, University College London, London, United Kingdom, [4]University of Nicosia, Cyprus, Nicosia, Cyprus.

Background/Purpose: SLE is an independent risk factor for cardiovascular disease (CVD). Traditional risk stratification tools underestimate CVD risk in patients with SLE. Previous vascular ultrasound (US) studies have reported intima-media thickness (IMT) and presence of plaques in the carotid arteries of patients with SLE. However, some patients have femoral but not carotid plaques and alternative measures such as plaque thickness (pT) and plaque area (pA) may be more sensitive and informative than IMT.

Methods: We carried out carotid and femoral US of 100 patients fulfilling ACR classification criteria for SLE with no history of CVD. Mean IMT of the common carotid artery (CCA) was measured using automated software. Plaque was defined as a focal structure of thickness >1.2 mm from media-adventitia interface to intima-lumen interface. Where plaque was present, pT was measured using manual callipers and pA measured using image analysis software.

Statistical analysis using Spearman's correlation was carried out to investigate association between IMT, pA, pT and auto-antibody profile, lipids and homocysteine levels, blood pressure (BP), treatment and smoking status. Anti-apolipoprotein A1 (anti-ApoA1) IgG and IgM and anti-HDL antibodies were measured using direct ELISA protocols. Other clinical/serological data were obtained from medical records/patient interview.

Results: No patients had thickened CCA IMT (>0.1cm) but 37 had plaque in at least one site and 15 had plaque in ≥3 sites. The factors associated with pT, pA and CCA IMT are summarized in Tables 1 and 2. Whereas CCA IMT was primarily influenced by traditional risk factors such as BP, total cholesterol and LDL, pT and pA correlated with a wider range of variables including higher disease activity, elevated homocysteine, cholesterol:HDL ratio and IgG anti-HDL level.

Table 1: Factors associated with CCA IMT

Variable	Spearman Correlation (r^2)	p-value
Age at scan (yrs)	0.55	<0.0001
Disease duration (yrs)	0.39	0.02
Systolic BP	0.4	<0.0001
Diastolic BP	0.22	0.03
Mean BP	0.32	0.001
Number of sites with plaque	0.39	<0.0001
Total plaque area (sq mm)	0.40	<0.0001
Total plaque thickness (mm)	0.40	<0.0001
Total cholesterol (mmol/l)	0.36	0.0002
LDL (mmol/l)	0.31	0.002
Anti-apoA1 IgG in early disease	0.24	0.02

Table 2: Factors associated with plaque area and thickness

Variable	Correlation with plaque area (Spearman r^2)	p-value	Correlation with plaque thickness (Spearman r^2)	p-value
Age at scan (yrs)	0.56	<0.0001	0.58	<0.0001
Disease duration (yrs)	0.29	0.004	0.32	0.0001
Systolic BP	0.27	0.007	0.29	0.004
No of sites with plaque	0.99	<0.0001	0.99	<0.0001
Mean CCA IMT	0.39	<0.0001	0.39	<0.0001
Anti-La positivity	-0.33	0.001	-0.33	0.001
Persistent moderate/high disease activity	0.21	0.035	0.18	0.07
Persistent low disease activity	-0.21	0.035	-0.18	0.07
Serum homocysteine	0.31	0.04	0.31	0.05
Serum triglyceride	0.27	0.007	0.28	0.005
Total cholesterol/HDL ratio	0.25	0.013	0.23	0.02
IgG anti-HDL	0.21	0.03	0.21	0.039
No of BILAG A flares of disease activity	0.23	0.023	0.21	0.03

Conclusion: Although some authors have hypothesised a link between disease activity and atherosclerosis in SLE, this has not been shown convincingly in studies of IMT. More sensitive measurements such as pA and pT may help in linking disease activity and serology with atherosclerosis in SLE. This could help us target CVD risk reduction therapies to appropriate patients.

Disclosure: S. Croca, None; **M. Griffin**, None; **D. Isenberg**, None; **A. Nicolaides**, None; **A. Rahman**, None.

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The Protective Effects of Statins for Thrombosis in Patients with Systemic Lupus Erythematosus Positive for Antiphospholipid Antibodies. Toshiyuki Watanabe, Kenji Oku, Olga Amengual, Eri Sugawara, Ryo Hisada, Kazumasa Ohmura, Tomoko Fukui, Sanae Shimamura, Ikuma Nakagawa, Atsushi Noguchi, Haruki Shida, Michihito Kono, Yuka Shimizu, Takashi Kurita, Toshiyuki Bohgaki, Tetsuya Horita, Shinsuke Yasuda and Tatsuya Atsumi. Hokkaido University Graduate School of Medicine, Sapporo, Japan.

Background/Purpose: Thrombosis is one of the most frequent manifestations in patients with systemic lupus erythematosus (SLE). Although antiphospholipid antibodies (aPL) are well recognized risk factors for thrombosis in SLE, few studies have addressed the potential effect of additional factors in the development or in the prevention of thrombosis in those patients.

Objective: To identify risk and protective factors for developing thrombosis in SLE with or without aPL.

Methods: One hundred fifty two newly diagnosed consecutive patients with SLE without history of thrombotic events were recruited at Hokkaido University Hospital from April, 1997 to February, 2014. All patients, 138 woman and 14 men, fulfilled the 1997 American College of Rheumatology revised criteria for SLE. Seventy-eight patients (51.3%) had aPL. The development of thrombosis and death caused by thrombosis were defined as the study endpoint.

Results: The median follow-up period in all patients was 58 months (IQR 20–115 months). In 78 patients with aPL, the median follow-up period was 69 months (IQR 27–118 months). Fifteen patients with aPL (19.2%) developed thrombosis during the follow-up period. Cerebral infarction (CI) was observed in 6 patients, pulmonary embolism (PE) in 5 and deep vein thrombosis (DVT) in 6. Multivariate analysis with Cox's proportional hazards model showed that older age at SLE onset and anticardiolipin antibodies (aCL)-IgG positivity, (HR 1.80 for every ten age, 95%C.I. 1.11–2.94) and (HR 6.87, 95%C.I. 1.74–27.1), respectively, are statistically significant risk factor for thrombosis. Statin therapy appears as a statistically significant protective factor against thrombosis (HR 0.12, 95%C.I. 0.01–0.97) (Figure 1.). Disease activity, anti-thrombotic drug therapy and classical risk factors for atherosclerosis were not related to thrombosis. On the other hand, in 74 patients without aPL (median follow-up period 46 months, IQR 15–110 months), 7 patients (9.5%) developed thrombosis. CI was observed in 4 patients, intestinal infarction in 1, PE in 1 and DVT in 1. With Cox's proportional hazards model, older age at SLE onset represents a statistically significant risk for thrombosis (HR 2.73 for every ten age, 95%C.I. 1.17–6.37).

Conclusion: This study suggests that, in aPL positive patients, the late disease onset and the presence of aCL-IgG represent additional risk factors for thrombosis. Statin treatment appeared as a thrombotic protective factor.

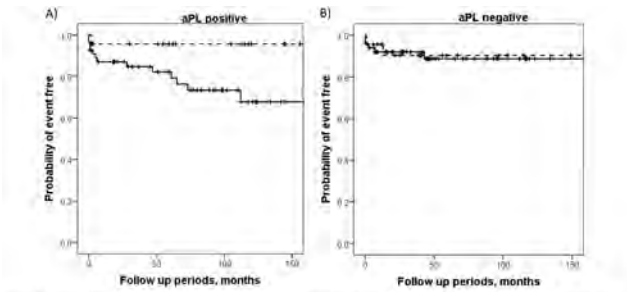

Figure 1. Kaplan-Meier survival curves for thrombotic events in patients treated (dashed line) and not treated (solid line) with statins. A) antiphospholipid antibodies (aPL) positive patients (Log-rank p=0.021) and B) aPL negative patients (Log-rank p=0.881)

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Coronary-Artery Atherosclerosis in Males with Systemic Lupus Erythematosus. Juanita Romero-Díaz[1], Sergio Criales-Vera[2], Eric Kimura-Hayama[2], Roberto Ivan Acosta-Hernandez[1], Maricruz Dominguez-Quintana[1] and Jorge Sánchez-Guerrero[3]. [1]Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico, [2]Instituto Nacional de Cardiologia, Mexico City, Mexico, [3]Mount Sinai Hospital and University Health Network, Toronto Canada, Toronto, ON.

Background/Purpose: Premature coronary-artery atherosclerosis is a major cause of morbidity and mortality in females with systemic lupus erythematosus (SLE), but little is known about the frequency, extent, risk-factors, and burden of coronary-artery disease in male patients.

Methods: We studied 96 male SLE patients attending our outpatient clinic and 94 healthy males w/o preexisting coronary heart disease, matched by age and race. Patients and controls had a standardized assessment of demographic characteristics and traditional cardiovascular risk factors. In addition, patients had an evaluation of lupus characteristics, medications, and laboratory tests including immunological, extended lipid profile, homocystein, and hsCRP. All patients and healthy controls were screened for coronary-artery calcifications using a 64-slice Multidetector Computed Tomography and the extent of calcification was measured by means of the Agatson score.

Results: Mean (SD) age of lupus patients and controls was 34.9 (10.5) and 35.3 (9.8) years, respectively. Coronary-calcifications were detected in 18 patients (18.8%) and 7 (7.5%) controls (OR 2.87, 95% CI 1.07–8.53). Median calcium score in patients was 68.75 (4.6–755.6), and 7.7 (1.1–140.2) in controls. Calcifications in lupus patients and controls were detected since age 31–40 and 41–50 years, respectively. In two patients, calcifications were detected within 3 years of diagnosis. Patients had more often hypertension (39% vs 4%, P<0.001) and higher levels of homocysteine (14.4+ 10.1 vs 9.3 + 2.5, P<0.001) than controls.

In comparison to patients w/o calcifications, patients with calcifications were older (32.7 + 9.5 vs 44.8 + 7.9 years, P<0.001), had a wider waist (89.1 + 14.4 vs 96.4 + 13.7 cm, P=0.008), higher systolic blood pressure (114.9 + 9.7 vs 121.7 + 12.0, P=0.02), higher Framingham risk score [2.2(1–17) vs 7.9(1–30), P<0.001] and current smokers (14% vs 39%, P=0.04). Lupus duration was longer (7.1 + 5.7 vs 13.4 + 9.6 years, P=0.01), had accrued more damage (SDI 1.0 + 1.2 vs 2.3 + 1.6, P=0.002), higher cumulative dose of prednisone [20.1 (0–56.1) vs 49.9(8.5–106.5 grams, P=0.001], and received Azathioprine more often (51% vs 78%, P=0.04). No difference was observed in lupus activity during the course of the disease, clinical manifestations, autoantibodies, and use of anti-malarials and aspirin.

Logistic regression adjusting by disease duration showed an independent association of age (OR 1.23, 95% CI 1.04–1.45) and SLICC score (OR 3.21, 95% CI 1.31–7.86) with calcifications.

Conclusion: Coronary-artery calcifications are more common, extensive, and present at younger age in male lupus patients than in the general population. Their association to traditional risk-factors and lupus characteristics, particularly chronic damage, raise the possibility of identifying modifiable risk-factors.

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Prevalence and Predictors of ECG Cardiovascular Abnormalities in Lupus Patients. Zahi Touma[1], Paula Harvey[2], Dafna D. Gladman[1], Dominique Ibanez[1], Arthy Sabapathy[1] and Murray B. Urowitz[1]. [1]University of Toronto, Toronto Western Hospital, Toronto, ON, [2]Women's College Hospital, Toronto, ON.

Background/Purpose: Patients with lupus are at increased risk for cardiovascular disease. Previous studies on healthy adults showed that abnormalities detected on resting electrocardiography (ECG) are associated with an increased risk for subsequent cardiovascular (CV) events. These **ECG-CV** abnormalities are: ST-segment and/or T-wave abnormalities, left ventricular hypertrophy (LVH), left-axis deviation and bundle branch block (BBB).

We aimed to determine the prevalence of ECG-CV abnormalities in a cohort of lupus patients and to examine the factors associated with ECG-CV abnormalities.

Methods: A standard digitally recorded 12-lead resting supine ECG was performed on consecutive patients attending the Lupus Clinic between October 2012-May 2014. Coded ECGs were reviewed and interpreted by a cardiologist using the Minnesota code classification system.

The frequency of the ECG-CV abnormalities was determined. In the univariate analysis normal ECG and ECG-CV abnormalities were compared (T-test and chi-squared test). Covariates with p<0.1 in addition to age, sex and ethnicity were evaluated with a stepwise logistic regression model to predict the ECG-CV abnormalities.

Results: 461 patients were studied. Of the 461 resting ECGs, 39.5% were abnormal: 7.6% axis deviation, 3.5% atrial enlargement, 11.3% arrhythmia and 6.7% pathological Q waves. ECG-CV abnormalities were present in 120 patients and included: ST-segment abnormalities and/or T-wave abnormalities in 17.4%, LVH in 8.9%, left-axis deviation in 4.1% and BBB in 6.3%.

Of the 120 patients with ECG-CV abnormalities, 65.0% had 1 abnormality, 26.7% had 2, 6.7% had 3 and 1.7% had all 4 abnormalities.

In the univariate analysis, in the group of ECG-CV abnormalities, patients were older, had a longer lupus duration, higher damage index, higher cumulative dose of corticosteroids, history of previous CAD event, presence of Coombs', La, LE cells, SCL70 and anti phospholipid lupus antibodies (table 1).

In the multivariate analysis, older age (OR =1.03; 95% CI: 1.01, 1.05; p=0.002), presence of damage (OR= 1.33; 95% CI: 1.17, 1.52; p<0.0001) and positive Coombs' (OR=2.37; 95% CI: 1.34, 4.21; p=0.003) were associated with ECG-CV abnormalities.

Conclusion: Of 461 resting ECGs 39.5% were abnormal. 26% had ECG-CV abnormalities. Older age, damage and Coombs' test were associated with ECG-CV abnormalities. These patients are at higher risk of developing CV events.

Table 1. Comparison of normal ECG and ECG-CV abnormalities

	Normal ECG (n=279)	ECG-CV abnormalities (n=120)	p
Sex			
Female	91.0%	88.3%	0.40
Race			
Caucasian	57.0%	60.0%	0.08
Black	15.8%	23.3%	
Asian	11.5%	7.5%	
Other	15.8%	9.2%	
Age @ SLE Dx at visit closest 30.3 ± 11.5	30.6 ± 11.2	0.84	
ECG	45.9 ± 13.0	52.3 ± 14.8	<0.0001
Disease Duration @ ECG	15.6 ± 10.2	21.7 ± 12.5	<0.0001
SLEDAI-2K First available in clinic at visit closest ECG	9.2 ± 8.1 3.7 ± 4.3	9.1 ± 7.5 3.5 ± 4.3	0.87 0.75
SDI > 0 at visit closest ECG	60.4%	80.3%	0.0001
SDI at visit closest ECG	1.29 ± 1.53	2.82 ± 2.62	<0.0001
SDI (Excluding Cardio) at visit closest ECG	1.24 ± 1.48	2.46 ± 2.39	<0.0001
Steroids at visit closest ECG	87.5%	91.7%	0.22
Cumulative Dose at visit closest ECG (gr)	33.8 ± 34.9	61.3 ± 55.6	<0.0001
CAD First available in clinic at visit closest ECG	0% 4.3%	1.7% 17.5%	0.09
Coombs First available in clinic at visit closest ECG	32.2% 63.8%	40.7% 80.5%	0.11 0.001
LA First available in clinic at visit closest ECG	18.3% 33.6%	22.2% 47.5%	0.44 0.009
LE First available in clinic at visit closest ECG	37.2% 58.1%	47.8% 73.0%	0.06 0.006

SCL70 First available in clinic at visit closest ECG	7.7% 19.7%	11.7% 35.8%	0.28 0.0006
APLA First available in clinic at visit closest ECG	26.3% 50.4%	27.4% 61.3%	0.82 0.045

Other studied variables: AMS 3 years prior ECG, antimalarials and immunosuppressants ever @ ECG, Jo1, RNP, Ro, ANCA, anti dsDNA and ANA ($p>0.05$).

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Cardiac Magnetic Resonance Imaging in Systemic Lupus Erythematosus. Alexa Meara[1], Namrata Dhillon[2], Kimberly Fisher[3], Paul Jensen[4] and Stacy P. Ardoin[5]. [1]The Ohio State University, Columbus, OH, [2]University of Pittsburgh Medical Center, Pittsburgh, PA, [3]The Ohio State University Wexner Medical Center, Columbus, OH, [4]The Ohio State University, Nationwide Children's Hospital, Columbus, OH, [5]Ohio State University College of Medicine, Columbus, OH.

Background/Purpose: Cardiac complications of SLE are common and include both acute and chronic manifestations: pericarditis, myocarditis, valvular disease, pulmonary hypertension, atherosclerosis, ischemic and non-ischemic cardiomyopathy. Cardiovascular magnetic resonance (CMR) imaging is a non-invasive, non-radiating imaging modality which can evaluate cardiac function and structure, myocardial inflammation, ischemia, and fibrosis. In this study we sought to assess indications for CMR use and CMR findings in SLE patients.

Methods: Chart review was performed for all patients with SLE diagnosis who underwent CMR for clinical indications from 2004 to 2014 at a single academic center. CMR results, cardiac risk factors, medications, SLE history, laboratory results, SLEDAI-2K (within 30 days of CMR) were recorded. Descriptive statistics were performed.

Results: During this time period, 31 SLE patients underwent 48 CMR. The patients were 45 ± 11.7 years, 77% female, duration SLE 9.5 ± 9.5 years, SLEDAI-2K5.5 ± 5.9, and 13% had antiphospholipid antibody syndrome. (Table 1). The following cardiovascular risk factors were present: diabetes mellitus (23%), hypertension (58%), dyslipidemia (16%), congestive heart failure (16.1%), current smoker (27%), history of myocardial infarction (6%). Clinical indications for obtaining CMR were chest pain (40%), dyspnea (4%), abnormal echocardiogram (31%), arrhythmia (4%) and other/unknown (12%). Half of the patients who underwent CMR stress testing had abnormal perfusion (Table 2). The most common abnormalities on non-stress CMR testing included abnormal myocardial T2 signal (29.8%), late gadolinium enhancement (21.3%), pericardial thickening (14.6%), and valvular abnormalities (21.7% aortic, 23.9% mitral, 17.4% tricuspid).

Conclusion: Cardiac complications of SLE are common and impart significant morbidity and mortality. In this study, CMR imaging identified several abnormalities not evident on other cardiovascular (CV) imaging modalities including increased T2 signal in myocardium (suggesting myocardial inflammation) and late gadolinium enhancement (suggesting fibrosis from prior ischemia or inflammation). CMR allows simultaneous evaluation of cardiac function, structure, inflammation, and fibrosis and, with stress imaging, ischemia. As SLE cardiac complications are myriad, CMR is a promising tool to assess the breadth of potential CV complications in the SLE patient presenting with CV symptoms.

Table 1 SLE Participant Characteristics

Age, mean ± SD years	44.9 ± 11.6
Sex, no. (%) female	31 (77.4%)
SLE Characteristics	
Duration SLE mean ± SD years	9.52 ± 8.8
SLEDAI-2K (within 30 days of CMR), mean ± SD	5.5 ± 5.9
History of lupus nephritis, no. (%)	5/31 (16.7%)
History of antiphospholipid antibody syndrome, no. (%)	4/31 (12.9%)
History of pericarditis, no. (%)	8/31 (28.8%)
History of positive anti-dsDNA antibody, no. (%)	15/25 (60.0%)
History of positive anti-Smith antibody, no. (%)	14/31 (58.3%)
Cardiovascular History	
Diabetes mellitus, no. (%)	7/31 (22.6%)
History of hypertension, no. (%)	18/31 (58.1%)
History of congestive heart failure, no. (%)	5/31 (16.1%)
History of ischemic stroke, no. (%)	3/31 (9.7%)
History of myocardial infarction, no. (%)	2/31 (6.5%)
History of dyslipidemia, no. (%)	5/31 (16.1%)
Current smoker, no. (%)	8/31 (26.7%)
Former smoker, no. (%)	10/30 (33.3%)
ECG abnormal within 30 days of CMR,no. (%)	21/38 (55.3%)
History of abnormal echocardiogram, no. (%)	40/45 (88.9%)
Medications at time of CMR	
Hydroxychloroquine, no. (%)	28/48 (65.1%)
No prednisone, no. (%)	15/48 (35.0%)
Azathioprine, no. (%)	7/48 (16.3%)
Mycophenolate mofetil, no. (%)	5/48 (11.6%)
Methotrexate, no. (%)	6/48 (13.9%)
Leflunomide, no. (%)	4/48 (9.3%)
Belimumab, no. (%)	2/48 (4.6%)
Cyclophosphamide, no. (%)	2/48 (4.6%)
Statin, no. (%)	20/48 (45.4%)
Other lipid lowering agent, no. (%)	4/48 (9.3%)
Aspirin, no. (%)	21/48 (48.8%)
Warfarin, no. (%)	8/44 (18.2%)
ACE-inhibitor, no. (%)	9/48 (20.9%)
Angiotensin receptor blocker, no. (%)	12/48 (27.9%)
Calcium channel blocker, no. (%)	15/48 (34.8%)
Diuretic, no. (%)	24/44 (54.5%)
Laboratory values within 30 days of CMR	
Erythrocyte sedimentation rate elevated, no. (%)	18/27 (66.7%)
C-reactive protein elevated, no. (%)	9/22 (40.9%)
Troponin I elevated, no. (%)	3/20 (15.0%)
Creatinine kinase elevated, no. (%)	3/12 (25.0%)
Brain natriuretic peptide elevated, no. (%)	5/14 (35.7%)
Hemoglobin, mean ± SD, mg/dL	10.4 ± 2.2
Serum albumin, mean ± SD, g/dL	3.2 ± 0.8
Serum creatinine, mean ± SD, mg/dL	1.2 ± 2.0

Abbreviations : ACE = angiotensin converting enzyme; CMR = cardiac magnetic resonance imaging; dsDNA = double stranded DNA; ECG = electrocardiogram; SLE = systemic lupus erythematosus, SLEDAI = systemic lupus erythematosus disease activity index.

Table 2: Cardiac Magnetic Resonance (CMR) Imaging in SLE Patients

Clinical Indications for Obtaining CMR	**N=48**
Chest pain, no. (%)	19 (39.5%)
Dyspnea, no. (%)	2 (4.2%)
Abnormal echocardiogram, no. (%)	15 (31.0%)
Arrhythmia, no. (%)	2 (4.2%)
Other/not available, no. (%)	6 (12.5%)
CMR Results	
CMR stress testing performed, no. (%)	11/48 (22.9%)
CMR stress with abnormal perfusion, no. (%)	5/36 (13.9%)
LV normal, no. (%)	40/46 (87.0%)
LV ejection fraction ± SD, %	56.4 ± 11.9
LV diastolic dysfunction present, no. (%)	3/46 (6.5%)
Abnormal LV peak circumferential strain, no. (%)	2/46 (4.4%)
RV function normal, no. (%)	44/46 (95.6%)
Myocardium with abnormal T2 signal, no. (%)	14/47 (29.8%)
Pericardial thickening, no. (%)	7/48 (14.6%)
Pericardial enhancement, no. (%)	1/47 (2.1%)
Late gadolinium enhancement, no. (%)	10/47 (21.3%)
Pulmonary artery enlargement, no. (%)	2/46 (4.4%)
Abnormal aortic valve, no. (%)	10/46 (21.7%)
Abnormal mitral valve, no. (%)	11/46 (23.9%)
Abnormal pulmonic valve, no. (%)	0%
Abnormal tricuspid valve, no. (%)	8/46 (17.4%)
Valvular vegetation present, no. (%)	0%

Abbreviations: CMR = cardiac magnetic resonance imaging; LV = left ventricle; RV = right ventricle.

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Risk of Cardiovascular Events in Patients with Cutaneous Lupus Erythematosus: A Population-Based Study. Abha G. Singh, Cynthia S. Crowson, Mark Davis, Hilal Maradit Kremers, Eric L. Matteson and Vaidehi Chowdhary. Mayo Clinic, Rochester, MN.

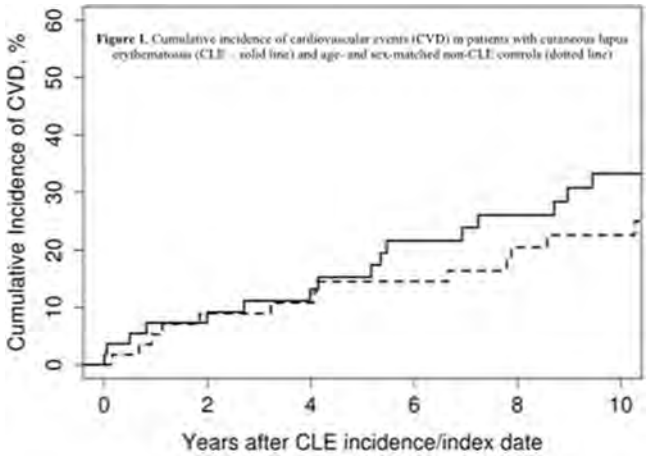
Background/Purpose: Systemic inflammation is an independent risk factor for atherosclerosis; chronic inflammatory diseases such as systemic lupus erythematosus (SLE) are associated with increased risk of cardiovascular disease (CVD). The pathogenesis of cutaneous lupus erythematosus (CLE) is similar to SLE, with complex gene-environment interactions, autoimmunity and immune-mediated cutaneous damage. It is not known whether CLE is associated with an increased risk of CVD. Hence, we estimated the cumulative incidence of CVD in a population-based cohort of patients with CLE, and compared the risk with an age- and sex-matched cohort without CLE.

Methods: Patients with subtypes of CLE (discoid, subacute cutaneous lupus, lupus panniculitis and bullous lupus) were identified from a population-based cohort from 1965–2005. Age- and sex-matched subjects without CLE were selected from the same population. Cardiovascular events (coronary artery disease [CAD], myocardial infarction, angina, heart failure, stroke,

transient ischemic attack, peripheral arterial disease) were collected via medical record review for a random sample of 66 of the 156 patients with CLE and the non-CLE subjects matched to them. The cumulative incidence of CVD was estimated using Kaplan-Meier methods. Cox models were used to estimate the relative risk of CVD in patients with CLE compared to non-CLE after adjustment for age, sex and calendar year.

Results: We identified 66 patients with CLE (mean age at time of CLE diagnosis, 55±14y; 64% females; 68% Caucasian; mean BMI, 27.3±7.2 kg/m^2; 35% current smokers), who were followed over a median follow-up of 12.0 years (interquartile range [IQR], 8.1–17.3y). Positive antinuclear antibody, anti-SSA and anti-SSB were seen in 48%, 47% and 18% of patients with CLE, respectively. Median ESR was 11 mm/hour (IQR, 4.0–25.0) and CRP 2.9 mg/dL (IQR 1.5–3.9). In this cohort, 9% were diabetic, 59% were hypertensive, 35% had hyperlipidemia and 8% had a family history of CAD; these risk factors were comparably distributed in 66 age- and sex-matched controls, except a higher prevalence of hyperlipidemia (53%, p=0.036). During follow-up, we observed 24 cardiovascular events (including 7 cases of myocardial infarction) in patients with CLE. The cumulative 1-, 5- and 10-year incidence of cardiovascular events after diagnosis of CLE was 7.3%, 15.3% and 33.2%, respectively. As compared to subjects without CLE, the risk of all cardiovascular events (hazard ratio [HR], 1.37; 95% confidence interval [CI], 0.77–2.49; p=0.29) or myocardial infarction (HR, 1.18; 95% CI, 0.77–2.49; p=0.29) was not significantly higher in patients with CLE (Figure).

Conclusion: The 10-year risk of cardiovascular events in a population-based cohort of patients with CLE is 33%. This risk is not increased as compared to age- and sex-matched non-CLE controls.



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Angiogenic and Antiangiogenic Factors in Patients with Systemic Lupus Erythematosus. Guilherme Ramires de Jesus[1], Camila Souto Oliveira[2], Flavia Cunha dos Santos[2], Nilson Ramires de Jesus[2], Luis Cristovao Porto[2], Roger A. Levy[3] and Evandro Mendes Klumb[2]. [1]Department of Obstetrics, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, [2]Hospital Universitario Pedro Ernesto, Rio de Janeiro, Brazil, [3]Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil.

Background/Purpose: SLE mainly affects young women and pregnancy in these patients has significant morbidity and mortality. Clinical and laboratory findings in lupus nephritis are similar to those found in patients with preeclampsia (PE), specifically hypertension, proteinuria and edema. It has been proposed the use of angiogenic factors, such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), and antiangiogenic factors, as soluble Fms-like tyrosine kinase-1 (sFlt-1), for the differential diagnosis between these two conditions, however available data in the literature about these cytokines in non-pregnant SLE patients are inconsistent. This study was designed to evaluate whether there are differences between serum levels of VEGF, PlGF and sFlt-1 in non-pregnant SLE patients with and without systemic disease activity and whether there are differences in these factors when comparing SLE patients with healthy women.

Methods: 54 women with SLE (according to ACR classification criteria) followed at an outpatient clinic of rheumatology were included. They had no other autoimmune disease diagnosed and were divided according to disease activity. 30 patients had inactive disease (mean SLEDAI: 0.7), and 24 had active disease (mean SLEDAI: 11.6). Twenty-three women in this latter group had active nephritis, while 20 patients with inactive disease had history of lupus nephritis. Control group consisted of 34 healthy women who attended a gynecology outpatient clinic.

Results: The mean values of VEGF, PlGF and sFlt-1 of all groups are described on Table 1. Considering the three studied cytokines, the SLE patients had significantly higher mean serum levels than the control group (VEGF: 319.0 + 226.0 × 206.2 + 119.4, p=0.02; PlGF: 42.2 + 54.1 × 13.6 + 21.6, p=0.02; sFlt-1: 107.9 + 49.2 × 70.2 + 95.0, p=0.01). The group of patients with active disease also had significantly higher mean levels of all three factors than controls (VEGF: 331.0 + 216.8 × 206.2 + 119.4, p=0.02; PlGF: 41.2 + 47.3 × 13.6 + 21.6, p=0.02; sFlt-1: 120.5 + 42.4 × 70.2 + 95.0, p=0.02), whereas no statistical difference was found between the group with inactive SLE and the control group. The mean sFlt-1 levels were higher in patients with active SLE than the mean levels of patients with inactive disease (120.5 + 54.9 × 97.8 + 42.4, p=0.02), but there was no significant difference in mean serum of VEGF and PlGF levels between these two groups.

Conclusion: Patients with active SLE have higher levels of VEGF, PlGF and sFlt-1 than controls. sFlt-1 was also higher in patients with active SLE than patients with inactive SLE. A better understanding of angiogenic and antiangiogenic factors in patients with SLE provided by this study allows the analysis of these cytokines in pregnant woman with SLE and possibly their subsequent application as differential method between PE and lupus nephritis.

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Carotid Intima-Media Thickness and Plaque in Mexican Mestizos with Systemic Lupus Erythematosus: A Case-Control Study. Iris J. Colunga-Pedraza, Dionicio A. Galarza-Delgado, Alberto Cardenas-de La Garza, Ana L. Sanchez-Nuñez, Samantha L. Segarra-Linares, Rocío A. Carrillo-Palacios, David Vega-Morales, Fernando Góngora-Rivera and Mario Alberto Garza-Elizondo. Hospital Universitario UANL, Monterrey, Mexico.

Background/Purpose: Systemic lupus erythematosus (SLE) patients are at risk of premature cardiovascular disease (CVD). The specific reason of this situation is still debatable. Subclinical atherosclerosis prevalence and characteristics in Mexican mestizo patients with SLE is unknown. The objective of this study is to evaluate the presence of carotid plaque (CP) and carotid intima-media thickness (CIMT) in Mexican mestizos with SLE and to compare them to a control group.

Methods: An observational, cross-sectional study in a Mexican mestizo population was realized. 69 SLE patients, age ranging from 18 to 53 years, and 69 age-sex-diabetes-hypertension matched controls were included. Their demographic profile, biochemical, anthropometric measurements, traditional risk factors for atherosclerosis and disease-related factors were recorded. Carotid evaluation was realized by B mode carotid Doppler ultrasonography. CP was defined as presence of focal thickening at least 50% greater than that of the surrounding wall or CIMT ≥ 1.2 cm. The CIMT was measured at 1 cm proximal to the start of the carotid bulb dilatation of the common carotid artery in the far wall. The maximum CIMT value was recorded.

Results: Demographic differences between groups included a higher prevalence of CVD familiar history in the SLE group (p≤0.001), higher diastolic and systolic blood pressure in the SLE group (p≤0.001), and higher weight in the control group (p=0.013). Only 2 subjects of each group had diagnosis of hypertension, and 1 subject of each group had diagnosis of diabetes at the time of the enrollment to the study.

The mean CIM value in SLE patients was 0.514 ± 0.098 mm while the control group had a mean of 0.518 ± 0.108 mm (p=0.830). CP was found in 11 patients with SLE and 4 in the control group (p=0.360). SLE patients with CP had lower levels of total cholesterol (p=0.021), low density lipoprotein cholesterol (p=0.030) and glucose (0.003) compared with the control group with CP.

Patients in the SLE group with steroid use for more than five years were more likely to have CP or increased CIMT (p=0.023). Use of synthetic DMARD was associated with lower probability of CP or increased CIMT (p=0.048). This association was not found with biological DMARD (p=0.422).

Conclusion: Our study has shown that despite high prevalence of traditional cardiovascular risk factors among Mexicans SLE patients, the CP/CIMT findings were not completely attributable to them. These findings

agree with most previously published reports in other populations including Asians, Caucasians and African-Americans. The actual evidence suggests that SLE itself is an independent predictor of atherosclerosis. The systematic carotid evaluation could be an important surrogate biomarker of premature atherosclerosis in our patients, and we recommend their systematic use.

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Long-Term Efficacy and Safety of Pulse Cyclophosphamide for Neuropsychiatric Systemic Lupus Erythematosus: A Two-Centre Experience. Antonis Fanouriakis[1], Cristina Pamfil[2], Laura O. Damian[3], Ioana Felea[3], Emmanuel Mihali[3], Ileana Filipescu[2], Theofanis Karageorgas[4], Prodromos Sidiropoulos[1], Simona Rednic[2], George Bertsias[1] and Dimitrios Boumpas[4]. [1]University of Crete, Heraklion, Greece, [2]University of Medicine and Pharmacy, Cluj-Napoca, Romania, [3]Emergency Clinical County Hospital Cluj, Cluj-Napoca, Romania, [4]"Attikon" University Hospital of Athens, Athens, Greece.

Background/Purpose: Cyclophosphamide (CYC) is often used in severe neuropsychiatric systemic lupus erythematosus. However, data on its use rely on small case series and a single randomized controlled trial with a limited number of patients and short follow-up.

Methods: SLE patients with active neuropsychiatric involvement from two tertiary European centers, who received CYC during the past 15 years and had regular follow-up were identified. Outcome at most recent follow-up visit (Likert scale from 1: remission to 6: worsening) and recurrences of the neuropsychiatric manifestation were assessed. Long-term complications of CYC therapy were also documented, with a focus on malignancies and severe infections.

Results: CYC was administered in 44 non-thrombotic neuropsychiatric events experienced by 43 patients (Table 1). Median age at NPSLE occurrence was 45 years (range 14–68 years), time lag from SLE onset was 1 year (range 0–7 years), and positivity for antiphospholipid antibodies was 42.9%. Most common indications were psychosis (9 cases), stroke (6 cases) and myelopathy, seizure disorder and polyneuropathy (5 cases each). In 95% of cases, CYC was administered as monthly intravenous pulses (the remaining 5% received oral CYC) and was chosen as first line immunosuppressive therapy in 36/44 events (81.8%). In the remaining 8 cases, CYC was used as second-line after non-response to other immunosuppressants [azathioprine (AZA) in 7/8 and steroid monotherapy in 1/8)]. The median number of CYC pulses was 8 (range 2–18) with a median cumulative dose of CYC of 7.1 gr (range 2–27 gr). After a median follow-up of 40.0 months (range 1–173), 85.4% of events had favorable outcome (Likert score <4, indicating at least moderate improvement from baseline). Recurrences of the neuropsychiatric manifestation occurred in 13.2% of events. No difference in outcome was observed when CYC was given as first or second line therapy. A total of 4 events (stroke, aseptic meningitis, myelopathy and psychosis) did not respond to CYC and were treated with rituximab as rescue therapy. In cases that responded to CYC after the induction phase, maintenance therapy consisted of AZA in 73.7%, bimonthly and quarterly pulses of CY in 21.0%, and mycophenolate mofetil in 5.3%. No malignancies were observed in our cohort, yet there were two cases of severe infections (one HBV reactivation and one fatal case of disseminated tuberculosis).

Conclusion: In a large case-series with long follow-up, cyclophosphamide was effective for severe non-thrombotic NPSLE but vigilant monitoring for infections is warranted.

Table 1

Manifestation (n)	Cumulative CYC dose (gr), median (IQR)	Duration of follow-up (months), median (IQR)	Outcome (Likert scale), median (IQR)	Major side-effects
Psychosis (9)	6.6 (6.3)	58 (99)	2.0 (2.7)	1 HBV reactivation
Stroke (6)	9.0 (9.8)	32 (100)	2.0 (3.0)	(−)
Myelopathy (5)	7.2 (8.1)	35 (69)	2.0 (1.5)	(−)
Seizures (5)	9.0 (10.3)	30 (52)	1.0 (2.0)	(−)
Polyneuropathy (5)	9.6 (10.4)	48 (35)	2.0 (1.5)	(−)
Mononeuritis multiplex (4)	4.2 (11.8)	90 (66)	1.0 (0.7)	(−)
Cranial neuropathy (3)	22.1*	67*	3.0*	(−)
Headache (2)	3.6*	27*	1.5*	(−)
Aseptic meningitis (1)	2.0	4	(−)	1fatal disseminated tuberculosis
Acute confusional state (1)	3.6	67	1.0	(−)
Acute demyelinating polyradiculopathy (1)	6.0	4	3.0	(−)
Mood disorder (1)	21.7	34	2.0	(−)
Severe cognitive impairment (1)	4.8	43	1.0	(−)

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Mood Disorders in Systemic Lupus Erythematousus (SLE): Results from an International, Inception Cohort Study. John G. Hanly for the Systemic Lupus International Collaborating Clinics[1], Li Su[2], Murray Urowitz[3], Juanita Romero-Diaz[4], Caroline Gordon[5], Sang-Cheol Bae[6], Sasha R. Bernatsky[7], Ann E. Clarke[8], Daniel J. Wallace[9], Joan T. Merrill[10], David A. Isenberg[11], Anisur Rahman[12], Ellen M. Ginzler[13], Paul Fortin[14], Dafna D. Gladman[15], Jorge Sanchez-Guerrero[3], Michelle A. Petri[16], Ian Bruce[17], Mary Anne Dooley[18], Rosalind Ramsey-Goldman[19], Cynthia Aranow[20], Graciela S. Alarcon[21], Barri J. Fessler[21], Kristján Steinsson[22], Ola Nived[23], Gunnar K. Sturfelt[23], Susan Manzi[24], Munther A. Khamashta[25], Ronald F. van Vollenhoven[26], Asad Zoma[27], Manuel Ramos-Casals[28], Guillermo Ruiz-Irastorza[29], S. Sam Lim[30], Thomas Stoll[31], Murat Inanc[32], Kenneth C. Kalunian[33], Diane L. Kamen[34], Peter Maddison[35], Christine A. Peschken[36], Søren Jacobsen[37], Anca Askanase[38], Jill P. Buyon[39], Chris Theriault[40], Kara Thompson[40] and Vernon Farewell[2]. [1]Dalhousie University and Capital Health, Nova Scotia, Canada, Halifax, NS, [2]MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Cambridge, United Kingdom, [3]Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital and University of Toronto, Toronto, ON, [4]Instituto Nacional de Ciencias Médicas y Nutricion, Mexico city, Mexico, [5]Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, [6]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [7]Division of Rheumatology and Clinical Epidemiology, McGill University, Montreal, Quebec, QC, [8]Division of Rheumatology, University of Calgary, Alberta, Calgary, AB, [9]Cedars-Sinai/David Geffen School of Medicine at UCLA, Los Angeles, CA, [10]Department of Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [11]Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom, [12]University College London, London, United Kingdom, [13]SUNY-Downstate Medical Center, Brooklyn, NY, [14]Division of Rheumatology, Centre Hospitalier Universitaire de Quebec et Universite Laval, Quebec, QC, [15]University of Toronto, Toronto Western Hospital, Toronto, ON, [16]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [17]Arthritis Research UK Epidemiology Unit, Institution of Inflammation and Repair, University of Manchester, NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [18]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, [19]Northwestern University and Feinberg School of Medicine, Chicago, IL, [20]Feinstein Institute for Medical Research, Mahasset, NY, [21]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [22]Centre for Rheumatology Research, Landspital University Hospital, Reykjavik, Iceland, [23]Department of Rheumatology, University Hospital Lund, Lund, Sweden, [24]Division of Rheumatology, University of Pittsburgh School of Medicine, Pittsburgh, PA, [25]Lupus Research Unit, The Rayne Institute, St Thomas Hospital, Kings College London School of Medicine, London, United Kingdom, [26]Unit for clinical therapy research (ClinTrid), Karolinska Institute, Stockholm, Sweden, [27]Lanarkshire Centre for Rheumatology, Hairmyres Hospital, East Kilbride, United Kingdom, [28]Josep Font Autoimmune Diseases Laboratory, IDIBAPS, Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Spain, [29]Autoimmune Diseases Research Unit, Department of Internal Medicine, BioCruces Health Research Institute, Hospital Universitario Cruces, University of the Basque Country, Barakaldo, Spain, [30]Emory University School of Medicine, Division of Rheumatology, Atlanta, GA, [31]Kantonsspital Geissbergstr, Schaffhausen, Switzerland, [32]Division of Rheumatology, Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey, [33]UCSD School of Medicine, La Jolla, CA, [34]Medical University of South Carolina, Charleston, SC, [35]Ysbyty Gwynedd Bangor, North Wales, United Kingdom, [36]University of Manitoba, Canada, Winnipeg, MB, [37]Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [38]Columbia University Medical Center, New York, NY, [39]New York University School of Medicine, New York, NY, [40]Department of Medicine, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, NS.

Background/Purpose: Neuropsychiatric (NP) events in patients with SLE include mood disorders. We determined the frequency, characteristics, clinical and autoantibody associations of mood disorders in a large, multiethnic/racial, inception cohort of SLE patients.

Methods: A prospective study of new onset SLE patients was performed by an international network of 32 academic centers in 11 countries. Patients were evaluated at enrollment and annually for up to 14 years. Data were

collected at each assessment on demographic and clinical manifestations, medications, SLE disease activity index-2000 (SLEDAI-2K) and Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index (SDI). Nervous system events were recorded using the ACR case definitions for 19 NP syndromes. These include mood disorders, determined by clinical judgment (based on Diagnostic and Statistical Manual, DSM-IV, criteria) and consisting of: (i) major depressive-like episode, (ii) mood disorder with depressive features, (iii) mood disorder with manic features and (iv) mood disorder with mixed features. Lupus anticoagulant, IgG autoantibodies to cardiolipin, β_2-glycoprotein I, ribosomal P and NMDA glutamate receptor 2 were measured at enrollment. Pre-defined rules determined the attribution of NP events to SLE and non-SLE causes. Cox regression was used to examine the associations of various factors with the occurrence of first mood disorder and first SLE-attributed mood disorder.

Results: Of 1,827 SLE patients, 88.9% were female, 48.9% Caucasian with mean±SD age 35.1±13.3 years. At enrollment, mean SLE duration was 5.6±4.8 months, SLEDAI-2K was 5.3±5.4, SDI was 0.31±0.74. The mean follow-up was 4.73±3.45 years. Over the study 863 (47.2%) patients had 1,627 NP events of which 503 (30.9%) were attributed to SLE. Mood disorders were the second most frequent NP event: 232 patients experienced 256 mood disorders of which 98/256 (38.3%) were attributed to SLE. The predominant mood disorders were major depressive-like episodes [134/256 (52.3%)], followed by mood disorder with depressive features [114/256 (44.5%)] and the remaining two mood disorders accounted for only 8/256 (0.03%) events. The estimated cumulative incidence of any mood disorder and any SLE-attributed mood disorder after 10 years was 17.7% (95%CI=[15.1%,20.2%]) and 7.9% (95%CI=[6.0%,9.9%]), respectively. A total of 110/256 (43.0%) mood disorders occurred in isolation without other concurrent NP events. Multivariate regression revealed a greater risk of mood disorder in patients with other concurrent NP events ($p \leq 0.01$) and a lower risk with Asian race/ethnicity ($p=0.01$) and immunosuppressive drugs taken in the absence of antidepressants ($p=0.003$). No association was found between mood disorders and SLEDAI-2K, SDI scores or lupus autoantibodies, whether or not the analysis was confined to mood disorders attributed to SLE.

Conclusion: Mood disorders are the second most frequent NP event in SLE patients and about one third are attributable to lupus. The lack of association of most mood disorders with global SLE disease activity, cumulative organ damage and lupus autoantibodies emphasize their multifactorial etiology and a role for non-lupus specific therapies.

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Predictors of Incident Seizure in Systemic Lupus Erythematosus. Xiangyang Huang[1], Laurence S. Magder[2] and Michelle Petri[3]. [1]Sichuan University School of Medicine, Sichuan, China, [2]University of Maryland, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: We identified the rate and risk factors for first occurrences of seizure based on a large closely followed longitudinal cohort of patients with systemic lupus erythematosus.

Methods: Rates of incident seizure were calculated overall and in subgroups defined by demographic and clinical variables. Adjusted estimates of association of risk factors were derived using pooled logistic regression.

Results: Of 2203 patients with no history of seizure prior to SLE diagnosis, 157 (7.1%) had the first seizure occurrence at the time of (37 patients, 1.63%) or after the diagnosis of (120 patients, 5.44%) SLE. The rate of incident seizure was 4.9 per 1000 person-years. The risk of seizure occurring around the time of SLE diagnosis was higher in patients with a history of malar rash ($p = 0.002$), proteinuria ($p = 0.004$), and psychosis ($p < 0.000$). Multivariable analysis of the first seizure occurring after the diagnosis of SLE showed that history of low C3 (RR = 1.763, $p = 0.0078$), psychosis (RR = 2.432, $p < 0.0001$), cranial or peripheral neuropathy (RR = 2.212, $p = 0.0043$), anti-Smith (RR = 1.518, $p = 0.0551$), renal involvement (urine dipstick protein positive 3+) (RR = 2.888, $p = 0.0177$) and current prednisone dose (RR = 9.960, $p < 0.0001$) were independently associated with a higher risk of incident seizure. SELENA-SLEDAI was not predictive and hydroxychloroquine was not protective after adjusting for the other variables in the model.

Conclusion: Seizure in SLE is multi-factorial. The risk of seizure in SLE is independently increased in those patients with prior psychosis, neuropathy, proteinuria, anti-Sm, low C3 and current corticosteroid use. Anti-Sm is of particular interest as it has also been incriminated in other CNS-SLE syndromes.

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Prednisone Is a Risk Factor for Incident Depression in Systemic Lupus Erythematosus. Xiangyang Huang[1], Laurence S. Magder[2] and Michelle Petri[3]. [1]Sichuan University School of Medicine, Sichuan, China, [2]University of Maryland, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Depression affects as many as 30% of SLE patients. Most studies of risk factors for depression among SLE patients have been cross-sectional, and thus unable to identify risk factors prospectively. The aim of this study was to identify the risk factors that preceded incident depression in a large prospective longitudinal cohort of patients without a history of depression.

Methods: A prospective study was performed using data from the Hopkins Lupus Cohort. Demographic variables, SLE manifestations, laboratory tests, Physician's Global Assessment (PGA), Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI), cumulative organ damage (SLICC/American College of Rheumatology Damage Index (SDI) and depression events were recorded at enrollment and each quarterly visit. A patient was considered to have depression if (1) there was a record of persistent depression (two or more mentions of depression separated by several weeks in rheumatology clinic notes) and/or a diagnosis of affective disorder was made by a psychiatric professional and (2) treatment for those symptoms with psychotherapy or antidepressant medications was documented. Rates of incident depression were calculated overall, and in subgroups defined by demographic and clinical variables. Adjusted estimates of association were derived using pooled logistic regression.

Results: The analysis was based on 1609 cohort members who did not have a history of depression prior to joining the cohort. Of these, we found that 282 (17%) experienced a first depression episode during follow-up. The incidence of depression was 29.7 episodes per 1000 person years. In the multivariable analysis, recent SLE diagnosis, non-Asian ethnicity, disability, cutaneous activity, longitudinal myelitis and higher doses of prednisone were independent predictors of incident depression (Table 1).

Table 1. Independent predictors of incident depression in the Hopkins Lupus Cohort based on a multivariate model

Variables	Comparison	Adjusted Rate Ratio (95% Confidence Interval)	P-value
Time since SLE dx	Per 10 year difference	0.7 (0.5, 0.9)	0.0006
Ethnicity	East Asian vs. others	0.1 (0.01, 0.8)	0.031
Disability	Yes vs. no	1.4 (1.0, 1.8)	0.034
Income	Income >100,000	0.7 (0.5, 1.1)	0.15
Year of enrollment	Year after 2005	0.6 (0.5, 0.8)	0.0008
Recent Cutaneous activity	Some vs. none	1.7 (1.2, 2.2)	0.0008
History of longitudinal myelitis	Yes vs. no	4.5 (1.6, 12.2)	0.0033
Recent dose of prednisone	20 mg/day+ vs. less	2.0 (1.3, 2.9)	0.0006

Conclusion: These results suggest that depression in SLE is multifactorial, with only certain types of SLE activity (skin and myelitis) playing a role. Interestingly, prednisone exposure appeared to increase the risk, even after adjustment for disease activity. This provides yet another motivation for prednisone sparing in management of SLE patients.

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"Point of Care" Neurocognitive Testing for Neuropsychiatric Systemic Lupus Erythematosis (NPSLE). Debbie Rybak, Nicole Jordan, Noa Schwartz, Tamar Rubinstein, Bryan Freilich, Irene Blanco and Chaim Putterman. Albert Einstein College of Medicine, Bronx, NY.

Background/Purpose: There is currently no standardized tool to assess for NPSLE, and comprehensive neuropsychological testing can be lengthy and expensive. The Automated Neuropsychological Assessment Metric (ANAM) is a computerized battery of tests which has been successfully used to test cognitive function in SLE. The Cognitive Stability Index (CSI) is a web-based tool for assessing neurocognitive function which measures similar domains to the ANAM; however, it has not been studied in patients with SLE. Furthermore, in contrast to ANAM, CSI summary scores are not solely based on response speed, and thus may have a significant advantage over ANAM. Additionally, CSI can auto-invalidate subtests performed with insufficient patient effort. We aimed to evaluate and compare the utility of ANAM and CSI to assess NPSLE in the outpatient setting.

Methods: Subjects enrolled in the Einstein Lupus Cohort were eligible to participate. Subjects completed an NPSLE screening questionnaire (Mosca et al, 2011), with the presence of NPSLE defined by a screening score of >17 (NPSLE (+)). Subjects completed the ANAM and CSI tests (each taking ~30 minutes to complete). Eight cognitive domains were assessed by the ANAM and four by the CSI. The ANAM composite score measures average performance on all domains and is reported as a z score; four individual CSI factor scores for each cognitive domain are reported as standard scores (mean 100±15). Mann Whitney U tests assessed differences between NPSLE (+) and NPSLE (−) subjects. Pearson correlations were obtained for ANAM and CSI scores.

Results: 31 subjects completed the CSI, of which 20 also completed the ANAM. Of the 31 subjects, median age was 39 years, 94% were female, 42% were Hispanic and 63% were black. 74% were treated with corticosteroids (median prednisone dose 10 mg).

The median composite ANAM z-score, adjusted for sex/age, was −1.39 [−2.59, −0.98]. Median age-adjusted CSI standard factor scores ranged from 84–98 across the four cognitive domains. The median composite ANAM score was significantly different in the NPSLE(+) patients compared to those who were NPSLE(−) (p=0.03). Of the eight domains evaluated by ANAM, learning, attention and spatial working memory differed significantly by screening score. Of the four CSI domains, response speed and memory differed significantly between the NPSLE(+) and NPSLE(−) subjects (p=0.03 and 0.01, respectively). The composite ANAM score and CSI factor scores correlated significantly with each other. Finally, anti-dsDNA antibodies, C3, C4, SLEDAI scores, and medications were not significantly associated with NPSLE.

Conclusion: Median cognitive test scores on both ANAM and CSI fell below the standard mean for normals, independent of NPSLE status. CSI factor memory scores were significantly lower in NPSLE(+) subjects, independent of their response speed. Since this cannot be inferred from the ANAM composite score, CSI may provide a more specific assessment of cognitive functioning. Overall, NPSLE was associated with significantly lower scores on both ANAM and CSI, suggesting that these are valuable "point of care" tools that can be easily implemented in the clinical setting for the diagnosis of NPSLE.

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Cognitive Impairment in SLE and Non-Criterion Anti-Phospholipid Antibodies. Michael Luggen[1], Gaurav Gulati[1], Rohan Willis[2] and Emilio B. Gonzalez[2]. [1]University of Cincinnati College of Medicine, Cincinnati, OH, [2]University of Texas Medical Branch, Galveston, TX.

Background/Purpose: The pathogenesis of cognitive impairment (CI) in patients with SLE is unknown. Anti-phospholipid antibodies (APL) have been implicated in some studies, but not in others. The APL which have been evaluated have variably included anti-cardiolipin (ACL) antibodies, lupus anticoagulant (LAC), and antibodies to beta-2 glycoprotein I (β2GPI). Few studies have examined all of the above and none has examined other APL (so-called non-criterion APL). We evaluated the association of CI with a broad spectrum of both criterion and non-criterion APL.

Methods: Subjects meeting the revised criteria for classification of SLE were recruited from 3 different patient populations. Cognitive function was assessed with the ANAM (Automated Neuropsychologic Assessment Metrics), a validated computer- based assessment tool which measures multiple cognitive domains. The TTS (total throughput score= number of correct responses/time) was used as the primary outcome measure. It was summed over 8 separate domains. Demographic, clinical, treatment, disease activity and damage information was obtained. The following APL of all three isotypes were assessed by ELISA using standardized techniques: ACL, anti-β2GPI, anti-phosphatidyl ethanolamine (aPE), anti-phosphatidyl choline (aPC), anti-phosphatidyl inositol (aPI), anti-phosphatidyl serine (aPS), anti-phosphatidyl glycerol (aPG), anti-phosphatidic acid (aPA). The data were analyzed by Fisher's exact test, Wilcoxon rank sum test, and multiple linear regression.

Results: Fifty-seven (57) patients were evaluated. Clinical characteristics are shown in Table 1. Of the 57, 12 had definite CI (<1.5 SD below the mean of an age, sex, and race matched RA population). The two groups were significantly different with regard to age, ethnicity, and family income. There was no significant difference between groups with regard to the presence or absence of any APL, or any specific APL, criterion or non-criterion. When titers of specific APL were compared with TTS, no significant correlations were found. Using multiple linear regression and adjusting for age, ethnicity, income, opioid and hydroxychloroquine use, and simple reaction time, neither the presence nor the titer of any APL significantly decreased TTS. However, the presence of aPG (IgM) (b'= 0.352, p =. 0007) and aPA (IgG) (b'=0.242,p=.02) appeared to increase TTS (model R^2=.731, p<0.0001).

Conclusion: In this cross-sectional study, neither criterion nor non-criterion APL of any isotype was associated with a significant decrease in cognitive performance as measured by the TTS of the ANAM. Somewhat surprisingly, aPG (IgM) and aPA (IgG) appeared to increase TTS, possibly reflecting protection against other pathogenic factors. Confirmation and further analysis of this finding is in progress.

Table 1.

Variable	ALL SUBJECTS (n=57)	CD (n=12)	NO CD (n=45)
Age (yrs [SD])	49.9 (11.2)	54.9 (8.8)	48.5 (11.5)*
Disease duration (yrs)	13.1 (10.1)	17.5 (13.9)	12.0 (8.6)
Family Income (% < $20K)	45.6	75.0	37.8*
Education (% ≤ 12 yrs)	36.8	50.0	33.3
Ethnicity (% Caucasian)	36.8	8.3	44.4*
SLEDAI	3.6 (3.4)	3.2 (4.3)	3.8 (3.3)
SLICC	2.75 (2.4)	3.4 (2.1)	2.4 (2.4)
Pain (100 mm VAS)	40.0 (28.2)	49.6 (29.1)	36.2 (27.7)
Patient global Assessment (100 mm VAS)	53.7 (22.6)	58.8 (22.6)	52.3 (22.7)
Depression (Beck Depression Inventory)	16.0 (12.3)	17.6 (10.2)	14.4 (12.6)
Fatigue (FACIT)	24.6 (13.5)	26.1 (10.8)	23.3 (14.3)
APL Positive (%)	38.6	25.0	42.2
Prednisone (% use)	53.7	54.5	53.9
Prednisone > 20 mg/d (%)	15.8	25.0	13.3
Immunosuppressants (%)	48.2	36.4	51.2
HCQ (%)	70.0	50.5	74.4
Warfarin (%)	14.8	18.2	14.0
ASA (%)	38.9	27.3	41.9
Antidepressant (%)	31.5	36.4	30.2
Opioid (%)	25.9	45.5	20.9
NSAID (%)	22.2	18.2	23.3

*C/D vs non-CD, p < .05

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Predictors of Therapeutic Outcomes in Patients with Neuropsychiatric Systemic Lupus Erythematosus. Kunihiro Ichinose[1], Kazuhiko Arima[2], Masataka Umeda[1], Shoichi Fukui[3], Ayako Nishino[1], Yoshikazu Nakashima[1], Takahisa Suzuki[1], Yoshiro Horai[4], Tomohiro Koga[4], Shin-ya Kawashiri[2], Naoki Iwamoto[1], Mami Tamai[1], Hideki Nakamura[1], Tomoki Origuchi[5] and Atsushi Kawakami[1]. [1]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki,

Japan, [2]Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [3]Departments of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, Nagasaki, Japan, [4]Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [5]Department of Health Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.

Background/Purpose: Neuropsychiatric systemic lupus erythematosus (NPSLE) is a serious organ disorder with a variety of symptoms. Despite advances in the understanding of the immunopathogenic and clinical aspects of SLE, NPSLE remains a diagnostic and therapeutic challenge. The therapeutic outcomes among very few published controlled studies are diverse, because of the variability in the manifestations of NPSLE and the absence of appropriate diagnostic criteria.

Methods: This study was conducted to investigate the immunopathogenic and clinical aspects and treatment outcomes of NPSLE. We analyzed the laboratory data, symptoms, treatment regimen, and therapeutic outcomes 1 year after treatment, and the prognostic factors of 28 NPSLE patients admitted to our hospital in an 8-year period from 2006 through 2013 and 27 cytokine, chemokines and growth factor profiles in pretreatment samples of their cerebrospinal fluid (CSF) using the Bio-Plex Human 27-plex panel.

Results: There were 26 females (92.9%) and two male. The median age at the onset of NPSLE was 35 years, ranging from 15 to 53 years old. The median duration from SLE onset to first neuropsychiatric event was 7 years. The median Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score at the disease onset of NPSLE was 13. Twelve patients were responders at 1 year post-treatment; their median age at NPSLE onset was 29 years versus 39 years in the non-responders (n=16, p=0.0260). The median duration from SLE onset of NPSLE was 1.5 years in responder versus 11 years in non-responder (p=0.0096). Patients with more than two NPSLE symptom types had significantly poorer outcomes (p=0.0159). The CSF interleukin (IL)-10, interferon (IFN)-γ and tumor necrosis factor (TNF)-α levels before the treatment were significantly higher in the non-responders (p=0.0051, p=0.0239 and p=0.0258, respectively). Ranking of the cytokines/chemokines to distinguish responder from non-responder by weighted-voting algorithm showed that the combination of IL-10, TNF-α, IL-6, IFN-γ, IL-4 and IL-13 had a highest Matthews correlation coefficient.

Conclusion: Younger, shorter disease duration and single-symptom NPSLE patients had significantly better therapeutic outcomes. The lower cytokine value of IL-10, IFN-γ and TNF-α before the treatment in CSF may provide better NPSLE outcomes. Additionally, measurement of multiple cytokines in pretreatment such as IL-10, TNF-α, IL-6, IFN-γ, IL-4 and IL-13 could distinguish responder from non-responder patients. Our findings may suggest the importance of making a diagnosis at an earlier phase for better therapeutic response and measuring multiple cytokines to predict therapeutic outcomes of NPSLE.

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Headache in Patients with Systemic Lupus Erythematosus Is Associated with Reduced Cerebral Grey Matter Volume, but not with Measures of Glial Activation, Anti-NR2-, or Anti-P Antibodies. Anne B Tjensvoll[1], Maria B Lauvsnes[1], Shunsei Hirohata[2], Jan T Kvaløy[1], Mona K Beyer[3], Erna Harboe[1], Lasse G Gøransson[1], Ole J Greve[1] and Roald Omdal[1]. [1]Stavanger University Hospital, Stavanger, Norway, [2]Kitasato University School of Medicine, Sagamihara, Japan, [3]Oslo University Hospital, National Hospital, Oslo, Norway.

Background/Purpose: Headache, especially migraine, is frequent and one of the most common neuropsychiatric manifestations in systemic lupus erythematosus (SLE). A possible mechanism for this is that the threshold for migraine activation could be lower in SLE patients due to immunological, biochemical or structural disturbances or changes. Glutamatergic neurotransmission, involving the NMDA-receptor is considered important in migraine pathophysiology, and antibodies (ab) against the NR2 subtype of the NMDA receptor (anti-NR2 ab) are found in SLE patients. Ab against ribosomal P proteins (anti-P ab) are potentially neuropathogenic and associated with diffuse and complex neuropsychiatric manifestations in SLE. Protein S100B, a biomarker of astro-glial cell activation, is linked to neuropsychiatric SLE in some studies. We investigated whether structural abnormalities of the brain as revealed by MRI volumetry, or anti-NR2 ab, anti-P ab or increased protein S100B in cerebrospinal fluid (CSF) were associated with primary headaches in SLE.

Methods: Sixty-seven SLE patients, all fulfilling the ACR criteria, and 67 age- and gender matched healthy subjects, participated in the study. Headache was assessed through a structured interview and classified according to the International Classification of Headache Disorders. Anti-NR2 ab, anti-P ab and protein S100B were measured in CSF. Global volumes of grey matter (GM) and white matter (WM) were estimated from cerebral MRI images by applying the SPM8 software.

Results: SLE patients in this cohort had, in accordance with other studies, more migraine than age- and gender matched healthy subjects (36% vs 19%, P = 0.03). In logistic regression analyses, higher GM volumes in the SLE patients reduced the odds for headache in general (OR 0.98, P = 0.05) and for migraine in particular (OR 0.95, P = 0.004). This was not evident for pure tension type headache. Higher WM volumes in the patients increased the odds for migraine (OR 1.04, P = 0.007). In contrast, no associations were found between headache and brain volumes in the healthy subjects. No associations were revealed between headache or headache categories and anti-NR2 ab, anti-P ab or S100B in the SLE patients.

Descriptive data in the SLE patients

	All headache	Migraine	No headache
GM volume	549 (450–680)	544 (450–633)	566 (516–675)
Anti-NR2 ab*	0.37 (0.1–1.7)	0.33 (0.1–1.4)	0.44 (0.2–2.2)
Anti-P ab*	< 0.001 (<0.001–0.08)	< 0.001 (<0.001–0.04)	< 0.001 (< 0.001–0.13)
S100B*	228 (110–420)	222 (110–393)	190 (127–302)

Data are given as median and range; GM, grey matter; volumes are given in cm≥; * measured in CSF; anti-NR2 ab, values are given as a ratio against an internal calibrator with defined signal intensity; anti-P ab in ug/mL; S100B in pg/mL

Conclusion: SLE patients with reduced GM volumes have higher probability for migraine and headache in general. However, no associations between headache or headache categories and anti-NR2 ab, anti-P ab or protein S100B were found. These results indicate that unknown disease processes in SLE resulting in GM loss may increase headache and migraine susceptibility.

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Clinical Features in Patients with Anti-Triosephosphate Isomerase Antibody-Positive Neuropsychiatric Systemic Lupus Erythematosus. Shuzo Sato, Hiroshi Watanabe, Tomoyuki Asano, Hiroko Kobayashi, Hiromasa Ohira and Makiko Yashiro. Fukushima Medical University School of Medicine, Fukushima, Japan.

Background/Purpose: Although several autoantibodies of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) have been reported, none of these autoantibodies were conclusively established as pathogenic. We have reported that autoantibodies to triosephosphate isomerase (TPI), which is an important glycolytic enzyme in red blood cells or neuronal cells, are associated with NPSLE pathogenesis. We have detected the presence of anti-TPI antibodies in sera of human NPSLE patients. However, clinical features regarding anti-TPI antibody-positive NPSLE patients are not known. The aim of this study was to determine the clinical features of anti-TPI antibody-positive NPSLE patients.

Methods: Clinical data was retrospectively collected from 24 NPSLE patients (mean age: 26.41 ± 8.93 years old, 4 males and 20 females). NPSLE manifestations were determined according to the ACR case definitions for NPSLE. NPSLE patients were divided into 2 groups (anti-TPI antibody-positive or negative), and compared clinical features as follows: age, sex, disease duration, NPSLE manifestation, other SLE manifestations, SLEDAI, and laboratory data. Serum samples collected from all NPSLE patients were analyzed by Western blotting to detect anti-TPI antibodies using rabbit muscle TPI protein.

Results: 7 of 24 NPSLE patients were positive for anti-TPI antibodies (29.1%). Age, the rate of female, and SLEDAI were not significantly different between 2 groups. In Laboratory data, the platelet count was significantly elevated in anti-TPI positive NPSLE patients (221,800 vs 158,300 /μl, p = 0.047). In NPSLE manifestation, Lupus headache was more frequently observed in anti-TPI antibody-positive NPSLE patients (28.5% vs 0%, p=

0.012) (Table). The frequency of Seizure, Organic Brain Syndrome and Psychosis was similar in both groups in this study. Myelopathy and aseptic meningitis were observed only in anti-TPI antibody-negative NPSLE patients.

Conclusion: General clinical features were similar between anti-TPI antibody-positive NPSLE patients and negative patients, however, anti-TPI antibody-positive patients may have higher platelet count and higher frequency of lupus headache, compared to anti-TPI antibody-negative NPSLE patients.

Table. Clinical features of anti-TPI antibody-positive NPSLE patients.

	Anti-TPI positive	Anti-TPI negative	*p*
Clinical items number	7	17	–
Age (years old)	30.85 ± 9.7	24.58 ± 8.2	0.16
Sex (female %)	100%	76.5%	0.08
SLEDAI	16.42 ± 7.82	15.41 ± 6.51	0.76
Laboratory Data			
WBC/μL	7857 ± 7054	6688 ± 3905	0.69
Hemoglobin g/dL	11.17 ± 3.25	11.17 ± 2.40	0.99
Platelet/μL	22.18 ± 6.05	15.83 ± 7.49	0.04
C3mg/dL	67.71 ± 44.8	56.11 ± 26.98	0.54
C4mg/dL	15.14 ± 14.95	13.76 ± 9.29	0.82
NPSLE manifestation			
Seizure	42.8%	23.5%	0.17
OBS	14.3%	23.5%	0.31
Psychosis	28.5%	17.6%	0.27
Headache	28.5%	0%	0.01

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Cognitive Function in Systemic Lupus Erythematosus Patients with Past History of Neuropsychiatric Manifestations : A Longitudinal Study. Yang Gao, Yi Lo, Jacky Wan, Esther YY Lau and Mo Yin Mok. University of Hong Kong, Hong Kong, Hong Kong.

Background/Purpose: Cognitive impairment is commonly reported in patients with systemic lupus erythematosus (SLE) and its associations with neuropsychiatric involvement (NPSLE) and psychiatric factors have been inconsistently reported in the literature.

Objective: To evaluate full neurocognitive function in relation to psychiatric factors including anxiety and depression in NPSLE patients longitudinally compared to matched controls.

Methods: Cognitive symptom inventory (CSI) was used to measure perceived cognitive impairment whereas full neurocognitive battery that covered 8 cognitive domains were performed by trained psychologist at 2 time-points 12 months apart. Depressive and anxiety symptoms were measured by HADS.

Results: 18 NPSLE and 18 non-NPSLE patients matched to age, sex and disease duration as well as 16 age- and sex- matched healthy subjects were recruited. NPSLE patients consistently reported more cognitive impairment and anxiety symptoms than non-NPSLE patients over both time-points. NPSLE patients had worse performance on 3 memory tests whereas non-NPSLE patients only showed significantly lower AVLT recognition compared with healthy subjects by post-hoc analysis. Applying age- and education- adjusted Chinese norms, NPSLE patients had significantly worse performance than non-NPSLE patients over 5 cognitive domains including simple and complex attention, memory, reasoning and visuospatial function which remained significant when adjusted for HADS-A. Anxiety contributed only to AVLT delay recall in regression analysis. Longitudinal analysis revealed improvement in some cognitive tests by non-NPSLE patients at re-evaluation whereas NPSLE patients did not show any difference in serial test performance.

Conclusion: Compared to non-NPSLE patients, NPSLE patients reported more cognitive and anxiety symptoms and had significantly worse cognitive functions involving simple and complex attention, memory, reasoning and visuospatial domains. Unlike non-NPSLE patients, they failed to demonstrate learning effect upon re-evaluation over 12 months.

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Cerebral Small Vessel Disease in Systemic Lupus Erythematosus: Histopathological Study. Jamal A. Mikdashi[1], Rupal I. Mehta[2] and Rudy J. Castellani[3]. [1]Univ of Maryland Schl of Med, Baltimore, MD, [2]University of Maryland School of Medicine, Baltimore, MD, [3]Univeristy of Maryland school of Medicine, Baltimore, MD.

Background/Purpose: Little is known about cerebral small vessel disease (CSVD) in SLE, compared to the mounting evidence of relating cardiovascular risk factors and inflammation to lager vessel disease and atherosclerosis. Our aim is to examine the clinical features of CSVD in SLE, and determine the risk factors associated with CSVD.

Methods: This is a postmortem study of consecutive autopsy brain of subjects drawn from the Maryland Lupus Cohort, between 2002 and 2014. A total of 15 eligible patients were identified, and central nervous system and systemic autopsy histopathology were reviewed. Four patients with limited autopsy data were excluded. Histopathological evidence of CSVD included microthromboemoli, glial hyperplasia, neuronal loss, microaneuryms, lacunar infarcts, and microbleeds. Demographics, clinical SLE features, cardiovascular risk factors, neuroimaging findings and therapeutic options were examined among those with CSVD and those with no CSVD. Multivariate analysis and non parametric studies were used to determine factors associated with CSVD. SLE disease activity (SLEDAI-2k), SLE damage index (SDI) and duration of SLE were adjusted for during analyses.

Results: Only four out of 11 SLE patients (36.4 %) had histopathological evidence of CSVD [n=4, mean age = 26.4 +/− 9.2 years, 100% women, 100% African American, and mean duration of disease = 3.4 +/− 0.9 years] as compared to SLE patients with no CSVD [n=7, mean age = 26.2 +/− 8.8 years, 86 % women, 86 % African American, and mean duration of disease = 3.7 +/− 1.7 years]. CSVD patients presented with less acute CNS disease process and tended to accumulate more damage overtime as compared with no CSVD patients. Stroke and cognitive impairment were more frequent among CSVD patients compared to no CSVD group.

Histopathological CSVD findings correlated well with neuroimaging evidence of CSVD including, the presence of recent subcortical infarcts, lacunae of vascular origin, white matter hyperintensity, and brain atrophy (Pearson correlation coefficient: 0.633; p value $<$ 0.036). CSVD was manifested largely as microinfarction in the subcortical and cortical areas of the frontal and parietal regions (75 %), with volume loss (50 %), non inflammatory vasculopathy (50 %), and inflammatory vessel disease (25 %).

Independent risk factors associated with the occurrence of CSVD included, elevated dsDNA and low levels of C3 (odds ratio; 2.0; 95 % CI: 0.8–5.6, p value $<$ 0.050). This association was independent of age, hypertension, diabetes, smoking, alcohol intake, anti-phospholipid antibodies, C-reactive protein, prior use of immunosuppressive therapy, or presence of microscopic evidence of small vessel disease in other organs such as the kidney, skin, cardiac, or pulmonary systems.

Conclusion: The present study highlights the nature of CSVD in SLE which is of considerable importance related to stroke and cognitive impairment. CSVD in SLE appears to be associated with chronic inflammation in the absence of classic cardiovascular risk factors, or effective treatment of hypertension and SLE. Identifying novel risk factors that shed light on CSVD pathogenesis in SLE may offer potential therapeutic targets.

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The Burden of Neuropsychiatric Symptoms in Systemic Lupus Erythematosus: Physician's and Patient's Perspectives. Chiara Tani[1], Maria Francisca Moraes-Fontes[2], Ana Carolina Araújo[2], Linda Carli[3], Manuel Pereira Gonçalves[4], Francesca Querci[1], Alexandra Mendes[5], Viola Signorini[6], Sabrina Vagnani[1], Rosaria Talarico[7], Céu Mateus[8], Stefano Bombardieri[9], Nuno Riso[2] and Marta Mosca[1]. [1]Rheumatology Unit, University of Pisa, Pisa, Italy, [2]Hospital de Curry Cabral, Centro Hospitalar Lisboa Central, Lisbon, Portugal, [3]GenOMeC PhD, University of Siena, Siena, Italy, [4]Mental Health Unit, Universidade Nova de Lisboa (UNL), Portugal, Lisboa, Portugal, [5]Clinical Psychology Unit, CHLC, Portugal, Lisboa, Portugal, [6]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [7]Rheumatology Unit, Pisa, Italy, [8]Health Economy, National School of Public Health (UNL), Portugal, Lisboa, Portugal, [9]University of Pisa, Pisa, Italy.

Background/Purpose: Neuropsychiatric symptoms (NPS) are observed in SLE with a variable prevalence depending on patient selection and

assessment methods. In 2010, a 27-item questionnaire was developed to identify NPS in SLE (1); in the present study we aim to compare the capability to detect NPS by means of this questionnaire and routine clinical assessment in SLE.

Methods: The questionnaire was administered to consecutive SLE patients from two European Countries as a physicians' administered tool in one cohort (PhQ) and a self-administered questionnaire in the other (PaQ). On the same day the routine clinical assessment was performed by a physician expert in SLE management blinded to the questionnaire result. The concordance level of NP symptoms as reported by questionnaires and clinical evaluation were calculated. The questionnaire was considered positive in presence of at least one symptom recorded.

Results: Overall, 137 patients were enrolled; the PhQ was administered to 70 patients (96% female, mean age at enrolment 42.3±12 years, disease duration 12.5±8.6 years) while the PaQ to 67 patients (92% female, mean age at enrolment 47±13 years, disease duration 14±9 years). Previous NP involvement was present in 25% of patients in PhQ cohort and in 21% in PaQ cohort. According to the clinical records and irrespectively from their attribution, NPS were reported in 23 patients (32%) in the PhQ cohort, and in 23 (34.3%) in the PaQ cohort; overall, there were neurologic symptoms in 15% and psychiatric symptoms in 14% of cases. According to questionnaires, at least one NPS was captured in 61 patients (87%) of the PhQ cohort and 62 (92%) in PaQ cohort. In the PhQ cohort, among the 61 patients with at least one symptom as captured by the questionnaire PhQ, 20 (32.7%) have also NPS recorded in the clinical chart; in all the 8 patients with negative questionnaire, no NPS were recorded in the clinical chart (agreement p=0.057). Similarly, among the 62 patients with positive PaQ, 20 (29.8%) have also NPS recorded in the clinical chart (agreement p=0.07). Cognitive impairment, depression and anxiety were the most overlooked symptoms in the clinical charts.

Conclusion: These data demonstrated that some NPS can be overlooked by the physician during routine clinical assessment. Although the clinical significance of these observations are under evaluation, this screening questionnaire can be a useful aid, for identifying patients with NPS requiring further evaluation.

1. Mosca M, et al. The development of a simple questionnaire to screen patients with SLE for the presence of neuropsychiatric symptoms in routine clinical practice. Lupus. 2011 Apr;20(5):485–92.

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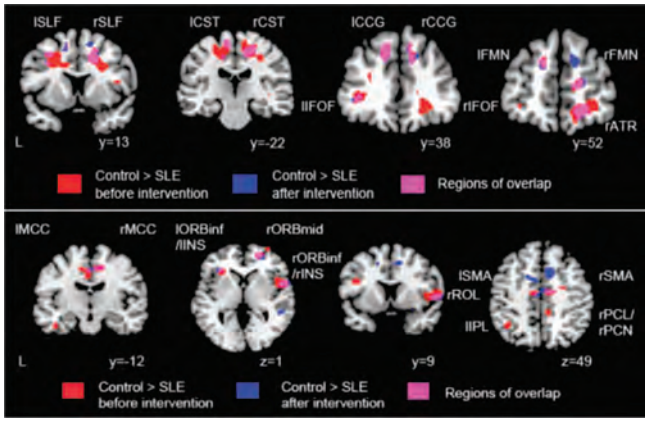
Brain Gray and White Matter Volume Losses and Their Associations with Glucocorticoid Use in Patients with Newly Diagnosed Systemic Lupus Erythematosus (SLE) – a Prospective MR Study. Anselm Mak[1], Roger CM Ho[1], Hanying Tng[2] and Juan Zhou[2]. [1]National University of Singapore, Singapore, Singapore, [2]Duke-NUS Graduate Medical School, Singapore, Singapore.

Background/Purpose: Data suggest that cerebral atrophy occurs in patients with SLE as early as within 9 months after disease onset. We aimed to address (1) if cerebral atrophy occurs even earlier after disease onset and (2) if glucocorticoid use early in the course of SLE would positively impact the brain gray matter (GMV) and white matter volumes (WMV).

Methods: Whole brain analyses of T1-weighted magnetic resonance (MR) images (1.5-T Siemen scanner) obtained ≤ 3 months of diagnosis and subsequently after sufficient disease control (SLEDAI<4) from 14 patients with new onset SLE (1997 ACR classification criteria) without clinically overt neuropsychiatric symptoms, traditional cardiovascular risk factors and antiphospholipid antibodies were performed. MR images of 14 demographically and intelligent-quotient matched healthy controls (HC) were used for comparison. An optimized voxel-based morphometry protocol was used to analyse the images. With thresholding at p<0.01 family-wise error (FWE) corrected, GMV and WMV between patients at diagnosis and HC were compared by 2-sample t-tests on 2-subject level probabilistic maps, while changes of GMV and WMV within the SLE group at diagnosis and after achieving sufficient disease control were compared by paired t-tests. Cumulative glucocorticoid doses were correlated with the changes of GMV and WMV of the regions of interest (ROI) within the SLE group.

Results: The mean±SD age of the patients at diagnosis and HC were 39.38±13.9 and 34.07±14.4 years respectively. The mean±SD SLEDAI and daily prednisolone dose were 9.93±5.7 and 15.32±18.4mg respectively. The mean±SD interval between diagnosis and the first MR scan was 36.86±35.5 days. Second MR scans in lupus patients were performed after a mean±SD of 504.92+267.0 days of treatment, with significant improvement of mean±SD SLEDAI and daily prednisolone dose to 2.64±1.4 (p<0.001) and 3.82±3.5mg (p=0.023) respectively. The mean±SD cumulative prednisolone was 1.76±2.10gm. Demonstrated in the first scans, lupus patients had significant GMV losses in both middle cingulate cortices and middle frontal gyrus, right rolandic operculum and the right supplementary motor area (lower panel of figure), and significant WMV losses in both superior longitudinal fasciculus, corticospinal tract, cingulum cingulate gyrus and inferior fronto-occipital fasciculus (upper panel of figure) as compared with HC. On ROI analyses, cumulative glucocorticoid dose was significantly correlated with improvement of brain volumes in the left inferior temporal gyrus, left cerebellum, and both anterior thalamic radiation in the SLE patients (all p<0.05).

Conclusion: In SLE patients, significant gray and white matter losses occurred as early as within a mean of 36.9 days of diagnosis. Glucocorticoid use early in the disease course improved GMV and WMV in certain areas, suggesting the potential benefit of glucocorticoids in brain plasticity and connectivity in early SLE.



Disclosure: A. Mak, None; **R. C. Ho**, None; **H. Tng**, None; **J. Zhou**, None.

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Cognitive Symptoms and Associated Disease and Non-Disease Related Factors in Patients with Systemic Lupus Erythematosus : A Longitudinal Study. Yang Gao, Yi Lo and Mo Yin Mok. University of Hong Kong, Hong Kong, Hong Kong.

Background/Purpose: Cognitive impairment is commonly reported in patients with systemic lupus erythematosus (SLE). Its associated disease and non-disease related factors have been inconsistently reported.

Objective: To examine cognitive symptoms and its relation to disease related factors including disease activity, antiphospholipid antibody, previous neuropsychiatric history (NPSLE) and non-disease related factors such as anxiety and depression over time.

Methods: Cognitive symptoms inventory (CSI) was used to measure perceived cognitive impairment serially at 3 time-points 12 months apart. Disease activity was measured by SLEDAI. Depressive and anxiety symptoms were measured by HADS-D and HADS-A respectively.

Results: 304 SLE patients were recruited at baseline (T0) among whom 144 had first re-evaluation (T1) and 34 had second re-evaluation (T2) at 12-month interval. Majority (73.5%, 25/34) of patients had stable CSI whereas 5.9% (2/34) of patients had persistently worsened CSI over 24 months. At T0, multivariate analysis revealed that higher CSI was associated with history of NPSLE (p=0.005) and psychiatric disease (p=0.04), higher HADS-A (p<0.001) and HADS-D (p<0.001) scores. CSI of active patients (SLEDAI>6) was not different from inactive patients and did not change despite regression of disease activity in 12 months. There was no difference in CSI between T0 and T1 regardless of history of NPSLE, psychiatric history, change in depressive status at T1 (HADS-D>11 as cutoff) but CSI was significantly different in patients who demonstrated change in anxiety status at T1 (HADS-A>11 as cutoff) (p=0.03). Multivariate linear regression analysis revealed change in HADS-A as the only significant predictive factor of change in CSI over time (β=0.774, 95% CI 0.43 – 1.12, p<0.001).

Conclusion: 5.9% of unselected SLE patients reported persistent cognitive symptoms. Patients with history of NPSLE and psychiatric illness, high

anxiety and depressive symptoms had worse CSI than those without these conditions. CSI was sensitive, but modestly, to change in anxiety symptoms over time.

Disclosure: Y. Gao, None; **Y. Lo**, None; **M. Y. Mok**, None.

2659

Neurofilament H Is Associated with White Matter Lesions in Childhood-Onset Systemic Lupus Erythematosus. Aline T. Lapa[1], Mariana Postal[1], Nailu A. Sinicato[1], Lucas Ferreti Silveira[1], Fernando Cendes[1], Roberto Marini[1] and Simone Appenzeller[2]. [1]State University of Campinas, Campinas, Brazil, [2]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: Imaging findings in systemic lupus erythematosus (SLE) patients are diverse; and diffuse or regional atrophy and white matter hyperintensities (WMH) have been described in variable frequency. Studies have shown that the subunit of high molecular weight neurofilament (NF-H) is more resistant to degradation and therefore can be found in large quantities in the serum of patients with CNS injury. However the prevalence and clinical significance of WMH and it′s association with serum NF-H levels in childhood-onset SLE (cSLE) is still unknown. We aimed to determine if serum NF-H protein levels are associated with WMH in cSLE patients.

Methods: We included consecutive cSLE patients (disease-onsebefore the age of 18)followed in a cohort at the Pediatric Rheumatology Unit at the StateUniversity of Campinas. The control group was consisted by age and sex matched healthy individuals. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. MRI scans were obtained through a standardized protocol (3Tessla Philips). WMH were analyzed in T2-weighted images using a semiautomated computer program developed in our laboratory (Neuroline) and validated against standard MRI segmentation programs. Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and cumulative SLE-related damage was determined using the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI) at time of blood withdrawal. NF-H protein levels were measured by enzyme-linked immunosorbent assay using commercial kits from BioVendor, Inc (Czech Republic). Data were compared by non-parametric tests.

Results: We included 70 consecutivecSLE patients [63(90%) female; median age=16 years (range 9–30)]. The median disease duration was 3 years (range 0–13 years). At time of study entry, 30 (42.5%) cSLE patients had active disease (SLEDAI $\geq$3) and 28 (40%) had a history of neuropsychiatric (NP) manifestations. Eighteen (25.7%) cSLE had cumulative damage [SDI scores$\geq$1 (range 1–3].The white matter lesions were identified in 63 (90%) patients. WMH lesions occurred more frequently in the subcortical WM. The median NF-H protein levels were significantly increased in cSLE(55.1 pg/mL; range 1.00–330.3) when compared to controls (60.68pg/mL; range 16.1–76.7; $p<0.001$).

Conclusion: The vast majority of cSLE patients presented WMH using an objective quantitative MRI method. The presence of WMH was associated withhigher NF-Hprotein levels, suggesting that these lesions are a result of CNS injuryand should be followed carefully.

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Metabolic Syndrome Features Can Influenciate Cognitive Functions and Brain Lesions in Childhood-Onset Systemic Lupus Erythematosus. Nailu A. Sinicato[1], Aline T. Lapa[1], Mariana Postal[1], Bruna Bellini[1], Paula T Fernandes[1], Roberto Marini[1] and Simone Appenzeller[2]. [1]State University of Campinas, Campinas, Brazil, [2]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: The underlying factor for an association between the metabolic syndrome (MetS) and cognitive decline might be a subclinical inflammation. Inflammatory mechanisms are hypothesized to be involved in the pathogenesis of cognitive impairment (CI) and in the development of diabetes and atherosclerosis. We aimed to correlate MetS, cognitive function and white matter hyperintensities (WMH) lesions in childhood-onset systemic lupus erythematosus (cSLE).

Methods: We performed a cross sectional study of 63 consecutive cSLE patients followed at the Pediatric Rheumatology Unit of the State University of Campinas and 63 age and sex matched healthy controls. All individuals were assessed for anthropometric and MetS features according to International Diabetes Federation (IDF) criteria. Body mass index (BMI) was calculated and blood was collected for the measurement of glucose, lipid profile including total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG), after a standard 12-hour fasting in all subjects. cSLE patients were further assessed for clinical and laboratory manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC)], current and cumulative drug exposures. Cognitive evaluation was performed in all participants using Wechsler Intelligence Scale for children (WISC-III) and Wechsler Intelligence Scale for adults (WAIS), according to age and validated in Portuguese. Cognitive impairment (CI) was defined when scores were $\leq$2 standard deviations from controls in 1 or more subtests. Magnetic resonance imaging (MRI) scans were performed in a 3T Phillips®scanner using a standardized protocol and T2 weighted images were used for analyze. Quantification of lesion load and volume of WMH were performed by using a semiautomatic computer program (Neuroline®). Non-parametric tests were used for statistical analysis.

Results: MetS was observed in 11 (17.4%) cSLE patients and in none of the controls ($p<0.001$). We observed a higher hip circumference ($p=0.030$), waist-to-hip ratio ($p<0.001$) and hypertriglyceridemia ($p=0.005$) in cSLE patients when compared to controls. Controls had a higher height ($p=0.003$) and higher levels of HDL ($p=0.004$). We observed an inverse correlation between height and total corticosteroid dose adjusted by weight in cSLE patients ($r=-0.285;p=0.022$). CI was present in 32 (50.8%) cSLE. No association between Mets and CI was observed ($p=0.3$). Rey complex picture on memory subtest correlated with BMI ($r=-0.249$; $p=0.05$) and TG levels ($r=0.282;p=0.028$) and Boston Naming Test had an inverse correlation with total cholesterol levels ($r=-0.258;p=0.047$). WMH were observed in 53 (82.5%) cSLE patients and in 4 (6.3%) controls. The presence of WMH lesions was associated with sera glucose levels ($p=0.039$).

Conclusion: MetS features such as lipid profile and glucose levels were associated with some cognitive functions and with WMH in cSLE. This findings suggest that MetS complications go beyond the cardiovascular risk factors and should be routinely screened and treated.

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2661

Serum Neuronal Biomarkers and Brain Atrophy in Childhood-Onset Systemic Lupus Erythematosus. Aline T. Lapa[1], Mariana Postal[1], Nailu A. Sinicato[1], Renata Barbosa[2], Fernando Cendes[1], Roberto Marini[1] and Simone Appenzeller[3]. [1]State University of Campinas, Campinas, Brazil, [2]Faculdade de Ciencias Medicas, Universidade Estadual de Campinas, Campinas, Germany, [3]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: We aimedto investigate the association of serum biomarkers and regional and diffuse brain atrophy in cSLE.

Methods: We included consecutive cSLE patients (disease-onset before the age of 18) followed in a cohort at the Pediatric Rheumatology Unit at the State University of Campinas and age and sex matched healthy controls. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and cumulative SLE-related damage was determined using the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI). Magnetic resonance imaging (MRI) scans were obtained through a standardized protocol (3Tessla Philips) and normalized volumetric 1mm Tl weighted images were used for manual volumetric measurements. Volumes $\leq$2 standard deviation from the means of controls were considered abnormal. Serum biomarkers (S100β, NF-H and antiribossomal P (Anti-P) and anticardiolipin antibodies levels were measured by enzyme-linked immunosorbent assay using commercial kits from BioVendor, Inc(Czech Republic). Anti-double stranded DNA (dsDNA) antibodies were determined by indirect immunofluorescen-

ceusingCrithidia as substrate and considered positive if ≥ 1:20.Precipitating antibodies to extractable nuclear antigens (ENAs),including Ro (SSA), La (SSB), and Sm were detected by a standardizedELISA method, and considered positive if higher than 1:40.Anticardiolipin antibodies (aCL) of theIgG and IgMisotypes were measured by an ELISA method. Thelupus anticoagulant (LA) activity was detected by coagulation assaysin platelet-free plasma obtained by double centrifugation. Non-parametric-tests and correlation were used for statistical analysis.

Results: We included 76 cSLE patients (69 women; median age 16 years; range 9–30), with median disease duration was 3 years (range 0–13 years). Neuropsychiatric manifestations were observed in 32 (42.1%). Structural brain abnormalities were identified in 51 (67%) cSLE patients and in in none of the controls ($p<0.001$). Cerebral atrophy was identified in 18 (23.7%), corpus callosum atrophy in 20 (26.3%) and hippocampal atrophy in 46 (60.5%). We did not observe an association between structural brain abnormalities and S100β, NF-H and anti-P protein. The presence of cerebral atrophy was associated with cumulative corticosteroid dose ($p=0.026$), active disease (SLEDAI≥3) ($p=0.044$), aCL ($p=0.024$), anti-dsDNA ($p=0.022$) and anti-Smith ($p=0.049$) antibodies. The presence of corpus callosum atrophy was associated with low complement levels ($p=0.011$). Hippocampal atrophy was associated with low complement levels ($p=0.014$) and LA ($p=0.019$).

Conclusion: Regional and diffuse brain atrophy is frequently observed in cSLE patients. We did not observe an association with neuronal biomarkers, however aPL, LA, low complement levels and cumulative corticosteroid dose were associated with atrophy in this cohort.

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Attribution Protocol and Clinical Significance of Neuropsychiatric Manifestations in Childhood-Onset Systemic Lupus Erythematosus. Renata Barbosa[1], Karina Oliveira Peliçari[2], Aline T. Lapa[2], Nailu A. Sinicato[2], Mariana Postal[2], Roberto Marini[2], Marcelo Govoni Sr.[3] and Simone Appenzeller[4]. [1]Faculdade de Ciencias Medicas, Universidade Estadual de Campinas, Campinas, Germany, [2]State University of Campinas, Campinas, Brazil, [3]University of Ferrara, Ferrara, Italy, [4]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: Systemic lupus erythematosus (SLE) is caused by an imbalance of the immune system and may lead to injury and dysfunction of various systems and organs, including the central nervous system. Different attribution protocols have been developed in adult-onset SLE, however, none has been validated for childhood-onset SLE (cSLE). This study aimed to validate an attribution protocol for NP manifestations and to determine clinical significance of NP manifestations in cSLE.

Methods: A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. Cognitive evaluation was performed in all participants using Wechsler Intelligence Scale according to age and validated in Portuguese. Mood disorders were determined through Becks Depression and Becks Anxiety Inventory. Disease activity was measured by the Systemic Lupus Erythematosus Disease Activity Index and cumulative damage was determined using the Systemic Lupus International Collaborating Clinics Damage Index (SDI). Serum biomarkers (antiribossomal P anticardiolipin Anti-double stranded DNA, Ro (SSA), La (SSB), Sm, anticardiolipin lupus anticoagulant were evaluated. Dose of corticosteroids and other immunosuppressant medications were obtained by review of the medical charts. The protocol was developed and validated in adult-onset SLE by one of the authors (MG). In this protocol each NP manifestations is categorized in unrelated to SLE, uncertain relation to SLE and as definitively related to SLE according to disease duration, disease activity and antibody profile. According to our chart review some modifications were made to the original protocol, such as inclusion of macrophage activation syndrome.

Results: A total of 161 NP were observed in 80 (73 female, mean age 19.13 SD± 4.57 years of 99 (80.8%) patients. Mean disease duration was 6.92(SD± 5.16) years. 39 (48.75%) of patients presented NPSLE during the first 6 months of disease. In decreasing order we observed the following NP manifestations: 68(85%) headache, 22(31.25%) cognitive impairment, 19 (23.75%) mood disorder, 16 (20%) seizure, 12 (15%) cerebrovascular disease, 12 (15%) anxiety, 3 (3.75%) acute confusional state, 3 (3.75%) psychosis, 2(2.5%) corea, 1 (1.25%) cranial neuropathy, 1 (1.25%) aseptic meningitis, 1 (1.25%) demyelinating syndrome and 1 (1.25%) polyneuropathy. Positive anticardiolipin antibodies were identified in 27 (27.27%), positive LA in 28 (28.28%) and positive anti-P in 9/34 (26.47%) cSLE patients. Using the attribution protocol NP manifestations were classified as unrelated to SLE in 1(1.25%) events, uncertain expressions to SLE in 47(58.75%) and as definitively related to SLE 32 (40.0%) events. The NPSLE were associated with azathioprine ($p = 0.011$), current age ($p = 0.006$), disease duration ($p=0.023$) and corticosteroid use (p 0.019).

Conclusion: Neuropsychiatric manifestations are prevalent in cSLE, however only 40% are definitively attributed to SLE. Results are similar to adult-onset SLE. This protocol has to be further validated in other cohorts, but may be useful in clinical practice.

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Sense of Smell, Anti-Ribosomal P Antibodies and Neuropsychiatric Manifestations in Systemic Lupus Erythematosus. Fernando Augusto Peres[1], Karina Oliveira Peliçari[1], Nailu A. Sinicato[1], Mariana Postal[1], Aline T. Lapa[1], Lilian Costallat[2] and Simone Appenzeller[3]. [1]State University of Campinas, Campinas, Brazil, [2]State University of Campinas, Campinas, United Kingdom, [3]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: Neuropsychiatric manifestations occur in 12–95% of SLE patients. Recent studies have demonstrated the high specificity of antiribosomal P antibodies for SLE. Antiribosomal P antibodies are able to bind to neuronal cells in areas of the limbic system which are responsible to the olfactory. We aimed to analyze the prevalence of olfactory disorder in SLE, correlate olfactory with presence of neuropsychiatric manifestations, disease activity and the presence of antiribosomal P antibodies.

Methods: Consecutive SLE patients followed at the rheumatology unit of the State University of Campinas were enrolled in this study. The control group was consisted by age and sex matched healthy individuals. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. Mood and anxiety disorders were determined through Becks Depression and Becks Anxiety Inventory. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index). Antiribosomal P antibody was performed by Enzyme Linked Immuno Sorbent Assay. Olfactory functions were evaluated using the Sniffin' Sticks test, in 3 stages: threshold, discrimination, and identification of different odors (TDI).

Results: We included 120 SLE patients (93.3% female; mean age 40.3 years; SD±11.3 years) and 135 healthy volunteers (91.1% female; mean age 37.6 years; SD±12.4 years). Anxiety was observed in 81(67.5%) SLE patients and in 49 (39.2%) controls ($p<0.001$). Depression was identified in 56 (46.6%) SLE patients and in 39 (28.8%) controls ($p=0.004$). Antiribosomal P antibodies were identified exclusively in SLE patients and were present in 13 (10.8%) of them ($p<0.001$). Olfactory changes were observed in 62 (51.6%) SLE patients and in 40 (29.6%) controls ($p=0.001$). SLE patients had significantly lower mean in all phases of the olfactory assessment. The olfactory was also inversely associated with anxiety ($p=0.004$, $R=-0.18$), depression ($p=0.01$, $R=-0.232$), cumulative damage ($p=0.002$, $R=-0.282$) and age ($p<0.001$, $R=-0.353$). The TDI was correlated with a CNS involvement, and patients with NP manifestations [mean of 28.35 (SD ± 5.30)] points, whereas patients without NP manifestations had a mean TDI of 30.8 (SD ± 4.51) points ($p<0.001$). Antiribosomal P antibodies were not associated with CNS involvement ($p=0.730$), but when we analyzed each manifestation separately, we observed an association between the presence of antiribosomal P antibodies and psychosis ($p<0.046$). We also observed an association between antiribosomal P antibodies and disease activity ($p=0.036$).

Conclusion: SLE patients have a significant decrease of smell when compared to healthy controls. Olfactory changes are associated with a history of neuropsychiatric symptoms, anxiety, depression, cumulative damage, and age. Antiribosomal P antibodies were exclusively observed in SLE patients compared to healthy controls and they were associated with psychosis and disease activity.

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Increased Risk of Hematological Malignancies in Children Born to Women with SLE. Evelyne Vinet[1], Ann E. Clarke[2], Christian A. Pineau[3], Susan Scott[3], Robert W. Platt[4] and Sasha Bernatsky[3]. [1]McGill University Health Center, Montreal, QC, [2]University of Calgary, Calgary, AB, [3]McGill University Health Centre, Montreal, QC, [4]McGill University, Montreal, QC.

Background/Purpose: Patients with SLE have an increased risk of hematological malignancies, particularly non-Hodgkin lymphoma, compared to the general population. Recently, in utero exposures, such as chronic maternal autoimmune conditions, have been associated with the development of childhood hematological malignancies. However, until now, no one has assessed the risk of hematological cancers in children born to women with SLE. Thus, in a large population-based study, we aimed to determine if SLE offspring have an increased risk of hematological malignancies, versus controls.

Methods: The "Offspring of SLE mothers Registry (OSLER)" includes all women who had ≥1 hospitalization for delivery after SLE diagnosis, identified through Quebec's universal healthcare databases (1989–2009). OSLER also includes a randomly selected control group of women, matched at least 4:1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery. We identified children born live to SLE mothers and their matched controls, and ascertained hematological malignancies based on ≥1 hospitalization or physician visit with a relevant diagnostic code, through to end of database follow-up.

We performed multivariate logistic regression analyses, using generalized estimating equations, to adjust for maternal demographics and comorbidities, sex of child, and gestational diabetes. In a subsample analysis of children with maternal drug coverage throughout pregnancy, we further assessed relevant in utero medication exposures.

Results: 509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Mean maternal age and follow-up were respectively 30.3 (SD 5.0) and 9.1 (SD 5.8) years. Children born to women with SLE experienced more hematological malignancies (9/719) compared to controls (38/8493) [1.25% (95% CI 0.61, 2.45) versus 0.45% (95% CI 0.32, 0.62), difference 0.80% (95% CI 0.14, 2.01)]. The most frequent type of hematological cancer in both groups was acute lymphoblastic leukemia. Of note, primary non-Hodgkin lymphoma of bone was observed in 2/719 SLE offspring as opposed to 6/8493 control children [0.28% (95% CI 0.05, 1.12) versus 0.07% (95% CI 0.01, 0.16), difference 0.21% (95% CI -0.04, 1.05)]. In multivariate analyses (n=9212), children born to women with SLE appeared to have an increased risk of hematological cancers versus controls (OR 2.80, 95% CI 1.33, 5.92).

In the subsample of children with drug coverage (n=1925), in utero medication exposures were rare in the 10 hematological cancer cases: none was exposed to antimalarials, corticosteroids, or immunosuppressants.

Conclusion: Our data suggest that compared to children from the general population, children born to women with SLE may have an increased risk of hematological malignancies. However, it must be emphasized that this outcome is extremely rare, and our findings remain to be confirmed by other study methods. The lack of association with in utero drug exposures may be viewed as somewhat re-assuring, though this too is preliminary.

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Risk of Hydrocephalus and/or Macrocephaly in Children Born to Mothers with SLE. Catherine Huang[1], Sasha Bernatsky[2], Christian A. Pineau[2], Susan Scott[2], Ann E. Clarke[3], Robert W. Platt[1] and Evelyne Vinet[4]. [1]McGill University, Montreal, QC, [2]McGill University Health Centre, Montreal, QC, [3]University of Calgary, Calgary, AB, [4]McGill University Health Center, Montreal, QC.

Background/Purpose: Evidence suggests that both hydrocephalus and macrocephaly could be potential manifestations of neonatal lupus. In a recent study of 87 children born to mothers with anti-Ro antibodies (Boros et al., *Arthritis Rheum*, 2007), prevalence of hydrocephalus was high at 8.0% and mean head circumference was substantially larger than the age-matched normal values. Although up to 40% of women with SLE display anti-Ro antibodies, to date, no one has assessed the occurrence of hydrocephalus and/or macrocephaly in SLE offspring. Thus, in a large population-based study, we aimed to determine if children born to women with SLE have an increased risk of hydrocephalus and/or macrocephaly compared to children born to women without SLE.

Methods: The "Offspring of SLE mothers Registry (OSLER)" includes all women who had ≥1 hospitalization for delivery after SLE diagnosis, identified through Quebec's universal healthcare databases (1989–2009). OSLER also includes a randomly selected control group of women, matched at least 4:1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery. We identified children born live to SLE mothers and their matched controls, and ascertained hydrocephalus and macrocephaly based on ≥1 hospitalization or physician visit with a relevant diagnostic code, through to end of database follow-up. We performed multivariate logistic regression analyses, using generalized estimating equations, to adjust for maternal demographics and comorbidities, sex of child, and gestational diabetes.

Results: A total of 719 children were born to 509 women with SLE, and 8493 children were born to the 5824 matched controls. Compared to controls, children born to women with SLE showed only a slight trend towards more records of hydrocephalus and/or macrocephaly diagnosis [8 per 1000 persons (95% CI 4, 18) versus 6 per 1000 persons (95% CI 5, 8), difference 2 per 1000 persons (95% CI -3,13)]. Similarly there was only a slight trend towards younger age at time of hydrocephalus and/or macrocephaly diagnosis in SLE offspring versus controls [respectively 0.6 year (95% CI 0.2, 1.0) and 1.1 years (95% CI 0.5, 1.7)]. Of note, among the 6 cases of hydrocephalus and/or macrocephaly identified in SLE offspring, none had a diagnosis of cardiac conduction disturbance, suggesting no strong association with neonatal lupus. In multivariate analysis, the point estimate for the outcome was consistent with a trend for higher risk of hydrocephalus and/or macrocephaly in SLE offspring compared to controls, although the confidence interval was wide and precluded definitive conclusions (OR 1.37, 95% CI 0.58, 3.22).

Conclusion: Compared to children from the general population, there was a slight trend for higher frequency (and earlier age at diagnosis) of hydrocephaly and/or macrocephaly among children born to mothers with SLE, but the results do not strongly suggest an important increase in the risk of hydrocephalus and/or macrocephaly.

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Causes of Stillbirths in Women with SLE. Evelyne Vinet[1], Geneviève Genest[2], Susan Scott[2], Christian A. Pineau[2], Ann E. Clarke[3], Robert W. Platt[4] and Sasha Bernatsky[2]. [1]McGill University Health Center, Montreal, QC, [2]McGill University Health Centre, Montreal, QC, [3]University of Calgary, Calgary, AB, [4]McGill University, Montreal, QC.

Background/Purpose: It is believed that pregnant women with SLE face an increased risk of stillbirths, although there are few precise or recent estimates of the magnitude of the effect. As well, no one to date has investigated the causes of stillbirths in SLE pregnancy. Using the "Offspring of Systemic Lupus Erythematous Registry (OSLER)", we examined stillbirths and the cause of their death in SLE mothers versus those without SLE.

Methods: OSLER is a large population-based cohort, which includes all women who had one or more hospitalizations for delivery after SLE diagnosis, identified through Quebec's healthcare databases (1989–2009). OSLER also includes a randomly selected control group of healthy women, matched at least 4:1 for age and year of delivery. We identified stillbirths (defined as intrauterine deaths occurring at or after 20 weeks of gestational age) from SLE mothers and their matched controls and ascertained the cause of death as indicated on the death certificate. We performed a multivariate logistic regression analysis, using generalized estimating equations, to estimate the risk of stillbirths in SLE offspring versus controls, adjusting for maternal education, comorbidities (i.e. hypertension, diabetes, asthma, depression), and multiple births.

Results: 509 women with SLE had 729 births, including 9 stillbirths (1.4%), while 5829 matched controls had 8541 births including 47 stillbirths (0.6%). Compared to controls, women with SLE had an increased risk of having a stillbirth (adjusted OR 2.16, 95% CI 1.05, 4.44). Among women having a stillbirth, median maternal age was identical for both SLE and control mothers [respectively 31.0 years (IQR 29.0, 32.0) and 31.0 years (IQR 26.5, 30.5)]. There was a trend for more female stillbirths born to women with SLE (6 of nine stillbirths were female) compared to controls (22/47) (OR 2.27, 95% CI 0.54, 9.41). In addition, stillbirths in SLE mothers occurred at a younger median gestational age compared to controls [29 weeks (IQR 28, 31) versus 35 weeks (IQR 27, 38)].

Causes of death in SLE and control stillbirths are illustrated in Table 1. We observed a trend for higher risk in SLE mothers versus controls for stillbirths due to maternal hypertensive disorders and placental abruption [respectively OR 6.43 (95% CI 0.8, 53.3) and OR 4.19 (95% CI 0.59, 29.72)].

Conclusion: Compared to women from the general population, women with SLE appear to have an increased risk of stillbirths, although it must be emphasized that most pregnancies in SLE are not complicated by this event. Stillbirths in mothers with SLE might be more often caused by maternal hypertensive disorders and placental abruption compared to stillbirths in mothers without SLE.

Table 1. Causes of death among SLE and control stillbirths

Causes[a]	SLE stillbirths (n=9)	Control stillbirths (n=47)
Hypertensive disorders, n (%)	2 (22)	2 (4)
Placental abruption, n (%)	2 (22)	3 (6)
Placental disorders, n (%)	0 (0)	3 (6)
Congenital abnormality, n (%)	1 (11)	3 (6)
Umbilical cord abnormality, n (%)	1 (11)	3 (6)
Obstetrical complications, n (%)	1 (11)	21 (45)
Maternal medical condition, n (%)	0 (0)	1 (2)
Infection, n (%)	1 (11)	1 (2)
Other, n (%)	1 (11)	3 (6)
Unknown n, (%)	0 (0)	7 (15)

[a]Reference for classification of causes of death: Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. JAMA. 2011 Dec 14; 306(22):2459–68.

Disclosure: E. Vinet, None; **G. Genest**, None; **S. Scott**, None; **C. A. Pineau**, None; **A. E. Clarke**, None; **R. W. Platt**, None; **S. Bernatsky**, None.

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First-Trimester Disease Activity Does Not Predict Pre-Eclampsia in SLE Pregnancy. Khaled Alderaan[1], Laurence S. Magder[2] and Michelle Petri[3]. [1]King Fahad Specilaist Hospital, Dammam, Saudi Arabia, [2]University of Maryland, Baltimore, MD, [3]Johns Hopkins University School of Medicine, Baltimore, MD.

Background/Purpose: Preeclampsia complicates up to 35% of lupus pregnancies compared to 8% of general population pregnancies. SLE has up to a 3-fold increased rate of preeclampsia. The aim of this cohort study was to determine whether variables measured in the first trimester could help predict which women will develop pre-eclampsia.

Methods: Only pregnancies with a clinic visit during the first trimester were included. All women were diagnosed with SLE either before or during the pregnancy, according to the American College of Rheumatology (ACR) revised classification criteria. Preeclampsia was defined according to the American College of Gynecology (ACOG), as follows: systolic blood pressure of 140 mm Hg or higher or diastolic of 90 mm Hg or higher in patients with previously normal blood pressure, taken on two occasions, measured after 20 weeks of gestation; and proteinuria, defined as urinary protein excretion of more than 0.3 g in a 24-hour urine collection. Rates of pre-eclampsia were calculated in subgroups defined by variables measured in the first trimester, defined as the first 13 weeks of pregnancy.

Results: A total of 280 pregnancies from 234 different women were included in this analysis. The patients were 62% Caucasian, 28% African American, and 10% other ethnicities. Twenty-nine (10%) of the pregnancies met the definition of preeclampsia. Table 1 shows the rates of pre-eclampsia by patient subgroups. There was not strong evidence of an association between lupus-related variables such as anti-dsDNA, low complement, global disease activity and risk of pre-eclampsia. Also, there was no strong evidence of a relationship between medications such as prednisone, hydroxychloroquine and risk of pre-eclampsia.

Conclusion: Preeclampsia development in SLE patients cannot be predicted in the first trimester. Disease activity, serologic activity, proteinuria, antiphospholipid antibodies and prednisone are not predictive.

Table 1. Number (%) with Preeclampsia Assessed in The First Trimester.

Pregnancy Characteristic	Number of Pregnancies[1]	Number (%) with pre-eclampsia	P-value
Systolic Blood Pressure			
<120	152	12 (8%)	0.56
120–129	65	9 (14%)	
130–139	28	3 (11%)	
140+	21	3 (20%)	
Diastolic Blood Pressure			
<70	112	10 (9%)	0.15
70–79	90	6 (7%)	
80+	64	11 (17%)	
Taking Hypertension Medication			
No	241	21 (9%)	0.097
Yes	33	7 (21%)	
BMI			
<20	25	1 (4%)	0.48
20–25	109	12 (11%)	
25–30	61	6 (10%)	
30+	47	8 (17%)	
SLEDAI			
0	105	10 (10%)	0.84
1–3	65	8 (12%)	
4+	103	10 (10%)	
PGA			
0–0.499	196	23 (12%)	0.25
0.5–1.0	42	4 (10%)	
>1.0	42	2 (5%)	
Log DNA titer			
0	179	18 (10%)	0.87
<5	48	5 (10%)	
5+	38	5 (13%)	
Low C4			
No	188	21 (11%)	0.55
Yes	80	7 (9%)	
RVVT			
<45	165	21 (13%)	0.98
45+	16	2 (13%)	
Anti-cardiolipin			
Not elevated	58	7 (12%)	0.54
> 10 for at least one isotype	47	4 (9%)	
Urine Protein Dip Stick			
0	194	19 (10%)	0.13
0.5	29	1 (3%)	
1	20	5 (25%)	
2+	22	1 (5%)	
Prednisone			
None	132	15 (11%)	0.80
1–9 mg/d	63	5 (8%)	
10–19 mg/d	47	4 (9%)	
20+ mg/d	30	4 (13%)	
Plaquenil			
No	146	17 (12%)	0.40
Yes	127	11 (9%)	
Serum Creatinine			
<0.7	98	8 (8%)	0.48
0.7–0.99	134	17 (13%)	
1.0+	36	3 (8%)	

[1] Numbers of pregnancies do not always add up to 280 due to missing values for predictors.

Disclosure: K. Alderaan, None; **L. S. Magder**, None; **M. Petri**, None.

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Maternal Clinical Characteristics of SLE and Pregnancy: Hopkins Lupus Pregnancy Cohort. Michelle Petri[1], Amanda Eudy[2], Marcy Powell[2], Greg Giguere[2], Qinggong Fu[2] and Deanna Hill[2]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]GlaxoSmithKline, Research Triangle Park, NC.

Background/Purpose: Systemic lupus erythematosus (SLE) typically presents in women of childbearing age. As such, it is important to understand how the clinical characteristics of SLE affect pregnancy outcomes. This research question is being assessed in a secondary analysis of the Hopkins Lupus Pregnancy Cohort.

Methods: Data from the Hopkins Lupus Pregnancy Cohort for pregnancies occurring on or after 01 Jan 2000. Maternal clinical characteristics in the 6 months prior to or during pregnancy that were analyzed included comorbidities (pregnancy-induced hypertension, placental abruption, preeclampsia, gestational diabetes, proteinuria, hypertension and thrombocyto-

penia), concomitant medications (corticosteroids, other immunosuppressants, NSAIDs, anti-malarials and heparin) and lab tests (low C3/C4, anticardiolipin antibodies and anti-dsDNA+). We evaluated whether maternal clinical characteristics were associated with low birth weight (LBW; <2500 g) pregnancy outcome for live births. Fischer exact p-values were calculated in this analysis (WEUKBRE5887 & WEUKBRE4566; 114256).

Results: In this analysis, there were 213 pregnancies in 190 women (median age: 30 years; median SLE duration: 5.5 years; 51% white, 37% black, 12% other). There were 16 (7.5%) spontaneous miscarriages, 6 (2.8%) stillbirths and 188 (88.3%) live births (median gestational age: 38 weeks). The outcome was unknown in three of the pregnancies. Of the live births, 38 (20.2%) were preterm, 15 (8.0%) were small for gestational age (SGA; defined as weight <10th percentile for gestational age) and 41 (21.8%) were LBW. Compared to mothers of infants with normal birth weight (Table 1), mothers of infants with LBW had a greater frequency of hypertension (34.1% vs. 17.0%; p=0.01), proteinuria (12.2% vs. 3.4%; p=0.03) and higher dose steroid use (≥7.5 mg/day) in the 6 months prior to or during pregnancy (63.4% vs. 47.6%; p=0.03).

Table 1 Association of maternal clinical characteristics[1] and low birth weight pregnancy outcome in the Hopkins Lupus Pregnancy Cohort

	Total Live Births n=188 n (%)	Normal Birth Weight (≥2500g) n=147 n (%)	Low Birth Weight (<2500g) n=41 n (%)	Fischer Exact p-value
Co-Morbidities				
Hypertension	39 (20.7)	25 (17.0)	14 (34.1)	**0.01**
Pregnancy-induced hypertension	7 (3.7)	5 (3.4)	2 (4.9)	0.3
Placental abruption	1 (0.5)	0 (0.0)	1 (2.4)	0.2
Pre-eclampsia	16 (8.5)	6 (4.1)	10 (24.4)	**<0.0001**
Proteinuria	10 (5.3)	5 (3.4)	5 (12.2)	**0.03**
Gestational diabetes	2 (1.1)	2 (1.4)	0 (0.0)	0.6
Thrombocytopenia	12 (6.4)	8 (5.4)	4 (9.8)	0.2
Medications[2]				
Corticosteroids[3]				
≥7.5 mg/day	96 (51.1)	70 (47.6)	26 (63.4)	**0.03**
<7.5 mg/day	91 (48.4)	76 (51.7)	15 (36.6)	**0.03**
Missing	1 (0.5)	1 (0.7)	0 (0.0)	–
Other immuno-suppressants	56 (29.8)	41 (27.9)	15 (36.6)	0.08
NSAIDs[4]	66 (35.1)	55 (37.4)	11 (26.8)	0.07
Antimalarials	154 (81.9)	121 (82.3)	33 (80.5)	0.2
Heparin	39 (20.7)	31 (21.1)	8 (19.5)	0.2
Lab Values				
Low C3/C4	110 (58.5)	84 (57.1)	26 (63.4)	0.1
Anticardiolipin antibodies	14 (7.4)	11 (7.5)	3 (7.3)	0.3
IgG	6 (3.2)	5 (3.4)	1 (2.4)	0.4
IgM	9 (4.8)	7 (4.8)	2 (4.9)	0.3
IgA	3 (1.6)	2 (1.4)	1 (2.4)	0.4
Anti-dsDNA+	100 (53.2)	78 (53.1)	22 (53.7)	0.1

[1]Observation period defined as the 6 months prior to and/or during pregnancy
[2]Medication use ever in the observation period
[3]Corticosteroid use categories are mutually exclusive. Patients with higher dose (≥7.5 mg/day) ever during the observation period were not included in the low dose (<7.5/mg day) category.
[4]NSAIDS: nonsteroidal anti-inflammatory drugs

Conclusion: In this analysis, certain maternal clinical characteristics were associated with LBW in infants born to mothers with SLE. Although a greater frequency of higher dose steroid use was observed in mothers of infants with low birth weight, it is possible that treatment with higher dose steroids (≥7.5 mg/day) was a proxy for more active SLE in the 6 months prior to or during pregnancy, rather high dose steroid use having a direct effect on low birth weight. Data from this analysis will complement planned analyses for the Belimumab Pregnancy Registry, an ongoing international, prospective cohort study of women exposed to commercially-supplied belimumab within 4 months prior to and/or during pregnancy (WEUKBRE6076; clinicaltrials.gov ID NCT01532310; 114256).

Disclosure: M. Petri, GlaxoSmithKline, 5; **A. Eudy**, GlaxoSmithKline, 3; **M. Powell**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **G. Giguere**, GlaxoSmithKline, 3; **Q. Fu**, GlaxoSmithKline, 1, GlaxoSmithKline, 3; **D. Hill**, GlaxoSmithKline, 1, GlaxoSmithKline, 3.

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Systemic Lupus Erythematosus and Lactation: Factors Affecting Infant Feeding Choices in Women with SLE. Sara Wasserman and Megan E. B. Clowse. Duke University Medical Center, Durham, NC.

Background/Purpose: Breastfeeding has been shown to improve maternal and infant wellbeing and long-term health, but it is currently unknown how often it is pursued in the SLE population. We sought to determine the rate of breastfeeding and factors that promote or discourage this in the postpartum period for women with SLE.

Methods: Lupus patients enrolled in a prospective pregnancy registry completed questionnaires about infant feeding intentions at enrollment and infant feeding practices post-partum. Throughout the pregnancy and postpartum, medications and disease activity were evaluated using the SLE pregnancy disease activity index (SLEPDAI).

Results: 86 pregnancies occurred in women who met the 2012 SLICC criteria for SLE. Of these, 13 resulted in a miscarriage or termination and 10 were lost to follow-up; postpartum feeding data is available for 51 pregnancies. 28 (54.9%) of pregnancies were in Caucasian women, 20 (39.2%) in African-American and 3 (5.9%) in Asian women. The average maternal age was 29.8yrs (SD 4.8), with a range from 21.5 to 42.2yrs. At study entry, 53 (64.6%) planned on breastfeeding, 19 (23.2%) planned on using formula, and 10 (12.2%) had no feeding plan.

By 6 weeks postpartum, 26 (51.0%) were formula feeding exclusively and 25 (49.0%) were breastfeeding. Of the women breastfeeding, 7 (28%) were supplementing with formula. Compared to women who formula fed only, those who were breastfeeding were older and had less disease activity post-partum (see table). Breastfeeding mothers also had deliveries that were more likely to be at term and their infants were less likely to have spent time in the intensive care unit.

African-American women were more likely to plan to use formula (45.0% AA vs 22.2% Caucasian, p=0.12) and to only use formula (65.0% AA vs 42.9% Caucasian, p=0.15). African-American women were also more likely to have high SLE activity post-partum (47.4% AA vs 15.6% Caucasian, p=0.04). In multivariate logistic regression, post-partum SLE activity (p=0.02) and whether breastfeeding was planned in pregnancy (p=0.03), but not race (p=0.6), predicted breastfeeding.

The key reasons that women breastfed included to keep the baby healthy (91.7%), to bond with the baby (66.7%), to keep infant feeding costs low (66.7%), to lose weight (58.3%), and for convenience (33%). The main reasons that women did not breastfeed were concern over medication effects on the infant (36%); 7 (27%) of the non-breastfeeding women were taking contraindicated medications (methotrexate, mycophenolate, or azathioprine) post-partum.

Conclusion: About half of women with lupus breastfeed for at least 6 weeks. Factors that influence this decision include pre-delivery intention to breastfeed, maternal age, SLE activity, and medications. Given the myriad of maternal and infant benefits seen with breastfeeding, finding approaches that facilitate this choice for women with SLE is an important goal.

	Breastfeeding	Formula Only	p-value
Number of pregnancies	25	26	
Maternal age	31.3 (SD 4.6)	28.4 (SD 4.7)	0.027
Maternal race			
Caucasian	16 (69.6%)	12 (48%)	0.154
African-American	7 (30.4%)	13 (52%)	
SLEPDAI post-partum average (SD)	2.7 (2.9)	5.5 (4.8)	0.03
SLEPDAI post-partum >4 (high SLE activity)	3 (15%)	10 (47%)	0.04
Preterm birth	3 (12%)	10 (38.5%)	0.05
Gestational Age at Delivery	38.1 (1.6)	37.1 (2.1)	0.05
C-section	11 (44%)	10 (38.5%)	0.9
Baby stayed in the intensive care unit	4 (16%)	8 (33%)	0.2
Pre-delivery Infant Feeding Plan			
Breastfeeding	21 (87.5%)	13 (50%)	0.016
Formula only	1 (4.2%)	7 (26.9%)	
No plan	2 (8.3%)	6 (23.1%)	

Disclosure: S. Wasserman, None; **M. E. B. Clowse**, UCB Pharma, 5.

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Premature Delivery in Patients with Systemic Lupus Erythematosus. Valeria Arturi, Pierina Sansinanea, Mariana Alejandra Pera, Adrian Pablo Salas, Josefina Marcos, Ana Carolina Costi, Claudia Elizabeth Pena and Mercedes Argentina García. HIGA San Martín La Plata, La Plata, Argentina.

Background/Purpose: Premature delivery (PD) is one of the most important difficultiess in perinatology. An incidence on developing countries of around 19% and 5–7% in developed nations is estimated. In Systemic Lupus Eritematosus (SLE) preterm delivery and stillbirth are still concerns, particularly in relation to pregnancies in patients with renal involvement, the presence of antiphospholipid antibodies (a-PL) or anti Phospholipidic Syndrome (APS). The aim of this study was to evaluate the prevalence of PD in patients with SLE and analyze the relationship between different factors related to the disease with fetal outcomes and neonatal mortality.

Methods: Patients with SLE (1997 ACR criteria) with ≥ 1 pregnancy between 1987–2011 were analyzed. Premature delivery was defined as live birth before 37 weeks of gestation. We compared the outcomes among PD pregnancies versus term pregnancies. The statistical analysis was performed with Chi-square test or test of Student as appropriate.

Results: 166 pregnancies were recorded in 124 SLE patients. In 132/166 (79.5%) pregnancies were live birth. 46/132 (34.8%) were PD. Main causes of PD were: premature rupture of fetal membranes (21.7%), gestosis (19.6%) and placental insufficiency with intrauterine growth restriction (13%). Eight preterm newborn (17.4%) died in the neonatal period, 4 of them were part of the seven cases of extreme preterm birth (< 32 weeks of gestation).

	Preterm 46	Term 98	p	OR	CI
APS	51%	32.65%	0.65	2.063	0.94–4.49
Previous nephropathy	32.6%	30.6%	1.000	1.063	0.46–2.39
Infections	24%	18.3%	0.505	1.39	0.54–3.52
Proteinuria	43.75%	10.2%	0.002	3.85	1.42–10.51
a-PL	77%	52.6%	0.006	3.06	1.27–7.49
Hydroxychloroquine	37%	40%	0.855	0.887	0.40–1.93
Pre-eclampsia	19.6%	11.2%	0.201	1.92	0.66–5.54
Cesarean delivery	58.7%	47%	0.212	1.61	0.74–3.48
Low birth weight	82.6%	10%	<0.0001	41.8	13.9–132
Neonatal Death	17.4%	4%	0.019	4.94	1.24–20.9

Conclusion: 34.8% of the 132 live newborns from mothers with SLE were preterm deliveries. Proteinuria during the course of the pregnancy and anti-phospholipid antibodies were significantly associated with PD. Patients with PD had increased the risk of having a newborn with low birth weight as well as increased mortality in the neonatal period, especially when the delivery occurred before 32 weeks of gestation.

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Impact of Glucocorticoid Dose on Maternal and Fetal Outcomes in Lupus Pregnancies. Dafhne Miranda[1], Miguel A. Saavedra[2], Eduardo Gomez[3], Alberto Daniel Rocha Muñoz[4], Jorge Gaspar Ramos[1] and Luis Javier Jara[5]. [1]Rheumatology Unit, Hospital de Especialidades. Centro Médico La Raza, IMSS, Distrito federal, Mexico, [2]Hospital de Especialidades Centro Médico La Raza, IMSS, Mexico City, Mexico, [3]Institute for Research in Rheumatology and Musculoskeletal System, Guadalajara, Mexico, [4]Institute for Research in Rheumatology and Musculoskeletal System, Guadalajara, Jalisco, Mexico, [5]Instituto Mexicano del Seguro Social, D.F., Mexico.

Background/Purpose:

- Lupus flares during pregnancy can be treated with short courses of low to moderate doses of glucocorticoids (GCs). GCs are associated with several maternal and fetal complications during pregnancy, however information about the role of the dose in the development of these complications is limited
- To analyze the role of GCs in the development of maternal and fetal complications in women with systemic lupus erythematosus (SLE) and if these complications are dose-related

Methods: We prospectively studied a cohort of pregnant women with SLE (ACR 1997) between January 2009 and August 2013. The patients were assessed every 4 to 6 weeks and postpartum by a rheumatologist and a gynecologist. Clinical, biochemical and immunological characteristics of women, along with maternal and fetal complications, were recorded. For analysis, the patients were first assigned to one of two groups: pregnancies exposed to GCs vs those not exposed. Secondly, to evaluate the dose effect of GCs, we compared three dose ranges throughout pregnancy: prednisone £10 mg daily, prednisone >10–24 mg daily and prednisone ≥25 mg daily. Statistical analysis included descriptive statistics, chi square, Student t test, Fisher's exact test, ANOVA and Scheffe's test as post-hoc and logistic regression; relative risk (RR) with confidence intervals (CI) of 95% were calculated. For the analysis each pregnancy was considered as an independent event.

Results:

- We included 143 pregnancies in 136 patients. There were 111 pregnancies exposed to GCs and a greater exposure to azathioprine (55% vs 21.9%, p=0.001) in comparison with those not exposed to GCs. There were no differences in maternal complications in the analyzed groups by dose ranges. Major fetal complications were dose-related: low weight, low height, and preterm birth. In the multivariable analysis, the use of prednisone >25mg daily was associated with preterm birth (RR 3.3, CI 95% 1.39–8.04, p=0.0002), low birth weight (RR 3.25, CI 95% 1.37–7.18, p=0.0001).

Conclusion:

- This study suggests that fetal complications associated with the use of prednisone are dose-related (>25 mg). The use of low to moderate doses of prednisone during pregnancy is safety.

Disclosure: D. Miranda, None; **M. A. Saavedra**, None; **E. Gomez**, None; **A. D. Rocha Muñoz**, None; **J. G. Ramos**, None; **L. J. Jara**, None.

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Characteristics of the Reproductive System in Systemic Lupus Erythematosus: A Cross-Sectional Survey with Pair-Matched Controls. Maria N. Antoniol[1], Cecilia Reimundes[1], Cecilia Catoggio[1], Analia V. Longo[2], Analia P. Alvarez[2] and Carlos Perandones[1]. [1]CEMIC, Buenos Aires, Argentina, [2]Hospital Penna, Buenos Aires, Argentina.

Background/Purpose: Patients with Systemic Lupus Erythematosus (SLE) present factors associated with the reproductive system that can increase the risk of the disease, but the literature is controversial.

The reproductive system variables are influenced by multiple social, ethnic, economic and cultural factors that can function as confounding variables. For this reason, the optimal SLE population control should be matched by age and sociodemographic features.

We compared reproductive variables of a group of women with SLE with pair-matched healthy controls.

Methods: A case-control study was performed using a cross-sectional survey to analyze variables of the reproductive system in patients with SLE. We included women over 18 years-old with SLE according to ACR criteria. Each case was matched with a healthy control belonging to her sociocultural environment and having her age ± 5 years.

The survey included multiple demographic and disease variables, as well as reproductive system features: age of menarche and menopause, number of pregnancies and fetal losses, and contraceptive methods. Paired t test and McNemar's test or Fisher exact test were applied for continuous and categorical variables, respectively.

Results: We included 83 cases with a mean age of 39.2 ± 10.8 years (range19–66) and the mean age at SLE diagnosis was 26.9 ± 10.3 years. Previous treatments were as follows: 91% hydroxychloroquine, 32% cyclophosphamide, 31% azathioprine, 24% mycophenolate mofetil, and 16% methotrexate.

	Cases	Controls	
Menarche (age ± SD)	12.8 ± 1.7	12.4 ± 1.4	paired t test p 0.15
Menopause (age ± SD)	43.12 ± 6.4	50.23 ± 3.7	paired t test p 0.01
Previous Oral Contraceptives (%)	42%	50%	McNemar's test 1.25 (p 0.26)
Pregnancies (mean ± SD)	1.7 ± 1.6	1.9 ± 1.9	paired t test p 0.34
Fetal Loss (%)	28	28	
Fetal Loss (mean ± SD)	0.43 ± 0.8	0.43 ± 0.8	paired t test p 1.0
Children (mean ± SD)	1.25 ± 1.2	1.45 ± 1.4	paired t test p 0.24
Gestational Age (weeks) (mean ± SD)	37.8 ± 3.1	37.9 ± 3.3	t test p 0.8
Infertility Treatment (%)	6.02	9.6	Fisher exact test p 0.17

When cyclophosphamide was analized as a risk factor for early menopause there were no difference between exposed and non exposed patients

Conclusion: There were no differences in the age of menarche, previous oral contraceptives, number of pregnancies, fetal losses and children, and the need of infertility treatment between SLE patientes and pair-matched controls.

The age of menopause is significantly different but cannot be related only to cyclophosphamide.

Disclosure: M. N. Antoniol, None; **C. Reimundes**, None; **C. Catoggio**, None; **A. V. Longo**, None; **A. P. Alvarez**, None; **C. Perandones**, None.

ACR/ARHP Poster Session C
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis: T and B Cell Signaling and Genetic Variants
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

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High-Throughput Sequencing of 219 Candidate Genes for Identification of SLE-Associated Risk Variants. Fabiana Farias[1], Maria Wilbe[1], Johanna Dahlqvist[1], Dag Leonard[2], Sergey Kozyrev[1], Gerli Pielberg[1], Maija-Leena Eloranta[2], Lars Rönnblom[2] and Kerstin Lindblad-Toh[1]. [1]Uppsala University, Science for Life Laboratory, Uppsala, Sweden, [2]Department of Medical Sciences, SciLife Lab, Rheumatology, Uppsala University, Uppsala, Sweden, Uppsala, Sweden.

Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease, believed to arise from environmental triggering events in genetically predisposed individuals. To date, more than 50 genes have been associated with SLE through genome-wide association studies. However, only about 15% of the heritability of SLE is explained by these findings. In this study we aimed to identify novel rare genetic variants of functional importance for SLE.

Methods: One hundred and forty Swedish SLE patients, fulfilling the ACR classification criteria for SLE, and 12 healthy controls were included in the study. We sequenced the exons, promoter regions and putative regulatory regions of 219 genes selected on basis of their role in immune response, autoimmunity or known association with SLE or SLE-related disease complex in dogs. Selected gene regions were targeted using Roche NimbleGen capture array and the DNA samples were then divided into 10 pools according to the disease manifestations of the patients, with the 12 healthy controls in a separate pool. The pools were paired-end sequenced using Illumina HiSeq2000 reaching approximately 250x coverage per individual.

Results: We detected 4276 novel single-nucleotide polymorphisms (SNPs; not present in 1000genomes or dbSNP137) out of which 1258 SNPs were case-only variants. Seventeen genes showed ≥ 5 novel variants private to cases. Of these, three genes have previously been associated with human SLE and 14 are novel candidate genes. Six SNPs (allele frequencies 0.01–0.03 in patients) located in non-coding sequences with potential regulatory function were selected for further studies based on their characteristics in terms of conservation, DNAse hypersensitivity, ENCODE data on histone marks and ChIP-Seq peaks. The SNPs were validated by genotyping in all patients and in 96 additional healthy controls, to confirm their increased frequency in the patient cohort. Using electrophoretic mobility shift assay, binding of protein complexes was investigated for all six SNPs and they are currently evaluated for their effect on gene expression. The clinical disease manifestations of the patients harboring each of the six SNPs are being analyzed in order to identify any phenotype-genotype correlations.

Conclusion: This proof-of-principle study highlights the importance of analysis of non-coding putative regulatory DNA regions for the identification of rare variants associated with complex disease.

Disclosure: F. Farias, None; **M. Wilbe**, None; **J. Dahlqvist**, None; **D. Leonard**, None; **S. Kozyrev**, None; **G. Pielberg**, None; **M. L. Eloranta**, None; **L. Rönnblom**, None; **K. Lindblad-Toh**, None.

2674

The Effect and Mechanisms of Icaritin on Regulating Foxp3/IL17a Expression in CD4$^+$ T Cells from SLE. Jieyue Liao[1], Yu Liu[2], Ming Zhao[3], hai Jing Wu[4] and Qianjin Lu[1]. [1]Department of Dermatology, Second Xiangya Hospital, Central South University, Changsha, China, [2]Department of Dermatology, Second Xiangya Hospital, Central South University, shangcha, China, [3]Department of Dermatology, Second Xiangya Hospital, Central South University, changsha, China, [4]Department of Dermatology, Second Xiangya Hospital, Central South University, sahngsha, China.

Background/Purpose: Systemic lupus erythematosus (SLE) is a female predominant autoimmune disease characterized by overproduction of autoantibodies. The pathogenesis of SLE is complex. Several studies have revealed that the balance between Treg cells and Th17 cells is destroyed in autoimmune diseases such as SLE.

Icaritin (ICT) is an active ingredient extracted from Chinese herbals Epimedium genus. It has been used as an aphrodisiac, tonic and antirheumatic in China. Our previous studies have found that ICT has a wide range of pharmacological and biological activities, including inhibiting T cell activation and enhancing Treg cells suppressive activities. In this study, we explored the the effect and mechanisms of Icaritin on regulating Foxp3/IL17a expression in systemic lupus erythematosus.

Methods:

1. CD4$^+$ T cells were isolated from SLE patients by positive selection using magnetic beads. CD4$^+$ T cells were treated with 40uM/L ICT for 72h. Foxp3 and IL17a mRNA levels were determined by real-time RT-PCR. Foxp3 protein level was examined by western blotting. Detection of IL17a level was performed by ELISA.
2. Amounts of H3K4me3 AH3K9me3 and H4 acethlation within the foxp3 and IL17a promoter were analyzed by chromatin immunoprecipitation (ChIP) and real-time PCR.
3. The transcription factor regulating both Foxp3 and IL17a expression was determined by microarray. STAT5b-siRNA and control-siRNA were transfected into CD4$^+$ T cells by transient electroporation. Then CD4$^+$ T cells were treated with 40uM/L ICT for 24h. STAT5b, Foxp3 and IL17a mRNA were evaluated by real-time PCR. STAT5b protein levels were examined by western blotting.

Results:

1. Compared to control group, Foxp3 mRNA and protein level were significantly increased in ICT- treated group, while IL17a mRNA and protein level were significantly decreased in ICT-treated group.
2. Compared to control group, H3K4me3 enrichment at the Foxp3 promoter was significantly increased in ICT-treated group; H3K9me3 enrichment at the IL17a promoter was significantly increased in ICT-treated group. There was no significant difference in H4 acethlation level at Foxp3 and IL17a promoter region.
3. Compared to control-siRNA group, STAT5b mRNA level and protein level were significantly decreased. After down-regulating STAT5b expression, Foxp3 and IL17a had no significant changes in ICT-treated group.

Conclusion:

1. ICT can increase the expression level of Foxp3 while decrease IL17a gene expression in CD4$^+$T cells from SLE.
2. ICT can increase H3K4me3 enrichment at the foxp3 promoter and H3K9me3 enrichment at the IL17a promoter in CD4$^+$T cells from SLE.
3. Down-regulating STAT5b in CD4$^+$ T cells can inhibit the effect of ICT on the modulation of Foxp3/ IL17a balance in CD4$^+$T cells from SLE.

Disclosure: J. Liao, None; **Y. Liu**, None; **M. Zhao**, None; **H. J. Wu**, None; **Q. Lu**, None.

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The Selective Loss of SLAMF4$^+$ CD8$^+$ T Cells Contributes to the Decreased Cytotoxic Capacity Observed in Systemic Lupus Erythematosus. Katalin Kis-Toth, Denis Comte, Maria Karampetsou, Lakshmi Kannan and George C. Tsokos. Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA.

Background/Purpose: Signaling lymphocytic activation molecule family member 4 (SLAMF4) engagement by its ligand SLAMF2 can mediate the cytotoxicity of CD8$^+$ T cells and natural killer cells. SLE CD8$^+$ T lymphocytes are reportedly defective in cytotoxicity. The aim of this study was to investigate the expression and function of SLAMF4 on SLE CD8$^+$ T cells.

Methods: The expression of SLAMF4 and its adaptor SAP in healthy and SLE T cells were measured by Q-PCR, flow cytometry and western blot. T cells were treated by immobilized anti-SLAMF4 antibodies and the cytotoxic capacity of the T cells was monitored by the cell surface expression of CD107a, reflecting exocytosis of lytic granules.

Results: We found significant downregulation of SLAMF4 and the adaptor molecule SAP gene and protein expression in SLE T cells compared to normal controls. Characterization of the T cell subsets revealed that SLE patients have significantly less $SLAMF4^+$ $CD8^+$ T cells compared to normal control T cells, switching the $SLAMF4^+/SLAMF4^-$ ratio in the favor of $SLAMF4^-$ $CD8^+$ T cells which have less SAP expression and decreased cytotoxic capacity. SLAMF4 engagement triggers the degranulation of $CD8^+$ T cells and SLE T cells have decreased degranulation capacity compared to normal controls. In the effort to explain the loss of $SLAMF4^+$ $CD8^+$ T cells in SLE we found that these cells are more likely become double negative T cells and/or die by apoptosis.

Conclusion: Based on our results we conclude that the selective loss of $SLAMF4^+$ $CD8^+$ T cells may contribute to the ineffective capacity of fighting against infections in SLE.

Disclosure: K. Kis-Toth, None; **D. Comte**, None; **M. Karampetsou**, None; **L. Kannan**, None; **G. C. Tsokos**, None.

2676

The E3 Ligase Casitas B Lineage Lymphoma b (Cbl-b) Modulates Peripheral Regulatory T Cell Function Via $p27^{kip1}$ in Patients with Systemic Lupus Erythematosus. Diana Gómez-Martín[1], Jorge Romo-Tena[2], Javier Merayo-Chalico[1], Ana Barrera-Vargas[1] and Jorge Alcocer-Varela[1]. [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico.

Background/Purpose: The interplay between effector and regulatory T cells (Tregs) is a key element among peripheral tolerance mechanisms in Systemic Lupus Erythematosus (SLE). Resistance to suppression has been recently acknowledged as part of the defects shown by T cells from SLE patients. The E3 ligase Cbl-b has been shown to modulate T cell unresponsiveness in SLE. However its potential role in the regulation of peripheral Tregs tolerance has not been fully addressed. The aim of this study was to assess the expression of Cbl-b and its relationship to the resistance to suppression phenotype in SLE patients.

Methods: We included 25 patients with SLE (10 in remission and 15 with active untreated disease) according to the classification criteria of the American College of Rheumatology and 25 age and gender-matched healthy controls. PBMCs were isolated by density gradient and effector ($CD4^+CD25^-$) and Tregs ($CD4^+CD25^+CD127^-$) were purified by magnetic selection. The expression of Cbl-b and $p27^{kip1}$ was analyzed by Western blotting. Interaction between Cbl-b and $p27^{kip1}$ was addressed by immunoprecipitation (IP). Proliferative responses were assessed in allogeneic and autologous cocultures by CFSE. Differences were assessed by t Student test. $p<0.05$ was considered as statistically significant. In all cases, an informed consent was obtained, and the ethics committee approved this study.

Results: We found diminished Cbl-b expression in Tregs from SLE patients in comparison to healthy controls (1.3 ± 1.0 vs 2.8 ± 1.8, $p=0.002$), which was associated with resistance to suppression in proliferation assays ($r=0.553$, $p=0.041$). Moreover, this phenomenon was related to deficient expression of the cell cycle regulator $p27^{kip1}$ in Tregs from SLE patients when compared to healthy controls. We also found by IP assays, that $p27^{kip1}$ interacts with Cbl-b in Tregs. We found no significant differences regarding to disease activity.

Conclusion: Our data suggest that the ligase Cbl-b is able to regulate the interplay between effector and Tregs, particularly, the resistance to suppression via ubiquitination of $p27^{kip1}$ in SLE patients. To our knowledge, this is the first study to demonstrate that $p27^{kip1}$ is able to interact with Cbl-b, which might constitute another mechanism by which this ubiquitin ligase is able to modulate the T cell receptor activation threshold.

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2677

Decreased Levels of SRSF1 (Serin/Arginine-Rich Splicing Factor1) Induced Lower Levels of RasGRP1 in T Cells from Patients with Systemic Lupus Erythematosus. Takashi Kurita[1], Shinsuke Yasuda[1], Vaishali Moulton[2], Yuka Shimizu[1], Michihito Kono[1], Hideyuki Koide[1], Kenji Oku[1], Toshiyuki Bohgaki[1], Olga Amengual[1], Tetsuya Horita[1], George C. Tsokos[3] and Tatsuya Atsumi[1]. [1]Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [3]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA.

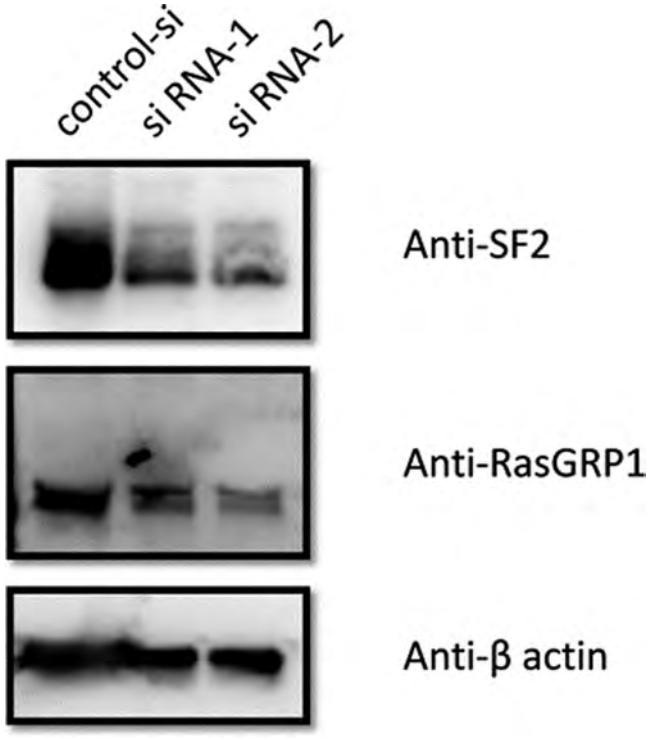
Background/Purpose: Down-regulation of MAP kinase pathway has been recognized in T cells from patients with SLE that results in hypo-methylation of DNA. RasGRP1 is an intracellular signaling protein highly expressed in T cells and activates the Ras signaling pathway downstream of TCR engagement. RasGRP1 deficient mice develop late-onset lymphoproliferative autoimmune syndrome. Previously we reported that defective (alternatively spliced) RasGRP1 transcripts correlate with lower levels of RasGRP1 protein in SLE T cells. Serin/arginine-rich splicing factor1 (SRSF1) is a member of the serine arginine family of splicing proteins that binds pre-mRNA to regulate alternative splicing. For instance, SRSF1 binds to the 3'UTR of CD3 zeta and enables normal splicing of this signaling protein. (Moulton V et.al. J Biol Chem. 2010). The purpose of this study is to determine the relationship between aberrant splicing of RasGRP1 and SRSF1 expression in SLE T cells.

Methods: Forty-five SLE patients and eighteen healthy subjects were included in this study. T cells were collected from peripheral blood of each subject and RNA was isolated. Expression levels of SRSF1, normally spliced RasGRP1 and DNMT1 transcripts were assessed by real time quantitative PCR. Immunoprecipitations (IP) were performed to confirm the direct binding of SRSF1 to RasGRP1 mRNA. SRSF1 specific siRNA was used to supress the expression levels of the RasGRP1 in Jurkat T cell.

Results: Expression levels of SRSF1 transcripts were significantly lower in SLE patients compared with healthy subjects ($p=0.001$, t-test). In patients with SLE, expression levels of SRSF1 correlated with those of normally spliced RasGRP1 and DNMT1 ($r=0.517$, $p=0.023$ [RasGRP1]; $r=0.557$, $p=0.013$ [DNMT1]). IP studies suggested that SRSF1 binds directly to RasGRP1 exon11 RNA. RasGRP1 protein level was decreased in Jurkat T cell when exposed to SRSF1 specific siRNA (Figure).

Conclusion: SRSF1 binds to RasGRP1 mRNA and controls its expression. Low SF2/ASF levels in SLE T cells correlate with the expression levels of RasGRP1 and DNMT1. We propose that SRSF1 regulates the alternative splicing of important genes in SLE T cells including RasGRP1 and CD3 zeta. (2238+250 < 2750 characters, one figure = 250 characters)

Figure



Disclosure: T. Kurita, None; **S. Yasuda**, None; **V. Moulton**, None; **Y. Shimizu**, None; **M. Kono**, None; **H. Koide**, None; **K. Oku**, None; **T. Bohgaki**, None; **O. Amengual**, None; **T. Horita**, None; **G. C. Tsokos**, None; **T. Atsumi**, None.

2678

UC-MSCs Inhibit T Cell Autophagy and Apoptosis in Patients with Systemic Lupus Erythematosus through Mitochondrial Transfer. Jinyun Chen, Xuebing Feng and Lingyun Sun. The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China.

Background/Purpose: This study is aimed to investigate the role of umbilical cord derived mesenchymal stem cells (UC-MSCs) on autophagy and apoptosis in T cells from SLE patients, and to explore the underline mechanisms involved in this process.

Methods: Peripheral blood mononuclear cells (PBMC) were isolated from SLE patients and healthy donors, and cultured under stimulation with anti-CD3/28 antibodies in the presence or absence of autophagy inhibitor 3-MA (5mM for 6h) or activator rapamycin (50nM for 48h). Autophagy levels and apoptotic rates were measured by flow cytometry with the detection of LC3IIB and Annexin V respectively. To determine the effects of MSCs on T cell autophagy and apoptosis, UC-MSCs were cocultured with T cells at the ratio of 1:10 directly or in transwell system. To observe the changes of pathways upstream of autophagy after MSC treatment, an AMPK activator was added to the cocultures. Meanwhile, mitochondria transmembrane potential (¦¤¦Øm), which was closely related to APPK activation, was marked and measured in MSCs and T cells by MitoTracker Deep Red (MDR).

Results: T cells from SLE patients had both elevated autophagy level and apoptotic rate compared with those from normal controls, which were further increased after anti-CD3/CD28 stimulation. Apoptotic rate of T cells significantly correlated with autophagy level ($r=0.570$, $p<0.0001$ for CD4+T; $r=0.508$, $p=0.0001$ for CD8+T). Inhibition of autophagy with 3-MA decreased the apoptotic rate of T cells, whereas activation of autophagy with rapamycin increased the apoptotic rate. UC-MSCs significantly inhibited T cell autophagy (22.5±2.4 vs. 36.4±6.3 for CD4+T; 27.2±1.9 vs. 39.2±5.4 for CD8+T, both $p<0.05$) and T cell apoptosis (22.2±2.6% vs. 49.1±5.7 % for CD4+T; 23.3±2.4% vs. 53.2±2.3 % for CD8+T, both $p<0.05$) after cell-to-cell contact coculturing, yet the effect was diminished in transwell system. When AMPK activator added to the cultures, the ability of UC-MSCs to regulated T cell apoptosis was greatly impaired. As shown in Figure 1, mitochondria in UC-MSCs could be transferred to SLE T cells when directly cocultured. Consequently, the elevation of ¦¤¦Øm in T cells was downregulated after MSC treatment (242.5±8.4 vs. 315.8±5.5, $p=0.003$ for CD4+T; 139.8±23.5 vs. 199±35.7, $p=0.06$ for CD8+T), along with the reduction of AMPK.

Conclusion: Autophagy levels are elevated in T cells from SLE patients, leading to aberrant apoptosis. UC-MSCs may inhibit T cell autophagy and apoptosis through mitochondrial transfer.

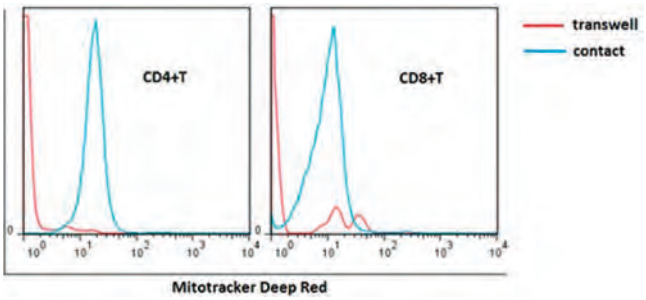


Figure 1 Transfer of MSC mitochondria to lupus T cells. Mitochondria in MSCs were marked by MitoTracker Deep Red. After cell-to-cell contact coculture, MSC-derived mitochondria were detectable in T cells.

Disclosure: J. Chen, None; **X. Feng**, None; **L. Sun**, None.

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Mucosal-Associated Invariant T Cell Deficiency in Systemic Lupus Erythematosus. Jeong-Hwa Kang, Young-Nan Cho, Hye Mi Jin, Hyun-Ju Jung, Sung-Ji Lee, Seung-Jung Kee and Yong-Wook Park. Chonnam National University Medical School and Hospital, Gwangju, South Korea.

Background/Purpose: Mucosal-associated invariant T (MAIT) cells contribute to protection against certain microorganism infections and play an important role in mucosal immunity. However, the role of MAIT cells remains enigmatic in autoimmune diseases. Here, we examined the level and function of MAIT cells in patients with rheumatic diseases.

Methods: MAIT cell, cytokine and programmed death-1 (PD-1) levels were measured by flow cytometry.

Results: Circulating MAIT cell levels were significantly reduced in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) patients. In particular, this MAIT cell deficiency was more prominent in CD8+ and double-negative T cell subsets, and significantly correlated with disease activity, such as SLE disease activity index (SLEDAI) and 28-joint disease activity score (DAS28). Interestingly, MAIT cell frequency was significantly correlated with natural killer T (NKT) cell frequency in SLE patients. Interferon-γ production in MAIT cells was impaired in SLE patients, but it was preserved in RA patients. In SLE patients, MAIT cells were poorly activated by α-galactosylceramide-stimulated NKT cells, thereby showing the dysfunction between MAIT cells and NKT cells. Notably, an elevated expression of PD-1 in MAIT cells and NKT cells was associated with SLE. In RA patients, MAIT cell levels were significantly higher in synovial fluid than in peripheral blood.

Conclusion: Our study primarily demonstrates that MAIT cells are numerically and functionally deficient in SLE. In addition, we report a novel finding that this MAIT cell deficiency is associated with NKT cell deficiency and elevated PD-1 expression. These abnormalities possibly contribute to dysregulated mucosal immunity in SLE.

Disclosure: J. H. Kang, None; **Y. N. Cho**, None; **H. M. Jin**, None; **H. J. Jung**, None; **S. J. Lee**, None; **S. J. Kee**, None; **Y. W. Park**, None.

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DNA Hydroxymethylation Changes in CD4+T Cells from Patients with Systemic Lupus Erythematosus. Ming Zhao, Wei Liao, Bochen Zhu, Ruifang Wu and Qianjin Lu. Department of Dermatology, Second Xiangya Hospital, Central South University, Changsha, China.

Background/Purpose: Recent studies have uncovered 5-hydroxymethylcytosine (5hmC) as the sixth base of the genome, and that the Ten-eleven translocation (TET) family proteins is responsible for the generation of 5hmC from 5mC in mammalian cells. 5hmC may function as another epigenetic mark by altering chromatin structure or contributing to the recruitment or exclusion of other DNA-binding proteins that affect transcription. However, the report about DNA hydroxymethylation in CD4+ T cell or SLE is poor, though DNA hypomethylation has been confirmed to contribute to SLE. In this study, we will investigate DNA hydroxymethylation in genome-wide in lupus CD4+ T cells.

Methods: 36 SLE patients and 36 healthy controls were recruited. CD4+ T cells were isolated by magnetic beads. The age and sex are matched. All patients fulfilled at least 4 of the SLE classification criteria of ACR. The content of 5hmC in genome was detected by dot blot. hMeDIP-NimbleGen Human 3×720K Promoter Plus CpG Island Arrays was completed for identification of genes with different 5hmC modifications between SLE CD4+ T cells and normal controls. mRNA expression levels were measured by real-time RT-PCR. Gene ontology (GO) was analyzed by the Database for Annotation, Visualization and Integrated Discovery (DAVID). Student's t-test for equality of means was used to compare values. P-values < 0.05 were considered as significant.

Results: Compared with normal controls, the content of 5hmC was increased significantly in lupus CD4+ T cells according to the result of dot blot. hMeDIP-chip and data analysis showed 2753 genes with increased 5hmC and 50 genes with decreased 5hmC within their promoter regions in lupus CD4+ T cells. Through the integrated analysis of DNA hydroxymethylation data with DNA methylation data from our previous study, we found 404 genes with increased 5hmC and decreased 5mC in promoter regions in lupus CD4+ T cells, such as UBE2A, IRF1, JUND. In addition, the integrated analysis of DNA hydroxymethylation data with gene expression data from our previous study showed 211 genes with increased promoter hydroxymethylation and expression in lupus CD4+ T cells, such as TNFRSF4, IL15RA and NR2F6, in which some significant GO enrichments, including T cell proliferation and cytokine-mediated signaling pathway, were observed. Furthermore, the results from real-time PCR showed that mRNA expression levels of TET2, TET3, UBE2A and JUND were up-regulated signficantly in CD4+T cells of SLE patients compared with normal controls. The positive correlation was observed between TET2 or TET3 and UBE2A or JUND expression levels.

Conclusion: The increased 5hmC may contribute to DNA demethylation and overexpression of some genes in lupus CD4+ T cells, which suggest DNA hydroxymethylation play an important role in the aberrant epigenetic mechanisms of SLE.

Disclosure: M. Zhao, None; **W. Liao**, None; **B. Zhu**, None; **R. Wu**, None; **Q. Lu**, None.

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Activated SLE-T Cells Enhance the Interferon-Alpha Production By Plasmacytoid Dendritic Cells Stimulated By RNA-IC. Dag Leonard[1], Maija-Leena Eloranta[1], Niklas Hagberg[1], Olof Berggren[1], Karolina Tandre[1], Gunnar Alm[2] and Lars Rönnblom[1]. [1]Department of Medical Sciences, SciLife Lab, Rheumatology, Uppsala University, Uppsala, Sweden, Uppsala, Sweden, [2]Department of Biomedical Sciences and Veterinary Public Health, Swedish University of Agricultural Sciences, Uppsala, Sweden, Uppsala, Sweden.

Background/Purpose: A prominent interferon-α (IFNα) signature is seen in several autoimmune diseases including systemic lupus erythematosus (SLE). Plasmacytoid dendritic cells (pDCs) are the main IFNα producing cells and produce large amounts of IFNα in response to immune complexes containing nucleic acids (ICs). Produced IFNα activates the immune system in a number of ways, including polarization of naïve T helper cells to Th1 cells, expansion and activation of cytotoxic CD8+ T cells and enhanced B-cell differentiation and antibody production. Thus, once pDCs are activated they strongly promote the adaptive immune response. However, much less is known about the effects on pDCs by different adaptive immune cells. Therefore, we asked if T cells can promote the IFNα production by pDCs stimulated by RNA containing ICs.

Methods: Human T cells were activated by anti-CD3/CD28 antibodies. T cells or supernatant from T cell cultures were co-cultured with pDCs stimulated with ICs containing U1 snRNP particles and SLE-IgG (RNA-IC). Cells were analyzed by flow cytometry and cytokines in supernatants were depleted or blocked by monoclonal antibodies. Supernatants were analyzed for IFNα and other cytokines.

Results: Activated T cells or supernatants from activated T cells increased the IFNα production by pDCs stimulated by RNA-IC >20-fold. The frequency of pDCs expressing intracellular IFNα increased when co-cultured with activated CD4+ T cells (5.8%) or CD8+ T cells (6.8%) compared to pDC cultured alone (0.2%). When cytokines were added to the RNA-IC stimulated pDCs at the same concentration as in the supernatant from activated T cells, both GM-CSF and IL-3 demonstrated a strong stimulatory effect on the IFNα response. The combination of both cytokines increased the IFNα production as much as supernatants from activated T cell. The stimulatory effect of supernatants was significantly reduced after depletion of GM-CSF (81%), blocking of GM-CSF (92%) or its receptor subunits CD131 and CD116 (55–81%), (all $p<0.05$). Blocking of IL-3 or its receptor subunit CD123 also reduced the stimulatory effect of the supernatant (31% and 32%, respectively). Supernatant from activated T cells increased the frequency of CD80 and CD86 expressing pDC from 6% to 35% ($p<0.05$) and 10% to 26% ($p<0.01$), respectively. Furthermore, when RNA-IC was added to pDCs cultured with GM-CSF and IL-3, an increased frequency of CD80 and CD86 ($p<0.05$) expressing pDCs were observed. Activated SLE T cells enhanced the IFNα production to the same extent as T cells from healthy controls. Detectable levels of serum-GM-CSF was found in 31% of SLE patients ($n=51$), who had a more active or severe disease.

Conclusion: Activated T cells enhance the IFNα production by RNA-IC stimulated pDCs via GM-CSF and IL-3, which induce maturation of the pDCs. Previous findings of activated T cells in patients with SLE and our observation of a subset of SLE patients expressing increased levels of serum-GM-CSF suggests that T cells contribute to the activated type I interferon system in SLE. Thus, a bidirectional crosstalk between the type I IFN system and the adaptive immune system seems to exist in SLE.

Disclosure: D. Leonard, None; **M. L. Eloranta**, None; **N. Hagberg**, None; **O. Berggren**, None; **K. Tandre**, None; **G. Alm**, None; **L. Rönnblom**, None.

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Serine Arginine-Rich Splicing Factor 1 (SRSF1) Regulates Transcriptional Activation of the T Cell Receptor CD3 Zeta Chain in Human T Cells. Vaishali Moulton[1], Andrew R. Gillooly[1] and George C. Tsokos[2]. [1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [2]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA.

Background/Purpose: T cells from patients with systemic lupus erythematosus (SLE) express reduced amounts of the critical CD3 zeta signaling chain, and are poor producers of the vital cytokine interleukin (IL)-2. Using oligonucleotide-pulldown and mass spectrometry approaches, we previously identified the serine arginine-rich splicing factor 1 (SRSF1) binding to the 3'UTR of CD3 zeta mRNA. We showed that SRSF1 regulates alternative splicing of the CD3 zeta 3'UTR to promote a full length 3'UTR over an unstable splice variant, and thus promotes expression of CD3 zeta chain. SLE T cells exhibit reduced expression of SRSF1, more so patients with worse disease as evidenced by higher SLE disease activity index (SLEDAI). SRSF1 and the serine arginine (SR) proteins have recently been suggested to regulate transcription, in addition to regulating post-transcriptional events in gene expression such as alternative splicing, mRNA stability and translation. CD3 zeta is regulated by the Ets transcription factor family member E-74-like factor (Elf)-1 via two Ets binding sites (EBS) within the CD3 zeta promoter. In this study, we asked whether SRSF1 could activate CD3 zeta transcription and if this involved the transcription factor Elf-1.

Methods: T cells were isolated by negative selection from peripheral blood of healthy individuals, and patients with SLE. Primary T cells were transfected with an SRSF1 or empty expression plasmid by nucleofection. mRNA and protein expression were assessed by real time quantitative pcr and immunoblotting respectively. To measure transcriptional activity, CD3 zeta promoter-luciferase constructs were co-transfected with increasing amounts of SRSF1 into 293T cells or into primary T cells, and luciferase activity measured using the dual luciferase assay system. Reporter chromatin immunoprecipitation (R-ChIP) assays were used to assess recruitment of proteins to the CD3 zeta promoter-luciferase construct. Specific antibodies were used to immunoprecipitate SRSF1, HA (tag present in the SRSF1 plasmid), and Elf-1 proteins. Quantitative real time pcr was performed to assess enrichment, and normalized to values obtained from inputs.

Results: We show that SRSF1 expression directly correlates with CD3 zeta chain expression in T cells from patients with SLE. Overexpression and silencing of SRSF1 in primary T cells results in corresponding increase and decrease in total CD3 zeta mRNA expression. SRSF1 increases activity of the CD3 zeta promoter-luciferase in a dose dependent manner. SRSF1 overexpression leads to increased Elf-1 expression in T cells. Recruitment of SRSF1 and Elf-1 (a known transcriptional activator of CD3 zeta) to the CD3 zeta promoter is observed in T cells that overexpress SRSF1 compared to control transfected cells.

Conclusion: Our results reveal a novel transcriptional mechanism by which SRSF1 regulates CD3 zeta and may represent a molecular mechanism that contributes to the reduced CD3 zeta expression in SLE.

Disclosure: V. Moulton, None; **A. R. Gillooly**, None; **G. C. Tsokos**, None.

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The Discovery of Novel Splicing Variants of Neurogranin and Their Role in the Pathogenesis of Systemic Lupus Erythematosus. Xiaofang Luo, Xuelan He, Chaonan Wu, Juan Ni, Ling li Dong and Shouxin Li. Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

Background/Purpose: Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease with a diverse array of clinical manifestations that is characterized by the production of antibodies to components of the cell nucleus. Neurogranin(Ng), a calmodulin binding protein, was thought to be a neural-specific factor involved in learning and memory, while, its ectopic expression was found in peripheral blood cells, like T lymphocytes, B lymphocytes, etc. And its role in SLE has not been reported yet. Our aim was to compare the expression and structure of Ng in peripheral blood and central nervous system (CNS), and to explore its role in SLE.

Methods: Thirty-four patients with SLE and 22 healthy controls were enrolled. Splicing variants of Ng gene in peripheral blood mononuclear cells(PBMCs) were screened with reverse transcription polymerase chain reaction (RT-PCR) combined with T/A clone, DNA sequencing, and reconfirmed using the primer-specific PCR. Expression of Ng splicing variants mRNA was detected by qRT-PCR. All subjects gave written informed consent prior to enrollment in the study, which was approved by the ethics committee of our hospital.

Results: Three splicing variants of Ng gene were cloned from SLE PBMCs, and two of which, named as Ng-mu1 and Ng-mu2 respectively, were not been reported yet. Compared to wild type of Ng (Ng-WT), Ng-mu1 containing of a 55 bp intron retention insertion with 256–392 base sites deleted, Ng-mu2 with second exon partially deleted and termination codon early emerged. The IQ motifs of Ng-mu1 which is the binding site of calmodulin were impaired (Fig 1). The ratio of Ng-WT to Ng-mu1 in healthy control PBMCs was lower than human brain total RNA. Further analysis showed the up-regulation of Ng-WT mRNA and the elevated ratio of Ng-WT to Ng-mu1 in SLE PBMCs, and the expression of Ng-WT was positively correlated with SLE disease activity index (SLEDAI) (Fig 2).

Conclusion: The novel splicing variants of Ng and their ectopic expression in PBMCs may contribute to the pathogenesis of SLE through mediating Ca2+ signal transduction.

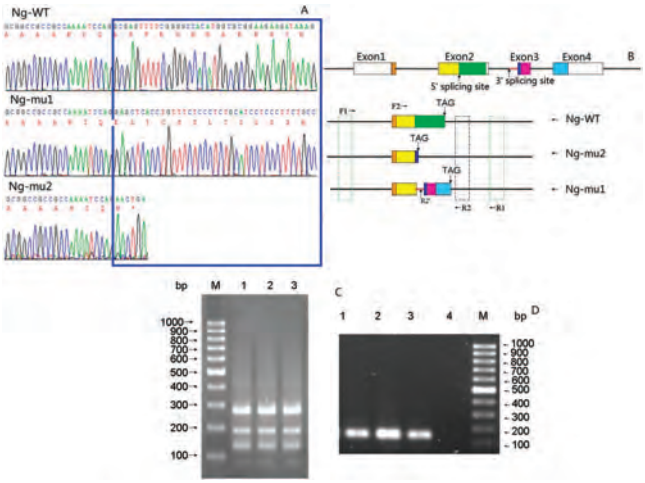

Fig 1. Three splicing variants of Ng gene. A: Comparison of IQ motif of Ng-WT, Ng-mu1 and Ng-mu2. B: Schematic diagram of forming of Ng-WT, Ng-mu1 and Ng-mu2. C: Agarose gels with the analysis of the cDNA of Ng gene fragment with primers F2 and R2 as in fig1B. D: Agarose gels with the analysis of the cDNA of Ng with specific primers F2 and R2' as in fig1B.

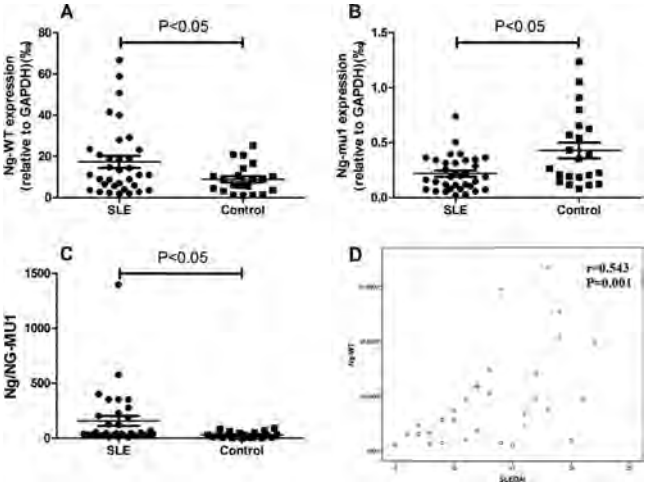

Fig 2. Relative expression of Ng-WT mRNA and Ng-mu1 mRNA in SLE PBMCs. A: Expression of Ng-WT mRNA. B: Expression of Ng-mu1 mRNA. C: The ratio of Ng-WT to Ng-mu1. D: Expression of Ng-WT was positively correlated with SLEDAI.

Disclosure: X. Luo, None; **X. He**, None; **C. Wu**, None; **J. Ni**, None; **L. L. Dong**, None; **S. Li**, None.

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Association of Adam33 Polymorphisms with Systemic Lupus Erythematosus. Seong-Wook Kang[1], Seung-Taek Song[1], Su-Jin Yoo[1], Mi-Kyoung Lim[2], Dong-Hyuk Sheen[2], In-Seol Yoo[1], Jinhyun Kim[1] and Seung-Cheol Shim[1]. [1]Chungnam National University School of Medicine, Daejeon, South Korea, [2]Eulji University Hospital, Daejeon, South Korea.

Background/Purpose: A Disintegrin and Metalloprotease 33 (ADAM33) is a member of a family of genes that encode membrane-anchored proteins with a disintegrin and a metalloprotease domain, and is located on chromosome 20p13. Recently, the polymorphisms in Adam33 have been found to be associated with asthma. Among the rheumatic diseases, systemic lupus erythematosus (SLE) is a prototypic Th2-mediated autoimmune disease like allergic disorders.

To assess whether genetic functional variants of ADAM33 are associated with susceptibility to SLE or development of specific phenotypes in patients with SLE.

Methods: We have identified 48 SNPs, and nine SNPs were selected with regard to the LD pattern. Genotyping for g.10918G>C, g.12433T>C and g.13506C>G in the ADAM33 gene was conducted with PCR RFLP methods, and genotyping for g.-330C>T, g.517 A>G, g.8227 G>A, g.9511 G>T, g.12462 C>T, g.12988 C>A polymorphisms was performed by single-base extension (SBE), using the ABI Prism SNaPshot Multiplex kit (Applied Biosystems). We conducted an association study for ADAM33 polymorphisms in 190 SLE patients, 469 healthy controls, and 390 rheumatoid arthritis (RA) patients as a disease control. Haplotype analyses of related variants were performed as well.

Results: Significant associations of ADAM33 polymorphisms with susceptibility to SLE were found at g.8227 G>A, g.12988 C>A, and g.13506 C>G (*P* value were all below 0.001). Polymorphisms at g.8227 G>A was associated with the ANA titers among SLE patients ($P = 0.012$). In addition, we analysed the haplotype, and found a positive association of susceptibility to SLE with the major haplotype CGCG ($P = 3.5E\text{-}11$). There was no association between ADAM33 polymorphisms and RA as expected.

Conclusion: ADAM33 polymorphisms were strongly associated with susceptibility to SLE and the development of specific clinical manifestations.

Table 1. Genotype and allele analyses of the polymorphisms of *Adam33*gene in SLE patients and healthy controls Position[a]

Position[a]	Genotype/ Allele	Control n (%)	SLE n (%)	Odds ratio[b] (95% CI)	P
g.-330C>T	CC	426 (90.8)	168 (88.4)	1.00	0.347
	CT	43 (9.2)	22 (11.6)	1.30 (0.75–2.24)	
	TT	0 (0.0)	0 (0.0)	–	
	C	895 (95.4)	358 (94.2)	1.00	0.399
	T	43 (4.6)	22 (5.8)	1.28 (0.75–2.17)	
g.517 A>G	AA	165 (38.4)	62 (32.6)	1.00	0.392
	AG	201 (46.7)	97 (51.1)	1.29 (0.88–1.88)	
	GG	64 (14.9)	31 (16.3)	1.29 (0.77–2.17)	
	A	531 (61.7)	221 (58.2)	1.00	0.256
	G	329 (38.3)	159 (41.8)	1.16 (0.91–1.49)	
g.8227 G>A	GG	300 (64.1)	122 (65.2)	1.00	**> 0.0001**
	GA	168 (35.9)	59 (31.6)	0.86 (0.60–1.24)	
	AA	0 (0.0)	6 (3.2)	–	
	G	768 (82.1)	303 (81.0)	1.00	0.692
	A	168 (17.9)	71 (19.0)	1.07 (0.79–1.46)	
g.9511 G>T	GG	390 (84.2)	156 (87.6)	1.00	0.093
	GT	71 (15.4)	19 (10.7)	0.67 (0.39–1.15)	
	TT	2 (0.4)	3 (1.7)	3.75 (0.62–22.66)	
	G	851 (91.9)	331 (93.0)	1.00	0.563
	T	75 (8.1)	25 (7.0)	0.86 (0.54–1.37)	
g.10918 G>C	GG	275 (59.4)	98 (61.3)	1.00	0.271
	GC	172 (37.1)	52 (2.5)	0.85 (0.58–1.25)	
	CC	17 (3.7)	10 (6.2)	1.65 (0.73–3.23)	
	G	722 (77.8)	248 (77.5)	1.00	0.938
	C	206 (22.2)	72 (22.5)	1.02 (0.75–1.38)	
g.12433 T>C	TT	391 (85.2)	178 (92.7)	1.00	**0.025**
	TC	66 (14.4)	13 (6.8)	0.43 (0.23–0.81)	
	CC	2 (0.4)	1 (0.5)	1.10 (0.10–12.19)	
	T	848 (92.4)	369 (96.1)	1.00	**0.013**
	C	70 (7.6)	15 (3.9)	0.49 (0.28–0.87)	
g.12462 C>T	CC	380 (84.5)	177 (93.2)	1.00	**0.009**
	CT	68 (15.1)	12 (6.3)	0.38 (0.20–0.72)	
	TT	2 (0.4)	1 (0.5)	1.07 (0.10–11.92)	
	C	828 (92.0)	366 (96.3)	1.00	**0.005**
	T	72 (8.0)	14 (3.7)	0.44 (0.25–0.79)	
g.12988 C>A	CC	327 (70.2)	170 (92.4)	1.00	**> 0.0001**
	CA	134 (28.8)	14 (7.6)	0.20 (0.11–0.36)	
	AA	5 (1.0)	0 (0.0)	–	
	C	788 (84.5)	354 (96.2)	1.00	**> 0.0001**
	A	144 (15.5)	14 (3.8)	0.22 (0.12–0.38)	
g.13506 C>G	CC	193 (43.3)	91 (49.5)	1.00	**> 0.0001**
	CG	207 (46.4)	48 (26.1)	0.49 (0.33–0.73)	
	GG	46 (10.3)	45 (24.4)	2.08 (1.28–3.36)	
	C	593 (66.5)	230 (62.5)	1.00	0.193
	G	299 (33.5)	138 (37.5)	1.19 (0.92–1.53)	

[a]Calculated from the translation start site.
[b]Logistic regression analyses were used for calculating OR (95% CI; confidence interval)

Table 2. The haplotype frequencies by *Adam33*polymorphisms in both SLE patients and controls

Haplotype	g.-330 C>G	g.8227 G>A	g.12988 C>A	g.13506 C>G	Frequency[a]		Chi-square	*P*[b]
					Control	SLE		
Ht 1	C	G	C	G	0.482	0.272	43.88	**3.5E-11**
Ht 2	C	G	C	C	0.259	0.484	56.53	**5.5E-14**
Ht 3	C	A	A	G	0.088	0.014	21.21	**4.1E-6**
Ht 4	C	A	C	G	0.057	0.043	0.915	0.339
Ht 5	G	G	C	C	0.030	0.022	0.517	0.472
Ht 6	C	G	A	G	0.027	0.003	6.655	**0.010**
others	–	–	–	–	0.057		–	–

Disclosure: S. W. Kang, None; **S. T. Song**, None; **S. J. Yoo**, None; **M. K. Lim**, None; **D. H. Sheen**, None; **I. S. Yoo**, None; **J. Kim**, None; **S. C. Shim**, None.

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Ten-Eleven Translocation 2 Protein Down-Regulates DNA Methylation of Interleukin-17A Promoter and Induces Its Expression in CD4$^+$t Cells of Patients with Systemic Lupus Erythematosus. Duo Li, Qian Tang, Lina Tan, Ming Zhao, Gongping Liang, Yang Yang and Qianjin Lu.Department of Dermatology, Second Xiangya Hospital, Central South University, Changsha, China.

Background/Purpose: Recent evidence indicates that IL-17A plays a key role in the pathogenesis of autoimmune diseases, such as systemic lupus erythematosus (SLE). SLE patients have a higher serum level of IL-17A which correlates with disease activity. However, the exact mechanisms of increased IL-17A level remain uncertain. Ten-eleven translocation (TET) family of dioxygenases catalyze the conversion of 5-methylcytosine into 5-hydroxymethylcytosine, and regulate DNA methylation and gene expression dynamicly. Our previous results showed that both TET1 and TET2, particularly TET2 were increased in SLE CD4$^+$T cells, which suggests TET2 may play a role in the pathogenesis of SLE. In this study, we aim to explore the effect of TET2 on IL-17A expression and the underlying mechanisms in SLE CD4$^+$T cells.

Methods: Fifteen SLE patients and fifteen healthy controls were recruited. All patients fulfilled at least 4 of the SLE classification criteria of the American College of Rheumatology. Naive T cells or CD4$^+$T cells were isolated by Ficoll-Hypaque density gradient centrifugation and magnetic sorting. The IL-17A levels in serum or culture supernatant were measured by ELISA kits. Bisulfite sequencing was done to assess the methylation status of the IL-17A promoter. Th17 cells were induced from Naive T cells of healthy donors in vitro. TET2-siRNA or TET2-expressing plasmid was transfected into CD4$^+$T cells by transient electroporation. The mRNA levels of IL-17A and TET2 were examined by real-time PCR.The protein levels of IL-17A and TET2 were measured by flow cytometric analysis or western blot, respectively. The enrichment of TET2 in the promoter region of IL-17A gene was investigated by chromatin immunoprecipitation and real-time PCR.

Results: Compared to controls, both the serum IL-17A levels and IL-17A mRNA levels in CD4$^+$T cells were elevated in SLE patients ($p<0.05$; $p<0.05$), the levels of Tet2 mRNA and protein were also increased in lupus CD4$^+$T cells ($p<0.05$; $p<0.05$). The IL-17A promoter region in SLE CD4$^+$T cells were found to be demethylated, which negatively correlated with the increased IL-17A mRNA expression ($r=0.725$; $p<0.05$). TET2 enrichment at IL-17A promoter was increased in SLE CD4$^+$T cells ($p<0.05$).Both IL-17A mRNA and protein levels were increased under the Th17 induction treatment on naive CD4$^+$T cells ($p<0.05$; $p<0.05$). TET2 mRNA and protein levels were also increased in a time-dependent manner during the process of Th17 differentiation($p<0.05$; $p<0.05$). IL-17A mRNA and protein levels were decreased in SLE CD4$^+$T cells transfected with TET2-siRNA ($p<0.05$; $p<0.05$), while increased in normal CD4$^+$T cells overexpressed TET2 ($p<0.05$; $p<0.05$). The methylation levels of IL-17A promoter were up-regulated in SLE CD4$^+$T cells transfected with TET2-siRNA ($p<0.05$), while down-regulated in normal CD4$^+$T cells overexpressed TET2 ($p<0.05$). TET2 enrichment at IL-17A promoter was reduced in SLE CD4$^+$T cells transfected with TET2-siRNA ($p<0.05$), while elevated in normal CD4$^+$T cells overexpressed TET2 ($p<0.05$).

Conclusion: Our results indicate that TET2 promotes IL-17A expression through demethylation of its promoter in SLE CD4$^+$T cells.

Disclosure: D. Li, None; **Q. Tang**, None; **L. Tan**, None; **M. Zhao**, None; **G. Liang**, None; **Y. Yang**, None; **Q. Lu**, None.

2686

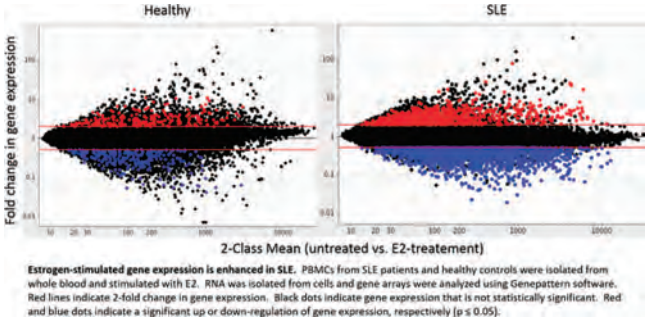
Gene Array Analysis Reveals Unique Estrogen Signature in Peripheral Blood Mononuclear Cells of Patients with Systemic Lupus Erythematosus. Stephanie Amici[1], Nicholas A. Young[2], Lai-Chu Wu[2], Mireia Guerau[1] and Wael N. Jarjour[2]. [1]The Ohio State University, Columbus, OH, [2]The Ohio State University Wexner Medical Center, Columbus, OH.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disorder predominately affecting females in the reproductive age range. Estrogen is present at higher levels in this population compared to pre-pubertal and postmenopausal women and has been shown to influence immune cell function by regulating the expression of multiple genes through activation of estrogen receptors (ER) a and b. Recent work using a chromatin immunoprecipitation with ERa has shown that this list may be much larger than what has been characterized to date. In this study, the effects of E2 were examined by comparing gene array expression in peripheral blood mononuclear cells (PBMCs) from premenopausal women with SLE and in healthy premenopausal individuals.

Methods: SLE patients meeting the revised criteria of the American College of Rheumatology and healthy volunteers were recruited through approved IRB protocols. Whole blood was collected into heparnized tubes and PBMCs were isolated. Cells were cultured with or without 10 nM of 17b-estradiol (E2) for 48 hours. PBMCs were then collected and purified as total RNA and submitted for gene array analysis using HG-U133 Affymetrix® Human Gene Chips. Untreated PBMC arrays served as the internal baseline control for each individual sample and was subtracted from the E2-treated expression values; thus, only the estrogen mediated effect was reported. Data was analyzed using the Multiplot function within the Genepattern software program and with Ingenuity Pathway Analysis Software.

Results: While over 1000 genes were significantly up-regulated over 2-fold in SLE samples when treated with E2, only 236 were identified in corresponding healthy controls. Furthermore, E2 stimulation significantly down-regulated 2530 genes in PBMCs from SLE patients, but only 244 in healthy samples under the same conditions. In concordance, 525 and 1629 genes were found to be uniquely up or down-regulated with E2 treatment in SLE, respectively. Significant E2-mediated regulation of several methyltransferases, including PCMTD1 and RG9MTD3, was identified in this analysis. Using Ingenuity Pathway Analysis Software, our results identified these gene sets to be associated with several pathways, including post-translational modification.

Conclusion: These results establish a clear estrogen effect over many genes to produce an estrogen signature, including several genes known to be associated with post-translational modification, and further reveals enhanced regulation in SLE patients when compared to healthy controls.



Estrogen-stimulated gene expression is enhanced in SLE. PBMCs from SLE patients and healthy controls were isolated from whole blood and stimulated with E2. RNA was isolated from cells and gene arrays were analyzed using Genepattern software. Red lines indicate 2-fold change in gene expression. Black dots indicate gene expression that is not statistically significant. Red and blue dots indicate a significant up or down-regulation of gene expression, respectively ($p \leq 0.05$).

Disclosure: S. Amici, None; **N. A. Young**, None; **L. C. Wu**, None; **M. Guerau**, None; **W. N. Jarjour**, None.

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Estrogen-Mediated STAT1 Activation By Estrogen Receptor a Induces TLR8 Expression: A Novel Pathogenic Mechanism in Systemic Lupus Erythematosus. Nicholas Young[1], Giancarlo Valiente[2], Lai-Chu Wu[2], Michael Bruss[2], Stacy Ardoin[2], Craig Burd[3] and Wael N. Jarjour[2]. [1]Ohio State University, Columbus, OH, [2]The Ohio State University Wexner Medical Center, Columbus, OH, [3]The Ohio State University, Columbus, OH.

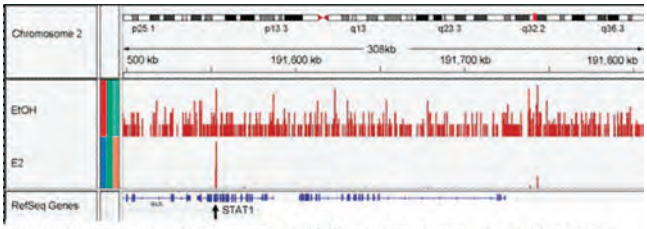
Background/Purpose: Many autoimmune disorders, including Systemic Lupus Erythematosus (SLE) display female gender predominance. Previous studies have demonstrated significant hormonal contributions to SLE pathogenesis, including estrogen, which influences gene expression by binding to

estrogen receptors (ERα and ERβ). E2 has been shown to regulate Signal Transducer and Activator of Transcription (STAT) 1 function and we have previously defined E2-mediated Toll-like receptor 8 (TLR8) expression in SLE. This study examined E2-induced STAT1 expression human peripheral blood mononuclear cells (PBMCs) and characterized the downstream effect on TLR8 expression.

Methods: Putative ERα binding sites in the human genome were identified from ChIP-seq data of MCF-7 cells stimulated with E2 for one hour. SLE patients and healthy controls were recruited for this study through approved IRB protocols. PBMCs were isolated and stimulated with a physiological dose of 17-b estradiol (E2). Radio-labeled probes were used in EMSA analysis to examine DNA-protein complex formation with recombinant ERα and in a human monocytic cell line (THP-1). STAT1 expression was blocked by siRNA with E2 treatment in THP-1 cells.

Results: ChIP-seq data identified an intragenic ERα binding peak within the STAT1 locus and EMSA analysis using this DNA sequence with recombinant ERα protein demonstrated enhanced DNA-protein complex formation. Levels of STAT1 were significantly elevated in SLE patients relative to healthy controls and E2 stimulation of both SLE and healthy PBMCs significantly induced STAT1 expression. In THP-1 cells, blocking STAT1 with siRNA significantly reduced TLR8 induction by E2. Using a *bona fide* STAT1 binding region located 24 kb from the 3'end of the TRL8 genetic locus, EMSA analysis showed enhanced DNA-protein complex formation with E2 stimulation in THP-1 cells.

Conclusion: E2 stimulates the expression of STAT1 in PBMCs, which could contribute to SLE pathogenesis by promoting TLR8 expression. These results identify a novel molecular target to inhibit the TLR8 inflammatory pathway; thus presenting a significant therapeutic opportunity.



Chromatin immunoprecipitation sequencing (ChIP-seq) identification of a putative estrogen receptor α (ERα) binding peak proximal to the STAT1 genetic locus. MCF7 cells were treated with vehicle (EtOH) or estrogen for 45 min and ChIP enriched DNA was sequenced on the Illumina platform. When compared to vehicle, the putative ERα binding peak is indicated with an arrow.

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Comparison of Systemic Lupus Erythematosus and Healthy Anti-Nuclear Antibody Positive African-Americans Reveals Distinct Differences in T Cell and Progenitor Populations. Rufei Lu[1], Samantha Slight-Webb[2], Holden T. Maecker[3], Paul J. Utz[3], Joel M. Guthridge[2] and Judith A. James[2]. [1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Stanford University School of Medicine, Stanford, CA.

Background/Purpose: Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder which arises from both genetic and environmental factors that likely affect phenotypic and functional characteristics of multiple cell lineages. Further, almost all SLE individuals are antinuclear antibody positive (ANA+) although ANA positivity does not obligate autoimmune disease. The differences in cellular physiology between ANA+ healthy individuals and individuals that go on to develop SLE remains a critical goal in the understanding of SLE development. A comprehensive view of immune cell phenotypes in disease is often challenging to ascertain due to limits of assay parameters and proper visualization tools to display cellular hierarchy for high-dimensional data sets. Using mass cytometry, we visualize the expression of 33 cell surface markers through hierarchical clustering using spanning-tree progression analysis of density-normalized events (SPADE) to provide a comprehensive view of the immune system between ANA- and ANA+ healthy controls and ANA+ patients with SLE.

Methods: Blood specimens and information on disease activity were collected from eight African American SLE patients. Patients were matched by age (±5 years), race, and gender to healthy individuals positive for ANA without classifiable lupus (ANA+, n=8) and ANA negative healthy controls (ANA-, n=8). Single-cell analysis of cell surface markers was completed by mass cytometry and cellular heterogeneity was analyzed using SPADE. Significant differences in cell population frequencies were determined using ANOVA and Wilcoxon rank test. Plasma samples isolated from patients at time of draw were analyzed for 51 cytokines using a multiplex immunoassay.

Results: Compared to both ANA+ and ANA- healthy controls, SLE patients had lower frequencies of cytotoxic CD8+ T cells, regulatory CD4+ T cells and early progenitor cell populations ($P<0.05$). Significant differences in progenitor cells nodes were found in CD4 and CD8 negative CD3+ T cells and surface marker null progenitor cells. Concentrations of serum sCD40 ligand were significantly lower in patients with SLE compared with ANA+ and ANA- healthy controls ($p<0.05$). Interestingly, sCD40L production positively correlated with a decrease in regulatory CD4+ T cell populations ($p<0.01$). Further, IL-7 levels were lower in both ANA+ controls and SLE patients compared with ANA- healthy individuals ($p<0.05$).

Conclusion: Our results indicate that early differences in progenitor cell populations may contribute to decreased levels of regulatory CD8+ and CD4+ T cells important for controlling systemic inflammation. Further, the decreased production of IL-7, which is important for the differentiation of hematopoietic stem cells into lymphoid progenitors, in SLE patients and ANA+ patients may contribute to early immune defects in progenitor lymphoid populations leading to loss of tolerance in autoimmunity.

Disclosure: R. Lu, None; **S. Slight-Webb**, None; **H. T. Maecker**, None; **P. J. Utz**, None; **J. M. Guthridge**, None; **J. A. James**, None.

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The CUL4^{CRBN} E3 Ubiquitin Ligase Modulator CC-220 Induces Degradation of the Transcription Factors Ikaros and Aiolos: Immunomodulation in Healthy Volunteers and Relevance to Systemic Lupus Erythematosus. Peter H. Schafer, Ying Ye, Lei Wu, Jolanta Kosek, Zhihong Yang, Liangang Liu, Michael Thomas, Maria Palmisano and Rajesh Chopra. Celgene Corporation, Summit, NJ.

Background/Purpose: CC-220 is an immunomodulatory compound that binds to cereblon (CRBN), part of the CUL4^{CRBN} E3 ubiquitin ligase complex, which has been shown to ubiquitinate the transcription factors Ikaros (IKZF1) and Aiolos (IKZF3). Polymorphisms at the IKZF1 and IKZF3 loci have been associated with risk of systemic lupus erythematosus (SLE). We explored CRBN, IKZF1, and IKZF3 gene expression in peripheral blood mononuclear cells (PBMC) from SLE patients, the effect of CC-220 on Ikaros and Aiolos protein levels and SLE autoantibody production in vitro, and the impact of CC-220 on immunological parameters in a phase 1, double-blinded, placebo-controlled, single ascending dose, healthy volunteer study.

Methods: CRBN, IKZF1, and IKZF3 gene expression was measured by qRT-PCR. Ikaros and Aiolos protein levels were measured by western blot and flow cytometry. Anti-dsDNA and anti-phospholipid autoantibodies were measured from SLE PBMC cultures treated for 7 days with CC-220. In the phase 1 healthy volunteer study, 56 subjects were randomized and enrolled in 7 cohorts, with 6 subjects per cohort receiving a single oral dose of CC-220 (0.03 to 6 mg) and 2 subjects per cohort receiving placebo. CD19+ B cells, CD3+ T cells, and intracellular Aiolos were measured by flow cytometry. IL-2 and IL-1β production were stimulated with anti-CD3 or lipopolysaccharide, respectively, in the TruCulture ex vivo whole blood assay system.

Results: Compared to normal PBMC, SLE PBMC expressed significantly higher levels of CRBN (1.5-fold), IKZF1 (2.1-fold), and IKZF3 (4.1-fold). CC-220 treatment of whole blood significantly reduced Ikaros and Aiolos protein levels in B cells, T cells, and monocytes, but not in granulocytes. In cultures of SLE PBMC, CC-220 inhibited anti-dsDNA and anti-phospholipid autoantibody production with an IC_{50} of ≈10 nM. Following administration of single doses of CC-220 to healthy volunteers, there was a treatment-related decrease in intracellular Aiolos, with minimum mean percent of baseline values of ≈12% to 28% in B cells and ≈0% to 33% in T cells for 0.3 to 6 mg. There was also a treatment-related decrease in absolute CD19+ B cells and CD3+ T cells, with minimum mean percent of baseline values of ≈41% to 67% for B cells and ≈66% to 73% for T cells for 2 to 6 mg. CC-220 administration also resulted in increased IL-2 (maximum mean percent of baseline values ranging from 247% to 1,896% for 0.1 to 6 mg), and a decrease in IL-1β (minimum mean percent of baseline values of ≈11% for 6 mg).

Conclusion: These results demonstrate that CRBN, IKZF1, and IKZF3 mRNA are overexpressed in PBMC from SLE patients. Targeting the CUL4^{CRBN} E3 ubiquitin ligase with CC-220 resulted in a potent reduction in Ikaros and Aiolos protein levels in B cells, T cells, and monocytes, and inhibited autoantibody production. Administration of single doses of CC-220 (0.3 to 6 mg) reduced intracellular Aiolos protein expression in B cells and T cells, reduced absolute B cell and T cell counts in the peripheral blood,

increased T cell-derived IL-2 production, and decreased LPS-induced IL-1β production in whole blood ex vivo. These findings support the further development of CC-220 for the treatment of SLE and other autoimmune diseases.

Disclosure: P. H. Schafer, Celgene, 3; **Y. Ye**, Celgene Corporation, 3; **L. Wu**, Celgene Corporation, 3; **J. Kosek**, Celgene Corporation, 3; **Z. Yang**, Celgene Corporation, 3; **L. Liu**, Celgene Corporation, 3; **M. Thomas**, Celgene Corporation, 3; **M. Palmisano**, Celgene Corporation, 3; **R. Chopra**, Celgene Corporation, 3.

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Autoregulatory Function of IL-10 Producing Pre-Naïve B Cells Is Defective in Systemic Lupus Erythematosus. Ji-Hyun Sim[1], Hang-Rae Kim[1], Soog-Hee Chang[1], In Je Kim[2], Peter E. Lipsky[3] and Jisoo Lee[2]. [1]Seoul National University, Seoul, South Korea, [2]Ewha Womans University School of Medicine, Seoul, South Korea, [3]AMPEL BioSolutions, Charlottesville, VA.

Background/Purpose: Pre-naive B cells represent an intermediate stage in human B cell development with some functions of mature cells, but their involvement in immune responses is unknown. The aim of this study was to determine the functional role of normal pre-naive B cells and possible abnormalities in systemic lupus erythematosus (SLE) that might contribute to disease pathogenesis.

Methods: Pre-naïve, naïve and memory B cells from healthy individuals and SLE patients were stimulated through CD40 and were analyzed for IL-10 production and co-stimulatory molecule expression, and their regulation of T cell activation. Autoreactivity of antibodies produced by pre-naïve B cells was tested by measuring IgM autoantibodies in culture supernatants after differentiation.

Results: CD40-stimulated pre-naive B cells produce large amounts of IL-10, but did not suppress $CD4^+$ T cell cytokine production. Activated pre-naive B cells demonstrated IL-10 mediated ineffective promotion of $CD4^+$ T cell activation, and IL-10 independent impairment of co-stimulatory molecule expression and TNF-a and IL-6 production. IgM antibodies produced by differentiated pre-naive B cells were reactive to ssDNA. SLE pre-naive B cells were defective in producing IL-10, and co-stimulatory molecule expression was enhanced, resulting in promotion of robust $CD4^+$T cell activation.

Conclusion: There is an inherent and IL-10 mediated mechanism that limits the capacity of normal pre-naïve B cells from participating in cellular immune response, but these cells can differentiate into autoantibody secreting plasma cells. In SLE, defects in IL-10 secretion permit pre-naive B cells to promote $CD4^+$ T cell activation, and may, thereby, enhance the development of autoimmunity.

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A Novel $CD123^-CD11c^-$ Dendritic Cell Subset Increased in Relation to Disease Activity in Patients with Systemic Lupus Erythematosus. Satoshi Kubo, Shingo Nakayamada, Naoki Yunoue, Maiko Yoshikawa, Kunihiro Yamaoka and Yoshiya Tanaka. University of Occupational and Environmental Health, Japan, Kitakyushu, Japan.

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by overproduction of autoantibodies by B cells and breaking self-tolerance of T cells and dendritic cells (DCs). However, little is known about the relationship between these immune cells in the etiology of SLE. Here, we found a novel DC subset and investigated the interaction among immune cell subsets in SLE.

Methods: Peripheral blood mononuclear cells were obtained from 44 patients with SLE, 20 with rheumatoid arthritis (RA), and 8 healthy donors (HD). Circulating B cells, T cells and DCs were defined based on comprehensive flow cytometric analysis for human immune system termed 'the Human Immunology Project' by NIH/FOCIS.

Results: The proportion of central memory B cells, effector B cells, and plasmablasts was higher ($p=0.04$, $p=0.001$, respectively), whereas the proportion of IgM memory B cells was lower ($p<0.001$) in SLE, compared to HD and RA. For T cell subsets, the proportion of effector memory T cells was highest in SLE ($p=0.04$). For DCs which were defined as $CD3^-CD14^-CD19^-CD20^-HLA\text{-}DR^{hi}$, the percentage of $CD11c^+$ myeloid DCs significantly decreased in SLE ($p<0.001$), while that of $CD123^+$ plasmacytoid DCs was comparable among SLE, HD and RA ($p=0.48$). Interestingly, DCs that expressed neither CD11c nor CD123 were detected exclusively in SLE but not in the control or RA ($p<0.001$). To assess pathological relevance of this double-negative DC subset in SLE, we calculated the Pearson product-moment correlation coefficient among immune cell subsets and also conducted correlation clustering analysis. Among them, Double-negative DCs characteristically clustered with the central memory B cells and plasmablasts, and was correlated positively with plasmablasts ($p=0.04$) and negatively with myeloid DCs ($p<0.001$) and plasmacytoid DCs ($p=0.04$). Furthermore, the percentage of double-negative DCs was correlated with scores of Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the British Isles Lupus Assessment Group (BILAG) index in patients. In 13 patients with treatment-naive in this cohort, the percentage of double-negative DCs was correlated positively with scores of SLEDAI and BILAG index as well as serum anti-dsDNA antibody levels and negatively with CH50 levels.

Conclusion: These results suggest that a novel $CD123^-CD11c^-$ DC subset characteristically increased in relation to central memory B cells and plasmablasts in patients with treatment-naïve SLE. Furthermore, the frequencies of novel DC subsets were correlated with scores of SLEDAI and BILAG and serum levels of anti-dsDNA antibody, indicating that this DC subset may contribute to disease activity and autoantibody production. Although further studies are required, our findings would shed light on the activation mechanism of autoantibody production through the interaction between a novel DC subset and central memory B cells/plasmablasts in SLE and could be potentially useful in the design of new therapeutic strategies.

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Up-Regulated Expression of CXCR4 on Circulating B Cells in Patients with Systemic Lupus Erythematosus. Hironari Hanaoka, Yuka Okazaki, Akinori Hashiguchi, Hidekata Yasuoka, Tsutomu Takeuchi and Masataka Kuwana. Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: It is increasingly appreciated that circulating B cells are functionally altered and are involved in pathogenic process in patients with systemic lupus erythematosus (SLE). We previously reported that anti-dsDNA antibody-secreting B cells and plasma cells were recruited into circulation in active disease phase in SLE patients. In this study, we evaluated roles of circulating B cells in pathogenic process of SLE by focusing on chemokines.

Methods: We studied peripheral blood samples from 38 patients with SLE and 13 healthy donors. We recorded the disease activity index (SLEDAI) at blood sampling by a retrospective chart review. According to the previous report, active disease was defined as SLEDAI ≥ 5. Peripheral blood mononuclear cells (PBMCs) were obtained by density gradient centrifugation and analyzed by flow cytometry for expression or mean fluorescence intensity of CXCR4, CXCR5 and CCR7 on CD19+ B cells. The concentration of serum CXCL12, which is a ligand for CXCR4, was also measured by enzyme immunoassay. Chemotaxis assay was conducted to test the chemotactic responsiveness of B cells toward the CXCL12. Infiltration of CD19+ B cells with expression of CXCR4 in renal tissue from patients with lupus nephritis ISN/RPS class IV was semi-quantitatively assessed by immunohistochemistry. In this experiment, renal specimens from patients with IgA nephropathy were used as a disease control.

Results: Seventeen active and 21 inactive patients with SLE were enrolled. Flow cytometric analysis revealed that expression of CXCR4 was higher in patients with SLE than normal healthy controls ($p = 0.035$). In patients with SLE, the expression of CXCR4 was higher in those with active disease than in those with inactive ($p = 0.001$). The expression levels of CXCR5 and CXCR7 were not different between patients with SLE and normal healthy controls. In contrast, there was no difference in circulating concentration of CXCL12 between patients with active and inactive disease (2113 vs 2201 pg/ml, $p = 0.263$). Migration ability of B cells toward CXCL12 was enhanced in SLE patients compared with normal healthy controls (33.9 vs 19.4 %, $p = 0.005$). Moreover, SLE patients with active disease represented more prominent chemotaxis towards CXCL12 than did

those with inactive disease (52.9 vs 27.6 %, p = 0.004). Finally, infiltration of CXCR4-expressing CD19+ B cells into the renal interstitium was more prominent in lupus nephritis than IgA nephropathy (p = 0.003).

Conclusion: In SLE patients with active disease, B cells with up-regulated expression of CXCR4 and enhanced chemotaxic responsiveness towards CXCL12 were increased in circulation. These aberrant B cells may be involved in the pathogenic process of SLE by infiltrating into the inflamed organs such as kidneys.

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Hyporesponsiveness to TLR9 in Term of Cytokines Production By B Cells in SLE-Patients. Julia Sieber[1], Capucine Daridon[1], Sarah J. Fleischer[1], Vanessa Fleischer[1], Falk Hiepe[1], Tobias Alexander[1], Guido Heine[2], Gerd Burmester[3], Simon Fillatreau[4] and Thomas Dörner[1]. [1]Charité University Medicine, Dept. Medicine/Rheumatology and Clinical Immunology/ German Rheumatism Research Center (DRFZ), Berlin, Germany, [2]Charité University Medicine, Dept. Dermatology, Venerology and Allergology, Berlin, Germany, [3]Charité University Medicine, Dept. Medicine/ Rheumatology and Clinical Immunology, Berlin, Germany, [4]German Rheumatism Research Center (DRFZ), Berlin, Germany.

Background/Purpose: The role of B cells in immunity has been mainly related to the generation of antibodies and formation of immune complexes. However, B cells can exert additional functions, such as antigen presentation, activation of T cells, formation of lymphoid organs and secretion of cytokines which has not been comprehensively explored in human autoimmunity. In systemic lupus erythematosus (SLE), which is a prototypic autoimmune disease characterized by a breakdown of tolerance toward nuclear antigens, cytokine production induced by toll-like receptor (TLR)9 is of great interest. It remains unclear to what extent B cells from SLE patients are able to produce cytokine in reaction to TLR9 stimulation.

Methods: Peripheral B cells from 18 SLE patients and 13 healthy donors (HD) were purified from peripheral blood mononuclear cells (PBMCs) by Magnetic Activated Cell Sorting and were stimulated with CpG 2006 *in vitro* for 48 hours. Subsequently, cell culture supernatants were tested for 28 cytokines (Bio-Plex). In a subgroup of subjects (6 SLE, 10 HD), activation status (CD38 expression), proliferation (% $Ki67^+$ B cells) and IL-10 producing B-cells were studied by flow cytometry after 48h of TLR9 stimulation of PBMCs. The response of B cells from SLE patients and HD upon TLR9 stimulation was compared regarding proliferation, activation and cytokine production and correlated with disease activity, anti-dsDNA titers and B cells subsets.

Results: SLE patients had a lower frequency of proliferating B cells upon TLR9 stimulation than HD ($p<0.05$). B cells from HD significantly up-regulated CD38, resulting in a 3-fold increase after TLR9 stimulation, while the response of B cells from SLE patients was significantly lower ($p<0.05$). Even though, the profiles of cytokine secretion observed in the supernatants of cultured B cells from SLE patients and HD were largely similar; the production of IL-6, IL-1ra, and VEGF by B cells was significantly reduced in active SLE patients (SLEDAI ≥ 6) compared to HD. In addition, correlation analyses of individual cytokines revealed significant inverse correlations between the SLEDAI and inducible amounts of IL-6, IL-9, IL-17A, IFN-γ, IP-10, MIP-1α, MIP-1β, TNF-α, and VEGF of TLR9-activated SLE B cells and between the serum anti-dsDNA titers as well as levels of IL-1ra, IL-6, IL-9, IL-17A, IFN-γ, MIP-1α, -1β, TNF-α, and VEGF produced by TLR9-activated SLE patients B cells. The secretion of IL-10 was also numerically reduced, although it just failed statistical significance ($p=0.051$). The generation of IL-10 producing B cells was not reduced in cultures of B cells from SLE patients.

Conclusion: The data show that TLR9-induced cytokine production by B cells is less efficient with increasing disease activity and either suggests exhaustion or loss of responsiveness of peripheral blood B cells in SLE.

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B Lymphocyte Stimulator (BLyS) Promotes Dysregulated Monocyte Function in Systemic Lupus Erythematosus(SLE). Eoghan M. McCarthy[1], Joan Ní Gabhann[2], Siobhán Smith[2], Lorraine O' Neill[3], Eamonn S. Molloy[4], Donough Howard[1], Paul G. O'Connell[1], S. Donnelly[5], Grainne M. Kearns[1] and Caroline Jefferies[2]. [1]Beaumont Hospital, Dublin, Ireland, [2]Royal College of Surgeons in Ireland, Dublin, Ireland, [3]Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland, [4]St. Vincent's University Hospital, Dublin 4, Ireland, [5]Mater Misericordiae University Hospital, Dublin 7, Ireland.

Background/Purpose: SLE involves complex interactions between the innate and adaptive immune systems. Monocytes are increasingly recognised to play a key role in the dysregulated immune response seen in SLE whilst more recently BLyS has been demonstrated to play a key role in the pathogenesis of SLE. Despite the fact that monocytes are one of the key producers of BLyS, the effect of BLyS on monocyte function in health and SLE is poorly understood. The aim of this study was to investigate the effect of BLyS on monocyte signalling and activation in healthy controls and to determine its role in the pathogenesis of SLE.

Methods: Signalling pathways following BLyS stimulation were investigated by Western Blotting in monocytes from healthy controls and SLE patients. qPCR was utilised to investigate pro-inflammatory gene expression. Monocyte supernatant and serum levels of proinflammatory cytokines were measured by ELISA. CD 14+ monocyte activation was assessed by Flow Cytometry. Differences between groups were examined using the Mann Whitney.

Results: Following stimulation with BLyS an increase in phosphorylated levels of STAT1, AKT, p42/44 MAPK and p38 MAPK was observed in healthy controls indicating BLyS signals via a number of pathways in monocytes. A corresponding decrease in total IkB levels was observed. Strikingly SLE patients exhibited significantly enhanced responses to BLyS stimulation compared to controls for the phospho-p42/44 MAPK, AKT and STAT pathways.

qPCR analysis revealed significant increases in BLyS, IL-6 and IFN-γ gene expression in SLE patients following stimulation, a finding that was not replicated in controls. Subsequent ELISA confirmed significantly enhanced IL-6 production in the supernatant of SLE patient monocytes compared to controls following BLyS stimulation. Furthermore the SLE patients exhibited significantly higher levels of IL-6 in their serum.

With regard to BLyS receptors, SLE patient monocytes demonstrated a significant upregulation of TACI expression following stimulation. Increased levels of BAFF-R were also seen in both patients and controls following stimulation.

With respect to monocyte activation SLE patients expressed significantly more CD80, CD86 and HLA-DR in the resting state compared to healthy controls. Despite this baseline hyperactivated state, BLyS stimulation resulted in significant increases in CD80, CD86 and MHC Class II in SLE patients. In contrast the healthy control volunteers failed to significantly upregulate any of the surface markers following BLyS stimulation indicating that SLE patients monocytes are more responsive to the effects of BLyS. Interestingly SLE patients with evidence of immunological activity (dsDNA +ve/Low C3/C4) exhibited enhanced HLA-DR and CD86 expression following BLyS stimulation compared to patients without evidence of such activity.

Finally co-culture of BLyS treated monocytes with T lymphocytes resulted in enhanced expression of the T cell activation marker CD69 on both CD8 and CD4+ T Cells, a finding that was significant in SLE patients.

Conclusion: BLyS promotes dysregulation of monocyte activation and signalling pathways in SLE with consequential excess production of pro-inflammatory cytokines and enhanced T cell activation.

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Alterations in B Cell Subsets and BAFF Levels in Autoimmune Rheumatic Diseases Treated with B Cell Depletion Therapy: Rituximab. Pamela M.K. Lutalo[1], David P. D'Cruz[2] and Jo Spencer[3]. [1]King's College London School of Medicine, London, United Kingdom, [2]Guy's and St Thomas' Hospital NHS Foundation Trust, London, United Kingdom, [3]King's College London, School of Medicine, London, United Kingdom.

Background/Purpose: Systemic lupus erythematosus (SLE) and granulomatosis with polyangiitis (GPA) are autoimmune diseases which develop secondary to immune self-tolerance failure. Both diseases are characterised in part by the production of pathogenic autoantibodies. Although they are different clinically, genetically and immunologically, SLE and GPA may be treated successfully with rituximab, an anti-CD20 monoclonal antibody B cell depleting drug.

The repopulation of B cells post-rituximab is of interest as the timing may differ in different autoimmune diseases and may be associated with serum factors, such as B cell activating factor (BAFF), which promotes B cell survival or with characteristics of specific B cell subsets.

Methods: A prospective longitudinal study of 12 patients with SLE and 12 patients with GPA pre-rituximab and at set intervals post-rituximab with matched autoimmune controls was conducted. Demographic, clinical and laboratory data was obtained in all patients with comparison to healthy controls.

Flow cytometry analysis of transitional B cell, naive mature B cell and memory B cell subsets was conducted in experiments staining isolated peripheral blood mononuclear cells with antibodies to CD19, IgD, CD27, CD24 and CD38. The expression of $\alpha4\beta7$ integrin by B cell subsets was analysed. Plasma BAFF levels were measured by ELISA at baseline, 3 months and 6 months post-rituximab. Statistical analysis was done using GraphPad Prism version 5.

Results: B cells were found to repopulate the blood earlier after rituximab in some cases of SLE compared to GPA. There was no statistically significant difference between the pre-rituximab CD19+ B cell percentage of total lymphocytes in SLE and GPA [$p=0.37$], however at 3 months and 6 months post-rituximab SLE patients had a greater population of CD19+ B cells in the peripheral blood compared to GPA patients [$p=0.02$, $p=0.001$, respectively]. Early repopulation was found to be independent of serum factors, but was related to the expression of $\alpha4\beta7$ integrin by subsets of B cells. $\alpha4\beta7$ integrin expression by T1 and T2 transitional B cells, naive mature B cells and memory B cells was significantly lower in SLE patients compared to GPA patients pre-rituximab [$p<0.0001$, $p=0.0003$, $p=0.0008$ and $p=0.0005$, respectively]. A separate analysis revealed significantly lower $\alpha4\beta7$ integrin expression in the early repopulation group, defined as B cell count >5 cells/μl ≤ 3 months post-rituximab, compared to SLE patients who repopulated the peripheral B cell pool later [$p=0.004$, $p=0.004$ and $p=0.003$, $p=0.7$ respectively].

Plasma BAFF levels were elevated in SLE and GPA patients pre-rituximab compared to HC [$p=0.008$, $p=0.001$ respectively] with a rise in BAFF levels detected in SLE 3 months post-rituximab [$p=0.006$] but no difference in SLE 6 months post-rituximab [$p=0.25$]. Plasma BAFF levels did not change significantly in the GPA cohort post-rituximab. Plasma BAFF levels were positively correlated with percentage transitional B cells [$r=0.44$, $p=0.04$].

Conclusion: There may be an association between the early repopulation of the peripheral blood B cell pool, $\alpha4\beta7$ integrin by subsets of B cells and rise in BAFF levels in a cohort of SLE patients.

Disclosure: P. M. K. Lutalo, None; **D. P. D'Cruz**, Investigator, 5; **J. Spencer**, None.

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Relationship Between Soluble sCD23 and B Cell Activation Factor in Patients with Systemic Lupus Erythematosus before and after Rituximab. Laura Heretiu[1], Maria J. Leandro[2], Venkat Reddy[3], David A. Isenberg[2] and Geraldine Cambridge[2]. [1]'Sf. Maria' Clinical Hospital, Bucharest, Romania, [2]Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom, [3]Centre for Rheumatology Research, Division of Medicine, University College London, London, United Kingdom.

Background/Purpose: CD23 is the low-affinity receptor for IgE (FceRII). The soluble form, sCD23 is released into the circulation and in vitro this is consistent with cleavage from naive B cells and expression of CD27 (a marker of memory B cells). BAFF (B cell activation factor) is a survival factor for predominantly naive B cells and is involved in B-cell proliferation, plasma cell differentiation and, with APRIL, also class switching. High levels of sCD23 and of BAFF can be present in sera from patients with Systemic Lupus Erythematosus (SLE) and other autoimmune diseases. The interrelation between sCD23 and BAFF has not been studied in relation to Rituximab (RTX) treatment.

Aim To investigate the relationship between sCD23 and serum BAFF at baseline and after RTX in patients with SLE.

Methods: Twenty eight patients with SLE (diagnosed according to the 1982 ACR revised criteria) were studied before B cell depletion therapy (BCDT) based on RTX and 18 SLE patients after RTX treatment. Twenty eight healthy controls (HC) were also included. Serum sCD23 (normal range given by manufacturers; 1235–5024pg/ml;) and BAFF levels were determined using ELISA. Results were analysed in relation with C3 level, anti-ds DNA titer, IgA, IgG, IgM level and CD19+ B cell count.

Results: Before RTX, sCD23 levels were positively correlated with serum BAFF ($p=0.05$, r^2 0.47). There was no correlation between sCD23 levels with C3, anti ds-DNA, total serum IgA, IgG or IgM. In HC, sCD23 levels did not correlate with serum BAFF ($r^2=0.23$: $p=0.10$). Further, in patients with levels of sCD23 above the normal range (>5024pg/ml; $n=7$) median BAFF levels were significantly higher than those with sCD23 within normal limits ($n=21$) (median BAFF levels: 3.37 and 1.35 ng/ml respectively).

In the 15/28 SLE patients with active disease (BILAG score), there was an even stronger correlation between sCD23 levels and serum BAFF ($r^2=0.56$, $p=0.001$) but no correlation between sCD23 and anti-ds-DNA, IgA, IgG or IgM levels. There was a tendency towards lower C3 values in those patients with sCD23 above the normal range. Median BAFF levels were significantly higher in this group ($n=6$; 5.75 ng/ml) compared to patients with sCD23 within the normal range ($n=9$; median BAFF: 1.25 ng/ml) ($p=0.001$).

After RTX, in 10 patients from whom serial samples were available, sCD23 decreased by a median of 39% at 3 months and 56% at 3–6 months consistent with removal of the majority of circulating B cells but levels did not fall below the normal range.

Conclusion: *In vitro*, the addition of BAFF to B cell cultures stimulated through either Toll-like receptors and the B-cell receptor significantly increases sCD23 cleavage from the B cell surface. Before RTX, serum BAFF levels were related to levels of sCD23 above the normal range in patients with SLE, most markedly in patients with active disease. Serum BAFF is raised in some SLE patients due to changes in availability of BAFF-R, B-cell lymphopenia, BAFF production, or induction by interferons. Germinal center structure is also disturbed in SLE, possibly related to high BAFF levels, which may result in decreased stringency for naïve B cell differentiation into memory phenotype, accompanied by release of sCD23. Levels of sCD23 may be a useful measure of B cell maturation *in vivo*.

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ACR/ARHP Poster Session C
Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics: Determinants of Disease, Classification and Response

Tuesday, November 18, 2014, 8:30 AM–4:00 PM

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Gender Disparities in Lung Transplantation in Patients with Systemic Sclerosis-Related Interstitial Lung Disease and Pulmonary Hypertension. Elizabeth Volkmann[1], Daniel E. Furst[2], Rajeev Saggar[3], Philip J. Clements[4], Bryant Torres[5], Lynne Yoder[1] and Rajan Saggar[1]. [1]University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [2]University of California, Los Angeles, CA, [3]University of Arizona College of Medicine, Phoenix, AZ, [4]University of California, Los Angeles, Department of Medicine, Los Angeles, CA, [5]Rollins School of Public Health, Emory University, Atlanta, GA.

Background/Purpose: Lung transplantation is often the most viable option for patients with severe systemic sclerosis (SSc)-associated interstitial lung disease (ILD) that is unresponsive to pharmacologic intervention. This study investigates gender differences in lung transplantation rates in patients with SSc-ILD with concomitant precapillary pulmonary hypertension (PH).

Methods: SSc patients with right heart catheterization (RHC)-diagnosed precapillary PH (mean pulmonary artery pressure (mPAP) $\geq$25 mmHg, pulmonary capillary wedge pressure (PCWP) $\leq$15 mmHg, and pulmonary vascular resistance (PVR) $\geq$240 dynesxsecond/cm^5) were included. All patients had extensive ILD based on review of high-resolution computed tomography (HRCT) chest imaging and spirometry. Independent t-tests and Fisher's Exact Test were used to compare differences in continuous and

categorical variables, respectively. Logistic regression was used to identify variables associated with lung transplantation.

Results: Of 71 patients with SSc-PH-ILD, 70% were women and 30% were men. Baseline characteristics (ethnicity, SSc type, SSc disease duration), co-morbidities (hypertension, coronary artery disease, diabetes mellitus), and hemodynamic and pulmonary parameters (mPAP, PCWP, PVR, FVC/DL_{CO}Ratio) were similar for men and women with the exception of age (Mean age (years): Women 56 vs. Men 50, p=0.03). There were no gender differences in median follow up time (All patients: 26 months). In all patients who underwent transplantation, the mPAP was 36.6 (SD 7.7) and the mean forced vital capacity (FVC)% predicted was 50.5 (SD 17.4); there were no differences in mPAP and FVC% predicted between patients who underwent transplantation and those who did not (all p-values =0.2). More men (38%) underwent transplantation than women (12%), p=0.016. The median time to transplantation from RHC was longer for women (21 months) than for men (10 months), p=0.09. In the logistic regression model, male gender (OR 2.3; p=0.02) was the only factor significantly associated with transplantation, even after controlling for severity of ILD and PH.

Conclusion: Among all patients with RHC-diagnosed precapillary PH and extensive ILD, there were no significant differences in mPAP and FVC% predicted between patients who underwent lung transplantation and those who did not. Lung transplantation occurred earlier and more frequently in men than in women with SSc-PH-ILD, even after accounting for severity of ILD and PH.

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Survival in Systemic Sclerosis-Pulmonary Arterial Hypertension By Serum Autoantibody Status. Monique Hinchcliff[1], Saira Khanna[1], Jungwha Lee[1], Orit Almagor[2], Rowland W. Chang[1], Virginia D. Steen[3] and Lorinda Chung[4]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Northwestern University, Chicago, IL, [3]Georgetown University Medical Center, Washington, DC, [4]Stanford University School of Medicine, Palo Alto, CA.

Background/Purpose: Previous studies have shown that anticentromere (AC) and isolated nucleolar (NUC) antibodies are the most common autoantibodies in patients with systemic sclerosis (SSc) and World Health Organization (WHO) group 1 pulmonary arterial hypertension (PAH). The goal of the present study was to determine the association between serum autoantibodies and survival in patients with newly diagnosed PAH who are enrolled in the PHAROS (**P**ulmonary **H**ypertension **a**nd **R**ecognition of **O**utcomes in **S**cleroderma) Registry.

Methods: We evaluated patients from the multi-center, prospective, observational PHAROS registry who had definite PAH diagnosed by right-heart catheterization (RHC) (mean pulmonary artery pressure (mPAP) ≥ 25mmHg and pulmonary capillary wedge pressure (PCWP)[2] 15mmHg) within 6 months of enrollment. Medical history, laboratory (including serum autoantibodies), pulmonary function test, echocardiogram, 6-minute walk distance, and RHC data were collected at baseline and biannually or as clinically indicated. Mortality data were collected from participating centers' electronic medical records and/or the Social Security Death Index. Kaplan-Meier estimates for survival were determined for 6 different autoantibody groups. Multivariable Cox regression analyses were performed to assess risk of death by hazard ratios (HR) in each autoantibody group, controlling for age, sex, SSc disease duration (defined as duration since first Raynaud symptom), forced vital capacity (FVC) % predicted, and skin score.

Results: 163 PHAROS subjects met WHO group 1 PAH criteria and had serum autoantibody information available (7 missing autoantibody data, 7 with negative autoantibody test). More than half had either AC or NUC; 61 (36%) subjects had AC, 39 (23%) NUC, 11 (6%) Scl70, 28 (16%) had mixed/other, 9 (5%) RNA polymerase III (RNApol), 8 (5%) U1RNP autoantibodies. The mean SSc disease duration at PAH diagnosis was longest for AC (19.3±13.4y) and shorter for NUC patients (12.2±9.8, compared to AC p=0.02). Thirty-two (21%) subjects died over a mean follow-up time of 2.4±1.7 (median 2.0, range 0–7.2) years. 1-, 3-year survival across all antibody groups was 93% and 77%; 1- and 3-year survival estimates were 94% and 72% for AC; 94% and 79% for NUC; 89% and 63% for Scl70; 100% and 86% for U1RNP; 92% and 79% for mixed/other. No patient with RNApol or negative autoantibodies died over the follow-up period. For all autoantibody groups, unadjusted and adjusted HR revealed no statistically significant association between risk of death and autoantibody positivity.

Conclusion: Anticentromere and NUC autoantibodies are prevalent in SSc patients with PAH. PAH may be a late complication in AC patients, but may occur earlier in SSc patients with other autoantibodies. There does not appear to be a significant association between SSc antibody type and survival in patients with PAH.

Table 1: Clinical Characteristics for World Health Organization Group 1 (PAH) Patients

Mean (SD) or as indicated	Overall N=170 (100%)	AC N=61 (36%)	NUC N=39 (23%)	Scl-70 N=11 (6%)	Mix/other N=28 (16%)	RNApol** N=9 (5%)	U1RNP** N=8 (5%)	Negative** N=7 (4%)	p-value*
Age (y)	60.1 (10.8)	62.9 (9.1)	55.7 (10.5)	57.0 (7.8)	62.2 (11.9)	61.7 (11.8)	49.1 (13.0)	61.1 (6.2)	0.001
Sex, n (% female)	145 (85)	57 (93)	32 (82)	9 (82)	24 (86)	6 (67)	6 (75)	6 (86)	0.34
Race, n (% Caucasian)	137 (81)	51 (84)	26 (67)	8 (73)	24 (86)	7 (78)	7 (88)	7 (100)	0.16
SSc disease duration: (y) From Raynaud onset	15.0 (12.1)	19.3 (13.4)	12.2 (9.8)	8.8 (10.2)	13.8 (12.5)	10.6 (9.2)	11.7 (10.6)	10.5 (4.1)	0.018
From non-Raynaud onset	10.8 (9.3)	13.5 (11.2)	7.6 (6.1)	8.4 (10.2)	9.6 (9.0)	10.5 (8.9)	10.2 (9.5)	11.2 (3.8)	0.13
SSc subtype: n (%) Limited cutaneous	124 (73)	59 (97)	28 (72)	5 (45)	15 (54)	2 (22)	5 (63)	3 (43)	<0.0001
Diffuse cutaneous	41 (24)	2 (3)	11 (28)	6 (55)	10 (36)	7 (78)	1 (13)	4 (57)	
Unclassified	5 (3)	0 (0)	0 (0)	0 (0)	3 (11)	0 (0)	2 (25)	0 (0)	
mRSS	8.4 (8.8)	5.8 (4.8)	10.3 (11.8)	13.9 (10.9)	7.2 (6.6)	18.1 (13.7)	8.1 (7.5)	7.8 (6.4)	0.0008
6MWD (m)	340.2 (125.3)	312.5 (121.0)	358.1 (125.3)	338.1 (159.4)	363 (111.9)	314.4 (104.6)	323.8 (203.9)	439.3 (70.7)	0.38
Echocardiogram SPAP (mmHg)	60.8 (21.2)	61.7 (20.9)	62.1 (22.8)	55.1 (17.0)	58.0 (20.8)	57.4 (13.0)	68 (30.4)	48.3 (11.3)	0.71
Heart catheterization mPAP (mmHg)	37.2 (10.4)	37.8 (10.4)	38.6 (11.4)	33.3 (10.1)	35.2 (9.0)	32.4 (5.5)	42.4 (10.0)	31.4 (7.1)	0.13
PCWP (mmHg)	10.00 (3.30)	9.9 (3.4)	10.3 (3.56)	11.3 (2.6)	9.3 (2.9)	11.3 (3.5)	8.6 (2.3)	10.3 (3.8)	0.41
Pulmonary function tests									
FVC % Predicted	80.1 (22.5)	85.4 (15.0)	75.9 (38.0)	75.1 (10.2)	76.6 (14.5)	69.9 (12.7)	80.8 (24.6)	87.5 (16.2)	0.27
DLCO % Predicted	42.3 (17.0)	44.4 (17.0)	41.6 (18.4)	37.6 (11.4)	41.4 (15.0)	33.5 (11.8)	50.3 (23.9)	53.8 (23.5)	0.27
% Survival Rate									
1-year	93%	94%	94%	89%	92%	100%	100%	100%	0.75***
3-year	77%	72%	79%	63%	79%	100%	86%	100%	

SSc=systemic sclerosis, mRSS=modified Rodnan skin score, 6MWD=6-minute walk distance, SPAP=systolic pulmonary artery pressure, mPAP=mean pulmonary artery pressure, PCWP=pulmonary capillary wedge pressure, FVC=forced vital capacity, DLCO=diffusion capacity for carbon monoxide, NUC=nucleolar, AC=anticentromere, Scl-70=anti-topoisomerase, RNApol=RNA Polymerase III.
* Comparing seven antibody groups.
**Three groups were collapsed into one 'combined group' for Kaplan Meier survival analyses due to similar survival rates.
*** Testing equality of survival curves over five antibody groups

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2699

Optimizing Scleroderma Centers of Excellence: Perspectives from Patients and Scleroderma (SSc) Experts. Veronika K. Jaeger[1], Andrew Aubin[2], Nancy Baldwin[3], Kim Fligelstone[4], Robyn Sims[5], Joep Welling[6], Ryan Burrill[7], Kerri Connolly[7], Tracy Frech[8], Jessica K. Gordon[9], Tanaka Ngcozana[10], Monika Kowalczyk[11], Matthew R. Lammi[12], Ulrich A. Walker[1] and Lesley Ann Saketkoo[13]. [1]Department of Rheumatology, University Hospital Basel, Basel, Switzerland, Basel, Switzerland, [2]Louisiana State University School of Medicine, New Orleans, LA, [3]Scleroderma Foundation-Chicago Support Group, Chicago, IL, [4]Royal Free Hospital, Scleroderma Unit and Scleroderma Society, London, United Kingdom, [5]Scleroderma Australia, Victoria, Australia, [6]The Dutch Patient Organization for Systemic Autoimmune Diseases, Utrecht, Netherlands, [7]Scleroderma Foundation, Boston, MA, [8]University of Utah, Salt Lake City, UT, [9]Hospital for Special Surgery, New York, NY, [10]Royal Free hospital, London, United Kingdom, [11]Tulane University School of Medicine, New Orleans, LA, [12]Louisiana State University Health Sciences Center, Pulmonary and Critical Medicine, New Orleans, LA, [13]Louisiana State University Health Sciences Center, New Orleans, LA.

Background/Purpose: SSc is a complex, diffuse, devastating health condition of vascular injury, inflammation and fibrosis resulting in multiple organ-system derangements with high impact on survival and quality of life. Demonstrated research activity tends to define SSc Centers of Excellence (SCoE) certification. However, SSc complications require coordinated high-level multi-specialty expert care. The Scleroderma Foundation in partnership with Scleroderma Australia and Scleroderma Society UK engaged SSc patients and SSc health providers (HPs) in a multi-tiered process to assess priorities in recognition of SCoEs.

Methods: A mixed methods design ensured comprehensive item collection in addressing 'important qualities and services in a certified SSc Center of Excellence'. A core of 35 patients, SSc HPs from 8 countries initiated the study through an iterative process using nominal group technique with rounds of item collection modification and review until saturation and satisfaction of proposed survey content was achieved and subsequently field-tested with a 5 point scale (critical to low importance). Participation was screened and 'gate-controlled' with online survey access through a unique one-time link. Telephone interview was offered for accessibility. Responses from SSc

patients and HPs were compared by Pearson's X2 or Fisher's exact tests as appropriate.

Results: Initial phases yielded a 54 item survey that was field-tested in 15 SSc patients and HPs. 400 patients and SSc HPs received surveys of which 299 from 19 countries (75% response rate) were completers. Expert care superseded research as a priority of 'critical importance' by HPs and patients respectively at 69% and 48% (p=0.02) and by 94% and 89% (p=0.8) when 'critical to very important' were collapsed. 3 questions provided internal cross-validation of this query. "SCoEs should engage in research" received 57% of patients and 48% of HPs (p=0.37) as being critical. Further, education, rehabilitative services and support networks were consistently highly rated items with topics stratified by ratings (tables 1 & 2). Discrepant areas of importance between patients and HPs are highlighted in tables.

Conclusion: Participation was robust in all project stages emphasizing the perceived global importance of this effort. Though research is of clear importance, quality expert care incorporating rehabilitative and educational provisions is a SCoE operational priority. These findings signal the need to redefine SCoE certification standards and provide a roadmap to SCoE development.

Table 1. Selected survey items. 5-point scale represented under 3 categories: 1. Critical importance, 2. Very important and 3. Moderate importance to not important collapsed. P value = between groups.

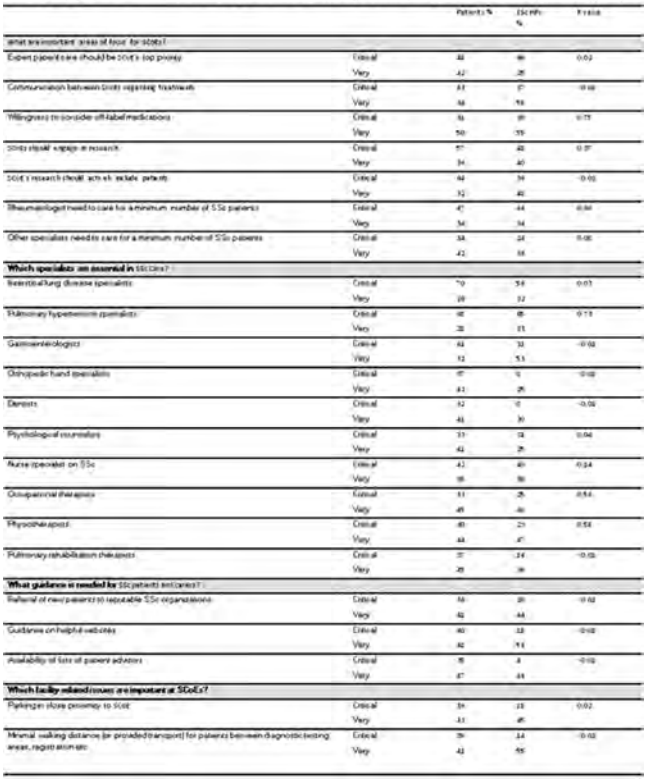

Table 2. Priority of Perceived Educational Needs

	Patients	HPs	Overall
'Red Flag Symptoms' to help patients recognize when to seek medical attention	54%	28%	49%
Overview of available treatments for SSc (with associated risks and benefits)	48%	17%	43%
Stress reduction, cold management, pain management strategies, and exercise	46%	21%	42%
Dietary/nutritional strategies to ease symptoms	38%	15%	34%
Current clinical trials available	36%	28%	35%
Over-the-counter medications or preparations for relieving symptoms	35%	13%	31%
Specialized treatment options (like hand surgeries or stem cell transplants)	34%	11%	30%
'Helping' tools and devices for assistance with daily living	31%	15%	28%

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2700

Clinical Phenotype of Systemic Sclerosis Patients with Anti-RNA Polymerase III Antibodies: A New French Cohort, Systematic Review and Meta-Analysis. Vincent Sobanski[1], Luc Dauchet[2], Guillaume Lefèvre[3], Marc Lambert[4], Sandrine Morell-Dubois[5], Thierno Sy[5], Eric Hachulla[1], Pierre-Yves Hatron[6], Sylvain Dubucquoi[7] and David Launay[8]. [1]Service de médecine interne, Centre National de Référence de la Sclérodermie Systémique, Hôpital Claude Huriez, CHRU Lille, Lille, France, [2]INSERM U744, LILLE, France, [3]EA 2686, Lille, LILLE, France, [4]Internal Medicine University Lille Hospital, Lille, Lille, France, [5]CHRU Lille, LILLE, France, [6]Internal Medicine, Lille, France, [7]Institut d'Immunologie, Centre de Biologie-Pathologie-Génétique, CHRU Lille, Lille, France, [8]EA 2686, Lille, Lille, France.

Background/Purpose: Anti-RNA polymerase III antibodies (anti-RNAP III) are one of the most frequent antinuclear antibodies identified in systemic sclerosis (SSc), with an estimated prevalence of 11% (95% CI: 8–14) (1). Anti-RNAP III has been associated with some clinical characteristics linked with a poor prognosis such as diffuse cutaneous involvement or renal crisis. More recently, anti-RNAP III have been suggested to play a role in immunological response to cancer (2). This study aimed to (i) confirm this clinical phenotype in a new French cohort followed by a systematic review and meta-analysis of the literature; (ii) test whether unknown clinical associations could be highlighted by a meta-analysis.

Methods: One hundred and thirty tree consecutive and unselected SSc patients were tested for anti-RNAP III. Clinical characteristics were retrieved from our database. PubMed and EMBase were searched for all references providing clinical characteristics of anti-RNAP III positive and negative (controls) SSc patients. Meta-analysis was performed using number of anti-RNAP III positive and controls patients, clinical characteristics and organ involvement.

Results: Twelve patients were found to be anti-RNAP III positive in our cohort. Anti-RNAP III was associated with diffuse cutaneous involvement (p=0.02), myositis, renal crisis and cancer (p=0.01). The systematic review retrieved 112 abstracts from 2003 references, which were read in full-text. Forty-five studies were finally included in the meta-analysis. The number of studies providing data for each clinical association was comprised between 4 and 26; between 256 to 1098 anti-RNAP III positive patients and 2088 to 6612 controls were included in analysis. Anti-RNAP III were positively associated with diffuse cutaneous involvement, joint involvement, renal crisis, heart involvement and cancer; and negatively associated with female sex. There was no association between anti-RNAP III and esophageal involvement, pulmonary hypertension, interstitial lung disease, digital ulceration, and myositis (Table 1).

Conclusion: This meta-analysis confirmed that SSc patients with anti-RNAP III are at higher risk of severe skin extension, renal crisis and cancer. Merging results from numerous studies also highlighted less known association such as joint and heart involvement. Patients carrying anti-RNAP III should benefit from an appropriate screening of these potentially severe complications.

(1) Sobanski V et al. Prevalence of Anti–RNA Polymerase III Antibodies in Systemic Sclerosis: New Data From a French Cohort and a Systematic Review and Meta-Analysis. *Arthritis & Rheumatology* 2014;66:407–417.

(2) Joseph CG et al. Association of the autoimmune disease scleroderma with an immunologic response to cancer. *Science* 2014;343:152–157.

Table 1. Results of the meta-analysis

Clinical association	No. of studies	Anti-RNAP III positive patients*	Anti-RNAP III negative patients*	Odds ratio (95% CI)
Female sex	18	506/633	3939/4654	0.46 (0.22–0.96)
Diffuse cutaneous SSc	26	666/956	2037/6612	4.12 (2.72–6.24)
Pulmonary hypertension	16	63/684	557/4769	0.94 (0.68–1.29)

Interstitial lung disease	20	232/714	1842/5056	0.77 (0.56–1.07)
Digital ulceration	11	144/352	1277/3138	0.90 (0.61–1.33)
Joint involvement	12	266/411	1446/3382	1.94 (1.20–3.14)
Myositis	10	65/453	625/3178	1.58 (0.92–2.73)
Esophageal involvement	10	196/256	1427/2088	0.90 (0.61–1.32)
Renal crisis	22	251/1098	256/6234	8.86 (6.48–12.13)
Heart involvement	16	113/583	509/3721	1.79 (1.10–2.91)
Cancer	4	59/361	165/2608	4.12 (2.26–7.51)

* number of events/number of patients

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2701

Relevance of the 6-Minute Walking Test in Assessing the Severity and Outcome of Pulmonary Arterial Hypertension Associated with Systemic Sclerosis, without Extensive Interstitial Lung Disease. Sébastien Sanges[1], David Launay[1], Rennie L. Rhee[2], Olivier Sitbon[3], Eric Hachulla[1], Luc Mouthon[4], Loïc Guillevin[4], Laurence Rottat[3], Pierre Clerson[5], Jean-Francois Cordier[6], Steven M. Kawut[2], Gérald Simonneau[7] and Marc Humbert[3]. [1]Université Lille Nord de France, Faculté de Médecine Henri Warembourg, Lille, Lille, France, [2]University of Pennsylvania, Philadelphia, PA, [3]Université Paris-Sud, Faculté de Médecine, Le Kremlin-Bicêtre, Le Kremlin-Bicêtre, France, [4]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France, [5]Orgametrie, Roubaix, France, [6]Division of Pneumology, Hôpital Louis-Pradel, Hospices Civils de Lyon, Lyon 1, Lyon, France, [7]INSERM U999, Centre Chirurgical Marie-Lannelongue, LabEx LERMIT, Le Plessis-Robinson, Le Plessis-Robinson, France.

Background/Purpose: In pulmonary arterial hypertension (PAH) associated with systemic sclerosis (SSc), no study has yet evaluated the correlation between the 6-minute walking test (6MWT) distance and the right-heart catheterization (RHC) hemodynamic data. This is an important matter, since the 6MWT is used as an outcome measure in SSc-PAH clinical trials, and can be biased by various comorbidities caused by the systemic disease. In this work, we assessed whether there is a correlation between the 6MWT and the RHC parameters at baseline and during follow-up, in SSc-PAH patients without extensive interstitial lung disease (ILD).

Methods: Patients with definite SSc (according to ACR 1987 and/or Leroy criteria), RHC-proven pre-capillary PAH and no extensive ILD on thoracic CT or pulmonary function tests (PFT) were included. Several data were collected regarding the clinical status (age, sex, BMI, NYHA class, SSc subtype), the 6WMT (total distance, heart rate and ΔHR, SaO_2 and ΔSaO_2, Borg score), the RHC (mRAP, mPAP, sPAP, dPAP, cardiac index (CI), PVR, TPR, stroke volume), the PFT and the transthoracic echocardiography, at baseline and during follow-up. The correlation of the 6MWT total distance with each hemodynamic parameter was studied, both at baseline and during follow-up, by linear regression.

Results: The statistical analysis was primarily conducted on a derivation cohort (83 patients from the French National SSc-PAH prospective network), and then confirmed on an independent validation cohort (329 patients from the FDA CTD-PAH register).

At baseline

In the derivation cohort, the univariate analysis showed that the 6MWT total distance was significantly correlated with all the RHC parameters, especially mPAP ($p=0.005$) and CI ($p=0.0001$), and with the NYHA class ($p<0.0001$). In multivariate analysis, the 6WMT total distance was significantly and independently correlated with the CI ($R^2=0.21$, $p=0.0002$) and NYHA classes 3&4 ($R^2=0.12$, $p=0.002$). In this regression model, the hemodynamic status explained only 21% of the distance walked during the test, suggesting the important weight of the confounding comorbidities. Those results were confirmed in the validation cohort, in which a significant, but weaker, correlation with the CI was also found ($R^2=0.08$, $p=0.0001$).

During follow-up

In the univariate analysis conducted on the derivation cohort, the Δ6MWT total distance was non-significantly and weakly correlated with ΔmPAP ($r = -0.20$, $p = 0.15$) and with ΔPVR ($r = -0.17$, $p = 0.22$). Similar results were found on the validation cohort, but reached statistical significance (ΔmPAP : $r = -0.20$, $p = 0.03$; ΔPVR : $r = -0.29$, $p= 0.008$). There were no correlation between Δ6MWT total distance and ΔCI in both cohorts.

Conclusion: To our knowledge, this study is the first to prove a correlation between the baseline 6MWT total distance and the RHC hemodynamic parameters, in SSc-PAH patients without extensive ILD. As the CI explains only 8–21% of the distance, the weight of confounding comorbidities remains important in this test. During follow-up, a weak correlation persists between Δ6MWT and ΔmPAP, but not with ΔCI. These results question the relevance of the 6MWT as an outcome measure for SSc-PAH patients.

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2702

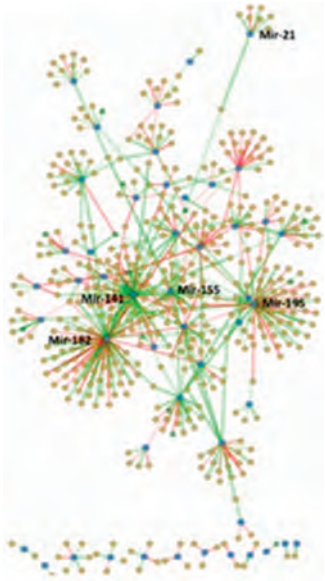
Key Roles for Mir-155 and Mir-21 in Progressive Lung Fibrosis Associated with Systemic Sclerosis (SSc-ILD). Romy Christmann[1], Percival D Sampaio-Barros[2], Claudia Borges[3], Carlos Carvalho[4], Ronaldo A Kairalla[5], Edwin R. Parra[4], Giuseppina Stifano[6], Avi Spira[7], Robert W. Simms[7], Vera L. Capelozzi[4] and Robert Lafyatis[8]. [1]Arthritis Center/Rheumatology, Boston, MA, [2]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [3]CEUMA University, Sao Luis do Maranhao, Brazil, [4]University of Sao Paulo School of Medicine, Sao Paulo, Brazil, [5]University of Sao Paulo, Sao Paulo, Brazil, [6]Boston University Medical Center, Boston, MA, [7]Boston University School of Medicine, Boston, MA, [8]Boston University, Boston, MA.

Background/Purpose: We have already reported that macrophage activation, and up-regulation of TGF-beta- and interferon-regulated genes are involved in progressive SSc-ILD. Micro-rnas (miRNA) are a class of small noncoding RNAs that control gene expression and are eventually involved in most biological processes. Therefore, we analyzed simultaneously mRNA and miRNA in the same prospective cohort of SSc-ILD patients in order to explore their complex network and the miRNA's involvement in progressive lung disease.

Methods: Lung tissue was obtained by open lung biopsy in 22 consecutive SSc-ILD patients (11 diffuse and 10 limited cutaneous SSc patients; 5 controls). High-resolution computerized tomography (HRCT) was performed on baseline and 2–3 years after treatment that was based on lung histologic classification. Microarray analysis (mRNA and miRNA) was performed and the results correlated (Pearson's) with changes in HRCT score (FibMax). MirConnX software was used to explore the gene regulatory network between mRNA and miRNA. The study was approved by the Institutional Review Boards from both universities (Brazil and USA).

Results: As already shown, despite treatment, most of SSc-ILD patients progressed based on delta FibMax ($p< 0.01$). Lung miRNA microarray analysis distinguished SSc-ILD from controls (FDR-corrected, $q<0.25$) with 185 miRNA genes (present in ≥25%) that had significant differential expression. The mRNA microarray analysis also confirmed the altered expression of hundreds of genes in our SSc-ILD cohort and MirConnX simultaneous analysis of mRNA and miRNA showed 4 relevant miRNAs in the center of this multifaceted regulation (graphic): mir-182, mir-141, mir-155, and mir-195 (graphic). Pearson's correlation between miRNAs and the top-50 most upregulated mRNAs in SSc-ILD compared to controls showed that mir-155 was strongly correlated ($r>0.5$) with 32/top-50 genes, such as IL13Ra2 ($r=0.75$) and TOP2A ($r=0.68$), mir-21 was the second most correlated (22/top-50 genes), followed by mir-195 (21/top-50 genes), mir-141 (22/top-50 genes), and mir-182 (19/top-50 genes). Mir-155 and mir-21 were also strongly negatively correlated with several top-downregulated mRNA genes, including IL12A, with r=-0.70. A heatmap of the most informative miRNAs showed mir-155 clustering together with mir-21, a known miRNA involved in idiopathic lung fibrosis; and both mir-155/mir-21 expression were strongly correlated ($r^2=0.6$). Surprisingly, only 4 miRNAs were correlated to the delta FibMax: mir-155 (r=0,65), mir-182 (r=0.49), mir-27a (r=0.49), and mir-21 (r=0.47).

Conclusion: Mir-155 and mir-21 were the center of this complex altered gene expression in the lungs of SSc-ILD. More importantly, these miRNAs were key for the progression of the lung fibrosis based on a CT score. Together, anti-miRNA therapy might be a novel target to prevent progressive SSc-ILD.



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2703

Elevated Serum Levels of Endostatin in Mixed Connective Tissue Disease - Association with Pulmonary Fibrosis and Digital Ulcers. Silje Reiseter[1], Ragnar Gunnarsson[2], Torhild Garen[2], May Brit Lund[3], T. Mogens Aalokken[4], Anna-Maria Hoffmann-Vold[2], Øyvind Molberg[1] and Thor Ueland[5]. [1]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [2]Department of Rheumatology, Oslo University Hospital Rikshospitalet, Oslo, Norway, [3]Department of Respiratory Medicine, Oslo University Hospital Rikshopitalet, Oslo, Norway, [4]Department of Radiology, Oslo University Hospital Rikshospitalet, Oslo, Norway, [5]Research Institute for Internal Medicine, University of Oslo, Oslo, Norway.

Background/Purpose: Mixed Connective Tissue Disease (MCTD) is a chronic, immune-mediated disorder defined by the combined presence of serum anti-RNP antibodies and selected clinical features of Systemic Sclerosis (SSc), Systemic Lupus Erythematosus and Polymyositis. Previous studies have revealed increased values of endostatin and Vascular Endothelial Growth Factor (VEGF) in MCTD (1) and SSc (2), suggesting that an altered angiogenic balance might play a pathogenic role in both diseases. The aim of this study was to examine the serum levels of endostatin and VEGF in MCTD, compared to SSc and Healthy Controls (HC).

Methods: Sera of MCTD patients (N=169) from the cross-sectional nationwide Norwegian MCTD cohort (n=136) and the Norwegian Systemic Tissue Disease and Vasculitides Registry (NOSVAR) (n=33) were assessed. SSc patients (N=310) were included from NOSVAR. Age- and sex-matched healthy blood donors were included as HC (N=100). Clinical parameters examined in MCTD patients were; digital ulcers (N=136), pulmonary fibrosis (N=158) and Forced Vital Capacity (FVC) % of predicted value (N=142). Pulmonary fibrosis was defined according to the Fleischner Society classification system for high-resolution CT Abnormalities. Serum levels of endostatin and VEGF were assessed by ELISA and compared by Means (M) and Standard Deviation (SD) in all groups. Statistical differences were analyzed by the independent sample t-test with significance level $P \leq .05$.

Results: The levels of endostatin were higher in the MCTD group M(SD) 83.0(24) ng/ml compared to HC 65.1(12) ng/ml ($P<.001$), but lower compared to SSc 93.0(37) ng/ml, ($P<.001$). The levels of VEGF in MCTD were not different compared to HC and SSc. However, levels of VEGF were elevated in SSc vs. HC (251.8(185) vs. 186.1(130) pg/ml, $P<.001$). MCTD patients with digital ulcers had higher endostatin levels (90.4(26) ng/ml) than MCTD patients without digital ulcers (79.6(21) ng/ml, $P<.05$). Mean endostatin levels were increased in MCTD patients with pulmonary fibrosis 90.5(33) ng/ml compared to MCTD without pulmonary fibrosis 79.9(20) ng/ml ($P<.05$). Correspondingly, MCTD patients with FVC< 80% had higher endostatin levels 94.5(33) ng/ml than MCTD patients with FVC ≥80% 81.8(21) ng/ml ($P<.05$).

Conclusion: MCTD patients have significantly elevated serum levels of endostatin, but not elevated serum levels of VEGF. Increased circulating levels of endostatin can indicate dysregulation of angiogenesis in MCTD, particularly in patient subgroups with digital ulcers and pulmonary fibrosis.

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2704

Fatigue in Systemic Sclerosis. Didem Uzunaslan[1], Caner Saygin[1], Tufan Torun[2], Mehmet Ozdemir[2] and Gulen Hatemi[3]. [1]University of Istanbul, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, [2]Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey, [3]Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey.

Background/Purpose: Fatigue is a frequently reported disabling symptom for patients with systemic sclerosis (SSc). It has a major impact on overall quality of life including work, family and social life. Our aim is to evaluate the frequency of fatigue among SSc patients compared to healthy and diseased controls and to delineate the factors associated with fatigue.

Methods: We included SSc and rheumatoid arthritis (RA) patients who visited our outpatient clinic for their routine follow-up and healthy controls recruited from hospital staff. Comprehensive physical examination with nailfold capillaroscopy and assessment of Rodnan skin score (RSS) were performed by a single physician. Health assessment questionnaire disability index (HAQ-DI), multidimensional assessment of fatigue (MAF) scale, fatigue severity scale (FSS), fatigue impact scale (FIS), and Beck depression inventory (BDI) were filed by all participants. Having a score of ≥5 in FSS was tabulated as having fatigue for statistical analysis. Multivariate regression analysis was performed to determine the factors associated with high fatigue scores in SSc.

Results: Seventy patients with SSc, 52 RA patients and 100 healthy controls were included in this study. MAF scores were significantly higher among RA patients ($p<0.0001$), followed by SSc patients ($p=0.013$) compared to healthy controls. Similarly, RA patients had higher FSS scores ($p<0.0001$), followed by SSc patients ($p<0.0001$) compared to healthy controls. FIS and BDI scores were highest in SSc patients ($p<0.0001$), followed by patients with RA ($p<0.0001$) and these were also significantly higher than healthy controls. The frequency of fatigue, determined by FSS score, was significantly higher with 77% among RA patients (40 out of 52 scored ≥5 in FSS) ($\chi^2=14.758$, df:2, $p<0.0001$), followed by SSc patients of whom 60% (42 out of 70) reported high FSS scores ($\chi^2=9.402$, df:1, $p=0.002$). SSc patients who experienced fatigue had higher frequency of skin pigmentation (72.9% vs. 45.5%, $p=0.02$), GI involvement (70% vs 35%, $p=0.007$), and higher HAQ (1.26 vs 0.54) and BDI scores (24.7 vs 12.1, $p<0.001$). The components of HAQ-DI which were significantly higher among SSc patients with fatigue were VAS-Raynaud (1.53 vs 0.32), VAS-digital ulcer (1.36 vs 0.32), VAS-GI (1.2 vs 0.39), and VAS-general (1.87 vs 0.76). In multivariate analysis, RSS ($p=0.016$, $\beta=0.365$, 95%CI=0.28–0.45), pulmonary arterial hypertension ($p=0.043$, $\beta=0.258$, 95%CI=0.009–0.504), VAS-digital ulcer ($p=0.036$, $\beta=0.339$, 95%CI=0.009–0.271), and VAS-GI ($p=0.016$, $\beta=0.169$, 95%CI=0.032–0.297) were independent predictors of fatigue.

Conclusion: Around two-thirds of our SSc patients reported higher levels of fatigue. This increase in fatigue correlated with the extent of skin sclerosis, pulmonary hypertension and patient-reported digital ulcer and gastrointestinal involvement severity.

	Systemic sclerosis (n=70)	Rheumatoid arthritis (n=52)	Healthy controls (n=100)	p value
Mean age, yrs	46.95 ± 11.96	54.07 ± 14.84	45.97 ± 10.39	<0.0001
Female/male ratio	65/5 (13)	40/12 (3.3)	96/4 (16)	0.001
Multidimensional assessment of fatigue scale	24.1 ± 14.08	33.9 ± 14.4	16.8 ± 6.06	<0.0001
Fatigue severity scale	4.61 ± 1.87	5.1 ± 1.8	3.97 ± 1.43	<0.0001
Fatigue impact scale	63.6 ± 39.4	61.69 ± 38.16	35.03 ± 28.67	<0.0001
Beck depression inventory	19.55 ± 12.34	17.15 ± 13.89	11.32 ± 9.55	<0.0001

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2705

Reduction of Cerebral and Corpus Callosum Volume in Systemic Sclerosis. a Volumetric Magnetic Resonance Imaging Study. Sergio Dertkigil[1], Tiago N. Amaral[1], Aline T. Lapa[1], Fernando Peres[1], Renan Frittoli[1], Ana Paula del Rio[1], João Francisco Marques-Neto[2] and Simone Appenzeller[3]. [1]State University of Campinas, Campinas, Brazil, [2]University of Campinas, Campinas, Brazil, [3]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: Systemic sclerosis (SSc) is a systemic disease characterized by cutaneous and visceral fibrosis, presence of autoantibodies and vasculopathy. The central nervous system has, however, been rarely studied. Therefore the aim of this study is to determine cerebral and corpus callosum abnormalities in SSc and to determine the possible relationship between atrophy and SSc related features.

Methods: A total of 41 SSc patients (37 female; mean age=50.8; SD=13.2) and sixty-six health age and sex matched volunteers (57 female; mean age=51.4; SD=12.3) were included. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Cognitive evaluation was performed using the Montreal Cognitive Assessment (MoCA). Individual with scores≤26 were considered impaired. Mood disorders were determined through Beck′s Depression and Beck′s Anxiety Inventories. SSc patients were further assessed for clinical and laboratory SSc manifestations, disease activity (Valentini Activity Index), severity activity (Medsger Severity Index). Total dose of corticosteroids and other immunosuppressant medications used since the onset of the disease were calculated. MRI scans were performed in a 3T Phillips® scanner. Sagittal T1 weighted were used for manual volumetric measurements. Volumes ≤ 2 standard deviations from the means of controls were considered abnormal. Non-parametric tests and correlation were used for statistical analysis.

Results: We included 27 (65.9%) limited SSc (lSSc) and 14 (34.1%) diffuse SSc (dSSc) with mean disease duration of 10.4 (SD 6.9) years. Active disease was identified in 12 (29.3%), abnormal neurological exam in 27 (65.8%) and cognitive impairment in 36 (87.8%) SSc patients. Mood disorders were identified in 25 (60.9%) SSC patients. All controls had normal neurological examinations. In SSc, cerebral (mean volume=8975.4 $cm^{3;}$; SD= 165.1) and corpus callosum (mean volume = 96.2 $cm^{3;}$; SD= 8,7) were significantly smaller when compared to cerebral (mean volume = 9514.2 $cm^{3;}$; SD= 176.1; p= 0.03) and corpus callosum (mean volume=114.3 $cm^{3;}$; SD=8,4 ; p=0.02) volumes of controls. When analyzed separately dSSc had significantly smaller cerebral and corpus callosum volumes than lSSc. Depression correlated with cerebral volume in dSSc (r=-0.31, p=0.03) and corpus callosum volume in both dSSc (r=-0.34, p=0.03) and lSSc (r=-0.30, p=0.04). Anxiety correlated with cerebral volume in dSSc (r=-0.30, p=0.02) and corpus callosum volume in both dSSc (r=-0.35, p=0.02) and lSSc (r=-0.26, p=0.04). MoCA scores correlated with corpus callosum volume in dSSc (r=0.57; p=0.002) and lSSc (r=0.29; p=0.04). No correlation was found between disease activity and cerebral volume (r=-0.05; p=0.14) or corpus callusum volume (r=-0.06; p=0.14).

Conclusion: dSSc have significant smaller cerebral and corpus callosum volumes when compared to lSSc and healthy controls. Structural abnormalities are observed in SSc patients with cognitive impairment and mood disorders. Disease activity and organ damage showed no correlation with cerebral volume and corpus callosum volume in this population.

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2706

Ulnar and Radial Stenosis in Systemic Sclerosis. María Eugenia Lara[1], Mariano Rivero[1], Julia Romero[1], Guadalupe Palacios[1], Ignacio Carrillo[2], Claudia L. Giraldo[3], Amalia Schiel[1], Hugo Armando Laborde[1], Marina Khoury[1], Saez Diego[1], Gustavo Citera[2], Oscar L. Rillo[4] and Juan C. Barreira[1]. [1]British Hospital, Buenos Aires, Argentina, [2]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [3]Hospital Gral. de Agudos Dr. E. Tornú, Buenos Aires, Argentina, [4]Hospital General de Agudos Dr. E. Tornú, Buenos Aires, Argentina.

Background/Purpose: Systemic sclerosis (SSc) is a chronic, autoimmune disease. Endothelial damage has been recognized as the initial pathogenic factor. The involvement of the microvasculature is well defined, whereas the prevalence of large vessels disease is still unknown. We aim to describe the frequency of ulnar and radial stenosis in SSc patients and analyze the correlation between arterial stenosis and digital ulcers.

Methods: We included 57 SSc consecutive patients who fulfilled ACR 1980 classification criteria, and 21 healthy controls. SSc patients were classified in two groups: those with present or past digital ulcers and those without them. We collected demographic, clinical and laboratory information. The control group was constituted with voluntaries who attended spontaneously to our hospital to make an image study. All participants have done an arterial ecodoppler of both arms, looking for ulnar and radial stenosis. Statistical analysis: Mann-Whitney, Fisher test $p<0.05$, Odds Ratio (OR), Forward Stepwise, Hosmer and Lemeshow test.

Results: The presence of stenosis in at least one ulnar artery was observed in 18 of 57 patients with SSc (31%) and in none of the 21 controls (p=0.003). Stenosis occurred in at least one radial artery in 9 of 57 SSc patients (15%) and in one of 21 controls (p=0.19). Univariate analysis is shown in Table 1. In the multivariate model, the best predictors of digital ulcers were age at onset of Raynaud phenomenon before 40 years (OR 5.3 95%CI 1.54–18.22, p=0.008) and presence of late SD pattern (OR 4.4 95%CI 1.29–15.63, p=0.018). The area under ROC=0.76 and the Hosmer and Lemeshow test was not significant (p=0.54). Ulcers probability calculated by the model and observed in the sample by combining groups with different predictors is presented in Table 2.

Conclusion: In the present series, ulnar stenosis was observed frequently in SSc patients. However, the size of the sample did not allow adjusting for potential confounders. Stenosis of large vessels in SSc patients was not associated with presence or history of digital ulcers. The best predictors of digital ulcers were age at onset of Raynaud phenomenon before 40 years and the presence of late SD pattern.

Table 1. Clinical features between SSc patients with present or past digital ulcers (A) versus those without them (B).

	A % (n=25)	B % (n=32)	p value	OR (95% CI)
Age > 45 years	20 (5)	34 (11)	**0.02**	4.2 (1.22–14.64)
Male	16 (4)	12 (4)	0.4	
Age at first non–Raynaud symptom years ± SD	37 ± 14	50 ± 9	**0.0018**	
Raynaud phenomenon onset <40 years=“ “ b=” ”>	28 (7)	46 (15)	**0.005**	**5.3 (1.68–17)**
Radial stenosis	12 (3)	18 (6)	0.4	0.59 (0.13–2.64)
Ulnar stenosis	32 (8)	31 (10)	0.9	1 (0.33–3.18)
Esophageal involvement	52 (13)	50 (16)	0.5	
Rodnan skin score >14	28 (7)	34 (11)	0.079	2.8 (0.88–8.87)
HAQ score ± SD	0.69 ± 0.7	0.46 ± 0.56	0.1	
Positive ANA (IFI)	84 (21)	81 (26)	0.5	
Anti-Scl70 positive (ELISA)	20 (5)	18 (6)	0.5	
Late SD pattern	70 (14)	30 (7)	0.013	**4.5 (1.43–14.37)**

Table 2. Chance of ulcers according to the combination of predictor factors.

Predictor factors	Value prediction model	Value observed in the sample
None	18.5%	20.8%
Raynaud phenomenon onset <40 years *or* late SD pattern	50.5–54.7%	47.8%
Raynaud phenomenon onset <40 years *and* late SD pattern	84.4%	90%

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2707

Systemic Sclerosis Related Calcinosis: Patients Provide What Specialists Want to Learn. Angela Christensen[1], Samara Khalique[2], Sophia Cenac[3], Kim Fligelstone[4], Anne Mawdsley[5], Tracy Frech[6], Jessica K. Gordon[7], Murray Baron[8], Evan Busman[9], Virginia D. Steen[10] and Lesley Ann

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Background/Purpose: Calcinosis is a disabling, rarely discussed manifestation of SSc for which the natural history and management is poorly understood. Last year, the Scleroderma Clinical Trials Consortium (SCTC) established a task force to develop a calcinosis specific patient reported measure (PROM). This investigation is the 1st phase of a multi-tiered project.

Methods: Four focus groups and individual interviews in the US and UK were recorded and transcribed verbatim. To capture both pathophysiologic and life impact, 2 questions were asked: 1. Since developing calcinosis how has your life changed over time? 2. How has the calcinosis changed over time? Patients were also asked to frame questions to help a physician learn if calcinosis was better, worse or the same.

Transcripts each underwent an iterative inductive process (no preconceived coding, content drives coding and analysis) by at least 5 independent analysts including at least one research team member with SSc. Concepts were triangulated to identify a comprehensive set of meaningful concepts with occurrence quantified per participant.

Results: Twenty-three patients (22/23 female, 19/23 white, with mean disease duration 14.8 years) were consented and interviewed. Responses spanned broadly to include concepts of self-management strategies and recurrent hypotheses relating calcinosis development to trauma, Raynaud's and cold exposure. We identified discrete concepts which are described in Table 1 along with the proportion of patients declaring personal relevance.

Cold exposure and Raynaud's were a perceived association to calcinosis severity - "when they are cold mine always open back up". Several described a disabling core body phenomenon involving decreased core temperature with a rapid physical decline requiring prolonged recovery potentially lasting hours – "it's like intense - it racks your whole body". Calcinosis tended to present along with or soon after SSc diagnosis and remained throughout disease duration.

A majority of patients engage in strategies to extrude calcinosis with either pressure +/− soaking or at home surgical techniques. "I actually have homemade surgical tools to get these out."

The following anchors were consistently indicated to assess calcinosis severity: pain level, size, frequency, number and functional impairment.

Conclusion: Patient observations and self-management behavior provide opportunities to learn from and to preemptively educate physicians and patients. Patients are eager for self-management guidance. These concepts provide the groundwork for PROM development. However, as suggested by patients, a composite of scales anchored in pain, size, frequency, number and related impairment may reasonably serve as an interim instrument for SSc calcinosis until that time.

Table 1. Concepts from patient focus groups and interviews. The participants not represented by either affirmations or denials did not discuss the designated issue.

Patient Characteristics			
Raynaud's (%)	100%		
Gender (female)	96%		
Race (white)	82%		
Time from Diagnosis (mean)	14.8 years		
Cold exposure decreases core body temperature with sensation of systemic symptoms	26%		
Patient Report	**Yes %**	**No %**	**Quotes**
Location			
Fingers	87%	–	"I got a spreading infection in there and then I had it amputated"
Palms	35%	–	
Wrists	26%	–	
Elbows	48%	–	"I thought it was a bone chip"
Scalp	26%	–	
Face, Lips, Eyelids or Ears	26%	–	"most painful ones are on the eyelid"
Feet (including toes)	26%	–	
Other (back, chest, buttock, armpit)	22%	–	
Calcinosis Physical Properties			
Rock-like/solid calcinosis	52%	–	". . . hard as a rock"
Paste-like	22%	–	"It was quite like toothpaste"
Fluid/Leaking	44%	–	"I've always had peeling and leaking"
Extrudes with warm soaking	23%	–	
Calcinosis always recurrent, once appears in any site	30%	–	
Effects/Sensations of Calcinosis			
Pain	96%	4%	"Paralyzing pain"
Constant	43%	4%	
Tender	91%	4%	
Throbbing	91%	–	
Like skin has been burned (hot coals, flame etc)	26%	–	
Sharp -'like glass shards'	22%		
Tight with pressure	57%	–	"feels like something is trying to get out"
Feel calcinosis growing	48%	–	
Relief with extrusion of calcinosis	78%		
Itchy	9%	–	
Development of Ulcer secondary to calcinosis	52%	–	
Infection related to calcinosis	70%	–	
Functional Effects of Calcinosis			
Interferes with ADLs	87%	–	"I can't even hold her"(referring to baby)
Interferes with hand use	91%	–	
Interferes with walking	22%	–	
Perceived Influencing Factors			
More frequent in cold or not practicing cold prevention	35%	–	"I know winter's coming because these come up.. Become tight"
Calcinosis occur in areas of trauma or pressure	61%	–	"I did notice that if I bang my finger. . .the red will stay and the calcium will develop"
More frequent when Raynaud's worse	43%	–	
Trauma or banging interferes with healing	43%	–	
Response to warmth or prevention against cold	35%	–	"I haven't taken the kind of care I'm used to with my gloves on . . . now it's the first time again with this"
Response to cyclophophamide	13%	–	"not since I was treated with Cytoxan-. . .they totally stopped coming"
Response to vasodilating medications	9%	–	
Response to colchicines	4%	–	"she gave me colchicine, it was doing exactly what she said softening the calcinosis"
Self-Management			
Self-Manages with topical antibiotics	30%	–	
Self-Manages with cushioning (if malet ial doesn't hurt)	70%	–	
SeIf-Managesby extrusion with pressure +/− warm soak	35%	–	"contact with viater helps them to drain"
Self-Manages by extrusion with instruments at home	22%	–	"I just got a large darning needle and pushed it in"
Need Self-Management Protocols for Calcinosis	87%	–	
Patient-suggested anchors to assessment questions			
Pain	91%	–	
Interferes with work / daily activities	74%	–	
Size	61%	–	
Number	43%	–	
Ask about wounds 1st then proceed to ask about calcinosis	13%	–	
Location	9%	–	

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2708

Post-Occlusive Reactive Hyperemia (PORH) Test Mirrors Vascular Changes in Systemic Sclerosis (SSc):a Laser Speckle Contrast (LASCA) Study. Alessandra Della Rossa[1], Anna d'Ascanio[1], Massimo Cagnoni[1], Chiara Stagnaro[1], Alice Parma[1], Marta Mosca[2] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: Vascular involvement is a key feature of Systemic sclerosis (SSc) and involves both the micro and macrovasculature. Vascular changes are central in the disease's pathogenesis and the assessment of vascular involvement has a prognostic value, therefore vascular assessment has a pivotal significance, both for research and clinical purpose.

A non invasive technique to monitor cutaneous vascular function is the response to a physiological challenge using laser speckle contrast imaging. This technique has proven effective and reproducible for the assessment of skin blood flow in SSc patients, either with or without dynamic challenge.

The aim of our study was to evaluate post-occlusive reactive hyperemia test (PORH) in consecutive SSc patients and to test whether PORH is a useful tool to discriminate different disease subsets within SSc population.

Methods:

Patients

Starting from to april 2011 to June 2014, 54 consecutive SSc patients were enrolled (mean age 56 ±15 years, F/M =18). Patients were divided into limited SSc (n=29), Diffuse SSc (n=8) and Very early SSc (VEDOSS) (n=17) according to literature definition.

Laser Speckle Contrast Analysis

Cutaneous blood flow was measured throughout the experiments using a high frame rate LSkI (Pericam PSI system, Perimed, Jarfalla). The occlusive/ischemic test was performed by inflating for 4 minutes a cuff placed on the left arm to 30 mm Hg above the systolic pressure. The recovery time (time needed to recover the basal flux after occlusion in seconds), the peak flux (hyperemic peak reached after occlusion) and the area under the hyperemic curve were recorded.

Statistical analysis

Correlation between clinical data and laser measurements were performed by non parametric tests and contingency tables for cathegorical variables (Stat-View, SAS). In view of the high number of comparisons involved, only p values equal or below 0,01 were considered significant.

Results: A statistical significant difference was detected in the post-ischemic hyperemic peak flow between very early SSc and established SSc (424 vs 137% p = 0,0001). PORH peak flow decreased according to capillaroscopic pattern (early=435%, active=173%, Late=145% P<0,005). Moreover a strong correlation between capillary density and peak flow was unveiled (rho=0,56, p < 0,0001).

Conclusion: These data show a different pattern of vascular involvement in early SSc as compared to established disease that mirror capillaroscopic changes. In this context, functional features of early and established disease seem to be the physiologic counterpart of abnormalities detected by capillaroscopy. POHR test might be a useful aid for further characterization of vascular involvement in SSc.

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2709

Could a Fibroblast-Free Environment Protect the Microcirculation in Systemic Sclerosis? Evidence from Retinal Vascular Imaging Research. Evaggelia K. Aissopou[1], Vasiliki-Kalliopi Bournia[1], Athanase D. Protogerou[1], Stylianos Panopoulos[1], Theodore G. Papaioannou[2], Panayiotis G. Vlachoyiannopoulos[1], Marco Matucci-Cerinic[3] and Petros P. Sfikakis[1]. [1]First Department of Propedeutic Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece, [2]Biomedical Engineering Unit, First University Dept. of Cardiology, Hippokration Hospital, Athens University Medical School, Athens, Greece, [3]University of Florence, Florence, Italy.

Background/Purpose: A primary endothelial cell dysfunction is thought to be involved in systemic sclerosis (SSc)-associated fibroproliferative vasculopathy of the microcirculation and small arterioles, even in sites not affected by fibrosis. Since, (i) the role of resident fibroblasts in the pathologic modifications and vascular wall remodeling is still unclear, and (ii) a fibroblast–free environment, such as the retina, provides a unique opportunity to assess the microcirculation, we systematically evaluated the retinal vessels in patients with SSc.

Methods: Digital retinal images were obtained from both eyes of 93 consecutive patients with fully characterized SSc and 29 healthy controls effectively matched 1:1 for age and gender with 29 selected patients without diabetes, hypertension history, or anti-hypertensive treatment. Internal microvascular calibers (erythrocyte column width in micro-m) by central retinal arteriolar and venular equivalents and arteriolar to venular ratio were measured using validated software.

Results: Arterioral and venular calibers were similar in patients and their matched controls (mean±SEM of 187±2 vs 184±3, p=0.444 and 211±2 vs 216±3, p=0.314, respectively). Both arterioral and venular calibers and their ratio in SSc patients were not associated with disease duration, the extent of skin involvement, the presence of pulmonary fibrosis, digital ulcers or absorptions, amputations, digital capillaroscopic findings, inflammatory indices, or autoantibodies.

Conclusion: The strong evidence that retinal microcirculation is spared in SSc suggests that the fibroproliferative vasculopathy depends on resident fibroblasts and/or other specific cellular or soluble factors not present in the retinal environment.

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2710

The New ACR-EULAR 2013 Systemic Sclerosis Classification Criteria Show Good Performance in a Capillaroscopy Clinic. Patricia E. Carreira[1], M Jesus Garcia de Yebenes[2], Beatriz E. Joven[1], Estibaliz Loza[2] and Loreto Carmona[2]. [1]Rheumatology Department. Hospital Universitario 12 de Octubre, Madrid, Spain, [2]Instituto de Salud Musculoesqueletica, Madrid, Spain.

Background/Purpose: To analyze the validity of the new 2013 ACR-EULAR Systemic Sclerosis (SSc) classification criteria versus SSc clinical diagnosis in patients from a capillaroscopy clinic.

Methods: All patients seen for capillaroscopy between Jan2010 and Oct2013 (before criteria publication) were included. Having as gold standard the SSc diagnosis done by a rheumatologist, the performance (sensitivity, specificity, likelihood ratios) of the ACR-EULAR 2013 criteria, in full, and by items was analyzed. Receiver Operating Characteristic (ROC) curve and area under the curve (AUC) were calculated for global score, and best cut-off for the criteria score obtained

Results: The study included 327 patients (84% women, 48±16 y). Reasons for capillaroscopy were Raynaud (40%), SSc evaluation (27%), other CTD with Raynaud (13%), CTD suspicion (10%), ischaemic lesions (1%) and others (9%). Final diagnosis was SSc in 106 (32%), idiopathic Raynaud (39%), SLE (13%), myopathy (8%), vascular related (6%), primary SS (3%) and others (30%).

The performance of the individual items in the criteria varied, being the best sclerodactily and capillaroscopic changes. The full criteria showed very high validity, with 98% sensitivity, 95% specificity and 18.6 positive likelihood ratio (Table 1). The best cut-offs of the criteria as a score were ≥8, ≥9 or ≥10 (Table 2). Finally, ROC curve showed an elevated discriminatory capacity for diagnosis of SSc, with AUC of 0.993 (Figure 1)

Conclusion: The new ACR-EULAR 2013 SSc classification criteria show high validity and discriminatory capacity for SSc clinical diagnosis done by rheumatologists in a capillaroscopy clinic setting

Table 1. Validity indexes for new ACR-EULAR 2013 SSc classification criteria global score, and by items and subitems

Criteria	Se (%)	Sp (%)	PPV (%)	NPV (%)	LHR+
Proximal and distal scleroderma	66.3	98.6	95.6	86.2	46.2
Sclerodactily	95.9	88.0	79.0	97.9	8.0
Finger edema	68.4	74.2	55.4	83.3	2.6
Any finger involvement	66.3	98.6	95.6	86.2	46.2
Digital Ulcers	43.9	92.3	72.9	77.8	5.7
Pitting Scars	42.9	98.1	91.3	78.5	22.4
Any ischaemiclesion	46.9	91.9	73.0	78.7	5.8
Telangiectasia	51.0	95.7	84.7	80.6	11.8
Capillaroscopic changes	81.6	90.4	80.0	91.3	8.5
PAH (confimed by RHC)	6.1	97.1	50.0	68.8	2.1
Lung fibrosis	25.5	95.2	71.4	73.2	5.3

PAH and/or Lung fibrosis	29.6	92.3	64.4	73.7	3.9
Raynaud	99.0	33.5	41.1	98.6	1.5
ACA	39.8	97.6	88.6	77.6	16.6
Scl70	24.5	96.2	75.0	73.1	6.4
Any antibody	66.3	93.8	83.3	85.6	10.7
Global (Fulfill/not fulfill)	98.0	94.7	89.7	99.0	18.6

Se=sensitivity; Sp=specificity; PPV=predictive positive value; NPV=predictive negative value; LHR: likelihood ratio PAH: pulmonary arterial hypertension; RHC: right heart catheterization

Figure 1: Receiver Operating Characteristic (ROC) Curve for global score of the new ACR-EULAR 2013 SSc classification criteria

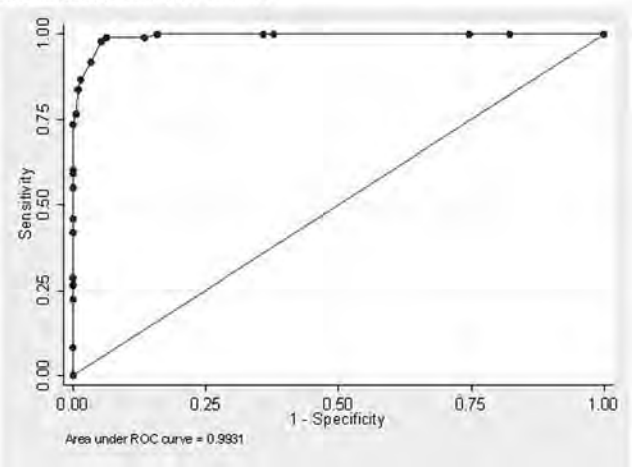

Table 2. Validity indexes for all cutpoints for the global score of the new ACR-EULAR 2013 SSc classification criteria

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR−
(>= 0)	100.00%	0.00%	31.92%	1.0000	
(>= 2)	100.00%	17.70%	43.97%	1.2151	0.0000
(>= 3)	100.00%	25.36%	49.19%	1.3397	0.0000
(>= 4)	100.00%	62.20%	74.27%	2.6456	0.0000
(>= 5)	100.00%	64.11%	75.57%	2.7867	0.0000
(>= 6)	100.00%	84.21%	89.25%	6.3333	0.0000
(>= 7)	98.98%	86.60%	90.55%	7.3881	0.0118
(>= 8)	98.98%	93.78%	95.44%	15.9129	0.0109
(>= 9)	97.96%	94.74%	95.77%	18.6123	0.0215
(>= 10)	91.84%	96.65%	95.11%	27.4198	0.0845
(>= 11)	86.73%	98.56%	94.79%	60.4254	0.1346
(>= 12)	83.67%	99.04%	94.14%	87.4386	0.1648
(>= 13)	76.53%	99.52%	92.18%	159.9487	0.2358
(>= 14)	73.47%	100.00%	91.53%		0.2653
(>= 15)	60.20%	100.00%	87.30%		0.3980
(>= 16)	59.18%	100.00%	86.97%		0.4082
(>= 17)	55.10%	100.00%	85.67%		0.4490
(>= 18)	45.92%	100.00%	82.74%		0.5408
(>= 19)	41.84%	100.00%	81.43%		0.5816
(>= 20)	28.57%	100.00%	77.20%		0.7143
(>= 21)	26.53%	100.00%	76.55%		0.7347
(>= 22)	22.45%	100.00%	75.24%		0.7755
(>= 24)	8.16%	100.00%	70.68%		0.9184
(>= 24)	0.00%	100.00%	68.08%		1.0000

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2711

Joint and Tendon Involvement Predict Severe Disease Progression in Systemic Sclerosis: A Prospective Study. Jerome Avouac[1], Ulrich Walker[2], Eric Hachulla[3], Gabriela Riemekasten[4], Giovanna Cuomo[5], Patricia E. Carreira[6], Paola Caramaschi[7], Lidiya P. Ananieva[8], Marco Matucci-Cerinic[9], Laszlo Czirjak[10], Christopher P. Denton[11], Ulf Muller-Ladner[12] and Yannick Allanore[13]. [1]Paris Descartes University and INSERM U1016, Rheumatology A department, Cochin Hospital, Paris, France, [2]Department of Rheumatology, Basel University, basel, Switzerland, [3]National Scleroderma Centre, Lille CEDEX, France, [4]Charité – University Hospital, Berlin, Germany, [5]Second University of Naples, Naples, Italy, [6]Rheumatology Department. Hospital Universitario 12 de Octubre, Madrid, Spain, [7]Rheumatology Unit, Azienda Ospedaliera Universitaria Integrata, Verona, Italy, [8]Research Institute of Rheumatology RAMS, Moscow, Russia, [9]University of Florence, Florence, Italy, [10]University of Pécs, Pécs, Hungary, [11]Centre for Rheumatology, Royal Free and University College Medical School, London, United Kingdom, [12]Univ Giessen/Kerckhoff-Clinic, Bad Nauheim, Germany, [13]Paris Descartes University, Rheumatology A Department and INSERM U1016, Cochin Hospital, Paris, France.

Background/Purpose: Joint involvement is frequent and strongly contributes to impaired quality of life in systemic sclerosis (SSc). In a previous cross-sectional study, synovitis and tendon friction rubs (TFRs) were associated with systemic inflammation and disease activity. Therefore, the aim of the present study was to determine whether joint synovitis and TFRs can predict the progression of SSc over time.

Methods: We included patients from the EUSTAR database (MEDS online) with early disease duration (first non Raynaud's symptom equal or less than 3 years) and with a follow-up of at least two years. We extracted data regarding the presence or not of synovitis and TFRs and data related to disease progression. Skin progression was defined by a ≥30% worsening of the modified Rodnan skin score (mRSS). Lung progression was defined by the new onset of pulmonary fibrosis on high resolution CT scan, or the deterioration of lung volume (≥10% of forced vital capacity, FVC). Cardiovascular worsening was defined for skin by new ischemic digital ulcers (DU), for lung by pre-capillary pulmonary arterial hypertension (PAH) on right heart catheterization, and for heart by the reduction of the left ventricular ejection fraction below 50% on echocardiography. Renal progression was defined by the occurrence of scleroderma renal crisis. Overall disease progression was defined according to the occurrence of at least one organ progression.

Results: From the 9165 patients included in the database, 1301 patients (1079 females) met our inclusion criteria (mean ± SD age of 55±15 years, mean ± SD follow-up: 4.5±2.2 years). During the follow-up period, 579 patients (45%) experienced skin and/or lung and/or cardiovascular progression with a mean time to development of 3.2±1.9 years.

Joint synovitis (Hazard Ratio, HR: 1.26, 95% confidence interval, CI, 1.01–1.59) and TFRs (HR: 1.32, 95%CI 1.03–1.70) were both independently predictive of overall disease progression, as were also the diffuse cutaneous subset (HR: 1.30, 95%CI 1.05–1.61) and positive antitopoisomerase-I antibodies (HR: 1.25, 95%CI 1.02–1.53).

The mean change of mRSS over the follow-up period was 9.4±4.11, and 99/123 patients (80%) had a progression of at least 5 points. Joint synovitis (HR: 1.63, 95%CI 1.05–2.55) and TFRs (HR: 1.67, 95%CI 1.01–2.75) were independently predictive of skin progression.

Joint synovitis was predictive of the occurrence of new digital ulcer(s) (HR: 1.45, 95%CI 1.08–1.96) and decreased left ventricular ejection fraction (HR: 2.20, 95%CI 1.06–4.57); TFRs were confirmed to be an independent predictor of scleroderma renal crisis (HR: 2.33, 95% CI 1.03–6.19).

Conclusion: This first report of the prospective follow-up of EUSTAR patients identified for the first time the merit of baseline synovitis and extended previous data for tendon friction rubs in early SSc patients. These results obtained through the largest worldwide database support the use of these easily detected clinical findings for the risk stratification of SSc patients. These parameters might be used in the future to select high-risk patients, guide therapies and might be regarded as potential surrogate markers for severity.

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2712

Nailfold Videocapillaroscopy in Healthy Children and Adolescents: Description of Patterns of Normality. Daniela Piotto[1], Juliana Sekiyama[2], Cristiane Kayser[3], Mariana Yamada[4], Claudio A. Len[5] and Maria Teresa Terreri[6]. [1]Assistant Doctor, Universidade Federal de São Paulo/UNIFESP, São Paulo, Brazil, [2]Universidade Estadual de Campinas, Campinas, Brazil, [3]Universidade Federal de São Paulo, São Paulo, Brazil, [4]Pediatric Resident, São Paulo, Brazil, [5]Universidade Federal de São Paulo/Escola Paulista de Medicina, São Paulo, Brazil, [6]Universidade Federal de São Paulo/UNIFESP, São Paulo, Brazil.

Background/Purpose: Video capillaroscopy (VCP) allows for the evaluation of capillary dimensions and to quantify the degree of microangiopathic alterations in autoimmune diseases. However, studies in healthy subjects and specially in children and adolescents are limited. To describe the normal pattern of capillaries by VCP in healthy children and adolescents, and to evaluate the inter and intraobserver concordance in capillary measurements.

Methods: Cross-sectional study of 100 healthy participants aged 5 to18 years by VCP. The capillary dimensions (capillary loop length, capillary width and inter capillary distance) and the number of capillaries/mm were evaluated under 100x magnification, acquiring three consecutive images of nine capillaries per individual, totaling 900 capillaries examined and photographed. Four age groups were studied: 5–7 years (17 individuals); 8–10 years (24 individuals); 11–14 years (30 individuals) and 15–18 years (29 individuals). The intra and inter observer concordance was tested in 25% of subjects by two professionals with experience in this method.

Results: The capillary dimensions (mean ± SD) were: capillary loop length 278.6 ± 60.3 μm, inter capillary distance 124.1 ± 28.1 μm, capillary width 15.0 ± 2.6 μm and 7.8 ± 1.5 number of capillaries /mm. The only significant difference between males and females was the inter capillary distance which was higher in girls ($p = 0.011$). When comparing the four age groups, only the intercapillary distance remained constant over time ($p=0.088$). Teenagers between 15 and 18 years had longer and thicker capillaries (318.7 ± 64.4 μm) and (16.2 ± 3.3 μm) resp. when compared to other age groups ($p < 0.001$ and $p = 0.012$ respectively). We also found an increase in the number of capillaries/mm with age: 6.1 capillaries/mm (5–7 years); 7.0 (8 to 10 years); 8.0 (11–14 years) and 9.3 (15–18 years) ($p < 0.001$). There was a good intra and interobserver concordance in the analysis of capillary dimensions and the number of capillaries/mm by VCP. In VCP, 11% had enlarged capillary (capillary width percentile> 97.5) and 10% avascular areas (inter capillary distance percentile> 97.5). There was a negative correlation between the distance and the number of capillaries/mm.

Conclusion: This study evaluated the normal pattern of VCP in healthy children and adolescents and stratified patients by age groups. The number of capillaries /mm, the length and thickness of the capillary increased with age, while the intercapillary distance was maintained over the years.

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2713

The Relationship of Patient Reported Skin Symptoms to the Scleroderma HAQ, the Modified Rodnan Skin Score and Skin Pathology.. Jessica Ziemek, Ada Man, Robert W. Simms and Robert Lafyatis. Boston University School of Medicine, Boston, MA.

Background/Purpose: Changes in skin are a cardinal feature of systemic sclerosis (SSc). However, there are no SSc specific patient reported outcome measures validated for use to measure changes in skin. Some of the current measures used for SSc are the Modified Rodnan Skin Score (MRSS), SHAQ, SF-36, and PROMIS-29. In addition, several PROs have been developed for use in other skin diseases such as Skindex-29. Our goal was to evaluate some of these current measures to determine their correlations with specific skin symptoms and skin pathology in diffuse cutaneous systemic sclerosis patients.

Methods: Patients were recruited from the Boston University Scleroderma Center. Data collection occurred between December 2005 to April 2014 and data collected included the SHAQ, Skindex-29, MRSS, and a skin symptom assessment questionnaire developed for this study. The Skin Symptom Assessment (SSA) consisted of patients' self-evaluation of six skin symptoms over the past week, each scored on a 5-level Likert Scale (tight, painful, red, rigid/stiff, itchy and overall). Correlations using Spearman's rho were assessed between SSA, SHAQ, MRSS, and Skindex-29, only when the compared measures were completed on the same date. A subgroup of patients had a skin biopsy from the same visit as the MRSS, SSA, and SHAQ ($n=20$), and the relationships between these measures, histological features and myofibroblast staining were evaluated. The first time point the subject completed each patient reported outcome measure was used for analysis.

Results: 99, 42, 99, and 45 patients completed the SHAQ, Skindex-29, MRSS, and SSA, respectively. In the 99 patients who had a SHAQ and MRSS from the same date, the SHAQ moderately correlated with MRSS ($r=0.403$, $p<0.001$). SSA had weak to moderate correlations with the MRSS ($n=45$): the MRSS correlated most highly with tight ($r= 0.410$, $p=0.0052$), rigid/stiff ($r=0.535$, $p=0.0002$), and overall skin symptoms ($r=0.389$, $p=0.0083$). In contrast, the SHAQ correlated most highly with painful ($r=0.524$, $p=0.0003$) skin symptoms ($n=43$). In the 20 patients with skin biopsies along with concurrent measures, the MRSS correlated strongly with hyalinized collagen ($r=0.679$, $p=0.001$), but the SHAQ did not correlate significantly with any of the histologic measures (inflammation, myofibroblast infiltration, or hyalinized collagen).

With the SSA, tight skin moderately correlated with myofibroblast infiltration ($r=0.485$, $p=0.030$), while rigid/stiff skin moderately correlated with inflammation ($r=0.514$, $p=0.02$), myofibroblast infiltration($r=0.450$, $p=0.036$) and hyalinized collagen($r=0.539$, $p=0.014$).

The three domains of Skindex-29, Symptoms, Emotions and Functioning did not correlate significantly with MRSS but did so moderately with SHAQ ($r=0.464$, $r=0.502$, and $r=0.472$ respectively all with $p<0.05$).

Conclusion: Patient reported skin symptoms correlate with both clinical and pathological measures. However, this Skin Symptom Assessment was exploratory, as it was not developed through the formal methodology needed for validation of a patient reported outcome measure. Further research is required to develop a patient reported skin symptom measure that is both validated and sensitive to change.

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2714

Application of the 2013 ACR/EULAR Classification Criteria for Systemic Sclerosis in Korean Patients with Raynaud Phenomenon. Jin Su Park, Hee-Jin Park, You Jung Ha, Yong-Beom Park, Soo-Kon Lee and Sang-Won Lee. Yonsei University College of Medicine, Seoul, South Korea.

Background/Purpose: The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) suggested the 2013 ACR/EULAR classification criteria for systemic sclerosis (SSc), due to the lack of sensitivity for early and limited SSc of the 1980 ACR classification criteria.

The aim of this study was to determine how many patients with Raynaud phenomenon are reclassified as SSc by the 2013 ACR/EULAR classification criteria for SSc and to analyze the predictive variables of the new classification criteria in those patients.

Methods: We applied the 2013 ACR/EULAR classification criteria for SSc to 60 patients who had been diagnosed as SSc according to the 1980 ACR classification criteria (SSc group) and 64 patients who presented Raynaud phenomenon with or without autoimmune disease, but did not fulfill the 1980 ACR classification criteria (Raynaud phenomenon group). We analyzed the discrepancy between the previous and the new classification criteria when subjects were categorized as those with SSc.

Results: All patients who were diagnosed as SSc according to the previous classifications criteria fulfilled the new criteria. Furthermore, 17 of 64 patients (26.5%) in Raynaud phenomenon group were reclassified as SSc by the new criteria. Reclassified SSc patients in Raynaud phenomenon group significantly showed less frequency of scleroderma, sclerodactyly, finger pitting scar, interstitial lung disease and higher frequency of telangiectasia than those in SSc group (Table 1). Eleven of 17 patients who were reclassified as SSc (64.7%) had anti-centromere antibody. But none of 17 patients had anti-topoisomerase 1, meanwhile 29 of 60 patients who had been diagnosed as SSc (43.8%) had anti-topoisomerase 1 (Table 1). On multivariate linear regression analysis using variables with significance, puffy finger, sclerodactyly and telangiectasia were significant predictive values for the new classification as SSc in Raynaud phenomenon (RR=23.7, 29.5, 14.2; p value=<0.001, 0.015, 0.031).

Conclusion: 26.5% patients, who presented Raynaud phenomenon but did not fulfill the 1980 ACR classification criteria for SSc, were reclassified as SSc according to the 2013 ACR/EULAR classification criteria. Also, we suggest that physicians should pay attention to puffy finger, sclerodactyly and telangiectasia in patients with Raynaud phenomenon for the early diagnosis of SSc.

Table 1. Comparison of characteristics, clinical manifestations and autoantibodies between reclassified systemic sclerosis patients in Raynaud phenomenon group (New SSc) and patients in systemic sclerosis group (SSc).

Variables	New SSc (n=17)	SSc (n=60)	*P* value
RP duration (years)	3.4 ± 2.4	9.6 ± 6.7	<0.001
Disease duration (years)	1.25 ± 1.25	6.4 ± 5.8	<0.001
2013 ACR/EULAR score	10.8 ± 1.8	19.1 ± 5.2	<0.001

Scleroderma (N(%))	0 (0)	40 (66.7)	<0.001
Puffy finger (N(%))	12 (70.5)	27 (45.0)	0.062
Sclerodactyly (N(%))	6 (35.3)	55 (91.6)	<0.001
Digital tip ulcer (N(%))	2 (11.8)	20 (33.3)	NS
Fingertip pitting scar (N(%))	0 (0)	19 (31.7)	0.008
Telangiectasia (N(%))	5 (29.4)	5 (8.3)	0.022
Abnormal nailfold capillaries (N(%))	17 (100)	56 (93.3)	NS
Pulmonary artery hypertension (N(%))	1 (5.9)	3 (5.0)	NS
Interstitial lung disease (N(%))	2 (11.8)	29 (48.3)	0.007
ANA (centromere) (N(%))	9 (52.9)	12 (20.0)	0.007
Anti-centromere (N(%))	11 (64.7)	13 (21.7)	0.001
Anti-topoisomerase 1 (N(%))	0 (0)	29 (48.3)	<0.001

Values given as n (%) or mean ± standard deviation. p values < 0.05
NS, not significant

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2715

Reliability and Validity of the Duruöz Hand Index in an Argentinian Population with Scleroderma. Vanesa Duarte, Gloria Crespo, Maritza Manzano, María Victoria Martire, Santiago Scarafia, Lucila Marino, Felix Romanini, Marta Mamani and Anastasia Secco. Hospital Bernardino Rivadavia, Buenos Aires, Argentina.

Background/Purpose: The Duruöz Hand Index (DIH) is a reliable tool for the evaluation of hand′s function in patients with scleroderma. The aim of our study was to adapt and to validate the DHI questionnaire in an Argentinian population with scleroderma.

Methods: For validation, 3 rheumatologists adapted and translated to Spanish the original version in French and the final version was re-translated to French by a bilingual person. To evaluate the construct validity, we used the patient global visual analogue scale (VAS), VAS for questions for the same activity, the health assessment questionnaire (HAQ) and the Rodnan. A subsample attended a second visit to evaluate reproducibility, with no modifications in the treatment in relation to the previous visit. Continuos variables were expressed as mean and standard desviation (SD) or medians with their interquartile range (IQR). Spearman′s correlation coefficient was used to quantify the degree of correlation between the different VAS, HAQ and Rodnan with the total score. The intraclass correlation coefficient(ICC) was used to assess reproducibility and Cronbach′s alfa to evaluate internal consistency.

Results: 45 patients diagnosed with scleroderma were included in the study. 84,44% were women, mean age of 51±13,72 years (SD), 48,89% were Mestizos, while 46,67% were Caucasians with a disease duration of 24 months (IQR: 18–60). 64,44% patients had diagnostic of limited scleroderma; 77,78% were right handed and 53,33% had extra cutaneous manifestations. Raynaud was present in 93,33%, pitting scars in 33,33% and digital ulcers in 26,67%. The median score of the total questionnaire was 4,5 (IQR: 0–26), of the global VAS 49 (IQR: 10–50), of HAQ 0,3 (IQR: 0–1) and of Rodnan 5 (IQR:2–11). The correlation between the total score of DHI and the patient global VAS was 0,58, with the HAQ was 0,63 and with Rodnan 0,08. The correlation coefficient between the VAS and each group of questions for the same activity in the DHI questionnaire, indicated good correlation for the questions that refer to activities of **kitchen** (0,60;0,71;0,67;0,67;0,59;0,62; 0,55), as well as for **dressing** (0,69;0,65;057), for **hygiene** (0,61;0,56), and for **the office** questions (o,56;0,73). There was excellent level of correlation with those related to **fine motor activities** with a maximun r value of 0,78. The reproducibility was 0,88 (CI 95% 0,76–0,99) and the internal consistency according to Cronbach′s alfa was 0,98.

Conclusion: The results from this study show the DHI to be a reliable and valid test for this Argentinian population with scleroderma.

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2716

Development of a "Renal Crisis Prevention Card" As an Educational Tool Aimed at Improving Outcomes in High-Risk Patients with Systemic Sclerosis. Lee S. Shapiro[1], Lesley Ann Saketkoo[2], Jessica F. Farrell[1] and Kim Fligelstone[3]. [1]The Center for Rheumatology, Albany, NY, [2]Louisiana State University Health Sciences Center, New Orleans, LA, [3]Royal Free Hospital, Scleroderma Unit and Scleroderma Society, London, United Kingdom.

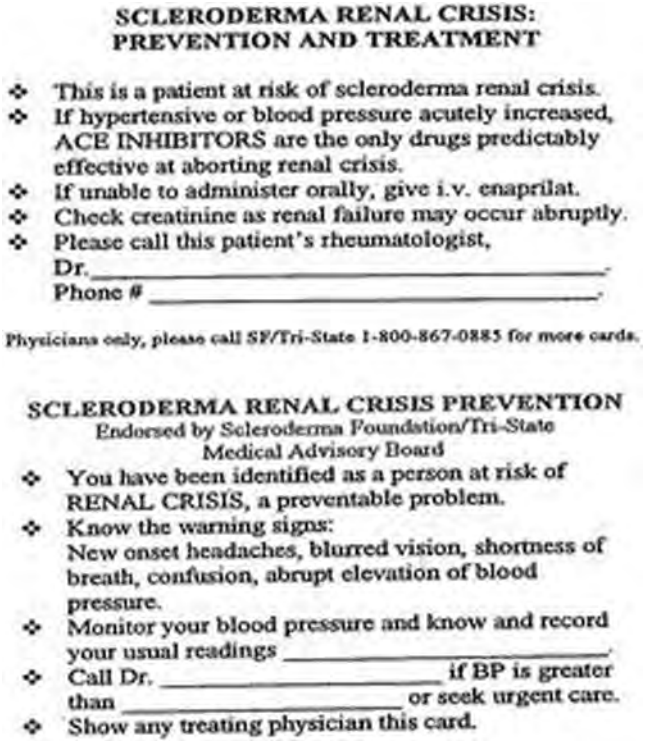
Background/Purpose: Scleroderma renal crisis (SRC) is a devastating complication of SSc. The introduction of effective treatment with ACE inhibition (ACE-I) in 1979 dramatically reduced death as a near-immediate consequence of SRC. However, poor outcomes still occur with great frequency including chronic or temporary dialysis or death. Individuals with early, rapidly progressive diffuse disease and RNA polymerase III antibody positivity are at high risk for SRC. Prophylactic use of ACE-I in high risk patients has not demonstrated improved outcomes and may have negative consequences. Our goals were to identify associative causes of poor outcome and develop a targeted preventive intervention to address in accordance with findings.

Methods: A retrospective chart review at Royal Free Hospital scleroderma clinic between 1994–1999 identified and stratified 44 cases of SRC for long term outcomes (death, long-term dialysis, short-term dialysis, and no dialysis). Cases were then assessed for factors potentially related to outcomes: onset of symptoms, time to medical attention, and therapeutic management. Results directed development of SRC preventive intervention.

Results: Death or long-term dialysis was the outcome in approximately 50% of the cases reviewed. Three subgroups emerged as associative with poor outcomes:

1. SSc patients with no previously established SSc diagnosis presenting as "malignant hypertension"
2. SSc patients with an established SSc diagnosis but uninformed about SRC and misinterpreted symptoms or failed to recognize the urgency of seeking medical attention
3. SSc patients who presented promptly for urgent outpatient medical care informing physician of SSc diagnosis, but were incorrectly treated with therapies other than ACE-I or initiation of ACE-I was without sufficiently rapid dose adjustment to achieve blood pressure control.

Poor outcomes were correlated to delayed therapy, rather than drug failure. All patients in the 'no dialysis/death' group were treated with ACE-I according to protocol. From these findings, a "scleroderma renal crisis prevention card" was developed. See image.



SCLERODERMA RENAL CRISIS:
PREVENTION AND TREATMENT

- This is a patient at risk of scleroderma renal crisis.
- If hypertensive or blood pressure acutely increased, ACE INHIBITORS are the only drugs predictably effective at aborting renal crisis.
- If unable to administer orally, give i.v. enaprilat.
- Check creatinine as renal failure may occur abruptly.
- Please call this patient's rheumatologist,
  Dr. _____.
  Phone # _____.

Physicians only, please call SF/Tri-State 1-800-867-0885 for more cards.

SCLERODERMA RENAL CRISIS PREVENTION
Endorsed by Scleroderma Foundation/Tri-State
Medical Advisory Board

- You have been identified as a person at risk of RENAL CRISIS, a preventable problem.
- Know the warning signs:
  New onset headaches, blurred vision, shortness of breath, confusion, abrupt elevation of blood pressure.
- Monitor your blood pressure and know and record your usual readings _____.
- Call Dr. _____ if BP is greater than _____ or seek urgent care.
- Show any treating physician this card.

Conclusion: Despite availability of effective therapy, SRC is associated with poor outcomes often consequential to treatment delay and lack of knowledge of initial treating physicians. A "renal crisis prevention card" may improve health outcomes of high-risk patients as a method of educating patients and health care providers.

Disclosure: L. S. Shapiro, None; **L. A. Saketkoo**, None; **J. F. Farrell**, None; **K. Fligelstone**, None.

2717

Comparison of PROMIS® survey Between Scleroderma Patients in an Academic Center and Patient-Based Scleroderma Foundations. Vivek Nagaraja[1], Veronica Berrocal[1], Kerri Connolly[2], Ann Kennedy[3], Daniela Seelmann[4] and Dinesh Khanna[1]. [1]University of Michigan, Ann Arbor, MI, [2]Scleroderma Foundation, Boston, MA, [3]Federation of European Scleroderma Associations, Tournai, Belgium, [4]Universidad de Los Andes, Santiago, Chile.

Background/Purpose: The National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS®) roadmap initiative is a cooperative research program designed to develop, evaluate, and standardize item banks to measure patient-reported outcomes (PROs) across different medical conditions as well as the US population (www.nihpromis.org). It has comprehensive items banks that assess physical, mental, and social well-being. The aim of this study was to compare the PROMIS survey between the scleroderma patients at an academic center and patient-based foundations as this has implications for large epidemiological studies (such as Scleroderma Patient Intervention Network).

Methods: A study titled 'PROMIS in rheumatology' was created in the Assessment center website. This study contained 13-PROMIS instruments. Patients seeking care in the academic Scleroderma clinic were approached to participate in the PROMIS survey. Patients were also recruited from the Scleroderma patient-based foundations (SF) namely – the Scleroderma Foundation and the Federation of European Scleroderma Associations, through the respective social media pages and e-newsletters. Average T-scores of the patient-based foundation scleroderma cohort were compared with those of the UM scleroderma patient cohort.

Results: Thirty-six patients at UM and 241 patients from SF have so far completed the survey. In both groups, the T-scores in the following domains were approximately 1 standard deviation worse than the United States (US) general population (GP) – fatigue, physical function, pain interference, satisfaction in roles and activities. Anger and social isolation banks were comparable to US GP. In comparison to the UM scleroderma cohort, the T-scores of the SF patient cohort was significantly worse for pain behavior and social isolation (Table, $p < 0.05$); however, the differences were not clinically meaningful.

Conclusion: The patients with SSc have decrements in health-related quality of life on PROMIS measures when compared to the US general population. There were no meaningful differences in the two cohorts, suggesting that patients from scleroderma clinic and patient foundations can be approached for non-pharmacologic intervention trials.

Table 1: Comparison of T-scores of UM and SF patient cohorts

	UM Scleroderma		Scleroderma patient foundations		
PROMIS item banks	**N**	**Mean**	**N**	**Mean**	**p-value**
Anger	36	51.4	238	52.0	0.75
Anxiety	36	55.1	238	54.5	0.57
Depression	36	54.4	241	54.5	0.57
Fatigue	35	60.4	240	60.9	0.49
Pain behavior	36	56.4	238	56.6	**0.04**
Pain interference	36	59.3	240	60.4	0.48
Physical function*	36	39.5	239	37.8	0.59
Physical function with mobility aid*	36	41.7	238	38.8	0.56
Satisfaction in roles and activities*	36	43.8	238	41.9	0.65
Sleep Disturbance	36	56.7	239	56.5	0.29
Sleep related impairment	36	58.1	239	56.8	0.19
Social activities (Ability to participate)*	36	45.2	238	43.8	0.74
Social isolation	36	48.7	238	50.8	**0.04**

* Lower score (T-score <50) means worse than average

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2718

The UCLA Gastrointestinal Tract Questionnaire (GIT)2.0 and GI Visual Analogue Scale(GI-VAS) Reflect Different Aspects of GI Involvement in Systemic Sclerosis. Yossra Suliman[1], Yasser Shaweesh[2], Suzanne Kafaja[3], Lewei Duan[4] and D. E. Furst[5]. [1]David Geffen School of Medicine, University of California Los Angeles,, Los Angeles, CA, [2]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, [3]University of California, Los Angeles, Department of Medicine, Los Angeles, CA, [4]David Geffen School of Medicine, University of California School of Medicine, Los Angeles, CA, [5]University of California at Los Angeles, Los Angeles, CA.

Background/Purpose: UCLA GIT2.0 is a validated measure for assessing the severity of gastrointestinal involvement in systemic sclerosis patients (SSc) patients; GI VAS is also a widely used measure of GI effect in patients as a component of SSc health assessment questionnaire (SHAQ). GIT2.0 includes 34 questions in 7 domains (reflux, distension, soilage, diarrhea, social function, emotional wellbeing and constipation). GI VAS is a 100 mm VAS that asks the patient; how much GI symptoms interfere with patient function. Both are measures of present state.

Objectives

1) Is there a correlation between GI-VAS and total GIT2.0?
2) Is a correlation between GI-VAS and GIT2.0 domains?
3) Does total GIT2.0 or GI-VAS predict patient global.

Methods: We extracted baseline data in 98 consecutive SSc patients, with respect to: age, sex, SSc subtype, disease duration, HAQ-DI, VAS for: pain, raynaud's, ulcer, breathing, GIT2.0 domains and patient global.

Analysis:-Correlation between GI VAS and GIT 2.0 (total and individual domains) by Pearson correlation Coefficient. Univariable linear regression using patient global as dependent variable against total GIT2.0 or GI-VAS as separate independent elements. Independent variables were: SSc subtype, age, gender, disease duration, VAS for: raynaulds, finger ulcers and breathing in each model.

Results: Of total 98 patients available for analysis, 84 were females, 59 were diffuse subtype, mean age 54.6 (SD 14), mean disease duration 9.6 years (7.6), total GIT2.0 mean0.51 (0.49) - moderate, GI-VAS mean2.34 (2.77)-mild, HAQ-DI mean 0.98 (0.76) and patient global mean 3.77(2.69). Correlation between GI VAS and GIT2.0 (total and individual domains) are listed in **table1**. Even though the correlation between GIT2.0 and GIT VAS is ($r=0.6$) and weighted kappa is 0.59 –moderate, thirty four percent of the patients showed disagreement between the two measures by at least 1 category (total of four categories). Linear regression analysis demonstrated that GIT2.0 and GI-VAS were independent predictors of patient global as were VAS for breathing and ulcer ($p<0.007$). Adjusted r squared for GIT2.0 was 0.49and for GI-VAS was0.51.

Table 1. Correlation between GI VAS and GIT2.0 (total and individual domains)

	GIT2.0	Reflux	Distension	Soilage	Diarrhea	Constipation	Social function	Emotional wellbeing
GI VAS	0.61	0.56	0.54	0.32	0.26	0.33	0.58	0.49

Conclusion: GIT2.0 and GI VAS reflect GIT involvement. Each separately is an independent predictor of patient global. They disagree sufficiently frequently that they may reflect different aspects of GI involvement and might be considered separately in clinical GI evaluation of SSc patients.

Disclosure: Y. Suliman, None; **Y. Shaweesh**, None; **S. Kafaja**, None; **L. Duan**, None; **D. E. Furst**, None.

2719

Performance of the New ACR Criteria in Systemic Sclerosis: A Multicenter Study. Necati Cakir[1], Omer Nuri Pamuk[2] and Mehmet Ali Balci[2]. [1]Fatih Sultan Mehmet State Hospital, Istanbul, Turkey, [2]Trakya University Medical Faculty, Edirne, Turkey.

Background/Purpose: Reliable and validated classification criteria are needed to conduct high quality clinical research in systemic sclerosis (SSc). The most widely used classification criteria for SSc are ACR criteria published in 1980. Recently, ACR and EULAR Collabarative Initiative has prpposed a new set of criteria for the classification of SSc. In our study, we aimed to compare the sensitivity and specificity of the new ACR/EULAR criteria to the ACR criteria in our SSc population.

Methods: Two rheumatology centers from Turkey participated in this study. The features present at disease onset in patients with SSc seen between 2008–2013 were retrospectively reviewed. For the evaluation of specificity, patients admitted to each center between the same time period for conditions other than SSc, in whom ANA was deemed necessary within the diagnostic work-up, were included as controls.

Results: Onehundredandtwo SSc patients (93 females, 9 males, mean age: 47.9 ± 13.9) and 80 controls (70 females, 10 males, mean age: 48.4 ± 11.6) were included into the study. ANA was positive in 89.2%,

anti-Scl-70 in 31.7%, and anti-centromere in 21.6% of the patients. Digital ulcers were present in 34.7% of SSc patients, pulmonary hypertension in 42.2%, interstitial lung disease in 38.3%, and renal crisis in 2%.

The sensitivity of ACR&EULAR and ACR1980 criteria were, respectively, 92.2% and 78.4%. The specificity of ACR/EULAR and ACR1980 criteria were, respectively, 89.3% and 76.7%. According to the new critera göre 10 patients were misclassified, and according to ACR1980 criteria 18 patients were misclassified. The sensitivity of ACR 1980 criteria was significantly better in SSc patients with interstitial lung disease when compared to others (91.7% vs. 74.%1, p=0.036). According to the New criteria set, however, the sensitivity tended to be higher in the group with anti-Scl-70 positivity (91.7% vs. 74.1%, p=0.09). The sensitivity and the specificity of the criteria were not different in patients with certain other clinical features or other antibody positivities.

Conclusion: We observed that the new ACR/EULAR SSc classification criterianın had better sensitivity and specifity in our SSc patients; and it led to misclassification in a less number of patients.

Disclosure: N. Cakir, None; **O. N. Pamuk**, None; **M. A. Balci**, None.

2720

Prevalence and Features of Metabolic Syndrome in Systemic Sclerosis. Tiago N. Amaral[1], Karina Pereira[2], Nailu A. Sinicato[1], Sandra Gasparini[1], Fernando Augusto Peres[1], Maria Carolina de Souza[1], Ana Paula del Rio[1], João Francisco Marques-Neto[3] and Simone Appenzeller[4]. [1]State University of Campinas, Campinas, Brazil, [2]State University of Campinas, Limeira, Brazil, [3]University of Campinas, Campinas, Brazil, [4]Faculty of Medical Science, State University of Campinas Unicamp, São Paulo, Brazil.

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by initial vascular injuries and resulted fibrosis of skin and internal organs. Vascular impairment in SSc involves both micro and macrovascular circulation and maybe a sign of endothelial dysfunction. Metabolic syndrome (MetS) is defined as a set of metabolic abnormalities which commonly manifests together and are considered to be cardiovascular risk factors. Each component by itself increases the risk for cardiovascular disease (CVD), however, when combined, a 1.5 – 2.5 increase in CVD mortality is observed.

Objective: To determine the prevalence and features of metabolic syndrome (MetS) in SSc.

Methods: We screened consecutive SSc patients followed in a longitudinal cohort from 2011 to 2013 and age and sex matched controls. We excluded patients with overlapping rheumatic diseases. Predefined outcome measures were collected. This included demographics (age, gender, disease duration), physical examination [skin score, joint count, blood pressure, height, weight, waist circumference (WC) and hip circunference (HC)], disease activity (Valentini Disease Activity Index) and severity (Medsger Disease Severity Scale) scores and laboratory data (total and fractions of cholesterol, fasting glucose levels, basal insulin, C3, C4, erythrocyte sedimentation rate and hemoglobin/hematocrit levels). MetS was assessed using the definition recommended by the 2009 Joint Interim Statement (JIS). Nonparametric tests and correlation were used for statistical analysis.

Results: A total of 131 SSc (121 female; mean age = 51.70; SD=13.12) and 79 health subjects (69 female; mean age=40.66; SD=13.38) (p=0.41) were included in the study. Seventy-eight (59.54%) patients had limited SSc (lSSc); 42(32.06%) had diffuse SSc (dSSc) and 11(8.4%) SSc sine scleroderma disease (ssSSc). Active disease was observed in 18(13.74%) SSc (10 lSSc and 8 dSSc) patients. Hypertension was identified in 35 (26.72%)SSc and in 3 (3.8%) controls (p<0.001), diabetes mellitus in 16 (12.21%) SSc patients and in 3 (3.8%) controls (p=0.04) and lipid profile abnormalities in 83 (63.36%) SSc patients and in 10 (12.6%) controls (p<0.001). Increased LDL [94 (71.76%)], increased triglycerides [49 (37.40%)] and reduced HDL [75 (57.25%)] were the lipid abnormalities more often observed in SSC when compared to controls (p<0.01). Abnormal abdominal circumference was observed in 105 (80.15%) SSc patients and in 54 (68.35%) controls (p=0.05). MetS was identified in 52 (39.69%) SSc patients and 7 (8.86%) controls (p<0.001). We did not observe an association between MetS and SSc subtype (p=0.76), disease activity (p=0.66), prednisone use (p=0.093) and severity index (p=0.1).

Conclusion: This is the first study to determine the prevalence and features of MetS in SSC. MetS is frequently observed in SSc and not associated with disease related features in this cohort. However MetS should be routinely screened since it can influence atherosclerosis and cardiovascular mortality in SSc.

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2721

Patients' Perspective of Skin Involvement in Systemic Sclerosis. Ada Man[1], Amy Wu[1], Jessica Ziemek[1], Romy Christmann[1], Robert W. Simms[1], David T. Felson[1] and Robert Lafyatis[2]. [1]Boston University School of Medicine, Boston, MA, [2]Boston University, Boston, MA.

Background/Purpose: Skin tightness and other abnormalities of the skin are the hallmark features of systemic sclerosis (SSc). While skin involvement may significantly impact a patient's quality of life, this impact is not well understood since current measures of SSc disease activity only address the objective measure of skin thickness (modified Rodnan skin score), and non-skin related SSc health status (scleroderma HAQ, SSc-GIT). We sought to identify key items of concern as related to skin disease in SSc from the patient's perspective.

Methods: Three directed focus groups with diffuse and limited cutaneous SSc patients (N=15) were conducted to facilitate free discussion around the patients' experience with skin-related quality of life in SSc. Transcripts were qualitatively analyzed using a Grounded Theory approach and emerging items of concern were coded with the aid of data analysis software (NVivo 10, QSR International). The items were sorted according to their frequency of citation combining all three focus sessions. We identified major constructs that formed a unifying conceptual framework for the items.

Results: The top cited concerns by patients included difficulty with gripping and moving parts of the body due to skin tightness, feeling self-conscious about the skin's appearance, uncomfortable skin tightness/restrictiveness, and difficulty opening and closing the mouth. Some skin-related concerns such as hand function may overlap with musculoskeletal involvement in SSc. Four major constructs were identified (in descending order of cited frequency): physical limitations imposed by skin tightness, physical skin effects, emotional effects, and social effects.

Conclusion: The subjective effects of skin involvement on SSc patients' quality of life are multidimensional and some important patient concerns such as discomfort from skin tightness, itch, and reduced mouth opening are not captured by existing disease outcome instruments in the dermatology and rheumatology literature. Hand function was a frequently cited skin-related concern and points to a possible need for SSc specific hand function assessment instruments as well.

Table 1. Top 20 concerns cited by systemic sclerosis patients (N=15) during three focus sessions relating to how skin affects their quality of life

Construct	Item	Number of times cited
Physical limitations	Difficulty with grip/fist	46
Physical limitations	Difficulty moving parts of the body	26
Emotional effects	Self-conscious	24
Physical skin effects	Tight or Restrictive	21
Physical limitations	Reduced ability to close or open mouth	18
Physical limitations	Difficulty with fine motor skills	18
Emotional effects	Fear of not knowing how disease will progress	14
Physical limitations	Difficulty putting on clothes and shoes	11
Physical skin effects	Itchy	11
Physical skin effects	Skin darkening	10
Physical skin effects	Swelling of skin on hands and fingers	10
Physical skin effects	Dry	7
Physical skin effects	Tingling or burning	6
Emotional effects	Depressed	6
Emotional effects	Different sense of self	6
Physical limitations	Difficulty opening hands	5
Physical skin effects	Change in facial appearance	5
Social effects	Decreased ability to work	5
Emotional effects	Feel misjudged by looks	4
Physical limitations	Change in ability and comfort in doing sports	4

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2722

Rapamycin Corrects GATA-3 Deficiency in Lupus Treg. Hiroshi Kato and Andras Perl. SUNY Upstate Medical University, Syracuse, NY.

Background/Purpose: As demonstrated by the negative correlation between Treg frequency or suppressive function and SLE disease activity index score, it is tempting to speculate that a Treg defect contributes to dysregulated immune response in SLE. GATA-3 is not only indispensable for Th2 differentiation, but also plays critical roles in homeostasis and function of Tregs as exemplified when Treg-specific deletion of GATA-3 leads to spontaneous development of inflammatory disorder. GATA-3 deficient Tregs have reduced FoxP3 expression and are poised to express IL-17 in the presence of IL-6. However, roles of GATA-3 in lupus Treg biology remain undefined.

Methods: $CD3^+$ T cells were isolated from 9 pairs of matched SLE and healthy control (HC) subjects. A part of the $CD3^+$ T cells were stained with CD4, CD8, and CD25 followed by GATA-3 and FOXP3. The rest of the cells were cultured in RPMI culture media with 10% FCS, 1% Penicillin/Streptomycin, and 1% L-glutamine for 3 days in the presence of plate-bound anti-CD3 and soluble anti-CD28 with or without 100 nM rapamycin. After 3 days of culture period, cells were stained as previously described. GATA-3 expression by $CD4^+$, $CD8^+$, and $CD4^-CD8^-$ double-negative (DN) T cells as well as $CD4^+CD25^+FOXP3^+$Treg was assessed by flow cytometry. Mean fluorescence intensity was normalized to that of HC samples on day 0. Frequency of GATA-3^+ cells was determined after 3-day T-cell-receptor stimulation.

Results: GATA-3 was overexpressed in freshly isolated SLE $CD3^+$ T cells (Relative MFI: 1.22±0.08, p=0.013), $CD8^+$ T cells (Relative MFI: 1.26±0.09, p=0.012), and DN T cells (Relative MFI: 1.70±0.33, p=0.033), whereas it was reduced in freshly isolated SLE Tregs (Relative MFI: 0.81±0.09, p=0.032). After 3-day T-cell-receptor stimulation, rapamycin suppressed GATA-3 expression by $CD3^+$ T cells in HC (% GATA-3^+ cells: 51.8±1.7% in rapamycin-untreated cells, 49.7±2.2% in rapamycin-treated cells, p=0.006), which appears to be the case in SLE (% GATA-3^+ cells: 49.8±5.6% in rapamycin-untreated cells, 48.1±6.9% in rapamycin-treated cells). In contrast, rapamycin augmented GATA-3 expression by Tregs in HC (% GATA-3^+ cells: 63.1±4.6% in rapamycin-untreated cells, 69.4±3.7% in rapamycin-treated cells, p=0.003) and appears to have restored that in SLE (% GATA-3^+ cells: 61.1±6.3% in rapamycin-untreated cells, 62.8±7.6% in rapamycin-treated cells).

Conclusion: The data points to GATA-3 deficiency in SLE Treg as a potential mechanism underlying the functional incompetence. Rapamycin may correct Treg function by restoring GATA-3 expression in SLE.

Disclosure: H. Kato, None; **A. Perl**, None.

2723

Programmed Death 1 Inhibits T-Cell Adhesion By Regulating Rap1. Inbar Alfaguter[1], Marianne Strazza[1] and Adam Mor[2]. [1]NYU, New York, NY, [2]NYU Langone Medical Center, New York, NY.

Background/Purpose: Programmed Death-1 (PD-1) is an inhibitory co-receptor that is highly expressed in T lymphocytes. The binding of PD-1 to its ligands, PD-L1 or PD-L2, is vital for the physiologic regulation of the immune system. Likewise, a major function of the PD-1 signaling pathway is the inhibition of self-reactive T cells, which serve to protect against autoimmune disease. PD-1 transmits its inhibitory effects by dephosphorylation of physically associated proximal signaling molecules that are downstream of the T cell receptor complex. At the cellular level, PD-1 activation can leads to depression of T-cell proliferation, impaired survival, and decreased interleukin-2 release.

Methods: Preliminary studies have shown that PD-1 also inhibits T cell adhesion, but little is known how this is mediated. In order to fill this gap, we investigated the role of PD-1 in T-cell adhesion by analyzing the major players in its TCR signaling pathway. We hypothesized that PD-1 inhibited adhesion by inhibiting Rap1, a small GTPase vital for effective T cell motility and adhesion.

Results: We identified that when PD-1 binds to its ligand PD-L2 there is an inhibition of Rap1 activation and LFA-1 mediated adhesion. We continued to show that C3G, a vital component of activating Rap1 and a more upstream element in the TCR signaling cascade, is dephosphorylated by PD-1.

Moreover, this was mediated by the phosphatases SHP-1 and SHP-2. Interestingly, we did not see these results downstream the inhibitory co-receptors, CTLA-4, proving that PD-1 works by a distinct mechanism.

Conclusion: We concluded that PD-1 inhibits Rap1 mediated adhesion by dephosphorylation of C3G utilizing the phosphatases SHP-1 and SHP-2. Further studies are underway to further characterize the regulation of these enzymes by PD-1.

Disclosure: I. Alfaguter, None; **M. Strazza**, None; **A. Mor**, None.

2724

Deficiency of Ro52/TRIM21 in Different Subsets of Peripheral Blood Mononuclear Cells from Patients with Inflammatory Myopathies. Angeles Shunashy Galindo-Feria, Diana Gómez-Martín, Ana Barrera-Vargas, Javier Merayo-Chalico and Jorge Alcocer-Varela. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.

Background/Purpose: The detection of Ro52/TRIM21 autoantibodies has been considered an independent prognostic marker in different rheumatic conditions. However, the information about the expression of Ro52/TRIM21 in subsets of peripheral blood mononuclear cells (PBMCs) in autoimmune diseases is scant. Specifically, its role in idiopathic inflammatory myopathies (IIM) has not been elucidated, and the evaluation of its expression in these diseases is the aim of the present study.

Methods: We included active, untreated patients with recent diagnosis (<1 month) of IIM according to Bohan and Peter's criteria, who attended a tertiary care center from March 2013 to April 2014. Patients with diagnosis of dermatomyositis (DM), polymyositis (PM) and antisynthetase syndrome (AAS), as well as age and gender-matched healthy controls were recruited. All subjects gave informed consent and the study was approved by the institutional ethics committee. PBMCs were isolated by Ficoll-Hypaque method and different subsets of PBMCs ($CD4^+$, $CD8^+$, $CD14^+$) were purified by magnetic selection. The expression of Ro52/TRIM21 was evaluated by Western Blot. Descriptive statistics are shown with mean and standard deviation. Student's T test or Mann-Whitney U test was used to analyze differences between groups.

Results: We included 14 patients with IIM (1 PM, 3 AAS, 10 DM), as well as 14 healthy controls. Sixty percent of subjects were female, with a mean age of 43±15 years. CPK levels at diagnosis were 4534±2235 UI/L and lymphocyte count was 1021±170 cells/uL. The presence of myositis-specific and associated autoantibodies was assessed by ELISA. The autoantibodies found in DM patients were anti-Ro52 (20%) anti-PL7 (20%), anti-Ku (20%), anti-PL12 (10%), anti-SRP (10%) and anti-Mi2 (10%). In AAS patients, anti-Ro52 (33.3%), anti-Jo1 (33.3%) and anti-PMScl75 (33.3%) were identified. We did not find any specific nor associated autoantibodies in the patient with PM. Patients with IIM showed decreased protein expression of Ro52/TRIM21 in comparison to healthy controls in different PBMC subsets: total PBMC (0.971±0.603 *vs* 1.849±0.927, p=0.016), $CD4^+$ lymphocytes (0.797±0.540 *vs* 2.413±0.786 p=0.017), and monocytes (0.875±0.358 *vs* 1.890±0.209 p<0.001). $CD8^+$ lymphocytes from IIM patients also showed a trend towards lower Ro52/TRIM21 expression (0.902±0.708 *vs*1.610±0.540, p=0.133). We did not find significant differences among each of the IIM groups.

Conclusion: Our findings suggest that patients with IIM are characterized by deficient expression of the ubiquitin ligase Ro52/TRIM21 in different PBMC subsets ($CD4^+$ lymphocytes and monocytes). Further insights into the function of this protein will have profound implications for the understanding of its role in IIM. TRIM21 deficiency could be particularly related to decreased IRF ubiquitination and degradation, which could enhance type 1 interferon signaling.

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Enhanced Expression of CCL25 to Facilitate Increased Numbers of CCR9-Expressing Tfh-like Cells in Salivary Glands of Primary Sjögren's Syndrome Patients. S.L.M. Blokland[1], M.R. Hillen[1], A.a. Kruize[1], A. Kislat[2], S. Meller[2], B. Homey[2], G.M. Smithson[3], J. Zalevsky[4], T.R.D.J. Radstake[1] and J.a.G. van Roon[1]. [1]University Medical Center Utrecht, Utrecht, Netherlands, [2]University of Düsseldorf, Medical Faculty, Düsseldorf, Germany, [3]Takeda Pharmaceuticals International, Chicago, IL, [4]Takeda California, San Diego, CA.

Background/Purpose: In primary Sjögren's syndrome (pSS) B cell activation and autoantibody secretion are hallmark immunopathological features. Specific lymphoid organization (including germinal centers) is associated with increased risk for development of extraglandular manifestations and lymphoma. Thus better understanding of the cellular and molecular pathways that underlie formation of ectopic lymphoid structures is of pivotal importance. Tfh cells, expressing ICOS and cytokines like IL-21 play a critical role in the formation of such structures and in activation of B cells. Recently, a novel subset of CD4+ T cells found to have Tfh-like characteristics was found to be specifically attracted to mucosal sites by CCL25, the ligand for CCR9.

Objective: To investigate the presence of CCL25 and CCR9-expressing Tfh-like cells in pSS patients.

Methods: Levels of CCL25 were measured in the serum of patients with pSS (n=13), non-Sjögren's sicca (nSS, n=15) and healthy controls (HC, n=6). Also, the correlation of CCL25 with other inflammatory mediators as assessed by Luminex was determined. Secretion of CCL25 by labial salivary gland (LSG) biopsy samples from pSS (n=14) and nSS (n=14) patients was assessed and CCL25 mRNA was quantified (n=9 vs n=9). CCR9-expressing cells were assessed in the circulation of HC and pSS patients and expression of Tfh markers including CXCR5, ICOS and PD-1 was analyzed.

Results: Increased CCL25 levels were observed in serum of pSS and nSS patients as compared to HC (pSS 2984 ± 286, nSS 2692 ± 177, HC 2140 ± 154, $p = 0.02$ and $p = 0.03$ resp). CCL25 serum levels in pSS correlated with the presence of chemokines involved in formation of ectopic lymphoid structures CXCL13 and CCL19 ($r=0.594$, $p=0.04$) and proinflammatory cytokines IL-12 ($r=0.615$, $p=0.03$) and TWEAK ($r=0.621$, $p=0.03$). In addition, pSS patients displayed a 10 fold increase in CCL25 mRNA levels in LSG ($p<0.05$) and an increase in CCL25 protein levels in LSG washouts compared to nSS patients (2029 ± 2986 vs 974 ± 188 pg/mL, $p=0.03$), correlating with CXCL13 ($r=0.832$, $p<0.001$). pSS patients had enhanced numbers of CCR9-expressing T cells in the circulation as compared to HC (14.1% vs 7.9%, $p=0.05$). Interestingly, comparable to Tfh a substantial proportion of CCR9+ cells expressed CXCR5, PD-1 and ICOS.

Conclusion: Our results suggest that enhanced expression of CCL25 in the labial salivary gland might promote elevation of CCR9-expressing Tfh-like cells at the site of inflammation. Considering the expression of ICOS and the capacity of CCL25 to induce proinflammatory cytokine secretion this suggests that the CCL25/CCR9-axis might play a role in the immunopathology of pSS, representing a novel therapeutic target in this disease.

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CD28null T Cells from Polymyositis Patients Are Cytotoxic to Autologous Muscle Cells *in Vitro* Via Perforin-Dependent Mechanisms. Jayesh Pandya[1], Paulius Venalis[1], Lubna Al-Khalili[2], Mohammad Shahadat Hossain[1], Ingrid E. Lundberg[1], Vivianne Malmström[1] and Andreas E. R. Fasth[1]. [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, [2]KTH - Royal Institute of Technology, Stockholm, Sweden.

Background/Purpose: Inflammatory infiltrates of muscles in polymyositis are dominated by CD4+CD28null and CD8+CD28null T cells. In contrast to conventional CD28+ T cells, these cells have a restricted T cell-receptor repertoire, rapidly release large amounts of IFN-γ and TNF, and can kill tissue cells by granzyme-B and perforin upon activation. Although their presence in myositis muscles have been demonstrated recently, their effect on muscle cells has not been clarified. Aim of the study was to investigate the potential myotoxic effect of CD28null T cells on muscle cells from patients with polymyositis, in a fully autologous co-culture system.

Methods: Muscle stem cells were extracted from biopsies from 6 patients with polymyositis (classified according to Bohan and Peter criteria) and differentiated into myotubes. T cell subsets from the same patients were isolated from peripheral blood by flow-cytometry. Co-cultures of autologous muscle cells were performed with un-stimulated or stimulated T cell subsets for 24–36 hours. Dead myotubes were quantified by calcein release assay and flow-cytometry. Blocking experiments were performed using relevant blocking antibodies to the co-cultures.

Results: CD28null T cells were spontaneously cytotoxic to autologous muscle cells in culture. The median cytotoxicity (induced muscle cell death) at 5:1 T cells-muscle cells ratio was 23.5% for CD4+CD28null and 22.3% for CD8+CD28null T cell subsets (n=4). In comparison, conventional CD4+ and CD8+ T cells displayed lower cytotoxicity (median CD4+CD28+ 10.3%, CD8+CD28+ 11.4%, n=4). Upon co-culture in stimulatory environment, both CD28null T cell subsets significantly induced more cell death in autologous muscle cells than CD28+ counterparts (n=5). Not only CD8+CD28null but also CD4+CD28null T cells displayed perforin polarization towards muscle cells and secreted higher levels of granzyme-B and IFN-γ in co-culture than CD28+ subsets (n=4). By blocking perforin, the myotoxicity was reduced by a median of 52% with CD4+CD28null T cells and by 56% in cultures with CD8+CD28null T-cells (n=3). TNF or IFN-γ did not induce death of muscle cells in the absence of T cells, but did upregulate HLA class I and II on muscle cells (n=3–5). Blockade of IFN-γ and TNF in co-cultures with T cells reduced the level of dead muscle cells by 46% (CD4+CD28null) and 53% (CD8+CD28null) (n=3). The reduced myotoxicity is likely attributed to reduced HLA expression, as HLA blockade resulted in a comparable reduction in myotoxicity, 61% (CD4+CD28null) and 55% (CD8+CD28null) (n=5).

Conclusion: The myotoxic effect by CD28null T cells in polymyositis may be mediated by perforin-dependent killing and regulated by IFN-γ-induced HLA expression by muscle cells. Together, this suggests that CD28null T cells are key effector cells directly contributing to the muscle cell damage in polymyositis, hence represent target candidate for future therapies

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T Cells Trigger Interstitial Pneumonia in Polymyositis. Akira Takeda[1], Yasutsugu Fukushima[2], Takaji Matsutani[3], Yoichiro Haji[1], Chisun Min[1], Ryo Rokutanda[1], Yasuhiro Suyama[1], Mitsumasa Kishimoto[1], Ken-ichi Yamaguchi[1] and Masato Okada[4]. [1]St. Luke's International Hospital, Tokyo, Japan, [2]Dokkyo University School of Medicine, Mibu, Japan, [3]Wakayama Medical University, Ibaraki, Japan, [4]St. Luke's International Hospital, tokyo, Japan.

Background/Purpose: The lung is frequently affected in connective tissue diseases (CTDs). Polymyositis (PM) is a major CTD characterized by idiopathic inflammatory lesions of muscle and other organs including critical pulmonary involvement. Interstitial lung diseases, mainly interstitial pneumonia (IP), have been recognized in 30–70% of PM patients, which often have a poor prognosis and a high risk of mortality. While the presence of myositis-specific autoantibodies suggests an autoimmune etiology of PM, the pathogenesis of PM-associated IP remains unclear. The aim of this study was to elucidate the role of T cells in this pulmonary complication. Lung tissue was utilized in this study with the approval of the IRB.

Methods: We had advantage of a rare opportunity to be able to precisely study the lung tissues which were obtained for the pathodiagnostic purpose by video-assisted thoracoscopy from the cases of earliest-stage IP associated with PM: one patient with IP of early usual IP (UIP) pattern and another patient with IP of nonspecific IP (NSIP) pattern. It lead us to immunohistochemically characterize the phenotype of lung-infiltrating lymphocytes from the lung biopsy specimens, and to analyze T-cell receptor α-chain (TCR Vα) and TCR β-chain (TCR Vβ) variable region repertoires of T-cells infiltrating the lung tissues using a validated adaptor ligation polymerase chain reaction (PCR)-based microplate hybridization assay, comparing these to peripheral blood lymphocytes (PBL). We considered it important to perform TCR analysis from lung tissue in the earliest stage of IP because TCRs diversify with disease progression due to "determinant spreading" in which autoreactive T-cell responses, initiated by a single antigenic epitope, evolve into multiepitopic responses.

Results: The study with lung tissues of the initial stage of IP demonstrated substantial pulmonary CD3+ predominated T cell infiltrates. In both cases, patient A (early UIP pattern) and patient B (NSIP pattern), most of the mononuclear cells were CD3+ T-cells, accompanied by a subtle infiltration of B-cells (CD20+), and a minimal number of monocytes (CD19+). Of infiltrating T-cells, more CD4+ than CD8+ cells (in the ratio of four to one) were noted in both patients. The usage of repertoires of TCR Vα/Vβ in the lung differed from those in PBL, with certain TCR V gene families detected more frequently in lung tissue, suggesting a pivotal role for T cells in the pathogenesis of IP associated with PM. This is the first robust demonstration of selective TCR repertoire usage and its differential expression in lung tissue

versus PBL. As expected, no TCR signals were detected from non-IP lung tissue controls.

Conclusion: These findings clearly suggest a pathogenic contribution of organ-specific oligoclonal T cell accumulation through antigen-driven immune responses, implying potential elucidation of causative antigens as well as development of immuno-specific treatments such as molecular-targeted therapies.

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Reduction of MAIT Cell Frequency Associated with Reduced Cell Proliferation and Enhanced Cell Death in Systemic Lupus Erythematosus. Asako Chiba, Naoto Tamura, Eri Hayashi, Ran Matsudaira, Yoshinari Takasaki and Sachiko Miyake. Juntendo University School of Medicine, Tokyo, Japan.

Background/Purpose: Mucosal-associated invariant T (MAIT) cells are innate-like lymphocytes which are restricted by the MHC-related molecule-1 (MR1) and express a semi-invariant TCRα chain: Vα7.2-Jα33 in humans and Vα19-Jα33 in mice. MAIT cells uniquely recognize microbial-derived vitamin B metabolites presented by MR1. Like other innate-like lymphocytes, MAIT cells have been suggested to play both proinflammatory and regulatory roles in autoimmune models. Although MAIT cells are rare in mice, human MAIT cells are more abundant and constitute approximately 5% of peripheral blood T cells, suggesting possible roles of MAIT cells in human autoimmune diseases. Previously we have revealed that the frequency of MAIT cells was reduced and reflected the disease activity in multiple sclerosis. In this study, we sought to investigate whether MAIT cells are involved in the pathogenesis of systemic lupus erythematosus (SLE).

Methods: Whole blood samples or peripheral blood mononuclear cells (PBMC) of SLE patients as well as healthy volunteers were stained with anti-human monoclonal antibodies(mAb) against CD3, $\gamma\delta$TCR, Vα7.2TCR, CD161, CD45RA, CCR7, CD69, CD95(FAS) and 7-AAD. MAIT cells were identified as $CD3^+\gamma\delta TCR^-V\alpha7.2TCR^+CD161^{high}$cells by FACS LSR Fortessa. In some experiments, costaining of intracellular active caspase-3 of MAIT cells was performed. MAIT cells and other T cell subsets were single-cell sorted by using FACS Aria II, and the usage of Vα7.2-Jα33 TCR of single-cell sorted cells was examined by PCR. PBMC labeled with Cell Trace Violet Dye were stimulated with anti-CD3mAb and anti-CD28mAb or IL-15, and the cell proliferation was analyzed by FACS.

Results: As previously reported, the frequencies of $\gamma\delta$T cells were slightly reduced in SLE. The percentages of MAIT cells from SLE patients were markedly decreased and about 7-fold lower compared with those from healthy subjects. Single-cell PCR analysis indicated that the decrease of lupus MAIT cells was not a result of downmodulation of surface markers. The proliferative capacity was slightly reduced in lupus MAIT cells. MAIT cells from lupus patients with active disease expressed high levels of CD69, and lupus MAIT cells had higher percentages of FAS^{high} cells, active caspase-3 or 7-AAD positive cells. These result suggest that more MAIT cells are undergoing activation-induced cell death in SLE. Activated MAIT cells failed to expand in a long term culture. Although the frequencies of naïve cells were increased in lupus $\gamma\delta$T cells, most MAIT cells displayed an effector memory phenotype and there was no increase of naïve cells among lupus MAIT cells.

Conclusion: This study demonstrates that the frequency of MAIT cells was significantly reduced in SLE. The increased cell death and reduced cell prolifeation of activated MAIT cells were in part responsible for the decrease of MAIT cells in SLE. The limited recruitment of recent thymic emigrants of naïve MAIT cells also contributed the profound reduction of these cells in SLE.

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To Live or Let Die... the Battle Between PD-1 and OX40 on SLE T Cells. Julie Kristine Laustsen[1], Stinne Greisen[1], Bent Deleuran[2] and Tue Kruse Rasmussen[1]. [1]Aarhus University, Aarhus C, Denmark, [2]Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: Programmed cell death 1 (PD-1) is a co-inhibitory receptor, which inhibits T cell proliferation and survival by inhibiting IL-2 signalling. By this PD-1 has been speculated as a key player in maintaining and restoring self-tolerance. In contrast, OX40 is a surface receptor that induces IL-2R expression and OX40 has been suggested to allow possible autoreactive effector T cells to develop into memory T cells. These two molecules could therefor represent two opposite sides of the balance in immune regulation -a balance crucial for maintaining peripheral tolerance. In systemic lupus erymathosus (SLE) this balance is disrupted, and disease progression is characterized by antibody production and autoreactive lymphocytes. In this study, we investigated cellular expression and soluble (s) levels of PD-1 and OX-40.

Methods: Plasma levels of sPD-1 and sOX40 from SLE patients (n=19) and healthy controls (HCs) (n=18) were quantified by ELISA. PBMCs from SLE patients and HC were stained with monoclonal antibodies against PD-1, OX40, CD4 and CD8. Cells where analyzed by flow cytometry. Skin biopsies from SLE patients and HCs were stained with anti-OX40 and anti-PD-1 antibodies and analyzed by confocal microscope. Statistics were assessed by Mann-Whitney's test, and Spearman's ranked correlation. Data are expressed as median (IQR).

Results: In SLE patients, sPD-1 was significantly increased (445 pg/ml (319 pg/ml – 897 pg/ml)) compared to HCs (244 pg/ml (173 pg/ml – 343 pg/ml), $p<0.001$) and correlated positively with the SLE disease activity score SLEDAI ($\rho=0.69$, $p=0.01$). Soluble OX40 was decreased (7.3 pg/ml (7.3 pg/ml – 16.4 pg/ml)) compared with HC (53,5 pg/ml (41.9 pg/ml – 72.5 pg/ml) $p<0.001$). Furthermore, did levels of sPD-1 and sOX40 inter-correlate positively in SLE patients ($\rho=0.59$, $p= 0.005$), which was not the case in HCs. Co-expression of PD-1 and OX40 was seen on (9.5%) $CD4^+$ T cells in SLE compared with (5.2%) in HCs ($P<0.01$). Immunofluorescence revealed that PD-1 and OX40 co-expressing cells were present in SLE skin, further supporting that the same cell expresses both PD-1 and OX40 (Fig 1).

Conclusion: In this study, we show that T-cells expressing both PD-1 and OX40 are increased in SLE, and that the levels of the soluble isoforms intercorrelate. We also show that sPD-1 correlates strongly with SLEDAI, suggesting sPD-1 as a marker of inflammation in SLE. The observed co-expresssion of the death receptor PD-1 and the survival receptor OX40, could in part explain why autoreactive effector T cells survive, despite receiving apoptosis signals, and help elucidate the lack of self-tolerance in SLE patients.

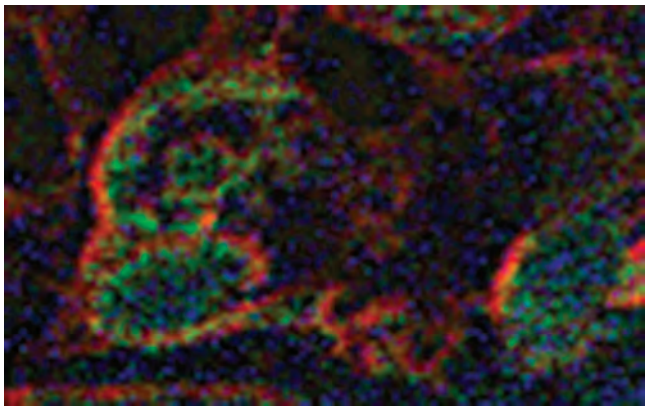

Fig 1: co-expression of PD-1 (green) and OX-40 (red)

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FcγRIIIa Ligation in Human Peripheral $CD4^+$ T-Cells Generate T_H17 like Population. Anil K. Chauhan[1], Terry Moore[2] and Chen Chen[1]. [1]Saint Louis University, St. Louis, MO, [2]St Louis University, Saint Louis, MO.

Background/Purpose: Cytokines produced during T_H17 response, IL-17A and IL17F drive inflammation and autoimmunity. They also act as a bridge between adaptive and innate immunity. Immune deposits are formed in vascular sites in autoimmunity and often demonstrate the excessive presence of immune complexes (ICs) and activated complement products. ICs drive nephropathic changes in SLE. Thus, we examined whether these immune reactants can activate naive $CD4^+$ T-cells to generate T_H17 like cells. Furthermore to elucidate the mechanism by which ICs triggered the generation of T_H17 like population, we also examined the presence of low affinity Fc-receptors on activated naïve $CD4^+$T-cells.

Methods: Naïve $CD4^+CD45RA^+$ T-cells obtained from SLE patients were activated using plate bound ICs (10 mg/ml) and soluble C5b-9 (2.5 mg/ml) in the presence of anti-CD3 (0.25 mg/ml). Post activation cells were cultured in the presence of IL-1β (25 ng) IL-2 (10 ng), IL-6 (50 ng), IL-23 (25 ng), and TGF-β1 (10 ng) in each ml of RPMI. On day 9th culture soups were analyzed for cytokines and flow analysis was performed for IL-17A, IL-17F, IL-21, and IL-22. qRT-PCR was performed for *rorc and ifng* IFN pathway genes were analyzed using qRT-PCR IFN-arrays (Applied Biosystems). Activated cells were analyzed for binding to labeled ICs and expression of *fcgr3a* gene transcripts.

Results and Conclusion: Our results demonstrate that ICs via FcγRIIIa ligation on activated naïve $CD4^+$ T-cells generate T_H17 like population. We observed increased expression of *rorc* transcripts and statistically significant increase in IL-17A, IL-17F, IL-21, and IL-22 in the culture supernatant and an increase in cytokine producing population in flow analysis in response to ICs treatment. In addition IC mediated signal in $CD4^+$ T-cells also generated an IFN-γ^{high+} population. ICs and complement provided a co-stimulatory signal that was strong and divergent from the traditional CD28 co-stimulatory signal. $CD4^+$ T-cells activated using anti-CD3+ICs+C5b-9 induced expression of *fcgr3a* transcripts and membrane FcγRIIIa protein. These activated cells showed statistically significant increase in binding to labeled ICs and AHG in flow analysis. These results for the first time demonstrate a possible role for FcγRIIIa in the generation of T_H17 like cells. Our IFN array analysis also showed increase in type 1 IFN genes. In autoimmune disease a co-operation between type 1 IFNs and T_H17 has been observed. Our data suggest that both of these responses are driven by ICs and complement in $CD4^+$ T-cells. Generation of T_H17 like population and IFN-γ producing cells will contribute to the development of lupus nephritis, which could occur locally in the kidney. These findings are important in that the activating membrane co-stimulatory signal from CD28 and ICOS are counteracted by CTLA4 and PD1 inhibitory signal during immune contraction. An activating signal from ICs and complement in immune contraction can tip the balance in favor of activating signal that may lead to breakdown of peripheral tolreance. Thus the data present identifies a new pathway by which ICs and complement will drive the autoimmune pathology.

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Th1 and Th17 Cytokines Drive Takayasu Arteritis Inflammation. David Saadoun[1], Marlène Garrido[2], Cloé Comarmond[3], Anne-Claire Desbois[4], Fanny Domont[4], Léa Savey[5], Benjamin Terrier[6], Michelle Rosenzwajg[2], David Klatzman[7], Pierre Fourret[8], Philippe Cluzel[9], Laurent Chiche[10], Julien Gaudric[11], Fabien Koskas[12] and Patrice Cacoub[13]. [1]DHU 2iB Internal Medicine Referal Center for Autoimmune diseases Pitie Hospital, Paris, France, [2]UMR 7211, INSERM U959, Hôpital Pitié-Salpêtrière, Paris, France, [3]Internal Medicine and Clinical Imunology, Hôpital Pitié Salpétrière, Paris, France, [4]Hôpital Pitié-Salpêtrière, Internal Medicine and Clinical Immunology, Paris, France, [5]Hôpital Pitié-Salpêtrière, Internal Medicine and Clinical Immunology, P, France, [6]Cochin Hospital, Paris, France, [7]UPMC Université Paris 06, UMR 7211, Paris, France, [8]Hôpital Pitié-Salpêtrière, Anathomopathology, Paris, France, [9]Vascular and Interventional Imaging Department, Paris, France, [10]Vascular Surgery, Paris, France, [11]Department of Vascular surgery GHPS, Paris, France, [12]Assistance Publique-Hôpitaux de Paris, Hopital Pitié-Salpétrière, Paris, France, [13]Groupe Hospitalier Pitié Salpétrière, Service de Médecine Interne, DHU i2B, Paris, France.

Background/Purpose: Takayasu arteritis (TA) is a large-vessel vasculitis inducing damage of the aorta and its branches. Glucocorticoids remain the gold standard of therapy in TA. However, the nature of T cell driving vascular inflammation and the effects of glucocorticoids on the systemic components of TA are not understood.

Methods: T cell homeostasis and cytokines production were analyzed in peripheral blood and aorta inflammatory lesions using Luminex, flow cytometry, and immunohistochemistry analysis. The study included 41 TA patients fulfilling the ACR criteria [17 active (aTA) and 24 in remission (rTA)], 30 giant cell arteritis (GCA) patients (disease control) and 20 age and sex-matched controls.

Results: We first demonstrated the promotion of Th1 and Th17 responses that correlates with TA activity. We determined whether serum from TA patients was able to modulate T cell differentiation in healthy controls. The addition of serum from active TA patients in sorted $CD4^+$ T cells culture of healthy donors induced a significant production of IFN-g and IL-17A. We demonstrated the the strong expression of IFN-g, and IL-6 producing T cells within vascular inflammatory infiltrates of TA. Glucocorticoid therapy were associated to decreased circulating Th1 cytokines with significantly lower IL-2 (mean±SEM; 2812±690.1 vs. 7228±1536 pg/ml, p=0.0196), IFN-g (1437±367.3 vs. 7124±1818pg/ml, p=0.0019) and TNF-a (643.3±106.4 vs. 1438±196.6pg/ml, p=0.01) in steroid treated TA compared to steroid free TA patients, respectively. However, glucocorticoids essentially left unaffected Th17 cytokines (i.e. IL-1b, IL-6, IL-17 and IL-23).

Conclusion: Our data provided the first evidence that Th1 and Th17 immunity seems to be important in driving TA inflammation, both systemically and in the blood vessels. In addition, only one of these pathways was amendable to glucocorticoid-mediated suppression. Glucocorticoids are associated to decrease Th1 cytokines and spared Th17 cytokines in TA.

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Massive Ex Vivo Expansion of Functionally Stable Behcet's Patient-Derived Regulatory T Cell Clones. Johannes Nowatzky, Olivier Manches, Yusuf Yazici and Juan Lafaille. New York University School of Medicine, New York, NY.

Background/Purpose: Adoptive transfer of regulatory T cells (Treg) is a promising strategy for the treatment of human autoimmune diseases. Most currently tested approaches focus on the polyclonal expansion of human thymus-derived Treg (tTreg), and are limited by potentially harmful and efficacy-limiting co-expansion of effector T cells (Teff). We hypothesized that the ex vivo isolation and massive expansion of $CD4^+/CD25^{high}/CD127^{low}/FoxP3^+/Helios^+$ tTreg clones results in maximal purity of the generated cellular product, preserving its suppressor function stability over several re-expansion cycles while yielding cell numbers sufficient for pre-clinical and clinical testing.

Methods: To validate our approach for a human rheumatic disease in which antigen-specific T effector responses have been implicated in target organ damage (uveitis), we chose to identify and expand Behcet's disease patient-derived tTreg clones. $CD4^+/CD25^{high}/CD127^{low}$ T cells were isolated by magnetic bead separation, subsequently cloned in a limiting dilution approach and massively expanded in at least four re-expansion cycles. Suppression was tested in suppression assays of CD3/CD28-stimulated effector T cells at repeated expansion cycles over at least 8 weeks. Clonality was demonstrated by Vβ staining.

Results: Cloning efficiency was 2–5/100 seeded cells. Treg clones were homogeneously $CD4^+/CD25^{high}/FoxP3^+/Helios^+$ and stained positive for one unique TCR Vβ chain. Clones maintained around 80% suppression at 1:4 Treg:Teff ratios over as long as 11 weeks in culture and at least 4 re-expansion cycles. Proliferation was in the 10^8 to 10^9-fold range at day 50. When compared to tTreg clones generated from healthy human donors there were no significant differences in suppressive capacity, suppressor function stability, or phenotype.

Conclusion: Our results suggest that tTreg are not intrinsically dysfunctional in Behcet's disease, and they deliver proof of principle that the massive monoclonal expansion of antigen-specific human Treg clones from patients with a rheumatic disease is possible and yields a functionally stable, ultra-pure cellular product for pre-clinical and clinical testing.

Disclosure: J. Nowatzky, None; **O. Manches**, None; **Y. Yazici**, None; **J. Lafaille**, None.

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Decreased CXCR3+CCR4-CCR6+ CD4+ Effector Memory T Cells in Patients with Granulomatosis with Polyangiitis. Lucas L. Lintermans, Coen A. Stegeman, Abraham Rutgers, Peter Heeringa and Wayel H. Abdulahad. University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: Persistent expansion of circulating $CD4^+$ effector memory T cells (T_{EM}) in patients with Granulomatosis with polyangiits (GPA) suggest their fundamental role in disease pathogenesis. The functional phenotype of these $CD4^+$ T_{EM} cells in GPA-patients is not known. Recent studies have shown that 4 distinct functional subsets of $CD4^+$ T_{EM} cell can be identified based on the expression pattern of the chemokine receptors CXCR3, CRTh2, CCR4, and CCR6. The current study aimed to identify

functionally reported different phenotypes within the expanded $CD4^+$ T_{EM} cell population in peripheral blood of GPA-patients.

Methods: Peripheral blood of 43 GPA-patients in remission and 16 healthy controls (HCs) was stained immediately after blood withdrawal with fluorochrome-conjugated antibodies for cell surface markers (CD3, CD4, CD45RO) and chemokine receptors (CCR4, CCR6, CCR7, CRTh2, CXCR3) followed by flow cytometry analysis. Positively and negatively stained populations were calculated by dot plot analysis, determined by the appropriate isotype controls. Expression patterns of chemokine receptors $CXCR3^+CRTh2^-CCR4^-CCR6^-$, $CXCR3^-CRTh2^+CCR4^+CCR6^-$, $CXCR3^-CRTh2^-CCR4^+CCR6^+$, and $CXCR3^+CRTh2^-CCR4^-CCR6^+$ were used to distinguish Th1, Th2, Th17, and Th1/17 cells, respectively.

Results: The percentage of $CD4^+$ T_{EM} ($CD3^+CD4^+CD45RO^+CCR7^-$) cells was significantly increased in GPA-patients in remission compared to HCs (median 41,93% vs 31,52%). Chemokine receptor co-expression analysis within the $CD4^+$ T_{EM} cell population demonstrated similar percentages of Th1 and Th2 cells between GPA-patients and HCs. Interestingly, the analysis revealed a significant decrease in the frequency of Th1/17 cells (median 9,28% vs 16,53%) with a concomitant significant increase in the Th17 cells (median 21,14% vs 16,93%) in GPA-patients compared to HCs. However, differences between these $CD4^+$ T_{EM} cell subsets were not related to generalized or localized disease, ANCA positivity at the time of inclusion, nor to immunosuppressive treatment regimens.

Conclusion: Based on chemokine receptor co-expression analysis we demonstrate an aberrant distribution in the $CD4^+$ T_{EM} cell compartment in GPA-patients. The identification of different phenotypes within the expanded $CD4^+$ T_{EM} cell population revealed a distinction between Th1/17 cells and Th17 cells. Interestingly, it has been described that the functional and molecular signature of Th1/17 cells is associated with a strong pathogenicity of this subset and may be important in mediating chronic inflammation. Analyzing the migration capacity of Th1/17 cells might reveal their distinct tissue homing characteristic to inflamed lesions in GPA-patients.

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B55β Regulates T Cell Survival through the Modulation of AKT during Cytokine Deprivation. José C. Crispin[1], Sokratis A. Apostolidis[1], Noe Rodriguez Rodriguez[1], Tran Nguyen[1] and George C. Tsokos[2]. [1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [2]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA.

Background/Purpose: The abundance of cytokines controls the length of immune responses through poorly defined mechanisms. B55β is a molecule that triggers apoptosis in activated T cells when cytokine levels decrease. T cells from a subset of patients with systemic lupus erythematosus (SLE) exhibit resistance to apoptosis that is associated to failure to express B55β. The aim of this study was to determine the molecular mechanisms through which B55β controls the survival of activated T cells.

Methods: Most experiments were performed in human primary T cells obtained from healthy donors. MCF7 cells were used in some experiments. T cells were activated with anti-CD3 and anti-CD28 (1 μg/mL). After day 3, fresh RPMI and IL-2 (100 U/mL) were replenished every 48 hours. Apoptosis was induced at day 10 by transferring the cells to fresh RPMI devoid of IL-2, in the presence of IL-2 blockade (anti-human IL-2). Apoptosis was quantified by flow cytometry (Annexin V/ propidium iodide staining). Forced expression and knockdown of B55β was induced by transducing activated T cells with lentiviruses encoding human B55β or B55β-specific shRNAs, respectively. Protein phosphorylation status was assessed by flow cytometry and Western blotting. Induction of pro-apoptotic genes was quantified by real time PCR.

Results: Maximal expression of B55β (protein) was reached after 2 hours of IL-2 deprivation. This induction was associated to dephosphorylation of AKT S473 and T308 that occurred 4 hours after IL-2 withdrawal. IL-2 deprivation-induced AKT dephosphorylation was abrogated in T cells infected with lentivirus encoding B55β-specific shRNA. Accordingly, apoptosis was significantly reduced by B55β knockdown. Complementary experiments showed that forced expression of B55β caused apoptosis of activated T cells that was associated to dephosphorylation of AKT S473. Simultaneous forced expression of AKT annulled apoptosis induced by B55β indicating that B55β induces cell death through inactivation of AKT. To determine the effects of IL-2 deprivation on the PI3K-AKT-mTOR axis, we assessed the phosphorylation status of 18 members of the pathway using an intracellular signaling array. The results confirmed that AKT is dephosphorylated by IL-2 deprivation but that the pathway is not uniformly downregulated. mTORC1 and its substrates were mostly not affected whereas other AKT substrates, in particular the pro-apoptotic protein Bad and the transcription factors FoxO1 and 3a, were activated by dephosphorylation. Accordingly, induction of pro-apoptotic genes regulated by FoxO factors was observed. Further experiments confirmed that B55β overexpression activates the FoxO factors inducing the upregulation of pro-apoptotic genes, in particular Noxa, Puma and HRK.

Conclusion: B55β is a key regulator of AKT. Upon its induction by IL-2 deprivation, it causes AKT dephophorylation triggering programmed cell death through the induction and activation of the BH3-only pro-apoptotic proteins Bad, Noxa, Puma, and HRK. Our results demonstrate a novel mechanism of how AKT is regulated in activated T cells in response to cytokine abundance.

Disclosure: J. C. Crispin, None; **S. A. Apostolidis**, None; **N. Rodriguez Rodriguez**, None; **T. Nguyen**, None; **G. C. Tsokos**, None.

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Association of a-Kinase Anchoring Protein-79 (AKAP79) to PKC Mediates Inhibition of IL2 Transcription and Erk Activation in T Cells. Gabriel Criado, María J. Pérez-Lorenzo, María Galindo, Jose L. Pablos and Abel Suarez-Fueyo. Instituto de Investigación Hospital 12 de Octubre (I+12), Madrid, Spain.

Background/Purpose: A-Kinase anchoring Protein AKAP79 associates to and regulates the activity of PKA, PKC and calcineurin, key regulators of T cell activation. We have previously described that AKAP79 is overexpressed in T cells from systemic lupus erythematosus lupus patients and inhibits IL2 transcription in Jurkat T cells (Criado et al., A&R 63 (Suppl10): S916). In the present study, we aim to analyze the effect of AKAP79 levels on IL2 production in SLE and normal T cells and characterize the role of the associations to PKA, PKC and calcineurin in T cell activation and IL2 transcription.

Methods:T cells were isolated by negative selection from SLE patients and healthy controls (HC). RNA was purified, retrotranscribed to cDNA and levels of AKAP79 and β-actin transcripts were quantified by quantitative real-time PCR using Sybr Green technology. AKAP79 protein expression was quantified in T cell lysates by ELISA. AKAP79 mutants deficient for association to PKA (ΔPKA-AKAP79), PKC (ΔPKC-AKAP79) and calcineurin (ΔCN-AKAP79) were generated with QuickChange Site Directed Mutagenesis kit and confirmed by sequencing. Jurkat T cells were transduced with dual promoter pRRL-AKAP79/GFP- or control pRRL-GFP-expressing lentiviruses. For functional assays, T cells were stimulated with plate-bound anti-CD3 and soluble anti-CD28 antibodies or PMA/ionomycin. RNA was isolated, IL2 transcripts quantified by quantitative real-time PCR (qPCR) and results calculated as fold change over non-stimulated cell (Mean +/− SEM). Statistical differences between groups were analysed by ANOVA and non-parametric Mann-Whitney U test, using GraphPad Prism software.

Results: IL2 transcription induced by anti-CD3/CD28 stimulation was not significantly different between SLE (n=6) and HC (n=6) T cells. However, a negative correlation between levels of AKAP79 protein and induction of IL2 transcription was found in T cells, regardless of their origin (R^2= 0.53, **p=0.0076). This was confirmed in Jurkat T cells by transduction with different amounts of AKAP79 (R^2= 0.57, *p=0.03, n= 8). Complementation of anti-CD3/CD28 stimulation by PMA, but not ionomycin, restored IL2 transcription in Jurkat cells overexpressing AKAP79, suggesting that inhibition of PKC by AKAP79 was responsible for the observed reduction of IL2 transcription. Consistent with this interpretation, overexpression of ΔPKC-AKAP79 partially rescued IL2 transcription when compared to WT-AKAP79 but ΔPKA-AKAP79 and ΔCN-AKAP79 had no significant effect (GFP: 11.59 +/− 2.21, AKAP79: 1.67 +/− 0.61, ΔPKC-AKAP79: 4.86 +/− 1.24, ΔPKA-AKAP79: 0.73 +/− 0.29, ΔCN-AKAP79: 0.88 +/− 0.35). Likewise, analysis of the kinetics of Erk activation in response to antiCD3/CD28 showed that Erk activation was blocked by AKAP79 overexpression and was recued by ΔPKC-AKAP79.

Conclusion: Overexpression of AKAP79 inhibits IL2 transcription and Erk activation in a PKC-dependent manner. Thus, targeting AKAP79-PKC interaction could provide a therapeutic approach to modulate T cell activation.

Disclosure: G. Criado, None; **M. J. Pérez-Lorenzo**, None; **M. Galindo**, None; **J. L. Pablos**, None; **A. Suarez-Fueyo**, None.

2736

Female Specific Increase in T Cell Glycosylation in Lupus. Gabriela Gorelik and Bruce Richardson. University of Michigan, Ann Arbor, MI.

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune inflammatory disease characterized by altered T cell signaling. SLE is characterized by epigenetic mechanisms that cause hypomethylation of the inactive X-chromosome predisposing females to the disease, and a global T cell DNA hypomethylation, which causes overexpression of immune-related genes.

OGT (O-linked N-acetylglucosamine transferase) is an X-linked gene overexpressed in female lupus T cells. OGT causes posttranslational modifications to proteins by adding β-N-acetyl-glucosamine (O-GlcNAc) to Ser or Thr residues in competition with phosphorylation. OGT mRNA and protein levels and O-GlcNAc-modified proteins are increased in CD4+ experimentally demethylated T cells and in T cells from active women with lupus.

Recent evidence shows that OGT plays a critical role in chromatin structure through O-GlcNAcylation of histones *in vivo* and *in vitro*, and GlcNAc is considered now part of the histone code.

Hypothesis: OGT overexpression in female lupus alters T cell signaling affecting posttranslational modifications of histones, thereby regulating chromatin remodeling and modifying gene expression.

Methods: PBMC from healthy donors were PHA-stimulated and treated with 5-azaC for 72 h. Then CD4+ T cells were isolated by negative selection and stimulated with PMA/Ionomycin for 6 h. T cells from lupus patients were activated with PMA/Ionomycin for 6 h. Cell fractions were obtained by using a nuclear extract kit (Active Motif) and the chromatin-bound proteins were isolated from the insoluble nuclear fraction. Subcellular fractions were subjected to SDS-PAGE gel electrophoresis followed by immunoblot. To detect glycosylated proteins we used CTD110.6 antibody (Abcam) and histone glycosylation was specifically detected by using anti-Histone H2B (glcnac S112) antibody (Abcam). T cells were nucleofected with 2μg of OGT siRNA using a nucleofector device (Amaxa).

Results: OGT and GlcNAcylated protein levels were increased in the nuclear fraction which correlates with translocation of OGT to the nucleus after lymphocyte activation, and the increment was higher in experimentally demethylated T cells, (OGT: $p=0.047$ control vs 5-AzaC T cells; GlcNAcylated proteins: $p=0.047$ control vs 5-AzaC T cells). OGT levels in T cells from males did not show any significant difference regardless of the treatment and/or cell fraction. We also found OGT bound to chromatin-bound proteins. H2B was GlcNAcylated at Ser112 in T cells and increased in women patients with active lupus with respect to healthy female donors (mean $\pm$ SEM: 2.85 ± 0.95; $p<0.05$ vs healthy donors; $n=3$). Histone glycosylation was inhibited in T cells transfected with OGT siRNA by $81 \pm 11\%$, indicating the specificity of the effect.

Conclusion: These results support our hypothesis that OGT overexpression in lupus T cells causes modifications in histone glycosylation that may result in altered gene expression.

Disclosure: G. Gorelik, None; **B. Richardson**, None.

2737

Microrna-155 Suppresses IL-21 Signaling and Production in Systemic Lupus Erythematosus. Tue K. Rasmussen[1], Thomas Andersen[1], Rasmus Bak[1], Gloria Yiu[2], Kristian Steengaard-Petersen[3], Jacob G. Mikkelsen[1], Paul J. Utz[2], Christian Holm[1] and Bent Deleuran[3]. [1]Aarhus University, Aarhus C, Denmark, [2]Stanford University School of Medicine, Stanford, CA, [3]Aarhus University Hospital, Aarhus, Denmark.

Background/Purpose: IL-21 is a key regulator of B cells functions and autoantibody production and is mainly produced by follicular T helper cells. The purpose of this study is to investigate the signaling capacity of interleukin (IL)-21 in T and B cells and assess its possible regulation by microRNA-155 and its target gene suppressor of cytokine signaling 1 (SOCS1) in systemic lupus erythematosus (SLE).

Methods: The signaling capacity of IL-21 was quantified by stimulating PBMCs with IL-21 and measuring phosphorylation of (p)STAT3 in CD4+ T cells, B cells, and NK cells. Induction of miR-155 by IL-21 was investigated by stimulating purified CD4+ T cells with IL-21 and measuring miR-155 expression levels. The functional role of miR-155 was assessed by overexpressing miR-155 in PBMCs from SLE patients and HCs and measuring its effects on STAT3 and IL-21 production in CD4+ and CD8+ T cells.

Results: Induction of pSTAT3 in CD4+ T cells in response to IL-21 was significantly decreased in SLE patients compared to HCs ($p<0.0001$). Further, expression levels of miR-155 were significantly decreased and SOCS1 correspondingly increased in CD4+ T cells from SLE patients. Finally, overexpression of miR-155 in CD4+ T cells increased STAT3 phosphorylation in response to IL-21 treatment ($p<0.01$) and differentially increased IL-21 production in SLE patients compared to HCs ($p<0.01$).

Conclusion: We demonstrate that SLE patients have reduced IL-21 signaling capacity, decreased miR-155 levels, and increased SOCS1 levels compared to HCs. The reduced IL-21 signaling in SLE could be rescued by overexpression of miR-155, suggesting an important role for miR-155 in the reduced IL-21 signaling observed in SLE.

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2738

Shk-186, a Kv1.3 channel inhibitor That Targets Effector Memory T Cells: Safety and Tolerability in Humans and Its Evaluation in a Model of Rapidly Progressive Glomerulonephritis. Ernesto J. Muñoz-Elías[1], Kayla Norton[1], John B. Grigg[1], Liz Bromley[1], David W. Peckham[1], Eric J. Tarcha[1], Jared Odegard[2], James Qin[2], Megan Yuasa[3], Anne Stevens[4], Wayel H. Abdulahad[5], Galina Schmunk[6], K. George Chandy[6] and Shawn P. Iadonato[1]. [1]Kineta Inc., Seattle, WA, [2]Benaroya Research Institute at Virginia Mason, Seattle, WA, [3]Seattle Children's Research Institute, Seattle, WA, [4]Seattle Children's Hospital, Seattle, WA, [5]University Medical Center Groningen, Groningen, Netherlands, [6]UC Irvine, Irvine, CA.

Background/Purpose: The voltage-gated potassium channel Kv1.3 is a novel target for the treatment of autoimmune disorders including psoriatic and rheumatic diseases. ShK-186 is an exquisitely specific, highly potent peptide inhibitor of Kv1.3 on activated effector memory T cells that has just entered clinical development. Here, we report on ShK-186's safety and tolerability in phase I trials and on the evaluation of its therapeutic potential in an autoimmune kidney disease model.

Methods: To evaluate the safety, tolerability and pharmacokinetics (PK) of ShK-186, we conducted single ascending dose and multiple ascending dose doubled-blind, placebo-controlled phase I trials in healthy volunteers. In the single ascending dose trial, individuals were given increasing doses of ShK-186 subcutaneously and characterized after a single dose of drug; in the multiple ascending dose trial, individuals were given 9 doses of drug twice weekly over 4 weeks and characterized throughout. To investigate ShK-186's potential therapeutic application in autoimmune kidney disease, we evaluated the drug in a glomerular basement membrane animal model of autoimmune glomerulonephritis. Moreover, we have begun evaluating peripheral blood and urine samples from patients with autoimmune kidney disease for expression of Kv1.3 and production of cytokines in the presence and absence of ShK-186.

Results: ShK-186 was well tolerated with no serious adverse events reported. PK analysis revealed that the doses and dose regimens evaluated provided drug exposure in plasma surpassing the predicated therapeutic range based on therapeutic drug exposures in preclinical models of disease. Supporting the therapeutic potential of ShK-186 to treat chronic autoimmune kidney diseases, we showed that ShK-186 could lower kidney disease parameters such as urine protein and creatinine in a model of autoimmune glomerulonephritis, as well as significantly reduced histopathological changes associated with disease such as crescent formation and inflammatory cellular infiltrate. *Ex vivo*immunophenotyping and functional studies of blood and urine from autoimmune kidney disease patients showed that Kv1.3 is present in effector memory T cells.

Conclusion: This first-in-human clinical trial suggests that ShK-186 is a well-tolerated drug when given at doses expected to provide a therapeutic benefit. In addition to previously described indications where Kv1.3 has been implicated including multiple sclerosis and rheumatoid arthritis, we provide evidence to support extending its therapeutic scope to the treatment of chronic kidney autoimmune diseases.

Disclosure: E. J. Muñoz-Elías, Kineta Inc, 3; **K. Norton**, Kineta Inc, 3; **J. B. Grigg**, Kineta Inc, 3; **L. Bromley**, Kineta Inc, 3; **D. W. Peckham**, Kineta Inc., 3; **E. J. Tarcha**, Kineta Inc, 3; **J. Odegard**, None; **J. Qin**, None; **M. Yuasa**, None; **A. Stevens**, None; **W. H. Abdulahad**, None; **G. Schmunk**, None; **K. G. Chandy**, Kineta Inc., 1; **S. P. Iadonato**, Kineta Inc, 3.

2739

SHP-1 Regulates the Activation Threshold of iNKT Cells. Meng Zhao[1] and Mitchell Kronenberg[2]. [1]UC-San Diego, La Jolla, CA, [2]La Jolla Institute for Allergy and Immunology, La Jolla, CA.

Background/Purpose: Autoreactive invariant Natural Killer T (iNKT) cells have been implicated in several rheumatic diseases, including Systemic lupus erythematosus and Rheumatoid arthritis. iNKT cells are a unique subgroup of lymphocytes that recognize glycolipids presented by CD1d, and that express an invariant T cell Ag receptor (TCR) a chain. As a result of activation, iNKT cells secrete copious amount of cytokines, including IFNγ, IL-4, IL-17 and IL-21 and they mediate immune responses in various pathological conditions. Although several potential lipid self-antigens for iNKT cell development and activation have been identified, the mechanism by which iNKT cells react to CD1d-self-antigen is not understood yet. Our discoveries therefore will help identify novel drug targets for potential translational intervention in patients with SLE, RA and other autoimmune diseases in which abnormal activation of iNKT cells is observed.

Methods: In detecting autoreactivity, instead of iNKT cell hybridomas that have many limitations, we will use primary cultured mouse iNKT cells. Sorted as αGalCer-CD1d tetramers$^+$ TCRb$^+$, iNKT cells grow exponentially *in vitro*, and can be transduced by retroviruses in order to modulate differential expressions of important regulators. Microarray was carried out to identify new regulators of iNKT cell autoreactivity.

Results: Our data show that the cultured iNKT cells have a greatly increased sensitivity to CD1d-lipid complexes derived from multiple sources, including soluble CD1d molecules produced in insect or mammalian cells, CD1d transfected cultured cells, and bone marrow-derived DCs. APCs that express a tail-deleted form of CD1d have a strongly diminished ability to stimulate the iNKT cell lines, indicating that the lines, like their primary cell counterparts *in vivo*, recognize auto-Ags loaded onto CD1d in endo/lysosomal compartments. Our results show that the iNKT cell lines preferentially respond to the auto Ags described previously when compared to the closely related homologs, despite their very different structures. Microarrays comparing the expression profiles of cultured and freshly isolated iNKT cells identifies SHP1/PTPN6, a tyrosine phosphatase that regulates TCR signaling, is down regulated in the iNKT cell lines. Reconstitution of the lines with the wild type but not the catalytically inactive SHP1 decreases the auto reactivity of the iNKT cell lines.

Conclusion: We hypothesize that iNKT cell TCR is intrinsically autoreactive, and instead of requiring a special autoantigens, many autologous Ags are capable of stimulating iNKT cells. The threshold of activation for iNKT cells are controlled during development and immune responses through key regulators, so that in the situation when this threshold is lowered, iNKT cells are activated by common lipid antigens that are present in the DP thymocytes or APCs. In the present study, taking advantage of a new system, we show the autoreactivity of polyclonal iNKT cells and we discover the protein tyrosine phosphatase SHP-1 (Ptpn6) is a critical regulator of the activation threshold of iNKT cells.

Disclosure: M. Zhao, None; **M. Kronenberg**, None.

2740

Microbiota Modulate Intraepithelial Lymphocyte Presence and Function. Kristine A. Kuhn and Sean P. Colgan. University of Colorado School of Medicine, Aurora, CO.

Background/Purpose: Microbiome studies in autoimmune diseases including rheumatoid arthritis and inflammatory bowel disease demonstrate alterations in relative abundance of specific bacterial species (dysbiosis). The immunologic influence of dysbiosis is only now being appreciated as important in disease pathogenesis. As intraepithelial lymphocytes (IELs) are anatomically positioned in intimate association with epithelial cells, it is intriguing to consider how the commensal flora might impact IEL function. In contrast to IELs of the small intestine, which have been better studied, the role of IELs in the colon during health and disease remains unclear.

Methods: Epithelial cells were harvested from wild type C57Bl/6 mice, lymphocytes stained for T cell surface markers, and cells evaluated by flow cytometry. IELs were also magnetically sorted from the epithelial cell harvest and stimulated ex vivo for five hours with PMA and ionamycin. Then IEL RNA was purified and analyzed by qRT-PCR. To model dysbiosis, mice were treated with 1 mg/ml ampicillin, metronidazole, and neomycin and 0.5 mg/ml vancomycin in the drinking water for one week. Recolonization of mice occurred by cohousing antibiotic treated mice with unmanipulated littermates. Trafficking of IELs was studied using the KiKGR transgenic mouse in which violet light exposure via colonoscopy photoconverts green fluorescent cells to red.

Results: Our studies demonstrate that the major subpopulation of IELs in the colon (52%) is CD3+ CD4- CD8- TCRβ+ (versus the small intestine where 72% are CD3+ CD8$\alpha\alpha$+ TCR$\gamma\delta$+). These colonic double negative IELs express cell surface markers consistent with activated lymphocytes (CD44+ CD69+ CD62L-) and produce a balance between inflammatory and regulatory cytokines. We next aimed to understand the role of colonic microbiota in shaping this population of cells. Treatment of mice with broad-spectrum antibiotics significantly decreased the number of IELs and shifted cytokine expression to a more pathogenic phenotype. Not only did the number of mature, activated T cells significantly decrease by about 75%, but also the remaining IELs expressed significantly more IL-17 (nearly 70-fold higher) in the antibiotic treated mice compared to untreated controls. The impact of antibiotics was reversible, as recolonization of mice resulted in normalization of the IEL numbers, phenotype, and cytokine expression. Finally, using a transgenic mouse in which colonoscopy-guided green-to-red photoconverstion labels IELs in the distal colon, we demonstrate that IELs traffic to extraintestinal sites, including the spleen, lung, and liver.

Conclusion: These data strongly support our hypothesis that colonic microbiota dynamically influence IEL function which, in turn, influences downstream systemic immune responses. By understanding the development and function of colonic IELs in health and disease, we hope to identify a potential pathway for the development of autoimmunity.

Disclosure: K. A. Kuhn, None; **S. P. Colgan**, None.

2741

The Role of Fli1 in Lupus T Cell Function and Nephritis. Thirumagal Thiyagarajan[1], Ivan Molano[1] and Tamara K. Nowling[2]. [1]Medical University of South Carolina, Charleston, SC, [2]Medical University of South Carolina and Ralph H. Johnson VA Medical Center, Charleston, SC.

Background/Purpose: The Ets factor Fli1 is implicated as a key modulator of lupus disease expression. Over-expressing Fli1 in healthy mice, results in the development of an autoimmune kidney disease similar to that observed in lupus. Lowering the global levels of Fli1 in two lupus mouse models significantly improved kidney disease and prolonged survival. Lowering the levels of Fli1 in hematopoietic cells in MRL/lpr lupus mice resulted in significantly improved kidney disease. We recently demonstrated that lowering the global levels of Fli1 in the MRL/lpr lupus model has specific effects on T cells, including reducing their activation and IL-4 production when stimulated through the T cell receptor. We further showed that this was likely a result of decreased glycosphingolipid (GSL) metabolism, specifically decreased Neuraminidase1 (Neu1) expression and activity and decreased lactosylceramide (LacCer) in T cells. GSLs are a heterogeneous class of lipids in the sphingolipid family that play a role in the regulation of cellular processes. LacCer is a GSL to which sialic acid residues are added by ganglioside synthases to generate gangliosides in the GSL synthesis pathway. Sialic acids are then removed by NEUs from gangliosides in the GSL catabolic pathway. Lipids with distinct chain lengths are thought to possess distinct biological activities. We now demonstrate that lowering Fli1 levels significantly decreases the number of CXCR3+ T cells, T cell migration to the kidney and GSL metabolism in the kidney of MRL/lpr lupus prone mice.

Methods: Kidney and/or spleen were harvested from 11, 14 and 18 week-old MRL/lpr Fli1+/+ and Fli1+/− mice. Kidneys and/or T cells isolated from spleen by negative selection were analyzed by flow cytometry. Supercritical Fluid Chromatography coupled with tandem mass spectrometry was performed on kidney cortex homogenates. Gene expression was analyzed by real-time RTPCR on RNA isolated from kidney cortex. Matrix-assisted laser desorption/ionization-imaging mass spectrometry (MALDI-IMS) imaging and immunohistochemistry (IHC) for LacCer was performed on frozen kidney sections.

Results: LacCer levels, which are elevated in the kidneys of MRL/lpr mice compared to controls, are significantly reduced by 50% in age-matched MRL/lpr mice that are heterozygote for Fli1 (Fli1+/−). This reduction in LacCer expression is observed across the kidney using MALDI-IMS. Although Neu1 expression and NEU activity is decreased in T cells, their levels are unchanged in the kidney of Fli1+/− compared to Fli1+/+ MRL/lpr mice. The percentage of T cells expressing CXCR3 is significantly reduced by ~30% in Fli1+/− compared to Fli1+/+ MRL/lpr mice and the percentage and overall number of T cells in the kidney are significantly reduced by ~50%.

Conclusion: Our results demonstrate that one mechanism by which reducing Fli1 levels may be protective in lupus kidney disease is to decrease GSL metabolism in T cells, reducing T cell activation, production of IL-4, expression of CXCR3, a receptor shown to be important in T cell migration

to the kidney in lupus, and migration to the kidney. This likely contributes to the decreased inflammation and GSL metabolism in the kidney and improved kidney disease of MRL/lpr Fli1+/− mice.

Disclosure: T. Thiyagarajan, None; **I. Molano**, None; **T. K. Nowling**, None.

2742

Polymorphisms in the Slam Family of Molecules Play a Role in the Development and Function of Invariant Natural Killer T Cells in New Zealand Black Mice. Yuriy Baglaenko[1], Kieran Manion[1], Nan-Hua Chang[2] and Joan E. Wither[3]. [1]University of Toronto, Toronto, ON, [2]Toronto Western Research Institute, Toronto Western Hospital, Toronto, ON, [3]Toronto Western Research Institute, Toronto Western Hospital, University of Toronto, Toronto, ON.

Background/Purpose: The family of signaling lymphocyte activating molecules (SLAM) have been shown to play a key role in the development of autoimmunity in spontaneous and induced mouse models. Previous work by others has shown that expression of two SLAM family members, CD150 and Ly108, plays a critical role in the development of Natural Killer T (NKT) cells, an innate-like semi-invariant population of lymphocytes, which quickly respond to lipids presented on non-classical MHCs. However, the impact of SLAM polymorphisms on NKT function is less clear. **The aim of this study was to characterize both the development and function of NKT cells in B6 congenic mice with an NZB chromosome 1 interval that is known to have polymorphisms in the SLAM family of molecules.**

Methods: NKT development and marker expression were examined by flow cytometry of *de novo* splenocytes and thymocytes. NKT cell function was examined by *in vivo* stimulation with 2μg of αGalCer, injected intravenously. Production of IFNγ and IL-4 was measured by intracellular flow cytometry. Bone marrow derived dendritic cells (BMDCs) were generated by 7–10 day culture with recombinant human FLT3 ligand.

Results: Congenic mice had significantly fewer splenic NKT cells when compared to B6 controls. However, NKT cell frequencies in the thymus did not differ. The frequency of double positive thymocytes, critical for homotypic interactions between NKT cell precursors, was also unchanged. In support of previous findings, cell surface expression of SLAM family members on this cell population was altered. When compared to control animals, NZB congenic mice had significantly decreased expression of positive signaling Ly108 and CD150 molecules and increased expression of the negative SLAM signaling molecule, Ly9. Since NKT cells have been shown to play a role in autoimmunity through production of cytokines such as IL-4 and IFNγ, the capacity of these cells to secrete cytokines was assessed. Upon stimulation with αGalCer, the prototypic NKT cell stimulating lipid, NKT cells from NZB congenic mice produced significantly less IL-4 and IFNγ when compared to control mice. Consistent with this being the result of the SLAM polymorphisms, analysis of subcongenic NZB strains with shorter chromosome 1 intervals revealed that both of these phenotypes localized to a small region between 171–177Mb containing the SLAM family. To determine whether the reduced NKT cytokine production in NZB congenic mice was due to altered antigen presentation or impaired NKT cell function, adoptive transfer experiments were conducted with αGalCer pulsed BMDCs from control or congenic mice. The results revealed that injection of BMDCs generated from either strain could equivalently stimulate IL- 4 and IFNγ production by NKT cells in control animals, whereas injection of control BMDCs into NZB congenic mice resulted in impaired production of these cytokines.

Conclusion: These data suggest that polymorphisms in the SLAM family result in reduced peripheral NKT cell numbers and an intrinsic NKT cell functional defect.

Disclosure: Y. Baglaenko, None; **K. Manion**, None; **N. H. Chang**, None; **J. E. Wither**, None.

2743

CD27 Is a Key Regulator of T Cell Responses. Michael Scully[1], Nicole Wunderler[2], Holger Babbe[1], Yevgeniya Orlovsky[1], Galina Obmolova[2], Ann Cai[1], Heath Guay[3], Jacqueline Benson[3] and Tatiana Ort[1]. [1]Immunology Research, Janssen Research and Development, LLC, Spring House, PA, [2]Janssen Research and Development, LLC, Spring House, PA, [3]Estrela Lupus Venture, Janssen Research and Development, LLC., Spring House, PA.

Background/Purpose: CD27 is a member of the TNF superfamily of receptors that is expressed on a majority of natural killer (NK) cells, T cells, memory B cells and antibody-secreting plasma cells in humans. CD70 is the only known ligand for CD27 and is transiently expressed on activated dendritic cells, B cells and T cells. Much of our understanding of the immunological role of CD27 comes from studies with mouse models, which suggest that CD27 is a key regulator of NK cell, T cell and B cell responses. Here, we used an in-house generated neutralizing, antagonistic antibody to evaluate the role of CD27 in regulating human and primate immune responses using in vitro and in vivo models.

Methods: To examine the role of CD27 in immune cell biology, we generated a neutralizing, antagonistic and non-depleting human anti-human CD27 antibody. To assess the contribution of CD27 signaling to human immune responses in vitro, we examined the effects of CD27 blockade on Ig-production by B cells, proliferation of naive $CD4^+$ T cells and cytokine production by healthy volunteer PBMCs in vitro. To understand the role of CD27 on immune responses in vivo, we examined the effects of CD27 blockade on T and B cell responses in a cynomolgus monkey Delayed Type Hypersensitivity (DTH) model. To further explore the contribution of CD27 to human T cell responses in vivo, we examined the effects of CD27 blockade on human T cell engraftment in the NSG (NOD/SCID IL-2R$\gamma^{-/-}$) human $CD45^+$ peripheral blood cell → mouse GVH model.

Results: We found that neutralizing the CD27 pathway inhibited CD70-induced Ig-secretion by activated human B cells, whereas blockade of CD27 in an autologous T cell:B cell co-culture model did not impact Ig-secretion in vitro (despite expression of CD70 on cells in this system). Treatment with an anti-CD27 antibody dose-dependently attenuated CD70-mediated induced proliferation of primary human $CD4^+$ T cells and decreased the production of pro-inflammatory cytokines by healthy control PBMCs in vitro. Treatment with an anti-CD27 antibody reduced human $CD45^+$ $CD4^+$ and $CD8^+$ cell numbers in the spleen and peripheral blood of host mice in the human cell → NSG mouse GVH model. Blockade of CD27 reduced T cell infiltration into the challenge site in response to a neo-antigen, but did not impact antigen-specific antibody titers in a cynomolgus monkey DTH model.

Conclusion: These data demonstrate that CD27 can promote Ig-production by human B cells, but may play a redundant role in some types of B cell responses. In contrast, CD27 appears to play a critical role in the generation of both $CD4^+$ and $CD8^+$ T cell responses. These data suggest that the CD27 pathway modulates the activity of multiple human immune cell types, and that blockade of the CD27 pathway may present a novel therapeutic strategy for the treatment of immune mediated diseases.

Disclosure: M. Scully, Janssen Research and Development, 3; **N. Wunderler**, Janssen Research and Development, 3; **H. Babbe**, Janssen Research and Development, 3; **Y. Orlovsky**, Janssen Research and Development, 3; **G. Obmolova**, Janssen Research and Development, 3; **A. Cai**, Janssen Research and Development, 3; **H. Guay**, Janssen Research and Development, 3; **J. Benson**, Janssen Research and Development, LLC., 3; **T. Ort**, Janssen Research and Development, 3.

ACR/ARHP Poster Session C
Vasculitis
Tuesday, November 18, 2014, 8:30 AM–4:00 PM

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Mi-RNA Profile of Active Vascular BEHÇET'S Patients. Ahmet Mesut Onat[1], Ozan Gerenli[2], Bunyamin Kisacik[1], Mustafa Ulasli[2], Gezmis Kimyon[1], Yavuz Pehlivan[3] and Serdar Oztuzcu[2]. [1]Gaziantep University School of Medicine, Gaziantep, Turkey, [2]Gaziantep UniversitySchool of Medicine, Gaziantep, Turkey, [3]Uludag University, School of Medicine, Bursa, Turkey.

Background/Purpose: Behçet's Disease (BD) is a systemic vasculitis that predominantly presented with oral aphtous ulcers and additionally at least two of the following findings like genital ulcers, eye involvement, skin lesions and pathergy reaction. Vascular involvement is devastating face of BD and thrombosis of the arterial and venous system and aneurismatic arterial disease is not rare. The flares are the typical nature of BD and the pathology of the disease is mostly constructed on vasculitis. However the satisfied mechanism of BD remains unknown. We herein tried to evaluate the micro RNA (miRNA) behavior in BD.

Methods: Eighty-five BD patients were enrolled in to the study group, which were divided to 3 groups of 20–20 and 25 with active vascular disease, active mucocutaneous disease and patients with at least 6 months remission, respectively. Additional 25 volunteers were the healthy controls and the 4 of the groups have no difference in the characteristics. The whole study population was male, due to difficulties of finding active women BD patients.

Serum samples were analyzed for miRNA with PCR assay and the data were analyzed statistically. Active vascular patients had significantly higher CRP and ESR results than active mucocutaneous ones and they both had significantly higher levels than remission and healthy groups.

	Active vasculer BD	Active mucocutaneous BD	Remission BD	Healthy controls
Age	32.60 ± 4.57	32.60 ± 6.36	35.72 ± 9.21	32.20 ± 1.71
Disease duration	4.30 ± 2.71	4.25 ± 3.31	4.68 ± 3.21	
CRP (mg/l)	29.35 ± 36.47	22.53 ± 21.38	4.92 ± 3.11	3.1 ± 1.8
ESR (/hour)	34.90 ± 26.46	30.0 ± 24.03	15.56 ± 11.85	10.02 ± 4.21

Results: There was no difference for any miRNA between BD patients with remission and healthy controls. The comparison of active BD patients and healthy controls revealed lower levels of miR-17-5p, miR-451A, miR-106b-5p, miR-16-5p, miR-19b-3p, miR-26b-5p, miR-93-5p, miR-20b, miR-25-3p in the disease activity. miR26b-5p was found lower only in mucocutaneous group inspite of vasculars.

Conclusion: The miRNA profile of active BDs especially the vascular group was remarkable. These miRNAs were related mainly with T and B lymphocytes and some apoptotic genes. miRNA studies might be beneficial for detecting better targets for treating the disease in the future.

Disclosure: A. M. Onat, None; **O. Gerenli**, None; **B. Kisacik**, None; **M. Ulasli**, None; **G. Kimyon**, None; **Y. Pehlivan**, None; **S. Oztuzcu**, None.

2745

Plasma of Patients with Active Behçet′s Disease (BD) Increases Neutrophil Extracellular Trap Formation, Oxidative Metabolism and NADPH-Oxidase Expression in Normal and BD Neutrophils, and Carries Several Neutrophil Stimulating Factors. Sandro F. Perazzio[1], Paulo Vitor Soeiro Pereira[2], Alexandre W. S. de Souza[3], Antonio Condino-Neto[2] and Luis Eduardo C. Andrade[3]. [1]Fleury Medicine and Health, Sao Paulo, Brazil, [2]ICB IV - Universidade de São Paulo, São Paulo, Brazil, [3]Escola Paulista de Medicina - Universidade Federal de São Paulo, Sao Paulo, Brazil.

Background/Purpose: Plasma factors seem to play a role in Behçet's disease (BD) pathogenesis, especially by increasing phagocyte oxidative profile. No data exists regarding neutrophil extracellular trap (NET) formation. We investigate the effect of plasma from patients with active BD (aBD) and inactive BD (iBD) on NET formation and oxidative burst, and searched for candidate soluble factors.

Methods: Neutrophils, peripheral blood mononuclear cells (PBMC) and plasma were obtained from patients with aBD (n=30), iBD (n=31), and healthy controls (HC; n=30). H_2O_2 and O_2^- production was determined by luminol/lucigenin luminescence with or without stimulation with phorbol myristate acetate (PMA), *Streptococcus pneumoniae, Streptococcus sanguinis*, *Candida albicans* or human plasma (from HC, iBD or aBD). Gene expression for the five NADPH-oxidase subunits was determined by qRT-PCR in resting cells, and protein expression by flow cytometry before and after stimulation with PMA or human plasma. NET formation was quantified after stimulus with PMA or human plasma, followed by labeling with anti-histones antibody, anti-neutrophil elastase antibody and Sytox Orange.

Results: Neutrophil production of O_2^-/H_2O_2 (Table 1) and NADPH-oxidase expression (Table 2) was higher after stimulus with aBD or iBD plasma than with HC plasma. PBMC displayed equivalent results. Resting and pathogen-stimulated phagocytes presented equivalent O_2^-/H_2O_2 production and NADPH-oxidase expression. NET formation was constitutively increased in aBD and iBD, compared to HC neutrophils (Table 3). Similarly, neutrophils from aBD and iBD produced more extensive NET than neutrophils from HC when stimulated with iBD plasma. In neutrophils from each group, aBD plasma induced greater NET formation than iBD or HC plasma. Eighteen soluble factors had increased concentration in aBD or BD plasma, and six were increased in both (Table 3). There was no significant difference in medication use between aBD and iBD patients.

Conclusion: Plasma from patients with aBD exerts a strong stimulus on NET formation and phagocyte oxidative burst. Increased concentration of MIP-1β, TNFα and other soluble plasma factors might be associated with neutrophil hyperactivity in BD. These findings warrant further studies in order to identify possible metabolic pathways involved in neutrophil activation in BD.

Disclosure: S. F. Perazzio, None; **P. V. S. Pereira**, None; **A. W. S. de Souza**, None; **A. Condino-Neto**, None; **L. E. C. Andrade**, None.

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The Importance of the Serum Visfatin Levels in Behcet's Disease Patients. M. Emin Enecik[1], Zeynep Ozbalkan[2], Goksal Keskin[3], Sevinc Can Sandikci[1] and Yasar Karaaslan[2]. [1]M.D., Ankara, Turkey, [2]Ankara Numune Education and Research Hospital, Ankara, Turkey, [3]Prof., Ankara, Turkey.

Background/Purpose: It's a known fact that serum levels of the tumor necrosis factor Alfa (TNF-α) interleucin-6 (IL-6) and other proinflammatory cytokines which are released from the adipose tissue are increased in Behcet's disease (BD). In BD adipose tissue is nor a passive energy depot, it is an active endocrine organ and releases adipositokines. Visfatine is one of them. Visfatin is realted to TNF-α and IL-6, IL-1 beta, co-stimulators like CD40, CD54 and CD 80 and endothelial ICAM-1 and ICAM-2. We aimed to search the relation among levels' of visfatin with activity of BD.

Methods: 60BD (30 patients were in active state and 30 were in remission) patients diagnosed according to The Criteria of Working Group on International BD and 20 health subjects as controls were involeved in to the study. The study of groups detected visfatin levels were compared among groups.

Results: Visfatin levels were significantly higer in both group of patients compared to the control group (both p<0,001). Serum visfatin levels in patients with active than in inactive patients were found statistically significantly higher (p <0.001). The same way in all cases statistically significant correlation between visfatin and CRP (p <0.001) and visfatin and ESR (p<0.01). Only according to the symptoms of the patients in the active group compared to visfatin levels in patients with genital aphth visfatin levels, a statistically significantly higher than in patients without genital aphth were detected (p<0,001).

Conclusion: Serum visfatin levels in patients with active and inactive causes are higher than the control group; visfatin proinflammatory cytokines have a role in chronic inflammatory reaction, and to sustain the cellular expression of the inflammatory stokinlerin concluded that induce or be due to different reasons.

Disclosure: M. E. Enecik, None; **Z. Ozbalkan**, None; **G. Keskin**, None; **S. C. Sandikci**, None; **Y. Karaaslan**, None.

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Identification of Potential Serum Biomarkers for Behcet Disease By High Resolution Quantitative Proteomic Analysis. Yongjing CHENG Jr.[1], Xiaolin Sun[2], Yuling Chen Jr.[3], Cibo Huang[4], Haiteng Deng[3] and Zhan-Guo Li[5]. [1]Beijing Hospital, Ministry of Health, Beijing, China, [2]People's hospital,Peking University, Beijing, China, [3]Tsing hua University, Beijing, China, [4]Beijing hospital, Beijing, China, [5]Peking University People's Hospital, Beijing, China.

Background/Purpose: Behcet's disease (BD) is a chronic, multisystemic vasculitis, pathogenesis of BD remains enigmatic. Diagnosis of BD is sometimes difficult, and until now, no specific serological markers have been established. Identification of antigens incorporated into CICs provides information that may be helpful in developing diagnostic and treatment strategies for autoimmune diseases, and such information might be more relevant than information on free antigens. The purpose of this study is to seek candidate autoantigens in CIC in BD, analyze autoantiges through Orbitrap mass spectrometry, and detect antibody levels of candidate autoantigens through ELISA in different autoimmune diseases.

Methods: A novel proteomic strategy (immune complexome analysis) was developed, in which circulating immune complexes (CICs) were separated from pooling serum sample of 10 BD patients and 10 healthy controls, digested directly with trypsin, and then subjected to Orbitrap mass spectrometry for identifying and profiling antigens in CICs. Anti-tubulin- a -1C antibody level were detected by Enzyme-linked immunosorbent assay (ELISA) in sera of 44 BD, 51 SLE, 51 SSc, 40 RA, 51 SS, 22 RAU, 13 TA, 25 AASV and 59 healthy volunteers.

Results: A totle of 22 antigens incorporated into CICs were found in CICs of BD patients, but not in RA and HC, including TAOK3, BAG3 and Tubulin-a-1C et al. The auto-antibody to one of the identified proteins, Tubulin-a-1C, was investigated by ELISA using a recombinant protein. The auto-antibody to Tubulin-a-1C were detected positive in 26 (59.0%) of the 44 patients with BD, 14 (27.5%) of the 51patients with SLE, 14 (27.5%) of the 51patients with SSc, 3 (7.5%) of the 40 patients with RA, 3(23.1%) of 13 TA, 1(4%) of 25 AASV and 2 (3.39%) of 59 HC. The sensitivity and specificity of Tubulin-a-1C antibody in the diagnosis of BD were 59.0% and 82.7% respectively. Further analysis demonstrated that Tubulin-a-1C antobody was correlated with complications of deep venous thrombosis and erythema nodosum of BD(p<0.05), and meanwhile, levels of anti- Tubulin-a-1C antibody were correlated with levels of ESR, CRP and BVAS(p<0.05).

Conclusion: Anti- Tubulin-a-1C antibody may be helpful in diagnosis and severity evaluation of BD, CIC relevant antigens may benefit understanding of the pathogenesis of venous thrombosis and erythema nodosum of BD.

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Microparticles May Play a Role in Causing Thrombosis in Behçet's Syndrome and Act As a Biomarker for Risk Management. Emon Khan, Nicola Ambrose, Michael A. Laffan and Dorian O. Haskard. Imperial College, London, United Kingdom.

Background/Purpose: Thrombosis occurs in 20% of patients with Behçet's Syndrome (BS) and leads to significant morbidity. There is no robust association between thrombosis in BS and the presence of hereditary thrombophilia or raised inflammatory markers. It remains a challenge to distinguish those at risk of thrombosis potentially requiring aggressive preventative therapy and those whose therapy can be reduced. There is a clear need to develop biomarkers for diagnosis and risk management in BS.

Plasma cell membrane derived microparticles (MPs) are released from cells undergoing apoptosis or activation. MPs are known to promote thrombosis in malignancy and cardiovascular disease, as a result of surface expression of phosphatidylserine (PS) and other cell surface markers, in particular tissue factor (TF). The aim of this study was to assess whether MPs are associated with thrombosis in Behçet's Syndrome (BS).

Methods: MPs were prepared following venepuncture of 88 BS patients who fulfilled International Study Group Criteria for diagnosis, 21 of whom had a history of thrombosis, and 39 healthy controls (HC). MPs were identified using flow cytometry by gating for particles less than 1μm in size and staining positively with Annexin V, which binds PS, giving a total MP count. Antibodies to CD14 (monocytes), TF, CD62P (platelets), CD144 (endothelial cells) and CD66b (neutrophils) were used to identify cellular origin. Endogenous thrombin potential (ETP) and peak thrombin (PT) were measured using calibrated automated thrombography, allowing analysis of the thrombotic potential of MPs.

Results: BS patients had higher total (4.3×10^5/ml vs 2.3×10^5/ml, $p=0.0072$), CD14+(2.7×10^5/ml vs 8.5×10^3/ml, $p<0.0001$), TF+ (4.5×10^4/ml vs 5.9×10^3/ml, $p<0.0001$) and CD14+TF+ (1.9×10^4/ml vs 4.5×10^3/ml, $p<0.0001$) MPs compared to HCs. Thrombotic BS (TBS) patients had higher total (8.8×10^5/ml vs 3.2×10^5/ml, $p=0.0028$), CD14+ (2.9×10^4/ml vs 2.5 x10^4/ml, $p=0.042$), TF+ (6.1×10^4/ml vs 4.3×10^4/ml, $p=0.041$) and CD14+ TF+ (2.6×10^4/ml vs 1.5×10^4/ml, $p=0.047$) than non-thrombotic BS (NTBS) patients.

BS patients also had higher CD62P+ (1.2×10^5/ml vs 4.7×10^4/ml, $p=0.0152$) and CD66b+ (1.9×10^4/ml vs 8.8×10^3/ml, $p=0.0389$) MPs than HCs. CD144 MPs were not significantly higher in BS patients than HCs (1.9×10^4/ml vs 1.1×10^4/ml, $p=0.0769$). TBS patients had higher CD62P+ (2.3×10^5/ml vs 7.1×10^4/ml, $p=0.0111$), CD144+ (3.8×10^4/ml vs 1.5×10^4/ml, $p=0.0342$) and CD66b+ (4.8×10^4/ml vs 1.7×10^4/ml, $p=0.0237$) MPs than NTBS patients.

ETP was significantly higher in BS patients than HCs (515.13 vs 383.52, $p=0.013$), but there was no difference in ETP between TBS and NTBS patients. PT was significantly higher in BS patients (20.08nM vs 9.92nM, $p=0.0022$) compared to HCs and in TBS (27.06nM vs 16.73nM, $p=0.041$) compared with NTBS patients, but did not correlate with MP numbers.

Conclusion: MPs are found in higher numbers in BS patients than in HCs, in particular in TBS patients. It is interesting that PT was raised in TBS compared with NTBS patients. These results suggest that MP counts and PT may be useful biomarkers in combination and may provide a scoring system for identifying patients at risk of thrombosis and risk management in patients with BS.

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The Clinical Course of Acute Deep Vein Thrombosis of the Legs in Behçet's Syndrome. Melike Melikoglu[1], Yesim Ozguler[2], Serdal Ugurlu[3], Firat Cetinkaya[4], Koray Tascilar[2], Emire Seyahi[3], Vedat Hamuryudan[3] and Hasan Yazici[1]. [1]Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, [2]University of Istanbul, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, [3]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [4]Colormed Radiology Center, Istanbul, Turkey.

Background/Purpose: To determine the prospective clinical course of lower extremity deep vein thrombosis (LEDVT) in patients with Behçet's syndrome (BS).

Methods: Consecutive BS patients with an acute episode of LEDVT were prospectively studied. Clinical examination and lower extremity Doppler ultrasonography (US) were done at 1, 3, 6, 18 and 24 months after the index event. A relapse was defined as a new episode of LEDTV and/or a superficial vein thrombosis (SVT).

Results: 40 patients (6F, 34M) with LEDVT were followed for a mean=33.2 ± 10.8 months. The mean age was 30.2 ± 7.3, and the median disease duration since disease onset was 33.3 months (IQR=8.0–60.8). A total of 50 relapses were observed in 27 patients. This was in the form of solo SVT in 8 patients, solo LEDVT in 10 and LEDV+SVT in 9 patients. Cox regression analysis revealed that a recanalization rate of $\geq$ 50% in LEDVT observed by US at month 3 was significantly associated with a lower relapse rate (HR=0.23; 95% CI =0.092–0.59).

The first line treatment had been with azathioprine (AZA) with moderate doses of glucocorticoids (0.5 mg/kg/d) in 34 (85%) patients, interferon-alpha (IFN-alpha) in 4 and cyclophosphamide in 2 patients (also with pulmonary vasculitis). 19 out of 34 (55%) remained on AZA, 10 were switched to IFN-alpha for resistant or recurrent disease during follow up. 8 of these 10 patients did not experience relapses after switching to IFN-alpha. 16 patients treated with IFN-alpha (including 3/4 initially treated with IFN-alpha) during follow-up and 12 of 16 (75%) patients were still on IFN-alpha therapy without relapses.

Conclusion: Relapses and resistant disease are frequent 27/40 (67.5%) in LEDTV in BS and is significantly associated with a failure to recanalize at 3 months. IFN-alpha can justifiably be tried in the treatment of LEDVT, refractory to AZA and glucocorticoid use.

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Effects of Anticoagulant Treatment on the Incidence of New Vascular Events in Patients with Behcet's Disease with Vascular Involvement. Fatma Alibaz-Oner[1], Aslı Karadeniz[1], Sema Yilmaz[2], Ayse Balkarli[3], Gezmis Kimyon[4], Ayten Yazici[5], Muhammed Cinar[6], Sedat Yilmaz[6], Fatih Yildiz[7], Sule Yasar Bilge[8], Emre Bilgin[9], Belkıs Nihan Şeniz[10], Ahmet Omma[11], Gozde Yildirim Cetin[12], Yonca Cagatay[13], Mehmet Sayarlioglu[14], Yavuz Pehlivan[15], Umut Kalyoncu[16], Omer Karadag[9], Timucin Kasifoglu[8], Eren Erken[7], Salih Pay[6], Ayse Cefle[5], Bunyamin Kisacik[17], Ahmet Mesut Onat[4], Veli Cobankara[18] and Haner Direskeneli[1]. [1]Marmara University, School of Medicine, Istanbul, Turkey, [2]Selcuk University School of Medicine, Konya, Turkey, [3]Pamukkale University School of Medicine, Denizli, Turkey, [4]Gaziantep University School of Medicine, Gaziantep, Turkey, [5]Kocaeli University, Kocaeli, Turkey, [6]Gulhane Military Medical Academy, Ankara, Turkey, [7]Cukurova University, School of Medicine, Adana, Turkey, [8]Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkey, [9]Hacettepe University Faculty of Medicine, Ankara, Turkey, [10]Uludağ University, School of Medicine, Bursa, Turkey, [11]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [12]Kahramanmaras University School of Medicine, Kahramanmaras, Turkey, [13]Bilim University Faculty of Medicine, Istanbul, Turkey, [14]Ondokuz Mayis University School of Medicine, Samsun, Turkey, [15]Uludag University, School of Medicine, Bursa, Turkey, [16]PsAID taskforce, EULAR, Zurich, Switzerland, [17]Gaziantep University, School of Medicine, Gaziantep, Turkey, [18]Pamukkale University, School of Medicine, Denizli, Turkey.

Background/Purpose: Vascular involvement (VI) is one of the major causes of mortality and morbidity in Behcet's Disease (BD). There are no controlled studies for the management of major vascular involvement in BD. According to the EULAR recommendations for the management of BD, only immunosuppressive (IS) agents such as corticosteroids, azathioprine, cyclophosphamide or cyclosporine A are recommended for VI. In this study, we aimed to investigate the effects of anticoagulant (AC) treatment on the development of new vascular events in patients with BD followed up for vascular disease (VBD), retrospectively.

Methods: In this retrospective study, 637 patients with BD (F/M: 283/354, mean age: 38.5 ± 11.1 years) classified according to ISG criteria from 8 Rheumatology centers in Turkey, were included. The demographic data, clinical characteristics of first vascular event and relapses, treatment protocols and data about complications were acquired from files, retrospectively.

Results: Two hundred eighty-one BD patients (44.1%) were of mucocutaneus type, whereas 356 patients (55.9%) had major organ involvement [Uveitis: 42.4% (n=270), neurologic involvement: 6.9% (n=44), gastrointestinal involvement 1.9%(n=12)]. VBD developed in 20.6% (N=131) patients during the follow-up. When the first vascular event developed, the mean disease duration was 3.5 (0–28) years and mean age 33.2±8 years. After the first vascular event, IS treatment was given to 88.5% (n=105) and AC treatment to 62.6% (n=76) of the patients. Minor hemorrhage (as a complication related to AC treatment) was observed in 3 (3.9%) patients. A second vascular event developed in 35.9% (n=47). The rate of new vascular event development was similar between the patients taking only ISs and AC+IS treatments after first vascular event (27.2% vs 29.6%, p=0.78). Relapse rate was significantly higher in group taking only ACs (91.6%, p=0.002). During follow-up, a third vascular event developed in 23.4% (n=11) patients. The rate of new vascular event development was again similar between the patients taking only IS and AC+IS treatments. There was no relationship between the total duration of AC treatment and number of vascular events. However, total number of vascular events negatively correlated with the age during the first vascular event (r:−0.215, p=0.02).

Conclusion: In this study, we did not find any additional positive effect of AC treatment used in combination with ISs in the course of vascular involvement in patients with BD. Severe complications related to AC treatment were also not detected. Our results suggest that short-duration of IS treatments is the major problem in BD patients associated with vascular relapses during follow-up.

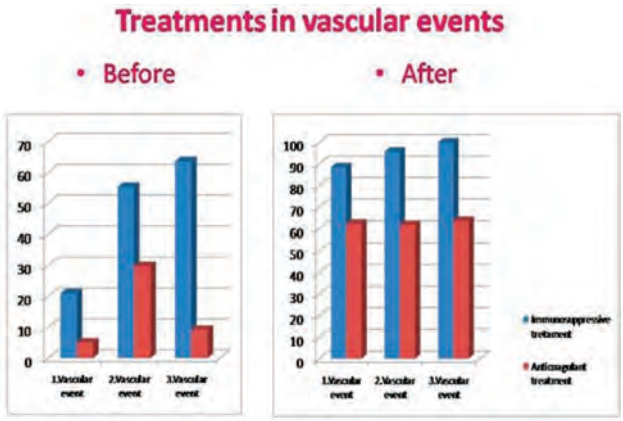

Figure 1: Immunosuppressive and anticoagulant treatment rates before and after vascular events.

Figure 1: Immunosuppressive and anticoagulant treatment rates before and after vascular events.

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18F-FDG PET/CT in Vascular Disease Due to Behçet's Syndrome.
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Background/Purpose: 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT is considered as a useful tool in assessing active vascular inflammation in large vessel vasculitis. Lower extremity vein thrombosis is the most common type of vascular disease in BS followed by vena cava thrombosis, pulmonary artery involvement and peripheral arterial aneurysms. Pulmonary artery involvement is mainly manifested by pulmonary artery aneurysms and solely by 'in situ' pulmonary artery thrombosis. Varying and multiple pulmonary parenchymal lesions such as nodules, consolidations and cavities make part of this involvement as well (1). Apart from a few case reports, information on the diagnostic value of PET/CT in vascular disease of BS is limited (2–3). We investigated the potential of PET/CT to evaluate the extent and activity of disease in vascular disease due to BS.

Methods: Thirty-three (30 M/3 F) patients with BS between March 2012 and April 2014 were studied. The mean age and the mean disease duration were 32±7 and 4±3 years, respectively. All patients had one or more type of large vessel disease such as: deep vein thrombosis of lower extremities (n=31), pulmonary artery involvement (n=14), vena cava superior (n=1) or inferior thrombosis (n =9) and Budd-Chiari syndrome (n=5). FDG PET/CT studies were performed within the first 2 weeks of diagnosis in 23 patients. In the remaining 10, scans were obtained for activity assessment during the follow-up. Maximum standardized uptake values (max SUVs) and visual analyses were used to interpret the FDG PET/CT images. In addition, non-enhanced CT findings obtained during FDG PET/CT were recorded.

Results: FDG PET/CT was positive (SUV ≥ 2; equal to or greater than liver uptake) in 15 (45 %) patients. These included 11 patients with pulmonary artery involvement (11/14, 79 %). Among these 11 patients, FDG uptake was observed in the lung parenchyma (in the form of nodules, consolidations or cavities) in 8, in the hilar region suggesting lymphadenopathy in 6 patients and in 1 patient, suggesting thrombus of a pulmonary artery aneurysm. Among the 19 patients with major venous vessel involvement, FDG uptake was observed in 4 patients (4/19, 21 %) and these was in the femoro-popliteal vessels.

Conclusion: This preliminary survey showed that in BS, FDG uptake was mainly observed at the pulmonary parenchyma while pulmonary arteries did not show increased uptake. Disease in peripheral major veins, on the other hand, can only occasionally be discerned by FDG PET/CT. Further studies might still be needed among immunosuppressive naïve patients.

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Budd-Chiari Syndrome Due to Behçet's Syndrome: Some Patients Present without Liver Related Symptoms and Have a Better Outcome.
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Background/Purpose: Behçet's syndrome (BS) is a well recognized cause of Budd–Chiari syndrome (BCS), however, information about its clinical characteristics and outcome is limited. We had presented the outcome of 40 patients with BCS due to BS at the ACR 2013 meeting (1). In further analyses, we better understood that there were patients in whom BCS could exist without the presence of any liver related symptoms/signs. In the current study we compared demographic, clinical, radiologic and prognostic characteristics of these patients to those presented with overt liver related symptoms.

Methods: We reviewed the records of about 9000 patients with BS who were registered at the multidisciplinary Behçet's syndrome outpatient clinic at Cerrahpasa Medical Faculty between July 1977 and October 2013. We identified 43 (40 male/ 3 female) patients who were diagnosed as having BCS. Their outcome was evaluated between September 2012 and October 2013.

Results: 43 (40 male/ 3 female) patients with BCS were identified. Thirty-three patients (77 %) had presented with liver related symptoms such as ascites and abdominal swelling for a median duration of 1 month [IQR:0.5–2.5 months]. These patients were defined as Group I. On the other hand, 10 (21%) were silent for liver disease at presentation and were found to have BCS while being investigated for fever (n=4), bilateral diffuse leg swelling (n = 4), and pulmonary symptoms like hemoptysis or dyspnea (n =4). None had liver dysfunction related symptoms/signs. These patients were classified as Group II. All were diagnosed after 1990. Group II patients were somewhat older (mean age: 32.2 vs 28.7, p=0.26) and had longer disease duration of BS at the onset of BCS (median: 5.1 vs 2.7, p =0.18) than Group I patients. The level of hepatic venous outflow obstruction in Group II

involved less frequently the combined IVC and hepatic veins (30 %) while was more likely to involve isolated hepatic veins (30 %) or isolated IVC (40 %) when compared to Group I (76 %, 26 % and 3 %, respectively) ($p = 0.05$). Besides that, the anatomical distribution of vessels other than those involved in BCS, and the clinical characteristics of BS were not very different than Group I. By the end of the survey, there was only 1 death in Group II, which was not due to hepatic failure. Mortality was significantly lower among Group I patients (1/10) as compared to Group II (19/33, 58 %), ($p = 0.025$).By the end of the survey, only 1 (1/13) in Group I, had ascites, while in the remaining surviving patients in Group I ascites had resolved within 6 to 8 months after the first visit. A final hepatic Doppler USG indicated that, the frequency of recanalisation and collateral formation was similar between the patients in Group I and II.

Conclusion: There is subgoup of patients in whom, BCS may exist without the presence of liver related symptoms/signs and these patients have a good prognosis. These patients could pass unnoticed, unless one looks carefully for hepatic veins or intra or suprahepatic segments of the IVC. The fact that, 8 of these10 patients were diagnosed after 2000, suggests that this subgroup was recognized after the recent availability of imaging techniques.

Reference:
Seyahi E et al. ACR 2013

Disclosure: E. Seyahi, None; **E. Caglar**, None; **S. Ugurlu**, None; **F. Kantarci**, None; **V. Hamuryudan**, None; **A. Sonsuz**, None; **M. Melikoglu**, None; **S. Yurdakul**, None; **H. Yazici**, None.

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Reduced Heart Rate Variability in Patients with Behcet's Disease. Joung-Wook Lee[1], Seung-Geun Lee[2], Eun-Kyoung Park[2] and Geun-Tae Kim[3]. [1]Divsion of Rheumatology, Department of Internal Medicine, Busan St. Marys center, Busan, South Korea, [2]Divsion of Rheumatology, Department of Internal Medicine, Pusan National University School of Medicine, Pusan National University Hospital, Busan, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Kosin University College of Medicine, Busan, South Korea.

Background/Purpose: The autonomic nervous system, including the sympathetic and parasympathetic nervous systems, has an important role in the triggering of ventricular arrhythmias and sudden cardiac death.

The aim to this study was to investigate autonomic regulations by means of heart rate variability(HRV), influence of conventional cardiovascular risk factors, and relationship with the disease activity in patients with Behcet's disease (BD).

Methods: 50 patients with BD (Age : 43.8 ± 18.6, female : 40) and 50 age-and sex-matched healthy controls were included in this study. All the participants were screened for basic cardiovascular risk factors.

BD activity was studied with Behcet's disease current activity form (BDCAF) and acute phase indices. HRV was calculated by time domain measures, frequency domain measures and nonlinear/complexity-based measures on 24 hours recording.

Results: Patients with BD had decreased HRV in comparison to healthy controls as reflected by decrease of the standard deviation of normal R-R intervals(SDNN) (74.0 ± 37.5 vs. 136.2 ± 62.3ms, respectively, $p < 0.01$) and of the high frequency(HF) power (130.0 ± 89.9 vs. 383.5 ± 154.2 ms2, respectively, $p < 0.005$).

SDNN ($r = -0.45$, $p < 0.005$ and $r = -0.37$, $p < 0.04$) and HF ($r = -0.42$, $p < 0.01$ and $r = -0.35$, $p < 0.02$) were significantly correlated with BDCAF and CRP, respectively.

Conclusion: HRV was shown to be significantly decreased, compared to healthy controls, among BD patients. Patients with BD had impaired autonomic cardiac regulation which is related to the disease activity and presence of systemic inflammation and which could contribute to the increased cardiovascular risk in these patients.

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Predictors of Quality of Life in Behçet's Syndrome. Selma Bozcan[1], Yesim Ozguler[1], Koray Tascilar[1], Caner Saygin[1], Didem Uzunaslan[1] and Gulen Hatemi[2]. [1]University of Istanbul, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, [2]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey.

Background/Purpose: Quality of life is commonly impaired in patients with chronic inflammatory diseases. The disease itself as well as the drugs used may be responsible for this impairment. Behçet's syndrome (BS) is a multisystem vasculitis with a wide variety of manifestations including oral ulcers, genital ulcers, nodular lesions, papulopustular lesions, arthritis, uveitis, venous thrombosis, arterial aneurysms, neurologic and gastrointestinal involvement. Determining the factors affecting quality of life in BS patients, would help developing effective management strategies.

Methods: Behçet Disease Quality of Life (BDQoL) and Short- Form 36 (SF-36) questionnaires were filled by consecutive BS patients attending our outpatient clinic. Socioeconomic factors, each type of organ involvement during the disease course, during the previous 4 weeks, disabilities caused by each, treatment modalities and overall disease activity were tested with regression analysis as possible determinants of quality of life. Men and women were also analyzed separately.

Results: 322 patients (M/F: 166/156, mean age: 37.9 ± 11.1 years) were included. 157 patients had eye involvement, 72 patients had vascular involvement, 67 patients had joint involvement, 20 patients had neurologic involvement, 2 patients had gastrointestinal involvement and 93 patients had only mucocutaneous involvement without major organ involvement. Determinants of BDQoL in the whole group were BSAS, household income, work disability, perception of insufficient income, neurologic damage (R^2:0.47, F: 48.76, $p<0.001$). Among women they were BSAS, perception of insufficient income, neurologic and mucocutaneous involvement (R^2:0.40, F: 19.75, $p<0.001$). Among men they were work disability, BSAS, household income, perception of insufficient income, vascular involvement during the last 4 week and damage caused by neurologic involvement (R^2:0.56, F: 29.70, $p<0.001$). SF-36 scores were well correlated with BDQoL scores ($r=-0.69$ for physical component and $r=-0.63$ for mental component).

Conclusion: In addition to overall disease activity and neurologic damage, mucocutaneous involvement in women and recent eye and vascular events in men seem to impair quality of life in BS. These findings are important for developing management strategies and outcome measures.

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Disease Activity and Quality of Life in BEHÇET'S Disease: The Role of Patients Reportedoutcomes. Elena Elefante[1], Rosaria Talarico[1], Chiara Stagnaro[2], Anna d'Ascanio[3], Antonio Tavoni[4], Chiari Tani[1], Chiara Baldini[1], Marta Mosca[5] and Stefano Bombardieri[1]. [1]Rheumatology Unit, Pisa, Italy, [2]Rheumatology Unit, University of Pisa, Pisa, Italy, [3]University of Pisa, Pisa, Italy, [4]Immunoallergology Unit, Pisa, Italy, [5]S. Chiara, Pisa, Italy.

Background/Purpose: Behçet's disease (BD) is a systemic vasculitis, typically characterised by recurrent oro-genital ulcers, ocular inflammation and skin manifestations; articular, vascular, gastro-enteric and neurological involvement may also occur. Since BD has a chronic-relapsing course and it can be very severe, debilitating and potentially life-threatening, it may without any doubt affect the quality of life of the patients. Moreover, it is well known that patient's perception of own disease represents an useful tool to help physicians to improve the understanding and management of the disease itself. The primary aim of this study was to explore the role of quality of life patients reported outcome (PRO) in better identifying the global status of BD.

Methods: The study enrolled 120 patients, all fulfilling the International Study Group (ISG) criteria for BD. The male/female ratio was 1.6:1, with a mean disease duration of 11 ± 6 years. Their mean age was 42 ± 8 years (min:18, max:77), while the mean age at disease onset was 24 ± 5 years. The primary end-point was to study any potential correlation between quality of life and disease activity. Disease activity was evaluated by means of the Behçet's Disease Current Activity Form (BDCAF), while the Italian version of the Short-form-36 (SF-36) was used to evaluate quality of life. Disease activity was compared with the global SF-36 score and with each dimension, that includes: physical functioning, physical disability, body pain, general health, vitality, social functioning, emotional disability, mental health. The statistical analysis was performed using Student t-test, Mann-Whitney-U test, ANOVA and Pearson correlation.

Results: At time of evaluation, according BDCAF, 47 BD patients (39%) had clinically active disease (18 ocular involvement, 8 joint involvement, 4 neurological involvement, 2 gastro-enteric, 15 muco-cutaneous involvement). As expected, the overall SF-36 scores were significantly lower in patients

with clinically active disease. Moreover, female BD patients had statistically significant lower scores in all SF-36 domains compared with male patients. When each domain of SF-36 was evaluated, we found that physical disability (p=0.004), body pain (p=0.006), general health (p=0.001), and vitality (p=0.001) were significantly lower in patients with disease activity. Notably, vitality (p=0.001), physical disability(p=0.004), social functioning (p=0.001), emotional disability (p=0.003) and mental health (p=0.001) were significantly lower in patients with muco-cutaneous active disease, compared with the other patients with active disease.

Conclusion: The clinicians who take care of any chronic disease would like to correctly know the current status of a patient to manage him properly. In this regard, the combination data of PRO measures and disease activity have been demonstrated to add more information compared to the evaluation of disease activity alone. These consideration suggest that the correct assessment of BD need a multi-dimensional approach, that fairly includes disease activity, disease damage and quality of life.

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Treatment of Mucocutaneous Manifestations in Behçet's Disease with Anakinra: A Pilot Open-Label Study. Peter C. Grayson[1], Yusuf Yazici[2], Elaine Novakovich[3], Elizabeth Joyal[3], Raphaela T. Goldbach-Mansky[3] and Cailin H. Sibley[3]. [1]National Institutes of Health, Bethesda, MD, [2]New York University School of Medicine, New York, NY, [3]National Institutes of Health Clinical Center, Bethesda, MD.

Background/Purpose: IL-1 blocking therapy shows promise in the treatment of Behçet's eye disease, but its effect on mucocutaneous manifestations is unknown.

Methods: 6 patients with Behçet's disease as determined by International Study Group criteria and active oral or genital ulcers for ≥2 months were enrolled in this open label phase I/II study. 2 patients had a history of inactive uveitis (anterior, panuveitis). Study duration was 3 months with extension up to 16 months (range 4–16). All were treated with anakinra 100mg subcutaneous daily with the option to escalate dose to 200mg in partial responders after 1 month and 300mg after 6 months. Patients recorded the number and severity of oral and genital ulcers in daily diaries. The primary outcome was remission defined as no ulcers on physical exam for 2 consecutive monthly visits from months 3–6. Secondary outcomes included the number of ulcers, the number and severity of patient-reported ulcers, patient/physician global scores, and standardized disease activity scores.

Results: 2 of 6 patients achieved the primary outcome of remission from months 3–6. All but 1 had improvement in the number of oral ulcers at month 3 (primary endpoint). Mean number of oral ulcers at baseline, month 3 and month 12 were 3.3, 1.5 and 0.5 and mean number of genital ulcers were 0.8, 0 and 0. Over the entire study, patients reported ≥1 oral and ≥1 genital ulcer on 665 (66%) and 139 (14%) days, respectively. Non-statistically significant improvements were seen in secondary outcomes including physician and patient visual analog scores and scores for Behcet's disease current activity form (BDCAF) patient index, and Behcet's disease quality of life (BDQOL). Behcet's syndrome activity scale (BSAS) showed significant changes at 3 and 9 months. (**Table**). Dose escalation to 200mg occurred in all patients prior to month 3 and was further increased in 3 to 300mg after month 6. 2 patients on baseline prednisone of 40mg and 20mg were tapered to 20mg and 0mg, respectively. On anakinra 200mg vs. 100mg, patients reported fewer days with oral ulcers (65% vs 74% days, p=0.02) and genital ulcers (10% vs 22% days, p<0.001) and milder ulcer severity (p<0.01). Increase of anakinra to 300mg did not result in fewer ulcers or milder ulcer severity. No ocular flares occurred during the study; however, 2 ocular flares (anterior uveitis, periorbital inflammation) occurred within a month after discontinuation of anakinra in the 2 patients with prior eye disease. Adverse events included a serious adverse event of pulmonary hypertension suspected prior to the study and frequent viral infections.

Conclusion: In this open-label pilot study, anakinra, at an optimal dose of 200mg daily, demonstrated partial efficacy in treatment of resistant oral and genital ulcers in Behçet's disease. Organ-specific differential effects of IL-1 blockade are likely.

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Table - Mean (SD) Values for Disease Activity Measurements

	Baseline (n=6)	Month 1 (n=6)	Month 2 (n=6)	Month 3 (n=6)	Month 6 (n=4)	Month 9 (n=4)	Month 12 (n=4)
Oral ulcer number	3.3 (0.8)	1.5 (1.2)	1.5 (1.4)	1.5 (2)	0.8 (1)	0.4 (0.5)	0.5 (0.6)
Genital ulcer number	0.8 (1.3)	0.5 (0.8)	0.3 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)
Physician global VAS (0–100)	26.5 (25.9)	19 (14.3)	19.8 (8.3)	14.5 (7.3)	12 (8)	9 (9.8)	10 (5.3)
Patient global VAS (0–100)	63.7 (28.9)	39.5 (32.1)	59.4 (25.9)	59.5 (32.5)	49.3 (40.1)	28.3 (18.3)	46 (72.5)
BDCAF (0–12)	6.7 (2.3)	6.2 (1.9)	5.5 (2.2)	5.8 (2.8)	5 (0.8)	4.3 (2.2)	5.3 (1.7)
BSAS (0–100)	50.1 (20.2)	34 (13.7)	42.6 (14)	26.9 (16.1)*	21.6 (18.7)	21.9 (9.3)*	41 (21)
BDQOL (0–30)	15.3 (5)	10.2 (7.3)	11 (8.1)	12.5 (10.3)	10.3 (10.9)	7.7 (5.7)	11.7 (4.9)

* $p < 0.05$ paired t-test from baseline

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Efficacy and Safety of ANTI-TNF ALPHA in BEHÇET Disease: A International Multicenter Registry of 122 Patients. Hélène Vallet[1], Sophie Rivière[2], Alban Deroux[3], Guillaume Moulis[4], Olga Addimanda[5], Carlo Salvarani[6], Marc Lambert[7], Philip Bielfeld[8], Pascal Sève[9], Jean Sibilia[10], Jean Baptiste Fraison[11], Yoland Schoindre[12], Isabelle Marie[13], Laurent Perard[14], Thomas Papo[15], Damien Sène[16], Gaelle Leroux[1], Valerie Royant[17], Antoinette Perlat[18], Xavier Mariette[19], Olivier Lidove[20], Olivier Fain[21], Claire De Moreuil[22], Gilles Blaison[23], Phuc LE Hoang[24], Eric Hachulla[25], Bertrand Wechsler[1], Barham Bodaghi[26], Patrice Cacoub[27] and David Saadoun[1]. [1]DHU 2iB Internal Medicine Referal Center for Autoimmune diseases Pitie Hospital, Paris, France, [2]Lapeyronie, Montpellier, France, [3]CHU Grenoble, Grenoble, France, [4]Internal Medicine department, Toulouse, Toulouse, France, [5]Arcispedale Santa Maria Nuova, I.R.C.C.S., Reggio Emilia, Italy, [6]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [7]CHRU Lille, Lille, France, [8]CHU de Dijon, Dijon, France, [9]CHU Lyon, Lyon, France, [10]University Hospital of Strasbourg, Strasbourg, France, [11]Hôpital Jean Verdier, Bondy, France, [12]DHU 2iB Internal Medicine Referal Center for Autoimmune diseases Pitie Hospital, PARIS, France, [13]CHU de Rouen, Rouen, France, [14]Hospices civils de Lyon, Lyon, France, [15]Hôpital Bichat, Paris, France, [16]Hopital Lariboisière, service de Médecine Interne, Paris, France, [17]Chartres, Chartres, France, [18]CHU de Rennes, Rennes, France, [19]Université Paris-Sud, Le Kremlin Bicêtre, France, [20]Hôpital Croix-Saint-Simon, PARIS, France, [21]Hôpital Saint Antoine, DHU i2B, Service de Médecine Interne, paris, France, [22]CHU, Brest, France, [23]CHR, Colmar, France, [24]Assistance Publique-Hôpitaux de Paris, Hôpital Pitié Salpétrière, Paris, France, [25]National Scleroderma Centre, Lille CEDEX, France, [26]Hôpital de la Pitié Salpêtrière, Paris, France, [27]Groupe Hospitalier Pitié Salpétrière, Service de Médecine Interne, DHU i2B, Paris, France.

Background/Purpose: Behçet's disease (BD) is a systemic large vessel vasculitis with recurrent genital and oral ulceration, uveitis, cardiovascular, joints, neurological or gut symptoms. Treatment of BD is dependent of the nature and the severity of clinical manifestations. Increased levels of TNF alpha and soluble TNF receptors have been found in the serum, plasma and in the aqueous humor of patients with BD. Although, anti-TNF alpha have proved effective in refractory uveitis, few data are available relative to its efficacy in extraocular manifestations of BD. The aim of this study is to report on the efficacy and the safety of anti-TNF alpha in BD.

Methods: We performed a retrospective multicenter study of main characteristics and outcomes of 122 patients with BD treated with anti-TNF alpha.

Results: One hundred twenty two observations were collected in 21 centers. Mean ± SD age at the anti-TNF alpha introduction was 35 ±12 years with 47% of men. Ninety one (75%) patients received at less one immunosuppressive therapy before the use of anti-TNF alpha.

The main indications of anti-TNF alpha were uveitis (n=80, 66%), mucocutaneous manifestations (n=26, 21%) [oral (n=21) and genital ulcerations (n=13)], articular (n=29, 24%), neurologic (n=12, 10%), cardiovascular (n=5, 4%) and digestive manifestations (n=9, 7%). Infliximab was frequently used (61%), followed by adalimumab (30%), etanercept (8%) and golimumab (1%). Associated therapy included prednisolone (84%), azathioprine (28%), mycophenolate mofetil (6%), and methotrexate (10%). Median duration of follow up was 31 months [11–55]. 96% and 81% of BD patients achieved a complete or partial response of uveitis and extraocular manifestations, respectively. Relapse free survival was similar regardless of anti-TNF alpha used. Anti-TNF alpha had a significant corticosteroid sparing effect (daily prednisolone dose of 40mg at time of introduction of anti-TNF alpha vs 10mg and 5mg at 6 and 12 months, respectively; p<0,0001). The median time for clinical improvement was 62 days [31–92]. Adverse events were reported in 28% of patients, mainly with infliximab (infliximab 61%, adalimumab 32%; p=0.02). They mainly included infections (52%) and

hypersensitivity reactions (16%). Serious adverse events were reported in 13% of patients and required treatment interruption in all cases.

Conclusion: These results show that TNF alpha inhibitors are highly and rapidly efficient in all BD manifestations. Although tolerance seems satisfactory, infliximab is associated with more frequent and more serious side effects.

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Predictive Factors for the Response to Infliximab Therapy in Patients with Behçet's Disease. Salvatore D'Angelo, Pietro Leccese, Angela Padula, Angelo Nigro, Michele Gilio, Antonio Carriero, Carlo Palazzi and Ignazio Olivieri. Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Potenza, Italy.

Background/Purpose: To identify the clinical factors predicting a good clinical response to Infliximab (IFX) therapy after 12 months in patients with Behçet's disease (BD) refractory to conventional therapy.

Methods: Patients receiving IFX (5 mg/kg intravenously at weeks 0, 2, 6, and every 6–8 weeks subsequently) for BD unresponsive to conventional therapy (corticosteroids plus at least two different immunosuppressive drugs) were prospectively included. Clinical response to IFX therapy was based on the expert opinion and was graded as follows: remission, response, no response and worsening. Remission was defined as the complete disappearance of symptoms and signs of inflammation and response as at least 50% of improvement. Univariate and multivariate analyses were performed to identify factors associated with IFX good response (remission, response) at 12 months. Logistic regression analysis was performed to analyse which of the following measures at the start of treatment were associated with a good response: sex; age; disease duration; HLA-B51 status; indication for IFX treatment including uveitis, CNS involvement, severe mucocutaneous manifestations or others including arthritis, intestinal and vascular involvement; concomitant drugs including steroids (Ster), colchicine (Col), azathioprine (AZA) or cyclosporine (CSA).

Results: The study included 73 BD patients (47 M/26 F; mean age 33.6±10.7 yrs; mean disease duration 12.3±9.3 yrs; 71.2% HLA-B51 positive). Indication for IFX treatment were uveitis in 38 patients, severe mucocutaneous manifestations in 13, CNS involvement in 16, intestinal involvement in 2, arthritis in 2, vascular involvement in the remaining 2. At 12 months, 56 patients (76.7%) had a good response to IFX, 4 (5.5%) patients had stopped for adverse events, and 13 (17.8%) had stopped for primary or secondary inefficacy. In the univariate analysis concomitant use of AZA (95.8% vs 67.3%, $p < 0.01$) was the only factor associated with a good response. In a multivariate logistic regression analysis concomitant use of AZA was independently associated with a good therapeutic response (OR = 34.2; 95% CI 2.7–435.8; $p = 0.007$). None of the other variables analysed predicted response to treatment.

Conclusion: This study has, for the first time, shown that concomitant use of AZA at the start of IFX treatment is a factor that seems to influence the probability of achieving a good therapeutic response in patients with refractory BD. Further support from larger studies is necessary so as to optimize the management of BD patients treated with IFX.

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Anti-TNF Treatment for Refractory Vascular Involvement of Behçet's Syndrome. Vedat Hamuryudan[1], Emire Seyahi[1], Melike Melikoglu[2], Serdal Ugurlu[1], Gulen Hatemi[1], Sebahattin Yurdakul[1] and Hasan Yazici[2]. [1]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [2]Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey.

Background/Purpose: The optimal management of major vascular involvement in patients with Behçet's syndrome (BS) is still a challenge.

Methods: We reviewed the charts of 16 BS patients (15 men) with vascular involvement who had been treated with anti-TNF agents following an inadequate response to traditional immunosuppressives (cyclophosphamide or azathioprine combined with glucocorticoids).

Results: Ten patients had pulmonary artery involvement (PAI), 5 had major vein involvement (multiple thromboses of vena cavae, deep veins and dural sinuses) and 1 had renal artery aneurysm. PAI was in the form of pulmonary artery aneurysm (PAA) in 2 patients, pulmonary artery thrombosis (PAT) in 6 patients and the combination of PAA with PAT in 2 patients. Six patients (5 with PAI) also had intracardiac thrombi formation. All patients were using immunosuppressives at the time of initiation of anti TNF therapy (for 11 ± 7 SD months in patients with PAI and for 50 ± 51 SD months in patients with other types of vascular involvement). The initial anti TNF agent was infliximab (5mg/kg) in 15 patients and adalimumab (40 mg eow) in 1 patient who had PAA and PAT in combination. Additionally, all patients used varying dosages of glucocorticoids and 10 used immunosuppressives (azathioprine = 7).

At the time of survey closure (December 2013) all patients were being followed, with all but 3 being still on anti TNF therapy. None of the patients experienced an exacerbation or new development of vascular involvement under anti TNF therapy during a mean of 16±13.6 SD months for PAI patients and 19.5±14.9 SD months for patients with other vascular involvement. Anti TNF treatment (all infliximab) had been discontinued in 5 patients (4 with PAI). In 3 patients (2 with PAI) this was due to stable disease after a mean of 22.7±12 SD months treatment. One of these patients with PAA is on maintenance treatment with azathioprine and is symptom free 8 months after withdrawal. The second patient with PAT experienced hemoptysis due to development of a new PAT 3 years after withdrawal. He responded to re-institution of infliximab, which was switched to adalimumab because of anaphylaxis during the second infusion. The third patient with extensive venous involvement developed new venous thrombosis and secondary amyloidosis 1 year after withdrawal. His clinical status improved with re-institution of infliximab but he was also switched to adalimumab because of the development of anaphylaxis. In the 2 remaining patients with PAI infliximab was withdrawn because of serious infections (lung tuberculosis and fungal infection). The patient developing tuberculosis is still receiving treatment for tuberculosis with no immunosuppressives and the second patient with fungal infection was subsequently prescribed interferon alpha.

Conclusion: Our uncontrolled experience suggests that anti TNF therapy effectively suppresses signs and symptoms of major vascular involvement in BS. Relapses can be seen after withdrawal. The development of serious infections underline the importance of close follow-up.

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Interferon Alfa-Associated Depression in Patients with Behçet's Syndrome. Yasin Keskin[1], Emire Seyahi[1], Cagri Poyraz[2], Serdal Ugurlu[1], Yilmaz Ozyazgan[3] and Hasan Yazici[4]. [1]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [2]Cerrahpasa Medical Faculty, University Of Istanbul, Istanbul, Istanbul, Turkey, [3]Cerrahpasa Medical Faculty University of Istanbul, Istanbul, Turkey, [4]Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey.

Background/Purpose: Interferon (IFN) is an effective immunemodulatory agent in the medical management of eye disease of Behçet's syndrome (BS). The agent is frequently associated with psychiatric adverse events, such as depressive disorders and suicide attempts are the most feared complication (1). We evaluated psychiatric status of a group of BS patients in whom IFN was used for the first time. As a control group we studied BS patients who started to use drugs other than IFN.

Methods: We studied BS patients who were seen between January 2012 and January 2014 at the Behçet's syndrome outpatient clinic at Cerrahpaşa Medical Faculty. Patients who have a history of psychiatric illness, who use illicit drugs/alcohol, or who have parenchymal neurological involvement due to BS were not included in the study. Patients who started to use IFN for the first time (Group 1) and those who started to use drugs other than IFN (Group 2) were studied. Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) were used to measure status of depression at baseline and at week 12.

Results: Group 1 included 17 (14 M, 3F) while Group 2 included 21 (13 M, 8 F) patients. During 12 weeks of follow-up, in Group 1, 6 patients used corticosteroids while 3 used colchicine in addition to IFN. Drugs that were started in Group 2, were azathioprine and cyclosporine combination (n=5), infliximab (n=2), methotrexate (n=1), azathoprine alone (n=6) and colchicine (n=7). Patients who used IFN were more likely to be male, to have longer disease duration and to have eye disease. Besides that, demographic, socio-economical and clinical characteristics were similar between the Groups. Among patients who used IFN, both BDI and HADS scores increased significantly after 3 months of follow-up. These scores did not change among patients who used other drugs (Table 2). (Table 1). Additionally, those who answered (I have thoughts of killing

myself but I would not carry them out) to question no: 9 was more common in the IFN group at week 12 (35 % vs 10 %, p =0.053). These were 24 % vs 10 %, respectively, (p = 0.24) at baseline.

Conclusion: We found that the depression scales increased among IFN users after 12 weeks of follow-up compared to those who used other drugs. Additionally, after 12 weeks of follow-up, the frequency of those with suicidal ideation also increased among the IFN users. A recent survey indicated that BS patients with major organ involvement have already increased risk for depression and suicidal behavior (2). Physicians should be cautious while using IFN in BS, since this drug may further increase this risk.

Table 1. Depression scales at baseline and at week 12

	Interferon, n = 17			Other drugs, n=21		
	Baseline	Week 12	p	Baseline	Week 12	p
BDI, mean ± SD	11.4 ± 8.7	14.7 ± 9.0	0.05	10.9 ± 9.6	10.0 ± 8.0	0.39
HADS, mean ± SD	5.0 ± 4.5	7.1 ± 4.2	0.04	5.5 ± 4.2	5.3 ± 3.2	0.71

BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale

References:
1) Schaefer M, et al. Ann Intern Med. 2012;157:94–103.
2) Uzunaslan D, et al. Ann Rheum Dis 2013;72(Suppl3):927.

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Increased Risk of Parenchymal Neurological Involvement in Behcet's Syndrome Patients with Panuveitis. Berivan Bitik[1], Berna Goker[1], Kubilay Sahin[2], Yesim Sucullu Karadag[2], Ridvan Mercan[1], Abdurrahman Tufan[1], Mehmet Akif Ozturk[1], Fikri Ak[2], Yasar Karaaslan[3] and Seminur Haznedaroglu[1]. [1]Gazi University School of Medicine, Ankara, Turkey, [2]Ankara Numune Education and Research Hospital, Ankara, Turkey, [3]Hitit University, Corum, Turkey.

Background/Purpose: Behcet's Syndrome (BS) is a systemic vasculitis which may involve multiple organ systems simultaneously. Most frequently, clinical findings in BS fit into well recognized patterns such as the association between papulopustular skin lesions and arthritis. Neurological involvement in BS is a serious condition which could lead to significant disability. It could either be parenchymal or vascular. The pathogenesis of these two types of Neuro-Behcet's Syndrome (NBS) are suggested to be different. The purpose of this study is to evaluate the association between the parenchymal Neuro-Behcet's Syndrome and panuveitis.

Methods: We retrospectively reviewed the clinical records of 288 patients with BS, who met the international classification criteria for BS, diagnosed at two major rheumatology clinics from 2000 to 2014. Patient demographics, ophthalmic examinations, clinical and radiologic patterns of neurological involvement were recorded. Pearson's Chi-square test was used for analysis.

Results: In this cohort of a total of 288 patients, 93 developed panuveitis and 38 had NBS (28 men and 10 women, median age 33 (28–54)). Of the 38 patients with neurological involvement, 28 had parenchymal and 10 had vascular disease. Venous sinus thrombosis was the only vascular involvement in NBS patients. Those with panuveitis were significantly more likely to have parenchymal neurological involvement compared to those without panuveitis (22.6% vs 3.6 %, p =0.001) (Table). 21 of the 28 parenchymal NBS patients had panuveitis either prior to or during the course of neurological involvement. Panuveitis was significantly associated with parenchymal-NBS (OR 7.83 95% CI 3.19–19.21).

Table. The association between panuveitis and parenchymal neurological involvement in patients with BS.

BS Patients		Parenchymal neurological involvement: Present	Absent	P-value
Panuveitis	Present	21	72	0.001
	Absent	7	188	

Conclusion: Among our 288 patients with BS, over one out of five cases with panuveitis had neurological involvement during their disease course. Our findings suggest a significant association between these two major organ involvements. This association might also be defined as a recognized clinical pattern, similar to the association of papulopustular skin lesions with arthritis. BS patients with panuveitis should be educated about possible signs and symptoms of neurological involvement which could progress quite rapidly and early initiation of treatment is the key for success.

Disclosure: B. Bitik, None; **B. Goker**, None; **K. Sahin**, None; **Y. S. Karadag**, None; **R. Mercan**, None; **A. Tufan**, None; **M. A. Ozturk**, None; **F. Ak**, None; **Y. Karaaslan**, None; **S. Haznedaroglu**, None.

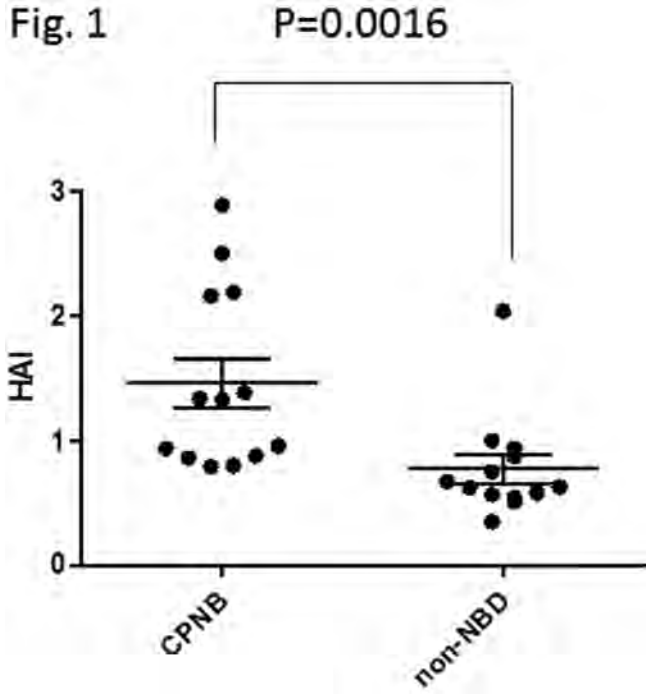
2762

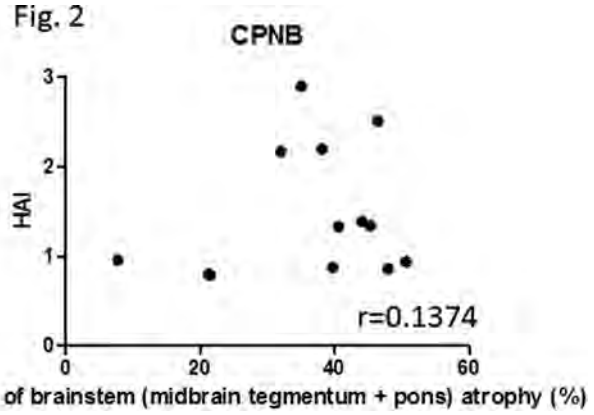
Atrophy of Hippocampal Region in Chronic Progressive Neuro-Behçet's Disease. Hirotoshi Kikuchi[1], Kurumi Asako[1], Maki Takayama[1], Yoshitaka Kimura[1], Akiko Okamoto[1], Toshihiro Nanki[2], Hajime Kono[1] and Shunsei Hirohata[3]. [1]Teikyo University School of Medicine, Tokyo, Japan, [2]Teikyo University, Tokyo, Japan, [3]Kitasato University School of Medicine, Sagamihara, Japan.

Background/Purpose: Central nervous system involvement in Behçet's disease, usually called neuro-Behçet's disease (NB), can be classified into acute NB (ANB) and chronic progressive NB (CPNB) based upon the differences in clinical courses and responses to corticosteroid treatment. Previous studies demonstrated that brainstem atrophy was significantly more frequently observed in CPNB than in ANB or non-NB. Noteworthy, in addition to truncal ataxia, neurobehavioral changes are frequently observed in CPNB, which cannot be accounted for by brainstem atrophy. In the present study we examined the volumes of hippocampus in order to determine the responsible lesions for neurobehavioral changes in CPNB.

Methods: A total of 26 patients were studied, including 13 patients with CPNB (11 males and 2 females, age 51.2 ± 12.1 [mean ± SD]) and 13 non-NBD (10 males and 3 females, age 54.4 ± 11.4). All the patients satisfied the international classification criteria for Behçet's disease. CPNB was defined as intractable, slowly progressive neurobehavioral changes and/or ataxia accompanied by the persistent elevation of cerebrospinal fluid of IL-6 more than 20 pg/mL on two different occasions at intervals of at least 2 weeks (3). The sagittal sections of T1-weighted images on brain MRI were obtained from each patient. Severity of gray matter loss in the hippocampal region and whole brain were investigated by the software for Voxel-Based Specific Regional Analysis System for Alzheimer's Disease (VSRAD) (Eisai Co., Ltd), calculating the indicators of the degrees of hippocampal region atrophy (HAI) and those of whole-brain atrophy (WBAI). The areas of midbrain tegmentum and pons were measured on mid-sagittal sections of T1-weightened images of brain MRI using image analysis software Image J (NIH, U.S.).

Results: The VSRAD analysis showed that HAI was significantly increased in CPNB (1.46 ± 0.70 [mean ± SD]) compared with in non-NB (0.77 ± 0.40) (p=0.0016) (Fig. 1). Although less markedly, WBAI was significantly higher in CPNB (10.6 ± 5.0) than in non-NB (6.9 ± 1.7) (p=0.0240). Neither HAI nor WBAI was correlated with age. Whereas all the patients with CPNB showed brainstem atrophy, there was no significant correlation between HAI and the rate of brainstem atrophy (Fig. 2).





Conclusion: These results indicate that hippocampus, in addition to brainstem, is a commonly affected lesion in CPNB, accounting for progressive neurobehavioral changes. The lack of correlation between brainstem atrophy and hippocampal atrophy suggest that there might be some predisposing factors determining the preference of affected lesions in CPNB.

Disclosure: H. Kikuchi, None; **K. Asako**, None; **M. Takayama**, None; **Y. Kimura**, None; **A. Okamoto**, None; **T. Nanki**, None; **H. Kono**, None; **S. Hirohata**, None.

2763

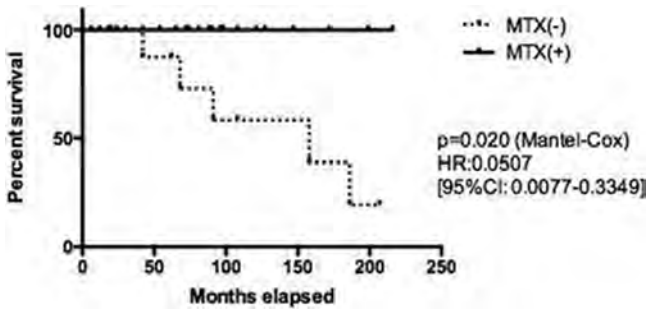
Long-Term Outcome of Chronic Progressive Neurological Manifestations in Behcet's Disease. Shunsei Hirohata[1], Hirotoshi Kikuchi[2], Tetsuji Sawada[3], Hiroko Nagafuchi[4], Msataka Kuwana[5], Mitsuhiro Takeno[6] and Yoshiaki Ishigatsubo[7]. [1]Kitasato Univ School of Med, Kanagawa, Japan, [2]Teikyo University School of Medicine, Tokyo, Japan, [3]Tokyo Medical University, Tokyo, Japan, [4]St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan, [5]Keio University School of Medicine, Tokyo, Japan, [6]Yokohama City University Hospital, Yokohama, Japan, [7]Yokohama City Grad Schl of Med, Yokohama, Japan.

Background/Purpose: Chronic progressive neurological manifestations in Behcet's disease (BD) is characterized by progressive deterioration leading to disability either with or without a history of previous attacks, thus called chronic progressive neuro-Behcet's disease (CPNBD). Although high doses of steroids, including steroid pulse therapy, cyclophosphamide and azathioprine have been anecdotally used in the treatment of CPNBD, the prognosis of the patients treated with such drugs have been usually miserable. Notably, methotrexate has been found effective for CPNBD in a prospective open trial with a small number of patients. However, its influences on the long-term outcome in a larger population remain unclear. The present study was designed to explore the effects of various treatment regimens, including methotrexate, on the prognosis of patients with CPNBD.

Methods: Thirty-seven patients, who met the international classification criteria for BD, and developed chronic progressive manifestations of NBD after 1988, were followed up until October 2013. The effects of various treatment regimens on prevention of death or severe disability of bedridden state were examined by Kaplan-Meier analysis and Cox's proportional hazard model.

Results: In 37 patients with CPNBD, 28 patients (75.7%) received methotrexate. Among the 28 patients with methotrexate, no patients died and only 5 patients progressed to disability with bedridden state. By contrast, among the 9 patients without methotrexate, 5 patients died and 3 patients progressed to the bedridden state. Thus, methotrexate significantly improved the survival of patients with CPNBD (HR 0.0507, 95% CI: 0.0077–0.334, p=0.020 as calculated by Mantel-Cox test) (figure), but any of steroid pulse, azathioprine or cyclophosphamide did not. Methotrexate also significantly reduced the proportion of the patients who were progressed into the bedridden state or death (HR 0.0694, 95% CI: 0.0047–0.7327, p=0.0258 as determined by multivariate analysis in Cox proportional hazard model).

Conclusion: These results indicate that methotrexate, but not high doses of steroids, azathioprine or cyclophosphamide, is effective to prevent the progression of CPNBD. Thus, it is recommended that methotrexate should be started as soon as possible the diagnosis of CPNBD is made.



Disclosure: S. Hirohata, None; **H. Kikuchi**, None; **T. Sawada**, None; **H. Nagafuchi**, None; **M. Kuwana**, None; **M. Takeno**, None; **Y. Ishigatsubo**, None.

2764

S100B Astrocyte Protein May Serve As a Prognostic Factor in Reversible Cerebral Vasoconstrictive Syndromes. Juan J. Maya[1], Vikram Puvenna[2], Chanda Brennan[2], Seby John[1], Ken Uchino[1], Leonard H. Calabrese[1], Damir Janigro[2] and Rula Hajj-Ali[1]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]Cleveland Clinic Lerner College of Medicine, Cleveland, OH.

Background/Purpose: Reversible Cerebral Vasoconstriction Syndromes (RCVS) are a group of disorders characterized by acute onset of recurrent thunderclap headaches with or without neurologic deficits. Radiologically, RCVS is characterized by reversible vasoconstriction; however at a molecular level the pathophysiology is poorly understood. Blood-Brain Barrier Disruption has been linked to a variety of neurological disorders. S100B is as an astrocytic protein considered to be an important peripheral blood marker of Blood-Brain Barrier Disruption and correlates with the presence or absence of enhancements on MRI scans. S100B serum levels have been used to study Blood-Brain Barrier Disruption after traumatic brain injury, and are even being used in emergency department settings to detect traumatic brain injury. Consequently, we assessed Blood-Brain Barrier Disruption in patients with RCVS by measuring the serum levels of S100B, and tested this protein for prognostic utility and risk stratification.

Methods: A total of 10 patients with RCVS from the Cleveland Clinic RCVS Biologic Repository were included in this study. A sample from each patient had been obtained during the ictal phase and samples of 3 patients were also obtained during the resolution of the vasoconstriction. S100B measurements were performed using S100B ELISA (Diasorin, Stillwater, MN). RCVS data was compared to age and gender matched historical controls, and subanalyses were performed using the data from the RCVS patients with ischemic stroke (n=5), and the RCVS patients with intracranial hemorrhages (n=4).

Results: Mean S100B level in RCVS patients during the ictal phase was statistically higher than the mean level in the control group (mean = 0.3644 vs. mean = 0.072, $p < 0.0001$). When the mean S100B level of RCVS patients with ischemic stroke (mean = 0.6588) was independently compared with the control group (mean = 0.072) and with RCVS patients with intracranial hemorrhages (mean = 0.048), the level was also statistically higher ($p < 0.0001$ for both comparisons). There was no statistical difference in the mean level of S100B between the control group and the group with intracranial hemorrhage ($p = 0.7271$). The levels of S100B in 2 out of 3 patients decreased when the initial levels were compared with the follow-up levels, in average from 0.08 to 0.05. The patient with the highest S100B level (> 3 SD above the mean) had multiple ischemic strokes and ultimately expired.

Conclusion: The elevation in S100B protein levels that was observed in RCVS patients implies that this condition can cause an alteration in the permeability of the Blood-Brain Barrier. S100B levels were higher in the ischemic stroke group as compared to the hemorrhagic group and to controls. This information implies that S100B may serve as a prognostic factor in a subgroup of RCVS patients. Furthermore, RCVS patients with intracranial hemorrhage did not have a significant increase in S100B levels, which is different from what other authors have observed in non RCVS intracranial hemorrhages. Further studies with larger number of subjects are needed in order to validate and further explore this data.

Disclosure: J. J. Maya, None; **V. Puvenna**, None; **C. Brennan**, None; **S. John**, None; **K. Uchino**, None; **L. H. Calabrese**, None; **D. Janigro**, Markers of Blood Brain Barrier Disruption and Methods of Using Same US 7,144,708, 9, Peripheral Markers of Blood Brain Barrier Permeability US 6,884,591 B2, 9; **R. Hajj-Ali**, None.

2765

Putative Blood Biomarkers of Reversible Cerebral Vasoconstriction Syndrome. Seby John, Belinda Willard, Leonard H. Calabrese, Ken Uchino, Tariq Hammad, Stewart Tepper, Mark Stillman and Rula A Hajj-Ali. Cleveland Clinic Foundation, Cleveland, OH.

Background/Purpose: The pathophysiology and molecular mechanisms of Reversible Cerebral Vasoconstriction Syndrome (RCVS) are unknown. Objective of the study was to identify putative biomarker proteins for RCVS.

Methods: Patients were recruited from our institution's prospective RCVS registry. Plasma samples were collected from 6 patients with RCVS during the acute cerebral vasoconstrictive phase, 2 patients at 6-month follow-up after resolution of vasoconstriction, and 4 patients with CNS vasculitis.

Plasma samples were immune-depleted for the most abundant plasma proteins, precipitated, and then digested overnight with trypsin and analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS). These LC-MS/MS experiments were carried out on a high resolution Orbitrap-Elite FT-MS system that allows the relative quantity of the proteins in these samples to be determined by a label free quantitative method. The quantitation is performed by searching the data with the programs Mascot and Sequest. These search results were then uploaded into the program Scaffold. The quantitation was performed by comparing the normalized spectral counts (SC) for the samples. The data was filtered based on several parameters including two matching peptides, a FDR of 1.0%, a protein threshold of 95%, and identified in at least 3 of the samples. The relative quantity of these proteins was determined by using the spectral counting method that has been described previously In order for a protein to be considered as a putative biomarker, the relative abundance needs to be at least two fold different with the T-test derived p-value less than 0.05.

Results: A total of 228 proteins were identified. Three, 5 and 4 proteins were found to be of higher abundance in a) follow-up samples of RCVS compared to baseline, b) CNS vasculitis samples compared to baseline RCVS, and c) baseline RCVS samples compared to CNS vasculitis respectively (Table 1).

Conclusion: This is a preliminary study looking at proteomic analysis of RCVS plasma samples. Results of this study show proteins that might be potential biomarkers for RCVS and which could help differentiate RCVS from its mimic CNS vasculitis. Further studies with larger number of patients are needed to assess reproducibility. The function and the pathways of these differentially expressed proteins should be further explored.

Table 1: List of differentially expressed proteins identified in LC-MS/MS analysis comparing i) Baseline vs follow-up RCVS and ii) Baseline RCVS vs CNS vasculitis

Protein	Average nSC Baseline RCVS	Average nSC Follow-up RCVS	Ratio Follow-up/ Baseline	T-Test P-Value
Neural cell adhesion molecule 1 isoform 5	0.8 ± 1.1	3.3 ± 1.5	4.1	0.0328
Structural maintenance of chromosomes protein 2	0.2 ± 0.4	1.3 ± 0.6	6.5	0.0201
Charged multivesicular body protein 4a	0 + 0	1.3 + 0.6	FU only	0.0015
	Baseline RCVS	**CNS Vasculitis**	**RCVS/CNS Vasculitis**	**P-Value**
Charged multivesicular body protein 4a	0.0 ± 0.0	1.8 ± 1.3	0.0	0.0158
Structural maintenance of chromosomes protein 2	0.2 ± 0.4	2.0 ± 0.0	0.1	0.0001
Poliovirus receptor isoform alpha	6.6 ± 4.1	14.0 ± 3.2	0.5	0.0211
Transthyretin	297.8 ± 75.5	602.0 ± 64.7	0.5	0.0004
Cystatin-C	5.4 ± 3.2	10.5 ± 2.4	0.5	0.0336
Lysozyme C	9.2 ± 1.1	3.8 ± 1.9	2.4	0.0010
Gamma-glutamyl hydrolase	9.2 ± 2.2	3.0 ± 3.8	3.1	0.0177
Uncharacterized protein C10orf92	4.6 ± 1.5	0.5 ± 0.6	9.2	0.0015
Ribonuclease 4	1.6 ± 0.9	0.0 ± 0.0	Base only	0.0096

Disclosure: S. John, None; **B. Willard**, None; **L. H. Calabrese**, None; **K. Uchino**, None; **T. Hammad**, None; **S. Tepper**, Please see notes, 9; **M. Stillman**, None; **R. A. Hajj-Ali**, None.

2766

Mycophenolate Mofetil in the Treatment of Primary Central Nervous System Vasculitis. Carlo Salvarani[1], Robert D. Brown Jr.[2], Teresa J. H. Christianson[2], John Huston III[2], Francesco Muratore[1], Caterina Giannini[2] and Gene G. Hunder[2]. [1]Arcispedale S Maria Nuova, Reggio Emilia, Italy, [2]Mayo Clinic, Rochester, MN.

Background/Purpose: The optimal management of primary central nervous system vasculitis (PCNSV) remains unclear. Cyclophosphamyde (CYC) in combination with glucocorticoids (GCs) or GCs alone are the most commonly used therapies. It is not proven if other immunosuppressants, used in other vasculitides, such as azathioprine (AZA), methotrexate (MTX) and mycophenolate mofetil (MMF), that are less toxic than CYC, can be used as induction and/or maintenance therapies. The aim of the study was to determine the efficacy and safety of MMF in PCNSV.

Methods: The study cohort consisted of 163 consecutive patients with PCNSV seen at Mayo Clinic (Rochester, MN) from 1983 to 2011. The diagnosis of PCNSV was based on findings of brain or spinal cord biopsy, cerebral angiography, or both. To assess treatment response, we used the treating physician's global opinion about the response to therapy. The degree of disability was defined using the modified Rankin scale. Outcomes, relapses, treatment response and ability to discontinue treatment at last follow-up were compared between patients treated with MMF and those receiving other therapies.

Results: 159/163 patients were treated at the time of diagnosis: 68 received GCs alone, 72 GCs and CYC, 2 CYC alone, 10 MMF and GCs, 6 AZA and GCs, and 1 rituximab and GCs. 6 more patients were treated with MMF after obtaining remission with CYC. In total, 16 patients were treated with MMF: 7 males and 9 females with a median age of 45.5 years (range: 20–72 years). Cerebral biopsy was performed in 10 and was positive in 9 (3 associated cerebral amyloid angiopathy). Clinical manifestations at presentation were: headache (9 patients), altered cognition (9 patients), persistent neurologic deficit or stroke (8 patients), seizures (6 patients) and 1 had intracranial hemorrhage. Cerebral MRI showed infarctions in 10 patients (bilateral in 7) and prominent leptomeningeal enhancement in 4 patients. CSF abnormalities were observed in 14/16 patients. The median duration of follow-up was 34 months (range: 10–78 months). Cerebral angiography was positive in 7/11 patients and large vessel involvement was observed in 4. The median dosage of MMF was 2 grams (range: 0.5–3 grams) and the median therapy duration 14.9 months (range: 1–31.6 months). Rankin disability scores at diagnosis were similar between patients treated with MMF and those receiving other therapies (Rankin score, 0–3: 68.7% versus 69.9%; Rankin score, 4–6: 31.3% versus 30.1%; p = 1.000). A significantly lower proportion of patients treated with MMF had severe disability at last follow-up compared to those receiving other therapies (Rankin score, 4–6: 0 versus 25.1%, p=0.023). No statistically significant differences were observed in patients treated with MMF compared to those receiving other therapies regarding relapses [7/16 (43.7%) versus 37/143 (25.9%), p = 0.146], ability to discontinue therapy at last follow-up [4/16 (25%) versus 36/142 (25.3%), p = 1.000], and treatment response [15/15 versus 111/142 (78.1%), p = 0.075]. Only 1 patient suspended MMF for a severe adverse event (leukopenia).

Conclusion: In this retrospective study of a small number of PCNSV patients, MMF was an effective and safe therapy.

Disclosure: C. Salvarani, None; **R. D. Brown Jr.**, None; **T. J. H. Christianson**, None; **J. Huston III**, None; **F. Muratore**, None; **C. Giannini**, None; **G. G. Hunder**, None.

2767

Core Outcome Domains and Potential Measurement Instruments in polymyalgia Rheumatica (PMR) Using Omeract Filter 2.0. Sarah Mackie[1], Toby Helliwell[2], Rodney Hughes[3], E Brouwer[4], Colin T. Pease[5], Christian Mallen[6], Maarten Boers[7] and John R. Kirwan[8]. [1]University of Leeds, Leeds, United Kingdom, [2]Keele University, Staffordshire, United Kingdom, [3]St. Peters Hospital, Chertsey Surrey, United Kingdom, [4]University Medical Center Groningen, Groningen, Netherlands, [5]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [6]Keele University, Keele, United Kingdom, [7]VU University Medical Center, Amsterdam, Netherlands, [8]Bristol Royal Infirmary, Bristol, United Kingdom.

Background/Purpose: The OMERACT PMR specialist interest group was established to develop a core outcome measurement set for PMR using the methods of OMERACT filter 2.0. This work builds on previous work undertaken to identify potential domains, which were presented at OMERACT 11.

Methods: A three-round Delphi survey was undertaken to identify domains of importance (Figure1). Additionally, meetings of patient and clinician participants were convened in order to scrutinise and finalise the candidate core domain set. A review of the PMR literature was undertaken to identify outcome measures and instruments used in previous PMR research. The candidate domains and identified instruments were presented and discussed at OMERACT 12.

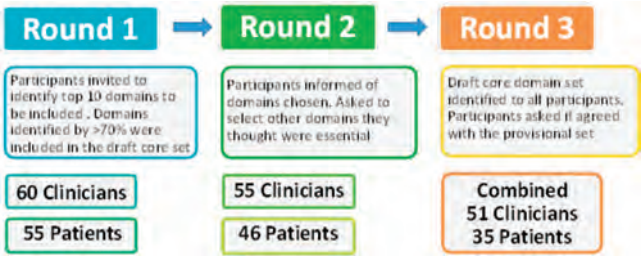


Figure 1.

Results: The literature review identified 28 studies for full review. The identified domains from the Delphi survey and corresponding measurement instruments are presented in Table 1.

Table 1.

Life Impact		Pathophysiological Manifestations		Rare/serious or adverse events	
Domain	Instrument used (N)	Domain	Instrument used (N)	Domain	Instrument
Pain/ache	VAS (11)	Blood tests	CRP or ESR (26)	Death	SAE reporting
Fatigue	VAS (2)	Physician Global	VAS (3)	Giant Cell Arteritis	Clinical diagnosis
Patient Global	VAS (3)	Stiffness	Duration (min) (7)	'Glucocorticoid AE'	None identified
Quality of Life	SF36 (2)				
ADL	HAQ (4)				

N: Number of studies; VAS: Visual analogue scale; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; SAE: Serious adverse event; AE: Adverse event; SF36: Short Form-36; ADL: Activities of daily living; HAQ: Health Assessment Questionnaire Disability Index

No study reported any patient involvement in the development of the outcome measures used. The candidate core domain set emerging after discussion at the OMERACT 12 PMR special interest group is shown in figure 2. Two studies undertook instrument validation and demonstrated poor test-retest reliability for fatigue VAS, morning stiffness duration, and SF36 mental component score and that the HAQ performed well for PMR.

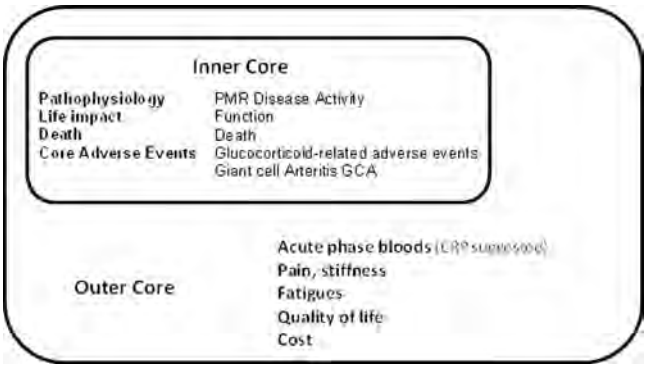


Figure 2.

Conclusion: The concern over glucocorticoid (GC) adverse effects (AEs) warrants their inclusion in the core set. No accepted measurement instrument for GC AEs was identified. GC AEs were not routinely reported in the studies identified. Review work by a EULAR Task Force found little evidence of their prevalence and severity at different daily and cumulative doses. Low dose GCs remain the cornerstone of PMR treatment and so the reporting of relevant associated AEs should be routine. The candidate core domain set is supported by substantial patient and clinician contributions, and by the previous use of these domains. Full evaluation of the instruments would now be worthwhile.

Disclosure: S. Mackie, None; **T. Helliwell**, None; **R. Hughes**, None; **E. Brouwer**, None; **C. T. Pease**, None; **C. Mallen**, None; **M. Boers**, None; **J. R. Kirwan**, Horizon Pharma USA Inc, 2.

2768

Patient Reported Outcomes and Acute Phase Reactants in Polymyalgia Rheumatica in Patients Treated with Prednisone Versus Modified-Release Prednisone. Mauro Betelli, Giulia Erba, Massimo Ricci, Carlo Valena, Elisabetta Allevi, Marta Riva, Giorgia Grosso, Simona Barbarossa, Federica Bonomi and Maria Rosa Pozzi. Rheumatology Outpatient Clinic - San Gerardo Hospital – Milano-Bicocca University, Monza, Italy.

Background/Purpose: Polymyalgia rheumatica (PMR) is a chronic inflammatory disorder of the elderly, characterised by morning stiffness, pain and aching in the hip and shoulder girdles and acute phase reactants increase. The response to low-dose prednisone (Pd) is marked and fast on both Patient Reported Outcomes (PROs) and acute phase reactants, but most patients require a treatment course of 1–3 years. A new modified-release delivery system Prednisone adapts the release of the administered glucocorticoid to the circadian rhythms and proved to be useful for morning stiffness, fatigue and disease activity control in Rheumatoid Arthritis. We compared Prednisone (Pd) to modified release Prednisone (MR-Pd) on PROs and acute phase reactants in Polymyalgia Rheumatica.

Methods: We studied 15 patients (5 men, mean age 70 years, SD 8.25) with newly diagnosed PMR and previously untreated. They received the same tapering dose of prednisone starting from 15 mg: 8 patients received a MR-Pd tablet, and 7 a Pd tablet. We observed no drop-outs but only ten patients have completed the 16-week assessment period by now (3 men, mean age 72 years, SD 5.48). CRP/ESR, VAS for stiffness duration/intensity and fatigue and HAQ-DI (PROs) were obtained at baseline and at week 4 and 16. We used Standardized Response Means (SRM), a measure of responsiveness, to evaluate acute phase response and clinical parameters improvement at week 4 and 16.

Results: The mean relative changes of the CRP/ESR and PROs from baseline to 4th and 16th week were not statistically different between Pd and MR-Pd ($p > 0.05$), confirming their same efficacy at the same dosage. We noticed that after 4 weeks CRP, fatigue, stiffness duration and HAQ assessment showed a better response in the group treated with modified release CS (CRP SRM 1.03–0.71, fatigue SRM 1.25–0.80; stiffness duration 1.40–0.40, HAQ SRM 1.74–1.10 for modified and immediate release Prednisone respectively). However at week 16 there were no significantly differences between CRP and HAQ (SRM 0.56 – 0.67 and 1.83 – 1.82 respectively), whereas fatigue and stiffness duration improved in patients treated with Pd (SRM 1.12– 7.03 and 0.72 – 1.01). Otherwise impact on stiffness intensity was constantly better in patients treated with Pd (after 4 and 16 weeks respectively: SRM 1.70–1.15 and 4.19–1.16).

Conclusion: Modified-Release Prednisone and Prednisone showed the same overall efficacy on Patient Reported Outcomes and acute phase reactants in patients with PMR, but with different timings and impacts on various disease aspects.

Disclosure: M. Betelli, None; **G. Erba**, None; **M. Ricci**, None; **C. Valena**, None; **E. Allevi**, None; **M. Riva**, None; **G. Grosso**, None; **S. Barbarossa**, None; **F. Bonomi**, None; **M. R. Pozzi**, None.

2769

Validation of New 2012 EULAR/ACR Classification Criteria for Polymyalgia Rheumatica: Comparison with the Previous Criteria in a Prospective Multi-Center Study. Gulsen Ozen[1], Seda Bas[1], Ali Ugur Unal[1], Gezmis Kimyon[2], Ahmet Mesut Onat[2], Meryem Can[3], Alperen Mengi[3], Ali Sahin[4], Sema Yilmaz[5], Havva Keskin[6], Sadiye Murat[6], Ayse Balkarli[7], Veli Cobankara[7], Omer Nuri Pamuk[8], Yonca Cagatay[9], Neslihan Yilmaz[9], Ilker Yagci[1], Pamir Atagunduz[1], Sibel Z. Aydin[10], Nevsun Inanc[1] and Haner Direskeneli[1]. [1]Marmara University School of Medicine, Istanbul, Turkey, [2]Gaziantep University School of Medicine, Gaziantep, Turkey, [3]Fatih Sultan Mehmet Education and Research Hospital, Istanbul, Turkey, [4]Cumhuriyet University Faculty of Medicine, Sivas, Turkey, [5]Selcuk University School of Medicine, Konya, Turkey, [6]Goztepe Medeniyet University Faculty of Medicine, Istanbul, Turkey, [7]Pamukkale University School of Medicine, Denizli, Turkey, [8]Trakya University School of Medicine, Edirne, Turkey, [9]Bilim University Faculty of Medicine, Istanbul, Turkey, [10]Koc University Faculty of Medicine, Istanbul, Turkey.

Background/Purpose: To evaluate the diagnostic and discriminative ability of the new 2012 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) polymyalgia rheumatica (PMR) classification criteria compared to previous four diagnostic/classification criteria for PMR in a multi-centre prospective study.

Methods: One-hundred and five patients older than 50 years of age, presenting with new onset (symptom duration ≤12 weeks) bilateral shoulder pain with elevated acute phase reactants were enrolled from 9 rheumatology clinics in Turkey. Patients were prospectively followed and the diagnosis of PMR was established when the diagnosis was maintained without an

alternative diagnosis at 6 months of follow-up. Those who were diagnosed as other than PMR at the 6thmonth were designated as control group. All patients were classified by each of the five different criteria for PMR and 2010 ACR/EULAR RA classification criteria.

Results: Of the 105 patients with new-onset (mean symptom duration 9.9±7.0 weeks) bilateral shoulder pain 65 (61.9%) patients were diagnosed as PMR and 40 (38.1%) were diagnosed as nonPMR (15 were RA). The discriminative ability as estimated by the area under the receiver operating characteristic (ROC) curve, was better for the Chuang criteria (0.86) than 2012 EULAR/ACR clinical criteria for PMR (0.69), Jones (0.67), Bird (0.66) and Nobunaga (0.75) criterias (Table 1). The 2012 EULAR/ACR clinical criteria for PMR had a sensitivity of 90.8% and a specificity of 47.5%. Jones and Chuang criteria had the highest specificity (90% and 92.5%, respectively). The specificity of the new 2012 EULAR/ACR clinical criteria for PMR further decreased to 40% in RA patients. Although the new 2010 ACR/EULAR RA classification criteria classified only 2 out of 65 PMR patients as RA, the new 2012 EULAR/ACR clinical criteria for PMR classified 9 out of 15 RA patients as PMR.

Conclusion: The new 2012 EULAR/ACR clinical classification criteria for PMR can classify PMR patients with high sensitivity, however, its ability to discriminate PMR from other inflammatory conditions with shoulder pain, especially RA is poor. Another criteria set, Chuang criteria, despite involvement of similar clinical parameters, perform better in discriminating PMR from RA and other inflammatory/noninflammatory articular diseases. This difference may be attributed to the involvement of a cut-off for ESR as 40 mm/h, exclusion of other diagnoses as criteria and classification of patients as PMR when all criteria are fulfilled unlike the new 2012 EULAR/ACR clinical criteria which require just four 4 points. Our results, therefore, suggest that in seronegative patients with bilateral shoulder pain and acute-phase response, differential diagnosis of PMR and RA may require imaging or biomarker studies.

Table 1. Sensitivity and specificity of each set of PMR criteria

Criteria	Sensitivity (%)	Specificity (%)	AUC (95% CI)	Specificity (%)	AUC (95% CI)
	PMR vs Total Cases			*PMR vs RA*	
Chuang	80	92.5	0.86 (0.78–0.93)	93.3	0.86 (0.77–0.96)
Bird	92.3	40	0.66 (0.54–0.77)	13.3	0.52 (0.36–0.69)
Jones	44.6	90	0.67 (0.57–0.77)	93.3	0.69 (0.56–0.81)
Nobunaga	73.8	77.5	0.75 (0.65–085)	80	0.76 (0.63–0.90)
EULAR/ACR	90.8	47.5	0.69 (0.58–0.80)	40	0.65 (0.48–0.82)

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Polymyalgia Rheumatica Relapse and 'Silence' Large Vessel Vasculitis. Is There Any Association? Stavros Chrysidis[1], Philip Rask Lage-Hansen[1] and Andreas P. Diamantopoulos[2]. [1]Department of Rheumatology, Hospital of Southwest Denmark, Esbjerg, Denmark, [2]Hospital of Southern Norway Trust, Kristiansand, Norway.

Background/Purpose: Large Vessel Vasculitis (LVV) can present with heterogeneous clinical manifestations, which range from general symptoms (fever, loss of weight) to the classic symptoms of Giant Cells Arteritis (GCA) (headache, jaw claudication, visual manifestations). Around 40% of GCA patients have concomitant Polymyalgia Rheumatica (PMR) and up to 40% of PMR patients have a positive biopsy of the temporal artery (TAB).

Studies evaluating ultrasound (US) as a diagnostic tool in GCA have reported a high sensivity and specificity.

The aim of this study was to investigate the association between disease's relapse and co-existing "silence" LVV in patients with pure PMR.

Methods: Patients with PMR who relapsed under corticosteroid (CS) tapering In Esbjerg Hospital, Denmark in the period of April 2013 to June 2014 have been prospectively included. In patients with PMR who relapsed under corticosteroid (CS) tapering, US examination of temporal (AT), axillary (AA), subclavian (AS) and carotid (AC) arteries was performed. US images were recorded and evaluated by an ultrasonographer experienced on vascular ultrasound (AD), who was blinded to patients' clinical and laboratory data.

US was considered positive when a homogeneous hypoechoic thickness >1.5 mm in AC and AS and >1mm in AA, in transverse and longitudinal view was observed. For the AT, the typical sign of halo (arterial wall swelling in transverse and longitudinal view) was considered as vasculitis. Relapse was defined as the reappearance of PMR clinical symptoms in addition to elevated ESR or CRP (ESR> 40 mm/h, CRP>10mg/lt) or persistent increased CRP/SR without any other explanation. All patients with positive US findings underwent a TAB.

Results: On a period of 14 months, 17 patients had been evaluated. All patients fulfilled the Bird's classifications criteria for PMR and all the patients responded appropriately to CS treatment at baseline. None of the patients had GCA- related clinical symptoms either on baseline or during the relapse. No significant differences were observed between the two groups of patients (PMR + LVV and PMR - LVV) in age, diseases duration, initial CRP/SR levels and initial CS dose (prednisolon 15–25mg).

Seven out of 17 (41%) patients had ultrasonographic sign of vasculitis. All patients had affection of the AA (6 of them bilateral), 3 of the AS, 1 of the AT none of the AC. The patient with the positive US of the AT was the only who had a positive TAB.

Conclusion: In our study, the relationship between PMR relapse and concomitant "silence" LVV has been evaluated. More than one-third of PMR patients who relapsed had a co-existing LVV. Thus, we recommend the use of vascular US in all patients with PMR suffering a relapse to investigate the possible co-existence of LVV.

Disclosure: S. Chrysidis, None; **P. R. Lage-Hansen**, None; **A. P. Diamantopoulos**, None.

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PET-CT Imaging and Association of Ferritin Autoantibodies in Polymyalgia Rheumatica. Niklas Thomas Baerlecken[1], Torsten Witte[2], Marco Amedeo Cimmino[3] and Dario Camellino[4]. [1]MD, Hannover, Germany, [2]MD, Hanover, Germany, [3]Università di Genova, Genova, Italy, [4]Clinica Reumatologica, Genova, Italy.

Background/Purpose: Previously we described antibodies against ferritin heavy chain peptide (anti-FHCP) in sera of patients with giant cell arteritis (GCA) and/or polymyalgia rheumatic (PMR) before glucocorticoid treatment was initiated. In that study, it remained unclear however, whether the PMR patients may have suffered from additional undiagnosed GCA. Therefore, we now measured antibodies against FHCP in PMR patients in whom GCA had been excluded by FDG-PET scan.

Methods: Sera of 63 patients were studied that presented initially with symptoms of PMR. A PET-CT had been performed in all patients and revealed large vessel vasculitis in 27 of these patients (GCA/PMR), whereas 36 had no signs of vasculitis (PMR). In a single-blinded study, we measured anti-FHCP in these patients and in a control group of patients with rheumatic diseases (RD, n=26), malignant diseases (MD, n=15) and infectious febrile diseases (IFD, n=22).

In the ELISA 3 peptides of the ferritin heavy chain were used as antigens: A19–45 (AAINRQINLELYASYVYLSMSYYFDRF), A79–104 (GRIFQDIKKPCDDWESGLNAMECA) and A105–143 (LHEKNVNQSLELHKLATDKNDPHLCFIETHYLNEQVK).

Results: The frequency of antibodies against A19–45 were 38/63 (60%) in all PMR patients and 14/63 (22%) in controls ($p<0.0001$), of antibodies against A79–104 30/63 (48%) in all PMR patients and 9/63 (14%) in controls ($p=0.0001$) and of antibodies against A105–143 38/63 (60%) in PMR and 12/63 (19%) in controls ($p<0.0001$). There were no differences within the controls considering all antigens.

Comparing the patients with and without vascular involvement in PET-CT, the frequencies of antibodies against A19–45 (18/27 (67%) and 20/36 (56%), ($p=0.53$)), against A79–104 (14/27 (52%) and 16/36 (44%) ($p=0.74$)) and against A105–143 (19/27 (70%) and 19/36 (53%) ($p=0.25$)) were not different.

Conclusion: This single-blinded study confirms the frequency of anti-FHCP in a different cohort. Anti-FHCP are associated with both GCA/PMR and PMR only.

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The Use of Imaging in the Diagnosis of Polymyalgia Rheumatica: Systematic Literature Review and Meta-Analysis. Sarah Mackie[1], Gouri Koduri[2], Catherine L. Hill[3], Andrew Hutchings[4], Richard J. Wakefield[5], Bhaskar Dasgupta[6] and Jeremy Wyatt[1]. [1]University of Leeds, Leeds, United Kingdom, [2]York Teaching Hospital NHS Foundation Trust, York, United Kingdom, [3]University of Adelaide, Adelaide, Australia, [4]London School of Hygiene and Tropical Medicine, London, United Kingdom, [5]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [6]Southend University Hospital, Essex, United Kingdom.

Background/Purpose: ACR/EULAR provisional classification criteria for polymyalgia rheumatica (PMR) incorporate musculoskeletal ultrasound of shoulder and hip (bursitis and synovitis given equal weight). Our objective was to systematically review diagnostic accuracy of imaging features of PMR: the reference standard was rheumatologist diagnosis.

Methods: Data sources were MEDLINE, EMBASE and PubMed searches; hand-searching; and experts in the field. Two authors independently reviewed search outputs and discussed disagreements. 1764 citations yielded 23 eligible studies. Data were extracted by two authors independently. Methodological quality was assessed by 3 authors using QUADAS-2. Hierarchical summary receiver operating curve (HSROC) models were constructed where appropriate, and positive/negative likelihood ratios (LR+/LR-) calculated.

Results: 23 studies with data from 2328 patients were evaluated: musculoskeletal ultrasound (9 studies), vascular ultrasound (6), magnetic resonance imaging (MRI) (6), and positron emission tomography (PET) (2). One further article (musculoskeletal ultrasound) was published during the preparation of this review. Internal and external validity varied, as did the clinical spectrum. All but one of the studies had a diagnostic case-control design. The most useful imaging features were subacromial-subdeltoid bursitis (SAB) on one or both sides (4 ultrasound studies: LR+ 2.5 (1.6 to 3.8); LR− 0.30 (0.11 to 0.81)), bilateral SAB (4 ultrasound studies: LR+ 6.2 (1.2 to 32); LR− 0.38 (0.15 to 0.97)), and presence of trochanteric bursitis (2 ultrasound, 1 MRI and 1 PET study: LR+ 5.4 (3.3 to 8.8), LR− 0.076 (0.002 to 2.8)). Hip or shoulder synovitis LRs were closer to the non-informative ratio of 1.0. Interspinous bursitis (LR+ 4.5 (1.5 to 13), LR− 0.26 (0.093 to 0.73)) and ischiogluteal bursitis (LR+ 3.6 (1.5 to 8.8), LR− 0.19 (0.05 to 0.69)) were detected by PET scans rather than ultrasound.

Conclusion: Based on current evidence, the most useful imaging features for the diagnosis of PMR appear to be SAB, bilateral SAB and trochanteric bursitis, rather than shoulder or hip synovitis.

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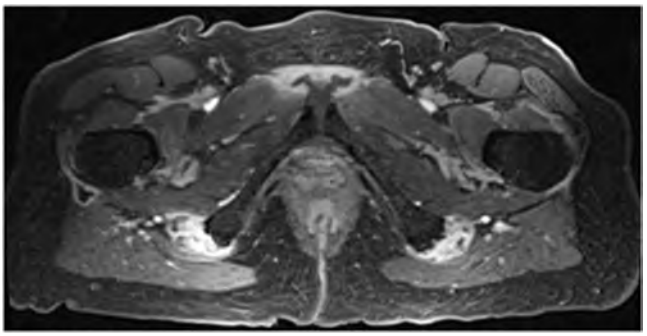
2773

Whole-Body MRI Reveals Characteristic Extracapsular Pattern of Inflammation in Polymyalgia Rheumatica. Sarah Mackie[1], Colin T. Pease[2], Eiki Fukuba[3], Paul Emery[4], Richard J. Hodgson[4], Jane E. Freeston[5] and Dennis McGonagle[6]. [1]University of Leeds, Leeds, United Kingdom, [2]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [3]Faculty of Medicine, Shimane University, Shimane, Japan, [4]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [5]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds., United Kingdom, Leeds, United Kingdom, [6]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Background/Purpose: Polymyalgia rheumatica (PMR) is a disease of widespread musculoskeletal inflammation characterized by pain and stiffness in shoulder and hip girdles. Here we report the first use of whole-body MRI to study the clinical spectrum of PMR in the rheumatology clinic. We hypothesized that PMR is characterized by an extracapsular pattern of inflammation.

Methods: 38 participants underwent whole-body MRI: 22 consecutive cases of clinically-diagnosed, active PMR identified by two rheumatologists with a special interest in PMR and followed up for a mean of 21 months; and 16 patients (controls) selected from a larger inflammatory arthritis (RA) cohort. 4 of the PMR patients did not have gadolinium enhancement, due to contra-indications. Anonymised gadolinium-enhanced MRI scans were consensus scored in axial view using semi-quantitative grading, and the features best discriminating PMR from RA were identified. Patients were treated after the MRI with 15mg prednisolone and then asked at follow-up whether they now felt back to normal.

Results: A characteristic pattern suggesting PMR was classified as "PMR pattern" by the blinded scorers; this could be identified both on the gadolinium-enhanced and non-enhanced scans. The features best discriminating PMR from RA were inflammation in the following sites: extending up around the rim of the acetabulum ("peri-acetabular"); around the ischial tuberosity; within the hip joint; around the greater trochanter; and around the symphysis pubis (Figure). Of all the MRIs performed in patients with a clinical diagnosis of PMR, "PMR pattern" was significantly associated with patient-defined glucocorticoid responsiveness ($p=0.01$).



Conclusion: A characteristic, extracapsular pattern of inflammation in PMR can be identified, and defines a subgroup of the clinical spectrum of PMR with excellent patient-reported glucocorticoid responsiveness. MRI is particularly useful in assessing inflammation of structures around the pelvis.

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Why Leg Ulcers Do Not Heal? a Prospective Study Showing High Proportion of Small Vessel Vasculitis. Vinod Ravindran[1], Sunil Rajendran[2] and Ranjish Vijayan[2]. [1]National Hospital, Kozhikode, Kerala, India, [2]PVS Hospital, Kozhikode, India.

Background/Purpose: Non healing cutaneous ulcers of lower limbs can have several different aetiologies [1]. It is likely that the patients with such ulcers would be treated with empirical therapies and may also undergo (unnecessary) venous procedures. Small vessel vasculitides (leucocytoclastic or non leucocytoclastic) are one of the important causes of non healing cutaneous leg ulcers [2]. The primary objective of this prospective study was to ascertain the cause of non healing cuatneous ulcers of the lower limbs.

Methods: Between May 2010 and April 2013 (3years) consecutive adult patients (age 18 to 75 years) who had one or more persistent leg ulcers (with or without a history of recurrent ulcerations in legs) for more than 2 years presenting to us were prospectively enrolled. Relevant details were extracted using a predefined proforma and included: demographic details, drug history, comorbidities, clinical features, investigations including ANCA, complement levels, cryoglobuilins, HIV and Hepatitis viral serology etc. and venous and arterial Dopplers, microscopy and culture of the ulcer swab in instances of infected looking ulcers. Previous biopsies were reveiwd and fresh biopsies were obtained from the ulcer edges and also from the nonulcerated sites where suitable skin lesions were also present. In cases of ulcers deemed to be a manifestation of a primary systemic vasculitis based on the EMEA classification, BVAS was used to assess disease activity.

Results: A total of 51 patients were assessed. Mean age was 53 ± 10.3 years and 39 (76%) were male. Eight (16%) patients were diabetic. History of some type of venous surgery was present in 30 (59%) and 9 had such procedures more than once. Biopsy confirmed small vessel vasculitis of various types in a majority (76%) of patients (table 1). Drug induced cutaneous vasculitis was not present in this cohort.

Table 1

Aeitiology	n(%)	Comments
Small vessel Vasculitis	39 (76%)	All biopsy proven
Chronic infections	4 (8%)	Mainly Stap. epidermidis
No apparent single cause	8 (16%)	Likely mixed aetiology

In 9 (18%) patients the leg ulcers were one of the manifestations of a primary systemic vasculitis i.e GPA (4), EGPA(2), MPA(2) and PAN (1). Leg ulcers in these patients ran an indolent course with a variety of low to moderate grade of activity features reflected also in the BVAS range of 9 to 15. All patients with small vessel vasculitis were treated with immunosuppressive therapy including glucocorticoids with good effect [complete healing of ulcer(s) in 21 patients with no relapse in 24 weeks of follow up period].

Conclusion: In this cohort of patients with chronic non healing leg ulcers small vessel cutaneous vasculitis emerged as the leading cause and majority benifitted from subsequently instituted specific measures of treatment.

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Disclosure: V. Ravindran, None; **S. Rajendran**, None; **R. Vijayan**, None.

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Cutaneous Vasculitis Associated with Severe Bacterial Infections. Study of 27 Patients from a Series of 766 Cutaneous Vasculitis. Leyre Riancho-Zarrabeitia[1], Javier Loricera[1], Ricardo Blanco[1], Jose L. Hernández[1], Vanesa Calvo-Río[1], Francisco Ortiz Sanjuan[1], Cristina Mata-Arnaiz[1], Javier Rueda-Gotor[1], Lino Álvarez[1], Carmen Gonzalez-Vela[1], Marcos A. González-López[1], Susana Armesto[1], Trinitario Pina Murcia[2], Montserrat Santos-Gómez[1] and Miguel A. González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [2]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain.

Background/Purpose: To assess the clinical spectrum of severe bacterial infections presenting as cutaneous vasculitis (CV) in a defined population.

Methods: Unselected series of 766 patients with CV diagnosed at a single university referral center.

Results: An underlying severe bacterial infection was diagnosed in 27 (22 men/5 women; mean age±SD: 53±18 years) of 766 cases presenting with CV (3.5%). These infections were: pneumonia (n=8), endocarditis (n=6), meningitis (n=4), intra-abdominal infections (n=3), septic arthritis (n=2), septicemia (n=2), septic bursitis (n=1), and urinary tract infection (n=1). All the patients were admitted for suspected CV. The median delay from admission to the diagnosis of infection was 4 days. A typical palpable purpura without relevant visceral vasculitic involvement was the main clinical manifestation. Patients with severe bacterial infections were older, with male predominance, had more frequently fever, constitutional symptoms, focal infectious features, and leukocytosis with left shift and anemia than the remaining patients with CV. Although antibiotics were prescribed in all the patients, seven of them also required the use of low-dose corticosteroids to achieve complete resolution of cutaneous lesions. Most patients experienced full recovery but two of them underwent prosthetic cardiac valve replacement, and another two died due to infection-related complications.

Conclusion: CV may be the presenting manifestation of a severe underlying bacterial infection. Physicians should keep in mind this fact to make an early diagnosis of infection and, consequently, prevent life-threatening complications.

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Drug-Associated Cutaneous Vasculitis: Study of 239 Patients from a Single Referral Center. Montserrat Santos-Gómez[1], Francisco Ortiz Sanjuan[1], Ricardo Blanco[1], Jose L. Hernández[1], Vanesa Calvo-Río[1], Javier Loricera[1], Carmen Gonzalez-Vela[1], Trinitario Pina Murcia[2], Hector Fernandez-Llaca[1], Susana Armesto[1], Victor Martínez-Taboada[1], Javier Rueda-Gotor[1], Leyre Riancho-Zarrabeitia[1] and Miguel A. González-Gay[1]. [1]Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Spain, Santander, Spain, [2]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, IDIVAL, Santander, Spain.

Background/Purpose: The 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides defined drug-associated immune complex vasculitis as a distinct entity included within the category of vasculitis associated with probable etiology. In the present study we assessed the clinical spectrum of patients with drug-associated cutaneous vasculitis (DACV).

Methods: Case records of patients with DACV attending to a tertiary referral hospital over a 36-year period were reviewed. A diagnosis of DACV was considered if the drug was taken within a week before the onset of the disease.

Results: 239 (30.9%) patients (133 men and 106 women with a mean age of 36 years) from a series of 773 unselected cutaneous vasculitis were diagnosed with DACV. Antibiotics (n=149; 62.3%) -mainly β-lactams-, and non-steroidal-anti-inflammatory drugs (NSAIDs) (n=24; 10%) were the most common drugs. Besides skin lesions (100%), the most common clinical features were joint (51%) and gastrointestinal (38.1%) manifestations, nephropathy (34.7%), and fever (23.8%). The most remarkable laboratory data were increased erythrocyte sedimentation rate (40.2%), presence of serum cryoglobulins (26%), leukocytosis (24.7%), positive antinuclear antibodies (21.1%), anemia (18.8%), and positive rheumatoid factor (17.5%). Despite drug discontinuation and bed rest, 108 patients (45.2%) required medical treatment, mainly corticosteroids (n=71) or immunosuppressive drugs (n=7). After a median follow-up of 5 months, relapses occurred in 18.4% of patients, and persistent microhematuria or renal insufficiency in 3.3% and 2.9%, respectively.

Conclusion: DACV is generally associated with antibiotics and NSAIDs. In most cases it has favorable prognosis, although a small percentage of patients may develop residual renal damage.

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Clinical-Biological Spectrum and Therapeutic Management of Hypocomplementemic Urticarial Vasculitis: Data from a French Nationwide Study on 57 Patients. Marie Jachiet[1], Alain Le Quellec[2], Alban Deroux[3], Pascal Godmer[4], Mikael Ebbo[5], Leonardo Astudillo[6], Beatrice Flageul[7], Nicolas Dupin[8], Selim Aractingi[1], Loïc Guillevin for the French Vasculitis Study Group[9], Luc Mouthon[9] and Benjamin Terrier[1]. [1]Cochin Hospital, Paris, France, [2]Division of internal Medicine, Hôpital Saint-Eloi, Centre Hospitalier Universitaire de Montpellier, Montpellier, Montpellier, France, [3]CHU Grenoble, Grenoble, France, [4]Department of Internal Medicine, Centre Hospitalier Bretagne Atlantique de Vannes, Vannes, France, [5]CHU, Marseille, France, [6]CHU, Toulouse, France, [7]Saint Louis, Paris, France, [8]Service de Dermatologie, Hôpital Cochin, AP-HP, Paris, France, [9]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France.

Background/Purpose: Hypocomplementemic urticarial vasculitis (HUV), an uncommon vasculitis of unknown etiology, is rarely reported. It is also called anti-C1q vasculitis in the 2012 revised International Chapel Hill Consensus Conference Nomenclature for Vasculitis. Information on its presentation and therapeutic management is scarce.

Methods: To analyze the clinical spectrum and therapeutic management of HUV patients, we conducted a French nationwide retrospective and transdisciplinary study on behalf of the FVSG that included 57 patients with chronic urticaria, histological leukocytoclastic vasculitis and hypocomplementemia as inclusion criteria.

Results: The 57 identified patients had a median age at diagnosis of 45 (range 15–83) years, and 42 (74%) were women (sex ratio 2.8). HUV was

isolated in 43 (75%) patients, while the remaining 14 (25%) were associated with systemic lupus erythematosus (n=10), primary Sjögren's syndrome (n=2), systemic sclerosis and lung cancer (n=1 each). Urticarial lesions were typically erythematous papules, more pruritic than painful, associated with angioedema (51%), purpura (35%) and/or livedo reticularis (14%). Extracutaneous manifestations included constitutional symptoms (56%), musculoskeletal (82%), ocular (56%), pulmonary (19%), gastrointestinal (18%) and/or kidney involvement (14%). HUV patients typically had low C1q-complement and normal C1-inhibitor levels, with 55% of them also having anti-C1q antibodies. Patients with anti-C1q antibodies had more frequent systemic HUV, angioedema, livedo reticularis, ocular, musculoskeletal and/or kidney involvement(s), and less frequent pulmonary and/or gastrointestinal involvement(s). Hydroxychloroquine (HCQ) or colchicine seemed to be as effective as corticosteroids as first-line therapy. For patients with relapsing and/or refractory HUV, higher cutaneous and immunological response rates were obtained with immunosuppressants, particularly azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide or rituximab (RTX)-based regimens, with the latter apparently more effective. Finally, cutaneous and immunological responses were strongly associated.

Conclusion: HUV is an uncommon systemic and relapsing vasculitis with various manifestations, mainly musculoskeletal and ocular. Half of the patients have anti-C1q antibodies. HCQ and colchicine should be the first-line therapy, whereas corticosteroids alone or combined with an immunosuppressant, preferentially AZA, MMF or RTX, could be alternative therapeutic options for relapsing and/or refractory disease.

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Non-Systemic Vasculitic Neuropathy: Presentation, Therapeutic Management and Outcome. Benjamin Terrier[1], Fleur Cohen[2], Aude Rigolet[3], Jean-Emmanuel Kahn[4], Alice Berezne[5], Olivier Benveniste[6], Alain Créange[7], Thierry Maisonobe[8], Zahir Amoura[9], Luc Mouthon[10] and Loïc Guillevin for the French Vasculitis Study Group[10]. [1]Cochin Hospital, Paris, France, [2]Pitié-Salpétrière, Paris, France, [3]Assistance Publique - Hôpitaux de Paris, Pitié-Salpêtrière University Hospital, Paris, France, [4]Internal Medicine, Foch Hospital, Suresnes, France, [5]Paris Descartes University, Internal Medicine department, Cochin Hospital, Paris, France, [6]Sorbonne Universités, University Pierre et Marie-Curie-Paris 6, INSERM, Paris, France, [7]Henri Mondor, Créteil, France, [8]Pitie-Salpetriere Hospital, Paris, France, [9]Pitié-Salpêtrière Hospital (AP-HP), Paris, France, [10]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, Paris, France.

Background/Purpose: Non-systemic vasculitic neuropathy (NSVN) is a small-to-medium–sized vessel vasculitis limited to the peripheral nervous system. It can be considered a single-organ vasculitis, as recently defined in the revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides in 2012. NSVN is probably an underdiagnosed entity that has rarely been reported. This descriptive study was undertaken to ascertain its presentation, therapeutic management and outcome.

Methods: We retrospectively analyzed 18 patients with NSVN fulfilling criteria proposed by Collins in 2010, including: 1) peripheral neuropathy, 2) vasculitis histologically proven on neuromuscular biopsy, 3) possible constitutional symptoms, and 4) absence of systemic manifestations or laboratory markers suggestive of systemic vasculitis or connective tissue disease.

Results: Ten women and 8 men, median age 51 (range 27–83) years, were included. Neurological manifestations were characterized by acute onset (78%), mononeuritis multiplex (88%), polyneuropathy (12%), sensory impairment (100%) and motor impairment (88%). Neurological manifestations were painful (88%) and asymmetrical (78%). Nerve trunks involved were external popliteal (94%), internal popliteal (44%), ulnar (33%), radial (17%) and median (11%). General symptoms included asthenia and weight loss >10% (22% each), arthralgias (12%) and fever (6%). Only 2 patients had elevated inflammatory parameters. Neuromuscular biopsy showed, in muscle or nerve, medium-sized-vessel vasculitis (56%) or small-sized-vessel vasculitis (44%), with fibrinoid necrosis (88%). Corticosteroids were prescribed to 94%, and their NSVN regressed significantly (65%), stabilized (2%) or progressed (24%). Cyclophosphamide was added to corticosteroids for refractory patients. Relapsing patients received methotrexate or azathioprine, with 3/4 patients showing improvement. After median follow-up of 47 months, neurological sequelae were noted in 83%, including sensory sequelae in 15 patients and motor sequelae in 6.

Conclusion: The results of this study describing NSVN presentation, therapeutic management and outcome indicated that acute onset, painful and asymmetrical manifestations are suggestive of NSVN. Half of the patients required immunosuppressive agents because of relapsing and/or refractory disease. Sensory and motor sequelae were common, suggesting that early diagnosis and initiation of therapy are critical.

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2779

Systemic Inflammatory and Autoimmune Manifestations Associated with Myelodysplastic Syndrome: A French Multicenter Retrospective Study. Arsene Mekinian[1], Eric Grignano[1], Thorsten Braun[2], Olivier Decaux[3], Eric Liozon[4], Nathalie Costedoat-Chalumeau[5], jean Emmanuel Kahn[6], Mohamed Hamidou[7], Geraldine Falgarone[8], Olivier Lortholary[9], Sophie Park[10], Zahir Amoura[11], A. Mathian[12], Bruno Gombert[13], Christian Rose[14], Xavier Puechal[5], David Launay[15], Guillaume Denis[16], Bertrand Lioger[17], Anne Laure Buchdaul[18], Sophie georgin Lavialle[19], Francois Montestruc[20], Mohammed Omouri[21], Julien Rossignol[22], Jean Marc Ziza[23], Pascal Cathebras[24], Serge Madaule[25], Benoit de Wazières[26], Nathalie Morel[5], Sebastien Trouillet[27], Loic Raffray[28], Yoland Schoindre[29], Eric Toussirot[30], jean Charles Piette[31], Claude Gardin[2], Lionel Ades[32], Pierre Fenaux[32] and Olivier Fain[33]. [1]Internal Medicine, DHUi2B Saint Antoine Hospital, paris, France, [2]Haematology department Avicenne Hospital, bobigny, France, [3]Rennes University Hospital, Rennes, France, [4]INTERNAL MEDICINE, DIJON, France, [5]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, [6]Internal medicine Hopital Foch, PARIS, France, [7]CHU Hôtel Dieu, Nantes, Nantes, France, [8]Rheumatology department Avicenne Hospital INSERM 1125, bobigny, France, [9]Service de maladies infectieuses, Hôpital Necker-Enfants malades, AP-HP, Paris, France, [10]Haematology Department, Grenoble University Hospital, grenoble, France, [11]Pitié-Salpêtrière Hospital (AP-HP), Paris, France, [12]Internal Medecine Department, Pitie-Salpetriere Hospital, Paris, France, [13]La Rochelle hospital, La Rochelle, France, [14]haematology, lille, France, [15]Service de médecine interne, Centre National de Référence de la Sclérodermie Systémique, Hôpital Claude Huriez, CHRU Lille, Lille, France, [16]Rochefoucault hospital, Rochefoucault, France, [17]INTERNAL MEDICINE, tours, France, [18]Douai hospital, Douai, France, [19]Internal Medicine Department Tenon Hospital, paris, France, [20]exystat, PARis, France, [21]Rheumatology Department Romilly Hospital, romilly, France, [22]haematology, paris, France, [23]Hopital Croix-Saint-Simon, Paris Cedex 20, France, [24]University Hospital St Etienne, St Etienne, France, [25]Chg, Albi, France, [26]Department of Internal Medicine and Gerontology, Hôpital Universitaire Carémeau, Nîmes, France, Nimes, France, [27]INTERNAL MEDICINE, aurillac, France, [28]INTERNAL MEDICINE, bordeaux, France, [29]DHU 2iB Internal Medicine Referal Center for Autoimmune diseases Pitie Hospital, PARIS, France, [30]Rheumatology Department, Univesity Hospital, besancon, France, [31]INTERNAL MEDICINE, PARIS, France, [32]Haematology department Saint Louis Hospital, paris, France, [33]Hôpital Saint Antoine, DHU i2B, Service de Médecine Interne, paris, France.

Background/Purpose: To describe characteristics, treatment and outcome of patients with systemic inflammatory or autoimmune diseases (SAID) and myelodysplastic syndrome (MDS).

Methods: For this retrospective study, a questionnaire was sent to SNFMI, CRI and GFM to report patients with SAID and MDS, concomitantly or successively. SAID were classified according to usual diagnostic criteria. Exclusion criteria included 1) MDS diagnosed > 12 months after immunosuppressive treatment for SAID 2) infectious, drug-related or neoplasm-related SAID. MDS characteristics, outcome, survival were compared between patients with MDS associated SAID and a cohort of 665 MDS without SAID diagnosed at Avicenne's university hospital between 2003 and 2013.

Results: 123 patients with both MDS and SAID (mean age, 70±13 years; 41 females and 82 males, baseline characteristics in table 1) were included. SAID was systemic vasculitis in 39 cases (32%), connective tissue diseases in 31 cases (25%), inflammatory arthritis in 28 cases (23%), neutrophilic disorder in 12 cases (10%) and unclassified in 13 cases (11%). Complete diagnostic SAID criteria were fulfilled in 66% of cases, remained incomplete

in 21% and SAID was unclassified in the remaining patients. The diagnosis of SAID and MDS was concomitant in 38 (31%) cases, diagnosis of SAID preceded MDS in 46 (37%) cases and was made after MDS in 39 (32%) cases, with the time between the diagnoses of the 2 diseases being 8.6±52 months. Apart from significant association between Chronic myelomonocytic leukemia (CMML) and systemic vasculitis (p=0.0024), no correlation was seen between specific types of SAID and of MDS. A response to SAID first line treatment (mainly steroids), was observed in 83% of the 118 treated cases, including 80% for steroids alone. A second-line treatment was required for steroid dependence or relapse in 48% of the patients. Among treated patients who received biologic targeted treatments at any time (n=27), overall response of SAID (partial or complete) was noted in 9/20 (45%) patients. Among 16 patients treated by azacytidine for their MDS, SAID remission was seen at 3 months in 75% of the cases, with a significant decrease of acute-phase reactants and steroid amounts required. At last follow-up, 37 patients (67%) with stable MDS had remission of SAID, and among patients with MDS progression, 23 patients (56%) also had active SAID (p=0.2).

Conclusion: The spectrum of SAID associated to MDS is variable, many cases remain difficult to classify. Presence of SAID has no impact on the overall survival of MDS patients. Azacitidine can improve SAID in 75% of the patients. Because of frequent steroid dependence and relapse of SAID, better therapeutic strategies with biological targeted drugs are required, while larger use of MDS specific dugs like azacitidine must be assessed prospectively.

Table 1. Baseline characteristics of patients with MDS-associated to SAID and MDS without SAID.

	MDS with SAID N=123	MDS without SAID N=665
Age (years)	70 ± 13	73 ± 11*
Female/Male	41/82 (50%)	291/374 (78%)*
Karyotype	62 (75%)	386 (69%)
Favorable	8 (10%)	111 (20%)*
Intermediate Poor	13 (16%)	64 (11%)*
Bone Marrow blasts (%)	6.5±9	4±5*
IPSS	0.9±0.9	0.8±0.9
IPSS low	18 (23%)	190 (34%)*
Intermediate-1	39 (49%)	181 (33%)*
Intermediate-2	15 (19%)	107 (19%)
Poor	7 (9%)	76 (14%)
RCUD	11 (9%)	73 (11%)
RARS	1 (1%)	57 (9%)*
RAEB-1	18 (15%)	130 (20%)
RAEB-2	10 (8%)	116 (17%)*
CMML 1/2	19 (16%)/5 (4%)	96 (14%)/7 (1%)
5q syndrome	6 (5%)	25 (4%)
RCMD	31 (26%)	136 (20%)
MDS-U	11 (9%)	22 (3%)
Progression to Acute Leukemia	26 (22%)	83 (21%)
Survival (medians, months)	72 [59-105]	75 [48-300]

*p<0.05

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Effectiveness of a Sequential Treatment with Intravenous Prostaglandins Followed By Bosentan in Patients with Buerger Disease and Severe Ischemic Lesions: A Case Series. Helena Borrell[1], Javier Narváez[2], Milagros Ricse[1], Eulalia Armengol[1], Andrea Zacarias[1], Sergi Heredia[1], Carmen Gomez Vaquero[1] and Joan Miquel Nolla[1]. [1]Hospital Universitario de Bellvitge, Barcelona, Spain, [2]Hospital Universitario de Bellvitge. Barcelona. Spain, Barcelona, Spain.

Background/Purpose: Buerger disease or tromboangitis obliterans (TAO) is a distinct form of systemic vasculitis of unknown etiology though strongly linked to cigarette smoking. It affects the small and medium-sized arteries and veins in the extremities of the limbs, frequently requiring amputation. Tobacco withdrawal is the only known effective treatment. Endothelial dysfunction appears to be of relevance in this condition and a report has even found that high serum levels of endothelin correlate with the presence of necrosis.

This prelimary study assessed the effectiveness and safety of a sequential treatment with intravenous prostaglandins followed by bosentan in patients with severe TAO.

Methods: A series of patients with TAO and severe ischemic ulcer or gangrene were treated with intravenous alprostadil (PGE-1) for 21 days, followed by bosentan p.o at dose of 62.5 mg twice daily during the first month, which was thereafter up-titrated to 125 mg twice daily. Bosentan was administered on a compassionate-use basis. The study endpoints were clinical improvement of the pain and trophic lesions and the need of amputation.

Results: To date, 4 patients have been included, all of them fulfilling the diagnostic criteria proposed by *De Olin (Current Opin Reumatol 2006;18: 18–24)*. Two patients were male and 2 women, with a mean age of 45 years. All patients were current smokers and withdrawn tobacco during follow-up as well as received antiaggregants.

In all cases a complete healing was achieded within the first 4 months after starting the sequential treatment, with disappearance of pain and complete healing of the ischemic lesions in the patient's toes. None of the patients required amputation. Bosentan could be stopped after a mean of 12 months (SD: 4.22, range 10–14), without relapses. After discontinuation of bosentan, patients were followed for a median of 21 months (4.54; 14–24) and none developed new ischemic lesions.

In all patients bosentan was well tolerated, without any observed adverse reaction.

Conclusion: This preliminary data suggest that a sequential treatment with intravenous prostaglandins followed by bosentan may be considered a therapeutic option for patients with TAO and severe ischemic lesions. Larger studies are required to confirm these results.

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ACR Plenary Session III: Discovery 2014

Tuesday, November 18, 2014, 11:00 AM–12:30 PM

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Cost-Effectiveness of Adding Etanercept Vs. Sulfasalazine and Hydroxychloroquine to Methotrexate Therapy: A Randomized Noninferiority Trial. Nick Bansback[1], Ciaran Phibbs[2], Huiying Sun[3], James R. O'Dell[4], Mary Brophy[5], Edward C. Keystone[6], Sarah Leatherman[7], Ted R. Mikuls[4] and Aslam H. Anis[3]. [1]University of British Columbia, Vancouver, BC, [2]Palo Alto VA Health Care System, Menlo Park, CA, [3]Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, [4]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [5]VA Boston Heathcare System, Boston, MA, [6]University of Toronto, Toronto, ON, [7]VA Boston Heatlhcare System, Boston, MA.

Background/Purpose: To estimate the incremental cost-effectiveness of etanercept plus methotrexate versus a triple regimen of disease-modifying anti rheumatic drugs (methotrexate, sulfasalazine, and hydroxychloroquine) over 24 weeks and 48 weeks in patients with active rheumatoid arthritis despite methotrexate therapy (RACAT).

Methods: In this double blind, noninferiority trial 353 patients were randomized to etanercept plus methotrexate or a triple regimen. After 24 weeks of treatment patients not achieving a DAS28 improvement of 1.2 were switched in a blinded fashion to the other therapy. Quality Adjusted Life Years (QALYs) were estimated using US societal values from the EQ-5D instrument which was measured every 24 weeks. Costs of drugs, hospitalizations, procedures, tests, visits and lost productivity were prospectively tracked and monetized from a societal perspective in 2014 US dollars. Incremental cost-effectiveness ratios were calculated using standard procedures assuming an intent-to-treat analysis, with missing data analyzed using multiple imputation and uncertainty assessed using bootstrapping.

Results: Both strategies showed significant improvements in EQ-5D, with etanercept providing marginally more accumulated QALYs (0.358 vs 0.354 over 24 weeks, and 0.742 vs 0.726 over 48 weeks for etanercept and triple regimen strategies respectively). The etanercept strategy accumulated

substantially higher drug costs even considering the switches between treatements at 24 weeks ($11,286 vs $369 cumulative costs from 0 to 24 weeks, and $19,625 vs $3,721 cumulative costs from 0 to 48 weeks for etanercept and triple regimen respectively). The differences in other health care and productivity costs across strategies were negligible. The resultant incremental cost-effectiveness ratios for etanercept vs. triple regimen were $2.7 million/QALY (95%CI 0.87 to ∞) gained over 24 weeks and $0.95 million/QALY (95%CI 0.41 to ∞) over 48 weeks.

Conclusion: This economic evaluation based on a prospective tracking of resource use and QALY measurement in a blinded, randomized trial demonstrates that the additional costs associated with using etanercept prior to a triple regimen does not provide good value for money at generally acceptable willingness to pay thresholds. A limitation of the study is its short time frame. However, even when considering the long-term perspective, since the incremental benefits are so small, even under the most optimistic scenarios imaginable, etanercept has only a small probability of being cost-effective compared to triple therapy. Given the opportunity cost associated with all health care spending, adapting a triple regimen prior to etanercept would free up scarce health dollars for use on alternative health care interventions that provide greater health benefits.

Table 1.

	24 Weeks			*48 Weeks*		
	Etanercept plus MTX	**Triple Regimen**	**Incremental**	**Etanercept plus MTX**	**Triple Regimen**	**Increment**
QALYs	0.358	0.354	0.004	0.742	0.726	0.016
Costs ($)	11,981	1,245	10,736	21,537	6,358	15.179
Diagnostic Test	84	87	−3	168	207	−39
Outpatient	102	180	−78	225	331	−106
Joint Procedure	26	117	−91	129	169	−40
Hospital	271	276	−5	1086	1527	−441
Drug	11,286	369	10,917	19,625	3,721	15,904
Absenteeism	212	217	−5	303	403	−100
Cost-effectiveness ratio ($)	–	–	2,665,851	–	–	950,628

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2782

Autoantibodies from Single Circulating Plasmablasts React with Citrullinated Antigens and *Porphyromonas Gingivalis* in Rheumatoid Arthritis.

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Background/Purpose: Anti-citrullinated protein antibodies (ACPAs) are highly specific for rheumatoid arthritis (RA) and also believed to play a pathogenic role in RA. *Porphyromonas gingivalis* (*P. gingivalis*), a Gram negative oral pathogen associated with periodontitis, has long been speculated as a trigger for the anti-citrulline autoimmune responses in RA patients. However, the detail relation between ACPA and *P. gingivalis* is still unclear.

Methods: In this study, we made 195 recombinant monoclonal antibodies from anti-cyclic citrullinated peptide (CCP)-positive RA patients (N=6), 23 recombinant monoclonal antibodies from CCP-negative RA patients (N=1), and 110 recombinant monoclonal antibodies from healthy controls (N=4) using a single cell-based antibody cloning approach. All the 7 RA patients satisfied the 2010 ACR classification criteria. Monoclonal ACPAs were determined by commercial anti-CCP test and fine specificity with 3 synthesized citrullinated peptides. Cross-reactivity of ACPA to *P. gingivalis* was tested by ELISA against *P. gingivalis* outer membrane protein and citrullinated peptide from *P. gingivalis* enolase. Immunoglobulin genes of 5 ACPAs were reverted to the germ line sequences and the corresponding antibodies were also expressed for the above tests.

Results: The relative frequencies of circulating plasmablasts were significantly higher in RA patients than in healthy donors ($p = 0.0015$). About 19.5% of circulating plasmablast-derived recombinant antibodies from CCP-positive RA patients, but none from the CCP-negative RA patient or healthy donors, specifically recognized citrullinated RA autoantigens ($p = 0.0001$). The immunoglobulin genes encoding these ACPAs were highly mutated with increased replacement/silent mutation ratios, suggesting that the generation of ACPAs involved active antigen selection. Interestingly, 63% of these ACPAs cross-reacted with the outer membrane antigens and/or citrullinated enolase from *P. gingivalis*. Germ-line reversions of some ACPAs completely eliminated their reactivity to citrullinated RA autoantigens but retained their reactivity to *P. gingivalis* antigens.

Conclusion: These results suggest that circulating plasmablasts in RA patients produce ACPAs and this process may be, in part, initiated by the anti-*P. gingivalis* immune responses.

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Effect of Synovitis, Effusion and Bone Marrow Lesions on Development of Sensitization in Knee OA: The Multicenter Osteoarthritis Study.

Tuhina Neogi[1], Michael C. Nevitt[2], Joachim Scholz[3], Lars Arendt-Nielsen[4], Clifford Woolf[5], Laurence A. Bradley[6], Emily K. Quinn[7] and Laura Frey-Law[8]. [1]Boston University School of Medicine, Boston, MA, [2]UCSF (University of California, San Francisco), San Francisco, CA, [3]Columbia University, New York, NY, [4]Center for Sensory-Motor Interaction, Aalborg, Denmark, [5]Children's Hospital Boston, Boston, MA, [6]Univ of Alabama-Birmingham, Birmingham, AL, [7]Boston University, Boston, MA, [8]University of Iowa, Iowa City, IA.

Background/Purpose: Alterations in the peripheral and central nervous systems including sensitization are thought to play an important role in the pain experience in knee OA. While sensitization could occur due to an underlying predisposition, it is hypothesized that joint inflammation and/or tissue injury in OA could provide sufficient peripheral nociceptive input to cause sensitization. We previously reported that radiographic knee OA severity or duration do not appear to be related to sensitization. However, whether specific MRI lesions related to inflammation (e.g., synovitis, effusion), or mechanical load or remodeling related to noninflammatory tissue injury (e.g., bone marrow lesions (BMLs)) are risk factors for development of sensitization is not yet known.

Methods: The Multicenter Osteoarthritis (MOST) Study is a NIH-funded longitudinal cohort of persons with or at risk of knee OA. Subjects had x-rays and MRIs (1.0 T) of each knee obtained at each study visit, and a standardized somatosensory evaluation of mechanical temporal summation and pressure pain thresholds (PPT) at the patella at 60- and 84-months. Temporal summation was defined by increased pain during repeated mechanical stimulation (1 Hz × 30-sec) with a 60g monofilament. PPT was assessed with an algometer (1 cm^2 tip, 0.5 Kg/sec) as the point at which the subject felt the pressure change to slight pain. Lower PPT indicates more sensitivity. Synovitis, effusion and BMLs on MRIs were scored using WORMS (one knee per person); these lesions were considered to be present if their score was ≥1 in any subregion. In sensitivity analyses, we assessed the sum of BML scores across all knee subregions as a measure of BML burden. We assessed the relation of presence of synovitis, effusion, and BMLs at 60-mo to incident temporal summation in the same knee at 84-mo among those who did not have temporal summation at 60-mo, and to change in PPT in the same knee between 60- and 84-mo in the whole sample using logistic and linear regression, respectively, adjusted for relevant potential confounders, including OA severity.

Results: There were 1111 subjects (mean age 66.9, mean BMI 29.7, 62% female) in the whole sample. 22.6% developed incident temporal summation at the 84-mo visit, and the range in change of PPT between the 60- and 84-mo visits was −7.35 to 7.15 kg/cm^2. Presence of synovitis was associated with a significant decrease in PPT (i.e., more sensitized) over 24 mo, while effusion was significantly associated with incident temporal summation (**Table**). BML presence or burden were not associated with temporal summation or PPT.

Conclusion: Inflammation, as evidenced by synovitis or effusion, may drive the occurrence of sensitization in knee OA. In contrast,

BMLs do not appear to contribute to sensitization in knee OA. Early targeting of inflammation in knee OA may be a reasonable strategy to test for its ability to prevent occurrence of sensitization, thereby reducing pain severity in knee OA.

MRI Lesion at 60-mo	Incident Temporal Summation at 84-mo (N=716)		Change in PPT (60- to 84-mo) (N=1111)	
	Prevalence of MRI Lesion	Adjusted* OR (95% CI)	Prevalence of MRI Lesion	Adjusted* Beta (95% CI)
Presence of synovitis	62%	1.12 (0.75, 1.66), p=0.6	60%	−0.30 (−0.52, −0.08), p=0.01
Presence of effusion	67%	1.54 (1.01, 2.36), p=0.04	66%	−0.04 (−0.28, 0.19), p=0.7
Presence of BMLs	79%	0.92 (0.56, 1.49), p=0.7	79%	0.03 (−0.25, 0.31), p=0.8
Sum of BMLs ('BML burden') (per unit increase)	Range: 0–19	1.00 (0.92, 1.07), p=0.9	Range: 0–19	−0.01 (−0.05, 0.04), p=0.8

*Analyses adjusted for age, sex, BMI, clinic site, race, catastrophizing, depressive symptoms, widespread pain, KL grade

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Contribution at the Spinal Level of Innate and Adaptive Immunity to the Development of Persistent Post-Inflammatory Mechanical Allodynia in Arthritic Mice. Sarah Woller[1], Cody Ocheltree[1], Tony Yaksh[1] and Marpiat Corr[2]. [1]UCSD, La Jolla, CA, [2]University of California at San Diego, La Jolla, CA.

Background/Purpose: Individuals with arthritis frequently develop persistent pain despite adequate treatment of synovitis. There is a need to better understand the mechanisms underlying pain occurring with arthritis. Recently, it has been shown that Toll-like receptor 4 (TLR4) mediates the transition from acute to chronic pain in a murine model of arthritis. Rather than developing persistent pain, animals deficient in TLR4 showed an attenuation of the late phase of pain. This receptor is unique in signaling through both MyD88-dependent and independent pathways. In order to further understand the role of TLR signaling, we examined the development of arthritis and persistent pain in mice deficient in these adaptor proteins.

Methods: Adult arthritic K/BxN mice were bled and the sera pooled. 100μl of the pooled sera was injected into recipient mice on Days 0 and 2. Clinical arthritis scores and mechanical reactivity, using the up-down method of von Frey testing, were assessed over a period of 28 days in male C57Bl/6, *Tlr4*$^{-/-}$, *Trif*^{lps2}, *Myd88*$^{-/-}$, *Tnf*$^{-/-}$, and *Ifnar1*$^{-/-}$ mice. Spinal cords were collected from WT and *Tlr4*$^{-/-}$ arthritic mice and changes in gene expression were measured using nanoString™ nCounter™ analysis. Behavioral data were analyzed using repeated measures ANOVAs, and Duncan New Multiple Range *post-hoc* analyses when appropriate.

Results: As shown previously, WT mice develop a persistent increase in mechanical reactivity that outlasts the period of inflammation; the 50% withdrawal thresholds dropped from 1.66 at baseline to 0.74 on day 28. In addition, *Tlr4*$^{-/-}$ mice develop an initial increase in reactivity, which resolves concurrent with inflammation (WT AUC 13.2 and TLR4 AUC 9.7, $p<.05$). MyD88 and TRIF play distinct roles in the development of pain: mice lacking MyD88 do not develop swelling or allodynia (AUC 2.6, $p<0.01$), while those deficient in TRIF develop a *prolonged* allodynia (AUC 12.2), similar to WT animals and outlasting the period of inflammation. NanoString™ nCounter™ analysis of 516 immune genes in the spinal cords of WT and *Tlr4*$^{-/-}$ mice harvested on Day 10 of arthritis showed differences in expression levels of IL2, RANKL, IFNβ, and TNF transcripts. Therefore, we also examined the development of pain resulting from arthritis in *Rag1*$^{-/-}$, *Ifnar1*$^{-/-}$, and *Tnf*$^{-/-}$ mice. In the *Tnf*$^{-/-}$ mice there was an attenuated development of pain (AUC 8.0, $p<.001$), the Rag1 (10.0, $p<.05$) mice developed pain, which resolved with the resolution of inflammation similar to *Tlr4*$^{-/-}$ mice and *Ifnar1*$^{-/-}$ mice developed pain that was not different than the WT mice (AUC 12.2).

Conclusion: These results suggest that pain can persist after resolution of inflammation. The innate and adaptive immune systems appear to have distinct roles in the development of the chronic pain state, and this pain cannot be attributed solely to increased TNF or IFNβ transcription.

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Joint Specific Positional Differences in Coding and Noncoding Transcriptome of Synovial Fibroblasts As a Determinant of the Susceptibility of Synovial Joints to Rheumatoid Arthritis. Caroline Ospelt[1], Maria Armaka[2], Giancarlo Russo[3], Anna Bratus[3], Michelle Trenkmann[4], Emmanuel Karouzakis[1], Christoph Kolling[5], Renate E. Gay[4], George Kollias[2], Steffen Gay[1] and Mojca Frank Bertoncelj[1]. [1]Center of Experimental Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]Biomedical Sciences Research Center 'Alexander Fleming', Vari, Greece, [3]Functional Genomics Center Zurich, ETH Zurich and University of Zurich, Zurich, Switzerland, [4]Zurich University Hospital, Zurich, Switzerland, [5]Schulthess Clinic, Zurich, Switzerland.

Background/Purpose: The molecular mechanisms underlying the topographic differences in the susceptibility of synovial joints to develop rheumatoid arthritis (RA) are unknown. Positional embryonic expression of Hox genes along proximal-distal and anterior-posterior body axes is critical for proper limb development. Adult skin fibroblasts retain the positional embryonic Hox code and exhibit major anatomic differences in their transcriptome, defining their unique positional identities. Synovial fibroblasts (SF) in the joints of RA patients drive joint destruction and inflammation locally. We hypothesized that SF from different joints show a joint specific, positional gene expression pattern, which can predispose joints to develop certain types of arthritides, like RA or osteoarthritis (OA).

Methods: SF were derived from knees, shoulders and metacarpophalangeal joints (MCPs) of RA and OA patients (n=9 each) undergoing joint replacement surgery. SF were obtained also from front paws, ankles and knees of wildtype (wt) and TNF transgenic (TNFtg) mice (n=7 each). Total RNA was extracted and RNA sequencing was performed with the Illumina HiSeq 2000 sequencing system followed by hierarchical clustering. Functional annotation clustering of mRNAs was done using Database for Annotation, Visualization, and Integrated Discovery (DAVID). Positionally expressed RNAs were validated by qPCR.

Results: Unsupervised hierarchical cluster analysis showed clustering of SF according to anatomic joint localization rather than disease. The positional embryonic HOX code was retained in SF, clearly differentiating between different joints. Among the Hox cluster residing long noncoding RNAs, HOTTIP was expressed in distal, MCP-derived SF and HOTAIR in posterior, knee-derived SF. Several positionally expressed mRNAs, e.g.HOXC8 and HOXD13, were differentially expressed in MCP-derived RA and OA SF. DAVID analysis showed positional enrichment of GOTERM limb development, anterior/posterior patterning, cartilage development, extracellular region part, cell adhesion, regulation of transcription. While some outliers where found when clustering was based on mRNA expression, clustering of SF into knee, shoulder and MCPs was perfect when based on miR expression. For example, miR-24 was positionally expressed in shoulder, miR-34c in MCP, and miR-137 in knee-derived SF, irrespective of disease. The positional expression of these miRs was confirmed in wt and TNFtg mice. Interestingly, miR-204 and miR-146a were positionally expressed in MCPs of OA but not of RA patients. These miRs were indeed positional also in wt mice but their MCP specific expression in humans correlated to ankle specific expression in wt mice. In addition, their expression was significantly changed in ankles of TNFtg compared to wt mice.

Conclusion: SF from joints of different anatomic sites exhibit particularly different mRNA and miR expression patterns suggesting that functionally unique subsets of SF populate different joints. The existence of positionally imprinted "risk" signatures of SF may account for the susceptibility of certain synovial joints to develop RA in humans and mice and may have major implications for synovial disease pathways operating early in RA.

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2786

Aortitis: Outcomes from a Cohort of 196 Patients. Alison Clifford, Amr Arafat, Jahanzaib Idrees, Eric Roselli, Carmela D. Tan, E. Rene Rodriguez, Lars Svensson, Eugene Blackstone and Gary S. Hoffman. Cleveland Clinic Foundation, Cleveland, OH.

Background/Purpose: Idiopathic aortitis is a rare diagnosis that may occur in the context of a primary systemic vasculitis, as part of a systemic autoimmune disease, or in isolation. In patients with focal isolated aortitis

(FIA), surgery alone may be curative; however, new vascular lesions have been reported to develop in between 5–47% of cases. The risk of progression to systemic disease and optimal management strategy for FIA patients is uncertain.

Methods: Patients with biopsy-proven aortitis, diagnosed following thoracic aortic surgery at the Cleveland Clinic between 1996 and 2012, were retrospectively reviewed. Patients were classified into clinical subgroups [Giant cell arteritis (GCA), Takayasu's arteritis (TAK), Focal Isolated Aortitis (FIA) or Other] at the time of surgery using pre-defined criteria. Symptoms, pathology, laboratory and imaging results were recorded at surgery and over time using a standardized database. Patients with FIA at surgery were followed for progression to systemic disease and outcomes of clinical subgroups were compared.

Results: Of 7,551 patients who underwent thoracic aortic surgery between 1996–2012, 196 patients with biopsy-proven aortitis were identified for review. Median age at surgery was 69 years (range 15–88) and 67% were female. At the time of surgery, 129 (65.8%) patients met criteria for FIA, 42 (21.4%) for GCA, 14 (7.1%) for TAK, and 11 (5.6%) for Other. A minimum of 6 months of clinical follow-up was available for 73 FIA patients. During follow-up (median 45 months, range 6–201 months), 14/73 (19.2%) FIA patients developed symptoms of systemic disease, 17/40 (42.5%) developed elevated inflammatory markers, 29/65 (44.6%) developed new vascular lesions on imaging, 30/73 (41.1%) required a second vascular surgery, 7(9.6%) dissected and 9 died (12.3%.) Ultimately 23 of 73 (31.5%) with FIA progressed to have features of a systemic disease: 21 GCA, 1 TAK, and 1 Other. When compared to patients with known systemic disease at surgery, patients with FIA were less likely to develop symptoms ($p=0.01$) but no different with respect to development of elevated inflammatory markers ($p=0.19$), new vascular lesions by imaging ($p=0.92$), need for further vascular surgery ($p=0.84$), dissection ($p=0.40$) or death ($p=0.76$) over time. Only 12 patients with FIA at surgery received immunosuppressive therapy post-operatively. Over time, 0/11 treated FIA patients with follow-up imaging developed aneurysms, but 2 (18.2%) developed new stenoses. Among the 54 untreated FIA patients with imaging available, 27 (50%) developed new lesions (23 aneurysms and 5 stenoses.) Additional tissue obtained after subsequent surgery in 2 untreated FIA patients revealed persistent inflammation in the distal aorta.

Conclusion: Over time, nearly one third of patients classified as FIA at the time of surgery progressed to have features of a systemic autoimmune disease. Patients with FIA are less likely to develop overt symptoms, but equally likely to develop elevated inflammatory markers or new vascular lesions on imaging when compared to GCA, TAK and Others. These patients require regular clinical follow-up and serial imaging to assess for progression.

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ACR Concurrent Abstract Session
2014 Rheumatology Research Foundation Edmond L. Dubois, MD Memorial Lectureship

Tuesday, November 18, 2014, 2:30 PM–4:00 PM

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Identification of Urinary Biomarkers for Lupus Nephritis. Carolina Landolt-Marticorena[1], Stephenie Prokopec[2], Heather Reich[3], James Scholey[4], Carmen Avila-Casado[3], Paul R. Fortin[5], Paul Boutros[2] and Joan Wither[6]. [1]Toronto Western Hospital, Toronto, ON, [2]Ontario Institute for Cancer Research, Toronto, ON, [3]University Health Network, Toronto, ON, [4]The Toronto Western Hospital, Toronto, ON, [5]Laval University, Division of Rheumatology, Centre de Recherche du CHU de Québec and Department of Medicine, Quebec City, QC, [6]University of Toronto, Toronto, ON.

Background/Purpose: Lupus nephritis (LN) is a major determinant of morbidity and mortality in Systemic Lupus Erythematosus (SLE). Variability in clinical course, underlying renal injury, and response to treatment pose therapeutic challenges. Management of LN would be served by the discovery of biomarkers that accurately reflect changes in disease activity, aiding in the prompt identification of flares and evaluation of response to therapy. Renal biopsy is the most reliable way to determine the extent and nature of renal injury, with serologic changes (anti-dsDNA antibodies) or measures of renal dysfunction (proteinuria) faltering in the diagnosis of impending flares and/or assessment of therapeutic response. We used a proteomics approach to identify potential urinary biomarkers associated with LN.

Methods: Urine was obtained from 60 LN patients within 2 weeks of biopsy, 25 active non-LN SLE patients, and 24 controls. The mean age and proportion of females (83–88%) was similar in the 3 groups. 128 distinct analytes were quantified by Luminex and normalized by scaling to urinary creatinine levels. Data was analyzed by hierarchical clustering using divisive analysis (DIANA), linear modeling, and non-parametric statistics, with appropriate corrections for multiple comparisons.

Results: LN and non-LN SLE patients had comparable SLEDAI-2K scores (13.8 ± 7.6 and 11.1 ± 3.9, respectively), with the majority of the SLEDAI-2K in LN patients arising from the renal indices (renal SLEDAI = 8 ± 4.3). The distribution of the renal biopsy classes (ISN-RPS) for the LN patients was: I – 1; II-3; III or III/V-12; IV or IV/V-32; V-9; VI-2; TIN-1. The mean biopsy activity and chronicity scores biopsy were 6.68 (range 0–19) and 3.13 (range 0–10), respectively. Following hierarchical clustering, significant clustering was seen for LN as compared to non-LN SLE patients and healthy. Linear modeling was used to determine the urinary proteins whose abundance differed significantly between disease states (SLE vs healthy control) and between the presence or absence of LN (active LN vs active non-LN). There were 9 analytes that differed significantly (q value <0.01) between SLE patients and controls and 42 between LN and non-LN, of which 37 differed only in LN patients as compared to active non-LN patients. A number of proteins, not previously proposed as urinary LN biomarkers (e.g., MMP-2, TIMP-1), and known candidate LN biomarkers (e.g., adiponectin), were identified, with several of the novel biomarkers showing an enhanced ability to discriminate between LN and non-LN patients over potential biomarkers reported in the literature. Ten proteins were found to significantly correlate with the activity score on renal biopsy ($q < 0.01$), 5 of which (IP-10, vWF, adiponectin, IL-16 and PAI-1) strongly discriminated between active proliferative and non-proliferative/chronic renal lesions.

Conclusion: Using a proteomics approach we identified promising urinary biomarkers that correlated with the presence of active renal disease and/or renal biopsy changes. Experiments to assess the ability of these candidate biomarkers to fluctuate over time and predict clinically significant changes in renal disease activity and outcome are ongoing.

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Preliminary Population- Based Incidence and Prevalence Estimates of SLE: The California Lupus Surveillance Project. Maria Dall'era[1], Kurt Snipes[2], Miriam Cisternas[3], C. Gordon[4] and Charles G. Helmick[5]. [1]University of California, San Francisco, San Francisco, CA, [2]California Department of Public Health, Sacramento, CA, [3]MGC Data Services, San Diego, CA, [4]Medical School, Birmingham, United Kingdom, [5]Centers for Disease Control and Prevention, Atlanta, GA.

Background/Purpose: Previous estimates of prevalence and incidence of systemic lupus erythematosus (SLE) in the United States have varied widely. The California Lupus Surveillance Project (CLSP) is part of a national effort funded by the Centers for Disease Control and Prevention (CDC) to determine more credible estimates of incidence and prevalence of SLE, with a special focus on Hispanics and Asians.

Methods: The CLSP is a population-based registry designed to determine the incidence and prevalence of SLE in San Francisco County, California. Sources of cases included hospitals, rheumatologists, nephrologists, commercial laboratories, and state population databases. Over 15,000 potential SLE patients were identified after the initial queries, and trained abstractors performed detailed medical chart reviews on the >5,500 patients who met the catchment criteria of residence in San Francisco County within the years of 2007–2009. Cases were defined as patients with documentation of $>$ 4/11 of the ACR Classification Criteria for SLE. Using SAS 9.3, we calculated prevalence and incidence rates and associated 95% confidence intervals (CI). Denominators for all rates were obtained from the U.S. Census data (revised 2000–2009 intercensal population files) for San Francisco County.

Results: Preliminary overall crude prevalence and incidence of SLE in San Francisco County were 90.4/100,000 and 5.1/100,000 respectively. The highest prevalence of disease was observed in Black women (430.6/100,000), followed by Hispanic and Asian (163.8/100,000 and 158.9/100,000, respectively), and White (111.3/100,000) women (Table I).

Table I: Preliminary Prevalence and Incidence Rates (per 100,000) of SLE in San Francisco County, CA

Race/ethnicity, sex	Prevalence (2007) # cases	Prevalence (2007) Crude rate (95% CI)	Incidence (2007–2009) # cases	Incidence (2007–2009) Crude rate (95% CI)
Overall	704	90.4 (84.0–97.3)	121	5.1 (4.3–6.1)
Women	623	162.0 (149.8–175.2)	112	9.6 (8.0–11.5)
Men	81	20.6 (16.5–25.5)	9	0.7 (0.4–1.4)
Black	138	243.0 (205.7–287.0)	27	15.9 (10.9–23.1)
Women	121	430.6 (360.5–514.2)	25	29.9 (20.3–44.2)
Men	17	59.2 (37.0–94.9)	2	2.3 (0.6–8.4)
White	255	58.1 (51.4–65.7)	43	3.2 (2.4–4.3)
Women	230	111.3 (97.8–126.6)	38	6.0 (4.4–8.3)
Men	25	10.8 (7.3–15.9)	5	0.7 (0.3–1.7)
Asian	264	95.8 (84.9–108.1)	39	4.6 (3.4–6.3)
Women	233	158.9 (139.8–180.7)	37	8.3 (6.0–11.4)
Men	31	24.0 (16.9–34.1)	2	0.5 (0.1–1.9)
Hispanic	99	87.7 (72.1–106.8)	17	4.9 (3.1–7.8)
Women	87	163.8 (132.9–202.0)	16	9.8 (6.0–15.9)
Men	12	20.1 (11.5–35.1)	1	0.5 (0.1–3.1)

Conclusion: The CLSP uses more complete case finding methods to provide current estimates of prevalence and incidence in a racially and ethnically diverse population. Racial and ethnic disparities in SLE were confirmed with the highest burden of disease in Black women, followed by Hispanic and Asians, and, finally, White women.

Disclosure: M. Dall'era, None; **K. Snipes**, None; **M. Cisternas**, None; **C. Gordon**, None; **C. G. Helmick**, None.

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Medical Marijuana Related Outcomes in Patients with Systemic Lupus Erythematosis. Basmah Jalil[1], Wilmer Sibbitt Jr[2], Romy Cabacangun[3], Clifford Qualls[3], Arthur Bankhurst[4] and Roderick Fields[5]. [1]University of New Mexico, Albuquerque, NM, [2]University of New Mexico HSC, Albuquerque, NM, [3]UNM, Albuquerque, NM, [4]University of NM Med Ctr, Albuquerque, NM, [5]University of New Mexico School of Medicine, Albuquerque, NM.

Background/Purpose: Medical cannabis is used extensively in the United States, usually in the form of smoked marijuana. There is growing research regarding the immunomodulatory effects of cannabinoids and the cannabinoid receptor system as a possible therapeutic target. Despite the increasing use of medical marijuana, almost all studies report short–term subjective effects of medical cannabis with little to no real outcome data in medical disease and systemic lupus erythematosus (SLE) in particular. Randomized, controlled trials of smoked cannibis are generally considered ethically problematic. This study determined whether cannabis was associated with important outcomes in SLE, including mortality and morbidity.

Methods: This is an analysis of a prospective de-identified 5 year longitudinal outcome study of a cohort of SLE patients at the University of New Mexico with a sample size of 276 patients with 30.4% using marijuana and 69.5% with no marijuana use. All patients had signed informed consent, but additional IRB approval was obtained prior to analyzing the de-identified database in relation to cannabis. Inclusion criteria were any patient with SLE, age 18–80. Exclusion criteria were any patient with a diagnosis other than SLE, age < 18 years, age > 80 years. The population sample was diverse and included all social and ethnic backgrounds, with Hispanics and Whites being the dominant participants. This analysis was supported by the University of New Mexico. Outcomes were determined at 5 years after enrollment in the study.

Results: No significant difference was observed in age, gender, SLE disease duration, SLE criteria, ANA titer, dsDNA titer, antiphospholipid Ig G, M, A, RF, anti-ribosomal P, incidence of Sjogren's syndrome between marijuana and non-marijuana users. Ethnically these groups were also similar.

However marijuana users were more likely to use opiate analgesics (p value 0.008), even though no differences were reported between pain scores, prednisone use, SLEDAI or joint pain/stiffness between the 2 groups. With marijuana use there was a 39% increase in neuropsychiatric SLE ($p=0.04$), a 85% increase in end-stage renal disease requiring dialysis ($p<0.006$) and a 40% increase in mortality ($p<0.12$). With multivariate analysis, the association of marijuana on the increase in ESRD could be explained completely by an increase in non-compliance/nonadherence to recommended therapy (non-marijuana: 3% noncompliance vs. marijuana use: 95% non-compliance, p value < 0.001).

Conclusion: This 5 year outcome study indicates that marijuana use in SLE is not associated with reduced pain, use of prednisone, narcotic analgesics or SLE disease activity. However, marijuana use in SLE is associated with an increased incidence of neuropsychiatric SLE, death, narcotic use, end stage renal disease, and noncompliance/nonadherence to recommended therapy. These epidemiologic data are not supportive of a beneficial role for medical cannabis in SLE.

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CMR with Quantitative T2 Mapping in Patients with Active SLE. Stacy P. Ardoin[1], Wael Jarjour[2], Subha V. Raman[2], Amanda Kibler[2] and Tam Tran[2]. [1]Ohio State University College of Medicine, Columbus, OH, [2]Ohio State University, Columbus, OH.

Background/Purpose: Cardiovascular (CV) disease is an important cause of morbidity in systemic lupus erythematosus (SLE). Myocarditis is considered an uncommon complication of SLE but autopsy studies suggest prevalence of up to 40%. With this study we used cardiac magenetic resonance (CMR) quantitative T2 mapping to assess for subclinical myocardial involvement during SLE flare.

Methods: Consecutive patients with active SLE (defined by SLEDAI $>$ 5 and clinician's intention to change therapy due to disease activity) without bias to CV symptoms were enrolled at a single academic center. Clinical, demographic and laboratory data were collected. CMR was performed on 1.5 Tesla scanner and included cine imaging, T2 mapping in long and short axes. Late gadolinium enhancement was assessed after contrast administration if GFR > 30. Left ventricular (LV) end diastolic volumes, end systolic mass and peak circumferential strain were measured. All images were scored by an experienced, blinded reader. To reduce artifactual findings, T2 mapping was limited to the 6 mid cardiac segments, and involvement of $\geq$2 mid-segments was considered abnormal. Based upon myocarditis literature, T2 scores > 59 ms were considered abnormal. Descriptive statistics were performed; means were compared using Student's t-test and correlation assessed with Pearsons' coefficient.

Results: 27 patients underwent CMR: mean age 32.4 years, 82% female, 44% black, mean SLEDAI-2K 10.4, mean SLICC DI 0.52 (see Table 1). 12/27 (44%) of patients had $\geq$ 2 mid cardiac segments with elevated T2 signal (Table 2). The mean T2 signal for mid cardiac segments was elevated compared to 40 historical healthy controls (57.0 ms $\pm$ 5 vs. 54.5 ms $\pm$ 2.2; $p= 0.010$) The mean LV circumferential strain was $-15.2\% \pm 5.4$ which is lower than accepted normal values (-20%). SLEDAI-2K scores positively correlated with mean mid cardiac T2 signal ($r = 0.57$); and mid cardiac maximum T2 signal ($r = 0.65$). Only 2/27 (7%) patients had positive LGE.

Conclusion: In this cohort of active SLE patients, CMR with quantitative T2 mapping identified a high prevalence (44%) of patients with abnormal T2 signal in $\geq$2 mid cardiac segments, suggesting subclinical myocardial inflammation may be common in SLE flare. Both mean and max mid segment T2 showed correlation with SLE disease activity measured by SLEDAI scores. Mean LV circumferential strain was lower than normal, suggesting impaired LV function. Very few CMR showed evidence of myocardial fibrosis as measured by LGE enhancement. Further study is needed to determine if abnormal quantitative T2 mapping during SLE flare foreshadows longer term CV complications.

Table 1: Patient Characteristics

Age, mean $\pm$ SD years	32.4 $\pm$ 9.7
Female, no. (%)	22 (82%)
Black/White/Other, no. (%)	12 (44%), 11 (41%), 4 (15%)
Hispanic, no. (%)	2 (7%)
History of hypertension, no. (%)	9 (33%)
History of hyperlipidemia, no. (%)	6 (22%)
History of myocardial infarction, no. (%)	0
History of ischemic stroke, no. (%)	3 (11%)
History of congestive heart failure, no. (%)	0
Current/former smoker, no. (%)	9 (33%)
Anti-phospholipid antibody positive, no. (%)	6 (22%)
Anti-phospholipid antibody syndrome, no. (%)	1 (4%)
SLEDAI-2K score, mean $\pm$ SD	10.4 $\pm$ 6.3
SLICC Damage Index, mean $\pm$ SD	0.5 $\pm$ 0.77
Troponin I, mean $\pm$, ng/mL	0.057 $\pm$ 0.009
CK, mean $\pm$ SD, U/L	146.8 $\pm$ 500.6
C-reactive protein $\pm$ mg/L	25.6 $\pm$ 16.1

Table 2: CMR Findings in Patients with Active SLE

≥ 2 mid segments with T2 59 ms, no. (%)	12 (44%)
Mean mid segment T2, mean ± ms	57.2 ± 5.0
Peak mid segment T2, mean ± ms	63.0 ± 7.7
Heart rate, mean ± SD	78.4 ± 16.0
LV end diastolic volume, mean ± SD	147.9 ± 35.5
LV end systolic volume, mean ± SD	61.9 ± 30.7
LV ejection fraction, mean ± SD, %	0.60 ± 0.10
LV mass, mean ± SD	86.5 ± 29.6

Disclosure: S. P. Ardoin, None; **W. Jarjour**, None; **S. V. Raman**, None; **A. Kibler**, None; **T. Tran**, None.

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Lung Cancer in SLE. Sasha Bernatsky[1], Rosalind Ramsey-Goldman[2], Michelle Petri[3], Murray B. Urowitz[4], Dafna D. Gladman[4], Edward H. Yelin[5], Christine Peschken[6], John G. Hanly[7], James E. Hansen[8], Jean-Francois Boivin[1], Lawrence Joseph[1], Patrice Chrétien Raymer[9], Mruganka Kale[10], Ann E. Clarke[11] and Systemic Lupus International Collaborating Clinics (SLICC)[12]. [1]McGill University, Montreal, QC, [2]Northwestern University, Chicago, IL, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]University of Toronto, Toronto Western Hospital, Toronto, ON, [5]University of California, San Francisco, San Francisco, CA, [6]University of Manitoba, Winnipeg, MB, [7]Dalhousie University and Capital Health, Halifax, NS, [8]Yale University, New Haven, CT, [9]McGill University Health Centre, Montreal, QC, [10]RI McGill Univ Health Ctr, Montreal, QC, [11]University of Calgary, Calgary, AB, [12]Systemic Lupus International Collaborating Clinics (SLICC), ON.

Background/Purpose: Lung cancer is 50% more common in SLE patients than their sex and age-matched counterparts. Our objective was to assess lung cancer risk in SLE, comparing demographics, drug exposures, and disease activity.

Methods: We used data from a very large multi-site international SLE cohort; this preliminary analysis is based on 6 centres: Halifax, Toronto, Montreal, Winnipeg, San Francisco, Baltimore. We used Cox proportional hazards regression to calculate the hazard ratio (HR) for lung cancer risk in SLE, relative to smoking, demographics (sex, age, race/ethnicity and time-dependent drug exposures and cumulative disease activity (based on adjusted mean SLEDAI-2K scores, assessed at baseline and annually). The adjusted mean SLEDAI score was assessed both as a continuous variable and (to aid in interpretation) and categorized using quartiles. Time zero for the observation interval was SLE diagnosis, so that our analyses adjusted for SLE duration. We included observation time and lung cancer events occurring after entry into the lupus cohort and up to the time of cohort exit (death, cancer, or date of last visits). Those developing a cancer other than lung during the interval, were censored at that time.

Results: Within the cohort (N=4,667) 34 lung cancers (7 male, 27 female) occurred. Versus SLE controls without cancer, lung cancer cases tended to be white (85.3% versus 63.3% in controls), and older at cohort entry (mean 52.3 years, median 52.9; versus mean 38.4, median 36.9 in controls). Among lung cancer cases 61.8% had high disease activity (highest SLEDAI quartile) at baseline (95% CI 43.6, 77.8), in contrast to only 40.1% (95% CI 38.6, 41.5) of SLE patients that went on to remain free of lung cancer. The vast majority (78.8%) of the lung cancer cases in SLE were ever-smokers, versus 40.7% of the SLE patients who did not develop lung cancer. The drug profiles seemed similar (in terms of steroids, immunomodulators, NSAIDs) in the SLE patients who developed lung cancer versus those who did not (though of note, none had been exposed to cyclophosphamide prior to a lung cancer). In both univariate and multivariate models, the principal factors associated with lung cancer risk were ever smoking and age. The adjusted analyses did suggest a trend for greater cancer risk in SLE patients with higher cumulative disease activity over time (HR 1.81, 0.90, 3.63) although the CI included the null value. The estimated adjusted effects of all drugs were relatively imprecise.

Conclusion: There was a trend for greater cancer risk in SLE patients with higher cumulative disease activity over time, although we saw no definite adverse effects of drugs on lung cancer risk in SLE. In particular we did not note prior cyclophosphamide exposure in the lung cancer cases. However, drug estimates were relatively imprecise. Smoking appears to be the most significant modifiable risk factor for lung cancer in SLE.

Case-cohort analysis	Unadjusted Hazard Ratios(95% CI)	Adjusted Hazard Ratios(95% CI)
Calendar year	0.98 (0.94, 1.02)	0.99 (0.94, 1.03)
Age	1.09 (1.06, 1.11)	1.09 (1.06, 1.12)
Male	2.52 (1.10, 5.77)	1.43 (0.59, 3.45)
White	2.52 (0.98, 6.44)	1.72 (0.64, 4.58)
Smoking ever	4.71 (2.04, 10.9)	4.07 (1.74, 9.49)
Steroids ever	0.76 (0.34, 1.70)	0.53 (0.14, 1.94)
Cumulative steroid 3.5 gm	1.15 (0.56, 2.38)	1.78 (0.55, 5.78)
Azathioprine ever	0.65 (0.29, 1.48)	0.45 (0.10, 2.10)
Azathioprine use > 1 year	0.87 (0.32, 2.34)	2.41 (0.37, 15.8)
Methotrexate ever	0.58 (0.17, 1.96)	1.13 (0.29, 4.49)
Mycophenolate ever	0.34 (0.05, 2.50)	0.74 (0.09, 5.86)
NSAIDS ever	0.79 (0.39, 1.61)	0.96 (0.46, 2.04)
Antimalarials ever	0.60 (0.29, 1.25)	1.15 (0.49, 2.72)
Antimalarial use > 5 yrs	0.50 (0.22, 1.14)	0.46 (0.19, 1.16)
Activity top quartile	1.58 (0.76, 3.31)	1.81 (0.90, 3.63)

Disclosure: S. Bernatsky, None; **R. Ramsey-Goldman**, None; **M. Petri**, None; **M. B. Urowitz**, None; **D. D. Gladman**, None; **E. H. Yelin**, None; **C. Peschken**, None; **J. G. Hanly**, None; **J. E. Hansen**, None; **J. F. Boivin**, None; **L. Joseph**, None; **P. Chrétien Raymer**, None; **M. Kale**, None; **A. E. Clarke**, None; **S. L. I. C. C. (SLICC)**, None.

ACR Concurrent Abstract Session
Biology and Pathology of Bone and Joint I: Bone Remodeling in Inflammation and Arthritis
Tuesday, November 18, 2014, 2:30 PM–4:00 PM

2792

Methotrexate Prevents Inflammatory Osteolysis By Activation of the Adenosine a_{2A} Receptor (A2AR). Aranzazu Mediero[1], Tuere Wilder[1] and Bruce N. Cronstein[2]. [1]NYU School of Medicine, New York, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Prior studies demonstrate that adenosine, acting at A2AR, mediates the anti-inflammatory effects of methotrexate (MTX) in models of both acute and chronic inflammation. We have previously reported that adenosine A2AR ligation diminishes wear particle-driven osteolysis. We asked whether MTX treatment could prevent bone resoprtion due to inflammatory osteolysis.

Methods: MTX (1mg/kg) was administered intraperitoneally to C57B/6 mice on a weekly basis starting 2 weeks prior to surgery. Control mice were injected with 0.9% saline. 1cm midline sagittal incisions were made over calvaria in 6–8 wk old C57Bl/6 mice. Calvaria were exposed to 20μl of PBS containing 3mg of UHMWPE followed by daily injections of either vehicle (Control and MTX) or ZM241385 1μM (A2AR antagonist) (n=5 each) for 14 days. XenoLight Rediject Bone Probe was injected IV and fluorescence of calvaria measured (IVIS) to assay bone formation. MicroCT and immunostaining for osteoclast and osteoblast markers were performed.

Results: XenoLight imaging revealed an 80±10% increase in bone formation after exposure to MTX when compared to UHMWPE alone ($p<0.001$, n=5) and ZM241385 completely reversed this effect (11±5% increase vs. control, p=NS, n=5). microCT analysis revealed increased porosity in particle-exposed mice that was inhibited by MTX treatment (54±6% decreased compared to saline treatment, $p<0.001$, n=5) an effect abrogated by ZM241385. MTX significantly increased bone volume/total volume (BV/TV) (9.54±0.1 vs 8.68±0.2, $p<0.05$), BV (5.31±0.3 vs 4.15±0.2, $p<0.05$), TV (5.90±0.2 vs 3.76±0.2, $p<0.001$) and Bone Mineral Density (BMD) (153.75±0.4 vs 144.63±1, $p<0.001$) when compared to WT, and ZM241385 completely reversed this effect. Histological examination of particle-exposed mouse calvarias demonstrated an inflammatory infiltrate on the bone surface that was significantly reduced by MTX and treatment with ZM241385 completely reversed this effect.

Conclusion: These results indicate that treatment with MTX, a well-tolerated and commonly used anti-inflammatory drug, may provide a novel therapeutic approach to enhance orthopedic implant survival, delaying or eliminating the need for revision arthroplasty surgery.

Disclosure: A. Mediero, None; **T. Wilder**, None; **B. N. Cronstein**, Canfite Pharma, 1, AstraZeneca, 2, Cellgene, 2, Gilead, 2, NIH, 2, NYU School of Medicine, 3, Bristol-Myers Squibb, 5, Pfizer Inc, 5, Eli Lilly and Company, 5, Rheumatology Reseach Foundation, 6, ACR, 6, Arthritis Foundation, 6.

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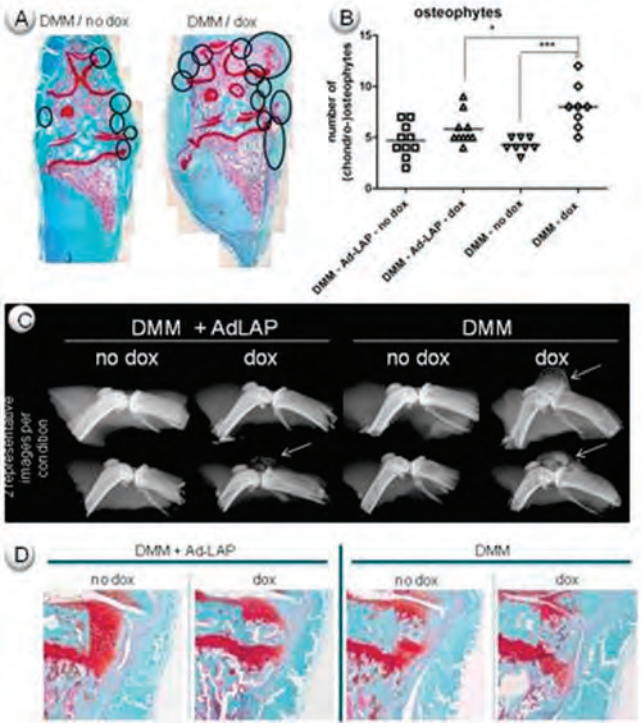
BMP2 Requires TGF-Beta to Induce Osteophytes during Experimental Osteoarthritis. Esmeralda Blaney Davidson[1], Arjen Blom[2], Arjan van Caam[1], Elly Vitters[2], Miranda Bennink[1], Wim van den Berg[2], Fons van de Loo[1] and Peter van der Kraan[2]. [1]Radboud university medical center, Nijmegen, Netherlands, [2]Radboud University Medical Center, Nijmegen, Netherlands.

Background/Purpose: Osteophytes are a major hallmark of osteoarthritis (OA). Both TGF-beta and BMP2 can induce osteophytes in murine knee joints. We demonstrated that TGF-beta could induce chondrogenesis in mesenchymal stem cells when BMPs were inhibited but not vice versa. This suggested that BMP2 might require a trigger like TGF-beta to induce initial stages of chondrogenesis. Therefore, we investigated whether BMP2 was still able to induce osteophyte formation in experimental OA when TGF-beta activity was blocked.

Methods: We made a unique transgenic mouse (Col2a1-rtTA-BMP2) expressing BMP2 under control of the Col2a1 promoter, only when exposed to doxycycline (dox) which results in only chondrocytes producing BMP2. These mice were fed dox-food up to 8 weeks to investigate BMP2 effects on osteophyte formation. We induced the DMM-model and investigated whether BMP2 augmented osteophyte formation. We combined the DMM-model with intra-articular injection of an adenovirus overexpressing TGF-beta-inhibitor LAP with or without dox. Knee joints were isolated 4 weeks after DMM for histology.

Results: There was no significant difference in osteophyte formation between dox and non-dox treated Col2a1-rtTA-BMP2 mice. However, dox treatment increased the number of osteophytes (8.0) during DMM compared to DMM non-dox (4.25). These "new" osteophytes were larger than DMM-induced osteophytes. The lack of osteophytes by dox compared to DMM+dox implied that DMM provided a trigger enabling BMP2-induced osteophyte formation. To investigate whether TGF-beta was that trigger, we injected Ad-LAP one day after DMM-induction. Without TGF-beta, BMP2 no longer augmented the number of osteophytes during DMM. Strikingly, inhibition of TGF-beta significantly reduced the pace of osteophyte formation. This was completely abolished by the presence of BMP2 restoring the speed of osteophyte formation and maturation.



Conclusion: Our data show that BMP2 is capable of inducing osteophyte formation, but is dependent on an additional trigger to achieve this, as present in OA. In OA conditions, BMP2 can severely aggravate osteophyte formation, both in number and size. However, when TGF-beta is blocked BMP2 is no longer capable of aggravating osteophyte formation during DMM. Strikingly, early inhibition of TGF-beta during OA impaired the speed of osteophyte formation, which could be compensated by the presence of BMP2. Our data show for the first time that BMP2 is dependent on TGF-beta to induce de novo osteophyte formation. This provides novel insight into the mechanism behind osteophyte formation and provides clues for future therapeutic application for osteophyte formation in OA.

Disclosure: E. Blaney Davidson, None; **A. Blom**, None; **A. van Caam**, None; **E. Vitters**, None; **M. Bennink**, None; **W. van den Berg**, None; **F. van de Loo**, None; **P. van der Kraan**, None.

2794

Deletion of the Inhibitory Receptor Motif, ITIM, on DC-STAMP Alters Osteoclast Differentiation and Function. Yahui Grace Chiu[1], Edward M. Schwarz[1], Dongge Li[1], Yuexin Xu[1], Minsoo Kim[1] and Christopher T. Ritchlin[2]. [1]University of Rochester, Rochester, NY, [2]University of Rochester Medical Center, Rochester, NY.

Background/Purpose: DC-STAMP (Dendritic Cell-Specific Transmembrane Protein), a 7-pass transmembrane protein essential for cell-to-cell fusion during osteoclast (OC) differentiation, is expressed on the cell surface of OC precursors (OCP). DC-STAMP knock-out (KO) mice form only mononuclear OC and have mild osteopetrosis due to the absence of functional multinucleated OC with bone erosion activity. Previously, we identified an Immunoreceptor Tyrosine-based Inhibitory Motif (ITIM) on the cytoplasmic tail of DC-STAMP, which suggested the potential role of DC-STAMP in signaling during osteoclastogenesis. A major hurdle in DC-STAMP research, however, is the absence of a known ligand. To overcome this barrier, we engineered DC-STAMP:Rhodopisn chimeric molecules that can be activated by light (photo-activatable). This approach enabled us to investigate the downstream events of DC-STAMP activation, and examine the importance and function of the ITIM in osteoclastogenesis.

Methods: DNA constructs were generated in which the four extracellular domains of DC-STAMP were replaced with the photo-activatable extracellular domains of rhodopsin. The functionality of two DC-STAMP chimeras (WT: original ITIM; TD: ITIM-deleted) was confirmed by: (1) activation of a calcium signal by 505-nm light, a wavelength that specifically excites rhodopsin; and (2) expression of mCherry protein (red), which was fused to the C'-terminus of DC-STAMP during engineering. These 2 chimeras were transfected into either murine 293T cells, or mouse bone marrow-derived macrophages (BMM) isolated from the DC-STAMP KO mice. To assess the role of the ITIM in signaling, we assessed the dynamic intracellular Ca^{2+} flux known to occur during normal osteoclastogenesis between the WT and TD transfected cells. Bone erosion was assessed by the bone wafer assay.

Results: The studies with the transfected chimeric molecules revealed the following. First, deletion of ITIM on DC-STAMP resulted in a significant and continuous (non-pulsatile) elevation (3-fold >WT DC-STAMP) in the intracellular Ca^{2+} level after light activation. Second, ITIM-deleted DC-STAMP did not complement the deficiency of cell-cell fusion in DC-STAMP KO cells, which was fully corrected and restored by the WT DC-STAMP. Most cells expressing ITIM-deleted DC-STAMP were unable to fuse, although rare cells with 3 nuclei were observed. Third, In contrast to an even distribution of wild-type DC-STAMP on the cell surface, ITIM-deleted DC-STAMP was expressed on the cell surface in a clustered and punctate distribution fashion. Fourth, bone resorption was decreased in cells expressing TD compared to WT DC-STAMP.

Conclusion: Our results suggest that the ITIM on the cytoplasmic tail of DC-STAMP functions (1) to induce pulsatile intracellular Ca^{2+} flux required for osteoclastogenesis after DC-STAMP activation; (2) to trigger cell-to-cell fusion between OCPs and form multinucleated mature OC; (3) to maintain an even distribution of DC-STAMP on the cell surface; (4) to support bone erosion activity of OC. Blocking the ITIM on DC-STAMP by targeted inhibition might serve as a novel strategy to inhibit pathologic bone resorption by OC in inflammatory and metabolic bone disorders.

Disclosure: Y. G. Chiu, None; **E. M. Schwarz**, Johnson & Johnson, 5, NIAMS-NIH, 2; **D. Li**, None; **Y. Xu**, None; **M. Kim**, None; **C. T. Ritchlin**, Eli Lilly and Company, 9, Eli Lilly and Company, 5.

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Blockade of IL-6R Signaling by Sarilumab Suppressed Circulating Markers of Bone Resorption and Synovial Damage in Rheumatoid Arthritis Patients from a Phase 3, Randomized, Double-Blind, Placebo-Controlled, International Study. Anita Boyapati[1], Jérôme Msihid[2], Emmanuelle Cousin[2], Ling Cai[3], Janet van Adelsberg[1], Jennifer D Hamilton[1], Neil Graham[1], Tanya Momtahen[4] and Stefano Fiore[4]. [1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [2]Sanofi R&D, France, Chilly-Mazarin, France, [3]Sanofi R&D, China, Beijing, China, [4]Sanofi, Bridgewater, NJ.

Background/Purpose: Rheumatoid arthritis (RA) patients develop bone and joint damage due to chronic inflammation mediated by critical cytokines, eg, IL-6. Pre-clinical studies have implicated IL-6 signaling in regulation of osteoclasts and fibroblast-like synoviocytes (FLS) to increase levels of bone resorptive molecules like receptor activated NF kB ligand (RANKL) and joint destructive proteins, such as matrix metalloproteinases (MMPs). Blockade of IL-6R signaling by sarilumab significantly reduced structural damage in RA patients, as measured by the modified van der Heijde total Sharp Score, including the erosion score and joint space narrowing components in the Phase 3 part of the MOBILITY study (NCT01061736). Most common TEAEs included infections and injection site reactions. A higher incidence of serious infections was observed with sarilumab. Lab abnormalities included decreases in neutrophils and increases in transaminases and lipids. To elucidate mechanisms of clinical reduction of bone and joint damage by sarilumab, we evaluated a panel of serum markers associated with bone resorption (RANKL and osteoprotegerin [OPG]), bone turnover (CTX-1 and C1M), osteoblast formation (osteocalcin [OC]), synovium (MMP-3 and C3M) and cartilage degradation (C2M) in patients enrolled in MOBILITY B.

Methods: Sera were analyzed from 128 patients treated with placebo (Pbo) + methotrexate (MTX), and 131 patients receiving subcutaneous 200 mg sarilumab every other week (q2w) + MTX. Serum biomarkers levels were measured by ELISA. All biomarkers were analyzed at baseline, and post-treatment at Wks 2 and 24, with the exceptions of CTX-1 and OC, which were analyzed at baseline, Wks 24 and 52 post-treatment. A mixed effect model with repeated measures on % change from baseline (after rank transformation) was performed for all biomarkers (ANOVA-type method). Treatments were compared at each visit. For samples above the limit of quantitation (LOQ), the LOQ was used in analyses, for samples below the LOQ, half the LOQ was used.

Results: Sarilumab + MTX treatment significantly reduced levels of MMP-3 and MMP generated fragments of collagen type 1 and type 3 (C1M and C3M) compared to Pbo + MTX at all timepoints analyzed (Table). RANKL levels were also reduced at Wk 24 in the sarilumab + MTX group, however approximately 15% of values were above the LOQ. In contrast, OC increased from baseline in the sarilumab 200 mg q2w + MTX group compared to Pbo + MTX but did not reach significance (Wk 52, p=0.0571).

Table Median percent change from baseline

Serum Biomarker	Tissue of Origin	Wk 2		Wk 24	
		Pbo + MTX (N=128)	Sarilumab 200 mg q2w + MTX (N=131)	Pbo + MTX (N=128)	Sarilumab 200 mg q2w + MTX (N=131)
C1M	Bone	2.30	−50.10*	−8.10	−60.30*
RANKL	Bone	0	−3.95†	0	−23.90†
OPG	Bone	0	−5.60	−1.80	−1.55
C3M	Synovium	−0.35	−23.75*	−5.25	−31.50*
MMP-3	Synovium	−0.35	−5.35†	−2.65	−44.20*
C2M	Cartilage	2.40	−4.30†	0	−4.35
		Wk 24		Wk 52	
CTX-1	Bone	−7.80	−6.65	−6.95	−7.70
OC	Bone	2.10	10.85	0.10	13.20

p-values generated for Sarilumab 200 mg q2w + MTX vs. Placebo + MTX comparison at each timepoint: * p<0.0001, † p<0.05.
Note: for RANKL, 15% of values were above the upper LOQ

Conclusion: Sarilumab reduced bone resorption and joint damage markers, and increased OC, a marker of bone formation, in RA patients. This is the first report that IL-6 inhibition leads to RANKL reduction in RA patients. This data supports a mechanism whereby increased IL-6 signaling promotes structural damage through osteoclasts and FLS and by reducing osteoblast bone formation.

Disclosure: A. Boyapati, Regeneron Pharmaceuticals, Inc, 3, Regeneron Pharmaceuticals, Inc, 1; **J. Msihid**, Sanofi R&D, 3, Sanofi R&D, 1; **E. Cousin**, Sanofi R&D, 3, Sanofi R&D, 1; **L. Cai**, Sanofi R&D, 3; **J. van Adelsberg**, Regeneron Pharmaceuticals, Inc., 3, Regeneron Pharmaceuticals, Inc., 1; **J. D. Hamilton**, Regeneron Pharmaceuticals, Inc., 1, Regeneron Pharmaceuticals, Inc, 3; **N. Graham**, Regeneron, 1, Regeneron, 3; **T. Momtahen**, Sanofi, 1, Sanofi, 3; **S. Fiore**, Sanofi, 3, Sanofi, 1.

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A Novel Mouse Model of Osteochondromagenesis By Deleting NFATc1 in Mesenchymal Progenitors and Postnatal Chondrocytes. Xian-Peng Ge, Susan Y. Ritter, Julia F. Charles, Kelly Tsang and Antonios O. Aliprantis. Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Osteochondromas are the most common benign bone tumor and are characterized by cartilage-capped bony projections from the external surface of bone. These lesions may cause pain, deformity, fracture and neurovascular compromise, and rarely undergo malignant transformation. The pathogenesis of osteochondroma remains poorly understood. Since we recently reported that transcription factor nuclear factor of activated T cells c1 (NFATc1) suppresses osteoarthritis in mice, we hypothesized that it controls other aspects of chondrocyte biology. The objective of this study was to further characterize potential roles of NFATc1 in mesenchymal progenitors and chondrocytes.

Methods: To investigate the role of NFATc1 in mesenchymal progenitors of the limb bud and in postnatal chondrocytes, *Nfatc1*$^{fl/fl}$ mice were bred to *Prx1-Cre* (hereafter *Nfatc1*^{Prx1}) or tamoxifen-inducible *Aggrecan-CreER*^{T2} (hereafter *Nfatc1*$^{Aggrecan\text{-}CreER}$) mice, respectively. *Nfatc1*$^{Aggrecan\text{-}CreER}$ mice were analyzed on either an NFATc2-sufficient (*Nfatc2*$^{+/-}$) or deficient (*Nfatc2*$^{-/-}$) background to check for redundancy among NFAT family members. *Nfatc1* was deleted in *Nfatc1*$^{Aggrecan\text{-}CreER}$ chondrocytes by administration of tamoxifen at 8 weeks or 12 weeks of age. The skeletal and joint phenotypes of these strains were determined by a combination of micro-CT and histology.

Results: *Nfatc1*^{Prx1} mice displayed ectopic cartilage and bone formation around the knee joints (osteochondromatosis) at 16 weeks of age. Similarly, within 1 month of tamoxifen injection, all *Nfatc1*$^{aggrecan\text{-}creER}$*Nfatc2*$^{+/-}$ mice displayed ectopic cartilage formation at the tibial attachment site of the medial collateral ligament. Three months after the administration of tamoxifen, *Nfatc1*$^{aggrecan\text{-}creER}$*Nfatc2*$^{+/-}$ mice showed clear osteochondroma-like exostoses at the ligament-bone attachment site, characterized histologically by cartilage-capped bony protrusions continuous with underlying bone. In some *Nfatc1*$^{aggrecan\text{-}creER}$*Nfatc2*$^{+/-}$ mice, cartilaginous protrusions outgrew from the epiphyses of knee joints at this time point. Lastly, the osteochondromagenesis previously reported around the hip joints in *Nfatc2*$^{-/-}$ mice, was exacerbated in *Nfatc1*$^{aggrecan\text{-}creER}$*Nfatc2*$^{-/-}$ double knockout mice.

Conclusion: Our data indicate that NFATc1 constitutively represses chondrogenesis and the formation of exostoses in mice. Reducing NFATc1 expression in mesenchymal progenitors or postnatal aggrecan-expressing chondrocytes represents a novel animal model of osteochondromagenesis.

Disclosure: X. P. Ge, None; **S. Y. Ritter**, None; **J. F. Charles**, None; **K. Tsang**, None; **A. O. Aliprantis**, None.

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Anti-Citrullinated Proteins Antibodies Promotes Osteoclastogenesis and Bone Destruction in Rheumatoid Arthritis. Akilan Krishnamurthy[1], Vijay Joshua[1], Heidi Wähämaa[1], Catia Cerqueira[1], Lars Klareskog[2], Vivianne Malmström[3], Jimmy Ytterberg[1] and Anca I Catrina[1]. [1]Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [2]Karolinska Institute, Stockholm, Sweden, [3]Rheumatology Unit, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Presence of anti-citrullinated protein antibodies (ACPA) is a major risk factor for bone erosion in rheumatoid arthritis (RA) and antibodies against modified citrullinated vimentin induce osteoclast (OC) formation from monocytes. Besides monocytes, dendritic cells (DC) are potent osteoclast precursors. We aimed to further characterize DC derived osteoclastogenesis and to explore the effect of pooled and individual monoclonal ACPAs on this pathway.

Methods: ACPA positive and negative IgGs were isolated from synovial fluid (SF, n=26) and peripheral blood (PB, n=38) samples of RA patients. $CD14^+$ monocytes from PB of $ACPA^+$ RA patients and healthy individuals were first cultured in the presence of GM-CSF and IL-4 to generate DC or M-CSF to generate MΦ, and then further differentiated to OC in the presence of RANKL and M-CSF. In parallel, cells were grown on osteoassay surfaces and bone resorption area was quantified by computer assisted image analysis. In house generated anti-citrullinated monoclonal antibodies obtained from SF B-cells were also tested. Cytokines were measured by cytometric bead arrays in cultures supernatants. Mass spectrometry analysis was performed on different stages of differentiation of DC derived OC. Immunohistochemistry (IHC) was used to stain the OCs with biotinylated ACPA IgG and monoclonal anti-citrullinated proteins antibodies. The effect of PAD inhibition (C.I.amidine) and IL-8 inhibition was tested in the osteoclasts cultures.

Results: SF derived ACPAs enhanced osteoclastogenesis and bone resorption from both DC (fold increase of 1.6±0.2 for osteoclasts number and 2.0±0.3 for bone resorption area) and MΦ (fold increase of 1.6±0.4 for osteoclasts number and 2.0±0.6 for bone resorption area) of healthy donors. Similar effect was observed when the precursor cells were derived from ACPA+ RA patients in both DC (fold increase of 2.3±0.9 for osteoclasts number and 2.6±0.1 for bone resorption area) and MΦ (fold increase of 1.8±0.6 for osteoclasts number and 2.3±0.7 for bone resorption) assays. PB

derived ACPAs were equally effective with SF ACPAs. Principal component analysis confirmed distinct proteomic profiles during osteoclasts maturation from DC and MΦ, respectively. Vimentin significantly increased during DC-OC maturation, with citrullinated vimentin peptides detectable in matured osteoclasts. Increased osteoclastogenesis was associated with significantly higher levels of IL-8 levels in cultures supernatants of both DC (fold increase of 2.4±0.5) and MΦ (fold increase of 2.0±0.5). Two of the tested anti-citrullinated monoclonal antibodies had similar effects, while a third one had no such effect. Fab fragments of these monoclonal antibodies retained similar effects. Binding of these antibodies on OC was confirmed using IHC. Both PAD activity and IL-8 appear to be required for ACPAs effects.

Conclusion: SF and PB derived ACPA IgGs with broad specificities enhanced osteoclastogenesis from both DC and MΦ. This effect appears to be restricted to certain ACPAs specificities and at least partially mediated through a Fab mediated mechanism.

Disclosure: A. Krishnamurthy, None; **V. Joshua**, None; **H. Wähämaa**, None; **C. Cerqueira**, None; **L. Klareskog**, None; **V. Malmström**, None; **J. Ytterberg**, None; **A. I. Catrina**, None.

ACR Concurrent Abstract Session
Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis I

Tuesday, November 18, 2014, 2:30 PM–4:00 PM

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***C5orf30* a Novel Regulator of Inflammation and Tissue Damage in Rheumatoid Arthritis.** Munitta Muthana[1], Sarah Hawtree[1], Holly Davies[1], Hannah Roberts[1], Sachin Khetan[1], Mohammed Akil[2], Fiona Wright[1], Barbara Ciani[1], Ursula Fearon[3], DJ Veale[4] and Anthony G. Wilson[5]. [1]University of Sheffield, Sheffield, United Kingdom, [2]Rheumatology Department, Sheffield South Yorkshire, United Kingdom, [3]Translational Rheumatology Research Group, Dublin, Ireland, [4]St. Vincent's University Hospital, Dublin, Ireland, [5]University College Dublin, Dublin, Ireland.

Background/Purpose: A recent genome wide association study identified the variant rs26232 in the first intron of the uncharacterized gene, *C5orf30*, as a rheumatoid arthritis (RA) susceptibility variant[1]. In addition, it has been associated with severity of radiological joint damage suggesting a role in tissue breakdown[2]. To date there is no function assigned for *C5orf30* and neither the gene or protein show homology to any known functional sequences. However, C5orf30 is highly conserved in chimpanzee, dog, cow, mouse, chicken, and zebrafish (orthologs).

Purpose - To determine the biological roles of *C5orf30* in rheumatoid arthritis.

Methods: Immunohistochemistry on synovial samples was used to determine expression of C5orf30 using anti-C5orf30 and antibodies to macrophages (CD68), fibroblasts (5B5), T (CD3) & B (CD19) cells. Real time PCR and western blotting were used to examine C5orf30 transcript and protein levels in RA PBMCs and fibroblast-like synovial cells (RASF) treated with TNF & hypoxia. To investigate gene function siRNA was used to knockdown (KD) either *C5orf30* or a non-targeting control (NTC) in RASF *in vitro*. After knockdown cell migration, invasion, and global gene expression (Illumina BeadChip array) were assessed. The disease-modulating activity of siRNA designed to silence C5orf30 was also investigated *in vivo*in a mouse model of collagen-induced arthritis (CIA). Clinical scores of CIA were measured daily (days 0–49) and the bones were analysed using a microCT scanner.

Results: Confocal microscopy revealed C5orf30 to be strongly expressed in the cytoplasmic compartment of RA synovial lining cells including macrophages and RASF but not T & B cells. C5orf30 was undetectable in arthroscopy sections obtained from osteoarthritis (OA) or OASFs. C5orf30 was found to be up-regulated by hypoxia (8-fold) and down-regulated by TNF treatment (0.5-fold) in RASF. We found that $C5orf30^{KD}$ increased the invasiveness of FLS assayed using Matrigel (N=6 p=0.01) and increased FLS migration in a scratch-wound assay (N=6 p=0.02). Gene profiling studies also revealed $C5orf30^{KD}$ resulted in upregulation of cell migration, adhesion, angiogenesis, and immune and inflammatory pathways. Finally, in mice with CIA, siRNA designed to inhibit C5orf30 strongly induced joint inflammation (n=10, p=0.0001) and bone erosion compared to irrelevant NTC siRNA.

Conclusion: Our data, in both RA and murine inflammatory arthritis, reveals C5orf30 to be a novel negative regulator of tissue breakdown modulating the autoaggressive phenotype that is characteristic of rheumatoid synovial fibroblasts.

1. Stahl EA, Raychaudhuri S, Remmers EF, et al. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. Nat Genet 2010;42:508–14.

2. Teare MD, Knevel R, Morgan MD, et al. Allele-Dose Association of the C5orf30 rs26232 Variant With Joint Damage in Rheumatoid Arthritis. Arthritis Rheum. 2013;65:2555–61.

Disclosure: M. Muthana, None; **S. Hawtree**, None; **H. Davies**, None; **H. Roberts**, None; **S. Khetan**, None; **M. Akil**, None; **F. Wright**, None; **B. Ciani**, None; **U. Fearon**, None; **D. Veale**, None; **A. G. Wilson**, None.

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The Differential Impact of Obesity on the Pathogenesis of RA or Preclinical Models Is Contingent on the Disease Status. Zhenlong Chen[1], Seung-jae Kim[1], Abdul Essani[1], Michael V. Volin[2], Suncica Volkov[1], William Swedler[1], Shiva Arami[1], Giamila Fantuzzi[1], Nadera J. Sweiss[1] and Shiva Shahrara[1]. [1]University of Illinois at Chicago, Chicago, IL, [2]Chicago College of Osteopathic Medicine Midwestern University, Downers Grove, IL.

Background/Purpose: Studies were performed to determine the significance of obesity in the pathogenesis of rheumatoid arthritis (RA) and experimental arthritis models.

Methods: Chronic and acute preclinical models of arthritis were utilized to examine the impact of obesity on different disease stages. Inflammatory mediators were identified in RA and mouse adipose condition media using ELISA. Role of IL-8/MIP2 was investigated in disease onset employing neutrophil chemotaxis. RA and mouse myeloid cells as well as ankle joints from preclinical arthritis models were utilized to assess the importance of proinflammatory M1 macrophage differentiation in disease remission using real-time RT-PCR, histology and Western blotting.

Results: We document that early onset of collagen induced arthritis (CIA) was impacted by high fat diet (HFD) on days 26, 28 and 30 post onset compared to mice fed with regular diet (RD). To elucidate the mechanism by which obesity affects the early stage of RA, inflammatory factors were quantified in adipose condition media extracted from RA synovial tissue and obese mouse gonadal adipose tissue. We uncovered that a great number of neutrophil (CXCL1, CXCL5 and IL-8/MIP2) and monocyte chemaoattractants (TNF-a, IL-17, IL-1b, CCL2) are present in RA and mouse adipose condition media, however levels of IL-8/MIP2 exceeded all other factors. We found that early arthritis exacerbated by obesity is due to elevated IL-8/MIP2 protein levels in the obese joint, as blockade of IL-8/MIP2 dysregulates neutrophil chemotaxis in response to RA and mouse adipose media, in contrast, neutralization of CXCL1 and CXCL5 was ineffective in this process. To elucidate the effect of obesity on arthritis progression, we chose to utilize the TLR4 induced arthritis model. We found that in the first 48h, TLR4 driven joint inflammation progresses similarly in obese and lean mice. Thereafter while arthritis resolves in the lean mice, ankle swelling is sustained in the obese mice at 72h post LPS injection. Histological studies confirm that mice on HFD have markedly greater joint inflammation and lining thickness compared to RD group. Corroborating with the higher levels of monocyte chemoattractants detected in the obese mice (TNF-a, IL-17, CCL20 and IL-6), joint myeloid cell recruitment was potentiated in the HFD arthritic mice compared to RD group. To better understand how obesity prolongs arthritis, joint myeloid cell phenotype was evaluated in the obese and the lean arthritic mice. We show that the obese arthritic mice, predominately express iNOS+ M1 macrophages; while iNOS+ cells are reduced and Arginase+ M2 macrophages are strongly expressed in the lean mice. Consistently, employing RA and mouse adipose condition media we show that RA or mouse naïve cells can be transformed into M1 macrophages. Hence, our results exhibit that obesity can sustain arthritis by reconstructing the newly recruited joint myeloid cells into proinflammatory M1 macrophages.

Conclusion: We show for the first time that early and late RA is impacted by obesity through differential mechanism of function.

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Tofacitinib Regulates Synovial Angiogenesis in Psoriatic Arthritis through Induction of Negative Feedback Inhibitors. Wei Gao, Jennifer McCormick, Carl Orr, Mary Connolly, Ursula Fearon and Douglas J. Veale. Translational Rheumatology Research Group, Dublin, Ireland.

Background/Purpose: Psoriatic Arthritis (PsA) is a common, chronic immune-mediated inflammatory disease, characterised by synovitis, progressive destruction of articular cartilage/bone, and is associated with psoriasis. Janus Kinase and Signal Transducer and Activator of Transcription (JAK/STAT), a critical signalling pathway involved in inflammatory mechanisms, has been implicated in the pathogenesis of PsA. This study was to examine the mechanistic effect of Tofacitinib (A novel JAK inhibitor CP-690,550) on pro-inflammatory pathways using *ex vivo* and *in vivo* models of PsA.

Methods: PsA whole tissue synovial explant cultures were established from PsA biopsies obtained under direct visualisation at arthroscopy. This explant model maintains the architecture and cell-cell contact of the synovial tissue, spontaneously releases pro-inflammatory mediators and therefore closely reflects the *in vivo* inflamed microenvironment. Primary PsA synovial fibroblasts (PsASFC) were also isolated from PsA synovial biopsies. Phospho-STAT3 (p-STAT3), phospho-STAT1 (p-STAT1), Suppressor of Cytokine Signaling 3 (SOCS3) and Protein Inhibitor of Activated Stat 3 (PIAS3) expression were quantified by Western Blot in PsA synovial explants and PsASFC following culture with Tofacitinib (1μM) or vehicle control. Cytokine expression of IL-6, IL-8 and IL-10 in *ex vivo* culture synovial explants in response to Tofacitinib (0.5μM-1μM) were assessed by ELISA. Furthermore the effect of Tofacitinib (0.5μM-1μM) on PsASFC migration, invasion, matrigel network formation and MMP2/9 were quantified by wound repair assays, transwell invasion chambers and zymography.

Results: Tofacitinib significantly decreased p-STAT3 and p-STAT1 expression in PsA synovial tissue explant cultures *ex vivo* and in primary PsASFC ($p<0.05$). In contrast Tofacitinib induced SOCS3 and PIAS3 expression in both models ($p<0.05$). In parallel Tofacitinib significantly decreased spontaneous secretion of IL-6 ($p<0.05$), IL-8 ($p<0.05$) and induced IL-10 ($p<0.05$) expression in PsA explant cultures. Functionally, PsASFC invasion, matrigel network/tube formation, migration, and pro-MMP-2/-9 activities, were inhibited in the presence of Tofacitinib ($p<0.05$).

Conclusion: This is the first study to demonstrate Jak/STAT signaling and the effect of Tofacitinib on these pathways in PsA synovial tissue and primary PsA synovial fibroblasts. Tofacitinib mediated specific JAK-STAT signaling components, inhibited key pro-inflammatory cytokines and invasion/migrational mechanisms. Thus this data further supports the use of JAK-STAT inhibition as a potential therapeutic agent for the treatment of PsA.

Disclosure: W. Gao, None; **J. McCormick**, None; **C. Orr**, None; **M. Connolly**, None; **U. Fearon**, None; **D. J. Veale**, Abbvie, 2, MSD, 2, Pfizer Inc, 2, Roche, 2, Pfizer, 5, Roche, 5, Abbott, 8, MSD, 8, Pfizer, 8, Roche, 8.

2801

IL-38: A New Factor in Rheumatoid Arthritis. Shinjiro Kaieda[1], Katsuya Kanezaki[2], Naomi Yoshida[1], Yukiko Kunitake[1], Hiroaki Ida[1] and Tomoaki Hoshino[1]. [1]Kurume University School of Medicine, Kurume, Japan, [2]Nagata orthopedic hospital, Omuta, Japan.

Background/Purpose: IL-38 (IL-1F10) was originally described as an IL-1 family cytokine, and named IL-1HY2. The *IL-38* gene is located in the *IL-1* family cluster on chromosome 2, next to the genes encoding the IL-1 receptor antagonist (IL-1Ra) and the IL-36 receptor antagonist (IL-36Ra). IL-38 shares 37% homology with IL-1Ra, 43% homology with IL-36Ra, and has a three-dimensional structure similar to IL-1Ra. IL-38 was recently shown to inhibit *Candida albicans*-induced IL-17 and IL-22 production by human memory T cells. However, the role of IL-38 in inflammatory diseases such as RA remains unclear.

Methods: We established several clones of mouse anti-human IL-38 mAb. One anti-human IL-38 mAb (H127C, mouse IgG2a) can be used for sandwich ELISAs and immunohistochemistry. To determine the expression pattern of the *IL-38* gene, a panel of cDNA derived from normal lung, pancreas, spleen, muscle, synoviocyte samples and peripheral blood mononuclear cells (PBMCs) was analyzed by quantitative real time-PCR (qRT-PCR), using primers specific to human IL-38. The serum levels of IL-38 in 137 RA and 26 OA patients, and in 56 healthy donors, were determined by ELISA. Synovial tissue samples were also obtained from 7 RA and 3 OA patients. We used immunohistochemistry to identify IL-38, prolyl-4-hydroxylase-positive fibroblasts, and CD68-positive macrophages. Arthritis was initiated in mice lacking IL-38, as well as their wild-type littermates, via intraperitoneal administration of K/BxN mouse serum. Total RNA was isolated from mouse ankle joints and *IL-1β* and *IL-6* mRNA were quantified by qRT-PCR.

Results: The *IL-38* transcripts were strongly expressed in the lung, spleen, and synoviocytes, and at a lower level in the pancreas and muscle**.** Further, strong mRNA expression of the *IL-38* gene was also observed in PBMCs obtained from 2 healthy donors**.** The serum levels of IL-38 were 5.7 $\pm$ 0.4 pg/mL, 2.8 $\pm$ 0.8 pg/mL, and 2.8 $\pm$ 0.7 pg/mL in RA patients, OA patients, and healthy donors, respectively. Twenty-one of the 137 RA (15.3%) patients, 1 of the 26 OA patients (3.9%), and 5 of the 56 controls (8.9%) had IL-38 levels that were above the limit of detection of our ELISA system (10 pg/mL). Further, IL-38 protein was strongly expressed in the synovial lining of RA synovium. Serial sections indicated that synovial fibroblasts highly expressed IL-38 protein; CD68-positive macrophages barely expressed IL-38 in the RA synovium. In contrast, IL-38 protein was barely expressed in the synovial lining of OA synovium. Moreover, we found that IL-38-deficient mice exhibited significant exacerbation of their arthritis clinical scores, compared with their wild-type littermates. Correspondingly, histological measures of arthritis were also exacerbated, and accompanied by increased *IL-1β* and *IL-6*gene expression in the ankles.

Conclusion: Our present study is the first to identify the presence of soluble IL-38 protein in the serum and its expression in the synovium of RA patients. IL-38 may play a role as an inhibitor in the pathogenesis of RA.

Disclosure: S. Kaieda, None; **K. Kanezaki**, None; **N. Yoshida**, None; **Y. Kunitake**, None; **H. Ida**, None; **T. Hoshino**, None.

2802

Non-Canonical NF-Kappab Signaling Promotes Angiogenesis in a Novel 3D Spheroid Model of Rheumatoid Arthritis Synovial Inflammation. Chrissta X. Maracle[1], Boy Helder[1], Ae-Ri Noort[1], Corine van der Horst[2] and Sander W. Tas[1]. [1]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [2]Arthrogen BV, Amsterdam, Netherlands.

Background/Purpose: Angiogenesis is regarded as a switch from acute to chronic inflammation and thus plays a crucial role in rheumatoid arthritis disease progression. This process is highly complex, involving interactions between several cell types in the inflamed synovium. Many of the current *in vitro* models of angiogenesis focus solely on endothelial cells (EC) and do not include interactions with other cell types. RA synovial fibroblasts (RASF) are important contributors to angiogenesis in synovial inflammation, and therefore a model including both RASF and EC would more accurately represent the pathophysiology of RA angiogenesis. We previously demonstrated that NF-κB inducing kinase (NIK) dependent non-canonical NF-κB signaling can induce angiogenesis in EC. This has not yet been studied in a co-culture model of angiogenesis.

Objective: To develop a 3D *in vitro* model to study the interaction between RASF and EC and to further delineate the role of the non-canonical NF-κB pathway in pathological angiogenesis.

Methods: We developed a novel 3 dimensional (3D) model in which human umbilical cord vein EC and RASF were labeled with green or orange cell tracker dye, respectively, and incubated overnight to form spheroids. Subsequently, the spheroids were harvested and plated in a collagen solution, and medium with or without lymphotoxin $\alpha1\beta2$ (LT) or LIGHT (both stimuli that induce non-canonical NF-κB signaling via the lymphotoxin beta receptor (LTβR)) or pro-angiogenic growth factors (bFGF/VEGF) was added. After 48 hours, spheroids were fixed and imaged through confocal microscopy. Cumulative EC sprout length and the number of sprouts was quantified using Leica QWin Plus software. To demonstrate NIK dependency of this process, EC were transfected with non-targeting or NIK targeting siRNA before addition into the model and subsequent sprout formation was quantified.

Results: Confocal analysis of the 3D model showed spheroids containing HUVEC and RASF formed sprouts under all conditions. Both LT and LIGHT caused significant increases in cumulative sprout length ($p<0.05$). Interestingly, the total number of sprouts formed by each spheroid also increased significantly. LT and LIGHT induced sprout formation was significantly decreased by siRNA-mediated knockdown of NIK in EC as compared to the non-targeting siRNA controls.

Conclusion: Our novel 3D model demonstrates that activation of the non-canonical pathway induces angiogenesis in spheroids of EC and RASF and that this process is strictly NIK dependent. This suggests that NIK targeting therapeutics may be able to reduce pathological angiogenesis in synovial inflammation and possibly halt disease progression. Further studies to test this, including the use of small molecule pharmacological NIK inhibitors, are currently underway. Of interest, the current 3D model is also optimized to include different subsets of immune cells in order to study their contributions to inflammation-induced angiogenesis, which makes this model a valuable tool for future studies.

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2803

Methotrexate Impacts the Effects of Tofacitinib, but Not Tocilizumab, on Clinically Relevant Biomarkers in Human Primary Cell–Based BioMAP® Disease Models: Can We Utilize in Vitro Models to Predict Clinical Outcomes? Alison O'Mahony[1], Ellen L. Berg[1], Xitong Li[1], Markus R. John[2], Kandeepan Ganeshalingam[2] and Ernest H. Choy[3]. [1]BioSeek, South San Francisco, CA, [2]F. Hoffmann-La Roche, Basel, Switzerland, [3]Cardiff University, Cardiff, United Kingdom.

Background/Purpose: A number of trials have shown that adding MTX benefits some, but not all, biologics and small molecules to treat RA. Specifically, though treatment of RA with an anti-TNF+MTX has been shown to be more beneficial than with the biologic alone,[1–3] the same was not consistently observed with tocilizumab (TCZ)+MTX.[4,5] Thus, it remains a challenge to determine whether cotreatment with MTX is a better option for patients. We have previously reported that BioMAP activities detected with TCZ alone were highly similar to those of TCZ+MTX, whereas the effects of adalimumab (ADA) alone differed from those of ADA+MTX.[6] Here we evaluate whether MTX alters the pattern of BioMAP activities of tofacitinib (TOF) in order to predict whether the effects of this drug can be modulated by cotreatment with MTX.

Methods: Human primary cell–based BioMAP disease models[7,8] were used to generate phenotypic activity profiles for compounds alone and in combination with MTX at concentrations that cover their clinical C_{max} ranges[9–11]: TCZ, 200 mg/mL; TOF_1, 1.1 mM; TOF_2, 0.12 μM; MTX, 10 mM. Agents and combinations were tested under standard[7] and soluble interukin-6 receptor–stimulated conditions. Changes in protein-based, clinically relevant end points (biomarkers)[7] and proliferation were evaluated by *t*-test and other statistical methods to determine whether activities of the combinations differed from those of the individual agents.

Results: Several activities detected with TOF_1+MTX or TOF_2+MTX were statistically significantly different ($p<0.01$) from those of TOF_1 or TOF_2 profiled alone. Cytokine and chemokine levels (M-CSF, G-CSF), inflammation markers (VCAM-1, E-selectin, and IP-10), and tissue-remodeling activities (thrombomodulin and PAI-1) were all modulated differently by TOF+MTX vs TOF alone. In contrast, the profile of TCZ+MTX was not significantly different from that of TCZ alone, with only MTX-mediated antiproliferative effects on endothelial cells (3C) and B cells (BT) contributing to the pattern of TCZ activities.

Conclusion: These data show that though TCZ has diverse effects on inflammatory responses, cotreatment with MTX elicits few additional activities and does not impact TCZ effects. In contrast, TOF+MTX impacts immune function, inflammation markers, and matrix-remodeling end points in human primary cell disease models differently than does TOF or MTX alone. The pharmacodynamic interactions between TCZ and MTX in BioMAP are significantly less pronounced than those between TOF and MTX. These data are consistent with the comparable efficacy of TCZ in monotherapy and combination therapy seen in some clinical trials[4,5] and in real life[12] and suggest that TOF could be more beneficial in combination with MTX.

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Disclosure: A. O'Mahony, DiscoveRx Corp (BioSeek division), 1, BioSeek, 3; **E. L. Berg**, BioSeek, 3; **X. Li**, BioSeek, 3; **M. R. John**, Roche Pharmaceuticals, 3; **K. Ganeshalingam**, Roche Pharmaceuticals, 1, Roche Pharmaceuticals, 3; **E. H. Choy**, Abbott Laboratories, Boehringer Ingelheim, Chelsea Therapeutics, Chugai Pharma, Ferring Pharmaceuticals, GSK, Jazz Pharmaceuticals, MSD, Novartis, Pierre Fabre Medicament, Novimmune, Roche, UCB, 2, Abbott Laboratories, Allergan, AstraZeneca, BMS, Boehringer Ingelheim, Chelsea Therapeutics, Chugai Pharma, Daiichi Sankyo, Eli Lilly, Ferring Pharmacuetical, GSK, ISIS, Jazz Pharmaceuticals, MedImmune, Merrimack Pharmaceutical, MSD, Novimmune, Novartis,, 5.

ACR Concurrent Abstract Session

Miscellaneous Rheumatic and Inflammatory Diseases/Innate Immunity and Rheumatic Disease: Assessing Outcomes of Infections in Rheumatic Disease

Tuesday, November 18, 2014, 2:30 PM–4:00 PM

2804

Rituximab in IgG4-Related Disease: A Large Single-Center Experience. Zachary Wallace, Mollie Carruthers and John H. Stone. Massachusetts General Hospital, Boston, MA.

Background/Purpose: IgG4-related disease (IgG4-RD) is an immune-mediated multiorgan, fibroinflammatory disease often associated with an elevated serum IgG4 concentration. The diagnosis hinges on characteristic histopathologic features. Glucocorticoids (GC) are an effective but non-curative treatment with many known toxicities, and many patients relapse on low doses. We report here an experience with the use of B cell depletion in 58 patients with biopsy-proven IgG4-RD.

Methods: All 58 patients were treated and followed for at least three months in the Massachusetts General Hospital Center for IgG4-RD. Patients' medical records were reviewed for details regarding demographics, clinical manifestations, prior treatment, response to treatment, and complications of treatment. The IgG4-RD Responder Index (IgG4-RD RI) was used to assess clinical improvement. Rituximab (RTX) (1gm) was administered on days 0 and 15. Three fourths of the patients in this cohort received no treatment except for RTX.

Results: Fifty-eight patients were included. Their mean age was 56 years (range: 32–83). The mean number of organs involved was 2.2 (range: 1–6). Thirty-two patients (55%) had an elevated serum IgG4 concentration at baseline (mean 712 mg/dL; range 154–4780; normal < 135 mg/dL). Thirty-two (55%) of the patients had undergone treatment courses – GC in 24 (41%) – prior to treatment with B cell depletion. The mean duration of follow-up after the first RTX infusion was 597 days (range: 90–1770). Forty-three (74%) of the patients were treated with RTX alone.

Clinical improvement was observed in 88% of patients following RTX administration. Among the 25 patients with post-RTX imaging studies, 24 (96%) demonstrated either improvement (68%) or stability (28%) in the radiologic features. Among the 15 (26%) patients on GC at the time their RTX began, 11 (73%) were able to discontinue GC completely following RTX treatment and 4 (27%) were able to taper the dose to below 5 mg/day of prednisone. Among the patients with an elevated serum IgG4 concentration before RTX, the value declined to a mean of 248 mg/dl (range: 20–985) after RTX among the 29 patients with follow up values assessed; the value normalized in only 13 patients (44%).

Among 33 patients followed for more than one year, 18 (55%) experienced disease flares, an average of 10 months (range 5–27) after the first RTX infusion. Nineteen patients received more than one course of RTX (a total of 36 re-treatments, 24 for flares and 12 for remission maintenance). RTX was well tolerated; there were 15 adverse events among 13 patients. Infusions reactions (4) and infection (4) were the most common adverse events.

Conclusion: RTX appears to be an effective and well-tolerated treatment for IgG4-RD. The majority of patients treated with RTX require no concomitant GC therapy. Serum IgG4 concentrations improve but the majority do not normalize following RTX treatment, despite clinical improvement.

Disclosure: Z. Wallace, None; **M. Carruthers**, None; **J. H. Stone**, Genentech and Roche, 5.

2805

IgG4-Related Disease: Baseline Features in 100 Patients with Biopsy-Proven Disease. Zachary Wallace[1], Vikram Deshpande[1], Hamid Mattoo[2], Vinay Mahajan[2], Mollie Carruthers[1], Maria Kulikova[1], Shiv Pillai[1] and John H. Stone[1]. [1]Massachusetts General Hospital, Boston, MA, [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: IgG4-related disease (IgG4-RD) has emerged as an immune-mediated disease that links multiple fibro-inflammatory conditions through common pathology and pathophysiologic mechanisms. Most of the literature on IgG4-RD is comprised of case reports and small case series focused on individual organ manifestations. We report detailed clinical features of the first 100 patients with IgG4-RD evaluated at our center.

Methods: We reviewed the cases of the first 100 patients included in a database maintained by the Massachusetts General Hospital Center for

IgG4-RD. All patients had biopsy-proven disease and 75 were on no immunosuppression at the time of evaluation yet had active disease. Clinical and laboratory data were extracted from the electronic medical record. An IgG4-RD responder index score > 3 defined active disease. Serum IgG4 concentrations were determined by nephelometry after serial dilution to prevent the prozone effect. Circulating plasmablasts and SLAMF7+ CD4+T cells were measured by flow cytometry.

Results: The average ages at evaluation and disease onset were 55 years (range: 24–83) and 49.9 years (range: 12–82), respectively. The majority of patients were white (75%) and male (63%); the mean number of organs affected was 2.8 (range 1–7). The most commonly involved organs were the submandibular glands, orbit, lymph nodes, pancreas, and retroperitoneum; fifty-five patients had sustained permanent damage due to IgG4-RD **(Table 1)**.

Forty-seven patients had received glucocorticoid therapy and all had either failed treatment or required ongoing treatment to maintain disease control. Only 38 (53%) of the 75 patients on no treatment at baseline had an elevated serum IgG4 concentration. Elevated serum IgG4 levels correlated with an inflammatory phenotype (increased acute phase reactants) and multi-organ disease. Regardless of the serum IgG4 concentrations, patients had elevated levels of circulating SLAMF7+ CD4+ T cells and plasmablasts. Male patients had a higher average serum IgG4 concentration (597mg/dL versus 233mg/dL; P=0.03) but neither the proportion with an elevated baseline value nor the number of organs involved differed. Patients with renal disease, lymphadenopathy, and retroperitoneal fibrosis represented distinctive subtypes on the basis of complement levels, serum IgG4 concentrations, number of organs involved, and inflammatory markers.

Conclusion: We report the baseline features of our first 100 patients with biopsy-proven IgG4-RD. The majority of the patients were on no treatment at the initial assessment, permitting insights into the pre-treatment features of IgG4-RD. Our study stands in contrast to all IgG4-RD publications to date as this is the first study to describe the clinical and laboratory features of a large, diverse cohort with IgG4-RD.

Table 1: Organ Involvement and Damage

Organ Involvement			
	# of cases		**# of Cases**
CNS	3	Aorta	9
Orbit	25	Heart	1
Parotid	15	Retroperitoneal fibrosis	19
Submandibular	29	Sclerosing mediastinitis	2
Mastoid	1	Sclerosing mesenteritis	1
Nasal Cavity	2	Pancreas	22
Sinusitis	5	Liver	3
Tonsilitis	1	Bile duct	8
Other ENT	6	Gallbladder	1
Thyroid	5	Skin	2
Lymph nodes	24	Prostate	3
Lung	16	Other	5
Kidney	8		
Damage			
Biliary	3	Pancreas	8
Nasal Septum	2	Kidney	8
Submandibular Gland	9	Lung	8
Sinus	4	Ureter	4
Palate	2	Vascular/SVC Syndrome	2
Thyroid	3	Chronic Pain	3
Aorta	2	Coronary	2
Other	9		

Disclosure: Z. Wallace, None; **V. Deshpande**, None; **H. Mattoo**, None; **V. Mahajan**, None; **M. Carruthers**, None; **M. Kulikova**, None; **S. Pillai**, None; **J. H. Stone**, None.

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Characteristic Phenotype of Peripheral Blood Lymphocytes in Patients with IgG4-Related Disease, Comparing to Primary Sjögren Syndrome and Healthy Controls. Shintaro Hirata, Shingo Nakayamada, Satoshi Kubo, Maiko Yoshikawa, Naoki Yunoue, Kazuhisa Nakano, Kunihiro Yamaoka, Kazuyoshi Saito and Yoshiya Tanaka. University of Occupational and Environmental Health, Japan, Kitakyushu, Japan.

Background/Purpose: IgG4-related disease (IgG4-RD) is a systemic disease that is characterized by the infiltration of IgG4-positive plasma cells and T cells into various organs. However, the characteristic and pathological role of immune cell subsets remains unclear. We have characterized peripheral blood immune cell subsets in patients with IgG4-RD by comparing with patients with primary Sjögren syndrome (pSS) and healthy controls (HC).

Methods: PBMCs were obtained from 8 IgG4-RD and 4 pSS patients as well as from 8 HC. The phenotype of immune cells was analyzed by 8-color staining flow cytometry. T helper cells were categorized as naive, central memory, effector memory and effector T cells by expression of CCR7 and CD45RA. B cells were categorized as naive, IgM memory, switched memory, effector B cell and plasmablast (PB) by expression of IgD, CD27 and CD38. DCs were categorized as myeloid and plasmacytoid DC by expression of CD11c and CD123. The proportion of immune cell subsets was assessed for correlations with serological parameters, including serum IgG, IgG4, and CRP.

Results: Baseline characteristics of patients with IgG4-RD (mean Â± SD) were; age 56 Â± 20 year, symptom duration 16.3 Â± 19.2 months, serum IgG4 628 Â± 549 mg/dl, CRP 1.3 Â± 2.6 mg/dl, respectively. There was no difference in the proportion of T helper cells (Th1, Th2, Th17, Treg), B cells or DC subsets between IgG4-RD, and pSS, HCï¼Œwhereas $CD3^+CD4^+CXCR5^+CD45RA^-$ Tfh cells were significantly higher in IgG4-RD than HC (p=0.033). In contrast, the proportion of $CD3^+CD4^+CCR7^-CD45RA^+$ effector T cells and $CD19^+CD27^+CD20^-CD38^+$ plasmablasts significantly increased in IgG4-RD compared to pSS and HC (*p* values: 0.008 and 0.013, respectively). Importantly, the proportion of $CD3^+CD4^+CCR7^-CD45RA^-$ effector memory T helper cells was strongly correlated with the ratio of serum IgG4/IgG ratio (rho=0.90, *p*=0.002), whereas it was not with that of plasmablasts (rho=0.17, p=0.67).

Conclusion: These results revealed that the higher proportion of effector T cells including Tfh cells and the increase of plasmablasts possibly induced by Tfh are characteristically observed in IgG4-RD, but not in pSS. Moreover, serum IgG4/IgG ratio was strongly correlated with ratio of effector memory T cells, but not plasmablasts. Taken together, IgG4 overproduction may be conducted by matured effector phase helper T cells, suggesting a pivotal role of effector phase T cells in pathogenesis of IgG4RD, especially in IgG4 specific production. Further studies are required to elucidate the detailed role of effector phase T cells in the pathogenesis of IgG4-RD.

Table 1.

	population	IgG4RD (n=8)	pSS (n=4)	HC (n=8)	p-value
Th cells	Naïve	42.1 ± 15.6	56.5 ± 16.5	52.2 ± 9.0	0.3732
	central memory	35.2 ± 8.6	29.8 ± 13.7	34.0 ± 8.3	0.8446
	effector memory	16.7 ± 6.5	12.3 ± 4.9	11.5 ± 6.5	0.1994
	effector	6.0 ± 4.3	1.5 ± 0.2	2.4 ± 1.9	0.0135
	activated	5.8 ± 3.0	3.1 ± 1.0	4.2 ± 1.7	0.1519
	Th1	18.8 ± 6.5	18.3 ± 7.7	21.9 ± 4.4	0.7856
	Th17	12.6 ± 4.2	9.1 ± 2.4	10.6 ± 3.9	0.5092
	Treg	6.2 ± 2.2	3.5 ± 0.8	4.1 ± 1.8	0.0805
	Tfh	1.6 ± 0.6	1.0 ± 0.6	1.1 ± 0.6	0.0682
	activated Tfh	18.8 ± 8.1	17.6 ± 8.3	17.9 ± 3.5	0.6828
B cells	Naïve	49.0 ± 22.7	56.7 ± 20.6	50.4 ± 13.3	0.7971
	IgM memory	9.9 ± 4.2	20.3 ± 10.7	27.9 ± 8.9	0.0065
	central memory	33.2 ± 22.5	15.2 ± 10.6	16.5 ± 7.3	0.1543
	effector	7.9 ± 3.2	7.9 ± 2.3	5.2 ± 1.8	0.0563
	Plasma blast	19.5 ± 18.7	3.5 ± 2.8	4.6 ± 5.7	0.0085
DCs	Myeloid DCs	58.1 ± 25.9	75.1 ± 16.0	80.0 ± 5.0	0.0654
	Plasmacytoid DCs	8.0 ± 5.2	7.8 ± 3.8	9.5 ± 3.6	0.4398

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Comparison of Outcomes in Septic Arthritis Caused By MRSA and MSSA. Deepa Panikkath[1], Sian Yik Lim[2], Swetha Gadwala[3], Ragesh Panikkath[3] and Kenneth Nugent[2]. [1]Texas Tech University of Health Sciences, Lubbock, LUBBOCK, TX, [2]Texas Tech University Health Sciences Center, Lubbock, TX, [3]Texas Tech University of Health Sciences, Lubbock, TX.

Background/Purpose: Staphylococcus aureus is the most common cause of adult septic arthritis and the incidence of methicillin-resistant Staphylococcus aureus (MRSA) infections continues to rise. There is a relative lack of information on clinical presentations and outcomes in MRSA septic arthritis and how it differs from methicillin-sensitive Staphylococcus aureus (MSSA) septic arthritis. Our aim was to evaluate the differences in clinical features and outcomes between patients with MRSA and MSSA septic arthritis.

Methods: This is a retrospective chart review study performed at a tertiary level referral hospital. We queried the electronic database for patients with a discharge diagnosis of pyogenic arthritis between Jan 1st 2000 and Dec 31st2013. We only included native joint septic arthritis. We collected data on patient demographics, clinical information, and patient outcomes. Statistical analysis was performed using SPSS staistics 20.0. The institutional review board at Texas Tech University approved this study.

Results: We identified 274 patients with native joint septic arthritis. Staphyloccocus aureus caused 122 cases. MRSA caused septic arthritis in 45 patients; MSSA caused septic arthritis in 77 patients. Patient characteristics, clinical features and outcomes of MRSA septic arthritis patients and MSSA septic arthritis patients are summarized in Table 1. MRSA and MSSA septic arthritis occurs predominantly in males. There were no differences between the two groups in mean age. MRSA septic arthritis patients had more comorbidities than MSSA septic arthritis patients. There were no statistically significant differences in the initial clinical presentation between both groups (fever, leukocytosis, presence of bacteremia, polyarticular involvement, mean leucocyte count on synovial analysis). Only 77.8% of MRSA patients were treated initially for MRSA. The MRSA septic arthritis patients had a higher mean number of joint surgeries and longer hospital lengths of stay. They also had worse patient and joint outcome and higher rates of development of osteomyelitis adjacent to the joint.

Conclusion: We recorded a significant number of MRSA septic arthritis cases from the year 2000 to 2013. MRSA septic arthritis affects patients with multiple comorbidities and is associated with worse outcomes. Only 77.8% of MRSA septic arthritis patients were covered empirically for MRSA on initial presentation. Since MRSA is an emerging clinical entity in septic arthritis, rheumatologists have to consider this pathogen in patients with septic arthritis and more research is needed to improve patient outcomes.

Table 1

	MSSA	MRSA	P
Male	61/77 (79.2%)	31/45 (68.9%)	0.201
Age, mean (SD*)	46.68 (22.6)	44.78 (21.0)	0.647
Number of comobidities, mean (SD*)	1.2 (2.3)	2.2 (2.6)	0.082
One or less than 1 co morbidity	39/77 (50.6%)	14/45 (31.3%)	0.036
Pre-existing joint disease	7/77 (9.1%)	5/45 (11.1%)	0.758
Fever (More than 100F)	21/77 (56.8)	16/45 (43.2)	0.347
Mean WBC count on presentation(/μL)	13399 (6980)	13615 (4147)	0.853
Mean ESR (mm/hr)	79.7 (32.3)	83.6 (35.0)	0.543
Mean Joint WBC on presentation (mm^3)	95461 (69768)	104784 (82679)	0.508
Polyarticular involvement	5/77 (6.5%)	4/45 (8.9%)	0.724
Bacteremia	25/77 (32.5%)	13/45 (28.9%)	0.680
Appropriate empiric coverage for MRSA	41/77 (53.2%)	34/45 (77.8%)	0.007
Mean number of weeks of antibiotics treatment (SD)	5.4 (1.8)	5.0 (1.3)	0.172
Mean number of joint surgeries (SD)	2.0 (1.3)	2.6 (1.7)	0.035
Mean number of admission days (SD)	10.2 (7.2)	16.2 (9.0)	0.001
Mortality	3/77 (3.9%)	4/45 (8.9%)	0.421
Poor patient outcome	7/77 (9.1%)	14/45 (31.1%)	0.002
Poor joint outcome	15/77 (19.5%)	15/45 (33.3%)	0.086
Development of osteomyelitis	8/77 (10.4%)	13/45 (28.9%)	0.009

Disclosure: D. Panikkath, None; **S. Y. Lim**, None; **S. Gadwala**, None; **R. Panikkath**, None; **K. Nugent**, None.

2808 WITHDRAWN

2809

Human Papilloma Virus and Chlamydia Trachomatis Infections in Rheumatoid Arthitis Under Anti-TNF Therapy. Mariana G Waisberg[1], Ana C.M. Ribeiro[2], Wellington M. Candido[1], Poliana B. Medeiros[1], Cezar N. Matsuzaki[1], Mariana C. Beldi[1], Maricy Tacla[1], Helio H. Caiaffa-Filho[1], Eloisa Bonfá[1] and Clovis A Silva[3]. [1]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [2]University of Sao Paulo, Sao Paulo, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: Cervical human papillomavirus (HPV) infection has been observed in 28% of rheumatoid arthritis (RA) patients in a cross-sectional study with no available data regarding *Chlamydia trachomatis* (CT) infection. Anti-TNF blockage may increase the risk of these gynecologic complications, in spite of a few case reports of HPV infection in chronic inflammatory arthritis and psoriasis under this therapy. Therefore, the purpose of our study was to evaluate HPV and CT infections in RA patients pre- and 6 months post-TNF blocker. The possible associations among these infections, demographic data, sexual function, disease parameters and treatment were also analyzed.

Methods: Fifty female RA patients (ACR criteria), who were eligible to anti-TNF therapy, [n=50 at baseline (BL) and n=45 after 6 months of treatment (6M)] and 50 age-matched healthy controls were prospectively enrolled. All RA patients and controls had previous sexual activity. Exclusion criteria were: current pregnancy, early post-partum period, diabetes mellitus, psychiatric diseases and cervical cancer. They were assessed for demographic data, gynecologic, sexual, cervical cytology and histological evaluations, disease parameters and current treatment. HPV DNA and CT DNA testing in cervical specimens were done using Hybrid Capture II assays.

Results: At BL, the median current age of RA patients and controls was 49(18–74) vs. 49(18–74) years, p=1.0. A trend of lower frequency of HPV infection was observed in AR patients pre anti-TNF compared to controls (14% vs. 30%, p=0.054). None of patients had genital warts. Further evaluation of AR patients with and without HPV infection before anti-TNF therapy showed that the former group had a higher frequency of sexual intercourses (100% vs. 48%, p=0.014), higher median number of sexual partners [1(1–1) vs. 0(0–1), p=0.032] and higher frequency of abnormal cervical cytology (43% vs. 7%, p=0.029). Current age, disease duration, physician and patient visual analogue scales, DAS 28, ESR, CRP and treatments were alike in both groups (p>0.05). At 6M after TNF blockage, HPV infection remained unchanged in five patients, whereas two became negative and one additional patient turn out to be positive (McNemar′s test p=1.0). None of them had cervical cancer in Pap smear. CT infection was uniformly negative in RA patients pre- and post-TNF blockage and in controls.

Conclusion: To our knowledge, this was the first study to assess prospectively genital infections in RA patients under TNF blockage therapy. Anti-TNF does not seem to increase short-term risk or severity of HPV and CT infections in RA patients.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects V: Mortality and Other Outcomes
Tuesday, November 18, 2014, 2:30 PM–4:00 PM

2810

Reduced Mortality Risk in Rheumatoid Arthritis: Findings from Two UK Inception Cohorts. Sam Norton[1], Elena Nikiphorou[2], Lewis Carpenter[2], David Walsh[3], Patrick Kiely[4], Josh Dixey[5] and Adam Young[6]. [1]King's College London, London, United Kingdom, [2]University of Hertfordshire, Hatfield, United Kingdom, [3]University of Nottingham, Nottingham, United Kingdom, [4]St. Georges Healthcare NHS Trust, London, United Kingdom, [5]New Cross Hospital, Wolverhampton, United Kingdom, [6]ERAS, St Albans City Hospital, St Albans, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) is associated with a 20 to 30% increased risk of mortality from all-causes compared to the general population. The aim of the present study is to examine whether, as observed in the general population, mortality rates in RA have decreased over the past 25 years. Furthermore, to assess whether changes are due to a potentially milder disease at presentation or change in treatment practise.

Methods: Data from 32 centres in the UK that recruited 2763 patients to two inception cohorts between 1986 and 2012 were combined for the analysis: Early RA Study and Early RA Network. Both recruited DMARD naïve patients at presentation to the rheumatology clinic. Death certificates were provided by the NHS central register. All-cause mortality was standardised against population rates (stratified by age, sex and calendar year) to examine whether excess mortality risk had changed with time. Pooled logistic survival models estimated the relative yearly reduction in mortality hazard. Marginal structural modelling was used to examine the effect on methotrexate on survival, adjusting for confounding by indication of the treatment effect.

Results: The excess mortality risk in RA compared to the general population reduced over time. Restricting the analysis to deaths within 10 years of onset, for ERAS (recruitment 1986 to 2001) the all-cause standardised mortality ratio (SMR) was significantly increased (1.21; 95%CI 1.10 to 1.34), whereas for ERAN (recruitment 2002 to 2012) it was non-significant (1.04; 95%CI 0.88 to 1.22). The difference between SMR's for the two cohorts was non-significant. Combining the two cohorts, year of symptom onset was significantly associated with all-cause mortality risk (HR = 0.96, p<.001; 95%CI. 95 to. 98). Controlling for demographic and clinical features at baseline did not reduce the magnitude of the effect for year of onset (HR = 0.95, p<.001; 95%CI. 93 to. 97). Extending the model to control for treatment using a marginal structural modelling approach, the use of methotrexate (use of which increased dramatically over the period of recruitment) was associated with a 60% reduction in the risk of death (HR = 0.40, p<.001; 95%CI. 25 to. 64). After controlling for methotrexate use the effect of year of onset was reduced to non-significant (Hazard ratio = 0.98, p<.001; 95%CI. 96 to 1.01).

Conclusion: Substantial gains in life expectancy have been observed for people with RA in the UK over the last 25 years. The excess mortality risk appears to have been greatly diminished. This is probably due to changes in treatment practise, rather than RA becoming milder at presentation.

Disclosure: S. Norton, None; **E. Nikiphorou**, None; **L. Carpenter**, None; **D. Walsh**, Pfizer Inc, 2; **P. Kiely**, None; **J. Dixey**, None; **A. Young**, None.

2811

Improvements in Rheumatoid Arthritis Related Fatigue Are Driven By Reductions in Pain, Not Disease Activity – Results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis.
Katie L Druce, Gareth T Jones, Gary J. Macfarlane and Neil Basu. University of Aberdeen, Aberdeen, United Kingdom.

Background/Purpose: Rheumatoid Arthritis (RA) patients commonly report reductions in fatigue after commencing Anti-TNF therapy. The mechanisms behind such reductions have not been determined, although it is assumed that changes in disease activity drive improvements. Nevertheless, to promote improvement in this patient priority, the true pathways to change in fatigue must be elucidated. Using Structural Equation Modelling (SEM), this study aimed to be the first to determine the pathways to improvement in fatigue among RA patients commencing Anti-TNF therapy.

Methods: Participants recruited to a long-term cohort study (the British Society for Rheumatology Biologics Register for RA) provided information on fatigue (SF 36 Vitality), disease activity (DAS 28) and other putative mediators of fatigue change (including disability, pain and mental health) at Anti-TNF therapy commencement and 6 month follow-up. A SEM path model, using the data of 2652 participants with high baseline fatigue (SF 36 Vitality ≤12.5,), was constructed employing a model generation approach. The total, direct and indirect effects of each putative mediator on improvement in fatigue were quantified using path co-efficients. Where indirect effects accounted for more than 50% of total effect, the variable was considered to be mediated by other variables in the model.

Results: Significant pathways to improvement in fatigue (Figure 1) were shown to originate from changes in disease activity, pain, mental health, and disability, as well as a history of depression and participant sex. The model accounted for 40% of the variance in change in fatigue and demonstrated a good model fit (χ^2=0.18, df=3,p=0.98). The largest absolute improvements in fatigue were associated with a one standard deviation improvement in pain and mental health (0.31 and 0.28 unit improvement in fatigue, respectively). As 82% of the total effect of change in disease activity was indirect, the variable was mediated by other variables in the model. Specifically, 50% of the indirect effect was mediated through a change in pain and an additional 14% through pain and mental health improvement.

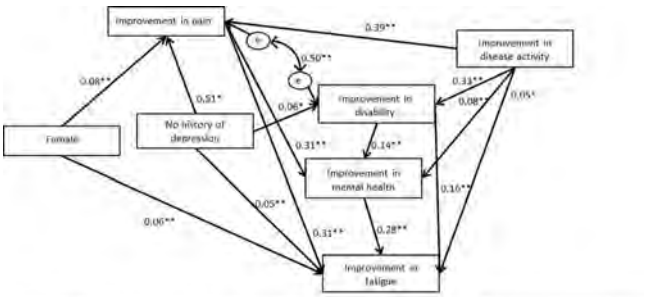

Figure 1. Path model diagram with standardized coefficients determining direct and indirect effects to improvement in fatigue (SF36 Vitality 0-100). e; 'error term' (unmeasured variable) p<0.01, **p<0.001

Conclusion: Improvement in RA related fatigue after commencing Anti-TNF therapy is driven by reductions in pain, rather than directly from disease activity. In addition, mental health and disability are important mediators in the pathway to fatigue improvement and should be targeted, in an attempt to further improve this patient priority.

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2812

Is Rheumatoid Arthritis the Same Disease in Women and Men?- Joint Damage in Patients with EARLY Rheumatoid Arthritis at 10 YEARS after Diagnosis.
Juha Asikainen[1], Kalevi Kaarela[2], Heidi Mäkinen[3], Hannu Kautiainen[4], Pekka Hannonen[5], Tuomas Rannio[6] and Tuulikki Sokka[7]. [1]Jyvaskyla Central Hospital, Jyväskylä, Finland, [2]Jyväskylä Central Hospital, Jyväskylä, Finland, [3]Tampere University Hospital, Tampere, Finland, [4]Medcare Oy, Äänekoski, Finland, [5]Jyväskylä Central Hospital, Jyvaskyla, Finland, [6]Kuopio University Hospital, Kuopio, Finland, [7]Jyvaskyla Central Hospital, Jyvaskyla, Finland.

Background/Purpose: Rheumatoid arthritis (RA) is suggested to be a more severe disease in women than in men as disease activity appears higher in women, and men meet remission criteria more often.

Long-term severity of RA can be analyzed from permanent joint damage in radiographs. Our purpose was to study possible differences in the extent of radiographic joint damage between women and men in an early RA cohort at 10 years after diagnosis.

Methods: Our early RA cohort includes 990 patients from a single clinic with a clinical diagnosis of early RA in 1997 – 2004. Radiographs of hands and feet were taken at a 10 year follow-up visit after diagnosis and were analyzed according to the Larsen score (0–100) including MCP I-V, wrists, and MTP II-V.

Results: Baseline characteristics of 990 patients were: the mean (SD) age 57(16) years, 67% female, 61% seropositive (RF/CCP+ any time over 10 years) and median (IQR) duration of symptoms before diagnosis 6(3, 12) months; 657(66%) patients were available for a 10 year follow up. Reasons for non-attendance among 333 patients included death (52%), high age, multi-comorbidity or institutionalization (10%), moving from the area (12%); 8% declined, 4% were lost to follow-up and 14% miscellaneous reasons. Thus, radiographs were available in 462 women and 195 men with a similar percentage of 66% being seropositive among genders. In seropositive patients, the mean (SD) Larsen score was 7.7(10) in women and 8.1(11) in men, p=0.12. The probability plot was similar for women and men (Figure 1). In seronegative patients, the mean (SD) Larsen score was 1.9(3.8) in women and 2.3(4.5) in men, p=0.29.

Conclusion: At 10 years after diagnosis, RA joint damage appears similar in both genders. RA severity is comparable between women and men.

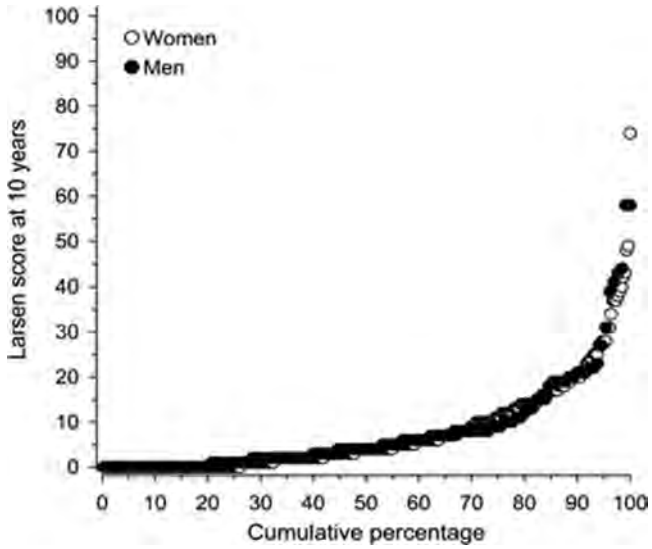

Figure. Larsen score in seropositive women and men with early RA at 10 years after diagnosis.

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2813

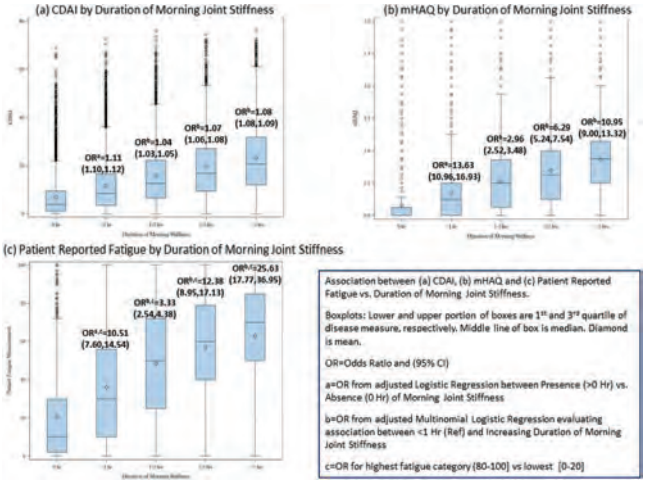
Correlation of Morning Stiffness with Measures of Higher Disease Activity in a Large US Registry Population of Rheumatoid Arthritis Patients. Vibeke Strand[1], Robert J. Holt[2], Katherine C. Saunders[3], Jeffery D. Kent[4], Ping Xu[5], Amy Y. Grahn[4], Marc Mason[3] and Carol J. Etzel[3]. [1]Stanford University, Palo Alto, CA, [2]University of Illinois - Chicago, Chicago, IL, [3]Corrona, LLC., Southborough, MA, [4]Horizon Pharma, Inc., Deerfield, IL, [5]Axio Research LLC, Seattle, WA.

Background/Purpose: Morning stiffness may not be specifically queried by rheumatologists in the course of their regular interactions with rheumatoid arthritis (RA) patients. This analysis investigated whether morning stiffness was correlated with measures of disease activity.

Methods: Data from the Corrona RA Registry included RA patients who initiated a new therapy: non-biologic or biologic DMARD, whether as monotherapy or in combination, and remained on treatment for ≥ 90 days. Patients were evaluated at initiation, 1 and 2 years after initiation and time of last visit. Correlations of measures of disease activity with presence and change in morning stiffness were modeled at the patients' last Corrona visit between January 2013 and February 2014. For patients with ≥ one visit during this interval, propensity score (PS) trimming of the top and bottom 5% was used to obtain comparable populations with and without morning stiffness. Thus data from 90% of RA patients (5379 subjects) were utilized to examine the association of measures of disease activity: remission (CDAI ≤2.8); low disease activity (2.8>CDAI≤10); moderate disease activity (10<CDAI≤22) and high disease activity (CDAI>22) with presence/absence of morning stiffness, after PS trimming at time of last visit.

Results: At baseline those with morning stiffness (n=9688) were less likely to be working, more likely to have received biologic therapy, Medicaid insurance, and to have higher measures of disease activity than those without (n=2865): CDAI high: 34.1 vs 10.3%; remission/low: 31.6 vs 66.3%, p<0.0001. At one year after initiation of treatment, these differences persisted (with morning stiffness (n=6148) without (n=2597), including statistically significantly higher mHAQ scores: 0.5 ± 0.5 vs 0.1 ±0.3, p<0.0001; more reporting disabled work status: 21.7 vs 5.2%, p<0.0001 and CDAI high: 21.7 vs 5.2%; remission/low: 48.0 vs 80.2% p<0.0001. These differences persisted even after 2 years of follow-up (with morning stiffness (n=4466) without (n=1895): mHAQ scores unchanged; disabled: 29.2 vs 9.4%; CDAI high:19.3 vs 3.9%; remission/low: 51.4 vs 82.0, all p<0.0001. At time of last Corrona visit, higher CDAI, mHAQ and patient reported fatigue were significantly associated with presence of morning stiffness and increased persistence of morning stiffness (Figure 1).

Conclusion: In this registry analysis, presence and persistence of morning stiffness consistently reflected higher disease activity associated with more impairment of physical function and self reported work disability.



Disclosure: V. Strand, AbbVie, Afferent, Amgen, Biogen Idec, Bioventus, BMS, Carbylan, Celgene, Celltrion, CORRONA, Crescendo, Genentech/Roche, GSK, Hospira, Iroko, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi, SKK, Takeda, UCB, Vertex, 5, Up to Date, 7; **R. J. Holt**, Horizon Pharma, Inc., 5; **K. C. Saunders**, Corrona, LLC., 3; **J. D. Kent**, Horizon Pharma, Inc., 1, Horizon Pharma, Inc., 3; **P. Xu**, Axio Research, LLC, 3; **A. Y. Grahn**, Horizon Pharma, Inc, 1, Horizon Pharma, Inc., 3; **M. Mason**, Corrona, LLC., 3, NIH, 6; **C. J. Etzel**, Corrona, LLC., 3.

2814

Time-to-Remission, Time-to-Relapse and Disease Severity at the Time of Relapse in RA- Results from the Ontario Best Practices Research Initiative (OBRI). Bindee Kuriya[1], Xiuying Li[2], Binu Jacob[2], Pooneh Akhavan[3], Jessica Widdifield[1], Mark Tatangelo[1], Janet E. Pope[4], Edward Keystone[5] and Claire Bombardier[6]. [1]University of Toronto, Toronto, ON, [2]University Health Network, Toronto General Research Institute, Toronto, ON, [3]Early Rheumatoid Arthritis Program, Mount Sinai Hospital and University of Toronto, Toronto, ON, [4]Western University, London, ON, [5]Mount Sinai Hospital, University of Toronto, Toronto, ON, [6]Institute for Work & Health, Toronto, ON.

Background/Purpose: Clinical remission in RA is the desired goal, however the ability to sustain remission and the timing and severity of relapse is not well known. We aimed to describe time to remission, time-to-relapse and disease activity at the time of relapse.

Methods: We performed a longitudinal data analysis of patients enrolled in the Ontario Best Practices Research Initiative (OBRI), a clinical registry of RA patients followed in routine care. The prevalence of a first occurrence of clinical remission according to the DAS28-ESR <2.6 or CDAI </=2.8 following cohort entry (baseline) was determined as was the average time-to-remission. Patients achieving remission with >/= 1 follow-up visit (typically spaced 3 to 6 months apart) were observed for the average time until relapse, defined as a DAS28 >2.6 or CDAI >2.8. The baseline disease activity level of those achieving remission and the disease activity level at the time of relapse was examined.

Results: The total cohort (N=2305) was 78% female with mean (SD) age 57 (13) years, disease duration 8.6 (9.6) years and mean DAS28 score 4.5 (1.5) at baseline. Remission was achieved in 1081 patients (47%); 140 of these patients had low baseline disease activity, 516 had moderate and 369 had high disease activity at baseline. The median time to remission was 279 days (interquartile range [IQR] 146 – 482) and remission was reached significantly faster among those starting with low disease activity (median 218 days, IQR 148–385) at baseline compared to more severe disease (median 357 days, IQR 173–563) (P<0.001). Nine hundred eighteen patients (85%) had continued follow up after remission and 582 (59%) went on to experience a relapse. The median time-to-relapse was 197 days (IQR 126–363). The majority switched from a state of remission to mild or moderate disease activity, in contrast to the moderate to severe levels of disease activity they experienced at baseline (Table).

Conclusion: Clinical remission in routine care is achievable and occurs fastest in those with low to moderate levels of disease activity at baseline. Remission is not sustained in the majority of individuals and relapse occurs, on average, by 7 months. Further work examining the predictors and characteristics of patients who relapse to a low disease state (which may be an acceptable substitute to remission) vs. relapse to a high disease state is needed to determine the nature and timing of therapeutic intervention that may be required to prevent and manage disease flares.

Table. Disease activity according to DAS28 or CDAI at time of relapse according to baseline level disease activity.

RA disease at baseline	Disease Activity at Time of Relapse (N=552)*		
	Low (N=257)	Moderate (N=245)	High (N=50)
Low (N=55)	26	25	4
Moderate (N=284)	140	127	17
High (N=213)	91	93	29

* 30 of the 582 patients were missing information at follow up to calculate disease activity

Disclosure: B. Kuriya, None; **X. Li**, None; **B. Jacob**, None; **P. Akhavan**, None; **J. Widdifield**, None; **M. Tatangelo**, None; **J. E. Pope**, None; **E. Keystone**, Abbott, Amgen, AstraZeneca, BMS, F. Hoffmann-La Roche, Janssen, Lilly, Novartis, Pfizer Sanofi-Aventis, UCB, 2, Abbott Laboratories, AstraZeneca, Biotest, BMS, F. Hoffmann-La Roche, Genentech, Janssen, Lilly, Merck, Pfizer, UCB, 5, Abbott, AstraZeneca, BMS Canada, F. Hoffmann-La Roche, Janssen, Pfizer, UCB, Amgen, 8; **C. Bombardier**, None.

2815

Better Functional Ability with Less Biologicals 2 years after Induction with Combination DMARD Therapy versus methotrexate Monotherapy. T. Martijn Kuijper[1], J.J. Luime[1], P.H.P. de Jong[1], A. H. Gerards[2], D. van Zeben[3], I. Tchetverikov[4], P.B.J. de Sonnaville[5], M. van Krugten[6], B. Grillet[7], J.M.W. Hazes[8] and A.E.a.M. Weel[9]. [1]Erasmus University Medical Center,

Rotterdam, Netherlands, [2]Vlietland Hospital, Schiedam, Netherlands, [3]Sint Franciscus Gasthuis, Rotterdam, Netherlands, [4]Albert Schweitzer Hospital, Dordrecht, Netherlands, [5]Admiraal de Ruyter Ziekenhuis, Goes, Netherlands, [6]Admiraal de Ruyter Hospital, Vlissingen, Netherlands, [7]ZorgSaam Hospital, Terneuzen, Netherlands, [8]Erasmus MC, Rotterdam, Netherlands, [9]MD, PhD, Rotterdam, Netherlands.

Background/Purpose: To assess differences in frequency of biological therapy use and functional ability in early RA patients two years after starting induction therapy according to three different treatment regimens.

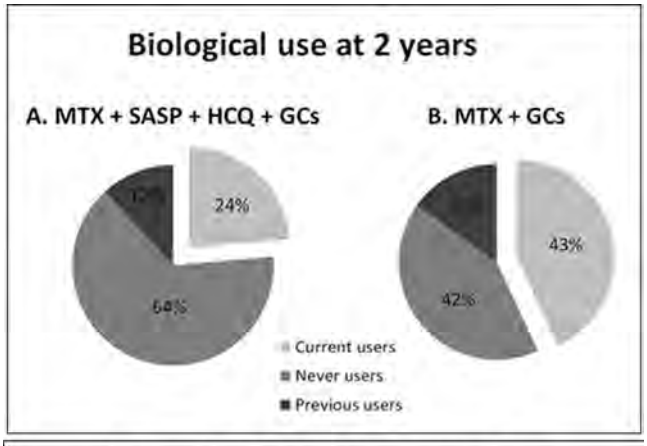
Methods: Data were used from patients with recent-onset arthritis participating in a single-blinded clinical trial (Treatment in the Rotterdam Early Arthritis CoHort (tREACH))(1) in which three induction therapy strategies were compared: (A1) combination therapy (methotrexate (MTX) + sulfasalazine + hydroxychloroquine) with glucocorticoids (GCs) intramuscularly; (A2) combination therapy with an oral GC tapering scheme and (B) MTX with oral GCs similar to B. As no difference in disease activity scores (DAS) was found between groups A1 and A2 at 3 and 12 months of follow-up(1), these groups were combined for this analysis (group A). Disease activity scores (original DAS) were assessed every 3 months. Functional ability was assessed using the Health assessment questionnaire (HAQ). Data were analysed using simple descriptive statistical techniques.

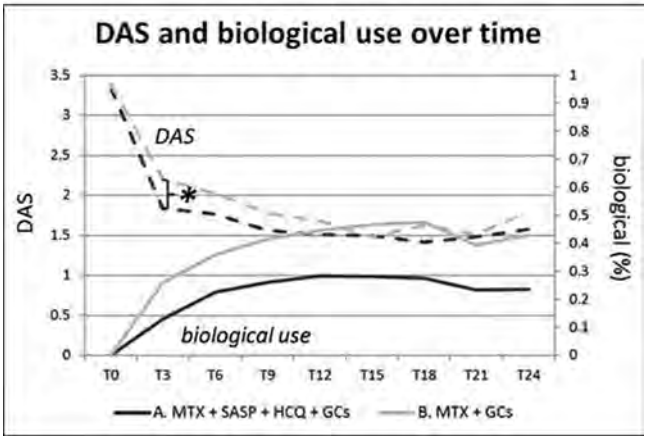
Results: 281 patients (91 men, 190 women; mean baseline DAS 3.3, median baseline HAQ 1.00) were initially randomized. Data on medication use at 2 years were available from 248 patients (88%), see figure 1. At 2 years, 24% of patients in group A versus 43% in group B were using a biological DMARD. Biological use and DAS over time are demonstrated in figure 2.

Equal mean DAS of 1.66 (95%CI 1.54–1.78) at 24 months was observed for the initial treatment groups at 24 months (group A: 1.58 (95%CI 1.43–1.73), group B: 1.80 (95%CI 1.58–2.02). DAS remission (DAS<1.6) was achieved by 53% of patients.

The median disability score (HAQ (min-max)) was 0.38 (0–2) for all patients but varied in the treatment groups: A. 0.25 (0–1.9) and B. 0.63 (0–2.1) (p=0.042).

Conclusion: We observed lower use of biological therapy and better functional ability in induction triple therapy compared to induction monotherapy MTX with GC bridging at 2 years of follow-up in the treat-to-target tREACH study. No differences were found for disease activity scores.





1. De Jong et al. Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. Ann Rheum Dis. 2014 Jul;73(7):1331–9.

Disclosure: T. M. Kuijper, None; **J. J. Luime**, None; **P. H. P. de Jong**, None; **A. H. Gerards**, None; **D. van Zeben**, None; **I. Tchetverikov**, None; **P. B. J. de Sonnaville**, None; **M. van Krugten**, None; **B. Grillet**, None; **J. M. W. Hazes**, None; **A. E. A. M. Weel**, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Human Etiology and Pathogenesis I: Mechanisms of Joint Damage
Tuesday, November 18, 2014, 2:30 PM–4:00 PM

2816

Distinctive DNA Methylome Signatures in Early Rheumatoid Arthritis (RA) Synoviocytes Compared with Longstanding (RA) and Other Inflammatory Arthritides. Rizi Ai[1], John W. Whitaker[2], David L. Boyle[3], Paul Peter Tak[4], Danielle M. Gerlag[5], Wei Wang[6] and Gary S. Firestein[3]. [1]UC San Diego, La Jolla, CA, [2]UCSD, San Diego, CA, [3]University of California at San Diego School of Medicine, La Jolla, CA, [4]Academic Medical Center / University of Amsterdam, Department of Clinical Immunology and Rheumatology & GlaxoSmithKline, Amsterdam, Netherlands, [5]Academic Medical Center/University of Amsterdam, Amsterdam, Netherlands, [6]UCSD, La Jolla, CA.

Background/Purpose: Epigenetics influences pathogenic mechanisms in autoimmunity. Recently, a stable RA DNA methylation signature in fibroblast-like synoviocytes (FLS) was defined in 2375 genes. The present study compared the DML patterns of early RA (ERA) and other inflammatory arthritides to the patterns in longstanding RA (LRA) and OA.

Methods: Genomic DNA from FLS was isolated from arthroscopic biopsies in ERA (1–13 months of symptoms; n=4), undifferentiated arthritis that progressed to RA (UA; n=2) and ACPA+ arthralgia that did not develop arthritis (Arthralg; n=2). FLS lines were obtained from juvenile idiopathic arthritis (JIA; n=3) and spondyloarthritis (SpA; n=2) at arthroplasty. Methylation was measured using the Illumina HumanMethylation450 chip. Hierarchical clustering using Pearson correlation as the metric was performed on the methylomes of 11 LRA and 11 OA FLS lines. Principle component analysis (PCA) assessed the relationships between the different FLS types. Feature selection was determined by random forest to define ERA and LRA differences. Pathway enrichment analysis was evaluated using Kyoto Encyclopedia of Genes and Genomes (KEGG).

Results: Differentially methylated loci (DMLs) for LRA and OA segregated from each other based on the methylation pattern of 15,220 DMLs. Other non-inflammatory arthritis FLS lines clustered with LRA rather than OA. Within the non-OA cluster, LRA were highly similar to each other. DML patterns for ERA FLS were closely related to each other, but differed from the LRA. FLS from other diseases, including UA, SpA and JIA had an intermediate pattern. They were more closely related to LRA but formed subgroups within the non-OA hierarchical clustering. PCA confirmed distinct methylation patterns for LRA and OA. ERA and LRA patterns partially overlapped, which could be consistent with a transition of ERA to LRA methylation. UA was in the center of the LRA region while SpA and JIA primarily localized at the edges of LRA. The 2 Arthalg FLS lines did not conform to either OA or LRA patterns. Feature selection was performed and showed that the difference between LRA and ERA was due to 317 CpG loci. Pathway analysis suggested that DML genes in ERA involving focal adhesion, chemokine signaling, complement and coagulation are differentially methylated compared with LRA, indicating that cell recruitment in synovium evolves during the transition from early to late disease.

Conclusion: These data show a methylation signature in longstanding RA, with patterns that could be differentiated from SpA and JIA. UA patients who ultimately develop RA have a longstanding RA pattern. Most interesting, early RA had a distinct but overlapping DML pattern compared with longstanding RA with changes in cell recruitment pathways that might indicate a change in how cells enter the joint as disease progresses. Therefore, differential methylation of RA FLS occurs early and evolves over time. Understanding the transition from early and established disease provides clues identifying targets causing disease progression.

Disclosure: R. Ai, None; **J. W. Whitaker**, None; **D. L. Boyle**, None; **P. P. Tak**, GlaxoSmithKline, 3; **D. M. Gerlag**, GlaxoSmithKline, 3; **W. Wang**, None; **G. S. Firestein**, None.

2817

Histone Deacetylase One Contributes to the Auto-Aggressive Phenotype of Rheumatoid Arthritis. Sarah Hawtree[1], Munitta Muthana[1], J. Mark Wilkinson[1], Anthony G. Wilson[1] and Mohammed Akil[2]. [1]University of Sheffield, Sheffield, United Kingdom, [2]Rheumatology Department, Sheffield South Yorkshire, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory disease that affects synovial joints. A key characteristic of RA is hyperplasia of fibroblast-like synoviocytes (FLS) which develop a stable, auto-aggressive phenotype that augments tissue destruction. It is unknown how this phenotype is stably maintained, however epigenetic changes have been implicated. Histone acetylation is a major epigenetic mechanism (HDACs). The objective of the study is to determine the role of histone deacetylates (HDACs) in regulating the auto-aggressive phenotype of RA FLS.

Methods: Real time-qPCR was used to compare levels of HDAC1–11 in RA compared with osteoarthritis (OA) FLS. Joint biopsies were co-stained with anti-HDAC1 and anti-fibroblast antibodies. HDAC1 and a non-targeting control (NTC) siRNA were transfected *in vitro* into RA FLS. Cell proliferation, migration and invasion after siRNA knockdown (KD) were assessed by using tritiated thymidine, a scratch assay and a matrigel invasion assay respectively. An Illumina BeadChip (47,000 transcripts) was used to analyse global gene expression changes after KD. The *in vivo* effect of $HDAC1^{KD}$ was investigated in a mouse model of collagen-induced arthritis (CIA) using *in vivo*siRNA. Clinical scores of CIA were measured daily (days 0–49) and the bones were analysed using a microCT scanner.

Results: The mRNA levels of HDACs 1–11 are higher in RA compared to OA FLS, with HDAC1 levels showing a 4.2-fold increase ($p=0.03$, n=7–10). $HDAC1^{KD}$ reduced FLS proliferation ($p=0.04$, n=6), migration ($p=0.01$, n=6) and invasion ($p=0.02$, n=6) compared to the NTC. Cluster analysis of the microarrays (n=3) revealed significant changes in genes involved in apoptosis ($p\leq0.009$, n=21), migration ($p\leq0.008$, n=4) and proliferation ($p\leq0.009$, n=9). In mice with CIA, $HDAC1^{KD}$ significantly inhibited joint inflammation ($p=0.0001$, n=10) and reduced bone erosion compared to the NTC.

Conclusion: Our data implicates HDAC1 in controlling the autoaggressive phenotype of FLS in RA and our data in murine inflammatory arthritis supports targeting HDACi as a potential therapy in RA.

Disclosure: S. Hawtree, None; **M. Muthana**, None; **J. M. Wilkinson**, None; **A. G. Wilson**, None; **M. Akil**, None.

2818

SH2 Domain-Containing Phosphatase 2 Promotes Aggressiveness of Rheumatoid Fibroblast-like Synoviocytes. Stephanie M. Stanford[1], German R. Aleman Muench[1], Cristiano Sacchetti[1], Lifan Zeng[2], David L. Boyle[3], Gen-Sheng Feng[4], Zhong-Yin Zhang[2], Maripat Corr[3], Gary S. Firestein[3] and Nunzio Bottini[1]. [1]La Jolla Institute for Allergy and Immunology, La Jolla, CA, [2]Indiana University School of Medicine, Indianapolis, IN, [3]University of California at San Diego School of Medicine, La Jolla, CA, [4]University of California at San Diego Division of Biological Sciences, La Jolla, CA.

Background/Purpose: In rheumatoid arthritis (RA), fibroblast-like synoviocytes (FLS) that line joint synovial membranes aggressively invade the extracellular matrix, destroying cartilage and bone. Although this cell type mediates RA pathogenesis, it is currently untapped as a drug target. Signal transduction in FLS is mediated through multiple pathways involving protein tyrosine phosphorylation, thus we sought to identify the protein tyrosine phosphatases (PTPs) regulating the aggressiveness of FLS from RA patients (RA FLS). We previously profiled the expression of all PTPs in FLS from RA and osteoarthritis (OA) patients, and found that the *PTPN11* gene, encoding the PTP SHP-2, is overexpressed in RA FLS. We also reported that SHP-2 promotes the aggressiveness of RA FLS by enhancing sensitivity of these cells to stimulation by platelet-derived growth factor (PDGF) or tumor necrosis factor (TNF). Here we sought to further explore the role of SHP-2 in mediating pathogenesis of RA.

Methods: Inhibition of SHP-2 enzymatic activity was achieved using a cell-permeable small-molecule chemical inhibitor. FLS migration was assessed in transwell assays in response to 5% fetal bovine serum. Inducible *in vivo* deletion of *Ptpn11* in hematopoietic cells was achieved by breeding *Ptpn11* floxed mice with mice expressing Cre recombinase under the *Mx1* promoter. Prior to experiments, deletion of the floxed alleles was induced by treating mice with 3 administrations of 300 μg poly(I:C) 2 days apart. *In vivo* inhibition of SHP-2 activity was achieved by administering mice with 7.5 mg/kg SHP-2 inhibitor once daily. Severity of arthritis in female mice was assessed every 2 days by ankle swelling in the K/BxN passive serum transfer arthritis mouse model following administration of 150 μl arthritogenic serum.

Results: We found that RA FLS migration was reduced 86% upon treatment with 25 μM SHP-2 chemical inhibitor (Median [IQR] % maximum cells per field: 56.58 [41.45–72.37] for vehicle-treated FLS and 7.90 [3.29–15.13] for SHP-2 inhibitor-treated FLS; $p<0.0001$ by Mann-Whitney test). Using the K/BxN mouse arthritis model, we found that inducible deletion of SHP-2 in hematopoietic cells led to >50% reduction in arthritis severity (Median [IQR] change in ankle thickness after 8 days: 3.62 [3.08–3.78] for Cre^- mice and 0.46 [0.11–1.69] for Cre^+ mice; $p<0.0001$ by two-way ANOVA test of 14-day arthritis course). Global inhibition of SHP-2 activity by daily administration of 7.5 mg/kg SHP-2 inhibitor also led to reduced arthritis severity (Median [IQR] change in ankle thickness after 8 days: 2.650 [1.81–3.27] for vehicle-treated mice and 2.14 [0.70–2.73] for inhibitor-treated mice; $p<0.01$ by two-way ANOVA test for 14-day arthritis course).

Conclusion: These data indicate that SHP-2 promotes the aggressiveness of RA FLS, a role that is dependent on the catalytic activity of the phosphatase. Both global inhibition and inducible deletion of SHP-2 in hematopoietic cells caused a reduction in arthritis severity, suggesting SHP-2 could be a potential target for therapy for RA.

Disclosure: S. M. Stanford, None; **G. R. A. Muench**, None; **C. Sacchetti**, None; **L. Zeng**, None; **D. L. Boyle**, None; **G. S. Feng**, None; **Z. Y. Zhang**, None; **M. Corr**, None; **G. S. Firestein**, None; **N. Bottini**, None.

2819

The YAP Pathway Regulates Fibroblast-like Synoviocyte Invasion. Beatrix Bartok. University of California, San Diego, La Jolla, CA.

Background/Purpose: Fibroblast like synoviocytes (FLS) in RA possesses unique transformed phenotype, such as cartilage invasion that is maintained independent of cytokines and other inflammatory cells. However-.the molecular mechanisms that regulate FLS behavior in RA are poorly understood. The transcriptional coactivator Yes-associated protein (YAP) was recently shown that is dysregulated in RA compared with OA FLS. Increased YAP activity might contribute to persistent activation and pathogenic behavior of RA FLS. Therefore, we assessed role of YAP in synoviocyte invasion.

Methods: We used siRNA knock down and chemical inhibition to assess effect of YAP iactivation on RA FLS invasion. We used Verteporfin to inhibit YAP transcriptional activity. For siRNA knockdown, YAP and control siRNA were transfected using AMAXA technology. FLS invasion was studied using Matrigel coated transwells, 3 days following transfection. YAP inhibitor or vehicle was added to the upper chamber and PDGF was used as chemoattractant in the lower chamber. The cytoskeleton and focal adhesions were visualized with confocal microscopy using Rhodamin phalloidin and anti-Vinculin staining. MMP expression was measured using qPCR.

Results: The YAP inhibitor Verteporfin significantly decreased number of invading cells in a concentration dependent manner, with 65+5% inhibition at 0.1 uM ($p< 0.02$, n=3). Similar results were obtained when YAP was knockdown by siRNA. Cells with reduced YAP activity displayed 52+6% ($p< 0.04$, n=3) decrease in invasion through Matrigel matrix compared with scramble control. To determine effect of YAP inactivation on cytoskeleton and focal adhesion formation, cells were stained with phalloidin and anti-Viculin. RA FLS treated with the YAP inhibitor Verteporfin displayed diminished stress fiber formation and decrease in focal adhesion formation by 56+5% ($p<0.04$, n=3) visualized with confocal microscopy. Similar findings were obtained when YAP was inactivated by siRNA knock down. To determine the effect on MMP production cells were stimulated with TNF and qPCR was performed for MMP1, 2, 3, 9 and MT1MMP. mRNA levels for MMP1 and MMP3 were significantly lower in YAP deficient cells compared with scramble control ($P<0.03$ and $p<0.05$, n=3), while MMP2,9 and MT1MMP mRNA were unchanged. Similar findings were obtained using chemical inhibition with Verteporfin.

Conclusion: YAP is a major regulator of RA FLS invasion by modulating focal adhesion formation and MMP production. These observations, together with our previous findings that increased YAP activity in RA FLS compared with OA suggest that YAP activity might contribute to persistent activation and pathogenic behavior of RA FLS. Therefore, modulating YAP pathway might represent a novel therapeutic approach for RA.

Disclosure: B. Bartok, None.

2820

Dual Role for B Cells in Promoting Bone Erosion in Rheumatoid Arthritis Via Effects on Osteoclast and Osteoblast Differentiation. Nida Meednu, Hengwei Zhang, Teresa Owen, Lianping Xing and Jennifer H. Anolik. University of Rochester, Rochester, NY.

Background/Purpose: Rheumatoid arthritis (RA) is a systemic autoimmune disease that often leads to joint damage, a process mediated by an imbalance between bone resorption and bone formation. Additional evidence implicates the role of B cells in joint destruction including the presence of B cell aggregates in RA synovium and subchondral bone and the efficacy of B cell depletion therapy in halting radiographic progression. However, B cell effects on bone have been described as mediated via indirect influences on other immune cell such as T cells. Whether B cells directly affect bone homeostasis in RA is not known. In this study we investigated the effects of B cells on osteoclast (OC) and osteoblast (OB) functions in RA.

Methods: Isolated B cells from peripheral blood of healthy controls (HC) or RA patients were stimulated with α-CD40 and PMA for 96 h, and RANKL and TNF production was assessed by flow cytometry, ELISA, and qPCR. Stimulated and un-stimulated B cells were fixed then co-cultured with CD14+ monocytes isolated from HC along with M-CSF and sub-optimal levels of exogenous RANKL (10ng/ml). OC formation *in vitro*was examined by TRAP staining. For OB differentiation assays, stimulated and un-stimulated B cells were co-cultured in Transwells with human mesenchymal stem cells (hMSCs) (Lonza, #PT-2501) for 24 h and the expression of OB transcription factor RUNX2 and Notch signaling molecules, Hes1 and Hey1 in hMSCs was detected by qPCR.

Results: HC B cells stimulated with α -CD40 and PMA produce significant amounts of RANKL as compare to un-stimulated B cells (%RANKL+: 4.9±0.94 *vs.* 0.413±0.095, $P<0.0001$). Stimulated HC B cells promoted more OC formation than that of un-stimulated B cells (#OC/well: 66±8 *vs.* 4±1, $P<0.0001$), which can be blocked by RANKL neutralizing antibody (#OC/well: 66±8 *vs.* 21±3, $P<0.0001$). Notably, stimulated RA B cells induced significantly more OC formation in comparison to HC B cells (using the same donor for OCP) (#OC/well: RA: 60±7 *vs.* HC: 12±7, $P<0.001$). In parallel, RA memory B cells expressed higher RANKL than memory B cells from HC (%RANKL+: 20.4±1.68 *vs.* 11.25±3.15, $P<0.05$). In addition to RANKL, stimulated B cells produce TNFα (91±11.6 pg/ml, n=4) a cytokine that we reported recently to inhibit OB differentiation of murine CD45- MSCs via up-regulating the Notch signaling pathway. In co-culture with hMSCs, stimulated RA B cells significantly reduced RUNX2 expression in hMSCs as compared to un-stimulated B cells (Runx2/actin: 0.21±0.01*vs.* 1±0.04 $P=0.002$, n=3), which was associated with increased levels of Hes1 and Hey1. In agreement with this finding, RA CD45- cells (MSC-enriched cells) isolated from peripheral blood have reduced expression of RUNX2 and increased expression of Hes1 and Hey1 compared to HC (n=11 for RA, n=14 for HC), suggesting abnormal OB function *in vivo*.

Conclusion: Our finding suggest that B cells play a critical role in promoting bone erosion in RA both by directly enhancing osteoclastogenesis and inhibiting osteoblast differentiation.

Disclosure: N. Meednu, None; **H. Zhang**, None; **T. Owen**, None; **L. Xing**, None; **J. H. Anolik**, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy V: Novel Therapies in Rheumatoid Arthritis - Late in Development

Tuesday, November 18, 2014, 2:30 PM–4:00 PM

2821

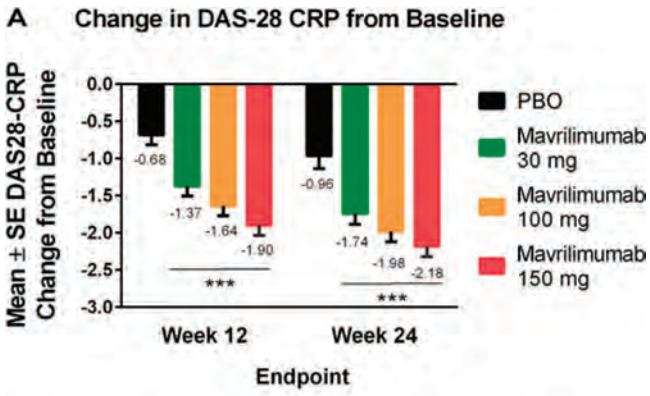
Efficacy and Safety/Tolerability of Mavrilimumab, a Human GM-CSFRá Monoclonal Antibody in Patients with Rheumatoid Arthritis.

Gerd Burmester[1], Iain B. McInnes[2], Joel M. Kremer[3], Pedro Miranda[4], Mariusz Korkosz[5], Jiri Vencovsky[6], Andrea Rubbert-Roth[7], Eduardo Mysler[8], Sara Sandbach[9], Matthew A. Sleeman[9], Alex Godwood[9], David Close[9] and Michael Weinblatt[10]. [1]Charité - University Medicine Berlin, Berlin, Germany, [2]University of Glasgow, Glasgow, United Kingdom, [3]Albany Medical College and the Center for Rheumatology, Albany, NY, [4]Centro de Estudios Reumatologicos, Santiago, Chile, [5]Malopolskie Centrum Medyczne, Krakow, Poland, [6]Charles University Institute of Rheumatology, Praha, Czech Republic, [7]University of Cologne, Koln, Germany, [8]OMI, Buenos Aires, Argentina, [9]MedImmune Ltd, Cambridge, United Kingdom, [10]Brigham & Women's Hospital, Harvard Medical School, Boston, MA.

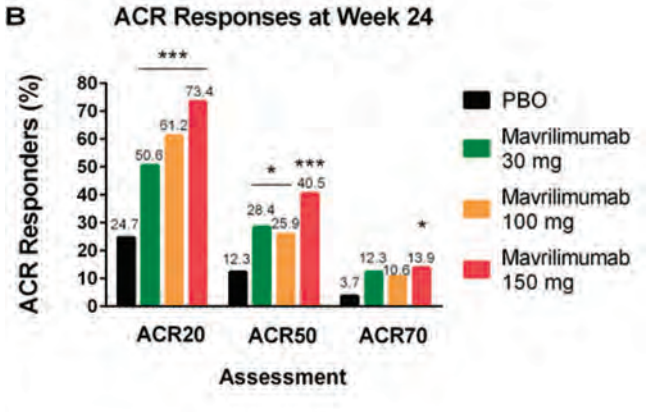
Background/Purpose: Granulocyte-macrophage colony-stimulating factor (GM-CSF) is implicated in RA pathogenesis via myeloid and granulocyte cell lineage activation. In a prior Phase 2a study (NCT01050998), mavrilimumab, a first-in-class inhibitor of the GM-CSF receptor α showed a rapid and sustained effect over the 12-week study duration. Here, we present results of a 24-week Phase 2b randomized, double-blind, placebo (PBO)-controlled, parallel-group, multicenter study (NCT01706926) that evaluated the efficacy and safety of mavrilimumab in patients with moderate-to-severe adult-onset RA.

Methods: Patients (18–80 years; inadequate response to ≥1 DMARD; DAS28-CRP ≥3.2; ≥4 swollen joints; receiving methotrexate [MTX]) were randomized 1:1:1:1 to receive 1 of 3 subcutaneous mavrilimumab doses (30, 100, 150 mg) or PBO every 2 weeks plus MTX (7.5–25.0 mg/week) for 24 weeks. Co-primary endpoints were change in DAS28-CRP (day 1 to week 12) and ACR20 response rate (week 24). Safety and tolerability were measured through assessment of adverse events (AEs) and pulmonary parameters. **Results** were analyzed using the modified intent-to-treat population.

Results: In total, 326 patients from Europe, South America and South Africa (mean [SD] age 51.8 [11.1] years; female 86.5%; mean [SD] DAS28-CRP 5.8 [0.9]; RF/ACPA+ 81.9%) were randomized to PBO or mavrilimumab 30, 100, or 150 mg (n=81, 81, 85, 79, respectively). At week 12, a statistically significant difference in DAS28-CRP ($p<0.001$) was seen for all doses of mavrilimumab vs PBO (Figure A). At week 24, a significantly higher percentage of all mavrilimumab-treated patients also met the ACR20 co-primary endpoint vs PBO (Figure B). A significant ($p<0.001$) separation vs PBO for these parameters was seen as early as week 1 for mavrilimumab 150 mg, which was also associated with significantly higher ACR50 and ACR70 response rates vs PBO at week 24 (Figure B). A dose response effect was observed across multiple secondary endpoints, with separation vs PBO evident from week 1 and 1 dose. The most common treatment-emergent AEs were headache (2.5%, 6.2%, 4.7%, 7.6%), nasopharyngitis (7.4%, 4.9%, 3.5%, 7.6%) and bronchitis (7.4%, 3.7%, 1.2%, 5.1%) for PBO and 30, 100, or 150 mg, respectively. There was no increase in pulmonary AEs for mavrilimumab vs PBO (6.2%, 3.5%, 6.3% vs 9.9%). No serious infections were observed in the 100 and 150 mg groups; 2 cases of pneumonia were seen (30 mg and PBO groups). There were no deaths or anaphylaxis, and no apparent dose relationship for AEs. >90% patients entered a long-term open-label study.



***p<0.001, mavrilimumab vs PBO
Mean [95% CI] adjusted difference from PBO at week 12: 150 mg -1.22 [-1.60, -0.84]; 100 mg -0.96 [-1.33, -0.58]; 30 mg -0.69 [-1.06, -0.31]
PBO, placebo; SE, standard error



*p<0.05, mavrilimumab vs PBO
***p<0.001, mavrilimumab vs PBO
PBO, placebo

Conclusion: This second Phase 2 study demonstrates the potential benefit of inhibiting macrophage activity via the GM-CSFRα pathway on RA disease activity. The study met both co-primary endpoints with a clear dose response effect. An acceptable tolerability profile was demonstrated over the 24-week study period.

Disclosure: G. Burmester, Medimmune, 5; **I. B. McInnes**, Medimmune, 5, Medimmune, AstraZeneca, 5; **J. M. Kremer**, Corrona, 1, Abbvie, Amgen, Genentech, Lilley, Pfizer, 2, Abbvie, Amgen, BMS, Genentech, Lilley, Pfizer, 5; **P. Miranda**, Medimmune, 2; **M. Korkosz**, None; **J. Vencovsky**, None; **A. Rubbert-Roth**, None; **E. Mysler**, Medimmune, 2; **S. Sandbach**, None; **M. A. Sleeman**, AstraZeneca, 1, Medimmune, 3; **A. Godwood**, AstraZeneca, 1, Medimmune, 3; **D. Close**, Medimmune, 3; **M. Weinblatt**, BMS, UCB, Crescendo Bioscience, 2, Medimmune, AstraZeneca, Amgen, Abbvie, BMS, Crescendo Bioscience, Lilly, Pfizer, UCB, Roche, 5.

2822

Safety and Efficacy of Baricitinib through 128 Weeks in an Open-Label, Long-Term Extension Study in Patients with Rheumatoid Arthritis.

Edward C. Keystone[1], Peter C. Taylor[2], Mark C Genovese[3], Douglas E. Schlichting[4], Inmaculada De La Torre[5], Scott D. Beattie[4] and Terence Rooney[4]. [1]Mount Sinai Hospital, Toronto, ON, [2]University of Oxford, Oxford, United Kingdom, [3]Stanford University Medical Center, Palo Alto, CA, [4]Eli Lilly and Company, Indianapolis, IN, [5]Eli Lilly and Company, Alcobendas, Spain.

Background/Purpose: Baricitinib is an oral inhibitor of JAK1/JAK2 being investigated as a treatment for rheumatoid arthritis (RA). In a phase 2b study, baricitinib treatment resulted in significant clinical improvements over 24 wks[1]. The safety and efficacy findings of baricitinib treatment in RA patients (pts) up to 128 wks are reported here.

Methods: Pts were randomized to placebo (PBO) or 1, 2, 4, or 8 mg baricitinib QD for 12 wks (Part A). Pts assigned to 2, 4, or 8 mg continued assigned treatment and pts assigned to PBO or 1 mg were reassigned to 4 mg QD or 2 mg BID for an additional 12 wks of blinded treatment (Part B). Pts completing Part B were eligible to enter a 52 wk open-label extension (OLE; Wks 24–76, Part C), where pts in the 8 mg group continued to receive 8 mg QD and all other pts received 4 mg QD. During Part C, doses could be escalated to 8 mg QD at 28 or 32 wks at the investigator's discretion when ≥6 tender and ≥6 swollen joints were present. Pts completing Part C were eligible to enter an additional 52 wk OLE (Wks 76–128, Part D) where pts received 4 mg QD regardless of previous dose.

Results: Of 204 pts at sites participating in Part C, 201 (99%) were treated and 169 (84%) completed 52 wks. Among pts who remained on 4 mg (N=108) in Part C, TEAEs occurred in 63%, SAEs in 16%, infections in 35%, and serious infections in 5%. Among pts who received 8 mg at any time (N=93) in Part C, TEAEs occurred in 68%, SAEs in 13%, infections in 40%, and serious infections in 3%. Of 150 pts at sites participating in Part D, 144 (96%) were treated and 133 (92%) completed an additional 52 wks. Among pts who remained on 4 mg (N=79) in Part D, TEAEs occurred in 53%, SAEs in 6%, infections in 32%, and serious infections in 3%. Among pts who decreased to 4 mg (N=65) in Part D, TEAEs occurred in 55%, SAEs in 6%, infections in 28%, and serious infections in 3%. The exposure-adjusted incidence rates for adverse events for all baricitinib groups in Part D were similar to or lower than those rates observed in Part C (Table 1). No opportunistic infections, tuberculosis cases, or lymphomas were observed through 128 wks. One death due to myocardial infarction occurred in the 8 mg group in Part C. Among all pts combined, the proportions of pts achieving ACR20 or disease improvement at Wk 24 were similar or increased at Wks 76 and 128 (Table 2).

Conclusion: Among pts completing 128 wks of a phase 2b study, clinical improvements observed at Wk 24 were maintained or improved through Wk 128. In addition, safety data collected during the OLE were consistent with previous baricitinib findings[1].

[1]Genovese M, et al. *Arth Rheum* 2012;64(Suppl 10):S1049-S1050.

Table 1 Safety Summary

	Weeks 24–76 (Part C)			Weeks 76–128 (Part D)		
				Remained on 4 mg	Decreased to 4 mg	
	4 mg (N=108)	8 mg* (N=93)	All Groups (N=201)	(N=79)	(N=65)	All Groups (N=144)
	n, (%)	n, (%)	IR†	n, (%)	n, (%)	IR†
TEAEs	68 (63)	63 (68)	73.4	42 (53)	36 (55)	57.6
SAEs	17 (16)	12 (13)	16.2	5 (6)	3 (6)	5.9
Infections	38 (35)	37 (40)	42.6	25 (32)	18 (28)	31.8
Serious Infections	5 (5)	3 (3)	4.9	2 (3)	2 (3)	3.0

*Randomized to 8 mg in Part A or escalated to 8 mg at Weeks 28 or 32 in Part C. Data after commencing 8 mg
†Incidence rate = number of events per 100 patient-years of exposure to treatment

Table 2 Disease Improvement

n (%)	Wk 24[a] (N=201)	Wk 76[b] (N=201)	Wk 128[c] (N=144)
ACR20	149 (74)	137 (68)	101 (70)
CDAI ≤ 2.8	34 (17)	38 (19)	31 (22)
SDAI ≤ 3.3	32 (16)	38 (19)	30 (21)
DAS28 ESR < 2.6	35 (17)	44 (22)	37 (26)
DAS28 ESR ≤ 3.2	55 (27)	69 (34)	56 (39)
DAS28 CRP < 2.6	61 (30)	76 (38)	56 (39)
DAS28 CRP ≤ 3.2	97 (48)	100 (50)	74 (51)

[a]Observed data for pts entering Part C at Wk 24
[b]Non-response imputed for discontinuing prior to Wk 76, but not for dose-escalation
[c]Among pts entering Part D, non-response imputed for discontinuing prior to Wk 128

Disclosure: E. C. Keystone, Abbott, Amgen, AstraZeneca, Bristol-Myers Squibb, Hoffmann-La Roche, Janssen, Eli Lilly and Company, Novartis, Pfizer, Sanofi-Adventis, UCB, 2, Abbott, AstraZeneca, Biotest, Bristol-Myers Squibb, Hoffmann-La Roche, Genetech, Janssen, Eli Lilly and Company, Merck, Pfizer, UCB, 5; **P. C. Taylor**, Eli Lilly and Company, Pfizer Inc, AstraZeneca, 5; **M. C. Genovese**, Eli Lilly and Company, 2, Eli Lilly and Company, 5; **D. E. Schlichting**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **I. De La Torre**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **S. D. Beattie**, Eli Lilly and Company, 1, Eli Lilly and Company, 3; **T. Rooney**, Eli Lilly and Company, 1, Eli Lilly and Company, 3.

2823

Comparable Efficacy with Sarilumab Plus Methotrexate in Biologic-Experienced and Biologic-Naïve Patients with Moderate-to-Severe Rheumatoid Arthritis from a Phase 3, Randomized, Double-Blind, Placebo-Controlled, International Study.

Roy Fleischmann[1], Dennis L. Decktor[2], Chunpeng Fan[3], Hubert Van Hoogstraten[3] and Mark C Genovese[4]. [1]Metroplax Clinical Research Center and University of Texas Southwestern Medical Center, Dallas, TX, [2]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [3]Sanofi, Bridgewater, NJ, [4]Stanford University Medical Center, Palo Alto, CA.

Background/Purpose: For patients with prior exposure to tumor necrosis factor-α inhibitor (TNF-I), the likelihood of response to subsequent treatment with a TNF-I declines with the increasing number of previous treatment failures.[1] Sarilumab, a fully human monoclonal antibody directed against interleukin-6R, has shown efficacy in a study of adult rheumatoid arthritis (RA) patients with moderate-to-severe disease and an inadequate response to methotrexate (MTX).[2] Sarilumab's safety and efficacy has been demonstrated at subcutaneous doses of 150 mg or 200 mg q2w + MTX. A further analysis of the clinical efficacy and safety of sarilumab in patients with/without prior biologic use (physician-reported) from this study is reported here. In the total population, 21.2% were exposed to biologics, of which 50% had received prior-TNF-I.

Methods: This was a subanalysis of the ACR20 (primary efficacy endpoint) and ACR50 and ACR70 responses, reduction of DAS28-CRP, and CDAI scores in patients with/without prior biologic use in the intention-to-treat population of the Phase 3 aspect of the MOBILITY study. Patients previously nonresponsive to biologic treatment were excluded from study participation.

Results: Both doses of sarilumab resulted in a statistically significant ACR20 response at Wk 24 vs placebo ($p<0.0001$); ACR50 and ACR70 responses were also statistically significant at Wk 24 (Fig 1). Statistically significant improvements in DAS28-CRP reduction were observed, with mean reductions at Wk 52 of –1.85, –2.80, and –3.15 in the placebo, sarilumab 150 mg, and 200 mg q2w groups, respectively, in patients with prior use of biologics, and –1.93, –3.24, and –3.29 in biologic-naïve patients (Figure 2). Similar improvements were seen in CDAI scores, with mean reductions at Wk 52 of –23.23, –28.45, and –28.81 in the placebo, sarilumab 150 mg, and 200 mg q2w groups, respectively, in patients with prior use of biologics, and –24.52, –31.35, and –30.33 in biologic-naïve patients (Fig 2). Most common TEAEs included infections and injection site reactions. A higher incidence of serious infections was observed with sarilumab. Lab

abnormalities included decreases in neutrophils and increases in transaminases and lipids.

Conclusion: Independent of prior use of a biologic, treatment with sarilumab resulted in clinically meaningful and statistically significant responses; given the modest number of biologic-experienced participants and the exclusion of prior non-responders, additional research is warranted.

References

1. Lloyd S et al. Rheumatology 2010;49(12):2313–2321.
2. Genovese M et al. Abstr. EULAR14-SCIE-3001, EULAR 2014.

Figure 1. ACR response rates at Week 24

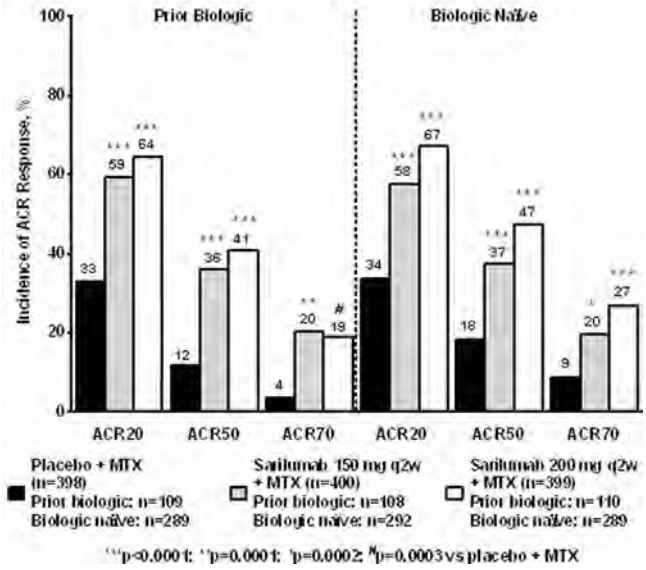
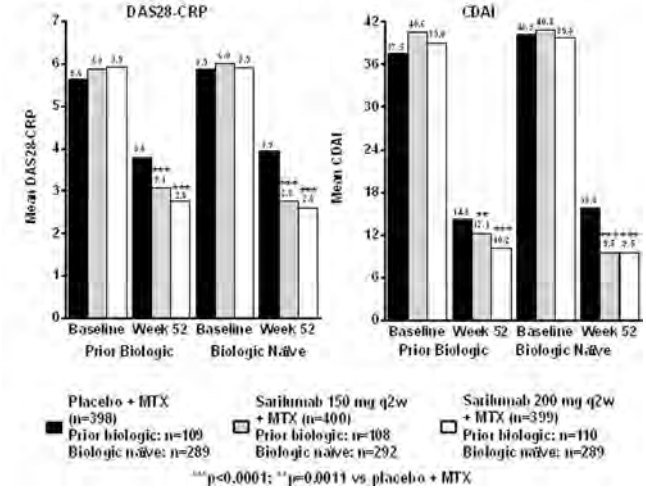


Figure 2. Mean DAS28-CRP and Mean CDAI scores in prior biologic versus biologic-naïve users at Week 52



Disclosure: R. Fleischmann, AbbVie, Amgen, Ardea, Astra Zeneca, BMS, Celgene, GSK, Janssen, Eli Lilly, Merck, Pfizer, Resolve, Roche, Sanofi Aventis, UCB., 2, AbbVie, Akros, Amgen, Antares, Ardea, Astra Zeneca, Augurex, BMS, Celgene, Covagen, Five Prime, GSK, Iroko, Janssen, Eli Lilly, McNeil, Merck, Pfizer, Plexxicon, Resolve, Roche, Sanofi Aventis, Teva, UCB, Vertex., 5; **D. L. Decktor**, Regeneron Pharmaceuticals, Inc., 3, Johnson & Johnson, 1; **C. Fan**, Sanofi, 1, Sanofi, 3; **H. Van Hoogstraten**, Sanofi, 3; **M. C. Genovese**, Eli Lilly and Company, 2, Eli Lilly and Company, 5, Sanofi, 2, Sanofi, 5, Regeneron, 2, Regeneron, 5.

2824

A Profile of the Efficacy of Sarilumab Plus Methotrexate in Rheumatoid Arthritis Patients: Results of a 52-Week, Phase 3, Randomized, Double-Blind, Placebo-Controlled, International Study. Arthur Kavanaugh[1], Dennis L. Decktor[2], Chunpeng Fan[3], Janet van Adelsberg[2], Renata Martincova[4] and Mark C. Genovese[5]. [1]University of California San Diego, La Jolla, CA, [2]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [3]Sanofi, Bridgewater, NJ, [4]Sanofi Czech Republic, Prague, Czech Republic, [5]Stanford University Medical Center, Palo Alto, CA.

Background/Purpose: Interleukin-6 (IL-6) regulates a diverse array of activities that may underlie systemic and local symptoms of rheumatoid arthritis (RA). The efficacy of sarilumab, a fully human monoclonal antibody (mAb) directed against IL-6R, has recently been investigated in the randomized, double-blind, placebo(pbo)-controlled, multicenter, phase 3 part of the MOBILITY study.[1] This analysis expands the profile to the entire 52-week duration of the trial.

Methods: Adults with active, moderate-to-severe RA and inadequate response to methotrexate (MTX) were randomized 1:1:1 to pbo + MTX, sarilumab 150 mg or 200 mg q2w + MTX for 52 wks. 3 co-primary endpoints associated with RA activity (signs & symptoms, physical function, and structural damage) were investigated: proportion of patients achieving ACR20 response at Wk 24; change from baseline in HAQ-DI at Wk 16; and change from baseline in mTSS at Wk 52. Secondary efficacy endpoints included major clinical response at Wk 52, ACR50 and ACR70 responses, reduction in DAS28-CRP, and CDAI.

Results: Sarilumab 150 mg and 200 mg q2w + MTX provided statistically significant, clinically meaningful improvement in all co-primary efficacy endpoints (ACR20, HAQ-DI, and mTSS) and secondary efficacy endpoints vs pbo + MTX (Table). ACR 20 response rates increased by Wk 2 and remained significantly higher in both sarilumab + MTX groups vs pbo + MTX through Wk 52 ($p<0.0001$). Change from baseline in the ACR core set of disease activity measures, swollen and tender joint counts, was significantly higher in the sarilumab + MTX groups vs pbo + MTX (Table). A significantly higher proportion of patients in the sarilumab + MTX groups maintained CDAI remission vs pbo + MTX (Wks 4–52; $p<0.0001$). DAS28-CRP scores were significantly improved vs pbo + MTX at Wks 2–52 ($p<0.0001$) in sarilumab + MTX-treated patients, who achieved DAS28-CRP remission at Wks 24 and 52 (Table). The proportion of HAQ-DI responders at Wks 16, 24 and 52 was significantly higher ($p<0.0001$) with sarilumab + MTX vs pbo + MTX at each timepoint (Table). Mean change from baseline in mTSS at Wk 52 with sarilumab + MTX was significantly higher vs pbo + MTX (Table). Most common TEAEs included infections and injection site reactions. A higher incidence of serious infections was observed with sarilumab. Lab abnormalities included decreases in neutrophils and increases in transaminases and lipids.

Conclusion: These additional analyses of patients with active RA and an inadequate response to MTX showed that treatment with subcutaneous sarilumab at 150 mg and 200 mg q2w + MTX improved the full range of reported outcomes in a robust and durable manner that was maintained over this 52 week-trial.

Reference:

1. Genovese M et al. Abstr. No. EULAR14-SCIE-3001 presented at EULAR 2014, Paris, France.

Table. Efficacy results

	Placebo + MTX (n=398)	Sarilumab 150 mg q2w + MTX (n=400)	Sarilumab 200 mg q2w + MTX (n=399)
ACR20 response – Wk 24, n (%)	133 (33.4%)	232 (58.0%)*	265 (66.4%)*
ACR50 response – Wk 24, n (%)	66 (16.6%)	148 (37.0%)*	182 (45.6%)*
ACR70 response – Wk 24, n (%)	29 (7.3%)	79 (19.8%)*	99 (24.8%)*
mTSS, mean change from BL – Wk 52	2.8	0.9*	0.3*
Major clinical response (ACR70 response maintained for 24 weeks), n (%)	12 (3.0%)	51 (12.8%)*	59 (14.8%)*
ACR disease activity measures, adj. mean change from BL – Wk 24			
Swollen joint count	–6.6	–10.6*	–11.2*
Tender joint count	–10.1	–16.9*	–17.4*
HAQ-DI, adj. mean change from BL			
– Wk 16	–0.3	–0.5*	–0.6*
– Wk 24	–0.4	–0.6*	–0.6*
– Wk 52	–0.5	–0.7*	–0.8*
DAS28–CRP			
LS mean change from BL – Wk 24	–1.17	–2.45*	–2.82*
LS mean change from BL – Wk 52	–1.36	–2.78*	–2.95*
Clinical remission# – Wk 24, n (%)	40 (10.1%)	111 (27.8%)*	136 (34.1%)*
Clinical remission# – Wk 52, n (%)	34 (8.5%)	124 (31.0%)*	136 (34.1%)*
CDAI			

LS mean change from BL – Wk 24	–14.47	–23.89*	25.79*
LS mean change from BL – Wk 52	–17.50	–26.96*	–27.26*
Remission (≤2.8) – Wk 24, n (%)	20 (5.0%)	41 (10.3%)†	55 (13.8%)*
Remission (≤2.8) – Wk 52, n (%)	19 (4.8%)	59 (14.8%)*	72 (18.0%)*
No radiographic progression at Wk 52, n (%)	154 (38.7%)	191 (47.8%)‡	222 (55.6%)*

*p<0.0001 vs placebo + MTX; †p=0.0053; ‡p<0.01 vs placebo + MTX; #score of <2.6; MTX, methotrexate; BL, baseline; LS, least squared; ACR 20/50/70, American College of Rheumatology 20%/50%/70% improvement criteria; mTSS, van der Heijde modified total Sharp score; HAQ-DI, Health Assessment Questionnaire-Disability Index; HAQ-DI responders, >0.3 improvement in HAQ-DI from baseline; DAS28-CRP, Disease Activity Score in 28 joints using C-Reactive Protein; DAS28-CRP remission, DAS28-CRP <2.6; CDAI, Clinical Disease Activity Index; CDAI remission, CDAI ≤2.8.

Disclosure: A. Kavanaugh, Sanofi, 2; **D. L. Decktor**, Regeneron Pharmaceuticals, Inc., 3, Johnson & Johnson, 1; **C. Fan**, Sanofi, 1, Sanofi, 3; **J. van Adelsberg**, Regeneron Pharmaceuticals, Inc., 3, Regeneron Pharmaceuticals, Inc., 1; **R. Martincova**, Sanofi, 3; **M. C. Genovese**, Eli Lilly and Company, 2, Eli Lilly and Company, 5, Sanofi, 2, Sanofi, 5, Regeneron, 2, Regeneron, 5.

2825

A Randomized, Double-Blind, Phase 3 Equivalence Trial Comparing the Etanercept Biosimilar, HD203, with Etanercept (Enbrel®), in Combination with Methotrexate (MTX) in Patients with Rheumatoid Arthritis (RA). Sang-Cheol Bae[1], Jinseok Kim[2], Jung-Yoon Choe[3], Won Park[4], So-Ra Lee[5], Yongho Ahn[6] and Yunjeong Seo[5]. [1]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [2]Jeju National University, Jeju, Korea, South Korea, [3]Catholic University of Daegu School of Medicine, Daegu, South Korea, [4]Inha University Hospital, Incheon, South Korea, [5]Hanwha Chemical, Seoul, South Korea, [6]Hanwha Chemical, Daejeon, South Korea.

Background/Purpose: Etanercept is a recombinant fusion protein that blocks TNF activity. HD203 is a biosimilar of etanercept. In a double-blind, randomized study in healthy volunteers, HD203 and a reference etanercept were comparable with regards to pharmacokinetics, safety and tolerability. The aim of this study was to evaluate the equivalence in efficacy and to compare the safety of HD203 (biosimilar etanercept) and a reference etanercept, in combination with MTX in patients with RA. (ClinicalTrials.gov identifier NCT01270997).

Methods: Patients (male or female aged ≥20 years) with active RA were randomly assigned (1:1) to 25 mg HD203 or reference etanercept, administered subcutaneously twice weekly with MTX for 48 weeks. The primary endpoint was the proportion of patients achieving ACR20 at week 24. Secondary endpoints included ACRn, change in DAS28, and EULAR response at week 24 and 48, safety and immunogenicity. Efficacy and safety were evaluated at screening, week 0, 2, 4, 8, 12, 16, 20, and 24. Immunogenicity, efficacy and safety were also evaluated at week 36 and 48.

Results: In total, 294 patients were randomized: 147 to HD203 and 147 to reference etanercept. The proportion of patients achieving ACR20 at week 24 (primary endpoint) was not significantly different for HD203 and reference etanercept (Table) and equivalence in efficacy was demonstrated within predefined margins. In addition, there were no statistically significant differences between proportions achieving ACR20 at weeks 12 and 48. Similar trends were seen for ACR50 and ACR70, however the proportion of patients achieving ACR50 at week 24 and 48 was higher with HD203 than with reference etanercept. There were no statistically significant differences between the groups for ACRn, change in DAS28, and EULAR response at week 24 and 48.

Table: Proportion of patients achieving ACR20 at week 24 and week 48

	HD203	Reference etanercept	Difference (95% CI)	P-value
24-week PPS	83.48% (96/115)	81.36% (96/118)	2.12 (–7.65,11.89)	0.6706†
FAS	79.10% (106/134)	75.56% (102/135)	3.55 (–6.45,13.55)	0.4870†
48-week PPS	86.27% (88/102)	81.90% (86/105)	4.37 (–5.57,14.31)	0.3905†

CI, confidence interval; PPS, per-protocol set; FAS, full analysis set; †Pearson's chi-square test

Analysis of the safety set (HD203, n=147; reference etanercept, n=146) revealed no statistically significant difference in the number of treatment-emergent (all-causality) adverse events (AEs): HD203 76.87% vs. reference etanercept 78.08% (p=0.8040). Furthermore, no statistically significant differences between HD203 and reference etanercept were observed with regards to adverse drug reactions, serious AEs, or discontinuations due to AEs. No unexpected AEs were observed, and few patients tested positive for anti-drug antibodies.

Conclusion: The study met the primary endpoint of demonstrating equivalence in efficacy of HD203 compared with a reference etanercept. HD203 was well tolerated, with a safety profile comparable to that of the reference etanercept in this population of Korean patients with RA.

Disclosure: S. C. Bae, Research grants from Abbott Ltd, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, MSD, and Pfizer, 2, Consulting fees from Pfizer, Hanwha Chemical, and Merck Serono, 5; **J. Kim**, None; **J. Y. Choe**, None; **W. Park**, None; **S. R. Lee**, Employee of Hanwha Chemical, 3; **Y. Ahn**, Employee of Hanwha Chemical, 3; **Y. Seo**, Employee of Hanwha Chemical, 3.

2826

A Phase 2b, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Dose-Finding, Multi-Center Study to Evaluate the Safety and Efficacy of ASP015K in Moderate to Severe Rheumatoid Arthritis Subjects Not on Concomitant Methotrexate. Mark C. Genovese[1], Maria Greenwald[2], Christine Codding[3], Mario H. Cardiel[4], Anna Zubrzycka-Sienkiewicz[5], Alan J. Kivitz[6], Steve Wisseh[7], Kathyjo Shay[8] and Jay P. Garg[8]. [1]Stanford University Medical Center, Palo Alto, CA, [2]Desert Medical Advances, PALM DESERT, CA, [3]Health Research of Oklahoma, Oklahoma City, OK, [4]Centro de Investigacion Clinica de Morelia, Morelia, Mexico, [5]ARS Rheumatica sp. Zo.o, Reumatika, Warszawa, Poland, [6]Altoona Center for Clinical Research, Duncansville, PA, [7]Biocis, Chicago, IL, [8]Astellas Pharma Global Development, Northbrook, IL.

Background/Purpose: ASP015K is a novel oral Janus kinase (JAK) inhibitor in development for the treatment of rheumatoid arthritis (RA). ASP015K inhibits JAK 1/3 with relative selectivity over JAK2 and can be dosed once daily (QD). This study evaluated the efficacy, safety and dose response of once daily ASP015K in patients (pts) with moderate to severe rheumatoid arthritis (RA) with an inadequate response/intolerance to DMARDs and not currently on concomitant methotrexate (MTX) (Clinical Trials Registration: NCT01565655).

Methods: In this 12-week, double-blind, placebo (PBO)-controlled study, pts 18 years or older who met ACR criteria for RA, were not on concomitant MTX, and had active RA (defined as either CRP [*** :possibility of New Font being added]' 0.8 mg/dL or ESR [*** :possibility of New Font being added]' 28 mm/hr and [*** :possibility of New Font being added]' 6 tender and swollen joints) were randomized 1:1:1:1:1 to ASP015K 25 mg, 50 mg, 100 mg, 150 mg or PBO. Allowed concomitant DMARD therapies were anti-malarials and/or sulfasalazine. The primary endpoint was ACR20 response at week 12.

Results: 289 pts (82% female; mean age 53.9 years) were randomized and dosed. Approximately half the subjects (48%) were enrolled in the U.S. and the remainder from Europe (41%) and Mexico (11%). 48% had used a biologic, with 36% exposed to ≥ 2. Mean baseline values: disease duration, 10.4 y, tender joint count 25.7 (of 68), swollen joint count 16.3 (of 66), CRP 1.69 mg/dL, ESR 44.36 mm/hr, DAS28-CRP 5.83, and DAS28-ESR 6.64. A statistically significant dose-response at week 12 was seen for ACR20 with the highest response seen in the ASP015K 100 mg and 150 mg groups. ACR50/70 response and DAS28-CRP remission were also higher in the 2 highest ASP015K dose groups as compared to PBO. Dose-dependent improvement in DAS28-CRP was seen, with statistically significant differences shown in the two highest dose groups as early as week 4. The incidence of adverse events (AEs) was similar between combined ASP015K groups and PBO (41.6% vs 43.1%). The most frequently reported AEs in the combined ASP015K groups as compared to PBO were upper respiratory tract infection (5.5% vs 3.9%), nausea (5.0% vs 0%), and diarrhea (3.8% vs 2.0%). The overall incidence of infections and serious adverse events was similar between ASP015K and PBO (13.4% vs 13.7% and 4.2% vs 3.9%, respectively). No meaningful differences in absolute neutrophil and lymphocyte counts or hemoglobin were seen between ASP015K and PBO. The safety profile was generally comparable among the ASP015K dose groups, except for a higher incidence of dyspepsia, headache, and blood creatinine phosphokinase increased (transient without associated symptoms) in the 100 mg and/or 150 mg groups.

Conclusion: In a population of RA pts with long-standing disease and previous treatment with multiple DMARDs, 12 weeks of treatment with ASP015K was well tolerated and efficacious, with the highest response seen at the 100 and 150 mg doses. These data support further development of ASP015K for the treatment of RA.

	Placebo (n=51)	ASP015K 25 mg (n=59)	ASP015K 50 mg (n=57)	ASP015K 100 mg (n=58)	ASP015K 150 mg (n=64)
Primary endpoint					
ACR20,n (%) [1]	15 (29.4)	13 (22.0)	21 (36.8)	28 (48.3)*	36 (56.3)**
Secondary endpoints					
ACR50, n (%)	5 (9.8)	9 (15.3)	14 (24.6)	16 (27.6)*	18 (28.1)**
ACR70, n (%)	4 (7.8)	4 (6.8)	9 (15.8)	11 (19.0)	7 (10.9)

Change from baseline in DAS28-CRP (LS mean)	−1.16	−1.24	−1.52	−2.11***	−2.01***
Key exploratory endpoints					
Change from baseline in DAS28-ESR (LS mean)	−1.42	−1.46	−1.74	−2.45***	−2.35***
Change from baseline in CRP (LS mean)	−0.46	−0.17	−0.46	−0.43	−0.85
Change from baseline in ESR (LS mean)	−12.14	−12.40	−12.47	−15.54	−19.41*
Change from baseline in HAQ-DI (LS mean)	−0.24	−0.22	−0.36	−0.34	−0.41

[1] Dose response, p<0.001.
P-values vs. placebo: *p<0.05; **p<0.01; ***p<0.001.
LS mean: Least squares mean

Disclosure: M. C. Genovese, Astellas, 2, Astellas, 5; **M. Greenwald**, Astellas, 2; **C. Codding**, None; **M. H. Cardiel**, Astellas, 8; **A. Zubrzycka-Sienkiewicz**, Astellas, paid by ICON CRO, 9, Janssen, 9, Roche, UCB, Sanofi, 9, Merck, 9; **A. J. Kivitz**, None; **S. Wisseh**, None; **K. Shay**, Astellas, 3; **J. P. Garg**, Astellas, 3.

ACR Concurrent Abstract Session
Spondyloarthropathies and Psoriatic Arthritis IV - Clinical Aspects Axial Spondyloarthritis
Tuesday, November 18, 2014, 2:30 PM–4:00 PM

2827

Cervical Spine Fracture and Mortality in Ankylosing Spondylitis. Katherine D. Wysham, Sara G. Murray, Nancy K. Hills, Edward H. Yelin and Lianne S. Gensler. University of California, San Francisco, San Francisco, CA.

Background/Purpose: Little data exist regarding mortality in Ankylosing Spondylitis (AS) patients. We performed a population-based study of diagnoses associated with hospital mortality in AS.

Methods: Data were abstracted from the Healthcare Cost and Utilization Project-National Inpatient Sample (HCUP-NIS) between 2007–2011. We identified hospital discharges with AS using a validated administrative definition. The primary outcome was mortality and we performed a subset analysis on cervical spine fracture (CSFX) associated conditions and fracture level. Chi-square and Wilcoxon rank sum tests were used when appropriate to identify diagnoses associated with mortality. Multivariable logistic regression, including socio-demographic variables, significant covariates and co-morbidities, was performed to identify independent factors associated with in-hospital mortality.

Results: There were 12,493 AS admissions, 422 CSFXs and 276 deaths between 2007–2011. The mean age of all hospitalized AS patients was 59.2±16.4 years, 71% were males and 24% were electively admitted. The mean age of those with CSFX was 67.8±15.1 years, 91% were males and 11% were electively admitted. The mean age of those who died was 73.0±12.9 years, 78% were males and 10% were electively admitted. In the multivariable model, bacteremia and CSFX were the diagnoses with the highest odds of death, 7.28 (95% CI 5.36–9.88) and 5.70 (95% CI 3.63–8.95), respectively. Of those with CSFX, 66% also had a diagnosis of fall, though there was no interaction between CSFX and falls in predicting mortality. Motor vehicle accidents accounted for another 16% of CSFX cases. The majority of CSFX occurred at the lower cervical spine (75%). Regardless of level of fracture, 11% of patients died with associated CSFX.

Conclusion: The diagnoses most strongly associated with mortality in hospitalized AS patients, were bacteremia and CSFX. CSFX appears to be most commonly associated with falls and the majority of fractures occur in the lower cervical spine. This is the first population-based study describing the significant mortality associated with CSFX in AS patients.

Table 1. Multivariable model of predictors of mortality in AS hospitalizations

Variable	Adjusted OR*	95% CI	P value
Age (per 1 year)	**1.05**	**1.03–1.06**	**<0.001**
Male Gender	0.97	0.71–1.33	0.87
Private insurance	0.77	0.53–1.11	0.16
Community population <50,000	**1.38**	**1.02–1.87**	**0.04**
Elective admission	**0.58**	**0.38–0.88**	**0.01**
Charlson Index (per 1 point on weighted scale)	**1.25**	**1.18–1.34**	**<0.001**
Bacteremia	**7.28**	**5.36–9.88**	**<0.001**
Pneumonia	**1.98**	**1.44–2.70**	**<0.001**
Cervical spine fracture	**5.70**	**3.63–8.95**	**<0.001**
Thoracic spine fracture	0.81	0.41–1.59	0.54
Lumbar spine fracture	1.88	0.81–4.41	0.14
Fall	0.98	0.63–1.51	0.92

*Odds ratios adjusted for all variables shown.

Disclosure: K. D. Wysham, None; **S. G. Murray**, None; **N. K. Hills**, None; **E. H. Yelin**, None; **L. S. Gensler**, UCB, 5, AbbVie, 5, Celgene Corporation, 9.

2828

A Physically Demanding Job May Amplify the Effect of Disease Activity on the Development of Syndesmophytes in Patients with Ankylosing Spondylitis. Sofia Ramiro[1], A.M. van Tubergen[2], Robert Landewé[3], Annelies Boonen[2], Carmen Stolwijk[2], Maxime Dougados[4], Filip Van den Bosch[5] and Desiree van der Heijde[6]. [1]Amsterdam Rheumatology Center/University of Amsterdam, Amsterdam, Netherlands, [2]Maastricht University Medical Center, Maastricht, Netherlands, [3]Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands, [4]Université Paris René Descartes and Hôpital Cochin, Paris, France, [5]Ghent University Hospital, Ghent, Belgium, [6]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: We have recently shown that disease activity is longitudinally associated with radiographic progression in AS. In animal models, it has recently been shown that mice that were tail suspended, in order to prevent mechanical loading on paws, had less new bone formation, thus providing a proof-of-concept that mechanical strain drives new bone formation in spondyloarthritis. Our aim was to investigate the complex relationship between inflammation, mechanical stress and radiographic progression in patients with ankylosing spondylitis (AS), using job type as a proxy for continuous mechanical stress.

Methods: Patients from OASIS were followed-up for 12 years, with 2-yearly assessments. Two readers independently scored the x-rays according to the mSASSS. Disease activity was assessed by the ASDAS-CRP. The relationship between ASDAS and spinal radiographic progression was investigated with longitudinal analysis, with job type at baseline (physically demanding ('blue collar') vs sedentary ('white collar') labor as a potential factor influencing this relationship. The effects of smoking status and socio-economic factors were also investigated.

Results: In total, 184 patients were included in the analyses (70% males, 83% HLA-B27 positive, 39% smokers, 48% blue-collar workers (65/136 patients in whom data on job type were available)). The relationship between disease activity and radiographic progression was significantly and independently modified by job type: In 'blue-collar' workers vs 'white collar' workers every additional unit of ASDAS resulted in an increase of 1.2 vs 0.2 mSASSS-units/2-years (p=0.014 for the difference between blue collar and white collar workers). In smokers vs non-smokers every additional unit of ASDAS resulted in an increase of 1.9 vs 0.4 mSASSS-units/2-years. Personal income also significantly modified the relationship ASDAS-mSASSS, but education and family income did not (Table).

Conclusion: Physically demanding jobs may amplify the driving effects of inflammation on radiographic progression, thus supporting the theory that mechanical stress leads to bone formation in AS. Smoking and personal income are likely classic confounders of this relationship but a separate detrimental effect of smoking on radiographic progression could not be excluded. If confirmed, these findings may have implications for our commonly given advice to patients with SpA to strenuously exercise.

Table: Effects of disease activity (one ASDAS-unit increase) on radiographic progression in subgroups

	2-year increase in mSASSS [units, (95% CI)]
A: Occupation: 'Blue collar' (n = 65)	1.19 (0.58; 1.79)
A: Occupation: 'White collar' (n = 71)	0.20 (−0.23; 0.64)
B: Smoking: Smokers (n = 49)	1.94 (1.00, 2.87)
B: Smoking: Non-smokers (n = 78)	0.35 (0.04; 0.65)
C: Education: 'non-university' (n = 167)	0.74 (0.41; 1.07)
C: Education: 'University' (n = 14)	−0.18 (−1.91, 1.55)
D: Personal income: <€1588 (n = 105)	0.93 (0.45, 1.41)
D: Personal income: ≥€1588 (n = 56)	0.14 (−0.21, 0.50)
E: Family income: <€3176 (n = 90)	0.49 (0.09, 0.89)
E: Family income: ≥€3176 (n = 21)	0.15 (−0.35, 0.65)

Disclosure: S. Ramiro, None; **A. M. van Tubergen**, None; **R. Landewé**, None; **A. Boonen**, None; **C. Stolwijk**, None; **M. Dougados**, None; **F. Van den Bosch**, None; **D. van der Heijde**, None.

2829

Spondyloarthritis Is Associated with Increased Cardiovascular and Cerebrovascular Mortality. Nigil Haroon[1], Nisha Nigil Haroon[2], Ping Li[3], Michael Paterson[3] and Robert D. Inman[4]. [1]Toronto Western Research Institute, Toronto, ON, [2]University of Toronto, Toronto, ON, [3]Institute of Clinical Evaluative Sciences, Toronto, ON, [4]University of Toronto and Toronto Western Hospital, Toronto, ON.

Background/Purpose: OnSpA is a population-based study of spondyloarthritis (SpA) based on a provincial population of over 13 million. Patients with SpA are thought to be at increased risk of cardiovascular disease but it is unknown if they have excess vascular mortality. We explored risk of vascular mortality and the contributing factors in AS.

Methods: We performed a population-based, retrospective cohort study on incident SpA patients, age 15 or above, living in Ontario, Canada between April 1995 and March 2011. There were 21,878 SpA cases and 87,504 controls (matched for age, gender and socioeconomic status). The primary outcome was a composite event of cardiovascular or cerebrovascular deaths coded as the primary cause on death certificates. Considering the large size of the cohorts, we used standardized differences to compare the baseline characteristics of those with AS and their matched controls. Cox proportional hazards model was used to estimate differences in vascular mortality between cases and controls. Crude and adjusted hazard ratios (HR) were calculated and adjustments were made for coronary and cerebrovascular disease (CAD, CVD), cancer, diabetes, dementia, inflammatory bowel disease, hypertension, chronic kidney disease (CKD) and peripheral vascular disease (PVD). Additionally, we used a separate model in those with AS to identify covariates associated with vascular mortality. Finally, we constructed survival curves using the Kaplan-Meier (KM) method and tested for survival differences among groups using the Log-Rank test.

Results: In the SpA cohort 53% were male, with a mean age of 46 ±16 years, and a follow-up of 169,307 patient-years. Follow-up for controls was 692,499 patient-years. Crude and adjusted HR (95%CI) for vascular deaths were 1.49 (1.26–1.77) and 1.36 (1.14–1.63) respectively, indicating a 36–49% higher risk of vascular mortality in AS. Crude HR (95%CI) in males and females were 1.63 (1.31–2.03) and 1.31(1.00–1.71) respectively. Cases and controls had similar prevalence of CAD, CVD, PVD, dementia and diabetes, but IBD (6% *vs* 4%), hypertension (24% *vs* 18%) and CKD (2% *vs* 0.8%) were more common in SpA. The predictors of vascular death were age, male sex, low income, CKD and PVD apart from CAD and CVD. The KM curve showing an increase in vascular mortality in AS patients is shown in figure 1.

Conclusion: This is the first population-based study to demonstrate SpA is associated with significantly risk of vascular mortality. These new findings should prompt a comprehensive strategy to screen and treat modifiable vascular risk factors in SpA patients.

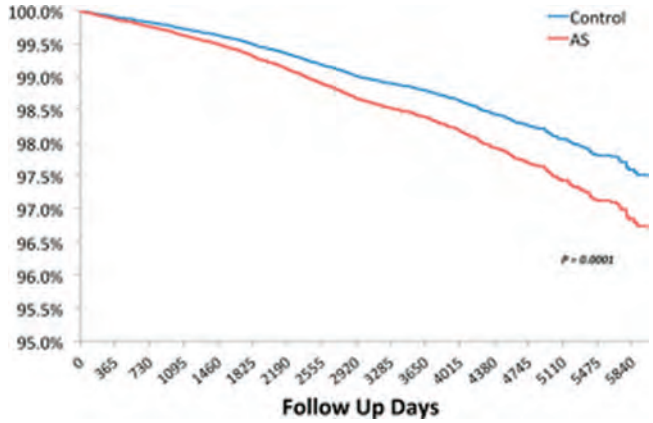


Figure 1. Kaplan-Meier Survival Curve of AS patients compared to non-AS controls after correcting for baseline variables

Disclosure: N. Haroon, None; **N. Nigil Haroon**, None; **P. Li**, None; **M. Paterson**, None; **R. D. Inman**, None.

2830

Progression to and Type of Orthopaedic Surgery in Juvenile *Vs.* Adult-Onset Ankylosing Spondylitis. Deepak R. Jadon[1], Gavin Shaddick[2], Amelia Jobling[2], Athimalaipet V Ramanan[3] and Raj Sengupta[1]. [1]Royal National Hospital for Rheumatic Diseases, Bath, United Kingdom, [2]University of Bath, Bath, United Kingdom, [3]University of Bristol Hospital Trust, Bristol, United Kingdom.

Background/Purpose: Juvenile-onset ankylosing spondylitis (JoAS) and adult-onset ankylosing spondylitis (AoAS) are subtypes of ankylosing spondylitis (AS) that may have different clinical outcome. We compared cohorts of JoAS and AoAS in terms of: (1) clinical characteristics; (2) clinical outcomes; (3) proceeding to and types of AS-related orthopaedic surgery.

Methods: A cohort study was conducted of all patients attending a dedicated AS clinic in a teaching hospital. Patients aged ≤16 years at symptom onset were categorised as JoAS, and ≥17 years as AoAS. Demographics, clinical parameters, composite indices ≤6 months of census, biological use, and history of AS-related orthopaedic surgery to the spine, root or peripheral joints were recorded. Univariate, multivariate logistic regression, and survival analyses were performed.

Results: 553 AS cases were studied: 162 JoAS; 391 AoAS. On univariate analyses (*Table 1*), no statistically significant differences were found between JoAS and AoAS in terms of *HLA-B*27 positivity, smoking, occurrence at any time of inflammatory bowel disease, psoriasis, enthesitis, or uveitis. JoAS cases had higher scores for two Bath AS Functional Index (BASFI) domains: bending forward from the waist (p=0.03); doing physically demanding activities (p=0.04).

On multivariate analyses adjusted for significant covariates (*Table 2*), compared to JoAS cases the AoAS cases were less likely to have: proceeded to surgery (odds ratio, OR 0.31; p<0.001); had a hip procedure (resurfacing or arthroplasty; OR 0.374; adjusted p=0.001); had a hip arthroplasty (OR 0.43; adjusted p=0.01). JoAS and AoAS were equally likely to have had hip resurfacing, bilateral hip arthroplasty, hip arthroplasty revision, hip arthroplasty re-revision, spinal orthopaedic surgery, and several (≥3) procedures.

Kaplan-Meier survival curves (log-rank test p=0.001) and Cox regression also demonstrated a significant difference in not having surgery between JoAS and AoAS (p=0.002) (*Figure 1*). A history of smoking was not associated with surgery. AS cases with older age at symptom onset were far less likely to have surgery than those with younger onset, in a non-linear manner.

Conclusion: JoAS are more likely than AoAS cases to proceed to AS-related orthopaedic surgery, especially hip resurfacing and arthroplasty.

Table 1. Comparison of clinical parameters and outcomes: Juvenile vs. adult-onset ankylosing spondylitis

		Juvenile-onset AS (n=162) n (%)	Adult-onset AS (n=391) n (%)	Odds Ratio	95% CI	p-value*
Clinical Characteristics	Males	115/162 (70.99%)	294/391 (75.19%)	0.86	0.60–1.25	0.36
	HLA-B27 positive	132/142 (92.96%)	276/316 (87.34%)	1.62	0.76–3.43	0.11
	Current/ex-smoker	60/159 (37.74%)	133/359 (34.19%)	1.11	0.78–1.59	0.49
	Psoriasis	31/162 (19.14%)	59/391 (15.09%)	1.22	0.80–1.85	0.30
	Inflammatory bowel disease	19/162 (11.73%)	31/391 (7.93%)	1.34	0.81–2.20	0.21
	Enthesities	36/161 (22.36%)	89/391 (22.76%)	0.98	0.65–1.48	0.99
	Uveitis	75/162 (46.30%)	173/390 (44.36%)	1.06	0.75–1.49	0.75
	Uveitis (HLA-B27 positive cases only)	64/132 (48.48%)	136/276 (49.25%)	0.98	0.68–1.42	0.97
Clinical Outcomes	Proceeded to AS-related surgery	30/162 (18.52%)	28/391 (7.16%)	1.94	1.30–2.83	<0.001
	Poor BASFI(≥5)	49/150 (32.67%)	109/346 (31.50%)	1.04	0.71–1.51	0.88
	Biological use ever	55/162 (33.95%)	116/391 (29.67%)	1.15	0.80–1.64	0.37

*Comparisons by continuty-adjusted Chi-squared test.
95% CI: 95% confidence interval AS: ankylosing spondylitis HLA: human leucocyte antigen
BASFI: Bath AS functional index BASDAI: Bath AS disease activity index BASMI: Bath AS metrology index

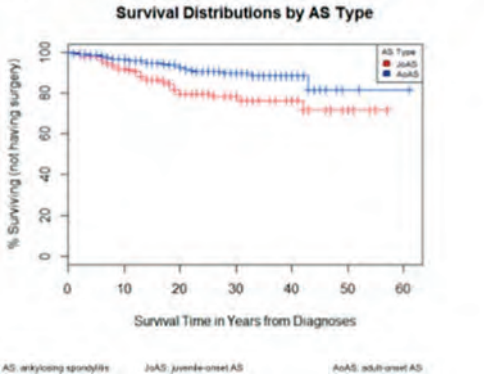
Table 2. Comparison of types of AS-related orthopedic surgeries in juvenile vs. adult-onset ankylosing spondylitis (multivariate analyses)

	JoAS (n = 142) n (%)	AoAS (n = 391) n (%)	Odds Ratio	95% CI	p-value
AS-related orthopsedic surgery	29/162 (17.90)	24/391 (6.14)	0.307*^	0.172–0.549	p<0.001
Hip procedures (resurfacing/arthroplasty)	29/162 (17.90)	24/391 (6.14)	0.374*^	0.205–0.578	p=0.001
Hip resurfacing	7/162 (4.32)	4/391 (1.02)	0.707☆	0.159–3.139	p=0.648
Hip arthroplasty	22/162 (13.58)	20/391 (5.12)	0.426☆	0.222–0.820	p=0.011
Bilateral hip arthroplasty	1/162 (0.62)	3/391 (0.76)	1.009☆	0.991–1.026	p=0.341
Hip arthroplasty revisions	21/162 (12.96)	16/391 (4.09)	0.347☆	0.031–3.853	p=0.389

Hip arthroplasty re-revisions ★	7/22 (31.82)	2/20 (10.00)	1.109☆	0.227–5.413	p=0.898
Spinal orthopaedic surgeries	1/162 (0.62)	4/391 (1.02)	1.664☆	0.185–14.998	p=0.650
Proceeding to several (≥3) surgeries	9/162 (5.56)	6/391 (1.53)	2.583☆	0.356–18.429	p=0.344

* adjusted for 'time since diagnosis'
^ adjusted for 'presence of psoriasis'
☆ no significant covariates requiring adjustment in the regression model
★ conditional on cases having had revision surgery in the first instance
AS: ankylosing spondylitis JoAS: Juvenile-onset AS AoAS: Adult-onset AS 95% CI: 95% confidence interval

Figure 1. **Kaplan-Meier survival curves for juvenile and adult-onset ankylosing spondylitis from 'age at diagnosis'**



Disclosure: D. R. Jadon, None; **G. Shaddick**, None; **A. Jobling**, None; **A. V. Ramanan**, None; **R. Sengupta**, None.

2831

Development of New Radiographic Vertebral Fractures in Patients with Ankylosing Spondylitis during 4 Years of TNF-α Blocking Therapy: Results from the Glas Cohort. Fiona Maas[1], Anneke Spoorenberg[1], Elisabeth Brouwer[2], Reinhard Bos[3], Rizwana N. Chaudhry[1], Freke Wink[3], Hendrika Bootsma[4], Eveline van der Veer[1] and Suzanne Arends[4]. [1]University Medical Center Groningen, Groningen, Netherlands, [2]University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [3]Medical Center Leeuwarden, Leeuwarden, Netherlands, [4]University Medical Center Groningen, University of Groningen, Groningen, Netherlands.

Background/Purpose: Previous studies have shown that the risk of vertebral fractures is increased in patients with ankylosing spondylitis (AS). Prospective longitudinal data about radiographic vertebral fractures are scarce and little is known about the effect of tumor necrosis factor-alpha (TNF-α) blocking therapy on the development of vertebral fractures in AS.

Our objective was to determine the prevalence of radiographic vertebral fractures in patients with AS before start of TNF-α blocking therapy and to investigate the incidence of vertebral fractures after 4 years of follow-up.

Methods: Consecutive AS patients from the Groningen Leeuwarden AS (GLAS) cohort with available thoracic and lumbar radiographs at baseline and after 4 years of TNF-α blocking therapy were included. Patients fulfilled the modified New York criteria for AS and the ASAS criteria to start with TNF-α blocking therapy. Vertebral fractures were assessed by two independent readers using the Genant method and were defined as ≥20% reduction in vertebral height (grade 1 (mild), 20–25% reduction; grade 2 (moderate), 25–40% reduction; grade 3 (severe), >40% reduction). Bone mineral density (BMD) was measured with DXA and spinal radiographic damage with the modified Stoke AS Spine Score (mSASSS).

Results: 105 AS patients were included: 72% male, mean age 42±11 years, median symptom duration 16 years (range 1–47), and 83% HLA-B27 positive. In 27 (26%) of 105 patients, vertebral fractures were observed at baseline (average 1.7 fractures per patient). These patients were significantly older, had larger occiput-to-wall distance, and more spinal radiographic damage.

After 4 years of follow-up, 21 (20%) patients had new vertebral fractures. Most fractures were mild and occurred in the thoracic spine. Older age, higher BASFI, low lumbar spine BMD, use of anti-osteoporotic treatment, and presence of moderate vertebral fractures at baseline were significantly associated with the development of new fractures. Lumbar spine and hip BMD increased significantly during treatment. Patients with new vertebral fractures showed significantly less improvement in lumbar spine BMD than patients without new fractures (median change in Z-score 0.4 vs. 0.8).

Conclusion: The prevalence of radiographic vertebral fractures was 26% in AS patients with active disease before start of TNF-α blocking therapy. Although a significant increase in BMD was found, 20% of patients developed new vertebral fractures during 4 years of TNF-α blocking therapy.

Disclosure: F. Maas, None; **A. Spoorenberg**, Pfizer Inc, 2, Pfizer Inc, 5, Abbvie, 5, UCB, 5; **E. Brouwer**, Pfizer Inc, 2; **R. Bos**, Pfizer Inc, 2, Pfizer Inc, 5; **R. N. Chaudhry**, None; **F. Wink**, None; **H. Bootsma**, None; **E. van der Veer**, None; **S. Arends**, Pfizer Inc, 2.

2832

The Effect of Co-Medication with Conventional Synthetic Disease Modifying Anti-Rheumatic Drugs on TNF Inhibitor Drug Survival in Patients with Ankylosing Spondylitis: Results from a Nationwide Prospective Study. Elisabeth Lie[1], Lars Erik Kristensen[2], Helena Forsblad-d'Elia[3], Johan Askling[4] and Lennart T. Jacobsson[3]. [1]Diakonhjemmet Hospital, Oslo, Norway, [2]Lund University, Malmö, Sweden, [3]Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden, [4]Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: For rheumatoid arthritis it is well established that co-medication (co-med) with methotrexate (MTX) increases the efficacy and drug survival of TNF inhibitors (TNFi), while there has been little evidence of such a beneficial effect of co-med for ankylosing spondylitis (AS). The purpose of this study was to assess the effect of co-med with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) on retention to TNFi therapy in AS.

Methods: Data on patients (pts) with AS starting adalimumab (ADA), etanercept (ETN) or infliximab (IFX) as their first TNFi from Jan 2003 through Dec 2010 were extracted from the Swedish Biologics Register ARTIS, including use of csDMARD co-med at baseline. Follow-up data through Dec 2011 were available at the time of analysis. Additional covariate data were obtained by linkage to the National Patient Register and Statistics Sweden. We analysed 5-year drug survival by multivariable Cox regression, including covariates that were selected a priori (Table). Additional potential confounders (ESR, CRP, patient global, 28-swollen joint count (SJC), and history of uveitis, psoriasis and inflammatory bowel disease) were also tested in the model.

Results: 1365 pts with AS were included (605 IFX, 406 ADA, 354 ETN). At baseline 557 pts (40.8%) used csDMARD co-med (429 used MTX), and co-med was more often given with IFX (55.4%) than with ADA (28.1%) or ETN (30.5%). Patients on co-med had higher levels of ESR and CRP and more often ≥1 swollen joint at baseline, and remained on therapy longer vs. pts on TNFi monotherapy. Estimated median survival time (based on Kaplan-Meier of overall drug survival) was 6.0 vs. 4.2 years (log rank test $p<0.001$). By separate analyses per drug (Kaplan-Meier with log rank test), statistically significantly better survival rates in pts on co-med were observed for IFX ($p=0.015$), ADA ($p=0.015$) and ETN ($p=0.020$). The multivariable Cox regression model is shown in the Table. The hazard ratio (HR) for TNFi discontinuation for pts on csDMARD co-med was 0.71 vs. those not on co-med. We also found statistically significant associations between drug survival and ESR, CRP, patient global, 28-SJC and uveitis, respectively, while the association with csDMARD co-med remained highly statistically significant ($p<0.001$) with a HR of 0.58–0.70 in the models with additional adjustments (data not shown). We also tested csDMARD co-med as MTX vs. other csDMARDs vs. no csDMARD in the model shown in the Table: MTX vs. no csDMARD HR (95% CI) 0.74 (0.61–0.91) ($p=0.004$), and other csDMARDs vs. no csDMARD 0.59 (0.41–0.83) ($p=0.002$).

Table. Multivariable Cox regression analysis of 5-year drug survival

	HR (95% CI)	p-value
Age (per 10 years)	1.01 (0.94–1.09)	0.739
Sex (ref. female)	0.66 (0.55–0.80)	**<0.001**
csDMARD co-medication (ref. none)	0.71 (0.59–0.85)	**<0.001**
TNFi type		**0.037**
ADA vs. IFX	0.90 (0.73–1.11)	0.317
ETN vs. IFX	0.75 (0.60–0.93)	**0.010**
Start year 2007–2010 vs. 2003–2006	1.22 (1.01–1.48)	**0.037**
Hospital days*	1.01 (1.00–1.01)	**0.008**
Number of outpatient visits*	1.02 (1.00–1.03)	**0.010**
Disposable income (per 1000 €)†	0.99 (0.99–1.00)	0.146
Education‡		0.087
10–12 years vs. ≤9 years	0.93 (0.73–1.17)	0.532
>12 years vs. ≤9 years	0.78 (0.60–1.01)	0.060
Missing vs. ≤9 years	2.55 (0.62–10.4)	0.192

*Number of days/visits the 2 years prior to TNFi start; data from the National Patient Register
†Income the year prior to TNFi start; data from Statistics Sweden
‡Data from Statistics Sweden

Conclusion: AS patients who received csDMARD co-med with their first TNFi remained on therapy significantly longer than those who were not on co-med. The association remained statistically significant when adjusting for potential confounders.

Disclosure: E. Lie, AbbVie, 5, UCB, 5, Bristol-Myers Squibb, 5, Hospira, 5, Pfizer Inc, 5, AbbVie, 8, UCB, 8; **L. E. Kristensen**, Pfizer Inc, 5, UCB, 5, AbbVie, 5, MSD, 5, Pfizer Inc, 8, UCB, 8, AbbVie, 8, MSD, 8; **H. Forsblad-d'Elia**, None; **J. Askling**, AstraZeneca; Pfizer;, 2; **L. T. Jacobsson**, Pfizer Inc, 5, AbbVie, 5, UCB, 5.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Novel Therapies for Systemic Lupus Erythematosus
Tuesday, November 18, 2014, 2:30 PM–4:00 PM

2833

SM101, a Novel Recombinant, Soluble, Human FcγIIB Receptor, in the Treatment of Systemic Lupus Erythematosus: Results of a Double-Blind, Placebo-Controlled Multicenter Study. Sascha Tillmanns[1], Claudia Kolligs[1], David P. D'Cruz[2], Andrea Doria[3], Eric Hachulla[4], Reinhard E. Voll[5], Michael Tansey[1] and Klaus Schollmeier[1]. [1]SuppreMol GmbH, Martinsried, Germany, [2]Louise Coote Lupus Unit, Guy's and St Thomas' Hospital, London, United Kingdom, [3]University of Padova, Padova, Italy, [4]Lille University, Lille, France, [5]University Hospital Freiburg, Freiburg, Germany.

Background/Purpose: SM101, which represents the human soluble non-glycosylated version of the Fcγ receptor IIB, binds to the Fc part of autoimmune complexes and inhibits the binding of immune complexes to cell-standing Fcg receptors. It has undergone preclinical and clinical safety and efficacy investigation, with evidence of efficacy in primary immune thrombocytopenia. The mode of action could make SM101 a safe and effective treatment for systemic lupus erythematosus (SLE).

Methods: The objectives of this phase IIa randomised, double-blind, placebo-controlled parallel-group study were to evaluate the safety, tolerability and efficacy of placebo and 2 doses of SM101 (6mg/kg and 12mg/kg), randomised 1:2:2, in patients with SLE. The main inclusion criteria were a diagnosis of SLE, evidence of serological activity (high anti-dsDNA activity or low C3), and a SELENA-SLEDAI score ≥ 6 points, with stratification to include patients with lupus nephritis (LN). Concomitant immunosuppressive therapy with corticosteroids, mycophenolate mofetil (MMF) or azathioprine and adjuvant SLE medication were allowed at constant doses during the study. Eligible patients received an infusion of study drug once a week for the first 4 weeks; study duration was 24 weeks. Data were reviewed regularly by an independent safety monitoring board. Response was measured at 24 weeks according to the SLE Responder Index (combination of SELENA-SLEDAI response ≥ 4 points, no BILAG A or 2 × B flares and no PGA score worsening).

Results: Fifty one eligible patients, 14 with LN, from 8 European countries and Australia, were randomized and received at least one dose of active investigational drug or placebo. Concomitant medications were corticosteroids (96% of patients), MMF (45%), azathioprine (20%) or combinations thereof. Patient numbers per group and response rates are shown in Table 1. The SLE Responder Index response rate was twice as high in the SM101-treated patients compared with placebo, and response in patients with LN was proportionately greater. The response rate on SM101 remains the same after exclusion of 15 patients who received rescue medication. The main clinical drivers for response were improvement in arthritis and in skin eruption (present in 75% and 50% patients respectively) according to the BILAG scale. Both worsened or remained unchanged in placebo patients; in SM101-treated patients improvement or resolution occurred in 57% with arthritis and 45% with skin eruption. No safety signals which could be attributed specifically to SM101 were reported, and no serious adverse events were probably or possibly related to the drug. No anti-drug antibodies were detected.

Conclusion: The encouraging results of this early phase study indicate that the novel biological SM101 warrants further investigation as a treatment for patients with SLE, including patients with LN.

Table 1. Percentage of Patients Responding According to the SLE Responder Index and its Components

	ALL PATIENTS			PATIENTS WITH LN		
	Placebo (n=11)	6mg/kg (n=22)	12mg/kg (n=18)	Placebo (n=3)	6mg/kg (n=6)	12mg/kg (n=5)
SLE Responder Index	18%	36%	39%	0%	50%	60%
SELENA-SLEDAI Reduction ≥ 4 Points	27%	41%	50%	0%	50%	80%
SELENA-SLEDAI Reduction ≥ 6 Points	9%	14%	28%	0%	17%	60%
BILAG No Worsening	91%	77%	100%	100%	83%	80%
PGA No Worsening	55%	77%	89%	67%	67%	80%

Disclosure: S. Tillmanns, SuppreMol GmbH, 3; **C. Kolligs**, SuppreMol GmbH, 3; **D. P. D'Cruz**, Investigator, 5; **A. Doria**, Investigator, 5; **E. Hachulla**, Investigator, 5; **R. E. Voll**, Investigator, 5; **M. Tansey**, SuppreMol GmbH, 3; **K. Schollmeier**, SuppreMol GmbH, 3.

2834

Correlation of Laboratory and Clinical Parameters with British Isles Lupus Assessment Group Response in an Open-Label Extension Study of Epratuzumab in Systemic Lupus Erythematosus. Richard A. Furie[1], Michelle A. Petri[2], Caroline Gordon[3], Vibeke Strand[4], Catrinel Galateanu[5], Sabine Bongardt[6], Willem Koetse[7] and Daniel J. Wallace[8]. [1]North Shore - Long Island Jewish Health System, Great Neck, NY, [2]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, [4]Biopharmaceutical Consultant, Portola Valley, CA, [5]UCB Pharma, Brussels, Belgium, [6]UCB Pharma, Monheim, Germany, [7]UCB Pharma, Raleigh, NC, [8]Cedars-Sinai Medical Center, Los Angeles, CA.

Background/Purpose: Epratuzumab is a monoclonal antibody in development for the treatment of systemic lupus erythematosus (SLE) that binds CD22, promoting the natural inhibitory function of CD22 on the B-cell receptor.[1,2] In EMBLEM™ (dose-ranging Phase 2b study [NCT00624351]), and its open-label extension (OLE; SL0008 [NCT00660881]), epratuzumab produced sustained, clinically relevant improvements in patients (pts) with moderate-to-severe SLE as measured by British Isles Lupus Assessment Group (BILAG) response. BILAG response forms the basis of BILAG-Based Composite Lupus Assessment (BICLA), described elsewhere.[3] This study aimed to correlate BILAG response with clinical and laboratory parameters during epratuzumab open-label therapy, and to examine maintenance of improvements in BILAG organ systems.

Methods: All EMBLEM™ pts completing 12 weeks (wks) of blinded treatment, or who discontinued due to lack of efficacy but completed ≥8 wks, were eligible for OLE entry, in which all pts received 1200mg epratuzumab at Wks 0 and 2 of repeating 12-wk cycles. Post-hoc analysis evaluated changes from EMBLEM™ baseline in clinical and laboratory parameters in BILAG responders (R) vs non-responders (NR) (OLE Wks 48 and 96). BILAG response was defined as BILAG A to B/C/D, all Bs to C/D, no new BILAG A or ≥2 new B scores; non-response as lack of improvement, worsening or withdrawal prior to assessment. Achievement and maintenance of a low disease activity state was defined as disease activity improvement in all systems with BILAG A or B scores at EMBLEM™ baseline to C or D in the OLE, with no categorical deterioration from baseline levels prior to improvement, and no reversion to baseline A or B levels once improvement had occurred.

Results: 203 pts entered the OLE; 80 (39%) achieved a BILAG response at Wk48, and 72 (36%) achieved a BILAG response at Wk96. At both timepoints, responders had significantly greater reductions in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Physician Global Assessment (PGA) and Patient Global Assessment (PtGA) scores, and improvements in greater numbers of BILAG organ domains than non-responders (Table). At Wk48, responders had greater reduction in concomitant steroid doses (not significant at Wk96 [Table]). Laboratory parameters associated with BILAG response are shown in the table. Improvements in individual BILAG organ systems were maintained in >50% of pts in 4/9 body systems.

Conclusion: BILAG responders in the OLE were more likely to achieve improvements in a range of clinical and laboratory parameters, including SLEDAI, PGA and PtGA scores, and show changes in absolute B-cell (CD19+) and T-cell (CD3+) counts. Additionally, improvements in individual body organ systems were maintained.

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Table 1. Clinical endpoints and laboratory parameters achieved by BILAG responders (R) and non-responders (NR) at Weeks 48 and 96

	Week 48			Week 96		
	BILAG R (N=80)	BILAG NR (N=123)	p value	BILAG R (N=72)	BILAG NR (N=130)	p value
Clinical parameters						
≥4-point SLEDAI reduction,[a] n (%)	67 (83.8)	43 (35.0)	<0.0001	67 (93.1)	30 (23.1)	<0.0001
≥7-point SLEDAI reduction,[a] n (%)	51 (65.4)	26 (21.8)	<0.0001	45 (67.2)	19 (14.6)	<0.0001
SLEDAI no worsening,[a] n(%)	76 (95.0)	68 (55.3)	<0.0001	71 (98.6)	43 (33.1)	<0.0001

No. BILAG organ domains improved,[a] mean (SD) [n]	3.0 (1.0) [80]	1.0 (1.1)[123]	<0.0001	3.2 (1.1) [72]	0.6 (1.0) [130]	<0.0001
ΔPGA,[b] mean (SD)	−34.3 (15.9)	−14.0 (21.4)	<0.0001	−33.9 (17.4)	−14.1 (22.0)	<0.0001
No worsening PGA,[b,c] n (%)	80 (100)	108 (87.8)	0.0012	71 (98.6)	115 (88.5)	0.0105
ΔPtGA,[b] mean (SD)	−22.8 (24.6)	−8.5 (25.8)	0.0001	−22.5 (25.9)	−8.0 (26.3)	0.0002
No worsening PtGA,[b,c] n (%)	72 (90.0)	93 (75.6)	0.0102	66 (91.7)	98 (75.4)	0.0046
Steroid dose						
Δ prednisone dose,[b]	−5.01 (10.5)	−0.18 (16.4)	0.0113	−4.28 (7.9)	−0.88 (17.4)	0.0579
Prednisone >7.5 mg/d with baseline prednisone ≤7.5 mg/d,[b] n/N (%)	0/29	2/45 (4.4)	0.2498	1/30 (3.3)	2/43 (4.7)	0.7802
Prednisone ≤7.5 mg/d with baseline prednisone >7.5 mg/d,[b] n/N (%)	12/51 (23.5)	14/78 (17.9)	0.4398	15/42 (35.7)	18/87 (20.7)	0.0668
Laboratory parameters						
Normalization of anti-dSDNA Ab,[b,d]n/N (%)	6/46 (13.0)	10/67 (14.9)	0.7780	12/38 (31.6)	11/74 (14.9)	0.0382
Reduction in anti-dSDNA,[d,e] n (%)	10/46 (21.7)	14/67 (20.9)	0.9142	15/38 (39.5)	17/74 (23.0)	0.0672
% Δ complement C3,[b,f]mean (SD) [n]	25.4 (88.4) [26]	8.6 (36.0) [51]	0.3597	52.5 (128.4) [19]	7.8 (30.6) [58]	0.1499
Normalization of complement C3, [b,f] n/N (%)	8/26 (30.8)	16/51 (31.4)	0.9569	7/19 (36.8)	15/58 (25.9)	0.3578
% Δ in absolute B cell (CD19+) counts, [b] mean (SD) [n]	−40.7 (41.9) [76]	−19.5 (88.8)[120]	0.0255	−39.1 (49.8) [69]	−23.9 (88.9) [126]	0.1288
% Δ in absolute T cell (CD3+) counts, [b] mean (SD) [n]	−4.1 (39.4) [76]	17.2 (126.1) [120]	0.0864	−2.7 (40.4) [69]	18.2 (157.8)[126]	0.1623
% Δ protein/creatinine ratio,[b] mean (SD) [n]	33.2 (215.4) [76]	157.5 (832.3) [123]	0.1177	−11.9 (55.7) [70]	206.3 (844.8) [128]	0.0043

[a]Non-responder imputation (NRI), last observed response is carried forward if any on-study component is missing; if patient discontinued prior to week analyzed, response is imputed to no response; [b]Last Observation Carried Forward (LOCF) imputation; [c]no worsening defined as <10-point worsening from baseline; [d]among patients positive at baseline; [e]reduction defined as ≥50% from baseline or reverting to negative; [f]among patients with low C3 at baseline. Abbreviations: SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; Δ: change from baseline; BILAG: British Isles Lupus Assessment Group; PGA: Physician's Global Assessment; PtGA: Patient's Global Assessment; Ab: Antibodies.

Disclosure: R. A. Furie, UCB Pharma, 5; **M. A. Petri**, UCB Pharma, 2, UCB Pharma, 5; **C. Gordon**, GlaxoSmithKline, MedImmune, Merck Serono, Paraxel and UCB Pharma, 5; **V. Strand**, AbbVie, Afferent, Amgen, Biogen Idec, Bioventus, BMS, Carbylan, Celgene, Celltrion, CORRONA, Crescendo, Genentech/Roche, GSK, Hospira, Iroko, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Sanofi, SKK, Takeda, UCB, Vertex, 5; **C. Galateanu**, UCB Pharma, 3; **S. Bongardt**, UCB Pharma, 3; **W. Koetse**, UCB Pharma, 1, UCB Pharma, 3; **D. J. Wallace**, Bristol-Myers Squibb, Genentech, Biogen IDEC Inc, GlaxoSmithKline, Human Genome Sciences Inc, MedImmune, Novo Nordisk, UCB Pharma, 5.

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A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Study to Evaluate the Efficacy and Safety of Sirukumab in Patients with Active Lupus Nephritis. Cynthia Aranow[1], R. van Vollenhoven[2], Brad H. Rovin[3], Carrie Wagner[4], Bei Zhou[4], Robert Gordon[4] and Benjamin Hsu[4]. [1]The Feinstein Institute, Manhasset, NY, [2]The Karolinska Institute, Stockholm, Sweden, [3]Ohio State University Medical Center, Columbus, OH, [4]Janssen Research & Development, LLC., Spring House, PA.

Background/Purpose: IL-6 is a pro-inflammatory cytokine that is over-expressed in lupus nephritis(LN). This proof-of-concept study examined the efficacy and safety of sirukumab, an anti-interleukin-6 monoclonal antibody, in patients (pts) with active, ISN/RPS class III or class IV lupus nephritis (LN).

Methods: Pts were enrolled if they had class III or IV LN on renal biopsy within 14 mo of randomization, persistent proteinuria (≥ 0.5 g/d) despite immunosuppression (MMF or AZA ± corticosteroids), and stable renin-angiotensin system blockade. Pts were randomized to IV sirukumab 10 mg/kg (n=21) or placebo (Pbo, n=4) q4wks through wk 24. Primary endpoint was % reduction from baseline in proteinuria (protein/creatinine (P/C) ratio in a 12hr urine collection) at wk 24; major secondary endpoints included the proportion of pts with: 1) ≥50% reduction of baseline proteinuria; 2) meaningful reduction in proteinuria; 3) no worsening of glomerular filtration rate (GFR) based on serum creatinine levels (defined as <15% decrease from baseline rate); all at any time through wk 24, as well as 4)% change from baseline in Patient's and Physician's Global Assessments of Disease Activity over time.

Results: Median time from biopsy collection to randomization was 116 days. 76% of pts (19/25) completed 2-wks of treatment. No median reduction in proteinuria at wk 24 (primary endpoint) was observed in the sirukumab group. In contrast, the Pbo group demonstrated median 43.3% increase in proteinuria(Table), largely driven by 1 Pbo-treated pt. Secondary endpoints indicated 20% (4/20) and 15% (3/20) of sirukumab-treated pts, vs 0% of Pbo-treated pts, demonstrated a ≥50% reduction or a meaningful reduction, respectively, in proteinuria at wk 24 (Table). In contrast, at wk 24, 10/18 (56%) of sirukumab-treated pts and 3/4 (75%) of Pbo-treated pts had no worsening in GFR (Table). Neither Physician nor Patient Global Assessment scores improved in either treatment group. Among the 12 sirukumab-treated pts positive for anti-dsDNA at baseline, there was a mean 62.3% reduction in anti-dsDNA at wk 24. Among 6 pts who discontinued study agent, 5 did so because of an adverse event(AE)(anaphylactic reaction, increased liver enzymes, neutropenia, pneumonia, and LN worsening). No deaths occurred. Approximately half (47.5%, 10/21) of sirukumab-treated pts had ≥1 serious AE, the majority of which were infections. No serious AE occurred with Pbo-treated pts, although 4/37 (10.8%) screen-failed pts had 1 or more SAEs during the 8 wk screening period.

Conclusion: IL-6 inhibition with sirukumab in pts with active LN did not result in a median improvement in proteinuria, however approx 15–20% of treated pts did show a notable reduction in proteinuria. A high frequency of serious AE was observed in this population of immunosuppressed pts with refractory LN.

Table. Summary of primary and major secondary efficacy endpoints at wk 24

	Placebo	CNTO 136
Modified intent-to-treat pts	4	20[a]
Proteinuria % change from baseline at wk24[a]		
Median		0.00
(95% CI)	43.3	(−61.8, 39.6)
Pts with decrease ≥50% in proteinuria at wk24[a]	0	4/20 (20.0%)
95% confidence interval		(5.7, 43.7)
Pts with meaningful reduction in proteinuria at wk24[a,b]	0	3/20 (15.0%)
95% confidence interval		(3.2, 37.9)
Pts with no worsening in GFR at wk24	3 (75.0%)	10/18 (55.6%)
95% confidence interval		(30.8, 78.5)

[a]A last-observation-carried-forward procedure was used to impute missing proteinuria values if a pt had data for ≥1 post- baseline evaluation. Of 21 randomized pts, 20 were included in the efficacy analyses.
[b]Meaningful reduction in proteinuria was defined as P/C (protein/creatinine) ratio < 0.5 for non-nephrotic pts; and ≥50% reduction in P/C ratio and P/C ratio < 3.0 for nephrotic pts.

Disclosure: C. Aranow, None; **R. van Vollenhoven**, Janssen Research and Development, LLC, 2; **B. H. Rovin**, Genentech and Biogen IDEC Inc., 2, Questcor, 2, Centocor, Inc., 5, Lilly, 5, GlaxoSmithKline, 5, Medimmune, 5, aurina, 5; **C. Wagner**, Janssen Research and Development, LLC, 3; **B. Zhou**, Janssen Research and Development, LLC, 3; **R. Gordon**, Janssen Research and Development, LLC, 3; **B. Hsu**, Janssen Research & Development, LLC., 3.

2836

Effects of Blisibimod, an Inhibitor of B Cell Activating Factor, on Patient Reported Outcomes and Disease Activity in Patients with Systemic Lupus Erythematosus. Michelle Petri[1], Renee S. Martin[2], Colin Hislop[2], Morton A. Scheinberg[3] and Richard Furie[4]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]Anthera Pharmaceuticals Inc, Hayward, CA, [3]Rheumatology Hospital Abreu Sodre Pesquisa Clínica, São Paulo, Brazil, [4]North Shore - Long Island Jewish Health System, Great Neck, NY.

Background/Purpose: To conduct secondary endpoint analyses of the effects of subcutaneously-administered blisibimod (A-623, AMG 623), an inhibitor of B-cell activating factor (BAFF), on patient-reported outcomes and indices of disease activity in patients with systemic lupus erythematosus (SLE) during the phase 2b clinical trial PEARL-SC (NCT01162681).

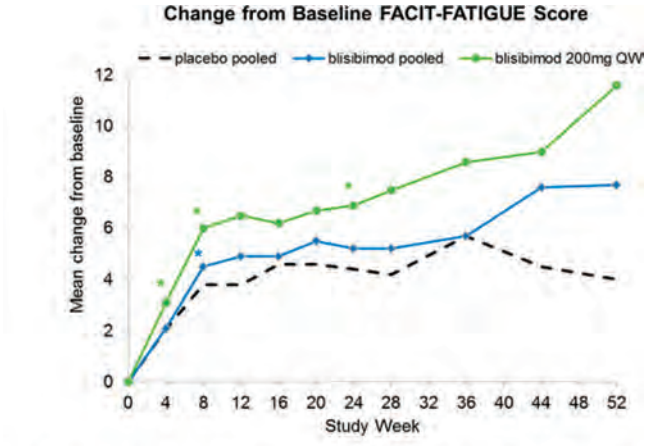
Methods: 547 SLE patients who met the ACR classification criteria, and had anti-double-stranded DNA or anti-nuclear antibodies, and SELENA-SLEDAI score ≥6 at baseline, were enrolled into the PEARL-SC study, and randomized 1:1 to receive placebo or blisibimod administered at 1 of 3 dose levels, 100 mg weekly (QW), 200 mg QW, or 200 mg every 4 weeks for up to 52 weeks (with a median of 37 weeks) or until the last subject completed 6 months of study drug therapy. Patient self-reported outcomes were evaluated using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, and disease activity evaluated within SELENA-SLEDAI organ domains.

Results: Significant improvements in measures of disease activity, including the SLE responder Index-8 (SRI-8) in subjects with severe baseline disease (defined at SELENA-SLEDAI score≥10 and receiving steroids), especially at the highest blisibimod dose of 200mg QW were reported previously (Furie et al. 2014). Approximately 76% of subjects had SELENA-SLEDAI musculoskeletal organ involvement at enrollment, and 89% of subjects had mucocutaneous organ involvement. At Week 24, approximately 12% and 39% of subjects randomized to the 200mg QW blisibimod arm had musculoskeletal or mucocutaneous organ involvement, compared with approximately 15% and 42% respectively in the placebo arm ($p<0.2$ to $p<0.05$ across manifestations evaluated over Weeks 12 through 24). A concomitant tendency toward improved self-reported fatigue was observed amongst subjects randomized to blisibimod based on the FACIT-Fatigue scale, especially in the 200mg QW group (N=80) where a mean 6.9-point improvement from baseline was reported at Week 24 ($p=0.065$) compared with 4.4 with placebo (N=229). Based on exploratory statistical analyses, the

effects of blisibimod on FACIT-fatigue were significantly better than placebo ($p<0.05$) as early as Week 8.

Blisibimod was safe and well-tolerated at all dose levels with no meaningful imbalances in serious adverse events or infections between blisibimod and placebo. Amongst the commonly-reported AEs, imbalance was observed only with injection site reactions (200mg QW blisibimod=15%, matched placebo=7%), but these were not serious or severe.

Conclusion: Fatigue remains a debilitating manifestation of lupus. In this trial, blisibimod showed a tendency toward improved mucocutaneous and musculoskeletal disease activity as well as patient self-reported fatigue. These data support further evaluation of blisibimod in patients with SLE.



Number at Week	4	8	12	16	20	24	28	36	44	52
Placebo Pooled	258	245	240	236	232	229	189	142	73	37
Blisibimod Pooled	267	254	246	246	240	239	191	132	70	44
Blisibimod 200QW	87	85	83	81	79	80	64	45	25	14

Disclosure: M. Petri, Anthera Pharmaceuticals Inc, 5, Anthera Pharmaceuticals Inc, 9; **R. S. Martin**, Anthera Pharmceuticals Inc, 1, Anthera Pharmaceuticals Inc, 3; **C. Hislop**, Antehra Pharmaceuticals Inc, 1, Anthera Pharmaceuticals Inc, 3; **M. A. Scheinberg**, Anthera Pharmaceuticals Inc, 9; **R. Furie**, Anthera Pharmaceuticals Inc, 5, Anthera Pharmaceuticals Inc, 9.

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Induction of Clinical Remission By Low-Dose Interleukin-2 in Refractory SLE. Jens Y. Humrich[1], Caroline von Spee-Mayer[1], Elise Siegert[1], Angelika Rose[1], Tobias Alexander[1], Falk Hiepe[1], Andreas Radbruch[2], Gerd Burmester[3] and Gabriela Riemekasten[1]. [1]Charité – University Hospital, Berlin, Germany, [2]German Rheumatism Research Centre Berlin (DRFZ), an institute of the Leibniz Association, Berlin, Germany, [3]Charité University Medicine, Dept. Medicine/Rheumatology and Clinical Immunology, Berlin, Germany.

Background/Purpose: Interleukin-2 (IL-2) is crucial for the growth and survival of regulatory T cells (Treg), and thus for the control of autoimmunity. In previous studies we have proven a causal relationship between an acquired IL-2-deficiency, defects in Treg biology and the development of systemic lupus erythematosus (SLE). Accordingly, we showed that compensation of IL-2 deficiency by IL-2 therapy corrects associated Treg defects and ameliorates already established disease in lupus-prone mice, providing the rationales for an IL-2-based immunotherapy of SLE in order to restore Treg activity an thus to re-establish endogenous mechanisms of tolerance that can counteract autoimmunity.

Here we report a rapid and robust reduction of disease activity in parallel to a remarkable expansion of the Treg population by an off-label therapy with low-dose IL-2 in two patients with a long-term history of SLE and increased disease activity refractory or intolerant to a large variety of approved and experimental therapies.

Methods: The therapeutic regimen consisted of four treatment cycles each with daily subcutaneous injections of recombinant human IL-2 (aldesleukin; Proleukin®) at single doses of 1.5 or 3.0 million IU on five consecutive days separated by washout-periods of 9–16 days and followed by a 9-week follow-up period. Disease activity was determined by the SLEDAI at defined time points during the study. Cells from peripheral blood were analyzed by flow cytometry at the indicated time points. Written informed consent was obtained from the patient prior to the initiation of the off-label treatment with IL-2.

Results: In the first treated patient, disease activity rapidly decreased already after one treatment cycle, while in the second patient a reduction in disease activity was observed two weeks later. During the following treatment cycles disease activity further decreased or remained low due to disappearance of clinical manifestations such as arthritis, myositis and skin rash. In addition and unexpectedly levels of anti-dsDNA-antibodies considerably declined in both patients. The clinical response was associated with cyclic and treatment-related increases of the CD25hiFoxp3+CD127lo Treg population in the peripheral blood. The therapy was very well tolerated and adverse events were generally mild and transient.

Conclusion: These data provide the first evidence for the clinical efficacy of low-dose IL-2-therapy in conjunction with the boosting of Treg activity in SLE and strongly support the rationales of this selective biological treatment strategy.

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2838

Exploratory Analysis of Pharmacokinetic Effects of Atacicept in Patients with Moderate to Severe Systemic Lupus Erythematosus. David Wofsy[1], Caroline Gordon[2], Yong Li[3], Stephen D. Wax[4] and David Isenberg[5]. [1]Division of Rheumatology, University of California, San Francisco, CA, [2]Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom, [3]R&D Global BioStatistics, EMD Serono, Billerica, MA, [4]Global Clinical Development Center - Immunology, EMD Serono Inc, Rockland, MA, [5]Centre for Rheumatology Research, University College Hospital London, London, United Kingdom.

Background/Purpose: Atacicept is a fusion protein that inhibits B-cell stimulating factors BLyS and APRIL. We previously reported the clinical effects of atacicept in lupus patients with active disease (the APRIL-SLE study). Here we report the exploratory analysis between mean drug concentration and clinical outcome in those subjects.

Methods: Patients with active SLE (≥1 BILAG A and/or B) were treated with corticosteroid taper for 12 weeks. Subjects reaching BILAG C or D at weeks 10 and 12 were randomized 1:1:1 to receive placebo (PLC), atacicept 75 mg (A75) or 150 mg (A150) twice weekly for 4 weeks then weekly for 48 weeks. All patients received standard of care. As previously reported, A150 reduced the frequency of BILAG A and B flares but was discontinued prematurely due to two infection-related deaths. This post-hoc analysis was performed among subjects in all groups randomized at least 52 weeks prior to discontinuation of A150 and who had an opportunity to complete the protocol (n=81, 84, and 81 for PLC, A75, and A150, respectively). For this analysis subjects in the two treatment arms were divided into four quartiles based on mean atacicept concentration, the 1st being the group with the lowest concentration.

Results: Subjects with the highest atacicept concentrations (3rd and 4th quartiles) experienced fewer flares during treatment compared to subjects with lower concentrations (1st and 2nd quartiles) and subjects in the PLC group (60, 63, 61, 49, and 29% in the PLC, 1st, 2nd, 3rd, and 4th quartiles, respectively). Similarly, the proportions of subjects using high-dose corticosteroids was lowest among subjects with higher concentrations of atacicept (32, 24, 17, 22 and 15% in the PLC, 1st, 2nd, 3rd and 4th quartiles). Time to first new flares was also longer for atacicept than the PLC. Despite their higher atacicept concentrations subjects in the 4th quartile experienced similar proportions of treatment-emergent serious or severe infectious adverse events vs PLC (4.9 vs 3.7%). Subjects with baseline free BLyS and APRIL concentrations both ≥median experienced fewer flares in the groups with higher atacicept concentrations (2nd, 3rd and 4th quartiles). Results are summarized in the Table 1. The two subjects in the A150 group who died due to infection had mean and max trough levels that were near or below the 25th percentile concentration.

Conclusion: Subjects in the APRIL-SLE study who achieved the highest concentrations of atacicept showed a reduced risk of SLE flares and increased time to flare. Atacicept was also associated with a reduction in corticosteroid use. Subjects with free BLyS and APRIL levels above median at baseline had an increased flare risk in the PLC group; among these subjects, there was an even greater treatment effect seen in the atacicept groups. These post-hoc results warrant further studies to assess the safety and efficacy of atacicept in SLE patients.

Table 1. Treatment response by quartiles of atacicept mean concentration (trough level): Potential Completer population

	Placebo n=81	Atacicept 1st Quartile n=41	Atacicept 2nd Quartile n=41	Atacicept 3rd Quartile n=41	Atacicept 4th Quartile n=41
Presence of flare* during treatment, n (%), [95% CI]	49 (60.5) [0.49, 0.71]	26 (63.4) [0.47, 0.78]	25 (61.0) [0.45, 0.76]	20 (48.8) [0.33, 0.65]	12 (29.3)# [0.16, 0.46]
Time to new flare (BILAG A or B only) by Kaplan-Meier curve, 25th percentile estimate (day)	97	141	196	167	>365+
Subjects who experienced a serious or severe infection during treatment period, n (%)	3 (3.7)	3 (7.3)	7 (17.1)	0	2 (4.9)
Subjects who had high-dose corticosteroids (≥20 mg/day) post-randomization during treatment period, n (%)	26 (32.1)	10 (24.4)	7 (17.1)	9 (22.0)	6 (14.6)
Baseline ≥median BLyS and ≥median APRIL‡	**n=30**	**n=5**	**n=13**	**n=16**	**n=12**
Presence of flare* during treatment, n (%), [95% CI]	23 (76.7) [0.58, 0.90]	4 (80.0) [0.28, 0.99]	6 (46.2) [0.19, 0.75]	7 (43.8) [0.20, 0.70]	1 (8.3)† [0.002, 0.38]

*Flare defined as having an adjudicated BILAG A or B score in any of the 8 organ systems during treatment, or imputed for subjects who had premature treatment discontinuation.
+25% percentile estimate is not reached during treatment period.
‡Categories determined by median of free BLyS (1.9 ng/mL) at baseline and median of free APRIL (2236.7 pg/mL).
Two-sided Fisher's exact test nominal p-value compared to placebo: □ #p=0.002, †p<0.0001

Disclosure: D. Wofsy, Merck Serono, 5, Genentech and Biogen IDEC Inc., 5, Anthera, 5, GlaxoSmithKline, 9, Medimmune, 5; **C. Gordon**, Merck Serono, 5, UCB Pharma, 5, Bristol-Myers Squibb, 5, Roche Pharmaceuticals, 5, GlaxoSmithKline, 5, MedImmune, 5, Amgen, 5; **Y. Li**, EMD Serono, 3; **S. D. Wax**, EMD Serono, 3; **D. Isenberg**, Merck Serono, 5.

ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Human Etiology and Pathogenesis II: Pathogenic Targets, Genetic Variants and Apoptosis
Tuesday, November 18, 2014, 2:30 PM–4:00 PM

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BCL-2 As a Potential Therapeutic Target in Human Lupus Tubulointerstitial Inflammation. Kichul Ko[1], Denisse Yanez[1], Natalya Kaverina[1], Vladimir M. Liarski[1], Yahui Peng[2], Li Lan[1], Stuart Perper[3], Annette Schwartz[3], Liz O'connor[3], Andrew Souers[4], Steven Elmore[4], Lisa Olson[3], Maryellen L. Giger[1], Li Chun Wang[3] and Marcus R. Clark[1]. [1]University of Chicago, Chicago, IL, [2]Beijing Jiaotong University, Beijing, China, [3]AbbVie Inc, AbbVie Bioresearch Center, Worcester, MA, [4]AbbVie Inc, North Chicago, IL.

Background/Purpose: Lupus nephritis (LuN) is the most common, severe manifestation of systemic lupus erythematosus (SLE). We have previously shown that glomerulonephritis appears to be a manifestation of systemic autoimmunity while tubulointerstitial inflammation (TII) is associated with additional, *in situ* adaptive immune cell networks that might amplify local inflammation and tissue damage. Furthermore, patients with significant TII are more likely to fail conventional therapy and progress to renal failure. Therefore, understanding the mechanisms of *in situ* adaptive immunity in lupus TII might provide new therapeutic opportunities for treating LuN. In mice, BCL-2 family proteins are key regulators of immune cell apoptosis and forced expression of BCL-2 in B cells promotes lupus-like nephritis. We hypothesized that dysregulated expression of the BCL-2 family proteins in human LuN TII might contribute to local adaptive immunity, inflammation and disease pathogenesis.

Methods: Frozen renal biopsy specimens from 26 patients with SLE (ISN/RPS Class III, IV or V LuN), 10 mixed cellular renal allograft rejection (MR) biopsy specimens and tonsil samples from healthy subjects and kidneys from IFNα-induced NZB/W F1 lupus mice were stained with antibodies specific for CD20, CD4, BCL-2, MCL-1 or BIM. Images were acquired using scanning laser confocal microscopy. IFNα-induced NZB/W F1 mice were treated daily with vehicle or 30 mg/kg of ABT-199 and analyzed for survival and the development of proteinuria.

Results: A recently developed imaging tool (*Science Translational Medicine* 2014, 6:230) was used to quantify the frequency of $CD20^+$ B and $CD4^+$ T cells expressing the anti-apoptotic molecules BCL-2, MCL-1 and the pro-apoptotic molecule BIM. In primary follicles of normal tonsils, both B and T cells frequently expressed BCL-2. However, upon entry into germinal centers (GC), BCL-2 was down-regulated and MCL-1 was induced. In marked contrast, in LuN and MR TII biopsies, the frequency of $BCL\text{-}2^+$ cells was increased in B and T cells while $MCL\text{-}1^+$ cells were rare. Observed differences between tonsil GC lymphocytes versus TII in LuN and MR for both BCL-2 and MCL-1 were highly significant ($p<0.001$). These expression differences were confirmed by laser capture microscopy coupled to qPCR. In contrast, the frequency of BIM^+ cells did not significantly vary among tissues. Consistent with these findings, BCL-2, but not MCL-1 expressing cells were detected in the inflamed kidney in IFNα-induced NZB/W F1 lupus mice. Furthermore, administration of ABT-199, a BCL-2 selective inhibitor, prevented the development of lupus nephritis by depleting intra-renal B and T cells in these animals.

Conclusion: Frequent BCL-2, but not MCL-1, expressing cells were present in LuN, MR TII tissues and IFNα-induced NZB/W F1 lupus mice. Treatment of these mice with the BCL-2 selective inhibitor ABT-199 resulted in the loss of renal B and T cells and the preservation of renal function. These data indicate that BCL-2, which is dysregulated in TII, is an attractive therapeutic target in cases of lupus nephritis manifesting tubulointerstitial inflammation.

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2840

Targeting the RhoA-Rock Pathway to Reverse T Cell Dysfunction in SLE. Cristina T. Rozo, Laura Leuenberger, Kyriakos A. Kirou, Margaret Robotham, Sanjay Gupta, Reena Khianey, Alessandra B. Pernis and Jane E. Salmon. Hospital for Special Surgery, New York, NY.

Background/Purpose: Aberrant expansion of T_H-17 cells and deregulated production of IL-17 and IL-21 are involved in the pathogenesis of SLE. Production of IL-17 and IL-21 is critically dependent on the transcription factor, IRF4 (Interferon Regulatory Factor 4). Rho-associated protein kinases (ROCKs) can phosphorylate IRF4 and regulate its activity. The finding that ROCK activity is elevated in SLE patients and is associated with human T_H-17 differentiation, coupled with the ability of ROCK inhibitors to ameliorate autoimmunity in murine models of lupus suggest that targeting the ROCK pathway might be a novel therapeutic strategy for the treatment of SLE. ROCK activation can be inhibited by Y27632 (a nonselective ROCK inhibitor that inhibits both ROCK isoforms, ROCK1 and ROCK2) or by statins (which inhibit ROCKs by interfering with their major upstream activator, RhoA). Here, we examined the ability of Y27632 and simvastatin to inhibit the production of IL-17 and IL-21 by human T_H-17 cells and SLE T cells.

Methods: We assessed the capacity of Y27632 (60uM–90uM) and simvastatin (0.2uM) to decrease ROCK activation and IL-17 and IL-21 production by cord blood $CD4^+$ T cells cultured under T_H-17-skewing conditions (5ng/mL TGFb, 10ng/mL IL1-b, 20ng/mL IL-6, 50ng/mL IL-23, 5ug/mL anti-IL-4 and 10ug/mL anti-IFN-g). We also assessed the ability of Y27632 and simvastatin to diminish IL-17 and IL-21 production by stimulated SLE $CD4^+$T cells. ROCK activation was determined by an ELISA-based ROCK activity assay. Plasma levels of IL-17, IL-21, and CCL20 were measured by ELISA. qPCR was used to determine gene expression of IRF4. All patients (N=24) met ACR criteria for SLE. Demographics and clinical features were as follows: mean age 37 ± 11 years, 96% female, 8% Asian, 21% African American, 21% Caucasian, 50% Hispanic, SLEDAI score 6 ± 4, and 42% with nephritis.

Results: Compared to T_H0 cells, cord blood $CD4^+$ T cells cultured under T_H-17-skewing conditions exhibited elevated ROCK activity that was inhibited by both Y27632 and simvastatin. IL-17 production was decreased by 60% in cord blood T_H-17 cells treated with either inhibitor. IL-21 production was decreased by 83% (90uM Y27632) and 65% (0.2uM simvastatin) in cord blood T_H-17 cells. Neither Y27632 nor simvastatin decreased IRF4 gene expression suggesting that their effects on IL-17 and IL-21 were not secondary to effects on cell viability. Both Y27632 and simvastatin decreased IL-17 and IL-21 cytokine production by purified SLE $CD4^+$T cells but neither treatment altered IFN-g protein production. We also confirmed our

previous findings that in a subset of SLE patients PBMCs showed elevated ROCK activity compared to PBMCs from healthy controls. In this new cohort, the majority (79%) of the SLE patients had ROCK values that were at least 2SD above the mean ROCK value for the healthy controls.

Conclusion: These data indicate that the production of IL-17 and IL-21 by SLE T cells can be selectively inhibited by targeting the RhoA-ROCK pathway providing a rationale to inhibit the ROCKs as a means to reverse T cell dysfunction in SLE.

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Identifying Novel Lupus Severity Risk Variants through Identification of Alleles with High Ethnic Variability Worldwide. Belinda A. Waltman[1], Kimberly E. Taylor[1], Julio Molineros[2], Sarah French[1], Joanne Nitiham[1], Jennifer Kelly[2], Adam Adler[2], Judith A. James[2], Swapan Nath[2], Marta Alarcon-Riquelme[2] and Lindsey A. Criswell[1]. [1]University of California, San Francisco, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, San Francisco, CA, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Substantial epidemiologic evidence demonstrates that SLE disproportionately affects minority patients in terms of incidence, prevalence, and disease severity. European ancestry has been associated with a lower risk of developing renal disease in SLE. We developed an approach to identify novel SLE risk variants that may influence disease severity by searching for single nucleotide polymorphisms (SNPs) with high ethnic variability worldwide and testing them in our multiethnic SLE cohort.

Methods: The Human Genome Diversity Project (HGDP) characterized the allele frequency of 650,000 SNPs in 938 people from 53 populations worldwide. Our multiethnic cohort of SLE patients was genotyped on the Illumina Immunochip (I-chip), covering over 160,000 SNPs across 185 autoimmune genes plus select non-autoimmune genes and ancestry informative markers. There were 32,907 SNPs common to the HGDP and I-chip. We selected the top 2% of those SNPs that met both an absolute mean frequency difference and a t-test criteria between Europeans and Non-Europeans. We tested these SNPs in our multiethnic cohort of 1427 SLE patients for severe disease outcomes (renal disease by ACR renal criterion, severe renal disease on biopsy or end-stage renal disease, and production of dsDNA antibodies) stratified by ethnicity: Caucasian, African American, Hispanic, and Asian. Logistic regression was performed, adjusting for disease duration and gender. Ethnic strata were refined via STRUCTURE analysis of 878 I-chip SNPs, excluding subjects with substantial ancestry outside of their self-identified ethnicity.

Results: This approach identified 13 SNPs with ethnicity-disease outcome associations (unadjusted p value < 0.001). Two SNPs, rs2099365 and rs2163882, which are in high linkage disequilibrium (LD) ($r2 = 0.98$) in Hispanics, also had significant false discovery rate p values (0.014) for association of renal disease in Hispanics (odds ratio 2.90). Both SNPs are 20kb from the 3' end of the endomucin (EMCN) gene, a glycoprotein involved in cell adhesion. These SNPs are predicted to disrupt 3–4 regulatory motifs. The EMCN gene is a non-autoimmune gene on the I-chip, not previously associated with SLE, but recently reported to be associated with susceptibility to RA. The association of the 2 SNPs with renal disease in Hispanics is consistent with an estimated 5.7 odds of renal disease per 100% Amerindian ancestry ($p = 3.5e\text{-}06$) compared to 0.23 odds per 100% European ancestry ($p=1.1e\text{-}22$) based on I-chip data. To validate the EMCN association results, we examined available EMCN gene SNPs in a large cohort of Hispanic patients, confirming an association with renal disease (5 SNPs with p values < 0.001, most significantly 4.5e-05).

Conclusion: Here we describe an approach to identify novel SLE severity risk variants. Testing these candidate alleles in our multiethnic SLE cohort identified 2 SNPs in high LD that were significantly associated with renal disease among Hispanic SLE patients. These SNPs are near the EMCN gene, a gene never before associated with SLE. Additional investigation is warranted to further validate these results and better characterize the association of this gene with renal disease in SLE.

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An Anti CD123 Monoclonal Antibody (CSL362) Depletes Plasmacytoid Dendritic Cells and Inhibits CpG Upregulated IFNα Production and IFNα-Inducible Gene Expression in Peripheral Blood Mononuclear Cells from Patients with Systemic Lupus Erythematosus. Shereen Oon[1], Nicholas Wilson[1] and Ian Wicks[2]. [1]The University of Melbourne, Melbourne, Australia, [2]The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia.

Background/Purpose: Plasmacytoid dendritic cells (pDCs) contribute to systemic lupus erythematosus (SLE) pathogenesis by producing Type 1 interferon (IFN), most likely induced by endosomal Toll like receptor (TLR) activation by immune complexes. In healthy donors, pDCs are known to express high levels of CD123, the IL3 receptor alpha chain. CSL362 is a novel monoclonal antibody (mAb) that binds to CD123, neutralizing IL3 signaling and causing antibody dependent cell mediated cytotoxicity (ADCC) of CD123 bearing cells. This study of SLE and healthy donors evaluates - 1) CD123 expression on pDCs and other cell types, 2) CSL362 mediated depletion of pDCs, and 3) the effect of CSL362 on IFNα production and IFNα-inducible gene expression from peripheral blood mononuclear cells (PBMCs) *in vitro*.

Methods: Quantitative flow cytometry with Quantibrite PE beads and an anti-CD123-PE antibody was used to assess CD123 expression on cell types from peripheral blood of SLE and healthy donors ($n=15$). PBMCs from SLE ($n=13$) and healthy ($n=10$) donors were isolated by Ficoll gradient centrifugation and incubated for 24 hours *in vitro* with CSL362, the Fab portion of CSL362 (Fab', which neutralizes IL3 signaling, but does not effect ADCC), or an isotype control mAb. The percentage of viable pDCs was enumerated by flow cytometry. PBMCs from SLE ($n=7$) and healthy ($n=6$) donors were pretreated with CSL362, Fab' or isotype control mAb for 24 hours, then stimulated with CpG, a TLR9 agonist, for 18 hours. IFNα production from culture supernatant was assessed by ELISA. A novel 'IFN gene score', based on 11 IFNα-inducible genes, was incorporated into a customized gene array, to serve as a 'gene signature' to stratify patients and assess drug efficacy. This score was evaluated by performing quantitative PCR on RNA extracted from SLE ($n=17$) and healthy ($n=9$) donor whole blood. The average of the log2 fold change for the 11 genes in the SLE patients was compared to healthy donors. This score was also evaluated in PBMCs ($n=2$ SLE, $n=2$ healthy) after CSL362 pretreatment followed by CpG stimulation. The average of the log2 fold change for the 11 genes of the treated samples was compared to the untreated samples.

Results: CD123 expression levels were highest on pDCs compared to other cell types. pDCs were depleted after *in vitro* culture with CSL362 ($8.3 \pm 2.4\%$ [mean $\pm$ SEM], $p < 0.0001$) compared to isotype control but were not depleted by Fab' ($96.8 \pm 5.5\%$, $p = 0.17$). In addition, CpG-induced IFNα production from PBMC was inhibited by CSL362 pretreatment ($1.1 \pm 0.8\%$, $p < 0.0001$) compared to isotype control, but was not inhibited by pretreatment with Fab' ($122.3 \pm 27.7\%$, $p = 0.78$). The IFN gene score was elevated in SLE (3.31 ± 0.46) compared to healthy (1.49 ± 1.1, $p = 0.07$) donors. CpG-induced upregulation of the IFN gene score (3.9 ± 0.9) was reduced by pretreatment of PBMC with CSL362 (-0.9 ± 1.9, $p = 0.12$).

Conclusion: A mAb targeting CD123 (CSL362) depletes pDCs and decreases CpG-induced IFNα production and IFNα-inducible gene expression from SLE and healthy donor PBMCs. These effects were not seen with IL3 blockade alone or isotype control mAb. Cytoreductive therapy with CSL362 may therefore represent a novel treatment strategy in SLE.

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SLE Patients Carrying a Disease-Associated *PTPN22* R620W Variant Show Reduced Interferon-Inducing Capacity. Yaya Wang, David Ewart, Ami Yamamoto, Emily C. Baechler, Parastoo Fazeli and Erik J. Peterson. University of Minnesota, Minneapolis, MN.

Background/Purpose: Type 1 interferons (IFN) are implicated in the pathogenesis of systemic lupus erythematosus (SLE). Increased expression of IFN-regulated genes, termed the IFN-signature, correlates with autoantibodies and disease activity in SLE. Likely sources of type 1 IFN in SLE include plasmacytoid dendritic cells (pDC), which produce IFNα following Toll-like receptor 7 (TLR7) activation. A coding variant in the protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*) gene is associated with SLE. *PTPN22* encodes lymphoid tyrosine phosphatase (Lyp). We showed previ-

ously that Lyp is required for TLR-driven type 1 IFN production in myeloid cells. Variant *PTPN22* encodes an R620W bearing protein ("LypW"). We recently established that LypW is associated with impaired TLR-driven type 1 IFN production and type 1 IFN-dependent immunity. However, the functional consequences of LypW carriage in human SLE patients remain unclear. The current study was designed to address the effect of LypW carriage on interferogenic TLR signaling in SLE patients.

Methods: Caucasian SLE patients satisfying 1987 ARA diagnostic criteria were genotyped for *PTPN22* LypW variant carriage. Plasma IFNα concentrations in 15 LypW carriers and 21 non-carriers were determined by ELISA. IFN gene signature in whole blood was also determined by quantitative PCR (qPCR). PBMC were stimulated with R848, a TLR7/8 agonist, and IFNα2 and TNFα expression in pDC ($Lin^{-}HLA\text{-}DR^{+}CD123^{+}$) were detected by FACS. We measured IFNα protein levels in the supernatant from R848-stimulated SLE PBMC by ELISA. We compared STAT1 activation in SLE PBMC from carriers and non-carriers by phospho-flow.

Results: In both LypW carrier and non-carrier SLE patients, we observed comparable IFNα protein in plasma and type 1 IFN gene "signatures" in whole blood. We found that the percentage of pDC that produce IFNα2 after R848 simulation was significantly reduced in LypW carrier SLE patients, while the percentage of pDC producing TNFα was comparable to that observed in non-carrier patients. Further, we observed that IFNα2 expression in pDC was decreased in LypW carriers. Supernatant IFNα protein levels from R848-stimulated PBMC were significantly reduced in LypW carriers. Moreover, activation of type 1 IFN-driven STAT1 was impaired in LypW carrier PBMC after R848 stimulation.

Conclusion: LypW carrier SLE patients have reduced capacity for TLR-induced type 1 IFN production, even as they exhibit elevated whole blood type 1 IFN signatures similar to those observed in non-carrier patients. The findings suggest that LypW carriage may identify a subset of SLE patients who harbor defects in type 1 IFN-dependent host defense or anti-inflammatory functions.

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Intracellular Complement C3 Is Exposed on the Cell Surface upon Apoptosis Induction and Participates in the Clearance of Apoptotic Cells By Phagocytes. Lucrezia Colonna[1], Christian Lood[1], YuFeng Peng[1], Xizhang Sun[1], Lena Tanaka[1], Sandip Panicker[2] and Keith B. Elkon[1]. [1]University of Washington, Seattle, WA, [2]True North Therapeutics, South San Francisco, CA.

Background/Purpose: The complement system has been viewed as a predominantly serum-derived host defense mechanism with multiple functions, including clearance of apoptotic cells. Defective function of the complement pathways have been implicated in the pathogenesis of systemic lupus erythematosus (SLE). Recently, intracellular complement C3 storage was demonstrated in many different cell types, and C3 activation products were shown to participate in the survival and effector cell differentiation of murine and human lymphoid cells. Despite the known role of serum-derived C3 activation products in the removal and immunosuppressive properties of dying cells, the role of intracellular C3 in clearance of apoptotic cells has never been explored. Thus, we asked whether human cells expose C3 and/or C3 activation products on their surface upon cell death induction, and whether such exposure functionally participates in their phagocytic clearance, independently of serum complement factors.

Methods: Apoptosis and secondary necrosis of human lymphoid cells was induced by both UV irradiation and serum starvation. C3/C3b/C3bi surface and intracellular expression on live and apoptotic human T and B primary cells as well as cell lines was monitored by flow cytometry (FACS), western blot and confocal microscopy. Macrophages were derived from circulating CD14+ monocytes by culture with M-CSF. Phagocytosis of apoptotic cells in presence or absence of serum was quantified by microscopy (phagocytic index) and by FACS with the aid of fluorescently labeled apoptotic cells.

Results: We observed that live human primary T and B cells, and human T and B cell lines expressed intracellular but not cell surface C3/C3bi. However, upon apoptosis induction, C3 activation products were exposed on the surface of dying cells in a time dependent manner. Detection of C3/C3bi correlated with later stages of apoptosis characterized by cell shrinkage and loss of membrane integrity (Annexin V+ PI+ cells). Confocal microscopy of unfixed cells revealed detection of C3/C3bi in a granular distribution, possibly in blebs and/or other endosomal compartments. To determine whether surface exposed C3/C3bi had functional relevance, we blocked the macrophage C3bi receptors CR3 and CR4 with antibodies, and compared phagocytosis of apoptotic cells in the absence of serum. Strikingly, functional blockade of CR3 and CR4 on human macrophages in the absence of serum specifically reduced the uptake of C3bi+ late apoptotic cells, and not that of latex beads (with an inhibition of 19.3% for CR3, 24.1% for CR4, and 48% for CR3+CR4 blockade; p= 0.182, 0.066; and 0.043, respectively).

Conclusion: Our results suggest that we have uncovered a novel function of intracellular complement C3 activation products in the removal of dying cells. C3 is a very large protein of 185,000 molecular mass and penetration into tissues is likely to be limited. Cell intrinsic, serum-independent, C3-mediated clearance of apoptotic cells may therefore be of particular relevance in tissues where there is accumulation of dead cells as observed in patients with SLE, as well as under other conditions such as hypoxia reperfusion injury and stroke.

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ACR Concurrent Abstract Session
T cell Biology and Targets in Autoimmune Disease
Tuesday, November 18, 2014, 2:30 PM–4:00 PM

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Altered Plasticity of Inflammatory CD4 T Cells Contributing to Th17 Shift in Rheumatoid Arthritis. Jan Leipe, Fausto Pirronello, Simon Hermann, Matthias Witt, Hendrik Schulze-Koops and Alla Skapenko. University of Munich, Munich, Germany.

Background/Purpose: Whereas T helper (Th) cell subsets were previously regarded as irreversibly differentiated endpoints, evidence suggests that Th cell differentiation is a plastic process in response to appropriate stimulation. Mechanisms leading to the pathogenetic important predominance of Th17 cells in rheumatoid arthritis (RA) are not yet understood. We hypothesized that an altered T cell plasticity contributes to the shift towards the Th17 phenotype in RA.

Methods: A unique cohort of 35 patients with early, active and untreated RA (to exclude effects of immunosuppressive drugs on T cells) and 33 age- and sex- matched healthy controls (HC) were studied. Viable *in vivo*-originated Th1, Th2 and Th17 cells were FACS-sorted and trans-differentiated under Th1-, Th2- or Th17-inducing conditions. The cytokine secretion profile of the trans-differentiated cells was assessed by flow cytometry. Analysis of histone modifications in *IL17* and *RORC* gene loci was performed by ChiP assay. The relative expression of cytokine and transcription factor genes was measured by qRT-PCR.

Results: Of interest, Th17 cells from RA patients demonstrated a strikingly diminished re-differentiation capacity into both Th1 and Th2 directions. Under Th1 conditions, RA Th17 cells retained significantly more IL-17-producing cells, whereas frequencies of newly generated Th1 cells in RA were diminished. Similarly, under Th2 conditions, frequencies of newly generated Th2 cells were significantly reduced in RA. Vice versa, RA Th1 and Th2 cells demonstrated an enhanced capacity to re-differentiate into Th17 cells. In order to analyze underlying mechanisms leading to increased re-differentiation of Th1 to Th17 cells in RA, expression of RORC was investigated. We found that *RORC* expression was higher after re-differentiation of Th1 cells. Moreover, in the *IL17* and *RORC* loci an overrepresentation of the permissive histone modification H3 actetylation over the repressive H3K27 methylation was found in T cells from RA patients. Investigation of the SGK1/ FOXO1/ IL23R pathway, known to be important for Th17 stability, revealed higher expression of SGK1 and IL23R in RA after re-differentiation of sorted Th1 cells.

Conclusion: Together these data indicate that in RA *in vivo*-originated Th17 cells are resistant to changes in their phenotype, whereas other Th subsets are prone to Th17 cell re-differentiation. Increased RORC expression and the presence of a permissive histone modification state at the RORC gene locus might contribute to the altered Th plasticity in RA, thereby forcing Th17 cell-mediated immunity of the disease.

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CaMK4 Inhibition Ameliorates the Development of Th17 Driven Inflammatory Diseases By Preventing Recruitment of IL-17 Producing Cells to Target Organs. Tomohiro Koga[1], Kotaro Otomo[2], Masayuki Mizui[2], Nobuya Yoshida[2], José C. Crispin[2], Atsushi Kawakami[1] and George C. Tsokos[3]. [1]Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [3]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA.

Background/Purpose: IL-17 producing T helper (Th17) cells have been closely associated with the development of organ damage in inflammatory and autoimmune diseases. We have previously reported that Calcium/calmodulin-dependent protein kinase IV (CaMK4) plays a crucial role in Th17 cell differentiation *invitro* and *invivo* and suggested that CaMK4 inhibition ameliorates clinical and pathological findings in experimental autoimmune encephalomyelitis (EAE) and MRL/*lpr* mice (1). We have also shown that Il-17 is important in the expression of anti-glomerular basement membrane Ab-induced glomerulonephritis (AIGN) (2). However, the effect of CaMK4 on recruitment of pathogenic T cells to target tissues in inflammatory settings has not been studied.

Methods: To determine the role of CaMK4 in the infiltration of inflammatory cells to target tissues, we induced experimental AIGN in *Camk4* sufficient or deficient mice and compared the kidney injury including the number of IL-17 producing cells in both groups. We also evaluated the effect of KN-93, a compound of CaMK4 antagonist in this AIGN model.

Results: *Camk4* deficient mice displayed less glomerular injury and less proteinuria at day 14 and at day 21 after induction of AIGN. Kidney infiltration by Th17 producing CD4 T cells was decreased significantly in *Camk4* deficient mice, suggesting that CaMK4 facilitated AIGN damage by promoting local inflammatory cells accumulation. In line with these observations, KN-93 treatment improved clinical and pathological finings in mice induced AIGN at dose dependent manner.

Conclusion: Collectively, our results indicate that CaMK4 inhibition might be a novel therapeutic strategy of Th17 cells-mediated inflammatory diseases.

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Survivin Co-Ordinates Formation of Follicular T-Cells in Rheumatoid Arthritis. Maria Bokarewa[1], Karin Andersson[2], Malin Erlandsson[2], Mattias Svensson[2], Nicola Cavallini[3] and Mikael Brisslert[2]. [1]University of Goteborg, Goteborg, Sweden, [2]University of Gothenburg, Gothenburg, Sweden, [3]University of Göteborg, Göteborg, Sweden.

Background/Purpose: Survivin is a proto-oncogene that regulates cell division and apoptosis. Recently, survivin has emerged as a biomarker of persistently active and joint destructive rheumatoid arthritis (RA). High serum levels of survivin are frequently associated with antibodies against cyclic citrullinated epitopes (ACPA).

Here we study the role of survivin in the formation of follicular T-cells and in the antibody production in RA.

Methods: The intracellular expression of survivin and Bcl-6 was studied in RA patients (age 21–71 years, disease duration 1–49 years) by flow cytometry and qPCR. DNA binding of survivin and Bcl-6 was studied in stimulated PBMC by chromatin immunoprecipitation.

The effect of survivin modulation on the follicular T-cells and on production of antigen-specific and autoantibodies was studied in collagen-immunized arthritis (CIA) mice, where Survivin transcription was inhibited by shRNA-lentiviral construct (shSurv, 10^6–10^7 particles/mouse). In separate experiments, CIA mice were vaccinated with survivin-peptides before the CII immunization. Control CIA mice received non-targeting transduction particles or were vaccinated with irrelevant peptides.

Results: The sSurv+RA group (n=76) was characterized by higher frequency of RF+ and ACPA+ patients, as well as by higher levels of ACPA compared to sSurv-RA (n=68). Intracellular survivin was present in the effector (CD45RA+CD27-) CD4+ T cells. Survivin co-expressed with Bcl-6 on lymphocytes of arthritic mice and in RA patients. Bcl-6+ subset comprised 7–38% of surv+CD4+ T-cells and was also CXCR5+. Bcl6+Surv+ subset of CD4 T cells and mRNA levels of Bcl-6 were lower in blood of sSurv$^+$patients.

Follicular (CXCR5+PD-1+) CD4 population in spleen and lymph nodes of arthritic DBA1 mice were mostly surv+Bcl6+. Mice vaccinated with survivin-derived peptides developed the phenotype similar to sSurv+RA patients and had high serum levels of survivin and higher levels of aCII and RF antibodies. Surv-vaccinated mice had significantly increased survivin expression and the subset of surv+Bcl-6+ within CXCR5+CD4+ cells in LN. shSurv-treated mice had reduced CD4+surv+ and CD19+surv+ populations in spleens, and smaller CXCR5+CD4+ and CXCR5+B220+ populations, while Bcl-6 gene transcription was increased. Inhibiting survivin led to lower levels of anti-CII antibodies and lower RF, suggesting insufficient Bcl-6 and poor Tfh development. Chromatin immunoprecipitation showed that survivin binds within Bcl-6 responsive element of Blipm-1 promoter potentially controlling transcriptional activity of Bcl-6.

Conclusion: In this study we demonstrate that RA patients have co-expression of survivin and Bcl-6 in the follicular T helper cells. Changes in survivin transcription modulate formation and function of the follicular T cells by regulating transcriptional activity of Bcl-6, essential factor of germinal center formation and autoantibody production.

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T-Cell Signaling Defects Can be Corrected By Manipulating 'TCR Signal Fine-Tuning Molecules' That Are Altered Due to Increased Ubiquitination in Systemic Autoimmune Disease. Julia Pinkhasov and Ram Raj Singh. UCLA, Los Angeles, CA.

Background/Purpose: T-cell selection in the thymus is primarily determined by the avidity of T cell receptor (TCR) for self-ligand-MHC. Since this process is dependent on the somatically generated receptors against the internal antigenic environment, all T-cells are inherently self-reactive to some degree. Hence, a signaling threshold must be established whereby overtly high self-avidity, potentially pathogenic, T-cells are removed, while allowing other lower self-avidity T-cells to survive. Using a avidity-based TCR transgenic model system, we found that besides the TCR, there are other signal regulating molecules that play a role in establishing signal threshold during a process known as TCR *tuning*, which modulates the intensity of TCR signaling (Pinkhasov et al, manuscript in preparation). Here, we determined the expression of potential TCR signal *fine-tuning* (TFT) molecules in a model of multi-system autoimmune disease, and investigated their role in T-cell signaling defects and mechanisms of their alteration.

Methods: The availability of murine strains that develop autoimmune disease resembling human SLE enables one to study the preclinical events in the pathogenesis. Here, we used MRL/MpJ-*Fas*$^{+/+}$ (MRL+/+) mice that develop SLE at 8–10-months of age, congenic MRL/MpJ-*Fas*$^{lpr/lpr}$ (MRL/lpr) mice that develop accelerated SLE due to a mutation of the *fas* gene, and MHC-matched C3H control mice. To analyze TFTs in antigen-specific T cells, studies were repeated in MRL/lpr, MRL+/+ and healthy B10.BR mice carrying the *AND* TCR transgene.

Results: We found the altered expression patterns of a battery of TFTs on thymocytes from MRL/lpr and MRL+/+ mice compared to C3H controls; specifically, negative regulator TFTs were reduced, while a positive regulator was increased. Thymocytes from young MRL+/+ and MRL/lpr mice showed increased activation and phosphokinase signal upon ex vivo stimulation, which were restored to near normal levels in the presence of a CD5 agonistic antibody. Unexpectedly, we observed a drastic reduction of TFTs in activated peripheral T-cells after disease onset. The reduced levels of negative TFTs correlated with increased responsiveness to TCR stimulation and to weak antigenic ligands. The reduced expression of TFTs in periphery was not due to their decreased transcripts, but rather, to activation-induced post-translational modification due to increased ubiquitination leading to targeted protein degradation. This was associated with an altered expression of E3 ubiquitin ligases *cbl-b*, *traf6*, *grail* and *itch* in MRL mice.

Conclusion: These results suggest that T-cells are able to tune the expression levels of TFTs post-development, likely by targeted protein degradation using the ubiquitin cycling pathway. We propose that the ability of T-cells to alter their internal signal threshold by altering TFT expression is a novel mechanism for

T-cells to escape peripheral tolerance and perpetuate autoimmune disease. Restoration of TCR signals to normal upon increased signaling through a TFT raises hope for a new avenue of treating systemic autoimmune diseases.

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Involvement of CD8$^+$ T Cells in the Pathogenesis of Giant Cell Arteritis and Polymyalgia Rheumatica. Maxime Samson[1], Sylvain Audia[1], Malika Trad[2], Marion Ciudad[2], Hervé Devilliers[3], Alexandrine Gautheron[2], Valérie Quipourt[4], Francois Maurier[5], Nadine Meaux Ruault[6], Patrick Manckoundia[4], Paul Ornetti[7], Jean-Francis Maillefert[8], Jean-François Besancenot[3], Christophe Ferrand[9], Philippe Saas[9], Laurent Martin[10], Nona Janikashvili[2] and Bernard Bonnotte[1]. [1]INSERM UMR 1098, Besançon ; University of Burgundy, Faculty of Medicine, IFR100 ; Department of Internal Medicine and Clinical Immunology, Dijon, France, [2]INSERM UMR 1098, Besançon, Dijon, France, [3]Department of internal medicine and systemic diseases, Dijon, France, [4]Department of Geriatric Internal Medicine, Dijon, France, [5]Department of Internal Medicine, Metz, France, [6]Department of Internal Medicine, Besançon, France, [7]Department of Rheumatology, Dijon, France, [8]University Hospital Dijon, Dijon, France, [9]INSERM UMR1098, Besançon, France, [10]INSERM UMR 1098, Besançon ; University of Burgundy, Faculty of Medicine, IFR100 ; Department of Pathology, Dijon, France.

Background/Purpose: Previous studies have demonstrated the implication of CD4$^+$ T cells, especially T helper (Th1) and Th17 cells, in the pathogenesis of giant cell arteritis (GCA) and polymyalgia rheumatica (PMR). However, very little is known concerning CD8$^+$ T cells. This study aimed to investigate their implication in the pathogenesis of GCA and PMR.

Methods: Thirty patients suffering from GCA (n=23) or PMR (n=7) and 21 age-matched healthy volunteers were enrolled. Blood samples were collected at diagnosis and after 3 months of glucocorticoid (GC) treatment. Percentages of circulating cytotoxic T lymphocytes (CTL) (CD3$^+$CD8$^+$Perforine$^+$ GranzymeB$^+$), Tc1 cells (CD3$^+$CD8$^+$IFN-γ^+), Tc17 cells (CD3$^+$CD8$^+$IL-17$^+$) and the expression of CD63, HLA-DR, CCR5, CCR6, CCR7, CD62L and CXCR3 by CD8$^+$ T lymphocytes were assessed by flow cytometry analysis. Levels of soluble Granzyme A, Granzyme B, CCL2, CCL20, CXCL9, CXCL10 and CXCL11 were determined by ELISA or Luminex® technology. Temporal artery biopsies (TAB) were stained for CD3, CD4 and CD8. Data are expressed by mean±SEM and *P* value is the result of the Mann Whitney U test or Wilcoxon matched-pairs signed rank test, when appropriate.

Results: Percentages of circulating CTL and Tc17 in total CD8$^+$ T cells were significantly increased in patients compared to controls: 36.6±4.1 vs. 16.3±3.1% (P=0.0004) and 0.59±0.11 vs. 0.15±0.03% (P<0.0001), respectively. The level of Tc1 cells was not different between two groups. CD63 expression, that is expressed at the membrane once CTL have degranulated, was higher in patients than in controls (29.3±3.5 vs. 14.8±2.9%; P=0.003). Levels of Granzyme A and B were also significantly increased in the serum of patients when compared to controls: 20.6±4.4 vs. 11.6±2.7 pg/mL (P=0.02) and 3.2±1.3 vs. 0.95±0.49 pg/mL (P=0.004), respectively. After 3 months of GC treatment, percentages of circulating CTL, Tc17 and soluble levels of Granzyme A and B were significantly decreased, whereas the percentages of Tc1 and CD63$^+$cells in total CD8$^+$ T lymphocytes remained stable. Expression of chemokine receptors was comparable between patients and controls except for CXCR3 that was expressed at a higher level by CD8$^+$ T cells from patients: 48.1±3.6 vs. 28.5±3.5% (P=0.0004). Levels of CXCR3 ligands were increased in the serum of patients compared to controls: 629.8±194.7 vs. 92.81±19.2 pg/mL (P<0.0001) for CXCL9, 31.4±6.9 vs. 9.2±1.5 pg/mL (P<0.0001) for CXCL10 and 12.0±4.1 vs. 3.5±2.7 pg/mL (P=0.0094) for CXCL11. Importantly, the levels of these 3 chemokines were decreased after 3 months of GC treatment. Immunohistochemical analyses of TAB (5 GCA patients) revealed a strong infiltration by CD4$^+$ and CD8$^+$ T cells in all the layers of the artery.

Conclusion: This study provides the first data that demonstrate an implication of CD8$^+$ T cells in the pathogenesis of GCA and PMR. In untreated patients, CD8$^+$ T cells, that infiltrate lesions of vasculitis, have an activated phenotype that is partly corrected by GC treatment. CXCR3 is upregulated on CD8$^+$ T cells from GCA and PMR patients while levels of CCL9, −10 and −11 are increased in the serum of patients, which argues for the implication of CXCR3 in the homing of CD8$^+$ T cells in the lesions of GCA.

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MiR-125a Is Critical Regulator for Controlling Autoimmunity in Multiple Autoimmune Diseases through Stabilizing Treg Mediated Immune Homeostasis. Wan Pan[1], Shu Zhu[1], Dai Dai[1], John Harley[2] and Nan Shen[1]. [1]Institute of Health Sciences, Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS) & Shanghai Jiao Tong University School of Medicine (SJTUSM), Shanghai, China, [2]The Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America, Cincinnati, OH.

Background/Purpose: Although different autoimmune diseases show distinct clinical phenotypes, common cellular and molecular immune pathways have been shown to be intimately involved in the autoimmune pathogenesis. Treg cells suppress inflammation and maintain immune homeostasis. Impairment of the development and function of Treg cells is a common immune defect that contributes to the development of multiple autoimmune diseases. MicroRNAs as novel epigenetic regulator of immune response play critical role on T cell mediated immune regulation. In this study we focus on defining the cellular and molecular mechanisms underlying microRNA(miR) mediated dysregulation of Treg cells on multiple autoimmune diseases and explore therapeutic potentials of miRs based intervention for re-program immune homeostasis on these disease relevant mouse models.

Methods: miR profiling for CD4+ T cells of multiple autoimmune diseases and their relevant mouse models were done by ABI miR array. miR125a KO and transgenic mice have been generated for testing Treg cell phenotype and function. EAE and T-cell mediated colitis models were conducted on both genetically modified mice and B6 controls mice for evaluating role of miR125a on Treg cell mediated tissue inflammation. mRNA profiling, IPA bioinformatics tool and several microRNA databases were used for miR targets predication. 3UTR report gene assay, western blot and FACS were used for miR125a targets's validation. We administrated miR 125a agomir(chemical modified miRNA mimics) into EAE and Lpr/MRL mice for evaluating its efficacy.

Results: Frist we identified a commonly down-regulated miRNA, miR-125a, in peripheral CD4+ T cells of multiple autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, and Crohn's diseases, as well as their relevant mouse models. Although the common dysregulation implied a shared mechanism of autoimmune pathogenesis, a function for miR-125a in either driving or constraining autoimmune pathology was still unclear. By using miR-125a deficient mice, we identified miR-125a as a key regulator that stabilizes the commitment and immunosuppressive capacity of Treg cells by restraining the differentiation programs of effector lineages, thus contributing to the suppression of inflammation, as well as the maintenance of immune homeostasis. Deficiency of miR-125a may ultimately result in more severe pathogenic consequences of T-cell mediated colitis and EAE development. Analysis of the genome-wide targets of miR-125a revealed that it suppressed several effector T cell factors that are detrimental to Treg cell differentiation, including Stat3, Il13 and Ifng. Moreover, manipulation of miR-125a level by chemically synthesized analogue of miR-125a showed therapeutic potentials to re-program the immune homeostasis and contributed to certain disease prevention or treatment in clinically-relevant animal models.

Conclusion: Our finding identify miR-125a as a commonly down-regulated miRNA critical for controlling autoimmune diseases through stabilizing Treg mediated immune homeostasis by repressing effector programs. miR-125a could be promsining therapeutic traget for treating multiple Treg cells mediated autoimmune diseases.

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The Relationship of ARMS2 Genotype with Idiopathic Inflammatory Vasculitis. Christopher Mecoli[1], Fan Wang[2], Christopher Pappas[3], Peter C. Grayson[4], David Cuthbertson[5], Simon Carette[6], Christian Pagnoux[6], Gary S. Hoffman[7], Nader A. Khalidi[8], Curry L. Koening[9], Carol A. Langford[10], Carol

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Background/Purpose: Patients with age-related macular degeneration (AMD), a leading cause of irreversible blindness, have a 10-fold increased prevalence of abdominal aortic aneurysms. Single nucleotide polymorphisms (SNPs) in a number of genes, including Complement Factor H (CFH) on chromosome 1 and age-related macular susceptibility protein 2 (*ARMS2)* and HTRA Serine Peptidase 1 *(HTRA1)* on chromosome 10, are strongly associated with increased risk for developing AMD. These AMD-associated loci are also strongly associated with vasculopathies, including choroidal neovascularization, polypoidal choroidal vasculopathy, and retinal angiomatous proliferation in both Caucasians and Japanese. These finding raise intriguing possibilities of a potential association between vascular pathology and AMD-associated genes. This study tested the hypothesis that AMD-associated gene variants may also be involved in the development of vasculitis, especially the large-vessel vasculitides (LVV), giant cell arteritis (GCA) and Takayasu's arteritis (TAK).

Methods: A candidate gene study was performed to investigate the relationship between AMD-associated variants and vasculitis. In a preliminary study, SNPs within CFH (rs1061170), Complement Component 3 (*C3*; rs2230199), *IL2/IL21* (rs1065489), *ARMS2* (rs10490924) and *HTRA1* (rs11200638) were examined for association with six phenotypes of vasculitis: GCA, TAK, granulomatosis with polyangiitis (Wegener's, GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (Churg-Strauss, EGPA), and polyarteritis nodosa (PAN). Among these 5 SNPs rs10490924 had the strongest association with the vasculitides and this SNP was pursued in the full analysis. The study included samples from 1196 patients with vasculitis and 1248 healthy controls matched for age, sex, race, and ethnicity. Additive p-values were calculated for each subtype of vasculitis.

Results: The main results of the study are reported in the Table. The controls had a minor allele frequency (MAF) of 21% for rs10490924. Overall there was a significant association of all vasculitis types with rs10490924 (p=0.0449). Large-vessel vasculitides were significantly associated with rs10490924 (p-value of 0.0177). The GCA and MPA groups were each independently associated with rs10490924 (p-values of 0.0199 and 0.039, respectively).

Conclusion: This candidate gene study demonstrated a significant association between variants in *ARMS2* and idiopathic forms of vasculitis, including large-vessel vasculitides. While further validation is needed, this study suggests the possibility of a common pathogenesis between aortic pathology in AMD and large-vessel vasculitis.

Association of rs10490924 with Vasculitis

Type of vasculitis	Cases, n	MAF in cases	MAF in controls	Additive OR (95% C.I.)	Additive p-value
GPA	584	0.23	0.21	1.11 (0.93–1.32)	0.2478
MPA	88	0.28	0.21	1.46 (1.03–2.08)	0.0390
EGPA	133	0.2	0.21	0.92 (0.67–1.26)	0.6222
PAN	62	0.21	0.21	0.99 (0.63–1.55)	0.9522
All Non-LVV (4 Vasculitides)	*867*	*0.23*	*0.21*	*1.10 (0.95–1.29)*	*0.2086*
TAK	116	0.25	0.21	1.26 (0.92–1.72)	0.1461
GCA	213	0.25	0.21	1.43 (1.07–1.92)	0.0199
All LVV (TAK+GCA)	*329*	*0.25*	*0.21*	*1.30 (1.05–1.60)*	*0.0177*
All 6 Vasculitides	*1196*	*0.23*	*0.21*	*1.15 (1.00–1.32)*	*0.0449*

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Evaluation of KIR3DL1/KIR3DS1 Association with Behçet's Disease in Turkish Individuals. Burak Erer[1], Elaine F. Remmers[1], Masaki Takeuchi[1], Colleen Satorius[1], Duran Ustek[2], Ilknur Tugal-tutkun[3], Emire Seyahi[4], Yilmaz Ozyazgan[5], Ahmet Gul[3], Daniel L. Kastner[6] and Michael J. Ombrello[7]. [1]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [2]Institute of Experimental Medicine, Istanbul University, Istanbul, Turkey, [3]Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, [4]Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey, [5]Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey, [6]National Human Genome Research Institute, Bethesda, MD, [7]National Institute of Arthritis Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD.

Background/Purpose: The Behçet's disease (BD)-associated HLA-B type, HLA-B*51 (B*51), is a ligand for a pair of allelic killer immunoglobulin-like receptors (KIR) present on cytotoxic cells —KIR3DL1, which inhibits their cytotoxicity, and KIR3DS1, which activates their cytotoxic activity. KIRs are inherited in evolutionarily conserved haplotypes in which KIR3DL1 and KIR3DS1 are mutually exclusive. We therefore tested the hypothesis that KIR-regulated cytotoxic mechanisms contribute to BD by testing for association between the presence of KIR3DL1 and KIR3DS1 alleles in Turkish individuals.

Methods: Turkish BD patients (n = 1,900) and controls (n = 1,779) were genotyped for the KIR3DL1 and KIR3DS1 alleles with two sequence-specific PCR assays. Genotypes of 6,994 SNPs from the HLA region were determined with the Immunochip (Illumina) and used to impute the individuals' HLA types using SNP2HLA and a reference panel of 5,225 European individuals. A chi squared test for association was used to evaluate the contribution of KIR3DL1 and KIR3DS1 to BD. A P-value less than 0.05 was considered significant.

Results: Classical HLA types were determined by imputation in all samples and types with posterior probability greater than 0.9 were included in analyses. KIR3DL1 and KIR3DS1 genotypes were determined for 1799 of the cases and 1710 of the controls. In these subjects, presence of the killing activating KIR3DS1 allele did not differ significantly between cases and controls (42.7% vs 41.0%, P = 0.29). Furthermore, the activating allele did not appear to interact with HLA-B alleles. It was present at similar frequencies in B*51-positive cases and controls (44.3% vs 43.0%, P = 0.63), in Bw4-positive cases and controls (43.0% vs 41.1%, P = 0.31), and in cases and controls bearing the Bw4 motif with isoleucine at position 80 (43.7% vs 41.4%, P = 0.32). Similarly, no disease association was found for the inhibitory KIR3DL1 allele in all the samples or in any of the HLA-B subsets.

Conclusion: We found no association of BD with the presence of the KIR3D activating (KIR3DS1) or inhibitory (KIR3DL1) receptors, which together regulate cytotoxic cell activity through binding of a subset of HLA class I molecules, including the BD-associated HLA-B*51. Due to the complexity of this locus (i.e. sequence variation, copy number variation), lack of association between BD and the presence/absence of KIR3DS1 or KIR3DL1 does not exclude a role for KIRs in the pathogenesis of BD. Further studies of KIR3DL1/KIR3DS1 types and copy number variants, as well as of other KIRs, are warranted.

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Comparative Study of Infliximab Versus Adalimumab in Patients with Refractory Uveitis Due to Behçet's Disease. Multicenter Study of 125 Cases. Leyre Riancho-Zarrabeitia[1], Vanesa Calvo-Río[1], Ricardo Blanco[1], Paz Rodríguez-Cundín[1], Emma Beltrán[2], Juan Sánchez Bursón Sr.[3], Marina Mesquida[4], Alfredo Adan[4], M. Victoria Hernández[5], Marisa Hernandez Grafella[6], Elia Valls Pascual[7], Lucía Martinez-Costa[8], Agusti Sellas-Fernandez[9], Miguel Cordero-Coma[10], Manuel Díaz-Llopis[11], Roberto Gallego[11], Jose Luis García Serrano[12], Norberto Ortego-Centeno[13], Jose M Herreras[14], Alejandro Fonollosa[15], Angel M. Garcia-Aparicio[16], Olga Maiz

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Background/Purpose: To compare the efficacy of infliximab (IFX) versus adalimumab (ADA) as first biologic drug in refractory uveitis due to Behçet's disease (BD) for 1-year period.

Methods: Multicenter study of patients with BDxs uveitis refractory to conventional treatment including high-dose corticosteroids and at least one standard immunosuppressive agent. IFX (3–5 mg/kg at 0, 2, and 6 weeks and then every 4–8 weeks) was used in 75 cases and ADA (usually 40 mg every 2 weeks) in 50 cases. The main comparative outcome measures were improvement of visual acuity (VA) (at least 20%), complete inactivity of anterior chamber inflammation, vitritis, and retinal vasculitis as well as macular thickness <250 microns. A bivariate and logistic regression analysis was performed for every previous outcome between ADA vs IFX (SPSS20.0 package).

Results: We studied 125 patients (223 affected eyes). No statistically significant differences at baseline were observed between IFX vs ADA groups in sex (♂/♀; 41/34 vs 29/21; p=0.71), mean age (39.2±9.39 vs 36.14±12.7 years; p= 0.12), HLA-B51 positive (75% vs 75%), uveitis duration before anti TNFα onset (median [IQR]; 36 [12–71] vs 24 months [12–60]; p=0.4), VA (0.47±0.26 vs 0.52±0.27; p=0.29), anterior chamber cells (median [IQR]; 0.5 [0–2] vs 1.5 [0–2]; p=0.2), retinal vasculitis (73.2% vs 75%; p=0.95); macular thickness (285.90±90.15 vs 312.02±106.57; p=0.25), combined treatment (82.7% vs 77.6%; p= 0.481), basal degree of immunosuppression (mean±SD; 11.35± 5.67 vs 9.65±4.68; p= 0.09). After 1 year of therapy**,** ADA yielded a non-statistically significant increased frequency of improvement of VA, complete inactivity of anterior chamber inflammation, and macular thickness < 250 microns when compared with IFX. In contrast, a slight increased frequency of inactive vitritis and improvement of retinal vasculitis was observed in IFX-treated patients but the difference was not statistically significant **(Table).**

Conclusion: After 1 year of therapy ADA and IFX do not show differences in the visual outcome of patients with refractory uveitis due to BD.

Table: Treatment results at 1 year of therapy: Differences between ADA and IFX

	ADA/IFX (%)	Crude Odds ratio (95% confidence interval)	p	Adjusted Odds ratio*	p
Visual acuity improvement (>20%)	66.7%/48.2%	2.148 (0.879–5.250)	0.094	1.84	0.214
Inactive anterior chamber inflammation	67.6%/61.2%	1.324 (0.528–3.323)	0.550	1.669	0.346
Inactive Vitritis	60.5%/66.7%	0.767 (0.330–1.782)	0.537	0.867	0.765
Improvement of retinal vasculitis	85.2%/93%	0.431 (0.089–2.099)	0.298	0.340	0.217
Macular thickness < 250 microns	36.8%/21.7%	2,100 (0.539–8.185)	0.285	1.447	0.620

* adjusted for age, sex, and disease duration.

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2854

Effect of Apremilast on Quality of Life and Physical Function in Patients with Behçet's Syndrome. Gulen Hatemi[1], Melike Melikoglu[1], Recep Tunc[2], Cengiz Korkmaz[3], Banu Turgut Ozturk[4], Cem Mat[5], Peter A. Merkel[6], Kenneth Calamia[7], Lilia Pineda[8], Ziqi Liu[8], Randall M. Stevens[8], Hasan Yazici[1] and Yusuf Yazici[9]. [1]Istanbul University, Cerrahpasa Medical Faculty, Rheumatology, Istanbul, Turkey, [2]Necmettin Erbakan University, Meram Medical Faculty,Division of Rheumatology, Konya, Turkey, [3]EskiÅŸehir Osmangazi University, EskiÅŸehir, Turkey, [4]Selçuk University, Konya, Turkey, [5]Istanbul University, Cerrahpasa Medical Faculty, Dermatology, Istanbul, Turkey, [6]Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [7]Mayo Clinic Health System in Waycross, Waycross, GA, [8]Celgene Corporation, Warren, NJ, [9]New York University School of Medicine, New York, NY.

Background/Purpose: The oral ulcers in Behçet's syndrome (BS) can be painful, causing difficulty in eating and speaking, and can impair the quality of life. Apremilast is an oral phosphodiesterase 4 inhibitor that modulates inflammatory pathways. A clinical trial demonstrated a beneficial effect on oral ulcers with this agent. For this study, we aimed to assess whether apremilast is effective in improving quality of life in patients with BS.

Methods: This was a phase 2, multicenter, controlled study of 111 patients with BS, without major organ involvement but with ≥2 oral ulcers, who were randomized to apremilast 30 mg BID or placebo for 12 weeks, followed by a 12-week active-treatment period for all patients. The primary outcome, which was the number of oral ulcers at Week 12, and secondary outcomes at Week 12, including oral ulcer pain, number of genital ulcers, number of patients with a complete or partial response, number of genital ulcers, and disease activity assessed by the BS activity scale (BSAS) and Behçet's disease current activity form, have already been reported. We now report the results of health related quality of life measurements from the trial as assessed using the Behçet's disease quality of life (BDQoL) questionnaire and the 36-item Short-Form Health Survey version 2 (SF-36v2). Patients in the trial completed each of these instruments at baseline and at Week 12.

Results: The mean ± SD BDQoL score showed a significantly greater improvement from baseline at Week 12 with apremilast vs. placebo (−4.5 ± 7.61 vs. −1.6 ± 5.30; p=0.0397). The mean ± SD SF-36v2 physical

component summary scores were significantly higher (improved) at Week 12 with apremilast vs. placebo (4.72 ± 9.45 vs. −1.70 ± 7.78; P=0.0011). The mean scores were significantly improved with apremilast for the SF-36v2 subscales of physical function, bodily pain, and general health perceptions at Week 12.

Conclusion: Treatment with Apremilast improved quality of life and physical function in patients with BS.

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2855

Efficacy and Safety of Rituximab Retreatment Regimen at Clinical Relapse in Severe Cryoglobulinemic Vasculitis. Luca Quartuccio[1], Francesca Zuliani[2], Patrizia Scaini[3], Marco Lenzi[4], Antonio Tavoni[5], Marco Sebastiani[6], Teresa Urraro[7], Francesco Saccardo[8], Costanza Sbreglia[9], Pietro Pioltelli[10], Paolo Fraticelli[11], Davide Filippini[12], Salvatore Scarpato[13], Oreste Perrella[9], Armando Gabrielli[14], Dario Roccatello[15], Anna Linda Zignego[7], Clodoveo Ferri[16], Stefano Bombardieri[17], Maurizio Pietrogrande[18], Massimo Galli[19], Giuseppe Monti[8] and Salvatore De Vita[1]. [1]DSMB, University Hospital Santa Maria della Misericordia, Udine, Italy, [2]Rheumatology Clinic, University Hospital of Udine, Udine, Italy, [3]Nephrology, Spedali Civili di Brescia, Brescia, Italy, [4]University of Bologna, Bologna, Italy, [5]Rheumatology Clinic, University of Pisa, Pisa, Italy, [6]Rheumatology Clinic, University of Modena and Reggio Emilia, Modena, Italy, [7]Center for Systemic Manifestations of Hepatitis Viruses (MASVE), Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, [8]Internal Medicine Unit, Saronno Hospital, Azienda Ospedaliera di Busto Arsizio, Saronno (VA), Italy, [9]Rheumatology Unit, AO Cotugno, Naples, Italy, [10]Hematology, S.Gerardo Hospital, Monza, Italy, [11]Istituto di Clinica Medica, Università Politecnica delle Marche, Ancona, Italy, [12]Rheumatology Unit, Ospedale Niguarda Ca' Granda, Milan, Italy, [13]Rheumatology Unit, M. Scarlato Hospital, Scafati, Salerno, Italy, [14]Università Politecnica delle Marche, Ancona, Italy, [15]UNIVERSITY OF TURIN (ITALY), TURIN, Italy, [16]Univ Modena Reggio Emilia, Modena, Italy, [17]Rheumatology Unit, University of Pisa, Pisa, Italy, [18]Internal Medicine Unit, Policlinico San Marco, Bergamo, Italy, [19]Istituto di Malattie Infettive e Tropicali, Università di Milano c/o Ospedale L. Sacco, Milano, Italy.

Background/Purpose: Two independent controlled randomized trials recently reported the efficacy and safety of rituximab (RTX) monotherapy in severe cryoglobulinemic vasculitis (CV) (1, 2), with one reporting a follow-up lasting two years (1). The aim of this study is to report the very long term efficacy and safety of a retreatment regimen with RTX administered at clinical relapse after the end of the abovementioned trial (1).

Methods: Long term follow up data of a trial of RTX in severe CV (1) were analysed, by considering patients managed with retreatent with RTX at clinical relapse. During this follow-up, only RTX monotherapy was used. Number of retreatments, disease activity at last follow up, adverse events and causes of deaths were registered. Clinical response was evaluated at the last follow-up visit, as follows: i) complete response (remission), partial response (response < 50% of at least one manifestation among glomerulonephritis, severe neuropathy or skin ulcers) (1), and active disease despite treatment.

Results: After the end of the 24-month controlled trial (1), follow-up data were analysed in 30 patients, all positive for hepatitis C virus infection. The mean follow up after the beginning of RTX therapy (1) was 72.6±20.4 months, including 24 (80%) patients followed for more than 4 years and 6 (20%) patients followed for 2.4–4 years. Of them, 21 patients were still under an active follow up, 3 patients were lost from follow-up shortly after the end of the trial, and 6 patients died. Survival of RTX regimen was 7.6±0.3 yrs (mean±standard error). Seventeen out of 30 (56.7%) patients needed a retreatment for relapse; of them, 6/30 were retreated during the trial, 10/30 only after the end of the trial and 1/30 during both follow-up periods, accounting for 25 retreatments in total, the first one at a mean of 22.3 ± 12.1 months from last RTX cycle during the trial. Patients were retreated for nephritis (7/25), neuropathy (12/25), skin ulcers (6/25) or widespread purpura (6/25). Of the 17 patients retreated, 6/17 (35.3%) showed complete response at the last follow-up, 5/17 (29.4%) a partial response, while 6/17 (35.3%) had an active disease. Interestingly, of the remaining 13/30 patients undergoing only one single course of RTX during the follow-up, 6/13 were still in active follow-up and in clinical remission at the last follow-up. Recurrent infections occurred in three patients (10%; urinary and upper respiratory), related to severe hypogammaglobulinemia (IgG < 3 g/l) in 2/3. Death occurred in 6 patients. However, only 2/6 deaths were linked to relapsed vasculitis, with new onset of intestinal vasculitis.

Conclusion: A long-term RTX monotherapy with a retreatment at relapse regimen is effective and safe in cryoglobulinemic vasculitis, with low rate of severe hypogammaglobulinemia. Clinicians should be aware to promptly recognize and treat clinical relapse, as well as concomitant infections. Relapses with life-threatening manifestations (i.e. intestinal vasculitis) were uncommon. Further investigation may be required to select patients where maintenance RTX therapy may be the best choice.

References:

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2856

Update on Long-Term Outcomes after Reversible Cerebral Vasoconstriction Syndrome (RCVS). Seby John[1], Aneesh Singhal[2], Leonard H. Calabrese[1], Ken Uchino[1], Tariq Hammad[1], Stewart Tepper[1], Mark Stillman[1] and Rula A Hajj-Ali[1]. [1]Cleveland Clinic Foundation, Cleveland, OH, [2]Massachusetts General Hospital, Boston, MA.

Background/Purpose: RCVS is characterized by acute onset of severe headaches, with or without neurologic deficit with evidence of reversible cerebral vasoconstriction. We have previously reported data on long-term outcome on 20 patients with RCVS. Herein, we are validating our previous report by including data from two large academic centers.

Objectives:

i) To assess stroke and headache outcomes using validated measures ii) To determine the impact of RCVS on health related quality of life (QoL).

Methods: The following validated questionnaires were mailed to patients recruited from RCVS registries of Cleveland Clinic and Massachusetts General Hospital: Headache screening form, Headache Impact Test (HIT-6), Migraine Disability Assessment Test (MIDAS), Barthel Index (BI), EuroQoL (EQ-5D-5L) and Patient Health Questionnaire (PHQ-9).

Results: Of the 191 patients in the RCVS registries, 109 could be contacted and 45 responded to the questionnaires. This included 41 (91%) females, with a median follow-up time after symptom onset of 78 months (range 4–254 months). Forty six % had prior migraine, 31% developed ischemic stroke, 18% intracerebral hemorrhage, and 44% had convexal subarachnoid hemorrhage. After RCVS resolution, 24 (53%) patients continued to have headache, but the majority (88%) reported improvement in its severity. Five (14%) patients reported severe impact on activities of daily living from headaches as measured by the HIT-6 and MIDAS scales. The majority (97.5%) of patients were functionally independent based on their BI scores. EQ-5D-5L measurements showed that patients did better in the domains of mobility, self-care and usual activities, as compared to pain and anxiety/depression. Patients with persistent headache had significantly higher levels of pain as measured by EQ-5D-5L. Depression assessment using the PHQ-9 revealed only 1 (3%) patient reporting severe depression. There was a trend towards greater patients with persistent headache having more severe degrees of depression. There was no difference among all the outcome measures between the two centers.

Conclusion: More than half of patients with RCVS will continue to have headache long-term. They are not similar to the RCVS onset headache and are markedly improved from the initial headache. Although close to two-thirds of patients suffered from an initial ischemic or hemorrhagic stroke, almost all were independent with little functional disability. However, pain and anxiety/depression might be associated with lower QoL Headache may be a potential factor aggravating pain and anxiety/depression in those patients with persistent headache. This larger data from two different centers validate our previous report.

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Restricting Back Pain Is Strongly Associated with Disability in Community-Living Older Persons over the Course of 13 Years. Una Makris[1], Liana Fraenkel[2], Ling Han[3], Linda Leo-Summers[3] and Thomas M. Gill[4]. [1]Dallas VA Medical Ctr, Dallas, TX, [2]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT, [3]Department of Medicine, New Haven, CT, [4]Yale University, New Haven, CT.

Background/Purpose: Although back pain is common and costly, few longitudinal studies have evaluated the association between back pain severe enough to restrict activity [hereafter referred to as restricting back pain (RBP)] and the development of disability. The objective of this study is to evaluate the association between RBP and subsequent episodes of disability in basic, instrumental, and mobility activities, respectively.

Methods: Participants included the 754 members of the Precipitating Events Project (median age 78 y, 64.6% women), a prospective study of community-living persons, aged 70+ years, who completed monthly telephone assessments of RBP and disability, and who were at risk for developing new and recurrent disability episode(s) for up to 159 months. RBP was defined as staying in bed for at least 1/2 day and/or cutting down on one's usual activities due to back pain. Disability was defined as needing help with/inability to complete ≥1 of the activities, listed in the Table, in any given month for each of the three outcome categories. The event rates for the three disability outcomes were estimated using a GEE Poisson model. A recurrent events Cox model was used to evaluate the association between RBP and each of the three disability outcomes. The model was adjusted for fixed-in-time (sex, education, ethnicity) and time-varying covariates (listed in Table) (age, chronic conditions, BMI, depressive symptoms, cognitive impairment, physical frailty) that were updated every 18 months.

Results: For the basic, instrumental and mobility activities, the disability event rates were: 3.6 per 100-person months (95% CI 3.37, 3.89), 8.5 per 100-person months (95% CI 8.05, 8.98), and 9.38 per 100-person months (95% CI 8.98,9.81), respectively, with a median duration of 2 months per disability episode for each of the three outcomes. The unadjusted and adjusted associations of restricting back pain with the 3 disability outcomes are listed in the Table.

Conclusion: In this longitudinal study, RBP was independently associated with disability in basic, instrumental and mobility activities among older persons. Interventions directed at preventing or decreasing RBP may reduce the likelihood of disability in activities across three key domains of function.

Disability Outcome	Activities Involved	Hazard Ratio: Association of Restricting back Pain with Disability	95% CI
Essential activities (N=754)	Bathing, dressing, walking inside house, transferring from chair	Unadjusted 3.83 Adjusted* 3.47	3.35, 4.37 3.01, 3.99
Instrumental activities (N=703)	Housework, meal preparation, shopping	Unadjusted 2.32 Adjusted* 2.33	2.05, 2.62 2.08, 2.61
Mobility activities (N=709)	Walking 1/4 mile, climbing flight of stairs, lifting or carrying 10 lb	Unadjusted 3.53 Adjusted* 3.23	3.13, 3.97 2.87, 3.64

*The model was adjusted for fixed (sex, education, ethnicity) and time-varying covariates (age, chronic conditions, body-mass index, depressive symptoms, cognitive impairment, and physical frailty) updated every 18 months.

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2858

Education Effects on Outcome Expectations for Exercise in Adults with Knee Osteoarthritis. Tressa Gamache, Lori Lyn Price, Jeffrey B. Driban, William F. Harvey and Chenchen Wang. Tufts Medical Center, Boston, MA.

Background/Purpose: Outside of a clinical trial setting, higher outcome expectations for exercise, more education, and greater physical activity are inter-related, and outcome expectations may partly explain why education level is associated with physical activity. In clinical trials with exercise interventions, where participants tend to have higher outcome expectations, it would be informative to know if these associations still hold true. Therefore, we assessed if higher education is associated with higher outcome expectations and if outcome expectations mediate the relationship between education and physical activity.

Methods: We conducted a secondary analysis of all baseline data from a randomized trial comparing Tai Chi and Physical Therapy among people with knee osteoarthritis (KOA) as defined by the ACR criteria. Participants completed the Outcome Expectations for Exercise (OES), CHAMPS Activities Questionnaire for Older Adults (CHAMPS), and demographics self-report questionnaires. The OES is a 9-item questionnaire, in which higher mean scores indicate higher expectations for exercise with a range from 1 to 5, CHAMPS is a 40-item questionnaire that measures physical activity, and education was categorized into the following: high school diploma or less, some college/trade school, college degree, graduate school.

We performed an analysis of variance (ANOVA) with OES as the dependent variable to explore the differences among education groups with graduate school as the reference group. We also performed a multivariable analysis to adjust for age and sex.

To examine the role of OES as a mediating factor between education and physical activity, we performed a mediation analysis between education and physical activity with OES as the mediator using a commonly accepted method (Baron & Kenney).

Results: Our analysis included data from 282 participants with an average age of 59.7 years (SD=10.4); 69% female, 51% white, 35% black, 29% working at least part time, 72% completed at least some college, and an average body mass index of 32 kg/m^2. In the ANOVA, participants with high school or less had lower OES than participants who completed graduate school (Table 1). Higher education attainment was associated with increased OES after adjusting for age and sex (p=0.002). Criteria were not met for the mediation analysis because education did not predict physical activity and OES did not predict physical activity when controlling for education.

Conclusion: Education is associated with OES; however, OES is not a mediator between education and physical activity among individuals with KOA who are enrolled in a clinical trial with an exercise intervention. The lack of mediation may be in part because the participants recruited into this trial had higher OES and most had at least some college education, therefore were not reflective of the general population.

Table 1. ANOVA with OES as Dependent Variable (p=0.003)

Variable	N	OES Mean	SD	p-value
High School or less	50	3.66	0.85	<0.01
Some College/Trade School	91	3.96	0.88	0.06
College Degree	51	4.13	0.50	0.75
Graduate School	64	4.24	0.55	Ref.

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2859

Randomized Controlled Trial of Postoperative Care Navigation in Total Knee Arthroplasty Patients: Does One Size Fit All? Elena Losina, Jamie E. Collins, John Wright, Meghan E. Daigle, Laurel Donnell-Fink, Doris Strnad, Vladislav Lerner, Stanley Abrams and Jeffrey N. Katz. Brigham and Women's Hospital, Boston, MA.

Background/Purpose: A number of TKA recipients have suboptimal improvements after surgery. Our objective was to establish the efficacy of a motivational-interviewing (MI)-based telephone intervention aimed at improving functional outcomes post-TKA and to identify subgroups especially likely (or unlikely) to benefit from the intervention.

Methods: We conducted the RCT to compare functional status in TKA recipients randomized to one of two strategies: 1) enhanced postoperative care with frequent follow-up by a care navigator; 2) usual postoperative care. Those who were randomized into the care navigation arm received ten calls from a trained non-clinician care navigator over the first 6 months post-TKA. The trained navigator used theory driven MI to engage TKA recipients in discussions about their rehabilitation goals, including plans for and confidence in achieving those goals. Patients in the usual care arm received standard postoperative care. Patients in both arms were assessed at baseline, 3 and 6 months post-TKA. The study enrolled subjects 40+ years of age with OA who were scheduled for TKA. Primary outcome was the difference between the arms in WOMAC function score change, over the 6 months post-TKA.

We defined a satisfactory functional improvement as either achieving WOMAC function scores <15 or reducing pre-operative functional score by 19+ points, suggested as MCID in TKA patients (Escobar, 2007). We examined whether sex, obesity and pain catastrophizing affected the efficacy of the care navigator intervention.

Results: We enrolled 309 TKA recipients, average age 67 years; 60% female, 84% Kellgren-Lawrence Grade 4, 50% obese (BMI>=30kg/m^2). Mean pre-operative WOMAC function score was 40 (18), on a 0–100 scale, 100-worst. Baseline characteristics did not differ between study arms. At 6 months, participants in care navigation arm improved by 29.4 (16.1) points compared to 26.1 (18.3) in control arm (p=0.1126). Overall, 21% of study participants did not achieve satisfactory functional improvements, with similar rates across arms. Greater pain catastrophizing led to less improvement overall and its association with poor outcome was more prominent among females compared to males (p value for interaction = 0.002). Further analysis, restricted to females, showed that greater pain catastrophizing modified the impact of the intervention: females with a low degree of pain catastrophizing improved by 8 points more (33 vs. 25) in the navigation arm than in the control arm, while females with a high degree of pain catastrophizing improved by five points less in the navigation arm than in the control arm (p-value for interaction= 0.0233).

Conclusion: The results of this RCT did not show benefits of the MI based enhanced postoperative care navigation in functional improvements in TKA recipients. The negative overall result could be explained by differential effect of intervention among females with high and low levels of pain catastrophizing. Greater focus on understanding the determinants of and effective therapies for reducing pain catastrophizing could improve the efficacy of interventions focused on better functional outcomes in TKA recipients.

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Randomised Comparison of the Effectiveness of a Non-Pharmacological Multidisciplinary Face-to-Face Group-Based Treatment Program Vs. a Telephone-Delivered Treatment Program on Daily Function in Patients with Generalized Osteoarthritis. Nienke Cuperus[1], Thomas Hoogeboom[2], Clarinda Kersten[1], Leonie Rietveld[1], Alfons den Broeder[1], Thea Vliet Vlieland[3] and Cornelia H.M. van den Ende[1]. [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]CAPHRI school for public health and primary care, CCTR centre for Care Technology Research, Maastricht University, Maastricht, Netherlands, [3]Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Generalized osteoarthritis (GOA) is a widely accepted and prevalent OA phenotype characterized by the involvement of multiple joints. However, current research and clinical practice mostly examine OA populations for a specific OA localization. The effectiveness of non-pharmacological interventions for GOA is therefore largely unknown. In addition, there is no evidence concerning the optimal mode of care delivery. Therefore, we compared the effectiveness of a non-pharmacological multidisciplinary face-to-face group-based treatment program versus a telephone-delivered treatment program on daily function for patients with GOA, until one year after treatment.

Methods: In this single blind randomized clinical superiority trial, individuals clinically diagnosed with GOA were randomly allocated to either a six week multidisciplinary face-to-face group-based treatment program or a six week telephone-delivered treatment program. Both programs aimed to improve daily function and to enhance self-efficacy to control the disease. The programs had comparable content but critically differed in mode of delivery and intensity. Primary (daily functioning; HAQ-DI) and secondary outcome measures were assessed at baseline, 6, 26 and 52 weeks. The 6-week time point was used to assess the short-term effects of both interventions. The average score obtained from the 6, 26 and 52 time points was used to assess the long-term effects. Directly after finishing the treatment patient satisfaction was measured. Multiple imputation was used to estimate missing values. Differences in effectiveness between both treatment programs were analysed using linear regressions adjusted for baseline, sex and age.

Results: Of 158 randomized patients (mean (SD) age 60 (8); female 85%), 147 (93%) completed at least the baseline measurement and were included in the intention to treat analysis. Of these patients, 75 were allocated to the face-to-face treatment program and 72 to the telephone-delivered treatment program. No difference in effectiveness between both treatment groups was found on the HAQ-DI at both the short (p = 0.59) and long-term (p = 0.65). Moreover, no differences in effectiveness between the two modes of care delivery on the secondary outcomes were found (p > 0.05). Patient satisfaction was significantly higher in the face-to-face treatment program than in the telephone-delivered treatment program.

Conclusion: In this trial we found no differences in effectiveness between two modes of delivery of non-pharmacological care for patients with GOA. Therefore, our results imply that the choice of mode of treatment delivery i.e. face-to-face versus telephone-delivered could be based on patients' preferences and/or costs.

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Changes in Knee Kinematics from a 6-Week Hip and Trunk Strengthening Program for Persons with Patellofemoral Osteoarthritis. Lisa Hoglund[1], Laura Pontiggia[1], John Kelly IV[2], Mark Arnott[1], Olumide Babalola[1], Andrew Gushen[1] and James Carey[2]. [1]University of the Sciences, Philadelphia, PA, [2]University of Pennsylvania, Philadelphia, PA.

Background/Purpose: Patellofemoral (PF) osteoarthritis (OA) is prevalent in middle-aged adults. Aberrant lower extremity (LE) biomechanics is one etiology of knee OA. Reduced peak knee flexion angles and increased peak tibial abduction angles were reported during sit-to-stand (STS) in persons with general knee OA and with PF OA, respectively. Additionally, reduced strength of the hip abductor, hip extensor, and knee extensor muscles was reported in PF OA, which may impact LE biomechanics. Studies have reported improved knee and hip biomechanics in persons with PF pain when treated with proximal LE strengthening. It is unknown if a proximal LE strengthening program with pelvic/abdominal stabilization training will alter LE kinematics, improve symptoms, and improve function in persons with PF OA. This study examined the impact of a 6-week hip and trunk muscle strengthening and stabilization program on knee and hip kinematics during STS and a step-down (StDn) task and self-reported symptoms and function in persons with PF OA.

Methods: Six female subjects with PF OA and anterior knee pain, median age (interquartile range [IQR]): 52 years (48–56 years) participated in the study. Subjects attended a biomechanical evaluation, 10 supervised exercise treatment sessions, and a reevaluation. Biomechanics of the most painful LE were examined during STS from a stool and StDn on a 3-step staircase. Subjects were treated with hip and abdominal/trunk strengthening exercises. In addition, subjects were instructed in proper LE position and pelvic stability. Outcome measures included triplanar knee and hip joint peak angles and the Knee Injury and Osteoarthritis Outcome Score (KOOS). Data analysis included group medians (IQR) and Wilcoxon Signed Rank tests.

Results: Peak knee flexion angle during STS increased: Initial: 76° (67, 86), Final: 93° (87, 97), p=.03. Peak knee extension angle during STS decreased: Initial: 2° (0.4, 9), Final: −7° (−11, −4), p=.03. Peak knee extension angle during StDn decreased: Initial: −0.2° (−5, 0.5), Final: −11° (−16, −6), p=.03. KOOS-Symptoms score improved: Initial: 62 (54, 68), Final: 75 (68, 89), p=.03. KOOS-Function score improved: Initial: 69 (47, 76), Final: 84 (79, 85), p=.03.

Conclusion: A hip and trunk strengthening program with education in proper LE alignment and pelvic stability resulted in increased knee flexion angles and reduced knee extension angles during two tasks that increase PF joint stress. In addition, subjects reported significant improvement in symptoms and function. The intervention may have improved subjects' ability to tolerate loading the PF compartment in activities requiring knee flexion. This may be one method to improve symptoms and function in persons with PF OA.

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Satisfaction Following Total Knee Replacement: Journey or Destination? Jeffrey N. Katz[1], Yan Dong[1], Jamie E. Collins[1], John Wright[1], David Dalury[2], Kirk Kindsfater[3] and Elena Losina[1]. [1]Brigham and Women's Hospital, Boston, MA, [2]Townson Orthopedics, Maryland, Baltimore, MD, [3]Orthopedic Center for the Rockies, Ft. Collins, CO.

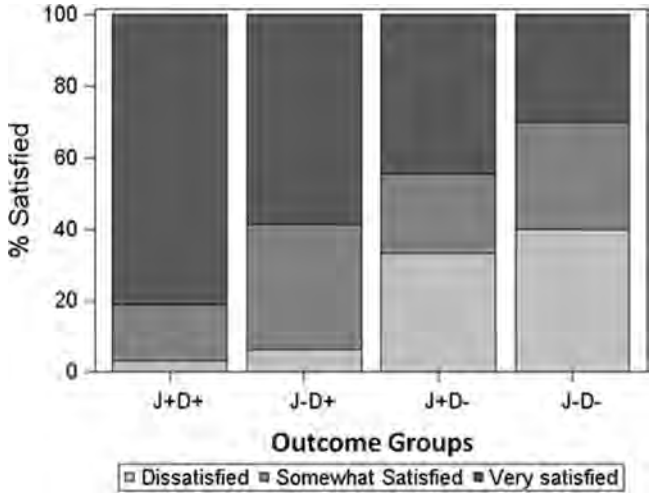
Background/Purpose: Total knee replacement (TKR) outcome is often assessed with measures of pain and function (fxn), but there is no consensus on whether surgery should be evaluated as extent of improvement on these scores ("journey") or final score ("destination"). We addressed this question

by evaluating whether improvement (journey) or final score (destination) is more closely associated with patient satisfaction with TKR.

Methods: We analyzed data from a prospective, multicenter cohort undergoing TKR. Subjects completed the WOMAC Pain and Fxn scales (0–100, 100 worst) preoperatively and 6 months postoperatively. At 6 months patients also completed a question on satisfaction with results of TKR. We defined the journey criterion as improvement by the minimal clinically important difference following TKR, ≥23 points on the WOMAC Pain or ≥19 on WOMAC Fxn Scale (Escobar et al). The destination criterion was the Patient Acceptable Symptom State following TKR, <31 on WOMAC Fxn (Tubach et al). We calculated the number of subjects who achieved the journey criterion, the destination criterion, both or neither. In each group, we calculated the proportion who reported being dissatisfied, somewhat satisfied and very satisfied with surgery. We used ordinal logistic regression to examine independent effects of achieving journey or of achieving destination criteria on satisfaction with TKR.

Results: 329 subjects were included, mean age 66, 57% female. Mean preoperative WOMAC Pain and Fxn scores were 40 (sd 18) and 42 (sd 17) respectively. 238 subjects (72%) met both journey and destination criteria for success while 10 (3%) met neither criterion. 63 subjects (19%) achieved the destination criterion but not journey, while 18 patients (5%) achieved the journey criterion but not destination. Among subjects who achieved the destination but not the journey criteria, 59% were very satisfied and only 6% were dissatisfied (Figure). Among those who achieved the journey but not the destination criteria, 44% were very satisfied and 33% were dissatisfied. In ordinal logistic regression models that adjusted for age, sex and baseline WOMAC Fxn, achieving the destination criterion had a stronger association with satisfaction (OR 7.7, 95% CI 3.2, 18) than the journey (OR 2.2, 95% CI 1.0, 4.7). This finding was essentially unchanged when we excluded the 30 subjects with preoperative WOMAC Fxn scores < 19, who were not eligible to achieve the journey criterion.

Conclusion: Improvement in outcome score (journey) and final score (destination) are distinct metrics for assessing results of surgery. In this TKR cohort, both metrics were associated with patient satisfaction with the results of TKR, with destination having a stronger association than journey. These data suggest that both journey and destination criteria should be integrated into patient-centered assessment of TKR.



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ACR Concurrent Abstract Session
Antiphospholipid Syndrome
Tuesday, November 18, 2014, 4:30 PM–6:00 PM

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IgG Antiphospholipid Antibodies Enhance Stroke Damage: An in Vivo Ischemia/Reperfusion Study. Charis Pericleous[1], Valerie Taylor[2], Lauren Bourke[3], Daniel Stuckey[2], Jed Wingrove[4], Mark Lythgoe[2], Silvia S. Pierangeli[5], Anisur Rahman[4], Ian Giles[1] and Yiannis Ioannou[6]. [1]Centre for Rheumatology, University College London, London, United Kingdom, [2]Centre for Advanced Biomedical Imaging (CABI), University College London, London, United Kingdom, [3]Centre for Rheumatology Research, University College London, London, United Kingdom, [4]University College London, London, United Kingdom, [5]University of Texas Medical Branch, Galveston, TX, [6]Centre for Rheumatology Research, University College Hospital London, London, United Kingdom.

Background/Purpose: Circulating pathogenic antiphospholipid antibodies (aPL) are the hallmark of antiphospholipid syndrome (APS) and a major risk factor for ischemic stroke, with up to one third of stroke cases in patients under 50 years of age due to APS. Additionally, stroke is the most common recurrent thrombotic manifestation in APS. While aPL are convincingly prothrombotic in both venous and arterial *in vivo* vessel thrombosis models, their effect upon stroke size post ischemia remains unexplored. We therefore employed an established rat model of ischemic / reperfusion (I/R) stroke injury utilizing transient endovascular filament middle cerebral artery (MCA) occlusion to assess the pathogenicity of APS-derived IgG.

Methods: Polyclonal IgG was purified from sera of two female patients with APS (triple positive for lupus anticoagulant, IgG anti-cardiolipin (aCL) and anti-beta-2-glycoprotein I (aβ_2GPI)) and four female healthy controls (HC). Two pooled IgG populations, APS-IgG and HC-IgG, were prepared at a final concentration of 1mg/ml and confirmed to be endotoxin-free (<0.1EU/mg).

Male Sprague-Dawley rats (200–215g) were injected once intravenously with 1mg APS-IgG or HC-IgG (5 rats per group). After 15min, a filament inserted through the common carotid artery was positioned so as to occlude the right MCA for 30min. The filament was then removed to allow reperfusion. After 24hr reperfusion, rats were sacrificed and histology was performed to determine brain infarct size, quantified by analyzing digital images scanned from 1mm brain slices stained with triphenyl tetrazolium chloride (TTC) which identifies metabolically active tissue. A small portion of the brain was kept for analysis of intracellular pathways by Western blot. Blood was collected prior to occlusion and at sacrifice. Researchers administering the IgG and performing TTC analysis were blinded to the groups.

Results: APS-IgG induced significantly larger infarcts compared to HC-IgG (mean infarct area as a percentage of total brain area ± SD: APS-IgG 32.2±4.6% versus HC-IgG 14.3±4.5%, $p<0.01$).

Reduced phosphorylation of the pro-survival kinase Akt was seen in brain tissue lysates of rats injected with APS-IgG compared to HC-IgG (ratio of phosphorylated : total Akt protein ± SD: APS-IgG 0.4±0.2 versus HC-IgG 0.9±0.2, $p=0.03$). Interestingly, there was a strong negative correlation between infarct size and the level of Akt activation ($r=-0.9$, $p<0.01$). Brain tissue lysates showed no difference in phosphorylation of ERK, JNK or p38-MAPK between APS-IgG and HC-IgG groups. Human IgG aCL/aβ_2GPI activity was present in the sera of rats treated with APS-IgG at sacrifice; human IgG was detected in brain tissue lysates from animals treated with APS-IgG and HC-IgG with no difference between the groups.

Conclusion: This study is the first to directly demonstrate the ability of APS-IgG to exacerbate stroke severity post I/R injury, causing larger infarcts compared to rats treated with HC-IgG. Furthermore, this finding correlated with inhibition of the pro-survival kinase Akt and warrants further validation studies to confirm Akt dependency and dissect mechanisms through which this inhibition may occur.

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Markers of Thrombotic Events in Autoimmune Diseases:Comparison of Antiphospholipid Score (aPL-S) and Global Anti-Phospholipid Syndrome Score (GAPSS). Kenji Oku, Olga Amengual, Ryo Hisada, Kazumasa Oomura, Ikuma Nakagawa, Toshiyuki Watanabe, Toshiyuki Bohgaki, Tetsuya Horita, Shinsuke Yasuda and Tatsuya Atsumi. Hokkaido University Graduate School of Medicine, Sapporo, Japan.

Background/Purpose: Recently, new scoring systems to quantify the probability for the diagnosis of antiphospholipid syndrome (APS) have been proposed in sequence: the Antiphospholipid Score(aPL-S) and the Global Antiphoshpholipid Syndrome Score (GAPSS). They are derived from the combinations of independent risks for thrombosis particularly focused on antiphospholipid antibodies profiles(aPL-S) or centered on the existence of each antiphospholipid antibodies taking into account with conventional cardiovascular disease risks (GAPSS). These scores, as well as tools for diagnosis, function as index for predicting future thrombosis in autoimmune diseases.

Methods: This study comprised 411 patients with autoimmune diseases who visited Hokkaido University Hospital Rheumatology Clinic between 2002 and 2003. Demographic, clinical data and cardiovascular risk factors were obtained from the medical charts. Lupus Anticoagulant (LAC) assays and IgG/M anticardiolipin antibodies, IgG/M anti-β_2-glycoprotein I antibodies and IgG/M phosphatidylserine dependent antiprothrombin antibodies were performed in all subjects. Among all the patients, 257 (62.5%) patients with follow-up period of more than 5 years (median follow-up periods: 126(IQR 92.5,133) months) were eligible. The disease profile of these patients was as follows; 17(7%) primary APS, 25(10%) APS with systemic lupus erythematosus(SLE), 84(33%) SLE (without APS), 45(18%) rheumatoid arthritis and 85 patients with other autoimmune diseases.

To evaluate the diagnostic powers for GAPSS and aPL-S, area under the curve (AUC) of receiver operating characteristic (ROC) curves were calculated. To evaluate the powers of the two scores for thrombosis prediction, Cox proportional hazard regression analyses were performed separately for each score with the cut off derived om the ROC curve. Each risk factor for the multivariate Cox analyses were assessed through separate univariate Cox regression test. To evaluate and compare the predictive powers of the two scores, Somer's d coefficient was calculated.

Results: Thirty-seven patients newly developed thrombosis during the observation period; 23 arterial thrombosis and 23 venous thrombosis. The ROC curve of GAPSS showed higher AUC than that of aPL-S (0.693 vs 0.656, respectively, $p<0.05$) indicating that GAPSS has better ability of diagnosing APS (GAPSS vs aPL-s: 0.693 vs 0.656, $p<0.05$).The cut off values of GAPSS and aPL-S for predicting future thrombosis were 10 and 31, respectively. The Cox multivariate proportional hazard regression analyses revealed that both scores, with appropriate cut off levels, accurately reflected the risks of the future thrombosis with statistic significance(GAPSS$>$10 $p=0.01$, aPL-S$>$31 $p<0.0001$). The aPL-S showed higher Somer's coefficient than GAPSS (0.497 vs 0.412, respectively, $p<0.05$).

Conclusion: The aPL-S and GAPSS accurately reflected the diagnosis of APS and the risk for future thrombotic events in patients with autoimmune diseases in our cohort. GAPSS may have relatively high potential for APS diagnosis and aPL-S might be superior to GAPSS in predicting future thrombosis.

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The Cellular Effects of ANTI-Factor Xa Antibodies Isolated from Patients with Antiphospholipid Syndrome ARE Inhibited By Factorxa Inhibitors, Hydroxychloroquine and Fluvastatin. Bahar Artim-Esen[1], Natalia Smoktunowicz[2], Vera M. Ripoll[3], Charis Pericleous[3], Rachel Chambers[2], Ian Mackie[4], David Isenberg[5], Anisur Rahman[6], Yiannis Ioannou[5] and Ian Giles[3]. [1]Rheumatology Division, Department of Internal Medicine, Istanbul Faculty of Medicine,Istanbul University, Istanbul, Turkey, [2]Respiratory Research Unit, University College London, London, United Kingdom, [3]Centre for Rheumatology, University College London, London, United Kingdom, [4]Haemostasis Research Unit, University College London, London, United Kingdom, [5]Centre for Rheumatology Research, University College Hospital London, London, United Kingdom, [6]University College London, London, United Kingdom.

Background/Purpose: Recently we showed that FXa reactive IgG in patients with the antiphospholipid syndrome (APS) displayed higher avidity binding to FXa and had greater functional effects upon the coagulant functions of FXa compared to patients with anti-FXa IgG isolated from patients with systemic lupus erythematosus (SLE) without APS. FXa signalling has been observed in many cell types via activation of protease-activated receptors (PAR) which stimulate an increase in intracellular calcium (Ca^{2+}) levels. Given that cellular responses elicited through activation of PARs are important in influencing pathways responsible for inflammation, tissue repair and haemostasis, FXa-reactive IgG may be important in the pathogenesis of SLE and APS. Therefore, we characterised the interaction between FXa and human umbilical vein endothelial cells (HUVEC) and the cellular effects of anti-FXa IgG isolated from patients with APS and SLE without APS.

Methods: IgG was purified from patients with APS (n=14) and SLE/no APS (n=14) who had medium or high serum levels of anti-FXa IgG and healthy controls (HC) (n=8). The effect of IgGs on FXa-mediated intracellular calcium release was measured using the fluorescent image plate reader (FLIPR). HUVECs were seeded in 96-well plates, for 48 hours until confluent and then incubated with Fluo-4AM calcium binding dye for one hour. Alterations in intracellular calcium release were monitored for 10 minutes following stimulation with α-Thrombin (Thr) or FXa +/− IgGs. PAR inhibitors, agonist peptides (AP), hydroxychloroquine (HCQ), fluvastatin and desensitisation experiments were also performed to characterise responses.

Results: We observed a dose-dependent induction of Ca^{2+} transients by FXa in HUVEC. FXa was a weaker agonist than Thr but the kinetics of response was different with a longer lag-time and duration. APS IgG significantly potentiated the FXa-induced Ca^{2+} release compared to SLE/no APS IgG ($p=0.04$), HC IgG ($p<0.05$) and FXa alone ($p<0.05$). FXa-mediated Ca^{2+} release was significantly reduced by PAR-1 inhibitors. When PAR-1 receptors were desensitised by Thr (10 nM) and cells were stimulated by PAR-2 AP, PAR-2 response was reduced by 47.5%. When Thr-desensitised cells were stimulated by FXa, response was reduced by 66% and residual response was not inhibited by PAR-1 or completely by 2 inhibitors. When cells were treated with: Antistasin, a specific FXa inhibitor; Hydroxychloroquine; or fluvastatin - FXa induced and IgG potentiated intracellular Ca^{2+} release was significantly reduced.

Conclusion: We confirmed FXa stimulation of HUVEC to be mediated mainly via PAR1 and 2 dependent signalling mechanisms that may be acting as a unit and this effect was enhanced by FXa-reactive APS-IgG. These effects were blocked by a FXa inhibitor which raises the exciting prospect that anti-FXa IgG positivity may be used as a novel biomarker to predict response to treatment with FXa inhibitors in patients with APS. Despite the need for the specificity to be investigated further, results also suggest that HCQ and fluvastatin may be beneficial in patients with APS.

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External Validation of the Global Anti-Phospholipid Syndrome Score in Comparison to IgG Antibodies Directed Against Domain I of β_2-Glycoprotein I. a Prospective Multicentre Cohort Study. Stephane Zuily[1], Bas De Laat[2], Veronique Regnault[3], Pierre Kaminsky[4], Hilde Kelchtermans[5], Zakera Shums[6], Roger Albesa[6], Gary L Norman[6], Philip de Groot[7], Anne-Christine Rat[8], Jacques Ninet[9], Nadine Magy-Bertrand[10], Jean-Louis Pasquali[11], Marc Lambert[12], Bernard Lorcerie[13], Thomas Lecompte[14], Francis Guillemin[15] and Denis Wahl[16]. [1]CHU de Nancy, Vascular Medicine Division and Regional Competence Center For Rare Vascular And Systemic Autoimmune Diseases, Nancy, F-54000, France; Inserm, UMR_S 1116, Nancy, F-54000, France; Université de Lorraine, Nancy, F-54000, France, Nancy, France, [2]Biochemistry, CARIM, Maastricht University, Maastricht, Netherlands, [3]Inserm, UMR_S 1116, Nancy, F-54000, France; Université de Lorraine, Nancy, F-54000, France; CHU de Nancy, Contrat d'interface, Nancy, F-54000, France, Nancy, France, [4]CHU Nancy, Vandoeuvre, France, [5]Biochemistry, CARIM, Maastricht University, The Netherlands; Synapse BV, Maastricht, The Netherlands, Maastricht, Netherlands, [6]INOVA Diagnostics, San Diego, CA, [7]Clinical Chemistry and Hematology, UMC Utrecht, The Netherlands, Utrecht, Netherlands, [8]University of Lorraine, Nancy, France, [9]Department of Nephrology and Internal Medicine, Hôpital Edouard Herriot, Lyon, France, Lyon, France, [10]Bensançon University Hospital, Besançon, France, [11]Nouvel Hospital Civil, Strasbourg Cedex, France, [12]Lille University Hospital, Lille, France, [13]Hopital Du Bocage, Service de Médecine Interne et Immunologie Clinique, Dijon, France, [14]Inserm, UMR_S 1116, Nancy, F-54000, France; Université de Lorraine, Nancy, F-54000, France; CHU de Nancy, Haematology Laboratory, Nancy, F-54000, France; Division of Haematology, HUG, Geneva, Switzerland (current address), Geneva, Switzerland, [15]INSERM, Centre d'Investigation Clinique - Epidémiologie Clinique (CIC-EC) CIE6, Nancy, France, [16]Nancy University Hospital and INSERM U961, Vandoeuvre-Les-Nancy, France.

Background/Purpose: Our objectives were 1- to perform an external validation of the Global Anti-Phospholipid Syndrome Score (GAPSS) and 2- to compare prognostic significances of GAPPS and a novel assays IgG antibodies directed against domain I of β_2-glycoprotein I (antiDI) in patients with antiphospholipid antibodies (aPL) and/or systemic lupus erythematosus (SLE).

Methods: We performed a prospective cohort study in French University Hospitals. Consecutive patients with aPL and/or SLE according to ACR classification without ongoing anticoagulant treatment were enrolled. The outcome was the time to the first incident thrombotic event. Blood was drawn at baseline. ELISA antiDI and anti-phosphatidyl/prothrombin antibodies assays were performed together with traditional assays (lupus anticoagulant,

anticardiolipin and anti-β_2-glycoprotein I antibodies). GAPSS was computed for each patient.

Results: One hundred and thirty eight patients (median age 43.5±15.3 years; 108 women) were followed-up for a mean duration of 43±20.7 months (493.9 patient-years). Thrombosis during follow-up occurred in 16 patients (3 strokes, 1 myocardial infarction, 1 splanchnic arterial thrombosis, 3 pulmonary embolisms, 3 deep vein, 5 small vessels thromboses). Higher values of GAPSS were seen in patients who experienced thrombosis compared to those without (10.9±4.8 vs 7.9±5.4, p=0.03). While triple positivity (HR=2.38 [CI95%; 0.83–6.80], p=0.11) and GAPSS above 10 (HR=1.56 [CI95%; 0.55–4.47], p=0.41) were not predictive of further incident thrombotic events, GAPSS above 16 (HR=5.27 [CI95%; 1.16–23.93], p=0.03) and high levels of antiDI above the 90th percentile of patients (HR=5.64 [CI95%; 1.94–16.42], p=0.002) were highly predictive of incident thrombotic events.

Conclusion: GAPSS and high levels of antiDI are significant predictors of thrombosis in aPL/SLE patients. These antibodies seem to add a substantial improvement in risk prediction of thrombosis independently of clinical variables assessed by GAPSS' components.

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Antiphospholipid Antibodies Promote the Release of Neutrophil Extracellular Traps: a New Mechanism of Thrombosis in the Antiphospholipid Syndrome. Srilakshmi Yalavarthi[1], Levi F. Mazza[1], Alexandra E. Morris[1], Carlos Núñez-Álvarez[2], Diego Hernández[2], Paula L. Bockenstedt[1], Antonio R. Cabral[2] and Jason S. Knight[1]. [1]University of Michigan, Ann Arbor, MI, [2]Instituto Nacional de Ciencias Medicas y Nutricion, Mexico City, Mexico.

Background/Purpose: Antiphospholipid antibodies (aPL), especially those targeting beta-2-glycoprotein I, are known to activate endothelial cells, monocytes, and platelets, with prothrombotic implications. However, the interaction of aPL with the most abundant leukocyte in human blood, the neutrophil, has only rarely been considered. Neutrophil extracellular trap (NET) release—a form of neutrophil cell death that results in the externalization of decondensed chromatin decorated with granular proteins—has recently been recognized as an important activator of the coagulation cascade, as well as an integral component of deep vein thrombi in both humans and animals. Here, we hypothesized that aPL activate neutrophils to release NETs, thereby predisposing to thrombosis.

Methods: Neutrophils, sera, and plasma were prepared from patients meeting criteria for primary antiphospholipid syndrome (APS) by the revised Sapporo classification criteria (n=50), or from healthy volunteers. Circulating NETs were quantified in sera and plasma by a myeloperoxidase-DNA sandwich ELISA. Neutrophils from APS patients were scored for their ability to release NETs by both immunofluorescence microscopy and fluorescence-based quantification of extracellular DNA. Neutrophils from healthy volunteers were stimulated with APS patient sera, purified IgG, or aPL monoclonal antibodies, and NET release was quantified; dependence on generation of reactive oxygen species was also determined. Expression of known aPL receptors, beta-2-glycoprotein and annexin A2, was measured on the neutrophil surface.

Results: Sera and plasma from APS patients have elevated levels of NETs as compared to healthy volunteers (2.7-fold increase when comparing means; p=0.0279). Neutrophils isolated from patients with primary APS are predisposed to spontaneous NET release when compared to healthy volunteers (p=0.0143). Importantly, APS-patient sera and IgG purified from patients with aPL, stimulate NET release from healthy-volunteer neutrophils (p=0.004 and 0.0187, respectively). Human aPL monoclonal antibodies, especially those that target beta-2 glycoprotein I, also enhance NET release; this enhancement can be abrogated by blockade of reactive oxygen species formation. At baseline, both APS-patient neutrophils and healthy-volunteer neutrophils display beta-2 glycoprotein I on their surface.

Conclusion: APS patients have more circulating NETs than healthy volunteers, even between thrombotic episodes. APS-patient neutrophils are predisposed to NET release, probably through exposure to aPL, since aPL can trigger NET release from healthy volunteer neutrophils *in vitro*. Future experiments will explore the role of annexin-A2/Toll-like-receptor-4 pathways in aPL-mediated NET release, while also assessing the thrombotic implications of APS NETs. Neutrophil netting warrants further investigation as a novel therapeutic target in APS patients.

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Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) Clinical Database and Repository Initial Analysis. Doruk Erkan[1], Danieli Andrade[2], Maria Tektonidou[3], Amaia Ugarte[4], Alessandra Banzato[5], Angela Tincani[6], Pier-Luigi Meroni[7], Ricard Cervera[8], Paul R. Fortin[9], Roger A. Levy[10] and On Behalf of APS Action[11]. [1]Hospital for Special Surgery, New York, NY, [2]University of São Paulo, São Paulo, Brazil, [3]First Department of Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece, [4]Hospital Universitario Cruces, Bizkaia, Spain, [5]Department of Cardiac Thoracic and Vascular Sciences, University of Padua, Padua, Italy, [6]Rheumatology and Clinical Immunology, Spedali Civili and University of Brescia, Brescia, Italy, [7]University of Milan, Milano, Italy, [8]Hospital Clinic, Barcelona, Spain, [9]Laval University, Division of Rheumatology, Centre de Recherche du CHU de Québec and Department of Medicine, Quebec City, QC, [10]Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, [11]APS ACTION, New York, NY.

Background/Purpose: APS ACTION International Clinical Database and Repository ("Registry") was created to study the natural course of disease over 10 years in persistently aPL-positive patients with/without other systemic autoimmune diseases. The objective of this preliminary analysis is to report the baseline characteristics of currently enrolled patients.

Methods: A secure web-based data capture system is used to store patient information including demographics, aPL/APS history, and aPL data. The inclusion criteria are positive lupus anticoagulant (LA) test based on the ISTH recommendations, medium-to-high titer (> 40U and/or > 99th percentile) anticardiolipin antibody (aCL) IgG/M/A, and/or medium-to-high titer anti-β_2Glycoprotein-I (aβ_2GPI) IgG/M/A tested at least twice within one year prior to enrollment. Clinical and blood collection (for core laboratory aPL confirmation and mechanistic studies) are performed once a year, or when patients develop new events. We used chi-square or Fisher's exact test for group comparisons, and linear-by-linear association test to analyze for trend.

Results: As of June 2014, 408 patients have been recruited from 17 centers globally (mean age at entry: 43.7±12.8y; female: 310 [76%]; white: 261 [69%]; and other systemic autoimmune diseases: 130 [32%]). Table shows the distribution of the aPL-related events (historically and/or at registry entry) as well as the association between the aPL-related events and the aPL profile (triple, double, or single positivity based on inclusion tests). The results did not change when the single aPL group was restricted to LA-positive patients only (data not shown). The percentages of patients tested for LA, aCL, and aβ_2GPI were 93%, 100%, and 76%, respectively in the double aPL-positive group; and 97%, 99%, and 77% in the single aPL-positive group. The percentages of the patients with positive LA, aCL, and aβ_2GPI were 65%, 89%, and 39%, respectively in the double aPL-positive group; and 72%, 23%, and 5% in the single aPL-positive group.

aPL-related Events (# of Patients)	Triple aPL	Double aPL	Single aPL	p-value*
N: 403 (5 excluded-pending aPL entry)	135 (34%)	123 (30%)	145 (36%)	
aPL, No Criteria Met (n:85)	30 (35%)	28 (33%)	27 (32%)	0.88
Thrombotic APS (n:221)	76 (34%)	64 (29%)	81 (37%)	0.21
Obstetric APS only (n:40)	12 (30%)	13 (33%)	15 (38%)	0.77
Thrombotic & Obstetric APS (n:57)	17 (30%)	18 (32%)	22 (39%)	0.57
Venous Thrombosis (n:169)	59 (35%)	44 (26%)	66 (39%)	0.34
Arterial Thrombosis (n:143)	47 (33%)	47 (33%)	49 (34%)	0.29
Catastrophic APS (n:3)	3 (100%)	0 (0%)	0 (0%)	*0.044*
Microthrombosis without CAPS (n:23)	9 (39%)	9 (39%)	5 (22%)	0.23
Fetal Loss (n:76)	25 (33%)	22 (29%)	29 (38%)	0.60
Premature Birth (EC/PEC/PI) (n:42)	13 (31%)	13 (31%)	16 (38%)	0.95
3 Consecutive Embryonic Losses (n:17)	4 (24%)	7 (41%)	6 (35%)	0.72
Livedo reticularis/racemosa (n:59)	19 (32%)	13 (22%)	27 (46%)	0.16
Persistent Thrombocytopenia[1] (n:73)	24 (33%)	28 (38%)	21 (29%)	0.22

Autoimmune Hemolytic Anemia (n:23)	9 (39%)	8 (35%)	6 (26%)	0.31
Cardiac Valve Disease[2] (n: 34)	18 (53%)	10 (29%)	6 (18%)	*0.02*
aPL-associated Nephropathy[2] (n:11)	2 (18%)	7 (64%)	2 (18%)	0.053
Skin Ulcers (n:21)	5 (24%)	8 (38%)	8 (38%)	0.58
Cognitive Dysfunction[3] (n: 10)	3 (30%)	4 (40%)	3 (30%)	0.27
MRI White Matter Changes (n:57)	18 (32%)	16 (28%)	23 (40%)	0.22

PEC: preeclampsia; EC: eclampsia; PI: placental insufficiency; (1) <100,000/mcL twice at least 12w apart; (2) Based on APS Classification Criteria Definitions; (3) neuropsychological test proven. * similar results with linear-by-linear association test for p-value trend.

Conclusion: Our preliminary analysis suggests that: a) there is no association between the aPL-related events and aPL profile (triple, double, or single positivity), except for Catastrophic APS and cardiac valve disease, based on a small number of patients; and b) LA positivity is the most important determinant of event risk in aPL-positive patients. Further analysis of the APS ACTION registry, i.e., detailed aCL/aβ_2GPI titers, potential confounders, and core laboratory aPL profile, will clarify if triple, double, and single aPL profiles are associated with different risk profiles.

Disclosure: D. Erkan, APS ACTION, 2, APS ACTION, 9; **D. Andrade**, APS ACTION, 2; **M. Tektonidou**, APS ACTION, 2; **A. Ugarte**, APS ACTION, 2; **A. Banzato**, APS ACTION, 2; **A. Tincani**, APS ACTION, 2; **P. L. Meroni**, APS ACTION, 2; **R. Cervera**, APS ACTION, 2; **P. R. Fortin**, APS ACTION, 2; **R. A. Levy**, APS ACTION, 2; **O. B. O. APS Action**, None.

ACR Concurrent Abstract Session
B cell Biology and Targets in Autoimmune Disease
Tuesday, November 18, 2014, 4:30 PM–6:00 PM

2869

TLR7 Influences Autoreactive B Cell Selection in the Germinal Center. Weiqing Huang[1], Megan Woods[1], Alexis Boneparth[2], Ramalingam Bethunaickan[1], Ranjit Sahu[1] and Anne Davidson[1]. [1]Feinstein Institute for Medical Research, Manhasset, NY, [2]Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ.

Background/Purpose: TLR7 is required for the generation of anti-RNA antibodies and excess TLR7 confers a SLE-like phenotype in mice. Recent studies have shown that TLR7 expression in B cells is sufficient for this phenotype and that TLR7 excess enhances germinal center (GC) maturation. The goal of this study was to determine how TLR7 influences the GC derived autoreactive B cell repertoire.

Methods: TLR7 deficiency was crossed into NZW mice for 13 generations. The 3H9 IgVH transgene that confers anti-DNA and anti-cardiolipin specificity was introduced into NZW/BXSB.Yaa and NZW.TLR7+/−/BXSB.Yaa lupus prone mice. The Yaa locus confers an extra copy of TLR7 in males and an accelerated lupus phenotype and NZW.TLR7+/−/BXSB.Yaa mice retain the Yaa locus but carry only one copy of TLR7. To create a physiologic setting in which autoreactive B cells compete for survival with non-autoreactive B cells, we generated 50% 3H9/50% wild type bone marrow chimeras in which transferred male 3H9. TLR7+/+ or TLR7+/−cells are GFP+ and can be easily identified. Mice were followed clinically and sacrificed at the onset of fixed proteinuria. Spleen cells were phenotyped and GC B cells were analyzed by single cell PCR for the repertoire of Vk light chains associated with the 3H9 heavy chain. Full length Vk5–43 encoded light chains were resequenced and their mutation frequency analyzed.

Results: Disease onset occurred with the same kinetics in TLR7+/+ and TLR7+/− chimeras and spleens from both sets of chimeras were phenotypically indistinguishable. We have previously shown a preferential selection of Vk5–43 and Vk5–48 light chains into the GCs of 3H9 SLE prone mice; these light chains confer anti-chromatin activity in their germline configuration whereas anti-DNA and anti-cardiolipin activity is acquired as a result of somatic mutations. We found that Vk5–48/Jk4 encoded light chains that have a high affinity for chromatin were preferentially selected into the GCs when 3H9 TLR7+/+ cells were transferred together with their non-3H9 counterparts but were found rarely when 3H9 TLR7+/− cells were transferred. By contrast, Vk5–43 encoded light chains were selected into the GCs in both TLR7+/+ and TLR7+/− chimeras. We therefore examined the frequency of somatic mutations in these light chains. The frequency of somatic mutations was significantly less in Vk5–43 light chains from 3H9+ GC cells from TLR7+/− chimeras than in 3H9+ GC cells from TLR7+/+ chimeras. Finally 3H9+ B cells were significantly more expanded in the GCs of TLR7+/+ than TLR7+/− chimeras.

Conclusion: We have demonstrated that TLR7 influences selection of autoreactive B cells into the GC, as well as their expansion and the frequency of somatic mutations. Our results suggest that TLR7 influences proliferation in the dark zone of the GC since this is linked to mutation frequency. These effects of TLR7 are independent of other genes in the Yaa locus.

Disclosure: W. Huang, None; **M. Woods**, None; **A. Boneparth**, None; **R. Bethunaickan**, None; **R. Sahu**, None; **A. Davidson**, None.

2870

B Cell-Intrinsic Deletion of the Type 1 Interferon Receptor Does Not Impact the Development of Murine Lupus. Shaun W. Jackson, Nicole Scharping, Socheath Khim and David Rawlings. Seattle Children's Research Institute, Seattle, WA.

Background/Purpose: Type 1 interferon (IFN) is strongly implicated in lupus pathogenesis, and patients with SLE frequently express a "type 1 IFN gene signature". Type 1 IFN promotes B cell activation *in vitro* suggesting a direct role for type 1 IFN in humoral autoimmunity. However, it is unclear whether type 1 IFN impacts lupus pathogenesis via B cell-intrinsic or –extrinsic mechanisms. We previously described the Wiskott Aldrich syndrome (WAS) model of B cell-driven autoimmunity (Becker-Herman et al., *JEM* 2011, Jackson et al. *J Immunol* 2014). An important advantage of the WAS chimera model is that dysregulated immune responses are limited to the B cell compartment, allowing genetic manipulation in a B cell-intrinsic fashion. In the current study, we describe the impact of B cell-intrinsic deletion of the type 1 interferon receptor (*ifnar*) in the WAS chimera model.

Methods: Proliferation of wild-type (WT), *was*−/−, *ifnar*−/− and double-deficient *was*−/−.*ifnar*−/− marginal zone B cells was quantified after stimulation with LPS (TLR4 agonist), R848 (TLR7 agonist) and CPG (TLR9 agonist) +/− IFN-β. To test the impact of B cell-intrinsic type 1 IFN activation in lupus pathogenesis *in vivo* we established bone marrow chimeras in which B cells were WT, *was*−/−, or *was*−/−.*ifnar*−/−; hereafter be referred to as B^{WT}, $B^{WAS-/-}$, and $B^{W/IFNAR-/-}$. Chimeras were analyzed for autoantibodies, immune activation and development of immune-complex glomerulonephritis by ELISA, flow cytometry and immunohistochemistry.

Results: We previously showed that autoimmunity in the WAS chimera model is dependent on B cell-intrinsic TLR7 activation (Jackson et al. *J Immunol* 2014). *Ifnar*-deficient B cells demonstrated a specific defect in TLR7-induced proliferation, while TLR4 and TLR9 responses were unaffected. In addition, recombinant IFN-β enhanced TLR7 responses, without impacting TLR4/TLR9 activation. These data suggest a role of B cell-intrinsic type 1 IFN signals in lupus pathogenesis. To test this hypothesis, we generated chimeras with B cells double-deficient in *was* and *ifnar*. Surprisingly, although type 1 IFN promoted B cell TLR7 activation *in vitro*, autoantibodies to RNA-associated antigen sm/RNP were equivalent in $B^{WAS-/-}$ and $B^{W/IFNAR-/-}$ animals. Further, B cell-intrinsic *ifnar* deletion had no impact on immune activation manifest by: splenomegaly; CD4+ T cell expansion; and generation of T follicular helper cells and germinal center B cells. Finally, we demonstrate that B cell-intrinsic *ifnar* deletion does not impact immune-complex glomerulonephritis.

Conclusion: The importance of type 1 IFN in the pathogenesis of SLE has been well established by both human studies and murine lupus models. Type 1 IFN promote TLR7-mediated B cell activation *in vitro*, suggesting a direct role for type 1 IFN on B cells in lupus pathogenesis. Despite these *in vitro* data, we demonstrate that TLR7-dependent humoral autoimmunity can develop independently of B cell-intrinsic *ifnar* activation. To our knowledge, this is the first study to directly address the impact of B cell type 1 IFN activation in murine lupus, of relevance to both the understanding of disease pathogenesis and to efforts to target type 1 IFN therapeutically in SLE.

Disclosure: S. W. Jackson, None; **N. Scharping**, None; **S. Khim**, None; **D. Rawlings**, None.

2871

Break of Anergy in Human Autoreactive B Cells By T Helper Signals Restores B Cell Receptor Signaling Capacity and Is Dependent on Upregulation of CD45 Phosphatase Activity-a Possible Novel Mechanism of Breech of B Cell Tolerance in Rheumatic Diseases. Peter Szodoray[1], Stephanie M. Stanford[2], Nunzio Bottini[2] and Britt Nakken[1]. [1]Institute of immunology, Rikshospitalet, Oslo University Hospital, Oslo, Norway, [2]La Jolla Institute for Allergy and Immunology, La Jolla, CA.

Background/Purpose: We recently identified a human B cell population, which is naturally autoreactive and tolerized by functional anergy. This population was naïve, fully mature, negative for surface IgM and expressing only IgD BCR (BND cells: naïve, D-only). The BND cells have antibody variable region genes in germline configuration and a proportion of anergic cells exhibit natural reactivity to antinuclear antigens and dsDNA. Break of B cell tolerance leading to presence of autoantibodies in rheumatic diseases may cause the initiation and perpetuation of various autoimmune processes. The aim of this study was therefore to investigate if anergy in BND cells could be overcome by T cell mediated signals as has been reported in murine systems, and furthermore, study the molecular mechanisms underlying this process.

Methods: Untouched naive and BND human B cells from healthy blood donors were purified and cultured in the presence of T cell help (e.g. IL-4 and CD40L) followed by various functional assays such as Ca2+-flux, phosphoflow (pSyk, pLyn) and standard flow cytometry measurements of intracellular and surface B cell markers. Finally, CD45 phosphatase activity was measured utilizing fluorescent peptide-based assay.

Results: Stimulation mimicking T cell help broke anergy and forced BND cells to fully respond to antigenic stimulation by restoring normal signaling through the BCR. This was dependent on *de novo* protein synthesis as opposed to direct crosstalk between the BCR, IL-4 and CD40 signaling pathways. We traced the restoration of BCR signaling from downstream signaling stages such as intracellular calcium release to phosphorylation of Syk and Lyn kinase, which is located proximal to the BCR. We observed an inability of activation of Lyn in BND cells upon BCR-stimulation, while subsequent to IL-4/CD40L treatment, the activation state of Lyn was restored. Lyn kinase activity is principally regulated by CD45 phosphatase (activating) and Csk kinase (inactivating). By inhibition studies, we identified CD45 phosphatase as a key component in the process of restoration of BCR signaling by T cell mediated signals. As a next step, we therefore investigated if T helper signals regulate CD45 expression in anergic B cells. A modest upregulation of CD45 surface expression on B cells stimulated with T cell mimicking signals was observed. Since CD45 is a complex molecule with many possible isoforms exhibiting different levels of phosphatase activity, quantitation of CD45 phosphatase activity of B cells upon T cell stimulation was performed. These analyses showed enhanced CD45 phosphatase activity upon T cell help in BND cells as well as in naive B cells, pinpointing CD45 as a key regulator of BCR signaling thresholds mediated by T cell help.

Conclusion: Our findings reveal a novel connection between T cell help, increased CD45 phosphatase activity and BCR signaling in human primary anergic and naïve B cells, and further implies that anergic BND cells may represent the precursors of autoantibody secreting plasma cells in B cell driven autoimmune conditions. Our data provide new insight in the break of humoral immune tolerance with possible diagnostic and therapeutic implications in patients with systemic autoimmune and rheumatic diseases.

Disclosure: P. Szodoray, None; **S. M. Stanford**, None; **N. Bottini**, None; **B. Nakken**, None.

2872

B-Cell Autoepitope and Tetramer Analysis Reveals Expansion of Apoptotic Autoantigen La and snRNP Reactive B Cells in BXD2 Mice. Jennie Hamilton[1], Jun Li[1], Qi Wu[1], PingAr Yang[1], Bao Luo[1], Hao Li[1], Troy Randall[1], John Edwin Bradley[1], Justin J. Taylor[2], John D. Mountz[3] and Hui-Chen Hsu[1]. [1]University of Alabama at Birmingham, Birmingham, AL, [2]Fred Hutchinson Cancer Research Center, Seattle, WA, [3]Birmingham VA Medical Center, Birmingham, AL.

Background/Purpose: Systemic lupus erythematous (SLE) is characterized by production of highly pathogenic IgG autoantibodies (autoAbs). While serum autoAb profiling is standard, it remains challenging to isolate authentic autoreactive B cells that give rise to these autoAbs. Similar autoAbs are spontaneously produced in lupus-prone BXD2 mice that display apoptotic cell clearance defects and heightened type I interferon (IFN) signals. The purpose of this study is to develop a comprehensive autoepitope and tetramer strategy to identify the dominant autoantigens (autoAg) and the underlying mechanisms promoting the development of autoreactive B cells in BXD2 mice.

Methods: A PEPperPRINT Autoimmunity Microarray covering 3,653 database derived, linear B-cell autoepitopes was probed with B6 and BXD2 serum to determine IgM and IgG binding reactivity. Top peptides were selected for 3D crystal structural analysis. A panel of over 50 peptide epitopes were verified by ELISA and ELISPOT. Two epitopes from RNA-binding lupus La and 70 kDa U1snRNP were used to generate B cell tetramers for characterization of Ag-specific subpopulations of B cells.

Results: The dominant epitopes recognized by BXD2 autoAbs are those commonly found in human SLE patients. Many immunodominant epitopes are located in cryptic regions of the native protein. The strongest autoAb response was observed with nuclear peptides from RNA binding proteins (RBP) including lupus La_{13-27} LEAKICHQIEYYFGD, $U1snRNP_{357-373}$ SHRSERERRRDRDRDRD, and $SmD1_{97-111}$RGRGRGRGRGRGRG. Other nuclear autoAgs include histones, centromere, and RNA polymerase III. Tetramer analysis revealed a significant expansion in La^+ and $snRNP^+$ memory B cells and marginal zone precursor (MZ-P) B cells in BXD2 vs. B6 in both the circulation and the spleen. Phenotype analysis of $tetramer^+$MZ-P B cells showed upregulation of type I IFN inducible activation molecules CD69 and CD86 in BXD2 mouse spleens.

Conclusion: The bona fide presence of RBP cryptic autoAgs that were not predicted by Ag prediction programs is consistent with the previous finding that defective clearance of apoptotic blebs in BXD2 mice leads to production of autoepitopes that break B cell tolerance. The potential activation of the TLR7 pathway by RBPs in combination with the upregulation of type I IFN response in Ag-specific MZ-P B cells further suggest that expanded $tetramer^+$ MZ-P B cells may be a result of apoptotic cell clearance defects. In light of our previous findings that MZ-P B cells are exceptional apoptotic Ag delivery $MHCII^{hi}$, $CD86^{hi}$cells and can stimulate CD4 T cells, these results suggest that specific targeting on TLR7 and type I IFNs may be important to eliminate autoAg-specific B cells.

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Epratuzumab Induces Broad Inhibition of B Cell Receptor Proximal Signaling but Has Opposing Effects on Distal Signaling in B Cell Subsets: A Profile of Effects on Functional Immune Signaling By Single Cell Network Profiling. Alison Maloney[1], Drew Hotson[2], Stephen Rapecki[1], Gianluca Fossati[1], Simon Lumb[1], David Rosen[2], Santosh Putta[2], Nikil Wale[2], David Spellmeyer[2], Alessandra Cesano[2], Rachael Hawtin[2] and Anthony Shock[1]. [1]UCB Pharma, Slough, United Kingdom, [2]Nodality Inc., South San Francisco, CA.

Background/Purpose: Epratuzumab is a humanized monoclonal antibody targeting the B cell-specific protein CD22 and is in Phase 3 clinical trials in patients with systemic lupus erythematosus (SLE). Epratuzumab does not deplete B cells, rather, the mechanism of action centers on CD22 regulatory activity of B cell receptor (BCR) modulation, via inhibition of specific BCR-driven phosphorylation events (Syk, PLCγ2) and Ca^{2+} flux.[1] The aim of this study was to assess the effects of epratuzumab on receptor activation and BCR signaling across multiple B cell subsets in peripheral blood mononuclear cells (PBMC) from a large cohort of healthy donors.

Methods: Single Cell Network Profiling (SCNP) is a multiparametric, flow cytometry-based technology that enables simultaneous analysis of signaling networks in multiple immune cell subsets.[2] BCR modulated signaling (anti-IgG/anti-IgM) was profiled by SCNP in PBMC from 60 healthy donors (HD) across naïve (CD27-/IgD+), switched memory (CD27+/IgD-) and unswitched memory (CD27+/IgD+) B cell subsets. Surface receptor (CD22, CD19), proximal (Syk, Slp76, BTK, PLCγ2) and distal (Akt, Erk, S6, p38, IkBa, NFκB-p105) signaling was interrogated 5 or 15 minutes post modulation in the presence and absence of epratuzumab (10mg/ml), which had been pre-incubated with cells for 1 hour.

Results: On-target epratuzumab activity in B cells was identified as induction of $pCD22\ Tyr^{807}$, most pronounced in naïve B cells ($p<0.001$). Broad inhibition of all examined BCR-proximal signaling ($p<0.0001$) was observed in the whole B cell population with the most pronounced effects observed in the switched memory population. Strong inhibition of BCR modulated pCD19 ($p<0.001$) was also seen in this population, which may contribute to inhibition of BCR activation events. Inhibition of distal signals was demonstrated specifically in the switched memory B cell population whilst conversely, in the naïve B cell subset, evidence for activation of distal signaling ($p<0.0001$) was observed. Interestingly, weak activation of pAkt was observed in both naïve and switched memory B cells.

Conclusion: Broad analysis of functional immune signaling across B cell subsets identified epratuzumab inhibition of BCR-proximal signaling, supporting an inhibitory role in BCR activation. Opposing effects on distal

signaling were identified in the naïve and memory populations. In switched memory B cells inhibition of pCD19 and downstream signals was demonstrated. In contrast, in naïve B cells activation of distal signals was observed. These data have implications for understanding the functional consequences of epratuzumab treatment on B cell pathologic activity in patients with autoimmune diseases such as SLE.

References

1. Sieger N. Arthritis Rheum 2013;65:770
2. Cesano A. Cytometry Part B 2012;82B:158

Disclosure: A. Maloney, UCB Pharma, 3; **D. Hotson**, Nodality Inc., 3; **S. Rapecki**, UCB Pharma, 3; **G. Fossati**, UCB Pharma, 3; **S. Lumb**, UCB Pharma, 3; **D. Rosen**, Nodality Inc., 3; **S. Putta**, Nodality Inc., 3; **N. Wale**, Nodality Inc, 3; **D. Spellmeyer**, Nodality Inc., 3, Nodality Inc., 1; **A. Cesano**, Nodality Inc., 3; **R. Hawtin**, Nodality Inc., 3; **A. Shock**, UCB Pharma, 3.

2874

Pro-Inflammatory FcRL4+ Memory B Cells in Joints of RA Patients: Immunoglobulin Gene Characteristics and Antigen Specificity. Khaled Amara[1], Lorraine Yeo[2], Natalie Sippl[1], Philip Titcombe[1], Andrew Filer[3], Karim Raza[3], Dagmar Scheel-Toellner[2] and Vivianne Malmström[4]. [1]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institutet, SE-17176 Solna, Stockholm, Sweden., Stockholm, Sweden, [2]Rheumatology Research Group, Centre for Translational Inflammation Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK, Birmingham, United Kingdom, [3]Rheumatology Research Group, MRC Centre for Immune Regulation, School of Immunity and Infection, University of Birmingham, Birmingham, United Kingdom, [4]Rheumatology Unit, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Our recent findings identified a subset of pro-inflammatory memory B cells in the RA synovium characterized by the expression of the surface protein Fc receptor like 4 (FcRL4)[1]. FcRL4+ve B cells produce RANKL, and express high levels of TNF mRNA, indicating a destructive, pro-inflammatory role for this B cell subpopulation. It is however unclear how synovial FcRL4+ve B cells develop, whether they have undergone hypermutation in germinal centers and the nature of their relationship with FcRL4-ve B cells at the same site. The aim of this project was to investigate whether autoreactive features would accumulate in the FcRL4+ve subset by investigating the antigen-specificity and Ig gene characteristics of FcRL4 +ve versus -ve B cells from both synovial tissue and fluid of RA patients.

Methods: Single FcRL4+ve and -ve memory B cells were sorted from synovial tissue (n=2) and synovial fluid (n=5) of patients with active RA. Their Ig variable region genes were sequenced and subsequently expressed to generate recombinant monoclonal antibodies. Antigen-specificities of the generated monoclonal antibodies were determined by ELISA.

Results: In total, we have cloned and sequenced B cell receptors from 332 individual B-cells (171 from FcRL4+ and 160 from FcRL4- cells). The Ig gene sequence analyses demonstrated that the Ig repertoire was highly diverse with no major differences in the *IGH* and *IGK* or *IGL* gene segment usage or *IGH*CDR3 features between FcRL4+ and FcRL4- memory B cells. From the sequenced clones we have so far generated 38 recombinant monoclonal antibodies (from both FcRL4+ve and FcRL4–ve B cells) and determined their specificity for citrullinated candidate autoantigens. We found no difference in the frequency of autoreactive Ig in the FcRL4 +ve versus -ve cells. 13 antibodies reacted to citrullinated antigens (including α-enolase, fibrinogen, and vimentin) without recognizing the unmodified arginine control peptides.

Conclusion: We conclude that the FcRL4+ve and FcRL4-ve memory B cells, while functionally and phenotypically distinct, are both post-germinal center hypermutated B cell subsets with similar Ig gene features. We have not identified a clonal relationship, but overall both B cell receptor characteristics and antigen specificities suggest that the two B cell subpopulations may originate from similar immune responses differentiating into functionally distinct subsets.

[1] Yeo L, Lom H, Juarez M, et al. Ann Rheum Dis (2014) doi:10.1136/annrheumdis-2013–204116

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ACR Concurrent Abstract Session
Cytokines, Mediators, Cell-cell Adhesion, Cell Trafficking and Angiogenesis II

Tuesday, November 18, 2014, 4:30 PM–6:00 PM

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Macrophage Expression of Hypoxia-Inducible Factor-2 Alpha Promotes Rheumatoid Arthritis Progression. Munitta Muthana[1], William Jacob Hardy[1], Sarah Hawtree[1], Fiona Wright[1], Ursula Fearon[2], DJ Veale[3], Mauro Perretti[4] and Anthony G. Wilson[5]. [1]University of Sheffield, Sheffield, United Kingdom, [2]Translational Rheumatology Research Group, Dublin, Ireland, [3]St. Vincent's University Hospital, Dublin, Ireland, [4]Barts and the London School of Medicine, London, United Kingdom, [5]University College Dublin, Dublin, Ireland.

Background/Purpose: Hypoxia exists in many diseased tissues including arthritic joints, atherosclerotic plaques and malignant tumours. Macrophages accumulate in these hypoxic sites where they possess broad pro-inflammatory, destructive and remodelling potential leading to inflammation and joint destruction. Macrophages respond to hypoxia by up regulating the hypoxia inducible transcription factors– HIF-1 and −2, which leads to the up-regulation of genes involved in proliferation, angiogenesis, and glucose metabolism.

The purpose of our study was to characterise the HIF-2 expressing macrophage populations in response to joint hypoxia, and in particular to dissect out the effects of HIF-2 in a murine model of arthritis.

Methods: Arthroscopy sections from RA patients with mild (~40mmHg) or severe (~3mmHg) joint hypoxia were immunostained with anti-HIF 2 and co-localised with the pan-macrophage marker CD68 as well as other M1 and M2 macrophage markers. Cell-specific RNA was purified from CD68+ve macrophages in RA tissue by laser capture microdissection (LCM) and differential gene expression was determined using the RT^2 Profiler PCR inflammatory arrays. The significance of HIF-2 was also evaluated in the K/BxN serum transfer model in mice bearing a targeted deletion of HIF-2 in myeloid cells including macrophages (HIF2fl/fl; LysM-Cre+' mice). Arthritis was assessed clinically and histologically.

Results: In patients with severely hypoxic joints macrophages predominately expressed HIF-2 as well receptors for VEGF (Flt1), angiopoietin 'Tie2' and mannose 'CD206' markers associated with M2-skewed macrophages. However, expression of CXCL-2, −4, −5, IL-1a, IL-6 IL-8 & TNFa were also all up regulated compared to macrophages from mildly hypoxic joints. *In vivo*, macrophages lacking HIF2 significantly suppressed disease development indicating an indispensable role for HIF2 in supporting macrophages in K/BxN serum-transfer arthritis.

Conclusion: HIF-2 expressing macrophages have an M1 & M2-like phenotype in patients with severely hypoxic joints and loss of HIF-2 in macrophages suppressed arthritis in mice. Collectively, our data identify HIF-2 as an important regulator of macrophage function, suggesting it may be a useful therapeutic target for treating RA.

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2876

Interleukin-10 Receptor Blockade during Lcmv Infection Results in Macrophage Activation Syndrome-like Disease in Mice. Lehn K. Weaver[1] and Edward M. Behrens[2]. [1]Children's Hospital of Philadelphia, Philadelphia, PA, [2]Childrens Hospital of Philadelphia, Philadelphia, PA.

Background/Purpose: Macrophage activation syndrome (MAS) is the rheumatic disease-associated member of a group of hyperinflammatory syndromes characterized by uncontrolled cytokine storm manifest as unremitting fevers, cytopenias, splenomegaly, hepatitis, coagulopathy, multisystem organ failure, and death in its most severe form. The clinical features of MAS are shared with other hyperinflammatory syndromes, of which genetic defects in cytotoxicity have provided insight into the pathogenesis driving viral-triggers of disease. However, severe defects in cellular cytotoxicity have not been found in patients with MAS making it unclear how viral infection can trigger hyperinflammation in this condition.

Methods: C57Bl/6, interferon (IFN)$\gamma^{-/-}$, and IFN$\alpha^{-/-}$mice were infected with LCMV Armstrong and treated with or without interleukin (IL)-10 receptor blockade. Survivial, weight loss, splenomegaly, cytopenias, and serum cytokine levels were measured after viral infection.

Results: Wildtype mice treated with IL-10 receptor blockade succumbed to MAS-like hyperinflammation manifest as weight loss, splenomegaly, bicytopenias, and hypercytokinemia during LCMV infection. IFN$\gamma^{-/-}$ and IFN$\alpha^{-/-}$mice were not protected from LCMV-induced disease in this model, as they developed severe weight loss, splenomegaly, cytopenias, hypercytokinemia, and more severe mortality when IL-10 receptor was blocked.

Conclusion: IL-10 receptor blockade leads to heightened immunopathology in the setting of LCMV infection similar to MAS-like hyperinflammatory disease. Unlike other hyperinflammatory syndromes, this immunopathology is independent of IFNγ and IFNα, and highlights the capacity of other inflammatory mediators to cause viral-induced hyperinflammation during IL-10 receptor blockade. Furthermore, these data highlight a novel mechanism that could contribute to MAS-like disease whereby defects in IL-10 production and/or sensing could exacerbate hyperinflammatory immunopathology induced by viral infection without genetic defects in cellular cytotoxicity.

Disclosure: L. K. Weaver, None; **E. M. Behrens**, None.

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Novel Function of Tocilizumab As a Modulator of Interleukin-27-Mediated Anti-Inflammatory Responses. Misato Hashizume[1], Jun Kikuchi[2], Keiko Yoshimoto[2] and Tsutomu Takeuchi[2]. [1]Chugai Pharmaceutical Co., Ltd., Gotemba, Japan, [2]Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: The immunological roles of interleukin 27 (IL-27) have been reported in the function of regulatory T cells (Treg), monocytes and osteoclasts, and these cells are involved in various autoimmune diseases, such as rheumatoid arthritis (RA), lupus, systemic sclerosis, and psoriasis. There was a paucity of information about how the function of IL-27 is regulates in autoimmune disease. IL-27 is a heterodimeric cytokine composed of IL-27p28 and EBI3, which are analogous to IL-6 and soluble IL-6 receptor (sIL-6R) respectively. In this study, we investigated whether a possible role of sIL-6R in regulating IL-27 function.

Methods: CD14$^+$ cells were isolated from peripheral blood in RA patients. MCP-1 was measured by ELISA in the culture supernatant of incubated with TNF-α, IL-27, sIL-6R, anti-IL-6 antibody and anti-IL-6R antibody (tocilizumab). In the experiments of osteoclasts, CD14$^+$cells were cultured with RANKL and M-CSF in the presence of IL-27, sIL-6R, anti-IL-6 antibody and tocilizumab for 4 days and the number of osteoclasts was counted. Consecutive RA patients who received 8mg/kg of tocilizumab every 4 weeks as first biologics between March 2010 and April 2012 after giving a written informed consent were included in this study (n=39). The proportions of Treg and monocytes at base line, week 24 and week 52 were sequentially measured by using the expression levels of differentiation markers, activation markers and co-stimulatory molecule markers in T cells and monocytes defined in previous report.

Results: Whereas IL-27 reduced MCP-1 production by CD14$^+$ cells stimulated with TNF-α, further addition of sIL-6R restored the production of MCP-1. To clarify which is an important unit either IL-6 or sIL-6R for modulating IL-27 function, we measured MCP-1 production in the presence of anti-IL-6 antibody or tocilizumab. Tocilizumab, but not an anti-IL-6 antibody, inhibited TNF-α-induced MCP-1 production in the presence of IL-27 and sIL-6R. RANKL-mediated osteoclast formation was suppressed by IL-27, and sIL-6R antagonized the activity of IL-27. Tocilizumab, but not anti-IL-6 antibody inhibited osteoclastgenesis in the presence of IL-27 and sIL-6R. Over the treatment with tocilizumab, the proportions of Treg and HLA-DR$^+$ activated Treg were significantly increased from baseline (Treg: $p=0.0034$, activated Treg: $p=0.0008$ by Wilcoxon rank test). The proportions of HLA-DR$^+$CD14$^+$ activated monocytes, CD69$^+$CD14$^+$ activated monocytes and CD16$^+$CD14$^+$ non-classical monocytes were significantly decreased from baseline to 52 weeks after treatment (HLA-DR$^+$ activated monocytes: $p=0.0006$, CD69$^+$activated monocytes: $p<0.0001$, non-classical monocytes: $p<0.0001$).

Conclusion: Our results suggest that sIL-6R antagonizes the IL-27 signaling, and blocks IL-27-mediated anti-inflammatory effects. In addition, tocilizumab, but not an anti-IL-6 antibody rescued IL-27-mediated anti-inflammatory effects in the presence of sIL-6R. And in vivo study demonstrates that tocilizumab showed differential effects on the proportions of circulating Treg and monocytes in RA patients. These data suggest that tocilizumab may be involved in modulating the anti-inflammatory responses of IL-27.

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2878

G Protein Signaling Modulator 3 (GPSM3) Deficiency Is Protective in Inflammatory Arthritis Models and Altered GPSM3 Gene Products Correlate with Single Nucleotide Polymorphisms in Humans. Teresa K. Tarrant[1], D. Stephen Serafin[1], Elizabeth Sugg[1], Roman Timoshchenko[1], Matthew J. Billard[1], David P. Siderovski[2] and Kristy Richards[3]. [1]Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]West Virginia University School of Medicine, Morgantown, WV, [3]Dept. of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC.

Background/Purpose: GPSM3, a newly described regulator of heterotrimeric G protein signaling, is selectively expressed in hematopoietic cells with high expression in monocytes. We have shown that *Gpsm3* deficient (−/−) mice are protected from Collagen Antibody Induced Arthritis due in part to their attenuated monocyte responses, including decreased *ex vivo* migration to the chemokines CX3CL1, CCL2, and chemerin, and enhanced apoptosis, which leads to an observed decrease in proinflammatory intra-articular *IL-6* and *IL-1b* transcripts in the joint. Given the restricted expression of *GPSM3* in leukocytes and the functional phenotypes observed in immune cells lacking *GPSM3* expression, we chose to examine effects of *GPSM3* deficiency in Collagen Induced Arthritis (CIA) and to analyze whether single nucleotide polymorphisms (SNPs) within the human *GPSM3* gene locus, associated with a decreased incidence of autoimmunity, correlate with altered *GPSM3* gene products.

Methods: *Gpsm3*−/− and *Gpsm3*+/+ DBA1-J mice were immunized with heterologous type II collagen in Freund's Adjuvant with a booster immunization at day 21 per published protocols. Arthritis was assessed by a blinded observer for paw swelling and clinical disease score (0–4). Paws were processed at day 42 for histopathology. Serum B-cell activating factor (BAFF) was measured by commercial ELISA (R&D Systems) per manufacturer's instructions on day 14. DNA and RNA was isolated from healthy human subject blood using Qiagen purification reagents. Genotyping for SNP (A (minor)/G (major) transition substitution) was performed using commercially available TaqMan SNP Genotyping Assay (SNP ID = rs204989) from Applied Biosystems by Life Technologies. qRT-PCR primers for known *GPSM3* transcripts *−001*, *−002*, *−003*, and *−004* were designed from NCBI (−001 and −002) and Ensembl (−003 and −004) databases, and validated by gel electrophoresis for sequence length, sequencing, melt curve analysis, and PrimerBlast. qRT-PCR of cDNA from healthy human subject blood was performed using a Biorad CFX96 Real-Time System and standard protocols. Data was calculated as relative expression compared to the housekeeping gene *IDUA*(ΔCt).

Results: *Gpsm3*−/− mice are protected from CIA and have significantly decreased serum BAFF levels. Healthy human subjects carrying protective SNP alleles that correlate with a decreased incidence of rheumatoid arthritis (RA) and four other autoimmune diseases have decreased levels of transcripts *GPSM3-001*, *−002*, and *−004*, but significantly increased levels of the transcript *GPSM3-003*, which is thought to be subjected to nonsense-mediated decay.

Conclusion: Our goal from these studies is to determine whether GPSM3 has immune system-modulating potential for the treatment of autoimmune diseases with particular focus on inflammatory arthritis. *Gpsm3*−/− mice are protected from two models of inflammatory arthritis through mechanisms involving monocyte function. *GPSM3* has altered mRNA transcripts in healthy human subjects with SNPs that correlate with decreased RA and other autoimmune diseases, suggesting differential gene regulation.

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2879

Epigallocatechin-3-Gallate (EGCG) Suppresses IL-1β-Induced IL-6 and IL-8 Synthesis By Selectively Inhibiting TAK1 Activation in Human Rheumatoid Arthritis Synovial Fibroblasts. Anil Singh[1], Sharayah Riegsecker[2], Sadiq Umar[1] and Salahuddin Ahmed[1]. [1]Washington State University, Spokane, WA, [2]University of Toledo, Toledo, OH.

Background/Purpose: In rheumatoid arthritis (RA), the role of interleukin-1β (IL-1β) signaling proteins (IRAK-1/TAK-1/TRAF-6) proximal to IL-1 receptor in mediating proinflammatory response is not completely understood. Using IL-1β-induced IL-6 and IL-8 production in RA synovial fibroblasts (RA-FLS), we examined the role of key signaling molecules critical in mediating its inflammatory response. We also tested if EGCG, a potent anti-inflammatory compound, inhibits IL-1β signaling protein to suppress IL-6 synthesis in RA-FLS.

Methods: RA-FLS were treated with IL-1β for different time alone or in the presence of EGCG. Western blotting analysis was utilized to study activation/phosphorylation of different IL-1β signaling proteins. In vitro kinase activity of IRAK-1 was determined using ADAPTA kinase assay. Changes in the ubiquitination patterns of IL-1β-stimulated RA-FLS was studied using immunoprecipitation (IP) assay. Using chemical inhibitors or siRNA for IRAK-1, TAK-1 or TRAF-6, their respective roles were examined in IL-1β-induced IL-6 and IL-8 expression by ELISA and qRT-PCR methods. Therapeutic effect of EGCG on these signaling events was evaluated.

Results: IL-1β-induced IL-6 and IL-8 production in RA-FLS was significantly inhibited by EGCG (2.5–20 μM) in a dose-dependent manner ($p<0.01$; $n=5$). IL-1β induced rapid degradation of IRAK-1 within 1–5 min followed by the activation of TAK-1 phosphorylation in RA-FLS. Using the chemical inhibitors for TAK-1, IRAK-1, and TRAF-6, our novel findings showed a complete blockade of IL-1β-induced IL-6 and IL-8 production by TAK-1, but only a modest inhibition with IRAK-1 or TRAF-6 inhibitors ($p<0.01$ for TAK-1; $n=4$). Confirmatory studies using siRNA method also showed a marked inhibition of IL-6 production by TAK-1 or IRAK-1 siRNA. Although EGCG inhibited *in vitro* IRAK-1 kinase activity by almost 65%, it did not prevent the IL-1β-induced proteasomal degradation of IRAK-1 in RA-FLS. To our surprise, EGCG selectively inhibited IL-1β-induced TAK-1 phosphorylation in a dose-dependent manner ($p<0.05$; $n=4$). Interestingly, we observed that the levels of TRAF-6 remained unchanged upon IL-1β stimulation. IP of RA-FLS cell lysates with global FK2 ubiquitin antibody and further Western blotting analysis showed that IL-1β activated TRAF-6 ubiquitination was not modulated by EGCG, suggesting TAK-1 as a potential therapeutic target in IL-1β signaling.

Conclusion: Our study provides a novel evidence of an important mediatory role of TAK-1 in IL-1β signaling in RA-FLS and warrants further testing of EGCG or it synthetic analogs as TAK-1 inhibitors for the treatment of RA.

Disclosure: A. Singh, None; **S. Riegsecker**, None; **S. Umar**, None; **S. Ahmed**, None.

2880

Elevated Levels of Soluble Inflammatory Mediators and Lupus-Specific Connective Tissue Disease Questionnaire Scores Discern Unaffected First Degree Relatives of Lupus Patients from Unaffected Individuals Not Related to Lupus Patients. Melissa E. Munroe[1], Kendra A. Young[2], Jennifer Fessler[1], Dustin Fife[1], Diane L. Kamen[3], Joel M. Guthridge[1], Timothy B. Niewold[4], Michael H. Weisman[5], Mariko L. Ishimori[5], Daniel J. Wallace[5], David R. Karp[6], John B. Harley[7], Gary S. Gilkeson[3], Jill M. Norris[2] and Judith A. James[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Colorado School of Public Health, Aurora, CO, [3]Medical University of South Carolina, Charleston, SC, [4]Mayo Clinic, Rochester, MN, [5]Cedars-Sinai Medical Center, Los Angeles, CA, [6]UT Southwestern Medical Center, Dallas, TX, [7]Cincinnati Children's Hospital Medical Center; US Department of Veterans Affairs Medical Center, Cincinnati, OH.

Background/Purpose: Identifying populations at risk of SLE is essential to curtail inflammatory damage and select individuals for prevention trials. First-degree relatives (FDRs) of lupus patients have an increased risk of developing SLE. Using a unique resource of SLE patient family members with longitudinal samples available, the goal of this study is to determine factors that distinguish FDRs who remain unaffected over time from unrelated, unaffected individuals.

Methods: We evaluated plasma samples from 154 unaffected FDRs of known SLE patients with samples available from previous genetic studies and who remained unaffected at follow-up evaluation (mean time to follow-up 6.8 years). FDRs were matched 2:1 by gender, race and age ($\pm$5 years) to 77 unaffected individuals unrelated to SLE patients (Controls). FDRs and Controls provided clinical and demographic information, and completed the SLE-specific portion of the Connective Tissue Disease Screening Questionnaire (CSQ) at baseline (BL) and follow-up (FU). BL and FU plasma samples were assessed for autoantibody production (ANA, anti-dsDNA, aCL, Ro, La, Sm, nRNP, and ribosomal P antibodies) and for 52 soluble inflammatory mediators (BLyS, APRIL, cytokines, chemokines, and shed TNF receptors). Logistic regression modeling of CSQ scores, number of autoantibody specificities, and select soluble mediators (via Random Forest) was utilized to evaluate whether certain factors distinguished unaffected FDRs from Controls.

Results: FDRs had significantly higher BL and FU CSQ scores than Controls ($p<0.0001$); CSQ scores were higher in female FDRs vs. male FDRs or female Controls ($p<0.0001$). No significant difference in the number of positive autoantibody specificities were noted between FDRs and Controls. FDRs had significant ($p\leq0.01$) alterations in 38 (of 52) soluble mediators compared to Controls, including innate and adaptive mediators of inflammation, chemokines, and TNF superfamily members. APRIL and BLyS, IFN-associated chemokines IP-10, MIG and MIP-1α, as well as the regulatory mediators IL-10 and TGF-β, were significantly higher in FDRs at BL and FU ($p\leq0.002$). A number of mediators (14 at BL and 18 at FU) found to best separate FDRs from Controls by Random Forest strongly correlated with CSQ scores ($p\leq0.0002$). Of these, levels of MIP-1α ($p=0.008$), MIG ($p=0.019$), GROα ($p=0.001$), ICAM-1 ($p=0.007$), and VEGF ($p=0.004$), along with CSQ scores ($p=0.010$), best distinguished FDRs from Controls in logistic regression models.

Conclusion: Unaffected FDRs of SLE patients demonstrate significantly altered levels of soluble inflammatory, as well as regulatory, mediators compared to matched, unrelated, unaffected Controls. These alterations are present despite lack of progression to classified SLE, suggesting that multiple perturbations in immune-mediated inflammatory processes present in family members of SLE patients may be offset by inhibitory factors, providing unique insights for potential autoimmune disease prevention or SLE disease treatment.

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ACR Concurrent Abstract Session
Education
Tuesday, November 18, 2014, 4:30 PM–6:00 PM

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The Center of Excellence in Musculoskeletal Care and Education: A Sustainable Interprofessional, Multidisciplinary Programmatic Innovation Developed with the Department of Veterans Affairs. Michael J. Battistone, Andrea M. Barker, Marissa Grotzke, Peter Beck, Jeffery Berdan, Caroline Milne, JoAnn Rolando and Grant W. Cannon. Salt Lake City VA and University of Utah, Salt Lake City, UT.

Background/Purpose: While musculoskeletal (MSK) problems are common in primary care, the current formal education in the evaluation and management of these conditions is inadequate. Through funding from the Veterans Affairs (VA) Office of Academic Affiliations, we developed an interprofessional, interdisciplinary, mixed-method program to enhance the clinical education of medical students, residents, fellows, and trainees of other health professions.

Methods: The week-long course begins with didactics, is reinforced through technology-enhanced simulation and peer-teaching in small-group settings, and culminates in supervised ambulatory clinical experiences and reflective practice.

Table 1

Monday	Tuesday	Wednesday	Thursday	Friday
Introduction	Back Pain	Gout	Orthopaedic Injection Clinic *-or-* PM&R Clinic	Center of Excellence Multidisciplinary Musculoskeletal Clinic
	-Didactic-	*-Didactic-*		
Introduction to the Evaluation of Rheumatic Disease	Physical Exam of the Knee	Rheumatology 101: Serologies and RA		
-Didactic-	*-Didactic-*	*-Didactic-*		
Physical Exam of the Shoulder	Physical Exam of the Knee	Arthrocentesis *-Didactic and Group Practice-*		
-Didactic-	*-Group Practice-*			
Physical Exam of the Shoulder	Approach to Knee Pain *-Didactic-*			
-Group Practice-				
Approach to Shoulder Pain				
-Didactic-				
Lunch	Lunch	Lunch	Lunch	Lunch

Bone Health I:	Bone Health II:	Rheumatology Clinic	Musculoskeletal Clinic	Rheumatoid Arthritis Clinic
Osteoporosis Risk Factors and Evaluation	Osteoporosis Treatment and Hypogonadism			
-Didactic-	*-Didactic-*			
	Shoulder Cases			OSCE
	-Group Practice-			

Participants learn to perform, describe, and document a systematic physical exam of the shoulder and knee, interpret these findings, and develop patient-centered management options in a framework of high value care. Faculty represent Internal Medicine (IM) (Primary Care, Rheumatology, Endocrinology), Orthopaedics, and Physical Medicine and Rehabilitation (PM&R) disciplines. Course assessments include written surveys, 2-station Objective Structured Clinical Examination, and individual exit interviews.

Results: Student and trainee participants in the 2013–14 academic year are summarized below. Survey response rate was 89%. Post-course competency in examining the shoulder and knee, and in reporting, interpreting, and managing the case using a framework of high-value care, was confirmed with 2-station OSCE.

Table 2

Discipline/ Profession	Post-Graduate Trainees							Students		
	IM	Rheum	Geri	Neuro	Ortho	PM&R	Occ Med	Med	APRN	PA
Number of Trainees	34	1	2	1	4	5	1	4	9	10
Percentage of Cohort	48%	1%	3%	1%	6%	7%	1%	6%	13%	14%

	Pre-MSK COE Week	Post-MSK COE Week
Able to evaluate and manage shoulder complaints	16%	98%
Able to evaluate and manage knee complaints	35%	94%
Competent to aspirate/inject knee or subacromial space	18%	76%

Conclusion: The MSK Intensive Education Week provides an interdisciplinary and interprofessional environment to teach trainees from multiple backgrounds in the evaluation and management of patients with complex MSK diseases through a cooperative practice model and evaluates their competency to practice in this system.

Disclosure: M. J. Battistone, None; **A. M. Barker**, None; **M. Grotzke**, None; **P. Beck**, None; **J. Berdan**, None; **C. Milne**, None; **J. Rolando**, None; **G. W. Cannon**, None.

2882

Using Decision-Based Learning to Highlight Rheumatic Disease for Third-Year Medical Students. Karen Law[1], J Richard Pittman[1] and Chad Miller[2]. [1]Emory University School of Medicine, Atlanta, GA, [2]Tulane University Health Sciences Center School of Medicine, New Orleans, LA.

Background/Purpose: Opportunities for exposure to rheumatology are limited in medical school, especially during the clinical years. In addition, because the rheumatic diseases represent a small portion of the National Board of Medical Examiners Subject Examination (SHELF exam) for the Internal Medicine clerkship, clerkship directors are reluctant to devote limited class time to rheumatology.

This project aims to improve medical student exposure to rheumatology during the third-year Internal Medicine Clerkship via Decision-Based Learning (DBL), a simulated case-based teaching technique. Learners work in teams on a challenging clinical case. Teams are given a description of the patient's history and physical examination; each team collaborates to generate a differential diagnosis, then order tests and studies to work up the case. A simulated "bank" of tests and studies is available, with each test coming with a "price" that the team is charged. The teams compete to solve the case by ordering and interpreting studies while also spending the least amount of money. Because of the cost-conscious and competitive nature of the exercise, learners are incentivized to employ prudent hypothesis testing and diagnostic reasoning to decide what is "the next best step" to arrive at the diagnosis.

DBL facilitates rheumatology exposure within the broad context of internal medicine, a format more appropriate for the medical student level than typical disease-specific rheumatology curricula. In addition, the DBL format highlights the diagnostic complexity of rheumatic cases. Students also practice critical thinking and cost consciousness, areas of medical education that are frequently lacking.

Methods: The project introduced DBL to third year medical students during their clerkship in Internal Medicine. Control sessions consisted of usual lecture-style didactics. Learners were given a survey after each session to rate their learning experience.

Results: Student feedback for DBL sessions was significantly higher than control didactic sessions ($p < 0.01$). 67% of learners rated DBL a "10" on a 10-point Likert scale compared to 35% for control ($p < 0.01$). Positive responses to DBL were also noted in the survey comments:

- "Really productive exercise; thought provoking"
- "Very high-yield, learned lots of new things"
- "Made us think about what to order & why- I don't feel we have gotten much experience with that during the rotation"

Conclusion: A novel case-based teaching technique facilitated medical student exposure to rheumatology during their clerkship in Internal Medicine. DBL resulted in significantly higher ratings of didactic sessions compared to traditional lecture-style didactics. Learners found the DBL sessions to be engaging and educationally valuable. This interactive teaching method can enhance the learning experience during the Internal Medicine clerkship; the realistic context in which Rheumatology topics are addressed may make it more appealing for Clerkship Directors to adopt. These findings support future evaluation of DBL with a case-control study to determine efficacy in the principal areas of Rheumatology-specific knowledge, diagnostic reasoning, and cost awareness.

Disclosure: K. Law, Rheumatology Research Foundation, 2; **J. R. Pittman**, None; **C. Miller**, None.

2883

Rheumatology-Specific Milestones for a Musculoskeletal Radiology Curriculum. Michelle Newkirk[1], Liem Mansfield[1], Jay B. Higgs[2] and Daniel Battafarano[1]. [1]San Antonio Military Medical Center, JBSA - Ft Sam Houston, TX, [2]San Antonio Military Medical Center, JBSA - Fort Sam Houston, TX.

Background/Purpose: In 2012, the Accreditation Council for Graduate Medical Education (ACGME) announced the required implementation of standardized milestones with entrustable professional activities (EPAs) for the semi-annual evaluation of resident/fellow performance which must be implemented by November 2014. However, little guidance was rendered as to the incorporation of these milestones and EPAs into the curriculum of a subspecialty training program. Our rheumatology fellowship has had a formal musculoskeletal (MSK) radiology rotation for the past five years as part of its core curriculum and has integrated internal medicine subspecialty curricular milestones with MSK radiology specific EPAs into this curriculum.

Methods: Utilizing a modified Delphi technique via e-mail, faculty and current fellows from the program established a consensus on EPAs for MSK radiology. The EPAs were individually rated using a nine-point Likert scale, with 1 being disagreement with the EPA and 9 being the most agreement. Agreed upon EPAs were then used as a foundation for the development of curricular milestones. These milestones were designed using a 5-level Dreyfus model which were defined as novice/critical deficiency, advance beginner, competent, proficient/ready for unsupervised practice, and expert/aspirational. The milestones were then incorporated into the core curriculum, with an emphasis placed on the "proficient" level and above for teaching purposes.

Results: Six faculty members and 2 rheumatology fellows participated in the process. Six EPAs were initially developed, and after two rounds of comments with rewording and scoring, all six EPAs rated in the highest agreement scores (see table). Curricular milestones for MSK radiology were then established in keeping with these EPAs. These curricular milestones were integrated into our core MSK radiology lecture series.

Entrustable Professional Activities (EPAs)	Mean Likert Score
1. Order and utilize appropriate diagnostic imaging studies for evaluation and management of patients with rheumatic disease.	8.9
2. Identify the optimal imaging modalities for patients with rheumatic disease within the context of patient comorbidities, preferences, treatment goals, financial considerations and insurance requirements.	8.3
3. Interpret signs of acute and/or chronic musculoskeletal disease on radiography and know when to consult a radiologist for further evaluation and interpretation.	7.7

4. Understand the written interpretation reports of radiography, computed tomography, ultrasound, magnetic resonance imaging, scintigraphy and bone mineral density studies and utilize the results to optimize the care of the patient with rheumatic disease.	8.6
5. Communicate directly with consulting radiologists when necessary to determine the optimal diagnostic studies to evaluate and manage patients with rheumatic disease.	8.1
6. Effectively communicate with patients their diagnostic imaging options, indications, alternatives and results in a clear and easily understood manner.	8.6

Conclusion: The interpretation and application of MSK radiology is critical in the training of a rheumatology fellow. Incorporating a dedicated radiology rotation which addresses specific milestones and EPAs is one way of ensuring trainees are exposed to a quality, uniform curriculum that meets the ACGME's next accreditation system requirements.

Disclosure: M. Newkirk, None; **L. Mansfield**, None; **J. B. Higgs**, None; **D. Battafarano**, None.

2884

Training the Rheumatologists of Tomorrow: The Canadian Experience. Alfred Cividino[1], Volodko Bakowsky[2], Susan Barr[3], Louis Bessette[4], Nader Khalidi[5], Christian A. Pineau[6], Janet E. Pope[7], David Robinson[8], Kam Shojania[9], Elaine Yacyshyn[10], Lynne Lohfeld[1] and Diane Crawshaw[1]. [1]McMaster University, Hamilton, ON, [2]Dalhousie University, Halifax, NS, [3]Heritage Medical Research Bldg, Calgary, AB, [4]Laval University, Québec, QC, [5]Division of Rheumatology, McMaster University, Hamilton, ON, [6]McGill University Health Center, Montreal, QC, [7]St Joseph Health Care, London, ON, [8]University of Manitoba, Winepeg, MB, [9]University of British Columbia, Vancouver, BC, [10]University of Alberta, Edmonton, AB.

Background/Purpose: Many countries face a shortage of rheumatologists. Based on an accepted benchmark of 1 specialist per 50,000 people as the number needed for effective patient care[1], recent figures show severe shortages in the U.S.[2]and Canada.[3]This qualitative environmental scan was designed to identify what faculty, administrators and learners associated with Canadian postgraduate rheumatology programs identify as appropriate means and messages that programs could use to attract future trainees.

Methods: Individual-level data from program faculty (F), administrators and learners (L) across Canada (n = 103) were collected via an online survey (n=78) and interviews (n = 25). Data were subjected to Thematic Framework Analysis to identify commonalities across sites to determine ways to address the rheumatology manpower shortage. Quotes are provided as examples.

Results: ***Participants:*** There were 103 respondents from nine programs including learners (medical students, junior residents (PGY1–3) rheumatology residents (PGY4–6) or new graduates); program and division directors and their assistants; and faculty in academic centres or community practices. Two-thirds of the survey respondents were female.

Ways to Increase Interest in Rheumatology: The need for rheumatologists was widely recognized. Respondents advocated targeting both undergraduates (*"People who influenced me were* [role models] *I had as a medical student"* [F]) and junior residents in Internal Medicine. Proposed methods included increasing exposure to rheumatology in undergraduate programs through formal lectures and courses, clinical skills and other hands-on training sessions, faculty available to shadow or mentor learners and postgraduate weekend information and training sessions, mandatory rotation for Internal Medicine residents, internships and career counseling.

Messaging to Promote Rheumatology: Messages to brand rheumatology as an attractive specialty included the intellectual challenge (*"This field fascinates me"* [L]; *"novel immunotherapies make it very exciting"* [F]), stimulating workday (*"nice mix of procedural and cerebral work"* [L]), positive relationships with colleagues and patients (*"According to a recent survey we are the happiest specialists"* [F]), alleviating suffering (*"We know how to treat arthritis now"* [L]), good quality of life and excellent job prospects (*"the health care system needs you"* [F]).

Conclusion: We found consensus on the need to inform potential trainees about rheumatology early in their education through a variety of messages and methods. Because of the shortage of rheumatologists it is important to increase awareness and information about the field by selectively using limited resources. The next step would be to collaboratively develop, test and evaluate tools designed to help increase the number of future rheumatologists, which will be applicable in many locales.

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2885

Clinical Training Opportunities in Two Innovative Ambulatory Resources: The Primary Care Musculoskeletal Clinic and Center of Excellence Multidisciplinary Clinic. Michael J. Battistone, Andrea M. Barker, Marissa Grotzke, Peter Beck, Jeffery Berdan, Phillip Lawrence and Grant W. Cannon. Salt Lake City VA and University of Utah, Salt Lake City, UT.

Background/Purpose: While musculoskeletal (MSK) problems are common in primary care, current training models do not adequately prepare primary care providers (PCP) to deal with these issues. With funding from the Veterans Affairs (VA) Office of Academic Affiliations (OAA), we developed a Center of Excellence (COE) for MSK Care and Education to meet this training need for health care professional trainees.

Methods: Two new weekly outpatient clinics, the Primary Care MSK (PC-MSK) and the Multidisciplinary (COE-MSK) Clinics were developed as key components of the COE. The PC-MSK is staffed by a rheumatologist and a physician assistant (PA) with orthopaedic experience. The COE-MSK is attended by a rheumatologist, endocrinologist, orthopaedic surgeon, physiatrist, and a PCP. All categorical internal medicine (IM) interns, orthopaedic interns, PM&R residents, and rheumatology fellows participate in this clinic over the course of the academic year. Additional IM residents, medical students, nurse practitioner students and physician assistant students are also included as space allows.

Results: In 2013–14, 80 trainees participated in the PC-MSK and COE-MSK clinics. The distribution of disciplines and professions represented in this multi-level cohort are shown in Table 1.

Table 1

	Post-Graduate Trainees							Students		
Discipline/Profession	**IM**	**Rheum**	**Geri**	**Neuro**	**Ortho**	**PM&R**	**Occ Med**	**Med**	**APRN**	**PA**
Number of Trainees	39	4	2	1	4	6	1	4	9	10
Percentage of Cohort	49%	5%	3%	1%	5%	8%	1%	5%	11%	12%

Since June 2013, 330 patients have been seen in these clinics. As shown in Table 2, most are referred from primary care, mainly by providers in non-resident clinics. Most non-resident referrals were to the PC-MSK clinic, all others tended to request the multidisciplinary COE-MSK clinic.

Table 2

		Referral Destinations	
Referral Sources	**Total**	**COE**	**MSK**
All Patients (n, %)	330 (100)	191 (58)	139 (42)
Primary Care	217	110	107
Resident Continuity Clinics	73	47	26
Faculty and Staff Clinics	138	60	78
Women's Clinics	6	3	3
Specialty Care	36	28	8
Medicine Subspecialties	25	18	7
Surgery	11	10	1
PC-MSK + COE-MSK (self-referrals)	23	19	4
Other	54	34	20
Procedures Performed (n, % of patients referred)	115 (35%)	43 (23%)	72 (52%)
Days to Consult Completion (mean, st.dev.)	47 (31.7)	55 (36.3)	36 (19.8)

Conclusion: These clinics provide unique and innovative opportunities for a broad range of trainees in a rich interdisciplinary and interprofessional educational environment. Additionally, these clinics are a valuable resource to primary care providers, specialty physicians, and patients for prompt and comprehensive care for veterans with either limited or complex MSK problems.

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Assessing Rheumatology Fellows' Teaching Skills Using the Objective Structured Teaching Exercise (OSTE). Eli M. Miloslavsky[1], Marcy B. Bolster[1], Kenneth S. O'Rourke[2] and Lisa G. Criscione-Schreiber[3]. [1]Massachusetts General Hospital, Boston, MA, [2]Wake Forest School of Medicine, Winston-Salem, NC, [3]Duke University Health System, Durham, NC.

Background/Purpose: The interaction between rheumatology fellows and Internal Medicine residents in the setting of a consult offers an important opportunity for resident learning. However, teaching in the setting of a consult interaction can be challenging due to time constraints and lack of a longitudinal relationship between the resident and fellow. Fellows' teaching skills in the setting of the consult interaction have not been evaluated. We conducted a pilot study utilizing the Objective Structured Teaching Exercise (OSTE)[1] to evaluate rheumatology fellows' teaching skills.

Methods: First and second year rheumatology fellows from 5 training programs participated in a one-station OSTE during a 7 station rheumatology Objective Structured Clinical Examination (OSCE) in February 2014. Following the OSCE format, fellows were given 10 minutes to teach a standardized resident in the setting of a simulated consult and relay their consult recommendations, followed by 2 minutes of feedback. Prior to beginning the station fellows were given written instructions on the objectives of the exercise as well as a resident admission note describing the patient (32 year old male with monoarthritis). The OSTE was proctored by 3 faculty members (including author [EMM]) and utilized 3 standardized residents. Each fellow was evaluated by one faculty member and the standardized resident using an 8-point instrument adapted from a validated OSTE rating tool.[1] Prior to the OSTE, faculty and standardized residents received written materials describing the station and the rating tool and underwent a 30–60 minute training.

Results: Nineteen rheumatology fellows participated in the OSTE (11 first years and 8 second years). Fellows' overall teaching effectiveness had a mean score of 3.75 out of 5 (Table). Of seven specific skills evaluated, fellows were rated highest on their ability to present organized material. The lowest rated skills were evaluating residents' factual knowledge, evaluating residents' ability to synthesize knowledge and giving feedback. No differences in teaching skill ratings were detected between first and second year fellows. Ratings of the two evaluators had a high degree of correlation for all items (0.85–1.0).

Skill evaluated	Average rating * (range)	Standard deviation
Listened to learner	3.95 (2–5)	0.90
Encouraged learner to participate actively in the discussion	3.75 (2–5)	0.95
Evaluated learner's knowledge of factual medical information	3.53 (1–5)	1.15
Evaluated learner's ability to analyze or synthesize knowledge	3.18 (1–5)	0.93
Presented well organized material	4.00 (2–5)	0.71
Paced the session well	3.92 (2–5)	0.70
Explained to learner why he/she was correct/incorrect	3.38 (1–5)	0.96
Overall teaching effectiveness	3.75 (2–5)	0.91

* Scores ranged from "1" as the lowest rating to "5" as the highest rating.

Conclusion: Rheumatology fellows may benefit from programs designed to improve their teaching skills, particularly in the consult setting where time pressure and lack of a longitudinal relationship with learners impede the teaching interaction. Such interventions should focus on improving fellows' ability to engage in learner-centered teaching and feedback. Our pilot study suggests that the OSTE may be a useful tool in assessing fellows' teaching skills.

References

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ACR Concurrent Abstract Session
Epidemiology and Public Health IV: Rheumatoid Arthritis Pathogenesis
Tuesday, November 18, 2014, 4:30 PM–6:00 PM

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Post-Menopausal Factors and the Risk of Seropositive and Seronegative Rheumatoid Arthritis Phenotypes: Results from the Nurses' Health Study. Camilla Bengtsson[1], Susan Malspeis[2], Jeffrey A. Sparks[2], Karen H. Costenbader[2] and Elizabeth W. Karlson[2]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: Among women, the peak incidence of rheumatoid arthritis (RA) is reported to be 45–74 years of age. In addition, it has been suggested that the post-menopausal transition, especially at younger ages (Pikwer, Ann Rheum Dis, 2012), is related to an increased risk of RA, but the literature is scarce. Whether menopause has different impact on seropositive/seronegative RA phenotypes remains to be elucidated. Our aim was to explore whether age and menopausal factors were independently associated with subsequent development of serologic RA phenotypes in 2 prospective cohorts.

Methods: Data were analyzed from Nurses' Health Study (NHS, 1976–2010) and NHSII (1989–2011). In NHS 121,701 female nurses aged 30–55and in NHSII 116,430 female nurses aged 25–42 were followed via biennial questionnaires on lifestyle factors and disease outcomes. In total, 1,089 incident RA cases were confirmed by questionnaire and chart review. Seropositive RA was defined as +RF or ACPA by chart review or lab measurement. We used Cox proportional hazards models to obtain HR (95% CI) of seropositive or seronegative RA associated with menopausal status, age at menopause, type of menopause, severity of hot flashes and ovulatory years, adjusting for age, income, BMI, smoking, breast-feeding, and parity.

Results: Women aged 45 or more had an increased risk of seronegative RA in all age-groups, compared with women aged 25–44, with peak HR at ages 55–59. Women aged 50 or more had an increased risk of seropositive RA, with peak HR at ages 55–59, but the risk attenuated after age 60. Post-menopausal women had an increased risk of seronegative RA after adjusting for age and other potential confounders (NHS: HR 1.8, 95% CI 1.1–3.0; NHSII: HR 2.5, 95% CI 1.5–4.2; pooled HR 2.1, 95% CI 1.5–3.1) without marked differences according to type of menopause. Early age at menopause associated with an increased risk of seronegative RA (NHS: HR 2.0, 95% CI 1.2–3.4; NHSII: HR 3.0, 95% CI 1.7–5.1; pooled HR 2.4, 95% CI 1.6–3.5), regardless of type of early menopause. Moderate/severe hot flashes was mainly associated with an elevated risk for seronegative RA (NHS HR=2.4, 95% CI 1.4–4.3; NHSII: 3.7, 95% CI 2.0–6.8; pooled HR 3.0, 95% CI 2.0–4.5). None of the menopausal factors were significantly associated with seropositive RA.

Conclusion: In these prospective cohorts, women of older ages have an increased risk of both RA phenotypes, but this risk attenuates after age 60 for seropositive RA. Post-menopausal factors are strongly associated with seronegative RA, but not seropositive RA, suggesting potential differences in disease etiology.

Table. Age and menopausal factors and the relative risk of seropositive RA and seronegative RA in the NHS (1976–2010) and NHSII (1989–2011) cohorts

	NHS I	NHS II	Pooled (NHS+NHSII)		
Factors	Seropositive RA (n=457)	Seronegative RA (n=267)	Seropositive RA (n=694)	Seronegative RA (n=395)	Seronegative RA (n=662)
Age*	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
25–44	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
45–49	1.2 (0.8–1.8)	**2.1 (1.3–3.4)**	1.5 (1.0–2.1)	**1.9 (1.2–3.0)**	**2.1 (1.5–3.0)**
50–54	**2.1 (1.5–2.9)**	**1.8 (1.1–2.9)**	**2.3 (1.6–3.2)**	**1.8 (1.1–2.9)**	**2.0 (1.4–3.1)**
55–59	**1.9 (1.3–2.6)**	**1.9 (1.2–3.1)**	**3.1 (2.1–4.6)**	**3.3 (1.9–5.5)**	**3.1 (1.3–7.4)**
60–64	1.5 (1.0–2.1)	**2.1 (1.3–3.3)**	0.8 (0.2–3.4)	2.4 (0.8–7.8)	**2.5 (1.5–4.2)**
≥65	1.3 (1.0–1.9)	**1.9 (1.2–2.9)**	N/A	N/A	N/A

Menopausal statusμ					
Pre-menopausal	1.0	1.0	1.0	1.0	1.0
Post-menopausal	1.3 (0.9–1.9)	**1.8 (1.1–3.0)**	1.1 (0.7–1.7)	**2.5 (1.5–4.2)**	**2.1 (1.5–3.1)**
Type of menopauseμ					
Pre-menopausal	1.0	1.0	1.0	1.0	1.0
Natural	1.3 (0.9–1.9)	**1.8 (1.1–3.0)**	1.0 (0.6–1.6)	**2.4 (1.3–4.4)**	**2.0 (1.4–3.0)**
Surgical	1.4 (0.9–2.2)	**1.8 (1.0–3.1)**	1.2 (0.8–1.9)	**2.7 (1.5–4.7)**	**2.2 (1.5–3.3)**
Age at menopauseμ					
Pre-menopausal	1.0	1.0	1.0	1.0	1.0
≤ 44 years	1.4 (0.9–2.1)	**2.0 (1.2–3.4)**	1.1 (0.7–1.8)	**3.0 (1.7–5.1)**	2.4 (1.6–3.5)
45–49 years	1.3 (0.9–2.0)	1.7 (1.0–2.9)	1.2 (0.7–1.9)	1.9 (0.9–4.0)	**1.7 (1.1–2.7)**
50–54 years	1.3 (0.9–2.0)	1.7 (1.0–3.0)	1.1 (0.6–1.8)	**2.4 (1.1–5.4)**	**1.9 (1.2–3.0)**
≥ 55 years	1.6 (0.9–2.9)	1.7 (0.8–3.9)	2.4 (0.9–6.4)	3.5 (0.9–14.0)	**2.1 (1.0–4.2)**
Type/age at menopauseμ					
Pre-menopausal	1.0	1.0	1.0	1.0	1.0
Natural ≤ 44	1.6 (1.0–2.5)	**2.2 (1.3–4.0)**	0.9 (0.4–2.3)	**3.0 (1.2–7.2)**	**2.5 (1.5–4.0)**
Natural ≥ 45	1.3 (0.9–1.9)	1.6 (1.0–2.8)	1.0 (0.6–1.7)	**2.1 (1.0–4.3)**	**1.8 (1.2–2.8)**
Surgical ≤ 44	1.2 (0.7–2.1)	1.6 (0.8–3.2)	1.1 (0.6–2.0)	**2.9 (1.6–5.4)**	**2.2 (1.2–4.0)**
Surgical ≥ 45	1.5 (1.0–2.4)	1.7 (0.9–3.1)	1.4 (0.7–2.5)	2.1 (0.9–5.0)	**1.8 (1.1–3.0)**
Hot flashesμ					
Pre-menopausal	1.0 (ref)	1.0 (ref)	1.0	1.0	1.0
Post-menopausal, none	1.1 (0.7–1.7)	**1.8 (1.1–3.1)**	1.0 (0.5–1.8)	**2.6 (1.3–5.3)**	**2.1 (1.3–3.2)**
Mild, moderate	1.0 (0.6–1.5)	1.7 (0.9–2.9)	1.2 (0.7–1.9)	1.7 (0.8–3.4)	**1.7 (1.1–2.6)**
Moderate, severe	1.5 (1.0–2.3)	**2.4 (1.4–4.3)**	1.2 (0.7–1.9)	**3.7 (2.0–6.8)**	**3.0 (2.0–4.5)**
Severe, 10+ years	1.5 (0.6–3.3)	2.0 (0.7–5.9)	1.4 (0.5–3.9)	**5.4 (1.8–15.8)**	**3.3 (1.2–8.7)**
Ovulatory yearsμ					
< 24 years	1.0	1.0	1.0	1.0	1.0
24–29 years	0.9 (0.7–1.3)	0.9 (0.6–1.4)	0.8 (0.4–1.4)	**0.4 (0.2–0.9)**	0.7 (0.3–1.3)
30–34 years	1.1 (0.7–1.5)	0.7 (0.5–1.1)	0.9 (0.5–1.8)	0.5 (0.2–1.0)	**0.7 (0.4–1.0)**
≥ 35 years	0.9 (0.6–1.3)	0.8 (0.5–1.3)	0.8 (0.4–1.7)	0.5 (0.2–1.2)	0.7 (0.5–1.1)

*Crude, unadjusted HR. μCox proportional hazards models adjusted for age, questionnaire cycle, median household income, BMI, smoking pack-years, breast-feeding, parity. Reference category is premenopausal women for menopausal variables.

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Amount of Smoking, Duration of Smoking Cessation, and Their Interaction with Silica Exposure in the Risk of Rheumatoid Arthritis: Results from the Swedish Epidemiological Investigation of Rheumatoid Arthritis Study. Xia Jiang[1], Camilla Bengtsson[1], Henrik Källberg[1], Lars Klareskog[2] and Lars Alfredsson[3]. [1]Karolinska Institutet, Stockholm, Sweden, [2]Karolinska University Hospital, Stockholm, Sweden, [3]The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

Background/Purpose: Exposure to silica is a well-defined inhalation exposure, and is known to be associated with moderately increased rheumatoid arthritis (RA) risk, with the effect confined to anti-citrullinated protein/peptide antibody (ACPA) positive RA. The interaction between silica exposure and current smoking, but not past smoking, in the etiology of ACPA-positive RA has also been described. Whereas the overall association of current smoking status, silica, and their interaction in RA could be regarded as established, considerably less is known about how much smoking is needed to bring about this synergistic effect, that is, the influence from cumulative dose (pack-years) among current smokers and the influence from cessation duration among past smokers. This study is to explore the interaction between silica exposure and smoking dose on one hand, as well as duration of smoking cessation on the other, with regard to the risk of developing RA defined by the presence/absence of ACPA.

Methods: We analyzed 927 incident male RA cases (fulfill 1987 ACR criteria) and 1403 randomly selected male controls, aged 18–70, from the Swedish EIRA study, a population based case-control study. Information on silica exposure and cigarette smoking were collected through self-reported questionnaires at the inclusion. Men with a history of having occupations as rock drilling and stone crushing were defined as silica exposed. Additive interaction (attributable proportion due to interaction (AP) and 95% confidence interval (95%CI)) between silica exposure, pack-years of smoking, and duration of smoking cessation (years after quit smoking) were calculated. ACPA status among cases was determined.

Results: A high risk of developing ACPA-positive RA was observed among silica-exposed current smokers (OR=8.03 (95%CI: 4.47–14.03)), and a statistically significant additive interaction was present (AP=0.41 (95%CI: 0.04–0.77)). The magnitude of the estimated silica-smoking interaction increased as the pack-year of smoking increased, with the highest AP observed for smoking ≥ 29 pack-years (AP=0.62 (95%CI: 0.29–0.94)). Although a relevant high risk of developing ACPA-positive RA was also observed for silica-exposed ex-smokers in general, no significant interaction was revealed (OR=4.09 (95%CI: 2.46–6.82); AP=0.07 (95%CI: −0.45–0.60)). Through further analysis, we found those ex-smokers who quit smoking no more than 10 years ago had a similarly high silica-smoking AP as current smokers (AP=0.46 (95%CI: −0.02–0.95), p=0.06). No significant interaction was observed after 10 years after smoking cessation. No statistically significant results were found for ACPA-negative RA.

Conclusion: Silica exposure and smoking interact significantly in a dose dependent manner regarding risk of developing ACPA-positive RA among men. It might take up to 10 years after smoking cessation for the diminishment of the smoking-silica interaction effect, and even longer for the main effect of smoking to return to the baseline. Since silica dust is hard to get rid of once in the lung, it is yet another reason to advise silica exposed persons not to start smoking, smoke less, and to quit smoking as early as possible.

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2889

The Association Between Changes in Inflammation and High Density Lipoprotein Cholesterol Efflux Capacity in Rheumatoid Arthritis. K P Liao[1], Martin Playford[2], Michelle A. Frits[1], Christine K. Iannaccone[1], Jonathan S. Coblyn[1], Michael E. Weinblatt[1], Nancy A. Shadick[3] and Nehal N. Mehta[4]. [1]Brigham and Women's Hospital, Boston, MA, [2]National Heart, Blood, and Lung Institute, Bethesda, MD, [3]Brigham and Women's Hospital/Harvard University, Cambridge, MA, [4]University of Pennsylvania, Philadelphia, PA.

Background/Purpose: High density lipoprotein (HDL) cholesterol efflux capacity measures the functional ability of HDL to remove cholesterol from atherosclerotic plaque. Low HDL efflux capacity is associated with an elevated risk of cardiovascular disease (CVD) independent of HDL levels and traditional CV risk factors in the general population. Recent cross-sectional studies suggest that inflammation is associated with impaired HDL efflux capacity. The objective of this study was to examine whether longitudinal changes in inflammation are associated with a change in HDL efflux capacity in rheumatoid arthritis (RA).

Methods: We conducted this study in a single center longitudinal RA cohort from a large academic center with RA clinical data, CRP and blood samples collected annually. We randomly selected 100 patients who experienced a reduction in inflammation defined as >10mg/L CRP decrease between any two time points one year apart. The first time point was defined as the baseline. Subjects on statin therapy one year before baseline or during the one-year follow-up period were excluded. We measured HDL efflux capacity in serum samples at baseline and one year follow-up quantified using a validated ex vivo system involving the incubation of macrophages with apolipoprotein B-depleted serum. We used the paired t-test to determine significant differences between baseline and follow-up HDL cholesterol efflux values. We assessed the correlation between the change in CRP levels [natural log (baseline CRP-1 year follow-up CRP)] with percentage (%) change in HDL cholesterol efflux capacity using a Spearman's correlation.

Results: We studied 92 subjects who experienced a reduction in inflammation as measured by CRP between baseline and one year follow-up with adequate serum volume. The mean age was 57.7 (SD 12.3), 89.3% were female, 78.5% were ACPA positive. The mean baseline CRP was 48.4mg/L (SD 59.3), and HDL efflux capacity was 1.04 (SD 0.17). At one year follow-up, the mean reduction in CRP was 41.0mg/L (SD 54.6). We observed an increase in HDL cholesterol efflux capacity of 6.7% (p<0.0001). A reduction in CRP was significantly correlated with an increase in HDL cholesterol efflux capacity (r=0.24, p=0.02) (Figure).

Conclusion: Although HDL cholesterol efflux capacity is considered to be a stable measure of HDL function over time in the general population, in RA subjects we observed a concomitant improvement in HDL function by efflux capacity with reductions in inflammation. These findings highlight a potential mechanism linking inflammation and CV risk in RA.

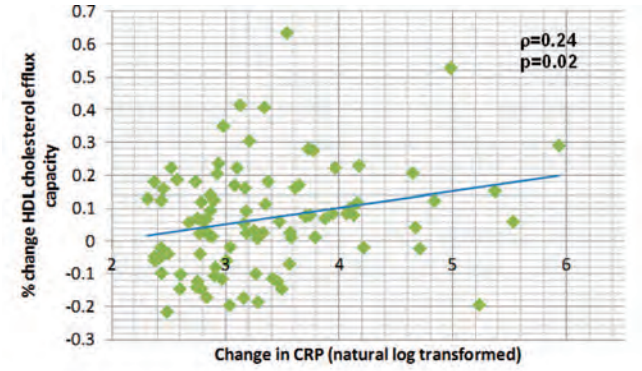

Figure. The correlation between reduction in CRP (natural log transformed) and percentage change in HDL cholesterol efflux capacity. (*Note:* A higher number change in CRP represents a larger reduction in CRP between baseline and one-year follow-up).

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Does a Family History of RA Influence the Clinical Presentation and Treatment Response in RA? Thomas Frisell[1], Saedis Saevarsdottir[2] and Johan Askling[3]. [1]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden, [3]Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden.

Background/Purpose: Since family history of RA is among the strongest risk factors for developing the disease, individuals suspected to have RA are routinely asked about their relatives' disease history. Being a summary measure of a range of genetic and non-genetic risk factors, it would seem likely that family history of RA carries information not only on risk of onset of RA, but also on prognosis, and/or that it may be more strongly associated to certain clinical features of this heterogenic criteria based syndrome. Despite the potential clinical value, and great interest from patients, the role of family history of RA as a clinical marker has been little studied, probably due to the difficulty in ascertaining valid information on familial RA and clinical outcomes.

Methods: We performed a cohort study using prospectively recorded data from Swedish nationwide registers. The cohort was defined as all early RA patients (symptom onset <12 months before inclusion) with a diagnosis of seropositive or seronegative RA in the Swedish Rheumatology register, who started methotrexate monotherapy as first DMARD treatment 2000–2011, and who had parents registered in the Swedish multi-generation register. First degree relatives of cohort members were identified through the Swedish Multi-Generation Register, and the presence of RA among relatives was assessed through the National Patient Register.

The association of RA in one or more first degree relatives to baseline clinical characteristics and treatment response (according to the DAS28-based EULAR response criteria), treatment switch, and change in disease activity measures at 3 and 6 months was estimated using linear regression and generalized logistic regression models.

Results: In our cohort, 380 (9%) of 4210 patients had a first degree relative with RA by their time of RA diagnosis. RA patients with compared to without a family history of RA were more often seropositive (75%/69%), but there were no other significant differences in baseline clinical characteristics (e.g., mean HAQ 0.95/1.01, mean DAS28 5.04/5.06, mean disease duration 0.48/0.49 years). Neither were there any significant differences in treatment response or disease progression at 3 or 6 months, a lack of association that remained after adjustment for sex, age, birth year, and disease duration, and also when further adjusting for baseline DAS28, HAQ, and CRP (Table).

Conclusion: Using a large population-based cohort, we found that despite being a strong predictor of RA itself, family history of RA is not associated with a more severe presentation of RA, nor with short term response to methotrexate monotherapy. Future studies could consider whether family history may be a predictor of long term prognosis or response to treatment other than methotrexate, and what this negative finding implies for the possibility of RA risk genes to also influence disease severity and treatment response.

Table. Association of family history of RA and response to methotrexate monotherapy at 3 and 6 months

Response Measure	Family History of RA		Crude OR or Mean Difference (95% CI)	Model 1.OR or Mean Difference (95% CI)	Model 2.OR or Mean Difference (95% CI)
EULAR Response at 3 Months	No (N=3830)	Yes (N=380)			
Switched Treatment	18%	14%	0.79 (0.56; 1.11)	0.82 (0.58; 1.17)	0.92 (0.64; 1.32)
No Response	11%	13%	1.15 (0.80; 1.64)	1.21 (0.84; 1.74)	1.40 (0.95; 2.08)
Moderate Response	19%	19%	0.96 (0.70; 1.32)	0.98 (0.72; 1.35)	1.03 (0.74; 1.43)
Good Response	27%	28%	Ref.	Ref	Ref
Response Missing	25%	26%	1.01 (0.76; 1.35)	0.98 (0.73; 1.31)	0.97 (0.71; 1.32)
Change from baseline in those remaining on MTX monotherapy at 3 Mths	*N=3157*	*N=326*			
ΔVAS Pain	−24.94	−24.93	0.01 (−4.00; 4.02)	0.55 (−3.42; 4.52)	0.47 (−3.24; 4.19)
ΔHAQ	−0.51	−0.47	0.04 (−0.05; 0.12)	0.05 (−0.03; 0.13)	0.02 (−0.04; 0.08)
ΔDAS28	1.96	1.93	−0.03 (−0.25; 0.19)	−0.06 (−0.27; 0.15)	−0.12 (−0.28; 0.05)
ΔTJC	−5.02	−5.11	−0.08 (−0.87; 0.70)	−0.07 (−0.85; 0.71)	−0.08 (−0.67; 0.51)
ΔSJC	−6.31	−6.11	0.20 (−0.55; 0.95)	0.21 (−0.53; 0.95)	0.33 (−0.32; 0.97)
ΔESR	−15.52	−12.83	2.70 (−0.14; 5.53)	2.85 (0.05; 5.65)	2.46 (0.28; 4.64)
ΔGH	−23.51	−22.70	0.80 (−3.09; 4.69)	1.32 (−2.52; 5.16)	1.84 (−1.77; 5.46)
EULAR Response at 6 Months					
Switched Treatment	25%	24%	1.06 (0.78; 1.45)	1.07 (0.78; 1.46)	1.15 (0.83; 1.60)
No Response	7%	7%	1.18 (0.75; 1.85)	1.19 (0.76; 1.87)	1.37 (0.85; 2.23)
Moderate Response	11%	9%	0.94 (0.62; 1.42)	0.94 (0.62; 1.44)	0.96 (0.62; 1.49)
Good Response	24%	21%	Ref.	Ref	Ref
Response Missing	34%	38%	1.26 (0.95; 1.67)	1.19 (0.89; 1.59)	1.21 (0.89; 1.64)
Change from baseline in those remaining on MTX monotherapy at 6 Mths	*N=2863*	*N=288*			
ΔVAS Pain	−24.34	−21.53	2.81 (−2.36; 7.98)	3.15 (−2.00; 8.29)	2.59 (−2.27; 7.44)
ΔHAQ	−0.53	−0.43	0.10 (−0.01; 0.21)	0.11 (0.00; 0.22)	0.05 (−0.02; 0.13)
ΔDAS28	2.17	2.10	−0.06 (−0.34; 0.21)	−0.07 (−0.34; 0.21)	−0.17 (−0.38; 0.03)
ΔTJC	−5.44	−5.52	−0.08 (−1.09; 0.92)	−0.07 (−1.07; 0.93)	0.10 (−0.63; 0.84)
ΔSJC	−6.85	−7.04	−0.19 (−1.14; 0.77)	−0.23 (−1.18; 0.72)	−0.12 (−0.91; 0.66)
ΔESR	−15.93	−13.64	2.28 (−1.34; 5.91)	2.23 (−1.37; 5.83)	0.85 (−1.87; 3.58)
ΔGH	−23.21	−19.44	3.77 (−1.18; 8.72)	4.08 (−0.85; 9.02)	4.28 (−0.43; 8.99)

Notes: TJC, Tender Joint Count; SJC, Swollen Joint Count; ESR, Erythrocyte Sedimentation rate; GH, Patient's Global Health. Model 1 adjusted for sex, age, birth year and disease duration. Model 2 further adjusted for baseline DAS28, HAQ, and CRP.

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2891

Inflammatory Genes Are Associated with Autoantibodies in Rheumatoid Arthritis-Free Individuals Who Are at-Risk for Future Disease. Ryan W. Gan[1], Kendra A. Young[1], M. Kristen Demoruelle[2], Michael H. Weisman[3], Jane H. Buckner[4], P. K. Gregersen[5], Ted R. Mikuls[6], James R. O'Dell[6], Richard M. Keating[7], Elizabeth W. Karlson[8], Kevin D. Deane[2], V. Michael Holers[2] and Jill M. Norris[1]. [1]Colorado School of Public Health, Aurora, CO, [2]University of Colorado School of Medicine, Aurora, CO, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]Benaroya Research Institute at Virginia Mason, Seattle, WA, [5]Feinstein Institute Medical Research and North Shore-Long Island Jewish Health System, Manhasset, NY, [6]Veteran Affairs Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, [7]Scripps Clinic, La Jolla, CA, [8]Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

Background/Purpose: We previously found that presence of rheumatoid arthritis(RA)-related autoantibodies is associated with systemic inflammation, and that decreased consumption of anti-inflammatory omega-3 fatty acids (n-3 FA) is associated with RA-related autoantibody positivity. We examined whether selected genes in inflammatory pathways in which n-3 FA also play a role are associated with the presence of RA-related autoantibodies in individuals without RA but at future risk for the disease.

Methods: Participants were enrolled in The Studies of the Etiology of RA (SERA), which is a multisite observational study following a cohort of first-degree relatives of RA probands and a cohort enriched with the HLA-DR4 genetic variant, both of which are RA-free at their baseline visit. Participant DNA was screened at the Benaroya Research Institute for specific shared epitope subtypes of HLA-DR4 and HLA-DR1. Participants were positive for the shared epitope if they were either DR4 or DR1 subtype positive. Serum was measured for the following autoantibodies: anti-cyclic citrullinated peptide version 2 (CCP2), CCP3.1 (in a subset), rheumatoid factor (RF) by nephelometry, and RF isotypes (RF-IgM, RF-IgG, RF-IgA). Participants were considered positive for RA-related autoantibodies if they tested positive for any of these autoantibodies at their baseline visit.

Participants were typed for single nucleotide polymorphisms (SNPs) in *Cox-2, TNFA, NF-KB, IkBkB, PPARA, and PPARG* at the Broad Institute using the Sequenom platform. The association between RA-related autoantibody positivity and inflammatory genes was assessed using logistic regression, accounting for the correlation within family members, and adjusting for age at visit, sex, and race.

Results: Demographic characteristics were similar between autoantibody positive (n=306) and autoantibody negative (n=1,576) participants (Table 1). We observed a significant association between increasing number of minor alleles for *Cox-2* and *NF-KB* and autoantibody positivity (Table 2).

Conclusion: Our results suggest that *Cox-2* and *NF-KB* could be associated with an increased likelihood of developing RA-related autoantibodies. The association observed with *Cox-2* is of interest due to the enzyme's role in producing inflammatory lipid molecules, while the association observed with *NF-KB* is of interest given the potential roles that NF-KB has in the RA disease process, including cytokine production and stimulating B cell differentiation to immunoglobulin-producing B cells. These results need to be explored in further detail.

Table 1: Demographic characteristics at baseline by autoantibody (Ab) positivity

Demographic	Ab Positive (n=306)	Ab Negative (n=1576)	p
Age at baseline visit (Mean ± SD)	43.9 ± 15.3	42.9 ± 13.4	0.22
Sex (% female)	71.6	68.2	0.25
Race (% NHW)	75.2	78.9	0.14
Ever Smoke (% Yes)	39.9	37.4	0.42
Current Smoker (% Yes)	12.1	10.9	0.55
Pack Years (Mean ± SD)	3.6 ± 6.8	3.5 ± 7.0	0.70
Shared Epitope (% Pos)	51.8	52.9	0.74
First-degree Relative of RA patient (%)	70.9	67.1	0.20

Table 2: Association between autoantibody positivity (CCP2, CCP3.1, or any RF) at baseline and increasing number of minor alleles (additive model). Adjusted for age, sex, and race, accounting for family correlation

Gene	SNP	Minor Allele	MAF*	OR	95%CI	p
Cox-2	rs5275	G	0.37	1.21	1.01–1.44	0.03
TNFA 857	rs1799724	T	0.11	1.15	0.89–1.50	0.29
NF-KB	rs997476	T	0.08	1.45	1.09–1.93	<0.01
IkBkB	rs6474388	A	0.09	0.87	0.64–1.18	0.36
PPARA L162V	rs1800206	G	0.06	0.97	0.68–1.39	0.89
PPARG Pro12Ala	rs1801282	G	0.12	1.14	0.88–1.48	0.33

*Minor Allele Frequency

Disclosure: R. W. Gan, None; **K. A. Young**, None; **M. K. Demoruelle**, None; **M. H. Weisman**, None; **J. H. Buckner**, None; **P. K. Gregersen**, None; **T. R. Mikuls**, None; **J. R. O'Dell**, None; **R. M. Keating**, None; **E. W. Karlson**, None; **K. D. Deane**, None; **V. M. Holers**, None; **J. M. Norris**, None.

2892

The Relative Risk of Incident NON-Ischemic Heart Failure in Prevalent Rheumatoid Arthritis. Ängla Mantel[1], Marie Holmqvist[2], Johan Askling[3], Lars Lund[4] and Daniel Andersson[5]. [1]Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Solna, Sweden, [2]Unit of Clinical Epidemiology, Department of medicine, Stockholm, Sweden, [3]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [4]Unit of Cardiology section for Heart Failure. Department of Medicine, Stockholm, Sweden, [5]Unit of Cardiology section for heart failure. Department of Medicine, Stockholm, Sweden.

Background/Purpose: Patients with rheumatoid arthritis (RA) may be at increased risk of developing heart failure (HF). Inflammatory activity has been linked to the pathogenesis of HF by inducing structural changes of the myocardium. Despite these indications of a potential link between RA-related factors and non-ischemic HF, the relative risk of non-ischemic HF in contemporary patients with RA has not yet been assessed. The objective of this study was therefore o assess the relative risk of incident non-ischemic heart failure in contemporary patients with prevalent RA.

Methods: Using the Swedish nationwide patient register, a cohort of patients with prevalent RA was identified between 2006 and 2012 and matched with up to 10 general population comparators based on sex, age and area of residency. An index-date, defined as the second visit listing RA (comparators received the same index-date as their corresponding case), was assigned to all study subjects and all study participants with ischemic heart disease (IHD) and/or HF prior to the index-date were excluded. Thereafter all study subjects were followed for the outcome, defined as a first-time hospitalization or outpatient visit listing a main diagnosis of HF. All subjects were followed until outcome, death, incident IHD, first emigration or 31 December 2012, whichever occurred first. Crude rates were calculated and presented as number of events per 1000 person-years. Cox regression models were used to assess the relative risk of HF in patients with RA and adjusted for potential confounders.

Results: In total, 41982 patients with RA and 360763 general population comparators free of IHD and HF at the index-date were identified. During the follow-up period (median follow-up for RA-patients 4.6 years [iqr 2.4–6.0] and comparators 4.8 years [iqr 2.5–6.1]), 630 (1.5 %) of patients with RA and 3058 (0.8%) of the comparators were registered with incident HF. The rate of HF was 3.6 HF/1000 person-years among the RA-patients and 2.0 HF/1000 person-years among the comparators. The corresponding risk increase of incident HF among the patients with RA was approximately 70% (Crude HR 1.69 [95% CI 1.56–1.85]) and remained statistically significantly increased after adjusting for potential confounders (Adjusted HR 1.53 [95% CI 1.40–1.67]). Stratifying RA patients by RF-positivity at index-date did not reveal any major differences between these two subgroups (Crude HR RF-positive subjects 1.66 [95% CI 1.51–1.84]; Crude HR RF-negative subjects 1.78 [95% CI 1.52–2.07]).

Conclusion: Patients with prevalent RA have an increased risk of developing non-ischemic HF. Our results support the proposed involvement of RA-related factors in the pathogenesis of HF, independent of vascular disease. The role of autoantibodies and other markers of RA disease is an important subject for further research.

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ACR Concurrent Abstract Session
Osteoarthritis - Clinical Aspects II: Osteoarthritis Risk Factors and Therapies

Tuesday, November 18, 2014, 4:30 PM–6:00 PM

2893

Genome-Wide Association Study of Osteoarthritis Progression: Results from the Osteoarthritis Initiative. Michelle S. Yau[1], Laura M. Yerges-Armstrong[1], Youfang Liu[2], David J. Duggan[3], Joanne M. Jordan[2], Braxton D. Mitchell[1], Rebecca D. Jackson[4] and Marc C. Hochberg[1]. [1]University of Maryland School of Medicine, Baltimore, MD, [2]University of North Carolina, Chapel Hill, NC, [3]Translational Genomics Research Institute, Phoenix, AZ, [4]The Ohio State University, Columbus, OH.

Background/Purpose: Most genome-wide association (GWA) studies have focused on OA prevalence, but few have focused on OA progression. GWA studies of OA progression may help reveal new biology and drug targets that can be used to develop treatments that slow disease progression in OA patients.

Methods: We used an agnostic GWA analysis of ~8 million 1000 genomes imputed single nucleotide polymorphisms (SNPs) to identify genetic variation associated with structural knee OA progression. Our analyses were conducted in Caucasian participants from the Osteoarthritis Initiative (OAI), a multi-center natural history study of individuals who have or are at high risk for developing radiographic knee OA. A total of 1,756 participants who returned for a follow-up exam and had evidence of radiographic OA (Kellgren-Lawrence (KL) grade ≥ 2) in one or more knees at baseline were included in the analyses (54% female, mean age=67±9 years). We defined progression as worsening of KL grade or progression to total joint replacement (TJR). As a secondary phenotype, we exclusively evaluated progression to TJR. Participants were followed annually for four years. About 27% had worsening of KL grade and 6% had TJR at follow-up. For these analyses, we used logistic regression models adjusted for age, sex, study site, and population stratification and assumed additive genetic models.

Results: We identified two SNPs that reached genome wide significance ($P < 5\times10^{-8}$). One SNP on chromosome 18, rs9964107 (OR=1.6, 95% CI=1.4–1.7, $P=3.2\times10^{-8}$), is associated with worsening of KL grade and another SNP on chromosome 4, rs76964101 (OR=10.8, 95% CI=10.0–11.7, $P=4.4\times10^{-8}$), is associated with progression to TJR. Both SNPs are located within intergenic regions, where rs9964107 is closest to *SYT4* and rs76964101

is closest to *SRD5A3* and *KDR*. *SYT4* encodes synaptotagamin 4, which is expressed in the brain and may play a role in calcium dependent vesicular trafficking and exocytosis. There is some evidence that this protein may be involved in body weight regulation through negative regulation of oxytocin release. *SRD5A3* encodes steroid 5 alpha-reductase 3, which is involved in maintenance of the androgen receptor activation pathway. *KDR* encodes a kinase insert domain receptor, which is a receptor for vascular endothelial growth factors and promotes proliferation, survival, migration, and differentiation of endothelial cells. There was no evidence for association of either SNP with OA prevalence, suggesting that these SNPs may be uniquely associated with OA progression.

Conclusion: We have identified two genome-wide significant SNPs that may be associated with structural knee OA progression. These SNPs reveal that neuronal regulation of obesity, androgen signaling, and vascular endothelial growth factors may play an important role in OA progression. None of these SNPs are associated with OA prevalence. Further work is ongoing to replicate these associations and identify the causative signal.

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2894

Relationship of Dermal Advanced Glycation End Products and Hand OA. Charles Eaton[1], Jeffrey Driban[2], Bing Lu[3], Mary Roberts[4] and Timothy E. McAlindon[2]. [1]Center for Primary Care and Prevention, Memorial Hospital of Rhode Island, Providence, RI, [2]Tufts Medical Center, Boston, MA, [3]Brigham and Women's Hospital, Foxboro, MA, [4]Center for Primary Care and Prevention, Pawtucket, RI.

Background/Purpose: Hand Osteoarthritis (HOA) is characterized by the progressive destruction of articular cartilage and bony changes and is strongly and positively associated with age but the mechanism by which aging contributes to this increased susceptibility is largely unknown. Recently the hypothesis that accumulation of advanced glycation endproducts (AGEs) that are associated with oxidative stress and aging might explain some or most of this association has been suggested. We compared skin autofluorescence as a measure of dermal AGEs and its association with the prevalence of HOA, symptomatic HOA, and the number of finger joints with osteophytes and joint space narrowing (JSN) as a measure of severity.

Methods: We performed a cross-sectional analysis of a purposeful sample of the Osteoarthritis Initiative (OAI) from a single site who had dermal AGEs measured by skin autofluoresence using SCOUT DS machine (Vera light Inc., Albuquerque, New Mexico) at the 36 month visit. We used an excitation wavelength of 375nm and emission wavelengths of 435–660nm. This wavelength is correlated with cross-links of collagen, FAD, and NADH. A mathematical algorithm is applied to spectrum results to adjust for age, hemoglobin, skin pigmentation and light scattering. Hand x-rays from the dominant hand were read for definite osteophytes with JSN at 48 months. We classified a person as having radiographic HOA if their hand x-ray had two or more finger joints (DIP, PIP, MCP) affected on different fingers. Symptomatic HOA was defined as having radiographic HOA and presence of hand/finger pain, aching or stiffness for more than half the days in past 30 days. Simple T tests or Pearson correlation coefficients were used to evaluate the the mean number of finger joints involved by tertiles of dermal AGE levels. Then Analysis of Covariance was performed to adjust for age and gender. T-tests comparing levels of dermal AGEs between those with and without HOA and with and without symptomatic HOA were performed.

Results: In a sub-sample from the OAI (n=200)with equal proportions of participants with and without abdominal adiposity had hand x-rays read. Of this sample, 171 had dermal AGEs measured and analyses performed. Mean levels of AGEs were greater both for those with radiographic HOA (n=114) [29.3(4.8) vs. 27.1(5.0), p = 0.005], and symptomatic HOA(n=35) [30.5(5.2) vs. 28.1(4.8), p=0.01] compared to those without HOA or symptomatic HOA. Furthermore level of AGEs correlated significantly with the number of joints affected per hand (r= 0.25, p<0.001) and exhibited a dose-response relationship in categorical analysis(with 2.34, 2.70 and 3.59 joints involved by increasing tertiles of dermal AGE levels after adjustment for age and gender (p trend <0.001).

Conclusion: Non-enzymatic glycation of dermal tissues as a proxy for the accumulation of AGEs in articular cartilage is associated with HOA, symptomatic HOA and the severity of HOA as measured by the number of finger joints affected in this cross-sectional study. Replication of these findings in prospective cohort studies and understanding of metabolic pathways that may modify or mediate the relationship of AGEs with HOA are indicated.

Disclosure: C. Eaton, None; **J. Driban**, None; **B. Lu**, None; **M. Roberts**, None; **T. E. McAlindon**, None.

2895

Habitual Running Any Time in Life Is Not Detrimental and May be Protective of Symptomatic Knee Osteoarthritis: Data from the Osteoarthritis Initiative. Grace H. Lo[1], Jeffrey B. Driban[2], Andrea Kriska[3], Kristi Storti[3], Timothy E. McAlindon[2], Richard Souza[4], Charles B. Eaton[5], Nancy J. Petersen[6] and Maria E. Suarez-Almazor[7]. [1]Michael E. DeBakey VA Medical Center, Baylor College of Medicine, Houston, TX, [2]Tufts Medical Center, Boston, MA, [3]University of Pittsburgh, Pittsburgh, PA, [4]University of California, San Francisco, San Francisco, CA, [5]Memorial Hospital of Rhode Island, Pawtucket, RI, [6]Baylor College of Medicine, Houston, TX, [7]The University of Texas, MD Anderson Cancer Center, Houston, TX.

Background/Purpose: Controversy exists regarding whether habitual running is beneficial versus harmful to the knee. Chronic mechanical overloading could potentially physically damage structures within the knee. Alternatively, runners have a lower body mass index (BMI), protective of knee osteoarthritis (OA). Most existing studies evaluating running and knee osteoarthritis (OA) have focused on elite male athletes, not generalizable to most of the population. Therefore, we aimed to evaluate the relationship of habitual running with symptomatic knee OA in the Osteoarthritis Initiative (OAI), a cohort recruited from the community not based on elite running status.

Methods: This is a cross-sectional study of OAI participants with knee x-ray readings, symptom assessments, and completed surveys on lifetime physical activity. At the 96-month visit, a modified version of the Lifetime Physical Activity Questionnaire (LPAQ) asked participants to identify the top 3 most frequently performed physical activities (≥ 20 times in life) from ages 12 – 18, 19 – 34, 35 – 49 and >50 years old. Those indicating running as an activity were defined as a runner in that time period. Running at any time in life included runners from all time periods. Posterior-Anterior semi-flexed knee radiographs were obtained at OAI 48-month visit and scored for Kellgren-Lawrence (KL) grade (0–4). Radiographic OA (ROA) was defined as KL ≥ 2. Frequent knee pain within a person required at least one knee have frequent knee pain at the OAI 48-month visit. Symptomatic radiographic OA (SOA) required that at least one knee had both ROA and frequent knee pain. Anyone with a total knee replacement was classified as having SOA.

We performed logistic regression analyses where the predictor was running any time in life and running in the specific age ranges. The outcomes were ROA, frequent knee pain, and SOA; adjusted analyses included covariates age, sex and BMI.

Results: 2439 participants were included, 55% were female, mean age was 64.7 (9.0) years and BMI was 28.5 (4.9) kg/m^2. 28% ran at some time in their lives; of those, 49%, 31%, 15% and 5% identified running in 1, 2, 3, and 4 of the time periods respectively. From lowest to highest BMI tertile, 35%, 28%, and 24% were runners at any time in life.

Table: Odds Ratios of Prevalent Symptomatic Knee Osteoarthritis (SOA) for Runners compared to Non-Runners

Running Time Period	Prevalence of SOA	Unadjusted Odds Ratios	Adjusted Odds Ratios*
Any time in Life			
No (n = 1528)	29.3%	Referent	Referent
Yes (n = 626)	22.7%	0.84 (0.76 – 0.94)	0.89 (0.79 – 1.00)
Ages 12 – 18 years old			
No (n = 1924)	27.7%	Referent	Referent
Yes (n = 212)	23.6%	0.81 (0.58 – 1.12)	0.94 (0.66 – 1.34)
Ages 19 – 34 years old			
No (n = 1806)	28.3%	Referent	Referent
Yes (n = 332)	22.0%	0.71 (0.54 – 0.94)	0.78 (0.58 – 1.05)
Ages 35 – 49 years old			
No (n = 1794)	28.2%	Referent	Referent

Yes (n = 374)	22.5%	0.74 (0.56 – 0.97)	0.85 (0.63 – 1.13)
Ages > 50 years old			
No (n = 1881)	28.2%	Referent	Referent
Yes (n = 221)	22.2%	0.73 (0.52 – 1.01)	0.85 (0.60 – 1.20)

*Adjusted for Age, Sex, and BMI.

For outcomes of frequent knee pain and ROA, the results were similar to that of SOA.

Conclusion: Our findings suggest an exposure to non-elite running at any time in life is not associated with a higher odds of prevalent ROA, knee pain, and SOA. Those with the lowest BMI were most likely to identify running as a habitual activity. These findings were observed in a cohort recruited from the community not based on elite running status making these findings potentially more applicable to a broader population. Non-elite running at any time in life does not appear detrimental, and may be protective of SOA.

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2896

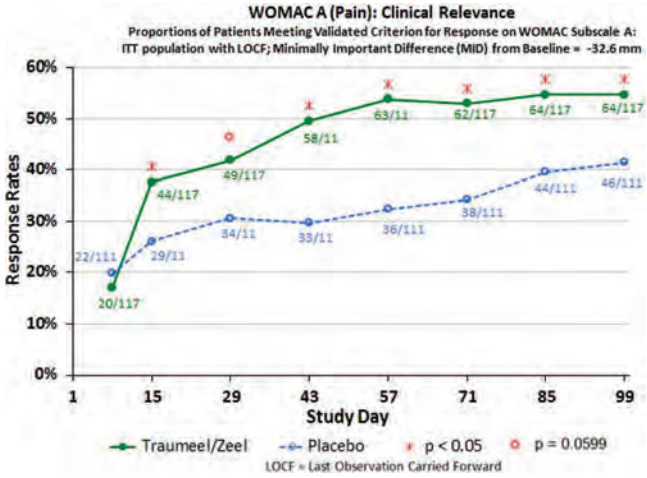
A Multi-Center Double-Blind, Randomized, Controlled Trial (db-RCT) to Evaluate the Effectiveness and Safety of Co-Administered Traumeel® (Tr14) and Zeel® (Ze14) Intra-articular (IA) Injections Versus IA Placebo in Patients with Moderate-to-Severe Pain Associated with OA of the Knee.

Carlos Lozada[1], Eve del Rio[2], Donald Reitberg[3], Robert Smith[3], Charles Kahn[4] and Roland W. Moskowitz[5]. [1]University of Miami Miller School of Medicine, Miami, FL, Miami, FL, [2]Rio Pharmaceutical Services, LLC, Bridgewater, Afghanistan, [3]Rio Pharmaceutical Services, LLC, Bridgewater, NJ, [4]South Florida Rheumatology, Hollywood, FL, [5]University Hospitals Case Medical Center, Cleveland, OH.

Background/Purpose: Tr14 & Ze14 is a combination of dilute biological and mineral extracts administered IA for painful knee OA. In response to clinician impressions of positive outcomes, a db-RCT to assess efficacy and safety compared to IA saline was deployed in the US.

Methods: Pts with moderate-to-severe chronic knee OA were randomized to 3 weekly IA injections of either Tr14 & Ze14 or saline by clinical investigators experienced with use of the IA injection route. The primary efficacy variable was change in knee pain from Baseline to End-of-Study (Week 17) as measured by the WOMAC OA Pain Subscale (Section A, 1–5) 100 mm VAS. Secondary measures included Total WOMAC and subscores for stiffness (B), and physical function (C), change in pain following a 50 ft walk (100 mm VAS), patient and physician global assessments. Clinical relevance was assessed by comparing proportions of patients with reductions from baseline in WOMAC A scores greater than a validated benchmark Minimal Clinically Important Difference (MCID). This was chosen as −32.6 mm (the most conservative value) based on a study of outpatients with knee or hip OA where WOMAC VAS MCIDs ranged from −7.9mm to −32.6mm [see reference 59 Tauback et al., *Ann Rheum Dis.* 2005; 64(1):29–33 in the description of the WOMAC index published by ACR]. Safety was assessed by monitoring of vital signs, physical examinations of the target knee, adverse events and concomitant medications.

Results: 232 patients were randomized and treated (All Tr14 & Ze14, n=119, All Placebo, n=113; Intention-to-Treat (ITT) Tr14 & Ze14, n=117, Placebo, n= 111). Treatment arms were well balanced across demographic and baseline characteristics. Tr14 & Ze14 did not discriminate for WOMAC A Pain as expected after only 1 of 3 injections on Day 8 (p=0.3715), but subsequently was significantly different (p<0.05) on Days 15, 43, 57, 71, 85 and 99 (primary endpoint day), and approached significance on Day 29 (p=0.0686). Logistic regressions showed the proportion of MCID responders was not significant on Day 8. As this was an expected finding, it served as a no-effect internal-model-validation. Tr14 & Ze14 was significantly different (p<0.05) on all subsequent days except Day 29 (approached significance, p=0.0599, Figure 1). 50' walk pain was similarly discriminating as was the physician global assessment. Total WOMAC and subscores B&C were directionally consistent with WOMAC A. There were no related SAEs. AEs were generally mild and unrelated to treatment. Local knee-related AEs, lab assessments, ECGs and vital signs were unremarkable and similar between treatments.



Conclusion: Tr14 & Ze14 provided statistically significant and clinically relevant pain relief on days 15 to 99 in comparison to placebo. In this double-blind, randomized, controlled trial, a biological/mineral multi-extract combination was shown to be a safe and effective treatment for pain in moderate-to-severe knee OA.

Disclosure: C. Lozada, Rio Pharmaceutical Services, 5, Heel USA, 5; **E. del Rio**, Biologische Heilmittel Heel GmbH, 5; **D. Reitberg**, Rio Pharmaceutical Services, LLC, 5; **R. Smith**, Rio Pharmaceutical Services, LLC, 5; **C. Kahn**, Biologische Heilmittel Heel GmbH, 5; **R. W. Moskowitz**, Rio Pharmaceutical Services, LLC, 5, Heel USA, 5.

2897

Exercise Therapy and/or Manual Therapy for Hip or Knee Osteoarthritis: 2-Year Follow-up of a Randomized Controlled Trial.

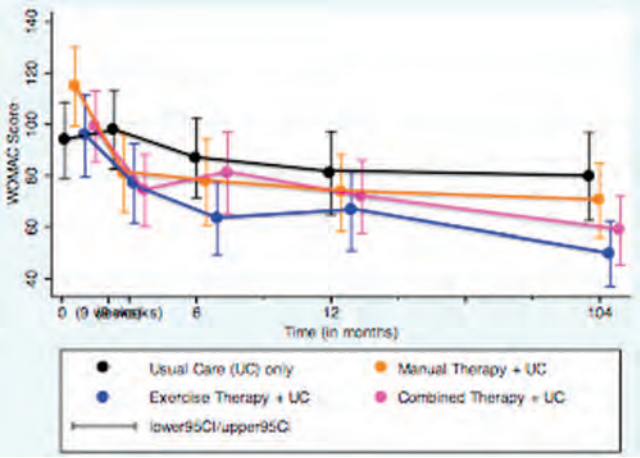
J. Haxby Abbott[1], Cathy Chapple[1], Daniel Pinto[2], Alexis Wright[3] and Jean-Claude Theis[1]. [1]University of Otago, Dunedin, New Zealand, [2]Northwestern University, Chicago, IL, [3]High Point University, High Point, NC.

Background/Purpose: Although both exercise therapy and manual therapy have evidence supporting their effectiveness in people with hip and knee osteoarthritis (OA), few clinical trials have reported their incremental effectiveness compared with usual medical care, or their long-term effects.

Methods: In this randomized controlled trial with 2-year follow-up, adults meeting the American College of Rheumatology criteria for hip or knee OA were randomly allocated to receive either a] exercise therapy; b] manual therapy; c] combined exercise therapy and manual therapy; or d] no trial intervention in addition to usual medical care. Groups a-c were provided 10 treatment sessions: 7 sessions within the first 9 weeks plus 3 booster sessions (2 at 4 months and 1 at 13 months). Assessors blinded to group allocation reassessed participants at 2 years. The primary outcome measures were the Western Ontario and McMaster (WOMAC) osteoarthritis index (24 questions, 0–10 scale, total range 0–240) and physical performance tests (timed up-and-go, 40m fast-paced walk, 30 second sit-to-stand).

Results: 186 (90.3%) of 206 participants recruited were retained at 2 years follow-up. At baseline, mean age was 66 years (range 37 to 92) and mean WOMAC was 100.8 (SD 53.8). Missing data were replaced using multiple imputation. Intention-to-treat analysis of covariance (ANCOVA) showed improvements in WOMAC at 2 years were superior for all three intervention groups compared with the usual care group (2-sided p<0.05). Participants receiving exercise therapy in addition to usual care showed gains of 31.7 WOMAC points (95% CI 10.0, 53.3); effect size 0.57 (Cohen's d; 95% CI. 17,. 97). Participants receiving manual therapy in addition to usual care showed gains of 30.1 (8.9, 51.3); effect size 0.55 (.16,. 94). Participants receiving combined exercise therapy and manual therapy in addition to usual care did not meet the *a priori* threshold for clinical significance (28 points), but were 26.2 (6.1, 46.3) WOMAC points better than usual care only, for a clinically significant effect size of 0.52 (.11,. 91). The exercise therapy group showed greater mean changes on most physical performance tests than did the other groups.

Conclusion: Both exercise physiotherapy and manual physiotherapy provided incremental benefit over usual care alone at 2 years follow-up. Physical performance test outcomes significantly favoured the exercise therapy group.



Disclosure: J. H. Abbott, None; **C. Chapple**, None; **D. Pinto**, None; **A. Wright**, None; **J. C. Theis**, None.

2898

New Insights into the Primary Care Osteoarthritis Consultation with Implications for Practice. Zoe Paskins, Tom Sanders, Peter Croft and Andrew Hassell. Keele University, Keele, United Kingdom.

Background/Purpose: Osteoarthritis (OA) is the commonest long term condition in primary care. Existing international guidance suggests that much can be done to improve patient outcomes but existing research suggests doctors and patients are pessimistic about OA treatment. How important is the primary care consultation in shaping and influencing this incongruity? Our study used innovative methods, a combination of video recorded consultations and post consultation interviews using video to prompt recall, to uncover what happens when patients with OA present to their General Practitioners (GPs). The study took place in the context of a programme of translational research and also aimed to characterise any unmet patient need to which interventions could be targeted.

Methods: With ethical approval, 15 GPs consented to have two routine consultation sessions video recorded. GP consultations with 190 consenting patients aged ≥ 45 were video recorded. 20 consultations contained reference to OA, and 17 of these patients and their GPs (n=13) consented to participate in post consultation interviews, during which the video was played to stimulate recall. Analysis involved comparing and contrasting patient and GP interviews with the matched consultation findings, using thematic analysis. The results in this abstract relate predominantly to the consultation findings.

Results: Four overarching themes emerged from analysis: complexity, heterogeneity, dissonance and the lack of a biomedical construct for OA. OA arises in the primary care consultation in complex contexts of multimorbidity, multiple and varied patient agendas which are often not explicit, and against a background of clinician agendas including time pressures, multiple guidelines and service commissioner requirements. Dissonance between doctors and patients was both observed and reported and was often underpinned by patient perception of lack of empathy and validation of their symptoms. Doctors and patients favour a 'lay' construct of OA where joint pain is seen as a normal part of life; this influences doctor and patient behaviour and acts as a significant barrier to formal recognition and hence treatment of the condition.

Conclusion: OA appears to be experiencing an identity crisis, with doctors and patients uncertain, (both consciously and subconsciously), of what constitutes OA and when to use the term 'osteoarthritis'. Further work is needed to establish whether primary care should adopt a more biomedical construct of OA in order to bring OA more in line with other long term conditions such as cancer or heart disease, which have clearer clinical pathways. The need for public health messages regarding OA and optimal models of primary care for these patients also needs to be explored.

Disclosure: Z. Paskins, None; **T. Sanders**, None; **P. Croft**, None; **A. Hassell**, None.

ACR Concurrent Abstract Session
Pediatric Rheumatology - Clinical and Therapeutic Aspects: Miscellaneous Pediatric Rheumatic Diseases
Tuesday, November 18, 2014, 4:30 PM–6:00 PM

2899

High Dose Aspirin for Treating Kawasaki Disease – Outdated Myth or Effective Aid? Gil Amarilyo[1], Yael Koren[2], Dafna Brik Simon[1], Maskit Bar-Meir[3], Hilla Bahat[4], Mona Hanna Helou[5], Amir Mendelson[6], Yackov Berkun[7], Eli Eisenstein[7], Yonatan butbul Aviel[5], Galia Barkai[8], Yoav Bolkier[8], Shai Padeh[8], Philip J. Hashkes[3], Riva Brik[5], Liora Harel[1] and Yosef Uziel[6]. [1]Schneider Children's Medical Center of Israel, Petach Tikvah, Israel, [2]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [3]Shaare-Zedek Medical Center, Jerusalem, Israel, [4]Assaf Harofeh Medical Center, Zerifin, Israel, [5]Rambam Medical Center, Haifa, Israel, [6]Meir Medical Center, Kfar Saba, Israel, [7]Hadassah Hebrew University Medical Center, Jerusalem, Israel, [8]Sheba Medical Center, Tel-Hashomer, Israel.

Background/Purpose: Kawasaki disease (KD) is generally treated with intravenous immunoglobulin (IVIG) together with high anti-inflammatory doses of acetyl salicylic acid (ASA), which is subsequently switched to low, anti-thrombotic dose ASA. However, there is still no evidence whether adding high dose ASA to IVIG increases the efficacy of the latter, especially concerning coronary artery outcome. We aimed to compare the efficacy and safety of IVIG+ anti-inflammatory high dose ASA regimen to IVIG with low dose ASA in a multicenter, national, retrospective study.

Methods: Medical record review of KD patients from our Pediatric Rheumatology Study Group units was conducted. Some hospitals do not use anti-inflammatory high dose ASA routinely, but rather add low dose ASA therapy to IVIG. Demographic data, clinical manifestations, coronary involvement, ASA and IVIG doses and adverse events were recorded. The primary efficacy outcome was defined as coronary aneurism 2–4 weeks after fever onset. Secondary outcomes were time from beginning of therapy to fever resolution and disease recurrence (defined as recurrence of fever after >72 hours). High dose and low dose ASA groups were compared using the Student's t-test for continuous variables and the Pearson Chi-square test for categorical variables.

Results: 336 KD patients, 287 in the high dose ASA group and 49 in the low dose ASA group were included. There were no demographic, clinical, or laboratory differences between the groups. In the high dose ASA group, 8% had coronary aneurisms, while no aneurisms were reported in the low dose ASA group ($P<0.2$). Regarding mild coronary findings, 22.8% of the high dose ASA group developed coronary ectasia 2–4 weeks after KD onset, compared to 3.6% in the low dose ASA group ($p<0.02$). No significant statistical differences were noted between the groups in time until fever resolution in days (high dose ASA 0.77 ± 1.84; low dose ASA 1.1 ± 3.34; $P=0.34$) or in KD recurrence (high dose ASA 32/287 (11%); low dose ASA 7/49 (14%); $P=0.58$). The need for use of rescue medications was similar in both groups. The number of adverse events in both groups were similar ($P=0.86$).

Conclusion: The efficacy and safety of treatment with IVIG and low-dose ASA was similar to that of IVIG and high dose ASA in patients with KD. We suggest that the routine use of high-dose ASA in addition to IVIG, will be re-evaluated in a prospective controlled study.

Disclosure: G. Amarilyo, None; **Y. Koren**, None; **D. Brik Simon**, None; **M. Bar-Meir**, None; **H. Bahat**, None; **M. Hanna Helou**, None; **A. Mendelson**, None; **Y. Berkun**, None; **E. Eisenstein**, None; **Y. butbul Aviel**, None; **G. Barkai**, None; **Y. Bolkier**, None; **S. Padeh**, None; **P. J. Hashkes**, None; **R. Brik**, None; **L. Harel**, None; **Y. Uziel**, None.

2900

Clinically Inactive Disease in Juvenile Dermatomyositis – a Proposed Revision to the Pediatric Rheumatology International Trials Organisation Criteria. Beverley Almeida[1], Raquel Campanilho-Marques[2], Katie Arnold[2], Lucy R. Wedderburn[3], Clarissa A Pilkington[1] and Kiran Nistala[4]. [1]Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [2]UCL Institute for Child Health, London, United Kingdom, [3]UCL, UCLH, GOSH NHS Trust, London, United Kingdom, [4]University College London, London, United Kingdom.

Background/Purpose: Juvenile dermatomyositis (JDM) affects 3 children/million/year with myositis and skin disease being the typical features. The Pediatric Rheumatology International Trials Organisation (PRINTO) have recently established criteria to classify JDM patients who are clinically inactive by meeting at least 3 out of the following 4 conditions – Creatine Kinase (CK) ≤150 U/L, Childhood Myositis Assessment Score (CMAS) ≥48, Manual Muscle Testing of 8 groups (MMT8) ≥78 and physician global Visual Analogue Scale (PGA) ≤0.2. CK, CMAS and MMT8 all measure muscle involvement, only PGA includes skin or other organ involvement. The hypothesis that these criteria may fail to detect patients who have active skin disease but normal muscle parameters was tested. The aim was to demonstrate the prevalence of clinically inactive disease in the UK JDM Cohort and Biomarker Study and to identify whether skin disease is still present in these patients on the basis of the PRINTO criteria.

Methods: Data were analysed from children who were recruited and met Bohan-Peter criteria. Data from patient episodes (either a clinic visit or hospital admission) were assessed using the PRINTO criteria. Using the PRINTO rules stipulating 3 of 4 criteria are required, all data entries were divided into 2 groups based on the criterion that was omitted. Each case was analysed to determine whether skin disease was present or absent.

Results: 682 data entries (DE) from 321 patients were identified as clinically inactive. 255 (37.4%) of these DE (119 patients) met all 4 criteria. 21.2% of DE had skin rash and 10.5% had nailfold changes (Table 1) at the time of assessment. 427 of the total DE (202 patients) met 3 of the 4 criteria. Of these, 320 (74.9%) had clinically inactive based on the 3 muscle criteria (PGA was not met). 61.6% of this group had ongoing skin rash present. Among the 107 remaining DE, which were clinically inactive by 3 criteria of which one was PGA, the frequency of skin changes was lower. The differences between the 3 groups were statistically significant in terms of rash (χ2 111.5, p<0.0001), nailfold changes (χ2 65.5, p<0.0001) and calcinosis (χ2 22.07, p<0.0001).

Table 1: Frequency of skin changes in JDM patients meeting PRINTO criteria (number of episodes, % in brackets)

No. of criteria met (DE=data entries, n=number of patients)	Rash	Nailfold changes	Calcinosis
All 4 criteria met (255 DE, n 119)	54 (21.2)	27 (10.5)	19 (7.5)
3 criteria met, but PGA not met (320 DE, n 131)	197 (61.6)	114 (35.6)	60 (18.8)
3 criteria met of which one was PGA (107 DE, n 71)	25 (23.3)	9 (8.4)	6 (5.6)

Conclusion: This study is one of the first to test the PRINTO criteria in a large independent cohort of JDM patients. When clinically inactive disease is defined by "muscle-based" criteria, without PGA, there is a greater frequency of skin disease. As a revision, we propose that PGA should be included as an essential criterion together with 2 of the 3 muscle criteria. This would prevent skin disease being overlooked in the clinical assessment which is important since it is often recalcitrant to treatment and may be associated with poor long-term disease outcomes. A revision of the criteria would need testing in independent cohorts.

Disclosure: B. Almeida, None; **R. Campanilho-Marques**, None; **K. Arnold**, None; **L. R. Wedderburn**, None; **C. A Pilkington**, None; **K. Nistala**, None.

2901

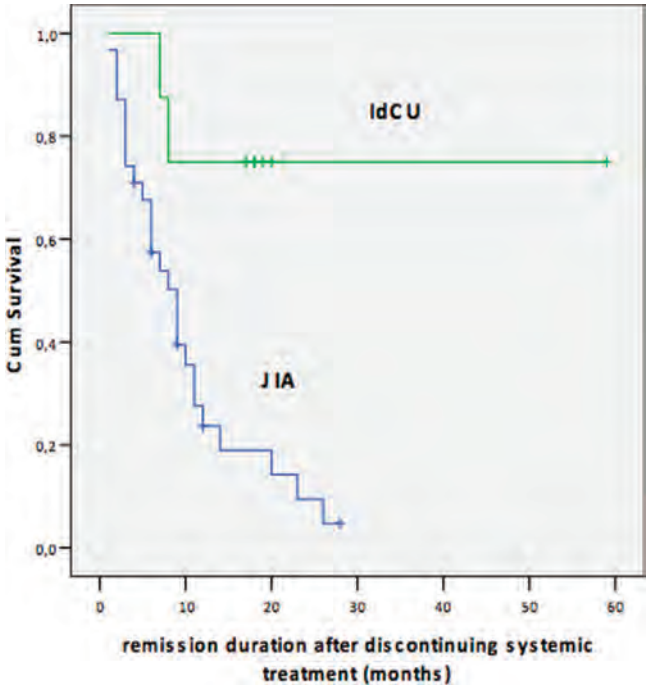
Predictors of Relapse after Discontinuing Systemic Treatment in Childhood Autoimmune Chronic Uveitis. Gabriele Simonini[1], Claudia Bracaglia[2], Marco Cattalini[3], Andrea Taddio[4], Alice Brambilla[1], Cinzia DeLibero[5], Denise Pires Marafon[6], Roberto Caputo[5] and Rolando Cimaz[1]. [1]Anna Meyer Children's Hospital-University of Firenze, Florence, Italy, [2]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, IRCCS, Rome, Italy, [3]Pediatric Immunology and Rheumatology Unit, Brescia, Italy, [4]Institute of Child Health, IRCCS Burlo Garofolo, University of Trieste, Trieste, Italy, [5]Anna Meyer Children's Hospital, Florence, Italy, [6]Ospedale Pediatrico Bambino Gesù, IRCCS, Roma, Italy.

Background/Purpose: Information regarding the natural clinical history of a child on systemic treatment due to auto-immune chronic uveitis would be helpful in driving duration therapy. Aim of our study was to assess the time on remission after discontinuing systemic therapy in a retrospective, comparative, multi-centre, cohort study of childhood non-infectious chronic uveitis.

Methods: 40 patients (30 F, 10 M; median age: 11.6 years, 31 JIA, 9 Idiopathic Chronic Uveitis [IdCU]) from 4 different paediatric rheumatology centres, with previously refractory, vision threatening, non-infectious *inactive* uveitis, which discontinued all related treatments for at least 3 months were enrolled. 23 children previously received Methotrexate, 17 TNF inhibitors. Primary outcome was to assess, once remission was achieved, the time on remission up to the first relapse after discontinuing treatment. Time to remission once systemic not-steroid treatment was started, time to steroid discontinuation, number of relapses before achieving remission and time on remission on therapy before discontinuing all treatments were also considered. Statistical Analysis. Mann–Whitney U-test, Wilcoxon signed-rank test for paired samples, c-square tests, and Fisher's exact test, when appropriate, were used to compare data. Pearson and Spearman correlation tests were used to determine correlation coefficients for different variables. In order to identify predictors of outcome Cox regression model and Kaplan–Meier curves were constructed, each one at mean of enter ed covariates.

Results: Median follow-up time on remission without treatment was 9 months (range 1–59 months). At last available follow-up after 1 year from discontinuation of treatment [49 months, range 15–168], 11/39 (28.2%) children maintained a complete remission over a median period of 18 months. At 49 months of follow-up, 6/8 children with IdCU (75%) compared to 5/31 children with JIA (16.1%) were still on remission without treatment (p<0.003). A higher probability of maintaining uveitis remission after discontinuing treatment was shown in IdCU compared to JIA group (Mantel-Cox c2 7.62, p<0.006) (Figure). ANA positivity was associated with a higher probability of flare in overall population (Mantel-Cox c2 6.68, p<0.01), but not in sub-analysis limited to JIA (Mantel-Cox c2 0.78, p=0.37) and IdCU (Mantel-Cox c2 1.18, p=0.27). None clinical variable, including time on remission on therapy, total length of treatment, and type of treatment, resulted significant predictors of long-lasting remission without therapy.

Conclusion: Even if limited to a relatively small group in retrospectively study design, our results suggest that type of disease, rather than the type or the length of treatment, can predict different duration of uveitis remission without systemic therapy.



Disclosure: G. Simonini, None; **C. Bracaglia**, None; **M. Cattalini**, None; **A. Taddio**, None; **A. Brambilla**, None; **C. DeLibero**, None; **D. Pires Marafon**, None; **R. Caputo**, None; **R. Cimaz**, None.

2902

The Health Status of Patients with Juvenile Idiopathic Arthritis (JIA) Significantly Worsens after Transfer from Pediatric to Adult Care. Kirsten Minden[1], Jens Klotsche[2], Martina Niewerth[2], Angela Zink[3] and Gerd Horneff[4]. [1]Charité University Medicine, Berlin, Germany, [2]German Rheumatism Research Center, Berlin, Germany, [3]German Rheumatism Research Centre and Charité University Medicine, Berlin, Germany, [4]Asklepios Klinik Sankt Augustin, Sankt Augustin, Germany.

Background/Purpose: A minority of patients with polyarticular JIA enter adulthood in drug free remission. Thus, patients are in need of care beyond adolescence. There is little information how patients' health status changes after discharge from pediatric care. We therefore investigated changes in the patients' health status before and after the transfer from pediatric to adult health care.

Methods: Data from patients were considered who were prospectively followed in the JIA biologic register BiKeR and in the follow-up register JuMBO for at least two additional years**.** Disease activity (physicians' global assessment on a numerical rating scale 0–10 [NRS]) and patient-reported outcomes (PROs; i.e. global assessment of disease activity, pain, overall well-being on NRS, functional status by CHAQ/HAQ) were assessed from inclusion in BiKeR up to the last follow-up in JuMBO.

Results: The eligible 654 patients were enrolled in BiKeR with a mean disease duration of 5.6 years (ys) at the start of a biologic (66.8%) or non-biologic DMARD (33.2%). The whole observation period of patients comprised 8.2 ys. During the years (mean 2.6) in pediatric care, i.e. from enrollment until the last visit in BiKeR, all PROs significantly improved: overall well-being from 4.5 to 2.1 (mean), pain level from 4.6 to 1.9, functional status (CHAQ-score) from 0.75 to 0.35. In contrast to this trend towards a steady improvement in patients' health state in pediatric care, PROs significantly worsened after discharge from pediatric care ($p < 0.001$). At the last follow-up in JuMBO, when patients were at the age of 23 ys (mean) and had a disease duration of 14.2 ys, the mean disease activity was 2.6, pain level 2.8, and overall well-being 2.9. At that time, more patients had an active disease (NRS0; 71 vs. 57%) and reported pain (78 vs. 56%) and restrictions in overall well-being (86 vs. 58%) than at the last visit in pediatric care.

Adult health care providers rated the patients' disease activity at first documentation in JuMBO lower than pediatric rheumatologists at the last visit in pediatric rheumatology care (1.8 vs. 2.1), which is in contrast to patients' self-reports. They also rated the disease activity lower than the patients did at last observation in JuMBO (1.9 vs. 2.6). The correlation between physician and patient scores for disease activity was better during pediatric than adult care (0.56 vs. 0.51).

Conclusion: The health state of patients with long-standing JIA significantly worsens after discharge from pediatric care. The reasons for this have to be explored. In addition, there are larger discrepancies between physician- and patient-reported outcomes in adult care than in pediatric care.

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2903

Early Outcomes in Pediatric Antineutrophil Cytoplasmic Antibody (ANCA) Associated Vasculitis (AAV). Kimberly Morishita[1], Susanne Benseler[2], Rae S.M. Yeung[3], Thomas Mason II[4], Dawn Wahezi[5], Kenneth N. Schikler[6], Erica F. Lawson[7], Susan Nielsen[8], Sirirat Charuvanij[9], Paul Dancey[10], Susan Shenoi[11], Linda Wagner-Weiner[12], Angelyne Sarmiento[1], David A. Cabral[1] and For the PedVas Initiative[1]. [1]BC Children's Hospital and University of British Columbia, Vancouver, BC, [2]Department of Pediatrics/University of Calgary, Calgary, AB, [3]The Hospital for Sick Children and University of Toronto, Toronto, ON, [4]Mayo Clinic, Rochester, MN, [5]Children's Hospital at Montefiore, Bronx, NY, [6]Univ of Louisville Schl of Med, Louisville, KY, [7]University of California, San Francisco, San Francisco, CA, [8]Rigshospitalet, Copenhagen, Denmark, [9]Siriraj Hospital, Bangkok, Thailand, [10]Janeway Children's Hospital, St. John's, NL, [11]Seattle Childrens Hospital, seattle, WA, [12]University of Chicago Hospital, Chicago, IL.

Background/Purpose: Childhood AAV is rare and outcome studies are limited. The PedVas Study is an international initiative collecting clinical data (to A Registry of Childhood Vasculitis -ARChiVe) and biological samples from children with primary systemic vasculitis. This is the largest study to date reporting early outcomes in pediatric AAV.

Methods: Patients diagnosed with granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA) and ANCA-associated pauci-immune glomerulonephritis before 18 years of age and with 12-month follow up data were included. Diagnoses were verified by applying a pediatric modification of the European Medicines Agency algorithm for classifying AAV (incorporating EULAR/PRINTO/PRES classification criteria). Descriptive statistics were used for baseline characteristics, remission-induction medications, and rates of remission at 4–6 months (post-induction) and at 12-months. Remission (on or off medications) was defined by a Pediatric Vasculitis Activity Score (PVAS) of 0. Relapse was defined as recurrence or new onset of disease activity (an increase in PVAS $\geq$1, from 0) attributable to active inflammation. Major relapse was defined as the recurrence, or new onset of potentially organ-or life-threatening disease activity requiring increased treatment, additional to corticosteroids (CS). Other relapses were considered minor.

Results: Among 40 patients eligible for inclusion in June 2014, 39 had verified AAV (35 GPA, 3 MPA, 1 EGPA), one patient became "unclassified" following verification. Median age at diagnosis was 12.4 years. 64% of patients were female. Median PVAS score at the time of diagnosis was 14 (IQR 11,19). 20 patients (51%) achieved remission 4–6 months after diagnosis and 25 patients (64%) were in remission at 12-months. 6 relapses occurred in 20 (30%) patients following remission, all were minor. At 12-months two patients were dialysis dependent and two patients had received renal transplants. No deaths occurred.

Primary treatments used for remission induction were: cyclophosphamide (CYC) in 29 (74%), methotrexate in 8 (21%), and rituximab (RTX) in 2 (5%). Plasmapheresis was used in conjunction with CYC or RTX in 8 patients. The most common maintenance treatments were azathioprine (38%), methotrexate (36%), and mycophenolate mofetil (18%). 37 (95%) of patients received CS in addition to their primary treatments. At 12-months, 22 patients (56%) were off (n=14) or on a low dose $\leq$ 0.1mg/kg/day (n=8) CS.

Following time-of-diagnosis, 20 patients required 31 hospitalizations: 16 in relation to underlying disease; 7 due to infection; 7 due to health problems unrelated to vasculitis; 1 due to medication effects.

The median score of a pediatric modification of the vasculitis damage index (pVDI) score completed for 21 patients at 12-months was 1 (range 0–5).

Conclusion: A significant proportion of children with AAV do not achieve remission following remission induction treatment, or at 12-months despite aggressive therapy. Compared to adults with AAV, remission rates may be lower in children and about half of children remain on corticosteroids at 12 months.

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2904

Clinical and Radiological Features of Down's Arthropathy. Charlene Foley, Orla Killeen and Emma Jane MacDermott. The National Centre for Paediatric Rheumatology, Dublin, Ireland.

Background/Purpose: The 'Arthropathy of Down syndrome' was first described in 1984. Three decades on we still have limited literature on the clinical & radiological features of this arthritis, despite the fact that it is thought to be 3–6 times more common than Juvenile Idiopathic Arthritis (JIA) in the general paediatric population. Down's Arthropathy (DA) is rarely recognised at onset, & remains under-diagnosed & largely under-reported in this population group. Ireland has one of the highest Trisomy 21 (T21) birth rates in Europe (1/547), and therefore provides an ideal setting for such a study.

Research Questions

1. What are the clinical & radiological features of DA?
2. Is DA missed, leading to a delay in diagnosis?

Objectives

To perform a musculoskeletal examination on children with T21, aged 0–18 years & document;

1. Presence of features to suggest old and/or present arthritis.
2. Radiological findings.

Methods: From May 2013 to September 2014, Children with T21 (aged 0–18 years) were invited to attend a screening clinic. Screening involved completion of a health questionnaire & musculoskeletal examination. Suspected cases of DA were invited to attend the National Centre for Paediatric Rheumatology (NCPR) for investigation, treatment & follow-up as per normal clinical practice.

Results: 370 children with T21 enrolled in the study, 56% Male. 17 new cases of DA were detected, only 3 (17.6%) of which were referred with suspected arthritis. In total, 28 children with DA now attend the NCPR for management of their arthritis, the largest cohort ever reported in the literature. We estimate the Point Prevalence of DA in Ireland to be 17–18/1000. For

comparison, the UK Prevalence of JIA is 1–2/1000. Table 1 compares characteristics of our DA cohort to a JIA comparison group.

Table 1: Comparison of Study Characteristic by Diagnosis

Characteristic		DA (n=28)		JIA (n=21)		p value
Small Joint Involvement	Mean (sd)	4.46 (1.95)		3.05 (2.29)		p<0.01
Time to Diagnosis	Mean (sd)	1.71 (1.47)		0.74 (0.86)		p<0.05
Characteristics		**n**	**(%)**	**n**	**(%)**	**p value**
Gender	Male	14	50.0	11	52.4	ns
	Female	14	50.0	10	47.6	
Rx MTX		8	28.5	7	33.3	ns
MTX Nausea		6	75.0	1	14.3	p<0.05

Features of DA – Summary of our findings

- Polyarticular Rheumatoid Factor negative presentation (69% of DA cohort).
- Finger involvement (77% of DA cohort) – significantly greater proportion than seen in the JIA comparison group.
- Erosive changes noted on X-Ray at presentation (27% of cohort).
- Methotrexate nausea common, but a good response to steroid intra-articular joint injections observed.
- General lack of awareness about the increased risk of arthritis in children with T21.

Conclusion: Children with T21 are at increased risk of developing arthritis, however there is often a delay in diagnosis. Reasons for this are multifactorial and include, failure of the child to express and localise pain, and changes in mobility attributed to the Down syndrome rather than a Rheumatological cause. Early diagnosis & treatment of DA is key to preventing irreversible joint destruction & long-term functional impairment. Methotrexate nausea is a significant barrier to successful treatment of DA with this DMARD. However, a good response to steroid joint injections has been observed. We advocate that children with T21 have an annual musculoskeletal assessment as part of their Health Screening Programme.

Disclosure: C. Foley, None; **O. Killeen**, None; **E. J. MacDermott**, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Animal Models II
Tuesday, November 18, 2014, 4:30 PM–6:00 PM

2905

The IL-6/Th17 Axis Promotes Autoantibody-Associated Autoimmune Valvular Carditis in Mice. Jennifer L. Auger, Brianna J. Engelson, Yaya Wang, Erik J. Peterson and Bryce A. Binstadt. University of Minnesota, Minneapolis, MN.

Background/Purpose: Autoimmune valvular carditis occurs in patients with systemic lupus erythematosus, rheumatoid arthritis and rheumatic fever, but the pathogenic mechanisms remain incompletely defined. Spontaneous autoimmune valvular carditis develops in the K/BxN T cell receptor transgenic mouse model of autoantibody-dependent inflammatory arthritis. CD4 T helper (Th) cells and macrophages cooperate to promote carditis in this model. We investigated which effector Th cell population was the predominant driver of cardiovascular pathology in K/BxN mice.

Methods: We first used RT-PCR to measure key cytokine transcript levels in cardiac valves of arthritic K/BxN mice and controls. We then used anti-cytokine blocking antibodies and gene knockout mice to determine which Th effector cells and cytokines were most critical for valve inflammation.

Results: We found increased expression of the genes encoding the Th17 differentiation factor IL-6 and IL-17A itself in K/BxN mitral valves relative to controls; IL-4 and IFNγ transcript levels were not different. Antibody blockade of IL-6 or IL-17A reduced the severity of valve inflammation, whereas blocking IL-4 had no effect. Genetic deficiency of IFNγ did not affect carditis severity. K/BxN mice lacking the key Th17 transcription factor RORγt had delayed onset of arthritis and were protected from valvular carditis.

Conclusion: Th17 cells are key drivers of autoimmune valvular carditis in K/BxN mice. We suggest a model in which autoantibodies engage Fc receptors on macrophages, leading to IL-6 production, which in turn promotes the differentiation of valve-infiltrating Th17 effector cells. Our results provide new insight into the mechanisms of valvular carditis in systemic autoantibody-mediated rheumatic diseases. More broadly, these findings may help guide the selection of therapies to reduce cardiovascular morbidity and mortality among patients with rheumatoid arthritis and systemic lupus erythematosus.

Disclosure: J. L. Auger, None; **B. J. Engelson**, None; **Y. Wang**, None; **E. J. Peterson**, None; **B. A. Binstadt**, None.

2906

Systemic Delivery of Short Hairpin RNA Targeting Calcium Release-Activated Calcium Channel 3 Down-Regulates Severity of Collagen-Induced Arthritis. Shuang Liu[1], Takeshi Kiyoi[2], Shohei Watanabe[3] and Kazutaka Maeyama[1]. [1]Informational Biomedicine, Ehime University Graduate School of Medicine, Toon-shi, Ehime, Japan, [2]Integrated Center for Sciences, Ehime University, Ehime, Japan, [3]Japan Community Health Care Organization Uwajima Hospital, Ehime, Japan.

Background/Purpose: In recent years, one widespread and potentially important Ca^{2+} channel, store-operated Ca^{2+}-release-activated Ca^{2+} (CRAC) channel is raised in drug discovery for rheumatoid arthritis (RA). Ca^{2+} entry through CRAC channels drives exocytosis, stimulates mitochondrial metabolism, activates gene expression and promote cell growth and proliferation in non-exitable cells. Downregulation of the CRAC channels lead to irregular functions of T cells, B cells and osteoclasts, which contribute to RA pathogenesis. The present study was undertaken to investigate the feasibility and efficiency of partially regulation of the Ca^{2+} influx via CRAC channel by CRACM3 gene-silencing for the treatment of RA.

Methods: We evaluated the therapeutic potential of CRACM3 gene-silencing by systemic delivery of lentivirus expressing CRACM3-shRNA (Lenti-M3shRNA) in a collagen-induced arthritis (CIA) mouse model. The inflammatory response was assessed by measuring the levels of inflammatory cytokines in joint and serum. The cytokine profile of T cells stimulated with autoantigen was also determined. Mature osteoclast function was analyzed using tartrate-resistant acid phosphatase (TRAP) staining and pit formation assay.

Results: The intraperitoneal injection (10^9 particles/7 days) of Lenti-M3shRNA was highly effective in treating CIA. Ca^{2+} influxes in splenocytes, thymocytes, and synovial cells were partially blocked by gene-silencing of CRACM3. CIA mice showed significant regression of the disease after Lenti-M3shRNA treatment. The autoimmune response, which was assessed using self-reactive Th1 cell activity and autoantibody production, was significantly suppressed by M3shRNA administration. Low level of the resorptive capacity in mature osteoclasts was also observed in Lenti-M3shRNA treated CIA mice according to the results of TRAP staining and pit formation assay.

Conclusion: Our findings indicate that *in vivo* gene-silencing CRACM3 by systemic delivery of Lenti-M3shRNA may have beneficial therapeutic effects on RA. Our findings provide valuable insight into the potential ways that CRACMs could contribute to RA pathogenesis and support the idea that targeting CRAC channels might offer an effective strategy for the treatment of RA.

Disclosure: S. Liu, None; **T. Kiyoi**, None; **S. Watanabe**, None; **K. Maeyama**, None.

2907

Loss of microRNA-146a Exacerbates Inflammatory Arthritis. Victoria Saferding[1], Antonia Puchner[1], Eliana Goncalvesalves[1], Birgit Niederreiter[1], Silvia Hayer[1], Gernot Schabbauer[2], Marije Koenders[3], Josef S. Smolen[1], Kurt Redlich[1] and Stephan Blueml[1]. [1]Medical University of Vienna, Vienna, Austria, [2]Medical University Vienna, Vienna, Austria, [3]Radboud University Nijmegen Medical Center, Nijmegen, Netherlands.

Background/Purpose: MicroRNA (MiR-) 146a is a key regulator of the innate immune response and has also been shown to suppress cancer development in myeloid cells. Elevated expression of miR-146a has been detected in synovial tissue of rheumatoid arthritis patients, but its role in the development of inflammatory arthritis is yet unknown.

Methods: We induced K/BxN serum transfer arthritis in wild type and miR-146a$^{-/-}$ mice. As a second inflammatory arthritis model we crossed miR-146a deficient into hTNFtg mice. Disease severity was assessed clinically and histologically in both arthritis models. Blood of arthritis animals was analyzed by flow cytometry. Serum cytokine levels were measured by Elisa.

Results: Absence of miR-146a leads to increased clinical signs of the induced serum transfer arthritis. In line, higher serum levels of the proinflammatory cytokines IL12 and TNF were measured in miR146a deficient mice compared to wt mice. When we crossed miR-146a$^{-/-}$ mice into hTNFtg mice, while detecting no clinical difference between hTNFtg and miR-146a/hTNFtg mice, we found a significant increase in circulating CD11b^{+} myeloid cells as well as CD11c^{+} dendritic cells in blood of miR-146a$^{-/-}$/hTNFtg mice compared to hTNFtg mice. Histological examination revealed a significant increase in synovial inflammation miR-146a$^{-/-}$/hTNFtg mice compared to hTNFtg mice. Even more striking, miR-146a$^{-/-}$/hTNFtg mice displayed a more than twofold increase in local bone destruction which was due to increased generation of osteoclasts in the tarsal joints of the mice. Measuring cytokine levels in serum, we show that IL-1β levels are increased in mice lacking miR-146a.

Conclusion: These data clearly demonstrate a negative regulatory role of the miR-146a in inflammatory arthritis. During arthritis, miR-146a is centrally involved in the regulation of proinflammatory cytokines as well as local bone destruction. These results identify an important anti-inflammatory role of miR-146a, which might possibly be exploited for therapeutic purposes.

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2908

Flip Deficiency in Dendritic Cells Promotes Spontaneous Arthritis Mediated By Reduced Treg and Increased Autoreactive CD4^{+}t Cells. Qiquan Huang[1], Harris R. Perlman[1], Robert Birkett[1], Renee E. Doyle[1], Deyu Fang[1], G. Kenneth Haines[2], William H. Robinson[3], Syamal K. Datta[1], Hyewon Phee[1] and Richard M. Pope[4]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Mount Sinai Hospital School of Medicine, New York, New York, NY, [3]VA Palo Alto Health Care System and Stanford University, Palo Alto, CA, [4]Northwestern University Feinberg school of Medicine, Chicago, IL.

Background/Purpose: *Flip (CFLAR)* has been identified as a rheumatoid arthritis (RA) risk allele and is important in preventing death receptor mediated apoptosis of dendritic cells (DCs). To examine the *in vivo*role of Flip in DCs in maintaining immune homeostasis, mice deficient in Flip in conventional DCs were generated (DC-Flip-KO). The DC-Flip-KO mice spontaneously develop erosive, inflammatory peripheral arthritis, resembling rheumatoid arthritis (RA). These studies were conducted to define the mechanisms that contribute to the development of arthritis in these mice.

Methods: Immune cell phenotyping was performed by flow cytometry. DC function was examined by antigen presentation and T regulatory cell (Treg) induction. Thymic T cell development, selection and tolerance were examined. T cell autoreactivity was determined by the syngeneic mixed lymphocyte response *in vitro* and by adoptive transfer *in vivo*, monitored by dilution of CFSE labelled T cells. Treg function was examined by suppression of CD4^{+} T cell proliferation. Autoantibodies to joint components were identified by immunoblotting. DC-Flip-KO mice were crossed with *Rag*$^{-/-}$ to generate DC-Flip-KO-*Rag*$^{-/-}$double mutant lines and arthritis was evaluated. All data are analyzed comparing indicated genotypes in age and gender matched groups.

Results: CD11c-cre mediated Flip deficiency resulted in consistent reduction of the CD11c^{+}CD8α^{+} subset of DCs in central and peripheral lymphoid organs before or after the onset of arthritis. No defects in thymic central tolerance were identified, however, increased autoreactive CD4^{+} T cells and plasmablasts are identified in the lymph nodes draining the inflamed joints, and both were positively correlated with the severity of arthritis. The DC-Flip-KO mice possessed autoantibodies specific for joint components. Further, Tregs were reduced in the thymus and spleen of DC-Flip-KO mice in a setting of lymphopenia. In addition, the number of Tregs in the spleen inversely correlated with the severity of the arthritis and adoptive transfer of Tregs ameliorated joint inflammation. DCs isolated from the DC-Flip-KO mice effectively presented antigen but were deficient in promoting the induction of Tregs. Supporting the role of T and B cells, DC-Flip-KO-*Rag*$^{-/-}$ mice, which lack of both T and B cells, develop significantly milder and self-resolving arthritis compared with the DC-Flip-KO-*Rag*$^{+/-}$mice.

Conclusion: Flip plays a key role in the survival of the CD8α^{+}CD11c^{+} DC subset *in vivo*. The loss of this subset impairs the generation and/or maintenance of Tregs, which in turn permits the expansion of antoreactive CD4^{+}T cells and autoantibody producing B cells, resulting in autoimmune arthritis. Our observations suggest that the DC-Flip-KO mouse is a novel model of RA that may provide important insights and permit in depth interrogation of the pathogenesis of RA.

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2909

Tolerogenic Splenic IDO+ Dendritic Cells from the Mice Treated with Induced-Treg Cells Could Suppress Collagen-Induced Arthritis. Jie Yang[1], Huahua Fan[2] and Hejian Zou[1]. [1]Division of Rheumatology, Huashan Hospital, Fudan University, Shanghai 200040, China, Shanghai, China, [2]Blood Engineering Laboratory, Shanghai Blood Center, Shanghai 200051, China, Shanghai, China.

Background/Purpose: As well known, Foxp3+ regulatory T cells play a crucial role in maintaining immune tolerance. It was reported that TGF-β-induced Tregs (iTregs) could retain Foxp3 expression and immune suppressive activity in the collagen-induced arthritis (CIA). However, the mechanisms whereby transferred iTregs suppressed immune response, especially the interplay between iTregs and DCs *in vivo*, remained incompletely understood. In this study, whether splenic DCs were involved in iTreg-based suppression and how these DCs further inhibited CIA were determined.

Methods: *In vitro*, iTregs were induced by TGF-β and adoptive transferred into established CIA mice. After 7 days, splenic CD11c^{+}DCs were isolated, termed 'DC_{iTreg}'. The phenotype, the expression of cytokines and function-associated molecules, the immunogenicity and the suppression on CD4/CD8 T cell differentiation of DC_{iTreg} were assessed. To determine the suppression *in vivo*, 5×10^5 of DC_{iTreg} were re-infused into the new CIA mice. Clinical and histopathologic scores, cytokine and anti-CII antibody secretion in serum were analyzed. And it also was determined the expression of Foxp3 and function of Tregs after IDO^{+}DCs transferred. Additionally, the role of IDO in the inhibitory effect of DC_{iTreg} was determined by 1-MT blocking *in vitro*and in CIA mice.

Results: After iTregs adoptive transferred, isolated DC_{iTreg} exhibited a series of tolerogenic characteristics. Compared with splenic DCs isolated from CIA mice (DC_{CIA}), DC_{iTreg} expressed obviously lower levels of MHC molecule (IA-IE) and co-stimulatory molecules (CD80, CD86 and CD40). And IL-12p40 and IL-6 production by DC_{iTreg} were negligible, while high levels of IL-10 and TGF-β were expressed; especially enhanced level of IDO by DC_{iTreg} was detected, and CD11b^{+}DCs were found as a major contributor of IDO expression in iTreg-treated CIA mice. In the proliferation assay, DC_{iTreg} showed the poor ability to expand effector T cells and had the effective inhibitory potency. Meanwhile, after CD11b^{+}IDO$^{+}DC_{iTreg}$ re-infused, a remarkable anti-arthritic activity, improved clinical scores and histological end-points were found. Also, serological levels of TNF-α, IL-6, IL-17 and anti-CII antibodies showed significantly low and TGF-β production was high in the DC_{iTreg}-treated group. Conversely, DC_{CIA} could not suppress CIA completely. And IDO^{+}DCs could induce the generation and proliferation of functional Foxp3^{+}Tregs *in vitro* and in CIA mice. Moreover, DC_{iTreg}lost the inhibitory ability on CIA when they pretreated 1-MT.

Conclusion: These findings suggested that iTregs could inhibit CIA via tolerogenic splenic DCs formation. These tolerogenic splenic DCs could further effectively dampen the severity and progression of CIA in the IDO-dependent manner, which was associated with modulation of inflammatory cytokine and anti-CII antibody secretion and induction of new iTregs. Thus, the potential therapeutic effect of iTreg in CIA and RA is likely to be maintained, even enlarged by their effects on DCs *in vivo*.

Disclosure: J. Yang, None; **H. Fan**, None; **H. Zou**, None.

2910

Tofacitinib Facilitates the Expansion of Myeloid-Derived Suppressor Cells and Ameliorates Arthritis in SKG Mice. Keisuke Nishimura, Jun Saegusa, Fumichika Matsuki, Kengo Akashi, Goichi Kageyama and Akio Morinobu. Kobe University Graduate School of Medicine, Kobe, Japan.

Background/Purpose: Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of cells that are characterized by the co-expression of Gr1 and CD11b in mice. MDSCs suppress T cell responses by producing arginase I (Arg I) and inducible nitric oxide synthase (iNOS). Tofacitinib is a Janus kinase (JAK) inhibitor that inhibits JAK1 and JAK3. Tofacitinib currently represents a novel therapeutic for treating rheumatoid arthritis. However, the anti-rheumatic effects of tofacitinib, especially its influence on

myeloid cells, are not fully understood. The aim of this study was to evaluate the effects of the Janus kinase inhibitor tofacitinib on MDSCs in a mouse model of rheumatoid arthritis.

Methods: Arthritis was induced in SKG mice by zymosan A (ZyA) injection. MDSCs isolated from the bone marrow (BM) of donor arthritic SKG mice were adoptively transferred to recipient arthritic mice. In a separate experiment, tofacitinib was administered to SKG arthritic mice subcutaneously via osmotic pump, in some cases followed by injection of an anti-Gr1 monoclonal antibody (mAb). BM cells from untreated mice were cultured for 5 days with granulocyte/macrophage colony-stimulating factor (GM-CSF), with or without tofacitinib, and then analyzed by flow cytometry.

Results: The BM and spleens of ZyA-treated mice contained increased numbers of $CD11b^{+}Gr1^{+}$ MDSCs, whereas polymorphonuclear (PMN)-MDSCs ($CD11b^{+}Ly6G^{+}Ly6C^{low}$) were significantly increased in the spleen of ZyA-treated mice. The number of monocytic-MDSCs ($CD11b^{+}Ly6G^{-}Ly6C^{high}$) was also significantly increased in the BM of ZyA-treated mice, although they represented only a small proportion of the BM cells. The BM cells from ZyA-treated SKG mice also expressed higher levels of iNOS and Arg I compared to untreated SKG mice. The adoptive transfer of MDSCs to recipient arthritic mice reduced disease severity compared to the untreated controls. Continuous administration of tofacitinib significantly ameliorated the arthritic scores of SKG mice. Tofacitinib treatment significantly increased the numbers of total- and PMN-MDSCs in the BM of arthritic mice. Furthermore, the anti-arthritic effect of tofacitinib was abrogated when MDSCs were depleted by anti-Gr1 mAb. *In vitro*, tofacitinib facilitated the differentiation of BM cells to MDSCs, and inhibited their differentiation to dendritic cells. Moreover, tofacitinib-treated BM cells were incapable of enhancing T cell proliferation, compared to mock-treated BM cells.

Conclusion: MDSCs play crucial roles in the regulation of SKG arthritis, and a JAK inhibitor, tofacitinib, enhances their expansion. Our results suggest a novel mode of anti-arthritic action for tofacitinib and a critical role for JAKs in the differentiation of MDSCs.

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ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects VI: Impact of Treatment and Other Interventions
Tuesday, November 18, 2014, 4:30 PM–6:00 PM

2911

Clinical Outcomes of Early RA after 7 Years – Does T2T Approach Overcome Delay of Therapy? Tuulikki Sokka[1], Hannu Kautiainen[2], Tuomas Rannio[3], Juha Asikainen[1] and Pekka Hannonen[1]. [1]Jyvaskyla Central Hospital, Jyväskylä, Finland, [2]Medcare Oy, Äänekoski, Finland, [3]Kuopio University Hospital, Kuopio, Finland.

Background/Purpose: Early vs. delayed referral/start of therapy within 3–4 months has been shown beneficial for outcomes in rheumatoid arthritis (RA) (Lard et al. AM J Med 2001, Gremese at al. ARD 2013, Ehrmann Feldman et al. Rheumatology 2013). However, in a real world setting, this applies for a minority of RA patients. In the FIN-RACo study, a delay of 4 months significantly influenced a 2-year remission rate in the monotherapy arm (remission rate was 11% vs 35%) while in the combination arm, 42% were in remission regardless of a delay indicating that early intensive therapy may overcome a delay (Möttönen et al. A&R 2002). Therefore, our aim was to study whether a delay of starting therapy in early RA affects long-term outcomes in a clinic with a T2T approach including preferring methotrexate based combinations over monotherapy, long-term low dose glucocorticoids over bridging, intra articular glucocorticoid injections to all swollen joints at every visit, patient education by specialist nurses, and routine monitoring including disease activity and self-reported outcomes.

Methods: A clinical database in a district of 275.000 population was analyzed for patients with a new diagnosis of RA in 1993–2013. Variables included demographics, clinical course, outcomes, medications and the date of first symptoms of RA, a question which was asked from the patient at the first visit and recorded in the database. Duration of symptoms (delay) at initiation of therapy was categorized as 0–3mo, 4–6mo, 7–12mo, 13–24mo, and >2yr. Outcome variables and medication data were available in 60–68% of patients at a mean of 7.3 years after diagnosis.

Results: In 1993–2013, 2374 patients (mean age 56yr, 67%F, 59%RF/CCP+) were diagnosed and treatment started with a median delay of 5.5mo (4.5mo in 2005 to 7.4 in 2003 with no trend of delay over years). Existing musculoskeletal disease and younger age were associated with longer delay, adjusted for sero+/−, gender, and year of diagnosis. Overall, 32%, 24%, 24%, 10%, and 10% of patients had a delay of 0–3mo, 4–6mo, 7–12mo, 13–24mo, and >2yr, respectively (in 98 patients delay data was missing).

After a mean follow-up of 7 years, the mean swollen and tender joint count (28JC) was <1, the mean ESR and CRP were normal, symptom level was low, functional capacity well maintained, and 66% of patients met the DAS28 remission (Table). No significant differences in outcomes and treatments were observed between the delay groups.

Conclusion: Clinical outcomes were good after 7 years in patients with early RA who were treated extensively using a T2T approach, including 66% of patients in DAS28 remission. Delay of treatment start did not influence outcomes in this clinic. Further analyses will include radiographic outcomes and work disability.

Mean values or % at evaluation	within 3mo	4–6mo	7–12mo	13–24mo	>2year	Total	P
N	737	553	544	212	231	2277	
Age, years	65.3	63.6	62.4	61.7	62.6	63.6	0.02
Disease duration, years	6.9	7.1	7.3	7.7	8.9	7.3	<0.001
SJC28	.33	.46	.54	.41	.44	.43	0.20
TJC28	.55	.74	.89	.50	.62	.68	0.06
ESR	13.7	13.6	13.8	12.2	14.1	13.6	0.78
CRP	4.8	4.8	4.7	4.1	5.2	4.8	0.87
InvGlobal VAS	9.2	9.9	10	10	11	9.9	0.56
Patientglobal VAS	31	29	27	29	30	29	0.31
Pain VAS	28	27	27	30	27	28	0.82
HAQ 0–3	.64	.63	.65	.65	.73	.65	0.62
DAS28 0–9.4	2.2	2.2	2.3	2.2	2.3	2.2	0.77
DAS28 remission <2.6	68%	67%	65%	67%	66%	66%	0.91
THERAPY NOW							
MTX, mono or combo	64%	68%	61%	70%	61%	64%	0.13
MTXcombo +any DMARD	38%	41%	40%	43%	31%	39%	0.15
Prednisolon	37%	44%	42%	37%	37%	40%	0.11
Biologic (+-DMARDs)	8.5%	8.5%	11%	13%	9.3%	9.6%	0.33
Without DMARDs	16%	13%	17%	12%	18%	15%	0.31

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2912

Impact of Failure to Adhere to Treat-to-Target of Rheumatoid Arthritis in Real World Practice: Data from the International Rheumatoid Arthritis Biomarker Program. WP Maksymowych[1], M. Østergaard[2], O Elkayam[3], R Landewé[4], J Homik[5], C Thorne[6], M Backhaus[7], S Shaikh[8], G Boire[9], M Larche[10], B Combe[11], T Schaeverbeke[12], A Saraux[13], G Ferraccioli[14], M Dougados[15], C Barnabe[16], M Govoni[17], PP Tak[18], D. van Schaardenburg[19], D van der Heijde[20], R Dadashova[1], E Hutchings[1], J Paschke[1] and Oliver FitzGerald[21]. [1]CaRE Arthritis, Edmonton, AB, [2]Copenhagen Center for Arthritis Research, Glostrup, Denmark, [3]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [4]Amsterdam Rheumatology Center, Amsterdam, Netherlands, [5]University of Alberta, Edmonton, AB, [6]Southlake Regional Health Centre, Newmarket, ON, [7]Charite University Hospital, Berlin, Germany, [8]Niagara Peninsula Arthritis Centre, Hamilton, ON, [9]CHUS-Sherbrooke University, Sherbrooke, QC, [10]St Joseph's Healthcare Hamilton, Hamilton, ON, [11]Hôpital Lapeyronie, Montpellier, France, [12]Bordeaux University Hospital, Bordeaux, France, [13]CHU Brest and EA 2216, UBO, Brest, France, [14]Catholic University of The Sacred Heart, Rome, Italy, [15]Hopital Cochin, Paris, France, [16]University of Calgary, Calgary, AB, [17]Universita di Ferrara, Ferrara, Italy, [18]Academic Medical Center, Amsterdam, Netherlands, [19]Jan van Breemen Research Institute, Amsterdam, Netherlands, [20]Leiden University Medical Center, Leiden, Netherlands, [21]St. Vincent's University Hospital, Dublin, Ireland.

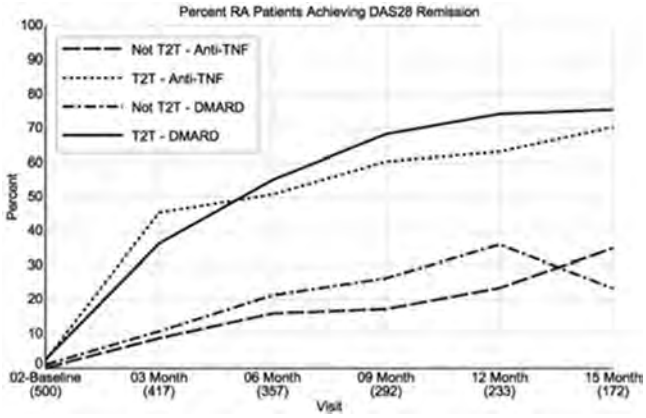
Background/Purpose: There is limited data on adherence to treat-to-target (T2T) strategies in RA in real world-practice and the impact of failure to adopt this best practice on clinical outcomes. We aimed to assess the impact of failure to adhere to T2T across 10 countries participating in the RA BIODAM program.

Methods: RA BIODAM is an international multicenter (35 sites, 620 patients) 2-year prospective study aimed at the clinical validation of biomarkers. Active RA patients are assessed for disease activity every 3 months with a prompt to make major treatment changes in order to achieve a DAS target

of ≤2.4. An internet-based data entry and management system (IDEMS) was designed to automate calculation of the DAS and alert sites to the requirement for treatment change. If a treatment change was not made a reason for that decision was required. RA outcomes (HAQ, RAID, SF36) and attainment of remission (DAS, CDAI, SDAI, ACR Boolean) were compared by adherence to T2T and according to treatment category (DMARD, anti-TNF).

Results: As of June 2014, 500 patients have been recruited of whom 172 have completed at least 15 months follow-up. Adherence to T2T was 52% and non-adherence 42% for at least 1 study visit (*the T2T failure visit*). Reasons for non-adherence were: physician decision that current treatment was acceptable (69%), physician decision (other) (14%), patient decision (9%), physician decision due to concern for adverse event (2%), other non-specific (6%). Starting at 6 months of follow up and continuing to diverge though 15 months, all outcomes were superior in T2T adhered patients: improvement in SJC/TJC, patient/physician global, HAQ, RAID, SF36. Remission at 15 months follow up was more frequent in T2T adhered patients at 75% (DAS), 41% (CDAI), 41% (SDAI), 40% (ACR Boolean) compared to non-adhered patients at 30% (DAS), 12% (CDAI), 13% (SDAI), 15% (ACR Boolean) irrespective of therapy (standard DMARD, anti-TNF). Median data for DAS components at *the T2T failure visit* was 9 and 4 for TJC and SJC, 5 for patient global, and 16 for ESR (40.0% with ESR >20). At the subsequent visit, there was still no change in treatment in 37% despite DAS > 2.4: median was 10 and 4 for TJC and SJC, 5 for patient global, and 22.5 for ESR (54.0% with ESR >20).

Conclusion: Adherence to T2T is associated with consistent improvement in RA outcomes and increased rates of remission. However, there remains a substantial gap in implementation even in protocol-specified clinical settings.



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2913

Does Corticosteroid Therapy at Disease Onset Influence Disease Progression of RA? Results from the Swiss Prospective Observational Cohort.

Ruediger Mueller[1], Nazim Reshiti[2], Toni Kaegi[1], Axel Finckh[3], Hendrik Schulze-Koops[4], Michael H. Schiff[5] and Johannes von Kempis[6]. [1]Kantonsspital St. Gallen, St. Gallen, Switzerland, [2]Division of Rheumatology, St. Gallen, Switzerland, [3]Geneva University Hospital, Geneva, Switzerland, [4]University of Munich, Munich, Germany, [5]University of Colorado, Denver, CO, [6]St. Gallen Hospital, CH-9007 St.Gallen, Switzerland.

Background/Purpose: Anti-inflammatory and disease-modifying properties of glucocorticoids (GCs) have been demonstrated in patients with rheumatoid arthritis (RA). Better outcomes in trials by combinations of synthetic DMARDs plus GCs versus DMARD monotherapy might be due GC. Since GCs are associated with adverse events, tapering of GCs is recommended in guidelines. There is almost no information on the benefits of GC in early arthritis outside the limitations of a clinical study.

To analyse whether initial GC therapy influences the course of the disease in early arthritis patients.

Methods: We included all patients from the Swiss RA registry SCQM with recent onset arthritis, (disease duration ≤1 year). Patients were categorized into two groups depending on their initial GC use. The primary outcome of this study was RA disease progression, as assessed by the evolution of disease activity (DAS28), radiographic erosion (Ratingen score) and HAQ-DI as a patient cantered outcome. The baseline disease characteristics were compared using standard descriptive statistics. The effect of initial glucocorticoid use on DAS 28 and HAQ-DI scores during follow up was estimated using linear mixed models with random slope and random intercept, and adjusted for various baseline factors in a univariate fashion. Slopes were compared between groups using the Mann-Whitney U-test.

Results: A total of 592 patients (pts) with early disease were available. Of these, 363 pts were initially treated with GC and 228 pts without (no-GC). DAS 28 (4.6 vs. 4.3, $p = 0.011$) and the HAQ-DI (0.94 vs. 0.82, $p = 0.0122$) were higher at the inclusion visit in GC patients, whereas average levels of CRP, swollen/tender joint counts, and erosion scores (Ratingen), presence of ACPA or rheumatoid factor at disease onset were not statistically different. Neither DAS 28, nor HAQ-DI, or the development of joint erosions differed between the two groups during follow up. Initial GC treatment was stopped in 201 patients during follow up after 680 days (mean). In parallel, GC treatment was initiated in 48 of the initial no-GC patients after 662 days (mean). Escalation of treatment employing biologics was documented in 18.0% of the no-GC patients and 27.3% of the GC patients ($p = 0.0097$). No differences in the number or kind of concomitant diseases were found.

We examined the probability of taking GC on the basis of baseline, parameters in a propensity score analysis. Even after adjusting for this propensity score, patients with and without use of GC did not have statistically significantly different DAS 28 (difference 0.04 on average, $p = 0.67$), erosion (0.75 higher Ratingen score with GC, $p = 0.29$), or HAQ-DI (0.03 higher with GC, $p = 0.47$).

Conclusion: It could be argued that initial GC use is not necessary in early RA patients, since disease progression, patient centred outcome, and the radiographic progression were comparable during follow up. Is has to be taken into consideration, however, that the patients with initial GC treatment had bad prognostic factors for the further disease course. Therefore we conclude that the treating rheumatologists have counterbalanced these factors by earlier and more frequent use of GC and subsequently by biologics.

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2914

The Clinical and Radiographic Course of Early Undifferentiated Arthritis Under Treatment Is Not Dependent on the Amount of Erosions at Diagnosis. Results from the Swiss Prospective Observational Cohort.

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Background/Purpose: To analyse whether early arthritis patients who do not fulfil the ACR/EULAR 2010 classification criteria for rheumatoid arthritis (RA) have a different course of the disease dependent on whether they can or cannot be classified as RA because of radiographic disease (as recently defined by the EULAR task force) at diagnosis.

Methods: For this observational study within the Swiss RA cohort SCQM, we included patients with early undifferentiated arthritis (disease duration ≤1 year), as diagnosed by the treating rheumatologist, who had not received any previous DMARDs. 2010 ACR/EULAR criteria negative patients were separated into 2 groups (radiographic vs. non radiographic arthritis) depending on whether or not they had radiographic changes recently defined as erosive disease by a EULAR task force (≥3 joints with erosions). The primary outcome measure was the radiographic progression detected employing the Ratingen erosion score. HAQ and DAS 28 were used as secondary outcome measures. The average observation period was 4 years.

Results: A total number 592 patients was analysed. 240 were not classifiable as RA by application of the 2010 ACR/EULAR criteria at baseline. 133 of these patients had radiographic arthritis and 50 non-radiographic arthritis. In 57 patients radiographs at the first visit were not available. Treatment was initiated in all patients with DMARDs, mostly MTX. There were no significant differences in the therapeutic strategies between radiographic and non-radiographic patients. No differences in DAS 28 and HAQ scores were found during follow up over 4 years. The average erosion scores were higher among patients with initially radiographic arthritis throughout the study. The progression of erosion scores over time, however,

was higher in initially non radiographic arthritis patients (3.3 erosions/year vs. 0.4, resp., $p<0.0001$).

Conclusion: The clinical and radiographic course of early undifferentiated arthritis under treatment was not dependent on the presence of erosions in 3 or more joints (i.e. the definition of radiographic disease by the EULAR taskforce) at diagnosis in our cohort.

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2915

Effects of Methotrexate on Anti-TNF Treatment in Rheumatoid Arthritis: An in-Depth Analysis of a Prospective Observational Study with Adalimumab. Marc Schmalzing[1], Frank Behrens[2], Eva C. Scharbatke[1], Michaela Koehm[3], Bianca Wittig[4], Gerd Greger[5], Harald Burkhardt[2] and Hans-Peter Tony[1]. [1]University of Würzburg, Würzburg, Germany, [2]Goethe-University Frankfurt, Frankfurt, Germany, [3]Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Project Group Translational Medicine & Pharmacology TMP, Frankfurt/Main, Germany, [4]Abbvie Deutschland GmbH & Co. KG, Wiesbaden, Germany, [5]AbbVie GmbH & Co KG, Wiesbaden, Germany.

Background/Purpose: Methotrexate (MTX) is currently the most frequently used drug in the treatment of rheumatoid arthritis (RA). MTX co-medication can improve the therapeutic benefit of adalimumab (ADA) in biologic-naïve RA patients. However, the impact of concomitant MTX has not been fully characterized in patients pretreated with biologics. Similarly, the influence of adding MTX to established ADA monotherapy has not been fully characterized.

Methods: We analyzed data from a large German multicenter, prospective, observational study of patients with active RA who are treated with ADA during routine clinical care. The effect of therapy on mean DAS28 scores was evaluated at baseline (month 0) and at months 3, 6, and 12 for patients receiving continuous ADA monotherapy, continuous ADA + MTX combination therapy, and MTX added to ADA therapy at 6 months (ADA monotherapy for the first 6 months and ADA + MTX combination therapy for months 6–12). Subgroup analyses for ADA monotherapy vs ADA + MTX were performed on biologic-naïve versus biologic-experienced patients. Stepwise forward and backward regression analyses were performed for identifying significant predictors.

Results: Combination therapy with ADA + MTX resulted in lower mean DAS28 scores at month 12 and a significant reduction in DAS28 scores from baseline than ADA monotherapy (Table). DAS28 improvements in patients who began the observation period on ADA monotherapy and added MTX at month 6 were similar to those receiving ADA + MTX continuously for 12 months. Subgroup analysis by prior biologic therapy indicated that both biologic-naïve and biologic-experienced patients achieved lower mean DAS28 scores with ADA + MTX than with ADA monotherapy ($p<0.0001$). However, patients treated previously with biologics did not show as much improvement in DAS28 scores as biologic-naïve patients, irrespective of MTX use.

Conclusion: Adding MTX to ADA monotherapy at month 6 resulted in DAS28 decreases similar to those observed with continuous ADA + MTX therapy, although patient numbers were small. Both biologic-naïve and biologic-experienced patients achieved lower DAS28 scores with ADA + MTX than with ADA monotherapy. These findings support the addition of MTX to ADA therapy for all patient populations.

Table 1. Effect of concomitant MTX on therapeutic response during ADA-treatment

Patient population	Therapy[a]	n	Mean DAS28 scores Month 0	Month 3	Month 6	Month 12	Mean DAS28 change at month 12[b]
All patients	Continuous ADA monotherapy	438	5.98	4.31	4.09	4.14	−1.85
	Continuous ADA + MTX	858	5.87	4.14	3.82	3.78	−2.08
	MTX added to ADA monotherapy at 6 months	51	5.84	4.31	3.83	3.70	−2.14
Biologic-naïve patients	Continuous ADA monotherapy	300	5.91	4.10	3.88	3.98	−1.93
	Continuous ADA + MTX	593	5.85	3.98	3.64	3.64	−2.21
Patients treated with ≥1 prior biologic	Continuous ADA monotherapy	138	6.15	4.77	4.55	4.47	−1.68
	Continuous ADA + MTX	265	5.90	4.51	4.21	4.10	−1.80

[a]Patients were considered to receive continuous therapy if they were recorded as receiving the stated therapy at each visit during the first 12 months of the observational study.
[b]Mean value calculated from the difference between DAS28 at month 12 and DAS28 at month 0 for each individual patient.

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2916

Effects of Exercise on Body Composition, Cardiovascular Fitness, Muscle Strength, and Cognition in Patients with Rheumatoid Arthritis: A Randomised Controlled Trial of a Patient-Specific Exercise Programme. Maha Azeez[1], Ciara Clancy[2], Tom O'Dwyer[2], Fiona Wilson[2] and Gaye Cunnane[1]. [1]St James's Hospital and Trinity College Dublin, Dublin, Ireland, [2]Trinity College Dublin, Dublin, Ireland.

Background/Purpose: Rheumatoid Arthritis (RA) patients have lower levels of physical activity compared to their non-RA counterparts. Large proportions of patients with RA are overweight or obese, and exhibit poor cardio-respiratory fitness and reduced muscle strength. These factors have been associated with poor function and increased mortality. A less well studied but important co-morbidity that affects RA patients is cognitive impairment, which can have a negative impact on patients' ability to manage their disease. We aimed to investigate the effects of a specifically designed exercise programme on body composition, aerobic capacity, muscle strength and cognition in RA patients.

Methods: Sixty-six patients with RA were randomised on a 1:1, case: control ratio. Assessments included body composition (waist circumference), fitness (VO_2max), muscle strength (hand-grip) and cognitive testing (Montreal Cognitive Assessment), in addition to disease related measures. Patients in the intervention group were enrolled for a three-month exercise programme. The control group received standard care.

Results: Twenty-eight cases and 24 controls attended for baseline testing. Seven patients were subsequently lost to follow up (4 cases and 3 controls). There were significant improvements in several measured outcomes in the intervention group compared to controls after three months. Median waist circumference was significantly reduced in cases, with median value 94.0 cm (range 67.3–124.5) at 0 months, compared to 91.4 cm (range 66.0–124.5) at 3 months, (2.8% reduction, $p<0.0001$). Aerobic capacity, as measured by VO2max, for cases was 23.2 ml/kg/min at 0 months compared to 27.6 ml/kg/min at 3 months (19% increase, $p=0.002$). Median right grip strength was 12kg (0–23) at 0 months, compared to 13kg (0–30) at 3 months (8.3% increase, $p=0.025$). For left grip strength, the median value was 8kg (0–20) at 0 months, compared to 10kg (0–32) at 3 months (25% increase, $p=0.005$). There was a significant improvement in cognitive function for cases, with median Montreal Cognitive Assessment value 25.5 (20–30) at 0 months compared to 28.0 (22–30) at 3 months (10% increase, $p=0.001$). There was also a significant reduction in C-reactive protein (median 2.8, range 1.0–27.4 at 0 months compared to 1.9, 1.0–18.4, at 3 months, equating to a reduction of 32.1%, $p=0.025$). Fatigue scores, measured by Global Fatigue Index were reduced from median 13.2 (range 6.4–34.1) at 0 months, to 10.9 (6.5–37.5) at 3 months ($p=0.047$). There was a significant reduction in trunk fat at 3 months (median 37.3, range 16.3–56.9) compared to 36.2, range 16.3–56.5 ($p=0.004$). For all above measures, there was no significant difference in median control values at 3 months.

Conclusion: There are significant benefits associated with physical activity for both general health and RA-related parameters, as evidence by the current data. This study has demonstrated for the first time that exercise has a significant impact on cognitive function in RA. We can conclude that physical activity is safe and effective in RA patients and should be a vital component of management protocols.

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2917

Inhibition of PAD4 Activity and the Formation of Neutrophil Extracellular Traps Via PTPN22, but Not Its Rheumatoid Arthritis-Prone W620 Variant. I-Cheng Ho[1], Hui-Hsin Chang[1], Nishant Dwivedi[1], Hsiao-Wei Tsao[1] and Anthony Nicholas[2]. [1]Brigham and Women's Hospital, Boston, MA, [2]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: One unique feature of rheumatoid arthritis (RA) is the presence of anti-citrullinated protein antibody (ACPA). Protein citrullination, a process mediated by peptidyl arginine deiminases, such as PAD4, not only yields antigens recognized by ACPA but also contributes to RA through several other mechanisms including promotion of neutrophil extracellular traps (NET) formation. A C-to-T single nucleotide polymorphism (SNP) located at position 1858 of human PTPN22, a protein tyrosine phosphatase, carries an odds ratio of 2–3 and, together with HLA alleles containing shared epitopes, synergistically increases the risk of RA 20- to 30-fold. The effect of this SNP is limited to ACPA+ RA. An explanation for this unique association is still lacking. We postulate that PTPN22 and the C1858T SNP, which converts an arginine (R620) to a tryptophan, influence protein citrullination.

Methods: The level of citrullinated proteins in wild type and PTPN22-deficient cells, as well as PBMC from healthy donors carrying or not carrying the risk T allele was examined with Western blotting using F95 antibody and anti-citrullinated histone H3. Co-immunoprecipitation was used to examine the physical interaction between PTPN22 and PAD4. The formation of neutrophil extracellular traps was analyzed with Sy-tox uptake and immunocytochemistry.

Results: Impaired expression of PTPN22 resulted in hypercitrullination in mouse and human immune cells. This effect was partly mediated by PAD4. PTPN22 did not regulate the expression or tyrosine phosphorylation of PAD4. Instead, PTPN22 physically interacted with and suppressed the activity of PAD4 independently of its phosphatase activity. Conversion of the R620 to a tryptophan disrupted the interaction between PTPN22 and PAD4, and completely ablated the ability of PTPN22 to suppress protein citrullination. Accordingly, the risk T allele is associated with hypercitrullination in PBMC and heightened propensity to form NET in healthy donors.

Conclusion: PTPN22 is a natural inhibitor of PAD, and the R620 is critical for this non-phosphatase function of PTPN22. The C1858T-mediated conversion of R620 to tryptophan increases the risk of ACPA+ RA through hypercitrullination and heightened propensity to form NET. Our data also identify a novel pathway regulating PAD activity and establish a molecular connection between the two RA risk genes PTPN22 and PAD4.

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2918

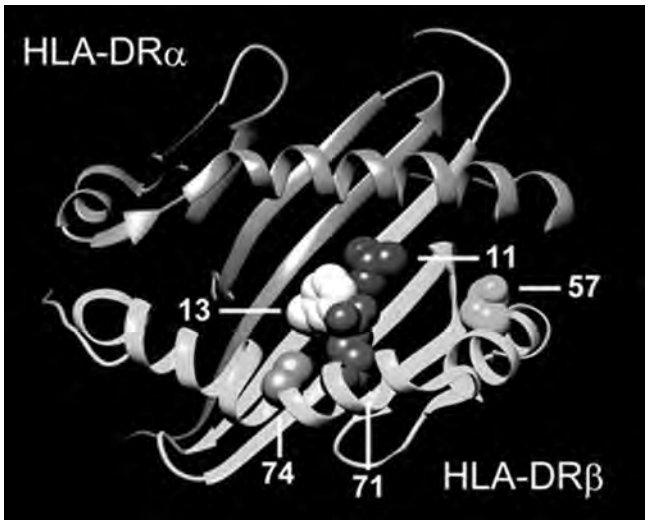
Fine-Mapping Major Histocompatibility Complex Associations in ACPA-Positive Rheumatoid Arthritis Identified Shared HLA Amino Acid Polymorphisms in Asian and European Populations. Yukinori Okada[1], Kwangwoo Kim[2], Buhm Han[3], Nisha E. Pillai[4], Rick T-H. Ong[4], Woei-Yuh Saw[4], Ma Luo[5], Lei Jiang[6], Jian Yin[6], So-Young Bang[7], Hye-Soon Lee[7], Matthew A. Brown[8], Sang-Cheol Bae[9], Huji Xu[10], Yik-Ying Teo[4], Paul IW. de Bakker[11] and Soumya Raychaudhuri[3]. [1]Tokyo Medical and Dental University, Tokyo, Japan, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]National University of Singapore, Singapore, Singapore, [5]University of Manitoba, Winnipeg, MB, [6]The Second Military Medical University, Shanghai, China, [7]Hanyang University Guri Hospital, Guri, South Korea, [8]University of Queensland Diamantina Institute, Brisbane, Australia, [9]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [10]Shanghai Changzheng Hospital, Shanghai, China, [11]University Medical Center Utrecht, Utrecht, Netherlands.

Background/Purpose: Rheumatoid arthritis (RA) risk is strongly associated with variations within the major histocompatibility complex (MHC) region, and in particular to *HLA-DRB1* alleles. We aimed to fine-map RA risk alleles within the MHC in Asian populations and conduct trans-ethnic risk comparison to those in European populations.

Methods: We analyzed 2,782 anti-citrullinated protein antibodies (ACPA)-positive RA cases and 4,315 controls from Chinese and Korean populations. We applied HLA imputation to infer genotypes at eight class I and II HLA genes (*HLA-A*, *HLA-B*, *HLA-C*, *HLA-DRB1*, *HLA-DQA1*, *HLA-DQB1*, *HLA-DPA1*, *HLA-DPB1*) using SNP2HLA software and a newly constructed pan-Asian imputation reference panel.

Results: We obtained highly accurate imputation of HLA classical alleles with this reference panel (95.1% and 82.4% concordance for two and four digit classical alleles respectively). We observed the most significant association in HLA-DRβ1 at amino acid position 13 ($P_{omnibus} = 6.9\times10^{-135}$), located outside the classical shared epitope (SE). The individual residues at position 13 have relative effects that are consistent with published effects in European populations (His>Phe<Arg>Tyr≈Gly>Ser) – but Asian effects are generally smaller. Applying stepwise conditional analysis, we identified additional associations at positions 57 (conditional $P_{omnibus} = 2.2\times10^{-33}$) and 74 (conditional $P_{omnibus} = 1.1\times10^{-8}$). Outside of HLA-DR$\beta$1, we observed independent effects for amino acid polymorphisms within HLA-B (Asp9, conditional $P = 3.8\times10^{-6}$) and HLA-DPβ1 (Phe9, conditional $P = 3.0\times10^{-5}$) concordant with European populations. While a common set of amino-acid residue effects in three HLA genes are shared between European and Asian populations, these same effects can induce different classical allelic associations (e.g. *HLA-DRB1*09:01*) in the two populations due to differences in allele frequencies.

Conclusion: Our trans-ethnic study reveals that a common set of amino-acid residue effects in three HLA genes are largely shared between European and Asian populations. Our study illustrates the value of high-resolution imputation for fine-mapping causal variants in the MHC.



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2919

The Novel Rheumatoid Arthritis (RA) Risk Gene, *LBH*, Is Regulated By TGFβ and PDGF and Modulates Cell Growth in Fibroblast-like Synoviocytes. Anna-Karin Ekwall[1], Deepa Hammaker[2], John W. Whitaker[3], William Bugbee[4], Wei Wang[5] and Gary S. Firestein[6]. [1]UC San Diego, La Jolla, CA, [2]University of California San Diego, La Jolla, CA, [3]UCSD, San Diego, CA, [4]Scripps Clinic, La Jolla, CA, [5]UCSD, La Jolla, CA, [6]University of California at San Diego School of Medicine, La Jolla, CA.

Background/Purpose: RA fibroblast-like synoviocytes (FLS) display an aggressive phenotype, such as increased cytokine production and cell growth. Currently no therapeutics specifically target FLS. To this end, we have taken an unbiased integrative omics approach to identify therapeutic candidate gene by combining three different genome-wide assays: (i) GWAS in RA, (ii) differentially expressed genes in RA vs. osteoarthritis (OA) FLS and, (iii) differential DNA methylation in RA vs. OA FLS. We identified and characterized one gene present in all three databases, namely *limb bud and*

heart development (LBH). LBH is a conserved putative protein with largely unknown functions.

Methods: FLS cultures were established from RA and OA synovial tissues from joint replacement surgery. Gene expression was measured by qPCR. *LBH* gene expression was silenced using siRNA (mean 91% decrease) or over-expressed (mean 13 fold increase) using an LBH expression vector. Differentially expressed genes of 4 RA FLS lines with modified *lbh* expression were determined by microarray. The affected pathways were identifed using Ingenuity Pathway Analysis. Effects of modified *lbh*gene expression were assessed by cell migration (scratch-wound assay), cell growth (MTT), apoptosis (caspase 3/7 activity) and TNF-stimulated gene expression.

Results: LBH is constitutively expressed in RA FLS as determined by qPCR. TGFβ stimulation (1 ng/ml, 18 hr) significantly increased *LBH* mRNA by 5.0±0.4 fold *(P*=0.02) and PDGF-BB (0.1 ng/ml,12 hr) significantly decreased *LBH* mRNA expression by 5.7±1.7 fold (*P*=0.04). Stimulating FLS with TNF, Wnt1, Wnt3a or Wnt 5a had no effect on *LBH* gene expression. LBH was then knocked down using siRNA, with no effects on cell migration or TNF-induced MMP3 or IL-6 expression. To determine potential functions, microarrays were performed using LBH-deficient FLS. Pathway analysis of gene expression profiles in LBH^{low} compared to control FLS identified "Cellular growth and proliferation" as the most significantly enriched pathway. Therefore, we performed cell growth assays. LBH-deficiency increased FLS proliferation by 92±15% (p=0.025). Conversely, LBH-overexpressing FLS significantly inhibited cell growth by 62±10% (*P*=0.018). LBH did not alter apoptosis.

Conclusion: We identified *LBH* as a candidate gene for RA by integrating multiple omics datasets. Microarray experiments focused our attention on cell growth as a potential LBH-regulated function, and this was confirmed using functional assays. Furthermore, the gene is highly regulated by growth factors that modulate the cell cycle. The data suggest that LBH contributes to synovial intimal hyperplasia and joint damage in RA.

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2920 WITHDRAWN

2921

Contraceptive Factors Are Associated with Serum Antibodies to Citrullinated Protein Antigens in Women at Elevated Risk for Future Rheumatoid Arthritis. Sonia Khatter[1], Mark C. Parish[1], Marie L. Feser[1], Jason R. Kolfenbach[1], Ryan W. Gan[2], Michael H. Weisman[3], James R. O'Dell[4], Ted R. Mikuls[5], Richard M. Keating[6], Peter K. Gregersen[7], Jane H. Buckner[8], V. Michael Holers[1], Kevin D. Deane[1], Jill M. Norris[2] and M. Kristen Demoruelle[1]. [1]University of Colorado School of Medicine, Aurora, CO, [2]Colorado School of Public Health, Aurora, CO, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]Veteran Affairs Nebraska Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, [5]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [6]Scripps Clinic, La Jolla, CA, [7]Feinstein Institute for Medical Research, Manhasset, NY, [8]Benaroya Research Institute at Virginia Mason, Seattle, WA.

Background/Purpose: The preclinical period of rheumatoid arthritis (RA) development is characterized by elevations of serum RA-related autoantibodies (Abs) including Abs to citrullinated protein antigens (ACPA) and rheumatoid factor (RF). Serum ACPAs are highly predictive of future inflammatory arthritis (IA) classifiable as RA, and recent data suggesting that ACPAs are directly pathogenic in joint disease highlight the need to understand the etiology of ACPA development. In addition, it remains unknown why RA disproportionately impacts women compared to men, and data suggest hormonal factors may influence the risk of developing RA. Importantly, prior data from our group identified that oral contraceptive pill (OCP) use was associated with a decreased risk for serum RF positivity in the absence of IA (Bhatia 2007). Therefore, we hypothesize that contraceptive factors will be associated with serum ACPA positivity among arthritis-free women at increased risk for RA.

Methods: In the Studies of the Etiology of RA (SERA) project, 1243 first degree relatives (FDR) of probands with RA are enrolled who are women. Of these FDRs, we studied women who at their baseline visit had serum ELISA testing for ACPA using anti-CCP3.1 (IgG/IgA, INOVA) and a detailed prior contraceptive and pregnancy history obtained using a standardized questionnaire (N=336). To avoid familial correlation, we also randomly selected only one subject per family; therefore, our final analyses included 297 FDRs. All subjects were without clinical IA at the time of serum testing. In cross-section, associations of ACPA and subject factors were analyzed using chi-squared and logistic regression.

Results: In multivariate analyses, prior use of OCPs was associated with a decreased risk of serum ACPA positivity (OR=0.34; 95% CI 0.15–0.79; adjusted for age, race and smoking). In addition, there was an increased risk of ACPA positivity in women who had a history of intrauterine device (IUD) use (OR=2.68; 95% CI 1.11–6.47; adjusted for age, race and smoking). ACPA(+) FDRs were slightly older than ACPA(−) FDRs, but were similar in race, smoking and shared epitope status (Table). No significant association was seen between ACPA positivity and pregnancy or breastfeeding.

Conclusion: Prior OCP use was associated with a decreased risk of ACPA positivity in these FDRs, and these results are in line with our prior findings of OCP use associated with a decreased risk of RF positivity. Of interest was the association of an increased risk of ACPA positivity with IUD use. While the mechanisms that link contraceptive factors to ACPA generation are unknown, unlike OCPs, IUDs have been shown to generate endometrial inflammatory responses. Therefore, the association of IUD use and ACPA suggest that IUD-induced endometrial inflammation may be a potential mucosal trigger of RA-related Abs. Mechanisms by which OCPs could protect and IUDs could increase risk for RA-related autoimmunity need further study.

Table. Contraceptive and Other Risk Factors for ACPA Positivity in Women at Elevated Risk for Future RA

	ACPA (+) (N=34)	ACPA (−) (N=263)	p-value*	Unadjusted OR (95% CI)	Adjusted OR (95% CI)**
History of OCP use (%)	**64.7**	**84.4**	**<0.01**	**0.34 (0.16–0.74)**	**0.34 (0.15–0.79)**
History of IUD use (%)	**26.5**	**12.9**	**0.03**	**2.42 (1.04–5.63)**	**2.68 (1.11–6.47)**
Age, mean (SD)	52 (17.3)	46 (15.8)	0.07	1.02 (1.0–1.05)	
Race, white non-Hispanic (%)	73.5	77.2	0.63	1.22 (0.54–2.75)	
History of ever smoking (%)	29.4	35.7	0.47	0.75 (0.34–1.63)	
≥1 shared epitope allele (%)	50.0	54.3	0.64	0.84 (0.41–1.72)	
History of pregnancy (%)	73.5	75.3	0.82	0.91 (0.40–2.05)	
Number of pregnancies, mean (SD)	2.0 (1.7)	2.1 (1.7)	0.66	0.95 (0.77–1.18)	
History of breastfeeding (%)	44.1	46.0	0.84	0.93 (0.45–1.90)	
Total duration breastfeeding, mean (SD)	8.6 (21.5)	7.3 (14.3)	0.63	1.01 (0.98–1.03)	
Age of menses onset, mean (SD)	13 (1.5)	13 (1.3)	0.85	0.98 (0.77–1.25)	

* Calculated comparing ACPA(+) versus ACPA (−) subjects, chi-squared and t-test used as appropriate.
**Odds ratios were adjusted for age, race and history of smoking.
Abbreviations: ACPA=antibodies to citrullinated protein antigen, OCP=oral contraceptive pill, IUD=intrauterine device.

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2922

Association of Single Nucleotide Polymorphisms of PADI4 Gene with Susceptibility to Rheumatoid Arthritis-Related Lung Disease. Seong-Wook Kang, Seung-Taek Song, Song Soo Kim, Ji Young Kim, So Young Lee, Su-Jin Yoo, In-Seol Yoo, Jinhyun Kim and Seung-Cheol Shim. Chungnam National University School of Medicine, Daejeon, South Korea.

Background/Purpose: Rheumatoid arthritis (RA) causes a myriad of pulmonary complications, including bronchiolitis and bronchiectasis, pleuritis, and interstitial lung disease (ILD). Recently, several studies have shown the association of rheumatoid arthritis-related lung disease (RA-LD) with the high titers of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) which are the most specific serologic marker for RA. Single nucleotide polymorphisms (SNPs) in a citrullinating (or deiminating) enzyme, peptidyl arginine deiminase type IV (PADI4) have been reproducibly associated with RA susceptibility in several populations.

The aim of the present study is to investigate if the SNPs in PADI4 gene are associated with RA-LD.

Methods: A total of 103 consecutive RA patients, who satisfied the 1987 American College of Rheumatology classification criteria, were genotyped for two nonsynonymous (padi4_89 and padi4_92) and one synonymous (padi4_104) SNPs in PADI4. RA-LD was diagnosed using high-resolution computed tomography of the chest. The following data were collected from medical records: Age, sex, disease duration, smoking history, use of disease-modifying anti-rheumatic drugs (DMARDs), RF, and ACPA. We used the t-test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Multivariate logistic regression analysis was performed to assess the relationship between the SNPs in the PADI4 gene and RA-LD.

Results: Of the 103 RA patients, 8 (7.8%) had interstitial lung disease (ILD) and 33 (32.0%) had small airway disease (AD). High titers of ACPA (≥80 U/mL; p=0.022) and RF (≥ULN×3; p=0.008) were significantly associated with susceptibility to RA-LD (Table 1). SNPs and genotypes in exon-3 (padi4_92) of PADI4 showed significant association with susceptibility to RA-LD (p=0.013, p=0.004, respectively) (Table 2)(Table 3). No statistically significant differences were seen between RA patients with LD and those without LD with respect to sex, smoking history, anti-Ro antibody, and use of DMARDs.

Conclusion: Our results suggest that SNPs and genotypes in exon-3 (padi4_92) of PADI4 are associated with susceptibility to RA-LD. Further studies are warranted to clarify the mechanisms by which SNPs in the PADI4 gene affect the development of RA-LD.

Table 1 Clinical characteristics of RA patients with or without lung disease

Characteristics	RA-no LD (n = 69)	RA-LD (n = 34)	*p*-value
Age (yrs)†	51.77±9.25	58.50±8.26	**0.001**
Female	62 (89.9)	30 (88.2)	1.000
RA duration (yrs)†	10.49±7.84	7.11±7.14	**0.037**
Smoking history	6 (9.1)	1 (3.1)	0.421
Positive ACPA	53 (77.9)	30 (88.2)	0.208
ACPA titer (U/mL)†	204.51±201.33	300.74±201.07	**0.025**
High-titier ACPA (≥80 U/mL)	40 (59.7)	28 (82.4)	**0.022**
Positive RF	53 (76.8)	30 (88.2)	0.168
RF titer (IU/mL)†	58.36±70.37	89.35±87.51	0.056
High-titer RF (≥ULN×3)	20 (20.9)	19 (55.9)	**0.008**
Positive anti-Ro Ab	12 (18.8)	4 (11.8)	0.567
anti-Ro titer	0.71±1.39	0.53±1.27	0.520
Use of DMARDs			
Biologic agents	17 (24.6)	11 (32.4)	0.408
Methotrexate	66 (95.7)	27 (79.4)	0.14
Leflunomide	7 (10.1)	4 (11.8)	1.000
Hydroxychloroquine	37 (53.6)	17 (50.0)	0.729
Sulfasalazine	5 (7.2)	2 (5.9)	1.000

Values are the number (%), †; (mean±SD). RA-LD group encompasses the interstitial lung disease (ILD) and small airway disease (AD). RA-no LD group includes RA patients without ILD or small AD. Smoking history is defined as positive for current or former smokers. In biologic agents, anti-tumor necrosis factor-α inhibitors (such as Etanercept, Adalimumab, and Golimumab), Abatacept, and Tocilizumab were included. Significance was determined by means of the independent *t*-test for continuous variables and the chi-square or Fisher's exact test for categorical variables.
RA, rheumatoid arthritis; ACPA, anti-citrullinated protein antibodies; RF, rheumatoid factor.

Table 2 Association of the alleles of *PADI4*SNPs with RA-LD susceptibility

SNP	Allele	RA-no LD	RA-LD	OR (95% CI)	*p*-value
padi4_89	A	0.52	0.61	1	0.418
	G	0.48	0.39	0.749 (0.372–1.508)	
padi4_92	C	0.18	0.41	1	**0.004**
	G	0.82	0.59	0.319 (0.147–0.692)	
padi4_104	C	0.61	0.67	1	0.809
	T	0.39	0.33	0.914 (0.441–1.896)	

Values are frequency. Age, sex-adjusted odds ratios (ORs) and *p* values for carriers of minor susceptibility alleles versus noncarriers were calculated by multivariate logistic regression. SNP, single nucleotide polymorphism; RA, rheumatoid arthritis; 95% CI, 95% confidence interval.

Table 3 Association of *PADI4*SNP genotypes with RA-LD susceptibility

SNP	Genotype	RA-no LD	RA-LD	OR (95% CI)	*p*-value
padi4_89	AA	0.25	0.39	1	0.087
	AG/GG	0.75	0.61	0.429 (0.162–1.132)	
padi4_92	CC	0.14	0.39	1	**0.004**
	CG/GG	0.86	0.61	0.195 (0.065–0.589)	
padi4_104	CC	0.32	0.46	1	0.081
	CT/TT	0.68	0.54	0.429 (0.166–1.110)	

Values are frequency. Age, sex-adjusted odds ratios (ORs) and *P*values for carriers of minor susceptibility alleles versus noncarriers were calculated by multivariate logistic regression. SNP, single nucleotide polymorphism; RA, rheumatoid arthritis; 95% CI, 95% confidence interval.

Disclosure: S. W. Kang, None; **S. T. Song**, None; **S. S. Kim**, None; **J. Y. Kim**, None; **S. Y. Lee**, None; **S. J. Yoo**, None; **I. S. Yoo**, None; **J. Kim**, None; **S. C. Shim**, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Small Molecules, Biologics and Gene Therapy VI: Biomarkers and Predictors of Rheumatoid Arthritis Disease Response and Outcomes
Tuesday, November 18, 2014, 4:30 PM–6:00 PM

2923

Protein Quantification Using Mass Spectrometry Methods to Predict Response to Abatacept and Methotrexate Combination Therapy in Rheumatoid Arthritis. A Obry[1], P Cosette[1], T Lequerré[2], Maria-Antonietta d'Agostino[3], C Gaillez[4], M Le Bars[5] and O Vittecoq[2]. [1]UMR 6270 CNRS, PISSARO Proteomic Facility, IRIB, Normandy University, University of Rouen, Rouen, France, [2]Rouen University Hospital, Rouen, France, [3]AP-HP Ambroise Paré Hospital, Boulogne-Billancourt, France, [4]Formerly of Bristol-Myers Squibb, Rueil-Malmaison, France, [5]Bristol-Myers Squibb, Rueil-Malmaison, France.

Background/Purpose: Targeted biologic therapies with different mechanisms of action are commonly used in RA. Abatacept is a recombinant fusion protein that inhibits T-cell co-stimulatory molecules required for T-cell activation. Overall, 57.1% of patients reached LDA (DAS28 [CRP] ≤3.2) after 6 months of treatment with abatacept and MTX in the open-label abatacept Power Doppler Ultrasonography APPRAISE study, in patients with RA and inadequate MTX response.[1] Treatment choice may be optimized by the identification of predictive protein markers of patient response to treatment. The aim of this study was to identify, by mass spectrometry-based quantification methods, a protein signature from peripheral blood mononuclear cells (PBMC) to predict abatacept/MTX response.

Methods: In total, 104 patients with active RA and inadequate MTX response were treated with approved doses of abatacept and MTX. For this analysis, patients were categorized as abatacept responders (DAS28 ≤3.2 [LDA]) (n= 30) or abatacept non-responders (DAS28 >3.2) (n=6) following 6 months of treatment. Proteins extracted from PBMCs from responders and non-responders at baseline and 6 months were analyzed. A 'label-free' approach was designed to compare the whole PBMC proteome for the 72 samples; the proteome of each sample was extracted and then in-gel digested. The resulting peptides were analyzed by high-resolution mass spectrometry (MS). Protein quantification was performed by comparing extracted ion currents with dedicated software for quantitation from MS data. Three differential analyses were conducted: (i) between responders and non-responders before treatment; (ii) between responders before and after treatment; (iii) between non-responders before and after treatment.

Results: These investigations revealed 30 proteins exhibiting differential expression between responders and non-responders before treatment: 28 proteins were down-regulated and 2 proteins were up-regulated in responders compared with non-responders. In our cohort, this combination of potential biomarkers could predict a good treatment response with 86.67% sensitivity and 66.67% specificity. In our second analysis, after 6 months of abatacept/MTX treatment 29 proteins were down-regulated in responders, while 30 proteins were up-regulated in non-responders, without overlap between these two sets of proteins. Several pathways were recruited in responders, including focal adhesion or leukocyte trans-endothelial migration, whereas immune system response was the main pathway among the over-expressed proteins in non-responders.

Conclusion: Our investigations identified a combination of potential biomarkers able to predict patient response to abatacept/MTX treatment in this dataset. We also demonstrated a decrease in the expression of proteins involved in cell migration in treatment responders and an enhanced immune response in treatment non-responders from our dataset. These exploratory findings require further validation and confirmation in another trial.

1. D'Agostino MA, et al. *Arthritis Rheum* 2012;**64**(Suppl):S352.

Disclosure: A. Obry, None; **P. Cosette**, None; **T. Lequerré**, Bristol-Myers Squibb, 2; **M. A. d'Agostino**, Bristol-Myers Squibb, AbbVie, 8; **C. Gaillez**, Bristol-Myers Squibb, Novartis, 1, Novartis Pharma AG, 3; **M. Le Bars**, Bristol-Myers Squibb, 3, Bristol-Myers Squibb, 1; **O. Vittecoq**, None.

2924

Clinical Utility of Random Anti-TNF Drug Level Testing and Measurement of Anti-Drug Antibodies on Long-Term Treatment Response in Rheumatoid Arthritis. Meghna Jani[1], Hector Chinoy[1], Richard B. Warren[2], Christopher E.M Griffiths[2], Ann W. Morgan[3], Anthony G. Wilson[4], Kimme L. Hyrich[1], John Isaacs[5], Darren Plant[1] and Anne Barton[6]. [1]Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom, [2]Dermatology Centre, University of Manchester, Manchester, United Kingdom, [3]University of Leeds, Leeds, United Kingdom, [4]University College Dublin, Dublin, Ireland, [5]Institute of Cellular Medicine, University of Newcastle, Newcastle, United Kingdom, [6]NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester Academic Health Science Centre, Manchester, United Kingdom.

Background/Purpose: Up to 40% of RA patients on anti-TNF treatment fail to respond either due to primary inefficacy or loss of response. One explanation is immunogenicity leading to the development of anti-drug antibodies (ADAb) and low drug levels, however the clinical utility of pharmacological monitoring is debated. One challenge is the practicality of obtaining trough drug levels in patients and the impact that would have on service delivery. Our aim was to evaluate whether the presence of ADAb and/or non-trough drug levels may predict treatment response in patients with RA treated with anti-TNF drugs.

Methods: 331 patients were selected from the Biologics in RA Genetics and Genomics Study Syndicate prospective cohort [n=160 adalimumab (ADL); n=171 etanercept (ETA)]. Serum samples were collected at 3, 6 and 12 months following initiation of therapy. ADAb were measured using RIA and drug levels using ELISA assays at 3, 6 and 12 months. Disease activity (DAS28) scores were measured at each visit. Multiple linear regression, logistic regression, generalised estimating equation and ROC curves were used to test the association and predictive value of ADAb and/or non-trough drug levels on treatment response as assessed by the change in DAS28 score between pre-treatment and 12 months post-treatment (ΔDAS28).

Results: 835 serial samples were suitable for pharmacological testing (n=414 ADL; n=421 ETA). Mean age: 56±13 years; 75% female; baseline DAS28 score 5.9±0.8; median BMI 27.5 (IQR 23.6–32.3). 85% were on a DMARD (56% MTX). ADAbs to ADL were detected in 24.8% (31/125 patients at ≥1 time points by 12 months) and in none of the ETA patients. The presence of ADAbs were significantly associated with lower ADL drug levels (ADAb titres>100AU p=0.0041; Spearman's rho −0.66). At 3 months, ADAb formation and low ADL levels were a significant predictor of no EULAR response at 12 months [ROC curve analysis, area under curve (AUC) 0.71, 95% confidence intervals (CI) 0.57–0.85]. Patients who developed ADAbs received lower median doses of concomitant MTX therapy (15mg/wk [IQR 10–20]) and had longer disease duration (14.0 years [6.7–19.4]) *vs.* patients who did not (20mg/wk [15–20] p= 0.01); (7.7 years [3.6–16.0] p=0.03). ADL drug level was the most significant independent predictor of ΔDAS28 at all time points after adjusting for confounders (p=0.003, regression coefficient (RC) 0.12, CI: 0.06–0.18). Patients on ETA with higher drug levels (>15μg/mL) were more likely to achieve a good EULAR response than patients with sub-therapeutic levels (<0.035 μg/mL) (p=0.01). However low ETA levels at 3 months were not a significant predictor of no EULAR response at 12 months (AUC 0.51; CI 0.41–0.61). BMI was the strongest predictor of low drug levels (ETA, p<0.001, RC −5.97; CI −8.75 to −3.19; ADL, p<0.001, RC −3.86; CI −5.72 to −2.00). Patients with a BMI>30 had significantly lower drug levels compared to those with a BMI<30 in both ADL and ETA cohorts (p<0.01).

Conclusion: Pharmacological testing in anti-TNF initiated patients is clinically useful even in the absence of trough levels. At 3 months ADAb formation and low ADL drug levels are a significant predictor for poor treatment response at 12 months. Patients with a BMI<30 were less likely to have therapeutic drug levels.

Disclosure: M. Jani, None; **H. Chinoy**, Abbvie, 8, Pfizer Inc, 8; **R. B. Warren**, Abbvie, 8, Pfizer Inc, 8; **C. E. M. Griffiths**, Abbvie, 8, Pfizer Inc, 8; **A. W. Morgan**, None; **A. G. Wilson**, Abbvie, 5, Pfizer Inc, 5; **K. L. Hyrich**, Pfizer Inc, 9, Abbott Immunology Pharmaceuticals, 9; **J. Isaacs**, None; **D. Plant**, None; **A. Barton**, None.

2925

Serum MMP-3 Predicts a Subgroup with No Radiographic Progression in Rheumatoid Arthritis Patients with Low-Dose Methotrexate (MTX) Monotherapy. Kazuko Shiozawa[1], Takashi Yamane[1], Miki Murata[1], Chihiro Tanaka[1], Noriaki Yo[1], Ryosuke Yoshihara[1], Yasushi Tanaka[1], Ken Tsumiyama[2] and Shunichi Shiozawa[2]. [1]Kohnan Kakogawa Hospital, Kakogawa, Japan, [2]Kyushu University Beppu Hospital, Beppu, Japan.

Background/Purpose: Studies have shown that treating rheumatoid patients with methotrexate (MTX) monotherapy initially and later providing an option to step up to combination therapy produces outcomes similar to those seen with combination therapies of conventional drugs and/or biologics provided immediately (O'Dell JR et al. Arthritis Rheum 65:1985, 2013). In their study, approximately 30% of the patients treated with MTX monotherapy did not require subsequent combination therapy. However, this subgroup was clinically and radiographically indistinguishable from those who required it.

The purpose of the present study was to assess the efficacy of low-dose MTX monotherapy, a regimen which is commonly prescribed in Japan, and to identify a subgroup of patients whose radiographic progression is halted in response to MTX monotherapy. In the present study, 161 rheumatoid patients were treated continuously with low-dose MTX monotherapy continuously for 3 yrs until significant adverse events or radiographic progression were suspected.

Methods: Rheumatoid patients treated with low-dose MTX monotherapy (n=161) were followed prospectively for 3 yrs. Their disease activity and radiographic progression were evaluated with reference to disease activity score 28 (DAS28), modified health assessment of questionnaire (mHAQ) and others and by the change in van der Heijde-modified total Sharp score per year (f¢TSS), by classifying patients into subgroups showing structural remission (REM; f¢TSS≤0.5), radiographic progression (f¢TSS>3) or rapid radiographic progression (RRP; f¢TSS>5).

Results: Disease activity was improved yearly, from baseline to 3 yrs: DAS28-ESR (3) improved from 5.2±1.1 to 3.9±1.4 (p<0.0001), %DAS28 remission from 1% to 19%, mHAQ from 0.54±0.47 to 0.18±0.32 (p<0.0001), mHAQ remission rate (f¢mHAQ<0.5) from 16% to 60%, and Boolean remission from 0.8% to 24.0%. During the 3-yrs of MTX monotherapy, the ratio of the patients classified into the REM group increased from 38.5% to 50.4% (p=0.0466), those in ΔTSS>3 decreased from 34.2% to 20.4% (p=0.0095), and those in RRP decreased from 21.7% to 10.9% (p=0.0190). In particular, the patients with active disease who required biologics arose mostly from the RRP group, followed by the CRRP group. This was, however, not the case when the patients were classified according to disease activity, i.e., DAS28. Receiver operating characteristic (ROC) curve analyses showed that serum matrix metalloproteinase-3 (MMP-3) levels of below 103.7 ng/ml at baseline predict a patient subgroup with no radiographic progression.

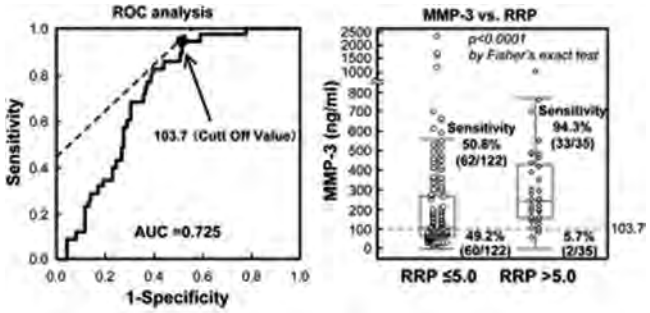

Fig.1 MMP-3 as a redictor identifying radiographic non-progression: cut off value for RRP and non-RRP

Conclusion: Approximately half of the patients given low-dose MTX monotherapy showed no radiographic progression over 3 yrs. A subgroup with no radiographic progression was predicted at outset by lower serum MMP-3.

Disclosure: K. Shiozawa, None; **T. Yamane**, None; **M. Murata**, None; **C. Tanaka**, None; **N. Yo**, None; **R. Yoshihara**, None; **Y. Tanaka**, None; **K. Tsumiyama**, None; **S. Shiozawa**, None.

2926

Calprotectin Serum Levels Reflect Residual Inflammatory Activity in Patients with Rheumatoid Arthritis and Psoriatic Arthritis on Clinical Remission or Low Disease Activity Undergoing TNF-Antagonists Therapy. Jose Inciarte-Mundo[1], M. Victoria Hernández[1], Sonia Cabrera-Villalba[1], Julio Ramirez[1], Andrea Cuervo[1], Virginia Ruiz-Esquide[1], Azucena González Navarro[1], Jordi Yagüe[2], Juan D. Cañete[1] and Raimon Sanmarti[1]. [1]Hospital Clínic of Barcelona, Barcelona, Spain, [2]Hospital Clinic Barcelona, Barcelona, Spain.

Background/Purpose: Calprotectin is a major S100 leucocyte protein, is associated to disease activity in rheumatoid arthritis (**RA**) and Psoriatic Arthritis (**PsA**) patients. Calprotectin is a potentially biomarker more sensitive of disease activity than conventional acute-phase proteins.

Objective: To analyze the relationship between calprotectin serum levels and inflammatory disease activity in patients with RA and PsA patients in clinical remission or low disease activity treated with TNF-antagonists. To correlate calprotectin levels with serum trough levels of TNF-antagonists.

Methods: Prospective cohort study of patients diagnosed with RA (ACR 1987 criteria) or PsA (CASPAR criteria) treated with adalimumab (**ADA**), etanercept (**ETN**) or infliximab (**IFX**) for ≥ 3 months in clinical remission or with low disease activity measured by DAS28-ESR in ≥ 2 consecutive visits. Clinical and laboratory data were analyzed. Calprotectin serum levels (using kits from Calpro AS, Norway) and TNF-antagonist serum trough levels, anti-drug antibodies (**Abs**) (using kits from Promonitor®, Progenika SA) were determined at 0, 4, 8 and 12 months of follow-up. We present the results at study entry (visit 0).

Results: 103 patients (47 RA, 56 PsA) were included. 61% female, mean age 58±12 years, mean DAS28-ESR 2.1±0.58, 76% were in clinical remission and 24% in low disease activity, 48% on monotherapy, 44% receiving reduced dosage of biologic (ADA 18 patients, ETN 22 patients and IFX 5 patients). Calprotectin levels were significantly lower in PsA than in RA patients (1.4±1 vs. 2.2±1, p=0.006). Patient on clinical remission (DAS28<2.6) showed lower calprotectin levels to those observed in those with low disease activity (1.2±1 vs. 3.4±1, *p<0.0001*), even when distributed by the most stringent remission criteria (patients with SDAI 3.3 1.9±2, p=0.005). Calprotectin strongly correlates with DAS28-ESR and SDAI in both RA (r_s=0.744, *p<0.0001* and r_s=0.328, *p=0.025* respectively) and PsA (r_s=0.777, *p<0.0001* and r_s=0.419, p=0.001 respectively), whereas no correlation was found between CRP serum levels or ESR with DAS28-ESR and SDAI in both populations. A trend for higher calprotectin levels in patients with low serum trough levels of ADA was showed (n=17, r_s=-0.413, p=0.09), that was statistically significant in those patients with RA treated with adalimumab at standard dose (r_s=-0.767, p=0.026). No correlations between calprotectin and serum trough levels ETN or IFX were observed.

Conclusion: Calprotectin was found to have high accuracy to discriminate RA or PsA patients in remission from those in low disease activity undergoing TNF-antagonists therapy, reflecting ongoing inflammatory activity. A strong correlation between disease activity measured by DAS28 and SDAI and calprotectin, but not with CRP or ESR, was found. No clear correlation between calprotectin levels and TNF-antagonists serum through levels was observed. Calprotectin emerges as a very useful biomarker to detect residual inflammatory activity in these patients.

Disclosure: J. Inciarte-Mundo, Premi Fi de Residencia "Emili Letang", 2, Beca MSD Societat Catalana de Reumatologia, 2; **M. V. Hernández**, None; **S. Cabrera-Villalba**, None; **J. Ramirez**, None; **A. Cuervo**, None; **V. Ruiz-Esquide**, None; **A. González Navarro**, None; **J. Yagüe**, None; **J. D. Cañete**, None; **R. Sanmarti**, unrestricted educational grant from Pfizer, 2.

2927

Baseline Serum Interferon Beta/Alpha Ratio Predicts Response to Tumor Necrosis Factor Alpha Inhibition in Rheumatoid Arthritis. Priyanka Vashisht[1], Jessica M. Dorschner[2], Mark A. Jensen[2], Beverly Chrabot[3], Theresa Wampler Muskardin[2], Marlena Kern[4], Tetrad Investigators[5], ABCoN Consortium[6], S. Louis Bridges Jr.[7], P.K. Gregersen[8] and Timothy B. Niewold[2]. [1]University of Nebraska Medical Center, Omaha, NE, [2]Mayo Clinic, Rochester, MN, [3]University of Chicago, Chicago, IL, [4]Feinstein Institute for Medical Research, Manhasset, NY, [5]AL, [6]NY, [7]University of Alabama at Birmingham, Birmingham, AL, [8]The Feinstein Institute for Medical Research, Manhasset, NY.

Background/Purpose: Response to tumor necrosis factor alpha (TNF-α) inhibition is variable in rheumatoid arthritis (RA). Previous studies have suggested that circulating type I interferon (IFN) levels may predict treatment response to TNF-α inhibitors and other biological agents in RA. Prediction of likely responders prior to initiating therapy would represent a major advance in biological treatment strategies for RA.

Methods: We studied a test set of 32 RA patients from the ABCoN registry and a validation set of 80 RA patients from the TETRAD registry. All subjects had serum available prior to treatment with a TNF-α inhibitor. In the test set, only those with a good response or no response at 14 weeks by EULAR criteria were included. In the validation set, subjects were included from the EULAR good, moderate, and non-response categories defined at 12 weeks post-treatment. Pre-treatment total serum type I IFN activity as well as IFN-α vs. IFN-β activity were measured using a functional reporter cell assay.

Results: In the test set, an increased ratio of IFN-β/IFN-α >1.3 in the pre-treatment serum sample was associated with lack of response by EULAR criteria at 14 weeks (p=0.009), and a receiver-operator curve supported a ratio of 1.3 as the optimal cut-off. Similarly, higher IFN-β/IFN-α ratio was positively correlated with higher DAS score at 14 weeks in the test set (Spearman's rho= 0.57, p=0.0075). In the validation set, subjects with an IFN-β/IFN-α ratio >1.3 were significantly more likely to have non-response by EULAR criteria at 12 weeks (p=0.0035), and no patient with this ratio or greater achieved a good response. In meta-analysis, IFN-β/IFN-α ratio >1.3 was a strong discriminator of good response vs. non-response at 12–14 weeks (OR = 18.0, $p=7.4\times10^{-5}$), and also a significant predictor of non-response vs. either moderate or good response at 12–14 weeks (OR = 4.34, p=0.0014). Anti-CCP antibody titer and mechanism of action (mAb vs etanercept) of TNF-α inhibitor did not influence this relationship.

Conclusion: Increased pre-treatment serum IFN-β/IFN-α ratio was strongly associated with non-response to TNF-α inhibition by EULAR criteria at 12–14 weeks. This blood test may be useful in making treatment decisions using TNF-α inhibitors in RA and other diseases.

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2928

Serum IL-33 Level Is Increased in Rheumatoid Arthritis and Predicts Response to Rituximab in Combination with High Serum IgG Level and Autoantibody Positivity: An Open-Label, Prospective, Multicentre Biological Trial. Jérémie Sellam[1], Houria Chavez[2], Stéphanie Rouanet[3], Nathalie Vernet[3], Bineta Ly[4], Sandrine Marion-Thore[5], Bernard Combe[6], Jean Sibilia[7], Jacques Tebib[8], Gilles Chiocchia[9], Maxime Dougados[10], Yassine Taoufik[2] and Xavier Mariette[11]. [1]AP-HP, Saint-Antoine Hospital, Rheumatology Department and DHU i2B, Paris, France, [2]Hopital Bicetre, Université Paris Sud, AP-HP, Kremlin Bicetre, France, [3]Roche France, Boulogne-Billancourt, France, [4]Universite Paris-Sud, Kremlin Bicetre, France, [5]Université Versailles Saint-Quentin, Montigny le Bretonneux, France, [6]Hôpital Lapeyronie, Montpellier, France, [7]University Hospital of Strasbourg, Strasbourg, France, [8]University Hospital Lyon, Lyon, France, [9]Université Versailles-Saint Quentin, Montigny le Bretonneux, France, [10]INSERM (U1153): Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, France., Paris, France, [11]Université Paris-Sud, Le Kremlin Bicêtre, France.

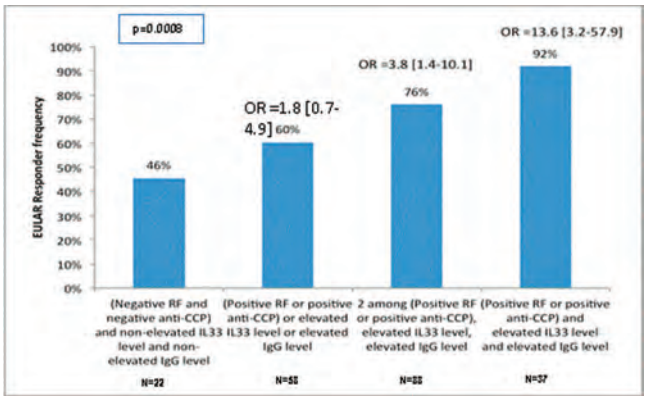
Background/Purpose: The recent discovered cytokine interleukin-33 (IL33) could be involved in B-cell activation as well as in RA pathophysiology. After a whole-blood transcriptomic analysis showing that baseline IL-33 mRNA upregulation was associated with clinical response to rituximab (RTX) (1), we investigated whether the serum level of IL-33 was associated with RA features and whether it may predict response to RTX.

Methods: We used ELISA to quantify serum IL-33 level and assessed B-cell–activation biomarkers (rheumatoid factor [RF], anti-CCP antibodies, free light chains, IgG, IgA, IgM, and BAFF levels), serum CXCL12, CXCL13 and CCL19 levels (all log transformed for analysis) in 205 RA patients before receiving a 1st course of RTX (1g on days 1 and 15) in the SMART trial and 63 controls (CT). Uni and multivariate analyses were performed to identify factors associated with a EULAR response 24 weeks after RTX.

Results: Serum IL-33 level was higher in patients with RA than in CT (median [interquartile range]: 258 [75;1345] *vs* 35 [22;664] pg/mL; p≤0.001) as well as in anti-CCP positive compared with anti-CCP negative patients (359 [87–1619] vs 102 [39–368] pg/mL, p=0.001). A similar result was observed for RF status (p=0.001). Serum IL-33 level was uncorrelated neither with DAS28 nor with CRP level. Unexpectedly, serum IL-33 level was highly correlated with CCL19 (r=0.7 ; p<0.0001) and CXCL13 levels (r=0.15 p=0.003). There were 146 (71%) responders (i.e. 44 good and 102 moderate). Using ROC curve analyze, 249 pg/mL was the optimal serum IL-33 level cut-off to discriminate responders from non-responders. Multivariate analysis indicated that IL33 level was independently associated with subsequent response to RTX (odds ratio [95% confidence interval]: 2.25 [1.14;4.43]; p=0.02), as well as the presence of anti-CCP antibodies or RF (OR: 2.76 [1.24;6.15]; p=0.01), with a similar trend for IgG level (OR: 2.00

[0.97;4.11]; p=0.059). These 3 parameters acted synergistically on the RTX response prediction since their simultaneous presence, observed in 20% of RA patients in SMART, frankly increased the likelihood of response (OR: 13.6 [3.2;57.9]) (Figure).

Conclusion: Serum IL-33 level, intrinsically increased in RA, represents a simple marker predicting accurately clinical response to RTX, independently of and synergistically with auto-antibodies and serum IgG level.



Disclosure: J. Sellam, Roche France, 2; **H. Chavez**, None; **S. Rouanet**, Reche France, 3; **N. Vernet**, Roche France, 3; **B. Ly**, None; **S. Marion-Thore**, None; **B. Combe**, Roche France, 2; **J. Sibilia**, Roche France, 2; **J. Tebib**, Reche France, 2; **G. Chiocchia**, Roche France, 2; **M. Dougados**, Roche France, 2; **Y. Taoufik**, Riche France, 2; **X. Mariette**, Roche France, 2.

ACR Concurrent Abstract Session
Sjögren's Syndrome I: Clinical Perspectives
Tuesday, November 18, 2014, 4:30 PM–6:00 PM

2929

Molecular Diagnostics for Patient Subsetting in Sjögren's Syndrome. John C. Hall[1], Alan N. Baer[1], Mi Y. Lam[2], Lindsey A. Criswell[3], Antony Rosen[1] and Livia Casciola Rosen[1]. [1]Johns Hopkins University School of Medicine, Baltimore, MD, [2]University of California San Francisco, San Francisco, CA, [3]University of California, San Francisco, Rosalind Russell/Ephraim P. Engleman Rheumatology Research Center, San Francisco, CA.

Background/Purpose: Sjögren's syndrome (SS) is a chronic autoimmune disease which targets exocrine glands, particularly salivary and lacrimal glands. While all SS patients have abnormal secretory function and inflammatory infiltration of their salivary glands, there is significant heterogeneity in terms of disease features, pathology and clinical course. Elucidating the inflammatory pathways which are active in pathologic tissues has important implications for defining disease subsets and monitoring disease activity. With the increasing availability of therapies which target specific immune pathways, defining the activity of distinct molecular pathways in target tissues will be important for selecting therapy. The type I and type II IFNs, which are implicated in SS pathogenesis, are particularly relevant in this regard.

Methods: Clinical data and a frozen labial salivary gland was obtained from each of 82 participants enrolled in the Sjögren's International Collaborative Clinical Alliance registry (NIH/NIDCR contract HHSN26S201300057C) with the following characteristics: (i) 53 individuals meeting ACR criteria for primary SS; (ii) 29 age and sex-matched controls lacking serologic and pathologic evidence of SS, of which 14 exhibited evidence of dry eye disease (OSS ≥3 for either eye). Protein lysates were generated from SS and control labial salivary glands, proteins were separated by SDS-PAGE and immunoblotted with specific markers of type I or type II IFN activity. Protein expression was normalized to the level of a loading control within the same sample and subject to hierarchical clustering to define patterns of IFN activity (high vs low). Correlations between IFN activity and categorical SS phenotypic features were analyzed using Fisher's exact test. Continuous phenotypic characteristics were compared between groups using a Wilcoxon rank sum test.

Results: IFN activity was low or absent in controls and detected at high levels in 31 of 53 (59%) SS patients. While patterns consistent with type I-predominant (n=9), type II-predominant (n=11) and mixed I/II (n=11) IFN activity were evident, these patients were indistinguishable in regards to key SS phenotypic features, except focus score which was highest in type II-predominant patients (p=0.024). Stratification of SS patients by high vs low IFN activity revealed associations of high IFN activity with high titer ANA (p=0.0016) and SSA (p=0.0161) antibodies, hyperglobulinemia (IgG ≥1445 mg/dl, p=0.0005; IgA ≥400 mg/dl, p=0.0335) and higher focus scores (p<0.0001). Additionally IFN high patients demonstrated greater evidence of glandular dysfunction as determined by a decreased ability to produce saliva (UWS; 0.164 vs 0.549 ml/5min, p=0.0003) and tears (Schirmer; 4 vs 6.5 mm/5min, p=0.0368).

Conclusion: Our data indicate that the parent phenotype in SS (chronic exocrine gland dysfunction, inflammatory infiltration and autoimmunity) includes distinct molecular subtypes, segregated by magnitude and pattern of IFN responses. While the resulting disease subtypes are clinically similar, therapies targeting type I and/or type II IFN may need to be selected based on prior analyses of which specific IFN pathway(s) are active *in vivo* in individual patients.

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2930

Precisely Quantified Fibrosis in Labial Salivary Glands Predicts Sjögren's Syndrome Classification in a Multiple Regression Model. Kerry M. Leehan[1], Michael Brown[2], Courtney Montgomery[2], Astrid Rasmussen[2], David M. Lewis[1], Lida Radfar[1], Donald U. Stone[1], Stephen Young[1], R. Hal Scofield[1], Kathy L. Moser Sivils[2] and A. Darise Farris[2]. [1]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Oklahoma Medical Research Foundation, Oklahoma City, OK.

Background/Purpose: Primary Sjögren's Syndrome (pSS) is a systemic, progressive autoimmune exocrinopathy that presents diagnostic challenges. Focal lymphocytic infiltrates in labial salivary gland (SG) biopsies, serum autoantibodies, objective measures of dryness, and patient-reported symptoms are used to classify pSS. Because focus score (FS) may vary with course of disease, we asked whether precisely quantified SG fibrosis can distinguish pSS from non-SS sicca.

Methods: Formalin-fixed biopsy sections (4–6 glandular cross-sections per subject) collected from symptomatically dry individuals attending the Oklahoma Sjögren's Syndrome Center of Research Translation clinic were stained with hematoxylin/eosin, imaged and digitally reconstructed. American European Consensus Group (AECG) classification status (n=50 pSS; n=28 non-SS) was blinded in order to eliminate bias by the scorer. AECG pSS exclusions were applied to all subjects. Fibrosis was quantified using a digital grid overlay; sections were scored and reported as average percent area per individual. Relationship of degree of fibrosis with age, focus score, whole unstimulated salivary flow, stimulated parotid flow, van Bijsterveld score and Schirmer's score was evaluated using Spearman correlations. Logistic regression was implemented using rank-transformed fibrosis scores to assess their predictive value for disease classification.

Results: Fibrosis was significantly increased (p=0.0004, Mann-Whitney U) in pSS salivary glands (median 25.39%, range 1.788%-70.45%) compared to non SS sicca subjects (median 15.52%, range 8.876%-31.38%). Among pSS subjects, fibrosis correlated with age (p=0.029, r=0.307), lip biopsy focus score (p=0.01, r=0.360) and van Bijsterveld Score (vBS, p=0.02, r=0.310). No significant correlation between fibrosis and salivary flow or Schirmer's score was observed. In a predictive model including fibrosis and age, degree of labial salivary gland fibrosis predicted disease classification with 68% accuracy irrespective of age (fibrosis, $p=3.91\times10^{-5}$; age, p=0.63).

Conclusion: Although age is associated with salivary gland fibrosis, multiple regression analysis suggests that labial salivary gland fibrosis is a significant feature of primary Sjögren's syndrome regardless of age.

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Longitudinal Examination with Salivary Gland Ultrasonography (SGUS) of Patients with Primary Sjogren's Syndrome: A Single Center Experience. Chiara Baldini[1], Nicoletta Luciano[1], Francesca Sernissi[1], Daniela Martini[1], Francesco Ferro[1], Marta Mosca[2] and Stefano Bombardieri[2]. [1]Rheumatology Unit, Pisa, Italy, [2]Rheumatology Unit, University of Pisa, Pisa, Italy.

Background/Purpose: Recently, convincing data have been published on the diagnostic value of salivary gland ultrasonography (SGUS) in primary Sjögren's syndrome (pSS). However, a limited number of information are available on the contribution of SGUS in the patients' prognostic assessment and in the monitoring of the response to therapy during the follow-up. Aim of the study was to prospectively evaluate if SGUS might have a role in the prognostic stratification and in the monitoring of the disease activity in patients with pSS over the follow-up.

Methods: The study population consisted of consecutive patients with a diagnosis of pSS (AECG 2002) who prospectively underwent clinical, laboratory and SGUS assessment at baseline, at 12 and at 24 months. An experienced rheumatologist scored the EULAR Sjögren's Syndrome Activity Index (ESSDAI) at each follow-up time point. Patients received the "best-available-therapy" according to the clinical practice. SGUS was performed by the same radiologist blinded to the rheumatologist clinical assessment. The parotid and submandibular glands were scanned on both sides by using a real-time US scanner (Esaote Technos MPX) with a 7.5–12.5 MHz transducer and the following US parameters were recorded: size, parenchymal echogenicity and inhomogeneity in the parotid and submandibular glands on both sides. A previously reported ultrasound scoring system (De Vita *et al* 1992) was used to grade the echostructure alterations of the salivary glands. Baseline, 12 months and 24 months SGUS results were compared using the non-parametric Friedman test for multiple comparisons. Correlation between SGUS and ESSDAI changes throughout the follow-up period was assessed using the Spearman linear correlation coefficient. Statistical significance was accepted at $p<0.05$.

Results: From January 2012 and January 2014, 68 pSS patients were enrolled in this study (median (IQR) age: 54 (45–64) years). At the baseline 28/68 (41.2%) presented a SGUS score ≥2. These patients, when compared to the group of patients with a SGUS score <2, presented more frequently low C4 levels ($p=0.04$), positivity for anti-Ro/SSA ($p<0.0001$) and higher mean ESSDAI scores, with the ESSDAI positively correlating with the SGUS score ($r=0.571$, $p<0.0001$). Over the follow-up we still observed a positive correlation between the changes in the ESSDAI and the changes in the SGUS score ($r=0.490$, $p<0.0001$). However, no statistically significant differences were detected over the follow-up in the SGUS score across the multiple test performed and at the end of the study patients with grossly inhomogenous glands still presented evident inhomogeneities.

Conclusion: This study highlighted the positive correlation between SGUS score and pSS disease activity. However, further research is needed before a conclusion can be made regarding the possibility of using SGUS in the assessment of the response to therapy in pSS.

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2932

Increased Risk of Deep Vein Thrombosis and Pulmonary Embolism in Sjögren's Syndrome: A General Population-Based Cohort Study. Marko Yurkovich[1], Hyon K Choi[2], Eric C. Sayre[3], Kamran Shojania[1] and J. Antonio Avina-Zubieta[3]. [1]University of British Columbia, Vancouver, BC, [2]Boston University School of Medicine, Boston, MA, [3]Arthritis Research Centre of Canada, Richmond, BC.

Background/Purpose: There is limited data available on the risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) in Sjögren's Syndrome (SjS). We estimated the population-based risk of **newly recorded DVT and PE** among **incident cases with SjS** compared to controls from the general population using physician-billing and hospitalization databases that cover the entire population of the province of British Columbia, Canada (~ 4.4 million).

Patients and Methods: Our data include all visits to health professionals and all hospital admissions from Jan 1, 1990 to Dec 31, 2010 and all dispensed medications from Sept 1, 1995 to Dec 31, 2010 for all individuals. We conducted a retrospective matched cohort study among patients satisfying at least one of the following criteria: **a)** diagnosis of SjS in adults on at least two visits within a two-year period between Jan 1996 and Dec 2010 by a non-rheumatologist physician; **b)** diagnosis of SjS on at least one visit by a rheumatologist or from hospitalization. To increase specificity we excluded cases that were not confirmed by a rheumatologist if they were seen at a later point. Ten non-SjS controls matched by birth year, sex and calendar year of follow-up were selected from the general population for each case. Outcomes: **incident PE, DVT, and PE or DVT** events based on hospitalization records (for PE and DVT), outpatient visits (DVT) or death certificates (all outcomes). For non-fatal outcomes, we also required the use of anticoagulant medication within six-months of the event as part of all outcome definitions. We estimated relative risks (RRs) comparing SjS with age-, sex- and entry time-matched comparison cohorts, adjusting for potential risk factors for PE and DVT. Sensitivity analyses were conducted to assess for unmeasured confounders.

Results: Among 1175 incident SjS cases, 14, 10 and 19 developed a first time PE, DVT, and PE or DVT event, respectively (incidence rates = 3.8, 2.7 and 5.2 per 1,000 person years, respectively) (**see table**). Compared with the age, sex, and entry-time-matched controls, the RRs were 4.1 (95% CI; 2.0 – 7.7), 3.0 (95% CI; 1.3 – 6.1) and 3.1 (95% CI; 1.8 – 5.3) for PE, DVT, and DVT or PE, respectively. After adjusting for covariates the results remained similar (**see table**). The risk of developing DVT, PE or either event was highest within the first year following diagnosis of SjS, decreasing over time to become not significantly increased after 5 years. Our results remained statistically significant after adjusting for the potential impact of an unmeasured confounder (adjusted RRs ranging between 1.58 – 1.98 in all sensitivity analyses).

Conclusion: This large population-based study indicates an increased risk of DVT and PE in patients with SjS. Our results support the need for increase monitoring for these complications in SjS patients.

Table: Risk of Incident PE, DVT or DVT or PE according to SjS Status

	PE		DVT		PE or DVT	
	SjS	**Non-SjS**	**SjS**	**Non-SjS**	**SjS**	**Non-SjS**
Sample size, n	1,175	11,958	1,175	11,958	1,175	11,958
Events, N	14	38	10	37	19	67
Incidence Rate/100 Person years	3.8	0.9	2.7	0.9	5.2	1.7
Age-, sex-, and entry time-matched RRs (95% CI)	**4.1 (2.0 – 7.7)**	**1.0**	**3.0 (1.3 – 6.1)**	**1.0**	**3.1 (1.8 – 5.3)**	**1.0**
Time After Initial Diagnosis:						
< 1 year	8.9 (2.7 – 28.0)	1.0	5.0 (1.4 – 16.3)	1.0	5.7 (2.3 – 12.9)	1.0
< 2 years	6.2 (2.4 – 15.0)	1.0	5.1 (1.8 – 13.6)	1.0	4.6 (2.1 – 9.4)	1.0
< 3 years	4.7 (2.0 – 10.4)	1.0	4.4 (1.7 – 10.5)	1.0	4.0 (2.0 – 7.5)	1.0
< 4 years	5.0 (2.3 – 10.5)	1.0	4.3 (1.8 – 9.8)	1.0	4.0 (2.0 – 7.1)	1.0
< 5 years	4.8 (2.2 – 9.7)	1.0	4.0 (1.6 – 9.0)	1.0	3.7 (1.9 – 6.6)	1.0
≥ 5 years	2.3 (0.3 – 10.6)	1.0	1.0 (0.0 – 6.5)	1.0	1.9 (0.4 – 6.5)	1.0
Multivariable RR* (95% CI)	**3.2 (1.6 – 6.5)**	**1.0**	**2.8 (1.2 – 6.4)**	**1.0**	**2.4 (1.3 – 4.4)**	**1.0**

*adjusted for alcoholism, liver disease, hypertension, varicose veins, trauma, fractures, surgery, glucocorticoids, hormone replacement therapy, COX-2 inhibitors, Charlson comorbidity score, number of hospitalizations, and number of outpatient visits.

Disclosure: M. Yurkovich, None; **H. K. Choi**, None; **E. C. Sayre**, None; **K. Shojania**, None; **J. A. Avina-Zubieta**, None.

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Metabolic Syndrome, Adipocytokines and Inflammation in Sjögren's Syndrome. Kristopherson Lustosa Augusto[1], Eloisa Bonfá[2], Rosa M. R. Pereira[1], Cleonice Bueno[1], Vilma S. T. Viana[3] and Sandra G. Pasoto[1]. [1]Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil, [2]University of Sao Paulo, Sao Paulo, Brazil, [3]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.

Background/Purpose: Systemic inflammation has been linked to increased frequency of metabolic syndrome (MetS) in autoimmune diseases. However, there are no studies concerning the frequency of this complication and adipocytokine sera profile in Primary Sjögren's syndrome (SS).

The aim of this study was to evaluate the frequency of MetS and serum levels of inflammatory cytokines, B-cell activating factor (BAFF) and adipocytokines in SS patients.

Methods: Seventy-one female SS patients (American-European Consensus Group Criteria), aged 18–65 years and 71 healthy women matched for age and race were enrolled in this case-control study. Clinical data were collected by a standardized questionnaire and physical examination at inclusion. Serum levels of glucose, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, interleukin-1 beta (IL-1b), IL-6, BAFF, insulin, leptin, adiponectin, visfatin, resistin, ghrelin and plasminogen activator inhibitor-1 (PAI-1) were determined for all patients and controls. MetS (International Diabetes Federation) and disease activity [(EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)] were also determined.

Results: Patients and controls were comparable regarding mean age (47.6 ± 10.3 vs. 47.2 ± 10.3 years, $p=0.833$), ethnicity (white: 77.5 vs. 77.5 %, $p=1.000$), body mass index (BMI) (27.6 ± 6.4 vs. 26.7 ± 3.6 kg/m^2, $p=0.783$), smoking ($p=0.538$), sedentary lifestyle ($p=0.847$) and menopause

(p=0.502). In contrast, MetS (39.4 vs. 16.9%, p=0.005), hypertension (32.4 vs. 11.3%, p=0.004) and dyslipidemia (22.5 vs. 4.2%, p=0.002) were more frequent in patients than controls in spite of similar abdominal and hip circumferences (p>0.05). No differences were observed regarding glucose (p=0.062), insulin (p=0.271) and HOMA-IR (p=0.662). Serum levels of IL-1b (p=0.008), IL-6 (p<0.0001), BAFF (p<0.0001), resistin (p<0.0001) and adiponectin (p=0.001) were higher in patients than in controls. Further analysis showed that SS patients with (n=28) and without (n=43) MetS were similar regarding age (p=0.111) and race (p=0,773). In contrast, the first group had higher BMI, abdominal circumference, cholesterol/LDL/VLDL, triglycerides, insulin and leptin levels, HOMA-IR score, and higher frequencies of hypertension and diabetes (p<0.05). ESSDAI (p=0.240), prednisone use (35.7 vs. 23.3%, p=0.289), current (3.0 ± 4.5 vs. 1.6 ± 3.2 mg/day, p=0.299) and cumulative dose (p=0.495) were similar in both groups. Otherwise, IL-1b levels were higher in SS patients with MetS than those without MetS (83.1 ± 187.6 vs. 8.4 ± 27.7 pg/mL, p=0.046). Multivariate analysis with adjustment for age, ethnicity, current and cumulative prednisone doses and usage time revealed that MetS group had higher values of hypertension (p=0.010), HOMA-IR (p=0.001), LDL (p=0.041), VLDL (p=0.001), triglycerides (p=0.001), glucose (p=0.045), insulin (p=0.006), leptin (p=0.008) and IL-1b (p=0.048).

Conclusion: This study identified a high frequency of MetS and an abnormal adipocytokine profile in SS patients. The interesting association of MetS with elevated IL-1b suggests that inflammation plays an important role in its pathogenesis in SS.

Disclosure: K. L. Augusto, None; **E. Bonfá**, None; **R. M. R. Pereira**, None; **C. Bueno**, None; **V. S. T. Viana**, None; **S. G. Pasoto**, None.

2934

Abatacept reduces Circulating Effector Memory T-Helper Cells in Patients with Primary Sjögren's Syndrome. Gwenny Verstappen[1], Wayel H. Abdulahad[2], Petra M. Meiners[1], Suzanne Arends[1], Silvia Beijer-Liefers[1], Arjan Vissink[1], Frans G.M. Kroese[1] and Hendrika Bootsma[1]. [1]University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [2]University Medical Center Groningen, Groningen, Netherlands.

Background/Purpose: In an open-label proof of concept study, Abatacept has been identified as an effective and safe treatment modality in primary Sjögren's syndrome (pSS). Abatacept is a fully human fusion molecule of IgG-Fc and CTLA-4 that modulates the costimulatory interaction between APCs and T-lymphocytes, thereby inhibiting full T-cell activation. Modifying T-helper (Th-) cell homeostasis may contribute to the therapeutic effect of Abatacept as Th-cell subset imbalances are involved in the emergence of autoimmune diseases. Therefore, the aim of this study was to assess Th-cell homeostasis in peripheral blood of pSS patients in response to Abatacept treatment.

Methods: Fifteen patients with pSS, diagnosed according to the revised American-European Concensus Group criteria, were treated with Abatacept on days 1, 15, 29 and every four weeks thereafter for five months (≈10 mg/kg of body weight i.v.). Absolute numbers and frequencies of circulating Th-cell subsets ($CD3^+CD4^+$) were examined in fresh blood samples by flow cytometry at baseline and 4, 12, 16, 24, 36 and 48 weeks after the first dose. Expression patterns of chemokine receptors CCR7 and CD45RO were used for distinction between naive, central memory, effector memory and terminally differentiated Th-cells. Generalized estimating equations (GEE) were used to analyze the presence of different subsets over time within subjects, viz. on treatment (week 0–24) and off treatment (week 24–48). Currently, the extent to which different subsets of effector memory Th-cells are affected by Abatacept is under investigation.

Results: On Abatacept treatment, numbers of peripheral blood $CD4^+$ T-cells did not significantly differ from baseline values. However, absolute numbers and frequencies of total memory Th-cells decreased significantly over time on treatment (p=0.001 and p<0.001, resp.). This was mainly a result of a decrease in effector memory Th-cells. On treatment, both absolute numbers and frequencies of effector memory Th-cells decreased significantly over time (p=0.011 and p=0.001, resp.), with the largest decrease seen at week 24. On the contrary, frequencies of naive Th-cells increased over time on treatment (p<0.001). From week 24 to week 48 (off treatment), a trend towards increased absolute numbers and frequencies of effector memory Th-cells was observed. Decrease and repopulation of this T-cell subset correspond to changes in disease activity as assessed with ESSDAI.

Conclusion: CTLA-4Ig treatment with Abatacept decreases the presence of circulating effector memory Th-cells of pSS patients. The observation that decrease and repopulation of effector memory Th-cells correspond to changes in disease activity suggests that these cells are -at least partially- responsible for the effects of Abatacept treatment seen in pSS patients.

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ACR Concurrent Abstract Session
Spondylarthropathies and Psoriatic Arthritis V - Clinical Aspects and Treatment
Tuesday, November 18, 2014, 4:30 PM–6:00 PM

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Attainment of Minimal Disease Activity Using Methotrexate in Psoriatic Arthritis. Barry J. Sheane, Arane Thavaneswaran, Dafna D. Gladman and Vinod Chandran. University of Toronto, Toronto Western Hospital, Toronto, ON.

Background/Purpose: Methotrexate (MTX) is used as first-line treatment in psoriatic arthritis (PsA); however, the extent of the disease-modifying effect of MTX on PsA, if any, is not established. Randomized controlled trials examining the efficacy of MTX have been either under-powered or have used dosages that may be sub-optimal. While TNF inhibitors (TNFi) are used as second-line therapies in PsA, they have proven efficacy and disease-modifying effect. Minimal disease activity (MDA) is achieved at 24 weeks in 39% and 52% of patients treated with adalimumab and infliximab, respectively. There is a need to establish the treatment effect of MTX. An international task force recently recommended that disease remission or MDA be the target of treatment and should be attained within 6 months of initiating medication.

The aims of this retrospective study were to: a) establish the percentage of PsA patients that achieve MDA after 6 months of treatment with MTX, and b) identify the dose of MTX most likely to achieve MDA.

Methods: All patients attending a large, tertiary referral centre for PsA who initiated MTX and were naïve to biological medication on or after January 2004 up until April 2014 were assessed for inclusion. The primary outcome was the achievement of MDA after 6 months of MTX. MDA is defined as: the presence of at least 5 out of the following 7 domains: tender joint count ≤ 1, swollen joint count (SJC) ≤ 1, Psoriasis Area Severity Index (PASI) ≤ 1 or body surface area ≤ 3%, tender entheseal points ≤ 1, Health Assessment Questionnaire score ≤ 0.5, patient global disease activity Visual Analogue Scale (VAS) score ≤ 20 and patient pain VAS ≤ 15.

Of 204 patients identified, 29 had insufficient duration on MTX to accurately assess outcome. These were excluded, leaving 175 for analysis. Of these, 167 patients had sufficient data for analysis at 6 months.

Results: Of 204 patients, 54% were male. At the start of MTX use (all mean (SD)), age was 47.1 (13.5) years, duration of PsA 6.2 (8.0) years, PASI 5.5 (8.0), tender joint count 10.2 (10.7) and swollen joints 6.0 (7.4). Oral MTX was prescribed in 77.5%; 22 (10.8%) had been prescribed a DMARD in the past.

After 6 months on MTX, 29 patients (17.4%) achieved MDA, despite 97 patients (58.1%) achieving a SJC ≤ 1 and 138 (82.6%) a PASI ≤ 1; Patient-reported outcomes were less responsive, with only 22 (13.2%) achieving the outcome for disease activity. For patients achieving MDA, mean dose was 17.8 (4.2) mg/week by 6 months, with 58.6% taking ≥ 17.5 mg/week (76% were taking oral MTX). This dose was similar in those not achieving MDA. Back pain (both inflammatory and mechanical) and dactylitis were associated with a lower probability of achieving MDA.

Conclusion: Based on this analysis, MTX use achieves the recommended treatment target of MDA by 6 months in less than 20% of patients. This low rate of achievement is explained by failure of response in the patient-reported outcome components of the MDA criteria. Adequately-powered randomized controlled trials are needed to establish the efficacy of MTX as a first line drug in PsA.

Disclosure: B. J. Sheane, None; **A. Thavaneswaran**, None; **D. D. Gladman**, None; **V. Chandran**, None.

2936

Is Ankylosing Spondylitis a Risk Factor for Cardiovascular Diseases, and How Does These Risks Compare to Those in Rheumatoid Arthritis?. Johan Askling[1], Lennart Jacobsson[2] and Jonas Eriksson[1]. [1]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]sahlrenska academy, gothenburg, Sweden.

Background/Purpose: Patients with RA are at increased risk of cardiovascular (CV) diseases, including acute coronary syndromes (ACS), deep venous thromboembolism (DVT) and pulmonary embolism (PE), and cerebrovascular diseases. Evidence suggests that traditional CV risk factors alone do not account for the entire risk increase. Instead, RA disease activity has been proposed to be of critical importance. Ankylosing Spondylitis (AS) is a chronic inflammatory disease with a different gender- and age-distribution, pathology, and phenotype yet often with a pronounced systemic inflammation. In contrast to the literature on CV risks in RA, data on CV risks in AS are less well studied, and because of the age/sex-differences between RA and AS, not directly comparable. The aim of this study was therefore to assess and compare CV risks, by CV phenotype, between prevalent patients with AS, RA and the general population, taking age and sex-differences into account.

Methods: We performed a nationwide population-based cohort study based on register linkage of prospectively recorded data from the Swedish Patient, Death, and Population Registers 2006–2011. We identified one cohort of prevalent patients with RA (n=37,245), one with AS (N=5,358) and one with general population comparator subjects (n=185,153). These cohorts were followed through 2011 for first ever occurrence of ACS, DVT/PE, and stroke, respectively (individuals with a history of the outcome were excluded). Age- and sex-specific rates for each outcome were calculated; rates were then standardised to the age/sex-distribution of the AS cohort.

Results: Crude rates were the lowest for AS. However, assuming all populations had the same age/sex distribution as the AS cohort, the rate for ACS was 30% higher among patients with AS, and 60% higher in patients with RA, than in the general population (Table). For stroke, the rate was 20% higher among patients with AS, and 30% higher in patients with RA, than in the general population. For thromboembolic events, the rate was 30% higher among patients with AS, and 80% higher in patients with RA, than in the general population.

Conclusion: Prevalent patients with AS in a population-based cohort are at a 20–30% increased risk of CV events compared to the general population. Whilst increased, the level of increase is around half that seen in the corresponding age/gender groups in RA.

Table. Crude rates of ACS, stroke, and DVT/PE in AS, RA and general population cohorts, and the corresponding standardised rates using the AS population as standard

	Acute Coronary Syndrome			Stroke			Thromboembolic events		
	AS	RA	GenPop	AS	RA	GenPop	AS	RA	GenPop
N patients at risk	4914	31 769	143 713	5252	35 528	169 224	5225	35 220	169 615
N incident events	95	1266	3438	62	1056	3790	68	1016	2866
Rates									
Crude rates	4.7 (2.8–6.6)	10.0 (8.9–11.1)	5.8 (5.4–6.2)	2.9 (1.4–4.3)	7.5 (6.6–8.4)	5.5 (5.1–5.8)	3.2 (1.6–4.7)	7.3 (6.4–8.2)	4.2 (3.9–4.5)
Standardised rate	4.7 (2.8–6.6)	6.1 (5.3–7.0)	3.7 (3.4–4.0)	2.9 (1.4–4.3)	3.2 (2.6–3.8)	2.4 (2.2–2.7)	3.2 (1.6–4.7)	4.4 (3.7–5.1)	2.4 (2.2–2.6)

Disclosure: J. Askling, AstraZeneca, Pfizer, MSD, 2; **L. Jacobsson**, Pfizer, Abbvie, UCB, 5, MSD, 2; **J. Eriksson**, None.

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Evaluation of Referral Models for Axial Spondyloarthritis in Primary Care in the Spondyloarthritis Caught Early Cohort. Ozair Abawi, Rosaline van den Berg, Désirée van der Heijde and Floris van Gaalen. Leiden University Medical Center, Leiden, Netherlands.

Background/Purpose: Several models have been proposed to refer patients (pts) with possible axial spondyloarthritis (axSpA) from primary care to the rheumatologist. Aim of the study was to evaluate performance of referral models for axSpA in the SPondyloArthritis Caught Early (SPACE) cohort.

Methods: Ten referral models were found in literature and tested in the *Leiden* SPACE cohort, including pts with back pain (≥3 months, ≤2 years, onset <45 years; n=192) referred to the rheumatology outpatient clinic of the LUMC. Imaging was omitted from all models if included as a referral parameter, as it is unfeasible for screening in primary care. **[table 1]**

Table 1. Characteristics of referral models. IBP, inflammatory back pain; IBD, inflammatory bowel disease

Model	Criteria	Refer if
Brandt I	HLA-B27, IBP (based on 3 criteria[1]; positive if 1/3 criteria fulfilled)	≥1 out of 2 positive
Brandt II	HLA-B27, IBP (positive if 2/3 criteria fulfilled)	≥1 out of 2 positive
Brandt III	HLA-B27, IBP (positive if 3/3 criteria fulfilled)	≥1 out of 2 positive
Braun[2]	Psoriasis, buttock pain, improvement of back pain by exercise (if ≤1 positive answer, HLA-B27 is tested)	≥2 positive or ≤1 positive and HLA-B27 positive
Braun alt.	Psoriasis, alternating buttock pain, improvement of back pain by exercise (if ≤1 positive answer, HLA-B27 is tested)	≥2 positive or ≤1 positive and HLA-B27 positive
MASTER[3]	HLA-B27, IBP, family history for ankylosing spondylitis, good response to NSAIDs	≥2 out of 4 positive
RADAR[4]	HLA-B27, IBP, family history for SpA, good response to NSAIDs, extra-articular manifestations (uveitis, psoriasis or IBD)	≥2 out of 5 positive
RADAR 2/3	IBP, good response to NSAIDs, extra-articular manifestations (uveitis, psoriasis or IBD)	≥2 out of 3 positive
CaFaSpA 1 pt[5]	IBP (ASAS), family history for SpA, good response to NSAIDs	≥1 out of 3 positive
CaFaSpA 2 pt	IBP (ASAS), family history for SpA, good response to NSAIDs	≥2 out of 3 positive

Performance of the models was evaluated (sensitivity, specificity, positive predictive value, positive likelihood ratio) using classification by ASAS axSpA criteria as external standard. For pts not fulfilling the ASAS criteria who are referred, post-test probability for axSpA was calculated based on the LR product for presence of SpA features. A LR product ≥78 equals a post-test probability ≥80% and was used as cut-off for probable axSpA. Pts who were incorrectly not referred met the ASAS axSpA criteria by fulfilling the clinical arm only or the imaging arm (imaging arm only or both arms). [table 2]

Table 2. Performance of referral models. Sens, sensitivity; Spec., specificity; PPV, positive predictive value; LR+, positive likelihood ratio; PTP, post-test probability

In SPACE: 74 patients fulfilling axSpA criteria 118 patients not fulfilling axSpA criteria							
Model	LR+	PPV	Referred patients fulfilling axSpA criteria n (sens.)	Referred patients not fulfilling axSpA criteria n (spec.)	Referred patients not fulfilling axSpA criteria with ≥80% axSpA n	Patients not referred but fulfilling axSpA criteria: imaging arm	Patients not referred but fulfilling axSpA criteria: clinical arm only
Brandt I	1.08	0.40	73 (0.99)	108 (0.08)	7	1/1	–
Brandt II	1.27	0.44	71 (0.96)	89 (0.24)	7	3/3	–
Brandt III	1.87	0.54	60 (0.82)	52 (0.56)	6	13/13	–
Braun	1.90	0.54	63 (0.85)	53 (0.55)	7	11/11	–
Braun alt.	3.04	0.66	61 (0.82)	32 (0.73)	6	13/13	–
MASTER	2.67	0.63	52 (0.70)	31 (0.74)	5	21/22	1/22
RADAR	2.27	0.59	64 (0.86)	45 (0.62)	6	10/10	–
RADAR 2/3	1.52	0.49	43 (0.58)	45 (0.62)	4	23/31	8/31
CaFaSpA 1 pt	1.27	0.44	69 (0.93)	87 (0.26)	6	5/5	–
CaFaSpA 2 pt	2.18	0.58	41 (0.55)	30 (0.75)	3	26/33	7/33

Results: In total, 74/192 pts fulfilled ASAS axSpA criteria; 48 with positive imaging (n=15 radiographic sacroiliitis). Most models performed well regarding sensitivity/specificity. Braun alt. model has the most balanced sensitivity/specificity and highest LR+. All models that include HLA B27 miss axSpA pts with positive imaging, 14–23% with radiographic sacroiliitis (depending on the model). PPV of the models is low, indicating that many pts are referred despite not fulfilling axSpA criteria. However, 6–16% (depending on the model) of these pts have a post-test probability ≥80% for axSpA. This reflects that these pts are rightly referred, despite not fulfilling the axSpA criteria.

Conclusion: Most referral models performed well in the SPACE cohort. However, this cohort includes pts already referred from primary care, probably causing overestimation of performance of all models. All models miss pts fulfilling the ASAS imaging arm, 14–23% of which have radiographic sacroiliitis, which is highly undesirable. Moreover, large numbers of pts referred unnecessarily might lead to a burden for health care systems. Further studies should be conducted in primary care to evaluate these models in their target population.

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2938

A Randomized, Double-Blind, Placebo-Controlled, 16-Week Study of Subcutaneous Golimumab in Patients with Active Nonradiographic Axial Spondyloarthritis. J Sieper[1], D van der Heijde[2], M Dougados[3], W Maksymowych[4], J Boice[5], G Bergman[5], S Curtis[5], A Tzontcheva[5], S Huyck[5]

and HH Weng[5]. [1]University Clinic Benjamin Franklin, Berlin, Germany, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Paris-Descartes University, Paris, France, [4]University of Alberta, Alberta, AK, [5]Merck & Co., Inc., Whitehouse Station, NJ.

Background/Purpose: Axial spondyloarthritis (axSpA), including ankylosing spondylitis and nonradiographic axial SpA (nr-axSpA), is a chronic inflammatory disease marked by back pain and progressive spinal stiffness. The goal of GO-AHEAD was to determine if golimumab (GLM) is superior to placebo (PBO) in patients with nr-axSpA.

Methods: GO-AHEAD was a Phase 3b, double-blind, randomized, PBO-controlled trial that evaluated subcutaneous (SC) GLM 50 mg vs PBO in patients aged 18–45 years with active nr-axSpA (Assessment of SpondyloArthritis international Society [ASAS] criteria and centrally-read SI joint X-rays; disease duration ≤5 years; chronic back pain; high disease activity [total back pain ≥40 mm on a 0–100 mm VAS and Bath Ankylosing Spondylitis Disease Activity Index {BASDAI} ≥4 cm]; and inadequate response or intolerance to NSAIDs). Patients were randomized 1:1 to GLM or PBO SC injections every 4 weeks. The primary endpoint was ASAS 20 attainment at week 16. Key secondary endpoints were ASAS 40, ASAS partial remission, and BASDAI 50 attainment; and Spondyloarthritis Research Consortium of Canada (SPARCC) magnetic resonance imaging (MRI) sacroiliac (SI) joint score change. AS Disease Activity Score based on C-reactive protein (ASDAS) was assessed. Treatment group differences for all patients-as-treated and the target populations (signs of inflammation by MRI or elevated CRP at baseline) were compared using the stratified Miettinen and Nurminen method for responder endpoints and the Mann-Whitney test for MRI SI joint score.

Results: Of 198 patients enrolled, 197 were treated (GLM=97; PBO=100). Mean age was 31 years; 57% were male. At baseline, mean BASDAI was 6.5 cm (SD=1.5), SPARCC MRI SI was 11.3 (SD=14.0), and ASDAS was 3.5 (SD=0.9). The primary endpoint was achieved by significantly more GLM patients (71.1%) than PBO patients (40.0%; table). Significantly more GLM patients also attained ASAS 40, ASAS partial remission, and BASDAI 50 (table). Mean ASDAS improvements were greater with GLM than PBO (−1.7 vs −0.6, respectively; P <.0001). Mean SPARCC MRI SI joint score improvements from baseline to week 16 were greater with GLM than PBO (−5.3 vs −0.9, respectively; P <.0001); improvements for the target population were −6.4 vs −1.2, respectively (P<.0001).

Table. Primary and Key Secondary Outcomes, Week 16

	All Patients as Treated			Target Population		
	GLM N=97 n (%)	PBO N=100 n (%)	Difference vs PBO,* % (95% CI)	GLM N=78 n (%)	PBO N=80 n (%)	Difference vs PBO,* % (95% CI)
ASAS 20	69 (71.1)	40 (40.0)	31.2 (17.5, 43.6) P <.0001	60 (76.9)	30 (37.5)	39.6 (24.6, 52.6) P <.0001
ASAS 40	55 (56.7)	23 (23.0)	33.8 (20.4, 46.1) P <.0001	47 (60.3)	18 (22.5)	37.9 (23.0, 51.2) P <.0001
ASAS Partial Remission	32 (33.0)	18 (18.0)	15.2 (3.2, 27.1) P =.0136	27 (34.6)	15 (18.8)	16.1 (2.5, 29.6) P =.0204
BASDAI 50	56 (57.7)	30 (30.0)	28.0 (14.4, 40.6) P <.0001	46 (59.0)	23 (28.8)	30.5 (15.4, 44.3) P <.0001

*Differences derived from the statistical model.

Adverse events (AEs) occurred in 41% of GLM and 47% of PBO patients. Serious AEs occurred in 1 GLM (female partner reported fetal death) and 2 PBO patients (cholelithiasis, back pain). There were no serious infections, serious opportunistic infections, active tuberculosis, malignancies, serious systemic hypersensitivity, or deaths.

Conclusion: Patients with active nr-axSpA treated with GLM had significantly greater improvements in disease activity and inflammation on MRI than patients treated with PBO. GLM was well-tolerated and generally had a favorable benefit-risk profile.

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2939

Increased Diagnosis of Spondyloarthritis in Female Patients Started in the Early Biologic Era: Data from the Ontario Spondyloarthritis (OnSpA) Study. Nisha Nigil Haroon[1], Ping Li[2], Michael Paterson[2] and Nigil Haroon[3]. [1]Department of Medicine, University of Toronto, Toronto, ON, [2]Institute of Clinical Evaluative Sciences, Toronto, ON, [3]Toronto Western Research Institute, Toronto, ON.

Background/Purpose: The health and economic impact of spondyloarthritis is considerable and growing. Over the past decade or more, there have been two major changes in this field that could potentially affect the diagnosis of new AS patients. The first was the introduction of Tumor Necrosis Factor inhibitors (TNFi), which dramatically changed the treatment paradigm in AS. The second was the introduction of a new entity called non-radiographic axial Spondyloarthritis (nr-AxSpA), defined based on the presence of MRI changes and HLA-B27, but without classic X-ray changes of AS. We studied the changes in incidence and prevalence of spondyloarthropathies (SpA) over time in Ontario, Canada.

Methods: We performed a population-based, retrospective cohort study on patients with SpA, age 15 or above, living in Ontario between 1995 and 2010. We used a stringent SpA definition of 2 outpatient claims within 2 years with at least one inpatient or rheumatologist claim. Incidence ratios, prevalence rates and confidence intervals were calculated using Poisson regression. The incidence of SpA in men and women were compared in the pre-biologic era (1995–2000), early biologic era (2000–2005) and late biologic era (2005–2010).

Results: A total of 21,878 SpA patients were identified. The age, sex and local health integration network (LHIN) standardized prevalence rates (per 100,000) for SpA were 79 in 1995, 132 in year 2000, 173 in 2005 and 213 in 2010. The male: female ratio was 1.7 in 1995, which progressively dropped to reach 1.25 by 2010. A significant increase in the diagnosis of female AS patients but not male patients occurred between 2000–2005. The male; female ratio in incident cases decreased from 1.3 in 1995 to 1.0–1.1 by 2005–2010. In both sexes, the incidence rates rose uniformly in all age groups (15–44 years, 45–64 years and above 65 years) with time.

Conclusion: In this large population-based study, the period specific adjusted prevalence of SpA progressively increased. More female patients were diagnosed with SpA from 2000 onwards which correlates with the introduction of TNFi therapy in AS. Thus the trend of increasing female SpA patients predates the introduction of MRI and the new ASAS classification criteria for axial SpA.

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2940

Do Patients with Non-Radiographic Axial Spondyloarthritis and Ankylosing Spondylitis Respond Similarly Well to Nsaids? – a Prospective Study Including Magnetic Resonance Imaging. Xenofon Baraliakos[1], Uta Kiltz[1], Frank Heldmann[1], Heiner Appel[2], Friedrich Dybowski[3], Manfred Igelmann[4], Ludwig Kalthoff[5], Dietmar Krause[6], Hans-Jürgen Menne[7], Ertan Saracbasi[8], Elmar Schmitz-Bortz[9] and Jürgen Braun[1]. [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Rheumatology and Nephrology Practice, Hamm, Germany, [3]Rheumatology Practice, Herne, Germany, [4]Rheumatology Practice, Bochum, Germany, [5]Rheumatology practice, Herne, Germany, [6]Rheumatology practice, Gladbeck, Germany, [7]Rheumatology practice, Dortmund, Germany, [8]Rheumatology practice, Oberhausen, Germany, [9]Rheumatology practice, Hattingen, Germany.

Background/Purpose: Patients classified as axial spondyloarthritis (axSpA) may have ankylosing spondylitis (AS) or non-radiographic axSpA (nr-axSpA). Treatment recommendations for AS consider non-steroidal anti-inflammatory drugs (NSAIDs) as first-line therapy. After an unsatisfactory response to at least 2 non-steroidal anti-inflammatory drugs (NSAIDs) within 4 weeks (wk), anti-TNF agents are to be considered. However, it is unknown whether patients with nr-axSpA and AS respond similarly well to NSAIDs.

Methods: Consecutive patients (pts) with axSpA (both n=50 for nr-axSpA and AS, respectively) were included in a prospective study if their BASDAI level was ≥4, and if they had not received the maximally approved dose of NSAIDs nor anti-TNF agents to date. After inclusion into the study the maximal dose of NSAIDs was administered over 1wk and the dose was then adapted in case of BASDAI<4. In case of BASDAI ≥4 of in case of NSAID intolerance, the NSAID was changed and the pt was treated for another 3 wk at the maximal dose. Clinical and laboratory parameters and dosage of drugs were assessed by using the ASAS NSAID-index. Magnetic resonance images (MRI) of the sacroiliac joints including STIR sequences were performed and scored by the Berlin score. Data were collected before (BL) and after 1 and 4 wk of treatment.

Results: Nr-axSpA pts were more often female (48% vs. 30%), younger (mean age 37.6±11.0 vs. 41.9±12.3 years), and had a shorter symptom duration than AS pts (7.3±9.1 vs. 14.6±11.8 years) but were similarly often HLA-B27+ (80% vs. 74%), respectively. Significant differences were found in the mean CRP levels (0.6±0.9 vs. 1.2±1.1) and mean SIJ-MRI scores (3.1±3.0 vs. 6.7±5.4) in nr-axSpA vs. AS pts, respectively (both $p<0.001$). Prior to treatment, an ASDAS-CRP >2.1 was found in 76% and 74% and a positive MRI was seen in 70% and 78% of pts with nr-axSpA and AS, respectively. Both groups responded similarly well to NSAIDs: after wk1 and wk4, the NSAID-index increased similarly in both groups. Significant improvement after 4 wks were found for all assessments with the exception of CRP levels and MRI-a scores, where almost no changes were observed. Between wks 1 and 4, the ASAS20% response rate increased in the entire group from 40% to 52%. At wk 4, there was a slight difference between pts with nr-axSpA and AS: 46% vs. 58% ($p=0.23$), and ASAS partial remission was only found in 16% (14% nr-axSpA and 18% AS, $p=0.59$). However, a BASDAI ≥4 was found in 49% and 44% of pts at wks 1 and 4, respectively, while, in comparison, an ASDAS-CRP of ≥2.1 was found in 37% and 33% at wk 1 and 4. Overall, there were no major differences in response to treatment between nr-axSpA and AS pts.

Conclusion: This study confirms that there are no major differences between pts with AS and nr-axSpA in most clinical aspects. For the first time we show that pts with nr-axSpA and AS show similar response rates to NSAIDs in recommended doses. Importantly, almost 50% of pts with axSpA still have BASDAI levels ≥4 after 4wk of NSAIDs and would, thus, be eligible for anti-TNF therapy. Bone marrow edema on MRI and CRP levels were not influenced by NSAIDs.

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ARHP Concurrent Abstract Session
Epidemiology/Public Health

Tuesday, November 18, 2014, 4:30 PM–6:00 PM

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Physical Function Is Independently Associated with Mortality Among Individuals with Knee and/or Hip OA: The Johnston County Osteoarthritis Project. Rebecca Cleveland[1], Todd Schwartz[1], Jordan B. Renner[2], Joanne M. Jordan[3] and Leigh F. Callahan[4]. [1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]University of North Carolina Department of Radiology, Chapel Hill, NC, [3]University of North Carolina Dept of Epidemiology, Chapel Hill, NC, [4]University of North Carolina, Chapel Hill, NC.

Background/Purpose: Declining physical function (PF) is a common consequence of osteoarthritis (OA), and poor PF is associated with death. It is possible that the resulting reduction in physical activity may increase an individual's risk of development or progression of life-threatening chronic diseases such as CVD and diabetes; however, we previously found that individuals with severe knee and/or hip OA were more likely to die, independent of comorbidities. We therefore sought to explore whether poorer PF among those with OA was associated with death at subsequent follow-up, independent of comorbidities associated with reduced PF.

Methods: Data were from 1,525 individuals aged 45 or older with radiographically confirmed (KL grade ≥2) knee and/or hip OA (rOA) who entered the cohort during the original study enrollment (1990–1997) and newly enrolled individuals recruited during the cohort enrichment (2003–2004). Vital status was assessed at first follow up period (1999–2004 for original participants; 2007–2010 for new enrolls). Severe rOA was defined as a KL grade ≥3; symptomatic OA (sxOA) was a subset of those with rOA and symptoms in the same joint. PF assessment was the 8-ft (2.4-m) walk test. Average number of steps needed to complete the walk and average times to the nearest tenth of a second across two trials were computed. Dichotomous variables based on medians were used for walk time (<3.4 sec and ≥3.4 sec) and number of steps (<5.5 steps and ≥5.5 steps). Multilevel logistic regression models controlling for the primary sampling unit (PSU) were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the associations between each PF measure at baseline and whether death occurred by the first follow-up evaluation. All models were adjusted for age, race, sex, BMI, smoking, depression, stroke, diabetes and CVD.

Results: Our sample was mostly women (63%), Caucasian (67%) and had a mean age of 65 years. At first follow-up, 18% of our sample had died. Walking time and number of steps above their medians were associated with about a doubling in the odds of death among those with knee and/or hip rOA (Table 1). Similar associations were observed when restricted to individuals with sxOA, and slightly attenuated ORs among those with severe disease that failed to reach statistical significance, possibly due to a smaller sample size. The highest odds of death with greater walking times were seen among individuals who had hip rOA whether with knee rOA (OR=2.33; 95% CI=1.20–4.51) or without knee rOA (OR=2.40; 95% CI=1.25–4.61).

Conclusion: Our findings suggest that poor PF among a cohort of individuals with knee and/or rOA is associated with death, findings which are independent of comorbidities linked to increased mortality. We observed associations with death were particularly strong for individuals with hip rOA, therefore suggesting a potential survival benefit through intervention among those individuals.

Table 1. Adjusted‡ odds ratios (95% CI) for death at first follow-up according to 8-foot walking test measures assessed at baseline among those with knee and/or hip rOA (n=1525)

	Knee and/or Hip rOA		Symptomatic Knee and/or Hip rOA		Severe Knee and/or Hip rOA	
	Dead/Alive	OR (95% CI)	Dead/Alive	OR (95% CI)	Dead/Alive	OR (95% CI)
Walking Time						
Time ≤3.4 sec	85/676	Referent	36/283	Referent	25/134	Referent
Time >3.4 sec	185/567	**1.94 (1.38–2.71)**	114/355	**2.15 (1.32–3.49)**	82/197	1.68 (0.92–3.09)
Number of Steps						
Steps ≤5.5	121/766	Referent	59/325	Referent	40/160	Referent
Steps >5.5	154/484	**2.13 (1.49–3.03)**	95/318	**1.77 (1.09–2.87)**	68/175	1.45 (0.79–2.64)

	Only Knee rOA		Only Hip rOA		Both Knee and Hip rOA	
	Dead/Alive	OR (95% CI)	Dead/Alive	OR (95% CI)	Dead/Alive	OR (95% CI)
Walking Time						
Time ≤3.4 sec	36/283	Referent	25/256	Referent	24/137	Referent
Time >3.4 sec	75/275	1.53 (0.90–2.58)	46/143	**2.40 (1.25–4.61)**	64/149	**2.33 (1.20–4.51)**
Number of Steps						
Steps ≤5.5	48/333	Referent	36/288	Referent	37/145	Referent
Steps >5.5	64/226	**2.25 (1.27–3.97)**	37/115	**2.98 (1.49–5.98)**	53/143	1.55 (0.79–3.02)

‡Adjusted for age, race, gender, BMI, smoking, diabetes, stroke, cardiovascular disease and depression at baseline; Controlling for PSU.

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2942

A Longitudinal Population-Based Study 1994–2010 of Age, Period, and Cohort Effects in the Prevalence of Arthritis: The Effect of Improving Socioeconomic Status and Increasing Obesity over Time. Elizabeth M. Badley[1], Mayilee Canizares[2], Anthony V. Perruccio[2], Sheilah. Hogg-Johnson[2] and Monique A.M. Gignac[2]. [1]Toronto Western Research Institute, Toronto, ON, [2]University of Toronto, Toronto, ON.

Background/Purpose: To examine birth cohort and period effects in the age-trajectories of reported arthritis from 1994 to 2010 in a representative sample of Canadians; and to determine whether any birth cohort or/and period effects in reported arthritis are associated with differences in SES (education and income), smoking, physical activity, or obesity over time.

Methods: Data from the Canadian Longitudinal National Population Health Survey, a nationally representative community sample followed every 2 years for 18 years. We used data for four birth cohorts (n =8,809 at baseline): World War II generation, born 1935–1944; older baby boomers, born 1945–1954; younger baby boomers, born 1955–64; and generation X, born 1965–74. Data at each interview included self-reported arthritis diagnosed by a health professional, years of education, household income, smoking, index of physical activity, and height (m) and weight (kg) (used to calculate body mass index (BMI: wt/ht^2)). Multilevel growth models were used to estimate the age-trajectory for reported arthritis for each cohort accounting for period. Once the age-trajectory was established, education, household income, smoking, physical activity, and BMI were separately introduced into the models to examine their influence on arthritis.

Results: There was a trajectory of increasing prevalence of arthritis with increasing age in all cohorts, with younger cohorts having successively greater prevalence. After accounting for period effects the cohort effect was no longer apparent. There were marked population-level cohort effects for increasing education, income, physical activity, and BMI and decreasing smoking from the youngest to oldest cohorts, which were much reduced (education, smoking, and physical activity) or removed (income and BMI) once period was taken into account. Including these variables in a multi-level growth model showed the prevalence of arthritis was significantly lower ($p<.001$) in those with higher education (OR: 0.54; 95% CI: 0.44 – 0.65: >16 years vs <12 years of school) or higher income (OR: 0.60; 95% CI: 0.53 – 0.68: highest vs lowest quartile) and the prevalence was significantly higher for obese individuals (OR: 2.63; 95% CI: 2.20 – 3.14: BMI>=35 vs normal

BMI (18.5–24.9) and current smokers vs non-smokers (OR: 1.63; 95% CI: 1.42 – 1.88). Physical activity was not significantly associated with arthritis. Further analysis showed that the population-level effects of increasing education and income on reducing the arthritis prevalence were almost counter-balanced by effects of increasing BMI (obesity).

Conclusion: The findings suggest that the cohort effect of more arthritis in younger cohorts is explained by period effects such that the potential benefits of increased education and income in reducing the prevalence of arthritis have been partially offset by increases in BMI over time. Our understanding of the impact of BMI on arthritis is therefore likely to be an underestimate. The cohort effect of increased arthritis in younger cohorts also suggests that previous population projections may be underestimated.

Disclosure: E. M. Badley, None; **M. Canizares**, None; **A. V. Perruccio**, None; **S. Hogg-Johnson**, None; **M. A. M. Gignac**, None.

2943

Severity of Foot Pain Is Linked to the Prevalence of Depressive Symptoms: The Framingham Foot Study. Arunima Awale[1], Alyssa B. Dufour[2], Patricia P. Katz[3], Virginia A. Casey[1] and Marian T. Hannan[4]. [1]Hebrew SeniorLife, Boston, MA, [2]Hebrew SeniorLife, Harvard Medical School & Beth Israel Deaconess Medical Center, Boston, MA, [3]University of California, San Francisco, CA, [4]Institute for Aging Research, Hebrew SeniorLife, Dept. of Medicine Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

Background/Purpose: While a number of risk factors for foot pain are established, the relation between depression and foot pain has not been well studied. The purpose of this study was to examine the associations of foot pain and severity of foot pain with depressive symptoms in a population-based study of older adults.

Methods: A validated foot assessment and the 20-item CES-D questionnaire were administered to Framingham Foot Study (2002–08) participants. Age (years) and body mass index (BMI, kg/m^2) were also collected. Foot pain was queried: "On most days, do you have pain, aching or stiffness in either of your feet?" Severity of foot pain was categorized as: none (referent), mild, moderate or severe pain. CES-D scores ≥ 16 were considered indicative of significant level of depressive symptoms. Sex-specific logistic regression was used to calculate odds ratios and 95% confidence intervals for the association of foot pain (y/n or severity of foot pain) with depressive symptoms (y/n) adjusting for age and BMI. In a subset of participants, further models adjusted for leg pain (hip, knee, ankle), back pain, or other joint pain (neck, shoulder, elbow, wrist).

Results: Of the 3321 participants (mean age: 66 ± 10 years), 1464 were men (BMI: 28.9 ± 4.7 kg/m^2) and 1857 were women (BMI: 28.0 ± 6.0 kg/m^2). 21% men and 27% women had depressive symptoms (CES-D score ≥ 16). Men with moderate foot pain vs. none had 2-fold increased odds (Table) of reporting depressive symptoms; men with severe foot pain had a 4-fold increased odds, independent of age and BMI. Women showed a similar trend in which women with moderate foot pain had 2-fold increased odds of depressive symptoms, and women with severe foot pain had 3-fold odds, independent of age and BMI. For both men and women, mild foot pain showed increased odds (ratios of = 1.3 and 1.4 respectively), but was only statistically significant for women (p =. 046). Models considering other regions of pain attenuated the odds ratios (Table); pain variables were non-significant for men, while in women, back pain (p =. 007), other pain (p =. 019) but not leg pain (p =. 775) added to the model.

Conclusion: Severity of foot pain, adjusting for age and BMI, was significantly associated with the prevalence of depressive symptoms in our study (i.e., those reporting worse foot pain were more likely to report depressive symptoms). Adding joint pain at other regions attenuated but did not change the pattern of results. Future studies should investigate the longitudinal aspects of the severity of foot pain and depressive symptoms in older adults.

Table: Odds ratios and 95% confidence intervals for the association between severity of foot pain and depressive symptoms, stratified by sex, and adjusted for age and BMI.*

	Men (n = 1464)		Women (n = 1857)	
	n (%)	OR (CI)	n (%)	OR (CI)
Foot pain (y/n)	277 (19)	1.84 (1.36, 2.48)	543 (29)	1.93 (1.55, 2.45)
Severity				
No foot pain (referent)	1187 (81)	1.0	1314 (71)	1.0
Mild foot pain	114 (8)	1.26 (0.79, 2.02)	208 (11)	1.40 (1.01, 1.94)
Moderate foot pain	126 (9)	1.88 (1.25, 2.86)	233 (13)	2.09 (1.55, 2.82)
Severe foot pain	37 (2)	4.34 (2.26, 8.48)	102 (5)	3.08 (2.02, 4.68)
Models further adjusted for leg pain, back pain and other joint pain				
	n (%)	OR (CI)	n (%)	OR (CI)
Foot pain (y/n)	198 (21)	1.56 (1.09, 2.23)	370 (31)	1.54 (1.17, 2.06)
Severity				
No foot pain (referent)	746 (79)	1.0	824 (69)	1.0
Mild foot pain	87 (9)	0.91 (0.54, 1.55)	141 (12)	1.08 (0.73, 1.59)
Moderate foot pain	81 (9)	1.87 (1.14, 3.06)	152 (13)	1.69 (1.16, 2.45)
Severe foot pain	30 (3)	3.64 (1.71, 7.75)	77 (6)	2.53 (1.54, 4.15)

*Depressive symptoms dichotomized as CES-D score ≥ 16 or <16.

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2944

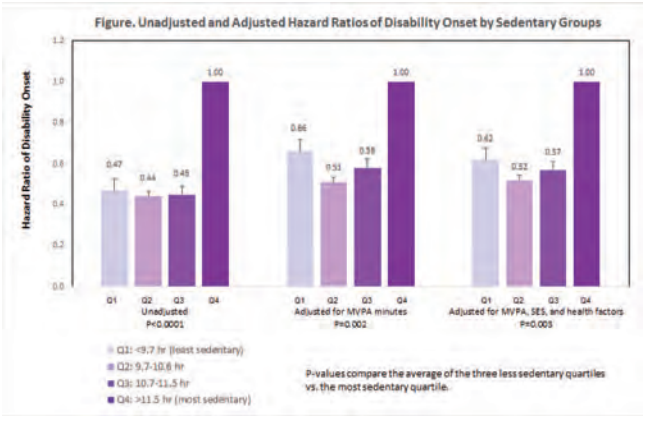
Sedentary Time Is an Independent Risk Factor for Disability Onset Among Adults at Elevated Risk: Prospective Cohort Study. Jungwha Lee[1], Jing Song[1], Barbara Ainsworth[2], Rowland W. Chang[1], Linda S. Ehrlich-Jones[3], Christine Pellegrini[1], Pamela Semanik[4], Dorothy D. Dunlop[1] and Leena Sharma[5]. [1]Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Arizona State University, Pheonix, AZ, [3]Rehabilitation Institute of Chicago, Chicago, IL, [4]Rush University, Chicago, IL, [5]Northwestern University, Chicago, IL.

Background/Purpose: Disability threatens personal independence and is a major driver of health care costs. Physical activity has been shown to prevent disability. Sedentary behavior, already associated with poor health outcomes, may have a unique relationship to the development of disability or simply reflect limited recommended moderate/vigorous physical activity (MVPA). If a separate and distinct risk factor, reducing sedentary behavior may provide an additional strategy to reduce disability among older adults.

Methods: Prospective multi-site cohort of 1680 community dwelling adults aged 49 years or older were at elevated risk to develop disability due to knee osteoarthritis or having knee osteoarthritis risk factors. Baseline sedentary and non-sedentary (e.g., light, moderate, vigorous) time were objectively measured using accelerometers. Participants were classified into sedentary time quartiles groups. Disability was ascertained from limitations in instrumental and basic activity of daily living (IADL/ADL) at baseline and two years. Hazard ratios for disability onset over 2 years follow-up were estimated from discrete time proportional hazards model controlling MVPA time, socioeconomic factors (age, sex, race/ethnicity, education, income), health factors (function, comorbidity, Center for Epidemiological Studies Depression score, body mass index category, current smoking, knee pain, knee OA severity, knee symptoms, knee injury, other lower extremity joint pain, gait speed).

Results: Incident disability was 147 versus 69, 62, and 72 per 1000 person-years over 2-years follow-up in the most sedentary quartile group (>11.5 sedentary hours per day) compared to the three less sedentary quartile groups, irrespectively. Less sedentary time was significantly associated with decreased risk of incident disability independent of moderate/vigorous minutes and other covariates (hazard ratios comparing three less sedentary quartiles vs. the most sedentary quartile, 0.62, 0.52, 0.57, irrespectively) (Figure). The average of the three less sedentary quartiles compared to the most sedentary quartile was associated with 44% decreased risk of disability (HR=0.56 [95% CI, 0.37–0.81], P=0.003). From further analyses using an isotemporal model, replacing one hour sedentary time with one hour light activity (e.g. walking) was associated with 51% decreased risk of disability onset for those in the most sedentary quartile group, independent of potential confounders and time spent in other activities (HR=0.49 [95% CI, 0.29–0.85], P=0.01; not shown in Figure).

Conclusion: Sedentary time appears to be a separate and distinct risk factor for incident disability among adults at elevated risk for disability. In addition to increasing MVPA physical activity, these findings suggest decreasing sedentary time may be an additional strategy to prevent disability onset.



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2945

Foot Structure and Function Show Associations with Lower Extremity Physical Function. Yvonne M. Golightly[1], Marian T. Hannan[2], Patricia P. Katz[3], Howard J. Hillstrom[4], Alyssa B. Dufour[5] and Joanne M. Jordan[1]. [1]University of North Carolina Dept of Epidemiology, Chapel Hill, NC, [2]Institute for Aging Research, Hebrew SeniorLife, Dept. of Medicine Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [3]University of California, San Francisco, San Francisco, CA, [4]Hospital Special Surgery (HSS), New York, NY, [5]Hebrew SeniorLife & Boston Univ, Boston, MA.

Background/Purpose: Foot pain is associated with poorer physical function in older adults, but few studies have examined how foot structure (high / low arches) and foot function (supination / pronation) are related to lower extremity physical function. The purpose of this cross-sectional study was to evaluate whether foot structure and function were associated with self-reported and performance-based physical function in a community-based study of Caucasian and African American men and women 50+ years old.

Methods: During the 2006–2010 exam of the Johnston County Osteoarthritis Project, foot pressure scans were obtained and physical function of participants was assessed via self-report and performance tests. Physical function measures included: the Foot and Ankle Outcome Score –Activities of Daily Living subscale (FAOS-ADL, 0 – 100 [extreme - no limitation]), 5 timed chair stands (unable and quartiles of completion time in seconds [s]), 8-foot walk (unable and quartiles of time in s), and standing balance (unable to stand without assistance, <10 s semi-tandem, semi-tandem 10 s but unable full tandem >2 s, full tandem 3–9 s, and full tandem 10 s). Foot pressure scans were used to determine foot structure (modified arch index) during standing and foot function (center of pressure excursion index) while walking. Based on population data, foot structure was categorized as high arch, low arch, and referent; foot function was categorized as over-pronated, over-supinated, and referent. The most extreme foot structure and function for each participant were used in analyses. Separate linear (continuous outcomes) and logistic (categorical outcomes) regression models were used to estimate the associations between foot types and physical function measures, adjusting for age, body mass index [BMI], sex, and race.

Results: 1571 participants had foot structure data and 1490 had foot function data (mean age 69 years, mean BMI 32 kg/m^2, 68% women, 30% African American). In standing, 22% had a low arch and 39% had high arch; during walking, 22% had an over-pronated foot and 31% had an over-supinated foot. Compared to the referent foot structure, higher FAOS-ADL scores (better physical function) were associated with a high arch in adjusted models, while a low arch was associated with worse physical performance on the chair stand and 8-foot walk tasks and with poorer balance (Table); these results were attenuated after controlling for age, BMI, sex, and race. Compared to the referent foot function, an over-supinated foot was associated with a faster 8-foot walk speed.

Conclusion: A high arch and an over-supinated foot were related to better lower extremity physical function. Longitudinal studies are needed to examine the effect of foot structure and function on changes in physical function and to assess interventions for modifying foot type (e.g., shoe orthotics) to limit physical decline in populations.

Table. Associations of Foot Structure and Foot Function with Physical Function

Physical Function		Foot Structure			Foot Function		
		Referent	Low Arch	High Arch	Referent	Over-Pronated	Over-Supinated
FAOS-ADL	n	580	587	324	662	296	427
	Mean (SD)	95.2 (9.3)	93.8 (9.7)	97.2 (6.8)	94.9 (9.3)	95.6 (8.3)	95.4 (8.7)
	Unadjusted beta (SE), p-value	–	−1.38 (0.53), <0.01	1.95 (0.62), <0.01	–	0.68 (0.62), 0.27	0.54 (0.55), 0.32
	Adjusted beta (SE), p-value	–	−0.44 (0.58), 0.45	1.47 (0.63), 0.02	–	0.55 (0.61), 0.37	0.21 (0.54), 0.70
Chair Stand	N	585	581	328	664	302	425
unable	%	11.8	19.6	7.6	12.5	15.6	11.8
≥ 15.8 s	%	20.9	23.8	19.5	22.3	23.8	19.5
12.8-<15.8 s	%	19.3	20.3	26.2	21.4	20.2	21.2
10.2-<12.8 s	%	25.6	19.1	20.4	22.7	21.5	23.5
<10.2 s	%	22.4	17.2	26.2	21.1	18.9	24.0
	Unadjusted OR (95% CI)	–	1.60 (1.31, 1.97)	0.86 (0.68, 1.10)	–	1.19 (0.94, 1.52)	0.86 (0.70, 1.07)
	Adjusted OR (95% CI)	–	1.08 (0.86, 1.36)	1.07 (0.83, 1.37)	–	1.03 (0.80, 1.32)	0.99 (0.79, 1.23)
8-foot walk	N	597	609	339	685	313	440
unable	%	0.2	0.3	0.3	0.3	0.0	0.5
≥ 4.2 s	%	21.4	29.9	15.3	21.6	32.6	18.2
3.3-<4.2 s	%	24.3	27.9	23	28.3	24.0	21.8
2.7-<3.3 s	%	27.5	22.5	27.1	24.8	21.7	28.9
<2.7 s	%	26.6	19.4	34.2	25.0	21.7	30.7
	Unadjusted OR (95% CI)	–	1.58 (1.29, 1.94)	0.71 (0.56, 0.91)	–	1.40 (1.10, 1.78)	0.74 (0.60, 0.92)
	Adjusted OR (95% CI)	–	1.10 (0.87, 1.39)	0.83 (0.64, 1.07)	–	1.17 (0.91, 1.51)	0.80 (0.64, 0.99)
Balance	N	599	609	339	686	313	441
unable	%	1.2	1.8	1.5	1.2	1.9	1.1
	%	5.7	6.6	3.2	4.4	7.0	5.2
semi-tandem 10 s, unable full tandem >2 s	%	16.4	19.9	16.5	18.2	20.5	14.3
full tandem 3-9 s	%	4.8	6.6	6.2	6.0	5.1	5.0
full tandem 10 s	%	72.0	65.2	72.6	70.3	65.5	74.4
	Unadjusted OR (95% CI)	–	1.35 (1.06, 1.71)	0.94 (0.70, 1.26)	–	1.29 (0.98, 1.71)	0.84 (0.64, 1.09)
	Adjusted OR (95% CI)	–	1.30 (0.98, 1.73)	0.97 (0.71, 1.34)	–	1.04 (0.77, 1.40)	0.92 (0.70, 1.22)

beta: negative sign indicates worse physical function.
OR = odds ratio (OR>1.0 indicates worse physical function).
CI=confidence interval; s = second; FAOS-ADL = Foot and Ankle Outcome Score –Activities of Daily Living subscale.
Adjusted models: control for age, BMI, race and sex.

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2946

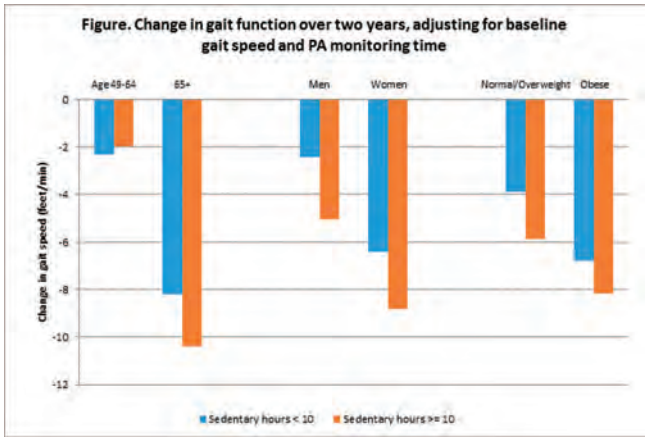
The Association Between Accelerometer Monitored Sedentary Behavior and Observed Physical Function Loss. Pamela Semanik[1], Rowland W. Chang[2], Jing Song[2], Jungwha Lee[2] and Dorothy D. Dunlop[2]. [1]Rush University College of Nursing, Chicago, IL, [2]Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Preservation of function in older adults is critical to maintaining independence. Physical activity interventions often focus on increasing activity while giving limited attention to reducing sedentary behaviors. This study examined whether time spent in objectively measured sedentary behaviors is related to subsequent physical function loss among independent community-dwelling adults with or at high risk for knee osteoarthritis (OA).

Methods: Longitudinal data (2008–2012) from 1659 Osteoarthritis Initiative participants ages 49–83 years were used to evaluate the relationship of baseline time spent in sedentary behaviors (percentage of awake hours and average daily hours) to functional loss (gait speed and chair stand testing) after 2 years of follow-up. Average daily hours of sedentary- and moderate-vigorous intensity physical activity were objectively assessed at baseline by ActiGraph accelerometer monitoring. The relationship of sedentary hours to functional loss was examined by multiple linear regression.

Results: This cohort spent almost 2/3 of their waking hours (average 9.8 hours) in sedentary behaviors. Sedentary time was significantly associated with subsequent functional loss in both gait speed (−1.66 feet/minute decrease per 10% increment increase in percentage sedentary waking hours, 95% confidence interval (CI): −3.15, −0.18) and chair stand rate (−0.75 repetitions/minute decrease, 95% CI: −1.30, −0.20) after controlling for baseline function, socioeconomic (age, sex, race/ethnicity, income, education), health factors (obesity, depression, comorbidities, knee symptoms, knee osteoarthritis severity), and time spent in moderate-vigorous activity. These findings were consistent across subgroups defined by gender and weight, and age among older adults (>65). (Figure)

Conclusion: Being more sedentary was related to more future decline in physical function. Importantly, this finding is independent of time spent in moderate-vigorous activity. This independent relationship supports a dual strategy for designing physical activity interventions. Both limiting sedentary activities and promoting physical activity in adults with knee osteoarthritis may be important in maintaining function.



Disclosure: P. Semanik, None; **R. W. Chang**, None; **J. Song**, None; **J. Lee**, None; **D. D. Dunlop**, None.

2947

Adenosine a_{2A} Receptor As a Potential New Therapeutic Target for the Prevention/Treatment of Osteoarthritis. Carmen Corciulo[1], Aranzazu Mediero[1], Tuere Wilder[1] and Bruce N. Cronstein[2]. [1]NYU School of Medicine, New York, NY, [2]NYU School of Medicine, Division of Rheumatology, New York, NY.

Background/Purpose: Osteoarthritis results from trauma, mechanical factors or metabolic changes in bone and cartilage. Adenosine, acting via the $A_{2A}R$, inhibits inflammation and plays a critical role in regulating bone metabolism. Aging $A_{2A}KO$ mice experience difficulty in movement, taking food and walking. We determined whether changes in their bone or joint structure or function could explain these changes.

Methods: 8, 12 and 16 weeks old C57Bl/6 wild type (WT) and $A_{2A}KO$ mice (n=5) were sacrificed and knee joints were prepared for microCT and histology. PAS (Periodic Acid Staining), Safranin-O and Trichrome staining were carried out. MicroCT analysis of knees was performed on the distal femur below the growth plate. Immunostaining for MMP-13 and Collagen-X were performed. Human immortalized chondrocytes (TC28a2) and primary osteoarthritic chondrocytes were treated with $A_{2A}R$ agonist CGS21680 1μM in the presence/absence of the $A_{2A}R$ antagonist ZM241385 1μM. Collagen-X, MMP-13 and b-catenin were analyzed by Western Blot and ELISA.

Results: microCT analysis of $A_{2A}KO$ mice knees showed osteophyte formation together with mild remodeling and subchondral sclerosis when compared to WT starting at 8 weeks of age. Bone volume/total volume was significantly decreased in $A_{2A}KO$ mice when compared to WT (33.324±0.56 vs 35.782±0.78, respectively, $p<0.01$). Trabecular thickness was also decreased (0.0685±0.0035 vs 0.081±0.002, $p<0.05$) together with bone mineral density (0.3795±0.003 vs 0.4265±0.01 respectively, $p<0.5$). Trichrome, Safranin-O and PAS staining of $A_{2A}KO$ articular cartilage showed chondrocyte hyperthrophy with a reduction of collagen and proteoglycans. Immunostaining for MMP-13 and Collagen-X showed an increase in these biomarkers in $A_{2A}KO$ mice. In both TC28a2 and primary human chondrocytes, activation of $A_{2A}R$ by CGS21680 induced a significant decrease in Collagen-X and MMP-13 expression and release, with an increase in b-catenin expression. These effects are reversed by the $A_{2A}R$ antagonist ZM241385.

Conclusion: Deficiency in adenosine $A_{2A}R$ leads to spontaneous osteoarthritis and stimulation of $A_{2A}Rs$ on chondrocytes diminishes changes associated with osteoarthritis, findings that suggest that $A_{2A}R$ may be novel targets for development of therapies to ameliorate or prevent osteoarthritis.

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2948

S100 Proteins Induce Canonical Wnt Signaling, Which Causes Increased Expression of MMPs in the Synovium. Martijn H. van den Bosch[1], Arjen B. Blom[1], R. Pelle Hoek[1], Rik F. Schelbergen[1], Sylvia W. Suen[1], Anke E. van Erp[1], Wim B. van den Berg[1], Peter M. van der Kraan[1] and Peter L. van Lent[2]. [1]Radboud university medical center, Nijmegen, Netherlands, [2]Experimental Rheumatology, Radboud University, Nijmegen, Netherlands.

Background/Purpose: Many osteoarthritis (OA) patients show synovial activation, which is thought to be involved in joint destruction. Previously, we found that the alarmins S100A8 and A9, and various members of the Wnt signaling pathway, including Wnt16, were highly increased in the synovium of knee joints during experimental OA. WISP1, a downstream protein of β-catenin-dependent canonical Wnt signaling, was increased in both synovium and cartilage. S100A9KO mice showed strongly reduced pathology in experimental OA. Wnt signaling has been linked to OA through activation of β-catenin, but the role of the synovium in OA pathology under the influence of Wnt signaling is unclear. In this study we investigated whether S100 proteins induce Wnt signaling and determined the potency of Wnts to increase expression of cartilage-degrading enzymes in the synovium.

Methods: Pathway analysis of microarray data from synovium of a collagenase-induced OA was done using DAVID. Activation of Wnt signaling was determined with β-catenin immunostaining of whole knee joint sections. Gene expression was analyzed by qPCR. Human OA synovial specimens were collected from joint replacement surgery and stimulated with S100 or members of the Wnt signaling pathway or blocked with the Wnt inhibitors FrzB and DKK-1.

Results: Pathway analysis showed enrichment of Wnt signaling in the synovium during experimental OA. Because upregulation of both S100 and Wnt proteins during experimental OA showed comparable kinetics, we determined if S100 proteins could induce Wnt signaling. We found that injections of S100A8 into mouse knee joints led to increased expression of Wnt16 and WISP1 in the synovium and β-catenin accumulation in the joint. Underlining an interrelationship between Wnt signaling and S100A8/9, we found less β-catenin accumulation during experimental OA in S100A9KO mice. To determine the effects of canonical Wnt signaling in the synovium, we overexpressed Wnt16 and WISP1 in the synovium with adenoviral vectors. This resulted in increased expression of various MMPs in the synovium. To translate these finding to a human situation, we stimulated human OA synovial tissues with Wnt3a, as a model for a canonical Wnt, and WISP1. This led to significantly increased expression of MMP3, MMP9 and MMP13, whereas the expression of the MMP inhibitors TIMP1 and 3 was not altered. Next, we hypothesized that if Wnt signaling was increased in OA synovium and that stimulation of synovium with members of the Wnt signaling pathway led to increased expression of various MMPs, that we should be able to decrease the expression of MMPs by blocking the Wnt signaling pathway. Inhibition of Wnt signaling by both FrzB, a general Wnt inhibitor, and DKK-1, selectively blocking canonical Wnt signaling, led to significantly decreased expression of MMPs.

Conclusion: S100 proteins are able to increase Wnt signaling. Canonical Wnts produced in the synovium may play an important role in OA pathology. Stimulation of human OA synovium with Wnts and WISP1 increases the expression of MMPs, whereas blocking Wnt signaling results in decreased expression of MMPs. This underlines synovial Wnt/WISP1 expression to be a potential target for OA therapy.

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Activation of AMP-Activated Protein Kinase (AMPK) By Berberine Limits Both Surgical Knee Instability-Induced and Aging-Related Osteoarthritis in Mice. Ru Bryan[1], Xianling Zhao[2], Yun Wang[3], Han Sol Lee[2], Hyunje Kim[4], Alifah Akasdi[2] and Robert Terkeltaub[5]. [1]VA Medical Center/University of California San Diego, San Diego, CA, [2]VAMC, San Diego, CA, [3]VA Medical Ctr/UCSD, San Diego, CA, [4]Yeungnam University, Daegu, South Korea, [5]VA Medical Ctr/University of California San Diego, San Diego, CA.

Background/Purpose: Human knee OA articular cartilage chondrocytes and aged mouse knee cartilage chondrocytes demonstrate decreased activation of master cellular energy bio-sensor AMPK. Moreover, inflammatory stimuli and biomechanical injury induce decreased chondrocyte AMPK activity, which transduces chondrocyte matrix pro-catabolic responses prevented by AMPK pharmacological activators *in vitro*. Therefore, we tested the hypothesis that activation of AMPK by berberine, an indirect AMPK activator that is employed in traditional medicine and as a dietary supplement, has chondroprotective effect in mice *in vivo*.

Methods: Two groups of male C57BL/6 mice (n=10 for each group), at age 3 months, were subjected to right knee destabilization of media meniscus (DMM) surgery, and left knee sham procedure. After surgery, 1 group was given berberine chloride (10 mg/kg body weight/day) via drinking water, with a no berberine treatment group serving as the control. Mice were sacrificed at 12 weeks after surgery. To study aging-related OA, 2 groups of five 6 month-old male mice were given berberine chloride as above, and 5 age-matched male mice for each group without berberine treatment were used as controls. Mice were sacrificed at age of 18 and 24 months. All mouse joints were fixed, decalcified, embedded in paraffin, and coronally sectioned (5 micron). We harvested 10–12 slides at ~75 micron intervals, and

stained with safranin-O and fast green for histologic scoring of the entire articular surface, using the OARSI grading system. Some knee sections also were analyzed by immunohistochemistry (IHC) for expression and -phosphorylation of AMPKα and appearance of NITEGE neoeitope of aggrecanase activity.

Results: After DMM surgery, non-treated mice developed OA in the knee medial compartment, with a mean score of 3.72, indicated by loss of safranin-O staining, fibrillation, and partial clefts/erosion down to the calcified cartilage of the articular surface. In comparison, mice receiving berberine treatment after surgery had a marked decrease in OA phenotype in the medial compartment with a mean score of 1.03 ($p<0.0001$, 95% CI of difference: 1.79 to 3.59). Our aging studies showed aging-related spontaneous OA development in non-treated mice, with mean total joint scores 1.5 and 6.6 ($p=0.002$, 95% CI of difference: -8.65 to -1.51) for 18 and 24 months-old mice, respectively. In contrast, berberine significantly reduced spontaneous OA development, and particularly so in 24 months-old mice. The mean total joint scores for the berberine treated mice were 0.38 and 2.2 ($p=0.008$, compared to non-treated mice at 24 months, 95% CI of difference: 0.84 to 7.97) at 18 and 24 months, respectively. Moreover, IHC analysis demonstrated that berberine inhibited both loss of phosphorylation of AMPKa and the appearance of NITEGE neoeitope in articular cartilage.

Conclusion: Maintenance of articular chondrocyte AMPK activity by berberine is therapeutically chondroprotective *in vivo* in mouse knee biomechanical injury and aging models. Targeted activation of AMPK by pharmacologic means, studied here using berberine, provides a novel approach to limiting OA development and progression in mice *in vivo*, and merits investigation in human OA.

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2950

Synovial Macrophages Promote TGF-β Activation after Intra-Articular Injections of Oxidized LDL in Naïve Murine Knee Joints, Preventing Production of Pro-Inflammatory Factors S100A8/9, Chemokines and Aggrecanase-Induced Neo-Epitopes. Wouter de Munter, Peter M. van der Kraan, Wim B. van den Berg and Peter L. van Lent. Radboud university medical center, Nijmegen, Netherlands.

Background/Purpose: In previous studies we found that synovial macrophages regulate joint pathology during experimental osteoarthritis (OA). Recently, we found that high systemic levels of LDL aggravate joint pathology during experimental OA with synovitis. LDL in inflamed synovium is oxidized and taken-up by macrophages via scavenger receptor A and CD36, leading to an activated macrophage phenotype. In this study, we investigate whether direct injection of oxLDL into a normal murine knee joint induces joint pathology and elucidate the role of synovial macrophages in that process.

Methods: Knee joints of C57BL/6 mice were injected at five consecutive days with 1.2 mg/mL oxLDL, LDL, or an equal volume of vehicle (PBS). This same procedure was done in mice which were depleted of synovial macrophages by intra-articular injection of clodronate liposomes seven days prior to the (ox)LDL or vehicle injections. Joint pathology was investigated by immunohistochemistry and RNA expression and protein production by synovium were determined using RT-PCR and luminex, respectively. Active TGF-β was measured using a functional CAGA-luciferase assay. Data are depicted as mean $\pm$ standard deviation.

Results: LDL and oxLDL injection in naïve knee joints did not increase synovial thickening, or production of pro-inflammatory factors (IL-1β, IL-6 and S100A8/9) compared to vehicle injection. Levels of active TGF-β in synovial wash-outs was, however, significantly increased by 33% (from 84.7 ng/mL/g synovium $\pm$ 14.4 to 113.0 ng/mL/g synovium $\pm$ 33.3; $p<0.05$). Immunohistochemistry of total knee joints showed that oxLDL injection decreased formation of aggrecanase-induced neo-epitopes (NITEGE) compared with vehicle injections, especially in areas along the bone margins that are prone to develop osteophytes (from arbitrary score 1.19 $\pm$ 0.57 to 0.33 $\pm$ 0.30; $p<0.05$).

In contrast, repeated injections of oxLDL in macrophage-depleted knee joints led to a 3.1 fold increase of synovial thickening (due to cell influx), compared with injection of vehicle ($p<0.01$), while LDL injections did not alter synovial thickening. Protein levels of S100A8/A9, markers for inflammation, were significantly increased in synovial wash-outs of oxLDL injected joints, compared with LDL (fold increase 5.6; $p<0.05$) or vehicle (fold increase 8.3; $p<0.01$) injection. RNA levels of chemokines CCL2 (Mcp-1) and CCL3 (Mip-1α) were also significantly upregulated after oxLDL injections (6.7 fold and 4.6 fold, respectively; $p<0.01$). No raise in active TGF-β was measured in macrophage-depleted joints. NITEGE expression was markedly increased (fold increase 1.92) in the synovial-cartilage contact areas after oxLDL injection ($p<0.05$).

Conclusion: Synovial macrophages promote anabolic effects after oxLDL injections in knee joints, supporting earlier studies which show increased ectopic bone formation during LDL-rich conditions in experimental osteoarthritis. In absence of synovial macrophages, however, oxLDL induces cell influx, production of pro-inflammatory mediators and aggrecanase activity.

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Syndecan-4 Regulates Chondrocyte Phenotype and Cartilage Homeostasis Via the WNT Signaling Pathway. Charlotte Kimberley Clarke[1], Annelena Held[1], Richard Stange[2], Uwe Hansen[2], Lars Godmann[2], Jessica Bertrand[2], Thomas Pap[3], Giovanna Nalesso[4], Frank Echtermeyer[5], Francesco Dell'Accio[6] and Joanna Sherwood[4]. [1]Institute of Experimental Musculoskeletal Medicine (IEMM), Muenster, 48149, Germany, [2]University Hospital Münster, Münster, Germany, [3]University Hospital Muenster, Muenster, Germany, [4]Queen Mary University London, London, United Kingdom, [5]University Hospital Hannover, Hanover, Germany, [6]William Harvey Research Institute, Barts and the London Queen Mary's School of Medicine and Dentistry, Centre for Experimental Medicine and Rheumatology, London, United Kingdom.

Background/Purpose: Syndecan-4 (Sdc4), family member of type I transmembrane heparan sulfate proteoglycans (HSPGs), is a regulator of various cartilage-related processes including osteoarthritis (OA). Blockade of Sdc4 signaling protects mice from cartilage degradation in experimentally induced OA. OA is characterized by hypertrophic differentiation of chondrocytes and matrix remodeling. Various signaling pathways including the WNT signaling pathway may trigger this induction of chondrocyte differentiation. Experiments investigating the effect of different WNT3a concentrations on WT and Sdc4 deficient chondrocytes have emphasized a complex dialogue between canonical and non-canonical WNT pathways. We hypothesize that Sdc4 controls the chondrocyte phenotype by specific modulation of WNT signaling pathways.

Methods: *In vitro* analyses were performed using neonatal wild type (wt) and Sdc4$-/-$ chondrocytes, or blocking antibodies against Sdc4. The influence of WNT3a on glycosaminoglycan (GAG) production was analyzed using alcian blue staining of micromass cultures. Expression of marker genes (e.g. aggrecan, collagen2, MMP13) was measured by quantitative RT-PCR. Effects of WNT3a on canonical and noncanonical WNT signaling were analyzed using Western Blot and luciferase reporter assay (AP-1, NFAT, TCF/Lef). The influence of WNT3a on the remodeling of the ECM was investigated by electron microscopy. Basal calcium concentrations without and upon WNT3a stimulation were examined using the Fura-2 method. *In vivo* relevance was investigated upon induction of OA using the DMM model.

Results: Micromass cultures revealed a higher basal GAG production by Sdc4$-/-$ chondrocytes. WNT3a stimulation led to a decrease in GAG production in wt cells, which was absent in Sdc4$-/-$ chondrocytes. qRT-PCR showed a 10$\times$ higher basal production of aggrecan and collagen2 in Sdc4$-/-$ chondrocytes. WNT3a increased the expression of both genes in Sdc-4 $-/-$, whereas it decreased the expression in wt chondrocytes. MMP13 was significantly less expressed in Sdc4$-/-$ chondrocytes and, unlike in wt cells, was not upregulated upon WNT3a stimulation. Western blot showed that β-catenin is strongly reduced and not upregulated upon stimulation with WNT3a in Sdc4$-/-$ chondrocytes. LRP6 was less phosphorylated and TCF/Lef promotor was less activated upon WNT3a stimulation in Sdc4$-/-$ chondrocytes. pCamKII was increased under basal conditions, but decreased upon WNT3a stimulation in Sdc4$-/-$. The same effects on canonical and noncanonical WNT signaling upon WNT stimulation were obtained by using a blocking anti-Sdc-4 antibody. Upon WNT3a stimulation, Sdc4$-/-$ cells displayed a finer, more condensed and disorganized ECM structure compared

to wt. Sdc4−/− chondrocytes had increased intracellular Ca^{2+} levels, which were reduced after 24h incubation with WNT3a. *In vivo* stainings confirmed *in vitro* results.

Conclusion: Sdc4 is a major regulator of the chondrocyte cellular response to WNT signalling through facilitating the induction of the canonical WNT signaling pathway. The blockade of Sdc4 protects from OA induced changes in chondrocyte phenotype by inhibiting WNT induced differentiation of chondrocytes.

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S100A9 Inhibitor Paquinimod (ABR-215757) reduces Joint Destruction in Experimental Osteoarthritis and Blocks Activating Effects of S100A9 in OA Synovium. Peter L. van Lent[1], Rik Schelbergen[1], Arjen B. Blom[1], Tomas Leanderson[2], Helena Eriksson[3] and Wim B. van den Berg[1]. [1]Radboud university medical center, Nijmegen, Netherlands, [2]Lund University, Lund, Sweden, [3]Active Biotech AB, Lund, Sweden.

Background/Purpose: Synovial activation is present in more than 50% of osteoarthritis (OA) patients and it is thought to be involved in the development of OA pathology. Previously, we found that alarmins S100A8 and S100A9 are elevated in synovium of OA patients and that high S100A8/A9 serum levels correlate with 2-year progression of the disease. Furthermore, in experimental OA, S100A8/A9 proteins regulate cartilage degradation and synovial activation. Paquinimod is a quinoline-3-carboxamide compound with immune modulatory properties that is currently in clinical development for treatment of systemic sclerosis. It targets the S100A9 protein and blocks the binding of S100A9 to RAGE and TLR-4. In the current study we investigated the effect of paquinimod in two experimental osteoarthritis models differing in synovial activation and its effect on S100A9 stimulated OA synovium.

Methods: Collagenase induced OA (CIOA) was induced by two times intra-articular injection of 1U collagenase and DMM was induced by transsection of the medial anterior meniscotibial ligament leading to destabilization of the medial meniscus (DMM), both in C57Bl6 mice. Paquinimod (3,75 mg/kg) was administered in the drinking water which was refreshed twice a week. Treatment started 4 days before induction of OA in both CIOA and DMM. Synovial thickening and cellularity was measured using an arbitrary score from 0–3. OA-like cartilage pathology was scored using a modified Pritzker OARSI score. Osteophyte size was assessed by a blinded observer using imaging software. Human OA synovium was anonymously obtained from patients undergoing arthroplasty and stimulated with S100A9 and/or paquinimod. Proteins released by synovium were measured with Luminex.

Results: Paquinimod treatment of CIOA expressing high synovial activation resulted in significantly reduced synovial thickening (57%), osteophyte size at the medial femur (66%) and cruciate ligament formation (67%). Moreover, cartilage damage was reduced by paquinimod in CIOA at the medial tibia (47%) and femur (75%). In contrast, paquinimod did not reduce cartilage damage and reduced osteophyte size only slightly (only at the medial femur) in DMM, in which synovial activation is scant. In addition, human OA synovium comprising lining macrophages, was incubated with human S100A9 and /or paquinimod. S100A9 significantly upregulated pro-inflammatory IL-6, IL-8 and TNFα (9-fold, 12-fold and 20 fold increase respectively) and catabolic factors MMP-1 and 3 (up to 2,5 fold). Adding paquinimod significantly inhibited S100A9-induced levels of IL-6 (35% reduction) and IL-8 (38% reduction) but not TNFα whereas MMP1 and MMP3 were reduced by 39% and 64% respectively.

Conclusion: Paquinimod reduces synovial activation, osteophyte formation and OA-like cartilage pathology in experimental OA with high synovial activation and ex vivo blocks pathological effects of S100A9 in OA synovium. Paquinimod could prove a very promising treatment for osteoarthritis patients expressing high synovial activation.

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International Immunochip Study in the Idiopathic Inflammatory Myopathies Identifies Novel Susceptibility Loci and Confirms HLA As Strongest Genetic Risk Factor. Simon Rothwell[1], Robert G. Cooper[2], Ingrid E. Lundberg[3], Frederick W. Miller[4], Peter K. Gregersen[5], Jiri Vencovsky[6], Katalin Danko[7], Lucy R Wedderburn[8], Vidya Limaye[9], Albert Selva O'Callaghan[10], Michael G. Hanna[11], Pedro Machado[11], Lauren M. Pachman[12], Ann M. Reed[13], Lisa G. Rider[4], Joanna Cobb[1], Hazel Platt[14], Øyvind Molberg[15], Olivier Benveniste[16], Pernille Mathiesen[17], Timothy Radstake[18], Andrea Doria[19], Jan De Bleecker[20], Boel De Paepe[20], Britta Maurer[21], William E. Ollier[14], Leonid Padyukov[3], Terrance P. O'Hanlon[4], Annette Lee[22], Hector Chinoy[1] and Janine Lamb[14]. [1]Centre for Genetics and Genomics, Arthritis Research UK, University of Manchester, Manchester, United Kingdom, [2]University of Liverpool, Liverpool, United Kingdom, [3]Rheumatology Unit, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden, [4]Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD, [5]The Feinstein Institute for Medical Research, Manhasset, NY, [6]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [7]University of Debrecen, Debrecan, Hungary, [8]Arthritis Research UK Centre for Adolescent Rheumatology, University College London, London, United Kingdom, [9]Royal Adelaide Hospital, Adelaide, Australia, [10]Vall d'Hebron General Hospital, Barcelona, Spain, [11]MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, United Kingdom, [12]Ann & Robert H. Lurie Children's Hospital of Chicago Research Center, Chicago, IL, [13]Mayo Clinic, Rochester, MN, [14]Centre for Integrated Genomic Medical Research, University of Manchester, Manchester, United Kingdom, [15]Department of Rheumatology, Oslo University Hospital Rikshospitalet, Oslo, Norway, [16]Pitié-Salpêtrière Hospital, APHP, Paris, France, [17]Paediatric Department, Holbaek University Hospital, Holbaek, Denmark, [18]University Medical Center Utrecht, Utrecht, Netherlands, [19]University of Padova, Padova, Italy, [20]University of Ghent, Ghent, Belgium, [21]Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [22]Feinstein Institute Med Rsch, Manhasset, NY.

Background/Purpose: The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of rare autoimmune diseases characterised by muscle weakness and extramuscular manifestations such as skin rashes and interstitial lung disease and with increased association with malignancy. Recent candidate gene studies in IIM and a genome-wide association study in dermatomyositis suggest a shared genetic architecture with other autoimmune diseases. We therefore conducted a genetic association study using the Immunochip; a custom Illumina array containing coverage of 186 established autoimmune susceptibility loci.

Methods: We genotyped 2,740 IIM cases of Caucasian descent comprising of dermatomyositis, juvenile dermatomyositis and polymyositis fulfilling Bohan and Peter classification criteria, and inclusion body myositis fulfilling Griggs/ENMC/Hilton-Jones criteria. Samples have been collected from 14 countries through the Myositis Genetics Consortium (MYOGEN). Data from all cases and 15,754 matched Caucasian control samples were combined for clustering, and SNPs were called using GenCall. SNP QC was based on a call rate >98% and/or cluster separation score >0.4. Sample QC was based on a call rate >98%. Samples with extreme heterozygosity, related individuals and ancestral outliers were also removed. Analysis was performed in PLINK v1.07 using logistic regression adjusting for the top 10 principal components.

Results: Initial analysis of 113,272 SNPs confirmed the MHC as the most strongly associated region. *PTPN22* was the only non-HLA region to reach genome-wide significance of $p=5\times10^{-8}$, previously associated in a candidate gene study. Using a second suggestive tier of significance at $p=5\times10^{-5}$, there was evidence for association at additional loci, including *STAT4, UBE2L3, SH2B3/ATXN2* and *RPL31P10*.

Conclusion: This is the largest genetic association study to date in IIM. The data confirm that *HLA* and *PTPN22* are associated at genome-wide significance, and identification of further novel loci at a suggestive level of significance indicates genetic overlap with other autoimmune diseases. These loci may differ from previously reported dermatomyositis specific associations. The IIMs are a heterogeneous set of diseases; additional clinical subgroup specific analyses are thus planned.

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The Amino Acid Positions 11, 13 and 26 of HLA-DR Beta Chain 1 Explain the Majority of the Association Between Systemic Lupus Erythematosus and the Major Histocompatibility Complex Locus. Kwangwoo Kim[1], So-Young Bang[2], Hye-Soon Lee[2], Yukinori Okada[3], Woei-Yuh Saw[4], Paul IW. de Bakker[5], Yik-Ying Teo[6], Soumya Raychaudhuri[7] and Sang-Cheol Bae[2]. [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea, [3]Broad Institute, Cambridge, MA, [4]National University of Singapore, Singapore, Singapore, [5]University Medical Center Utrecht, Utrecht, Netherlands, [6]Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore, Singapore, [7]Broad Institute of MIT and Harvard, Cambridge, MA.

Background/Purpose: Genetic association of the major histocompatibility complex (MHC) locus is well-established in systemic lupus erythematosus (SLE), but the causal functional variants in this region remain yet to be identified. This study aimed to examine the contribution of amino acid variants in major HLA genes (HLA-A, -B, -C, -DPA1, -DPB1, -DQA1, -DQB1 and -DRB1) to SLE susceptibility and dissect the association signals within the extended MHC locus.

Methods: We inferred HLA classical alleles, amino acid residues and MHC SNPs from the genotyped data of 5,342 unrelated Korean subjects including 849 SLE cases and 4,493 controls. For accurate imputation for the Korean population, we newly constructed an Asian HLA reference panel from two recent HLA reference panels from Korean (n=413; unpublished) and Southeast Asian (n=441) for use with the SNP2HLA software. The dosage effect of binary markers on SLE risk was assessed by a logistic regression and the overall difference of amino acid residues at each amino acid position between case and control groups was examined by a log-likelihood ratio test comparing the fit between null model and full model with amino acids effects.

Results: The new Asian reference panel demonstrated a reliable imputation accuracy, showing high concordance rates between genotyped and imputed alleles of 61 East Asian HapMap3 individuals (98.5% at 2-digit resolution and 93.2% at 4-digit resolution) and a subset of the study subjects (n=1306; 97.9% at 2-digit resolution and 94.1% at 4-digit resolution at HLA-DRB1). We found the primary association signal within HLA-DRB1. When adjusted with all classical alleles of HLA-DRB1, no signal passed a genome-wide significance threshold in our study. At the amino acid level, the most significant association with SLE susceptibility was mapped to the amino acid position 13 of HLA-DR beta chain 1 (HLA-DRβ1; $P = 2.48\times10^{-17}$). The amino acid position 13 explained the SLE risk better than any single HLA allele or SNP. Among six possible residues at the position 13, Arg/Tyr and Ser/His conferred the risk and protective effects on SLE susceptibility, respectively (OR=1.63, $P=1.15\times10^{-15}$ for Arg+Tyr and OR=0.65, $P=4.15\times10^{-14}$ for Ser+His). We validated the association and residue effects at the position 13 using an independent Korean population including 105 SLE cases and 391 controls who were genotyped for HLA-DRB1. In a conditional analysis, the position 26 was remained to be significantly associated with SLE ($P=2.42\times10^{-9}$) after conditioning on the amino acid positions 13 and its tightly correlated position 11. We observed 10 common haplotypes defined by the amino acid position 11-13-26. The reported SLE-risk *HLA-DRB1* alleles *15:01 and *03:01 belong to the SLE-risk haplotypes Pro-Arg-Phe and Ser- Ser-Tyr, respectively.

Conclusion: Our study identified the three amino acid positions 11, 13 and 26 at the antigen-binding groove of HLA-DRβ1 were responsible for most of the association between SLE and MHC.

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The Impact of Northern European Ancestry and Susceptibility Loci on the Risk of Lupus Nephritis. Sarah French[1], Kimberly E. Taylor[1], Sharon A. Chung[1], Joanne Nitiham[1], Michelle Petri[2], Peter K. Gregersen[3], Ward Ortmann[4], Annette T. Lee[3], Timothy W. Behrens[4], Susan Manzi[5], F. Yesim Demirci[6], M. Ilyas Kamboh[6], Robert R. Graham[4], Michael F. Seldin[7] and Lindsey A. Criswell[1]. [1]University of California, San Francisco, Rosalind Russell / Ephraim P. Engleman Rheumatology Research Center, San Francisco, CA, [2]Johns Hopkins University School of Medicine, Baltimore, MD, [3]Feinstein Institute for Medical Research, Manhasset, NY, [4]Genentech, Inc., South San Francisco, CA, [5]Division of Rheumatology, University of Pittsburgh School of Medicine, Pittsburgh, PA, [6]University of Pittsburgh, Pittsburgh, PA, [7]University of California, Davis, Davis, CA.

Table 1.

Model	OR (95% CI) for 25% increase in N. European ancestry	P-value	BIC*
Model 1 (N. European ancestry + disease duration, gender)	0.84 (0.72, 0.99)	0.04	1305.6
Model 1 + European PCs	0.83 (0.70, 0.98)	0.03	1317.3
Model 1 + susceptibility loci (2 SLE risk alleles, 7 renal GWAS SNPs)	0.85 (0.72, 1.01)	0.07	1291.9
Model 1 + renal GRS	0.83 (0.70, 0.99)	0.03	1243.9

Multivariate logistic regression with odds ratios (OR) for LN associated with a 25% increase in proportion of northern European ancestry. Successive models incorporated other measures of genetic variance including European PCs (EIGENSTRAT), susceptibility loci, and a renal genetic risk score (GRS) = sum of number of risk alleles. * BIC = Bayesian information criterion, with lower BIC scores indicating a better fitting model.

Background/Purpose: Lupus nephritis (LN) has a higher prevalence among African Americans, Hispanics, and Asians compared to Caucasians. Significant differences in SLE severity also exist within continental groups, with northern European genetic ancestry conferring protection against autoantibody production and renal disease, which we have previously shown to be independent of socioeconomic status (SES). The goal of our study was to test whether the effect of northern European ancestry is mediated by known SLE risk alleles or recently identified LN susceptibility loci.

Methods: We studied 1142 SLE patients from four independent case collections with genotype data obtained from a previous genome-wide association study (GWAS). A set of continental and intra-European ancestry informative markers (AIMs) was analyzed using the program STRUCTURE to define percent European and northern European ancestry. Subjects with <90% European ancestry were excluded. Multivariate logistic regression of LN risk was performed including percent northern European and other covariates (Table 1). Susceptibility loci were incorporated as potential mediators of the effect of genetic ancestry on the risk of LN. Forty-nine established SLE susceptibility loci and 12 single nucleotide polymorphisms (SNPs) with the strongest association with LN in a recent renal GWAS of SLE subjects were tested for association with LN. A $p<0.05$ was required for SNPs in multivariate logistic regression with other putative risk SNPs to be included in the model of LN risk. A polygenic risk score (PRS), a statistical method for calculating the effect of many common variants in aggregate, was generated from a random 2/3 of individuals using the program PLINK to select 12,935 SNPs with evidence of cumulative association with LN ($p<0.05$).

Results: The overall rate of LN in the study population was 27.3%. A 25% increase in the proportion of northern European ancestry was associated with a 16% reduction in the odds of having renal disease, after adjustment for disease duration and gender (OR 0.84, 95% CI 0.72–0.99, p=0.04). Two previously reported SLE susceptibility loci (BANK1, HLA-DR3) and 7 of 12 LN risk SNPs were significantly associated with LN in our dataset. Adjustment for all 9 putative LN susceptibility loci did not substantially alter the association between northern European ancestry and LN (Table 1). Exploratory analyses incorporating the PRS were underpowered in our study but suggested that a more comprehensive set of genetic variants, as captured by the PRS, may explain more of the effect of Northern European ancestry on the risk of LN.

Conclusion: Northern European ancestry has a significant protective effect for renal disease among SLE patients of European ancestry; this

appears to be independent of currently known SLE risk alleles and LN susceptibility loci, but may be partially explained by a PRS.

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Identification of Autoimmune Functional Variants Under Positive Selection in the Gullah African American Population of South Carolina. Paula S. Ramos[1], Satria Sajuthi[2], Jasmin Divers[2], Yiqi Huang[3], Uma Nayak[3], Wei-Min Chen[3], Kelly J. Hunt[1], Diane L. Kamen[1], Gary S. Gilkeson[1], Jyotika K. Fernandes[1], Ida J. Spruill[1], W. Timothy Garvey[4], Michèle M. Sale[3] and Carl D. Langefeld[2]. [1]Medical University of South Carolina, Charleston, SC, [2]Wake Forest School of Medicine, Winston-Salem, NC, [3]University of Virginia, Charlottesville, VA, [4]University of Alabama at Birmingham, Birmingham, AL.

Background/Purpose: The reasons for the ethnic disparities in rheumatologic and autoimmune diseases (ADs) are largely unknown. We posit that population-specific selection influencing the allele frequencies at some loci contribute to ethnic disparities. Relative to other African-Americans (AA), the Gullah population has lower European admixture and higher ancestral homogeneity from the Sierra Leone (SL) area in Far-West Africa. The shorter genetic distance between the Gullahs and SL suggests that population genetic signals, such as regions under recent selection, may be more easily detected in the Gullahs than in other AA populations. Since both protein-coding and regulatory variation have important roles in recent human adaptation, our goal was to integrate evidence for natural selection with functional annotation for the identification of biologically relevant signals that may harbor risk loci for ADs.

Methods: We computed the cross population extended haplotype homozygosity test (XP-EHH) to identify alleles with higher than expected frequency relative to their haplotype length in Gullah population controls (n=277) relative to SL population controls (n=400), to HapMap Phase II Africans (YRI, n=203), and Caucasians (CEU; n=165). In total 679,513 SNPs met standard GWAS quality control criteria. Variants that met suggestive significance ($|$XP-EHH$|>4$, P<E-04) were annotated and prioritized based on the potential impact of amino acid changes and regulatory functions using RegulomeDB and HaploReg, as well as overlap with immune/autoimmune-related genes and regions associated with ADs.

Results: Nearly the same number of loci showed suggestive evidence for selection between the Gullah and YRI (0.15% of all SNPs), and Gullah and SL (0.14%), although only 106 SNPs in 12 regions showed evidence for selection in both comparisons. Fewer loci showed evidence for selection between Gullah and CEU (0.06%). This is reflected in the enrichment of different pathways in each comparison. Enhancer enrichment analysis of all suggestive SNPs revealed a significant enrichment of strongest enhancers in H1 human embryonic stem cells. Several regions showing evidence of selection between the Gullah and the YRI harbor missense SNPs in AD-relevant genes (*CENPO, IKBKA, USP31*). Other autoimmune-related genes harbor multiple SNPs with high regulatory scores based on the simultaneous presence of eQTLs, transcription factor binding and DNase sites, including those showing evidence of selection between Gullah and YRI (*CCR2, ADCY2, HLA, CD36, CAV1*, GLG1, FXR2), Gullah and SL (*CCR2, ADCY2*), and Gullah and CEU (*TET3*).

Conclusion: These results reveal several autoimmune-related genes with evidence for selection and concomitant high functional potential in the Gullah AA population. Given the increased prevalence of several ADs in AAs and the homogeneity of the Gullah, identification of functional regions under selection in the Gullah has the potential to elucidate AD risks in AA and help explain the ethnic disparity.

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The Rheumatoid Arthritis -Risk Locus CCR6 and Its SNP-Dependent Response to Estrogen: A Possible Genomic Link Between Sex Hormones and the IL-17 Inflammatory Pathway. Ming-Fen Ho, Richard M. Weinshilboum, Liewei Wang and Tim Bongartz. Mayo Clinic, Rochester, MN.

Background/Purpose: The CCR6-CCL20–mediated migration of Th17 cells to inflamed tissues may represent an important mechanism in the etiology of rheumatoid arthritis (RA). The CCR6 SNP rs3093023 is associated with RA disease risk. Variation in the *CCR6* locus has been found to affect CCR6 expression and influence the IL17 serum concentration in RA patients (1). Importantly, an analysis of disease risk stratified by gender revealed opposing effects in Asian subjects: Specifically a *CCR6*SNP (rs3093024), which is in almost complete linkage disequilibrium with rs3093023, was associated with an increased risk of RA in women, but appeared to have a protective effect in men (2). We set out to determine whether variation in estrogen levels might influence the expression of CCR6 and other IL-17 pathway related genes. Furthermore, we aimed to clarify if such estrogen dependent regulation might be influenced by the presence of the variant *CCR6*genotype that is associated with RA disease risk in Europeans.

Methods: We genome-wide genotyped human lymphoblastoid cells using the Illumina 550K and 510S SNP BeadChip and the Affymetrix SNP array 6.0. We then cultured eight LCLs homozygous for the wild-type (WT) SNP rs3093023 sequence and eight LCLs homozygous for the variant (V) allele with increasing concentrations of estradiol (E2). Expression of CCR6, CCL20, IL17A and IL17RA mRNA was measured by qPCR. We then performed siRNA knockdown experiments for CCR6 to explore the downstream effects. To predict putative estrogen receptor binding sites in the *CCR6*gene, we queried the TRANSFEC database. The functional relevance of putative binding sites was confirmed using ChIP assays.

Results: The basal expression levels of CCR6, CCL20, IL17A and IL17RA showed no differences when comparing cell lines with *CCR6* WT versus V genotypes. Knockdown of CCR6 resulted in upregulation of CCL20 and IL-17A, but downregulation of IL-17RA expression. Treatment with E2 for 24 hours resulted in a significant increase in CCR6 expression in a dose-dependent manner, but only in cells with the V allele. CCL20, IL-17A and IL17 RA expression was also SNP-dependent: in cells with the variant genotype, E2 treatment resulted in higher IL-17RA expression. Conversely, CCL20 and IL-17A expression decreased with estrogen treatment only in cells homozygous for the V allele. The TRANSFEC database predicted the presence of two estrogen response elements in the *CCR6*intronic region flanking the rs3093023 SNP. Chip essays demonstrated increased binding of estrogen receptor alpha when the V allele was present.

Conclusion: Our results indicate that a *CCR6*variant, which is associated with RA disease risk, can modulate the CCR6/CCL20/IL-17 axis in an estrogen-dependent manner. Enhanced binding of estrogen receptor alpha to the variant CCR6 genotype may contribute to the mechanism underlying this observation. Such a genomic link between variation in sex hormone levels and variation in cytokine/chemokine expression may provide new insights into the gender differences in RA prevalence and prognosis.

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(2) Teng E et al.: DNA Cell Biol. 2012.

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Polygenic Analysis of Transport, Metabolism and Immune Related Genomic Compartments in Serum Urate and Gout. Eli A. Stahl[1], Tony R. Merriman[2], Amanda Dobbyn[3], David B. Mount[4], Peter Kraft[5] and Hyon Choi[6]. [1]Mt Sinai School of Medicine, New York City, NY, [2]University of Otago, Dunedin, New Zealand, [3]Icahn School of Medicine at Mount Sinai, New York, NY, [4]Brigham and Women's Hospital, Boston, MA, [5]Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, MA, [6]Harvard Medical School, Boston, MA.

Background/Purpose: Genome wide association studies (GWAS) have identified loci associated with complex traits, and the current challenge is to glean biological insights from these findings. A GWAS in 110,347 samples discovered ~30 loci associated with serum urate; however, only two loci were associated with gout in 2,115 cases (*SLC2A9, ABCG2*)[1]. The strongest effects lie in renal urate transporter loci, with additional loci thought to include metabolic genes. Here we systematically assess polygenic effects of urate transport, metabolic and immune-related genes, excluding known associated loci, in both serum urate and gout.

Methods: GWAS results (2.2M HapMap2-imputed SNPs) for serum urate (110,347 individuals) and for gout case/control status (2,115 cases in 14 studies), were utilized to construct polygenic scores. After removal of the 31 significant urate GWAS loci (1Mb each), non-overlapping genomic compart-

ments were defined by SNPs in proximity (+− 50Kb) to genes involved in 1. Urate transport: ABCG and SLC family members of urate-associated transporters and their direct connections in Inweb and String network databases[2] (348 genes), 2. Urate metabolism: purine metabolism and glycolysis KEGG pathways (256 genes), 3. Immune-related: genes targeted by the Immunochip array (184 genes), 4. All other genic regions, and 5. Intergenic regions. Polygenic scores based on GWAS P-value thresholds[3] were calculated in Nurses Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) samples, with incident gout cases having met ACR criteria for diagnosis, and were tested in multivariate analysis with sex, age, BMI and a 31 SNP urate genetic risk score as covariates.

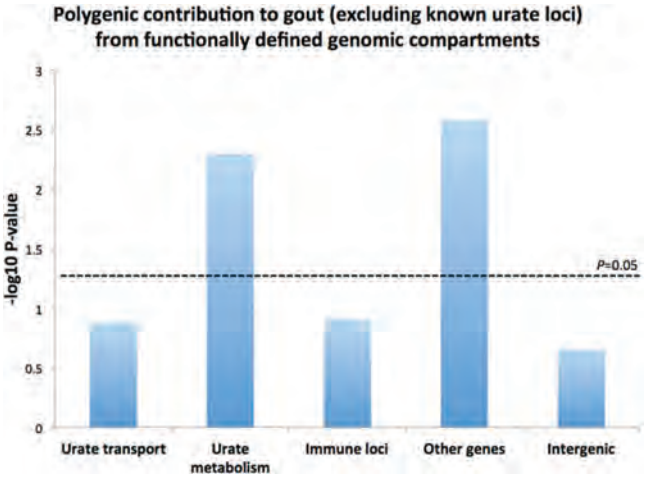
Results: Polygenic scores were significantly associated with gout in metabolic genes (n=797 SNPs with $P_{GWAS}<10^{-2}$; P=0.005) and other genic regions (n=570,599 SNPs with $P_{GWAS}<0.5$; P=0.001), with similar results for association with serum urate (P=0.0025 and P=0.007 for metabolic and other genes respectively). The immune gene compartment was not significant in gout (P>0.12). The urate transporter compartment (excluding known significantly associated urate transporter loci) was not significant in gout or urate (P>0.13 and P=0.20, respectively).

Conclusion: Our results demonstrate an important role for metabolism in both serum urate and risk of gout, with genes outside of the defined compartments also contributing. Excluding known loci, we find no additional evidence for polygenic variation in urate transport or immune-related functions contributing to serum urate or gout. Genomic compartments defined on function can provide additional discoveries and further biological insights into the etiologies of urate and gout.

1. Köttgen, Nat Genet 45: 145 (2013).

2. Lage, Nat Biotechnol 25: 309 (2007); Franceschini, Nucleic Acids Res 41: D808 (2013).

3. Purcell, Nature 460: 748 (2009).



Disclosure: E. A. Stahl, None; **T. R. Merriman**, None; **A. Dobbyn**, None; **D. B. Mount**, None; **P. Kraft**, None; **H. Choi**, Takeda, 5, AstraZeneca, 5.

ACR Concurrent Abstract Session

Metabolic and Crystal Arthropathies II: Mechanisms of Disease

Wednesday, November 19, 2014, 9:00 AM–10:30 AM

2959

Twenty-Eight Loci That Influence Serum Urate Levels: Analysis of Association with Gout. Tony R. Merriman[1], Marilyn E. Merriman[1], Ruth Topless[1], Sara Altaf[1], Grant Montgomery[2], Christopher Franklin[3], Gregory T. Jones[1], Andre M. van Rij[1], Douglas HN White[4], Lisa K. Stamp[5], Nicola Dalbeth[3] and Amanda Phipps-Green[1]. [1]University of Otago, Dunedin, New Zealand, [2]Queensland Institute of Medical Research, Brisbane, Australia, [3]University of Auckland, Auckland, New Zealand, [4]Waikato Clinical School, Waikato Hospital, Hamilton, New Zealand, [5]University of Otago, Christchurch, New Zealand.

Background/Purpose: Twenty-eight genetic loci are associated with serum urate levels in Europeans. Ten are established, with a further 18 of weaker effect more recently detected. *SLC2A9*, *ABCG2*, *SLC17A1* and *GCKR*, with stronger effect sizes, have been consistently associated with gout. Evidence for association with gout at the other 24 loci is absent, equivocal or not replicated, with one explanation likely to be non-clinical ascertainment of gout. Our aim was to test the loci with prevalent gout meeting the ACR gout classification criteria in Aotearoa New Zealand (NZ) European and Polynesian case-control sample sets.

Methods: 648 NZ European cases and 1550 controls, and 888 Polynesian (Māori and Pacific) cases and 1095 controls were genotyped. Association with gout was tested by logistic regression adjusting for age and sex, and ancestry estimate for Polynesians. Power was adequate (>0.7) to detect effects of OR>1.3.

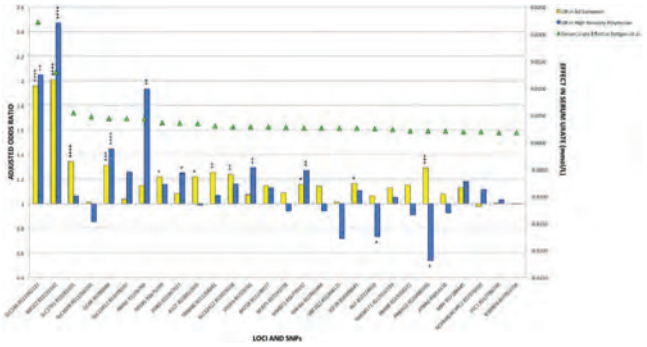
Results: We focused on the 24 loci without consistent evidence for association with gout. Association was detected at seven loci in Europeans, one of which was the first report of association with gout (*IGFR1*) (Figure). In combined Polynesians association with gout was detected at three loci (*SLC22A12, SFMBT1, VEGFA*). Meta-analysis of Europeans and Polynesians revealed association at nine loci, two which had not previously been associated with gout (*PDZK1* and *MAF*). In participants with higher Polynesian ancestry, there was association in an opposing direction to Europeans at *PRKAG2* and *HLF* (Figure). In Europeans there was obvious inconsistency of gout association at four loci (*GCKR, INHBC, SLC22A11, SLC16A9*) that display very similar effects on urate levels.

Conclusion: We provide the first evidence for association with gout at four (*IGRF1, PDZK1, MAF, HLF*) serum urate loci not previously associated with gout. Understanding reasons for lack of correlation between urate and gout effect sizes will be important in understanding the etiology of urate control and risk of gout.

Reference:

Kottgen et al. Nat Genet. 2013;45:145–54.

Figure Adjusted odds ratio of association of 28 serum loci with gout in NZ Europeans (yellow) and people with higher Polynesian ancestry (blue). Serum urate effect sizes taken from Kottgen et al. are shown (green triangles). * P^2 0.05, ** P^2 0.01, *** P^2 0.001, **** P^2 0.0001.



Disclosure: T. R. Merriman, None; **M. E. Merriman**, None; **R. Topless**, None; **S. Altaf**, None; **G. Montgomery**, None; **C. Franklin**, None; **G. T. Jones**, None; **A. M. van Rij**, None; **D. H. White**, None; **L. K. Stamp**, None; **N. Dalbeth**, Ardea, 5, AstraZeneca, 5, Takeda, 5, Metabolex, 5, Menarini, 8, Savient, 8, Novartis Pharmaceutical Corporation, 8, Fonterra, 2, Novartis Pharmaceutical Corporation, 2, Ardea, 2, Fonterra, 9; **A. Phipps-Green**, None.

2960

Urate Genetic Loci and the Risk of Incident Cases of Confirmed Gout in Two Prospective Cohort Studies. Hyon K Choi[1], Gary Curhan[2], Ying Bao[3], Eli A. Stahl[4], Peter Kraft[5], Robert M. Plenge[3], Yuqing Zhang[1] and Tony R. Merriman[6]. [1]Boston University School of Medicine, Boston, MA, [2]Harvard Medical School, Boston, MA, [3]Brigham and Women's Hospital, Boston, MA, [4]Mt Sinai School of Medicine, New York City, NY, [5]Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, MA, [6]University of Otago, Dunedin, New Zealand.

Background: Gout is the most common inflammatory arthritis and is caused by hyperuricemia. The Global Urate Genetics Consortium (GUGC) has recently validated 28 SNP associations in serum urate. However, most corresponding data for the risk of gout have been based on suboptimal definitions (e.g., self-report, by the presence of hyperuricemia, or by anti-gout drug use) and prevalent cases (thus potentially selecting survivors given the risk of premature death associated with gout). To address these issues, we examined two large prospective cohorts and estimated the impact of the

GUGC urate genetic loci on the risk of incident gout, which was ascertained by a widely-used standard definition.

Methods: The Health Professionals Follow-up Study (HPFS) and Nurses' Health Study (NHS) have systematically collected a wide range of exposures and health outcome data, including incident cases of gout, regularly for several decades. We ascertained incident gout cases using the American College of Rheumatology survey criteria. Using GWAS data from the two cohorts (4223 men from the HPFS and 6850 women from the NHS), we calculated a weighted genetic risk score (GRS) based on GUGC urate loci (possible range 0 to 58). Cox proportional hazards models were used to examine the association of GRS as well as individual urate loci with the risk of incident gout in these cohorts separately and together.

Results: Over a total of 262,805 person years, we documented 1081 confirmed cases of incident gout (727 in the HPFS and 354 in the NHS). The GRS ranged from 12.2 to 44.5 among our study participants. Increasing GRS scores were associated with an increasing risk of incident gout in both cohorts (P for heterogeneity > 0.17), and the pooled relative risks (RRs) for incident gout according to increasing GRS categories were 0.34, 0.66, 1.00 (referent), 1.37, 2.01, and 3.48 (P for trend < 0.001) (**Table 1**). Our analyses for individual loci (**Table 2**) showed that *SLC2A9, ABCG2,* and *GCKR* were significantly associated with the risk of incident gout in each cohort as well as in the pooled cohort. *TMEM171, SLC17A1, INHBC, VEGFA,* and *UBE2Q2* were modestly associated only in men (HPFS), and *PRKAG2, B4GALT1, MAF,* and *HLF* were modestly associated only in women (NHS). Heterogeneity between the sexes of these loci was significant for *INHBC, PRKAG2, B4GALT1,* and *HLF*.

Conclusion: These two large prospective cohort studies confirm that the urate GRS scores are strongly associated with the risk of incident cases of confirmed gout among men as well as among women. *SLC2A9, ABCG2,* and *GCKR* were most strongly associated with the risk of incident gout, and nine additional urate loci are more modestly associated with the risk as well.

Table 1. Relative risks (RRs) of Incident Gout According to Genetic Risk Score

Genetic Risk Score	<20.5	20.5–<25.5	25.5–<30.5	30.5–<35.5	35.5–<40.5	≥40.5	P_{trend}
HPFS (Men)							
No. of Cases/Person Years	11/3025	83/14241	232/29717	316/26820	79/4866	6/208	
RR (95% CI)	0.47 (0.25–0.85)	0.75 (0.58–0.96)	1.00 (referent)	1.51 (1.27–1.78)	2.08 (1.61–2.68)	3.68 (1.64–8.28)	<0.001
NHS (Women)							
No. of Cases/Person Years	2/6344	34/32605	133/70479	143/62986	40/11148	2/366	
RR (95% CI)	0.17 (0.04–0.67)	0.55 (0.38–0.80)	1.00 (referent)	1.20 (0.95–1.52)	1.90 (1.33–2.70)	2.93 (0.73–11.83)	<0.001
Pooled Cohort							
RR (95% CI)	0.34 (0.14–0.86)	0.66 (0.50–0.89)	1.00 (referent)	1.37 (1.10–1.70)	2.01 (1.64–2.48)	3.48 (1.72–7.00)	<0.001
$P_{heterogeneity}$	0.19	0.19	–	0.13	0.68	0.78	

Table 2. RR of Incident Gout According to Individual Urate Loci (Limited to 12 Loci with Significance in at Least One or the Pooled Cohort)

SNP	Gene	Risk allele	HPFS RR (95% CI)	HPFS P	NHS RR (95% CI)	NHS P	Pooled RR (95% CI)	Pooled P	$P_{heterogeneity}$
rs12498742	SLC2A9	A	1.44 (1.26–1.64)	<0.001	1.76 (1.43–2.17)	<0.001	1.57 (1.29–1.90)	<0.001	0.11
rs2231142	ABCG2	T	1.71 (1.49–1.96)	<0.001	1.41 (1.15–1.74)	0.001	1.58 (1.32–1.90)	<0.001	0.14
rs1260326	GCKR	T	1.17 (1.06–1.30)	0.002	1.28 (1.10–1.48)	0.001	1.21 (1.11–1.31)	<0.001	0.35
rs17632159	TMEM171	C	0.89 (0.79–0.99)	0.04	0.97 (0.82–1.14)	0.692	0.91 (0.83–1.00)	0.057	0.38
rs1165151	SLC17A1	T	0.86 (0.77–0.95)	0.004	0.91 (0.79–1.06)	0.216	0.88 (0.80–0.95)	0.002	0.52
rs729761	VEGFA	T	0.84 (0.75–0.95)	0.005	1.00 (0.85–1.18)	0.99	0.91 (0.77–1.07)	0.27	0.10
rs3741414	INHBC	T	0.84 (0.74–0.95)	0.007	1.10 (0.93–1.31)	0.25	0.96 (0.73–1.25)	0.74	0.01
rs1394125	UBE2Q2	A	1.16 (1.05–1.29)	0.006	1.07 (0.92–1.25)	0.39	1.13 (1.04–1.24)	0.006	0.38
rs10480300	PRKAG2	T	1.05 (0.94–1.17)	0.42	0.83 (0.70–0.99)	0.04	0.94 (0.75–1.18)	0.60	0.03
rs10813960	B4GALT1	T	0.99 (0.88–1.11)	0.84	0.73 (0.62–0.88)	0.001	0.86 (0.64–1.15)	0.31	0.01
rs7188445	MAF	A	0.91 (0.82–1.02)	0.12	0.84 (0.72–0.99)	0.041	0.89 (0.81–0.98)	0.015	0.43
rs7224610	HLF	A	1.00 (0.90–1.11)	0.97	0.79 (0.68–0.91)	0.001	0.89 (0.71–1.13)	0.348	0.01

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2961

Conditional Analysis of 30 Serum Urate Loci Identifies 25 Additional Independent Effects. Eli Stahl[1], Hyon Choi[2], Murray Cadzow[3], Tanya Flynn[3], Ruth Topless[3] and Tony R. Merriman[3]. [1]Mt Sinai School of Medicine, New York City, NY, [2]Harvard Medical School, Boston, MA, [3]University of Otago, Dunedin, New Zealand.

Background/Purpose: Single variants in 30 genetic loci have been associated with serum urate levels in Europeans by meta-analysis of summary statistics of 48 individual genome-wide association study (GWAS) data sets.[1] Identifying independent effects can help fine map causal genes and reveal functional mechanisms of genetic variation, and has been successful in other complex phenotypes. Our aim was to test for the presence of independent effects at the 30 urate loci.

Methods: Summary level statistics from the Kottgen et al. GWAS[1] were used in collaboration with the Global Urate Genetics Consortium. The Genome-Wide Complex Trait Analysis (GCTA) package[2] was used to test for association conditional on the lead single nucleotide polymorphism (SNP). A total of 9713 HapMap2 genome-wide imputed genotypes from European participants of the Atherosclerosis Risk in Communities study were used as a reference. An independent effect at each locus was defined as an association signal, after conditional analysis, of $P<0.05$ divided by the number of SNPs analyzed. Further rounds of analysis were conducted if SNPs remained significant after conditioning. The percent variance explained for each SNP was calculated by the formula b^2*(var(X)/var(Y)).

Results: Twenty-five additional independent effects were detected at 14 of the 30 urate loci (Table). The percent variance explained by the 30 lead SNPs was calculated to be 4.83%, with the additional SNPs explaining a further 0.81% of variance (total 5.64%).

Conclusion: The independent effects provide evidence for multiple etiological variants at the serum urate loci in Europeans, emphasizing the complex genetic control of serum urate levels. These results are an important initial step in fine-mapping the causal variants. For example, one of the independent effects at *SLC2A9* (*rs3775948*) was the lead SNP in a urate GWAS in East Asian individuals,[3] indicating both shared and unique genetic effects between East Asians and Europeans. The use of multiple ancestral groups will be important in fine-mapping.

1. Köttgen et al. Nat Genet 2013;45:145.
2. Yang et al. Am J Hum Genet 2011;88:76.
3. Okada et al. Nat Genet 2012;44:904.

Lead SNP (locus), P	Additional SNP(s)	Residual P^1
rs1260326 (GCKR), 1×10^{-24}	*rs11891554, rs17709034*	3×10^{-3}
rs12498742 (SLC2A9), $<1\times10^{-700}$	*rs3775948, rs11724112, rs10939614, rs9990701, rs13115661*	9×10^{-16}
rs2231142 (ABCG2), 1×10^{-134}	*rs2622629, rs2725256, rs3109823, rs4693211*	1×10^{-4}
rs17632159 (TMEM171), 4×10^{-11}	*rs575416*	>0.05
rs675209(RREB1), 1×10^{-23}	*rs501510*	1×10^{-3}
rs1165151 (SLC17A1), 7×10^{-70}	*rs12182983, rs6923367*	8×10^{-5}
rs2941484 (HNF4G), 4×10^{-17}	*rs2941478*	>0.01
rs10821905 (A1CF), 7×10^{-17}	*rs10761587*	4×10^{-3}
rs1171614 (SLC16A9), 2×10^{-28}	*rs1171606, rs1171620*	7×10^{-5}
rs2078267 (SLC22A11), 9×10^{-38}.*rs3782099 (NRXN2),* 4×10^{-11}	*rs3782099, rs10897518, rs480617*	9×10^{-3}
rs642803 (OVOL1), 3×10^{-13}	*rs12289836*	1×10^{-3}
rs3741414 (INHBC), 2×10^{-25}	*rs1106766*	3×10^{-3}
rs1394125 (UBE2Q2), 3×10^{-13}	*rs1976748*	2×10^{-3}
rs7193778 (NFAT5), 8×10^{-10}	*rs732021*	>0.05

[1]*P* corresponds to the strongest associated SNP after the final round of conditioning at each locus.

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2962

Association of the Toll-like Receptor 4 (TLR4) Gene with Gout. Humaira Rasheed[1], Ruth Topless[1], Richard Day[2], Diluk Kannangara[3], Kenneth Williams[3], Linda Bradbury[4], Matthew Brown[5], Catherine Hill[6], Susan Lester[7], Maureen Rischmueller[8], Malcolm Smith[6], Mariano Andrés[9], Thomas Bardin[10], Michael Doherty[11], Matthijs Janssen[12], Tim Jansen[13], Leo Joosten[13], Fernando Perez-Ruiz[14], Timothy Radstake[15], Philip L. Riches[16], Ed Roddy[17], Anne-Kathrin Tausche[18], Lisa K. Stamp[19], Nicola Dalbeth[20], Frederic Lioté[21], Alex So[22], Cushla McKinney[1] and Tony R. Merriman[1]. [1]University of Otago, Dunedin, New Zealand, [2]St. Vincent's Hospital, Sydney, Australia, [3]University of New South Wales, Sydney, Australia, [4]The University of Queensland, Brisbane, Australia, [5]University of Queensland Diamantina Institute, Brisbane, Australia, [6]Queen Elizabeth Hospital, Adelaide, Australia, [7]Queen Elizabeth Hospital, Woodville South, Australia, [8]The Queen Elizabeth Hospital, SA, Australia, [9]Hospital General Universitario de Alicante, Alicante, Spain, [10]Hôpital Lariboisière, Paris, France, [11]City Hospital, Nottingham, United Kingdom, [12]Rijnstate Hospital, Arnhem, Netherlands, [13]Radboud University Medical Center, Nijmegen, Netherlands, [14]Hospital De Cruces, Baracaldo, Spain, [15]University Medical Center Utrecht, Utrecht, Netherlands, [16]University of Edinburgh, Edinburgh, United Kingdom, [17]Keele University, Staffordshire, United Kingdom, [18]Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Dresden, Germany, [19]University of Otago, Christchurch, New Zealand, [20]University of Auckland, Auckland, New Zealand, [21]Université Paris Diderot, Paris, France, [22]CHUV, Lausanne, Switzerland.

Background/Purpose: Gout results from innate immune response to monosodium urate (MSU) crystals that form in the context of supersaturation of urate. Identification of genetic risk factors for hyperuricemia and the MSU immune response is therefore important for insight into the etiology of gout. Genome-wide association studies have provided significant insights into the causes of hyperuricemia, however there are no confirmed loci for non-serum urate pathways in gout. Association of *rs2149356* in the TLR4 locus with gout was reported in a Chinese sample set (odds ratio TT genotype = 1.88)[1]. TLR4 triggers innate immune response to endogenous ligands, including MSU crystals. To replicate, we tested *rs2149356* for association with gout in 2,501 European and Polynesian cases and 9,105 controls.

Methods: All gout cases were clinically ascertained according to the American Rheumatism Association criteria. European cases (n=1614) were recruited from New Zealand (n=647), by the Eurogout consortium within the European Crystal Network (n=779) and by the Arthritis Genomics Recruitment Initiative in Australasia (AGRIA; n=188). European non-gouty controls (n=8017) were recruited from NZ (n=875) and sourced from the Atherosclerosis Risk in Communities (n=4143) and Framingham Heart (n=2999) studies. There were 872 New Zealand Māori and Pacific Island (Polynesian) cases and 1088 controls.

Genotyping of *rs2149356* was done by Taqman in the New Zealand samples and imputed in ARIC and FHS from Affymetrix genome-wide data. Association analysis was done by STATA and adjusted by age, sex and (as appropriate) estimate of Polynesian ancestry.

Results: Using controls unstratified for urate status, there was no evidence for allelic or genotypic association in the European sample sets (Table). However the TT genotype was associated with gout in Polynesians ($OR_{TTgenotype}$=0.68, P=0.012). Comparison of cases to hyperuricemic controls revealed evidence for association with gout in Europeans ($OR_{Tallele}$=1.26, P=0.005; $OR_{TTgenotype}$=1.63, P=0.009), but weakened evidence for association in Polynesians ($OR_{Tallele}$= 0.88, P=0.25; $OR_{TTgenotype}$=0.77, P=0.21).

Conclusion: The previous report of association of *TLR4* with gout in Chinese[1] was replicated in Europeans with the T allele of *rs2149356* conferring risk in both populations. Evidence for association was weaker in Polynesians, with the G-allele conferring risk. The strengthening of association in Europeans using hyperuricemic controls is consistent with a role for this locus in gouty inflammation in the presence of hyperuricemia. Subject to further replication, *TLR4* represents the first replicated non-serum urate genetic risk locus identified in gout, and provides support for a role of TLR4 in the etiology of gout.

1 Qing et al. Association of TLR4 gene rs2149356 polymorphism with primary gouty arthritis in a case-control study. PLoS One 2013;5:e64845.

	Gout Cases				Control (All)					
	GG	GT	TT	T	GG	GT	TT	T	OR (T allele), *P*	OR (TT genotype), *P*
European	722 (0.443)	706 (0.433)	201 (0.123)	1108 (0.340)	3773 (0.471)	3408 (0.426)	821 (0.103)	5050 (0.316)	1.13 [1.00–1.28], 0.059	1.26 [0.85–1.67], 0.10
Polynesian	237 (0.272)	431 (0.494)	204 (0.234)	831 (0.481)	288 (0.265)	518 (0.476)	282 (0.259)	1082 (0.497)	0.96 [0.79–1.17], 0.70	0.68 [0.50–0.92], 0.012
	Gout Cases				Control (Hyperuricemic)					
European	722 (0.443)	706 (0.433)	201 (0.123)	1108 (0.340)	593 (0.496)	495 (0.414)	108 (0.090)	711 (0.297)	1.26 [1.07–1.47], 0.005	1.63 [1.13–2.34], 0.009
Polynesian	237 (0.272)	431 (0.494)	204 (0.234)	831 (0.481)	76 (0.295)	107 (0.415)	75 (0.291)	257 (0.498)	0.88 [0.72–1.09], 0.25	0.77 [0.52–1.16], 0.21

Disclosure: H. Rasheed, None; **R. Topless**, None; **R. Day**, None; **D. Kannangara**, None; **K. Williams**, None; **L. Bradbury**, None; **M. Brown**, None; **C. Hill**, None; **S. Lester**, None; **M. Rischmueller**, None; **M. Smith**, None; **M. Andrés**, None; **T. Bardin**, Novartis, SOBI, 5, Novartis, 8; **M. Doherty**, Manarini, 5; **M. Janssen**, None; **T. Jansen**, Abbvie, 2, UCB, 2, Abbvie, 5, AstraZeneca, 5, UMS, 5, Janssen Pharmaceutica Product, L.P., 5, Menarini, 5, Novartis Pharmaceutical Corporation, 5, Pfizer Inc, 5, Roche Pharmaceuticals, 5, Abbvie, 8; **L. Joosten**, None; **F. Perez-Ruiz**, None; **T. Radstake**, None; **P. L. Riches**, None; **E. Roddy**, None; **A. K. Tausche**, None; **L. K. Stamp**, None; **N. Dalbeth**, Ardea, 5, AstraZeneca, 5, Takeda, 5, Metabolex, 5, Menarini, 8, Savient, 8, Novartis Pharmaceutical Corporation, 8, Fonterra, 2, Novartis Pharmaceutical Corporation, 2, Ardea, 2, Fonterra, 9; **F. Lioté**, None; **A. So**, None; **C. McKinney**, None; **T. R. Merriman**, None.

2963

The URAT1 Uric Acid Transporter Is Important in Uric Acid Homeostasis and Its Activity May be Altered in Gout Patients and in Drug-Induced Hyperuricemia. Philip K. Tan, Sha Liu and Jeffrey N. Miner. Ardea Biosciences, Inc., San Diego, CA.

Background/Purpose: Gout results from chronic hyperuricemia. Most gout patients exhibit an increased renal reabsorption of uric acid which leads to elevated levels of serum uric acid (SUA). SUA levels are controlled in part through URAT1, a transporter that is essential for the renal reabsorption of uric acid. Our current research suggests that the renal uric acid reabsorption system is more completely saturated in normal healthy individuals but not in gout patients. We hypothesize that this difference may be due to differences in URAT1 activity, and present evidence that in gout patients as well as in hyperuricemia induced by certain drugs, the activity of uric acid transport by URAT1 is altered by the presence of other URAT1 substrates.

Methods: An analysis based on data from 4 Phase I/Ib studies, in which xanthine oxidase inhibitors (XOI) were given to either normal healthy volunteers (NHV) or gout patients, was conducted. The relationship between change in reabsorption of uric acid versus baseline reabsorption, as well as reabsorption of uric acid versus SUA, was examined. Uric acid transport activity of URAT1 was measured in HEK-293T cells transiently transfected with URAT1 in the absence or presence of salicylate, nicotinate, and other URAT1 substrates.

Results: From the SUA lowering effect of XOI treatment, gout patients experienced a greater change in reabsorption compared to NHV. This indicates that in gout patients the reabsorption of uric acid may be more responsive to changes in SUA levels, and that in NHV the reabsorption of uric acid is less responsive and hence more saturated. URAT1 transported uric acid with an affinity (equilibrium dissociation constant or K_d) of 154 μM. At 500 μM uric acid, the uric acid transport activity of URAT1 was greater than 90% of the maximal activity, approaching saturation for total transport activity. Therefore, URAT1 is highly saturated for transport of uric acid at levels present in NHV (at or below 6.8 mg/dL or 408 μM), and the total transport activity of uric acid by URAT1 is reduced slightly upon physiologically-relevant reductions of uric acid, similar to the highly saturated renal reabsorption of uric acid observed in NHV. However, in the presence of other URAT1 substrates such as salicylate, URAT1 transported uric acid with a 2- to 4-fold lower affinity ($K_d$was increased), and at 500 μM uric acid, the uric acid transport activity of URAT1 was around 60% of the maximal activity.

Conclusion: The presence of other substrates leads to greater reductions in total uric acid transport by URAT1 as uric acid levels are reduced, as seen with the less saturated and more responsive renal reabsorption of uric acid in gout patients. The reabsorption profiles before and after XOI treatment in NHV or gout patients can be mimicked by the activity of the uric acid reabsorption transporter URAT1 *in vitro*, in the absence or presence of other URAT1 substrates, respectively. The results suggest the the possibility that the enhanced reabsorption of uric acid in gout patients and in drug-induced hyperuricemia may be due to the presence of other URAT1 substrates that alter the uric acid transport kinetics of URAT1, which may lead to, or sustain, hyperuricemia.

Disclosure: P. K. Tan, Ardea Biosciences, Inc., 3; **S. Liu**, AstraZeneca, 1, Ardea Biosciences, Inc., 3; **J. N. Miner**, AstraZeneca, 1, Ardea Biosciences, Inc., 3, ARTA Bioscience, 6.

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Association Analysis of Apolipoprotein B and Very Low-Density Lipoprotein with Hyperuricemia and Gout. Humaira Rasheed[1], Angela Hsu[1], Nicola Dalbeth[2], Lisa K. Stamp[3], Sally McCormick[1] and Tony R. Merriman[1]. [1]University of Otago, Dunedin, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]University of Otago, Christchurch, New Zealand.

Background/Purpose: Gout results from an innate immune response to monosodium urate (MSU) crystals deposited in joints. Increased very low-density lipoprotein (VLDL) has been associated with gout. Apolipoprotein B (apoB), present on VLDL, regulates neutrophil response to MSU crystals. ApoB has been positively associated with gout and the *APOB* mRNA-editing gene, *A1CF*, is associated with urate levels. However the relationship of ApoB and VLDL with gout in the presence of hyperuricemia has not previously been tested. Therefore we tested the association of VLDL and apoB with gout in the presence of hyperuricemia (HU).

Methods: New Zealand European (n=90) and Māori and Pacific Island (Polynesian) (n=90) male gout case and control sample sets were divided into normouricemia (NU: serum urate <0.41mmol/L), asymptomatic hyperuricemia (HU: serum urate ≥0.41mmol/L) and gout groups. Gout was classified using the 1997 American Rheumatism Association criteria. Size exclusion chromatography and enzyme-linked immunosorbant assay were used to measure VLDL and apoB. Multivariate linear regression was used to assess the risk of gout and HU per unit change in VLDL and apoB.

Results: Increased levels of VLDL triglycerides (Tg) were observed in the gout sample set compared to NU and HU in European ($P=1\times10^{-4}$ and 2×10^{-3}, respectively) and Polynesian subjects (P=0.042 and 0.019, respectively). This increase was driven by overproduction of VLDL particles in the European subjects and by the Tg-enrichment of existing VLDL particles in the Polynesian subjects. Each mmol/L increase in VLDL Tg was significantly associated with gout in the presence of HU in Europeans, with a similar trend

in Polynesians (OR=6.82, P=0.017 and 2.85, P=0.066, respectively). Each μmol/L increase in apoB was associated with a decreased risk of HU (OR=0.47; P=0.046) and, conversely, with increased risk of gout in the presence of HU (OR=4.79; P=0.005: Table 1) in combined sample set.

Conclusion: Increased VLDL Tg is associated with the risk of gout in the presence of HU. If genetic approaches indicate evidence for causality of VLDL in gout, this would provide further justification for clinical trials examining the effects of fibrates as a treatment option in gout.

Table 1: Analysis of association of VLDL Tg and apo B associated traits with gout and hyperuricemia

	Association with gout risk				Association with Hyperuricemia	
	NU vs. Gout		HU vs. Gout		NU vs. HU and gout	
	OR [95%CI]	P	OR [95%CI]	P	OR [95%CI]	P
VLDL Tg						
Europeans	3.51 [0.94–13.18]	0.063	6.82 [1.40–33.12]	0.017	2.51 [0.66–9.55]	0.18
Polynesians Combined	1.05 [0.37–2.97]	1.92	2.85 [0.93–8.72]	0.066	0.89 [0.39–2.07]	0.80
	1.92 [0.95-3.86]	0.068	3.43 [1.56–7.56]	0.002	1.28 [0.67–2.43]	0.45
Total apo B						
Europeans	1.24 [0.32–4.87]	0.76	3.13 [0.92–10.65]	0.067	0.58 [0.20–1.67]	0.32
Polynesians	0.23 [0.04–1.34]	0.10	12.43 [0.68–227.45]	0.089	0.19 [0.05–0.82]	0.026
Combined	0.85 [0.37–1.97]	0.70	4.79 [1.60–14.37]	0.005	0.47 [0.22–0.99]	0.046

All associations are adjusted for age, BMI, type 2 diabetes, SSB intake (drinks/day), alcohol intake (drinks/week), estimated glomerular filtration rate (eGFR) and prescription of lipid-lowering medication. The Polynesian data are also adjusted by number of self-reported Polynesian grandparents. Combined sample sets are additionally adjusted for ethnic class. VLDL Tg and total FPLC Tg are measured in mmol/L. Apo B is measured in μmol/L.

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ACR Concurrent Abstract Session
Pain: Basic and Clinical Aspects II/Orthopedics, Low Back Pain and Rehabilitation
Wednesday, November 19, 2014, 9:00 AM–10:30 AM

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Effects of Anti-NGF Strategies in Two Animal Models of Osteoarthritis (OA). Lilian Ngozi Nwosu[1], Paul Mapp[1], Karyn Bouhana[2], Steven Andrews[2], Victoria Chapman[1] and David Walsh[1]. [1]Arthritis Research UK Pain Centre, University of Nottingham, Nottingham, United Kingdom, [2]Array BioPharma, Boulder, CO.

Background/Purpose: Levels of endogenous nerve growth factor (NGF) are increased in osteoarthritic (OA) joints in patients and animal models and may be an important cause of pain associated with OA. NGF binds to the high-affinity tropomyosin kinase A (Trk A) and low affinity p75 receptors. Analgesic benefits of the humanized antibody tanezumab in clinical trials have encouraged development of NGF blockade as a novel analgesic strategy for OA, although rare and currently unexplained adverse effects on joint structure have been a concern. Blocking antibodies against NGF inhibit signalling through both Trk A and p75. The ability of selective inhibitors of Trk A tyrosine kinase activity to inhibit OA pain has not previously been reported. We investigated the effect of a selective Trk A inhibitor on pain behaviour, synovial inflammation and joint structure in a chemically induced monosodium iodoacetate (MIA) model and a surgically induced medial meniscal transection (MNX) model of OA.

Methods: Male Sprague Dawley rats (n=10/group, 200–300g) were briefly anaesthetised and given a single intra-articular injection of (1mg/50μl) MIA or saline or underwent MNX or SHAM surgery. The development of pain behaviour was assessed using weight bearing asymmetry (difference in hind limb weight bearing (%)). Two weeks after OA induction, rats were stratified according to their pain responses and received a selective Trk A inhibitor (AR00475786) or vehicle for the remainder of the study. Alterations in knee structure and inflammation were examined by macroscopic visualisation of articular surfaces (Guingamp classification) and histology. Differences between groups were analysed using Kruskal Wallis test followed by post hoc Dunn's test and presented as mean (95% confidence interval).

Results: Rats receiving intra-articular injection of MIA or that underwent MNX surgery developed significant increases in %weight-bearing asymmetry (saline v MIA; day 3 = 2.9 [−4.7 – 11] v 36 [22–51], day 7 = 3.3 [−3 – 9.6] v 24 [14–35] *p<0.05, SHAM v MNX; day 3 = 11.5 [−0.78 – 3.9] v 20 [9.3–31], day 7 = 1.4 [−0.83 – 3.7] v 18 [9.4–26] *p<0.05) with significant increases in synovial inflammation (saline v MIA; 0.78 [0.14–1.4] v 2.3 [2–2.6] **p<0.01). Following drug treatment with AR00475786, there was a significant reversal of %weight-bearing asymmetry (MIA + Vehicle v MIA + drug; day 21 = 27 [21–23] v 3.7 [−1.4 – 8.8] **p<0.01, MNX + Vehicle v MNX + drug; day 21 = 27 [21–32] v 4.8 [1.1–8.6] **p<0.01) and reduced synovial inflammation (MIA + Vehicle v MIA + drug; day21 = 2.3 [2–2.6] v 1.2 [0.32–2.1] *p<0.05). Administration of the Trk A inhibitor did not significantly affect macroscopic chondropathy.

Conclusion: NGF may mediate pain behaviour in rats with MIA or MNX-induced OA through diverse mechanisms. Reductions in weight bearing asymmetry suggest effects of blockade of endogenous NGF activity through Trk A inhibition on peripheral pain processing. Reductions in synovitis suggest additional analgesic mechanisms of NGF inhibition. Trk A inhibition has therapeutic potential in the treatment of OA. Better understanding of the contributions of NGF to OA pathology may help realise the potential of NGF inhibition for OA treatment.

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2966

Genome-Wide Association Analysis of Pain Reduction in Rheumatoid Arthritis Patients Treated with TNF Inhibitors. Marieke J. H. Coenen[1], Maša Umicevic-Mirkov[1], Sophine B. Krintel[2], Julia Johansen[3], Corinne Miceli-Richard[4], Henrik Kallberg[5], Hans Scheffer[1], Wietske Kievit[1], Mart A. van de Laar[6], Piet L. C. M. van Riel[1], X. Mariette[7], Saedis Saevarsdottir[8], Merete Lund Hetland[9], Sita Vermeulen[1] and Cornelis A. Albers[1]. [1]Radboud university medical center, Nijmegen, Netherlands, [2]Copenhagen University Hospital at Glostrup, Glostrup, Denmark, [3]University of Copenhagen, Frederiksberg, Denmark, [4]Université Paris-Sud 11, Bicêtre Hospital,, Kremlin Bicêtre, France, [5]Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [6]University Twente & Medisch Spectrum Twente, Enschede, Netherlands, [7]Paris-Sud University, Paris, France, [8]Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden, [9]DANBIO, Center for Rheumatology and Spine Diseases, Glostrup Univ Hospital, Glostrup, Denmark.

Background/Purpose: Pain is the dominant and prevailing symptom of rheumatoid arthritis (RA). Tumor necrosis factor inihibitors (TNFi) have proven very successful in pain reduction. Interestingly, improvement of pain, is notable rapidly after administration of TNFi agents, and well before anti-inflammatory effects of treatment can be observed. The vast majority of pharmacogenetic studies of response to TNFi utilized the clinical outcome measure, disease activity score 28 (DAS28). This measure is very useful for clinical practice, however it might be less heritable as compared to individual, potentially more homogeneous, disease measures. Usage of less complex phenotypes, such as pain (heritability 28–71%), might significantly aid the identification of genetic markers predicting differential response to TNFi. We aimed to identify and replicate genetic factors predicting pain reduction upon TNFi treatment in patients with RA using genome-wide association approach.

Methods: We included 508 TNFi treated RA patients. Association analysis of change of visual analogue scale of pain (VAS-pain) after 14 weeks of treatment was performed on imputed genome-wide genotyping data under additive genetic model with adjustment for baseline VAS-pain. We also conducted a meta-analysis including 1287 RA patients. Gene-based analysis was performed using VEGAS.

Results: No findings reached the threshold for genome-wide significance (P-value≤1×10-8) in the discovery cohort. Meta-analysis revealed 213 SNPs suggestively associated (P<10-4) with change in VAS-pain after fourteen weeks of TNFi treatment. The most significant SNP rs2295739 (p=2.21×10-6), located ~50kb upstream from the *KCNK10* gene. Which belongs to a family of genes involved in sensory perception. The top hit in the gene-based analysis was RET, known to regulate ion channels and receptors participating in detection and transduction of sensory stimuli. Besides Ret-deficient mice show elevated pain responses.

Conclusion: We have identified several suggestive genomic regions, further studies are required to validate if these regions play a role in pain reduction upon TNFi treatment.

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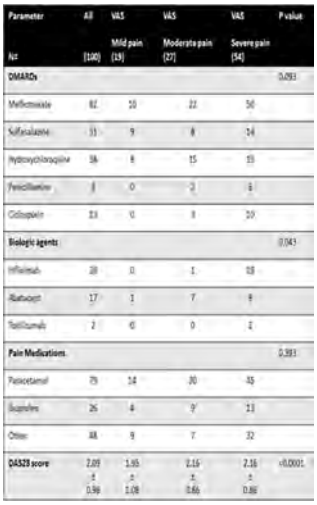
Patient Reported Pain By the Paindetect Questionnaire Reveals Multimodal Elements to Pain Perception in Rheumatoid Arthritis. Saqa Ahmed[1], Tejal Magan[1], Mario Vargas[1], Abiola Harrison[1] and Nidhi Sofat[2]. [1]St George's, University of London, London, United Kingdom, [2]St. George's University of London, London, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) is an inflammatory autoimmune condition typified by systemic inflammation targeted towards synovial joints. Inhibition of pro-inflammatory networks by disease-modifying anti-rheumatic drugs e.g. methotrexate and biologic therapies including TNFα inhibitors, often leads to suppression of disease activity. However, despite the era of widespread use of disease-modifying treatments, there remain significant groups of patients who continue to experience pain.

Methods: Our study formulated a pain assessment tool to be used in the arthritis clinic to assess feasibility of measurements including the visual analogue scale (VAS) for pain (range 0–100 mm) and painDETECT questionnaires (range 0–38) to evaluate neuropathic features of pain in people with established RA (n=100). Clinical measures of disease activity (DAS28), disease-modifying medication use, body mass index (BMI) and worst pain ever were also recorded. Continuous data was described and analysed using parametric statistics, with ANOVA and Chi-squared tests for groups with 3 or more categories.

Results: We found that participants with RA reported relatively high pain levels, despite widespread use of disease-modifying drugs (Table 1). The majority, 54%, reported 'severe pain' on the visual analogue scale (VAS), which identifies people with a VAS of 54–100 mm as having the highest severity of pain. The mean DAS28 in the group was 2.09 $\pm$ 0.96. The majority of subjects had duration of diagnosis greater than or equal to 5 years (84%), suggesting that pain was a persisting symptom despite sustained use of disease-modifying agents and a DAS28 score suggesting clinical remission. All participants evaluated had been stable on DMARD therapy for at least 3 months prior to completing the study and had not required a change in their treatment, or addition of corticosteroid therapy during that time. The majority of participants were being treated with disease-modifying drugs, including the commonest agent, methotrexate (82%). Using the painDETECT questionnaire, 67% of patients had unlikely neuropathic pain. A significantly high proportion of 28% subjects had possible neuropathic pain and 5% had features of likely neuropathic pain by painDETECT scoring. We found a positive correlation between VAS and painDETECT (r^2=0.757). Of note, the group who had likely or probable neuropathic pain also showed significantly increased pain reporting by VAS ($p < 0.01$). Subjects who were clinically obese (BMI > 30) had statistically higher proportions of pain reporting (VAS 89.0 $\pm$ 0.7) compared with subjects who had a normal BMI (VAS 45.2 $\pm$ 21.8), p<0.05.

Conclusion: Our findings suggest that multimodal features of pain perception exist in RA, including neuropathic and sensitisation elements, perhaps explaining why a subgroup of people with RA continue to experience ongoing pain, despite their apparent suppression of inflammation.



Parameter	All	VAS	VAS	VAS	P value
		Mild pain	Moderate pain	Severe pain	
N=	(100)	(19)	(27)	(54)	
DMARDs					0.093
Methotrexate	82	10	22	50	
Sulfasalazine	11	9	0	14	
Hydroxychloroquine	16	0	15	13	
Penicillamine	0	0	0	0	
Ciclosporin	13	0	0	19	
Biologic agents					0.043
Infliximab	20	0	1	18	
Abatacept	17	1	7	9	
Tocilizumab	2	0	0	2	
Pain Medications					0.393
Paracetamol	79	14	30	35	
Ibuprofen	26	4	9	13	
Other	48	9	7	32	
DAS28 score	2.09 ± 0.96	1.95 ± 1.08	2.16 ± 0.66	2.16 ± 0.86	<0.0001

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2968

Improvement Following Total Knee Replacement (TKR) Surgery: Exploring Preoperative Symptoms and Change in Preoperative Symptoms. Ernest R. Vina[1], Michael J. Hannon[2] and C. Kent Kwoh[3]. [1]University of Pittsburgh and VA Healthcare System, Pittsburgh, PA, [2]University of Pittsburgh School of Medicine, Pittsburgh, PA, [3]University of Arizona, Tucson, AZ.

Background/Purpose: Few have examined the trajectories of preoperative health-related quality of life (HRQL) measures in osteoarthritis (OA) patients who undergo TKR. Yet, the type and rate of preoperative decline may predict the outcomes of TKR. The objectives of the study are to determine whether changes in preoperative HRQL measures are associated with improvement after TKR and to identify important predictors of clinically significant improvement.

Methods: Data from people who underwent TKR were obtained from the Osteoarthritis Initiative (OAI), a study which annually assessed participants. T0 was the assessment prior to TKR while T-1 was the assessment prior to that. T+2 was the second assessment after TKR. We compiled data on OA-related symptoms (i.e. pain/aching/stiffness most days of the month in the last year), the WOMAC, activities, and radiographic severity (i.e. Kellgren-Lawrence grade, KLG). We defined clinically significant improvement as improvement in WOMAC total score $\geq$ to the minimal important difference (0.5 standard deviation of mean change in the study data) between T0 and T+2. After conducting bivariate tests for differences, logistic regression models were performed to evaluate the relationship between improvement and preoperative measures. Only variables associated with improvement at $p \leq 0.2$ in a series of stepwise regressions were included.

Results: Our sample consists of 211 improved & 58 unimproved patients. Improved, compared to unimproved, patients had higher preoperative (T0) WOMAC pain (39.31 $\pm$ 17.86 vs. 22.73 $\pm$ 17.92, p<0.001), disability (39.17 $\pm$ 15.08 vs. 18.23 $\pm$ 16.86, p<0.001) and stiffness (46.45 $\pm$ 20.21 vs. 27.37 $\pm$ 20.47, p<0.001) scores in the index knee (i.e. TKR knee). Those who had improvement were more likely to report OA-related symptoms in the index knee (96.68% vs. 77.59%, p<0.001). They also had greater worsening of their WOMAC pain (9.65 $\pm$ 19.53 vs. 2.48 $\pm$ 13.19, p=0.002), disability (9.87 $\pm$ 17.22 vs. $-$0.16 $\pm$ 13.38, p<0.001) and stiffness (9.11 $\pm$ 23.23 vs. $-$0.24 $\pm$ 20.34, p=0.009) scores from T-1 to T0 in the index knee.

Preoperative measures as predictors of improvement in our multivariate model included: Higher WOMAC disability (OR 1.09, 95% CI [1.05–1.13], p<0.001), presence of OA-related symptoms in the index (OR 7.13, 95% CI [1.77–28.67], p=0.006) but absence in the contralateral (OR 8.07, 95% CI [2.75–23.74], p<0.001) knee, exposure to frequent knee bending (OR 3.01, 95% CI [1.02–8.87], p=0.045), having a KLG of 4 (vs. 0, 1, 2 or 3) in the contralateral (OR 4.40, 95% CI [1.24–15.56], p=0.022) and index (p=0.124) knee, and worse SF-12 Mental Health score (p=0.209).

Conclusion: More than 75% of OAI patients had clinically significant improvement after TKR. Improved patients had more self-reported pain and disability prior to surgery and were more likely to have escalation of these symptoms than unimproved patients. Worse OA-related disability prior to surgery, presence of OA symptoms in the surgical knee, prior exposure to frequent knee bending, and having marked radiographic features of OA but without OA-related symptoms in the contralateral knee all increase the likelihood of achieving clinically significant improvement after TKR.

Disclosure: E. R. Vina, None; **M. J. Hannon**, None; **C. K. Kwoh**, None.

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Mortality after Knee Replacement Surgery for Osteoarthritis in a Population-Based Propensity-Score Matched Cohort. Devyani Misra[1], Tuhina Neogi[1], Na Lu[1], David T. Felson[1], Thomas Einhorn[1], Hyon Choi[2], Jessica Maxwell[3] and Yuqing Zhang[1]. [1]Boston University School of Medicine, Boston, MA, [2]Harvard Medical School, Boston, MA, [3]Boston University, Boston, MA.

Background/Purpose: Knee replacement (KR) surgery for osteoarthritis (OA) provides improvement in symptoms and function. Whether these improvements translate into survival benefit has been unclear, likely related to selection of healthier patients for surgery, exclusion of the post-operative immortal time, and inadequate length of follow-up in prior studies. The purpose of this study was to determine risk of mortality related to KR by comprehensive adjustment for confounders using a propensity-score (PS) matched cohort approach and long follow-up.

Methods: Participants ages 50–89 years with a diagnosis of knee OA (from Read Codes) were included from The Health Improvement Network

(THIN), an electronic medical records database representative of the UK general population. High risk subjects who are less likely to be surgical candidates (BMI>40, history of joint infection, high risk cancers (pancreatic, esophageal, gastric or other metastatic), end-stage renal disease on dialysis, use of nasal cannula oxygen, or DMARD therapy) were excluded. PS for KR was calculated using logistic regression with KR as the dependent variable and the confounders listed in the table as independent variables, that reflect indications for KR and risk for poor outcomes. One year cohort-accrual blocks were created, and each KR subject was matched 1:1 by PS with a non-KR subject. Follow-up started from the index date, which was the date of surgery for KR subjects and a random date within the cohort accrual block for non-KR subjects, and continued until death or censoring. We examined the association of KR with mortality by calculating crude incidence rates (IR) and Hazard ratios (HR) using Cox proportional hazard regression. We also examined the association stratified by age category (<70 years, ≥70years) as well as within percentile categories of the PS.

Results: There were 14,675 pairs of subjects with knee OA (mean age 71yrs; 57% women; mean BMI 29kg/m^2) in the PS-matched cohort. The follow-up years were 63769 and 60582 for matched KR and non-KR subjects, respectively. Overall there was 31% lower risk of mortality among subjects with KR (HR 0.69, 95% CI 0.64–0.75). The lower risk remained in subjects ≥70 years but no such relation was noted in subjects <70 years (table). The crude IR for mortality among KR subjects decreased as PS percentile category increased, while no such trend was noted for the non-KR subjects. Mortality risk was lowest (HR 0.29, 95% CI 0.13–0.63) in the highest PS percentile (>98%) category (table).

Conclusion: We found KR to be protective for mortality risk among subjects ≥70 years and among those with the highest propensity for KR. Although a protective effect of KR cannot be ruled out, there likely remains confounding by indication despite comprehensive adjustment of covariates. Patients, physicians, and surgeons consider additional factors in performing KRs that are not adequately captured within administrative databases.

Table: Association of Knee Replacement Surgery and Mortality Risk, stratified by age and by percentiles of propensity scores, in a propensity-score matched cohort of men and women with knee osteoarthritis

			KR			Non-KR			
	* Score	No. of Pairs	Death	Followup-years	IR	Death	Followup-years	IR	HR(95% CI)
Overall	–	14,675	1233	63769.3	0.019	1636	60581.7	0.027	0.69 (0.64–0.75)
Age < 70 years	0.057	6,553	270	29413.0	0.009	291	30372.3	0.010	1.00 (0.78–1.31)
Age 70-90 years	0.055	7,911	963	34356.3	0.028	1345	30209.4	0.045	0.59 (0.52–0.68)
Propensity-score percentile category									
<2%	0.005	293	40	1391.9	0.029	50	1306.9	0.038	0.76 (0.48–1.21)
2%-10%	0.012	1174	129	5536.4	0.023	148	5231.2	0.028	0.78 (0.60–1.03)
10%-20%	0.019	1467	153	6703.1	0.023	175	6280.3	0.028	0.77 (0.60–0.98)
20%-30%	0.025	1468	142	6565.0	0.022	165	6289.7	0.026	0.76 (0.59–0.98)
30%-40%	0.032	1467	125	6510.3	0.019	157	6170.1	0.025	0.78 (0.60–1.02)
40%-50%	0.040	1468	110	6255.3	0.018	152	6088.7	0.025	0.74 (0.56–0.97)
50%-60%	0.049	1467	126	6453.4	0.019	151	6130.2	0.025	0.83 (0.63–1.08)
60%-70%	0.060	1468	118	6314.7	0.019	168	5997.9	0.028	0.60 (0.46–0.80)
70%-80%	0.075	1467	95	6301.0	0.015	149	6074.4	0.025	0.57 (0.42–0.76)
80%-90%	0.097	1468	106	6065.1	0.017	174	5639.8	0.031	0.52 (0.40–0.68)
90%-98%	0.136	1174	79	4546.6	0.017	117	4350.9	0.027	0.65 (0.47–0.90)
>98%	0.208	293	10	1120.9	0.009	30	1021.6	0.029	0.29 (0.13–0.63)

* Mean propensity score within the percentile
Confounders used for calculation of propensity score: 1) **OA severity and duration** 2) **General** (age, gender, BMI, socio-economic status); 3) **Comorbidities** (hypertension, diabetes (including severity), hyperlipidemia, ischemic heart disease (including severity), heart failure, atrial fibrillation, stroke, dementia/cognitive impairment, depression, seizure disorder, peripheral vascular disease, venous thrombo-embolism, chronic obstructive lung disease, lung infection, renal disease, liver disease, cancers except skin cancer, cellulitis, falls, hip fracture, anemia and peptic ulcer disease); 4) **Habits** (smoking status and alcohol use); 5) **Health status** (number of GP visits and hospitalization, albumin level); and 6) **Medication use** (Non-steroidal anti-inflammatory medications, opioid or non-opioid analgesics, anti-hypertensive, cholesterol lowering, insulin/ oral hypoglycemic, bisphosphonates, raloxifene, strontium, glucocorticoids and anti-epileptics).

Disclosure: D. Misra, None; **T. Neogi**, None; **N. Lu**, None; **D. T. Felson**, None; **T. Einhorn**, None; **H. Choi**, Takeda, 5, AstraZeneca, 5; **J. Maxwell**, None; **Y. Zhang**, None.

2970

Psoriatic Arthritis is Associated with Heterotopic Ossification after Total Hip Arthroplasty.

Mario Cedillo[1], Arielle Fein[2], Susan M. Goodman[2], Rebecca Zhu[2], Mark P. Figgie[2], Michael Alexiades[2], Jayme C. Burket[2] and Lisa A. Mandl[2]. [1]Weill Cornell Medical College, New York, NY, [2]Hospital for Special Surgery, New York, NY.

Background/Purpose: Heterotopic ossification (HO), the pathologic deposition of ectopic bone in soft tissues, is a feared complication of total hip arthroplasty (THA). HO is strongly associated with ankylosing spondylitis. However, whether rates of HO are also increased in psoriatic arthritis (PsA), another seronegative spondyloarthopathy with a predisposition to build bone, is unknown.

Methods: We performed a case–control study of validated PsA THA cases, each matched 2:1 on age and date of surgery with osteoarthritis (OA) controls. All THA were performed between May 2007 and June 2012. Radiographs taken ≥ 6 months after surgery were reviewed to detect evidence of HO, based on Brooker classification criteria. Chart review was conducted to identify potential known risk factors for HO, which were evaluated in univariate models. A logistic regression model was constructed to evaluate independent predictors of HO. Risk factors considered for inclusion in the model were those with p-values < 0.20 from the univariate models, which were then removed in a step-wise fashion until only terms with p < 0.1 remained.

Results: 242 PsA THA were identified and matched to 484 OA controls. No PsA THA received prophylactic radiation to prevent HO. 94.2% of PsA surgeries were primary THA and 5.8% were revisions while 93.8% of OA surgeries were primary THA and 6.2% were revisions. Average age was 62.3 for PsA ± 11.7 years and 62.8 for OA ± 11.5. 55.2% of PsA were male while 44.4% of OA were male. More PsA THA than OA THA developed HO (42.2% vs. 29.6%; p-value = 0.012). In univariate models, PsA diagnosis, primary vs. revision surgery, inpatient NSAID use, ASA use, blood transfusions, sex, age, BMI, and length of stay were associated with HO. In the final logistic regression model, HO was significantly associated with PsA (OR: 1.62; 95% CI 1.16–2.27; p-value = 0.005), age (OR for each 10-year increase in age 1.15; 95% CI 1.00–1.3; p-value = 0.047), and being discharged on Coumadin for DVT prophylaxis (OR: 1.86; 95% CI 1.23–2.65; p-value = 0.0007). Inpatient Lovenox was associated with an over 4-fold increase in the odds of having HO (OR: 4.16; 95% CI 1.05–16.6; p-value = 0.043). Female gender was protective against HO (OR: 0.44: 95% CI 0.32– 0.62; p-value < 0.001).

Conclusion: To our knowledge, this is the first study to show that psoriatic arthritis is associated with increased odds of HO following THA. Being older, receiving inpatient Lovenox, or being discharged on Coumadin also increased the risk of HO. Being female decreased the risk of developing HO. This is important information to convey to THA surgeons and patients with PsA contemplating THA.

Table 1. Incidence of heterotopic ossification

		Brooker Classification Criteria for HO						p-value (Fisher's Exact Test)
		0	1	2	3	4	Total	
								0.0121
OA	N	341	62	59	18	4	484	
	%	70.5	12.8	12.2	3.7	0.8		
PsA	N	140	44	47	9	2	242	
	%	57.9	18.2	19.4	3.7	0.8		

OA = Osteoarthritis; PsA = Psoriatic Arthritis

Disclosure: M. Cedillo, None; **A. Fein**, None; **S. M. Goodman**, None; **R. Zhu**, None; **M. P. Figgie**, None; **M. Alexiades**, None; **J. C. Burket**, None; **L. A. Mandl**, None.

ACR Concurrent Abstract Session
Rheumatoid Arthritis - Clinical Aspects VII: New Aspects of Monitoring Disease
Wednesday, November 19, 2014, 9:00 AM–10:30 AM

2971

Patient's Self-Monitoring Via Smartphone: The Compass Study Correlation Between Patient Self-Assessment of Rheumatoid Arthritis Disease Activity Via Smartphone Technology and Physicians' Validated Scores.

Ruediger Mueller[1], Ulrich Walker[2], Diego Kyburz[3], Robert Theiler[4], Adrian Forster[5], Fabiana Ganz[6] and Patrick Dufner[6]. [1]Kantonspital St. Gallen, St. Gallen, Switzerland, [2]Department of Rheumatology, Basel University, basel, Switzerland, [3]University Hospital, Basel, Switzerland, [4]Triemli spital, Zurich, Switzerland, [5]Spital Thurgau AG, Diessenhofen, Switzerland, [6]Abbvie AG, Baar, Switzerland.

Background/Purpose: In clinical practice, patients with RA are usually seen every 3 to 6 months[1]. Although desirable, monthly visits with assessments of disease activity are often not possible due to limited physician resources[2]. However, patients increasingly wish to be actively involved in treatment decisions. Therefore, the development of an internet-based tool for disease activity score assessments by patients could represent an innovative solution. The COmPASS study aims to demonstrate a correlation between the patient assessments of RA disease activity via smartphone and the disease activity done by the physician using traditional scores.

Methods: Adult RA patients under current non-intravenous DMARD treatment were included in the prospective, single-arm, multicentre study. Patients were equipped with smartphones and educated to use a web application (WebApp) for self-assessment. Patients were assessed clinically by the treating physician at baseline. The assessment included joint counts, global assessment, laboratory values, along with simultaneous WebApp questionnaires (RAPID3/4) that were filled in by the patient. During the subsequent 3 months, patients were asked to fill in the WebApp questionnaires at least once a week. Descriptive statistics for RA disease activity according to the WebApp and rheumatologist evaluation at the baseline visit were analysed with the Pearson Correlation. Sensitivity analysis was performed. The correlation between RAPID3/4 scores and DAS44 as well as CDAI and SDAI was evaluated.

Results: Ninety patients were recruited in five Swiss clinics [mean (SD): RA duration: 7.1 years (8.6); age: 54.7 years (13.5); 60% male]. The data showed a strong correlation between patient and rheumatologist assessment of disease activity when comparing RAPID3 with DAS44 at baseline (Fig 1, R=0.60; 95% CI 0.43 – 0.73), CDAI (R=0.53; 95% CI 0.34 – 0.68) and SDAI (R=0.49; 95% CI 0.28 – 0.65). The sensitivity analysis demonstrated that this correlation was independent of disease characteristics, treatment type, demographics, and centre effects, as well as unaffected by a delay of the smartphone data entries up to 7 days after baseline assessment by the rheumatologist. A similar correlation was seen for RAPID4 and DAS44 (R=0.61; 95% CI 0.45 – 0.74), CDAI (R=0.55; 95% CI 0.37 – 0.70) and SDAI (R=0.50; 95% CI 0.30 – 0.66).

Conclusion: In this multicentre study patients' self-assessment of disease activity (RAPID3 and 4) correlated strongly with that of rheumatologists (DAS44, CDAI, SDAI), indicating that patients are able to self-assess their disease activity. This provides a rationale to further explore the use of smartphone technology for tight disease monitoring in order to help the rheumatologist to optimize RA management. Whether or not the use of a WebApp for self-assessment will lead to better treatment outcomes will have to be shown in future studies.

Figure 1: Pearson Correlation at Baseline – RAPID3 and DAS44 at baseline as primary endpoint.

Disclosure: R. Mueller, None; **U. Walker**, None; **D. Kyburz**, None; **R. Theiler**, None; **A. Forster**, None; **F. Ganz**, None; **P. Dufner**, None.

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Elevations of Certain Memory-Effector T Cell and Inflammatory Monocyte Subpopulations in Rheumatoid Arthritis Are Associated with the Presence of Subclinical Coronary Artery Atherosclerosis. Robert Winchester[1], Jon T. Giles[1], Simona Nativ[2], Hui-Zhu Zhang[1], Kendall Downer[1] and Joan Bathon[1]. [1]Columbia University, New York, NY, [2]Morristown Medical Center, Morristown, NJ.

Background/Purpose: Factors that identify cardiovascular disease (CVD) fully in RA are lacking. Peripheral blood mononuclear cell (PBMC) subsets in RA patients differ markedly, on average, from non-RA controls in T-cell activation/differentiation to memory effector status and in the degree monocytes exhibit an intermediate 'inflammatory' phenotype. We hypothesized that elevations in these subpopulations would distinguish those with subclinical atherosclerosis.

Methods: Patients with RA and no clinical CVD underwent cardiac computed tomography (CT). Coronary arterial calcium (CAC) was quantified by the Agatston method. PBMC subsets were assessed by multiparameter flow cytometry. Multivariable linear and logistic regression were used to assess the associations between PBMC subpopulations and CAC, adjusting for relevant confounders associated both with PBMC subsets of interest and CAC. The area under the receiver operator curve (AUC) was used to estimate the contribution of covariates on the prediction of any CAC.

Results: 72 RA patients [mean age 54±14 years; 84% female; shared epitope positive=64%, median RA duration=6.6 years; median DAS28=3.9; current biologic use in 31%] were studied. Any CAC [CAC>0] was observed in 34%. In univariate analyses, compared with patients with no CAC, those with CAC had significantly higher percentages of circulating CD4 T cell subsets denoting activation ($CD4^+HLA\text{-}DR^+$, $CD4^+CD28^-HLA\text{-}DR^+$), differentiation to memory effector ($CD4^+CD28^-HLA\text{-}DR^+$, $CD4^+CD56^+CD57^+$), and acquisition of NK receptors ($CD4^+CD56^+CD57^+$) and similar increases of analogous CD8 T cell subsets, along with increases in the proportion of intermediate $CD14^{++}CD16^+$monocytes. The CD4 and CD8 subsets were highly correlated, while the $CD14^{++}CD16^+$monocyte subset was independent of the CD4 and CD8 subsets. In multivariable models including all non-collinear PBMC subsets of interest, only levels of $CD4^+CD56^+CD57^+$ T cells and $CD14^{hi}CD16^+$monocytes remained significantly associated with the presence of CAC after adjusting for relevant RA and CVD risk factors (Figure). CRP, serum IL-6 and DAS28 were not associated with CAC. The AUC for any CAC for the model containing only the two PBMC subsets of interest was 0.76 (95%CI=0.64–0.87), this increased to 0.89 (95%CI 0.82–0.96) with the addition of age and systolic blood pressure to the model. Neither PBMC subset of interest was associated with the extent of CAC within those with a positive CAC score.

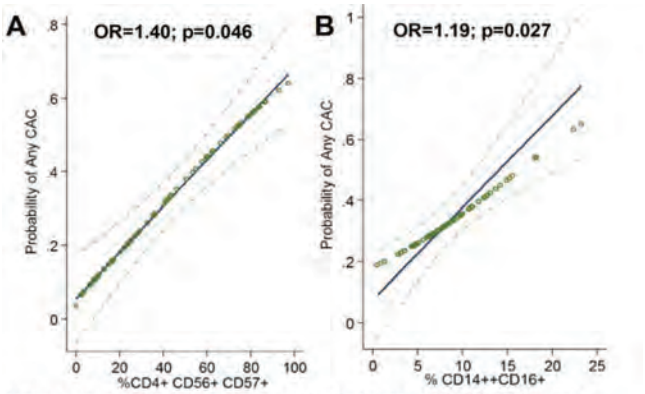

Figure. Crude and Adjusted Associations of the Proportions of $CD4^+CD56^+CD57^+$ and $CD14^{++}CD16^+$ Cells with the Probability of Any CAC. Crude associaitons are depicted by open circles. Adjusted associations are depicted with the solid least squares indicator and 95% confidence interval (light dashed line). Each unit increase in the square root of $\%CD4^+CD56^+CD57^+$ was associated with a 40% higher adjusted odds of any CAC (Panel a; p=0.046) while each unit increase in $\%CD14^{++}CD16^+$ was associated with a 19% higher adjusted odds of any CAC (Panel b.; p=0.027). Adjustments for age, systolic blood pressure, and the other PBMC subset. Other RA and CVD risk factors were not retained in adjusted models as they were not associated with both the PBMC subsets of interest and the presence of CAC.

Conclusion: Subclinical atherosclerosis was robustly associated with levels of circulating PBMCs reflecting differentiation to memory effector status/acquisition of NK receptors and higher levels of intermediate (inflammatory) monocytes, independent of demographics, CVD risk factors, and, importantly, RA disease activity and severity. These factors may account for a portion of the unexplained contributors to enhanced atherogenesis in RA.

Disclosure: R. Winchester, None; **J. T. Giles**, None; **S. Nativ**, None; **H. Z. Zhang**, None; **K. Downer**, None; **J. Bathon**, None.

2973

The Multi-Biomarker Disease Activity Score As a Predictor of Radiographic Progression in a Registry of Patients with Rheumatoid Arthritis. Eric H. Sasso[1], George Wu[1], CC Hwang[1], Michael E. Weinblatt[2], Nancy A. Shadick[2], Claire Alexander[1] and Oscar Segurado[1]. [1]Crescendo Bioscience Inc., South San Francisco, CA, [2]Brigham and Women's Hospital, Boston, MA.

Background/Purpose: This study evaluated the association between baseline disease activity, as assessed with the multi-biomarker disease activity (MBDA) blood test, CRP or clinical measures, and the rate of radiographic progression over 2 years for patients with rheumatoid arthritis (RA) receiving stable therapy in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) Registry.

Methods: MBDA scores, CRP, DAS28-CRP, CDAI, RAPID3, and radiographic progression were analyzed at baseline (defined as the initial visit in the BRASS registry), for 143 patients with RA who had received a stable treatment, i.e., with no addition or removal of DMARDs and irrespective of dosing, over 2 years. Radiographs of hands and wrists only, taken within 3 months of baseline in BRASS and 2 years later, were evaluated to determine the change per year in total Sharp score (ΔTSS). Radiographic progression (RP) was defined as ΔTSS >3 per year over 2 years. Predictive performance was assessed using AUROC. Associations with RP were evaluated using univariate and multivariate logistic regression adjusted for potential confounders.

Results: For 143 patients, mean age and disease duration were 59 and 18 years, respectively, with 84% female, 80% seropositive (RF+ and/or anti-CCP+), and 52% receiving MTX/non-biologic DMARD monotherapy, 19% a TNF inhibitor alone, 27% both in combination, and 2% not on any DMARD therapy. Mean baseline values were MBDA score=39, CRP=0.86 mg/dL,

DAS28-CRP=4.1, CDAI=24.8, RAPID3=8.1 and TSS=68. RP was observed in 18% (26/143) of patients. Better predictive accuracy for RP was observed for baseline MBDA score (AUROC=0.75), compared with baseline clinical CRP (AUROC=0.71), DAS28-CRP (AUROC=0.62), CDAI (AUROC=0.59) or RAPID3 (AUROC=0.50). Adjusting for BMI and baseline TSS, the significant independent predictors for RP were MBDA score (OR_{1SD}=2.90, 95% CI=1.69–4.97), CRP (OR_{1SD}=2.36, 95% CI=1.46–3.82), and DAS28-CRP (OR_{1SD}=1.74, 95% CI=1.04–2.93), but not CDAI (OR_{1SD}=1.46, 95% CI=0.89–2.41) and RAPID3 (OR_{1SD}=0.97, 95% CI=0.61–1.55). For patients with low CRP (≤1 mg/dL) at baseline, RP was observed in 34.8% (8/23) with high MBDA score (>44) versus 8.1% (7/86) with low/moderate MBDA score (≤44) (p=0.003).

Conclusion: Baseline MBDA score was a better predictor of radiographic progression over 2 years than CRP, DAS28-CRP, CDAI or RAPID3 in patients with RA on stable therapy from the BRASS registry.

Disclosure: E. H. Sasso, Crescendo Bioscience, 3; **G. Wu**, Crescendo Bioscience, 3; **C. Hwang**, Crescendo Bioscience, 3; **M. E. Weinblatt**, UCB, 2, Bristol-Myers Squibb, 2, Crescendo, 2, UCB, 5, Bristol-Myers Squibb, 5, Crescendo, 5; **N. A. Shadick**, Crescendo Bioscience, 2, Amgen, 2, UCB, 2, Abbvie, 2, Bristol Myers Squibb, 2, Genentech, 2; **C. Alexander**, Crescendo Bioscience, 3; **O. Segurado**, Crescendo Bioscience, 3.

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Multi-Biomarker Disease Activity Score Is Associated with Power Doppler Ultrasound in Patients with Rheumatoid Arthritis in Low Disease Activity State. Margaret H. Ma[1], Toby Garrood[2], Wanying Li[3], Nadine A. Defranoux[3], Gabrielle H. Kingsley[4], Andrew P. Cope[5] and David L. Scott[6]. [1]King's College Hospital, London, United Kingdom, [2]Guy's and St. Thomas' Foundation Hospital NHS Trust, London, United Kingdom, [3]Crescendo Bioscience Inc., South San Francisco, CA, [4]Kings College London, London, United Kingdom, [5]King's College London, London, United Kingdom, [6]King's College London, Department of Rheumatology, London, United Kingdom.

Background/Purpose: Rheumatoid arthritis (RA) patients increasingly achieve clinical remission with intensive treatment regimens. However, ultrasound (US) subclinical synovitis has been reported in remission states. The multi-biomarker disease activity (MBDA) blood test assesses overall RA disease activity.

The purpose of this study was to evaluate associations between US signals, MBDA score and its component biomarkers in the REMIRA cohort, a 1 year prospective observational study of patients with RA in low disease activity.

Methods: We studied 95 patients with RA on stable therapy for ≥6 months with DAS28 ≤3.2 for ≥1 month. Clinical measurements and serum samples were collected every 3 months for 1 year and US were conducted at baseline (BL) and 1 year. MBDA scores (range 1–100) were calculated from the serum concentrations of VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, YKL-40, MMP-1, MMP-3, leptin, resistin, SAA and CRP using the validated Vectra® DA algorithm. MBDA disease activity thresholds have been defined as remission (<26), low (26–29), moderate (30–44), and high (>44). Power doppler (PD) and synovial hypertrophy (SH) of bilateral MCP joints and wrists were assessed by the same sonographer on the same machine and scored 0–3 for each joint and summed to provide total PD and SH scores (range 0–36). More stringent modified PD (mPD) and SH (mSH) scores were derived, based on MCP joint measures only, using signal thresholds determined from the distributions of BL PD and SH signals measured in a subset of patients who maintained no swollen joints (SJC28=0) without intensification of therapy over 1-year follow-up. Correlations between PD or SH and DAS28, MBDA scores or their components were evaluated by Spearman's rank correlation.

Results: Mean (±SD) BL disease activity measures were: DAS28 2.1 (±1.0), MBDA score 30 (±13), PD score 3.7 (±5.1), mPD 1.1 (±2.7), SH score 12.1 (±4.7), and mSH 0.4 (±1.1). At BL, 67% of patients were in DAS28 remission, 43% were in MBDA remission, 91% had PD>0 (31% had mPD>0) and 100% had SH>0 (21% had mSH>0). Statistically significant correlations (p<0.05) with PD and mPD were observed at both time points for MBDA scores (correlations ranged from 0.22–0.36), DAS28 (r=0.22–0.30), SJC28 (r=0.28–0.39), and four MBDA biomarker components: CRP (r=0.21–0.31), SAA (r=0.21–0.35), IL-6 (r= 0.26–0.39) and MMP-3 (r=0.24–0.36). The frequency of having MBDA score <26 was significantly greater in patients with mPD=0 than those with mPD>0 (52% vs. 24% at BL; 36% vs. 9% at 1 year). Correlations at BL or 1 year between SH or mSH and DAS28, MBDA score or components were weak or non-significant.

Conclusion: Ultrasound PD and SH signals could be detected in most RA patients of the REMIRA cohort. After applying a modified, more stringent, scoring system, 21% to 31% had detectable US signals. We have shown, for the first time, significant correlations with PD and mPD scores for MBDA scores and some of its component biomarkers. Correlations were also found with DAS28 and SJC28. Remission by MBDA score was significantly associated with mPD=0. These results suggest that MBDA score detect low grade inflammation and subclinical synovitis in patients with RA in clinical remission or low disease activity.

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Residual Large Joint Synovitis By Power Doppler Ultrasonography Is Associated with Higher Disease Activity and Significant Impact of Disease in Multi-Ethnic Asian Patients with Established Rheumatoid Arthritis. Yu Xiao Guo[1], Manjari Lahiri[2] and Peter Cheung[2]. [1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore, [2]Division of Rheumatology, National University Hospital, Singapore, Singapore.

Background/Purpose: Regular monitoring of disease activity with appropriate modification of disease-modifying anti-rheumatic drug (DMARD) therapy results in improved radiographic and functional outcomes in patients with rheumatoid arthritis (RA). Large joint involvement has been shown to impact significantly on both disease activity and disability. Power Doppler ultrasound (PDUS) can effectively detect subclinical active synovitis not appreciated by clinical examination. The objective is to evaluate the presence of residual large joint disease in established RA patients in a multi-ethnic Asian cohort using PDUS as the reference standard, and whether there is increased impact and disability.

Methods: Patients with established RA (ACR 1987 criteria) and stable disease were recruited as part of a randomized controlled single centre study, evaluating the use of ultrasonography feedback as training tool for patient self-assessment of synovitis. At baseline, 28 joints (2 shoulders, 2 elbows, 2 wrists, 10 MCP, 10 PIP, 2 knees) of each patient were assessed for synovitis in B-mode (from 0=absence of synovial thickening to 3=marked synovial thickening) and PDUS (from 0=absence of signal, no intra-articular flow to 3=marked signal in more than half of the synovial area). Semiquantitative grade ≥1 on PDUS was considered as active synovitis. Patients with residual large joint disease (shoulders, elbows, knees) on PDUS were evaluated for differences in baseline demographics, disease activity, physical function (modified Health Assessment Questionnaire, mHAQ and SF12-physical component score) and impact of disease (Rheumatoid Arthritis Impact of Disease Score, RAID) with patients that did not have large joint involvement. Measures of association were evaluated using logistic regression.

Results: Of the 101 patients included, median (IQR) age was 54 (48, 63) years old, Chinese (73%), female (81%), non-smokers (85%), and 77% were positive for either rheumatoid factor or anti citrullinated peptide antibody. Median disease duration was 5 (2, 9) years with PDUS-DAS28 of 3.2 (2.6, 4.2). PDUS indicated a large proportion of patients with residual large joint involvement (44%) – 21% of shoulders, 20% of elbows and 6% of knees involved. The most common small joint involvement was the wrist (27%) with MCP and PIP joints rarely involved (both 2% respectively). A higher proportion of Chinese patients had large joint involvement (p=0.03). No significant differences in other baseline patient characteristics such as age, sex and seropositivity were seen. Patients with large joint disease had higher PDUS-DAS28 (p<0.001), ESR (p=0.002) and were more likely to receive combination triple therapy (DMARDs) (p=0.008). Residual large joint involvement was significantly associated with mHAQ>0.5 (p=0.03), lower SF12 physical component scores (p=0.02) and higher RAID score (p<0.001).

Conclusion: Multi-ethnic Asian RA patients with relatively stable established disease have a high proportion of residual PDUS large joint activity that significantly impacts on patients. Physicians should aggressively treat this subset of patients with either systemic/local therapies to prevent further disability.

Disclosure: Y. X. Guo, None; **M. Lahiri**, None; **P. Cheung**, None.

2976

Lung Ultrasound Screening for Interstitial Lung Disease in Rheumatoid Arthritis. Comparison with Usual Detection Algorithms in Clinical Practice. Marco Antivalle, Michel Chevallard, Michele Battellino, Maria-Chiara Ditto, Valentina Varisco, Federica Rigamonti, Alessandra Mutti, Fabiola Atzeni, Alberto Batticciotto and Piercarlo Sarzi-Puttini. L. Sacco University Hospital, Milano, Italy.

Background/Purpose: Interstitial lung disease (RA-ILD) is one of the most serious extraarticular complications of rheumatoid arthritis (RA). Presently, it is not clear which is the best strategy for the detection of RA-ILD. We have previously reported on the feasibility and accuracy of lung ultrasound (LUS) in the detection of RA-ILD (1). Aim of the present study was to assess the performance of LUS in the detection of RA-ILD in clinical practice, and to compare its accuracy with the detection algorithms usually adopted.

Methods: 147 unselected RA patients (114 F and 33 M) were studied. In all patients, LUS was performed as previously described (1) by an expert physician (MC), blinded to clinical and HRCT data, using a standard commercially available US equipment (Esaote MyLabFive) with a 7.5–12 MHz probe. By LUS, RA-ILD was defined by a B-lines score >10. The results of the LUS study were compared to clinical, pulmonary function tests, chest X-ray, and lung CT (HRCT) data, as available from clinical records. Four clinical algorithms (ALG) were identified: ALG 1: presence of dyspnea (NYHA class >=2) and/or bibasilar crackles; ALG 2: as ALG 1 + FVC < 80%; ALG 3 as ALG 1 + DLCO<80%; ALG 4 as ALG 1 + evidence of ILD at chest X-ray. Sensitivity, specificity, and predictive values of LUS and clinical algorithms with reference to HRCT were calculated, and compared by McNemar test.

Results: RA-ILD was detected by LUS in 41/146 (28.1%) patients. Clinical data, FVC, DLCO, X-ray, and CT were available in 146(100%), 63(43%), 61(42%), 102(70%), and 67(46%) cases respectively. LUS showed a significantly higher accuracy in the detection of RA-ILD than clinical algorithms (Table 1). 33/64(52%) asymptomatic patients, and 31/82(38%) patients with clinical suspicion of RA-ILD, were not further evaluated by neither PFTs nor by HRCT. Overall, LUS detected unsuspected signs of RA-ILD in 9/146(6%) patients (Fig 1).

Conclusion: LUS is more accurate than usual clinical algorithms in the evaluation of RA-ILD, and allows the detection of a substantial number of unsuspected cases.

Tab. 1 – Sensitivity, specificity, and predictive power of LUS and clinical algorithms in the detection of RA-ILD. HRCT is the gold standard.

		LUS	ALG 1 (crackles a/o dyspnea)	ALG 2 (ALG 1 +FVC < 80%)	ALG 3 (ALG 1 + DLCO < 80%)	ALG 4 (ALG 1 + X-ray +)
Sensitivity % (IC 95%)		87.0 (76.0–93.6)	78.3 (66.2–87.0)	9.5 (3.3–22.7)	47.6 (32.9–62.7)	41.7 (26.7–58.2)
Specificity, % (IC 95%)		72.7 (60.3–82.6)	43.2 (31.3–55.8)	96.0 (84.4–99.4)	52.0 (37.0–66.7)	89.3 (74.5–96.3)
PPV % (IC 95%)		62.5 (49.8–73.8)	41.9 (30.1–4.5)	66.7 (51.1–79.4)	45.5 (31.0–60.7)	62.5 (45.8–76.8)
PPN% (IC 95%)		91.4 (81.4–96.5)	79.2 (67.2–87.8)	55.8 (40.5–70.1)	54.2 (39.0–68.7)	78.1 (61.8–89.1)
p*	total	–	0.02	0.005	0.05	0.05
	sensitivity	–	0.687	0.000	0.021	0.070
	specificity	–	0.007	0.039	0.549	0.227

McNemar test: * = p refers to the comparison of LUS with clinical algorithms

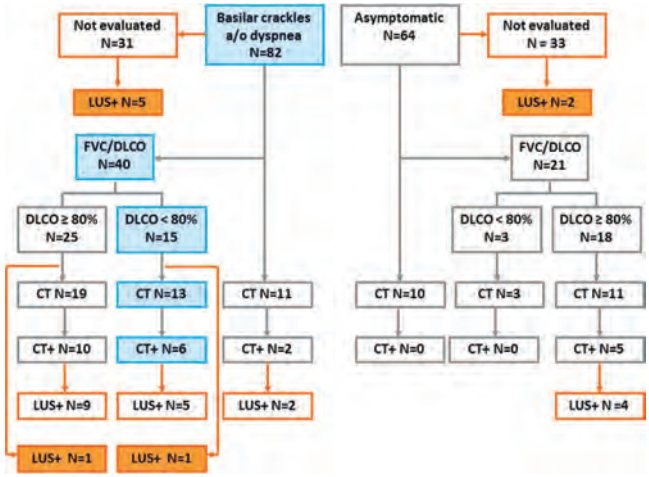

Fig. 1: LUS RA-ILD in the population (LUS+). Orange-filled boxes show LUS-positive patients which were unsuspected on clinical ground

References:
Cogliati C, et al. Rheumatology (Oxford). 2014 Mar 31. [Epub ahead of print]

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ACR Concurrent Abstract Session
Sjögren's Syndrome II: Insights into Pathophysiology
Wednesday, November 19, 2014, 9:00 AM–10:30 AM

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Distinct Serum Protein Signature and Novel Biomarkers of primary Sjogren's Syndrome Revealed by comprehensive High-Throughput Proteomic Analysis. Ayumi Nishikawa[1], Katsuya Suzuki[1], Yoshiaki Kassai[2], Yuumi Gotou[3], Takahiro Miyazaki[2], Maiko Takiguchi[4], Masaru Takeshita[1], Atsuko Murota[1], Rimpei Morita[5], Akihiko Yoshimura[5] and Tsutomu Takeuchi[1]. [1]Keio University School of Medicine, Tokyo, Japan, [2]Takeda Pharmaceutical Company Limited, Kanagawa, Japan, [3]Takeda Pharmaceutical Company Limited, Tokyo, Tokyo, Japan, [4]Takeda Pharmaceutical Company Limited, Tokyo, Japan, [5]Department of Microbiology and Immunology, Keio University School of Medicine, Tokyo, Japan.

Background/Purpose: The EULAR SS Disease Activity Index (ESSDAI) is currently used as an objective evaluation method of clinical disease activity in clinical research into primary Sjogren's syndrome (pSS). This comprehensive indicator reflects patient signs and symptoms and organ involvement. However, a useful substitute serum biomarker of disease activity has not been established. Although several proteomic investigations of small and large salivary and lachrymal glands have been recently reported, information on serum protein is insufficient. Here, we aimed to reveal a distinct serum protein signature of pSS and identify novel biomarkers of disease activity.

Methods: We studied 90 serum samples from 30 pSS patients, 30 untreated rheumatoid arthritis (RA) patients as non-SS autoimmune disease controls, and 30 healthy control (HC) subjects. 1128 serum proteins, including inflammatory cytokines and chemokines, were quantitatively measured by comprehensive high-throughput proteomics assay using nucleic acid aptamers (SOMAscan™ Assay; Somalogic Inc., CO, USA). Associations between serum protein concentrations, clinical indicators and laboratory test results were statistically analyzed.

Results: After exclusion of 28 proteins for statistical reasons, 1100 of 1128 proteins in 90 subjects were analyzed. We first screened differentially up- and down-regulated proteins among the three groups, by which 195 proteins, including some overlap (85; pSS vs HC, 124; RA vs HC, 81; pSS vs RA), were statistically extracted ($p<0.05$ in the t-test and U-test, and fold change ≥ 1.2 or ≤ 0.83). Sixty proteins were up-regulated in pSS compared with HC, including BAFF (pSS patients/healthy control subjects: 9.4-fold), I-Tac (1.82-fold), vWF (1.57-fold), β2-microglobulin (1.47-fold), while 25 were down-regulated, including Immunoglobulin (Ig) D (0.21-fold), CTAP-III (0.79-fold), and GPIIbIIIa (0.83-fold). Enrichment analysis for characterization of up-regulated genes identified these as cytokines and chemokines including TNF-associated molecules and coagulation factors, indicating a serum protein signature in pSS. Multivariate analysis of these 60 proteins and ESSDAI identified 15 proteins with a statistically positive correlation, including TNF-associated molecules (BAFF, sCD163, TRAIL1-R4 and others), LAG-3, β2-microglobulin, and others.

Conclusion: This comprehensive proteomics analysis highlighted a dysregulated immunity and coagulation signature in patients with pSS. Fifteen up-regulated proteins were found to be correlated with disease activity. These proteins are candidate serum biomarkers for use in the clinical prediction of disease activity of pSS.

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Characterization of the Sjögren's Syndrome Intergenic Non-Coding RNA 1 (SSINCR1). John A. Ice[1], He Li[1], Indra Adrianto[1], Mikhail G. Dozmorov[1], Astrid Rasmussen[1], Graham B. Wiley[1], Jennifer A. Kelly[1], Kimberly S. Hefner[2], Donald U. Stone[3], Raj Gopalakrishnan[4], David M. Lewis[3], Stephen Young[3], Michael D. Rohrer[4], Juan-Manuel Anaya[5], Swamy Venuturupalli[6], Barbara M. Segal[7], Nelson L. Rhodus[4], Lida Radfar[3], Michael H. Weisman[8], Judith A. James[1], Courtney G. Montgomery[1], R. Hal Scofield[9], Patrick M. Gaffney[1], Linda F. Thompson[1], A. Darise Farris[10], Susan Kovats[1], Jonathan D. Wren[1], Kathy L. Sivils[3] and Christopher J. Lessard[1]. [1]Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Hefner Eye Care and Optical Center, Oklahoma City, OK, [3]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [4]University of Minnesota, Minneapolis, MN, [5]Center for Autoimmune Diseases Research (CREA), Universidad del Rosario., Bogota, Colombia, [6]Cedars-Sinai Medical Center, West Hollywood, CA, [7]Hennepin County Medical Center, Minneapolis, MN, [8]Cedars-Sinai Medical Center, Los Angeles, CA, [9]US Department of Veterans Affairs Medical Center, Oklahoma City, OK, [10]Oklahoma Medical Research Foun, Oklahoma City, OK.

Background/Purpose: Sjögren's syndrome (SS) is a common autoimmune disorder characterized by immune-mediated exocrine gland destruction and systemic inflammatory responses that contribute to clinical heterogeneity. Widespread dysregulation of transcribed RNAs in SS, including coding and non-coding elements, has been identified, but the complex regulatory mechanisms governing these responses are poorly understood. We performed an RNA-sequencing (RNA-seq) study that identified over 2,600 differentially expressed (DE) transcripts associated with SS, including 969 long non-coding RNAs (lncRNAs). This study sought to validate, replicate, and functionally characterize one upregulated lncRNA mapped to chromosome 2p25.1, SSINCR1, to better understand its role in SS pathogenesis.

Methods: Whole blood RNA from 27 healthy controls and 57 SS patients was sequenced, and 2,632 statistically significant DE transcripts were identified. Technical validation and replication of SSINCR1 upregulation was assessed by qRT-PCR in an independent set of 36 SS patients and 21 controls. Bioinformatic analyses using GAMMA-seq and the lncRNAtor database were performed to identify co-expression patterns of SSINCR1 with other coding and non-coding transcripts and to identify candidate protein binding partners. To determine cellular expression patterns of SSINCR1, we employed fluorescence-assisted cell sorting (FACS) staining for 10 distinct immune cell subsets in a healthy control followed by RNA isolation and assessed SSINCR1 expression by qRT-PCR. Statistical comparisons were made using t-tests and Pearson correlations.

Results: RNA-seq showed significant upregulation of SSINCR1 when comparing healthy controls and SS patients ($P_{adj}=3.69\times10^{-5}$; Fold Change=2.4). Technical validation by qRT-PCR using the RNA-seq cDNA library confirmed this finding ($P=0.0096$), and correlation with RNA-seq results was observed ($r=0.869$). Transcript expression in an independent sample set replicated and confirmed SSINCR1 upregulation ($P=0.0183$). Co-expression patterns by GAMMA-seq showed T, NK, and dendritic cell activation, development, and proliferation, and assessment of SSINCR1 using lncRNAtor suggested protein binding with cyclin T1 and FIP1L1. FACS analysis showed that SSINCR1 expression levels were highest in the $CD3^+CD56^+$ compartment (containing NKT cells; relative units [RU]= 8.25), followed by $CD8^+$ T cells (RU=3.34), CD56int NK cells (RU=2.08), CD56hi NK cells (RU=0.83), and $CD4^+$ T cells (RU=0.81). Expression was not detected in $CD141^+$ and $CD1c^+CD11c^+$ myeloid DCs, monocytes, B cells, or pDCs.

Conclusion: We have identified, technically validated, and independently replicated the upregulation of a novel SS lncRNA, SSINCR1. We show that transcript expression is highly enriched in CD4+ and CD8+ T cells, NKT cells, and NK cells. Ongoing studies are assessing potential protein binding partners and SSINCR1 expression in refined T and NK subsets and in expanded groups of affected and healthy individuals to determine subset-specific DE. This study establishes SSINCR1 as the first lncRNA associated with SS and lays the groundwork for further functional characterization in the pathogenesis of this complex disorder.

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Nucleic Acid Sensing Receptors TLR7, RIG-I and MDA5 Collaborate in Driving the Systemic IFN Signature and Amplify the Pathogenic Loop: Potential New Targets for Therapy in Primary Sjogrens Syndrome. Naomi I Maria[1], Cornelia G. van Helden-Meeuwsen[1], Eline C. Steenwijk[1], Arne S. IJpma[2], Wouter Beumer[1], Zana Brkic[1], Virgil A. Dalm[1], Paul L. van Daele[1], P. Martin van Hagen[1], Peter J. van der Spek[2], Hemmo A. Drexhage[1] and Marjan A. Versnel[1]. [1]Erasmus Medical Center, Immunology, Rotterdam, Netherlands, [2]Erasmus Medical Center, Bioinformatics, Rotterdam, Netherlands.

Background/Purpose: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by autoantibodies targeting RNA-associated antigens, anti-SSA/SSB. The IFN-signature is present in over half of pSS patients, and is associated with higher disease-activity and autoantibody presence. Endosomal Toll-like receptors, TLR7 and TLR9, are crucial for both the generation of auto-antibodies by B-cells and immunecomplex-mediated IFN production by plasmacytoid Dendritic Cells (pDCs) in autoimmunity. Recently opposing effects were described for TLR7 and TLR9 in murine lupus-models, where TLR7-deletion limited autoimmunity and TLR9-deletion paradoxically exacerbated disease. Interestingly, we recently found the TLR7-pathway upregulated in IFNpositive pDCs of pSS patients, whereas TLR9 was not. Here we set out to further investigate this imbalanced endosomal TLR-signaling in IFN-driven pSS.

Methods: Blood samples were obtained from 33 Healthy controls (HC) and 58 pSS patients, diagnosed according to the 2002 American-European criteria, and stratified according to their IFNsignature. Fluorescence-activated cell sorting was used to isolate CD123+BDCA4+ pDCs, CD14+ monocytes, CD3+ T-cells and CD19+ B-cells >98% purity, from peripheral blood mononuclear cells (PBMCs). Genome-wide Microarray analysis conducted on sorted pDCs and monocytes revealed increased expression of cytoplasmic and endosomal pattern recognition receptors: TLR7, retinoic acid inducible gene-I (RIG-I/*DDX58*), melanoma differentiation associated gene-5 (MDA-5/*IFIH1*), and further downstream MyD88-dependent signaling, confined to IFNpositive patients. mRNA expression of the resulting differentially expressed genes (DEGs), as assessed by Ingenuity pathway analysis (IPA), was validated in sorted cell-suspensions and whole blood (Paxgene) using real-time quantitative PCR. To further clarify the possible TLR7-driven activation of the IFN signature, PBMCs of HC were stimulated *in vitro*with imiquimod, a TLR7 agonist, and inhibited with the TLR7 antagonist IRS661.

Results: Confirming our microarray results, we found an upregulation of TLR7 ($p<0.05$), *but not TLR9*, in IFNpositive pDCs, monocytes, B-cells and in whole blood ($p<0.0001$) as well as further downstream MyD88, RSAD2 and IRF7 ($p<0.001$). We also observed the upregulation of intracellular RNA-sensing receptors RIG-I and MDA-5 ($p<0.01$), recently described to collectively initiate effective IFN signaling. This widespread upregulation of TLR7 and its downstream signaling pathway is confined to IFNpositive pSS patients. *In vitro*studies with HC-PBMCs reveal that triggering of the TLR7-pathway by Imiquimod causes further upregulation of the other RNA-sensing receptors RIG-I and MDA5, inflammatory cytokines, IFN-inducible genes and also BAFF. Specific TLR7-inhibition subsequently showed a dose-dependent decrease.

Conclusion: Taken together, these RNA-sensing receptors — TLR7, RIG-I and MDA5 — seem to collaborate in amplifying the pathogenic IFN-driven loop in pSS. A better understanding of this unrestrained and potentially autoreactive loop reveals novel targets for therapeutic interventions in pSS.

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Genome-Wide DNA Methylation Analysis of CD19+ B Cells in Primary Sjögren's Syndrome. Gunnel Nordmark[1], Juliana Imgenberg-Kreuz[2], Jonas Carlsson Almlöf[2], Jessica Nordlund[2], Roald Omdal[3], Katrine B. Norheim[3], Maija-Leena Eloranta[4], Lars Rönnblom[4] and Johanna K. Sandling[2]. [1]Rheumatology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden, [2]Molecular Medicine and Science for Life Laboratory, Department of Medical Sciences, Uppsala University, Uppsala, Sweden, [3]Clinical Immunology Unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway, [4]Department of Medical Sciences, SciLife Lab, Rheumatology, Uppsala University, Uppsala, Sweden, Uppsala, Sweden.

Background/Purpose: Increasing evidence suggests an epigenetic contribution to the pathogenesis of autoimmune diseases, including primary Sjögren's Syndrome (pSS) (1). A genome-wide DNA methylation study in T cells from patients with pSS and controls identified a large number of differentially methylated genes (2). B cells play an important role in pSS with production of autoantibodies and the potential development of B cell lymphomas. The aim of this study was to investigate DNA methylation profiles in purified CD19+ B cells from patients with pSS and healthy controls.

Methods: Seventeen female patients with pSS, mean age 53.2 years and 28 healthy blood donors, 11 females/17 males, mean age 46.7 years were included. All patients fulfilled the AECG criteria for pSS, 94.1 % were anti-SSA and/or -SSB positive and none of the patients had lymphoma. DNA was prepared from CD19+ B cells positively selected from fresh blood samples. Genome wide DNA methylation profiles were generated on the Illumina HumanMethylation450 BeadChip array. After quality control and normalization, 383 258 CpG sites remained. A threshold of 10% difference between cases and controls in average methylation level per CpG site was applied. Age and sex were included as covariates and a Bonferroni corrected p-value of $<1\times10^{-7}$ was considered significant.

Results: We identified 482 differentially methylated CpG sites, 91 hypomethylated annotated to 63 genes and 391 hypermethylated annotated to 316 genes. Pathway analysis of genes with hypomethylated sites showed over-representation in Interferon signalling genes, and for genes with hypermethylated sites Syndecan-1-mediated signalling events and the EGF receptor signalling pathway. Disease association of genes with differentially methylated sites showed enrichment for genes implicated in cancer, viral infections and B cell and follicular lymphomas. The most distinct difference in average methylation was observed in the interferon-induced gene *IFI44L* with 31 % decreased methylation in pSS CD19+ B cells compared to control B cells.

Conclusion: Our results demonstrate that DNA methylation is altered in CD19+ B cells from patients with pSS, which underscores the importance of these cells in the pathogenesis of the disease. The significance of genes in the interferon system is highlighted and the enrichment of genes involved in B cell lymphoma is intriguing and warrants further investigation.

References:

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Prognostic Value of the Complex P2X7 Receptor-Inflammasome in Patients with Primary Sjögren's Syndrome at Lymphoma Risk. Chiara Baldini[1], Eleonora Santini[2], Chiara Rossi[2], Francesca Sernissi[1], Daniela Martini[1], Alessia Gallo[3], Valentina Donati[2], Nicoletta Luciano[1], Francesco Ferro[1], Illias Alevizos[3], Anna Solini[2] and Stefano Bombardieri[2]. [1]Rheumatology Unit, Pisa, Italy, [2]Rheumatology Unit, University of Pisa, Pisa, Italy, [3]NIDCR, Bethesda, MD.

Background/Purpose: Pro-inflammatory P2X7-receptor has been recently implicated in the pathogenesis of primary Sjögren's syndrome (pSS), suggesting that it may be involved in the initiation and amplification of the innate immune response in salivary glands. In particular, previous studies have shown that the expression of P2X7R message in minor salivary glands was significantly higher in patients with positive anti-Ro-SSA and that it correlated with the minor salivary gland biopsy focus score. To date, however, no data are available on the role of the complex P2X7 receptor-inflammasome in the prognostic stratification of patients with pSS, specifically concerning their risk for lymphoma. The aim of this study was, therefore, to explore any eventual association or correlation between P2x7 mRNA levels in pSS minor salivary glands and in blood peripheral lymphocytes and traditional histological and serological risk factors for lymphoma in pSS.

Methods: Consecutive, unselected patients with a diagnosis of pSS made according to the AECG 2002 were enrolled in this study. All subjects had a standardized evaluation for pSS which included oral and ophthalmologic examinations, laboratory testing and a rheumatologic evaluation. Mononuclear cells were isolated from fresh blood by density gradient centrifugation. Total RNA was extracted from the frozen salivary gland tissue and from the frozen pellet of lymphocytes and expression of the P2X7R mRNA was determined by real-time PCR. Minor salivary gland biopsies were re-evaluated by light microscopy in order to identify GC-like structures. For statistical comparisons, non parametric Mann-Whitney test and Spearman's rank correlation coefficient were employed.

Results: Twenty pSS subjects were enrolled in the study. At diagnosis, 20% of pSS patients had GC-like structures in their salivary glands. P2X7R mRNA expression was significantly higher in the salivary glands of pSS with GC-like structures than in those without GC-like structures and correlated significantly with minor salivary gland focus score ($r=0.688$, $p=0.000$), beta-2 microglobulin levels ($r=0.538$, $p=0.02$) and IgG levels ($r=0.452$, $p=0.02$). Moreover, P2X7R mRNA salivary expression levels were significantly higher in patients with clinically evident major salivary glands enlargement and/or disease specific parenchyma dyshomogeneity documented by salivary gland ultrasonography. No significative correlations were found between P2X7R expression in peripheral lymphomonocytes and all the histological and laboratory risk factors for lymphoma examined in the study.

Conclusion: The results of this proof of concept study reinforce the potential involvement of the salivary P2X7R in pSS chronic salivary inflammation which have consistently been associated with an increased risk of malignant lymphomas. Further investigation are mandatory to clarify whether salivary P2X7R expression might be useful to identify pSS patients at lymphoma risk.

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Identification of Whole Blood Gene Expression Signature in Primary Sjögren's Syndrome Associated Lymphoma. Shereen Al-Ali[1], Simon Cockell[2], Andrew Skelton[3], Katherine James[2], Jessica Tarn[2], David Young[3], Bridget Griffiths[4], Simon Bowman[5], James Locke[2] and Wan-Fai Ng[2]. [1]University of Basrah, Basrah, Iraq, [2]Newcastle University, Newcastle upon Tyne, United Kingdom, [3]Newcastle University, Newcastle Upon Tyne, United Kingdom, [4]Freeman Hospital, Newcastle Upon Tyne, United Kingdom, [5]University Hospital Birmingham, Birmingham, United Kingdom.

Background/Purpose: Primary Sjögren's syndrome (pSS) is associated with a substantially increased risk of lymphoma development. The aim of our study is to identify a whole blood gene expression signature of pSS-associated lymphoma and to explore the potential biological significance of such signature using pathway and network analysis.

Methods: Whole blood RNA samples (n=144) from pSS patients and healthy controls taken part in the UK primary Sjögren's syndrome registry (UKPSSR). All patients fulfilled the AECG criteria and were stratified into five clinical subsets (pSS = 61, pSS with lymphoma = 16, pSS with other cancers=21, pSS with paraproteinemia = 23 and healthy controls = 23). RNA was extracted and globin mRNA were removed using GLOBINClear kit. Whole genome microarray (illumina, HumanHT-12 v4 BeadChips) was used for gene expression profiling. Microarray data were analyzed by R Bioconductor. The differentially expressed genes between the pSS-associated lymphoma group and pSS patients without lymphoma were validated using RT-PCR.

Results: Distinct gene expression profiles and similar differentially expressed genes were observed when comparing each clinical subset with healthy controls. Comparison between the "Lymphoma" group and those without lymphoma revealed 25 upregulated genes and 43 downregulated genes. When compared with pSS patients with other cancers, only one gene was differentially expressed and it was

downregulated in the "lymphoma" group. No differentially expressed gene were found when comparisons were made between other clinical subsets. Go terms and KEGG pathway analysis revealed 14 biological processes and 23 different biological pathways that might be important which included (e.g. mismatch Repair, T-cell receptor signaling pathway and pathways in cancer).

Conclusion: A potential gene expression signature for pSS-associated lymphoma was identified. Further experiments to validate the biosignature with another cohort and to evaluate the sensitivity and specificity of such signature are in progress.

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ACR Concurrent Abstract Session
Spondyloarthropathies and Psoriatic Arthritis VI - Imaging and Biomarkers
Wednesday, November 19, 2014, 9:00 AM–10:30 AM

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Infliximab Added to Naproxen Does Not Increase Frequency of New Fatty Lesions on MRI of the Sacroiliac Joints and of the Spine As Compared to Naproxen Alone in Early Axial Spondyloarthritis. Denis Poddubnyy and Joachim Sieper. Charité Universitätsmedizin Berlin, Berlin, Germany.

Background/Purpose: Fatty lesions of the bone marrow in the axial skeleton (sacroiliac joints – SIJ, and spine) on magnetic resonance imaging (MRI) are considered nowadays as earliest post-inflammatory changes preceding new bone formation in axial spondyloarthritis (axSpA). It has been shown in several trials with tumour necrosis factor (TNF) α inhibitors that resolution of inflammation under anti-TNF therapy is associated with an increase of a fatty lesion score. This raised concerns that TNF blockers might therefore promote the process of new bone formation in axSpA. The aim of the current analysis was to investigate the difference in fatty lesions formation rates in patients treated with the TNF inhibitor infliximab (IFX) added to naproxen (NPX) as compared to NPX alone given over 28 weeks in patients with early axSpA.

Methods: Part I of the INFAST study was a double-blind, randomized controlled trial of IFX in biologic-naïve patients 18–48 years of age with early (<3 years symptom duration), active axSpA with signs of active sacroiliitis on MRI. A total of 158 patients were randomized (2:1) to receive 28 weeks of treatment with either intravenous IFX 5 mg/kg (weeks 0, 2, 6, 12, 18, and 24) + NPX 1000 mg/d (n=106) or intravenous PBO+NPX 1000 mg/d (n=52). MRIs of the SIJ and of the spine were performed at baseline and week 28 and were scored according to the Berlin scoring system for active inflammation and for fatty lesions, including a detailed fatty degeneration score for the SIJ by a reader who was blinded for clinical data including treatment allocation.

Results: Complete MRI sets (baseline and week 28, both STIR and T1-weighted sequences) were available in 147 patients for the spine (n=99 IFX+NPX, n=48 NPX alone) and in 143 patients for the SIJ (n=97 IFX+NPX, n=46 NPX alone). At baseline there were no meaningful differences between treatment group neither in osteitis nor in fatty lesion scores. In both treatment groups there was a significant reduction of inflammation in the spine and in the SIJ at week 28 as compared to baseline – ***table***, which was however more prominent in the combined treatment group since after 28 weeks patients in the IFX+NPX group had significantly lower osteitis scores in the SIJ ($p=0.001$) and in the spine ($p<0.001$). Similarly, in both groups there was a significant and comparable increase in the fatty lesion score (***table***) in the spine and in the SIJ at week 28 as compared to baseline, but no statistically significant difference between treatment groups was observed in the fatty lesion status score at week 28.

Conclusion: Effective anti-inflammatory treatment of axSpA in this study was associated with an increase in the fatty lesion score in the SIJ and in the spine that was independent of the treatment arm. The results suggest that fatty lesion formation after resolution of inflammation is possibly a universal pathogenetic mechanism in axSpA and not a direct effect of anti-TNF therapy.

Table. Changes in MRI scores over 28 weeks in patients with active axSpA in the INFAST study.

	IFX+NPX			NPX		
Parameter	**Baseline**	**Week 28**	**p-value***	**Baseline**	**Week 28**	**p-value***
Spine osteitis score (0–69)	3.7 ± 5.4	0.8 ± 1.9	<0.001	4.7 ± 5.7	2.7 ± 4.0	0.001
Spine fatty lesion score (0–69)	4.9 ± 7.4	5.7 ± 8.2	<0.001	6.2 ± 8.0	7.2 ± 8.9	<0.001
SIJ osteitis score (0–24)	5.3 ± 5.3	1.0 ± 1.9	<0.001	6.1 ± 4.0	2.2 ± 2.6	<0.001
SIJ fatty lesion score (0–24)	9.2 ± 7.6	10.8 ± 7.3	<0.001	11.2 ± 8.6	12.5 ± 8.1	<0.001

*Wilcoxon-Test, Week 28 vs. Baseline

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Degenerative Changes of the Spine on MRI in Patients with Inflammatory Back Pain from the DESIR Cohort. F. de Bruin[1], Marc Olivier Treyvaud[2], Antoine Feydy[2], Maxime Dougados[3], Laure Gossec[4], J.L Bloem[1], Désirée van der Heijde[1] and Monique Reijnierse[1]. [1]Leiden University Medical Center, Leiden, Netherlands, [2]Paris Descartes University, Radiology B department, Cochin Hospital, Paris, France, [3]Descartes University, Cochin Hospital, Paris, France, [4]UPMC Paris 06 University, GRC 08, Paris France and Pitié Salpétrière Hospital Paris France, Paris, France.

Background/Purpose: MRI is a sensitive method to detect early signs of axial spondyloarthritis (axSpA). A positive MRI of the sacroiliac joints is part of the imaging arm of the ASAS criteria. However, the exact role of MRI of the spine in screening for axSpA needs to be determined. Degenerative changes (DCs) are a common finding in the spine of adults; they might be an alternative explanation for complaints and might interfere with diagnostic decision making. Purpose of this study was to describe the prevalence of DCs on spine MRI in axSpA and no axSpA patients in the DESIR cohort

Methods: The DESIR cohort is a prospective longitudinal cohort study of adults aged 18–50 with inflammatory back pain (IBP) ≥3 months, ≤3 years. Patients (pts) were categorized as axSpA or no axSpA, based on the ASAS criteria for axial spondyloarthritis. Baseline 1.5T MRI (sagittal T1TSE and STIR) of the spine were scored independently by two blinded readers, for: degree of disc degeneration (DD) (Pfirrmann 5 point scale, class ≤2 considered normal), endplate changes (Modic 3 point scale) and presence of a high intensity zone (HIZ), disc protrusion or extrusion, canal stenosis, spondylolisthesis, facet joint osteoarthritis (FJOA) and Schmorls nodes (±edema). In case of disagreement, a third reader acted as adjudicator. AxSpA and no axSpA pts were compared using chi2 test, regression analysis was used for association between age and DCs

Results: 648 pts (303 male, 47%) with mean age 34 (±9) had a MRI spine available and were evaluated. Of these, 454 (70%) had axSpA. 456 pts (70%) showed one or more DCs (range 1–39). In 366 (57%) pts, DCs were observed in the lumbar spine and in 292 (45%) pts in L4-S1 (fig 1). Less pts had DCs in the cervical spine (119, 18%), and thoracic spine (253, 39%). DD and Schmorls nodes were most prevalent (table 1, fig 1). Modic type 3 was not observed. Table 1 lists the number of pts with none, one or multiple changes.

192(30%) pts with no DCs were evenly distributed between the axSpA and no axSpA groups (56/194, 29% and 136/456, 30%) (P=.854). With increasing age, the total number of DCs increased (b=0.11; P<.001) and this was also for canal stenosis, extrusion, HIZ, FJOA, Modic I and Pfirrmann (b=.002 to. 058; *P*=.047 to <.001).

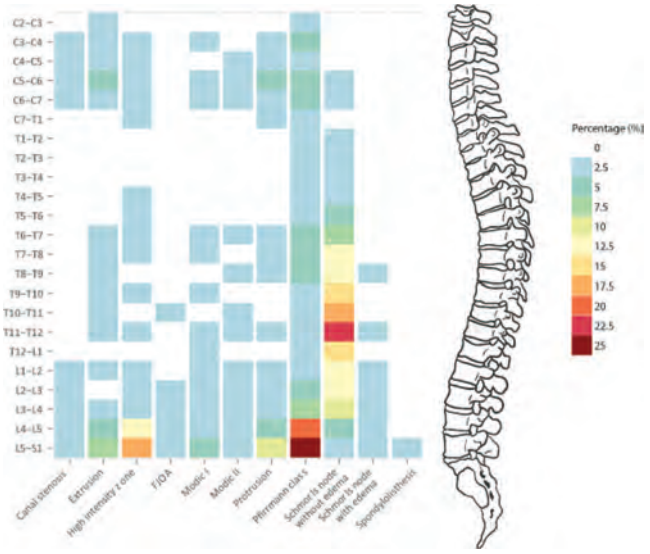
Conclusion: Prevalence of DCs is high in pts with IBP in the DESIR cohort and in accordance with literature. Most DCs are found in the (lower) lumbar spine. With age, the prevalence of DCs increased. No difference was found between axSpA and no axSpA pts.

Table 1

	Number of changes					
	0 (%)		1 (%)		≥2 (%)	
	No axSpA (n=194)	AxSpA (n=454)	No axSpA (n=194)	AxSpA (n=454)	No axSpA (n=194)	AxSpA (n=454)
Pfirrmann class ≥3	107 (55)	263 (58)	43 (22)	97 (21)	44 (23)	94 (21)
High intensity zone	148 (76)	328 (72)	34 (18)	95 (21)	12 (6)	31 (7)
Disc Extrusion	154 (79)	338 (74)	31 (16)	44 (10)	9 (5)	22 (5)
Disc Protrusion	157 (81)	383 (84)	26 (13)	48 (11)	11 (6)	23 (5)
Canal stenosis	189 (97)	447 (99)	2 (1)	1 (0)	4 (2)	5 (1)

Modic 1 (edema)	174 (90)	426 (94)	20 (10)	26 (6)	0 (0)	2 (0)
Modic 2	185 (95)	432 (95)	8 (4)	19 (4)	1 (1)	3 (1)
Schmorls node	127 (66)	283 (62)	19 (10)	46 (10)	48 (25)	125 (28)
Schmorls node (edema)	188 (97)	442 (97)	5 (3)	7 (2)	1 (1)	5 (1)
Facet joint osteoarthritis	192 (99)	452 (100)	0 (0)	1 (0)	2 (1)	1 (0)
Spondylolisthesis	194 (100)	450 (99)	0 (0)	4 (1)	0 (0)	0 (0)

Figure 1: The prevalence of all degenerative changes for each vertebral unit is shown on this heatmap. The darker the colour, the higher its prevalence (as indicated in the colour key on the right).



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2985

Autoantibodies to 14-3-3η Are Novel Biomarkers Associated with Inflammation and Radiographic Progression in Ankylosing Spondylitis. WP Maksymowych[1], Stephanie Wichuk[1], RG Lambert[1], Mairead Murphy[2] and Anthony Marotta[2]. [1]University of Alberta, Edmonton, AB, [2]Augurex Life Sciences Corp., North Vancouver, BC.

Background/Purpose: 14-3-3η is a ubiquitous intracellular chaperone protein that is expressed extracellularly in rheumatoid arthritis and mediates inflammatory cascades that result in expression of inflammatory factors and metalloproteinases. An autoantibody response (AAb) is elicited to a range of epitopes on the native protein both within and outside the ligand-binding groove. We aimed to determine whether autoantibodies to the native protein were generated in AS and which specific autoantibody might be associated with inflammation and have diagnostic and prognostic properties.

Methods: Sera from 116 patients with AS followed prospectively and 106 healthy controls were screened against ten 14-3-3η peptides (Pan 1–10) using an electrochemiluminescent multiplex assay platform. Inflammation was assessed by CRP and MRI of the sacroiliac joint (SIJ) and spine, which was performed by two central readers and an adjudicator using the Spondyloarthritis Research Consortium of Canada (SPARCC) score. Radiographic progression over 2 years was assessed by two central readers and an adjudicator using the modified Stoke AS Spine Score (mSASSS). Patients had mean age of 39.7 years, 73% male, mean symptom duration 16.9 years, and 51 (44%) received TNF blocker therapy. Mean (SD) baseline mSASSS was 13.8 (17.6), mean change in mSASSS was 1.8 (2.7), and 52.5% had mSASSS change $>$ 0. Mann-Whitney U-test was used to determine group differences and ROC analysis (AUC) was used to assess diagnostic utility. Potential associations were assessed by Pearson correlation. Multivariate regression analyses were used to examine associations significant in univariate analyses.

Results: Discrimination by AUC ranged from 0.81–0.89 for all 10 autoantibodies ($p<0.0001$ for all). For example, median (SD) expression of the Pan-1 14-3-3η autoantibody was significantly higher in SpA than in healthy controls (838 U/ml (605–1287) vs. 456 U/ml (346–568), $p=0.0001$) and area under the ROC curve was 0.86, 95%CI (0.82–0.91). A cut-off of 803 U/ml delivered 95% specificity and 53% sensitivity (LR+ 11.2, LR- 0.5). For inflammation parameters, Pan-1 and Pan-5 correlated significantly with CRP ($r=0.23, p=0.02$; $r=0.27, p=0.005$) and Pan-1 correlated with SPARCC SIJ MRI score ($r=0.21, p=0.04$). For radiographic progression measured by change in mSASSS, significant correlations were observed with all 10 Pan specificities, notably, Pan-2 ($r=0.39, p<0.0001$), Pan-3 ($r=0.34, p=0.0004$), and Pan-10 ($r=0.35, p=0.0003$). Independent predictors of MRI inflammation were sex ($p=0.006$) and Pan 1 autoantibody ($p=0.008$) (adjusted for age, sex, symptom duration, CRP). Controlling for baseline mSASSS CRP, age, sex, symptom duration, and treatment, Pan antibodies were the only significant predictors of the change in mSASSS at 2 years in multivariate regression analysis: Pan composite score ($p=0.001$), Pan-1 ($p=0.0008$), Pan-2 ($p=0.0001$), Pan-3 (0.0005), Pan-10 ($p=0.0003$).

Conclusion: 14-3-3η autoantibodies are novel serum markers that are differentially expressed in AS versus healthy controls. They are significantly associated with MRI inflammation and baseline expression of several autoantibody specificities predicts radiographic progression.

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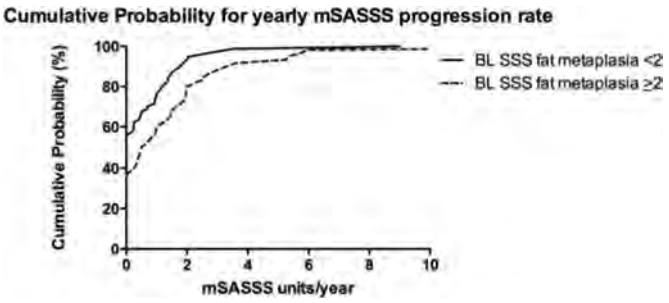
2986

Fat Metaplasia on MRI of the Sacroiliac Joints Is a Lead Indicator of Radiographic Progression in the Spine of Patients with Ankylosing Spondylitis. WP Maksymowych[1], S Wichuk[1], P Chiowchanwisawakit[2], RG Lambert[1] and Sj Pedersen[3]. [1]University of Alberta, Edmonton, AB, [2]Mahidol University, Bangkok, Thailand, [3]Copenhagen Center for Arthritis Research, Copenhagen, Denmark.

Background/Purpose: Fat metaplasia in the SIJ on MRI is an early feature of sacroiliitis and occurs both in subchondral bone marrow and also in the excavated area caused by erosion, when it is called backfill. Recent data has shown that these lesions are key intermediaries in the development of SIJ ankylosis. We aimed to test the hypothesis that these lesions may also be lead indicators of new bone formation in the spine of patients with axial SpA. This could provide an important target for therapeutic intervention.

Methods: Bone marrow fat metaplasia and backfill were scored using the SPARCC MRI SIJ structural score (SSS) by two readers and an adjudicator using pre-specified rules for adjudication. 137 pairs of MRI scans blinded to time point (baseline, 2 years) were assessed from a prospective cohort of AS patients (mean age 40.5years, mean symptom duration16.9 years, 53% on anti-TNF) followed for mean 2.3 years. Two readers and an adjudicator independently scored pairs of radiographs (baseline, 2 years) from the same patients using the mSASSS. Radiographic progression was compared in patients with and without positive SIJ MRI for fat metaplasia (SSS score ≥ 2 or <2) and the degree of SIJ fat metaplasia at baseline (absolute SSS score) was compared in patients with and without radiographic progression (mSASSS >0 or $=0$) using Mann-Whitney and cumulative probability. Multivariate regression analyses included variables significant in univariate analyses (age, sex, symptom duration, CRP, baseline mSASSS) and treatment.

Results: Radiographic progression was significantly greater in those with positive SIJ fat metaplasia ($p=0.015$) (figure), and especially in patients who only received non-biologic therapy ($p=0.023$). Baseline SSS SIJ fat metaplasia scores were significantly higher in those who developed radiographic progression compared to those without (1.58 vs 0.65, $p=0.008$). Both positive SIJ MRI for fat metaplasia and the degree of fat metaplasia were significantly associated with radiographic progression in multivariate analyses ($\beta=0.38$ ($p=0.005$) and $\beta=0.06$ ($p<0.0001$) respectively). SSS score for backfill was also significantly associated with radiographic progression in multivariate analysis ($\beta=0.04$ ($p=0.019$)).



Conclusion: The appearance of fat metaplasia in SIJ subchondral bone marrow and/or at sites of erosion in the SIJ may identify AS patients at increased risk of radiographic progression in the spine.

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2987

Value of Color Doppler Ultrasound Assessment of Sacroiliac Joints in Patients with Inflammatory Chronic Low Back Pain. Maximiliano Bravo[1], Leandro Ferreyra Garrott[1], David A. Navarta[1], Emmanuel Bertiller[1], Ricardo Garcia-Monaco[2], Santiago Ruta[1], Javier Rosa[3] and Enrique Soriano[1]. [1]Rheumatology Unit, Internal Medical Services, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, [2]Radiology and Imagenology Department, Hospital italiano de Buenos Aires, Buenos Aires, Argentina, [3]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.

Background/Purpose: The utility of ultrasound in the evaluation of sacroiliitishas not been extensively studied yet. To evaluate the diagnostic value of color Doppler ultrasound (US) for the detection of sacroiliac (SI) active inflammatory lesions in patients with inflammatory chronic low back pain (LBP).

Methods: Consecutive patients older than 18 years, with chronic inflammatory low back pain, defined as LBP with more than 3 months of continuous duration, of insidious onset, with improvement with exercise, no improvement with rest, and pain at night (with improvement upon getting up), without a definitive diagnosis (patients at risk of having undetected spondyloarthritis (SpA)), referred from orthopedics or general practitioners clinics for an axial magnetic resonance imaging (MRI), were included. Patients with Ankylosing spondylitis (AS) according to modified New York criteria, were included as control group.Clinical assessment included BASDAI, BASFI, and HAQ. Ultrasound evaluation was performed by a blinded rheumatologist experienced in this technique with a My lab 70 machine (Esaote) with a multi-frequency convex array transducer (1–8 MHz). Standardized scanning method was used to investigate increased local perfusion with color Doppler US. When color Doppler signal was found in or around the SI joints, spectral Doppler was used and the resistive index (RI) was measured. Color Doppler US sacroiliitis was defined as a positive color Doppler signal with a RI <0.75 at any of the SI joints.

The following sequences were used on the MRI assessment: T1-weighted spinecho (SE) and short-tau inversion recovery (STIR). MRI sacroiliitis was defined according to ASAS definition of active sacroiliac inflammatory lesions.

Sensitivity, specificity, positive and negative predictive values for the diagnosis of sacroiliitisbycolor Doppler US features was calculated, using MRI as the gold standard.

Results: Forty-four patients were included. Twenty-four (54%) were males. Mean age was: 40 years (SD: 11 yrs). Median disease duration was 2 years (IQR: 0.5–10 yrs). Mean BASDAI was 4.8 (SD: 2.4), mean BASFI: 3.6 (SD: 2.7), and mean HAQ was 0.6 (SD: 0.5).Ten patients had AS. Among all patients, 21 (48%) had active sacroiliitis by MRI. Active sacroiliitis by MRI was present in 4 (40%) of AS patients, and in 17 (50%) of patients with inflammatory LBP, respectively.

Color Doppler US sensitivity for the diagnosis of sacroiliitis among all patients was 62 % (95% CI: 48–76%) and specificity was 91%. (95% CI: 83–99.6%). Positive predictive value (PPV) was 87% (95% CI: 77–97%) and negative predictive value (NPV) was: 72% (95% CI: 59–86%). Among AS patients observed values were: sensitivity 75% (95% CI:48–100%), specificity 83% (95% CI: 60–99), PPV: 75% (95% CI:48–100%) and NPV: 83% (95% CI: 60–99%) and among inflammatory LBP patients diagnostic test values were: sensitivity 59 % (95% CI:42–75%), specificity: 94% (95% CI:86–100%), PPV: 91% (95% CI;81–100%) and NPV: 70% (95% CI: 54–89%).

Conclusion: color Doppler US seems to be a practical and useful tool for the diagnosis of active sacroiliitis. Larger studies would be needed to confirm these results.

Disclosure: M. Bravo, UCB, 2; **L. Ferreyra Garrott**, UCB, 2; **D. A. Navarta**, UCB, 2; **E. Bertiller**, UCB, 2; **R. Garcia-Monaco**, UCB, 2; **S. Ruta**, UCB, 2; **J. Rosa**, UCB, 2; **E. Soriano**, UCB, 2.

2988

Calgranulin Levels Are Elevated in Spondyloarthritis and Reflect the Presence of Acute Microscopic Gut Inflammation. Heleen Cypers[1], Gaëlle Varkas[1], Liesbet Van Praet[1], Johannes Roth[2], Thomas Vogl[2], Claude Cuvelier[3], Dirk Föll[4], Miha Lavric[4], Filip van Den Bosch[1] and Dirk Elewaut[1]. [1]Department of Rheumatology Ghent University Hospital, Ghent, Belgium, [2]Institute of Immunology University of Muenster, Muenster, Germany, [3]Department of Pathology Ghent University Hospital, Ghent, Belgium, [4]University Children's Hospital Muenster, Muenster, Germany.

Background/Purpose: Microscopic gut inflammation is present in about 50% of spondyloarthritis (SpA) patients. Two types can be distinguished: an acute type resembling infectious enterocolitis, and a chronic type similar to early Crohn's disease. Although subclinical, microscopic gut inflammation appears to be a prognostic factor in SpA, linked with more extensive disease and a less favorable outcome. At this moment, however, reliable biomarkers are missing. The calgranulins S100A8/S100A9 and S100A12 are very sensitive markers of innate immune activation. They are released from monocytes and granulocytes in the early phase of the immune response and exert important pro-inflammatory effects via Toll-like receptor 4 dependent mechanisms. Calgranulins can be measured in serum and stool. Moreover, the S100A8/S100A9 heterodimer, also called calprotectin, has been established for a long time as a fecal marker of disease activity in inflammatory bowel disease. Our aim was to assess whether calgranulins can be used as biomarkers for microscopic gut inflammation in SpA.

Methods: Serum levels of calgranulins were measured in 103 newly diagnosed SpA patients and 24 healthy controls. Ninety seven SpA patients underwent an ileocolonoscopy to assess the presence of microscopic gut inflammation. Ileal and colonic biopsies were histologically scored and subsequently immuno-stained for S100A8 and S100A9.

Results and Conclusion: Serum levels of S100A8/S100A9 and S100A12 were significantly higher in SpA patients versus healthy controls ($p= 0,035$ and $p = 0,024$). Levels correlated moderately with CRP, but not with ASDAS, BASDAI or swollen joint count. SpA patients with the acute type of microscopic gut inflammation ($N= 17$) had significantly higher calgranulin levels compared to those with normal gut histology ($N= 56$) ($p = 0,021$ for S100A8/S100A9 and $p = 0,05$ for S100A12). Furthermore, immunohistology showed high staining of S100A8 and S100A9 on acutely inflamed gut biopsies, compared to absent/minimal staining on normal biopsies. Chronically inflamed biopsies ($N=24$) stained positive only when they had high inflammatory activity (in $\sim$ 50% of cases). Importantly, NSAID intake had neither influence on immunohistology stainings nor on serum levels of calgranulins. To conclude, we found that calgranulin levels, both systemically and locally, marked the presence of acute microscopic gut inflammation in SpA. These results illustrate their high sensitivity as they reflected inflammation present only on a subclinical level. Therefore we anticipate that they may be of particular value in detecting (or excluding) latent (systemic) disease.

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ACR Concurrent Abstract Session
Systemic Lupus Erythematosus - Clinical Aspects and Treatment: Central Nervous System and Other Clinical Aspects
Wednesday, November 19, 2014, 9:00 AM–10:30 AM

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Lupus Impact Tracker Is Responsive to Changes in Disease Activity in Lupus. David Giangreco[1], Hervé Devilliers[2], Narender Annapureddy[1], Joel A. Block[1] and Meenakshi Jolly[1]. [1]Rush University Medical Center, Chicago, IL, [2]Department of internal medicine and systemic diseases, Dijon, France.

Background/Purpose: Patient reported outcomes (PRO) are important to understand, educate, manage and follow patients with systemic lupus erythematosus (SLE). Lupus Impact Tracker (LIT) is a ten-item tool developed to facilitate patient-physician communication. Herein, we present its responsiveness to physician and patient assessed changes in disease status from data obtained during routine SLE patient care visits.

Methods: Longitudinal data on LupusPRO, physician assessed disease activity assessment, and patient reported changes in SLE health status was collected during 182 SLE patient routine clinical care visits. LIT score was derived from PRO data. Disease activity assessments used as anchors for testing responsiveness were the SLEDAI physician global assessment (PGA), Total SELENA-SLEDAI score, SELENA-Flare Index (SFI), and Patient reported changes in SLE health status. Cut-offs used to determine change in disease activity were as follows: PGA (change of 0.3), Total SELENA-SLEDAI (change of 4), SFI (remitting, stable, and flaring) and Patient reported changed in SLE health status (−7 to 7). For patient reported change in SLE health status, we categorized −2 to 2 as unchanged, −3 to −7 as worsening and 3 to 7 as improvement. Mixed model regression analysis was used to compare changes in LIT against disease activity and patient reported changes in SLE health status anchors.

Results: There were 658 visit data available for 182 SLE patients. Consecutive visits were 2–5 months apart with a median number of visits per patient of 7. PGA was available for 630 visits; Total SLEDAI was available for 249 visits; SFI was available for 610 visits; Patient reported change in SLE health status was available for 449 visits. Mean (SD) age and SELENA-SLEDAI were 43.5 (13.2) years and 6.4 (7.3), respectively. PGA changed significantly for 269 visit data (increased in 125, decreased in 144) while 361 visit data had unchanged PGA. Total SELENA-SLEDAI changed significantly among 66 visits (29 increased, 37 decreased) and remained stable among 183 visits. Significant changes in SFI were observed in 149 visit data (80 remitting, 69 flaring) while 461 visit data was unchanged. Patient reported change in SLE health status changed significantly for 221 (150 improved, 71 worsened) and remained stable for 228 visits. LIT scores responded significantly and in the appropriate direction for changes in PGA ($p<0.05$), Total SLEDAI ($p=0.01$), and SFI ($p<0.05$) and patient reported changes in SLE health status ($p=0.001$).

Conclusion: LIT is responsive to physician- and patient-assessed changes in disease status in SLE. In addition to being used in clinical trials, LIT is an effective tool that may be used by patients and physicians in facilitating communication and tracking disease impact in SLE.

Disclosure: D. Giangreco, None; **H. Devilliers**, None; **N. Annapureddy**, None; **J. A. Block**, None; **M. Jolly**, None.

2990

Risk Factors for Posterior Reversible Encephalopathy Syndrome in Systemic Lupus Erythematosus Patients: A Single Center Study. Javier Merayo-Chalico[1], Elia Apodaca[2], Ana Barrera-Vargas[1], Jorge Alcocer-Varela[1] and Diana Gómez-Martín[1]. [1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Instituto Nacional de Ciencias Médicas y Nutrición, Mexico City, Mexico.

Background/Purpose: Posterior reversible encephalopathy syndrome (PRES) is a well-known but rare complication in systemic lupus erythematosus (SLE) patients (<1%). However, current epidemiologic data is quite scant. The aim of the present study was to describe potentially unrecognized risk factors.

Methods: We performed a single-center retrospective case-control study in a tertiary care center in Mexico City between 1999 and 2014. We included 48 patients (cases) with SLE diagnosis (≥4 ACR criteria) who presented with reversible neurological manifestations (seizures, visual abnormalities, acute confusional state, among others) associated with changes by magnetic resonance (MRI) (iso or hypointensity in T1 and hyperintensity in T2/FLAIR). Controls (n=96) were patients with SLE without evidence of PRES that were hospitalized during the same period as cases (± 3 months) and matched by gender. Association between variables was calculated by X^2 test and OR (95% CI). Multivariate analysis was performed by logistic regression.

Results: SLE patients with PRES were younger (27.9±1.05 vs 36.2±1.36 years, $p<0.001$). Ninety percent of the cases occurred in women. PRES occurred in 28/48 patients (40%) after 24 hours of admission (2–30 days). The vast majority (80.2%) of cases presented with seizures, and up to 18% showed "atypical" MRI images. Decrease or resolution of MRI images in the first 12 weeks after the event occurred in 88.8% of cases. Variables associated with the development of PRES, three months prior to hospitalization and at the time of the event are summarized in Table 1. After multivariate analysis, hypertension at admission [OR 16.3, 95% CI 4.03–65.85, $p<0.001$], renal replacement therapy at discharge [OR 6.65, 95% CI 1.24–35.64, $p=0.027$], persistent lymphopenia (<1,000 cells/uL in at least two consecutive measurement previous to the event) [OR 5.76, 95% CI 1.36–24.40, $p=0.017$], SLEDAI≥6 prior to admission [OR 1.11, 95% CI 1.01–1.22, $p=0.031$] and age [OR 0.863, 95% CI 0.81–0.91, $p<0.001$] were independent risk factors for the development of PRES in SLE. Length of hospital stay was similar between groups (17.2±2.07 vs 14.60±1.11 days, $p=0.26$) and none of the cases died during hospitalization.

Conclusion: Our data is in agreement with prior studies that link end-stage renal disease, hypertension and high SLEDAI scores to the development of PRES in SLE. Furthermore, we found that persistent lymphopenia is a novel independent risk factor for PRES in SLE, which could be related to endothelial dysfunction in these patients.

Table 1. Variables associated with development of PRES in SLE patients (univariate analysis)

Three months prior to admission	OR	95% CI	p value
SLEDAI ≥6 points	4.41	1.87–10.40	<0.001
Hypertension	3.50	1.68–7.32	0.001
Lymphopenia	3.36	1.36–8.29	0.006
Low C3 levels	2.71	1.21–6.07	0.013
History of renal replacement therapy	2.66	1.15–6.12	0.019
At admission	**OR**	**95% CI**	**p value**
SLEDAI ≥6 points	33.80	4.43–257.54	<0.001
Hypertension	13.63	5.88–31.56	<0.001
GFR ≤60 mL/min/1.73 m^2	4.75	1.93–11.65	<0.001
Renal replacement therapy at discharge	4.27	1.97–9.24	<0.001
Low C3 levels	2.22	1.02–4.81	0.041

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2991

Anti-Ribosomal P Antibody Is a Key Autoantibody Associated with Complications of NP-SLE with High-Levels of CSF IL-8. Hidenaga Kawasumi[1], Takahisa Gono[1], Yasushi Kawaguchi[1], Yasuhiro Katsumata[1], Hisae Ichida[1], Akiko Tochimoto[1], Masanori Hanaoka[1], Yuko Okamoto[1], Sayuri Kataoka[1] and Hisashi Yamanaka[2]. [1]Tokyo Women's Medical University, Tokyo, Japan, [2]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

Background/Purpose: Complications of neuropsychiatric systemic lupus erythematosus (NP-SLE) are associated with the morbidity and mortality of patients with SLE. Although the detailed pathophysiology of NP-SLE remains unknown, complements, autoantibodies, and cytokines are involved in the inflammation of the central nervous system (CNS) or the peripheral nervous system (PNS) in SLE. Previous studies have demonstrated that anti-phospholipid (PL), anti-ribosomal P, anti-*N*-methyl-D-aspartate receptor subunit 2 (NR2), and anti-U1-RNP antibodies are associated with the development of NP-SLE. In addition, cerebrospinal fluid (CSF) proinflammatory cytokines, such as IL-6, are increased in NP-SLE. In this study, we evaluated the associations between several serum autoantibodies and CSF proinflammatory cytokines in NP-SLE.

Methods: In the present study, seventy patients with SLE who had been admitted to our hospital from 2001 to 2013 were enrolled. SLE was diagnosed according to the 1997 ACR revised criteria for the classification of SLE. Disease activity was measured using the SLE disease activity index 2000 (SLEDAI-2k). NP-SLE manifestations were classified according to the 1999 ACR nomenclature and case definitions for NP-SLE syndromes. Serum and CSF samples were obtained from all enrolled patients with SLE. We measured serum autoantibodies, including anti-PL, anti-ribosomal P, anti-NR2, anti-U1-RNP and anti-Sm antibodies, and CSF cytokines (IL-6, IL-8, and IFN-α).

Results: Of the 70 patients with SLE, all patients were female, and their median age was 32 years. The median score on the SLEDAI-2k was 12. NP-SLE was diagnosed in 24 patients. Serum anti-PL, anti-ribosomal P, anti-NR2, anti-U1-RNP, and anti-Sm antibodies were detected in 15, 23, 23, 24, and 13 patients, respectively. The CSF levels of IL-8 were significantly higher in the NP-SLE subset compared with the non-NP-SLE subset ($p<0.05$). There were no significant differences in the CSF levels of IL-6, IFN-α, total protein, or IgG index between the two subsets. High levels of CSF IL-8 (>30 pg/ml) were significantly ($p<0.001$) associated with the complications of NP-SLE. No patient was diagnosed with NP-SLE when the CSF levels of IL-8 were less than 30 pg/ml. To identify the specific autoantibodies associated with high levels of CSF IL-8, a multivariate analysis was conducted. Anti-ribosomal P was the most significant autoantibody involved in the high levels of CSF IL-8.

Conclusion: High levels of CSF IL-8 are associated with the complications of NP-SLE. Anti-ribosomal P is a key autoantibody associated with NP-SLE with high levels of CSF IL-8.

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2992

Usefulness of Diagnostic Biomarker for Neuropsychiatric Systemic Lupus Erythematosus By Anti-Microtubule Associated Protein 2 Antibody in Cerebrospinal Fluid. Yusuke Yamada, Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, Tokyo, Japan.

Background/Purpose: Microtubule associated protein-2 (MAP-2) is found exclusively in nerve cells. MAP-2 has been shown to stabilize microtubules by binding to the outer surface and participate in determining the structure of nerve cells. Interestingly, a previous report has shown that an autoantibody against MAP-2 has been reported to be found in sera with SLE patients especially having neuropsychiatric manifestations. However, there are no additional reports concerning anti-MAP-2 antibody. NPSLE involves a wide range of focal and diffuse central and peripheral nervous system disorders. The diagnosis of NPSLE is often clinically difficult because discrimination of secondary causes such as infection, medication side-effects, and metabolic abnormalities was required. The diagnostic inference of NPSLE can be made only after these secondary causes have been excluded. There is no one single diagnostic tool specific to NPSLE so far. Multiple diagnostic examinations such as IL-6 measurement in cerebrospinal fluid or Magnetic Resonance Imaging (MRI) have been used for diagnosis with NPSLE. However, the findings from these examinations are not specific for NPSLE. Therefore, novel diagnostic biomarkers have been expected to be established. Herein, we conducted this study to clarify that anti-MAP-2 antibody in cerebrospinal fluid can be used for a diagnostic biomarker of NPSLE.

Methods: Anti-MAP-2 antibody, anti-ribosomal P antibody, and IL-6 was measured by ELISA in cerebrospinal fluid from NPSLE patients (n=24) or non NPSLE controls (n=18). The diagnosis with NPSLE was made by the nomenclature system proposed by American College of Rheumatology (ACR, 1999). Non NPSLE controls consisted of SLE patients with CNS disorders caused by the secondary causes such as steroid psychosis, and other tissue connective diseases with CNS disorder.

Results: Titer of anti-MAP-2 antibody in cerebrospinal fluid was significantly higher in NPSLE patients compared to non NPSLE controls. When the cutoff value was designed as average + 3SD of the controls, the prevalence of anti-MAP-2 antibody in NPSLE patients was 33.3% (8/24), and none of patients with non NPSLE controls (0/18) had an anti-MAP-2 antibody. Furthermore, titer of anti-ribosomal P antibody and IL-6 concentration in cerebrospinal fluid, which are other diagnostic biomarker for NPSLE, were significantly higher in NPSLE patients with anti-MAP-2 antibody compared to NPSLE patients without anti MAP-2 antibody or non NPSLE controls.

Conclusion: Anti-MAP-2 antibody in cerebrospinal fluid was recognized in 33.3% patients with NPSLE and the appearance was highly specific for NPSLE. We propose that anti-MAP-2 antibody in cerebrospinal fluid is a novel diagnostic biomarker for NPSLE.

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MRI in Neuropsychiatric Lupus: Correlations with the 1999 ACR Case Definitions. Minyoung Her[1], Dongyook Kim[1], Na young Park[1], Seong-Kyu Kim[2], Lee Sung Won[3] and Lee sang Yeob[3]. [1]Inje University, Pusan Paik Hospital, Busan, South Korea, Busan, South Korea, [2]Catholic University of Daegu, Daegu, South Korea, Daegu, South Korea, [3]Dong-A university, Busan, South Korea, Pusan, South Korea.

Background/Purpose: Neurological manifestations in SLE are diverse. Because of its varied manifestations and low prevalence, the ACR has developed nomenclature and case definitions for neuropsychiatric SLE (NPSLE) to facilitate clinical research. Brain MRI has been used for the evaluation of neurologic symptoms. The purpose of this study was to identify characteristic brain MRI findings in NPSLE and to investigate the association between brain MRI findings and NPSLE manifestations.

Methods: All brain MRI cases that received the diagnosis of SLE at three tertiary university-based hospitals from August 2002 to August 2013 were screened. 219 brain MRIs with diagnosis of SLE were screened. All clinical manifestations found by brain MRI were retrospectively assessed and were classified as NPSLE according to the 1999 NPSLE ACR nomenclature and case definitions. In total, 139 brain MRIs in 121 patients with NPSLE from 2002 to 2013 were retrospectively reviewed. The images were evaluated for the presence of white matter hyperintensity (WMH), gray matter hyperintensity(GMH), parenchymal defects, atrophy, enhancement, and the abnormalities in diffusion-weighted image (DWI). The number, size and location of WMH, GMH and parenchymal defects were evaluated. The NPSLE manifestations of each patient were classified according to the 1999 ACR case definitions for NPSLE syndromes. The associations between MRI findings and manifestations of NPSLE were examined.

Results: In total, 97 MRIs (69.8%) demonstrated abnormalities among the 139 brain MRIs reviewed. There were 164 NP events that encompassed 16 of 19 NP syndromes. The most common MRI abnormalities were WMHs. One or more WMHs were found in 78 MRIs (56.1 %) among the total 139 MRIs. GMHs were observed in 42 MRIs (32.0%). GMHs tended to involve much larger areas than WMHs. Patients with cerebrovascular disease or seizures were more likely to have GMHs than patients with other NP manifestations. 33 MRIs among 42 MRIs which had GMHs also exhibited WMHs. Parenchymal defects were found in 34 MRIs (24.5%). Atrophy was detected in 20 MRIs (14.4%). Brain MRIs were enhanced in 21 of the 122 cases that had undergone enhancement. Patients who had seizures were more likely to demonstrate MRI enhancement than patients with other NP manifestations. DWIs were obtained in 97 MRIs and abnormal DWIs were obtained in 17 MRIs cases. Patients with cerebrovascular disease were more likely to have GMH, parenchymal defects and abnormal DWI than patients with other NP manifestations.

°°	Number of MRIs (%)	Abnormalities of MRI	WMH	GMH	Parenchymal defect	Atrophy	Enhancement
Acute confusion	9 (6.5%)	6	3	3	3	1	3
Anxiety disorder	1 (0.7%)	0	0	0	0	0	0
Aseptic meningitis	6 (4.3%)	4	3	0	1	0	2
Cerebrovascular disease	32 (23.0%)	32	26	15	15	4	4
Cognitive dysfunction	4 (2.9%)	3	3	0	1	3	0
Demyelinating disease	2 (1.4%)	2	2	1	1	0	1
Headache	33 (23.7%)	17	12	6	2	4	2
Mood disorder	1 (0.7%)	0	0	0	0	0	0
Movement disorder	4 (2.9%)	3	3	0	0	0	0
Psychosis	4 (2.9%)	3	2	0	1	1	1
Seizure	23 (16.6%)	17	14	12	5	5	7
Autonomic disorder	3 (2.2%)	0	0	0	0	0	0
Cranial neuropathy	12 (8.6%)	7	7	2	2	0	0
Mononeuropathy	3 (2.2%)	1	1	1	1	0	0
Myasthenia gravis	0 (0%)	0	0	0	0	0	0
Polyneuropathy	2 (1.4%)	2	2	2	2	2	1
Total	139 (100%)°°	97	78	42	34	20	21

Conclusion: Diverse brain MRI abnormalities were observed in the brain MRI of patients with NPSLE. In addition to WMHs, which were previously known as SLE findings, we also noted the presence of GMHs, parenchymal defects and abnormal DWI in a substantial portion of SLE patients, particularly in those with cerebrovascular disease or seizure.

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Blood Brain Barrier and Anti-NR2 Antibody in SLE Patients with Cognitive Impairment. Gaurav Gulati[1], Philip Iffland[2], Vikram Puvenna[2], Damir Janigro[2] and Michael Luggen[1]. [1]University of Cincinnati College of Medicine, Cincinnati, OH, [2]Cleveland Clinic Lerner College of Medicine, Cleveland, OH.

Background/Purpose: Cognitive Impairment (CI) is one of the most common manifestations of neuropsychiatric SLE (NPSLE) and one of the most devastating. The pathogenesis of CI in SLE is not known, but in animal models, antibody to the NR2 subunit of the N-methyl D-aspartate receptor (aNR2) can cause memory impairment. However, this effect can only be demonstrated if the blood brain barrier (BBB) has been disrupted or if the antibody is introduced intrathecally. Several studies in SLE patients have failed to find an association of aNR2 with CI. None, however, has assessed the integrity of the BBB as a potential pathogenic cofactor. S100B protein is an astrocyte specific protein that has been used as biomarker of BBB disruption in traumatic brain injury and some neurodegenerative disorders. And, antibodies to this protein may indicate previous exposure to this immunologically privileged protein and might be used as an indicator of preceding BBB disruption. We hypothesized that aNR2 antibody is pathogenic in SLE patients only if there evidence of previous or ongoing BBB disruption as indicated by increased levels of S100B or anti-S100B.

Methods: Patients who fulfilled the revised American College of Rheumatology (ACR) criteria for SLE and were stable for at least 4 weeks were recruited from three different settings. Basic demographic, clinical and laboratory data was collected. The Automated Neuropsychological Assessment Metrics (ANAM), a computerized and validated tool, was utilized to measure cognitive function. The Total Throughput Score (TTS = number of correct responses/time) was used as the primary outcome measure. CI was defined as a score of less than 1.5 SD below the age, sex, and race matched RA population mean. Patients also had assessment of fatigue, depression, SLE activity and SLE damage using the FACIT fatigue score, Becks Depression Inventory (BDI), SLEDAI 2K, and SLICC respectively. Serum was analyzed by established ELISA techniques for aNR2 antibody, anti-S100B antibody and intact serum S100B protein.

Results: A total of 57 patients were evaluated. Demographic and clinical data is summarized in TABLE 1. The age, ethnicity, and family income were significantly different between the two groups ($p<0.05$). In a multiple regression model using the above independent variables together with simple reaction time and opioid use, no significant effects of aNR2, S100b, or aS100b on decreasing TTS were found. However, aNR2 antibodies significantly decreased TTS at higher, but not lower, levels of S100b ($p<.01$, model R^2 of 0.657, $p<.0001$).

Conclusion: Antibody to NR2 may play a role in the pathogenesis of CI in SLE patients, but it does so only if there is disruption of the blood brain barrier as has been previously suggested. Confirmation of these findings and further investigation of the causes of BBB damage in these patients may improve our understanding of this important problem.

Table 1. Clinical and Demographic Characteristics of Study Patients

Variable	ALL SUBJECTS	CD (n=12)	NO CD (n=45)
Age (SD)	49.9 (11.2)	54.9 (8.8)	**48.5 (11.5)***
Disease duration (yrs)	13.1 (10.1)	17.5 (13.9)	12.0 (8.6)
Family Income (% < $20K)	45.6	75.0	**37.8***
Education (% ≤ 12 yrs)	36.8	50.0	33.3
Ethnicity (% Caucasian)	36.8	8.3	**44.4***
SLEDAI	3.6 (3.4)	3.2 (4.3)	3.8 (3.3)
SLICC	2.75 (2.4)	3.4 (2.1)	2.4 (2.4)
Pain (100 mm VAS)	40.0 (28.2)	49.6 (29.1)	36.2 (27.7)
Patient global Assessment (100 mm VAS)	53.7 (22.6)	58.8 (22.6)	52.3 (22.7)
Depression (Beck Depression Inventory)	16.0 (12.3)	17.6 (10.2)	14.4 (12.6)
Fatigue (FACIT)	24.6 (13.5)	26.1 (10.8)	23.3 (14.3)
APL Positive (%)	38.6	25.0	42.2
Prednisone (% use)	53.7	54.5	53.9
Prednisone > 20 mg/d (%)	15.8	25.0	13.3
Immunosuppressants (%)**	48.2	36.4	51.2
HCQ (%)	70.0	50.5	74.4
Warfarin (%)	14.8	18.2	14.0
ASA (%)	38.9	27.3	41.9
Antidepressant (%)	31.5	36.4	30.2
Opioid (%)	25.9	45.5	20.9
NSAID (%)	22.2	18.2	23.3

* CD vs non-CD, $p < .05$
** Immunosuppressant medications include methotrexate, mycophenolate mofetil, cyclophosphamide, leflunomide and azathioprine.

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ACR Concurrent Abstract Session
Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Clinical Aspects and Therapeutics III: Updates in Predictors and Outcomes in Systemic Sclerosis

Wednesday, November 19, 2014, 9:00 AM–10:30 AM

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Surrogate Measures of Extent of Interstitial Lung Disease As Measured By Quantitative Radiographic Analysis in Patients with Systemic Sclerosis.

Elizabeth Volkmann[1], Donald Tashkin[2], Chi-hong Tseng[1], Kim Hyun[1], Jonathan Goldin[1], Philip J. Clements[3], Daniel E. Furst[1], Dinesh Khanna[4], Eric Kleerup[1], Michael Roth[1] and Robert Elashoff[5]. [1]University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [2]University of California at Los Angeles, Los Angeles, CA, [3]University of California, Los Angeles, Department of Medicine, Los Angeles, CA, [4]University of Michigan Health System, Ann Arbor, MI, [5]University of California, Los Angeles, Los Angeles, CA.

Background/Purpose: Extent of systemic sclerosis (SSc)-related interstitial lung disease (ILD) predicts disease course, mortality and treatment response. While quantitative analyses of total extent of ILD (QILD) are more sensitive and reproducible than visual assessments of SSc-ILD, these analyses are not widely available. This study evaluates the relationship between disease parameters and QILD scores to identify potential surrogate measures of QILD.

Methods: Using baseline data from the Scleroderma Lung Study I (SLS I) (N=158), multivariate regression analyses were performed using the best subset selection method to identify 1 to 5 variable-models that best predict QILD scores in both whole lung (WL) and the zone of maximal involvement (ZM). These models were subsequently validated using baseline data from SLS II (N=142). SLS I&II did not include patients with clinically significant pulmonary hypertension (PH).

Results: Diffusing capacity for carbon monoxide (DLCO) was the single best predictor of QILD in the WL and ZM in all of the best subset models (Tables 1, 2). Adding other disease parameters to the models did not substantially improve model performance. Forced vital capacity (FVC) did not predict QILD scores in any of the models.

Conclusion: In the absence of PH, DLCO provides the best overall estimate of HRCT-measured QILD in patients from 2 large SSc cohorts. FVC, which is commonly used to monitor disease course in SSc-ILD, may not be the best surrogate measure of extent of QILD.

Table 1. Multivariate regression analyses of the best 1 to 5 variable models that predict extent of quantitative interstitial lung disease (QILD) in the zone of maximal involvement (ZM).

Variable	Estimate	SE	p value	Adjusted r^2 for SLS I	Correlation SLS I	Correlation SLS II
From best 1- variable model						
DLCO% predicted	−0.87	0.13	<0.0001	0.29*	0.55*	0.44*
From best 2-variable model						
Diffuse disease	6.70	3.23	0.04	0.32*	0.57*	0.39*
DLCO% predicted	−0.91	0.13	<0.0001			
From best 3-variable model						
Diffuse disease	6.72	3.21	0.039	0.33*	0.59*	0.44*
DLCO% predicted	−0.75	0.16	<0.0001			
TLC% predicted	−0.24	0.16	0.13			
From best 4-variable model						
Diffuse disease	6.22	3.23	0.057	0.33*	0.60*	0.46*
DLCO% predicted	−0.67	0.18	0.0003			
TLC% predicted	−0.28	0.16	0.085			
Breathing VAS	0.077	0.066	0.24			
From best 5-variable model						
Diffuse disease	10.61	4.51	0.021	0.33*	0.60*	0.46*
DLCO% predicted	−0.76	0.17	<0.0001			
TLC% predicted	−0.24	0.16	0.14			
mRSS[à]	−0.28	0.21	0.18			
Disease duration[¤]	−0.90	0.73	0.22			

* $p<0.0001$.
Visual analog scale for breathing (Range of scores 0–100).
à Modified Rodnan Skin Score (Range of scores 0–51).
¤ Disease duration = Number of years since diagnosis of first non-Raynaud's symptom to randomization.

Table 2. Multivariate regression analyses of the best 1 to 5 variable models that predict extent of quantitative interstitial lung disease (QILD) in the whole lung (WL).

Variable	Estimate	SE	p value	Adjusted r^2 for SLS I	Correlation SLS I	Correlation SLS II
From best 1- variable model						
DLCO% predicted	−0.59	0.12	<0.0001	0.19*	0.44*	0.37*
From best 2-variable model						
DLCO% predicted	−0.49	0.12	0.0001	0.24*	0.50*	0.38*
Breathing VAS	0.15	0.057	0.0081			
From best 3-variable model						
DLCO% predicted	−0.51	0.12	<0.0001	0.25*	0.52*	0.37*
Breathing VAS	0.15	0.056	0.0067			
Age (years)	−0.20	0.12	0.086			
From best 4-variable model						
DLCO% predicted	−0.54	0.12	<0.0001	0.25*	0.53*	0.38*
Breathing VAS	0.14	0.057	0.010			
Age (years)	−0.20	0.12	0.088			
Diffuse disease	2.89	2.86	0.32			
From best 5-variable model						
DLCO% predicted	−0.56	0.12	<0.0001	0.26*	0.54*	0.40*
Breathing VAS	0.15	0.057	0.010			
Age (years)	−0.21	0.12	0.085			
Diffuse disease	6.29	4.01	0.12			
mRSS[à]	−0.22	0.18	0.23			

* $p<0.0001$
Visual analog scale for breathing (Range of scores 0–100).
à Modified Rodnan Skin Score (Range of scores 0–51).

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Intestinal Pseudo-Obstruction in Patients with Systemic Sclerosis: An Analysis of the Nationwide Inpatient Sample. Antonia Valenzuela[1], Shufeng Li[1], Laren Becker[1], Nielsen Fernandez-Becker[1], Dinesh Khanna[2], Linda Nguyen[1] and Lorinda Chung[1]. [1]Stanford University School of Medicine, Palo Alto, CA, [2]University of Michigan Health System, Ann Arbor, MI.

Background/Purpose: Intestinal pseudo-obstruction accounted for 3.7% of hospitalizations of patients with systemic sclerosis (SSc), and led to death in 10% of patients in a previous dual-center study. We aimed to determine the prevalence of intestinal pseudo-obstruction in hospitalized patients with SSc in a large US national database and to compare outcomes between patients with intestinal pseudo-obstruction and SSc, patients with intestinal pseudo-obstruction secondary to other causes, and SSc patients without intestinal pseudo-obstruction.

Methods: This is a case-control study using the Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS) for the period 2002–2011. We included patients using the previously validated International Classification of Diseases-Clinical Modification-9 code 710.1 for SSc in combination with codes for intestinal pseudo-obstruction. We used multivariate logistic and linear regression, adjusting for potential confounders and comorbidities using a modified Charlson comorbidity index, to determine the risks for surgical procedures (total or partial resection of small or large intestine), use of parenteral nutrition, and in-hospital mortality, and to estimate the length of stay in SSc patients compared with controls.

Results: A total of 193610 SSc hospitalizations occurred in the US between 2002 and 2011, of which 5.4% (n=10386) were associated with a concurrent intestinal pseudo-obstruction diagnosis (cases). The mean age of this group was 62.5±0.4 years, 81% were female, and 55% Caucasian. In-hospital mortality was 7.3%, mean length of stay was 9.3±0.3 days, 13.5% received parenteral nutrition, and 6% underwent surgical procedures (Table 1). In multivariate analyses, cases were more likely to die during the inpatient stay and to receive parenteral nutrition than patients with idiopathic intestinal pseudo-obstruction (control group 1), patients with intestinal pseudo-obstruction and diabetes (control group 2), and SSc patients without intestinal pseudo-obstruction (control group 3). Cases had longer in-hospital stay than control groups 2 and 3, and were less likely to undergo surgical procedures than control groups 1 and 2 (Table 2).

Conclusion: The prevalence of intestinal pseudo-obstruction in patients with SSc was 5.4% in this large US-based hospitalization database. SSc patients with intestinal pseudo-obstruction are more likely to die and to receive parenteral nutrition than patients with intestinal pseudo-obstruction secondary to other causes and SSc patients without intestinal pseudo-obstruction.

Table 1

	Cases n (%)	Controls 1 n (%)	Controls 2 n (%)	Controls 3 n (%)
Length of stay (days ± SD)	9.3 ± 0.3	8.4 ± 0.1	8.3 ± 0.1	6.0 ± 0.1
In-hospital mortality	757 (7.3)	200154 (5.1)	54322 (4.7)	9394 (5.1)
Surgical procedures	620 (6)	307976 (7.8)	89292 (7.7)	1088 (0.6)
Parenteral nutrition	1397 (13.5)	243752 (6.2)	66665 (5.7)	3765 (2.1)

Table 2

	In-hospital mortality		Parenteral nutrition		Surgical Procedures		Length of stay					
	OR	95%CI	*p*-value	OR	95%CI	*p*-value	OR	95%CI	*p*-value	b	95%CI	*p*-value
Cases vs Controls 1	1.3	1.02–1.52	0.029	2.3	1.95–2.63	<.0001	0.8	0.68–0.98	0.66	0.2	−0.26–0.72	0.355
Cases vs controls 2	2.4	1.99–2.8	<.0001	2.8	2.39–3.22	<.0001	0.8	0.67–0.96	0.017	1.4	0.88–1.85	<.0001
Cases vs control 3	1.3	1.12–1.60	0.002	7.4	6.25–8.66	<.0001	10.9	8.7–13.7	<.0001	3.2	2.74–3.71	<.0001

OR=Odds ratios, b= b-coefficient, Cases= patients with SSc and intestinal pseudo-obstruction, Controls 1=patients with idiopathic intestinal pseudo-obstruction, Controls 2=patients with intestinal pseudo-obstruction and diabetes, Controls 3=patients with SSc without intestinal pseudo-obstruction. All multivariate model included age, gender, race and modified Charlson comorbidity index

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Development and External Validation of a Five-Year Mortality Risk Stratification Tool for Early Diffuse Systemic Sclerosis Patients. Robyn T. Domsic[1], Svetlana I. Nihtyanova[2], Mary Lucas[1], Stephen R. Wisniewski[3], Michael J. Fine[4], C. Kent Kwoh[5], Christopher P. Denton[6] and Thomas A. Medsger Jr.[1]. [1]University of Pittsburgh, Pittsburgh, PA, [2]Royal Free and University College Medical School, London, United Kingdom, [3]University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, [4]University of Pittsburgh and Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare, Pittsburgh, PA, [5]The University of Arizona Arthritis Center, Tucson, AZ, [6]Centre for Rheumatology, Royal Free and University College Medical School, London, United Kingdom.

Background/Purpose: Knowledge of mortality risk and predictors is important in systemic sclerosis (SSc) patient care and clinical trial design. There is no validated 5-year mortality model in early diffuse SSc (dcSSc); a high risk population. The objective of this study was to derive and externally validate a 5-year mortality risk stratification tool in early dcSSc patients.

Methods: The derivation cohort was a prospectively enrolled inception cohort of adult early dcSSc patients first seen between 1980 and 2009 and enrolled in a US Scleroderma Center databank. Early dcSSc was defined as <2 years from the first SSc symptom and proximal skin thickening. Predefined candidate predictor variables at the first visit (demographic, history, exam, lab values, organ system objective tests) were placed into a stepwise multivariable logistic regression model. Regression diagnostics were performed. Beta-estimates were rounded to the nearest 1, and then summed for a total score, which was then classified into low, moderate and high risk morality categories. The external validation cohort was a large UK Scleroderma Center databank, with patients meeting identical inclusion criteria and an initial visit between 2000 and 2008. Area under the curve (AUC) was calculated to assess discrimination in the derivation and validation cohorts, and stratum-specific chi-square analysis performed.

Results: In the US derivation cohort, 760 early dcSSc patients were identified, of whom 388 were Caucasian and had all objective testing required to assess internal organ involvement at the first visit. The mean age was 50.4±13.3 years, 76% female and median disease duration 0.93 years (IQR 0.63, 1.33). The mean skin thickness score was 26.1 ± 11.7. After 5 years, 110 of the 388 (28.4%) had died. 144 patients composed the UK validation cohort, with no significant differences in age, gender or skin score from the US cohort. Median disease duration was longer at 1.02 (0.78,1.45) years (p=0.03). At 5 years 38/144 (26.4%) had died, which was not different (p=0.65) from the US cohort.

Table 1: Multivariable model and risk point assignment for 5-year mortality

Characteristics	β	Odds Ratio	95% Confidence Interval	p-value	Point Assigned
Age at first visit (years)	−0.66	0.56	0.20–1.53	<0.001	−1
<35	−0.38	0.69	0.31–1.54		0
35-44	–	1	–		0
45-54	0.76	1.96	0.94–4.10		1
55-64	1.4	4.12	1.92–8.85		1
>65					
Male gender	0.55	1.8	1.01–3.20	0.05	1
Tendon friction rubs	0.73	1.94	1.02–3.70	0.002	1
2-Jan	1.34	3.36	1.71–6.59		1
≥3					
GI involvement*	0.93	2.42	1.39–4.21	0.002	1
RNA polymerase III antibody†	−0.86	0.41	0.23–0.72	0.002	−1
Anemia (hemoglobin < 12 mg/dL)	0.62	2.17	1.25–3.76	0.0006	1
Total Sum Score					

*defined as any one of the following: heartburn *plus* dysphagia, abnormal esophagram or manometry, antibiotics for or documented small bowel bacterial overgrowth, small bowel dysmotility by radiographic imaging, pseudoobstruction, malabsorption or necessity for hyperalimentation.
†note that RNA polymerase III is protective.

Significant independent predictors of 5-year mortality at first visit were age, gender, tendon friction rubs, GI involvement, RNA polymerase III antibody and anemia (Table 1). The AUC in the US derivation cohort was 0.79 (95% CI 0.74–0.84) for the overall model and 0.74 (0.65–0.82) in the UK cohort. Using the total sum score, risk stratification was defined as low (≤0), moderate (1–2) and high (≥3) risk. The AUC for the 3-level risk stratification in the US derivation cohort was 0.76 (0.72–0.81) compared to 0.68 (0.60–0.76) in the UK validation cohort (p=0.24). There were no significant differences in mortality rate between each strata of the risk stratification model in the US and UK cohorts.

Conclusion: We have developed and externally validated an easy-to-use 3-level risk stratification tool for 5-year mortality in *early* dcSSc patients. This tool requires only history, exam and bloodwork.

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Screening for Interstitial Lung Disease in Systemic Sclerosis: Performance of High-Resolution Computed Tomography with Limited Number of Slices – a Prospective Study. Thomas Frauenfelder[1], Anna Winklehner[1], Thi Dan Linh Nguyen[1], Rucsandra Dobrota[2], Stephan Baumüller[1], Britta Maurer[3] and Oliver Distler[3]. [1]Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, Zurich, Switzerland, [2]Department of Internal Medicine and Rheumatology, Dr.I.Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, [3]Division of Rheumatology, University Hospital Zurich, Zurich, Switzerland.

Background/Purpose: Early diagnosis of interstitial lung disease (ILD), currently the main cause of death in systemic sclerosis (SSc), is needed. The gold standard is high resolution computed tomography (HRCT) of the chest, but regular screening faces the risk of increased radiation exposure. We perform a prospective validation of a dedicated, 9-slice HRCT protocol with reduced radiation dose for the detection of ILD in patients with SSc.

Methods: We analysed 170/205 consecutive patients with SSc. Whole chest HRCT, serving as standard of reference, and the reduced HRCT with 9 slices allocated according to a basal-apical gradient were obtained. ILD presence, extent (>or<20%) and diagnostic confidence were assessed. The reduced CT was independently analysed by 2 blinded radiologists, who also evaluated image quality. The effective radiation doses and the test performance parameters of the reduced HRCT were calculated.

Results: The study cohort included early (n=66), limited cutaneous SSc (n=66) and diffuse cutaneous SSc (n=34) patients, with a median disease duration of 60 months (Q1;Q3 28,120). Standard chest HRCT showed ILD in 77/170 patients. With the reduced HRCT, 68/77 cases with ILD were identified (sensitivity 88.3%, both readers). The accuracy (91.8%-reader1, 94.7%-reader2), diagnostic confidence (98.8%-reader1, 95.3%-reader2) and image quality rates were high (Table 1). Missed cases were exclusively borderline to minimal ILD on standard CT. Minimal ILD was correctly quantified in 73.1% (reader1) /71.2% (reader2) and extensive ILD in 88% (reader 1) /100% (reader 2) (Table 2). Importantly, the reduced CT had a significantly lower radiation dose. The mean DLP (effective dose) was only 5.66±4.46 mGycm (0.08±0.06 mSv), compared with the standard protocol dose of 149.00±95.90 mGycm (2.09±1.34 mSv).

The presence of associated lung pathology was also assessed. In this cohort, 8/10 lung nodules were also detected on the reduced CT (all <6 mm diameter and stable at follow-up).

Table 1. Estimated accuracy and diagnostic certainty in detecting ILD on reduced CT scans

	Reader 1	Reader 2
Sensitivity (95% CI)	88.3% (78.5%–94.2%)	88.3% (78.5%–94.2%)
Specificity (95% CI)	94.6% (87.3%–98.0%)	100% (95.1%–100%)
Accuracy	91.8%	94.7%
NPV (95% CI)	90.7% (82.7%–95.4%)	91.2% (83.5%–95.6%)
High diagnostic confidence*	98.8%	95.3%

* degree of confidence score 1 or 2 (i.e. 1 = fully confident; 2 = probably confident); CI = Confidence interval (in parenthesis), NPV = Negative predictive value

Table 2. Estimated extent of ILD in standard CT and reduced CT scans

	Estimated extent in reduced CT			
Lung involvement in standard CT	**No ILD** Reader 1/2	**Minimal (<20%)** Reader 1/2	**Extensive (>20%)** Reader 1/2	**Indeterminate** Reader 1/2
Minimal (<20%) n = 52	n = 9/9	**n = 38/37***	n = 5/6	n = 0/0
Extensive (>20%) n = 25	n = 0/0	n = 3/0	**n = 22/25***	n = 0/0

ILD was present in 77 patients in standard CT. *Correctly estimated extent in reduced CT as compared to standard CT.

Conclusion: The above-described reduced chest HRCT protocol reliably detects even mild SSc-ILD in clinical practice, with the advantage of a much lower radiation dose compared to standard whole chest HRCT. This makes it an attractive protocol for periodical screening for ILD in SSc.

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2999

Development of a Composite Index for Clinical Trials in Early Diffuse Cutaneous Systemic sclerosis—the Combined Response Index in Systemic Sclerosis. Dinesh Khanna[1], Veronica Berrocal[2], Edward Giannini[3], Maureen Mayes[4], Peter A. Merkel[5], Jeffrey Siegel[6], James R. Seibold[7], Murray Baron[8], Philip J. Clements[9], Yannick Allanore[10], Virginia D. Steen[11], Christopher P. Denton[12], Oliver Distler[13], Sindhu R. Johnson[14], Marco Matucci-Cerinic[15], Lazlo Czirjak[16], Janet E. Pope[17], Susanna Proudman[18], Weng Kee Wong[19], Athol U. Wells[20] and Daniel E. Furst[9]. [1]University of Michigan Scleroderma Program, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI, [3]Childrens Hosp Med Ctr, Cincinnati, OH, [4]University of TX Health Science Center -Houston, Houston, TX, [5]Boston University School of Medicine, Boston, MA, [6]Genentech, South San Francisco, CA, [7]Scleroderma Research Consultants LLC, Avon, CT, [8]Lady David Institute for Medical Research and Jewish General Hospital, Montreal, QC, [9]University of California, Los Angeles, Department of Medicine, Los Angeles, CA, [10]Department of Rheumatology, University Paris Descartes and Cochin Hospital, Paris, France, [11]Georgetown University Medical Center, Washington, DC, [12]UCL Medical School Royal Free Campus, London, United Kingdom, [13]University Hospital Zurich, Zurich, Switzerland, [14]Division of Rheumatology, Toronto Western Hospital, University Health Network Pulmonary Hypertension Programme, Toronto General Hospital, Mount Sinai Hospital and University of Toronto, Toronto, ON, [15]University of Florence, Florence, Italy, [16]University of Pécs, Pécs, Hungary, [17]Western University, London, ON, [18]Royal Adelaide Hospital, Adelaide, Australia, [19]UCLA Fielding School of Public Health, Los Angeles, CA, [20]Department of Radiology, London, United Kingdom.

Background/Purpose: Diffuse systemic sclerosis (dcSSc) is a multisystem disease that involves skin and internal organs. Our objective was to develop a composite response index in dcSSc (CRISS) for use in clinical trials using expert consensus and data driven approaches.

Methods: Consensus was achieved on core set measures for a 1-year multicenter trial where 11 domains and 31 core items were proposed. Subsequently, a prospective NIH-funded observational cohort of 200 early dcSSc (disease duration < 5 years) was established to assess psychometric properties of the core measures. Using data from the cohort study and literature review, the steering committee assessed the feasibility, reliability, validity, and sensitivity to change for each core set measure. For endorsed core measures, paper patient profiles (n=150) were developed using cohorts from NIH and the Canadian Scleroderma Research Group. The literature was searched to assess the most prevalent/ bothersome issues faced by patients with SSc. 54 SSc experts were invited to participate in web-based evaluation to rate 20 patient profiles each on: 1. whether each patient had improved, worsened, or stabilized, and 2. rank the 3 most important variables that influenced their decision regarding change. Cluster analysis was conducted on the experts' answers to determine clusters that identified the most influential core items. We defined consensus as 75% agreement among the experts of a patient's status (improved, worsened or stabilized). Using only profiles where consensus was reached, we fit logistic regression models to the experts' ratings for patients being improved vs. not and the core items as covariates. For each model, sensitivity, specificity and AUC were computed and predicted probabilities of improvement were derived for each patient profile. CRISS algorithm was subsequently evaluated in a RCT of methotrexate vs. placebo of dcSSc (Pope A&R 2001).

Results: 16 of 31 variables were chosen to be included as part of the patient profiles after review of test characteristics and available literature by the Steering Committee. Literature review suggested pain and fatigue as important attributes in SSc and were also included. 40 experts rated patient profiles and consensus was achieved in 118 of 150 profiles. Patients were not considered improved if they developed: 1. New renal crisis; 2. New decline in FVC% predicted by 15% (relative) and confirmed after 1 month; and 3. New onset left ventricular failure (systolic ejection fraction <45%) or PAH. Ranking and cluster analysis indicated that the change in the modified Rodnan skin score, FVC% predicted, patient and physician global assessments, and HAQ-DI had an AUC of 0.986; sensitivity of 0.982 (95%CI 0.981–0.983) and specificity of 0.931 (95% CI 0.929–0.932). A cut-off at 0.6 in the predicted probability of being improved yielded the smallest misclassification error. In the patients with complete data in the MTX

trial, 58% of MTX group vs. 19% in placebo group were considered improved.

Conclusion: We've developed a feasible composite response index with strong ability to discriminate patients who have improved vs. those who have not. The CRISS is currently being validated in RCTs of dcSSc.

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3000

Comparison of Systemic Sclerosis Subsets As Predictors of Mortality and Morbidity. Hebah Alhajeri[1], Marie Hudson[1], Canadian Scleroderma Research Group CSRG[1] and Murray Baron[2]. [1]McGill University, Montreal, QC, [2]Lady David Institute for Medical Research and Jewish General Hospital, Montreal, QC.

Background/Purpose: Identifying systemic sclerosis (SSc) subsets that predict mortality and morbidity could provide useful prognostic information. We undertook this study to compare the predictive ability of different approaches to subsetting SSc.

Methods: SSc subjects from the Canadian Scleroderma Research Group cohort were studied. Three approaches to subsetting were used: Leroy subsets based on skin involvement (limited (lcSSc) and diffuse cutaneous (dcSSc) subsets), serological subsets (anti-centromere (ACA), anti-topoisomerase I (ATA) and anti-RNA polymerase III (RNAP)), and unsupervised cluster analysis based on the items in the ACR/EULAR 2013 classification criteria, of which 3 clusters were identified (cluster 1 (ACA negative subjects with digital ulcers (DU)), cluster 2 (ACA positive subjects), and cluster 3 (ACA negative subjects with no DU)). Morbidity was defined as forced vital capacity (FVC) $<$ 70% predicted, interstitial lung disease (ILD), pulmonary hypertension (PH) and impaired health-related quality of life (defined as SF-36 Physical Component Summary (PCS) score $<$ 40). Kaplan Meier curves were generated to compare the time to event between the various subsets. Log rank p values $<$ 0.05 were considered statistically significant.

Results: 805 subjects were included (86.1% (N=693) female, 49.8% (N=401) dcSSc, disease duration since onset of first non-Raynaud's disease manifestation 10.8±9.2 years). Subsetting based on autoantibodies and unsupervised clustering (but not Leroy classification) predicted mortality, with ACA having better survival than RNAP and cluster 1 having better survival than the 2 other clusters. All three approaches to subsetting predicted FVC $<$ 70% and development of ILD: dcSSc was worse than lcSSc, ACA was better than ATA and RNAP, and cluster 1 was better than the other clusters. None of the 3 approaches to subsetting predicted time to PH. Subsetting based on Leroy classification and autoantibodies, but not clusters, predicted time to SF-36 PCS $<$ 40, with dcSSc worse than lcSSc, and ATA worse than ACA.

Conclusion: Different approaches to subsetting provide different prognostic information. Subsetting based on clinical and serological profiles remains a challenge in SSc. In the future, subsetting based on molecular profiles may improve the predictive ability of SSc subsets.

	Mortality				FVC<70% predicted				ILD				PH				SF-36 PCS < 40			
	N	N of events	Time to event (years)	P	N	N of events	Time to event (years)	P	N	N of events	Time to event (years)	P	N	N of events	Time to event (years)	P	N	N of events	Time to event (years)	P
Leroy subsets																				
dcSSc	384	66	13.0	ns	251	30	12.7	*	215	68	11.8	*	258	18	12.4	ns	145	69	12.0	*
lcSSc	350	50	13.9		228	15	13.4		229	34	13.1		233	19	13.3		126	36	12.8	
Serology																				
ACA	250	31	14.2		176	14	14.0		185	26	13.6		162	10	13.3	ns	102	37	12.4	
ATA	107	16	11.6		68	21	11.7	*	46	17	10.1	*	68	5	11.1		40	18	9.6	*
RNAP	127	29	11.9	*	80	9	11.0	*	74	27	10.6	*	87	8	11.5		37	17	12.3	
Clusters#																				
Cluster 1	240	26	14.1		173	3	14.0		187	27	13.7		159	11	13.3	ns	103	37	12.6	ns
Cluster 2	237	44	12.1	*	161	19	11.8	*	153	44	11.3	*	174	15	11.7		91	36	11.9	
Cluster 3	268	49	14.0	*	150	24	13.5	*	108	32	12.1	*	163	11	13.7		79	32	12.5	

ns – not statistically significant; * p value $<$ 0.05; ACA is the reference group; # Cluster 1 is the reference group

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ACR Concurrent Abstract Session
Systemic Sclerosis, Fibrosing Syndromes and Raynaud's - Pathogenesis, Animal Models and Genetics II
Wednesday, November 19, 2014, 9:00 AM–10:30 AM

3001

Targeting IL-6 By Both Passive or Active Immunization Strategies Prevents Inflammation-Driven Skin Fibrosis. Jerome Avouac[1], Lucille Desallais[2], Maxime Fréchet[3], Muriel Elhai[3], Jean François Zagury[2] and Yannick Allanore[1]. [1]Paris Descartes University, Rheumatology A Department and INSERM U1016, Cochin Hospital, Paris, France, [2]Chaire de Bioinformatique, Laboratoire Génomique, Bioinformatique et Applications, EA 4627, Conservatoire National des Arts et Métiers, Paris, France, [3]INSERM U1016, Cochin Institute, Paris, France.

Background/Purpose: Interleukin 6 (IL-6) is a pleiotropic cytokine involved in inflammatory and autoimmune processes. Preliminary data have suggested that IL-6 might contribute to systemic sclerosis (SSc). Our aims were to investigate i) IL6 expression in SSc patients ii) the efficacy of both passive and active immunization against IL-6 to reduce skin fibrosis in complementary mouse models of SSc.

Methods: Human serum levels and skin expression of IL-6 were determined by ELISA and immunohistochemistry, respectively. We evaluated the monoclonal IL-6R antibody MR16-1 in the mouse model of bleomycin-induced dermal fibrosis, reflecting early and inflammatory stages of SSc. Six-week-old DBA/2 mice received in parallel subcutaneous injections bleomycin (0,5 mg/ml) and intraperitoneal (ip.) injection of MR16-1 or control antibody at a dose of 2 mg at day 0 followed by one ip. injection of 1 mg at day 7 and 14. Then, we assessed the merit of MR-16 in the tight skin (Tsk-1) mice, an inflammation-independent mouse model of skin fibrosis. Tsk-1 mice received a first ip. injection of 2 mg of MR16-1 or control antibody at the age of 5 weeks followed by one ip. injection of 1 mg once a week for 5 weeks. Thereafter, because of the drawbacks of anti-cytokine monoclonal antibodies, we developed an innovative strategy using active immunization against a small peptide derived from murine IL-6, which was performed in the mouse model of bleomycin-induced dermal fibrosis. Infiltrating leukocytes, T cells and B cells were quantified, and IL-6 levels were measured in the serum and lesional skin of mice after passive or active immunization.

Results: Serum and skin levels of IL-6 were significantly increased in patients with early SSc. Passive immunization with MR16-1 exerted antifibrotic effects in the mouse model of bleomycin-induced dermal fibrosis: dermal thickness, hydroxyproline content and myofibroblast counts were reduced by 25±4% (P=0.02), 30±6% (P=0.007) and 45±7% (P=0.005) respectively, compared to mice receiving control antibody. MR16-1 demonstrated no efficacy in Tsk-1 mice. Mice immunized against the mIS200 peptide derived from murine IL-6 exhibited in the bleomycin mouse model similar antifibrotic effects as passive immunization. We observed a significant reduction of dermal thickness by 20±3% (P=0.02), hydroxyproline content by 25±4% (P=0.005) and myofibroblast counts by 41±9% (P=0.01), compared to the group immunized against the carrier protein alone. Passive and active immunization led to decreased T cell infiltration in the lesional skin of mice challenged with bleomycin. Upon bleomycin injections, serum and skin IL-6 levels were increased after treatment with MR16-1, and were significantly reduced after the anti-IL-6 active immunization.

Conclusion: Our results support the relevance of targeting IL-6 in patients with early SSc since IL-6 is overexpressed in early stages of the disease. Targeting IL-6 by both passive or active immunization strategies prevented the development of bleomycin-induced dermal fibrosis in mice. Our results highlight the therapeutic potential of active immunization against IL-6, which is a seducing alternative to passive immunization.

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3002

Anti-Fibrotic Effects of a Newly Discovered HGF Receptor Carboxy-Terminal Fragment in Systemic Sclerosis. Yuichiro Shirai[1], Ilia Atanelishvili[2], Tanjina Akter[1], Richard Silver[3] and Galina Bogatkevich[1]. [1]Medical University of South Carolina, Charleston, SC, [2]Medical University of South Carolina, Charleston, USA, Charleston, SC, [3]Medical University of South Carolina, Charleston, SC.

Background/Purpose: Systemic sclerosis (SSc) is an irreversible fibrotic disorder with interstitial lung disease (ILD) being a major complication and leading cause of mortality. African American SSc patients exhibit higher prevalence of ILD and worse outcomes than those of other races. We previously reported that a cell-protective and antifibrotic factor, hepatocyte growth factor (HGF), is downregulated in bronchoalveolar lavage fluid and plasma from African American SSc-ILD patients compared with white SSc-ILD patients. Here we report a newly identified C-terminal fragment of the HGF receptor, designated as "M10", as a peptide with robust antifibrotic properties that is lacking in certain African American SSc-ILD patients.

Methods: Lung tissue was collected postmortem from SSc patients with ILD and RNA was extracted from lung fibroblasts. The coding exons of the HGF receptor, MET (mesenchymal-epithelial transition factor), were amplified by PCR, and sequences were analyzed. Adenoviruses carrying wild type MET gene or the D1398G mutant observed in African American patients were generated. Lung fibroblasts were infected by either type of adenovirus and treated with HGF, transforming growth factor-β (TGF-β), and the M10 peptide. MET phosphorylation, connective tissue growth factor (CTGF, CCN2) and collagen expression was examined by immunoblotting. Potential peptide-protein interactions were modulated *in-silico*.

Results: We have identified the D1398G mutation in African American SSc-ILD patients whose MET signaling is impaired. When we compared MET phosphorylation following HGF treatment between normal lung fibroblasts expressing wild type or the D1398G MET, we found that the D1398G mutant showed reduced MET phosphorylation. Additionally, normal fibroblasts expressing the D1398G mutant exhibited a diminished reduction in CTGF and collagen expression following HGF treatment compared with wild type. Sequence analysis revealed that the D1398G mutation is located at the terminal amino acid sequence of "DEVD" which is a Caspase-3 cleavage motif, suggesting that the D1398G MET mutant is incapable of generating the terminal 10-amino-acid-fragment of MET, M10. We found that synthetic M10 effectively reduces, in a dose-dependent manner, collagen and CTGF in SSc fibroblasts. Computational molecular modeling based on the peptide-binding sites from protein surfaces predicts that M10 may negatively regulate TGF-β signaling by an interaction with protein domains identified as 2KXQ and 1U7V (Protein Data Bank).

Conclusion: A D1398G mutation in MET is associated with impaired phosphorylation and reduced HGF signaling in African American SSc-ILD lung fibroblasts. On the other hand, the M10 peptide generated from wild type MET signaling demonstrates strong antifibrotic effects and should be considered as a potential therapeutic agent for SSc-ILD and other fibrosing diseases.

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3003

Am80 Ameliorates Bleomycin-Induced Dermal Fibrosis By Suppressing the Pro-Fibrotic Phenotype of Fibroblasts, Endothelial Cells, and Immune Cells. Tetsuo Toyama[1], Yoshihide Asano[1], Takehiro Takahashi[1], Ryosuke Saigusa[1], Yohei Ichimura[1], Takashi Taniguchi[1], Shinji Noda[1], Kaname Akamata[1], Shinichi Sato[1], Takafumi Kadono[1] and Koichi Shudo[2]. [1]University of Tokyo Graduate School of Medicine, Tokyo, Japan, [2]Reseach Foundation ITSUU Laboratory, Tokyo, Japan.

Background/Purpose: Am80 is a synthetic retinoid serving as an agonist for retinoic acid receptor α/β with chemical and pharmacological advantages over all-trans retinoic acid, such as higher chemical stability, a lower affinity for cellular retinoic acid-binding protein, and a lack of affinity for retinoic acid receptor-γ. Am80 has been shown to modulate the pathological processes of various autoimmune and inflammatory diseases and their animal models. The aim of this study was to investigate the effect of Am80 on dermal fibrosis of a bleomycin (BLM)-induced animal model of systemic sclerosis (SSc), normal dermal fibroblasts treated with TGF-β1 and SSc dermal fibroblasts.

Methods: A BLM-induced murine model of SSc was generated with wild type C57BL/6 mice in the presence or absence of oral administration of Am80. The mRNA and protein levels of target molecules were determined by quantitative reverse transcription-PCR, immunostaining, and immunoblotting in the skin and cultured cells. Th1/Th2/Th17 polarization of immune response and macrophages polarization were evaluated by flow cytometry.

Results: Am80 significantly decreased tissue fibrosis and mRNA levels of the *Tgfb* and *Ctgf* genes in the lesional skin of BLM-treated mice. In response to Am80, the expression levels of cytokines and chemokines, including IL-4, IL-10, IL-13, IL-17A, TNF-α, IFN-γ, and MCP-1, in the lesional skin were decreased and the differentiation of naïve $CD4^+$ T cells into cytokine producing effector T cells, such as Th1/Th2/Th17 cells, and regulatory T cells were suppressed in BLM-treated mice. In addition, the infiltration of macrophages, mast cells, and T cells was attenuated by Am80 in BLM-treated mice. Am80 also exerted on dermal microvascular endothelial cells through attenuating the induction of endothelial-to-mesenchymal transition and the expression of intercellular adhesion molecule-1, and shifted macrophages from M2 phenotype to M1 phenotype. Furthermore, Am80 directly reversed the pro-fibrotic phenotype of normal dermal fibroblasts treated with TGF-β1 and SSc dermal fibroblasts via suppressing the transcription and reducing the mRNA stability of *COL1A2* gene, increasing mRNA levels of *MMP-1* gene, and decreasing mRNA levels of *CTGF* gene.

Conclusion: These results suggest that Am80 inhibits the development of experimental dermal fibrosis via reversing the pro-fibrotic phenotype of fibroblasts, dermal microvascular endothelial cells, and immune cells and would be a candidate of new therapeutic drugs against dermal fibrosis of SSc.

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3004

Autoantibody-Mediated Raynaud's Phenomenon: Animal Model and Human Disease. Dana P. Ascherman[1], Yunjuan Zang[2], Laisel Martinez[1], Judith Pignac-Kobinger[2], Irina Fernandez[2] and Eric L. Greidinger[2]. [1]Miami VAMC, Miami, FL, [2]University of Miami, Miami, FL.

Background/Purpose: Raynaud's Phenomenon (RP) is frequently seen in autoimmune conditions, but an autoimmune basis for RP has not been established.

Methods: Sera derived from anti-RNP+ individuals were screened for antibodies associated with RP by immunoprecipitation, western blot, and ELISA. Autoantigen targets were then identified by mass spectrometry. Biological effects of antigen-specific monoclonal antibodies as well as human and murine antisera were assessed in in vitro endothelial cell culture and in vivo adoptive transfer experiments involving various wild type and knockout mice.

Results: Immunoprecipitation and mass spectrometric sequencing identified cytokeratin 10 (K10) as a putative antigen linked to RP in anti-RNP+ sera. Subsequent ELISA-based screening of 123 anti-RNP+ patients demonstrated that antibodies to K10 were strongly linked to the presence of RP (present in 92% of RP patients; Odds Ratio of RP in anti-K10+ patients = 4.6 (95% confidence interval 1.6–13.4). In vitro endothelial expression of K10 was confirmed at the mRNA and protein level by rtPCR and western blot, respectively. Fluorescence microscopy further demonstrated that anti-K10 antibodies bound to the surface of K10-expressing endothelial cells, with corresponding induction of endothelial cell apoptosis not observed with control antibodies. Endothelial cell K10 expression (but not other cytokeratins) was found to be dramatically upregulated by cold exposure in vitro. Consistent with these observations, in vivo passive transfer of anti-K10+ antisera or anti-K10 monoclonal antibodies to wild type recipient mice induced a high rate of ischemia and damage of thermoregulatory tissues (ears and tail) that was exacerbated by preconditioning with cold exposure. These effects were not observed in K10 knockout mice, which were resistant to tissue ischemia induced by either anti-K10 antisera or mAb.

Conclusion: Anti-K10 antibodies induce endothelial apoptosis, mediate a murine model of RP via their recognition of the K10 antigen, and are strongly linked with clinically evident RP in human anti-RNP autoimmunity. These findings suggest that RP may be driven by anti-K10 or other endothelial apoptosis-inducing antibodies, establishing the foundation for development of novel diagnostic and treatment modalities in this frequent complication of systemic autoimmune disease.

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3005

Essential Role for Alternately Spliced Tenascin C and TLR4 Signaling in Persistent Organ Fibrosis. Swati Bhattacharyya[1], Wenxia Wang[1], Luisa Morales-Nebreda[1], Katja Lakota[1], Robert Lafyatis[2], Monique E. Hinchcliff[1], GR Scott Budinger[1], Zenshiro Tamaki[1] and John Varga[3]. [1]Northwestern University, Feinberg School of Medicine, Chicago, IL, [2]Boston University School of Medicine, Boston, MA, [3]Northwestern University Feinberg School of Medicine, Chicago, IL.

Background/Purpose: Transforming growth factor-beta stimulates collagen synthesis and myofibroblast differentiation, and is implicated as a key initiating factor in pathological tissue remodeling in scleroderma. However, the mechanism responsible for the persistence fibrotic response associated with scleroderma is not well understood. Recent studies provide evidence for activated innate immunity in patients with scleroderma. Many alternately spliced factors that govern normal embryonic and fetal development are currently recognized as being central to postnatal repair and injury responses. We hypothesized that tissue injury in scleroderma leads to generation and accumulation of alternately spliced extracellular matrix molecules such as tenascin C that are recognized by, and serve as endogenous ligands for TLR4 to drive persistent fibrosis.

Methods: Tissue expression of tenascin C was investigated in scleroderma skin biopsies by microarray, immunofluorescence and real-time qPCR. Tenascin C was assayed in 3-D human skin equivalents reconstituted with scleroderma fibroblasts and in scleroderma serum. Cellular responses elicited by tenascin C in human and mouse skin fibroblasts and in 3-D organotypic human skin equivalents were examined. The role of tenascin C in scleroderma skin and lung fibrosis was investigated using tenascin C-null mouse.

Results: Levels of an alternately spliced full-length tenascin C isoform (TN-FL) were markedly elevated in scleroderma serum and skin biopsies, as well as in fibrotic skin and lung tissues from mice. TN-FL mRNA level correlated with the skin score. The splicing factor serine/arginine-rich (SR)-rich splicing factor SRSF6, implicated in alternate splicing of tenascin C, was elevated in scleroderma skin biopsies as well as in scleroderma fibroblasts populating skin equivalents. Treatment with TGF-β stimulated the expression of both SRSF6 and TN-FL. In vitro, TN-FL stimulated collagen synthesis and myofibroblasts differentiation, and induced dermal sclerosis in skin equivalents. All of these profibrotic responses were abolished by genetic or pharmacological disruption of TLR4 signaling. Importantly, tenascin C-null mice treated with bleomycin were protected from development of skin and lung fibrosis and loss of lung compliance.

Conclusion: Increased SRSF6-driven alternate splicing of tenascin C leads to aberrant TN-FL accumulation in scleroderma. TN-FL triggers TLR4-dependent fibroblasts activation, contributing to intractable skin and lung fibrogenesis. Disrupting the tenascin C-TLR4 signaling axis by preventing tenascin C accumulation through SRSF6 blockade, or by blocking TLR4 signaling using selective small molecule inhibitors, represent appealing novel strategies for attenuating progressive fibrosis as treatment for scleroderma.

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3006

Activation of the Thromboxane A2 Receptor By 8-Isoprostane Inhibits the Pro-Angiogenic Effect of Vascular Endothelial Growth Factor in Scleroderma. Pei-Suen Tsou[1], George Zakhem[2], Beatrix Balogh[2], M. Asif Amin[3], Phillip Campbell[3], Gautam Edhayan[3], Ray A. Ohara[3], Elena Schiopu[3], Dinesh Khanna[1], Alisa E. Koch[4] and David A. Fox[3]. [1]University of Michigan Scleroderma Program, Ann Arbor, MI, [2]University of Michigan Medical School, Ann Arbor, MI, [3]Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI, [4]Department of Veteran's Affairs and University of Michigan, Ann Arbor, MI.

Background/Purpose: Scleroderma (SSc) is a complex disease characterized by inflammation, vasculopathy, and excessive deposition of extracellular matrix. Various studies have demonstrated a paradoxical increase in angiogenic mediators, such as vascular endothelial growth factor (VEGF), in both the skin and serum of patients with SSc. Despite this, angiogenesis does not occur normally. 8-isoprostane is an oxidized lipid created by excessive oxidative stress, and has been shown to be elevated in SSc. The thromboxane A2 receptor (TXAR) and ROCK pathway, which can be activated by 8-isoprostane (8-IP), inhibits VEGF-induced endothelial cell (EC) differentiation and migration. However, its role in SSc has not been examined. In this study we determined whether the TXAR pathway was activated by 8-IP in SSc ECs. Its effect on VEGF-induced angiogenesis was also determined.

Methods: Dermal ECs were isolated from punch biopsies from healthy subjects or patients with diffuse cutaneous SSc. Angiogenesis was assessed by chemotaxis and *in vitro*Matrigel tube formation assays. TXAR expression was determined by qPCR and Western blotting. Knockdown studies were performed using TXAR siRNAs.

Results: SSc patients had significantly higher 8-IP plasma levels (60.9 ± 8.4 pg/ml) compared to healthy subjects (24.9 ± 5.0 pg/ml, $p<0.05$). Increased oxidative stress was detected in SSc ECs as increased 8-IP in SSc EC conditioned media and excessive superoxide in SSc ECs were observed. In healthy ECs, 8-IP inhibited VEGF-induced EC migration, and the inactivation of TXAR or ROCK pathways restored VEGF-induced angiogenesis inhibited by 8-IP. In SSc ECs, VEGF did not induce EC migration, however, addition of the TXAR or ROCK inhibitors restored the pro-angiogenic effect of VEGF. This was further confirmed by TXAR siRNA experiments which showed that TXAR-knockdowned SSc ECs migrated towards VEGF while the SHAM-transfected ECs did not. We then measured ROCK activity in healthy and SSc ECs before and after VEGF or 8-IP stimulation. Basal ROCK activity was significantly higher in SSc ECs compared to healthy ECs. Moreover, 8-IP-induced ROCK activation was significantly higher in SSc ECs while VEGF induced significantly higher ROCK activation in healthy ECs. The expression of key players in this pathway was also examined. The protein expression of TXAR, RhoA, ROCK1/2 were all elevated in SSc ECs compared to healthy ECs.

Conclusion: We show that 8-IP inhibits VEGF-induced migration in healthy ECs through the TXAR/ROCK pathway. ECs not only produce high levels of 8-IP, but also show elevated expression of TXAR and RhoA/ROCK levels. This could explain the increased activation of the TXAR pathway in terms of ROCK activity in SSc ECs compared to healthy ECs. This hyper-activation leads to inhibition of VEGF-induced EC migration, as using the TXAR or ROCK inhibitor, as well as specific knockdown of TXAR, results in restoration of VEGF activity. These results suggest that the TXAR pathway plays a crucial role in angiogenesis and that 8-IP is not just a by-product as a result of oxidative stress, but instead plays a significant role in impaired angiogenesis that characterizes SSc.

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ARHP Concurrent Abstract Session
Clinical Practice/Patient Care
Wednesday, November 19, 2014, 9:00 AM–10:30 AM

3007

Can Knee Pain be Prevented through Diet and Exercise Among Those at High Risk? the Look Ahead Study. Daniel White[1], Tuhina Neogi[2], W. Jack Rejeski[3], Michael Walkup[3], Cora E. Lewis[4], Michael Nevitt[5], Capri Foy[3] and David T. Felson[2]. [1]Boston Univ School of Med, Boston, MA, [2]Boston University School of Medicine, Boston, MA, [3]Wake Forest University, Winston-Salem, NC, [4]The University of Alabama at Birmingham, Birmingham, AL, [5]UCSF, San Francisco, CA.

Background/Purpose: Weight loss combined with exercise is effective for reducing pain and improving function in adults with knee pain. However, it is not known if this same approach prevents the development of knee pain among those at high risk. We examined whether an intensive weight loss and exercise intervention prevented the development of knee pain among overweight and obese adults with type II diabetes, a group at risk for knee pain due to excess weight.

Methods: We carried out a secondary analysis of the Look AHEAD study, a multi-center randomized intervention trial of an intensive lifestyle intervention (ILI) vs. diabetes support and education (DSE) comparison group in adults with a BMI > 25 kg/m^2 and type II diabetes. Participants in the ILI had goals of reducing weight by 7% and participating in > 175 minutes/week of physical activity by one year. We included subjects with no knee pain at baseline and examined to what extent the ILI

group protected against developing knee pain at year 1 and 4. Knee pain was assessed by asking "Have you had any pain or discomfort in your knees in the past month?" In a second separate analysis, we examined whether meeting treatment goals, i.e., weight loss only, physical activity only, or both weight loss and physical activity, reduced the risk of developing knee pain compared with those not meeting any goal at year 1 and 4. This second analysis was performed in a subset of 989 participants whose clinic sites provided an accelerometer.

Results: Of the 2998 participants with no knee pain at baseline (age 58.5±6.7, men 44.9%, BMI 35.1±5.6) 50.1% were assigned to the ILI group and the remainder to the DSE. Subject characteristics were similar between groups at baseline. At year 1, ILI participants were 15% less likely to develop knee pain compared with. At year 4, this decreased to 5% and was not statistically significant. In the second analysis, participants meeting both weight loss and physical activity goals had 47% less risk of developing knee pain at year 1. Only those meeting the weight loss goal at year 1 had less risk that met statistical significance of developing knee pain at year 4.

Conclusion: An intensive lifestyle intervention of diet and exercise prevented the development of knee pain among those at high risk in the short-term. Weight loss appears to have the most relevant for preventing the development of knee pain over four years.

Table: (A) Association of an Intensive Lifestyle Intervention vs. Diabetes Support and Education control with developing knee pain (n = 2998). (B) Association of meeting treatment goals at one year with the development of knee pain at one and four years among all participants who were an accelerometer (n = 989).

	Knee Pain at Year 1		Knee Pain at Year 4	
A: Intervention vs control n = 2889	**n (%)**	**Adjusted* Risk Ratio [95% CI]**	**n (%)**	**Adjusted* Risk Ratio [95% CI]**
Diabetes Support and Education control n = 1441 (49.9%)	329 (22.8)	1.00 [REF]	393 (27.2)	1.00 [REF]
Intensive Lifestyle Intervention n = 1448 (50.1%)	281 (19.4)	0.85 [0.74, 0.98]	375 (25.9)	0.95 [0.84, 1.07]
B: Meeting treatment goals n = 989	**n (%)**	**Adjusted* Risk Ratio [95% CI]**	**n (%)**	**Adjusted* Risk Ratio [95% CI]**
Did not meet either treatment goal at 1 year n = 549 (55.5%)	**137 (25.0)**	**1.00 [REF]**	**166 (30.2)**	**1.00 [REF]**
Met only the weight loss goal at year 1 n = 229 (23.1%)	37 (16.2)	0.63 [0.46, 0.88]	44 (19.2)	0.62 [0.47, 0.83]
Met only the physical activity goal at year 1n = 106 (10.7%)	15 (14.2)	0.69 [0.42, 1.13]	21 (19.8)	0.79 [0.53, 1.20]
Met both treatment goals at year 1 n = 106 (10.7%)	13 (12.3)	0.53 [0.31, 0.90]	22 (20.8)	0.76 [0.51, 1.13]

*Adjusted for age, sex, BMI, race, NSAID use, and depressive symptoms

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3008

High Prevalence of Subclinical Ultrasonographic Enthesopathy and Synovitis in Patients with Inflammatory Bowel Disease without Clinical Signs or Symptoms of Spondyloarthritis. Esther Vicente[1], Silvia Pérez-Esteban[2], María Chaparro[1], Francisco Rodríguez-Salvanés[1], Lorena Vega[1], Santos Castañeda[1] and Javier P Gisbert[3]. [1]Hospital Universitario de La Princesa, IISP, Madrid, Spain, [2]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain, [3]Hospital Universitario de La Princesa. IIS La Princesa, Madrid, Spain.

Background/Purpose: Musculoskeletal manifestations as peripheral arthritis, axial disease and enthesitis are present in 10–62% of Inflammatory Bowel Disease (IBD) patients. Ultrasonography is more sensitive than physical examination to detect enthesopathy and synovitis, so we believe it may be useful to identify subclinical involvement.

Our Purpose is to evaluate the presence of subclinical enthesitis and synovitis with power Doppler ultrasonography (PDUS) in IBD patients and to investigate its correlation with IBD variables.

Methods: Cross-sectional study that recruited prospectively IBD patients, without clinically overt musculoskeletal disease, attended by Gastroenterology during 2013. Gastroenterological, rheumatological and PDUS evaluation, blind to each other, were performed. Clinical assessment included demographics, comorbidities, IBD characteristics and musculoskeletal clinical examination. PDUS evaluation consisted of the detection of grey scale (GS) and power Doppler (PD) signs of enthesopathy and synovitis in 12 enthesis scored according to the Madrid Ankylosing Spondylitis Enthesitis Index (MASEI) and in 44 joints using a LOGIQ7 General Electric machine with a 12-MHz linear array transducer. Statistical analysis: continuous variables are expressed as mean±SD or range and categorical variables as number of cases (%). The associations between PDUS and clinical variables were evaluated by the Student's t test, Mann-Whitney test, $\chi 2$ test or Pearson and Spearman correlations as appropriate. The intra-reader agreement for US was estimated in all the images obtained. Statistical significance was set at $p<0.05$ (Stata 10).

Results: A number of 23 (56.5% male) IBD patients [9 Crohn's disease and 14 ulcerative colitis] have been included so far. Clinical variables: Age 42±12 years, evolution time 9 years (range: 0.1–33), CDAI 28±21, Mayo index 0.4±1, DMARD therapy in 91.3% for 5.5±5.3 years, ESR 12±8.8 mm/h and CRP 0.12±0.14 mg/dL. A positive MASEI was present in 95.7%, with a mean score of 35.2±9.5. GS enthesal abnormalities were found in at least 1 enthesis in 100% of patients: enthesophytes or calcifications (100%), altered echoestructure (100%), increased thickness (100%), erosion (13%) and bursitis (34.8%). GS joint effusion and synovial hypertrophy in at least 1 joint were present in 91.3% and 100%, respectively, with poliarticular (≥5 joints) involvement in 47.8% and 74%, respectively. Entheseal and joint PD signal was positive in 52.2% and 47.8% of patients, respectively. Joint effusion and synovial hypertrophy were more frequent in MTF, MCF and carpal joints and PD signal in carpal and knee joints. We found no association between PDUS variables and clinical or analytical IBD variables, probably due to the yet small sample size. The intra-reader agreement was high (0.8 intra-class correlation variability).

Conclusion: Subclinical joint and entheseal PDUS abnormalities are common in IBD patients, regardless of clinical subtype, evolution time and intestinal activity. Prospective longitudinal studies are needed to define its predictive value of clinically overt musculoskeletal disease and its association with structural deterioration.

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3009

Stem Cell Augmentation for Cardiovascular Risk in Rheumatoid Arthritis. Nidhi Garg[1], Ashit Syngle[2] and Pawan Krishan[1]. [1]Punjabi University Patiala, India, Patiala, India, [2]Healing Touch City Clinic, Fortis Multispeciality Hospital, Chandigarh, India.

Background/Purpose: Bone marrow derived stem cells, endothelial progenitor cells (EPCs), protect against atherosclerotic vascular damage by overcoming endothelial damage. However, EPCs are depleted in RA and contribute to the enhanced cardiovascular (CV) risk. Therapeutic potential of augmenting EPCs to treat the heightened CV risk of RA has not yet been exploited. We aimed to investigate the effect of rosuvastatin on EPCs population, endothelial dysfunction, nitrite, adhesion molecules and on markers of inflammation in RA.

Methods: 50 RA patients were randomized to receive 24 weeks of treatment with rosuvastatin (10mg/day, n=25) or placebo (n=25) as an adjunct to existing stable antirheumatic drugs. EPCs (CD34+/CD133+) were quantified by Flow Cytometry. Flow mediated dilatation (FMD) was assessed by AngiodefenderTM (Everest Genomic Ann Arbor, United States). Inflammatory measures included DAS28, CRP, ESR and Pro-inflammatory cytokines (TNF-α, IL-6 and IL-1) were measured at baseline and after treatment. Estimation of serum nitrite, Lipids, and adhesion molecules (ICAM-1 and VCAM-1) was done at baseline and after treatment.

Results: At baseline, inflammatory measures, pro-inflammatory cytokines, adhesion molecules and nitrite levels were elevated and EPCs and endothelial function were impaired among both groups. At 24 wks: DAS28, ESR, CRP, TNF-α and IL-6 improved significantly ($p<0.05$) in rosuvastatin group. Concentration of serum nitrite ($p=0.02$) and ICAM-1 ($p=0.01$) was significantly lower in the rosuvastatin group compared with placebo. EPCs increased significantly from ($CD34^+/CD133^+$, 0.01 ± 0.001 to 0.035 ± 0.001, $p<0.01$) after treatment with rosuvastatin as compared with placebo and after 24 wks percentage change in EPCs was 71.4% and 22.2% in the rosuvastatin and placebo groups respectively (Fig.1). After treatment with rosuvastatin there was significant improvement in FMD ($p<0.01$) as compared to placebo. Rosuvastatin exerted positive effect on lipid spectrum by signicantly increasing HDL cholesterol levels ($p=0.01$) and decreasing LDL cholesterol ($p=0.02$). Significant inverse correlation was observed between EPCs and CRP ($r=-0.44$, $p=0.02$), TNF-α ($r=-0.42$, $p=0.03$), ICAM-1($r=-0.45$, $p=0.03$) and FMD($r=-0.47$, $p=0.01$) after treatment with rosuvastatin.

Conclusion: First study to show that rosuvastatin augments EPCs population in RA mediated by lowering the levels of cytokines, especially IL-6 and TNF-α, which downregulates adhesion molecule, CRP and nitric oxide production. This defines a novel mechanism of rosuvastatin treatment

in patients with RA: the augmentation of EPCs with improvement in inflammatory disease activity and endothelial dysfunction. The augmentation of EPCs by rosuvastatin represents a fascinating new approach for the management of RA.

Disclosure: N. Garg, None; **A. Syngle**, None; **P. Krishan**, None.

3010

The Development and Evaluation of a Self-Monitoring and Patient-Initiated Follow-up Service for People with Rheumatoid or Psoriatic Arthritis on Methotrexate. Hayley McBain[1], Michael Shipley[2], Abigail Olaleye[2], Samantha Moore[3], Shashi Hirani[4] and Stanton Newman[4]. [1]East London Foundation Trust, London, United Kingdom, [2]University College Hospital London, London, United Kingdom, [3]University College London, London, United Kingdom, [4]City University London, London, United Kingdom.

Background/Purpose: Patient-initiated services in rheumatology have been found to be cost-saving without compromising the clinical or psychosocial well-being of patients with rheumatoid arthritis. Self-monitoring is a technique used in many other long-term conditions and is associated with reductions in healthcare utilisation and mortality and has been found to be satisfactory from the patient's perspective. The aim of this study was to evaluate the efficacy of a service which integrates self-monitoring into patient-initiated follow-ups for patients with RA or PsA on methotrexate; in terms of healthcare utilisation and clinical outcomes; using a mixed methods approach including a randomised controlled trial (RCT) and qualitative semi-structured interviews.

Methods: One hundred patients with RA or PsA (according to ACR/EULAR/CASPAR criteria)on methotrexate were randomised to either an intervention group or usual care. All participants were assessed over 6 blood tests. Those in the intervention group attended one training session where they were taught how to monitor their blood test results and which symptoms and side effects they should report. These participants had no scheduled appointments with their rheumatology nurse during the trial period, but continued with their consultant appointments as usual. Blood test results were sent to intervention participants and along with their assessment of symptoms and side effects; patients initiated a review with their nurse, when necessary. If these reviews were required an immediate outpatient appointment was made. Healthcare utilisation was monitored throughout the trial period. Poisson regressions and multi-level modelling were used to explore the impact of the intervention on healthcare usage and clinical outcomes.

Results: There were no significant differences in clinical or demographic variables between the two groups at baseline. Across the trial period 77% of decisions made by intervention participants were considered to be safe. At the end of the trial period participants in the intervention group had 54.55% fewer appointments with their rheumatology nurse specialist ($p<0.0001$). There were no significant differences in the number of appointments with the rheumatologist or GP. Levels of pain, fatigue, ESR, CRP and disease activity did not differ between groups ($p>0.05$). Intervention participants were positive about the new model of care, valuing its efficiency and tailored approach. The service allowed patients to gain new knowledge and use this information along with the skills they obtained to take control of their health and arthritis.

Conclusion: After brief training patients with RA and PsA can successfully understand and interpret their blood test results and use this information along with reports of their symptoms and side effects to initiate appropriate reviews with their rheumatology nurse. Participants in the intervention group had fewer hospital appointments with their nurse specialist with no detrimental effects to their clinical status and with no increase in visits to the rheumatologist or GP. This model of care offers a viable alternative for established RA and PsA patients on DMARD therapy.

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3011

Ambulatory Gait Analysis in Clinical Practice: Single or Dual Task Conditions? Bernard Auvinet[1], Claude Touzard[2] and Vincent Goëb[3]. [1]Polyclinic, LAVAL, France, [2]Hospital of Laval, LAVAL, France, [3]Amiens University Hospital, Amiens, France.

Background/Purpose: Interest in ambulatory gait analysis is increasing thanks to validated gait analysis apparatus dedicated to clinical practice. Such methodology has to be reproducible, sensitive, specific and pertinent. Traditionally gait analysis was carried out during a walking test with no additional tasks (called single task (ST)). Recently due to the fact that gait control involves the cognitive domain, gait analysis has additionally been carried out using the dual task paradigm, when a task demanding attention is performed during walking - this type of gait analysis is known as Dual Task (DT). We hypothesize that gait analysis under ST or DT conditions has to be chosen according to the objectives of the clinician, as well as that of the choice of gait variables.

Methods: Locometrix is a validated accelerometric device which allows the measurement of the following gait variables: walking speed (WS, m/s), stride frequency (SF, Hz), stride length (SL, m), step symmetry (SS, dimensionless), stride regularity, an index of similarity of successive strides (SR, dimensionless), cranio-caudal power (CCP, W/Kg), high frequency energy modulus at heel contact (HFEM,%: a measurement of shock wave (SW)).

ST gait analysis was performed in three pathological conditions: 1- knee osteoarthritis compared to a control group (41 patients, age: 65 ± 10y, BMI 28 ± 4 kg/m^2, mean Lequesne index: $9\pm4/24$); 2- newly diagnosed Parkinson patients with no treatment, compared to a control group (22 patients, age 69 ± 9y, BMI: 26 ± 3 kg/m^2, mean motor score: 23.5 ± 3.0); 3-Fibromyalgia patients (52 matched pairs of female patients and controls, age: 44 ± 7y, BMI: 24 ± 4 kg/m^2).

DT gait analysis was performed in 80 elderly patients (age 68 ± 14y, BMI 25 ± 5 kg/m^2). suffering from gait instability, memory impairment, recurrent falls.

Results: Study 1: In knee osteoarthritis two gait variables are highly significant and relevant: area under the ROC curve (SR: 0.79 ± 0.05), SW: 0.78 ± 0.06)

Study 2: In Parkinson's disease two gait variables are highly significant and correlated to motor score: SR ($r=0.59$, $p<0.01$); CCP ($r=-0.65$, $p<0.003$)

Study 3: Fibromyalgia patients

- ROC curves confirmed the utility of SF (0.74 ± 0.04), SR (0.68 ± 0.05) and CCP (0.69 ± 0.05) in the identification of fibromyalgia patients,
- SR is correlated to the Fibromyalgia Impact Questionnaire ($r=-0.33$, $p=0.01$)
- SR is correlated to cognitive dysfunction measured by the Coping Strategy Questionnaire ($r=0.31$, $p=0.003$)
- CCP is correlated to pain (weekly VAS: $r=-0.33$, $p=0.01$)

Study 4: Gait exhibited no abnormality under ST in 13 patients. Gait abnormalities occurred under DT in each patient, moreover the decrease of one or more of the following gait variables (WS, SR, SF) alerted the clinician to an underlying neurological pathology.

Conclusion: The Single Task Gait Analysis condition is well adapted to knee osteoarthritis (SR and SW: a measurement of shock wave), to Parkinson's disease (SR, CCP: a measurement of kinesia); to fibromyalgia patients (SR, SF, CCP: a method for the identification of homogenous subgroups). Gait Analysis Test under Dual Task conditions is of major interest in exploring the cognitive reserve and explaining gait instability in the elderly.

Disclosure: B. Auvinet, CentaureMetrix, 1; **C. Touzard**, None; **V. Goëb**, None.

3012

Needs Assessment Survey – Evaluation of Sexual Dysfunction Among Patients at a Tertiary Rheumatology Clinic. Sharon Nesher Peleg[1], Ori Elkayam[2], Bruria Yahini[1] and Jacob N. Ablin[1]. [1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]Tel-Aviv Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

Background/Purpose: Sexual function is a major component of wellbeing and is adversely affected by many disease states. Previous studies have demonstrated various aspects of sexual dysfunction among rheumatological patients. These may include reduced libido, pain upon intercourse (dyspareunia) and erectile dysfunction; tenderness, limitations of range of motion and depression may have a compounding negative effect. In a previous study we have demonstrated aspects of sexual dysfunction found among fibromyalgia patients. The aim of the current preliminary study was to evaluate aspects of sexual dysfunction among rheumatological patients. We also wished to evaluate the needs of rheumatological patients vis-à-vis sexological counseling, in order to assess the need for establishing a reproductive health clinic at our rheumatology center and design future interventions in this field. A similar approach has been previously used for evaluation the needs of cancer patients.

Methods: Patients: patients were recruited among those attending the rheumatology clinic at the Tel Aviv Sourasky Medical Center from a broad range of rheumatological diagnoses. Participants filled out the following questionnaires:

1. A demographic questionnaire
2. Self-report Sexual questionnaire which was translated into Hebrew and adapted for the needs of the patients at the rheumatology institute-. This questionnaire included questions regarding common domains of sexual dysfunction, including decreased libido, difficulty achieving arousal, difficulty in achieving an erection (males) or vaginal dryness (females) pain during intercourse, difficulty in achieving an orgasm, and feeling unattractive sexually.

Results: Forty three patients were recruited, (8 males and 35 females). The most frequent age group of the patients was 41–50.

Diagnoses included Rheumatoid arthritis (50%), Osteoarthritis (3.2%), Fibromyalgia (13%), Systemic Lupus Erythematosus (3.2%) Psoriatic arthritis (13%), Other. 31% reported being currently active sexually.

41 % expressed interest in receiving attention for their sexual issues by the attending rheumatologist and 19% would be interested in receiving specialized sexual consultation with their partner, in the context of the rheumatology follow up.

Among female patients, 25.7% reported a decrease in libido. 17.1% reported pain during sexual intercourse and 17.1% reported difficulty achieving sexual arousal. 14.3% reported vaginal dryness and a decrease sense of attractiveness respectively. 11.4% reported difficulty in achieving an orgasm.

Conclusion: Sexual dysfunction is highly prevalent among rheumatology patients. While not routinely evaluated in clinical practice, this issue appears to be pertinent for many patients who also express interest in receiving specific advice and treatment, as part of their rheumatological follow up. Rheumatological health care providers should be aware of this important aspect of the quality of life of their patients and should feel comfortable about raising the topic during the course of follow up. Further research is warranted into the specific causes of sexual dysfunction in various rheumatological populations and regarding the optimal treatment of these problems.

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3013

The Reserve Capacity Model in Patients with Rheumatoid Arthritis: Understanding the Relationship of Socioeconomic Status, Psychosocial Resources, Mood, and Pain. Desiree Azizoddin[1], Taylor Draper[1], Sarah Ormseth[1], Perry M. Nicassio[1], Michael R. Irwin[1], Michael Weisman[2] and Hilary Wilson[1]. [1]University of California, Los Angeles, Los Angeles, CA, [2]Cedars-Sinai Medical Center, Los Angeles, CA.

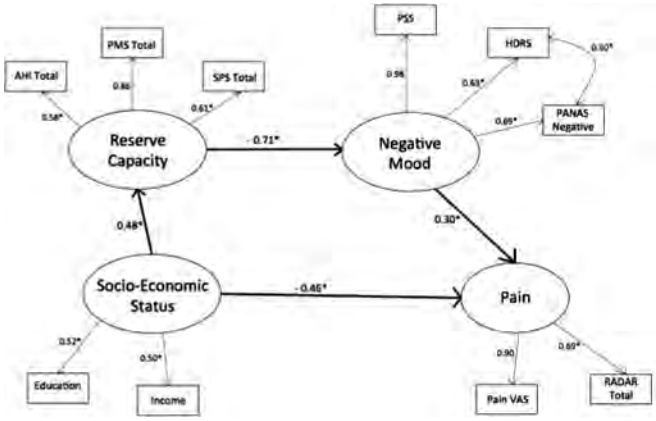
The Reserve Capacity Model in Patients with Rheumatoid Arthritis: Understanding the Relationship of Socioeconomic Status, Psychosocial Resources, Mood, and Pain.

Background/Purpose: The reserve capacity model is a framework for understanding how low SES may affect health outcomes through both positive and negative emotions separately and the depletion of psychosocial resources. The purpose of this study was to explore the reserve capacity model in persons with rheumatoid arthritis, using structural equation modeling (SEM; see Figure 1). It was hypothesized that SES would be negatively related to self-reported pain directly and/or indirectly through the potential mediators of positively related psychosocial resources (reserve capacity) and negatively related negative mood.

Methods: Data of 106 participants were drawn from a randomized comparative efficacy trial of psychosocial interventions for RA. In the hypothesized model, SES (years of education and annual income) predicted pain (Pain VAS and Rapid Assessment of Disease Activity in Rheumatology total joint score) through reserve capacity (Personal Mastery Scale, Arthritis Helplessness Index, and Social Provisions Scale), and negative mood (Hamilton Depression Rating Scale, Perceived Stress Scale and the Positive and Negative Affect Schedule), using EQS 6.1 to evaluate the structural model.

Results: SEM revealed a confirmed the hypothesized relations among model constructs (see Figure 1). Higher SES was positively associated with reserve capacity, which predicted lower levels of negative mood and related directly and positively to pain severity. The indirect effect of SES on pain via reserve capacity and negative mood was significant ($\beta_{indirect} = -.10$, $p = .027$). Evidence supported a partial mediation of reserve capacity and negative mood between SES and pain, as the direct effect of SES on pain remained significant after controlling for the attenuating mediators of reserve capacity and negative mood.

Conclusion: These findings underscore the importance of a multidimensional framework in evaluating pain in RA using a structural-equation approach. The mediating variables of reserve capacity and negative mood may play major roles in explaining pain in RA, and represent modifiable factors for targeted interventions.



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3014

Does the Order or Amount of Risk-Benefit Information Presented Influence patients' Perceived Value of a Proposed New Medication? Liana Fraenkel[1], Richard Street[2], Harjinder Chowdhary[3], Sarah Swift[3] and Ellen Peters[4]. [1]Yale University School of Medicine, Veterans Affairs Connecticut Healthcare Systems, New Haven, CT, [2]Texas A&M University, College Station, TX, [3]Yale University, New Haven, CT, [4]Ohio State University, Columbus, OH.

Background/Purpose: The order and amount of information has been shown to influence risk perceptions related to hazards. In this study we sought to examine whether order and amount of risk and benefit information influences patients' perceived value of a proposed new medication.

Methods: We created 5 videos of a physician describing a new medication. The videos were identical except for the order and number of side effects (SEs) and benefits presented (see Table). Subjects with a systemic inflammatory rheumatic disease were randomly assigned to view one of the videos. Perceived medication value (PMV) was assessed by having subjects choose: the risks outweigh the benefits, the risks and benefits are equally balanced or the benefits outweigh the risks. We subsequently examined whether differences in the order and amount of information was associated with subjects' PMV. This outcome was chosen because one's overall impression more strongly predicts behavior than recall of verbatim information. We also examined the association of demographic characteristics (age, minority status, and difficulty paying for medications), attitudes towards illness and treatment (factor analysis of illness perceptions, patient activation and trust resulting in 4 factors: worry about illness, perceived treatment efficacy, impact of illness, patient activation), and current medications on PMV using bivariate analyses. Variables found to be significant ($p<0.05$) were included in a multinomial logistic regression model. Because of the known influence of numeracy on risk perception, all analyses were stratified by high versus low subjective numeracy (dichotomized at the median).

Results: 389 subjects participated: mean (SD) age= 55 (14), 75% female, 40% minority (African American and/or Hispanic). In bivariate analyses, the order and number of SEs and benefits, current use of prednisone, and minority status were associated with PMV in subjects with high numeracy (n=242). Presenting SEs first or between benefits were both associated with more negative PMV compared to the reference video (3 benefits followed by 6 SEs) (See Table). Among subjects with low numeracy (n=142), the order and

number of risk and benefits presented were not associated with PMV. In bivariate analyses, use of a biologic, difficulty paying for medications, perceived treatment efficacy, patient activation, and minority status, were associated with PMV in subjects with low numeracy. Except for current use of a biologic, all remained significant in the multivariate model (see Table).

Conclusion: Order and amount of information matter, but only in patients with high subjective numeracy. Minority patients have a much more negative PMV compared to Caucasian, non-Hispanic patients, regardless of their level of numeracy.

Table: Multinomial logistic regression model examining association of risk-benefit presentation and patients characteristics on perceived medication value.

Variable	Perceived Medication Value (Ref= Risks outweigh Benefits)	Adjusted Odd Ratio (95% CI)
High Numeracy		
Video (Ref= 3 benefits → 6 SEs)		
6 benefits → 6 SEs	Balanced	1.87 (0.59–5.98)
	Benefits outweigh Risks	0.45 (0.14–1.48)
6 benefits → 3 SEs	Balanced	0.79 (0.24–2.64)
	Benefits outweigh Risks	0.60 (0.19–1.83)
6 SEs → 3 benefits	Balanced	0.47 (0.16–1.40)
	Benefits outweigh Risks	**0.20 (0.07–0.58)**
3 benefits → 6 SEs → 3 benefits	Balanced	0.54 (0.18–1.66)
	Benefits outweigh Risks	**0.26 (0.09–0.78)**
Currently on prednisone	Balanced	0.75 (0.34–1.67)
	Benefits outweigh Risks	1.77 (0.82–3.80)
Minority vs Caucasian	Balanced	0.95 (0.48–1.89)
	Benefits outweigh Risks	**0.25 (0.11–0.58)**
Low Numeracy		
Perceived treatment efficacy	Balanced	1.46 (0.90–2.37)
	Benefits outweigh Risks	**2.22 (1.28–3.83)**
Patient activation	Balanced	**1.75 (1.09–2.81)**
	Benefits outweigh Risks	1.05 (0.62–1.78)
Currently on a biologic	Balanced	1.13 (0.35–3.66)
	Benefits outweigh Risks	2.64 (0.87–8.04)
Difficulty paying for medications	Balanced	**0.17 (0.07–0.44)**
	Benefits outweigh Risks	0.73 (0.27–2.00)
Minority vs Caucasian	Balanced	**0.23 (0.09–0.62)**
	Benefits outweigh Risks	**0.22 (0.08–0.63)**

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3015

Evaluation of the effuc Educational Needs Assessment Tool (ENAT) Focused Patient Education on Health Outcomes in Patients with Rheumatolid Arthritis - a Randomised Controlled Trial. Adewale O. Adebajo[1], Dawn Johnson[2], Hardware Bernadette[3], Claire Hale[4] and Mwidimi Ndosi[4]. [1]University of Sheffield, Sheffield, United Kingdom, [2]Barnsley Hospital NHS Foundation Trust, Barnsley, United Kingdom, [3]Barnsley Hospital NHS Foundation Trust, Baarnsley, United Kingdom, [4]University of Leeds, Leeds, United Kingdom.

Background/Purpose: The Educational Needs Assessment Tool (ENAT) is a quick and simple, self completed questionnaire that ensures that patient education is relevant, appropriate and timely for people with Rheumatoid Arthritis (RA). It has been validated for use in RA and six other rheumatic diseases and has been cross-culturally adapted into nine European languages. Our aims were (i) to evaluate the effectiveness of ENAT focused patient education on self-efficacy, patient knowledge and health outcomes (physical function, symptoms, role/work, social interaction and psychological status/affect) (ii) to evaluate the usability of the ENAT in clinical practice, from both a practitioner and patient perspective.

Methods: This was a mixed methods (quantitative and qualitative) study conducted in seven rheumatology centres across the United Kingdom. Patients were randomised to either the ENAT group (EG) where patients completed the ENAT which was then used as a template by the Nurse Practitioner (NP) to meet their educational needs; or usual care (UC) by NP without the ENAT. Patients were seen at baseline then at weeks 16 and 32. The outcomes were self-efficacy (ASES), health status (AIMS2-SF) and patient knowledge (PKQ). The primary outcome was self-efficacy (ASES) at week 32. The ASES has two subscales: ASES-Pain and ASES-Other symptoms.

Results: A total of 132 patients were entered into the study of which 70 received ENAT (53%) and 62 usual care (47%). At week 16, there were no significant between-group differences. By week 32, the ASES mean scores, were higher for the ENAT group than the usual care group; ASES-Pain, MD=4.36(95%CI: 1.17, 7.55), t=2.72, P=0.008; ASES-Other symptoms, MD=5.84(95%CI: 2.07,9.62), t=3.07, P=0.003). (Bonferroni-adjusted P-value = 0.025 for significance at the alpha level). While there were no significant changes in ASES scores in the usual care group over the whole follow-up period, the ENAT group saw significant improvements in ASES-pain and ASES-Other symptoms scores, suggesting that the ENAT helped improve patients' self-efficacy. Initially, patients were asked if they wanted any education about their arthritis (yes/no); at week 0, 33 patients (48%) said 'yes' and this dropped to 13 (21%) at week 16 and 9 (16%) by week 32 (Chi Sq.=18.76, $p < 0.001$). Trends over time reveal significant decrease in the overall ENAT score for all domains (managing pain, movement, arthritis process, self-help measures and support) except the feelings domain. The decrease in the total ENAT score by the end of the study, indicates that patients' educational needs were being met effectively.

Qualitative interviews were undertaken with patients and Nurse Practitioners. All found the ENAT to be a comprehensive and easy to use tool. For most patients, the process helped them to focus on what they needed to know from the NP and for some, it made them think of additional questions to ask and topics to think about. Both the EG and the CG perceived that they were getting a good and adequate education provision from their NP.

Conclusion: This is the first study to report the effects of ENAT-focused education in people with RA. The results of the primary outcome (ASES-Pain and ASES-Other symptoms) suggest that the ENAT could be a useful addition to usual care.

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3016

Measuring the Impact of an Early RA Support and Education Program Using a Program Evaluation with Patient Identified Outcomes. Adena Batterman[1], Kathryn Klingenstein[1], Roberta Horton[1], Linda Leff[1], Theodore R. Fields[2] and Vivian P. Bykerk[1]. [1]Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery Weill Cornell Medical College, New York, NY.

Background/Purpose: The Early RA Support and Education Program addresses the unique psycho-educational needs of people recently diagnosed (<2yr) with RA. This free monthly program is co-facilitated by an MSW and RN and was developed based on a needs assessment with patient input; it features an RA- focused lecture followed by a support group, aimed at enhancing emotional coping and disease management. In order to measure program impact on concerns most relevant to new RA patients, we developed an evaluation tool incorporating patient identified outcomes (Hewlett, 2003), on which we previously reported. Since that time, we have piloted the evaluation and now report on the results.

Methods: Through a multi-level collection of data, we identified patient derived program outcomes and language most relevant to participants. This process yielded 3 key domains: Managing RA, Connecting with Others with RA and Coping with the Emotional Impact (Wolrich, 2011). From this data we created a 20-item evaluation, using a 6 point Likert scale and open-ended questions, which incorporates patient identified outcomes under each of the domains. This new tool was administered to participants after each of 12 monthly sessions.

Results: 127 evaluations were completed from 180 participants. Demographics: Gender: 93%F; Mean age: 49; Ethnicity: White 59%; African American 19%; Asian American 11%; Latino 11%; Education: College or higher: 92%. Results indicate % of participant agreement (either "completely" or "a great deal") with the following Likert scale question statements, which represent each of the 3 key domains. I. MANAGING RA: As a result of this session, I feel. . . *"more prepared to discuss my RA treatment with my doctor"* (84%); *"I can make informed choices about my RA"* (90%). II.CONNECTING WITH OTHERS: *"Speaking with other group members, I feel more hopeful about my RA"* (77%). *"Sharing information and feelings in the group helps me cope with RA"* (89%). III EMOTIONAL IMPACT: Participating in this program makes me feel. . ."*more confident in managing my RA"(79%); "my RA is less disruptive to my daily life than it was before"* (61%).

Responses to open ended questions re learning and impact supported the program's value within the 3 domains: Managing ("will follow up with MD

about what I learned"); Connecting ("I don't feel so alone"); Emotional Coping ("learned ways to deal with stress of RA").

Conclusion: Evaluation results indicate that in domains I and II, and in domain III, "more confident in managing my RA", the program is making a strong positive impact. In domain III, " RA is less disruptive to my daily life," results reflect positive impact, though not as marked as in other questions. Future work is needed to explore how patients define "disruptive" and develop targeted content to address this for future groups. Future research might also follow participants longitudinally, to determine how program participation over time, and other variables, impact this outcome. This tool was administered to measure how effectively the program meets patient identified needs. Our process can serve as a model for including the patient perspective in evaluating outcomes in other disease specific support and education programs.

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3017

Program Evaluation of 'the Joint Clinic': An Innovative Clinical Service for Patients with Hip or Knee Osteoarthritis. J. Haxby Abbott[1], Helen Harcombe[1], Chris Crane[2], Liam Hutton[2], Kirsten Stout[2], Cathy Chapple[1] and David Gwynne-Jones[1]. [1]University of Otago, Dunedin, New Zealand, [2]Southern District Health Board, Dunedin, New Zealand.

Background/Purpose: In socialized healthcare systems with free public access to healthcare, there are circumstances wherein patients referred by general medical practitioners (GPs) for specialist physician consultation may not be not offered a first specialist appointment (FSA), when demand exceeds supply. Thus, clinical prioritization is necessary. To address unmet need for FSA in patients with hip or knee osteoarthritis, we initiated and evaluated a physical therapist-led clinic offering non-surgical management of osteoarthritis and outpatient treatment.

Methods: We conducted a program evaluation comprising: a proof-of-concept evaluation, an implementation evaluation, a process evaluation, and an outcomes evaluation. Mixed-methods qualitative and quantitative methodology grounded in health services research were used. Patients, GPs, surgeons, and hospital clinical, management and administrative staff were interviewed and/or surveyed. Patient trajectories were analysed and patient-reported outcome measures were assessed.

Results: The concept model was supported by best-practice literature, and was implemented in close concordance with the model proposed. Qualitative interviews and survey data indicate the "Joint Clinic" has been well accepted by key stakeholders and end-users, is functioning well within the host organisation, is accessible and operating at close to intended capacity. In the 2-year evaluation period, the clinic served 358 new patients [53% female, mean(sd) age 66(10), BMI 29.9(7.5)] in 637 consultations. Unmet need was reduced by 80% compared with pre-implementation for hip/knee OA patients; 30% overall. 31% of patients experienced clinically significant (>20%) improvement on patient-reported outcome measures. 25% of patients were referred for FSA (mean wait 77 days) for fast-track access to joint replacement surgery. 70% of patients were satisfied to be seen by the "Joint Clinic" instead of an orthopaedic surgeon; 98% were satisfied with the knowledge and expertise of the "Joint Clinic" staff; 80% would recommend the clinic to others. Cost-per-patient was NZ$384 (year 2). The host organisation has accepted the service as value-for-money and sustainable.

Conclusion: These data indicate successful implementation and functioning of an innovative service. The service is achieving satisfactory outcomes benefiting patients through clinically significant improvement, monitoring on optimal non-surgical management, or fast-tracked referral for joint replacement surgery.

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3018

Testing of a Newly Developed Computerized Animated Activity Questionnaire for Assessing Activity Limitations in Patients with Hip and Knee Osteoarthritis. Wilfred FH Peter[1], Mick Loos[1], Henrica de Vet[1], Maarten Boers[1], Jaap Harlaar[1], Leo D. Roorda[2], Rudolf Poolman[3], Vanessa Scholtes[3], Jan Bogaard[1], Hilda Buitelaar[1], Martijn P.M. Steultjens[4], Ewa M. Roos[5], Anne-Christine Rat[6], Francis Guillemin[7], Maria Grazia Benedetti[8], Antonio Escobar Martinez[9], Nina Østerås[10] and Caroline Terwee[1]. [1]VU University Medical Center, Amsterdam, Netherlands, [2]Amsterdam Rehabilitation Research Center Reade, Amsterdam, the Netherlands, Amsterdam, Netherlands, [3]Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands, [4]Glasgow Caledonian University, Glasgow, Scotland, [5]University of Southern Denmark, Odense, Denmark, [6]University of Lorraine, Nancy, France, [7]INSERM, Centre d'Investigation Clinique - Epidémiologie Clinique (CIC-EC) CIE6, Nancy, France, [8]Istituto Ortopedico Rizzoli, Bologna, Italy, [9]Basurto University Hospital, Bilbao, Spain, [10]Diakonhjemmet Hospital, Oslo, Norway.

Background/Purpose: Self-report questionnaires and performance-based tests correlate moderately in measuring activity limitations, indicating that they measure different aspects. Self-reports measure mainly how patients think they perform an activity, and is influenced by pain, fatigue or situations they are referring to. This may lead to cross-cultural differences. Performance-based tests measure an artificial situation, is resource-intensive and burdensome for patients. To overcome these drawbacks we developed and tested a pilot version of an Animated Activity Questionnaire (AAQ), which demonstrated some promising features[1]. The aim of this study was to develop a computerized Animated Activity Questionnaire (AAQ) to assess activity limitations in patients with hip/ knee osteoarthritis and preliminary testing of its validity and reliability.

Methods: Based on the pilot version, International Classifications of Functioning core set for osteoarthritis, focus groups of patients, and existing measurement instruments, the AAQ was developed. In 482 patients correlations were calculated between the Animated Activity Questionnaire (AAQ) and self-reported Hip disability and Knee injury Osteoarthritis Outcome physical functioning score. In addition internal consistency was calculated. In 65/482 patients also correlations with performance based tests (Stair Climbing Test, Timed Up and Go test, and the 30 second Chair Stand Test) were calculated. Test-retest reliability was assessed by repeated scoring in 56/482 patients.

Results: The Animated Activity Questionnaire (AAQ) includes animated videos of 17 basic daily activities with four levels of increasing difficulty (check the following link for two examples: http://kmin-vumc.nl/_14_0.html). Patients were asked to select the video that best matched their own performance. Cronbach's alpha was 0.95. Correlation with self-reported physical functioning scores was high (0.72). The AAQ correlated moderately with the performance based tests (0.49, 0.44, and 0.57, respectively). Correlations of the AAQ score with pain was lower (0.51) than the correlation of the self-reported physical functioning score with pain (0.75). For test-retest reliability, a Intraclass Correlation Coefficient of 0.97 (95% Confidence Interval 0.93–0.98) was found.

Conclusion: A computerized Animated Activity Questionnaire (AAQ) was developed showing a high internal consistency and excellent test-retest reliability. Content validity was considered good, and construct validity is supported by high correlations with self-reported physical functioning and moderate correlations with performance-based tests. The AAQ seems to be less influenced by pain compared with self-reported physical functioning. Since the AAQ needs no reading ability or translation, it has potential for international use. Continuing research will focus on construct validity and cross-cultural validity.

Reference

Terwee CB et al. Development and Validation of the Computer-Administered Animated Activity Questionnaire to Measure Physical Functioning of Patients With Hip or Knee Osteoarthritis. Phys Ther. 2014 Feb;94(2):251–61.

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